

Vaccinia virus–specific molecular signature in atopic dermatitis skin

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Background: Eczema vaccinatum (EV), a disseminated viral skin infection, is a life-threatening complication of vaccinia virus (VV) inoculation in patients with atopic dermatitis (AD) and is thought to be associated with a defective innate immune response. However, the precise mechanism or mechanisms and key factor or factors of EV are unknown.

Objective: Given that patients with psoriasis, another inflammatory skin disorder, are not susceptible to EV, we compared the global transcriptional response of skin to VV in healthy subjects, patients with psoriasis, and patients with AD, focusing on AD-specific genes. We hypothesized that differences in the transcriptional response to VV between patients with AD and patients with psoriasis or healthy subjects would identify a defective pathway or pathways that might be associated with the development of EV.

Methods: Gene expression profiling of sham-treated and VV-treated unaffected skin explants from patients with AD (n = 12), patients with psoriasis (n = 12), or healthy subjects (n = 13) were generated with U133_Plus2 (54,613 probe sets) GeneChips and analyzed with the GCOS_1.4/SAM_2.1/MAPPFinder_2.0 pipeline.

Results: Sixty-seven genes were significantly affected by VV in AD skin but not in psoriatic and healthy skin. Genes associated with defense response, response to wounding, and immune response were the most affected by VV in AD skin. All genes in these ontologies were downregulated, including the innate immunity genes leukotriene B₄ receptor (*LTB4R*), orosomucoid 1 (*ORM1*), coagulation factor II (thrombin) receptor (*F2R*), complement component 9 (*C9*), and LPS-binding protein (*LBP*). These findings were confirmed by means of real-time PCR and validated by means of PubMatrix analysis. *ORM1*, Toll-like receptor 4 (*TLR4*), and NLR family pyrin domain containing 1 (*NLRP1*) genes were also linked to AD severity.

Conclusion: This study identified groups of innate immunity genes that are associated with the aberrant response of AD skin to VV and represent potential targets for EV pathogenesis. (*J Allergy Clin Immunol* 2010;125:153-9.)

Key words: *Eczema vaccinatum, vaccinia virus, atopic dermatitis, genomics*

The recent bioterrorist attacks with anthrax suggested potential use of other infectious agents, such as smallpox, by terrorist groups. Given that smallpox vaccination was discontinued in the early 1970s, there are more than 120 million smallpox-susceptible residents in the United States. An epidemic of smallpox on US soil could result in catastrophic numbers of infected victims. Although the healthy population in the United States can be vaccinated against smallpox, patients with atopic dermatitis (AD) cannot be vaccinated because of their high risk of eczema vaccinatum (EV), a disseminated viral skin infection that occurs after inoculation of AD skin with vaccinia virus (VV), the main active component of smallpox vaccine.¹ In contrast, patients with psoriasis, another chronic inflammatory skin disorder, do not have frequent skin infections and are not susceptible to EV.^{2,3} The role of potential innate immune defects in patients with AD has been suggested.⁴ To investigate the detailed mechanisms responsible for EV in patients with AD, the National Institute of Allergy and Infectious Diseases launched the Atopic Dermatitis and Vaccinia Network, which funded this study.⁵

Global gene expression profiling is a powerful tool for dissecting differences between AD and psoriasis at the molecular level. Using this technique, our group has previously demonstrated that these disorders have distinct transcriptional signatures.³ These differences might explain several features of AD and psoriasis, including the specific inflammatory cell infiltrates observed in these disorders and disparity in the innate immune component.^{6,7} Furthermore, the induction of a battery of inflammatory genes was recently identified in AD lesions.⁸ We predict that patients with AD, compared with patients with psoriasis or healthy subjects, will have a compromised innate immune response to VV similar to that observed in VV animal models.⁴

As a follow-up to our previous transcriptomics studies of AD and psoriasis, we have used this powerful technique for analysis of VV-associated global transcriptional response of skin samples from patients with AD, patients with psoriasis, and healthy subjects. In the current studies we investigated VV-induced transcriptional changes in skin biopsy specimens from the aforementioned groups with a focus on AD-specific genes. We hypothesized that differences in the transcriptional response to VV between patients with AD and patients with psoriasis or healthy subjects would identify the defective pathway or pathways that might be associated with the development of EV.

