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This information is current as of December 19, 2011

J Immunol; Prepublished online 14 December 2011;
doi:10.4049/jimmunol.1102349
<http://www.jimmunol.org/content/early/2011/12/14/jimmunol.1102349>

Supplementary Data	http://www.jimmunol.org/content/suppl/2011/12/14/jimmunol.1102349.DC1.html
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The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
9650 Rockville Pike, Bethesda, MD 20814-3994.
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Print ISSN: 0022-1767 Online ISSN: 1550-6606.



Shifting of Immune Responsiveness to House Dust Mite by Influenza A Infection: Genomic Insights

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Respiratory viral infections have been associated with an increased incidence of allergic asthma. However, the mechanisms by which respiratory infections facilitate allergic airway disease are incompletely understood. We previously showed that exposure to a low dose of house dust mite (HDM) resulted in enhanced HDM-mediated allergic airway inflammation, and, importantly, marked airway hyperreactivity only when allergen exposure occurred during an acute influenza A infection. In this study, we evaluated the impact of concurrent influenza infection and allergen exposure at the genomic level, using whole-genome microarray. Our data showed that, in contrast to exposure to a low dose of HDM, influenza A infection led to a dramatic increase in gene expression, particularly of TLRs, C-type lectin receptors, several complement components, as well as FcεR1. Additionally, we observed increased expression of a number of genes encoding chemokines and cytokines associated with the recruitment of proinflammatory cells. Moreover, HDM exposure in the context of an influenza A infection resulted in the induction of unique genes, including calgranulin A (*S100a8*), an endogenous damage-associated molecular pattern and TLR4 agonist. In addition, we observed significantly increased expression of serum amyloid A (*Saa3*) and serine protease inhibitor 3n (*Serpina3n*). This study showed that influenza infection markedly increased the expression of multiple gene classes capable of sensing allergens and amplifying the ensuing immune-inflammatory response. We propose that influenza A infection primes the lung environment in such a way as to lower the threshold of allergen responsiveness, thus facilitating the emergence of a clinically significant allergic phenotype. *The Journal of Immunology*, 2012, 188: 000–000.

Allergic asthma is a chronic immune-inflammatory disease of the airways that occurs following sensitization to common aeroallergens, such as house dust mite (HDM), the most ubiquitous indoor aeroallergen worldwide. However, despite universal exposure, only ~20% of the population develops the disease (1). This suggests that the natural response to allergens

is immunologic homeostasis and that additional factors contribute to triggering aberrant immune responses to these allergens (2). In addition to a genetic predisposition, environmental factors, such as respiratory viral infections, have been implicated with the clinical expression of allergic airway inflammation (3, 4). In this regard, there is abundant evidence in humans of an association between viral infections and the expression of asthma (5, 6). In mice, we previously reported that exposure to a concentration of HDM, which by itself elicits negligible airway inflammation and no changes in lung function, results in a phenotype characterized by robust allergic airway inflammation, enhanced mucus production, and marked lung dysfunction in the context of an acute influenza A virus (Flu) infection (7).

In this study, we used genome-wide transcriptional profiling to investigate the nature of the Flu-induced environment in the lung, by examining global gene expression during the early phase (EP; 4 d) and late phase (LP; 7 d) of HDM exposure. We found that exposure to a low concentration of HDM alone elicited minimal alterations in the gene profile, whereas Flu infection led to a pervasive upregulation of genes associated with the general response to stimuli and stress. In particular, Flu infection dramatically increased the expression of a number of cell surface receptors, notably TLRs, C-type lectin receptors (CLRs), and FcRs, and a prolific number of chemokines and chemokine receptors. Interestingly, exposure to HDM in the context of this Flu-induced environment led to the increased expression of several hundred genes, which were not expressed in mice exposed to allergen alone. These data suggested that Flu lowered the threshold of HDM responsiveness by establishing a global, heightened state of immune sensing in the lung and launching multiple pathways involved in inflammatory responses to exogenous Ags.

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Received for publication August 12, 2011. Accepted for publication November 4, 2011.

This work was supported in part by the Canadian Institute of Health Research and MedImmune LLC. A.A.-G. holds a scholar award from the King Abdullah University of Science and Technology, and M.J. holds a Senior Canada Research Chair in Immunobiology of Respiratory Disease and Allergy.

The sequences presented in this article have been submitted to the European Molecular Biology Laboratory-European Bioinformatics Institute ArrayExpress database (<http://www.ebi.ac.uk/microarray-as/ae>) under accession number E-MEXP-3325.

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The online version of this article contains supplemental material.

Abbreviations used in this article: CLR, C-type lectin receptor; DC, dendritic cell; EP, early phase; Flu, influenza A virus; Flu+HDM, house dust mite in the context of influenza A virus infection; GO, gene ontology; HDM, house dust mite; LP, late phase; qPCR, quantitative real-time PCR.

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Materials and Methods

Animals

Female BALB/c mice (6–8 wk old) were purchased from Charles River Laboratories (Saint-Constant, QC, Canada). The mice were housed under specific pathogen-free conditions and maintained on a 12-h light-dark cycle, with food and water ad libitum. All experiments described in this study were approved by the Animal Research Ethics Board of McMaster University.

Flu and infection protocol

Flu strain A/PR/8/34 (H1N1) was prepared, as described previously (8), and kindly provided by MedImmune. The viral stock suspension (10^9 PFU/ml) was diluted, and 10 PFU was administered intranasally to isoflurane-anesthetized BALB/c mice in 35 μ l sterile PBS solution. Animals were monitored for signs of illness twice daily for 10 d following infection.

Sensitization protocols

Allergen administration. HDM extract (Greer Laboratories, Lenoir, NC) was resuspended in sterile PBS at a concentration of 0.5 mg (protein)/ml, and 10 μ l (5- μ g dose) was administered to isoflurane-anesthetized mice intranasally. Groups of mice were infected with Flu or exposed to PBS. Seven days later, separate groups of mice were exposed to saline or HDM for 3 or 6 d, and lungs were harvested 24 h after the last exposure, at day 4 (EP) or day 7 (LP) (Fig. 1).

RNA isolation and hybridization of Affymetrix GeneChip array

Lungs were harvested 24 h after the last allergen challenge, snap-frozen in liquid nitrogen, and stored at -80°C until further processing. Total RNA was extracted using RNA-STAT60 reagent (Tel-Test, Friendwood, TX), as per the manufacturer's protocol. The extracted total RNA was further purified using an RNeasy Mini Kit (QIAGEN, Valencia, CA), and quality was assessed with the Agilent Bioanalyzer 2100 (Agilent Technologies, Santa Clara, CA). Preparation of wild-type sense cDNA targets, hybridization to Affymetrix Mouse Gene 1.0 ST arrays (Affymetrix, Santa Clara, CA), and scanning were performed according to standard Affymetrix protocols. In brief, 100 ng total RNA from each sample was used for the synthesis of dsDNA with random hexamers tagged with a T7 promoter sequence. The double-stranded cDNA was subsequently used as template and amplified by T7 RNA polymerase, producing many copies of antisense cRNA. In the second cycle of cDNA synthesis, random hexamers were used to prime reverse transcription of the cRNA from the first cycle to produce ssDNA in the sense orientation with incorporated deoxyuridine triphosphate. Fragmentation of the ssDNA was performed using a combination of uracil DNA glycosylase and apurinic/apyrimidine endonuclease 1 that breaks DNA at deoxyuridine triphosphate residues. Labeling of fragmented DNA by terminal deoxynucleotidyl transferase with the Affymetrix DNA labeling reagent covalently linked to biotin was used in the final step of target preparation. Fragmented and biotin-labeled cDNA was hybridized at 45°C for 17 h to Affymetrix Mouse Gene 1.0 ST arrays. The arrays were washed and stained with streptavidin-PE, followed by signal amplification with a biotinylated anti-streptavidin Ab. The arrays were scanned according to the manufacturer's instructions.

Processing of image files and gene-expression analysis

Gene-expression measurements were generated from quantified Affymetrix image files ("*.CEL" files) using the robust multiarray analysis algorithm (9) and GeneSpring 10.0 software (Agilent Technologies). All 21 CEL files were analyzed simultaneously with quantile normalization and median polish probe summarization using the PBS samples as a baseline (control). Transcripts with expression levels in the first quantile were filtered out to remove noise from downstream statistical analyses. One-way ANOVA was applied to the filtered and log₂-transformed probe sets. A Tukey post hoc test was applied successively to identify transcripts with a statistically significant expression among the treatment groups. Genes were defined as differentially expressed if they had fold changes of at least ± 1.5 , with p values ≤ 0.05 . This selection criterion includes the maximum number of differentially expressed genes used to identify biologically relevant gene families and pathways. Functional annotations of the differentially expressed genes were identified using NetAffx (Affymetrix) and the Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.7 (10, 11). Gene ontology (GO) analysis of the differentially expressed genes was performed using GoMiner software (12), and GO biological processes that had a Fisher exact p value < 0.05 (false discovery rate

corrected; $p < 0.05$) were considered significantly enriched. Microarray data files from this study are available at European Molecular Biology Laboratory-European Bioinformatics Institute ArrayExpress database (<http://www.ebi.ac.uk/microarray-as/ae>). ArrayExpress accession number for these files is E-MEXP-3325.

Quantitative real-time PCR for gene validation

RNA was quantified and normalized, and RNA integrity was assessed by Agilent Bioanalyzer. cDNA was generated using the Super Script III Reverse Transcriptase kit (Life Technologies, Carlsbad, CA), according to the manufacturer's instructions. Relative transcript expression assay was conducted, as described previously (13), using the Fluidigm Biomark system (Fluidigm, San Francisco, CA). BestKeeper (version 1) (14) was used to identify the stably expressed housekeeping gene to be used as an internal reference. Among the four housekeeping genes, β -actin (*Actb*), β -2-microglobulin (*B2m*), *Gapdh*, and hypoxanthine phosphoribosyl-transferase 1 (*Hprt1*), *Hprt1* emerged as the most stably expressed and, thus, was selected for normalizing genes of interest. Data analysis of cycle threshold values was conducted using the Relative Expression Software Tool-384 (REST-384) version 1, and the pair-wise fixed reallocation randomization test was performed to determine the fold changes and statistical significance (15).

Results

Impact of Flu infection and HDM exposure on global gene-expression profiles

To investigate the global impact of exposure to a low dose of HDM, Flu, and HDM in the context of Flu infection (Flu+HDM) on gene-expression profiles (Fig. 1), we conducted a principal component analysis, which allows visualization of the effects of multiple treatments on gene-expression profiles. To this end, the analysis included all genes from all arrays without any prior filtering. Our analysis revealed the differential effects of HDM exposure, Flu infection, or Flu+HDM coexposure, during the EP and LP of the response, on gene expression by placing them along the planes of the x -, y -, and z -axes (Fig. 2). Our data showed that EP and LP HDM treatment falls in close proximity to the PBS control group along the x - and z -axes, thus suggesting that exposure to such a low dose of HDM (5 μ g) for 3 or 6 d had only minimal effects

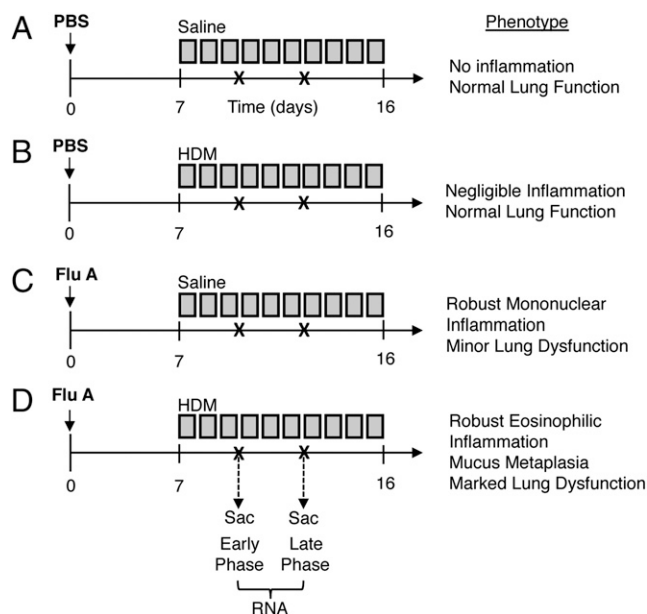
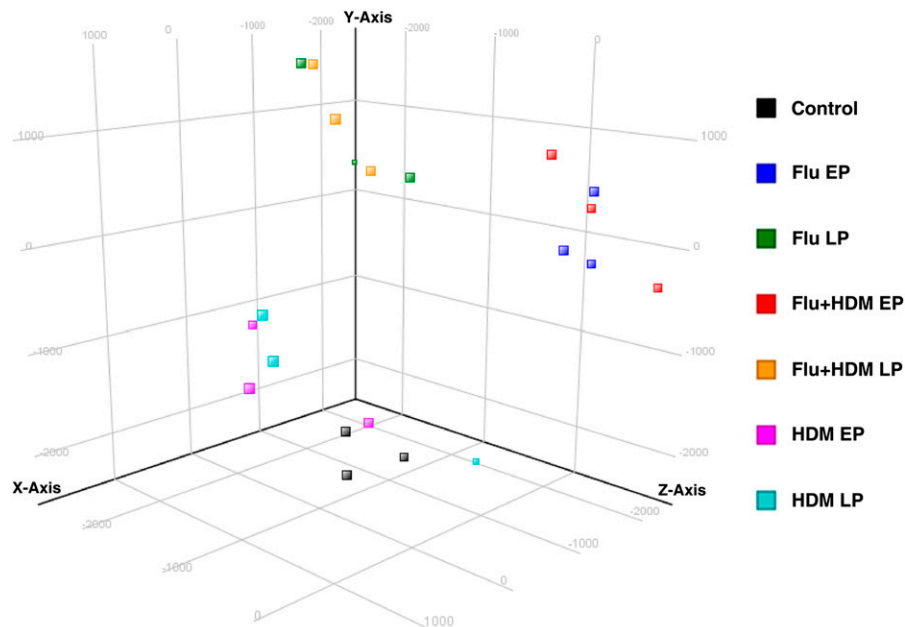


FIGURE 1. Experimental plan. A–D, Separate groups of mice were infected with Flu or exposed to PBS. Seven days later, mice were either exposed to saline or HDM for 10 d, resulting in four treatment groups: PBS (A), HDM (B), Flu (C), and Flu+HDM (D) (7). Lungs were harvested, and RNA was isolated 24 h after the third or sixth dose of HDM at day 4 or 7, representing the EP or LP response, respectively.

FIGURE 2. Principal component analysis evaluating the impact of treatment and time on gene expression. Separate groups of mice were either infected with Flu or exposed to PBS; 7 d later, they were exposed to 5 μ g HDM or treated with saline for 3 or 6 d. Gene-expression profiles were evaluated 24 h after the last exposure, at day 4 (EP) or 7 (LP) ($n = 3$ mice/group).



on gene expression. In contrast, Flu LP and Flu+HDM LP groups clustered together along the y-axis, farthest from the x-z plane; similarly, the expression profile during the EP of Flu and Flu+HDM clustered together along the y-z plane, indicating that Flu infection and Flu+HDM coexposure during EP or LP had similar effects on lung gene-expression profiles, which is distinct from that observed in the lungs of mice exposed to PBS or HDM. Interestingly, the genes expressed during the EP in Flu and Flu+HDM groups were clustered apart from those expressed during the LP, highlighting the impact of time on gene expression in these two treatment groups.

To quantify the number of genes differentially regulated in response to HDM, Flu, or Flu+HDM, each individual treatment group was compared with PBS controls. Genes with a differential regulation of at least ± 1.5 -fold changes ($p \leq 0.05$) were considered statistically significant. Using this selection criterion, we identified a total of 51 differentially expressed genes in mice exposed to HDM only during the EP (Fig. 3A). In contrast, we identified a total of 1443 genes in mice infected with Flu only at the same time point. Exposure to Flu+HDM led to the regulation of a total of 1592 genes compared with PBS controls. However, a majority of the genes regulated in the Flu+HDM group (1235 genes) were also expressed in mice infected with Flu only (common genes), whereas 330 genes were only expressed in the Flu+HDM group. Heretofore, we refer to these 330 genes as “unique genes” (Fig. 3A). During the LP of the response, representing the time point at which Flu infection enters into the resolving phase (i.e., 14 d after the initial infection), the number of differentially expressed genes was reduced to 1378 in the Flu-only group and 1362 in the Flu+HDM-treated group. In addition, during the LP, Flu and Flu+HDM groups shared 1038 genes, whereas a total of 240 genes was uniquely expressed in the Flu+HDM group (Fig. 3B).

Evaluation of differentially expressed genes

To gain an appreciation of the various functions associated with the dramatic increase in differentially expressed genes following Flu and Flu+HDM exposure, we next performed a GO analysis and compared the biological profiles between these two groups (Fig. 4). Our data showed that, during both the EP and LP of the response, Flu- and Flu+HDM-treated mice have similar profiles with respect to various GO biological processes (Fig. 4). Interestingly, at least

five of these GO processes, including “response to stimulus” (GO:0050896), “response to stress” (GO:0006950), “response to wounding” (GO:0009611), “inflammatory response” (GO:0006954), and “chemotaxis” (GO:0006935) were enriched with a greater number of genes in the Flu+HDM-treated group compared with the Flu-alone-treated group in both EP and LP; specifically, the “response to stimulus” process was enriched with 265 and 218 genes during EP and LP, respectively, in mice infected with Flu only, whereas in the Flu+HDM group this same process was enriched with 283 (EP) and 243 (LP) genes. To gain greater insight into the biological significance of these diverse processes, we identified specific genes associated with these functional groups. Our analysis revealed that these biological processes are associated with the expression of genes encoding complement components and their receptors (Table I) or various C-type lectins (including CLRs), FcRs, and TLRs (Table II). In addition, we identified genes encoding chemokines and chemokine receptors (Table III), as well as various cytokines and cytokine receptors (Table IV). The majority of these genes was found to be upregulated in both Flu and Flu+HDM groups, during both the EP and LP responses.

