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Sanna-Kaisa Häkkinen

Microarray Study

Gene Expression in Endothelial Cell Cultures and Intracranial Aneurysms

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SANNA-KAISA HÄKKINEN

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ABSTRACT

DNA microarray technology has proven to be a very useful and important tool in the field of molecular biology. The possibility to measure expression levels of thousands of genes simultaneously has facilitated the research of polygenic diseases. Vascular diseases are the main cause of mortality and morbidity in the western world. Therefore it is necessary to clarify the mechanisms of pathogenesis of these diseases. Large scale gene expression profiling will enhance the development of therapeutic strategies for the treatment of vascular diseases.

Vascular endothelial growth factors (VEGFs) have important roles in the growth, differentiation, and maintenance of blood vessels. They are also involved in many pathological conditions such as in atherosclerosis. The endothelium is a major regulator of vascular tone and remodelling as well as arterial inflammation and thrombosis. Endothelial dysfunction in considered as an early sign of atherosclerosis. In this study the effects of overexpression of one important human VEGF, VEGF-$D^{\Delta N\Delta C}$, was studied in human vascular endothelial cells (HUVECs) to elucidate the role and significance of VEGF-$D^{\Delta N\Delta C}$ in vascular biology. Intracranial aneurysm (IA) is a life-threatening condition. Rupture of IA causes subarachnoid hemorrhage which is associated with high mortality. It is not known why aneurysms rupture. In this study Affymetrix microarrays was used to analyze the difference in the gene expression of ruptured and unruptured intracranial aneurysms.

Overexpression of VEGF-$D^{\Delta N\Delta C}$ caused activation of three signalling cascades downstream from VEGFR-2 (vascular endothelial growth factor receptor -2) which induces vasodilatation and endothelial survival. Also, upregulation of VEGF-A, neuropilin 2 (NRP2) and stanniocalcin 1(STC1) was evident and it seemed to regulate and amplify the effects of VEGF-$D^{\Delta N\Delta C}$. In the aneurysm study there was significant upregulation of 686 genes and downregulation of 740 genes in the ruptured aneurysms. Significantly upregulated biological processes included: chemotaxis, leukocyte migration, oxidative stress, vascular remodelling, and extracellular matrix (ECM) degradation.

In HUVECs possible mechanism for VEGF-$D^{\Delta N\Delta C}$ regulation was found that will increase understanding about the biology of VEGF-$D^{\Delta N\Delta C}$. Especially VEGF-A, NRP2 and STC1 particularly seem to have key roles in VEGF-$D^{\Delta N\Delta C}$ signalling and regulation. In the aneurysm expression analysis, pathways and candidate genes associated to the rupture of human saccular IA (sIA) was identified. The results provide clues to the molecular mechanisms in sIA wall rupture and insight for novel therapeutic strategies to prevent rupture. Gene expression profiling is a convenient and modern research tool that will help us to understand mechanisms behind complex diseases.

National Library of Medicine Classification: QS 532.5.E7, QU 58.5, QU 107, QU 450,QU 475, WG 500, WL 355

Medical Subject Headings: Genomics; Gene Expression; Gene Expression Profiling; Gene Expression Regulation; Blood Vessels; Endothelial Cells; Endothelium, Vascular/pathology; Cerebrovascular Disorders; Atherosclerosis; Vascular Endothelial Growth Factors; Microarray Analysis; Signal Transduction; Intracranial Aneurysm; Rupture, Spontaneous; Inflammation; Cell Movement; Leukocytes; Chemotaxis; Extracellular Matrix/pathology; Oxidative Stress

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TIIVISTELMÄ

Mikrosiruteknologia on osoittautunut hyvin hyödylliseksi ja tärkeäksi menetelmäksi molekyylibiologisessa tutkimuksessa. Mahdollisuus tutkia kymmenien tuhansien geenien ilmentymistä yhdellä kertaa on nopeuttanut monigeenisten tautien tutkimista. Erilaiset verisuonisairaudet ovat suurin sairastuvuuden ja kuolleisuuden aiheuttaja länsimaissa. Siksi on tärkeää selvittää näiden tautien syntymisen mekanismeja. Laaja-alainen geenien ilmentymisen tutkiminen tulee nopeuttamaan kaikentyypisten verisuonisairauksien terapeuttisten strategioiden kehittämistä.

Verisuonen endoteelikasvutekijöillä (vascular endothelial growth factor, VEGF) on tärkeä rooli verisuonten muodostumisessa, erilaistumisessa ja ylläpidossa. Niillä on vaikutusta myös useisiin sairauksiin kuten valtimonkovettumatautiin. Endoteelillä on tärkeä rooli verisuonen paineen säätelyssä ja uudelleen muodostumisessa sekä valtimon tulehduksessa ja verisuonitukoksissa. Endoteelin toimintahäiriötä pidetään valtimonkovettumataudin varhaisena merkkinä. Tässä tutkimuksessa tutkittiin yhden tärkeän VEGF:n, VEGF-$D^{\Delta N\Delta C}$:n, yli-ilmentymisen vaikutuksia ihmisen endoteelisolulinjassa (HUVEC) VEGF-$D^{\Delta N\Delta C}$:n verisuonibiologian kannalta keskeisen roolin ja merkityksen selventämiseksi. Aivovaltimoaneurysma (IA) puolestaan on verisuonen seinämän sairaus, joka puhjetessaan subaraknoidaalitilaan aiheuttaa hengenvaarallisen tilan, jolla on suuri kuolleisuusriski. Syytä aneurysmien puhkeamiseen ei tiedetä. Tässä tutkimuksessa analysoitiin puhjenneiden ja puhkeamattomien aivovaltimoanerysmien geenien ilmentymisten eroja Affymetrix:in mikrosiruilla.

VEGF-$D^{\Delta N\Delta C}$:n yli-ilmentyminen aiheutti kolmen signalointireitin aktivoitumisen VEGFR-2:n (verisuonen endoteelikasvutekijä reseptori -2) alajuoksussa, jotka saavat aikaan verisuonten laajenemista ja parantaa endoteelin eloonjäämistä. Lisäksi havaittiin VEGF-A:n, neuropiliini-2:n (neuropilin-2, NRP2) ja stanniokalsiini-1:n (stanniocalcin-1, STC1) ilmentymisen lisääntyminen, mikä näyttäisi säätelevän ja lisäävän VEGF-$D^{\Delta N\Delta C}$:n vaikutuksia. Aneurysmatutkimuksessa havaittiin 686 geenin ilmentymisen lisääntyneen ja 740 geenin ilmentymisen vähentyneen puhjenneissa aneurysmissa. Merkittävästi ilmentyminen oli lisääntynyt seuraavissa biologisissa prosesseissa: kemotaksis, leukosyyttien migraatio, oksidatiivinen stressi, verisuonen uudelleen muokkautuminen ja ekstrasellulaarimatriksin hajoaminen.

Tutkimuksessa löydettiin VEGF-$D^{\Delta N\Delta C}$:n säätelyn mahdollinen mekanismi ihmisen endoteelisoluissa, joka auttaa meitä ymmärtämään paremmin VEGF-$D^{\Delta N\Delta C}$:n biologiaa. Erityisesti VEGF-A:lla, NRP2:lla ja STC1:llä näyttäisi olevan tärkeä rooli VEGF-$D^{\Delta N\Delta C}$:n signaloinnissa ja säätelyssä. Aneurysmien geenien ilmentymisen analyysissa löydettiin reittejä ja kandidaattigeenejä, joilla voi olla vaikutusta IA:n puhkeamiseen. Tulokset auttavat selvittämään IA:n puhkeamisen molekulaarisia mekanismeja ja parantavat merkittävästi mahdollisuuksia uusien terapeuttisten puhkeamista estävien menetelmien kehittämiseen.

Yleinen suomalainen asiasanasto: genomiikka; geenitutkimus; geenit; endoteeli; verisuonet; verisuonitaudit; ateroskleroosi; aneurysma; kasvutekijät; DNA-sirut; tulehdus; valkosolut; sidekudokset - - hajoaminen; hapettuminen

"If you can't convince them, confuse them."
- Harry S. Truman

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Contents

ABBREVIATIONS

AcomA anterior communicating artery
Ad adenovirus
Arp actin related protein
aSAH aneurysmal subarachnoid hemorrage
Bcl-2 B-cell lymphoma 2
cDNA complementary deoxyribonucleic acid
cRNA complementary ribonucleic acid
CO_2 carbon dioxide
COL collagen
COX cyclooxygenase
CMV cytomegalovirus
CSF colony stimulating growth factors
DAB 3′-5′-diaminobenzidine
DACA distal anterior cerebral artery
DAVID Database for Annotation, Visualization and Integrated Discovery
DNA deoxyribonucleic acid
dscDNA double stranded complementary deoxyribonucleic acid
EBI European Bioinformatics
ECM extracellular matrix
EGF epidermal growth factor
ELISA enzyme-linked immunosorbent assay
eNOS endothelial nitric oxide synthase
ERK1/2 extracellular signal regulated kinase 1/2
FDR false discovery rate
FGED Functional Genomics Data Society
FGF fibroblast growth factor
HBSS Hank's Buffered Salt Solution
HDL high density lipoprotein
HPSE heparan sulfate proteoglycan degrading enzyme heparanase
HRP horseradish peroxidase
HUGO Human Genome Organization
HUVEC human umbilical vein endothelial cell
IA intracranial aneurysm
ICA internal carotid artery
ICAM intercellular adhesion molecule
IGF-1 insulin growth factor 1
IHC immunohistochemistry
IL-1 interleukin 1
INF-γ interferon γ
ITGB2 integrin beta 2
IVT in vitro transcription
kDa kilo dalton
KEGG Kyoto Encyclopedia of Genes and Genomes
LDL low density lipoprotein
mAb monoclonal antibody
MAQC MicroArray Quality Control
MCA middle cerebral artery
MCP-1 monocyte chemoattractant protein 1
MGED Microarray Gene Expression Data Society
MIAME Minimum Information About a Microarray Experiment
miRNA micro ribonucleic acid
MMP matrix metalloproteinase
MOI multiplicity of infection
mRNA messenger ribonucleic acid
MUPP1 multiple PDZ domain protein 1
NA not available
NADPH nicotinamide adenine dinucleotide phosphate
NF-κB nuclear factor κB
NO nitric oxide
NRP neuropilin
NS not stained
oxLDL oxidized low density lipoprotein
pAb polyclonal antibody
PCA principal component analysis
PComA posterior communicating artery
PDGF platelet derived growth factor
PECAM platelet endothelial cell adhesion molecule
PGI_2 prostacyclin
PI3K phosphatidylinositol 3-kinase
PLAUR plasminogen activating receptor
PlGF placental growth factor
PPAR peroxisome proliferators-activated receptor
qRT-PCR quantative real time polymerase chain reaction
r recombinant
RNA ribonucleic acid
rRNA ribosomal ribonucleic acid
ROS reactive oxygen species
RU ruptured
SAH subarachnoid hemorrage
sIA saccular intracranial aneurysm
SMC smooth muscle cell
SOM self organizing maps
STC1 stanniocalcin 1
SVD singular value decomposition
THBS1 thrombospondin 1
TIMP tissue inhibitor of matrix metalloproteinases
TNFα tumor necrosis factor alpha
TNFRSF tumor necrosis factor receptors superfamily
tPA tissue plasminogen activator
T-PER tissue protein extraction reagent
tRNA transfer ribonucleic acid
UR unruptured
VCAM vascular cell adhesion molecule
VEGF vascular endothelial growth factor
VEGFR vascular endothelial growth factor receptor
ZAK leucine zipper- and sterile alpha motif-containing kinase
ZO1 tight junction protein 1

1 Introduction

Vascular diseases are caused mainly by pathological changes that take place in the vascular walls. Two common vascular diseases, atherosclerosis and aneurysm, are both diseases of blood vessel wall. Great emphasis has been placed in the role of the endothelium in the triggering and development of vascular diseases. VEGFs are important for endothelial integrity and thus for vascular function. The role of VEGFs, especially VEGF-D, in atherosclerosis has not been extensively studied. They are important factors in proliferation, migration and survival of endothelial cells (Breen, 2007) and thus they might prevent endothelial dysfunction. Dilatation of the vessels can cause weakening of the wall leading to aneurysm formation and even to rupture. The presence of endothelial dysfunction also in aneurysms has been shown (Libby et al., 1995). Several risk factors promote the development and progression of vascular diseases and aneurysms but the significance of genes in disease pathology is considered highly important. Although *in vivo* studies of the risk factors are essential effects of different factors are generally easier to study *in vitro* as the conditions are easier to control.

Vascular diseases are polygenic diseases. Therefore to study the pathology, advanced methods are needed. Microarrays can be used to study gene expression of tens of thousands of genes at the same time. The method can help to clarify mechanisms of regulation, biochemical pathways and wider connections between cells. The completion of human genome project has made it possible to study the whole human genome in a single experiment. Microarrays have been utilized in disease diagnostics, novel gene identification, drug discovery and understanding complex biological systems. So far, microarrays are perhaps the most successful and mature technologies for high-throughput and large-scale genomic analyses. The real challenge for research is how to process the large data amount obtained from the experiments that might help to understand pathogenesis of the disease and identify potential therapeutic targets (Clarke et al., 2001).

2 Review of the literature

2.1 GENOMICS

Genomics is the study of the molecular characteristics of the whole genome. It aims to understand the structure and function of the genome, including mapping genes and sequencing the deoxyribonucleic acid (DNA). Genomics examines the molecular mechanisms and the interplay of genetic and environmental factors in disease. It includes functional genomics, which is the characterization of genes and their messenger ribonucleic acid (mRNA) and protein products. Structural genomics focuses on the dissection of the architectural features of genes and chromosomes. In comparative genomics the evolutionary relationships between the genes and proteins of different species are studied. Epigenomics or epigenetics is the study of DNA methylation patterns, imprinting, DNA packaging and histone modification. In pharmacogenomics new biological targets and new ways to design drugs and vaccines are discovered (Devlin, 2010).

2.1.1 Genome

The genome is the organism's complete set of hereditary information either in DNA or RNA form. Genomes differ widely in size and they include both genes and non-coding sequences of DNA. The smallest known genome for a free-living organism, (a bacterium) contains about 600,000 DNA base pairs (Fadiel et al., 2007), while human and mouse genomes consist of about 3 milliard base pairs (Mouse Genome Sequencing Consortium et al., 2002). In humans the DNA is packed in 46 chromosomes forming 23 chromosome pairs containing the entirety of hereditary information (Devlin, 2010).

2.1.1.1 Human Genome Organization (HUGO)

Human Genome Organization (http://www.hugo-international.org/) is an organization involved in the Human Genome Project which has the global initiative to map and sequence the human genome (Fig 1). HUGO was established in 1989 as an international organization, primarily to promote collaboration between genome scientists around the world. HUGO has many activities ranging from support of data collation for constructing genetic and physical maps of the human genome, to the organization of workshops to promote the consideration of a wide range of ethical, legal, social and intellectual property issues. HUGO provides an interface between the Human Genome Project and groups and organizations interested or involved in the human genome initiative. A working draft of the Human Genome Project was announced in 2000 (Lander et al., 2001; Venter et al., 2001) and the complete one in 2003. It was a huge collaboration between publicly and privately funded research teams. It was considered the first large scale project of biology and had a huge impact on development of an array of new technologies microarrays being one of them (Collins et al., 2003).

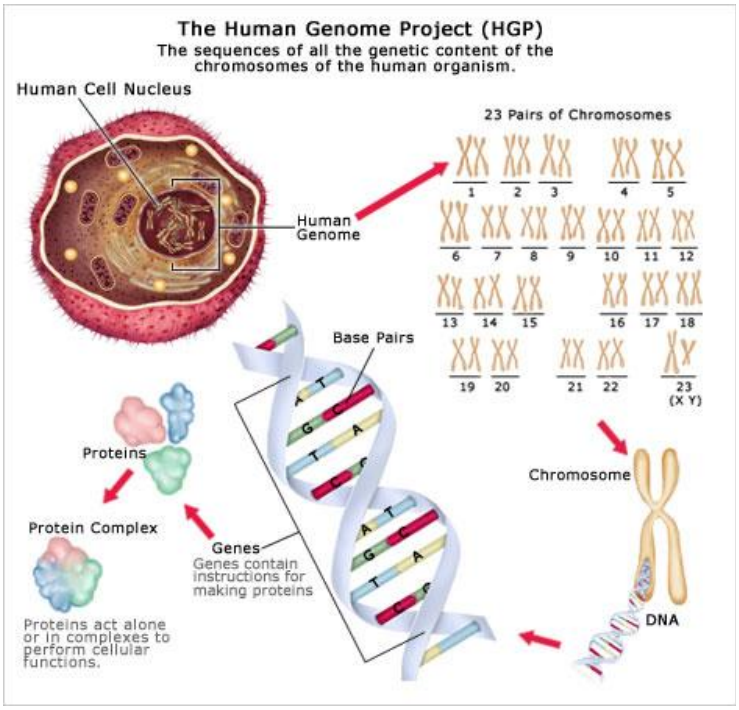


Figure 1. From genome to protein (www.familyhelix.com)

2.1.2 Gene expression

Gene expression is the process where information from a gene is used in the synthesis of a functional gene product (protein or RNA). Expressed genes include genes that are transcribed into mRNA and then translated into protein as well as genes that are transcribed into different kinds of RNAs such as transfer RNA (tRNA), ribosomal RNA (rRNA), short non-coding RNA and microRNA (miRNA) that are not translated into proteins. Gene expression is a highly regulated process where genes are switched on and off at certain times which leads to changes in the amounts of corresponding gene products. The process of gene expression is used by almost all known life to generate the macromolecular machinery of life. Gene expression is regulated at many different levels in transcription, RNA splicing, translation and post-translational modification of a protein. Gene regulation is a way of controlling different biological mechanisms. It is involved in cellular differentiation and morphogenesis and it is the basis of the versatility and adaptability of organisms (Devlin, 2010).

2.1.2.1 Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)

DNA is located in the nucleus as a DNA-protein complex, chromatin, which is organized into chromosomes and it contains all the genetic information. DNA consists of two long chains of nucleotides in a double-helical structure joined together by hydrogen bonds. Each nucleotide is composed of a deoxyribose sugar, a phosphate and a nitrogenous base. RNA differs to DNA by being single-stranded, containing ribose instead of deoxyribose and having a uracil as a base rather than thymine which is present in DNA. RNA is transcribed from DNA and

there are different types of RNAs which have their own roles in gene expression, gene regulation and protein synthesis (Devlin, 2010).

2.1.2.2 Transcription

Transcription is the process where information is transferred from the DNA to the messenger RNA after which the RNA's information is translated into specific proteins. The DNA is made up of two strands, linked together in the shape of a double helix (Watson and Crick, 1953). When the transcription starts, the two strands separate, and a strand of mRNA forms with the help of RNA polymerase. Transcription starts from the promoter sequence which has to be accessible to the transcription machinery. For a gene to be active, it needs binding of transcription factors to DNA sequences in the promoter region. Also, enhancers and other cis-acting transcriptional control elements need to bind other factors in order to stimulate transcription. Transcription factors bound to DNA recruit RNA polymerase II to the promoter and the forming of mRNA begins. RNA copies the information into its own system of bases. The new mRNA then moves on to the ribosome area of the cell where translation will take place (Devlin, 2010).

2.1.2.3 Translation

The mRNA translates the information it has gleaned from the DNA into amino acid sequence and then proteins at the ribosomes in the cell's cytoplasm. The mRNA, as well as DNA, is divided into codons, three-letter combinations made up of nucleotide bases and each codon matches up with a particular tRNA. The tRNA then takes the codon carrying the corresponding amino acid and links it together with other amino acids in a protein chain. Initiation requires bringing together a small (40S) ribosomal subunit, mRNA and tRNA complex, all in proper orientation. Association of the large (60S) subunit to the complex forms a completed initiation complex. The process starts when eukaryotic initiation factor 2 binds to GTP and forms a complex with the initiator tRNA, Met-$tRNA_i^{met}$. The order of the amino acids in the chain is dictated by the sequence of codons in the mRNA. Amino acids are linked together by peptide bonds. When the protein is complete, a stop codon will indicate that the protein chain can detach from the ribosome making it a fully functioning molecule of protein (Devlin, 2010).

2.2 DNA MICROARRAYS

DNA microarray technology allows simultaneous measurement of the mRNA levels of thousands of genes. Microarray based expression profiling is a powerful technology for studying biological mechanisms and for developing valuable predictive classifiers. Microarrays can be used to study a wide variety of objectives that can be categorized into one of three broad categories: class comparison, class prediction, and class discovery (Ballman, 2008). Class comparison is also known as differential analysis and it involves the comparison of gene expression profiles of predefined and dissimilar sample groups to identify the genes that are differentially expressed among the groups. In class prediction the objective is to find genes that differ across predefined classes. The aim is to identify a small set of genes able to accurately distinguish among the distinct groups. Class discovery studies try to determine whether subsets of samples with seemingly homogenous phenotypes can be detected on the basis of differences in their gene expression profiles.

2.2.1 History

Microarray technology evolved from Southern blotting where a mixed pool of DNA sequences is immobilised on a membrane and then probed with a known gene or fragment (Southern, 1975). It is difficult to establish an

exact and uncontroversial origin for microarray technology but the first described use of a collection of distinct DNAs for expression profiling was in 1987 by Kulesh et al (Kulesh et al., 1987) where they identified genes whose expression was modulated by interferon. The gene arrays used in the experiment were made by spotting complementary DNA (cDNA) onto filter-paper with a pin-spotting device. The use of miniaturized microarrays for gene expression profiling was first reported in 1995 (Schena et al., 1995) and a complete eukaryotic genome (Saccaharomyces cerevisiae) on a microarray was published in 1997 (Lashkari et al., 1997). Technological improvements have been essential for the production of convenient and reproducible microarrays. These include the use of a nonporous solid support, usually glass, enabling array miniaturization, the development of fluorescence-based detection (Lockhart et al., 1996), and the introduction of high-speed spatial synthesis of oligonucleotides, allowing simultaneous synthesis of thousands of probes *in situ* on arrays (Fodor et al., 1991; Lipshutz et al., 1999).

2.2.2 Principles

Microarrays are based on the ability of nucleic acids to specifically pair with each other by forming hydrogen bonds between complementary nucleotide acid pairs allowing the hybridization between two DNA strands. Hybridization occurs on a solid support where a probe (cDNA or oligonucleotides) forms a pair with its complementary sample RNA which is labelled with fluorescence. The level of binding between a probe and its target is quantified by emitted fluorescence from the hybridized target when scanned (Coppee, 2008). DNA microarrays can be small custom arrays designed to monitor expression of a few hundred genes, very large arrays that represent tens of hundreds of genes, or arrays that represent the entire genome (Katagiri and Glazebrook, 2009a). There are many different types of arrays and the most distinct difference between the arrays is whether they are spatially arranged on a surface or on coded beads.

2.2.2.1 Solid-phase arrays

In solid-phase arrays, nucleic acid samples (probes) are attached on a solid support such as glass, plastic or silicon biochip. Several thousands of targets can be attached on a single DNA microarray in known locations.

2.2.2.1.1 Spotted

Spotted arrays are usually printed directly onto a glass slide (Fig 2). The spotted probes can be cDNA or oligos (approximately 30-70 basepairs). Array printers required for manufacturing are widely available making this technology also suitable for custom array printing in academic laboratories (Elvidge, 2006). Although the quality and the probe density is quite limited compared to commercial arrays the advantages of this technology, flexibility and relatively low cost, are making them rather attractive for academic laboratories. However, commercial arrays have become less expensive and availability of made-to-order custom arrays might diminish the advantage of in-house spotted arrays (Katagiri and Glazebrook, 2009a).

2.2.2.1.2 In situ synthesised

In situ synthesised arrays are manufactured by synthesising a sequence designed to represent a single gene or a family of gene splice-variants directly on the array surface. The synthesized oligonucleotides can be long (50 to 70 mer) or short (about 25 mer) depending on the desired purpose. Longer probes are said to be more specific to individual target genes whereas shorter probes may be spotted in higher density across the array and are cheaper to manufacture. Agilent uses longer oligonucleotide probes (60 mer) which are manufactured *in situ*

using ink-jet technology in their arrays and it allows great flexibility in the design of each array (Katagiri and Glazebrook, 2009a). Affymetrix uses a photolithographic method with masks to manufacture their arrays (GeneChips) (Fig 2). Light-directed synthesis is employed by passing adenosine, guanine, cytosine or thymine nucleotides that contain a light-sensitive protecting group over a quartz wafer. Lithographic masks are used to either block or transmit light onto specific locations on the array and the coupling of the nucleotide will happen only in the illuminated areas. This process is repeated with different nucleotides so that the sequences are built by one base per round. The standard design of GeneChip has multiple (at least 11) short (about 25 mer) sequences matching perfectly to target sequences per gene. There also are 11 probes that have one basepair change in the centre of the probe known as mismatch probes. Intensity readings from multiple probes are used to detect each transcript and the degree of nonspecific hybridization can be estimated from the mismatch probes (Rattray et al., 2006).

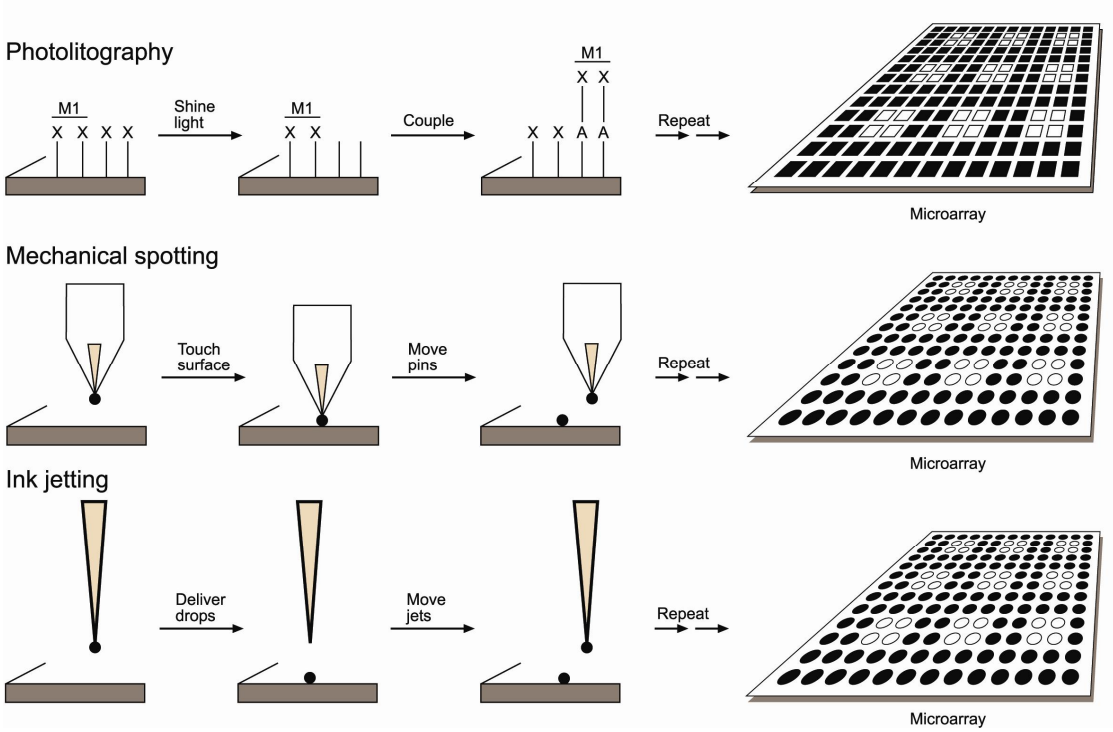


Figure 2. Microarray technologies. Photolitography (top) is a process by which oligonucleotides are synthesized directly on the surface. A photomask (M1) protects some of the reactive groups but leaves others exposed to ultraviolet light, allowing for coupling of photoprotected nucletotides (X, A) on the chip surface. In the next step, a second photomask protects other reactive groups and unprotects the formerly shielded ones, allowing for another round of synthesis. The step is repeated until the wanted length of the oligonucleotides is achieved. This technique is used by Affymetrix. Mechanical microspotting (middle): a biochemical sample is loaded into spotting pin by capillary action, and a small volume is transferred to a solid surface by physical contact between the pin and the solid substrate. Robotic control systems and multiplexed printheads allow automated microarray fabrication. Ink jetting (bottom): releases cDNA by employing electric current delivered by a piezoelectric element onto the platform without touching it. A repeated series of cycles with multiple jets enables rapid microarray production. This technique is used in making of Agilent arrays. Modified from Schena et al. (Schena et al., 1998).

2.2.2.1.3 Two-channel and one-channel detection

Methods that analyze two RNA samples on a single array are called two channel methods. Two RNA samples are labelled with different coloured dyes and cohybridized to the array to obtain the ratio of the mRNA levels for each probe between the two samples. Because the array must be scanned at two wavelength channels for two colours, the method is called two-channel and it is mostly used with spotted arrays. Several different dyes are used for labelling, the most popular being the Cy-dyes or Alexa-dyes. With two colour labelling various different labelling methods and colours can be used but the disadvantage of these methods are that a large amount of total RNA is needed and incorporation of bulky dye-tagged nucleotides into the growing cDNA chain is inefficient. In one-channel method one mRNA sample is labelled with one dye and the labelled sample is hybridized to obtain the mRNA amount for each probe. It is the most popular method for both spotted and

one colour commercial arrays and it is based in the in vitro transcription (IVT) described by Eberwine (Eberwine, 1996). During cDNA synthesis modified nucleotides are incorporated in the strand that enables the detection which can be direct detection of the amplified RNA, for example using fluorescence tagged nucleotides or indirect detection by afterwards coupling dye molecules. Advantages of this method are a relative low amount of starting material and a standardized protocol.

2.2.2.2 Bead array

Bead arrays are created by either impregnating beads with different concentrations of fluorescent dye, or by a type of barcoding technology. The beads are addressable and used to identify specific binding events that occur on their surface. Illumina is the best known manufacturer of bead arrays (BeadChip). In BeadChips a multicore optical 'imaging' fiber is etched so that a bead can fit into the resulting micron-sized etched wells on the tip of the fiber. Different oligonucleotide sequences are attached to each bead and thousands of beads can be self-assembled on the fiber bundle. A subsequent decoding process is carried out to determine which bead occupies which well. Complementary oligonucleotides present in the sample bind to the beads, and bound oligonucleotides are measured by using a fluorescent label (Elvidge, 2006; Gunderson et al., 2004). The biggest current advantage of the BeadChip is the lower costs compared with e.g. Affymetrix and the ability to process more samples in parallel.

2.2.3 Gene expression profiling using Affymetrix GeneChip

Within the commercial one-channel microarray platforms available on the market, Affymetrix is the oldest, with the largest panel of microarrays (GeneChips) designed for a variety of different organisms and the highest number of publicly available data sets (Cordero et al., 2007).

2.2.3.1 Experimental design

Effective use of microarrays requires clear objectives and a well constructed design. Clearly stated study objectives are needed to determine the appropriate type of specimens, an adequate sample size, and a suitable analysis plan (Ballman, 2008). Good experimental design minimizes potential bias. Study groups should be created, if possible, so that they differ only with respect to the variable of interest and all other variables should be as similar as possible. Consideration should be taken to the equality of the characteristics of individuals, specimen or sample collection, isolation, handling, and storage. Throughout the experiment the protocols should be similar to all study groups. One very important aspect in the study design is determining an adequate sample size to address the question of interest. The large cost of arrays is the most common reason for having too few samples in the experiment. However, having enough arrays is essential to obtain reliable and accurate results from the microarray experiment. Several different statistical analyses can be used to determine the adequate sample size for each experiment (Simon et al., 2002) where source of the samples and the objectives of the study are the most influential factors. Technical replication where the same biological material is hybridized independent times are generally no longer performed as the analyses have shown that the results will be relatively consistent overall (MAQC Consortium et al., 2006).

2.2.3.1.1 Probe preparation, hybridization, washing and scanning

Messenger RNA is isolated from a specimen which can be for example, cultured cells, tissue from animal models, or human tissue. The mRNA is converted to cDNA, labelled with biotin, and hybridized to the chosen

Affymetrix GeneChip. After hybridization GeneChip is washed with two different types of buffers to remove unbound probes and stained with streptavidin phycoerythrin conjugate in GeneChip Fluidics Station and scanned with GeneChip Scanner. The level of gene expression is estimated from the raw intensities of the streptavidin phycoerythrin conjugate emitted by the labelled sequence which is bound to probes representing genes from which mRNAs were transcribed.

2.2.4 Standardization

After the new microarray technology had become more widely used, the research community faced a new big problem which was the wide scale of parameters involved in interpreting a microarray experiment and the lack of global comparability of results. The microarray datasets cannot be compared meaningfully if the signals associated with related array elements are not on equal footing. It became evident that there was a need for standards for microarray analysis in order to solve the problem of comparability (Bammler et al., 2005; Brazma, 2001; Star and Rasooly, 2001). Extremely large data sets produced from a single experiment make it difficult to get reliable, reproducible, and comparable results. The enormous matrices produced by each array inevitably contain noise and uncertainty which will complicate analysis of results (Rogers and Cambrosio, 2007).

2.2.4.1 Microarray Gene Expression Data Society (MGED)

In order to bring scientists closer to understanding and comparing microarray data a movement called Microarray Gene Expression Data Society was founded in November 1999. The founders of the society were European Bioinformatics (EBI), Affymetrix and Stanford University who were at the time the leading players in microarray field (Brazma, 2001). The basic aim was to standardize the field. In the first meeting of the society, the frames for "Minimum Information About a Microarray Experiment" (MIAME) were agreed. In July 2010, the name of the group was changed to Functional Genomics Data Society (FGED) to reflect its current mission which embraces functional genomics and not just microarrays or gene expression (http://www.mged.org/index.html).

2.2.4.2 Minimum Information About Microarray Experiment (MIAME)

In December 2001 MIAME was completed and published (Brazma et al., 2001). The aim was to describe the information that researchers should provide to explain the procedures and biological purpose of their microarray data in adequate detail. The data received from microarray experiments is highly context-dependent. To understand the data, experimental information must be provided, including what transcripts are represented, the details of the sample and any treatments, and information on other factors which might have influenced the results. Information about the data processing must be also provided. The complication is that each study has different types of associated information that are relevant and judgements must be made about what is relevant (Stoeckert et al., 2002). The original version of MIAME has been updated several times allowing for more detailed specifications of the software and tools which support it as well as for more precise experimental descriptions (Rogers and Cambrosio, 2007).

2.2.4.3 MicroArray Quality Control (MAQC)

Serious concerns about reproducibility and accuracy of microarrays were raised in publications reporting a lack of concordance in lists of differentially expressed genes that were obtained at different laboratories or using different platforms (Tan et al., 2003). Microarray technology was no longer considered very reliable and this motivated the Food and Drug Administration to launch the MicroArray Quality Control (MAQC) project

(MAQC Consortium et al., 2006). It involved researchers from government, academia, and industry who established strictly controlled standard comparisons of microarray systems. The MAQC project demonstrated that the key factors influencing variations are biological samples and human factors rather than technical diversity (Shi et al., 2008).

2.2.5 Statistical analysis

Proper statistical analysis is vital to the successful use of arrays. Because microarray datasets are very large, statistical analysis is influenced by a number of variables. Variations of experimental conditions inherent systematic biases and the microarray outputs are associated with distinguishing features like high dimensionality (making simultaneous inferences on thousands of genes) and scarcity (only a small fraction of genes are statistically differentially expressed) (Fan and Ren, 2006).

2.2.5.1 Image analysis

After hybridization of the fluorescence-labelled targets on microarrays, the fluorescence image of the array is scanned and the fluorescence image data are generated (Katagiri and Glazebrook, 2009a). The goal is to identify the spots in the microarray image, quantify the signal, and record the quality of each spot. The digital images are analyzed by specialized software with a pre-loaded design of the microarray and grid layout, which instructs the software to consider number, position, shape and the dimension of each spot. With the help of the grid, fine tuning can be done as well as finding possible artefacts like bubbles or scratches which are quite common.(Trevino et al., 2007).

2.2.5.2 Data processing

Automated integration function of the software is used to convert the actual spot readings to a numerical value. The integration function considers the signal and background noise for each spot. Background is caused by optical noise, non-specific hybridization, probe-specific effects, and measurement errors. The output file is commonly a tab-limited text file or a specific file format ((Katagiri and Glazebrook, 2009a; Trevino et al., 2007). Data from different arrays are usually not directly comparable even after background adjustment. Systematic errors will occur in labelling, hybridization, and scanning procedures. Normalization is used to correct these errors, preserving the biological information and to generate values that can be compared between experiments when they are generated in and with different places, times, technicians, reagents and arrays. Also controls used in different steps of probe preparation help to evaluate the consistency of the process.

2.2.5.3 Identification of statistically significant changes

After data normalization, the levels of gene expression can be compared between samples to identify genes that are differentially expressed. Usually, differentially expressed genes are inferred by a fixed threshold cut off method (for example a two-fold increase or decrease) but it is statistically inefficient, the main reason being that there are numerous systemic and biologic variations that occur during microarray experiments. Because of the variations, merely using a fixed threshold to infer the significance might increase the proportion of false positives or false negatives. A better framework of significance includes statistics based on replicate array data for ranking genes according to their possibility of differential expression and selection cut-off value for rejecting the null-hypothesis that the gene is not differentially expressed (Leung and Cavalieri, 2003). Several different statistical methods can be used such as Student's t-test and its variants (Baldi and Long, 2001) , ANOVA (Kerr et

al., 2000), Bayesian method (Baldi and Long, 2001; Long et al., 2001) , and Mann-Whitney test (Wu, 2001) which take into account multiple comparisons.

2.2.5.4 Network-based methods

Exploratory data analysis does not require the incorporation of any prior knowledge of the process. It is a grouping technique aiming to find genes with similar expression profiles (behaving similarly) (Katagiri and Glazebrook, 2009b). Some commonly used methods include principal component analysis (PCA) (Raychaudhuri et al., 2000) or singular value decomposition (SVD) (Alter et al., 2000) for dimensionality reduction, as well as hierarchical clustering (Eisen et al., 1998), K-means clustering (Tavazoie et al., 1999) and self organizing maps (SOMs) (Tamayo et al., 1999) for clustering. There is no exploratory data analysis that will suit all situations. Different analysis or even different parameters of the same analysis can reveal unique aspects of the same data.

2.2.6 Advantages and disadvantages

DNA microarray is a powerful, mature, versatile, and easy-to-use genomic tool that can be applied to biomedical and clinical research. It has shown its usefulness in drug discovery e.g. in profiling transcriptional responses after different drug analogues (Elmouelhi et al., 2009), disease diagnosis e.g. in characterization of gene expression in B-cell malignancies (Alizadeh et al., 2000), disease characterization e.g. analyzing the autoimmune process characterizing child's progression toward type 1 diabetes (Elo et al., 2010), novel gene identification e.g. finding novel cytokine-induced genes in pancreatic beta-cells (Cardozo et al., 2001), and understanding complex biological systems e.g. carcinogen identification (Afshari et al., 1999). There are however several limitations related to microarray technology (Table 1). DNA microarrays detect changes in mRNA levels which are rapidly changeable in response to different stimuli and are also prone to rapid degradation. Messenger RNA levels do not always reflect protein concentrations and microarrays cannot detect the post-translational modifications or the function of the protein after that (Ewis et al., 2005), therefore differential RNA expression may not always lead to biological differences. Several replicate microarray measurements are required to obtain accurate results but the cost of extensive replicates is too high for many academic laboratories. General consensus is that at least three replicates have to be used when gene expression data from single specimens are being analyzed (Lee et al., 2000), although more replicates are necessary when studying for example clinically heterogeneous diseases. Although the research community has formed with great effort guidelines to standardize microarray experiments, comparison of different studies is still quite challenging. One of the most important problems that arose already during early microarray studies was incorrect annotation of probes on the various microarray platforms. For many cDNA platforms, sequencing of clones revealed that many of them were incorrect or contaminated (Halgren et al., 2001; Taylor et al., 2001). Closer examination of mammalian Affymetrix microarray revealed that greater than 19 % of the probes on each platform did not correspond to their appropriate mRNA reference sequence (Mecham et al., 2004). Several other studies about incorrect probe information or annotation of Affymetrix microarrays has been published (Dai et al., 2005; Harbig et al., 2005). These findings reveal that many of the conclusions derived from the earlier microarray studies could be significantly flawed. Major improvements have been made as more sequence information is created, validated, and annotated in high-quality data-bases. Improvements have been made in annotation and subsequent probe refinement. Fewer probes on commercial arrays will hybridize to multiple splice variants, show cross-hybridization to other genes in the same family and hybridize to non-specific probes (Yauk and Berndt, 2007). Interpreting microarray experiments is very taxing because of large data sets created

within the studies and the lack of easy-to-use bioinformatics tools. Existing statistical problems range from image analysis to pattern discovery and classification. Several different commercial and non-commercial bioinformatics tools have been developed during the years to help with interpretation of the results. Still after all the data analyses have been done, remains the question: do the results have real biological significance? It has been speculated that microarray technology will soon be replaced by next generation sequencing in which the transcripts are directly sequenced by low cost, high-throughput sequencing technologies (Wang et al., 2009). Though at the moment the technology is still quite expensive and in its relative infancy. Thus, until sequencing based methods become more cost-effective and easy to use microarrays will remain a desirable method for gene expression profiling for many researchers.