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Abbreviations used

AD: Atopic dermatitis
 AGP-A: α_1 -Acid glycoprotein
 C9: Complement component 9 gene
 EASI: Eczema Area and Severity Index
 EV: Eczema vaccinatum
 FC: Fold change
 F2R: Coagulation factor II (thrombin) receptor gene
 GO: Gene ontology
 LBP: LPS-binding protein gene
 LTBR: Leukotriene B₄ receptor gene
 NLRP1: NLR family pyrin domain containing 1 gene
 ORM1: Orosomucoid 1 gene
 SAM: Significance Analysis of Microarrays
 TLR4: Toll-like receptor 4 gene
 VV: Vaccinia virus

METHODS**Study subjects**

Subjects included 12 patients with AD, 12 patients with psoriasis, and 13 healthy subjects with no history of skin disease (Table I). None of the patients had previously received oral corticosteroids or cyclosporin, and topical corticosteroids were not allowed for greater than 1 week before enrollment. All patients with AD were determined to have the extrinsic (allergic) form based on positive serum IgE levels to allergens. The current research was carried out according to the principles of the Declaration of Helsinki. The Institutional Review Board at National Jewish Health reviewed and approved the conduct of this study, and informed consent was obtained from each patient.

Virus source and culture

The Wyeth strain of VV was obtained from the Centers for Disease Control and Prevention (Atlanta, Ga). VV was propagated with HeLa S3 cells (ATCC#CCK-2.2), as previously described.⁶ Virus was harvested, yielding infectious virions in the form of intracellular mature virions.

Human skin explant cultures

Two-millimeter punch biopsy specimens were obtained from nonlesional skin (the upper arm or quadriceps area) of each donor and placed in a 96-well plate and RPMI (Cellgro; Mediatech, Herndon, Va) supplemented with 10% FCS (Gemini Bio Products, West Sacramento, Calif). Biopsy specimens were cultured in the presence of media alone containing virus diluent or 2×10^5 pfu VV for 24 hours, as previously described.⁹ After the exposure period, medium was removed, and biopsy specimens were submerged in Tri-Reagent (Molecular Research Center, Inc, Cincinnati, Ohio) for RNA isolation.

Transcript profiling with Affymetrix oligonucleotide arrays

Affymetrix GeneChip profiling was performed at the Lowe Family Genomics Core. Total RNA (7–10 μ g) was isolated with TRIzol (Gibco-BRL, Invitrogen, Carlsbad, Calif) and RNeasy columns (Qiagen, Hilden, Germany). The quality of RNA was confirmed on the Agilent 2100 bio-analyzer (Agilent Technologies, Palo Alto, Calif) and hybridized to an Affymetrix GeneChip U133_Plus2 (54,613 probe sets for 38,500 genes). Hybridization signals were measured with the Agilent Gene Array Scanner. The resulting digitized matrix (CEL files) was processed, masked, and normalized, as described previously.^{10,11}

Computational identification of significant transcriptional changes

Affymetrix probe sets that aligned to the same exon were clustered, as described previously,¹² and considered as a combined statistical entity. Significance Analysis of Microarrays (SAM 2.20)¹³ was conducted by using 500 permutations without application of arbitrary restrictions.¹⁴ Gene candidates were selected in 2 analytic runs. During the first run, each probe set was treated as an individual gene. In the second run probes that were targeting the same gene were analyzed together, and the blocking feature of SAM was used, as described previously.¹⁵

Fold change (FC) cutoffs were calculated by using power prediction analysis for minimum array requirements,¹⁶ as described previously.¹⁷ The resulting cutoff values for significance of VV effects are presented in Table E1 (available in this article's Online Repository at www.jacionline.org).

Selection of VV-specific gene candidates for AD

Identification of VV-specific genes in AD skin samples was conducted in 3 steps. First, AD-specific genes were selected. For this, we generated gene expression profiles for sham (media)-treated skin samples from healthy control subjects, patients with AD, and patients with psoriasis. Significant changes in gene expression of AD samples compared with either control or psoriatic samples were considered AD specific. Genes that were significant in both comparisons were selected as our first-line candidates. Second, we identified VV-specific genes using the same approach. Gene expression profiles for VV-treated skin samples from healthy control subjects, patients with AD, and patients with psoriasis were generated. VV-responsive genes in patients with AD but not in control subjects or patients with psoriasis were considered VV/AD specific. Those that were called "significant" by both comparisons (VV/AD vs VV/healthy skin and VV/AD vs VV/psoriatic skin) became our first-line candidates. The AD-specific genes were subtracted from the VV/AD-specific genes to further narrow our candidate list, resulting in a VV-specific pool.

Gene ontology analysis

The MAPPFinder compatible files were prepared by using the GenMAPP converting tool, as described previously.¹⁸ Significant bioprocesses were selected by choosing gene ontology (GO) terms containing greater than 5% of the total number of genes linked by MAPPFinder. A z score of greater than 2 and first GO node greater than 0 were also applied as filtering criteria. Generalized terms, such as "development" and "signal transduction," were not considered.