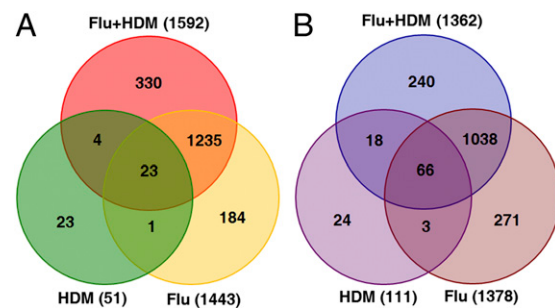


FIGURE 3. Venn analysis of differentially expressed genes. Separate groups of mice were either infected with Flu or exposed to PBS; 7 d post-infection, they were either exposed to 5 μ g HDM or saline treated for 3 or 6 d. Gene-expression profiles were evaluated 24 h after the last exposure, at day 4 (EP) or 7 (LP). Venn diagram showing number of common and unique genes expressed following Flu, HDM, and Flu+HDM treatment during EP (A) and LP (B) ($n = 3$ mice/group). Genes were filtered based on fold change (≥ 1.5). $p < 0.05$, one-way ANOVA, Tukey post hoc test.

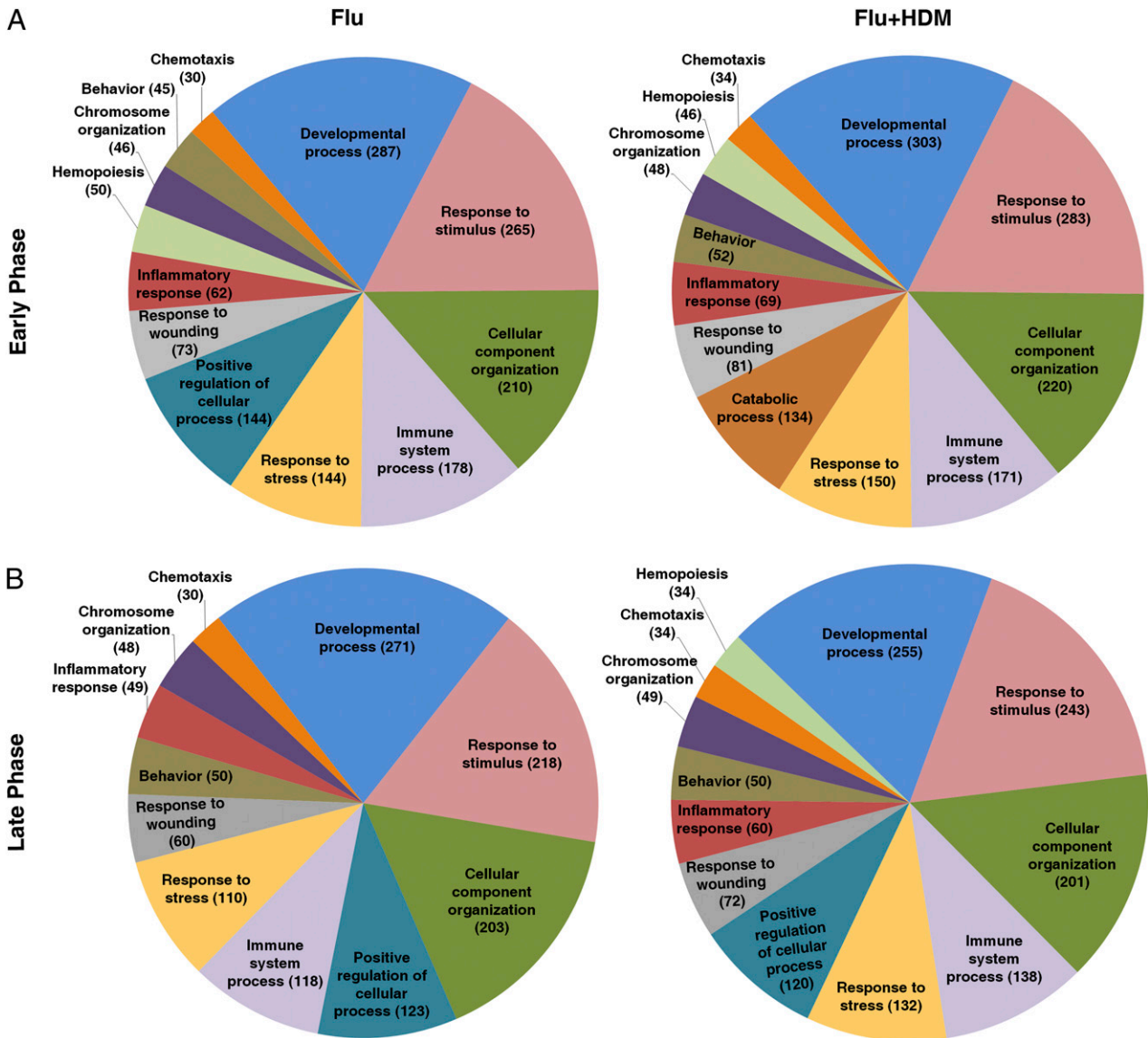


FIGURE 4. GO biological processes in mice infected with Flu and exposed to HDM. GO biological processes enriched with genes from Flu and Flu+HDM during EP (A) and LP (B) response. Numbers in parentheses represent the number of genes enriching each process ($n = 3$ mice/group). $p < 0.05$, Fisher exact test (false discovery rate corrected).

Impact of HDM exposure on gene expression during ongoing Flu infection

In addition to the 330 and 240 uniquely expressed genes in the Flu+HDM-treated mice during the EP and LP, respectively (Fig. 3), we selected genes whose expression was shared among the three treatment groups but that exhibited additional regulation in response to HDM when allergen exposure occurred during ongoing Flu infection. A selection criterion of a 1.5-fold difference in expression was applied to the 1262 commonly expressed genes in the EP that resulted in the inclusion of 34 genes shared between Flu and Flu+HDM groups and 2 genes shared among all three treatments (HDM, Flu, and Flu+HDM). Collectively, a total of 366 genes were additionally regulated in response to HDM exposure in the context of Flu infection (Supplemental Table I). The same selection criterion was applied to the genes commonly expressed in the LP, which resulted in a total of 263 genes (240 were unique to Flu+HDM; 11 were common among all three treatments; 8 were common among Flu and Flu+HDM; 4 were

common among HDM and Flu+HDM) (Supplemental Table I). According to available functional annotations, these genes could be classified into 13 major functional categories. Functional annotations for 146 genes from EP and 86 genes from LP are not available and, thus, were classified in the “other” category (Table V).

To further understand the contribution of immune genes in regulating the response to HDM during acute viral infection, we examined in more detail those genes that were part of the “immune/inflammatory response” category. Our data identified 32 genes in the EP, of which 8 genes were shared between Flu and Flu+HDM (Table VI), and 46 genes expressed during the LP, of which 7 genes were shared between these two treatment groups (Table VII). These shared genes showed additional regulation to HDM exposure, resulting in additional fold increases in expression levels following HDM exposure in mice infected with influenza (Flu+HDM) compared with those infected with influenza only. Importantly, for the majority of these immune/inflammatory-responsive genes, the expression levels were up-

Table I. Differentially expressed genes associated with complement pathway during EP and LP responses after exposure to HDM, Flu, or Flu+HDM

Gene Symbol	Gene Name	EP			LP		
		HDM	Flu	F+H	HDM	Flu	F+H
<i>C3ar1</i>	Complement component 3a receptor 1	–	8.66	8.71	1.56	4.47	3.71
<i>C1qc</i>	Complement component 1, q C chain	–	5.73	6.59	–	5.46	4.70
<i>C1qb</i>	Complement component 1, q, β polypeptide	–	6.11	5.67	1.53	4.30	4.52
<i>C1qa</i>	Complement component 1, q, α polypeptide	–	5.17	4.91	–	4.26	3.76
<i>Cfb</i>	Complement factor B	–1.52	3.55	3.68	–	–	1.69
<i>C5ar1</i>	Complement component 5a receptor 1	–	–	1.89	–	–	–
<i>C1rb</i>	Complement component 1, r	–	1.74	1.88	–	–	–
<i>C4b/C4a</i>	Complement component 4B /4A	–	1.70	1.80	–	–	–
<i>C1s</i>	Complement component 1, s	–	2.36	1.80	–	–	–
<i>C2</i>	Complement component 2 (within H-2S)	–	–	1.78	–	–	–
<i>C1qbp</i>	Complement component 1, q binding protein	–	–	1.59	–	1.84	1.79
<i>C1r</i>	Complement component 1, r	–	–	1.56	–	–	–
<i>Cr2</i>	Complement receptor 2	–	–	–1.68	–	–	–
<i>C1qtnf7</i>	C1q and TNF related protein 7	–	–1.71	–2.16	–	–1.72	–1.67
<i>Cfd</i>	Complement factor D (adipsin)	–	–2.12	–2.38	–2.78	–1.60	–2.12
<i>C7</i>	Complement component 7	–	–	–	–	–2.24	–1.75
<i>C3</i>	Complement component 3	–	1.51	–	1.74	–	1.55
<i>Cfh</i>	Complement component factor h	–	–	–	–	–1.83	–

Values represent mean fold changes compared with PBS ($n = 3$ mice/group).

$p < 0.05$, one-way ANOVA, Tukey post hoc test.

–, Genes that showed no significant regulation in that treatment group; F+H, Flu+HDM.

regulated and, for only a few of these genes (11 genes in EP; 4 genes in LP), the levels were downregulated. We identified serum amyloid A (*Saa3*), tissue inhibitor of metalloproteinase 1 (*Timp1*), and serine protease inhibitor A3 (*Serpina3n*) among those genes that were additionally upregulated by HDM exposure during EP and LP, whereas S100 calcium-binding protein A8 (*S100a8*) was one of the uniquely expressed genes that emerged during the EP.

Gene validation by quantitative real-time PCR

To validate the gene-expression data obtained by microarray analysis, we examined gene-expression levels for a number of genes using quantitative real-time PCR (qPCR). To this end, we chose to examine genes with various fold changes across different gene classes as representative samples; these included a selection of genes expressed following Flu infection, as well as representative genes from the “uniquely expressed” list of genes following HDM

Table II. Differential expression of genes encoding cell surface receptors during EP and LP responses after exposure to HDM, Flu, or Flu+HDM

Gene Symbol	Gene Name	EP			LP		
		HDM	Flu	F+H	HDM	Flu	F+H
C-Type Lectins							
<i>Clec12a</i>	C-type lectin domain family 12, a	–	5.56	4.48	–	2.74	2.81
<i>Clec5a</i>	C-type lectin domain family 5, a	–	4.34	4.11	–	2.93	3.75
<i>Clec4a2</i>	C-type lectin domain family 4, a2	–	2.74	3.03	–	1.66	1.81
<i>Clec4a1</i>	C-type lectin domain family 4, a1	–	4.23	2.95	–	1.75	1.97
<i>Clec4a3</i>	C-type lectin domain family 4, a3	–	3.81	2.54	1.63	1.79	1.75
<i>Clec4d</i>	C-type lectin domain family 4, d	–	2.07	2.39	–	1.84	2.38
<i>Clec4n</i>	C-type lectin domain family 4, n	–	2.39	2.10	–	2.81	3.45
<i>Clec7a</i>	C-type lectin domain family 7, a	–	2.63	1.77	–	2.49	2.99
<i>Clec14a</i>	C-type lectin domain family 14, a	–	–2.92	–3.07	–	–4.26	–3.74
<i>Clec1a</i>	C-type lectin domain family 1, a	–1.86	–2.09	–	–2.59	–2.23	–
FcRs							
<i>Fcgr4</i>	FcR, IgG, low affinity IV	–	8.10	8.18	–	2.68	2.56
<i>Fcgr1</i>	FcR, IgG, high affinity I	–	5.42	6.24	–	2.37	2.30
<i>Fcer1g</i>	FcR, IgE, high affinity I, γ	–	3.17	3.80	–	2.44	2.25
<i>Fcgr2b</i>	FcR, IgG, low affinity IIb	–	3.14	3.17	2.12	2.43	3.88
<i>Fcgr3</i>	FcR, IgG, low affinity III	–	2.60	2.26	–	2.04	2.09
<i>Fcer2a</i>	FcR, IgE, low affinity II, α	–	–1.51	–2.20	–	–	–
TLRs							
<i>Tlr13</i>	TLR13	–	3.40	3.70	–	2.05	2.41
<i>Tlr2</i>	TLR2	–	2.02	2.10	–	–	–
<i>Tlr7</i>	TLR7	–	1.81	1.91	–	–	–
<i>Tlr1</i>	TLR1	–	2.15	1.80	–	–	–
<i>Tlr8</i>	TLR8	–	1.88	1.77	–	–	–

Values represent mean fold changes compared with PBS ($n = 3$ mice/group).

$p < 0.05$, one-way ANOVA, Tukey post hoc test.

–, Genes that showed no regulation in that treatment group; F+H, Flu+HDM.

Table III. Differential expression of genes encoding chemokines and chemokine receptors during EP and LP responses after exposure to HDM, Flu, or Flu+HDM

Gene Symbol	Common Name	Receptor	EP			LP		
			HDM	Flu	F+H	HDM	Flu	F+H
<i>Cxcl10</i>	IP-10	CXCR3	–	22.20	23.30	2.26	5.91	7.41
<i>Cxcl9</i>	MIG	CXCR3	–	14.50	12.93	–	7.03	6.64
<i>Ccl8</i>	MCP-2	CCR1, CCR2b, CCR5	–	11.81	9.78	4.37	7.54	6.62
<i>Ccl3</i>	MIP1a	CCR1	–	7.36	7.69	–	2.62	3.78
<i>Ccl12</i>	MCP-5	–	–	5.34	6.12	1.74	2.82	2.82
<i>Cxcl13</i>	BCA-1/BLC	CXCR5	–	5.34	5.57	1.64	3.37	5.62
<i>Ccl2</i>	MCP-1	CCR2	–	5.21	5.46	–	1.64	1.68
<i>Ccl7</i>	MCP-3/MARC	CCR2	–	4.00	5.13	1.61	1.56	1.94
<i>Ccl5</i>	RANTES	CCR5	–	3.32	2.69	–	2.11	1.54
<i>Cxcl16</i>	SRPSOX	CXCR6	–	2.44	2.26	–	1.79	1.83
<i>Cxcl5</i>	ENA-78	CXCR2	–	2.46	2.26	2.02	2.33	4.18
<i>Ccl9</i>	RP-2, CCF18, MIP-1?	CCR1	–	1.67	2.04	1.70	1.72	2.25
<i>Cxcl17</i>	DMC, VCC-1	–	–	–	1.51	–	2.48	2.49
<i>Cx3cl1</i>	Fractalkine	CX3CR1	–	–1.75	–1.55	–	–	–
<i>Ccl21a</i>	6Ckine, Exodus-2	CCR7	1.51	–	–	–	1.69	1.50
<i>Ccl22</i>	MDC	CCR4	–	–	–	–	–	1.58
<i>Ccl11</i>	Eotaxin	CCR2, CCR3, CCR5	–	–	–	2.88	–	1.59
<i>Ccl20</i>	LARC, Exodus-1	CCR6	–	–	–	–	–	1.71
<i>Ccl17</i>	TARC	CCR4	–	–	–	–	1.64	1.81
<i>Ccl6</i>	C10, MRP-2	CCR1	–	–	–	–	1.89	1.90
<i>Ccl19</i>	ELC, Exodus-3	CCR7	2.20	–	–	–	–	–
Receptors			Cellular Expression					
<i>Ccr5</i>	DC and memory Th1 cells	CCL2, CCL3, CCL4, CCL5, CCL11, CCL13, CCL14, CCL16	–	9.28	8.78	1.71	3.21	3.56
<i>Cxcr6</i>	–	CXCL16	–	6.54	4.58	–	2.84	3.56
<i>Cxcr3</i>	T, NK, and B cell	CXCL9, CXCL10, CXCL11	–	4.37	4.17	–	2.58	2.14
<i>Ccr2</i>	Monocytes, memory T cells, B cells, basophils, macrophages	CCL2, CCL8, CCL16	–	3.06	2.28	–	–	1.72
<i>Cxcr7</i>	T and B cells	CXCL12	–	–	1.69	–	–	–
<i>Cxcr2</i>	Neutrophils	CXCL1 to CXCL7	–	–	1.63	1.63	–	1.62
<i>Ccl11</i>	–	CCL19/CCL21/SLC and CCL25/TECK	–	–1.71	–2.07	–	–	–1.75
<i>Cxcr4</i>	Hematopoietic cells	CXCL12	–	–1.68	–2.11	–	–1.73	–1.71
<i>Ccl2</i>	Neutrophils and monocytes	–	–	–	–	–	–1.69	–1.87
<i>Xcr1</i>	–	–	–	2.11	–	–	1.50	1.59
<i>Cx3cr1</i>	–	CX3CL1	–	1.68	–	–	1.83	–

Values represent mean fold changes compared with PBS ($n = 3$ mice/group).

$p < 0.05$, one-way ANOVA, Tukey post hoc test.

–, Genes that showed no significant regulation in that treatment group; F+H, Flu+HDM.

exposure in the context of an ongoing Flu infection. These included complement component 1, q subcomponent, C chain (*C1qc*); chemokine (CC motif) ligand 7 (*Ccl7*); chemokine (CC motif) ligand 8 (*Ccl8*); C-type lectin domain family 14, member a (*Clec14a*); chemokine (CXC motif) ligand 10 (*Cxcl10*); chemokine (CXC motif) ligand 5 (*Cxcl5*); chemokine (CXC motif) ligand 9 (*Cxcl9*); chemokine (CXC motif) receptor 3 (*Cxcr3*); FcR, IgG, low affinity IV (*Fcgr4*); Ig μ chain V region AC38 205.12 (*IghmAC38.205.12*); *Saa3*; and *Timp1* (Fig. 5). All of these genes demonstrated the same directional fold changes (11 genes upregulated and 1 gene downregulated) analyzed by qPCR as that observed by microarray analysis. *Ccl7*, *Ccl8*, *Cxcl10*, *Cxcl5*, *Saa3*, and *Timp1* from the microarray experiment were found to be upregulated in the HDM-treatment group in the LP only, which was confirmed by qPCR analysis. Furthermore, none of these genes was significantly expressed in the HDM treatment group in the EP, as analyzed either by microarray or qPCR.

