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Gene expression profiling in peripheral blood cells of patients with rheumatoid arthritis in response of anti-TNF-alpha treatments.

E. Meugnier[1,2,3,4*], F. Coury [1,2*], J. Tebib[1,2], C. Ferraro-Peyret[1,2], S. Rome[1,3], J. Bienvenu[1,2,5], H. Vidal[1,2,3,4], J. Sibilia[6], and N. Fabien[1,2,5]

[1]Lyon 1 University, F69002 Lyon, France; [2] Hospices Civils de Lyon, Department of Rheumatology and Department of Autoimmunity & Immunology, Centre Hospitalier Lyon-Sud, F-69495 Pierre-Benite, France; [3] INSERM U870, F-69600 Oullins, France; [4] INRA U1235, F-69600 Oullins, France [5] INSERM U851, F-69007, France and [6] Department of Rheumatology, CHU Hautepierre, 67098 STRASBOURG cedex.

*: *the first two authors contributed equally to the work.*

Running head:

Gene expression in rheumatoid arthritis with anti-TNF-alpha

Correspondence : Dr. Nicole Fabien, Department of Immunology, UF Autoimmunity, Centre Hospitalier Lyon-Sud, 69495 Pierre-Bénite Cedex, France. Tel. +33 478 866 681; Fax +33 478 863 344; nicole.fabien@chu-lyon.fr

The efficacy of anti-TNF-alpha therapies highlights the role of TNF-alpha in the pathogenesis of rheumatoid arthritis (RA). However the mechanism of action of these agents is poorly understood at the molecular level. The aim of this study was to characterize the effects of anti-TNF-alpha treatment on the global gene expression profile in peripheral blood mononuclear cells (PBMCs) of responder RA patients. Changes in gene expression was determined using oligonucleotide microarrays (25,341 genes) in PBMCs obtained before and after 12 weeks of treatment with either etanercept or adalimumab from responder RA patients. Two hundred fifty one genes displayed significant changes (FDR < 0.1%) in expression level (178 up-regulations with mean fold change = 1.5 and 73 down-regulations with mean fold change = -1.50) after 12 weeks of treatment. Importantly, the expression of several genes, including those coding for the calcium binding proteins S100A12 and A8, CD14 antigen, Selectin P or ribosomal protein L39, reported to be upregulated in RA patients, were found to be decreased after anti-TNF-alpha treatment. Globally, inflammation, immune response, apoptosis, protein synthesis and mitochondrial oxido-reduction were the most affected pathways in response to anti-TNF-alpha treatment. The obtained gene expression signature in PBMCs provides new information to better understand the mechanisms of action of anti-TNF-alpha treatment in RA patients.

Keywords: Anti-TNF-alpha therapies, Rheumatoid arthritis, Gene expression

The development of tumor necrosis factor alpha (TNF-alpha) inhibitors has led to major advances in the management of rheumatoid arthritis (RA). The efficacy of these therapies highlights the key role of TNF-alpha in the pathogenesis of RA. No notable difference in clinical efficacy was observed between the two classes of agents: anti-TNF-alpha antibody (infliximab, adalimumab) and soluble TNF-alpha receptor (etanercept)(31). Both block TNF-alpha actions, but the downstream molecular effects involved in the inhibition of the inflammatory process of RA are not clearly understood (38).

To exert its complex actions on immune system, inflammation or apoptosis, TNF-alpha is thought to control the expression of gene networks through the activation of intracellular signalling pathways and specific transcription factors (18). The identification of these transcriptional events using microarrays and large scale gene expression analysis can therefore help to better understand the mechanisms of action of therapeutic agents, as successfully performed in various chronic inflammatory diseases (23, 32). Studies of gene expression have been also recently reported in patients with RA and Sjögren syndrome, in peripheral blood mononuclear cells (PBMCs) leading to identification of genes with altered expression pattern using these cells (6, 7, 11, 12, 27, 35, 41). Therefore PBMCs can be chosen as a relevant model for a transcriptomic investigation of RA since they express more than 75% of the human genome and, being an important part of the immune system, they can play a central role in the pathogenesis of RA (16).

With the aim of gaining insight into the molecular events participating in the beneficial effects of anti-TNF-alpha therapies in good responder RA patients, we performed microarray gene expression profiling using oligonuclotide microarrays in PBMCs during treatment with adalimumab and etanercept. PBMCs were isolated before and after 12 weeks of treatment in RA patients showing a reduction in the Disease Activity Score 28 joints (DAS 28) as clinical indicator of a good response to the therapy (14).

Patients and methods

Patients. Eight patients (8 women, mean age of 51±9 years and mean disease duration of 4.8 years), fulfilling the American Rheumatism Association 1987 revised criteria for RA (4) and having an active RA disease (DAS28 > 5.1) were included. None has been treated with anti-TNF-alpha before the study. During the study, the patients maintained the same doses of methotrexate as used before. Four of them were treated (subcutaneous infusion of 25 mg at initiation and every 2 weeks thereafter) with adalimumab (Humira®,Abbott-France,France) and the 4 others (subcutaneous infusion of 25 mg/kg at initiation and twice a week thereafter) with etanercept (Enbrel®,Wyeth-Lederlé,France). Before and after 12 weeks of anti-TNF-alpha treatment, the number of swollen and tender joints, the patient's assessment of disease activity (0 to 100 mm visual analogue scale) and the erythrocyte sedimentation rate in the first hour, were recorded to calculate the DAS28. All patients were treatment responders because either their DAS28 was lower than 3.2 or their DAS28 decreased of more than 1.2 after 12 weeks of treatment (25). Clinical and demographic characteristics of the RA patients are reported in Table I. Informed consent was obtained from each of them. The study was approved by the Research and the Ethical Committees of the Hospices Civils de Lyon.

PBMC isolation. Ten mL samples of venous blood were collected before the first injection of anti-TNF-alpha and after 12 weeks of treatment. Blood was drawn just prior to injection. Samples were layered onto Ficoll-Paque Plus® (GEHealthcare Biosciences, Saclay, France) and PBMCs were separated by density gradient centrifugation at 2,500 rpm at room temperature for 20 min. The resulting buffy coat at the interface was added to 5 ml PBS, pH 7.4, (Invitrogen, Cergy-Pontoise, France) and cells were centrifuged at 1,000 rpm for 10 min at room temperature. The pellets were stored at -80°C to be used for RNA extraction.

Total RNA preparation and amplification. Total RNA was extracted from the PBMCs using phenol/chloroform/ethanol procedure (9) and quantified by spectrophotometry. The 260/280 nm absorbance ratio were higher than 1.8. RNA integrity (28S/18S ratio) was determined with the Agilent 2100 Bioanalyzer and RNA 6000 labChip Kit (Agilent Technologies, Massy, France). Only total RNA preparations with a 28S/18S ratio above 1.7 were used for gene expression analysis.

Probe labelling and microarray hybridization . Total RNA (500ng) was amplified using the Amino-Allyl-Message-Amp-II antisense RNA (aRNA) kit (Applied Biosystem, Courtaboeuf, France), according to manufacturer's instructions. After purification using Rneasy Mini Kit (Qiagen, Courtaboeuf, France), fluorescent probes synthesized by coupling of 5µg aminoallyl aRNA with cyanine 3 or 5 dyes (GEHealthcare Biosciences), were fragmented with the 25X RNA Fragmentation Reagents (Agilent Technologies, Massy, France) and hybridized in 2X Agilent Hybridization Buffer (Agilent Technologies) in an Agilent oven at 62°C for 16 h to human oligonucleotide microarrays produced by the French Genopole Network (RNG) (22). This platform is referred to GPL1456 in GEO. Microarrays were washed and scanned with a Genepix 4000B scanner (Molecular Devices Inc, Sunnyvale, CA, US) as previously reported (27).

Microarray Analysis. The human pangenomic oligonucleotide microarrays produced by RNG consisted of oligonucleotides of 50mers printed on glass slides representing 25,341 distinct genes listed in the Unigene database (24). Images were analyzed using Genepix Pro4.0 software (Molecular Devices Inc). The signal intensities of the microarray spots were loaded to R, lowess normalized within arrays and log transformed using the limma package from BioConductor (15). To compare results from the different subjects, data from each slide

were normalized in log-space to have a mean of zero using Cluster 3.0 software. Flagged spots and spots with fluorescence intensities below 3-fold above the background for both dyes were not taken into account. Only spots which passed these quality controls on all slides were selected for analysis. Then 12,825 spots were used for further analysis. Microarrays data are available in the GEO database under accession number GSE12897. The list of genes with significant changes in mRNA levels in the PBMCs of the 8 good responders during the treatment was determined using the one-class significance analysis of microarray (SAM) procedure (39).

Real-time quantitative PCR. First-strand cDNAs were synthesized from 500 ng of total RNA in the presence of 100 units of Superscript II (Invitrogen, Cergy-Pointoise, France) using a mixture of random hexamers and oligo (dT) primers (Promega, Charbonnières les bains, France). Real-time PCR assays were performed using a Light-Cycler (Roche-Diagnostics, Meylan, France) as previously reported (30). The list of the PCR primers is presented in Supplementary Table 1.

Measurement of S100 proteins. The serum levels of S100A8 were measured before and after 12 weeks of anti-TNF-alpha treatment using a sandwich immunoenzymatic technique (ELISA) according to the manufacturer's instructions (Buhlmann, Schönenbuch, Switzerland). The normal range was 0.5 to 5 µg/mL.

Statistical analysis

Wilcoxon's test was used to compare S100A8 levels before and after 12 weeks of treatment. Spearman's rank correlation coefficient was used to test correlation between the drop in DAS, swollen joints or S100A8 mRNA and serum S100A8 levels. A *P* value of less than 0.05 was considered statistically significant.

Results

The two anti-TNF-alpha therapies have similar effects on gene expression in PBMCs of RA patients. The patients were all responders, as assessed by the change in DAS28 at 12 weeks (Table 1). The time period of 12 weeks was chosen according to the consensus statement on biological agents for the treatment of RA (14). The decrease of DAS28 was similar for all the patients (2.3±0.7), independently from their treatment (Table 1).

No statistical difference could be observed between treatments by comparing the global changes in gene expression in the subgroup treated by adalimumab and in the subgroup treated by etanercept (supplementary Fig. 1).

Changes in PBMCs gene expression during anti-TNF-alpha therapies. As there is no difference between the gene profiles in the 8 RA patients after treatment either with adalimumab or etanercept, the microarray data were further analysed for the 8 patients together, to compare the expression of genes in PBMC before the initiation of the treatment and 12 weeks after. With a False Discovery Rate of 0.1% and taking into account only genes with fold change higher than 1.5 (both up- or down-regulated), the one-class SAM resulted in the selection of 251 genes that were significantly regulated in response to the treatments, in a similar manner in all the subjects. 178 and 73 genes were up-regulated and down-regulated respectively. By manual assignment using SOURCE, Gene Ontology, OMIM and PUBMED, we found functional annotation or information for more than 90% of the genes, allowing their classification into functional groups (supplementary Table 2). The remaining genes (n=20) were assigned as “unknown function”.

Among the classified genes, 31 were related to immune response and inflammation, 24 encoded ribosomal proteins, 24 corresponded to transcription factors, 19 were related to oxido-reduction and electron transfer, including 6 members of the NADH dehydrogenase

complex 1 of the mitochondria, and 15 genes encoded proteins that could be involved in the regulation of apoptosis (supplementary Table 2).

Table 2 shows the list of the 30 most up- and down-regulated genes during the anti-TNFalpha treatments. This selection of highly regulated genes amplified the over-representation of genes related to ribosomes (23%), immune response and inflammation (20%) and apoptosis (15%).

