

AUS DEM LEHRSTUHL  
FÜR DERMATOLOGIE  
PROF. DR. MED. DR. H. C. M. LANDTHALER  
DER FAKULTÄT FÜR MEDIZIN  
DER UNIVERSITÄT REGENSBURG

IDENTIFICATION OF NEW GENES ASSOCIATED WITH MELANOMA

Inaugural – Dissertation  
zur Erlangung des Doktorgrades  
der Medizin

der  
Fakultät für Medizin  
der Universität Regensburg

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# Identification of new genes associated with melanoma

Andreas Mauerer<sup>§\*</sup>, Alexander Roesch<sup>§<sup>o</sup></sup>, Christian Hafner\*, Thomas Stempf<sup>#</sup>, Peter Wild<sup>Φ</sup>, Stefanie Meyer\*, Michael Landthaler\* and Thomas Vogt<sup>o+</sup>

*\* Department of Dermatology, University of Regensburg, Franz-Josef Strauss-Allee 11, D-93053 Regensburg, Germany*

*<sup>o</sup> Department of Dermatology, University of Saarland, Kirrberger Strasse, D-66421 Homburg/Saar, Germany*

*# Center of Excellence for Fluorescent Bioanalysis, University of Regensburg, D-93053 Regensburg, Germany*

*Φ Institute of Surgical Pathology, University Hospital Zurich, CH-8091 Zurich, Switzerland*

**§ These authors contribute equally.**

**+ Corresponding author:**

Thomas Vogt, MD

Department of Dermatology,

Homburg/Saar University Medical Center,

Building 18,

D-66421 Homburg/ Saar,

Germany

E-mail: thomas.vogt@uniklinikum-saarland.de

## **Abbreviations:**

PM: primary melanoma

MM: melanoma metastases

MN: melanocytic nevi

GDF15: growth differentiation factor 15

TLE1: transducin-like enhancer of split 1 (E(sp) homolog, Drosophila)

CNTN1: contactin 1

FRZB: frizzled-related protein

MMP1: matrix metalloproteinase 1

ALM: acral lentiginous melanoma

LMM: lentigo maligna melanoma

SSM: superficial spreading melanoma

NMM: nodular melanoma

FFPE: formalin-fixed, paraffin-embedded

PFS: progression free survival

## **Abstract:**

**Purpose:** Repeated failures in melanoma therapy made clear that the molecular mechanisms leading to melanoma are still poorly understood. Here, we aim to provide a more comprehensive understanding of the transcriptional profiles and signaling pathways associated with melanoma.

**Methods:** Gene expression was analyzed using the Affymetrix Human Genome U133A 2.0 GeneChip arrays. To avoid culture artifacts, we used microdissected fresh frozen material of 18 melanocytic nevi (MN), 20 primary melanomas (PM) and 20 metastatic melanomas (MM). Statistical analysis was performed with Genomatix Chipinspector, Ingenuity™ Software, SPSS Software and Partek Genomic Suite 6.4. Expression levels of selected transcripts were verified by quantitative real-time RT-PCR and immunostaining of a tissue microarray sampling more than 280 cases of MN, PM, and MM with known clinical outcome.

**Results:** A total of 284 differentially expressed genes was detected in PM compared to MN and 189 genes in MM compared to PM affecting common cancer pathways such as MAPK-, Wnt-, and Notch-signaling. Using principal component analysis, the samples could be grouped according to their histological entity. We identified a panel of novel melanoma-associated markers: FRZB, an antagonist of Wnt; TLE1, a transcription factor partner of TCF/LEF-1; CNTN1, an activator of Notch signaling; two Serpin peptidase inhibitors, Serpin B3/B4, and the TGF- $\beta$  family member GDF15, the latter with association to MAPK-signaling.

**Key words:**

Melanoma, FRZB, TLE1, Serpin B3, Serpin B4



## Introduction

Melanoma is increasing in incidence with 68,130 cases expected for 2010 in the United States and an annual death rate of 4.07 per 100,000, corresponding to a total of 8700 estimated deaths [1]. Melanoma patients with a tumor thickness of < 1mm have a favorable cure rate but once melanoma has progressed into systemic disease, median survival drops below 7-8 months and the 5 year survival is less than 5% [2]. Since cellular homeostasis in melanoma is deregulated by a concert of genes [3], it is important to develop new diagnostic and therapeutic strategies taking into account the entire tumor signature rather than one single marker. To gain insights into genome-wide gene expression patterns in cancer, microarray technology became a powerful instrument and the recent progress in computational analysis allows investigating whole networks of signaling pathways in individual patient samples at the same time. Since single pathways, e.g. MAPK signaling, have been targeted so far only with limited success [4], a better understanding of the entire spectrum of signaling networks and their interconnection is highly needed for the design of future therapies [5].

Although applied for years now, the benefit of microarrays for melanoma research is still limited, because the majority of studies has been based on cultured cell lines. Certainly, experimental conditions can be stably controlled in cell culture, but on the downside, gene expression is affected by the selected culture media leading to artifacts in the results. Among the few studies that have analyzed in vivo patient samples, e.g. Jaeger et al. [6] compared gene expression patterns of 19 primary melanomas (PM) and 22 melanoma metastases (MM). Their results showed that PM and MM were characterized by distinct gene expression patterns and represent different biological stages of tumor progression. However, since benign nevi (MN) were not included, an interpretation with regard to initial malignant processes was not possible. A former study of our group on a limited number of laser-microdissected patient samples, indicated that particularly the comparison to MN could reveal significant changes in the transcriptional profiles of PM [7].

Here, we aim to detect new gene expression alterations in PM and MM compared to MN, which may contribute to tumor initiation and progression of this deadly disease. We applied high throughput transcriptional profiling followed by network analysis to a large number of fresh frozen patient specimens of MN, PM and MM and subsequently performed validation experiments to a panel of significantly regulated and promising new candidate genes.

## Methods

### *Patient Material*

For microarray analysis, tissue samples from 18 MN, 20 PM (2 acral lentiginous melanomas, 3 lentigo maligna melanomas, 4 nodular melanomas, 5 secondary nodular melanomas, and 6 superficial spreading melanomas) and 20 MM (cutaneous and lymph node metastases) were collected at the Department of Dermatology, University of Regensburg, Germany (Table 1). Patients' written consent was obtained prior to surgery. The tissue specimens were immediately frozen in liquid nitrogen and stored at  $-80^{\circ}\text{C}$ . Histological diagnoses were routinely assessed by two expert dermatopathologists (M.L. and T.V.) prior to RNA extraction.

### *RNA Isolation and microarray hybridization*

RNA was extracted using QIAshredder columns (Quiagen, Hilden, Germany) and the RNeasy Mini Kit (Quiagen) as previously described [8]. RNA quality control was done with an Agilent Bioanalyzer 2100 (Agilent Technologies, Palo Alto, USA). 1 to 5 micrograms of total RNA from each tissue specimen were used to generate double-stranded cDNA and biotin-labeled cRNA (One Cycle Target Labeling Kit, Affymetrix). The length of the cRNA products was assessed using the Agilent 2100 bioanalyzer (Agilent Technologies, Palo Alto, USA). Following fragmentation, cRNA products (10  $\mu\text{g}$ ) were hybridized to Affymetrix Human Genome U133A 2.0 GeneChip® (Affymetrix, Santa Clara, USA) arrays for 16 h at  $45^{\circ}\text{C}$  in a rotating chamber. The array contained about 22,000 probe sets representing 14,500 human genes. Hybridized arrays were washed and stained in Affymetrix Washing Station FS400 using Streptavidin Phycoerythrin conjugate (Molecular Probes, Eugene, USA) together with biotinylated anti-streptavidin antibody (Vector Laboratories, Burlingame, USA), and the fluorescent signals were measured with the Affymetrix GeneChip® Scanner 3000. Quality control of the isolated RNA samples and sample processing were performed at a regional German Affymetrix Service Provider and Core Facility, "KFB - Center of Excellence for Fluorescent Bioanalytics" ([www.kfb-regensburg.de](http://www.kfb-regensburg.de)).

### ***Tissue microarrays and Immunohistochemistry***

Tissue microarrays were constructed as described previously [9] and contained formalin-fixed, paraffin-embedded (FFPE) human tissue samples of 127 MN, 73 PM, and 89 MM. The University of Regensburg institutional review board granted approval for the project. In brief, tissues were deparaffinized and rehydrated, according to standard protocols and subsequently incubated with a 1:600 dilution of anti-GDF15 polyclonal antibody (Abcam, Cambridge, UK) and a 1:2000 dilution of mouse anti-MMP1 monoclonal antibody (Millipore Corporation, Billerica, USA) overnight at 4°C. The secondary antibody [biotinylated polyvalent antibody, Zytochem Plus (HRP) Broad Spectrum Kit, Zytomed Systems, Berlin, Germany] was incubated for 30 minutes at room temperature, followed by incubation with horseradish peroxidase [Zytochem Plus (HRP) Broad Spectrum Kit] for 15 minutes at room temperature. Antibody binding was visualized using AEC solution (Zytochem Plus HRP Broad Spectrum Kit). Tissues were counterstained with hematoxylin. Immunostaining was confirmed in a series of ‘whole tumor sections’ to exclude spatial restriction of marker expression in TMAs (not shown). To avoid experimental bias within the set of tumor samples, immunohistochemistry of all examined tissue samples was performed under identical experimental conditions. Immunostaining was assessed by two independent investigators (A.M., T.V.). Cytoplasmic GDF15 and MMP1 staining intensity was estimated using a 5-step scoring system (range 0-4) with regard to staining intensity: 0, negative; 1(+) weakly positive (<50% positive cells and weak intensity); 2 + positive (<50% and moderate); 3 ++ strongly positive (<50% and strong intensity or >50% and weak intensity); 4 +++ very strongly positive (>50% moderate and strong intensity). The Pearson Chi square test was used for statistical analyses,  $p < 0.05$  was considered significant.

### ***Quantitative real-time RT-PCR***

For microarray validation, quantitative real-time RT-PCR (QPCR) was performed as described previously [8]. RNA was isolated from 5 representative MN, 5 PM, and 5 MM that were included before in the microarray analysis. One microgram of RNA was reversely transcribed using the SuperScript II reverse transcription system (Invitrogen, Carlsbad, USA) in combination with random hexa primers. The resulting cDNA was used as template for RT-PCR on an ABI 7000 Sequence Detection System (Applied Biosystem, Foster City, USA). The ddCT method was applied for quantitation of gene expression. Expression signals were normalized to 18S rRNA. The analyses were done in triplicates using commercial TaqMan™ assays (Applied Biosystems) and custom-designed primer pairs (Apara Bioscience,

Denzlingen, Germany): Serpin B3: Hs00199468\_m1; Serpin B4: Hs01691258\_g1; 18S rRNA: Hs99999901\_s1; FRZB proximal forward: 5'-AAACTGTAGAGGGGCAAGCA-3', reverse: 5'-GGCAGCCAGAGCTGGTATAG-3', TLE1 proximal forward: 5'-CACGACTTCACCTCCCAGAT-3', reverse: 5'-CTGGAATATGCTGGCTCCAT-3', CNTN1 proximal forward: 5'-CCCTTCCCGGTTTACAAAT-3', reverse: 5'-TCAGGTGGGAAAGGATCAAG-3'.

### ***Statistical analysis***

ChipInspector version 1.3 (Genomatix Software GmbH, Munich, Germany) was used for single probe based analysis of gained CEL files as described earlier [10]. For testing statistical significance false discovery rate (FDR) was set to 0, minimal probe coverage was set to 3, minimal probe change <-2 and >2. To reveal functional connections between the regulated transcripts, a network and pathway analysis of the pre-filtered genes was performed as described [11] using the Ingenuity™ Pathways Analysis online application ([www.ingenuity.com](http://www.ingenuity.com), Ingenuity™ Systems, Mountain View, USA). The significance of networks was calculated by integrated Ingenuity™ algorithms [11]. Principal component analysis (PCA) was performed with Partek Genomic Suite 6.4 (Partek Inc., St. Louis, USA). Comparison of the survival curve with low and high expressing melanoma was performed with SPSS V.18.0 (SPSS Inc., Chicago, USA). Values of  $p < 0.05$  were considered to be significant. All specimens on the TMAs were considered independently. Progression free survival (PFS) curves comparing patients with GDF15 and MMP1 staining patterns were calculated by the Kaplan–Meier method, with significance evaluated by two-sided log rank statistics as described earlier [12].

## Results

### *Comparative gene expression profiling*

To investigate the transcriptional profiles that are associated with malignant progression in melanoma, we compared 18 MN to 20 PM and 20 MM using a single probe based microarray analysis. CEL files were analyzed by Chipinspector version 1.3 (Genomatix Software GmbH, Munich, Germany), which is based on single probe analysis and *de novo* gene annotation that bypasses probe set definitions. After elimination of probes that could cross-hybridize to other transcripts, Chipinspector (CI) identified significantly regulated individual probes using default settings. At least 3 probes had to match per annotated transcript and minimal probe coverage was set to 3 with a fold change of  $<-2$  and  $>2$ . In the comparison of PM with MN, Chipinspector identified 52055 probes significantly up- and 48713 probes significantly down-regulated after elimination of probes that could cross-hybridize to other transcripts. We received 691 transcripts matching 284 significantly regulated genes; 167 up- and 117 down-regulated in PM compared to MN. Comparing MM to PM we found 39016 and 35455 probes significantly up- and down-regulated (586 transcripts matching 189 genes, 26 up-, 163 down-regulated in MM compared to PM) (Supplemental Table 1).

Among the 167 genes that were up-regulated in PM compared to MN, we found a high overlap with previously reported genes, e.g. PRAME, SSP1 [13, 14], CXCL9, PHACTR1, CITED-1, BCL2A1 [13, 15] S100A9, MMP1, FN1 [16], NNMT, SERPIN A3 [13], MCAM [17], ISG15 [18], CDK-2, and CDK-4 [19], GDF15 [13, 15, 20] and Hey1 [15, 16]. Comparing genes that were down-regulated from PM to MN with previous studies, we found consensus for CIRBP, FEZ1, PPP1R3C, LDOC1, TRPM1 [16], Desmoglein [17], KRT-15 [13], FABP7 [20], p57KIP2, and CDKN1 [21]. In MM, only a few genes have been described so far to be up-regulated compared to PM. Interestingly, we also found only 26 up-regulated genes. Of these, significant regulation has been described before for VEGFA [22, 23], FN1 [6, 24], IGFBP2 [25], SPP1, MAGEA12, c-MET [6, 15, 26], STC1, and PLOD2 [6]. Down-regulation in MM included the previously published genes Serpin B5 [27], SPRR1A, KRT 16/17/6B, CD 24, LOR, DSC1 [26], KRT 1/14/6A/5, CXCL14 and SPINT2 [6]. For the full list of regulated transcripts, see Supplemental Table 1.

### ***Expression profile-based sample classification***

To classify the tumor specimens based on their transcriptional profiles, we used principal component analysis (PCA) anticipating that the specimens would group according to their histological origin, i.e. MN, PM, and MM. Indeed, PCA displayed a clear spatial separation between the three histological entities reflecting considerable differences in respective gene expression signatures. The most significant difference was seen between PM and MN (Supplemental Figure 1) confirming previous data of our group [7] which pointed out that gene expression patterns differ dramatically between MN and PM and not so much between PM and MM.

### ***Identification of signaling pathways and networks***

To further unravel functions and networks of the regulated transcripts, we mapped the microarray ‘hits’ according to biological functions in Ingenuity’s<sup>TM</sup> Knowledge Base. Comparing PM to MN, particularly such genes were differentially regulated that play a role in cancer, dermatological diseases and conditions, cellular growth and proliferation, cellular movement, inflammatory response (Supplemental Table 2). Applying Ingenuity’s Network Algorithm<sup>TM</sup>, 15 functional gene networks could be constituted in total. Each of them contained more than 10 regulated focus genes with significant Ingenuity scores [11] of 11 and more (for example, maximum score of network 1 was 42, see Supplemental Figure 2A). Within these networks several genes were comprised with known relevance for melanoma biology, e.g. SPP1, STAT1, MMP1, or CDK2. Consequently, we found an affection of canonical pathways that are known to play a role in melanoma development, such as MAPK-signaling, apoptosis, Notch-, WNT/beta catenin- and integrin-signaling, as well as G1/S and G2/M checkpoint control [28, 29] (Table 2). When we grouped the 189 genes that were differentially regulated between MM and PM according to biological functions in Ingenuity’s<sup>TM</sup> Knowledge Base, we found an association to hair and skin development and function, dermatological diseases and conditions, cancer, cellular development, cellular movement, cellular growth and proliferation and inflammatory response (Supplemental Table 3). Also in MM, these functions were linked to melanoma-typical signaling pathways such as WNT/beta catenin-, integrin-, VEGF-, PI3/AKT- and cell-to-cell signaling (Table 2, Supplemental Figure 2B).

### ***Novel melanoma-associated genes***

To filter out novel genes with relevance for melanoma, we performed a separate Ingenuity™ pathway analysis that only comprised the most significant transcripts, i.e. showing an up- and down-regulation with a minimum log ratio of 1.5 (Supplemental Figure 2C). Based on our comprehensive GO analysis (Table 2), we primarily expected to find genes with relationship to major melanoma pathways like MAPK-, Notch- or Wnt-signaling. Indeed, we found a relatively new player of the Notch pathway, the cell adhesion molecule contactin 1 (CNTN1), to be significantly down-regulated in PM compared to MN. In the Wnt/beta catenin pathway, we found frizzled-related protein (FRZB) and the transducin-like enhancer of split 1 (TLE1) to be differentially expressed (both down in PM). Also included in the strongest up-regulated genes in PM, we found the Serpin peptidase inhibitors Serpin B3 and B4, both-linked to MAPK signaling [30]. At last, we could confirm the recently described up-regulation of the TGF-β family member growth differentiation factor 15 (GDF15) in PM [13, 15, 16].

To verify the expression levels of FRZB, TLE1, CNTN1, Serpin B3 and Serpin B4 we performed quantitative real-time RT-PCR (QPCR) using the same mRNA templates as for the microarrays. The down-regulation of FRZB, TLE1, and CNTN1 from benign MN to malignant PM and MM was largely confirmed with high statistical significance (Supplemental Figure 3). Also in case of Serpin B4, the up-regulation in PM compared to MN and MM could be reproduced by QPCR (p=0.028 and p=0.001, respectively). The Serpin B3-QPCR confirmed the significant down-regulation in MM compared to PM (p=0.001) and showed a trend towards up-regulation in PM (p=0.422).

For proof-of-principle that the observed transcriptional changes also translate into different protein levels, we picked one candidate marker with particularly interesting biology, GDF15 (up-regulated in melanoma), for further tissue microarray analysis (Figure 1). As control gene with known regulation, MMP1 was selected. Two independent investigators (A.M., T.V.) evaluated immunostaining of >280 human tissue specimens based on a 5-step scoring system (for details, see *Methods*, Supplemental Table 4). Inter- and intra-examiner reproducibility was 86.2 % (GDF15) and 79.5 % (MMP1), respectively. In accordance with the microarray data, PM and MM revealed a high expression of GDF15 protein (average scores 2.52 and 2.21, respectively), whereas GDF15 expression in MN was almost negligible (average score 0.91). The differences in expression were highly significant with p=1.8 E-20 for MN vs. PM and p<0.05 for PM vs. MM, respectively (Chi square test). To our knowledge this is the first

time that GDF15 protein expression was analyzed in a large panel of melanocytic tumors. Interestingly, progression free survival (PFS) in melanoma patients with low GDF15 staining (0 to 2+) was significantly higher compared to patients with high GDF15 expression (3+ to 4+) ( $p=0.037$ ; Figure 2A). Confirming previous reports on matrix metalloproteinases [31, 32], we observed a high immunoreactivity for MMP1 in PM (average score 3.02) with a significant decrease in MM (2.46,  $p=1.26 \text{ E-}5$ , Chi square test) and MN (mean 2.29,  $p=2 \text{ E-}12$ , Chi square test). Here, no significant difference in PFS was observed between melanoma patients with low and high MMP1 (Figure 2B).



## Discussion

In this study, we performed gene expression profiling and computational network analysis of a large series of patient samples derived from MN, PM and MM to gain new insights into melanoma biology. Our experiments discovered a panel of new candidate markers that are associated with melanoma-relevant signaling pathways such as MAPK-, Notch-, and Wnt-signaling.

Since the discovery of activating BRAF mutations in high percentage of melanoma [33-35], the MAPK signal transduction (with its various cascades of MAPKKKs, MAPKKs, and MAPKs) has been put into focus of melanoma research, not least, because of its highly drug-targetable potential. However, recent failures in BRAF-targeting therapy [4] disclosed our considerable lack in understanding this pathway and its interaction with other signaling networks [5]. As expected, also in our set of samples, we found differential expression of genes with known association to MAPK signaling. For example, STAT1 and SPP1 were up-regulated in PM compared to MN whereas PPP1R3C was down-regulated. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate to the cell nucleus, where they act as transcription activators. In former studies, SPP1 was found to be strongly up-regulated in PM and MM [6, 13, 36], which is in accordance with our data. Little is known about the function and role of PPP1R3C in human cancer. It is supposed to have tumor suppressor function since promoter hypermethylation and reduced mRNA expression were shown in melanoma compared to melanocytes [37].

As novel progression-related markers with association to MAPK signaling, we identified two Serpin peptidase inhibitors, Serpin B3 (squamous cell carcinoma antigen 1, SCCA1) and Serpin B4 (SCCA2, leupin). Both were strongly up-regulated in PM compared to MN and down-regulated in MM. Recently, it has been shown that Serpin B3 is a specific endogenous inhibitor of c-Jun-NH<sup>2</sup>-terminal kinase-1 (JNK1/MAPK8) and protects UV-exposed keratinocytes from apoptotic cell death after sun exposure [38]. Little is known about the role of Serpin B3 and Serpin B4 in melanoma. In squamous cell carcinomas of the cervix, lung, head and neck, however, Serpin B3 is already used as a tumor marker [39, 40]. Serpin B4 could be a general marker for tumor invasion and metastasis because its suppression by antisense cDNA, e.g. in uterine cancer cells, is followed by a decrease of E-cadherin

expression, which determines a common step in loss of cell-cell adhesion [41]. Since also melanoma cells can escape from keratinocyte control through down-regulation of E-cadherin [17], we assume that Serpins play an important role also during melanoma progression. This conclusion is further supported by our observation that another family member, Serpin B5 (maspin), was additionally decreased in MMs. Loss of Serpin B5 is another marker for invasion and migration in a variety of other tumors such as breast, prostate, and pancreatic cancer [42].

Next to the MAPK pathway, TGF- $\beta$  signaling is critical for tumor cell invasion and metastasis [43]. We found GDF15, a member of the TGF- $\beta$  superfamily, to be dramatically up-regulated in PM and MM compared to MN. In addition, we found that low GDF15 expression in melanoma patients is associated with higher progression free survival compared to high GDF15 expression. This matches previous reports on GDF15 suggesting a role in invasiveness of gastric cancer cells through up-regulation of the urokinase-type plasminogen activator system in an ERK1/2- dependent pathway [44]. Just recently, Boyle and co-workers started to mechanistically unravel the role of GDF15 in melanoma. They showed that shRNA knockdown in three different melanoma cell lines resulted in significantly decreased tumorigenicity in a mouse xenograft model [45]. This is also in accordance with a former finding by Talantov et al. who proposed that GDF15 is a better marker for differentiation between melanomas from benign nevi than the conventional markers tyrosinase, me20m and MART1 [15]. Because of its additional connection to other cancer pathways such as p53 [46], MITF [47], and PI3K/AKT signaling [45, 48, 49], it may represent a new key player in the development of metastatic melanoma associated with poor prognosis and survival [50].

With FRZB and TLE1 we also detected two players of the Wnt signaling pathway to be down-regulated in PM compared to MN. FRZB (sFRP3) belongs to the secreted Frizzled-related protein family, whose members prevent ligand-receptor interaction by binding to extracellular Wnt ligands [51, 52]. It has been suggested that FRZB exhibits tumor suppressor activity since down-regulation of FRZB has been shown to be involved in pleural mesothelioma [53] and prostate cancer [54]. TLE1 is a member of the Groucho/TLE/Grg family of corepressors that operate in many signaling pathways [55, 56]. It has important transcription factor partners, e.g. TCF/LEF-1 in the case of the Wnt signaling pathway [57]. TLE1 inactivation was suggested to contribute to the development of hematologic

malignancies by disrupting critical differentiation and growth suppressing pathways [58]. In Notch signaling, TLE1 functions as a co-repressor for HES1, which is activated in some human malignancies and allows tumor cells to evade differentiation and irreversible cell cycle arrest [52, 59]. Although there is increasing evidence for the critical role of Wnt signaling in tumor development, there are only a few studies available on Wnt in melanoma [60-63]. According to our data, particularly FRZB and TLE1 would represent promising future study targets in this context.

CNTN1, a member of the immunoglobulin superfamily, is a GPI- anchored neuronal membrane protein that functions as a cell adhesion molecule and acts as a functional ligand for Notch, e.g. during oligodendrocyte maturation [64]. Depending on the tissue context, Notch signaling can exhibit tumor initiating or tumor suppressive properties through complex modulation of tumor cell differentiation, proliferation, and apoptosis [65, 66]. In melanoma, activation of Notch signaling seems to be important throughout tumor progression. For example, stable overexpression of Nic, the active form of Notch, in benign melanocytes leads to transformation into a malignant phenotype whereas activation of Notch1 in primary melanoma cells resulted in a more metastatic phenotype [67, 68]. Hence, CNTN1 could be a so far overlooked critical progression factor in melanoma and should be investigated in follow up studies.

In confirmation with previous profiling studies by others and us, the present data support the concept that primary and metastatic melanomas are characterized by distinct gene expression patterns, in particular when compared to benign melanocytic nevi. These expression patterns reflect the activation/deactivation of cancer signaling pathways that are well-known for melanoma, such as MAPK-, Wnt-, or Notch-signaling. However, novel molecular players are still emerging and need to be further evaluated to get a better and more comprehensive understanding of melanoma for future diagnostics and therapy.

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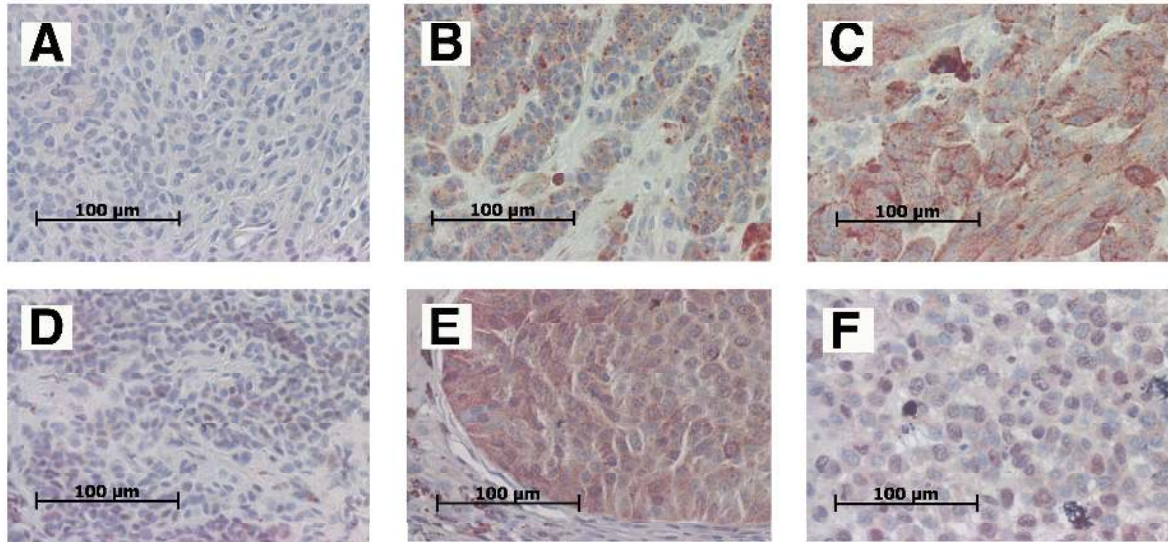
| <b>Characteristics</b>                      |               | <b>PM (%)</b> | <b>MM (%)</b> | <b>MN (%)</b> |
|---|---------------|---------------|---------------|---------------|
| <b>Tissue samples</b>                       |               | 20            | 20            | 18            |
| <b>Mean age</b>                             |               | 68.5 +-13.4   | 55 +- 15.63   | 23.33 +- 13.6 |
| <b>Gender</b>                               |               |               |               |               |
|   | <b>Female</b> | 10 (50)       | 4 (29)        | 8 (50)        |
|   | <b>Male</b>   | 10 (50)       | 10 (71)       | 8 (50)        |
| <b>PM subtypes</b>                          |               |               |               |               |
|   | <b>ALM</b>    | 2 (10)        |               |               |
|   | <b>LMM</b>    | 3 (15)        |               |               |
|   | <b>NMM</b>    | 4 (20)        |               |               |
|   | <b>SNM</b>    | 5 (25)        |               |               |
|   | <b>SSM</b>    | 6 (30)        |               |               |
| <b>Tumor thickness according to Breslow</b> |               |               |               |               |
|   | <b>≤1mm</b>   | 4 (20)        |               |               |
|   | <b>1-2mm</b>  | 4 (20)        |               |               |
|   | <b>≥2mm</b>   | 12 (60)       |               |               |
| <b>Clark Level</b>                          |               |               |               |               |
|   | <b>I</b>      |               |               |               |
|   | <b>II</b>     |               |               |               |
|   | <b>III</b>    | 3 (15)        |               |               |
|   | <b>IV</b>     | 13 (65)       |               |               |
|   | <b>V</b>      | 4 (20)        |               |               |
| <b>T stage</b>                              |               |               |               |               |
|   | <b>T1</b>     | 4 (20)        |               |               |
|   | <b>T2</b>     | 6 (30)        |               |               |
|   | <b>T3</b>     | 4 (20)        |               |               |
|   | <b>T4</b>     | 6 (30)        |               |               |

**Table 1:** Patient information with PM subtypes (ALM= acral lentiginous melanoma; LMM= lentigo maligna melanoma; NMM= nodular melanoma; SNM= secondary nodular melanoma; SSM= superficial spreading melanoma).

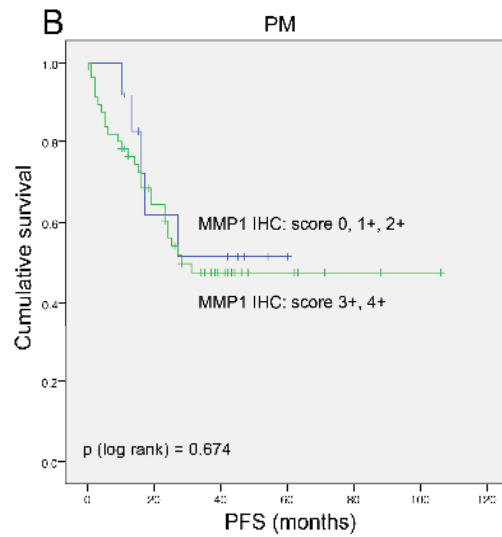
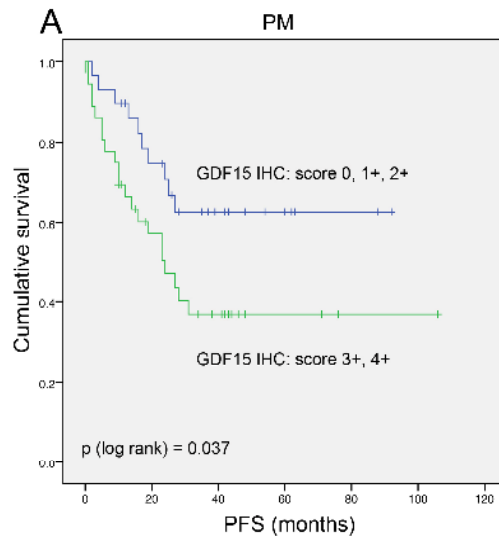
| Pathway                   | PM c/t MN  | MM c/t PM                         |
|---------------------------|--|-----------------------------------|
| <b>MAPK</b>               | (e.g. STAT1 ↑, SPP1 ↑, PPP1R3C ↓, GDF15 ↑, MMP1 ↑, Serpin B3 ↑, Serpin B4 ↑) | (Serpin B3 ↓, Serpin B4 ↓)        |
| <b>PI3/AKT</b>            |  | (e.g. SFN ↓)                      |
| <b>Cell cycle control</b> | (e.g. cyclin B1 ↑, cyclin B2 ↑, CDKN1C ↓, CDK2 ↑)                            | (e.g. SFN ↓)                      |
| <b>Apoptosis</b>          | (e.g. SPP1 ↑, TNFRSF21 ↑, BCL2A1 ↑)  |                                   |
| <b>Cell-cell adhesion</b> |  | (e.g. E-cadherin ↓, P-cadherin ↓) |
| <b>Wnt</b>                | (e.g. TLE1 ↓, FRZB ↓)  | (e.g. E-cadherin ↓, P-cadherin ↓) |
| <b>Notch</b>              | (e.g. CNTN1 ↓, HEY1 ↑)   |                                   |
| <b>Integrin</b>           | (e.g. ACTN1 ↑, ITGB2 ↑, FN1 ↑, LAMB4 ↓, COL4A1 ↑, COL4A2 ↑)                  | (e.g. FN1 ↑, LAMC2 ↓, LAMA3 ↓)    |
| <b>VEGF</b>               |  | (e.g. VEGFA ↑)                    |

**Table 2:** Melanoma-typic pathways are found regulated within the set of differentially expressed genes. ↑↓ refers to up- or down-regulated genes in PM (column 2), MM (column 3)





**Figure 1:** Immunohistochemical staining of GDF15 (A, B, C) and MMP1 (D, E, F) based on a 5-step scoring system (range 0-4+). Negative staining of GDF15 in a MN (A), positive (4+) staining in a PM (B) and MM (C), positive (2+) staining of MMP1 in a MN (D), positive (4+) staining in a PM (E) and positive (2+) staining in a MM (F). Original magnification x 200.