Table 1. Advantages and disadvantages of microarrays

ADVANTAGES	DISADVANTAGES
Powerful	Fast degradation of starting material
Highly developed	Not measuring the real biological function
Versatile	Technical variation
Easy-to-use	Problems in standardization
Many applications	Problems in validation
Accessibility	Problems in data analysis
Large amount of data obtainable	Problems in comparison between different experiments
Lots of users	Expensive

2.3 BLOOD VESSELS

Blood vessels are complex networks of hollow tubes that transport blood throughout the entire body. Blood vessels carry blood from the heart to all areas of the body. The blood travels from the heart via arteries to smaller arterioles, then to capillaries, to venules, to veins and back to the heart. Lymph vessels distribute lymph fluid back from the tissues to the circulatory system (Gray, 2003).

2.3.1 Structure and function

Circulatory network maintain cellular function, absorption of essential nutrients and removal of cellular and metabolic waste (Pugsley and Tabrizchi, 2000). The structure of vasculature varies and reflects distinct functional requirements at different locations. Arterial walls are thick because of constant pulsatile and high blood pressure. The thickness of arterial wall diminishes gradually as the vessels become smaller but the ratio of wall thickness to lumen diameter becomes greater. Veins are larger in diameter, have larger lumen and a thinner wall than corresponding arteries and they contain valves. Lymph vessels are thin walled and also valved structures. (Robbins et al., 2010; Vito and Dixon, 2003). The arteries are divided into three types based on their size and structural features: 1) large or elastic arteries, including the aorta and its large branches; 2) medium-sized or muscular arteries comprising other branches of the aorta; and 3) small arteries that deliver for the most part blood to the tissues.

2.3.1.1 Anatomy

The arterial wall (Fig 3A) is a layered structure with distinct sections known as the intima, media and adventitia. The innermost layer, called the tunica intima, is composed of a monolayer of endothelial cells called the

endothelium. The tunica intima helps to restrict the entry of substances into the vascular wall, control blood vessel diameter, and regulate coagulation. The middle layer is called the tunica media and is separated from the tunica intima by a dense elastic membrane called the internal elastic lamina. The tunica media is composed of a circular arrangement of smooth muscle cells (SMC), collagen, and elastic fibers; it composes the bulk of the wall of most arteries but in veins is thinner and contains fewer SMCs. Smooth muscle contains contractile elements that are responsible for contraction and relaxation (vasodilation). They also produce collagen and elastin. The tunica media imparts strength, elasticity, and contractile abilities to the vessel wall. Surrounding the tunica media is the tunica adventitia. The two layers are separated by the external elastic lamina. This outermost layer contains a matrix of collagen and elastic fibers that support fibroblasts, the cells that secrete the fibrous proteins collagen and elastin, nerves, and vasa vasorum, which are small blood vessels that supply the walls of large arteries and veins with oxygen and nutrients. Veins (Fig 3B) are large-calibre but thin-walled vessels with a poorly defined internal elastic membrane and tunica media not as well developed as that of arteries. Lymph vessels are lined by endothelial cells under which they have a thin layer of smooth muscle and adventitia that bind the lymph vessel to the surroundings (Borysenko and Beringer, cop. 1989; Robbins et al., 2010).

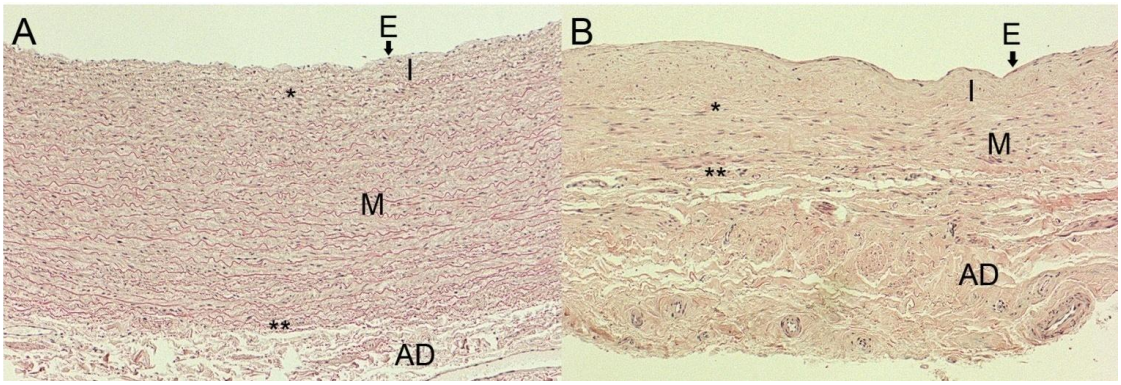


*Figure 3: Histological sections of normal human artery (A) and vein (B). Staining hematoxylin-eosin, magnification 40x E = endothelium, I = intima, M = media, A = adventitia, * = internal elastic lamina, ** = external elastic lamina.*

2.3.1.2 Physiology

Blood vessels do not actively transport blood because they have no appreciable peristalsis but arteries, and also veins to a degree can regulate their inner diameter by contraction of the muscular layer. This changes the blood flow to downstream organs and is determined by the autonomic nervous system and hormones. Oxygenated blood returning from the lungs, flows from the left ventricle of the heart into large network of arteries starting from larger arteries moving to low-resistance conducting vessels to small arteries and arterioles, which lower blood pressure and protect the capillaries. The arterial vascular system transitions to the venous system through a capillary network where the exchange of nutrients and waste products takes place between tissue and blood, a process that requires a very large surface area. The return of blood to the heart via the venous system begins with its movement into postcapillary venules which connect to form larger veins. They provide a volume buffer that acts as a capacitance for the vascular circuit. Lymph vessels act as a reservoir for plasma and other

substances including cells that leaked from the vascular system and transport lymph fluid back from the tissues to the circulatory system (Guyton and Hall, 2006).

2.3.1.3 Endothelial dysfunction

Endothelium is the monolayer covering the inner surface of blood vessels. Normal functions of endothelium include regulation of vascular tone and structure, mediation of coagulation, platelet adhesion and immune function. Endothelial dysfunction has been identified as a hallmark of vascular diseases and it is regarded as the early step in the development of atherosclerosis as well as being fundamental in maintaining vascular inflammation. Thus the integrity of the endothelial monolayer plays an important role in counteracting such inflammatory events (Deanfield et al., 2005). There are several mechanisms behind endothelial dysfunction, the most prevailing being the diminishing of nitric oxide (NO) and an increase in reactive oxygen species (ROS). Endothelial cells release NO in response to mechanical stress, causing vasodilatation which is impaired in vascular inflammation in part due to increased vascular oxidant stress. It has been shown to promote a pro-inflammatory and prothrombotic phenotype of the endothelium (Azuma et al., 1986; De Caterina et al., 1995). ROS contributes to endothelial dysfunction in several ways such as upregulation of adhesins and cytokines, reducing NO synthase activity and increasing NO breakdown, thereby reducing the bioactivity of NO (Deanfield et al., 2005). VEGFs in low physiological concentrations are endothelium and vasculoprotective because they induce constitutive NO production (Yla-Herttuala et al., 2007).

2.3.1.4 VEGFs

There are several factors that are involved in the regulation of the vascular system. The VEGF family members VEGF-A, -B, -C, -D and placental growth factor (PlGF) and their receptors VEGFR-1, -2 and -3 are important factors in vasculogenesis and angiogenesis (Fig 4). VEGF-A binds to VEGFR-1 and -2 as well as neuropilin-1 and -2. It induces proliferation, sprouting, migration and tube formation of endothelial cells (Ferrara et al., 2003). VEGF-B is a ligand for VEGFR-1 and Nrp-1 and its precise role *in vivo* is not known but it seems to induce myocardium specific angiogenesis and arteriogenesis. It might also have a role in cellular energy metabolism (Lahteenvuo et al., 2009). Binding of PlGF to its receptors, VEGFR-1 and Nrp-1, induces angiogenesis but its role is still controversial (Nagy et al., 2008). The unprocessed forms of VEGF-C and -D bind to and activate preferably VEGFR-3 and they have lymphangiogenic effects, but after proteolytic cleavage the binding affinity to the VEGFR-2 is notably increased (Achen et al., 1998) inducing mitogenesis, migration and survival of endothelial cells (Saharinen et al., 2004). The role of a novel member of the VEGF family, VEGF-D, has not yet been fully elucidated. The processed form of VEGF-D (VEGF-$D^{\Delta N\Delta C}$) has been shown to be an effective factor in inducing capillary enlargement and vascular permeability *in vivo* (Rissanen et al., 2003b). In human arteries, VEGF-D is mainly expressed in SMCs in large arteries and in macrophages in complicated lesions. VEGF-D has also been shown to have vascular protective features that participate in vascular maintenance (Rutanen et al., 2003). Recently found VEGF homologues VEGF-E, produced by Orf viruses, and VEGF-F, isolated from snake venom, bind only to VEGFR-2 and their role in vascular biology is still unclear (Ogawa et al., 1998; Yamazaki et al., 2003).

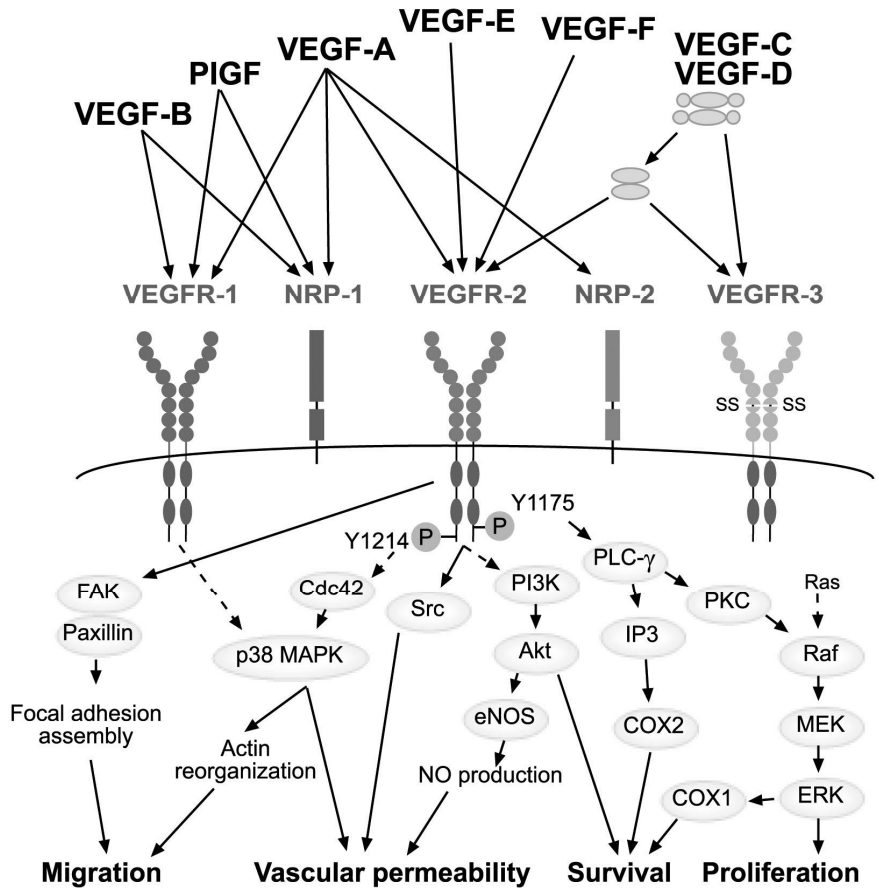


Figure 4. Schematic illustration of receptor binding specificity and VEGF family members and the VEGFR-2 signalling pathway modified from (Takahashi and Shibuya, 2005).

2.3.2 Diseases of blood vessels

Blood vessels play a huge role in virtually every medical condition. Diseases of the blood vessels are primarily the result of adverse changes in the vessel walls, such as hardening of the arteries, aneurysms, vasculitis, malformations, stroke, and varicose veins. A healthy circulation depends to a large extent not only on the condition of the blood-forming organs but on the pipelines through which blood flows. Blood vessels may become inflamed, as in the case of vasculitis, phlebitis, and varicose veins; or they may become clogged, especially the arteries, as a result of atherosclerosis (hardening of the arteries) or blood clots (thrombosis and embolism), which can prevent the blood from reaching a vital organ; or they may weaken resulting the dilation of the vessel wall (aneurysm), high blood pressure, or congenital defects (Robbins et al., 2010).

2.3.2.1 Atherosclerosis

Atherosclerosis is a disease which affects large and medium-sized arteries. Typical features of atherosclerosis are accumulation of intra- and extracellular lipids, foam cell formation, proliferation of SMCs and accumulation of

connective tissue. Atherosclerosis plays a major role in the development of myocardial infarction, stroke, claudication, gangrene and aneurysms. Epidemiological studies have revealed several important environmental and genetic risk factors associated with atherosclerosis such as age, male sex, high plasma low density lipoprotein (LDL) level, low plasma high density lipoprotein (HDL) level, high blood pressure, smoking and diabetes. Development of lesions is the pivotal factor in atherogenesis. Atherosclerosis is not simply an inevitable degenerative consequence of aging but rather a chronic inflammatory condition that can convert into an acute clinical event by plaque rupture and thrombosis (Lusis, 2000; Ross, 1999).

2.3.2.1.1 Pathogenesis of atherosclerosis

There have been several different hypotheses for the development of atherosclerosis. The most accepted theories for the pathogenesis of atherosclerosis are the lipid hypothesis (Steinberg et al., 1989), the monoclonal hypothesis (Benditt and Benditt, 1973; Schwartz et al., 1995), and the response-to-injury hypothesis (Ross, 1986). The lipid hypothesis underlines the importance of lipids, especially LDL, in the development of atherosclerosis (Steinberg et al., 1989). In the monoclonal hypothesis, the clonal expansion of SMC in developing plaques is considered significant (Schwartz et al., 1995). Response-to-injury hypothesis reviews atherosclerosis to be a chronic inflammatory response of the arterial wall initiated by some form of injury to the endothelium (Ross and Glomset, 1976). The endothelial dysfunction that results from the injury leads to compensatory responses that alter the normal homeostatic properties of the endothelium. The injuries increase the adhesion of blood monocytes, T-lymphocytes, and platelets as well as permeability (Ross, 1999). Monocytes and T-lymphocytes attach to specific adhesive glycoproteins that appear on the surface of the endothelial cells and migrate between the cells under the influence of growth-regulatory molecules and chemoattractants released both by the altered endothelium, its adherent leukocytes, and possibly by underlying SMCs. Migrating cells reach further beneath the arterial surface where the monocytes become macrophages, accumulate lipid, become foam cells, and together with the accompanying lymphocytes, become the fatty streak. (Ross, 1993). Fatty streak is the earliest form of atherosclerotic lesion (Stary, 1992). They precede intermediate lesions, which are composed of macrophages and SMC. They tend to form a fibrous cap that walls of the lesion from the lumen. The fibrous cap covers a mixture of leukocytes, lipid and depris, which form a necrotic core. These lesions expand at their shoulders by means of continued leukocyte adhesion and entry of adhesion molecules and growth factors. Lesions proceed to develop to more advanced, complex occlusive plaques that contain macrophages, SMCs, T-cells, atheromatous core and calcium (Fig 5). Complicated lesions occlude the artery and may be ruptured resulting in thrombus formation. The rupture usually occurs at sites of thinning of the fibrous cap that covers the advanced lesion. Thinning of the fibrous cap might be due to the continuing influx and activation of macrophages which release metalloproteinases and other proteolytic enzymes at these sites. These enzymes cause degradation of the matrix which can lead to haemorrhage from the lumen of the artery. Also, intraplaque angiogenesis often occurs in these regions which might make the plaque even more fragile (Lusis, 2000; Ross, 1993; Ross, 1999).

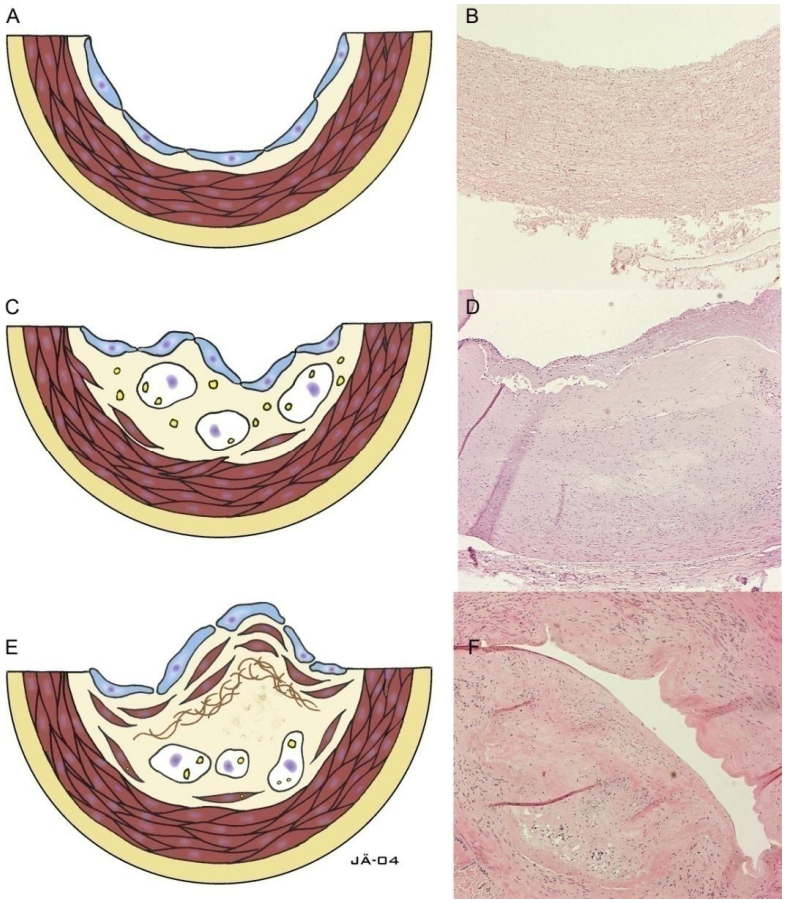


Figure 5. Development of atherosclerotic lesion. A) Normal artery with intact endothelial cell lining (upper cell layer) and organized medial layer composed of SMC. C) Medial SMCs migrate toward intima and start to proliferate. Monocytes migrate between endothelial cells to intima from the lumen and become activated. E) SMCs continue proliferation and synthesize ECM. Plaque now contains lipid debris from dying macrophages with necrotic compartments and inflammatory cells. B, D and F, histological sections of normal human artery, intermediate lesion and complicated lesion, respectively. Staining hematoxylin-eosin, magnification 40x.

2.3.2.1.2 Gene expression in atherosclerosis

Atherosclerotic lesions consist of different cell types which produce many proteins that are involved in atherogenesis. These proteins include lipoprotein receptors, growth factors, cytokines, matrix metalloproteinases (MMPs), and cell adhesion molecules. Macrophage scavenger receptors are membrane glycoproteins that are involved in internalisation of unmodified and modified LDL. They mediate accumulation of modified lipoproteins in macrophages and participate in foam cell formation in atherosclerotic lesions (Yla-Herttuala et al., 1991; Kodama et al., 1990). They are involved in cell adhesion and recognition of glycosylation end products, apoptotic cells and bacteria (Yamada et al., 1998). Growth factors can stimulate cell proliferation and act as chemoattractants. Platelet derived growth factors (PDGFs), fibroblast growth factors (FGFs), VEGFs and insulin like growth factor-1 (IGF-1) are involved in several important cellular processes in atherogenesis. They can

induce SMC proliferation and are generally expressed in normal arteries whereas they are upregulated in atherosclerotic lesions (Ross, 1993; Waltenberger, 1997). In chemotaxis, leukocytes move into the artery wall and SMC from the media to intima. Leukocyte chemotaxis can be induced by colony stimulating growth factors (CSFs) (Rosenfeld et al., 1992) and SMC chemotaxis by PDGF and IGF-1 (Gerszten et al., 2000). Chemokines are activators and attractants to leukocytes and their expression is induced by a number of atherogenic stimuli such as oxidized LDL (oxLDL), vascular injury, growth factors and cytokines (Gerszten et al., 2000). Monocyte chemoattractant protein-1 (MCP-1) is a chemokine expressed in macrophage-rich areas and SMCs in atherosclerotic lesions and is actively involved in the recruitment of new monocytes into lesions (Yla-Herttuala et al., 1991). Cellular adhesion molecules mediate the interaction between endothelium and blood cells via cell-cell or cell-matrix interactions. They can also function in cell migration, signalling, and other vascular responses. The endothelium expresses adhesion molecules like integrins and selectins that increase the adhesion of monocytes and T-lymphocytes to the endothelium (Price and Loscalzo, 1999). Vascular cell adhesion molecule (VCAM) (Cybulsky and Gimbrone, 1991), intercellular adhesion molecules (ICAMs) (Dustin et al., 1986) and platelet-endothelial cell molecule (PECAM) (DeLisser et al., 1994) can serve as ligands for integrins. Adhesion molecule expression can be regulated by different cytokines. Leukocyte adhesion is mediated by E-, L-, and P-selectins which interact with ligands on leukocytes (Bevilacqua et al., 1985). Cytokines like interleukin 1 (IL-1) and interferon γ (INFγ) modulate inflammatory processes (Ross, 1993). Peroxisome proliferators-activated receptors (PPARs) are nuclear receptor-type transcription factors that modulate inflammation and influence lipid metabolism such as cholesterol efflux and foam cell formation (Schoonjans et al., 1996). Nuclear factor κB (NF-κB) is a transcription factor associated with oxidative stress and inflammation. NF-κB regulates the expression of many important proatherogenic genes including VCAM-1 and ICAM-1(Collins and Cybulsky, 2001). Macrophages, SMCs, and T-cells in atherosclerotic lesions undergo apoptosis. Apoptosis is controlled by a number of different genes or gene families for example B-cell lymphoma-2 (Bcl-2), caspases, and NO (Rossig et al., 2001). MMPs degrade ECM components which are essential for matrix remodelling, infiltration of inflammatory cells, plaque rupture, and angiogenesis (George, 1998). VEGF-D has been shown to be present in atherosclerotic arteries. Its expression in early lesions is abundant but in advanced lesions the expression is diminished and mainly localized in macrophages (Rutanen et al., 2003). It is not known if the role of VEGF-D in the artery is protective or pro-atherogenic.

2.3.2.2 Intracranial aneurysms

An aneurysm is an abnormal widening or ballooning of a portion of an artery due to weakness in the wall of the blood vessel. It is not clear what causes aneurysms. Some aneurysms are present at birth and defects in some of the parts of the artery wall may be responsible. The aneurysm can be located commonly at the aorta, the brain (cerebral aneurysm), in the leg behind the knee (popliteal artery aneurysm), intestine (mesenteric artery aneurysm), and an artery in the spleen (Splenic artery aneurysm). Intracranial aneurysm commonly arises at a branch site on a parent artery. Aneurysms are usually discovered after they rupture, producing subarachnoid haemorrhage (SAH). The most common type of aneurysm is saccular (berry) aneurysm. Other rare types of aneurysms are arteriosclerotic (fusiform), inflammatory (mycotic), traumatic, and dissecting. This study focuses only in sIAs. Saccular aneurysms account for 95 % of aneurysms that rupture. They occur at bifurcations of the major cerebral arteries, the most common sites being the junction of the carotid and posterior communicating arteries, the anterior communicating artery, and the major bifurcation of the middle cerebral artery in the Sylvian fissure (Fig 6) (Gasparotti and Liserre, 2005). Saccular aneurysms consist of outpouching of deficient

collagenized tunica media that bulges through a localized defect in the internal elastic lamina. The tunica media and the elastic lamina terminate at the aneurysm neck and the aneurysm wall is very thin, consisting only of intima and adventitia (Stehbens et al., 1989). About two percent of the general population have an intracranial aneurysm (Rinkel et al., 1998) and the risk of rupture is estimated to be 1-2 % per year for asymptomatic lesions (Wiebers et al., 1987) which increases with age, size of the aneurysm, and the presence of symptoms. The incidence of SAH is the highest in the world in Finland, especially in Eastern Finland and also in Japan (de Rooij et al., 2007; Fogelholm, 1981). Symptoms from aneurysms can be caused in three ways, by rupture and SAH, expansion of the aneurysm, or compression of adjacent structures or vascular compromise of circulation distal to the aneurysm (Gilbert and Sergott, 2006). Most aneurysms are symptom free until the first leakage. That is why most of the sIAs are found incidentally when the brain is scanned for diagnostic purposes or because of the first SAH. In special anatomic locations, like posterior communicating artery, sIAs can press surrounding cranial nerves thus inflicting neurological deficiency symptoms (Friedman et al., 2001). Exceptional giant aneurysms (> 2 cm) often partly thrombose and may cause ischemic symptoms by sending emboli in the distal vessel network (Krings and Choi, 2010). Mortality from SAH is around 35-50 % despite modern intensive care and neurosurgical therapy. Approximately 10 % of patients die acutely of their SAH (Hop et al., 1997).

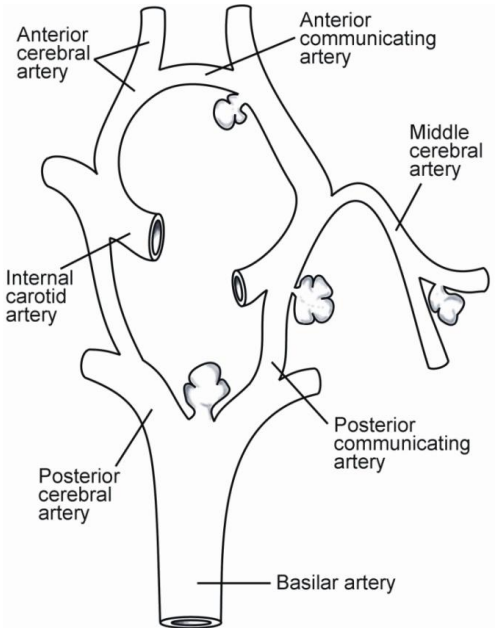


Figure 6. Common sites of saccular aneurysms in the Circle of Willis modified from Robbins et al. (Robbins et al., 2010).

2.3.2.2.1 Pathogenesis of intracranial aneurysms

The etiologic basis of sIAs is unknown. Three different hypotheses exist regarding the pathogenesis of the aneurysms: 1) congenital weakness of the muscular layer, 2) degenerative alternations of inner elastic membrane or 3) a combination of both (Gasparotti and Liserre, 2005). Although the majority of cases occur sporadically, genetic factors may be important in their pathogenesis. This is suggested by the fact that the first-degree relatives of patients with the disorder are seven times more at risk than the general population (Ronkainen et al., 1997). Cigarette smoking and hypertension are accepted predisposing factors for the development of sIAs

(Robbins et al., 2010). Other risk factors are heavy alcohol consumption and female gender (Juvela et al., 1993). The majority of carriers of sIAs are asymptomatic and it seems that most of these aneurysms do not rupture during their lifetime (Juvela et al., 2008). Mechanisms of how these factors predispose to the formation or rupture of the intracranial wall are not known. The degree to which each contributes to an individual's aneurysm is likely to be patient-specific. Identification of new genes important in sIA pathogenesis would provide new insights into the primary determinants of this disease, and might result in new opportunities for early diagnosis in the preclinical setting. This would also assist in the understanding of disease pathogenesis whilst allowing clinicians the opportunity to modify treatment based risk.

2.3.2.2.2 Gene expression in intracranial aneurysms

The cellular and molecular mechanisms of the formation and rupture of sIA are not known but the contribution of complement activation, infiltration of inflammatory cells, intimal hyperplasia, proteolysis, atherosclerosis, and angiogenesis have been suggested (Chyatte et al., 1999; Frosen et al., 2006 Mar; Frosen et al., 2004; Skirgaudas et al., 1996; Tulamo et al., 2006; Tulamo et al., 2010; Tulamo et al., 2010) The role of MMPs in the pathogenesis of sIA has been studied extensively (Bruno et al., 1998)(Aoki et al., 2007a). The degradation of ECM is a hallmark of a sIA. MMPs degrade most of the arterial ECM components, hence being largely involved in remodelling of ECM. Tissue inhibitors of MMPs (TIMPs) regulate the proteinase activity of MMPs via forming complexes and are considered the most potent inhibitors of MMPs. The imbalance of MMPs and TIMPs has been suggested to be one of the key factors in the progression and rupture of sIAs (Aoki et al., 2007b; Jin et al., 2007). Reduction of the number of SMCs is a distinctive feature of sIA. Apoptosis in medial SMCs has been shown in sIA which leads to further ECM degradation (Hara et al., 1998; Kondo et al., 1998). Inflammation might have a significant role in the development and rupture of aneurysms. Presence of complement C3c and C9, immunoglobulin IgG and IgM, macrophages and T lymphocytes and complement activation have been reported (Chyatte et al., 1999; Tulamo et al., 2006). Leukocyte infiltration has been associated with the rupture of sIA (Frosen et al., 2004). It has been speculated that the inflammatory process elicited by activated endothelial cells and recruited monocytes/macrophages is one of the major pathological events of intracranial aneurysm development (Kataoka and Aoki, 2010). Expression of MCP-1 has been suggested to play a role in sIA formation as a major chemoattractant for monocytes/macrophages (Aoki et al., 2009). The upregulation of adhesion molecule VCAM-1 expression has been shown in sIAs (Chyatte et al., 1999), but the role of it and other adhesion molecules in sIA development is still unclear. The presence of endothelial dysfunction was supported by studies that analyzed inflammatory cytokines in sIA. Tumor necrosis factor α (TNF-α) is a potent proinflammatory cytokine that triggers endothelial dysfunction with increased monocyte recruitment (Libby et al., 1995). Increased expression on TNF-α has been seen in sIAs (Jayaraman et al., 2005 Sep) but its role in enlargement and rupture of aneurysm is still unclear. NF-κB is a family of transcriptional factors regulating the expression of a variety of genes in response to inflammatory mediators (Pahl, 1999). Activation of NF-κB has been shown in sIA especially in intima (Aoki et al., 2007c), and it has been hypothesized to be caused by excessive hemodynamic stress and inflammatory cytokines.

3 Aims of the study

1) To evaluate the usefulness of microarrays in studying molecular biology of complex diseases

2) To elucidate molecular biology of VEGF-$D^{\Delta N \Delta C}$ and its possible role in endothelial cells

3) To identify reasons and factors behind rupture of intracranial aneurysms

4 Materials and methods

4.1 RECOMBINANT PROTEINS AND ADENOVIRAL VECTORS

Recombinant human (r) VEGF-A_{165} was obtained from R&D Systems (Minneapolis, MN). For rVEGF-$D^{\Delta N\Delta C}$ production the DNA sequences encoding human tissue plasminogen activator (tPA), signal peptide (amino acids 1-21), human VEGF-D mature form (amino acids 93-201) and a polyhistidine tag were cloned in frame into pDonr201 (Invitrogen, Carlsbad, CA) vector and subcloned using BVboost system (Laitinen et al., 2005) LR reaction into pBVboostFGII expression vector. A recombinant baculovirus was produced and the rVEGF-$D^{\Delta N\Delta C}$ protein was expressed and purified (Toivanen et al., 2009). AdVEGF-$D^{\Delta N\Delta C}$ and AdVEGF-A_{165} are serotype 5 adenoviruses that contain human VEGF-$D^{\Delta N\Delta C}$ or human VEGF-A_{165} cDNAs, respectively, driven by a cytomegalovirus (CMV) promoter. The AdCMV control virus contains the CMV promoter and the poly (A) tail. Adenoviruses were produced in 293 cells and the virus was concentrated and purified via two CsCl gradients, dialyzed, and stored at -20 °C (Kossila et al., 2002).

4.2 CELL CULTURE

Collagenase treatment was used to isolate human endothelial cells (HUVECs) from the interior of umbilical veins. The cells were harvested from the cord veins with the help of Phosphate Buffered Saline (PBS; GibcoBRL, Grand Island, NY) which was perfused to the vein. The umbilical cord, ligated with both ends and containing PBS, was incubated at +37 °C. After incubation, the collagenase solution containing the endothelial cells was flushed from the cords by perfusion of PBS and pelleted with centrifugation (Jaffe et al., 1973). HUVECs were grown in Endothelial Cell Growth medium (EGM; Cambrex Biosciences, East Rutherford, NJ) on cell culture flasks coated with 10 μg/ml fibronectin (Sigma, St. Louis, MO) and 0.05% gelatin (Sigma) in PBS. Cell culture studies with HUVECs were done at passages 3-5. Isolation of HUVECs from umbilical veins was approved by the Ethics Committee of the Kuopio University Hospital (Kuopio, Finland).

4.3 CELL SURVIVAL ASSAY

HUVECs were plated at the density of 15 000 cells/cm^2 and allowed to attach for 24 h. Cells were washed with Hanks' Balanced Salt Solution (HBSS; Gibco BRL) and MCDB131 medium (Sigma) was added to the wells. HUVECs were starved for 16 h and treated with rVEGF-$D^{\Delta N\Delta C}$ (100 ng/ml) in the presence of varying concentrations of NRP antagonist. The peptide has been produced to inhibit the binding of VEGF-A_{165} to NRP1 but it blocks NRP2-mediated responses as well (Jia et al., 2006). Relative amount of living cells was measured with MTS-reagent (Promega, Madison, WI).

4.4 ADENOVIRAL GENE TRANSFER

Cells were plated as described above. Transductions with AdVEGF-$D^{\Delta N\Delta C}$, AdVEGF-A_{165} and AdCMV were performed in serum-free conditions at the multiplicity of infection (MOI) 50. Normal cell culture supplements were added after an hour and cell culture was continued for an additional 12 h. Cells were washed with HBSS and fresh cell culture medium was added.

4.5 EXPERIMENTAL SETTING FOR HUVECs

The experiment was done with HUVECs pooled from three separate donors. Adenoviral transduction was performed with AdVEGF-$D^{\Delta N\Delta C}$ and AdCMV as described above. Samples were done in triplicates. Cells were harvested 36 h or 72 h after adenoviral transduction.

4.6 PATIENTS AND INTRACRANIAL ANEURYSM SAMPLES

Tissue samples from the aneurysm walls were obtained from the Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland. Fundi of 25 ruptured and 20 unruptured sIAs were resected during microsurgical clipping of the aneurysm neck (Table 2) (Frosen et al., 2006 Mar; Frosen et al., 2004; Tulamo et al., 2006; Tulamo et al., 2010; Tulamo et al., 2010). All of the subjects were of Finnish ethnicity. The samples were immediately snap frozen in liquid nitrogen, and stored in the Helsinki Neurosurgery sIA Tissue Bank. The medical records of the 45 sIA patients were collected (Table 2). The study was approved by the Ethical Committee of Neurology, Ophthalmology, Otorhinolaryngology, and Neurosurgery of the Helsinki University Central Hospital.

Table 2. Patients, sIA samples and methods

Sample No.	Sex	Age Years	Location of sIA	Rupture of sIA*	Time from Rupture (h)	Micro-array**	qRT-PCR ***	IHC ****
1	F	60	MCA	no		+	-	-
2	F	64	ICA	no		+	-	-
3	M	47	MCA	no		+	-	-
4	F	37	MCA	no		+	-	-
5	M	42	MCA	no		+	+	-
6	F	62	MCA	no		+	+	-
7	M	56	PCoA	no		+	+	-
8	F	65	MCA	no		+	+	-
9	F	56	MCA	no		-	+	-
10	M	42	MCA	no		-	+	+
11	F	59	MCA	no		-	+	-
12	M	28	ACoA	no		-	-	+
13	F	48	MCA	no		-	-	+
14	F	55	MCA	no		-	-	+
15	F	54	MCA	no		-	-	+
16	M	37	ACoA	no		-	-	+
17	F	57	DACA	no		-	-	+
18	M	53	MCA	no		-	-	+
19	F	54	MCA	no		-	-	+
20	F	50	MCA	no		-	-	+
21	F	54	MCA	yes	16	+	-	-
22	F	46	ACoA	yes	96	+	-	-
23	M	58	MCA	yes	24	+	+	-
24	F	71	ACoA	yes	216	+	+	-
25	F	52	ICA	yes	168	+	+	-
26	F	32	MCA	yes	3	+	+	-
27	F	38	MCA	yes	2.6	+	+	-
28	M	73	MCA	yes	3.6	+	+	-
29	F	69	MCA	yes	6.7	+	+	-
30	F	53	MCA	yes	NA	+	+	-
31	M	70	MCA	yes	14	+	+	+
32	F	57	PCoA	yes	6.4	-	+	-
33	F	58	MCA	yes	12	-	+	-
34	F	44	MCA	yes	11	-	+	-
35	F	53	MCA	yes	24	-	+	+
36	F	47	ACoA	yes	5.2	-	+	-
37	M	41	ACoA	yes	9.1	-	+	-
38	F	62	PCoA	yes	72	-	+	-
39	M	84	ACoA	yes	360	-	-	+
40	M	58	ICA	yes	3.75	-	-	+
41	F	64	ACoA	yes	11	-	-	+
42	F	71	MCA	yes	72	-	-	+
43	F	46	PCoA	yes	48	-	-	+
44	F	36	MCA	yes	24	-	-	+
45	F	72	MCA	yes	4	-	-	+

F = female; M = male; MCA = middle cerebral artery; PComA = posterior communicating artery, AComA = anterior communicating artery; ICA = internal carotid artery; DACA = distal anterior cerebral artery; NA = not available; *aneurysm unruptured no or ruptured yes; **microarray yes + or no -; ***quantitative real time PCR yes + or no -; ****immunohistochemistry (IHC) yes + or no -

4.7 ISOLATION OF mRNA AND MICROARRAY HYBRIDIZATION

Total RNA was extracted with Trizol Reagent (Invitrogen) according to the manufacturer's instructions. The amounts and purity of total RNAs were measured with NanoDrop ND-1000 Spectrophotometer (NanoDrop Technologies Inc, Wilmington, DE). The probes for gene expression analysis were made according to the Affymetrix protocol. From HUVECs, five micrograms and from intracranial aneurysms, hundred nanograms of total RNA was first reverse transcribed to double stranded cDNA using a T7-oligo(dT) promoter primer in the first-strand cDNA synthesis reaction. Following RNase H-mediated second-strand cDNA synthesis, the double-stranded cDNA was purified and it served as a template in the subsequent *in vitro* transcription (IVT) reaction. The IVT reaction was carried out in the presence of T7 RNA polymerase and a biotinylated ribonucleotide mix for complementary RNA (cRNA) amplification and biotin labelling. For aneurysms, Affymetrix two-cycle amplification protocol was used because of the smaller amount of starting total RNA therefore an additional cycle of cDNA synthesis and IVT amplification was done to obtain sufficient amounts of labelled cRNA target for analysis with arrays. The biotinylated cRNA targets were cleaned up, fragmented, and hybridized for 16 h to Human Genome U133 Plus 2.0 GeneChips (Affymetrix, Santa Clara, CA). The chips were stained with streptavidin phycoerythrin conjugate, washed (Affymetrix Fluidics Station 400) and scanned (Affymetrix GeneChip Scanner 3000) according to manufacturer's instructions (Fig 7).

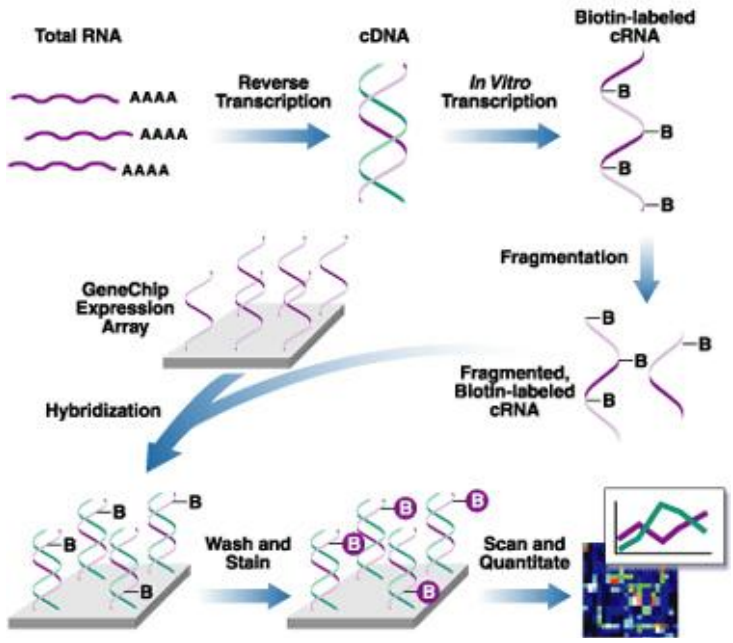


Figure 7. Schematic illustration of Affymetrix standard eukaryotic gene expression assay from www.affymetrix.com.