Real-time RT-PCR validation

Transcript levels of 10 selected candidate genes were measured by using the TaqMan Gold RT-PCR Core Reagents Kit/ABI Prism 7700 Sequence Detector System (Perkin-Elmer/Applied Biosystems, Foster City, Calif), as previously described.¹¹ The significance of the obtained differences were assessed by using t tests in which a P value of less than .05 was considered significant.

Biomarker-association analysis

Transcriptional signals of sham (media)-treated AD skin explants were pairwise subtracted from corresponding VV-affected samples. Resulting changes in expression were correlated with the Eczema Area and Severity Index (EASI) score of the population with AD. To reduce the level of type II error,¹⁹ because of the small sample size, the symmetric trimming of the highest and the lowest EASI scores was conducted. The R (correlation coefficient) and P (2-tailed probability) values were identified by using the `linregress()` function of the Python Statistical Module.¹⁰ EASI-associated changes in gene expression were evaluated as the FC differences among the 3 samples with the lowest and the 3 samples with the highest EASI scores, as described previously.¹¹ Genes with R values of greater than

TABLE I. Summary of patient demographics

	Healthy subjects (n = 13)	Patients with AD (n = 12)	Patients with psoriasis (n = 12)
Age (y)	30 (9)*	36 (10)	43 (12)
Female sex, no. (%)	7 (54)	7 (58)	9 (75)
White race, no. (%)†	11 (85)	10 (83)	7 (58)
EASI score	—	15.2 (18.1)	—

*All values are expressed as means (SDs) unless otherwise specified.

†Nonwhite subjects are represented by the following categories: black or African American, American Indian/Alaska Native, and other.

0.7 and FCs of greater than 2 or *R* values of less than -0.7 and FCs of less than -2 were considered significantly associated with the EASI score, as defined by Beck et al.⁵ The full list of *R* and FC values is provided in Table E4 (available in this article's Online Repository at www.jacionline.org). Detailed GO analysis of AD severity-associated genes is combined in Table E4.

PubMatrix analysis

VV-affected transcripts in AD samples were searched against “skin,” “dermatitis,” and “atopic dermatitis” terms in the PubMed database by using the PubMatrix automated literature search engine.²⁰

Detailed methods are provided in the Methods section in this article's Online Repository at www.jacionline.org.

RESULTS

Patient demographics and clinical data

Twelve consecutive patients with AD or psoriasis and 13 healthy nonatopic subjects were included in the study (Table I). The average ages of the patients with AD, patients with psoriasis, and healthy subjects were 36 ± 10 , 43 ± 12 , and 30 ± 9 years, respectively. Age differences between these groups were not significant ($P > .05$). Two-tailed *t* tests assuming equal variances generated a *P* value of .155 for patients with AD versus healthy subjects and a *P* value of .123 for patients with AD versus patients with psoriasis. Ten of 12 patients with AD self-reported as white, and 10 (83%) were women. The average EASI score was 15.2 ± 18.1 , suggesting moderate-to-severe AD.

Gene candidate selection and validation

A total of 34,208 probe sets of 54,613 tested identified their targets in human skin biopsy specimens. These skin-specific probe sets covered 17,921 genes, which demonstrated that each gene, on average, is targeted by 2 probe sets. A conventional analytic approach (ie, considering the signal of each probe set as an individual entity) identified 225 genes that significantly differed in AD skin compared with healthy skin and 258 genes that differed from psoriatic skin. The probe set clustering approach (considering signals from probe sets for the same gene as a combined value) identified another 30 and 55 genes, respectively (Fig 1, A and B). Similarly, after *in vitro* stimulation of skin samples with VV, the clustering approach recovered 125 and 52 genes after comparison of AD samples with healthy or psoriatic skin, respectively (Fig 1, C and D), totaling 459 and 192 VV-associated transcripts for the respective comparisons (Fig 2 and see Tables E2-E4). Comparison of VV effects between psoriatic and healthy skin detected 174 genes, of which 59 were also responsive in AD samples (see Fig E1 in this article's Online

Repository at www.jacionline.org). This cross-referencing identified 399 and 115 VV-specific genes in AD and psoriatic samples, respectively. The observed subdued reaction of psoriatic samples to VV compared with AD samples is in perfect concordance with the well-known low reactivity of psoriatic skin to VV. This finding confirmed the reliability of our array data. The filtering by subtraction of the first-line AD-specific genes (Fig 2, A) from 88 first-line VV/AD-specific genes (Fig 2, B) resulted in a VV-specific pool of 71 transcripts (Fig 2, C), of which 67 represented known genes.

