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Perfusion of human placenta with hemoglobin introduces preeclampsia-like injuries that are prevented by α_1-microglobulin

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Short Title:**”Free hemoglobin causes preeclampsia-like injuries *ex vivo*”**

Key words: hemoglobin, oxidative stress, dual placental perfusion, microarray, electron microscopy, α_1-microglobulin

Abbreviations

A1M	α_1-microglobulin
ECM	extra-cellular matrix
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
PE	preeclampsia
Hb	hemoglobin
HbA	adult hemoglobin
OxyHb	oxygenated hemoglobin
HbF	fetal hemoglobin
ROS	reactive oxygen species
EM	electron microscopy
BASE	BioArray Software Environment
RIA	radioimmunoassay

Abstract

Background: Preeclamptic women have increased plasma levels of free fetal hemoglobin (HbF), increased gene expression of placental HbF and accumulation of free HbF in the placental vascular lumen. Free hemoglobin (Hb) is pro-inflammatory, and causes oxidative stress and tissue damage.

Methodology: To show the impact of free Hb in PE, we used the dual *ex vivo* placental perfusion model. Placentas were perfused with Hb and investigated for physical parameters, Hb leakage, gene expression and morphology. The protective effects of α_1-microglobulin (A1M), a heme- and radical-scavenger and antioxidant, was investigated.

Results: Hb-addition into the fetal circulation led to a significant increase of the perfusion pressure and the feto-maternal leakage of free Hb. Morphological damages similar to the PE placentas were observed. Gene array showed up-regulation of genes related to immune response, apoptosis, and oxidative stress. Simultaneous addition of A1M to the maternal circulation inhibited the Hb leakage, morphological damage and gene up-regulation. Furthermore, perfusion with Hb and A1M induced a significant up-regulation of extracellular matrix genes.

Significance: The *ex vivo* Hb-perfusion of human placenta resulted in physiological and morphological changes and a gene expression profile similar to what is observed in PE placentas. These results underline the potentially important role of free Hb in PE etiology. The damaging effects were counteracted by A1M, suggesting a role of this protein as a new potential PE therapeutic agent.

Introduction

Preeclampsia (PE) is a leading cause of maternal and fetal morbidity and mortality. Despite extensive research, PE still remains enigmatic and is called the disease of theories by many obstetricians [1]. Clinical manifestations, i.e. hypertension and proteinuria, appear from 20 weeks of gestation and onwards, but the underlying mechanisms may begin already at the time of implantation [2]. Up to date, there are no established prognostic and/or diagnostic markers for the disease. The only cure still is termination of pregnancy with delivery of the fetus and removal of the placenta.

PE evolves in two stages where the first stage is initiated by a defective placentation. A growing body of studies shows that uneven blood perfusion, hypoxia and oxidative stress follow as a consequence of the defect in placentation, further aggravating the impairment of placental functions [3, 4]. Stage two is characterized by the appearance of clinical symptoms such as hypertension, proteinuria and edema, which are caused by a general vascular endothelial dysfunction leading to a general organ failure and damage. The link between stage one and two is still unclear but several different factors and explanations have been suggested [5].

By using gene and protein profiling techniques, we have previously been able to show increased mRNA levels of fetal hemoglobin (HbF) in the placental tissue and evidence of free HbF in the placental vascular lumen in PE [6]. Furthermore, we have shown increased plasma and serum concentrations of HbF in the mother, suggesting that free HbF leaks over the blood-placenta barrier, into the maternal circulation where the plasma concentration is increasing from early pregnancy and later correlates to the severity of the the disease [7, 8].

Free Hb is a highly reactive molecule that is capable of damaging and disrupting cell membranes [9]. Also, it binds and inactivates nitric oxide (NO)[10], with vasoconstriction as a consequence. The metabolites of Hb, free heme and iron, damage lipids, protein and DNA through direct oxidation and/or generation of reactive oxygen species (ROS) [11]. In fact, free heme, bilirubin, and biliverdin have been identified among 14 metabolites in a metabolomic signature of preeclampsia using first trimester plasma [12]. Due to the lipophilic nature of the heme-group, it intercalates membranes and has destabilizing effects on the cytoskeleton [13]. Heme is also a pro-inflammatory molecule that activates neutrophils [11]. Several important Hb-detoxification systems work in parallel to prevent Hb-induced oxidative stress and tissue damage. Haptoglobin is a glycoprotein that forms a complex with free Hb, and is one of the primary Hb scavengers in plasma. In fact, a haptoglobin polymorphism has been associated with essential hypertension, which is predisposing for developing PE [14]. Free heme is primarily scavenged by hemopexin, but this activity is reduced in PE [15]. The haptoglobin-Hb and hemopexin-heme complexes are cleared from the circulation by the two receptor-mediated pathways CD163 and CD91, and subsequently degraded in lysosomes [16].

α_1-microglobulin (A1M), a 26kDa plasma and tissue protein, has recently been described as a heme- and radical scavenger with antioxidative, cell-protective and repair properties [17-20]. A1M is mainly synthesized in the liver and distributed via the blood-stream to the extra-vascular compartment in all tissues [21]. Due to its small size, A1M is filtered in the renal glomeruli and partially re-absorbed in the tubuli [21, 22]. Recent reports have shown that A1M is a heme- and radical-scavenger, involved in the defense against

oxidative stress induced by free Hb and participating in the degradation of heme [18, 19, 23]. Its synthesis is up-regulated, both in liver and peripheral cells, as a consequence of elevated concentrations of free Hb, heme and ROS [24].

We have hypothesized, that early events, including hypoxia, during development of PE cause over-production and release of free HbF, which induces oxidative stress with damage to the blood-placenta barrier and leakage of free HbF into the maternal circulation. Thus, circulating free HbF may be one of the important factors, linking stage 1 to stage 2, leading to endothelial dysfunction and subsequently the clinical manifestations characterizing PE. The levels of A1M are elevated in maternal plasma, serum, urine and placental tissue from women with PE suggesting that the protein is involved in a defence reaction against the Hb-insult [8]. Hypothesizing that A1M, and other defence systems, are overwhelmed in PE, we propose that the disease may be treated by addition of exogeneous A1M.

In this study we used the dual placental perfusion system, which is a well-established model to study the placental function *ex vivo* [25], in order to systematically decipher the effects of free Hb in an isolated healthy placenta. We have previously shown that *ex vivo* perfusion of human placenta under control conditions leads to mild oxidative stress with changes resembling those described *in vivo* in PE, such as increased secretion of pro-inflammatory cytokines and release of syncytiotrophoblast membranes [26-28]. Physical and morphological parameters were recorded and related to the global gene expression and electron microscopy (EM) data. Furthermore, the protective and potentially therapeutic effects of A1M were evaluated.

Material and Methods

Sample Collection

Fifteen human term placentas (gestational age 38-42 weeks, placenta weight 438-1102 g) obtained from uncomplicated singleton pregnancies delivered by Caesarean section (n=3) or vaginal delivery (n=12) were used for the perfusion experiments. All mothers gave their written informed consent for the experimental use of their placentas prior to delivery. The ethical review committee of Lund University approved the study.

Tissue samples from the placenta were taken from an adjacent cotyledon before the perfusions were initiated and from the perfused cotyledon after the completion of the perfusion. Furthermore, placental tissue samples were also collected from three patients with severe PE (diastolic pressure >110mmHg and proteinuria >3g/L). Small pieces, 3x3mm, were obtained from a central, non-necrotic, part of the placenta and immersed in fixative as described below. The tissue samples were immediately cryopreserved for gene expression and protein analysis.

The Placental Perfusion Model and Experimental Design

The perfusions of a placental cotyledon using the dual perfusion model were performed as previously described [25](Supplementary figure 1). When the volumes and pressures of both the maternal and fetal circuits were stable the circuits were closed and perfusion continued with mean flow rates of 12 and 4 ml/min on the maternal and fetal side respectively and 140 ml perfusion medium were recycled in each circulation. The perfusion medium consisted of NTCT 153 (Sigma-Aldrich, Steinheim, Germany) in

Earl's buffer (1:3, v/v), 4% albumin (PAA, Laboratories, Linz, Austria), 0.2% glucose (Merck, Darmstadt, Germany), 1% dextrane 40 (Carl Roth, Karlsruhe, Germany), 2500 units/l heparin (Leo Pharma, Malmö, Sweden), and 250 mg/l clamoxyl (AstraZeneca, Lund, Sweden). To mimic intrauterine conditions, two gas exchange devices were connected (Mera Silox-S 0.3, Senko Medial Instruments, Tokyo, Japan). The fetal circulation was equilibrated with 95% nitrogen and 5% carbon dioxide and an atmospheric gas mixture was used for the maternal side.

The experiments were terminated if any of the following criteria was observed: fetal perfusion pressure above 50 mmHg, loss of perfusate > 4 ml/h, and in case of mismatch of materno-fetal circulation as measured by inadequate oxygen transfer (pO_2 maternal side < 100 mmHg, pO_2 fetal side < 20 mmHg). After 60 minutes of the initial equilibration of the placental preparation, the medium was exchanged in both circuits and the actual experiment consisted of three phases lasting 120 min each with medium exchange between the phases. Experiments were performed using medium only in phase I and III. In phase II the medium was supplemented with one of the following substances: 3 mg/ml free human adult Hb (HbA; corresponding to 55 μM Hb or 220 μM heme) in the fetal circulation (n=6, Hb), 0.5 mg/ml A1M (22 μM) in the maternal circulation (n=2, A1M) or 3 mg/ml free HbA in the fetal + 0.5 mg/ml A1M in the maternal circulations respectively (n=4, Hb+A1M). Control experiments were performed using medium only in all three phases (n=3).

HbA was purified from whole blood, freshly drawn from healthy subjects as described [29]. Recombinant human A1M was expressed in *E.coli*, purified and re-folded as described by Kwasek et al [30], but with an additional ion-exchange chromatography

step. This was performed by applying A1M to a column of DEAE-Sephadex A-50 (GE Healthcare, Uppsala, Sweden) equilibrated with 20 mM Tris-HCl, pH8.0. A1M was eluted with a linear salt gradient (from 20 mM Tris-HCl, pH8.0 to 20mM Tris-HCl+0.2 M NaCl) at a flow rate of 1 ml/min. A1M-containing fractions, according to absorbance at 280 nm, were pooled, concentrated and dialyzed against perfusion medium.

Medium samples were taken at regular intervals from the maternal and fetal circulation and stored at -20°C for further analysis. Glucose consumption and lactate production were used as parameters reflecting the placental energy metabolism. Antipyrine (0.4 mM) and creatinine (1.3 mM) permeability were measured in phase I, as reference parameters for trans-placental transfer of flow- respectively diffusion limited molecules to ensure a match of the materno-fetal circulation. Glucose, lactate and creatinine concentration as well as oxygen and carbon dioxide pressure were measured using a blood-gas-analyzer (Radiometer, Copenhagen, Denmark); antipyrine concentration was measured using an HPLC method [31]. The arterial fetal perfusion pressure and the feto-maternal leakage were recorded as viability characteristics.

Transmission Electron Microscopy

The ultra-morphology of the placental samples were analyzed by ultra-thin sectioning and transmission EM. The placenta specimens were immersed in 1.5% paraformaldehyde, 1.5% glutaraldehyde in 0.1M sodium-phosphate buffer pH 7.2 for 1h at room temperature, and then overnight at 4 °C. Samples were washed in the fixation buffer and then postfixed for 1h at room temperature in 1% osmium tetraoxide in 0.1M sodium-phosphate buffer, dehydrated in a graded series of ethanol, and then embedded in Epon

812 using acetone as an intermediate solvent. Specimens were cut into 50-70 nm-thick ultrathin sections with a diamond knife on an LKB ultramicrotome. The sections were stained with uranyl acetate and lead citrate. Specimens were observed in a JEOL JEM 1230 electron microscope operated at 80 kV accelerating voltage, and images were recorded with a Gatan Multiscan 791 CCD camera. The analysis was carried out in a blinded fashion by an independent investigator. For quantitative evaluation of tissue damage by oxidative stress, the surface areas of mitochondria and extracellular matrix space as well as the ratio of damaged and intact plasma and nuclear membrane stretches were determined for 30 cell profiles (Table 1). The values for the surface area for these structures were determined using Adobe Photoshop CS5.

Gene Expression

RNA Extractions and Integrity

Total RNA was extracted using TRIZOL® (Invitrogen, Carlsbad, USA) and E.Z.N.A™ total RNA Kit (Omega Bio-tek, Doraville, USA) according to manufacturer's instructions. RNA concentration was spectrophotometrically determined using a Nanodrop (NanoDrop technologies, Wilmingon, USA). RNA integrity was assessed on an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, USA). Only samples with a RNA integrity number over 6 were used for expression profiling.

cDNA Synthesis

RNA was transcribed using either the Taqman Reverse Transcription Reagents from Applied Biosystems (Applied Biosystems Inc., Foster City, CA, USA) or Fermentas RevertAid H Minus first strand cDNA synthesis kit (Fermentas AB, Helsingborg,

Sweden) according to the manufactures instructions. The cDNA samples were stored at -20°C until further use.

Arrays

Human whole genome bead microarrays, HumanHT-12 v3 Expression BeadChip (Illumina Inc., San Diego, CA, USA) were ordered from SCIBLU Genomics at the Lund University, Sweden and used according to the manufacturer's instructions. Following hybridization and scan, the arrays were imaged on an Illumina BeadArray™ Reader (Illumina Inc.).

Array Analysis

Expression data was exported into BioArray Software Environment (BASE) for statistical analysis [32]. Data was normalized using average normalization and non-specific hybridizations were removed by filtering with a p-value < 0.01 using the Illumina p-value detection analysis. Arrays were then background corrected and exported into TM4 MeV for further analysis [33].

Firstly, all genes not present in 95% of the arrays were filtered out. Then, data were log2 transformed and the differential gene expression was calculated with a false discovery rate modified t-test. P-values were set to be based on the maximum number of permutations for the analysis, and the cut-off was set to $q < 0.05$ and $p < 0.05$. Fold change was calculated by dividing the mean intensity for each gene between the groups.

Real-time PCR

Gene transcripts for verification of microarray results were quantified in the StepOnePlus™ Realtime PCR System (Applied Biosystems) using commercially available TaqMan®Gene Expression Assays (Applied Biosystems) (Supplementary table 1). The PCR reactions were carried out in duplicates including negative controls (without template) in each run as previously described [6]. Gene transcript of the A1M gene was quantified using SYBR green in an iCycler Thermal Cycler (Bio-Rad Laboratories, Hercules, CA, USA) as previously described [20].

Protein Measurements

Measurement of Hb in medium

Hb was measured in the perfusion medium using HemoCue Plasma/Low Hb according to the manufacturer (Hemocue, Ängelholm, Sweden).

Protein extraction

Total protein from the placental tissues was isolated using TRIZOL® (Invitrogen) according to the manufacturer's instructions. The total protein concentration was determined by BCA™ protein assay kit (Pierce, Thermo scientific Rockford IL USA). The protein solutions were corrected to the same concentrations before analysis.

Radioimmunoassay (RIA) of A1M

Radiolabelling of A1M with ^{125}I was done using the chloramine T method [34]. Labeled A1M was separated from free iodide by gel-chromatography on Sephadex G-25 columns (PD10, GE Healthcare, Uppsala, Sweden). A specific activity of 0.1-0.2 MBq/µg protein was obtained. RIA was performed as previously described [35].

SDS-PAGE and Western blotting

SDS-PAGE (T=12%, C=3.3%) was performed as described by Laemmli [36]. The gels were run under non-reducing conditions. The separated proteins were transferred to polyvinylidene difluoride (PVDF) membranes (Immobilon-P, Millipore, Bedford, MA, USA). The PVDF membranes were then incubated over-night as described [37] with mouse monoclonal anti-A1M antibodies (BN11.10, 10 μg/ml) [38], followed by incubation with ^{125}I-labelled rabbit anti-mouse IgG (10 ng/ml; Dako, Denmark). The membranes were developed in a Fuji FLA3000 phosphoimaging system (Fujifilm Sweden AB, Stockholm, Sweden). Human free, monomeric plasma A1M, used as control, was purified by affinity chromatography and gel chromatography as described [39].

Statistical Analysis

All statistical analysis was performed using Origin 8 software (Microcal, Northampton, MA, USA). The significance of differences between groups was evaluated using both Student´s t-test and Mann-Whitney U-test. Values of $p<0.05$ were considered statistically significant.