To verify whether our manual assignment was correct and corresponded to significant enrichments in functions or biological pathways, we then used the PANTHER classification system (www.pantherdb.org). Among the 251 regulated genes, 192 had annotation in this data-base. Table 3 shows the significantly enriched biological processes and molecular functions found in the list of regulated genes by comparison to the 25,341 genes present on the microarray. The same results were obtained when the NCBI whole human genome gene list (25,431 genes with unique IDs) was used as a reference instead of the genes represented on the microarray (data not shown). Although this analysis did not take into account all the regulated genes, the data presented in Table 3 confirmed our manual classification and demonstrated a significant impact of the anti-TNF alpha therapy on specific functional groups of genes, mainly related to ribosomes and protein synthesis, immune response, oxido-reduction and mitochondrial electron transfer.

Validation of microarray data using real-time PCR. A validation of the microarray data was performed using real-time quantitative PCR on a subset of 10 genes, focusing on the candidate biomarkers in RA (S110A8, S100A12, CD14 and selectin P) (6, 7, 11, 41) and on some genes known to play a role in immune response, inflammation or apoptosis and known to be up-regulated in RA (IL1-Beta, TNFreceptors) (21) .

The changes in mRNA expression detected using microarrays were confirmed for 9 out of the

198 10 tested genes (Table 4). Only the change in somatic cytochrome C was not verified. Of note,
199 regarding the TNF receptors, TNFR1 mRNA expression was decreased by anti-TNF-alpha
200 treatments, while expression of TNFR2 was not affected, as observed both on microarrays and
201 by quantitative PCR (Table 4).
202
203 *Measurement of S100 proteins.* S100A8 serum level was significantly reduced after the
204 treatment with a decrease in all but 1 patient ($p = 0.015$) (Table 5). No significant correlation
205 was found between the changes in S100A8 serum levels and the changes in DAS28, number
206 of swollen joints or S100A8 mRNA measured by RT-qPCR ($p = 0.659$; $p = 0.140$;$p = 0.231$
207 respectively).
208

209 ## Discussion

210
211 Effectiveness of anti-TNF-alpha therapy in RA has recently strongly modified the
212 therapeutic approach and treatment paradigms of this disease. However, despite extensive
213 investigation, their mechanisms of action remain incompletely understood (1, 38). In the
214 present study, we used a global transcriptomic approach to characterize the changes in gene
215 expression in PBMCs of RA patients who successfully responded to anti-TNF-alpha
216 therapies. It was important to study patients with rather similar responses to the therapy to
217 avoid confounding effects due to differential treatment effectiveness. Despite the fact that
218 some patients still have high DAS28 at the end of the study, we did not observe major
219 difference in their individual gene expression response in PBMCs. There was also no
220 significant difference in the response to the two anti-TNF-alpha treatments (adalimumab or
221 etanercept).
222 We demonstrated that 12 weeks of treatment modify the expression levels of 251 genes in
223 PBMCs, without significant difference between anti-TNF-alpha antibody (adalimumab) or

soluble TNF-alpha (etanercept) receptor. A majority of these genes were related to immune response and inflammation, as it might be expected from inhibition of TNF-alpha actions. However, several other functional groups also emerged, including genes encoding ribosomal proteins, apoptosis, oxido-reduction and electron transfer.

We demonstrated that the treatment with anti-TNF-alpha modified the expression of 10 of genes in opposite direction to observed alterations in previous studies comparing RA and control subjects, suggesting restoration or improvement of the gene expression profile in response to the therapy (6, 7, 11, 41). Among them, the genes coding for calgranulin C (S100A12) and calgranulin A (S100A8), were strongly repressed in our study. S100 proteins represent a new class of chemoattractants, which contribute to monocytic cells and leukocyte migration in chronic inflammatory responses (43). S100A8 has also been associated with RA pathogenesis as a possible amplifier of proinflammatory cytokine responses (28, 37). Interestingly S100 A8 and A12 have been shown to be elevated in serum from patients with established RA in comparison with healthy controls (9). In addition, S100A8 has been shown to be a marker of subclinical disease activity and relapse in patients with juvenile idiopathic arthritis (13, 34). We demonstrated in our study that there is a clear decrease of S100A8 serum level in 7 out of 8 patients following the 12 weeks anti-TNF alpha treatment. However, we did not find correlation between changes in S100A8 mRNA levels in PBMC and serum levels. This lack of correlation could be due to several factors, such as the regulation of S100A8 production in other tissue (44) or eventually the regulation of the protein stability in the plasma. Nevertheless, since circulating levels of S100A8 proteins could be reliable markers of inflammation it will be of interest to determine whether they can also be novel biomarkers of effectiveness of anti-TNF-alpha treatment between responder and non-responder RA patients.

TNF-alpha therapy also affected the expression of 4 other genes, selectin P (SELP), lysosomal-associated membrane protein 1 (LAMP1), ferritin heavy polypeptide 1 (FTH1) and

vestigial like 4 (VGLL4), found deregulated in PBMCs and in synovia from RA patients (6, 7, 11, 26, 41). An increase in the levels of SELP and FTH1 has been detected in SF from RA (19, 33). SELP and LAMP1 have also been shown to mediate leucocytes migration to sites of inflammation (20, 29). Anti-TNF-alpha treatment may thus diminish leucocyte migration, reducing the local synovial inflammation.

The strong impact of the anti-TNF-alpha agents by inhibiting the expression of these genes emphasize the importance of the leucocyte migration pathway in the pathogenesis of RA disease. Interestingly a recent study reported that increased expression of B cell genes as we found for CD79A, could reflect a block of migration of B cells to the tissue (40).

In addition to these genes, we found that TNF-alpha inhibitors affected the expression of a number of other genes related to the immune response and/or inflammation. The gene coding for Interleukin-1beta (IL-1b), was down-regulated and this effect might be important for the effectiveness of anti-TNF-alpha treatment as the serum concentration of IL-1b is significantly increased in RA (3). Expression of the gene coding CXCL1, the chemokine (C-X-C motif) ligand 1, described to be up-regulated in an autoimmune model of RA was here decreased, thus indicating that TNF-alpha blockade can reduce the expression of various pro-inflammatory factors (2).

Anti-TNF-alpha treatment seemed also to affect the ribosome biogenesis pathway with 24 genes coding for various ribosomal components differentially expressed after anti-TNF-alpha treatment in our study. The expression of RPL39, shown to be up-regulated in PBMCs of RA patients (11) was significantly reduced after treatment in our study. In a recent report, some other ribosomal components identified in our study (RPS16 and MRPL) were shown to be differentially expressed following anti-TNF-alpha treatment (27). Interestingly, the expression of the gene coding for bystin (BYSL) was also increased after anti-TNF-alpha treatment while it has been shown to be down-regulated in PBMCs from RA patients (6). It has been reported

that bystin promotes cell proliferation by facilitating ribosome biogenesis, specifically the production of the 40S subunit (28). All together, these data strongly suggest that TNF-alpha inhibitors affect regulatory pathways involved in the control of translation and protein synthesis. Further studies are required to define the role of this pathway in anti-TNF alpha response.

Another important pathway that is affected by anti-TNF-alpha treatment is the programmed cell death process that plays a critical role in the development of RA (5, 10, 42). A pro-apoptotic role of the treatment can be suggested by the up-regulation of the gene coding the protein AIM2 (Absent in melanoma 2) that was shown to induce tumor cell apoptosis (8). However, increased expression of other genes (BIRC7, FAIM2, TXNDC5) that code for proteins involved in anti-apoptosis processes and decreased expression of pro-apoptotic genes (TNFRSF10C, NGFRAP1,SNCA) were demonstrated in our study (17, 36). These contrasting observations on apoptosis-related genes illustrated the complexity of the regulation of this process in inflammatory disease.

Previous transcriptomic studies recently reported sets of genes with distinct regulation in PBMCs between responder and non-responder RA patients to anti-TNF-alpha treatment (22, 27, 35). Compared to our results, there was a consistent variation in up-regulation in transcript levels of 3 genes (PSMB9, COX7A2L and RPL35) (27) and downregulation in transcript levels of 2 genes (IL1B, SNCA) (22). Regarding the list of predictors of good response several interferon related genes were identified (35). No gene from this report was found to be regulated in our study except IFI27 (interferon, alpha-inducible protein 27). IFNs are known to be important immune system mediators that initiate or modulate autoimmunity and tissue damage through diverse actions on cells with immune function.

It would be interesting to know how the panel of genes identified in our study is regulated in non-responder RA patients in order to assess whether the changes in the expression levels

of some genes are not only a consequence of a general anti-TNF-alpha response but are also directly linked with the clinical benefits of the treatment. Here, only good responders were explored. Additional studies with different groups and with more subjects are now needed to go further and validate the hypotheses emerging from the present work. Further studies will be also required to better characterize patient subsets or to define more precisely biomarkers of outcome and response to anti-TNF therapies.

In conclusion, the present study provides, for the first time, a global transcriptomic analysis of the response to anti-TNF-alpha treatment in PBMCs of RA patients. Using oligonucleotide microarray, we identified 251 genes with significant regulation of expression after 12 weeks of TNF-alpha blockade with either etanercept or adalimumab. Functional analysis of the regulated genes revealed that immune response, inflammation, apoptosis, protein synthesis and mitochondrial electron transfer were the most affected pathways in PBMCs during therapy and confirmed a major impact of anti-TNF-alpha on inflammatory processes. Although this initial study will require confirmation and extension in a larger study, the obtained results confirm the potential feasibility and usefulness of using a genomic approach in PBMC of RA patients to gain insight into the molecular defects of this pathology and into the mechanisms of action of the anti-TNF-alpha therapies.

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Table 1 Demographic and clinical data of patients

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (year)	49	67	53	38	55	50	41	57
RA duration (years)	3	13	6	1	1	4	4	6
Anti-TNF alpha								
Treatment	Ada	Ada	Eta	Eta	Eta	Eta	Ada	Ada
Methotrexate (mg/week)	15	15	12.5	15	15	12.5	10	15
Steroids (mg/day)	-	-	-	-	10	-	-	-
ACPA (baseline)	pos	pos	pos	pos	pos	pos	pos	pos
RF (baseline)	pos	neg	pos	pos	pos	pos	pos	pos
DAS 28 (baseline)	5.12	6.48	7.02	5.97	6.85	5.13	5.21	6.48
DAS 28 (12 weeks)	2.84	2.78	5.40	3.71	4.32	3.47	2.81	4.49
∆DAS 28	- 2.26	- 3.70	- 1.62	- 2.26	- 2.53	- 1.66	- 2.40	- 1.99

Abbreviation :Ada, Adalimumab ; Eta, Etanercept, DAS = Disease Activity Score; The DAS28 considers 28 tender and swollen joint counts, general health (patient assessment of disease activity using a 100 mm visual analogue scale) and the erythrocyte sedimentation rate in the first hour; ACPA: anti-citrullinated peptide antibodies; RF: rheumatoid factor; pos: positive; neg:negative.

Table 2 List of the most regulated genes in PBMCs during anti-TNF-alpha therapy.