These 67 genes (Fig 2, C) were dynamically linked by MAPP-Finder to GO terms to evaluate the effect of VV on biologic pathways and processes in human skin. GO analysis identified 6 significant pathways affected by VV in AD skin. Among the most implicated pathways were response to wounding and defense response (Table II). For validation, we selected a total of 9 genes. Five were from the first-line candidates, complement component 9 (*C9*), chemokine (C-C) ligand 22 (*CCL22*), orosomucoid 1 (*ORM1*), coagulation factor II (thrombin) receptor (*F2R*), and leukotriene B₄ receptor (*LTB4R*), and another 4 were from the second-line candidates. TNF receptor superfamily, member 25 (*TNFRSF25*), and keratin 15 (*KRT15*) were specific for AD versus healthy skin, and LPS-binding protein (*LBP*) and *HLA-DRB1* were specific for the AD versus psoriasis comparisons. Seven of 9 selected genes were successfully validated (Fig 3), with similar validation percentages between first-line (80%) and second-line (75%) candidates. Expression of all validated genes was previously reported for skin, and most were linked to dermatitis. Only *ORM1* was previously associated with dermatitis but not with AD (Table III).

Identifying genes associated with AD severity

Linear regression studies identified 305 genes that were significantly negatively associated with EASI scores (ie, lower gene expression was associated with greater AD severity). GO analysis of these genes identified defense response as most associated with AD severity (Table IV). This pathway was represented by 17 genes, including innate immunity-related candidates: C-type lectin domain family 4 member C (*CLEC4C*), NLR family pyrin domain containing 1 (*NLRP1*), *ORM1*, chemokine (C-C motif) receptor 2 (*CCR2*), and Toll-like receptor 4 (*TLR4*). Among our candidates (Fig 3), aside from *ORM1*, only *C9* demonstrated an expressional trend toward EASI (see Table E5 in this article's Online Repository at www.jacionline.org). The EASI score association patterns with VV-inflicted transcriptional changes of *ORM1*, *NLRP1*, and *TLR4* genes are depicted in Fig 4.

DISCUSSION

The main finding of this study is that VV-specific transcriptional changes in unaffected skin explants from patients with AD are detectable by using microarray techniques, and these molecular signatures are distinguishable from those in patients with psoriasis and healthy subjects. We acknowledge that the volume of large data sets generated during this study posed a challenge with respect to accurate data interpretation; however, the pipeline of consecutive cutting-edge *in silico* and *in vitro* analyses efficiently reduced the noise of the system and greatly improved gene candidate identification. Altogether, this provides evidence

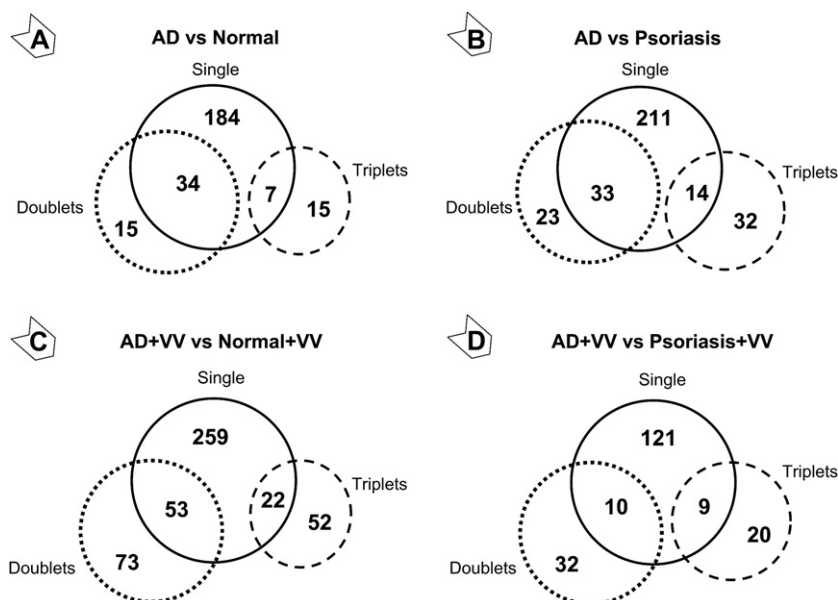


FIG 1. AD-specific (A and B) and VV-induced (C and D) transcriptional changes in skin biopsy specimens from unaffected areas. Gene expression analysis was conducted with standard (solid circle) and clustering (dashed circles) approaches (see the Methods section). The *single* pool represents the number of significantly different genes that were detected by using information from individual probe sets per gene (generating >1 expression value per gene). The *doublets* and *triplets* pools represent the number of significantly different genes that are targeted by 2 or 3 probe sets, respectively, and were analyzed by using combined values of those probe sets (generating only 1 expression value per gene).