Discussion

The conditions under which allergen sensitization and ultimately, allergic inflammation, occur remain to be fully elucidated. HDM, the most ubiquitous aeroallergen worldwide, comprises a biochemically complex mixture of hundreds of protein and nonprotein components that confer immunogenic activities (16). Studies ex-

amining mechanisms associated with HDM-induced inflammation have identified various molecular constituents capable of activating innate defense mechanisms at mucosal surfaces (17, 18). However, these studies relied on the administration of concentrations of allergen designed to elicit maximal immune responses. In this regard, we recently reported detailed dose responses to HDM in a mouse system (19). Our data showed that although exposure to a concentration of 25 μ g daily elicited near-maximal responses, exposure to 1 μ g represented the threshold of visible responsiveness. Although it is exceedingly difficult to determine, on clinical and epidemiological grounds, the precise amount of HDM that humans inhale, it is reasonable to argue that most individuals are exposed to amounts that are insufficient to elicit allergic sensitization and, particularly, allergic asthma. Furthermore, we must be mindful that, in humans, allergen exposure rarely occurs in isolation but, rather, coupled to concurrent exposures to a plethora of chemicals (e.g., pollution) and biological entities, such as respiratory viruses, which can elicit substantial immune changes in the lung. Thus, priming of the immune environment of the lung through environmental coexposures may shift HDM responsiveness and, thus, increase the susceptibility to develop allergic sensitization and, eventually, allergic asthma.

The research we report in this article is based on a previous study in which we described a distinctive asthmatic phenotype in mice

Table IV. Differential expression of genes encoding cytokines and cytokine receptors during EP and LP responses after exposure to HDM, Flu, or Flu+HDM

Gene Symbol	Gene Name	EP			LP		
		HDM	Flu	F+H	HDM	Flu	F+H
Receptors							
<i>Tnfrsf12a</i>	TNFR superfamily, member 12a	–	1.72	2.75	–	1.60	1.50
<i>Il1r2</i>	IL-1R, type II	–	1.61	2.48	–	–	2.14
<i>Il2rb</i>	IL-2R, β -chain	–	2.22	2.43	–	–	–
<i>Il1rn</i>	IL-1R antagonist	–	2.00	1.97	–	1.58	2.03
<i>Tnfrsf9</i>	TNFR superfamily, member 9	–	2.00	1.87	–	–	1.97
<i>Il21r</i>	IL-21R	–	1.90	1.82	–	1.67	1.72
<i>Il2rg</i>	IL-2R, γ -chain	–	2.18	1.55	–	–	1.63
<i>Tnfsf10</i>	TNF (ligand) superfamily, member 10	–	–	–1.72	–	–1.94	–1.63
<i>Il17rd</i>	IL-17R D	–	–1.68	–1.88	–	–1.62	–1.68
<i>Ifngr2</i>	IFN- γ R 2	–	–	–	–	–	1.52
<i>Il18rap</i>	IL-18R accessory protein	–	1.57	–	–	–	–
<i>Il10ra</i>	IL-10R α	–	1.63	–	–	–	–
Cytokines							
<i>Irf7</i>	IFN regulatory factor 7	–	3.03	4.44	–	1.72	1.86
<i>Irf1</i>	IFN regulatory factor 1	–	2.22	2.40	–	–	1.51
<i>Il18bp</i>	IL-18 binding protein	–	2.07	2.38	–	–	1.51
<i>Tnf</i>	TNF	–	2.11	2.24	–	–	1.56
<i>Il1b</i>	IL-1 β	–	1.95	2.00	1.57	2.23	2.93
<i>Tnfrsf1b</i>	TNFR superfamily, member 1b	–	1.82	1.99	–	–	1.67
<i>Irf8</i>	IFN regulatory factor 8	–	1.99	1.83	–	–	1.61
<i>Tnfaip6</i>	TNF- α -induced protein 6	–	–	–	1.85	–	1.56
<i>Il1f9</i>	IL-1 family, member 9	–	–	–	–	–	1.59
<i>Tnfaip2</i>	TNF- α -induced protein 2	–	–	–	–	1.63	1.88
<i>Il33</i>	IL-33	–	1.64	–	1.58	–	1.93
<i>Il6st</i>	IL 6 signal transducer	–	–	–	–	–1.63	–
<i>Tnfsf13b</i>	TNF (ligand) superfamily, member 13b	–	1.63	–	–	–	–
<i>Il1a</i>	IL-1 α	–	–	–	–	–	–

Values represent mean fold changes compared with PBS ($n = 3$ mice/group).

$p < 0.05$, one-way ANOVA, Tukey post hoc test.

–, Genes that showed no significant regulation in that treatment group; F+H, Flu+HDM.

exposed to a low concentration of HDM (5 μ g daily) in the context of an acute influenza infection (7). In this model, exposure to HDM alone elicits minimal allergic sensitization and airway eo-

Table V. Functional categories of uniquely expressed genes in mice concurrently exposed to Flu+HDM during the EP and LP response

Biological Function	F+H Treatment Group	
	EP	LP
	No. of Genes	No. of Genes
Translation regulation	3	8
Other metabolic genes	4	9
Nucleotide/DNA/chromosome binding	4	5
Lipid/fatty acid metabolism	10	6
Ion transport/binding	11	12
Carbohydrate metabolism	11	6
Protein transport	16	6
Tissue/muscle development or reorganization	19	16
Transcription regulation	22	19
Cell division/cell cycle regulation	22	16
Protein metabolism/regulation	30	16
Immune/inflammatory response	32	46
Intracellular signaling	36	12
Others	146	86
Total genes	366	263

Genes were selected based on a mean fold change of ± 1.5 compared with PBS control-, HDM only-, or Flu-only-treated groups ($n = 3$ mice/group).

$p < 0.05$, one-way ANOVA, Tukey post hoc test.

F+H, Flu+HDM.

sinophilia and, importantly, does not alter lung function. Hence, we define this dose as a subclinical dose of allergen exposure. However, if HDM exposure takes place during the course of an ongoing acute influenza infection, strong Th2-mediated immunity, robust eosinophilia and, importantly, the generation of marked lung dysfunction ensue. We sought to investigate the genomic basis of this phenotype. As shown in Fig. 2, our data indicated that the global gene-expression profile in the lungs of mice exposed to HDM alone approximated the expression profile of mice exposed to PBS. In contrast, infection with Flu led to a gene-expression profile that was remarkably different from that observed in mice exposed to either HDM alone or PBS. Interestingly, the expression pattern in the lungs of Flu+HDM-treated mice was similar, but not identical, to that induced by Flu alone, despite the overt differences in phenotype observed between these two groups (7). Venn analysis revealed that 80% of genes expressed in Flu+HDM-treated mice were also expressed in the lungs of mice infected with Flu only (Fig. 3). A similar examination revealed that mice exposed to HDM alone or Flu+HDM shared only 1.5% and 6% of expressed genes in the EP and LP, respectively. In contrast to shared genes, we identified a set of 330 and 240 unique genes expressed only in mice exposed to Flu+HDM during the EP and LP of the response, respectively; these genes represent 23% and 19% of the total regulated genes in this treatment group. These data revealed that, compared with the minimal impact elicited by a subclinical dose of allergen, Flu infection has a major impact on global gene regulation, involving hundreds of genes involved in the regulation of a number of distinct biological pathways.

Table VI. Immune inflammatory genes with additional responsiveness to HDM in the lungs of mice infected with Flu and exposed to HDM for 3 d (EP)

Gene Symbol	Gene Name	Flu	F+H
<i>Saa3</i>	Serum amyloid A 3	15.74	17.35
<i>Cxcl9</i>	Chemokine (CXC motif) ligand 9	14.50	12.93
<i>Timp1</i>	Tissue inhibitor of metalloproteinase 1	8.01	10.07
<i>Ccl8</i>	Chemokine (CC motif) ligand 8	11.81	9.78
<i>Serpina3n</i>	Serine (or cysteine) peptidase inhibitor, clade A, member 3N	4.09	9.25
<i>IghmAC38.205.12</i>	Ig μ chain V region AC38 205.12	3.65	5.65
<i>Igh-1a</i>	IgH 1a	2.96	4.94
<i>Cd163</i>	CD163 Ag	–	2.54
<i>C5ar1</i>	Complement component 5a receptor 1	–	1.89
<i>C2</i>	Complement component 2 (within H2S)	–	1.78
<i>S100a8</i>	S100 calcium binding protein A8 (calgranulin A)	–	1.70
<i>Ndr1</i>	Nmyc downstream regulated gene 1	–	1.68
<i>Il8rb</i>	IL-8R, β	–	1.63
<i>Nupr1</i>	Nuclear protein 1	–	1.62
<i>G6pdx</i>	Glucose-6 phosphate dehydrogenase X-linked	–	1.62
<i>Enpp1</i>	Ectonucleotide pyrophosphatase/phosphodiesterase 1	–	1.58
<i>C1r</i>	Complement component 1, r subcomponent	–	1.56
<i>H2Q2 H2I9 H2D1</i>	MHC class Ib T9	–	1.54
<i>Fnl</i>	Fibronectin 1	–	1.53
<i>Cxcl17</i>	Chemokine (CXC motif) ligand 17	–	1.51
<i>H2T24</i>	Histocompatibility 2, T region locus 24	–	1.50
<i>Bpgm</i>	2,3 bisphosphoglycerate mutase	–	–1.62
<i>Cr2</i>	Complement receptor 2	–	–1.68
<i>Tnfrsf10</i>	TNF (ligand) superfamily, member 10	–	–1.72
<i>Cbfa2t3</i>	Core-binding factor, runt domain, α subunit 2, translocated to 3 (human)	–	–1.72
<i>Enpp2</i>	Ectonucleotide pyrophosphatase/phosphodiesterase 2	–	–1.74
<i>Ms4a1</i>	Membrane spanning 4 domains, subfamily A, member 1	–	–1.79
<i>Bank1</i>	B cell scaffold protein with ankyrin repeats 1	–	–1.80
<i>Itga1</i>	Integrin α 1	–	–1.82
<i>Lyz1</i>	Lysozyme 1	–	–1.94
<i>Cd209a</i>	CD209a Ag	–	–2.14
<i>Hc</i>	Hemolytic complement	–2.00	–5.56

Values represent mean fold changes compared with PBS ($n = 3$ mice/group).

$p < 0.05$, one-way ANOVA, Tukey post hoc test.

–, Genes that showed no significant regulation in that treatment group; F+H, Flu+HDM.

Based on the initial global gene-expression analysis, we sought to uncover potential pathways by which influenza may enhance allergen responsiveness. To this end, we analyzed in greater detail the biological roles of genes induced following influenza infection and, then, focused our analysis on specific gene classes that may facilitate innate responsiveness to allergen exposure. From a functional perspective, the gene-expression profile observed following Flu and Flu+HDM treatment showed that these genes pertained to a wide range of biological processes. Major categories included response to stimuli, stress, and wounding and genes mainly associated with inflammatory responses and chemotaxis (Fig. 4). Many of these processes were highly enriched with genes associated with the initiation of immune inflammatory responses encoding proteins for pattern recognition receptors and damage-associated molecular patterns, such as TLRs, CLRs, and several members of the complement pathway (Tables I, II). Among the TLRs, our study showed that Flu infection particularly led to increased and sustained expression of *TLR13*, a recently described member of the TLR family, shown to be expressed largely by myeloid cells, particularly dendritic cells (DCs) (20, 21). Similarly, we observed increased expression for a number of CLR family members, most notably Dectin 1 (*Clec7a*) and Dectin 2 (*Clec4n*) expressed on DCs and macrophages (22, 23). These receptors were shown to respond to complex carbohydrate structures, including glycans present on HDM aeroallergens, such as *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* (24). Interestingly, we detected increased expression of a number of FcR molecules, most notably *FcεR1*. Grayson et al. (25) reported, in a mouse model of sendai virus infection, increased type-1 IFN α -dependent upregulation of

FcεR1 on lung DCs, which, upon receptor cross-linking, led to the production of CCL28, a Th2-associated chemokine. Furthermore, evidence from a microarray analysis of PBMCs isolated during acute virus-associated asthma exacerbations from HDM-sensitized children, revealed increased *FcεR1* gene expression on monocytes and DCs (26); interestingly, this was associated with increased expression of *CCR2*, a chemokine receptor necessary for the recruitment of monocytes and DCs to inflamed tissues. In accordance with these findings, our study showed that influenza infection triggers the expression of *FcεR1* in the lung, along with concomitant increases in *CCR2* and type I IFN-stimulated genes (Table III). The nature of our study prevented identification of the specific cell types expressing these molecules. However, these findings collectively suggested that viral infections may amplify the allergic immune-inflammatory response through a mechanism that involves type-1 IFN and *FcεR1* and the recruitment of monocytes and DCs into the inflamed lung environment.

Lastly, our data revealed increased expression of several components of the complement pathway, most notably several *C1q* subunits (*C1qa*, *C1qb*, *C1qc*), *C3*, and *C3ar*, which are key components necessary for the generation and signaling of anaphylatoxins C3a and C5a. Anaphylatoxins are involved in the recruitment and activation of a number of leukocytes, including mast cells, eosinophils, and basophils, and were also implicated in the regulation of DC and T cell signaling (27). Thus, Flu infection enhanced the expression of a substantial number of innate molecules involved in the sensing and response to HDM.

Activation of innate-immune pathways through signaling of cell surface receptors leads to the recruitment of immune inflammatory

Table VII. Immune inflammatory genes with additional responsiveness to HDM in the lungs of mice infected with Flu and exposed to HDM for 6 d (LP)

Gene Symbol	Gene Name	Flu	F+H
<i>Igj</i>	Ig joining chain	9.61	11.17
<i>IghmAC38.205.12</i>	Ig μ chain V region AC38 205.12	8.72	10.80
<i>Saa3</i>	Serum amyloid A 3	5.88	10.61
<i>Cxcl10</i>	Chemokine (CXC motif) ligand 10	5.91	7.41
<i>Timp1</i>	Tissue inhibitor of metalloproteinase 1	5.27	6.82
<i>Cxcl13</i>	Chemokine (CXC motif) ligand 13	3.37	5.62
<i>Cxcl5</i>	Chemokine (CXC motif) ligand 5	2.33	4.18
<i>Irg1</i>	Immunoresponsive gene 1	–	2.22
<i>Orml</i>	Orosomucoid 1	–	1.91
<i>Itgax</i>	Integrin α X	–	1.79
<i>Mpa2l</i>	Guanylate binding protein 10	–	1.77
<i>Mpa2l</i>	Macrophage activation 2 like	–	1.74
<i>Oasl2</i>	2'5' oligoadenylate synthetase-like 2	–	1.73
<i>H2Eb1</i>	Histocompatibility 2, class II Ag E β	–	1.72
<i>Ccr2</i>	Chemokine (CC motif) receptor 2	–	1.72
<i>Cd274</i>	CD274 Ag	–	1.72
<i>Igbbp1</i>	Ig (CD79A) binding protein 1	–	1.71
<i>Ccl20</i>	Chemokine (CC motif) ligand 20	–	1.71
<i>Gbp2</i>	Guanylate binding protein 2	–	1.71
<i>Cfb</i>	Complement factor B	–	1.69
<i>Tnfrsf1b</i>	TNFR superfamily, member 1b	–	1.67
<i>Oasl1a</i>	2'5' oligoadenylate synthetase 1A	–	1.65
<i>H2Q8</i>	Histocompatibility 2, Q region locus 1	–	1.63
<i>Il2rg</i>	IL-2R, γ -chain	–	1.63
<i>Irf8</i>	IFN regulatory factor 8	–	1.61
<i>Vav1</i>	Vav 1 oncogene	–	1.61
<i>Gbp3</i>	Guanylate binding protein 3	–	1.61
<i>H2Q2 H2gs10 H2Q1</i>	Histocompatibility 2, Q region locus 5	–	1.61
<i>Il1f9</i>	IL-1 family, member 9	–	1.59
<i>H2Aa</i>	Histocompatibility 2, class II Ag A, α	–	1.59
<i>Ccl22</i>	Chemokine (CC motif) ligand 22	–	1.58
<i>Plek</i>	Pleckstrin	–	1.57
<i>Psmel</i>	Proteasome (prosome, macropain) 28 subunit, α	–	1.57
<i>Ptafr</i>	Platelet-activating factor receptor	–	1.57
<i>Fn1</i>	Fibronectin 1	–	1.56
<i>Lsp1</i>	Lymphocyte specific 1	–	1.54
<i>Sirpa</i>	Signal regulatory protein α	–	1.54
<i>Lax1</i>	Lymphocyte transmembrane adaptor 1	–	1.53
<i>Mx1</i>	Myxovirus (influenza virus) resistance 1	–	1.52
<i>Il18bp</i>	IL-18 binding protein	–	1.51
<i>Irf1</i>	IFN regulatory factor 1	–	1.51
<i>Pomp</i>	Proteasome maturation protein	–	1.51
<i>H2T24</i>	Histocompatibility 2, T region locus 24	–	–1.50
<i>Mfge8</i>	Milk fat globule EGF factor 8 protein	–	–1.53
<i>Ear2</i>	Eosinophil-associated, RNase A family, member 3	–	–1.56
<i>Alas2</i>	Aminolevulinic acid synthase 2, erythroid	–	–1.87

Values represent mean fold changes compared with PBS ($n = 3$ mice/group).

$p < 0.05$, one-way ANOVA, Tukey post hoc test.

–, Genes that showed no significant regulation in that treatment group; F+H, Flu+HDM.

cells capable of producing a plethora of cytokines. Consistent with our previous report of increased expression of proinflammatory cytokines and the accumulation of neutrophils, DCs, and monocytes into the lung of mice during the acute phase of the response (7), influenza infection at day 10 postinfection regulated the expression of a substantial number of chemokines and their receptors involved in the recruitment of various leukocytes, such as monocytes, macrophages, DCs' Th cells, eosinophils, and mast cells (Table III). The cytokine gene profile elicited by influenza reflects its potent Th1 cell-promoting effects, with strong induction of members of the type I IFN family, as well as proinflammatory cytokines, such as *TNF- α* and several members of the IL-1 family of proteins, including *IL-1 β* , *IL-18bp* and, notably, *IL-33* (7, 28) (Table IV). Interestingly, *IL-33* was shown to amplify both Th1- and Th2-type responses by targeting mast cells, basophils, and Th2 cells, as well as NK and NK T cells, hence suggesting an important role in asthma pathogenesis (29). Importantly, our study showed that this cytokine is also increased 7 d

following HDM exposure, and its expression is further enhanced in mice exposed to HDM in the context of an ongoing Flu infection. Thus, through the activation of innate and adaptive immune pathways, influenza infection induces a number of gene families involved in the initiation and propagation of a variety of Th-mediated inflammatory responses.