A- List of the 30 most up-regulated genes

INTERNAL_ID	*GENE NAME*	*SYMBOL*	*FOLD CHANGE*
12577	Interferon, alpha-inducible protein 27	IFI27	**3.58**
57066	Immunoglobulin J polypeptide	IGJ	**3.09**
27656	Proapoptotic caspase adaptor protein	PACAP	**2.36**
172818	Thioredoxin domain containing 5	TXNDC5	**2.33**
101332	CD79a molecule, immunoglobulin-associated alpha	CD79A	**2.15**
87376	Ribosomal protein L5	RPL5	**2.05**
85906	Immunoglobulin kappa constant	IGKC	**2.00**
77769	Immunoglobulin heavy constant gamma 1 (G1m marker)	IGHG1	**1.99**
95294	Lactate dehydrogenase B	LDHB	**1.94**
58441	Testis expressed sequence 261	TEX261	**1.93**
36999	Mitochondrial ribosomal protein S12	MRPS12	**1.88**
19319	Cytoplasmic FMR1 interacting protein 2	CYFIP2	**1.88**
17996	Killer cell lectin-like receptor subfamily K, member 1	KLRK1	**1.87**
40185	Polymerase (RNA) II (DNA directed) polypeptide L, 7.6kDa	POLR2L	**1.83**
36942	Ribosomal protein L36a	RPL36A	**1.83**
87389	Ribosomal protein L18	RPL18	**1.81**
57479	Selenoprotein M	SELM	**1.81**
171646	Eukaryotic translation elongation factor 1 beta 2	EEF1B2	**1.81**
93719	Ribosomal protein SA	RPSA	**1.80**
131476	Tumor necrosis factor, alpha-induced protein 8	TNFAIP8	**1.80**
5422	Mitochondrial ribosomal protein L33	MRPL33	**1.79**
7844	CD81 molecule	CD81	**1.79**
106068	Baculoviral IAP repeat-containing 7 (livin)	BIRC7	**1.79**
49123	Gamma-aminobutyric acid (GABA) A receptor, gamma 3	GABRG3	**1.78**
97600	Ras-related C3 botulinum toxin substrate 2	RAC2	**1.77**
38690	Proline dehydrogenase (oxidase) 2	PRODH2	**1.76**
6499	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa	NDUFB4	**1.76**
19948	Fas apoptotic inhibitory molecule 2	FAIM2	**1.75**
47818	Growth arrest and DNA-damage-inducible, gamma interacting protein 1	GADD45 GIP1	**1.75**
13180	CD164 molecule, sialomucin	CD164	**1.75**

Table 2 List of the most regulated genes in PBMCs during anti-TNF-alpha therapy.
B- List of the 30 most down-regulated genes

INTERNAL_ID	*GENE NAME*	*SYMBOL*	*FOLD CHANGE*
8707	Potassium inwardly-rectifying channel, subfamily J, member 4	KCNJ4	**-3.80**
40554	Prokineticin 2	PROK2	**-3.39**
73003	Ferritin, heavy polypeptide 1	FTH1	**-3.20**
14117	FBJ murine osteosarcoma viral oncogene homolog B	FOSB	**-3.08**
98155	Tumor protein, translationally-controlled 1	TPT1	**-3.01**
87362	Prostaglandin-endoperoxide synthase 2	PTGS2	**-2.81**
99252	S100 calcium binding protein A8 (calgranulin A)	S100A8	**-2.75**
7423	Beta-2-microglobulin	B2M	**-2.59**
12678	S100 calcium binding protein A12 (calgranulin C)	S100A12	**-2.43**
169581	Ribosomal protein L41	RPL41	**-2.41**
66498	Keratin associated protein 13-1	KRTAP13-1	**-2.33**
88992	Ribosomal protein L19	RPL19	**-2.26**
88435	Interleukin 1, beta	IL1B	**-2.22**
169722	Synuclein, alpha (non A4 component of amyloid precursor)	SNCA	**-2.13**
87423	Ribosomal protein S6	RPS6	**-2.03**
29497	Erythroid associated factor	ERAF	**-2.02**
90570	Ribosomal protein S29	RPS29	**-2.01**
78590	Lysozyme (renal amyloidosis)	LYZ	**-2.00**
7867	Chondroitin sulfate proteoglycan 2 (versican)	CSPG2	**-1.99**
101364	Dual specificity phosphatase 6	DUSP6	**-1.98**
88452	CD14 molecule	CD14	**-1.96**
90532	Ribosomal protein L37	RPL37	**-1.91**
146540	Taste receptor, type 2, member 38	TAS2R38	**-1.87**
87403	Ribosomal protein L32	RPL32	**-1.87**
90560	Ribosomal protein S16	RPS16	**-1.86**
12508	Potassium voltage-gated channel, Isk-related family, member 3	KCNE3	**-1.86**
87380	Ribosomal protein L6	RPL6	**-1.84**
10742	Hemoglobin, zeta	HBZ	**-1.84**
20921	Nerve growth factor receptor (TNFRSF16) associated protein 1	NGFRAP1	**-1.82**
10879	Nuclear receptor coactivator 4	NCOA4	**-1.80**

Table 3 Biological processes and molecular functions over-represented among the list of regulated genes in PBMCs during anti-TNF-alpha therapy.

Analyses were performed using PANTHER classification system (www.pantherdb.org). The reference gene list consists in the list of with 25,341 genes present on the microarray. Expected is the number of genes randomly expected for the PANTHER category based on the reference list, and Ratio corresponds to the number of regulated genes divided by the expected number. The P values were determined using the Bonferroni correction for multiple testing.

Biological Process

	Reference	Regulated genes	Expected	Ratio	*P value*
Protein biosynthesis	591	24	5.76	4.17	*8.73E-07*
Protein metabolism and modification	3040	58	29.65	1.96	*1.22E-05*
MHCI-mediated immunity	22	6	0.21	28.57	*2.11E-05*
Immunity and defense	1318	30	12.85	2.33	*5.14E-04*
Oxidative phosphorylation	78	7	0.76	9.21	*2.04E-03*
T-cell mediated immunity	194	10	1.89	5.29	*3.77E-03*
Electron transport	252	10	2.46	4.07	*6.77E-03*

Molecular Function

	Reference	Regulated genes	Expected	Ratio	*P value*
Nucleic acid binding	2850	56	27.79	2.02	*7.43E-06*
Ribosomal protein	465	19	4.53	4.19	*3.60E-05*
Major histocompatibility complex	46	5	0.45	11.11	*1.63E-02*
Oxidoreductase	603	15	5.88	2.55	*2.84E-02*
Defense/immunity protein	369	11	3.60	3.06	*3.31E-02*

Table 4 Comparison of microarray results with real-time RT-PCR

The fold changes in mRNA levels during the anti-TNF treatments were measured in PBMCs from 8 RA patients. RT-qPCR was performed as indicated in the Method section. Values were corrected by the mRNA level of hypoxanthine phosphoribosyl transferase (HPRT) used as a reference gene. P values were determined using a paired t-test. NS: non significantly regulated on the microaray.

		Microarray	**RT-qPCR**	
GENE NAME	*SYMBOL*	*Fold change*	*Fold Change*	*p value*
S100 calcium binding protein A8 (calgranulin A)	S100A8	**-2.75**	**-1.97 ± 0.23**	0.011
S100 calcium binding protein A12 (calgranulin C)	S100A12	**-2.43**	**-1.61 ± 0.29**	0.007
Selectin P ligand	SLEP	**-1.50**	**-2.22 ± 0.31**	0.005
CD14 antigen	CD14	**-1.96**	**-1.92 ± 0.14**	0.0001
Interleukin 1, beta	IL1B	**-2.22**	**-2.63 ± 0.79**	0.005
CCAAT/enhancer binding protein (C/EBP), delta	CEBPD	**-1.62**	**-1.89 ± 0.23**	0.005
TNF receptor 1	TNFR1	**-1.57**	**-1.38 ± 0.08**	0.0005
TNF receptor 2	TNFR2	**NS**	**1.4 ± 0.46**	0.369
Ribosomal protein L5	RPL5	**2.05**	**1.58 ± 0.21**	0.006
Cytochrome c, somatic	CYCS	**1.59**	**1.04 ± 0.21**	0.485

532 **Table 5:** Measurement of serum level of S100 A8 proteins during anti-TNF-alpha therapy

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Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Serum level of S100A8 protein µg/mL (baseline)	449	405	1122	849	2521	1571	1221	1287
Serum level of S100A8 protein µg/mL(12 weeks)	479	351	512	160	655	453	741	352
Δ Serum level of S100A8 protein µg/mL	+30	-54	-610	-689	-1866	-1118	-480	-935
Δ S100A8 mRNA level	-4.30	-4.21	-2.81	-3.55	-2.82	-1.27	-1.13	-1.88
Δ Swollen joints number	-14	-11	-15	-13	-15	-14	-15	-17
ΔDAS 28	- 2.26	-3.70	- 1.62	-2.26	- 2.53	- 1.66	- 2.40	- 1.99
Anti-TNFalpha treatment	Ada	Ada	Eta	Eta	Eta	Eta	Ada	Ada

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Supplementary Material

Table 1: List of the PCR primers

Table 2: List of the 251 genes significantly regulated after 12 weeks of anti-TNF alpha treatments in the PBMCs of RA patients.

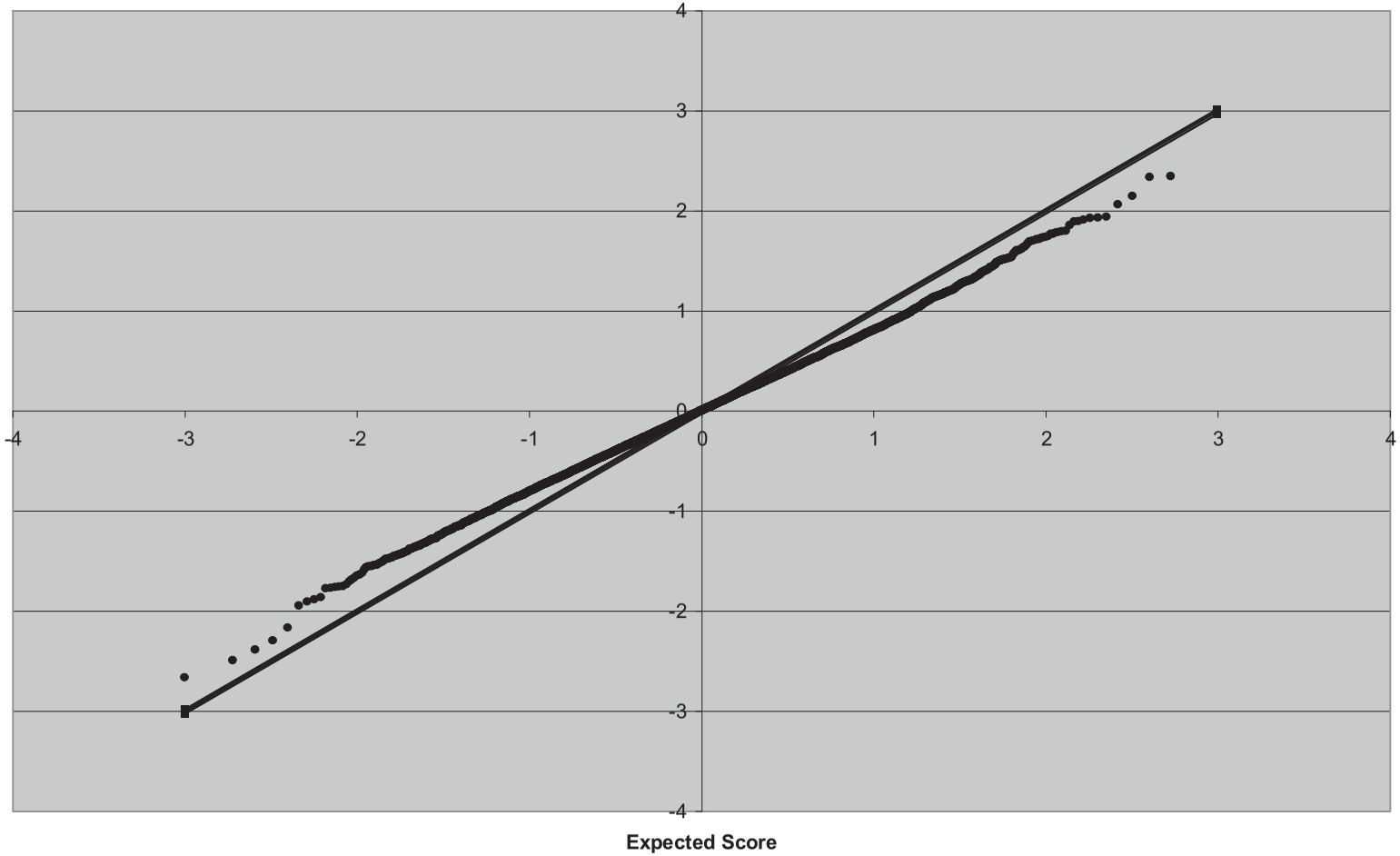
Legend to supplementary Figure

Supplementary Figure 1: SAM plot showing the lack of differential effects between the two treatments and obtained by comparing the changes in gene expression induced by adalimumab (n = 4) and by etanercept (n = 4) using the two-classes significance analysis of microarrays.