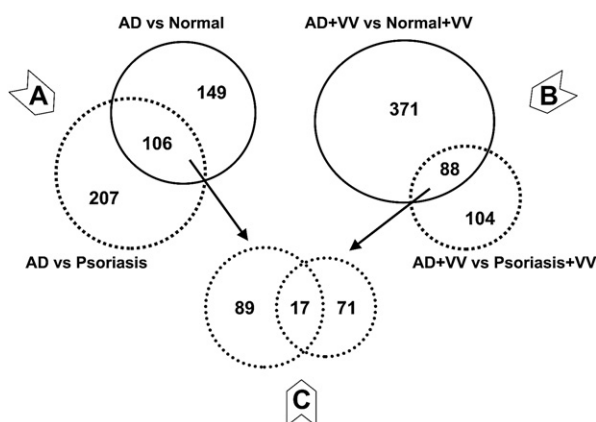


FIG 2. Selection of first-line VV-specific gene candidates using a cross-referencing approach. Eighty-three genes that were significantly affected by VV treatment in AD samples compared with both normal and psoriatic samples were cross-referenced with 106 genes that were significantly associated with AD in both comparisons with normal and psoriatic skin. The resulting pool of 71 genes represents VV-specific response in AD samples.

for the use of this practical assay to discover new molecular targets and biomarkers in a large population of patients with AD who are at risk for EV. In addition, we demonstrated that gene expression patterns and specific biologic processes in skin might be associated with stages of AD severity, thus providing mechanistic insight into the AD development and potential susceptibility to EV. EASI scores were significantly correlated with expression of defense- and immune/inflammation-related genes in the skin.

This is the first attempt to identify differences in global patterns of gene expression in response to VV from patients with AD,

patients with psoriasis, and healthy subjects with a particular focus on processes associated with innate immunity. The probe set-guided clustering approach of gene expression profiles provided additional candidates for both patient populations (Figs 1 and 2). This technique identified novel candidate genes, including *ORM1*, which was missed by the standard SAM analysis (see Fig E2 in this article's Online Repository at www.jacionline.org). Cross-referencing of thus enriched gene candidates yielded 67 genes that were particularly relevant to VV stimulation (Fig 2).

GO analysis of these genes identified several bioprocesses (Table II) potentially involved in VV susceptibility. Wound healing and defense response were among the most heavily involved in AD-specific responses to VV. These findings are in agreement with our previous observation that there is a defective response of the antiviral defensive peptide cathelicidin (LL-37) in patients with AD^{9,21} and a report by others that LL-37 is required for wound healing.²² Interestingly, the overwhelming majority of genes in these aforementioned ontologies were downregulated, including the innate immunity genes *LTB4R*, *ORM1*, *F2R*, *C9*, and *LBP*. This observation was confirmed by means of real-time PCR studies, which demonstrated significantly lower transcript abundance of key VV-responsive genes in skin from patients with AD compared with that seen in skin from healthy subjects or patients with psoriasis (Fig 3). When VV's effects in the well-known innate immunity genes *C9* and *LBP* in patients with AD were compared with those in healthy volunteers, there was an approximately 400-fold decrease in expression (Fig 3). Although *C9* is a somewhat unexpected candidate, there are data supporting this finding. One report associated hereditary deficiency in *C9* with dermatomyositis manifesting as skin pruritic erythema²³ and another study in animals demonstrated amplified antiviral response to recombinant VV in mice deficient in natural

TABLE II. Significant pathways affected by VV in AD skin

GO ID	GO name	No. of measured genes	No. of significant genes	Percentage of significant genes	z Score
9611	Response to wounding	282	11	3.90	8.211
6954	Inflammatory response	160	8	5.00	8.138
6952	Defense response	596	16	2.68	7.782
6955	Immune response	546	15	2.75	7.644
9607	Response to biotic stimulus	631	16	2.54	7.474
6950	Response to stress	761	15	1.97	5.969

