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# DISSERTATION

# Mechanism of action of intravenous immunoglobulins in Multiple Sclerosis Studies of gene expression profiles in peripheral T cells

Ausgeführt zum Zweck der Erlangung des akademischen Grades eines Doktors der Naturwissenschaften unter der Leitung von

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"From the brain and the brain alone arise our pleasures, joys, laughter and jests, as well as our sorrows, pains and griefs" *Hippocrates* 

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#### Zusammenfassung

Polyspezifische humane IgG Produkte (Intravenöses Immunglobulin, IVIG) werden erfolgreich bei der Behandlung von zahlreichen Autoimmunerkrankungen, die das zentrale Nervensystem betreffen, eingesetzt. Ein relativ neues Anwendungsgebiet für IVIG in diesem Sektor ist Multiple Sklerose (MS).

Obwohl IVIG einen substantiellen Effekt bei Kurzzeit- und Langzeitbehandlungen zeigt, sind die genauen Wirkungsmechanismen noch weitgehend unbekannt.

Der positive Effekt der IVIG Behandlung könnte durch eine Veränderung der T-Zell-Antwort im Zuge der Immunantwort verursacht werden.

Deshalb war das Ziel meiner Dissertation die Identifizierung und Charakterisierung von Genen, die in den immunmodulatorischen Altivitäten von IVIG bei der Behandlung von Schüben bei Patienten, die an rezidivierend-remittierender MS (RRMS) leiden, involviert sind.

Mit Hilfe von Microarrays konnten wir die Expressions-Profile von T-Zell-Fraktionen untersuchen. Die T-Zellen wurden aus peripheren Blut-Mononucleären Zellen (PBMC) der 10 Patienten, die an unserer klinischen Studie teilgenommen haben, isoliert. Zur Kontrolle wurde eine Gruppe von 5 Patienten mit intravenösem Methylprednisolone (IVMP) behandelt. Unter den 22.000 Genen, die auf dem Chip lokalisiert sind, fanden wir 152 verschiedenen Gene oder 176 verschiedenen Probe-Sets, die zumindest in 40% der Patienten mindestens 2-fach verändert waren und somit differentiell expremiert wurden. Die meisten der Proteine, die durch die Gene codiert werden, spielen eine Rolle in Immunantwort, Entzündungserscheinungen, Proliferation, Apoptose, Zellzyklus, Signaltransduktion oder Regulierung von Transkription. All diese biologischen Aktivitäten könnten mit der Regulation der Krankheits-Aktivität in Patienten, die an RRMS leiden, assoziiert sein.

Zur Verifizierung der Microarray-Daten wurde ebenfalls eine statistische Untersuchung des Datensatzes durchgeführt, bei der die Daten mit Hilfe eines parametrischen t-tests analysiert wurden. Dieser Ansatz ergab eine gänzlich unterschiedliche Anzahl an differentiell expremierten Genen. Ein Vergleich der zwei verschiedenen Ansätze ergab nur eine geringe Zahl an Genen, die in beiden Methoden gleich verändert waren. Diese Unterschiede in den Ergebnissen der Genespressions-Studie ist ein bekanntes Problem in der Literatur. Um

reproduzierbare und vergleichbare Expressions-Daten einer Microarray-Analyse zu bekommen, ist eine internationale Standardisierungs-Richtlinie nötig.

Zusammenfassend glauben wir, durch diese zwei Methoden Gen-Sets gefunden zu haben, die bei der biologischen Aktivität von IVIG bei der Behandlung von Patienten, die an einem akuten MS-Schub leiden, eine zentrale Rolle spielen.

#### Abstract

Intravenous immunoglobulins (IVIG) have been used successfully in the treatment of a number of autoimmune diseases of the central nervous system including multiple sclerosis (MS).

Although IVIG seems to have a substantial effect on short- and long-term treatment potential, the underlying mechanisms of action are not elucidated.

The benefical effects of IVIG treatment might be caused by a modulation of the T cell immune response. Therefore, the aim of my PhD-thesis was the identification and characterization of genes involved in the immunomodulatory activity of IVIG in the treatment of exacerbations in Relapsing-Remitting MS (RRMS).

Using microarrays we investigated the expression profiles of T cell fractions of peripheral blood mononuclear cells (PBMC) isolated from 10 RRMS patients treated with IVIG as well as five control patients treated with intravenous methylprednisolone (IVMP). Among the approximately 33.000 genes examined, we found 152 different genes (176 probe-sets) which were differentially regulated by a minimum of a two-fold change in at least 40% of patients. Most of the proteins encoded by these genes are known to be involved in immune response, inflammatory response, proliferation, apoptosis, cell cycle, signal transduction or regulation of transcription. All these biological activities might be associated with the regulation of disease activity in patients with RRMS. Statistical analysis by parametric t-test revealed a different number of significantly differentially regulated genes. When comparing the results obtained with both approaches, only a few genes were in common. Differences in the results obtained from gene expression profiles using different approaches for the evaluation of the data are a known problem in the literature. International standartization of statistical approaches for the evaluation of gene expression data obtained from microarray analysis will be necessary to generate reproducible and comparable results in different laboratories.

In conclusion we believe to have identified two set of genes by using two different methods – a non statistical and a statistical approach - that are likely involved in the biological activity of IVIG in patients suffering from acute exacerbations.

# INTRODUCTION

# 1.1 Intravenous Immunoglobulins (IVIG)

#### 1.1.1 Introduction

Immunoglobulins are proteins produced by cells of the B lymphocyte lineage of the immune system and are the major effector molecules of the humoral immune response.

Intravenous immunoglobulins (IVIG) are prepared from plasma pools of 15.000-

50.000 healthy donors and contain > 97% of intact IgG molecules and, depending on the product, small traces of IgM and IgA molecules. The IgG subclasses are distributed similar to normal serum.

Therefore, IVIG comprises a broad range of immune antibodies directed to pathogens and foreign antigens that are essential for substitution-treatment of patients with primary and secondary immune deficiencies.

Primary immunodeficiency disorders are a group of genetic diseases in which the body is unable to produce adequate amounts of its own antibodies and is at increased risk of severe and partially life-threatening infections. Among these diseases there are agammaglobulinemia and hypoglobulinemia, common variable immunodeficiency (CVID), severe combined immunodeficiencies (SCID) and Wiskott-Aldrich syndrome.

Secondary immunodeficiencies are disorders in which the patients are unable to produce antibodies due to another underlying condition, and they suffer from severe infections. Among these diseases there are myeloma or chronic lymphocytic leukemia, children with congenital AIDS and recurrent infections, bone marrow and other transplantations in which chemotherapy can result in a period of immunodeficiency.

IVIG has proven efficiency in controlled clinical trials for the treatment of autoimmune thrombocytopenic purpura, Guillain Barrè syndrome, chronic inflammatory demyelinating polyneuropathy, acute myasthenia gravis, multifocal

motor neuropathy, steroid-resistant dermatomyesitis, autoimmune uveitis, Kawasaki syndrome and ANCA-associated vasculitides (1).

Pharmacokinetics of most IVIG preparations reflect metabolic properties of normal IgG. After infusion in normal individuals and patients, serial determinations of total IgG result in biphasic plasma or serum disappearance curves with an initial  $\alpha$  phase, which represents early catabolism and distribution between body compartments, and a final  $\beta$  phase representing catabolism.

In immunologically normal persons the half-life values of IVIG preparations were between 14 – 24 days, while those of various IgG antibodies were between 12 – 35 days (A).

In general there was a prolonged half-life of infused IgG in patients with congenital humoral immunodeficiencies (A).

#### 1.1.2 History of IVIG

Immunotherapy was started at the Charitè Hospital in Berlin more than 100 years ago with the administration of diphtheria antitoxin sera of animal origin under the supervision of von Berhring, Ehrlich and Kitasato from the Robert Koch Institute.

Initially, immunoglobulin was used as a prophylaxis or treatment against measles, tetanus, diphtheria, hepatitis B and pertussis. In 1952 for the first time immunoglobulin preparations from human blood were used in clinical medicine to treat immune deficiency conditions. The only available preparations at that time required intramuscular administration (IMIG). But intramuscular administration was painful for the patient, muscle proteases degraded many of the infused immunoglobulins and the remaining IGs only reached the circulation after delay. The injections were also limited in dose and frequency.

Nowadays there are preparations for intravenous administration available. Initially IVIG preparations were used for substitution of immune deficiencies but they are now used as therapeutic and prophylactic reagents, too.

Because the concentration of any single antibody in a normal IVIG preparation is relatively low, high doses are required to be clinically effective.

The process of fractionating large volumes of human plasma was developed by E.J. Cohn in the 1940s in the Department of Physical Chemistry at Harvard Medical School. Originally, the Cohn fractionation procedure was developed to produce albumin solutions as blood substitution during World War II. But it has proven to be useful in large-scale separation of other classes of therapeutic plasma proteins.

This cold ethanol fractionation process which was developed by Cohn is used to produce three protein fractions: an IgG concentrate, an intermediate in the production of coagulation factors VII and IX, and human serum albumin, the only fraction which does not require additional purification steps. The process might produce an IgG fraction with a purity of > 97% (w/w).

IgG produced by Cohn ethanol fractionation was historically freeze-dried to remove ethanol and to produce a stable intermediate fraction. But this promotes the formation of IgG aggregates at the expense of monomeric IgG.

In 1962 the formation of IgG aggregates which lead to spontaneous complement activation was proposed as the principal cause of adverse side effects when intramuscular immunoglobulin (IMIG) was injected intravenously. Therefore anticomplement activity hemolytic tests became routinously used.

From this time on commercial IVIG preparations tended to reduce the anticomplement activity, either by enzymatic digestion or chemical modification.

In 1986 McCue and co-workers developed stable IVIG solutions by adjustment of the pH (4).

Cold ethanol fractionation has been considered as a sufficient process for the elimination and inactivation of viruses due to high concentrations of ethanol at low temperature. In the 80s plasma pools were contaminated with HIV and patients treated for hemophilia with other blood products made out of the same pool, were transmitted with AIDS.

Today IVIG preparations are manufactured in accordance with standardized safety measures to ensure a maximum of safety, beginning with strict selection of only highly qualified donors and prescreening and screening for viruses by PCR. Donations containing high titers of human parvovirus B19 nucleic acids, HIV, HCV or HBV are rejected. The plasma is also screened for alanine aminotransferase

(ALT) levels, a measurement for liver function. All plasma units are held for at least 60 days and released only after the donor returns for subsequent donation of plasma. This procedure ensures that a donor infected by a certain pathogen, but does not show any clinical symptoms at the time of donation, is identified by the subsequent testing and screening.

The manufacturing process of, for example Endobulin S/D includes plasma collection with HIQ-PCR testing of plasma pilot pools and plasma production pools for HIV-1, HIV-2, HBV and HCV, Cohn-Oncley Fractionation for isolating the immunoglobulins from coagulation factors and inhibitors, DEAE-Sephadex chromatography for IgA depletion - yielding a product with a high level of monomeric and dimeric IgG and virus removal against some lipid (HIV, pseudo rabies virus PRV) and all investigated non-lipid enveloped viruses (HAV, MMV), sovent/detergent treatment for viral inactivation of all lipid-enveloped viruses tested to date (HIV, HCV, HBV) by incubating fraction II with solvent tri(n-butyl) phosphat (TNBP) and the detergents Triton X-100 and Tween 80, removal of the solvent/detergent by binding of IgG to an electrostatic matrix while the rest of the either negatively or neutral chemicals is washed away, incubation of fraction II with hydrolases at 37° for the inactivation of vaso active substances, PEG precipitation with polyethylene glycol for removal of aggeregates which may have been formed during incubation, and finally sterile filtration and addition of stabilizing agents like sodiumchloride and glucose to preserve antibody activity and prevention of aggregation of the monomeric IgG and freeze drying.

Open-label studies of pharmacokinetics and tolerance in primary immunodeficiency patients showed no occurrence of virus transmission, a low number and no serious adverse side effects. The risk of adverse/anaphylactic reactions is minimized by testing for parameters known to cause reactions. Furthermore, there are also animal models to assess the potential for adverse events caused by hypotensive and bronchospastic substances (like aggregates). All these actions taken today are to ensure maximal safety and tolerability for patients.

# 1.1.3 Mode of action of IVIG

IVIG preparations have shown to be effective in the treatment and prophylaxis of infectious complications in patients with primary or secondary humoral immunodeficiencies as well as in the treatment of various autoimmune diseases. But the precise mechanism of action underlying these immunomodulatory activities has not been elucidated.

There are at least four models to explain the immunomodulatory potential of IVIG in patients suffering from autoimmune and inflammatory diseases:

- I. Fcγ-Receptor-Mediated Immunomodulation
- II. Influence on Idiotype/Anti-Idiotype Network
- III. Elimination of Immunostimulating Microbial Products
- IV. Immunomodulatory Effects of Ig-associated Molecules

## I. Fcγ-Receptor-Mediated Immunomodulation

IG preparations available on the market mainly consist of IgG (in particular IgG1 and IgG2). IgG1 especially can bind via the Fc part not only to Fc receptors I-III (CD64, CD32, CD16) but also to C1q. IgG1 is also able to bind to cell-bound complement receptors (CD11b, CD11c) by activation and binding of other complement factors, but the best complement activator is IgG3 which is only contained to a small amount in IVIG preparations. IgG1 and IgG3 bind with high-affinity to FcyRI expressed on macrophages, neutrophils and also eosinophils. In general, there are three distinct FcyR classes: FcyRI, FcyRII and FcyRIII with different IgG class specificities and binding affinities. The only high affinity receptor due to its third extracellular domain is FcyRI (CD64) with its specifity for IgG1 and IgG3. It can bind monomeric and aggregated Ig and functions mainly in phagocytosis. FcyRII (CD32) is a low affinity receptor which binds IgG in the form of immune complexes with a specificity for IgG1 and IgG3. FcyRIIA is mainly

expressed by macrophages and neutrophils and functions in phagocytosis and cell activation while Fc<sub>γ</sub>RIIB is mainly expressed by B lymphocytes and functions in feedback inhibition of B cells. Fc<sub>γ</sub>RIII (CD16) bind immune complexes with low to

medium affinitiy.  $Fc\gamma RIIIA$  is expressed by Natural Killer cells (NK) cells and functions in ADCC,  $Fc\gamma RIIIB$  is expressed by neutrophils and functions in phagocytosis (2).

As  $Fc\gamma$  and complement receptors are mainly expressed by immune cells like B cells, T cells, NK, monocytes/macrophages, dendtritic cells and granulocytes, activation can lead to intracellular signaling cascades resulting in immunomodulatory consequences.

Fc receptors can bear either activation (ITAMs) or inhibiting (ITIMs) motifs in their intracytoplasmic domains. Especially the FcyRIIB receptor possesses such an inhibitory signal. It is a low-affinity receptor binding immune complexes.(3) Antigen-IgG antibody complexes are thus able to inactivate B lymphocytes and inhibit differentiation in IG producing plasma cells through a negative regulation via their ITIMs. This negative feedback reaction might be an explanation for the IG-induced inhibition of autoantibody synthesis (B).

IG preparations can contain anti-idiotypic antibodies and thus have an influence on the idiotype/anti-idiotype network (B). Therefore, therapeutic IG antibodies bind directly to (auto-)antigen receptors and then also to the  $Fc\gamma$  receptors of B lymphocytes (B) which may lead to negative regulation of B cell proliferation in response to the inhibitory signals mediated by ITIMs through binding to the FcyRIIB receptor.

There is also experimental evidence that IgG-containing complexes can modulate the cytokine production of monocytes/macrophages through binding to the  $Fc\gamma$ receptor IIA. In addition there seems to be an indirect inhibition of T cell function, which might explain the anti-inflammatory effect seen after IG administration, that could be due to a latent association with TGF- $\beta$ . This binding can occur directly in antibody-producing B cells and also in plasma. IgG-TGF- $\beta$  complexes can inhibit the activation of inflammatory TH1 cells and CD8<sup>+</sup> cells (4).

Finally, antigen presentation can be influenced by the formation of immune complexes. Antigens in these complexes are increasingly eliminated by scavenger cells like macrogphages resulting in reduction of presentation on dendritic cells.

II. Influence on Idiotype/Anti-Idiotype Network

It has been demonstrated by several investigators that the sera of healthy people contain anti-idiotypic antibodies binding to idiotypic autoantibodies.

III. Elimination of Immunostimulating Microbial Products

Neutralization of inflammation-inducing microbial products may also be the cause of the anti-inflammatory effects caused by IG. When bacterial superantigens (e.g.SEB) are administered, an inflammatory reaction through oligoclonal T cell stimulation leads to septic shock. Specific anti-SEB hyperimmune globulin preparations inhibit this inflammatory reaction by neutralization of bacterial toxins. So the efficiency of IG preparations in inflammatory conditions could be determined by the content of neutralizing toxin (superantigen) antibodies.

IV. Immunomodulatory Effects of Ig-associated Molecules

Mouse studies have shown that IgG is often associated with latent TGF- $\beta$ . This binding happens directly in IgG-producing B cells and also in plasma. These IgG-TGF- $\beta$  complexes can inhibit the activation of inflammatory TH1 cells and cytotoxic T cells.

# **1.2** Autoimmunity

Diseases caused by a failure of self-tolerance and subsequent pathologic immune responses against self are called autoimmune diseases.

Autoimmune diseases are classified into three subgroups according to the type of immune response, and nature and location of the antigen target.

- I. Antibody mediated diseases
- II. Immune complex mediated diseases
- III. T cell mediated diseases

# I. Antibody mediated diseases

The pathologic mechanism underlying this type of autoimmunity are IgG and IgM molecules directed against the cell surface or extracellular matrix antigens.

This leads to opsonization and phagocytosis of cells, complement- and Fcreceptor mediated recruitment and activation of leukocytes (neutrophils, macrophages) leading to an enormous immune response. Also impaired cellular functions, e.g. hormone receptor signaling might be a result.

Examples for antibody mediated disorders include autoimmune thrombocytopenic purpura, acute rheumatic fever and myasthenia gravis, where self-antibodies to the acetylcholine receptor inhibit the binding of acetylcholine followed by a down-modulation of the receptor by antibodies which leads to symptoms like muscle weakness and paralysis (B).

## II. Immune complex mediated diseases

Here immune complexes of circulating antigens as well as IgG and IgM antibodies are the mechanisms resulting in complement- and Fc-receptor-mediated recruitment and activation of leukocytes resulting in inflammation, and injury to the vessels and the adjacent tissues.

Many systemic immunologic diseases are caused by this deposit of immune complexes in blood vessels, e.g. systemic lupus erythemathodes (SLE).

In SLE pathogenic T Helper (TH) cells seem to react with peptides derived from nucleosomal proteins. Self-DNA specific B cells bind nucleosomal protein-DNA complexes leading to the production of anti-DNA antibodies via T cell activation.

The immune complexes cause inflammation and complement activation in various tissues throughout the human body. Many patients show low numbers of suppressor T cells, suggesting a loss of immune tolerance due to decreased inhibition by suppressor cells (C) (5-7).

#### III. T cell mediated diseases

T lymphocyte can cause injury either by triggering delayed type hypersensitivity reactions (DTH) or by directly killing target cells.

CD4<sup>+</sup> T cells mediate macrophage activation and cytokine-mediated inflammation resulting in DTH reactions while CD8+ cells directly cause cell lysis

(T cell-mediated cytolysis) or also cytokine-mediated inflammation.

Examples for disorders caused by T cells are insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis and the animal model of multiple sclerosis, experimental autoimmune encephalitis (EAE), a neurologic disease where autoimmune T cells directed against myelin lead to destruction and neurologic deficits in the brain.

Therefore, also multiple sclerosis, the human equivalent to EAE might be a T cell mediated autoimmune disease (C)(8-10).

Autoimmune diseases are also caused by a (partially strong) genetic predisposition. For instance a concordance rate of 35%-50% in monozygotic twins for IDMM. Among the genes strongest associated with autoimmunity are the genes within the MHC locus, especially the HLA genes in the MHC II locus. Finally, viral and bacterial infections are discussed to contribute to the

development or exacerbation of autoimmune diseases through enhanced expression of costimulators in tissues and cross-reactions between the pathogenic antigens and self antigens.

# 1.3 Multiple Sclerosis

1.3.1 The Human Brain

Multiple Sclerosis (MS) is an autoimmune disease affecting the Central Nervous System (CNS).

The CNS consist of the brain and the spinal cord, immersed in the cerebrospinal fluid (CSF). The brain itself consists of three parts, the cerebrum, the cerebellum and the brainstem.

The <u>cerebrum</u> is divided into two hemispheres (left and right). Each consists of four lobes (frontal, parietal, occipital and temporal). The outer brain layer, or the cerebral cortex, is also known as "grey matter". It covers the nuclei which lie in the so-called "white matter", in the cerebral hemisphere.



Fig. 1 The cerebrum The main portion of the brain, made up of two cerebral hemispheres united by the corpus callosum, forming the largest part of the CNS. (www.brainexplorer.org) The <u>grey matter</u>, formed by neurons, includes regions of the brain involved in muscle control and sensory perceptions.

The <u>white matter</u> or diencephalons is situated between the brainstem and the cerebellum. It is a neuronal tissue containing myelinated axons.

White matter nuclei are involved in the conduction of sensory information to the cerebral cortex as well as in the regulation of autonomic functions.

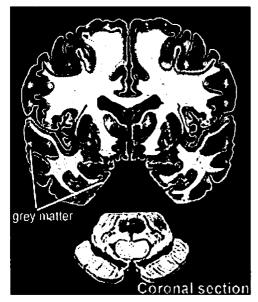


Fig. 2a Normal grey matter (www.brainexplorer.org)

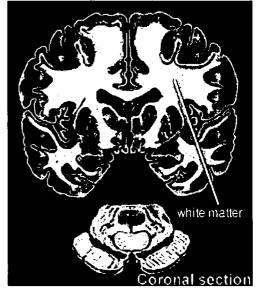


Fig. 2b Normal white matter (www.brainexplorer.org)

The <u>cerebellum</u> is responsible for psychomotor function while the <u>brainstem</u> forms the link between cerebral cortex, white matter and spinal cord contributing to regulation of breathing, sleeping and circulation.

#### 1.3.1.1 Cells of the CNS:

#### I. Neurons

II. Glial cells

#### I. <u>Neurons</u>:

Neurons are cells specialized in the conduction and transmission of electric signals. They are organized into circuits that innervate the body to transmit sensory and motor signals to all areas.

Neurons consists of efferent axons, long nerve-fibers which extend from the cell body and are covered by a myelin sheath. At the end of the axon, the nerve impulses are transmitted to other neurons or effector organs.

Myelin enables nerve impulses to be conducted at a faster rate. A thin myelinated axon transmits impulses at anything from 5 to 30 meters per second whereas an unmyelinated one transmits them at 0.5 to 2 meters per second. It does this both by insulating and containing the nerves. The insulating properties of myelin are due to its structure, the low  $H_20$  content (40%), the thickness and the lipid enrichment.

A nerve impulse is a wave of depolarising current called an action potential that travels along the entire neuron by allowing charged ions of sodium and potassium to flood through channels in the semi-permeable membrane around the nerve cell. At rest (resting potential), the neuron and the surrounding space act as a "capacitor" storing current which is released during the action potential.

Myelin increases the speed of the transmission by containing the current (as positively charged ions) in a small space surrounding the axon. This means that the sodium and potassium ions that contribute to the resting potential do not need to move far when the action potential occurs. Myelin also prevents current from being lost as sodium ions drift away from the neuron.

The myelin sheath is broken at intervals called the nodes of Ranvier which are rich in sodium channels. This makes the nerve impulses move in a stepwise fashion called "salutatory conduction".

Myelin is composed of about 80% lipid fats (cholesterol, phospholipids and glycolipids) and about 20% proteins. Some of the proteins that make up myelin are Myelin Basic Protein (MBP), Myelin Oligodendrocyte Glycoprotein (MOG) and Proteolipid Protein (PLP). Myelin is produced by Oligodendrocytes.

Myelin damage as in MS-patients, results in a severely impaired transmission efficacy.

Dendrites are afferent neuron extensions containing neurofilaments and neurotubuli, typically highly branched and responsible for receiving information and formation of synaptic contacts with the terminals of other nerve cells to allow nerve impuls transmission.

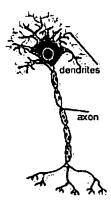


Fig. 3 Neuron (www.brainexplorer.org)

## II. Glial cells

Glial cells are major constituents of the central nervous system.

They can be divided into two groups: microglia and macroglia.

Microglia are phagocytes which are recruited to the CNS by infection or injury.

They do not have a direct role in neurotransmission but microglial cells play a supporting role that helps define synaptic contacts and maintain the signaling abilities of neurons. Their functions are phagocytosis (removal of damaged or

developmental cells), antigen presentation, cytotoxicity and they also act neurotrophic.

Various types of macroglial cells can be found in the brain (or CNS) including astrocytes, oligodendrocytes and Schwann cells. The total number of glial cells exceeds that of neurons by approximately three-fold.

Glial cells are smaller than neurons and lack axons and dendrites. Functions of the glia include: modulating the rate of nerve impulse propagation; controlling the uptake of neurotransmitters; and playing a pivotal role during development and adulthood. Some evidence also suggests that glial cells aid (or, in some cases, prevent) recovery from neuronal injury and that they are involved in a number of diseases, such as Alzheimer's disease, multiple sclerosis and other central and peripheral neuropathies. (D) (E)

<u>Oligodendrocytes (ODCs)</u>, formed by Oligodendrocyte Precursor Cells (OPCs), are found in the CNS. Their main function is insulation of axons by forming a myelin sheath and thus increasing nerve impuls velocity. One oligodendrocyte myelinates around 30-50 axons (D) (E).

<u>Schwann cells</u> occur in the peripheral nervous system and do also form myelin sheaths but only envelope one internode of only one axon (D) (E).

<u>Astrocytes</u> represent the highest number of glial cells and responsible for brain homeostastis. Some form end-feet on the surface of neurons in the brain and spinal cord may play a role in bringing nutrients to these cells. Others play endfeet on the brain's blood vessels and cause the vessel's endothelial cells to form tight junctions, thus creating the blood-brain barrier (BBB).

They also help in maintaining the right potassium ion concentration in the extracellular space between neurons. They are highly permeable to potassium and can take up an excess of potassium and so protect the neighbouring neurons. An

additional feature is the up-take of neurotransmitters from synaptic zones after release and thereby regulating the synaptic activities.

Astrocytes also provide energy reserves by glycogen storage (D) (E).

#### 1.3.1.2 The Blood-Brain Barrier

The brain is separated from blood only by a very large surface of endothelial cell membranes, the Blood-Brain Barrier (BBB). This barrier maintains a stable environment for neurons by excluding toxic substances. The exclusion results primarily from specialized anatomic properties of brain endothelial cells that limit passive diffusion of water-soluble substances across the vessel walls.

Endothelial cells are interconnected by complex arrays of tight junctions which block diffusion.

Therefore, the BBB is, first of all, a barrier for hydrophobic molecules (proteins, peptides), allowing only the entry of lipophilic substances.

This provides restricted CNS entry of antibodies and inflammatory mediators but also restricted exit of CNS molecules.

Second, the BBB restricts the entry of leucocytes (immune cells) and the exit of CNS derived cells into lymphatic vessels or circulation. An exception are activated T cells and they are able to cross the BBB.

The BBB consists of endothelial cells as a central diffusion barrier, the basement membrane which functions as a molecular filter for size and charge, the membrane glia limitans perivascularis which acts as a ion buffer and allows an active metabolic transport and finally, perivasculare macrophages/microglia cells for phagocytosis and removal of debris (D) (E).

#### 1.3.1.3 Brain Inflammation

The inflammatory process which takes place in the brain is mainly induced and regulated by Class II MHC-restricted T cells.

But inflammation is not only caused by MHC II-restricted CD4<sup>+</sup>  $T_{H-1}$  cells, but also by MHC I-restricted  $T_c-1$  cells as well as by  $T_{H-2}/T_c-2$  cells.

 $T_H$ 1-restricted T cells release pro-inflammatory cytokines as INF- $\gamma$  or TNF- $\alpha$  while  $T_H$ 2-restricted T cells produce anti-inflammatory cytokines as IL-10, TGF- $\beta$ . The main effector cells of non antigen-specific bystander damage are tissue-damage microglial cells.

The main elicitor of brain inflammation is the entry of activated T cells across the BBB into the CNS by emperiploesis.

Normally, endothelial cells express a low amount of adhesion molecules and resting T cells have only few binding partners.

During an inflammatory process the expression of adhesion molecules like VCAM, ICAM or LFA-3 is up-regulated by pro-inflammatory cytokines which facilitate the entry of activated T cells into the CNS. These mediators cause tight binding of leucocytes to integrins which results in activation of endothelial cells and stable adhesion of leucocytes. They actively facilitate the entry by dissolving the basal membrane of the BBB.

Inside the CNS chemokines are released which diffuse into the periphery and bind to the surface of endothelial cells, resulting in enhancement of the migratory process.

normal endothelium	T cell mediated inflammation
LFA-3	VCAM
PECAM	ICAM
ICAM	PECAM
	P-Selectin
	ΤΝΕ-α
	chemokines
	neuropeptides
	INF-γ, ΙL-1β

Tab. 1 Adhesion molecules at the BBB

(source: H. Lassmann: Immunology of neurologic diseases: <u>ftp.hifo.univie.ac.at</u> May, 10<sup>th</sup>, 2004)

Effector T cells entering the CNS display a migratory phenotype, characterized by the up-regulation of MHC II and the chemokines CCR1, CCR2b, CCR3, CCR5 and CCR7 while Ox 40 and IL-12 are down-regulated. CD4, the TCR and the chemokines CCR4 and CXCR3 remain unchanged.

The expression of MHC molecules in the brain was not discovered until 15 years ago.

Today it is known that the expression of MHC is dependent on the electrical activity, regulated by neurotrophines.

MHC I and MHC II are constitutively expressed by meningeal and perivascular macrophages. MHC I is also expressed by endothelial cells. After stimulation also microglial cells express MHC I and II. During acute inflammation MHC molecules are expressed by all former mentioned cell types as well as by astrocytes.

In summary T cell mediated inflammation on the CNS plays a physiological role by ensuring immune surveillance and tissue degeneration/destruction which allows clearance of debris and supports the regeneration through neurotrophic factors.

The pathologic consequences are either infections like meningitis or the development of autoimmune diseases like multiple sclerosis or Guillane-Barre syndrome.

But autoreactive T cells also might act as a therapeutic target for site-directed drug delivery.

## 1.3.1.4 CNS Autoimmunity

Autoreactive T cells are a component of the normal immune repertoire.

An autoimmune T cell mediated response against brain proteins may help reducing brain damage, e.g. trauma. Therefore inflammation may act neuroprotective through neurotrophins like NGF, NT3, NT4 or BDNF which are released by inflammatory cells (11;12).

Neuroprotective autoimmunity is mediated by  $T_{H}$ -1 cells and suppressed by CD4<sup>+</sup>/CD25<sup>+</sup> regulatory T cells (13).

It has shown that there are gender differences displaying a more efficient neuroprotective autoimmunity in females compared to males (14).

# 1.3.1.5 Mechanisms of inflammatory tissue damage in the CNS

## T cell cytotoxicity

Inflammation is characterized by the presence of T cells and activated microglial cells which cause specific damage of antigen containing target cells but can be induced by activated CD8<sup>+</sup> cells alone. Without macrophage recruitment no bystander damage is induced. Cytotoxic T cells can cause severe lesions with vasculitis and ischemia.

This is in contrast to CD4+ mediated inflammation where macrophage recruitment leads to massive bystander damage.

# T cell mediated inflammation by antibodies

Inflammation in the CNS caused by T cells leads to disruption or disturbances of the Blood-Brain Barrier which leads to an influx of antibodies and complement into the brain. As a result local effector cells are activated.

Antibodies against targets as well as macrophages and sometimes granulocytes, are accessible from the extracellular space and cause selective destruction of antigen-specific target through complement and/or antibody-dependent cellular cytotoxicity (ADCC).

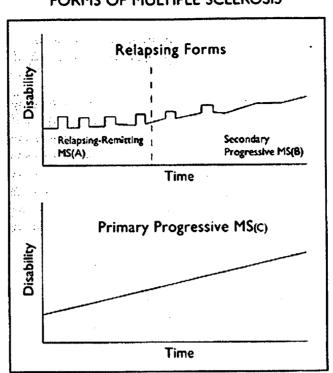
## 1.3.2 Multiple Sclerosis as a disease

The disease Multiple Sclerosis (MS) was first described by Jean-Marie Charcot (1825-1893) as "la sclerose en plaques desseminées" (F, G, H).

MS is an inflammatory autoimmune disease affecting the Central Nervous System (CNS), i.e. the brain and spinal cord, with an onset in early adulthood – between 20 and 40 years of age and women being affected more often than men (2:1).

The disease is normally not life-shortening but leads to substantial defects in sensation as well as in motor, autonomic and neurocognitive functions.

There are two major forms: Relapsing-Remitting (RR), which is the most frequent form (85-90%) and chronic-progressive. Most of RR patients develop secondary-progressive MS within the years, but about 10-15% develop an insidious onset characterized by steady progression, termed primary-progressive MS.



#### FORMS OF MULTIPLE SCLEROSIS



MS is characterized by the infiltration of autoreactive T cells into the CNS, localized myelin-destruction, axonal damage and a loss of oligodendrocytes.

Patients have white matter lesions which are detectable by magnetic resonance imaging (MRI).

MS is a heterogenous disease where environmental and genetic factors interact in the pathogenesis. The incidence increases with latitude away from the equator, therefore, areas like northern-Europe or southern Australia being at the highest risk (prevalence varies about factor 10/100.000 persons) (15). A causative factor might be the decrease in sunlight depending on the latitude. UV radiation influences the biosynthesis of vitamin D. Therefore vitamin D receptor polymorphisms have been associated with MS (16;17).

Migration studies have shown that emigration from an area of high prevalence to an area of low prevalence before age 15-16, adapts to the low risk area, whereas migration after that age does not change the risk (18).

That fact might be related to an infectious event aquired during childhood.

The susceptibility to MS varies in different ethnic groups, with people of Caucasian origin displaying the highest disease-rates.

The concordance rate among monozygotic twins is approximately 20-35%, and about 2-5% in first-degree relatives like dizygotic twins and siblings (19;20).

## 1.3.2.1 Genetic factors

To search for susceptibility genes more than 20 whole genome screens in different MS populations and different geographic areas have been performed e.g. the GAMES study (21), but the results so far are not promising.

HLA-DR2 or-DQ on chromosome 6 is the predominant susceptibility allele associated with MS but even here the frequency varies among patients in different populations (22). Especially in Caucasians the HLA-DR15 haplotype carries a higher risk factor.

There are several other risk-confering genes which have been pointed out as candidate genes for MS, like polymorphisms of CCR2, CCR5, IL-10 receptor  $\alpha$ ,

IL-10, FAS-L, IL-4 receptor  $\alpha$ , IL-2 receptor  $\beta$ , INF- $\gamma$ , NOTCH4 or an allele of apolipoprotein E (APOE4) (19).

Adhesion molecules	Interleukines/Cytokines	Other
B7-1	IL-1Ra/IL-1B (progression)	CD45
CD40L	IL-2ra/rb/rg (progression)	Apo B/C2/H
CTLA-4	IL-4/R (susceptibility)	Apo E (progression)
(progression)		
ICAM-1	II-7	HLA-DM/DP (susceptibility)
PECAM	Il-9	HLA-DR/DQ (susceptibility)
	IL-10/R	C3/C4
	IL-12 R/p355/p40 (resistence)	TCR A/B (susceptibility)
×	INF-α/β	Hsp70
	INF-γ R1/R2	NOS1
	TGF-BR1/BR2/BR3	IgH/V/C
	TNF-α (susceptibility)	FcR (resistence)
<u></u>	CCR5 (severity)	Rh blood group
	CCL7(MCP-3) resistance	Vitamin D R
	CNTF (severity)	25(OH)D3
		Oestrogen R (severity)
CNS proteins	Apoptosis	α-2-macroglobulin
MBP	Apo-1	TIMP-3
PLP	FAS-670 (resistance)	Sca2/3/6/8/11
MOG	p53	Gelatinase B
MAG	Bax, bcl-2, bcl-x	Myeloperoxidase
OMGP		Trk-C
Golli-MBP		GABA A3R
NF2		erb B4
<del>,</del> <del>,</del>		CYP2D6
		mt DNA

Tab. 2: Candidate genes for MS-susceptibility [Compston, 2003]

#### 1.3.2.2 Non genetic factors

As the concordance rate of monozygotic twins is relatively low, environmental factors are generally suggested to contribute to the etiology of MS.

The higher risk of women to develop MS might be due to the hormonal status. This suggestion is supported by the fact that women during pregnancy have a lower risk for relapses (23).

The geographical distribution is also reflected by the economic level of the country and higher prevalence rates are connected with the increasing socioeconomic development (industrialization, urban living, pollution, diet changes, ..), and reduced exposure to infections in developed countries also gave rise to the "hygiene hypothesis" which suggests an increased risk to develop allergies or autoimmune reactions/diseases.

*Viral or bacterial infections* have long been discussed as candidates for triggering MS. Especially human-pathogenic viruses that induce persistent infections have been investigated, among them Human Herpes Virus 6 (HHV6) or Epstein-Barr Virus (EBV) which have lymphotrophic (HHV6) and neurotrophic properties that cause tissue damage and also have the ability to activate autoimmune responses directed at the myelin tissue. HHV6-DNA has been detected more often in serum and CF of MS-patients than in controls and they exhibit a significantly different cytokine profile (Th1) compared to controls (Th2) (24-27). Some viruses share sequence-homologies with myelin proteins leading to *molecular mimicry*-induced activation of T cells (28). The recognition of self-antigens at intermediate level affinity by T cells during thymic selection results in positive selection and the export of these potentially autoreactive T cells to the periphery where they can crossreact with foreign antigen. The activated T cells now can cross the BBB and infiltrate the CNS. Upon recognition inside the brain tissue damage or the development of autoimmune diseases like MS may be the outcome.

In addition viral CNS infections can also induce autoimmune reactions by epitope spreading and superantigen activity (29).

There are two ways of bystander activation mechanisms to induce autoreactive T cells.

First, TCR-independent bystander activation by inflammatory cytokines, superantigens and molecular pattern recognition, e.g. toll-like receptor (TLR) activation.

During infection chemokines and proinflammatory cytokines are produced which are thought to be the main activators of virus-specific CD8<sup>+</sup> cells and inducers of autoimmune processes. Binding of infectious agents to TLRs results in an innate immune response which leads to increased expression of cytokines and reactive oxygen intermediates. For example TLR4 in the CNS is expressed on microglia. During a bacterial infection TLR4 interacts with LPS which may lead not only to the

activation of monocytes and mircroglia but also to the activation of autoreactive T cells in the periphery.

Second, viral tissue damage leads to the unveiling of host antigens.

Here, activated virus-specific T cells travel to the side of infection, recognize viral epitopes and kill the infected cells. The consequence is destruction of self-tissue and release of autoantigens. If these autoantigens are presented together with the adjuvant effect of the infectious agents it will result in de-novo activation of autoreactive T cells and later epitope spreading (15).

#### 1.3.2.3 Main effector cells of MS

Multiple Sclerosis is believed to be a chronic inflammatory autoimmune demyelinating disease of the CNS, which is characterized by patchy inflammatory infiltrates containing blood-derived myelin-specific T cells, B cells secreting antimyelin component antibodies and various non specific effector mononuclear cells (mostly macrophages).

Current hypothesis revolve around an induction of the autoimmune inflammatory response by T cells in response to one or more infectious agents (molecular mimicry), with the beginning of the disease in the periphery (30).

The first hints that MS is an T cell-derived disorder came from the animal model experimental autoimmune encephalomyelitis (EAE) in the early 1980ies (31;32).

It was observed that EAE could be transferred by in vitro reactivated myelinspecific CD4<sup>+</sup>T cells, either adoptive or passive.

EAE can be directly induced by autoreactive T cells in naïve animals, but not by antibodies. This leads to the conclusion that MS is probably a T cell-mediated autoimmune disease (15;33).

#### CD4<sup>+</sup> T cells

CD4+ T cells play a major role in the immunology of the disease.

They are found in the CNS- and CSF-infiltrating inflammatory cells, the genetic risk for MS is partly conferred by HLA-DR and HLA-DQ molecules which code for the T cell related MHCII and antibody production, CD8<sup>+</sup> maturation as well as many other innate and adaptive immune reactions are, at least partly, controlled by CD4<sup>+</sup>.

In the CNS, CD4<sup>+</sup> cells target myelin proteins, among them myelin-basic protein (MBP), the best-studied one. There are five isoforms of MBP, according to different splicing sites. The protein is highly basic and positioned at the intracellular surface of myelin membranes in both central and peripheral myelin. It is involved in the maintenance of the myelin structure by forming interactions with acidic lipid moieties.

The most immunodominant epitopes for high-avidity myelin-specific CD4<sup>+</sup> T cells are MBP<sub>(13-32)</sub>, MBP<sub>(111-129)</sub> and MBP<sub>(146-170)</sub> (34).

The most abundant myelin protein in the CNS is Proteolipid Protein (PLP), a highly hydrophobic and evolutionary conserved protein.

The main targets of PLP-specific high-avidity Th<sub>1</sub> cells are PLP<sub>(139-151)</sub> and PLP<sub>(178-191)</sub> (34).

Another target of CD4<sup>+</sup> cells in the CNS is Myelin Oligodendrocyte Glycoprotein (MOG), which is located on the outer surface of the oligodendrocyte membrane, which makes it directly accessible to antibodies. Therefore, MOG is a relevant target for both cellular and humoral immune responses. The expression of MOG is less abundant, it is only found in the brain/spinal cord and retina but not in the peripheral lymphoid tissues (35). Immunodominant epitopes are located in the Ig-like extracellular domain as well as in the intracellular parts.

There are several further myelin and non myelin antigens which serve as targets for CD4<sup>+</sup> T cells. Among them there are for example *myelin-associated glycoprotein (MAG)* located at the inner surface of the myelin sheath, 2`3`-cyclic *nucleotide* 3`*phosphodiesterase (CNPase)* located in oligodendrocytes, but also expressed by Schwann cells and partly by the lymphoid tissue, *myelin-associated oligodendrocytic basic protein (MOBP)*, an exclusively oligodendrocyte-expressed protein which appears late in myelination, *oligodendrocyte-specific glycoprotein (OSP)*, the third most abundant myelin protein, expressed in the CNS and testis. The majority of myelin-specific CD4<sup>+</sup> T cells are restricted by HLA-DR molecules (15) and display a Th1 phenotype (34).

CD4<sup>+</sup> T cells also exhibit cytotoxic activity. They mediate perforin- and Fas/Fas-Ligand-mediated cytotoxicity of MBP. It is considered unlikely that CD4+ cells are directly involved in the lysis of oligodendrocytes or neurons because neither type of CNS cells expresses HLA class II (36;37).

# Regulatory CD4<sup>+</sup>CD25<sup>+</sup> T cells

MS may result from the failure of tolerance mechanisms that prevent the expansion of pathogenic T cells that react against myelin. Tolerance mechanisms include regulatory T cells expressing the transcription factor FoxP3. Studies had shown a decrease in FoxP3 expression in MS patients suggesting impaired immunoregulation by T reg cells (C) (38).

Experiments in animal models have shown that regulatory T cells (Tregs,  $CD4^{+}CD25^{+}$ ) are responsible for the prevention of the disease (39).

They suppress T cell proliferation by both cell-cell contact and cytokine-mediated mechanisms. CD4<sup>+</sup>Th2/3 cells and their cytokines II-4, II-10 and TGF- $\beta$  are therefore thought to be beneficial in MS.

Tregs contribute to the maintenance of peripheral tolerance and breakdown of this tolerance due to neural self-antigens is a main factor in the development of an autoaggressive immune response. Deletion of the CD4<sup>+</sup>CD25<sup>+</sup> population causes spontaneous autoimmune disease in mice (40).

# CD8+ T cells

It is considered that cytotoxic T cells are important effector cells for mediation of pathological immune reaction that induce CNS damage.

CD8<sup>+</sup> cells outnumber CD4<sup>+</sup> cells in all lesions, not only in active plaques.

	Acute MS % of CD3	Chronic MS % of CD3
Active	67.6% CD8	83.7% CD8
Inactive	52.0% CD8	72.1% CD8

source: H. Lassmann: Immunology of neurologic diseases: <u>ftp.hifo.univie.ac.at</u> May, 10<sup>th</sup>, 2004

Clonally expanded CD8+ cells (65% compared to 24% CD4<sup>+</sup> cells) are found within MS lesions and in the cerebrospinal fluid of MS patients (41).

The TCR repertoire of CD8+ T cells in the CSF resembles the TCR repertoire of brain infiltrating T cells (42). Leukocyte entry into the CNS is tightly regulated by the BBB, but there are at least three different entry routes: from blood to CSF across the choroidal plexus, from blood to subarachnoid space and form blood to parenchymal perivascular space.

MHCI is expressed by oligodendrocytes, astrocytes, axons, neurons and endothelial cells in active lesions, while MHCII is expressed only by microglia cells in the CNS.

That points to the importance of CD8<sup>+</sup> cells compared to CD4<sup>+</sup> cells.

Some  $CD8^{+}$  T cells can attack neurons and axons directly - by polarizing their cytotoxic granules towards the contact zone – which are expressing MHCI and are therefore susceptible to antigen-specific lysis by cytotoxic T cells (42).

There are also CD8+ virus-specific T cells which are directly capable of lysing neuron via Fas/Fas-L-mediated cytolysis (43).

The CD8+ response to MBP is elevated in MS patients, as there are a number of HLAI – restricted myelin epitopes been described for MBP, PLP, MAG and other proteins (44).

In summary it seems that both T cell populations, CD4<sup>+</sup> and CD8<sup>+</sup> cells, have an important role in MS.

#### **B** cells

The detection of oligoclonal bands in the CSF of MS patients has long been considered as an important clinical parameter in detecting the disease.

Under normal conditions B cells are not able to cross an intact Blood-Brain Barrier.

But under inflammatory conditions B cells, antibodies and complement factors enter the CNS. The activation of B cells can either be due to stimulation with foreign antigen or self antigen through a bystander effect or superantigen stimulation.

There are different ways for B cells to contribute to the pathogenesis of MS.

They can act as antigen-presenting cells (APC) for autoreactive T cells which is underlined by the fact that T cells and B cells often share the same immunodominant epitopes in humans (45).

B cells and tissue bound Ig can also recruit autoreactive T cells into the CNS (46). Finally, the production of myelin-specific antibodies and the myelin destruction within the MS plaques seem to be the most important way of the contribution of B cells to the pathogenesis of MS.

Antibodies cause demyelination by opsonization of myelin or by complement activation, leading to formation of the membrane-attack complex (MAC) and complement-mediated cytolysis (47).

The most interesting B cell autoantigen in MS is MOG, a target for autoantibody mediated demyelination in experimental autoimmune encephalomyelitis (EAE).

Pathogenic anti-MOG antibodies are mainly directed against conformationdependent epitopes present on the extracellular immunoglobulin domain of the protein. The autoimmune response might be partly regulated by polymorphisms in the MOG gene itself (48).

The intrathecal IgG response in MS patients also consists of high-affinity anti-DNA antibodies. The mechanisms underlying this triggering of anti-DNA antibodies is still unknown, but may follow the release of large quantities of host DNA from damaged tissue by a primary infection. As under normal conditions DNA is a poor antigen, the production of high-affinity anti-DNA antibodies might be closely related to the autoimmune state in MS (49).

Antibodies may also have a beneficial effect on MS. They can shift the immune response from a TH1-driven to a TH2-driven response (50).

Furthermore, antibodies against CNS components can induce myelin repair.

Intravenous immunoglobulins (IVIG) have also been shown to be effective in autoimmune diseases like MS, as will be discussed below (51;52).

# 1.3.2.4 MS and innate immune mechanisms

# Toll-like receptors (TLR)

The main function of the innate immune system is self-protection and maintenance of homeostasis but under special circumstances it can also result in destructive autoimmunity.

TLRs recognize conserved pathogen-associated molecules and induce proinflammatory signals that induce the adaptive immunity.

They might play a role in breaking peripheral tolerance to self-antigens during chronic infections or inhibit immunosuppressive effects of CD4+CD25+ regulatory T cells on effector T cells via IL-6 by their engagement on dendritic cells (DC) (15).

# Mast cells

Mast cell-released mediators (e.g. tryptase and histamine) are increased in the CSF and in acute lesions of MS patients. They act on the disrupted BBB and enhance the entry of leucocytes into the CNS by increased recruitment, adhesion and rolling.

Mast cell proteases such as tryptase and chymase act on the activation of matrix metalloproteinase (MMP) precursors.

In vitro mast cell degranulation in response to MBP leads to demyelination (15).

# Nitric Oxide Synthase

Phagocytes (macrophages and granulocytes) are able to generate highly toxic reactive oxygen and nitrogen intermediates which exert strong antimicrobial activities.

Inducible nitric oxide synthase (iNOS) generates nitric oxide (NO), a free radical that is toxic to bacteria. NO, found in MS lesions, can mediate microglia-induced cytotoxicity (53).

# Natural Killer Cells (NK)

The association between decreased NK cell activity and MS has been known for over 20 years. Prior and during acute exacerbations NK lysis is reduced which is due to a significantly reduced number of NK cells in general in MS (54). NK cells could suppress autoimmunity because of their cytokine profile (IL-5, IL-13, TGF-ß) or by target lysis via perforin-and/or TRAIL-dependent mechanisms. Therefore NK cells may exert important immunoregulatory functions in MS (15).

## **Complement**

Most of the complement found in the CNS is produced by the cells localized in the brain with astrocytes being the major source. The main function of complement is to ensure immune defense against pathogens.

Demyelination results from direct complement activation after complement-binding to myelin and from an autoimmune response against myelin via the classical pathway.

The classical pathway can be activated by purified myelin.

Complement activation, e.g. by MOG, results in oligodendrocyte lysis and chemoattraction of macrophages (15).

## Cytokines and Chemokines

Cytokines are proteins that mediate many different responses of innate and adaptive immunity. They are synthesized in response to inflammatory or antigenic stimuli and usually act locally in an autocrine or paracrine fashion by binding to high-affinity receptors on target cells.

For homeostasis a dynamic balance between pro- and anti-inflammatory cytokines is required. Proinflammatory cytokines like INF- $\gamma$ , TNF- $\alpha$ , IL-12, IL-17, etc. are supposed to play a role in the pathogenesis of MS via activation of the immune system in the periphery and/or by directly damaging the oligodendrocytes or myelin.

Anti-inflammatory cytokines like IL-4 and IL-10 are in contrast considered to be benefical in MS by augmenting B cell proliferation, differentiation and antibody production.

Data on proinflammatory cytokines in MS are contradictory.

Elevated numbers of TNF- $\alpha$  have been reported in blood and serum of MS patients.

But therapy with anti-TNF- $\alpha$  leads to increased exacerbations.

Some data show higher INF- $\gamma$  levels in MS patients, but a therapeutic trial with INF- $\gamma$  resulted in exacerbations as well. Also EAE data report different results (15). Data on anti-inflammatory cytokines are not less divergent.

Especially the role of IL-10 remains unclear.

IL-10 production seems to drop in PBMC, CNS plaques and CSF of MS patients.

It has been reported that IL-10 production is blocked by type I interferons in activated monocytes but stimulated in activated T cells (type I interferons reduce disease exacerbations in early MS). Therefore, it was hypothesized that II-10 might be differentially regulated in monocytes and T cells (55).

TNF- $\alpha$  belongs to the proinflammatory cytokines but is also involved in tissue repair in the brain. Active demyelinating lesions in the brain of MS patients show elevated levels compared to inactive/remyelinating lesions (56).

Transgenic animal models overexpressing TNF- $\alpha$  and INF- $\gamma$  induce demyelination, because these cytokines might be toxic for oligodendrocytes. They may activate microglia and macrophages which phagocytose myelin and the proinflammatory

cytokines may be involved in induction of apoptosis with subsequent demyelination (15).

The cystein protease caspase-1 is responsible for processing inflammatory cytokines and is associated with the induction of apoptosis. It might also play a role in the inflammatory and apoptotic processes associated with MS (57).

Chemokines are important for the recruitment of leukocytes and other cells during inflammation. Only disruption of the BBB allows inflammatory cells to enter the CNS.

Trafficking of activated T cells into the brain starts with a weak adhesion and rolling on the endothelial side of the BBB, a firm arrest on the luminal side of the endothelium and finally crossing through the BBB into the CNS. All of these individual steps are induced by chemokines which also form a chemotactic concentration gradient. (source: H. Lassmann: Immunology of neurologic diseases: <u>ftp.hifo.univie.ac.at</u> May, 10<sup>th</sup>, 2004)

Major receptors on TH1 cells are CCR5 and CXCR3 and on Th2 cells CCR3 and CCR4.

CCR5 might play a pathogenic role in MS, as levels are elevated in circulating T cells. But increased expression of CCR5 was only shown in some studies (58).

T cells of MS patients expressing CCR5 produce high levels of the proinflammatory cytokines INF- $\gamma$  and TNF- $\alpha$  (59).

A CCR5 Delta32 deletion mutation abolishes functional CCR5 on the cell surface and therefore may reduce the entry of cells into the lesions. But data showed that a lack of CCR5 does not protect from MS but rather predispose to the chronic disease course (60).

The chemokines CCL5 (RANTES) and CXCL10 (IP10) show increased levels in the CSF of MS patients, while CCL2 (MCP-1) is decreased, which correlates with active MRI. This occurs during MS exacerbations but not during remissions and suggests a mainly Th1-driven response in MS (61).

Monocyte chemoattractant protein-1 (MCP-1) plays an important role in many inflammatory and autoimmune diseases and loss of its effector-function alone is sufficient to impair monocyte trafficking in inflammation models. MCP-1 knockout

mice show no clinical and histological EAE disease signs, even if transferred with encephalitogenic T cells. This emphasizes the importance of MCP-1 in the effector phase of the disease (62).

CXCR3 expression may facilitate the entry of T cells into the CSF, while CXCL10 (IP-10) mediates retention in the inflamed brain (15).

EAE data have shown that often the increase of chemokines or their receptors is associated with disease progression while depletion in vivo improves EAE.

#### 1.3.2.5 Pathogenesis of MS

Multiple sclerosis is primarily a demyelinating disease. But acute axonal damage in demyelinating lesions is a frequent event. Demyelination can be partly repaired by mechanisms of remyelination whereas the axonal destruction is irreversible.

The functional impairment in patients with relapsing-remitting MS is mainly caused by inflammation and demyelination in contrast to the accumulations of irreversible neurological deficits which are caused by axonal destruction and loss.

The events leading to demyelination are summarized here:

In the periphery potentially autoreactive T cells are activated, probably by molecular mimicry. Activated T cells, mainly CD4+ cells, can cross the BBB by adhesion to endothelial adhesion molecules (VLA-4, LFA-1) which facilitate their entry into the CNS by transmigration. It is still uncertain if this step involves also a chemokine gradient. Inside the CNS local factors may upregulate the expression of endothelial adhesion molecules which facilitate further entry of autoreactive T cells.

The following brain-inflammation leads to upregulation of proinflammatory cytokines like INF- $\gamma$ , IL-23, TNF- $\alpha$  or LT as well as of chemokines like RANTES or IL-8. They activate the resident CNS microglia and astrocyte cells, recruit more immune cells (monocytes, mast cells, B cells, CD8<sup>+</sup> cells) from the peripheral blood and mediate the formation of inflammatory lesions. The open BBB is a characteristic of acute inflammation and results in tissue edema due to mediator/protease release from mast cells, monocytes and T cells under the

influence of proinflammatory cytokines and oxygen/nitrogen radicals. Several effector mechanisms contribute to myelin damage like direct macrophagemediated myelin phagocytosis, anti-myelin antibodies secreted by B cells, myelintoxic cytokines and nitric oxide components. These early inflammatory events already lead to massive CNS (myelin sheath, oligodendrodytes and axons) damage (15).

Recently, inflammation has been questioned to be the exclusive factor leading to demyelination. EAE data showed an increase from 20-80% of morbidity rate in mice treated with an antibody neutralizing INF $\gamma$  (63). CNS-specific NF $\gamma$  production can protect mice from progression of disease by inducing a fast clearance of encephalitogenic T cells infiltrating the CNS parenchyma via apoptosis, associated with up-regulation of TNF-Receptor 1 (64).

 $CD4^{+}$  T cells can induce microglia to secrete IL-12 inhibiting factors like PGE<sub>2</sub>, thus selflimiting the inflammation (65).

Macrophages may remove myelin debris, therefore, promoting remyelination. They can also induce remyelination by secretion of proinflammatory cytokines (TNF- $\alpha$ ) which are able to promote proliferation of oligodendrocyte progenitors via TNFRII signaling (66;67).

Therefore, inflammation in MS is more complex than thought before and includes detrimental and protective components.

Processes leading to myelin damage and axonal loss include direct complement deposition, ADCC via Fc-receptors, antibody-mediated complement activation, myelin phagocytosis, direct axonal lysis by CD8<sup>+</sup> cells, secretion of proteases and apoptosis of oligodendrocytes. In addition an increase in glutamate production and a decrease in its degradation leads to glutamate-mediated exocytotoxicity of oligodendrocytes via glutamate-receptor mediated calcium influx (68).

The early phase of MS is in 85% of patients characterized by an acute attack leading to white matter lesions. Axonal loss is predominant in these early appearing lesions and decreases over time. There seems to be a correlation between inflammation and axonal damage as a high amount of damage occurs in areas with large T cell (mainly CD8<sup>+</sup>) infiltration and the macrophage extent (69).

During the time that follows an inflammatory event demyelinated axons, apoptotic oligodendrocytes and T cells and axonal transsections appear. Astrocytes are activated to proliferate, and macrophages are loaded with phagocytosed myelin

lipids. Th2/Th3 cytokines dominate in lesion resolution and various growth factors, like CNTF and brain-derived neurotrophic factor, are secreted.

Remyelination starts with the activation of oligodendrocyte precursors so that the surviving oligodendrocytes can start repairing the demyelinated areas. Repaired myelin does not possess its former density and therefore conduction velocity is slower.

There is evidence which shows a secondary axonal degeneration, both inside lesions and in the normal appearing white matter (NAWM). Naked, demyelinated axons may be more susceptible to degeneration because of their lost support from oligodendrocytes, a hypothesis supported by the observation of remyelinated axons being protected from further damage (69).

Another assumption is that secondary degeneration might appear due to a decreased remyelination efficacy of oligodendrocytes because of repeated demyelination episodes (70).

Following an inflammatory event the cellular composition of the plaques changes. Chronic plaques show some inflammation but are devoid of inflammatory cells and characterized by myelin loss, axonal damage, an increase in astrocytes and the deposition of scar tissue (15).

Analysis of immunopathological material of actively demyelinated lesions has revealed great heterogeneity in the demyelination patterns among patients. Four different patterns of pathologic MS have been identified (71).

Pattern I:

Demyelination is macrophage-mediated and lesions are distributed perivenous. Inflammatory infiltrates are composed of T cells and macrophages which are considered, together with microglia, responsible for myelin-degeneration. The putative mechanisms are T cell-mediated inflammation with

macrophage/micorglia activation and demyelination induced by macrophage toxins.

# Pattern II:

Demyelination is antibody mediated, and lesions resemble pattern I lesions. In addition they show deposition of immunoglobulins and activated complement at the sites of active destruction. The mechanisms underlying this pattern are T cell-mediated inflammation with macrophage/microglia activation as well as complement-mediated lysis of antibody-targeted myelin.

# Pattern III:

Demyelination is due to distal oligodendrogliopathy with inflammation by T cells and macrophages. Small vessel vasculitis with endothelial cell damage and microvessel thrombosis have been seen. Lesions show degeneration of distal oligodendrocyte processes, followed by oligodendrocyte apoptosis and demyelination.

Underlying mechanisms are characterized by T cell-mediated small vessel vasculitis with secondary ischemic damage in the white matter.

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# Pattern IV:

Similar lesions like in pattern III, but oligodendrocyte degeneration is prominent in a small rim of the white matter. Mechanisms include T cell-mediated inflammation with macrophage/microglia activation. Demyelination is induced by macrophage toxins on the background of metabolically impaired oligodendrocytes. Oligodendrocytes might be genetically defect.

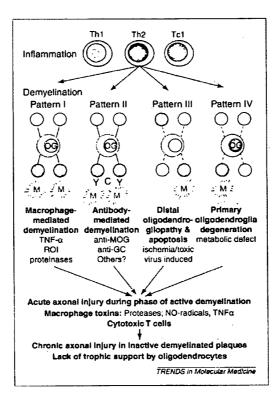


Fig. 5: Heterogenity of MS pathogenesis (source: Lassmann H., Trends in Molecular Medicine, Vol 7. No.3. March 2001)

Multiple sclerosis is a highly heterogeneous disease in which multiple factors interact in the pathogenesis, and influence the neurological impairment.

First, the number of brain-lesions, their dimension and their location in the CNS.

A lesion at the first relais of the spinal cord effects all other relais, for example.

Surprisingly brain Magnetic Resonance Imaging (MRI) and disability correlate only modest.

Second, the pathology of the lesions and their four different patterns also affect the disease course. Areas with previous inflammation reveal the greatest brain damage.

A new hypothesis proposes that lesion might begin with pattern III and is then followed by an abrupt loss of oligodendrocytes (72).

Normally one patient reveals different lesion types during his/her disease, but it is also possible to find different lesion types at the same time in one patient.

MRI may predict changes in the white matter (WM) almost 18 weeks before lesions appear. Therefore, neurological changes already appear in the preclinical phase of MS.

Third, WM abnormalities affect impairment. Abnormalities are not only seen within lesions, but also in the normal appearing white matter. These are increasingly seen in more disabled patients.

Forth, also the normal appearing grey matter (NAGM) shows damages on MRI of MS patients.

And fifth, the recovery mechanisms, mainly remyelination, play an important role in the pathogenesis of MS. Acute axonal damage is already seen in the early phase of the disease due to inflammation in the brain. The first attack (relapse) can cause severe damage, but may be reversible. Less lesions in the brain mean less brain atrophy. Bone marrow transplantation might stop inflammation, but brain atrophy keeps continuing. The reason are axons, which survive but continue to degenerate which leads to secondary axonal degeneration.

Secondary axonal damage is the predominant factor in the second phase of the disease. While very good results can be achieved by treating patients in the first, acute inflammatory phase with anti-inflammatory drugs, treatment in the second phase shows no results.

Inflammation in the early disease-phase is the key for reversible damage and therefore should be treated (I).

#### **Remyelination**

Experimental evidence indicates that surving oligodendrocytes are not the producers of new myelin after a demyelinating event, but oligodendrocyte precursor cells (ODPC) present throughout the adult brain (I).

In response to demyelination these cells proliferate and migrate towards affected areas on neurons to start remyelination of the myelin sheath. This phase is called recruitment phase. For complete remyelination these cells must engage demyelinated axons, differentiate into myelin-sheath forming oligodendrocytes and restore the myelin sheath. This final phase is called differentiation phase.

ODPCs are a normal part of the adult WM and remain mostly quiescent. Only in response to CNS injury they become activated and proliferate. Activation involves an increase in the expression of transcription factor genes, which are associated with developmental myelination. In the NAWM ODPCs express bHLH transcription factor Olig1 but expression of Olig2 and Nkx2.2 is at low level. Following an acute demyelinating event, the expression of both Olig2 and Nkx2.2 dramatically increases. Their expression is confined to the ODPC population. At differentiation of ODPCs into oligodendrocytes and PLP, their expression decreases again. Therefore, it was hypothized that the increased expression of the genes Olig2 and Nkx2.2 in response to demyelination is a critical genetic switch required to convert ODPCs into cells able to differentiate auiescent into remyelinating oligodendrocytes (73).(A)

As there are substantial numbers of premyelinating oligodendrocytes in CNS lesions, the repair-potential seems not to be limited by the loss of these cells. Therefore, interactions between the surrounding environment and oligodendrocytes might be important for the repair process and its success. A micorarray study investigated the links between astrocyte reactivity and lesion repair (74).

During CNS development, contact-mediated activation of Notch1 receptors on ODPCs by the ligand Jagged1 induces Hes5, which in turn inhibits their maturation.

The study found out that TGF- $\beta$ , which is upregulated in MS patients, specifically reinduced Jagged1 in primary cultures of human astrocytes. Within and around

active plaques, where no remyelination occurs, reactive astrocytes express high levels of Jagged1 and Notch1 and Hes5 were expressed by cells with an immature oligodendrocyte phenotype. TGF- $\beta$  localized to perivascular extracellular matrix. In contrast to remyelinated areas astrocytes there showed no Jagged1 immunoreactivity. These data suggest that Jagged1-expressing astrocytes may be causally related to the limited remyelination in MS.

Another aspect concerning remyelination is inflammation.

At least some aspects of the inflammatory response associated with demyelination seem to be somehow responsible for subsequent repair processes. This was demonstrated by toxin-induced demyelination models, where the inflammatory response occurs as a consequence of demyelination rather than being the cause of it, like in EAE. Studies on knock-out mice showed an impaired efficiency of remyelination in the absence of proinflammatory cytokines (IL-1 and TNF- $\alpha$ ) (67). Thus, inflammatory mediators seem to be necessary for creating a proremyelination environment.

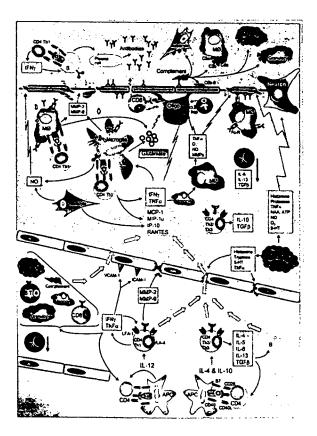


Fig.6 Summary of the pathogenesis of MS (source: Sospedra M. and Martin R., Annu. Rev. Immunol. 2005, 23: 683-747)

# 1.3.2.6 Treatment and Therapy

During the last decade several disease-modifying agents have been used as approved therapies for the treatment of relapsing-remitting (RR) MS. Their effectiveness is based on class I evidence – prospective, randomized, controlled clinical trials.

The following drugs are considered as first line therapy:

- interferon beta-1a: Avonex® (Biogen)
- interferon beta-1a: Rebif® (Serono)
- interferon beta-1b: Betaferon® (Schering)
- glatirameracetat: Copaxone® (Teva Pharmaceuticals)

All these drugs have been demonstrated to decrease the relapse rate, slow the progression of disability and improve markers of lesion load observed on MRI. Concerning disability a study comparing all immunomodulatory drugs did not find a significant reduction in EDSS score (75).

As a second line treatment mitoxandrone (Novandrone® by Serono) - approved only in the USA and natalizumab (Tysabri® by Biogen) are currently used.

For the treatment of inflammatory mediated health-problems, methylprednisolone is widely used.

Intravenous immunoglobulin (IVIG) has shown to be effective in the treatment of MS and will be discussed below in more detail.

Initially, treatment of the disease with modifying drugs was started when "clinically well-established RR disease with high relapse activity" was diagnosed.

Today, due to knowledge on the axonal damage which occurs already in the very early phase of the disease and the percentage of axonal loss, which has a significantly higher percentage than in later stages, there are discussions on whether to start treatment earlier, at signs of the first "clinically isolated syndrome".

# **Interferons**

The benefical effects of interferons in the treatment of MS are due to inhibition of proinflammatory cytokines, induction of anti-inflammatory biological products, reduction of cellular migration and inhibition of autoreactive T cells (76;77).

The INF $\beta$ -1b molecule differs from the natural human INF $\beta$  by missing a carbohydrate side chain and a serine for cysteine substitution at position 17.

INF $\beta$ -1a is glycosylated and basically indistinguishable from natural human INF $\beta$  (78).

Experiences have shown that the earlier the treatment is started and the younger the age of the patients, the better the response chances of the interferon therapy.

The EVIDENCE study has shown that a higher dosage and more frequent administration seem to be more effective (79).

A problem of interferon treatment is its immunogenicity. Interferon therapy may induce the appearance of neutralizing antibodies (NABs) already after 6 months of treatment. At the end of a one-year treatment 90% of patients are tested positive for the presence of NABs. The presence of NABs blocks activation of the interferon-receptor and interferon therapy will no longer be effective. Patients tested positive for NABs will also reveal a slightly higher relapse rate compared to patients tested negative for the presence of NABs (80).

## <u>Glatirameracetat</u>

It was the third treatment for RR-MS to be approved by the US FDA.

Glatirameracetat (GA) is a standardized, randomized mixture of synthetic polypeptides consisting of L-glutamic acid, L-lysine, L-alanine and L-tyrosine with a defined molecular ratio of 0.14 : 0.34 : 0.43 : 0.09 and an average molecular mass of 4.7 to 11.0kDa, and an average length of 45 to 100 amino acids.

GA has both suppressive and protective effects in EAE and has shown to be effective on clinical and MRI-defined MS patients when daily adiministered s.c.

It is supposed that GA competes in some way with MBP at the antigen-presenting cell level for binding to MHC and GA/MHC competes with MBP/MHC for binding to the TCR. GA induces a shift from a TH1-mediated immune response to a TH2-mediated immune response. The TH2 reactive T cells are able to cross the BBB because of daily immunization. In the CNS they release anti-inflammatory cytokines like IL-4, IL-5, IL-13 and TGF- $\beta$  which have a benefical effect on the ongoing inflammation in the brain (81).

#### **Mitoxandrone**

Patients experiencing relapses while on interferon-therapy are often treated with mitoxandrone, an anthracenedione cytotoxic drug with immunosuppressive properties. Clinical trial showed positive effects for both clinical and MRI-measured endpoints. Mitoxandrone inhibits RNA and DNA synthesis, B cell activity, reduces Th1 activity while enhancing suppressor-T cell activity.

Unfortunately the drug may cause some serious side-effects like cardiotoxicity or even the development of leukemias.

## <u>Natalizumab</u>

Natalizumab (Antegren) is a humanized monoclonal antibody against the four subunits of 41-Integrin (VLA-4) and 47-Integrin expressed on leucoytes. The antibody blocks the interaction of the integrins with their ligands VCAM and MadCAM. This causes and inhibition of the transmigration of leucoytes through the BBB.

Clinical trials have shown significant positive effect on the development of new inflammatory lesions in the CNS.

The 2-year AFFIRM study (phase III trial) showed good results in reduction of relapse-rate, reduction of the EDSS score as well as on MRI (data not published yet).

In the SENTINEL study (phase III) natalizumab was compared to placebo in patients using interferon beta-1a where it also showed positive effects concerning relapse-rate and MRI outcomes. (data not published yet).

Natalizumab (Tysabri®) was approved by the FDA in November 2004 but was very recently (February 2005) been taken voluntarily from the market due to severe side-effects of 3 patients in the SENTINEL study (source: <u>www.nationalmssociety.org</u>).

# Glucocorticosteroids

Intravenously or orally administered glucocorticosteroids shorten the duration of acute relapses and high dose treatment can delay the development of clinically definite MS for 2 years following the first attack of optic neuritis (78).

Methylprednisolone (MP) shows clinical effects by reducing inflammation and myelin-breakdown as seen on MRI, where the number of gadolinium-enhancing lesions is decreased.

Data indicate that MP suppresses the expression of the adhesion molecules LFA-1, VLA-4 and ICAM-1 on mononuclear cells. Therefore, MP might inhibit the ability, of immune cells to adhere to the endothelium leading to restricted transmigration into the CNS which leads to clinical improvement of patients (82).

## New treatments

FTY20 (sphingosine-1-phosphate receptor (S1P) modulator) is an oral immunomodulator capable of reversible sequestering tissue damaging T and B cells away form blood and the CNS to peripheral lymph nodes. The new drug has shown both preventive and therapeutic efficacy in several MS animal models. A proof of concept study demonstrated the effectiveness of both MRI and relapse-related endpoints. It seems that FTY20 has the potential to be an efficious disease modifying treatment for RRMS when administered once daily (A).

# Treatment in the progressive phase of MS

Unfortunately disease modifying drugs used for treatment of patients suffering from progressive MS show far less impressive results.

Two large, placebo-controlled studies with interferon beta-1a revealed no effect on sustained disability progression measured by EDSS score though an effect was seen on relapses (I).

Two similar studies using interferon beta-1b came up with divergent results:

The EU-SPMS trial measured a sustained effect on disability while the NA-SPMS trial could not confirm these results. But both studies showed similar positive results concerning the relapse rate and MRI endpoints (I).

Researchers and clinicians assumed that only RRMS was related to inflammation in the brain, while SPMS was thought to be the chronical phase of MS. But evidence shows diffuse WM injuries with severe inflammation in the CNS of SPMS patients. The question why these patients do not respond to immunomodulatory drugs remains open (I).

## 1.3.3 Intravenous immunoglobulins and MS

Intravenous immunoglobulins (IVIG) have been used for the treatment of several autoimmune disorders as immunomodulating agents.

In MS IVIG decreases the relapse-rate and the number of gadolinium-enhancing lesions on MRI. It suppresses the proliferation of activated T cells without modulating the apoptosis rate. Interactions between IVIG and variable regions of autoantibodies seem to be responsible for the ability of IVIG to regulate autoreactive B cell clones in vivo (83). The interaction of IVIG with complement prevents the formation of the C5b-9 membrane attack complex and therefore subsequent tissue damage (83).

EAE-studies indicate that these effects are mediated by modulation of the cytokine network and T cell response. IVIG might also protect oligodendrocytes from phagocytosis mediated by antibodies (84).

Introduction

The benefical effect of IVIG was shown by a number of open trials (85) and four randomized double-blind studies (52;86-88).

The largest trial, the AIMS study, was performed by Fazekas et al. (85) with 150 patients suffering from RRMS. Patients were treated with either IVIG 0.15-0.20g/kg/month or placebo for a 2-year period. The primary outcome endpoint were changes in EDSS. The patients showed a significant reduction in their EDSS score but the most significant result was a reduction in the mean annual relapse rate. The difference to the placebo group was 59%. Side effects with this low-dose treatment were mild and infrequent.

In the Achiron trial (51) 40 patients participated who were either treated with IVIG 0.4g/kg/day for 5 days followed by 0.4g/kg every 2 month or placebo. The primary endpoint were changes in the annual relapse rate which was achieved in a highly statistically significant way when compared to placebo (from 1.50 to 0.75 in the first year, and to 0.52 in the second year) meaning a reduction of the relapse rate of 63%. T2-weighted MRI images measured semi-quantitatively showed no significant differences.

The study performed by Sorensen (84) on 26 patients suffering from RRMS had new gadolinium-enhancing lesions on MRI as the primary endpoint. Half of the patients were treated with IVIG 2g/kg monthly for 6 months and a 3 months washout period after which they were treated with placebo for 6 month. The other half was treated in reverse order. MRI was measured monthly. The outcome was a reduction of ~60% of new lesions in the treatment group. The high-dose IVIG treatment was associated with a high number of side effects.

Lewanska et al. (87) investigated three different IVIG-treatment groups on 49 patients suffering from RRMS. They were treated either with IVIG 0.2g/kg, IVIG 0.4g/kg or placebo monthly over the period of one year. The annual relapse rate decreased significantly, also the EDSS score showed a reduction compared to placebo.

In summary, all four studies confirmed the benefical effect of IVIG on the annual relapse rate of RRMS patients.

Therefore IVIG can be considered as an alternative second-line therapy for the treatment of RRMS (89).

A review summarizing all four trials concluded, that IVIG has indeed beneficial effects on relapses and disability changes in patients suffering from RRMS. The results of all studies, despite the differences in their set-up, were remarkably consistent.

IVIG is a valuable alternative to established therapies for RRMS. Advantages of IVIG treatment include monthly infusions and only mild side-effects if applied in small doses of 0.2-0.4g/kg (85;90).

Nevertheless, the effects of IVIG treatment for RRMS patients is still controversial: as some investigators could show that IVIG is able to enhance CNS remyelination in animal models, a double-blind, placebo controlled trial to evaluate the effect of IVIG treatment in MS patients with a stable clinical deficit was conducted. 10 patients were treated first with placebo and later with IVIG 0.4g/kg for 5 days with a separation periodof 6 weeks between the treatments. The primary outcome parameter was the change in central motor conduction time as an indirect measurement of remyelination. The results of this pilot-study did not support a role for IVIG in the remyelination of patients with stable neurological deficits (91).

Another pilot study, a double-blind, randomized placebo-controlled trial, measured the effectiveness of a combination treatment with IVIG and MP for RRMS patients.

As some patients did not show significant improvements of acute relapses after IVMP treatment, the investigators wanted to know if combination therapy with IVIG on top of IVMP would lead to a better efficacy. Patients were randomized for IVMP 500mg directly followed by IVIG 0.4g/kg or placebo for five days. The primary outcome criterion was the EDSS score at four weeks. The results of the study could show no superiority of IVMP-IVIG therapy in the treatment of MS (92).

A recently performed clinical study using MRI as primary outcome measurement for IVIG treatment of patients, suffering from an established clinical neurological deficit caused by RRMS, did not show any significant benefits (93).

Three other small trials studying IVIG treatment at the time of acute relapse of MS patients showed that IVIG did not have any cliniclal influence on the duration of relapses, if given directly after the relapse or optic neuritis. The author of a summarizing review concludes that IVIG is not indicated for the treatment of relapses in MS (94).

Based on the controversial results published in literature, it was the aim of our study to investigate the effects of IVIG treatment in patients suffering from an acute relapse of MS at the level of gene-expression in peripheral T cells, as

autoreactive T cells which cross the blood-brain-barrier are the main target of demyelinating antibodies. The aim of my PhD-thesis is the evalutation of differentially expressed genes in peripheral T cells of patients before and after treatment with IVIG.

Initially we intended to use a new method called "subtractive suppression hybridization (SSH)". This method is a PCR-based technique for identifying and isolating cDNAs of differentially expressed genes. It is used to selectively amplify target cDNA fragments which are differentially expressed and simultaneously suppress non target DNA amplification (95).

For further identification of the differentially expressed library created with this method, differential screening must be performed. Finally the identified clones must be confirmed by Northern Blot thus meaning a tedious and lengthy process all together. The initial results that I obtained with this method were not convincing. Furthermore, it was recently suggested that the primary application of this method should be the detection of dramatic alteration in gene expression. The application of this method for the comparison of expression profiles in a set-up where small changes in gene expression are to be expected, was considered to be highly ineffective. Moreover, it was suggested that the target mRNA should be at least 0.1% of the total RNA which means that low abundance genes would not be detected (96). Therfore, we decided to use a more appropriate method and chose a completely different approach – microarray analysis.