4.8 MICROARRAY DATA ANALYSIS

For HUVECs, data analysis was performed with dChip1.3 which uses a probe-sensitivity index to capture the response of a specific probe pair and calculates model-based expression indexes (Li and Wong, 2001).

Transcripts up- or downregulated by 1.5-fold (false discovery rate (FDR) 0% and $p < 0.05$) were analyzed further with NetAffx software and OMIM. For aneurysms microarray analyses were performed with R statistical software version 2.9.1 (R Dev Core Team, 2009) and Bioconductor version 2.4.1 (Gentleman R. C. et al., 2004). Data import was done using Affy package version 1.22 (Gautier et al., 2004) using BrainArray CustomCDF version 12 custom Chip Description File (CDF) for probe set matching and gene annotations (Dai et al., 2005; Sandberg and Larsson, 2007). There were 17788 distinct genes defined by the custom CDF. To normalize expression values between arrays and to generate a single expression measure for each gene from individual probes robust multi-array average algorithm was used (Irizarry et al., 2003). Non-specific filtering was applied to filter out less informative probe sets not linked to genes and probe sets with small variance across samples (50% of probe sets with the least variation). The differentially expressed genes between sample groups were detected with Linear Models for Microarray Data version 2.18.3 analysis package (Smyth, 2004) using fitting of linear models and applying empirical Bayes variance smoothing to each probe set. Due to anticipated large biological gene specific variation between individuals, a robust MM-estimator was applied, which is not as sensitive to outliers as least squares estimation. Benjamini & Hochberg FDR (Benjamini and Hochberg, 1995) was used to adjust for multiple testing and adjusted $P < 0.05$ was considered significant.

4.9 FUNCTIONAL ANALYSIS OF DIFFERENTIALLY EXPRESSED GENES

An overrepresentation analysis (aneurysms only) was performed for the up- and downregulated gene lists separately. Gene Ontology terms and KEGG pathways, GOstats R package version 2.1 (Falcon and Gentleman, 2007) and DAVID (Dennis et al., 2003; Huang da et al., 2009) bioinformatics resource was used for this enrichment analysis. All of the distinct 17788 genes in the array were utilized as a background gene set. A conditional Gene Ontology analysis strategy was employed to avoid reporting redundant ontologies which announces only the most specific Gene Ontology terms in the hierarchy that are statistically overrepresented in the differentially expressed gene sets (Falcon and Gentleman, 2007). Benjamini & Hochberg FDR (Benjamini and Hochberg, 1995) was used to adjust for multiple testing and adjusted $P < 0.05$ was considered significant. To assess the similarity of differentially expressed gene sets to genes genetically associated to different diseases and disease classes The Database for Annotation, Visualization and Integrated Discovery program was applied (Dennis et al., 2003) using Genetic Association Database as the data source for disease association. In the ruptured sIA wall samples, the time elapsed from the rupture to the resection of the sample may affect the gene expression levels. The levels were compared between the early (2.6h - 14h) and the delayed (24h - 216h) time groups. The correlation was calculated between the elapsed time and the expression level of each gene. In both tests the p-values were adjusted for multiple testing correction with Benjanimi & Hochberg FDR (Smyth, 2004) and corrected p-values < 0.05 were considered significant. Kruskal's non-metric multidimensional scaling method implemented in MASS R package (Venables and Ripley, 2002) was used to arrange each sample according to expression level differences of all genes between samples, and clustering according to the elapsed time was visually assessed.

4.10 ANIMAL EXPERIMENTS

In the study LDLR$^{-/-}$ApoB$^{100/100}$ mice fed with standard chow diet were used. All animal experiments were approved by the Experimental Animal Committee of the University of Kuopio (Kuopio, Finland). Fifty microlitres of AdVEGF-D$^{\Delta N\Delta C}$ or AdCMV control virus ($1x10^{11}$ viral particles) were injected in hind limb skeletal muscles (musculus caput gastrocnemii) (n=4, both hind limbs of each animal transduced with the same virus).

On day 5, gene transfer animals were sacrificed by CO_2 inhalation and transduced muscles were snap frozen in liquid nitrogen (Kholova et al., 2007). Half of each sample was used for total RNA extraction with Trizol Reagent (Invitrogen) and the other half was used for protein extraction with T-PER tissue protein extraction reagent (Pierce Biotechnology) The total tissue homogenates from AdCMV and AdVEGF-$D^{\Delta N\Delta C}$ -transduced muscles were used to measure the VEGF-$D^{\Delta N\Delta C}$ expression levels with VEGF-D ELISA.

4.11 VEGF-D ELISA

The expression levels of VEGF-$D^{\Delta N\Delta C}$ protein in conditioned media of HUVECs or in total tissue homogenate of mouse hind limb skeletal muscles were measured with Human Quantikine VEGF-D ELISA (R&D Systems) according to the manufacturer's instructions.

4.12 QUANTITATIVE REAL-TIME PCR

One microgram (HUVECs) or 500 nanograms (aneurysms) of total RNA was reverse transcribed into cDNA using random hexamers (Promega) and M-MuLV reverse transcriptase (MBI Fermentas, Hanover, MD). Quantitative measurements of mRNA levels were done using the Assays-on-Demand gene expression products (Table 3) (Applied Biosystems, Foster City, CA) with the ABI PRISM 7700 Sequence Detection System (Applied Biosystems). Each real-time RT-PCR reaction contained 10 ng of cDNA sample, 1x TaqMan Master Mix (Applied Biosystems) and 1x gene expression product target (Applied Biosystems) in the final volume of 23 μl. Measurements were done in duplicates. Amplification of 18S ribosomal RNA was used as an endogenous control to standardize the amount of RNA in each sample.

Table 3. Genes for the quantative RT-PCR

Accession	Gene	Assay ID
BE622627	Phosphoinositide-3-kinase, regulatory subunit 3 (p55, gamma)	Hs01103591_m1
NM_002646	Phosphoinositide-3-kinase, class 2, beta polypeptide (PIK3C2B)	Hs00153248_m1
AF022375	Vascular endothelial growth factor-A (VEGF-A)	Hs00173626_m1/Hs00900055_m1
NM_003155	Stanniocalcin 1 (STC1)	Hs00174970_m1
NM_018534	Neuropilin 2 (NRP2)	Hs00187290_m1
NM_009505	Vascular endothelial growth factor-A (VEGF-A)	Mm00437306_m1
AF099098	Stanniocalcin 1 (STC1)	Mm00436798_m1
NM_009285	Neuropilin 2 (NRP2)	Mm00803099_m1
NM_008969	Prostaglandin-endoperoxide synthase 1 (COX1)	Mm00477214_m1
NM_011198	Prostaglandin-endoperoxide synthase 2 (COX2)	Mm00478374_m1
NM_000610	CD44 molecule	Hs00153304_m1
NM_003246	Thrombospondin 1 (THBS1)	Hs00170236_m
NM_001065	Tumor necrosis factor receptor superfamily, member 1A (TNFRSF1A)	Hs01042313_m1
NM_001066	Tumor necrosis factor receptor superfamily, member 1B (TNFRSF1B)	Hs00153550_m1

4.13 SDS-PAGE ELECTROPHORESIS AND WESTERN BLOT

Following AdVEGF-$D^{\Delta N\Delta C}$ and AdCMV transductions, conditioned media was collected 36 and 72 h post-transduction and used for the analysis of VEGF-$D^{\Delta N\Delta C}$ and STC1 proteins. For other analyses transduced or rVEGF-$D^{\Delta N\Delta C}$ -stimulated cells were treated with lysis buffer [50 mM Tris, pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% Triton X-100, 0.5% sodium deoxycholate, 0.1% SDS, 10% glycerol, 1 mM sodium orthovanadate (Na_3VO_4, Sigma), with protease inhibitors (Complete Mini proteinase inhibitor cocktail tablets, Roche, Basel, Switzerland)]. From each sample equal amounts of total protein (30 μg) were used for analysis on SDS-PAGE and Western Blot. Primary antibodies used for the immunodetection are shown in Table 3. Horseradish peroxidase (HRP)-conjugated secondary antibodies were purchased from Pierce. Antigen-antibody complexes were detected either by chemiluminescence (SuperSignal West Dura Extended Duration Substrate, Pierce) and exposed to high performance chemiluminescence film (Amersham Biosciences) or ECL Plus detection system (GE Healthcare, Buckinghamshire, UK) and detected with Typhoon 9400 (GE Healthcare) scanner.

4.14 IMMUNOHISTOCHEMICAL STAININGS

Immunohistochemical stainings were performed with the avidin-biotin-HRP system (Vector Laboratories) using the 3′-5′-diaminobenzidine (DAB, Zymed) color subsrate from 4μm thick frozen sections of sIA samples of selected proteins. The primary antibodies used for immunohistochemistry are listed in Table 4. All histological quantifications were performed blinded for the rupture status. The percentage of positively stained area was analyzed semi-quantitatively (Rutanen et al., 2003).

Table 4. Antibodies used in Western blot and immunohistochemistry

Antibody	Specificity	Code/ Clone	Species	Ig isotype	Dilution	Company
VEGF-D	VEGF-D	78923	mAb mouse anti-human	IgG_1	1:1000	R&D
p-eNOS	phospho eNOS	9571	pAb rabbit		1:1000	Cell Signaling
eNOS	eNOS	Type III	mAb mouse	IgG_1	1:4000	Transduction Laboratories
VEGF-A	VEGF-A	sc-7269	mAb mouse anti-human	IgG_{2a}	1:500	Santa Cruz
STC1	STC1	sc-30183	pAb rabbit anti-human	IgG	1:1000	Santa Cruz
NRP2	NRP2	257103	mAb mouse anti-human	IgG_{2a}	1:1000	R&D
β-actin	β-actin	4967	pAb rabbit anti-human		1:1000	Cell Signaling
αSMA	α-smooth muscle actin	1A4	mAb mouse anti-human	IgG_{2a}	1:300	Sigma
CD31/ PECAM1	endothelium	JC70A	mAb mouse anti-human	$IgG_{1,\kappa}$	1:50	DAKO
CD68	macrophages	KP1	mAb mouse anti-human	$IgG_{1,\kappa}$	1:250	DAKO
CD44	lymphocytes, T- and B-cells, monocytes, granulocytes, erythrocytes, epithelial cells, mast cells	DF1485	mAb mouse anti-human	$IgG_{1,\kappa}$	1:100	DAKO
CD 36	CD36	FA6-152	mAb mouse anti-human	IgG_1	1:100	Abcam
ICAM1	ICAM1	BBIG-I1 (11C81)	mAb mouse anti-human	IgG_1	1:100	R&D

mAb = monoclonal antibody, pAb = polyclonal antibody

4.15 STATISTICAL ANALYSIS

Results are expressed as means ± SD and analyzed for the statistical significance using One-way ANOVA (HUVEC data), Dunnett's multiple comparison test (HUVEC data) and Welch t-test (aneurysm data). $P < 0.05$ was used to define a significant difference between groups.

5 Results

5.1 GENE EXPRESSION STUDY WITH VEGF-D$^{\Delta N\Delta C}$

The role and regulation of VEGF-D$^{\Delta N\Delta C}$ in the vascular system has not been fully elucidated. Studying the function of VEGF-D$^{\Delta N\Delta C}$ in molecular level might help us to understand the mechanism. To clarify the target genes of VEGF-D$^{\Delta N\Delta C}$ in endothelial cells gene expression analysis was done with Affymetrix Human Genome U133 Plus 2.0 GeneChips. HUVECs treated with AdVEGF-D$^{\Delta N\Delta C}$ and AdCMV control virus were harvested 36 h and 72 h post-transduction. Data analysis was performed using dCHIP1.3 software. The criteria for the genes to be further analyzed were: up- or downregulation by 1.5-fold ($p < 0.05$) and FDR 0 %. With this criteria the expression of 673 genes was significantly altered at 36 h (219 up- and 454 downregulated) and at 72 h the expression of 256 genes was altered (148 up- and 108 downregulated). The significantly up- and downregulated genes are presented in Annex 1. VEGFR-2 downstream signalling factors leading to protective effect against vascular damage together with angiogenesis-related growth factors and NRP2 were mostly upregulated at 36 h time point. After 72 hours the change in the expression of most of the genes in question was lost.

The changes of VEGFR-2 downstream signalling factors from GeneChip analysis are shown in Figure 8 and 9A. The activation of VEGFR-2 intracellular signalling cascade was evident 36 h after AdVEGF-D$^{\Delta N\Delta C}$ -transduction, but no changes in the expression level of VEGFR-2 downstream signalling factors were detected at 72 h (data not shown).

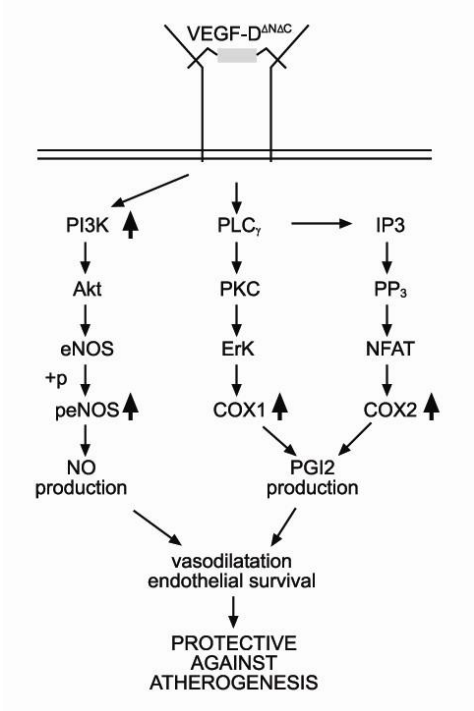


Figure 8. Downsteam signalling of VEGFR-2. Upregulation of several genes was detected (indicated as arrow). Binding of VEGF- D$^{\Delta N\Delta C}$ to VEGFR-2 activates three different pathways leading to upregulation of NO and PGI$_2$ production.

To verify the findings, quantitative measurements of mRNA levels were done using qRT-PCR. The enhanced expression of COX1, VEGF-A, STC1 and NRP2 at 36 h was also confirmed with qRT-PCR from AdVEGF-$D^{\Delta N\Delta C}$ and AdCMV-transduced HUVECs (Fig 9C). Significant change in endothelial NO synthase (eNOS) gene expression was not seen but increased phosphorylation of eNOS, the crucial step in eNOS function, was seen in the protein level measurements from HUVEC extract at 36 h time point with Western Blot. After 72 h the difference in phosphorylation was gone (Fig 9B). The correlation of the gene expression between GeneChip analysis (Fig 9A) and qRT-PCR (Fig 9C) was very good.

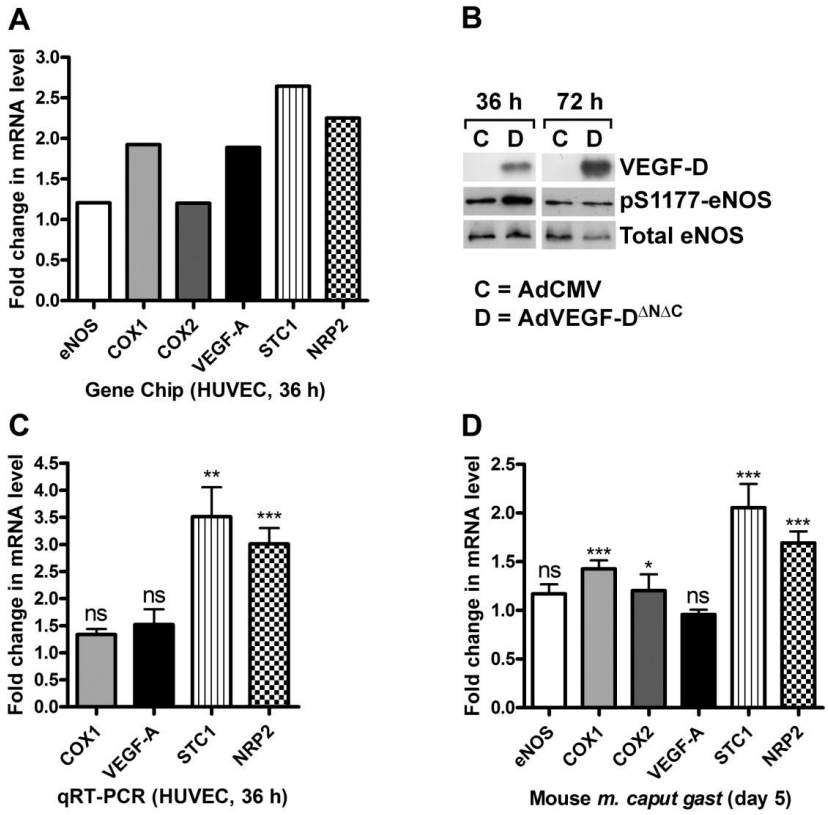


*Figure 9. A) Genes from GeneChips 36 h post-transduction in HUVECs. The data is presented as mean ±SD. B) Target protein secretion from the AdVEGF-$D^{\Delta N\Delta C}$ –transduced HUVECs confirmed by Western Blot 36 h and 72 h post-transduction. Increased phosphorylation of eNOS was seen in AdVEGF-$D^{\Delta N\Delta C}$ –transduced cells 36 h after gene delivery (total eNOS was used as a loading control) showing the activation of HUVECs by VEGF-$D^{\Delta N\Delta C}$. C) AdVEGF-$D^{\Delta N\Delta C}$ –induced fold changes in COX1, VEGF-A, STC1 and NRP2 mRNA levels analysed with qRT-PCR. D) In vivo confirmation of specific genes in mouse skeletal muscle. For all experiments *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.005$, Dunnett's multiple comparison test.*

For *in vivo* confirmations, mouse hind limb skeletal muscles (m. caput gastrognemius) were transduced with AdVEGF-$D^{\Delta N\Delta C}$ and AdCMV control virus. This model has been shown to have angiogenic effects from day 4 until day 28 after AdVEGF-$D^{\Delta N\Delta C}$ gene delivery (Kholova et al., 2007). Animals were sacrificed at day 5 and the transgene expression was analyzed by VEGF-D ELISA. COX1, COX2, STC1 and NRP2 were shown to be up-regulated at mRNA level in mouse skeletal muscle (Fig 9D).

To further confirm that STC1, VEGF-A, and NRP2 expression was altered also at the protein level, HUVECs were stimulated for 48 h with different concentrations of rVEGF-$D^{\Delta N\Delta C}$. Western blot analysis showed a dose-dependent increase in STC1 protein expression (Fig 10A). In addition, maximal upregulation for VEGF-A was achieved with 250 ng/ml and for NRP2 already with 100 ng/ml of rVEGF-$D^{\Delta N\Delta C}$ (Fig 10A).

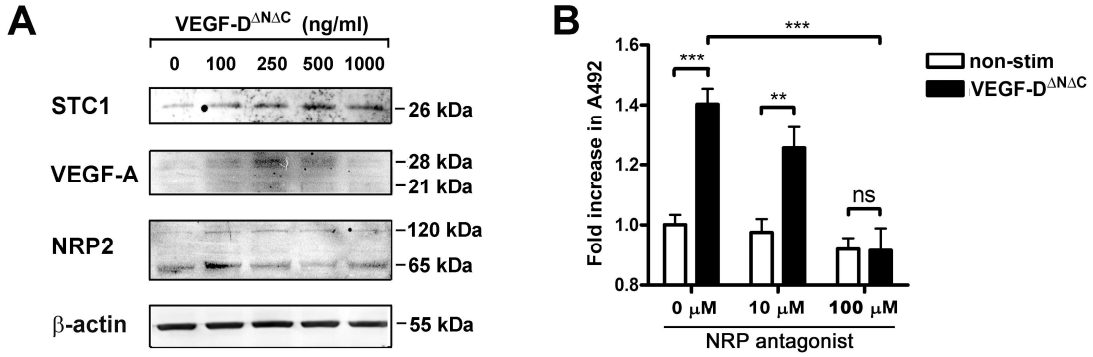


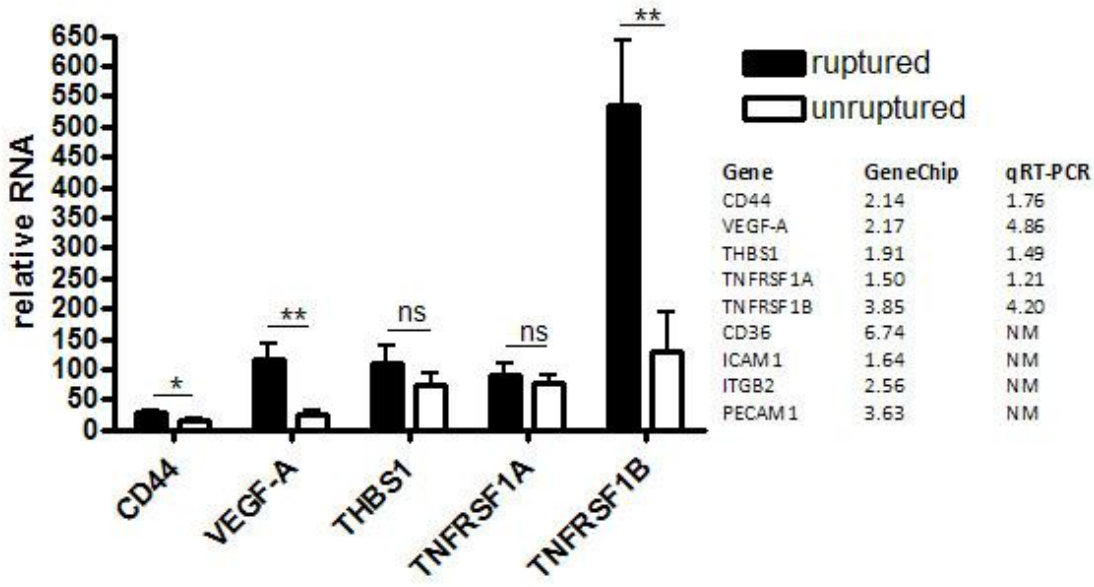
*Figure 10. A) Western Blot analysis for the STC1, VEGF-A and NRP2 protein expression levels. HUVECs were serum-starved for 16 h and treated with different concentrations of rVEGF-$D^{\Delta N\Delta C}$. Conditioned media from the cells were collected after 48 h of stimulation and used for the analysis of STC1 which is a secreted protein. VEGF-A and NRP2 analysis were performed from cell extracts harvested at the same time point and β-actin was used to confirm the equal loading of the samples. Data is representative of two independent experiments done in triplicates. B) NRP antagonist blocked rVEGF-$D^{\Delta N\Delta C}$ –induced survival of HUVECs at dose-dependent manner. HUVECs were serum-starved for 16 h and treated with rVEGF-$D^{\Delta N\Delta C}$ (100 ng/ml) in the presence of varying concentrations of NRP-antagonist. The amount of the living cells in the wells was measured with MTS-reagent. Non-stimulated cells without NRP antagonist were set to be 1.0. The data from three experiments done in triplicates is presented as mean ±SD; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.005$, One-way ANOVA.*

5.2 VEGF-$D^{\Delta N\Delta C}$-INDUCED SURVIVAL OF HUVECs WAS BLOCKED WITH NRP ANTAGONIST

In gene expression studies, upregulation of NRP2 was seen in VEGF-$D^{\Delta N\Delta C}$ -stimulated HUVECs at mRNA as well as protein levels and in AdVEGF-$D^{\Delta N\Delta C}$ -transduced mouse skeletal muscle at mRNA level. NRP1 expression level was not altered. To study the importance of NRP2 in VEGF-$D^{\Delta N\Delta C}$ signalling, blocking experiments were performed with a NRP antagonist. HUVECs were stimulated with or without rVEGF-$D^{\Delta N\Delta C}$ (100 ng/ml) at the presence of varying concentrations of NRP antagonist. A dose-dependent decrease in rVEGF-$D^{\Delta N\Delta C}$ -induced cell survival was observed. The NRP antagonist did not have any significant effects on the survival of non-stimulated HUVECs (Fig 10B). Total inhibition of rVEGF-$D^{\Delta N\Delta C}$ -induced cell survival was achieved with 100 μM NRP antagonist (Fig 10B).

5.3 GENE EXPRESSION STUDY OF INTRACRANIAL ANEURYSMS

The reason why aneurysms erupt is not known. Understanding the molecular mechanism behind rupture of aneurysms might help us to prevent ruptures and to identify the aneurysms that are at risk to rupture. To study the mechanism a comparison of the gene expression profiles was done of eleven ruptured (average age 60 years) and eight unruptured (average age 54 years) sIA walls from patients of Finnish ethnicity and screening of the expression of 17788 distinct genes. Upregulation of 686 genes and downregulation of 740 genes in the ruptured sIA walls compared to unruptured was detected (Annex 2). The upregulation of five representative genes were verified by qRT-PCR (Fig 11). In the ruptured sIA wall group, the time elapsed from the rupture to the resection of the sample did not seem to affect the gene expression levels. There were no statistically significant differences in the gene expression levels between the early and the delayed sample groups.



Gene	GeneChip	qRT-PCR
CD44	2.14	1.76
VEGF-A	2.17	4.86
THBS1	1.91	1.49
TNFRSF1A	1.50	1.21
TNFRSF1B	3.85	4.20
CD36	6.74	NM
ICAM1	1.64	NM
ITGB2	2.56	NM
PECAM1	3.63	NM

*Figure 11. Comparison of the expression of five selected genes in 16 ruptured and seven unruptured sIA wall samples by quantative RT-PCR. The differential expression was tested by Welch t-test; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.005$, ns= not significant, NM = not measured. Gene expression ratios in GeneChip and qRT-PCR have the same trend.*

Significantly enriched pathways among the upregulated genes in the ruptured sIA walls were cytokine-receptor interaction, toll-like-receptor signalling, hematopoietic cell lineage, and leukocyte transendothelial migration (Annex 3). The most relevant enriched ontologies were related to the immune system and to the chemotaxis of cells. Of the cellular compartment ontologies, the Arp2/3 protein complex and the NADPH oxidase complex were enriched.

General increase in pro-apoptotic and pro-inflammatory genes was seen after data analysis. Upregulation of tumor necrosis factor receptors superfamily member 1A (TNFRSF1A) and 1B (TNFRSF1B), plasma membrane

receptors that activate intracellular signalling pathways leading to apoptosis by activation of caspase proteases, was found. Changes in gene expression were also detected in thrombospondin 1 (THBS1) and transmembrane receptor CD36. Their interaction leads to apoptosis-dependent inhibition of angiogenesis (Jimenez et al., 2000). The expression changes in pro-apoptotic genes THBS1, TNFRSF1A and 1B were confirmed at RNA level with qRT-PCR (Fig 11). Upregulation of CD 36 was verified at protein level with immunohistochemistry (Fig 12, Table 5).

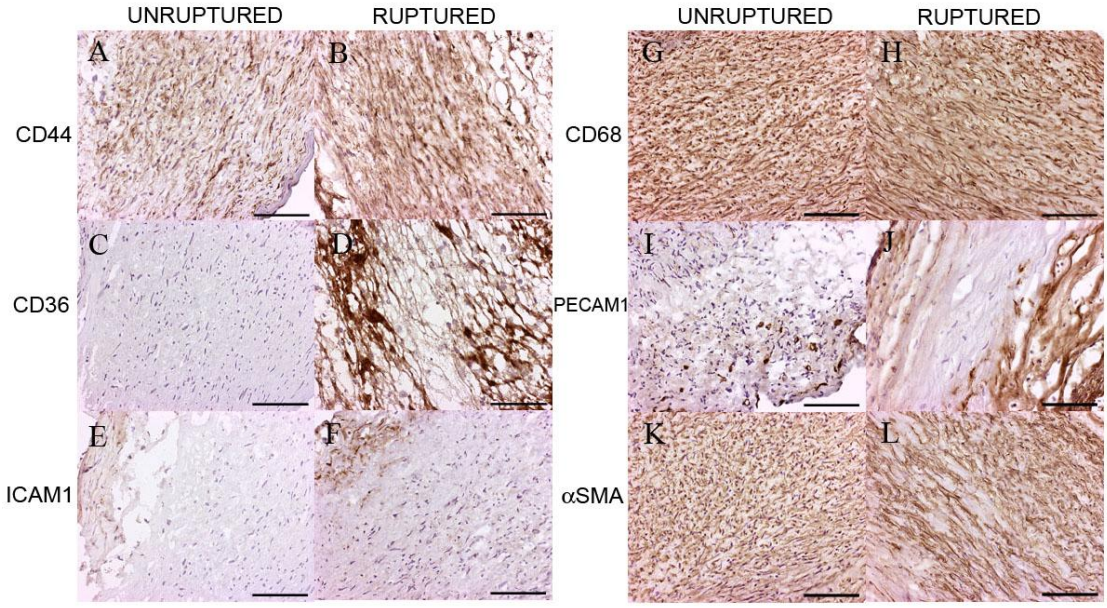


Figure 12. Immunohistochemistry was performed from 4 μm thick frozen sections of unruptured (A, C, E, G, I, K) and ruptured (B, D, F, H, J, L) sIAs. Protein expression of CD44 (A, B), CD36 (C, D) and ICAM1 (E, F) was higher in ruptured sIAs than in unruptured. sIAs were also stained against CD68 (G, H), PECAM1 (I, J) and αSMA (K, L).

Table 5. Grading of the immunohistochemical staining

Sample No.	Sex	Age Years	Location of sIA	UR/ RU	CD44	CD36	ICAM1	VCAM1
10	M	42	MCA	UR	**	*	-	-
12	M	28	ACoA	UR	*	-	*	-
13	F	48	MCA	UR	**	*	*	**
14	F	55	MCA	UR	**	*	*	-
15	F	54	MCA	UR	NS	-	-	-
16	M	37	ACoA	UR	**	**	**	*
17	F	57	DACA	UR	**	*	**	**
18	M	53	MCA	UR	**	*	*	**
19	F	54	MCA	UR	NS	-	-	*
20	F	50	MCA	UR	**	**	**	-
31	M	70	MCA	RU	**	*	NS	-
35	F	53	MCA	RU	NS	**	NS	-
39	M	84	ACoA	RU	***	*	NS	-
40	M	58	ICA	RU	***	**	***	*
41	F	64	ACoA	RU	***	**	*	*
42	F	71	MCA	RU	**	-	*	*
43	F	46	PCoA	RU	NS	*	**	-
44	F	36	MCA	RU	*	-	*	-
45	F	72	MCA	RU	**	-	**	*

UR = unruptured; RU = ruptured; NS = not stained; (-) = no detectable staining, (*) = weak staining, meaning that less than 10 % of the area was positive for the studied signal; (**) = moderate staining, meaning that 10-50 % of the area was positive for the studied signal; (***) = strong staining, meaning that more than 50 % of the area was positive for the studied signal.

Several adhesion molecules were upregulated in ruptured aneurysms compared to unruptured (Annex 2). ICAM1 is engaged during firm adhesion by leukocyte integrin beta 2 (ITGB2). Induction of both was evident after data analysis. Interestingly, the other well known adhesion molecule, VCAM1, was not upregulated. However, PECAM1, which interacts with ITGB2 in transendothelial migration was upregulated. CD44 mediates the attachment of circulating lymphocytes to activated endothelium (Jalkanen et al., 1987) and it was induced 2.1-fold in ruptured aneurysms. Upregulation of CD44 was confirmed both at RNA (Fig 11) and protein (Fig 12, Table 5) levels. Expression of ICAM1 (Fig 12, Table 5) and VCAM1 (Table 5) was checked at protein level. No statistically significant differences in expression of inflammatory markers were found with X^2-test between male and female or young (≤ 50 years) and old (> 50 years). The significant differences were seen only between ruptured and unruptured IA samples. VEGF-A, also known as vascular permeability factor, is a cytokine and heparin-binding glycoprotein with potent angiogenic activity specific for endothelial cells and it has major roles in several cellular functions. VEGF-A was upregulated 2.2-fold in ruptured sIAs and the trend was confirmed at RNA level (Fig 11). After multiple testing correction there were no significantly enriched pathways among the genes significantly downregulated in the ruptured sIA walls. However, there were significantly enriched gene ontologies, revealing strong enrichment of zinc finger proteins of transcription factor activity (Annex 2) and genes of tight junction and adherens junction (Annex 3).

6 Discussion

Studying the mechanisms of polygenic diseases is a demanding task. To clarify the true factors behind the disease both *in vivo* and *in vitro* methods are needed. Human tissue samples and animal models are commonly used but cell cultures are easier when controlling of different factors and conditions is needed. Microarrays are convenient method when studying of large scale gene expression is necessary. Microarray experiment usually after data analysis produces large amounts of interesting differentially expressed genes which leads to a problem which genes to study further. There is no general rule what to choose. The genes more specifically studied in this study were chosen because they formed a clear pathway, they clustered nicely together or they are known to have a role in already known events (e.g. regulation of angiogenesis, apoptosis, inflammation) in vascular diseases.

6.1 GENE EXPRESSION STUDY WITH VEGF-D$^{\Delta N \Delta C}$

VEGF-D$^{\Delta N \Delta C}$ seems to have a role in the vascular system but its mechanism of action is unknown. This is due to the relatively low efficiency of recombinant VEGF-D$^{\Delta N \Delta C}$ to activate VEGFR-2 in cell cultures. Especially target genes and signalling mechanisms of VEGF-D$^{\Delta N \Delta C}$ are poorly understood. It is essential to clarify the functions and mechanisms of VEGF-D$^{\Delta N \Delta C}$ to elucidate its role in vascular diseases. In this array study, three VEGFR-2 downstream signalling cascades were found to be upregulated. Activation of these cascades may lead to vasodilation and endothelial cell survival via upregulation of NO and prostacyclin (PGI_2) production which are key factors in protection against vascular damage. PGI_2 plays a major physiologic role as a potent mediator of vasodilation and inhibitor of platelet activation. It is a labile metabolite of arachidonic acid produced in concert with the bis-enoic prostaglandins via the cyclooxygenase (COX) pathway (Vane and Corin, 2003). COX is the key enzyme in the metabolism of arachidonic acid. Two COX-isozymes have been identified, COX1 which is constitutively expressed and COX2 which is induced in response to inflammatory stimuli (Santovito et al., 2009). COX1 was upregulated in this array data and it was verified with qRT-PCR. Both COXs were upregulated in the mouse skeletal muscle. The COXs are located in the end of two signalling cascades which were activated upon VEGFR-2 stimulation. Upregulation of these two factors may lead to an increase in PGI_2 production which functions as a powerful vasodilator. Activation of VEGFR-2 might also lead to the upregulation of important signalling factor, phosphatidylinositol 3-kinase (PI3K), which functions upstream from eNOS. To induce NO production, eNOS needs to be phosphorylated. In AdVEGF-D$^{\Delta N \Delta C}$ transduced cells increase in the phosphorylation of eNOS was evident in the Western Blot (Fig 8B). NO is a potent vasodilator and promotes endothelial survival. Especially in endothelial injury, NO induces rapid repairing of endothelial layer which inhibits excess neointima formation delaying lesion progression (Rutanen et al., 2005). VEGF-D has not been previously shown to have atheroprotective effects. Rutanen et al. (Rutanen et al., 2003) showed that VEGF-D is abundant in arteries regardless of the stage of atherosclerosis with only a reduction in the most advanced lesions. This might indicate that VEGF-D is atheroprotective in early stage lesions and it is able to slow down the lesion development but in advanced lesions the protective effect is lost.

Upregulation of VEGF-A, NRP2 and STC1, three important factors in vascular biology, was found in the present study. Several other growth factors, for example epidermal growth factor (EGF), PlGF, PDGF and FGF4 have been shown to upregulate VEGF-A (Orlandini et al., 1996; Rissanen et al., 2003a; Roy et al., 2005) but this has not previously been shown for VEGF-D. NRP2 is normally expressed in venous endothelial cells and in adult

lymphatic vessels (Herzog et al., 2001; Yuan et al., 2002). It binds VEGF-D and closely related lymphatic growth factor VEGF-C and is internalized with VEGFR-3 after VEGF-D or VEGF-C stimulation (Karpanen et al., 2006). The capability of NRP2 to form complexes with VEGFR-1 and VEGFR-2 has been noticed and NRP2 has also been shown to enhance the effects of two angiogenic growth factors, VEGF-A and PlGF, in endothelial cell signalling by an isoform specific manner (Gluzman-Poltorak et al., 2000; Gluzman-Poltorak et al., 2001; Neufeld et al., 2002). According to the results of this study, NRP2 mRNA level is increased by VEGF-D$^{\Delta N\Delta C}$ -stimulation in HUVECs as well as in mouse hind limb skeletal muscle. The Western blot from HUVEC extract showed upregulation of two distinct bands corresponding to the cell surface bound form (120 kDa) and the soluble form (66 kDa) (Fig 10A). Cell surface bound form of NRP2 could have a role in enhancing the effects of VEGF-D$^{\Delta N\Delta C}$ or related factors in endothelial cell signalling. The soluble form of NRP2 is generated by alternative splicing from the same gene and it has been proposed to have an inhibitory effect on the functions of VEGFs and semaphorins, although some studies suggest that soluble NRP could be sufficient to enhance the angiogenic responses of VEGFs (Geretti and Klagsbrun, 2007; Rossignol et al., 2000; Yamada et al., 2001). The importance of NRP2 upregulation in VEGF-D$^{\Delta N\Delta C}$ signalling was shown with a NRP antagonist which was able to block the rVEGF-D$^{\Delta N\Delta C}$ -induced responses.

Calcium and phosphate homeostasis regulating factor STC1 is related to angiogenesis and is shown to be upregulated in response to rVEGF-A and hypoxia (Holmes and Zachary, 2008; Manalo et al., 2005). It has also been vaguely connected to atherosclerosis (Sato et al., 1998). In these studies, the transient upregulation of STC1 mRNA was noticed in AdVEGF-D$^{\Delta N\Delta C}$ -transduced HUVECs at 36 h time point and in mouse skeletal muscles five days after AdVEGF-D$^{\Delta N\Delta C}$ -treatment. In HUVECs, STC1 protein expression level was also increased by rVEGF-D$^{\Delta N\Delta C}$ -stimulation in a dose-dependent manner. Very little is known about the effects of STC1 on the vascular system, however, regulatory roles for inflammatory responses, endothelial permeability and apoptosis have been suggested (Chakraborty et al., 2007; Chen et al., 2008; Kanellis et al., 2004). Interestingly, a recent publication suggested that STC1 could work as a negative feedback effector for growth factor-induced phosphorylation of ERK1/2 (Wu et al., 2006) which is also an important factor in VEGFR-2-mediated proliferative responses.

Although VEGF-A and VEGF-D$^{\Delta N\Delta C}$ both bind to the VEGFR-2 and stimulate angiogenic responses at the same efficiency, *in vivo* their actions in vascular system are not equal. A major difference is that VEGF-A mRNA and protein synthesis is stimulated under hypoxic conditions or by inflammatory responses whereas VEGF-D is constitutively expressed in normal adult arteries and atherosclerotic lesions but in advanced lesion the expression is lost (Bates and Harper, 2002; Rutanen et al., 2003; Tammela et al., 2005; Rutanen et al., 2003; Tammela et al., 2005). Still the role of VEGF-D in atherogenesis is unknown. Furthermore, VEGF-D$^{\Delta N\Delta C}$ has slower kinetics in the stimulation of VEGFR-2 tyrosine phosphorylation as well as its downstream signalling cascade but the effects last longer than those induced by VEGF-A (Jia et al., 2006; Nagy et al., 2008). This data suggests that VEGF-D$^{\Delta N\Delta C}$ might have a protective role against vascular dysfunction. After endothelial injury VEGF-D$^{\Delta N\Delta C}$ will be released from the vessel wall and upregulate VEGF-A, NRP2 and STC1 which might there after regulate and amplify the effects of VEGF-D (Fig 13). This would explain the slower effects of VEGF-D$^{\Delta N\Delta C}$ compared to VEGF-A. VEGF-D$^{\Delta N\Delta C}$ might need to be amplified via other factors to achieve high enough stimuli to induce the effects and making them also last longer. Although it is not clear whether the effects go through VEGFR-2 or VEGFR-3 or both, binding of VEGF-D$^{\Delta N\Delta C}$ together with positive stimulation of VEGF-A, positive or

negative stimulation of STC1 and co-operation of NRP2 with VEGFR-2 or 3 seem to induce vasodilatation and endothelial survival.