In addition to the pervasive upregulation of genes involved in innate immune responsiveness following influenza infection, we identified a subset of genes uniquely expressed as a result of Flu+HDM coexposure; these consisted of 366 and 263 genes during the EP and LP of the response, respectively (Table V, Supplemental Table I). Of these, 330 and 240 genes were identified as unique genes in mice exposed to Flu+HDM and were not expressed in any other treatment groups (Fig. 3). An additional 36 and 23 genes were shared among HDM-, Flu-, and Flu+HDM-treated groups; however, these shared genes were found to be significantly up- or downregulated in Flu-infected mice concurrently exposed to HDM. Although 30–40% of these genes do not have ascribed

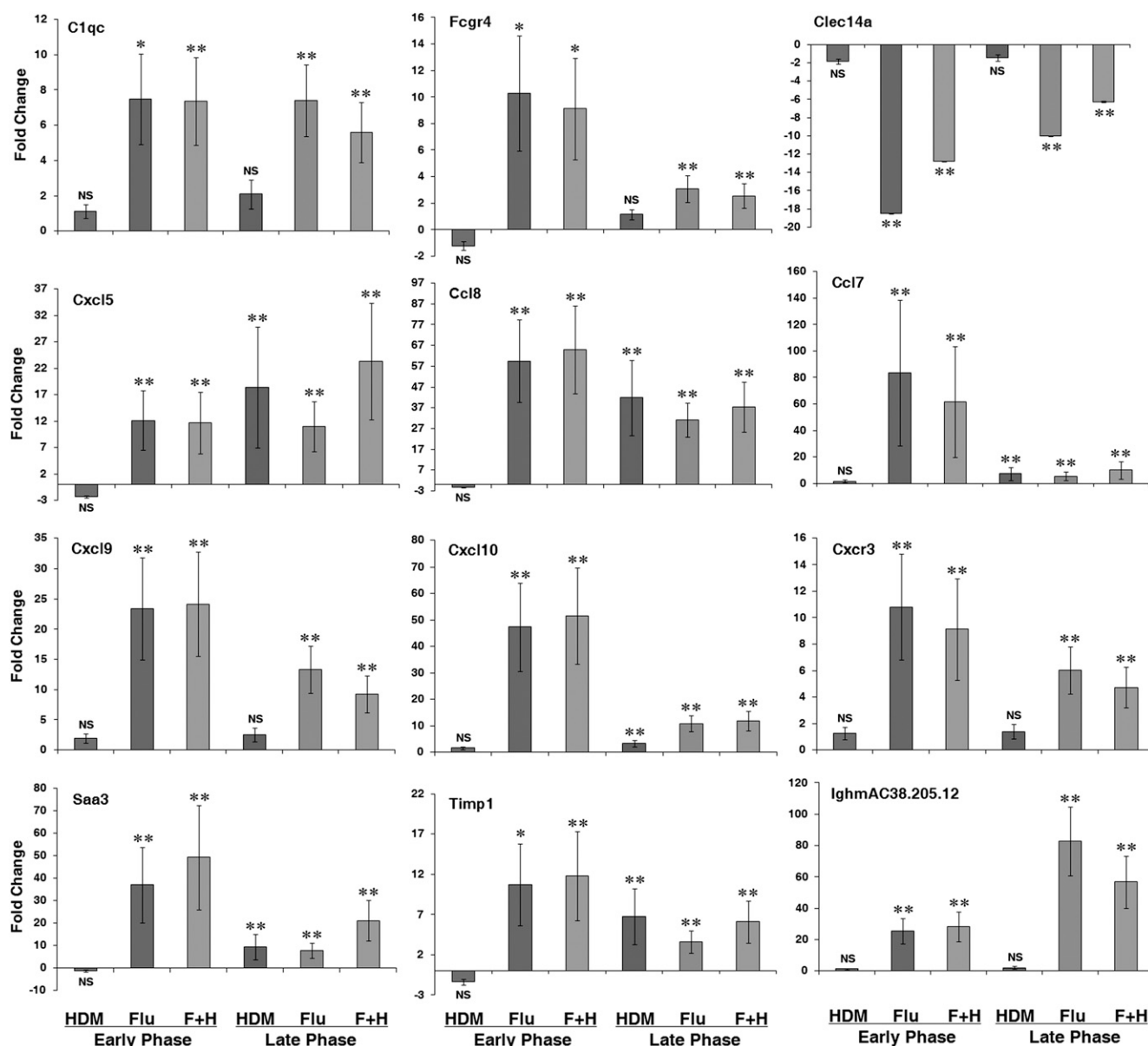


FIGURE 5. Representative genes from microarray experiment validated by qPCR. Data are expressed as mean $\pm$ SEM ($n = 4$). * $p < 0.05$, ** $p < 0.01$, pair-wise fixed reallocation randomization test.

functions, the remaining 60–70% are known to be involved in a wide range of biological processes; these could be divided into 13 functional categories, including immune inflammatory responses, intracellular signaling, metabolism, and transcriptional and translational regulation, as well as tissue/muscle development and reorganization. These data showed that a subclinical dose of HDM, which by itself did not lead to significantly altered gene expression, elicited distinct, unique changes when administered in the context of an ongoing Flu infection.

To further understand how the interaction between HDM and Flu affected gene expression from an immunological perspective, we evaluated the contribution of genes expressed within the functional group “immune inflammatory-responsive genes.” In addition to the increased expression of several members of the chemokine and cytokine family and genes encoding additional complement components, we particularly observed increased expression of genes encoding proteins, such as *Saa3*, *Timp1*, and serine peptidase inhibitor, clade A, member 3N (*Serpina3n*). Although *Timp1* was reported to play a role in extracellular matrix remodeling, and

its role in the development of allergic asthma is well described (30, 31), the functional role of *Serpina3n* has not been established. In humans, SERPIN3A, commonly known as antichymotrypsin, is produced by a variety of cell types, including hepatocytes and bronchial epithelial cells during acute inflammatory responses, and studies showed that serum levels of two other serpin family members, SERPINB3 and SERPINB4, are elevated in patients with asthma (32, 33). Interestingly, in a recent animal model of allergic asthma, the murine ortholog, *Serpina3ba*, was shown to mediate HDM-induced mucus production (34). Thus, our study suggested that, similar to other serpin family members, *Serpina3n* may likely play an important role in HDM-mediated allergic disease, particularly in the context of an acute viral infection.

Saa3, is a major acute-phase protein that can act as a chemo-attractant for phagocytes (35) and recently was shown to promote Th17-mediated allergic asthma through the activation of the NLRP3 inflammasome complex (36). Our data showed that this gene was significantly upregulated following Flu infection, with an additional 2-fold increase following HDM exposure during the

EP that was sustained through the LP, where we observed a 5-fold difference in expression level between Flu- and Flu+HDM-treated mice (Tables VI, VII). Interestingly, the expression of *Saa3* in the lung is regulated by *S100a8* (37), which was also found to be exclusively expressed in Flu+HDM-treated mice, albeit at lower levels. Indeed, S100A8 was recently identified as an important damage-associated molecular pattern released by activated phagocytes and was shown to be an endogenous activator of TLR4 on monocytes (38, 39). Although the functional role of *S100a8* remains to be elucidated, our findings intimate the potential importance of the *Saa3*–*S100a8* axis in allergic disease. Considering that S100A8 can activate TLR4 signaling, the increased expression of these genes may amplify inflammatory responses (40). Thus, HDM exposure in the context of a prior Flu infection leads to the expression of a number of unique immune genes that collectively function to either facilitate or amplify allergic inflammatory responses.

We describe the concentration of HDM used in this study as “subclinical” because, per se, it induced minimal immune-inflammatory responses and no airway physiological changes. In this study, we investigated the impact of an ongoing Flu infection on the response to such low concentration of HDM at the genomic level. Under these conditions, the phenotype elicited is characterized by robust allergic airway inflammation and airway hyperreactivity. Our data showed that the potential mechanisms by which Flu infection may facilitate this phenotype are manifold and impact different processes in the generation of allergic-inflammatory responses. A first repercussion may be conceptualized as a heightened state of immune alertness, illustrated by the enhanced expression of a number of innate molecules involved in Ag sensing. A second repercussion may be visualized as an amplification event exhibited by the enhanced expression of chemokines and chemokines receptors that facilitate the recruitment of a variety of immune-inflammatory cell types. We suggest that the overall consequence of these effects is a significant lowering of the threshold of allergen responsiveness required to manifest a clinically meaningful phenotype. Indeed, this outcome is depicted by the increased expression of molecules distinctly associated with features of the allergic phenotype. Clearly, the immune priming induced by Flu, and likely other respiratory viruses, is archetypically complex because it involves the expression of hundreds of genes and multiple interacting pathways and, moreover, additional posttranscriptional and translational regulation. Thus, it seems unlikely that the generation of an allergic phenotype under these conditions could be conceptualized linearly or attributed to a single critical signal. This notion has implications for the design and expectations of therapeutic strategies to prevent viral-induced allergic asthma.

Acknowledgments

We thank Tina Walker and Ashley E. Keller for technical help and Marie Bailey for administrative assistance.

Disclosures

A.A.H. and R.K. are employees of MedImmune, LLC. A.J.C. is an employee of Pfizer, Inc.

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Supplementary table 1: Differentially expressed genes that showed additional responsiveness to house dust mite exposure in the context of flu infection (Flu+HDM) during the early phase (EP) and late phase (LP).

Affy Transcript ID	Accession ID	Gene Name	Gene Symbol	Biological Function	Fold Change					
					HDM [EP]	Flu [EP]	Flu + HDM [EP]	HDM [LP]	Flu [LP]	Flu + HDM [LP]
Immune/Inflammatory Response										
10541644	NM_001170395	CD163 antigen	Cd163	Acute inflammatory response	-	-	2.54	-	-	-
10355403	NM_010233	Fibronectin 1	Fn1	Acute inflammatory response	-	-	1.53	-	-	1.56
10567995	NM_019738	Nuclear protein 1	Nupr1	Acute inflammatory response	-	-	1.62	-	-	-
10505438	NM_008768	Orosomucoid 1	Orm1	Acute inflammatory response	-	-	-	-	-	1.91
10563597	NM_011315	Serum amyloid A 3	Saa3	Acute inflammatory response	-	15.74	17.35	4.14	5.88	10.61
10398075	NM_009252	Serine (or cysteine) peptidase inhibitor, clade A, member 3N	Serpina3n	Acute inflammatory response	-	4.09	9.25	-	-	-
10541678	NM_023143	Complement component 1, r subcomponent	C1r	Adaptive immune response	-	-	1.56	-	-	-
10450344	NM_013484	Complement component 2 (within H2S)	C2	Adaptive immune response	-	-	1.78	-	-	-
10450325	NM_008198	Complement factor B	Cfb	Adaptive immune response	-	-	-	-	-	1.69
10361292	NM_007758	Complement receptor 2	Cr2	Adaptive immune response	-	-	-1.68	-	-	-
10450154	NM_010378	Histocompatibility 2, class II antigen A, alpha	H2Aa	Adaptive immune response	-	-	-	-	-	1.59
10481962	NM_010406	Hemolytic complement	Hc/C5	Adaptive immune response	-	-2.00	-5.56	-	-	-
10403018	---	Immunoglobulin heavy chain Ia	Igh-Ia	Adaptive immune response	-	2.96	4.94	-	-	-
10403015	---	Ig mu chain V region AC38 205.12	IghmAC38.205.12	Adaptive immune response	-	3.65	5.65	-	8.72	10.80
10566050	NM_010531	Interleukin 18 binding protein	Il18bp	Adaptive immune response	-	-	-	-	-	1.51
10415282	NM_011189	Proteasome (prosome, macropain) 28 subunit, alpha	Psme1	Antigen processing and presentation	-	-	-	-	-	1.57
10444298	NM_010382	Histocompatibility 2, class II antigen E beta	H2Eb1	Antigen processing and presentation of exogenous peptide antigen	-	-	-	-	-	1.72
10502335	NM_001033350	Bcell scaffold protein with ankyrin repeats 1	Bank1	B cell activation	-	-	-1.80	-	-	-

Affy Transcript ID	Accession ID	Gene Name	Gene Symbol	Biological Function	Fold Change					
					HDM [EP]	Flu [EP]	Flu + HDM [EP]	HDM [LP]	Flu [LP]	Flu + HDM [LP]
10600973	NM_008784	Immunoglobulin (CD79A) binding protein 1	Igbp1	B cell activation	-	-	-	-	-	1.71
10466172	NM_007641	Membranespanning 4domains, subfamily A, member 1	Ms4a1	B cell activation	-	-	-1.79	-	-	-
10560242	NM_001173550	Complement component 5a receptor 1	C5ar1	Chemotaxis	-	-	1.89	-	-	-
10347888	NM_016960	Chemokine (CC motif) ligand 20	Ccl20	Chemotaxis	-	-	-	-	-	1.71
10574213	NM_009137	Chemokine (CC motif) ligand 22	Ccl22	Chemotaxis	-	-	-	-	-	1.58
10379535	NM_021443	Chemokine (CC motif) ligand 8	Ccl8	Chemotaxis	-	11.81	9.78	-	-	-
10531415	NM_021274	Chemokine (CXC motif) ligand 10	Cxcl10	Chemotaxis	-	-	-	2.26	5.91	7.41
10561047	NM_153576	Chemokine (CXC motif) ligand 17	Cxcl17	Chemotaxis	-	-	1.51	-	-	-
10523120	NM_009141	Chemokine (CXC motif) ligand 5	Cxcl5	Chemotaxis	-	-	-	2.20	2.33	4.18
10414262	NM_007895	Eosinophilassociated, ribonuclease A family, member 3	Ear2	Chemotaxis	-	-	-	-	-	-1.56
10428619	NM_015744	Ectonucleotide pyrophosphatase/phosphodiesterase 2	Enpp2	Chemotaxis	-	-	-1.74	-	-	-
10347291	NM_009909	Interleukin 8 receptor, beta	Il8rb	Chemotaxis	-	-	1.63	-	-	-
10412298	NM_001033228	Integrin alpha 1	Itga1	Chemotaxis	-	-	-1.82	-	-	-
10559207	NM_019391	Lymphocyte specific 1	Lsp1	Chemotaxis	-	-	-	-	-	1.54
10493831	NM_013650	S100 calcium binding protein A8 (calgranulin A)	S100a8	Chemotaxis	-	-	1.70	-	-	-
10605338	NM_008062	Glucose6phosphate dehydrogenase Xlinked	G6pdx	Cytokine production	-	-	1.62	-	-	-
10508734	NM_001081211	Plateletactivating factor receptor	Ptafr	Cytokine production	-	-	-	-	-	1.57
10531407	NM_008599	Chemokine (CXC motif) ligand 9	Cxcl9	Defense response	-	14.50	12.93	-	-	-
10372652	NM_013590	Lysozyme 1	Lyz1	Defense response	-	-	-1.94	-	-	-
10441233	NM_010846	Myxovirus (influenza virus) resistance 1	Mx1	Defense response	-	-	-	-	-	1.52
10518300	NM_011610	Tumor necrosis factor receptor superfamily, member 1b	Tnfrsf1b	Defense response	-	-	-	-	-	1.67
10576784	NM_133238	CD209a antigen	Cd209a	Endocytosis	-	-	-2.14	-	-	-
10468898	NM_001159649	Lymphocyte transmembrane adaptor 1	Lax1	Immune effector process	-	-	-	-	-	1.53
10368289	NM_008813	Ectonucleotide pyrophosphatase/phosphodiesterase 1	Enpp1	Immune response	-	-	1.58	-	-	-
10496592	NM_010260	Guanylate binding protein 2	Gbp2	Immune response	-	-	-	-	-	1.71
10496580	NM_018734	Guanylate binding protein 3	Gbp3	Immune response	-	-	-	-	-	1.61
10444814	---	Histocompatibility 2, Q region locus 5	H2Q2 H2gs10 H2Q1	Immune response	-	-	-	-	-	1.61
10450699	AB359227	MHC class Ib T9	H2Q2 H2t9 H2D1	Immune response	-	-	1.54	-	-	-