Microarray technology has tremendously improved over the last few years. The inclusion of a series of internal controls on the microarray provide a reliable method for gene expression analysis and it was shown by 1064 published articles in the year 2003, the year we started using this method.

(http://www.affymetrix.com/community/publications/full\_list.affx?year=2003&result \_page=1).

We decided to use the human HU-133 genechip provided by Affymetrix® that allows the detection of ~ 33.000 differentially expressed genes.

# 2.4 Objectives of my project

Intravenous immunoglobulin (IVIG) have been used successfully in the treatment of several autoimmune disorders, including relapsing-remitting Multiple Sclerosis (RRMS). MS is an inflammatory-mediated disease and a modulation of T cell responses might be involved in the immunomodulatory activities of IVIG.

The aim of my PhD project was to explain the effects of IVIG on gene expression levels. Therefore, I studied the expression profiles of peripheral T cells in patients with RRMS in exacerbation before and after treatment with IVIG using microarrays to identify differentially expressed genes.

My part of the project was the establishment of all cell isolation methods for obtaining total RNA from T cells obtained from peripheral blood mononuclear cells (PBMC), isolation of RNA, data analysis of microarrays and confirmation of microarray results using Real Time PCR.

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# 1.3.2.6 Treatment and Therapy

During the last decade several disease-modifying agents have been used as approved therapies for the treatment of relapsing-remitting (RR) MS. Their effectiveness is based on class I evidence – prospective, randomized, controlled clinical trials.

The following drugs are considered as first line therapy:

- interferon beta-1a: Avonex® (Biogen)
- interferon beta-1a: Rebif® (Serono)
- interferon beta-1b: Betaferon® (Schering)
- glatirameracetat: Copaxone® (Teva Pharmaceuticals)

All these drugs have been demonstrated to decrease the relapse rate, slow the progression of disability and improve markers of lesion load observed on MRI. Concerning disability a study comparing all immunomodulatory drugs did not find a significant reduction in EDSS score (75).

As a second line treatment mitoxandrone (Novandrone® by Serono) - approved only in the USA and natalizumab (Tysabri® by Biogen) are currently used.

For the treatment of inflammatory mediated health-problems, methylprednisolone is widely used.

Intravenous immunoglobulin (IVIG) has shown to be effective in the treatment of MS and will be discussed below in more detail.

Initially, treatment of the disease with modifying drugs was started when "clinically well-established RR disease with high relapse activity" was diagnosed.

Today, due to knowledge on the axonal damage which occurs already in the very early phase of the disease and the percentage of axonal loss, which has a significantly higher percentage than in later stages, there are discussions on whether to start treatment earlier, at signs of the first "clinically isolated syndrome".

# **Interferons**

The benefical effects of interferons in the treatment of MS are due to inhibition of proinflammatory cytokines, induction of anti-inflammatory biological products, reduction of cellular migration and inhibition of autoreactive T cells (76;77).

The INF $\beta$ -1b molecule differs from the natural human INF $\beta$  by missing a carbohydrate side chain and a serine for cysteine substitution at position 17.

INF $\beta$ -1a is glycosylated and basically indistinguishable from natural human INF $\beta$  (78).

Experiences have shown that the earlier the treatment is started and the younger the age of the patients, the better the response chances of the interferon therapy.

The EVIDENCE study has shown that a higher dosage and more frequent administration seem to be more effective (79).

A problem of interferon treatment is its immunogenicity. Interferon therapy may induce the appearance of neutralizing antibodies (NABs) already after 6 months of treatment. At the end of a one-year treatment 90% of patients are tested positive for the presence of NABs. The presence of NABs blocks activation of the interferon-receptor and interferon therapy will no longer be effective. Patients tested positive for NABs will also reveal a slightly higher relapse rate compared to patients tested negative for the presence of NABs (80).

## Glatirameracetat

It was the third treatment for RR-MS to be approved by the US FDA.

Glatirameracetat (GA) is a standardized, randomized mixture of synthetic polypeptides consisting of L-glutamic acid, L-lysine, L-alanine and L-tyrosine with a defined molecular ratio of 0.14 : 0.34 : 0.43 : 0.09 and an average molecular mass of 4.7 to 11.0kDa, and an average length of 45 to 100 amino acids.

GA has both suppressive and protective effects in EAE and has shown to be effective on clinical and MRI-defined MS patients when daily adiministered s.c.

It is supposed that GA competes in some way with MBP at the antigen-presenting cell level for binding to MHC and GA/MHC competes with MBP/MHC for binding to the TCR. GA induces a shift from a TH1-mediated immune response to a TH2-mediated immune response. The TH2 reactive T cells are able to cross the BBB because of daily immunization. In the CNS they release anti-inflammatory cytokines like IL-4, IL-5, IL-13 and TGF- $\beta$  which have a benefical effect on the ongoing inflammation in the brain (81).

# **Mitoxandrone**

Patients experiencing relapses while on interferon-therapy are often treated with mitoxandrone, an anthracenedione cytotoxic drug with immunosuppressive properties. Clinical trial showed positive effects for both clinical and MRI-measured endpoints. Mitoxandrone inhibits RNA and DNA synthesis, B cell activity, reduces Th1 activity while enhancing suppressor-T cell activity.

Unfortunately the drug may cause some serious side-effects like cardiotoxicity or even the development of leukemias.

## <u>Natalizumab</u>

Natalizumab (Antegren) is a humanized monoclonal antibody against the four subunits of 41-Integrin (VLA-4) and 47-Integrin expressed on leucoytes. The antibody blocks the interaction of the integrins with their ligands VCAM and MadCAM. This causes and inhibition of the transmigration of leucoytes through the BBB.

Clinical trials have shown significant positive effect on the development of new inflammatory lesions in the CNS.

The 2-year AFFIRM study (phase III trial) showed good results in reduction of relapse-rate, reduction of the EDSS score as well as on MRI (data not published yet).

In the SENTINEL study (phase III) natalizumab was compared to placebo in patients using interferon beta-1a where it also showed positive effects concerning relapse-rate and MRI outcomes. (data not published yet).

Natalizumab (Tysabri®) was approved by the FDA in November 2004 but was very recently (February 2005) been taken voluntarily from the market due to severe side-effects of 3 patients in the SENTINEL study (source: <u>www.nationalmssociety.org</u>).

# <u>Glucocorticosteroids</u>

Intravenously or orally administered glucocorticosteroids shorten the duration of acute relapses and high dose treatment can delay the development of clinically definite MS for 2 years following the first attack of optic neuritis (78).

Methylprednisolone (MP) shows clinical effects by reducing inflammation and myelin-breakdown as seen on MRI, where the number of gadolinium-enhancing lesions is decreased.

Data indicate that MP suppresses the expression of the adhesion molecules LFA-1, VLA-4 and ICAM-1 on mononuclear cells. Therefore, MP might inhibit the ability, of immune cells to adhere to the endothelium leading to restricted transmigration into the CNS which leads to clinical improvement of patients (82).

# New treatments

FTY20 (sphingosine-1-phosphate receptor (S1P) modulator) is an oral immunomodulator capable of reversible sequestering tissue damaging T and B cells away form blood and the CNS to peripheral lymph nodes. The new drug has shown both preventive and therapeutic efficacy in several MS animal models. A proof of concept study demonstrated the effectiveness of both MRI and relapse-related endpoints. It seems that FTY20 has the potential to be an efficious disease modifying treatment for RRMS when administered once daily (A).

# Treatment in the progressive phase of MS

Unfortunately disease modifying drugs used for treatment of patients suffering from progressive MS show far less impressive results.

Two large, placebo-controlled studies with interferon beta-1a revealed no effect on sustained disability progression measured by EDSS score though an effect was seen on relapses (I).

Two similar studies using interferon beta-1b came up with divergent results:

The EU-SPMS trial measured a sustained effect on disability while the NA-SPMS trial could not confirm these results. But both studies showed similar positive results concerning the relapse rate and MRI endpoints (I).

Researchers and clinicians assumed that only RRMS was related to inflammation in the brain, while SPMS was thought to be the chronical phase of MS. But evidence shows diffuse WM injuries with severe inflammation in the CNS of SPMS patients. The question why these patients do not respond to immunomodulatory drugs remains open (I).

## 1.3.3 Intravenous immunoglobulins and MS

Intravenous immunoglobulins (IVIG) have been used for the treatment of several autoimmune disorders as immunomodulating agents.

In MS IVIG decreases the relapse-rate and the number of gadolinium-enhancing lesions on MRI. It suppresses the proliferation of activated T cells without modulating the apoptosis rate. Interactions between IVIG and variable regions of autoantibodies seem to be responsible for the ability of IVIG to regulate autoreactive B cell clones in vivo (83). The interaction of IVIG with complement prevents the formation of the C5b-9 membrane attack complex and therefore subsequent tissue damage (83).

EAE-studies indicate that these effects are mediated by modulation of the cytokine network and T cell response. IVIG might also protect oligodendrocytes from phagocytosis mediated by antibodies (84).

Introduction

The benefical effect of IVIG was shown by a number of open trials (85) and four randomized double-blind studies (52;86-88).

The largest trial, the AIMS study, was performed by Fazekas et al. (85) with 150 patients suffering from RRMS. Patients were treated with either IVIG 0.15-0.20g/kg/month or placebo for a 2-year period. The primary outcome endpoint were changes in EDSS. The patients showed a significant reduction in their EDSS score but the most significant result was a reduction in the mean annual relapse rate. The difference to the placebo group was 59%. Side effects with this low-dose treatment were mild and infrequent.

In the Achiron trial (51) 40 patients participated who were either treated with IVIG 0.4g/kg/day for 5 days followed by 0.4g/kg every 2 month or placebo. The primary endpoint were changes in the annual relapse rate which was achieved in a highly statistically significant way when compared to placebo (from 1.50 to 0.75 in the first year, and to 0.52 in the second year) meaning a reduction of the relapse rate of 63%. T2-weighted MRI images measured semi-quantitatively showed no significant differences.

The study performed by Sorensen (84) on 26 patients suffering from RRMS had new gadolinium-enhancing lesions on MRI as the primary endpoint. Half of the patients were treated with IVIG 2g/kg monthly for 6 months and a 3 months washout period after which they were treated with placebo for 6 month. The other half was treated in reverse order. MRI was measured monthly. The outcome was a reduction of ~60% of new lesions in the treatment group. The high-dose IVIG treatment was associated with a high number of side effects.

Lewanska et al. (87) investigated three different IVIG-treatment groups on 49 patients suffering from RRMS. They were treated either with IVIG 0.2g/kg, IVIG 0.4g/kg or placebo monthly over the period of one year. The annual relapse rate decreased significantly, also the EDSS score showed a reduction compared to placebo.

In summary, all four studies confirmed the benefical effect of IVIG on the annual relapse rate of RRMS patients.

Therefore IVIG can be considered as an alternative second-line therapy for the treatment of RRMS (89).

A review summarizing all four trials concluded, that IVIG has indeed beneficial effects on relapses and disability changes in patients suffering from RRMS. The results of all studies, despite the differences in their set-up, were remarkably consistent.

IVIG is a valuable alternative to established therapies for RRMS. Advantages of IVIG treatment include monthly infusions and only mild side-effects if applied in small doses of 0.2-0.4g/kg (85;90).

Nevertheless, the effects of IVIG treatment for RRMS patients is still controversial: as some investigators could show that IVIG is able to enhance CNS remyelination in animal models, a double-blind, placebo controlled trial to evaluate the effect of IVIG treatment in MS patients with a stable clinical deficit was conducted. 10 patients were treated first with placebo and later with IVIG 0.4g/kg for 5 days with a separation periodof 6 weeks between the treatments. The primary outcome parameter was the change in central motor conduction time as an indirect measurement of remyelination. The results of this pilot-study did not support a role for IVIG in the remyelination of patients with stable neurological deficits (91).

Another pilot study, a double-blind, randomized placebo-controlled trial, measured the effectiveness of a combination treatment with IVIG and MP for RRMS patients.

As some patients did not show significant improvements of acute relapses after IVMP treatment, the investigators wanted to know if combination therapy with IVIG on top of IVMP would lead to a better efficacy. Patients were randomized for IVMP 500mg directly followed by IVIG 0.4g/kg or placebo for five days. The primary outcome criterion was the EDSS score at four weeks. The results of the study could show no superiority of IVMP-IVIG therapy in the treatment of MS (92).

A recently performed clinical study using MRI as primary outcome measurement for IVIG treatment of patients, suffering from an established clinical neurological deficit caused by RRMS, did not show any significant benefits (93).

Three other small trials studying IVIG treatment at the time of acute relapse of MS patients showed that IVIG did not have any cliniclal influence on the duration of relapses, if given directly after the relapse or optic neuritis. The author of a summarizing review concludes that IVIG is not indicated for the treatment of relapses in MS (94).

Based on the controversial results published in literature, it was the aim of our study to investigate the effects of IVIG treatment in patients suffering from an acute relapse of MS at the level of gene-expression in peripheral T cells, as

autoreactive T cells which cross the blood-brain-barrier are the main target of demyelinating antibodies. The aim of my PhD-thesis is the evalutation of differentially expressed genes in peripheral T cells of patients before and after treatment with IVIG.

Initially we intended to use a new method called "subtractive suppression hybridization (SSH)". This method is a PCR-based technique for identifying and isolating cDNAs of differentially expressed genes. It is used to selectively amplify target cDNA fragments which are differentially expressed and simultaneously suppress non target DNA amplification (95).

For further identification of the differentially expressed library created with this method, differential screening must be performed. Finally the identified clones must be confirmed by Northern Blot thus meaning a tedious and lengthy process all together. The initial results that I obtained with this method were not convincing. Furthermore, it was recently suggested that the primary application of this method should be the detection of dramatic alteration in gene expression. The application of this method for the comparison of expression profiles in a set-up where small changes in gene expression are to be expected, was considered to be highly ineffective. Moreover, it was suggested that the target mRNA should be at least 0.1% of the total RNA which means that low abundance genes would not be detected (96). Therfore, we decided to use a more appropriate method and chose a completely different approach – microarray analysis.

Microarray technology has tremendously improved over the last few years. The inclusion of a series of internal controls on the microarray provide a reliable method for gene expression analysis and it was shown by 1064 published articles in the year 2003, the year we started using this method.

(http://www.affymetrix.com/community/publications/full\_list.affx?year=2003&result \_page=1).

We decided to use the human HU-133 genechip provided by Affymetrix® that allows the detection of ~ 33.000 differentially expressed genes.

### 2.4 Objectives of my project

Intravenous immunoglobulin (IVIG) have been used successfully in the treatment of several autoimmune disorders, including relapsing-remitting Multiple Sclerosis (RRMS). MS is an inflammatory-mediated disease and a modulation of T cell responses might be involved in the immunomodulatory activities of IVIG.

The aim of my PhD project was to explain the effects of IVIG on gene expression levels. Therefore, I studied the expression profiles of peripheral T cells in patients with RRMS in exacerbation before and after treatment with IVIG using microarrays to identify differentially expressed genes.

My part of the project was the establishment of all cell isolation methods for obtaining total RNA from T cells obtained from peripheral blood mononuclear cells (PBMC), isolation of RNA, data analysis of microarrays and confirmation of microarray results using Real Time PCR.

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#### 3.1 Abstract

Intravenous immunoglobulins (IVIG) have been used successfully in the treatment of a number of autoimmune diseases of the central nervous system including multiple sclerosis (MS).

Although IVIG seems to have a substantial effect on short- and long-term treatment potential, the underlying mechanisms of action are not elucidated.

It has been suggested that a modulation of the T cell immune responses might be involved in the benefical effects of IVIG therapy and therefore we focused on the identification and characterization of genes involved in the immunomodulatory activity of IVIG in the treatment of exacerbations in Relapsing-Remitting MS (RRMS).

Using microarrays we investigated the expression profiles of T cell fractions of peripheral blood mononuclear cells (PBMC) isolated from 10 RRMS patients treated with IVIG as well as five control patients treated with intravenous methylprednisolone (IVMP). Among the approximately 33.000 genes examined, we found 152 different genes (176 probe-sets) which were differentially regulated by a minimum of a two-fold change in at least 40% of patients. They included genes involved in immune response, inflammatory response, proliferation, apoptosis, cell cycle, signal transduction or regulation of transcription. Statistical analysis by parametric t-test revealed a different number of significantly differentially regulated genes. When comparing the results obtained with both approaches, only a few genes were in common. Differences in the results obtained from gene expression profiles using different approaches for the evaluation of the data are a known problem in the literature. International standartization of statistical approaches for the evaluation of gene expression data obtained from microarray analysis will be necessary to generate reproducible and comparable results in different laboratories.

## 3.2 Introduction

Multiple Sclerosis (MS) is the most common inflammatory disease of the central nervous system (CNS). It is characterized by the infiltration of immune cells, mainly activated T cells, into the brain accompanied by a disruption of the blood-brain-barrier (BBB). In the white matter of the CNS demyelinating lesions lead to neurological deficits.

Intravenous immunoglobulins (IVIG) have been shown to be effective in the treatment of a number of autoimmune diseases including MS (1).

But the precise mechanism of action underlying the immunomodulatory activities of IVIG has not been elucidated. There are several models to explain the immunomodulatory potential of IVIG in patients suffering from autoimmune and inflammatory diseases, including  $Fc\gamma$ -receptor-mediated immunomodulation, influence on idiotype/anti-idiotype network, elimination of immunostimulating microbial products or neutralizing antibodies against cytokines and chemokines.

A potential to modify the balance of TH1 and TH2 cells and an inhibition of the formation of antibody/complement complexes have also been shown (2).

In MS IVIG decreases the relapse-rate and the number of gadolinium-enhancing lesions on brain-MRI. Furthermore, it suppresses the proliferation of activated T cells without modulating the apoptosis rate (3-6).

The benefical effect of IVIG in MS was shown by a number of open trials (3) and four randomized double-blind studies (5;7-9).

It was the aim of our study to investigate the effects of IVIG treatment in patients suffering from an acute relapse of MS at the level of gene-expression in peripheral T cells, as auto-reactive T cells can cross the blood-brain-barrier and are the main effector cells causing brain inflammation.

To investigate the mechanism of action of IVIG, a small clinical study including 10 patients suffering from RRMS was performed. Patients were treated with IVIG for 5 days and magnetic-resonsance imaging (MRI) - for measurement of treatment efficacy - was taken before treatment, 1 day after completion of therapy on day 6 as well as 3 weeks after termination of therapy on day 21. A group of five patients treated with methylprednisolone (IVMP) were used as a control.

Microarray technology has significantly improved over the last few years and allows a systematical analysis of the expression of a great number of genes. Especially Affymetrix technology has shown high correlation among replicates and low levels of variance when compared to other microarray platforms (10).

Analysis of microrarrays applying a filter criteria of a 2-fold change of expression revealed 152 differentially regulated genes and a number of 176 different probesets in at least 40% of the patients, including 57 genes involved in regulation of immune responses or inflammatory response.

Statistical analysis of the same data set using a parametric t-test detected 360 different probe-sets. These results show that data-analysis is not unique and discrepancies are possible for data-sets of human diseases (11). The results of two data-sets were confirmed by Real Time PCR.

The efficacy of IVIG treatment was also confirmed by the clinical results, which showed a reduction in the Enhanced Disability Status Scale (EDSS) of MS patients after IVIG treatment.

## 3.3 Materials and Methods

### 3.3.1 Patients involved in the study

All patients included in the study were suffering from clinically and laboratorysupported definite MS of Relapsing-Remitting type. The diagnosis of MS was based on Poser's criteria. The neurological disability was evaluated by the Expanded Disability Status Scale (EDSS). Patients characteristics are listed in table 1. Before entry into the study each patient signed a form of consent to participate in the study. The study was approved by the Ethical Committee of Tampere University, Tampere, Finnland.

Patients who received prior treatment with immunosuppressants in the preceding nine months or patients who received corticosteroids in the preceding eight weeks were excluded.

All patients received Endobulin® (Baxter AG, Vienna, Austria) in a 5-day course of 0.4g/kg/day.

Clinical evaluation of the patients was done before treatment with IVIG, 1 day after completion of therapy on day 6 as well as 3 weeks after completion of therapy on day 21. It included neurological examination, determination of the EDSS score, arm index and Ambulation index.

The primary outcome of the study was changes in the EDSS score from baseline (before IVIG) to week 3.

Secondary outcome measurement points were changes in the volume or number of several MRI-measures (T1-, T2-, FLAIR- and Gadolinium-enhancing lesions as well as brain volume).

A control-group of 5 patients was treated with 1g/day of intravenous methylprednisolone (IVMP) for 3 days what represents the current standard of care.

#### Table. 1

Characteristics of study population

Characteristics	IVIG Patients	IVMP Controls
Number of study population	10	5
Age average ± SD, year)	40 ± 10.6	35.3 ± 8.8
Sex (male vs female)	3 vs 7	0 vs 5
Disease duration (average ± SD, year)	5.6 ± 3.5	5.2 ± 3.6
Time current vs previous relapse (average ± SD, month)	17.6 ± 21.0	5 ± 3.2
EDSS score at remission (average ± SD, score)	3.7 ± 1.1	3.2 ± 2.4
EDSS score at acute relapse (average ± SD, score)	3.7 ± 1.1	4.2 ± 2.0

A total of 10 patients suffering from Multiple Sclerosis in acute relapse were selected for a clinical trial to confirm the efficacy of a 5-day course of IVIG-treatment on EDSS score and brain-MRI to improve disease-condition.

A total of 5 patients RRMS patients were treated with a 3-day course of IVMP as a control.

#### 3.3.2 Sample Preparation

Peripheral blood mononuclear cells (PBMC) were separated from peripheral blood in Vacutainer® CPTTM Cell Preparation Tubes (Becton Dickinson, Franklin Lakes,

N.J.) within 60 min after blood sampling using standard procedures of density gradient (Lymphoprep, Nycomed, Roskilde, DK) centrifugation.

PBMCs were separated into T cells and non T cells using a mixture of nonstimulating anti-CD4<sup>+</sup> and anti-CD8<sup>+</sup> magnetic Dynabeads (Dynal Biotech, Oslo, N) at 4°C.

Aliquots of ~  $5 \times 10^6$  cells were pelleted and the pellets were thoroughly mixed with 1ml TRIzol (Invitrogen, Carlsbad, CA). Aliquots were stored and frozen at  $-80^\circ$  until further processing.

Total RNA was isolated according to the manufacturer's protocol and RNA pellets were dissolved in Nuclease-free water (Invitrogen, Carlsbad, CA), measured and stored at –80°.

# 3.3.3 Microarrays

For this study we used the HU-133A Genechip (Affymetrix, Santa Clara, CA) containing approximately 33.000 genes. 5µg of total T cell RNA were in-vitro transcribed, labelled and hybridized on the array according to the manufacturer's protocol (see Affymetrix.com) RNA quality was checked before in-vitro processing with a Bioanalyzer (Agilent Technologies, Palo Alto, CA).

## 3.3.4 Data Analysis

Data were analyzed with Gene chip Operating software (GCOS) and Data Mining Tool software (DMT) (Affymetrix, Santa Clara, CA). We searched for genes which were either up- or down-regulated in 40%, 50%, 60%, 80% and 100% of patients. Cut-off values were a 2-fold differential expression with a p-value of  $\leq 0.006$  or  $\geq 0.994$ .

# 3.3.5 Real Time Polymerase chain reaction

The microarray data for 8 genes were confirmed by quantitative real-time PCR. 1µg of total T cell RNA was used for reverse transcription into cDNA according to the manufacturer's protocol (MBI Fermentas, Burlington, Canada). 100ng cDNA in 5µl nuclease-free water (Invitrogen, Carlsbad, CA) were quantitatively analyzed using different TaqMan® Assays-on-Demand (Applied Biosystems, Foster City, CA) with the ABPrism 7000 (Applied Biosystems). Data analysis was performed using the ^^CT-Method, a method commonly used

for relative quantification (12). For normalization of expression data human GPDH

was used as a housekeeping gene. For verification of normalization, a second housekeeping gene,  $\beta$ -2microglobulin, was used as a control (data not shown).

3.3.6 Statistical Analysis

Our data set of 30 arrays (3 time points /10 replicates each) was analyzed using a parametric t-test (Welch t-test with unpaired variances). First, all arrays were normalized followed by normalization of genes and logarithmic transformation of all data. Genes with a fold change  $\geq 2$  as well as a p-value <0.5 were significantly changed. The same method was used for analyzing the control group with a lower-sample number (5 patients).

# 3.4 Results

## 3.4.1 Clinical outcome

The clinical outcome of the study showed that a 5-day course of IVIG therapy of patients resulted in a significant reduction of the EDSS score in all 10 patients from a mean of 3.8 to 2.6 (Fig. 1, Tab.2) as well as in an improvement of MRI measurements (Tab. 3a), for example from a median of 1.76 down to 1.73 on T1-weighted images (used for the detection of axonal loss) or from a median of 5.49 down to 5.08 on T2-weighted images (used for the detection of new lesion in the brain). Data for MRI-measurements of the control group are given in Tab. 3b. Here, IVMP does not have an overall reducing effect on MRI measurements as seen on the median for the T1-weighted images.

Treatment was save and well-tolerated. Based on these data, we could confirm the benefical effects of IVIG in patients with RRMS during relapse.

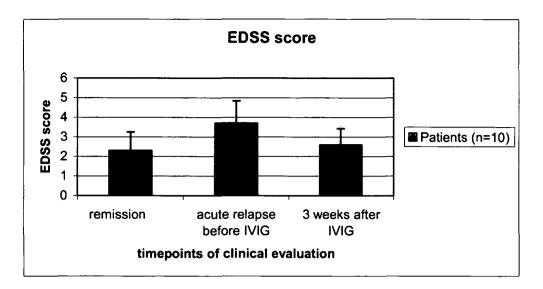


Figure. 1 Treatment effect of IVIG on mean EDSS score of patients

Names	Group	EDSS	EDSS	EDSS
		at day 0	at day 6	_at day 21
NK	IVIG	2	4	3
MP	IVIG	0.5	2	1
AH	IVIG	4	5	4
PJ	IVIG	2	3	2.5
MN	IVIG	2.5	3	2.5
LM	IVIG	3	4	3
TV	IVIG	2.5	3	2.5
IL	IVIG	3	5	2
AT	IVIG	2.5	3	2.5
PL	IVIG	3	5.5	4
HA	IVIG	1.5	3.5	1.5
<u>LT</u>	IVIG	_ 3	5	3

Table. 2 Treatment efficacy of IVIG on mean EDSS score of patients

# <u>Table 3a</u>

Parameter	Before IVIG	After IVIG
Lesion vol cm3	mean ± SE	mean ± SE
T1	1. 76 ± 0.55	1.73 ± 0.59
T2	5.49 ± 1.09	5.08 ± 1.03*
Flair	15.76 ± 2.23	14.09 ± 1.94**
Gd-enhanced	0.32 ± 0.27	0.21 ± 0.24**
Brain volume	1124.94 ± 40.61	1120.31± 40.72
Gd+lesion N	2.83 ± 0.71	2.00 ± 0.60**
EDSS° score	$3.8 \pm 0.3$	2.6 ± 0.2**

MRI measurements of brain abnormalities before and after IVIG

\* p<0.05; \*\* p<0.01

° EDSS = Kurtzke's Expanded Disability Status Scale

Table 3b:

MRI measurements of brain abnormalities before and after IVMP

Parameter	Before IVMP	After IVMP	P value
Lesion vol cm3	mean ± SE	mean ± SE	
T1	1.41 ± 0.60	1.64 ± 0.84	1
T2	11.15 ± 4.59	9.83 ± 4.17	0.17
Flair	24.37 ± 8.19	23.18 ± 8.05	0.25
Gd-enhanced	0.70 ± 0.39	0.63 ± 0.37	0.59
Brain volume	1056.32 ± 47.78	1045.07 ± 52.53	0.35
Gd+lesion N	3.0 ± 1.5	2.7 ± 1.4	0.16
EDSS* score	Not available	Not available	

\*EDSS = Kurtzke's Expanded Disability Status Scale

#### 3.4.2 Gene expression profiles

Microarray analysis of gene expression analysis examined ~22.000 transcripts and resulted in 176 differentially expressed probe-sets and 152 differentially expressed genes after application of a 2-fold criteria and a concomitance of a minimum of 40% in all patients after treatment with IVIG (Tab. 4). The majority of probe-sets (134) were down-regulated between day 6 and day 21 after beginning of IVIG therapy, while the only up-regulations (29) occurred at day 6 compared to day 0 after start of treatment (Tab. 5). A complete list of genes is given in the attachment section (see table A1).

Out of these genes, 49 probe-sets are involved in either immune response or inflammatory response (see Tab. A1). An example of two immune-relevant genes which were common in 60% of patients (6 out of 10) were the Fc fragment of IgG receptor 1 - FCGR1 (CD64) - and the Fc fragment of IgG receptor 2A - FCGR2A (CD32). Both genes were down-regulated at day 21 compared to day 6, while CD64 was up-regulated at day 6 compared to day 0 as well.

FCGR1 (CD64) is the only high affinity receptor in the immunoglobulin receptor superfamily due to its third extracellular domain and has a specifity for IgG1 and IgG3. It can bind monomeric and aggregated Ig and functions mainly in phagocytosis. FCGR2 (CD32) is a low affinity receptor which binds IgG in form of immune complexes with a specificity for IgG1 and IgG3. FCGR2A is mainly expressed by macrophages and neutrophils and functions in phagocytosis and cell activation but it is also expressed by a small subset of activated T cells where it fuctions as a cytolytic receptor in ADCC (Antibody-dependent cell-mediated cytotoxicity).

Probe-sets not involved in immune or inflammatory response reveal their main function in signalling, transcription, regulation of proliferation or cell cycle.

Microarray analysis of gene expression of the control-group showed 784 differentially regulated prob-sets after application of a 2-fold criteria and a concomitance of a minimum of 40% in all patients after treatment with IVMP (Tab. 6). Again, the majority of genes showing a change in expression was downregulated. The highest number of down-regulation occurred at day 6 compared to day 0 after beginning of IVMP treatment (Tab. 7). Out of the list containing probe-sets differentially regulated upon IVIG treatment. 8

Out of the list containing probe-sets differentially regulated upon IVIG treatment, 8 genes were selected according to the criteria of either immune relevancy or common in a high percentage of samples for confirmation of expression data (see 3.5) and to show their progression during the time course (Fig. 2).

For probe-sets differentially regulated in the control-group, 7 genes were selected according to the criteria of either immune relevancy or common in a high percentage of samples for confirmation of expression data (see 3.5) and to show their progression during the time course (Fig. 3).

<u>Table 4</u> Number of differentially expressed probe-sets on the HU-133A Genechip (Affymetrix) after IVIG treatment according to 2-fold induction/reduction criteria and a minimum of presence of at least 40% (4 out of 10) of patients;

Fold change in gene expression	Number of probe-sets	affected by IVIG
	Increases	Decreases
$\geq$ 2–change in any patient	4403	8356
$\geq$ 2–change in at least 40% of patients	26	104
$\geq$ 2-change in at least 50% of patients	3	32
≥ 2-change in at least 60% of patients	0	11
$\geq$ 2–change in at least 80% of patients	0	0
$\geq$ 2–change in at least 100% of patients	0	0

<u>Table 5</u> Number of differentially expressed probe-sets at the three different time-points of blood sampling after IVIG treatment; Criteria applied are a 2-fold change and a minimum of presence of at least 40% (4 out of 10 patients);

≥ 2-fold changes in at	comparison	comparison	comparison
least 40% of patients	day 6 to day 0	day 21 to day 0	day 21 to day 6
increases	29	0	0
decreases	6	7	134
total	35	7	134
total all		176	

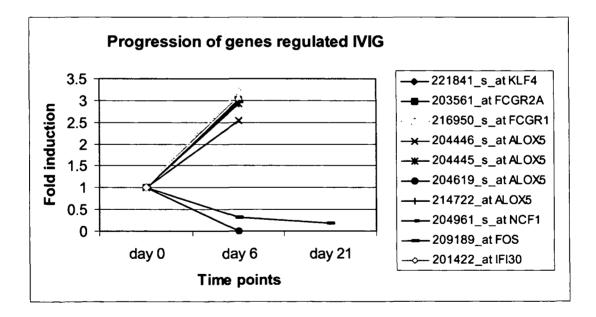
<u>Table 6</u> Number of differentially expressed probe-sets on the HU-133A Genechip (Affymetrix) after IVMP treatment according to 2-fold induction/reduction criteria and a minimum of presence of at least 40% (2 out of 5) of control-patients;

Fold change in gene expression	Number of probe-sets affected by IVMP		
	Increases	Decreases	
$\geq$ 2–change in any patient	3178	6197	
$\geq$ 2-change in at least 40% of patients	204	494	
$\geq$ 2-change in at least 60% of patients	20	52	
$\geq$ 2-change in at least 80% of patients	7	7	
$\geq$ 2-change in at least 100% of patients	0	0	

<u>Table 7</u> Number of differentially expressed probe-sets at the three different time-points of blood sampling after IVMP treatment; Criteria applied are a 2-fold change and a minimum of presence of at least 40% (2 out of 5 control-patients);

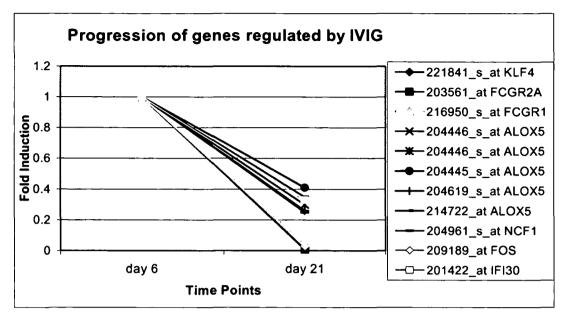
Differentially expressed g	enes		
≥ 2-fold changes in at least 40% of patients	comparison day 6 to day 0	comparison day 21 to day 0	comparison day 21 to day 6
increases	78	18	135
decreases	422	69	42
total	520	87	177
total all		784	

#### Figure. 2



#### Figure 2a:

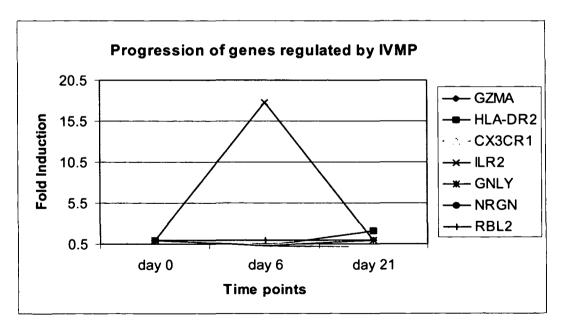
Progression of genes used for Real Time PCR confirmation under the influence of IVIG; Microarray data are displayed as fold-inductions; Day 0 was set as 1; Data are given for the following time points: Day 6 compared to day 0 and day 21 compared to day 0 after beginning of IVIG treatment;



#### Figure 2b:

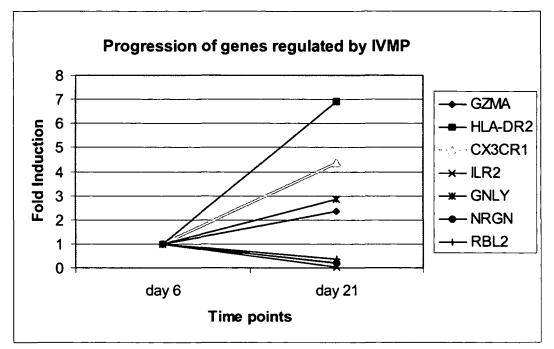
Progression of genes used for Real Time PCR confirmation under the influence of IVIG; Microarray data are displayed as fold-inductions; Day 0 was set as 1; Data are given for the following time points: Day 21 compared to day 6 after beginning of IVIG treatment;

### Figure 3



#### Figure 3a:

Progression of genes used for Real Time PCR confirmation under the influence of IVMP;Microarray data are displayed as fold-inductions; Day 0 was set as 1; Data are given for the following time points: Day 6 compared to day 0 and day 21 compared to day 0 after beginning of IVMP treatment;



#### Figure 3b:

Progression of genes used for Real Time PCR confirmation under the influence of IVIG; Microarray data are displayed as fold-inductions; Day 0 was set as 1; Data are given for the following time points: Day 21 compared to day 6 after beginning of IVIG treatment;

## 3.4.3 Statistical evaluation of gene expression data

Statistical analysis of the same data set consisting of microarray results of T cells of 10 patients suffering from MS in acute relapse gave a completely different number of significant differentially regulated genes: 360 probe-sets showed a change in expression upon IVIG treatment using a parametric t-test and 176 probe-sets showed a change using Data Mining Tool for analysis. In the control group treated with IVMP the parametric t-test revealed 583 probe-sets differentially regulated and the approach using Data Mining Tool showed 784 probe-sets of significantly differential regulated genes (Tab. 8 und Tab. 9).

The complete lists of all statistically significant genes differentially regulated upon IVIG and IVMP treatment are given in the attachment section (see Tab. A3 for IVIG and Tab. A4 for IVMP).

These list include immune or inflammatory related genes like PTGER4 (Prostaglandin E receptor 4), encoding a protein which is a member of the G-protein

coupled receptor family and being one of four receptors identified for prostaglandin E2 (PGE2), a receptor which can activate T-cell signalling or the IL11 gene encoding a protein which is a member of the gp130 family of cytokines and it is shown to stimulate the T-cell-dependent development of immunoglobulin-producing B cells and it is also found to support the proliferation of haematopoietic stem cells and megakaryocyte progenitor cells.

Probe-sets not involved in immune or inflammatory response function mainly in signalling, transcription, regulation of proliferation or cell cycle.

The two approaches for the analysis of differentially regulated genes only had 2 genes in common for patients treated with IVIG: STAT1 and CDKN1 (Tab. 10). For patients treated with IVMP the two approaches shared 5 different genes in common: IRF8, CX3CR1, GZMB, ILT7 and PTGDS (Tab. 11).

<u>Table 8:</u> Number of differentially regulated probe sets after IVIG treatment obtained by the statistical approach; Data have a minimum of a 2-fold change in 100% of all patients (10 out of 10)

Differentially expresse	ed		· · · · · · · · · · · · · · · · · · ·
≥ 2-fold changes in 100% of patients	compariso day 6 to day	compariso day 21 to	compariso day 21 to day
increase	52	71	54
decrease	39	76	68
total	91	147	122
ltotal		360	

<u>Table 9:</u> Number of differentially regulated probe.sets after IVMP treatment obtained by the statistical approach; Data have a minimum of a 2-fold change in 100% of all patients (5 out of 5)

Differentially expressed	ed		·
≥ 2-fold changes in 100% of patients	compariso day 6 to day	compariso day 21 to	compariso day 21 to day
increase	83	78	117
decrease	135	85	85
	040	400	000
total	218	163	202
total		583	

<u>Table 10:</u> Comparison of the two methods for analyzing differentially expressed genes upon IVIG treatment; Method 1: Analysis of data using Data Mining Tool software;

Criteria: minimum of 2-fold change in at least 40% of patients;

Method 2: Analysis of data using parametric t-test;

Criteria: minimum of 2-fold change in 100% of patients;

Intersection: genes in common by these two approaches;

Intersection of differentially expressed genes upon IVIG treatment by DMT-analysis and parametric t-test:

	Probe-Set ID	Biological Process
STAT1	209969_s_a	regulation of cell cycle, regulation of transcription,
		DNA-dependent transcription from RNA polymerase II promotor caspase activation
		intracellularsignaling cascade
		STAT protein nuclear translocation
		response to pest, pathogen or parasite
CDKN1	213348 at	regulation of cyclin dependent protein kinase activity,
	-	G1 phase of mitotic cell cycle
		cell cycle
		cell cycle arrest
		negative regulation of cell proliferation,
		negative regulation of cell cycle

r

<u>Table 11:</u> Comparison of the two methods for analyzing differentially expressed genes upon IVMP treatment; Method 1: Analysis of data using Data Mining Tool software;

Criteria: minimum of 2-fold change in at least 60% of patients;

Method 2: Analysis of data using parametric t-test;

Criteria: minimum of 2-fold change in 100% of patients; Intersection: genes in common by these two approaches;

Intersection of differentially expressed genes upon IVMP treatment by DMT-analysis and parametric t-test:

	Probe-Set ID	Biological Process
IRF8	204057_at	negative regulation of transcription from RNA polymerase II promotor regulation of transcription DNA-dependent immune response
CX3CR1	205898_at	chemotaxis cellular defense response cell adhesion signal transduction G-protein coupled receptor protein singalling pathway
GZMB	210164_at	proteolysis and peptidolysis apoptosis cleavage of lamin cytolysis
ILT7	210313_at	immune response
PTGDS		prostaglandin biosynthesis fatty acid biosynthesis transport regulation of circadian sleep/wake cycle

### 3.4.4 Comparison between patients treated with IVIG and the control group

To analyse if the differentially expressed genes obtained by microarray analysis are due to IVIG treatment or the pathologic MS background of the patients, a group of five patients was included as a control. These patients also suffered from MS in acute relapse, but were not treated with IVIG but intravenous methylprednisolone, a glucocorticoid used as an anti-inflammatory drug. By comparison of both expression-data sets, an exclusion of genes differentially regulated upon IVMP treatment only was possible. By performing an intersection of both gene lists, common genes differentially regulated upon immunomodulatory/immunosuppressive treatment in general were filtered out. The intersection between the genes obtained from IVIG treated patients and the genes obtained from IVMP treated patients revealed a list of 2 probe-sets in common (Tab. 12): MARCKS, coding for a protein involved in cell motility and KLF4 encoding a protein involved in the negative regulation of cell proliferation. KLF4 was increased at day 6 compared to day 0 in 50% of all patients during IVIG treatment and decreased again at day 21 compared to day 6 in 60% of all patients during IVIG and IVMP treatment. It plays a role in cell cycle regulation and epithelial differentiation. It is also an essential mediator of p53 in controlling G1/S progression of the cell cycle following DNA damage, thus acting as a tumor suppressor gene necessary for preventing the entry into mitosis following DNA damage. This is consistent with a clonal expansion of specific cell clones (T cells and B cells) which is a result of immune stimulation. Up-regulation of KLF4 amplifies the negative regulation of proliferation leading to immune suppression.

<u>Table 12:</u> Intersection (common genes) between IVIG treatment and IVMP treatment according to Data Mining Criteria for IVIG treatment: a minimum of a 2-fold change in at least 60% of patients (6 out of 10); Criteria for IVMP treatment: a minimum of a 2-fold change in at least 60% of patients (3 out of 5);

Probe Set ID Gene Symb	ol Gene Title	Chromosomal Location
201669_s_at MARCKS	myristoylated alanine-rich protein kinase C substrate	6q22.2
221841_s_at KLF4	Kruppel-like factor 4 (gut)	9q31

The intersection between the two lists - genes differentially regulated upon IVIG and IVMP treatment - of the statistical approach using the t-test showed 18 genes in common (Table 13), most of them involved in intracellular signalling, replication and cell adhesion.

<u>Table 13:</u> Intersection (common genes) between IVIG treatment and IVMP treatment according to the parametric t-test Criteria for IVIG treatment: a minimum of 2-fold change in 100% of patients; Criteria for IVMP treatment: a minimum of 2-fold change in 100% of patients;

Probe Set ID Gene Symbo	I Gene Title	Chromosomal Location
202837 at FLN29	FLN29 gene product	12g
203862_s at ACTN2	actinin, alpha 2	1q42-q43
204677_at CDH5	cadherin 5, type 2, VE-cadherin (vascular epithelium)	16q22.1
205085_at ORC1L	origin recognition complex, subunit 1-like (yeast)	1p32
205151_s_at KIAA0644	KIAA0644 gene product	7p15.1
206175_x_at ZNF222	zinc finger protein 222	19q13.2
208546_x_at HIST1H2BH	histone 1, H2bh	6p21.3
209819_at HABP4	hyaluronan binding protein 4	9q22.3-q31
209969_s_at STAT1	signal transducer and activator of transcription 1, 91kDa	2q32.2
210415_s_at ODF2 213991_s_at HS3ST1 215409_at LOC254531	outer dense fiber of sperm tails 2 Heparan sulfate (glucosamine) 3-O-sulfotransferase 1 PLSC domain containing protein	9q34.11 4p16 15q14
215767_at C2orf10	chromosome 2 open reading frame 10	2q32.1
216814_at		
217082_at	Unknown protein	
219534_x_at CDKN1C	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	11p15.5
220425_x_at ROPN1B	ropporin, rhophilin associated protein 1B	3q21.2
222258_s_at SH3BP4	SH3-domain binding protein 4	2q37.1-q37.2

Subtraction of genes differentially regulated upon IVMP treatment from genes differentially expressed upon IVIG treatment revealed 11 IVIG-specific probe-sets or 9 different genes (Tab. 14). Examples are FCGR2A involved in immune response or ALOX5 involved in inflammatory response.

The Fc fragment of IgG, the low affinity receptor IIa (FCGR2A, CD32), was upregulated at day 6 compared to day 0 and became down-regulated again at day 21 compared to day 6. Receptors for the Fc portion of IgG play an essential role in the protection of the organism against foreign antigens by removing antigenantibody complexes from the circulation. Receptors are present on T and B lymphocytes, monocytes, macrophages, neutrophils and natural killer (NK) cells. The receptor may also act in an inhibitory way terminating activation signals via the ITIM-motives in the cytoplasmatic tail. An up-regulation of this Fc receptor after IVIG treatment, which consist of > 90% of IgG seems to be a normal consequence of the input of human antibodies into the circulation. As the IVIG-antibodies become cleared out of the body, the receptor becomes down-regulated again. By binding of IVIG antibodies to the receptor, inhibitory signal may act on the acute inflammatory response taking place in the CNS during the relapse, thus downregulating the acute immune response.

FOS is a member of the FOS gene family and can dimerize with members of the JUN family, thereby forming the transcription factor complex AP-1. FOS is a regulator of cell proliferation, differentiation, transformation and has also been associated with apoptotic cell death. FOS/JUN regulate themselves. Influences from outside increase their synthesis. For example c-FOS is induced at the beginning of cell proliferation. The activity of FOS/JUN can also be regulated by the transfer of phosphate-groups on amino-acids in either the transactivation-domain or the DNA-binding-domain. The transcription factor AP-1 is one of the three factors activated in T cells by antigen recognition via TCR-signaling. Activation of AP-1 leads to transcription of IL-2. IL-2 is responsible for the proliferation of antigen-specific T cells, promotes proliferation and differentiation of other immune cells and potentiates apoptotic death of antigen- activated T cells. FOS is down-regulated in 60% of all patients at day 21 compared to day 6.

Down-regulation of FOS leads to down-regulation of AP-1 followed by decreased induction of IL-2 resulting in decreased proliferation of immune cells. This finding is in line with the immunosuppresent effect of IVIG on immune cells.

Here IVIG seems to induce a long-term effect on the down-regulation of immune cells thus maybe preventing the further entry of autoreactive T cells into the CNS, which causes the relapses of the patients.

<u>Table 14:</u> Subtraction of IVMP-specific genes from IVIG-specific genes according to the DMT-approach; Criteria: minimum of a 2-fold change in at least 60% of patients: 6 out of 10 for the IVIG group; 3 out of 5 for the IVMP group;

Probe Set ID	Gene Symbol	Gene Title	Chromosomal Location
201422_at			
201798_s_at	FER1L3	fer-1-like 3, myoferlin (C. elegans)	10q24
203561_at	FCGR2A	Fc fragment of IgG, low affinity IIa, receptor (CD32)	1q23
204445_s_at	ALOX5	arachidonate 5-lipoxygenase	10q11.2
204446_s_at	ALOX5	arachidonate 5-lipoxygenase	10q11.2
208018_s_at	HCK	hemopoietic cell kinase	20q11-q12
208890_s_at	PLXNB2	plexin B2	22q13.33
209189_at	FOS	v-fos FBJ murine osteosarcoma viral oncogene homolog	14q24.3
210873_x_at	APOBEC3A	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A	22q13.1-q13.2
214366_s_at	ALOX5	arachidonate 5-lipoxygenase	10q11.2
214511_x_at			

Using the statistical approach, there were 253 probe-sets specific for IVIG treatment after subtraction of the probe-sets differentially regulated upon IVMP therapy (Tab. A6, see attachment) like for example the chemokine ligands CXCL3 and CXCL5.

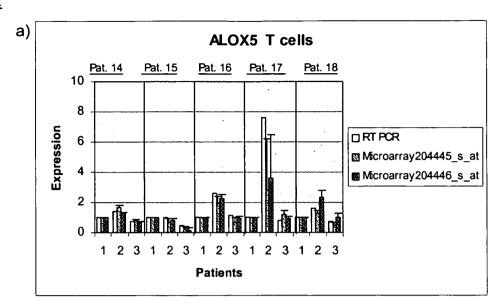
## 3.4.5 Confirmation of microarray data by Real-time PCR

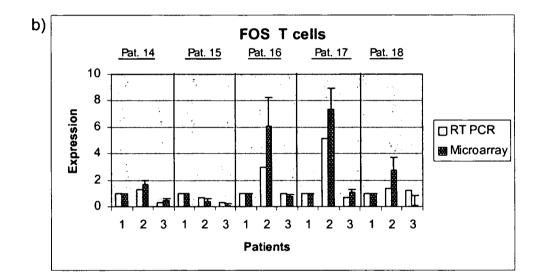
Microarray analysis was confirmed by quantitative Real-time PCR,

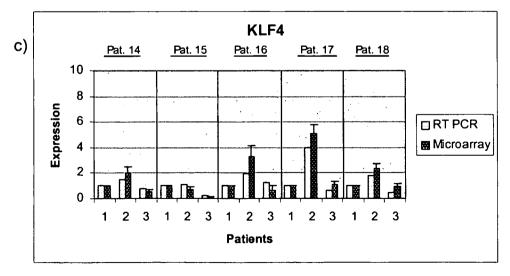
using primers for 8 genes as an example according to the criteria of either immune relevancy or common in a high percentage of samples (at least in a minimum of 50% of all patients): Fc fragment of IgG, low affinity IIa-receptor (FCGR2A), Fc fragment of IgG, high affinity Ia, receptor (FCGR1A), arachidonate 5-lipoxygenase (ALOX5), v-fos murine osteosarcoma viral oncogene homolog (FOS), neutrophil cytosolic factor 1 (NCF1), interferon, gamma-inducible protein 30 (IFI30) and Kruppel-like factor 4 (KLF4) for the analysis performed using the 2-fold filtering criteria (Fig. 4a-h).

Microarray results are given in fold-induction in comparison to Real Time PCR results that are given in relative expression normalized to an endogenous control according to the ^^CT-method. Therefore an exact comparison of both data sets is not possible, but the trend of an up- or down-regulation should be the same in both methods (13). Indeed, Real Time PCR results could confirm the microrarray data. Discrepancies were only seen for ALOX5/patient 17.2, FOS/patient 16.2 and 17.2, NCF1/patient 18.2, FCGR2A/ patient 18.2 and FCYR1/patient 16.3 and 17.2 . FCYR1 is annotated by two probe sets: 216950\_s\_at and 214511\_x\_at. The discrepancy can also be due to the x-annotation — which allows cross-hybridization with other genes – or the alternative splice site of the s-annotation. Most differences were seen at day 6 compared to day 0 after IVIG treatment. As analysis was performed with patient material, one has to consider that patients are a very heterogeneous group, all having a different immunological state and reacting in a different way to IVIG.

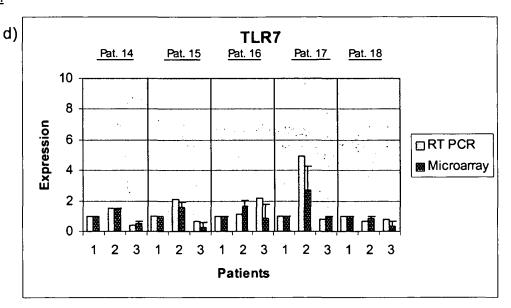
Figures 4a-c:

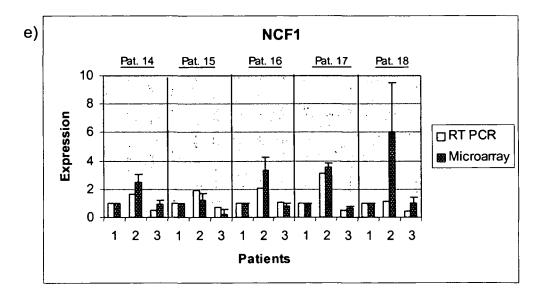


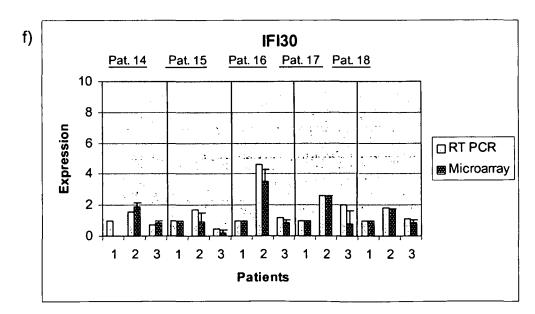




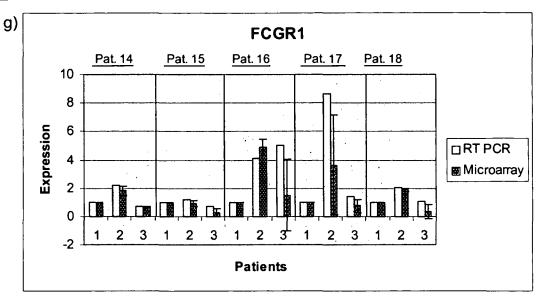
Figures 4d-f:

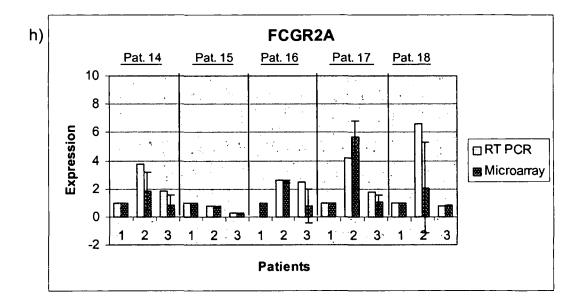






Figures 4g-h:





# Figures 4a-h:

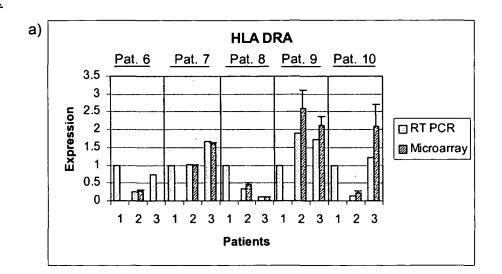
Verification of differential expression of genes affected by IVIG treatment of MSpatients in acute relapse by Real Time PCR. All primers used were pre-designed assays-on-demand. Presented data are given in fold-changes for microarray results and in relative expression normalized to the endogenous control (GPPH) for PCR results. Standard deviation is given for comparison of both data sets. Real Time experiments were taken in triplets and confirmed by a second round. For confirmation of expression of the genes in the group treated with IVMP, 7 genes were confirmed by Real Time PCR as an example using primers for the following genes according to the criteria of either immune relevancy or common in a high percentage of samples: GZMA, HLA-DRA, CX3CR1, ILR2, GNLY, NRGN and RBL2. The trend towards an increase or a decrease in the differential regulation of microarray and Real Time PCR could be confirmed (Figures 5a-g). Only with the gene RBL2 there were some noticeable differences between expression fold-changes. Patient 8.2 showed an increase in expression by 1.6-fold in Real Time PCR but by 2-fold on the microarray. The most amazing increases were seen for the IL1R2 gene at day 6 compared to day 0 after IVMP treatment. It was increased by >10-fold in Real Time PCR (patient 7.2) and by >20-fold on the microarray as well as by >25-fold in Real Time PCR (patient 8.2) and >30-fold on the microarray.

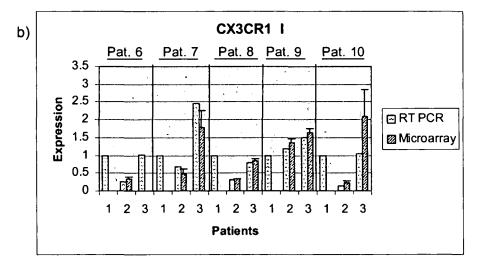
Another gene which was highly up-regulated in one patient (#9) was NRGN.

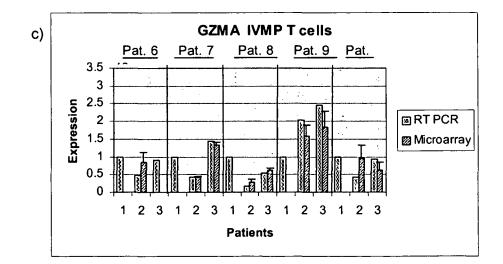
At day 6 compared to day 0 after IVMP treatment, it was up-regulated by ~ 10-fold and at day 21 compared to day 0 it was down-regulated again by 5-fold.

Unfortunately there was no micorarray signal for patient # 6 at day 21 after beginning of treatment (time point 6.3) for all genes selected for confirmation. This could be due to unsuccessful binding of target cRNA to the probes, or even bad quality of cRNA by itself. Therefore, it was impossible to compare results obtained by Real Time PCR at day 21 with the microarray results for patient 6.3.

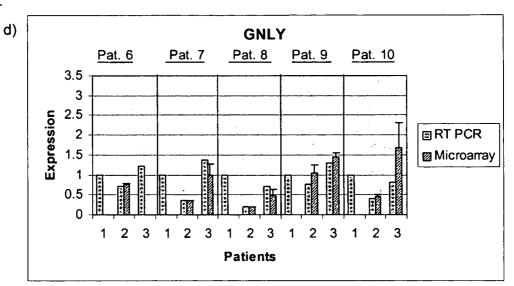
Figures 5a-c:

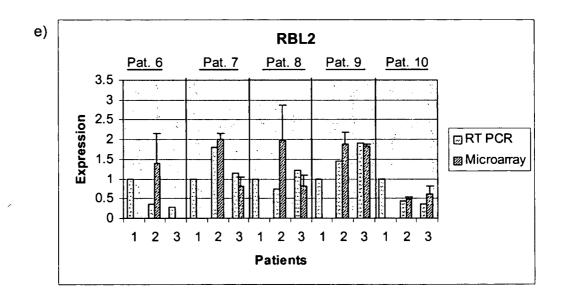




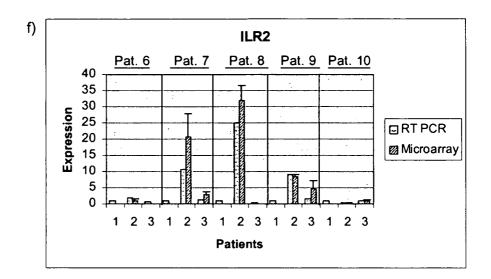


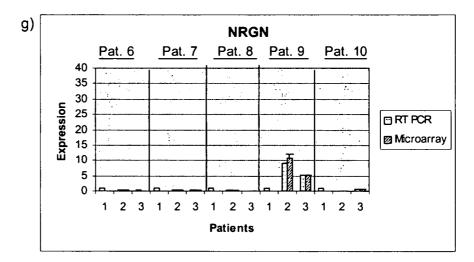
Figures 5d-e:





# Figures 5f-g:





### Figures 5a-g:

Verification of differential expression of genes affected by IVMP treatment of MS-patients in acute relapse by Real Time PCR. All primers used were pre-designed assays-on-demand. Presented data are given in fold-changes for microarray results and in relative expression normalized to the endogenous control (GPPH) for PCR results. Standard deviation is given for comparison of both data sets. Real Time experiments were taken in triplets and confirmed by a second round. Figures 3f and 3g use a different scale due to high increases;

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### 4.1 Discussion

Multiple sclerosis is the most common chronic inflammatory neurological disease. Despite major advances in aetiology of this disease, it is still not completely understood. Epidemiological studies and magnetic resonance imaging have provided important inside into the natural course and prognostic factors of MS, but the ability to predict different courses of the disease, and especially its response to treatment, is still very limited (1).

Peripheral blood mononuclear cells, in particular peripheral T cells, have been shown to be involved in the disease pathogenesis and induce active demyelination. Recently it was shown that a number of genes in peripheral blood mononuclear cells of patients were differentially expressed when compared to healthy subjects (2). These results support the involvement of peripheral cells in the pathogenesis of the disease.

The present study was designed to identify genes differentially expressed in T cells of patients with RRMS in acute exacerbation after treatment with IVIG. The clinical outcome of the study showed that IVIG given in a 5-day course at 0.4g/kg per day was effective and caused significant changes in EDSS score as well as changes in disease activity. Furthermore, the treatment was safe and well tolerated.

Using GCOS- and Data Mining Tool software for data analysis, I found 176 genes to be at least 2-fold up- or down-regulated in a minimum of 40% of all patients (4 out of 10). The majority of these genes was down-regulated (147) and the differential regulation occurred mostly at day 21 compared to day 6 after beginning of IVIG therapy. Most of the proteins encoded by these genes are involved in the regulation of immune- and inflammatory responses, signal transduction, transcription, apoptosis or cell proliferation. Prominent examples are genes coding for chemokines or chemokine ligands that are involved in the regulation of leukocyte migration, genes coding for proteins involved in synthesis and regulation of prostaglandins, genes coding for toll-like receptors, genes coding for Fc receptors or genes coding for cytokines.

All these biological activities are likely to be involved in the regulation of disease activity in patients with RRMS. To differentiate between genes regulated upon

IVIG treatment and genes differentially expressed due to the pathologic background of MS, we included a control group treated with an immunosupressive drug (IVMP) that represents the current standard of care. There were 784 genes differentially regulated in peripheral T cells upon IVMP treatment showing at least a 2-fold change in expression. The majority of these genes were down-regulated, most often at day 6 compared to day 0 after beginning of therapy. When I compared differentially expressed genes found in peripheral T cells under IVIG treatment with those found under IVMP treatment, I found a total of 133 genes to be regulated only in patients treated with IVIG. Therefore, I believe that I have identified a set of genes that might be associated with the biological activity of IVIG in patients with RRMS. Further evaluation of these genes in a larger group of patients will be necessary to confirm our data and to eventually define a set of differentially expressed genes that can be clearly associated with the clinical efficacy of IVIG in RRMS.

Statistical analysis using a parametric-t test gave a rather different result when compared to the analysis using GCOS- and Data Mining Tool software. A total of 360 genes were differentially expressed with a minimum of a 2-fold change in expression. Both methods had only 2 genes in common: STAT1 and CDKN1, both encoding proteins that are involved in intracellular signalling or cell cycle regulation. There might be two reasons for the observed differences. First, our approach using the Data Mining Tool Software was more restrictive, having the criteria of either 2-fold increase or decrease, a minimum of change in at least 40% of all patients, a requirement for present calls of 100% as well as a p-value cut off of 0.004 or 0.096.

The statistical approach had a minimum requirement for present calls in at least 50% of patients and used data of all 100% of patients. Second, it is a well-known problem in the literature, that comparing different methods for statistical analysis of microarray data can give rather conflicting results (3-5). The issue of high dimensionality in microarray data has been, and remains, a hot topic in statistical and computational analysis. Efficient gene filtering and differentiation approaches can reduce the dimension of data, help to remove redundant genes and noises, and highlight the most relevant genes that are major players in the development of certain diseases or the effect of drug treatment. A significant body of data on gene

expression patterns in autoimmune diseases such as MS has been generated by microarray analysis (1;3-18). Although the results are considered to be very promising, there are many factors that have detracted from the data. No common methodological directions are available. Collection techniques, processing methods, and statistical approaches are often very different (19).

Recently, Liang et al (3) investigated the efficiency of parametric, non-parametric and semi-parametric gene filtering methods through the application of time course microarray data from MS patients being treated with interferon-beta-1a. Their results show that the presented methods used for the analysis of data performed significantly differently from each other. Therefore, commonly approved standardguidelines for the statistical evaluation of gene expression data would be helpful for better reproducibility and comparability in the evaluation of microarray data.

Another problem with our clinical study was the small number of patients included (10 patients in the group treated with IVIG and 5 patients in the group treated with IVMP). Clearly, our data have to be confirmed in a larger study.

In conclusion, treatment of patients suffering from RRMS in acute exacerbations with IVIG showed beneficial effects, as shown by the significant reduction of EDSS scores and by the significant reduction in active brain lesions illustrated by MRI. IVIG had a significant down-regulatory effect on many genes involved in immune or inflammatory responses. Selection of the most important genes affected by IVIG could help in establishing a clinically relevant micorarray for testing the immunomodulatory effects of IVIG in RRMS.

# Gene expression data in MS

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1422 at	(F130	interferon, gemma-incucible protein 30	19p13.1	immune response
3561_#t	FCGR2A FOS	Fc fragment of IgG, low affinity Ita, receptor (CD32)	1q23	immune response DNA methylation, regulation of transcription from RNA polymerase II promoter, inflammatory respo
4511 x at	FCGR1	v-fos FBJ marine osteoseroome viral oncogene homolog Fc fragment of IgG, low effinity ta, receptor (CD64)	14q24.3 1q21.2-q21.3	phegocytosis. enguliment, immune response, signal transduction
366 s at 841 s at		arachidonate S-lipoxygenese Kruppel-like factor 4 (gut)	10q11.2 9q31	electron transport, inflammatory response. leukotriene biosynthesis transcription, meeoderm cell fate determination, negative regulation of cell proliferation
669 s at	MARCKS	myristoylated alanina-rich protain kinase C substrate	6q22.2	cell motility
798 s at 018 s at		fer-1-like 3, myoferlin (C. elegans)	10q24 20q11-q12	muscle contraction, circulation protain amino acid phosphorylation, intracetlular signaling cascade, mesoderm development
890 s_at	PLXNB2 APOBEC3A	plexin 52 epolipoprotein 8 mRNA edding enzyme, catelytic polypeptide-black	22q13.33 22q13.1-q13.2	development
743 at	CD14	CD14 antigen	5q22-q32 5q31.1 10q11.2	phegocytosis: apoptosis; inflammatory response; cell surface receptor linked signal transduction electron transport; inflammatory response; leukotriana biosynthesis
533 at	CXCL10	chemokine (C-X-C motif) ligand 10	4a21	cell motility: chemotaxis; inflammatory response; cell surface receptor linked signal transduction
	<u> </u>		<b>├</b> ────────	cell-cell signaling: muscle development sensory perception; circulation
950 s_st		Fc fragment of IgG, high affinity ta, receptor (CD84)	1q21 2-q21.3	phagocytosis, engulfment; immune response
619 s_at		tofi-like receptor 7	20p13 Xp22.3	inflammatory response, cel-matrix adhesion, cell-cell adhesion
858 s_at	ECGF1	endothelial cell growth factor 1 (platelet-derived)	22q13.33	mitochondrial genome maintenance; angiogenesis; pyrimidine base metabolism; chamotaxis
	<u> </u>		<u></u>	pyrimidine nucleotide metabolism: DNA replication: cell surface receptor linked signal transduction cell-cell signaling; sensory perception: metabolism; cell differentiation
961_s at	NCF1	neutrophil cytosolic factor 1 (47kDa, chronic granulomatous disease, autosomal 1)	7q11 23	electron transport; superoxide metabolism; cellular defense response; intracellular signaling cascad
763_8_at		member RAS oncogene family	18p11.3	small GTPase mediated signal transduction
088_at	C5R1	complement component 5 receptor 1 (C5a ligand)	19q13.3-q13 4	activation of MAPK:chamotaxis; G-protein coupled receptor protein signaling pathway phospholipase C activation; positive regulation of cytosolic calcium ion concentration
				sensory perception of chemical stimulus
439 at		v-maf musculoaponeurotic fibrosarcoma oncogene homolog B_ interferon-induced protein 44-like	20q11.2-q13.1 1p31 1	transcription: regulation of transcription. DNA-dependent: sensory organ development
1084 x #1			-	m
360_at 670_s_at	CST3 MARCKS	cystatin C myristoyfated alanine-rich protein kinese C substrate	20p11.21 6q22.2	cell motifity
510 s at	TNFAIP2	tumor necrosis factor, alpha-induced protein 2	14q32	angiogenesis: cell differentiation
	SERPINA1	serine (or cysteine) proteinase inhubitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	14q32.1	acute-phase response
833 s_st	SERPINAL	serine (or cysteine) proteinase inhibitor, clade A	14q32.1	acute-phase response
936 s at		(alpha-1 antiproteinase, antitrypsin), member 1 hexokinese 3 (white cell)	5q35.2	glycolysis
488 s_el		CD38 antigen (collagen typel receptor thrombospondin receptor) (heterogeneous nuclear ribonucleopratein H1 (H)	7q11 2 5q35 3	lipid metabolism: fatty acid metabolism: transport; cell adhesion: blood coegulation
9788_at		paired immunoglobin-like type 2 receptor alpha	7q22.1	transmembrane receptor protein tyrosune kinase, activation (dimerization)
088 **	SERDING	serine (or cysteine) proteinase inhibitor	11012-013.1	immune response, complement activation, classical pathway, blood coegulation, circulation
		clade G (C1 inhibitor), member 1, (angioedema, hereditary)		
2269 x at 3066 at		guanylate binding protein 1, interferon-inducible, 67kDa B cell RAG associated protein	1p22 2 10q26	immune response regulation of DNA recombination, regulation of B-cell differentiation
3535 at	S100A9 1	S100 calcium binding protein A9 (caloranulin B)	1921	inflammatory response, cell-cell signaling
1415 at 1446 s at	G1P3	interferon, alpha-inducible protein (clone IFI-6-18) erechidonate 5-lipoxygenase	1p36 10g11.2	immune response, response to pest, pethogen or perasite electron transport, inflammatory response, leukotriane biosynthesis
747 at	IFIT3 1	interferon-induced protein with tetratricopeptide repeats 3	10g24	immune response
5483 s at 146 s at	G1P2 1 PPBP	interferon, alpha-inducible protein (clone IFI-15K) pro-platelet basic protein (chemokine (C-X-C motif) ligand 7)	1p36 33 4q12-q13	protein modification, immune response, cell-cell signaling regulation of cell cycle, chemotaxis, immune response, sensory perception
				cell proliferation, glucose transport, defense response to becteria
3066_at 3153_at	GALNAC45-6ST	B cell RAG associated protein	10q28	regulation of DNA recombination, havose biosynthesis, regulation of B-cell differentiation
3535_st	S100A9	interferon-induced protein with tetratricopeptide repeats 1	10q25-q26	immune response
3922_s_at		S100 calcium binding protein A9 (calgranutin B) cytochrome b-245, beta polypeptide (chronic granutomatous deeses)	1q21 Xp21.1	inflammatory response, cell-cell signeling electron transport, ion transport, inflammatory response, antimicrobial humoral response
3923 s at	CYBB	cytochrome b-245, beta polypeptide (chronic granutomatious disease)	Xp21.1	(aersu Vertebrata) electron transport, ion transport, inflammatory response, antimicrobial humoral response
				(sensu Vertebreta)
4232 at 7104 x at	IFCER1G	Fc fragment of igE, high attenty I, receptor for, gamma polypeptide feukocyte immunoglobulin-like receptor, subfamily B	1923	Immune response, cell surface receptor linked signal transduction
		(with TM and ITIM domains), member 1	19q13.4	immune response, response to virus
4924 at 5715 at	TLR2 BST1	toll-like receptor 2 bone marrow stromal cell antigen 1	4q32	induction of apoptosis, inflammatory response, signal transduction
5789 at	CD10	CD1D antigen, d polypeptide	4p15	humoral immune response, development detection of becteria, T-cell selection, positive regulation of innete immune response,
5863_et	S100A12	S100 celcium binding protein A12 (calgranulin C)	1q22-q23 1q21	antigen presentation, endogenous peptide antigen, antigen presentation, endogenous lipid antigen
6360_s_st	PEC	properdin P factor, complement		xenobiotic metabolism, inflammatory response, defense response to becteria,
6710 s st	EPB41L3	erythrocyte membrane protein band 4.1-like 3	Xp11.3-p11.23	immune response, complement activation, alternative pathway, defense response to bectaria
9906_a1	C3AR1	complement component 3a receptor 1	12p13.31	cell motility, chemotaxis, amonth muscle contraction, inflammatory response, cellular defense response, signal transduction, G-protein coupled receptor protein signaling pathws
				neuropeptide signaling pathway, positive regulation of cytosolic calcium ion concentration.
7857 at	LILRA2	leukocyte immunogłobulin-like receptor, subfamily A	19013.4	sensory perception, circulation
		(with TM domain), member 2		
3594 x at		leukocyte immunoglobulin-like receptor, subfamity B	19q13.4	
	TNFSF13	tumor necrosis factor (ligand) superfamily, member 13	17p13.1	immune response, signal transduction, positive regulation of cell proliferation
655_s_at 629_x_at	LST1	CD36 antigen (cotagen type I receptor, thrombospondin receptor)	7q11.2 6p21.3	upid metabolism, fatty ecid metabolism, transport, cell adhesion, blood coegulation
		leukocyte immunoglobulun-like receptor, subfamily A	19913.4	negative regulation of lymphocyte proliferation
	<u> </u>	(with TM domain), member 1		
0895_s_at	CD86	CD86 entigen (CD28 antigen ligend 2, B7-2 entigen)	3q21	immune response, cell-cell agneting, positive regulation of cell proliferation, T-cell activation, positi regulation of tumor necrosis factor-beta biosynthesis, positive regulation of interleukin-2 biosynthe
	1		I	positive regulation of interleukin-4 biosynthesis, positive regulation of T-helper 2 cell differentiation
982 a st	HLA-DRA	major histocompatibility complex, class II, DR alpha	6p21.3	positive regulation of transcription immune response, immune response, antigen presentation, exogenous antigen,
				antigen processing, exogenous antigen via MHC class II
1336 x_at 1582 x_at	LST1	leukocyte immunoglobulin-like receptor, subfamily B	19q13.4 6p21.3	immune response, response to virus cellular morphogenesis, immune response, immune response, dendrite morphogenesis,
3716 s at		secreted and transmembrane 1	17q25	negative regulation of tymphocyte proliferation immune response, mesoderm development, positive regulation of HuppeB kineseNF-tuppeB casced
6710_8_at 1038_at		chemokine (C-C motif) ligend 8	1/g25 17g11.2	calcium ion transport, exocytosis, chemotaxis, inflammatory response, signal transduction,
5833 ×_at	ISTI	laukocyte specific transcript 1	6p21.3	cell cycle errest. cellular morphogenesis, immune response, immune response, dendrite morphogenesis,
_				negative regulation of lymphocyte proliferation
1696 s at	CLEC7A	C-type lectin domain family 7, member A	12p13.2-p12.3	phegocytosia, recognition, cell recognition, carbohydrate mediated algnaling, antibacterial humoral response (sensu Vertebrata), antifungal humoral response (sensu Vertebrata
	t			T-cell activation, defense response to pathogenic protozoa, reduction of virulence
1060 s_at	TLR4	toll-like receptor 4	9q32-q33	inflammatory response, signal transduction, activation of NF-kappaB-inducing kinese, detection of pethogenic becteria, detection of fungi. T-helper 1 type immune response, macrophage activation,
	-		1	positive regulation of interleukin-12 biosynthesis, positive regulation of interleukin-1 biosynthesis,
				positive regulation of interleukin-13 biosynthesis, positive regulation of interleukin-8 biosynthesis mast cell activation, negative regulation of osteoclast differentiation
		tryptophany4-tRNA synthetase	14932 31	_ protein biosynthesis, tryptophenyl-tRNA aminoacylation, negative regulation of cell proliferation
	WARS 1	dual specificity phosphatase 6	12022-023	regulation of cell cycle, Inactivation of MAPK, protein amino acid dephosphorylation
3891 at	DUSP6			
5891_et	DUSP6 TGFBI	transforming growth factor, bata-induced, 68kDa	5q31	cell adhesion, negative regulation of cell adhesion, sensory perception, visual perception,
3891_at 1506_at	DUSP6		5q31	cell proliferation transcription, regulation of transcription, DNA-dependent, protein amino acid phosphorylation,
0829 st 8891 st 1508 st 0148 st 3524 s st 0678 x st	DUSP6 TGF8i HIPK3 G0S2	transforming growth factor, bata-induced, 68kDa		cell proliferation

Tab. A1:

		· · · · · · · · · · · · · · · · · · ·		
207540 s at	SYK	spleen tyrosine kinsse	9q22	protein complex assembly, protein amino acid phosphorylation, leukocyte cell adhesion,
		·····		integrin-mediated, signaling pathway, intracellular signaling cascade, call proideration,
				cell proliferation, organogenesis, neutrophil chemotaxis
213182 x #	CDKN1C	arythrocyte membrane protein band 4.1-like 3	18p11.32	conticel actin cytoskeleton organization and biogenesis
		cyclin-dependent kinese inhibitor 1C (p57, Kip2)	11p15.5	regulation of cyclin dependent protein kinese activity, G1 phase of mitotic cell cycle, cell cycle, cell cycle arrest, negative regulation of cell proliferation, negative regulation of cell cycle
216894 x at	COKNIC	cyclin-dependent kinase inhibitor 1C (p67, Kip2)	11p15.5	regulation of cyclin dependent protein kinese activity, G1 phase of mitotic cell cycle, cell cycle,
				cell cycle arrest, negative regulation of cell proliferation, negative regulation of cell cycle
219534 x at	CDKN1C	cyclun-dependent kinese inhibitor 1C (p57, Kip2)	11p15.5	regulation of cyclin dependent protein kinese activity, G1 phase of mitotic cell cycle, cell cycle,
			20-44-42	cell cycle arrest, negative regulation of cell proliferation, negative regulation of cell cycle
208018 s at 202626 s at		hemopoietic cell kinase v-yes-1 Yamaguchi sercoma virel related oncogene homolog	20q11-q12 8q13	protein amino acid phosphorylation, intracellutar signaling cascade, mesoderm development protein amino acid phosphorylation, intraceltutar signaling cascade
204858 s at	ECGF1 A	endothelial cell growth factor 1 (platelet-derived)	22q13/22q13.33	mitochondrial genome maintenance, angiogenesis, pyrimidine bese metabolism
			1	pyrimidine nucleotide metabolism, DNA replication, chemotaxis, cell surface receptor linked
				signal transduction, cell-cell signaling, sensory perception, metabolism, cell differentiation
220088 at	C5R1 1	complement component 5 receptor 1 (C5a ligand)	19q13.3-q13.4	activation of MAPK, chemotaxis, cellular defense response, signal transduction,
				G-protein coupled receptor protein signaling pathway, phospholipese C activation, positive regulation of cytosolic calcium ion concentration, sensory perception of chemical sumulus -
09969 s at	STAT1 1	signal transducer and activator of transcription 1, 91kDa	2q32.2	regulation of cell cycle, transcription, regulation of transcription, DNA-dependent
	_			transcription from RNA polymerase II promoter, caspase activation,
				intracellular signaling cascade, I-kappeB kinase/NF-kappeB cascade, tyrosine phosphorylation
02388 at	RGS2	regulator of G-protein signalling 2, 24kDa	1q31	of STAT protein, STAT protein nuclear translocation, response to pest, pathogen or parasite oall cycle, signal transduction, regulation of G-protein coupled receptor protein signaling pathway
02626 s at		v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	8q13	protein amino acid phosphorylation, intracellular signaling cascade
03104_at		colony stimulating factor 1 receptor, formerly McDonough	5q33-q35	protein amino acid phosphorylation, signal transduction, transmembrane receptor protein tyrosine
		feline sarcoma viral (v-fms) oncogane homolog		kinase signaling pathway, development, cell proliferation, antimicrobial humoral response
	TYROBP	TYRO protein tyrosine kinase binding protein	19q13.1	cellular defense response, intracellular signaling cascade
09684_at 10222_s_st	RIN2 RTN1	Res and Reb interactor 2	14q23.1	endocytosis, intracellular signaling cascade, small GTPase mediated signal transduction signal transduction, neuron cell differentiation
10754 s at		v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	8q13	protein amino acid phosphorylation, intracellular signaling cascade
11284 s at	GRN	grandin	17q21.32	signal transduction, cell-cell signaling, cell proliferation, positive regulation of cell proliferation
15041 x at		granulin	17q21.32	signal transduction, cell-cell signaling, cell proliferation, positive regulation of cell proliferation
19607 s at		membrane-spanning 4-domains, subfamily A, member 4	11q12	signal transduction
216899 s at 21581 s at		erc family associated phosphoprotein 2 Williama-Beuren syndrome chromosome region 5	7p21-p15 7q11 23	protein complex assembly, signel transduction intracellular signaling cascade, celcium-mediated signaling, B-cell activation
17764 s at		RAB31, member RAS oncogene family	18p11.3	small GTPsse mediated signal transduction
17853_at	TENS1	tensin-like SH2 domain containing 1	7p13-p12.3	protein amino acid dephosphorylation, cell cycle, intracellular signaling cascade
18559 s at		v-mail musculosponeurotic fibrosarcoma oncogene homolog B	20q11.2-q13.1	transcription, regulation of transcription, DNA-dependent, sensory organ development
204959 at		myeloid cell nuclear differentiation antigen	1922	transcription, regulation of transcription, DNA-dependent, cellular defense response
04039_at	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	19q13.1	generation of precursor metabolites and energy, transcription, regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter
04959_at	MNDA	myeloid cell nuclear differentiation antigen	1g22	transcription, regulation of transcription, DNA-dependent, callular defense response
	SPI1	epieen focus forming virus (SFFV) provinsi enlegration oncogene epi1	11p11.2	negative regulation of transcription from RNA polymerase II promoter, transcription,
	HHEX	hematopoletically expressed homeobox	10q23.33	regulation of transcription, DNA-dependent, development, antimicrobial humoral response
15433 8 81				
	021		71-22.2	(sensu Vertebrata)
221211_s_st		chromosome 21 open reeding frame 7	21q22.3	regulation of transcription, DNA-dependent
221211 s at 205936 s at	нкз	hexokinase 3 (white cell)	5q35.2	regulation of transcription, DNA-dependent glycolysis
221211_s_et 205936_s_et 208130_s_et	HK3 TBXAS1	hexokinase 3 (white cell) thromboxane A synthese 1 (platelet, cytochrome P450, family 5, subfamily A)	5q35.2 7q34-q35	regulation of transcription, DNA-dependent
221211_s_st 205936_s_st 208130_s_st 213566_st	HK3 TBXAS1 RNASE6	hexokinase 3 (white cell) (Inromboxane A syrihase 1 (platelet, cytochrome P450, family 5, subfamily A) ribonuclease, RNase A family, k6	5q35.2 7q34-q35 14q11.2	regulation of transcription, DNA-dependent glycolysis
221211_s_at 205936_s_at 208130_s_at 213566_at 219093_at	HK3 TBXAS1 RNASE8 FLJ20701	flexokinase 3 (white cell) (i/combourne A synthase 1 (platalet, cytochrome P450, family 5, sublamily A) riboruclease, RNase A family, k6 mpotimiscal protein FLJ20701	5g35.2 7g34-g35 14g11.2 2g38.3	reguletion of transcription, DNA-dependent glycolysis prostagtandin biosynthesis, efectron transport, fatty acid biosynthesis, transport, alcod coegulation RNA catabolism, defense response 
221211_s_at 205936_s_at 208130_s_at 213566_at 219093_at	HK3 TBXAS1 RNASE8 FLJ20701	hexokinase 3 (white cell) (Inromboxane A syrihase 1 (platelet, cytochrome P450, family 5, subfamily A) ribonuclease, RNase A family, k6	5q35.2 7q34-q35 14q11.2	regulation of transcription, DNA-dependent glycolysis prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, aloos coegulation
221211 s et 205936 s et 208130 s et 213566 et 219093 et 204619 s et 204619 s et	HK3 TBXAS1 RNASE6 FLJ20701 CSPG2	fixexbinase 3 (while cell)     firomboxane A synthese 1     (glatelet, cytochrome P450, family 5, sublamily A)     riboruclesse, RNase A family, k6     mpothatical protein FL20701     (chordrotin suffate proteoglycan 2 (versicen)     ficolin (collegen/fibrinogen domain containing) 1	5q35.2 7q34-q35 14q11.2 2q36.3 5q14.3 9q34	reguletion of transcription, DNA-dependent glycolysis prostagtandin biosynthesis, electron transport, fatty acid biosynthesis, transport, blood coegulation RNA catabolism, defense response 
221211 s st 205936 s at 208130 s st 213566 at 219093 at 204619 s st 205237 at 201798 s at	HK3 TBXAS1 RNASE6 FLJ20701 CSPG2 FCN1 FER1L3	hexokinase 3 (white cell) (i/ateries, cytochrome P450, family 5, subfamily A) (i/ateries, cytochrome P450, family 6, irbonuclesse, RNase A family, 85 irbonuclesse, RNAse A	5q35 2 7q34-q35 2q36 3 5q14 3 9q34 10q24	regutation of transcription, DNA-dependent glycolysis prostagiancin biosynthesis, electron transport, fatty acid biosynthesis, transport, alood coegutation RNA catabolism, defense response ~ development, call recognition
221211 s at 205936 s at 208130 s at 213666 at 219093 at 204619 s at 205237 at 201798 s at 201798 s at 201798 s at	HK3 TBXAS1 RNASE6 FLJ20701 CSPG2 FCN1 FER1L3 FER1L3	Invokinses 3 (white cell) If combourse A synthese 1 (platelet, cytochrome P450, family 5, subfamily A) Indonuclease. RNase A family, k6 Importinistical protein FLJ20701 chondroitin suffate proteoglycan 2 (versican) If colin (collegen/fibrinogen domain containing) 1 [ifer-1ite 3, myöferlin (C, elegans) IARP essociate factor-1	5q35.2 7q34-q35 14q11.2 2q36.3 5q14.3 9q34 10q24 17p13.1	regutation of transcription, DNA-dependent dycotyse prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, atoos coegutation RNA catabolism, defense response 
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21211 s et 25236 s et 15660 s et 13566 et 13566 et 13660 et	HK3 TBXA51 TBXA51 FL20701 CSPG2 FL20701 CSPG2 FER1L3 FER1L	Inexotinase 3 (white cell) (increated a synthase 1 (platietic, cytochrome P450, family, 5, subfamily, A) informations, Rhase A family, 58 Propublicated protein FL120701 chordrotion suffate proteogycan 2 (versican) [isolin (collegen/fibrinogen domain containing) 1 [isolin (collegen/fibrinogen domain containing) 1 [isolinocated factor-1 [isolinocated promoter region (to activated MET oncogene) 	5q35.2 7q34-q35 14411.2 2q36.3 5q14.3 9q34 10q24 17p13.1 12q24.2 11q25 4 6q23 20p13 2q35 22q13.1-q13.2 	regutation of transcription, DNA-dependent glycolysis prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, accor coegutation RNA catabolism, defense response 
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221211 5 et           221211 5 et           005936 s et           005936 s et           13566 at           10303 at           13567 at           005237 at           005237 at           005237 at           00133 at           00133 at           00125 at           0125 at           01253 at           01253 at           01267 at           10287 at           10433 at           01285 at           02457 at           02457 at           02458 at           04459 at           04254 at           04257 at           04267 at      <	HK3 TBXA51 TBXA51 FL20701 CSPG2 FCN1 4 FER113 4 HSXAPA51 T HSXAPA51 T HSXAPA51 T HSXAPA51 T SGK PTPNS1 SLC11A1 4 APOBECSA 7 	Inexotinase 3 (white cell) (inormboare A synthase 1 (fatelist, cytochrome P450, famity 5, subfamity A) (fatelist, cytochrome P450, famity 5, subfamity A) (footnicolin suffate protein FLJ20701 chordrootin suffate proteoglycan 2 (versicen) (fcolin (collegen/fibringen domain containing) 1 (fer-1-like 3, myoffarin (C, elegans) XIAP associated factor-1 aldenyce dehydrogeness 2 famity (mitochondriai) Versitocated factor-1 aldenyce dehydrogeness 2 famity (mitochondriai) Versitocated promoter region (to activated MET oncogene) 	5q35.2 7q34-q35 14411.2 2q36.3 5q14.3 9q34 10q24 17p13.1 12q24.2 11q25 	regutation of transcription, DNA-dependent glycolysis prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, alood coegutation RNA catabolism, defense response 
21211 5 et 205236 a et 205236 a et 205236 a et 205237 at 205237 at 205237 at 201258 at 201218 at 201218 at 201218 at 201238 at 201238 at 201239 at 20287 at 2	HK3 TBXAS1 TBXAS1 FLJ20701 CSPG2 FCN1 ↑ FEN13 ↑ HSXAPAF1 ↑ ALDH2 TPR SGK PTPNS1 SLC11A1 ↑ FCN1 ↑ FIL44L SLC7A7 CSPG2 CSPG2 CSPG2 CSPG2 FGL2 LMG2 CSFA CSFA CSFA CSFA CSFA CSFA CSFA CSFA	Invoktinase 3 (white cell) (invomboaren 4 synthase 1 (plantek, cytochrome P450, famity 5, subfamity A) (plantek, cytochrome P450, famity 5, subfamity A) (plantek, cytochrome P450, famity 5, subfamity A) (plantek, cytochrome P450, famity 6, subfamity A) (plantek, cytochrome P450, famity 6, subfamity A) (plantek, cytochrome P450, famity 6, subfamity 7, (plantek, cytochrome P450, famity 7, subfamity 7, cytochrome 1, solute carrier famity 11 (proten-induced protein 44-tike solute carrier famity 1, 1 (proten-cytochrome famity 7, cettoric attransporter, yr system), member 7 chondroitin suffate proteoglycen 2 (versicen) chondroitin suffate proteoglycen 1 (versicen) chondroitin suffate proteoglycen 2 (versicen)	5q35.2         7q34-q35         14q11.2         2q36.3         5q14.3         9q34         10q24         17p13.1         12q24.2         1q24.2         1q25	regulation of transcription, DNA-dependent divelopment, cell recognition prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, allocd coegulation RNA catabolism, defense response 
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221211         5         st           205236         5         st           205236         5         st           205237         st         st           135566         at         st           10363         at         st           10373         at         st           10125         at         st           10287         at         st           10483         at         st           204439         at         st           204267         at         st           20427         at         st           205278         at         st           205453         at         st           205453         at         st           205453         at         st </td <td>HK3 TBXA51 TBXA51 FL20701 CSPG2 FCN1 4 FER113 1 HSXAPA51 TPR TPR FKN1 SLC11A1 4 APOBECSA 1 SLC1A1 4 APOBECSA 1 SLC7A7 CSPG2 CSPG2 CSPG2 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 FCA1 SLC</td> <td>Invoktinase 3 (white cell) (invomboare A synthase 1 (fatelist, cytochrome P450, family 5, subfamily A) (fatelist, cytochrome P450, family 5, subfamily A) (forunciess, RNase A family, 5, intonucless, RNase A family, 5, intonucless, RNase A family, 5, (foolin (collegen/fibringen domain containing) 1 (foolin collegen/fibringen domain containing) 1 (foolin collegen/fibringe</td> <td>5q35.2 7q34-q35 14 2q36.3 5q14.3 5q14.3 5q34 10q24 17p13.1 12q24 2 11q25 </td> <td>regulation of transcription, DNA-dependent divelopment, cell recognition resultation biosynthesis, electron transport, fatty acid biosynthesis, transport, acod coegulation RNA catabolism, defense response </td>	HK3 TBXA51 TBXA51 FL20701 CSPG2 FCN1 4 FER113 1 HSXAPA51 TPR TPR FKN1 SLC11A1 4 APOBECSA 1 SLC1A1 4 APOBECSA 1 SLC7A7 CSPG2 CSPG2 CSPG2 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 FCA1 SLC7A7 CSPG2 FCA1 SLC7A7 FCA1 SLC	Invoktinase 3 (white cell) (invomboare A synthase 1 (fatelist, cytochrome P450, family 5, subfamily A) (fatelist, cytochrome P450, family 5, subfamily A) (forunciess, RNase A family, 5, intonucless, RNase A family, 5, intonucless, RNase A family, 5, (foolin (collegen/fibringen domain containing) 1 (foolin collegen/fibringen domain containing) 1 (foolin collegen/fibringe	5q35.2 7q34-q35 14 2q36.3 5q14.3 5q14.3 5q34 10q24 17p13.1 12q24 2 11q25 	regulation of transcription, DNA-dependent divelopment, cell recognition resultation biosynthesis, electron transport, fatty acid biosynthesis, transport, acod coegulation RNA catabolism, defense response 
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21211 5 et           21211 5 et           05530 5 et           05530 5 et           13566 at           108130 5 et           13567 at           05031 7 at           05130 7 at           05130 3 et           05137 at           05138 at           05125 at           0125 at           0125 at           0125 at           0125 at           0125 at           0125 at           04523 at           04523 at           04524 at           04525 at           05627 at           05627 at           05627 at           05623 at           05623 at           0563	HK3 TBXAS1 TBXAS1 TBXAS1 FL20701 CSPG2 FCN1 4 FER113 4 HSXAPA71 7 ALDH2 TPR SLC11A1 4 ADH2 TPR SLC11A1 4 APO8ECSA 7 FCM1 SLC7A7 CSPG2 CSPG	Invoktinase 3 (white cell) (invomboare A synthase 1 (fatelist, cytochrome P450, family 5, subfamily A) (fatelist, cytochrome P450, family 5, subfamily A) (footnicess, RNase A family 5, subfamily A) (footnicess, RNase A family 6, (footnicess, RNase A family 6, subfamily 1) (footnicess, RNase A family (mitochondrial) Variatocated factor-1 aldenyde dehydrogeness 2 family (mitochondrial) Variatocated promoter region (to activated MET oncogene) 	5q35.2           5q35.2           7q34-q35           1           2q36.3           5q14.3           5q34           10q24           17p13.1           12q24.2           1q25	regutation of transcription, DNA-dependent divelopment, cell recognition, DNA-dependent Prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, alloca coegviston RNA catabolism, defense response 
21211 5 et           21211 5 et           05526 a et           05526 a et           05526 a et           13566 et           13566 et           13063 et           13567 et           04619 s et           05237 et           05133 et           01238 et           01218 et           01228 et           01238 et           02459 et           04620 et           04620 et           04634 et           05076 a at           1527 et           05638 et           05638 et           1571 et           15226 et           12162 et           12225 et           12238 et           17388 et at           17388 et at	HK3 TBXA51 TBXA51 FL20701 CSPG2 FFL20701 FFER1L3 FFER1	Investing as a synthese 1 (platets, cytochrome P450, family, 5, subfamily, A) (platets, cytochrome P450, family, 5, subfamily, A) Indonuclesse, Rhase A family, 86 Importinetical protein FL120701 chordrotin suffate proteogycan 2 (versican) (isolin (collagen/fibrinogen domain containing) 1 (isolin collagen/fibrinogen domain containing) 1 (isolin collagen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen domain containing) 1 (isolin collagen/fibrinogen domain containing) 1 (forthordin suffate proteoglycen 2 (versicen) chordrotin suffate proteoglycen 2 (versicen) fibrinogen-fibrinogen/fibrinogen domain containing) 1 (forthordin suffate proteoglycen 2 (versicen) fibrinogen-fibrinogen formal transporter, ye system), member 7 condicion suffate proteoglycen 2 (versicen) fibrinogen-fibrinogen domain containing) 1 (folin collagen/fibrinogen domain containing) 1 (folinogen-fibrinogen domain containing) 1 (folinogen/fibrinogen domain containing) 1 (folinofibrinogen domain containing) 1 (forthorin suffate proteoglycen 2 (versicen) (folinogen/fibrinogen domain containing) 1 polasibut of fibrinogen domain containing 1 polasibut of fibrinogen do	5q35.2 7q34-q35 14q11.2 2q36.3 5q14.3 5q14.3 9q34 10q24 17p13.1 12q24 2 1q25 	regutation of transcription, DNA-dependent divelopment, cell recognition, DNA-dependent Prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, alloca coegutation RNA catabolism, defense response 
21211 5 et           221211 5 et           005936 s et           005936 s et           005936 s et           13566 et           113566 et           00633 s et           113566 et           00633 s et           10363 et           00633 et           00633 et           00633 et           00739 s et           01218 et           01739 et           01228 et           01238 et           01439 et           01450 et           01420 et <td>HK3 TBXAS1 TBXAS1 FL20701 CSPG2 FCN1 4 FER113 4 HSXAPA71 7 ALDH2 TPR SLC11A1 4 APO8ECSA 7 FCN1 5 FCN1 4 HSXAPA71 7 HSXAPA71 7 SLC11A1 4 APO8ECSA 7 FCN2 SLC7A7 CSPG2 CSP</td> <td>Investinase 3 (white cell) (inventosane A synthase 1 (platietic, cytochrome P450, famity 5, subfamity A) (platietic, cytochrome P450, famity 5, subfamity A) Intoruciaese, Rhase A famity, 16 Thypothetical protein FLJ20701 (chordroin suffate proteinglycan 2 (versicen) (incellingen/fibrinogen domain containing) 1 (incellingen/fibrinogen domain containing) 1 (incellingen/fibrinogen</td> <td>5q35.2         7q34-q35         14q11.2         2q36.3         5q14.3         9q34         10q24         17p13.1         12q24.2         1q24.2         1q25        </td> <td>regulation of transcription, DNA-dependent glycolysis prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, according prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, according RNA databolism, defense response </td>	HK3 TBXAS1 TBXAS1 FL20701 CSPG2 FCN1 4 FER113 4 HSXAPA71 7 ALDH2 TPR SLC11A1 4 APO8ECSA 7 FCN1 5 FCN1 4 HSXAPA71 7 HSXAPA71 7 SLC11A1 4 APO8ECSA 7 FCN2 SLC7A7 CSPG2 CSP	Investinase 3 (white cell) (inventosane A synthase 1 (platietic, cytochrome P450, famity 5, subfamity A) (platietic, cytochrome P450, famity 5, subfamity A) Intoruciaese, Rhase A famity, 16 Thypothetical protein FLJ20701 (chordroin suffate proteinglycan 2 (versicen) (incellingen/fibrinogen domain containing) 1 (incellingen/fibrinogen domain containing) 1 (incellingen/fibrinogen	5q35.2         7q34-q35         14q11.2         2q36.3         5q14.3         9q34         10q24         17p13.1         12q24.2         1q24.2         1q25	regulation of transcription, DNA-dependent glycolysis prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, according prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, according RNA databolism, defense response 
21211         5         st           22211         5         st           005930         5         st           005930         5         st           13566         st         st           10430         st         st           00430         st         st           004319         st         st           004319         st         st           00133         st         st           01126         st         st           01238         st         st           01239         st         st           01329         st         st           01425         st         st           01238         st         st           01239         st         st           04439         st         st           04619         st         st           04620         st         st           04623         st         st           04638         st         st           04639         st         st           04630         st         st           04638         st         st	HK3 TBXAS1 TBXAS1 TBXAS1 FL20701 CSPG2 FCN1 4 FER1L3 4 HSXL0721 TPR HSXL0747 TPR HSXL0747 TPR SLC11A1 4 APOBEC3A SLC11A1 4 APOBEC3A SLC11A1 4 APOBEC3A FCN1 SLC11A1 4 FL44L SLC7A7 CSPG2 CSPG4 CSPG2 C	Investing as a synthese 1 (platets, cytochrome P450, family, 5, subfamily, A) (platets, cytochrome P450, family, 5, subfamily, A) Indonuclesse, Rhase A family, 86 Importinetical protein FL120701 chordrotin suffate proteogycan 2 (versican) (isolin (collagen/fibrinogen domain containing) 1 (isolin collagen/fibrinogen domain containing) 1 (isolin collagen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen/fibrinogen domain containing) 1 (isolin collagen/fibrinogen domain containing) 1 (forthordin suffate proteoglycen 2 (versicen) chordrotin suffate proteoglycen 2 (versicen) fibrinogen-fibrinogen/fibrinogen domain containing) 1 (forthordin suffate proteoglycen 2 (versicen) fibrinogen-fibrinogen formal transporter, ye system), member 7 condicion suffate proteoglycen 2 (versicen) fibrinogen-fibrinogen domain containing) 1 (folin collagen/fibrinogen domain containing) 1 (folinogen-fibrinogen domain containing) 1 (folinogen/fibrinogen domain containing) 1 (folinofibrinogen domain containing) 1 (forthorin suffate proteoglycen 2 (versicen) (folinogen/fibrinogen domain containing) 1 polasibut of fibrinogen domain containing 1 polasibut of fibrinogen do	5q35.2 7q34-q35 14q11.2 2q36.3 5q14.3 5q14.3 9q34 110q24 117p13.1 12q24.2 11q25 	regulation of transcription, DNA-dependent glycotyse prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, adoot coegulation RNA catabolism, defense response 
221211 5         still           221211 5         still           2005206 5         still           2005207 8         still           213566 41         still           200420 7         still           200420 7         still           200421 8         still           200523 7         still           200523 7         still           200523 7         still           20125 8         still           20125 8         still           20127 8         still           20128 8         still           20129 8         still           2012001 8         still           <	HK3 TBXA51 TBXA51 TBXA51 FL20701 CSPG2 FCN1 4 FER113 4 HSXAPA51 TPR 	Invokrinse 3 (white cell) (invomboare A synthese 1 (fatelist, cytochrome P450, family 5, subfamily A) (fatelist, cytochrome P450, family 5, subfamily A) (formotion suffate protein FLJ20701 chordrootin suffate proteoglycan 2 (versicen) (foolin (collegen/fibringen domain containing) 1 (fer - like 3, myoffatin (C. elsegans) XIAP associated fector-1 aldenyde dehydrogenesa 2 family (mitochondriae) translocated promoter region (to ectivated MET oncogene) - - serun/glucocorticoid regulated kinase protein tyrosine phosphatase, non-receptor type substrate 1 solute carrier family 11 (proton-coupled visient motel on transporters), member 1 epoliporotein B mRNA adding enzyme catalytic polyspetide-like 3A    Condroidin aufiate proteoglycan 2 (versicen) chordroidin aufiate proteoglycan 2 (versicen) Condocin augifate proteoglycan 2 (versicen) Carbonypapitase, vitallogenc-like 3 Elitin, galacitade-binding, aouble, 2 (galactin 2) Family with sequence asmilarity 48, member A neutrophic cycloci factor 2 (foStDe, chronic granidometous disease, autosomal 2) synuratinase (L-synuremen hydrolase) 	5q35.2           5q35.2           7q34-q35           14q11.2           2q36.3           5q14.3           5q14.3           10q24           17p13.1           12q24.2           1q25	regulation of transcription, DNA-dependent prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, abox coegulation RNA catabolism, defense response 
2120623 at 2004219 s at 201728 s at 201728 s at 201728 s at 201728 s at 201728 s at 201729 s at 215220 s at 215220 s at 210423 s at 204219 s at 204229 s at 204229 s at 204229 s at 210577 s at 201757 s at 210923 s at 210933 s at 210933 s at 210033 s at 21003	HK3 TBXA51 TBXA51 TBXA51 FL20701 CSPG2 FCN1 FER1L3 F FER1L3 F FER1L3 F HSXAPA71 T ALDP2 TPR SLC11A1 T AP08EC3A F FTPNIS1 SLC11A1 T AP08EC3A F FIFIAL SLC7A7 CSPG2 CSPG2 CSPG2 CSFG2	Investing and a synthese 1 (platielit, cytochrome P450, famity S, subfamity A) (platielit, cytochrome P450, famity S, subfamity A) indonuclesse, Rhase A famity, K6 Typothetical protein FLJ20701 (chordroin suffate proteing/can 2 (versicen) ficclin (collegen/fibrinogen domain containing) 1 (fer-14ite 3, modefini (C, elegans) XIAP associated factor-1 eldenyde dehydrogenesse 2 famity (mitochondrial) Variatocated protein region (to activated MET oncogene) 	5q35.2         7q34-q35         14911.2         2q36.3         5q14.3         9q34         10q24         17p13.1         12q24.2         1q24.2         1q25	regutation of transcription, DNA-dependent glycolysis prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, aloos coegutation RNA catabolism, defense response 
21211         5         st           22211         5         st           2005203         5         st           2005203         5         st           2005203         5         st           200527         st         st           200527         st         st           200720         st         st           200721         st         st           200773         st         st           200773         st         st           200773         st         st           200774         st         st           200775         st         st           200776         st         st           200776         st         st           200778         st	HK3 TBXA51 TBXA51 TBXA51 FL20701 CSPG2 FCN1 4 FER113 4 HSXAPA71 1 HSXAPA71 1	Invokinase 3 (white cell) (invombourne A synthase 1 (platietic, cytochrome P450, famity 5, subfamity A) (platietic, cytochrome P450, famity 5, subfamity A) Intoruciaese, Rhase A famity, 46 Pypolhatical protein FLJ20701 (chordroin suffate proteinglycan 2 (versicen) (incellingen/fibrinogen domain containing) 1 (incellingen/fibrinogen 2 (versicen) (incellingen/fibrinogen 2 (versicen)	5q35.2         7q34-q35         14911.2         2q36.3         5q14.3         5q34         10q24         17p13.1         12q24.2         1q24.2         1q25	regutation of transcription, DNA-dependent glycolysis prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, abox coegutation RNA catabolism, defense response 

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Tab. A1: Complete list of all probe-sets differentially regulated after IVIG-treatment. Probe-Sets are selected using following criteria a minimum of either a 2-fold increase or decrease, in a minimum of 40% (4 out of 10 patients); Probe-Sets common in 60% of patients are written in purple, probe-sets common in 50% of patients are written in blue;

Immune-related probe-sets are highlighted in light blue; Proliferation-, apoptosis- or cell cyfe-related probe-sets are highlighted in grey; Signalling-related probe-sets are highlighted in yellow; Transcription-related probe-sets are highlighted in green;

Tab. A2

Tab. A2				<u></u>
Probe Set ID	Gene Symbol	Gene Title	Chromosomal Location	GO Biological Process
206390 x_at	PF4	pistelet factor 4 (chemokine (C-X-C motil) ligand 4)	4q12-q21	mmune response, sensory perception, negative regulation of engingenesis,
				cytokine and chemokine mediated signaling pathway, platelet activation, immune cell chemotaxia negative regulation of megakanyocyte differentiation
210313_at	£17	leukocyte immunoglobulin-like receptor, subfamily A	19q13.4	immune response
205033_s_a1	DEFA1, DEFA3	(without TM domain), member 4 defensin, alpha 1, myeloid-related sequence, defensin,	8p23.1, 8pter-p23.3	xanobiotic metabolism, response to pest, pathogen or parasite,
		alpha 3, neutrophil-specific		defense response to becteria, defense response to fungi
	CX3CR1	neurogranin (protein kinase C substrate, RC3) chemokine (C-X3-C motif) receptor 1	11q24 3p21j3p21.3	signal transduction, neurogenesis chemotaxis, cellular defense response, cell adhesion, signal transduction,
206207 at	CLC	Charcol-Leyden crystal protein	19q13 1	G-protein coupled receptor protein signaling pathway phospholipid metabolism, development, lipid catabolism, antumicrobial humoral response
208450_at	LGALS2	lectin, galactoside-binding, soluble, 2 (galectin 2)	22q12-q13j22q13.1	
212187 x at 205495 s at			9q34.2-q34.3 2p12-q11	prostagtandin biosynthesis, fatty acid biosynthesis, transport, regutation of circadian eleep/wake cycle xanobicitic metabolism, cellular defense response. defense response to bactaria and fungi
	CX3CR1		3p21j3p21.3	chemotaxis, cellular defense response, cell adhesion, signal transduction,
210164 at	GZMB	granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated	14q11.2	G-protein coupled receptor protein signaling pathway proteolysis and peptidolysis, apoptosis, cleavage of tamin. cytolysis
		serine esterase 1)		
	GZMH NKG7	granzyme H (cathepsin G-lue 2, protein h-CCPX) natural killer cell group 7 sequence	14q11 2 19q13 41	proteolysis and peptidolysis, epoptosis, cytolysis
37145_at	GNLY		2p12-q11	xenobictic metabolism, cellular defense response, defense response to bacteria and fung
205403 at	IL1R2 1	interlessun 1 receptor, type II	2q12-q22	immune response
	FCGR3A/B	Fc fragment of IgG, low affinity Illa, receptor (CD16a).	1q23	immune response
209312_x_at	HLA-DRB1	Fc fragment of IgG. low affinity IIIb, receptor (CD16b) major histocompatibility complex, class II, DR beta 1	6p21.3	immune response, antigen presentation, exogenous antigen, antigen processing,
200728 -4			4-01.0	exogenous antigen via MHC class II
			6p21.3	animune response, signal transduction, pethogenesis, antigen presentation, exogenous antigen, antigen processing, exogenous antigen via MHC class II
210982_s_at	HLA-DRA	major histocompatibility complex, class II, DR alpha	6p21.3	immune response, immune response, artigen presentation, exogenous antigen, artigen processing, exogenous antigen via MHC class II
211990_st	HLA-OPA1	major histocompatibility complex, class II, DP alpha 1	6p21 3	immune response, antigen presentation, exogenous antigen, antigen processing.
211991 sat	HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	6p21 3	exogenous antigen via MHC class II immune response, antigen presentation, exogenous antigen, antigen processing,
				exogenous antigen via MHC class II
204006 s at 204057 at		Fc fragment of IgG, low affinity Illa, receptor (CD16a) interferon regulatory factor 8	1q23 18q24 1	immune response negative regulation of transcription from RNA polymerase II promoter, transcription,
				regulation of transcription. DNA-dependent, immune response
214181_x_at			6p21 3	cellular morphogenesis, immune response, immune response, dendrite morphogenesis, negative regulation of tymphocyte proliferation
215071 s at 215193 x at			6p21.3 6p21.3	nucleosome assembly, chromosome organization and biogenesis (sensu Eukaryota) mmune response, antigen presentation, exogenous antigen, antigen processing,
				exogenous antigen via MHC class il
211991_s_at	HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	6p21 3	immune response, antigen presentation, exogenous antigen, antigen processing, exogenous artigen va MHC class II
			хр22	inflammatory response. IkB kinase/NFkB cascade, detection of virus, innete immunity
201506_at 208893_s_at		transforming growth factor, beta-induced, 68kDa dual specific phosphatase 6	5q31 12q22-q23	cell adhesion, neg. regulation of cell adhesion, sensory perception, visual perception, cell profferation regulation of cell cyle, inactivation of MAPK, protein amino acid dephosphorylation
207206_s_at		arachidonate 12-lipoxygenase	17p13 1	electron transport, oxygen and reactive oxygen species metabolism, anti-epoptosis, cell motility
		· · · · · · · · · · · · · · · · · · ·		positive regulation of cell proliferation, positive regulation of cell proliferation, anachidonic acid metabolism, leukotriene biosynthesis, fatty acid oxidation, pos. regulation of cell growth, regulation of
	0000		4+42 +42	membrane potential, superoxide release, pos. regulation of cell adhesion, neg. regulation of cell volume
214146 s at		pro-platelet basic protein (chemokine (C-X-C motif) ligand 7)	4q12-q13	regulation of cell cycle, chemotaxis, immune response, sensory perception, cell proliferation, glucose transport, defense response to bacteria
205488 at 213348 at	GZMA CDKN1C	granzyme A (granzyme 1, cytotoxic T-lymphocyte-essociated Cyclin-dependent kinase inhibitor 1C (p57, Kip2)	5q11-q12 11p15 5	proteolysis and peptidolysis, apoptosis, cleavage of lamin, immune response, cytolysis regulation of cyclin dependent protein kinase activity, G1 phase of mitotic cell cycle, cell cycle,
				cell cycle arrest, negative regulation of cell proliferation, negative regulation of cell cycle
	RGS2 CSF1R	regulator of G protein signalling 2, 24kDa colony stimulating factor 1 receptor, formerly McDonough feline	1q31 5q33-q35	cell cycle, signal transduction, regulation of G-protein coupled receptor protein signaling pathway protein amino acid phosphorylation, signal transduction, transmembrane receptor protein tyrosine
		sarcoma viral (v-fms) oncogene homolog		kinase signaling pathway, development, cell protiferation, antimicrobial humoral response
	RTN1 PRKAR2B	reticulon 1 protein kinase, cAMP-dependent, regulatory, type II, beta	14q23 1 7q22	signal transduction, neuron ceil differentiation protein amino acid phosphorylation, signal transduction, intracellular signaling cascade
205159 at	CSF2RB	colony stanutating factor 2 receptor, beta.	22q13 1	signal transduction, respiratory gaseous exchange, cytokine and chemokine mediated signaling pathway, antimicrobial humoral response (sensu Vertebrata)
206493_at	ITGA2B	iow-affinity (granubcyte-macrophage) integrin, atpha 2b	17q21 32	cell-matrix adhesion, integrin-mediated signaling pathway
206655_s_at	GP188	(platelet glycoprotein lib of lib/lila complex, antigen CD41B) glycoprotein lb (platelet), beta polypeptide	22011 21-011 23/22011	cell adhesion, cell surface receptor linked signal transduction, platelet activation
214146_s_at	PPBP	pro-platelet basic protein (chemokine (C-X-C motif) ligand 7)	4q12-q13	regulation of cell cycle, chemotaxis, immune response, sensory perception,
203680_at	PRKAR2B	protein kinase, cAMP-dependent, regulatory, type II, beta	7922	cell proliferation, glucose transport, defense response to bacteria
219529_at	CLIC3	chloride intracellular channel 3	9q34.3	ion transport, chlonde transport, signal transduction
21456/_s_at	XCL1/XCL2	chemokine (C motif) ligand 1	1q23/1q23-q25	calcium ion homeostasis, chemotaxis, immune response, signal transduction, cell-cell signaling, sensory perception, antimicrobial humoral response, chemotaxis, signal transduction,
203140 at	BCL6	B-cell CLL/Ivmphoma 6 (zinc finger protein 51)	3q27	cell-cell signaling, circulation negative regulation of transcription from RNA polymerase II promoter, transcription, regulation of
				transcription, DNA-dependent, inflammatory response, positive regulation of cell proliferation
204057_at	IRF8	Interferon regulatory factor 8	16q24.1	negative regulation of transcription from RNA polymerase II promoter, transcription, regulation of transcription, DNA-dependent, immune response
204115_at	GNG11	guanine nucleotide binding protein (G protein), gamma 11	7q31-q32	signal transduction. G-protein coupled receptor protein signaling pathway
212331_at 221841_s_at	RBL2 KLF4	retinoblastome-like 2 (p130) Kruppel-like factor 4 (gut)	16q12.2 9q31	transcription, regulation of transcription, negative regulation of cell cycle. DNA-dependent cell cycle transcription, mesoderm cell fate determination, negative regulation of cell proliferation, negative
				regulation of transcription, DNA-dependent, negative regulation of transcription, DNA-dependent
221211_s_at 205861_at	SPIB	chromosome 21 open reading frame 7 Spi-B transcription factor (Spi-1/PU.1 related)	21q22.3 19q13.3-q13.4	regulation of transcription, DNA-dependent transcription, regulation of transcription from RNA polymerase II promoter
200596_s_at	EIF3S10 1	eukaryotic translation initiation factor 3, subunit 10 theta, 150/170kDa	10q26	protein biosynthesis, regulation of translational initiation
200727_8_at		ARP2 actin-related protein 2 homolog (yeast)	2p14	
203845 s at 204900 x at		CD163 antigen sin3-associated polypeptide, 30kDa	12p13.3 4q34 1	antimicrobial humoral response (sensu Vertebrata)
212188_at	KCTD12	potassium channel tetramerisation domain containing 12	13q22.3	potassium ion transport
215049 x at 203645 s at		CD163 antigen	12p13.3 12p13.3	artimicrobial humoral response (sensu Vertebrata)
215646 s at	t]CSPG2 ↑	chondroitin sulfate proteoglycan 2 (versican)	5q14 3	development, cell recognition
200665 s at 201669 s at		secreted protein, acidic, cysteine-rich (osteonectin)	5q31 3-q32 6q22 2	cell motitity
203305_at	F13A1	coegutation factor XIII, A1 polypeptide	6p25 3-p24.3	blood coegulation, peptide cross-linking
204439_at 204838_s_at	I MLH3	mterferon-induced protein 44-like mutL homolog 3 (E. coli)	1p31.1 14q24.3	msmatch repair, metotic recombination
205495_s_at		granutysin histone 1, H3h	2p12-q11 6p22-p21-3	xenobiotic metabolism, cellular defense response, defense response to bacteria and fungi
	t CD36	CD36 antigen (collagen type I receptor, thrombospondin receptor)	7q112	lipid metabolism, fatty acid metabolism, transport, cell adhesion, blood opegulation
206488 s at	t CPVL	carboxypeptidase, vitellogenic-like	7p15-p14 21g22.3	proteolysis and peptidolysis
208146 s at	H28FS	tubulan, beta 1	20q13.32	microtubule-based movement, protein polymerization tipid metabolism, apoptosis, immune response, complement activation, classical pathway,
208146 s at 208579 x at 208601 s at	TUBBI			
208146 s at 208579 x at	TUBBI	Clusterin (complement lysis inhibitor, SP-40,40, suffated glycoprot. 2, testosterone-represed prostate message 2, apolipoproten J)	.  8p21-p12	(entrization (sensu Metazoa), cell death
208146 s at 208579 x at 208601 s at 208791 at 209555 s at	1 TUBB1 CLU 1 CD36	clusterin (complement lysis inhibitor, SP-40,40, suffated glycoprot. 2. testosterone-repressed prostate message 2, apolipoprotein J) CD36 antigen (collagen type I receptor, thrombospondin receptor	) 7q11 2	fertization (sonsu Metazoa), cell death lipid metabolism, fatty acid metabolism, transport, cell adhesion, blood coegulation
208146 s at 208579 x at 208601 s at 208791 at 209555 s at 210164_at	CLU CLU CO36 CZMB	clusterin (complement lysis inhibitor, SP-40,40, suffated glycoprot. 2. testosterone-repressed prostate message 2, apolipoprotein J)		fertilization (sensu Metazoa), cell desth lipid metabolism. fatty ecid metabolism, transport, cell adhesion, blood coegulation proteolysis and peptidolysis, apoptosis, cleavage of lamin, cytolysis
208146 s at 208579 x at 208601 s at 208791 at 209555 s at	1 TUBB1 CLU 1 CD36 GZMB	chusterin (complement tysis inhibitor, SP-40,40, suffated glycoprot. 2. testosterone-repressed prostate message 2, apolopoproten J) CD36 antigen (collagen type I receptor, thrombospondin receptor granzyme B (granzyme 2, cytotox C+/mphocyte-ssociated	) 7q11 2	fertization (sonsu Metazoa), cell death lipid metabolism, fatty acid metabolism, transport, cell adhesion, blood coegulation

208450_at [LGALS2	lectin, galactoside-binding, soluble, 2 (galectin 2)	22q12-q13/22q13.1	
211571_s_st CSPG2	chondroiun sulfate proteoglycan 2 (versican)	5q14.3	development, cell recognition
203799_at CD302	CD302 antigen	2024.2	
204860_s_at BIRC1	baculoviral IAP repeat-containing 1	5q13.1	cet motity
208450_at LGALS2	lectin, gatactoside-binding, soluble, 2 (galectin 2)	22q12-q13 22q13.1	
	prostaglandin D2 synthase 21kDa (brain)	9q34.2-q34.3	prostaglandin biosynthesis, fatty acid biosynthesis, transport, regulation of circadian sleep/wake cycle
212187_x_at PTGDS	prostaglandin 02 synthese 21kDa (brain)	9q34.2-q34.3	prostaglandin biosynthesis, fatty acid biosynthesis, transport, regulation of circadian sleep/wake cycle
217979_at TSPAN13	tetraspanin 13	7p21.1	

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Tab. A2: Complete list of all probe-sets differentially regulated after IVMP-treatment; Probe-Sets are selected using following criteria: a minimum of either a 2-fold increase or decrease, in a minimum of 60% (3 out of 5 patients); Probe-Sets common in 80% of patients are written in purple, probe-sets common in 60% of patients are written in blue,

Immuno-related probe-sets are highlighted in light blue; Prolferation-, apoptosis- or cell cyle-related probe-sets are highlighted in grey. Signaling-related probe-sets are highlighted in yetow; Transcription-related probe-sets are highlighted in green;

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Probe Set ID	log2 (fold change)	Fold Change	Gene Title	Gene Symbol	Chromosomal Location	GO Biological Process Description
219534_x_at			cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C		regulation of cyclin dependent protein kinase activity /// G1 phase of mitotic cell cycle /// cell cycle /// cell cycle arrest /// negative regulation of cell proliferation /// negative regulation of cell cycle
219534_x_at 213904_at	1.999		Clone 23555 mRNA sequence		11p15.5	
213307_8(	1.930	3,83174007	collagen, type III, alpha 1 (Ehlers Danlos syndrome type IV,			phosphate transport /// circulation
215076_s_at	1.809	3,50399326	autosomal dominant)	COL3A1	2q31	/// organogenesis
213458_at	1.637	3,11018414	KIAA0974	KIAA0974	10q22.2	
209 <u>169_</u> at	1.589	3,0084075	glycoprotein M6B	GPM6B	Xp22.2	neurogenesis /// cell differentiation
220084_at	1. <u>5</u> 42	2,9119791		C14orf105	14q22.3	
220178_at	1.516	2,85996997	chromosome 19 open reading frame 28	C19orf28	19p13.3	
201616_s_at	1.497	2,82255169	caldesmon 1	CALD1	7q33	muscle contraction /// muscle development
	1.442	2,71697257				
221233_s_at	1.438	2,70944995	KIAA1411 /// KIAA1411	KIAA1411	6q12-q13	
215308_at 210880_s_at	<u>1.422</u> 1.416	2,6795672 2,66844634	embryonal Fyn-associated substrate	<u>G22P1</u> EFS	22q13.2-q13.31 14q11.2-q12	DNA ligation /// DNA repair /// double-strand break repair via nonhomologous end-joining /// DN recombination /// positive regulatic of transcription, DNA-dependent cell adhesion /// intracellular signaling cascade
			SH3 and multiple ankyrin repeat			
215830_at	1.404	2,64634288		SHANK2	11q13.3-q13.4	intracellular signaling cascade
216814_at	1.395	2,62988552	<u></u>			
204887 <u>s_at</u> 215759 at	1.375 1.369		polo-like kinase 4 (Drosophila) hypothetical protein FL112056	PLK4 FLJ12056	4q27-q28 2p13.3	regulation of cell cycle /// protein amino acid phosphorylation
		_,	CDNA: FLJ23604 fis, done			
221183_at	1.354	2,55619873	LNG15857			
208291_s_at	1.337	2,52625452	tyrosine hydroxylase	тн	11p15.5	synaptic transmission /// aromatic amino acid family metabolism /// morphogenesis /// neurotransmitte biosynthesis /// catecholamine biosynthesis
222305_at	1.311	2,4811346	hexokinase 2	нк2	2p13	regulation of cell cycle /// glycolysi
211448_s_at 206446_s_at		2,4435862 2,41998818	regulator of G-protein signalling 6 elastase 24	RGS6 ELA2A	14q24.3 1p36.21	G-protein coupled receptor protein signaling pathway /// intracellular signaling cascade /// regulation of protein coupled receptor protein signaling pathway proteolysis and peptidolysis
	1.273	2,41930018				
2200303_at 220411_x_at			hypothetical protein FLJ23447	FLJ23447	19p13.12	
215070_x_at	1.263	2,39994276	RAB GTPase activating protein 1	RABGAP1	<del>9</del> q33.2-q33.3	cell cycle protein biosynthesis /// cytoskeleta
214099_s_at	1.256	2,38832637	phosphodiesterase 4D interacting protein (myomegalin)	PDE4DIP	1q12	organization and biogenesis /// act cytoskeleton organization and biogenesis rRNA modification /// rRNA
210801_at	1.237	2,35707882	dimethyladenosine transferase FAT tumor suppressor homolog 2	HSA9761	5q11-q14	processing
208153_s_at	1.231	2,34729636	(Drosophila) /// FAT tumor suppressor homolog 2 (Drosophila) fer-1-like 3, myoferlin (C.	FAT2	5q32-q33	cell adhesion /// homophilic cell adhesion
217518_at	1.221	2,3310824	elegans)	FER1L3	10q24	muscle contraction /// circulation
215211_at	1.217		Clone 23832 mRNA sequence			
	1.198		latrophilin 3	LPHN3	4q13.1	signal transduction /// neuropeptic signaling pathway

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220382_s_at			Rho GTPase activating protein 28	ARHGAP28	18p11.23	viral release
216856_s_at 214133_at	1.162	2,2376742	mucin 6, gastric	MUC6	11p15.5-p15.4	
214135_al	1.140	2,2100047	Solute carrier family 16		111p15.5-p15.4	
			(monocarboxylic acid			transport /// organic anion transport
217685_at	1.145	2 24146121	transporters), member 3	SLC16A3	17q25	/// monocarboxylic acid transport
217005_80	1.145	2,21140131	A kinase (PRKA) anchor protein	3661040	17425	
213516_at	1.145	2,21146131		AKAP13	15q24-q25	intracellular signaling cascade
213310_80	1.145	2,21140131	15		15424-425	
			thrombopoietin (myeloproliferative leukemia virus			
			oncogene ligand, megakaryocyte			
211154_at	1.129	2,18707091	growth and development factor)	THPO	3q27	development /// cell proliferation
						transcription /// regulation of transcription from RNA polymerase
						II promoter /// heart development
207662_at	1.128	2,18555548	T-box 1	твх1	22q11.21	/// morphogenesis
209819 at	1.119	2 17196371	hyaluronan binding protein 4	HABP4	9q22.3-q31	
205015_0	1.110	2,17100011		17.051		regulation of cell cycle ///
209969_s_at	1.119	2,17196371	signal transducer and activator of transcription 1, 91kDa	STAT1	2q32.2	transcription /// regulation of transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// caspase activation /// intracellular signaling cascade /// I-kappaB kinase/NF-kappaB cascade /// tyrosine phosp
210019_at	1.113	2,16294953	calmodulin-like 3	CALML3	10pter-p13	
205249_at	1.095	2,13613082	early growth response 2 (Krox-20 homolog, Drosophila)	EGR2	10q21.1	transcription /// regulation of transcription, DNA-dependent /// brain development /// peripheral nervous system development /// mechanosensory behavior
			mitochondrial solute carrier			
218978_s_at	1.089	2,12726535	CDNA: FLJ21997 fis, clone	MSCP	8p21.2	transport
216165_at	1.086	2,12284642				
						fatty acid biosynthesis /// fatty acid desaturation /// fatty acid
204257_at	1.065		fatty acid desaturase 3	FADS3	11q12-q13.1	desaturation
217363_x_at	1.048	2,06766147				
215013_s_at	1.035	2,04911365	ubiquitin specific protease 34	USP34	2p15	ubiquitin-dependent protein catabolism /// ubiquitin cycle
215942_s_at			G-2 and S-phase expressed 1	GTSE1	22q13.2-q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process
204015	4		DEAH (Asp-Glu-Ala-His) box	DUNCE	10-12-2	
204816_s_at		2,03778239	polypeptide 34	DHX34	19q13.3	electron transport
217395_at	1.023	2,03214029	metallothionein IV	MT4	16q13	
						cation transport /// calcium ion transport /// calcium ion homeostasis /// muscle contraction /// signal transduction /// regulation
207557_s_at	1.022	2,0307322	ryanodine receptor 2 (cardiac)	RYR2	1q42.1-q43	of heart contraction rate
204677_at	1.015	2.02090289	cadherin 5, type 2, VE-cadherin (vascular epithelium)	CDH5	16q22.1	cell adhesion /// homophilic cell adhesion
206926_s_at			interleukin 11	IL11	19q13.3-q13.4	cell-cell signaling /// positive regulation of cell proliferation /// platelet activation /// B-cell differentiation /// megakaryocyte differentiation /// adipocyte differentiation

Tab. A3a: Probe-sets up-regulated regulated upon IVIG treatment at day 6 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients;

Tab. A3a			· · · · · · · · · · · · · · · · · · ·		L	
	fold: change)		Gene Title	Gene Symbol	Chromosomal	* GO'Biological Process Description*
219534_x_at			cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C	11p15.5	regulation or cyclin dependent protein kinase activity /// G1 phase of mitotic cell cycle /// cell cycle /// cell cycle arrest /// negative regulation of cell proliferation /// negative regulation of cell cycle
213904 at	1.938	3.83174087	Clone 23555 mRNA sequence			
215076_s_at			collagen, type III, alpha 1 (Ehlers Danlos syndrome type IV, autosomal dominant)	COL3A1	2q31	phosphate transport /// circulation /// organogenesis
213458_at	1.637	3.11018414		KIAA0974	10q22.2	
213.50_ut	1.001	3,11010414			10422.2	····=
209169_at	1.589		glycoprotein M6B chromosome 14 open reading	GPM6B	Xp22.2	neurogenesis /// cell differentiation
220084_at	1.542	2,9119791	frame 105	C14orf105	14q22.3	
			chromosome 19 open reading			
220178_at	1.516	2,85996997	frame 28	C19orf28	19p13.3	
201616_s_at 220687_at		2,82255169	caldesmon 1	CALD1	7q33	muscle contraction /// muscle development
221233_s_at	1.442		KIAA1411 /// KIAA1411	KIAA1411	 6q12-q13	
215308_at	1.422	2,6795672	Thyroid autoantigen 70kDa (Ku	G22P1	22q13.2-q13.31	DNA ligation /// DNA repair /// double-strand break repair via nonhomologous end-joining /// DNA recombination /// positive regulation of transcription, DNA-dependent cell adhesion /// intracellular
210880_s_at	1.416	2,66844634		EFS	14q11.2-q12	signaling cascade
			SH3 and multiple ankyrin repeat			
215830_at	1.404	2,64634288	domains 2	SHANK2	11q13.3-q13.4	intracellular signaling cascade
216814_at	1.395	2,62988552				
						regulation of cell cycle /// protein
204887_s_at	1.375	2,59367911	polo-like kinase 4 (Drosophila)	PLK4	4q27-q28	amino acid phosphorylation
215759_at	1.369	2,5829147	hypothetical protein FLJ12056	FU12056	2p13.3	
			CDNA: FLJ23604 fis, done			
221183_at 208291_s_at	1.354 1.337	2,55619873 2,52625452	tyrosine hydroxylase	тн	11p15.5	synaptic transmission /// aromatic amino acid family metabolism /// morphogenesis /// neurotransmitter biosynthesis /// catecholamine biosynthesis
222305_at	1.311	2 4811346	hexokinase 2	нк2	2p13	regulation of cell cycle /// glycolysis
211448_s_at 206446_s_at	1.289		regulator of G-protein signalling 6	RGS6	14q24.3 1p36.21	G-protein coupled receptor protein signaling pathway /// intracellular signaling cascade /// regulation of G- protein coupled receptor protein signaling pathway proteolysis and peptidolysis
	1.274	2,41831135				
220411_x_at		2,40660605	hypothetical protein FLJ23447		19p13.12	
215070_x_at	1.263	2,39994276	RAB GTPase activating protein 1	RABGAP1	9q33.2-q33.3	cell cycle
 214099_s_at			phosphodiesterase 4D interacting		1q12	protein biosynthesis /// cytoskeleton organization and biogenesis /// actin cytoskeleton organization and biogenesis rRNA modification /// rRNA
210801_at	1.237	2.35707882	dimethyladenosine transferase	HSA9761	5q11-q14	processing
208153_s_at		2,34729636	FAT tumor suppressor homolog 2 (Drosophila) /// FAT tumor suppressor homolog 2			cell adhesion /// homophilic cell adhesion
217518_at	1.221	2,3310824		FER1L3	10q24	muscle contraction /// circulation
	1.217		Clone 23832 mRNA sequence			
209866_s_at		2,29421405		LPHN3		signal transduction /// neuropeptide signaling pathway

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220382_s_at		2,27521046	Rho GTPase activating protein 28	ARHGAP28	18p11.23	viral release
216856_s_at	1.162	2,2376742				
214133_at	1.148	2.2160647	mucin 6, gastric	MUC6	11p15.5-p15.4	
-			Solute carrier family 16			
			(monocarboxylic acid			transport /// organic anion transpo
217685_at	1.145	2 211/6131	transporters), member 3	SLC16A3	17q25	/// monocarboxylic acid transport
217005_00	1.145	2,21140131	A kinase (PRKA) anchor protein	5001045	11/425	I'll monocarboxyne acid danspore
212616 at	4 4 4 5	0.01446424		AVADIO	15-24 -25	intracellular cignalian carcado
213516_at	1.145	2,21146131	13	AKAP13	15q24-q25	intracellular signaling cascade
			thrombopoietin			
			(myeloproliferative leukemia virus			
				'		
			oncogene ligand, megakaryocyte	-		
211154_at	1.129	2,18707091	growth and development factor)	ТНРО	3q27	development /// cell proliferation
						transcription /// regulation of
						transcription from RNA polymerase
						II promoter /// heart development
207662_at	1.128	2,18555548	T-box 1	TBX1	22q11.21	/// morphogenesis
209819_at	1.119	2,17196371	hyaluronan binding protein 4	HABP4	9q22.3-q31	
			<b></b>	<u> </u>		regulation of cell cycle ///
						transcription /// regulation of
						transcription, DNA-dependent ///
						transcription from RNA polymerase
						II promoter /// caspase activation
						/// intracellular signaling cascade //
			·····			
			signal transducer and activator of			I-kappaB kinase/NF-kappaB cascad
209969_s_at			transcription 1, 91kDa	STAT1	2q32.2	/// tyrosine phosp
210019_at	1.113	2,16294953	calmodulin-like 3	CALML3	10pter-p13	
						transcription /// regulation of
						transcription, DNA-dependent ///
						brain development /// peripheral
			early growth response 2 (Krox-20	1		nervous system development ///
205249_at	1.095	2 13613082	homolog, Drosophila)	EGR2	10q21.1	mechanosensory behavior
203219_0	1.000	2,10010002	mitochondrial solute carrier		10421.1	Intechanosensory ochavior
110070 c at	4 000	0.40700505		MCCD	0-21.2	A
218978_s_at	1.069	2,12726535		MSCP	8p21.2	transport
			CDNA: FLJ21997 fis, clone			
216165_at	1.086	2,12284642	HEP06590			
		· ·				fatty acid biosynthesis /// fatty acid
						desaturation /// fatty acid
	1.065	2,09216988	fatty acid desaturase 3	FADS3	11q12-q13.1	desaturation
217363_x_at	1.048	2,06766147				
						ubiquitin-dependent protein
215013_s_at	1.035	2 04011365	L			
			udiquitin specific protease 34	IUSP34	2015	Icatabolism /// ubiquitin cycle
		2,04311303	ubiquitin specific protease 34	USP34	2p15	catabolism /// ubiquitin cycle G2 phase of mitotic cell cycle ///
		_2,04911303	ubiquitin specific protease 34	USP34	2p15	G2 phase of mitotic cell cycle ///
		_2,04511505	ubiquitin specific protease 34	USP34	2p15	G2 phase of mitotic cell cycle /// DNA damage response, signal
		_2,04311303	ubiquian specific protease 34	USP34	2p15	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator
						G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest ///
			G-2 and S-phase expressed 1	USP34 GTSE1	2p15 22q13.2-q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator
215942_s_at	1.033	2,04627494	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box	GTSE1	22q13.2-q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process
2 <u>15942_s_at</u> 204816_s_at	<u>1.033</u> 1.027	2,04627494 2,03778239	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34	GTSE1 DHX34	22q13.2-q13.3 19q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport
2 <u>15942_s_at</u> 204816_s_at	1.033	2,04627494 2,03778239	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box	GTSE1	22q13.2-q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process
2 <u>15942_s_at</u> 204816_s_at	<u>1.033</u> 1.027	2,04627494 2,03778239	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34	GTSE1 DHX34	22q13.2-q13.3 19q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport
2 <u>15942_s_at</u> 204816_s_at	<u>1.033</u> 1.027	2,04627494 2,03778239	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34	GTSE1 DHX34	22q13.2-q13.3 19q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport
2 <u>15942_s_at</u> 204816_s_at	<u>1.033</u> 1.027	<u>2,04627494</u> 2,03778239	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34	GTSE1 DHX34	22q13.2-q13.3 19q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport
2 <u>15942_s_at</u> 204816_s_at	<u>1.033</u> 1.027	<u>2,04627494</u> 2,03778239	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34	GTSE1 DHX34	22q13.2-q13.3 19q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion
2 <u>15942_s_at</u> 204816_s_at	<u>1.033</u> 1.027	<u>2,04627494</u> 2,03778239	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34	GTSE1 DHX34	22q13.2-q13.3 19q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis /// muscle contraction
215942_s_at 204816_s_at 217395_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV	GTSE1 DHX34 MT4	22q13.2-q13.3 19q13.3 16q13	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport 
2 <u>15942_s_at</u> 204816_s_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029 2,0307322	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV	GTSE1 DHX34	22q13.2-q13.3 19q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis /// muscle contraction /// signal transduction /// regulation of heart contraction rate
215942_s_at 204816_s_at 217395_at 207557_s_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029 2,0307322	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV ryanodine receptor 2 (cardiac) cadherin 5, type 2, VE-cadherin	GTSE1 DHX34 MT4 RYR2	22q13.2-q13.3 19q13.3 16q13 1q42.1-q43	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis /// muscle contraction /// signal transduction /// regulation of heart contraction rate cell adhesion /// homophilic cell
215942_s_at 204816_s_at 217395_at 207557_s_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029 2,0307322	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV ryanodine receptor 2 (cardiac) cadherin 5, type 2, VE-cadherin	GTSE1 DHX34 MT4	22q13.2-q13.3 19q13.3 16q13	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis // muscle contraction /// signal transduction /// regulation of heart contraction rate cell adhesion /// homophilic cell adhesion
215942_s_at 204816_s_at 217395_at 207557_s_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029 2,0307322	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV ryanodine receptor 2 (cardiac) cadherin 5, type 2, VE-cadherin	GTSE1 DHX34 MT4 RYR2	22q13.2-q13.3 19q13.3 16q13 1q42.1-q43	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis // muscle contraction /// signal transduction /// regulatior of heart contraction rate cell adhesion /// hostive
215942_s_at 204816_s_at 217395_at 207557_s_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029 2,0307322	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV ryanodine receptor 2 (cardiac) cadherin 5, type 2, VE-cadherin	GTSE1 DHX34 MT4 RYR2	22q13.2-q13.3 19q13.3 16q13 1q42.1-q43	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis // muscle contraction /// signal transduction /// regulation of heart contraction rate cell adhesion /// hostive regulation of cell proliferation ///
215942_s_at 204816_s_at 217395_at 207557_s_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029 2,0307322	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV ryanodine receptor 2 (cardiac) cadherin 5, type 2, VE-cadherin	GTSE1 DHX34 MT4 RYR2	22q13.2-q13.3 19q13.3 16q13 1q42.1-q43	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis // muscle contraction /// signal transduction /// regulation of heart contraction rate cell adhesion /// hostive
215942_s_at 204816_s_at 217395_at 207557_s_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029 2,0307322	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV ryanodine receptor 2 (cardiac) cadherin 5, type 2, VE-cadherin	GTSE1 DHX34 MT4 RYR2	22q13.2-q13.3 19q13.3 16q13 1q42.1-q43	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis // muscle contraction /// signal transduction /// regulation of heart contraction rate cell adhesion /// hostive regulation of cell proliferation ///
04816_s_at 04816_s_at 17395_at 07557_s_at	1.033 1.027 1.023	2,04627494 2,03778239 2,03214029 2,0307322	G-2 and S-phase expressed 1 DEAH (Asp-Glu-Ala-His) box polypeptide 34 metallothionein IV ryanodine receptor 2 (cardiac) cadherin 5, type 2, VE-cadherin	GTSE1 DHX34 MT4 RYR2	22q13.2-q13.3 19q13.3 16q13 1q42.1-q43	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process electron transport  cation transport /// calcium ion transport /// calcium ion homeostasis // muscle contraction /// signal transduction /// regulatio of heart contraction rate cell adhesion /// homophilic cell adhesion cell-cell signaling /// positive regulation of cell proliferation /// platelet activation /// B-cell

Tab. A3a:

Probe-sets up-regulated regulated upon IVIG treatment at day 6 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients;

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ALC: A DE TAIX L'A	. A	A. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.		133.000	die werten in fak in	
Probe Set IE	log2	Fold Change	Gene Title	Gene Symbol	Chromosoma Location	GO Biological Process Description
		a, ord, or or or ige	Statistics of concentrate fragmentation			protein amino acid dephosphorylation
						dephosphorylation /// cell cycle ///
215793_at	-2.268	4 91654052	myotubularin related protein 7	MTMP7	8p22	phospholipid dephosphorylation
215/95_8	-2.200	-4,01054952	transmembrane protein with			
			EGF-like and two follistatin-like			
205122_at	-1.985	-3,95862663		TMEFF1	9q31	
				1		
			Tissue factor pathway inhibitor			
ļ			(lipoprotein-associated			
213258_at	-1.64	-3,11665832	coagulation inhibitor)	TFPI	2q31-q32.1	blood coagulation
			p21/Cdc42/Rac1-activated			protein amino acid phosphorylation ///
			kinase 1 (STE20 homolog,			protein amino acid phosphorylation ///
209615_s_at	-1.494	-2,81668845		PAK1	11q13-q14	apoptosis /// JNK cascade
			alcohol dehydrogenase IB			
209612_s_at	-1.403	-2,64450921	(class I), beta polypeptide	ADH1B	4q21-q23	ethanol oxidation
						nucleobase, nucleoside, nucleotide and
201420				<b>DDV</b> (2) <b>D</b>		nucleic acid metabolism /// signal
201430_s_at	-1.403	-2,64450921	dihydropyrimidinase-like 3 Similar to Hypothetical zinc	DPYSL3	5q32	transduction /// neurogenesis
222125 -+	4 200	2 6252500	finger protein KIAA1956		10-12 42	
222135_at	-1.398	-2,0353599	cell adhesion molecule with		19q13.43	·
			homology to L1CAM (dose			
204591_at	-1.329	2 51220476		CHL1	3p26.1	cell adhesion /// signal transduction
220258_s_at		-2,51220470	homolog of L1) hypothetical protein FLJ10385	FLJ10385	17p13.1	
217082_at	-1.288	-2,51054396	Unknown protein		17p13.1	
217002_at	-1.200	-2,44189303	thrombopoletin			
			(myeloproliferative leukemia			
			virus oncogene ligand,			
711071 c -+	4 000		megakaryocyte growth and	TUM	2	development (// coll proliferation
211831_s_at 214160_at	-1.200	-2,43851019	development factor)	THPO	3q27	development /// cell proliferation
217386_at	-1.271	-2,36854322				
17500_at	-1.244	-2,30054322				
			FK506 binding protein 12-			regulation of cell cycle /// DNA repair
			rapamycin associated protein 1	EDAD1	1p36.2	/// DNA recombination
215381 at	1 229	2 24242026				
	-1.228					
		-2,3343162	KIAA1109		4q27	
		-2,3343162	KIAA1109 solute carrier organic anion			
214929 <u>s</u> at	-1.223	-2,3343162	KIAA1109 solute carrier organic anion transporter family, member	KIAA1109	4q27	transport /// ion transport /// organic
214929 <u>s</u> at	-1.223	-2,3343162	KIAA1109 solute carrier organic anion transporter family, member	KIAA1109		transport /// ion transport /// organic anion transport
215381_at 214929_s_at 211480_s_at	-1.223	-2,3343162 -2,30697121	KIAA1109 solute carrier organic anion transporter family, member 1A2	KIAA1109	4q27	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron
214929_s_at	-1.223 -1.206	-2,3343162 -2,30697121	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin)	KIAA1109 SLCO1A2	4q27 12p12	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty
214929 <u>s</u> at	-1.223 -1.206	-2,3343162 -2,30697121 -2,27521046	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase	KIAA1109 SLCO1A2	4q27	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron
214929_s_at 211480_s_at 210702_s_at	-1.223 -1.206 -1.186	-2,3343162 -2,30697121 -2,27521046	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187	KIAA1109 SLCO1A2 PTGIS	4q27 12p12 20q13.13	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis
214929_s_at 211480_s_at 210702_s_at 216596_at	-1.223 -1.206 -1.186 -1.178	-2,3343162 -2,30697121 -2,27521046 -2,26262893	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein	KIAA1109 SLCO1A2 PTGIS LOC440265	4q27 12p12 20q13.13 15q13.3	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis
214929_s_at 211480_s_at 210702_s_at 216596_at	-1.223 -1.206 -1.186	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1	KIAA1109 SLCO1A2 PTGIS LOC440265	4q27 12p12 20q13.13	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis
214929_s_at	-1.223 -1.206 -1.186 -1.178	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division	KIAA1109 SLCO1A2 PTGIS LOC440265	4q27 12p12 20q13.13 15q13.3	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at	-1.223 -1.206 -1.186 -1.178 -1.161	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae,	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1	4q27 12p12 20q13.13 15q13.3 2p13.1	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis
214929_s_at 211480_s_at 210702_s_at 216596_at	-1.223 -1.206 -1.186 -1.178 -1.161	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog)	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1	4q27 12p12 20q13.13 15q13.3	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at 214381_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLJ14293 fis, done	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12	 transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis  cell cycle
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLJ14293 fis, done PLACE1007866	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1	4q27 12p12 20q13.13 15q13.3 2p13.1	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at 214381_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin 12 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLD14293 fis, clone PLACE1007866 glutathione peroxidase 5	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12 	 transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis  cell cycle
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at 214381_at 222202_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin 12 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLD14293 fis, clone PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12 	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at 214381_at 222202_at 208028_s_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864 -2,22684324	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FL014293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein)	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601  GPX5	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12  6p22.1	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to oxidative stress
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at 214381_at 222202_at 208028_s_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FL014293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein)	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12 	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at 214381_at 222202_at 208028_s_at 06519_x_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155 -1.144	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864 -2,22684324 -2,20992897	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FL014293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein)	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601  GPX5 	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12  6p22.1 	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to oxidative stress
214929_s_at 211480_s_at 210702_s_at 216596_at 216525_at 214381_at 22202_at 08028_s_at 06519_x_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155 -1.144	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864 -2,22684324 -2,20992897	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FL014293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein)	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601  GPX5 	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12  6p22.1	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to oxidative stress
214929_s_at 211480_s_at 210702_s_at 216596_at 216525_at 214381_at 22202_at 08028_s_at 06519_x_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155 -1.144	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864 -2,22684324 -2,20992897 -2,18404109	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLJ14293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein) 	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601  GPX5  RHD	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12  6p22.1  1p36.11	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to oxidative stress ion transport /// potassium ion
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at 214381_at 222202_at 208028_s_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155 -1.144	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,23457428 -2,23147864 -2,22684324 -2,20992897 -2,18404109	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLJ14293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein)  Rhesus blood group, D antigen potassium voltage-gated	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601  GPX5  RHD	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12  6p22.1  1p36.11 21q22.1-	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to oxidative stress ion transport /// potassium ion transport /// muscle contraction ///
214929_s_at 211480_s_at 210702_s_at 216596_at 216596_at 216525_at 214381_at 222202_at 208028_s_at 208028_s_at 206519_x_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155 -1.144 -1.127	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,2361237 -2,23457428 -2,23147864 -2,22684324 -2,20992897 -2,18404109	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLJ14293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein) 	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601  GPX5  RHD	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12  6p22.1  1p36.11 21q22.1- q22.2 21q22.	<pre> transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to oxidative stress ion transport /// potassium ion transport /// muscle contraction /// perception of sound /// regulation of</pre>
214929_s_at 211480_s_at 210702_s_at 216596_at 216596_at 216525_at 214381_at 222202_at 208028_s_at 208028_s_at 206519_x_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155 -1.144 -1.127	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,2361237 -2,23457428 -2,23147864 -2,22684324 -2,20992897 -2,18404109 -2,18252775	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLJ14293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein) 	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601  GPX5  RHD	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12  6p22.1  1p36.11 21q22.1- q22.2 21q22. 12	transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis 
214929_s_at 211480_s_at 210702_s_at 216596_at 216225_at 216225_at 214381_at 222202_at 208028_s_at 208028_s_at 208028_s_at 200429_at 210429_at	-1.223 -1.206 -1.186 -1.178 -1.161 -1.16 -1.158 -1.155 -1.144 -1.127 -1.126	-2,3343162 -2,30697121 -2,27521046 -2,26262893 -2,2361237 -2,2361237 -2,23457428 -2,23147864 -2,22684324 -2,20992897 -2,18404109 -2,18252775	KIAA1109 solute carrier organic anion transporter family, member 1A2 prostaglandin I2 (prostacyclin) synthase similar to DKFZP434L187 protein Anthrax toxin receptor 1 similar to CDC10 (cell division cycle 10, S.cerevisiae, homolog) CDNA FLJ14293 fis, done PLACE1007866 glutathione peroxidase 5 (epididymal androgen-related protein) 	KIAA1109 SLCO1A2 PTGIS LOC440265 ANTXR1 LOC441601  GPX5  RHD KCNE1	4q27 12p12 20q13.13 15q13.3 2p13.1 11p11.12  6p22.1  1p36.11 21q22.1- q22.2 21q22. 12	<pre> transport /// ion transport /// organic anion transport prostaglandin biosynthesis /// electron transport /// lipid metabolism /// fatty acid biosynthesis cell cycle lipid metabolism /// response to oxidative stress ion transport /// potassium ion transport /// muscle contraction /// perception of sound /// regulation of</pre>

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1						transmembrane receptor protein
		[				tyrosine phosphatase signaling
			pleiotrophin (heparin binding		1	pathway /// neurogenesis /// cell
			growth factor 8, neurite growth			proliferation /// positive regulation of
209465_x_at	1 002	2 12217156	promoting factor 1)	PTN	7q33-q34	cell proliferation
203405_x_at			actinin, alpha 2	ACTN2	1042-043	
205002_5_00	-1.000	-2,11043007	Microfibrillar-associated protein		1412 413	
214588_s_at	-1 081	-2,11550193		MFAP3	5q32-q33.2	
<u></u>	1-1.001	2,11000100	·····		5452 45512	signal transduction /// G-protein
			G-protein signalling modulator			coupled receptor protein signaling
221922_at	-1.065	-2.09216988	2 (AGS3-like, C. elegans)	GPSM2	1p13.3	pathway
	+		CDNA done IMAGE:4152983,			
214803_at	-1.055	-2,07771821	· · · ·			
	1.000				1	proteolysis and pepudolysis ///
						phosphate transport /// induction of
						apoptosis /// caspase activation /// cell
•				•		adhesion /// cell surface receptor linked
1						signal transduction /// perception of
T			collagen, type IV, alpha 3			sound /// circulation /// cell
216896_at	-1.045	-2.06336636	(Goodpasture antigen)	COL4A3	2q36-q37	proliferation /// negative regul
		1	uroporphyrinogen			<u> </u>
222074_at	-1.028	-2,03919537	decarboxylase	UROD	1p34	heme biosynthesis
	1		<b>i</b> , <u>-</u> -			transcription /// regulation of
						transcription, DNA-dependent ///
205906_at	-1.028	-2,03919537	forkhead box J1	FOXJ1	17q22-17q25	spermatogenesis
						ossification /// cell adhesion ///
221681_s_at	-1.019	-2,0265138	dentin sialophosphoprotein	DSPP	4q21. <u>3</u>	development /// perception of sound
						coll mide checkesist (// DNA roppin ///
1						cell cycle checkpoint /// DNA repair ///
l	ļ				Į.	regulation of transcription from RNA
						polymerase II promoter /// regulation
						of transcription from RNA polymerase
1						III promoter /// DNA damage response,
						signal transduction by p53 class
204531_s_at			breast cancer 1, early onset	BRCA1	17q21	mediator resulting in transcrip
204414_at	-1.004	-2,00555287				
217688_at	-1.002	-2,00277451				

Tab. A3b:

Probe-sets down-regulated regulated upon IVIG treatment at day 6 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients;

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Tab.	A3c
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	log2				Chromosoma	. GO Biological Process Description
Probe Set)ID	Change)	Fold Change	GeneiTitie	Gene Symbol	Location	GO Biological Process Description
220178_at	2.091		chromosome 19 open reading frame 28 UDP-Gal:betaGicNAc beta	C19orf28	19p13.3	
217452_s_at	1.768	3,40581483	1,3-galactosyltransferase, polypeptide 2	B3GALT2	1q31	protein amino acid glycosylation
215554_at	1.738	3,33572418	glycosylphosphatidylinositol specific phospholipase D1 DEAH (Asp-Glu-Ala-His)	GPLD1	6p22.3-p22.2	cell-matrix adhesion
204816_s_at	1.607	3,04617748	box polypeptide 34	DHX34	19q13.3	electron transport
<u>215200_x_at</u> 206863_x_at		2,97316597	Villin 2 (ezrin)	VIL2	6q25.2-q26	cellular morphogenesis /// cytoskeletal anchoring
			chromosome 14 open			· · · · · · · · · · · · · · · · · · ·
220084_at 214676_x_at	1.514	2,85600796	reading frame 105	C14orf105 MUC3B	14q22.3 7q22	
214070_A_at	1.5	2,02042112	Clone 23555 mRNA		/422	
213904_at	1.498	2,82450881	sequence			
208580_x_at	1.447	2,72640521	1, H4j	HIST1H4K /// HIST1H4J	6р22-р21.3	
214126_at	1.404	2,64634288	Mitochondrial carrier triple repeat 1	MCART1	9p13.3-p12	transport
217539_at	1.402	2,64267681	chromosome 18 open reading frame 25	C18orf25	18q21.1	
202563_at	1.38		chromosome 14 open reading frame 1	C14orf1	·	sterol biosynthesis
221233_s_at			KIAA1411 /// KIAA1411	KIAA1411	14q24.3 6q12-q13	
220077_at	1.353	2,55442752	hypothetical protein FLJ22349	FL)22349	22q13.2	 nucleosome assembly ///
208546_x_at	1.343	2,5367828	histone 1, H2bh	HIST1H2BH	6p21.3	nucleosome assembly /// chromosome organization and biogenesis (sensu Eukaryota)
			hypothetical protein			
220411_x_at 203806_s_at			Fanconi anemia, complementation group A /// Fanconi anemia,	FLJ23447 FANCA		DNA repair /// protein complex
216740_at	1.327	2,50880441	Transcriptional regulating factor 1	TRERF1		regulation or transcription, DNA- dependent /// steroid biosynthesis /// cholesterol catabolism /// development /// homeostasis /// positive regulation of transcription, DNA-dependent /// regulation of hormone biosynthesis
214133_at	1.325		mucin 6, gastric cation channel, sperm	MUC6	p15.4	
217588_at	1.323	2,50185816	•••	CATSPER2	15q14	cation transport
206423_at	1.307		angiopoietin-like 7 A kinase (PRKA) anchor	ANGPTL7	1р36.3-р36.2	response to oxidative stress
213516_at	1.299	2,46058269	· · ·	AKAP13	15q24-q25	intracellular signaling cascade blood coagulation /// regulation of
205649_s_at		2,44697608			4q28	blood pressure /// positive regulation of cell proliferation
	1.29 1.283	2,44528056 2,43344472	Hypothetical protein	 MGC11061	 2p22.3	
	1.277		embryonal Fyn-associated		· ·	regulation of cell cycle /// glycolysis cell adhesion /// intracellular
10880_s_at	<u>1.271</u> 1.27	2,41328784				signaling cascade
17363_x_at		2,41161566				