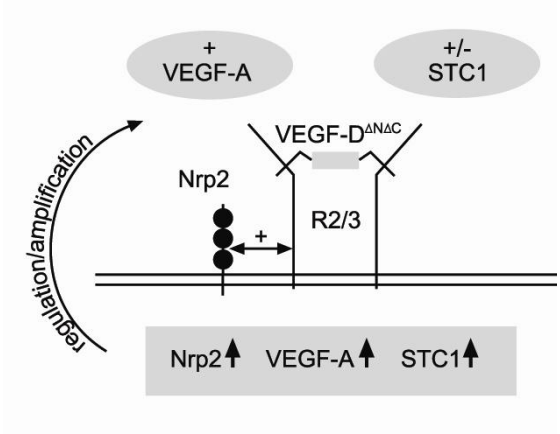


Figure 13. *Illustration of the possible mechanism of VEGF-A, NRP2 and STC1 to regulate and amplify the effects of VEGF-D.*

6.2 GENE EXPRESSION STUDY OF INTRACRANIAL ANEURYSMS

Despite modern therapy, aneurysmal SAH (aSAH) remains one of the most severe forms of cerebrovascular disease, with mortality approaching 50%. aSAH can be prevented with microsurgery or endovascular therapy, if rupture prone sIAs are identified in time. Why some sIAs rupture, while many remain unruptured, is unknown. Also the molecular mechanisms leading to sIA wall rupture remain mostly unknown. Comparison of the transcriptomes of eleven ruptured and eight unruptured human sIA walls to identify pathways that are associated to the rupture was done. The processes significantly overrepresented in the ruptured sIA walls were: chemotaxis; leukocyte migration; oxidative stress; vascular remodelling; and ECM degradation (Annex 3).

Comparison of gene expression profiles of human ruptured and unruptured sIA walls have been performed by Krischek et al. (Krischek et al., 2008) (six vs. four samples, oligonucleotide microarray, Agilent), Shi et al. (Shi et al., 2008) (three vs. three samples, beadchip microarray, Illumina), Pera et al. (Pera et al., 2010) (eight vs. six samples, oligonucleotide microarray, Affymetrix), and Marchese et al. (Marchese et al., 2010) (12 vs. 10 samples, oligonucleotide microarray, Affymetrix). Krischek et al. and Shi et al. did not find significant differences between the ruptured and unruptured walls, Pera et al. found only one upregulated gene in the ruptured walls, and Marchese et al. reported ten upregulated and four downregulated genes in the ruptured walls. Significant upregulation of 686 genes and downregulation of 740 genes in the ruptured sIA walls was identified. The larger number of differentially expressed genes in this study is most likely due to increased sample size combined with different statistical analyses and up to date custom annotations for microarray oligonucleotide probes.

It is possible that some of the differences in gene expression in this study could be caused by the reaction of the sIA wall to rupture, but there seemed to be no significant effect in differential gene expression of different times from the rupture to the resection of the sIA wall samples. This was also the conclusion of Kataoka et al who did a comparison of 44 ruptured and 27 unruptured aneurysm walls (Kataoka et al., 1999). They found no correlation between the time from the rupture to the resection and the scores of histological inflammation and aneurysm wall fragility. Frösen et al. studied the walls of 42 ruptured and 24 unruptured sIAs. Comparison of

leukocyte density and the time from the rupture to sample resection revealed that leukocytes might be present in the sIA wall before the rupture (Frosen et al., 2004). Also one limitation in this differential transcriptome profiling is that the sIA wall samples contain a mixture of cell types, including endothelial cells, SMCs, fibroblasts, and leukocytes. Consequently, it is difficult to tell for certain which cell populations are responsible for the overall differential profile. The genetically homogenous Finnish population has a high incidence of aSAH (de Rooij et al., 2007) the causes of which have not been fully elucidated. The tendency to sIA wall rupture may partially be related to the Finnish genetic pool, but we are confident that the pathways identified in our study are relevant irrespective of study population.

Turbulent flow and low shear stress may cause inflammation, leukocyte migration, and oxidative stress at arterial bifurcations, (Chiu et al., 2009) the site of sIAs as well. Inflammation is associated to atherosclerosis and many cardiovascular diseases, (Sprague and Khalil, 2009) as well as experimental cerebral aneurysm formation (Aoki et al., 2009). The signalling pathway of the pro-apoptotic inflammatory cytokine, TNFα, was differentially expressed in ruptured and unruptured sIAs and this may partly explain the increased cell death in the ruptured sIA wall. TNFα expression has been previously shown in ruptured sIA walls by Jayaraman et al. (2005). In these series TNFα was expressed in both ruptured and unruptured sIA walls with no significant difference, but TNFα receptors TNFRSF1A and TNFRSF1B, were upregulated in ruptured sIA walls. This suggests increased sensitivity to apoptosis via the TNFα pathway in the sIA wall. TNFα is produced by macrophages. Since increased macrophage infiltration of the sIA wall is associated with rupture (Frosen et al., 2004), inflammatory cells in the sIA wall seem the likely source of the pro-apoptotic TNFα cytokine in the sIA wall.

Leukocyte migration is a characteristic feature of an inflammatory response, and has been associated with the pathogenesis of a number of vascular diseases, such as atherosclerotic plaque ruptures and aortic aneurysms (Galkina and Ley, 2007; Maiellaro and Taylor, 2007). The migration of leukocytes from the blood stream into the extravascular space is mediated by the interaction of adhesion molecules expressed on the cell surface of leukocytes with their counter ligands on endothelial cells and perivascular basement membrane components (Carlos and Harlan, 1994). The comparison of gene expression of unruptured and ruptured sIA walls showed upregulation of several leukocyte adhesion molecules in ruptured sIA walls, especially those of CD44, ICAM-1, and PECAM-1 (Fig 14).

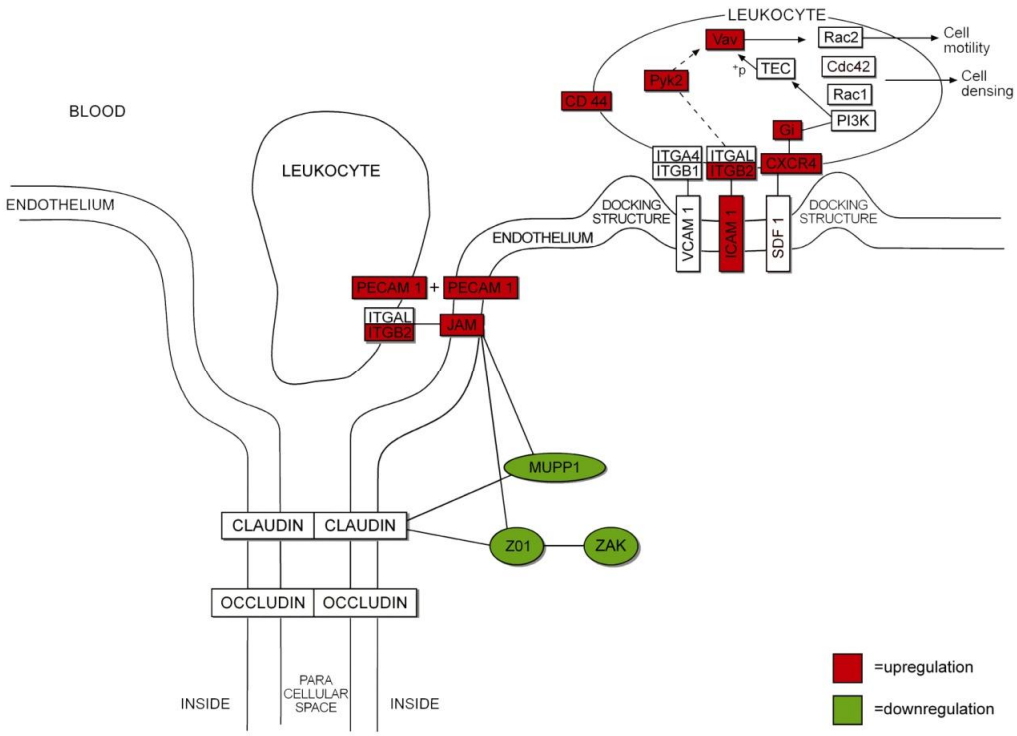


Figure 14. Differentially expressed genes in leukocyte transendothelial migration and tight junctions between ruptured vs. unruptured intracranial aneurysms. Upregulation of several leukocytes adhesion molecules and downregulation of tight junction and adherens junction genes was evident which might indicate loosening of tight junctions thus making leukocyte migration to the extravascular space easier.

CD44 is known to mediate tethering and rolling of lymphocytes on endothelium under physiological shear stress (DeGrendele et al., 1996). Shear stress also increases ICAM1 expression, and suppresses TNFα induced VCAM1 expression (Chiu et al., 2004). The observed upregulation of CD44 and ICAM1 in ruptured sIAs, together with no observed changes in VCAM1 expression either at RNA or protein level despite upregulation of TNFα-pathway, suggests that the ruptured sIA wall is subjected to increased shear stress that induces the changes in adhesion molecule expression.

Tight junction and adherens junction genes were downregulated in the ruptured sIA walls (Annex 3), suggesting loosening of contact between endothelial cells and SMCs. Elastin and collagen degrading enzymes (cathepsins A, L1, S, B, C), MMP9, MMP19, heparan sulfate proteoglycan degradating enzyme heparanase (HPSE), and plasminogen activating receptor (PLAUR) were highly upregulated while three collagen genes (COL4A5, COL21A1, COL14A1) were strongly downregulated together with multiple PDZ domain protein 1 (MUPP1), tight junction protein 1 (ZO1 or TJP1) and leucine zipper- and sterile alpha motif -containing kinase

(ZAK) (Annex 2). MUPP1, ZO1 and ZAK are located downstream from tight junction or adherens junction genes (Fig 14). Their downregulation might loosen off tight junctions hence helping the migration of leukocytes to the extravascular space. This data suggests that ECM degradation predisposes to or follows the sIA wall rupture, or both. ECM degradation is known to be central in many arterial wall diseases (Lutgens et al., 2007; Raffetto and Khalil, 2008).

One likely key mediator of increased vascular permeability in the sIA wall is VEGF-A. The actions of VEGF-A are thought to initiate changes that favour leakage at endothelial intercellular junctions and the secondary activation of pathways causing enzymatic breakdown of matrix proteins (Unemori et al., 1992). VEGF-A has been previously shown in sIA walls at the protein level (Skirgaudas et al., 1996) and was found in this study at the mRNA level in both the microarray and in the qRT-PCR. Downregulation of several tight junction proteins together with upregulated VEGF-A expression might indicate increased vascular permeability.

6.3 MICROARRAYS IN STUDYING GENE EXPRESSION

Microarray technology has enabled simultaneous investigation of the expression of thousands of genes. It can easily be applied for biomedical and clinical research. Microarrays have made it possible to study biological systems directed at definitions of functions and behaviour of genes in health and disease. In biomedical research, the scope of microarrays extends to gene expression profiling, gene expression localization, studies of gene function, gene characterization and detection of single nucleotide polymorphisms. Because the technology is flexible, it has been widely used in many fields of biology ranging from plants to animals and humans. It provides vast amounts of data that has to be biologically interpreted which requires the integration of several sources of information. Microarrays have also been reported to produce contradictory results on the analysis of the same RNA samples hybridized on different microarray platforms (MAQC Consortium et al., 2006). Scepticism has arisen regarding the reliability and the reproducibility of this technique. In reality many of those divergent results reflect the complex nature of the data generated by high-throughput systems and the analytical methods used without necessarily meaning that the results are unreliable and false. However, lots of the results still deviate because of technical issues in array preparation, sample processing or data analysis (Hardiman, 2006). It is therefore imperative to confirm the results by other independent methods to avoid wrong interpretations. It has been suggested that results of microarray experiments should be verified by two principal methods: *in silico* method or laboratory-based validation method (Chuaqui et al., 2002). In *in silico* method array results are compared with previous information thus providing an opportunity to validate the data without further experiments. Previous information is not always appropriate or available and laboratory-based validation needs to be used to verify the results (e.g RT-PCR, in-situ hybridization, immunohistochemistry, Northern and Western blots, enzymatic assays, animal models, human samples). However, while these methods might help to validate the results, it must be critically assessed whether the observed phenomenon is universal and an accurate description of the biological process studied. Microarrays have also been widely used in clinical research but successful application of the technology in clinical medicine depends upon technological developments and also in the agreement of joint standards and best practices. In clinical settings, microarrays can be useful for disease diagnosis, pharmacogenomics and toxicogenomics. Microarrays might have great impact on the treatment of diseases because the data will help to identify subtypes of diseases, disease risks, treatments, prognosis and outcome, moving biomedical research to the era of personalized medicine (Sotiriou and Piccart, 2007; Trevino et al., 2007).

7 Conclusions

It has been shown that the microarray is a very useful tool in studying gene expression of complex diseases. Here the method was used to study the genes related to two common vascular diseases, atherosclerosis and intracranial aneurysms. Pathogenesis of both diseases is very complicated and studies have revealed involvement of various genes. GeneChips enabled the screening of thousands of genes simultaneously and generated large amounts of data where identification of biologically relevant mechanisms, pathways and genes could be made.

Microarray is fast and quite a simple method in which to generate large amounts of data. One of the biggest problems with microarrays is still data analysis. There is no single right method to analyze the data which makes the comparison of different experiments very difficult. Also, the handling of vast amounts of data might be overwhelming and finding the significant and biologically relevant results is a challenging task. That is why all results should be verified in RNA and protein level with other methods.

GeneChips were used to study the effects of overexpression of VEGF-$D^{\Delta N\Delta C}$ in HUVECs and it revealed a possible role of VEGF-$D^{\Delta N\Delta C}$ as an atheroprotective factor. Overexpression of VEGF-$D^{\Delta N\Delta C}$ activated three signalling cascades downstream from VEGFR-2 that induce vasodilatation and endothelial survival both of which have been associated in vascular protection. VEGF-$D^{\Delta N\Delta C}$ overexpression also upregulated several other factors like VEGF-A, NRP2 and STC1 which all seem to regulate and amplify the effects of VEGF-$D^{\Delta N\Delta C}$. This feedback regulation might explain differences in kinetics and effects of the two VEGFR-2 ligands, VEGF-A and $D^{\Delta N\Delta C}$. The biology of VEGF-$D^{\Delta N\Delta C}$ has not been studied much at the cellular level and the role of VEGF-$D^{\Delta N\Delta C}$ in vascular system has been unclear because of its low efficiency to activate VEGFR-2. Better knowledge of VEGF-$D^{\Delta N\Delta C}$ signalling and regulation is important in order to clarify the role of VEGF-$D^{\Delta N\Delta C}$ in cardiovascular diseases so that possible new therapeutic applications could be developed.

Gene expression profiles of unruptured and ruptured sIAs were compared with GeneChips. Because in this study the number of samples was higher compared to the previous sIA gene expression studies, higher number of differentially expressed genes was also found. Upregulation of several genes related to inflammation, leukocyte migration and adhesion was seen. Rupture of sIA seems to involve many similar events as various other vascular diseases. In ruptured aneurysms expression of endothelial adhesion molecules was upregulated helping leukocytes to migrate through endothelium. Expression of tight junction proteins was downregulated which leads to loosening of the cell-to-cell junctions allowing the migration of leukocytes to extravascular space. Genes involved in degradation of ECM were upregulated which might facilitate the rupture of sIA or be the consequence of the rupture or both. It is vital to elucidate what makes sIAs rupture so that the rupture could be prevented or that the rupture-prone aneurysms could be identified in time. Molecular biology of sIAs and its rupture is quite complicated and studies have been hindered by the difficulty of sample collection and lack of animal models. The resection of sIA sample requires a very skilful neurosurgeon and the processing of the sample needs to be well organized. In this study high numbers of sIAs were used to elucidate the mechanisms behind rupture. Results correlate with previous studies and also reveal new possible therapeutic targets for prevention of sIA rupture.

8 References

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Annex 1: Significantly up- and downregulated genes after overexpression of VEGF-$D^{\Delta N\Delta C}$ at 36 h and 72 h time points

Annex 2: Differentially expressed genes between ruptured and unruptured sIA wall

Annex 3: Biological processes in ruptured sIA wall samples.

Annex 1: Significantly up- and downregulated genes after overexpression of VEGF-D$^{\Delta N\Delta C}$ at 36 h and 72 h time points

36 h timepoint

Accession	Gene	Fold change	P value
NM_025170	DEP domain containing 2	220.56	2.71E-04
BC004405	pseudogene MGC10997 /// pseudogene MGC10997	209.3	7.70E-03
AF215907	interleukin 18 binding protein	161.73	3.69E-03
AK098076	ATPase, Na+/K+ transporting, alpha 4 polypeptide	123.33	8.08E-03
AC006371	Homo sapiens BAC clone RP11-304C24 from Y	107.49	1.76E-03
AW663885	suppressor of hairy wing homolog 2 (Drosophila)	90.11	3.09E-03
AL442092	leucine rich repeat neuronal 3	73.33	2.42E-04
AI539459	V-myb myeloblastosis viral oncogene homolog (avian)-like 1	71.09	8.00E-06
NM_015603	coiled-coil domain containing 9	59.15	1.58E-03
AF086258	Full length insert cDNA clone ZD41F01	35.26	2.30E-05
BF508325	FLJ41603 protein	31.91	5.20E-05
AE000659	hypothetical protein MGC40069	30.37	2.43E-02
AI379514	Homo sapiens cDNA FLJ11154 fis, clone PLACE1006932	29.43	1.67E-03
AL833246	Homo sapiens mRNA; cDNA DKFZp761C2420 (from clone DKFZp761C2420).	27.17	3.65E-04
BE675241	phosphatidylinositol-specific phospholipase C, X domain containing 1	22.67	3.50E-03
AI374739	hyaluronan synthase 2	22.62	4.55E-04
AL109817	formiminotransferase cyclodeaminase	15.78	3.02E-03
AI693153	gamma-aminobutyric acid (GABA) A receptor, beta 3	15.35	6.89E-04
BE965418	hypothetical protein MGC20806	12.34	2.10E-04
AI278629	zinc finger protein 444	11.9	7.70E-05
NM_014465	sulfotransferase family, cytosolic, 1B, member 1	11.52	9.17E-04
BF440025	nephroblastoma overexpressed gene	11.11	2.09E-03
AU147317	30 kDa protein	9.78	8.41E-03
AF288391	chromosome 1 open reading frame 24	8.77	1.03E-03
AA588400	ovo-like 1(Drosophila)	8.6	3.04E-03
AK097997	leucine zipper, putative tumor suppressor 2	7.04	9.12E-04
AK022316	parvin, alpha	6.39	2.45E-03
NM_000089	collagen, type I, alpha 2	6.06	1.22E-03
NM_024111	hypothetical protein MGC4504	6.06	7.40E-05
AI733120	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 18	6.05	3.59E-03
AI859267	Homo sapiens, clone IMAGE:4703872, mRNA	5.72	1.12E-03
AU119437	hypothetical protein LOC144997	5.27	1.99E-03
AL136588	hypothetical protein /FL=gb:AL136588.1	5.24	2.63E-03
BC015770	solute carrier family 39 (zinc transporter), member 14	4.88	1.70E-03
AI654224	Hypothetical protein FLJ38508	4.85	1.69E-04
NM_004411	dynein, cytoplasmic, intermediate polypeptide 1	4.63	6.94E-03
NM_014368	LIM homeobox 6	4.62	1.80E-05
NM_006877	guanosine monophosphate reductase /// guanosine monophosphate reductase	4.54	1.08E-03
NM_001090	ATP-binding cassette, sub-family F (GCN20), member 1 /// ATP-binding cassette, sub-family F (GCN20), member 1	4.49	5.84E-03
NM_173664	cyclin-dependent kinase 8	4.36	6.00E-06
AI870617	CD82 (suppressor of tumorigenicity 6)	4.35	1.00E-02
BC003637	DNA-damage-inducible transcript 3	4.32	4.80E-05
AB032967	zinc finger protein 473	3.98	2.62E-02
NM_139054	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 18	3.67	1.43E-03
AA115278	potassium channel tetramerisation domain containing 1	3.52	2.73E-03
AK098337	Hypothetical LOC401131	3.51	4.67E-04
AK091990	putative UST1-like organic anion transporter	3.48	3.59E-03
AW015573	exosome component 3	3.46	4.32E-03
AL542359	LSM10, U7 small nuclear RNA associated	3.36	1.96E-03
BE549732	likely ortholog of mouse zinc finger protein EZI	3.26	3.29E-04
NM_018149	hypothetical protein FLJ10587	3.23	4.27E-03
AA088177	KIAA1913	3.17	4.47E-04
AA716425	jun dimerization protein 2	3.1	1.37E-03
AK023795	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 1	3.09	9.93E-04
N74607	aquaporin 3	3.09	4.38E-04
BC036362	Hypothetical LOC387905	3.04	3.56E-04
NM_006260	DnaJ (Hsp40) homolog, subfamily C, member 3	2.99	3.02E-03
BC001193	histone 3, H2a	2.99	3.55E-03
AF060152	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 1	2.97	2.12E-03
BC000893	histone 1, H2bk	2.81	1.60E-05
AF115512	DnaJ (Hsp40) homolog, subfamily B, member 9	2.8	4.34E-03
NM_024324	Homo sapiens hypothetical protein MGC11256 (MGC11256)	2.78	1.00E-06
BC035170	Homo sapiens, clone IMAGE:5265791, mRNA.	2.78	6.81E-03
NM_003155	stanniocalcin 1	2.77	5.20E-05
U36501	nuclear antigen Sp100	2.75	4.33E-03
NM_018004	hypothetical protein FLJ10134	2.75	2.07E-04
AI377271	nucleobindin 2	2.7	4.32E-03
AW003173	stanniocalcin 1	2.66	1.52E-03
NM_004723	rho/rac guanine nucleotide exchange factor (GEF) 2	2.61	1.54E-03
AF155508	myoneurin	2.6	1.12E-02
NM_002661	phospholipase C, gamma 2 (phosphatidylinositol-specific)	2.59	1.46E-03
AA526904	KIAA0924 protein	2.59	2.86E-03
NM_005461	v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)	2.57	5.10E-05
AW204712	chromosome 10 open reading frame 128	2.56	1.93E-03
NM_001673	asparagine synthetase	2.55	1.34E-03
AB039327	calcium/calmodulin-dependent serine protein kinase (MAGUK family)	2.54	1.93E-03
NM_019058	DNA-damage-inducible transcript 4	2.51	1.47E-04
AL353759	H2A histone family, member L	2.51	5.47E-04
BF973568	selenoprotein M	2.51	2.00E-02

AI300520	stanniocalcin 1	2.5	1.10E-03
NM_017445	H2B histone family, member S	2.48	1.59E-03
NM_004563	phosphoenolpyruvate carboxykinase 2 (mitochondrial)	2.46	2.12E-04
NM_014459	protocadherin 17	2.42	1.47E-03
AK001782	CXXC finger 5	2.42	2.07E-03
NM_004221	natural killer cell transcript 4 (interleukin 32)	2.37	2.59E-03
NM_003896	sialyltransferase 9 (CMP-NeuAc:lactosylceramide alpha-2,3-sialyltransferase; GM3 synthase)	2.36	5.40E-05
NM_005114	heparan sulfate (glucosamine) 3-O-sulfotransferase 1	2.33	4.13E-03
NM_006134	chromosome 21 open reading frame 4	2.31	3.51E-04
AW135013	v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)	2.3	1.28E-04
NM_018534	Neuropilin 2	2.29	2.89E-03
AL080081	DnaJ (Hsp40) homolog, subfamily B, member 9	2.25	2.09E-04
AK024680	Neuropilin 2	2.24	4.36E-04
BC002490	CXXC finger 5	2.22	1.04E-02
AF280545	neuropilin 2	2.22	5.78E-03
BC006112	ADP-dependent glucokinase	2.21	1.13E-02
BE550486	solute carrier family 2 (facilitated glucose transporter), member 3	2.18	1.36E-02
AA910945	peroxisome proliferative activated receptor, alpha	2.18	7.87E-04
BC019266	Dystrophia myotonica-containing WD repeat motif	2.17	6.96E-03
BF131886	sestrin 2	2.15	1.12E-02
AW071793	MAX dimerization protein 1	2.15	2.51E-04
NM_005013	nucleobindin 2	2.13	6.59E-04
NM_000355	transcobalamin II; macrocytic anemia	2.13	3.33E-04
U94592	uncoupling protein 2 (mitochondrial, proton carrier)	2.13	2.89E-03
AL050297	Hypothetical protein LOC203069	2.13	9.53E-04
AL050069	docking protein 5	2.12	5.73E-03
NM_006855	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	2.1	1.52E-04
NM_002133	heme oxygenase (decycling) 1	2.08	8.30E-05
AA778684	solute carrier family 2 (facilitated glucose transporter), member 3	2.08	4.20E-03
NM_016657	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	2.07	4.18E-04
AL541302	serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2	2.07	1.23E-03
AI130969	collagen, type V, alpha 1	2.06	2.27E-04
AA812232	thioredoxin interacting protein	2.03	1.33E-02
AF169676	fibronectin leucine rich transmembrane protein 2	2.03	3.52E-02
NM_016594	FK506 binding protein 11, 19 kDa	2.03	5.74E-03
NM_006931	solute carrier family 2 (facilitated glucose transporter), member 3	2.02	2.97E-03
NM_022044	stromal cell-derived factor 2-like 1	2.01	8.63E-03
AC004010	amphoterin induced gene 2	2	5.96E-03
AF052059	sel-1 suppressor of lin-12-like (C. elegans)	1.99	8.81E-03
AK026966	Adenylate kinase 3	1.99	7.70E-05
BF110588	FERM domain containing 3	1.99	4.11E-03
NM_001864	cytochrome c oxidase subunit VIIa polypeptide 1 (muscle)	1.98	4.65E-03
AW052084	WD40 repeat protein Interacting with phosphoInositides of 49kDa	1.98	1.02E-04
S36219	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)	1.97	6.96E-04
NM_014061	melanoma antigen, family H, 1	1.97	3.90E-05
NM_020650	reticulocalbin 3, EF-hand calcium binding domain	1.97	1.59E-03
AL359601	ELMO domain containing 1	1.96	2.06E-04
N30339	Collagen, type V, alpha 1	1.95	1.44E-03
NM_031301	anterior pharynx defective 1B-like /// anterior pharynx defective 1B-like	1.95	6.49E-04
BC008034	chromosome 14 open reading frame 34	1.93	1.10E-02
BE645771	glutamine-fructose-6-phosphate transaminase 1	1.92	7.31E-04
BC003654	solute carrier family 27 (fatty acid transporter), member 3	1.92	1.18E-03
AW026379	Tumor necrosis factor receptor superfamily, member 11a, activator of NFKB	1.92	1.95E-04
NM_021643	tribbles homolog 2 (Drosophila)	1.91	3.10E-02
BF514079	Kruppel-like factor 4 (gut)	1.91	1.43E-03
BC008992	docking protein 5	1.91	5.63E-04
NM_030777	solute carrier family 2 (facilitated glucose transporter), member 10 /// solute carrier family 2 (facilitated glucose transporter), member 10	1.9	7.40E-04
AF212233	similar to signal peptidase complex (18kD)	1.9	7.66E-04
AF022375	vascular endothelial growth factor	1.89	5.34E-03
AV725328	prion protein (p27-30) (Creutzfeld-Jakob disease, Gerstmann-Strausler-Scheinker syndrome, fatal familial insomnia)	1.89	7.03E-03
AB037823	chondroitin sulfate glucuronyltransferase	1.89	3.23E-03
X15357	natriuretic peptide receptor A/guanylate cyclase A (atrionatriuretic peptide receptor A)	1.89	1.59E-04
NM_000962	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)	1.88	7.26E-03
AA037766	Hypothetical LOC388610	1.88	2.60E-02
NM_007213	PRA1 domain family 2	1.87	1.14E-03
NM_016041	Der1-like domain family, member 2	1.87	2.78E-04
BC002356	nucleobindin 1	1.86	3.19E-03
NM_012446	single-stranded DNA binding protein 2	1.86	5.44E-04
NM_019116	similar to ubiquitin binding protein	1.86	1.23E-03
AI378647	coagulation factor II (thrombin) receptor-like 2	1.86	7.01E-04
NM_000499	cytochrome P450, family 1, subfamily A, polypeptide 1	1.85	1.72E-03
AI983428	Collagen, type V, alpha 1	1.85	1.28E-03
BC000425	protein disulfide isomerase related protein (calcium-binding protein, intestinal-related)	1.84	8.50E-05
AL354872	cystathionase (cystathionine gamma-lyase)	1.84	2.46E-04
BF589413	FERM domain containing 3	1.84	8.80E-05
BE858787	HTPAP protein	1.83	2.20E-03
AI807917	Hypothetical protein DKFZp761B107	1.82	5.40E-03
AI631159	solute carrier family 2 (facilitated glucose transporter), member 3	1.81	1.48E-03
NM_003494	dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive)	1.81	2.94E-03
NM_016594	FK506 binding protein 11, 19 kDa	1.81	8.30E-05
NM_012434	solute carrier family 17 (anion/sugar transporter), member 5	1.81	4.33E-03

BC001144	DnaJ (Hsp40) homolog, subfamily B, member 11	1.81	1.27E-03
AK026921	solute carrier family 17 (anion/sugar transporter), member 5	1.81	2.38E-03
BC006428	CXXC finger 5 /// CXXC finger 5	1.81	1.34E-04
AB037810	signal-induced proliferation-associated 1 like 2	1.81	1.16E-02
AB035172	sialyltransferase 7D	1.8	1.11E-02
NM_017983	WD40 repeat protein Interacting with phosphoInositides of 49kDa	1.79	5.84E-04
AL041124	hypothetical protein PP1665	1.79	1.12E-03
AI431730	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 9	1.79	1.51E-03
NM_000043	tumor necrosis factor receptor superfamily, member 6	1.78	1.01E-03
AF212238	HTPAP protein	1.78	1.49E-03
AA844682	synovial apoptosis inhibitor 1, synoviolin	1.78	4.02E-03
AI984061	hypothetical protein LOC90637	1.78	5.55E-04
AL544576	similar to RIKEN cDNA 2600017H02	1.78	7.92E-04
BE622627	phosphoinositide-3-kinase, regulatory subunit 3 (p55, gamma)	1.77	8.20E-03
AF077048	single-stranded DNA binding protein 2	1.77	1.38E-03
NM_022464	endoplasmic reticulum chaperone SIL1, homolog of yeast	1.77	2.66E-03
BF970287	chromosome 20 open reading frame 160	1.77	4.55E-04
NM_017901	two-pore channel 1, homolog /FL=gb:NM_017901.1	1.76	1.35E-04
NM_012252	transcription factor EC	1.75	2.82E-03
AB018580	aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II)	1.75	4.19E-03
AL110298	solute carrier family 2 (facilitated glucose transporter), member 3	1.75	2.07E-03
NM_014403	sialyltransferase 7D ((alpha-N-acetylneuraminyl-2,3-beta-galactosyl-1,3)-N-acetyl galactosaminide alpha-2,6-sialyltransferase)	1.75	1.37E-03
W93554	Neuralized-like (Drosophila)	1.75	7.82E-04
NM_013410	adenylate kinase 3	1.73	7.85E-03
NM_002646	phosphoinositide-3-kinase, class 2, beta polypeptide	1.73	1.95E-04
U08032	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	1.73	1.74E-03
AL041124	hypothetical protein PP1665	1.73	2.45E-03
BC001451	testis derived transcript (3 LIM domains)	1.72	3.17E-03
AI797684	reticulocalbin 3, EF-hand calcium binding domain	1.72	1.38E-04
NM_015641	testis derived transcript (3 LIM domains)	1.7	5.62E-03
D21254	cadherin 11, type 2, OB-cadherin (osteoblast)	1.7	1.22E-02
AA534198	chondroitin sulfate glucuronyltransferase	1.7	2.04E-03
AF162769	glutaredoxin (thioltransferase)	1.69	3.18E-04
M33376	aldo-keto reductase family 1, member C2	1.68	2.67E-04
AI683900	amplified in osteosarcoma	1.68	1.38E-03
AI825800	glucose regulated protein, 58kDa	1.68	8.06E-04
AW149417	zinc finger protein 423	1.67	2.61E-03
NM_002064	glutaredoxin (thioltransferase)	1.65	1.60E-03
NM_006472	thioredoxin interacting protein	1.64	1.11E-03
NM_013231	fibronectin leucine rich transmembrane protein 2	1.64	5.11E-04
BF111651	HTPAP protein	1.64	8.90E-05
AI628657	Weakly similar to PIHUSD salivary proline-rich glycoprotein precursor PRB4 (H.sapiens)	1.64	3.83E-04
NM_004199	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide II	1.63	7.41E-04
NM_004353	serine (or cysteine) proteinase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1)	1.62	1.57E-04
AF217990	homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	1.59	2.49E-04
AI738556	tumor necrosis factor receptor superfamily, member 10d, decoy with truncated death domain	1.59	9.90E-05
NM_025146	Mak3 homolog (S. cerevisiae)	0.65	1.20E-05
NM_005342	high-mobility group box 3	0.64	3.40E-05
AF053641	CSE1 chromosome segregation 1-like (yeast)	0.63	3.63E-04
NM_001033	ribonucleotide reductase M1 polypeptide	0.63	8.80E-05
AB003476	A kinase (PRKA) anchor protein (gravin) 12	0.63	2.50E-05
W72220	hypothetical protein FLJ12806	0.63	2.05E-04
NM_004728	DEAD (Asp-Glu-Ala-Asp) box polypeptide 21 /// DEAD (Asp-Glu-Ala-Asp) box polypeptide 21	0.62	1.10E-03
AF063020	PC4 and SFRS1 interacting protein 1	0.62	7.70E-05
AY014272	Similar to FKSG30	0.62	1.12E-04
BF195526	heterogeneous nuclear ribonucleoprotein A3	0.62	8.95E-04
AI741392	Importin 7	0.62	4.70E-05
BF001670	ephrin-B2	0.62	1.71E-04
NM_004427	polyhomeotic-like 2 (Drosophila)	0.61	1.24E-03
NM_003799	RNA (guanine-7-) methyltransferase	0.61	3.38E-04
BE407516	cyclin B1	0.61	6.00E-05
NM_017702	hypothetical protein FLJ20186	0.61	4.67E-04
NM_017665	zinc finger, CCHC domain containing 10	0.61	6.34E-04
BE622897	Kinase interacting with leukemia-associated gene (stathmin)	0.61	1.91E-04
AB020690	Paraneoplastic antigen MA2	0.61	5.55E-04
BF671894	hypothetical protein FLJ13910	0.61	7.06E-04
AI859865	MCM4 minichromosome maintenance deficient 4 (S. cerevisiae)	0.61	1.77E-03
AA525163	phosphatidic acid phosphatase type 2A	0.61	2.65E-04
AB023173	ATPase, Class VI, type 11B	0.61	3.86E-04
NM_020401	nucleoporin 107kDa	0.61	3.17E-04
NM_004456	enhancer of zeste homolog 2 (Drosophila)	0.60	3.56E-04
NM_012242	dickkopf homolog 1 (Xenopus laevis)	0.60	6.13E-04
AL043571	RAN binding protein 2-like 1	0.60	4.98E-04
AL136750	hypothetical protein FLJ20425	0.60	7.80E-05
NM_003589	cullin 4A	0.60	3.80E-04
AI742789	eukaryotic translation initiation factor 4E	0.60	9.70E-03
NM_006461	sperm associated antigen 5	0.60	8.35E-04
NM_012192	fracture callus 1 homolog (rat)	0.60	1.01E-03
NM_016052	CGI-115 protein	0.60	4.22E-04
AL132665	BCL2/adenovirus E1B 19kDa interacting protein 3-like /// BCL2/adenovirus E1B	0.60	7.70E-04

	19kDa interacting protein 3-like		
AA524072	hypothetical protein FLJ31153	0.60	1.37E-03
NM_021953	forkhead box M1	0.60	4.95E-04
AW272611	thymopoietin	0.60	1.33E-03
NM_014746	ring finger protein 144	0.60	6.25E-04
X98743	DEAD (Asp-Glu-Ala-Asp) box polypeptide 18	0.60	4.66E-03
BC001282	high mobility group nucleosomal binding domain 4	0.60	1.16E-03
NM_024619	fructosamine-3-kinase-related protein	0.60	6.13E-04
NM_004645	coilin	0.59	1.51E-03
NM_000947	primase, polypeptide 2A, 58kDa	0.59	1.16E-03
BG290646	ubiquitin-conjugating enzyme E2N (UBC13 homolog, yeast)	0.59	2.89E-04
BG109746	Dicer1, Dcr-1 homolog (Drosophila)	0.59	1.12E-03
NM_022451	chromosome 10 open reading frame 117	0.59	9.54E-04
AL136770	claudin 12	0.59	4.10E-04
BG483966	HP1-BP74	0.59	2.25E-03
AI129320	sterile alpha motif and leucine zipper containing kinase AZK	0.59	1.15E-03
BC029360	suppressor of variegation 3-9 homolog 2 (Drosophila)	0.59	4.70E-04
AK055438	Transmembrane 6 superfamily member 1	0.59	4.15E-03
AB010427	WD repeat domain 1	0.59	3.69E-04
NM_001379	DNA (cytosine-5-)-methyltransferase 1	0.59	1.80E-05
NM_000574	decay accelerating factor for complement (CD55, Cromer blood group system)	0.59	1.47E-03
NM_004111	flap structure-specific endonuclease 1	0.59	3.16E-03
NM_005758	heterogeneous nuclear ribonucleoprotein A3	0.59	1.73E-03
U62136	ubiquitin-conjugating enzyme E2 variant 2	0.59	4.63E-04
D26069	centaurin, beta 2	0.59	3.57E-04
AI765445	BTG family, member 3	0.59	1.70E-04
NM_015895	geminin, DNA replication inhibitor	0.59	1.81E-04
NM_024053	chromosome 22 open reading frame 18	0.59	1.37E-03
NM_022831	hypothetical protein FLJ12806	0.59	1.14E-03
AI735576	ROD1 regulator of differentiation 1 (S. pombe)	0.59	1.89E-03
AI885466	Similar to RIKEN cDNA 2410129H14	0.59	3.78E-03
BG492359	CDNA clone IMAGE:4452583, partial cds	0.59	2.47E-03
AI275605	phosphatidylinositol glycan, class K	0.59	7.85E-04
NM_004701	cydin B2	0.58	1.26E-03
NM_007057	ZW10 interactor	0.58	4.23E-04
BC001188	transferrin receptor (p90, CD71)	0.58	1.31E-04
AA534860	H2A histone family, member V	0.58	3.00E-04
AI796581	KIAA0056 protein	0.58	1.62E-04
AA121481	TWIST neighbor	0.58	3.19E-03
NM_003472	DEK oncogene (DNA binding)	0.58	2.50E-05
NM_001826	CDC28 protein kinase regulatory subunit 1B	0.58	5.19E-04
AA648913	baculoviral IAP repeat-containing 5 (survivin)	0.58	3.41E-04
NM_004237	thyroid hormone receptor interactor 13	0.58	1.79E-02
BC001886	ribonucleotide reductase M2 polypeptide	0.58	3.68E-03
AL043631	CDNA FLJ33469 fis, clone BRAMY2002005 /// Dynamin 1-like	0.58	1.80E-05
AF213040	cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)	0.58	2.09E-03
NM_000584	interleukin 8	0.58	2.08E-02
NM_016126	chromosome 1 open reading frame 41	0.58	4.42E-03
U77949	CDC6 cell division cycle 6 homolog (S. cerevisiae)	0.58	1.30E-03
AF053640	CSE1 chromosome segregation 1-like (yeast)	0.58	1.62E-03
AA527502	heterogeneous nuclear ribonucleoprotein A3	0.58	2.10E-03
AL050205	c-Mpl binding protein	0.58	2.59E-03
AL050136	TATA element modulatory factor 1 /// Similar to family with sequence similarity 9, member C	0.58	1.72E-04
NM_024624	SMC6 structural maintenance of chromosomes 6-like 1 (yeast)	0.58	2.35E-03
AJ238379	TH1-like (Drosophila)	0.58	1.23E-03
AJ238376	TH1-like (Drosophila)	0.58	1.65E-03
BF590117	human T-cell leukemia virus enhancer factor	0.58	5.73E-04
NM_003642	histone acetyltransferase 1	0.57	5.97E-03
BC001866	replication factor C (activator 1) 5, 36.5kDa	0.57	4.59E-04
NM_003600	serine/threonine kinase 6	0.57	3.86E-04
N92507	high-mobility group box 1	0.57	2.76E-03
AI963083	hypothetical protein MGC26963	0.57	1.34E-04
BC031695	deleted in a mouse model of primary ciliary dyskinesia	0.57	2.35E-03
NM_001316	CSE1 chromosome segregation 1-like (yeast)	0.57	3.88E-04
NM_001255	CDC20 cell division cycle 20 homolog (S. cerevisiae)	0.57	5.85E-04
NM_005033	exosome component 9	0.57	2.78E-04
NM_002425	matrix metalloproteinase 10 (stromelysin 2)	0.57	1.05E-03
NM_017760	more than blood homolog	0.57	2.99E-03
NM_007027	topoisomerase (DNA) II binding protein 1	0.57	9.30E-05
AL031778	nuclear transcription factor Y, alpha	0.57	1.28E-03
AF113020	nucleoporin like 1	0.57	1.46E-04
BF679966	Hypothetical protein FLJ38426	0.57	5.47E-04
AW299250	Hypothetical protein LOC90624	0.57	1.99E-04
AI760760	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 3	0.56	2.18E-04
AI263909	ras homolog gene family, member B	0.56	6.33E-03
BE045993	Opa-interacting protein 5	0.56	2.18E-03
AK023411	fidgetin-like 1	0.56	7.75E-04
AI129328	deleted in a mouse model of primary ciliary dyskinesia	0.56	1.08E-02
AI743511	likely ortholog of mouse TORC2-specific protein AVO3 (S. cerevisiae)	0.56	1.44E-02
NM_005915	MCM6 minichromosome maintenance deficient 6 (MIS5 homolog, S. pombe) (S. cerevisiae)	0.56	1.15E-04
NM_003630	peroxisomal biogenesis factor 3	0.56	3.63E-04
NM_006716	activator of S phase kinase	0.56	7.00E-05
NM_004414	Down syndrome critical region gene 1	0.56	4.34E-04
AL582836	Paternally expressed 10	0.56	1.52E-02

