Original Article Maternal peripheral blood gene expression in early pregnancy and preeclampsia

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Received November 3, 2010; accepted December 28, 2010; Epub December 29, 2010; published January 1, 2011

Abstract: We investigated associations of early pregnancy maternal peripheral blood gene expression with preeclampsia. In a nested case control study, gene expression of peripheral blood, collected at 16weeks of gestation on average from 16 women destined to develop preeclampsia and 16 women who had normotensive pregnancies was profiled using Affymetrix GeneChip Arrays. Fold change and Student's T-test analyses were used to compare differential gene expression across the groups. Functions and functional relationships as well as common regulatory sequences of differentially expressed genes were investigated. Genes participating in abnormal placentation (e.g COL1A1), immune/inflammation response (e.g. IKBKB) and cellular development (including cell cycle) (e.g. RB1) were differentially expressed in early pregnancy peripheral blood in preeclampsia. We identified transcription factors (i.e. Sp1, MAZ and MZF1) that may account for co-expression of differentially expressed genes. Preeclampsia is associated with differential gene expression in early pregnancy peripheral blood.

Keywords: preeclampsia; early pregnancy; gene; expression

Introduction

The pathogenesis of preeclampsia, a pregnancy -related vascular disorder, is a complex process that has been associated with angiogenesis, immune dysfunction, inflammation and oxidative stress [1-3]. While preeclampsia is a disorder of the second half of pregnancy, accumulating evidence supports the multi-stage developmental phases of preeclampsia that start early in pregnancy [1-3]. For instance, immune sensitivity and abnormal placentation in early pregnancy contribute to placental hypoxemia which promotes diffuse inflammation, oxidative stress and endothelial dysfunction later in pregnancy [1-4]. However, significant gaps in knowledge persist on preeclampsia related events and risk factors in early pregnancy that is critical for prevention and early detection of disease [5].

Increasingly, gene expression studies are being used to investigate pathophysiologic processes underlying preeclampsia [5]. Several investigators, including our team, have conducted gene expression profiling of preeclamptic placenta after delivery [6-9]. Although results from these studies provide new insights about preeclampsia pathophysiology, inferences are limited by critical questions concerning temporal relationships between gene expression profiles, onset of the clinical disorder, and its management. Few gene expression studies investigating preeclampsia were conducted in early pregnancy [10-12] and even fewer were conducted using early pregnancy peripheral blood [12], a tissue that may reflect local and systemic pathophysiological changes associated with preeclampsia.

Taking into account the potential significance of this research area, in 2003, we expanded an on -going pregnancy cohort study by prospectively collecting and storing peripheral blood samples in Paxgene[™] Blood RNA tubes for gene expression studies. In this report, we describe findings of a nested case control study that investigated early pregnancy maternal peripheral blood gene expressions among 16 women destined to develop preeclampsia and 16 women who had normotensive pregnancies. We also compared similarities and differences between preeclampsia related underlying pathomechanisms in early and late pregnancy using gene expression profiles of peripheral blood (early pregnancy) and placenta (at-delivery), respectively.

Materials and methods

Study population

This nested case control study was conducted using information collected from participants of the Omega study (1996-2007), a prospective study designed to examine risk factors of pregnancy complications. Participants were recruited from women who initiate prenatal care before 20 weeks gestation at Swedish Medical Center (SMC) affiliated clinics. Ineligibility criteria included < 18 years of age, not speaking or reading English, not planning to carry the pregnancy to term, and/or not planning to deliver at SMC. The study for this report was conducted among selected preeclampsia cases (N=16) and controls (N=16) from Omega cohort members enrolled during the period of July 2003 to May 2007. During this interval, > 80% of approached women consented to participate in the study and > 95% of enrolled participants were followed through pregnancy completion.

Preeclampsia cases were selected using the then current 1996 ACOG guidelines when both pregnancy-induced hypertension (PIH) and proteinuria were present. PIH was defined as a sustained (≥2 measures 6 hrs apart) blood pressure (Bp) elevation (>140/90 mmHg) after 20 weeks of gestation or a sustained 15-mm Hg rise in diastolic Bp or a 30-mm Hg rise in svstolic Bp above 1st trimester values. Proteinuria was defined as a sustained (≥2 measures 4 hrs apart) presence of elevated protein in the urine (>30 mg/dL or >1+on a urine dipstick). Controls were selected among women who had normotensive pregnancies uncomplicated by proteinuria or gestational diabetes. Women who were multiparous or had history of chronic hypertension and/or pre-gestational diabetes as well as women with non-singleton pregnancies were excluded. The Institutional Review Board of the SMC approved study protocols. All participants provided written informed consent.

Data collection

Information on risk factors was collected using in-person interviews, blood collection and medi-

cal records abstraction. Following enrollment, in -person interviews were conducted to collect data on socio-demographic characteristics and reproductive and medical histories. At or near the time of in-person interviews (16 weeks of gestation on average), trained phlebotomists collected peripheral blood samples. PAXgene™ Blood RNA tubes (Qiagen Inc, Valencia, CA) [13] were used to collect blood samples for gene expression studies. After delivery, trained personnel abstracted maternal and infant medical records to ascertain pregnancy outcomes.

Total RNA extraction, target preparation and hybridization

The PAXgene Blood RNA Kit (Qiagen Inc., Valencia, CA) was used for extraction and purification of total RNA. Total RNA concentration was determined by UV absorbance at 260 nm (A₂₆₀) by direct measurement on a NanoDrop ND1000 spectrophotometer (ThermoFisher Scientific, Wilmington, DE). RNA purity was assessed by evaluating readings at 260 nm and 280 nm (A₂₆₀/ A₂₈₀). All samples had A₂₆₀/ A₂₈₀ values > 2.0 indicating high level of purity. Samples were then kept in frozen storage at -80°C. All RNA samples, including reference RNAs, underwent quality control checks and were labeled using same standardized protocols.

RNA target preparations were conducted using guidelines of the NuGEN™ Ovation™ RNA Amplification System V2 (amplification) and the Nu-GEN™ FL-Ovation™ cDNA Biotin Module V2 (fragmentation and labeling) (NuGen Technologies Inc., San Carlos, CA). The resultant fragmented and labeled cDNA was added to the hybridization cocktail in accordance with the NuGEN and Affymetrix guidelines for hybridization onto Affymetrix Human Genome U133 Plus 2.0 GeneChip® Arrays (Affymetrix, Sunnyvale, CA). The arrays were washed and stained on the GeneChip® Fluidics Station 450 (Affymetrix, Sunnyvale, CA), before being inserted into the Affymetrix autoloader carousel and scanned using the GeneChip® Scanner 3000 (Affvmetrix. Sunnyvale, CA). Data from each array was guantified using GeneChip® Operating Software (Affymetrix, Sunnyvale, CA).

GeneChip quality controls and normalization

GeneChip quality control procedures included the following. First, background values of Ge-

neArray scanners calibrated to the new PMT setting (10% of maximum) were assessed for comparability. Second, GAPDH gene was used to assess RNA sample and assay quality. Third, controls on the GeneChip array (four E.Coli genes, bioB, bioC and bioD and the cre gene) were spiked into each sample to evaluate hybridization efficiency. Fourth, raw noise (Q value), a measure of pixel-to-pixel variation of probe cells due to operation-associated electrical noise, was evaluated. Fifth, PolyA control genes (dap, lys, phe, thr and trp genes from B. subtilis) were amplified and spiked into the RNA samples prior to amplification to serve as internal control genes. Finally, data were normalized using an error-weighted model based on Rosetta Resolver Error Models (Rosetta, Seattle, WA) [14].

Real time quantitative polymerase chain reaction (RT-qPCR) experiment

RT-qPCR experiment was conducted to confirm microarray based expression measures of selected genes. Initially, 1 µg total RNA was reverse transcribed using the Transcriptor first strand cDNA synthesis kit (Roche Applied Science, Indianapolis, IN). The gPCR reactions were performed using the Roche LightCycler 480® Probes kit and the LightCycler 480® instrument (Roche Applied Science, Indianapolis, IN). Pre-designed exon spanning Taqman® assays for each gene target were obtained from Applied Biosystems (Foster City, CA). Each individual assay was run on an individual 96-well plate in duplicate for each sample; and, 2 reverse transcription negative controls and 2 no template control wells were included with each assay. Individual reactions were characterized by the PCR cycle at which fluorescence first rises above threshold background fluorescence (the threshold cycle, Ct). ACTB and GAPDH genes, selected based on their non-variant gene expression across cases and controls in the microarray experiment, were used for normalization.

Statistical analysis

Analysis was conducted on normalized and logtransformed data. Fold change (FC) expression differences (absolute FC \geq 1.5) and Student's Ttest (two sample, unequal variances) p-values (<0.05) were used to identify differentially expressed genes across the two groups (cases and controls). Two-Dimensional hierarchical clustering, using Cluster and TreeView softwares [16], and Principle components analysis (PCA) techniques were used to evaluate whether differentially expressed genes cluster arrays into groups (case and control groups) [15]. Functions and functional relationships between differentially expressed genes were investigated using Ingenuity Pathway Analysis (IPA), as described before (Ingenuity, Redwood City, CA) [7]. Gene-enrichment of networks (network score) based on a modified Fisher's exact test, measured in IPA, was used to rank biological significance of gene function networks in relation to preeclampsia. In the confirmatory RT-gPCR experiment, we used fold change analysis and Student's T-test to compare whether results were consistent with those obtained from microarray experiments. Common regulatory sequences for the differentially expressed genes as well as their cognate regulators (transcription factors (TFs)) were searched using ConTra (conserved transcription factor binding sites, TFBs) and MAPPER [17]. Finally, using GeneGO pathway analysis tools (GeneGO Inc., St Joseph, MI), we compared gene ontology (GO) processes represented by differentially expressed genes in maternal early pregnancy peripheral blood in the current study with differentially expressed genes in preeclamptic placenta we reported before [7].

Results

Selected study population characteristics are summarized in **Table 1**. Mean age of preeclampsia cases and normotensive controls were 35.1 and 32.1 years, respectively. Maternal whole blood samples were collected from participants at 16 weeks of gestation, on average. Preeclampsia cases had higher pre-gestational BMI compared with controls.

Of the total >38,500 genes represented by ~47,400 probe sets on the GeneChip, 247 genes (<1%) represented by 356 probes that met the following criteria were up (N=86) or down (N=161) regulated in preeclampsia cases compared to controls; Student's T-test p-value < 0.05 and absolute fold change > 1.5 (**Table 2** and **3**). These differentially expressed genes included genes involved in abnormal placentation (e.g. COL1A1 and NRTK2) and immune response/inflammation (e.g. CLEC12B and IKBKB). The range of fold change differences in

| Characteristics | Preeclampsia cases (N=16) | Normotensive controls (N=16) |
|---|---|---|
| GA at blood collection, weeks* | 16.2 (1.7) | 16.2 (2.5) |
| Maternal Age, years* 20-34 years 35 and above years | 35.1 (5.3) 8 (50.0) 8 (50.0) | 32.1 (4.4) 13 (81.3) 3 (13.7) |
| Maternal Race/Ethnicity White African American Other | 14 (87.5) 2 (12.5) 0 (0.0) | 13 (81.3) 1 (6.3) 2 (12.5) |
| Pre-gestational BMI, kg/m²* <20 20-24.99 25-29.99 ≥30 | 29.6 (11.9) 2 (12.5) 7 (43.8) 5 (31.3) 2 (12.5) | 23.8 (6.2) 1 (6.3) 12 (75.0) 2 (12.5) 1 (6.3) |
| Smoked in pregnancy | 0 (0.0) | 1 (6.3) |
| Family history of chronic hypertension | 10 (62.5) | 6 (37.5) |
| Family history of diabetes mellitus | 3 (18.8) | 1 (6.3) |
| Gestational diabetes | 2 (12.5) | 0 (0.0) |

Table 1 Characteristics of study population

*Mean (standard deviation), otherwise n (%). Abbreviations: GA: gestational age, BMI: body mass index; kg/m²: kilogram/meter²

expression between preeclampsia cases and controls was -5.40 (DKFZp666G057) to 2.78 (TMEM176B). In hierarchical clustering, based on expressions measured by probes representing differentially expressed genes, all but three preeclampsia cases and all but one normotensive controls clustered in to the two main cluster groups of cases and controls, respectively (**Figure 1**). Similarly, in PCA, we demonstrated that preeclampsia cases and controls can be classified into two groups using expressions measured by probes representing differentially expressed genes (**Figure 2**).