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202837_at	1.258	2,39163959	FLN29 gene product	FLN29	12q	
206366_x_at		2,3817137	chemokine (C motif) ligand	XCL2	1g23-g25	chemotaxis /// immune response /// signal transduction /// cell-cell signaling /// sensory perception /// circulation
204026 -+	4.000		mitogen-activated protein kinase kinase kinase kinase			protein amino acid phosphorylation /// vesicle targeting /// response to stress /// immune response /// protein kinase cascade /// JNK
204936_at 205223_at	1.232	2,34892394	DEP domain containing 5	MAP4K2 DEPDC5	11q13 22q12.3	cascade /// hemocyte development intracellular signaling cascade
212478_at	1.226	2,33917533	hypothetical protein FLJ13910	FLJ13910	2p11.2	
215759_at	1.219	2,32785307		FLJ12056	2p13.3	
			glucocorticoid modulatory	0.150.		
220938_s_at 214692_s_at	1.211		element binding protein 1 jerky homolog (mouse)	GMEB1 JRK	1p35.3 8q24.3	
204896_s_at			prostaglandin E receptor 4 (subtype EP4)	PTGER4	5p13.1	immune response /// signal transduction /// G-protein coupled receptor protein signaling pathway /// G-protein signaling, coupled to cAMP nucleotide second messenger
203759_at	1.189	2,27994655	ST3 beta-galactoside alpha- 2,3-sialyltransferase 4	ST3GAL4	11q23-q24	protein amino acid glycosylation
010066 c -+		0.00457465		1004	18q11.2-	transport /// neurogenesis ///
210066_s_at	1.16	2,23457428	aquaporin 4	AQP4	q12.1	excretion
215942_s_at	1.153	2,22375832	G-2 and S-phase expressed 1	GTSE1	22q13.2- q13.3	G2 phase of mitotic cell cycle /// DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest /// microtubule-based process
210960_at	1.136	2,19770844	adrenergic, alpha-1D-, receptor	ADRA1D	20p13	DNA metabolism /// signal transduction /// G-protein coupled receptor protein signaling pathway /// G-protein signaling, coupled to cAMP nucleotide second messenger /// cell-cell signaling /// development /// cell proliferation /// positive regulation of
204643_s_at	1.133	2,19314318	cytosolic ovarian carcinoma antigen 1	COVA1	Xq25-q26.2	regulation of cell growth /// electron transport /// transport /// ultradian rhythm
205056_s_at	<u>1.129</u>		gene rich cluster, A gene lectin, mannose-binding, 1	GRCA	12p13	G-protein coupled receptor protein signaling pathway /// protein metabolism
20420_at	1.125	2,18101547		LMAN1L	15q24.1	
04811_s_at	1.117	2,16895482	dependent, alpha 2/delta	CACNA2D2	3p21.3	ion transport /// calcium ion transport autophagic vacuole formation ///
04833_at	1.113		APG12 autophagy 12-like (S. cerevisiae)	APG12L	5q21-q22	ubiquitin cycle /// autophagy /// apoptosis
07557_s_at	1.109	2,15696086		RYR2	1q42.1-q43	cation transport /// calcium ion transport /// calcium ion homeostasis /// muscle contraction /// signal transduction /// regulation of heart contraction rate
11259_s_at		2,13317156		BMP7	20q13	skeletal development /// cell differentiation /// growth
08324_at '	1.087	2,12431837				
09299_x_at 1	1.086		peptidylprolyl isomerase (cyclophilin)-like 2	PPIL2	22q11.21	protein folding

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216258_s_at	1.065	2,09216988	serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 13	SERPINB13	18q21.3-q22	response to UV /// regulation of proteolysis and peptidolysis
						double-strand break repair via homologous recombination /// double-strand break repair via homologous recombination /// DNA unwinding /// DNA unwinding ///
			RAD51 homolog (RecA			DNA repair /// mitotic recombination
			homolog, E. coli) (S.	ľ		/// meiosis /// meiotic
205024_s_at	1 065	2,09216988		RAD51	15q15.1	recombination /// positive regulation
20502 1_5_00	1.000	2,002,0000	chromosome 4 open			
214123_s_at	1.058	2,0820432	reading frame 10	C4orf10	4p16.3	
			amyloid beta precursor		<u> </u>	
			protein (cytoplasmic tail)			
215402_at	1.055	2,07771821	binding protein 2	APPBP2	17q21-q23	intracellular protein transport
	[		daudin 5 (transmembrane			
			protein deleted in			calcium-independent cell-cell
204482_at	1.054	2,07627854	1*	CLDN5	22q11.21	adhesion
			······································	1	<u>                                       </u>	protein folding /// endocytosis ///
215624_at	1.051	2,07196553	Tuberous sclerosis 2	TSC2	16p13.3	negative regulation of cell cycle
			PLSC domain containing			
215409_at	1.05	2,07052985	SH3 and multiple ankyrin	LOC254531	15q14	metabolism
215830_at	1.05	2.07052095	repeat domains 2	SHANK2	11q13.3- q13.4	intracellular signaling cascade
213030_80	1.05	2,07052965		JIANKZ	<u>413.4</u>	indiacendial signaling cascade
214520 v at	1.047	0.00000070	erythrocyte membrane protein band 4.1	50041	1-22 -22	circulation /// cortical actin cytoskeleton organization and
214530_x_at	1.047	2,06622878	(elliptocytosis 1, RH-linked)	EPB41	1p33-p32	biogenesis cytoskeletal anchoring ///
			spectrin, beta, non-			cytoskeletal anchoring /// vesicle- mediated transport /// vesicle-
220185_at	1.034	2,0476938	erythrocytic 4	SPTBN4	19q13.13	mediated transport
222250+	4 000	0.04405700	SH3-domain binding protein	CU2004	2-274 -27.2	
222258_s_at 206595_at	1.032	2,04485706	cystatin E/M	SH3BP4 CST6	11q13	endocytosis /// cell cycle morphogenesis
200333_at	1.020	2,03919337	chromosome 14 open		11415	
219203_at	1.027	2.03778239	reading frame 122	C14orf122	14q11.2	
			mevalonate kinase			protein amino acid phosphorylation /// cholesterol biosynthesis ///
204056_s_at	1.025		(mevalonic aciduria) Bernardinelli-Seip	МУК	12q24	isoprenoid biosynthesis
				BSCL2 ///		
				DKFZp762N1	11q12-q13.5	
208906_at	1.019		protein DKFZp762N1910	910	/// 11q12.3	
			caspase 2, apoptosis- related cysteine protease			proteolysis and peptidolysis ///
			(neural precursor cell			proteolysis and peptidolysis /// anti-
			expressed, developmentally			apoptosis /// apoptotic program ///
211140_s_at	1.017		down-regulated 2)	CASP2	7q34-q35	regulation of apoptosis
			serine			glycine metabolism /// L-serine
24.4005			hydroxymethyltransferase 2			metabolism /// one-carbon
214095_at	1.013	2,01810327	(mitochondrial)	SHMT2	12q12-q14	compound metabolism
206175_x_at	1 000	2 01251555	zinc finger protein 222	ZNF222	19q13.2	transcription /// regulation of transcription, DNA-dependent
2001/J_A_dt	1.009	2,01201000	cyclin-dependent kinase	-111 222	1.541.5.2	cell cycle /// cell cycle arrest ///
			inhibitor 2C (p18, inhibits			negative regulation of cell
211792_s_at	1.003	2,00416321		CDKN2C	1p32	proliferation

Tab. A3c:

Probe-sets up-regulated regulated upon IVIG treatment at day 21 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients;

Prohe Set II	(fold	Fold	Gene Title	Gene Symbo	Chromosoma	P GO Biological Process Description
Probe Secul	Unange		NADH dehydrogenase (ubiguinone) 1	Gene Symbo	Taki Locauon /	Process Description
215850_s_at	-1.962	-3,89601707	alpha subcomplex, 5, 13kDa	NDUFA5	7q32	electron transport
	1	1				chemotaxis /// inflammatory response /// signal
	ļ					transduction /// cell-cell signaling /// positive
207852_at	-1.741		chemokine (C-X-C motif) ligand 5	locas	4q12-q13	regulation of cell proliferation
219780_at	-1.739	-3,33803712	2 mesenchymal stem cell protein DSC43	LOC51333	16p11.2	
						regulation of mitotic recombination /// double-stra break repair via nonhomologous end-joining ///
	ļ		MRE11 meiotic recombination 11 homolog			telomerase-dependent telomere maintenance ///
211334_at	-1.636	-3 10802908	A (S. cerevisiae)	MRE11A	11g21	meiosis /// meiotic recombination
211551_00	1-1.000	-0,10002300	elongation of very long chain fatty acids		11421	
213712_at	-1.592	-3.01466982	(FEN1/Elo2, SUR4/Elo3, yeast)-like 2	ELOVL2	6p24.1	fatty acid biosynthesis
216003_at	-1.519		CMT1A duplicated region transcript 1	CDRT1	17p12	
			natriuretic peptide receptor C/guanylate		1	
			cyclase C (atrionatriuretic peptide receptor			
219789_at	-1.511	-2,85007523		NPR3	5p14-p13	skeletal development
216948_at_	-1.483	-2,79529394			<u> </u>	
						transcription /// regulation of transcription, DNA-
219312_s_at	-1.464	-2,75872184	zinc finger and BTB domain containing 10	ZBTB10	8q13-q21.1	dependent
			1	]	ļ	protein amino acid dephosphorylation /// protein
215793_at	-1.458	2 74707047	myotubularin related protein 7	MTMP7	8022	amino acid dephosphorylation /// cell cycle /// phospholipid dephosphorylation
15/93_at	-1.458		BMP2 inducible kinase	MTMR7 BMP2K	8p22 4q21.21	prospholipid deprosphorylation
at	1.432	1-2,1330/001			17421.21	
					1	regulation of transcription, DNA-dependent ///
				ł		regulation of transcription, DNA-dependent /// sig
				ſ		transduction /// cell growth /// estrogen receptor
211627_x_at	-1.442	-2,71697257	estrogen receptor 1 /// estrogen receptor 1	ESR1	6q25.1	signaling pathway /// negative regulation of mitos
05151_s_at	-1.441		KIAA0644 gene product	KIAA0644	7p15.1	
		1				ion transport /// chloride transport /// cell surface
						receptor linked signal transduction /// synaptic
07462_at	-1.44	-2,71320865	glycine receptor, alpha 2	GLRA2	Xp22.1-p21.3	
		1				vesicle docking during exocytosis /// protein
22246_at	-1.427	-2,68886999	Syntaxin binding protein 3	STXBP3	1p13.3	transport /// vesicle-mediated transport
05030 -1	1				Xp11.22-	cell adhesion /// homophilic cell adhesion /// emb
05028_at	-1.405	-2,64817782		TRO	p11.21	implantation
21136_at	-1.381	-2,00448838	growth differentiation factor 2 a disintegrin and metalloproteinase domain	GDF2	10q11.22	growth
11238_at	-1.371	-2,58649786		ADAM7	8p21.2	proteolysis and peptidolysis
.112.30_at	-1.571	-2,30049700	proprotein convertase subtilisin/kexin type			
10553_x_at	-1.356	-2,55974483		PCSK6	15q26.3	proteolysis and peptidolysis /// cell-cell signaling
			hydroxy-delta-5-steroid dehydrogenase, 3			
06294_at	-1.343	-2,5367828	beta- and steroid delta-isomerase 2	HSD382	1p13.1	C21-steroid hormone biosynthesis
16634_at	-1.336	-2,52450406	phospholipase C-like 3	PLCL3	3q25.31	lipid metabolism /// intracellular signaling cascade
16419_at	-1.329		ciliary rootlet coiled-coil, rootletin	CROCC	1pter-p36.11	
06344_at	-1.325	-2,50532888	paraoxonase 1	PON1	7g21.3	response to external stimulus
			notactium voltage, gated channel. Ick		21q22.1-	ion transport /// potassium ion transport /// musc
08514_at	-1.324	2 50250202	potassium voltage-gated channel, Isk- related family, member 1	KCNE1		contraction /// perception of sound /// regulation
00314_0	-1.524	-2,30335252	related ranking, member 1	NUNEI	12	heart contraction rate chemotaxis /// inflammatory response /// G-prote
						coupled receptor protein signaling pathway ///
07850_at	-1.297	-2 45717396	chemokine (C-X-C motif) ligand 3	aas	4q21	sensory perception
	1.201	2,101 11000	tachykinin, precursor 1 (substance K,	0.00	1921	tachykinin signaling pathway /// neuropeptide
			substance P, neurokinin 1, neurokinin 2,			signaling pathway /// cell-cell signaling /// synapt
			neuromedin L, neurokinin alpha,			transmission /// insemination /// detection of abio
06552_s_at	-1.296	-2,45547137	neuropeptide K, neuropeptide gamma)	TAC1	7q21-q22	stimulus
						regulation of cell cycle /// transmembrane receptor
						protein tyrosine phosphatase signaling pathway /
			pleiotrophin (heparin binding growth factor			neurogenesis /// cell proliferation /// positive
)9465_x_at	-1.281	-2,43007358		PTN	7q33-q34	regulation of cell proliferation
	4 000	2 40007 170	solute carrier family 15 (H+/peptide	ci ci ci ci c		han an an 111 attack and the house of
05317_s_at	-1.208	-2,40827476	transporter), member 2	SLC15A2	3q13.33	transport /// oligopeptide transport signal transduction /// G-protein signaling, couple
						to IP3 second messenger (phospholipase C
)7333_at	-1.259	2 30320702	neuromedin B receptor	NMBR	6q21-qter	activating)
10429_at	-1.255		Rhesus blood group, D antigen	RHD	1p36.11	
9984_s_at			HRAS-like suppressor	HRASLS	3q29	
		2,00044000			16q22.3-	regulation of transcription, DNA-dependent ///
08033_s_at	-1.231	-2,34729636	AT-binding transcription factor 1	ATBF1		transcription from RNA polymerase II promoter
			Similar to Hypothetical zinc finger protein			
2135_at	-1.228	-2,34242036	KIAA1956		19q13.43	
20180_at	-1.218			SE57-1	18q21	
						cell-matrix adhesion /// integrin-mediated signalir
	-1.216			ITGB5	3q21.2	pathway /// development
	-1.214	-2,31979931		GPC5	13q32	
.1353_at	-1.213			LRRC21	10q23	
Π.			transcription factor AP-2 beta (activating			transcription /// regulation of transcription from R
4451_at	-1.212			TFAP28		polymerase II promoter /// neurogenesis
			solute carrier family 22 (organic cation			ion transport /// sodium ion transport /// organic
7201_s_at			transporter), member 1	SLC22A1	6q26	cation transport

	-1.009		transmembrane protein with EGF-like and two follistatin-like domains 1	TMEFF1	9q31	
20425_x_at 16420_at	-1.018 -1.015	-2,02510961		ROPN1B	3q21.2	membrane /// cell-cell adhesion /// sperm motility
						cytokinesis /// signal transduction /// Rho protein signal transduction /// spermatogenesis /// acrosome reaction /// fusion of sperm to egg plasm
14590_s_at	-1.018		ubiquitin-conjugating enzyme E2D 1 (UBC4/5 homolog, yeast)	UBE2D1	10q11.2-q21	ubiquitin-dependent protein catabolism /// ubiquitin cycle
20471_s_at		-2,03495938	myc target 1	MYCT1	6q25.2	
03499_at	-1.028		EPH receptor A2	EPHA2	1p36	protein amino acid phosphorylation /// signal transduction /// transmembrane receptor protein tyrosine kinase signaling pathway /// development
16801_at	-1.03	-2,04202425	/// hypothetical gene supported by BC033316	/// LOC <u>440</u> 572	1p36.13	•••
	- 1.032		hypothetical gene supported by BC033316	LOC400742	A420	
<u>09437_s_at</u> 06609_at	-1.038		spondin 1, extracellular matrix protein melanoma antigen family C, 1	SPON1 MAGEC1	11p15.2 Xq26	cell adhesion /// development
16132_at	-1.045	-2,06336636	Astrotactin 2	ASTN2	9q33.1	
10359_at	-1.066	-2 09362056	metastasis suppressor 1	MTSS1	8p22	cell mobility /// cell cycle /// cell adhesion /// transmembrane receptor protein tyrosine kinase signaling pathway /// neurogenesis /// muscle development /// microspike biogenesis /// actin cytoskeleton organization and biogenesis /// negative regulatio
05754_at	-1.067	-2,09507225	coagulation factor II (thrombin)	F2	11p11-q12	regulation of cell cycle /// proteolysis and peptidolysis /// apoptosis /// caspase activation /// acute-phase response /// tyrosine phosphorylation of STAT protein /// STAT protein nuclear translocation /// development /// response to wounding /// platel
205962_at	-1.067	-2,09507225	p21 (CDKN1A)-activated kinase 2	PAK2	3q29	protein amino acid phosphorylation /// protein amino acid phosphorylation /// negative regulation of protein kinase activity /// signal transduction
210702_s_at	-1.069	-2,09797866	prostaglandin I2 (prostacyclin) synthase	PTGIS	20q13.13	lipid metabolism /// fatty acid biosynthesis
203431_s_at			Rho GTPase-activating protein	RICS	11q24-q25	 prostaglandin biosynthesis /// electron transport /
<u>11831_s_at</u> 16782_at	-1.076	-2,10818285	factor) Potassium inwardly-rectifying channel, subfamily J, member 15	THPO KCNJ15	<u>3q27</u> 21q22.2	development /// cell proliferation
			thrombopoietin (myeloproliferative leukemia virus oncogene ligand, megakaryocyte growth and development			
209612_s_at	-1.078	-2,11110744		ADH1B	4q21-q23	ethanol oxidation
214360 <u>at</u>	-1.079	-2,11257125	dependent regulator of chromatin, subfamily a, member 4	SMARCA4	19p13.2	transcription /// regulation of transcription from R polymerase II promoter
211223_at	-1.09	-2,12874036	transcription factor SWI/SNF related, matrix associated, actin	PROP1	5q35.3	central nervous system development
210364_at	-1.091	-2,13021641		SCN2B	11q23	transmission regulation of transcription, DNA-dependent ///
204591_at	-1.104	-2,14949835	L1CAM (close homolog of L1) sodium channel, voltage-gated, type II,	CHL1	3p26.1	cell adhesion /// signal transduction ion transport /// sodium ion transport /// synaptic
209590_at	-1.107	-2,15397275	protein 1) cell adhesion molecule with homology to	BMP7	20q13	growth
205085_at	-1.107	-2,15397275	Bone morphogenetic protein 7 (osteogenic	ORC1L	1p32	DNA replication /// DNA replication initiation skeletal development /// cell differentiation ///
			origin recognition complex, subunit 1-like	<u> </u>	1	
215311_at	-1.125		MRNA full length insert cDNA clone EUROIMAGE 21920			
206104 at	-1.132	1	ISL1 transcription factor, LIM/homeodomain, (islet-1)	ISL1	5q11.2	regulation of transcription, DNA-dependent /// development
205517_at 213991_s_a	-1.144 t -1.138	1	GATA binding protein 4 Heparan sulfate (glucosamine) 3-O- sulfotransferase 1	GATA4	8p23.1-p22 4p16	of trans
						transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// development /// heart development /// positive regulation of transcription, DNA-dependent /// positive regulation
208028_s_a	t -1.158	-2,23147864	androgen-related protein)	GPX5	6p22.1	lipid metabolism /// response to oxidative stress transcription /// transcription /// regulation or
205360_at	-1.158	-2,23147864	prefoldin 4 Jalutathione peroxidase 5 (epididymal	PFDN4	20q13.2	folding
217504_at	-1.159	-2,23302592		ABCA6	17q24.3	transport protein folding /// chaperonin-mediated tubulin
219859_at 216225_at	-1.174		C-type lectin domain family 4, member E Anthrax toxin receptor 1 ATP-binding cassette, sub-family A (ABC1),	CLEC4E ANTXR1	12p13.31 2p13.1	immune response /// antimicrobial humoral response (sensu Vertebrata)
47550_at 216577_at	-1.204	-2,30377528	leucine zipper, putative tumor suppressor	LZTS1	8p22	celi cycle

,

						neuropeptide signaling pathway /// synaptic
206803_at	-1.007	-2,00972764	prodynorphin	PDYN	20pter-p12	transmission
			X-ray repair complementing defective			DNA repair /// double-strand break repair /// DNA
205072_s_at	-1.004	-2,00555287	repair in Chinese hamster cells 4	XRCC4	5q13-q14	recombination /// DNA recombination

Tab. A3d: Probe-sets down-regulated regulated upon IVIG treatment at day 21 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients;

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Tab. A3e

Tab. A3e				<u></u>		
Probe Set ID	fold 3	Fold Change	1 d'in Gene Title	Gene Symbol	Chromosoma LLocation	GO Biological Process Description
						/// steroid biosynthesis /// cholesterol catabolism /// development /// homeostasis /// positive regulation of transcription, DNA-
216740_at	2.129	4,37414183	Transcriptional regulating factor 1	TRERF1	6p21.1-p12.1	dependent /// regulation of hormone biosynthesis
						regulation of transcription from RNA polymerase II promoter /// regulation of
						transcription from RNA polymerase III promoter /// DNA damage response, signal transduction by p53 class mediator resulting
204531_s_at 204414_at	1.947 1.823	3,85571923 3,53816174	breast cancer 1, early onset	BRCA1	17q21 	in transcrip 
222258_s_at	1.816	3,52103605	SH3-domain binding protein 4	SH3BP4	2q37.1-q37.2	endocytosis /// cell cycle
215554_at	1.748		glycosylphosphatidylinositol specific phospholipase D1	GPLD1		cell-matrix adhesion
220258_s_at			hypothetical protein FLJ10385	FL)10385	17p13.1	•••
214019_at	1.631	3,09727611				
			tubulin tyrosine ligase-like			
203702_s_at	1.558	2,94445372	family, member 4	ΠЦ4	•	protein modification chemotaxis /// immune response /// signal transduction /// cell-cell signaling ///
206366_x_at	1.542	2,9119791	chemokine (C motif) ligand 2 [serine (or cysteine) proteinase	xci.2	1q23-q25	sensory perception /// circulation
216258_s_at	1 524	2 90597624	inhibitor, clade B (ovalbumin), member 13	SERPINB13	18021 3-022	response to UV /// regulation of proteolysis and peptidolysis
222202_at	1.518		CDNA FLJ14293 fis, done PLACE1007866			
222202_al	1.310	2,00393740	PLACE1007800		18q11.2-	
210066_s_at	1.493	2,81473675	aquaporin 4 UDP-Gal:betaGlcNAc beta 1,3-	AQP4	q12.1	transport /// neurogenesis /// excretion
217452_s_at	1.469	2,76829943	galactosyltransferase, polypeptide 2	B3GALT2	1q31	protein amino acid glycosylation
212396_s_at	1.467	2,76446441	KIAA0090	KIAA0090	1p36.13	
204936_at	1.42	2.67585511	mitogen-activated protein kinase kinase kinase kinase 2	MAP4K2	11q13	protein amino acid phosphorylation /// vesicle targeting /// response to stress /// immune response /// protein kinase cascade /// JNK cascade /// hemocyte development
		-				
222074_at	1.408		uroporphyrinogen decarboxylase chromosome 14 open reading		1p34	heme biosynthesis
	1.38		Solute carrier family 26, member			transport /// anion transport /// excretion
	1.376	2,59547753	3	SLC26A3	7q31	/// sulfate transport
221487_s_at	1.355	2,55797116		ENSA	1q21.2	transport /// response to nutrients
			SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily			transcription /// regulation of transcription, DNA-dependent /// regulation of transcription from RNA polymerase II
212258_s_at	1.313	2,48457656	a, member 2	SMARCA2	9p22.3	promoter /// cell cycle
			prostaglandin E receptor 4			immune response /// signal transduction /// G-protein coupled receptor protein signaling pathway /// G-protein signaling, coupled to
204896_s_at	1.304	2,46912521	(subtype EP4)	PTGER4	5p13.1	cAMP nucleotide second messenger
214126_at	1.294	2,45206972	Mitochondrial carrier triple repeat	MCART1	9р13.3-р12	transport
217 <u>566_s_at</u>	1.279	2,42670712	transglutaminase 4 (prostate)	TGM4	3p22-p21.33	peptide cross-linking /// protein amino acid polyamination protein amino acid phosphorylation ///
207228_at	1.269		protein kinase, cAMP-dependent, catalytic, gamma		9q13	spermatogenesis /// male gonad development
201961_s_at	1.257	2,38998241			12q13.2- q13.3	protein ubiquitination
			killer cell immunoglobulin-like			
			receptor, two domains, short			

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			Bernardinelli-Seip congenital		1	
		•	lipodystrophy 2 (seipin) ///	BSCL2 ///		
			hypothetical protein	DKFZp762N1	1	
208906_at	1.244	2,36854322	DKFZp762N1910	910	/// 11q12.3	
			caspase 2, apoptosis-related			
			cysteine protease (neural			proteolysis and peptidolysis /// proteolysis
			precursor cell expressed,			and peptidolysis /// anti-apoptosis ///
			developmentally down-regulated			apoptotic program /// regulation of
211140_s_at	1 229	2,34404457	· · ·	CASP2	7q34-q35	apoptosis
211110_3_00	1.223	2,04404437	z,		1/45/455	proteolysis and pepudolysis /// phosphate
216896_at	1.159		collagen, type IV, alpha 3 (Goodpasture antigen)	COL4A3	2q36-q37	transport /// induction of apoptosis /// caspase activation /// cell adhesion /// cell surface receptor linked signal transduction /// perception of sound /// circulation /// ce proliferation /// negative regul
217082_at	1.158	2,23147864	Unknown protein			
214160_at	1.158	2,23147864				
			Mesenchymal stem cell protein	1		
221968_s_at	1.138	2,20075722	DSC43	LOC51333	16p11.2	
		+ <u>-,</u>	+		1p36.12	······································
214579_at	1.128	2 18555540	hypothetical protein dJ462O23.2	C 55059410		
2143/9_dL	1.120	2,10000048	chromosome 14 open reading	05102023.2	1,22.1	
202563_at	1.121	2,17497678	Irrame 1	C14orf1	14q24.3	sterol biosynthesis
			potassium channel, subfamily K,			
220448_at	1.114	2,16444929	member 12	KCNK12	2p22-p21	ion transport /// potassium ion transport
214507_s_at	1.109	2,15696086	exosome component 2	EXOSC2	9q34	rRNA processing
220070_at	1.099		hypothetical protein FLJ13798	FLJ13798	16p12.1	
203862_s_at			actinin, alpha 2	ACTN2	1q42-q43	
200002_0_0	1.030	2,10011100	phosphatidylinositol 4-kinase		1912 913	
209346_s_at	1.09	2,12874036		PI4KII	10q24	phosphatidylinositol biosynthesis protein amino acid phosphorylation ///
			mevalonate kinase (mevalonic			cholesterol biosynthesis /// isoprenoid
204056_s_at	1.07	2,09943337		MVK	12q24	biosynthesis
			mitochondrial ribosomal protein			
218890_x_at	1.069	2,09797866	L35	MRPL35	2p11.2	
						nucleosome assembly /// nucleosome
						assembly /// chromosome organization and
208546_x_at	1 056	2 07015887	histone 1, H2bh	HIST1H2BH	6p21.3	biogenesis (sensu Eukaryota)
200340_x_at	1.000	2,07313007		112011	0021.5	
210415	4 055	0.07774.004	auton danas filma af anoun taila 3	0050	0-24.11	
210415_s_at	1.055	2,07771821	outer dense fiber of sperm tails 2	UDF2	9q34.11	
			erythrocyte membrane protein			
			band 4.1 (elliptocytosis 1, RH-			circulation /// cortical actin cytoskeleton
214530_x_at	1.048	2.06766147	linked)	EPB41	1p33-p32	organization and biogenesis
215645_at	1.046	2.06479707	Hypothetical protein MGC13008	FLCN	17p11.2	
		· · · · · · · · · · · · · · · · · · ·	······································			
			hypothetical protein FLJ12748 ///			
221713_s_at	1 030	2 05480280		FLJ12748	3q27.1	
	1.009		lysosomal associated protein			
			•			
			transmembrane 4 beta ///			
			lysosomal associated protein			
208029_s_at	1.037		transmembrane 4 beta	LAPTM4B	8q22.1	
			protein arginine N-			
219408_at	1.037	2,05195629	methyltransferase 7	PRMT7	16q22.1	
206863_x_at		2,03919537				
	1.025			LOC254531	15q14	metabolism
206519_x_at		2,02230416				
		2,02230410	CDNA FLJ12359 fis, clone			
	4 000	0.04054565				
215965_at	1.009	2,01251565	MAMMA1002355			
			chromosome 2 open reading			
15767_at	1.002	2,00277451	frame 10	C2orf10	2q32.1	
1			serine hydroxymethyltransferase			glycine metabolism /// L-serine metabolism
14095_at	1.002			SHMT2	12q12-q14	/// one-carbon compound metabolism
w. [		-,00211401				III ene consert compound mediconom

Tab. A3e: Probe-sets up-regulated regulated upon IVIG treatment at day 21 compared to day 6; Probe-sets have a minimum change of 2-fold in 100% of patients;

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1 10				10.19	Chromosoma Location	
Probe Set II	change)	Fold Change	collagen, type III, alpha 1 (Ehlers	Gerie Symbo	I FLocation :	GO Biological Process Description
	4.050		Danlos syndrome type IV,			
215076_s_at	-1.958	3,88522998	B autosomal dominant) FAT tumor suppressor homolog 2	COL3A1	2q31	phosphate transport /// circulation /// organogenesis
			(Drosophila) /// FAT tumor			
208153_s_at	-1.845	-3,59252949	suppressor homolog 2 (Drosophila)	FAT2	5q32-q33	cell adhesion /// homophilic cell adhesion
	1		DNA damage repair and	1		
215312_at	-1.836	-3,57018789	recombination protein RAD52			
			natriuretic peptide receptor C/quanylate cyclase C			
		1	(atrionatriuretic peptide receptor			
219789_at	-1.703	-3,25577274	<u>(</u> )	NPR3	5p14-p13	skeletal development
			early growth response 2 (Krox-20			transcription /// regulation of transcription, DNA-depender /// brain development /// peripheral nervous system
205249_at	-1.686		homolog, Drosophila)	EGR2	10q21.1	development /// mechanosensory behavior
213458_at	-1.62	-3,07375036	glycosylphosphatidylinositol	KIAA0974	10g22.2	
206265_s_at	-1.62	-3,07375036	specific phospholipase D1	GPLD1	6p22.3-p22.2	cell-matrix adhesion
				1	1	calcium ion homeostasis /// chemotaxis /// inflammatory response /// signal transduction /// cell-cell signaling ///
206407_s_at	-1.613	-3,05887256	chemokine (C-C motif) ligand 13	CQ 13	17q11.2	sensory perception
216474_x_at	-1 554	-2,93630127	tryptase alpha/beta 1 /// tryptase	TPSAB1 /// TPSB2	16p13.3	proteolysis and peptidolysis /// defense response /// proteolysis and peptidolysis
209819_at	-1.554		hyaluronan binding protein 4	HABP4	9q22.3-q31	
						chemotaxis /// inflammatory response /// signal transduction /// cell-cell signaling /// positive regulation of
207852_at	-1.546	-2,92006402	chemokine (C-X-C motif) ligand 5	aas	4q12-q13	cell proliferation
215013_s_at		-2,90996137	ubiquitin specific protease 34	USP34	2p15	ubiquitin-dependent protein catabolism /// ubiquitin cycle
220270_at	-1.521	-2,86989907	tudor domain containing 4	TDRD4	<u>13q12.12</u>	[ [regulation of transcription, DNA-dependent /// regulation c
						transcription, DNA-dependent /// signal transduction /// ce
211627_x_at	-1 494	-2,81668845	estrogen receptor 1 /// estrogen	ESR1	6q25.1	growth /// estrogen receptor signaling pathway /// negativ regulation of mitosis
	1.101	2,01000040	<b>·</b>		0423.1	
			thrombopoietin (myeloproliferative leukemia virus			
			oncogene ligand, megakaryocyte			
11154_at	-1.468	-2,76638126	growth and development factor)	THPO	3q27	development /// cell proliferation
14361_s_at	-1.441	-2,71508996	regulator of G-protein signalling	RGS12	4p16.3	signal transduction /// regulation of G-protein coupled receptor protein signaling pathway /// protein transport
20920_at	-1.44	-2,71320865	ATPase, Class V, type 10B	ATP10B	5q34	cation transport
21091_at	-1.414	-2,66474965	insulin-like 5	INSL5	1p31.1-p22.3	physiological process
16201		0.05004.000	CDNA: FLJ21586 fis, done			
16201_at	-1.411	-2,65921422	cytochrome P450, family 2,			
19903_s_at	-1.407	-2,65185152	subfamily C, polypeptide 8		10q23.33	electron transport /// electron transport /// transport
16206_x_at	-1.406	-2,65001403	mitogen-activated protein kinase kinase 7		19p13.3- p13.2	protein amino acid phosphorylation /// response to stress /// signal transduction
06446_s_at		-2,64084568	elastase 2A	ELA2A	1p36.21	proteolysis and peptidolysis
06414_s_at	-1 396	-2 63170905	development and differentiation enhancing factor 2	DDEF2	2p25 2p24	regulation of GTPase activity
			RNA binding protein with multiple			
07836_s_at	-1.376	-2,59547753	splicing	RBPMS	8p12-p11	RNA processing
						protein amino acid phosphorylation /// transmembrane
08222_at 04694_at	-1.342		activin A receptor, type IB alpha-fetoprotein		12q13 4q11-q13	receptor protein serine/threonine kinase signaling pathway
<u></u> dl	-1.34	-2,00101019	transcription factor AP-2 beta	AFP	-111-012	transport /// immune response
14451		0 50400070	(activating enhancer binding	TEADOD	C=21 =12	transcription /// regulation of transcription from RNA
14451_at 16329_at	-1.334 -1.331	-2,52100678	protein 2 beta)	TFAP2B 	6p21-p12	polymerase II promoter /// neurogenesis
			transglutaminase 2 (C			
01042_at	-1.327	-2.50880441	polypeptide, protein-glutamine- gamma-glutamyltransferase)	TGM2	20q12	G-protein coupled receptor protein signaling pathway /// peptide cross-linking /// positive regulation of cell adhesion
09866_s_at		-2,50532888	latrophilin 3		4q13.1	signal transduction /// neuropeptide signaling pathway
T	ſ		NADH dehydrogenase (ubiquinone) 1 alpha subcomplex,			
15850_s_at		-2,49320239	5, 13kDa	NDUFA5	7q32	electron transport
		-2,48974847	hydroxy-delta-5-steroid			
			dehydrogenase, 3 beta- and	ļ	Í	
06294_at	1 307		steroid delta-isomerase 2	HSD3B2	1p13.1	C21-steroid hormone biosynthesis
20382_s_at	1 286	-2,43851019	Rho GTPase activating protein 28	ARHGAP28	18p11.23	viral release
						vesicle docking during exocytosis /// protein transport ///
2246_at	1.262	-2,39827983	Syntaxin binding protein 3	STXBP3	1p13.3	vesicle-mediated transport

	[·····					
711774 6 -	1 226	2 22047522	ATP-binding cassette, sub-family	ARCR11	2024	transport
211224_s_at 205498_at	-1.226		B (MDR/TAP), member 11 growth hormone receptor	ABCB11 GHR	2q24 5p13-p12	transport skeletal development /// endocytosis /// growth
205953_at	-1.207	-2,30537269				
	1.200	2,00007200	/	í		cation transport /// calcium ion transport /// metabolism //
206043_s_at	-1.202	-2.30058379	KIAA0703 gene product	KIAA0703	16q24.1	proton transport
	1		syntrophin, beta 1 (dystrophin-	· · · · · · · · · · · · · · · · · · ·	1	
	1		associated protein A1, 59kDa,			
214708_at	-1.191	-2,28310941	basic component 1)	SNTB1	8q23-q24	muscle contraction
						regulation of cell growth /// regulation of cell growth ///
						proteolysis and peptidolysis /// proteolysis and peptidolysis
214689_at	-1.189		pappalysin 2	PAPPA2	1q23-q25	/// cell differentiation
222383_s_at			arachidonate lipoxygenase 3	ALOXE3	17p13.1	electron transport /// leukotriene biosynthesis
220223_at	-1.157	-2,22993244	hypothetical protein FLJ12735 solute carrier family 13 (sodium-	FU12735	17q11.2	protein folding
	1		dependent dicarboxylate			
207567_at	-1.153	2 22375832	transporter), member 2	SLC13A2	17p13.2	ion transport /// sodium ion transport
<u></u>	1-1.100	-2,2207 0002	ATPase, Ca++ transporting,	10010/02	17913.2	
215911_x_at	-1.148	-2,2160647	plasma membrane 3	ATP2B3	Xq28	cation transport /// calcium ion transport /// metabolism
220687_at	-1.144	-2,20992897				
214716_at	-1.141	-2,20533833	BMP2 inducible kinase	BMP2K	4q21.21	protein amino acid phosphorylation
			Patatin-like phospholipase	<u> </u>		
213862_at	-1.136	-2,19770844	domain containing 2	PNPLA2	11p15.5	
			fms-related tyrosine kinase 1	Į		angiogenesis /// protein amino acid phosphorylation ///
			(vascular endothelial growth	[		transmembrane receptor protein tyrosine kinase signaling
04405 -1		0.45005040	factor/vascular permeability	F1 T4	1.2.12	pathway /// pregnancy /// positive regulation of cell
204406_at	-1.111	-2,15995312	factor receptor) tissue factor pathway inhibitor	FLT1	13q12	proliferation /// cell differentiation
	1		(lipoprotein-associated			
209676_at	-1.109	-2 15696086	coagulation inhibitor)	TFPI	2q31-q32.1	blood coagulation
207834_at	-1.103	-2,14652057		FBLN1	22q13.31	chitin metabolism /// development
	1.102	2,14002007			122413.31	signal transduction /// G-protein signaling, coupled to IP3
207333_at	-1.101	-2,14503323	neuromedin B receptor	NMBR	6q21-qter	second messenger (phospholipase C activating)
206951_at	-1.098		histone 1, H4e	HIST1H4E	6p21.3	
		1	Dicer1, Dcr-1 homolog			RNA processing /// RNA interference, targeting of mRNA for
216280_s_at	-1.086	-2,12284642	(Drosophila)	DICER1	14q32.13	destruction
				1		regulation of cyclin dependent protein kinase activity /// G
				1		phase of mitotic cell cycle /// cell cycle /// cell cycle arrest
	4 005		cyclin-dependent kinase inhibitor	COVING 1	1.1-15 5	/// negative regulation of cell proliferation /// negative
219534_x_at 206609_at	-1.085		1C (p57, Kip2)	CDKN1C MAGEC1	11p15.5	regulation of cell cycle
19984_s_at			melanoma antigen family C, 1 HRAS-like suppressor	HRASLS	Xq26 3q29	
19901_3_80	-1.035	1-2,00340000			Juzz	regulation of mitotic recombination /// double-strand break
						repair via nonhomologous end-joining /// telomerase-
			MRE11 meiotic recombination 11	]		dependent telomere maintenance /// meiosis /// meiotic
11334_at	-1.057	-2,08060053	homolog A (S. cerevisiae)	MRE11A	11q21	recombination
			cadherin 5, type 2, VE-cadherin		1	
04677_at	-1.053	-2,07483987		CDH5	16q22.1	cell adhesion /// homophilic cell adhesion
			transportin 2 (importin 3,			
15844_at	-1.049	-2,06909516	karyopherin beta 2b)	TNPO2	19p13.13	protein-nucleus import, docking /// protein transport
			Development and differentiation			
15435_at	-1.035	-2,04911365	enhancing factor 1 solute carrier family 6	DDEF1	18q24.1-q24.2	regulation of GTPase activity
			(neurotransmitter transporter,		11p15.2-	
10810_s_at	1.03		alycine), member 5	SLC6A5	p15.1	neurotransmitter transport /// synaptic transmission
01616_s_at		-2,04202425	caldesmon 1	CALD1	7q33	muscle contraction // muscle development
01010_3_dl	-1.021	-2,03770239	solute carrier family 22 (organic		,,,,,,,	ion transport /// sodium ion transport /// organic cation
07201_s_at	-1.026	-2.0363704	cation transporter), member 1	SLC22A1	6q26	transport
		1 2,0000,04				cell-matrix adhesion /// integrin-mediated signaling pathwa
01124_at	-1.014	-2,0195026	integrin, beta 5	ITGB5	3q21.2	/// development
			chromosome X open reading		1	μι <u>ν</u>
22269_at	-1.011	-2,01530752	frame 33	CXorf33	Xq21.1	
	-1.007	0.00070704	Maternally expressed 3	MEG3	14q32	

Tab. A3f: Probe-sets down-regulated regulated upon IVIG treatment at day 21 compared to day 6; Probe-sets have a minimum change of 2-fold in 100% of patients;

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Probe Set ID	log2 FC	Fold Change	Gene Title	Gene	Chromosoma I Location	CO Biological Process Description
		<b>-</b>	leukocyte immunoglobulin-like receptor, subfamily A (without TM			<u>na na na kaominina dia kao</u>
210313_at	-3.526	-11,52	domain), member 4	1.17	19q13.4	immune response
215047_at	-3.282	-9,73	tripartite motif-containing 58	TRIM58		protein ubiquitination
207989_at	-2.775	-6,84			<del> -</del>	prostaglandin biosynthesis /// fatty acid
212187_x_at	-2.77	-6,82	prostaglandin D2 synthase 21kDa (brain) prostaglandin D2 synthase 21kDa	PTGDS	9q34.2-q34.3	biosynthesis /// transport /// regulation of circadian sleep/wake cycle, sleep prostaglandin biosynthesis /// fatty acid
211748_x_at	-2.466	-5,53	(brain) /// prostaglandin D2 synthase 21kDa (brain)	PTGDS	9g34.2-g34.3	biosynthesis /// transport /// regulation of circadian sleep/wake cycle, sleep
207781_s_at	-2.368	-5 18	zinc finger protein 6 (CMPX1)	ZNF6	Xq13-q21.1	regulation of transcription, DNA- dependent /// regulation of transcription
211812_s_at	-2.336		UDP-Gal:betaGicNAc beta 1,3- galactosyttransferase, polypepode 3	B3GALT	3q25	protein amino acid glycosylation
220803_at	-2.3		Associated molecule with the SH3 domain of STAM (AMSH) like protein	AMSH	10q23.31	
	-2.28		UDP-glucose ceramide			protein amino acid glycosylation ///
218801_at	-2.20	4,80	glucosyltransferase-like 2 OCR4-NOT transcription complex,	00002	13q32.1	posttranslational protein folding regulation of transcription, DNA- dependent /// regulation of global transcription from RNA polymerase II
210928_at	-2.258	-4,78	subunit 2	CNOT2	12q15	promoter
222258_s_at	-2.248	-4,75	SH3-domain binding protein 4	SH38P4	2q37.1-q37.2	endocytosis /// cell cycle cytokinesis /// microtubule-based
204444_at	-2.206	4,61	Idnesin family member 11	KIF11	10q24.1	movement /// cell cycle /// mitotic spindle organization and biogenesis regulation of transcription, DNA-
204525_at	-2.162	-4,48	PHD finger protein 14	PHF14	7p21.3	dependent
215613_at	-2.135	-4.39	A disintegrin and metalloproteinase domain 12 (metrin alpha)	ADAM12	10q26.3	proteolysis and peptidolysis /// cell adhesion /// myoblast fusion
19387_at	-2.132		KIAA1212	KIAA121		
19387_at 07744_at	-2.132	-4,38			2p16.3	
						ion transport /// potassium ion transport /// signal transduction /// synaptic
211520_s_at	-2.064		glutamate receptor, ionotropic, AMPA 1		5q33 5q31.1	transmission
213568_at	-2.055	4,18	odd-skipped related 2 (Drosophila)	OSR2	8q22.2	
203753_at	-2.036	4,10	transcription factor 4	TOF4	18q21.1	transcription from RNA polymerase II promoter
15695_s_at	-2.027		glycogenin 2	GYG2	Хр22.3	glycogen biosynthesis /// carbohydrate biosynthesis
						smooth muscle contraction /// Signal transduction /// positive regulation of cytosolic calcium ion concentration /// response to nutrients /// digestion ///
211174_s_at	-2.024	-4,07	cholecystokunin A receptor	COKAR	4p15.1-p15.2	feeding behavior chemotaxis /// cellular defense response
						(I) cholester of metabolism /// cell proliferation /// B-cell differentiation /// The proliferation /// B-cell differentiation /// The helper 2 type immune response /// connective tissue growth factor biosymthesis /// regulation of isotype
07539_s_at	-2.008	-4,02	interleukin 4	IL4	5q31.1	switching
13395_at	-1.994	-3,98	megalencephalic leukoencephalopathy with subcortical cysts 1	MLC1	22q13.33	protein biosynthesis /// ion transport
06637_at	-1.993		purinergic receptor P2Y, G-protein coupled, 14	P2RY14	3q21-g25_	signal transduction /// G-protein coupled receptor protein signaling pathway
04939_s_at	-1.993	-3,98	phospholamban	PLN	6q22.1	calcium ion transport /// muscle contraction /// circulation
09981 at	-1.973	.3 01	PNA-binding protein ningin	PTPPIN	22q13.2-	regulation of transcription, DNA- dependent /// mRNA processing /// bistone mRNA 3-end processing
09981_at		-3,83	RNA-binding protein pippin	PIPPIN		regulation of cyclin dependent protein
			cyclin-dependent kinase inhibitor 1C			regulation of cyclin dependent protein kinase activity /// G1 phase of mitotic cel cycle /// cell cycle /// cell cycle arrest /// negative regulation of cell protiferation
16894_x_at	-1.971			CDKNIC		negative regulation of cell protiferation /// negative regulation of cell cycle
			cyclin-dependent knase inhibitor 1C			regulation of cyclin dependent protein kinase activity /// G1 phase of mitotic cel cycle /// cell cycle /// cell cycle arrest /// negative regulation of cell proliferation
19534_x_at	-1.966	-3,91	(p57, Kip2)	CDKN1C	11p15.5	/// negative regulation of cell cycle
21062_at	-1.963			H\$35T3 B1	17p12-p11.2	heparan sulfate proteoglycan biosynthesis, enzymatic modification
09655_s_at	-1.96	-3,89	transmembrane protein 47	TMEM47	Xp11.4	<del></del>
14660_at	-1.957				5q11.2	protein biosynthesis regulation of transcription, DNA-
6623_x_at	-1.916	-3,77	trinucleotide repeat containing 9	TNRC9		dependent
6613_at	-1.914		MRNA; cDNA DKFZp566L0824 (from clone DKFZp566L0824)			_
5767_at	-1.911			C2orf10	2032.1	
)3443_at	-1.904			FL)3582	11q12.3	
						actylcholine catabolism in synaptic cleft /// DNA replication /// cell adhesion /// synaptogenesis /// muscle development /// cell protiferation /// response to wounding /// neurotransmitter catabolism /// amyfoid precursor protein
)5378_s_at	-1.89	-3,71	cetylcholinesterase (YT blood group)	ACHE	7q22	metabolism /// positiv cell adhesion /// homophilic cell adhesion
0572_at	-1.856	-3,62	protocadherin alpha 2	PCDHAZ	5q31	/// neurogenesis
						transcription /// regulation of

					T	angiogenesis /// transcription /// regulation of transcription, DNA- dependent /// transcription from RNA
200878_at 213426_s_at	-1.844 -1.799		endothelial PAS domain protein 1 caveolin 2	EPAS1 CAV2	2 <u>p21-p16</u> 7q31.1	polymerase II promoter /// signal transduction /// cell differentiation
216468_s_at			zinc finger protein 682	ZNF682		regulation of transcription, DNA- dependent
		•,••	wingless-type MMTV integration site			signal transduction /// frizzled-2 signalit pathway /// cell-cell signaling ///
205990_s_at	-1.778	-3,43	family, member 5A	WNTSA	3p21-p14 12p13.3-	morphogenesis intracellular protein transport /// protein
217757_at	-1.762	<u>-3</u> ,39	alpha-2-macroglobulin	A2M	p12.3	homooligomerization
219661_at	-1.761	-3,39	RAN binding protein 17	RANBP1 7	5q34	protein-nucleus import, docking /// protein transport
206065_s_at	-1.75		dihydropyrimidinase	DPYS	8q22	nucleobase, nucleoside, nucleotide and nucleic acid metabolism /// response to toxin
221086_s_at	-1.741		zinc finger protein 312		3p14.2	 transcription /// regulation of
204753 6 31	-1.732		hanstin to do in forma	HLF	17922	transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// development /// rhythmic
204753_s_at			hepatic leukemia factor			process branschpbon /// regulation of transcription, DNA-dependent /// regulation of transcription, DNA- dependent /// celi cycle /// chromatin
213966_at	-1.715	-3,28	High-mobility group 208	HMG208	19p13.3	modification regulation of cyclin dependent protein kinase activity /// G1 phase of mitotic of cycle /// cell cycle /// cell cycle arrest //
213182_x_at	-1. <b>696</b>	-3,24	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C	11p15.5	negative regulation of cell proliferation /// negative regulation of cell cycle
205533_s_at	-1.669		cadherin 6, type 2, K-cadherin (fetal kidney)	CDH6	5p15.1-p14	cell adhesion /// homophilic cell adhesio
216180_s_at	-1.667	-3,18	synaptojanin 2	SYNU2	6q25.3	
220774_at 221397_at	-1.661		dymeclin	DYM TAS2R1	18q12-q21.1	 signal transduction /// G-protein couplec receptor protein signaling pathway /// sensory perception /// perception of taste
210726_at	-1.647		cytochrome P450, family 3, subfamily A, polypeptide 4	Сурзая		electron transport /// lipid metabolism // xenobiotic metabolism /// xenobiotic metabolism /// transport
214702_at	-1.632	-3,10	fibronectin 1	FN1	2q34	acute-phase response /// cell adhesion /// metabolism /// response to woundin /// cell migration
220061_at	-1.615	-3,06	hypothetical protein FLJ20581	1 HISTIH	16p12.3	metabolism
207156_at	-1.614		histone 1, H2ag	2AG	6p22.1	
216291_at	-1.606	-3,04			-	 
220911_s_at	-1.599	-3,03	KIAA1305	5	14q11.2	DNA recombination cellular defense response /// cell surface
210228_at	-1.579		colony stimulating factor 2 (granulocyte-macrophage)	CSF2	5q31.1	receptor linked signal transduction /// development
216644_at 207481_at	-1.578	-2,99	CDNA FLJ20178 fis, clone COL09990	-	-	
210397_at	-1.57		defensin, beta 1	DEFB1	8p23.2-p23.1	response to pest, pathogen or parasite /// defense response to bacteria /// innate immune response /// innate immune response
216681_at	-1.561	-2,95	<b>—</b>	-	-	 transcription /// regulation of
222172_at	-1.559		neuronal PAS domain protein 3 FERM, RhoGEF (ARHGEF) and	NPAS3	14q12-q13	transcription, DNA-dependent /// signal transduction
201911_s_at	-1.557	-2,94	pleckstrin domain protein 1 (chondrocyte-derived)	FARP1	13q32.2	-
215105_at	-1.554		hypothetical gene CG030	CG030_	13q12-q13	
209544_at	-1.545	-2,92	kinase 2 tumor necrosis factor receptor	ripk2 TNFRSF	8q21	kinase/NF-kappaB cascade
218856_at	-1.54	-2,91	superfamily, member 21	21	6p21.1-12.2	apoptosis /// signal transduction
217400_at	-1.524		keratin 5 (epidermolysis bullosa simplex, Dowling-Meara/Kobner/Weber			
201820_at	-1.52		Cockayne types)	KRTS	12q12-q13	epidermis development
- T		-2,87	Cockayne types)			protein modification /// protein
201820_at 211412_at 222025_s_at	-1.52 -1.518 -1.518	-2,87 -2,86 -2,86	Cockayne types) peptidyl arginine deiminase, type IV S-oxoprolinase (ATP-hydrolysing)	PADI4	12q12-q13 1p36.13 8q24.3	protein modification /// protein modification 
211412_at	-1.518	-2,87 -2,88 -2,86 -2,84	Cockayne types) peptidyl arginine deiminase, type IV S-oxoprolinase (ATP-hydrolysing) WNT1 Inducible signaling pathway protein 1	PADI4 OPLAH	1p36.13	protein modification /// protein modification  regulation of cell growth /// cell adhesio /// signal transduction /// cell-cell signaling /// Wht receptor signaling
211412_at 22025_5_at 206796_at	-1.518 -1.518 -1.504	-2,87 -2,88 -2,88 -2,88	Cockayne types) peptidyl arginine deiminase, type IV S-oxoprolinase (ATP-hydrolysing) WNT1 Inducible signaling pathway protein 1 CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small	PADI4 OPLAH WISP1	1 <u>p36.13</u> 8q24.3 8q24.1-q24.3	protein modification /// protein modification  regulation of cell growth /// cell adhesio /// signal transduction /// cell-cell signaling /// Wht receptor signaling
211412_at 222025_s_at	-1.518 -1.518	-2,87 -2,86 -2,86 -2,86 -2,84 -2,80	Cockayne types) peptidyl arginine deiminase, type IV S-oxoprolinase (ATP-hydrohysing) WNT1 Inducible signaling pathway protein 1 CTD (carboxy-terminal domain, RNA polymerase II, polyneptide A) small phosphatase-like grantymie B (granzyme 2, cytotoxx 1- tymphocyte-associated serine esterase 1) /// granzyme B (granzyme 2,	PADI4 OPLAH	1 <u>p36.13</u> 8q24.3 8q24.1-q24.3	protein modification /// protein modification regulation of cell growth /// cell adhesion /// signal transduction /// cell-cell signaling /// Wnt receptor signaling pathway 
211412_at 22025_5_at 206796_at	-1.518 -1.518 -1.504	-2,87 -2,88 -2,88 -2,88 -2,84	Cockayne types) peptidyl arginine deiminase, type IV 5-oxoprolinase (ATP-thydrohysing) WNT1 Inducible signaling pathway protein 1 CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like grantyme B (granzyme 2, cytótoxic 1- ymphocyte-associated serine esterase	PADI4 OPLAH WISP1 CTDSPL	1 <u>p36.13</u> 8q24.3 8q24.1-q24.3	protein modification /// protein modification regulation of cell growth /// cell adhesio /// signal transduction /// cell-cell signaling /// Wnt receptor signaling pathway 
211412_at 222025_s_at 206796_at 201906_s_at	-1.518 -1.518 -1.504 -1.486	-2,87 -2,86 -2,86 -2,86 -2,86 -2,86 -2,80 -2,80	Cockayne types) peptidyl arginine deiminase, type IV S-oxoprolinase (ATP-hydrohysing) WNT1 Inducible signaling pathway protein 1 CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like grantyme B (granzyme 2, cytotoxic 1- ymphocyte-associated servine esterase 1) /// granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated servine esterase 1) sperm associated antigen 11	PADI4 OPLAH WISPI CTDSPL	1p36.13 8q24.3 8q24.1-q24.3 3p21.3	protein modification /// protein modification regulation of cell growth /// cell adhesio /// signal transduction /// cell-cell signaling /// Wnt receptor signaling pathway  proteolysis and peptidolysis /// apoptosis /// cleavage of lamin /// cytolysis
211412_at 22025_s_at 206796_at 201906_s_at 201906_s_at	-1.518 -1.519 -1.504 -1.486 -1.485	-2,87 -2,88 -2,88 -2,88 -2,80 -2,80 -2,80 -2,80	Cockayne types) peptidyl arginine deiminase, type IV S-oxoprolinase (ATP-hydrohysing) WNT1 Inducible signaling pathway protein 1 CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like grantyme B (granzyme 2, cytotoxic 1- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 1, cytotoxic T- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 1, cytotoxic T- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 1, cytotoxic T- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 1, cytotoxic T- ymphocyte-associated serine (the serine serine serine (the serine serine)	PADI4 OPLAH WISPI CTDSPL	1p36.13 8q24.3 8q24.1-q24.3 3p21.3 14q11.2	protein modification /// protein modification regulation of cell growth /// cell-cell signaling // Wht receptor signaling pathway proteolysis and peptidolysis /// apoptosis /// deavage of lamin /// cytolysis defense response /// spermatogenesis //
211412_at 22025_s_at 206796_at 201906_s_at 201906_s_at 201906_s_at	-1.518 -1.510 -1.504 -1.486 -1.485 -1.462	-2,87 -2,88 -2,88 -2,88 -2,88 -2,80 -2,80 -2,80 -2,80 -2,75 -2,75 -2,75	Cockayne types) peptidyl arginine deiminase, type IV S-oxoprolinase (ATP-hydrohysing) WNT1 Inducible signaling pathway protein 1 CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like grantyme B (granzyme 2, cytotoxic 1- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 1, cytotoxic T- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 1, cytotoxic T- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 1, cytotoxic T- ymphocyte-associated serine esterase 1) /// granzyme B (granzyme 1, cytotoxic T- ymphocyte-associated serine (the serine serine serine (the serine serine)	PAD14 OPLAH WISP1 CTDSPL GZMB SPAG11 SFRS1	1p36.13 8g24.3 8g24.1-g24.3 3p21.3 14g11.2 8p23-p22	protein modification /// protein modification regulation of cell growth /// cell adhesio /// signal transduction /// cell-cell signaling /// Wnt receptor signaling pathway 

	<u> </u>			T	<del></del>	muscle contraction /// peptidyl-amino
209135_at	-1.433		aspartate beta-hydroxylase	ASPH	8q12.1	acid modification
206661_at	-1.43	-2,69	Db/4-related factor 1	DRF1	17q21.31	signal transduction /// G-protein coupled
						receptor protein signaling pathway /// digestion /// feeding behavior ///
210956_at	-1.428	-2,69	pancreatic polypeptide receptor 1	PPYR1	10q11.2	circulation regulation of transcription, DNA-
219851_at	-1.427	-2,69	zinc finger protein 613	ZNF613	19q13.41	dependent
210545_at	-1.419	-2,67	Intersectin 2	ITSN2	2pter-p25.1	endocytosis regulation of cell cycle /// angiogenesis
						/// cell proliferation /// positive
206742_at	-1.384	-2 61	c-fos induced growth factor (vascular endothelial growth factor D)	FIGF	Xp22.31	regulation of cell proliferation /// cell differentiation
			potassium channel, subfamily K,			ion transport /// potassium ion transport
210261_at	1.381	-2,60	member 2	KCNK2	1941	/// potassium ion transport micouc sister chromatid Segregation ///
						regulation of cell cycle /// cytokinesis /// proteolysis and peptidolysis /// apoptosis
						/// chromosome segregation ///
			extra spindle poles like 1 (S.			establishment of mitotic spindle localization /// positive regulation of
204817_at	-1.375	-2,59	cerevisiae)	ESPL1	i2q	mitotic metaphase/anap
220903_at	-1.361	-2,57	G elongation factor, mitochondrial 1	GFM1	3q25.1-q26.2	protein biosynthesis /// translational elongation
220790_s_at	-1.352	.2.55	membrane-spanning 4-domains, subfamily A, member 5	MS4A5	11q12	signal transduction
			sublinity of memoer s			transcription /// regulation of
						transcription, DNA-dependent /// signal transduction /// central nervous system
213462_at	-1.33	-2,51	neuronal PAS domain protein 2	NPAS2	2q11.2	development ion transport /// potassium ion transport
						/// glutamate signaling pathway ///
215655_at	-1.328	-2,51	Glutamate receptor, ionotropic, kainate	GRIK2	6a16.3-a21	synaptic transmission /// synaptic transmission
213035_81	-1.520	-2,51	<u> </u>	GRANZ_	0410.3421	development /// Wnt receptor signaling
206619_at	-1.305	.7 47	dickkopf homolog 4 (Xenopus laevis)	DKK4	8p11.2-p11.1	pathway /// negative regulation of Wnt receptor signaling pathway
u	11	-2,71				L-phenylalanine catabolism /// tyrosine
206024_at	-1.298	-2.46	4-hydroxyphenylpyruvate_dioxygenase_	HPD	12q24-qter	catabolism /// aromatic amino acid family metabolism
220200_s_at 211813_x_at		-2,45	PR/SET domain containing protein 8 decorin	SET8 DCN	12q24.31 12q21.33	chromatin modification organogenesis
			chromosome 20 open reading frame	C20orf1		
219463_at	-1.283	-2,43	103	03	20p12	protein amino acid phosphorylation ///
			Triple functional domain (PTPRF			transmembrane receptor protein tyrosine
215406_at	-1.282	-2,43	interacting)	TRIO	5p15.1-p14	phosphatase signaling pathway regulation of transcription, DNA-
216023_at	-1.279	-2,43	jumonji domain containing 2B	JMJD2B KIAA057	19p13.3	dependent
213997_at	-1.279		KIAA0574 protein	4	15q12	
217276_x_at 202837_at	-1.274		serine hydrolase-like 2 FLN29 gene product	SERHL2 FLN29	22q13	aromatic compound metabolism
			beaded filament structural protein 2,			
207399_at	-1.259	-2,39	phakinin	BFSP2	3q21-q25	sensory perception /// visual perception transcription /// regulation of
216991_at	-1.237	-2,38	zinc finger protein 224 synovial sarcoma, X breakpoint 3 ///	ZNF224	19q <u>1</u> 3.2	transcription, DNA-dependent
211670_x_at	-1.228	-2,34	synovial sarcoma, X breakpoint 3	\$\$73	Χφ11.23	transcription, DNA-dependent
217511_at	-1.217	-2.32	Kazal-type serine protease inhibitor domain 1	KAZALD	10q24.32	regulation of cell growth
						cytokinesis /// protein amino acid
			cell division cycle 2, G1 to 5 and G2 to			phosphorylation /// mitosis /// traversing
203214_x_at	-1.206	-2,31	M	0002	10q21.1	start control point of mitotic cell cycle transcription /// regulation of
			recombining binding protein suppressor	RBPSUH		transcription, DNA-dependent /// signal
221377_s_at	-1.193	-2,29	of hairless (Drosophila)-like	L	20q12-q13.1 18p11.22-	transduction
202684_s_at	-1.187	-2,28	RNA (guanine-7-) methyltransferase	RNMT	p11.23	mRNA capping regulation of transcription, DNA-
						dependent /// signal transduction ///
203220_s_at	-1.181		transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)	TLE1	9q21.32	frizzied signaling pathway /// development /// organogenesis
						negative regulation of transcription from
206578_at	-1.171	-2,25	NK2 transcription factor related, locus 5 (Drosophila)	NKX2-5	5q34	RNA polymerase II promoter /// development /// heart development
204765_at	-1.168		Rho guanine nucleotide exchange factor (GEF) 5	ARHGEF 5	7q33-q35	
207/05_a(	-1.100	-2,25		,	7033-0235	proteolysis and peptidolysis /// sterol
		,	thyrotropin-releasing hormone			depletion response, sterol regulatory element binding-protein cleavage ///
219937_at	-1.166		degrading ectoenzyme	TRHDE	12q15-q21	signal transduction /// cell-cell signaling regulation or cell cycle /// transcription
		1				/// regulation of transcription, DNA-
						dependent /// transcription from RNA polymerase II promoter /// casoase
						activation /// intracellular signaling
209969_s_at	-1.16		signal transducer and activator of transcription 1, 91kDa	STAT1	2032.2	cascade /// I-kappaB kinase/NF-kappaB cascade /// tyrosine phosp
				FLJ3156	-	
222274_at	-1.158	-2,23	hypothetical protein FLJ31568	8 LOC196	22q11.23	<u></u>
214418_at	-1.145		hypothetical protein LOC196993	993	15q22.32	
209819_at	-1.137		hyaluronan binding probein 4	HABP4 MGC112	9q2 <u>2.3-q31</u>	····
19127_at	1.132	-2,19	hypothetical protein MGC11242	42	17q21.32	
[			<b>.</b>			carbohydrate metabolism /// glycogen
16079_at	-1.128		epilepsy, progressive myocionus type 2A, Lafora disease (laforin)	EPM2A	6q24	metabolism /// regulation of translation /// protein amino acid dephosphorylation
			sodium channel, voltage-gated, type			cation transport /// sodium ion transport
:06981_at	1.123	-2,18	IV, alpha	SCN4A DKFZP5	17q23-q25.3	/// muscle contraction
16028_at	-1.115		DKFZP564C152 protein	64C152	11	
16655_s_at	-1.114	-2,16	ectonucleoside triphosphate			
	1	, i i				
06191_at	-1.108		diphosphohydrolase 3	ENTPD3	3p⊋1.3	<u> </u>

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	— Т		· · · · · · · · · · · · · · · · · · ·	1	I	chemotaxis /// cellular defense response
				1		/// cell adhesion /// signal transduction
						/// G-protein coupled receptor protein
205898_at	-1.09	-2,13	chemokine (C-X3-C motif) receptor 1	03031	3p21(3p21.3	signaling pathway
	r		chorionic somatomammotropin			
207285_x_at	-1.07	-2,10	hormone-like 1	CSHLL	17q24.2	
					1	transcription /// regulation of
			]		ļ	transcription, DNA-dependent ///
				FOXG18		regulation of transcription, DNA-
			forkhead box G1B /// forkhead box	///	14q12-q13	dependent /// development /// brain
207658_s_at	-1.065	-2,09	GIA		/// 14q13	development /// brain development
				FLJ2356		
219487_at	-1.065	-2,09	hypothetical protein FLJ23560	0	12q21.2	protein folding
			cadherin 5, type 2, VE-cadherin		I	
204677_at	-1.031	-2,04	(vascular epithelium)	CDH5	16q22.1	cell adhesion /// homophilic cell adhesion
			synuclein, alpha (non A4 component of			
			amyloid precursor) /// synuclein, alpha			
			(non A4 component of amyloid		ł .	anti-apoptosis /// central nervous system
204467_s_at	-1.023	-2,03	precursor)	SNCA	4q21	development
	1	1			1	negative regulation of transcription from
						RNA polymerase II promoter ///
						transcription /// regulation of
			interferon regulatory factor 8 ///			transcription, DNA-dependent /// immune
204057_at	-1.018	-2,03	interferon regulatory factor 8	IRF8	16q24.1	response
215409_at	-1.012		D CC demois metaining anotain	531	15014	wate balling
215409_at	-1.012	-2,02	PLSC domain containing protein neuronoromin 1 (neuronoromatosis,	221	19014	metabolism
			von Recklinghausen disease, Watson			
		1	disease) /// neurofibromin 1		[	cell cycle /// Ras protein signal
			(neurofibromatosis, von			transduction /// negative regulation of
			Recklinghausen disease, Watson			cell proliferation /// negative regulation
211914 x at	-1.012		disease)	NF1	17011.2	of cell cycle
2					1, 411.5	inflammatory response /// signal
	1		1			transduction /// G-protein coupled
						receptor protein signaling pathway ///
					14a32.1-	positive regulation of cytosolic calcium
207510 at	-1.011	-2 02	bradykinin receptor B1	BDKRB1		ion concentration
						skeletal development /// cell adhesion ///

Tab. A4a: Probe-sets down-regulated regulated upon TVMP treatment at day 6 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients;

Probe Set ID		Eald Openia	Gene Title	Gene Symbol	Chromosoma	GO Biological Process Description
	1002 FC	Fold Change	Gene Hoe a state	Gene Synuos	Location	xenobiotic metabolism /// response t
			defensin, alpha 1, myeloid-		8p23.1 ///	pest, pathogen or parasite /// defens response to bacteria /// defense
205033_s_at	2.873	7,32586949	related sequence /// defensin, alpha 3, neutrophil-specific	DEFA1 /// DEFA3		response to fungi
						regulation of transcription, DNA- dependent /// transcription from RN
			POU domain, class 1,			polymerase II promoter /// negative
207846 34	7 607	8 48452008	transcription factor 1 (Pit1,	POU1F1	3p11	regulation of cell proliferation ///
207846_at	2.697	0,40452080	growth hormone factor 1)	room	16q24.2-	organogenesis cell adhesion /// homophilic cell
204726_at	2.586		cadherin 13, H-cadherin (heart)	CDH13 CAV2	q24.3 7q31.1	adhesion
203324_s_at	2.101	5,59446433	CDNA: FLJ22786 fis, clone	0.12	/431.1	
216427_at	2.422			 THAP9	 4q21.3	
220360_at 203862_s_at	2.359		actinin, alpha 2	ACTN2	1042-043	
215944_at	2.338	5,05601239				
219872_at	2.281		DKFZp434L142	DKFZp434L142	4q32.1	•••
217196_s_at	2.276	4,84333234	KIAA1078 protein	KIAA1078	1q32.1	 intracellular protein transport /// sm
			RAB40A, member RAS			GTPase mediated signal transduction
217589_at	2.249	4,75353242	oncogene family prostate and breast cancer	RAB40A	Xq22.1	/// protein transport
208329_at	2.241	4,72724619	overexpressed 1	PBOV1	6q23-q24	
213591_at	2.227	4.68159457	aldehyde dehydrogenase 7 family, member A1	ALDH7A1	5q31	aldehyde metabolism /// perception sound /// metabolism
			intersectin 1 (SH3 domain		21q22.1-	
209298_s_at	2.212	4,63317122	protein) phorbol-12-myristate-13-	ITSN1	q22.2	synaptic vesicle endocytosis
204286_s_at	2.209	4,62354683	acetate-induced protein 1	PMAIP1	18q21.32	
						response to unfolded protein ///
110000			chromosome 1 open reading	Clardin	1.071	metabolism /// response to heat ///
220090_at	2.204	4,60755057	frame 10	Clorf10	1q21	cell-cell adhesion /// cell-cell adhesic
		1				angiogenesis /// immune response /, cell-cell signaling /// induction of
						apoptosis via death domain receptor
						/// regulation of cell adhesion /// sleep /// chemokine biosynthesis ///
			interleukin 18 (interferon-		11q22.2-	helper 2 type immune response ///
206295_at	Z 159	4,46605185	gamma-inducing factor)	11,18	q22.3	interleukin-2 biosynthesis /// inte regulation of cen cycle /// negative
						regulation of transcription from RNA
						polymerase II promoter /// negative moutation of transmission from BNA
						regulation of transcription from RNA polymerase II promoter /// protein
1			Mdm2, transformed 3T3 cell			complex assembly /// negative
205385_at	2.065	4,18433976	double minute 2, p53 binding protein (mouse)	MDM2	12q14.3-q15	regulation of cell proliferation /// prote
215107_s_at	2.027	4,07556479	hypothetical protein FLJ20619	FLJ20619	1p32.3	
216814_at	1.914	3,7685251		<del>.</del>		eye morphogenesis (sensu Mammali
170504 -1			Lauthana	VEDA	17077	/// sensory perception /// visual
220504_at		3,73213197	Keratocan	KERA	12q22	perception synaptic transmission /// synaptic
			neuro-oncological ventral			transmission /// locomotory behavio /// locomotory behavior /// RNA
207437_at		3,72696172		NOVA1	14q	splicing /// RNA splicing
	1 898					
			chordin	CHED	3077	skeletal development /// development
221674_s_at 206480_at	1 898 1 861 1.855	3,63259367	chordin leukotriene C4 synthase	CHRD LTC4S	3q27 5q35	skeletal development /// development leukotriene biosynthesis
221674_s_at	1 861	3,63259367			5q35	leukotriene biosynthesis regulation of cell growth /// DNA
221674_s_at 206480_at	1 861	3,63259367			5q35	leukotriene biosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidermis development
221674_s_at 206480_at	1 861 1.855	3,63259367 3,61751751		LTC4S	5q35 6q23.1	leukotriene biosynthesis regulation of cell growth /// DNA metabolism /// cell mobility /// cell adhesion /// epidermis development /// response to wounding
221674_s_at 206480_at	1 861 1.855	3,63259367 3,61751751	leukotriene C4 synthase	LTC4S	5q35 6q23.1	leukotriene biosynthesis regulation of cell growth /// DNA metabolism // cell motility /// cell adhesion /// epidermis development /// response to wounding complement activation, fectin pathw /// phosphate transport /// immune
221674_s_at 206480_at	1 861 1.855	3,63259367 3,61751751	leukotriene C4 synthase	LTC4S	5q35 6q23.1	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development /// response /// boyon, lectin pathiw /// phosphate transport /// immune response /// complement activation,
221674_s_at	1 861 1.855 1.848	3,63259367 3,81751751 3,60000772	leukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein	LTC4S	5q35 6q23.1 10q11.2-q21	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell mobility /// cell adhesion /// puidemis development complement activation, lectin pathiwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress.
221674_5_at 206480_at 209101_at	1 861 1.855 1.848	3,63259367 3,81751751 3,60000772	leukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein	LTC4S	5q35 6q23.1 10q11.2-q21	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell mobility /// cell adhesion /// epidermis development /// response to wounding complement activation, lectin pathw /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription /// regulation of
221674_5_at 206480_at 209101_at 207256_at	1 861 1.855 1.848 1.763	3,63259367 3,61751751 3,60000772 3,39403161	leukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2,	LTC4S CTGF MBL2	5q35 6q23.1 10q11.2-q21	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development complement activation, lectin pathiw /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription from RNA polymerase I transcription from RNA polymerase I promoter /// lipid metabolism ///
221674_5_at 206480_at 209101_at 207256_at 15073_5_at	1 861 1.855 1.848 1.763	3,63259367 3,61751751 3,60000772 3,39403161 3,38825181	leukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2	LTC4S CTGF MBL2 NR2F2	5q35 6q23.1 10q11.2-q21 15q26	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell mobility /// cell adhesion /// epidemis development /// response to wounding complement activation, lectin pathiw /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stness transcription /// regulation of transcription from RNA polymerase 1
221674_s_at 206480_at 209101_at 207256_at 215073_s_at	1 861 1.855 1.848 1.763	3,83259387 3,81751751 3,80000772 3,39403181 3,38825181 3,31727818	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor	LTC4S CTGF MBL2	5q35 6q23.1 10q11.2-q21	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motbilly /// cell adhesion /// epidemis development /// response to wounding complement activation, lectin pathw /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oudative stress transcription from RNA polymerase I promoter /// regulation of transcription from RNA polymerase I signal transduction 
221674_5_at 206480_at 209101_at 207256_at 215073_5_at	1 861 1.855 1.848 1.763	3,63259367 3,61751751 3,60000772 3,39403161 3,30825181 3,31727618	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 ///	LTC4S CTGF MBL2 NR2F2	5q35 6q23.1 10q11.2-q21 15q26	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell mobility /// cell adhesion /// epidemis development /// response bo wounding complement activation, fechn pathw. /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription /// regulation of transcription /// page /// immune
221674_s_at 206480_at 209101_at 207256_at 215073_s_at 217786_at	1 861 1.855 1.848 1.763 1.752 1.752 1.73	3,63259367 3,81751751 3,80000772 3,39403161 3,38625181 3,31727618 3,28296644	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 9	LTC45 CTGF MBL2 NR2F2 BENE TNFRSF9	5q35 6q23.1 10q11.2-q21 15q26 2q13 1p36	leukoriene bosynthess regulation of cell growth /// DNA metabolism /// cell mobility /// cell adhesion /// epidermis development /// response to wounding complement activation, lectin pathwi /// peoprese to wounding complement activation, lectin pathwi response /// complement activation, classical pathway /// response to oxidative stress oxidative stress promoter /// regulation of transcription from RNA polymerase I promoter /// lepid metabolism /// signal transduction 
221674_5_at 206480_at 209101_at 207256_at 207256_at 215073_5_at 209373_at	1 861 1.855 1.848 1.763 1.752 1.73	3,63259387 3,61751751 3,60000772 3,39403161 3,34625181 3,31727816 3,28296644 3,28208643	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 tumor necrosis factor receptor superfamily, member 9 tippartite motif-containing 46	LTC45 CTGF MBL2 NR2F2 BENE TNFRSF9	5q35 6q23.1 10q11.2-q21 15q26 2q13 1p36 1q22	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, dassical pathway /// response to oxidative stress transcription from RNA polymerase I promoter /// lipid metabolism /// signal transduction 
221674 <u>s</u> at 206480 at 209101 at 207256 at 207256 at 207256 at 2073 <u>s</u> at 209373 at 20909 at	1 861 1.855 1.848 1.763 1.752 1.752 1.73	3,63259387 3,81751751 3,60000772 3,39403181 3,39403181 3,38625181 3,3727818 3,2829644 3,2829844 3,2829844	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 9	LTC45 CTGF MBL2 NR2F2 BENE TNFRSF9	5q35 6q23.1 10q11.2-q21 15q26 2q13 1p36 1q22	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development adhesion /// epidemis development /// phosphate transport /// immune response /// complement activation, classical pathway /// response to owidative stress transcription from RNA polymerase I transcription from RNA polymerase I transcription from RNA polymerase I monoter /// high metabolism /// signal transduction 
221674 <u>s</u> at 206480 at 209101 at 207256 at 207256 at 207256 at 2073 <u>s</u> at 209373 at 20909 at	1 861 1.855 1.848 1.763 1.752 1.752 1.73 1.715 1.705	3,63259387 3,81751751 3,60000772 3,39403181 3,39403181 3,38625181 3,3727818 3,2829644 3,2829844 3,2829844	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 pripartite motif-containing 46 frascoulation and elongation	LTC45 CTGF MBL2 NR2F2 BENE TN/FRSF9 TRJM46	5q35 6q23.1 10q11.2-q21 15q26 2q13 1p36 1q22 11q24.2	leukotrene bosynthess regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development complement activation, lectin pathiw /// phosphate transport /// immune response /// complement activation, dasskal pathway /// response to oxidative stress transcription from RNA polymerase I promoter /// lipid metabolism /// signal transduction 
221674 <u>s</u> at 206480 at 209101 at 207256 at 207256 at 207256 at 2073 <u>s</u> at 209373 at 20909 at	1 861 1.855 1.848 1.763 1.752 1.752 1.73 1.715 1.705	3,63259387 3,81751751 3,60000772 3,39403181 3,39403181 3,38625181 3,3727818 3,2829644 3,2829844 3,2829844	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 pripartite motif-containing 46 frascoulation and elongation	LTC45 CTGF MBL2 NR2F2 BENE TN/FRSF9 TRJM46	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q26 1q22 11q24.2	leukotrene bosynthess regulation of cell growth /// DNA metabolism /// cell motility /// cell adheson /// epidermis development complement activation, lectin pathwi complement activation, lectin pathwi // phosphate transport /// immune response /// complement activation, dasskal pathway /// response to oxidative stress transcription from RNA polymerase I promoter /// lipid metabolism /// signal transduction 
221674 <u>s</u> at 206480 at 209101 at 207256 at 207256 at 207256 at 2073 <u>s</u> at 209373 at 20909 at	1 861 1.855 1.848 1.763 1.752 1.752 1.73 1.715 1.705	3,63259387 3,81751751 3,60000772 3,39403181 3,39403181 3,38625181 3,3727818 3,2829644 3,2829844 3,2829844	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 pripartite motif-containing 46 frascoulation and elongation	LTC45 CTGF MBL2 NR2F2 BENE TN/FRSF9 TRJM46	5q35 6q23.1 10q11.2-q21 15q26 2q13 1p36 1q22 11q24.2	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidermis development gromplement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription from RNA polymerase I promoter /// kpid metabolism /// signal transduction 
221674_5_at 206480_at 209101_at 207256_at 207256_at 207256_at 207256_at 207256_at 209373_at 20999_at 20999_at	1 861 1.855 1.848 1.763 1.763 1.763 1.763 1.775 1.705 1.704	3,63250367 3,61751751 3,60000772 3,30403161 3,30625181 3,28296644 3,28028033 3,25603025	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 timor necrosis factor receptor superfamily, member 9 tipartite motif-containing 46 fasoiculation and elongation protein zeta 1 (zygin 1) fibroblast growth factor	LTC45 CTGF MBL2 NR2F2 BENE TNFRSF9 TRJM46 FEZ1	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q26 1q22 11q24.2	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription from RNA polymerase I promoter /// lipid metabolism /// signal transduction septonese /// negative regulation of cell proliferation cell adhesion /// neurogenesis /// transmitmation ecopital axion guidance signal oralisoticom /// transmitmate receptor protein protein ubiquitation cell adhesion /// neurogenesis /// transmembrane receptor protein fibroblast growth factor receptor
221674 <u>s</u> at 06480 at 109101 at 107256 at 15073 <u>s</u> at 109373 at 11786 at 20909 at 05973 at 21308 at	1 861 1.855 1.848 1.763 1.752 1.752 1.73 1.715 1.705	3,63250367 3,61751751 3,60000772 3,30403161 3,30625181 3,28296644 3,28028033 3,25603025	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 protein and elongation protein zeta 1 (zygin 1) fibroblast growth factor receptor substrate 2	LTC45 CTGF MBL2 NR2F2 BENE TN/FRSF9 TRJM46	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q26 1q22 11q24.2	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell mobility /// cell adhesion /// epidermis development /// response to wounding complement activation, lectin pathwi /// propose to wounding complement activation, lectin pathwi /// response /// complement activation, classical pathway /// response to oxidative stress promoter /// regulation of transcription from RNA polymerase I promoter /// figli metabolism /// signal transduction 
221674 <u>s</u> at 206480 at 209101 at 209101 at 209256 at 209256 at 209373 at 20909 at 20909 at 05973 at 21308 at 06537 at	1 861 1.855 1.846 1.763 1.752 1.755 1.705 1.705 1.706 1.699 1.68	3,63259387 3,81751751 3,60000772 3,39403181 3,38625181 3,38625181 3,28296944 3,28296944 3,28298032 3,28603025 3,24675832 3,20427851	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 /// timor necrosis factor receptor superfamily, member 9 /// fibroblast growth factor receptor substrate 2	LTC45 CTGF MBL2 NR2F2 BENE TNIFRSF9 TRIM46 FEZ1 FRS2 	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 12q15 	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription from RNA polymerase I promoter /// lipid metabolism /// signal transduction septonese /// negative regulation of cell proliferation cell adhesion /// neurogenesis /// transmitmation ecopital axion guidance signal oralisoticom /// transmitmate receptor protein protein ubiquitation cell adhesion /// neurogenesis /// transmembrane receptor protein fibroblast growth factor receptor
221674_s_at 206480_at 209101_at 207256_at 215073_s_at 217786_at	1 861 1.855 1.848 1.763 1.752 1.752 1.73 1.715 1.705 1.704	3,63259367 3,61751751 3,60000772 3,39403161 3,30825161 3,31727616 3,28296644 3,28028933 3,25603025 3,226078512 3,20427951 3,10235647	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 protein and elongation protein zeta 1 (zygin 1) fibroblast growth factor receptor substrate 2	LTC45 CTGF MBL2 NR2F2 BENE TNIFRSF9 TRIM46 FEZ1 FRS2 	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 11q24.2	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription from RNA polymerase I promoter /// lipid metabolism /// signal transduction septonese /// negative regulation of cell proliferation cell adhesion /// neurogenesis /// transmitmation ecopital axion guidance signal oralisoticom /// transmitmate receptor protein protein ubiquitation cell adhesion /// neurogenesis /// transmembrane receptor protein fibroblast growth factor receptor
221674 <u>s</u> at 206480 at 209101_at 209101_at 207256_at 207256_at 207256_at 2073_s_at 207256_at 207566_at 207566_at 207566_at 207566_at 2075	1 861 1.855 1.848 1.763 1.752 1.752 1.755 1.705 1.704 1.699 1.689 1.661	3,63259367 3,81751751 3,80000772 3,39403161 3,30825181 3,31727818 3,28296844 3,28028933 3,25803025 3,24675832 3,20427951 3,18235647	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 protein and elongation protein zeta 1 (zygin 1) fibroblast growth factor receptor substrate 2 	LTC45 CTGF MBL2 NR2F2 BENE TN/FRSF9 TRJM46 FE21 FRS2 	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 11q24.2 11q24.2 11q24.2	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidermis development adhesion /// epidermis development /// response to wounding complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription from RNA polymerase I transcription from RNA polymerase to woldative stress transcription from RNA polymerase I promoter /// lipid metabolism /// signal transduction 
221674 <u>s</u> at 206480 at 209101 at 209101 at 209256 at 209256 at 209373 at 20909 at 20909 at 05973 at 21308 at 06537 at	1 861 1.855 1.848 1.763 1.752 1.752 1.755 1.705 1.704 1.699 1.689 1.661	3,63259367 3,81751751 3,80000772 3,39403161 3,30825181 3,31727818 3,28296844 3,28028933 3,25803025 3,24675832 3,20427951 3,18235647	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 protein and elongation protein zeta 1 (zygin 1) fibroblast growth factor receptor substrate 2 	LTC45 CTGF MBL2 NR2F2 BENE TNIFRSF9 TRIM46 FEZ1 FRS2 	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 11q24.2 11q24.2 11q24.2	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidemis development complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to oxidative stress transcription from RNA polymerase I promoter /// lipid metabolism /// signal transduction septonese /// negative regulation of cell proliferation cell adhesion /// neurogenesis /// transmitmation ecopital axion guidance signal oralisoticom /// transmitmate receptor protein protein ubiquitation cell adhesion /// neurogenesis /// transmembrane receptor protein fibroblast growth factor receptor
221674 s at 206480 at 209101 at 209101 at 207256 at 215073 s at 215073 s at 211786 at 20909 at 205973 at 21308 at 21308 at 21308 at 13717 at 10610 at	1 861 1.855 1.848 1.763 1.752 1.752 1.735 1.705 1.705 1.704 1.699 1.685 1.661 1.615	3,63259367 3,81751751 3,80000772 3,39403161 3,38625181 3,31727818 3,28296844 3,28028933 3,25803025 3,24675832 3,20427951 3,18235647 3,08311599	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, and elongation protein zeta 1 (zygin 1) fibroblast growth factor receptor substrate 2 	LTC45 CTGF MBL2 NR2F2 BBNE TNFRSF9 TRIM46 FEZ1 FRS2 	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion i// epidermis development /// response to wounding complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to outdative stress transcription from RNA polymerase I promoter /// trgiu metabolism /// signal transduction 
221674 <u>s</u> at 206480 at 209101_at 209101_at 207256_at 207256_at 207256_at 2073_s_at 207256_at 207566_at 207566_at 207566_at 207566_at 2075	1 861 1.855 1.848 1.763 1.752 1.752 1.735 1.705 1.705 1.704 1.699 1.685 1.661 1.615	3,63250387 3,61751751 3,60000772 3,39403181 3,39403181 3,34625181 3,34625181 3,28296944 3,28028933 3,25803025 3,26475832 3,20427951 3,08311599 3,03984971	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily, member 9 /// fasoculation and elongation protein zeta 1 (zygin 1) fibroblast growth factor receptor substrate 2 LIM domain binding 3 carcinoembryonic antigen- related cell adhesion molecule 1 (bilary glycoprotein) potassium inwardly-rectifyling channel, subfamily 1, member 3	LTC45 CTGF MBL2 NR2F2 BBNE TNFRSF9 TRIM46 FEZ1 FRS2 	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2	leukotriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion /// epidermis development adhesion /// epidermis development complement activation, tectin pathwi /// phosphate transport /// immune response /// complement activation, dassical pathway /// response to oxidative stress transcription from RNA polymerase I transcription from RNA polymerase I transcription from RNA polymerase I promoter /// ipid metabolism /// signal transduction 
221674 s at 206480 at 209101 at 209101 at 207256 at 215073 s at 215073 s at 211786 at 20909 at 205973 at 21308 at 21308 at 21308 at 13717 at 10610 at	1 861 1.855 1.848 1.763 1.752 1.752 1.753 1.715 1.705 1.704 1.699 1.681 1.661 1.615	3,63250387 3,81751751 3,60000772 3,39403161 3,39425181 3,31727618 3,282296844 3,28028933 3,25803025 3,26028933 3,25803025 3,26028933 3,25803025 3,26028933 3,25803025 3,26028933 3,25803025 3,26028933 3,26028933 3,26028933 3,26028933 3,26028933 3,26028933 3,26028933 3,26028933 3,26028934 3,26028933 3,26028934 3,26028933 3,26028934 3,26028944 4,360444 4,5604944 4,5604944 4,5604944 4,5604944 4,56049444 4,56049444 4,56049444 4,56049444 4,56049444 4,56049444 4,56049444 4,56049444 4,560494444 4,560494444 4,5604944444 4,5604944444444444444444444444444444444444	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein O, 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily member 9 /// tumor necrosis factor receptor superfamily member 9 /// tumor necrosis factor receptor superfamily and elongation protein zeta 1 (zygin I) 	LTC45 CTGF MBL2 NR2F2 BENE TN/FRSF9 TRJM46 FEZ1 FRS2  LD83 CEACAM1 KONU3	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2 11q24.2	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion i// epidermis development /// response to wounding complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to outdative stress transcription from RNA polymerase I promoter /// trgiu metabolism /// signal transduction 
221674 _s_at 206480_at 209101_at 209101_at 209256_at 15073 _s_at 209373_at 20909_at 05973_at 21308_at 05973_at 13717_at 10610_at 07142_at 11584_s_at 21308_s_at	1 861 1.855 1.846 1.763 1.763 1.763 1.763 1.752 1.705 1.705 1.705 1.705 1.705 1.705 1.705 1.609 1.661 1.615 1.604 1.602	3,63259387 3,81751751 3,80751751 3,80000772 3,39403181 3,38625181 3,31727818 3,282260342 3,29427553 3,006311599 3,033946971	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein bumor necrosis factor receptor superfamily, member 9 partie motif-containing 46 fasculation and elongation protein zeta 1 (zygin I) fibroblast growth factor receptor substrate 2 	LTC45 CTGF MBL2 NR2F2 BENE TNFRSF9 TRJM46 FE21 FRS2 FRS2 CEACAM1 KCNU3 NPAT	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 12q15 10q22.3- q23.2 19q13.2 2q24.1 11q22-q23	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion i// epidermis development /// response to wounding complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to outdative stress transcription from RNA polymerase I promoter /// trgiu metabolism /// signal transduction 
221674 <u>s</u> at 106480 at 109101 at 107256 at 107256 at 1073 <u>s</u> at 1073 <u>s</u> at 11786 at 20909 at 05973 at 13717 at 10610 at 107142 at	1 861 1.855 1.848 1.763 1.763 1.763 1.763 1.763 1.775 1.705 1.705 1.706 1.609 1.661 1.615 1.604 1.602 1.596	3,63250387 3,61751751 3,60000772 3,39403181 3,30625181 3,30625181 3,30625181 3,28296944 3,28296944 3,28296944 3,28296933 3,25803025 3,20427951 3,20427951 3,08311599 3,03984971 3,03583851	Ieukotriene C4 synthase connective tissue growth factor mannose-binding lectin (protein C) 2, soluble (opsonic defect) nuclear receptor subfamily 2, group F, member 2 BENE protein tumor necrosis factor receptor superfamily, member 9 /// tumor necrosis factor receptor superfamily member 9 /// tumor necrosis factor receptor superfamily and elongation protein zeta 1 (zygin 1) fibroblast growth factor receptor substrate 2 	LTC45 CTGF MBL2 NR2F2 BENE TN/RSF9 TRJM46 FEZ1 FRS2 CEACAM1 KCNU3 NPAT DDX25	5q35 6q23.1 10q11.2-q21 15q26 2q13 1q22 11q24.2 11q24.2 11q24.2 11q24.2 19q13.2 2q24.1	leukoriene bosynthesis regulation of cell growth /// DNA metabolism /// cell motility /// cell adhesion i// epidermis development /// response to wounding complement activation, lectin pathwi /// phosphate transport /// immune response /// complement activation, classical pathway /// response to outdative stress transcription from RNA polymerase I promoter /// trgiu metabolism /// signal transduction 