**Figure 2:** Distribution of time (months) to melanoma progression among patients with low (0, 1+, 2+) and high (3+, 4+) immunoreactivity as estimated by the Kaplan-Meier method. IHC, immunohistochemistry; PFS, progression free survival. (A) GDF15 staining; (B) MMP1 staining.

| Search Term                                   | Gene Id | Symbol      | Gene Name   | logRatio PM minus MN | Fold change |
|---|---------|-------------|---|----------------------|-------------|
| <b>Gene up regulated in PM compared to MN</b> |         |             |   |                      |             |
| 23532   | 23532   | PRAME       | preferentially expressed antigen in melanoma  | 3.297                | 9.82869584  |
| 6696  | 6696    | SPP1        | secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1) | 2.815                | 7.03719261  |
| 4283  | 4283    | CXCL9       | chemokine (C-X-C motif) ligand 9  | 2.743                | 6.69460994  |
| 221692  | 221692  | PHACTR1     | phosphatase and actin regulator 1   | 2.628                | 6.1816844   |
| 6280  | 6280    | S100A9      | S100 calcium binding protein A9   | 2.628                | 6.1816844   |
| 4312  | 4312    | MMP1        | matrix metalloproteinase 1 (interstitial collagenase)   | 2.624                | 6.16456887  |
| 3854  | 3854    | KRT6B       | keratin 6B  | 2.474                | 5.55582054  |
| 10537   | 10537   | UBD         | ubiquitin D   | 2.349                | 5.0947099   |
| 7453  | 7453    | WARS        | tryptophanyl-tRNA synthetase  | 2.263                | 4.79988553  |
| 6318  | 6318    | SERPINB4    | serpin peptidase inhibitor, clade B (ovalbumin), member 4                                     | 2.256                | 4.77665275  |
| 3627  | 3627    | CXCL10      | chemokine (C-X-C motif) ligand 10   | 2.121                | 4.34995356  |
| 5996  | 5996    | RGS1        | regulator of G-protein signalling 1   | 2.106                | 4.3049605   |
| 2335  | 2335    | FN1         | fibronectin 1   | 2.102                | 4.29304115  |
| 3868  | 3868    | KRT16       | keratin 16 (focal non-epidermolytic palmoplantar keratoderma)                                 | 2.091                | 4.26043281  |
| 3853  | 3853    | KRT6A       | keratin 6A  | 2.087                | 4.24863675  |
| 6698  | 6698    | SPRR1A      | small proline-rich protein 1A   | 2.061                | 4.17275437  |
| 9518  | 9518    | GDF15       | growth differentiation factor 15  | 2.037                | 4.10391258  |
| 2   | 2       | A2M         | alpha-2-macroglobulin   | 1.987                | 3.96411825  |
| 713   | 713     | C1QB        | complement component 1, q subcomponent, B chain   | 1.936                | 3.82643263  |
| 5266  | 5266    | PI3         | peptidase inhibitor 3, skin-derived (SKALP)   | 1.841                | 3.58258268  |
| 91316   | 91316   | LOC91316    | similar to bK246H3.1 (immunoglobulin lambda-like polypeptide 1, pre-B-cell specific)          | 1.829                | 3.55290718  |
| 3371  | 3371    | TNC         | tenascin C (hexabrachion)   | 1.79                 | 3.45814893  |
| 3492  | 3492    | IGH@        | immunoglobulin heavy locus  | 1.785                | 3.44618464  |
| 27299   | 27299   | ADAMDEC1    | ADAM-like, decysin 1  | 1.78                 | 3.43426175  |
| 6279  | 6279    | S100A8      | S100 calcium binding protein A8   | 1.724                | 3.30351066  |
| 91353   | 91353   | CTA-246H3.1 | similar to omega protein  | 1.685                | 3.21540396  |
| 10563   | 10563   | CXCL13      | chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)                                    | 1.66                 | 3.16016525  |
| 712   | 712     | C1QA        | complement component 1, q subcomponent, A chain   | 1.63                 | 3.09512999  |
| 9232  | 9232    | PTTG1       | pituitary tumor-transforming 1  | 1.615                | 3.06311599  |
| 6241  | 6241    | RRM2        | ribonucleotide reductase M2 polypeptide   | 1.593                | 3.01676015  |
| 3937  | 3937    | LCP2        | lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)             | 1.557                | 2.94241349  |
| 6699  | 6699    | SPRR1B      | small proline-rich protein 1B (cornifin)  | 1.55                 | 2.92817139  |
| 6317  | 6317    | SERPINB3    | serpin peptidase inhibitor, clade B (ovalbumin), member 3                                     | 1.54                 | 2.90794503  |
| 4837  | 4837    | NNMT        | nicotinamide N-methyltransferase  | 1.52                 | 2.8679105   |
| 55872   | 55872   | PBK         | PDZ binding kinase  | 1.506                | 2.84021472  |
| 3838  | 3838    | KPNA2       | karyopherin alpha 2 (RAG cohort 1, importin alpha 1)  | 1.487                | 2.8030549   |
| 4435  | 4435    | CITED1      | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1             | 1.481                | 2.79142153  |
| 7037  | 7037    | TFRC        | transferrin receptor (p90, CD71)  | 1.475                | 2.77983644  |
| 3872  | 3872    | KRT17       | keratin 17  | 1.474                | 2.77791027  |
| 3429  | 3429    | IFI27       | interferon, alpha-inducible protein 27  | 1.469                | 2.76829943  |
| 597   | 597     | BCL2A1      | BCL2-related protein A1   | 1.466                | 2.7625489   |
| 10437   | 10437   | IFI30       | interferon, gamma-inducible protein 30  | 1.462                | 2.75490009  |
| 6772  | 6772    | STAT1       | signal transducer and activator of transcription 1, 91kDa                                     | 1.46                 | 2.75108364  |
| 3512  | 3512    | IGJ         | immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides     | 1.456                | 2.74346658  |
| 11065   | 11065   | UBE2C       | ubiquitin-conjugating enzyme E2C  | 1.449                | 2.73018744  |
| 3595  | 3595    | IL12RB2     | interleukin 12 receptor, beta 2   | 1.448                | 2.72829567  |
| 7378  | 7378    | UPP1        | uridine phosphorylase 1   | 1.448                | 2.72829567  |
| 7262  | 7262    | PHLDA2      | pleckstrin homology-like domain, family A, member 2   | 1.436                | 2.70569646  |
| 963   | 963     | CD53        | CD53 molecule   | 1.422                | 2.6795672   |
| 23327   | 23327   | NEDD4L      | neural precursor cell expressed, developmentally down-regulated 4-like                        | 1.402                | 2.64267681  |
| 2633  | 2633    | GBP1        | guanylate binding protein 1, interferon-inducible, 67kDa                                      | 1.383                | 2.60810147  |
| 2537  | 2537    | IFI6        | interferon, alpha-inducible protein 6   | 1.382                | 2.6062943   |
| 7805  | 7805    | LAPTM5      | lysosomal associated multispinning membrane protein 5   | 1.378                | 2.59907812  |
| 1508  | 1508    | CTSB        | cathepsin B   | 1.377                | 2.59727721  |
| 6362  | 6362    | CCL18       | chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)                          | 1.369                | 2.5829147   |
| 813   | 813     | CALU        | calumenin   | 1.369                | 2.5829147   |

|       |       |          |   |       |            |
|-------|-------|----------|---|-------|------------|
| 4162  | 4162  | MCAM     | melanoma cell adhesion molecule   | 1.362 | 2.57041267 |
| 3108  | 3108  | HLA-DMA  | major histocompatibility complex, class II, DM alpha                                      | 1.356 | 2.55974483 |
| 9636  | 9636  | ISG15    | ISG15 ubiquitin-like modifier   | 1.355 | 2.55797116 |
| 2207  | 2207  | FCER1G   | Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide                      | 1.351 | 2.55088878 |
| 822   | 822   | CAPG     | capping protein (actin filament), gelsolin-like   | 1.344 | 2.53854177 |
| 6947  | 6947  | TCN1     | transcobalamin I (vitamin B12 binding protein, R binder family)                           | 1.343 | 2.5367828  |
| 929   | 929   | CD14     | CD14 molecule   | 1.343 | 2.5367828  |
| 1687  | 1687  | DFNA5    | deafness, autosomal dominant 5  | 1.339 | 2.52975908 |
| 6363  | 6363  | CCL19    | chemokine (C-C motif) ligand 19   | 1.331 | 2.51576994 |
| 1282  | 1282  | COL4A1   | collagen, type IV, alpha 1  | 1.32  | 2.4966611  |
| 891   | 891   | CCNB1    | cyclin B1   | 1.314 | 2.48629934 |
| 9332  | 9332  | CD163    | CD163 molecule  | 1.293 | 2.45037066 |
| 1164  | 1164  | CKS2     | CDC28 protein kinase regulatory subunit 2   | 1.291 | 2.44697608 |
| 11015 | 11015 | KDEL3    | KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3                 | 1.288 | 2.44189303 |
| 6574  | 6574  | SLC20A1  | solute carrier family 20 (phosphate transporter), member 1                                | 1.287 | 2.44020102 |
| 22996 | 22996 | C1orf34  | chromosome 1 open reading frame 34  | 1.284 | 2.43513204 |
| 5653  | 5653  | KLK6     | kallikrein-related peptidase 6  | 1.282 | 2.43175857 |
| 6035  | 6035  | RNASE1   | ribonuclease, RNase A family, 1 (pancreatic)  | 1.279 | 2.42670712 |
| 684   | 684   | BST2     | bone marrow stromal cell antigen 2  | 1.273 | 2.41663569 |
| 6352  | 6352  | CCL5     | chemokine (C-C motif) ligand 5  | 1.271 | 2.41328784 |
| 914   | 914   | CD2      | CD2 molecule  | 1.26  | 2.39495741 |
| 22974 | 22974 | TPX2     | TPX2, microtubule-associated, homolog ( <i>Xenopus laevis</i> )                           | 1.259 | 2.39329793 |
| 6955  | 6955  | TRA@     | T cell receptor alpha locus   | 1.258 | 2.39163959 |
| 51303 | 51303 | FKBP11   | FK506 binding protein 11, 19 kDa  | 1.254 | 2.38501774 |
| 55379 | 55379 | LRRC59   | leucine rich repeat containing 59   | 1.249 | 2.37676621 |
| 962   | 962   | CD48     | CD48 molecule   | 1.239 | 2.36034869 |
| 3778  | 3778  | KCNMA1   | potassium large conductance calcium-activated channel, subfamily M, alpha member 1        | 1.234 | 2.3521825  |
| 9133  | 9133  | CCNB2    | cyclin B2   | 1.232 | 2.34892394 |
| 55062 | 55062 | WIPI1    | WD repeat domain, phosphoinositide interacting 1  | 1.229 | 2.34404457 |
| 5698  | 5698  | PSMB9    | proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2) | 1.226 | 2.33917533 |
| 5315  | 5315  | PKM2     | pyruvate kinase, muscle   | 1.225 | 2.3375545  |
| 51514 | 51514 | DTL      | denticleless homolog ( <i>Drosophila</i> )  | 1.224 | 2.33593479 |
| 57103 | 57103 | C12orf5  | chromosome 12 open reading frame 5  | 1.211 | 2.31498043 |
| 7298  | 7298  | TYMS     | thymidylate synthetase  | 1.209 | 2.31177341 |
| 344   | 344   | APOC2    | apolipoprotein C-II   | 1.204 | 2.30377528 |
| 9404  | 9404  | LPXN     | leupaxin  | 1.204 | 2.30377528 |
| 7305  | 7305  | TYROBP   | TYRO protein tyrosine kinase binding protein  | 1.204 | 2.30377528 |
| 3576  | 3576  | IL8      | interleukin 8   | 1.198 | 2.29421405 |
| 9768  | 9768  | KIAA0101 | KIAA0101  | 1.198 | 2.29421405 |
| 23406 | 23406 | COTL1    | coactosin-like 1 ( <i>Dictyostelium</i> )   | 1.197 | 2.29262437 |
| 3001  | 3001  | GZMA     | granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)              | 1.197 | 2.29262437 |
| 9787  | 9787  | DLG7     | discs, large homolog 7 ( <i>Drosophila</i> )  | 1.193 | 2.28627667 |
| 5327  | 5327  | PLAT     | plasminogen activator, tissue   | 1.183 | 2.2704842  |
| 4318  | 4318  | MMP9     | matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)    | 1.174 | 2.25636427 |
| 3059  | 3059  | HCLS1    | hematopoietic cell-specific Lyn substrate 1   | 1.172 | 2.25323846 |
| 397   | 397   | ARHGDIB  | Rho GDP dissociation inhibitor (GDI) beta   | 1.159 | 2.23302592 |
| 972   | 972   | CD74     | CD74 molecule, major histocompatibility complex, class II invariant chain                 | 1.157 | 2.22993244 |
| 9833  | 9833  | MELK     | maternal embryonic leucine zipper kinase  | 1.157 | 2.22993244 |
| 1284  | 1284  | COL4A2   | collagen, type IV, alpha 2  | 1.156 | 2.2283873  |
| 6790  | 6790  | AURKA    | aurora kinase A   | 1.152 | 2.22221746 |
| 4069  | 4069  | LYZ      | lysozyme (renal amyloidosis)  | 1.15  | 2.21913894 |
| 87    | 87    | ACTN1    | actinin, alpha 1  | 1.146 | 2.21299471 |
| 23462 | 23462 | HEY1     | hairy/enhancer-of-split related with YRPW motif 1   | 1.143 | 2.20839769 |
| 1017  | 1017  | CDK2     | cyclin-dependent kinase 2   | 1.141 | 2.20533833 |
| 1033  | 1033  | CDKN3    | cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)        | 1.141 | 2.20533833 |
| 4939  | 4939  | OAS2     | 2'-5'-oligoadenylate synthetase 2, 69/71kDa   | 1.134 | 2.19466388 |
| 6890  | 6890  | TAP1     | transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)                               | 1.133 | 2.19314318 |
| 3669  | 3669  | ISG20    | interferon stimulated exonuclease gene 20kDa  | 1.13  | 2.1885874  |
| 27242 | 27242 | TNFRSF21 | tumor necrosis factor receptor superfamily, member 21                                     | 1.128 | 2.18555548 |

|   |       |           |   |        |            |
|---|-------|-----------|---|--------|------------|
| 4111  | 4111  | MAGEA12   | melanoma antigen family A, 12   | 1.127  | 2.18404109 |
| 6490  | 6490  | SILV      | silver homolog (mouse)  | 1.121  | 2.17497678 |
| 11332   | 11332 | ACOT7     | acyl-CoA thioesterase 7   | 1.121  | 2.17497678 |
| 3003  | 3003  | GZMK      | granzyme K (granzyme 3; tryptase II)  | 1.121  | 2.17497678 |
| 51338   | 51338 | MS4A4A    | membrane-spanning 4-domains, subfamily A, member 4  | 1.119  | 2.17196371 |
| 6271  | 6271  | S100A1    | S100 calcium binding protein A1   | 1.119  | 2.17196371 |
| 6347  | 6347  | CCL2      | chemokine (C-C motif) ligand 2  | 1.114  | 2.16444929 |
| 3959  | 3959  | LGALS3BP  | lectin, galactoside-binding, soluble, 3 binding protein   | 1.114  | 2.16444929 |
| 57016   | 57016 | AKR1B10   | aldo-keto reductase family 1, member B10 (aldose reductase)                                     | 1.104  | 2.14949835 |
| 12  | 12    | SERPINA3  | serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3             | 1.099  | 2.14206165 |
| 3002  | 3002  | GZMB      | granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1)                    | 1.087  | 2.12431837 |
| 7852  | 7852  | CXCR4     | chemokine (C-X-C motif) receptor 4  | 1.084  | 2.11990557 |
| 3394  | 3394  | IRF8      | interferon regulatory factor 8  | 1.08   | 2.11403608 |
| 6373  | 6373  | CXCL11    | chemokine (C-X-C motif) ligand 11   | 1.075  | 2.10672207 |
| 10095   | 10095 | ARPC1B    | actin related protein 2/3 complex, subunit 1B, 41kDa  | 1.071  | 2.10088909 |
| 5265  | 5265  | SERPINA1  | serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1             | 1.071  | 2.10088909 |
| 5214  | 5214  | PFKP      | phosphofructokinase, platelet   | 1.069  | 2.09797866 |
| 3123  | 3123  | HLA-DRB1  | major histocompatibility complex, class II, DR beta 1   | 1.067  | 2.09507225 |
| 51056   | 51056 | LAP3      | leucine aminopeptidase 3  | 1.065  | 2.09216988 |
| 6402  | 6402  | SELL      | selectin L (lymphocyte adhesion molecule 1)   | 1.064  | 2.0907202  |
| 533   | 533   | ATP6V0B   | ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b  | 1.064  | 2.0907202  |
| 58986   | 58986 | TMEM8     | transmembrane protein 8 (five membrane-spanning domains)  | 1.062  | 2.08782385 |
| 717   | 717   | C2        | complement component 2  | 1.061  | 2.08637719 |
| 8836  | 8836  | GGH       | gamma-glutamyl hydrolase (conjugase, folylpolyglutamyl hydrolase)                               | 1.057  | 2.08060053 |
| 11031   | 11031 | RAB31     | RAB31, member RAS oncogene family   | 1.056  | 2.07915887 |
| 51330   | 51330 | TNFRSF12A | tumor necrosis factor receptor superfamily, member 12A  | 1.056  | 2.07915887 |
| 9263  | 9263  | STK17A    | serine/threonine kinase 17a   | 1.055  | 2.07771821 |
| 3122  | 3122  | HLA-DRA   | major histocompatibility complex, class II, DR alpha  | 1.044  | 2.06193664 |
| 948   | 948   | CD36      | CD36 molecule (thrombospondin receptor)   | 1.041  | 2.05765342 |
| 1893  | 1893  | ECM1      | extracellular matrix protein 1  | 1.04   | 2.05622765 |
| 3689  | 3689  | ITGB2     | integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)                              | 1.04   | 2.05622765 |
| 11145   | 11145 | HRASLS3   | HRAS-like suppressor 3  | 1.034  | 2.0476938  |
| 10962   | 10962 | MLLT11    | myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11 | 1.033  | 2.04627494 |
| 4314  | 4314  | MMP3      | matrix metalloproteinase 3 (stromelysin 1, progelatinase)                                       | 1.032  | 2.04485706 |
| 915   | 915   | CD3D      | CD3d molecule, delta (CD3-TCR complex)  | 1.031  | 2.04344017 |
| 3113  | 3113  | HLA-DPA1  | major histocompatibility complex, class II, DP alpha 1  | 1.026  | 2.0363704  |
| 6999  | 6999  | TDO2      | tryptophan 2,3-dioxygenase  | 1.025  | 2.03495938 |
| 3109  | 3109  | HLA-DMB   | major histocompatibility complex, class II, DM beta   | 1.019  | 2.0265138  |
| 1123  | 1123  | CHN1      | chimerin (chimaerin) 1  | 1.019  | 2.0265138  |
| 8870  | 8870  | IER3      | immediate early response 3  | 1.018  | 2.02510961 |
| 2745  | 2745  | GLRX      | glutaredoxin (thioltransferase)   | 1.018  | 2.02510961 |
| 79139   | 79139 | DERL1     | Der1-like domain family, member 1   | 1.01   | 2.0139111  |
| 3713  | 3713  | IVL       | involucrin  | 1.01   | 2.0139111  |
| 332   | 332   | BIRC5     | baculoviral IAP repeat-containing 5 (survivin)  | 1.009  | 2.01251565 |
| 1503  | 1503  | CTPS      | CTP synthase  | 1.007  | 2.00972764 |
| 1601  | 1601  | DAB2      | disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)                              | 1.006  | 2.00833509 |
| 9055  | 9055  | PRC1      | protein regulator of cytokinesis 1  | 1.006  | 2.00833509 |
| 10112   | 10112 | KIF20A    | kinesin family member 20A   | 1.006  | 2.00833509 |
| 1476  | 1476  | CSTB      | cystatin B (stefin B)   | 1.005  | 2.0069435  |
| 29887   | 29887 | SNX10     | sorting nexin 10  | 1.003  | 2.00416321 |
| 5641  | 5641  | LGMN      | legumain  | 1.001  | 2.00138677 |
| 5476  | 5476  | CTSA      | cathepsin A   | 1      | 2          |
| <b>Gene down regulated in PM compared to MN</b> |       |           |   |        |            |
| 6137  | 6137  | RPL13     | ribosomal protein L13   | -1.004 | 2.00555287 |
| 80201   | 80201 | HKDC1     | hexokinase domain containing 1  | -1.005 | 2.0069435  |
| 4501  | 4501  | MT1X      | metallothionein 1X  | -1.005 | 2.0069435  |
| 29997   | 29997 | GLTSCR2   | glioma tumor suppressor candidate region gene 2   | -1.005 | 2.0069435  |
| 5803  | 5803  | PTPRZ1    | protein tyrosine phosphatase, receptor-type, Z polypeptide 1                                    | -1.013 | 2.01810327 |
| 91851   | 91851 | CHRD1     | chordin-like 1  | -1.014 | 2.0195026  |

|        |        |              |   |        |            |
|--------|--------|--------------|---|--------|------------|
| 23650  | 23650  | TRIM29       | tripartite motif-containing 29  | -1.016 | 2.02230416 |
| 10351  | 10351  | ABCA8        | ATP-binding cassette, sub-family A (ABC1), member 8                                 | -1.019 | 2.0265138  |
| 2628   | 2628   | GATM         | glycine amidinotransferase (L-arginine:glycine amidinotransferase)                  | -1.021 | 2.02932509 |
| 3590   | 3590   | IL11RA       | interleukin 11 receptor, alpha  | -1.024 | 2.03354935 |
| 6304   | 6304   | SATB1        | SATB homeobox 1   | -1.029 | 2.04060932 |
| 23461  | 23461  | ABCA5        | ATP-binding cassette, sub-family A (ABC1), member 5                                 | -1.031 | 2.04344017 |
| 120    | 120    | ADD3         | adducin 3 (gamma)   | -1.033 | 2.04627494 |
| 3480   | 3480   | IGF1R        | insulin-like growth factor 1 receptor   | -1.033 | 2.04627494 |
| 55638  | 55638  | FLJ20366     | hypothetical protein FLJ20366   | -1.034 | 2.0476938  |
| 92211  | 92211  | PCDH21       | protocadherin 21  | -1.037 | 2.05195629 |
| 23705  | 23705  | CADM1        | cell adhesion molecule 1  | -1.037 | 2.05195629 |
| 1153   | 1153   | CIRBP        | cold inducible RNA binding protein  | -1.039 | 2.05480288 |
| 9638   | 9638   | FEZ1         | fasciculation and elongation protein zeta 1 (zygin I)                               | -1.04  | 2.05622765 |
| 3316   | 3316   | HSPB2        | heat shock 27kDa protein 2  | -1.044 | 2.06193664 |
| 7102   | 7102   | TSPAN7       | tetraspanin 7   | -1.045 | 2.06336636 |
| 10278  | 10278  | EFS          | embryonal Fyn-associated substrate  | -1.047 | 2.06622878 |
| 5325   | 5325   | PLAGL1       | pleiomorphic adenoma gene-like 1  | -1.048 | 2.06766147 |
| 2947   | 2947   | GSTM3        | glutathione S-transferase M3 (brain)  | -1.049 | 2.06909516 |
| 7306   | 7306   | TYRP1        | tyrosinase-related protein 1  | -1.049 | 2.06909516 |
| 55366  | 55366  | LGR4         | leucine-rich repeat-containing G protein-coupled receptor 4                         | -1.054 | 2.07627854 |
| 56967  | 56967  | C14orf132    | chromosome 14 open reading frame 132  | -1.057 | 2.08060053 |
| 81578  | 81578  | COL21A1      | collagen, type XXI, alpha 1   | -1.057 | 2.08060053 |
| 23075  | 23075  | SWAP70       | SWAP-70 protein   | -1.069 | 2.09797866 |
| 3131   | 3131   | HLF          | hepatic leukemia factor   | -1.071 | 2.10088909 |
| 51309  | 51309  | ARMCX1       | armadillo repeat containing, X-linked 1   | -1.074 | 2.10526231 |
| 23037  | 23037  | PDZD2        | PDZ domain containing 2   | -1.076 | 2.10818285 |
| 1474   | 1474   | CST6         | cystatin E/M  | -1.083 | 2.11843667 |
| 23641  | 23641  | LDOC1        | leucine zipper, down-regulated in cancer 1  | -1.088 | 2.12579135 |
| 224    | 224    | ALDH3A2      | aldehyde dehydrogenase 3 family, member A2  | -1.092 | 2.13169347 |
| 1028   | 1028   | CDKN1C       | cyclin-dependent kinase inhibitor 1C (p57, Kip2)                                    | -1.098 | 2.1405774  |
| 84909  | 84909  | C9orf3       | chromosome 9 open reading frame 3   | -1.11  | 2.15845647 |
| 1828   | 1828   | DSG1         | desmoglein 1  | -1.113 | 2.16294953 |
| 7991   | 7991   | TUSC3        | tumor suppressor candidate 3  | -1.115 | 2.16595009 |
| 79652  | 79652  | C16orf30     | chromosome 16 open reading frame 30   | -1.124 | 2.17950422 |
| 7704   | 7704   | ZBTB16       | zinc finger and BTB domain containing 16  | -1.126 | 2.18252775 |
| 26053  | 26053  | AUTS2        | autism susceptibility candidate 2   | -1.129 | 2.18707091 |
| 7101   | 7101   | NR2E1        | nuclear receptor subfamily 2, group E, member 1                                     | -1.129 | 2.18707091 |
| 22798  | 22798  | LAMB4        | laminin, beta 4   | -1.134 | 2.19466388 |
| 23678  | 23678  | SGK3         | serum/glucocorticoid regulated kinase family, member 3                              | -1.136 | 2.19770844 |
| 1832   | 1832   | DSP          | desmoplakin   | -1.138 | 2.20075722 |
| 25854  | 25854  | DKFZP564J102 | DKFZP564J102 protein  | -1.14  | 2.20381023 |
| 1974   | 1974   | EIF4A2       | eukaryotic translation initiation factor 4A, isoform 2                              | -1.145 | 2.21146131 |
| 8796   | 8796   | SCEL         | sciellin  | -1.156 | 2.2283873  |
| 6662   | 6662   | SOX9         | SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal) | -1.156 | 2.2283873  |
| 7088   | 7088   | TLE1         | transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)                    | -1.163 | 2.23922578 |
| 738    | 738    | C11orf2      | chromosome 11 open reading frame2   | -1.168 | 2.24699981 |
| 2153   | 2153   | F5           | coagulation factor V (proaccelerin, labile factor)                                  | -1.169 | 2.24855785 |
| 51302  | 51302  | CYP39A1      | cytochrome P450, family 39, subfamily A, polypeptide 1                              | -1.177 | 2.26106113 |
| 9890   | 9890   | LPPR4        | plasticity related gene 1   | -1.186 | 2.27521046 |
| 563    | 563    | AZGP1        | alpha-2-glycoprotein 1, zinc-binding  | -1.187 | 2.27678806 |
| 114088 | 114088 | TRIM9        | tripartite motif-containing 9   | -1.194 | 2.28786195 |
| 4897   | 4897   | NRCAM        | neuronal cell adhesion molecule   | -1.195 | 2.28944832 |
| 9413   | 9413   | C9orf61      | chromosome 9 open reading frame 61  | -1.197 | 2.29262437 |
| 23635  | 23635  | SSBP2        | single-stranded DNA binding protein 2   | -1.207 | 2.30857084 |
| 65982  | 65982  | ZSCAN18      | zinc finger and SCAN domain containing 18   | -1.218 | 2.32624008 |
| 1823   | 1823   | DSC1         | desmocollin 1   | -1.245 | 2.37018554 |
| 3400   | 3400   | ID4          | inhibitor of DNA binding 4, dominant negative helix-loop-helix protein              | -1.269 | 2.40994463 |
| 2261   | 2261   | FGFR3        | fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)        | -1.269 | 2.40994463 |
| 55227  | 55227  | LRR1         | leucine rich repeat containing 1  | -1.271 | 2.41328784 |
| 1825   | 1825   | DSC3         | desmocollin 3   | -1.274 | 2.41831135 |
| 3861   | 3861   | KRT14        | keratin 14 (epidermolysis bullosa simplex, Dowling-Meara, Koebner)                  | -1.275 | 2.41998818 |
| 25875  | 25875  | LETMD1       | LETM1 domain containing 1   | -1.282 | 2.43175857 |