We further evaluated functions and functional relationships of differentially expressed genes. In IPA, 12 networks with network scores > 3 were over represented by differentially expressed genes. These networks are involved in cellular development (particularly of the hematological system), cell signaling, cell cycle regulation, metabolism (lipid, vitamin, carbohydrates and nucleic acids), inflammation and cellular response (**Table 4**). In particular, the RB1_E2F1

cell cycle pathway that regulates cellular development (e.g in the hematological system) was significantly over represented (**Figure 3**).

In the qRT-PCR experiment to confirm microarray-based measurements conducted on selected differentially expressed genes (of CLEC family of genes or functionally related genes), similar direction of fold change differences (and for some, similar size of fold change differences) between preeclampsia cases and controls were observed for most genes (6/8, 75%) (**Table 5**). However, most of the p-values in Student's T-test comparisons were not statistically significant.

In the promoter analysis of common regulatory sequences (motifs) of differentially expressed genes, binding sites of transcription factors Sp1 (specificity protein 1), MAZ (MYC associated zinc finger protein) and MZF1 (myeloid zinc finger 1) were identified (**Figure 4**).

Results of GO comparisons of preeclampsia

| Gene Symbol | Gene Name | FC* | P-value* | | |
|--------------------------|---|-------|----------|--|--|
| De la contrata da contra | | | | | |
| Down regulated genes | | | | | |
| DKFZp666G057 | hypothetical protein DKFZp666G057 | -5.40 | 0.0245 | | |
| HSD17B12 | Hydroxysteroid (17-beta) dehydrogenase 12 | -3.39 | 0.0121 | | |
| PLEKHG2 | pleckstrin homology domain containing, family G (with RhoGef domain) member 2 | -2.79 | 0.0157 | | |
| COL5A3 | collagen, type V, alpha 3 | -2.69 | 0.0432 | | |
| LOC400581 | GRB2-related adaptor protein-like | -2.64 | 0.0037 | | |
| ACCN2 | amiloride-sensitive cation channel 2, neuronal | -2.38 | 0.0078 | | |
| GTSF1L | gametocyte specific factor 1-like | -2.35 | 0.0033 | | |
| CLEC12B | C-type lectin domain family 12, member B | -2.33 | 0.0010 | | |
| COL1A1 | collagen, type I, alpha 1 | -2.26 | 0.0466 | | |
| ZNF496 | zinc finger protein 496 | -2.21 | 0.0003 | | |
| VN1R1 | vomeronasal 1 receptor 1 | -2.13 | 0.0006 | | |
| PTPRM | protein tyrosine phosphatase, receptor type, M | -2.05 | 0.0012 | | |
| IKBKB | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta | -2.02 | 0.0124 | | |
| PTPRM | protein tyrosine phosphatase, receptor type, M | -2.02 | 0.0003 | | |
| Up regulated genes | | | | | |
| NTRK2 | neurotrophic tyrosine kinase, receptor, type 2 | 2.01 | 0.0185 | | |
| L0C728806 | Similar to N-ethylmaleimide-sensitive factor | 2.10 | 0.0081 | | |
| MSL-1 | Male-specific lethal-1 homolog | 2.10 | 0.0018 | | |
| VEPH1 | ventricular zone expressed PH domain homolog 1 (zebrafish) | 2.24 | 0.0107 | | |
| B9D1 | B9 protein domain 1 | 2.41 | 0.0106 | | |
| MGC50559 | hypothetical protein MGC50559 | 2.41 | 0.0493 | | |
| RAB6A | RAB6A, member RAS oncogene family | 2.50 | 0.0159 | | |
| NALCN | sodium leak channel, non-selective | 2.67 | 0.0022 | | |
| PTPRD | protein tyrosine phosphatase, receptor type, D | 2.67 | 0.0106 | | |
| TMEM176B | Transmembrane protein 176B | 2.78 | 0.0046 | | |

| Table 2. Selected* | list of differentiall | v expressed genes |
|--------------------|-----------------------|----------------------|
| | | , one occor a Borroo |

**Selected (absolute fold change > 2.0 [FC] and Student's T test p-value [p-value] < 0.05) list of differentially expressed genes.

related differentially expressed genes in the current experiment with preeclampsia related differentially expressed genes in placenta atdelivery, reported before [7], are presented in **Figure 5**. GO processes of cell proliferation, response to hypoxia and smooth muscle contraction were over represented in preeclamptic placenta while GO processes of vasculature (blood vessel) development were over represented in early pregnancy peripheral blood among women who later developed preeclampsia.

Discussion

We demonstrated that preeclampsia is associated with differential gene expression in early pregnancy maternal peripheral blood. Genes participating in abnormal placentation (e.g COL1A1), immune/inflammation response (e.g. IKBKB) and cellular development (including cell cycle) (e.g. RB1) were differentially expressed. We identified transcription factors (e.g. Sp1, MAZ and MZF1) that may account for coexpression of differentially expressed genes. Comparison of preeclampsia related gene expression profiles of early pregnancy peripheral blood and placenta (at-delivery) suggest gestational age and tissue specific differences in pathophysiological processes (vasculature development versus hypoxia response, respectively) involved in preeclampsia.

Previous studies have investigated peripheral blood gene expression in relation to preeclampsia [10, 12, 18-20]. Okazaki et al reported upregulation of pregnancy specific beta-1 glycoprotein and trophoblast glycoprotein in peripheral blood of women with preeclampsia at 38-

| Gene Symbol | Gene Name | FC* | P-value* |
|----------------|---|-------|----------|
| • | | | |
| DKF7p6666G057 | hypothetical protein DKFZp666G057 | -5.4 | 0.0245 |
| HSD17B12 | Hydroxysteroid (17-beta) dehydrogenase 12 | -3.39 | 0.0121 |
| PLEKHG2 | nleckstrin homology domain containing family G (with RhoGef | -2 79 | 0.0157 |
| TEERINGZ | domain) member 2 | 2.10 | 0.0101 |
| | collagen type V alpha 3 | -2.69 | 0 0/32 |
| 100/00581 | GRB2-related adaptor protein-like | -2.60 | 0.0432 |
| | amiloride sensitive cation channel 2 neuronal | -2.38 | 0.0078 |
| CTSE11 | dametocyto specific factor 1 liko | 2.30 | 0.0078 |
| | C type lectin domain family 12, member B | -2.33 | 0.0033 |
| | colladon type I alpha 1 | -2.33 | 0.0010 |
| | collagen, type I, alpha I | -2.20 | 0.0400 |
| | Zinc miger protein 490 | -2.21 | 0.0003 |
| | | -2.13 | 0.0006 |
| | protein tyrosine phosphatase, receptor type, w | -2.05 | 0.0012 |
| INBNB | innibitor of kappa light polypeptide gene enhancer in B-cells, kinase | -2.02 | 0.0124 |
| DIVNIA | Deta | 1.00 | 0.0040 |
| PLXNA1 | | -1.99 | 0.0040 |
| LIK | leukocyte tyrosine kinase | -1.96 | 0.0268 |
| ULK4 | unc-51-like kinase 4 (C. elegans) | -1.96 | 0.0160 |
| AGRN | agrin | -1.94 | 0.0293 |
| GIMAP5 | GTPase, IMAP family member 5 | -1.93 | 0.0027 |
| RAB40A | RAB40A, member RAS oncogene family | -1.93 | 0.0187 |
| CLEC12A | C-type lectin domain family 12, member A | -1.92 | 0.0023 |
| DKFZP761N09121 | hypothetical protein DKFZp761N09121 | -1.9 | 0.0050 |
| RAB3IP | RAB3A interacting protein (rabin3) | -1.89 | 0.0002 |
| MUC5B | mucin 5B, oligomeric mucus/gel-forming | -1.88 | 0.0019 |
| PICK1 | protein interacting with PRKCA 1 | -1.88 | 0.0282 |
| FAM70A | family with sequence similarity 70, member A | -1.87 | 0.0275 |
| DUSP2 | dual specificity phosphatase 2 | -1.86 | 0.0000 |
| LOC161527 | promyelocytic leukemia | -1.86 | 0.0209 |
| PTGDS | prostaglandin D2 synthase 21kDa (brain) | -1.85 | 0.0004 |
| MLZE | melanoma-derived leucine zipper, extra-nuclear factor | -1.83 | 0.0018 |
| UACA | uveal autoantigen with coiled-coil domains and ankyrin repeats | -1.83 | 0.0481 |
| MTHFSD | Methenyltetrahydrofolate synthetase domain containing | -1.82 | 0.0484 |
| TTC28 | tetratricopeptide repeat domain 28 | -1.82 | 0.0011 |
| LRRC23 | leucine rich repeat containing 23 | -1.81 | 0.0094 |
| CA3 | carbonic anhydrase III, muscle specific | -1.8 | 0.0155 |
| CENTG2 | centaurin, gamma 2 | -1.8 | 0.0003 |
| GPR4 | G protein-coupled receptor 4 | -1.8 | 0.0011 |
| LDB2 | LIM domain binding 2 | -1.8 | 0.0204 |
| SOX15 | SRY (sex determining region Y)-box 15 | -1.8 | 0.0436 |
| GIPC3 | GIPC PDZ domain containing family, member 3 | -1.79 | 0.0189 |
| LYPD3 | LY6/PLAUR domain containing 3 | -1.79 | 0.0081 |
| DSTN | Destrin (actin depolymerizing factor) | -1.78 | 0.0015 |
| KLHDC4 | Kelch domain containing 4 | -1.78 | 0.0176 |
| PCOLCE | procollagen C-endopeptidase enhancer | -1.77 | 0.0132 |
| ZNF542 | zinc finger protein 542 | -1.77 | 0.0418 |
| FLJ44606 | hypothetical gene supported by AK126569 | -1.75 | 0.0093 |
| FAM120A0S | family with sequence similarity 120A opposite strand | -1.74 | 0.0191 |
| HFI 308 | DNA helicase HFI 308 | -1.74 | 0.0057 |
| HLCS | holocarboxylase synthetase (hiotin-(proprionyl-Coenzyme A- | -1 74 | 0.0044 |
| TIL00 | carboxylase (ATP-hydrolysing)) ligase) | ±., 4 | 0.0044 |
| TMFM46 | transmembrane protein 46 | -1 74 | 0 0064 |
| TRIM47 | tripartite motif-containing 47 | -1 74 | 0.0119 |
| CASP10 | caspase 10 apontosis-related cysteine pentidase | -1 73 | 0.0124 |
| CFL | carboxyl ester linase (hile salt-stimulated linase) | -1 72 | 0.0300 |
| GPRASP2 | G protein-coupled recentor associated sorting protein 2 | -1 73 | 0.0018 |
| | retinol dehydrogenase 16 (all trans) | -1.72 | 0.0010 |
| DHCR7 | 7-debydrocholesterol reductase | -1.70 | 0.0202 |
| ENI1 | fibronactin 1 | -1.72 | 0.0000 |
| | DO loop repeat containing 3 | -1.72 | 0.0140 |
| 1 QL00 | i y iooh iehear coirtaining o | -1.12 | 0.0219 |