AW188464	Ubiquitin specific protease 53	0.56	4.85E-04
BF438799	Homo sapiens, clone IMAGE:3887266, mRNA	0.56	2.27E-03
AI860012	Growth arrest-specific 2 like 3	0.56	1.02E-04
AK024896	Mitochondrial ribosomal protein S6	0.56	8.65E-04
NM_024680	FLJ23311 protein	0.56	4.60E-04
AA642341	KIAA1333	0.56	1.59E-03
BF940270	likely ortholog of mouse TORC2-specific protein AVO3 (S. cerevisiae)	0.56	5.92E-04
AA736452	phosphoglucomutase 2-like 1	0.56	1.07E-03
AW173157	progestin and adipoQ receptor family member III	0.56	8.13E-04
NM_012382	osmosis responsive factor	0.56	2.57E-03
AI808345	mitogen-activated protein kinase 9	0.56	1.34E-03
AI684747	PX domain containing serine/threonine kinase	0.56	1.96E-04
AJ293392	choroideremia-like (Rab escort protein 2)	0.56	2.26E-03
AF020043	chondroitin sulfate proteoglycan 6 (bamacan)	0.55	1.37E-04
AI861788	citron (rho-interacting, serine/threonine kinase 21)	0.55	1.62E-03
AA807529	MCM5 minichromosome maintenance deficient 5, cell division cycle 46 (S. cerevisiae)	0.55	1.88E-04
NM_006342	transforming, acidic coiled-coil containing protein 3	0.55	2.27E-03
NM_017692	aprataxin	0.55	4.42E-04
BC005004	hypothetical protein FLJ10156	0.55	2.68E-04
BC000973	KIAA1333	0.55	7.21E-04
AW294894	Hypothetical protein FLJ21924	0.55	1.29E-03
AI458313	Hypothetical protein AF301222	0.55	4.08E-03
AI798098	ring finger protein (C3HC4 type) 159	0.55	1.57E-03
NM_002608	platelet-derived growth factor beta polypeptide (simian sarcoma viral (v-sis) oncogene homolog)	0.55	8.66E-04
AI587307	mannosidase, endo-alpha	0.55	2.21E-04
AB032931	HSPC150 protein similar to ubiquitin-conjugating enzyme	0.55	3.58E-04
AI026938	thyroid hormone receptor associated protein 6	0.55	1.81E-04
AI276663	hypothetical protein LOC201725	0.55	4.34E-03
BE620598	hypothetical protein LOC201725	0.55	2.86E-04
AA890373	Dishevelled associated activator of morphogenesis 1	0.55	2.39E-02
AI093579	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	0.55	1.60E-04
AF269167	hypothetical protein FLJ20364	0.55	6.71E-04
AF015043	SH3-domain binding protein 4	0.55	6.82E-03
BF034206	hypothetical protein LOC339745	0.55	4.90E-04
AI469788	kinetochore protein Spc24	0.55	1.54E-03
NM_007080	LSM6 homolog, U6 small nuclear RNA associated (S. cerevisiae)	0.54	4.94E-04
NM_022406	X-ray repair complementing defective repair in Chinese hamster cells 4	0.54	1.43E-03
NM_001147	angiopoietin 2	0.54	1.98E-03
AF097159	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 6	0.54	2.89E-03
U82756	PRP4 pre-mRNA processing factor 4 homolog (yeast)	0.54	1.16E-02
AW513286	Hypothetical protein FLJ30655	0.54	6.93E-04
BC001422	placental growth factor, vascular endothelial growth factor-related protein	0.54	1.77E-03
BE500942	MRNA full length insert cDNA clone EUROIMAGE 1509279	0.54	1.02E-03
BF511276	A kinase (PRKA) anchor protein (gravin) 12	0.54	3.62E-03
AW151538	chromosome 21 open reading frame 45	0.54	2.83E-03
NM_006739	MCM5 minichromosome maintenance deficient 5, cell division cycle 46 (S. cerevisiae)	0.54	8.08E-04
AF080255	transcription termination factor, RNA polymerase II	0.54	5.34E-03
AL513759	recombining binding protein suppressor of hairless (Drosophila)	0.54	6.53E-03
NM_014321	origin recognition complex, subunit 6 homolog-like (yeast)	0.54	1.36E-03
NM_024745	SHC SH2-domain binding protein 1	0.54	3.19E-04
N63709	lin-7 homolog C (C. elegans)	0.54	9.03E-04
AJ238374	TH1-like (Drosophila)	0.54	1.01E-03
AU155565	choroideremia-like (Rab escort protein 2)	0.54	1.29E-04
BF108964	microtubule associated serine/threonine kinase-like	0.54	3.85E-04
H25097	ubiquitin specific protease 53	0.54	4.49E-03
AA489041	CDNA clone IMAGE:4333081, partial cds	0.54	4.16E-03
NM_004526	MCM2 minichromosome maintenance deficient 2, mitotin (S. cerevisiae)	0.53	5.94E-04
NM_014791	maternal embryonic leucine zipper kinase	0.53	2.78E-04
NM_003035	TAL1 (SCL) interrupting locus	0.53	1.57E-03
AV752215	sorcin	0.53	1.59E-04
AW958593	hypothetical protein FLJ20425	0.53	8.34E-03
BF511276	A kinase (PRKA) anchor protein (gravin) 12	0.53	3.35E-04
NM_004896	vacuolar protein sorting 26 (yeast)	0.53	9.80E-05
NM_013229	apoptotic protease activating factor	0.53	9.20E-05
BG484789	programmed cell death 6 interacting protein	0.53	1.78E-03
BE218980	v-ets erythroblastosis virus E26 oncogene homolog 1 (avian)	0.53	4.20E-05
BE644830	Rho GTPase activating protein 18	0.53	9.80E-05
AV705805	hypothetical protein MGC13159	0.53	1.70E-05
AL529634	nucleoporin 35kDa	0.53	4.08E-04
AW138157	hypothetical protein MGC24665	0.53	1.17E-03
BE466145	CDNA FLJ31513 fis, clone NT2RI1000127	0.53	1.47E-03
AU157716	Transcribed locus, moderately similar to NP_689573.2 zinc finger protein 573 [Homo sapiens]	0.53	4.98E-03
AV724329	phosphoglucomutase 2-like 1	0.53	7.98E-04
AL354612	hypothetical protein FLJ10407	0.53	9.01E-04
AI141802	mitogen-activated protein kinase-activated protein kinase 2	0.53	3.19E-03
NM_002894	retinoblastoma binding protein 8	0.53	2.87E-04
D55716	MCM7 minichromosome maintenance deficient 7 (S. cerevisiae)	0.53	4.16E-04
BF062223	chromatin assembly factor 1, subunit A (p150)	0.53	9.14E-04
AL520908	Synaptotagmin binding, cytoplasmic RNA interacting protein	0.53	5.30E-05
AI935647	Hypothetical protein FLJ10312	0.53	4.50E-04
NM_002388	MCM3 minichromosome maintenance deficient 3 (S. cerevisiae)	0.53	1.29E-04
NM_014873	Family with sequence similarity 34, member A	0.53	4.42E-04
NM_001237	cyclin A2	0.52	7.41E-04
NM_002916	replication factor C (activator 1) 4, 37kDa	0.52	7.97E-04

AF098158	TPX2, microtubule-associated protein homolog (Xenopus laevis)	0.52	2.12E-02
AF187858	angiopoietin 2	0.52	3.81E-03
NM_016048	CGI-111 protein	0.52	1.57E-04
AA633196	carbon catabolite repression 4 protein	0.52	1.83E-04
NM_001168	baculoviral IAP repeat-containing 5 (survivin)	0.52	7.80E-05
NM_003158	serine/threonine kinase 6	0.52	1.95E-04
D26488	WD repeat domain 43	0.52	4.29E-03
BF111719	Alkylglycerone phosphate synthase	0.52	1.61E-04
W49629	likely ortholog of mouse TORC2-specific protein AVO3 (S. cerevisiae)	0.52	2.31E-02
NM_006938	small nuclear ribonucleoprotein D1 polypeptide 16kDa	0.52	5.61E-04
NM_016426	G-2 and S-phase expressed 1	0.52	1.31E-03
BC000323	flap structure-specific endonuclease 1	0.52	5.52E-04
NM_005590	MRE11 meiotic recombination 11 homolog A (S. cerevisiae)	0.52	1.37E-03
AB011446	aurora kinase B	0.52	1.67E-03
AI669947	hypothetical protein LOC286148	0.52	1.59E-03
NM_016359	nucleolar and spindle associated protein 1	0.52	5.68E-04
NM_018410	hypothetical protein DKFZp762E1312	0.52	8.04E-04
NM_007019	ubiquitin-conjugating enzyme E2C	0.52	9.10E-05
NM_003504	CDC45 cell division cycle 45-like (S. cerevisiae)	0.52	2.92E-04
NM_001186	BTB and CNC homology 1, basic leucine zipper transcription factor 1	0.52	8.43E-04
AF279900	MCM7 minichromosome maintenance deficient 7 (S. cerevisiae)	0.52	2.54E-03
NM_003981	protein regulator of cytokinesis 1	0.52	8.35E-04
NM_016397	TH1-like (Drosophila)	0.52	3.82E-03
AA876372	Solute carrier family 7 (cationic amino acid transporter, y+ system), member 2	0.52	1.71E-04
AK025867	CDK5 regulatory subunit associated protein 2	0.52	7.13E-03
AL514445	regulator of G-protein signalling 4	0.51	3.60E-04
AF043294	BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast)	0.51	3.38E-04
NM_012310	kinesin family member 4A	0.51	2.06E-03
AK023129	HP1-BP74	0.51	1.02E-04
NM_007317	kinesin family member 22	0.51	6.21E-04
NM_001211	BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)	0.51	8.20E-05
W94952	CCR4-NOT transcription complex, subunit 7	0.51	1.69E-04
NM_014635	GRIP and coiled-coil domain containing 2	0.51	1.95E-03
NM_003914	cyclin A1	0.51	8.44E-04
BC002703	centromere protein A, 17kDa	0.51	7.11E-04
NM_017647	FtsJ homolog 3 (E. coli)	0.51	1.04E-03
NM_018204	cytoskeleton associated protein 2	0.51	9.40E-05
NM_017768	hypothetical protein FLJ20331	0.51	6.68E-04
AU153848	Rac GTPase activating protein 1	0.51	1.90E-04
AW007694	KIAA1333	0.51	9.60E-04
AL572471	centromere protein H	0.51	1.20E-03
BC000149	replication factor C (activator 1) 3, 38kDa	0.51	5.20E-05
NM_002875	RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)	0.51	3.03E-03
NM_003234	transferrin receptor (p90, CD71)	0.51	3.32E-04
NM_024945	chromosome 9 open reading frame 76	0.51	1.84E-04
N63551	male sterility domain containing 2	0.51	6.50E-04
BF700678	cyclin-dependent kinase 8	0.51	6.63E-04
AY026505	kinesin family member 2C	0.50	2.75E-03
BC001651	cell division cycle associated 8	0.50	2.05E-02
AW517711	Hypothetical protein LOC286148	0.50	1.84E-04
NM_019081	limkain b1	0.50	5.80E-03
NM_000321	retinoblastoma 1 (including osteosarcoma)	0.50	1.35E-04
NM_002358	MAD2 mitotic arrest deficient-like 1 (yeast)	0.50	1.61E-04
NM_006733	FSH primary response (LRPR1 homolog, rat) 1	0.50	1.18E-02
AU148274	Hypothetical protein DKFZp566H0824	0.50	1.40E-05
NM_018201	TBC1 domain family, member 13	0.50	3.10E-03
AI761561	hexokinase 2	0.50	2.18E-03
AI346350	cyclin A2	0.50	4.70E-05
AI932370	spastic ataxia of Charlevoix-Saguenay (sacsin)	0.50	1.21E-03
BC001425	differential display and activated by p53	0.49	6.22E-04
AI635449	solute carrier family 39 (zinc transporter), member 6	0.49	4.92E-04
NM_001442	fatty acid binding protein 4, adipocyte	0.49	1.96E-02
D89678	heterogeneous nuclear ribonucleoprotein D-like	0.49	5.61E-04
BC000764	chromosome 6 open reading frame 166	0.49	4.89E-03
AU158022	Rho GTPase activating protein 18	0.49	4.49E-03
BF697734	TUDOR gene similar	0.49	1.17E-03
AF258562	deoxythymidylate kinase (thymidylate kinase)	0.49	1.32E-03
BC040700	E1A binding protein p300	0.49	1.14E-03
NM_014708	kinetochore associated 1	0.49	4.39E-03
D38553	barren homolog (Drosophila)	0.49	1.18E-03
AA252512	hypothetical protein FLJ23861	0.49	4.13E-03
AL136877	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)	0.48	4.00E-05
NM_003384	vaccinia related kinase 1	0.48	6.94E-04
NM_000465	BRCA1 associated RING domain 1	0.48	3.04E-03
NM_018154	ASF1 anti-silencing function 1 homolog B (S. cerevisiae)	0.48	4.21E-04
AY029179	cell division cycle associated 7 /// cell division cycle associated 7	0.48	7.80E-05
AF106069	ubiquitin specific protease 15	0.48	2.74E-03
AJ130972	small nuclear ribonucleoprotein polypeptide A'	0.48	3.92E-03
NM_017975	Zwilch	0.48	1.31E-02
NM_018454	nucleolar and spindle associated protein 1	0.48	8.73E-03
NM_004702	cyclin E2	0.48	1.81E-03
W74442	hypothetical protein FLJ10719	0.48	1.07E-03
AI859865	MCM4 minichromosome maintenance deficient 4 (S. cerevisiae)	0.48	2.28E-02
AI823905	KIAA1333	0.48	2.42E-03
AI375486	adenomatosis polyposis coli	0.48	2.88E-03
NM_022346	chromosome condensation protein G	0.48	5.29E-04

NM_017858	timeless-interacting protein	0.48	7.48E-04
BF062139	Polymerase (RNA) III (DNA directed) polypeptide G (32kD)	0.47	1.06E-03
NM_003021	small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha	0.47	1.07E-02
NM_015874	recombining binding protein suppressor of hairless (Drosophila)	0.47	1.08E-02
BC003186	DNA replication complex GINS protein PSF2	0.47	1.26E-03
NM_002692	polymerase (DNA directed), epsilon 2 (p59 subunit)	0.47	1.41E-04
BC000712	Kinesin family member C1	0.47	7.20E-04
BF447705	RNA binding motif protein 12	0.47	2.30E-04
BG403615	hypothetical protein FLJ10719	0.47	2.50E-04
AL135396	Similar to RIKEN cDNA 2700049P18 gene	0.47	2.02E-04
AW003297	Ral GEF with PH domain and SH3 binding motif 2	0.47	5.43E-04
NM_001786	cell division cycle 2, G1 to S and G2 to M	0.47	5.14E-04
NM_001809	centromere protein A, 17kDa	0.47	7.50E-05
U29343	hyaluronan-mediated motility receptor (RHAMM)	0.47	6.80E-05
D88357	cell division cycle 2, G1 to S and G2 to M	0.47	4.61E-04
AB046794	family with sequence similarity 29, member A	0.47	2.60E-03
NM_017645	family with sequence similarity 29, member A	0.46	1.35E-03
AK001166	DEP domain containing 1B	0.46	4.29E-04
BG283921	hypothetical protein MGC33382	0.46	2.31E-04
AF394735	MAD2 mitotic arrest deficient-like 1 (yeast)	0.46	9.60E-04
NM_021067	KIAA0186 gene product	0.46	3.70E-05
NM_012145	deoxythymidylate kinase (thymidylate kinase)	0.46	2.73E-04
BC000737	regulator of G-protein signalling 4	0.46	2.42E-03
NM_012177	F-box protein 5	0.46	2.13E-04
BC005400	leucine zipper protein FKSG14	0.46	1.60E-03
AK025578	ubiquitin-like, containing PHD and RING finger domains, 1	0.46	6.60E-05
BF062175	chromosome 14 open reading frame 106	0.46	6.52E-04
AI184802	PRP4 pre-mRNA processing factor 4 homolog (yeast)	0.45	1.13E-03
NM_017669	hypothetical protein FLJ20105	0.45	1.75E-03
AL138828	DUF729 domain containing 1	0.45	5.71E-03
NM_004703	rabaptin, RAB GTPase binding effector protein 1	0.45	4.63E-03
AA292789	hypothetical protein LOC146909	0.45	1.12E-03
AW965339	shugoshin-like 2 (S. pombe)	0.45	7.27E-03
NM_007036	endothelial cell-specific molecule 1	0.45	1.28E-04
NM_018131	chromosome 10 open reading frame 3	0.45	1.36E-04
NM_018492	T-LAK cell-originated protein kinase	0.45	8.81E-04
N90191	cyclin B1	0.45	6.40E-05
NM_005496	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)	0.45	1.98E-04
BF059556	hypothetical protein MGC33382	0.45	2.18E-04
U63743	kinesin family member 2C	0.44	5.75E-04
NM_017779	DEP domain containing 1	0.44	3.46E-02
BE614410	cell division cycle associated 5	0.44	4.02E-04
NM_006444	SMC2 structural maintenance of chromosomes 2-like 1 (yeast)	0.44	3.82E-03
NM_018098	epithelial cell transforming sequence 2 oncogene	0.44	8.00E-05
NM_005613	regulator of G-protein signalling 4	0.44	1.85E-02
AK021890	dishevelled associated activator of morphogenesis 1	0.44	4.87E-03
AJ278112	DEP domain containing 1	0.44	4.44E-03
AA236927	neural precursor cell expressed, developmentally down-regulated 1	0.44	3.62E-04
NM_014750	discs, large homolog 7 (Drosophila)	0.44	4.00E-05
AK000490	DEP domain containing 1	0.44	4.85E-04
AL561834	topoisomerase (DNA) II alpha 170kDa	0.44	2.91E-04
NM_006055	LanC lantibiotic synthetase component C-like 1 (bacterial)	0.44	3.59E-04
AI889959	Helicase, lymphoid-specific	0.44	2.63E-03
AF327722	transcriptional coactivator tubedown-100	0.43	1.89E-02
AI829603	chromosome 13 open reading frame 3	0.43	1.42E-03
AK026197	F-box protein 5	0.43	1.22E-02
AL079310	high-mobility group protein 2-like 1	0.43	5.05E-03
AV700332	LYRIC/3D3	0.43	1.70E-05
NM_003318	TTK protein kinase	0.43	1.97E-03
R59697	Cyclin-dependent kinase 8	0.43	1.70E-05
AL524035	cell division cycle 2, G1 to S and G2 to M	0.42	1.51E-04
AF225416	kinetochore protein Spc25	0.42	3.03E-03
BC003068	solute carrier family 19 (folate transporter), member 1	0.42	5.75E-03
NM_022346	chromosome condensation protein G	0.42	2.41E-03
AF155827	helicase, lymphoid-specific	0.42	6.54E-04
BC005170	MCM8 minichromosome maintenance deficient 8 (S. cerevisiae)	0.42	8.25E-04
NM_014875	Kinesin family member 14	0.42	4.78E-03
BF248364	AF15q14 protein	0.42	6.60E-05
NM_018518	MCM10 minichromosome maintenance deficient 10 (S. cerevisiae)	0.41	2.55E-04
AK023208	anillin, actin binding protein (scraps homolog, Drosophila)	0.41	3.90E-05
AI150000	CDNA clone IMAGE:4797120, partial cds	0.41	2.35E-04
AK055438	Transmembrane 6 superfamily member 1	0.41	9.20E-04
NM_012485	hyaluronan-mediated motility receptor (RHAMM)	0.41	1.51E-03
NM_020242	kinesin-like 7	0.41	4.16E-04
AI343467	Inhibin, beta A (activin A, activin AB alpha polypeptide)	0.41	1.21E-03
NM_014264	polo-like kinase 4 (Drosophila)	0.41	1.93E-03
BE966236	ribonucleotide reductase M2 polypeptide	0.41	1.90E-04
NM_018132	chromosome 6 open reading frame 139	0.41	1.36E-03
NM_007295	breast cancer 1, early onset	0.40	5.64E-03
AU145746	esterase D/formylglutathione hydrolase	0.40	4.27E-03
AW439242	Similar to hypothetical protein, MGC:7199	0.40	1.49E-03
NM_002497	NIMA (never in mitosis gene a)-related kinase 2	0.40	1.60E-03
NM_002915	replication factor C (activator 1) 3, 38kDa	0.40	2.87E-02
NM_000057	Bloom syndrome	0.40	1.24E-03
AA126446	F-box protein 45	0.40	9.90E-05
AL556909	transcriptional coactivator tubedown-100	0.40	3.70E-04

AI418293	Cbl-interacting protein Sts-1	0.40	5.39E-04
AU147044	antigen identified by monoclonal antibody Ki-67	0.39	1.04E-03
NM_004523	kinesin family member 11	0.39	3.90E-05
AU152107	antigen identified by monoclonal antibody Ki-67	0.39	3.18E-03
AF114264	nexilin (F actin binding protein)	0.39	5.05E-04
NM_006101	kinetochore associated 2	0.39	6.30E-05
NM_024629	MLF1 interacting protein	0.39	7.80E-05
NM_016195	M-phase phosphoprotein 1	0.38	6.24E-03
AU132185	antigen identified by monoclonal antibody Ki-67	0.38	4.95E-03
N62196	zinc finger protein 367	0.38	8.40E-05
NM_022445	thiamin pyrophosphokinase 1	0.38	4.30E-05
U30872	centromere protein F, 350/400ka (mitosin) /// centromere protein F, 350/400ka (mitosin)	0.38	1.70E-03
BF001806	antigen identified by monoclonal antibody Ki-67	0.37	9.36E-03
AL136560	ankyrin repeat domain 32	0.37	3.83E-04
NM_018685	anillin, actin binding protein (scraps homolog, Drosophila)	0.37	1.18E-04
NM_004856	kinesin family member 23	0.37	1.10E-03
AL043646	polo-like kinase 4 (Drosophila)	0.37	3.28E-03
AU154486	SMC2 (structural maintenance of chromosomes 2, yeast)-like 1	0.37	1.08E-04
AF348491	chemokine (C-X-C motif) receptor 4 /// chemokine (C-X-C motif) receptor 4	0.37	3.88E-03
NM_014109	ATPase family, AAA domain containing 2	0.37	1.52E-03
AA041298	Similar to Caspase-4 precursor (CASP-4) (ICH-2 protease) (TX protease) (ICE(rel)-II)	0.36	1.85E-02
AF326731	cell division cycle associated 1	0.36	2.35E-03
NM_018123	asp (abnormal spindle)-like, microcephaly associated (Drosophila)	0.36	5.29E-04
AI925583	ATPase family, AAA domain containing 2	0.36	8.90E-05
NM_006520	t-complex-associated-testis-expressed 1-like	0.35	5.30E-05
AW088063	hypothetical protein FLJ40629	0.34	9.56E-04
AL136827	WD repeat domain 37	0.34	4.14E-03
AI804930	chromosome 10 open reading frame 4	0.34	2.49E-03
AJ224869	chemokine (C-X-C motif) receptor 4	0.34	8.41E-04
NM_031217	kinesin family member 18A /// kinesin family member 18A	0.34	8.03E-04
AB051530	DAB2 interacting protein	0.33	3.61E-03
L01639	chemokine (C-X-C motif) receptor 4	0.32	2.01E-03
AB042719	MCM10 minichromosome maintenance deficient 10 (S. cerevisiae)	0.32	1.03E-03
NM_017915	hypothetical protein FLJ20641	0.32	2.30E-05
AI829927	hypothetical protein LOC285148	0.32	2.30E-05
NM_002060	gap junction protein, alpha 4, 37kDa (connexin 37)	0.31	1.11E-04
NM_001813	centromere protein E, 312kDa	0.31	2.70E-03
AB037724	raptor	0.30	1.32E-03
BE966146	RAD51 associated protein 1	0.28	9.10E-04
M96789	gap junction protein, alpha 4, 37kDa (connexin 37)	0.28	1.46E-03
NM_005196	centromere protein F, 350/400ka (mitosin)	0.27	1.97E-03
BC002493	Homo sapiens, Similar to transcription factor 19 (SC1), clone MGC:2575	0.27	5.03E-03
NM_022767	hypothetical protein FLJ12484	0.23	2.55E-03
N31982	hypothetical protein LOC285636	0.22	2.02E-03
NM_000222	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	0.12	2.56E-03
AK025325	Transcribed locus, moderately similar to NP_689573.2 zinc finger protein 573 [Homo sapiens]	0.03	2.23E-03
AA150107	COBL-like 1	0.01	4.73E-04

72 h time point

Accession	gene	fold change	P value
BC004405	pseudogene MGC10997 /// pseudogene MGC10997	353.79	8.85E-03
NM_020995	haptoglobin-related protein	313	1.16E-03
NM_015603	coiled-coil domain containing 9	63.8	2.30E-05
U27336	fucosyltransferase 6 (alpha (1,3) fucosyltransferase)	63.04	1.90E-05
BG337478	Hypothetical protein LOC220929	42.81	7.80E-05
NM_015622	chromosome 7 open reading frame 28A	31.57	9.49E-04
BC042052	C-MYC proto-oncogene regulatory region	31.36	4.00E-06
AI539459	V-myb myeloblastosis viral oncogene homolog (avian)-like 1	27.6	1.91E-04
NM_145042	alpha tubulin-like	26.13	1.52E-03
AA884069	LVLF3112	25.91	1.52E-04
AF238488	olfactory receptor, family 8, subfamily B, member 8	22.98	1.85E-03
AA135522	glycerol-3-phosphate dehydrogenase 1-like	20.86	2.46E-02
NM_002612	pyruvate dehydrogenase kinase, isoenzyme 4	18.74	1.40E-02
AI278629	zinc finger protein 444	16.93	2.30E-05
AI654224	Hypothetical protein FLJ38508	15.88	7.51E-03
AB063187	dual specificity phosphatase 19	14.93	4.89E-03
NM_018465	chromosome 9 open reading frame 46	10.62	2.22E-02
AF288391	chromosome 1 open reading frame 24	9.73	2.30E-05
NM_001673	asparagine synthetase	9.13	9.53E-04
AW293356	Neurofibromin 1 (neurofibromatosis, von Recklinghausen disease, Watson disease)	8.06	1.20E-02
NM_007076	Huntingtin interacting protein E	7.43	2.61E-03
AK097997	leucine zipper, putative tumor suppressor 2	7.02	4.60E-03
AW136901	Bromodomain containing 4	6.88	3.48E-04
AK026247	hypothetical protein FLJ22594	6.63	1.27E-03
NM_024111	hypothetical protein MGC4504	6.53	3.41E-04
R56894	Phosphofructokinase, platelet	5.91	2.24E-02
NM_017482	adducin 2 (beta)	5.87	8.31E-03
BF732683	breast cancer membrane protein 101	5.76	1.70E-03
AI590926	solute carrier family 35, member B4	5.76	5.69E-03
U48705	discoidin domain receptor family, member 1	5.67	5.50E-03
NM_006623	phosphoglycerate dehydrogenase	5.39	1.25E-04
NM_001090	ATP-binding cassette, sub-family F (GCN20), member 1 /// ATP-binding cassette, sub-family F (GCN20), member 1	5.27	3.94E-03

AF155508	myoneurin	5.01	4.87E-03
AF182275	cytochrome P450, family 2, subfamily A, polypeptide 6	4.82	7.44E-03
NM_022044	stromal cell-derived factor 2-like 1	4.52	1.60E-03
AW300045	Homeodomain interacting protein kinase 2	4.37	4.74E-03
BG500611	hypothetical protein MGC21416	4.04	5.92E-03
BC003637	DNA-damage-inducible transcript 3	3.62	1.73E-04
BC001441	S-phase kinase-associated protein 2 (p45)	3.62	5.25E-03
AI927944	Hypothetical protein FLJ10618	3.6	3.95E-03
NM_018149	hypothetical protein FLJ10587	3.59	3.78E-03
BC006112	ADP-dependent glucokinase /// ADP-dependent glucokinase	3.53	4.63E-03
M95541	ATPase, Ca++ transporting, plasma membrane 1	3.45	2.99E-03
BC019266	Dystrophia myotonica-containing WD repeat motif	3.43	4.87E-03
BC004863	phosphoserine aminotransferase 1	3.39	1.14E-03
AL050297	Hypothetical protein LOC203069	3.36	1.20E-03
AI129328	deleted in a mouse model of primary ciliary dyskinesia	3.35	3.69E-03
NM_004723	rho/rac guanine nucleotide exchange factor (GEF) 2	3.32	1.63E-03
BC001331	KIAA0652 gene product	3.32	2.16E-02
NM_002661	phospholipase C, gamma 2 (phosphatidylinositol-specific)	3.05	1.83E-02
AF339834	RAN binding protein 5	3.05	1.17E-03
AF255304	membrane associated DNA binding protein	2.95	2.51E-03
AI829927	hypothetical protein LOC285148	2.94	7.97E-03
BF939727	sorting nexin family member 27	2.91	4.41E-03
BC030524	claudin 19	2.9	4.47E-04
S69738	chemokine (C-C motif) ligand 2	2.85	3.19E-03
AA115278	potassium channel tetramerisation domain containing 1	2.81	1.22E-02
BF573638	Similar to CG32736-PA	2.81	1.22E-02
AF212233	similar to signal peptidase complex (18kD)	2.79	7.04E-04
NM_002283	keratin, hair, basic, 5	2.78	1.67E-03
NM_021158	tribbles homolog 3 (Drosophila)	2.73	3.93E-04
AB033007	endoplasmic reticulum-golgi intermediate compartment 32 kDa protein	2.72	1.12E-03
BE796327	nucleolar protein 5A (56kDa with KKE/D repeat)	2.67	1.92E-03
AY042224	CD209 antigen	2.67	3.20E-04
AA716425	jun dimerization protein 2	2.59	3.05E-03
BE549732	likely ortholog of mouse zinc finger protein EZI	2.54	9.32E-03
AA488687	solute carrier family 7, (cationic amino acid transporter, y+ system) member 11	2.51	1.34E-03
AB040875	solute carrier family 7, (cationic amino acid transporter, y+ system) member 11	2.48	1.69E-04
AB029004	Rab6-interacting protein 2	2.48	1.40E-02
AI693193	Metaxin 1	2.47	6.40E-03
NM_016594	FK506 binding protein 11, 19 kDa	2.44	5.70E-03
BC000569	chromosome 21 open reading frame 4	2.43	1.33E-03
AL355685	chromosome 21 open reading frame 4	2.4	6.10E-05
NM_001511	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	2.36	4.88E-03
AV715993	HESB like domain containing 1	2.34	1.95E-02
AI571298	exosome component 4	2.32	2.05E-03
BG473130	kinesin family member 1A	2.31	2.71E-03
NM_006134	chromosome 21 open reading frame 4	2.3	3.24E-03
NM_005951	metallothionein 1H	2.26	1.79E-02
NM_021154	phosphoserine aminotransferase 1	2.23	1.02E-03
NM_012243	solute carrier family 35 (UDP-N-acetylglucosamine (UDP-GlcNAc) transporter), member A3	2.22	2.37E-03
BC001144	DnaJ (Hsp40) homolog, subfamily B, member 11	2.22	1.36E-04
BE794699	Chromosome 6 open reading frame 129	2.2	1.91E-03
AI377271	nucleobindin 2	2.2	1.16E-03
NM_006907	pyrroline-5-carboxylate reductase 1	2.18	5.21E-04
NM_004563	phosphoenolpyruvate carboxykinase 2 (mitochondrial)	2.17	1.89E-04
NM_013417	isoleucine-tRNA synthetase	2.15	1.57E-04
AB039327	calcium/calmodulin-dependent serine protein kinase (MAGUK family)	2.15	1.84E-03
D31887	solute carrier family 39 (zinc transporter), member 14	2.12	1.18E-04
AJ224869	chemokine (C-X-C motif) receptor 4	2.12	2.46E-03
NM_003197	S-phase kinase-associated protein 1A (p19A)	2.11	5.32E-03
NM_006636	methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase	2.1	3.05E-03
NM_006855	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	2.09	3.27E-04
NM_016594	FK506 binding protein 11, 19 kDa	2.03	1.79E-03
D30658	glycyl-tRNA synthetase	2	1.52E-03
N51405	chromosome 21 open reading frame 4	2	9.20E-03
AF217990	homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	1.98	9.90E-05
AA429615	hypothetical protein FLJ23233	1.98	5.99E-03
NM_005952	metallothionein 1X	1.95	7.93E-03
NM_020169	latexin	1.94	3.78E-03
AF115512	DnaJ (Hsp40) homolog, subfamily B, member 9	1.94	7.15E-04
AB044548	eukaryotic translation initiation factor 4E binding protein 1	1.93	7.22E-04
NM_001605	alanyl-tRNA synthetase	1.92	9.40E-05
AI927770	sel-1 suppressor of lin-12-like (C. elegans)	1.91	3.54E-04
AW052044	heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	1.9	7.98E-04
NM_006010	arginine-rich, mutated in early stage tumors	1.88	3.59E-03
AF085359	selenoprotein K	1.87	1.13E-04
AW242820	Exportin, tRNA (nuclear export receptor for tRNAs)	1.87	1.60E-03
NM_021014	synovial sarcoma, X breakpoint 3	1.86	2.91E-03
M57731	chemokine (C-X-C motif) ligand 2	1.85	3.03E-03
NM_005013	nucleobindin 2	1.82	8.30E-03
NM_016657	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	1.82	3.11E-03
AU144243	phosphatidylinositol glycan, class B	1.82	2.63E-03
AA844682	synovial apoptosis inhibitor 1, synoviolin	1.8	1.71E-03
NM_003359	UDP-glucose dehydrogenase	1.79	8.40E-05
BE613178	cystathionine-beta-synthase	1.79	1.41E-02

NM_000584	interleukin 8	1.78	1.09E-03
BC003048	peptidylprolyl isomerase (cyclophilin)-like 1	1.74	2.39E-03
AK025062	solute carrier family 12 (sodium/potassium/chloride transporters), member 2	1.73	9.10E-05
AL080081	DnaJ (Hsp40) homolog, subfamily B, member 9	1.72	2.87E-04
AW052084	WD40 repeat protein Interacting with phosphoInositides of 49kDa	1.72	9.22E-04
NM_014059	response gene to complement 32	1.72	3.73E-03
NM_006389	hypoxia up-regulated 1	1.71	4.07E-04
NM_000421	keratin 10 (epidermolytic hyperkeratosis; keratosis palmaris et plantaris)	1.71	4.64E-04
AI984005	exportin, tRNA (nuclear export receptor for tRNAs)	1.71	6.28E-04
AL564683	CCAAT/enhancer binding protein (C/EBP), beta	1.7	1.04E-03
AA584310	collagen triple helix repeat containing 1	1.7	1.59E-03
AA910945	peroxisome proliferative activated receptor, alpha	1.7	8.59E-04
NM_021127	phorbol-12-myristate-13-acetate-induced protein 1	1.69	3.06E-03
AB033080	cell cycle progression 1	1.69	2.65E-03
NM_138627	BCL2-like 11 (apoptosis facilitator)	1.68	3.04E-03
NM_016041	Der1-like domain family, member 2	1.66	5.41E-04
NM_004184	tryptophanyl-tRNA synthetase	1.63	2.59E-04
M19156	keratin 10 (epidermolytic hyperkeratosis; keratosis palmaris et plantaris)	1.61	2.69E-04
BC001173	eukaryotic translation initiation factor 3, subunit 9 eta, 116kDa	0.62	1.58E-04
AU145277	hypothetical protein LOC139886	0.60	3.41E-04
NM_002380	matrilin 2	0.60	1.02E-03
NM_000877	interleukin 1 receptor, type I	0.60	5.31E-04
D21254	cadherin 11, type 2, OB-cadherin (osteoblast)	0.60	1.53E-04
AF131747	KIAA0830 protein	0.60	3.34E-04
BE747815	CREBBP/EP300 inhibitor 2	0.60	2.24E-04
NM_014033	DKFZP586A0522 protein	0.59	7.50E-03
BF437750	epithelial V-like antigen 1	0.59	1.41E-03
AL050331	TSPY-like 4	0.58	3.12E-04
BE971383	spermidine/spermine N1-acetyltransferase	0.58	3.62E-03
NM_014183	dynein, cytoplasmic, light polypeptide 2A	0.58	1.22E-03
NM_002166	inhibitor of DNA binding 2, dominant negative helix-loop-helix protein	0.58	5.58E-04
AI885109	bromodomain containing 7	0.58	1.67E-03
BC001068	chromosome 20 open reading frame 129	0.58	5.60E-03
AF459643	filamin-binding LIM protein-1	0.58	1.53E-03
NM_000930	plasminogen activator, tissue	0.57	3.60E-04
NM_000240	monoamine oxidase A	0.57	4.50E-04
AI653037	cleavage stimulation factor, 3' pre-RNA, subunit 3, 77kDa	0.57	1.87E-02
NM_006494	Ets2 repressor factor	0.56	9.09E-04
NM_003155	stanniocalcin 1	0.56	5.88E-03
AI334128	NAD kinase	0.56	2.33E-03
AW964972	Placenta-specific 9	0.56	1.88E-02
BC032347	Hypothetical gene supported by BC055092	0.56	3.90E-03
AY028896	caspase recruitment domain family, member 10	0.56	4.58E-03
AI479175	sulfatase 1	0.56	3.62E-04
NM_016109	angiopoietin-like 4	0.56	1.53E-03
AL581473	exosome component 7	0.56	4.61E-03
NM_002923	regulator of G-protein signalling 2, 24kDa	0.55	9.90E-04
NM_002939	ribonuclease/angiogenin inhibitor	0.55	3.91E-03
AA628586	phosphatidic acid phosphatase type 2B	0.55	6.35E-04
AA702016	hypothetical protein FLJ13105	0.55	1.25E-03
AW338933	tissue inhibitor of metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory)	0.54	7.33E-03
U16797	ephrin-B2	0.54	3.82E-03
NM_004995	matrix metalloproteinase 14 (membrane-inserted)	0.53	1.68E-03
NM_021151	carnitine O-octanoyltransferase	0.53	2.20E-05
AL574194	extracellular link domain containing 1	0.53	1.38E-03
AK023795	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 1	0.53	2.03E-04
NM_001394	dual specificity phosphatase 4	0.53	3.48E-02
L29511	growth factor receptor-bound protein 2	0.52	3.65E-03
NM_000435	Notch homolog 3 (Drosophila)	0.52	4.44E-03
NM_012342	BMP and activin membrane-bound inhibitor homolog (Xenopus laevis)	0.52	6.44E-03
AA761181	CD24 antigen (small cell lung carcinoma cluster 4 antigen)	0.52	2.62E-04
AA133341	chromosome 14 open reading frame 87	0.51	3.53E-03
W93728	guanylate cyclase 1, soluble, beta 3	0.51	1.35E-03
AU145746	esterase D/formylglutathione hydrolase	0.51	9.20E-03
AK000168	CD24 antigen (small cell lung carcinoma cluster 4 antigen)	0.51	1.36E-04
AK025009	BTB (POZ) domain containing 9	0.51	1.31E-03
H05240	neuregulin 3	0.50	4.87E-03
BE500977	sulfatase 1	0.50	1.27E-03
NM_017790	Regulator of G-protein signalling 3	0.49	7.41E-04
AB000889	phosphatidic acid phosphatase type 2B	0.49	6.72E-04
L33930	CD24 antigen (small cell lung carcinoma cluster 4 antigen)	0.49	5.51E-03
NM_001797	cadherin 11, type 2, OB-cadherin (osteoblast)	0.49	3.04E-03
N74607	aquaporin 3	0.49	1.38E-03
AW073672	catenin (cadherin-associated protein), delta 1	0.48	7.36E-03
M31159	insulin-like growth factor binding protein 3	0.48	1.97E-03
AJ278150	hypothetical protein FLJ10842	0.47	3.09E-03
NM_003516	histone 2, H2aa	0.47	4.31E-04
NM_006033	lipase, endothelial	0.47	1.04E-04
D49958	glycoprotein M6A	0.46	1.87E-04
AF055585	slit homolog 2 (Drosophila)	0.46	5.86E-03
AI300520	stanniocalcin 1	0.45	7.68E-03
AI313324	histone 2, H2aa	0.44	2.18E-03
M96789	gap junction protein, alpha 4, 37kDa (connexin 37)	0.44	1.43E-03
NM_002060	gap junction protein, alpha 4, 37kDa (connexin 37)	0.43	9.61E-04
AI343467	Inhibin, beta A (activin A, activin AB alpha polypeptide)	0.42	1.56E-03

M58664	CD24 antigen (small cell lung carcinoma cluster 4 antigen)	0.41	9.90E-05
AF098951	ATP-binding cassette, sub-family G (WHITE), member 2	0.41	8.60E-05
NM_005824	leucine rich repeat containing 17	0.40	2.19E-04
AI250910	FLJ44635 protein	0.40	3.79E-03
AI423201	BMP-binding endothelial regulator precursor protein	0.40	4.65E-04
BG327863	CD24 antigen (small cell lung carcinoma cluster 4 antigen)	0.39	1.44E-02
BC000764	chromosome 6 open reading frame 166	0.39	5.56E-03
BF340228	insulin-like growth factor binding protein 3	0.38	9.01E-04
NM_003021	small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha	0.38	2.23E-03
AB037724	raptor	0.38	2.74E-03
AI950007	hypothetical protein MGC42630	0.36	1.26E-03
NM_003278	tetranectin (plasminogen binding protein)	0.36	1.61E-02
AJ005866	solute carrier family 35, member D2	0.34	1.75E-03
AW005298	CDNA clone IMAGE:30332316, partial cds	0.33	3.12E-04
AW118175	pre-mRNA cleavage complex II protein Pcf11	0.33	1.64E-03
AI758408	Homo sapiens, clone IMAGE:5302158, mRNA	0.33	7.00E-05
NM_012193	frizzled homolog 4 (Drosophila)	0.31	1.17E-03
AI719730	guanylate cyclase 1, soluble, alpha 3	0.31	3.27E-03
AK091506	hypothetical protein LOC200169	0.30	7.59E-03
AI805050	RAB6B, member RAS oncogene family	0.30	2.34E-03
AL136827	WD repeat domain 37	0.27	1.78E-03
NM_032816	hypothetical protein FLJ14640	0.25	1.93E-03
NM_000104	cytochrome P450, family 1, subfamily B, polypeptide 1	0.25	2.20E-04
NM_018286	hypothetical protein FLJ10970	0.23	2.50E-05
AI692880	gap junction protein, alpha 5, 40kDa (connexin 40)	0.22	3.48E-03
BF218922	Chondroitin sulfate proteoglycan 2 (versican)	0.15	2.29E-04
AK000847	Zinc finger protein 236	0.08	1.56E-02
NM_000237	lipoprotein lipase	0.08	1.10E-04
AK025325	Transcribed locus, moderately similar to NP_689573.2 zinc finger protein 573 [Homo sapiens]	0.03	6.60E-04

Annex 2. Differentially expressed genes between ruptured and unruptured saccular intracranial aneurysm walls.