|        |        |               |  |        |            |
|--------|--------|---------------|--|--------|------------|
| 1308   | 1308   | COL17A1       | collagen, type XVII, alpha 1   | -1.292 | 2.44867278 |
| 8470   | 8470   | SORBS2        | sorbin and SH3 domain containing 2   | -1.299 | 2.46058269 |
| 4014   | 4014   | LOR           | loricrin   | -1.3   | 2.46228883 |
| 80310  | 80310  | PDGFD         | platelet derived growth factor D   | -1.303 | 2.46741434 |
| 259217 | 259217 | HSPA12A       | heat shock 70kDa protein 12A   | -1.306 | 2.47255052 |
| 51765  | 51765  | RP6-213H19.1  | serine/threonine protein kinase MST4   | -1.32  | 2.4966611  |
| 23382  | 23382  | KIAA0828      | adenosylhomocysteinase 3   | -1.329 | 2.51228476 |
| 4023   | 4023   | LPL           | lipoprotein lipase   | -1.33  | 2.51402675 |
| 2878   | 2878   | GPX3          | glutathione peroxidase 3 (plasma)  | -1.345 | 2.54030197 |
| 3769   | 3769   | KCNJ13        | potassium inwardly-rectifying channel, subfamily J, member 13                        | -1.347 | 2.54382601 |
| 3852   | 3852   | KRT5          | keratin 5 (epidermolysis bullosa simplex, Dowling-Meara/Kobner/Weber-Cockayne types) | -1.349 | 2.54735495 |
| 51673  | 51673  | CGI-38        | brain specific protein   | -1.355 | 2.55797116 |
| 5836   | 5836   | PYGL          | phosphorylase, glycogen; liver (Hers disease, glycogen storage disease type VI)      | -1.366 | 2.57754926 |
| 2625   | 2625   | GATA3         | GATA binding protein 3   | -1.377 | 2.59727721 |
| 113146 | 113146 | C14orf78      | chromosome 14 open reading frame 78  | -1.401 | 2.64084568 |
| 8404   | 8404   | SPARCL1       | SPARC-like 1 (mast9, hevin)  | -1.403 | 2.64450921 |
| 5348   | 5348   | FXYD1         | FXYD domain containing ion transport regulator 1 (phospholemmann)                    | -1.41  | 2.65737163 |
| 3080   | 3080   | CFHR2         | complement factor H-related 2  | -1.435 | 2.70382167 |
| 63928  | 63928  | LOC63928      | hepatocellular carcinoma antigen gene 520  | -1.45  | 2.73208051 |
| 688    | 688    | KLF5          | Kruppel-like factor 5 (intestinal)   | -1.456 | 2.74346658 |
| 10218  | 10218  | ANGPTL7       | angiopoietin-like 7  | -1.46  | 2.75108364 |
| 9355   | 9355   | LHX2          | LIM homeobox 2   | -1.499 | 2.82646729 |
| 667    | 667    | DST           | dystonin   | -1.506 | 2.84021472 |
| 83604  | 83604  | TMEM47        | transmembrane protein 47   | -1.533 | 2.89386977 |
| 1272   | 1272   | CNTN1         | contactin 1  | -1.542 | 2.9119791  |
| 1428   | 1428   | CRYM          | crystallin, mu   | -1.561 | 2.95058291 |
| 3849   | 3849   | KRT2          | keratin 2 (epidermal ichthyosis bullosa of Siemens)                                  | -1.574 | 2.97729051 |
| 23086  | 23086  | EXPH5         | exophilin 5  | -1.608 | 3.04828966 |
| 9547   | 9547   | CXCL14        | chemokine (C-X-C motif) ligand 14  | -1.619 | 3.07162054 |
| 2487   | 2487   | FRZB          | frizzled-related protein   | -1.642 | 3.12098192 |
| 4308   | 4308   | TRPM1         | transient receptor potential cation channel, subfamily M, member 1                   | -1.646 | 3.12964713 |
| 5507   | 5507   | PPP1R3C       | protein phosphatase 1, regulatory (inhibitor) subunit 3C                             | -1.66  | 3.16016525 |
| 10391  | 10391  | CORO2B        | coronin, actin binding protein, 2B   | -1.664 | 3.16893924 |
| 2259   | 2259   | FGF14         | fibroblast growth factor 14  | -1.673 | 3.18876991 |
| 445    | 445    | ASS1          | argininosuccinate synthetase 1   | -1.697 | 3.24226048 |
| 4118   | 4118   | MAL           | mal, T-cell differentiation protein  | -1.711 | 3.27387673 |
| 10850  | 10850  | CCL27         | chemokine (C-C motif) ligand 27  | -1.756 | 3.37760355 |
| 3848   | 3848   | KRT1          | keratin 1 (epidermolytic hyperkeratosis)   | -1.77  | 3.41053957 |
| 55118  | 55118  | CRTAC1        | cartilage acidic protein 1   | -1.776 | 3.42475314 |
| 11341  | 11341  | SCRG1         | scrapie responsive protein 1   | -1.956 | 3.87984764 |
| 2861   | 2861   | GPR37         | G protein-coupled receptor 37 (endothelin receptor type B-like)                      | -1.957 | 3.88253788 |
| 25891  | 25891  | DKFZP586H2123 | regeneration associated muscle protease  | -1.976 | 3.9340083  |
| 64131  | 64131  | XYLT1         | xylosyltransferase I   | -1.985 | 3.95862663 |
| 2173   | 2173   | FABP7         | fatty acid binding protein 7, brain  | -2.009 | 4.02503129 |
| 10752  | 10752  | CHL1          | cell adhesion molecule with homology to L1CAM (close homolog of L1)                  | -2.124 | 4.35900845 |
| 7021   | 7021   | TFAP2B        | transcription factor AP-2 beta (activating enhancer binding protein 2 beta)          | -2.479 | 5.57510895 |
| 3866   | 3866   | KRT15         | keratin 15   | -2.662 | 6.32909841 |
| 5764   | 5764   | PTN           | pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)    | -2.895 | 7.43843954 |
| 3075   | 3075   | CFH           | complement factor H  | -2.949 | 7.7221362  |

| Search Term                                     | Gene Id | Symbol      | Gene Name  | logRatio MM minus PM | Fold Change |
|---|---------|-------------|--|----------------------|-------------|
| <b>Gene up regulated in MM compared to PM</b>   |         |             |  |                      |             |
| 6696  | 6696    | SPP1        | secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1)  | 1.797                | 3.47496874  |
| 4745  | 4745    | NELL1       | NEL-like 1 (chicken)   | 1.697                | 3.24226048  |
| 6192  | 6192    | RPS4Y1      | ribosomal protein S4, Y-linked 1   | 1.554                | 2.93630127  |
| 91353   | 91353   | CTA-246H3.1 | similar to omega protein   | 1.515                | 2.85798828  |
| 91316   | 91316   | LOC91316    | similar to bK246H3.1 (immunoglobulin lambda-like polypeptide 1, pre-B-cell specific)   | 1.499                | 2.82646729  |
| 4256  | 4256    | MGP         | matrix Gla protein   | 1.392                | 2.62442251  |
| 216   | 216     | ALDH1A1     | aldehyde dehydrogenase 1 family, member A1   | 1.367                | 2.5793365   |
| 4111  | 4111    | MAGEA12     | melanoma antigen family A, 12  | 1.333                | 2.51925996  |
| 3426  | 3426    | CFI         | complement factor I  | 1.278                | 2.42502564  |
| 2947  | 2947    | GSTM3       | glutathione S-transferase M3 (brain)   | 1.262                | 2.39827983  |
| 23336   | 23336   | DMN         | desmuslin  | 1.247                | 2.3734736   |
| 12  | 12      | SERPINA3    | serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3  | 1.211                | 2.31498043  |
| 3485  | 3485    | IGFBP2      | insulin-like growth factor binding protein 2, 36kDa  | 1.206                | 2.30697121  |
| 3492  | 3492    | IGH@        | immunoglobulin heavy locus   | 1.191                | 2.28310941  |
| 6781  | 6781    | STC1        | stanniocalcin 1  | 1.157                | 2.22993244  |
| 730   | 730     | C7          | complement component 7   | 1.151                | 2.22067767  |
| 7422  | 7422    | VEGFA       | vascular endothelial growth factor A   | 1.14                 | 2.20381023  |
| 4233  | 4233    | MET         | met proto-oncogene (hepatocyte growth factor receptor)   | 1.136                | 2.19770844  |
| 2138  | 2138    | EYA1        | eyes absent homolog 1 (Drosophila)   | 1.087                | 2.12431837  |
| 2335  | 2335    | FN1         | fibronectin 1  | 1.071                | 2.10088909  |
| 7991  | 7991    | TUSC3       | tumor suppressor candidate 3   | 1.044                | 2.06193664  |
| 5352  | 5352    | PLOD2       | procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2   | 1.038                | 2.05337909  |
| 7078  | 7078    | TIMP3       | TIMP metalloproteinase inhibitor 3 (Sorsby fundus dystrophy, pseudoinflammatory)   | 1.026                | 2.0363704   |
| 7018  | 7018    | TF          | transferrin  | 1.024                | 2.03354935  |
| 1E+05   | 114088  | TRIM9       | tripartite motif-containing 9  | 1.022                | 2.0307322   |
| 5740  | 5740    | PTGIS       | prostaglandin I2 (prostacyclin) synthase   | 1.002                | 2.00277451  |
| <b>Gene down regulated in MM compared to PM</b> |         |             |  |                      |             |
| 27065   | 27065   | D4S234E     | DNA segment on chromosome 4 (unique) 234 expressed sequence  | -1.011               | 2.01530752  |
| 6283  | 6283    | S100A12     | S100 calcium binding protein A12   | -1.013               | 2.01810327  |
| 2878  | 2878    | GPX3        | glutathione peroxidase 3 (plasma)  | -1.017               | 2.0237064   |
| 7286  | 7286    | TUFT1       | tuftelin 1   | -1.019               | 2.0265138   |
| 909   | 909     | CD1A        | CD1a molecule  | -1.022               | 2.0307322   |
| 4155  | 4155    | MBP         | myelin basic protein   | -1.024               | 2.03354935  |
| 445   | 445     | ASS1        | argininosuccinate synthetase 1   | -1.027               | 2.03778239  |
| 11254   | 11254   | SLC6A14     | solute carrier family 6 (amino acid transporter), member 14  | -1.028               | 2.03919537  |
| 23593   | 23593   | HEBP2       | heme binding protein 2   | -1.033               | 2.04627494  |
| 26085   | 26085   | KLK13       | kallikrein-related peptidase 13  | -1.033               | 2.04627494  |
| 3557  | 3557    | IL1RN       | interleukin 1 receptor antagonist  | -1.036               | 2.05053448  |
| 55040   | 55040   | EPN3        | epsin 3  | -1.037               | 2.05195629  |
| 306   | 306     | ANXA3       | annexin A3   | -1.038               | 2.05337909  |
| 1E+05   | 131578  | LRRC15      | leucine rich repeat containing 15  | -1.038               | 2.05337909  |
| 2707  | 2707    | GJB3        | gap junction protein, beta 3, 31kDa  | -1.044               | 2.06193664  |
| 6401  | 6401    | SELE        | selectin E (endothelial adhesion molecule 1)   | -1.048               | 2.06766147  |
| 55612   | 55612   | C20orf42    | chromosome 20 open reading frame 42  | -1.051               | 2.07196553  |
| 3983  | 3983    | ABLIM1      | actin binding LIM protein 1  | -1.062               | 2.08782385  |
| 563   | 563     | AZGP1       | alpha-2-glycoprotein 1, zinc-binding   | -1.064               | 2.0907202   |
| 646   | 646     | BNC1        | basonuclin 1   | -1.065               | 2.09216988  |
| 1646  | 1646    | AKR1C2      | aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase, type III) | -1.065               | 2.09216988  |
| 3918  | 3918    | LAMC2       | laminin, gamma 2   | -1.067               | 2.09507225  |
| 10276   | 10276   | NET1        | neuroepithelial cell transforming gene 1   | -1.076               | 2.10818285  |
| 288   | 288     | ANK3        | ankyrin 3, node of Ranvier (ankyrin G)   | -1.076               | 2.10818285  |
| 10850   | 10850   | CCL27       | chemokine (C-C motif) ligand 27  | -1.077               | 2.10964463  |
| 4499  | 4499    | MT1M        | metallothionein 1M   | -1.078               | 2.11110744  |
| 51458   | 51458   | RHCG        | Rh family, C glycoprotein  | -1.08                | 2.11403608  |
| 1515  | 1515    | CTSL2       | cathepsin L2   | -1.083               | 2.11843667  |
| 3117  | 3117    | HLA-DQA1    | major histocompatibility complex, class II, DQ alpha 1   | -1.085               | 2.12137548  |
| 6362  | 6362    | CCL18       | chemokine (C-C motif) ligand 18 (pulmonary and activation-   | -1.094               | 2.13465068  |



|       |       |           |  |        |            |
|-------|-------|-----------|--|--------|------------|
|       |       |           | regulated)   |        |            |
| 80004 | 80004 | RBM35B    | RNA binding motif protein 35B  | -1.097 | 2.13909418 |
| 51228 | 51228 | GLTP      | glycolipid transfer protein  | -1.106 | 2.15248025 |
| 1040  | 1040  | CDS1      | CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 1                                   | -1.124 | 2.17950422 |
| 3909  | 3909  | LAMA3     | laminin, alpha 3   | -1.129 | 2.18707091 |
| 202   | 202   | AIM1      | absent in melanoma 1   | -1.132 | 2.19162353 |
| 5655  | 5655  | KLK10     | kallikrein-related peptidase 10  | -1.134 | 2.19466388 |
| 9314  | 9314  | KLF4      | Kruppel-like factor 4 (gut)  | -1.14  | 2.20381023 |
| 4856  | 4856  | NOV       | nephroblastoma overexpressed gene  | -1.14  | 2.20381023 |
| 1359  | 1359  | CPA3      | carboxypeptidase A3 (mast cell)  | -1.159 | 2.23302592 |
| 1718  | 1718  | DHCR24    | 24-dehydrocholesterol reductase  | -1.164 | 2.24077843 |
| 51200 | 51200 | CPA4      | carboxypeptidase A4  | -1.176 | 2.25949443 |
| 1001  | 1001  | CDH3      | cadherin 3, type 1, P-cadherin (placental)   | -1.199 | 2.29580483 |
| 11187 | 11187 | PKP3      | plakophilin 3  | -1.201 | 2.2989897  |
| 242   | 242   | ALOX12B   | arachidonate 12-lipoxygenase, 12R type   | -1.209 | 2.31177341 |
| 3934  | 3934  | LCN2      | lipocalin 2 (oncogene 24p3)  | -1.211 | 2.31498043 |
| 222   | 222   | ALDH3B2   | aldehyde dehydrogenase 3 family, member B2   | -1.238 | 2.35871318 |
| 10974 | 10974 | C10orf116 | chromosome 10 open reading frame 116   | -1.238 | 2.35871318 |
| 3120  | 3120  | HLA-DQB2  | major histocompatibility complex, class II, DQ beta 2  | -1.245 | 2.37018554 |
| 53905 | 53905 | DUOX1     | dual oxidase 1   | -1.256 | 2.38832637 |
| 8673  | 8673  | VAMP8     | vesicle-associated membrane protein 8 (endobrevin)   | -1.258 | 2.39163959 |
| 6785  | 6785  | ELOVL4    | elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 4                     | -1.265 | 2.4032721  |
| 1956  | 1956  | EGFR      | epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian) | -1.265 | 2.4032721  |
| 25797 | 25797 | QPCT      | glutaminy-peptide cyclotransferase (glutaminy cyclase)   | -1.268 | 2.40827476 |
| 1824  | 1824  | DSC2      | desmocollin 2  | -1.273 | 2.41663569 |
| 8626  | 8626  | TP73L     | tumor protein p73-like   | -1.281 | 2.43007358 |
| 771   | 771   | CA12      | carbonic anhydrase XII   | -1.288 | 2.44189303 |
| 26154 | 26154 | ABCA12    | ATP-binding cassette, sub-family A (ABC1), member 12   | -1.296 | 2.45547137 |
| 7851  | 7851  | MALL      | mal, T-cell differentiation protein-like   | -1.303 | 2.46741434 |
| 6820  | 6820  | SULT2B1   | sulfotransferase family, cytosolic, 2B, member 1   | -1.324 | 2.50359292 |
| 2261  | 2261  | FGFR3     | fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)                       | -1.329 | 2.51228476 |
| 5646  | 5646  | PRSS3     | protease, serine, 3 (mesotrypsin)  | -1.331 | 2.51576994 |
| 7051  | 7051  | TGM1      | transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase)   | -1.338 | 2.5280062  |
| 80740 | 80740 | LY6G6C    | lymphocyte antigen 6 complex, locus G6C  | -1.344 | 2.53854177 |
| 688   | 688   | KLF5      | Kruppel-like factor 5 (intestinal)   | -1.35  | 2.54912125 |
| 7447  | 7447  | VSNL1     | visinin-like 1   | -1.356 | 2.55974483 |
| 6286  | 6286  | S100P     | S100 calcium binding protein P   | -1.374 | 2.59188193 |
| 57758 | 57758 | SCUBE2    | signal peptide, CUB domain, EGF-like 2   | -1.4   | 2.63901582 |
| 5275  | 5275  | SERPINB13 | serpin peptidase inhibitor, clade B (ovalbumin), member 13   | -1.404 | 2.64634288 |
| 4493  | 4493  | MT1E      | metallothionein 1E   | -1.412 | 2.66105808 |
| 1634  | 1634  | DCN       | decorin  | -1.414 | 2.66474965 |
| 3613  | 3613  | IMPA2     | inositol(myo)-1(or 4)-monophosphatase 2  | -1.418 | 2.67214816 |
| 3898  | 3898  | LAD1      | ladinin 1  | -1.419 | 2.67400099 |
| 6337  | 6337  | SCNN1A    | sodium channel, nonvoltage-gated 1 alpha   | -1.427 | 2.68886999 |
| 1308  | 1308  | COL17A1   | collagen, type XVII, alpha 1   | -1.427 | 2.68886999 |
| 760   | 760   | CA2       | carbonic anhydrase II  | -1.431 | 2.69633546 |
| 5055  | 5055  | SERPINB2  | serpin peptidase inhibitor, clade B (ovalbumin), member 2  | -1.454 | 2.73966596 |
| 5653  | 5653  | KLK6      | kallikrein-related peptidase 6   | -1.466 | 2.7625489  |
| 7739  | 7739  | ZNF185    | zinc finger protein 185 (LIM domain)   | -1.469 | 2.76829943 |
| 10653 | 10653 | SPINT2    | serine peptidase inhibitor, Kunitz type, 2   | -1.473 | 2.77598544 |
| 2205  | 2205  | FCER1A    | Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide                               | -1.474 | 2.77791027 |
| 79852 | 79852 | ABHD9     | abhydrolase domain containing 9  | -1.481 | 2.79142153 |
| 999   | 999   | CDH1      | cadherin 1, type 1, E-cadherin (epithelial)  | -1.513 | 2.85402901 |
| 3429  | 3429  | IFI27     | interferon, alpha-inducible protein 27   | -1.566 | 2.9608266  |
| 8710  | 8710  | SERPINB7  | serpin peptidase inhibitor, clade B (ovalbumin), member 7  | -1.57  | 2.96904714 |
| 9022  | 9022  | CLIC3     | chloride intracellular channel 3   | -1.575 | 2.97935493 |
| 8424  | 8424  | BBOX1     | butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1              | -1.591 | 3.01258093 |
| 25984 | 25984 | KRT23     | keratin 23 (histone deacetylase inducible)   | -1.627 | 3.08870053 |
| 10874 | 10874 | NMU       | neuromedin U   | -1.646 | 3.12964713 |
| 6382  | 6382  | SDC1      | syndecan 1   | -1.652 | 3.14269007 |
| 79983 | 79983 | POF1B     | premature ovarian failure, 1B  | -1.683 | 3.21094955 |
| 2697  | 2697  | GJA1      | gap junction protein, alpha 1, 43kDa   | -1.691 | 3.2288043  |
| 23086 | 23086 | EXPH5     | exophilin 5  | -1.691 | 3.2288043  |

|       |        |          |  |        |            |
|-------|--------|----------|--|--------|------------|
| 3397  | 3397   | ID1      | inhibitor of DNA binding 1, dominant negative helix-loop-helix protein               | -1.703 | 3.25577274 |
| 57152 | 57152  | SLURP1   | secreted LY6/PLAUR domain containing 1   | -1.71  | 3.27160823 |
| 3728  | 3728   | JUP      | junction plakoglobin   | -1.759 | 3.38463439 |
| 7306  | 7306   | TYRP1    | tyrosinase-related protein 1   | -1.766 | 3.40109664 |
| 822   | 822    | CAPG     | capping protein (actin filament), gelsolin-like                                      | -1.769 | 3.40817638 |
| 1525  | 1525   | CXADR    | coxsackie virus and adenovirus receptor  | -1.786 | 3.44857418 |
| 9890  | 9890   | LPPR4    | plasticity related gene 1  | -1.789 | 3.45575275 |
| 11012 | 11012  | KLK11    | kallikrein-related peptidase 11  | -1.797 | 3.47496874 |
| 4312  | 4312   | MMP1     | matrix metalloproteinase 1 (interstitial collagenase)                                | -1.831 | 3.55783597 |
| 667   | 667    | DST      | dystonin   | -1.832 | 3.56030293 |
| 9982  | 9982   | FGFBP1   | fibroblast growth factor binding protein 1   | -1.837 | 3.57266341 |
| 934   | 934    | CD24     | CD24 molecule  | -1.859 | 3.62756132 |
| 7277  | 7277   | TUBA4A   | tubulin, alpha 4a  | -1.862 | 3.63511247 |
| 8796  | 8796   | SCEL     | sciellin   | -1.893 | 3.71406741 |
| 1E+05 | 113146 | C14orf78 | chromosome 14 open reading frame 78  | -1.931 | 3.81319418 |
| 79755 | 79755  | ZNF750   | zinc finger protein 750  | -1.951 | 3.86642439 |
| 1041  | 1041   | CDSN     | corneodesmosin   | -1.964 | 3.90142185 |
| 57016 | 57016  | AKR1B10  | aldo-keto reductase family 1, member B10 (aldose reductase)                          | -2.013 | 4.03620654 |
| 57111 | 57111  | RAB25    | RAB25, member RAS oncogene family  | -2.021 | 4.05865019 |
| 11202 | 11202  | KLK8     | kallikrein-related peptidase 8   | -2.056 | 4.15831774 |
| 3858  | 3858   | KRT10    | keratin 10 (epidermolytic hyperkeratosis; keratosis palmaris et plantaris)           | -2.096 | 4.27522396 |
| 1382  | 1382   | CRABP2   | cellular retinoic acid binding protein 2   | -2.101 | 4.29006647 |
| 3815  | 3815   | KIT      | v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog                        | -2.11  | 4.31691295 |
| 1672  | 1672   | DEFB1    | defensin, beta 1   | -2.173 | 4.50960165 |
| 25818 | 25818  | KLK5     | kallikrein-related peptidase 5   | -2.201 | 4.59797939 |
| 3034  | 3034   | HAL      | histidine ammonia-lyase  | -2.21  | 4.62675274 |
| 26239 | 26239  | LCE2B    | late cornified envelope 2B   | -2.272 | 4.82992237 |
| 3866  | 3866   | KRT15    | keratin 15   | -2.301 | 4.92799229 |
| 6590  | 6590   | SLPI     | secretory leukocyte peptidase inhibitor  | -2.372 | 5.17658262 |
| 360   | 360    | AQP3     | aquaporin 3 (Gill blood group)   | -2.386 | 5.22706102 |
| 64065 | 64065  | PERP     | PERP, TP53 apoptosis effector  | -2.412 | 5.32211616 |
| 23650 | 23650  | TRIM29   | tripartite motif-containing 29   | -2.425 | 5.37029001 |
| 5493  | 5493   | PPL      | periplakin   | -2.488 | 5.609997   |
| 383   | 383    | ARG1     | arginase, liver  | -2.522 | 5.74377804 |
| 57402 | 57402  | S100A14  | S100 calcium binding protein A14   | -2.527 | 5.763719   |
| 5650  | 5650   | KLK7     | kallikrein-related peptidase 7   | -2.552 | 5.86446703 |
| 4070  | 4070   | TACSTD2  | tumor-associated calcium signal transducer 2   | -2.589 | 6.01681501 |
| 5266  | 5266   | PI3      | peptidase inhibitor 3, skin-derived (SKALP)  | -2.618 | 6.13898438 |
| 84525 | 84525  | HOP      | homeodomain-only protein   | -2.682 | 6.41744933 |
| 1825  | 1825   | DSC3     | desmocollin 3  | -2.682 | 6.41744933 |
| 1474  | 1474   | CST6     | cystatin E/M   | -2.69  | 6.45313407 |
| 810   | 810    | CALML3   | calmodulin-like 3  | -2.698 | 6.48901724 |
| 27076 | 27076  | LYPD3    | LY6/PLAUR domain containing 3  | -2.708 | 6.53415193 |
| 3849  | 3849   | KRT2     | keratin 2 (epidermal ichthyosis bullosa of Siemens)                                  | -2.727 | 6.62077453 |
| 1830  | 1830   | DSG3     | desmoglein 3 (pemphigus vulgaris antigen)  | -2.826 | 7.09105359 |
| 9635  | 9635   | CLCA2    | chloride channel, calcium activated, family member 2                                 | -2.902 | 7.47461878 |
| 4014  | 4014   | LOR      | loricrin   | -2.953 | 7.74357622 |
| 6317  | 6317   | SERPINB3 | serpin peptidase inhibitor, clade B (ovalbumin), member 3                            | -2.993 | 7.96127777 |
| 3713  | 3713   | IVL      | involucrin   | -3.116 | 8.66980773 |
| 2810  | 2810   | SFN      | stratifin  | -3.132 | 8.76649413 |
| 6318  | 6318   | SERPINB4 | serpin peptidase inhibitor, clade B (ovalbumin), member 4                            | -3.147 | 8.85811668 |
| 1828  | 1828   | DSG1     | desmoglein 1   | -3.177 | 9.04424454 |
| 9547  | 9547   | CXCL14   | chemokine (C-X-C motif) ligand 14  | -3.24  | 9.44794129 |
| 51806 | 51806  | CALML5   | calmodulin-like 5  | -3.451 | 10.9358996 |
| 1832  | 1832   | DSP      | desmoplakin  | -3.469 | 11.0731977 |
| 1823  | 1823   | DSC1     | desmocollin 1  | -3.491 | 11.2433496 |
| 3868  | 3868   | KRT16    | keratin 16 (focal non-epidermolytic palmoplantar keratoderma)                        | -3.564 | 11.8268995 |
| 11005 | 11005  | SPINK5   | serine peptidase inhibitor, Kazal type 5   | -3.587 | 12.0169594 |
| 6280  | 6280   | S100A9   | S100 calcium binding protein A9  | -3.629 | 12.3719414 |
| 1475  | 1475   | CSTA     | cystatin A (stefin A)  | -3.647 | 12.5272687 |
| 6698  | 6698   | SPRR1A   | small proline-rich protein 1A  | -3.774 | 13.6800348 |
| 3872  | 3872   | KRT17    | keratin 17   | -3.966 | 15.6273365 |
| 6273  | 6273   | S100A2   | S100 calcium binding protein A2  | -4.102 | 17.1721646 |
| 5268  | 5268   | SERPINB5 | serpin peptidase inhibitor, clade B (ovalbumin), member 5                            | -4.134 | 17.557311  |
| 3852  | 3852   | KRT5     | keratin 5 (epidermolysis bullosa simplex, Dowling-Meara/Kobner/Weber-Cockayne types) | -4.462 | 22.0392007 |

|      |      |        |  |        |            |
|------|------|--------|--|--------|------------|
| 3854 | 3854 | KRT6B  | keratin 6B   | -4.663 | 25.3339477 |
| 3848 | 3848 | KRT1   | keratin 1 (epidermolytic hyperkeratosis)                           | -4.865 | 29.1414347 |
| 6699 | 6699 | SPRR1B | small proline-rich protein 1B (cornifin)                           | -4.865 | 29.1414347 |
| 6279 | 6279 | S100A8 | S100 calcium binding protein A8                                    | -4.928 | 30.4421848 |
| 3853 | 3853 | KRT6A  | keratin 6A   | -4.965 | 31.2330163 |
| 3861 | 3861 | KRT14  | keratin 14 (epidermolysis bullosa simplex, Dowling-Meara, Koebner) | -5.868 | 58.4041913 |

| Search Term                                   | Gene ID | Gene Symbol | Gene Name   | Log Ratio MM minus MN | Fold Change |
|---|---------|-------------|---|-----------------------|-------------|
| <b>Gene up regulated in MM compared to MN</b> |         |             |   |                       |             |
| 6696  | 6696    | SPP1        | Secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1) | 4.612                 | 24.4540243  |
| 23532   | 23532   | PRAME       | Preferentially expressed antigen in melanoma  | 3.907                 | 15.0011375  |
| -1  | -1      | N.N.        |   | 3.574                 | 11.909162   |
| 91316   | 91316   | LOC91316    | Similar to bK246H3.1 (immunoglobulin lambda-like polypeptide 1, pre-B-cell specific)          | 3.328                 | 10.0421759  |
| 91353   | 91353   | CTA-246H3.1 | Similar to omega protein  | 3.2                   | 9.18958684  |
| 2335  | 2335    | FN1         | Fibronectin 1   | 3.173                 | 9.0192033   |
| 3492  | 3492    | IGH@        |   | 2.976                 | 7.86801659  |
| 7453  | 7453    | WARS        | Tryptophanyl-tRNA synthetase  | 2.921                 | 7.57370905  |
| 221692  | 221692  | PHACTR1     | Phosphatase and actin regulator 1   | 2.807                 | 6.99827812  |
| 10537   | 10537   | UBD         | Ubiquitin D   | 2.722                 | 6.59786839  |
| 9518  | 9518    | GDF15       | Growth differentiation factor 15  | 2.645                 | 6.25495715  |
| 2   | 2       | A2M         | Alpha-2-macroglobulin   | 2.639                 | 6.22899753  |
| 713   | 713     | C1QB        | Complement component 1, q subcomponent, B chain   | 2.486                 | 5.60222528  |
| 4111  | 4111    | MAGEA12     | Melanoma antigen family A, 12   | 2.46                  | 5.50216727  |
| 4283  | 4283    | CXCL9       | Chemokine (C-X-C motif) ligand 9  | 2.329                 | 5.02456952  |
| 12  | 12      | SERPINA3    | Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3           | 2.31                  | 4.9588308   |
| 5996  | 5996    | RGS1        | Regulator of G-protein signaling 1  | 2.253                 | 4.7667303   |
| 3512  | 3512    | IGJ         | Immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides     | 2.243                 | 4.73380409  |
| 712   | 712     | C1QA        | Complement component 1, q subcomponent, A chain   | 2.102                 | 4.29304115  |
| 51303   | 51303   | FKBP11      | FK506 binding protein 11, 19 kDa  | 2.079                 | 4.2251425   |
| 6035  | 6035    | RNASE1      | Ribonuclease, RNase A family, 1 (pancreatic)  | 2.062                 | 4.17564771  |
| 4435  | 4435    | CITED1      | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1             | 1.967                 | 3.90954307  |
| 3627  | 3627    | CXCL10      | Chemokine (C-X-C motif) ligand 10   | 1.934                 | 3.82113175  |
| 4162  | 4162    | MCAM        | Melanoma cell adhesion molecule   | 1.907                 | 3.75028439  |
| 597   | 597     | BCL2A1      | BCL2-related protein A1   | 1.899                 | 3.72954595  |
| 344   | 344     | APOC2       | Apolipoprotein C-II   | 1.873                 | 3.66293475  |
| 7076  | 7076    | TIMP1       | TIMP metalloproteinase inhibitor 1  | 1.839                 | 3.57761961  |
| 10563   | 10563   | CXCL13      | Chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)                                    | 1.827                 | 3.54798522  |
| 7852  | 7852    | CXCR4       | Chemokine (C-X-C motif) receptor 4  | 1.822                 | 3.53571012  |
| 55872   | 55872   | PBK         | PDZ binding kinase  | 1.803                 | 3.48945082  |
| 4311  | 4311    | MME         | Membrane metallo-endopeptidase  | 1.763                 | 3.39403161  |
| 3426  | 3426    | CFI         | Complement factor I   | 1.757                 | 3.37994554  |
| 10763   | 10763   | NES         | Nestin  | 1.746                 | 3.35427274  |
| 1282  | 1282    | COL4A1      | Collagen, type IV, alpha 1  | 1.724                 | 3.30351066  |
| 5327  | 5327    | PLAT        | Plasminogen activator, tissue   | 1.712                 | 3.27614679  |
| 4318  | 4318    | MMP9        | Matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)        | 1.706                 | 3.26254997  |
| 929   | 929     | CD14        | CD14 molecule   | 1.698                 | 3.24450862  |
| 11065   | 11065   | UBE2C       | Ubiquitin-conjugating enzyme E2C  | 1.654                 | 3.14704978  |
| 3485  | 3485    | IGFBP2      | Insulin-like growth factor binding protein 2, 36kDa   | 1.647                 | 3.13181719  |
| 6241  | 6241    | RRM2        | Ribonucleotide reductase M2 polypeptide   | 1.641                 | 3.11881937  |
| 1284  | 1284    | COL4A2      | Collagen, type IV, alpha 2  | 1.633                 | 3.10157283  |
| 51514   | 51514   | DTL         | Denticleless homolog (Drosophila)   | 1.633                 | 3.10157283  |
| 9232  | 9232    | PTTG1       | Pituitary tumor-transforming 1  | 1.632                 | 3.09942372  |
| 10437   | 10437   | IFI30       | Interferon, gamma-inducible protein 30  | 1.622                 | 3.07801444  |
| 4100  | 4100    | MAGEA1      | Melanoma antigen family A, 1 (directs expression of antigen MZ2-E)                            | 1.599                 | 3.02933263  |
| 2207  | 2207    | FCER1G      | Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide                          | 1.589                 | 3.0084075   |
| 813   | 813     | CALU        | Calumenin   | 1.588                 | 3.00632296  |
| 7805  | 7805    | LAPTM5      | Lysosomal associated multispinning membrane protein 5   | 1.568                 | 2.96493402  |
| 10788   | 10788   | IQGAP2      | IQ motif containing GTPase activating protein 2   | 1.564                 | 2.95672486  |