 Table 3. List of differentially expressed genes

| | ubiautia ana ifia mantidaga 40 | 1 71 | 0.0405 |
|----------------|--|-------|---------|
| USP18 | ubiquitin specific peptidase 18 | -1.71 | 0.0485 |
| L0C150837 | hypothetical protein LOC150837 | -1.7 | 0.0311 |
| | transmombrano protoin 177 | 17 | 0.0084 |
| | | -1.7 | 0.0004 |
| L0C283859 | hypothetical protein LOC283859 | -1.69 | 0.0039 |
| TAPBP | TAP binding protein (tapasin) | -1.69 | 0.0481 |
| 100283666 | hypothetical protein LOC283666 | -1 68 | 0 0059 |
| 100200000 | hypothetical protein E00200000 | 1.00 | 0.0000 |
| HEYL | nairy/ennancer-of-split related with YRPW motif-like | -1.67 | 0.0283 |
| SERHL | serine hydrolase-like | -1.67 | 0.0073 |
| 7CCHC2 | zinc finger. CCHC domain containing 2 | -1 67 | 0.0118 |
| 10014 | and Call this set areas 4 | 1.66 | 0.0020 |
| ACU14 | acyl-coa thioesterase 4 | -1.00 | 0.0020 |
| C10orf58 | chromosome 10 open reading frame 58 | -1.66 | 0.0079 |
| CXCR6 | chemokine (C-X-C motif) receptor 6 | -1.66 | 0.0017 |
| MKLO | MKL /myocardin like 2 | 1 66 | 0.0356 |
| | | -1.00 | 0.0330 |
| OSGIN1 | oxidative stress induced growth inhibitor 1 | -1.66 | 0.0496 |
| ZNF804A | zinc finger protein 804A | -1.66 | 0.0091 |
| ARI 3 | ADP-ribosylation factor-like 3 | -1 65 | 0.0011 |
| 00422 | Abr hoosylation hadden inte o | 1.00 | 0.0011 |
| GPA33 | giycoprotein A33 (transmembrane) | -1.65 | 0.0215 |
| LOC751071 | hypothetical protein LOC751071 | -1.65 | 0.0043 |
| RNF157 | CDNA FL J36181 fis. clone TESTJ2026794 | -1.65 | 0.0176 |
| SE240 | opliging factor 20. subunit 2. GG/Do | 1.65 | 0.0075 |
| SFSAZ | Splicing lactor 5a, subulit 2, bokDa | -1.65 | 0.0075 |
| 7A5 | putative binding protein 7a5 | -1.64 | 0.0016 |
| PTPN20A | protein tyrosine phosphatase, non-receptor type 20B | -1.64 | 0.0396 |
| | Homk mothyltransforace family member 1 | 1.62 | 0.0052 |
| | | -1.05 | 0.0055 |
| PMS2L4 | postmeiotic segregation increased 2-like 4 | -1.63 | 0.0252 |
| TDRKH | tudor and KH domain containing | -1.63 | 0.0028 |
| CD248 | CD2/18 molecule endosialin | -1.62 | 0.0186 |
| 00240 | | -1.02 | 0.0100 |
| FLJ35934 | FLJ35934 protein | -1.62 | 0.0322 |
| OIP5 | Opa interacting protein 5 | -1.62 | 0.0125 |
| C5orf20 | chromosome 5 open reading frame 20 | -1 61 | 0.0312 |
| 5001120 | FL 14E004 protoin | 1.01 | 0.0012 |
| FLJ45224 | FLJ45224 protein | -1.01 | 0.0083 |
| HDAC5 | histone deacetylase 5 | -1.61 | 0.0031 |
| PDZD4 | PDZ domain containing 4 | -1.61 | 0.0231 |
| ATCOR | ATCO autophagy related 0 hamalag P (S. aarovisiaa) | 1.6 | 0.0102 |
| AIG9D | Arda autophagy related a normolog B (3. cerevisiae) | -1.0 | 0.0185 |
| CASKIN2 | CASK interacting protein 2 | -1.6 | 0.0006 |
| FBX015 | F-box protein 15 | -1.6 | 0.0250 |
| FL 137512 | similar to Contactin-associated protein-like 3 precursor (Cell | -16 | 0.0307 |
| 1031312 | | -1.0 | 0.0307 |
| | recognition molecule Caspr3) | | |
| GRAMD1B | GRAM domain containing 1B | -1.6 | 0.0112 |
| 10025845 | hypothetical LOC25845 | -16 | 0 0208 |
| 100701100 | ting finder protoin 700 | 1.0 | 0.0200 |
| LUC/91120 | Zinc linger protein 783 | -1.0 | 0.0180 |
| LRRC56 | leucine rich repeat containing 56 | -1.6 | 0.0102 |
| ZNF10 | zinc finger protein 10 | -1.6 | 0.0210 |
| C3orf39 | chromosome 3 open reading frame 39 | -1 50 | 0.0016 |
| 0001100 | Chorbert of Den reduing frame 35 | -1.55 | 0.0010 |
| CYP4V2 | Cytochrome P450, family 4, subfamily V, polypeptide 2 | -1.59 | 0.0027 |
| HEY2 | hairy/enhancer-of-split related with YRPW motif 2 | -1.59 | 0.0168 |
| PMS1 | PMS1 postmeiotic segregation increased 1 (S. cerevisiae) | -1 59 | 0.0192 |
| | tronomombrono protoin 120E | 1 50 | 0.0204 |
| TIVIEIVI132E | | -1.59 | 0.0224 |
| TRIM46 | tripartite motif-containing 46 | -1.59 | 0.0301 |
| CACNB1 | calcium channel, voltage-dependent, beta 1 subunit | -1.58 | 0.0096 |
| OBSCN | obscurin, outoskolotal calmodulin and titin interacting PhoCEE | 1 5 8 | 0.0085 |
| | | -1.50 | 0.0000 |
| ANKSO | ankyrin repeat and sterile alpha motif domain containing 6 | -1.57 | 0.0279 |
| BNIPL | BCL2/adenovirus E1B 19kD interacting protein like | -1.57 | 0.0137 |
| IAG2 | jagged 2 | -1.57 | 0.0007 |
| KDTN | kantin (actin hinding protoin) | 1 57 | 0.0245 |
| | | -1.57 | 0.0240 |
| ME3 | malic enzyme 3, NADP(+)-dependent, mitochondrial | -1.57 | 0.0172 |
| MPI | mannose phosphate isomerase | -1.57 | 0.0098 |
| RNF12 | Ring finger protein 12 | -1 57 | 0.0122 |
| | O the lost proton to the 11 member A | 4 5 0 | 0.00122 |
| ULEUTIA | U-type lectin domain family 11, member A | -1.56 | 0.0059 |
| COL23A1 | collagen, type XXIII, alpha 1 | -1.56 | 0.0188 |
| DOCK4 | dedicator of cytokinesis 4 | -1.56 | 0.0169 |
| | CTDace activating Pan / PanCAD domain like 2 | 1 56 | 0.0019 |
| GARINES | arrase activating Rap/ RandAr domain-like 3 | 0C.1- | 0.0018 |
| SPHK2 | sphingosine kinase 2 | -1.56 | 0.0170 |
| TMEM117 | transmembrane protein 117 | -1.56 | 0.0128 |
| | | | |