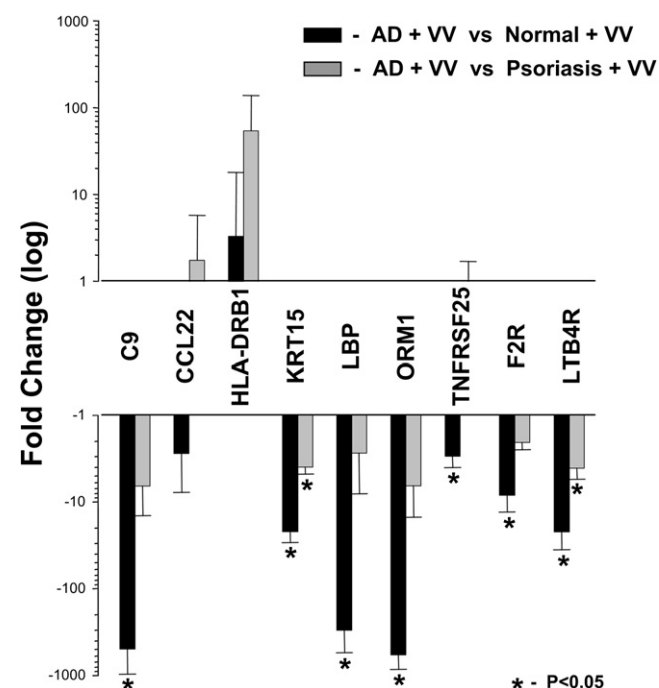


FIG 3. Expression level of VV-specific gene candidates in unaffected skin from patients with AD detected by means of real-time RT-PCR. The relative message abundance of 9 genes that are listed on the x-axis was evaluated with real-time RT-PCR and compared with internal controls (3 housekeeping genes), as described in the Methods section, by using total RNA isolated from skin stimulated with VV in 3 randomly selected patients with AD. The changes in transcript abundance were identified by comparing AD values with randomly selected VV-stimulated control samples ($n = 3$, solid bar) or psoriatic samples ($n = 3$, gray bar) and expressed as mean FCs, with error bars representing SDs. Significant changes ($P < .05$) in transcript abundance are identified with asterisks. Full gene names are reported in Table III.

C9 inhibitor.²⁴ A similar to *C9* expression pattern and amplitude was demonstrated for the *ORM1* gene (Fig 3) that encodes a well-known acute-phase plasma component, α_1 -acid glycoprotein (AGP-A). Interestingly, a recent study demonstrated innate immune properties of this protein.²⁵ The *ORM1* gene was also the only candidate associated with dermatitis but not AD (Table III). Taken together, these observations support the notion that VV-induced responses in AD skin are associated with alterations in innate immunity-related genes. Furthermore, these findings are in agreement with a recently described transcriptional signature of AD lesions based on a study using a cDNA microarray targeting 24,500 genes.⁸ In our studies, however, we analyzed unaffected skin regions using an oligonucleotide microarray that targets 47,000 transcripts and variants, including more than 38,500 well-characterized genes. Despite these differences, a

TABLE III. PubMatrix search for gene candidates

Gene	Symbol	PubMatrix terms		
		Skin	Dermatitis	AD
Keratin 15	<i>KRT15</i>	14	0	0
LPS-binding protein	<i>LBP</i>	30	1	1
TNF receptor superfamily, member 25	<i>TNFRSF25</i>	1	0	0
Complement component 9	<i>C9</i>	81	13	1
Orosomucoid 1	<i>ORM1</i>	2	1	0
Coagulation factor II (thrombin) receptor	<i>F2R</i>	1	0	0
Leukotriene B ₄ receptor	<i>LTB4R</i>	2	1	1
Chemokine (C-C) ligand 22	<i>CCL22</i>	69	45	36
Major histocompatibility complex class II DRB1	<i>HLA-DRB1</i>	108	20	6

sizable group of genes identified in our study were also reported for lesional skin in the aforementioned report, including but not limited to the concordantly upregulated genes *HLA-DRB1*, *CALML5*, *COL6A2*, *RNASE1*, *CCL18*, and *FGL2* and the downregulated genes *ACAA2*, *FBP1*, *APOC1*, *LOVL5*, *FADS1*, and *FADS2* (see Table E7 in this article's Online Repository at www.jacionline.org). Interestingly, our second-line AD-specific candidate, *HLA-DRB1*, was further upregulated by VV (Fig 3). Although a number of identified transcriptional changes of candidate genes might be secondary to the skin barrier dysfunction, their ultimate effects are contributory to VV susceptibility.

We also observed variability in the expression of VV-affected genes according to AD severity (Fig 4). This finding demonstrated that stratifying VV transcriptional effects based on AD severity (EASI score) allows detection of significant changes in expression of genes involved in AD-specific pathogenic processes, which can serve as potential biomarkers for the severity of the response to smallpox vaccine. Our genomics findings were in agreement with reports on a key role for compromised innate immunity in susceptibility to EV in patients with AD.^{6,21,26} We identified *ORM1*, *TLR4*, and *NLRP1* genes, which belong to the innate immune response, as associated with AD severity (Fig 4).