Affy Transcript ID	Accession ID	Gene Name	Gene Symbol	Biological Function	Fold Change					
					HDM [EP]	Flu [EP]	Flu + HDM [EP]	HDM [LP]	Flu [LP]	Flu + HDM [LP]
10450675	NM_008207	Histocompatibility 2, T region locus 24	H2T24	Immune response	-	-	1.50	-	-	-1.50
10531126	NM_152839	Immunoglobulin joining chain	Igj	Immune response	-	-	-	-	9.61	11.17
10469786	NM_153511	Interleukin 1 family, member 9	Il1f9	Immune response	-	-	-	-	-	1.59
10531994	NM_194336	Guanylate binding protein 10	Mpa2l	Immune response	-	-	-	-	-	1.77
10532019	NM_001039647	Macrophage activation 2 like	Mpa2l	Immune response	-	-	-	-	-	1.74
10533256	NM_145211	2'5' oligoadenylate synthetase 1A	Oas1a	Immune response	-	-	-	-	-	1.65
10524621	NM_011854	2'5' oligoadenylate synthetaselike 2	Oasl2	Immune response	-	-	-	-	-	1.73
10527598	NM_025624	Proteasome maturation protein	Pomp	Immune response	-	-	-	-	-	1.51
10491091	NM_009425	Tumor necrosis factor (ligand) superfamily, member 10	Tnfsf10	Immune response	-	-	-1.72	-	-	-
10602372	NM_009653	Aminolevulinic acid synthase 2, erythroid	Alas2	Immune system development	-	-	-	-	-	-1.87
10537179	NM_007563	2,3bisphosphoglycerate mutase	Bpgm	Immune system development	-	-	-1.62	-	-	-
10582429	NM_009824	Corebinding factor, runt domain, alpha subunit 2, translocated to, 3 (human)	Cbfa2t3	Immune system development	-	-	-1.72	-	-	-
10590631	NM_009915	Chemokine (CC motif) receptor 2	Ccr2	Immune system development	-	-	-	-	-	1.72
10576034	NM_008320	Interferon regulatory factor 8	Irf8	Immune system development	-	-	-	-	-	1.61
10598976	NM_001044384	Tissue inhibitor of metalloproteinase 1	Timp1	Immune system development	-	8.01	10.07	3.55	5.27	6.82
10523359	NM_018866	Chemokine (CXC motif) ligand 13	Cxcl13	inflammatory response	-	-	-	1.64	3.37	5.62
10564713	NM_008594	Milk fat globuleEGF factor 8 protein	Mfge8	Phagocytosis	-	-	-	-	-	-1.53
10476021	NM_007547	Signalregulatory protein alpha	Sirpa	Phagocytosis	-	-	-	-	-	1.54
10446253	NM_011691	Vav 1 oncogene	Vav1	Phagocytosis	-	-	-	-	-	1.61
10444821	NM_023124	Histocompatibility 2, Q region locus 1	H2Q8	Regulation of cytokine production	-	-	-	-	-	1.63
10376060	NM_008390	Interferon regulatory factor 1	Irf1	Regulation of cytokine production	-	-	-	-	-	1.51
10557895	NM_021334	Integrin alpha X	Itgax	T cell proliferation	-	-	-	-	-	1.79
10384458	NM_019549	Pleckstrin	Plek	Platelet degranulation	-	-	-	-	-	1.57
10429140	NM_008681	Nmyc downstream regulated gene 1	Ndrp1	Mast cell activation	-	-	1.68	-	-	-
10416837	NM_008392	Immunoresponsive gene 1	Irg1	Response to molecule of bacterial origin	-	-	-	-	-	2.22
10606016	NM_013563	Interleukin 2 receptor, gamma chain	Il2rg	Positive regulation of immune system process	-	-	-	-	-	1.63

Affy Transcript ID	Accession ID	Gene Name	Gene Symbol	Biological Function	Fold Change					
					HDM [EP]	Flu [EP]	Flu + HDM [EP]	HDM [LP]	Flu [LP]	Flu + HDM [LP]
10462390	NM_021893	CD274 antigen	Cd274	Negative regulation of immune system process	-	-	-	-	-	1.72
Ion Transport/Binding										
10540241	NM_022992	ADPribosylation factorlike 6 interacting protein 5	Arl6ip5	Ion transport	-	-	1.55	-	-	-
10442691	NM_011930	Chloride channel 7	Clcn7	Ion transport	-	-	1.52	-	-	-
10562211	NM_052992	FXYP domaincontaining ion transport regulator 1	Fxyd1	Ion transport	-	-	-	-	-	-1.57
10385083	NM_146017	Gammaaminobutyric acid (GABA) A receptor, pi	Gabrp	Ion transport	-	-	-1.53	-	-	1.53
10607403	NM_175429	Potassium channel tetramerisation domain containing 12b	Kctd12b	Ion transport	-	-	-	-	-	-1.56
10431326	NM_133241	Megalencephalic leukoencephalopathy with subcortical cysts 1 homolog (human)	Mlc1	Ion transport	-	-	-1.65	-	-	-1.54
10483353	NM_009135	Sodium channel, voltagegated, type VII, alpha	Scn7a	Ion transport	-	-1.82	-3.45	-	-	-
10599719	NM_172780	Solute carrier family 9 (sodium/hydrogen exchanger), member 6	Slc9a6	Ion transport	-	-	-	-	-	-1.52
10356886	NM_172658	Solute carrier organic anion transporter family, member 4C1	Slco4c1	Ion transport	-	-	-1.71	-	-	-
10357239	NM_019432	Transmembrane protein 37	Tmem37	Ion transport	-	-	1.78	-	-	-
10439268	NM_001013371	Deltex 3like (Drosophila)	Dtx3l	Zinc ion binding	-	-	-	-	-	1.52
10466659	NM_010266	Guanine deaminase	Gda	Zinc ion binding	-	-	-	-	-	1.56
10509596	NM_025786	Ring finger protein 186	Rnf186	Zinc ion binding	-	-	-1.62	-	-	-
10399588	ENSMUST00000	Zinc finger protein 125	Zfp125	Zinc ion binding	-	-	-	-	-	1.61
10505270	NM_025286	Solute carrier family 31, member 2	Slc31a2	Transition metal ion transport	-	-	1.52	-	-	-
10470948	NM_013901	Solute carrier family 39 (zinc transporter), member 1	Slc39a1	Transition metal ion transport	-	-	1.58	-	-	-
10421309	NM_001135151	Solute carrier family 39 (zinc transporter), member 14	Slc39a14	Transition metal ion transport	-	-	-	-	-	1.67
10399854	NM_011867	Solute carrier family 26, member 4	Slc26a4	Sulfate transport	-	-	-	8.65	3.19	6.43
10502622	NM_017474	Chloride channel calcium activated 3	Clca3	Calcium ion transport	-	-	-	61.17	-	8.42
10363157	NM_001141927	Phospholamban	Pln	Calcium ion transport	-	-	-1.91	-	-	-
10521830	NM_026404	Solute carrier family 35, member A4	Slc35a4	Carbohydrate transport	-	-	-	-	-	-1.61

Affy Transcript ID	Accession ID	Gene Name	Gene Symbol	Biological Function	Fold Change					
					HDM [EP]	Flu [EP]	Flu + HDM [EP]	HDM [LP]	Flu [LP]	Flu + HDM [LP]
Lipid/Fatty Acid Metabolism										
10439442	NM_134102	Phospholipase A1 member A	Pla1a	Lipid catabolic process	-	2.45	6.00	-	-	-
10394538	NM_133360	Acetyl-Coenzyme A carboxylase alpha	Acaca	Lipid metabolism	-	-	-2.03	-	-	-
10580649	NM_133660	Esterase 22	Es22	Lipid metabolism	-	-	-1.98	-	-	-
10514221	NM_007408	Adipose differentiation related protein	Adfp	Lipid transport	-	-	1.92	-	-	-
10466606	NM_010730	Annexin A1	Anxa1	Lipid transport	-	-	-	-	-	1.65
10424695	NM_026730	GPIanchored HDLbinding protein 1	Gpihbp1	Lipid transport	-	-	-	-	-	-1.64
10475845	NM_028765	AcylCoenzyme A oxidaselike	Acox1	Fatty acid metabolic process	-	-2.15	-3.88	-	-	-
10387838	NM_145684	Arachidonate lipoxygenase, epidermal	Alox12e	Fatty acid metabolic process	-	-	-	1.75	2.88	4.56
10457071	NM_025797	Cytochrome b5	Cyb5	Fatty acid metabolic process	-	-	-1.58	-	-	-
10481518	NM_022415	Prostaglandin E synthase	Ptges	Fatty acid metabolic process	-	-	1.77	-	-	1.60
10467979	NM_009127	StearoylCoenzyme A desaturase 1	Scd1	Fatty acid metabolic process	-	-	-2.20	-	-	-
10474526	NM_207206	Lysophosphatidylcholine acyltransferase 4	Agpat7	Phospholipid metabolic process	-	-	-	-	-	1.52
10524698	NM_011107	Phospholipase A2, group IB, pancreas	Pla2g1b	Phospholipid metabolic process	-	-	-2.24	-	-	-
10516765	NM_172702	Serine incorporator 2	Serinc2	Phospholipid metabolic process	-	-	1.66	-	-	-
10565712	NM_025408	Alkaline ceramidase 3	Phca	Membrane lipid metabolic process	-	-	-	-	-	1.58
Transcription Regulation										
10391504	NM_010791	Mesenchyme homeobox 1	Meox1	Regulation of transcription	-	-	-1.68	-	-	-
10472514	NM_181547	Nitric oxide synthase trafficker	Nostrin	Regulation of transcription	-	-	-1.77	-	-	-
10520950	NM_016861	PDZ and LIM domain 1 (elfin)	Pdlim1	Regulation of transcription	-	-	-	-	-	1.53
10566926	NM_025999	Ring finger protein 141	Rnf141	Regulation of transcription	-	-	-1.65	-	-	-
10552740	---	Nucleoporin 62	Nup62	RNA localization	-	-	1.57	-	-	-
10574033	NM_172410	Nucleoporin 93	Nup93	RNA localization	-	-	1.60	-	-	-
10394353	NM_025323	RIKEN cdna 0610009D07 gene	0610009D07Rik	RNA processing	-	-	-	-	-	1.65
10397081	NM_027349	RNA binding motif protein 25	Rbm25	RNA processing	-	-	-	-	-	1.89
10358454	NM_001166409	RNA binding motif protein 3	Rbm3	RNA processing	-	-	-	-	-	1.55

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10501649	NM_025517	RNA terminal phosphate cyclase domain 1	Rtcd1	RNA processing	-	-	1.58	-	-	-
10529299	NM_009193	Stemloop binding protein	Slbp	RNA processing	-	-	-	-	-	1.79
10476620	NM_021335	U2 small nuclear ribonucleoprotein B	Snrpb2	RNA processing	-	-	-	-	-	1.54
10442341	NM_175229	Serine/arginine repetitive matrix 2	Srrm2	RNA processing	-	-	-1.50	-	-	-
10472605	NM_009278	Sjogren syndrome antigen B	Ssb	RNA processing	-	-	-	-	-	1.51
10541091	NM_026053	Gem (nuclear organelle) associated protein 6	Gemin6	RNA splicing	-	-	-	-	-	1.74
10392098	NM_025310	Ftsj homolog 3 (E. Coli)	Ftsj3	rRNA modification	-	-	1.63	-	-	-
10449971	NM_028543	Zinc finger protein 763	1700065O13R ik	Transcription	-	-	-1.68	-	-	-
10490302	NM_001162922	RIKEN cdna 2810021G02 gene	2810021G02R ik	Transcription	-	-	-1.59	-	-	-
10586064	NM_009672	Acidic (leucinerich) nuclear phosphoprotein 32 family, member A	Anp32a	Transcription	-	-	-1.63	-	-	-
10421950	NM_007826	Dachshund 1 (Drosophila)	Dach1	Transcription	-	-	-1.99	-	-	-
10375358	ENSMUST00000	Early Bcell factor 1	Ebf1	Transcription	-	-	-2.07	-	-	-
10358027	NM_001163131	E74like factor 3	Elf3	Transcription	-	-	1.50	-	-	-
10584142	NM_011808	E26 avian leukemia oncogene 1, 5' domain	Ets1	Transcription	-	-	-1.53	-	-	-
10404404	NM_010225	Forkhead box F2	Foxf2	Transcription	-	-	-	-	-	-1.61
10402063	BC029185	Forkhead box N3	Foxn3	Transcription	-	-	-1.50	-	-	-
10399897	NM_153198	High mobility group box transcription factor 1	Hbp1	Transcription	-	-	-	-	-	-1.54
10542750	NM_025315	Mediator complex subunit 21	Med21	Transcription	-	-	-	-	-	1.60
10507529	NM_020000	Mediator of RNA polymerase II transcription, subunit 8 homolog (yeast)	Med8	Transcription	-	-	-	-	-	1.54
10539574	NM_008723	Nucleoplasmin 3	Npm3ps1	Transcription	-	-	1.51	-	-	-
10510215	NM_001083918	RIKEN cdna 1700029I01 gene	OTTMUSG000 00010657	Transcription	-	-	-	-	-	1.73
10601878	NM_146236	Transcription elongation factor A (SII)like 1	Tceal1	Transcription	-	-	-2.21	-	-	-1.61
10543239	NM_031198	Transcription factor EC	Tcfec	Transcription	-	-	-	-	-	1.56
10566358	NM_009099	Tripartite motifcontaining 30	Trim30	Transcription	-	-	-	-	-	1.58
10442250	---	Zinc finger protein	---	Transcription	-	-	-1.62	-	-	-
10408693	NM_028784	Coagulation factor XIII, A1 subunit	F13a1	tRNA metabolic process	-	-	2.06	-	-	-
10432006	NM_019572	Histone deacetylase 7	Hdac7	Negative regulation of transcription from RNA polymerase II promoter	-	-	-1.50	-	-	-

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10417713	NM_011243	Retinoic acid receptor, beta	Rarb	Negative regulation of transcription from RNA polymerase II promoter	-	-	-1.53	-	-	-
10489127	NM_011249	Retinoblastomalike 1 (p107)	Rbl1	Negative regulation of transcription from RNA polymerase II promoter	-	-	-	-	-	1.55
10450501	NM_013693	Tumor necrosis factor	Tnf	Negative regulation of transcription from RNA polymerase II promoter	-	-	-	-	-	1.56
10491036	NM_026623	Nudix (nucleoside diphosphate linked moiety X)type motif 21	Nudt21	mRNA cleavage	-	-	-	-	-	1.60
Translation Regulation										
10397543	NM_001177565	eukaryotic translation initiation factor 1A	Eif1a	Translation	-	-	1.54	-	-	-
10396795	NM_026114	Eukaryotic translation initiation factor 2, subunit 1 alpha	Eif2s1	Translation	-	-	-	-	-	1.61
10578683	NM_026030	Eukaryotic translation initiation factor 2, subunit 2 (beta)	Eif2s2	Translation	-	-	-	-	-	1.65
10425226	NM_145139	Eukaryotic translation initiation factor 3, subunit L	Eif3eip	Translation	-	-	-	-	-	1.55
10407870	NM_029271	Mitochondrial ribosomal protein L32	Mrpl32	Translation	-	-	-	-	-	1.64
10497703	NM_029017	Mitochondrial ribosomal protein L47	Mrpl47	Translation	-	-	-	-	-	1.76
10450640	NM_025878	Mitochondrial ribosomal protein S18B	Mrps18b	Translation	-	-	-	-	-	1.54
10436694	NM_007475	Ribosomal protein, large, P0	Rplp0	Translation	-	-	1.52	-	-	-
10586604	NM_026467	Ribosomal protein S27like	Rps27l	Translation	-	-	1.64	-	-	-
10385043	NM_008722	Nucleophosmin 1	Npm1	Ribosome export from nucleus	-	-	-	-	-	1.62
10462623	NM_008331	Interferoninduced protein with tetratricopeptide repeats 1	Ifit1	Posttranslational modification, protein turnover, chaperones,	-	-	-	-	-	1.51
Cell Division/Cell Cycle Regulation										
10562709	NM_001111058	CD33 antigen	Cd33	Cell adhesion	-	-	1.56	-	-	-
10402211	NM_011812	Fibulin 5	Fbln5	Cell adhesion	-	-	-1.58	-	-	-
10584827	NM_007962	Myelin protein zerolike 2	Mpzl2	Cell adhesion	-	-	1.66	-	-	-
10449000	NM_018857	Mesothelin	Msln	Cell adhesion	-	-	2.46	-	-	-
10498018	NM_130448	Protocadherin 18	Pcdh18	Cell adhesion	-	-	-1.93	-	-	-
10392221	NM_008816	Platelet/endothelial cell adhesion molecule 1	Pecam1	Cell adhesion	-	-	-1.65	-	-	-
10492021	NM_015784	Periostin, osteoblast specific factor	Postn	Cell adhesion	-	-	-1.51	-	-	-

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10352792	XR_033810	predicted gene 10124	Gm10124	Cell cycle	-	-	1.50	-	-	-
10346810	NM_001081050	Par3 partitioning defective 3 homolog B (C. Elegans)	Pard3b	Cell cycle	-	-	-1.51	-	-	-
10358389	NM_009061	Regulator of Gprotein signaling 2	Rgs2	Cell cycle	-	-	-1.54	-	-	-
10493820	NM_011313	S100 calcium binding protein A6 (calcyclin)	S100a6	Cell cycle	-	-	2.11	-	-	-
10576140	NM_026014	Chromatin licensing and DNA replication factor 1	Cdt1	Cell cycle checkpoint	-	-	-	-	-	1.58
10456490	NM_027556	Centrosomal protein 192	Cep192	Cell cycle checkpoint	-	-	-	-	-	1.62
10586184	NM_025372	Timeless interacting protein	Tipin	Cell cycle checkpoint	-	-	-	-	-	1.89
10443463	NM_007669	Cyclindependent kinase inhibitor 1A (P21)	Cdkn1a	Cell cycle process	-	-	-	-	-	1.67
10497731	NM_026222	Coiledcoil domain containing 39	Ccdc39	Cell division and chromosome partitioning,	-	-	-1.57	-	-	-
10512470	NM_001110320	CD72 antigen	Cd72	Cell division and chromosome partitioning,	-	5.12	2.95	-	-	-
10515808	NM_026789	WD repeat domain 65	LOC674677	Cell division and chromosome partitioning,	-	-	-1.63	-	-	-
10422728	NM_023118	Disabled homolog 2 (Drosophila)	Dab2	Cell morphogenesis	-	-	1.50	-	-	-
10439514	NM_008083	Growth associated protein 43	Gap43	Cell morphogenesis	-	-	-1.93	-	-	-
10396421	NM_010431	Hypoxia inducible factor 1, alpha subunit	Hif1a	Cell morphogenesis	-	-	-	-	-	1.51
10519717	NM_009152	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	Sema3a	Cell morphogenesis	-	-	-1.57	-	-	-
10438049	NM_015773	Sperm associated antigen 6	Spag6	Cell motion	-	-	-1.50	-	-	-
10440794	NM_025642	RIKEN cdna 2610039C10 gene	2610039C10Rik	M phase of mitotic cell cycle	-	-	1.60	-	-	1.53
10605674	NM_008892	Polymerase (DNA directed), alpha 1	Pola1	S phase of mitotic cell cycle	-	-	-	-	-	1.73
10380067	NM_011129	Septin 4	Sep4	Germ cell development	-	-	-	-	-	-1.54
10492558	NM_133786	Structural maintenance of chromosomes 4	Smc4	Mitotic sister chromatid segregation	-	-	-	-	-	1.60
10409240	NM_013660	Sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	Sema4d	Positive regulation of cell development	-	-	-	-	-	1.60
10451993	NM_080837	DNA segment, Chr 17, Wayne State University 104, expressed	D17Wsu104e	Positive regulation of cell proliferation	-	-	1.52	-	-	-