HGNC * Symbol	Fold change	*P* value **	Gene Description
CD163	49.46	1.88E-06	CD163 molecule
PPBP	23.95	4.85E-03	pro-platelet basic protein (chemokine (C-X-C motif) ligand 7)
C15orf48	21.66	4.92E-08	chromosome 15 open reading frame 48
PF4	21.47	3.78E-03	platelet factor 4
SPP1	16.62	5.28E-03	secreted phosphoprotein 1
ADFP	15.55	2.53E-07	adipose differentiation-related protein
S100A8	13.90	9.28E-03	S100 calcium binding protein A8
CSTA	11.69	7.42E-05	cystatin A (stefin A)
PTX3	11.53	8.90E-03	pentraxin-related gene, rapidly induced by IL-1 beta
SGK1	10.93	5.68E-04	serum/glucocorticoid regulated kinase 1
PCOLCE2	10.87	2.38E-06	procollagen C-endopeptidase enhancer 2
BCL2A1	10.50	3.98E-05	BCL2-related protein A1
HMOX1	10.06	2.60E-04	heme oxygenase (decycling) 1
IL8	9.89	1.40E-04	interleukin 8
NCF2	9.76	1.35E-03	neutrophil cytosolic factor 2
IFI30	8.83	6.68E-04	interferon, gamma-inducible protein 30
LAPTM5	8.58	9.31E-03	lysosomal multispanning membrane protein 5
SLC16A10	8.57	5.97E-07	solute carrier family 16, member 10 (aromatic amino acid transporter)
SOD2	8.41	6.84E-06	superoxide dismutase 2, mitochondrial
HCLS1	8.38	5.27E-03	hematopoietic cell-specific Lyn substrate 1
C1orf162	8.33	2.02E-04	chromosome 1 open reading frame 162
SLA	8.31	1.06E-03	Src-like-adaptor
FPR1	7.86	1.72E-03	formyl peptide receptor 1
SLC16A6	7.46	7.10E-05	solute carrier family 16, member 6 (monocarboxylic acid transporter 7)
COTL1	7.42	7.19E-05	coactosin-like 1 (Dictyostelium)
CD14	7.32	2.86E-03	CD14 molecule
TIMP1	7.14	5.46E-04	TIMP metallopeptidase inhibitor 1
FCGR3B	6.85	3.58E-02	Fc fragment of IgG, low affinity IIIb, receptor (CD16b)
CD36	6.74	5.10E-04	CD36 molecule (thrombospondin receptor)
C13orf18	6.73	4.21E-04	chromosome 13 open reading frame 18
CLEC5A	6.59	5.60E-03	C-type lectin domain family 5, member A
TYROBP	6.54	1.13E-02	TYRO protein tyrosine kinase binding protein
LYZ	6.53	1.60E-03	lysozyme (renal amyloidosis)
NP	6.29	1.89E-04	nucleoside phosphorylase
AQP9	6.28	4.56E-04	aquaporin 9
CD53	6.20	1.12E-02	CD53 molecule
MAFB	6.15	5.03E-04	v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)
CXCL2	5.97	3.07E-02	chemokine (C-X-C motif) ligand 2
UPP1	5.92	2.69E-04	uridine phosphorylase 1
C13orf15	5.83	9.82E-03	chromosome 13 open reading frame 15
SAT1	5.81	2.02E-04	spermidine/spermine N1-acetyltransferase 1
C19orf59	5.54	4.61E-03	chromosome 19 open reading frame 59
RGS1	5.54	4.34E-02	regulator of G-protein signaling 1

FGR	5.52	4.69E-03	Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
CTSS	5.47	8.03E-03	cathepsin S
TLR2	5.41	1.79E-02	toll-like receptor 2
CCR1	5.33	3.42E-03	chemokine (C-C motif) receptor 1
VAMP8	5.17	4.45E-02	vesicle-associated membrane protein 8 (endobrevin)
CXCR4	5.04	1.26E-02	chemokine (C-X-C motif) receptor 4
CCL20	5.03	1.60E-03	chemokine (C-C motif) ligand 20
GLUL	4.91	2.53E-04	glutamate-ammonia ligase (glutamine synthetase)
ADM	4.87	6.80E-04	adrenomedullin
C5AR1	4.84	4.33E-03	complement component 5a receptor 1
NPL	4.83	5.02E-03	N-acetylneuraminate pyruvate lyase (dihydrodipicolinate synthase)
CEBPD	4.71	1.22E-04	CCAAT/enhancer binding protein (C/EBP), delta
HPSE	4.71	8.00E-03	heparanase
MS4A7	4.69	1.41E-03	membrane-spanning 4-domains, subfamily A, member 7
PLAUR	4.69	3.09E-04	plasminogen activator, urokinase receptor
ITGAX	4.68	6.25E-04	integrin, alpha X (complement component 3 receptor 4 subunit)
CXorf21	4.65	4.74E-02	chromosome X open reading frame 21
CCDC109B	4.61	3.98E-04	coiled-coil domain containing 109B
VSIG4	4.60	4.34E-02	V-set and immunoglobulin domain containing 4
UCP2	4.58	1.04E-02	uncoupling protein 2 (mitochondrial, proton carrier)
COL11A1	4.55	2.90E-02	collagen, type XI, alpha 1
IL6	4.52	7.34E-03	interleukin 6 (interferon, beta 2)
F13A1	4.51	2.41E-03	coagulation factor XIII, A1 polypeptide
LY96	4.47	1.07E-02	lymphocyte antigen 96
TCIRG1	4.39	1.80E-03	T-cell, immune regulator 1, ATPase, H+ transporting, lysosomal V0 subunit A3
RGS10	4.37	2.06E-02	regulator of G-protein signaling 10
ALOX5AP	4.34	1.52E-02	arachidonate 5-lipoxygenase-activating protein
ITGAM	4.34	1.74E-02	integrin, alpha M (complement component 3 receptor 3 subunit)
HMHA1	4.33	2.60E-02	histocompatibility (minor) HA-1
TYMP	4.31	1.83E-03	thymidine phosphorylase
LCP2	4.29	5.38E-03	lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)
AGPAT9	4.29	6.36E-03	1-acylglycerol-3-phosphate O-acyltransferase 9
TNFAIP3	4.27	3.81E-04	tumor necrosis factor, alpha-induced protein 3
TNFRSF1B	4.22	3.06E-03	tumor necrosis factor receptor superfamily, member 1B
APOBEC3A	4.19	1.42E-03	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A
FERMT3	4.15	1.93E-03	fermitin family homolog 3 (Drosophila)
AIM1	4.14	3.81E-02	absent in melanoma 1
GMFG	4.14	1.84E-02	glia maturation factor, gamma
MARCO	4.10	1.41E-02	macrophage receptor with collagenous structure
S100A9	4.08	2.28E-02	S100 calcium binding protein A9
C13orf33	4.07	1.60E-03	chromosome 13 open reading frame 33
WDFY4	4.05	1.15E-02	WDFY family member 4
IL7R	4.03	3.07E-02	interleukin 7 receptor
ANPEP	4.01	3.41E-03	alanyl (membrane) aminopeptidase
IL1R2	3.97	3.07E-03	interleukin 1 receptor, type II
TNFSF13B	3.95	2.94E-02	tumor necrosis factor (ligand) superfamily, member 13b
SPHK1	3.94	1.73E-03	sphingosine kinase 1
DOCK4	3.90	2.57E-02	dedicator of cytokinesis 4
SYK	3.84	3.45E-02	spleen tyrosine kinase
RGS2	3.79	1.14E-02	regulator of G-protein signaling 2, 24kDa
OBFC2A	3.78	5.75E-03	oligonucleotide/oligosaccharide-binding fold containing 2A
RRM2	3.77	2.65E-03	ribonucleotide reductase M2 polypeptide
BCAT1	3.76	1.21E-02	branched chain aminotransferase 1, cytosolic
SCO2	3.75	1.49E-04	SCO cytochrome oxidase deficient homolog 2 (yeast)
CPVL	3.71	1.82E-02	carboxypeptidase, vitellogenic-like
G0S2	3.67	1.21E-02	G0/G1switch 2
MYO1F	3.66	2.20E-03	myosin IF
CXCL3	3.66	2.86E-02	chemokine (C-X-C motif) ligand 3
CXCL1	3.65	9.61E-03	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)
LYN	3.64	1.84E-02	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog
PECAM1	3.63	2.46E-03	platelet/endothelial cell adhesion molecule
FOSB	3.57	1.70E-02	FBJ murine osteosarcoma viral oncogene homolog B
ARL4C	3.56	1.37E-03	ADP-ribosylation factor-like 4C
LILRB2	3.56	1.59E-03	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 2
CTSB	3.53	9.53E-03	cathepsin B
ANGPTL4	3.51	1.81E-03	angiopoietin-like 4
C4orf48	3.48	7.72E-04	chromosome 4 open reading frame 48
HK3	3.46	2.83E-03	hexokinase 3 (white cell)
CTSL1	3.45	3.78E-03	cathepsin L1
C16orf54	3.44	2.18E-02	chromosome 16 open reading frame 54
MS4A6A	3.43	2.76E-02	membrane-spanning 4-domains, subfamily A, member 6A
HCK	3.41	1.92E-02	hemopoietic cell kinase
GNA15	3.37	1.23E-03	guanine nucleotide binding protein (G protein), alpha 15 (Gq class)
NANS	3.36	7.46E-07	N-acetylneuraminic acid synthase
LCP1	3.35	1.04E-02	lymphocyte cytosolic protein 1 (L-plastin)
MPP1	3.35	5.79E-04	membrane protein, palmitoylated 1, 55kDa
SLC2A3	3.34	5.75E-03	solute carrier family 2 (facilitated glucose transporter), member 3
ABCA1	3.33	7.06E-03	ATP-binding cassette, sub-family A (ABC1), member 1
IER3	3.32	2.65E-03	immediate early response 3
RASSF2	3.29	2.79E-02	Ras association (RalGDS/AF-6) domain family member 2
C17orf60	3.27	5.87E-03	chromosome 17 open reading frame 60
CECR1	3.26	3.08E-02	cat eye syndrome chromosome region, candidate 1
BMP2K	3.26	4.47E-03	BMP2 inducible kinase
AIF1	3.24	6.17E-03	allograft inflammatory factor 1
CXCL16	3.22	2.01E-02	chemokine (C-X-C motif) ligand 16
CTSC	3.21	2.37E-03	cathepsin C

OLR1	3.19	3.19E-03	oxidized low density lipoprotein (lectin-like) receptor 1
MPEG1	3.14	2.31E-02	macrophage expressed 1
C3AR1	3.13	9.57E-03	complement component 3a receptor 1
CXCL6	3.10	4.34E-02	chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2)
OSTF1	3.10	2.76E-05	osteoclast stimulating factor 1
IL10RA	3.10	3.62E-02	interleukin 10 receptor, alpha
HLA-DQB1	3.09	1.77E-02	major histocompatibility complex, class II, DQ beta 1
NFKBIZ	3.09	5.79E-04	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta
ARHGAP30	3.09	1.12E-02	Rho GTPase activating protein 30
MST150	3.07	4.18E-03	MSTP150
FCER1G	3.06	7.69E-03	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide
SDS	3.04	1.37E-03	serine dehydratase
ADAP2	3.04	1.12E-02	ArfGAP with dual PH domains 2
FTL	3.04	7.65E-03	ferritin, light polypeptide
RGS18	3.03	4.54E-02	regulator of G-protein signaling 18
SLC7A7	3.03	1.69E-02	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7
MAP3K8	3.03	2.23E-02	mitogen-activated protein kinase kinase kinase 8
SH3BGRL3	3.03	1.66E-03	SH3 domain binding glutamic acid-rich protein like 3
MT2A	3.02	4.83E-03	metallothionein 2A
CD48	3.02	2.94E-02	CD48 molecule
LGMN	3.01	9.17E-03	legumain
FBP1	3.00	7.92E-03	fructose-1,6-bisphosphatase 1
NAMPT	3.00	4.86E-02	nicotinamide phosphoribosyltransferase
FKBP11	3.00	6.06E-03	FK506 binding protein 11, 19 kDa
MMP9	2.97	2.32E-02	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)
PLBD1	2.97	2.67E-02	phospholipase B domain containing 1
MYC	2.96	1.04E-02	v-myc myelocytomatosis viral oncogene homolog (avian)
C11orf75	2.96	2.31E-03	chromosome 11 open reading frame 75
CAPG	2.94	9.82E-03	capping protein (actin filament), gelsolin-like
DUSP5	2.94	3.67E-03	dual specificity phosphatase 5
GPR171	2.93	4.77E-02	G protein-coupled receptor 171
CFD	2.92	8.47E-03	complement factor D (adipsin)
SAMSN1	2.92	1.84E-02	SAM domain, SH3 domain and nuclear localization signals 1
MLLT11	2.92	4.55E-02	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11
SLC22A15	2.90	5.53E-03	solute carrier family 22, member 15
PLEK	2.89	2.43E-02	pleckstrin
RNASE6	2.89	4.10E-02	ribonuclease, RNase A family, k6
GK	2.86	3.57E-02	glycerol kinase
SYTL3	2.85	1.14E-02	synaptotagmin-like 3
SLC31A2	2.85	1.63E-02	solute carrier family 31 (copper transporters), member 2
MS4A4A	2.85	1.62E-02	membrane-spanning 4-domains, subfamily A, member 4
ACSL1	2.83	4.70E-02	acyl-CoA synthetase long-chain family member 1
CMTM7	2.83	1.12E-02	CKLF-like MARVEL transmembrane domain containing 7
BLOC1S2	2.83	3.23E-03	biogenesis of lysosomal organelles complex-1, subunit 2
LHFPL2	2.83	1.65E-02	lipoma HMGIC fusion partner-like 2
HIF1A	2.80	5.85E-06	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)
SRPX2	2.80	3.12E-02	sushi-repeat-containing protein, X-linked 2
FYB	2.78	1.87E-02	FYN binding protein (FYB-120/130)
LRRC8D	2.76	2.53E-03	leucine rich repeat containing 8 family, member D
ST14	2.75	1.27E-02	suppression of tumorigenicity 14 (colon carcinoma)
SLC11A1	2.75	7.34E-03	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1
IL1R1	2.74	1.81E-03	interleukin 1 receptor, type I
EFHD2	2.73	1.38E-03	EF-hand domain family, member D2
ARHGAP18	2.73	7.59E-03	Rho GTPase activating protein 18
IMPDH1	2.73	2.20E-03	IMP (inosine monophosphate) dehydrogenase 1
FAM26F	2.71	8.89E-04	family with sequence similarity 26, member F
MYD88	2.70	1.38E-03	myeloid differentiation primary response gene (88)
SRGN	2.68	1.38E-03	serglycin
PIM1	2.67	6.55E-05	pim-1 oncogene
CD86	2.67	1.52E-02	CD86 molecule
F11R	2.67	3.23E-03	F11 receptor
RNASET2	2.65	2.72E-02	ribonuclease T2
SPOCD1	2.64	3.07E-03	SPOC domain containing 1
PRAGMIN	2.62	1.11E-02	homolog of rat pragma of Rnd2
TMEM2	2.62	6.98E-04	transmembrane protein 2
LAIR1	2.61	1.76E-02	leukocyte-associated immunoglobulin-like receptor 1
DPEP2	2.60	7.54E-03	dipeptidase 2
TMEM158	2.60	6.88E-03	transmembrane protein 158
SNORD114-3	2.59	4.53E-02	small nucleolar RNA, C/D box 114-3
PTPRE	2.59	2.96E-02	protein tyrosine phosphatase, receptor type, E
SERPINB1	2.58	1.49E-02	serpin peptidase inhibitor, clade B (ovalbumin), member 1
TREM1	2.58	8.15E-03	triggering receptor expressed on myeloid cells 1
PSME4	2.57	4.08E-04	proteasome (prosome, macropain) activator subunit 4
C12orf5	2.57	5.25E-03	chromosome 12 open reading frame 5
ITGB2	2.56	4.44E-02	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)
HN1	2.56	1.10E-03	hematological and neurological expressed 1
DUSP6	2.55	2.65E-03	dual specificity phosphatase 6
PTGS1	2.55	3.99E-02	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)
EMP3	2.54	1.58E-02	epithelial membrane protein 3
MYB	2.54	1.81E-03	v-myb myeloblastosis viral oncogene homolog (avian)
VASP	2.54	3.05E-03	vasodilator-stimulated phosphoprotein
H2AFY	2.52	4.73E-04	H2A histone family, member Y
TIAM1	2.51	1.08E-02	T-cell lymphoma invasion and metastasis 1
CCL5	2.50	8.30E-03	chemokine (C-C motif) ligand 5
STK10	2.50	3.35E-03	serine/threonine kinase 10
ATP6V0B	2.49	2.21E-03	ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b
CD300LF	2.48	3.34E-02	CD300 molecule-like family member f

CSF1R	2.48	1.99E-02	colony stimulating factor 1 receptor
ABCC3	2.46	2.32E-04	ATP-binding cassette, sub-family C (CFTR/MRP), member 3
EHD4	2.46	7.76E-03	EH-domain containing 4
BID	2.45	1.36E-02	BH3 interacting domain death agonist
PMAIP1	2.45	8.88E-04	phorbol-12-myristate-13-acetate-induced protein 1
SLC20A1	2.44	1.20E-02	solute carrier family 20 (phosphate transporter), member 1
VAV1	2.44	3.07E-02	vav 1 guanine nucleotide exchange factor
CSNK1D	2.44	2.60E-04	casein kinase 1, delta
PIK3AP1	2.44	3.94E-02	phosphoinositide-3-kinase adaptor protein 1
FPR3	2.43	3.06E-03	formyl peptide receptor 3
DOCK2	2.42	4.31E-02	dedicator of cytokinesis 2
LOC100133315	2.41	1.93E-02	similar to hCG1640299
CCRL2	2.41	5.24E-03	chemokine (C-C motif) receptor-like 2
BAZ1A	2.41	8.15E-03	bromodomain adjacent to zinc finger domain, 1A
STAB1	2.41	3.91E-02	stabilin 1
C1orf38	2.41	1.70E-02	chromosome 1 open reading frame 38
ARHGAP9	2.40	1.16E-02	Rho GTPase activating protein 9
SASH3	2.39	2.12E-02	SAM and SH3 domain containing 3
MMD	2.38	3.05E-02	monocyte to macrophage differentiation-associated
ARHGAP25	2.38	3.45E-02	Rho GTPase activating protein 25
ABHD5	2.37	2.17E-03	abhydrolase domain containing 5
S100A10	2.36	1.73E-03	S100 calcium binding protein A10
HK2	2.36	1.99E-02	hexokinase 2
CEBPB	2.36	1.74E-02	CCAAT/enhancer binding protein (C/EBP), beta
MAN2B1	2.36	6.22E-03	mannosidase, alpha, class 2B, member 1
CD55	2.35	2.89E-02	CD55 molecule, decay accelerating factor for complement (Cromer blood group)
MAPK13	2.34	2.13E-02	mitogen-activated protein kinase 13
PAPSS2	2.34	4.94E-02	3'-phosphoadenosine 5'-phosphosulfate synthase 2
MS4A14	2.34	2.72E-02	membrane-spanning 4-domains, subfamily A, member 14
AKR1C1	2.33	3.34E-02	aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)
SMPDL3A	2.33	4.41E-02	sphingomyelin phosphodiesterase, acid-like 3A
ANKRD9	2.33	1.38E-03	ankyrin repeat domain 9
B3GNT5	2.33	1.94E-02	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5
ISG20	2.32	1.80E-02	interferon stimulated exonuclease gene 20kDa
TMEM167A	2.32	4.63E-03	transmembrane protein 167A
SLC7A5	2.32	4.87E-02	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5
MGAT4A	2.31	2.60E-02	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme A
GMFB	2.30	4.86E-02	glia maturation factor, beta
METRNL	2.30	5.73E-03	meteorin, glial cell differentiation regulator-like
MOBKL1B	2.29	1.81E-03	MOB1, Mps One Binder kinase activator-like 1B (yeast)
TSPAN13	2.28	4.34E-02	tetraspanin 13
LPXN	2.28	2.64E-02	leupaxin
ARHGDIB	2.26	2.02E-02	Rho GDP dissociation inhibitor (GDI) beta
DOK2	2.24	1.46E-02	docking protein 2, 56kDa
KIAA0746	2.24	3.26E-02	KIAA0746 protein
TGIF1	2.23	4.36E-04	TGFB-induced factor homeobox 1
CKLF	2.22	2.86E-03	chemokine-like factor
EMILIN2	2.22	1.38E-03	elastin microfibril interfacer 2
ST3GAL1	2.22	1.70E-03	ST3 beta-galactoside alpha-2,3-sialyltransferase 1
CA2	2.22	3.06E-02	carbonic anhydrase II
CASP4	2.22	1.16E-02	caspase 4, apoptosis-related cysteine peptidase
GRB2	2.21	5.86E-03	growth factor receptor-bound protein 2
EDNRB	2.21	3.51E-02	endothelin receptor type B
RAB20	2.21	1.55E-02	RAB20, member RAS oncogene family
PFKFB3	2.21	2.18E-02	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3
TGFBI	2.20	4.05E-02	transforming growth factor, beta-induced, 68kDa
IFNGR2	2.20	4.73E-04	interferon gamma receptor 2 (interferon gamma transducer 1)
ARHGAP22	2.19	2.52E-02	Rho GTPase activating protein 22
GSTO1	2.19	1.32E-03	glutathione S-transferase omega 1
ATP6V1B2	2.19	3.91E-02	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B2
DENND4B	2.19	2.90E-02	DENN/MADD domain containing 4B
TOP1	2.18	6.63E-04	topoisomerase (DNA) I
TLR1	2.18	3.75E-02	toll-like receptor 1
DGKZ	2.17	3.47E-02	diacylglycerol kinase, zeta 104kDa
VEGFA	2.17	3.91E-02	vascular endothelial growth factor A
NOD2	2.17	4.47E-02	nucleotide-binding oligomerization domain containing 2
SEC14L1	2.17	3.92E-03	SEC14-like 1 (S. cerevisiae)
TNFRSF21	2.17	6.06E-03	tumor necrosis factor receptor superfamily, member 21
C17orf62	2.17	1.30E-02	chromosome 17 open reading frame 62
AGFG1	2.16	7.65E-03	ArfGAP with FG repeats 1
CCR5	2.15	3.50E-02	chemokine (C-C motif) receptor 5
CSK	2.15	1.08E-02	c-src tyrosine kinase
MYO1G	2.14	1.16E-02	myosin IG
CD44	2.14	2.36E-03	CD44 molecule (Indian blood group)
PLA2G7	2.14	1.60E-02	phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)
GLRX	2.13	1.60E-03	glutaredoxin (thioltransferase)
GLA	2.13	9.14E-03	galactosidase, alpha
SLC22A4	2.11	2.86E-02	solute carrier family 22 (organic cation/ergothioneine transporter), member 4
CYBB	2.11	4.54E-02	cytochrome b-245, beta polypeptide
C6orf62	2.11	2.98E-03	chromosome 6 open reading frame 62
BASP1	2.11	1.20E-02	brain abundant, membrane attached signal protein 1
PTP4A2	2.11	1.03E-03	protein tyrosine phosphatase type IVA, member 2
KLF4	2.11	1.10E-02	Kruppel-like factor 4 (gut)
ATP6V0D1	2.10	3.16E-02	ATPase, H+ transporting, lysosomal 38kDa, V0 subunit d1
IRAK3	2.10	4.18E-02	interleukin-1 receptor-associated kinase 3
RBM47	2.10	6.37E-03	RNA binding motif protein 47

DAB2	2.09	4.47E-03	disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)
PNPLA6	2.09	2.05E-02	patatin-like phospholipase domain containing 6
IRAK1	2.09	3.43E-03	interleukin-1 receptor-associated kinase 1
IL6R	2.09	3.67E-02	interleukin 6 receptor
CIB1	2.08	3.51E-04	calcium and integrin binding 1 (calmyrin)
DPH3	2.08	3.27E-03	DPH3, KTI11 homolog (S. cerevisiae)
SERPINA1	2.08	4.98E-02	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1
WIPF1	2.07	1.59E-02	WAS/WASL interacting protein family, member 1
PLEKHB2	2.07	1.04E-02	pleckstrin homology domain containing, family B (evectins) member 2
FAM49A	2.07	3.50E-02	family with sequence similarity 49, member A
MLKL	2.07	1.04E-02	mixed lineage kinase domain-like
GLIPR2	2.06	2.89E-03	GLI pathogenesis-related 2
M6PRBP1	2.06	9.64E-04	mannose-6-phosphate receptor binding protein 1
GPR65	2.06	3.01E-02	G protein-coupled receptor 65
CYBA	2.06	2.31E-02	cytochrome b-245, alpha polypeptide
RAB27A	2.06	1.22E-02	RAB27A, member RAS oncogene family
NRIP3	2.05	3.27E-03	nuclear receptor interacting protein 3
RHBDF2	2.05	2.01E-02	rhomboid 5 homolog 2 (Drosophila)
FCGRT	2.05	9.75E-03	Fc fragment of IgG, receptor, transporter, alpha
MXD1	2.04	2.11E-02	MAX dimerization protein 1
PDK4	2.04	1.84E-02	pyruvate dehydrogenase kinase, isozyme 4
MGAT1	2.04	6.29E-03	mannosyl (alpha-1,3-)-glycoprotein beta-1,2-N-acetylglucosaminyltransferase
QSOX1	2.04	8.46E-03	quiescin Q6 sulfhydryl oxidase 1
LAMP3	2.03	5.12E-03	lysosomal-associated membrane protein 3
GNL3	2.03	2.63E-02	guanine nucleotide binding protein-like 3 (nucleolar)
C20orf24	2.03	1.09E-02	chromosome 20 open reading frame 24
RHOG	2.03	6.22E-03	ras homolog gene family, member G (rho G)
KPNA2	2.03	4.78E-02	karyopherin alpha 2 (RAG cohort 1, importin alpha 1)
SLC25A37	2.03	3.19E-02	solute carrier family 25, member 37
SUSD1	2.02	1.99E-02	sushi domain containing 1
CYB5R4	2.02	2.11E-02	cytochrome b5 reductase 4
LOC729806	2.02	2.41E-02	similar to hCG1725380
WARS	2.02	1.71E-02	tryptophanyl-tRNA synthetase
MCOLN1	2.01	1.22E-02	mucolipin 1
IRF1	2.00	3.36E-02	interferon regulatory factor 1
TYK2	2.00	2.90E-02	tyrosine kinase 2
KIAA0101	1.99	2.88E-02	KIAA0101
SRXN1	1.99	2.89E-02	sulfiredoxin 1 homolog (S. cerevisiae)
FHOD1	1.99	2.15E-02	formin homology 2 domain containing 1
RBBP8	1.99	6.04E-03	retinoblastoma binding protein 8
VDR	1.98	1.02E-02	vitamin D (1,25- dihydroxyvitamin D3) receptor
GPR160	1.98	2.23E-02	G protein-coupled receptor 160
ASPHD2	1.98	2.61E-02	aspartate beta-hydroxylase domain containing 2
ITGA5	1.97	1.25E-02	integrin, alpha 5 (fibronectin receptor, alpha polypeptide)
S100A11	1.97	2.64E-02	S100 calcium binding protein A11
PIM3	1.96	5.79E-04	pim-3 oncogene
TBC1D8	1.96	2.67E-02	TBC1 domain family, member 8 (with GRAM domain)
CTSA	1.96	8.15E-03	cathepsin A
SPPL2A	1.96	1.90E-02	signal peptide peptidase-like 2A
RPL22L1	1.96	1.50E-02	ribosomal protein L22-like 1
SRM	1.95	1.49E-02	spermidine synthase
SNX8	1.94	4.85E-03	sorting nexin 8
ZNF267	1.94	4.71E-02	zinc finger protein 267
ALPK2	1.94	1.41E-02	alpha-kinase 2
SOAT1	1.94	3.01E-02	sterol O-acyltransferase 1
NEK6	1.94	7.34E-03	NIMA (never in mitosis gene a)-related kinase 6
TACC3	1.94	3.90E-02	transforming, acidic coiled-coil containing protein 3
NCF4	1.94	4.55E-02	neutrophil cytosolic factor 4, 40kDa
PLEKHO2	1.93	4.19E-03	pleckstrin homology domain containing, family O member 2
NUSAP1	1.93	2.01E-02	nucleolar and spindle associated protein 1
MELK	1.93	3.47E-02	maternal embryonic leucine zipper kinase
NCKAP1L	1.93	2.64E-02	NCK-associated protein 1-like
C9orf30	1.93	6.17E-03	chromosome 9 open reading frame 30
TNFAIP2	1.93	2.34E-02	tumor necrosis factor, alpha-induced protein 2
ALOX5	1.91	4.88E-02	arachidonate 5-lipoxygenase
OAS1	1.91	3.21E-02	2',5'-oligoadenylate synthetase 1, 40/46kDa
CD300A	1.91	3.88E-02	CD300a molecule
EMR2	1.91	6.07E-03	egf-like module containing, mucin-like, hormone receptor-like 2
PIK3CD	1.91	2.15E-02	phosphoinositide-3-kinase, catalytic, delta polypeptide
SH2B3	1.91	4.36E-02	SH2B adaptor protein 3
RNF149	1.90	1.76E-02	ring finger protein 149
KIAA1949	1.90	2.31E-02	KIAA1949
S100A16	1.89	3.34E-02	S100 calcium binding protein A16
KYNU	1.89	4.83E-03	kynureninase (L-kynurenine hydrolase)
LYVE1	1.89	4.00E-02	lymphatic vessel endothelial hyaluronan receptor 1
AMPD2	1.89	1.35E-03	adenosine monophosphate deaminase 2 (isoform L)
RPN2	1.88	2.44E-03	ribophorin II
TAF1D	1.88	4.03E-03	TATA box binding protein (TBP)-associated factor, RNA polymerase I, D, 41kDa
RGS19	1.87	8.57E-03	regulator of G-protein signaling 19
GMPPB	1.87	2.50E-03	GDP-mannose pyrophosphorylase B
SDCBP	1.86	1.91E-02	syndecan binding protein (syntenin)
TPST2	1.85	3.31E-02	tyrosylprotein sulfotransferase 2
CXorf38	1.85	8.67E-03	chromosome X open reading frame 38
HIST1H2BK	1.85	3.69E-02	histone cluster 1, H2bk
AMPD3	1.84	1.61E-03	adenosine monophosphate deaminase (isoform E)
NFKBIE	1.84	6.26E-03	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon
ME2	1.84	9.01E-03	malic enzyme 2, NAD(+)-dependent, mitochondrial
3-Mar	1.84	3.66E-02	membrane-associated ring finger (C3HC4) 3
WIPI1	1.83	6.07E-03	WD repeat domain, phosphoinositide interacting 1
SLCO4A1	1.83	3.19E-02	solute carrier organic anion transporter family, member 4A1

NPC2	1.83	3.42E-02	Niemann-Pick disease, type C2
GTF3A	1.83	2.52E-02	general transcription factor IIIA
ADCY7	1.83	1.53E-02	adenylate cyclase 7
ARAP1	1.83	8.63E-04	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 1
TRIB1	1.83	9.87E-03	tribbles homolog 1 (Drosophila)
STX4	1.83	1.76E-02	syntaxin 4
MMP19	1.82	1.22E-02	matrix metallopeptidase 19
ATP1B3	1.82	2.31E-02	ATPase, Na+/K+ transporting, beta 3 polypeptide
HGS	1.82	5.53E-03	hepatocyte growth factor-regulated tyrosine kinase substrate
MAPKAPK3	1.82	1.11E-02	mitogen-activated protein kinase-activated protein kinase 3
C6orf150	1.82	8.57E-03	chromosome 6 open reading frame 150
ODF3B	1.81	2.90E-02	outer dense fiber of sperm tails 3B
CHST2	1.81	7.51E-03	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2
OSBPL3	1.81	2.02E-02	oxysterol binding protein-like 3
METTL1	1.81	1.89E-02	methyltransferase like 1
SULT1B1	1.81	2.15E-02	sulfotransferase family, cytosolic, 1B, member 1
C12orf59	1.81	3.58E-02	chromosome 12 open reading frame 59
SLC25A19	1.80	1.46E-02	solute carrier family 25 (mitochondrial thiamine pyrophosphate carrier), member 19
FES	1.80	1.82E-02	feline sarcoma oncogene
ZNF469	1.80	3.31E-02	zinc finger protein 469
ACADVL	1.80	4.07E-02	acyl-Coenzyme A dehydrogenase, very long chain
FXYD5	1.80	1.95E-02	FXYD domain containing ion transport regulator 5
FLVCR2	1.80	9.63E-03	feline leukemia virus subgroup C cellular receptor family, member 2
PNKP	1.80	1.35E-03	polynucleotide kinase 3'-phosphatase
SLC43A3	1.79	3.16E-02	solute carrier family 43, member 3
DYSF	1.79	4.75E-02	dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive)
MAP2K3	1.79	2.31E-02	mitogen-activated protein kinase kinase 3
PPRC1	1.79	1.74E-02	peroxisome proliferator-activated receptor gamma, coactivator-related 1
CYTH1	1.79	2.57E-02	cytohesin 1
PHLDA1	1.79	1.40E-03	pleckstrin homology-like domain, family A, member 1
PLOD3	1.78	1.61E-03	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3
ARNTL	1.78	4.16E-02	aryl hydrocarbon receptor nuclear translocator-like
CCM2	1.78	6.56E-03	cerebral cavernous malformation 2
KCNN4	1.78	2.57E-02	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4
NOP10	1.78	5.19E-03	NOP10 ribonucleoprotein homolog (yeast)
SDSL	1.78	2.66E-02	serine dehydratase-like
ACP2	1.78	3.43E-02	acid phosphatase 2, lysosomal
EFTUD2	1.77	9.82E-03	elongation factor Tu GTP binding domain containing 2
C3orf52	1.77	3.75E-02	chromosome 3 open reading frame 52
DDX3X	1.77	7.08E-04	DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked
PTPN1	1.77	2.90E-02	protein tyrosine phosphatase, non-receptor type 1
IL1RL1	1.76	4.47E-02	interleukin 1 receptor-like 1
EREG	1.76	1.20E-02	epiregulin
CCNL1	1.76	4.67E-02	cyclin L1
PI4K2A	1.76	3.76E-03	phosphatidylinositol 4-kinase type 2 alpha
ZCCHC6	1.76	1.50E-02	zinc finger, CCHC domain containing 6
HAVCR2	1.76	3.48E-02	hepatitis A virus cellular receptor 2
MED25	1.76	1.90E-03	mediator complex subunit 25
UBE2D3	1.76	1.79E-02	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)
DDX39	1.75	3.90E-02	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39
PPAN	1.75	5.53E-03	peter pan homolog (Drosophila)
JHDM1D	1.75	1.74E-02	jumonji C domain containing histone demethylase 1 homolog D (S. cerevisiae)
HSD3B7	1.75	9.28E-03	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 7
GRB10	1.75	3.48E-02	growth factor receptor-bound protein 10
KIAA1539	1.74	1.63E-02	KIAA1539
NFKBIA	1.74	4.44E-02	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
ABCG1	1.74	3.26E-02	ATP-binding cassette, sub-family G (WHITE), member 1
NOP2	1.74	2.95E-02	NOP2 nucleolar protein homolog (yeast)
MGAT4B	1.74	1.13E-02	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme B
LGALS8	1.74	3.39E-03	lectin, galactoside-binding, soluble, 8
SRA1	1.73	1.12E-02	steroid receptor RNA activator 1
UBASH3B	1.73	3.48E-03	ubiquitin associated and SH3 domain containing, B
GAS7	1.72	3.05E-02	growth arrest-specific 7
SLC16A3	1.72	2.66E-02	solute carrier family 16, member 3 (monocarboxylic acid transporter 4)
APOBEC3B	1.72	1.22E-02	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B
ERO1L	1.72	1.76E-02	ERO1-like (S. cerevisiae)
MICALL1	1.71	1.56E-02	MICAL-like 1
TNFAIP8L2	1.71	4.20E-02	tumor necrosis factor, alpha-induced protein 8-like 2
PSAP	1.71	4.86E-02	prosaposin
C7orf43	1.71	3.00E-02	chromosome 7 open reading frame 43
PSMD12	1.71	1.04E-02	proteasome (prosome, macropain) 26S subunit, non-ATPase, 12
FBXL11	1.71	5.40E-03	F-box and leucine-rich repeat protein 11
RPN1	1.71	1.12E-02	ribophorin I
SPNS1	1.71	7.05E-03	spinster homolog 1 (Drosophila)
HOMER3	1.71	1.20E-02	homer homolog 3 (Drosophila)
TMSB10	1.71	2.18E-02	thymosin beta 10
LYL1	1.70	4.43E-02	lymphoblastic leukemia derived sequence 1
NETO2	1.70	4.71E-02	neuropilin (NRP) and tolloid (TLL)-like 2
GRN	1.70	3.69E-02	granulin
PTAFR	1.70	3.29E-02	platelet-activating factor receptor
SYAP1	1.70	1.34E-02	synapse associated protein 1, SAP47 homolog (Drosophila)
HAS1	1.69	3.96E-02	hyaluronan synthase 1
ELF4	1.69	3.19E-03	E74-like factor 4 (ets domain transcription factor)
NOP16	1.69	1.57E-02	NOP16 nucleolar protein homolog (yeast)