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211347_at	1.578			CDC14B	9922.33	protein amino acid dephosphorylation
220843_s_at 206898_at			gene model 83 cadherin 19, type 2	Gm83 CDH19	8q22.3 18q22-q23	homophilic cell adhesion
216214_at	1.505	2,83824671	Clone 24504 mRNA sequence		-	
213550_s_at	1.501	2,83038832	CDNA FLJ20827 fis, done	<u> </u> −		
216461_at	1.5	2,62842712				
				PCDHAC2 /// PCDHAC1 ///		
				PCDHA13 ///		
				PCDHA12 /// PCDHA11 ///		
			protocadherin alpha 9 ///	PCDHA10 ///		
			protocadherin alpha subfamily	PCDHA8 ///		
			C, 2 /// protocadherin alpha subfamily C, 1 /// protocadherir	PCDHA7 /// PCDHA6 ///		
			alpha 13 /// protocadherin	PCDHA5 ///		1
			alpha 12 /// protocadherin alpha 11 /// protocadherin	PCDHA4 /// PCDHA3 ///		cell adhesion /// homophilic cell
			alpha 10 /// protocadherin	PCDHA2 ///		adhesion /// cell adhesion ///
210674_s_at 40489_at	1.465			PCDHA1 ATN1	5q31 12p13.31	neurogenesis central nervous system development
			Chromosome 10 open reading			
213381_at	1.462	2,75490009	r revenueracing process,	C10orf72	10q11.23	
			binding protein 1 (liprin beta 1) /// similar to PTPRF interacting	ł	1	
			protein binding protein 1	1		
			isoform 1; liprin-beta 1; liprin			
			related protein; protein-tyrosine phosphatase receptor-type f	1	12p11.23-	
			polypeptide-Interacting protein-		p11.22 ///	auli adhasian
214375_at	1.444	2,7207417	binding laminin, gamma 1 (formerly	LOC440091	12p11.23	cell adhesion protein complex assembly /// cell
200770_s_at	1.433	2,70007597	LAMB2)	LAMCI	1q31	adhesion /// endoderm development
220815_at	1.43	2,69446715	catenin (cadherin-associated protein), alpha 3	CTNNA3	10g22.2	cell adhesion
						cell adhesion /// homophilic cell
205535_s_at 222363_at	1.403		BH-protocadherin (brain-heart) Transcribed locus	1rcuri7 —	4p15	adhesion
			sema domain, immunoglobulin			
			domain (Ig), short basic domain, secreted, (semaphorin)			
215324_at	1.396	2,63170905	3D	SEMAJD	7q21.11	neurogenesis /// cell differentiation
214668_at	1.383	2,60810147	chromosome 13 open reading frame 1	C13orf1	13q14	
						regulation of cyclin dependent protein
						kinase activity // cytokinesis ///
04606			call division and DEA	CONCORA.	2-21	protein amino acid dephosphorylation
204696_s_at	1.381	2,00440030	cell division cycle 25A hypothetical protein	CDC25A	3p21	/// mitosis /// cell proliferation
214905_at	1.363	2,57219497	LOC145899	LOC145899	15q24.2	
			aminoadipate-semialdehyde			electron transport /// lysine
10852_s_at	1.36	2,5668518	synthase	AASS	7q31.3	catabolism /// protein tetramerization
						skeletal development /// embryonic
						development (sensu Mammalia) /// cell fate determination /// Notch
						signaling pathway /// Notch signaling
19537_x_at	1.357	2 58151072	delta-like 3 (Drosophila)	DUJ	19q13	pathway /// development /// neurogenesis /// cell differentiation
		2,00101012	proline-rich protein BstNI	200		
11531_x_at	1 335	2 52275482	subfamily 1 /// proline-rich protein BstNI subfamily 2	PRB1 /// PRB2	12p13.2	G-protein coupled receptor protein signaling pathway
		2,3221 3402	Similar to Group X secretory			Squarray partitions
			phospholipase A2 precursor (Phosphatidylcholine 2-			
			acylhydrolase GX) (GX sPLA2)			
1737_at	1.318	2,49320239	(SPLAZ-X)	<u> </u>	16p13.11	 Cytokinesis /// signal transduction ///
						Rho protein signal transduction ///
						spermatogenesis /// acrosome reaction /// fusion of sperm to egg
	]		ropporin, rhophilin associated			plasma membrane /// cell-cell
20425_x_at	1.315	2,48802331	protein 1B	ROPNIB	3q21.2	adhesion /// sperm motility transcription /// transport ///
	ļ				ļ	intracellular protein transport ///
1						regulation of cholesterol biosynthesis /// positive regulation of transcription,
04541_at	1.31	2,4794154	SEC14-like 2 (S. cerevisiae)	SEC14L2	22q12.2	DNA-dependent
			glutamate receptor,		1	ion transport /// potassium ion transport /// glutamate signaling
17565_at		2,47598058	ionotrophic, AMPA 3	GRIA3	Xq25-q26	pathway /// synaptic transmission
19744_at 12942_s_at		2,46058269 2,38336515	ructosamine 3 kinase KIAA1199	FN3K KIAA1199	17q25.3 15q24	fructoselysine metabolism perception of sound
						negative regulation of Wnt receptor
20277_at			myo-inositol monophosphatase	CXXC4	4q22-q24	signaling pathway
18516_s_at	1.218	2,32624008	A3 mesenchyme homeo box 2	IMPA3	8q12.1	 regulation of transcription, DNA-
	1	1	growth arrest-specific homeo			dependent /// development ///
06201_s_at	1.216	2,32301746		MEOX2	7p22.1-p21.3	circulation nuclear mKNA splicing, via
		1				spliceosome /// transcription ///
	1		splicing factor, arginine/serine- rich 8 (suppressor-of-white-			regulation of transcription, DNA- dependent /// mRNA splice site
02773_s_at	1.202		apricot homolog, Drosophila)	SFRS8	12q24.33	selection
				· · ·		carbohydrate metabolism /// D-ribose
19222_at	1.133	2,28627667	thromosome 19 open reading	RBKS	2p23.3	metabolism
12575_at	1.187	2,27678806		C19orf6	19p13.3	<u> </u>
ļ			variable heavy chain /// IgM		.	
1640 -	, . <i>.</i> .		heumatoid factor RF-TT1,			
1640_x_at	1.151		ATPase, Ca++ transporting,			cation transport /// calcium ion

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217081_at	1.127	2,18404109	olfactory receptor, family 2, subfamily H, member 2	OR2H2	6p21.3	regulation of transcription, DKA- dependent /// defense response /// signal bransduction /// G-protein coupled receptor protein signaling pathway /// perception of smell /// mating
			mannosyl (alpha-1,6-)- glycoprotein beta-1,6-N-acetyl-	Ĩ		
206720_at	1.094	2,13465068		MGAT5	2921	N-linked glycosylation
217600_at	1.092	2,13169347	Signal peptide, CUB domain, EGF-like 3	SCUBE3	6p21.3	_
			cytochrome P450, family 2, subfamily B, polypeptide 7			
210272_at	1.083	2,11843687	pseudogene 1	CYP2B7P1	19q13.2	electron transport
			similar to cervical cancer			
217104_at	1.057	2,08060053	suppressor-1	LOC400410	15q25.1	
212338_at	1.028	2,03919537	myosin ID	MYO1D	17q11-q12	
207894_s_at	1.026	2,0363704	T-cell leukemia/lymphoma 6	TCL6	14q32.1	
208007_at	1.023	2,03214029		-		

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Tab. A4b: Probe-sets up-regulated regulated upon IVMP treatment at day 6 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients:

Tab. A4c Probe Set ID	Log2 FC of	Fold Change	S THE Gene Title S	Gene Symbol	Chromosoma #1 Location	GO Biological Process Description
214660_at	3.043		Integrin, alpha 1	PELO	5q11.2	protein biosynthesis regulation of transcription, DNA-dependent /// regulatio
207781_s_at	-2.975	-7,86256479	zinc finger protein 6 (CMPX1)	ZNF6	Xq13-q21.1	of transcription
209655_s_at 221086_s_at	-2.864	-7,28031059	transmembrane protein 47 zinc finger protein 312	TMEM47 ZNF312	Xp11.4 3p14.2	<u> </u>
218349_s_at	2.553	-5,86853338	Zwilch	FL110036	15q22.31	-
217400_at	-2.392	-5,24884502				Ion transport /// potassium ion transport /// glutamate
215655_at 207156_at	-2.378		Glutamate receptor, ionotropic, kainate 2 (histone 1, H2ag	GRIK2 HIST1H2AG	6q16.3-q21 6p22.1	signaling pathway /// synaptic transmission /// synaptic transmission
216681_at		-4,89734557				
214702_at	.2.26	-4,76991482	fibrogentin 1	FN1	2q34	acute-phase response /// cell adhesion /// metabolism / response to wounding /// cell migration
215047_at			tripartite motif-containing 58	TRIM58	1944	proten ubiquitination proteolysis and peptidolysis /// sterol depletion respons
1			thyrotropin-releasing hormone degrading			sterol regulatory element binding-protein cleavage ///
219937_at 214078_at		-4,55357612	ectoenzyme P21 (CDKN1A)-activated kinase 3	PAK3	12q15-q21 Xq22.3-q23	signal transduction /// cell-cell signaling
			cadherin 5, type 2, VE-cadherin (vascular	1		
204677_at 216180_s_at	-2.168	-4,49399961 -4,31691295	synaptojanin 2	CDH5 SYNU2	16q22.1 6q25.3	cell adhesion /// homophilic cell adhesion
		;				acetylcholine catabolism in synaptic cleft /// DNA replication /// cell adhesion /// synaptogenesis /// musi development /// cell proliferation /// response to
						wounding /// neurotransmitter catabolism /// amyloid
05378_s_at	-2.025		acetylcholinesterase (YT blood group)	ACHE PADI4	7q22 1p36.13	precursor protein metabolism /// positiv protein modification /// protein modification
11412_at 19474_at	-1.941		peptidyl arginine deiminase, type IV TPA-induced transmembrane protein	TTMP	3q13.2	
05532_s_at	-1.922	-3,78948028	cadherin 6, type 2, K-cadherin (fetal kidnev)	CDH6	5p15.1-p14	cell adhesion /// homophilic cell adhesion
						transcription /// regulation of transcription, DNA-
16991_at	-1.919	-3,78160847	zinc finger protein 224 potassium channel, subfamily K, member	ZNF224	19q13.2	dependent ion transport /// potassium ion transport /// potassium
10261_at	-1.851	-3,60750151	2	KCNK2 FLN29	1041	ion transport
02837_at	-1./49	-3,36125501	FLN29 gene product	FUN29 _	<u>12q</u>	
						transcription /// regulation of transcription, DNA- dependent /// signal transduction /// transforming grow
05188_s_at	-1.736	-3,33110308	SMAD, mothers against DPP homolog 5 (Drosophila)	SMAD5	5q31	factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway
16708_x_at 04525_at	-1.726	-3,30809347	Immunoglobulin lambda variable 3-21	IGLC2 PHF14	22q11.2	immune response regulation of transcription, DNA-dependent
			PHD finger protein 14		7p21.3	protein amino acid phosphorylation /// intracellular
13770_at 22274_at			kinase suppressor of ras hypothetical protein FLJ31568	KSR FLJ31568	17q11.2 22q11.23	signating cascade /// Ras protein signal transduction
14378_at		-3,21986455		-		••••
			FERM, RhoGEF (ARHGEF) and pleckstrin			
01911_s_at 19851_at		-3,12964713	domain protein 1 (chondrocyte-derived)	FARP1 ZNF613	13q32.2 19q13.41	
19051_80	-1.019	-3,0/102034	zinc finger protein 613	201013	19013.41	nucleosome assembly /// nucleosome assembly ///
08546_x_at	-1 615	-3 06311599	histone 1, H2bh	HIST1H2BH	6p21.3	chromosome organization and biogenesis (sensu Eukaryota)
20061_at	-1.607	-3,04617748	hypothetical protein FLJ20581	FLJ20581	16p12.3	metabolism
14261_s_at	-1.59	-3,01049349	alcohol dehydrogenase 6 (class V)	ADH6	4q23	ethanol oxidation signal transduction /// G-protein coupled receptor prote
21397_at	-1 581	-2 00177152	taste receptor, type 2, member 10	TAS2R10		signaling pathway /// sensory perception /// perception taste
05572_at 21148_at		-2,97935493 -2,92008402	angiopoietin 2	ANGPT2	8p23.1	angiogenesis /// signal transduction /// cell differentiati
18748_s_at	-1 545	2.01804060	SEC10-like 1 (S. cerevisiae)	SEC10L1	14q22.3	exocytosis /// post-Golgi transport /// protein transport /// vesicle docking
10/ 10_3_0(		-2,01001000				
						membrane protein ectodomain proteolysis ///
	1					chromosome organization and biogenesis (sensu
						Eukaryota) /// chromosome segregation /// Notch
)4261_s_at	-1.542	-2,9119791	presenilin 2 (Alzheimer disease 4)	PSEN2	1q31-q42	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade // apoptotic program /// protein processing /// amylold pr
<u> </u>	-1.542	1		PSEN2	1q31-q42	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade /, apoptotic program /// protein processing /// amyloid pr carbohydrate metabolism /// ghycogen metabolism ///
			epilepsy, progressive myoclonus type 2A,		1q31-q42 6q24	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade // appottor: program /// protein processing /// amyloid by carbohydrate metabolism /// glycogen metabolism /// regulation of translation /// protein amino acid dephosphorvitation
			epilepsy, progressive myoclonus type 2A,		1q31-q42 6q24	Eukaryota) /// chromosome segregaton /// Notch receptor processing /// intracellular signaling cascade / apoptor program /// protein processing /// amyloid by carbohydrate metabolism /// glycogen metabolism /// regulation of translation /// protein amino acid dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor
			epilepsy, progressive myoclonus type 2A,		1g31-g42 6g24	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade / appottor: program /// protein processing /// amytoide carbohydrate metabolism /// pytogen metabolism /// regulation of translation /// protein amino acid dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke
6079_at	-1.538	-2,90391656	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor		<u>1q31-q42</u> 6q24	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade / appottor: program /// protein processing /// amytoide carbohydrate metabolism /// pytogen metabolism /// regulation of translation /// protein amino acid dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke
6079_at	-1.538 -1.523	-2,90391656	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3	EPM2A PRLR	<u>1q31-q42</u> 6q24 5p14-p13	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade / apoptoc. program /// protein processing /// amyoldy or carbohydrate metabolism /// plycogen metabolism /// regulation of translation /// protein amino acid dephosphorytetion Steroid biosynthesis /// steroid biosynthesis /// amb- apoptosis /// amb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor protein
.6079_at 0476_s_at 0803_at 5409_at	-1.538 -1.523 -1.519 -1.497	-2,90391656	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) protactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein	EPM2A PRLR AMSH-LP LOC254531	1q31-q42 6q24 5p14-p13 10q23.31 15q14	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade / apoptoc. program /// protein processing /// amyoldy or carbohydrate metabolism /// plycogen metabolism /// regulation of translation /// protein amino acid dephosphorytetion Steroid biosynthesis /// steroid biosynthesis /// amb- apoptosis /// amb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor protein
6079_at 0476_s_at 0803_at 5409_at	-1.538 -1.523 -1.519 -1.497	-2,00301656	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein PLSC domain containing protein chromosome 2 open reading frame 10	EPM2A PRLR AMSH-LP LOC254531	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1	Eularyota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade / apottotic program /// protein processing /// amyloid jo carbohydrate metabolism /// plycogen metabolism /// equidation of translation /// plycogen metabolism /// deptosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// resismembrane receptor protein tyrosine kinase activation (di
6079_at 0476_s_at 0803_at 5409_at 5767_at 0959_s_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.486	-2,90391658	epilepsy, progressive myocionus type 2A, Lafora disease (laforn) prolactin receptor Associated molecule with the SH3 domain of STAM (AMS4) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A	EPM2A PRLR AMSH-LP LOC254531 C20710 OBP2B /// OBP2B ///	1 <u>q31-q42</u> 6 <u>q24</u> 5 <u>p14-p13</u> 10 <u>q23.31</u> 15 <u>q14</u> 2 <u>q32.1</u> 9 <u>q34</u>	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade / apoptotic program /// protein processing /// amyloid by carbohydrate metabolism /// phycogen metabolism /// regulation of translation /// protein amino acid dephosphorytetion Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anti-apoptosis /// cell surface receptor inked signal transduction /// cell surface receptor inke signal transduction /// transmembrane receptor protein tyrosine kinase activation (di 
6079_at 0476_s_at 0803_at 5767_at 0959_s_at 0959_s_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.486 -1.474	-2,90391656 -2,87388035 -2,8659233 -2,8255168 -2,82059592 -2,80111204 -2,777910271 -7,77219977	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) protactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxyfase	EPM2A PRLR AMSH-LP LOC254531 C2orf10 OBP2B 7// OBP2A KIJA1212	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3	Eularyota) /// chromosome segregaton /// Notch receptor processing /// intracellular signaling cascade / apottotic program /// protein processing /// amyloid ju carbohydrate metabolism /// olycogen metabolism /// engulation of translation /// protein amino acid dephosphorytation Sterod biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// reli surface receptor linke signal transduction /// cell surface receptor protein hyrosine kinase activation (di 
6079_at 0476_s_at 0803_at 5767_at 0959_s_at 9387_at 0896_s_at	-1.538 -1.523 -1.519 -1.496 -1.496 -1.474 -1.474 -1.471 -1.471	-2,90391656 -2,87388035 -2,8659233 -2,8225169 -2,82059592 -2,8011284 -2,77213977 -2,77213977	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3 domain of STAN (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 Sapartate beta-hydroxylase Homo sapiens, done IMAGE:4824772, mRNA	EPM2A PRLR AMSH-LP LOC254531 C2orf10 OBP2B 7// OBP2A KIJA1212	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3	Eularyota) /// chromosome segregaton /// Notch receptor processing /// intracellular signaling cascade / apottotic program /// protein processing /// amyloid ju carbohydrate metabolism /// olycogen metabolism /// engulation of translation /// protein amino acid dephosphorytation Sterod biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// reli surface receptor linke signal transduction /// cell surface receptor protein hyrosine kinase activation (di 
6079_at 0476_5_at 0803_at 5409_at 5767_at 0959_5_at 9387_at 0996_5_at 6543_at 9661_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.496 -1.474 -1.474 -1.471 -1.471	-2,90391656 -2,87388035 -2,8659233 -2,8255169 -2,82059592 -2,82059592 -2,80111284 -2,77791027 -2,77213977 -2,77213977 -2,77213977	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) protactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxylase Homo sapiens, clone IMAGE:4824772, mRNA RAN binding protein 17	EPM2A PRLR AMSH-LP LOC254531 C20710 OBP2B /// OBP2B /// OBP2B /// OBP2A KIAA1212 ASPH 	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1  5q34	Eukaryota) /// chomosome segregation /// Notch receptor processing /// intracellular signaling cascade // apoptor program /// protein processing /// amytoid pro- carbohydrate metabolism /// pivogen metabolism /// regulation of translation /// protein amino acid dephosphorylation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anti-poptosis /// cell surface receptor linked signal transduction /// cell surface receptor protein tyrosine kinase activation (di 
6079 at 0476 s at 0803 at 5767 at 9387 at 0959 s at 9387 at 0996 s at 6543 at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.496 -1.474 -1.474 -1.471 -1.471	-2,90391656 -2,87388035 -2,8659233 -2,8255169 -2,82059592 -2,82059592 -2,80111284 -2,77791027 -2,77213977 -2,77213977 -2,77213977	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3 domain of STAN (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 Sapartate beta-hydroxylase Homo sapiens, done IMAGE:4824772, mRNA	EPM2A PRLR AMSH-LP LOC254531 C20710 OBP2B /// OBP2B /// OBP2B /// OBP2A KIAA1212 ASPH 	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1  5q34 19p12	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade // apoptor program /// protein processing /// amyloid pro- carbohydrate metabolism /// phoceen metabolism /// dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor protein tyrosine kinase activation (di metabolism 
6079 at 0476 s at 0803 at 5767 at 9387 at 0959 s at 9387 at 0996 s at 6543 at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.496 -1.474 -1.474 -1.471 -1.471	-2,90391656 -2,87388035 -2,8659233 -2,8255169 -2,82059592 -2,82059592 -2,80111284 -2,77791027 -2,77213977 -2,77213977 -2,77213977	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) protactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxylase Homo sapiens, clone IMAGE:4824772, mRNA RAN binding protein 17	EPM2A PRLR AMSH-LP LOC254531 C20710 OBP2B /// OBP2B /// OBP2B /// OBP2A KIAA1212 ASPH 	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2q16.3 8q12.1  5q34 19p12	Eularyota) /// chromosome segregaton /// Notch receptor processing /// intracellular signaling cascade // apoptotic program /// protein processing /// amyloid go carbohydrate metabolism /// glycogen metabolism /// ergulation of translation /// protein amino acid dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor protein tyrosine kinase activation (di 
6079_at 0476_s_at 0803_at 5409_at 5767_at 0959_s_at 9387_at 09561_at 6458_s_at 1174_s_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.486 -1.474 -1.474 -1.471 -1.4744 -1.4744 -1.4744 -1.4744 -1.4744 -1.4744 -1.4744 -1	-2,90391656 -2,87388035 -2,8659233 -2,8659233 -2,82059592 -2,82059592 -2,82059592 -2,80111264 -2,777910271 -2,77213977 -2,77213977 -2,77213977 -2,770912571 -2,70944995 -2,70944995	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) protactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant timiding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxyfase Homo sapiens, clone IMAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystokinin A receptor	EPM2A PRLR AMSH-LP LOC254531 C2or10 OBP28 /// OBP2A KIAA1212 ASPH RANBP17 ZNF682 CCXAR	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1 5q34 19p12 4p15.1-p15.2	Eukaryota) /// chromosome segregatorn /// Notch receptor processing /// intracellular signaling cascade // apoptor processing /// intracellular signaling cascade // apoptors processing /// amyloid processing /// amyloid pro- carbohydrate metabolism /// pycogen metabolism /// equidation of translation /// protein amino acid dephosphorylation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor finkes signal transduction /// transmembrane receptor protein tyrosine kinase activation (di 
6079_at 0476_s_at 0803_at 5409_at 5767_at 0959_s_at 9387_at 9661_at 6468_s_at 1174_s_at 9887_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.474 -1.474 -1.471 -1.474 -1.471 -1.438 -1.438	-2,90391656 -2,87388035 -2,8659233 -2,8659233 -2,8255168 -2,82059592 -2,8011264 -2,8011264 -2,77213977 -2,77213977 -2,771697257 -2,77944905 -2,70944995 -2,87029681	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2A binding protein 2A /// odorant KIAA1212 aspartate beta-hydroxyfase Homo sapiens, clone IMAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystoklinin A receptor hypothetical protein FLJ10786	EPM2A PRLR AMSH-LP LOC254531 C2orf10 OBP2B /// OBP2B /// OBP2A KIAA1212 ASPH 	1q31-q42 6q24 5p14-p13 10q23-31 15q14 2q32.1 9q34 2p16.3 8q12.1  5q34 15p12 4p15.1-p15.2 11q13.2 11p15.4	Eukaryota) /// chomosome segregation /// Notch receptor processing /// intracellular signaling cascade // apoptor processing /// intracellular signaling cascade // apoptors processing /// anyloid pro- carbohydrate metabolism /// photein amino acid dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// ahb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// transmembrane receptor protein typosine kinase activation (di 
6079 at 0476 s at 0803 at 5767 at 0959 s at 9387 at 0996 s at 6543 at 9661 at 6468 s at 1174 s at 9887 at 7525 at	-1.538 -1.523 -1.519 -1.496 -1.486 -1.474 -1.474 -1.471 -1.471 -1.471 -1.471 -1.471 -1.473 -1.438 -1.417 -1.385	-2,90391656 -2,87388035 -2,8659233 -2,8255169 -2,82059592 -2,82059592 -2,80111284 -2,777910271 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77944995 -2,70944995 -2,87029661 -2,81171867 -2,81184 -2,81184 -2,8118 -2,81185 -2,8118	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) protactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxylase Homo sapiens, clone IMAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystokinin A receptor hypothetical protein FL10786 offors stimulating factor 2 (granulocyte-	EPH2A PRLR AMSH-LP LOC254531 C2or10 OBP28 /// OBP28 /// OBP28 /// OBP28 /// OBP28 /// C0P28 /// COP28 // COP28 // COP28 /// COP28 /// COP28 // COP28 //	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1 	Eularyota) /// chromosome segregatorn /// Notch receptor processing /// intracellular signaling cascade // apoptoto: program /// protein processing /// amyloid gra- carbohydrate metabolism /// glycogen metabolism /// ergulation of translation /// protein amino acid dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor protein tyrosine kinase activation (di 
16079_at 16079_at 16079_at 10803_at 15767_at 10959_5_at 10959_5_at 10959_5_at 10965_at 10965_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_at 1174_5_5_5_at 1174_5_5_5_5_5_5_5_5_5_5_5_5_5_5_5_5_5_5_5	-1.538 -1.523 -1.519 -1.496 -1.486 -1.474 -1.474 -1.471 -1.471 -1.471 -1.471 -1.471 -1.473 -1.438 -1.417 -1.385	-2,90391656 -2,87388035 -2,8659233 -2,8659233 -2,8255169 -2,82059592 -2,82059592 -2,82059592 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77944995 -2,670296611 -2,61771957 -2,61771957 -2,58112498	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxylase Homo sapiers, clone IMAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystokinin A receptor hypothetical protein PL10786 offactomedin-like 1 colony stimulating factor 2 (granulocyte- macrophage)	EPH2A PRLR AMSH-LP LOC254531 C2or10 OBP2B /// OBP2A KIAA1212 ASPH  RANBP17 ZNF682 COKAR FU10786 OLFML1 CSF2	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1  5q34 19p12 4p15.1-p15.2 11q13.2 11p15.4 5q31.1	Eukaryota) /// chromosome segregation /// Notch receptor processing /// intracellular signaling cascade // apoptor processing /// intracellular signaling cascade // apoptor processing /// anyloid pro- carbohydrate metabolism /// phoceen metabolism /// eigulation of translation /// protein amino acid dephosphorylation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor finke signal transduction /// transmembrane receptor protein tyrosine kinase activation (di miscle contraction of smell /// chemosensory behavior /// perception of cytosotic calcium ion concentratio /// regulation of cytosotic calcium ion concentratio /// response to nutrients /// digestion /// feeding behavior /// regulation of cranscription, DNA- transcription/// regulation of cranscription, DNA- transcription/// regulation of cranscription, DNA-
M261_s_at 16079_at 16079_at 10803_at 10803_at 15767_at 10959_s_at 9387_at 09965_at 10965_s_at 1174_s_at 9887_at 1174_s_at 9887_at 1174_s_at 9887_at 1163_s_at 1163_s_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.474 -1.474 -1.474 -1.471 -1.471 -1.472 -1.438 -1.471 -1.438 -1.438 -1.438 -1.385 -1.365	-2,90391656 -2,87388035 -2,8659233 -2,8659233 -2,8255169 -2,82059592 -2,82059592 -2,82059592 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77944995 -2,670296611 -2,61771957 -2,61771957 -2,58112498	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxylase Homo sapiers, done IMAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystokinin A receptor hypothetical protein F210786 offactomedin-like 1 colony stimulating factor 2 (granulocyte- macrophage)	EPH2A PRLR AMSH-LP LOC254531 C2or10 OBP2B /// OBP2A KIAA1212 ASPH  RANBP17 ZNF682 COKAR FU10786 OLFML1 CSF2	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1  5q34 19p12 4p15.1-p15.2 11q13.2 11p15.4 5q31.1	Eukaryota) /// chromosome segregatorn /// Notch receptor processing /// intracellular signaling cascade // apoptor processing /// intracellular signaling cascade // apoptors processing /// amyloid processing /// amyloid pro- steroid biosynthesis /// optoren metabolism /// optors /// anti-apoptosis /// cell surface receptor inked signal transduction /// cell surface receptor inked signal transduction /// transmembrane receptor protein tyrosine kinase activation (di metabolism 
16079_at 16079_at 10803_at 5767_at 10995_s_at 9387_at 0996_s_at 6543_at 9661_at 6468_s_at 1174_s_at 9887_at 9887_at 0228_at 1163_s_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.486 -1.474 -1.474 -1.471 -1.471 -1.472 -1.438 -1.438 -1.438 -1.417 -1.385 -1.368 -1.368 -1.342	-2,90391656 -2,87388035 -2,8659233 -2,8659233 -2,82059592 -2,82059592 -2,82059592 -2,82059592 -2,82059592 -2,82059592 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77249257 -2,70944995 -2,87029661 -2,87029661 -2,87029661 -2,87029661 -2,87029661 -2,53502504 -2,5350	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxyfase Homo sapiens, clone IMAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystoklinin A receptor hypothetical protein FL10786 otfactomedin-like 1 colony stimulating factor 2 (granulocyte- macrophage) Williams Beuren syndrome chromosome region 14	EPH2A PRLR AMSH-LP LOC254531 C2or10 OBP28 /// OBP28 /// OBP28 /// OBP28 /// OBP28 /// OBP28 /// C20F28 C20	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1 	Eularyota) /// chromosome segregatorn /// Notch receptor processing /// intracellular signaling cascade // apoptotic program /// protein processing /// amyloid gra- carbohydrate metabolism /// glycogen metabolism /// ergulation of translation /// protein amino acid dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor linke signal transduction /// cell surface receptor protein tyrosine kinase activation (di 
16079_at 10476_5_at 10803_at 5409_at 5767_at 10959_5_at 9387_at 09561_at 6543_at 9661_at 6468_5_at 1174_5_at 9887_at 7525_at 0228_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.486 -1.474 -1.474 -1.471 -1.471 -1.472 -1.438 -1.438 -1.438 -1.417 -1.385 -1.368 -1.368 -1.342	-2,90391656 -2,87388035 -2,8659233 -2,8659233 -2,82059592 -2,82059592 -2,82059592 -2,82059592 -2,82059592 -2,82059592 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77249257 -2,70944995 -2,87029661 -2,87029661 -2,87029661 -2,87029661 -2,87029661 -2,53502504 -2,5350	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxyfase Homo sapiens, clone IMAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystoklinin A receptor hypothetical protein FL10786 otfactomedin-like 1 colony stimulating factor 2 (granulocyte- macrophage) Williams Beuren syndrome chromosome region 14	EPH2A PRLR AMSH-LP LOC254531 C2or10 OBP28 /// OBP28 /// OBP28 /// OBP28 /// OBP28 /// OBP28 /// C20F28 C20	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1  5q34 19p12 4p15.1-p15.2 11q13.2 11p15.4 5q31.1 7q11.23 Xp11.2	Eukaryota) /// chromosome segregatorn /// Notch receptor processing /// intracellular signaling cascade // apoptor processing /// intracellular signaling cascade // apoptors processing /// intracellular signaling cascade // apoptors /// translation /// protein amion acid dephosphorylation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptors /// and-papotosis /// cell surface receptor inked signal transduction /// cell surface receptor linke signal transduction /// transmembrane receptor protein tyrosine kinase activation (dir metabolism 
6079 at 0476 s at 0803 at 5409 at 5767 at 0959 s at 9387 at 0956 s at 6543 at 9661 at 6458 s at 1174 s at 9887 at 0228 at 1163 s at	-1.538 -1.538 -1.519 -1.497 -1.496 -1.474 -1.474 -1.474 -1.471 -1.471 -1.472 -1.438 -1.471 -1.438 -1.417 -1.385 -1.365 -1.365 -1.342 -1.337	-2,90391656 -2,87388035 -2,8659233 -2,8659233 -2,8255169 -2,82059592 -2,82059592 -2,82059592 -2,87219277 -2,772139777 -2,772139777 -2,772139777 -2,772139777 -2,772139777 -2,771697257 -2,779449955 -2,670290611 -2,53502504 -2,53502504 -2,4986611	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3 domain of STAM (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2B /// odorant tiltichal 212 aspartate beta-hydroxyfase Homo sapiens, done IPAAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystoklinin A receptor hydrothecial protein FL10786 otharcophage Williams Beuren syndrome chromosome region 14 A klinase (PRKA) anchor protein 4 Nuclear factor 1/8	EPH2A PRLR AMSH-LP LOC254531 C2or10 OBP2B /// OBP2A KIAA1212 ASPH RANBP17 ZNF682 CCKAR FU10786 OLFML1 CSF2 WBSCR14 AKAP4	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1 5q34 19p12 4p15.1-p15.2 11q13.2 11q13.2 11q15.4 5q31.1 7q11.23 Xp11.2	Eularyota) /// chromosome segregaton /// Notch receptor processing /// intracellular signaling cascade // apoptoto: program /// protein processing /// amyloid yr carbohydrate metabolism /// olycogen metabolism /// ergulation of translation /// protein amino acid dephosphorytation Steroid biosynthesis /// steroid biosynthesis /// anb- apoptosis /// anb-apoptosis /// cell surface receptor linked signal transduction /// cell surface receptor inkes signal transduction /// cell surface receptor inkes signal transduction /// cell surface receptor protein tyrosine kinase activation (di 
6079_at 0476_s_at 0803_at 5409_at 5767_at 0959_s_at 9387_at 0956_at 6543_at 1174_s_at 9887_at 7525_at 1163_s_at 7019_s_at 7019_s_at	-1.538 -1.523 -1.519 -1.497 -1.496 -1.471 -1.471 -1.471 -1.471 -1.471 -1.472 -1.438 -1.438 -1.438 -1.438 -1.438 -1.438 -1.337 -1.32	-2,90391656 -2,87388035 -2,8659233 -2,8255169 -2,82059592 -2,82059592 -2,82059592 -2,82059592 -2,82059592 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,77213977 -2,771097257 -2,77044995 -2,67029661 -2,58112498 -2,52825452 -2,4986811 -2,4986811	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) prolactin receptor Associated molecule with the SH3 domain of STAN (AMSH) like protein PLSC domain containing protein chromosome 2 open reading frame 10 odorant binding protein 2B /// odorant binding protein 2A KIAA1212 aspartate beta-hydroxylase Homo sapiers, done IMAGE:4824772, mRNA RAN binding protein 17 zinc finger protein 682 cholecystokinin A receptor hydrothecal protein CD107866 offactmedin-like 1 colony stimulating factor 2 (granulocyte- macrophage) Williams Beuren syndrome chromosome region 14 A kinase (PRKA) anchor protein 4 Nuclear factor 1/8 IDP-Gal-bedGNA beta 1,3-	EPH2A PRLR AMSH-LP LOC254531 C2or10 OBP28 /// OBP2A KIAA1212 ASPH RANBP17 ZNF682 CCKAR FL10786 OUFHL1 CSF2 WBSCR14 AKAP4 NFIB	1q31-q42 6q24 5p14-p13 10q23.31 15q14 2q32.1 9q34 2p16.3 8q12.1 	Eukaryota) /// chomosome segregation /// Notch receptor processing /// intracellular signaling cascade // apoptor processing /// intracellular signaling cascade // apoptor processing /// anyloid pro- carbohydrate metabolism /// photein amino acid dephosphorylation /// protein amino acid dephosphorylation /// protein amino acid dephosphorylation /// cell surface receptor finke signal transduction /// cell surface receptor finke signal transduction /// cell surface receptor protein tyrosine kinase activation (di 

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<b></b>				· · · ·		regulation of cell growth /// intracellular signaling
				1		cascade /// JAK-STAT cascade /// negative regulation of
						signal transduction /// cytokine and chemokine mediated
						signaling pathway /// positive regulation of T-helper 1
200540				CONTE	1	
209648_x_at	-1.242		suppressor of cytokine signaling 5	50CS5	2p21	cell differentiation /// negative
217082_at	-1.242	-2,365262	Unknown protein synuclein, alpha (non A4 component of			••••
1						
			amyloid precursor) /// synuclein, alpha	1	1	1
			(non A4 component of amyloid		4-74	
204467_s_at	-1.259	-2,36034869	precursor)	SNCA	4q21	anti-apoptosis /// central nervous system development ion transport /// potassium ion transport /// signal
311530				CO	C-3315-33.4	
211520_s_at	-1.221	+2,3310824	glutamate receptor, ionotropic, AMPA 1 zinc finger, X-linked, duplicated A /// zinc	GRIA1	5q33 5q31.1 Xp11.1 ///	transduction /// synaptic transmission
	4 304			2008	Xp11.1 ///	
216014_s_at			finger, X-linked, duplicated B			and the second s
209135_at	-1.205	-2,30217898	aspartate beta-hydroxylase	ASPH	8q12.1 18p11.22-	muscle contraction /// peptidyl-amino acid modification
202000						
202684_s_at	-1.195	-2,28944832	RNA (guanine-7-) methyltransferase	RNMT	p11.23	ImRNA capping (regulation of transcription, DNA-dependent /// signal
			transducin-like enhancer of split 1		1	transduction /// frizzled signaling pathway ///
					0-21.22	
203220_5_at			(E(sp1) homolog, Drosophila)	TLE1	9921.32	development /// organogenesis
216023_at	-1.165	-2,24233216	jumonji domain containing 2B	JMJD2B	19p13.3	regulation of transcription, DNA-dependent transcription /// regulation of transcription, DNA-
105724					0-13.3	
205731_s_at			nuclear receptor coactivator 2	NCOA2	8q13.3	dependent /// signal transduction
220278_at			jumonji domain containing 2D	JMJD2D	11921	
205980_s_at	-1.126	-2,16252775	Rho GTPase activating protein 8	ARHGAP8	22q13.31	intracellular protein transport /// Golgi organization and
316303			CCC2 internation and the		10.75 .26	
216392_s_at	-1.119	-2,1/1963/1	SEC23 interacting protein	SEC23IP	10q25-q26_	biogenesis
1		i i	Mediaton of DNA ashiman as 11	ľ	1	transcription /// regulation of transcription, DNA-
			Mediator of RNA polymerase II		4-10	
214831_at	<u>•1.11/</u>	-2,16895482	transcription, subunit 28 homolog (yeast)	MED28	4p16	dependent L-phenylalanine catabolism /// tyrosine catabolism ///
206024_at			d hudana ahaa da	нро	1	aromatic amino acid family metabolism
200024_81	-1.101	-2,14503323	4-hydroxyphenylpyruvate dioxygenase	nru	12q24-qter_	regulation of transcription, DNA-dependent /// defense
						response /// signal transduction /// G-protein coupled
	1		olfactory receptor, family 2, subfamily H,			receptor protein signaling pathway /// perception of smell
217081_at		-2,14503323		OR2H2	6021.3	/// mating
217001_at	-1.101	-2,14503323	heat shock 70kDa protein 98 (mortalin-		10p21.3	/// maong
200690 at						anatolia datata a
215481_s_at		-2 12726535	2) percodsomal biogenesis factor 5	HSPA9B PEX5	5031.1	protein folding
211813 x at				DON	12p13.3	protein bransport
		-2,10380356			12q21.33	organogenesis
214612_x_at	-1.038	-2,05337909	melanoma antigen family A, 6	MAGEA6	Xq28	CAMP biosynthesis /// intracellular signaling cascade ///
117607		0.04000400	adamidata matana 2 (haria)	4000	F-15 3	
217687_at	-1.03	-2,04202425	adenylate cyclase 2 (brain)	ADCY2	5p15.3	cyclic nucleotide biosynthesis
215034_s_at	1 000	2 04080020	transmembrane 4 L six family member 1	TM4SF1	2021-025	l
215039_5_at	•1.029		amiloride-sensitive cation channel 2.	101951	3q21-q25	ion transport /// sodium ion transport /// signal
7057	1 0 2 7					
37953_s_at	-1.02/	-2.03778239		ACCN2	12q12 22q13.2-	transduction /// response to pH regulation of transcription, DNA-dependent /// mRNA
000001 -+	1.024	2 0225 4025	Data binding emtain single	010070		
209981_at	-1.024	-2,03354935	RNA-binding protein pippin membrane-spanning 4-domains,	PIPPIN	q13.31	processing /// histone mRNA 3'-end processing
10700					1	alaant an ood ooloo
20790_s_at	-1.02	-2,02791896	subfamily A, member 5	MS4AS	11q12	signal transduction
			CTD (carboxy-terminal domain, RNA			
			polymerase II, polypeptide A) small			
13597_s_at	-1.017	<u>-2,0237064</u>	phosphatase-like	CTDSPL	3p21.3	<u> </u>

Tab. A4c: Probe-sets down-regulated regulated upon IVMP treatment at day 21 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients;

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in a strill	111 X5 46-196	Cana The State		Chromosoma	GO Biological Process Description
1.1002 FC.	, roio Change	States and the states of the	Gene symbo	Location"	So bological Process Description 3
		potassium inwardly-rectifying		1	
2.52			KCNU3	2q24.1	ion transport /// potassium ion transport
2.518	5,73	fasciculation and elongation			cell adhesion /// neurogenesis /// axon
2.411			FEZ1	11g24.2	guidance
2.384	5,22			7q31.1	-
		family, member D /// acidic			
				15022.3-023	
		member C /// similar to acidic	ANP32C ///		  nucleocytoplasmic transport /// intracelluli
2.253	4,77		LOC440272	15q14	signaling cascade
,			MMP238 ///		reproduction /// proteolysis and peptidolys
2.221	4,66		MMP23A	1p36.3	/// proteolysis and peptidolysis
2.152	4.44		POSTN	13013.3	skeletal development /// cell adhesion /// adhesion
		chromosome 19 open reading	1		
2.105	4,30	frame 6	C190mb	19013.3	response to unfolded protein /// metabolis
		chromosome 1 open reading			/// response to heat /// cell-cell adhesion ,
2.042			Clorf10	1q21	cell-cell adhesion
2.034	4,10	sema domain, immunoglobulin		1932.1	
		domain (Ig), short basic			
2.026	4.07		SEMA3D	7021.11	neurogenesis /// cell differentiation
		mesenchyme homeo box 2		h-1-2-2-2	
1 061	3 84		MEOY2	1077 1-071	regulation of transcription, DNA-dependen /// development /// circulation
1.901			NAV1		DNA methylation
		secretagogin, EF-hand calcium	1		
1.821				19022.3-022.1	
				t	regulation of cyclin dependent protein kina
				1	activity /// cytokinesis /// protein amino ac dephosphorylation /// mitosis /// cell
1.799	3,48	cell division cycle 25A	CDC25A	3p21	proliferation
1.795	3,47	hypothetical protein FL113912	FLJ13912	16q21	
1.788	3,45	translocase of inner	TRUMHO	1q22	protein ubiquitination
		mitochondrial membrane 50			
1.777			MYOID	17q11-q12	-
1.744		phosphodiesterase 9A	PDE9A	21q22.3	signal transduction /// signal transduction
1.723	3.30		NBL1		cell cycle /// negative regulation of cell cyc
		aldehyde dehydrogenase 7		ſ	aldehyde metabolism /// perception of sou
1.676	3,20	family, member A1	ALDH7A1		///_metabolism
1.639	3,11	spermatogenesis associated 2	SPATA2	q13.2	spermatogenesis /// cell differentiation
					N-acetylglucosamine metabolism
1.01		COL-14 prodem	0.01-11	10013.5	
F					angiogenesis /// immune response /// cell- cell signaling /// induction of apoptosis via
					death domain receptors /// regulation of o
		Interder for 10 finter dames			adhesion /// sleep /// chemokine biosynth
1.621	3.08	• • • • •	11.18		/// T-helper 2 type immune response /// interleukin-2 biosynthesis /// inte
1.6				4p15	cell adhesion /// homophilic cell adhesion
1 504	2.02	cadharia 12 M.cadhada (haad)	00413	16q24.2-	cell adherion /// homophilit cell adherion
1.566				15q24	perception of sound
					regulation of cell cycle /// transcription /// regulation of transcription, DNA-dependent
				· · · · ·	regulation of transcription, UNA-dependen /// inflammatory response /// chromatin
					modification /// histone deacetylation /// E
1 530	2.00	histone descelutore 0	нолго	7071 1	cell differentiation /// negative regulation of mynametic
		tumor necrosis factor receptor	11.004.3	· pe 1.1	myogenesis
					induction of anostanic III immuna
1			TNFRSF9	1p36	induction of apoptosis /// immune respons /// negative regulation of cell proliferation
1.536		Superiantily, memoer 9			regulation of transcription, DNA-dependen
1.536	2,90	superfamily, member 9			
1.536	2,90	homeo box C8	HOXC8	12q13.3	/// development eve morphogenesis (sensu Mammalia) ///
	2,90 2,87		HOXC8	12q13.3 12q22	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception
1.519	2,90 2,87	homeo box C8			eye morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of transcription
1.519	2,90 2,87 2,82 2,80	homeo box C8			eye morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of transcription DNA-dependent /// transcription from RVA polymerase 11 promoter
1.519 1.498 1.484	2,90 2,87 2,82 2,80	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semiaklehyde	KERA	12q22 15q12	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of branscription DNA-dependent /// transcription from RNA polymerase II promoter electron transport /// hysine catabolism ///
1.519 1.498 1.484 1.484	2,90 2,87 2,82 2,80 2,80	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semiaklehyde	KERA	12q22	eye morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of transcription DNA-dependent /// transcription from RNA polymerase 11 promoter
1.519 1.498 1.484	2,90 2,87 2,82 2,80 2,80	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA	KERA KLF13 AASS	12q22 15q12	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription of branscription DNA-dependent /// transcription from RNA polymerase II promoter electron transport /// lysine catabolism /// protein tetramerization
1.519 1.498 1.484 1.484	2,90 2,87 2,82 2,80 2,80	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA	KERA KLF13 AASS	12q22 15q12 7q31.3	eve morphogeness (sensu Manmalia)/// sensory perception /// visual perception transcription /// regulation of transcription DNA-dependent /// transcription from RVA polymerase III promoter electron transport /// lysine catabolism /// protein tetramerization 
1.519 1.498 1.484 1.484	2,90 2,87 2,82 2,80 2,80 2,80 2,79	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA	KERA KLF13 AASS CHD1L	12q22 15q12 7q31.3	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription of branscription DNA-dependent /// transcription from RNA polymerase II promoter electron transport /// lysine catabolism /// protein tetramerization 
1.519 1.498 1.484 1.484 1.484	2,90 2,87 2,82 2,80 2,80 2,80 2,79	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde symthase chromodomain helicase DNA binding protein 1-like	KERA KLF13 AASS CHD1L	12q22 15q12 7q31.3 1q12	eve morphogenesis (sensu Manmalia) /// sensory perception /// visual perception transcription /// regulation of branscription DNA-dependent /// transcription from RVA polymerase II promoter electron transport /// lysine catabolism /// protein tetramerization 
1.519 1.498 1.484 1.484 1.484	2,90 2,87 2,82 2,80 2,80 2,80 2,79 2,78	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde symthase chromodomain helicase DNA binding protein 1-like	KERA KLF13 AASS CHD1L	12q22 15q12 7q31.3 1q12	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of branscription DNA-dependent /// transcription from RNA polymerase II promoter dectron transport /// hysine catabolism /// protein tetramerization 
1.519 1.498 1.484 1.484 1.484	2,90 2,87 2,82 2,80 2,80 2,79 2,78 2,78	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA binding protein 1-like growth differentiation factor 15 ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide	KERA KLF13 AASS CHD1L	12q22 15q12 7q31.3 1q12	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of branscription DNA-dependent /// transcription from RNA polymerase II promoter electron transport /// hysine catabolism /// protein tetramenzation — signal transduction /// transforming growth factor beta receptor signaling pathway /// cell signaling potassium ion transport /// sodium ion transport /// metabolism /// ATP hydrohysi
1.519 1.498 1.484 1.484 1.484 1.477 1.477	2,90 2,87 2,82 2,80 2,80 2,80 2,76 2,78	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA binding protein 1-like growth differentiation factor 15 ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide Heparan sulfate (glucosarrine) 3	KERA KLF13 AASS CHD1L GDF15 ATP1A2	12q22 15q12 7q31.3 1q12 19p13.1-13.2 1q21-q23	eve morphogeness (sensu Manmalia)//// sensory perception /// visual perception transcription /// regulation of branscription DNA-dependent /// transcription from RVA polymerase III promoter electron transport /// hysine catabolism /// protein tetramerization 
1.519 1.498 1.484 1.484 1.484 1.477 1.476 1.475	2,90 2,87 2,82 2,80 2,80 2,80 2,79 2,78 2,78 2,78 2,78	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA binding protein 1-like growth differentiation factor 15 ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide Heparan sulfate (glucosamine) 3 D-sulfotransferase 1 origin recognition complex,	KERA KLF13 AASS CHD1L GDF15 ATP1A2 HS3ST1	12q22 15q12 7q31.3 1q12 19p13.1-13.2 1q21-q23 4p16	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of transcription DNA-dependent /// transcription from RNA polymerase II promoter electron transport /// lysine catabolism /// protein tetramerization 
1.519 1.498 1.484 1.484 1.484 1.477 1.477	2,90 2,87 2,82 2,80 2,80 2,80 2,80 2,78 2,78 2,78 2,78 2,78 2,78 2,78	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA binding protein 1-like growth differentiation factor 15 ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide Heparan sulfate (glucosamine) 3 O-sulfotransferase 1 origin recognition complex, subunt 1-like (yeast)	KERA KLF13 AASS CHD1L GDF15 ATP1A2 HS3ST1	12q22 15q12 7q31.3 1q12 19p13.1-13.2 1q21-q23	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of transcription DNA-dependent /// transcription from RNA polymerase II promoter electron transport /// lysine catabolism /// protein tetramerization 
1.519 1.498 1.484 1.484 1.484 1.477 1.476 1.475	2,90 2,87 2,82 2,80 2,80 2,80 2,79 2,78 2,78 2,78 2,78 2,78	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA binding protein 1-like growth differentiation factor 15 ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide Heparan sulfate (glucosamine) 3 O-sulfboarnsferase 1 origin recognition complex, subunit 1-like (yeast) nterphotoreceptor matrix	KERA KLF13 AASS CHD1L GDF15 ATP1A2 HS3ST1	12q22 15q12 7q31.3 1q12 19p13.1-13.2 1q21-q23 4p16 1p32	eve morphogenesis (sensu Manmalia) /// sensory perception /// visual perception transcription /// regulation of branscription DNA-dependent /// transcription from RNA polymerase III promoter electron transport /// lysine catabolism /// protein tetramerization 
1.519 1.498 1.484 1.484 1.484 1.477 1.476 1.475 1.476 1.473 1.406	2,90 2,87 2,82 2,80 2,80 2,80 2,79 2,78 2,78 2,78 2,78 2,65 2,65 2,64	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA binding protein 1-like growth differentiation factor 15 ATPase, Na + /K + transporting, alpha 2 (+) polypeptide Reparan sulfate (glucosarrine) 3 O-sulfotransferase 1 origin recognition complex, subunt 1-like (yeast) interphotoreceptor matrix proteoghycan 2 solute carrier family 27 (fatty	KERA KLF13 AASS CHD1L GDF15 ATP1A2 HS3ST1 ORC1L IMPG2	12q22 15q12 7q31.3 1q12 19p13.1-13.2 1q21-q23 4p16 1p32 3q12.2-q12.3	eve morphogenesis (sensu Manmalia) /// sensory perception /// visual perception transcription /// regulation of transcription DNA-dependent /// transcription from RNA polymerase III promoter electron transport /// lysine catabolism /// protein tetramentation 
1.519 1.498 1.484 1.484 1.484 1.477 1.476 1.473 1.406	2,90 2,87 2,82 2,80 2,80 2,79 2,78 2,78 2,78 2,78 2,78 2,65 2,64 2,60	homeo box C8 keratocan Kruppel-like factor 13 aminoadipate-semialdehyde synthase chromodomain helicase DNA binding protein 1-like growth differentiation factor 15 ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide Heparan sulfate (glucosamine) 3 D-sulfotransferase 1 origin recognition complex, subunit 1-like (yeast) niterphotoreceptor matrix proteoghycan 2 solute carrier family 27 (fatty acid transporter), member 6	KERA KLF13 AASS CHD1L GDF15 ATP1A2 HS3ST1 ORC1L IMPG2 SLC27A6	12q22 15q12 7q31.3 1q12 19p13.1-13.2 1q21-q23 4p16 1p32	eve morphogenesis (sensu Mammalia) /// sensory perception /// visual perception transcription /// regulation of branscription DNA-dependent /// transcription from RNA polymerase II promoter dectron transport /// lysine catabolism /// protein tetramerization 
	2.518 2.411 2.384 2.253 2.253 2.221 2.152 2.055 2.042 2.034 2.026 1.961 1.906 1.821 1.815 1.799 1.795 1.788 1.799 1.777 1.774 1.774 1.774 1.774 1.621 1.621 1.621 1.621 1.621	2.52 2.52 5.74 2.518 5.73 2.411 5.32 2.384 5.72 2.411 5.32 2.384 5.72 2.411 5.32 2.384 5.72 2.253 4.77 2.221 4.66 2.152 4.44 2.105 4.30 2.042 4.12 2.034 4.10 2.026 4.07 1.961 3.69 1.906 3.75 1.821 3.52 1.799 3.43 1.779 3.43 1.779 3.43 1.779 3.43 1.779 3.43 1.774 3.45 1.779 3.43 1.774 3.43 1.774 3.43 1.774 3.43 1.774 3.43 1.774 3.43 1.774 3.06 1.624 3.06 1.624 3.084 1.624 3.084 1.624 3.084 1.624 3.085 1.624 3.084 1.624 3.085 1.624 3.085 1.624	2.52 5,74 channel, subfamily J, member 3 2.518 5,73 fasciculation and elongation 2.411 5,32 protein zeta 1 (rygin I) 2.386 5,22 Caveolin 2 Gravestin 2 Gravestin 2 Gravestin 2 Gravestin 2 Gravestin 2 Gravestin 2 Gravestin 2 Gravestin 32 family, member A// acids (leucine- rich) nuclear phosphoprotein 32 family, member D /// acids (leucine-rich) nuclear phospho nabris metalloproteinase 23B /// matter metalloproteinase 23B /// 30 fame 6 chromosome 1 open reading 2.042 4,12 frame 10 2.034 4,10 KIAA1078 protein Gravesteed, (semaphorin) 2.026 4,07 30 mesenchyme homeo box 2 (growth arrest-specific homeo 1.961 3,69 box) 1.906 3,75 Neuron navigator 1 scretapogin, EF-hand calcium 1.815 3,52 Transcribed locus 1.799 3,48 tell division cycle 25A 1.799 3,43 Myosin IE 1.799 3,43 Myosin IE 1.797 3,431 myosin IE 1.794 3,20 Rematogenesis associated 2 1.624 3,08 TBP-1 interacting protein 1.621 3,00 Gi-14 protein 1.621 3,00 Gi-14 protein 1.621 3,00 Gi-14 protein 1.621 3,00 KIAA1199 interleukin 18 (interferon- 1.621 3,00 KIAA1199	C22         1.11         1.12	2.52         5.74         Example - Protectifying         2.52         5.74         Example - Protectifying         2.52         1.12 <th1.12< th=""> <th1.12< th=""> <th1.12< td="" th<=""></th1.12<></th1.12<></th1.12<>

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201452_at	1.342	2.54	Ras homolog enriched in brain	RHEB	7q36	signal transduction /// small GTPase mediated signal transduction
				· · · ·		
214418_at	1.336	2,52	hypothetical protein LOC196993	LOC196993	15q22.32	signal transduction /// frizzled-2 signaling
	1		wingless-type MMTV integration	ł		pathway /// cel-cell signaling ///
205990_s_at	1.333	2.52	site family, member 5A	WNTSA	3p21-p14	morphogenesis
203918_at	1.333	2,52	protocadherin 1 (cadherin-like	PCDH1	5q32-q33	regulation of transcription, DNA-dependent /// cell adhesion /// homophilic cell adhesion /// cell-cell signaling /// neurogenesis
203862_s_at	1.332	2,52	actinin, alpha 2	ACTN2	1q42-q43	
211347_at	1.324	2,50	CDC14 cell division cycle 14 homolog B (S. cerevisiae)	CDC14B	9q22.33	protein amino acid dephosphorylation
210610_at	1.319	2,49	carcinoembryonic antigen- related cell adhesion molecule 1 (biliary glycoprotein) insulin-like growth factor	CEACAM1	19q13.2	immune response /// pregnancy
215712_5_at	1.298		binding protein, acid tabile subunit	IGFALS	16p13.3	cell adhesion /// signal transduction
207894_s_at	1.287	2,44	T-cell leukemia/lymphoma 6	TCL6	14q32.1	
			chromosome 12 open reading			
207754_at	1.279	2,43	frame 2	C12orf2	12p12.3	signal transduction
217616_at	1.268	2 4 1	SNF1-like kinase	SNF1LK	21q22.3	protein amino acid phosphorylation /// cell cycle /// protein kinase cascade /// regulation of mitotic cell cycle /// regulation of cell differentiation
205151_s_at	1.26		KIAA0644 gene product	KTAA0644	7015.1	
217032_at	1.254		forkhead box D4 like 1	FOXD4L1	2q14.1	transcription /// regulation of transcription, DNA-dependent
40489_at	1.245	2,37	atrophin 1	ATN1	12p13.31	central nervous system development
216214_at	1.225		Clone 24504 mRNA sequence	'—		
221674_s_at	1.212	2,32	chordin	CHRD	3q27	skeletal development /// development
216245_at	1.193	2,29	Interleukin 1 receptor antagonist	ILIRN	2q14.2	inflammatory response
219832_s_at	1.176	2,26	homeo box C13 chromosome 7 open reading	HOXC13	12q13.3	regulation of transcription, DNA-dependent /// morphogenesis
53202_at	1.176	2,26	frame 25 pleckstrin homology-like	C7orf25	7p14-p11.2	
209803_s_at	1.164	2.24	domain, family A, member 2	PHLDA2	11015.5	imprinting /// apoptosis
217123_x_at	1.16		pro-melanin-concentrating hormone-like 1	PMCHL1	5p14.3	Synaptic transmission /// behavior
212923_s_at	1.154	2,23	chromosome 6 open reading frame 145	C6orf145	6p25.2	_
			Hypothetical gene supported by			
217625_x_at	1.143		AK024177	-	9q34.11	
221863_at	1.125	2,18	KIAA1193	KIAA1193	19p13.3	[—
216017_5_at	1.103	2,15	NGFI-A binding protein 2 (EGR1 binding protein 2) Cas-Br-M (murine) ecotropic	NABZ	12q13.3- q14.1	transcription /// regulation of transcription, DNA-dependent /// neurogenesis /// cell proliferation /// negative regulation of transcription
220638_s_at	1.098	2,14	retroviral transforming sequence c	CBLC	19q13.2	-
217633_at	1.095	2,14	chromosome 21 open reading frame 108	C21orf108	21q22.11	
216690_at	1.062		olfactory receptor, family 7, subfamily C, member 1	OR7C1	19p13.1	l
209373_at	1.052			BENE	2013	
		£,50	golgi associated, gamma		1	protein complex assembly /// intracellular
213772_s_at	1.047		adaptin ear containing, ARF binding protein 2	GGA2	16p12	protein transport /// intracellular protein transport /// intra-Golgi transport
219534_x_at	1.024		cyclin-dependent kinase Inhibitor 1C (p57, Kip2)	CDKN1C	11p15.5	regulation of cyclin dependent protein kinase activity /// G1 phase of mitotic cell cycle /// cell cycle /// cell cycle arrest /// negative regulation of cell pycle regulation of cell cycle
13997_at	1.008			KIAA0574	11p15.5	-
	1.000	∡,01]		TELEVILLE	142414	

Tab. A4d: Probe-sets up-regulated regulated upon IVMP treatment at day 21 compared to day 0; Probe-sets have a minimum change of 2-fold in 100% of patients;

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205731_s_at	I					transcription /// regulation of transcriptio
			nuclear receptor coactivator 2	NCOA2	8q13.3	DNA-dependent /// signal transduction
209353_s_at	-1.156	-2,2283873	hypothetical protein MGC16664	MGC16664	1925.2	<u> </u>
			chromosome 13 open reading frame	1		
214668_at	-1.164	-2,24077843	1	C13orf1	13q14	
		1			1	regulation of cell cycle /// mitosis /// sign
1 1		1	fibroblast growth factor 4 (heparin			transduction /// cell-cell signaling /// cell
1		1	secretory transforming protein 1,	1	1	proliferation /// positive regulation of cell
206783_at	-1.164	2 24077042	Kaposi sarcoma oncogene)	FGF4	110133	proliferation
200/00_8(	1.104	-2,2401/843	rapusi saturna uncogene/		11q13.3	ubiguitin-dependent protein catabolism //
1 1		1	1		1	
		1		I	1	ubiquitin cycle /// signal transduction ///
222374_at	-1.168		beta-transducin repeat containing	BTRC	10q24.32	Wnt receptor signaling pathway
206480_at	-1.175	-2,25792881	leukotnene C4 synthase	LTC4S	5q35	leukotriene biosynthesis
1	· · · · ·		catenin (cadherin-associated	1	1	
220815_at	-1.184	-2,27205853	protein), alpha 3	CTNNA3	10q22.2	cell adhesion
		1	Chromosome 10 open reading		1	1
213381_at	-1.202	-2,30058379		C100rf72	10q11.23	
		-,	cytochrome P450, family 2,		1	
		1	subfamily B, polypeptide 7		1	
	4.74	0.04007		0000000	1.0-12.2	
210272_at	-1.21	-2,3133/637	pseudogene 1	CYP2B7P1	19q13.2	electron transport
. 1		1				nucleosome assembly /// nucleosome
. 1		I.	1	1	1	assembly /// chromosome organization
208546_x_at	1.216	-2,32301748	histone 1, H2bh	HIST1H2BH	6p21.3	and biogenesis (sensu Eukaryota)
						nuclear mRNA splicing, via spliceosome //
		1	splicing factor, arginine/serine-rich	1	I	transcription /// regulation of transcription
1		1	8 (suppressor-of-white-apricot		1	DNA-dependent /// mRNA splice site
202773_s_at	.1 240	-2,37676821		SFRS8	12924.33	selection
	-1 289		regulated in COPD kinase	RCK	2021.3	protein amino acid phosphorylation
444100_6L	-1 208	+2,4430662	CTD (carboxy-terminal domain, RNA	nun	2421.3	
		[	polymerase II, polypeptide A) small			
213597_s_at			phosphatase-like	CTDSPL	3p21.3	
220360_at	-1 366	2,57754926	THAP domain containing 9	THAP9	4q21.3	<u> -</u>
			TPA-induced transmembrane			
219474_at	-1.373	-2,590088	protein	TTMP	3013.2	
		1	<u> </u>		1	
					í .	skeletal development /// cell-cell signaling
205290_s_at	1 375	2 50287014	bone morphogenetic protein 2	BMP2	20p12	/// cell differentiation /// growth
220843_s_at	-13/6	-2,5854//53	gene model 83	Gm83	8q22.3	transcription /// regulation of transcription
		1 1			1	
					1	DNA-dependent /// protein amino acid
		I	homeodomain interacting protein			
210148_at	-1 402	-2,64267681		ніркз	11p13	phosphorylation /// apoptosis
210148_at	-1 402	-2,64267681		ніркз	11p13	phosphorylation /// apoptosis
210148_at	-1 402	-2,64267681		HIPK3	11p13	phosphorylation /// apoptosis transcription /// regulation of transcription
210148_at	-1 402	-2,64267681		ніркз	11p13	phosphorylation /// apoptosis transcription /// regulation of transcription
210148_at	-1 402	-2,64267681		ніркз	11p13	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction ///
210148_at	-1 402	-2,64267681	kinase 3	ніркз	11p13	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor
			kinase 3			phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern
205188_s_at	-1 422	-2,6795872	kinase 3	HIPK3	11p13 5q31	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor
205188_s_at			kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila)			phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway
205188_s_at 206537_at	<u>-1 422</u> -1 423	-2,6795672 -2,68142518	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) 	SMAD5	5q31	phosphorylation /// apoptosis transcription /// regulation of transcription DNA dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway 
205188_s_at 206537_at	-1 422	-2,6795872	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) 			phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway specification /// BMP signaling pathway ion transport /// sodium ion transport /// signal transduction /// response to pH
205188_s_at 206537_at	<u>-1 422</u> -1 423	-2,6795672 -2,68142518	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) amiloride-sensitive cation channel 2, neuronal	SMAD5	5q31	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway ion transport /// sodium ion transport /// signal transduction /// response to pH ion transport /// polassium ion transport
205188_s_at 206537_at	<u>-1 422</u> -1 423	-2,6795672 -2,68142518	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) 	SMAD5	5q31	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway specification /// BMP signaling pathway ion transport /// sodium ion transport /// signal transduction /// response to pH
205188_s_at 206537_at	<u>-1 422</u> -1 423	-2,6795672 -2,68142518 -2,72262823	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) 	SMAD5  ACCN2	5q31	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway ion transport /// sodium ion transport /// signal transduction /// response to pH ion transport /// polassium ion transport
205188_s_at 206537_at 37953_s_at 217565_at	<u>-1 422</u> -1 423 -1 445 -1 449	-2,6795672 -2,68142518 -2,72262823 -2,73018744	kinase 3 SMAD, mothers against DPP homogg 5 (Drosophila) 	SMAD5	5q31  12q12 Xq25-q26	phosphorylation /// apoptosis transcription /// regulation of transcription DNA dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway 
205188_s_at 206537_at 37953_s_at 217565_at	<u>-1 422</u> -1 423 -1 445	-2,6795672 -2,68142518 -2,72262823	kinase 3 SMAD, mothers against DPP homogg 5 (Drosophila) 	SMAD5  ACCN2	5q31  12q12	phosphorylation /// apoptosis transcription /// regulation of transcription DNA dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway 
205188_s_at 206537_at 37953_s_at 217565_at	<u>-1 422</u> -1 423 -1 445 -1 449	-2,6795672 -2,68142518 -2,72262823 -2,73018744	kinase 3 SMAD, mothers against DPP homogg 5 (Drosophila) 	SMAD5	5q31  12q12 Xq25-q26	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic patterm specification /// BMP signaling pathway  
205188_s_at 206537_at 37953_s_at 217565_at	<u>-1 422</u> -1 423 -1 445 -1 449	-2,6795672 -2,68142518 -2,72262823 -2,73018744	kinase 3 SMAD, mothers against DPP homogg 5 (Drosophila) 	SMAD5	5q31  12q12 Xq25-q26	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway ion transport /// sodium ion transport /// signal transduction /// response to pM ion transport /// polassium ion transport /// glutamate signaling pathway /// synaptic transmission 
205188_s_at 206537_at 37953_s_at 217565_at	<u>-1 422</u> -1 423 -1 445 -1 449	-2,6795672 -2,68142518 -2,72262823 -2,73018744	kinase 3 SMAD, mothers against DPP homogg 5 (Drosophila) 	SMAD5	5q31  12q12 Xq25-q26	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway 
205188_s_at 206537_at 37953_s_at 217565_at	<u>-1 422</u> -1 423 -1 445 -1 449	-2,6795672 -2,68142518 -2,72262823 -2,73018744	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila)  amitoride-sensitive cation channel 2, neuronal glutamate receptor, ionotrophic, AMPA 3 visinin-like 1	SMAD5	5q31  12q12 Xq25-q26	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway 
205188_s_at 206537_at 37953_s_at 217565_at 203797_at	-1 422 -1 423 -1 445 -1 445 -1 453	-2,6795072 -2,68142518 -2,72262823 -2,73018744 -2,73776763	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) amiloride-sensitive cation channel 2, neuronal glutamate receptor, ionotrophic, AMPA 3 visinin-like 1 ropponn, rhophilin associated	SMAD5	5q31  12q12 Xq25-q26	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway ion transport /// sodium ion transport /// signal transduction /// response to pH ion transport /// sodium ion transport /// synaptic transmission 
205188_s_at 206537_at 37953_s_at 217565_at	-1 422 -1 423 -1 445 -1 445 -1 453	-2,6795072 -2,68142518 -2,72262823 -2,73018744 -2,73776763	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) amiloride-sensitive cation channel 2, neuronal glutamate receptor, ionotrophic, AMPA 3 visinin-like 1 ropponn, rhophilin associated	SMAD5	5q31  12q12 Xq25-q26	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway ion transport /// sodium ion transport /// signal transduction /// response to pH ion transport /// sodium ion transport /// synaptic transmission 
205188_s_at 206537_at 37953_s_at 217565_at 203797_at	-1 422 -1 423 -1 445 -1 445 -1 453	-2,6795672 -2,68142518 -2,72262823 -2,73018744	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) amiloride-sensitive cation channel 2, neuronal glutamate receptor, ionotrophic, AMPA 3 visinin-like 1 ropponn, rhophilin associated	SMADS 	5q31  12q12 Xq25-q26 2p24.3	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway
205188_s_at 206537_at 37953_s_at 217565_at 203797_at	-1 422 -1 423 -1 445 -1 445 -1 453	-2,6795072 -2,68142518 -2,72262823 -2,73018744 -2,73776763	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) amiloride-sensitive cation channel 2, neuronal glutamate receptor, ionotrophic, AMPA 3 visinin-like 1 ropponn, rhophilin associated	SMADS 	5q31  12q12 Xq25-q26 2p24.3	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway ion transport /// sodium ion transport /// signal transduction /// response to pH ion transport /// sodium ion transport /// synaptic transmission 
205188_s_at 206537_at 37953_s_at 217565_at 203797_at	-1 422 -1 423 -1 445 -1 445 -1 453	-2,6795072 -2,68142518 -2,72262823 -2,73018744 -2,73776763	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) amiloride-sensitive cation channel 2, neuronal glutamate receptor, ionotrophic, AMPA 3 visinin-like 1 ropponn, rhophilin associated	SMADS 	5q31  12q12 Xq25-q26 2p24.3	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming prowth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway 
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205188_s_at 206537_at 37953_s_at 217565_at 203797_at	-1 422 -1 423 -1 445 -1 445 -1 453	-2,6795672 -2,68142518 -2,72262823 -2,73018744 -2,73776763 -2,75108384	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) amboride-sensitive cation channel 2, neuronal glutamate receptor, ionotrophic, AMPA 3 visinin-like 1 ropponn, rhophilin associated protein 18	SMADS 	5q31  12q12 Xq25-q26 2p24.3	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway
205188_s_at 206537_at 37953_s_at 217565_at 203797_at	-1 422 -1 423 -1 445 -1 445 -1 453	-2,6795672 -2,68142518 -2,72262823 -2,73018744 -2,73776763 -2,75108384	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) 	SMADS 	5q31  12q12 Xq25-q26 2p24.3	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transformung growth factor beta receptor signaling pathway /// embryonic patterm specification /// BMP signaling pathway  ion transport /// sodium ion transport /// signal transduction /// response to pH ion transport /// polassium ion transport /// glutamate signaling pathway /// synaptic transmission  cytokinesis /// signal transduction /// Rho protein signal transduction /// Rho protein signal transduction /// Rho protein signal transduction /// Roportein signal transduction /// husion of sperm to egg plasma membrane (// cell-cell adhesion /// sperm motility regulation of transcription from RNA polymerase II promoter /// negative
205188 <u>s</u> at 206537_at 37953_s_at 217565_at 203797_at 220425_x_at	-1 422 -1 423 -1 445 -1 449 -1 453 -1 453	-2,6795672 -2,68142518 -2,72262823 -2,73018744 -2,73776763 -2,75108364	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) 	SMADS 	5q31  12q12 Xq25-q26 2p24.3 3q21.2	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway
205188 <u>s</u> at 206537_at 37953_s_at 217565_at 203797_at 220425_x_at	-1 422 -1 423 -1 445 -1 445 -1 453	-2,6795672 -2,68142518 -2,72262823 -2,73018744 -2,73776763 -2,75108384	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) amiloride-sensitive cation channel 2, neuronal glutamate receptor, ionotrophic, AMPA 3 visinin-like 1 ropportin, rhophilin associated protein 18 Mdm2, transformed 3T3 cell double minute 2, p53 binding protein (mouse)	SMADS 	5q31  12q12 Xq25-q26 2p24.3	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway
205188 <u>s</u> at 206537_at 37953_s_at 217565_at 203797_at 220425_x_at	-1 422 -1 423 -1 445 -1 449 -1 453 -1 453	-2,6795672 -2,68142518 -2,72262823 -2,73018744 -2,73776763 -2,75108384	kinase 3 SMAD, mothers against DPP homolog 5 (Drosophila) 	SMADS 	5q31  12q12 Xq25-q26 2p24.3 3q21.2	phosphorylation /// apoptosis transcription /// regulation of transcription DNA-dependent /// signal transduction /// transforming growth factor beta receptor signaling pathway /// embryonic pattern specification /// BMP signaling pathway