Results

Validation Parameters and Characteristics of the Placental Perfusions

Initially, in phase I, antipyrine and creatinine permeability were monitored in all four perfusion groups (control, Hb, Hb+A1M and A1M) to ensure that there was no mismatch of the maternal and fetal circulation before the supplements were added in phase II. No difference between the perfusions was detected (Supplementary table 2). The validation parameters for placental carbohydrate metabolism, glucose consumption and lactate production, were investigated for all perfusion groups in phase I-III (Supplementary table 2). None of the supplements influenced any of these parameters and no difference between the individual phases of the perfusion experiments was detected. Antipyrine and creatinine permeability and glucose consumption and lactate production were all found to be consistent with previous studies [31].

Hemoglobin Increases Perfusion Pressure and Feto-Maternal Hemoglobin Leakage.

Addition of Hb into the fetal circulation led to significant increase of the mean arterial fetal perfusion pressure compared to control perfusions (14.3 ± 2.9mmHg vs. 3.7 ± 2.0 mmHg, p=0.019, Fig. 1A). The elevated perfusion pressure in the fetal circulation caused a tendency to higher feto-maternal leakage, measured as a volume increase in the maternal circulation, although this change was not statistically significant (Fig 1B). The specific leakage of free Hb from the fetal into the maternal circulation increased with time (Fig 1C).

Free Hemoglobin Damages Placental Ultra Morphology

The morphology of cytothrophoblasts and syncytiotrophoblasts in placental villi of Hb-perfused and control placentas was analyzed by EM (overview Figure 2, quantification Table 1). Exposure to free Hb resulted in severe cell-damage revealed by alterations of the extracellular matrix (ECM) architecture (Fig. 3B), signs of apoptosis manifested by the presence of vast amounts of apoptotic vesicles (Fig. 3D) and enlarged mitochondria (Fig. 3F). In the pericellular environment the Hb-perfusion caused impaired cellular barrier functions including plasma membrane rupture (Fig. 3D). Intracellularly, the Hb-perfusion caused enlarged mitochondria, altered endoplasmatic reticulum structure and a fuzzy morphology of nuclear membranes (Fig. 3F, H). For further details see legend of figures.

The damages observed in the Hb-perfused placentas were compared to non-perfused placenta samples taken at delivery from patients with severe PE. The morphology seen in PE-placentas (Fig. 4C) was similar to the morphology of placentas perfused with Hb (Fig. 4B). The controls and the non-perfused placentas from healthy subjects showed no signs of damage and no difference in morphology (Fig. 4A).

Microarray Analysis

The gene expression was analyzed by microarray before and after perfusions. The differential gene expression between Hb vs. controls, Hb+A1M vs. Hb, Hb+A1M vs. A1M and A1M vs. control, respectively, showed a significantly differential gene

expression of in total 818 genes when a cut-off was set to $p < 0.05$ and $q < 0.05$ (supplementary table 3). For the complete list of genes with significantly changed expression see supplementary table 4.

Free Hemoglobin Up-regulates Placental Gene Expression.

Simply by looking at the numbers of the microarray Hb vs. control comparison, it can be concluded that Hb perfusion resulted in a general up-regulation of genes (184 up and 5 down). The major gene categories affected were genes related to immune response, apoptosis, oxidative stress, structure and cytoskeleton (Table 2). This suggests that Hb perfusion results in oxidative stress, apoptosis and tissue damage, supporting the morphological changes observed by EM. Among the down-regulated genes, the pregnancy specific beta-1-glycoproteins 3 and 7 are of particular interest because down-regulation of these has previously been correlated to PE and poor pregnancy outcome [40].

To confirm the microarray data we quantified the expression of genes of particular interest (i.e. greatest and/or most statistically significant differentially expression, gene ontology and expression pattern) using quantitative real-time PCR. The addition of Hb led to a significant up-regulation of DNA repair/apoptosis pathways (represented by poly-(ADP-ribose)-polymerase family, member 3; PARP3 and immune response pathways (represented by Fc-fragment of IgG, high affinity IA, receptor (CD64); FCGR1A. We also found a strong tendency to down-regulation of pregnancy specific beta-1-glycoprotein 3 and 7 genes (PSG3 and 7).

A1M-Addition Protects the Placenta from the Hemoglobin insult

Addition of A1M into the maternal circulation simultaneous to addition of free Hb to the fetal circulation did not reverse the increased perfusion pressure caused by Hb. A slight increase, but not statistically significant, was seen by addition of A1M alone (Fig 1A). No significant change in leakage of fluid was seen by addition of A1M (Fig 1B). However, A1M significantly prevented the specific leakage of free Hb from the fetal into the maternal circulation (Fig 1C).

A protective effect by A1M-addition was also supported by the EM observations. The ECM architecture in the placentas perfused with Hb+A1M was indistinguishable from the controls (Fig. 5D, B, Table 1). Likewise, the cell organelle structures were intact in the groups, i.e. no swelling of mitochondria, no disruption of the membranes, and absence of apoptotic vesicles could be seen (data not shown). Placentas perfused with A1M alone could not be distinguished from the control placentas (data not shown).

A1M Influence on Hemoglobin-Induced Gene Expression in Placenta

In an attempt to explore the mechanisms behind the protective effects of A1M, the microarray data from perfusions with Hb+A1M, Hb (alone) and Hb+A1M vs. Hb were compared. The analysis shows a general down-regulation of genes (236 down and 42 up) (supplementary table 3). This suggests that the simultaneous addition of A1M to the maternal circulation counteracted the general gene up-regulation caused by Hb perfusion. In order to confirm this finding we compared the list of genes up-regulated in Hb vs. control to the list of genes down-regulated in Hb+A1M vs. Hb. In total, twelve genes that were up-regulated in Hb vs. control, were down-regulated in Hb+A1M vs. Hb (see supplementary table 4). Among these were genes related to oxidative stress-response and

apoptosis e.g. arginine-rich, mutated in early stage tumors, (ARMET) and immune response e.g. RAS-like, family 11, member B (RASL11B) (Table 3). The expression of these genes was not affected by the addition of A1M alone. Interestingly, several genes coding for ECM components e.g. collagen, type VIII, alpha 2, (COL8A2), were up-regulated in placentas perfused with Hb+A1M. These genes were not up-regulated when Hb or A1M were added separately to the circulations.

To confirm the microarray data, we quantified a selection of genes by real-time PCR. The results confirmed that A1M-addition counteracted the up-regulation of oxidative genes (represented by ARMET) and immune response genes (represented by RASL11B). Also, the up-regulation of ECM genes (represented by COL8A2) by Hb+A1M, but not by either protein separately, was confirmed.

All together, the gene expression data suggest that A1M acts protectively by counteracting harmful oxidative consequences of the Hb-perfusion by down-regulating oxidative, apoptotic and immune related genes and up-regulation of ECM protective/repair genes.

Expression of A1M mRNA and A1M Protein Variants in Placenta

To further explore the mechanism of A1M-protection in the Hb-perfusion insult, we investigated A1M mRNA and protein content and the qualitative presence of various A1M variants in the placental tissue from the study groups.

Real-time PCR revealed an up-regulation of A1M mRNA expression in the Hb perfused placentas (Fig. 6A). Furthermore, addition of exogenous A1M resulted in decreased A1M mRNA expression, almost to the same level as the control placentas. Perfusion with A1M

alone did not yield a significant change in A1M mRNA expression compared to control perfusions.

The A1M-protein concentration in the placental tissue was also increased by Hb-perfusion as compared to controls (Fig. 6B). The addition of A1M to the maternal circulation resulted in a dramatic increase of the A1M-concentration in the placental tissue. This was observed both with and without the addition of free Hb to the fetal circulation and could reflect A1M-protein in the medium from the intervillous space and/or in the tissue.

Variants of the A1M-protein in (Hb+A1M)-perfused placental tissues were also qualitatively analyzed by Western blotting (Fig. 6C). Monomeric plasma A1M (lane 2) migrates as a 31 kDa-band and is found in whole plasma (lane 1) and placental tissue (lane 3). Also, high molecular weight A1M-complexes with IgA, albumin and prothrombin {Berggård, 1997 #2368}, migrating between 100-400 kDa, were found in plasma and placenta tissue. Non-glycosylated recombinant *E.coli*-A1M, migrating as a 24 kDa band, was found in large amounts in the placental tissue (lane 3), suggesting an uptake of A1M from the maternal circulation, or the presence of A1M-containing medium. In addition to these previously described forms, several novel variants were seen in the placental tissue (lane 3). The most prominent of these forms migrated at 33, 35, 45 and 100 kDa. The former three bands were seen in all perfusions, whereas the latter was seen only in some, but not all, Hb+A1M-perfusions.

Discussion

Placental tissue may be subjected to different degrees of oxidative stress. Recently, it was shown that labor initiates oxidative stress which, depending on length and intensity, varies with the lowest degree of stress found in placental tissue from elective cesarean section [41]. As far as the gene profile is concerned, there apparently is no unanimous opinion [42]. Oxidative stress related changes in placental tissue is a typical hallmark of PE [3]. *Ex vivo* dual perfusion of placental tissue, even under control conditions, induces mild oxidative stress, which may be explained by reperfusion following the postpartum ischaemia [27]. We have also shown that addition of xanthine + xanthine oxidase to the medium only resulted in a minor increase of oxidative stress indicating a considerable antioxidant capacity of the tissue [43]. The gene expression profile in *ex vivo* perfused placental tissue shows similarities with tissue from PE placenta [28].

In this paper we have obtained results supporting our hypothesis that free Hb may have a central role in the etiology of PE. Perfusion with free Hb led to increased perfusion pressure, feto-maternal Hb leakage, ultra-structural changes of the ECM and general cell damage. Gene array analysis showed an up-regulation of genes related to apoptosis and oxidative stress-response. The morphological alterations showed a high similarity to those observed in PE placentas [44]. Furthermore, the results also suggest that the heme- and radical scavenger A1M can prevent several of the harmful effects of the Hb-insult.

The similarity between the ultra-structural alterations in our *ex vivo* Hb-perfused placental tissue and unperfused placental tissue from PE patients suggests that our model

is relevant and underline the impact of Hb in the PE etiology. In addition, the observed ultra-structural alterations are, to some extent, in agreement with a previously published study on endothelial cell damage in PE [44]. In our EM analysis we have mainly focused on the plasma membrane structure, ECM architechture and organelle morphology of syncytio-/cyto-throphoblasts. However, several additional ultra-structural observations were seen in the syncytiothrophoblast layer in the Hb-perfused placentas. Signs of cell death, dilated endoplasmatic reticulum and swollen cells with damaged plasma membranes are some of the changes that are agreement with findings from villous explants subjected to oxidative stress [45].

Our observations of the effects of Hb-perfusion in placental tissue may be explained in terms of known toxic effects of free Hb and its metabolites. As described above, cell-free Hb and its metabolites are known to be harmful because of their oxidative properties. OxyHb, i.e. ferrous Hb (Fe^{2+}) binding oxygen (O_2), is known to undergo spontaneous intramolecular oxidation–reduction reactions which generate superoxide radicals. Further reactions lead to formation of ferryl Hb (Fe^{4+}), free heme, and various ROS. All these compounds are toxic because they can cause oxidative damage on DNA, matrix molecules, cell membranes, and other tissue components [46]. Thus, it is reasonable to assume that Hb-induced oxidations are explanatory mechanisms of the disruption of the placental ultrastructure as well as the increased feto-maternal leakage.

The results of the genome wide array analysis support the idea that free Hb mediates the placental damage via oxidation. Hb-perfusion, in general, led to a massive up-regulation

of genes. The gene ontology-analyses showed that apoptosis-, oxidative stress-, and immune-related genes were frequently represented, confirming data from previously reported findings based on gene array studies on PE placentas [6, 47-49].

Assuming that Hb mediates the placental damage via heme and oxidative stress, the heme- and radical scavenging and cyto-protective properties of A1M could explain the inhibition of Hb-induced damage [18, 19, 21, 50]. For example, when cell cultures were exposed to free Hb, heme, Fenton reaction-generated ROS and irradiation, addition of A1M led to heme-binding, decreased ROS-levels and inhibition of cell death and oxidative stress markers in the cells [8, 20]. The exact mechanism behind the scavenging effects by A1M still remains to be explored. Besides radical scavenging, our results suggest that A1M exerts protective effects by up-regulation of genes related to ECM components, (e.g. collagen, type VIII, alpha 2, COL8A2) in the presence of Hb. It may be speculated that A1M in this way also activates systems that repair tissue damages caused by oxidation.

The increase in arterial pressure by the Hb-perfusion may be a result of oxidative endothelial damage but it is also likely to be an effect of the NO-scavenging properties of free Hb. It has previously been shown that hemolysis and increased levels of cell-free Hb in sickle-cell anemia results in binding of NO by oxy-Hb, thus inhibiting the vasodilatory function of NO [51]. The addition of A1M did not prevent the rise in perfusion pressure induced by Hb. A possible explanation for this may be that the protective effects of A1M does not include inhibition of the NO-scavenging properties of

Hb. This speculation seems reasonable, since A1M has not been reported to bind directly to the Hb molecule itself.

The concentration of Hb in the perfusion media was 3 mg/ml, which is equivalent to 220 μM heme-groups. This is much higher than the Hb-concentrations, 3-10 μg/ml, measured in PE-patients at 20 weeks of gestation or at term [7, 8]. A higher concentration was chosen for several reasons. First, the local concentration of free Hb in the placental villi can be expected to be much higher than in the maternal blood and secondly, the exposure time of the perfused placental tissue to free Hb is only a few hours compared to several weeks in the clinical situation. An A1M concentration of 22 μM, corresponding to a tenfold excess of Hb, *visavi* A1M, was chosen because, as mentioned above, A1M does not interact with Hb itself but rather with free heme and radicals expected to be generated at a much lower steady-state concentration. In addition, the radical-scavenging capacity of A1M was shown to be approximately 8-9 radicals / A1M-molecule [24]. It has also been shown previously that a molar deficit of A1M is sufficient to protect cultured cells against oxidation by an excess of Hb or free heme [20].

Interestingly, several unique forms of A1M were identified in the placenta tissue extracts (33, 35, 45 and 100 kDa bands in Western blotting). The former three variants were seen in all samples, suggesting that they are constitutively present in placenta, and not derived from exogenously added recombinant A1M. The 45 and 100 kDa bands have been described previously and were suggested to be complexes between A1M and other proteins [52]. The previously un-detected 33 and 35 kDa-bands are, due to their small

size, unlikely to be complexes with other proteins and they may represent A1M-forms with larger placenta-specific glycosylation modifications. Our results thus show the presence of unique placental variants of A1M suggesting a placenta-specific role of the protein.

A physiological role of A1M in the protection of human placenta is further supported in previous studies on the immunohistochemical distribution of A1M [20, 52]. The protein was found to be present throughout the villous stroma, with an accumulation on the apical surface of the syncytiotrophoblast layer and in the basal membrane around the fetal blood vessels. This distribution is consistent with the hypothesis that A1M plays a role in local protection against oxidative stress at the maternal/placental and fetal/placental interfaces. Interestingly, high concentrations of A1M were found at sites of "syncytial injury", i.e. where the syncytiotrophoblast layer was ruptured, and at fibrin deposits around intravillous blood vessels [52]. This suggests an accumulation/up-regulation of A1M where the integrity of the placental barrier is breached and the placental tissue is exposed to oxidants from fetal or maternal blood. This is supported by this study where Hb-perfusion led to up-regulation of placental A1M-mRNA expression and accumulation of A1M protein in the placental tissue. Accordingly, increased production of (unique placental variants) of A1M may be a normal response to Hb-induced oxidative stress in placental cells, which is in line with a previous report of an up-regulated A1M-expression in blood cells exposed to Hb and ROS [24].

The up-regulation of A1M previously reported in PE suggests a natural antioxidative response that fails to neutralize the oxidative stress in PE. By supplementing the body with a bolus dose of A1M, a therapeutic level might be reached. The idea of preventing PE development by anti-oxidative treatment is not new. Several studies have evaluated the use of vitamin C and E in high-risk pregnancies in order to prevent the oxidative stress seen in PE. The results have failed to show a reduction in the rate of adverse maternal or perinatal outcomes related to pregnancy-associated hypertension [53, 54]. This does not disprove the oxidative nature of the disease, however, since the scavenging capacity of vitamin C is limited and the oxidized form, dihydroascorbate, which is formed by its oxidation, may also present an oxidative challenge in the tissues during the disease.

In summary, PE is a pathologic condition that is in need of improved, early diagnosis and therapeutic treatment. Recently, we have shown that elevated levels of free HbF and A1M in maternal plasma are indicators for PE, and a prognostic/diagnostic test based on these two parameters is under development [7, 8]. The results presented in this paper further underlines that Hb is a potential important etiological factor in the onset and progression of PE. We also show that a heme- and radical scavenger protein may protect the placenta from cell-damage. Therefore, we suggest heme- and radical-scavenging as a possible treatment of PE. The inhibition of Hb damage by A1M in our *ex vivo* model suggests A1M as a promising candidate for future PE therapy.