The dramatic downregulation of the *ORM1* gene by VV in AD skin (Fig 3) makes this new candidate an especially appealing target. The involvement of the *ORM1* product AGP-A protein in psoriatic pathogenesis was reported in recent studies, which demonstrated an association of plasma AGP-A levels with an acute phase of the disease.²⁷ Another study confirmed the ability of skin to be a target tissue for AGP-A by suggesting linkage of increased levels of AGP-A with the intensity of pruritus.²⁸ Although the mechanism of AGP-A's action in skin remains unclear, there was a report on the protective role of AGP-A against allergy

TABLE IV. Significant VV-affected pathways associated with EASI scores

GO ID	GO name	No. of measured genes	No. of significant genes	Percentage of significant genes	z Score
6952	Defense response	590	17	2.88	2.859
6955	Immune response	540	15	2.78	2.525
15980	Energy derivation by oxidation of organic compounds	117	5	4.27	2.494
6954	Inflammatory response	160	6	3.75	2.372
30154	Cell differentiation	308	9	2.92	2.099

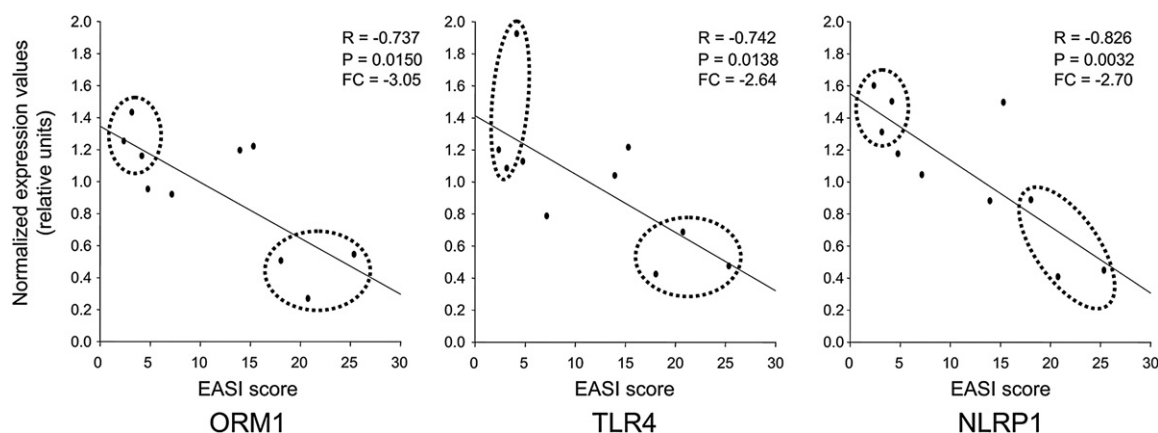


FIG 4. EASI-associated linear regression graphs of the most representative genes involved in defense response. Expression values (y-axis) of *ORM1*, *TLR4*, and *NLRP1* genes were plotted against EASI scores (x-axis), and correlation coefficients (*R*) and 2-tailed probability (*P*) values were calculated by using the Python Statistical package (see the Methods section). FCs were calculated as the ratio between expression values corresponding to the 3 lowest and 3 highest EASI scores (dashed ovals). Full gene names are reported in Table III.

mediator (ie, histamine and platelet-activating factor)-induced vascular leak in skin.²⁹ Therefore the potential AGP-A mechanism might be antagonizing increased vascular permeability during inflammation. Immunomodulatory properties of AGP-A have also been suggested. It has been demonstrated that AGP-A increases resistance to infection and skin graft survival in murine models.³⁰ Although there is evidence for the association of 2 isoforms of the *ORM1* gene with contact dermatitis,³¹ knowledge on the relationship of this gene to atopy is limited. However, the recent report on polymorphisms in orosomucoid 1-like 3 (*ORMDL3*, homolog of *ORM1*), which might contribute to childhood asthma,³² suggests that *ORM1* might have a potential role in atopy.

Another candidate, *NLRP1*, belongs to a new class of pattern-recognition receptors. The classical pattern-recognition receptors, such as TLRs, play an important role in innate immune response to microorganisms and their toxins. The transcriptional levels of expression for one of the TLRs, *TLR4*, was associated with EASI (Fig 4). This is in concert with our recent report on the involvement of this gene in atopy.³³ Recently, another group of pattern-recognition receptors was discovered. They were coined “domain present in NAIP, CIITA, HET-E, TP-1-leucine-rich repeat” (NACHT-LRRs or NLRs).^{34,35} In contrast to TLRs, which are mainly transmembrane receptors (except *TLR3*), all members of this group are located in the cytosol but possess intriguing similarities with TLRs and are considered to be a complementary system for the nonspecific recognition of microbial toxins. Some members contain a baculovirus inhibitor of