|       |       |          |   |       |            |
|-------|-------|----------|---|-------|------------|
| 6574  | 6574  | SLC20A1  | Solute carrier family 20 (phosphate transporter), member 1  | 1.563 | 2.95467613 |
| 3838  | 3838  | KPNA2    | Karyopherin alpha 2 (RAG cohort 1, importin alpha 1)  | 1.546 | 2.92006402 |
| 27242 | 27242 | TNFRSF21 | Tumor necrosis factor receptor superfamily, member 21   | 1.531 | 2.8898608  |
| 1164  | 1164  | CKS2     | CDC28 protein kinase regulatory subunit 2   | 1.52  | 2.8679105  |
| 10112 | 10112 | KIF20A   | Kinesin family member 20A   | 1.519 | 2.8659233  |
| 7422  | 7422  | VEGFA    | Vascular endothelial growth factor A  | 1.518 | 2.86393748 |
| 7298  | 7298  | TYMS     | Thymidylate synthetase  | 1.514 | 2.85600796 |
| 11015 | 11015 | KDEL3    |   | 1.504 | 2.83628007 |
| 9787  | 9787  | DLG7     | Discs, large homolog 7 (Drosophila)   | 1.491 | 2.8108374  |
| 684   | 684   | BST2     | Bone marrow stromal cell antigen 2  | 1.479 | 2.78755448 |
| 22974 | 22974 | TPX2     | TPX2, microtubule-associated, homolog (Xenopus laevis)  | 1.479 | 2.78755448 |
| 6515  | 6515  | SLC2A3   | Solute carrier family 2 (facilitated glucose transporter), member 3                                 | 1.476 | 2.78176394 |
| 11145 | 11145 | HRASLS3  | HRAS-like suppressor 3  | 1.468 | 2.76638126 |
| 891   | 891   | CCNB1    | Cyclin B1   | 1.467 | 2.76446441 |
| 9133  | 9133  | CCNB2    | Cyclin B2   | 1.464 | 2.75872184 |
| 4745  | 4745  | NELL1    | NEL-like 1 (chicken)  | 1.447 | 2.72640521 |
| 4233  | 4233  | MET      | Met proto-oncogene (hepatocyte growth factor receptor)  | 1.44  | 2.71320865 |
| 23643 | 23643 | LY96     | Lymphocyte antigen 96   | 1.437 | 2.70757256 |
| 9332  | 9332  | CD163    | CD163 molecule  | 1.433 | 2.70007597 |
| 4256  | 4256  | MGP      | Matrix Gla protein  | 1.432 | 2.69820507 |
| 6271  | 6271  | S100A1   | S100 calcium binding protein A1   | 1.428 | 2.69073442 |
| 9123  | 9123  | SLC16A3  | Solute carrier family 16, member 3 (monocarboxylic acid transporter 4)                              | 1.42  | 2.67585511 |
| 4837  | 4837  | NNMT     | Nicotinamide N-methyltransferase  | 1.414 | 2.66474965 |
| 7262  | 7262  | PHLDA2   | Pleckstrin homology-like domain, family A, member 2   | 1.412 | 2.66105808 |
| 9768  | 9768  | KIAA0101 | KIAA0101  | 1.403 | 2.64450921 |
| 5450  | 5450  | POU2AF1  | POU class 2 associating factor 1  | 1.396 | 2.63170905 |
| 1687  | 1687  | DFNA5    | Deafness, autosomal dominant 5  | 1.384 | 2.6099099  |
| 963   | 963   | CD53     | CD53 molecule   | 1.379 | 2.60088029 |
| 6772  | 6772  | STAT1    | Signal transducer and activator of transcription 1, 91kDa   | 1.368 | 2.58112498 |
| 397   | 397   | ARHGDI3  | Rho GDP dissociation inhibitor (GDI) beta   | 1.366 | 2.57754926 |
| 7037  | 7037  | TFRC     | Transferrin receptor (p90, CD71)  | 1.354 | 2.55619873 |
| 57103 | 57103 | C12orf5  | Chromosome 12 open reading frame 5  | 1.353 | 2.55442752 |
| 2026  | 2026  | ENO2     | Enolase 2 (gamma, neuronal)   | 1.35  | 2.54912125 |
| 3576  | 3576  | IL8      | Interleukin 8   | 1.35  | 2.54912125 |
| 4321  | 4321  | MMP12    | Matrix metalloproteinase 12 (macrophage elastase)   | 1.348 | 2.54558987 |
| 5351  | 5351  | PLOD1    | Procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1  | 1.346 | 2.54206338 |
| 63915 | 63915 | MUTED    |   | 1.337 | 2.52625452 |
| 81575 | 81575 | APOLD1   | Apolipoprotein L domain containing 1  | 1.329 | 2.51228476 |
| 2138  | 2138  | EYA1     | Eyes absent homolog 1 (Drosophila)  | 1.324 | 2.50359292 |
| 94239 | 94239 | H2AFV    | H2A histone family, member V  | 1.32  | 2.4966611  |
| 2633  | 2633  | GBP1     | Guanylate binding protein 1, interferon-inducible, 67kDa  | 1.317 | 2.49147483 |
| 5265  | 5265  | SERPINA1 | Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1                 | 1.317 | 2.49147483 |
| 5329  | 5329  | PLAUR    | Plasminogen activator, urokinase receptor   | 1.316 | 2.48974847 |
| 1063  | 1063  | CENPF    | Centromere protein F, 350/400ka (mitosin)   | 1.315 | 2.48802331 |
| 7980  | 7980  | TFPI2    | Tissue factor pathway inhibitor 2   | 1.314 | 2.48629934 |
| 9500  | 9500  | MAGED1   | Melanoma antigen family D, 1  | 1.312 | 2.48285498 |
| 871   | 871   | SERPINH1 | Serpin peptidase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1) | 1.298 | 2.45887773 |
| 7052  | 7052  | TGM2     | Transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)                     | 1.296 | 2.45547137 |
| 3937  | 3937  | LCP2     | Lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)                   | 1.294 | 2.45206972 |
| 2181  | 2181  | ACSL3    | Acyl-CoA synthetase long-chain family member 3  | 1.292 | 2.44867278 |
| 6790  | 6790  | AURKA    | Aurora kinase A   | 1.287 | 2.44020102 |
| 5920  | 5920  | RARRES3  | Retinoic acid receptor responder (tazarotene induced) 3   | 1.286 | 2.43851019 |
| 51338 | 51338 | MS4A4A   | Membrane-spanning 4-domains, subfamily A, member 4  | 1.281 | 2.43007358 |
| 7545  | 7545  | ZIC1     | Zic family member 1 (odd-paired homolog, Drosophila)  | 1.28  | 2.42838977 |
| 10019 | 10019 | SH2B3    | SH2B adaptor protein 3  | 1.278 | 2.42502564 |
| 11326 | 11326 | VSIG4    | V-set and immunoglobulin domain containing 4  | 1.278 | 2.42502564 |
| 55379 | 55379 | LRRC59   | Leucine rich repeat containing 59   | 1.278 | 2.42502564 |
| 9833  | 9833  | MELK     | Maternal embryonic leucine zipper kinase  | 1.277 | 2.42334532 |
| 23327 | 23327 | NEDD4L   | Neural precursor cell expressed, developmentally down-regulated 4-like                              | 1.27  | 2.41161566 |
| 28959 | 28959 | TMEM176B | Transmembrane protein 176B  | 1.263 | 2.39994276 |
| 1033  | 1033  | CDKN3    | Cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)                  | 1.26  | 2.39495741 |

|        |        |          |   |       |            |
|--------|--------|----------|---|-------|------------|
| 3006   | 3006   | HIST1H1C | Histone cluster 1, H1c  | 1.254 | 2.38501774 |
| 23406  | 23406  | COTL1    | Coactosin-like 1 (Dictyostelium)  | 1.253 | 2.38336515 |
| 6781   | 6781   | STC1     | Stanniocalcin 1   | 1.25  | 2.37841423 |
| 7153   | 7153   | TOP2A    | Topoisomerase (DNA) II alpha 170kDa   | 1.25  | 2.37841423 |
| 3669   | 3669   | ISG20    | Interferon stimulated exonuclease gene 20kDa  | 1.245 | 2.37018554 |
| 142    | 142    | PARP1    | Poly (ADP-ribose) polymerase family, member 1   | 1.243 | 2.36690204 |
| 7378   | 7378   | UPP1     | Uridine phosphorylase 1   | 1.235 | 2.35381347 |
| 991    | 991    | CDC20    | Cell division cycle 20 homolog (S. cerevisiae)  | 1.232 | 2.34892394 |
| 6745   | 6745   | SSR1     | Signal sequence receptor, alpha (translocon-associated protein alpha)                     | 1.231 | 2.34729636 |
| 6352   | 6352   | CCL5     | Chemokine (C-C motif) ligand 5  | 1.23  | 2.3456699  |
| 23516  | 23516  | SLC39A14 | Solute carrier family 39 (zinc transporter), member 14                                    | 1.224 | 2.33593479 |
| 29887  | 29887  | SNX10    | Sorting nexin 10  | 1.224 | 2.33593479 |
| 3959   | 3959   | LGALS3BP | Lectin, galactoside-binding, soluble, 3 binding protein                                   | 1.222 | 2.33269874 |
| 10095  | 10095  | ARPC1B   | Actin related protein 2/3 complex, subunit 1B, 41kDa                                      | 1.219 | 2.32785307 |
| 7305   | 7305   | TYROBP   | TYRO protein tyrosine kinase binding protein  | 1.211 | 2.31498043 |
| 116372 | 116372 | LYPD1    | LY6/PLAUR domain containing 1   | 1.211 | 2.31498043 |
| 8091   | 8091   | HMGA2    | High mobility group AT-hook 2   | 1.21  | 2.31337637 |
| 10486  | 10486  | CAP2     | CAP, adenylate cyclase-associated protein, 2 (yeast)                                      | 1.209 | 2.31177341 |
| 1601   | 1601   | DAB2     | Disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)                        | 1.206 | 2.30697121 |
| 5577   | 5577   | PRKAR2B  | Protein kinase, cAMP-dependent, regulatory, type II, beta                                 | 1.206 | 2.30697121 |
| 9055   | 9055   | PRC1     | Protein regulator of cytokinesis 1  | 1.203 | 2.30217898 |
| 23213  | 23213  | SULF1    | Sulfatase 1   | 1.198 | 2.29421405 |
| 10211  | 10211  | FLOT1    | Flotillin 1   | 1.196 | 2.2910358  |
| 87     | 87     | ACTN1    | Actinin, alpha 1  | 1.193 | 2.28627667 |
| 1846   | 1846   | DUSP4    | Dual specificity phosphatase 4  | 1.191 | 2.28310941 |
| 3371   | 3371   | TNC      | Tenascin C (hexabrachion)   | 1.189 | 2.27994655 |
| 6876   | 6876   | TAGLN    | Transgelin  | 1.179 | 2.2641978  |
| 27299  | 27299  | ADAMDEC1 | ADAM-like, decysin 1  | 1.178 | 2.26262893 |
| 8406   | 8406   | SRPX     | Sushi-repeat-containing protein, X-linked   | 1.174 | 2.25636427 |
| 1508   | 1508   | CTSB     | Cathepsin B   | 1.173 | 2.25480082 |
| 6402   | 6402   | SELL     | Selectin L (lymphocyte adhesion molecule 1)   | 1.173 | 2.25480082 |
| 6947   | 6947   | TCN1     | Transcobalamin I (vitamin B12 binding protein, R binder family)                           | 1.167 | 2.24544284 |
| 3357   | 3357   | HTR2B    | 5-hydroxytryptamine (serotonin) receptor 2B   | 1.166 | 2.24388696 |
| 5476   | 5476   | CTSA     | Cathepsin A   | 1.166 | 2.24388696 |
| 5352   | 5352   | PLOD2    | Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2  | 1.165 | 2.24233216 |
| 962    | 962    | CD48     | CD48 molecule   | 1.15  | 2.21913894 |
| 3491   | 3491   | CYR61    | Cysteine-rich, angiogenic inducer, 61   | 1.149 | 2.21760129 |
| 11014  | 11014  | KDEL2    | KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 2                 | 1.149 | 2.21760129 |
| 717    | 717    | C2       | Complement component 2  | 1.136 | 2.19770844 |
| 5698   | 5698   | PSMB9    | Proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2) | 1.131 | 2.19010494 |
| 4017   | 4017   | LOXL2    | Lysyl oxidase-like 2  | 1.127 | 2.18404109 |
| 9928   | 9928   | KIF14    | Kinesin family member 14  | 1.123 | 2.17799403 |
| 10656  | 10656  | KHDRBS3  | KH domain containing, RNA binding, signal transduction associated 3                       | 1.123 | 2.17799403 |
| 1978   | 1978   | EIF4EBP1 | Eukaryotic translation initiation factor 4E binding protein 1                             | 1.122 | 2.17648488 |
| 2020   | 2020   | EN2      | Engrailed homeobox 2  | 1.122 | 2.17648488 |
| 11004  | 11004  | KIF2C    | Kinesin family member 2C  | 1.119 | 2.17196371 |
| 51203  | 51203  | NUSAP1   | Nucleolar and spindle associated protein 1  | 1.114 | 2.16444929 |
| 2258   | 2258   | FGF13    | Fibroblast growth factor 13   | 1.111 | 2.15995312 |
| 3108   | 3108   | HLA-DMA  | Major histocompatibility complex, class II, DM alpha                                      | 1.109 | 2.15696086 |
| 3689   | 3689   | ITGB2    | Integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)                        | 1.106 | 2.15248025 |
| 6351   | 6351   | CCL4     | Chemokine (C-C motif) ligand 4  | 1.105 | 2.15098878 |
| 7018   | 7018   | TF       | Transferrin   | 1.105 | 2.15098878 |
| 4104   | 4104   | MAGEA5   | Melanoma antigen family A, 5  | 1.103 | 2.14800894 |
| 719    | 719    | C3AR1    | Complement component 3a receptor 1  | 1.102 | 2.14652057 |
| 6347   | 6347   | CCL2     | Chemokine (C-C motif) ligand 2  | 1.102 | 2.14652057 |
| 4085   | 4085   | MAD2L1   | MAD2 mitotic arrest deficient-like 1 (yeast)  | 1.1   | 2.14354693 |
| 6999   | 6999   | TDO2     | Tryptophan 2,3-dioxygenase  | 1.099 | 2.14206165 |
| 64092  | 64092  | SAMSN1   | SAM domain, SH3 domain and nuclear localization signals 1                                 | 1.098 | 2.1405774  |
| 3383   | 3383   | ICAM1    | Intercellular adhesion molecule 1 (CD54), human rhinovirus receptor                       | 1.096 | 2.13761198 |
| 701    | 701    | BUB1B    | BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)                         | 1.095 | 2.13613082 |
| 6891   | 6891   | TAP2     | Transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)                               | 1.094 | 2.13465068 |

|        |        |           |  |       |            |
|--------|--------|-----------|--|-------|------------|
| 58986  | 58986  | TMEM8     | Transmembrane protein 8 (five membrane-spanning domains)                                       | 1.094 | 2.13465068 |
| 8836   | 8836   | GGH       | Gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)                         | 1.093 | 2.13317156 |
| 10954  | 10954  | PDIA5     | Protein disulfide isomerase family A, member 5   | 1.093 | 2.13317156 |
| 85236  | 85236  | HIST1H2BK | Histone cluster 1, H2bk  | 1.092 | 2.13169347 |
| 3059   | 3059   | HCLS1     | Hematopoietic cell-specific Lyn substrate 1  | 1.09  | 2.12874036 |
| 5315   | 5315   | PKM2      | Pyruvate kinase, muscle  | 1.09  | 2.12874036 |
| 3017   | 3017   | HIST1H2BD | Histone cluster 1, H2bd  | 1.085 | 2.12137548 |
| 5272   | 5272   | SERPINB9  | Serpin peptidase inhibitor, clade B (ovalbumin), member 9                                      | 1.085 | 2.12137548 |
| 7184   | 7184   | HSP90B1   | Heat shock protein 90kDa beta (Grp94), member 1  | 1.085 | 2.12137548 |
| 9404   | 9404   | LPXN      | Leupaxin   | 1.083 | 2.11843667 |
| 7351   | 7351   | UCP2      | Uncoupling protein 2 (mitochondrial, proton carrier)   | 1.082 | 2.11696879 |
| 8905   | 8905   | AP1S2     | Adaptor-related protein complex 1, sigma 2 subunit   | 1.082 | 2.11696879 |
| 165    | 165    | AEBP1     | AE binding protein 1   | 1.08  | 2.11403608 |
| 4811   | 4811   | NID1      | Nidogen 1  | 1.078 | 2.11110744 |
| 6890   | 6890   | TAP1      | Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)                                    | 1.073 | 2.10380356 |
| 10440  | 10440  | TIMM17A   | Translocase of inner mitochondrial membrane 17 homolog A (yeast)                               | 1.073 | 2.10380356 |
| 5721   | 5721   | PSME2     | Proteasome (prosome, macropain) activator subunit 2 (PA28 beta)                                | 1.071 | 2.10088909 |
| 1462   | 1462   | VCAN      | Versican   | 1.067 | 2.09507225 |
| 3099   | 3099   | HK2       | Hexokinase 2   | 1.066 | 2.09362056 |
| 23194  | 23194  | FBXL7     | F-box and leucine-rich repeat protein 7  | 1.066 | 2.09362056 |
| 5690   | 5690   | PSMB2     | Proteasome (prosome, macropain) subunit, beta type, 2  | 1.064 | 2.0907202  |
| 23484  | 23484  | LEPROTL1  | Leptin receptor overlapping transcript-like 1  | 1.064 | 2.0907202  |
| 149111 | 149111 | CNIH3     | Cornichon homolog 3 (Drosophila)   | 1.064 | 2.0907202  |
| 7077   | 7077   | TIMP2     | TIMP metalloproteinase inhibitor 2   | 1.062 | 2.08782385 |
| 533    | 533    | ATP6V0B   | ATPase, H <sup>+</sup> transporting, lysosomal 21kDa, V0 subunit b                             | 1.057 | 2.08060053 |
| 50515  | 50515  | CHST11    | Carbohydrate (chondroitin 4) sulfotransferase 11   | 1.057 | 2.08060053 |
| 54828  | 54828  | BCAS3     | Breast carcinoma amplified sequence 3  | 1.057 | 2.08060053 |
| 9263   | 9263   | STK17A    | Serine/threonine kinase 17a  | 1.053 | 2.07483987 |
| 3620   | 3620   | INDO      | Indoleamine-pyrrole 2,3 dioxygenase  | 1.05  | 2.07052985 |
| 54927  | 54927  | CHCHD3    | Coiled-coil-helix-coiled-coil-helix domain containing 3  | 1.049 | 2.06909516 |
| 60481  | 60481  | ELOVL5    | ELOVL family member 5, elongation of long chain fatty acids (FEN1/Elo2, SUR4/Elo3-like, yeast) | 1.049 | 2.06909516 |
| 6782   | 6782   | STCH      | Stress 70 protein chaperone, microsomal-associated, 60kDa                                      | 1.048 | 2.06766147 |
| 79801  | 79801  | SHCBP1    | SHC SH2-domain binding protein 1   | 1.048 | 2.06766147 |
| 10460  | 10460  | TACC3     | Transforming, acidic coiled-coil containing protein 3  | 1.047 | 2.06622878 |
| 23530  | 23530  | NNT       | Nicotinamide nucleotide transhydrogenase   | 1.047 | 2.06622878 |
| 983    | 983    | CDC2      | Cell division cycle 2, G1 to S and G2 to M   | 1.037 | 2.05195629 |
| 50999  | 50999  | TMED5     | Transmembrane emp24 protein transport domain containing 5                                      | 1.036 | 2.05053448 |
| 55647  | 55647  | RAB20     | RAB20, member RAS oncogene family  | 1.036 | 2.05053448 |
| 2305   | 2305   | FOXO1     | Forkhead box M1  | 1.034 | 2.0476938  |
| 9212   | 9212   | AURKB     | Aurora kinase B  | 1.034 | 2.0476938  |
| 29028  | 29028  | ATAD2     | ATPase family, AAA domain containing 2   | 1.033 | 2.04627494 |
| 8934   | 8934   | RAB7L1    | RAB7, member RAS oncogene family-like 1  | 1.032 | 2.04485706 |
| 256227 | 256227 | MGC87042  | Similar to Six transmembrane epithelial antigen of prostate                                    | 1.029 | 2.04060932 |
| 64151  | 64151  | NCAPG     | Non-SMC condensin I complex, subunit G   | 1.026 | 2.0363704  |
| 5641   | 5641   | LGMN      | Legumain   | 1.025 | 2.03495938 |
| 3074   | 3074   | HEXB      | Hexosaminidase B (beta polypeptide)  | 1.021 | 2.02932509 |
| 332    | 332    | BIRC5     | Baculoviral IAP repeat-containing 5 (survivin)   | 1.019 | 2.0265138  |
| 1503   | 1503   | CTPS      | CTP synthase   | 1.018 | 2.02510961 |
| 9447   | 9447   | AIM2      | Absent in melanoma 2   | 1.017 | 2.0237064  |
| 914    | 914    | CD2       | CD2 molecule   | 1.014 | 2.0195026  |
| 11013  | 11013  | TMSL8     | Thymosin-like 8  | 1.013 | 2.01810327 |
| 50486  | 50486  | G0S2      | G0/G1switch 2  | 1.012 | 2.01670491 |
| 5230   | 5230   | PGK1      | Phosphoglycerate kinase 1  | 1.01  | 2.0139111  |
| 6185   | 6185   | RPN2      | Ribophorin II  | 1.009 | 2.01251565 |
| 528    | 528    | ATP6V1C1  | ATPase, H <sup>+</sup> transporting, lysosomal 42kDa, V1 subunit C1                            | 1.008 | 2.01112116 |
| 3309   | 3309   | HSPA5     | Heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)                                  | 1.006 | 2.00833509 |
| 4192   | 4192   | MDK       | Midkine (neurite growth-promoting factor 2)  | 1.005 | 2.0069435  |
| 728    | 728    | C5AR1     | Complement component 5a receptor 1   | 1.003 | 2.00416321 |
| 1020   | 1020   | CDK5      | Cyclin-dependent kinase 5  | 1.002 | 2.00277451 |
| 5696   | 5696   | PSMB8     | Proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)      | 1.002 | 2.00277451 |
| 10384  | 10384  | BTN3A3    | Butyrophilin, subfamily 3, member A3   | 1.002 | 2.00277451 |
| 7873   | 7873   | ARMET     | Arginine-rich, mutated in early stage tumors   | 1.001 | 2.00138677 |
| 23753  | 23753  | SDF2L1    | Stromal cell-derived factor 2-like 1   | 1.001 | 2.00138677 |

| Gene down regulated in MM compared to MN |        |          |  |        |            |
|--|--------|----------|--|--------|------------|
| 6136                                     | 6136   | RPL12    | Ribosomal protein L12  | -1     | 2          |
| 7001                                     | 7001   | PRDX2    | Peroxiredoxin 2  | -1     | 2          |
| 59338                                    | 59338  | PLEKHA1  | Pleckstrin homology domain containing, family A (phosphoinositide binding specific) member 1 | -1.002 | 2.00277451 |
| 170680                                   | 170680 | PSORS1C2 | Psoriasis susceptibility 1 candidate 2   | -1.003 | 2.00416321 |
| 116039                                   | 116039 | OSR2     | Odd-skipped related 2 (Drosophila)   | -1.004 | 2.00555287 |
| 6261                                     | 6261   | RYR1     | Ryanodine receptor 1 (skeletal)  | -1.006 | 2.00833509 |
| 55214                                    | 55214  | LEPREL1  | Leprecan-like 1  | -1.006 | 2.00833509 |
| 79056                                    | 79056  | PRRG4    | Proline rich Gla (G-carboxyglutamic acid) 4 (transmembrane)                                  | -1.008 | 2.01112116 |
| 1294                                     | 1294   | COL7A1   | Collagen, type VII, alpha 1 (epidermolysis bullosa, dystrophic, dominant and recessive)      | -1.009 | 2.01251565 |
| 56288                                    | 56288  | PARD3    | Par-3 partitioning defective 3 homolog (C. elegans)  | -1.012 | 2.01670491 |
| 60495                                    | 60495  | HPSE2    | Heparanase 2   | -1.013 | 2.01810327 |
| 9651                                     | 9651   | PLCH2    | Phospholipase C, eta 2   | -1.014 | 2.0195026  |
| 9796                                     | 9796   | PHYHIP   | Phytanoyl-CoA 2-hydroxylase interacting protein  | -1.015 | 2.02090289 |
| 51232                                    | 51232  | CRIM1    | Cysteine rich transmembrane BMP regulator 1 (chordin-like)                                   | -1.02  | 2.02791896 |
| 3557                                     | 3557   | IL1RN    | Interleukin 1 receptor antagonist  | -1.021 | 2.02932509 |
| 10924                                    | 10924  | SMPDL3A  | Sphingomyelin phosphodiesterase, acid-like 3A  | -1.021 | 2.02932509 |
| 80303                                    | 80303  | EFHD1    | EF-hand domain family, member D1   | -1.021 | 2.02932509 |
| 23461                                    | 23461  | ABCA5    | ATP-binding cassette, sub-family A (ABC1), member 5  | -1.023 | 2.03214029 |
| 23259                                    | 23259  | DDHD2    | DDHD domain containing 2   | -1.025 | 2.03495938 |
| 1638                                     | 1638   | DCT      | Dopachrome tautomerase (dopachrome delta-isomerase, tyrosine-related protein 2)              | -1.027 | 2.03778239 |
| 7162                                     | 7162   | TPBG     | Trophoblast glycoprotein   | -1.027 | 2.03778239 |
| 10602                                    | 10602  | CDC42EP3 | CDC42 effector protein (Rho GTPase binding) 3  | -1.027 | 2.03778239 |
| 55040                                    | 55040  | EPN3     | Epsin 3  | -1.028 | 2.03919537 |
| 3119                                     | 3119   | HLA-DQB1 | Major histocompatibility complex, class II, DQ beta 1  | -1.029 | 2.04060932 |
| 2152                                     | 2152   | F3       | Coagulation factor III (thromboplastin, tissue factor)                                       | -1.035 | 2.04911365 |
| 10810                                    | 10810  | WASF3    | WAS protein family, member 3   | -1.038 | 2.05337909 |
| 5603                                     | 5603   | MAPK13   | Mitogen-activated protein kinase 13  | -1.04  | 2.05622765 |
| 4692                                     | 4692   | NDN      | Necdin homolog (mouse)   | -1.043 | 2.06050791 |
| 9414                                     | 9414   | TJP2     | Tight junction protein 2 (zona occludens 2)  | -1.05  | 2.07052985 |
| 1028                                     | 1028   | CDKN1C   | Cyclin-dependent kinase inhibitor 1C (p57, Kip2)   | -1.053 | 2.07483987 |
| 5126                                     | 5126   | PCSK2    | Proprotein convertase subtilisin/kexin type 2  | -1.054 | 2.07627854 |
| 1842                                     | 1842   | ECM2     | Extracellular matrix protein 2, female organ and adipocyte specific                          | -1.058 | 2.0820432  |
| 3655                                     | 3655   | ITGA6    | Integrin, alpha 6  | -1.06  | 2.08493152 |
| 4897                                     | 4897   | NRCAM    | Neuronal cell adhesion molecule  | -1.062 | 2.08782385 |
| 23189                                    | 23189  | ANKRD15  | Ankyrin repeat domain 15   | -1.063 | 2.08927153 |
| 928                                      | 928    | CD9      | CD9 molecule   | -1.065 | 2.09216988 |
| 4675                                     | 4675   | NAP1L3   | Nucleosome assembly protein 1-like 3   | -1.065 | 2.09216988 |
| 5652                                     | 5652   | PRSS8    | Protease, serine, 8  | -1.066 | 2.09362056 |
| 51309                                    | 51309  | ARMCX1   | Armadillo repeat containing, X-linked 1  | -1.067 | 2.09507225 |
| 91851                                    | 91851  | CHRDL1   | Chordin-like 1   | -1.071 | 2.10088909 |
| 57146                                    | 57146  | TMEM159  | Transmembrane protein 159  | -1.072 | 2.10234582 |
| 1124                                     | 1124   | CHN2     | Chimerin (chimaerin) 2   | -1.075 | 2.10672207 |
| 1906                                     | 1906   | EDN1     | Endothelin 1   | -1.077 | 2.10964463 |
| 4086                                     | 4086   | SMAD1    | SMAD family member 1   | -1.077 | 2.10964463 |
| 1808                                     | 1808   | DPYSL2   | Dihydropyrimidinase-like 2   | -1.084 | 2.11990557 |
| 4128                                     | 4128   | MAOA     | Monoamine oxidase A  | -1.084 | 2.11990557 |
| 85458                                    | 85458  | DIXDC1   | DIX domain containing 1  | -1.084 | 2.11990557 |
| 154                                      | 154    | ADRB2    | Adrenergic, beta-2-, receptor, surface   | -1.087 | 2.12431837 |
| 1515                                     | 1515   | CTSL2    | Cathepsin L2   | -1.089 | 2.12726535 |
| 7503                                     | 7503   | XIST     | X (inactive)-specific transcript   | -1.09  | 2.12874036 |
| 288                                      | 288    | ANK3     | Ankyrin 3, node of Ranvier (ankyrin G)   | -1.091 | 2.13021641 |
| 3918                                     | 3918   | LAMC2    | Laminin, gamma 2   | -1.091 | 2.13021641 |
| 3769                                     | 3769   | KCNJ13   | Potassium inwardly-rectifying channel, subfamily J, member 13                                | -1.093 | 2.13317156 |
| 80206                                    | 80206  | FHOD3    | Formin homology 2 domain containing 3  | -1.1   | 2.14354693 |
| 57758                                    | 57758  | SCUBE2   | Signal peptide, CUB domain, EGF-like 2   | -1.104 | 2.14949835 |
| 11211                                    | 11211  | FZD10    | Frizzled homolog 10 (Drosophila)   | -1.105 | 2.15098878 |
| 25976                                    | 25976  | TIPARP   | TCDD-inducible poly(ADP-ribose) polymerase   | -1.108 | 2.15546629 |
| 3205                                     | 3205   | HOXA9    | Homeobox A9  | -1.111 | 2.15995312 |
| 6509                                     | 6509   | SLC1A4   | Solute carrier family 1 (glutamate/neutral amino acid transporter), member 4                 | -1.111 | 2.15995312 |
| 55227                                    | 55227  | LRRC1    | Leucine rich repeat containing 1   | -1.111 | 2.15995312 |
| 6280                                     | 6280   | S100A9   | S100 calcium binding protein A9  | -1.112 | 2.1614508  |
| 6665                                     | 6665   | SOX15    | SRY (sex determining region Y)-box 15  | -1.112 | 2.1614508  |