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Tables

Table 1: Quantification of values for surface areas obtained by EM.

Structures	Control	Hemoglobin	Hemoglobin + A1M
ECM integrity	93%	16%	78%
Plasma membrane integrity	96%	36%	83%
Nuclear membrane integrity	95%	37%	88%
Mitochondrial cross section area (square μm)	0.4	1.3	0.6

Table 2: Selection of differentially expressed genes in Hb perfusion compared to control medium perfusions.

Gene	Symbol	P-value	FC	Gene ontology
IMMUNE RESPONSE				
FC fragment of IgG, high affinity IA, receptor (CD64)	FCGR1A	0.006	2.8	high-affinity Fc-gamma receptor, pivotal role in the immune response
intercellular adhesion molecule 3	ICAM3	0.007	2.3	regulates leukocyte adhesion to blood vessels at sites of inflammation/injury
APOPTOSIS, OXIDATIVE STRESS				
BCL2-associated athanogene 4	BAG4	0.008	2.3	silencer of death domains
carbonyl reductase 1	CBR1	0.005	1.6	catalyzes reduction of carbonyl compounds
poly (ADP-ribose) polymerase family, member 3	PARP3	0.008	2.4	Activated as early response to DNA breaks, required for DNA repair & apoptosis regulation
CELL ADHESION/CELL-CELL CONTACT				
nexilin	NEXN	0.0080	3.8	Actin filament binding, focal contact, cell adhesion, migration
PROTEIN/VESICLE TRANSPORT				
synaptogamin-like 2	SYTL2	0.008	1.9	RAB27A-dependent vesicle transport, secretion in e.g.NK and CTL cells
HEME SYNTHESIS				
uroporphyrinogen III synthase	UROS	0.009	2.2	Enzyme in heme synthesis pathway
PLACENTA FUNCTION				
pregnancy specific beta-1-glycoprotein 3	PSG3	0.0090	-1.2	female pregnancy, low expression indicates bad placental function
pregnancy specific beta-1-glycoprotein 2	PSG7	0.010	-1.3	Female pregnancy, low expression indicates bad placental function

FC= Fold change. A positive FC corresponds to an increased gene expression in the Hb perfusion

Table 3: Selection of genes with altered expression after addition of A1M to the maternal side in the perfusion.

Gene	Symbol	FC Hb vs. med.	FC Hb+A1M vs. Hb	Gene ontology
IMMUNE RESPONSE				
RAS-like, family 11, member B	RASL11B	2.0	0.53	intracellular signaling, GTP binding, cell communication
carboxypeptidase M	CPM	NC	0.61	proteolysis, catalytic activity
OXIDATIVE STRESS				
connexin 40	GJA5	2.0	0.52	gap junction channel activity, blood vessel development
arginine-rich, mutated in early stage tumors	ARMET	1.6	0.59	receptor binding, growth factor activity
homocystein-/ER stress inducible, ubiquintin-like domain member 1	HERPUD 1	1.4	0.52	biopolymer & protein metabolic process at ER membrane, stress inducible
CELL ADHESION/EXTRACELLULAR MATRIX				
VAV 3 oncogene*	VAV3	NC	0.060	integrin-mediated signaling pathway, cellular structure, morphogenesis, regulation of cell adhesion
collagen, type VI, alpha 2	COL6A2	NC	1.7	ECM structural constituent, cell adhesion, inorganic anion transport
collagen, type VIII, alpha 2	COL8A2	NC	2.0	ECM structural constituent, cell adhesion, collagen

FC = Fold change. A positive fold change means the expression is increased in Hb (vs. medium) or Hb+A1M (vs. Hb only) respectively. NC=no statistically significant change in expression can be detected. *Also affected by A1M alone; A1M vs. medium FC 2.8.

Supplementary table 1: Data on primers used for real-time PCR amplification

mRNA	Accession number	Size (NT)	TaqMan®Gene Expression Assay ID
GJA5	NM_005266.5	89	Hs00979198_m1
ARMET	NM_006010.2	57	Hs00180640_m1
HERPUD1	3RefSeqs	126	Hs01124269_m1
RASL11B	NM_023940.2	80	Hs00225132_m1
CPM	3RefSeqs	92	Hs00266395_m1
VAV3	2RefSeqs	64	Hs00196125_m1
COL6A2	NM_001849.3	89	Hs00242484_m1
COL8A2	NM_005202.1	85	Hs00697025_m1
SYTL2	6RefSeqs	107	Hs00909223_m1
UROS	NM_000375.2	124	Hs00165992_m1
NEXN	NM_144573.3	95	Hs00332124_m1
FCGR1A	NM_000566.3	105	Hs00174081_m1
ICAM3	NM_002162.3	66	Hs00233674_m1
BAG4	NM_004874.2	130	Hs00362193_m1
CBR1	NM_001757.2	73	HS00156323_m1
PARP3	3RefSeqs	88	Hs00193946_m1
PSG3	NM_021016.3	96	Hs00360732_m1
PSG7	NM-002783.2	101	Hs00818333_m1
GAPDH	NM_002046.3	122	Hs99999905_m1
ACTB	NM_001101.3	171	Hs99999903_m1

Supplementary table 2: Viability characteristics during *ex vivo* perfusions of the human placenta. Means ± S.D. are given.

Protocol	Control	3mg/ml Hb (fetal circulation)	0.5mg/ml A1M (maternal circulation)	3mg/ml Hb (fetal circulation)+ 0.5mg/ml A1M (maternal circulation)
	n=3	n=6	n=2	n=4
antipyrine permeability ($ml \times min^{-1} \times g^{-1}$)[A]	0.103 ± 0.035	0.064 ± 0.021	0.070 ± 0.033	0.047 ± 0.013
creatinine permeability ($ml \times min^{-1} \times g^{-1}$)[A]	0.038 ± 0.026	0.026 ± 0.070	0.027 ± 0.090	0.017 ± 0.007
glucose consumption ($\mu mol \times min^{-1} \times g^{-1}$)[B]	0.392 ± 0.343	0.333 ± 0.106	0.422 ± 0.140	0.196 ± 0.063
lactate production ($\mu mol \times min^{-1} \times g^{-1}$)[B]	0.605 ± 0.430	0.526 ± 0.080	0.747 ± 0.180	0.306 ± 0.058

[A] The materno-fetal permeability of antipyrine and creatinine were assessed in perfusion phase I, before addition of any of the supplements to ensure a match of the maternal and fetal circulation.

[B] The overall (maternal and fetal) glucose consumption and lactate production are given as means of perfusion phase I-III, as there was no difference between the individual phases of the perfusion experiments.

Supplementary table 3: **Overview of the differential gene expression between the various perfusion conditions detected by microarray.**

Perfusion condition	Number of up-regulated genes*	Number of down-regulated genes*
Hb vs. medium	184	5
Hb+A1M vs. Hb	42	236
Hb+A1M vs. A1M	67	106
A1M vs. medium	137	47

*The numbers of differential expressed genes when a cut off of $p < 0.05$ and $q < 0.05$ was used in the analysis.

Supplementary table 4: Genes with altered gene expression in the group comparisons. The p-value and fold change (within parenthesis) are presented. The fold change is always relative to the second group in the comparison, where a negative value represents decreased gene expression.

Figure Legends

Figure 1. Mean arterial fetal perfusion pressure, feto-maternal leakage of medium and Hb during *ex vivo* perfusions of the human placenta. The increase in fetal circulation pressure was detected at the end of phase II, and the feto-maternal leakage was detected at the end of phase III. The specific leakage of Hb in phase II is shown as concentration of Hb in the maternal circulation at various time-points. Means ± S.E.M are given. *$p<0.05$, **$p<0.01$, ***$p<0.001$ in Hb vs. control. (*), (**), (***) represent the corresponding significance levels in Hb vs Hb+A1M perfusions.

Figure 2. Overview of ultrathin sectioning and transmission electron microscopy of human placenta. A and B shows an overview of a placental villus with the syncytiotrophoblast layer and the intervillous space seen at the top, from control medium (A) and Hb-perfused (B) placentas, respectively. The scale bar represents 5 μm. A higher magnification of A is shown in 2C and the frame in 2B is shown in 2D. The scale bars in Figure 2C and 2D represent 2 μm. The frames in Figure 2C (control medium perfused) and 2D (Hb-perfused) are shown as higher magnified areas in Figure 3A, C, E, G and 3B, D, F and H, respectively.

Figure 3. Ultrathin sectioning and transmission electron microscopy of human placenta perfused with control medium (A, C, E, G) or with Hb (B, D, F, H). The scale bar represents 0.2 μm. A, B: structural changes in the ECM upon Hb-perfusion with a dramatically reduced number of cross-striated collagen fibrils(c) in 3B. C, D: In control perfused placenta (3C) individual cells are surrounded by intact plasma membranes (PM) and adjacent, multi-layered electron dense structures (arrowheads). In contrast, Hb-

perfusion (3D) induces a massive presence of apoptotic vesicles (AV) and plasma membrane stretches of fuzzy electron density (arrow). E-F: after Hb-treatment (3F) mitochondria (M) increase considerably in volume and the morphology of the endoplasmatic reticulum (ER) with attached ribosomes changes from round, necklace-like structures (3E,3G) to an overall more extended shape (3F, 3H). In control specimens the nuclear membrane (NM) exhibits a typical double-layered structure with inner and outer membrane aspects (3G). After Hb-perfusion this is changed to a fuzzy and less defined appearance (3H).

Figure 4 Transmission electron microscopy of ultrathin sections of non-perfused healthy control placentas (A), as compared to placentas perfused *ex vivo* with Hb (B) or non-perfused PE placentas (C). The scale bar represents 0.5 µm. The ECM undergoes severe morphological changes upon Hb-perfusion, which resemble the morphology of non-perfused PE placentas, where for example an abundance of collagen fibrils in the healthy placenta (A) is altered to a relative thinness of matrix filaments and a massive presence of apoptotic membrane structures (B, C).

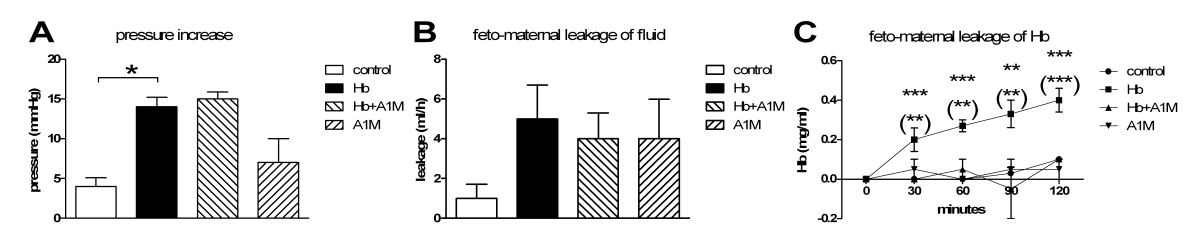
Figure 5. A1M prevents the damaging effects of Hb *ex vivo* on extracellular matrix as visualized by transmission electron microscopy of placenta specimens. The scale bar represents 0.2 µm. (A) non-perfused placenta, (B) perfusion with medium, (C) perfusion with Hb, (D) perfusion with Hb+A1M.

Figure 6. Expression of A1M as mRNA and protein and its variants in placental tissue. (A) A1M mRNA expression in placental tissue. The mRNA expression of A1M was analysed by real time PCR. The expression was related to the housekeeping gene

GAPDH. The data are presented as ΔΔCt (ΔCtA1M - ΔCtGAPDH). Hb vs control: $p<0.01$ and Hb+A1M vs Hb: $p<0.07$. (B) A1M protein concentrations in placental tissue. The A1M protein concentration in total protein extracts of placental tissue was analysed by RIA. The data are presented as µg A1M/mg of total protein. Hb vs control: $p<0.03$. (C) A1M variants in placental tissue. The A1M protein in placentas perfused with Hb+A1M was analyzed by Western blotting. 46 g total protein extracted from Hb+A1M perfused placenta were separated by SDS-PAGE (lane 3). As references 0.02 L human plasma (lane1) and 10 g plasma free, monomeric A1M (lane 2) were co-analyzed. The A1M variants were detected with anti-A1M.