Significant: 0
Median number of false positives: 0
False Discovery Rate (%): 1

SAM Plotsheet

Tail strength (%): -31,4
se (%): 22,3



Supplementary Figure 1

Supplementary Table 1: List of the primers used for qPCR

SYMBOL	*FORWARD PRIMER*	*REVERSE PRIMER*
S100A8	TAGAGACCGAGTGTCCTCAG	GAATGAGGAACTCCTGGAAG
S100A12	TCCACCAATACTCAGTTCGG	GAAAGTCGACCTGTTCATC
SLEP	CAGGACCATTGACTATCCAG	TGTTCCTAGGTGGCTGTGAG
CD14	AGCTCAGAGGTTCGGAAGAC	CTGAGGTTCGGAGAAGTTGC
IL1B	GGCAATGAGGATGACTTGTT	TGTAGTGGTGGTCGGAGATT
CEBPD	AGGAGCGCAAAGAAGCTACAG	CTTAGCTGCATCAACAGGAG
TNFR1	CCTGCCAGGAGAAACAGAAC	CAATCTGGGGTAGGCACAAC
TNFR2	ACATGCCGGCTCAGAGAATA	CCTCACAGGAGTCACACACG
RPL5	TGAAGGGAGCTGTGGATGG	CATCTCCTCCATCATGTCTG
CYCS	GTAATCAGCCCAGTAGTAAC	GTGAGATTGCACCACTGTAC

<u>Supplementary Table 2 :</u> List of the 251 regulated genes in PBMC during anti-TNF-alpha therapies

Genes were selected with the SAM procedure. using a FDR of 0.1 %. The list was limited to genes with a fold change higher than 1.5