|        |        |              |  |        |            |
|--------|--------|--------------|--|--------|------------|
| 738    | 738    | C11orf2      | Chromosome 11 open reading frame2  | -1.115 | 2.16595009 |
| 10351  | 10351  | ABCA8        | ATP-binding cassette, sub-family A (ABC1), member 8  | -1.117 | 2.16895482 |
| 25878  | 25878  | MXRA5        | Matrix-remodelling associated 5  | -1.118 | 2.17045874 |
| 2150   | 2150   | F2RL1        | Coagulation factor II (thrombin) receptor-like 1   | -1.121 | 2.17497678 |
| 1580   | 1580   | CYP4B1       | Cytochrome P450, family 4, subfamily B, polypeptide 1  | -1.122 | 2.17648488 |
| 79686  | 79686  | C14orf139    | Chromosome 14 open reading frame 139   | -1.122 | 2.17648488 |
| 1646   | 1646   | AKR1C2       | Aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase, type III) | -1.123 | 2.17799403 |
| 6662   | 6662   | SOX9         | SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal)  | -1.126 | 2.18252775 |
| 10278  | 10278  | EFS          | Embryonal Fyn-associated substrate   | -1.126 | 2.18252775 |
| 5349   | 5349   | FXD3         | FXD domain containing ion transport regulator 3  | -1.127 | 2.18404109 |
| 23382  | 23382  | KIAA0828     | Adenosylhomocysteinase 3   | -1.127 | 2.18404109 |
| 2013   | 2013   | EMP2         | Epithelial membrane protein 2  | -1.129 | 2.18707091 |
| 55107  | 55107  | TMEM16A      | Transmembrane protein 16A  | -1.129 | 2.18707091 |
| 2069   | 2069   | EREG         | Epiregulin   | -1.13  | 2.1885874  |
| 283638 | 283638 | KIAA0284     | KIAA0284   | -1.132 | 2.19162353 |
| 1153   | 1153   | CIRBP        | Cold inducible RNA binding protein   | -1.133 | 2.19314318 |
| 5792   | 5792   | PTPRF        | Protein tyrosine phosphatase, receptor type, F   | -1.133 | 2.19314318 |
| 55294  | 55294  | FBXW7        | F-box and WD repeat domain containing 7  | -1.136 | 2.19770844 |
| 26298  | 26298  | EHF          | Ets homologous factor  | -1.138 | 2.20075722 |
| 23002  | 23002  | DAAM1        | Dishevelled associated activator of morphogenesis 1  | -1.141 | 2.20533833 |
| 1359   | 1359   | CPA3         | Carboxypeptidase A3 (mast cell)  | -1.144 | 2.20992897 |
| 23242  | 23242  | COBL         | Cordon-bleu homolog (mouse)  | -1.146 | 2.21299471 |
| 242    | 242    | ALOX12B      | Arachidonate 12-lipoxygenase, 12R type   | -1.151 | 2.22067767 |
| 2941   | 2941   | GSTA4        | Glutathione S-transferase A4   | -1.152 | 2.22221746 |
| 51090  | 51090  | PLLP         | Plasma membrane proteolipid (plasmolipin)  | -1.155 | 2.22684324 |
| 11075  | 11075  | STMN2        | Stathmin-like 2  | -1.156 | 2.2283873  |
| 23593  | 23593  | HEBP2        | Heme binding protein 2   | -1.156 | 2.2283873  |
| 26330  | 26330  | GAPDHS       | Glyceraldehyde-3-phosphate dehydrogenase, spermatogenic  | -1.158 | 2.23147864 |
| 694    | 694    | BTG1         | B-cell translocation gene 1, anti-proliferative  | -1.16  | 2.23457428 |
| 9413   | 9413   | C9orf61      | Chromosome 9 open reading frame 61   | -1.16  | 2.23457428 |
| 2770   | 2770   | GNAI1        | Guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1  | -1.161 | 2.2361237  |
| 26018  | 26018  | LRIG1        | Leucine-rich repeats and immunoglobulin-like domains 1   | -1.161 | 2.2361237  |
| 4915   | 4915   | NTRK2        | Neurotrophic tyrosine kinase, receptor, type 2   | -1.163 | 2.23922578 |
| 7056   | 7056   | THBD         | Thrombomodulin   | -1.168 | 2.24699981 |
| 6513   | 6513   | SLC2A1       | Solute carrier family 2 (facilitated glucose transporter), member 1  | -1.173 | 2.25480082 |
| 3590   | 3590   | IL11RA       | Interleukin 11 receptor, alpha   | -1.174 | 2.25636427 |
| 29091  | 29091  | STXBP6       | Syntaxin binding protein 6 (amisyn)  | -1.175 | 2.25792881 |
| 2153   | 2153   | F5           | Coagulation factor V (proaccelerin, labile factor)   | -1.176 | 2.25949443 |
| 2709   | 2709   | GJB5         | Gap junction protein, beta 5, 31.1kDa  | -1.178 | 2.26262893 |
| 3816   | 3816   | KLK1         | Kallikrein 1   | -1.178 | 2.26262893 |
| 3775   | 3775   | KCNK1        | Potassium channel, subfamily K, member 1   | -1.18  | 2.26576777 |
| 7022   | 7022   | TFAP2C       | Transcription factor AP-2 gamma (activating enhancer binding protein 2 gamma)  | -1.184 | 2.27205853 |
| 25854  | 25854  | DKFZP564J102 | Family with sequence similarity 149, member A  | -1.185 | 2.27363395 |
| 23015  | 23015  | GOLGA8A      | Golgi autoantigen, golgin subfamily a, 8A  | -1.187 | 2.27678806 |
| 10579  | 10579  | TACC2        | Transforming, acidic coiled-coil containing protein 2  | -1.188 | 2.27836675 |
| 3248   | 3248   | HPGD         | Hydroxyprostaglandin dehydrogenase 15-(NAD)  | -1.189 | 2.27994655 |
| 6137   | 6137   | RPL13        | Ribosomal protein L13  | -1.189 | 2.27994655 |
| 6385   | 6385   | SDC4         | Syndecan 4   | -1.195 | 2.28944832 |
| 1112   | 1112   | CHES1        | Forkhead box N3  | -1.196 | 2.2910358  |
| 390    | 390    | RND3         | Rho family GTPase 3  | -1.2   | 2.29739671 |
| 2202   | 2202   | EFEMP1       | EGF-containing fibulin-like extracellular matrix protein 1   | -1.201 | 2.2989897  |
| 26154  | 26154  | ABCA12       | ATP-binding cassette, sub-family A (ABC1), member 12   | -1.202 | 2.30058379 |
| 79850  | 79850  | FAM57A       | Family with sequence similarity 57, member A   | -1.203 | 2.30217898 |
| 9891   | 9891   | NUAK1        | NUAK family, SNF1-like kinase, 1   | -1.206 | 2.30697121 |
| 2196   | 2196   | FAT2         | FAT tumor suppressor homolog 2 (Drosophila)  | -1.209 | 2.31177341 |
| 56998  | 56998  | CTNBP1       | Catenin, beta interacting protein 1  | -1.209 | 2.31177341 |
| 2114   | 2114   | ETS2         | V-ets erythroblastosis virus E26 oncogene homolog 2 (avian)  | -1.212 | 2.31658561 |
| 117247 | 117247 | SLC16A10     | Solute carrier family 16, member 10 (aromatic amino acid transporter)  | -1.212 | 2.31658561 |
| 25875  | 25875  | LETMD1       | LETM1 domain containing 1  | -1.214 | 2.31979931 |
| 4610   | 4610   | MYCL1        | V-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)  | -1.215 | 2.32140783 |
| 53335  | 53335  | BCL11A       | B-cell CLL/lymphoma 11A (zinc finger protein)  | -1.216 | 2.32301746 |



|        |        |          |  |        |            |
|--------|--------|----------|--|--------|------------|
| 5593   | 5593   | PRKG2    | Protein kinase, cGMP-dependent, type II  | -1.217 | 2.32462822 |
| 1050   | 1050   | CEBPA    | CCAAT/enhancer binding protein (C/EBP), alpha  | -1.22  | 2.32946717 |
| 7088   | 7088   | TLE1     | Transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)   | -1.22  | 2.32946717 |
| 3400   | 3400   | ID4      | Inhibitor of DNA binding 4, dominant negative helix-loop-helix protein   | -1.224 | 2.33593479 |
| 4477   | 4477   | MSMB     | Microseminoprotein, beta-  | -1.231 | 2.34729636 |
| 6692   | 6692   | SPINT1   | Serine peptidase inhibitor, Kunitz type 1  | -1.231 | 2.34729636 |
| 396    | 396    | ARHGDI   | Rho GDP dissociation inhibitor (GDI) alpha   | -1.234 | 2.3521825  |
| 3480   | 3480   | IGF1R    | Insulin-like growth factor 1 receptor  | -1.234 | 2.3521825  |
| 4147   | 4147   | MATN2    | Matrilin 2   | -1.235 | 2.35381347 |
| 51228  | 51228  | GLTP     | Glycolipid transfer protein  | -1.236 | 2.35544558 |
| 2125   | 2125   | EVPL     | Envoplakin   | -1.237 | 2.35707882 |
| 23150  | 23150  | FRMD4B   | FERM domain containing 4B  | -1.237 | 2.35707882 |
| 9194   | 9194   | SLC16A7  | Solute carrier family 16, member 7 (monocarboxylic acid transporter 2)   | -1.238 | 2.35871318 |
| 10391  | 10391  | CORO2B   | Coronin, actin binding protein, 2B   | -1.243 | 2.36690204 |
| 1902   | 1902   | EDG2     | Endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2                                       | -1.25  | 2.37841423 |
| 11341  | 11341  | SCRG1    | Scrapie responsive protein 1   | -1.252 | 2.3817137  |
| 26053  | 26053  | AUTS2    | Autism susceptibility candidate 2  | -1.256 | 2.38832637 |
| 5453   | 5453   | POU3F1   | POU class 3 homeobox 1   | -1.257 | 2.38998241 |
| 1645   | 1645   | AKR1C1   | aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase) | -1.258 | 2.39163959 |
| 1944   | 1944   | EFNA3    | Ephrin-A3  | -1.26  | 2.39495741 |
| 10512  | 10512  | SEMA3C   | Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C                                 | -1.26  | 2.39495741 |
| 3080   | 3080   | CFHR2    | Complement factor H-related 2  | -1.262 | 2.39827983 |
| 10529  | 10529  | NEBL     | Nebulette  | -1.262 | 2.39827983 |
| 79977  | 79977  | GRHL2    | Grainyhead-like 2 (Drosophila)   | -1.262 | 2.39827983 |
| 53832  | 53832  | IL20RA   | Interleukin 20 receptor, alpha   | -1.268 | 2.40827476 |
| 9124   | 9124   | PDLIM1   | PDZ and LIM domain 1 (elfin)   | -1.269 | 2.40994463 |
| 29997  | 29997  | GLTSCR2  | Glioma tumor suppressor candidate region gene 2  | -1.269 | 2.40994463 |
| 7447   | 7447   | VSNL1    | Visinin-like 1   | -1.27  | 2.41161566 |
| 55118  | 55118  | CRTAC1   | Cartilage acidic protein 1   | -1.274 | 2.41831135 |
| 7704   | 7704   | ZBTB16   | Zinc finger and BTB domain containing 16   | -1.279 | 2.42670712 |
| 7101   | 7101   | NR2E1    | Nuclear receptor subfamily 2, group E, member 1  | -1.28  | 2.42838977 |
| 5348   | 5348   | FXYD1    | FXYD domain containing ion transport regulator 1 (phospholemmann)  | -1.283 | 2.43344472 |
| 161291 | 161291 | TMEM30B  | Transmembrane protein 30B  | -1.283 | 2.43344472 |
| 9231   | 9231   | DLG5     | Discs, large homolog 5 (Drosophila)  | -1.294 | 2.45206972 |
| 54873  | 54873  | PALMD    | Palmelphin   | -1.297 | 2.45717396 |
| 5742   | 5742   | PTGS1    | Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)                                  | -1.3   | 2.46228883 |
| 9076   | 9076   | CLDN1    | Claudin 1  | -1.302 | 2.46570465 |
| 224    | 224    | ALDH3A2  | Aldehyde dehydrogenase 3 family, member A2   | -1.319 | 2.49493114 |
| 26751  | 26751  | SH3YL1   | SH3 domain containing, Ysc84-like 1 (S. cerevisiae)  | -1.326 | 2.50706604 |
| 54361  | 54361  | WNT4     | Wingless-type MMTV integration site family, member 4   | -1.327 | 2.50880441 |
| 54566  | 54566  | EPB41L4B | Erythrocyte membrane protein band 4.1 like 4B  | -1.337 | 2.52625452 |
| 6095   | 6095   | RORA     | RAR-related orphan receptor A  | -1.341 | 2.53326851 |
| 259217 | 259217 | HSPA12A  | Heat shock 70kDa protein 12A   | -1.345 | 2.54030197 |
| 10628  | 10628  | TXNIP    | Thioredoxin interacting protein  | -1.347 | 2.54382601 |
| 54829  | 54829  | ASPN     | Asporin  | -1.349 | 2.54735495 |
| 7850   | 7850   | IL1R2    | Interleukin 1 receptor, type II  | -1.351 | 2.55088878 |
| 217    | 217    | ALDH2    | Aldehyde dehydrogenase 2 family (mitochondrial)  | -1.354 | 2.55619873 |
| 10218  | 10218  | ANGPTL7  | Angiopoietin-like 7  | -1.356 | 2.55974483 |
| 10265  | 10265  | IRX5     | Iroquois homeobox 5  | -1.358 | 2.56329585 |
| 222    | 222    | ALDH3B2  | Aldehyde dehydrogenase 3 family, member B2   | -1.363 | 2.57219497 |
| 23037  | 23037  | PDZD2    | PDZ domain containing 2  | -1.365 | 2.57576326 |
| 51302  | 51302  | CYP39A1  | Cytochrome P450, family 39, subfamily A, polypeptide 1   | -1.365 | 2.57576326 |
| 6820   | 6820   | SULT2B1  | Sulfotransferase family, cytosolic, 2B, member 1   | -1.375 | 2.59367911 |
| 4493   | 4493   | MT1E     | Metallothionein 1E   | -1.383 | 2.60810147 |
| 8710   | 8710   | SERPINB7 | Serpin peptidase inhibitor, clade B (ovalbumin), member 7  | -1.386 | 2.61353051 |
| 999    | 999    | CDH1     | Cadherin 1, type 1, E-cadherin (epithelial)  | -1.394 | 2.62806325 |
| 10848  | 10848  | PPP1R13L | Protein phosphatase 1, regulatory (inhibitor) subunit 13 like  | -1.394 | 2.62806325 |
| 85453  | 85453  | TSPYL5   | TSPY-like 5  | -1.401 | 2.64084568 |
| 10418  | 10418  | SPON1    | Spondin 1, extracellular matrix protein  | -1.403 | 2.64450921 |
| 1287   | 1287   | COL4A5   | Collagen, type IV, alpha 5 (Alport syndrome)   | -1.405 | 2.64817782 |

|        |        |              |  |        |            |
|--------|--------|--------------|--|--------|------------|
| 1012   | 1012   | CDH13        | Cadherin 13, H-cadherin (heart)  | -1.407 | 2.65185152 |
| 1675   | 1675   | CFD          | Complement factor D (adipsin)  | -1.41  | 2.65737163 |
| 80004  | 80004  | RBM35B       | RNA binding motif protein 35B  | -1.419 | 2.67400099 |
| 51200  | 51200  | CPA4         | Carboxypeptidase A4  | -1.42  | 2.67585511 |
| 2861   | 2861   | GPR37        | G protein-coupled receptor 37 (endothelin receptor type B-like)  | -1.421 | 2.67771051 |
| 10089  | 10089  | KCNK7        | Potassium channel, subfamily K, member 7   | -1.421 | 2.67771051 |
| 3606   | 3606   | IL18         | Interleukin 18 (interferon-gamma-inducing factor)  | -1.422 | 2.6795672  |
| 55638  | 55638  | FLJ20366     | Golgi-localized protein  | -1.422 | 2.6795672  |
| 651872 | 651872 | LOC651872    |  | -1.422 | 2.6795672  |
| 7286   | 7286   | TUFT1        | Tuftelin 1   | -1.425 | 2.68514501 |
| 79026  | 79026  | AHNAK        | AHNAK nucleoprotein  | -1.432 | 2.69820507 |
| 646    | 646    | BNC1         | Basonuclin 1   | -1.433 | 2.70007597 |
| 57447  | 57447  | NDRG2        | NDRG family member 2   | -1.433 | 2.70007597 |
| 11187  | 11187  | PKP3         | Plakophilin 3  | -1.439 | 2.71132865 |
| 3909   | 3909   | LAMA3        | Laminin, alpha 3   | -1.44  | 2.71320865 |
| 83604  | 83604  | TMEM47       | Transmembrane protein 47   | -1.445 | 2.72262823 |
| 5325   | 5325   | PLAGL1       | Pleiomorphic adenoma gene-like 1   | -1.448 | 2.72829567 |
| 6317   | 6317   | SERPINB3     | Serpin peptidase inhibitor, clade B (ovalbumin), member 3  | -1.453 | 2.73776763 |
| 1272   | 1272   | CNTN1        | Contactin 1  | -1.454 | 2.73966596 |
| 9022   | 9022   | CLIC3        | Chloride intracellular channel 3   | -1.461 | 2.7529912  |
| 55612  | 55612  | C20orf42     | Chromosome 20 open reading frame 42  | -1.463 | 2.75681031 |
| 4948   | 4948   | OCA2         | Oculocutaneous albinism II (pink-eye dilution homolog, mouse)  | -1.465 | 2.76063471 |
| 57152  | 57152  | SLURP1       | Secreted LY6/PLAUR domain containing 1   | -1.47  | 2.77021894 |
| 3868   | 3868   | KRT16        | Keratin 16 (focal non-epidermolytic palmoplantar keratoderma)  | -1.473 | 2.77598544 |
| 2628   | 2628   | GATM         | Glycine amidinotransferase (L-arginine:glycine amidinotransferase)   | -1.474 | 2.77791027 |
| 218    | 218    | ALDH3A1      | Aldehyde dehydrogenase 3 family, member A1   | -1.476 | 2.78176394 |
| 2263   | 2263   | FGFR2        | Fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome) | -1.483 | 2.79529394 |
| 22798  | 22798  | LAMB4        | Laminin, beta 4  | -1.49  | 2.80888975 |
| 81578  | 81578  | COL21A1      | Collagen, type XXI, alpha 1  | -1.496 | 2.82059592 |
| 4023   | 4023   | LPL          | Lipoprotein lipase   | -1.499 | 2.82646729 |
| 9355   | 9355   | LHX2         | LIM homeobox 2   | -1.5   | 2.82842712 |
| 1634   | 1634   | DCN          | Decorin  | -1.502 | 2.83235088 |
| 1382   | 1382   | CRABP2       | Cellular retinoic acid binding protein 2   | -1.506 | 2.84021472 |
| 28231  | 28231  | SLCO4A1      | Solute carrier organic anion transporter family, member 4A1  | -1.517 | 2.86195304 |
| 10276  | 10276  | NET1         | Neuroepithelial cell transforming gene 1   | -1.52  | 2.8679105  |
| 3397   | 3397   | ID1          | Inhibitor of DNA binding 1, dominant negative helix-loop-helix protein   | -1.521 | 2.86989907 |
| 760    | 760    | CA2          | Carbonic anhydrase II  | -1.528 | 2.88385774 |
| 6785   | 6785   | ELOVL4       | Elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 4   | -1.534 | 2.89587634 |
| 7123   | 7123   | CLEC3B       | C-type lectin domain family 3, member B  | -1.534 | 2.89587634 |
| 5055   | 5055   | SERPINB2     | Serpin peptidase inhibitor, clade B (ovalbumin), member 2  | -1.537 | 2.90190442 |
| 1956   | 1956   | EGFR         | Epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)   | -1.556 | 2.94037467 |
| 25797  | 25797  | QPCT         | Glutamyl-peptide cyclotransferase (glutamyl cyclase)   | -1.557 | 2.94241349 |
| 7164   | 7164   | TPD52L1      | Tumor protein D52-like 1   | -1.559 | 2.94649537 |
| 64919  | 64919  | BCL11B       | B-cell CLL/lymphoma 11B (zinc finger protein)  | -1.562 | 2.95262881 |
| 2940   | 2940   | GSTA3        | Glutathione S-transferase A3   | -1.563 | 2.95467613 |
| 1040   | 1040   | CDS1         | CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 1   | -1.569 | 2.96698987 |
| 2707   | 2707   | GJB3         | Gap junction protein, beta 3, 31kDa  | -1.573 | 2.97522752 |
| 2051   | 2051   | EPHB6        | EPH receptor B6  | -1.589 | 3.0084075  |
| 23641  | 23641  | LDOC1        | Leucine zipper, down-regulated in cancer 1   | -1.592 | 3.01466982 |
| 79852  | 79852  | ABHD9        | Abhydrolase domain containing 9  | -1.597 | 3.02513599 |
| 53905  | 53905  | DUOX1        | Dual oxidase 1   | -1.603 | 3.03774338 |
| 92211  | 92211  | PCDH21       | Protocadherin 21   | -1.604 | 3.03984971 |
| 3898   | 3898   | LAD1         | Ladinin 1  | -1.605 | 3.04195751 |
| 8857   | 8857   | FCGBP        | Fc fragment of IgG binding protein   | -1.605 | 3.04195751 |
| 80740  | 80740  | LY6G6C       | Lymphocyte antigen 6 complex, locus G6C  | -1.615 | 3.06311599 |
| 4501   | 4501   | MT1X         | Metallothionein 1X   | -1.616 | 3.06523992 |
| 79652  | 79652  | C16orf30     | Chromosome 16 open reading frame 30  | -1.633 | 3.10157283 |
| 202    | 202    | AIM1         | Absent in melanoma 1   | -1.635 | 3.1058755  |
| 8626   | 8626   | TP73L        | Tumor protein p63  | -1.639 | 3.11449876 |
| 51765  | 51765  | RP6-213H19.1 | Serine/threonine protein kinase MST4   | -1.644 | 3.12531152 |
| 358    | 358    | AQP1         | Aquaporin 1 (Colton blood group)   | -1.648 | 3.13398875 |

|       |       |               |   |        |            |
|-------|-------|---------------|---|--------|------------|
| 6337  | 6337  | SCNN1A        | Sodium channel, nonvoltage-gated 1 alpha  | -1.655 | 3.14923191 |
| 51195 | 51195 | RAPGEFL1      | Rap guanine nucleotide exchange factor (GEF)-like 1                                   | -1.66  | 3.16016525 |
| 2173  | 2173  | FABP7         | Fatty acid binding protein 7, brain   | -1.661 | 3.16235647 |
| 3131  | 3131  | HLF           | Hepatic leukemia factor   | -1.665 | 3.17113655 |
| 10752 | 10752 | CHL1          | Cell adhesion molecule with homology to L1CAM (close homolog of L1)                   | -1.67  | 3.18214594 |
| 5507  | 5507  | PPP1R3C       | Protein phosphatase 1, regulatory (inhibitor) subunit 3C                              | -1.682 | 3.20872467 |
| 10974 | 10974 | C10orf116     | Chromosome 10 open reading frame 116  | -1.683 | 3.21094955 |
| 1396  | 1396  | CRIP1         | Cysteine-rich protein 1 (intestinal)  | -1.688 | 3.22209716 |
| 1718  | 1718  | DHCR24        | 24-dehydrocholesterol reductase   | -1.689 | 3.22433133 |
| 6698  | 6698  | SPRR1A        | Small proline-rich protein 1A   | -1.712 | 3.27614679 |
| 2259  | 2259  | FGF14         | Fibroblast growth factor 14   | -1.719 | 3.29208138 |
| 64131 | 64131 | XYLT1         | Xylosyltransferase I  | -1.725 | 3.30580127 |
| 909   | 909   | CD1A          | CD1a molecule   | -1.726 | 3.30809347 |
| 7739  | 7739  | ZNF185        | Zinc finger protein 185 (LIM domain)  | -1.777 | 3.42712782 |
| 1041  | 1041  | CDSN          | Corneodesmosin  | -1.781 | 3.43664302 |
| 3983  | 3983  | ABLIM1        | Actin binding LIM protein 1   | -1.812 | 3.51128719 |
| 9314  | 9314  | KLF4          | Kruppel-like factor 4 (gut)   | -1.849 | 3.60250392 |
| 3613  | 3613  | IMPA2         | Inositol(myo)-1(or 4)-monophosphatase 2   | -1.859 | 3.62756132 |
| 51673 | 51673 | CGI-38        | Tubulin polymerization-promoting protein family member 3                              | -1.86  | 3.63007662 |
| 3120  | 3120  | HLA-DQB2      |   | -1.864 | 3.6401553  |
| 7277  | 7277  | TUBA4A        | Tubulin, alpha 4a   | -1.864 | 3.6401553  |
| 10653 | 10653 | SPINT2        | Serine peptidase inhibitor, Kunitz type, 2  | -1.871 | 3.65786036 |
| 771   | 771   | CA12          | Carbonic anhydrase XII  | -1.886 | 3.69609029 |
| 4308  | 4308  | TRPM1         | Transient receptor potential cation channel, subfamily M, member 1                    | -1.896 | 3.72179863 |
| 25984 | 25984 | KRT23         | Keratin 23 (histone deacetylase inducible)  | -1.914 | 3.7685251  |
| 25833 | 25833 | POU2F3        | POU class 2 homeobox 3  | -1.931 | 3.81319418 |
| 5650  | 5650  | KLK7          | Kallikrein-related peptidase 7  | -1.938 | 3.83174087 |
| 3815  | 3815  | KIT           | V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog                         | -1.944 | 3.84770982 |
| 84909 | 84909 | C9orf3        | Chromosome 9 open reading frame 3   | -1.952 | 3.86910532 |
| 2487  | 2487  | FRZB          | Frizzled-related protein  | -1.967 | 3.90954307 |
| 11202 | 11202 | KLK8          | Kallikrein-related peptidase 8  | -1.987 | 3.96411825 |
| 6382  | 6382  | SDC1          | Syndecan 1  | -1.99  | 3.97236998 |
| 6590  | 6590  | SLPI          | Secretory leukocyte peptidase inhibitor   | -2.004 | 4.01110574 |
| 9982  | 9982  | FGFBP1        | Fibroblast growth factor binding protein 1  | -2.01  | 4.0278222  |
| 8424  | 8424  | BBOX1         | Butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1 | -2.077 | 4.21928927 |
| 79983 | 79983 | POF1B         | Premature ovarian failure, 1B   | -2.082 | 4.23393758 |
| 3713  | 3713  | IVL           | Involucrin  | -2.107 | 4.3079455  |
| 1428  | 1428  | CRYM          | Crystallin, mu  | -2.148 | 4.43212939 |
| 3034  | 3034  | HAL           | Histidine ammonia-lyase   | -2.153 | 4.44751663 |
| 4118  | 4118  | MAL           | Mal, T-cell differentiation protein   | -2.208 | 4.62034314 |
| 2205  | 2205  | FCER1A        | Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide                  | -2.229 | 4.68808913 |
| 563   | 563   | AZGP1         | Alpha-2-glycoprotein 1, zinc-binding  | -2.251 | 4.76012679 |
| 63928 | 63928 | LOC63928      | Calcineurin B homologous protein 2  | -2.253 | 4.7667303  |
| 1672  | 1672  | DEFB1         | Defensin, beta 1  | -2.265 | 4.8065442  |
| 10874 | 10874 | NMU           | Neuromedin U  | -2.286 | 4.87702038 |
| 383   | 383   | ARG1          | Arginase, liver   | -2.306 | 4.94510104 |
| 2878  | 2878  | GPX3          | Glutathione peroxidase 3 (plasma)   | -2.323 | 5.00371632 |
| 3728  | 3728  | JUP           | Junction plakoglobin  | -2.323 | 5.00371632 |
| 25818 | 25818 | KLK5          | Kallikrein-related peptidase 5  | -2.327 | 5.01760882 |
| 2625  | 2625  | GATA3         | GATA binding protein 3  | -2.336 | 5.04900813 |
| 25891 | 25891 | DKFZP586H2123 | Regeneration associated muscle protease   | -2.351 | 5.10177757 |
| 2261  | 2261  | FGFR3         | Fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)          | -2.386 | 5.22706102 |
| 11012 | 11012 | KLK11         | Kallikrein-related peptidase 11   | -2.393 | 5.2524845  |
| 57111 | 57111 | RAB25         | RAB25, member RAS oncogene family   | -2.398 | 5.27071981 |
| 2697  | 2697  | GJA1          | Gap junction protein, alpha 1, 43kDa  | -2.422 | 5.35913441 |
| 810   | 810   | CALML3        | Calmodulin-like 3   | -2.507 | 5.68436817 |
| 3854  | 3854  | KRT6B         |   | -2.553 | 5.86853338 |
| 10850 | 10850 | CCL27         | Chemokine (C-C motif) ligand 27   | -2.637 | 6.22036829 |
| 1308  | 1308  | COL17A1       | Collagen, type XVII, alpha 1  | -2.719 | 6.58416276 |
| 445   | 445   | ASS1          | Argininosuccinate synthetase 1  | -2.724 | 6.60702132 |
| 3872  | 3872  | KRT17         | Keratin 17  | -2.745 | 6.70389708 |
| 79755 | 79755 | ZNF750        | Zinc finger protein 750   | -2.748 | 6.71785194 |
| 1525  | 1525  | CXADR         | Coxsackie virus and adenovirus receptor   | -2.766 | 6.80219328 |

|        |        |          |  |        |            |
|--------|--------|----------|--|--------|------------|
| 688    | 688    | KLF5     | Kruppel-like factor 5 (intestinal)   | -2.814 | 7.03231649 |
| 7306   | 7306   | TYRP1    | Tyrosinase-related protein 1   | -2.815 | 7.03719261 |
| 5764   | 5764   | PTN      | Pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)    | -2.846 | 7.19004101 |
| 1830   | 1830   | DSG3     | Desmoglein 3 (pemphigus vulgaris antigen)  | -2.867 | 7.29546532 |
| 3853   | 3853   | KRT6A    | Keratin 6A   | -2.878 | 7.35130307 |
| 27076  | 27076  | LYPD3    | LY6/PLAUR domain containing 3  | -2.925 | 7.59473697 |
| 9890   | 9890   | LPPR4    | Plasticity related gene 1  | -2.974 | 7.85711676 |
| 360    | 360    | AQP3     | Aquaporin 3 (Gill blood group)   | -3.022 | 8.12292881 |
| 57402  | 57402  | S100A14  | S100 calcium binding protein A14   | -3.029 | 8.16243727 |
| 9635   | 9635   | CLCA2    | Chloride channel, calcium activated, family member 2                                 | -3.035 | 8.19645458 |
| 8796   | 8796   | SCEL     | Sciellin   | -3.048 | 8.27064589 |
| 3075   | 3075   | CFH      | Complement factor H  | -3.057 | 8.32240213 |
| 3858   | 3858   | KRT10    | Keratin 10 (epidermolytic hyperkeratosis; keratosis palmaris et plantaris)           | -3.086 | 8.49138567 |
| 26239  | 26239  | LCE2B    | Late cornified envelope 2B   | -3.094 | 8.5386027  |
| 23650  | 23650  | TRIM29   | Tripartite motif-containing 29   | -3.133 | 8.77257271 |
| 4070   | 4070   | TACSTD2  | Tumor-associated calcium signal transducer 2   | -3.172 | 9.01295383 |
| 6279   | 6279   | S100A8   | S100 calcium binding protein A8  | -3.204 | 9.21510114 |
| 7021   | 7021   | TFAP2B   | Transcription factor AP-2 beta (activating enhancer binding protein 2 beta)          | -3.225 | 9.35021799 |
| 64065  | 64065  | PERP     | PERP, TP53 apoptosis effector  | -3.274 | 9.67324541 |
| 5493   | 5493   | PPL      | Periplakin   | -3.28  | 9.71355908 |
| 23086  | 23086  | EXPH5    | Exophilin 5  | -3.299 | 9.84233076 |
| 6699   | 6699   | SPRR1B   | Small proline-rich protein 1B (cornifin)   | -3.314 | 9.94519735 |
| 113146 | 113146 | C14orf78 | AHNAK nucleoprotein 2  | -3.332 | 10.0700574 |
| 667    | 667    | DST      | Dystonin   | -3.339 | 10.1190363 |
| 51806  | 51806  | CALML5   | Calmodulin-like 5  | -3.449 | 10.9207497 |
| 2810   | 2810   | SFN      | Stratifin  | -3.479 | 11.1502179 |
| 6273   | 6273   | S100A2   | S100 calcium binding protein A2  | -3.555 | 11.7533491 |
| 84525  | 84525  | HOP      | HOP homeobox   | -3.679 | 12.808237  |
| 11005  | 11005  | SPINK5   | Serine peptidase inhibitor, Kazal type 5   | -3.68  | 12.817118  |
| 1474   | 1474   | CST6     | Cystatin E/M   | -3.774 | 13.6800348 |
| 1475   | 1475   | CSTA     | Cystatin A (stefin A)  | -3.843 | 14.3502106 |
| 8581   | 8581   | LY6D     | Lymphocyte antigen 6 complex, locus D  | -3.905 | 14.980356  |
| 1825   | 1825   | DSC3     | Desmocollin 3  | -4.051 | 16.5757242 |
| 3849   | 3849   | KRT2     | Keratin 2 (epidermal ichthyosis bullosa of Siemens)                                  | -4.171 | 18.0134174 |
| 1828   | 1828   | DSG1     | Desmoglein 1   | -4.196 | 18.3282864 |
| 4014   | 4014   | LOR      | Loricrin   | -4.252 | 19.0537096 |
| 1832   | 1832   | DSP      | Desmoplakin  | -4.607 | 24.3694198 |
| 1823   | 1823   | DSC1     | Desmocollin 1  | -4.736 | 26.6488247 |
| 9547   | 9547   | CXCL14   | Chemokine (C-X-C motif) ligand 14  | -4.86  | 29.040613  |
| 3866   | 3866   | KRT15    | Keratin 15   | -4.963 | 31.1897482 |
| 5268   | 5268   | SERPINB5 | Serpin peptidase inhibitor, clade B (ovalbumin), member 5                            | -5.042 | 32.9452827 |
| 3852   | 3852   | KRT5     | Keratin 5 (epidermolysis bullosa simplex, Dowling-Meara/Kobner/Weber-Cockayne types) | -5.812 | 56.180595  |
| 3848   | 3848   | KRT1     | Keratin 1 (epidermolytic hyperkeratosis)   | -6.635 | 99.388016  |
| 3861   | 3861   | KRT14    | Keratin 14 (epidermolysis bullosa simplex, Dowling-Meara, Koebner)                   | -7.142 | 141.239519 |

**Supplemental Table 1:** Significantly regulated genes in PM compared to MN, MM compared to PM, MM compared to MN with a minimum fold change of  $<-2$  and  $>2$ .