PRELID1	1.69	4.14E-02	PRELI domain containing 1
KCNK6	1.69	3.48E-02	potassium channel, subfamily K, member 6
EIF4EBP1	1.69	4.78E-02	eukaryotic translation initiation factor 4E binding protein 1
CD82	1.69	2.31E-02	CD82 molecule
ARPC5L	1.69	1.00E-02	actin related protein 2/3 complex, subunit 5-like
PLA2G15	1.68	4.44E-02	phospholipase A2, group XV
SDF2L1	1.68	1.97E-02	stromal cell-derived factor 2-like 1
NAGK	1.68	2.44E-02	N-acetylglucosamine kinase
FAM20A	1.68	1.63E-02	family with sequence similarity 20, member A
ARPC1B	1.68	1.61E-02	actin related protein 2/3 complex, subunit 1B, 41kDa
FRAT1	1.68	3.15E-02	frequently rearranged in advanced T-cell lymphomas
IGF2BP3	1.68	4.85E-02	insulin-like growth factor 2 mRNA binding protein 3
SIK1	1.67	2.31E-02	salt-inducible kinase 1
GARS	1.67	1.40E-02	glycyl-tRNA synthetase
MT4	1.67	1.22E-02	metallothionein 4
C19orf10	1.67	1.84E-02	chromosome 19 open reading frame 10
CLEC10A	1.67	3.52E-02	C-type lectin domain family 10, member A
XPO6	1.67	4.85E-03	exportin 6
GAK	1.67	1.74E-02	cyclin G associated kinase
PHC2	1.67	2.64E-02	polyhomeotic homolog 2 (Drosophila)
SIPA1L2	1.67	2.86E-02	signal-induced proliferation-associated 1 like 2
OAZ1	1.66	2.04E-02	ornithine decarboxylase antizyme 1
MRPL14	1.66	1.19E-03	mitochondrial ribosomal protein L14
CHKA	1.66	1.21E-02	choline kinase alpha
DPAGT1	1.66	1.21E-02	dolichyl-phosphate (UDP-N-acetylglucosamine) N-acetylglucosaminephosphotransferase 1 (GlcNAc-1-P transferase)
SLC7A6	1.65	1.58E-02	solute carrier family 7 (cationic amino acid transporter, y+ system), member 6
SLC37A2	1.65	2.65E-02	solute carrier family 37 (glycerol-3-phosphate transporter), member 2
SLCO2B1	1.65	4.77E-02	solute carrier organic anion transporter family, member 2B1
GSPT1	1.65	4.36E-02	G1 to S phase transition 1
OAS3	1.65	4.26E-02	2'-5'-oligoadenylate synthetase 3, 100kDa
TPI1	1.65	3.03E-02	triosephosphate isomerase 1
P2RX4	1.65	9.19E-03	purinergic receptor P2X, ligand-gated ion channel, 4
RNPEP	1.65	4.11E-02	arginyl aminopeptidase (aminopeptidase B)
ZSWIM6	1.64	3.22E-02	zinc finger, SWIM-type containing 6
GPR172A	1.64	5.53E-03	G protein-coupled receptor 172A
GGA1	1.64	2.27E-02	golgi associated, gamma adaptin ear containing, ARF binding protein 1
WDR81	1.64	2.57E-02	WD repeat domain 81
COX5A	1.64	3.28E-02	cytochrome c oxidase subunit Va
STK11IP	1.64	1.18E-02	serine/threonine kinase 11 interacting protein
ICAM1	1.64	1.49E-02	intercellular adhesion molecule 1
ERCC1	1.64	1.74E-02	excision repair cross-complementing rodent repair deficiency, complementation group 1 (includes overlapping antisense sequence)
PFKFB4	1.63	4.39E-02	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4
IL10RB	1.63	1.89E-02	interleukin 10 receptor, beta
SFT2D2	1.63	3.63E-02	SFT2 domain containing 2
AP2S1	1.63	3.69E-02	adaptor-related protein complex 2, sigma 1 subunit
ARFGAP1	1.63	1.54E-02	ADP-ribosylation factor GTPase activating protein 1
RAB32	1.63	1.12E-02	RAB32, member RAS oncogene family
LOC1001324 30	1.63	1.74E-02	hypothetical LOC100132430
TNFRSF10A	1.63	4.44E-02	tumor necrosis factor receptor superfamily, member 10a
CD84	1.63	4.36E-02	CD84 molecule
NUAK2	1.63	2.21E-02	NUAK family, SNF1-like kinase, 2
RIT1	1.63	4.12E-02	Ras-like without CAAX 1
GALE	1.63	1.79E-02	UDP-galactose-4-epimerase
JMJD3	1.63	2.85E-02	jumonji domain containing 3, histone lysine demethylase
MATK	1.63	2.25E-02	megakaryocyte-associated tyrosine kinase
FAM100B	1.62	1.13E-02	family with sequence similarity 100, member B
RIN3	1.62	2.23E-02	Ras and Rab interactor 3
LIMS1	1.62	1.63E-02	LIM and senescent cell antigen-like domains 1
SIRT7	1.61	1.63E-02	sirtuin (silent mating type information regulation 2 homolog) 7 (S. cerevisiae)
HEATR3	1.61	3.00E-02	HEAT repeat containing 3
E2F3	1.61	1.01E-02	E2F transcription factor 3
GNG5	1.61	5.44E-03	guanine nucleotide binding protein (G protein), gamma 5
GUSB	1.61	6.82E-03	glucuronidase, beta
HPCAL1	1.61	7.69E-03	hippocalcin-like 1
PLK3	1.61	1.38E-02	polo-like kinase 3 (Drosophila)
ACTR2	1.60	2.19E-02	ARP2 actin-related protein 2 homolog (yeast)
GGA3	1.60	3.07E-02	golgi associated, gamma adaptin ear containing, ARF binding protein 3
APOB48R	1.60	3.60E-02	apolipoprotein B48 receptor
KIAA0020	1.60	1.68E-02	KIAA0020
CMTM6	1.60	4.16E-02	CKLF-like MARVEL transmembrane domain containing 6
IL4I1	1.60	4.63E-02	interleukin 4 induced 1
C10orf125	1.60	3.91E-02	chromosome 10 open reading frame 125
ADA	1.60	2.73E-02	adenosine deaminase
C10orf11	1.60	4.77E-02	chromosome 10 open reading frame 11
ARPC2	1.60	1.39E-02	actin related protein 2/3 complex, subunit 2, 34kDa
SLC25A20	1.59	2.91E-02	solute carrier family 25 (carnitine/acylcarnitine translocase), member 20
CHST11	1.59	1.32E-02	carbohydrate (chondroitin 4) sulfotransferase 11
RP3-402G11.5	1.59	3.26E-02	selenoprotein O
ADRM1	1.59	5.75E-03	adhesion regulating molecule 1
NADK	1.59	1.70E-02	NAD kinase
ARMET	1.59	4.98E-02	arginine-rich, mutated in early stage tumors
RAB8A	1.59	3.01E-02	RAB8A, member RAS oncogene family
ZDHHC18	1.58	6.82E-03	zinc finger, DHHC-type containing 18
ZGPAT	1.58	2.85E-02	zinc finger, CCCH-type with G patch domain
DBNL	1.58	5.75E-03	drebrin-like

MR1	1.58	1.46E-02	major histocompatibility complex, class I-related
TWF2	1.58	1.50E-02	twinfilin, actin-binding protein, homolog 2 (Drosophila)
KCNE3	1.58	4.63E-02	potassium voltage-gated channel, Isk-related family, member 3
KIAA0664	1.58	3.75E-02	KIAA0664
CSNK1G2	1.58	1.70E-02	casein kinase 1, gamma 2
MVP	1.57	3.02E-02	major vault protein
SURF4	1.57	3.30E-02	surfeit 4
CDCP1	1.57	2.12E-02	CUB domain containing protein 1
FOSL2	1.57	3.10E-03	FOS-like antigen 2
TFRC	1.57	2.13E-02	transferrin receptor (p90, CD71)
PPP4C	1.57	9.57E-03	protein phosphatase 4 (formerly X), catalytic subunit
SLC35B1	1.57	4.18E-02	solute carrier family 35, member B1
ATP6V0C	1.57	1.50E-02	ATPase, H+ transporting, lysosomal 16kDa, V0 subunit c
RRP7A	1.56	2.31E-02	ribosomal RNA processing 7 homolog A (S. cerevisiae)
PTGES	1.56	1.88E-02	prostaglandin E synthase
DUSP23	1.56	2.65E-02	dual specificity phosphatase 23
FGFR1OP	1.56	1.35E-02	FGFR1 oncogene partner
HTRA3	1.56	2.13E-02	HtrA serine peptidase 3
HPRT1	1.56	4.81E-02	hypoxanthine phosphoribosyltransferase 1
NADSYN1	1.56	4.42E-02	NAD synthetase 1
HYOU1	1.56	2.41E-02	hypoxia up-regulated 1
TMEM106A	1.56	4.74E-02	transmembrane protein 106A
SAMHD1	1.56	4.79E-02	SAM domain and HD domain 1
VPS16	1.56	2.63E-02	vacuolar protein sorting 16 homolog (S. cerevisiae)
CSGLCA-T	1.55	4.98E-02	chondroitin sulfate glucuronyltransferase
PDXK	1.55	2.31E-02	pyridoxal (pyridoxine, vitamin B6) kinase
LOC100133362	1.55	4.94E-02	similar to heterogeneous nuclear ribonucleoprotein A1
CREM	1.55	3.45E-02	cAMP responsive element modulator
IMP4	1.55	3.07E-02	IMP4, U3 small nucleolar ribonucleoprotein, homolog (yeast)
ACTR3	1.55	3.12E-02	ARP3 actin-related protein 3 homolog (yeast)
SIGLEC10	1.55	4.88E-02	sialic acid binding Ig-like lectin 10
PLEKHM2	1.55	3.34E-02	pleckstrin homology domain containing, family M (with RUN domain) member 2
TCP11L1	1.55	1.49E-02	t-complex 11 (mouse)-like 1
ABCC1	1.55	3.16E-02	ATP-binding cassette, sub-family C (CFTR/MRP), member 1
DPP3	1.55	4.33E-03	dipeptidyl-peptidase 3
ADIPOR1	1.54	1.73E-02	adiponectin receptor 1
ADAM8	1.54	4.94E-02	ADAM metallopeptidase domain 8
MTMR14	1.54	2.43E-02	myotubularin related protein 14
PPIL5	1.54	1.46E-02	peptidylprolyl isomerase (cyclophilin)-like 5
SLC12A6	1.54	3.15E-02	solute carrier family 12 (potassium/chloride transporters), member 6
TSPAN17	1.53	7.77E-03	tetraspanin 17
KPNB1	1.52	1.58E-02	karyopherin (importin) beta 1
SPCS3	1.52	3.46E-02	signal peptidase complex subunit 3 homolog (S. cerevisiae)
NIPA2	1.52	2.63E-02	non imprinted in Prader-Willi/Angelman syndrome 2
IL10	1.52	3.63E-02	interleukin 10
TNIP2	1.52	1.89E-02	TNFAIP3 interacting protein 2
ADPGK	1.52	2.53E-02	ADP-dependent glucokinase
C19orf28	1.52	1.75E-02	chromosome 19 open reading frame 28
TBC1D9	1.52	3.11E-02	TBC1 domain family, member 9 (with GRAM domain)
DNMT1	1.51	2.43E-02	DNA (cytosine-5-)-methyltransferase 1
HSD17B14	1.51	2.15E-02	hydroxysteroid (17-beta) dehydrogenase 14
HM13	1.51	8.57E-03	histocompatibility (minor) 13
TTC38	1.51	3.16E-02	tetratricopeptide repeat domain 38
ARPC5	1.51	2.09E-02	actin related protein 2/3 complex, subunit 5, 16kDa
ERCC5	1.51	4.94E-02	excision repair cross-complementing rodent repair deficiency, complementation group 5
UBR4	1.50	1.20E-02	ubiquitin protein ligase E3 component n-recognin 4
CHIC2	1.50	1.26E-02	cysteine-rich hydrophobic domain 2
PLEKHM1	1.50	2.31E-02	pleckstrin homology domain containing, family M (with RUN domain) member 1
2-Mar	1.50	3.07E-02	membrane-associated ring finger (C3HC4) 2
TNFRSF1A	1.50	1.70E-02	tumor necrosis factor receptor superfamily, member 1A
SLC2A6	1.50	3.34E-02	solute carrier family 2 (facilitated glucose transporter), member 6
PXN	1.50	1.12E-02	paxillin
CSGALNACT2	1.50	2.15E-02	chondroitin sulfate N-acetylgalactosaminyltransferase 2
CHFR	1.49	1.11E-02	checkpoint with forkhead and ring finger domains
CDV3	1.49	3.39E-02	CDV3 homolog (mouse)
IL17RA	1.49	2.31E-02	interleukin 17 receptor A
SH3TC1	1.49	3.05E-02	SH3 domain and tetratricopeptide repeats 1
PCSK7	1.49	3.82E-02	proprotein convertase subtilisin/kexin type 7
RALB	1.49	1.49E-02	v-ral simian leukemia viral oncogene homolog B (ras related; GTP binding protein)
FLOT1	1.49	2.12E-02	flotillin 1
AP1B1	1.48	4.87E-02	adaptor-related protein complex 1, beta 1 subunit
DNAJC3	1.48	2.51E-02	DnaJ (Hsp40) homolog, subfamily C, member 3
CCDC137	1.48	2.28E-02	coiled-coil domain containing 137
SNX11	1.48	2.91E-02	sorting nexin 11
BYSL	1.48	3.52E-02	bystin-like
C19orf22	1.48	2.47E-02	chromosome 19 open reading frame 22
TAGLN2	1.48	2.16E-02	transgelin 2
KIAA0100	1.48	3.00E-02	KIAA0100
SERPINB8	1.47	2.71E-02	serpin peptidase inhibitor, clade B (ovalbumin), member 8
LRRC33	1.47	3.84E-02	leucine rich repeat containing 33
FAM110A	1.47	3.00E-02	family with sequence similarity 110, member A
PHRF1	1.47	1.18E-02	PHD and ring finger domains 1
BCKDK	1.47	1.97E-02	branched chain ketoacid dehydrogenase kinase
GATAD2A	1.47	4.03E-02	GATA zinc finger domain containing 2A
ZMYND15	1.47	2.44E-02	zinc finger, MYND-type containing 15
GLTSCR1	1.47	3.65E-02	glioma tumor suppressor candidate region gene 1
NOP14	1.47	2.88E-02	NOP14 nucleolar protein homolog (yeast)

SRRT	1.46	3.83E-02	serrate RNA effector molecule homolog (Arabidopsis)
IRAK4	1.46	3.00E-02	interleukin-1 receptor-associated kinase 4
STX6	1.46	1.91E-02	syntaxin 6
CORO2A	1.46	4.63E-02	coronin, actin binding protein, 2A
PDCD11	1.46	2.31E-02	programmed cell death 11
SLC25A44	1.46	3.06E-02	solute carrier family 25, member 44
CR1	1.45	4.14E-02	complement component (3b/4b) receptor 1 (Knops blood group)
RFWD3	1.45	2.50E-02	ring finger and WD repeat domain 3
LMNB2	1.45	4.83E-02	lamin B2
CDC42SE1	1.45	2.31E-02	CDC42 small effector 1
MCL1	1.45	1.73E-02	myeloid cell leukemia sequence 1 (BCL2-related)
STK40	1.44	3.26E-02	serine/threonine kinase 40
XIRP1	1.44	4.87E-02	xin actin-binding repeat containing 1
C12orf49	1.44	2.44E-02	chromosome 12 open reading frame 49
B4GALT3	1.44	4.16E-02	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 3
LACTB	1.44	2.31E-02	lactamase, beta
INPPL1	1.43	2.42E-02	inositol polyphosphate phosphatase-like 1
ANKRD11	1.43	3.60E-02	ankyrin repeat domain 11
STARD3	1.43	4.77E-02	StAR-related lipid transfer (START) domain containing 3
SERINC2	1.42	3.36E-02	serine incorporator 2
GALNT12	1.42	2.49E-02	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 12 (GalNAc-T12)
PIP5K1C	1.42	1.66E-02	phosphatidylinositol-4-phosphate 5-kinase, type I, gamma
ORAI1	1.41	2.66E-02	ORAI calcium release-activated calcium modulator 1
BATF3	1.41	4.75E-02	basic leucine zipper transcription factor, ATF-like 3
TMEM93	1.41	4.32E-02	transmembrane protein 93
RRP12	1.41	1.58E-02	ribosomal RNA processing 12 homolog (S. cerevisiae)
ZNF513	1.41	2.60E-02	zinc finger protein 513
DNAJC5B	1.40	3.67E-02	DnaJ (Hsp40) homolog, subfamily C, member 5 beta
SCAMP3	1.40	4.01E-02	secretory carrier membrane protein 3
JTB	1.40	3.08E-02	jumping translocation breakpoint
YRDC	1.40	4.54E-02	yrdC domain containing (E. coli)
DNM2	1.39	4.84E-02	dynamin 2
UBD	1.39	2.43E-02	ubiquitin D
ZNF8	1.39	4.31E-02	zinc finger protein 8
SMARCD2	1.39	4.57E-02	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2
PIGW	1.38	4.34E-02	phosphatidylinositol glycan anchor biosynthesis, class W
SLC7A8	1.37	3.53E-02	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8
MLEC	1.36	3.01E-02	malectin
VPS35	0.73	3.14E-02	vacuolar protein sorting 35 homolog (S. cerevisiae)
MRPL45	0.73	4.83E-02	mitochondrial ribosomal protein L45
RHBDD1	0.72	4.54E-02	rhomboid domain containing 1
EPB41L5	0.72	4.69E-02	erythrocyte membrane protein band 4.1 like 5
CRIPT	0.71	3.48E-02	cysteine-rich PDZ-binding protein
DUT	0.71	2.43E-02	deoxyuridine triphosphatase
ZDHHC17	0.71	4.37E-02	zinc finger, DHHC-type containing 17
TMEM68	0.71	4.31E-02	transmembrane protein 68
TRDMT1	0.71	4.74E-02	tRNA aspartic acid methyltransferase 1
ZNF347	0.71	3.37E-02	zinc finger protein 347
PAQR7	0.70	4.05E-02	progestin and adipoQ receptor family member VII
GLRB	0.70	4.31E-02	glycine receptor, beta
ALDH3A2	0.70	4.36E-02	aldehyde dehydrogenase 3 family, member A2
ASTE1	0.70	3.05E-02	asteroid homolog 1 (Drosophila)
C21orf91	0.70	4.65E-02	chromosome 21 open reading frame 91
DPH5	0.70	2.47E-02	DPH5 homolog (S. cerevisiae)
C5	0.70	3.69E-02	complement component 5
GLTSCR2	0.70	4.67E-02	glioma tumor suppressor candidate region gene 2
CCDC8	0.70	4.29E-02	coiled-coil domain containing 8
PDE4C	0.70	4.77E-02	phosphodiesterase 4C, cAMP-specific (phosphodiesterase E1 dunce homolog, Drosophila)
C8orf48	0.70	4.07E-02	chromosome 8 open reading frame 48
TNRC6A	0.69	4.98E-02	trinucleotide repeat containing 6A
ZFP3	0.69	2.32E-02	zinc finger protein 3 homolog (mouse)
C18orf18	0.69	1.25E-02	chromosome 18 open reading frame 18
LOC645513	0.69	2.96E-02	hypothetical LOC645513
ZNF337	0.69	4.36E-02	zinc finger protein 337
STOML1	0.69	2.43E-02	stomatin (EPB72)-like 1
S100PBP	0.69	2.43E-02	S100P binding protein
PIN4	0.69	4.90E-02	protein (peptidylprolyl cis/trans isomerase) NIMA-interacting, 4 (parvulin)
LGI4	0.69	3.44E-02	leucine-rich repeat LGI family, member 4
ICK	0.69	2.15E-02	intestinal cell (MAK-like) kinase
ORC4L	0.68	2.57E-02	origin recognition complex, subunit 4-like (yeast)
ZNF10	0.68	4.89E-02	zinc finger protein 10
ING4	0.68	4.35E-02	inhibitor of growth family, member 4
C10orf4	0.68	2.00E-02	chromosome 10 open reading frame 4
CLUAP1	0.68	4.16E-02	clusterin associated protein 1
TNRC6B	0.68	3.06E-02	trinucleotide repeat containing 6B
SPIN3	0.67	2.68E-02	spindlin family, member 3
ARMC1	0.67	2.19E-02	armadillo repeat containing 1
FAM13A	0.67	4.96E-02	family with sequence similarity 13, member A
IFT74	0.67	1.74E-02	intraflagellar transport 74 homolog (Chlamydomonas)
ALDH5A1	0.67	2.67E-02	aldehyde dehydrogenase 5 family, member A1
WDR60	0.67	4.25E-02	WD repeat domain 60
ZSCAN21	0.67	4.90E-02	zinc finger and SCAN domain containing 21
TUG1	0.67	3.29E-02	taurine upregulated 1 (non-protein coding)
TSN	0.67	2.16E-02	translin
CTPS2	0.67	2.31E-02	CTP synthase II
PER2	0.67	1.63E-02	period homolog 2 (Drosophila)
XPO1	0.67	2.77E-02	exportin 1 (CRM1 homolog, yeast)
EBAG9	0.67	3.59E-02	estrogen receptor binding site associated, antigen, 9
NTF3	0.67	3.60E-02	neurotrophin 3
SNX25	0.66	1.78E-02	sorting nexin 25
TUSC4	0.66	2.10E-02	tumor suppressor candidate 4
AFAP1L2	0.66	3.91E-02	actin filament associated protein 1-like 2

PRKG1	0.66	1.70E-02	protein kinase, cGMP-dependent, type I
CACNA1C	0.66	2.17E-02	calcium channel, voltage-dependent, L type, alpha 1C subunit
POLK	0.66	1.74E-02	polymerase (DNA directed) kappa
SUV420H1	0.66	3.51E-02	suppressor of variegation 4-20 homolog 1 (Drosophila)
SNX21	0.65	4.94E-02	sorting nexin family member 21
NT5C3L	0.65	2.51E-02	5'-nucleotidase, cytosolic III-like
HYI	0.65	3.02E-02	hydroxypyruvate isomerase homolog (E. coli)
ASH1L	0.65	1.91E-02	ash1 (absent, small, or homeotic)-like (Drosophila)
C8orf83	0.65	2.00E-02	chromosome 8 open reading frame 83
DYNC2LI1	0.65	3.00E-02	dynein, cytoplasmic 2, light intermediate chain 1
ACACB	0.65	2.83E-02	acetyl-Coenzyme A carboxylase beta
PHLPP	0.65	3.60E-02	PH domain and leucine rich repeat protein phosphatase
SUSD2	0.65	9.64E-03	sushi domain containing 2
RNASEN	0.65	1.84E-02	ribonuclease type III, nuclear
BOLA1	0.65	1.70E-02	bolA homolog 1 (E. coli)
RAB5B	0.65	5.75E-03	RAB5B, member RAS oncogene family
CCDC102A	0.65	3.28E-02	coiled-coil domain containing 102A
ABHD10	0.65	2.11E-02	abhydrolase domain containing 10
TUBG2	0.65	1.77E-02	tubulin, gamma 2
SMARCC2	0.65	1.78E-02	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 2
ZNF585A	0.65	9.85E-03	zinc finger protein 585A
MAK10	0.65	4.83E-02	MAK10 homolog, amino-acid N-acetyltransferase subunit (S. cerevisiae)
BHLHB9	0.64	3.21E-02	basic helix-loop-helix domain containing, class B, 9
CCDC46	0.64	4.94E-02	coiled-coil domain containing 46
OFD1	0.64	3.52E-02	oral-facial-digital syndrome 1
TM7SF3	0.64	4.22E-02	transmembrane 7 superfamily member 3
ZNF34	0.64	3.65E-02	zinc finger protein 34
C5orf33	0.64	3.07E-03	chromosome 5 open reading frame 33
OBSL1	0.64	1.02E-02	obscurin-like 1
SCAMP1	0.64	4.75E-02	secretory carrier membrane protein 1
RTTN	0.64	4.50E-02	rotatin
PANK1	0.64	1.50E-02	pantothenate kinase 1
KRCC1	0.64	2.31E-02	lysine-rich coiled-coil 1
SV2A	0.64	4.02E-02	synaptic vesicle glycoprotein 2A
PGM5	0.64	1.44E-02	phosphoglucomutase 5
NRBP2	0.64	3.11E-02	nuclear receptor binding protein 2
SNCAIP	0.64	4.63E-02	synuclein, alpha interacting protein
C1orf102	0.64	2.43E-02	chromosome 1 open reading frame 102
BPNT1	0.64	4.13E-02	3'(2'), 5'-bisphosphate nucleotidase 1
SPAG16	0.63	3.76E-03	sperm associated antigen 16
SASS6	0.63	4.80E-02	spindle assembly 6 homolog (C. elegans)
IPP	0.63	2.31E-02	intracisternal A particle-promoted polypeptide
SEMA4C	0.63	5.73E-03	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C
FLJ41603	0.63	2.79E-03	FLJ41603 protein
CBY1	0.63	3.96E-02	chibby homolog 1 (Drosophila)
WASL	0.63	1.51E-02	Wiskott-Aldrich syndrome-like
STX17	0.63	3.29E-03	syntaxin 17
NALCN	0.63	1.31E-02	sodium leak channel, non-selective
LOC201229	0.63	1.12E-02	hypothetical protein LOC201229
ZNF793	0.63	8.23E-03	zinc finger protein 793
ZC3H6	0.63	1.90E-02	zinc finger CCCH-type containing 6
LRP6	0.63	2.51E-02	low density lipoprotein receptor-related protein 6
PWWP2A	0.63	5.75E-03	PWWP domain containing 2A
MDM1	0.63	1.22E-02	Mdm1 nuclear protein homolog (mouse)
MTX3	0.63	2.22E-02	metaxin 3
ANKRD50	0.63	2.32E-02	ankyrin repeat domain 50
COL14A1	0.63	4.39E-02	collagen, type XIV, alpha 1
C11orf67	0.63	1.04E-02	chromosome 11 open reading frame 67
TMX4	0.62	8.50E-03	thioredoxin-related transmembrane protein 4
DSTYK	0.62	1.22E-02	dual serine/threonine and tyrosine protein kinase
C2orf67	0.62	1.32E-02	chromosome 2 open reading frame 67
NTHL1	0.62	4.54E-02	nth endonuclease III-like 1 (E. coli)
ZHX2	0.62	4.60E-02	zinc fingers and homeoboxes 2
GPR125	0.62	1.52E-02	G protein-coupled receptor 125
CCDC66	0.62	8.16E-03	coiled-coil domain containing 66
ZNF232	0.62	2.65E-02	zinc finger protein 232
RAPGEF2	0.62	4.94E-02	Rap guanine nucleotide exchange factor (GEF) 2
DLX2	0.62	2.63E-02	distal-less homeobox 2
ERLIN2	0.62	2.44E-02	ER lipid raft associated 2
SEC62	0.62	3.13E-02	SEC62 homolog (S. cerevisiae)
ZNF507	0.62	4.55E-02	zinc finger protein 507
RUNX1T1	0.62	9.19E-03	runt-related transcription factor 1; translocated to, 1 (cyclin D-related)
LOC728737	0.62	1.21E-02	similar to CDA11
C9orf123	0.62	1.62E-02	chromosome 9 open reading frame 123
C21orf34	0.62	1.91E-02	chromosome 21 open reading frame 34
SPOP	0.62	3.07E-02	speckle-type POZ protein
C4orf27	0.62	5.15E-03	chromosome 4 open reading frame 27
DZIP3	0.61	1.41E-02	DAZ interacting protein 3, zinc finger
RBM4B	0.61	2.17E-02	RNA binding motif protein 4B
MAGEF1	0.61	1.60E-02	melanoma antigen family F, 1
SKP1	0.61	2.73E-02	S-phase kinase-associated protein 1
AASDH	0.61	8.98E-03	aminoadipate-semialdehyde dehydrogenase
MTERFD3	0.61	7.06E-03	MTERF domain containing 3
ZNF30	0.61	1.99E-02	zinc finger protein 30
DCUN1D4	0.61	1.87E-02	DCN1, defective in cullin neddylation 1, domain containing 4 (S. cerevisiae)
SPTAN1	0.61	2.34E-02	spectrin, alpha, non-erythrocytic 1 (alpha-fodrin)
TTC23	0.61	5.88E-03	tetratricopeptide repeat domain 23
ZRANB2	0.61	3.00E-02	zinc finger, RAN-binding domain containing 2
ZNF436	0.61	5.87E-03	zinc finger protein 436
LOC285550	0.61	1.47E-02	hypothetical protein LOC285550
CC2D2A	0.61	4.17E-03	coiled-coil and C2 domain containing 2A
SALL2	0.61	2.44E-02	sal-like 2 (Drosophila)
HES1	0.61	2.42E-02	hairy and enhancer of split 1, (Drosophila)

ZNF32	0.60	4.36E-02	zinc finger protein 32
XPA	0.60	3.08E-02	xeroderma pigmentosum, complementation group A
ZNF137	0.60	4.46E-02	zinc finger protein 137
VEZF1	0.60	3.05E-02	vascular endothelial zinc finger 1
ZMAT1	0.60	7.34E-03	zinc finger, matrin type 1
tcag7.903	0.60	9.41E-03	hypothetical protein LOC729852
RPLP2	0.60	3.48E-02	ribosomal protein, large, P2
EIF3L	0.60	3.94E-02	eukaryotic translation initiation factor 3, subunit L
GPRC5C	0.60	3.34E-02	G protein-coupled receptor, family C, group 5, member C
SIN3A	0.60	2.31E-02	SIN3 homolog A, transcription regulator (yeast)
PMS1	0.60	2.67E-02	PMS1 postmeiotic segregation increased 1 (S. cerevisiae)
FUNDC1	0.60	4.55E-02	FUN14 domain containing 1
ZNF404	0.60	1.09E-02	zinc finger protein 404
PCCA	0.60	4.18E-02	propionyl Coenzyme A carboxylase, alpha polypeptide
ZNF33A	0.60	3.29E-02	zinc finger protein 33A
SPATA18	0.60	1.43E-02	spermatogenesis associated 18 homolog (rat)
MRPS27	0.60	3.91E-02	mitochondrial ribosomal protein S27
NEK1	0.60	3.70E-02	NIMA (never in mitosis gene a)-related kinase 1
ZNF14	0.60	3.96E-02	zinc finger protein 14
POGZ	0.60	7.69E-03	pogo transposable element with ZNF domain
MTERF	0.60	4.11E-02	mitochondrial transcription termination factor
SLC6A16	0.60	1.30E-02	solute carrier family 6, member 16
PART1	0.59	2.57E-02	prostate androgen-regulated transcript 1
TSHZ1	0.59	1.39E-02	teashirt zinc finger homeobox 1
PCMTD1	0.59	4.16E-02	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 1
C1orf216	0.59	3.86E-02	chromosome 1 open reading frame 216
OSGEPL1	0.59	1.55E-02	O-sialoglycoprotein endopeptidase-like 1
FANCL	0.59	9.00E-03	Fanconi anemia, complementation group L
KIAA1429	0.59	3.59E-02	KIAA1429
CLYBL	0.59	3.83E-02	citrate lyase beta like
ZNF187	0.59	1.29E-02	zinc finger protein 187
NOL3	0.59	5.25E-03	nucleolar protein 3 (apoptosis repressor with CARD domain)
CAMLG	0.59	2.79E-02	calcium modulating ligand
KLHDC9	0.59	2.22E-02	kelch domain containing 9
UPF3B	0.59	1.74E-02	UPF3 regulator of nonsense transcripts homolog B (yeast)
COX6C	0.59	2.96E-02	cytochrome c oxidase subunit VIc
ARMCX3	0.59	4.46E-02	armadillo repeat containing, X-linked 3
SEC63	0.59	4.98E-02	SEC63 homolog (S. cerevisiae)
MYBL1	0.59	2.57E-02	v-myb myeloblastosis viral oncogene homolog (avian)-like 1
ARV1	0.59	2.24E-02	ARV1 homolog (S. cerevisiae)
ZNF673	0.59	2.12E-02	zinc finger family member 673
PTH1R	0.59	1.06E-02	parathyroid hormone 1 receptor
MEF2C	0.59	2.94E-02	myocyte enhancer factor 2C
NUDT12	0.58	5.78E-03	nudix (nucleoside diphosphate linked moiety X)-type motif 12
NKIRAS1	0.58	2.44E-02	NFKB inhibitor interacting Ras-like 1
GTF2H5	0.58	1.73E-02	general transcription factor IIH, polypeptide 5
INTS2	0.58	2.43E-02	integrator complex subunit 2
PKN2	0.58	1.41E-02	protein kinase N2
ATP8B2	0.58	1.87E-02	ATPase, class I, type 8B, member 2
BPTF	0.58	1.08E-02	bromodomain PHD finger transcription factor
DHFRL1	0.58	1.56E-02	dihydrofolate reductase-like 1
ZNF615	0.58	6.82E-03	zinc finger protein 615
RFC1	0.58	2.96E-02	replication factor C (activator 1) 1, 145kDa
C4orf3	0.58	2.57E-02	chromosome 4 open reading frame 3
LOC729970	0.58	2.44E-02	hypothetical LOC729970
PEX3	0.58	1.12E-02	peroxisomal biogenesis factor 3
LZTFL1	0.58	2.51E-02	leucine zipper transcription factor-like 1
HCFC1R1	0.58	8.01E-03	host cell factor C1 regulator 1 (XPO1 dependent)
C12orf29	0.58	4.22E-02	chromosome 12 open reading frame 29
KAT2B	0.58	3.05E-02	K(lysine) acetyltransferase 2B
MPHOSPH8	0.58	1.62E-02	M-phase phosphoprotein 8
FMO4	0.58	1.22E-02	flavin containing monooxygenase 4
ZFHX3	0.58	4.54E-02	zinc finger homeobox 3
ZFP90	0.58	9.14E-03	zinc finger protein 90 homolog (mouse)
EFS	0.57	1.91E-02	embryonal Fyn-associated substrate
BDH2	0.57	1.73E-02	3-hydroxybutyrate dehydrogenase, type 2
FAM164A	0.57	1.49E-02	family with sequence similarity 164, member A
DTNA	0.57	5.53E-03	dystrobrevin, alpha
ZBTB4	0.57	2.05E-02	zinc finger and BTB domain containing 4
HIST1H4C	0.57	3.43E-02	histone cluster 1, H4c
MSRB2	0.57	4.83E-03	methionine sulfoxide reductase B2
MACF1	0.57	4.96E-02	microtubule-actin crosslinking factor 1
SYF2	0.57	5.33E-03	SYF2 homolog, RNA splicing factor (S. cerevisiae)
PDZRN4	0.57	4.15E-02	PDZ domain containing ring finger 4
ZNF177	0.57	2.80E-03	zinc finger protein 177
ZFP30	0.57	8.67E-03	zinc finger protein 30 homolog (mouse)
MRPL1	0.57	3.36E-02	mitochondrial ribosomal protein L1
ZNF23	0.57	1.02E-02	zinc finger protein 23 (KOX 16)
NAB1	0.57	4.63E-03	NGFI-A binding protein 1 (EGR1 binding protein 1)
DHX40	0.57	2.54E-02	DEAH (Asp-Glu-Ala-His) box polypeptide 40
ZNF606	0.57	5.60E-03	zinc finger protein 606
MUM1	0.56	5.09E-03	melanoma associated antigen (mutated) 1
ISYNA1	0.56	9.72E-03	inositol-3-phosphate synthase 1
ZNF540	0.56	5.69E-03	zinc finger protein 540
RWDD2A	0.56	1.21E-02	RWD domain containing 2A
USP16	0.56	1.63E-02	ubiquitin specific peptidase 16
FBXO17	0.56	4.86E-02	F-box protein 17
LOC100132884	0.56	4.45E-03	hypothetical protein LOC100132884
THUMPD1	0.56	2.16E-02	THUMP domain containing 1
LOC644589	0.56	3.45E-02	similar to DnaJ (Hsp40) homolog, subfamily C, member 19
NAPEPLD	0.56	9.67E-03	N-acyl phosphatidylethanolamine phospholipase D
CYHR1	0.56	5.29E-04	cysteine/histidine-rich 1