UNIGENE_ID	SYMBOL	GENE NAME	MEAN	SD	SE	Cytoband	LLID	INTERNAL_ID	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7	Patient-8
Apoptosis related proteins																
Hs.409563	PACAP	Proapoptotic caspase adaptor protein	2.36	0.82	0.29	5q23-5q31	51237	27656	3.61	1.62	4.02	2.76	1.74	2.16	1.97	1.03
Hs.256126	BIRC7	Baculoviral IAP repeat-containing 7 (livin)	1.79	0.27	0.09	20q13.3	79444	106068	2.01	2.37	1.33	1.93	1.91	1.54	1.6	1.63
Hs.567424	FAIM2	Fas apoptotic inhibitory molecule 2	1.75	0.27	0.09	12q13	23017	19948	2.04	1.87	0.92	1.94	1.68	1.57	1.95	2.01
Hs.515164	GADD45GIP1	Growth arrest and DNA-damage-inducible, gamma interacting protei	1.75	0.25	0.09	19p13.13	90480	47818	2.12	1.75	1.36	2.36	1.61	1.75	1.68	1.35
Hs.348264	GZMH	Granzyme H (cathepsin G-like 2, protein h-CCPX)	1.71	0.39	0.14	14q11.2	2999	47696	1.52	1.37	1.68	2.59	1.17	1.49	1.45	2.37
Hs.127799	BIRC3	Baculoviral IAP repeat-containing 3	1.69	0.47	0.17	11q22	330	87599	2.23	1.97	2.17	1.17	2.28	1.02	1.25	1.45
Hs.281898	AIM2	Absent in melanoma 2	1.67	0.17	0.06	1q22	9447	5342	1.9	1.21	2.03	1.6	1.56	1.69	1.66	1.75
Hs.522817	BCAP31	B-cell receptor-associated protein 31	1.62	0.17	0.06	Xq28	10134	9740	1.79	1.44	1.48	1.72	1.7	1.25	1.65	1.96
Hs.183684	EIF4G2	Eukaryotic translation initiation factor 4 gamma, 2	1.62	0.21	0.07	11p15	1982	40290	2.04	1.33	1.66	1.4	1.95	1.65	1.29	1.62
Hs.614326	BIRC5	Baculoviral IAP repeat-containing 5 (survivin)	1.60	0.17	0.06	17q25	332	89221	1.55	1.68	1.27	1.92	1.39	1.82	1.52	1.67
Hs.150107	BIRC6	Baculoviral IAP repeat-containing 6 (apollon)	1.58	0.17	0.06	2p22-p21	57448	29079	1.77	1.88	1.21	1.78	1.51	1.51	1.46	1.51
Hs.131226	BNIP3L	BCL2/adenovirus E1B 19kDa interacting protein 3-like	-1.50	0.15	0.05	8p21	665	7812	-1.7	-1.54	-1.38	-1.67	-1.63	-1.12	-1.41	-1.57
Hs.145269	TNFRSF10C	Tumor necrosis factor receptor superfamily, member 10c	-1.51	0.23	0.08	8p22-p21	8794	74789	-1.68	-1.6	-1.72	-1.35	-1.41	-1.15	-1.19	-1.94
Hs.448588	NGFRAP1	Nerve growth factor receptor (TNFRSF16) associated protein 1	-1.82	0.49	0.17	Xq22.2	27018	20921	-1.21	-1.97	-3.19	-2.16	-1.15	-1.84	-1.15	-1.89
Hs.271771	SNCA	Synuclein, alpha (non A4 component of amyloid precursor)	-2.13	0.34	0.12	4q21	6622	169722	-2.15	-2.23	-2.09	-2.8	-1.94	-1.93	-1.18	-2.71
Immune response and inflammation																
Hs.532634	IFI27	Interferon, alpha-inducible protein 27	3.58	2.07	0.73	14q32	3429	12577	10.65	1.33	4.46	2.51	1.21	3.93	2.91	1.68
Hs.643431	IGJ	Immunoglobulin J polypeptide	3.09	1.50	0.53	4q21	3512	57066	3.47	1.26	7.62	3.44	0.97	3.83	2.64	1.46
Hs.631567	CD79A	CD79a molecule, immunoglobulin-associated alpha	2.15	0.55	0.19	19q13.2	973	101332	1.27	2.51	3.04	2.08	3.09	1.84	1.84	1.52
Hs.449621	IGKC	Immunoglobulin kappa constant	2.00	0.27	0.10	2p12	3514	85906	1.98	1.61	2.27	2.63	1.99	2.21	1.98	1.36
Hs.510635	IGHG1	Immunoglobulin heavy constant gamma 1 (G1m marker)	1.99	0.37	0.13	14q32.33	3500	77769	2.44	1.9	2.81	1.98	2.12	2.05	1.36	1.24
Hs.387787	KLRK1	Killer cell lectin-like receptor subfamily K, member 1	1.87	0.66	0.23	12p13.2-p12.3	22914	17996	2.94	1.81	1.41	2.34	0.85	1.3	1.33	2.98
Hs.271955	TNFAIP8	Tumor necrosis factor, alpha-induced protein 8	1.80	0.38	0.13	5q23.1	25816	131476	2.51	2.01	1.22	2.17	1.3	2.01	1.83	1.36
Hs.403857	LY9	Lymphocyte antigen 9	1.69	0.34	0.12	1q21.3-q22	4063	53216	2.4	2.06	1.4	2	1.57	1.22	1.37	1.51
Hs.435579	BRDG1	BCR downstream signaling 1	1.68	0.23	0.08	4q13.2	26228	18066	1.74	1.45	1.89	1.87	1.89	1.43	1.23	1.93
Hs.370937	TAPBP	TAP binding protein (tapasin)	1.66	0.27	0.09	6p21.3	6892	98011	1.53	1.76	2.13	1.61	1.75	1.12	1.28	2.04
Hs.405667	CD8B	CD8b molecule	1.65	0.42	0.15	2p12	926	173203	2.44	1.83	1.06	2.37	1.22	1.43	1.56	1.31
Hs.416848	CTSW	Cathepsin W (lymphopain)	1.64	0.31	0.11	11q13.1	1521	94025	1.42	1.9	1.56	1.63	1.94	1.22	1.12	2.3
Hs.521903	LY6E	Lymphocyte antigen 6 complex, locus E	1.64	0.37	0.13	8q24.3	4061	93772	2.27	0.99	2.39	1.55	1.49	1.21	1.71	1.47
Hs.438040	MS4A1	Membrane-spanning 4-domains, subfamily A, member 1	1.60	0.34	0.12	11q12	931	169532	1.87	1.32	1.55	1.01	1.83	2.12	1.94	1.19
Hs.53155	CFP	Complement factor properdin	1.59	0.34	0.12	Xp11.3-p11.23	5199	97262	1.3	1.81	1.99	1.24	2.12	1.32	1.8	1.11
Hs.61265	FAM3D	Family with sequence similarity 3, member D	1.53	0.09	0.03	3p14.2	131177	56703	1.72	1.66	1.41	1.53	1.45	1.39	1.57	1.53
Hs.181244	HLA-A	Major histocompatibility complex, class I, A	1.52	0.30	0.11	6p21.3	3105	93502	2.55	1.16	1.11	1.42	1.37	1.68	1.42	1.45
Hs.409934	HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	1.52	0.16	0.05	6p21.3	3119	91974	1.27	1.37	1.48	1.36	1.48	1.92	1.68	1.58
Hs.465643	TNFAIP8L1	Tumor necrosis factor, alpha-induced protein 8-like 1	1.50	0.28	0.10	19p13.3	126282	61046	1.98	1.68	1.09	1.78	1.23	1.69	1.28	1.31
Hs.520048	HLA-DRA	Major histocompatibility complex, class II, DR alpha	-1.55	0.24	0.09	6p21.3	3122	34658	-1.78	-1.76	-1.41	-1.73	-1.14	-1.15	-1.8	-1.66
Hs.279594	TNFRSF1A	tumor necrosis factor receptor superfamily, member 1A	-1.57	0.30	0.11	12p13.2	7132	90622	-1.21	-1.33	-2.21	-1.76	-1.4	-1.59	-1.12	-1.93
Hs.169998	BST1	Bone marrow stromal cell antigen 1	-1.61	0.26	0.09	4p15	683	7816	-1.73	-2.15	-1.58	-1.41	-1.97	-1.43	-1.18	-1.4
Hs.789	CXCL1	Chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating act	-1.66	0.44	0.16	4q21	2919	94236	-2.57	-1.39	-2.23	-1.1	-1.95	-1.3	-1.57	-1.16
Hs.463483	MMD	Monocyte to macrophage differentiation-associated	-1.66	0.32	0.11	17q	23531	19979	-1.95	-1.76	-2.55	-1.63	-0.99	-1.48	-1.29	-1.64
Hs.77961	HLA-B	Major histocompatibility complex, class I, B	-1.79	0.34	0.12	6p21.3	3106	91960	-1.38	-2.06	-2.27	-1.22	-1.67	-2.33	-1.88	-1.51
Hs.163867	CD14	CD14 molecule	-1.96	0.47	0.17	5q22-q32|5q31.1	929	88452	-1.68	-3.04	-2.41	-1.7	-2.1	-1.08	-1.5	-2.19
Hs.126256	IL1B	Interleukin 1, beta	-2.22	1.01	0.36	2q14	3553	88435	-2.76	-2.4	-1.22	-1.35	-4.88	-1.18	-2.9	-1.08
Hs.19413	S100A12	S100 calcium binding protein A12 (calgranulin C)	-2.43	0.72	0.25	1q21	6283	12680	-3.7	-3.48	-1.82	-2.2	-2.52	-1.6	-1.22	-2.9
Hs.333388	B2M	Beta-2-microglobulin	-2.59	1.28	0.45	15q21-q22.2	567	82509	-0.99	-5.13	-4.41	-1.79	-3.37	-1.47	-1.98	-1.62
Hs.416073	S100A8	S100 calcium binding protein A8 (calgranulin A)	-2.75	0.99	0.35	1q21	6279	99252	-4.3	-4.21	-2.81	-3.55	-2.82	-1.27	-1.13	-1.89
Hs.196384	PTGS2	Prostaglandin-endoperoxide synthase 2	-2.81	1.20	0.43	1q25.2-q25.3	5743	87362	-3.66	-2.11	-1.49	-3.13	-4.44	-2.14	-4.84	-0.71
Transcription and Translation																
Transcription factors, co-factors and polymerases																
Hs.441072	POLR2L	Polymerase (RNA) II (DNA directed) polypeptide L, 7.6kDa	1.83	0.18	0.06	11p15	5441	40185	1.77	2.33	1.83	1.76	1.95	1.51	1.91	1.55
Hs.555947	LEF1	Lymphoid enhancer-binding factor 1	1.73	0.42	0.15	4q23-q25	51176	30758	2.79	2.24	1.04	1.8	1.24	1.7	1.28	1.79
Hs.7158	RNF167	Ring finger protein 167	1.73	0.40	0.14	17p13.2	26001	23553	1.46	2.43	2.11	2.27	1.45	1.3	1.32	1.5
Hs.473152	TFAP2C	Transcription factor AP-2 gamma	1.69	0.20	0.07	20q13.2	7022	96513	1.79	1.52	1.65	2.15	1.66	1.18	1.62	1.95
Hs.174050	EDF1	Endothelial differentiation-related factor 1	1.65	0.18	0.07	9q34.3	8721	170923	1.79	1.66	1.43	2.25	1.33	1.61	1.64	1.53
Hs.435755	PDRG1	P53 and DNA damage regulated 1	1.63	0.17	0.06	20q11.21	81572	44350	1.81	1.55	1.61	1.91	1.86	1.5	1.45	1.37
Hs.524828	ZNF664	Zinc finger protein 664	1.61	0.24	0.09	12q24.31	144348	61149	1.91	1.93	0.91	1.74	1.45	1.74	1.49	1.68
Hs.443465	TCERG1	Transcription elongation regulator 1	1.58	0.22	0.08	5q31	10915	15693	1.91	1.22	1.52	1.5	1.64	1.36	1.4	2.09
Hs.184298	CDK7	Cyclin-dependent kinase 7 (MO15 homolog, Xenopus laevis)	1.58	0.19	0.07	5q12.1	1022	91544	1.7	1.33	1.69	1.89	1.26	1.42	1.53	1.77
Hs.194157	ZC3HC1	Zinc finger, C3HC-type containing 1	1.57	0.19	0.07	7q32.2	51530	29299	1.96	1.44	1.62	1.43	1.87	1.42	1.39	1.4
Hs.632472	RFX5	Regulatory factor X, 5 (influences HLA class II expression)	1.56	0.19	0.07	1q21	5993	88255	1.77	1.36	1.65	1.71	1.22	1.71	1.33	1.73
Hs.191482	CUTL1	Cut-like 1, CCAAT displacement protein (Drosophila)	1.55	0.15	0.05	7q22.1	1523	187207	1.2	1.53	1.83	1.75	1.62	1.39	1.48	1.58
Hs.3530	FUSIP1	FUS interacting protein (serine/arginine-rich) 1	1.54	0.30	0.11	1p36.11	10772	165260	2.06	1.25	1.23	1.89	1.11	1.68	1.36	1.77
Hs.7395	TFB2M	Transcription factor B2, mitochondrial	1.54	0.25	0.09	1q44	64216	39180	1.78	1.38	1.4	1.82	1.2	2.03	1.39	1.35
Hs.436578	POLR2F	Polymerase (RNA) II (DNA directed) polypeptide F	1.54	0.19	0.07	22q13.1	5435	37398	1.57	1.58	1.27	2.15	1.13	1.58	1.59	1.44
Hs.632575	YEATS2	YEATS domain containing 2	1.54	0.22	0.08	3q27.1	55689	28677	1.7	1.26	1.63	1.72	1.56	1.2	1.26	1.98
Hs.436350	ZNF302	Zinc finger protein 302	1.52	0.24	0.09	19q13.11	55900	169409	2.41	1.4	1.38	1.35	1.61	1.5	1.2	1.33
Hs.333348	ZNF441	Zinc finger protein 441	1.50	0.22	0.08	19p13.2	126068	62578	1.08	1.82	1.73	1.52	1.82	1.18	1.43	1.45
Hs.190477	ZC3H6	Zinc finger CCCH-type containing 6	-1.51	0.20	0.07	2q13	376940	161066	-1.93	-1.55	-1.56	-1.38	-1.35	-1.28	-1.25	-1.82
Hs.440829	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	-1.62	0.27	0.09	8p11.2-p11.1	1052	10543	-2.46	-1.6	-1.65	-1.81	-1.65	-1.52	-0.98	-1.33
Hs.629812	TPRX1	Tetra-peptide repeat homeobox 1	-1.66	0.26	0.09	19q13.32	284355	76697	-2.01	-1.65	-1.77	-1.46	-1.48	-1.23	-1.44	-2.26
Hs.468908	MXD1	MAX dimerization protein 1	-1.79	0.55	0.20	2p13-p12	4084	85356	-3.48	-2.32	-1.17	-1.33	-1.77	-1.49	-1.62	-1.15