Suppl. Figure 1. Diagrammatic figure of the dual perfusion model

The maternal and fetal side respectively containing 140 ml perfusion medium that was recycled in each circulation.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pressure increase
pressure (mmHg)
20
15
10
5
0
*
control
Hb
Hb+A1M
A1M
B
feto-maternal leakage of fluid
leakage (ml/h)
8
6
4
2
0
control
Hb
Hb+A1M
A1M
C
feto-maternal leakage of Hb
Hb (mg/ml)
0.6
0.4
0.2
0.0
-0.2
***
(**)
***
(**)
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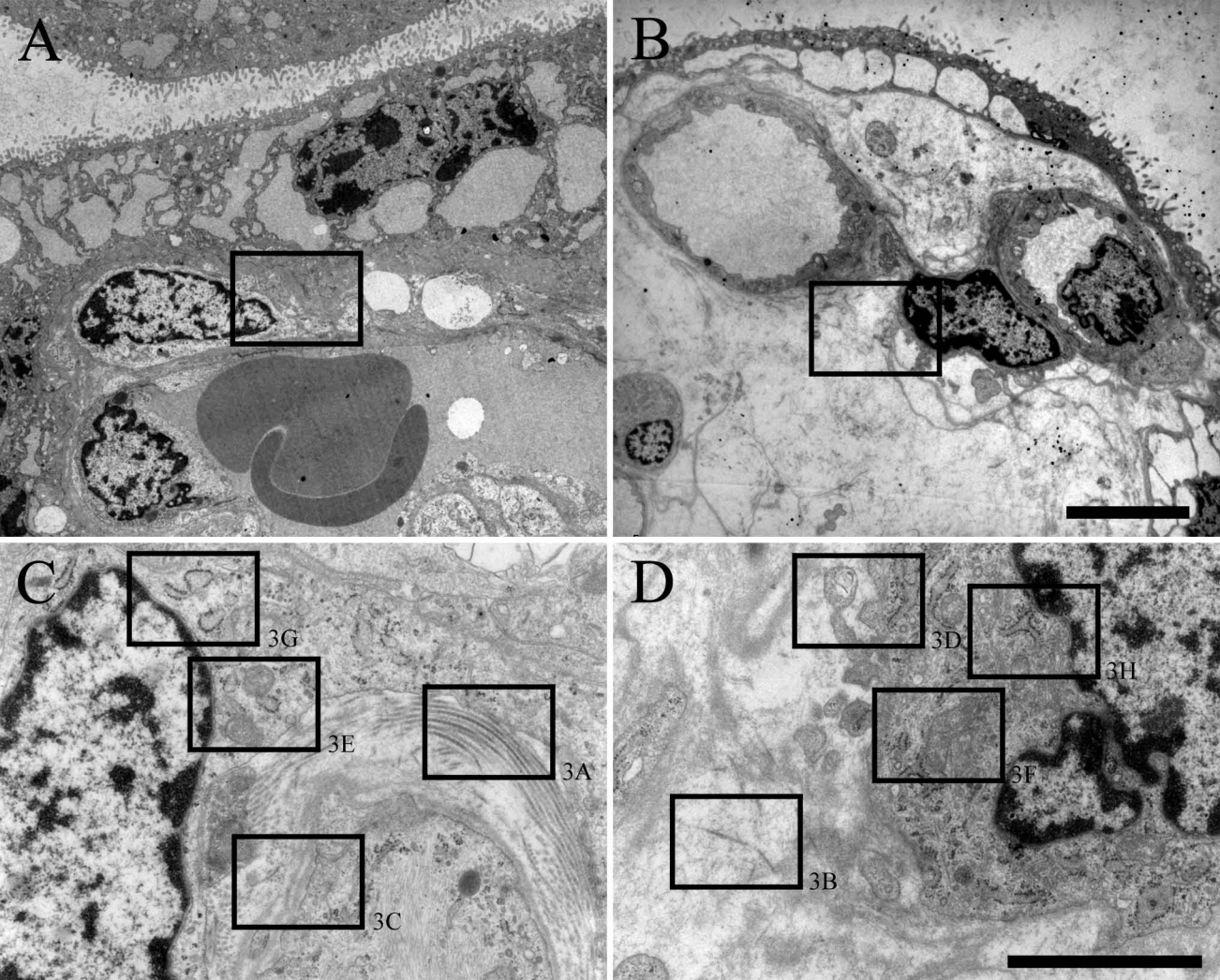
(**)
***
(***)
0
30
60
90
120
minutes
control
Hb
Hb+A1M
A1M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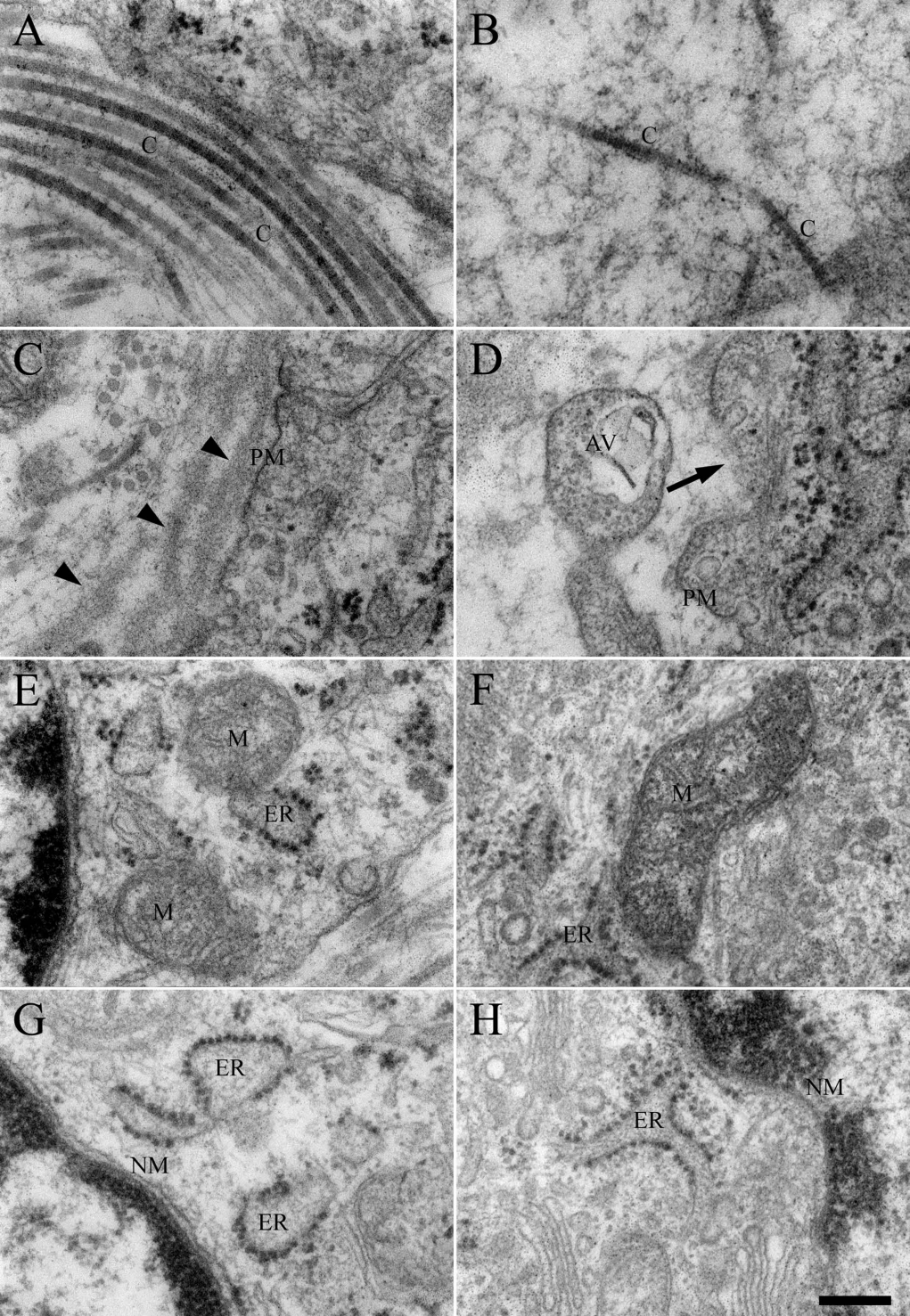
3G
3E
3A
3C
D
3D
3H
3F
3B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C
C
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H
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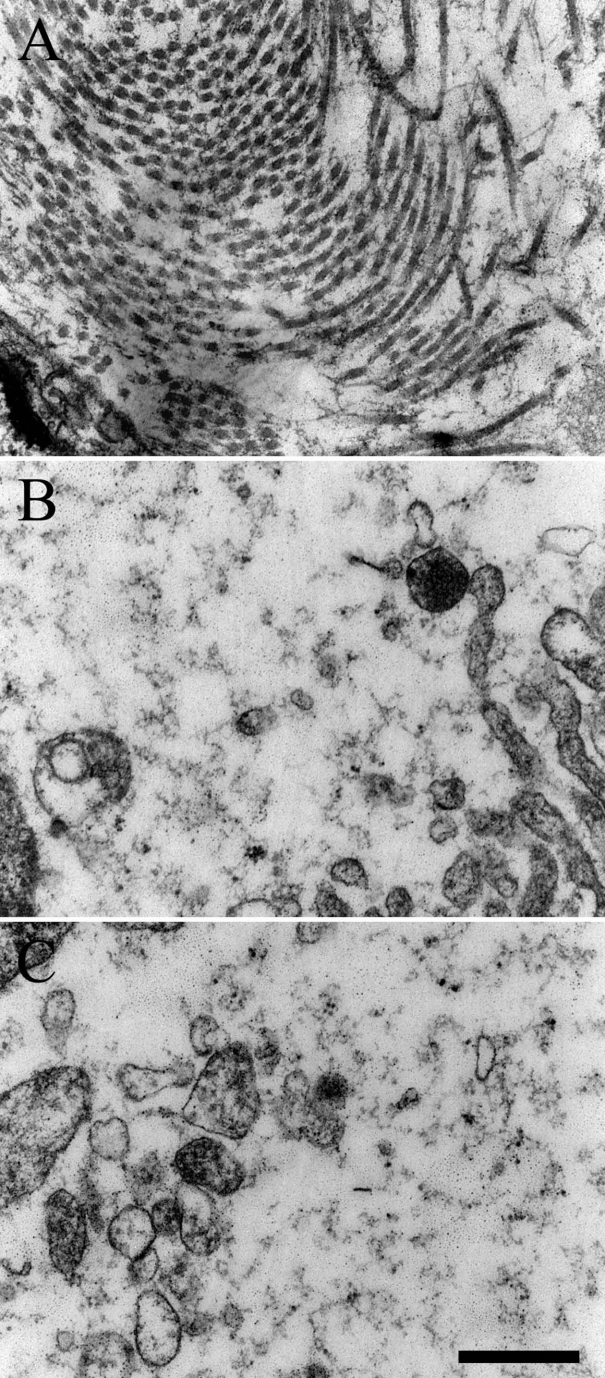
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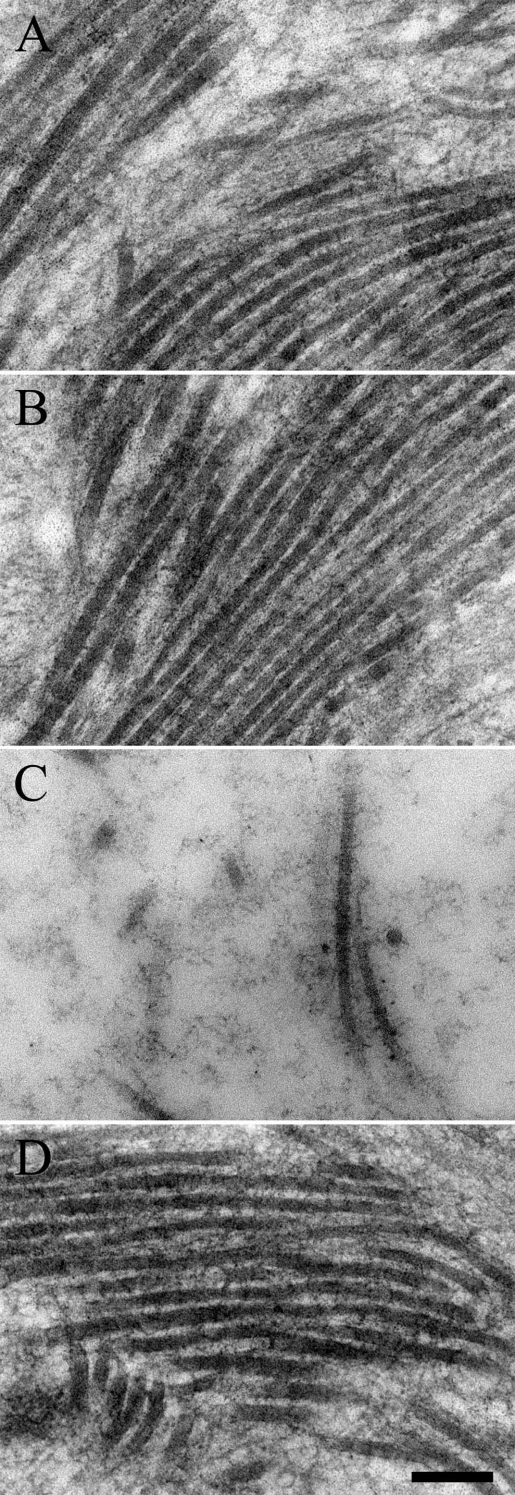
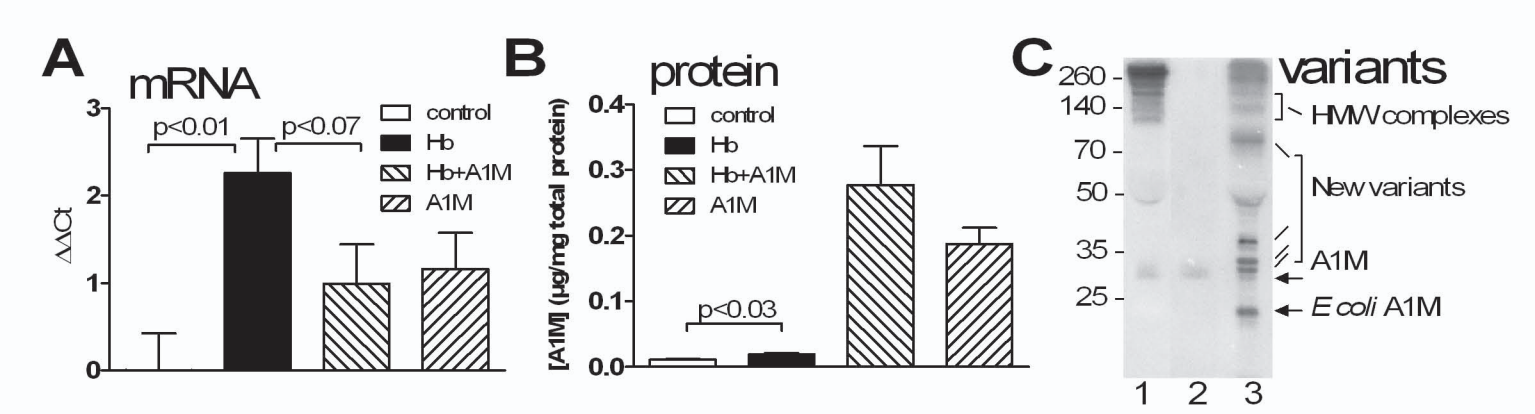
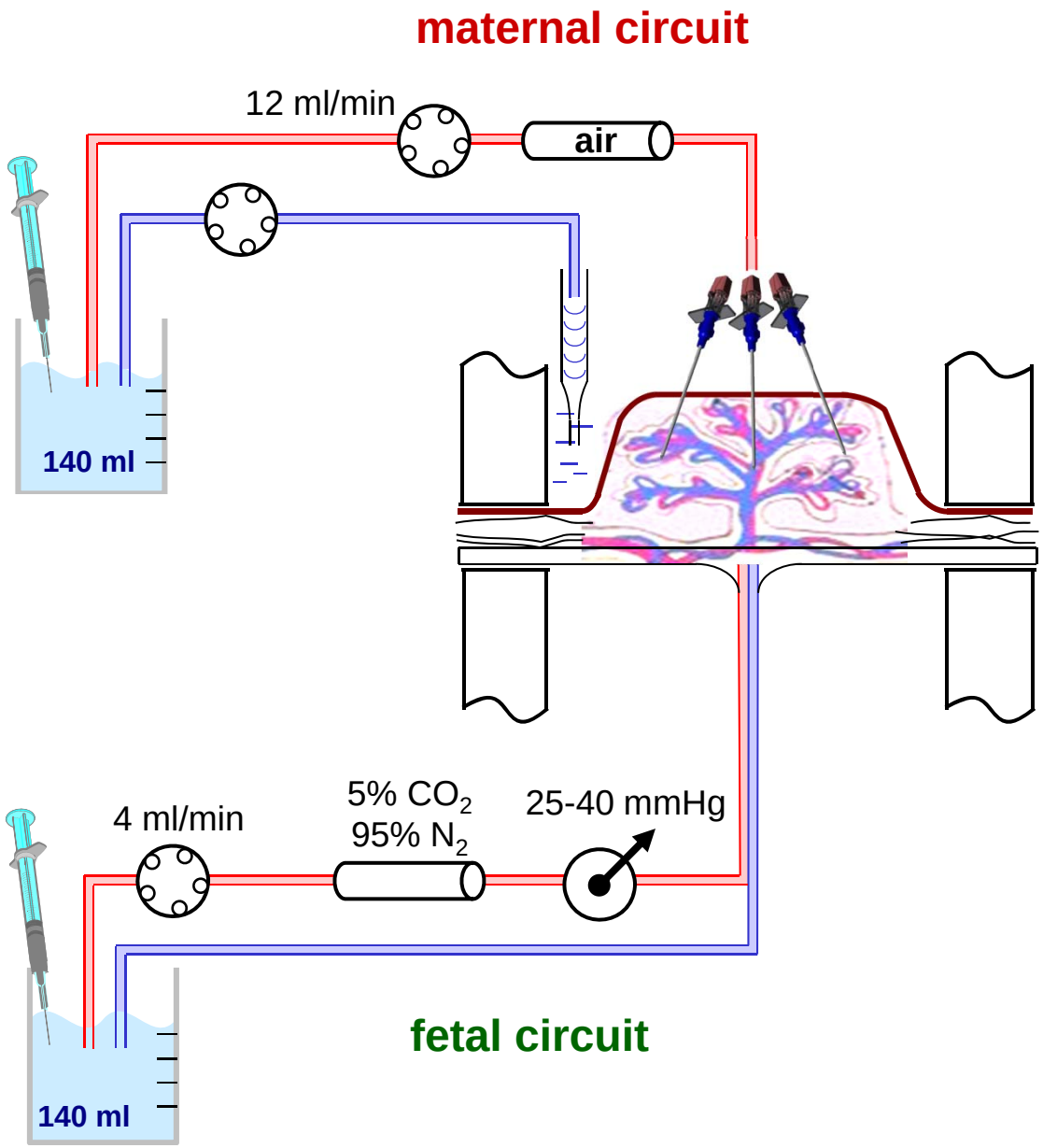
B
C


A
B
C
D


A
mRNA
ΔΔCt
3
2
1
0
p<0.01
p<0.07
control
Hb
Hb+A1M
A1M
B
protein
[A1M] (µg/mg total protein)
0.4
0.3
0.2
0.1
0.0
p<0.03
control
Hb
Hb+A1M
A1M
C
260
140
70
50
35
25
variants
HMW complexes
New variants
A1M
E coli A1M
1
2
3


maternal circuit
12 ml/min
air
140 ml
4 ml/min
5% CO_2
95% N_2
25-40 mmHg
140 ml
fetal circuit

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Supplementary table 1. Genes with altered gene expression in the group comparisons. The p-value and fold change (within parenthesis) are presented. The fold change is always relative to the second group in the comparison, where a negative value represents decreased gene expression.