| Category                               | p-value           | Molecules   |
|--|-------------------|---|
| Cancer                                 | 3,82E-27-1,08E-03 | SELL, KRT6A, ASS1, KLK6, CCNB2, EIF4A2, SERPINA3, CXCL10, GPR37, CXCL13, CDKN3, FABP7, TYMS, TDO2, CKS2, GSTM3 (includes EG:2947), MT1X, IGH@, RRM2, IER3, RAB31, ARHGDIB, NRCAM, CTSB, TFRC, TCN1, PDGFD, ECM1, UBE2C, KIF20A, PRAME (includes EG:23532), FN1, GBP1 (includes EG:2633), PHLDA2, PPP1R3C, KPNA2, PTN, GDF15, CCL5, CD74, COL4A2, ABCA5, CCL2, STK17A, MAL, HLA-DRA, IGF1R, DAB2, SERPINA1, ADAMDEC1, TRIM29, MMP1 (includes EG:4312), PLAT, HEY1, PLA2G16, S100A1, PKM2, PSMB9, CCNB1, TNC, GZMK, KRT6B, KRT17, TYROBP, DST, ISG15, ITGB2, SERPINB4, S100A9, KRT5, CIRBP, SORBS2, GATA3, SGK3, GZMB, DLGAP5, RGS1, MMP3, TRIM9, PTTG1, RNASE1, MELK, LYZ, CD163, PBK, BIRC5, FGFR3, NNMT, GPX3, CCL27, CXCL14, IFI30, SCRG1, KRT1, CDKN1C, GZMA, KRT16, IL8, SPP1, CXCL9, COL4A1, GGH, SERPINB3, CAPG, AURKA, TUSC3, BST2, EFS, SPARCL1, ABCA8, AKR1B10, CD14, IRF8, CCL19, DSC1, TRA@, LGR4, CDK2, IFI27, FRZB, LETMD1, CD2, KIAA0101, TFAP2B, ACOT7, GLRX, TNFRSF12A, HLF (includes EG:3131), SOX9, KCNMA1, MCAM, F5, S100A8, CFH, STAT1, SILV, KRT14, COTL1, CXCR4, C9ORF3, PRC1, UPP1, CD36, CD48, PFKF, HCLS1, CD3D, MST4, WARS, IGF1, LGALS3BP, KLF5, ISG20, MMP9 |
| Dermatological Diseases and Conditions | 4,48E-14-1,2E-03  | RGS1, SELL, KRT6A, MMP3, HLA-DRB1, KLK6, BIRC5, CCL27, CXCL13, IFI30, KRT1, DSP, TYMS, IL8, KRT16, SPP1, COL4A1, CXCL9, SERPINB3, DSG1, UBD, COL21A1, TCN1, CD14, DSC1, ECM1, LCP2, CDK2, FN1, CD2, GDF15, CCL5, CD74, COL4A2, HLA-DRA, KRT2, S100A8, SERPINA1, LOR, STAT1, MMP1 (includes EG:4312), IL11RA, PLAT, KRT14, KRT6B, CXCR4, KRT17, CD36, COL17A1, TYRP1, ITGB2, S100A9, KRT5, FCER1G, MMP9  |
| Cellular Growth and Proliferation      | 1,32E-13-1,19E-03 | KLK6, HLA-DRB1, CXCL10, LGMN, CDKN3, FABP7, ZBTB16, TNFRSF21, TYMS, CKS2, IL12RB2, IER3, LDOC1, NRCAM, CTSB, TFRC, BCL2A1, PDGFD, ECM1, LCP2, UBE2C, KIF20A, PRAME (includes EG:23532), FN1, GBP1 (includes EG:2633), PHLDA2, GDF15, PTN, COL4A2, CCL5, CD74, TAP1, GLTSCR2, CCL2, IGF1R, DAB2, KRT2, SERPINA1, IL11RA, HEY1, PLAT, S100A1, PKM2, PLAGL1, CCNB1, TNC, KRT17, TYROBP, ISG15, ITGB2, SWAP70, S100A9, CIRBP, FCER1G, GATA3, ID4, GZMB, SGK3, DLGAP5, MMP3, PTTG1, CD163, PBK, BIRC5, FGFR3, GPX3, CCL27, IFI30, CDKN1C, DSP, KRT16, IL8, CXCL9, COL4A1, SPP1, FXYD1, CITED1, AURKA, BST2, TPX2, EFS, CD14, IRF8, CCL19, CST6, CDK2, TRA@, LGR4, FRZB, CD2, KIAA0101, TFAP2B, TNFRSF12A, SOX9, MCAM, S100A8, STAT1, ACTN1, DTL, CXCR4, UPP1, CD36, CD48, HCLS1, CADM1, MST4, TYRP1, WARS, NR2E1 (includes EG:7101), SATB1, KLF5, A2M, MMP9, ISG20   |
| Gastrointestinal Disease               | 6,92E-13-3,41E-04 | DLGAP5, MMP3, TRIM9, PTTG1, CCNB2, KLK6, SERPINA3, MELK, EIF4A2, LYZ, PBK, BIRC5, NNMT, FGFR3, CXCL10, CDKN3, TYMS, IL8, SPP1, COL4A1, TDO2, MT1X, GGH, RRM2, CAPG, AURKA, BST2, RAB31, EFS, CTSB, TCN1, CD14, TFRC, LGR4, UBE2C, KIF20A, FN1, KIAA0101, KPNA2, GDF15, ABCA5, CD74, COL4A2, ACOT7, GLRX, CCL2, MCAM, HLA-DRA, IGF1R, STAT1, PLAT, PKM2, KRT14, TNC, TYROBP, CXCR4, CD36, HCLS1, WARS, CIRBP, MMP9, ISG20  |
| Cellular Movement                      | 1,17E-12-1,2E-03  | RGS1, SELL, KRT6A, MMP3, PTTG1, KLK6, CCNB2, SERPINA3, PBK, CXCL10, LGMN, CCL27, CXCL13, CXCL14, FABP7, ZBTB16, TNFRSF21, KRT16, IL8, CXCL9, SPP1, COL4A1, SERPINB3, AURKA, ARHGDIB, EFS, NRCAM, CTSB, CD14, CCL19, PDGFD, CST6, CCL18, LGR4, LCP2, C2, FN1, GBP1 (includes EG:2633), ARPC1B, CD2, GDF15, PTN, CD74, CCL5, COL4A2, TNFRSF12A, CCL2, MCAM, IGF1R, DAB2, PTPRZ1, S100A8, SERPINA1, CFH, STAT1, CHL1, MMP1 (includes EG:4312), PLAT, CXCL11, HEY1, CD53, S100A1, TNC, CXCR4, COL17A1, CD48, CD36, CADM1, ITGB2, NR2E1 (includes EG:7101), WARS, SWAP70, S100A9, KLF5, FCER1G, GATA3, A2M, MMP9, GZMB   |
| Inflammatory Response                  | 1,24E-12-1,2E-03  | RGS1, SELL, MMP3, ASS1, PTTG1, HLA-DRB1, C1QA, HLA-DMB, SERPINA3, C1QB, LYZ, CD163, CXCL10, CCL27, CXCL13, CXCL14, IFI30, GZMA, TNFRSF21, IL8, SPP1, CXCL9, IL12RB2, CAPG, IER3, ARHGDIB, CTSB, CD14, IRF8, CCL19, CCL18, DSC1, TRA@, LCP2, C2, FN1, CD2, CD74, CCL5, TAP1, TNFRSF12A, CCL2, F5, HLA-DRA, IGF1R, IFI6, S100A8, SERPINA1, CFH, STAT1, CXCL11, IL11RA, PLAT, SILV, PSMB9, HLA-DMA, TNC, TYROBP, CXCR4, CD48, CD36, COL17A1, ISG15, TYRP1, ITGB2, S100A9, SATB1, PI3, FCER1G, GATA3, A2M, MMP9, GZMB   |
| Cell-To-Cell Signaling and Interaction | 1,87E-12-1,2E-03  | RGS1, SELL, LHX2, HLA-DRB1, KLK6, HLA-DMB, C1QA, LYZ, CD163, CXCL10, FGFR3, CXCL13, CCL27, ALDH3A2, CXCL14, LPL, FABP7, CDKN1C, KRT1, GZMA, KRT16, IL8, CXCL9, SPP1, SERPINB3, IL12RB2, BST2, ARHGDIB, ANGPTL7, NRCAM, TFRC, CD14, IRF8, CCL19, BCL2A1, CST6, CCL18, LGR4, TRA@, LCP2, CDK2, UBE2C, FN1, CD2, GDF15, CCL5, CD74, TNFRSF12A, SOX9, CCL2, KCNMA1, MCAM, HLA-DRA, F5, IGF1R, KRT2, DAB2, PTPRZ1, S100A8, CFH, STAT1, CHL1, GATM, MMP1 (includes EG:4312), PLAT, DSC3, CXCL11, PSMB9, HLA-DMA, TNC, FEZ1, TYROBP, CXCR4, FGF14, COL17A1, CD48, CD36, AZGP1, CADM1, SYBU, ITGB2, SWAP70, S100A9, LGALS3BP, SATB1, PI3, FCER1G, GATA3, A2M, MMP9, GZMB  |
| Genetic Disorder                       | 2,58E-12-7,09E-04 | SELL, KRT6A, AUTS2 (includes EG:26053), ASS1, LRRC1, TLE1, CCNB2, EIF4A2, SERPINA3, CRYM, TYMS, RRM2, IL12RB2, DSG1, ARHGDIB, C14ORF132, CTSB, TFRC, ECM1, UBE2C, CYP39A1, GBP1 (includes EG:2633), GDF15, CCL5, CD74, CCL2, KRT2, DAB2, SERPINA1, TRIM29, CHL1, MMP1 (includes EG:4312), S100A1, PKM2, MLLT11, KRT17, DST, COL17A1, PAMR1, CSTB, ISG15, PDZD2, SWAP70, KRT5, WIP1, DERL1, GATA3, ID4, GZMB, DLGAP5, MMP3, LHX2, PTTG1, RNASE1, LYZ, CD163, GPX3, CXCL14, LPL, CDKN1C, NEDD4L, IL8, FXYD1, CAPG, AURKA, TUSC3, TMEM204, SPARCL1, ABCA8, AKR1B10, IRF8, C2, LGR4, LETMD1, FRZB, KIAA0101, TFAP2B, GLRX, MCAM, CFH, STAT1, KRT14, SLC20A1, HLA-DMA, FEZ1, PRC1, CD36, PYGL, HSPA12A, CADM1, TYRP1, KLF5, A2M, ISG20, KLK6, HLA-DRB1, HLA-DMB, EXPH5, CXCL10, LGMN, GPR37, CDKN3, FABP7, ZBTB16, DFNA5, CKS2, TDO2, CHN1 (includes EG:1123), MT1X, IER3, RAB31, UBD, NRCAM, MS4A4A, TCN1, TRPM1, PDGFD, LCP2, FN1, TSPAN7, KPNA2, PTN, COL4A2, ABCA5, CORO2B, HLA-DRA, MAL, IGF1R, SNX10, IFI6, ADAMDEC1, LAMB4,   |

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|   |                   | RPL13, DSC3, PLAT, IL11RA, CD53, PSMB9, PLAGL1, CCNB1, TNC, CNTN1, KRT6B, OAS2, TYROBP, FGF14, CRTAC1, ITGB2, S100A9, CIRBP, FCER1G, SORBS2, TRIM9, LPPR4, MELK, PBK, BIRC5, FGFR3, CCL27, ALDH3A2, IFI30, SCEL, KRT1, DSP, GZMA, KRT16, COL4A1, SPP1, CXCL9, XYLT1, PHACTR1, GGH, SERPINB3, TMEM47, BST2, COL21A1, CD14, DSC1, CCL18, CDK2, TRA@, CD2, CDHR1, APOC2, ACOT7, TNFRSF12A, SOX9, KCNMA1, F5, PTPRZ1, S100A8, LOR, GATM, ACTN1, FAM149A, COTL1, CXCR4, C9ORF3, CD48, AHCYL2, PFKP, CD3D, KCNJ13, SYBU, NR2E1 (includes EG:7101), IGJ, MMP9  |
| Hematological System Development and Function | 1,14E-11-1,2E-03  | RGS1, SELL, MMP3, CCNB2, HLA-DRB1, HLA-DMB, C1QA, SERPINA3, LYZ, CD163, BIRC5, CXCL10, CCL27, CXCL13, CXCL14, ZBTB16, GZMA, TNFRSF21, IL8, COL4A1, SPP1, CXCL9, IL12RB2, IER3, EFS, CTSB, CD14, CCL19, IRF8, DSC1, CCL18, BCL2A1, C2, CDK2, LCP2, TRA@, FN1, CD2, CD74, CCL5, TAP1, CCL2, HLA-DRA, F5, IGF1R, DAB2, S100A8, SERPINA1, CFH, STAT1, MMP1 (includes EG:4312), CXCL11, PLAT, IL11RA, PSMB9, HLA-DMA, TNC, CCNB1, CXCR4, TYROBP, COL17A1, CD36, CD48, HCLS1, CD3D, ISG15, CADM1, TYRP1, ITGB2, SWAP70, S100A9, PI3, SATB1, FCER1G, GATA3, A2M, MMP9, ISG20, GZMB   |
| Immune Cell Trafficking                       | 1,14E-11-1,2E-03  | RGS1, SELL, MMP3, HLA-DRB1, SERPINA3, C1QA, HLA-DMB, LYZ, CD163, CXCL10, CXCL13, CCL27, CXCL14, ZBTB16, GZMA, TNFRSF21, IL8, COL4A1, SPP1, CXCL9, SERPINB3, IER3, EFS, CTSB, CD14, CCL19, CCL18, DSC1, LCP2, C2, FN1, CD2, CCL5, CD74, CCL2, HLA-DRA, F5, SERPINA1, S100A8, CFH, STAT1, CXCL11, PLAT, HLA-DMA, PSMB9, TNC, TYROBP, CXCR4, CD48, COL17A1, CD36, ITGB2, SWAP70, S100A9, SATB1, FCER1G, GATA3, MMP9, GZMB  |
| Tissue Morphology                             | 5,1E-11-1,2E-03   | SELL, MMP3, PTTG1, C1QA, BIRC5, FGFR3, CXCL10, CXCL13, CDKN1C, ZBTB16, TYMS, TNFRSF21, IL8, SPP1, COL4A1, IL12RB2, CTSB, IRF8, CCL19, BCL2A1, TRA@, LCP2, CDK2, FN1, GDF15, COL4A2, CCL5, TAP1, SOX9, CCL2, IGF1R, SERPINA1, S100A8, CFH, STAT1, MMP1 (includes EG:4312), PLAT, S100A1, TNC, CCNB1, CXCR4, TYROBP, PRC1, CD3D, ISG15, CADM1, ITGB2, NR2E1 (includes EG:7101), SWAP70, S100A9, IGJ, PI3, SATB1, FCER1G, GATA3, MMP9  |
| Cellular Development                          | 3,77E-10-1,2E-03  | SELL, KRT6A, LPXN, SSBP2, SERPINA3, CXCL10, FABP7, ZBTB16, TYMS, DFNA5, CHN1 (includes EG:1123), IL12RB2, IER3, CTSB, TRPM1, TFRC, BCL2A1, LCP2, PRAME (includes EG:23532), FN1, TSPAN7, PTN, GDF15, CD74, CCL5, SPRR1A, CCL2, MAL, IGF1R, DAB2, CHL1, MMP1 (includes EG:4312), HEY1, PLAT, IL11RA, S100A1, PSMB9, PLAGL1, IVL, CCNB1, TNC, TYROBP, ITGB2, S100A9, FCER1G, GATA3, CHRDL1, ID4, GZMB, DLGAP5, MMP3, LHX2, RNASE1, CD163, BIRC5, FGFR3, SCEL, CDKN1C, DSP, GZMA, IL8, SPP1, COL4A1, CAPG, CITED1, CD14, IRF8, CCL19, DSC1, TRA@, CDK2, FRZB, TFAP2B, TNFRSF12A, SOX9, KCNMA1, F5, PTPRZ1, S100A8, STAT1, LOR, CXCL11, HLA-DMA, CXCR4, FEZ1, SPRR1B, CD36, CD3D, HCLS1, CADM1, MST4, TYRP1, NR2E1 (includes EG:7101), SATB1, KLF5, A2M, MMP9                               |
| Reproductive System Disease                   | 1,25E-09-5,64E-04 | SELL, KRT6A, ASS1, KLK6, CXCL10, LGMN, CXCL13, FABP7, ZBTB16, TYMS, MT1X, GSTM3 (includes EG:2947), RRM2, IER3, ARHGDIB, CTSB, TCN1, TFRC, PDGFD, ECM1, UBE2C, PRAME (includes EG:23532), KIF20A, FN1, PHLDA2, KPNA2, GDF15, CD74, ABCA5, CCL5, CCL2, IGF1R, DAB2, SERPINA1, ADAMDEC1, MMP1 (includes EG:4312), S100A1, PSMB9, CCNB1, TNC, CNTN1, KRT6B, KRT17, DST, ISG15, SERPINB4, S100A9, CIRBP, KRT5, SORBS2, GATA3, SGK3, RGS1, MMP3, TRIM9, PTTG1, LYZ, CD163, PBK, BIRC5, FGFR3, GPX3, CXCL14, IFI30, SCRG1, KRT1, CDKN1C, GZMA, IL8, CXCL9, SPP1, COL4A1, SERPINB3, AURKA, TUSC3, ABCA8, CD14, CCL19, CCL18, LGR4, CDK2, LETMD1, IFI27, KIAA0101, SOX9, KCNMA1, MCAM, S100A8, CFH, STAT1, CXCR4, C9ORF3, PRC1, UPP1, CADM1, IGJ, MMP9, ISG20                                   |
| Hair and Skin Development and Function        | 1,39E-09-4,66E-04 | KRT14, KRT16, IVL, FN1, SPRR1B, KRT17, COL17A1, CITED1, SPRR1A, TYRP1, KRT5, ALDH3A2, TRPM1, KRT2, SCEL, LOR, CST6, KRT1, KRT15, DSP  |
| Organ Development                             | 1,39E-09-1,39E-09 | KRT14, KRT16, SPRR1B, KRT17, COL17A1, SPRR1A, KRT5, ALDH3A2, KRT2, SCEL, CST6, KRT1, KRT15, DSP   |
| Immunological Disease                         | 4,2E-09-1,2E-03   | SELL, MMP3, TRIM9, AUTS2 (includes EG:26053), LRRC1, HLA-DRB1, C1QA, SERPINA3, HLA-DMB, LYZ, BIRC5, FGFR3, CXCL10, CXCL13, CXCL14, IFI30, NEDD4L, TYMS, TNFRSF21, GZMA, IL8, SPP1, COL4A1, CXCL9, XYLT1, RRM2, IL12RB2, TUSC3, TPX2, DSG1, RAB31, ARHGDIB, NRCAM, CTSB, CD14, TFRC, IRF8, CCL19, CCL18, DSC1, CDK2, LCP2, C2, FN1, CD2, FRZB, CCL5, COL4A2, CD74, ACOT7, TAP1, HLA-DPA1, TNFRSF12A, CCL2, KCNMA1, HLA-DRA, IGF1R, S100A8, CFH, STAT1, CHL1, MMP1 (includes EG:4312), RPL13, LAMB4, PLAT, S100A1, CD53, PSMB9, HLA-DMA, CCNB1, TYROBP, CXCR4, C9ORF3, FGF14, COL17A1, CD36, HCLS1, CD3D, CADM1, PDZD2, ITGB2, WARS, SWAP70, S100A9, FCER1G, SORBS2, GATA3, A2M, MMP9, GZMB   |
| Cell-mediated Immune Response                 | 5,9E-09-6,23E-04  | SELL, FN1, CD2, CCNB2, CD74, CCL5, BIRC5, CXCL10, CXCL13, CCL27, CCL2, F5, IGF1R, STAT1, CXCL11, GZMA, TNFRSF21, HLA-DMA, PSMB9, IL8, SPP1, CCNB1, COL4A1, CXCL9, CXCR4, CD48, SERPINB3, IL12RB2, IER3, CD3D, EFS, ITGB2, SATB1, FCER1G, IRF8, CCL19, GATA3, CCL18, BCL2A1, LCP2, TRA@, CDK2, GZMB  |
| Cell Death                                    | 8,25E-09-1,2E-03  | HSPB2, HLA-DRB1, SERPINA3, C1QA, CXCL10, GPR37, ZBTB16, TYMS, TNFRSF21, MT1X, RRM2, IL12RB2, IER3, DSG1, UBD, NRCAM, CTSB, TFRC, BCL2A1, UBE2C, PRAME (includes EG:23532), FN1, PHLDA2, GDF15, PTN, CCL5, COL4A2, CD74, SPRR1A, TAP1, CCL2, STK17A, MAL, IGF1R, DAB2, IFI6, SERPINA1, CHL1, MMP1 (includes EG:4312), IL11RA, HEY1, PLAT, PLA2G16, PKM2, CD53, S100A1, PLAGL1, GZMK, TNC, CCNB1, TYROBP, SERPINB4, ITGB2, SWAP70, S100A9, FCER1G, SORBS2, ID4, GZMB, SGK3, MMP3, PTTG1, RNASE1, LYZ, PBK, BIRC5, FGFR3, CCL27, CDKN1C, DSP, GZMA, IL8, CXCL9, SPP1, SERPINB3, AURKA, CD14, IRF8, CCL19, CDK2, TRA@, FRZB, CD2, TFAP2B, CDHR1, GLRX, TNFRSF12A, HLF (includes EG:3131), SOX9, KCNMA1, MCAM, PTPRZ1, S100A8, CFH, STAT1, CXCL11, HLA-DMA, CXCR4, CD36, CD48, HCLS1, CADM1, |

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|  |                   | MST4, NR2E1 (includes EG:7101), LGALS3BP, KLF5, SATB1, A2M, MMP9  |
| Tissue Development                             | 1,32E-08-1,2E-03  | RGS1, SELL, MMP3, PTTG1, KLK6, C1QA, BIRC5, FGFR3, CXCL10, CDKN1C, TNFRSF21, IL8, KRT16, COL4A1, CXCL9, SPP1, IER3, AURKA, CITED1, TPX2, ARHGDIB, NRCAM, CCL19, DSC1, CST6, LCP2, FN1, CD2, PTN, COL4A2, CCL5, TNFRSF12A, SOX9, CCL2, MCAM, IGF1R, DAB2, PTPRZ1, S100A8, STAT1, CHL1, MMP1 (includes EG:4312), IL11RA, PLAT, DSC3, CXCL11, TNC, FEZ1, CXCR4, CD36, CD48, AZGP1, HCLS1, CADM1, ITGB2, SWAP70, S100A9, LGALS3BP, KLF5, FCER1G, MMP9, GZMB   |
| Inflammatory Disease                           | 2,62E-07-1,2E-03  | SELL, AUTS2 (includes EG:26053), LRRC1, TLE1, HLA-DRB1, C1QA, SERPINA3, HLA-DMB, CXCL10, CXCL13, TYMS, TNFRSF21, TDO2, RRM2, IL12RB2, ARHGDIB, RAB31, CTSS, TFRC, BCL2A1, LCP2, FN1, CCL5, COL4A2, CD74, TAP1, HLA-DPA1, CCL2, HLA-DRA, IGF1R, KRT2, IFI6, SERPINA1, MMP1 (includes EG:4312), RPL13, LAMB4, IL11RA, PLAT, CD53, PSMB9, CCNB1, TNC, OAS2, TYROBP, DST, FGF14, ITGB2, PDZD2, SWAP70, S100A9, FCER1G, SORBS2, GATA3, GZMB, MMP3, LHX2, TRIM9, LYZ, CD163, BIRC5, FGFR3, CXCL14, IFI30, NEDD4L, GZMA, IL8, SPP1, CXCL9, COL4A1, XYLT1, TMEM47, CD14, CCL19, DSC1, CCL18, C2, TRA@, LGR4, CDK2, CD2, FRZB, CDHR1, ACOT7, TNFRSF12A, KCNMA1, F5, PTPRZ1, S100A8, CFH, STAT1, HLA-DMA, CXCR4, COTL1, C9ORF3, CD48, CD36, AZGP1, CD3D, HCLS1, CADM1, A2M, MMP9  |
| Infection Mechanism                            | 3,8E-07-5,09E-04  | IL8, CXCL9, FN1, CXCR4, CD74, CCL5, BST2, CXCL10, ITGB2, S100A9, CCL2, PI3, SNX10, S100A8, SERPINA1, IRF8, CXCL11   |
| Infectious Disease                             | 3,8E-07-8,81E-04  | TRIM9, PTTG1, C1QA, LYZ, CD163, CXCL10, LPL, IFI30, NEDD4L, TYMS, IL8, SPP1, CXCL9, MT1X, RRM2, IL12RB2, IER3, RAB31, UBD, MS4A4A, CTSS, TFRC, TCN1, CD14, IRF8, C2, LCP2, UBE2C, FN1, LAPTM5, GDF15, CD74, CCL5, GLTSCR2, CCL2, F5, IGF1R, PTPRZ1, SERPINA1, TRIM29, STAT1, ACTN1, CXCL11, PLAT, SLC20A1, S100A1, CXCR4, CD36, PYGL, ITGB2, S100A9, PI3, FCER1G, GATA3, A2M, MMP9  |
| Respiratory Disease                            | 5,8E-07-7,09E-04  | PTTG1, KLK6, CCNB2, HLA-DRB1, RNASE1, LYZ, BIRC5, FGFR3, CXCL10, IFI30, CDKN1C, TYMS, IL8, SPP1, CKS2, SERPINB3, RRM2, AURKA, IER3, RAB31, AKR1B10, TCN1, CD14, CCL19, IRF8, UBE2C, FN1, CCL5, SOX9, CCL2, KCNMA1, HLA-DRA, F5, IGF1R, SERPINA1, STAT1, ACTN1, CXCL11, PLAT, IVL, TNC, CCNB1, KRT6B, CXCR4, PYGL, PFKP, AZGP1, ITGB2, S100A9, KRT5, IGJ, GATA3, MMP9, GZMB  |
| Neurological Disease                           | 6,54E-07-6,6E-04  | SELL, KRT6A, AUTS2 (includes EG:26053), HLA-DRB1, TLE1, EIF4A2, C1QA, HLA-DMB, SERPINA3, CXCL10, GPR37, CRYM, FABP7, ZBTB16, TYMS, TNFRSF21, DFNA5, CHN1 (includes EG:1123), MT1X, RRM2, IL12RB2, IER3, ARHGDIB, RAB31, C14ORF132, NRCAM, MS4A4A, CTSS, TCN1, TRPM1, PDGFD, ECM1, UBE2C, TSPAN7, GBP1 (includes EG:2633), PTN, COL4A2, CD74, CCL5, CORO2B, CCL2, HLA-DRA, MAL, SNX10, IGF1R, SERPINA1, CHL1, MMP1 (includes EG:4312), RPL13, LAMB4, PLAT, DSC3, S100A1, PKM2, PSMB9, MLLT11, CCNB1, TNC, CNTN1, TYROBP, KRT17, DST, FGF14, CSTB, PAMR1, ITGB2, PDZD2, SWAP70, S100A9, CIRBP, WIPI1, FCER1G, SORBS2, GATA3, ID4, GZMB, DLGAP5, PTTG1, LPPR4, FGFR3, CCL27, LPL, SCEL, CDKN1C, DSP, KRT16, IL8, SPP1, COL4A1, PHACTR1, FXYD1, TMEM47, CAPG, TUSC3, TMEM204, SPARCL1, CD14, IRF8, DSC1, TRA@, CDK2, LETMD1, APOC2, ACOT7, GLRX, TNFRSF12A, SOX9, KCNMA1, F5, STAT1, GATM, FAM149A, KRT14, HLA-DMA, FEZ1, CXCR4, CD36, PYGL, PFKP, HSPA12A, KLF5, A2M, MMP9 |
| Cell Signaling                                 | 9,66E-07-1,55E-04 | RGS1, SELL, FN1, CD2, PTN, APOC2, CCL5, LYZ, CXCL10, CCL27, CXCL13, CCL2, MCAM, IGF1R, S100A8, MMP1 (includes EG:4312), CXCL11, S100A1, IL8, CNTN1, SPP1, CXCL9, TYROBP, CXCR4, CD36, CD48, FXYD1, CD3D, ITGB2, S100A9, FCER1G, CCL19, A2M, TRA@, LCP2  |
| Molecular Transport                            | 9,66E-07-1,08E-04 | RGS1, SELL, FN1, CD2, CCL5, LYZ, CXCL10, CCL27, CXCL13, CCL2, MCAM, S100A8, MMP1 (includes EG:4312), CXCL11, S100A1, IL8, SPP1, CXCL9, TYROBP, CXCR4, FXYD1, CD3D, ITGB2, S100A9, FCER1G, CCL19, A2M, TRA@, LCP2  |
| Vitamin and Mineral Metabolism                 | 9,66E-07-1,08E-04 | RGS1, SELL, FN1, CD2, CCL5, LYZ, CXCL10, CCL27, CXCL13, CCL2, MCAM, S100A8, MMP1 (includes EG:4312), CXCL11, S100A1, IL8, SPP1, CXCL9, TYROBP, CXCR4, FXYD1, CD3D, ITGB2, S100A9, FCER1G, CCL19, A2M, TRA@, LCP2  |
| Tumor Morphology                               | 1,04E-06-1,19E-03 | CD53, FN1, MMP3, CXCR4, MCAM, GDF15, CD14, ZBTB16, MMP1 (includes EG:4312), MMP9, GZMB  |
| Cardiovascular System Development and Function | 1,33E-06-1,2E-03  | SELL, FN1, GBP1 (includes EG:2633), MMP3, PTN, C1QA, CCL5, COL4A2, TNFRSF12A, FGFR3, CXCL10, CCL2, F5, CXCL14, MMP1 (includes EG:4312), HEY1, CXCL11, PLAT, S100A1, IL8, SPP1, COL4A1, CXCL9, CXCR4, CD36, CITED1, ITGB2, WARS, NR2E1 (includes EG:7101), KLF5, CTSS, ECM1, MMP9  |
| Cell Morphology                                | 1,91E-06-1,19E-03 | SELL, FN1, KRT6A, TSPAN7, LPXN, SERPINA3, CCL5, CD74, CXCL10, CCL2, KRT2, DAB2, IL8, SPP1, TNC, CXCL9, KRT17, CHN1 (includes EG:1123), IL12RB2, CAPG, ITGB2, SWAP70, CCL19, GATA3, A2M, MMP9, GZMB  |
| Antigen Presentation                           | 1,95E-06-1,2E-03  | RGS1, SELL, FN1, HLA-DRB1, HLA-DMB, CCL5, CD74, CXCL10, CCL2, CXCL13, CXCL14, HLA-DRA, IFI30, S100A8, SERPINA1, CFH, STAT1, CXCL11, PSMB9, IL8, HLA-DMA, CXCL9, SPP1, CXCR4, TYROBP, CD36, IL12RB2, ITGB2, S100A9, PI3, FCER1G, CD14, IRF8, CCL19, CCL18, MMP9  |
| Cellular Function and Maintenance              | 2,12E-06-1,19E-03 | FN1, CD2, CCNB2, CCL5, CD74, BIRC5, CCL2, CXCL13, F5, IGF1R, STAT1, IL11RA, GZMA, HLA-DMA, PSMB9, IL8, SPP1, CCNB1, CXCR4, TYROBP, IL12RB2, IER3, CD3D, ITGB2, SATB1, FCER1G, CCL19, IRF8, GATA3, BCL2A1, LCP2, TRA@, CDK2, GZMB  |
| Lymphoid Tissue Structure and Development      | 3,08E-06-1,19E-03 | IL8, SELL, CXCL9, SPP1, MMP3, C1QA, CCL5, BIRC5, CXCL10, ITGB2, CCL2, CXCL13, S100A9, CXCL14, PI3, FCER1G, S100A8, SERPINA1, IRF8, CFH, ZBTB16, MMP9  |
| Hematopoiesis                                  | 5,05E-06-1,2E-03  | SELL, FN1, CD2, CCL5, CD74, BIRC5, CXCL10, CCL2, F5, IGF1R, SERPINA1, S100A8, STAT1, ZBTB16, IL11RA, CXCL11, GZMA, HLA-DMA, PSMB9, IL8, SPP1, CCNB1, CXCL9, CXCR4, IL12RB2, IER3, CD3D, ITGB2, S100A9, SATB1, FCER1G, CD14, IRF8, CCL19, GATA3, BCL2A1, TRA@, LCP2, CDK2, MMP9, GZMB  |