| ZNPcos 21.01: Inger protein bos 1.55 0.0325 CARD11 cabsse recruitment domain family, member 11 1.55 0.0428 CDL6A1 collagea 1.55 0.0248 CARD11 collagea 1.55 0.0229 H2AFY H2A histone family, member Y 1.55 0.0236 IGSFL1 transcription factor 19 (SC1) 1.55 0.0045 UBQUNL ubquilin-like 1.55 0.0011 CSord42 chromosome 5 open reading frame 42 1.54 0.00142 LIPNN1 neuronal cell adhesion molecule 1.54 0.00142 LIPNN1 patrophenologia (Drosophila) 1.54 0.0013 RASGRP3 RAS guaryl releasing protein 3 (calcium and DAG-regulated) 1.54 0.0029 RVM2 runstrelated transcription factor 2 1.54 0.0019 CSNK1E casein Misse 1, esption 1.53 0.00191 CSNK1E casein Misse 1, esption 1.53 0.0112 CSNK1E casein Misse 1, esption 1.53 0.0122 CSNK1E </th <th>7115000</th> <th>in Grade and the OOO</th> <th>4 50</th> <th>0.0005</th> | 7115000 | in Grade and the OOO | 4 50 | 0.0005 |
|---|------------------|---|-------|--------|
| CARD11 caspase recruitment domain family, member 11 -1.55 0.0076 CHD9 chromodomain helicase DNA binding protein 9 -1.55 0.0229 COLGA1 collagen, type VI, alpha 1 -1.55 0.0249 IGSF11 immunoglobulin superfamily, member 11 -1.55 0.0239 IGSF11 immunoglobulin superfamily, member 11 -1.55 0.005 UBQLNL ubiquilin-like 9.001 -1.55 0.0055 IFRG15 interferon responsive gene 15 -1.54 0.0052 MGC15705 hypothetical protein MCC15705 -1.54 0.0029 RCAM neuronal cell adhesion molecule -1.54 0.0029 RUN2 runt-related transcription factor 2 -1.54 0.0029 RUN2 runt-related transcription factor 2 -1.54 0.0029 RUN2 runt-related transcription factor 2 -1.54 0.0029 CSN41 cossen kinase 1, epsilon -1.53 0.0191 CSN41 cossen kinase 1, epsilon -1.53 0.0024 CSN41 cossen kinase 1, epsilon | ZNF668 | zinc finger protein 668 | -1.56 | 0.0325 |
| CH09 chromodomain helicase DNA binding protein 9 -1.55 0.0428 C016A1 collsgan -1.55 0.0429 H2AFY H2A histone family, member Y -1.55 0.04459 IGSF11 transcription factor 19 (SC1) -1.55 0.005 UBQLNL ubiquilin-like -1.55 0.011 C5ord42 chromosome 5 open reading frame 42 -1.54 0.0042 LPHN1 latrophilin 1 -1.54 0.0042 MGC13705 hypothetical protein MGC15705 -1.54 0.00451 NRCAM neuronal cell adhesion molecule -1.54 0.0029 USN43 ubiquitin specific peptidase 43 -1.54 0.0029 CSNK1E casein Misses 1, epsion -1.53 0.0139 CSNK1E casein Misses 0, epsion -1.53 0.0191 CSNK1E casein Misses 0, epsion -1.53 0.0192 CSNK1E casein Misses 0, epsion -1.53 0.0192 CSNK1E casein Misses 0, epsion -1.53 0.0192 DKFZP4340153 D | CARD11 | caspase recruitment domain family, member 11 | -1.55 | 0.0076 |
| COL6A1 collegen, type W, alpha 1 1.55 0.0229 H2AFY H2A histone family, member 1 1.55 0.0459 IGSF11 immunoglobulin superfamily, member 11 1.55 0.005 UBQLNL ubiquilin-like 1.55 0.005 UBQLNL ubiquilin-like 1.55 0.005 UBQLNL ubiquilin-like 1.55 0.0451 CSorf42 chromosome 5 open reading frame 42 1.54 0.0052 MGCL5705 hypothetical protein MGCL5706 1.54 0.0051 MRCAM neuronal call adhesion molecule 1.54 0.0029 PTCH1 patched homolog 1 (Drosophila) 1.54 0.0029 RUN22 runt-related transcription factor 2 1.53 0.0141 CST4 cystatin S 1.53 0.0142 CST4 <td< td=""><td>CHD9</td><td>chromodomain helicase DNA binding protein 9</td><td>-1.55</td><td>0.0428</td></td<> | CHD9 | chromodomain helicase DNA binding protein 9 | -1.55 | 0.0428 |
| M2APV H2A bitstore family, member Y 1.55 0.0459 IGSF11 immunoglobulin superfamily, member 11 1.55 0.0459 IGSF11 immanglobulin superfamily, member 11 1.55 0.005 IURQUNL 1.55 0.005 0.005 IVRG15 interferon responsive gene 15 1.54 0.0052 IVRCAM neuronal cell adhesion molecule 1.54 0.0055 NRCAM neuronal cell adhesion molecule 1.54 0.0065 PTCH1 latrophilin 1 1.154 0.0055 RASGRP3 RAS guny releasing protein 3 (calcium and DAG-regulated) 1.54 0.0029 RUNX2 uniquim specific perptidae 43 1.54 0.0029 RUNX2 uniquim specific perptidae 43 1.53 0.0135 DKF2P434C153 DKF2P434C153 0.0135 0.0135 DKF2P434C153 DKF2P434C153 0.0134 1.53 0.0032 C1Sr650 chromosome 15 open reading frame 40 1.52 0.0032 C1Sr640 chromosome 15 open reading frame 50 1.52 0.0032 | COL 641 | collagen type VI alpha 1 | -1 55 | 0 0209 |
| PLAPT PLAPT <th< td=""><td></td><td>UQA history family member V</td><td>1.55</td><td>0.0200</td></th<> | | UQA history family member V | 1.55 | 0.0200 |
| ILSN11 immunoglobulin superformity, member 11 1.55 0.00236 UEQLNL ubiquilin-like 1.55 0.005 UEQLNL ubiquilin-like 1.55 0.005 UEQLNL ubiquilin-like 1.55 0.0055 IFRG15 interferon responsive gene 15 1.54 0.00252 MGC15705 hypothetical protein MGC15705 1.54 0.0025 MRCAM neuronal cell adhesion molecule 1.54 0.0029 RASGRP3 RAS guany releasing protein 3 (aclicum and DAG-regulated) 1.54 0.0029 RUNX2 runt-related transcription factor 2 1.54 0.0027 CSN41E casein kinase 1, epsilon 1.53 0.0191 CSN41E casein kinase 1, epsilon 1.53 0.0022 CSN41E casein kinase 1, epsilon 1.53 0.0034 CGST4 cystatin 5 1.53 0.0034 CGST4 cystatin 5 1.53 0.0034 CGST4 cystatin 5 1.52 0.0017 CGST4 cystatin 5 1.52 </td <td></td> <td>HZA historie family, member Y</td> <td>-1.55</td> <td>0.0459</td> | | HZA historie family, member Y | -1.55 | 0.0459 |
| TCF19 transcription factor 19 (SC1) -1.55 0.005 USQUN ubiquilin-like -1.55 0.0101 CSorf42 chromosome 5 open reading frame 42 -1.54 0.0055 IFRG15 interform responsive gene 15 -1.54 0.00142 LPHN1 latrophilin 1 -1.54 0.0052 MGC15705 hypothetical protein MGC15705 -1.54 0.0057 TCCH1 patchetical protein MGC15705 -1.54 0.0029 RUNX2 runt-related transcription factor 2 -1.54 0.0029 USP43 ubiquitin specific peptidase 43 -1.53 0.0191 CSIA1E caster insea 1, epsion -1.53 0.0191 CSIA4 cystatin S -1.53 0.0191 DK72P434C153 DK72P434C153 DK72P434C153 0.0022 DK72P434C153 DK72P434C153 OK72P434C153 0.0032 LOG388963 similar to short-chain dehydrogenase/reductase 1 -1.53 0.0032 CSorf50 chromosome 15 open reading frame 40 -1.52 0.0025 < | IGSF11 | immunoglobulin superfamily, member 11 | -1.55 | 0.0236 |
| UBQUNL ubiquini-like -1.55 0.0101 CSorf42 chromosome 5 open reading frame 42 -1.54 0.0055 IFRG15 interferon responsive gene 15 -1.54 0.0065 MGCL5705 hypothetical protein MGC15705 -1.54 0.0065 MGCL15705 hypothetical protein MGC15705 -1.54 0.0075 PTCH1 patched homolog 1 (Drosophila) -1.54 0.0029 RUXX2 runt-related transcription factor 2 -1.54 0.0029 RUXX2 runt-related transcription factor 2 -1.54 0.0029 RUXX2 runt-related transcription factor 2 -1.54 0.0021 CSIK41E casinin Kinase 1, epsion -1.53 0.0131 CSIK41E casinin Kinase 1, epsion -1.53 0.0022 EDI.3 EGF-like repeats and discolin Hilke domains 3 -1.53 0.0032 EDI.4 floroblast growth factor receptor 4 -1.53 0.0022 C2or40 chromosome 2 open reading frame 40 -1.52 0.0227 C15r65 chromosome 2 open reading frame 50 -1 | TCF19 | transcription factor 19 (SC1) | -1.55 | 0.005 |
| CSort42 .154 0.0055 IFRGL5 .154 0.0042 IPRN1 latrophilin 1 .154 0.0042 MGC15705 hypothetical protein MGC15705 .154 0.0055 MGC15705 hypothetical protein MGC15705 .154 0.0057 RASGRP3 RASgumy releasing protein 3 (calcium and DAG-regulated) .154 0.0029 RUNX2 runt-related transcription factor 2 .154 0.0029 RUNX2 runt-related transcription factor 2 .154 0.0029 RUNX2 runt-related transcription factor 2 .153 0.0195 CSNK1E casein kinase 1, epsilon .153 0.0314 CSNK1E casein kinase 1, epsilon .153 0.0321 DKEZP434C153 DKEZP434C153 DKEZP434C153 0.00321 CC3R686 similar to short-chain dehydrogenase/reductase 1 .153 0.00321 C15orf50 chromosome 2 open reading frame 50 .152 0.0179 C2ord40 chromosome 1 open reading frame 40 .152 0.0022 PRR6 Pol | UBOLNI | ubiquilin-like | -1.55 | 0.0101 |
| Contra2 Chronosome 30 pain reading ratine 92 1.54 0.0013 IFR015 interform responsive gene 15 1.54 0.0052 LPNN1 latrophilin 1 1.54 0.0052 NRCAM neuronal cell adhesion molecule 1.54 0.0055 PTCH1 patched homolog 1 (Drosophila) 1.54 0.0029 RUNX2 runt-related transcription factor 2 1.54 0.0029 USP43 ubiquitin specific peptidase 43 1.53 0.0019 CST4 cystatin S 1.53 0.0191 CST4 cystatin S 1.53 0.0191 DKF2P434CL53 DKF2P434CL53 protein 1.53 0.0032 EDL3 EGF-like repeats and discolidn-like domains 3 1.53 0.0032 LOC388963 similar to short-chain dehydrogenase/reductase 1 1.53 0.0032 C15orf50 chronosome 2 open reading frame 50 1.52 0.0022 C2orf40 chronosome 1 open reading frame 50 1.52 0.0022 CATA GATA binding protein 3 1.52 0.0022 | CEorf42 | chromosomo 5 open reading frame 42 | 1.57 | 0.0055 |
| Interferon 1.54 0.0142 LPHN1 interferon responsive gene 10 1.54 0.0052 MGCL5705 hypothetical protein MGC15705 1.54 0.0055 MRCAM neuronal cell adhesion molecule 1.54 0.0029 RMSQR RASGRPS RAS guny releasing protein 3 (calcium and DAG-regulated) 1.54 0.0029 RUNX2 runt-related transcription factor 2 1.54 0.0027 RUNX2 runt-related transcription factor 2 1.54 0.0027 CSNK1E casein kinase 1, epsilon 1.53 0.0136 CSNK1E casein kinase 1, epsilon 1.53 0.0034 CSRF4 Gibrobiast growth factor receptor 4 1.53 0.0034 LOG388963 similar to short-chein dehydrogenase/reductase 1 1.52 0.0032 CL5orf50 chromosome 12 open reading frame 40 1.52 0.0032 CL5orf50 chromosome 2 open reading frame 40 1.52 0.0034 SPON1 spondin 1, extracellular matrix protein 1.52 0.0032 CL5orf50 chromosome 12 open reading frame | | | -1.54 | 0.0000 |
| LPHN1 istrophilin 1 .1.54 0.0052 MGC15705 hypothetical protein MGC15705 .1.54 0.00451 NRCAM neuronal cell adhesion molecule .1.54 0.00451 PTCH1 patched homolog 1 (Drosophila) .1.54 0.0029 RMSQRP3 RAS guaryl releasing protein 3 (calcium and DAG-regulated) 1.54 0.0029 USP43 ubiquitin specific peptidase 43 .1.53 0.00191 CSTM casenik mase 1, epsilon .1.53 0.0022 CSTA cystatin 5 .1.53 0.0024 COS38903 similar to short-chain dehydrogenase/reductase 1 .1.53 0.00341 LO389903 similar to short-chain dehydrogenase/reductase 1 .1.53 0.0032 C15orf50 chromosome 2 open reading frame 50 .1.52 0.0227 FGFR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, .1.52 0.0022 CPr40 chromosome 2 open reading frame 50 .1.52 0.0227 GATA binding protein 3 .1.52 0.0314 SPON1 spondin 1, extracellular matrix protein | IFRG15 | Interferon responsive gene 15 | -1.54 | 0.0142 |
| MGCL3705 hypothetical protein MGCL3705 1.54 0.0451 NRCAM neuronal cell adhesion molecule 1.54 0.0055 PTCH1 patched homolg 1 (Drosophila) 1.54 0.0029 RASGRP3 RAS guary releasing protein 3 (calcum and DAG-regulated) 1.54 0.0029 RUNX2 runt-related transcription factor 2 1.54 0.0057 CSNK1E casein kinase 1, epsilon 1.53 0.0195 CST44 cystatin 5 1.53 0.0195 DKFZP434C153 DKFZP434C153 protein 1.53 0.0321 EDL3 EGF-like repeats and discodin kike domains 3 1.53 0.0341 C15orf50 chromosome 15 open reading frame 50 1.52 0.0179 C2ord40 chromosome 2 open reading frame 40 1.52 0.0022 CRTA3 GATA binding protein 3 1.52 0.0022 PRR6 Proline rich 6 1.52 0.0021 SPON1 spondin 1, extracellular matrix protein 1.51 0.0404 MCOLN3 mucolipin 3 1.51 0.0404 | LPHN1 | latrophilin 1 | -1.54 | 0.0052 |
| INFCM neuronal cell adhesion molecule 1.54 0.0055 PTCH1 patched homolog 1 (Drosophila) 1.54 0.019 RASGRP3 RAS guanyl releasing protein 3 (calcium and DAG-regulated) 1.54 0.0029 RUNX2 runt-related transcription factor 2 1.54 0.0087 RUNX2 runt-related transcription factor 2 1.54 0.0087 CSNK1E casein kinase 1, epsilon 1.53 0.0195 CSNK1E casein kinase 1, epsilon 1.53 0.0022 DKZPP434C153 DKFZP434C153 protein 1.53 0.0022 CISA cystatin 6 discoldin Hilke domains 3 1.53 0.0032 C1Sorf50 chromosome 15 open reading frame 50 1.52 0.0179 C2orl40 chromosome 2 open reading frame 40 1.52 0.022 FGR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, to.025 1.52 0.0179 C2orl40 chromosome 15 open reading frame 40 1.52 0.022 FRR6 Proline rich 6 1.52 0.022 PRR6 Proline rich 6 | MGC15705 | hypothetical protein MGC15705 | -1.54 | 0.0451 |
| International induction of the second of the seco | NRCAM | | -1 5/ | 0.0055 |
| Prich1 patched infinition patched infinition patched infinition patched infinition RASGRP3 RASGRP3 <td>DTCU1</td> <td>netched hemales 1 (Dresenbile)</td> <td>1 5 4</td> <td>0.0000</td> | DTCU1 | netched hemales 1 (Dresenbile) | 1 5 4 | 0.0000 |
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| RUNX2 runt-related transcription factor 2 1.54 0.0089 USP43 ubiquitn specific peptidase 43 -1.54 0.0057 CSNM1E caseim kinase 1, epsilon -1.53 0.0191 DKFZP434C153 DKFZP434C153 protein -1.53 0.0022 EDL13 EGF-like repeats and discoldin Hilke domains 3 -1.53 0.00341 L00388963 similar to short-chain dehydrogenase/reductase 1 -1.53 0.0032 C15orf50 chromosome 15 open reading frame 50 -1.52 0.0179 C2orf40 chromosome 2 open reading frame 40 -1.52 0.0022 GATA GATA binding protein 3 -1.52 0.0022 FGFR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, -1.52 0.0021 PRR6 Proline rich 6 -1.52 0.0022 SPON1 spondin 1, extracellular matrix protein -1.52 0.0042 PPP1R13L protecadherin 7 -1.51 0.0134 SL224A1 solute carrier family 24 (sodium/potassium/calcium exchanger), -1.51 0.0332 DMPK dystrophia myotonica-prote | RASGRP3 | RAS guanyl releasing protein 3 (calcium and DAG-regulated) | -1.54 | 0.0029 |
| USP43 ubiquitin specific peptidase 43 1.54 0.0057 CSNM1E casein kinase 1, epsilon 1.53 0.0195 CST4 cystatin S 1.53 0.0022 DMFZP434C153 DKFZP434C153 protein 1.53 0.0034 FGFR4 fibroblast growth factor receptor 4 1.53 0.0032 LOC3889663 similar to short-chain dehydrogenase/reductase 1 1.53 0.0032 C15orf50 chromosome 15 open reading frame 50 1.52 0.0179 C2ori40 chromosome 15 open reading frame 40 1.52 0.0257 FGFR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, | RUNX2 | runt-related transcription factor 2 | -1.54 | 0.0089 |
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| CSI4L Costen knikes L, Epsilon -1.53 0.0131 CSI4L Costen knikes L, Epsilon -1.53 0.0131 DKFZP434C153 DKFZP434C153 protein -1.53 0.0022 EDIL3 EGF-like repeats and discoidin Hike domains 3 -1.53 0.00341 FGFR4 fibroblast growth factor receptor 4 -1.53 0.0032 LOC388963 smilia to short-chain dehydrogenase/reductase 1 -1.53 0.0032 C15orf50 chromosome 15 open reading frame 40 -1.52 0.0179 C2orf40 chromosome 2 open reading frame 40 -1.52 0.0021 FGFR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, -1.52 0.0021 PR6R6 Proline rich 6 -1.52 0.0025 CATA3 GATA binding protein 3 -1.51 0.0404 MCOLN3 mucolipin 3 -1.51 0.0404 MCOLN3 mucolipin 3 -1.51 0.0322 CATA14 protocatherin 7 protocatherin 7 1.51 0.0332 PPE1R12 protocatherin 7 protocatherin 7 | | ascoin kinaco 1. oncilon | 1 5 2 | 0.0101 |
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| EDL3 EGF-like repeats and discoldin Hike domains 3 -1.53 0.0341 FGFR4 fibroblast growth factor receptor 4 -1.53 0.0189 LOC388963 similar to short-chain dehydrogenase/reductase 1 -1.53 0.0094 NOS3 nitric oxide synthase 3 (endothelial cell) -1.52 0.0179 C25orf50 chromosome 12 open reading frame 50 -1.52 0.0179 C2orf40 chromosome 2 open reading frame 40 -1.52 0.0021 C3743 GATA binding protein 3 -1.52 0.0022 PRR6 Proline rich 6 -1.52 0.0014 SP0N1 spondin 1, extracellular matrix protein -1.51 0.0015 PCDH7 protocacherin 7 -1.51 0.0134 SLC24A1 solute carrier family 24 (sodium/potassium/calcium exchanger), -1.51 0.0332 Member 1 -1.51 0.0344 SLC24A1 solute carrier family 24 (sodium/potassium/calcium exchanger), -1.51 0.0392 SNRP70 small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) -1.51 0.0373 DCST2 DC-STAMP domain containi | DKFZP434C153 | DKFZP434C153 protein | -1.53 | 0.0022 |
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| Horva Horva by the factor feedpulor 4 1.153 0.01189 LOC388963 similar to short-chain dehydrogenase/reductase 1 1.153 0.0032 CLSorf50 chromosome 15 open reading frame 50 1.52 0.0179 C2orf40 chromosome 2 open reading frame 40 1.52 0.0227 FGFR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, 1.52 0.0022 PRR6 Proline rich 6 1.52 0.0022 PRR6 Proline rich 6 1.52 0.0025 CACHD1 cache domain containing 1 -1.51 0.0404 MCOLN3 mucolipin 3 -1.51 0.0404 MCOLN3 mucolipin 3 -1.51 0.0022 PPP1R13L protice in phosphatase 1, regulatory (inhibitor) subunit 13 like -1.51 0.0332 SNRP70 small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) -1.51 0.0392 ATP13A4 ATPase type 13A4 -1.5 0.0374 DCST2 DCSTAWP domain containing 2 -1.5 0.0374 DMPK dystrophia myotonica-protein kinase < | ECER/ | fibrablact growth factor recentor 4 | 1 5 2 | 0.0190 |
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| NOS3 nitric oxide synthase 3 (endothelial cell) -1.52 0.0032 CL5orf50 chromosome 15 open reading frame 50 -1.52 0.0179 C2orf40 chromosome 2 open reading frame 40 -1.52 0.0257 FGFR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Prefifer syndrome) -1.52 0.0022 GATA3 GATA binding protein 3 -1.52 0.0021 SPR6 Proline rich 6 -1.52 0.0021 CACHD1 cache domain containing 1 -1.51 0.0404 MCOLN3 mucolipin 3 -1.51 0.0404 MCOLN3 mucolipin 3 -1.51 0.0115 SUC24A1 protein phosphatase 1, regulatory (inhibitor) subunit 13 like -1.51 0.0322 SNRP70 small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) -1.51 0.0324 SNRP70 small nuclear rNA activating complex, polypeptide 4, 190kDa -1.5 0.0274 INADL InaD-like (Drosophila) -1.5 0.0372 DMPK dystrophia myotonica-protein 4 1.5 0.0372 GL1A4 | L0C388963 | similar to short-chain dehydrogenase/reductase 1 | -1.53 | 0.0094 |
| C150rf50 chromosome 15 open reading frame 50 1.52 0.0179 C2orf40 chromosome 2 open reading frame 40 -1.52 0.0257 FGFR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, PR6 -1.52 0.0021 GATA3 GATA binding protein 3 -1.52 0.0025 CACHD1 cache domain containing 1 -1.52 0.0025 CACHD1 cache domain containing 1 -1.51 0.0149 MCOLN3 mucolipin 3 -1.51 0.0149 PPDH7 protocadherin 7 -1.51 0.0134 SL2Z4A1 solute carrier family 24 (sodium/potassium/calcium exchanger), member 1 -1.51 0.0392 SNR7O small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) -1.51 0.0392 ATP13A4 ATPase type 13A4 -1.5 0.0274 DVPK dystrophia myotonica-protein kinase -1.5 0.0274 INADL Inab-like (Drosophila) -1.5 0.0372 SNAPC4 small nuclear RNA activating complex, polypeptide 4, 190kDa -1.5 0.0372 GOLM4 | NOS3 | nitric oxide synthase 3 (endothelial cell) | -1.53 | 0.0032 |