Gene symbol	Gene Name	Medium ↔ Hb	Hb ↔ Hb+A1M	A1M ↔ Hb+A1M
ABCF1	ATP-BINDING CASSETTE, SUB-FAMILY F (GCN20), MEMBER 1		0.0027 (-1.6)	
ACADM	ACYL-COENZYME A DEHYDROGENASE, C-4 TO C-12 STRAIGHT CHAIN	0.010 (1.6)		
ACLY	ATP CITRATE LYASE			0.0070 (-1.2)
ACOT11	ACYL-COA THIOESTERASE 11		0.0021 (-6.1)	
ACOT2	ACYL-COA THIOESTERASE 2	0.0047 (1.9)	0.0047 (-1.8)	
ACSL5	ACYL-COA SYNTHETASE LONG-CHAIN FAMILY MEMBER 5		0.0036 (-1.9)	
ACTG1	ACTIN, BETA	0.0096 (1.5)		
ADORA1	N/A	0.0026 (2.1)		
ADPRHL2	ADP-RIBOSYLHYDROLASE LIKE 2	0.014 (2.2)		
AFMID	ARYLFORMAMIDASE	0.0083 (2.4)		
AHNAK	AHNAK NUCLEOPROTEIN (DESMOYOKIN)		0.0035 (-3.1)	
ALG14	ASPARAGINE-LINKED GLYCOSYLATION 14 HOMOLOG (YEAST)		0.00032 (-1.7)	
AMY1B	"AMYLASE, ALPHA 1A; SALIVARY"	0.011 (2.2)		
ANKMY2	ANKYRIN REPEAT AND MYND DOMAIN CONTAINING 2			0.039 (1.4)
ANKRD16	ANKYRIN REPEAT DOMAIN 16			0.025 (1.9)
ANXA8	ANNEXIN A8			0.014 (-2.5)
APP	AMYLOID BETA (A4) PRECURSOR PROTEIN (PEPTIDASE NEXIN-II, ALZHEIMER DISEASE)			0.041 (-1.6)
ARF1	ADP-RIBOSYLATION FACTOR 1			0.036 (-1.2)
ARF4	ADP-RIBOSYLATION FACTOR 4		0.0029 (-1.7)	0.037 (-1.7)
ARF4	ADP-RIBOSYLATION FACTOR 4		0.00014 (-1.6)	0.040 (-1.5)
ARID4B	AT RICH INTERACTIVE DOMAIN 4B (RBP1- LIKE)		0.002 (-1.9)	
ARL4A	ADP-RIBOSYLATION FACTOR-LIKE 4A		0.0013 (-2.2)	

ARL4A	ADP-RIBOSYLATION FACTOR-LIKE 4A	0.012 (1.9)		
ARMET	ARGININE-RICH, MUTATED IN EARLY STAGE TUMORS	0.0041 (1.6)	0.0014 (-1.7)	
ARPC1B	ACTIN RELATED PROTEIN 2/3 COMPLEX, SUBUNIT 1B, 41KDA	0.0029 (2.3)		
ARSD	ARYLSULFATASE D			0.040 (-1.4)
ATE1	ARGINYLTRANSFERASE 1		0.000099 (-4.5)	
ATF1	ACTIVATING TRANSCRIPTION FACTOR 1			0.034 (-1.5)
ATF3	ACTIVATING TRANSCRIPTION FACTOR 3		0.0012 (-1.7)	
ATG10	HYPOTHETICAL PROTEIN FLJ13954		0.0031 (-1.8)	
ATG4A	ATG4 AUTOPHAGY RELATED 4 HOMOLOG A (S. CEREVISIAE)	0.0096 (1.8)		
ATP5F1	ATP SYNTHASE, H+ TRANSPORTING, MITOCHONDRIAL F0 COMPLEX, SUBUNIT B1	0.012 (1.4)		
ATP5L	ATP SYNTHASE, H+ TRANSPORTING, MITOCHONDRIAL F0 COMPLEX, SUBUNIT G	0.0088 (1.4)		
ATP6V0B	ATPASE, H+ TRANSPORTING, LYSOSOMAL 21KDA, V0 SUBUNIT B		0.0012 (-1.5)	
AXIIR	SIMILAR TO ANNEXIN II RECEPTOR	0.0043 (2.1)		
AXIN2	AXIN 2 (CONDUCTIN, AXIL)	0.015 (2.6)		
AYP1p1	N/A	0.012 (1.6)		
AZI1	5-AZACYTIDINE INDUCED 1			0.021 (1.6)
B3GALNT2	UDP-GALNAC:BETAGLCNAC BETA 1,3-GALACTOSAMINYLTRANSFERASE, POLYPEPTIDE 2			0.048 (-1.6)
B3GNT2	UDP-GLCNAC:BETAGAL BETA-1,3-N-ACETYLGLUCOSAMINYLTRANSFERASE 1	0.013 (1.7)		
BAG4	SILENCER OF DEATH DOMAINS	0.0083 (2.3)		
BMP7	BONE MORPHOGENETIC PROTEIN 7 (OSTEOGENIC PROTEIN 1)			0.024 (1.3)
BNIP1	BCL2/ADENOVIRUS E1B 19KDA INTERACTING PROTEIN 1		0.0016 (-2.5)	
BNIP1	BCL2/ADENOVIRUS E1B 19KDA INTERACTING PROTEIN 1		0.00053 (-2.4)	
BOLA2	BOLA-LIKE 2 (E. COLI)	0.0068 (1.8)		
BTBD16	CHROMOSOME 10 OPEN READING		0.0032	

	FRAME 87		(-6.5)	
BTBD3	BTB (POZ) DOMAIN CONTAINING 3			0.018 (1.5)
C10orf32	ARSENIC (+3 OXIDATION STATE) METHYLTRANSFERASE		0.00027 (-1.5)	
C11orf10	CHROMOSOME 11 OPEN READING FRAME 10		0.001 (-1.5)	
C12orf43	CHROMOSOME 12 OPEN READING FRAME 43		0.0018 (-1.7)	0.034 (-1.5)
C13orf7	CHROMOSOME 13 OPEN READING FRAME 7		0.0022 (-1.6)	
C14orf122	CHROMOSOME 14 OPEN READING FRAME 122	0.0061 (1.8)		
C14orf151	CHROMOSOME 14 OPEN READING FRAME 151		0.0023 (-11.2)	
C15orf24	CHROMOSOME 15 OPEN READING FRAME 24		0.00023 (-1.6)	
C15orf44	CHROMOSOME 15 OPEN READING FRAME 44		0.0000078 (-1.7)	
C17orf81	CHROMOSOME 17 OPEN READING FRAME 81	0.0051 (2)		
C19orf10	CHROMOSOME 19 OPEN READING FRAME 10	0.0041 (1.5)		
C19orf58	DDA1			0.016 (-1.2)
C1GALT1	CORE 1 SYNTHASE, GLYCOPROTEIN-N-ACETYLGALACTOSAMINE 3-BETA-GALACTOSYLTRANSFERASE, 1		0.0048 (-1.5)	0.011 (-1.5)
C1orf198	CHROMOSOME 1 OPEN READING FRAME 198			0.0061 (1.7)
C1orf77	CHROMOSOME 1 OPEN READING FRAME 77		0.00019 (-1.5)	
C1QB	COMPLEMENT COMPONENT 1, Q SUBCOMPONENT, B CHAIN			0.031 (1.6)
C2	COMPLEMENT COMPONENT 2			0.031 (1.5)
C2orf4	CHROMOSOME 2 OPEN READING FRAME 4	0.0044 (2)		
C3AR1	COMPLEMENT COMPONENT 3A RECEPTOR 1			0.023 (3.3)
C3orf38	CHROMOSOME 3 OPEN READING FRAME 38	0.0037 (1.6)		
C4orf14	CHROMOSOME 4 OPEN READING FRAME 14	0.0092 (1.5)		
C6orf106	CHROMOSOME 6 OPEN READING FRAME 106		0.0011 (-4.4)	
C6orf166	CHROMOSOME 6 OPEN READING FRAME 166		0.0029 (-1.6)	
C6orf48	CHROMOSOME 6 OPEN READING FRAME 48	0.0055 (1.4)		
C6orf48	CHROMOSOME 6 OPEN READING	0.002		

	FRAME 48	(1.6)		
C7orf28B	DKFZP586I1023 PROTEIN			0.033 (-3.2)
C9orf58	CHROMOSOME 9 OPEN READING FRAME 58			0.035 (2.9)
C9orf6	CHROMOSOME 9 OPEN READING FRAME 6	0.0081 (1.7)		
C9orf72	HYPOTHETICAL PROTEIN FLJ11109			0.037 (-1.9)
CACYBP	CALCYCLIN BINDING PROTEIN	0.0077 (1.9)		
CASC2	CANCER SUSCEPTIBILITY CANDIDATE 2			0.046 (2.1)
CASK	CALCIUM/CALMODULIN-DEPENDENT SERINE PROTEIN KINASE (MAGUK FAMILY)			0.042 (3.5)
CAV1	CAVEOLIN 1, CAVEOLAE PROTEIN, 22KDA	0.0033 (2)		
CAV2	CAVEOLIN 2	0.0033 (2.1)		
CBR1	CARBONYL REDUCTASE 1	0.0054 (1.6)		
CBX3	CHROMOBOX HOMOLOG 3 (HP1 GAMMA HOMOLOG, DROSOPHILA)	0.0081 (1.8)		
CCBL2	KYNURENINE AMINOTRANSFERASE III		0.0034 (-1.7)	0.047 (-1.6)
CCDC101	HYPOTHETICAL PROTEIN BC011981		0.0025 (-1.7)	
CCDC104	SIMILAR TO RIKEN CDNA 4931428D14 GENE		0.0043 (-2)	
CCDC23	COILED-COIL DOMAIN CONTAINING 23		0.0021 (-1.6)	
CCNB1IP1	CYCLIN B1 INTERACTING PROTEIN 1	0.012 (1.5)		
CDC42EP1	CDC42 EFFECTOR PROTEIN (RHO GTPASE BINDING) 1			0.020 (-1.4)
CDCA8	CELL DIVISION CYCLE ASSOCIATED 8	0.013 (2)		
CDH1	CADHERIN 1, TYPE 1, E-CADHERIN (EPITHELIAL)			0.0081 (-1.3)
CDK5R1	CYCLIN-DEPENDENT KINASE 5, REGULATORY SUBUNIT 1 (P35)		0.0019 (-8.3)	
CDKN2D	CYCLIN-DEPENDENT KINASE INHIBITOR 2D (P19, INHIBITS CDK4)		0.0023 (-3)	
CGGBP1	CGG TRIPLET REPEAT BINDING PROTEIN 1			0.036 (-1.2)
CKS2	CDC28 PROTEIN KINASE REGULATORY SUBUNIT 2			0.045 (-2.2)
CLK3	CDC-LIKE KINASE 3		0.00057 (-1.7)	
CLK3	CDC-LIKE KINASE 3		0.00096	

			(-1.6)	
CLPP	CLPP CASEINOLYTIC PEPTIDASE, ATP-DEPENDENT, PROTEOLYTIC SUBUNIT HOMOLOG (E. COLI)			0.034 (1.4)
CMAS	CYTIDINE MONOPHOSPHATE N-ACETYLNEURAMINIC ACID SYNTHETASE			0.035 (-1.5)
CNIH	CORNICHON HOMOLOG (DROSOPHILA)	0.0057 (1.5)		
COL6A2	COLLAGEN, TYPE VI, ALPHA 2		0.011 (1.7)	0.024 (2)
COL6A3	COLLAGEN, TYPE VI, ALPHA 3		0.00026 (1.7)	
COL8A2	COLLAGEN, TYPE VIII, ALPHA 2		0.011 (2.2)	0.033 (1.4)
COMMD5	COMM DOMAIN CONTAINING 5	0.014 (1.5)		
COQ2	COENZYME Q2 HOMOLOG, PRENYLTRANSFERASE (YEAST)	0.015 (1.5)		
COX6C	CYTOCHROME C OXIDASE SUBUNIT VIC			0.046 (-1.2)
CPM	CARBOXYPEPTIDASE M	0.012 (2)	0.008 (-1.7)	
CREG1	CELLULAR REPRESSOR OF E1A-STIMULATED GENES 1			0.027 (-1.3)
CSHL1	CHORIONIC SOMATOMAMMOTROPIN HORMONE-LIKE 1		0.0016 (-1.7)	
CSNK2A1P	CASEIN KINASE 2, ALPHA 1 POLYPEPTIDE PSEUDOGENE		0.00022 (-1.5)	
CST6	CYSTATIN E/M			0.0034 (-4)
CSTB	CYSTATIN B (STEFIN B)		0.002 (-1.7)	
CTPS	CTP SYNTHASE	0.0014 (2.1)		
CXorf38	CHROMOSOME X OPEN READING FRAME 38		0.0003 (-1.8)	
CXorf39	CHROMOSOME X OPEN READING FRAME 39	0.010 (1.6)		
CYP2J2	CYTOCHROME P450, FAMILY 2, SUBFAMILY J, POLYPEPTIDE 2	0.013 (1.5)		
DAAM1	DISHEVELLED ASSOCIATED ACTIVATOR OF MORPHOGENESIS 1		0.0047 (-1.8)	
DAXX	DEATH-ASSOCIATED PROTEIN 6		0.0045 (-1.6)	
DBT	DIHYDROLIPOAMIDE BRANCHED CHAIN TRANSACYLASE E2	0.011 (1.8)		
DCTN3	DYNACTIN 3 (P22)			0.024 (-1.2)
DDR1	DISCOIDIN DOMAIN RECEPTOR FAMILY, MEMBER 1			0.050 (-1.3)

DDX52	DEAD (ASP-GLU-ALA-ASP) BOX POLYPEPTIDE 52	0.0036 (1.5)		
DEDD2	DEATH EFFECTOR DOMAIN CONTAINING 2	0.0076 (1.5)		
DERL1	DER1-LIKE DOMAIN FAMILY, MEMBER 1		0.0023 (-1.6)	
DHX9	DEAH (ASP-GLU-ALA-HIS) BOX POLYPEPTIDE 9		0.00042 (-1.6)	
DIMT1L	N/A	0.0098 (1.7)		
DIP2A	DIP2 DISCO-INTERACTING PROTEIN 2 HOMOLOG A (DROSOPHILA)			0.035 (-1.3)
DKFZp434K1815	HYPOTHETICAL PROTEIN DKFZP434K1815		0.00017 (-1.8)	
DNAJA1	DNAJ (HSP40) HOMOLOG, SUBFAMILY A, MEMBER 1	0.010 (1.7)		
DNAJA5	DNAJ HOMOLOGY SUBFAMILY A MEMBER 5		0.000053 (-7)	0.026 (-6.1)
DNAJB9	DNAJ (HSP40) HOMOLOG, SUBFAMILY B, MEMBER 9		0.000037 (-1.7)	
DPM2	DOLICHYL-PHOSPHATE MANNOSYLTRANSFERASE POLYPEPTIDE 2, REGULATORY SUBUNIT		0.0002 (-3)	
DPP7	DIPEPTIDYL-PEPTIDASE 7			0.030 (2.7)
DSCAM	DOWN SYNDROME CELL ADHESION MOLECULE		0.00077 (-2.1)	
DSCR10	DOWN SYNDROME CRITICAL REGION GENE 10			0.00066 (1.6)
DSCR2	DOWN SYNDROME CRITICAL REGION GENE 2	0.0099 (1.4)		
DVL1	DISHEVELLED, DSH HOMOLOG 1 (DROSOPHILA)			0.044 (-3.5)
DYNLT1	DYNEIN, LIGHT CHAIN, TCTEX-TYPE 1	0.014 (1.5)		
E2F6	E2F TRANSCRIPTION FACTOR 6		0.0012 (-2)	
EBP	EMOPAMIL BINDING PROTEIN (STEROL ISOMERASE)	0.0034 (1.6)		
EEA1	EARLY ENDOSOME ANTIGEN 1, 162KD		0.00066 (-1.8)	
EFNA4	EPHRIN-A4		0.00018 (-1.7)	
EIF2A	EUKARYOTIC TRANSLATION INITIATION FACTOR 2A, 65KDA		0.0027 (-1.6)	
EIF2S2	EUKARYOTIC TRANSLATION INITIATION FACTOR 2, SUBUNIT 2 BETA, 38KDA		0.00071 (-2)	
ELAVL1	ELAV (EMBRYONIC LETHAL, ABNORMAL VISION, DROSOPHILA)-		0.00072 (-10.5)	