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10371607	NM_027878	RIKEN cdna 1200002N14 gene	1200002N14Ri	Apoptosis	-	-	-1.51	-	-	-
10345666	NM_026850	Phosducinlike 3	Pdcl3	Apoptosis	-	-	-	-	-	1.54
10418480	NM_153547	Guanine nucleotide binding proteinlike 3 (nucleolar)	Gnl3	Regulation of cell proliferation	-	-	-	-	-	1.59
10534667	NM_008871	Serine (or cysteine) peptidase inhibitor, clade E, member 1	Serpine1	Regulation of cell proliferation	-	-	-	-	-	1.64
10436304	NM_001014423	ABI gene family, member 3 (NESH) binding protein	Abi3bp	Regulation of cellsubstrate adhesion	-	-2.46	-4.03	-	-	-
10474201	NM_008505	LIM domain only 2	Lmo2	Regulation of myeloid cell differentiation	-	-	-	-	-	-1.53
10379630	NM_011408	Schlafen 2	Slfn2	Negative regulation of cell proliferation	-	-	-	-	-	1.74
10558325	NM_025392	BRCA2 and CDKN1A interacting protein	Bccip	Regulation of cyclin-dependent protein kinase activity	-	-	-	-	-	1.52
Cell Signaling										
10473444	NM_011784	Apelin receptor	Agtrl1	Cell surface receptor linked signal transduction	-	-3.24	-4.92	-	-	-
10604375	NM_013912	Apelin	Apln	Cell surface receptor linked signal transduction	-	-	-1.61	-	-	-
10590623	NM_030712	Chemokine (CXC motif) receptor 6	Cxcr6	Cell surface receptor linked signal transduction	-	6.54	4.58	-	-	-
10348451	NM_007722	Chemokine (CXC motif) receptor 7	Cxcr7	Cell surface receptor linked signal transduction	-	-	1.69	-	-	-
10445953	NM_139138	EGFLike module containing, mucinlike, hormone receptorlike sequence 4	Emr4	Cell surface receptor linked signal transduction	-	-	-1.92	-	-	-1.67
10416340	NM_008115	Glial cell line derived neurotrophic factor family receptor alpha 2	Gfra2	Cell surface receptor linked signal transduction	-	-	-	-	-	-1.56
10502780	NM_001081298	Latrophilin 2	Lphn2	Cell surface receptor linked signal transduction	-	-	-1.65	-	-	-
10414271	NM_008964	Prostaglandin E receptor 2 (subtype EP2)	Ptger2	Cell surface receptor linked signal transduction	-	-	1.66	-	-	-

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10350733	NM_011267	Regulator of Gprotein signaling 16	Rgs16	Cell surface receptor linked signal transduction	-	-	-	-	-	1.54
10537789	NM_207028	Taste receptor, type 2, member 126	Tas2r126	Cell surface receptor linked signal transduction	-	-	-1.61	-	-	-
10418729	NM_009937	Collagenlike tail subunit (single strand of homotrimer) of asymmetric acetylcholinesterase	Colq	Cell-cell signaling	-	-	-	-	-	-1.73
10480459	NM_080462	Histamine Nmethyltransferase	Hnmt	Cell-cell signaling	-	-	-1.64	-	-	-
10433114	NM_010577	Integrin alpha 5 (fibronectin receptor alpha)	Itga5	Cell-substrate junction assembly	-	-	1.82	-	-	-
10574027	NM_013602	Metallothionein 1	Mt1	Cellular ion homeostasis	-	1.73	3.65	-	-	-
10574023	NM_008630	Metallothionein 2	Mt2	Cellular ion homeostasis	-	3.08	9.58	-	-	-
10450038	NM_020581	Angiopietinlike 4	Angptl4	Cellular response to starvation	-	-	1.70	-	-	-
10413419	NM_027871	Rho guanine nucleotide exchange factor (GEF) 3	Arhgef3	Intracellular signaling cascade	-	-	-1.51	-	-	-1.51
10352348	NM_030131	Cornichon homolog 4 (Drosophila)	Cnih4	Intracellular signaling cascade	-	-	1.55	-	-	-
10585982	NM_173018	myosin IXa	MYO9A	intracellular signaling cascade	-	-	-1.51	-	-	-
10476401	NM_019677	Phospholipase C, beta 1	Plcb1	Intracellular signaling cascade	-	-	-2.58	-	-	-
10578986	NM_030263	Pleckstrin and Sec7 domain containing 3	Psd3	Intracellular signaling cascade	-	-	-1.64	-	-	-
10497358	NM_001173460	Signalregulatory protein beta 1	Sirpb1	Intracellular signaling cascade	-	-	-	-	-	1.67
10472289	NM_011529	TRAF family memberassociated Nfkappa B activator	Tank	Intracellular signaling cascade	-	-	-	-	-	1.83
10496789	NM_022983	Lysophosphatidic acid receptor 3	Lpar3	MAPKKK cascade	-	-	-	-	-	-1.50
10536505	NM_008591	Met protooncogene	Met	MAPKKK cascade	-	-	-1.77	-	-	-
10606532	NM_021330	Acid phosphatase 1, soluble	Acp1	Protein amino acid dephosphorylation	-	-	1.55	-	-	-
10478897	NM_011201	Protein tyrosine phosphatase, nonreceptor type 1	Ptpn1	Protein amino acid dephosphorylation	-	-	1.67	-	-	-
10357191	NM_019933	Protein tyrosine phosphatase, nonreceptor type 4	Ptpn4	Protein amino acid dephosphorylation	-	-	-2.07	-	-	-
10513957	NM_011211	Protein tyrosine phosphatase, receptor type, D	Ptprd	Protein amino acid dephosphorylation	-	-	-1.85	-	-	-

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10412667	NM_008981	Protein tyrosine phosphatase, receptor type, G	Ptprg	Protein amino acid dephosphorylation	-	-	-1.51	-	-	-
10356880	NM_009183	ST8 alphaNacetylneuraminide alpha2,8sialyltransferase 4	St8sia4	Protein amino acid glycosylation	-	-	-1.78	-	-	-
10606235	NM_175358	Zinc finger, DHHC domain containing 15	Zdhhc15	Protein amino acid lipidation	-	-	1.55	-	-	-
10563014	NM_019830	Protein arginine Nmethyltransferase 1	Prmt1	Protein amino acid methylation	-	-	1.57	-	-	-
10532630	NM_177078	Adrenergic receptor kinase, beta 2	Adrbk2	Protein amino acid phosphorylation	-	-	-1.50	-	-	-
10443408	NM_011950	Mitogenactivated protein kinase 13	Mapk13	Protein amino acid phosphorylation	-	-	1.67	-	-	-
10461934	NM_153417	Transient receptor potential cation channel, subfamily M, member 6	Trpm6	Protein amino acid phosphorylation	-	-	-1.94	-	-	-
10498576	NM_016753	Latexin	Lxn	Sensory perception	-	-	-	-	-	1.56
10510197	NM_144880	protein phosphatase 2, regulatory subunit B (B56), alpha isoform	Ppp2r5a	Signal transduction	-	-	-1.51	-	-	-
10492798	NM_009144	Secreted frizzledrelated protein 2	Sfrp2	Response to extracellular stimulus	-	-	-1.55	-	-	-
10519527	NM_011076	ATP binding cassette, subfamily B (MDR/TAP), member 1A	Abcb1a	Response to inorganic substance	-	-	-1.56	-	-	-
10519555	NM_011075	ATP binding cassette, subfamily B (MDR/TAP), member 1B	Abcb1b	Response to inorganic substance	-	-	-	-	-	1.77
10409031	NM_025900	DEK oncogene (DNA binding)	Dek	Response to organic substance	-	-	-	-	-	1.53
10596575	NM_029103	Mesencephalic astrocytederived neurotrophic factor	Armet	Response to unfolded protein	-	-	1.58	-	-	1.70
10441718	NM_016694	Parkinson disease (autosomal recessive, juvenile) 2, parkin	Park2	Regulation of neurotransmitter levels	-	-	-1.53	-	-	-
10402435	NM_008458	Serine (or cysteine) peptidase inhibitor, clade A, member 3C	Serpina3c	Response to endogenous stimulus	-	-	1.59	-	-	-
Tissue/Muscle Development or Re-organization										
10414537	NM_021472	Angiogenin, ribonuclease, rnase A family, 5	Ang	Angiogenesis	-	-	-1.50	-	-	-
10401607	NM_008827	Placental growth factor	Pgf	Angiogenesis	-	-	-	-	-	1.53
10584288	NM_028783	Roundabout homolog 4 (Drosophila)	Robo4	Angiogenesis	-	-	-1.51	-	-	-
10490731	NM_009236	SRYbox containing gene 18	Sox18	Angiogenesis	-	-	-	-	-	-1.53
10404429	NM_009256	Serine (or cysteine) peptidase inhibitor, clade B, member 9	Serpinb9	Antiapoptosis	-	-	-	-	-	1.54
10458894	NM_010728	Lysyl oxidase	Lox	Blood vessel development	-	2.13	4.04	-	-	1.71

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10519886	NM_013657	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C	Sema3c	Blood vessel development	-	-	-1.80	-	-	-
10393449	NM_007707	Suppressor of cytokine signaling 3	Socs3	Blood vessel development	-	-	-	-	-	1.71
10489204	NM_009373	Transglutaminase 2, C polypeptide	Tgm2	Blood vessel development	-	-	1.74	-	-	-
10387932	NM_011072	Profilin 1	Pfn1	Embryonic epithelial tube formation	-	-	1.59	-	-	-
10575976	NM_030209	Cysteinerich secretory protein LCCL domain containing 2	Crispld2	Extracellular matrix organization	-	-	1.53	-	-	-
10559043	NM_010844	Mucin 5, subtypes A and C, tracheobronchial/gastric	Muc5ac	Extracellular matrix organization	-	-	-	6.94	-	2.33
10485982	NM_009608	Actin, alpha, cardiac muscle 1	Actc1	Cytoskeleton organization	-	-	-2.73	-	-	-
10534343	NM_007925	Elastin	Eln	Cytoskeleton organization	1.67	1.97	4.20	-	-	-
10412260	NM_008046	Follistatin	Fst	Hair follicle development	-	2.41	4.53	-	-	-
10391036	NM_008471	Keratin 19	Krt19	In utero embryonic development	-	-	1.67	-	-	-
10543273	NM_080285	Cortactin binding protein 2	Cttnbp2	Microtubule cytoskeleton organization	-	-	-	-	-	-1.60
10450605	NM_011655	Tubulin, beta 5	Tubb5	Microtubule cytoskeleton organization	-	-	-	-	-	1.63
10458428	NM_013840	Ubiquitously expressed transcript	Uxt	Microtubule cytoskeleton organization	-	-	1.50	-	-	-
10545515	NM_001164669	Dynein, axonemal, heavy chain 6	Dnahc6	Microtubule based process	-	-	-2.01	-	-	-
10354563	NM_001160386	Dynein, axonemal, heavy chain 7B	Dnahc7b	Microtubule based process	-	-	-1.58	-	-	-
10587107	NM_010864	Myosin VA	Myo5a	Regulation of action potential	-	-	-	-	-	1.75
10447708	NM_021881	Quaking	Qk	Regulation of action potential	-	-	-1.50	-	-	-
10406598	NM_172588	Serine incorporator 5	Serinc5	Regulation of action potential	-	-	-	-	-	-1.60
10354309	NM_007737	Collagen, type V, alpha 2	Col5a2	Skeletal system development	-	-	-	-	-	1.53

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10494548	NM_008121	Gap junction membrane channel protein alpha 5	Gja5	Skeletal system development	-	-	-2.14	-	-	-
10606714	NM_013463	Galactosidase, alpha	Gla	Skeletal system development	-	-	-	-	-	1.52
10445119	NM_013819	Histocompatibility 2, M region locus 3	H2M3	Skeletal system development	-	-	-	-	-	1.54
10520362	NM_153526	Insulin induced gene 1	Insig1	Skeletal system development	-	-	-	-	-	-1.74
10456046	NM_001146268	Platelet derived growth factor receptor, beta polypeptide	Pdgfrb	Skeletal system development	-	-	-	-	-	-1.50
10554693	NM_023377	Starrelated lipid transfer (START) domain containing 5	Stard5	Steroid biosynthetic process	-	-	1.54	-	-	-
10452815	NM_011723	Xanthine dehydrogenase	Xdh	Tissue homeostasis	-	-	1.54	-	-	-
10423388	NM_133365	Dynein, axonemal, heavy chain 5	Dnahc5	Ciliary or flagellar motility	-	-	-1.65	-	-	-
10493850	NM_011468	Small prolinerich protein 2A	Sprr2a	Ectoderm development	-	-	-	2.11	4.37	5.93
Carbohydrate Metabolism										
10471675	NM_025374	Glyoxalase 1	Glo1	Carbohydrate metabolic process	-	-	-	-	-	1.57
10422655	ENSMUST00000	Glyceraldehyde3phosphate dehydrogenase pseudogene	Gapdh	Carbohydrate Metabolism	-	-	1.55	-	-	-
10498405	NR_002890	glyceraldehyde-3-phosphate dehydrogenase	Gapdh LOC433845	Glucose metabolic process	-	-	1.51	-	-	-
10474239	ENSMUST00000	glyceraldehyde-3-phosphate dehydrogenase	Gm2606	Glucose metabolic process	-	-	-	-	-	1.58
10497321	NM_023418	phosphoglycerate mutase 1	Pgam1	Glucose metabolic process	-	-	1.71	-	-	-
10605571	NM_212444	Glycerol kinase	Gyk	Glycerol metabolic process	-	-	-	-	-	1.65
10595718	NM_018763	Carbohydrate sulfotransferase 2	Chst2	Monosaccharide metabolic process	-	-	-1.62	-	-	-
10473240	NM_023119	Enolase 1, alpha nonneuron	Eno1	Monosaccharide metabolic process	-	-	-	-	-	1.63
10368612	NM_008084	Glyceraldehyde3phosphate dehydrogenase	Gapdh	Monosaccharide metabolic process	-	-	-	-	-	1.59
10458547	NM_011937	Glucosamine6phosphate deaminase 1	Gnpda1	Monosaccharide metabolic process	-	-	1.54	-	-	-
10585932	NM_011099	Pyruvate kinase, muscle	Pkm2	Monosaccharide metabolic process	-	-	1.75	-	-	-
10502522	NM_011828	Heparan sulfate 2 O sulfotransferase 1	Hs2st1	Polysaccharide biosynthetic process	-	-	-1.61	-	-	-
10349968	NM_007695	Chitinase 3 like 1	Chi3l1	Polysaccharide catabolic process	-	-	-2.28	-	-	-

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10501020	NM_009892	Chitinase 3 like 3	Chi3l3	Polysaccharide catabolic process	-	-	2.13	-	-	-
10501026	NM_145126	Chitinase 3 like 4	Chi3l4	Polysaccharide catabolic process	-	-	-	9.65	-	2.69
10413615	NM_018746	Inter alphasubtrypsin inhibitor, heavy chain 4	Itih4	Polysaccharide metabolic process	-	-	-2.08	-	-	-
10458569	NM_008173	Nuclear receptor subfamily 3, group C, member 1	Nr3c1	Regulation of carbohydrate metabolic process	-	-	-1.74	-	-	-
Protein or Amino Acid Metabolism/Regulation										
10368343	NM_007482	Arginase, liver	Arg1	Arginine metabolic process	-	1.82	3.83	-	-	-
10487011	NM_025961	Glycine amidinotransferase (Larginine:glycine amidinotransferase)	Gatm	Cellular amino acid derivative metabolic process	-	6.96	4.89	-	-	-
10345203	NM_153783	Polyamine oxidase (exoN4amino)	Paox	Cellular amino acid derivative metabolic process	-	-	1.57	-	-	-
10362129	NM_011979	Vanin 3	Vnn3	Cellular amino acid derivative metabolic process	-	-	-	-	-	1.57
10546113	NM_016906	Sec61 alpha 1 subunit (S. Cerevisiae)	Sec61a1	Intracellular protein transport	-	-	1.54	-	-	-
10360225	NM_016897	Translocase of inner mitochondrial membrane 23 homolog (yeast)	Timm23	Intracellular protein transport	-	-	1.52	-	-	1.60
10539119	NM_019802	Gammaglutamyl carboxylase	Ggcx	Peptidylglutamic acid carboxylation	-	-	-1.65	-	-	-
10543686	NM_009459	Ubiquitin-conjugating enzyme E2H	Ube2h	Protein catabolic process	-	-	-1.54	-	-	-
10469712	NM_019501	Prenyl (solanesyl) diphosphate synthase, subunit 1	Pdss1	Protein complex assembly	-	-	1.78	-	-	-
10434675	NM_026400	Dnaj (Hsp40) homolog, subfamily B, member 11	Dnajb11	Protein folding	-	-	-	-	-	1.53
10381122	NM_010221	FK506 binding protein 10	Fkbp10	Protein folding	-	-	1.78	-	-	-
10544885	NM_153573	FK506 binding protein 14	Fkbp14	Protein folding	-	-	1.82	-	-	-
10449452	NM_010220	FK506 binding protein 5	Fkbp5	Protein folding	-	2.06	5.76	-	-	1.62
10359034	NM_001024945	Quiescin Q6 sulfhydryl oxidase 1	Qsox1	Protein folding	-	-	1.91	-	-	-
10415844	NM_007798	Cathepsin B	Ctsb	Proteolysis	-	-	-	-	-	1.52
10410124	NM_009984	Cathepsin L	Ctsl	Proteolysis	-	-	1.89	-	-	-
10490212	NM_022325	Cathepsin Z	Ctsz	Proteolysis	-	-	-	-	-	1.64
10581434	NM_176913	Dipeptidase 2	Dpep2	Proteolysis	-	-	1.80	-	-	-
10406817	NM_007930	Ectodermalneural cortex 1	Enc1	Proteolysis	-	-	1.76	-	-	-