Tab. A4e
Probe Set ID 1002 FC Fold Change 11; A grant Gene Title; Gene Symbol Chromosoma FC GO Biological Process Description; F1
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NPAT

12q15-g21 1q42-q43

6q16.3-q21 1p32.3

19q13

2p23.3 5q11.2

6q23.1

9p24.1

16q22.1

1p22.3

11g22-g23

thyrotropin-releasing hormone

Glutamate receptor, ionotropic,

219937\_at -1 021 -2,02932509 degrading ectoenzyme 203862\_s\_at -1.027 -2,03778239 actinun, alpha 2

215655\_at -1.05 -2,07052985 kainate 2 215107\_s\_at -1.054 -2,07827854 hypothetical protein FL120619

-1 082 -2,11696879 ribokinase -1 086 -2,12284642 Integrin, alpha 1

209101\_at -1 09 -2,12874038 connective tissue growth factor

-2,0820432 delta-like 3 (Drosophila)

-2,17648488 Nuclear factor I/B cadherin 5, type 2, VE-cadherin

Caonern 5, type 2, Vi-Caonern 2,1992323 (Vascular getthelium) Synovial sarcoma, X breakpoint 2 -2,20381023 interacting protein nuclear protein, ataxia--2,20686748 telangiectasia locus

depletion response, sterol regulatory element binding-protein cleavage /// signal

---ion transport /// potassium ion transport /// glutamate signaling pathway /// synaptic transmission /// synaptic

transduction /// cell-cell signaling

---skeletal development 7/7 emoryonic

skeletai development /// emoryonic development (sensu Mammala) /// cell fate determination /// Notch signaling pathway /// Notch signaling pathway /// development /// neurogenesis /// cell differentiation antiohydrate metabolism /// D-nbose

protein biosynthesis regulation of cell growth /// DNA metabolism /// cell mobility /// cell adhesion /// epidermis development ///

regulation of transcription, DNA-dependent

cell adhesion /// homophilic cell adhesion

transcription /// regulation of transcription DNA-dependent /// signal transduction

transmission

metabolism

cell adhesion

response to wounding DNA replication /// transcription ///

Tab. A4e

219537\_x\_at -1.058

219222\_at 214660\_at

213032\_at

204677\_at

210871\_x\_at -1.14

211584\_s\_at -1.142

-1.122

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21259_att         1.460         24.217305         prode         24.217307           213770_att         1.500         -2.84912002         base suggerssor of res         SR         17211.2         prode transport           213770_att         1.500         -2.84912002         base suggerssor of res         SR         17211.2         prode transport         If an interpretation of transport           210715_1_1_1_1_1_1_1_1_1							
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21370_at         1500         2.44912802         Name sugnets made signification           21370_at         1501         2.48912802         Name sugnets made signification         Name sugnets made signification           210715_1_at         1516         2.48912802         Project made signification         Name sugnets         Name sugnets           210715_1_at         1516         2.48912802         Project made signification         Name sugnets         Name sugnets         Name sugnets           210715_1_at         1542         2.29752702         Project made sugnets         Name sugnets							
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210175 5. al.         1516         2.8509807         product in montor         PBLR         501-51         S0175 5. al.         1516         2.8509807         product in montor         PBLR         501-51         S0175 5. al.         1524         2.8509807         product in montor         PBLR         501-51         S0175 5. al.         1524         2.85098274         CMINE in montor         PBLR         501-51         S0175 5. al.         S01		1					
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20076 a. al.         150         2.8599007         production memotion         PDL         Sp1+p1         Interactional receptor production memotion           20078 J. al.         151         2.859912 (model)         152         2.879712 (model)         152         2.87972 (model)         152         2.8999000         152         2.8999000         152         2.8999000         152         2.89990000         152         2.89990000         152         2.89990000         152         2.89990000         152         2.89990000         152         2.89990000         152         2.89990000         152         2.89990000         152         2.899900000         152         2.89990000000000000000000000000000000000	1				•		
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205175_s.g.         1.950         -2.4646037         thin finger protein 222         2/87222         19:132         DNA-dependent           208379_att         1.957         -2.002106 (weeppessed)         PROVI         5023-924         -           21576_att         1.957         -2.002106 (weeppessed)         PROVI         5023-924         -           21576_att         1.95         -2.002106 (weeppessed)         PROVI         5023-924         -           21576_att         1.95         -2.002106 (weeppessed)         SC231 Intracting protein         SC231 Intracting protein         SC231 Intracting protein         SC231 Intraction and bogenesis           21632_ccll_1.01_03_3.0652106 (weeppessed)         ILS6         2023         arransport         IlL025-926			1	similar to cervical cancer suppressor	ł		
206175_z_ell         1.550         2.9484537         Pict Inc. Mag. protein         222         276722         1991.32         DNA-degendent           208379_d_t         1.567         2.028279 (a) vertragesed I         PB7V1         692.3-Q2         —           21576_d_t         1.50         2.0898905         Tetracycline transporter-Mag. protein         Tetracycline transport         PB7V1         692.3-Q2         —           21576_d_t         1.50         2.0898905         Tetracycline transporter-Mag. protein         SEC31P         Tetracycline transport /// Colgi           21612_a_st         1.60         3.06932890         meteorian or processor /// Similar to         NACEAS         3Q8         —           20816_3_st         1.60         3.0693281         Tetrackins in receptor /// Similar to         NACEAS         3Q8         —           208256_st         1.60         3.10016222         product (protein C)         MB2         10g11.2-Q2         pathway /// (mit more reporter)           208256_st         1.60         3.10074246         Tetrackin in receptor // Tit, variable         —         —         —           208274_st         1.60         3.10674246         Tetrackin in receptor // Tit, variable         —         —         —           208274_st         1.607	217104_at	-1 545	-2,91804069		LOC400410	15q25.1	<b>—</b>
203309_att         -1.507         -2.022160 methods         -1.507         -2.02176         -1.507         -2.02176         -1.507         -2.02176         -1.508 <td>206176</td> <td>1.000</td> <td>204040500</td> <td>Tine finner centein 333</td> <td>7NE222</td> <td>10012.2</td> <td></td>	206176	1.000	204040500	Tine finner centein 333	7NE222	10012.2	
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215746_att         158         -2,0690685         Tetracycline transporter-tike protein         TETRAH         4p16.3         transport           216372_att         1010         -3,06523927         relations antigen family A_6         62/31         transport           216372_att         1010         -3,06523927         relations antigen family A_6         62/38         42/38	208329_at	-1 567	-2,9628796		PBOV1	6q23-q24	
216392_s_gl - 1.600         -3.0604033         SEC21 interacting protein         SEC21P         Log2-s_Q2         organization and bogenesis           216402_s_gl - 1.603         -3.0604033         SEC21 interacting interacting interacting interaction interacting interaction interactinteractintex interaction interaction interactintex interaction in		1	1			- 1	
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214612_r_al         1916         3.08523982         melanoma antigen family, A         MACEA         YQ28 and YQ28	316703				CE (73.31F	10-35 -35	
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208164         5         1         623         3,308147         Interlexitin 9 receptor         UCX00481         16p13.3         depart transduction /// cell proliferation           208164         5,3081487         Interlexitin 9 receptor         UCX00481         16p13.3         depart transduction /// cell proliferation           207256         at         1.66         3,1691452         jobble toponic defect)         HBL2         10p11.2-q21         philmay /// response to oxidable stress           207256_at         1.66         3,169146         beary dual	217012_X_80	1-1010	-3,00323882	Instanting an user raining A, 0			
207255_at         -1.66         -3.10015225         -3.0015222         -3.0015222         -3.0015222         -3.0015222         -3.0015222         -3.0015222         -3.0015222         -3.0015222         -3.0015222         -3.0015222         -3.00172	ļ		•	interleukin 9 receptor /// similar to	IL9R ///		
207256_at         166         3_16015529         2_solute (opsonk defca)         MB2         10g11.2g21         phosphate transport (/// moure response /// complement activation, cassical /// cassical /// complement activation, cassical /// cassica //// cassical ///// cassical ////// cassical //// cassical ////	208164_s_at	-1 623	-3,0801487	interleukin 9 receptor	LOC400481	16p13.3	signal transduction /// cell proliferation
207256_at         166         3_16018529         2_solutie (opconk defca)         MB2         10g11.2g1         phosphate transport (/// immune response /// immune response /// immune response /// immune response           201640_x_at 1 (603         -3_16674268 (heavy chain /// ight memmatical factor RP-TTL, variable heavy chain /// ight memmatical factor RP-TTL, variable /// immune response         -         -         -         -           201640_x_at 1 (603         -3_16674268 (heavy chain // immomentary is 1.5k family // immomentary immomentary is 1.5k family // immomentary immomentary immomentary // immomentary immomentary immomentary // immomentary immomentary immomentary // immomentary immomentary /			1				complement activation lectic pathway ///
20725 st.         166         3,1601252 South (concerned and // Logh         /// complement address on cassial           20725 st.         168         3,1601261 South (concerned and // Logh         10g11.2-211         10g11.2-211         10g11.2-211           211640		1					
20725 at.         160         -3,16016522 (2, solute (opconic defect))         MB2         10(11.2-21) [at/way/// response to oxidative stress.           211640 z. at.         1637 Addition (2011)         Variable heavy chain // 1041         -         -           211640 z. at.         1637 Addition (2011)         Variable heavy chain // 1041         -         -           211640 z. at.         1637 Addition (2011)         Variable heavy chain // 1041         -         -           21090 j.at.         1678 -3,1080707         -         -         -         -           20000 j.at.         1677 - 3,21986455         neuro-oncological ventral antigen 1         NOVA1         14g         RNA splicing /// Synaptic transmission /// Norontory behavior /// Norottory behavior /// Norontory behavior //				mannose-binding lectin (protein C)			
variable heavy chain	207256_at	-1 66	-3,16016525	2, soluble (opsonic defect)	MBL2	10q11.2-q21	
21640_2,zt         1.963         -3,16734b Reay chain             21504_2,zt         1.963         -3,16734b Reay chain             21504_2,zt         1.963         -3,17944b Reay chain             20007_att         1.976         -3,19540767              2014_2,zt         1.976         -3,19540767              2014_3,zt         1.976         -3,21984555 neuro-oncological ventral antigen 1         NOVA1         14g         RMX sploring /// tocomotory behavior /// KAS sploring /// tocomotory behavior /// RAS sploring /// tocomotory behavior // RAS s							
211640_x_at							
21504 sst         -1609        517041        51044	211640 × 31	1 661	3 18674346				_
215024, s_ati, 1.669         -3,176941 member 1         TH4SF1         321-225	2	11005	-5,100/4340				
207437_st         1.887         -3,21884455         neuro-oncological ventral antigen 1         NOVA1         14g         RNA splicing           207437_st         1.1887         -3,21884455         neuro-oncological ventral antigen 1         NOVA1         14g         RNA splicing         Iteramitisson /// sources/ splaining catalogical seatures/ splaining catalogical seatur			-3,179941		TH4SF1	3q21-q25	
207437_at         -1.697         -3,21986455         neuro-oncological ventral antigen 1         NOVA1         14g         RNA splicing         regulation of cell growth /// intracellular signaling cascade /// negative engulation of signal transduction /// cytokine and chemokine mediated signaling cascade // negative mokine mediated caspaling negative of cell growth // intracellular signaling cascade // negative mokine mediated signalit masport           209648_x_at         -1.74         -3,34032566         decombor Network // sector negative of cell growth // intracellular signalit (TPase mediated signal transduction // peptidyl-amino acid contraction // peptidyl-amino acid fact 1, ratio - 3,349217 sector 1 (Rt1, growth hormone fact 2 q21         N-linked glycosylabon           20720_at         -1.78         -3,432420175 sector // sectorsor (hormogon segregative sectorsor // prodem transcription Rt1 // sectorsor // prodem transcription // regative sectorsor // prodem transcription grows sectorsor // interactive grows sectorsor // predidyl-amino sectorsor // intrasectorsor // regative se	208007_at	-1 676	-3,19540767		-	-	
207437_at         -1.687         -3,21980455         neuro-oncological ventral antigen 1         NOVA1         14g         RNA splcing         RNA splcing           207437_at         -1.687         -3,21880455         neuro-oncological ventral antigen 1         NOVA1         14g         RNA splcing         regulation of cell growth /// intracellular signaling cascade /// JNA-STAT cascade // JNA-STAT cas							
207437_at         1.687         -3,21986455         neuro-oncological ventral artigen 1         NOVA1         14q         RNA splcing           207437_at         1.687         -3,21986455         neuro-oncological ventral artigen 1         NOVA1         14q         RNA splcing           209648_x_at         1.74         -3,34035168         suppressor of cytokine signaling 5         SOC55         2p21         Thelper 1 cell differentiation /// negative           20955_s_at         1.75         -3,3635666         family         RA838         1p32-p31         /// cytokine and chemokine mediated signal transduction           20955_s_at         1.761         -3,38932674         spantate beta-hydroxytase         ASPH         8g12.1         modification         modification /// peptidyl-amino acid           210955_s_at         1.761         -3,389274         spantate beta-hydroxytase         ASPH         8g12.1         modification /// peptidyl-amino acid           210427_at         1.765         -3,39874 KAIA2150           exocytosis /// post-Goigi transport ///           218748_s_st         1.78         -3,43428175         SEC10-like 1 (S. cerevisiae)         SEC10.1         14g22.3         protein transport /// prost-Goigi transport /// prost-Goigi transport /// prost-Goigi transport /// prost-Goigi transport /// pranscription non RNA polymerase II protein transport i/							
206648_x_at         -1.74         -3.34035168         suppressor of cytokine signaling 5         SOC55         2221         Thelger 1 cell differentiation /// negative regulation of Signal transduction /// cytokine and chemokine mediated signaling pathway // postive regulation of Signal transduction /// cytokine and chemokine mediated signaling pathway // postive regulation of Xignal transduction /// egative           20954.5_x.at         1.74         -3.34035168         Suppressor of cytokine signaling 5         SOC55         2221         Thelger 1 cell differentiation /// negative           20952.5_x.at         1.764         -3.34035168         Suppressor of cytokine signaling 5         SOC55         Thelger 1 cell differentiation /// negative           20952.5_x.at         1.764         -3.34035168         Suppressor of cytokine signaling 5         SOC55         Social These mediated signal transduction /// negative           210956_s.at         1.761         -3.38032074         aspartate beta-hydroxylase         ASPH         Bg12.1         modification         modification           210427_at         1.785         -3.3492(175         SEC10.1         14g22.3         modification         modification         modification           216427_at         -1.781         -3.43426(175         SEC10.1         14g22.3         modification         modification           207846_s.t         -1.781         -3.433484302 <t< td=""><td></td><td></td><td></td><td></td><td></td><td>140</td><td></td></t<>						140	
209648_x_at     1.74     -3,34035168     suppressor of cytokine signaling 5     SOCSS     2p21     Thetiper 1 cell differentiation /// potkine regulation of signaling pathway /// potkine regulation of cell profileration /// peptidyl-amino acid       20966_s_t     -1.781     -3,43426175 SEC10-4ike 1 (5. cerevisiae)     SEC10.1 14q22.3     protein transport /// peptidyl-amino acid       207846_st     -1.781     -3,43426175 SEC10-4ike 1 (5. cerevisiae)     SEC10.1 14q22.3     protein transport /// potkine regulation of cell       207846_st     -1.781     -3,43604302 ffactor 1 (Pc1, growth hormone Poulfs)     POU formain, class 1, transcription factor 1 (Pc1, growth hormone Poulfs)     protein transport /// regulation of cell       207846_st     -1.781     -3,4535823 glucosaminytransferase     MGATS     2021     N-linked glycosylabon       207846_st     -1.788     -3,50156532 hypothetical prot	207437 at	1-1 687	-3.21986455	neuro-oncological ventral antioen 1	INOVAL I		
209648_x_at         -174         -3,34035186         suppressor of cytokine signaling 5         SOCSS         2p1           209548_x_at         -174         -3,3402566         decomptionuclease I+like 2         DRASE112         16p13.3         DRA catabolism           20952_s_st         -174         -3,34802566         decomptionuclease I+like 2         DRASE112         16p13.3         DRA catabolism           20955_s_at         -175         -3,3885866         framity         RAB3B         Ip32-p31         I// protein transport           210956_s_at         -1761         -3,38932074         asparate beta-hydrox/tase         ASPH         8g12.1         modification           210956_s_at         -178         -3,43420175         SEC10-like 1 (S. cerevisiae)         SEC10.1         14g22.3         protein transport /// transport // transport /// transport // transport /	207437_at	-1 687	-3,21986455	neuro-oncological ventral anugen 1	NOVA1	A-TN	
209648_x at 1.74         -3,34035186 suppressor of cytokine signaling 5         SOCSS         2021         T-Helper 1.cell differentiation /// negative.           2097192_at         1.744         -3,34035186 suppressor of cytokine signaling 5         SOCSS         2021         T-Helper 1.cell differentiation /// negative.           209525_s_at         1.75         -3,3835866         decomptionuclease 14/ke 2         ONASE112         16p13.3         DMA catabolism           209525_s_at         1.76         -3,3835866         denominative regulation of // negative regulated signal transduction           210996_s_at         1.761         -3,3892074         assative het-hydroxylase         ASPH         8q12.1         modification           210427_at         1.765         -3,38924         AUA2150              216427_at         1.785         -3,3492175         SEC10-like 1 (S. cerevisiae)         SEC10.1         14g22.3         protein transport /// veskie docking           218748_s_at         -1.78         -3,43484175         SEC10-like 1 (S. cerevisiae)         SEC10.1         14g22.3         protein transport /// veskie docking           207846_at         -1.781         -3,4535823 glucosaminytransferase         MGATS         2q21         N-linked glycosylabon           207846_at         -1.788         <	207437_at	-1 687	-3,21986455	neuro-oncological ventral anugen 1	NUVAI	<u></u>	regulation of cell growth /// intracellular
209648_x.tl         174         -3.34035189         suppressor of cytokine signaling 5         SOCS5         2021         T-Helper         Identifiable         T-Helper         Identifiable	207437_at	<u>-1 687</u>	-3,21986455	neuro-oncological ventral anogen 2		<u> </u>	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade ///
207192_at         1.744         -3,34982565 (accomboundess L-like 2         DNA catabolism           20592_5_st         1.75         -3,3355666 family         RAB3B, member RAS oncogene         Small CTPses mediated signal transduction           210996_s_at         1.761         -3,3832974 aspartate beta-hydroxylase         ASPH         Bq12.1         modification           210996_s_at         1.761         -3,38932974 aspartate beta-hydroxylase         ASPH         Bq12.1         modification           210996_s_at         1.776         -3,38932974 aspartate beta-hydroxylase         ASPH         Bq12.1         modification           216427_at         1.776         -3,34974 (KAL2150              218748_s_at         1.78         -3,43428175 SECIO-like 1 (S. cerevisiae)         SECI0.1         14g22.3         protein transport /// viside docking           207846_at         -1.781         -3,43428175 SECIO-like 1 (S. cerevisiae)         SECI0.1         14g22.3         protein transport /// exployed endent /// transcription, DNA-dependent /// transcription, from RNA polymerase II provider about /// capanogeness           207846_at         -1.781         -3,43428175         SECI0-like 1 (S. cerevisiae)         SECI0.1         14g22.3         Hinked glycosylabon           207846_at         -1.788         -3,47256091 (situal -1,6-)-glyco	207437_at	-1 687	-3,21986455	neuro-oncological ventral anugen 1			regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction
AB38, member RAS oncogene         small GTPase mediated signal transduction           205925_s_at         -175         -3,36356566 family         RA838         1p32-p31         /// potelin transport           210996_s_at         -1.761         -3,38932974         spantate beta-hydroxylase         ASPH         8g12.1         mudification           210996_s_at         -1.761         -3,38932974         spantate beta-hydroxylase         ASPH         8g12.1         modification           216427_at         -1.765         -3,38974         KALN2150           excytosis /// post-Golgi transport /// veskic docking           218748_s_at         -1.78         -3,4426175         SEC10-like 1 (Sc. cerevisiae)         SEC10L1         14g22.3         protein transport /// veskic docking           207846_at         -1.781         -3,43664302         factor 1 (Pt1, growth hormone         POU domain, class 1, transcription         /// requision of transcription, RNA ophrenses II           207846_at         -1.781         -3,45335822         glucosimintransferase         MGAT5         2q21         N-linked glycosylabon           206720_at         -1.788         -3,45335823         glucosimintransferase         MGAT5         2q21         N-linked glycosylabon           219887_at         -1.808         -3,50156552	207437_at	-1 687	-3,21986455	neuro-oncological ventral anugen 1	NOVAI	<u>.</u>	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chemokine mediated
205925_5_at         1.75         -3.36356566         family         FA838         1p32-p31         /// protein transport           210896_5_at         -1.761         -3.38932974         aspartate beta-hydroxylase         ASPH         Bq12.1         mudification           210896_5_at         -1.761         -3.38932974         aspartate beta-hydroxylase         ASPH         Bq12.1         mudification           216427_at         -1.765         -3.38914         KALX150	209648_x_at	-1 74	-3,34035168	suppressor of cytokine signaling 5	50C55	2p21	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chemokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative.
210896_5_at     -1.761     -3.38932074     aspariate beta-hydroxylase     ASPH     8g12.1     modification       210427_at     -1.785     -3.38974     kIA2150         216427_at     -1.785     -3.38974     kIA2150         216427_at     -1.785     -3.43426175     SEC10-like 1 (S. cerevisiae)     SEC10L1     14g22.3     protein transport /// veskie docking       218748_s_at     -1.78     -3.43864302     factor 1 (Pc1, growth homone     POU domain, class 1, transcription     /// transcription nRNA polymerse II       POU domain, class 1, transcription     matness (1) protein transport /// veskie docking     regulation of transcription nRNA polymerse II       207846_at     -1.781     -3.43864302     factor 1 (Pc1, growth homone     POUIF1       206720_at     -1.788     -3.4535820     glucosiminytransferase     MGAT5     2q21       206720_at     -1.788     -3.4535820     glucosiminytransferase     MGAT5     2q21     N-linked glycosylabon       81737_at     -1.788     -3.47256021 (gPL2×X)          219887_at     -1.818     -3.52592063     presenilin 2 (Alzheimer disease 4)     PSEN2     1g31-g42       204261_5_s_at     -1.818     -3.52592063     presenilin 2 (Alzheimer disease 4)     PSEN2     1g3	209648_x_at	-1 74	-3, <u>34035168</u> -3,34982595	suppressor of cytokine signaling 5 decxyribonuclease 1-like 2	50C55	2p21	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine and chemokine mediated signaling pathway /// positive regulation of T-heiper 1 cell differentiation /// negative DNA catabolism
210996_5_at         1.761         -3,38932974 asparate beta-hydroxytase         ASPH         8q12.1         modification           216427_at         -1.761         -3,38932974 asparate beta-hydroxytase         ASPH         8q12.1         modification           216427_at         -1.765         -3,38974 (KLQ2150            exocytosis /// post-Golgi transport /// vesked docking           218748_5_at         -1.78         -3,43426175 SEC10-like 1 (S. cerevisiae)         SEC10L1         14q22.3         protein transport /// vesked docking           207846_at         -1.781         -3,43864302 factor 1)         POU domain, class 1, transcription from RNA pohymerase II promoter /// regaine regulation of cell promoter /// regaine regulation of cell protein transport /// vesked docking           207846_at         -1.781         -3,43864302 factor 1)         POUI for annone         POUIF1         aptification /// organogenesis           206720_at         -1.788         -3,4385823 glucosaminytransferase         MGAT5         2q21         N-linked glycosylabon           3tmärt borophy Secretory phospholipase A2 precursor (Phosphathylchiotine 2- acylthydrotase CA) (Cill SPLA2)          16p13.11            219887_at         -1.808         -3,50156532 hypothetical protein FU10786         FU10786         11q13.2            21987_at	209648_x_at 207192_at	- <u>1 74</u> - <u>1 744</u>	-3,34035168 -3,34982595	suppressor of cytokine signaling 5 decoyribonuclease I-like 2 RAB3B, member RAS oncogene	SOCS5 DNASE1L2	2p21 16p13.3	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chemokine mediated signaling pathway /// positive regulation of T-heiper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction
216427_at         1.765         -3,39874 K4IA2150	209648_x_at 207192_at	- <u>1 74</u> - <u>1 744</u>	-3,34035168 -3,34982595	suppressor of cytokine signaling 5 decoyribonuclease I-like 2 RAB3B, member RAS oncogene	SOCS5 DNASE1L2	2p21 16p13.3	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine and chernokine mediated signaling pathway /// positive regulation of T-heiper 1 cell differentiation /// negative_ DNA catabolism small GTPase mediated signal transduction /// protein transport
218748_s_at       -1.78       -3,43426175       SEC10-like 1 (S. cerevisiae)       SEC10.1       14q22.3       protein transport /// vesice docking         218748_s_at       -1.78       -3,43426175       SEC10-like 1 (S. cerevisiae)       SEC10.1       14q22.3       protein transport /// vesice docking         207846_at       -1.781       -3,43684302 factor 1)       -3,43684302 factor 1)       POUI form RNA polymerase II         207846_at       -1.781       -3,43684302 factor 1)       POUI factor 1)       POUI f1       3p11       protein transport /// vesice docking         206720_at       -1.788       -3,45335823 plucosaminytransferase       MGAT5       2q21       N-linked glycosylabon         206720_at       -1.788       -3,45335823 plucosaminytransferase       MGAT5       2q21       N-linked glycosylabon         206720_at       -1.788       -3,45335823 plucosaminytransferase       MGAT5       2q21       N-linked glycosylabon         219887_at       -1.696       -3,50156352 hypothetical protein FLJ10786       11q13.2	209648_x_at 207192_at 205925_5_at	-1 74 -1 744 -1.75	-3,34035168 -3,34982595 -3,38358566	suppressor of cytokine signaling 5 deoxyribonuclease I-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase	SOCS5 DNASE1L2 RAB3B	2p21 16p13.3 1p32-p31	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chemokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid
218748_s_at       -1.78       -3,43428175       SEC10-like 1 (S. cerevisiae)       SEC10.1       14g22.3       protein transport /// vesicle docking         207846_at       -1.781       -3,43484302       factor 1 (Prt.1, growth hormone factor 1 (Prt.1, growth hormone promoter /// negative regulation of cell promoter /// negative regulation of cell         20720_at       -1.788       -3,4533827 at -1.788       -3,4533827 at -3,4533827 at -1.808       -3,4533828 at -3,47256091 (SPLA2-X)       MGAT5       2q21       N-linked glycosylation         219887_at       -1.808       -3,47256091 (SPLA2-X)       -       16p13.11          219887_at       -1.808       -3,52582083       presenilin 2 (Alzheimer disease 4)       PSEN2       11q13.2          204261_5_at       -1.818       -3,52582083       presenilin 2 (Alzheimer disease 4)       PSEN2       1q31-q42       protein processing /// amyloid prec         214375_at       -1.818       -3,52582083       presenilin 2 (Alzheimer disease 4)       PSEN2       1q31-q42       protein processing /// amyloid prec         214375_at       -1.872       -3,68039697       protein 1 lippin beta 1 /// similar to PTPRF interacting protein protein protein processing /// amyloid prec       12p11.23- protein processing ///	209648_x_at 207192_at 205925_s_at 210896_s_at	-1 74 -1 744 -1.75 -1.761	-3,34035168 -3,34902595 -3,38358566 -3,38932974	suppressor of cytokine signaling 5 decxyritbonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDM4: FU22786 fis, clone	SOCS5 DNASE1L2 RAB3B	2p21 16p13.3 1p32-p31	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chemokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid
207846_st         -1.781         -3,43864302 factor 1 factor 1 (Pt1, growth homone peter 2,644-acty)         POU formain, class 1, transcription factor 1 (Pt1, growth homone peter 2,644-acty)         POUIF1         3p11         proinferstion (// regardgenesis protein 2,644-acty)           206720_at         -1.781         -3,43864302 factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,644-acty)         POUIF1         3p11         proliferation (// organogenesis           206720_at         -1.788         -3,45335823 glucosaminytransferase Similar to Group X secretary phospholipase QX (GX SPL2)         N-linked glycosylabon         N-linked glycosylabon           81737_at         -1.796         -3,47256001 (PHL/A2-X)         -         16p13.11            219887_at         -1.808         -3,50156532 hypothetical protein FLJ10786         FLJ10786         11q13.2            219887_at         -1.818         -3,52592083 presenilin 2 (Alzheimer disease 4) Proken L1 (// in the target 1) // in the ceptor processing /// anyloid prec          16p13.11            204261_5_at         -1.816         -3,52592083 presenilin 2 (Alzheimer disease 4) Proken L1 (lipit hetta 1) // in the target protein protein processing /// anyloid prec             214375_at         -1.872         -3,66039607 binding to PTRFi Interacting protein binding protein 1 lipith beta 1) // in the ceptor rype f pohypeptide-interacting protein- torsine phosphatase receptor rype f po	209648_x_at 207192_at 205925_s_at 210896_s_at	-1 74 -1 744 -1.75 -1.761	-3,34035168 -3,34902595 -3,38358566 -3,38932974	suppressor of cytokine signaling 5 decxyritbonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDM4: FU22786 fis, clone	SOCS5 DNASE1L2 RAB3B	2p21 16p13.3 1p32-p31	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chemokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification
207846_at     -1.781     -3,43864302 factor 1 (Pt1, growth hormone factor 1 (Pt1, growth hormone     POUIF1     3p11     proliferation (// reparciption from RNA polymerase II provider regulation of cell provider regulation regulation of cell provider regulation regulation of cell provider regulation regulation of cell provider regulation regulation regulation regulation provider regulation regulation regulation regulation regulation regulation regulation regulation regulation provider regulation regulation regulation regulation regulation provider regulation regulation regulation regulation provider regul	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at	-1 74 -1 744 -1.75 -1.761 -1.765	-3,34035168 -3,34962565 -3,38358566 -3,38932974 -3,39974	suppressor of cytokine signaling 5 decxyribonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDNA: FLJ22786 frs, clone KALA2150	SOCS5 DNASE1L2 RAB3B ASPH 	2p21 16p13.3 1p32-p31 8q12.1	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine and chernokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification — execotosis /// post-Golgi transport ///
207846_at     -1.781     -3,43864302 factor 1     Point (Pt1, growth hormone pouliferation of cell proliferation (// organogenesis       207846_at     -1.781     -3,43864302 factor 1     Poul F1     3p11     promoter /// negative regulation of cell proliferation (// organogenesis       206720_at     -1.788     -3,45335823 plucosaminytransferase     MGAT5     2q21     N-linked glycosylabon       206720_at     -1.788     -3,45335823 plucosaminytransferase     MGAT5     2q21     N-linked glycosylabon       206720_at     -1.788     -3,45335823 plucosaminytransferase     MGAT5     2q21     N-linked glycosylabon       206720_at     -1.788     -3,45335823 processing/lipase A2 precursor (Phosphatdylcholine 2- acylhydrolase G7) (GX SPLA2)     -     16p13.11        219887_at     -1.808     -3,50156532 hypothetical protein FLD10786     FLD10786     11q13.2        219887_at     -1.818     -3,52592093 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein recessing /// anyloid prec       204261_5_at     -1.818     -3,52592093 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// anyloid prec       214375_at     -1.8172     -3,66039607 binding	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at	-1 74 -1 744 -1.75 -1.761 -1.765	-3,34035168 -3,34962565 -3,38358566 -3,38932974 -3,39974	suppressor of cytokine signaling 5 decxyribonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDNA: FLJ22786 frs, clone KALA2150	SOCS5 DNASE1L2 RAB3B ASPH 	2p21 16p13.3 1p32-p31 8q12.1	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chemokine mediated signaling pathway /// positive regulation of T-heiger 1 cell differentiation /// negative DNA catabolism small CTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-armino acid modification 
207846_at     -1.781     -3,43684302     factor 1) mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl-     POUIF1     3p11     protiferation /// organogenesis       206720_at     -1.788     -3,4533823     glucosaminytransferase     MGAT5     2q21     N-linked glycosylabon       206720_at     -1.788     -3,4533823     glucosaminytransferase     MGAT5     2q21     N-linked glycosylabon       2077_at     -1.788     -3,47258091 (SPLA2-X)     -     16p13.11        219887_at     -1.808     -3,50156532     hypothetical protein FL110786     FL10786     11q13.2       204261_5_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       204261_5_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       204261_5_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       214375_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       214375_at     -1.872     -3,68039897     binding     1/// protein binding     1// protein protein protein protein-tyrosine phosphatase receptor-type f polypept	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at	-1 74 -1 744 -1.75 -1.761 -1.765	-3,34035168 -3,34962565 -3,38358566 -3,38932974 -3,39974	suppressor of cytokine signaling 5 decxyribonuclease 1-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CON4: FU22786 fis, clone KALA2150 SEC10-like 1 (S. cerevisiae)	SOCS5 DNASE1L2 RAB3B ASPH 	2p21 16p13.3 1p32-p31 8q12.1	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chernokine mediated signaling pathway /// positive regulation of Thelper 1 cell differentiation /// negative PMA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification  excoytosis /// post-Golgi transport /// protein transport /// vesicle docking regulation of transcription, DNA-dependent
206720_at     -1.788     -3,45335823 glucosaminytransferase     MGAT5     2q21     N-linked glycosylabon       206720_at     -1.788     -3,45335823 glucosaminytransferase     MGAT5     2q21     N-linked glycosylabon       81737_at     -1.788     -3,45335823 glucosaminytransferase     MGAT5     2q21     N-linked glycosylabon       81737_at     -1.786     -3,47256091 (5PLA2:X)     -     -     16p13.11        219887_at     -1.808     -3,50156532 hypothetisal protein FU10786     FU10786     11q13.2        219887_at     -1.818     -3,52592083 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// intracellular signaling cascade /// apoptotic program /// chromosome organization and biogenesis (sensu Eukarysta) /// chromosome organization and biogenesis /// apoptotic program /// protein i fiorin teta 1) /// similar to PTPRF interacting protein binding protein 1	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at	-1 74 -1 744 -1.75 -1.761 -1.765	-3,34035168 -3,34962565 -3,38358566 -3,38932974 -3,39974	Suppressor of cytokine signaling 5 decoyntbonuclease 1-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CONA: FU22786 fis, clone KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription	SOCS5 DNASE1L2 RAB3B ASPH 	2p21 16p13.3 1p32-p31 8q12.1	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine and chemokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification 
206720_at     -1.788     -3,45335823 glucosaminytransferase     MGAT5     2q21     N-linked glycosylation       206720_at     -1.788     -3,45335823 glucosaminytransferase     MGAT5     2q21     N-linked glycosylation       206720_at     -1.788     -3,45335823 glucosaminytransferase     MGAT5     2q21     N-linked glycosylation       20720_at     -1.788     -3,47258091 (sPLA2-X)     -     16p13.11        219887_at     -1.808     -3,5015832 hypothetical protein FU10786     FU10786     11q13.2        219887_at     -1.808     -3,5015832 hypothetical protein FU10786     FU10786     11q13.2        204261_5_at     -1.818     -3,52592083 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       204261_5_at     -1.818     -3,52592083 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       204261_5_at     -1.818     -3,52592083 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       204261_5_at     -1.818     -3,62592083 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       204261_5_at     -1.818     -3,62592083 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing ///	209648 <u>x_at</u> 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at	-1 74 -1 744 -1.75 -1.761 -1.765 -1.78	-3,34035168 -3,34962566 -3,38358566 -3,38932974 -3,38974 -3,43426175	Suppressor of cytokine signaling 5 decxyribonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDNA: FLJ22786 frs, done KALA2150 SEC10-like 1 (S, cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone	SOCSS DNASE112 RA838 ASPH  SEC10L1	2p21 16p13.3 1p32-p31 8q12.1  14q22.3	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification — — exocytosis /// post-Golgi transport /// protein transport /// vesicle docking regulation of transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// negative regulation of cell
206720_at     -1.788     -3,45335823     glucosaminytransferase     MGATS     2q21     N-linked glycosylation       Similar to Group X secretory phospholipase A2 precursor (Phosphatdycholine 2- acylhydrotase GX) (GX SPLA2)     -     16p13.11        219887_at     -1.808     -3,50156532     hypothetical protein FU10786     FU10786     11g13.2        219887_at     -1.808     -3,50156532     hypothetical protein FU10786     FU10786     11g13.2        204261_s_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4) protein 1 (tiprin beta 1) /// similar to PTRF interacting protein binding protein 1 (tiprin beta 1) /// similar to PTRF interacting protein binding protein 1 isoform 1; liprin-beta 1; liprin related protein; protein- tyrosine phosphatase receptor type f potypeptide-interacting protein- to RTRF, distase receptor type f potypeptide-interacting protein- to RTRF, distase receptor type f potypeptide-interacting protein- to RTRF, distase receptor type f potypeptide-interacting protein- to RTRF, membrane 2     12p11.23- AT282     cell adhesion anglogenesis (// signal transport /// calcium ion transport /// metabolism       216120_s_at     -1.847     -3,65571923     anglopoletin 2 anglopoletin 2     ANGPT2     8p23.1     differentiation	209648 <u>x_at</u> 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at	-1 74 -1 744 -1.75 -1.761 -1.765 -1.78	-3,34035168 -3,34962566 -3,38358566 -3,38932974 -3,38974 -3,43426175	Suppressor of cytokine signaling 5 decxyritbonuclease 1-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU22786 fris, clone KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone factor 1)	SOCSS DNASE112 RA838 ASPH  SEC10L1	2p21 16p13.3 1p32-p31 8q12.1  14q22.3	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification — — exocytosis /// post-Golgi transport /// protein transport /// vesicle docking regulation of transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// negative regulation of cell
Similar to Group X secretory phospholipase QX procursor (Phosphatdytcholine 2- arythydroixase GX) (GX sPL2) 119887_at -1.808 -3,50156532 hypothetical protein FL110786 FL110786 11q13.2 219887_at -1.808 -3,50156532 hypothetical protein FL110786 FL110786 11q13.2 219887_at -1.808 -3,50156532 hypothetical protein FL110786 FL110786 I1q13.2 204261_s_at -1.816 -3,52592083 presenilin 2 (Alzheimer disease 4) PSEN2 1q31-q42 protein processing /// amytoid prec FTrKP Interacting protein binding protein 1 (liprin beta 1) /// similar to PTPRF Interacting protein binding protein 1 isoform 1; liprin-beta 1; liprin related protein; protein- to PTPRF interacting protein binding protein 1 isoform 2; liprin-beta 1; liprin related protein; protein- to 214375_at -1.872 -3,66039667 binding 214375_at -1.872 -3,66039667 binding 216120_s_at -1.809 -3,72854566 membrane 2 205572_at -1.947 -3,65571923 angiopoletin 2 DEAD (Asp-Glu-Ala-Asp) box	209648 <u>x_at</u> 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at	-1 74 -1 744 -1.75 -1.761 -1.765 -1.78	-3,34035168 -3,34962566 -3,38358566 -3,38932974 -3,38974 -3,43426175	suppressor of cytokine signaling 5 decoyntbonuclease I-like 2 RAB3B, member RAS oncogene family asparate beta-hydroxylase CDNA: FLJ22786 frs, clone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (Pk1, growth hormone factor 1) mannosyl (alpha-1,5-)-ghycoprotein	SOCSS DNASE112 RA838 ASPH  SEC10L1	2p21 16p13.3 1p32-p31 8q12.1  14q22.3	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification — — exocytosis /// post-Golgi transport /// protein transport /// vesicle docking regulation of transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// negative regulation of cell
81737_at       -1.796       .3,47256091 (sPhosphatidykcholine 2- aryfhydrolase CX) (GX SPLA2)	209648 <u>x</u> at 207192 at 205925 <u>s</u> at 210896 <u>s</u> at 216427 at 218748 <u>s</u> at 207846 <u>at</u>	-1 74 -1 744 -1 75 -1 761 -1 765 -1 78 -1 78	-3,34035168 -3,34902565 -3,383585666 -3,38932974 -3,39874 -3,43426175 -3,43426175	Suppressor of cytokine signaling 5 decxyribonuclease I-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase CONA: FJJ22786 frs, clone KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- glucosaminytransferase	SOCSS DNASE112 RA83B ASPH  SEC10L1 POU1F1	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-aimino acid modification 
81737_at     -1.796     -3,47256091 (sPLA2:X)	209648 <u>x</u> at 207192 at 205925 <u>s</u> at 210896 <u>s</u> at 216427 at 218748 <u>s</u> at 207846 <u>at</u>	-1 74 -1 744 -1 75 -1 761 -1 765 -1 78 -1 78	-3,34035168 -3,34902565 -3,383585666 -3,38932974 -3,39874 -3,43426175 -3,43426175	Suppressor of cytokine signaling 5 decxyribonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDNA: FLI22786 frs, clone KAL2150 SEC10-like 1 (S, cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone factor 1) mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl- glucosaminyturansferase Similar to Group X secretory	SOCSS DNASE112 RA83B ASPH  SEC10L1 POU1F1	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-aimino acid modification 
81737. at     -1.798     -3.47258091 (SPLA2-X)      16p13.11        219887. at     -1.808     -3.50158532 hypothetical protein FLJ10786     FLJ10786     11q13.2        219887. at     -1.808     -3.50158532 hypothetical protein FLJ10786     FLJ10786     11q13.2        204261.s.at     -1.818     -3.52582083 presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// intracellular signaling cascade /// apottoic program /// protein processing /// antytoic program /// protein processing /// antytoic program /// protein i fugrin beta 1) /// similar to PTPRF interacting protein binding protein 1 isoformeta 1; iliprin beta 1; iliprin related protein 1; iprin-beta 1; iliprin related protein 1; iprin-beta 1; iliprin related protein 1; ibrin-beta 1; iliprin related protein 1; ibrin-beta 1; iliprin traception 1; ibrin-beta 1; iliprin traception 1; ibrin-beta 1; iliprin related protein 1; ibrin-beta 1; iliprin traception 1; ibrin-beta 1; iliprin-beta 1;	209648 <u>x</u> at 207192 at 205925 <u>s</u> at 210896 <u>s</u> at 216427 at 218748 <u>s</u> at 207846 <u>at</u>	-1 74 -1 744 -1 75 -1 761 -1 765 -1 78 -1 78	-3,34035168 -3,34902565 -3,383585666 -3,38932974 -3,39874 -3,43426175 -3,43426175	suppressor of cytokine signaling 5 decxyritbonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU32786 fis, clone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone factor 1) mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl- glucosaminy/transferase similar to Group X secetory phospholipase A2 precursor	SOCSS DNASE112 RA83B ASPH  SEC10L1 POU1F1	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-aimino acid modification 
219887_at     -1.808     -3,50156532 hypothetical protein FU10786     FU10786     11q13.2	209648 <u>x</u> at 207192 at 205925 <u>s</u> at 210896 <u>s</u> at 216427 at 218748 <u>s</u> at 207846 <u>at</u>	-1 74 -1 744 -1 75 -1 761 -1 765 -1 78 -1 78	-3,34035168 -3,34902565 -3,383585666 -3,38932974 -3,39874 -3,43426175 -3,43426175	Suppressor of cytokine signaling 5 decoyribonuclease 1-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase CONA: FU22786 fis, clone KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- ghucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Mosphatidycholine 2-	SOCSS DNASE112 RA83B ASPH  SEC10L1 POU1F1	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-aimino acid modification 
204261_s_at1.818 -3,52592083 presenilin 2 (Alzheimer disease 4) 204261_s_at1.818 -3,52592083 presenilin 2 (Alzheimer disease 4) PTRF interacting protein	209648 x_at 207192 at 205925 s_at 210896 s_at 216427 at 218748 s_at 207846_at 206720_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.78 -1.781	-3,34035168 -3,34982595 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43454302 -3,45335823 -3,47256091	Suppressor of cytokine signaling 5 decoyribonuclease 1-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU22786 frs, done KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- glucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidy/choline 2- axylhydrolase G2) (GX SPLA2) (SPLA2X)	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-aimino acid modification 
204261_5_at -1.818 -3,52592083 presenilin 2 (Alzheimer disease 4) PSEN2 1q31-q42 protein processing /// intraceBular signaling cascade /// apoptotic program /// protein 1 (lippin beta 1) /// similar to PTPRP interacting protein binding protein 1 (lippin beta 1) /// similar to PTPRP interacting protein	209648 x at 207192 at 205925 <u>s at</u> 210896 <u>s at</u> 216427 at 218748 <u>s at</u> 207846 <u>at</u> 207846 <u>at</u> 206720 <u>at</u>	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.781 -1.788	-3,34035168 -3,34982595 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43454302 -3,45335823 -3,47256091	Suppressor of cytokine signaling 5 decoyribonuclease 1-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU22786 frs, done KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- glucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidy/choline 2- axylhydrolase G2) (GX SPLA2) (SPLA2X)	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of 7-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-armino acid modification 
204261_5_at     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     increasing /// intracellular       204261_5_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// intracellular       204261_5_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// intracellular       204261_5_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// intracellular       204261_5_at     1 (liprin beta 1) /// similar to PTPRF interacting protein-timolog     protein 1 (softmal 1)     interacting protein-timolog     protein 1       214375_at     -1.872     -3,66039867     binding     LOC440091     12p11.23     cell adhesion       216120_5_at     -1.899     -3,72854586     membrane 2     ATP282     3p25.3     /// metabolim       205572_at     -1.947     -3,85571923     anglopoletin 2     ANGPT2     8p23.1     differentiation	209648 x at 207192 at 205925 <u>s at</u> 210896 <u>s at</u> 216427 at 218748 <u>s at</u> 207846 <u>at</u> 207846 <u>at</u> 206720 <u>at</u>	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.781 -1.788	-3,34035168 -3,34982595 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43454302 -3,45335823 -3,47256091	Suppressor of cytokine signaling 5 decoyribonuclease 1-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU22786 frs, done KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- glucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidy/choline 2- axylhydrolase G2) (GX SPLA2) (SPLA2X)	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine mediated signaling pathway /// positive regulation of T-heiper 1 cell differentiation /// negative BNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification 
204261_s_at     -3.52592003     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     signaling cascade /// apoptotic program /// protein processing /// amytoid prec       204261_s_at     -1.818     -3.52592003     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amytoid prec       PTRF interacting protein binding protein 1 isofrom 1; isprin-beta 1; liprin related protein; protein-tyrosine phosphatase receptor-type f polypeptide-intracting protein-tyrosine phosphatase receptor-type f polypeptide-intracting protein-tocc440091     12p11.23     cell adhesson       214375_at     -1.872     -3,66039607     binding     LOC440091     12p11.23     cell adhesson       216120_s_at     -1.899     -3,72854566     membrane 2     ATP282     3p25.3     /// metabolism       205572_at     -1.947     -3,85571923     anglopoletin 2     ANGPT2     8p23.1     differentiation	209648 x at 207192 at 205925 <u>s at</u> 210896 <u>s at</u> 216427 at 218748 <u>s at</u> 207846 <u>at</u> 207846 <u>at</u> 206720 <u>at</u>	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.781 -1.788	-3,34035168 -3,34982595 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43454302 -3,45335823 -3,47256091	Suppressor of cytokine signaling 5 decoyribonuclease 1-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU22786 frs, done KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- glucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidy/choline 2- axylhydrolase G2) (GX SPLA2) (SPLA2X)	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-heiper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification — — — — — — — — — — — — — — — — — — —
204261_5_at     -1.818     -3,52582083     presenilin 2 (Alzheimer disease 4)     PSEN2     1q31-q42     protein processing /// amyloid prec       protein 1 (liprin beta 1) /// similar to PTPRF interacting protein- binding protein 1 isoform beta 1; liprin related protein; protein- tyrosine phosphatase receptor type f potypeptide-interacting protein- tyrosine phosphatase receptor type f potypeptide-interacting protein- LOC440091     12p11.23- (ali dhesion LOC440091     rotein ransport /// calcium ion transport /// metabolism       214375_at     -1.872     -3,66039867     binding ATPase, Ca++ transporting, plasma     Calion transport /// calcium ion transport /// metabolism       216120_5_at     -1.847     -3,85571923     angloppetide12     ANGPT2     8p23.1     differentiation	209648 x at 207192 at 205925 <u>s at</u> 210896 <u>s at</u> 216427 at 218748 <u>s at</u> 207846 <u>at</u> 206720 at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.781 -1.788	-3,34035168 -3,34982595 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43454302 -3,45335823 -3,47256091	Suppressor of cytokine signaling 5 decoyribonuclease 1-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU22786 frs, done KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- glucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidy/choline 2- axylhydrolase G2) (GX SPLA2) (SPLA2X)	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine mediated signaling pathway /// positive regulation of T-heiper 1 cell differentiation /// negative BNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification 
protein 1 (ipprin beta 1) /// similar         protein 1 (ipprin beta 1) /// similar           to PTPRF interacting protein 1 isofrin-beta 1; lipprin related protein; protein- tyrosine phosphatase receptor-type         12p11.23- p1.22 ///           214375_at         -1.872         -3,66039667           216120_5_at         -1.899         -3,72854596 membrane 2           216120_5_at         -1.947         -3,85571923 anglopoletin 2           ATP282         ANGPT2         8p23.1           differentiation         DEAD (Asp-Giu-Ala-Asp) box	209648 x at 207192 at 205925 <u>s at</u> 210896 <u>s at</u> 216427 at 218748 <u>s at</u> 207846 <u>at</u> 206720 at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.781 -1.788	-3,34035168 -3,34982595 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43454302 -3,45335823 -3,47256091	Suppressor of cytokine signaling 5 decoyribonuclease 1-like 2 RAB3B, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU22786 frs, done KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- glucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidy/choline 2- axylhydrolase G2) (GX SPLA2) (SPLA2X)	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification 
protein 1 (ipprin beta 1) /// similar         protein 1 (ipprin beta 1) /// similar           tb PTPRF interacting protein- protein 1 isoform 1; iiprin-beta 1; iiprin-beta 1	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 207846_at 206720_at 81737_at 219887_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.78 -1.788 -1.796 -1.808	-3,34035168 -3,34902565 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43426175 -3,43854302 -3,45335823 -3,45335823 -3,47256091 -3,50158532	suppressor of cytokine signaling 5 decoynibonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDM4: FU22786 fis, clone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone factor 1) mannosyl (alpha-1,5-)-ghycoprotein beta-1,6-N-acetyl- ghucosaminyttransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidytcholine 2- acythydrobase GX) (GX sPLA2) (SPLA2-X) hypothetiscal protein FLJ10786	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5  FL110786	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway // positive regulation of T-helper 1 cell differentiation /// negative /// protein transport muscle contraction /// peptidyl-armino acid modification 
214375_at         -1.872         -3,66039697         binding         LOC440091         12p11.23           214375_at         -1.872         -3,66039697         binding         LOC440091         12p11.23           216320_s_at         -1.872         -3,65039697         binding         LOC440091         12p11.23           216120_s_at         -1.899         -3,72654596         membrane 2         ATP282         3p25.3         /// metabolism           205572_at         -1.947         -3,85571923         angiopoletin 2         ANGPT2         8p23.1         differentiation	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 207846_at 206720_at 81737_at 219887_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.78 -1.788 -1.796 -1.808	-3,34035168 -3,34902565 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43426175 -3,43854302 -3,45335823 -3,45335823 -3,47256091 -3,50158532	suppressor of cytokine signaling 5 decoynibonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDM4: FU22786 fis, clone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone factor 1) mannosyl (alpha-1,5-)-ghycoprotein beta-1,6-N-acetyl- ghucosaminyttransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidytcholine 2- acythydrobase GX) (GX sPLA2) (SPLA2-X) hypothetiscal protein FLJ10786	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5  FL110786	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway // positive regulation of T-helper 1 cell differentiation /// negative /// protein transport muscle contraction /// peptidyl-armino acid modification 
214375_at         -1.872         -3,66039667         binding         LDC440091         12p11.23         cell adhesion           216325_at         -1.872         -3,66039667         binding         LDC440091         12p11.23         cell adhesion           216120_5_at         -1.899         -3,72854596         membrane 2         ATP282, Ca++ transporting, plasma         Cation transport /// calcium ion transport           205572_at         -1.947         -3,85571923         anglopenesis /// signal transduction /// cell           DEAD (Asp-Glu-Ala-Asp) box         DEAD (Asp-Glu-Ala-Asp) box         anglopenesis /// signal transduction /// cell	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 207846_at 206720_at 81737_at 219887_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.78 -1.788 -1.796 -1.808	-3,34035168 -3,34982595 -3,36358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,434654302 -3,45335823 -3,45335823 -3,47256091 -3,50156532 -3,50156532	Suppressor of cytokine signaling 5 decoyritbonuclease 1-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU32786 fis, done KAIA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1) mannosyl (alpha-1, 6-)-glycoprotein beta-1, 6-N-acetyl- glucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (PhosphatidyAcholine 2- axylhydrolase G2) (GX SPLA2) (SPLA2:X) hypothetical protein FLJ10786 presenilin 2 (Alzheimer disease 4) rrmkr mitter acurry protein (Lismilar	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5  FL110786	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway // positive regulation of T-helper 1 cell differentiation /// negative /// protein transport muscle contraction /// peptidyl-armino acid modification 
214375_at         -1.872         -3,6603967         binling         LOC440091         12p11.22           214375_at         -1.872         -3,6603967         binling         LOC440091         12p11.22           216120_s_at         1.899         -3,72954566         membrane 2         ATP282         3p25.3         /// metabolism           205572_at         -1.947         -3,65571923         angiogenesis /// signal transduction /// cell           DEAD (Asp-Glu-Ala-Asp) box         DEAD (Asp-Glu-Ala-Asp) box         angiogenesis /// signal transduction /// cell	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 207846_at 206720_at 81737_at 219887_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.78 -1.788 -1.796 -1.808	-3,34035168 -3,34962595 -3,38932974 -3,38932974 -3,43426175 -3,43426175 -3,43654302 -3,45335823 -3,47256091 -3,50156532 -3,52592063	suppressor of cytokine signaling 5 decxyribonuclease I-like 2 RAB38, member RAS oncogene family separtate beta-hydroxylase CDNA: FLJ22786 fs, cone KAL2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (Pr1, growth hormone factor 1) mannosyl (alpha-1,6-)-ghcoprotein beta-1,6-h-acetyl- glucosaminytransferase Similar to Group X secretary phospholipase A2 precursor (Phosphatidy(choline 2- acylhydrokses GX) (GX SPLA2) (SPLA2-X) hypothetical protein FLJ10786 presenilin 2 (Azhelmer disease 4) Friermittefacting protein binding protein 1 (liprin beta 1) /// similar	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5  FL110786	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway // positive regulation of T-helper 1 cell differentiation /// negative /// protein transport muscle contraction /// peptidyl-armino acid modification 
f polypeptide-interacting protein- 214375_at         PPFIBP1 /// LOC440091         p11.22 /// 12p1.23         cell adhesion           ATP28c         C3++ transporting, plasma         Cation transport /// calcium lon transport         cation transport /// calcium lon transport           216120_s_at         -3,285571923         anglopoletin 2         ATP2B2         3p25.3         /// metabolism           205572_at         -1.947         -3,85571923         anglopoletin 2         ANGPT2         8p23.1         differentiation	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 207846_at 206720_at 81737_at 219887_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.78 -1.788 -1.796 -1.808	-3,34035168 -3,34902565 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43426175 -3,43854302 -3,45335823 -3,45335823 -3,52592063	suppressor of cytokine signaling 5 decoyribonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDNA: FU22786 fis, cone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (Pr1, growth hormone factor 1) mannosyl (alpha-1,5-)-ghcoprotein beta-1,6-N-acetyl- ghcosaminytransferase Similar ID croug X secretory phospholipase A2 precursor (Phosphatidytcholine 2- acythydrokase GX) (GX SPLA2) (SPLA2-X) hypothetical protein FLJ10786 presenilin 2 (Azheimer disease 4) rrnkr mitte during protein 1 (liprin beta 1) /// similar to PTPRF interacting protein 1 (softm 1; liprin-beta 1;	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5  FL110786	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway // positive regulation of T-helper 1 cell differentiation /// negative /// protein transport muscle contraction /// peptidyl-armino acid modification 
214375_at         -1.872         -3,66039867         binding         LOC440091         12p11.23         cell adhesion           ATP3ce, Ca++ transporting, plasma         Cation transport /// calcium ion transport         Cation transport /// calcium ion transport           216120_s_at         -1.899         -3,72854586         membrane 2         ATP282         3p25.3         /// metabolism           205572_at         -1.947         -3,85571923         anglopenesis /// signal transduction /// cell         anglopenesis /// signal transduction /// cell           DEAD (Asp-Glu-Ala-Asp) box         DEAD (Asp-Glu-Ala-Asp)         box         application	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 207846_at 206720_at 81737_at 219887_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.78 -1.788 -1.796 -1.808	-3,34035168 -3,34982596 -3,38932974 -3,38932974 -3,38932974 -3,43426175 -3,43426175 -3,43426175 -3,43854302 -3,45335823 -3,45335823 -3,45335823 -3,52592063	Suppressor of cytokine signaling 5 decxyribonuciease 1-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDNA: FLJ22786 ffs, clone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- glucosaminytransferase Smillar to Lorop X secretory phospholipase A2 precursor (Phosphatidycholine 2- aylhydrolase GX) (GX sPLA2) (Phosphatidycholine 2- aylhydrolase GX) (GX sPLA2) (sPLA2-X) hypothetical protein FLJ10786 presenilin 2 (Alzheimer disease 4) Friver-mitte aduring protein binding protein 1 (softm 1); liprih-beta 1; liprin related protein-	SOCSS DNASE112 RA838 ASPH  SEC10L1 POU1F1 MGAT5  FL110786 PSEN2	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2 1q31-q42	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway // positive regulation of T-helper 1 cell differentiation /// negative /// protein transport muscle contraction /// peptidyl-armino acid modification 
ATPase, Ca++ transporting, plasma         Cation transport /// calcium ion transport           216120_s_at         -3,72954596 membrane 2         ATP2B2         3p25.3         /// metabolism           205572_at         -1.947         -3,85571923 angiopetin 2         ANGPT2         8p23.1         differentiation           DEAD (Asp-Glu-Ala-Asp) box         DEAD (Asp-Glu-Ala-Asp) box         Angiopetic ang	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 207846_at 206720_at 81737_at 219887_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1.78 -1.78 -1.788 -1.796 -1.808	-3,34035168 -3,34962595 -3,38932974 -3,38932974 -3,43426175 -3,43426175 -3,43426175 -3,43426175 -3,4364302 -3,45335823 -3,47256091 -3,50156532 -3,52592063	suppressor of cytokine signaling 5 decoyribonucease I-like 2 RAB38, member RAS oncogene family appartate beta-hydroxylase CDNA: FLJ22786 fs, clone KAL2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (Pr1, growth hormone factor 1) mannosyl (alpha-1,6-)-ghcoprotein beta-1,6-N-acetyl- glucosaminytransferase Similar to Croup X secretory phospholipase A2 procursor (Phosphatidycholine 2- acylhydroises GX) (GX SFA2) (SPL2-X) hypothetical protein FLJ10786 protein 1 (liprin beta 1) /// similar to PTPRF interacting protein binding protein 1 isoform 1; liprin-beta 1; liprin related protein, protein-	SOCSS DNASE112 RA83B ASPH  SEC10L1 MGATS  FLJ10786 PSEN2	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2 1q31-q42 12p11.23-	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway // positive regulation of T-helper 1 cell differentiation /// negative /// protein transport muscle contraction /// peptidyl-armino acid modification 
216120_s_at         -1.899         -3,72954595         membrane 2         ATP282         3p25.3         /// metabolism           205572_at         -1.947         -3,85571923         angiopoletin 2         ANGPT2         8p23.1         differentiation           DEAD         (Asp-Glu-Ala-Asp)         box         Image: Alage of the second	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 206720_at 81737_at 219887_at 204261_s_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1 78 -1 78 -1 786 -1 808 -1 808	-3,34035168 -3,34982565 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43426175 -3,43426175 -3,4335823 -3,45335823 -3,45335823 -3,52592083	suppressor of cytokine signaling 5 decayritbonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDMA: FU32786 fis, clone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl- glucosaminytransferase similar to Group X secetory phospholipase A2 precursor (Phosphatidytcholine 2- avylhydrolase GX) (GX SPLA2) (SPLA2-X) hypothetiscal protein FLJ10786 presenilin 2 (Alzheimer disease 4) protein 1 (liprin beta 1) /// similar to PTPRF interacting protein-binding protein 1 (liprin beta 1) /// similar to PTPRF interacting protein-binding protein 1 signin beta 1) /// similar	SOCSS DNASE1L2 RA83B ASPH 	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2 1q31-q42 12p11.23- p1.22 ///	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction /// cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative Small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification 
205572_at -1.947 -3,85571923 angiopoletin 2 ANGPT2 8p23.1 differentiation	209648_x_at 207192_at 205925_s_at 210896_s_at 216427_at 218748_s_at 207846_at 206720_at 81737_at 219887_at 204261_s_at	-1 74 -1 744 -1 75 -1 761 -1 765 -1 78 -1 78 -1 786 -1 808 -1 808	-3,34035168 -3,34962595 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43654302 -3,45335623 -3,45335623 -3,55592063 -3,52592063 -3,52592063	Suppressor of cytokine signaling 5 decxyribonuclease I-like 2 RAB38, member RAS oncogene family appartate beta-hydroxylase CDNA: FLJ22786 fs, clone KAL2150 SEC10-like 1 (S, cerevisiae) POU domain, class 1, transcription factor 1 (Pr1, growth hormone factor 1) mannosyl (alpha-1,6-)-ghcoprotein beta-1,6-N-acetyl- ghcosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidy(choline 2- ayrthydrolase GX) (GX SPLA2) (SPLA2:X) hypothetical protein FLJ10785 protein 1 (liptin beta 1) /// similar to PTPRF linteracting protein- brosphatose choline to a secretory protein 1 isoform 1; liptin-beta 1; protein 1 isoform 1; liptin-beta 1; protein 1 isoform 1; liptin-beta 1; protein 1 isoform 1; liptin-beta 1;	SOCSS DNASE1L2 RA83B ASPH 	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2 1q31-q42 12p11.23- p1.22 ///	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-simino acid modification 
DEAD (Asp-Gtu-Ala-Asp) box	209648 x at 207192 at 205925 s at 210896 s at 216427 at 218748 s at 207846 at 207846 at 206720 at 81737 at 219887 at 204261 s at 204261 s at	-1.74 -1.744 -1.75 -1.761 -1.765 -1.78 -1.78 -1.788 -1.788 -1.808 -1.808	-3,34035168 -3,34902595 -3,38358566 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43426175 -3,43426175 -3,43654302 -3,45335823 -3,45335823 -3,52592063 -3,52592063 -3,52592063	suppressor of cytokine signaling 5 decoryribonuclease 1-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDNA: FU22786 fis, clone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (Pt1, growth hormone factor 1) mannosyl (alpha-1,6-)-ghycoprotein beta-1,6-N-acetyl- ghucosaminytransferase Similar to Croup X secretory phospholipase A2 precursor (Phosphatidycholine 2- acyflwdrobase C3) (GX SFLA2) (SPL2-X) hypothetical protein FU10786 presenilin 2 (Atzheimer disease 4) protein 1 (liprin beta 1) /// similar to PTPRF inteacting protein- binding protein 1 isoform 1; liprin-beta 1; liprin related protein; protein- ting protein-tracting protein- hinding ATP3se, Ca++ transporting, plasma	SOCSS DNASE1L2 RA83B ASPH  SEC10L1 POU1F1 MGAT5  FLJ10786 PSEN2 PPFIBP1 /// LOC440091	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2 1q31-q42 12p11.23- p11.22 /// 12p11.23	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative DNA catabolism small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-amino acid modification 
	209648 x at 207192 at 205925 s at 210896 s at 216427 at 218748 s at 207846 at 207846 at 207846 at 207846 at 207846 at 204261 s at 204261 s at 214375 at 214375 at at	-1.74 -1.761 -1.761 -1.765 -1.78 -1.78 -1.781 -1.788 -1.808 -1.808 -1.808	-3,34035168 -3,34962595 -3,38932974 -3,38932974 -3,43426175 -3,43426175 -3,43426175 -3,43426175 -3,43954302 -3,45335823 -3,45335823 -3,47256091 -3,50156532 -3,52592063 -3,52592063 -3,52592063	suppressor of cytokine signaling 5 decoyribonucease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CONA: FLJ2786 fs, clone KAL2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone factor 1) mannosyl (alpha-1,6-)-ghoporotein beta-1,6-N-acetyl- ghucosaminytransferase Similar to Croup X secretory phospholipase A2 precursor (Phosphatidycholine 2- acythydroises GX) (GX SFA2) (SPL2-X) hypothetical protein FLJ10786 protein 1 (liprin beta 1) /// similar to DrPRF interacting protein- binding ATPase, Ca++ transporting, plasma membrane 2	SOCSS DNASE1L2 RA83B ASPH 	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2 1q31-q42 12p11.23- p11.22 /// 12p11.23 3p25.3	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative Small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-armino acid modification — execytosis /// post-Golgi transport /// protein transport /// veskcle docking regulation of transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// negative regulation of cell proliferation /// organogenesis N-linked glycosylabon // chromosome segregation /// Notch receptor processing /// thracellular signaling cascade /// apoptotic program /// protein processing /// thracellular signaling cascade /// apoptotic program /// protein processing /// amydold prec
	209648 x at 207192 at 205925 s at 210896 s at 216427 at 218748 s at 207846 at 207846 at 207846 at 207846 at 207846 at 204261 s at 204261 s at 214375 at 214375 at at	-1.74 -1.761 -1.761 -1.765 -1.78 -1.78 -1.781 -1.788 -1.808 -1.808 -1.808	-3,34035168 -3,34902565 -3,38932974 -3,38932974 -3,39874 -3,43426175 -3,43426175 -3,43426175 -3,43426175 -3,43854302 -3,45335823 -3,45335823 -3,52592063 -3,52592063 -3,66039667 -3,72954556 -3,85571923	suppressor of cytokine signaling 5 decayritbonuclease I-like 2 RAB38, member RAS oncogene family aspartate beta-hydroxylase CDM4: FU32786 fis, clone KALA2150 SEC10-like 1 (S. cerevisiae) POU domain, class 1, transcription factor 1 (PR1, growth hormone factor 1) mannosyl (alpha-1,5-)-glycoprotein beta-1,6-N-acetyl- glucosaminytransferase Similar to Group X secretory phospholipase A2 precursor (Phosphatidytcholine 2- acythydrobase GX) (GX sPLA2) (SPLA2-X) hypothetical protein FLJ10786 presenilin 2 (Alzheimer disease 4) protein 1 (liprin beta 1) /// similar to PTPRF interacting protein- binding ATPase, Ca++ transporting, plasma membrane 2 anglopoletin 2	SOCSS DNASE1L2 RA83B ASPH 	2p21 16p13.3 1p32-p31 8q12.1  14q22.3 3p11 2q21 16p13.11 11q13.2 1q31-q42 12p11.23- p11.22 /// 12p11.23 3p25.3	regulation of cell growth /// intracellular signaling cascade /// JAK-STAT cascade /// negative regulation of signal transduction // cytokine mediated signaling pathway /// positive regulation of T-helper 1 cell differentiation /// negative Small GTPase mediated signal transduction /// protein transport muscle contraction /// peptidyl-armino acid modification — execytosis /// post-Golgi transport /// protein transport /// veskcle docking regulation of transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// negative regulation of cell proliferation /// organogenesis N-linked glycosylabon // chromosome segregation /// Notch receptor processing /// thracellular signaling cascade /// apoptotic program /// protein processing /// thracellular signaling cascade /// apoptotic program /// protein processing /// amydold prec

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	[		Williams Beuren syndrome	[		transcription /// regulation of transcription,
221163_s_at	-2 052	-4,1468044	chromosome region 14	WBSCR14	7q11.23	DNA-dependent /// morphogenesis
214831_at	-2 068	-4,1930499	Mediator of RNA polymerase II transcription, subunit 28 homolog (west)	MED28	4016	transcription /// regulation of transcription, DNA-dependent
220278 at	-2 074		jumonji domain containing 20	JMJD2D	11021	
215944_at	-2 125	-4.36203093		_		t
214078_at	-2 159		P21 (CDKN1A)-activated kinase 3	PAK3	Xq22.3-q23	protein amino acid phosphorylation
219872_at	-2.164		hypothetical protein DKFZp434L142	DKFZp434L1	4q32.1	-
205532_s_at		-4,57572389	cadherin 6, type 2, K-cadherin (fetal		5p15.1-p14	cell adhesion /// homophilic cell adhesion
216814_at	-2 205	-4,61074539			-	
217081_at	-2.228	-4,68484072	olfactory receptor, family 2, subfamily H, member 2	OR2HZ	6p21.3	regulation of transcription, DRA-dependent /// defense response /// signal transduction /// G-protein coupled receptor protein signaling pathway /// perception of smell /// mating
205033_s_at	-2 371	-5,17298573	defensin, alpha 1, myeloid-related sequence /// defensin, alpha 3, neutrophil-specific	DEFA1 /// DEFA3	8p23.1 /// 8pter-p23.3	xenobiobic metabolism /// response to pest, pathogen or parasite /// defense response to bacteria /// defense response to fungi
15073_s_at	-2.425	-5,37029001	nuclear receptor subfamily 2, group F, member 2	NR2F2	15q26	transcription /// regulation of transcription from RNA polymerase II promoter /// lipid metabolism /// signal transduction
204286 s at	2 868	.7 30052301	phorbol-12-myristate-13-acetate- induced protein 1	PMAIP1	18921.32	
					21022.1-	
09298_s_at			Intersectin 1 (SH3 domain protein)	ITSN1	g22.2	synaptic vesicle endocytosis
18349_s_at	-3.187	-9,10715223	Zwilch	FL110036	15q22.31	

Tab. A4e: Probe-sets down-regulated regulated upon IVMP treatment at day 21 compared to day 6; Probe-sets have a minimum change of 2-fold in 100% of patients;