|   |                   |  |
|---|-------------------|--|
| Humoral Immune Response                               | 6,32E-06-1,2E-03  | RGS1, EFS, CXCL9, CXCL13, CCL19, CCL18, MMP9   |
| Cellular Compromise                                   | 6,36E-06-6,36E-04 | IL8, FN1, KRT6A, SPP1, TYROBP, TYRP1, ITGB2, CCL2, PI3, FCER1G, CD14, IRF8, CFH  |
| Connective Tissue Disorders                           | 6,46E-06-1,82E-04 | MMP3, AUTS2 (includes EG:26053), TRIM9, LRRC1, HLA-DRB1, HLA-DMB, SERPINA3, C1QA, LYZ, BIRC5, FGFR3, CXCL10, CXCL13, CXCL14, TNFRSF21, GZMA, IL8, COL4A1, SPP1, CXCL9, XYLT1, ARHGDIB, RAB31, COL21A1, CTSB, TFRC, CCL19, DSC1, CCL18, CDK2, TRA@, C2, FN1, FRZB, CCL5, COL4A2, CD74, ACOT7, TAP1, HLA-DPA1, CCL2, KCNMA1, HLA-DRA, S100A8, STAT1, MMP1 (includes EG:4312), RPL13, LAMB4, PLAT, IL11RA, CD53, HLA-DMA, PSMB9, CCNB1, CXCR4, C9ORF3, FGF14, COL17A1, CD36, AZGP1, HCLS1, CD3D, CADM1, PDZD2, ITGB2, SWAP70, S100A9, FCER1G, SORBS2, A2M, MMP9, GZMB   |
| Skeletal and Muscular Disorders                       | 6,46E-06-1,82E-04 | AUTS2 (includes EG:26053), ASS1, LRRC1, HLA-DRB1, C1QA, SERPINA3, HLA-DMB, EIF4A2, CXCL10, CXCL13, CRYM, FABP7, ZBTB16, TNFRSF21, TYMS, CKS2, CHN1 (includes EG:1123), MT1X, RRM2, IER3, RAB31, ARHGDIB, C14ORF132, CTSB, TFRC, UBE2C, FN1, GBP1 (includes EG:2633), CD74, COL4A2, CCL5, TAP1, CORO2B, HLA-DPA1, CCL2, HLA-DRA, IGF1R, SNX10, SERPINA1, LAMB4, RPL13, MMP1 (includes EG:4312), IL11RA, PLAT, CD53, PKM2, PSMB9, CCNB1, TYROBP, DST, FGF14, ITGB2, PDZD2, SWAP70, S100A9, CIRBP, FCER1G, SORBS2, ID4, GZMB, MMP3, TRIM9, MELK, LYZ, PBK, BIRC5, FGFR3, CXCL14, LPL, SCEL, CDKN1C, DSP, GZMA, IL8, CXCL9, SPP1, COL4A1, XYLT1, TMEM204, SPARCL1, CD14, CCL19, IRF8, CCL18, DSC1, C2, TRA@, CDK2, FRZB, TFAP2B, ACOT7, TNFRSF12A, SOX9, KCNMA1, F5, S100A8, STAT1, HLA-DMA, CXCR4, C9ORF3, PRC1, CD36, PYGL, AZGP1, CD3D, HCLS1, CADM1, A2M, MMP9 |
| Post-Translational Modification                       | 1,1E-05-1,72E-04  | IL8, SELL, FN1, SPP1, CNTN1, TSPAN7, CD2, TYROBP, PTN, CD36, CD48, APOC2, CCL5, TUSC3, FGFR3, ITGB2, SATB1, FCER1G, IGF1R, SERPINA1, STAT1, CDK2, MMP1 (includes EG:4312), UBE2C   |
| Hematological Disease                                 | 1,52E-05-6,23E-04 | SELL, FN1, CD2, KPNA2, PTTG1, C1QA, CCL5, CD74, BIRC5, CXCL10, FGFR3, CCL2, CXCL13, KCNMA1, F5, CXCL14, LPL, PTPRZ1, CFH, PLAT, IL11RA, IL8, CXCL9, COL4A1, SPP1, CXCR4, CD36, RRM2, HCLS1, CD3D, ITGB2, ABCA8, S100A9, SATB1, FCER1G, CD14, IRF8, GATA3, CDK2, C2, MMP9   |
| Organismal Injury and Abnormalities                   | 1,52E-05-1,06E-03 | SELL, KRT6A, LHX2, IFI27, HSPB2, CXCL10, CCL2, LPL, HLA-DRA, SERPINA1, IFI6, STAT1, DSP, CXCL11, IL11RA, IL8, PSMB9, SPP1, CXCL9, OAS2, CXCR4, UPP1, COL17A1, CD36, ITGB2, S100A9, KLF5, CTSB, DSC1, MMP9, CDK2  |
| Cell Cycle  | 5,02E-05-1,2E-03  | KIF20A, TYMS, DLGAP5, PLAGL1, CCNB1, FN1, TNC, CKS2, PTTG1, GDF15, SSBP2, IER3, AURKA, BIRC5, NR2E1 (includes EG:7101), SOX9, STAT1, CDKN1C, NEDD4L, ZBTB16, CDK2, MMP9  |
| Hypersensitivity Response                             | 7,46E-05-1,19E-03 | CXCL10, IL8, ITGB2, CXCL9, CD2, CCL2, CD48, CCL5, CXCL11   |
| Nucleic Acid Metabolism                               | 1,55E-04-1,55E-04 | CXCL10, CXCL9, CXCL11  |
| Small Molecule Biochemistry                           | 1,55E-04-1,55E-04 | CXCL10, CXCL9, CXCL11  |
| Carbohydrate Metabolism                               | 2,4E-04-2,4E-04   | KRT14, CXCL10, IL8, TNC, SPP1, FN1, CD14   |
| Organismal Development                                | 2,54E-04-8,06E-04 | IL8, COL4A1, FN1, MMP3, CXCR4, CD36, COL4A2, CITED1, TNFRSF12A, CXCL10, ITGB2, WARS, NR2E1 (includes EG:7101), CCL2, KLF5, CXCL14, CTSB, ECM1, MMP1 (includes EG:4312), MMP9, HEY1, PLAT   |
| Cellular Assembly and Organization                    | 2,68E-04-2,68E-04 | SWAP70, CCL2, CCL5   |
| Endocrine System Disorders                            | 3,11E-04-3,11E-04 | RGS1, COL4A1, SPP1, FN1, SERPINA3, CD74, A2M, C2   |
| Metabolic Disease                                     | 3,11E-04-3,11E-04 | RGS1, COL4A1, SPP1, FN1, SERPINA3, CD74, A2M, C2   |
| Organismal Survival                                   | 3,79E-04-3,79E-04 | S100A1, CXCL9, CNTN1, CD2, CD48, LYZ, CD74, TAP1, BIRC5, CXCL10, CCL2, HLA-DRA, LPL, CTSB, CD14, BCL2A1, STAT1, DSP, MMP9, CXCL11, PLAT  |
| Embryonic Development                                 | 4,05E-04-4,05E-04 | COL4A1, COL4A2   |
| Nervous System Development and Function               | 4,05E-04-4,05E-04 | FN1, CHL1  |
| Visual System Development and Function                | 4,05E-04-4,05E-04 | NR2E1 (includes EG:7101), CDKN1C   |
| Cardiovascular Disease                                | 4,22E-04-1,06E-03 | MMP3, HSPB2, LPL, CD36, MMP1 (includes EG:4312), MMP9, DSP   |
| Organismal Functions                                  | 4,94E-04-4,94E-04 | GZMA, PTPRZ1, PLAT, GZMB   |
| Connective Tissue Development and Function            | 6,23E-04-6,23E-04 | FGFR3, SOX9, MMP9  |
| Skeletal and Muscular System Development and Function | 6,23E-04-1,2E-03  | FGFR3, S100A1, SOX9, FN1, SERPINA3, A2M, MMP9, MMP1 (includes EG:4312)   |
| Renal and Urological                                  | 1,06E-03-         | CXCL10, IL8, CXCR4, CCL5   |



|                                 |                   |  |
|---------------------------------|-------------------|--|
| System Development and Function | 1,06E-03          |  |
| Renal and Urological Disease    | 1,08E-03-1,08E-03 | PKM2, FGFR3, TYMS, PRC1, RRM2, AURKA, MMP9, PLAT, UBE2C, BIRC5 |
| Antimicrobial Response          | 1,2E-03-1,2E-03   | GZMA, GZMB   |
| Organ Morphology                | 1,2E-03-1,2E-03   | S100A1, MMP1 (includes EG:4312)                                |

**Supplemental Table 2:** The Functional Analysis according to Ingenuity's™ Knowledge Base identified the biological functions that were most significant to regulated genes in PM compared to MN comprising cancer, cellular growth and development.

| Category                               | p-value           | Molecules  |
|--|-------------------|--|
| Hair and Skin Development and Function | 7.99E-26-1,4E-02  | CSTA, KRT6A, KLK6, CTSL2, VEGFA, KLK5, SCEL, JUP, KRT1, DSP, KRT16, SELE, GJA1, CDSN, KRT10, KLF4, KLK7, CDH1, TGM1, SPINK5, LAMA3, DSC1, CST6, KRT15, ALOX12B, FN1, SPRR1A, ID1, DSG3, CDH3, KRT2, KIT, LOR, EGFR, KRT14, TIMP3, CALML5, IVL, TP63, KRT17, SPRR1B, COL17A1, LAMC2, KLK8, TYRP1, DHCR24, KRT5, BNC1, CRABP2, SFN   |
| Organ Development                      | 7.99E-26-1,23E-02 | ALOX12B, FN1, SPRR1A, CTSL2, VEGFA, FGFR3, ALDH1A1, KLK5, KIT, KRT2, SCEL, DSC2, LOR, KRT1, DSP, EGFR, KRT14, KRT16, GJA1, CALML5, TP63, SPRR1B, KRT17, COL17A1, CDSN, KRT10, LAMC2, MET, HOPX, KLK7, CDH1, SPINK5, TF, DHCR24, KRT5, BNC1, CRABP2, LAMA3, CST6, SFN, KRT15  |
| Dermatological Diseases and Conditions | 3,73E-19-1,43E-02 | KRT6A, FCER1A, KLK6, SERPINB2, CTSL2, VEGFA, SLURP1, CCL27, ZNF750, JUP, KRT1, DSP, KRT16, GJA1, SELE, SPP1, SERPINB3, CDSN, KRT10, DSG1, CDH1, SPINK5, TGM1, IL1RN, FERMT1, LAMA3, DSC1, ABCA12, ALOX12B, FN1, GJB3, HLA-DQA1, SLPI, DSG3, CD1A, KIT, KRT2, S100A8, LOR, MMP1 (includes EG:4312), EGFR, KRT14, SDC1, TP63, KRT6B, KRT17, PERP, COL17A1, TUBA4A, S100A12, LAMC2, TYRP1, S100A9, KRT5   |
| Cancer                                 | 5,73E-16-1,21E-02 | KRT6A, ASS1, KLK6, SERPINA3, RPS4Y1, SERPINB2, CTSL2, VEGFA, KLK5, MGP, PTGIS, SELE, IGH@, DCN, GSTM3 (includes EG:2947), KRT23, KRT10, S100A2, MET, KLK7, CDH1, SPINT2, ANK3, CA2, FN1, SLPI, AQP3, KLK11, DSG3, ID1, MT1E, CDH3, TRIM29, KLK10, MMP1 (includes EG:4312), EGFR, TACSTD2, PLOD2, KRT6B, KRT17, DST, DEFB1, S100A14, C10ORF116, LAMC2, SERPINB4, NOV, S100A9, DHCR24, KRT5, BNC1, SFN, CXADR, EYA1, QPCT (includes EG:25797), TRIM9, MBP, SCUBE2, FCER1A, LAD1, FGFR3, GPX3, ALDH1A1, CCL27, CXCL14, CFI, JUP, SERPINB5, KRT1, AIM1 (includes EG:202), KRT16, GJA1, SPP1, LCN2, SERPINB3, CAPG, ZNF185, TUSC3, AKR1C2, KLF4, IGFBP2, STC1, IL1RN, AKR1B10, LAMA3, DSC1, S100P, IFI27, CD1A, C7, KIT, S100A8, CD24, KRT14, KLK13, TIMP3, TP63, SDC1, TUBA4A, PERP, PPL, CPA4, KLK8, HOPX, CRABP2, KLF5   |
| Reproductive System Disease            | 5,73E-16-4,17E-03 | NELL1, KRT6A, TRIM9, MBP, ASS1, SCUBE2, LAD1, KLK6, VEGFA, FGFR3, CTSL2, GPX3, ALDH1A1, CXCL14, KLK5, CFI, MGP, SERPINB5, JUP, KRT1, AIM1 (includes EG:202), SELE, SPP1, GSTM3 (includes EG:2947), DCN, LCN2, KRT23, SERPINB3, AKR1C2, TUSC3, KLF4, S100A2, IGFBP2, MET, STC1, CDH1, KLK7, LAMA3, SPINT2, CCL18, S100P, ANK3, FN1, IFI27, SLPI, KLK11, ID1, MT1E, CDH3, C7, KIT, S100A8, CD24, MMP1 (includes EG:4312), KLK10, EGFR, TACSTD2, POF1B, TIMP3, TP63, KRT6B, KRT17, DST, TUBA4A, DEFB1, S100A14, KLK8, SERPINB4, HOPX, S100A9, DHCR24, KRT5, BNC1, CRABP2, SFN, EYA1, CXADR  |
| Cellular Development                   | 2,54E-13-1,43E-02 | NELL1, CSTA, KRT6A, MBP, SERPINA3, SERPINB2, FGFR3, CTSL2, VEGFA, SLURP1, ALDH1A1, MGP, SERPINB7, SCEL, JUP, DSP, GJA1, SPP1, PKP3, DCN, LCN2, CAPG, KRT10, KLF4, IGFBP2, MET, STC1, CDH1, SPINK5, TGM1, IL1RN, LAMA3, CST6, DSC1, CA2, FN1, HLA-DQA1, SPRR1A, SYNM, ID1, KIT, S100A8, LOR, CD24, MMP1 (includes EG:4312), EGFR, TIMP3, IVL, SDC1, TP63, SPRR1B, TYRP1, HOPX, NOV, S100A9, CRABP2, KLF5, SFN, CXADR, EYA1  |
| Genetic Disorder                       | 1,38E-11-1,43E-02 | NELL1, KRT6A, ASS1, CA12, KLK6, SERPINA3, EXPH5, VEGFA, SCNN1A, SLURP1, HAL, KLK5, MGP, SERPINB7, PTGIS, MALL, SELE, DCN, CPA3, KRT10, S100A2, DSG1, MET, KLK7, CDH1, TGM1, SPINT2, VSNL1, ANK3, CA2, FN1, HLA-DQA1, SLPI, ABLIM1, DSG3, KLK11, ID1, AQP3, HLA-DQB2, MT1E, CDH3, KRT2, CLIC3, TRIM29, MMP1 (includes EG:4312), KLK10, EGFR, TACSTD2, NMU, DSC3, POF1B, PLOD2, KRT6B, KRT17, DST, COL17A1, ELOVL4, DEFB1, LAMC2, S100A9, TF, DHCR24, KRT5, BNC1, ANXA3, EYA1, QPCT (includes EG:25797), TRIM9, SLC6A14, MBP, SCUBE2, FCER1A, LPPR4, MT1M, FGFR3, GPX3, ALDH1A1, ZNF750, CCL27, CXCL14, CFI, IMPA2, SCEL, SERPINB5, JUP, KRT1, DSC2, DSP, AIM1 (includes EG:202), KRT16, BBOX1, GJA1, SPP1, LCN2, SERPINB3, CDSN, CAPG, ZNF185, AKR1C2, TUSC3, IGFBP2, SPINK5, FERMT1, IL1RN, AKR1B10, LAMA3, DSC1, CCL18, ABCA12, ARG1, S100P, ALOX12B, GJB3, TUFT1, CDS1, CD1A, C7, KIT, S100A8, LOR, CD24, KRT14, TIMP3, TP63, SDC1, PERP, TUBA4A, S100A12, KLK8, TYRP1, HOPX, KLF5, RHCG |
| Cellular Movement                      | 1,79E-08-1,43E-02 | KRT6A, FCER1A, KLK6, SERPINA3, SERPINB2, CTSL2, VEGFA, CCL27, CXCL14, MGP, SERPINB5, JUP, KRT16, SELE, GJA1, SPP1, PKP3, DCN, LCN2, SERPINB3, KRT10, S100A2, KLF4, IGFBP2, STC1, MET, CDH1, IL1RN, LAMA3, SPINT2, CCL18, CST6, VSNL1, S100P, FN1, SLPI, SYNM, ID1, CDH3, KIT, S100A8, CD24, CALML3, MMP1 (includes EG:4312), NMU, EGFR, TIMP3, TP63, SDC1, PRSS3 (includes EG:5646), COL17A1, DEFB1, LRRC15, LAMC2, LYPD3, NOV, S100A9, KLF5   |
| Cellular Growth and Proliferation      | 2,83E-08-1,43E-02 | NELL1, MBP, FCER1A, KLK6, SERPINB2, CTSL2, FGFR3, VEGFA, SLURP1, ALDH1A1, CCL27, MGP, SERPINB7, SERPINB5, JUP, CLCA2 (includes EG:9635), KRT16, GJA1, SPP1, PKP3, DCN, LCN2, KRT10, FGF1, KLF4, IGFBP2, MET, STC1, CDH1, IL1RN, LAMA3, SPINT2, CST6, ARG1, S100P, FN1, SLPI, SYNM, ID1, DSG3, MT1E, KIT, KRT2, S100A8, CD24, EGFR, TACSTD2, KLK13, TIMP3, TP63, DEFB1, KLK8, TYRP1, NOV, S100A9, TF, DHCR24, BNC1, CRABP2, KLF5, SFN, CXADR  |
| Respiratory Disease                    | 4,28E-08-1,16E-02 | CA2, FN1, CA12, KLK6, SLPI, RPS4Y1, SCNN1A, FGFR3, VEGFA, ID1, DSG3, KLK11, KLK5, MGP, IMPA2, KIT, SERPINB5, CD24, KLK10, EGFR, PTGIS, TIMP3, IVL, SELE, SPP1, TP63, KRT6B, LCN2, SERPINB3, TUBA4A, S100A12, AZGP1, KLK8, MET, CDH1, KLK7, TF, S100A9, IL1RN, KRT5, ANXA3, AKR1B10, LAMA3, ARG1, S100P   |
| Cell-To-Cell Signaling and Interaction | 1,1E-07-1,43E-02  | MBP, FCER1A, KLK6, SERPINB2, CTSL2, VEGFA, SLURP1, CCL27, SERPINB5, JUP, KRT1, DSC2, DSP, CLCA2 (includes EG:9635), KRT16, SELE, GJA1, SPP1, DCN, LCN2, SERPINB3, CDSN, KLF4, IGFBP2, STC1, MET, CDH1, SPINK5, IL1RN, LAMA3, VSNL1, CST6, ANK3, FN1, HLA-DQA1, SLPI, ID1, DSG3, CD1A, CDH3, KRT2, KIT, S100A8, CD24, MMP1 (includes EG:4312), NMU, EGFR, DSC3, TIMP3, SDC1, TP63, COL17A1, PERP, S100A12, AZGP1, LAMC2, LYPD3, S100A9, PI3, CXADR  |

|   |                   |  |
|---|-------------------|--|
| Tissue Development                                    | 1,1E-07-1,43E-02  | NELL1, KRT6A, KLK6, SERPINB2, FGFR3, VEGFA, SLURP1, ALDH1A1, SERPINB5, JUP, DSC2, CLCA2 (includes EG:9635), KRT16, SELE, GJA1, SPP1, DCN, LCN2, CDSN, STC1, MET, CDH1, SPINK5, IL1RN, LAMA3, DSC1, VSNL1, CST6, CA2, FN1, SLPI, ID1, DSG3, CDH3, C7, KIT, S100A8, CD24, EGFR, DSC3, TIMP3, TP63, SDC1, KRT6B, KRT17, PERP, AZGP1, LAMC2, DHCR24, S100A9, KLF5, EYA1, CXADR   |
| Endocrine System Disorders                            | 1,39E-07-9,55E-03 | CA2, SELE, FN1, SPP1, LCN2, CA12, SERPINA3, KLF4, IGFBP2, VEGFA, ID1, CDS1, TF, IL1RN, EYA1, EGFR  |
| Metabolic Disease                                     | 1,39E-07-7,7E-04  | CA2, SELE, FN1, SPP1, LCN2, CA12, SERPINA3, KLF4, IGFBP2, VEGFA, ID1, CDS1, TF, IL1RN  |
| Connective Tissue Development and Function            | 1,63E-06-1,18E-02 | NELL1, GJA1, FN1, SPP1, PKP3, DCN, VEGFA, STC1, FGFR3, MET, CDH1, IL1RN, CDH3, MGP, JUP, EGFR  |
| Renal and Urological Disease                          | 3,84E-06-1,21E-02 | CA2, FN1, MBP, CA12, SERPINA3, VEGFA, FGFR3, AQP3, MT1E, CFI, KIT, JUP, AIM1 (includes EG:202), EGFR, TIMP3, SPP1, LCN2, TUBA4A, PPL, DEFB1, IGFBP2, MET, STC1, CDH1, IL1RN, VAMP8   |
| Inflammatory Response                                 | 4,82E-06-1,28E-02 | FN1, FCER1A, SERPINA3, SLPI, VEGFA, CTSL2, DSG3, CCL27, CXCL14, C7, S100A8, NMU, EGFR, SELE, GJA1, SDC1, SPP1, COL17A1, DEFB1, CAPG, S100A12, TYRP1, S100A9, TF, IL1RN, PI3, DSC1, CCL18   |
| Neurological Disease                                  | 8,18E-06-1,43E-02 | NELL1, KRT6A, MBP, SCUBE2, LPPR4, CA12, MT1M, SERPINA3, FGFR3, CTSL2, VEGFA, ALDH1A1, CCL27, MGP, IMPA2, SCEL, DSP, AIM1 (includes EG:202), PTGIS, KRT16, SELE, GJA1, BBOX1, SPP1, DCN, LCN2, CAPG, CDSN, TUSC3, AKR1C2, ZNF185, KRT10, IGFBP2, TGM1, IL1RN, FERMT1, LAMA3, VSNL1, DSC1, S100P, ARG1, ABCA12, ANK3, CA2, GJB3, HLA-DQA1, TUFT1, ABLIM1, HLA-DQB2, CDS1, MT1E, CD1A, C7, CLIC3, KIT, CD24, MMP1 (includes EG:4312), DSC3, EGFR, POF1B, KRT14, TIMP3, PLOD2, SDC1, TP63, KRT17, DST, PRSS3 (includes EG:5646), PERP, TUBA4A, DEFB1, S100A12, DHCR24, TF, S100A9, KLF5, ANXA3, EYA1 |
| Gastrointestinal Disease                              | 1,27E-05-1,18E-02 | ANK3, CA2, FN1, TRIM9, KLK6, SERPINA3, FGFR3, CTSL2, VEGFA, AQP3, MT1E, KLK5, KIT, SERPINB5, CD24, KLK10, AIM1 (includes EG:202), EGFR, KRT14, KLK13, PLOD2, TIMP3, GJA1, SDC1, SPP1, TP63, LCN2, TUBA4A, CAPG, KRT10, AKR1C2, KLF4, CPA4, C10ORF116, MET, CDH1, IL1RN, CRABP2, LAMA3, SFN, QPCT (includes EG:25797)   |
| Organismal Injury and Abnormalities                   | 1,52E-05-1,06E-02 | CA2, NELL1, KRT6A, IFI27, CA12, SLPI, FGFR3, VEGFA, CTSL2, SCNN1A, DSG3, MT1E, KIT, DSP, MMP1 (includes EG:4312), EGFR, NMU, PTGIS, PLOD2, SELE, GJA1, SPP1, PRSS3 (includes EG:5646), COL17A1, TUBA4A, SERPINB3, KRT10, STC1, HOPX, S100A9, IL1RN, KLF5, DSC1, ARG1   |
| Cell Morphology                                       | 1,56E-05-1,43E-02 | NELL1, KRT6A, FN1, KLK6, SERPINA3, SYNM, VEGFA, ID1, MGP, KRT2, SERPINB5, CD24, CALML3, EGFR, KRT16, TIMP3, SELE, GJA1, SPP1, SDC1, TP63, KRT17, DCN, LCN2, CAPG, KLF4, IGFBP2, STC1, MET, CDH1, SPINK5, IL1RN, BNC1, KLF5, LAMA3, ARG1  |
| Immunological Disease                                 | 2,42E-05-1,43E-02 | SPP1, FN1, MBP, FCER1A, COL17A1, HLA-DQA1, DSG1, VEGFA, FGFR3, DSG3, SPINK5, S100A9, IL1RN, KIT, CD24, CXADR   |
| Skeletal and Muscular System Development and Function | 2,71E-05-1,18E-02 | NELL1, GJA1, SDC1, FN1, SPP1, DCN, SERPINA3, KLF4, MET, CTSL2, STC1, FGFR3, VEGFA, NOV, IL1RN, KLF5, MGP, KIT, SERPINB5, CXADR, MMP1 (includes EG:4312), ARG1, EGFR  |
| Hematological System Development and Function         | 2,81E-05-1,2E-02  | FN1, MBP, FCER1A, SERPINA3, SLPI, CTSL2, VEGFA, CCL27, CDH3, CXCL14, C7, KIT, S100A8, NMU, EGFR, TIMP3, GJA1, SELE, SPP1, LCN2, PRSS3 (includes EG:5646), COL17A1, DEFB1, CAPG, KRT10, STC1, TF, S100A9, IL1RN, PI3, CCL18, DSC1   |
| Immune Cell Trafficking                               | 2,81E-05-1,2E-02  | FN1, FCER1A, SERPINA3, SLPI, VEGFA, CTSL2, CCL27, CDH3, CXCL14, C7, KIT, S100A8, CD24, NMU, EGFR, TIMP3, SELE, SPP1, SDC1, PRSS3 (includes EG:5646), SERPINB3, COL17A1, DEFB1, KRT10, STC1, S100A9, IL1RN, DSC1, CCL18   |
| Organismal Functions                                  | 3,81E-05-4,11E-03 | MET, VEGFA, HOPX, GJA1, SPP1, FN1, IL1RN, SLPI, SERPINB2   |
| Inflammatory Disease                                  | 4,7E-05-7,5E-03   | VEGFA, CA2, SPP1, S100A9, IL1RN, CA12, S100A8, S100A12, SERPINB2   |
| Nutritional Disease                                   | 4,7E-05-4,7E-05   | SCNN1A, DSG3, SPINK5   |
| Cardiovascular System Development and Function        | 6,06E-05-1,4E-02  | PTGIS, TIMP3, SELE, GJA1, SPP1, FN1, DCN, KLF4, VEGFA, MET, CTSL2, STC1, SLURP1, ID1, S100A9, KLF5, KIT, SERPINB5, KRT1, CXADR, MMP1 (includes EG:4312), EGFR  |
| Ophthalmic Disease                                    | 8,11E-05-8,95E-03 | CA2, SELE, DCN, ELOVL4, CA12, TUBA4A, VEGFA, FGFR3, TYRP1, TF, IL1RN, KIT, TACSTD2   |
| Tumor Morphology                                      | 9,35E-05-1,43E-02 | SELE, FN1, DCN, PERP, LRRC15, IGFBP2, SERPINB2, CTSL2, VEGFA, CDH1, NOV, IL1RN, JUP, SERPINB5, MMP1 (includes EG:4312), EGFR   |
| Cell Death  | 1,73E-04-1,43E-02 | CSTA, NELL1, MBP, FCER1A, SERPINA3, SERPINB2, VEGFA, CTSL2, FGFR3, ALDH1A1, CCL27, CFI, MGP, JUP, SERPINB5, DSP, CLCA2 (includes EG:9635), PTGIS, GJA1, SPP1, DCN, LCN2, SERPINB3, KRT10, KLF4, IGFBP2, DSG1, STC1, MET, CDH1, TGM1, IL1RN, S100P, ARG1, RAB25, FN1, SPRR1A, ID1, DSG3, MT1E, C7, KIT, S100A8, CD24, MMP1 (includes EG:4312), EGFR, TIMP3, SDC1, TP63, PERP, DEFB1, KLK8, SULT2B1, SERPINB4, TF, DHCR24, S100A9, KLF5, CRABP2, SFN, EYA1   |
| Cardiovascular Disease                                | 2,53E-04-1,43E-02 | PTGIS, CA2, SELE, GJA1, KRT6A, LCN2, CA12, S100A12, SLPI, CTSL2, VEGFA, SCNN1A, S100A9, IMPA2, SERPINB5, JUP, DSC2, VSNL1, DSP, AIM1 (includes EG:202), S100P  |
| Cellular Compromise                                   | 2,53E-04-3,09E-03 | TYRP1, SELE, GJA1, SPP1, KRT6A, MT1E, IL1RN, PI3, EGFR   |
| Connective Tissue Disorders                           | 2,56E-04-2,75E-03 | VEGFA, SPP1, S100A9, IL1RN, S100A8, S100A12, SERPINB2  |

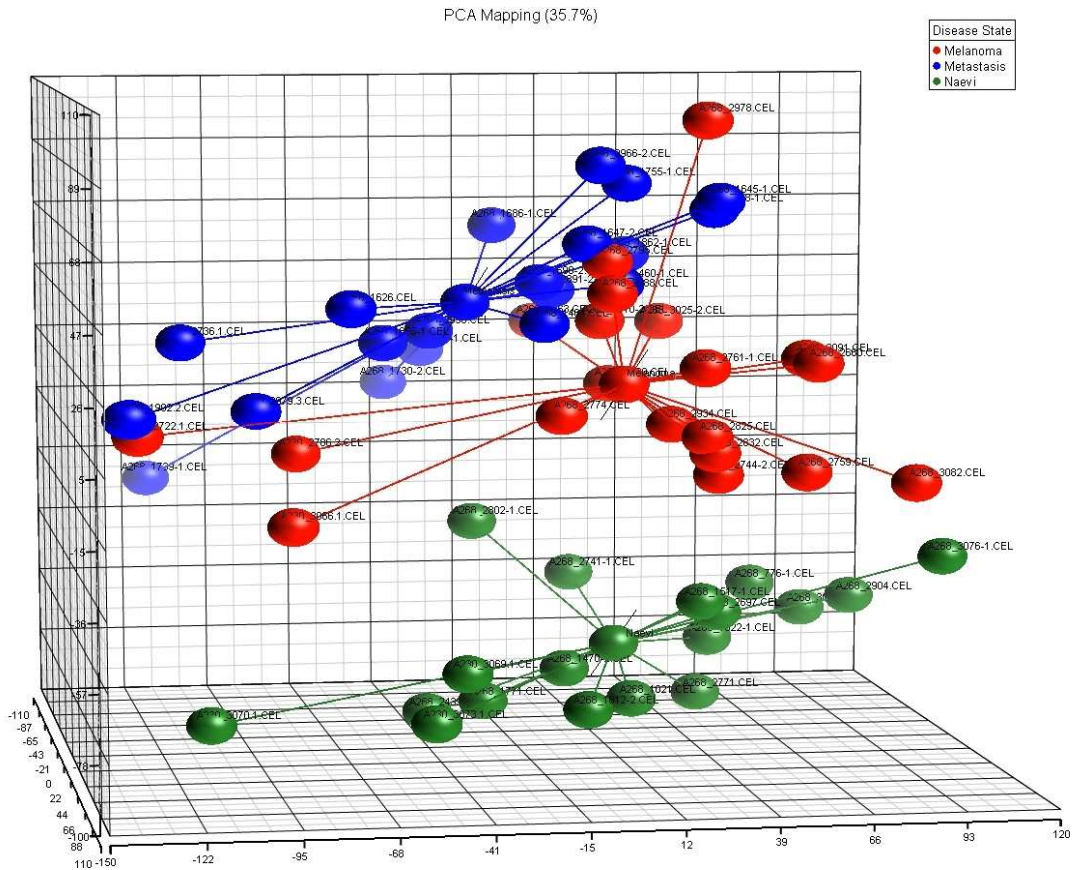
|  |                   |  |
|--|-------------------|--|
| Cell Cycle   | 3,75E-04-1,43E-02 | VEGFA, ID1, CDH1, SPP1, FN1, TF, KIT, SERPINB5, SFN, KLF4, EGFR  |
| Carbohydrate Metabolism                              | 4,72E-04-8,42E-03 | KRT14, VEGFA, CDH1, SPP1, FN1, SLPI  |
| Infectious Disease                                   | 8,37E-04-1,43E-02 | FN1, S100A9, PI3, LCN2, IMPA2, S100A12, SLPI, RPS4Y1, CXADR, CD24, S100P   |
| Cellular Assembly and Organization                   | 8,51E-04-1,43E-02 | GJA1, KRT6A, FN1, SPP1, KRT17, LAMC2, VEGFA, MET, CDH1, CCL27, MGP, LAMA3, JUP, DSP, EGFR  |
| Cellular Function and Maintenance                    | 8,51E-04-1,43E-02 | VEGFA, CDH1, KRT6A, IL1RN, KRT17, MBP, LAMA3, FCER1A, VAMP8, DSC2, LAMC2   |
| Embryonic Development                                | 8,51E-04-1,31E-02 | TIMP3, GJA1, KRT6A, FN1, TP63, KRT6B, LCN2, KLK6, MET, VEGFA, FGFR3, SLURP1, ALDH1A1, MGP, SERPINB5, EYA1, EGFR                        |
| Organ Morphology                                     | 8,51E-04-8,5E-03  | KRT16, GJA1, FN1, TP63, KRT10, CTSL2, TYRP1, VEGFA, CDH1, TGM1, ALDH1A1, DHCR24, IL1RN, DSC2, DSC1, MMP1 (includes EG:4312), DSP, EGFR |
| Post-Translational Modification                      | 8,51E-04-9,4E-03  | FGFR3, VEGFA, GPX3, TP63, ALDH1A1, TGM1, FCER1A, KIT, CD24, EGFR   |
| Protein Folding                                      | 8,51E-04-8,51E-04 | VEGFA, TGM1  |
| Reproductive System Development and Function         | 8,51E-04-1,43E-02 | VEGFA, SELE, GJA1, CDH1, TP63, ALDH1A1, TF, KLF5, KIT, DSC2, CLCA2 (includes EG:9635)  |
| Tissue Morphology                                    | 8,51E-04-8,43E-03 | GJA1, SELE, SPP1, FCER1A, KLF4, MET, CTSL2, VEGFA, STC1, TF, S100A9, PI3, S100A8, SFN, MMP1 (includes EG:4312), ARG1                   |
| Organismal Development                               | 8,98E-04-8,42E-03 | MET, VEGFA, STC1, TIMP3, SLURP1, FN1, KLF5, SERPINB5, MMP1 (includes EG:4312)  |
| Hepatic System Disease                               | 1,68E-03-1,68E-03 | MT1E, IL1RN  |
| Renal and Urological System Development and Function | 1,68E-03-1,43E-02 | MET, TIMP3, CDH1, FN1, TP63, ALDH1A1, LCN2, KLK6   |
| Hematological Disease                                | 2,24E-03-1,43E-02 | VEGFA, PLOD2, SELE, SPP1, FN1, S100A9, IL1RN, KIT, CXADR   |
| Skeletal and Muscular Disorders                      | 2,51E-03-9,63E-03 | GJA1, SPP1, ASS1, LCN2, TUBA4A, S100A12, RPS4Y1, FGFR3, S100A9, CRABP2, IMPA2, KIT, S100A8, VSNL1, AIM1 (includes EG:202), S100P       |
| Cell Signaling                                       | 2,77E-03-7,51E-03 | ASS1, FCER1A, VAMP8, ARG1  |
| Drug Metabolism                                      | 2,77E-03-2,77E-03 | PTGIS, VEGFA   |
| Lipid Metabolism                                     | 2,77E-03-1,08E-02 | VEGFA, PTGIS, ALOX12B, SPP1, S100A9, FCER1A, S100A8, AKR1C2, NMU   |
| Molecular Transport                                  | 2,77E-03-1,18E-02 | SPP1, TF, MT1E, S100A9, SLC6A14, FCER1A, S100A8, VAMP8, ARG1, NMU  |
| Small Molecule Biochemistry                          | 2,77E-03-1,18E-02 | PTGIS, ALOX12B, SPP1, SLC6A14, FCER1A, AKR1C2, FGFR3, VEGFA, CDH1, ALDH1A1, S100A9, AKR1B10, KIT, S100A8, CD24, EGFR, NMU, ARG1        |
| Lymphoid Tissue Structure and Development            | 2,83E-03-6,44E-03 | PTGIS, SELE, GJA1, S100A9, TF, KLF5, PI3, FCER1A, S100A8, KLF4   |
| Visual System Development and Function               | 4,11E-03-4,11E-03 | MET, VEGFA   |
| Hematopoiesis  | 4,44E-03-1,18E-02 | VEGFA, SELE, IL1RN, MBP, LCN2, KIT, EGFR   |
| Infection Mechanism                                  | 5,7E-03-5,7E-03   | PI3, CXADR   |
| Cell-mediated Immune Response                        | 7,05E-03-1,18E-02 | CTSL2, SELE, SPP1, FN1, CCL27, IL1RN, MBP, DEFB1, CCL18  |
| Amino Acid Metabolism                                | 7,51E-03-1,18E-02 | FGFR3, ASS1, SLC6A14, FCER1A, KIT, CD24, EGFR, ARG1  |
| Protein Degradation                                  | 7,51E-03-7,51E-03 | TIMP3, KLK6  |
| Respiratory System Development and Function          | 8,42E-03-8,42E-03 | FGFR3, VEGFA, HOPX   |
| Developmental Disorder                               | 9,4E-03-9,55E-03  | FGFR3, VEGFA, EYA1, EGFR   |
| Protein Synthesis                                    | 9,4E-03-9,4E-03   | GPX3, TP63, ALDH1A1  |
| Endocrine System Development and Function            | 9,55E-03-9,55E-03 | SPP1, NMU  |
| Antigen Presentation                                 | 1,18E-02-1,18E-02 | FN1, CAPG  |