Hs.522932	NCOA4	Nuclear receptor coactivator 4	-1.80	0.25	0.09	10q11.2	8031	10879	-1.83	-2.21	-2.1	-1.98	-1.92	-1.45	-1.17	-1.78
Hs.590958	FOSB	FBJ murine osteosarcoma viral oncogene homolog B	-3.08	1.21	0.43	19q13.32	2354	14117	-5.23	-1.33	-2.74	-3.03	-4.34	-4.15	-3.44	-0.42
DNA or chromatine associated proteins																
Hs.612774	DCLRE1C	DNA cross-link repair 1C (PSO2 homolog, S. cerevisiae)	1.71	0.20	0.07		64421	37731	1.69	1.52	2.08	1.82	1.72	1.33	1.53	2.03
Hs.128686	NUCB2	Nucleobindin 2	1.71	0.36	0.13	11p15.1-p14	4925	8754	2.46	1.74	1.17	1.97	1.09	1.89	1.42	1.96
Hs.156519	MSH2	MutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)	1.57	0.27	0.10	2p22-p21	4436	89552	2.07	1.59	1.42	1.9	0.94	1.47	1.37	1.82
Hs.410228	ORC3L	Origin recognition complex, subunit 3-like (yeast)	1.56	0.31	0.11	6q14.3-q16.1	23595	18385	1.99	1.28	1.44	2.31	1.03	1.48	1.3	1.62
Hs.288798	MUS81	MUS81 endonuclease homolog (S. cerevisiae)	1.50	0.18	0.06	11q13	80198	42419	1.55	1.31	1.54	1.66	1.62	1.2	1.26	1.84
Hs.591778	HIST1H3H	Histone 1, H3h	-1.59	0.29	0.10	6p22-p21.3	8357	99982	-1.71	-1.73	-1.88	-2.09	-0.95	-1.42	-1.23	-1.68
Hs.420272	H2AFY	H2A histone family, member Y	-1.62	0.35	0.12	5q31.3-q32	9555	167895	-1.74	-2	-1.43	-2.28	-1.29	-1.22	-1.13	-1.83
Hs.546259	H3F3A	H3 histone, family 3A	-1.80	0.46	0.16	1q41	3020	91945	-1.6	-2.64	-2.72	-1.88	-1.7	-1.27	-1.08	-1.48
RNA processing																
Hs.632554	SF3B1	Splicing factor 3b, subunit 1, 155kDa	1.75	0.36	0.13	2q33.1	23451	21631	1.86	1.37	1.57	2.22	1.42	1.62	1.34	2.6
Hs.441124	APOBEC3C	Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3F	1.73	0.29	0.10	22q13.1	200316	19483	1.65	1.89	1.99	2.1	1.38	2.09	1.46	1.26
Hs.91579	IMP4	IMP4, U3 small nucleolar ribonucleoprotein, homolog (yeast)	1.68	0.16	0.06	2q21.1	92856	122939	1.84	1.9	1.54	1.9	1.48	1.73	1.56	1.49
Hs.369761	DAZAP2	DAZ associated protein 2	1.64	0.24	0.08	12q12	9802	22881	1.66	1.26	1.76	2.01	1.13	1.58	1.85	1.85
Hs.464734	SNRPD1	Small nuclear ribonucleoprotein D1 polypeptide 16kDa	1.57	0.12	0.04	18q11.2	6632	14431	1.57	1.57	1.45	1.98	1.36	1.62	1.42	1.57
Hs.25892	SNORA9	Small nucleolar RNA, H/ACA box 9	1.56	0.21	0.07	7p13	677798	162843	1.97	1.29	1.53	1.36	1.44	1.37	1.56	1.98
Hs.105465	SNRPF	Small nuclear ribonucleoprotein polypeptide F	1.53	0.18	0.06	12q22	6636	97898	1.8	1.56	1.42	1.59	1.42	1.27	1.3	1.9
Hs.546304	SNRPN	Small nuclear ribonucleoprotein polypeptide N	1.53	0.21	0.07	15q11.2	6638	104118	1.34	1.58	1.99	1.38	1.71	1.22	1.68	1.37
Hs.496279	ZCRB1	Zinc finger CCHC-type and RNA binding motif 1	1.51	0.11	0.04	12q12	85437	49022	1.7	1.38	1.38	1.5	1.35	1.49	1.59	1.68
Hs.373959	VGLL4	Vestigial like 4 (Drosophila)	-1.52	0.23	0.08	3p25.2	9686	72242	-2	-1.53	-1.62	-1.44	-1.28	-1.26	-1.18	-1.82
Hs.489287	CPSF4	Cleavage and polyadenylation specific factor 4, 30kDa	-1.57	0.30	0.11	7q22.1	10898	17228	-2.21	-1.33	-1.21	-1.76	-1.4	-1.93	-1.12	-1.59
Hs.533712	RBM4	RNA binding motif protein 4	-1.67	0.22	0.08	11q13	5936	96063	-2	-1.5	-1.5	-2.01	-1.47	-1.89	-1.63	-1.36
Translation regulation																
Hs.421608	EEF1B2	Eukaryotic translation elongation factor 1 beta 2	1.81	0.33	0.12	2q33-q34	1933	171646	1.89	2.6	1.12	2.24	1.63	1.73	1.73	1.54
Hs.411641	EIF4EBP1	Eukaryotic translation initiation factor 4E binding protein 1	1.70	0.25	0.09	8p12	1978	100235	1.77	2.04	1.11	2.22	1.55	1.79	1.61	1.55
Hs.516023	EIF3S5	Eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa	1.70	0.21	0.07	11p15.4	8665	7082	1.75	2.01	1.51	1.94	1.45	1.81	1.85	1.31
Hs.503787	DARS	Aspartyl-tRNA synthetase	1.53	0.24	0.09	2q21.3	1615	90981	2.03	1.54	1.49	1.25	1.12	1.26	1.99	1.52
Ribosomal proteins																
Hs.532359	RPL5	Ribosomal protein L5	2.05	0.37	0.13	1p22.1	6125	87376	1.66	2.68	1.65	2.85	1.76	1.7	2.11	1.96
Hs.411125	MRPS12	Mitochondrial ribosomal protein S12	1.88	0.24	0.09	19q13.1-q13.2	6183	36999	1.86	1.9	1.42	2.62	1.64	1.67	1.85	2.07
Hs.432485	RPL36A	Ribosomal protein L36a	1.83	0.21	0.07	Xq22.1	6173	36942	1.94	2.4	1.45	1.77	1.78	1.63	1.67	1.95
Hs.515517	RPL18	Ribosomal protein L18	1.81	0.28	0.10	19q13	6141	87389	2.26	1.78	1.29	2.49	1.78	1.66	1.72	1.53
Hs.560655	RPSA	Ribosomal protein SA	1.80	0.34	0.12	3p22.2	3921	93719	2.37	1.9	1.08	2.39	1.41	1.8	1.91	1.57
Hs.515879	MRPL33	Mitochondrial ribosomal protein L33	1.79	0.25	0.09	2p21	9553	5422	1.75	2.12	1.26	2.22	1.5	1.8	1.68	2.02
Hs.632726	RPS26	Ribosomal protein S26	1.74	0.38	0.14	12q13	6231	87440	1.91	2.61	1.53	2.23	1.68	1.11	1.26	1.56
Hs.182825	RPL35	Ribosomal protein L35	1.72	0.36	0.13	9q34.1	11224	16251	1.89	2.25	1.45	2.45	1.53	1.03	1.61	1.56
Hs.311190	MRPL14	Mitochondrial ribosomal protein L14	1.64	0.24	0.08	6p21.3	64928	43343	2.06	1.96	1.26	1.71	1.57	1.25	1.51	1.77
Hs.284286	MRPS24	Mitochondrial ribosomal protein S24	1.61	0.22	0.08	7p14	64951	46451	1.79	1.91	1.38	1.36	1.83	1.25	1.61	1.79
Hs.381123	RPL21	Ribosomal protein L21	1.61	0.23	0.08	13q12.2	6144	87393	1.63	2.28	1.25	1.72	1.72	1.53	1.25	1.47
Hs.182698	MRPL20	Mitochondrial ribosomal protein L20	1.51	0.13	0.05	1p36.3-p36.2	55052	31910	1.67	1.58	1.26	1.76	1.39	1.41	1.56	1.48
Hs.558387	RPL39	Ribosomal protein L39	-1.53	0.24	0.09	Xq22-q24	6170	90533	-1.34	-1.34	-1.97	-1.71	-1.16	-1.86	-1.36	-1.46
Hs.523463	RPL27A	Ribosomal protein L27a	-1.56	0.16	0.06	11p15	6157	145631	-1.25	-1.29	-2.1	-1.53	-1.52	-1.6	-1.55	-1.61
Hs.322473	RPS28	Ribosomal protein S28	-1.63	0.35	0.12	19p13.2	6234	90568	-1.06	-1.34	-2.02	-2.07	-1.41	-2.17	-1.31	-1.65
Hs.388664	RPL11	Ribosomal protein L11	-1.70	0.26	0.09	1p36.1-p35	6135	88982	-1.31	-1.56	-2	-1.99	-1.84	-1.53	-1.39	-2.02
Hs.546283	RPL6	Ribosomal protein L6	-1.84	0.27	0.10	12q24.1	6128	87380	-1.51	-1.89	-2.4	-1.85	-2.22	-1.41	-1.52	-1.92
Hs.397609	RPS16	Ribosomal protein S16	-1.86	0.36	0.13	19q13.1	6217	90560	-1.65	-1.17	-2.41	-2.12	-1.83	-1.8	-1.44	-2.48
Hs.265174	RPL32	Ribosomal protein L32	-1.87	0.31	0.11	3p25-p24	6161	87403	-1.43	-1.48	-2.47	-1.8	-1.74	-2.03	-1.66	-2.33
Hs.80545	RPL37	Ribosomal protein L37	-1.91	0.45	0.16	5p13	6167	90532	-1.49	-1.59	-2.48	-2.44	-2.09	-1.23	-1.54	-2.42
Hs.156367	RPS29	Ribosomal protein S29	-2.01	0.33	0.12	14q	6235	90570	-1.63	-1.57	-2.89	-1.77	-2.12	-1.88	-1.87	-2.34
Hs.408073	RPS6	Ribosomal protein S6	-2.03	0.59	0.21	9p21	6194	87423	-1.66	-1.28	-3.08	-2.44	-2.17	-1.46	-1.34	-2.78
Hs.381061	RPL19	Ribosomal protein L19	-2.26	0.36	0.13	17q11.2-q12	6143	88992	-2.04	-1.62	-2.66	-1.83	-2.44	-2.41	-2.13	-2.98
Hs.632703	RPL41	Ribosomal protein L41	-2.41	0.41	0.14	12q13	6171	169581	-1.55	-1.63	-3.24	-2.65	-2.41	-2.44	-2.53	-2.79
Protein folding and post-translational modifications																
Hs.172791	UXT	Ubiquitously-expressed transcript	1.74	0.31	0.11	Xp11.23-p11.22	8409	6014	1.82	2.55	1.44	2.08	1.64	1.66	1.41	1.29
Hs.191887	SEC61B	Sec61 beta subunit	1.66	0.20	0.07	9q22.32-q31.3	10952	15825	1.98	1.51	1.46	2	1.41	1.71	1.46	1.77
Hs.207459	ST6GAL1	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	1.61	0.27	0.10	3q27-q28	6480	96248	2.02	2.01	1.39	1.87	1.54	1.42	1.23	1.35
Hs.29169	HSPBAP1	HSPB (heat shock 27kDa) associated protein 1	1.56	0.16	0.06	3q21.1	79663	74945	1.69	1.7	1.14	1.83	1.41	1.5	1.63	1.55
Hs.192374	HSP90B1	Heat shock protein 90kDa beta (Grp94), member 1	1.55	0.22	0.08	12q24.2-q24.3	7184	96628	1.97	1.42	1.49	1.81	1.04	1.64	1.4	1.67
Hs.632539	HSPD1	Heat shock 60kDa protein 1 (chaperonin)	1.52	0.16	0.06	2q33.1	3329	95116	2	1.59	1.55	1.38	1.31	1.41	1.6	1.33
Hs.523560	HSP90AA1	Heat shock protein 90kDa alpha (cytosolic), class A member 1	1.51	0.30	0.11	14q32.33	3320	9215	2.01	1.34	1.15	1.19	1.18	1.97	1.66	1.6
Hs.53066	HSPBP1	Hsp70-interacting protein	1.50	0.15	0.05	19q13.42	23640	21452	1.79	1.51	1.21	1.57	1.68	1.27	1.54	1.43
Hs.274309	ERAF	Erythroid associated factor	-2.02	0.75	0.27	16p11.2	51327	29497	-1.67	-1.49	-1.02	-3.72	-2.25	-1.69	-1.23	-3.1
Oxido-reduction and electron transfer																
Hs.150837	TXNDC5	Thioredoxin domain containing 5	2.33	0.63	0.22	6p24.3	81567	172818	3.97	1.55	2.98	2.56	1.68	1.9	2.35	1.69
Hs.515366	PRODH2	Proline dehydrogenase (oxidase) 2	1.76	0.30	0.11	19q13.1	58510	38690	1.71	1.98	1.07	2.56	1.42	1.87	1.84	1.65
Hs.594079	NDUFB4	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa	1.76	0.27	0.10	3q13.33	4710	6499	2.16	1.7	1.43	2.4	1.38	1.67	1.5	1.81
Hs.401903	COX5A	Cytochrome c oxidase subunit Va	1.74	0.18	0.06	15q25	9377	7700	1.67	1.86	1.62	2.34	1.6	1.57	1.66	1.63
Hs.406510	ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta	1.74	0.23	0.08	12q13.13	506	137097	2.11	1.38	1.84	2.03	1.42	1.75	1.86	1.51
Hs.632385	NDUFS5	NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15kDa	1.72	0.20	0.07	1p34.2-p33	4725	6514	2.06	1.86	1.5	2.01	1.41	1.64	1.72	1.52
Hs.83383	PRDX4	Peroxiredoxin 4	1.59	0.26	0.09	Xp22.11	10549	15278	2.35	1.28	1.51	1.88	1.2	1.58	1.55	1.37
Hs.437060	CYCS	Cytochrome c, somatic	1.59	0.37	0.13	7p15.2	54205	110162	2.15	1.2	1.07	2.06	1.07	1.8	1.53	1.82
Hs.15977	NDUFB9	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22kDa	1.58	0.23	0.08	8q13.3	4715	11877	1.37	1.74	1.29	2.36	1.37	1.56	1.58	1.38
Hs.518424	NDUFB5	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa	1.57	0.24	0.08	3q26.33	4711	95515	1.52	1.54	1.68	2.09	0.93	1.82	1.67	1.35
Hs.84549	NDUFC1	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 1, 6kD	1.55	0.16	0.06	4q28.2-q31.1	4717	93968	1.72	1.4	1.26	1.86	1.61	1.67	1.45	1.44