| C2orf40 chromosome 2 open reading frame 40 -1.52 0.0257 FGFR1 fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Prefiffer syndrome) -1.52 0.0022 GATA3 GATA binding protein 3 -1.52 0.0022 PRR6 Proline rich 6 -1.52 0.0022 GATA3 GATA binding protein 3 -1.52 0.0022 GACHD1 cache domain containing 1 -1.51 0.0404 MCOLN3 mucolipin 3 -1.51 0.0042 PPP1R13L protein phosphatase 1, regulatory (inhibitor) subunit 13 like -1.51 0.0332 SURP70 small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) -1.51 0.0392 ATP13A4 ATPase type 13A4 -1.5 0.0173 0.0394 DMPK dystrophia myotonica-protein kinase -1.5 0.0275 TMEM182 transmembrane protein 182 -1.5 0.0372 GOLM4 golg integral membrane protein 4 1.5 0.0372 GOLM4 golg integral membrane protein 1 1.5 0.0372 GATA9 | C15orf50 | chromosome 15 open reading frame 50 | -1.52 | 0.0179 |
| Description Constants 2 properties of the constant of the second stress of | C_{2} orf 40 | chromosome 2 open reading frame 10 | -1.52 | 0.0257 |
| Freikfild Thoronalist growth factor receptor 1 (tms-felated tyrosine kinase 2, 1.52 0.0131 GATA3 GATA binding protein 3 -1.52 0.0022 PRR6 Proline rich 6 -1.52 0.0021 SP0N1 spondin 1, extracellular matrix protein -1.52 0.0022 CACHD1 cache domain containing 1 -1.51 0.0404 MC0LN3 mucolipin 3 -1.51 0.0115 PCDH7 protecadherin 7 -1.51 0.0134 SLC24A1 solute carrier family 24 (sodium/potassium/calcium exchanger), -1.51 0.0332 member 1 - - - SNRP70 small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) -1.51 0.0392 ATP13A4 ATPase type 13A4 -1.5 0.0204 - DCST2 DC STAMP domain containing 2 -1.5 0.0275 DMFK dystrophia myotonica-protein kinase -1.5 0.0394 SNAPC4 small nuclear RNA activating complex, polypeptide 4, 190kDa -1.5 0.0372 GOLM4 golgi integral membrane protein 1 1.5 | 6201140 | Chronicsome 2 open reduing name 40 | -1.52 | 0.0207 |
| Preiffer syndrome) 1.52 0.0022 PRR6 Proline rich 6 -1.52 0.0314 SP0N1 spontin 1, extracellular matrix protein -1.52 0.0025 CACHD1 cache domain containing 1 -1.51 0.0404 MCOLN3 mucolipin 3 -1.51 0.0404 MCOLN3 mucolipin 4 -1.51 0.0115 PCDH7 protein phosphatase 1, regulatory (inhibitor) subunit 13 like -1.51 0.0134 SLC24A1 solute carrier family 24 (sodium/potassium/calcium exchanger), -1.51 0.0392 ATP13A4 ATPase type 13A4 -1.5 0.0369 DCST2 DC-STAMP domain containing 2 -1.5 0.0173 DMPK dystrophia myotonica-protein kinase -1.5 0.0394 SNAP70 small nuclear RNA activating complex, polypeptide 4, 190kDa -1.5 0.0372 INEM182 transmembrane protein 1 1.5 0.0372 GOLM1 golgi imethorane protein 1 1.5 0.0372 GOLM4 golgi membrane protein 1 1.51 0.0066 | FGFR1 | fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, | -1.52 | 0.0131 |
| GATA3 GATA binding protein 3 -1.52 0.0022 PRR6 Proline rich 6 -1.52 0.0314 SPON1 spondin 1, extracellular matrix protein -1.52 0.0025 CACHD1 cache domain containing 1 -1.51 0.0044 MCOLN3 mucolipin 3 -1.51 0.0115 PCDH7 protocaldherin 7 -1.51 0.0042 PPPR131 protein phosphatase 1, regulatory (inhibitor) subunit 13 like -1.51 0.0032 SLC24A1 solute carrier family 24 (sodium/potassium/calcium exchanger), member 1 -1.51 0.0332 SNRP70 small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) -1.51 0.0369 DCST2 DC-STAMP domain containing 2 -1.5 0.0173 DMPK dystrophia myotonica-protein kinase -1.5 0.0204 INADL InaD-like (Drosophila) -1.5 0.0372 GOLM1 golgi integral membrane protein 4 1.5 0.0372 GOLM1 golgi integral membrane protein 1 1.5 0.0203 TMEM182 transmebrane protein 1 | | Pfeiffer syndrome) | | |
| PRR6 Proline rich 6 1.52 0.0314 SP0N1 spontin 1, extracellular matrix protein 1.52 0.0025 CACHD1 cache domain containing 1 1.51 0.0404 MCOLN3 mucolipin 3 1.51 0.0115 PCDH7 protocadherin 7 1.51 0.0134 SLC24A1 solute carrier family 24 (sodium/potassium/calcium exchanger), member 1 1.51 0.0332 SNRP70 small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) 1.51 0.0392 ATP13A4 ATPase type 13A4 -1.5 0.0173 DMPK dystrophia myotonica-protein kinase -1.5 0.0394 SNAPC4 small nuclear RNA activating complex, polypeptide 4, 190kDa 1.5 0.0372 GOLM4 golgi integral membrane protein 1 1.5 0.0372 GOLM4 golgi integral membrane protein 1 1.5 0.0273 TGM4 transglutaminase 4 (prostate) 1.51 0.0185 ADAM3A ADAM metallopeptidase domain 3A (cyritestin 1) 1.51 0.0185 BCAS1 breast carcinoma amplifi | GATA3 | GATA binding protein 3 | -1.52 | 0.0022 |
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| MCOLN3 mucolipin 3 -1.51 0.0115 PCDH7 protocadherin 7 -1.51 0.0042 PPP1R13L protein phosphatase 1, regulatory (inhibitor) subunit 13 like -1.51 0.0134 SLC24A1 solute carrier family 24 (sodium/potassium/calcium exchanger), member 1 -1.51 0.0332 SNRP70 small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen) -1.51 0.0369 DCST2 DC-STAMP domain containing 2 -1.5 0.0173 DMPK dystrophia myotonica-protein kinase -1.5 0.0204 INADL InaD-like (Drosophila) -1.5 0.0334 SNAPC4 small nuclear RNA activating complex, polypeptide 4, 190kDa -1.5 0.0372 GOLIM4 golgi integral membrane protein 1 1.5 0.0372 GOLM1 golgi integral membrane protein 1 1.5 0.0253 TGM4 transglutaminase 4 (prostate) 1.51 0.0111 ADAM metallopeptidase domain 3A (cyritestin 1) 1.51 0.0266 HIST1H2BG histone cluster 1, H2bg 1.51 0.00266 HIST1H2BG | CACHD1 | cache domain containing 1 | -1.51 | 0.0404 |
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| PDP1R13Lprotein phosphatase 1, regulatory (inhibitor) subunit 13 like1.510.0134SLC24A1solute carrier family 24 (sodium/potassium/calcium exchanger), member 1-1.510.0332SNRP70small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen)-1.510.0392ATP13A4ATPase type 13A4-1.50.0369DCST2DC-STAMP domain containing 2-1.50.0173DMPKdystrophia myotonica-protein kinase-1.50.0204INADLInaD-like (Drosophila)-1.50.0346SNAPC4small nuclear RNA activating complex, polypeptide 4, 190kDa-1.50.0346GOLIM4golgi integral membrane protein 11.50.0372GOLM1golgi integral membrane protein 41.50.0185BCAS1breast carcinoma amplified sequence 11.510.0185BCAS1breast carcinoma amplified sequence 11.510.0026HIST1H2BGhistone cluster 1, H2bg1.510.0026MGC13005hypothetical protein NGC130051.510.0026MGC13005hypothetical protein NGC130051.510.0026MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.540.0229HUS1HUS1 checkpoint homolg b (S. pombe)1.540.0229HUS1HUS1 checkpoint homolg b (S. pombe)1.540.0259MIPOL1mirror-image polydactyly 11.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227 | PCDH7 | nrotocadherin 7 | -1 51 | 0 0042 |
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| DMPKdystrophia myotonica-protein kinase-1.50.0204INADLInaD-like (Drosophila)-1.50.0394SNAPC4small nuclear RNA activating complex, polypeptide 4, 190kDa-1.50.0075TMEM182transmembrane protein 182-1.50.0346GOLIM4golgi integral membrane protein 41.50.0372GOLM1golgi membrane protein 11.50.0253TGM4transglutaminase 4 (prostate)1.50.0011ADAM3AADAM metallopeptidase domain 3A (cyritestin 1)1.510.0185BCAS1breast carcinoma amplified sequence 11.510.0066HIST1H2BGhistone cluster 1, H2bg1.510.0006MGC13005hypothetical protein MGC130051.510.0066KBTBD2kelch repeat and BTB (POZ) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234WNK13WNK lysine deficient protein kinase 31.560.0234 | DCS12 | DC-STAMP domain containing 2 | -1.5 | 0.0173 |
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| SNAPC4small nuclear RNA activating complex, polypeptide 4, 190kDa-1.50.0075TMEM182transmembrane protein 182-1.50.0346GOLIM4golgi integral membrane protein 41.50.0372GOLM1golgi membrane protein 11.50.0253TGM4transglutaminase 4 (prostate)1.50.0011ADAM3AADAM metallopeptidase domain 3A (cyritestin 1)1.510.0185BCAS1breast carcinoma amplified sequence 11.510.0056HIST1H2BGhistone cluster 1, H2bg1.510.0056MGC13005hypothetical protein MGC130051.510.0056KBTBD2kelch repeat and BTB (POZ) domain containing 21.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0227SAMD5WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | INADI | InaD-like (Drosophila) | -1.5 | 0.0394 |
| Sintain Hotelar Niva activating complex, polybeptide 4, 150Aba1.50.0013TMEM182transmembrane protein 182-1.50.0346GOLIM4golgi integral membrane protein 11.50.0372GOLM1golgi membrane protein 11.50.0253TGM4transglutaminase 4 (prostate)1.50.0011ADAM3AADAM metallopeptidase domain 3A (cyritestin 1)1.510.0185BCAS1breast carcinoma amplified sequence 11.510.0066HIST1H2BGhistone cluster 1, H2bg1.510.0056MGC13005hypothetical protein MGC130051.510.0056KBTBD2kelch repeat and BTB (PO2) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0192MIPOL1mirror-image polydactyly 11.550.0211LOC728142hypothetical protein LOC7281421.550.0021PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | SNAPC4 | small nuclear RNA activating complex networtide 4, 190kDa | 15 | 0.0075 |
| IMEM182 transmembrane protein 182 -1.5 0.0346 GOLIM4 golgi integral membrane protein 4 1.5 0.0372 GOLM1 golgi membrane protein 1 1.5 0.0253 TGM4 transglutaminase 4 (prostate) 1.5 0.0011 ADAM3A ADAM metallopeptidase domain 3A (cyritestin 1) 1.51 0.0185 BCAS1 breast carcinoma amplified sequence 1 1.51 0.0066 HIST1H2BG histone cluster 1, H2bg 1.51 0.0026 MGC13005 hypothetical protein MGC13005 1.51 0.0034 MUC20 Mucin 20, cell surface associated 1.52 0.0034 MUC20 Mucin 20, cell surface associated 1.54 0.0259 HUS1 E2F1 E2F transcription factor 1 1.54 0.0259 CENPN centromere protein N 1.54 0.0192 HUS1 checkpoint homolog b (S. pombe) 1.54 0.0192 MIPOL1 mirror-image polydactyly 1 1.55 0.0211 LOC728142 hypothetical protein LOC728142 1.55 0.0227 PAPD phosphatidic acid phosphatase type 2 <t< td=""><td></td><td></td><td>-1.5</td><td>0.0075</td></t<> | | | -1.5 | 0.0075 |
| GOLIM4golgi integral membrane protein 41.50.0372GOLM1golgi membrane protein 11.50.0253TGM4transglutaminase 4 (prostate)1.50.0011ADAM3AADAM metallopeptidase domain 3A (cyritestin 1)1.510.0185BCAS1breast carcinoma amplified sequence 11.510.0066HIST1H2BGhistone cluster 1, H2bg1.510.0056MGC13005hypothetical protein MGC130051.510.0056KBTBD2kelch repeat and BTB (POZ) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.560.0227PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | IMEM182 | transmembrane protein 182 | -1.5 | 0.0346 |
| GOLM1golgi membrane protein 11.50.0253TGM4transglutaminase 4 (prostate)1.50.0011ADAM3AADAM metallopeptidase domain 3A (cyritestin 1)1.510.0185BCAS1breast carcinoma amplified sequence 11.510.0066HIST1H2BGhistone cluster 1, H2bg1.510.0206MGC13005hypothetical protein MGC130051.510.0056KBTBD2kelch repeat and BTB (POZ) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactlyl 11.550.0211LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0227LAPTM4Bhypothetical protein LOC7281421.560.0227PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | GOLIM4 | golgi integral membrane protein 4 | 1.5 | 0.0372 |
| TGM4transglutaminase 4 (prostate)1.50.0011ADAM3AADAM metallopeptidase domain 3A (cyritestin 1)1.510.0185BCAS1breast carcinoma amplified sequence 11.510.0066HIST1H2BGhistone cluster 1, H2bg1.510.0206MGC13005hypothetical protein MGC130051.510.0056KBTBD2kelch repeat and BTB (POZ) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.560.0227PAP2Dphosphatidic acid phosphatase type 21.560.0492WNK3WNK lysine deficient protein kinase 31.560.0224PAPPApregnancy-associated protein A, pappalysin 11.570.0023 | GOLM1 | golgi membrane protein 1 | 1.5 | 0.0253 |
| ADAM3AADAM metallopeptidase domain 3A (cyritestin 1)1.510.0011BCAS1breast carcinoma amplified sequence 11.510.0185BCAS1breast carcinoma amplified sequence 11.510.0066HIST1H2BGhistone cluster 1, H2bg1.510.0206MGC13005hypothetical protein MGC130051.510.0056KBTBD2kelch repeat and BTB (POZ) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.560.0227PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | TGM4 | transolutaminase 4 (prostate) | 15 | 0.0011 |
| ADAM/SAADAM metallopeptidase domain SA (cyntestin 1)1.510.0185BCAS1breast carcinoma amplified sequence 11.510.0066HIST1H2BGhistone cluster 1, H2bg1.510.0206MGC13005hypothetical protein MGC130051.510.0056KBTBD2kelch repeat and BTB (POZ) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.550.0211LOC728142hypothetical protein LOC7281421.550.0027PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | | ΔDAM motollenentidene demoin $2A$ (suritantia 1) | 1.5 | 0.0011 |
| BCAS1breast carcinoma amplified sequence 11.510.0066HIST1H2BGhistone cluster 1, H2bg1.510.0206MGC13005hypothetical protein MGC130051.510.0056KBTBD2kelch repeat and BTB (POZ) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | ADAM3A | ADAM metallopeptidase domain 3A (cyritestin 1) | 1.51 | 0.0185 |
| HIST1H2BG histone cluster 1, H2bg 1.51 0.0206 MGC13005 hypothetical protein MGC13005 1.51 0.0056 KBTBD2 kelch repeat and BTB (POZ) domain containing 2 1.52 0.0034 MUC20 Mucin 20, cell surface associated 1.52 0.0142 E2F1 E2F transcription factor 1 1.53 0.0431 CENPN centromere protein N 1.54 0.0259 HUS1B HUS1 checkpoint homolog b (S. pombe) 1.54 0.0192 LAPTM4B lysosomal associated protein transmembrane 4 beta 1.55 0.0211 LOC728142 hypothetical protein LOC728142 1.56 0.0227 PAP2D phosphatidic acid phosphatase type 2 1.56 0.0227 SAMD5 sterile alpha motif domain containing 5 1.56 0.0234 WNK3 WNK lysine deficient protein kinase 3 1.56 0.0234 PAPPA pregnancy-associated plasma protein A, pappalysin 1 1.57 0.0023 | BCAS1 | breast carcinoma amplified sequence 1 | 1.51 | 0.0066 |
| MGC13005 hypothetical protein MGC13005 1.51 0.0056 KBTBD2 kelch repeat and BTB (POZ) domain containing 2 1.52 0.0034 MUC20 Mucin 20, cell surface associated 1.52 0.0142 E2F1 E2F transcription factor 1 1.53 0.0431 CENPN centromere protein N 1.54 0.0259 HUS1B HUS1 checkpoint homolog b (S. pombe) 1.54 0.0192 LAPTM4B lysosomal associated protein transmembrane 4 beta 1.55 0.0211 LOC728142 hypothetical protein LOC728142 1.56 0.0227 SAMD5 sterile alpha motif domain containing 5 1.56 0.0234 WNK3 WNK lysine deficient protein kinase 3 1.56 0.0234 PAPPA pregnancy-associated plasma protein A, pappalysin 1 1.57 0.0023 | HIST1H2BG | histone cluster 1, H2bg | 1.51 | 0.0206 |
| KBTBD2kelch repeat and BTB (PO2) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.560.0227PAP2Dphosphatidic acid phosphatase type 21.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | MGC13005 | hypothetical protein MGC13005 | 1 51 | 0.0056 |
| KBTBD2Keich repeat and BTB (PO2) domain containing 21.520.0034MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | KRTRD2 | keleb repeat and BTB (DOZ) domain containing 2 | 1 5 0 | 0.0000 |
| MUC20Mucin 20, cell surface associated1.520.0142E2F1E2F transcription factor 11.530.0431CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.550.0211LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0234WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | KDIDD2 | keich repeat and BTB (POZ) domain containing 2 | 1.52 | 0.0034 |
| E2F1 E2F transcription factor 1 1.53 0.0431 CENPN centromere protein N 1.54 0.0259 HUS1B HUS1 checkpoint homolog b (S. pombe) 1.54 0.0096 MIPOL1 mirror-image polydactyly 1 1.54 0.0192 LAPTM4B lysosomal associated protein transmembrane 4 beta 1.55 0.0211 LOC728142 hypothetical protein LOC728142 1.55 0.0059 PAP2D phosphatidic acid phosphatase type 2 1.56 0.0227 SAMD5 sterile alpha motif domain containing 5 1.56 0.0234 WNK3 WNK lysine deficient protein kinase 3 1.56 0.0234 PAPPA pregnancy-associated plasma protein A, pappalysin 1 1.57 0.0023 | MUC20 | Mucin 20, cell surface associated | 1.52 | 0.0142 |
| CENPNcentromere protein N1.540.0259HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | E2F1 | E2F transcription factor 1 | 1.53 | 0.0431 |
| HUS1BHUS1 checkpoint homolog b (S. pombe)1.540.0096MIPOL1mirror-image polydactyly 11.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | CENPN | centromere protein N | 1.54 | 0.0259 |
| MIPOL1mirror-image polydactyly 11.540.0096LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | | HUS1 checknoint homolog h (S. nombo) | 1 54 | 0.0006 |
| MIPOL1mirror-image polydactyly 11.540.0192LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | | nust checkpoint nomolog b (S. poinbe) | 1.54 | 0.0090 |
| LAPTM4Blysosomal associated protein transmembrane 4 beta1.550.0211LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalvsin 11.570.0023 | MIPOL1 | mirror-image polydactyly 1 | 1.54 | 0.0192 |
| LOC728142hypothetical protein LOC7281421.550.0059PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | LAPTM4B | lysosomal associated protein transmembrane 4 beta | 1.55 | 0.0211 |
| PAP2Dphosphatidic acid phosphatase type 21.560.0227SAMD5sterile alpha motif domain containing 51.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | L0C728142 | hypothetical protein LOC728142 | 1.55 | 0.0059 |
| SAMD5sterile alpha motif domain containing 51.560.0227WNK3WNK lysine deficient protein kinase 31.560.0492PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | | nhoenhatidic acid nhoenhataea type 2 | 1 56 | 0.0227 |
| SAIVUSSterile alpha motif domain containing 51.560.0492WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | | | 1.50 | 0.0221 |
| WNK3WNK lysine deficient protein kinase 31.560.0234PAPPApregnancy-associated plasma protein A, pappalysin 11.570.0023 | SAMDS | sterile alpha motif domain containing 5 | 1.56 | 0.0492 |
| PAPPA pregnancy-associated plasma protein A, pappalvsin 1 1.57 0.0023 | WNK3 | WNK lysine deficient protein kinase 3 | 1.56 | 0.0234 |
| | PAPPA | pregnancy-associated plasma protein A, pappalysin 1 | 1.57 | 0.0023 |