	LIKE 1 (HU ANTIGEN R)			
ELF2	E74-LIKE FACTOR 2 (ETS DOMAIN TRANSCRIPTION FACTOR)		0.0017 (-5.1)	
ELF2	E74-LIKE FACTOR 2 (ETS DOMAIN TRANSCRIPTION FACTOR)		0.0018 (-2.1)	
ETFA	ELECTRON-TRANSFER-FLAVOPROTEIN, ALPHA POLYPEPTIDE (GLUTARIC ACIDURIA II)	0.0085 (1.6)		
ETNK1	ETHANOLAMINE KINASE 1			0.040 (-1.6)
EXOC1	EXOCYST COMPLEX COMPONENT 1		0.0000042 (-8.2)	
F2R	COAGULATION FACTOR II (THROMBIN) RECEPTOR		0.0006 (-1.6)	
FAM136A	HYPOTHETICAL PROTEIN FLJ14668	0.013 (1.6)		
FAM18B2	FAMILY WITH SEQUENCE SIMILARITY 18, MEMBER B2		0.00073 (-2.4)	
FAM20C	FAMILY WITH SEQUENCE SIMILARITY 20, MEMBER C			0.0086 (1.7)
FAM36A	FAMILY WITH SEQUENCE SIMILARITY 36, MEMBER A			0.014 (-1.3)
FAM3C	FAMILY WITH SEQUENCE SIMILARITY 3, MEMBER C			0.040 (-1.7)
FAM83B	CHROMOSOME 6 OPEN READING FRAME 143		0.0031 (-3)	0.019 (-2.8)
FBLN1	FIBULIN 1		0.0033 (-1.8)	0.021 (-2)
FBXO5	F-BOX PROTEIN 5	0.012 (1.6)		
FCGR1A	FC FRAGMENT OF IGG, HIGH AFFINITY IA, RECEPTOR (CD64)	0.0057 (2.8)		
FCGR1B	FC FRAGMENT OF IGG, HIGH AFFINITY IB, RECEPTOR (CD64)	0.0074 (2)		
FCGR1B	FC FRAGMENT OF IGG, HIGH AFFINITY IB, RECEPTOR (CD64)	0.0073 (2.5)		
FGFR3	FIBROBLAST GROWTH FACTOR RECEPTOR 3 (ACHONDROPLASIA, THANATOPHORIC DWARFISM)			0.038 (1.9)
FKBP1A	FK506 BINDING PROTEIN 1A, 12KDA		0.0035 (-2)	
FLJ10769	HYPOTHETICAL PROTEIN LOC51254		0.002 (-1.8)	
FLJ12078	HYPOTHETICAL PROTEIN FLJ12078		0.0024 (-3.8)	0.045 (-3.2)
FLJ12716	FLJ12716 PROTEIN		0.00047 (1.8)	
FLJ20035	HYPOTHETICAL PROTEIN FLJ10787		0.0047 (-2.6)	
FLJ22222	HYPOTHETICAL PROTEIN FLJ22222		0.0043 (-2)	

FLJ33790	HYPOTHETICAL PROTEIN FLJ33790		0.0038 (-2.8)	
FLJ43663	HYPOTHETICAL PROTEIN FLJ43663		0.0022 (-1.6)	
FLJ46838	FLJ46838 PROTEIN			0.023 (-1.5)
FLJ90709	HYPOTHETICAL PROTEIN FLJ90709	0.012 (1.5)		
FTL	FERRITIN, LIGHT POLYPEPTIDE		0.00065 (-1.6)	
FTSJ3	HYPOTHETICAL PROTEIN FLJ20062			0.029 (-2.5)
GABARAPL2	GABA(A) RECEPTOR-ASSOCIATED PROTEIN-LIKE 2		0.00024 (1.9)	
GAST	GASTRIN		0.0032 (-2.3)	
GCA	GRANCALCIN, EF-HAND CALCIUM BINDING PROTEIN	0.0051 (1.6)		
GDAP2	GANGLIOSIDE INDUCED DIFFERENTIATION ASSOCIATED PROTEIN 2		0.00016 (-3.7)	
GDF15	GROWTH DIFFERENTIATION FACTOR 15		0.000022 (-1.6)	0.023 (-1.3)
GFM2	G ELONGATION FACTOR, MITOCHONDRIAL 2		0.00046 (-3)	
GJA5	GAP JUNCTION PROTEIN, ALPHA 5, 40KDA (CONNEXIN 40)	0.010 (2)	0.015 (-1.9)	
GLMN	GLOMULIN, FKBP ASSOCIATED PROTEIN		0.0039 (-1.5)	
GLYCTK	CG9886-LIKE		0.0016 (-2.1)	
GPBP1	GC-RICH PROMOTER BINDING PROTEIN 1		0.0021 (-1.7)	
GPBP1L1	GC-RICH PROMOTER BINDING PROTEIN 1-LIKE 1		0.00016 (-1.7)	
GPC6	GLYPICAN 6		0.00024 (-2.6)	
GPR37	G PROTEIN-COUPLED RECEPTOR 37 (ENDOTHELIN RECEPTOR TYPE B-LIKE)		0.0029 (-2.6)	
GPR89C	G PROTEIN-COUPLED RECEPTOR 89A	0.0061 (1.7)		
GRHL1	GRAINYHEAD-LIKE 1 (DROSOPHILA)		0.0023 (-2.2)	
GTF2I	GENERAL TRANSCRIPTION FACTOR II, I	0.0052 (1.4)		
GTF2IRD1	GTF2I REPEAT DOMAIN CONTAINING 1			0.042 (2.7)
GTF2IRD2	GTF2I REPEAT DOMAIN CONTAINING 2		0.0014 (-2.3)	
H19	H19, IMPRINTED MATERNALLY EXPRESSED UNTRANSLATED MRNA			0.020 (-1.2)

HACL1	PHYTANOYL-COA 2-HYDROXYLASE 2		0.000043 (-1.5)	
HAVCR2	HEPATITIS A VIRUS CELLULAR RECEPTOR 2	0.015 (1.7)		
HAX1	HCLS1 ASSOCIATED PROTEIN X-1	0.0063 (1.7)		
HEATR2	HYPOTHETICAL PROTEIN FLJ20397	0.010 (2.1)		
HEATR3	HYPOTHETICAL PROTEIN FLJ20718			0.024 (-3.1)
HELLS	HELICASE, LYMPHOID-SPECIFIC			0.018 (-1.6)
HERPUD1	HOMOCYSTEINE-INDUCIBLE, ENDOPLASMIC RETICULUM STRESS-INDUCIBLE, UBIQUITIN-LIKE DOMAIN MEMBER 1	0.015 (1.4)	0.0011 (-1.9)	
HIGD1A	HIG1 DOMAIN FAMILY, MEMBER 1A			0.027 (-1.5)
HIGD1A	HIG1 DOMAIN FAMILY, MEMBER 1A		0.00059 (-1.6)	
HIST1H3A	HISTONE 1, H3A			0.024 (-3.4)
HIST1H4K	H4 HISTONE, FAMILY 2	0.010 (2.5)		
HIST2H2AA3	HISTONE 2, H2AA		0.0023 (-1.6)	
HIST2H2AC	HISTONE 2, H2AC		0.00063 (-1.7)	
HNRPK	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN K		0.0016 (-1.6)	
HPS5	HERMANSKY-PUDLAK SYNDROME 5	0.014 (1.6)		
HSCB	J-TYPE CO-CHAPERONE HSC20	0.014 (1.6)		
HSP90AA1	HEAT SHOCK PROTEIN 90KDA ALPHA (CYTOSOLIC), CLASS A MEMBER 1	0.0097 (1.6)	0.00051 (-2.1)	
HSP90B1	HEAT SHOCK PROTEIN 90KDA BETA (GRP94), MEMBER 1		0.0017 (-1.5)	
HSPC171	HSPC171 PROTEIN			0.041 (-1.2)
HSPE1	HEAT SHOCK 10KDA PROTEIN 1 (CHAPERONIN 10)	0.013 (1.6)		
HSPH1	HEAT SHOCK 105KDA/110KDA PROTEIN 1	0.0069 (2.6)		
HSZFP36	ZFP-36 FOR A ZINC FINGER PROTEIN		0.00038 (-1.9)	
HTRA2	HTRA SERINE PEPTIDASE 2	0.0083 (1.8)		
ICA1	ISLET CELL AUTOANTIGEN 1, 69KDA			0.019 (-1.7)
ICAM3	INTERCELLULAR ADHESION	0.0074		

	MOLECULE 3	(2.3)		
IFITM2	INTERFERON INDUCED TRANSMEMBRANE PROTEIN 2 (1-8D)	0.0063 (1.6)		
IFITM3	INTERFERON INDUCED TRANSMEMBRANE PROTEIN 3 (1-8U)	0.0088 (1.6)		
IFNGR1	INTERFERON GAMMA RECEPTOR 1		0.004 (-1.6)	
IFRG15	INTERFERON RESPONSIVE GENE 15		0.0024 (-1.6)	
IIP45	INVASION INHIBITORY PROTEIN 45		0.0019 (-1.7)	
INPP5F	N/A	0.0039 (2.8)		
IRF6	INTERFERON REGULATORY FACTOR 6	0.0035 (2.4)		
ITIH5	INTER-ALPHA (GLOBULIN) INHIBITOR H5		0.003 (-1.6)	
ITM2B	INTEGRAL MEMBRANE PROTEIN 2B			0.026 (-1.4)
ITM2C	INTEGRAL MEMBRANE PROTEIN 2C	0.0073 (2.1)	0.014 (-1.7)	
KCNMB4	POTASSIUM LARGE CONDUCTANCE CALCIUM-ACTIVATED CHANNEL, SUBFAMILY M, BETA MEMBER 4			0.039 (3.3)
KHDRBS3	KH DOMAIN CONTAINING, RNA BINDING, SIGNAL TRANSDUCTION ASSOCIATED 3			0.028 (-2.9)
KIAA0427	KIAA0427			0.0085 (2.7)
KIAA1276	KIAA1276 PROTEIN			0.036 (-7)
KREMEN1	KRINGLE CONTAINING TRANSMEMBRANE PROTEIN 1	0.0039 (1.4)		
KRT19	KERATIN 19		0.0016 (-1.7)	
KRT27	KERATIN 25C			0.020 (-2.3)
KRT86	KERATIN, HAIR, BASIC, 1			0.019 (2)
KRTCAP2	KERATINOCYTE ASSOCIATED PROTEIN 2		0.00031 (-1.5)	
Kua-UEV	UBIQUITIN-CONJUGATING ENZYME E2 VARIANT 1		0.0022 (-2)	
KYNU	KYNURENINASE (L-KYNURENINE HYDROLASE)		0.000038 (-2)	0.013 (-1.7)
LACTB	HYPOTHETICAL PROTEIN FLJ14902		0.0038 (-3.1)	
LAMA4	LAMININ, ALPHA 4		0.0016 (1.9)	
LATS1	LATS, LARGE TUMOR SUPPRESSOR, HOMOLOG 1 (DROSOPHILA)			0.050 (-3.6)

LIAS	LIPOIC ACID SYNTHETASE	0.0099 (1.9)		
LOC153222	ADULT RETINA PROTEIN		0.0034 (-2.4)	
LOC162073	HYPOTHETICAL PROTEIN LOC162073		0.0046 (-1.9)	
LOC220686	HYPOTHETICAL PROTEIN LOC220686		0.0013 (-1.6)	
LOC341457	SIMILAR TO PEPTIDYLPROLYL ISOMERASE A ISOFORM 1	0.013 (1.5)		
LOC347544	SIMILAR TO RIBOSOMAL PROTEIN L18A	0.012 (1.6)		
LOC387820	SIMILAR TO DNAJ (HSP40) HOMOLOG, SUBFAMILY B, MEMBER 6 ISOFORM A		0.0048 (-1.6)	
LOC387841	SIMILAR TO RIBOSOMAL PROTEIN L13A			0.011 (-1.2)
LOC387921	HYPOTHETICAL PROTEIN LOC283506		0.00041 (-2.7)	
LOC388654	SIMILAR TO LAMININ RECEPTOR 1 (RIBOSOMAL PROTEIN SA)	0.0018 (1.5)		
LOC388948	HYPOTHETICAL GENE SUPPORTED BY BC062774		0.0041 (-2)	
LOC389286	SIMILAR TO FKSG62		0.0014 (-2.4)	
LOC389517	*no*			0.049 (-6.9)
LOC389517	N/A			0.043 (-5.5)
LOC390354	N/A	0.0041 (1.6)		
LOC402694	SIMILAR TO RIBOSOMAL PROTEIN L15	0.0093 (1.4)		
LOC441050	SIMILAR TO UNACTIVE PROGESTERONE RECEPTOR, 23 KD	0.004 (1.9)		
LOC442454	UBIQUINOL-CYTOCHROME C REDUCTASE BINDING PROTEIN PSEUDOGENE			0.038 (-1.2)
LOC51136	PTD016 PROTEIN	0.011 (1.9)		
LOC642033	SIMILAR TO ATP-BINDING CASSETTE, SUB-FAMILY F, MEMBER 1 ISOFORM B		0.0016 (-2.2)	
LOC642236	SIMILAR TO FRG1 PROTEIN (FSHD REGION GENE 1 PROTEIN)	0.014 (2.3)		
LOC642299	HYPOTHETICAL PROTEIN LOC642299			0.031 (-1.3)
LOC642299	HYPOTHETICAL PROTEIN LOC642299		0.0022 (-1.6)	
LOC642393	SIMILAR TO MITOCHONDRIAL RIBOSOMAL PROTEIN L20			0.0035 (-3)
LOC643035	SIMILAR TO CG33096-PB, ISOFORM B		0.00028 (1.8)	

LOC643433	SIMILAR TO 60S RIBOSOMAL PROTEIN L29 (CELL SURFACE HEPARIN BINDING PROTEIN HIP)	0.006 (1.5)		
LOC644033	SIMILAR TO SIMILAR TO RPL23AP7 PROTEIN	0.0071 (1.5)		
LOC644584	SIMILAR TO RNA-BINDING PROTEIN EWS		0.00002 (-2.9)	
LOC644634	HYPOTHETICAL PROTEIN LOC644634		0.0017 (1.7)	
LOC645261	HYPOTHETICAL PROTEIN LOC645261		0.0041 (-2.1)	
LOC647108	HYPOTHETICAL PROTEIN LOC647108	0.010 (2.2)		
LOC647197	HYPOTHETICAL PROTEIN LOC647197		0.0036 (-2.7)	
LOC647784	HYPOTHETICAL PROTEIN LOC647784			0.010 (4.4)
LOC649049	SIMILAR TO ACIDIC RIBOSOMAL PHOSPHOPROTEIN P0	0.0082 (1.5)		
LOC649150	SIMILAR TO EUKARYOTIC TRANSLATION ELONGATION FACTOR 1 ALPHA 2		0.00000031 (-1.5)	
LOC649447	SIMILAR TO 60S RIBOSOMAL PROTEIN L29 (CELL SURFACE HEPARIN BINDING PROTEIN HIP)	0.012 (1.5)		
LOC649555	SIMILAR TO EUKARYOTIC TRANSLATION INITIATION FACTOR 4E	0.0071 (1.6)		
LOC651429	HYPOTHETICAL PROTEIN LOC651429		0.0041 (-2.5)	
LOC651576	SIMILAR TO TUBULIN, ALPHA 8 LIKE		0.0014 (-8.1)	0.029 (-5)
LOC652844	SIMILAR TO PHOSPHODIESTERASE 4D INTERACTING PROTEIN ISOFORM 2		0.0045 (-2.9)	
LOC652846	SIMILAR TO ANNEXIN A8 (ANNEXIN VIII) (VASCULAR ANTICOAGULANT-BETA) (VAC-BETA)			0.049 (-2.1)
LOC652864	SIMILAR TO MITOCHONDRIAL IMPORT INNER MEMBRANE TRANSLOCASE SUBUNIT TIM23	0.014 (1.6)		
LOC653232	SIMILAR TO RIBOSOMAL PROTEIN L15	0.0088 (1.5)		
LOC653489	SIMILAR TO RAN-BINDING PROTEIN 2 (RANBP2) (NUCLEAR PORE COMPLEX PROTEIN NUP358) (NUCLEOPORIN NUP358) (358 KDA NUCLEOPORIN) (P270)		0.0011 (-8)	
LOC653505	SIMILAR TO PEPTIDYLPROLYL ISOMERASE A (CYCLOPHILIN A)-LIKE 4	0.0068 (1.7)		
LOC653566	SIMILAR TO SIGNAL PEPTIDASE COMPLEX SUBUNIT 2 (MICROSOMAL SIGNAL PEPTIDASE 25 KDA SUBUNIT)		0.0000074 (-1.5)	0.040 (-1.3)