Hs.199625	HAX1	HCLS1 associated protein X-1	1.54	0.14	0.05	1q21.3	10456	14899	1.89	1.63	1.56	1.48	1.44	1.64	1.48	1.21
Hs.339639	COX7A2L	Cytochrome c oxidase subunit VIIa polypeptide 2 like	1.53	0.17	0.06	2p21	9167	8324	1.54	1.45	1.38	1.88	1.14	1.57	1.79	1.46
Hs.513803	CYBA	Cytochrome b-245, alpha polypeptide	1.52	0.23	0.08	16q24	1535	83479	1.66	1.08	1.3	2.12	1.34	1.55	1.66	1.44
Hs.501578	MTG1	Mitochondrial GTPase 1 homolog (S. cerevisiae)	1.50	0.17	0.06	10q26.3	92170	132575	1.91	1.6	1.65	1.33	1.31	1.27	1.43	1.51
Hs.418668	ATP5D	ATP synthase, H+ transporting, mitochondrial F1 complex, delta sub	1.50	0.27	0.09	19p13.3	513	91392	1.3	2.12	1.3	1.57	1.87	1.29	1.37	1.18
Hs.464572	NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa	1.50	0.20	0.07	18p11.31-p11.2	4729	36965	1.93	1.46	1.46	1.84	1.21	1.53	1.38	1.19
Hs.516830	SRXN1	Sulfiredoxin 1 homolog (S. cerevisiae)	-1.52	0.25	0.09	20p13	140809	56000	-2.15	-1.61	-1.53	-1.18	-1.82	-1.28	-1.38	-1.24
Hs.464071	PGD	Phosphogluconate dehydrogenase	-1.64	0.31	0.11	1p36.3-p36.13	5226	98808	-1.91	-2.36	-1.43	-1.35	-1.73	-1.2	-1.33	-1.8
Hs.368254	HGD	Homogentisate 1,2-dioxygenase (homogentisate oxidase)	-1.71	0.44	0.15	3q21-q23	3081	89464	-2.72	-1.87	-2.28	-1.55	-1.18	-1.39	-1.32	-1.36
Other enzymes																
Hs.446149	LDHB	Lactate dehydrogenase B	1.94	0.62	0.22	12p12.2-p12.1	3945	95294	3.76	2.33	0.99	2.23	1.09	1.94	1.55	1.65
Hs.356769	MAN2B1	Mannosidase, alpha, class 2B, member 1	1.60	0.32	0.11	19cen-q13.1	4125	88343	0.91	1.28	1.89	1.9	1.91	1.57	1.37	1.98
Hs.631920	CAPN7	Calpain 7	1.59	0.37	0.13	3p24	23473	19203	1.49	1.33	1.26	2.37	1.09	1.93	1.26	1.95
Hs.104123	PRPS2	Phosphoribosyl pyrophosphate synthetase 2	1.56	0.30	0.11	Xp22.3-p22.2	5634	97442	1.92	1.67	1.3	2.31	1.01	1.5	1.25	1.54
Hs.368960	NGLY1	N-glycanase 1	1.55	0.24	0.08	3p24.2	55768	32344	1.61	1.38	1.43	1.74	1.31	1.32	1.36	2.24
Hs.168799	METTL3	Methyltransferase like 3	1.55	0.17	0.06	14q11.1	56339	36292	2.14	1.2	1.41	1.55	1.54	1.56	1.36	1.59
Hs.123461	AS3MT	Arsenic (+3 oxidation state) methyltransferase	1.52	0.18	0.06	10q24.32	57412	33616	1.59	1.87	1.12	1.75	1.47	1.57	1.31	1.44
Hs.480364	METAP1	Methionyl aminopeptidase 1	1.51	0.21	0.07	4q23	23173	23253	1.82	1.58	1.4	1.74	1.23	1.26	1.31	1.7
Hs.50727	HSD17B1	Hydroxysteroid (17-beta) dehydrogenase 1	1.51	0.11	0.04	17q11-q21	3292	89810	1.45	1.69	1.49	1.35	1.28	1.56	1.66	1.57
Hs.250616	ACSBG1	Acyl-CoA synthetase bubblegum family member 1	-1.58	0.22	0.08	15q23-q24	23205	26470	-1.87	-1.58	-1.97	-1.79	-1.25	-1.46	-1.19	-1.54
Hs.524579	LYZ	Lysozyme (renal amyloidosis)	-2.00	0.65	0.23	12q15	4069	78590	-2.86	-3.03	-1.72	-1.46	-2.73	-1.13	-1.49	-1.6
Ubiquitin or proteasome pathways																
Hs.132682	PSMB9	Proteasome (prosome, macropain) subunit, beta type, 9	1.72	0.28	0.10	6p21.3	5698	54197	2.73	1.45	1.33	1.79	1.33	1.76	1.65	1.74
Hs.513244	FBXL16	F-box and leucine-rich repeat protein 16	1.72	0.28	0.10	16p13.3	146330	62011	2.03	1.77	1.46	2.32	1.68	1.1	1.53	1.9
Hs.75348	PSME1	Proteasome (prosome, macropain) activator subunit 1 (PA28 alpha)	1.72	0.40	0.14	14q11.2	5720	110886	1.8	1.35	1.39	2.4	0.94	2.29	1.58	1.98
Hs.525084	HECTD3	HECT domain containing 3	1.63	0.37	0.13	1p34.1	79654	41669	1.51	1.87	2.07	1.32	2.43	1.05	1.25	1.57
Hs.250758	PSMC3	Proteasome (prosome, macropain) 26S subunit, ATPase, 3	1.63	0.40	0.14	11p12-p13	5702	140247	1.12	2.42	1.87	1.16	2.07	1.29	1.76	1.34
Hs.420529	UBE2V1	Ubiquitin-conjugating enzyme E2 variant 1	1.61	0.20	0.07	20q13.2	7335	107723	1.2	2.04	1.6	1.78	1.73	1.33	1.5	1.71
Hs.31387	ARIH2	Ariadne homolog 2 (Drosophila)	1.58	0.25	0.09	3p21.2-p21.3	10425	50885	1.93	1.73	1.55	1.38	1.78	1.01	1.39	1.89
Hs.531064	NEDD8	Neural precursor cell expressed, developmentally down-regulated 8	1.51	0.10	0.04	14q12	4738	16485	1.6	1.52	1.34	1.62	1.36	1.68	1.53	1.41
Hs.69554	RNF126	Ring finger protein 126	1.50	0.17	0.06	19p13.3	55658	30138	1.51	1.52	1.27	2.06	1.6	1.28	1.32	1.49
Signaling pathways																
Hs.517601	RAC2	Ras-related C3 botulinum toxin substrate 2 (small GTP binding prote	1.77	0.15	0.05	22q13.1	5880	97600	2.13	1.68	1.91	1.86	1.69	1.67	1.64	1.6
Hs.5662	GNB2L1	Guanine nucleotide binding protein (G protein), beta polypeptide 2-li	1.74	0.36	0.13	5q35.3	10399	14867	2.02	1.55	1.07	2.68	1.33	1.9	1.81	1.6
Hs.11169	ERRFI1	ERBB receptor feedback inhibitor 1	1.66	0.35	0.13	1p36.12-36.33	54206	36024	2.2	1.88	1.23	2.32	1.56	1.27	1.17	1.67
Hs.591968	FZD4	Frizzled homolog 4 (Drosophila)	1.62	0.18	0.06	11q14.2	8322	21372	1.6	1.86	1.69	2.01	1.59	1.28	1.41	1.51
Hs.444468	CTDSP1	CTD (carboxy-terminal domain, RNA polymerase II) small phosphata	1.59	0.27	0.10	2q35	58190	37082	1.29	2.02	1.89	1.79	1.76	1.09	1.34	1.57
Hs.337242	CENTB1	Centaurin, beta 1	1.59	0.22	0.08	17p13.1	9744	22798	1.84	1.76	1.62	1.18	1.85	1.2	1.51	1.79
Hs.508514	STK24	Serine/threonine kinase 24 (STE20 homolog, yeast)	1.57	0.18	0.06	13q31.2-q32.3	8428	98509	1.6	1.55	1.41	2.03	1.31	1.31	1.63	1.73
Hs.41086	PLEKHA3	Pleckstrin homology domain containing, family A member 3	1.56	0.33	0.12	2q31.2	65977	36200	1.76	1.43	1.24	2.55	1.05	1.67	1.27	1.5
Hs.502004	RRAS2	Related RAS viral (r-ras) oncogene homolog 2	1.51	0.19	0.07	11p15.2	22800	18241	2.08	1.43	1.29	1.63	1.31	1.5	1.23	1.58
Hs.268530	GPS1	G protein pathway suppressor 1	1.50	0.16	0.06	17q25.3	2873	5949	1.8	1.55	1.35	1.36	1.28	1.71	1.59	1.38
Hs.435291	ARHGAP6	Rho GTPase activating protein 6	-1.58	0.23	0.08	Xp22.3	395	89228	-2.39	-1.41	-1.55	-1.66	-1.06	-1.63	-1.51	-1.43
Hs.475963	CTDSPL	CTD (carboxy-terminal domain, RNA polymerase II) small phosphata	-1.64	0.28	0.10	3p21.3	10217	12925	-2.56	-1.28	-1.56	-1.72	-1.24	-1.76	-1.52	-1.47
Hs.298654	DUSP6	Dual specificity phosphatase 6	-1.98	0.42	0.15	12q22-q23	1848	101364	-2.88	-2.41	-1.73	-2.27	-1.59	-1.11	-1.8	-2.03
Adhesion molecules and extracellular matrix																
Hs.591335	CD164	CD164 molecule, sialomucin	1.75	0.36	0.13	6q21	8763	13180	2.06	1.34	1.32	2.37	1.13	1.95	1.85	1.95
Hs.90107	ADRM1	Adhesion regulating molecule 1	1.56	0.23	0.08	20q13.33	11047	14496	1.67	1.95	1.92	1.4	1.39	1.63	1.35	1.21
Hs.106880	BYSL	Bystin-like	1.53	0.25	0.09	6p21.1	705	4307	1.77	1.57	1.83	1.28	1.97	1.5	1.22	1.1
Hs.73800	SELP	Selectin P (granule membrane protein 140kDa, antigen CD62)	-1.50	0.20	0.07	1q22-q25	6403	97770	-1.79	-1.55	-1.63	-1.37	-1.16	-1.55	-1.17	-1.75
Hs.494419	LAMP1	Lysosomal-associated membrane protein 1	-1.55	0.16	0.06	13q34	3916	11092	-1.29	-1.71	-1.4	-1.87	-1.55	-1.73	-1.52	-1.37
Hs.64016	PROS1	Protein S (alpha)	-1.68	0.29	0.10	3q11.2	5627	88023	-1.9	-1.98	-2.27	-1.7	-1.17	-1.66	-1.06	-1.69
Hs.3745	MFGE8	Milk fat globule-EGF factor 8 protein	-1.74	0.30	0.10	15q25	4240	13094	-1.52	-1.56	-1.29	-1.91	-1.44	-2.24	-2.26	-1.71
Hs.443681	CSPG2	Chondroitin sulfate proteoglycan 2 (versican)	-1.99	0.58	0.20	5q14.3	1462	7867	-1.87	-3.42	-2.12	-2.54	-2.19	-1.31	-1.18	-1.3
Structural proteins and cytoskeleton																
Hs.12967	SYNE1	Spectrin repeat containing, nuclear envelope 1	1.69	0.38	0.13	6q25	23345	173286	2.4	1.81	1.51	1.93	1.27	1.2	1.26	2.13
Hs.501012	ADD3	Adducin 3 (gamma)	1.67	0.31	0.11	10q24.2-q24.3	120	170248	2.4	1.71	1.24	1.89	1.09	1.69	1.42	1.9
Hs.533059	TUBB	Tubulin, beta	1.64	0.32	0.11	6p21.33	203068	112531	1.74	2.03	2.17	1.51	1.9	1.23	1.29	1.26
Hs.381099	LCP1	Lymphocyte cytosolic protein 1 (L-plastin)	1.61	0.25	0.09	13q14.3	3936	95285	1.6	1.11	1.54	1.83	1.18	1.89	1.76	1.98
Hs.56145	TMSL8	Thymosin-like 8	1.56	0.28	0.10	Xq21.33-q22.3	11013	38935	1.26	1.61	2.23	1.55	1.76	1.08	1.23	1.75
Hs.183706	ADD1	Adducin 1 (alpha)	1.55	0.20	0.07	4p16.3	118	173102	1.73	1.57	1.56	1.55	1.49	1.21	1.15	2.15