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10427904	BC050864	Fbox and leucinerich repeat protein 7	Fbxl7	Proteolysis	-	-	-1.55	-	-	-
10583056	NM_008605	Matrix metallopeptidase 12	Mmp12	Proteolysis	-	-	-	-	3.30	4.62
10570855	NM_008872	Plasminogen activator, tissue	Plat	Proteolysis	-	-	2.05	-	-	-
10448409	NM_133731	Protease, serine, 22	Prss22	Proteolysis	-	-	2.01	-	-	1.60
10585474	NM_011966	Proteasome (prosome, macropain) subunit, alpha type 4	Psma4	Proteolysis	-	-	-	-	-	1.62
10365426	NM_011967	Proteasome (prosome, macropain) subunit, alpha type 5	Psma5	Proteolysis	-	-	-	-	-	1.52
10508182	NM_011970	Proteasome (prosome, macropain) subunit, beta type 2	Psmb2	Proteolysis	-	-	1.53	-	-	1.66
10380815	NM_011971	Proteasome (prosome, macropain) subunit, beta type 3	Psmb3	Proteolysis	-	-	1.56	-	-	-
10419810	NM_011186	Proteasome (prosome, macropain) subunit, beta type 5	Psmb5	Proteolysis	-	-	1.56	-	-	-
10561679	NM_026545	Proteasome (prosome, macropain) 26S subunit, nonatpase, 8	Psmd8	Proteolysis	-	-	1.56	-	-	-
10354191	NM_001033135	Ring finger protein 149	Rnf149	Proteolysis	-	-	-	-	-	1.55
10389719	NM_029023	Serine carboxypeptidase 1	Scpep1	Proteolysis	-	-	1.58	-	-	-
10520124	NM_133354	SMT3 suppressor of mif two 3 homolog 2 (yeast)	Sumo2	Proteolysis	-	-	-	-	-	1.50
10516735	NM_023476	Tubulointerstitial nephritis antigenlike 1	Tinagl	Proteolysis	-	-	2.00	-	-	-
10394532	NM_026454	Ubiquitinconjugating enzyme E2F (putative)	Ube2f	Proteolysis	-	-	-	-	-	1.70
10350489	NM_019562	Ubiquitin carboxylterminal esterase L5	Uchl5	Proteolysis	-	-	1.53	-	-	1.80
10599369	NM_009688	Xlinked inhibitor of apoptosis	Xiap	Proteolysis	-	-	-1.51	-	-	-
10412251	NM_010887	NADH dehydrogenase (ubiquinone) FeS protein 4	Ndufs4	Regulation of protein amino acid phosphorylation	-	-	-	-	-	1.57
10492689	NM_019971	Platelet derived growth factor, C polypeptide	Pdgfc	Regulation of protein amino acid phosphorylation	-	-	1.60	-	-	-
10583021	NM_027924	Platelet derived growth factor, D polypeptide	Pdgfd	Regulation of protein amino acid phosphorylation	-	-	-2.30	-	-	-
10408557	NM_025429	Serine (or cysteine) peptidase inhibitor, clade B, member 1a	Serpinb1a	Regulation of protein catabolic process	-	-	-1.61	-	-	-
10365769	NM_010401	Histidine ammonia lyase	Hal	Histidine metabolic process	-	3.28	4.78	-	-	-

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Protein Transport										
10498024	NM_011990	Solute carrier family 7 (cationic amino acid transporter, y+ system), member 11	Slc7a11	Amino acid transport	-	-	-	-	-	2.21
10582275	NM_011404	Similar to solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Slc7a5	Amino acid transport	-	-	-	-	-	1.54
10574985	NM_178798	Solute carrier family 7 (cationic amino acid transporter, y+ system), member 6	Slc7a6	Amino acid transport	-	-	1.87	-	-	-
10462822	NM_175353	Exocyst complex component 6	Exoc6	Exocytosis	-	-	-1.51	-	-	-
10374106	NM_019661	YKT6 homolog (S. Cerevisiae)	Ykt6	Exocytosis	-	-	1.50	-	-	-
10531383	NM_172713	SDA1 domain containing 1	Sdad1	Protein localization	-	-	-	-	-	1.60
10538290	NM_028035	Sorting nexin 10	Snx10	Protein localization	-	-	-	-	-	1.73
10488237	NM_024225	Sorting nexin 5	Snx5	Protein localization	-	-	-	-	-	1.51
10501762	NM_029655	Sorting nexin 7	Snx7	Protein localization	-	-	-	-	-	1.53
10420637	NM_008466	Karyopherin (importin) alpha 3	Kpna3	Protein targeting	-	-	-	-	-	1.61
10346634	NM_018868	NOP58 ribonucleoprotein homolog (yeast)	Nol5	Protein targeting	-	-	-	-	-	1.79
10606689	NM_013898	Translocase of inner mitochondrial membrane 8 homolog a1 (yeast)	Timm8a1	Protein targeting	-	-	1.58	-	-	-
10477370	NM_024214	Similar to Translocase of outer mitochondrial membrane 20 homolog (yeast)	Tomm20	Protein targeting	-	-	-	-	-	1.87
Other Metabolic Processes										
10433494	NM_011955	Nucleotide binding protein 1	Nubp1	Cofactor metabolic process	-	-	1.62	-	-	-
10414522	NM_009687	Apurinic/apyrimidinic endonuclease 1	Apex1	DNA metabolic process	-	-	1.59	-	-	-
10451225	NM_030715	Polymerase (DNA directed), eta (RAD 30 related)	Polh	DNA metabolic process	-	-	1.61	-	-	-
10461487	NM_201351	Cytochrome b, ascorbate dependent 3	Cybasc3	Generation of precursor metabolites and energy	-	-	-	-	-	-1.61
10353624	---	NADHubiquinone oxidoreductase chain 4L	ND4L	Generation of precursor metabolites and energy	-	-	-1.79	-	-	-
10598067	---	Predicted gene 4076	ND5	Generation of precursor metabolites and energy	-	-	-1.56	-	-	-

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10452525	NM_028388	NADH dehydrogenase (ubiquinone) flavoprotein 2	Ndufv2	Generation of precursor metabolites and energy	-	-	-	-	-	1.55
10536931	NM_021414	Sadenosylhomocysteine hydrolaselike 2	Ahcyl2	One-carbon metabolic process	-	-	-1.51	-	-	-
10490913	NM_007606	Carbonic anhydrase 3	Car3	One-carbon metabolic process	-	-2.38	-5.61	-	-	-
10556302	NM_009667	Adenosine monophosphate deaminase 3	Ampd3	Purine base metabolic process	-	-	1.65	-	-	-
10413086	NM_134079	Adenosine kinase	Adk	Purine nucleotide metabolic process	-	-	-1.55	-	-	-
10587639	NM_011851	5' nucleotidase, ecto	Nt5e	Purine nucleotide metabolic process	-	-	1.53	-	-	-
10515164	NM_025647	Cytidine monophosphate (UMPCMP) kinase 1	Cmpk1	Pyrimidine nucleotide metabolic process	-	-	-	-	-	1.65
10395039	NM_020557	Cytidine monophosphate (UMPCMP) kinase 2, mitochondrial	Cmpk2	Pyrimidine nucleotide metabolic process	-	-	1.57	-	-	-
10515943	NM_016748	Cytidine 5'triphosphate synthase	Ctps	Pyrimidine nucleotide metabolic process	-	-	-	-	-	1.71
10427461	NM_001136079	Prostaglandin E receptor 4 (subtype EP4)	Ptger4	Regulation of nucleotide metabolic process	-	-	-	-	-	1.64
10561008	NM_001039185	Carcinoembryonic antigenrelated cell adhesion molecule 1	Ceacam1	Regulation of phosphate metabolic process	-	-	-	-	-	1.51
10395273	BC052902	Gangliosideinduced differentiationassociatedprotein 10	Gdap10	Response to nutrient	-	-	1.51	-	-	-
10472538	NM_175512	Dehydrogenase/reductase (SDR family) member 9	Dhrs9	Retinoid metabolic process	-	-	1.81	-	-	-
10463836	NM_010362	Glutathione Stransferase omega 1	Gsto1	Vitamin metabolic process	-	-	1.59	-	-	-
10483439	NM_001081088	Low density lipoprotein receptorrelated protein 2	Lrp2	Vitamin metabolic process	-	-	-1.72	-	-	-
10453057	NM_009994	Cytochrome P450, family 1, subfamily b, polypeptide 1	Cyp1b1	Xenobiotic metabolic process	-	-	2.03	-	-	-
Nucleotide/DNA/Chromosome Binding										
10472782	NM_026115	Histone aminotransferase 1	Hat1	Chromatin organization	-	-	-	-	-	1.83
10530759	NM_080560	Ubiquitinconjugating enzyme E2N	Ube2n	DNA doublestrand break processing	-	-	-	-	-	1.66
10494407	NM_175666	Histone cluster 1, h2bg	Hist2h2bb	DNA packaging	-	-	1.55	-	-	-
10500333	NM_033596	Histone cluster 1, h4k	Hist2h4	DNA packaging	-	-	1.72	-	-	-

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10505894	NM_024433	Methylthioadenosine phosphorylase	Mtap	Nucleoside metabolic	-	-	-	-	-	1.54
10607877	NM_026662	Phosphoribosyl pyrophosphate synthetase 2	Prps2	Nucleoside metabolic process	-	-	-1.59	-	-	-
10381458	NR_004414	U2 small nuclear RNA	Rnu2	Nucleotide binding	-	-	-	-	-	2.22
10523012	NM_007832	Deoxycytidine kinase	Dck	Nucleotide transport and metabolism	-	-	-	-	-	1.62
10359851	NM_030724	Uridine-cytidine kinase 2	Uck2	Nucleotide transport and metabolism	-	-	1.70	-	-	-
Others										
10542953	NM_009364	Tissue factor pathway inhibitor 2	Tfpi2	Blood coagulation	-	-	1.62	-	-	1.62
10395365	NM_011783	Anterior gradient 2 (xenopus laevis)	Agr2	Body fluid secretion	-	-	-	5.41	1.92	4.33
10533504	NM_009879	Intraflagellar transport 81 homolog (chlamydomonas)	lft81	Gamete generation	-	-	-1.54	-	-	-
10432986	NM_153416	Achalasia, adrenocortical insufficiency, alacrimia	Aaas	Nucleocytoplasmic transport	-	-	1.73	-	-	-
10537146	NM_008012	Aldoketo reductase family 1, member b8	Akr1b8	Oxidation reduction	-	-	1.50	-	-	-
10346410	NM_023617	Aldehyde oxidase 3	Aox3	Oxidation reduction	-	-3.45	-5.64	-	-	-
10551226	NM_009997	Cytochrome p450, family 2, subfamily a, polypeptide 21, pseudogene	Cyp2a4 Cyp2a5	Oxidation reduction	-	-	-	-	-	-1.61
10367691	NM_027391	Iodotyrosine deiodinase	lyd	Oxidation reduction	-	-	-1.67	-	-	-
10518408	NM_011122	Procollagenlysine, 2oxoglutarate 5dioxygenase 1	Plod1	Oxidation reduction	-	-	1.72	-	-	-
10545682	NM_183138	Tet oncogene family member 3	Tet3	Oxidation reduction	-	-	-1.51	-	-	-
10537316	NM_009729	ATPase, h+ transporting, lysosomal v0 subunit c atpase, h+ transporting, lysosomal v0 subunit c, pseudogene 2	Atp6v0c Atp6v0c-ps2	Oxidative phosphorylation	-	-	1.66	-	-	-
10479411	NM_031373	Opioid growth factor receptor	Ogfr	Regulation of growth	-	-	1.58	-	-	-
10414202	NM_023134	Surfactant associated protein a1	Sftpa1	Respiratory gaseous exchange	-	-	-1.79	-	-	-
10492682	NM_133187	Riken cDNA 1110032e23 gene	1110032E23Ri	-	-	-	-	-	-	-1.54
10588109	NR_028123	Riken cDNA 1600029i14 gene	1600029I14Ri	-	-	-	-1.58	-	-	-
10481272	BC099566	Riken cDNA 1700007k13 gene	1700007K13Ri	-	-	-	-1.50	-	-	-
10565241	NM_029335	Riken cDNA 1700026d08 gene	1700026D08Ri	-	-	-	-1.72	-	-	-

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10354275	BC119032	Riken cDNA 1700029f09 gene	1700029F09Rik	-	-	-	-	-	-	1.94
10493626	NM_028567	Riken cDNA 1700094d03 gene	1700094D03Rik	-	-	-	-1.58	-	-	-
10565210	NM_177894	Family with sequence similarity 154, member b	1700129I04Rik	-	-	-	-1.52	-	-	-
10569877	NM_026985	Riken cDNA 1810033b17 gene	1810033B17Rik	-	-	-	1.52	-	-	-
10526452	NM_027158	Riken cDNA 2310043j07 gene	2310043J07Rik	-	-	-	1.68	-	-	-
10485378	NM_001083810	Proline rich 5 like	2600010E01Rik	-	-	-	-1.83	-	-	-
10415377	NM_026403	Riken cDNA 2610027l16 gene	2610027L16Rik	-	-	-	1.50	-	-	-
10601335	BC035042	WD repeat domain 43	2610029G23Rik	-	-	-	-	-	-	1.50
10595614	BC032970	Riken cDNA 2810026p18 gene	2810026P18Rik	-	-	-	1.53	-	-	-
10436598	---	Riken cDNA 2810055g20 gene	2810055G20Rik	-	-	-	-1.70	-	-	-
10397230	NM_028377	Riken cDNA 2900006k08 gene	2900006K08Rik	-	-	-	-1.51	-	-	-
10368041	NM_028440	Riken cDNA 3110003a17 gene	3110003A17Rik	-	-	-	-	-	-	1.76
10425903	---	Riken cDNA 3110043j09 gene similar to glyceraldehyde-3-phosphate dehydrogenase (gapdh)	3110043J09Rik	-	-	-	-	-	-	1.66
10374578	NM_028672	Family with sequence similarity 161, member a	4930430E16Rik	-	-	-	-1.58	-	-	-
10438178	NM_029053	Riken cDNA 4930451c15 gene	4930451C15Rik	-	-	-	-1.55	-	-	-
10371916	ENSMUST00000	(Riken cDNA 4930485b16 gene	4930485B16Rik	-	-	-	-1.51	-	-	-
10527285	ENSMUST00000	(Radial spoke head 10 homolog b (chlamydomonas)	4930526H21Rik	-	-	-	-1.67	-	-	-
10476795	BC048610	Riken cDNA 4930529m08 gene	4930529M08Rik	-	-	-	-1.54	-	-	-
10562368	BC060233	Riken cDNA 4931406p16 gene	4931406P16Rik	-	-	-	-1.52	-	-	-
10439881	NR_028300	Riken cDNA 5330426p16 gene	5330426P16Rik	-	-	-	-1.53	-	-	-

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10586484	NM_026635	Family with sequence similarity 96, member a	5730536A07Ri	-	-	-	-	-	-	1.59
10584561	NM_133733	Riken cDNA 9030425e11 gene	9030425E11Ri	-	-	-	1.68	-	-	-
10488409	NM_029960	Riken cDNA 9230104l09 gene	9230104L09Ri	-	-	-2.23	-3.80	-	-	-
10577388	NM_001039553	RIKEN cDNA 4930467E23 gene pr	4930467E23Ri	-	-	-	-1.56	-	-	-
10466963	NM_172836	Riken cDNA 9930021j03 gene	9930021J03Ri	-	-	-	-1.51	-	-	-
10356271	NM_213615	RIKEN cDNA A530032D15Rik gene	A530032D15Ri	-	-	-	-	-	-	1.71
10519951	NM_175437	Pigeon homolog (drosophila)	A530088l07Ri	-	-	-	-1.51	-	-	-
10355998	ENSMUST00000	Family with sequence similarity 124, member b	A830043J08Ri	-	-	-	-	-	-	-1.51
10443027	NM_029870	Riken cDNA a930001n09 gene	A930001N09Ri	-	-	-	-1.63	-	-	-
10356995	---	Ensmusg00000073605	AC157923.3	-	-	-	-1.65	-	-	-
10415019	---	---	AK030929	-	-	-	-	-	-	1.50
10421749	NM_001164503	A kinase (prka) anchor protein 11	Akap11	-	-	-	-1.52	-	-	-
10604094	NM_001033785	A kinase (prka) anchor protein 14	Akap14	-	-	-	-1.66	-	-	-
10449854	NM_017476	A kinase (prka) anchor protein 8like	Akap8l	-	-	-	-1.55	-	-	-
10479979	NM_138756	Ensmusg00000082953	AL929440.1	-	-	-	-1.80	-	-	-
10578515	NM_001039562	Ankyrin repeat domain 37	Ankrd37	-	-	-	-	-	-	1.52
10439009	NM_007470	Apolipoprotein d	Apod	-	-	-	1.66	-	-	-
10538753	NM_028035	Atonal homolog 1 (Drosophila)	Atoh1	-	-	-	-	-	-	1.63
10570201	NM_015804	ATPase, class vi, type 11a	Atp11a	-	-	-	-1.54	-	-	-
10516966	NM_001033308	cDNA sequence bc013712	BC013712	-	-	-	-	-	-	1.50
10500276	BC028528	cDNA sequence bc028528	BC028528	-	-	-	-1.67	-	-	-
10584691	NM_001081369	Coiledcoil domain containing 153	BC038167	-	-	-	-1.50	-	-	-
10521667	NM_009763	Bone marrow stromal cell antigen 1	Bst1	-	-	-	1.66	-	-	-
10388010	NM_007573	Complement component 1, q subcomponent binding protein	C1qbp	-	-	-	1.59	-	-	-
10404939	ENSMUST00000	(Riken cDNA 2010001k21 gene	C78339	-	-	-	-	-	-	-1.62
10519855	NM_001110843	Calcium channel, voltage-dependent, alpha2/delta subunit 1	Cacna2d1	-	-	-	-1.59	-	-	-
10586118	NM_138304	Calmodulinlike 4	Calml4	-	-	-	-1.66	-	-	-
10509568	NM_025451	Calcium/calmodulindependent protein kinase ii inhibitor 1	Camk2n1	-	-	-	-	-	-	-1.56
10475378	NM_177054	Cancer susceptibility candidate 4	Casc4	-	-	-	-1.72	-	-	-
10536273	NM_145398	Cas1 domain containing 1	Casd1	-	-	-	-1.63	-	-	-