ZNF148	0.56	9.28E-03	zinc finger protein 148
KIAA0831	0.56	1.25E-02	KIAA0831
LOC202781	0.56	2.47E-02	hypothetical protein LOC202781
LOC644538	0.56	2.43E-02	hypothetical protein LOC644538
C11orf54	0.56	4.31E-02	chromosome 11 open reading frame 54
VPS45	0.56	2.60E-02	vacuolar protein sorting 45 homolog (S. cerevisiae)
FTO	0.56	3.00E-02	fat mass and obesity associated
ITGB3BP	0.56	3.34E-02	integrin beta 3 binding protein (beta3-endonexin)
MBD5	0.56	1.37E-03	methyl-CpG binding domain protein 5
ETAA1	0.56	2.61E-02	Ewing tumor-associated antigen 1
OBFC1	0.56	3.05E-02	oligonucleotide/oligosaccharide-binding fold containing 1
KBTBD6	0.56	1.00E-02	kelch repeat and BTB (POZ) domain containing 6
RNF20	0.56	2.90E-02	ring finger protein 20
MOCS1	0.56	7.34E-03	molybdenum cofactor synthesis 1
ZNF260	0.55	2.98E-02	zinc finger protein 260
C15orf52	0.55	3.18E-02	chromosome 15 open reading frame 52
TOMM7	0.55	3.04E-03	translocase of outer mitochondrial membrane 7 homolog (yeast)
METTL14	0.55	2.60E-02	methyltransferase like 14
TACC2	0.55	3.08E-02	transforming, acidic coiled-coil containing protein 2
TRIB2	0.55	3.47E-02	tribbles homolog 2 (Drosophila)
LOC100133166	0.55	4.11E-02	similar to neighbor of BRCA1 gene 1
MAP9	0.55	9.14E-03	microtubule-associated protein 9
TULP3	0.55	1.35E-02	tubby like protein 3
C2orf64	0.55	1.78E-02	chromosome 2 open reading frame 64
ZDHHC14	0.54	4.63E-02	zinc finger, DHHC-type containing 14
PRDX2	0.54	2.98E-02	peroxiredoxin 2
BBX	0.54	5.75E-03	bobby sox homolog (Drosophila)
RUFY3	0.54	1.58E-02	RUN and FYVE domain containing 3
PXMP2	0.54	3.92E-03	peroxisomal membrane protein 2, 22kDa
ZHX1	0.54	3.23E-02	zinc fingers and homeoboxes 1
ZNF596	0.54	1.90E-02	zinc finger protein 596
RERGL	0.54	5.53E-03	RERG/RAS-like
ZSCAN29	0.54	2.91E-03	zinc finger and SCAN domain containing 29
TNKS	0.54	4.69E-03	tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase
FBXW4	0.54	4.75E-04	F-box and WD repeat domain containing 4
C1QTNF7	0.54	1.64E-02	C1q and tumor necrosis factor related protein 7
ZC3H14	0.54	1.22E-02	zinc finger CCCH-type containing 14
GARNL3	0.54	1.38E-03	GTPase activating Rap/RanGAP domain-like 3
ACADL	0.54	4.14E-03	acyl-Coenzyme A dehydrogenase, long chain
LOC730124	0.54	2.44E-02	similar to hCG2041586
LUC7L2	0.54	1.74E-02	LUC7-like 2 (S. cerevisiae)
SSBP2	0.54	4.83E-02	single-stranded DNA binding protein 2
LOC100128550	0.54	4.16E-03	hypothetical protein LOC100128550
THAP10	0.53	1.29E-02	THAP domain containing 10
FILIP1	0.53	1.58E-02	filamin A interacting protein 1
CRYZL1	0.53	3.89E-03	crystallin, zeta (quinone reductase)-like 1
LOC730098	0.53	4.27E-02	similar to chemokine (C-C motif) ligand 27
LOC100127983	0.53	3.39E-03	hypothetical protein LOC100127983
FREM1	0.53	1.60E-03	FRAS1 related extracellular matrix 1
WDSUB1	0.53	4.31E-02	WD repeat, sterile alpha motif and U-box domain containing 1
CCDC109A	0.53	7.65E-03	coiled-coil domain containing 109A
SYNJ2BP	0.53	4.62E-02	synaptojanin 2 binding protein
ZNF292	0.53	1.91E-02	zinc finger protein 292
SECISBP2L	0.53	1.61E-02	SECIS binding protein 2-like
MARVELD1	0.53	4.27E-02	MARVEL domain containing 1
TRIM68	0.53	5.60E-03	tripartite motif-containing 68
NDUFA5	0.53	3.16E-02	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa
KIAA0776	0.53	1.46E-02	KIAA0776
SGCB	0.53	3.86E-02	sarcoglycan, beta (43kDa dystrophin-associated glycoprotein)
KIAA1712	0.53	2.79E-03	KIAA1712
SVIL	0.53	3.64E-02	supervillin
WDR19	0.53	8.30E-03	WD repeat domain 19
CLDN12	0.53	4.31E-02	claudin 12
ZCCHC18	0.52	1.51E-03	zinc finger, CCHC domain containing 18
KIF3A	0.52	1.12E-02	kinesin family member 3A
LYRM5	0.52	1.24E-02	LYR motif containing 5
C12orf26	0.52	8.67E-03	chromosome 12 open reading frame 26
ZBTB10	0.52	2.83E-02	zinc finger and BTB domain containing 10
NAP1L2	0.52	2.24E-02	nucleosome assembly protein 1-like 2
ZNF680	0.52	9.29E-03	zinc finger protein 680
SEPW1	0.52	3.25E-02	selenoprotein W, 1
TUBE1	0.52	2.83E-02	tubulin, epsilon 1
ESD	0.52	3.13E-02	esterase D/formylglutathione hydrolase
PLAC9	0.52	4.31E-02	placenta-specific 9
VCL	0.52	2.59E-02	vinculin
FYCO1	0.52	6.22E-03	FYVE and coiled-coil domain containing 1
ZNF528	0.52	4.83E-03	zinc finger protein 528
MTMR11	0.52	2.01E-02	myotubularin related protein 11
TJP1	0.51	1.39E-02	tight junction protein 1 (zona occludens 1)
HMGN3	0.51	1.09E-02	high mobility group nucleosomal binding domain 3
PCDHB15	0.51	1.35E-02	protocadherin beta 15
FAM33A	0.51	8.42E-03	family with sequence similarity 33, member A
SAP18	0.51	3.15E-02	Sin3A-associated protein, 18kDa
C2orf74	0.51	4.41E-02	chromosome 2 open reading frame 74
LRRN3	0.51	4.19E-03	leucine rich repeat neuronal 3
FAM50B	0.51	5.25E-03	family with sequence similarity 50, member B
PER3	0.51	2.19E-03	period homolog 3 (Drosophila)
TBCKL	0.51	8.47E-03	TBC domain-containing protein kinase-like
PCDHB14	0.51	3.67E-02	protocadherin beta 14
ZNF618	0.51	4.36E-02	zinc finger protein 618
TANC1	0.51	4.76E-02	tetratricopeptide repeat, ankyrin repeat and coiled-coil

			containing 1
LRIG1	0.51	3.95E-02	leucine-rich repeats and immunoglobulin-like domains 1
HABP4	0.51	2.06E-03	hyaluronan binding protein 4
THRB	0.50	1.73E-02	thyroid hormone receptor, beta (erythroblastic leukemia viral (v-erb-a) oncogene homolog 2, avian)
SUCLG2	0.50	3.66E-02	succinate-CoA ligase, GDP-forming, beta subunit
CRBN	0.50	5.53E-03	cereblon
GSPT2	0.50	3.63E-02	G1 to S phase transition 2
ZNF662	0.50	1.05E-02	zinc finger protein 662
AKAP1	0.50	5.53E-03	A kinase (PRKA) anchor protein 1
LNP1	0.50	1.21E-04	leukemia NUP98 fusion partner 1
PABPC4L	0.50	4.78E-02	poly(A) binding protein, cytoplasmic 4-like
HSPB2	0.50	1.41E-02	heat shock 27kDa protein 2
ACADM	0.50	4.33E-02	acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain
TCF7L2	0.50	3.06E-03	transcription factor 7-like 2 (T-cell specific, HMG-box)
IMMP2L	0.50	1.39E-02	IMP2 inner mitochondrial membrane peptidase-like (S. cerevisiae)
PRPSAP1	0.50	3.05E-02	phosphoribosyl pyrophosphate synthetase-associated protein 1
LMO7	0.50	3.70E-02	LIM domain 7
SLC16A9	0.50	1.17E-02	solute carrier family 16, member 9 (monocarboxylic acid transporter 9)
MAP1B	0.50	4.27E-02	microtubule-associated protein 1B
UNC13B	0.50	3.62E-02	unc-13 homolog B (C. elegans)
SERGEF	0.50	3.07E-03	secretion regulating guanine nucleotide exchange factor
PPP1R12B	0.50	9.34E-03	protein phosphatase 1, regulatory (inhibitor) subunit 12B
FAM36A	0.50	4.45E-03	family with sequence similarity 36, member A
ZBTB41	0.50	2.15E-02	zinc finger and BTB domain containing 41
PDE5A	0.49	1.38E-03	phosphodiesterase 5A, cGMP-specific
CRELD1	0.49	9.82E-03	cysteine-rich with EGF-like domains 1
NKAIN2	0.49	1.33E-02	Na+/K+ transporting ATPase interacting 2
TMEM55A	0.49	1.11E-02	transmembrane protein 55A
ZNF514	0.49	1.07E-02	zinc finger protein 514
ESAM	0.49	1.04E-02	endothelial cell adhesion molecule
TIGD7	0.49	1.00E-03	tigger transposable element derived 7
GLIS2	0.49	2.63E-02	GLIS family zinc finger 2
ACP6	0.49	1.95E-02	acid phosphatase 6, lysophosphatidic
CYFIP2	0.49	1.92E-02	cytoplasmic FMR1 interacting protein 2
CWF19L2	0.49	4.83E-02	CWF19-like 2, cell cycle control (S. pombe)
JUB	0.49	1.50E-02	jub, ajuba homolog (Xenopus laevis)
ZNF204	0.49	4.03E-03	zinc finger protein 204 pseudogene
TINAGL1	0.49	2.01E-02	tubulointerstitial nephritis antigen-like 1
KIAA1377	0.49	7.34E-03	KIAA1377
ZNF559	0.49	2.51E-02	zinc finger protein 559
MANSC1	0.49	2.71E-02	MANSC domain containing 1
NPHP3	0.48	8.97E-03	nephronophthisis 3 (adolescent)
APP	0.48	3.81E-02	amyloid beta (A4) precursor protein
UTP14C	0.48	4.84E-02	UTP14, U3 small nucleolar ribonucleoprotein, homolog C (yeast)
TRIM2	0.48	1.40E-03	tripartite motif-containing 2
PPM1K	0.48	4.63E-03	protein phosphatase 1K (PP2C domain containing)
TENC1	0.48	1.50E-02	tensin like C1 domain containing phosphatase (tensin 2)
MRPS9	0.48	3.54E-02	mitochondrial ribosomal protein S9
CCDC111	0.48	2.30E-03	coiled-coil domain containing 111
ENTPD1	0.48	5.87E-03	ectonucleoside triphosphate diphosphohydrolase 1
AMOTL2	0.48	8.57E-03	angiomotin like 2
CCDC112	0.48	1.38E-02	coiled-coil domain containing 112
PABPC5	0.48	1.71E-04	poly(A) binding protein, cytoplasmic 5
MRPS6	0.48	2.66E-02	mitochondrial ribosomal protein S6
ATPAF1	0.48	7.23E-03	ATP synthase mitochondrial F1 complex assembly factor 1
C7orf60	0.48	2.55E-02	chromosome 7 open reading frame 60
ZFP1	0.48	1.52E-02	zinc finger protein 1 homolog (mouse)
LOC644285	0.48	1.22E-02	hypothetical LOC644285
TMOD1	0.48	4.47E-02	tropomodulin 1
SORT1	0.48	2.07E-02	sortilin 1
KLHDC5	0.47	4.14E-03	kelch domain containing 5
LRRCC1	0.47	3.37E-04	leucine rich repeat and coiled-coil domain containing 1
WFS1	0.47	3.50E-04	Wolfram syndrome 1 (wolframin)
ZNF25	0.47	5.23E-04	zinc finger protein 25
FABP3	0.47	2.55E-02	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)
AP3M2	0.47	3.22E-02	adaptor-related protein complex 3, mu 2 subunit
ANKRD37	0.47	2.06E-03	ankyrin repeat domain 37
ZFYVE21	0.47	1.07E-02	zinc finger, FYVE domain containing 21
JRKL	0.47	2.16E-03	jerky homolog-like (mouse)
C9orf5	0.47	3.86E-02	chromosome 9 open reading frame 5
ALMS1	0.47	9.03E-03	Alstrom syndrome 1
SASH1	0.47	3.05E-02	SAM and SH3 domain containing 1
PLEKHA5	0.47	1.55E-02	pleckstrin homology domain containing, family A member 5
PPP1R12A	0.47	3.43E-02	protein phosphatase 1, regulatory (inhibitor) subunit 12A
EPC2	0.47	3.23E-03	enhancer of polycomb homolog 2 (Drosophila)
FBXO8	0.47	4.93E-02	F-box protein 8
CASD1	0.47	1.89E-02	CAS1 domain containing 1
TMEM106B	0.47	2.50E-02	transmembrane protein 106B
C5orf53	0.47	4.38E-03	chromosome 5 open reading frame 53
RANBP6	0.47	2.31E-02	RAN binding protein 6
SMARCD3	0.47	3.91E-02	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 3
C2orf76	0.47	1.72E-02	chromosome 2 open reading frame 76
ZNF512	0.46	4.36E-04	zinc finger protein 512
C14orf28	0.46	7.24E-03	chromosome 14 open reading frame 28
SLC5A3	0.46	1.72E-02	solute carrier family 5 (sodium/myo-inositol cotransporter), member 3
GUCY1B3	0.46	3.09E-03	guanylate cyclase 1, soluble, beta 3
KBTBD7	0.46	4.13E-02	kelch repeat and BTB (POZ) domain containing 7
MAP7D3	0.46	9.75E-03	MAP7 domain containing 3

CEP68	0.46	2.32E-04	centrosomal protein 68kDa
DUSP26	0.46	1.69E-02	dual specificity phosphatase 26 (putative)
ACTR6	0.46	4.55E-02	ARP6 actin-related protein 6 homolog (yeast)
KLHDC2	0.46	3.01E-02	kelch domain containing 2
LOC120376	0.46	4.05E-03	Uncharacterized protein LOC120376
NFIB	0.46	1.71E-02	nuclear factor I/B
PRRT2	0.46	2.72E-02	proline-rich transmembrane protein 2
ZNF627	0.46	3.43E-03	zinc finger protein 627
MAP2	0.46	3.38E-02	microtubule-associated protein 2
TRPC1	0.46	8.46E-03	transient receptor potential cation channel, subfamily C, member 1
IRAK1BP1	0.46	1.42E-03	interleukin-1 receptor-associated kinase 1 binding protein 1
ZBTB20	0.46	3.19E-03	zinc finger and BTB domain containing 20
GPD1L	0.46	2.56E-02	glycerol-3-phosphate dehydrogenase 1-like
NCRNA00153	0.45	8.91E-04	non-protein coding RNA 153
RAB11FIP2	0.45	3.32E-02	RAB11 family interacting protein 2 (class I)
DIP2C	0.45	2.21E-02	DIP2 disco-interacting protein 2 homolog C (Drosophila)
RBMS3	0.45	9.22E-03	RNA binding motif, single stranded interacting protein
PHF16	0.45	4.55E-02	PHD finger protein 16
PHOSPHO2	0.45	4.86E-02	phosphatase, orphan 2
IGF1R	0.45	5.36E-03	insulin-like growth factor 1 receptor
PCDHB7	0.45	1.04E-02	protocadherin beta 7
FAM13B	0.45	3.68E-02	family with sequence similarity 13, member B
NTRK3	0.45	1.21E-04	neurotrophic tyrosine kinase, receptor, type 3
AS3MT	0.45	3.32E-03	arsenic (+3 oxidation state) methyltransferase
C9orf150	0.45	3.57E-02	chromosome 9 open reading frame 150
TEX9	0.45	6.85E-03	testis expressed 9
C7orf58	0.45	5.54E-04	chromosome 7 open reading frame 58
ITGA7	0.45	7.24E-03	integrin, alpha 7
ZNF138	0.45	2.34E-05	zinc finger protein 138
8-Sep	0.45	2.65E-02	septin 8
DLX1	0.45	1.32E-03	distal-less homeobox 1
COBLL1	0.45	7.34E-03	COBL-like 1
LAYN	0.45	2.43E-02	layilin
MPP7	0.44	1.32E-03	membrane protein, palmitoylated 7 (MAGUK p55 subfamily member 7)
CX3CL1	0.44	1.45E-02	chemokine (C-X3-C motif) ligand 1
AEBP2	0.44	2.86E-02	AE binding protein 2
EPM2AIP1	0.44	2.02E-04	EPM2A (laforin) interacting protein 1
ST13	0.44	2.34E-02	suppression of tumorigenicity 13 (colon carcinoma) (Hsp70 interacting protein)
ZNF706	0.44	1.11E-02	zinc finger protein 706
ZNF420	0.44	1.97E-02	zinc finger protein 420
SESTD1	0.44	2.13E-02	SEC14 and spectrin domains 1
SHPRH	0.44	3.58E-02	SNF2 histone linker PHD RING helicase
CBR3	0.44	5.09E-03	carbonyl reductase 3
CFL2	0.44	3.24E-02	cofilin 2 (muscle)
LOC169834	0.44	1.38E-03	hypothetical protein LOC169834
AIF1L	0.44	9.97E-05	allograft inflammatory factor 1-like
ATP1A2	0.44	2.79E-02	ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide
DZIP1	0.44	1.74E-02	DAZ interacting protein 1
TTC32	0.44	9.14E-03	tetratricopeptide repeat domain 32
ARHGEF17	0.44	4.49E-04	Rho guanine nucleotide exchange factor (GEF) 17
ARHGAP5	0.44	3.12E-02	Rho GTPase activating protein 5
LIPT1	0.44	2.16E-03	lipoyltransferase 1
ZSCAN18	0.44	1.91E-02	zinc finger and SCAN domain containing 18
ZAK	0.44	2.66E-03	sterile alpha motif and leucine zipper containing kinase AZK
MFAP4	0.44	3.34E-02	microfibrillar-associated protein 4
NR3C2	0.44	4.41E-03	nuclear receptor subfamily 3, group C, member 2
LYRM7	0.44	1.16E-03	Lyrm7 homolog (mouse)
C1QTNF2	0.43	2.49E-02	C1q and tumor necrosis factor related protein 2
LANCL1	0.43	9.83E-03	LanC lantibiotic synthetase component C-like 1 (bacterial)
ZFP82	0.43	2.51E-02	zinc finger protein 82 homolog (mouse)
LOC375190	0.43	4.19E-03	hypothetical protein LOC375190
RAB33B	0.43	1.12E-02	RAB33B, member RAS oncogene family
INTU	0.43	5.86E-03	inturned planar cell polarity effector homolog (Drosophila)
NDN	0.43	3.05E-02	necdin homolog (mouse)
C9orf125	0.43	1.67E-04	chromosome 9 open reading frame 125
FAM149A	0.43	1.08E-03	family with sequence similarity 149, member A
LOC92270	0.43	2.06E-03	V-type proton ATPase subunit S1-like protein
BBS2	0.43	3.68E-02	Bardet-Biedl syndrome 2
GARNL1	0.43	3.50E-02	GTPase activating Rap/RanGAP domain-like 1
RPL22	0.43	5.60E-03	ribosomal protein L22
EEF1A1	0.43	3.29E-02	eukaryotic translation elongation factor 1 alpha 1
CTDSPL	0.43	4.34E-02	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like
EIF4A2	0.42	1.60E-02	eukaryotic translation initiation factor 4A, isoform 2
ZNF573	0.42	5.53E-03	zinc finger protein 573
DAAM1	0.42	4.07E-03	dishevelled associated activator of morphogenesis 1
CYP2U1	0.42	4.21E-04	cytochrome P450, family 2, subfamily U, polypeptide 1
VPS13A	0.42	1.30E-02	vacuolar protein sorting 13 homolog A (S. cerevisiae)
DYNC1I1	0.42	2.61E-02	dynein, cytoplasmic 1, intermediate chain 1
IFT80	0.42	4.75E-04	intraflagellar transport 80 homolog (Chlamydomonas)
EMILIN1	0.42	1.41E-03	elastin microfibril interfacer 1
ANKMY2	0.42	2.01E-02	ankyrin repeat and MYND domain containing 2
C16orf45	0.42	3.01E-02	chromosome 16 open reading frame 45
GGTA1	0.42	1.81E-02	glycoprotein, alpha-galactosyltransferase 1
PDGFRB	0.41	4.42E-02	platelet-derived growth factor receptor, beta polypeptide
PHLDB2	0.41	6.38E-03	pleckstrin homology-like domain, family B, member 2
ZFP62	0.41	1.27E-03	zinc finger protein 62 homolog (mouse)
LRCH2	0.41	7.30E-03	leucine-rich repeats and calponin homology (CH) domain containing 2
ZNF280D	0.41	3.92E-03	zinc finger protein 280D
SETBP1	0.41	2.35E-02	SET binding protein 1
ZNF423	0.41	3.57E-02	zinc finger protein 423

NXN	0.41	5.82E-03	nucleoredoxin
MAGEE1	0.41	2.75E-03	melanoma antigen family E, 1
EHD3	0.41	5.88E-03	EH-domain containing 3
PARP2	0.41	2.60E-04	poly (ADP-ribose) polymerase 2
CAMK2G	0.40	2.55E-05	calcium/calmodulin-dependent protein kinase II gamma
NCRNA00117	0.40	5.02E-03	non-protein coding RNA 117
MAGEH1	0.40	1.70E-02	melanoma antigen family H, 1
HLF	0.40	8.21E-04	hepatic leukemia factor
OXR1	0.40	1.73E-02	oxidation resistance 1
SLC25A12	0.40	9.85E-03	solute carrier family 25 (mitochondrial carrier, Aralar), member 12
PM20D2	0.40	1.57E-02	peptidase M20 domain containing 2
MN1	0.40	1.64E-02	meningioma (disrupted in balanced translocation) 1
EEF2K	0.40	4.39E-02	eukaryotic elongation factor-2 kinase
BARD1	0.40	6.25E-04	BRCA1 associated RING domain 1
C2CD2	0.40	3.65E-02	C2 calcium-dependent domain containing 2
HACE1	0.40	1.50E-02	HECT domain and ankyrin repeat containing, E3 ubiquitin protein ligase 1
TXNDC16	0.40	5.19E-03	thioredoxin domain containing 16
PLK2	0.40	4.94E-02	polo-like kinase 2 (Drosophila)
MXI1	0.40	5.53E-03	MAX interactor 1
ZNF415	0.40	3.34E-02	zinc finger protein 415
TRNP1	0.40	1.81E-03	TMF1-regulated nuclear protein 1
CCDC104	0.40	7.03E-05	coiled-coil domain containing 104
SERP2	0.40	3.92E-03	stress-associated endoplasmic reticulum protein family member 2
RABGAP1	0.40	4.07E-03	RAB GTPase activating protein 1
DLG5	0.40	1.99E-02	discs, large homolog 5 (Drosophila)
NEO1	0.40	8.57E-03	neogenin homolog 1 (chicken)
POLI	0.40	2.02E-04	polymerase (DNA directed) iota
FAM133A	0.40	1.79E-04	family with sequence similarity 133, member A
MARK1	0.40	1.34E-03	MAP/microtubule affinity-regulating kinase 1
DMXL1	0.40	2.92E-02	Dmx-like 1
EML1	0.39	3.01E-02	echinoderm microtubule associated protein like 1
PLCL1	0.39	3.34E-02	phospholipase C-like 1
PCDHB5	0.39	1.32E-03	protocadherin beta 5
AMN1	0.39	2.41E-03	antagonist of mitotic exit network 1 homolog (S. cerevisiae)
FLJ13197	0.39	1.14E-04	hypothetical FLJ13197
C2orf68	0.39	2.44E-02	chromosome 2 open reading frame 68
SRPX	0.39	3.04E-02	sushi-repeat-containing protein, X-linked
SCAPER	0.39	2.20E-03	S phase cyclin A-associated protein in the ER
ZNF362	0.39	2.41E-03	zinc finger protein 362
PTK2	0.39	8.94E-03	PTK2 protein tyrosine kinase 2
SELENBP1	0.39	1.60E-02	selenium binding protein 1
BBS10	0.39	4.22E-02	Bardet-Biedl syndrome 10
CETN3	0.39	9.82E-03	centrin, EF-hand protein, 3 (CDC31 homolog, yeast)
hCG_1806964	0.39	5.85E-03	hypothetical LOC401093
KCNMB1	0.39	3.69E-02	potassium large conductance calcium-activated channel, subfamily M, beta member 1
TMEM130	0.39	3.62E-02	transmembrane protein 130
PRDM6	0.39	1.11E-02	PR domain containing 6
NEURL1B	0.39	2.96E-02	neuralized homolog 1B (Drosophila)
THYN1	0.38	3.91E-03	thymocyte nuclear protein 1
STEAP2	0.38	5.27E-03	six transmembrane epithelial antigen of the prostate 2
DACT3	0.38	1.87E-03	dapper, antagonist of beta-catenin, homolog 3 (Xenopus laevis)
C21orf63	0.38	1.00E-02	chromosome 21 open reading frame 63
PDZRN3	0.38	1.76E-02	PDZ domain containing ring finger 3
TMEM200B	0.38	1.77E-02	transmembrane protein 200B
ID3	0.37	3.69E-02	inhibitor of DNA binding 3, dominant negative helix-loop-helix protein
PELI2	0.37	3.84E-02	pellino homolog 2 (Drosophila)
OSBPL9	0.37	2.64E-02	oxysterol binding protein-like 9
PCDH18	0.37	3.29E-03	protocadherin 18
CDKN1B	0.37	1.53E-02	cyclin-dependent kinase inhibitor 1B (p27, Kip1)
ANKRD46	0.37	2.43E-02	ankyrin repeat domain 46
TTLL7	0.37	8.19E-03	tubulin tyrosine ligase-like family, member 7
PFN2	0.37	8.50E-03	profilin 2
GSTA4	0.37	1.41E-02	glutathione S-transferase alpha 4
C1orf198	0.37	2.20E-02	chromosome 1 open reading frame 198
C3orf70	0.37	4.76E-03	chromosome 3 open reading frame 70
NFIA	0.37	8.99E-03	nuclear factor I/A
AMOT	0.37	1.45E-02	angiomotin
SLC25A4	0.36	1.23E-02	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4
RIMKLB	0.36	4.69E-03	ribosomal modification protein rimK-like family member B
TMSB15B	0.36	1.25E-02	thymosin beta 15B
NFYB	0.36	4.53E-03	nuclear transcription factor Y, beta
FXYD1	0.36	7.67E-03	FXYD domain containing ion transport regulator 1
UNC84A	0.36	3.43E-02	unc-84 homolog A (C. elegans)
SHROOM3	0.36	8.76E-03	shroom family member 3
PSIP1	0.36	1.30E-03	PC4 and SFRS1 interacting protein 1
ACYP1	0.36	4.80E-03	acylphosphatase 1, erythrocyte (common) type
SLC20A2	0.36	7.11E-03	solute carrier family 20 (phosphate transporter), member 2
ITIH5	0.36	9.59E-03	inter-alpha (globulin) inhibitor H5
TSPYL4	0.36	8.90E-03	TSPY-like 4
MPDZ	0.36	1.03E-02	multiple PDZ domain protein
STARD10	0.35	1.21E-04	StAR-related lipid transfer (START) domain containing 10
C2orf40	0.35	3.69E-02	chromosome 2 open reading frame 40
TMEM133	0.35	1.13E-03	transmembrane protein 133
MOBKL2B	0.35	1.60E-03	MOB1, Mps One Binder kinase activator-like 2B (yeast)
ZNF302	0.35	4.36E-04	zinc finger protein 302
FAM8A1	0.35	8.76E-03	family with sequence similarity 8, member A1
MAGI2	0.35	5.75E-03	membrane associated guanylate kinase, WW and PDZ domain containing 2

NHS	0.35	1.76E-02	Nance-Horan syndrome (congenital cataracts and dental anomalies)
FOXC1	0.35	7.10E-03	forkhead box C1
CDC14B	0.35	6.29E-03	CDC14 cell division cycle 14 homolog B (S. cerevisiae)
SETMAR	0.35	1.19E-02	SET domain and mariner transposase fusion gene
RICH2	0.34	2.93E-02	Rho-type GTPase-activating protein RICH2
HLTF	0.34	4.00E-03	helicase-like transcription factor
MYH10	0.34	3.07E-02	myosin, heavy chain 10, non-muscle
PRDM16	0.34	3.01E-05	PR domain containing 16
DAAM2	0.34	9.75E-03	dishevelled associated activator of morphogenesis 2
MAP3K5	0.33	5.10E-04	mitogen-activated protein kinase kinase kinase 5
SCRN1	0.33	2.43E-02	secernin 1
RAB40B	0.33	1.41E-02	RAB40B, member RAS oncogene family
LHFP	0.33	3.75E-02	lipoma HMGIC fusion partner
FLJ30375	0.33	9.65E-03	hypothetical gene supported by AK054937
BMPR1A	0.33	1.76E-02	bone morphogenetic protein receptor, type IA
ZIC1	0.33	9.19E-03	Zic family member 1 (odd-paired homolog, Drosophila)
PRICKLE2	0.33	1.23E-02	prickle homolog 2 (Drosophila)
LOC283174	0.33	8.18E-06	hypothetical LOC283174
NRIP2	0.33	2.02E-04	nuclear receptor interacting protein 2
ATP9A	0.33	9.82E-03	ATPase, class II, type 9A
NT5DC1	0.32	4.83E-03	5'-nucleotidase domain containing 1
EFCAB7	0.32	6.71E-04	EF-hand calcium binding domain 7
ITPR1	0.32	7.64E-05	inositol 1,4,5-triphosphate receptor, type 1
LRRC49	0.32	4.68E-04	leucine rich repeat containing 49
KRT17	0.32	7.34E-03	keratin 17
ZNF285A	0.32	9.23E-06	zinc finger protein 285A
RBPMS	0.32	2.43E-02	RNA binding protein with multiple splicing
FILIP1L	0.32	4.05E-02	filamin A interacting protein 1-like
GUCY1A3	0.32	7.03E-03	guanylate cyclase 1, soluble, alpha 3
KANK2	0.32	1.55E-02	KN motif and ankyrin repeat domains 2
LDB3	0.32	1.81E-03	LIM domain binding 3
HEPH	0.32	2.11E-02	hephaestin
NUAK1	0.32	3.47E-03	NUAK family, SNF1-like kinase, 1
LOC100128288	0.31	5.86E-03	hypothetical protein LOC100128288
TMEM14A	0.31	1.95E-02	transmembrane protein 14A
SYNC	0.31	2.30E-03	syncoilin, intermediate filament protein
EBF1	0.31	6.33E-03	early B-cell factor 1
GPRASP2	0.31	2.44E-03	G protein-coupled receptor associated sorting protein 2
FAM26E	0.31	5.82E-03	family with sequence similarity 26, member E
SLC16A14	0.31	7.34E-03	solute carrier family 16, member 14 (monocarboxylic acid transporter 14)
BAMBI	0.30	2.01E-02	BMP and activin membrane-bound inhibitor homolog (Xenopus laevis)
RAPGEF5	0.30	1.06E-03	Rap guanine nucleotide exchange factor (GEF) 5
GJA4	0.30	3.06E-03	gap junction protein, alpha 4, 37kDa
TSPAN2	0.30	2.63E-02	tetraspanin 2
LRRC1	0.30	2.56E-03	leucine rich repeat containing 1
GPRASP1	0.30	4.16E-03	G protein-coupled receptor associated sorting protein 1
FBXL2	0.29	5.27E-03	F-box and leucine-rich repeat protein 2
PLCE1	0.29	1.26E-03	phospholipase C, epsilon 1
CNNM2	0.29	8.18E-06	cyclin M2
PDLIM3	0.29	4.47E-02	PDZ and LIM domain 3
CBX7	0.28	1.13E-02	chromobox homolog 7
FIBIN	0.28	5.19E-03	fin bud initiation factor homolog (zebrafish)
MYLK	0.28	4.68E-02	myosin light chain kinase
PLSCR4	0.28	1.88E-02	phospholipid scramblase 4
CX3CR1	0.28	3.63E-02	chemokine (C-X3-C motif) receptor 1
INMT	0.28	4.89E-02	indolethylamine N-methyltransferase
MAMDC2	0.28	1.71E-02	MAM domain containing 2
MRGPRF	0.28	1.46E-02	MAS-related GPR, member F
SYNPO2	0.28	1.81E-03	synaptopodin 2
MYLIP	0.27	2.83E-02	myosin regulatory light chain interacting protein
WTIP	0.27	1.33E-03	Wilms tumor 1 interacting protein
TCEA3	0.27	5.75E-03	transcription elongation factor A (SII), 3
INPP4B	0.27	3.27E-03	inositol polyphosphate-4-phosphatase, type II, 105kDa
SYNM	0.27	1.78E-02	synemin, intermediate filament protein
CAND2	0.27	5.79E-04	cullin-associated and neddylation-dissociated 2 (putative)
PCDHB10	0.27	3.19E-03	protocadherin beta 10
KANK1	0.27	4.74E-02	KN motif and ankyrin repeat domains 1
RAMP1	0.26	1.23E-03	receptor (G protein-coupled) activity modifying protein 1
LMOD1	0.26	6.98E-04	leiomodin 1 (smooth muscle)
PPP2R2B	0.26	1.73E-04	protein phosphatase 2 (formerly 2A), regulatory subunit B, beta isoform
NCALD	0.26	2.06E-04	neurocalcin delta
ZNF248	0.26	1.02E-05	zinc finger protein 248
ZNF135	0.26	1.89E-04	zinc finger protein 135
RASL11B	0.26	1.35E-03	RAS-like, family 11, member B
ANK3	0.26	5.99E-04	ankyrin 3, node of Ranvier (ankyrin G)
ANKRD6	0.26	1.72E-02	ankyrin repeat domain 6
LOC100133323	0.26	9.46E-05	hypothetical LOC100133323
RASL12	0.26	2.60E-04	RAS-like, family 12
PLCB4	0.26	5.10E-04	phospholipase C, beta 4
SGIP1	0.25	2.83E-02	SH3-domain GRB2-like (endophilin) interacting protein 1
KCNS3	0.25	1.04E-02	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3
OLFML2A	0.25	6.39E-04	olfactomedin-like 2A
SERPINI1	0.25	9.83E-03	serpin peptidase inhibitor, clade I (neuroserpin), member 1
GLDN	0.25	1.50E-02	gliomedin
SSPN	0.24	3.92E-03	sarcospan (Kras oncogene-associated gene)
SYTL2	0.24	6.23E-04	synaptotagmin-like 2
SHC4	0.24	4.96E-02	SHC (Src homology 2 domain containing) family, member 4
NPNT	0.24	5.64E-04	nephronectin
SLC14A1	0.24	2.22E-02	solute carrier family 14 (urea transporter), member 1

			(Kidd blood group)
ANGPT1	0.24	4.75E-04	angiopoietin 1
HSPA2	0.24	4.34E-02	heat shock 70kDa protein 2
NR2F2	0.24	1.31E-03	nuclear receptor subfamily 2, group F, member 2
ITGA8	0.23	3.11E-02	integrin, alpha 8
EFHD1	0.23	2.57E-02	EF-hand domain family, member D1
COL21A1	0.23	1.95E-02	collagen, type XXI, alpha 1
DKFZP564O0823	0.23	3.75E-02	DKFZP564O0823 protein
OPCML	0.23	1.48E-04	opioid binding protein/cell adhesion molecule-like
ID4	0.23	5.82E-03	inhibitor of DNA binding 4, dominant negative helix-loop-helix protein
HSDL2	0.23	5.09E-06	hydroxysteroid dehydrogenase like 2
TRIM36	0.22	2.41E-03	tripartite motif-containing 36
MRAP2	0.22	2.01E-02	melanocortin 2 receptor accessory protein 2
CAP2	0.22	1.32E-02	CAP, adenylate cyclase-associated protein, 2 (yeast)
ENPP2	0.22	2.22E-02	ectonucleotide pyrophosphatase/phosphodiesterase 2
GULP1	0.22	2.45E-03	GULP, engulfment adaptor PTB domain containing 1
MYH11	0.21	6.59E-03	myosin, heavy chain 11, smooth muscle
CYP4X1	0.21	3.23E-03	cytochrome P450, family 4, subfamily X, polypeptide 1
NPY1R	0.21	2.76E-05	neuropeptide Y receptor Y1
EFHA2	0.21	4.75E-04	EF-hand domain family, member A2
NRN1	0.21	6.32E-04	neuritin 1
TSPAN8	0.20	2.17E-03	tetraspanin 8
SGCE	0.20	2.57E-02	sarcoglycan, epsilon
RGS5	0.20	1.85E-02	regulator of G-protein signaling 5
CSRP2	0.20	2.82E-02	cysteine and glycine-rich protein 2
GNAI1	0.19	8.24E-04	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1
SLC6A1	0.19	5.99E-04	solute carrier family 6 (neurotransmitter transporter, GABA), member 1
AOC3	0.19	2.70E-02	amine oxidase, copper containing 3 (vascular adhesion protein 1)
NAP1L3	0.19	8.50E-03	nucleosome assembly protein 1-like 3
PCDHB16	0.18	8.30E-03	protocadherin beta 16
AK5	0.18	5.10E-04	adenylate kinase 5
PRUNE2	0.17	1.64E-04	prune homolog 2 (Drosophila)
FZD7	0.17	3.06E-02	frizzled homolog 7 (Drosophila)
FMO2	0.17	4.67E-04	flavin containing monooxygenase 2 (non-functional)
HEY2	0.17	3.42E-05	hairy/enhancer-of-split related with YRPW motif 2
EMX2	0.16	2.44E-05	empty spiracles homeobox 2
LOC100133319	0.16	1.56E-04	PRO1804
SMOC2	0.16	1.14E-02	SPARC related modular calcium binding 2
PPP1R14A	0.16	2.43E-02	protein phosphatase 1, regulatory (inhibitor) subunit 14A
PPP1R3C	0.16	1.56E-02	protein phosphatase 1, regulatory (inhibitor) subunit 3C
DACT1	0.15	6.38E-03	dapper, antagonist of beta-catenin, homolog 1 (Xenopus laevis)
NET1	0.15	2.60E-04	neuroepithelial cell transforming 1
RBM20	0.12	1.09E-04	RNA binding motif protein 20
NR1D2	0.12	5.85E-06	nuclear receptor subfamily 1, group D, member 2
RGS7BP	0.11	3.45E-04	regulator of G-protein signaling 7 binding protein
C5orf54	0.11	5.06E-09	chromosome 5 open reading frame 54
MUSTN1	0.11	9.23E-06	musculoskeletal, embryonic nuclear protein 1
PNMAL1	0.11	4.73E-04	PNMA-like 1
ECM2	0.10	1.69E-02	extracellular matrix protein 2, female organ and adipocyte specific
HMCN1	0.10	6.38E-03	hemicentin 1
SUSD5	0.10	1.50E-02	sushi domain containing 5
KCNAB1	0.10	5.06E-09	potassium voltage-gated channel, shaker-related subfamily, beta member 1
RCAN2	0.10	3.25E-02	regulator of calcineurin 2
PLN	0.10	2.77E-03	phospholamban
MYOM1	0.08	4.92E-08	myomesin 1, 185kDa
REEP1	0.07	1.87E-07	receptor accessory protein 1
FAM13C	0.06	7.10E-05	family with sequence similarity 13, member C
RRAD	0.05	3.51E-07	Ras-related associated with diabetes

* identification code; ** p-value uncorrected for multiple testing

Annex 3. Biological processes in ruptured sIA wall samples. Gene Ontology (www.geneontology.org) and KEGG (www.genome.jp/kegg) databases were used to identify biological processes related to the 686 upregulated and 740 downregulated genes) between ruptured and unruptured sIA wall samples.

UPREGULATED GENES

Gene Ontology (GO) biological processes	**GO ID***	***P* value****	**FDR *****	**OR**	**Count ********	**Size *********
chemotaxis	GO:0006935	2.60E-14	5.66E-11	7	30	125
immune response	GO:0006955	5.70E-14	6.26E-11	4	49	333
response to external stimulus	GO:0009605	1.00E-13	7.41E-11	3	74	651
inflammatory response	GO:0006954	1.40E-13	7.52E-11	4.2	46	296
locomotory behavior	GO:0007626	1.50E-11	6.46E-09	4.5	35	208
response to stress	GO:0006950	3.60E-09	1.31E-06	2.1	99	1224
response to other organism	GO:0051707	4.70E-08	1.49E-05	5.7	18	87
positive regulation of tumor necrosis factor production	GO:0032760	5.80E-08	1.60E-05	127	6	7
locomotion	GO:0040011	1.30E-07	3.18E-05	4.7	20	114
cytokine production	GO:0001816	2.50E-05	5.49E-03	3.8	16	108
phosphate metabolic process	GO:0006796	5.30E-05	1.06E-02	1.8	66	893
positive regulation of interleukin-6 production	GO:0032755	5.90E-05	1.08E-02	42	4	6
regulation of cell proliferation	GO:0042127	1.80E-04	3.10E-02	1.9	44	550
intracellular lipid transport	GO:0032365	2.60E-04	3.55E-02	21	4	8
neutrophil chemotaxis	GO:0030593	2.70E-04	3.55E-02	12	5	14
regulated secretory pathway	GO:0045055	2.70E-04	3.55E-02	12	5	14
Protein amino acid phosphorylation	GO:0006468	2.70E-04	3.55E-02	1.8	47	613
regulation of cytokine biosynthetic process	GO:0042035	3.90E-04	4.55E-02	4.2	10	61
Purine ribonucleoside monophosphate biosynthetic process	GO:0009168	3.90E-04	4.55E-02	11	5	15

KEGG biological process	**KEGG ID**	**P value**	**FDR**	**OR**	**Count**	**Size**
Cytokine-cytokine receptor interaction	4060	8.50E-06	7.82E-04	2.7	31	245
toll-like receptor signaling pathway	4620	1.10E-05	7.82E-04	4	17	94
hematopoietic cell lineage	4640	1.70E-05	8.10E-04	4.3	15	78
epithelial cell signaling in Helicobacter pylori infection	5120	5.80E-05	2.03E-03	4.3	13	67
fructose and mannose metabolism	51	3.30E-04	8.81E-03	5.6	8	33
leukocyte transendothelial migration	4670	3.80E-04	8.81E-03	3	16	112

Gene Ontology cellular compartment	**GO ID**	**P value**	**FDR**	**OR**	**Count**	**Size**
membrane	GO:0016020	2.50E-07	5.30E-05	1.5	325	6028
vacuole	GO:0005773	3.30E-07	5.30E-05	3.5	26	193
Arp2/3 protein complex	GO:0005885	9.30E-07	9.80E-05	110	5	6
cytoplasm	GO:0005737	5.10E-05	3.80E-03	1.4	329	6428
integral to plasma membrane	GO:0005887	6.00E-05	3.80E-03	1.7	72	1053
NADPH oxidase complex	GO:0043020	2.20E-04	1.18E-02	22	4	8
extracellular space	GO:0005615	3.20E-04	1.43E-02	1.9	39	497
membrane raft	GO:0045121	5.60E-04	2.23E-02	3.9	10	66
lysosome	GO:0005764	8.10E-04	2.85E-02	3.1	13	108
cytosol	GO:0005829	1.30E-03	4.09E-02	1.6	55	827
Proton-transporting V-type ATPase, V0 domain	GO:0033179	1.50E-03	4.40E-02	22	3	6

DOWNREGULATED GENES

Gene Ontology cellular compartment	**GO ID**	**P value**	**FDR**	**OR**	**Count**	**Size**

nucleus	GO:0005634	1.40E-05	4.81E-03	1.5	235	4487
intracellular part	GO:0044424	5.90E-05	1.04E-02	1.8	79	1487
costamere	GO:0043034	9.60E-05	1.11E-02	31	4	7
adherens junction	GO:0005912	5.90E-04	4.36E-02	3.6	11	82
tight junction	GO:0005923	6.30E-04	4.36E-02	5.6	7	36

* identification code; ** p-value uncorrected for multiple testing; *** false discovery rate, p-value after multiple testing correction; **** number of differentially expressed genes in each biological category; ***** total number of genes assayed in the present study in each category.

Sanna-Kaisa Häkkinen

Microarray Study

Gene Expression in Endothelial Cell Cultures and Intracranial Aneurysms

The molecular biology of vascular diseases is very complex. To develop better therapeutic strategies, it is important to understand the mechanisms behind the disease. In this thesis new mechanisms for regulation of vascular growth factor important for vascular diseases was found using large scale gene expression analysis. In addition candidate genes and pathways behind rupture of intracranial aneurysm were identified.

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