Hs.134602	TTN	Titin	-1.50	0.20	0.07	2q31	7273	54667	-1.73	-1.53	-1.62	-1.4	-1.3	-1.16	-1.32	-1.91
Hs.21213	MYO5A	Myosin VA (heavy polypeptide 12, myoxin)	-1.50	0.27	0.10	15q21	4644	162416	-2.31	-1.26	-1.28	-1.38	-1.3	-1.78	-1.45	-1.24
Hs.370392	MYO1E	Myosin IE	-1.52	0.29	0.10	15q21-q22	4643	151109	-2.1	-1.6	-1.58	-1.3	-1.29	-1.19	-1.14	-2
Hs.515094	TRIP10	Thyroid hormone receptor interactor 10	-1.60	0.27	0.10	19p13.3	9322	6097	-2.52	-1.67	-1.6	-1.7	-1.35	-1.2	-1.19	-1.58
Hs.631558	TNNT1	Troponin T type 1 (skeletal, slow)	-1.69	0.33	0.12	19q13.4	7138	98132	-1.18	-2.38	-2.05	-1.63	-1.61	-1.26	-1.46	-1.95
Hs.407653	KRTAP13-1	Keratin associated protein 13-1	-2.33	0.93	0.33	21q22.1	140258	66498	-2.3	-2.02	-4.03	-1.32	-4.35	-1.93	-1.35	-1.34
Hs.374596	TPT1	Tumor protein, translationally-controlled 1	-3.01	0.40	0.14	13q12-q14	7178	98155	-2.67	-1.84	-3.8	-2.96	-3.25	-3.1	-2.95	-3.51
Vesicle traffking and membrane fusion																
Hs.81964	SEC24C	SEC24 related gene family, member C (S. cerevisiae)	1.60	0.24	0.09	10q22.2	9632	8638	1.38	1.45	1.96	1.91	1.7	1.24	1.34	1.81
Hs.216226	SYNGR1	Synaptogyrin 1	1.53	0.19	0.07	22q13.1	9145	114838	1.7	1.3	1.54	1.51	1.26	1.39	1.41	2.11
Hs.213389	GOLGB1	Golgi autoantigen, golgin subfamily b, macrogolgin, 1	1.52	0.18	0.06	3q13	2804	8036	1.69	1.43	1.5	1.47	1.63	1.17	1.32	1.98
Hs.631827	ANXA7	Annexin A7	1.51	0.23	0.08	10q21.1-q21.2	310	177172	1.62	1.36	1.18	1.95	1.11	1.71	1.66	1.46
Membrane receptors																
Hs.54457	CD81	CD81 molecule	1.79	0.34	0.12	11p15.5	975	7844	2.42	1.87	1.79	2.43	1.52	1.37	1.33	1.61
Hs.569475	GABRG3	Gamma-aminobutyric acid (GABA) A receptor, gamma 3	1.78	0.40	0.14	15q12	2567	49123	1.1	2.55	2.02	1.44	2.01	1.45	2.13	1.54
Hs.643584	IGSF10	Immunoglobulin superfamily, member 10	1.64	0.28	0.10	3q25.1	285313	71222	1.32	2.13	1.95	1.47	1.96	1.04	1.61	1.65
Hs.632045	MSR1	Macrophage scavenger receptor 1	1.55	0.16	0.06	8p22	4481	92351	1.37	1.41	1.38	1.41	1.91	1.54	1.7	1.67
Hs.122785	TAS2R38	Taste receptor, type 2, member 38	-1.87	0.61	0.22	7q34	5726	6686	-4.11	-1.85	-1.06	-1.62	-2.08	-1.84	-1.42	-1
Carriers and transporters																
Hs.500761	SLC16A3	Solute carrier family 16 (monocarboxylic acid transporters), member	-1.52	0.19	0.07	17q25	9123	7626	-1.82	-1.62	-1.54	-1.79	-1.05	-1.33	-1.4	-1.61
Hs.567337	SLC22A3	Solute carrier family 22 (extraneuronal monoamine transporter), mer	-1.53	0.23	0.08	6q26-q27	6581	131716	-2.28	-1.39	-1.2	-1.39	-1.26	-1.65	-1.5	-1.59
Hs.433670	FTL	Ferritin, light polypeptide	-1.79	0.17	0.06	19q13.3-q13.4	2512	142146	-1.67	-2.01	-1.94	-1.67	-1.84	-2.04	-1.55	-1.57
Hs.585357	HBZ	Hemoglobin, zeta	-1.84	0.56	0.20	16p13.3	3050	154067	-1.66	-1.48	-0.93	-3.6	-1.9	-1.54	-1.32	-2.26
Hs.524910	FTH1	Ferritin, heavy polypeptide 1	-3.20	0.46	0.16	11q13	2495	141972	-3.04	-4.58	-3.37	-3.14	-3.4	-3.29	-1.98	-2.78
Ion and water channels																
Hs.259048	AQP10	Aquaporin 10	1.70	0.44	0.16	1q21.3	89872	54317	1.14	2.32	2.25	1.18	2.26	1.11	1.73	1.58
Hs.574026	MIP	Major intrinsic protein of lens fiber	-1.48	0.21	0.07	12q13	4284	19632	-1.91	-1.45	-1.7	-1.34	-1.32	-1.13	-1.32	-1.67
Hs.523899	KCNE3	Potassium voltage-gated channel, Isk-related family, member 3	-1.86	0.37	0.13	11q13-q14	10008	12508	-2.54	-2.56	-1.44	-1.57	-1.79	-1.44	-1.58	-1.99
Hs.32505	KCNJ4	Potassium inwardly-rectifying channel, subfamily J, member 4	-3.80	1.92	0.68	22q13.1	3761	8707	-2.4	-4.41	-0.79	-4.21	-8.99	-5.27	-1.39	-2.91
Miscelaneous																
Hs.55940	SELM	Selenoprotein M	1.81	0.50	0.18	22q12.2	140606	57479	2.22	2.64	1.23	2.07	2.31	1.29	1.41	1.33
Hs.637001	SRP19	Signal recognition particle 19kDa	1.65	0.33	0.12	5q21-q22	6728	97953	1.79	1.36	1.18	2.6	1.26	1.87	1.51	1.61
Hs.339831	PENK	Proenkephalin	1.62	0.37	0.13	8q23-q24	5179	13415	2.07	1.2	1.1	2.42	1.2	1.78	1.52	1.69
Hs.556077	MUSTN1	Musculoskeletal, embryonic nuclear protein 1	1.62	0.27	0.10	3q21.1	389125	155956	2.06	1.47	1.87	1.51	1.48	1.14	1.41	2
Hs.303055	TTC8	Tetratricopeptide repeat domain 8	1.61	0.23	0.08	14q31.3	123016	139958	2.45	1.62	0.92	1.67	1.5	1.52	1.6	1.61
Hs.5062	TSPAN3	Tetraspanin 3	1.57	0.19	0.07	15q24.3	10099	129599	1.48	1.89	1.34	1.39	1.99	1.46	1.47	1.5
Hs.631572	TTC9B	Tetratricopeptide repeat domain 9B	1.53	0.16	0.06	19q13.2	148014	79156	1.71	1.91	1.16	1.62	1.49	1.37	1.5	1.5
Hs.534363	UCN	Urocortin	1.51	0.15	0.05	2q33-q21	7349	99760	1.46	1.61	1.7	1.21	1.33	1.45	1.72	1.63
Hs.520070	CUTA	CutA divalent cation tolerance homolog (E. coli)	1.50	0.26	0.09	6pter-p21.31	51596	27017	2.14	1.79	1.04	1.32	1.53	1.39	1.56	1.22
Hs.510262	MTAC2D1	Membrane targeting (tandem) C2 domain containing 1	1.50	0.26	0.09	14q32.12	123036	62537	2.36	1.45	1.35	1.12	1.14	1.4	1.68	1.48
Hs.591976	PANX1	Pannexin 1	-1.50	0.12	0.04	11q21	24145	24980	-1.62	-1.75	-1.52	-1.25	-1.45	-1.32	-1.6	-1.48
Hs.431099	PDZK1IP1	PDZK1 interacting protein 1	-1.68	0.31	0.11	1p33	10158	137288	-2.35	-1.45	-1.98	-1.62	-1	-1.94	-1.55	-1.56
Hs.528665	PROK2	Prokineticin 2	-3.39	2.23	0.79	3p21.1	60675	40554	-12.27	-3.44	-2.54	-1.79	-2.5	-1.85	-1.4	-1.34
Unknown function																
Hs.516087	TEX261	Testis expressed sequence 261	1.93	0.54	0.19	2p13.3	113419	58441	3.21	2.71	1.42	2.02	1.45	1.64	1.61	1.35
Hs.519702	CYFIP2	Cytoplasmic FMR1 interacting protein 2	1.88	0.31	0.11	5q33.3	26999	19319	1.96	1.99	1.93	2.35	1.79	1.12	1.46	2.4
Hs.111577	ITM2C	Integral membrane protein 2C	1.71	0.33	0.12	2q37	81618	46004	3	1.41	1.69	1.7	1.44	1.74	1.61	1.1
Hs.592091	FLJ00180	NOD3 protein	1.71	0.34	0.12	16p13.3	197358	72264	2.74	1.64	1.51	1.87	1.39	1.31	1.34	1.88
Hs.460487	CCDC101	Coiled-coil domain containing 101	1.67	0.22	0.08	16p11.2	112869	54900	1.87	1.92	1.36	1.92	1.84	1.5	1.54	1.37
Hs.620802	CTAGEP	CTAGE family pseudogene	1.62	0.12	0.04	10q26.3	119437	82749	1.68	1.49	1.74	1.83	1.33	1.54	1.64	1.69
Hs.514500	FAM100B	Family with sequence similarity 100, member B	1.60	0.28	0.10	17q25.1	283991	83936	2.02	1.46	1.42	1.55	1.45	1.03	1.79	2.11
Hs.503666	GPKOW	G patch domain and KOW motifs	1.60	0.29	0.10	Xp11.23	27238	26889	2.26	1.49	1.46	2.09	1.18	1.45	1.46	1.39
Hs.306291	DLEU8	Deleted in lymphocytic leukemia 8	1.59	0.20	0.07	13q14.3	79621	38420	1.84	1.44	1.47	2.02	1.3	1.72	1.45	1.51
Hs.508266	COMMD6	COMM domain containing 6	1.59	0.20	0.07		170622	154593	1.57	1.94	1.23	1.88	1.55	1.37	1.46	1.74
Hs.592292	RIC8A	Resistance to inhibitors of cholinesterase 8 homolog A (C. elegans)	1.58	0.24	0.08	11p15.5	60626	38858	1.58	1.91	1.57	2.18	1.42	1.08	1.3	1.62
Hs.495918	FAM5B	Family with sequence similarity 5, member B	1.58	0.22	0.08	1q24.1-q25.3	57795	37042	1.82	2.18	1.1	1.45	1.57	1.31	1.61	1.59
Hs.116419	MEI1	Meiosis defective 1	1.56	0.23	0.08	22q13.2	150365	61274	1.96	1.49	1.52	2.06	1.28	1.43	1.27	1.44
Hs.137459	SHRM	Shroom	1.55	0.24	0.09	4q21.1	57619	35291	1.71	1.75	1.58	1.1	1.91	1.04	1.6	1.73
Hs.591694	BBS7	Bardet-Biedl syndrome 7	1.54	0.30	0.11	4q27	55212	28937	1.1	2.06	1.78	1.21	1.93	1.13	1.58	1.52
Hs.271695	NOB1	NIN1/RPN12 binding protein 1 homolog (S. cerevisiae)	1.53	0.21	0.08	16q22.3	28987	18923	1.7	1.91	1.43	1.85	1.28	1.37	1.45	1.3
Hs.135805	MIB2	Mindbomb homolog 2 (Drosophila)	1.52	0.18	0.06	1p36.33	142678	57680	1.93	1.49	1.27	1.68	1.3	1.37	1.48	1.67
Hs.376046	BTN3A2	Butyrophilin, subfamily 3, member A2	1.51	0.23	0.08	6p22.1	11118	14576	1.99	1.45	1.49	1.56	1.29	1.1	1.32	1.91
Hs.509264	KLHDC2	Kelch domain containing 2	1.50	0.20	0.07	14q22.1	23588	20815	1.73	1.49	1.07	1.8	1.67	1.32	1.32	1.61
Hs.512668	TSCOT	Thymic stromal co-transporter	-1.62	0.24	0.08	9q32	57864	50524	-2.2	-1.95	-1.43	-1.25	-1.52	-1.61	-1.65	-1.34