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Tab. A4f	9	1.1.1.1	The life to the state of the state of the	12002	Chromosom	
	5 1002 FC/2			Gene Symbol	Location	GO Biological Process Description
220798_x_a	t 1.401	2,64084568	plasticity-related gene 2 cadherin 6, type 2, K-	PRG2	19p13.3	
205533_5_a	1.158	2,23147864		CDH6	5p15.1-p14	cell adhesion /// homophilic cell adhesion
			pleckstrin homology-like			
209803_s_a	1 802	3,48703296	domain, family A, member	PHLDAZ	11p15.5	imprinting /// apoptosis
		1 0,40,0000	splicing factor,			
			arginine/serine-rich 1 (splicing factor 2, alternate		1	nuclear mRNA splicing, via spliceosome /// mRNA splice site
201741_x_a	1.235	2,35381347	splicing factor)	SFRS1	17921.3-922	selection
1000(1				40.00		anti-apoptosis /// signal transduction /// cell-cell signaling ///
208062_s_a	1.305	2,47083727	neuregulin 2 wingless-type MMTV	NRG2	5q23-q33	embryonic development
			integration site family,			signal transduction /// frizzled-2 signaling pathway /// cell-cel
205990_s_a	3.111	8,63981248	member 5A interphotoreceptor matrix	WNTSA	3p21-p14	signaling /// morphogenesis
220830_at	1.15	2,21913894	proteoglycan 2	IMPG2	3q12.2-q12.1	visual perception
	1					protein amino acid phosphorylation /// inflammatory response
			receptor-interacting serine-			/// signal transduction /// regulation of apoptosis /// positive
209544_at 213951_s_at	1.576		threonine kinase 2	RIPK2 TBPIP	8q21 17q12-q21	regulation of I-kappaB kinase/NF-kappaB cascade
213951_5_8		2,20992097	TBP-1 interacting protein PR/SET domain containing	1 BPIP	1/012-021	
220200_s_at	1.698	3,24450882	protein 8	SET8	12024.31	chromatin modification
206148_at	1.418	2 66944634	Interleukin 3 receptor, alpha (low affinity)	IL3RA	Xp22.3 or Yp11.3	protein amino acid phosphorylation /// development
200210_8(	1.410	2,00044004				
			c-fos induced growth factor (vascular endothelial	1		regulation of cell cycle /// angiogenesis /// cell proliferation /// positive regulation of cell proliferation /// cell
206742_at	1.306	2,47255052	growth factor D)	FIGF	Xp22.31	differentiation
						inflammatory response /// signal transduction /// G-protein
207510_at	1.372	2 58820131	bradylonin receptor B1	BDKRB1	14q32.1- q32.2	coupled receptor protein signaling pathway /// positive regulation of cytosolic calcium ion concentration
10/ 510_01	[				432.2	DNA repair /// transcription-coupled nucleotide-excision repair
218110_at	1.11	2,15845647	XPA binding protein 2 megalencephalic	XAB2	19p13.2	/// transcription /// RNA processing
			leukoencephalopathy with			
213395_at	1,305	2,47083727	subcortical cysts 1	MLC1	22q13.33	protein biosynthesis /// ion transport protein complex assembly /// protein amino acid
						phosphorylation /// leukocyte cell adhesion /// integrin-
						mediated signaling pathway /// intracellular signaling cascade
209269_s_at	1 105	3 37383306	Spleen tyrosine kinase	SYK	9q22	/// cell proliferation /// organogenesis /// neutrophil chemotaxis
209209_3_80	1.165	2,21,303380	5-oxoprolinase (ATP-	316	5422	
222025_s_at	1.684	3,21317599	hydrolysing)	OPLAH	8q24.3	-
						regulation of cyclin dependent protein kinase activity /// G3 phase of mitotic cell cycle /// cell cycle /// cell cycle arrest ///
			cyclin-dependent kinase			negative regulation of cell proliferation /// negative regulation
213182_x_at	2.21	4,62675274	inhibitor 1C (p57, Kip2) chromosome 12 open	CDKN1C	11p15.5	of cell cycle
207754_at	1.998	3,99445866	reading frame 2	C12orf2	12p12.3	signal transduction
			G elongation factor,			
220903_at	2.143	4,41679539	mitochondrial 1 neuronal PAS domain	GFM1	3q25.1-q26.2	protein biosynthesis /// translational elongation transcription /// regulation of transcription, DNA-dependent
222172_at	1 107	2,15397275	protein 3	NPAS3	14g12-q13	/// signal transduction
212923_s_at	1 4 2 9	2 80073442	chromosome 6 open reading frame 145	C6orf145	6025.2	
	1.420	2,000/ 0442	MRNA; ODNA	0001115	0023.2	
216613_at	1.664	3 16903024	DKFZp566L0824 (from clone DKFZp566L0824)			
		0,10000024	Chine Did approacher 17			regulation of cell cycle /// branscription /// regulation of
						transcription, DNA-dependent /// inflammatory response /// chromatin modification /// histone deacetylation /// B-cell
			histone deacetylase 9	HDAC9	7p21.1	differentiation /// negative regulation of myogenesis
:05659_at	1.229	2,34404457				
105059_at	1.229		granzyme B (granzyme 2,			
03039_at	1.229		granzyme B (granzyme z, cytotoxoc T-lymphocyte-			
05059_at	1.229		granzyme B (granzyme z, cytotoxoc T-lymphocyte- associated serine esterase 1) /// granzyme B			
<u>.02029_81</u>	1.229		granzyme B (granzyme z, cytotoxoc T-lymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T-			ombook ale and particles ale /// scorbacie /// deacons of
	1.229		granzyme B (granzyme z, cytotoxoc T-lymphocyte- associated serine esterase 1) /// granzyme B	GZMB	14q11.2	proteolysis and peptidolysis /// apoptosis /// cleavage of Jamin /// cytolysis
		4,23687334	granzyme B (granzyme 2, cytotoxoc T-lymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor	GZMB	14q11.2	lamin /// cytolysis negative regulation of transcription from RNA polymerase II
10164_at	2 083	4,23687334	granzyme B (granzyme z. cytotoxoc T-lymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory			lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA-
<u>10164_at</u> 04057_at	2 083	4,23687334 2,66105808	granzyme B (granzyme 2, cytotoxo T-hymphocyte associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- hymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide	IRF8	16q24.1	lamin /// cytolysis negative regulation of transcription from RNA polymerase II
10164_at	2 083	4,23687334 2,66105808	granzyme B (granzyme 2, cytotoxo T-hymphocyte associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- hymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide	IRF8		lamin /// cytubysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response
10164_at 04057_at 15139_at	2 083 1 412 1 26	4,23687334 2,66105808 2,39495741	granzyme B (granzyme 2, cytotoxoc T-lymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10	IRF8 ARHGEF10	16q24.1	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response  transcription /// regulation of transcription, DNA-dependent /// regulation of transcription, DNA-dependent /// cell cycle
<u>10164_at</u> 04057_at	2 083	4,23687334 2,66105808 2,39495741	granzyme B (granzyme z. cytotoxo T-Ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 208	IRF8 ARHGEF10	16q24.1 8p23 19p13.3	lamin /// cytubysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at	2 083 1 412 1 26 1 596	4,23687334 2,66105808 2,39495741 3,02303986	granzyme B (granzyme z cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme z. cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 208 sperm associated antigen 11	IRF8 ARHGEF10 HMG208	16q24.1 8p23 19p13.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at	2 083 1 412 1 26 1 596	4,23687334 2,66105808 2,39495741 3,02303986 2,19466388	granzyme B (granzyme 2, cytotoxo T-hymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- hymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 208 sperm associated antigen 11 networpromum 1	IRF8 ARHGEF10 HMG208	16q24.1 8p23 19p13.3	lamin /// cytubysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at	2 083 1 412 1 26 1 596	4,23687334 2,66105808 2,39495741 3,02303986 2,19466388	granzyme B (granzyme 2, cytotoxo T-lymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 208 sperm associated antigen 11 meuronoromatosis, von	IRF8 ARHGEF10 HMG208	16q24.1 8p23 19p13.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at	2 083 1 412 1 26 1 596	4,23687334 2,66105808 2,39495741 3,02303986 2,19496388	granzyme B (granzyme 2, cytotoxo T-hymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- hymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 R/b guanine nucleobide exchange factor (GEF) 10 High-mobility group 208 sperm associated antigen 11 netwonorcommr 2 (neurofibromatosis, von Recklinghausen disease, Watson disease) ///	IRF8 ARHGEF10 HMG208	16q24.1 8p23 19p13.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at	2 083 1 412 1 26 1 596	4,23687334 2,66105808 2,39495741 3,02303986 2,19486388	granzyme B (granzyme 2, cytotoxo T-lymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 208 sperm associated antigen 11 meuronoromatosis, von Recklinghausen disease, Watson disease) /// neurofibrorin 1	IRF8 ARHGEF10 HMG208	16q24.1 8p23 19p13.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at	2 083 1 412 1 26 1 596	4,23687334 2,66105808 2,39485741 3,02303986 2,19486388	granzyme B (granzyme 2, cytotoxo T-hymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- hymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 R/b guanine nucleobide exchange factor (GEF) 10 High-mobility group 208 sperm associated antigen 11 netwonorcommr 2 (neurofibromatosis, von Recklinghausen disease, Watson disease) ///	IRF8 ARHGEF10 HMG208	16q24.1 8p23 19p13.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at	2 083 1 412 1 25 1 596 1 134	4,23687334 2,68106808 2,39496741 3,02303986 2,19466388 2,84415482	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 neuronibromatosis, von Recklinghausen disease, Watson disease)	IRF8 ARHGEF10 HMG208 SPAG11	16q24.1 8p23 19p13.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at 11381_x_at	2 083 1 412 1 26 1 598 1 134 1 508	4,23687334 2,66105808 2,39495741 3,02303996 2,19466388 2,19466388	granzyme B (granzyme 2, cytotoxo T-hymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- hymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 Recollinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) solitesese, Watson disease, watson disease, Watson disease)	IRF8 ARHGEF10 HMG208 SPAG11 NF1	16q24.1 8p23 19p13.3 8p23-p22	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// innume response 
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at	2 083 1 412 1 28 1 598 1 134 1 508 1 19	4,23687334 2,66105808 2,39495741 3,02303986 2,19466388 2,19466388 2,84415482 2,84415482	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage- gated, type IV, alpha outer dense fiber of sperm	IRF8 ARHGEF10 HMG208 SPAG11 NF1 SCN4A	16q24.1 8p23 19p13.3 8p23-p22 17q11.2 17q23-q25.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at 10415_s_at	2 083 1 412 1 25 1 596 1 134 1 508 1 19 1 149	4,23687334 2,66105808 2,39495741 3,02303986 2,19496388 2,19496388 2,84415482 2,28152743 2,21780120	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage- gated, type IV, alpha outer dense fiber of sperm	IRF8 ARHGEF10 HMG208 SPAG11 NF1 SCN4A	16q24.1 8p23 19p13.3 8p23-p22	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at	2 083 1 412 1 25 1 596 1 134 1 508 1 19 1 149	4,23687334 2,68105808 2,39495741 3,02303986 2,19466388 2,84415482 2,28152743 2,21720120 3,33341283	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage- gated, type IV, alpha outer dense fiber of sperm	IRF8 ARHGEF10 HMG208 SPAG11 NF1 SCN4A	16q24.1 8p23 19p13.3 8p23-p22 17q11.2 17q23-q25.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at 10415_s_at 16655_s_at	2 083 1 412 1 25 1 596 1 134 1 508 1 19 1 149 1 737	4,23687334 2,66105808 2,39495741 3,02303986 2,19466388 2,84415482 2,28152743 2,21760129 3,33341283	granzyme B (granzyme 2, cytotoxo T-hymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- hymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 208 sperm associated antigen 11 neurofibromatosis, von Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage- gated, type IV, alpha outer dense fiber of sperm tails 2 	IRF8 ARHGEF10 HMG208 SPAG11 NF1 SCN4A ODF2 -	16q24.1 8p23 19p13.3 8p23-p22 17q11.2 17q23-q25.3 9q34.11	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at 10415_s_at	2 083 1 412 1 25 1 596 1 134 1 508 1 19 1 149 1 737	4,23687334 2,66105808 2,39495741 3,02303986 2,19466388 2,19466388 2,28152743 2,28152743 2,21760129 3,33341283 2,13813082	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage- gated, type IV, alpha outer dense fiber of sperm tails 2 	IRF8 ARHGEF10 HMG208 SPAG11 NF1 SCN4A ODF2 -	16q24.1 8p23 19p13.3 8p23-p22 17q11.2 17q23-q25.3	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at 10415_s_at 16655_s_at 21705_s_at	2 083 1 412 1 26 1 596 1 134 1 508 1 19 1 149 1 737 1 095	4,23687334 2,68105808 2,39495741 3,02303986 2,19466388 2,19466388 2,284415482 2,28152743 2,2780129 3,33341283 2,13813082	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 neuronibromatosis, von Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage gated, hype IV, alpha outer dense fiber of sperm tals 2 	IRF8 ARHGEF10 HIMG208 SPAG11 SPAG11 NF1 SCN4A ODF2 - - FU21168	16q24.1 8p23 19p13.3 8p23-p22 17q11.2 17q23-q25.3 9q34.11 1p13.1 1p36.13-	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// infumune response transcription /// regulation of transcription, DNA-dependent /// regulation of transcription, DNA-dependent /// cell cycle /// cheomatin modification defense response /// spermatogenesis /// response to pest, pathogen or parasite cell cycle /// Ras protein signal transduction /// negative regulation of cell proliferation /// negative regulation of cell cycle cation transport /// sodium ion transport /// muscle contraction
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at 10415_s_at 16655_s_at 21705_s_at	2 083 1 412 1 25 1 596 1 134 1 508 1 19 1 149 1 737	4,23687334 2,68105808 2,39495741 3,02303986 2,19466388 2,19466388 2,284415482 2,28152743 2,2780129 3,33341283 2,13813082	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 neuronibromatosis, von Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage aoter disease fiber of sperm tals 2 	IRF8 ARHGEF10 HIMG208 SPAG11 SPAG11 NF1 SCN4A ODF2 - - FU21168	16q24.1 8p23 19p13.3 8p23-p22 17q11.2 17q23-q25.3 9q34.11 1p13.1 1p36.13-	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// immune response 
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at 10415_s_at 16655_s_at 21705_s_at	2 083 1 412 1 26 1 596 1 134 1 508 1 19 1 149 1 737 1 095	4,23687334 2,66105808 2,39495741 3,02303986 2,19496388 2,19496388 2,84415482 2,28152743 2,21780129 3,33341283 2,13813082 2,5793385	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 neuronibromatosis, von Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage aoter disease fiber of sperm tals 2 	IRF8 ARHGEF10 HIMG208 SPAG11 SPAG11 NF1 SCN4A ODF2 - - FU21168	16q24.1 8p23 19p13.3 8p23-p22 17q11.2 17q23-q25.3 9q34.11 1p13.1 1p36.13-	lamin /// cytolysis negative regulation of transcription from RNA polymerase II promoter /// transcription /// regulation of transcription, DNA- dependent /// inmune response 
10164_at 04057_at 15139_at 13966_at 11381_x_at 11914_x_at 06981_at 16655_5_at 21705_s_at 21705_s_at	2 083 1 412 1 26 1 596 1 134 1 508 1 19 1 149 1 737 1 095	4,23687334 2,66105808 2,39495741 3,02303986 2,19496388 2,19496388 2,28152743 2,21780120 3,33341283 2,13813082 2,5793385 4,23393758	granzyme B (granzyme 2, cytotoxo T-ymphocyte- associated serine esterase 1) /// granzyme B (granzyme 2, cytotoxic T- lymphocyte-associated serine esterase 1) interferon regulatory factor 8 /// interferon regulatory factor 8 Rho guanine nucleotide exchange factor (GEF) 10 High-mobility group 20B sperm associated antigen 11 Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) /// neurofibromatosis, von Recklinghausen disease, Watson disease) sodium channel, voltage- gated, type IV, alpha outer dense fiber of sperm tails 2 	IRF8 ARHGEF10 HMG208 SPAG11 NF1 SCN4A ODF2 - FLJ21168 NBL1 IRF8	16q24.1 8p23 19p13.3 8p23-p22 17q11.2 17q23-q25.3 9q34.11 1p36.13- p36.11	Iamin /// Cytolysis         negative regulation of transcription from RNA polymerase II         negative regulation of transcription from RNA polymerase II         promoter /// transcription /// regulation of transcription, DNA-dependent /// infurmation of transcription, DNA-dependent /// cell cycle

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	1		phosphoprotein 32 family,			
			member A /// acidic			
			(leucine-rich) nuclear			
			phosphoprotein 32 family,			
		1	member D /// acidic (leucine-rich) nuclear			
			phosphoprotein 32 family,	ANP32A ///	15922.3-923	
			member C /// similar to	ANP32D ///	/// 12q13.11	
208571_at	1 578	2,98555677	acidic (leucine-rich) nuclea 7 phospho	LOC440272	/// 4q32.3 // 15q14	/ nucleocytoplasmic transport /// intracellular signaling cascad
207481_at	2 143	4,4167953		-		
217276 <u>x</u> a	t 1 623	3,0801487	7 serine hydrolase-like 2	SERHIL2	22q13	aromatic compound metabolism
			insulin-like growth factor binding protein, acid labile			
215712_s_a	t 1 146	2,21299471		IGFALS	16p13.3	cell adhesion /// signal transduction
206065_s_a		2 95 20475	dihydropyrimidinase	DPYS	8922	nucleobase, nucleoside, nucleotide and nucleic acid metabolism /// response to toxin
200003_3_0	<u> </u>				10424	chemotaxis /// cellular defense response /// cell adhesion //
			chemokine (C-X3-C motif)			signal transduction /// G-protein coupled receptor protein
205898_at 215408_at	1 809		Receptor 1	MY01E	3p21 3p21.3 15q21-q22	signaling pathway actin filament-based movement
			chromodomain helicase			
207645_s_a	t 1.759	3,38463439	DNA binding protein 1-like	CHDIL	1q12	<u> </u>
			cytochrome P450, family 3	,		electron transport /// lipid metabolism /// xenobiotic
210726_at	1.682	3,20872467	Subfamily A, polypeptide 4 CDNA FLJ20178 fis, clone	CYP3A4	7q21.1	metabolism /// xenobiotic metabolism /// transport
216644_at	1.304		CONA HU20178 hs, clone			
	1	1 2,000,0001			1	
			3-hydroxy-3-methylglutary	H		
204607_at	1.695	3,23776887	Coenzyme A synthase 2 (mitochondrial)	HMGCS2	1p13-p12	acetyl-CoA metabolism /// cholesterol biosynthesis
						transcription /// regulation of transcription, DNA-dependent
219878_s_at	1.603	3,03774338	Kruppel-like factor 13 translocase of Inner	KLF13	15q12	/// transcription from RNA polymerase II promoter
	1		mitochondrial membrane			1
217612_at	1 124	2,17950422	50 homolog (yeast)	TIMMSO	19q13.2	
206637 =+	1 997	3 00180089	purinergic receptor P2Y, G-	P2014	3071-075	signal transduction /// G-protein coupled receptor protein
206637_at	1.997		protein coupled, 14	P2RY14	3q21-q25	signaling pathway [transcription /// regulation of transcription, DNA-dependent]
						/// transcription from RNA polymerase II promoter ///
204753_s_at	1777	3,42712782	hepatic leukernia factor katanin p80 (WD repeat	HLF	17q22	development /// rhythmic process cytokinesis /// cell motility /// microtubule depolymerization
203163_at	1.04	2,05622765	containing) subunit B 1	KATNB1	16q13	/// cell cycle /// mitosis
220774_at	1.737	3,33341283		DYM	18q12-q21.1	
206619_at	1.406	2 65001403	dickkopf homolog 4 (Xencpus laevis)	DKK4	8p11.2-p11.1	development /// Wnt receptor signaling pathway /// negative regulation of Wnt receptor signaling pathway
207744_at	2.127	4,36808218				
			transmembrane protein			
220111_s_at	1.243	2,36690204	168 solute carrier family 22	TMEM168	12p13.3	<b>↓</b> ¯
			(organic anion			ion transport /// sodium ion transport /// organic anion
221662_s_at	1.066	2,09362056	transporter), member 7	SLC22A7	6p21.2-p21.1	transport negative regulation of transcription from RNA polymerase II
	1					promoter /// transcription /// regulation of transcription, DNA
						dependent /// transcription initiation from RNA polymerase I
209476 c -++	1.018	1 2 20000448	interferon regulatory factor	1057	11-15 5	promoter /// inflammatory response /// response to DNA
208436_s_at 204939_s_at		2,02230418	/ phospholamban	IRF7 PLN	11p15.5 6q22.1	damage stimulu calcium ion transport /// muscle contraction /// circulation
						chemotaxis /// cellular defense response /// cholesterol metabolism /// cell proliferation /// B-cell differentiation /// 1
						helper 2 type immune response /// connective tissue growth
207539_s_at			interleukin 4	IL4	5q31.1	factor biosynthesis /// regulation of isotype switching
216291_at	1.311	2,4811346				orotein amino acid phosphorylation /// signal transduction //
						transmembrane receptor protein tyrosine kinase signaling
11898_s_at	1,059	2,08348688	EPH receptor B1	EPHB1	3q21-q23	pathway /// neurogenesis
			heparan sulfate (glucosamine) 3-O-			heparan sulfate proteoglycan biosynthesis, enzymatic
21062_at	1.112	2,1614508	sulfotransferase 381	HS3ST3B1	17p12-p11.2	modification
01452			Ras homolog enriched in	0.450	7-36	signal transduction /// small GTPase mediated signal
01452_at	1.125	2,18101547	olfactory receptor, family	RHEB	7q36	transduction
16690_at	2 058	4,16408639		OR7C1	19p13.1	488
			growth associated protein			regulation of cell growth /// protein kinase C activation ///
04471_at	1 514	2,85600796	43	GAP43	3013.1-013.2	regulation of cell growth /// protein innase C activation /// neurogenesis /// response to wounding /// cell differentiation
			Cas-Br-M (murine)			
20638_s_at	1 292	2.44887278	ecotropic retroviral transforming sequence c	CBLC	19q13.2	
		<u></u> /2/0	glutamic-pyruvate			
ACTON			transaminase (alanine	cm.	0.74 7	gluconeogenesis /// nitrogen compound metabolism ///
06709_x_at 19082_at	1 374		aminotransferase) CGI-14 protein	GPT CGI-14	8q24.3 16p13.3	biosynthesis N-acetylglucosamine metabolism
						cytokinesis /// microtubule-based movement /// cell cycle ///
04444_at	1 622	3,07801444	kinesin family member 11 Rho guanine nucleotide	KIF11	10q24.1 _	mitotic spindle organization and biogenesis
	1 251	2,38006339	exchange factor (GEF) 5	ARHGEF5	7q33-q35	
				PCDHA2	5q31	cell adhesion /// homophilic cell adhesion /// neurogenesis
04765_at	1 949		protocadherin alpha 2			
04765_at 10572_at	1 949		hypothetical protein	FI 113017	16071	
04765_at 10572_at 18719_s_at	1 949 2 282	4,86351713	hypothetical protein	FL)13912 GREB1	16q21 2p25.1	
04765_at 10572_at 18719_s_at 10562_at	1 949 2 282 1.629	4,86351713 3,09298535 4,31990624	hypothetical protein FLJ13912 GREB1 protein KIAA0644 gene product			
04765_at 10572_at 18719_s_at 10562_at 05151_s_at	1 949 2 282 1 629 2,111	4,88351713 3,09298535 4,31990824	hypothetical protein FLJ13912 GREB1 protein KIAA0644 gene product SH3-domain binding	GREB1 KLAA0644	2p25.1 7p15.1	
04765_at 10572_at 18719_s_at 10562_at 05151_s_at	1 949 2 282 1 629 2,111	4,86351713 3,09298535 4,31990624	hypothetical protein FLJ13912 GREB1 protein KIAA0644 gene product SH3-domain binding	GREB1	2p25.1 7p15.1	
04765_at 10572_at 18719_s_at 10562_at 05151_s_at 22258_s_at	1 949 2 282 1 629 2.111 1 852	4,86351713 3,09298535 4,31990624 3,61000291	hypothetical protein FU13912 GREB1 protein KKAA0644 gene product SH3-domain binding protein 4 pro-melanin-concentrating	GREB1 KIAA0644 SH3BP4	2p25.1 7p15.1 2q37.1-q37.2	endocytosis /// cell cycle
04765_at 10572_at 18719_s_at 10562_at 05151_s_at 22258_s_at	1 949 2 282 1 629 2.111 1 852	4,86351713 3,09298535 4,31990624 3,61000291 4,41985794	hypothetical protein PLJ13912 GREB1 protein KIAA0644 gene product SH3-domain binding protein 4 pro-melanin-concentrating hormone-like 1	GREB1 KLAA0644	2p25.1 7p15.1 2q37.1-q37.2 5p14.3	
04765_at 10572_at 18719_5_at 10562_at 05151_s_at 22258_s_at 17123_x_at	1 949 2 282 1.629 2.111 1 852 2 144	4,86351713 3,09298535 4,31990624 3,61000291 4,41985794 2,93426669	hypothetical protein FLJ13912 GREB1 protein KIAA0644 gene product SH3-domain binding protein 4 pro-melanin-concentrating hormone-like 1 spermatogenesis associated 2	GREB1 KIAA0644 SH3BP4	2p25.1 7p15.1 2q37.1-q37.2	endocytosis /// cell cycle
04765_at 10572_at 18719_5_at 10562_at 05151_5_at 22258_5_at 17123_x_at 04433_5_at	1 949 2 282 1 629 2 111 1 852 2 144 1 553	4,88351713 3,09298535 4,31990624 3,81000291 4,41985794 2,93426669	hypothetical protein PLJ13912 GREB1 protein KIAA0644 gene product SH3-domain binding protein 4 pro-melanin-concentrating hormone-like 1 spermatogenesis associated 2 Perfostin, osteoblast	GREB1 KIAA0644 SH3BP4 PMCHL1 SPATA2	2p25.1 7p15.1 2q37.1-q37.2 5p14.3 20q13.1- q13.2	endocytosis /// cell cycle synaptic transmission /// behavior spermatogenesis /// cell differentiation
04765_at 10572_at 18719_5_at 10562_at 05151_5_at 22258_5_at 17123_x_at 04433_5_at 14981_at	1 949 2 282 1 .629 2.111 1 .652 2 144 1 .553 3 .156	4,86351713 3,09298535 4,31990624 3,61000291 4,41985794 2,93428669 8,91354921	hypothetical protein FLJ13912 GREB1 protein KIAA0644 gene product StI3-doman binding protein 4 pro-melanin-concentrating hormone-like 1 secondary 2 permatogenesis associated 2 Perfositin, osteoblast specific factor	GREB1 KIAA0644 SH3BP4 PMCHL1 SPATA2 POSTN	2p25.1 7p15.1 2q37.1-q37.2 5p14.3 20q13.1- q13.2 13q13.3	endocytosis /// cell cycle synaptic transmission /// behavlor
04765_at 10572_at 18719_5_at 10562_at 05151_5_at 22258_5_at 17123_x_at 04433_5_at 14981_at	1 949 2 282 1 629 2.111 1 852 2 144 1 553	4,88351713 3,09298535 4,31990624 3,61000291 4,41985794 2,93426669 8,91354921 2,09943337	hypothetical protein FD13912 GREB1 protein KIAA0644 gene product St43-domain binding protein 4 pro-melanin-concentrating hormone-like 1 sperosting concentrating hormone-like 1 perfosting, osteoblast specific factor KIAA1193	GREB1 KIAA0644 SH3BP4 PMCHL1 SPATA2 POSTN KIAA1193	2p25.1 7p15.1 2q37.1-q37.2 5p14.3 20q13.1- q13.2 13q13.3 19p13.3	endocytosis /// cell cycle synaptic transmission /// behavior spermatogenesis /// cell differentiation skeletal development /// cell adhesion /// cell adhesion mittranscription /// regulation of transcription, DNA-dependent
04765_at 10572_at 18719_5_at 10562_at 05151_5_at 22258_5_at 17123_x_at 04433_5_at 14981_at 21963_at	1 949 2 282 1 629 2.111 1 852 2 144 1 553 3 158 1.07	4,88351713 3,09298535 4,31990824 3,61000291 4,41985794 2,93428669 8,91354921 2,09943337	hypothetical protein FLJ13912 GREB1 protein KIAA0644 gene product StI3-domain binding protein 4 pro-melanin-concentrating hormone-like 1 spermatogenesis associated 2 Periostin, osteoblast specific factor KIAA1193 forthead box G1B ///	GREB1 KIAA0644 SH3BP4 PMCHL1 SPATA2 POSTN KIAA1193 FOXG18 ///	2p25.1 7p15.1 2q37.1-q37.2 20q13.1- q13.2 13q13.3 19p13.3 14q12-q13	endocytosis /// cell cycle synaptic transmission /// behavior spermatogenesis /// cell differentiation skeletal development /// cell adhesion /// cell adhesion transcription /// regulation of transcription, DNA-dependent /// regulation of transcription, DNA-dependent ///
04765_at 10572_at 18719_5_at 10562_at 05151_5_at 22258_5_at 17123_x_at 04433_5_at 14981_at	1 949 2 282 1 629 2.111 1 852 2 144 1 553 3 158 1.07	4,88351713 3,09298535 4,31990824 3,61000291 4,41985794 2,93428669 8,91354921 2,09943337	hypothetical protein FD13912 GREB1 protein KIAA0644 gene product St43-domain binding protein 4 pro-melanin-concentrating hormone-like 1 sperosting concentrating hormone-like 1 perfosting, osteoblast specific factor KIAA1193	GREB1 KIAA0644 SH3BP4 PMCHL1 SPATA2 POSTN KIAA1193	2p25.1 7p15.1 2q37.1-q37.2 5p14.3 20q13.1- q13.2 13q13.3 19p13.3	endocytosis /// cell cycle synaptic transmission /// behavior spermatogenesis /// cell differentiation sketetal development /// cell adhesion /// cell adhesion transcription /// regulation of transcription, DNA-dependent /// regulation of transcription, DNA-dependent /// development /// train development /// brain development
04765_at 10572_at 18719_5_at 10562_at 05151_5_at 22258_5_at 17123_x_at 14935_at 14981_at 21963_at	1 949 2 282 1 629 2.111 1 852 2 144 1 553 3 158 1.07	4,88351713 3,09298535 4,31990824 3,61000291 4,41985794 2,93428669 8,91354921 2,09943337	hypothetical protein FLJ13912 GREB1 protein KIAA0644 gene product StI3-domain binding protein 4 pro-melanin-concentrating hormone-like 1 spermatogenesis associated 2 Periostin, osteoblast specific factor KIAA1193 forthead box G1B ///	GREB1 KIAA0644 SH3BP4 PMCHL1 SPATA2 POSTN KIAA1193 FOXG18 ///	2p25.1 7p15.1 2q37.1-q37.2 20q13.1- q13.2 13q13.3 19p13.3 14q12-q13	endocytosis /// cell cycle synaptic transmission /// behavior spermatogenesis /// cell differentiation skeletal development /// cell adhesion /// cell adhesion transcription /// regulation of transcription, DNA-dependent /// regulation of transcription, DNA-dependent ///

			UDP-Gal:betaGicNAc beta	1	T	·····
	1		1,3-galactosyltransferase,			
21 <u>1812_s_</u> a	t 1.023	2.03214029	polypeptide 3	B3GALT3	3q25	protein amino acid glycosylation
216155_at			Neuron navigator 1	NAV1	-	DNA methylation
			UDP-glucose ceramide	1	1	protein amino acid glycosylation /// posttranslational protei
218801_at	2.071	4,20177816	glucosyltransferase-like 2	UGCGL2	13q32.1	folding
203753_at	1.511	2,85007523	transcription factor 4	TCF4	18q21.1	transcription /// regulation of transcription from RNA polymerase II promoter
207484_5_a	t 1.099	2,14208165	HLA-B associated transcript	BATS	6021.31	chromatin modification
			Triple functional domain	r	1	protein amino acid phosphorylation /// transmembrane
<u>21</u> 5406_at	2.238	4,71742637	(PTPRF Interacting) prostaglandin D2 synthase 21kDa (brain) ///	TRIO	5p15.1-p14	receptor protein tyrosine phosphatase signaling pathway
211663_x_a	t 1.528	2,88385774	prostaglandin D2 synthase 21kDa (brain)	PTGDS	9q34.2-q34.3	prostaglandin biosynthesis /// fatty acid biosynthesis /// transport /// regulation of circadian sleep/wake cycle, sleep
200979 at			endothelial PAS domain	EDACI	2p21-p16	angiogenesis /// transcription /// regulation of transcription, DNA-dependent /// transcription from RNA polymerase II
200878_at	2.002	4,00554902	hypothetical protein	EPAS1	12p21-p16	promoter /// signal transduction /// cell differentiation
20 <u>3443_at</u>	1.923	3,79210786		FU35827	11q12.3	
219463_at	2.197	4,58524874	reading frame 103	C20orf103	20p12	
209989_at	2.376	5,19095507	zinc finger protein 268 hypothetical protein	ZNF268	12q24.33	transcription /// regulation of transcription, DNA-dependent
214418_at	2.481	5,58284306	LOC196993	LOC196993	15q22.32	
210928_at	2.131	4,38020988	CCR4-NOT transcription	CNOTZ	12q15	regulation of transcription, DNA-dependent /// regulation of global transcription from RNA polymerase II promoter
210920_at	2.131	4,38020988	complex, subunit 2 fumor necrosis factor receptor superfamily,		112013	global transcription non none polymerase 11 promote
21 <u>8856_at</u>	2 045	4,12673272	member 21	TNFRSF21	6p21.1-12.2	apoptosis /// signal transduction
219832_5_at	1.75	3,36358568	homeo box C13 regulator of telomere	HOXC13	12q13.3	regulation of transcription, DNA-dependent /// morphogenes nucleobase, nucleoside, nucleotide and nucleic acid
216325_x_at	1 054	2,07627854		RTEL1	20q13.3	metabolism /// nucleotide-excision repair
			cydin-dependent kinase			regulation of cyclin dependent protein kinase activity /// GI phase of mitotic cell cycle /// cell cycle /// cell cycle arrest // negative regulation of cell proliferation /// negative regulatio
219534_x_at	2 99	7,94473998	inhibitor 1C (p57, Kip2)	CDKN1C	11p15.5	of cell cycle
216623_x_at	1 254	2,38501774		TNRC9	16q12.1	regulation of transcription, DNA-dependent
213568_at	1 385	2,61171957	odd-skipped related 2 (Drosophila)	OSR2	8922.2	
201655_s_at	1 57	2,96904714	heparan sulfate proteoglycan 2 (perlecan)	HSPG2	1p36.1-p34	cell adhesion
			prostaglandin D2 synthase 21kDa (brain) /// prostaglandin D2 synthase			prostaglandin biosynthesis /// fatty acid biosynthesis ///
2 <u>11748_x_at</u>	3.055	8,31067283	21kDa (brain) keratin 5 (epidermolysis butlosa simplex, Dowling-	PTGDS	9q34.2-q34.3	transport /// regulation of circadian sleep/wake cycle, sleep_
201820_at	1.984	3 05589387	Meara/Kobner/Weber- Cockayne types)	KRT5	12q12-q13	epidermis development
216894_x_at			cyclin-dependent kinase inhibitor 1C (p57, Kip2)	COKNIC	11p15.5	regulation of cyclin dependent protein kinase activity /// GT phase of mitotic cell cycle /// cell cycle /// cell cycle arrest // negative regulation of cell proliferation /// negative regulatio of cell cycle
	1 086		tripartite motif-containing 58	TRIM58		
215047_at	1 000	2,14204042	matrix metalloproteinase		1q44	protein ubiquitination
07118	1 842	1 59766394	238 /// matrix	MMP236 /// MMP23A	1036.2	reproduction /// proteolysis and peptidolysis /// proteolysis and peptidolysis /// proteolysis
207 <u>118_s_at</u> 20837_at	2.411	3,58755264 5,31842843	metalloproteinase 23A		1p36.3	and peptidolysis
		0,01042040	A disintegrin and		<u> </u>	
			metalloproteinase domain			proteolysis and peptidolysis /// cell adhesion /// myoblast
15613_at	1 422		12 (metuin alpha)	ADAM12	10q26.3	fusion
07989_at	2 129	4,37414183		-		
			extra spindle poles like 1			/// cytokinesis /// proteolysis and peptidolysis /// apoptosis /// chromosome segregation /// establishment of mitotic spindle localization /// positive regulation of mitotic
04817_at	1 629		(S. cerevisiae)	ESPL1	12q	metaphase/anap
			leukocyte immunoglobulin- like receptor, subfamily A			
	3 995	15,9446442	(without TM domain), member 4	11.17	19q13.4	immune response
10313 at		10,000042	lymphocyte antigen 6			
10313_at	3 880			1.464	8q24.3	cellular defense response /// neurogenesis
10313_at	1 246	2,371829	complex, locus H	LY6H	0042 1.3	and the standing biographics of the second biographics and
06773_at	1 246		complex, locus H prostaglandin D2 synthase			prostaglandin biosynthesis /// fatty acid biosynthesis ///
06773_at 12187_x_at	1 246 3.211	9,25992174	complex, locus H prostaglandin D2 synthase 21kDa (brain)	PTGDS	9g34.2-g34.3	prostaglandin biosynthesis /// fatty acid biosynthesis /// transport /// regulation of circadian sleep/wake cycle, sleep
06773_at	1 246 3.211	9,25992174	complex, locus H prostaglandin D2 synthase 21kDa (brain) KIAA0574 protein			prostaglandin biosynthesis /// fatty acid biosynthesis ///
06773_at 12187_x_at	1 246 3.211	9,25992174 4,88040204	complex, locus H prostaglandin D2 synthase 21kDa (brain)	PTGDS	9g34.2-g34.3	prostaglandin biosynthesis /// fatty acid biosynthesis ///

Tab. A4f: Probe-sets up-regulated regulated upon IVMP treatment at day 21 compared to day 6; Probe-sets have a minimum change of 2-fold in 100% of patients;