| | tronomodulin 2 (nouronal) | 1 5 7 | 0 0303 |
|---------------|---|-------|--------|
| | (10pontouunin 2 (neuronal)) | 1.57 | 0.0392 |
| CDH10 | cadherin 10, type 2 (12-cadherin) | 1.58 | 0.0316 |
| GAS2L3 | growth arrest-specific 2 like 3 | 1.58 | 0.0409 |
| HIPK1 | homeodomain interacting protein kinase 1 | 1.58 | 0.0336 |
| LOC151877 | hypothetical protein LOC151877 | 1.58 | 0.0136 |
| LONRF2 | LON peptidase N-terminal domain and ring finger 2 | 1.58 | 0.0412 |
| CTD-2248C21 2 | G antigen 1 | 1 59 | 0.0415 |
| | adonulato kinaso 7 | 1.61 | 0.0114 |
| | transformin recenter (n00, CD71) | 1.01 | 0.0114 |
| | | 1.01 | 0.0081 |
| IMC1 | transmembrane channel-like 1 | 1.61 | 0.0216 |
| ABCC4 | ATP-binding cassette, sub-family C (CFTR/MRP), member 4 | 1.62 | 0.0052 |
| HIST1H4E | histone cluster 1, H4e | 1.62 | 0.0038 |
| PAK7 | p21(CDKN1A)-activated kinase 7 | 1.62 | 0.0326 |
| EGLN3 | egl nine homolog 3 (C. elegans) | 1.63 | 0.0009 |
| XYLB | xylulokinase homolog (H. influenzae) | 1.63 | 0.0219 |
| CDC20B | Cell division cycle 20 homolog B (S. cerevisiae) | 1.60 | 0.0428 |
| DD020D | retinghlastema 1 (including actopactoona) | 1.64 | 0.0420 |
| | | 1.64 | 0.0001 |
| SPAG4L | sperm associated antigen 4-like | 1.64 | 0.0176 |
| ARHGEF12 | Rho guanine nucleotide exchange factor (GEF) 12 | 1.65 | 0.0201 |
| TSPAN17 | tetraspanin 17 | 1.65 | 0.0146 |
| CHD7 | chromodomain helicase DNA binding protein 7 | 1.66 | 0.0204 |
| IGSF3 | immunoglobulin superfamily, member 3 | 1.66 | 0.0187 |
| KIAA0644 | KIAA0644 gene product | 1.66 | 0.0167 |
| | DEAD (Aco Clu Ala Aco) box polypoptido 54 | 1.67 | 0.0107 |
| | DEAD (ASP-GIU-AId-ASP) box polypeptide 54 | 1.07 | 0.0069 |
| | ieukotriene B4 12-nydroxydenydrogenase | 1.67 | 0.0416 |
| DCBLD2 | discoldin, CUB and LCCL domain containing 2 | 1.68 | 0.01 |
| KRT33A | keratin 33A | 1.68 | 0.0312 |
| PSG4 | pregnancy specific beta-1-glycoprotein 4 | 1.68 | 0.0371 |
| KIAA0746 | KIAA0746 protein | 1.69 | 0.0034 |
| MFAP5 | microfibrillar associated protein 5 | 1 7 1 | 0.0238 |
| OR2B2 | olfactory recentor family 2 subfamily 8 member 2 | 1 71 | 0.0457 |
| SCN2D2 | codium obannal voltage gated type III beta | 1 71 | 0.0407 |
| | Souluin chainer, voltage-galeu, type III, beta | 1.71 | 0.0493 |
| LUC283194 | nypotnetical protein LUC283194 | 1.72 | 0.0499 |
| SHC4 | SHC (Src homology 2 domain containing) family, member 4 | 1.72 | 0.0146 |
| SRGAP2P1 | SLIT-ROBO Rho GTPase activating protein 2 pseudogene 1 | 1.72 | 0.0454 |
| TAT | Tyrosine aminotransferase | 1.72 | 0.0366 |
| KRT25 | keratin 25 | 1.73 | 0.0084 |
| ATP13A3 | ATPase type 13A3 | 1.74 | 0.0463 |
| TTC7A | Tetratricopentide repeat domain 7A | 1 74 | 0.0178 |
| EMCN | endomucin | 1 75 | 0.0254 |
| | Transmembrane protein 624 | 1.75 | 0.0234 |
| | | 1.75 | 0.0300 |
| EVI1 | Ecotropic viral integration site 1 | 1.77 | 0.0365 |
| KCNB2 | potassium voltage-gated channel, Shab-related subfamily, member | 1.77 | 0.0333 |
| | 2 | | |
| FLJ14959 | hypothetical protein FLJ14959 | 1.78 | 0.0072 |
| UNC119B | Unc-119 homolog B (C. elegans) | 1.78 | 0.0352 |
| PHTF2 | putative homeodomain transcription factor 2 | 1 79 | 0.0159 |
| | LITP11-like LI3 small nucleolar ribonucleonrotein (veast) | 1.8 | 0.0496 |
| | defension hete 1074 | 1.01 | 0.0400 |
| | leur deneitu linenretein recenter releted protein C | 1.01 | 0.0303 |
| LRPO | iow density inpoprotein receptor-related protein 6 | 1.85 | 0.0161 |
| RNF32 | ring finger protein 32 | 1.86 | 0.0377 |
| KIAA2022 | KIAA2022 | 1.87 | 0.0241 |
| ANKRD30B | ankyrin repeat domain 30B | 1.88 | 0.0446 |
| EDN1 | endothelin 1 | 1.91 | 0.0163 |
| RNF150 | ring finger protein 150 | 1.91 | 0.0197 |
| MMP25 | matrix metallonentidase 25 | 1 95 | 0.0191 |
| | nhank metallopopulado 20 nhosphodiostaraso 11 calmodulin dapandant | 1.00 | 0.0201 |
| | μ of the product of the set of | 1 00 | 0.0244 |
| | onactory receptor, ranning 5, subranning n, member 1 | T.90 | 0.0429 |
| | neurotrophic tyrosine kinase, receptor, type 2 | 2.01 | 0.0185 |
| LUC/28806 | Similar to N-ethylmaleimide-sensitive factor | 2.1 | 0.0081 |
| MSL-1 | Male-specific lethal-1 homolog | 2.1 | 0.0018 |
| VEPH1 | ventricular zone expressed PH domain homolog 1 (zebrafish) | 2.24 | 0.0107 |
| B9D1 | B9 protein domain 1 | 2.41 | 0.0106 |