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10474437	NM_026613	Coiledcoil domain containing 34	Ccdc34	-	-	-	1.52	-	-	-
10596222	NM_145700	Chemokine (c-c motif) receptor-like 1	Ccr1	-	-	-	-	-	-	-1.75
10435907	NM_021325	Cd200 receptor 1	Cd200r1	-	-	-	-	-	-	1.54
10482920	NM_025422	Cd302 antigen	Cd302	-	-	-	1.54	-	-	1.50
10588091	NM_023873	Centrosomal protein 70	Cep70	-	-	-	-1.98	-	-	-
10384956	NM_026527	Chac, cation transport regulator homolog 2 (e. Coli)	Chac2	-	-	-	-	-	-	1.67
10380398	NM_007689	Chondroadherin	Chad	-	-	-	-1.79	-	-	-
10347915	NM_001081746	Predicted gene 2635	Csprs	-	-	-	-	-	-	1.51
10582879	NM_033616	Component of sp100-rs	Csprs	-	-	-	-	-	-	1.50
10409876	NM_007796	Cytotoxic t lymphocyteassociated protein 2 alpha	Ctla2a	-	-	-	-1.62	-	-	-
10551282	NM_007812	Similar to cytochrome p450 2a5 (cyp1a5) (coumarin 7-hydroxylase) (p450-15-coh) (p450-ia3.2)	Cyp2a5	-	-	-	-	-	-	-1.57
10345368	---	DNA segment, chr 1, erato doi 448, expressed	D1Ertd448e	-	-	-	-	-	-	-1.52
10595953	NM_177775	Family with sequence similarity 62 (c2 domain containing), member c	D9Ertd280e	-	-	-	-	-	-	-1.62
10502359	NM_011932	Dual adaptor for phosphotyrosine and 3phosphoinositides 1	Dapp1	-	-	-	-	-	-	1.61
10417829	NM_134081	DNAj (hsp40) homolog, subfamily c, member 9	Dnajc9	-	-	-	-	-	-	1.52
10511541	NM_001081201	Dpy19like 4 (c. Elegans)	Dpy19l4	-	-	-	-1.53	-	-	-
10452450	NM_001008973	Riken cDNA e130009j12 gene	E130009J12Rik	-	-	-	-1.65	-	-	-
10419154	NM_007894	Eosinophilassociated, ribonuclease a family, member 8	Ear8	-	-	-	-	-	-	-1.50
10518069	NM_025994	Ef hand domain containing 2	Efhd2	-	-	-	-	-	-	1.81
10501492	ENSMUST00000	Leptin receptor overlapping transcript	EG433643	-	-	-	-	-	-	-1.59
10520390	ENSMUST00000	Proline rich 8	EG545741	-	-	-	1.51	-	-	-
10403021	---	---	EG629908	-	-	3.34	6.67	-	7.74	12.34
10498972	NM_001146328	RNA binding motif protein 46	EG633285	-	-	-	1.51	-	-	-
10466843	---	similar to glyceraldehyde-3-phosphate dehydrogenase	EG667806 LOC634019	-	-	-	1.50	-	-	-
10566583	AK172683	Predicted gene 8995	EG668139	-	-	-	-	-	-	1.51
10362902		Glyceraldehyde3phosphate dehydrogenase	EG668192	-	-	-	1.59	-	-	-

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10523058	NM_001166589	Eukaryotic translation initiation factor 5a	Eif5a	-	-	-	1.53	-	-	1.67
10462111	---	Ensmusg00000054178	ENSMUSG0000054178	-	-	-	-1.61	-	-	-
10504755		Hypothetical protein loc641050	ENSMUSG0000056897	-	-	-	-	-	-	1.69
10542594	---	Ensmusg00000067389	ENSMUSG0000067389	-	-	-	-1.56	-	-	-
10503709	---	Riken cDNA d130062j21 gene	ENSMUSG0000073981	-	-	-	-2.02	-	-	-
10406452	---	---	ENSMUSG0000074792	-	-	-	-1.71	-	-	-
10344674	AK087278	Family with sequence similarity 150, member a	Fam150a	-	-	-	-	-	-	1.54
10518075	NM_177868	Forkheadassociated (fha) phosphopeptide binding domain 1	Fhad1	-	-	-	-1.64	-	-	-
10447649	NM_001081416	Fibronectin type iii domain containing 1	Fndc1	-	-	-	-1.59	-	-	-
10435641	NM_008047	Follistatinlike 1	Fstl1	-	-	-	-	-	-	1.66
10351035	NR_002840	Growth arrest specific 5	Gas5	-	-	-	1.76	-	-	1.53
10544583	NM_153175	GTPase, imap family member 6	Gimap6	-	-	-	-1.63	-	-	-
10492658	ENSMUST000000000000	---	Gm10291	-	-	-	-	-	-	1.51
10374764	NR_002890	Glyceraldehyde-3-phosphate dehydrogenase	Gm12070	-	-	-	-	-	-	1.51
10417667	---	Gene model 281, (NCBI)	Gm281	-	-	-	-1.69	-	-	-
10545182	---	---	Gm459	-	-	-	1.57	-	-	-
10361710	---	---	Gm5177	-	-	-	-	-	-	1.58
10601537	---	Similar to ubiquitin-conjugating enzyme e2n	Gm5943	-	-	-	-	-	-	1.64
10413977	XM_985917	Gene model 626, (NCBI)	Gm626	-	-	-	-1.51	-	-	-
10593490	NM_008084	glyceraldehyde-3-phosphate dehydrogenase	Gapdh	-	-	-	-	-	-	1.54
10466735	NM_001114174	---	Gm967	-	-	-	-	-	-	-1.79
10360415	NM_011825	Gremlin 2 homolog, cysteine knot superfamily (xenopus laevis)	Grem2	-	-	-	-1.73	-	-	-
10577882	NM_029884	Heparanalphagglucosaminidase	Hgsnat	-	-	-	-	-	-	-1.59
10368527	NM_025798	Histidine triad nucleotide binding protein 3	Hint3	-	-	-	-1.54	-	-	-
10404051	NM_175654	histone cluster 1, H4d	Hist1h4d	-	-	-	1.90	-	-	-
10575380	NM_172916	Hydrocephalus inducing	Hydin	-	-	-	-1.70	-	-	-
10346799	NM_017480	Inducible tcell costimulator	Icos	-	-	-	-	-	-	1.91
10436865	NM_008338	Interferon gamma receptor 2	Ifngr2	-	-	-	-	-	-	1.52

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10403034	---	Immunoglobulin heavy chain complex	Igh	-	-	8.64	12.32	-	14.49	19.42
10403054	ENSMUST00000	Similar to monoclonal antibody heavy chain	Ighla	-	-	2.46	5.12	-	-	-
10403060	---	Immunoglobulin heavy variable v1-72	Ighv1-72	-	-	2.04	4.26	-	-	-
10545220	BC019474	Immunoglobulin kappa chain variable 12-41	Igk	-	-	-	-	-	6.87	9.11
10545239	---	Immunoglobulin kappa chain variable 8 (v8)-21	Igk-V8-21	-	-	-	3.35	-	-	-
10345752	NM_010555	Interleukin 1 receptor, type ii	Il1r2	-	-	-	-	-	-	2.14
10576692	NM_010568	Insulin receptor	Insr	-	-	-	-1.63	-	-	-
10548409	NM_001136068	Killer cell lectinlike receptor subfamily c, member 1	Klrc1	-	-	5.94	2.80	-	-	-
10438435	NM_177356	Lysosomalassociated membrane protein 3	Lamp3	-	-	-	-2.59	-	-	-
10360745	NM_133815	Lamin b receptor	Lbr	-	-	-	-	-	-	-1.50
10360542	NM_025511	Hypothetical loc100270747	LOC100270747	-	-	-	-1.54	-	-	-
10497372	DQ055451	Similar to sirp beta 1 like 1 protein	LOC381484	-	-	-	-	-	-	1.51
10506652	NM_001081272	Similar to low density lipoprotein receptor a domain containing 1	LOC546840	-	-	-	-1.59	-	-	-
10362751	XR_032514	Adenylate kinase domain containing	Akd1	-	-	-	-1.52	-	-	-
10595109	NM_001146048	Leucine rich repeat containing 1	Lrrc1	-	-	-	-1.51	-	-	-
10380403	NM_133807	Leucine rich repeat containing 59	Lrrc59	-	-	-	-	-	-	1.62
10429100	NM_019457	Leucine rich repeat containing 6 (testis)	Lrrc6	-	-	-	-1.51	-	-	-
10429573	NM_010741	Lymphocyte antigen 6 complex, locus c2	Ly6c2	-	-	-	1.53	-	-	-
10429560	NM_020498	Lymphocyte antigen 6 complex, locus i	Ly6i	-	-	6.53	3.61	-	2.65	4.61
10424113	NM_178920	Mal, tcell differentiation protein 2	Mal2	-	-	-	-1.51	-	-	-
10465244	NR_002847	Metastasis associated lung adenocarcinoma transcript 1 (non-coding RNA)	Malat1	-	-	-	-1.55	-	-	-
10463224	NM_183195	Marvel (membraneassociating) domain containing 1	Marveld1	-	-	-	-	-	-	-1.60
10400460	NM_145442	Map3k12 binding inhibitory protein 1	Mbip	-	-	-	-1.69	-	-	-
10452860	NM_133771	Mediator of cell motility 1	Memo1	-	-	-	-	-	-	1.68

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10377774	NM_145137	Macrophage galactose nacytylgalactosamine specific lectin 2	Mgl2	-	-	-	-1.72	-	-	-
10380135	NR_029555	microRNA 142	Mir142	-	-	-	1.55	-	-	-
10435791	NR_030576	microRNA 568	Mir568	-	-	-	-1.70	-	-	-
10607774	NM_029730	Motile sperm domain containing 2	Mospd2	-	-	-	-1.72	-	-	-
10461587	XM_889011	Membrane-spanning 4-domains, subfamily a, member 4a	Ms4a4a	-	-	4.53	7.21	2.38	1.88	3.45
10461629	NM_025658	Membranespanning 4domains, subfamily a, member 4d	Ms4a4d	-	-	-	1.52	-	-	-
10466130	NM_022430	Membranespanning 4domains, subfamily a, member 8a	Ms4a8a	-	-	-	2.09	-	-	-
10367591	NM_026793	Myc target 1	Myct1	-	-	-1.86	-3.39	-	-	-
10381798	NM_010858	Myosin, light polypeptide 4	Myl4	-	-	-	-	-	-	-1.51
10501895	NM_021503	Myozenin 2	Myoz2	-	-	-	-1.73	-	-	-
10549647	NM_010746	Natural cytotoxicity triggering receptor 1	Ncr1	-	-	-	-1.80	-	-	-
10598087		Predicted gene 4076	ND6	-	-	-	-	-	-	-1.51
10490551	NM_021426	Na+/k+ transporting atpase interacting 4	Nkain4	-	-	-	-1.58	-	-	-1.69
10532390	NM_153570	Nucleolar complex associated 4 homolog (s. Cerevisiae)	Noc4l	-	-	-	1.74	-	-	-
10448748	NM_011956	Nucleotide binding protein 2	Nubp2	-	-	-	1.63	-	-	-
10375234	NM_026023	Nudc domain containing 2	Nudcd2	-	-	-	-	-	-	1.82
10469070	NM_016918	Nudix (nucleoside diphosphate linked moiety x)type motif 5	Nudt5	-	-	-	-	-	-	1.70
10483648	NM_025942	Obglike atpase 1	Ola1	-	-	-	1.56	-	-	1.82
10544133	NM_172893	Poly (adpribose) polymerase family, member 12	Parp12	-	-	-	1.63	-	-	-
10344707	NM_183028	Proteinlisoaspartate (daspartate) omethyltransferase domain containing 1	Pcmt1	-	-	-	-1.52	-	-	-
10497646	NM_001165954	Polyhomeotic-like 3 (drosophila)	Phc3	-	-	-	-1.62	-	-	-
10344981	NM_053191	Peptidase inhibitor 15	Pi15	-	-	-	1.84	-	-	-
10473022	NM_019755	Proteolipid protein 2	Plp2	-	-	-	1.59	-	-	-
10606495	NM_181579	Premature ovarian failure 1b	Pof1b	-	-	-	-1.67	-	-	-
10355115	NM_025596	Preli domain containing 1	Preli1	-	-	-	1.50	-	-	1.63
10520388	NM_028234	Proline rich 8	Prr8	-	-	-	-1.72	-	-	-
10607004	NM_016883	Proteasome (prosome, macropain) 26s subunit, nonatpase, 10	Psmd10	-	-	-	-	-	-	1.57
10578027	NM_026453	Mak16 homolog (s. Cerevisiae)	Rbm13	-	-	-	-	-	-	1.65
10436095	NM_020509	Resistin like alpha	Retnla	-	-	-	-	7.32	1.92	4.31

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10436100	NM_181596	Resistin like gamma	Retnlg	-	-	-	1.77	-	-	-
10569057	NM_001172101	Ribonuclease/angiogenin inhibitor 1	Rnh1	-	-	-	1.73	-	-	-
10406250	NM_009084	Ribosomal protein l37a	Rpl37a	-	-	-	-	-	-	1.50
10589695	NM_153100	Receptor transporter protein 3	Rtp3	-	-	-	-	-	-	-1.60
10493995	NM_009112	S100 calcium binding protein a10 (calpactin)	S100a10	-	-	-	1.52	-	-	-
10428594	NM_177225	Sterile alpha motif domain containing 12	Samd12	-	-	-	-2.20	-	-	-
10440393	NM_023380	Sam domain, sh3 domain and nuclear localization signals, 1	Samsn1	-	-	-	-	-	-	1.87
10461642	NR_028560	small Cajal body-specific RNA 17	Scarna17	-	-	-	-1.53	-	-	-
10450904	NM_001039137	Short coiledcoil protein	Scoc	-	-	-	-	-	-	1.71
10355984	NM_009255	Serine (or cysteine) peptidase inhibitor, clade e, member 2	Serpine2	-	-	-	1.65	-	-	-
10459905	NM_053099	Set binding protein 1	Setbp1	-	-	-	-1.59	-	-	-
10347734	NM_001004173	Sphingosine1phosphate phosphotase 2	Sgpp2	-	-	-	-1.54	-	-	-
10561721	NM_001081028	Signalinduced	Sipa1l3	-	-	-	-1.62	-	-	-
10497349	NM_001002898	Signal-regulatory protein beta 1	Sirpb1a	-	-	-	-	-	-	1.53
10377372	NM_028048	Solute carrier family 25, member 35	Slc25a35	-	-	-	-1.55	-	-	-
10379650	AF099974	Schlafen 3	Slfn3	-	-	-	-1.75	-	-	2.60
10389143	NM_181545	Schlafen 8	Slfn8	-	-	-	-	-	-	1.64
10489463	NM_011414	Secretory leukocyte peptidase inhibitor	Slpi	-	-	-	2.27	-	-	-
10584580	NR_028275	small nucleolar RNA, C/D box 14E	SNORD14	-	-	-	1.50	-	-	-
10522445	NM_178387	Spermatogenesis associated 18	Spata18	-	-	-	-1.54	-	-	-
10427681	NM_177123	Sperm flagellar 2	Spef2	-	-	-	-1.51	-	-	-
10542740	NM_010656	Sarcospan	Sspn	-	-	-	-	-	-	-1.50
10389795	NM_011505	Syntaxin binding protein 4	Stxbp4	-	-	-	-2.15	-	-	-
10481147	NM_011512	Surfeit gene 4	Surf4	-	-	-	1.68	-	-	-
10545168	NM_020047	Tumorassociated calcium signal transducer 2	Tacstd2	-	-	-	1.69	-	-	1.56
10596900	NM_133986	Tcell leukemia translocation altered gene	Tcta	-	-	-	-	-	-	-1.58
10449661	NM_009363	Trefoil factor 2 (spasmolytic protein 1)	Tff2	-	-	-	-	3.35	-	1.52
10565609	NM_009381	Thyroid hormone responsive spot14 homolog (rattus)	Thrsp	-	1.92	-1.61	-3.44	-	-	-
10498273	NM_008536	Transmembrane 4 superfamily member 1	Tm4sf1	-	-	-	-1.68	-	-	-

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10565514	NM_025460	Transmembrane protein 126a	Tmem126a	-	-	-	-	-	-	1.63
10553324	NM_026436	Transmembrane protein 86a	Tmem86a	-	-	-	1.52	-	-	-
10510580	NM_011612	Tumor necrosis factor receptor superfamily, member 9	Tnfrsf9	-	-	-	-	-	-	1.97
10538791	NM_001001495	Tnfaip3 interacting protein 3	Tnip3	-	-	-	-	-	3.55	5.56
10362420	NM_029726	Triadin	Trdn	-	-	-	-	-	-	1.64
10515282	NM_133681	Tetraspanin 1	Tspan1	-	-	-	-	-	-	1.61
10558961	NM_053082	Tetraspanin 4	Tspan4	-	-	-	1.87	-	-	-
10425808	NM_009775	Translocator protein	Tspo	-	-	-	1.84	-	-	-
10590212	NM_028735	Tetratricopeptide repeat domain 21a	Ttc21a	-	-	-	-1.53	-	-	-
10396064	NM_172054	Thioredoxin domain containing 9	Txndc9	-	-	-	-	-	-	1.53
10480714	NM_001033293	Udpnacteylglucosamine pyrophosphorylase 1like 1	Uap1l1	-	-	-	1.50	-	-	-
10478012	NM_011665	Ubiquitin-conjugating enzyme e2i	Ube2i	-	-	-	-	-	-	1.55
10364109	NM_009514	Preb lymphocyte gene 3	Vpreb3	-	-	-	-1.63	-	-	-
10419296	NM_172598	WD repeat and hmgbox dna binding protein 1	Wdhd1	-	-	-	-	-	-	1.54
10435862	NM_001033247	WD repeat domain 52	Wdr52	-	-	-	-1.71	-	-	-
10399632	---	RIKEN cDNA F630048H11 gene	F630048H11Ril	-	-	-	-1.52	-	-	-