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Probe Set ID	Gene Symbo	Gene Title	Chromosomal Locatio	GO Biological Process
0629_at	WARS	tryptophanyl-tRNA synthetase	14q32.31	protein biosynthesis, tryptophanyl-tRNA aminoacylation, negative regulation of cell profferation
00678_x_a	GRN	granuán	17q21.32	signal transduction, cell-cell signaling, cell probleration, positive regulation of cell probleration
	SERPING1	serine (or cysteine) proteinase inhibitor, clade G (C1 inhibitor), me		immune response, complement activation, classical pathway, blood coegulation, circulation
01041_s_at 01218_at	DUSPI	dual specificity phosphatase 1	5q34	protein amino acid dephosphorylation, response to oxidative stress, cell cycle
1360_at	CST3	cystatin C (amyloid angiopathy and cerebral hemorrhage)	20p11.21	
01422_at	-	-	_	
01425_at	ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	12924.2	carbohydrate metabolism, alcohol metabolism, metabolism
01670_6_8 01739_81	SGK	myristoylated alanine-rich protein kinase C substrate serum/glucocorticoid regulated kinase	6q22.2 6q23	cell motility protein amino acid phosphorytation, aodium ion transport, apoptosis, response to stress
01743_at	CD14	CD14 antigen	5q22-q32 5q31.1	phagocytosis, apoptosis, inflammatory response, cell surface receptor inked signal transduction
01798_s_at		fer-1-like 3, myoferlin (C. elegans)	10q24	muscle contraction, circulation
02269_x_at 02510_s_at		guanylate binding protoin 1, interferon-inducible, 67kDa tumor neorosis factor, alpha-induced protein 2	1p22.2 14q32	immune response angiogenesis; cell differentiation
02626_s_at		v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	8q13	protein amino acid phosphorytation, intracellular signaling cascade
	SERPINAI	serine (or cysteine) proteinase inhibitor, clade A	14q32.1	acute-phase response
~~~~	PTPNS1	(alphe-1 antiproteinase, antitrypsin), member 1		
02897_at 03066 at		protein tyrosine phosphatase, non-receptor type substrate 1 B cell RAG associated protein	20p13 10q26	regulation of DNA recombination, hexase biosynthesis, regulation of B-cell differentiation
03153_at	IFTT 1	interferon-induced protein with tetratricopeptide repeats 1	10q25-q26	immune response
03535_at	S100A9	S100 calcium binding protein A9 (calgranulin B)	1q21	inflammatory response, cell-cell signaling
03561_at 03922_s_at		Fc fragment of IgG, low affinity fla, receptor (CD32) cytochrome b-245, beta polypeptide	1q23 Χρ21.1	immune response electron transport, ion transport, inflammatory response, antimicrobial humoral response
·····	0100	(chronic granulomatous disease)	Apr (.)	(sensu Vertebrata)
03923_s_at	CYBB	cytochrome b-245, beta polypeptide	Xp21.1	electron transport, ion transport, inflammatory response, antimicrobial humoral response
		(chronic granulomatous disease)		(sensu Vertebrata)
04039_at	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	19q13.1	generation of precursor metabolites and energy, transcription, regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter
04122_at	TYROBP	TYRO protein tyrosine kinase binding protein	19q13.1	cellular defense response, intracellular signaling cascade
D4232_at	FCER1G	Fc fragment of IgE, high affinity I, receptor for; y-polypeptide	1q23	immune response, cell surface receptor linked signal transduction
04249_s_at	LMO2	LIM domain only 2 (rhombotin-like 1)	11p13	development
)4415_a1 )4445_s_at		interferon, alpha-inducible protein (clone IFI-6-16) arachidonate 5-lipoxygenase	1p35 10g11.2	Immune response, response to pest, pathogen or parasite electron transport, inflammatory response, leukotriene biosynthesis
04446_s_at		arachidonate 5-spoxygenase	10q11.2	electron transport, inflammatory response, leukotriene biosynthesis
04533_st	CXCL10	chemokine (C-X-C mot/) ligand 10	4q21	cell motility; chemotaxis; inflammatory response; cell surface receptor linked signal transduction
04588_s_at	SLC7A7	solute carrier family 7 (cartionic amino acid transporter,	14q11.2	protein complex assembly, amino acid metabolism, transport, transport, amino acid transport
04619_s_at	CSPG2	y+ system), member 7 chondroitin suffate proteoglycan 2 (versican)	5q14.3	development, cell recognition
24620_s_at		chondroitin sulfate proteoglycan 2 (versican)	5q14.3	development, cell recognition
)4747_at	IFTT3	interferon-induced protein with tetratricopeptide repeats 3	10q24	immune response
A834_at		fibrinogen-like 2 andethefel and amouth factor 1 (alstatet dark ad)	7q11.23	mitechandrial manage maintenance analyzance and interaction
04858_8_81	ECOP1	endothelial cell growth factor 1 (platelet-derived)	22q13 22q13.33	mitochondrial genome maintenance, angiogenesis, pyrimidine base metabolism pyrimidine nucleotide metabolism, DNA replication, chemotaxis, cell surface receptor linked
				signal transduction, cell-cell signaling, sensory perception, metabolism, cell differentiation
04924_at		toll-like receptor 2	4q32	induction of apoptosis, inflammatory response, signal transduction
4959_at	MINDA	myeloid cell nuclear differentiation antigen	1q22	transcription, regulation of transcription, DNA-dependent, cellular defense response
14961_s_at 14971_at		neutrophil cytosofic factor 1 (47kDa, chronic granufomatous diseas cystatin A (stefin A)	3q21	electron transport; superoxide metabolism; cellular defense response; intracellular signaling cascade
5076_s_at		myotubularin related protein 11	1012-021	phospholipid dephosphorylation
5119_s_at	FPR1	formyl peptide receptor 1	19q13.4	activation of MAPK, cell motility, chemotaxis, inflammatory response, signal transduction
5237_at		ficolin (collagen/fibrinogen domain containing) 1	9q34	phosphate transport, cell adhesion, opsonization
05312_at	SPI	spleen focus forming virus (SFFV) provinal integration oncogene sp	110112	negative regulation of transcription from RNA polymerase II promoter, transcription, regulation of transcription, DNA-dependent
5483_s_at	G1P2	interferon, alpha-inducible protein (clone IFI-15K)	1p36.33	protein modification, immune response, cell-cell signaling
)6715_at	BST1	bone marrow stromal cell antigen 1	4p15	humoral immune response, development
)5789_at	CD1D	CD1D antigen, d polypeptide	1q22-q23	detection of bacteria, T-cell selection, positive regulation of innate immune response,
05863_at	5100412	S100 calcium binding protein A12 (calgranulin C)	1q21	antigen presentation, endogenous peptide antigen, antigen presentation, endogenous lipid antigen xenobiotic metabolism, inflammatory response, defense response to bacteria,
0000_ai	3100412	Shoe calcium birding protein Krz (calgranium C)	iqz i	defense response to fungi
05936_s_at	нкз	hexokinase 3 (white cell)	5q35.2	głycołysia
		XIAP associated factor-1	17p13 1	
06380_s_at		properdin P factor, complement erythrocyte membrane protein band 4.1-like 3	Xp11.3-p11.23 18p11.32	immune response, complement activation, alternative pathway, defense response to bacteria cortical actin cytoskeleton organization and biogenesis
06710_s_at 07078_at		mediator of RNA polymerase II transcription, subunt 6 homolog (y		regulation of transcription from RNA polymerase II promoter
07104_x_at		leukocyte immunoglobulin-like receptor, subfamily B	19q13.4	immune response, response to virus
		(with TM and ITIM domains), member 1		
07540_s_at	SYK	spieen tyrosine kinase	9q22	protein complex assembly, protein amino acid phosphorytation, leukocyte cell adhesion,
				integrin-mediated, signaling pathway, intracellular signaling cascade, cell proliferation, cell proliferation, organogenesis, neutrophil chemotaxis
7610 s at	EMR2	egf-like module containing, mucin-like, hormone receptor-like 2	19p13 1	signal transduction; G-protein coupled receptor protein signaling pethway;
				neuropeptide signaling pathway
7697_x_at		leukocyte immunoglobulin-like receptor, subfamily B	19q13.4	cellular defense response; cell surface receptor signal transduction; antimicrobial humoral response
7857_at		(with TM and ITIM domains), member 2 leukocyte immunoglobu <u>än-like receptor, subfamily</u> A	19g13.4	immune response; signal transduction
1007_ <b>a</b> t		ieukocyte immunogiobuzn-ake receptor, subramity A (with TM domain), member 2	14410.4	
8018_s_a1		hemopoletic cell kinase	20q11-q12	protein amino acid phosphorylation, intracellular signaling cascade, mesoderm development
8130_s_at	TBXAS1	thromboxane A synthese 1 (platelet, cytochrome P450, family 5, si		prostaglandin biosynthesis, electron transport, fatty acid biosynthesis, transport, biood coegulation
8594_x_at		ieukocyte immunoglobulin-like receptor, subfamily B (with TM and (TMA domains) member 6	19q13.4	
8890 sat		(with TM and ITIM domains), member 6 plexin B2	22q13 33	development
8891_at	DUSP6	dual specificity phosphatase 6	12q22-q23	regulation of cell cycle; inactivation of MAPK protein amino acid dephosphorylation
8892_s_at	DUSPE	dual specificity phosphatase 6	12022-023	regulation of cell cycle; inactivation of MAPK protein amino acid dephosphorylation
9189_at	FOS	v-fos FBJ murine osteosarcoma viral oncogene homolog	14q24 3	DNA methylation, regulation of transcription from RNA polymerase II promoter,
9500 x at	TNFSF13	tumor necrosis factor (ligand) superfamily, member 13	17p13 1	inflammatory response immune response, signal transduction, positive regulation of cell proliferation
9683_at		Family with sequence similarity 49, member A	2p24.3-p24.2	
9684_at	RIN2	Ras and Rab interactor 2	-	endocytosis, intracelular signaling cascade, small GTPase mediated signal transduction
9906_at	C3AR1	complement component 3a receptor 1	12p13 31	cell motility, chemotaxis, smooth muscle contraction, inflammatory response,
				cellular defense response, signal transduction, G-protein coupled receptor protein signaling pathway, neuropeptide signaling
				pathway, positive regulation of cytosolic celcium ion concentration, sensory perception, circulation
9949_at		neutrophil cytosofic factor 2	1q25	superoxide metabolism, cellular defense response
		(65kDa, chronic granulomatous disease, autosomal 2)	0-22.0	and dation of and much temperaturing providetion of temperaturing. Only descendent successively date
9969_s_at	SIAI1 :	signal transducer and activator of transcription 1, 91kDa	2q32.2	regulation of cell cycle transcription regulation of transcription, DNA-dependent transcription from RNA polymerase (I promoter, caspase activation, intracellular signaling cascade,
				HappaB kinase/NF-kappaB cascade, tyrosine phosphorylation of STAT protein,
				STAT protein nuclear translocation, response to pest, pathogen or parasite
01 <b>48_x_a</b> t		leukocyte immunoglobulin-like receptor, subfamily B	19q134	celtular defense response; cell surface receptor signal transduction; antimicrobial humoral response
		(with TM and FTIM domains), member 2	**-12	transmission manufation of transmission DNA-dependent rentain amine and observice dation
0148_at	nuPK3	homeodomain interacting protein kinase 3	11p13	transcription, regulation of transcription, DNA-dependent, protein amino acid phosphorylation, apoptosis
02222_s_at	RTN1	reticulon 1	14g23.1	apoprosis signal transduction, neuron cell differentiation
0423_s_at		solute carrier family 11 (proton-coupled divatent metal ion transport		transport, iron ion transport, response to pest, pathogen or parasite, response to bacteria
			6p21.3	cellular morphogenesis, immune response, immune response, dendrite morphogenesis,
				negative regulation of lymphocyte proliferation
0629_x_at		eukocyte immunoglobulin-like receptor, subfamily A	19q13.4	immune response, cell surface receptor linked signal transduction
X629_x_at∣				
0629_x_at   0660_at		(with TM domain), member 1 Iom reminese (L-long remine bytmisse)	2022 3	notein amino acid phoenhopdation, intra-calidar simplifin cascade
0629_x_at   0660_at ( 0663_a_at		kynureninase (L-kynurenine hydrolase)	2q22.3 8q13	protein amino acid phosphorylation, intracellular signaling cascade immune response, cell-cell signaling, positive regulation of cell profiferation, T-cell activation, positive
0629_x_at  0660_at  0663_s_at  0754_s_at	KYNU I	kynureninase (L-kynurenine hydrolase)	2q22.3 8q13 22q13 1-q13.2	
0629_x_at   0660_at   0663_s_at   0754_s_at	KYNU I LYN APOBEC3A I	kynureninase (L-kynurenine hydrolase) ⊬yes-1 Yamaguchi sarcoma viral related oncogene homolog	8q13	protein amino acid phosphorylation, intraceBular signaling cascade immune response, cell-cell signaling, positive regulation of cell profiferation, T-cell activation, positive immune response, cell-cell signaling, positive regulation of cell profiferation, T-cell activation, positive

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211100_1_0	ULRA2	leukocyte immunoglobulin-like receptor, subfamily A	19g13.4
	ubve	(with TM domain), member 2	100110.0
211101_x_et	LILRA2	leukocyte immunoglobulin-like receptor, subfamily A	19q13.4
		(with TM domain), member 2	
211284_s_at		granuán	17q21.32
211338_x_a1	LILKB1	leukocyte immunoglobutin-like receptor, subfamily B	19q134
211429 5 81	SEDDINA	(with TM and ITIM domains), member 1 serine (or cysteine) proteinase inhibitor, clade A	14q32.1
211460_0_0	OCIO NOST	(alpha-1 antiproteinase, antitrypsin), member 1	1440E
211582 x at	LSTI	leukocyte specific transcript 1	6p21.3
212099_at	RHOB	ras homolog gene family, member B	2p24
212192 at	KCTD12	potassium channel tetramerisation domain containing 12	13q22 3
212225_at	SUI1	putative translation initiation factor	17021 2
212636_at	QKI	quaking homolog, KH domain RNA binding (mouse)	6q26-27
212681_at	EPB41L3	erythrocyte membrane protein band 4.1-like 3	18p11.32
213182_x_at	CDKN1C	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	11p15 5
213418_at	HSPA6	heat shock 70kDa protein 6 (HSP708')	1923
213472_at	HNRPH1	heterogeneous nuclear ribonucleoprotein H1 (H)	5q35.3
213524_s_at		putative lymphocyte G0/G1 switch gene	1g32.2-g41
213566_at	RNASE6	ribonuclease, RNase A family, k6	14q11 2
213716_s_at		secreted and transmembrane 1	17q25
214038_at	CCL8	chemokine (C-C motif) ligand 8	17q11.2
214084_x_at			-
214366_s_at 214511 x at		arachidonate 5-lipoxygenase	10q11_2
214722 at	NOTCH2NL	Notch homolog 2 (Drosophila) N-terminal like	 1g21.2
215123 at	-		
215220_s_at	TPR	translocated promoter region (to activated MET oncogene)	1q25
215633_x_at	LST1	leukocyte specific transcript 1	6p21 3
215933_s_at		hematopoietically expressed homeobox	10q23.33
216041_x_at 216109_at		granulin Thyroid hormone receptor associated protein 2	17q21.32 12q24.21
216109_at 216894_x_at		cyclin-dependent kinase inhibitor 1C (p57, Kip2)	12q24.21 11p15.5
2.000.7.2		of the second	11010
216899_s_at	SCAP2	arc family associated phosphoprotein 2	7p21-p15
216050 s at	FCGR1A	Fc fragment of IgG, high affinity Ia, receptor (CD64)	1021.2-021.3
		kynureninase (L-kynurenine hydrolase)	2q22 3
217388_s_at			
217388_s_at 217679_x_at		-	-
217388_s_st 217679_x_st 217763_s_st	RAB31		 18p11.3
217388_s_at 217679_x_at 217763_s_at 217764_s_at	 RAB31 RAB31	 RAB31, member RAS oncogene family RAB31, member RAS oncogene family	
217388_s_st 217679_x_st 217763_s_st	 RAB31 RAB31 TENS1	- RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-like SH2 domain containing 1 RNA-binding protein	 18p11.3
217388 s_at 217679 x_at 217763 s_at 217764 s_at 217764 s_at 218035 s_at 218035 s_at 218559 s_at	 RAB31 RAB31 TENS1 FLJ20273 MAFB	— RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Ro SH2 domain containing 1	
217388_s_mt 217679_x_at 217763_s_at 217764_s_at 217853_st 218055_s_at 218559_s_at 219093_at	 RAB31 RAB31 TENS1 FLJ20273 MAFB FLJ20701	- RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-like SH2 domain containing 1 RNA-binding protein RNA-binding protein wmaf musculesponeurotic fibrosarcoma oncogene homolog B hypothetical protein FL/20701	
217388_s_st 217679_x_st 217763_s_st 217763_s_st 217764_s_st 217753_s_st 218035_s_st 2180559_s_st 219093_st 219519_s_st	 RAB31 RAB31 TENS1 FLJ20273 MAFB FLJ20701 SN	- RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Rus SH2 domain containing 1 RNA-binding protein v-maf musculoaponeurotic fibrosarcoma oncogene homolog B hypothetical protein FL/20701 satas/thesis	— 18p11.3 18p11.3 7p13-p12.3 4p13-p12 20q11.2-q13.1 2q36.3 20p13
217388_s_mt 217679_x_at 217763_s_at 217764_s_at 217853_st 218055_s_at 218559_s_at 219093_at	 RAB31 RAB31 TENS1 FLJ20273 MAFB FLJ20701 SN	- RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-like SH2 domain containing 1 RNA-binding protein Wmaf musculesponeurotic fibrosarcoma oncogene homolog B hypothetical protein FL/20101	
217388_s_st 217679_x_st 217763_s_st 217763_s_st 217853_st 218035_s_st 2180559_s_st 219003_st 219519_s_st 219534_x_st	AB31 RAB31 TENS1 FLJ20273 MAFB FLJ20701 SN CDKN1C	- RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-like SH2 domain containing 1 RNA-binding protein v-maf musculesponeurutic fibrosarcoma oncogene homolog B hypothetical protein FLJ20701 salaadhesin cyclin-dependent kinase inhibitor 1C (p57, Kip2)	
217388_s_et 217676_x_et 217763_s_et 217764_s_et 217853_et 218035_s_et 218055_s_et 219093_et 2190534_x_et 219607_s_et	AB31 RAB31 TENS1 FLJ20273 MAFB FLJ20701 SN CDKN1C	- RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Bue SH2 domain containing 1 RNA-binding protein wmaf musculeaponeurotic fibrosarcoma oncogene homolog B hypothetical protein Fu/20701 sabadhesin cyctin-dependent kinase inhibitor 1C (p57, Kip2) membrane-spanning 4-domains, subfamily A, member 4	
217388_s_et 217679_x_et 217763_s_et 217764_s_et 218035_s_et 218035_s_et 219003_et 219534_x_et 219534_x_et 219607_s_et 219788_et			
217388_s_et 217679_x_et 217763_s_et 217764_s_et 218035_s_et 218035_s_et 219003_et 219534_x_et 219534_x_et 219607_s_et 219788_et	AB31 RAB31 TENS1 FLI20273 MAFB FLI20701 SN CDKN1C MS4A4A PLRA	- RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Bue SH2 domain containing 1 RNA-binding protein wmaf musculeaponeurotic fibrosarcoma oncogene homolog B hypothetical protein Fu/20701 sabadhesin cyctin-dependent kinase inhibitor 1C (p57, Kip2) membrane-spanning 4-domains, subfamily A, member 4	
217388_g.mt 217679_x.mt 217763_g.mt 217764_g.mt 218035_g.mt 218035_g.mt 218035_g.mt 218035_g.mt 219039_mt 219534_x.mt 219667_g.mt 219667_g.mt 219688_mt	 RAB31 RAB31 TENS1 FLI20273 MAFB FLI20701 SN CDKN1C MS4A4A PILRA CSR1	 RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Bus 5H2 domain containing 1 RNA-briefing protein v-maf musculesponeurotic fibrosancoma oncogene homolog B hypothetical protein FLJ20701 saibadhesin cycEn-dependent kinase inhibitor 1C (p57, Kip2) membrane-spanning 4-domains, subfamily A, member 4 peind immunoglobin-Bits type 2 receptor a beha complement component 5 receptor 1 (C5a ligand)	
217388et 217679sit 217763sit 217764sit 217553_sit 218035_sit 218035_sit 218059_sit 219519_sit 219519_sit 219534_x_sit 219675_sit 220085_st 220091_st	 RAB31 RAB31 TENS1 FL/20273 MAFB FL/20701 SN CDKN1C MS4A4A PILRA C5R1 SLC2A6		
217388_g.mt 217679_x.mt 217763_g.mt 217764_g.mt 218035_g.mt 218035_g.mt 218035_g.mt 218035_g.mt 219059_g.mt 219519_g.mt 219554_x.mt 21967_g.mt 21967_g.mt 220088_mt 220091_mt 220146_st			
217388_a_mt 217670_x_at 217676_a_mt 217763_a_mt 217763_a_mt 218555_a_mt 218053_s_at 218051_a_mt 219534_x_mt 219534_x_mt 219676_a_mt 220088_mt 220091_mt 220146_at 220548_a_mt	 RAB31 RAB31 TENS1 FL/20273 MAFB FL/20701 SN CDKN1C MS4A4A PILRA C5R1 SLC2A6  LR8		
217388_g.mt 217679_x.mt 217763_g.mt 217764_g.mt 218035_g.mt 218035_g.mt 218035_g.mt 218035_g.mt 219059_g.mt 219519_g.mt 219554_x.mt 21967_g.mt 21967_g.mt 220088_mt 220091_mt 220146_st	 RAB31 RAB31 TENS1 FL/20273 MAFB FL/20701 SN CDKN1C MS4A4A PILRA C5R1 SLC2A6  LR8		
217388_a_mt 217670_x_at 217676_a_mt 217763_a_mt 217763_a_mt 218555_a_mt 218053_s_at 218051_a_mt 219534_x_mt 219534_x_mt 219676_a_mt 220088_mt 220091_mt 220146_at 220548_a_mt	 RAB31 RAB31 TENS1 FL/20273 MAFB FL/20701 SN CDKN1C MS4A4A PILRA C5R1 SLC2A6  LR8		
217388_a_mt 217670_x_at 217676_a_mt 217763_a_mt 217763_a_mt 218555_a_mt 218053_s_at 218051_a_mt 219534_x_mt 219534_x_mt 219676_a_mt 220088_mt 220091_mt 220146_at 220548_a_mt	 RAB31 RAB31 TENS1 FL/20273 MAFB FL/20701 SN CDKN1C MS4A4A PILRA C5R1 SLC2A6  LR8		
217388_s_et 217679_x_et 217679_s_et 217763_s_et 217764_s_et 218555_s_et 218035_s_et 21903_s_et 2190519_s_et 219578_et 219788_et 220088_et 220091_et 220146_st 220146_st 22052_s_et 22056_s_et		 RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-ikes 5H2 domain containing 1 RNA-binding protein v-maf musculeaponeurotic fibrosarcoma oncogene homolog B hypothetical protein FL/20701 saibadhesin cycEn-dependent kinase inhibitor 1C (p57, Kip2) membrane-spanning 4-domains, subfamily A, member 4 peind immunoglobin-like type 2 receptor alpha complement component 5 receptor 1 (C5s ligand) solutie carrier family2 (facilitated glucose transporter), member 6  LR8 protein tol-like receptor 4	
217388_s_et 217679_x_et 217679_x_et 217763_s_et 217764_s_et 218559_st 218055_s_et 218055_s_et 219053_s_et 219554_x_et 219554_x_et 219785_st 220091_et 220146_st 220532_s_et 221581_s_et		 RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Bus SH2 domain containing 1 RNA-binding protein v-maf musculoaponeurotic fibrosarcoma oncogene homolog B hypothetical protein FLJ20701 sabaedhesin cycfin-dependent kinase inhibitor 1C (p57, Kip2) membrane-spanning 4-domains, subfamily A, member 4 period immunojobin-Bus type 2 roceptor a lighta complement component 5 receptor 1 (C5s ligand) solute carrier family2 (facilitated glucose transporter), member 6  LR8 protein tol-Bite receptor 4 Williams-Beuren syndrome chromosome region 5	
217388_s_et 217679_x_et 217679_s_et 217764_s_et 217763_s_et 218559_s_et 218035_s_et 21903_s_et 219059_s_et 219548_st 219788_et 220088_et 220091_et 220146_st 220146_st 22055_s_et		 RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-ikes 5H2 domain containing 1 RNA-binding protein v-maf musculeaponeurotic fibrosarcoma oncogene homolog B hypothetical protein FL/20701 saibadhesin cycEn-dependent kinase inhibitor 1C (p57, Kip2) membrane-spanning 4-domains, subfamily A, member 4 peind immunoglobin-like type 2 receptor alpha complement component 5 receptor 1 (C5s ligand) solutie carrier family2 (facilitated glucose transporter), member 6  LR8 protein tol-like receptor 4	
217388_s_et 217679_x_et 217679_x_et 217763_s_et 217764_s_et 218559_st 218055_s_et 218055_s_et 219053_s_et 219554_x_et 219554_x_et 219785_st 220091_st 220146_st 220552_s_et 221581_s_et		 RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Bus SH2 domain containing 1 RNA-binding protein v-maf musculoaponeurotic fibrosarcoma oncogene homolog B hypothetical protein FLJ20701 sabaedhesin cycfin-dependent kinase inhibitor 1C (p57, Kip2) membrane-spanning 4-domains, subfamily A, member 4 period immunojobin-Bus type 2 roceptor a lighta complement component 5 receptor 1 (C5s ligand) solute carrier family2 (facilitated glucose transporter), member 6  LR8 protein tol-Bite receptor 4 Williams-Beuren syndrome chromosome region 5	
217388_s_et 217679_x_et 217679_x_et 217763_s_et 217764_s_et 218559_st 218055_s_et 218055_s_et 219053_s_et 219554_x_et 219554_x_et 219785_st 220091_st 220146_st 220552_s_et 221581_s_et		 RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Bus SH2 domain containing 1 RNA-binding protein v-maf musculoaponeurotic fibrosarcoma oncogene homolog B hypothetical protein FLJ20701 sabaedhesin cycfin-dependent kinase inhibitor 1C (p57, Kip2) membrane-spanning 4-domains, subfamily A, member 4 period immunojobin-Bus type 2 roceptor a lighta complement component 5 receptor 1 (C5s ligand) solute carrier family2 (facilitated glucose transporter), member 6  LR8 protein tol-Bite receptor 4 Williams-Beuren syndrome chromosome region 5	
217388_9_4 217679_x at 217763_8_at 217764_8_at 218035_8_at 218035_8_at 218059_8_at 219059_8_at 219059_8_at 21967_9_4 219678_at 220088_at 220091_at 220148_at 220148_at 220148_at 220148_at 221680_8_at		 RAB31, member RAS oncogene family RAB31, member RAS oncogene family tensin-Bus SH2 domain containing 1 RNA-briding protein v-maf musculoaponeurutic florosarcoma oncogene homolog B hypothetical protein FLJ20701 saloadhesin cycEn-dependent kinase inhibitor 1C (p57, Kip2) membrane-spenning 4-domains, subfamily A, member 4 peired immunojobin-Bus type 2 receptor a byte complement component 5 receptor 1 (C5s ligand) solute carrier family2 (facilitated glucose transporter), member 6  LR8 protein tol-Bite receptor 4 Williams-Beuren syndrome chromosome region 5 C-type lectin domain family 7, member A	

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Tab. A5: Subtraction of IVMP-specific genes after treatment of IVIG-specific genes after treatment; Probe-sets listed above are specifically differentially regulated upon IVIG therapy; Criteria for IVIG treatment: a minimum of a 2-fold change in at leat 40% of patients (4 out of 10); Criteria for IVIP treatment: a minimum of a 2-fold change in at leat 60% of patients (3 out of 5);

immune response; signal transduction
eignal transduction, cell-cell signaling, cell proliferation, positive regulation of cell proliferation immune response, response to virus
acute-phase response
celular morphogenesis, immune response, immune response, dendrite morphogenesis,
negative regulation of lymphocyte proliferation
angiogenesis; programmed cell death; transformed cells; cell cycle; cell adhesion small GTPase mediated signal transduction; endosome to lysosome transport; protein transport
cell differentiation; positive regulation of angiogenesis; negative regulation of cell cycle
potassium ion transport
protein biosynthesis, translational initiation, regulation of translation, regulation of
translational initiation, response to stress
contical actin cytoskeleton organization and biogenesis
regutation of cyclin dependent protein kinase activity, G1 phase of mitotic cell cycle, cell cycle,
cell cycle arrest, negative regulation of cell proliferation, negative regulation of cell cycle
protein folding; response to unfolded protein RNA processing
regulation of cell cycle
RNA catabolism, defense response
immune response, mesoderm development, positive regulation of HuppeB kinase/NF-kappeB cascade
calcium ion transport, exocytosis, chemotaxis, inflammatory response, signal transduction,
cell cycle arrest,
electron transport, inflammatory response, leukotriene biosynthesis
protein-nucleus import, transport celular morphogenesis, immune response, immune response, dendrite morphogenesis,
regative regulation of lymphocyte profferation
regulation of transcription, DNA-dependent, development, antimicrobial humoral response
signal transduction, cell-cell signaling, cell proliferation, positive regulation of cell proliferation
regulation of cyclin dependent protein kinase activity, G1 phase of mitotic cell cycle, cell cycle,
cell cycle arrest, negative regulation of cell proliferation, negative regulation of cell cycle
protein complex assembly, signal transduction
phagocylosis, enguafment; immune response tryptophan catabolism, NAD biosynthesis
small GTPase mediated signal transduction
small GTP ase mediated signal transduction
protein amino acid dephosphorylation, cell cycle, intracellular signaling cascade
transcription, regulation of transcription, DNA-dependent, sensory organ development
inflammatory response, cell-matrix adhesion, cell-cell adhesion
regulation of cyclin dependent protein kinase activity, G1 phase of mitotic cell cycle, cell cycle,
cell cycle arrest, negative regulation of cell proliferation, negative regulation of cell cycle
signal transduction
transmembrane receptor protein tyrosine kinase, activation (dimerization) activation of MAPK;chemotaxis; G-protein coupled receptor protein signaling pathway
phospholipese C activation; positive regulation of cytosolic calcium ion concentration
sensory perception of chemical stimulus
carbohydrate transport
organogenesis
inflammatory response, signal transduction, activation of NF-kappaB-inducing kinase, detection of
pathogenic bacteria, detection of fungi, T-helper 1 type immune response, macrophage activation,
positive regulation of interleukin-12 biosynthesis, positive regulation of interleukin-1 biosynthesis,

positive regulation of interleukin-4 biosynthesis, positive regulation of T-helper 2 cell differentiation, positive regulation of transcription immune response; signal transduction

inflammatory response, signal transduction, activation of NF-kappaB-inducing kinase, detection of
pathogenic bacteria, detection of fungi, T-helper 1 type immune response, macrophage activation,
positive regulation of interleukin-12 biosynthesis, positive regulation of interleukin-1 biosynthesis,
positive regulation of interleukin-13 biosynthesis, positive regulation of interleukin-6 biosynthesis
mast cell activation, negative regulation of osteoclast differentiation
intracellular signaling cascade, calcium-mediated signaling, B-cell activation
phagocytosis, recognition, cell recognition, carbohydrate mediated signaling,
antibacterial humoral response (sensu Vertebrata), antifungal humoral response (sensu Vertebrata),
T-cell activation, defense response to pathogenic protozoa, reduction of virulence
development, cell recognition

6398 x et XC 6407 s et XC 6407 s et CC 18198 x et XIF 17850 st CX 17852 st CX 17852 st CX 17853 st CX 17853 st CX 17854 st F2 16625 s et L1 194455 x et PT 19445 x et PT	P GGER4 AP4K2 DL2 DL2 DL13 R2DS1 KCL3 KCL3 EC4E R2GA1 		Chromosomal Location 4q11-q13 5p13.1 11q13 1q23-q25 17q11.2 19q13.4 4q12-q13 12p13.31 17q21	CO Biological Process Description transport, immune response, signal transduction, C-protein coupled receptor protein signaling pathway, Coprotein signaling, coupled to cAMP nucleotide second messenger protein amino acd phosphonfation, vesicle langeling, response to stress, immune response, protein transe cascade, JNK cascade, hemocyte dovelopment chemotaxis, immune response, signal transduction, cel-cell signaling, sensory perception mmune response, capatite cascade, inflammatory response, signal transduction, cel-cell signaling, sensory perception fmmune response, capatite cascade, inflammatory response, signal transduction, cel-cell signaling, sensory perception chemotaxis, inflammatory response, C-protein coupled receptor protein signaling pathway, sensory perception chemotaxis, inflammatory response, signal transduction, cel-cell signaling, positive regulation of cell proderation immune response, attimicrobial humoral response (sensu Vertebrata) cell cycle checkpoint, DMA regark, resparise of transportation from RNA polymerase ii promoter,
44634         af           44636         af           44636         af           44636         af           44636         af           44338         af           44338         af           44338         af           78550         af           78552         af           78552         af           78552         af           78553         af           78552         af           78553         af           78554         af           78574         af           78626         af           14405         af           69226         af           194405         x           194405         x           194405         x           19445         x	P GGER4 AP4K2 DL2 DL2 DL13 R2DS1 KCL3 KCL3 EC4E R2GA1 	alpha-fatoprotein prostaglandin E receptor 4 (autitype EP4) mitogen-activited protein kinase kinase kinase kinase 2 chemokune (C mot/) ligand 2 chemokune (C-C mot/) ligand 13 killer cell mmunoglobulin-tike receptor, heo dornains, short cytoplasmic tail, 1 chemokune (C-X-C mot/) ligand 3 chemokune (C-X-C mot/) ligand 5 C-type lectin domain family 4, member E breast cancer 1, early onset	4q11-q13 5p13.1 11q13 1q23-q25 17q11.2 18q13.4 4q21 4q12-q13 12p13.31	transport, immune response immune response, signal transduction, G-protein coupled receptor protein signaling pathway, G-protein signaling, coupled to cAMP nucleotide second messenger protein immune response, signal transduction, ce8-ce8 signaling, sensory perception, circulation calcum on homeostasis, chemotasis, inflammatory response, signal transduction, ce8-ce8 signaling, sensory perception immune response chemotasis, inflammatory response, G-protein coupled receptor protein signaling pathway, sensory perception immune response chemotasis, inflammatory response, G-protein coupled receptor protein signaling pathway, sensory perception chemotasis, inflammatory response, G-protein coupled receptor protein signaling positive regulation of ce8 proteintion immune response, antimicrobil humoral response (sensu Vertebrata)
H4896         s. et         PT.           H4335         at         MA           H6336         s. et         XC           H6407         s. et         XC           H6550         et         XC           H6550         et         XC           H6550         et         XC           H4605         et         FL           H4605         et         FL           H6627         s. et         LL           H6626         s. et         LL	rger4 AP4K2 2L2 2L13 R2DS1 KCL3 KCL5 LEC4E RCA1 .T1 .K4	prostaglandin E receptor 4 (authype EP4) mitogen-ectivated protein kinase kinase kinase kinase 2 chemokine (C mot/) ligand 2 chemokine (C-C mot/) ligand 13 kifer cell mmunogibolim-kike receptor, hero domains, short cytopilamic tak. 1 chemokine (C-X-C mot/) ligand 3 chemokine (C-X-C mot/) ligand 5 C-type lectin domain family 4, member E breast cancer 1, early onset	5p13.1 11q13 1q23-q25 17q11.2 19q13.4 4q21 4q12-q13 12p13.31	Immune response, signal transduction, G-protein coupled receptor protein signaling pathway, G-protein signaling, coupled to CAMP nucleotide accord messenger protein minor acid phosphorylation, vesicle targeting, response to stress, immune response, protein minor ensponse, signal transductori, cel-cell signaling, sensory perception, circulation calcum on homeostasis, chemotaxis, inflemmatory response, signal transduction, cel-cell signaling, sensory perception immune response chemotaxis, inflemmatory response, G-protein coupled receptor protein signaling pathway, sensory perception chemotaxis, inflemmatory response, G-protein coupled receptor protein signaling pathway, sensory perception chemotaxis, inflemmatory response, G-protein coupled receptor protein signaling positive regulation of cell proteintion immune response, antimicrobili humorali response (sensu Vertebrata)
M936 at         MA           6366 x at         XC           6407 s at         CC           8198 x at         XIF           7850 at         CX           7852 at         CX           9859 at         CL           4406 at         FL           4406 at         FL           6857 a at         PL           6926 a at         LL           6926 a at         LT	AP4K2 5L2 5L13 R2051 KCL3 KCL3 ECC4E RCA1 .T1 .K4	prostaglandin E receptor 4 (aubtype EP4) mitogen-activeited protein kinase kinase kinase kinase 2 chemokine (C-C motif) ligand 2 chemokine (C-C motif) ligand 13 killer cell mmunoglobulin-tike receptor, heo domairs, short cytoplesmic tail, 1 chemokine (C-X-C motif) ligand 3 chemokine (C-X-C motif) ligand 5 C-type lectin domain family 4, member E breast cancer 1, early onset	5p13.1 11q13 1q23-q25 17q11.2 19q13.4 4q21 4q12-q13 12p13.31	Immune response, signal transduction, G-protein coupled receptor protein signaling pathway, G-protein signaling, coupled to CAMP nucleotide accord messenger protein minor acid phosphorylation, vesicle targeting, response to stress, immune response, protein minor ensponse, signal transductori, cel-cell signaling, sensory perception, circulation calcum on homeostasis, chemotaxis, inflemmatory response, signal transduction, cel-cell signaling, sensory perception immune response chemotaxis, inflemmatory response, G-protein coupled receptor protein signaling pathway, sensory perception chemotaxis, inflemmatory response, G-protein coupled receptor protein signaling pathway, sensory perception chemotaxis, inflemmatory response, G-protein coupled receptor protein signaling positive regulation of cell proteintion immune response, antimicrobili humorali response (sensu Vertebrata)
6398 x et XC 6407 s et XC 6407 s et CC 18198 x et XIF 17850 st CX 17852 st CX 17852 st CX 17853 st CX 19859 st CL 14405 st FL 14405 st FL 14405 st FL 14605 s et L1 199465 x et PT	CL2 CL13 R2OS1 KCL3 KCL5 EC4E RCA1 T1 X4	chemokine (C motif) igand 2 chemokine (C-C motif) igand 13 killer cell immunogibbulin-kille receptor, two domains, short cytoplasmic tail, 1 chemokine (C-X-C motif) igand 3 chemokine (C-X-C motif) igand 5 C-type loctin domain family 4, member E breast cancer 1, early onset	1q23-q25 17q11.2 19q13.4 4q21 4q12-q13 12p13.31	protein amino sod phosphonfation, vesicle largeting, response to gress, immune response, protein kinase cascade, JNK cascade, hemocyte dovelopment chemotaxis, immune response, signal transductor, cet-ceti signaling, sensory perception, circulation calcium on homeostasis, chemotaxis, inflemmatory response, signal transduction, cet-ceti signaling, sensory perception immune response chemotaxis, inflammatory response, G-protein coupled receptor protein signaling pethway, sensory perception chemotaxis, inflammatory response, signal transduction, cet-ceti signaling positive regulation of ceti protein coupled receptor protein signaling positive regulation of ceti proteinin and transduction, cet-ceti signaling, positive regulation of ceti proteinin response (sensu Vertebrata)
6398 x et XC 6407 s et XC 6407 s et CC 18198 x et XIF 17850 st CX 17852 st CX 17852 st CX 17853 st CX 19859 st CL 14405 st FL 14405 st FL 14405 st FL 14605 s et L1 199465 x et PT	CL2 CL13 R2OS1 KCL3 KCL5 EC4E RCA1 T1 X4	chemokine (C motif) igand 2 chemokine (C-C motif) igand 13 killer cell immunogibbulin-kille receptor, two domains, short cytoplasmic tail, 1 chemokine (C-X-C motif) igand 3 chemokine (C-X-C motif) igand 5 C-type loctin domain family 4, member E breast cancer 1, early onset	1q23-q25 17q11.2 19q13.4 4q21 4q12-q13 12p13.31	protein kinase cascade, JNK cascade, hemocyte dovelopment chemotaxis, immune response, signal transduction, cel-cel signaling, sensory perception, circulation calcum on homostasis, chemotaxis, inflammatory response, signal transduction, cel-cel signaling, sensory perception immune response chemotaxis, inflammatory response, C-protein coupled receptor protein signaling pathway, sensory perception chemotaxis, inflammatory response, G-protein coupled receptor protein signaling positive regulation of cell proteintion immune response, antimicrobal humoral response (sensu Vertebrata)
6407 s. et         CC           8198 x. et         KIF           7850 et         CX           7852 at         CX           7853 at         FL           4405 at         FL           4405 at         L1           46825 at         L1           96425 x at         PT	CL 13 R2DS1 KCL3 KCL5 LEC4E RCA1 	chemokine (C-C motif) ligand 13 killer cell immunoglobulin-tike receptor, hvo domains, short sytoplasmic tall, 1 chemokine (C-X-C motif) ligand 3 chemokine (C-X-C motif) ligand 5 C-type loctin domain family 4, member E breast cancer 1, early onset	17q11.2 19q13.4 4q21 4q12-q13 12p13.31	chemotaxis, immune response, signal transducton, cel-cel signaling, sensory perception, circulation calcium ion homeostasis, chemotaxis, inflammatory response, signal transduction, cel-cel signaling, sensory perception immune response chemotaxis, inflammatory response, G-protein coupled receptor protein signaling pet/way, sensory perception chemotaxis, inflammatory response, G-protein coupled receptor protein signaling demotaxis, inflammatory response, signal transduction, cell-cell signaling, possilve regulation of cell proteintion immune response, antimicrobial humoral response (sensu Vertebrata)
8198 x et XIF 7850 et XIF 7852 et XIF 9859 et CL 4531 e et BR 4406 et FL 4406	R2DS1 KCL3 KCL5 LEC4E RCA1 	killer cell immunogibbulin-kke receptor, two dorneins, short cytoplasmic tell, 1 chemokine (C-X-C motif) figand 3 chemokine (C-X-C motif) figand 5 C-type lectin domain family 4, member E breast cancer 1, early onset	19q13.4 4q21 4q12-q13 12p13.31	sensory perception immune response chemotaxis, inflammatory response, C-protein coupled receptor protein signaling pathway, sensory perception chemotaxis, inflammatory response, signal transduction, cell-cell signaling, possilve regulation of cell proteint ramonal response (sensu Vertebrata)
77850 et CX 17852 et CX 17852 et CX 19859 et CL 44331 s. et BR 44406 et FL 44406 et FL 44406 et FL 44687 s. et PL 6754 et F2 69226 s. et IL1 19465 x. et PT	KCL3 KCL5 EC4E RCA1 T1	hiro domains, short cytoplesmic tail, 1 chemokine (C-X-C motif) ligand 3 chemokine (C-X-C motif) ligand 5 C-type loctin domain family 4, member E breast cancer 1, early onset	4q21 4q12-q13 12p13 31	Immune response chemotaxis, inflammatory response, G-protein coupled receptor protein signaling pathway, sensory perception chemotaxis, inflammatory response, signal transduction, cell-cell signaling, positive regulation of cell proteination immune response, antimicrobial humoral response (sensu Vertebrata)
7852 at CX 9859 at CL 4531 a at BR 4405 at FL 4405 at FL 6626 a at LL 96465 x at PT	KCL3 KCL5 LEC4E RCA1 	chemokine (C-X-C motif) ligand 3 chemokine (C-X-C motif) ligand 5 C-type lectin domain family 4, member E breast cancer 1, early onset	4q12-q13 12p13 31	sensory perception chemotaxis, inflammatory response, signal transduction, cell-cell signaling, positive regulation of cell problemation immune response, antimicrobial humoral response (aensu Vertebrata)
7852 at CX 9859 at CL 4531 a at BR 4405 at FL 4405 at FL 6626 a at LL 96465 x at PT	KCL5 LEC4E RCA1	chemokune (C-X-C motif) igand 5 C-type lectin domain family 4, member E breast cancer 1, early onset	4q12-q13 12p13 31	sensory perception chemotaxis, inflammatory response, signal transduction, cell-cell signaling, positive regulation of cell problemation immune response, antimicrobial humoral response (aensu Vertebrata)
9859 et CLI 4531 s. et BR 4406 et FL1 4687 s. et PL 6754 et FL 8026 s. et L1 90485 x. et PT	TI	C-type loctin domain family 4, member E breast cancer 1, early onset	12p13 31	dhemotaxis, inflammatory response, signal transduction, cell-cell signaling, positive regulation of cell proliferation immune response, antimicrobial humoral response (aensu Vertebrata)
4405 at FL 4405 at FL 44857 s at PL 6754 at F2 6926 s at L1 19485 x at PT	T1 K4	breast cancer 1, early onset	12p13 31	positive regulation of cell problemation immune response, antimicrobial humoral response (sensu Vertebrate)
4405 at FL 4405 at FL 44857 s at PL 6754 at F2 6926 s at L1 19485 x at PT	T1 K4	breast cancer 1, early onset		
4406 at FL 14887 s at PU 15754 at F2 16926 s at L1 19485 x at PT	Т1 .К4			
14687 <u>a</u> at PU 16754 at F2 16926 <u>a</u> at U.1 16465 <u>x</u> at PT	.K4	ma-related tyrosine kimise 1 (vascular endothelial growth		regulation of transcription from RNA polymerase III promoter, DNA damage response,
14687 <u>a</u> at PU 16754 at F2 16926 <u>a</u> at U.1 16465 <u>x</u> at PT	.K4	ma-relinted tyrosine kinese 1 (vescular endothelia) growth		signal transduction by p53, class mediator resulting in transcription of p21 class mediator, cell cycle ,
14687 <u>a</u> at PU 16754 at F2 16926 <u>a</u> at U.1 16465 <u>x</u> at PT	.K4	ma-related tyrosine kinese 1 (vascular endothelial growth	┝─────	protein ubiquitination, regulation of cell proliferation, regulation of apoptosis, regulation of cell positive regulation of DNA repair, negative regulation of cell cycle, negative regulation of centricle replication
6754 at F2 18926 a at LL1 19485 x at PT	.K4		13012	angiogenesis, protein amino acid phosphorylation, transmembrane receptor protein tyrosine kinase
6754 at F2 18926 a at LL1 19485 x at PT		factor/vascular permembility factor receptor)		signaling pathway, pregnancy, positive regulation of cell proliferation, cell differentiation
6926 sat LL1 9465 x at PT		polo-like kinase 4 (Drosophia)	4q27-q28	regulation of cell cycle, protein amino acid phosphorylation
19485 <u>x</u> et PT		congulation factor II (thrombin)	11p11-q12	regulation of cell cycle, protectysis and peptidolysis, apoptosis, caspase activation, acute-phase , response, tyrosine phosphorylation of STAT protein, STAT protein nuclear translocation, development
19485 <u>x</u> et PT	1			response to wounding, platelet activation, regulation of blood coegulation, fibrinolysis
	11	nterleukin 11	19q13 3-q13.4	cell-cell signaling, positive regulation of cell proliferation, piztelet activation, B-cell differentiation,
		pleiotrophin (heparin binding growth factor 8,	7933-934	megakaryocyte differentiation, adipocyte differentiation regulation of cell cycle, transmembrane receptor protein tyrosine phosphatase signaling pathway,
0359_at MT		neurite growth-promoting factor 1)		neurogenesis, cell proliferation, positive regulation of cell proliferation
	TSS1	metastasis suppressor 1	8p22	cell motility, cell cycle, cell adhesion, transmembrane receptor protein tyrosine kinase signaling
1			<u> </u>	pathway, neurogenesis, muscle development, microsplice biogenesis, actin cytoskeleton organization and biogenesis, negative regulation of cell cycle
0960_at AD	DRA1D	adrenergic, alpha-1D-, receptor	20p13	DNA metabolism, signal transduction, G-protein coupled receptor protein signaling pethway,
				G-protein signaling, coupled to cAMP nucleotide second messenger,
1154_at TH	iro l	thrombopolistin (mysloproliferative leukernis virus oncogene	3q27	cell-cell signaling, development, cell proliferation, positive regulation of cell proliferation development, cell proliferation
		igand, megakaryocyte growth and development factor)		
1792 s at CD			1p32	cell cycle, cell cycle arrest, negative regulation of cell proliferation
1831 s at TH		thrombopoistin (myeloproliferative leukemia virus oncogene ligand, megalarvocyte growth and development factor)	3q27	development, cell proliferation
4381_at LO			11p11.12	cell cycle
5070 x at RA			9q33.2-q33.3	cell cycle
5381_at FR 5624 at TS		FK506 binding protein 12-rapemycin associated protein 1 Tuberous aclerosis 2	1p36.2	regulation of cell cycle, DNA repair, DNA recombination protein folding, endocytosis, negative regulation of cell cycle
			8p22	protein amino acid dephosphorylation, protein amino acid dephosphorylation, cell cycle,
				phospholipid dephosphorytetion
5942_s_st GT	ISE1	G-2 and S-phase expressed 1	22q13.2-q13.3	G2 phase of mitotic cell cycle, DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest, microtubule-based process
6896_at CO	01.443	collagen, type IV, alpha 3 (Goodpesture antigen)	2938-937	proteolysis and peptidolysis, phosphilita transport, induction of apoptosis, caspase activation,
				cell adhesion, cell surface receptor linked signal transduction, perception of sound, circulation,
2305 at HK	<del>;</del> {	hexoldnese 2	2p13	cell profiferation, negative regulation of cell profiferation and angiogenesis regulation of cell cycle, glycolysis
4833771 AP		APG/2010001017/12-00(5(corev100)	5621-622	
UNACIDITAL CA			26622685	protection in the protection of the protection o
1042 et TG	M2	precuisor(cellexpressed) developmentally,down-regulated/2)	20012	G-protein coupled receptor protein signaling pathway, peptide cross-linking,
				positive regulation of cell adhesion
1124_at ITC		integrin, beta 5	3q21.2	cell-matrix adhesion, integrin-mediated signaling pathway, development
1430_s_at_DP			5q32	nucleobase, nucleoside, nucleotide and nucleic acid metabolism, signal transduction, neurogenesis protein ammo acid phosphorytation, signal transduction, transmembrane receptor protein tyrosine
				kinese signaling pathway, development
			3p26 1	cell adhesion, signal transduction
16056_s_at_GR 16223_at_DE			12p13 22q12.3	G-protein coupled receptor protein signaling pathway, protein metabolism
0223 at TA		techylunin, precursor 1 (substance K, substance P, neurokinin 1, n		tachykinin signaling pathway, neuropeptide signaling pathway, cell-cell signaling, synaptic
				transmission, insemination, detection of abiotic stimulus
06803_atPD 07333_atNM	UYN T		20pter-p12 6q21-qter	neuropeptide signaling pathway, synaptic transmission signal transduction, G-protein signaling, coupled to IP3 second messenger (phospholipase C activating)
7557 a at RY	YR2	ryanodine receptor 2 (cardiac)	1q42 1-q43	cation transport, calcium ion transport, calcium ion homeostasis, muscle contraction,
				signal transduction, regulation of heart contraction rate
x8222_at AC	CVR1B	activin A receptor, type IB	12q13	protein amino acid phosphorylation, transmembrane receptor protein serine/threonine kinase signaling pathway
9866 s at LP	HN3	tatrophilin 3	4q13.1	signel transduction, neuropeptide signeling pethway
A4600 8 81 1 LP	FS	embryonal Fyn-associated substrate	14q11.2-q12	cell adhesion, intracellular signaling cascade
0880 s at EF	GS6	regulator of G-protein signaling 8	14q24.3	G-protein coupled receptor protein signaling pathway, intracellular signaling cascade, regulation of G-protein coupled receptor protein signaling pathway
	KAP13	A kinase (PRKA) anchor protein 13	15q24-q25	intracefutar signaling cascade
0880 s at EF	GS12	regulator of G-protein signating 12	4p16.3	signal transduction, regulation of G-protoin coupled receptor protein signaling pathway, protein transport
10880 s at EF 11448 s at RO 13516 at AK 14361 s at RO		Res suppressor protein 1 SH3 and multiple ankyrin repeat domains 2	10p13 11g13.3-g13.4	signal transduction intracellular signaling cascade
0880 s at EF 11448 s at RG 13516 at AK 14361 s at RG 5618 at RS		manan atti atad amtain kinasa kinan 7	19p13.3-p13.2	protein amino acid phosphorylation, response to stress, signal transduction
0880 s at EF 11448 s at RC 13516 at AK 14361 s at RC 15618 at RS 15830 at SH 16206 x at M	HANK2 AP2K7	mitogen-activated protein kinase kinase 7	3q25.31	tipid metabolism, intracellular signaling cascada
0880 s at EF 1448 s at RC 13516 at AK 4361 s at RC 15618 at RS 15630 at SH 16206 x at MU 16634_at PL	HANK2 AP2K7 LCL3	phospholipase C-like 3		signal transduction, G-protein coupled receptor protein signaling pathway
0880 s at EF 1448 s at RC 13516 at AK 4361 s at RC 5618 at RS 58830 at SH 16206 x at MU 16634 at PL 21922 at GF	HANK2 AP2K7 LCL3 PSM2	phospholipase C-like 3 G-protein signalling modulator 2 (AGS3-like, C. elegans)	1p13.3	
0880 s at EF 1448 s at RC 13516 at AK 4361 s at RC 5618 at RS 58830 at SH 16206 x at MU 16634 at PL 21922 at GF	HANK2 AP2K7 LCL3	phospholipase C-like 3 G-protein signalling modulator 2 (AGS3-like, C. elegans) early growth response 2 (Krox-20 homolog, Drosophila)	1p13.3 10g21.1	transcription, regulation of transcription, DNA-dependent, brain development,
0980 s at EF 11448 s at RC 13516 at AK 14361 s at RC 15618 at RC 15636 at SH 16206 x at MU 16634 at PL 21922 at GF 25249 at EC	HANK2 AP2K7 LCL3 PSM2	phospholipase C-like 3 G-protein signalling modulator 2 (AGS3-like, C. elegans)	1p13.3	Iranscription, regulation of transcription, DNA-dependent, brain development, peripheral nencous system development, mechanosensory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymensse II
0880 s at EF 11448 s at RC 13516 at AK 14381 s at RC 15618 at RS 15830 at RC 15830 at RC 19922 at RC 19922 at RC 19922 at RC 19922 at RC	HANK2 AP2K7 LCL3 PSM2 GR2 ATA4	phospholipase C-Bis 3 G-protein signaling modulator 2 (AGS3-Bis, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4	1p13.3 10q21.1 8p23.1-p22	transcription, regulation of transcription, DNA-dependent, brain development, peripheral nervous system development, mechanosensory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymentse II formoter, development, heart development, possive regulation of transcription, DNA-dependent
0880 s at EF           11448 s at RC           13516 at AK           14361 s at RC           15618 at RS           1580 at RS           1580 at RS           16205 x at MM           16834 at PL           21922 at GF           55517 at GA           35517 at GA           35906 at FC	HANK2 AP2K7 LCL3 PSM2 GR2 ATA4	phospholipase C-Bke 3 Geproten signaling modulator 2 (AGS3-Bke, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4 fortheed box J1	1p13.3 10q21.1 8p23.1-p22 17q22-17q25	transcription, regulation of transcription, DNA-dependent, brain development, peripheral nervous system development, mechanoseroory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymentase II promoter, development, heart development, possible regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, spermatogenesis
10880 s et EF           11448 s et RC           13516 et AK           13516 et AK           13516 s et RC           13516 et AK           13516 et AK           13518 et RC           13518 et RC           13518 et RC           15619 et RC           15630 et RC           15830 et RC           15830 et RC           15830 et RC           15831 et RC           15832 et RC           15834 et RC           16234 et RC           16234 et RC           16334 et RC           1634 et RC           16350 et RC           1636 et RC           1636 et RC           1636 et RC           1637 et RC           1638 et RC           1638 et RC           1639 et RC           1630 et RC           1630 et RC           1630 et RC           1630 et RC </td <td>HANK2 AP2K7 LCL3 PSM2 GR2 ATA4</td> <td>phospholipase C-Bis 3 G-protein signaling modulator 2 (AGS3-Bis, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4</td> <td>1p13.3 10q21.1 8p23.1-p22</td> <td>transcription, regulation of transcription, DNA-dependent, brain development, perpineral nervous system development, mechanosensory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymentse II promoter, development, heart development, positive regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, spermatogenesis regulation of transcription, DNA-dependent, development transcription, regulation of transcription from RNA polymentse II promoter,</td>	HANK2 AP2K7 LCL3 PSM2 GR2 ATA4	phospholipase C-Bis 3 G-protein signaling modulator 2 (AGS3-Bis, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4	1p13.3 10q21.1 8p23.1-p22	transcription, regulation of transcription, DNA-dependent, brain development, perpineral nervous system development, mechanosensory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymentse II promoter, development, heart development, positive regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, spermatogenesis regulation of transcription, DNA-dependent, development transcription, regulation of transcription from RNA polymentse II promoter,
10980 s. ett         EF           1448 s. ett         RC           13516 ett         AK           13516 st         RS           15610 ett         RS           15630 ett         RS           16334 st         RS           16234 st         RL           16234 st         RL           25517 st         GA           25600 ett         FC           26104 st         IS           26204 st         TE	HANK2 AP2K7 LCL3 PSM2 GR2 ATA4 OXJ1 LL1 BX1	phospholipase C-Bke 3 G-protein signalling modulator 2 (AGS3-Bke, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4 forthread box J1 ISL1 transcription factor, LIM/homeodomain, (silet-1) T-box 1	1p13.3 10q21.1 8p23.1-p22 17q22-17q25 5q11.2 22q11.21	Iranscription, regulation of transcription, DNA-dependent, brain development, peripheral nervous system development, mechanosersory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymenase II promoter, development, heart development, possible regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, spermatogenesis regulation of transcription, DNA-dependent, development transcription, regulation of transcription, DNA-dependent, development transcription, regulation of transcription, DNA-dependent, development transcription, regulation of transcription, from RNA polymerase II promoter, heart development, morphogenesis
10980 s et EF           11448 s et RC           13516 et Atk           13500 et Atk           13020 x et Atk	HANK2 AP2K7 LCL3 PSM2 GR2 ATA4 OXJ1 L1 BX1 TBF1	phospholipase C-Bis 3 G-protein signafing modulator 2 (AGS3-Bis, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA binding protein 4 fortheed box J1 ISL1 transcription factor, LIM/homeodomain, (stel-1) T-box 1 AT-binding transcription factor 1	1p13.3 10q21.1 8p23.1-p22 17q22-17q25 5q11.2 22q11.21 18q22.3-q23.1	Izanscription, regulation of transcription, DNA-dependent, brain development, peripheral nervous system development, mechanisaersory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter, development, heart development, possible regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, apermatogenesis regulation of transcription, DNA-dependent, development transcription, regulation of transcription from RNA polymerase II promoter, heart development, morphogenesis regulation of transcription from RNA polymerase II promoter, heart development, morphogenesis
10980 s. ett         EF           1448 s. ett         RC           13516 ett         AK           13516 st         RS           15610 ett         RS           15630 ett         RS           16334 st         RS           16234 st         RL           16234 st         RL           25517 st         GA           25600 ett         FC           26104 st         IS           26204 st         TE	HANK2 AP2K7 LCL3 PSM2 GR2 GR2 OXU1 DXU1 DXU1 DXU1 DXU1 DXU1 DXU1 DXU1 D	phospholipase C-Bke 3 G-protein signalling modulator 2 (AGS3-Bke, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4 forthread box J1 ISL1 transcription factor, LIM/homeodomain, (silet-1) T-box 1	1p13.3 10q21.1 8p23.1-p22 17q22-17q25 5q11.2 22q11.21	Iranscription, regulation of transcription, DNA-dependent, brain development, peripheral nanous system development, mechanosensory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter, development, heart development, positive regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, spermatogenesis regulation of branscription, DNA-dependent, spermatogenesis regulation of branscription, DNA-dependent, approximate II promoter, heart development, morphogenesis regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter regulation of transcription, DNA-dependent, central nervous system development regulation of transcription, DNA-dependent, regulation of transcription, DNA-dependent regulation of transcription, DNA-dependent, regulation of transcription, DNA-
10980 s. ett         EF           11448 s. ett         RC           13516 ett         AK           13518 ett         RS           15618 ett         RS           15630 ett         SH           16334 ett         PL           19525 x. ett         MA           18634 ett         PL           19525 t. ett         MA           18634 ett         PL           205517 ett         GA           26006 ett         FC           26104 ett         ISI           26033 ett         PL           11627 x. ett         ES	HANK2 AP2K7 LCL3 PSM2 GR2 ATA4 OXJ1 LL BX1 TBF1 ROP1 SR1	phospholipase C-Bio 3 Goroten signaling modulator 2 (AGS3-Bio, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4 fortheed box J1 ISLI transcription factor, LIM/homeodomain, (slet-1) T-box 1 AT-binding transcription factor 1 propher of P41, paired-like homeodomain transcription factor estrogen receptor 1	1p13.3 10q21.1 8p23.1-p22 17q22-17q25 5q11.2 22q11.2 22q11.21 16q22.3-q23.1 5q36.3 6q25.1	Iranscription, regulation of transcription, DNA-dependent, brain development, peripheral nervous system development, mechanosarooxy behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter, development, heart development, possible regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, spermatogenesis regulation of transcription, DNA-dependent, development (transcription, regulation of transcription, DNA-dependent, development transcription, regulation of transcription, DNA-dependent, development regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter regulation of transcription, DNA-dependent, regulation of transcription,
10980 s at EF 1448 s at RC 13516 at Atk 13518 at RS 15618 at RS 15618 at RS 15638 at RS 16034 at PL 10922 at RS 10926 at RS 1	HANK2 AP2K7 LCL3 PSM2 GR2 ATA4 OXJ1 L1 BX1 TBF1 ROP1 SR1 MARCA2	phospholipsise C-Bie 3 G-protein signaling modulator 2 (AGS3-Bie, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4 forthread box J1 ISL1 transcription factor, LIM/homeodomain, (slet-1) T-box 1 AT-bening transcription factor 1 prophet of P41, paired-Bie homeodomain transcription factor eating on receptor 1 SWUSNF related, matrix associated, actin dependent regulator of	1p13.3 10q21.1 8p23.1-p22 17q22-17q25 5q11.2 22q11.21 18q22.3-q23.1 5q35.3 6q25.1 0p22.3	Iranscription, regulation of transcription, DNA-dependent, brain development, peripheral nervous system development, mechanosersory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymenase II promoter, development, heart development, possible regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, spermatogenesis regulation of transcription, DNA-dependent, development transcription, regulation of transcription, DNA-dependent, development transcription, regulation of transcription, DNA-dependent, development transcription, regulation of transcription from RNA polymenase II promoter, heart development, morphogenesis regulation of transcription, DNA-dependent, transcription from RNA polymenase II promoter regulation of transcription, DNA-dependent, central nervous system development mogulation of transcription, DNA-dependent, regulation of transcription, DNA-dependent, regulation of transcription, cell anowh, estrogen receptor signaling pethway, negative regulation of mitosis transcription, DNA-dependent, regulation from RNA polymenase II promoter transcription, DNA-dependent, regulation of transcription, DNA-dependent, signal transcription, DNA-dependent, regulation of transcription, DNA-dependent, ecologian promoter transcription, DNA-dependent, regulation of transcription, DNA-dependent, signal transcription, DNA-dependent, regulation of transcription, DNA-dependent, signal
10980 s at EF 1448 s at RC 13516 at At At 13516 at RS 15618 at RS 15618 at RS 15630 at RC 15618 at RS 15630 at RC 15631 at RS 15630 at RS 15630 at RS 15630 at RS 15630 at RS 15630 at RS 16034 at RS	HANK2 AP2K7 LCL3 PSM2 GR2 ATA4 OXJ1 LL BX1 TBF1 ROP1 SR1	phospholipase C-Bio 3 Goroten signaling modulator 2 (AGS3-Bio, C. elegans) early growth response 2 (Krox-20 homolog, Drosophile) GATA bunding protein 4 fortheed box J1 ISLI transcription factor, LIM/homeodomain, (slet-1) T-box 1 AT-binding transcription factor 1 propher of P41, paired-like homeodomain transcription factor estrogen receptor 1	1p13.3 10q21.1 8p23.1-p22 17q22-17q25 5q11.2 22q11.2 22q11.21 16q22.3-q23.1 5q36.3 6q25.1	Iranscription, regulation of transcription, DNA-dependent, brain development, peripheral nanouus system development, mechanosensory behavior transcription, regulation of transcription, DNA-dependent, transcription from RNA polymense II promoter, development, heart development, positive regulation of transcription, DNA-dependent transcription, regulation of transcription, DNA-dependent, spermatogenesis regulation of branscription, DNA-dependent, development transcription, regulation of transcription from RNA polymerase II promoter, heart development, morphogenesis regulation of transcription, DNA-dependent, transcription from RNA polymerase II promoter, Insert development, morphogenesis regulation of transcription, DNA-dependent, central nervous system development regulation of transcription, DNA-dependent, central nervous system development

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nation, meiosis,	
merization	

Appendix

201010_8_81		caldesmon 1	7q33	muscle contraction, muscle development
201961_s_st 202563_st	C14orf1	ring finger protein 41	12q13 2-q13.3 14q24 3	protein ubiquitination
03431_s_at	RICS	chromosome 14 open reading frame 1 Rho GTPase-ectivating protein	11q24-q25	
03702_s_at 03759_at	ST3GALA	tubulin tyrosine ligase-like family, member 4 ST3 beta-galactoside alpha-2,3-sialytmansferase 4	2p24 3-p24.1 11q23-q24	protein modification protein amino acid glycosylation
3806 s at	FANCA	Fanconi anemia, complementation group A	16q24 3	DNA repair, protein complex assembly
040,56_s_at 042,57_at	FADS3	mevalonate kinase (mevalonic aciduria)	12024	protein amino acid phosphorylation, cholesterol biosynthesis, isoprenoid biosynthesis fatty acid biosynthesis, fatty acid desaturation, fatty acid desaturation
4414_st	-		11q12-q13.1	-
4462_81	CLDN5	claudin 5 (transmembrane protein deleted	22q11 21	calcium-independent cell-cell adhesion
4643_s_at	COVA1	in velocardiofacial syndrome) cytosotic ovarian carcinoma antigen 1	Xq25-q28.2	regulation of cell growth, electron transport, transport, utradian rhythm
4811_s_at 4816_s_at	CACNA2D2	caloium channel, vollage-dependent, alpha 2/delta subunit 2 DEAH (Asp-Glu-Ala-His) box polypeptide 34	3p21 3 19q13 3	ion transport, calcium ion transport
5024 s at		RAD51 homolog (RecA homolog, E. coli) (S. cerovisiae)	15q15.1	double-strand break repair via homologous recombination, double-strand break repair via homologous
				recombination, DNA unwinding, DNA unwinding, DNA repair, mitotic recombination, moiosis,
5028_at	TRO	trophinin	Xp11.22-p11.21	meiotic recombination, positive regulation of DNA ligation, protein homooligomerization cell adhesion, homophilic cell adhesion, embryo implantation
6072 s at		X-ray repair complementing defective repair in	5q13-q14	DNA repair, double-strand break repair, DNA recombination
6122 at	TMEFF1	Chinese hamster cells 4 transmembrane protein with EGF-like and	9q31	
	1	two folistatin-like domains 1	ad 21	
5317_s_at 5360 at	SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	3q13 33	transport, ofigopeptide transport
5498 at		prefoldin 4 growth hormone receptor	20q13.2 5p13-p12	protein folding, chaperonin-mediated tubulin folding skeletal development, endocytosis, growth
6649_s_at	FGA	fibrinogen, A atoha polypeptide	4q28	blood coegulation, regulation of blood pressure, positive regulation of cell proliferation
5962_at	PAK2	p21 (CDKN1A)-activated kinase 2	3q29	protein amino acid phosphorytation, protein amino acid phosphorytation, negative regulation of protein kinase activity, signal transduction
6043_8_at	KIAA0703	KIAA0703 gene product	16q24 1	cation transport, calcium ion transport, metabolism, proton transport
6265_s_at	GPLD1	glycosylphosphatidylinositol specific phospholipese D1	6p22 3-p22.2	cell-matrix adhesion
6294_st	HSU382	hydroxy-deita-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2	1p13 1	C21-steroid hormone biosynthesis
6344_at	PON1	paraoxonase 1	7q21 3	response to external stimulus
6414 s at 6423 at	DDEF2 ANGPTL7	development and differentiation enhancing factor 2 angiopolietin-like 7	2p25j2p24 1p36 3-p36 2	regulation of GTPase activity response to caldative stress
6446 s at	ELA2A	olastase 2A	1p36.21	proteolysis and peptidolysis
6519_x_at	<u> </u>		-	
6595_at 6609_at	MAGEC1	cystatin E/M melanoma antigen family C, 1	11q13 Xq28	morphogenesis
6863 x_at	-		-	
6903_at 6951_at	— HIST1H4E	histone 1, H4e	6p21 3	
	GPC5	glypican 5	13q32	
7201_s_at 7228_at	SLC22A1	solute carrier family 22 (organic cation transporter), member 1	6q26	ion transport, addium ion transport, organic cation transport
	GLRAZ	protein kinase, cAMP-dependent, catalytic, gamma glycine receptor, alpha 2	9q13 Xp22 1-p21.3	protein amino acid phosphorylation, spermatogenesis, male gonad development ion transport, chloride transport, cell surface receptor linked signal transduction, synaptic transmission
	SEC13A2	solute carrier family 13 (sodium-dependent dicarboxylate	17p13.2	ion transport, sodium ion transport
7834_at	FBLN1	transporter), member 2 fibutin 1	22q13 31	chitin metabolism, development
7836 s at	RBPMS	RNA binding protein with multiple splicing	8p12-p11	RNA processing
8153 s_at	FAT2	FAT tumor suppressor homolog 2 (Drosophila)	5q32-q33	cell adhesion, homophilic cell adhesion
3291_s_at	<u></u>	tyrosine hydroxytase	11p15.5	synaptic transmission, aromatic amino acid family metabolism, morphogenesis, neurotransmitter biosynthesis, catecholamine biosynthesis
8324_at	-	-		
8514_at	KCNE1	potassium voltage-gated channel, isk-related family, member 1	21q22.1-q22.2	ion transport, potassium ion transport, muscle contraction, perception of sound, regulation of heart contraction rate
		histone 1, H4k/j	6p22-p21.3	
3906_at 169_at		Bernardinelli-Seip congenital lipodystrophy 2 (seipin)	11012-013.5,11012.3	neurogenesis, cell differentiation
299 x at	PPIL2	popoprotein M68 peptidylprolyl isomerase (cyclophilin)-like 2	Xp22 2 22q11 21	protein fokting
346 s at	PHKI	phosphatidylinositol 4-kinase type II	10q24	phosphatidylinositol biosynthesis
1437_s_at	BMP7	spondin 1, extracellular matrix protein Bone morphogenetic protein 7 (osteogenic protein 1)	11p15.2 20q13	cell adhesion, development skeletal development, cell differentizion, growth
612_s_at	ADH1B	alcohol dehydrogenase IB (class !), beta polypeptide	4q21-q23	ethanol oxidation
615 s at 676 at	PAK1	p21/Cdc42/Rac1-activated kinase 1 (STE20 homolog, yeast) tissue factor pathway inhibitor	11q13-q14 2q31-q32.1	protein amino acid phosphorylation, protein amino acid phosphorylation, apoptosis, JNK cascade blood cosgulation
		(lipoprotein-essociated coagulation inhibitor)	2431-432.1	
		calmodulin-like 3	10pter-p13	
066_s_at / 364_at \$		sodium channel, voltage-gated, type II, beta	18q11.2-q12.1 11q23	transport, neurogenesis, excretion ion transport, sodiam ion transport, synaptic transmission
429 at	RHD	Rhesus blood group, D antigen	1p36 11	-
553_x_at   702_s_at		proprotein convertase subtilisin/kexin type 6	15q26.3	proteolysis and peptidolysis, cell-cell signaling prostagtandin biosynthesis, electron transport, lipid metabolism, fatty acid biosynthesis
795 s at I	MEG3	prostaglandin I2 (prostacyclin) synthese Matemally expressed 3	20q13.13 14q32	
301_at / 310 в at 3		dimethyladenosine transferase	5q11-q14	rRNA modification, rRNA processing
SIU_B_AL		solute carrier family 6 (neurotransmitter transporter, glycine), member 5	11p15.2-p15.1	neurotransmitter transport, syneptic transmission
224_8_at /	ABCB11	ATP-binding cassette, sub-family 8 (MDR/TAP), member 11	2q24	transport
238_at / 259_s_at 6		a disintegrin and metalloproteinase domain 7 bone morphogenetic protein 7 (osteogenic protein 1)	8p21.2 20g13	protectysis and peptidolysis skeletal development, cell differentiation, growth
239 <u>s</u> at 1 334_at 1		MRE11 meiotic recombination 11 homolog A (S. cerevisiae)	11q21	regulation of mitotic recombination, double-strand break repair via nonhomologous end-joining,
353_at				telomerase-dependent telomere maintenance, meiosis, meiotic recombination
353_art   480_s_art \$		leucine rich repeat containing 21 solute carrier organic anion transporter family, member 1A2	10q23	transport, ion transport, organic anion transport
396_s_at	KIAA0090	KJAA0090	1p36 13	
478_at   258_at	FLJ13910 TFPI	hypothetical protein FLJ13910 Tissue factor pathway inhibitor	2p11 2 2q31-q32.1	blood coegutation
		(lipoprotein-essociated coagulation inhibitor)		
		KIAA0974	10q22.2	
712_at E	ELOVL2	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 2	6p24.1	fatty acid biosynthesis
862_at   F		Patatin-like phospholipase domain containing 2	11p15.5	-
904_at - 999_at	- MGC11061	Clone 23555 mRNA sequence		
019_st -				
095_at 5		sorine hydroxymethytransferase 2 (mtochondrial)	12q12-q14	glycine metabolism, L-serine metabolism, one-carbon compound metabolism
099_s_at F 123_s_at 0		phosphodiesterase 4D interacting protein (myomegalin) chromosome 4 open reading frame 10	1q12 4p16 3	protein biosynthesis, (actin) cytoskeleton organization and biogenesis
126_at	MCART1	Mitochondrial carrier triple repeat 1	9p13 3-p12	transport
133_at     160_at   -	MUC6	mucin 8, gastric	11p15.5-p15.4	
507_s_at E		expsome component 2		rRNA processing
530 x at E		erythrocyte membrane protein band 4.1	1p33-p32	circulation, cortical actin cytoskeleton organization and biogenesis
579 at 1	0,462023.2	(eliptocytosis 1, RH-linked) hypothetical protein dJ482023.2	1p36 12-p35.1	
588_s_at N	WFAP3	Microfibrillar-associated protein 3	5q32-q33.2	
590_s_atL 676_x_ath		ubiquitin-conjugating enzyme E2D 1 (UBC4/5 homolog, yeast)	10q11.2-q21	ubiquitin-dependent protein catabolism, ubiquitin cycle
	PAPPA2	mucin 38	7q22 1q23-q25	regulation of cell growth, regulation of cell growth, proteolysis and peptidolysis, cell differentiation
689 at P			8q24 3	
689_at P 692_s_at J	IRK			
689 at P 692 s at J 708 at S	SNTB1	Syntrophin, beta 1	8q23-q24	muscle contraction
689_at P 692_s_at J 708_at S	SMTB1			muscle contraction protein amino acid phosphorylation

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11665, al.         CDMA 7,21397 fra, down 14760800					
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Number         Construction         Construction         Construction           Number         Construction         Construction         Construction<		I	(Ehlers-Danios syndrome type IV, autosomal dominant)		
NUM         Control         Theore states (PAS (P. 2013))         Control (P. 2013)         Control (P. 2014)           NUM         And Mark Mark Control (P. 2014)				6q25.2-q26	cellular morphogenesis, cytoskeletal anchoring
1111 1.1		G22P1		22q13.2-q13.31	DNA ligation, DNA repair, double-strand break repair via nonhomologous end-joining,
10194 P       Parton Point Point Professional Profession					DNA recombination, positive regulation of transcription, DNA-dependent
1110000000000000000000000000000000000		<u> </u>			
Dist J         Provide state of the set of th			amyloid beta precursor protein (cytoplasmic tal) binding protein 2		
1992 A. 1992 A. 1992 A. 1992 A. 1993 A.					
1993.4     Sold Sold Sold Sold Sold Sold Sold Sold					
Dist L         Interpret			Solute carrier family 26, member 3	7q31	transport, anion transport, excretion, sulfate transport
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Dist of a second seco	215850_s_at	NDUFA5	NADH dehydrogenase (ubiquinone) 1 slpha subcomplex, 5, 13kDa		
1993 Control         Control         Control         Part Part Part Part Part Part Part Part		ATP2B3		Xq28	cation transport, caloium ion transport, metabolism
Number         Authors 2         Authors 2         Authors 2           NUMBER         Authors 2		CORT1		17p12	-
Context         Context (Context)         Context (Context)         Context (Context)           Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context)           Context (Context)         Context (Context)         Context (Context)         Context)         Context (Context)         Context (Context)           Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)           Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)         Context (Context)		ASTN2	Astrotactin 2		
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Image 2         The product control of the product control	216280 s at	DICER1		14032.13	RNA processing, RNA interference, targeting of mRNA for destruction
1000 a	216329_at		-	-	
No. 1         PSSAU (2)         PS		CROCC	totiary rootlet coiled-coil, rootletin	1pter-p36.11	
Biology Jack         Control	216474 x_at	TPSAB1/2	tryptase alpha/bela , tryptase beta 2	16p13 3	proteolysis and peptidolysis, defense response, proteolysis and peptidolysis
198.94         WEEP1         Transportant registring labor 1         5p.1 (p / 1)         Transport 1 <thtransport 1<="" th=""> <thtransport 1<="" th=""> <tht< td=""><td>216577 at</td><td>_</td><td>-</td><td></td><td></td></tht<></thtransport></thtransport>	216577 at	_	-		
Notes         Notes <th< td=""><td></td><td></td><td></td><td></td><td>regulation of transcription, DNA-dependent, sterrini biosynthesis, cholecterol catabolism, development</td></th<>					regulation of transcription, DNA-dependent, sterrini biosynthesis, cholecterol catabolism, development
Control (Control (Contro) (Control (Control (Control (Control (Control (Control					homeostasis, positive regulation of transcription, DNA-dependent, regulation of hormone biosynthesis
10815 m         -         -         -         -           10816 m         -         -         -         -           1081 m         -         -         -         -         -         -					ion transport, potassium ion transport
11865 A. #         -         -         -         -           11865 A. #         -         -         -         -           11866 A. #         -         -         -         -           11866 A. #         -         -         -         -           11866 A. #         -         -         -         -           1186 A. #         AFEMING State of the state state state of the state of the state of the state of the stat		-	-	-	
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1766 J. A. S. [GM4]         Inspatianess (products)         Sp2-21 33         pages acces 4 kan present anno act programmed mediation (products)           1786 J. B. S. Chiko.         Section.         Section.<	217518_at	FER1L3	fer-1-like 3, myoferlin (C. elegans)	10g24	
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2044 et         KCNK12         potassam channel, subfamly K, member 12         2p22-p21         ion transport, potasslam ion transport           20507. gt         MC71         myc larget 1		FLJ23447	Rho GTPase activating protein 28	18p11.23	
2008/2       at       -       -       -         2009/2       at       PTP06       ATPase, Class V. type 108       5q34         2009/2       at       PTP106       ATPase, Class V. type 108       5q34         2009/2       at       PTP106       ATPase, Class V. type 108       1p35         2009/2       at       PDP106       AtPase, Class V. type 108       5q34         2019/2       at       PDP106       AtPase, Class V. type 108       -         2118       at       CDNA: FLJ22004 fs, cons LNG15857       -       -         2123       at       EXA1411       Eq12-q13       -         21467       at       ExA54       endosuffre at/ba       1q21 2       transport, response to nutrients         2168       at ICNSA       endosuffre at/ba       1q21 2       -       -         2118.5       at       EXA54       3q27.1       -       -         2119.6       at ICCS1333       Mesenchymal stan cell protein DSC43       16p11 2       -       -         2120.4       at       CDNA typothetical zinc finger protein KUA1656       1fig13 4       -       -         2204.4       STXDP3       Syntaxin brinding protein 3       1fig13 4       -		LMANIL	Rho GTPase ectivating protein 28 hypothetical protein FLJ23447 lectin, mannose-binding, 1 Bke	18p11.23 19p13.12 15q24.1	
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21457 s at ENSA       endosuline alpha       1021 2       transport, response to nutrients         21681 s at DSPP       dentin sistophosphoprotein       4021 3       castification, cell adhesion, development, perception of sound         21681 s at EU12748       hypothetical protein FL12746       3027.1       -         21698 s at LOC51333       Mesenchymal istem cell protein DSC43       16p11.2       -         21747 at UROD       uropophyrinogen decarboxylase       1p34       heme biosynthesis         22135 at       Similar to Hypothetical zinc finger protein KUA1956       1021.3.3          22202 at       CDNA FL14233 ls, clone PLACE100/886           22248 at STXBP3       Syntaxin binding protein 3       1p13.3       vesicle doking during excrytosis, protein transport, vesicle-mediated transport         22248 at STXBP3       Syntaxin binding protein 3       17p13.1       electron transport, laukotriene biosynthesis         22383 s at ALOXE3       arachidonisis lipoxygenese 3       17p13.1       electron transport, laukotriene biosynthesis         ab. At: IVKG-specifig genes         -         abstraction of IVMP-specific genes after treatment of MIG-specific genes after treatment according to parametric Less;       -       -         robe-exts listed above ars specificaby differuiaby regulated upon MIG therapy;	20448 et     20471 s et   20687 et   20920 et   20938 s et 0 21091 et    21136 et   0	LMAN1L KCNK12 MYCT1 	Rho GTPase echeting protein 28 hypothetical protein FL/23447 lectin, mannose-binding, 1 Bite potassum channel, subfamily K, member 12 myc target 1	18p11.23 19p13.12 15q24.1 2p22-p21 6q25.2 - 5q34 1p35.3 1p31.1-p22.3	
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### 5.2 Publications

5.2.1

### Mechanisms of action of intravenous immunoglobulins (IVIG) in patients with relapsing-remitting Multiple Sclerosis

N.Pigard, H.Kuusisto, I.Elovaara, R. Paalavuo, H.P. Scharz, B.Reipert

will be submitted to the Journal of Allergy and Clinical Immunology in November 2005;

### 5.3 Posters

### 5.3.1

N.Pigard, H.Kuusisto, I.Elovaara, R. Paalavuo, K. Zimmermann, H.P. Scharz, B.Reipert (2004): **Mechanisms of action of intravenous immunoglobulins in** patients with relapsing-remitting multiple sclerosis

Poster presentation at the 14<sup>th</sup> Meeting of the European Neurological Society, 26-30 June 2004, Barcelona, Spain

Journal of Neurology, Volume 251, Suppl.3, June 2004: Poster 723

### 5.3.2

Pigard N, Kuusisto H, Elovaara I, Paalavuo R, Zimmermann K, Schwarz HP and Reipert BM (2004): Gene expression profiles of peripheral T cells in patients with relapsing-remitting multiple sclerosis after treatment with intravenous immunoglobulins (IVIG)

Poster presentation at the 8th Congress of the European Federation of Neurological Societies (EFNS), September 2004, Paris, France Eur J Neurol 2004; 11(suppl 2): P2437

### 5.3.3

Pigard N, Kuusisto H, Elovaara I, Paalavuo R, Zimmermann K, Schwarz HP and Reipert BM (2004): Intravenous immunoglobulin (IVIG) in patients with Relapsing-Remitting Multiple Sclerosis – towards a better understanding of the mechanism of action

Poster presentation at the Annual meeting of the Austrian Society for Allergology and Immunology (ÖGAI), December 2004, Vienna, Austria

### 5.3.4

Effects of intravenous immunoglobulins (IVIg) treatment of patients with relapsing-remitting multiple sclerosis on gene expression profiles of their peripheral t cells

Abstract submitted for Poster presentation at the 9th Congress of the European Federation of Neurological Societies (EFNS), September 2005, Athens, Greece the abstract will be published in the European Journal of Neurology;

### 5.3.5

N. Pigard, H. Kuusisto, R. Paalavuo, I. Elovaara, H.P. Schwarz, B. Reipert; BMT Research, Tampere University Hospital, Baxter Bioscience (Vienna, A; Tampere, FIN): Differentially expressed genes in peripheral T cells obtained from patients with relapsing-remitting multiple sclerosis after treatment with intravenous immunoglobulins

Poster presentation at the 21th Congress of the European Committee / 10th Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), taking place in Thessaloniki, 28 September - 1 October 2005;

# Mechanisms of action of intravenous immunoglobulins (IVIG) in patients with relapsing-remitting multiple sclerosis

Pigard Nadine', Kuusisto Hanna?, Elovaara Irina?, Zimmermann Klaus?, Schwarz Hans-Peter 3, Reipert Birgit 3

BMT-Research, Vienna, Austria; "Department of Neurology, Tampere University Hospital, Tampere, Finnland; "Baxter BioScience, Vienna, Austria

## INTRODUCTION

Promerous Immuropolouline pMG/here been used scorestafy in the treamerous of announce of information and and the calences of the campa of an announce system including actionate pMG approximation of the calence of announce and the calence of the campa of the calence of the announce of the campa of the calence of the phone of the calence of the phone of the calence of the calence of the calence of the phone of the calence of the patient web to calence (NG). NG the calence of the patient web to calence (NG) the phone of the calence of the patient web to calence (NG) there are not account of the patient web to calence (NG).

## AIM OF THE STUDY

(dentification and characteritation of genes expressed in V-7208 PBMC obtained from patients with Relaxing Remarking MS (PRMS) in acute execentration before and effect treatment with IVIG.

## I. Patients included in the study

METHODS

Inclusion criteria: - chriedhy or taboratory-supported definite PRMS in acute - experimentation - eigen fai and So years Scale (EDSS) 0-5.5 - eigen 18 and So years

- Exchastion criterite Heatens with provid treatment Emmanascorporesarsa within 6 month controsterotus 8 weeks controsterotus 8 weeks Sowee concurrent classes

- All 10 patients included in the study necessed a 5-day course of 0-glogg coursely Einchold SO (Baurs) V Vanna Austria 0-glogg coursel of Databate as well as Catrica relation was per city. Thermark of Institute as well as Catrica relation was core at the Landau Catria of Nauvdogy, Tampore University Hoopsa. Tampare, Finteriad. 2. Theetment of patients

## **3. Blood sempling**

Blood semples were taken immediately before the first dose X MO as well as 24 hours and three weeks after the tast dose.

- Clinical examination
- Interview
   EDSS
   EDSS
   EDSS
   EDS1 and spiral cont
   Thinking of chincal examination:
   Thinking of chincal examination:
   24.h after test cose of MG
   3 weeks a site test cose of MG

5. Properation of CD4'/CD6' PBMC

Pertrans tood morouclers cells PEAK) was preared with 60 mm after boot strong of cells was expressed from REMC at YC using a mixture of non-sumulating anti-COA REMC at am-COB (preadeds (pread) Putry of separated cells was continued by FACS-analysis.

6. Preparation of RNA and gane chip analysis

Purified Cails were immediately transferred into TRIzol (diboration) Cathorial Cathorial and stand at a 40°C transform Cathorial Cathorial RAM was in the presentation of RAM samples, Edge of total RAM was in the presentation of RAM samples, Samples of Cathorial Ram Processon (The Cathorial Raman With Samples) and Samples of Cathoria Samples) and Samples with stream of the Samples of Cathoria Samples of Raman VII 33 + Cenerchy (Minnetrof)

## 7. Date enabysis

Data obtained from the processing of the chick were example with CCCSS forware (why memory and ECDust) (may/sep aid/se utd?FFECUS15) from co) we second for genes that were up or dominisplated at 21 clust of week burd in a least of % of the particulation of following the FOLCING transmission of the particulation of the particulation of the second by an endowed the antip-particulation of the second by the second by an endowed the particulation of the second by the second by antion.

## RESULTS

The report of microwness of IVID treatment The EDSS score was significantly rectored in pairs after MID-restrict (specificant), base bobared in Mid analysis correlated with the introvement of the EDSS score.

bible 1: Citnical outcome: EDSS score before and after MG treatment.

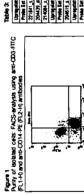
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10,01
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Purity of CD4//CD8<sup>-</sup> PBMC cells after magnetic bead separation

Using FACS enalysis we could show that the majority of othe constraints of the start cass, starts of the other shorts of the costs were depleted, including CO19 is each CO29 costs were depleted, including CO19 is each CO29 costs and the CO13 casts were CO14' casts FACS-enalysis shorts afron T casts (CO1 casts) were CO14' casts FACS-enalysis shorts afron T casts (CO1 casts) were CO14' casts FACS-enalysis shorts afron T casts (CO1 casts) were CO14' casts fACS-enalysis shorts afron T casts (CO1 casts) were CO14' casts fACS-enalysis

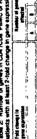
# 3. Gene expression analysis

Morcoaray-analysis revealed a number of otherantially expressed genese state MOS treatment (tabled), Table 5, Cartains a complete Ist of all genese that were at lasts 2, S-troit up-or down-regulated in expression in all least 50% of all patients.



	Dtha 2: Number of genes In CDV /CDP PBNC of RBNS patients with at least 2-road change in gene expression.
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A 34 hours differ completion of ING herary compared to day 0 hours MC herary B 3 webs completion of ING herary compared to day 0 holon MG herary C 24 hours compared to their weeks after completion of ING the day

Euclideen distance/K-means custering of all geness differentially distansi in a list differ of the partients revealed 2 mails effects of MG on gene expression ( Fig. 2), namely up-reputation and down-regulation of centarin genes.

I. Analysis of gene clusters

Constraints and an analysis of the constraint could be ductived than 3 sub-projection ductors compared than 3 sub-projection ductors and an analysis of the constraints of NG thereby compared to any 10 benefician of NG thereby compared to the NG thereby NG thereby NG thereby compared to the NG thereby NG thereby NG thereby NG thereby compared to any 10 benefician of NG thereby regulated them thereby compared to any 10 benefician NG thereby compared to any 10 benefician of NG thereby compared to any

Genes that were down-regulated upon IVID the transmost could be categorid into 3 happones. • press down-regulation if 3 weeks compared to 24 hours after comparison of IVID transmit (128 dyna). • press down-regulated at 24 hours after dompared to 10 VID entry contrasting to 124 hours after 3 weeks. The regulation of the distribution of the 34 hours after orthogonic dyna the distribution of the 34 hours after entry of press matrixed busine levels after 3 weeks. The regulation of IVID treating (8 gyna).

genes down-regulated at 24 hours after completion of MIG genes down-regulated bid by Deter MIG teamset, remained down-regulated until 3 weeks after comparison of MIG thready compared to day 0 before MIG thready (48 genes);

Приле 3 Бългано ставатова / к-товото създенту од облачението правано Бълганова и 24 полот Казу Од ило 1. ченото Кралия (2 мар. ИО) велена и 24 полота Кази Од ило 1. ченото краливана и к-товато сталички създен в братовато Соказија на ставато Стал. Соказа Саказа създен в братовато Саказија на ставато Стал. Соказа Саказа създен в братовато Саказија на ставато Стал. Соказа Саказа създен в братовато Саказија на ставато саказа създението та вратовато Саказија на ставато саказа соказет та вратовато братовато саказато саказато саказа соказет та вратовато братовато саказато саказато саказа соказет та вратовато саказа саказа саказато саказа саказа саказато саказа създението създението саказато саказа саказа саказато саказато саказато саказа саказа саказа саказа саказа саказато саказа саказа саказа саказа саказа саказа саказа саказа саказато саказа саказа саказа саказа саказа саказа саказа саказато саказа саказа саказа саказа саказа саказа саказа саказа саказато саказа с



## DISCUSSION

The mechanisms of action of IVIG in autoimmute claorders and MS is support yourseling of the machine claorder from Rhots profession in Carlo Car

The chrical outporte of the study showed that (MG phen in a Schrousset of Aphto show as discharge at chrane at cargo IESS score than tocather levels (by Obton MD reactment) to weit 2 after MIO statement is an weil as changes in the current exist of annual MB reactman. Futhermont, the reactment was safe and well obsertaid.

## REFERENCES

1. Atazs et al., 2001: J.Neuroimmunol 114 (160-167) 2. Modiano et al., 1997: J.Immunol Immunosthol 63 (1): 77-85

### Gene expression profiles of peripheral T-cells in patients with relapsing-remitting multiple sclerosis after treatment with intravenous immunoglobulins (IVIG)

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### INTRODUCTION

Intravenous immunoglobulins (IVIG) have been used successfully in the treatment of a number of inflammatory and autoimmune diseases of the central nervous system including multiple sclerosis (MS)

(mos), Athough MIGs appear to have substantial short- and long-term therapeutic potential, the mechanisms underlying these effects are not elucidated.

Recent studies suggested a modulation of T-cell response is involved in the immunomodulatory activities of IVIG in MS (1) (2).

### AIM OF THE STUDY

Identification and characterization of genes expressed in T cells that might be involved in reimmunomodulatory activity of MG in the treatment exacerbations in Relapsing Remitting MS

### METHODS

1. Patients included in the study

- Inclusion criteria:
- clinically or laboratory-supported definite RRMS in acute exacerbation Expanded Disability Status Scale (EDSS) 0-5.5
- age 18 and 55 years

Exclusion criteria: Patients with prior treatment

immunosuppressants within 9 month
 corticosteroids 8 weeks

- acute exacerbation within 8 weeks before entry Severe concurrent disease

### 2. Treatment of patients

All 10 patients included in the study received a 5-day

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Blood samples were taken immediately before the first dose of IVIG as well as 24 hours and three weeks fter the last dose.

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EDSS

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- 24 h after course - 3 weeks after course

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### 7. Data analysis

Data obtained from the processing of the chips were analyzed with GCOS-Software (Affymetrix) and EPClust (http://ep.ebi.ac.uk/EP/EPCLUST/index.cg)). We searched for genes that were up-or down-regulated  $\geq 2$ -fold and were found in at least 40% of the patients

(4 out of 10) Using the EPClust programme we grouped differentially regulated genes in clusters using the signal log

### RESULTS

1. Therapeutic effectiveness of IVIG treatment

Monitoring of RRMS patients regarding the clinical data, especially the EDSS score which was significantly reduced after IVIG-treatment, and MRI analysis (data not shown) did show a therapeutic effect of IVIG.

Table 1: Clinical outcome: Change in EDSS score

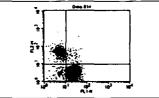
EDSS	EDSS	EDSS
in stable phase	before IVIG	at 3 weeks
2.42 ± 0.28	3.83 ± 0.32**	2.6 ± 0.25**

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from PBMC were purified T cells with depletion of most other lymphoid cells including CD19<sup>-</sup> cells, CD11b<sup>-</sup> and CD56<sup>-</sup> cells.

Amost all CD3 cells are CD14: cells (Fig. 1), FACS-Analysis using CD3-FITC and CD14-PE dye showed a proportion of 75% CD3: cells, a proportion of 15.6% CD14: cells. The and 2.7% double-positive CD3/CD14: cells. The remaining 6.8% may be due to unspecific binding of the antibodies to various Fc-Receptors.

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3. Gene expression analysis

Microarray-Analysis revealed a number of differentially expressed genes after IVIG treatment (Table2).

Table 2: Number of genes in CD4<sup>+</sup> or CD8<sup>+</sup> PBMC of RRMS patients with at least 2-fold change in gene expression.

Fold change in gene expression	Number of genes affected		
	A	B	C
≥ 2-fold change in any patient	2605	4602	3855
≥ 2-fold change in at least 40% of patients	35	7	134
≥ 2-fold change in at least 50% of patients	3	1	43
≥ 2-fold change in at least 60% of patients	0	0	11

Legend: A: 24 hours after completion of IVIG therapy compared to day 0 before IVIG

- therapy B. 3 weeks after completion of IVIG therapy compared to day 0 before IVIG
- therapy C: 3 week 3 weeks after completion of IVIG therapy compared to 24 hours after completion of IVIG therapy

### 4. Analysis of gene clusters

Euclidean distance/K-means clustering of all genes differentially regulated in at least 40% of the patients revealed 2 main effects of IVIG on gene expression (Fig. 2).

- Genes that are up-regulated upon MG treatment can be clustered into 3 sub-groups: genes were up-regulated 24 hours after completion of IVIG therapy compared to day 0 before IVIG treatment and remained up-regulated at 3 weeks after completion of MG therapy compared to day 0, genes were up-regulated 24 hours after completion of IVIG therapy compared to day 0 before IVIG treatment and returned to baseline-levels at 3 weeks after completion of MG therapy compared to day 0 before IVIG therapy (14 genes)

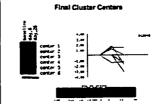
		ines at 24 hours a	ther completion of IVIG therapy compared to day 0 before IVIG therapy
	Expression	Gene Symbol	Gene Title
221841 <u>_S_</u> R	1 t	KLF4	Kruppel-like factor 4 (gut)
204439_#	1 t _	Ctorf29	chromosome 1 open reading frame 29
اللي (14084	t		Homo sepiens similar to Neutrophil cytosolic factor 1 (LOC378112), mRNA
Upregulated/ Di	ownregulated g	ines at 3 works a	har completion of MIG therapy compared to day 0 before MIG therapy
Probe Set ID	Expression	Gene Symbol	Gene Title
الرد 204619		CSPG2	chondroitin sulfate proteoglycan 2 (versican)
Upregulated/ De	menregulated g	ines al 24 hours o	compared to 3 weeks after completion of IVIG therapy
Probe Set ID	Expression	Gene Symbol	Cene Title
201422_st	L +	F130	Intenteron, garante-inductible protein 30
203561_#	+	FCGR2A	Fc fragment of IgG, low affinity Ra, receptor for (CD32)
تىرى204445		ALOX5	electron transport.inflammatory responseleukotriene biosynthesis
204533_#	L L	CXCL10	cell motilitychemotaxisinflammatory responseimmune responsecell surface receptor linked signal transduction
207697_x_#	1	LILRE?	Isukacyte immunoglobulin-like receptor, subfamily 8 (with TM and ITIM domains), member 2
210146_x_M	<b>T</b>	LIL982	leukocyte immunoglobulm-like receptor, subfamily B (with TM and ITIM domains), member 2
211100_1_#	T T	ULR81	Isukocyte immunoglobulin-like receptor. subfamily 8 (with TM and ITIM domains), member 1
211101_1_0	L L	ULR81	leukocyte immunoglobulan-like receptor, subfamily B (with TM and ITIM domains), member 1
214366_5_8	1-1	ALOXS	arachidonate 5-Roongenase
214511_1_8	1	FCGR1A	Fe fragment of IqG, high affinity (a, receptor for (CD64)
216950 s #	1	FOGR1A	Fc fragment of IgG, high affinity Ia. receptor for (CD64)
219519_5_#	1	SN	subuchesin
220145 #	I I	TLR7	toll-like receptor 7
201669	- T	MARCKS	myntstoylated alanine-rich protein lanese C substrate
201670_5_#	1 1	MARCKS	myntstoylated alanino-rich protein lonase C substrate
205119_3_#		FPR1	formyl peptide receptor 1
206891_#		DUSP6	dual specificity phosphause 6
208892_5_#	1	DUSP6	dual specificity phosphalase 6
208893 5.4	1	OUSP6	Qual specificity phosphatase 6
221841.5.0	<u>i</u>	ILF4	Knyppel-Riz factor 4 (gut)
204858 3 #	t i	ECCFI	endothetial cell growth factor 1 (plastet-derived)
204961_5_#	<u> </u>	NCT1	neutrophil cytosolic factor 1 (47kDa, chronic granulomatous disease, autosomal 1)
207610 5 #	t i	EMR2	edi-tite module contaming, mucin-fite, hormone receptor-lite 2
208018_5_#	<del>  i -</del>	HCK	hemopoletik cefi kinase
209189_#	t i	FOS	v-fos FBJ munitie ostaosarcoma vital oncogene homolog
212099_#	<del>  i</del>	ARHB	ras homolog gene (amily, member 8
217763_5_#	+ <u>i</u>	RAB31	RAB31, member RAS encogene family
219788_#	t i	PILRA	pared immunodióbin-kie type 2 receptor alpha
220068_#	+ $-$	CSR1	condement component 5 receptor 1 (CSa ligand)
201350 #	t ī	CST3	cystaun C (amytoid angiopathy and cerebral hemorrhage)
201736_5_#	<del>l i</del>	FERILS	for 1-like 3, myclorine (C, elecands)
202510_5_#		THEALP2	tumor neorosis factor, alpha-induced protein 2
202833_5_#	ti	SERPINAL	serine (or cysteine) proteinase inhubror, clade A (alpha-1 antiproteinase, antiprypsin), member 1
205936_5_4	+ i	HIG	Source (or cystolic) proteinase annual, calve in (aprile) a amproteinase, and ystar), memory i hexolorase 3 (white cell)
206468 3 #	t-i-	0036	CD36 antigen (collagen type I receptor, thrombospondin receptor)
206890_5_#	1 <u>-</u>	PL36	dexin B2
210423_5_#	<u>+</u>	SLCIVAL	solute canter family 11 (proton-coupled divatent metal ion transporters), member 1
210873_x_#	+	APOBECSA	applipoprotein B raiktikk editing enzyme, catalytic polytoppide-tika 3A
211429_5_#		-ruarusi	Acceptopose is taken exempler cauge porpepose and sh
213418_8	+ i -	HSPN6	hast shock. 70kDe gratein 6 (HSP7081)
213418_8 213472_8	1-:-	HNRPH1	htterageneous nuclear rikonucleopratein H1 (H)
	<u> </u>	MAFB	v-mail musculoaponeurotic fabrosarcoma oncogene homolog B (avian)
218559_5_#	•	1000	A set responsible real rest conclusion currently in careful a faularit

The following table contains a complete list of all genes that were at least 2-fold up-or down-regulated in expression in at least 50% of all patients.

genes were up-regulated 24 hours after completion of IVIG therapy compared to day 0 before IVIG

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### DISCUSSION

The mechanism of action of IVIG in autoimmune-disorders like MS is still poorly understood. The increasing efficacy of this immunomodulatory treatment requires to elucidate the mode of action underlying the enesis of the disease

pathogenesis of the disease. In MS, auto-reactive T-cells which cross the blood-brain-barrer are the main target of demyelinating antibodies. Therefore we investigated the impact of human IVIG on gene-expression in T-cells of RRMS patients. The clinical outcome of the study shows that IVIG given in a 5-day course of 0.4g/kg once daily was efficacious in the treatment of multiple sclerosis. It caused a change in EDSS score from baseline (before MG) to week 3 (after IVIG) as well as changes in the volume or number of several IMR measures. The treatment also was safe and well tolerated. Therefore MC is a well as a tranget for treatment of

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All these physiological processes might be important for the therapeutic efficiency of MG in the treatment of acute exacerbations in MS.

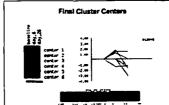
### REFERENCES

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2 Euclidean distance / k-means clustering of differentially regulated genes after 6 days and 26 days of IVIG

The K-means procedure assigns all genes to their respective clusters (the cluster to whose center they are



### Intravenous immunoglobulin (IVIG) in patients with **Relapsing-Remitting Multiple Sclerosis - towards a better** understanding of the mechanism of action

Pigard Nadine\*, Kuusisto Hanna\*, Elovaara Irina\*, Raija Paalavuo\*, Zimmermann Klaus\*, Schwarz Hans-Peter \*\*, Reipert Birgit \*\*

'BMT-Research, Vienna, Austria

In at least 50% of all patients

<sup>2</sup>Neuroimmunology Unit, Department of Neurology, Medical School, University of Tampere and Tampere University Hospital, Tampere, Finland <sup>2</sup>Baxter BioScience, Vienna, Austria

### INTRODUCTION

Intravenous immunoglobulins (IVIG) have been used successfully in the treatment of a number of Inflammatory and autoimmune diseases of the central nervous system including multiple sclerosis (MS

Although IVIGs appear to have substantial short- and long-term therapeutic potential, the mechanisms underlying these effects are not elucidated.

Recent studies suggested a modulation of T-cell response is involved in the immunomodulatory activities of IVIG in MS (1) (2).

### AIM OF THE STUDY

Identification and characterization of genes expressed in T cells that might be involved in the immunomodulatory activity of ING in the treatment of exacerbations in Relapsing Remitting MS RRMS)

### METHODS

1. Patients included in the study

### Inclusion criteria:

- clinically or laboratory-supported definite RRMS in acute exacerbation
- nded Disability Status Scale (EDSS) 0-5.5 age 18 and 55 years

### Exclusion criteria:

Patients with prior treatment

- immunosuppressants within 9 month
- continuesteroids 8 weeks - acute exacerbation within 8 weeks before entry Severe concurrent disease

### 2. Treatment of patients

All 10 patients included in the study received a 5-day course of 0.4g/kg bodyweight Endobulin S/D (Baxter AG, Vienna, Austria) per day.

Treatment of patients as well as clinical evaluation was done at the Department of Neurology, Tampere University Hospital, Tampere, Finnland, Patients were also subjected to MRI diagnosis of brain and spinal cord before and three weeks after IVIG

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Blood samples were taken immediately before the first dose of IVIG as well as 24 hours and three taken the last dose.

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- Interview
- EDSS
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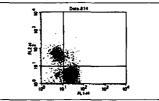
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Proba Sel ID	Expression	Gene Symbol	Gene Title
221841_5_21	1	KLF4	Kruppel-ake factor 4 (guf)
204439_81		C1orf29	chromosome 1 open reading trame 29
214084_x_at		Ciunca	Homo sacients samilar to Neutrophil cytosolic factor 1 (LOCS78112), mRNA
		in es at 3 meetrs a	fter completion of IVIG therapy compared to day 0 before IVIG therapy
Protes Set 10	Expression	Gene Symbol	Gene Title
204619 5 21		CSPG2	chondroxim Suffate proteophycan 2 (versican)
			compared to 8 weeks after completion of MG therapy
Toba Set ID	Expression	Gene Symbol	Gene Title
101422 at		POD	interferon, gamma-inducible protein 30
203561_11	<u> </u>	FCGR2A	Fc tragment of IgG, low affinity ills, receptor for (CD32)
204445 5 22		ALOXS	electron transportantiammatory responseleutotriene biosynthesis
204533_81	i	000.10	cell mobilitychemotaxis.inflammatory responsermmune responsecell surface receptor linked signal transducte
207697_x_at	1	LILAB2	leukocyte immunopiobylin-kka receptor, subfamily B (with TM and (TIM domains), member 2
210145 x at		ULR82	leukocyle kmimunoolobulun-ika radeptor, subfamily 8 (with TM and TTM domains), member 2
211100 x 21	i	LULAB1	leukocyte immunopiobulin-like receptor, subfamely 8 (with TM and ITIM domains), member 1
211101 x at		LULRB1	eukocyte immunoplobulin-like receptor, subfamily 8 (with TM and ITMA domains), member 1
214365 5.8	i -	AL005	anachidorate 5-Boorganase
214511_1_8	i i	FCGB1A	Fc tracment of kg6, high attinity is, receptor for (CD64)
216950 sat		FCGR1A	Fc fragment of IoG, high attinuty la, receptor for (CD64)
219519_5_#	<u> </u>	SN	suboditesan
220145 41	i	TLA7	toll-like receptor 7
201569 5 21		MARCKS	myntsallyfiathdi albanine-ricch protein kinase C substrate
201670_5_#		MARCKS	mynskoylated alanne-nch protein lonase C substrate
205119 5 20	i	FPRI	tormyl peptide naceptor 1
206891_a1		DUSP6	dual specificity phosphatase 6
208692 5 24		DUSPS	dual specificity phosphatase 6
206893_5_#	1	DUSP6	dual specificity phosphatase 6
221841 5.0	1	KQ_F4	Kruppel-like factor 4 (put)
204858_5_#	i i	ECGF1	endothelial cell growth factor 1 (platelet-derived)
204961_s_at		NCF1	neutrophil cytosolic factor 1 (47kDa, chronic granulomatous disease, autosomal 1)
207610_5_21	ł	EMR2	eof-lika module containing, mucun-lika, hormone receptor-lika 2
208018_5_4		HCK	temopoletic cell lassa
209189_41	i	FOS	v-fos F8J monthe osteosarcoma vizzi oncogene homotido
212099 al		ARHS	ras homoloo gene tamev, member B
217763 5 #1	1	RAB31	RAB31, member RAS oncogene taméy
219788_at	-	PILRA	paind immunopiobin-like type 2 receptor alpha
220088_at		CSR1	complement component 5 receptor 1 (CSa ligand)
201360_at	1	C\$13	cystatin C (amyloid angiopathy and cerebral hemorrhage)
201798_1.#	1	FERILS	ter-1-6ka 3. mychistin (C. elegans)
202510_5_21	1	TNFAIP2	turnor mecrosis tactor, alpha-induced protein 2
202833_5_#	+	SERPINAL	Serme (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antibrypsin), member 1
205936_5_#		HK3	hexolonase 3 (while cell)
206488_5_#		C036	CD36 antigen (collagen type I receptor, thrombospondin receptor)
206890_1_#		PLXN82	plipsin 62
210423_5_#		SLC11A1	Solute carrier family 11 (proton-coupled divatent metal ion transporters), member 1
210873_1_8		APOBECSA	apolipopretein & refetA editing enzyme, catalytic polypepide-lika 3A
211429_5_#	1		Homo sapiens PR02275 mRNA, complete cds
213418_41		HSPA6	heat shock 70kDa protein 6 (HSP70B')
213472_21		HNRPH1	hetarogeneous nuclear ribonucleoprotein H1 (H)
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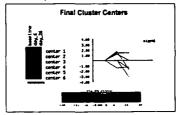
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### REFERENCES

2011. Polyapicali: mmunopolusina AVG augotess profileation of numeritaurate cells: without inducing appropriate; J. of Neurommunology 114 (160-167) et al., 1997. Posstanco-holowe Reputation of 3-cell 6-2 production by Human I guider, J. of Immunology and Immunopercology 53 (1), 77-65.

In either of the following: regulation of immune resporses, regulation of prolifetation, regulation of apoptoss, regulation of cell signaling or regulation of transcription (Fig. 4). Examples of proteins involved in regulation of immune responses are ligands for chemokine receptors, cytokines and proteins involved in biosynthests or bioactivity of given in a 5-day course at 0.4g/kg per day was score as well as changes in disease activity as analyzed by MRI. Furthermore, the treatment was 1. Aktas et al.: J Neuroimmunol 2001;114:160-167 2. Modiano et al.: J Immunoi Immunpathol 1997;83 77-85 expressed in T cells of patients with RRMS in acute The clinical outcome of the study showed that IVIG effective and caused a significant change in EDSS specifically in patients after IVIG treatment. Most of the proteins encoded by these genes are known to cell proliferation, apoptosis, cell signaling and transcription. All these biological activities are likely to be involved in the regulation of disease activity we have identified a set of genes that might be associated with the biological activity of IVIG in patients with RRMS. Further evaluation of these genes in a larger group of patients will be necessary to This study was designed to identify genes differentially We identified 253 genes differentially expressed be involved in the regulation of immune responses, in patients with RRMS. Therefore, we believe that confirm our data and to define a set of differentially expressed genes that correlate with the clinical BMT Biological function of proteins encoded by genes differentially expressed during IVIG therapy. ntiatly expressed genes (in%) DISCUSSION AND CONCLUSIONS Function of proteins encoded by genes differentiatly expressed upon IVIG treatment exacerbation after treatment with IVIG. efficacy of IVIG in RRMS. safe and well tolerated. region of wheelphan STRUCT COMPLETE REFERENCES prostaglandines. Pigard Nadine', Kuusisto Hanna', Elovaara Irina', Raija Paalavuo ', Schwarz Hans-Peter', Reipert Birgit'<sup>, J</sup> BMT-Research, Vienna, Austria - 'Neuroimmunology Unit, Department of Neurology, Medical School, University of Tampere and Tampere University Hospital, Tampere, Fintand - 'Baxter BioScience, Vienna, Austria ż using microarray analysis was investigated by Real Time PCR, Results obtained with the Real Time PCR showed the same trend of either up- or down-regulation as data obtained by microarray analysis. Confirmation of microarray data by Real Time Polymerase chain reaction (PCR) Biological activity of proteins encoded by differentially expressed genes in patients after treatment with IVIG Expression of 13 genes found to be differentially expressed Proteins encoded by most genes found to be differentially Number of differintally expressed genes in C04-/C08-Number of differintally expressed genes in C04-/C08-Common genes were found in both groups of pariants. WIO Specific and WMP-specific genes were only lound in pairents treated with WMP-specific genes were only lound in pairents treated with WMP or WMM- respectively. All genes were al Number of differentially expressed genes of different time points during treatment with IVIG (Fig. 3a) or IVMP (Fig. 3b). All genes were at least 2-told up- or down-regulated e conmon genes a MVC-specific genes a MMP-specific genes sclerosis after treatment with intravenous immunoglobulins (IVIG) manual OW 8 8 Number of differentiality expressed genes upon ING treatment at different time points Number of differentially expressed genes upon IMMP treatment at different time points Differentially expressed genes upon I/VG and I/MP treatment TTI Number of perm 1. 14. 52.4.4 ייים מן קיימניון אייי One 21 company in any O o has a measure of the day il compared to day 0 dey 21 compared to day 6 day 21 conquered in day i ary 21 compared to day 0 ¥ ¥ ¥ ¥ ¥ ¥ ¥ ¥ a Ž \* ĩ 

Table 2. MRI measurements of brain abnormalities Differentially expressed genes after IVIG Um efficient and clinical evaluation Um efficient evaluation Kurtek e Expanded Dissbility Status Scale (EDSS) in patients after treatment with MOG. • PoOO1 measurements of hrain about stable phase acute release 3 wr before IV/O after 1 

between patients treated with NIG and patients treated with patients treated with NIG most the PFIG, as and 3D, in patients treated with NIG most differentially expressed genes were found on day 21 when compared to either day 0 or day 6 (Fig 3a).

expressed in patients after treatment with IVIG are involved

expressed genes after IVIG treatment (Fig. 2). 271 genes expressed genes after IVIG treatment (Fig. 2). 271 genes were differentially expressed in CD4/CD8• FBMC in patients after treatment with WMP (Fig. 2). 18 genes were patients after treatment with WMP (Fig. 2). 18 genes were patients after treatment with WMP (Fig. 2). 2010 genes patients and 23 genes to be differentially expressed patients, leaving 233 genes to be differentially expressed specifically in patients after WIG treatment (Fig. 2). Microarray-analysis revealed a number of differentially

treatment N

The kunetic distribution of differentially expressed genes differed

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Penpheral blood mononuclerar cells (PBMC) were prepared Preparation of peripheral T cells

within 60 min after blood sampling. T cells were isolated from PBMC at 4°C using a mixture of non-stimulating anti-CD4 Purity of separated cells was confirmed by FACS-analysis. and anti-CD8 Dynabeads (Dynal, Oslo, Norway)

# 6. Preparation of RNA and gene chip analysis

Purified cells were immediately transferred into TRIzol (Gibcor/Invitrogen.Carlsbad, California) and stored at -80° until preparation of RNA samples. 5µg of total RNA were in vitro-transcribed using the Artymetrix Eurkaryotic Target Protocol. The CRNA was labeled with streptavdin-phycocrythrin conjugate and hybridized to the Human U133-A Genechip (Artymetrix, Santa Clata, CA)

## 7. Data analysis

significant. Initially, all arrays were normalized for comparison between expression data obtained on day 0 (before All data obtained were analyzed using a parametric t-test (Welch t-test with unpaired variances). Differences with pvalues of less than 0.05 were considered to be statistically treatment) and on days 6 and 21. All data were transformed logarithmically and all genes with a fold change > 2 were included in the analysis.

# 8. Real Time Polymerase chain reaction

The microarray data for 13 genes were confirmed by quantitative real-time PCR. 1 µg of total T cell RNA was used for reverse transcription

into cDNA according to the manufacturer's protocol (MBI Fermentas, Burlington, Canada). 100ng cDNA in 5µ nuclease-free water (Invitrogen, Carlsbad,

CA) were quantitatively analyzed using different TaqMan<sup>6</sup> Assays-on-benand Applied Biosystems, Forster City, CA) with the APPhsen 7000 (kopsied Biosystems). For monization of expression data human GPDH and β-2 microglobulin were used as housekeeping genes.

## RESULTS

The EDSS score was significantly reduced in patients correlated with the improvement of EDSS scores (table 2). For comparison, MRI analysis in control patients who neceived IMMP treatment old not show significant improvement after IVIG-treatment (Fig. 1). Data obtained in MRI analysis Therapeutic effectiveness of IVIG treatment of disease activity (table 3).

## Blood samples were taken immediately before the first dose of IVIG or IVMP as well as on days 6 and 21 after the first 3. Blood sampling

INTRODUCTION

Differentially expressed genes in peripheral T cells obtained from patients with relapsing-remitting multiple

**Clinical examination** dose. Intravenous immunoglobulins (IVIG) have been used successfully in the treatment of a number of inflammatory

and autoimmune diseases of the central nervous system including multiple sclerosis (MS). Recent studies suggested that a modulation of T-cell responses was involved in the immunmodulatory activities of IVIG in MS (1; 2). To explain the effects of IVIG

Interview

In more detail, we studied gene expression profiles of perioheral T cells in patients with relapsing-remitting MS (FRMS) in expendion before and after treatment with NGC. For comparison we studied patients who received intravenous methylprednisolone (IVMP)

 6 days after the first dose of IVIG or IVMP 3 weeks after first dose of IVIG or IVMP

before first dose of IVIG or IVMP Timing of clinical examination. EDSS MRI of brain and spinal cord

## PURPOSE OF THE STUDY

Identification of genes differentially expressed in perpheral T cells obtained from patients with relapsing remitting MS (RRMS) in acute exacerbation before and after treatment with IVIG.

## METHODS

# . Patients included in the study

- clinically or laboratory-supported definite RRMS in acute nclusion criteria:
  - Expanded Disability Status Scale (EDSS) 0-5.5 exacerbation
    - age 18 and 55 years
      - Exclusion criteria:
- immunosuppressants within 9 month prior treatment with.
- acute exacerbation within 8 weeks before entry. severe concurrent disease corticosteroids within 8 weeks

## 2. Treatment of patients

All 10 patients included in the study received a 5-day course of 0.4g/kg bodyweight Endobulin S/D (IVIG; Baxter AG, Vienma, Austria) per day. The control group of 5 patients received 1gday intravenous methypreditisoion (IVMP). Treatment of patients as well as clinical evaluation was done at the Department of Neurology. Tampere University Hospital, Tampere, Finnland. The characteristics of patients included in the study are given in table 1.

# Table 1. Characteristics of study population

Character ristics	patients treated with IVIG with IVIP (controls)	patients treated with IVMP (controts)
Number of study population	10	5
Age average ± SD, year)	40 ± 10.6	35.3 ± 8.8
Sex (male vs female)	3 15 7	0 v5 5
Disease dwation (average ± SO, year)	56+35	52±36
Time current vs previous relapse (average ± S0, month)	17.6 ± 21.0	5 * 3 2
EDSS score at remission (average ± SO, score)	3.7 ± 1.1	32±24
EDSS score at acute relapse (average ± SD, score)	3.7±1.1	4.2±2.0)

# Canical evaluation of patients before and after treatment with IVIG

	After IVIG	mean ± SE	1.73±0.59	5 08 * 1.03
	Betone IVIG	mean ± SE	1.76±0.55	5.49 ± 1.09
erore and aner Ivid	Parameter	Lesion vol cm <sup>2</sup>		2

Parametter	Before IVIG	After IVIG
Lesion vol cm <sup>2</sup>	mean ± SE	mean ± SE
n	1.76±0.55	1.73 ± 0.59
2	5.49 ± 1.09	5.08 ± 1.03*
fair	15.76±2.23	14.09 ± 1.94**
Gd-enhanced	0.32±0.27	0.21 ± 0.24.
Brain votume	1124.94 ± 40.61	1120.31± 40.72
Gd+lesion N	2.63 ± 0.71	2.00±0.60.1
EDSS* score	3.8±0.3	2.6±0.2**

p<0.05; \*\* p<0.01 EDSS = Kurtzke's Expanded Disability Status Scale

ore and after IVMP		
amater	Betere IVMP	After IVMP
ion voi cm <sup>2</sup>	mean ± SE	mean ± SE
	1.41 ± 0.60	1.64±0.84
	11.15 ± 4.59	9.83 ± 4.17
	24.37 ± 8.19	23.18 ± 8.05
enhanced	0.70±0.39	063±037
in votume	1056.32 ± 47.78	1045 07 ± 52 53
lesion N	3.0 ± 1.5	27±1.4

Para Para

### 6. CURRICULUM VITAE

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01/2001 - 11/2005	PhD Thesis " Genexpression studies in patients with Relapsing Remitting Multiple Sclerosis" at the Department of Immunology at Baxter Bioscience, Vienna, Austria; Employed by Biomolecular Therapeutics (BMT), Vienna, Austria;
09/1999 – 11/2000	Diploma Thesis at the Department of Medical Biochemistry, Vienna Biocenter, Universtity of Vienna, Austria;
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