**Supplemental Table 3:** The Functional Analysis according to Ingenuity's™ Knowledge Base identified the biological functions that were most significant to regulated genes in MM compared to PM comprising cancer, cellular movement, cellular growth and proliferation.

| GDF 15                     | MN   |      |      | PM   |      |      | MM   |      |      |
|----------------------------|------|------|------|------|------|------|------|------|------|
|                            | A.M. | T.V. | mean | A.M. | T.V. | mean | A.M. | T.V. | mean |
| - negative                 | 48   | 45   | 46,5 | 7    | 5    | 6    | 17   | 15   | 16   |
| (+) weakly positive        | 45   | 51   | 48   | 2    | 3    | 2,5  | 3    | 4    | 3,5  |
| + positive                 | 32   | 28   | 30   | 26   | 23   | 24,5 | 31   | 25   | 28   |
| ++ strongly positive       | 2    | 3    | 2,5  | 27   | 28   | 27,5 | 26   | 31   | 28,5 |
| +++ very strongly positive | 0    | 0    | 0    | 11   | 14   | 12,5 | 12   | 14   | 13   |

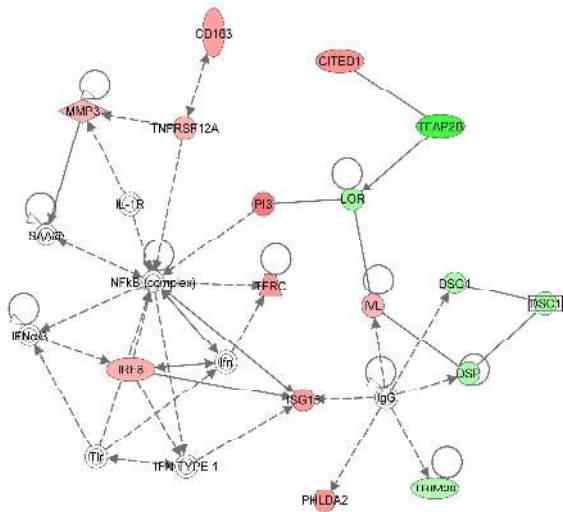
| MMP 1                      | MN   |      |      | PM   |      |      | MM   |      |      |
|----------------------------|------|------|------|------|------|------|------|------|------|
|                            | A.M. | T.V. | mean | A.M. | T.V. | mean | A.M. | T.V. | mean |
| - negative                 | 1    | 5    | 3    | 0    | 0    | 0    | 2    | 5    | 3,5  |
| (+) weakly positive        | 14   | 22   | 18   | 1    | 0    | 0,5  | 11   | 14   | 12,5 |
| + positive                 | 51   | 47   | 49   | 14   | 12   | 13   | 27   | 33   | 30   |
| ++ strongly positive       | 54   | 48   | 51   | 44   | 50   | 47   | 32   | 25   | 28,5 |
| +++ very strongly positive | 6    | 4    | 5    | 17   | 14   | 15,5 | 19   | 14   | 16,5 |

**Supplemental Table 4:** Two independent investigators (A.M., T.V.) evaluated immunostaining of tissue specimens based on a 5-step scoring system.



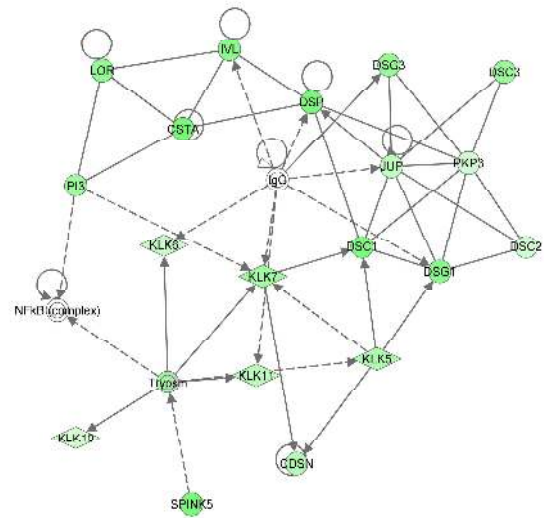
**Supplemental Figure 1:** Principal component analysis displays spatial separation of melanocytic nevi (MN), primary melanomas (PM), and melanoma metastases (MM). Results of PCA are shown in the three-dimensional contribution scores, which discriminate the three entities.

A: PMvsMN all



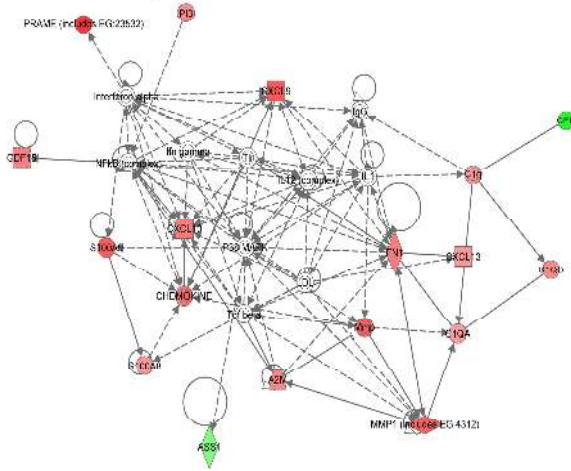
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B: MMvsPMall



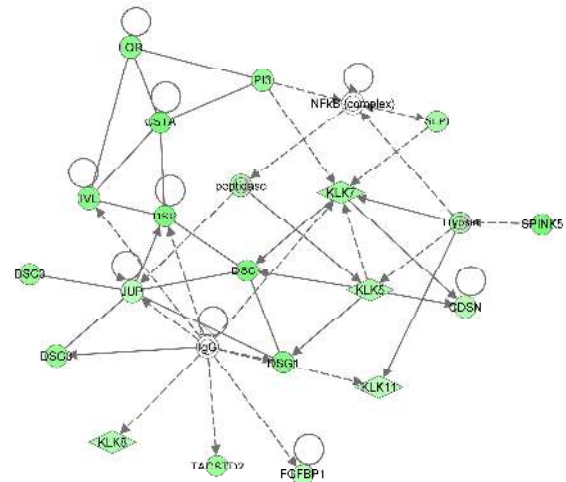
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C: PMvsMN ratio 1,5



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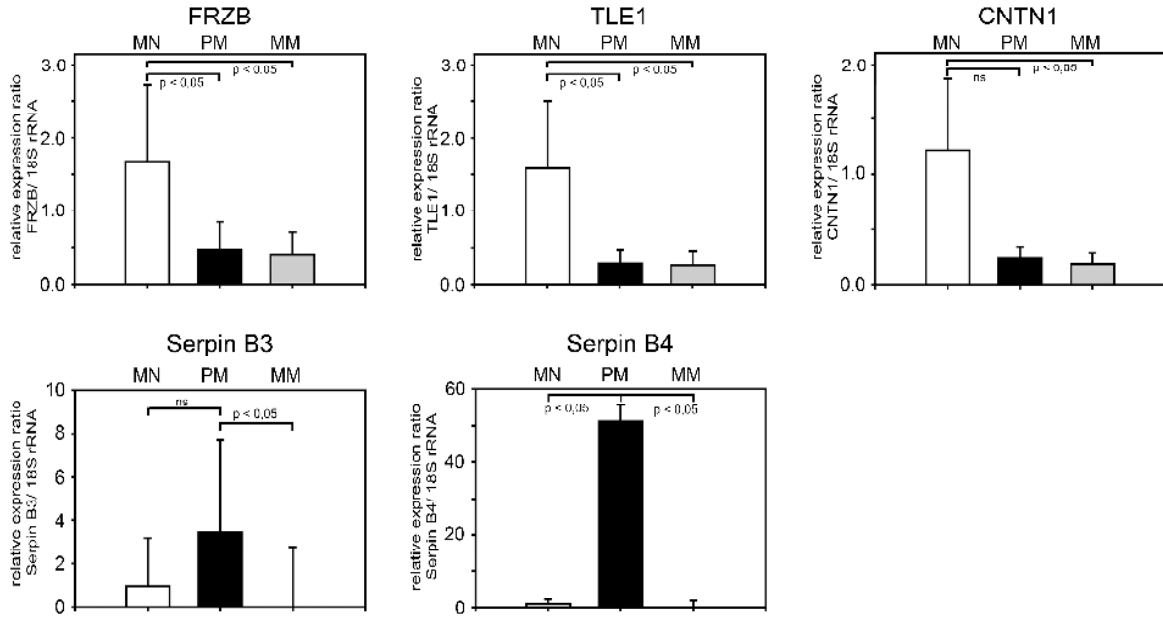
D: MMvsPM ratio 1,5



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**Supplemental Figure 2A/B/C/D:** Ingenuity Network analysis of all significantly regulated genes in PM compared to MN (Figure A), MM compared to PM (Figure B). Analysis of genes with a minimum log ratio of 1.5 in PM compared to MN (Figure C), MM compared to PM (Figure D). Green symbols show down-regulation, red symbols show up-regulation in PM compared to MN (Figure A/ C) and in MM compared to PM (Figure B/ D).





**Supplemental Figure 3:** Confirmation of differential gene expression by quantitative real-time RT-PCR (ns= not significant).

# Deutsche Zusammenfassung der Promotionsarbeit

mit dem publizierten Titel:

## **“Identification of new genes associated with melanoma”**

### **Identifizierung neuer melanomassoziierter Gene**

Andreas Mauerer

Mit der vorliegenden Arbeit sollen neue Erkenntnisse über die Genexpressionsmuster und Signalkaskaden des malignen Melanoms gewonnen werden. Während Melanom-Patienten mit einer Tumordicke von unter 1 mm (Stadium I) eine gute Prognose haben, sinkt die Fünfjahresüberlebensrate bei Vorliegen von Fernmetastasen (Stadium IV) unter 10 % [1]. Auf eine Standardchemotherapie sprechen nur zwischen 5,3 und 23% der Patienten an [2, 3]. Wegen dieser geringen Ansprechrate werden neue Therapieansätze verfolgt, die auf der Blockade molekularer Prozesse in der Signaltransduktion der Zelle beruhen. Die Selbstregulation der Melanomzelle wird von einer Vielzahl an Genen gesteuert. Deshalb ist es für neue diagnostische und therapeutische Ansätze wichtig, bevorzugt das Gesamtexpressionsmuster zu betrachten anstatt nur ein Einzelgen zu verfolgen [4]. Seit der Entwicklung der Mikroarray-Technologie ist es möglich die Expression einer Vielzahl von Genen in einer Gewebeprobe zu untersuchen. Mit einer geeigneten Software können Netzwerke von Signalkaskaden in den einzelnen Proben analysiert und verglichen werden.

In dieser Arbeit wurden humane Gewebeproben von 18 melanozytären Nävuszellnävus (MN), 20 Melanomen (PM) und 20 Melanommetastasen (MM) aus der Abteilung für Dermatologie der Universität Regensburg verwendet. Ein Teil des entfernten Patientengewebes wurde nach der Gewinnung kryokonserviert. Nach Abschluss der Diagnosestellung wurde mittels Mikrodissektion Gewebe zur weiteren Untersuchung isoliert. Anschließend erfolgte die Isolierung der RNA und Überschreibung in zweisträngige cDNA und Biotin markierte cRNA. Nach deren Fragmentierung erfolgte die Hybridisierung auf Mikroarrays (Affymetrix Human Genome U133A 2.0 GeneChip®; Affymetrix, Santa Clara, USA). Zur Analyse und statistischen Untersuchung der gewonnenen CEL Files wurde Chipinspector Version 1.3 (Genomatix Software GmbH, München, Germany) verwendet [5]. Mit Ingenuity™ Pathways

Analysis ([www.ingenuity.com](http://www.ingenuity.com), Ingenuity<sup>TM</sup> Systems, Mountain View, USA) [6] wurden funktionelle Verbindungen der signifikant regulierten Gene, Netzwerke und eingebundene Signalkaskaden aufgedeckt. Eine Hauptkomponentenanalyse erlaubte die dreidimensionale Darstellung der Einzelproben in Abhängigkeit von ihrem Expressionsmuster (Partek Genomic Suite 6.4, Partek Inc., St. Louis, USA).

Zur Validierung der Mikroarray Daten wurden zusätzlich quantitative Echtzeit-PCR (QPCR) Untersuchungen durchgeführt. Hierfür wurde RNA von fünf repräsentativen MN, von fünf PM und von fünf MM isoliert und in cDNA (SuperScript II, Invitrogen, Carlsbad, USA) übersetzt. Die Untersuchung erfolgte in dreifacher Ausführung mit Hilfe der kommerziell erhältlichen TaqMan<sup>TM</sup>-Assays (Applied Biosystem, Foster City, USA) und individueller Primer (Apara Bioscience, Denzlingen, Germany).

Um die Genprodukte von GDF15 und MMP1 nachzuweisen, führten wir Tissue-Mikroarrays (TMA) durch [7]. Diese enthielten Gewebezyylinder von 127 MN, 73 PM, und 89 MM auf einem Paraffinblock. Anhand von Standardprotokollen erfolgte eine Inkubierung mit polyklonalen anti-GDF15 Antikörpern (Abcam, Cambridge, UK) und monoklonalen anti-MMP1 Antikörpern (Millipore Corporation, Billerica, USA); danach Färbung mit Hilfe von biotinylierten Sekundärantikörpern (Zytochem Plus HRP Broad Spectrum Kit, Zytomed Systems, Berlin, Germany). Die Auswertung erfolgte durch zwei unabhängige Untersucher (A.M., T.V.) anhand eines fünfstufigen Bewertungssystems (0 bis 4+). Um die Überlebenszeit mit niedrigen und hohen Expressiongraden der Gene Serpin B3 und Serpin B4 zu vergleichen, verwendeten wir SPSS V.18.0 (SPSS Inc., Chicago, USA). Ein p-Wert <0.05 wurde als signifikant gewertet [8].

Bei der Auswertung der CEL Files wurden die Gruppe der PM mit der Gruppe der MN und die Gruppe der MM mit der Gruppe der PM verglichen. Die Werte mussten sich hierbei um den Faktor zwei unterscheiden, um als signifikant zu gelten. Chipinspector identifizierte für die Gruppe der PM im Vergleich mit der Gruppe der MN 167 Gene, die vermehrt, und 117 Gene, die vermindert exprimiert wurden. Beim Vergleich der Gruppe der MM mit der Gruppe der PM ergaben sich 26 vermehrt und 163 vermindert exprimierte Gene.

Beim Vergleich der Ergebnisse mit bereits publizierten Daten zeigten sich große Übereinstimmungen. Erhöhte Expressionswerte bei Melanomen im Vergleich mit melanozytären Nävi sind bekannt für PRAME, SSP1 [9, 10], CXCL9, PHACTR1, CITED-1, BCL2A1 [9, 11] S100A9, MMP1, FN1 [12], NNMT, SERPIN A3 [9], MCAM [13], ISG15 [14], CDK-2, und CDK-4 [15], GDF15 [9, 11, 16] und Hey1 [11, 12]. Erniedrigte Werte sind für CIRBP,

FEZ1, PPP1R3C, LDOC1, TRPM1 [12], Desmoglein [13], KRT-15 [9], FABP7 [16], p57KIP2 und CDKN1 [17] beschrieben.

Für die Gruppe der Melanometastasen im Vergleich mit Melanomen ergab die Literaturrecherche ebenfalls erhöhte Expressionswerte für VEGFA [18, 19], FN1 [20, 21], IGFBP2 [22], SPP1, MAGEA12, c-MET [11, 21, 23], STC1, und PLOD2 [21] sowie verminderte Werte für Serpin B5 [24], SPRR1A, KRT 16/17/6B, CD 24, LOR, DSC1 [23], KRT 1/14/6A/5, CXCL14 und SPINT2 [21].

Wir nahmen an, dass die drei histologisch unterschiedlichen Gruppen anhand ihres Transkriptoms klassifiziert werden können und untersuchten dies mit Hilfe der Hauptkomponentenanalyse. Hierbei wurden die 58 Patientenproben anhand ihres Expressionsmusters räumlich dargestellt. Tatsächlich ergab sich in der dreidimensionalen Darstellung eine klare räumliche Trennung der drei Entitäten.

Um die Funktion der transkribierten Gene und deren Verbindungen untereinander zu analysieren nutzten wir die Datenbank der Ingenuity<sup>TM</sup> Software. Bei PM im Vergleich mit MN waren insbesondere die Gene exprimiert, die für Tumoren, dermatologische Erkrankungen, Zellwachstum, Zellwanderung und Entzündungsreaktionen eine Rolle spielen. Darüberhinaus konnten mit Hilfe des Ingenuity Network Algorithm<sup>TM</sup> 15 funktionelle Gennetzwerke erstellt werden. Darunter waren Gene, die in wichtige Zellfunktionen und in Signalkaskaden des malignen Melanoms involviert sind, insbesondere in die Apoptose, die Kontrolle der G1/S und G2/M Phasen, den Notch-, den MAP-Kinase-, den WNT/beta Catenin- und Integrin-Signalweg [25, 26]. Die beim Vergleich der MM mit den PM signifikant regulierten Transkripte sind laut Ingenuity<sup>TM</sup> Datenbank beteiligt an Haar und Hautentwicklung, dermatologischen Erkrankungen, Tumoren, Zellwachstum, Zellwanderung und Entzündungsreaktionen. Auch hier konnten wichtige Signalwege identifiziert werden, unter anderen VEGF-, PI3/AKT-, WNT/beta Catenin- und Integrin-Signalwege.

Um bisher noch nicht für das Melanom beschriebene Gene zu identifizieren, führten wir eine Ingenuity<sup>TM</sup> Analyse durch, bei der nur diejenigen differentiell exprimierten Transkripte einbezogen wurden, die eine minimale log- Ratio von 1,5 aufwiesen. Basierend auf intensiven Gene-Ontology Recherchen erwarteten wir insbesondere Gene, die in die bedeutenden Melanom-Signalwege MAP-Kinase-, Notch- und Wnt-Signalweg involviert sind. Hierbei identifizierten wir Contactin1 (CNTN1), ein Adhäsionsmolekül, das in den Notch- Signalweg eingebunden ist und bei PM im Vergleich mit MN geringer exprimiert war. Frizzled-related Protein (FRZB) und transducin-like enhancer of split 1 (TLE1) sind in den Wnt-Signalweg eingebunden und waren bei PM im Vergleich mit MN geringer exprimiert. Die Serpin

Peptidase Inhibitoren Serpin B3 und B4 waren bei PM im Vergleich mit MN sehr stark exprimiert und sind assoziiert mit dem MAP-Kinase Weg [27]. Zudem konnten wir die kürzlich beschriebene verstärkte Expression des growth differentiation factor 15 (GDF15) in PM [9, 11, 12] verifizieren.

Diese Beobachtung validierten wir mit Hilfe der Echtzeit-PCR Methode. Die von MN über PM bis hin zu MM abnehmenden Expressionswerte für CNTN1, FRZB und TLE1 wurden weitgehend mit hoher statistischer Signifikanz bestätigt. Auch die hohen Serpin B4 Expressionswerte bei PM verglichen mit MN und MM konnten reproduziert werden. Für Serpin B3 fanden wir signifikant erhöhte Werte bei PM verglichen mit MM und einen Trend in Richtung erhöhter Werte bei PM verglichen mit MN.

GDF15, ein potenzieller Marker mit interessanter Biologie, wurde exemplarisch ausgewählt, um unsere auf transkribierten Genen basierenden Daten auf Proteinebene zu überprüfen. Hierfür wählten wir Tissue-Mikroarrays (TMA) mit mehr als 280 humanen Gewebeproben. Als Kontrolle verwendeten wir MMP1, deren Genregulation bereits bekannt ist. Die immun-histochemischen Färbungen wurden anhand eines fünfstufigen Bewertungssystems (0 bis 4+) kategorisiert und zeigten hohe GDF15 Werte bei PM und MM, während das GDF15 Protein bei MN kaum nachweisbar war. Diese Beobachtungen stimmten mit den Werten des GeneChips® überein. Interessanterweise war die progressionsfreie Überlebenszeit der Melanom Patienten mit niedrigen GDF15 Protein Werten (0 bis 2+) signifikant höher als die der Patienten mit hohen GDF15 Werten (3+ bis 4+;  $p=0.037$ ). Übereinstimmend mit früheren Berichten über Metalloproteinasen [28, 29] beobachteten wir hohe Werte für MMP1 bei PM und signifikant niedrigere Werte bei MM und MN. Beim Vergleich der Färbeintensität mit der Zeit des progressionsfreien Überlebens zeigte sich für MMP1 kein signifikanter Unterschied.

Wie bereits oben erwähnt, findet man in praktisch jeder Melanomzelle Veränderungen im MAP-Kinase-Weg, die zu einer Aktivierung dieses Signalwegs führen [30]. Seit der Entdeckung aktivierender Mutationen des BRAF Proteins beim Melanom [31-33] stand der MAP-Kinase-Weg im Mittelpunkt des Forschungsinteresses. Auch in unseren Daten fanden wir differentiell exprimierte Gene mit Bezug zu MAP-Kinase Signalen. So waren STAT1 und SPP1 bei PM verglichen mit MN verstärkt exprimiert, während PPP1R3C vermindert exprimiert wurde. Mitglieder der STAT-Familie werden als Antwort auf Zytokine und Wachstumsfaktoren phosphoryliert und können daraufhin dimerisieren und am Zellkern als Transkriptionsfaktoren agieren. Wie auch in früheren Studien gezeigt wurde, wird SPP1 bei

PM und MM sehr stark exprimiert [9, 21, 34]. Dagegen ist relativ wenig über PPP1R3C bei Tumoren bekannt. PPP1R3C werden Tumor-Suppressorfunktionen zugeschrieben, da bei Melanomen verglichen mit Melanozyten eine Promotor-Hypermethylierung und eine geringere mRNA Expression beobachtet wurden [35]. Als neue progressionsassoziierte Marker mit Bezug zu MAP-Kinase Signalen konnten wir zwei Serpin-Peptidase-Inhibitoren, Serpin B3 und Serpin B4, identifizieren. Beide waren bei PM verglichen mit MN stark hochreguliert und bei Metastasen herunterreguliert. Kürzlich wurde gezeigt, dass Serpin B3 ein spezifischer endogener Inhibitor der c-Jun-NH<sup>2</sup>-Terminal Kinase-1 (JNK1/MAPK8) ist und UV-exponierte Keratinozyten vor apoptotischem Zelltod nach Sonnenexposition bewahrt [36]. Über die Rolle von Serpin B3 und B4 beim Melanom ist wenig bekannt. Bei Plattenepithelkarzinomen der Zervix, der Lunge, des Kopf-Hals-Bereichs wird Serpin B3 bereits als Tumormarker verwendet [37, 38]. Serpin B4 könnte ein allgemeiner Marker für Tumorinvasion und Metastasierung sein. Eine Inaktivierung durch Antisense cDNA führt bei humanen Zervixkarzinom-Zellkulturen zu einem Abfall der E-Cadherin-Expression, was allgemein einen bekannten Schritt für den Verlust der Zell-Zell-Adhäsion darstellt. [39]. Da auch Melanomzellen durch Herunterregulation von E-Cadherin der Keratinozytenkontrolle entkommen können [13], nehmen wir an, dass Serpine eine wichtige Rolle in der Melanomprogression spielen. Diese Annahme wird durch die Beobachtung bekräftigt, dass ein weiteres Mitglied der Familie der Serpine, Serpin B5 (Maspin), bei MM vermindert exprimiert wurde. Der Verlust von Serpin B5 gilt als Marker für Invasion und Migration bei anderen Tumorentitäten wie Brust-, Prostata- und Pankreaskarzinomen [40].

Ein weiteres signifikant reguliertes Gen in unseren Daten mit Verbindungen zum MAP-Kinase Signalweg ist GDF15, ein Mitglied der TGF- $\beta$  Superfamilie [41]. Wir fanden deutlich erhöhte Expressionswerte für PM und MM verglichen mit MN; gleichzeitig konnten wir nach Auswertung unserer Patientendaten feststellen, dass erhöhte GDF15 Werte mit einer verkürzten progressionsfreien Überlebenszeit assoziiert waren. Wie Boyle et al. bereits feststellen konnten, kann die Tumorigenität von unterschiedlichen Melanom-Zelllinien in einem Maus-Xenograft Model durch Inhibierung von GDF15 reduziert werden [42]. Erhöhte GDF15 Werte bei PM und MM wurden auch von Talantov et al. beschrieben, die zudem GDF15 als geeigneten Marker zur Differenzierung von Melanomen und Nävi vorschlugen [11]. Da GDF15 in weitere Tumor-Signalwege eingebunden ist, wie z. B. p53 [43], MITF [44], und PI3K/AKT-Signalwege [42, 45, 46], könnte es eine Schlüsselposition für die Entwicklung von Melanommetastasen mit schlechter Prognose und Überlebenszeit besitzen [47].

Beim Melanom wurden zudem aberrante Aktivierungen des Wnt-Signalwegs beobachtet [48]. Mit FRZB und TLE1 wurden in unseren Daten zwei wichtige Bausteine des Wnt-Signalwegs bei PM verglichen mit MN geringer exprimiert. FRZB (sFRP3) gehört zur Familie der secreted Frizzled-related Proteine, deren Mitglieder eine Ligand-Rezeptor Interaktion durch die Bindung extraxellulärer Wnt-Liganden verhindern [49, 50]. Da FRZB bei Pleuramesotheliomen [51] und Prostatakarzinomen [52] geringer exprimiert wird, wurde eine Tumor-Suppressorfunktion vermutet.

TLE1, ein Corepressor, ist Mitglied der Groucho/TLE/Grg Familie und an einigen Signalwegen beteiligt [53, 54]. Im Wnt-Signalweg interagiert es mit wichtigen Transkriptionsfaktoren, unter anderen mit TCF/LEF-1 [55]. Es wird angenommen, dass eine Inaktivierung von TLE1 an der Entwicklung hämatookologischer Erkrankungen beteiligt ist, da entscheidende Differenzierungswege und wachstumshemmende Signalwege unterbrochen werden [56]. Im Notch-Signalweg fungiert TLE1 als Corepressor von HES1, einem Gen, das bei einigen humanen Tumorerkrankungen aktiviert ist und Tumorzellen erlaubt, der Differenzierung und der irreversiblen Ruhephase zu entkommen [50, 57]. Auch CNTN1 ist am Notch-Signalweg beteiligt. Es ist ein Mitglied der Immunglobulin-Superfamilie und ein neuronales Membranprotein, das als Adhäsionsmolekül und funktioneller Ligand von Notch wirkt. Es ist unter anderem an der Oligodendrozytenreifung beteiligt [58]. Abhängig vom Gewebe können Notch-Signalwege durch die Beeinflussung von Tumorzeldifferenzierung, Proliferation und Apoptose sowohl tumorinitiierende als auch tumorsupprimierende Effekte auslösen. [59, 60]. Bei Melanomen scheint eine Aktivierung von Notch-Signalwegen wichtig für die gesamte Tumorprogression. So führt eine verstärkte Expression von Nic, der aktiven Form von Notch, in Melanozyten zu einer malignen Transformation, während eine Aktivierung von Notch1 bei Melanomzellen eher einen metastatischen Phänotyp bewirkt [61, 62].

Die Studie konnte zeigen, dass sich Primärtumoren und Metastasen des Melanoms durch unterschiedliche Genexpressionsmuster unterscheiden, insbesondere auch im Vergleich mit gutartigen Melanozyten. Die differentiell regulierten Gene spiegeln die Aktivierung und Inaktivierung wichtiger Tumor-Signalwege wider. Hierbei fanden sich die für Melanome bereits beschriebenen MAP-Kinase-, Wnt- und Notch- Signalwege mit bisher noch nicht beteiligten Genen. Um daraus diagnostischen und therapeutischen Nutzen ziehen zu können, bedarf es weiterer zukünftiger Untersuchungen.

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# Curriculum Vitae

Andreas Leo Mauerer

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Geburtsdatum: 23.07.1981  
Nationalität: Deutsch

## Beruf

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seit 07/2008 Assistenzarzt, Universitätsklinikum Regensburg, Abteilung für Dermatologie

## Studium

---

06/2008 Staatsexamen Medizin  
02/2007- 01/2008 Praktisches Jahr  
10/2006- 01/2007 Forschungssemester, Uniklinikum Regensburg

## Schule

---

07/2001 Abitur, Carl-Friedrich-Gauß-Gymnasium Schwandorf

Regensburg, den 08.09.11