| MGC50559 | hypothetical protein MGC50559 | 2.41 | 0.0493 | |
|--|--|------|--------|--|
| RAB6A | RAB6A, member RAS oncogene family | 2.5 | 0.0159 | |
| NALCN | sodium leak channel, non-selective | 2.67 | 0.0022 | |
| PTPRD | protein tyrosine phosphatase, receptor type, D | 2.67 | 0.0106 | |
| TMEM176B | Transmembrane protein 176B | 2.78 | 0.0046 | |
| *List of differentially expressed genes in fold change (FC) and Students' T-test (p-value) analyses. | | | | |

Table 4. Gene networks overrepresented by differentially expressed genes Focus # Genes in Network* Score genes Functions 26s Proteasome, ARHGEF12, CARD11, CASP10, Caspase, Cdc2, CLEC11A, Cyclin A, DUSP2, E2f, E2F1, EGLN3, FGFR1, Filamin, Hdac, HDAC5, Histone h3, Histone h4, MECOM, Mek, NFkB (complex), OIP5, OSGIN1, Pi3-kinase, PML, PPP1R13L, Cellular Development, Hematological System 1 Ras, Rb, RB1, RORA, RUNX2, Shc, SNRNP70, TMOD2, Vegf 32 19 Development and Function, Hematopoiesis CA3, CD28, CENPN, COL23A1, CSGALNACT1, CSNK1E, CSNK1G2, dihydrotestosterone, EPS15, GRB2, HEYL, KCNB2, LRP6, LRRC23, NAA38, ONECUT1, PMS1, PPP1R3D, PPP2R1A, 2 PRNP, RDH5, RDH16, REPS1, RNF20, RPS28, SGIP1, SLC24A1, SMAD3, SOST, SVIL, TGM4, TMF1, UGT2B11, UGT2B15, Lipid Metabolism, Small Molecule UGT2B@ 22 14 Biochemistry, Vitamin and Mineral Metabolism AGAP1, Alp, Ap1, COL5A3, Collagen type I, Collagen(s), DCBLD2, EDN1, ERK, ERK1/2, Fgf, FGFR4, FN1, Focal adhesion kinase, HEY2, Ifn gamma, IL1, Laminin, LYPD3, Mapk, MUC5B, Cellular Development, Visual System 3 NTRK2, PCDH7, PCOLCE, Pdgf, PDGF BB, PI3K, Pkc(s), PLC Development and Function, Cellular Assembly gamma, PLEKHG2, Rac, Rap1, RASGRP3, TCR, Tgf beta 22 14 and Organization Actin, Actin-Nrf2, BCL2, BNIPL, CD248, DSTN, EMCN, ENDOG, FMO1, FOXF2, GFI1B, GIMAP5, GSTT1, JAG2, JARID2, LGALS3BP, MCOLN3, MEGF6, MEGF8, MFAP5, MYH14, NCALD, 4 NFE2L2, NQO2, PDZD4, SERPINB8, SLC1A4, SNAPC4, STARD3, Cell Morphology, Cell-To-Cell Signaling and TBP, TNF, TROPONIN, UACA, Vacuolar H+ ATPase, ZNF496 20 13 Interaction, Cell Death CASKIN2, CDH6, CDH7, CDH8, CDH9, CDH10, CDH15, CDH17, CDH18, CDH22, CLYBL, CTNNAL1, CTNNB1, EDIL3, FBX08, FBX015, GNB2L1, GOLM1, GPX2, Groucho, HLCS, HNF1A, 5 KRT33A, MIRLET7D (includes EG:406886), MKL2, NRCAM, PCCA, PTCH1, Scf Trcp beta, SKP1, SRF, TRIM46, TSG101, Cell-To-Cell Signaling and Interaction, Tissue **TSPAN17**, ZNF365 19 13 Development, Embryonic Development ARL3, C100RF58, CD70, CEL, CST4, DGKA, GIP2, GPA33, Hlaabc, IFNA2, IGSF3, IkB-Tp53, KLF4, LAPTM4B, MT1L, NFKBIA, PQLC3, PROM1, PYHIN1 (includes EG:149628), SCN3B, SLC19A2, SOD2, SPHK2, SPON1, TACC3, TBX3, TEP1, TERT, Cellular Growth and Proliferation, Cell Cycle, TMC1, TP53, TRIM14, TRIM22, TRIM28, Ube3, ZNF10 19 13 Cell Death 6 ABCC4, ACCN1, ACCN2, ATXN1, BCAS1, beta-estradiol, BICD1, CACNB1, DDX54, GMEB2, GRM2, GRM3, HSD17B12, HUS1B, 7 IFT122, MAL, MATN2, MIR133A-1, NAPB, NARS, NR1I3, NR3C1, NSF, OBSCN (includes EG:84033), PAPSS2, PICK1, PTP4A2, RAB6A, SAPS2, SEPT3, SLC1A6, SULT1A1, TGTP1, ZCCHC2, Cancer, Psychological Disorders, Cell-To-Cell **ZNF804A** 18 12 Signaling and Interaction 4930444G20RIK, ADAMTS14, alcohol group acceptor phosphotransferase, amino acids, ASTL, CPA5, DMPK, DPEP3, FAM70A, GRAMD1B, HIPK1, IMMP2L, KIAA2022, LTK, MIR129-8 2 (includes EG:406918), MIR195 (includes EG:406971), MIR362 (includes EG:574030), MMP1B, NAALADL1, PAK7, PEPC (includes EG:109616), peptidase, PRKX, PRPF4B, PRT5, Genetic Disorder, Skeletal and Muscular

18

| 12 | Disorders, Protein Degradation |
|----|--------------------------------|
|----|--------------------------------|