	(SPASE 25 KDA SUBUNIT)			
LOC653629	SIMILAR TO WILLIAMS BEUREN SYNDROME CHROMOSOME REGION 19			0.030 (-5.1)
LOC654074	SIMILAR TO HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN C ISOFORM B		0.004 (1.7)	
LOC654174	SIMILAR TO CG4775-PA		0.00014 (-3.1)	
LOC728492	SMALL EDRK-RICH FACTOR 1A (TELOMERIC)	0.007 (1.6)	0.0019 (-2.2)	
LOC728739	N/A	0.014 (1.4)		
LOC730256	*no*		0.0039 (-1.9)	
LOC84661	DPY-30-LIKE PROTEIN	0.011 (1.5)		
LRP1	LOW DENSITY LIPOPROTEIN-RELATED PROTEIN 1 (ALPHA-2-MACROGLOBULIN RECEPTOR)			0.029 (3.2)
LRRN3	LEUCINE RICH REPEAT NEURONAL 3		0.0016 (-3.1)	
LSM1	LSM1 HOMOLOG, U6 SMALL NUCLEAR RNA ASSOCIATED (S. CEREVISIAE)	0.0052 (1.5)		
MAD2L2	MAD2 MITOTIC ARREST DEFICIENT-LIKE 2 (YEAST)			0.036 (-1.6)
MAGEL2	MAGE-LIKE 2	0.013 (2.2)		
MALL	MAL, T-CELL DIFFERENTIATION PROTEIN-LIKE			0.015 (-2.3)
MAP7D3	HYPOTHETICAL PROTEIN FLJ12649	0.0099 (-1.8)		
MAPK1	MITOGEN-ACTIVATED PROTEIN KINASE 1	0.0058 (1.8)		
MAPRE3	MICROTUBULE-ASSOCIATED PROTEIN, RP/EB FAMILY, MEMBER 3	0.013 (-1.5)		
MAX	MYC ASSOCIATED FACTOR X			0.038 (12.6)
MBD2	METHYL-CPG BINDING DOMAIN PROTEIN 2		0.0043 (-1.9)	
MBTD1	MBT DOMAIN CONTAINING 1			0.021 (1.4)
MCART1	MITOCHONDRIAL CARRIER TRIPLE REPEAT 1		0.0013 (-5.9)	
MDM2	MDM2, TRANSFORMED 3T3 CELL DOUBLE MINUTE 2, P53 BINDING PROTEIN (MOUSE)		0.0038 (-7.6)	
ME2	MALIC ENZYME 2, NAD(+)-DEPENDENT, MITOCHONDRIAL	0.0079 (1.6)		
MELK	MATERNAL EMBRYONIC LEUCINE ZIPPER KINASE	0.0088 (1.6)		

METTL9	DORA REVERSE STRAND PROTEIN 1		0.0017 (-1.8)	0.039 (-1.8)
MGC3731	HYPOTHETICAL PROTEIN MGC3731	0.005 (1.7)		
MGC7036	HYPOTHETICAL PROTEIN MGC7036			0.050 (-1.2)
MGC72104	SIMILAR TO FRG1 PROTEIN (FSHD REGION GENE 1 PROTEIN)	0.010 (1.9)		
MIB2	MINDBOMB HOMOLOG 2 (DROSOPHILA)		0.00012 (-1.7)	0.041 (-1.5)
MLLT11	"MYELOID/LYMPHOID OR MIXED-LINEAGE LEUKEMIA (TRITHORAX HOMOLOG, DROSOPHILA); TRANSLOCATED TO, 11"			0.030 (-1.5)
MOBKL2C	MOB1, MPS ONE BINDER KINASE ACTIVATOR-LIKE 2C (YEAST)		0.0011 (-1.9)	
MORC4	MORC FAMILY CW-TYPE ZINC FINGER 4		0.00016 (1.7)	
MORN2	MORN REPEAT CONTAINING 2		0.00022 (-2.4)	
MRPL22	MITOCHONDRIAL RIBOSOMAL PROTEIN L22	0.0099 (1.6)		
MRPL32	MITOCHONDRIAL RIBOSOMAL PROTEIN L32	0.013 (1.5)		
MRPL44	MITOCHONDRIAL RIBOSOMAL PROTEIN L44	0.010 (1.4)		
MRPS9	MITOCHONDRIAL RIBOSOMAL PROTEIN S9	0.0016 (1.9)		
MTG1	MITOCHONDRIAL GTPASE 1 HOMOLOG (S. CEREVISIAE)		0.00074 (-5.5)	
MTMR11	MYOTUBULARIN RELATED PROTEIN 11		0.0041 (-1.8)	
MTP18	MITOCHONDRIAL PROTEIN 18 KDA	0.012 (1.6)		
MTP18	MITOCHONDRIAL PROTEIN 18 KDA	0.011 (2.5)		
MTRR	5-METHYLTETRAHYDROFOLATE-HOMOCYSTEINE METHYLTRANSFERASE REDUCTASE	0.0066 (1.8)		
MYL6B	MYOSIN LIGHT CHAIN 1 SLOW A	0.012 (1.8)		
MYL9	MYOSIN, LIGHT POLYPEPTIDE 9, REGULATORY			0.0085 (3.4)
MYO18A	TGFB1-INDUCED ANTI-APOPTOTIC FACTOR 1			0.015 (3.2)
NA	N/A			0.028 (-4.5)
NA	N/A			0.042 (-3.3)
NA	N/A			0.031 (-2.9)

NA	N/A			0.028 (-2.3)
NA	N/A			0.048 (-2)
NA	HYPOTHETICAL PROTEIN LOC150837			0.030 (-2)
NA	N/A			0.045 (-1.3)
NA	N/A			0.028 (1.9)
NA	N/A			0.029 (2.3)
NA	HYPOTHETICAL PROTEIN LOC121838			0.016 (3.3)
NA	N/A			0.041 (3.8)
NA	N/A		0.00075 (-8.4)	
NA	N/A		0.0016 (-5.6)	
NA	N/A		0.0015 (-4.2)	
NA	N/A		0.0029 (-4)	
NA	N/A		0.0029 (-2.5)	
NA	N/A		0.0005 (-2.5)	
NA	N/A		0.0015 (-2.4)	
NA	HYPOTHETICAL PROTEIN LOC150837		0.00084 (-1.8)	
NA	N/A	0.0023 (2)		
NAG18	NAG18 PROTEIN		0.0000027 (-1.5)	
NARG2	NMDA RECEPTOR REGULATED 2		0.0012 (-3.4)	
NCAPH2	KLEISIN BETA			0.031 (1.8)
NCF4	NEUTROPHIL CYTOSOLIC FACTOR 4, 40KDA	0.0021 (1.6)		
NEDD9	NEURAL PRECURSOR CELL EXPRESSED, DEVELOPMENTALLY DOWN-REGULATED 9		0.0008 (-3.5)	
NET1	NEUROEPITHELIAL CELL TRANSFORMING GENE 1		0.0033 (-1.7)	
NEXN	NEXILIN (F ACTIN BINDING PROTEIN)	0.0081 (3.8)		
NFIX	NUCLEAR FACTOR I/X (CCAAT-BINDING TRANSCRIPTION FACTOR)		0.000011 (2.9)	

NFKBIE	NUCLEAR FACTOR OF KAPPA LIGHT POLYPEPTIDE GENE ENHANCER IN B-CELLS INHIBITOR, EPSILON		0.0024 (-3.2)	
NFYA	NUCLEAR TRANSCRIPTION FACTOR Y, ALPHA		0.0019 (-2)	
NKIRAS1	NFKB INHIBITOR INTERACTING RAS-LIKE 1		0.0015 (-1.7)	
NOC3L	NUCLEOLAR COMPLEX ASSOCIATED 3 HOMOLOG (S. CEREVISIAE)	0.013 (1.7)		
NOL14	CHROMOSOME 4 OPEN READING FRAME 9	0.0071 (1.5)		
NOL5A	NUCLEOLAR PROTEIN 5A (56KDA WITH KKE/D REPEAT)	0.014 (1.7)		
NP	NUCLEOSIDE PHOSPHORYLASE	0.011 (1.7)		
NPM3	NUCLEOPHOSMIN/NUCLEOPLASMIN, 3	0.011 (1.6)		
NPSR1	G PROTEIN-COUPLED RECEPTOR 154	0.013 (1.7)		
NRBP2	NUCLEAR RECEPTOR BINDING PROTEIN 2		0.0018 (1.9)	
NSDHL	NAD(P) DEPENDENT STEROID DEHYDROGENASE-LIKE	0.012 (1.8)		
NSL1	CHROMOSOME 1 OPEN READING FRAME 48	0.0092 (1.6)		
NSUN5	NOL1/NOP2/SUN DOMAIN FAMILY, MEMBER 5		0.0047 (-4.4)	
NUMA1	NUCLEAR MITOTIC APPARATUS PROTEIN 1		0.00006 (1.7)	
NUP35	NUCLEOPORIN 35KDA	0.011 (2)		
ODC1	ORNITHINE DECARBOXYLASE 1		0.00054 (-2.2)	
OR8H3	OLFACTORY RECEPTOR, FAMILY 8, SUBFAMILY H, MEMBER 3		0.0032 (2)	
ORC6L	ORIGIN RECOGNITION COMPLEX, SUBUNIT 6 HOMOLOG-LIKE (YEAST)	0.0025 (2.4)		
OSBPL11	HYPOTHETICAL PROTEIN FLJ13164			0.011 (1.6)
OSBPL1A	OXYSTEROL-BINDING PROTEIN-RELATED PROTEIN 1			0.0097 (-2.4)
OSBPL1A	OXYSTEROL-BINDING PROTEIN-RELATED PROTEIN 1	0.0013 (3.5)		
OSTF1	OSTEOCLAST STIMULATING FACTOR 1		0.001 (-1.5)	
PABPC1	POLY(A) BINDING PROTEIN, CYTOPLASMIC 2		0.0021 (-1.6)	
PAK1IP1	PAK1 INTERACTING PROTEIN 1		0.0025 (-2)	
PARP3	POLY (ADP-RIBOSE) POLYMERASE FAMILY, MEMBER 3	0.0078 (2.4)		

PCDH10	PROTOCADHERIN 10			0.034 (2.6)
PDCD10	PROGRAMMED CELL DEATH 10	0.0043 (1.8)		
PDCL3	PHOSDUCIN-LIKE 3	0.015 (1.9)		
PDE4C	PHOSPHODIESTERASE 4C, CAMP-SPECIFIC (PHOSPHODIESTERASE E1 DUNCE HOMOLOG, DROSOPHILA)			0.043 (-1.3)
PDGFRL	PLATELET-DERIVED GROWTH FACTOR RECEPTOR-LIKE		0.0016 (-2.2)	
PDLIM3	PDZ AND LIM DOMAIN 3	0.014 (1.8)		
PDLIM5	PDZ AND LIM DOMAIN 5		0.00085 (-3)	
PEA15	PHOSPHOPROTEIN ENRICHED IN ASTROCYTES 15		0.0039 (-1.5)	
PELO	PRO1770 PROTEIN	0.0053 (1.6)		
PFDN6	PREFOLDIN SUBUNIT 6		0.0036 (-2)	
PGM5	PHOSPHOGLUCOMUTASE 5			0.048 (2.6)
PIGC	N/A	0.0052 (1.6)		
PIK3C3	PHOSPHOINOSITIDE-3-KINASE, CLASS 3		0.00081 (2.3)	
PITPNM2	PHOSPHATIDYLINOSITOL TRANSFER PROTEIN, MEMBRANE-ASSOCIATED 2			0.040 (1.6)
PITX1	PAIRED-LIKE HOMEODOMAIN TRANSCRIPTION FACTOR 1			0.022 (2.4)
PKD1	POLYCYSTIC KIDNEY DISEASE 1 (AUTOSOMAL DOMINANT)			0.042 (3.9)
PLEKHB2	PLECKSTRIN HOMOLOGY DOMAIN CONTAINING, FAMILY B (EVECTINS) MEMBER 2		0.0033 (-1.8)	
PODXL	PODOCALYXIN-LIKE		0.00098 (2.2)	
POLB	POLYMERASE (DNA DIRECTED), BETA	0.011 (1.6)		
POLD3	POLYMERASE (DNA-DIRECTED), DELTA 3, ACCESSORY SUBUNIT		0.00091 (-3.9)	
POLDIP2	POLYMERASE (DNA-DIRECTED), DELTA INTERACTING PROTEIN 2		0.0023 (-1.8)	
POLR2K	POLYMERASE (RNA) II (DNA DIRECTED) POLYPEPTIDE K, 7.0KDA			0.046 (2.8)
POLR3D	POLYMERASE (RNA) III (DNA DIRECTED) POLYPEPTIDE D, 44KDA		0.00043 (-2.5)	
PPA1	N/A	0.011 (1.6)		
PPARG	PEROXISOME PROLIFERATIVE			0.011

	ACTIVATED RECEPTOR, GAMMA			(-1.5)
PPIG	PEPTIDYLPROLYL ISOMERASE G (CYCLOPHILIN G)		0.000051 (-1.6)	
PPL	PERIPLAKIN			0.011 (1.9)
PPP1R14B	PROTEIN PHOSPHATASE 1, REGULATORY (INHIBITOR) SUBUNIT 14B		0.0023 (-1.6)	
PPP2CB	PROTEIN PHOSPHATASE 2 (FORMERLY 2A), CATALYTIC SUBUNIT, ALPHA ISOFORM		0.00068 (-9.7)	
PPP3R1	PROTEIN PHOSPHATASE 3 (FORMERLY 2B), REGULATORY SUBUNIT B, 19KDA, ALPHA ISOFORM (CALCINEURIN B, TYPE I)		0.0048 (-1.5)	
PQLC3	PQ LOOP REPEAT CONTAINING 3			0.041 (-1.9)
PQLC3	PQ LOOP REPEAT CONTAINING 3		0.0036 (-2)	
PRDM6	PR DOMAIN CONTAINING 6		0.0028 (5.4)	
PRG2	PROTEOGLYCAN 2, BONE MARROW (NATURAL KILLER CELL ACTIVATOR, EOSINOPHIL GRANULE MAJOR BASIC PROTEIN)		0.0024 (-6.9)	
PRKAG1	N/A	0.014 (1.5)		
PROM1	PROMININ 1			0.029 (1.4)
PRRG4	PROLINE RICH GLA (G-CARBOXYGLUTAMIC ACID) 4 (TRANSMEMBRANE)		0.0028 (1.9)	
PSG3	PREGNANCY SPECIFIC BETA-1-GLYCOPROTEIN 3	0.0095 (-1.2)		
PSG4	PREGNANCY SPECIFIC BETA-1-GLYCOPROTEIN 4		0.0046 (-1.7)	
PSG7	PREGNANCY SPECIFIC BETA-1-GLYCOPROTEIN 2	0.010 (-1.3)		
PSG9	PREGNANCY SPECIFIC BETA-1-GLYCOPROTEIN 9		0.000016 (-1.7)	
PSMA4	PROTEASOME (PROSOME, MACROPAIN) SUBUNIT, ALPHA TYPE, 4	0.0028 (1.6)		
PSMB8	PROTEASOME (PROSOME, MACROPAIN) SUBUNIT, BETA TYPE, 8 (LARGE MULTIFUNCTIONAL PEPTIDASE 7)	0.0092 (2.5)		
PSMB8	PROTEASOME (PROSOME, MACROPAIN) SUBUNIT, BETA TYPE, 8 (LARGE MULTIFUNCTIONAL PEPTIDASE 7)	0.0088 (2.7)		

PSMD13	PROTEASOME (PROSOME, MACROPAIN) 26S SUBUNIT, NON-ATPASE, 13		0.0028 (2.5)	
PTHR1	PARATHYROID HORMONE RECEPTOR 1			0.023 (1.8)
PTMA	PROTHYMOSIN, ALPHA (GENE SEQUENCE 28)		0.0041 (1.7)	
PTPN2	PROTEIN TYROSINE PHOSPHATASE, NON-RECEPTOR TYPE 2		0.00012 (-3.2)	
PTPRA	PROTEIN TYROSINE PHOSPHATASE, RECEPTOR TYPE, A			0.0032 (1.4)
PTPRA	PROTEIN TYROSINE PHOSPHATASE, RECEPTOR TYPE, A		0.0048 (-1.7)	
PTS	6-PYRUVOYLTETRAHYDROPTERIN SYNTHASE	0.0066 (1.7)	0.0032 (-1.7)	
PVRL3	POLIOVIRUS RECEPTOR-RELATED 3		0.00054 (-1.6)	
PXN	PAXILLIN			0.028 (-1.9)
QKI	QUAKING HOMOLOG, KH DOMAIN RNA BINDING (MOUSE)			0.044 (-1.7)
R3HCC1	R3H DOMAIN AND COILED-COIL CONTAINING 1	0.0091 (1.9)		
RAB12	RAB12, MEMBER RAS ONCOGENE FAMILY		0.0028 (-2.7)	
RABEPK	RAB9 EFFECTOR PROTEIN WITH KELCH MOTIFS	0.013 (1.7)		
RAD17	RAD17 HOMOLOG (S. POMBE)		0.00033 (-2.2)	
RAD21	RAD21 HOMOLOG (S. POMBE)		0.0044 (-1.7)	
RAG1AP1	RECOMBINATION ACTIVATING GENE 1 ACTIVATING PROTEIN 1		0.0000031 (-2.1)	
RANBP2	RAN BINDING PROTEIN 2			0.021 (4.1)
RANBP3	RAN BINDING PROTEIN 3		0.0042 (-2.9)	
RASL11B	RAS-LIKE, FAMILY 11, MEMBER B	0.0036 (1.7)	0.0012 (-1.9)	
RBBP4	N/A	0.011 (1.7)		
RBPJ	RECOMBINING BINDING PROTEIN SUPPRESSOR OF HAIRLESS (DROSOPHILA)	0.0081 (1.7)		
RDBP	RD RNA BINDING PROTEIN		0.0023 (-1.5)	
RECQL	RECQ PROTEIN-LIKE (DNA HELICASE Q1-LIKE)	0.0092 (1.4)		
RECQL	RECQ PROTEIN-LIKE (DNA HELICASE Q1-LIKE)	0.0035 (2)		
REEP3	RECEPTOR ACCESSORY PROTEIN 3		0.0015	