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PRT6, PTPRD, PTPRM, RNF150, SENP5 (includes EG:303874),

| | SOLH, TMEM132E, TMPRSS11D, UPG2, YME1L1 | | | |
|----|---|----------|-----------|--|
| | ABLIM, Akt, ATP9A, CREBL2, DHCR7, DHRS3, DYRK3, FASN, | | | |
| | FSH, GATA3, GK7P, IFN Beta, IgG, IGKV1-117, IKBKB, IL12 | | | |
| | (complex), Insulin, Interferon alpha, Jnk, Jun-ATF2, Lh, | | | Cellular Response to Therapeutics, Lipid |
| 9 | LOC81691, MAS1, P38 MAPK, PI4K2A, Pka, QRFP, RASAL2, | | | Metabolism, Reproductive System |
| | RPA1, TAPBP, TFRC, TP53I11, TRIL, USP18, ZNF668 | 16 | 11 | Development and Function |
| | ACOT2, ACOT4, ACOT5, ACOT7, ACOT8, ACOT9, ACOT1 (includes | | | |
| | EG:26897), ACOT1 (includes EG:641371), BAAT, C220RF28, | | | |
| | C20RF47, C30RF26, CLEC12B, FASTKD2, GOLIM4, GPX7, | | | |
| | GSTK1, HNF4A, LAS1L, MTR, OGFR, palmitoyl-CoA hydrolase, | | | |
| 10 | PPT1, PTPN11, SEL1L3, TCF19, TDRKH, TLN1, TMEM63A, | | | |
| | TOR1AIP2, TSC22D1, USMG5, UTP11L (includes EG:51118), | | | Lipid Metabolism, Nucleic Acid Metabolism, |
| | VEPH1, VN1R1 | 16 | 11 | Small Molecule Biochemistry |
| | ADAMTS3, ADAMTS13, ADK, AKT1, Akt-Calmodulin-Hsp90- | | | |
| | Nos3, ATG9B, ATP13A3 (includes EG:79572), C1QC, CACHD1, | | | |
| | CASP3, COL6A1, CORO1C, cyclic AMP, F2, FGL2, FXYD5, Lamin, | | | |
| 11 | LOXL2, LPHN1, MAGI2, NOS3, PDE11A, PDE1A, PDE4C, PDE7A, | | | |
| | PLANAI, PPTI, PIGDS, SLUIZAT, SULH, SUAIS, IGFBI, | 10 | 4.4 | Reproductive System Disease, Cell |
| | USP25, WINKS, ZIVIZI | 10 | 11 | Morphology, Inflammatory Disease |
| | AGRN, ARPP19, B9D1, CEBPB, CENPV, CLPA, COPG2, CIED, CYCRE (includes EC:10662) DDV12 DDD1 ENO2 ENTRD2 | | | |
| | CDD192 HSDD1 HTT KLE16 KDTN LDD2 LMO4 MVL4 | | | |
| 10 | MENTOS, NOLUL, NII, KLELO, KEIN, LUDZ, LIVIU4, MILLA, NDUEAS DOTD DECA DIIM SCHIDI SEDDI SESAS SMADOAA | | | Carbohydrata Matabalism, Call Signaling |
| 12 | NDULAS, FUTE, FOR4, REINI, SUFIEL, SEFFL, SESAZ, SMARUA4, SPGAD3 SPRT TNNI2 TRAD1 VIDR2 7NE675 | 1/ | 10 | Nucleic Acid Metabolism |
| | *The networks were deperted using Indeputity Dethways Analysis | | | |
| | "The networks were generated using ingenuity Pathways Analysis | (ingenui | iye Syste | ems, www.ingenuity.com). Each gene |

* The networks were generated using Ingenuity Pathways Analysis (Ingenuity® Systems, www.ingenuity.com). Each gene identifier was mapped to its corresponding gene object in the Ingenuity Pathways Knowledge Base (IPKB). These genes were overlaid onto a global molecular network developed from information contained in the IPKB. Network enrichment is then assessed using a network score (negative log of p-values of Fisher tests). Focus genes (in bold) are genes identified in our list of differentially expressed genes. Networks shown here are those with network scores > 3.0.

| Table 5. WICI | Table 5. Microarray and griffer expression measurement comparisons | | | | | |
|---------------|--|--------------------|---------|-------------|---------|--|
| Gene symbol | Gene description | qRT-PCR Microarray | | | | |
| | | Fold change | P-value | Fold change | P-value | |
| | | | | | | |
| CLEC11A | C-type lectin domain family 11, member A | 1.06 | 0.763 | -1.56 | 0.006 | |
| CLEC12A | C-type lectin domain family 12, member A | -1.52 | 0.22 | -1.54 | 0.018 | |
| CLEC12B | C-type lectin domain family 12, member B | -2.08 | 0.024 | -1.59 | 0.001 | |
| MMP25 | Matrix metallopeptidase 25 | 1.09 | 0.705 | 1.95 | 0.019 | |
| FGFR1 | Fibroblast growth factor receptor 1 | -1.24 | 0.247 | -1.52 | 0.013 | |
| LTK | Leukocyte receptor tyrosine kinase | -1.25 | 0.428 | -1.96 | 0.027 | |
| PML | Promyelocytic leukemia protein | -1.08 | 0.685 | -1.86 | 0.021 | |
| PPP1R13L | Protein phosphatase 1, regulatory subunit 13 like | 1.05 | 0.813 | -1.51 | 0.013 | |

Table 5. Microarray and qRT-PCR expression measurement comparisons



Figure 1 Hierarchical clustering of participants and differentially expressed genes. Probes (N=356) representing differentially expressed genes (N=247) (upregulated: shades of red and downregulated: shades of green) (rows) and participants (columns, cases=pink and controls=green) grouped according to level and nature of expression and similarity of expression profiles (participants) and subjected to hierarchical tree clustering.



39 weeks of gestation [18]. Purwosunu et al, in a qRT-PCR based study of peripheral blood samples collected around 39 weeks of gestation, reported that expression of CRH, PLAC1 and P-Selectin were up-regulated in women with preeclampsia [19]. In another qRT-PCR based study, Purwosunu and colleagues have reported differential regulation of angiogenesis-related genes including Flt-1 and VEGF in peripheral blood of women with preeclampsia at 38-39 weeks of



Cellular development, hematological system development and function, hematopoiesis

Figure 3. Top network overrepresented by differentially expressed genes. The networks were generated using Ingenuity Pathways Analysis (Ingenuity® Systems, www.ingenuity.com). Each gene identifier was mapped to its corresponding gene object in the Ingenuity Pathways Knowledge Base (IPKB). These genes were overlaid onto a global molecular network developed from information contained in the IPKB. Network enrichment is then assessed using a network score (negative log of p-values of Fisher tests). Focus genes (shaded) are genes identified in our list of differentially expressed genes.

gestation [20]. Sun et al reported that 72 genes involved in cell proliferation, smooth muscle contraction and immune response were differentially expressed in peripheral blood of women with preeclampsia at 24-32 weeks of gestation [21]. In a follow-up study of chorionic villus gene expression study in early pregnancy (11 weeks), Farina et al investigated expressions of selected genes in third trimester peripheral blood of women who developed preeclampsia [10]. They reported up regulation of ADD1, BTD7, CLDN6, LTF and MAS1 in third trimester peripheral



Figure 4. Promoter analysis results of differentially expressed genes. Inferred network of differentially expressed genes (Red=up regulated and Green=down regulated) in preeclampsia and transcription factors (White). Transcription factors were identified by their binding to over expressed promoter sequences in the differentially expressed genes.



Note: Yellow: Preeclamptic placenta, and Blue: Early pregnancy peripheral blood

blood of women with preeclampsia. Recently, Sekizawa et al investigated expressions of selected candidate genes in peripheral blood at 16-17 weeks to identify early pregnancy markers of preeclampsia [12]. In their study, expressions of FLT-1, ENG, P-Selectin, PLAC1, P1GF and HO-1 were deregulated in the case group while no differences were present between cases and controls in expressions of TGFB1, VEGF and SOD [12].

Investigators have also studied gene expression profiles in chorionic villus tissue samples collected in early pregnancy in relation to risk of preeclampsia [10-11]. Farina et al reported preeclampsia related differential expression of genes involved in trophoblast invasion, inflammation, endothelial dysfunction, angiogenesis and blood pressure control in chorionic villus samples in early pregnancy (11 weeks) [10]. Similarly, Founds et al reported deregulation of genes related to inflammation/immune regulation in early pregnancy (10-12 weeks) chorionic villus samples in women who later developed preeclampsia [11]. Genes involved in hypoxia or

> oxidative stress responses were not differentially expressed in their samples, similar to our findings. In sum, review of current and preeclampsia previous related gene expression profiles from blood and placental tissues suggest early pregnancy changes consistent with alterations in angiogenesis and immune/inflammatory response in contrast to late pregnancy changes which are consistent with alterations in response to hyoxidative poxemia or stress and subsequent endothelial dysfunction.

In our study, several genes that participate in abnormal placentation were differentially expressed in preeclampsia. In their candidate gene study, Goddard et al reported associations of variations in the COL1A1

Figure 5. Comparison of gene ontology processes. Gene ontology (GO) processes over represented by differentially expressed genes in early pregnancy maternal peripheral blood (blue) and preeclamptic placenta (yellow).

gene with risk of preeclampsia [22]. COL1A1 is a gene coding for a protein in collagen metabolism (similar to COL5A3, also differentially expressed in our study) which influence maternal extracellular matrix composition and subsequently trophoblast migration [23]. NRTK2 is a brain derived neurotrophin family of proteins known to activate the high-affinity tyrosine kinase [24]. Kawamura et al, using *in vitro* and *in vivo* studies, have previously demonstrated important roles of the tyrosine kinase B signaling system and related neurotrophins in implantation and placental development through regulation of trophoblast cell growth [24].

Several genes in the immune response/ inflammation and cell cycle pathways were also differentially expressed related to preeclampsia in our study. For instance, genes constituting the CLEC family of genes (e.g. CLEC11A, CLEC12A and CLEC12B) were down regulated. These C-type lectin receptors play crucial roles in immunity and homeostasis, particularly in recognition, pathogen and self-antigen pathomechanisms that have been implicated in preeclampsia [25-27]. Regulatory signal pathways of the inflammatory system involving TNFRSF1ATRAFs, IKBKB and NFKB genes have been described [28]. IKBKB was differentially expressed in our study, while NFKB plays a central role in the top network that was over represented by differentially expressed genes. Genes participating in the RB E2R1 cell cycle pathway were also differentially expressed in our study. While most research in this pathway has been done in cancer research, recently, interest in this pathway related to vascular disorders has increased following identification of E2F1 binding sites in promoters of angiogenesis related genes (e.g. FLT-1) [29].

We identified putative transcription factors (i.e., Sp1, MAZ and MZF1) that may be responsible for co-expression of differentially expressed genes. Sp1 has been associated with transcription of genes involved in syncytiotrphoblast differentiation such as the PSG family of genes (e.g. PSG4 up regulated in our study), endoglin and TGF β 1 and 2 other genes [30]. Further research in this area may enhance understanding of mechanisms of abnormal syncytiotrophoblast differentiation and related pathologies such as preeclampsia.

Our study has several strengths and limitations.

It is the first global microarray based study investigating risk of preeclampsia and early pregnancy differential gene expression in peripheral blood, to our knowledge. Evaluation of functions and functional relationships of differentially expressed genes, for example using GO processes, as observed in past reports, enhances comparison of findings across studies [31]. By comparing preeclampsia related differential gene expression in early pregnancy peripheral blood and placenta at-delivery, we were able to present corroborative evidence for recent hypotheses that seek to elucidate gestational age and/or tissue specific gene expression changes associated with preeclampsia [4].

Several limitations of our study deserve mention. Single measurement of peripheral blood gene expression may not provide a full picture of gene expression changes across gestation. Evaluation of whole blood gene expression, a potentially heterogeneous cell population, does not allow comparisons of expression differences across similar cell subtypes. We were able to confirm microarray-based measurement for approximately 75% of genes in our confirmatory gRT-PCR study. This is comparable to other previous reports that range between 60-75% [32-33]. Further, most fold change differences observed were in the same direction in both experiments. For the two genes with different fold change directions (up or down regulation) between the two experiments, the qRT-PCR based gene expression differences were close to 1 (1.05 for PPP1R13L and 1.06 for CLEC11A).

In summary, we demonstrated maternal early pregnancy peripheral blood gene expression in early pregnancy. Differentially expressed genes participate in cellular processes of placentation, immune function/inflammation and cell growth (cell cycle). Besides improving understanding of pathogenesis of preeclampsia, early pregnancy peripheral blood gene expression profiling may provide critical windows of opportunity for disease prevention, early detection and/or treatment.

Acknowledgments

The authors are indebted to the participants of the Omega study for their cooperation. They are also grateful for the technical expertise of staff of the Center for Perinatal Studies, Swedish Medical Center. This work was supported by grants from the National Institute of Child Health and Human Development, National Institutes of Health (HD/HL R01-32562 and R01-055566).

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