			(-1.7)	
REXO4	REX4, RNA EXONUCLEASE 4 HOMOLOG (S. CEREVISIAE)	0.0099 (2.3)		
RFESD	LOC317671		0.0043 (-3.1)	
RGS20	REGULATOR OF G-PROTEIN SIGNALLING 20		0.0031 (-3.3)	
RHOQ	RAS HOMOLOG GENE FAMILY, MEMBER Q		0.0046 (-1.6)	
RN7SK	RNA, 7SK, NUCLEAR		0.001 (2.4)	
RNF13	RING FINGER PROTEIN 13		0.003 (-6)	
RNF141	RING FINGER PROTEIN 141			0.016 (-1.4)
RNF5	RING FINGER PROTEIN 5			0.035 (1.5)
RNF7	RING FINGER PROTEIN 7		0.000064 (-1.6)	0.035 (-1.3)
RPL14	RIBOSOMAL PROTEIN L14		0.0019 (1.7)	
RPL39L	RIBOSOMAL PROTEIN L39-LIKE	0.011 (2.4)		
RPN1	RIBOPHORIN I		0.0037 (-1.5)	
RPS27	RIBOSOMAL PROTEIN S27 (METALLOPANSTIMULIN 1)			0.045 (-1.3)
RPS27A	RIBOSOMAL PROTEIN S27A			0.043 (-1.2)
RRAD	RAS-RELATED ASSOCIATED WITH DIABETES			0.0071 (-3)
RRS1	RRS1 RIBOSOME BIOGENESIS REGULATOR HOMOLOG (S. CEREVISIAE)		0.00082 (-2)	
S100P	S100 CALCIUM BINDING PROTEIN P			0.033 (-1.3)
SAMM50	SORTING AND ASSEMBLY MACHINERY COMPONENT 50 HOMOLOG (S. CEREVISIAE)	0.014 (1.8)		
SCAMP2	SECRETORY CARRIER MEMBRANE PROTEIN 2		0.0017 (-1.6)	
SCO2	SCO CYTOCHROME OXIDASE DEFICIENT HOMOLOG 2 (YEAST)		0.0015 (-1.7)	
SCP2	STEROL CARRIER PROTEIN 2		0.0032 (-5)	
SEC11A	SEC11-LIKE 1 (S. CEREVISIAE)	0.012 (1.5)		
SELS	SELENOPROTEIN S		0.0011 (-1.6)	
SELT	SELENOPROTEIN T		0.00052 (-1.7)	

SEPSECS	SOLUBLE LIVER ANTIGEN/LIVER PANCREAS ANTIGEN			0.044 (1.3)
SERF1B	SMALL EDRK-RICH FACTOR 1A (TELOMERIC)		0.0025 (-2)	0.034 (-4.5)
SETBP1	SET BINDING PROTEIN 1		0.002 (1.9)	
SETD1A	SET DOMAIN CONTAINING 1A			0.038 (1.5)
SETD3	SET DOMAIN CONTAINING 3		0.00023 (-2.2)	
SETP7	SEPTIN 7		0.003 (1.7)	
SH2D5	SH2 DOMAIN CONTAINING 5			0.046 (-1.6)
SHMT2	SERINE HYDROXYMETHYLTRANSFERASE 2 (MITOCHONDRIAL)	0.014 (1.4)		
SLC25A17	"SOLUTE CARRIER FAMILY 25 (MITOCHONDRIAL CARRIER; PEROXISOMAL MEMBRANE PROTEIN, 34KDA), MEMBER 17"		0.0032 (-1.6)	
SLC2A11	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 11			0.045 (-3.3)
SLC31A2	SOLUTE CARRIER FAMILY 31 (COPPER TRANSPORTERS), MEMBER 2		0.0012 (-1.6)	
SLC46A2	THYMIC STROMAL CO-TRANSPORTER			0.049 (1.3)
SLC5A3	SOLUTE CARRIER FAMILY 5 (INOSITOL TRANSPORTERS), MEMBER 3		0.0016 (-8.6)	
SLMAP	SARCOLEMMA ASSOCIATED PROTEIN	0.010 (1.5)		
SLTM	HYPOTHETICAL PROTEIN FLJ10005		0.0026 (-2.3)	
SNORD68	HBII-202 SMALL NUCLEOLAR RNA	0.011 (1.6)		
SP100	SP100 NUCLEAR ANTIGEN		0.00028 (-24.7)	
SP100	SP100 NUCLEAR ANTIGEN	0.0014 (1.9)		
SPA17	SPERM AUTOANTIGENIC PROTEIN 17		0.0022 (-2.5)	
SPAG1	SPERM ASSOCIATED ANTIGEN 1			0.020 (-4.6)
SPCS2	SIGNAL PEPTIDASE COMPLEX SUBUNIT 2 HOMOLOG (S. CEREVISIAE)		0.000054 (-1.7)	
SPIN1	SPINDLIN		0.0029 (-1.7)	
SRGAP2	SLIT-ROBO RHO GTPASE ACTIVATING PROTEIN 2			0.044 (1.4)
SRP14P1	SIMILAR TO SIGNAL RECOGNITION	0.0076		

	PARTICLE 14KDA (HOMOLOGOUS ALU RNA BINDING PROTEIN)	(1.4)		
STAM2	SIGNAL TRANSDUCING ADAPTOR MOLECULE (SH3 DOMAIN AND ITAM MOTIF) 2			0.033 (-2)
STC1	STANNIOCALCIN 1	0.014 (2.9)		
STEAP3	STEAP FAMILY MEMBER 3		0.00096 (1.9)	0.036 (2.1)
STRA13	N/A	0.0033 (1.8)		
STT3B	STT3, SUBUNIT OF THE OLIGOSACCHARYLTRANSFERASE COMPLEX, HOMOLOG B (S. CEREVISIAE)			0.047 (-1.2)
SUGT1	SGT1, SUPPRESSOR OF G2 ALLELE OF SKP1 (S. CEREVISIAE)	0.0088 (1.6)		
SULT1A3	SULFOTRANSFERASE FAMILY, CYTOSOLIC, 1A, PHENOL-PREFERRING, MEMBER 3		0.00086 (-1.7)	
SUPT6H	SUPPRESSOR OF TY 6 HOMOLOG (S. CEREVISIAE)		0.0000017 (1.8)	0.020 (1.9)
SYTL2	SYNAPTOTAGMIN-LIKE 2	0.014 (1.9)	0.000046 (1.6)	
SYTL2	SYNAPTOTAGMIN-LIKE 2	0.0078 (1.9)		
TAF13	TAF13 RNA POLYMERASE II, TATA BOX BINDING PROTEIN (TBP)-ASSOCIATED FACTOR, 18KDA		0.00023 (-3.5)	
TAPBPL	TAP BINDING PROTEIN-LIKE		0.0039 (-1.8)	
TBCC	TUBULIN-SPECIFIC CHAPERONE C		0.00058 (-4.1)	
TCEA3	TRANSCRIPTION ELONGATION FACTOR A (SII), 3			0.0097 (2.3)
TCEAL3	TRANSCRIPTION ELONGATION FACTOR A (SII)-LIKE 3			0.040 (1.9)
TCEAL8	TRANSCRIPTION ELONGATION FACTOR A (SII)-LIKE 8	0.0085 (1.6)		
TCTA	T-CELL LEUKEMIA TRANSLOCATION ALTERED GENE			0.039 (-1.3)
TES	TESTIS DERIVED TRANSCRIPT (3 LIM DOMAINS)		0.0015 (-3.6)	
TFAP2A	TRANSCRIPTION FACTOR AP-2 ALPHA (ACTIVATING ENHANCER BINDING PROTEIN 2 ALPHA)		0.0003 (-2.4)	
TGIF1	TGFB-INDUCED FACTOR (TALE FAMILY HOMEOBOX)			0.040 (-1.6)
TIMM22	TRANSLOCASE OF INNER MITOCHONDRIAL MEMBRANE 22 HOMOLOG (YEAST)	0.0037 (1.6)		

TIMM23	TRANSLOCASE OF INNER MITOCHONDRIAL MEMBRANE 23 HOMOLOG (YEAST)	0.013 (1.4)		
TLR7	TOLL-LIKE RECEPTOR 7			0.028 (2)
TM4SF18	TRANSMEMBRANE 4 L SIX FAMILY MEMBER 18		0.0044 (-1.7)	
TMBIM4	TRANSMEMBRANE BAX INHIBITOR MOTIF CONTAINING 4			0.030 (-1.2)
TMEM185A	FAMILY WITH SEQUENCE SIMILARITY 11, MEMBER A		0.0033 (-1.5)	
TMEM41A	TRANSMEMBRANE PROTEIN 41A	0.0086 (1.9)		
TMEM5	TRANSMEMBRANE PROTEIN 5	0.0029 (1.7)	0.0031 (-1.6)	
TMEM54	TRANSMEMBRANE PROTEIN 54			0.0094 (1.7)
TMUB2	HYPOTHETICAL PROTEIN MGC3123		0.0023 (-1.6)	
TNNT3	TROPONIN T TYPE 3 (SKELETAL, FAST)			0.040 (2)
TPMT	THIOPURINE S-METHYLTRANSFERASE			0.011 (-1.7)
TPRKB	TP53RK BINDING PROTEIN	0.0064 (1.5)		
TPT1	TUMOR PROTEIN, TRANSLATIONALLY-CONTROLLED 1			0.046 (-1.2)
TRIM32	TRIPARTITE MOTIF-CONTAINING 32	0.002 (1.8)		
TRIM5	TRIPARTITE MOTIF-CONTAINING 5		0.0011 (-3.1)	
TRIM5	TRIPARTITE MOTIF-CONTAINING 5		0.001 (-2.9)	
TRIM69	RING FINGER PROTEIN 36	0.0089 (2.3)	0.006 (-3.5)	
TTC25	TETRATRICOPEPTIDE REPEAT DOMAIN 25			0.031 (2.1)
TTC32	SIMILAR TO CG14894-PA		0.0031 (-1.9)	
TUBB2B	TUBULIN, BETA 2B	0.0071 (1.8)		
TUSC1	TUMOR SUPPRESSOR CANDIDATE 1		0.0021 (-1.7)	0.038 (-1.6)
TWF1	PTK9 PROTEIN TYROSINE KINASE 9		0.0019 (-1.6)	
TXN	THIOREDOXIN		0.0036 (-2)	
U1SNRNPBP	U11/U12 SNRNP 35K		0.00064 (-4)	0.046 (-2.2)
U1SNRNPBP	U11/U12 SNRNP 35K			0.0086 (-1.5)

U2AF1	U2(RNU2) SMALL NUCLEAR RNA AUXILIARY FACTOR 1	0.011 (1.6)		
U2AF1L3	U2(RNU2) SMALL NUCLEAR RNA AUXILIARY FACTOR 1-LIKE 3		0.00002 (-4.6)	
U2AF1L4	U2(RNU2) SMALL NUCLEAR RNA AUXILIARY FACTOR 1-LIKE 3		0.00027 (-1.8)	
UBC	UBIQUITIN C		0.0000069 (-1.6)	0.031 (-1.2)
UBC	UBIQUITIN C		0.0033 (-1.5)	
UBE2D3	UBIQUITIN-CONJUGATING ENZYME E2D 3 (UBC4/5 HOMOLOG, YEAST)		0.0041 (-1.6)	
UBE2E3	UBIQUITIN-CONJUGATING ENZYME E2E 3 (UBC4/5 HOMOLOG, YEAST)		0.00067 (-6.3)	
UBTD2	DENDRITIC CELL-DERIVED UBIQUITIN-LIKE PROTEIN		0.004 (-3.8)	
UCHL3	UBIQUITIN CARBOXYL-TERMINAL ESTERASE L3 (UBIQUITIN THIOLESTERASE)			0.041 (-1.2)
UCK2	URIDINE-CYTIDINE KINASE 2		0.00024 (-1.7)	
UROS	N/A	0.009 (2.2)		
USF2	UPSTREAM TRANSCRIPTION FACTOR 2, C-FOS INTERACTING			0.049 (1.5)
USP10	UBIQUITIN SPECIFIC PEPTIDASE 10	0.0072 (1.5)		
USP26	UBIQUITIN SPECIFIC PEPTIDASE 26			0.044 (1.8)
USP30	UBIQUITIN SPECIFIC PEPTIDASE 30		0.00036 (-2.2)	
USP33	UBIQUITIN SPECIFIC PEPTIDASE 33		0.00014 (-1.6)	
UTP11L	UTP11-LIKE, U3 SMALL NUCLEOLAR RIBONUCLEOPROTEIN, (YEAST)		0.0001 (-1.7)	
VAMP4	VESICLE-ASSOCIATED MEMBRANE PROTEIN 4			0.014 (-2.6)
VAV3	VAV 3 ONCOGENE		0.010 (-16.7)	0.033 (-32.6)
WDR45	WD REPEAT DOMAIN 45		0.0024 (-4.1)	
WDR47	WD REPEAT DOMAIN 47		0.0015 (-2.3)	
WDSUB1	WD REPEAT, STERILE ALPHA MOTIF AND U-BOX DOMAIN CONTAINING 1			0.048 (-1.2)
VEZT	VEZATIN, ADHERENS JUNCTIONS TRANSMEMBRANE PROTEIN		0.0007 (-1.8)	
WNT7A	WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 7A	0.0029 (1.7)		
VPS33A	VACUOLAR PROTEIN SORTING 33A (YEAST)		0.001 (-1.6)	

VRK3	VACCINIA RELATED KINASE 3	0.014 (1.7)		
VSIG4	V-SET AND IMMUNOGLOBULIN DOMAIN CONTAINING 4			0.0052 (1.7)
WTIP	WILMS TUMOR 1 INTERACTING PROTEIN	0.012 (1.7)		
XBP1	X-BOX BINDING PROTEIN 1		0.0023 (-1.7)	
YWHAE	TYROSINE 3-MONOOXYGENASE/TRYPTOPHAN 5-MONOOXYGENASE ACTIVATION PROTEIN, EPSILON POLYPEPTIDE			0.038 (1.3)
ZADH2	HYPOTHETICAL PROTEIN BC010734		0.0011 (-1.8)	
ZC3H14	NUCLEAR PROTEIN UKP68		0.0012 (-1.5)	
ZCD1	CHROMOSOME 10 OPEN READING FRAME 70	0.014 (1.6)		
ZDHHC6	ZINC FINGER, DHHC-TYPE CONTAINING 6		0.00087 (-1.6)	0.042 (-1.3)
ZFAND2A	ZINC FINGER, AN1-TYPE DOMAIN 2A	0.0063 (2.2)		
ZFAT1	ZINC FINGER PROTEIN 406			0.037 (-3.1)
ZNF154	ZINC FINGER PROTEIN 154 (PHZ-92)	0.012 (-1.8)		
ZNF160	ZINC FINGER PROTEIN 160		0.0038 (-1.7)	
ZNF195	ZINC FINGER PROTEIN 195		0.0025 (-5)	
ZNF200	ZINC FINGER PROTEIN 200		0.000063 (-2.3)	
ZNF200	ZINC FINGER PROTEIN 200		0.0021 (-1.7)	
ZNF277P	ZINC FINGER PROTEIN 277		0.000047 (-3)	0.029 (-2.5)
ZNF292	ZINC FINGER PROTEIN 292		0.00013 (-22.3)	
ZNF444	ZINC FINGER PROTEIN 444		0.00058 (-2)	
ZNF511	ZINC FINGER PROTEIN 511	0.011 (1.8)		
ZNF526	ZINC FINGER PROTEIN 526			0.048 (-1.6)
ZNF557	ZINC FINGER PROTEIN 557		0.000042 (1.9)	
ZNF644	HYPOTHETICAL PROTEIN BM-005		0.0013 (-1.8)	
ZNF649	ZINC FINGER PROTEIN 649	0.014 (1.4)		
ZNF654	ZINC FINGER PROTEIN 654		0.0027	

			(-2.4)	
ZNF682	ZINC FINGER PROTEIN 682		0.00066 (-2.4)	
ZNF776	HYPOTHETICAL PROTEIN FLJ38288		0.0046 (-3)	
ZNF784	SIMILAR TO ZINC FINGER PROTEIN			0.042 (-1.9)
ZNHIT4	ZINC FINGER, HIT TYPE 4		0.00089 (-2.1)	
ZRANB2	ZINC FINGER PROTEIN 265		0.0014 (-1.6)	