apoptosis repeat domain and can function as signal transducers.³⁶ Recent genetic studies of this gene identified promoter polymorphisms in *NLRP1*, which interact with other NLR genes and might play a role in AD pathogenesis.³⁶ The cytoplasmic cellular location of the *NLRP1* product suggests the potential antiviral activity of this protein, similar to that of *TLR3*, which has been shown by us to be involved in anti-VV activity.⁹ These findings warrant further studies of *ORM1* and *NLRP1* genes and their role in host defense against VV. Moreover, our EASI score association studies make these genes even more appealing candidates. We demonstrated that both *ORM1* and *NLRP1* are negatively associated with the EASI score (Fig 4), which has recently been suggested to be a predictor for the increased risk of adverse reactions to VV in patients with severe forms of AD.⁵

To our knowledge, this is the first global transcriptional study of the effects of VV in AD, psoriatic, and normal skin biopsy specimens. The data presented herein suggest that dysregulation of the wounding and defense responses in skin might contribute to adverse reactions of patients with AD to VV. Downregulation of the innate immune component of these bioprocesses might underlie the aberrant response of AD skin to VV. We have identified genes that code for the novel defense peptide *ORM1* and the pattern-recognition receptor *NLRP1* that represent new potential targets for further investigation. Our findings warrant further detailed studies of other members of the identified pathways as well, which can lead to the discovery of new molecular targets for correcting immune response to VV in patients with AD.

We recognize that this pilot study represents data from a small subset of the population of patients with AD and that comparison with samples from patients with documented EV would be ideal. Certainly, multiple other factors might influence gene expression, including drugs, comorbid conditions, and extra-skin diseases. It would also be important to follow a population of patients with both mild and severe AD over time and to study patients with AD who are at risk for EV. However, the reported data provide strong evidence that gene expression can be studied in unaffected AD skin biopsy specimens and that biologically relevant genes are detected and associated with disease severity. We also demonstrated that our severity-based correlation can link VV-responsive genes with the stage of AD, thus providing potential EV targets and facilitating clinical research.

In summary, our findings indicate that alterations in gene expression in response to VV are detectable by using microarray techniques in unaffected skin biopsy specimens from patients with AD versus patients with psoriasis and healthy subjects. The skin gene expression was highly correlated with the EASI score and demonstrated association of VV-affected innate immune and defensive properties of this tissue with the severity of AD. Deciphering the role of these pathways and their components in the response to VV might reveal new targets for early detection, prevention, and treatment of EV.

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Key messages

- New evidence for an AD-specific transcriptional signature and biologic processes associated with AD severity were revealed.
- Novel molecular targets for early detection, prevention, and treatment of EV were identified.
- These data provide mechanistic insight into AD development and potential susceptibility to EV.

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METHODS

Study subjects

Subjects included 12 patients with AD, 12 patients with psoriasis, and 13 healthy subjects with no history of skin disease (Table I). None of the patients had previously received oral corticosteroids or cyclosporin, and topical corticosteroids were not allowed for greater than 1 week before enrollment. All patients with AD were determined to have the extrinsic (allergic) form based on a positive RAST result. The current research was carried out according to the principles of the Declaration of Helsinki. The Institutional Review Board at National Jewish Health reviewed and approved the conduct of this study, and informed consent was obtained from each patient.

Virus source and culture

The Wyeth strain of VV was obtained from the Centers for Disease Control and Prevention (Atlanta, Ga). VV was propagated with HeLa S3 cells (ATCC#CCK-2.2), as previously described.⁶ Virus was harvested, yielding infectious virions in the form of intracellular mature virions.

Human skin explant cultures

Two-millimeter punch biopsy specimens were obtained from nonlesional skin (the upper arm or quadriceps area) of each donor and placed in a 96-well plate and RPMI (Cellgro) supplemented with 10% FCS (Gemini Bio Products). Biopsy specimens were cultured in the presence of media alone containing virus diluent or 2×10^5 pfu VV for 24 hours, as previously described.⁹ After the exposure period, medium was removed, and biopsy specimens were submerged in Tri-Reagent (Molecular Research Center, Inc) for RNA isolation. Total RNA (7–10 μ g) was isolated from each sample with TRIzol (Gibco-BRL) and RNeasy columns (Qiagen), and RNA quality was confirmed on the Agilent 2100 bio-analyzer (Agilent Technologies).

Clustering Affymetrix HG_U133_plus probe sets

Probe sets that shared exonic regions of their corresponding targets were clustered, as described previously.¹² Briefly, the genomic alignments of known human genes (knownGene.txt.gz 05-Sep-2008) were retrieved from the GoldenPath database <http://hgdownload.cse.ucsc.edu/goldenPath/hg18/database> of the University of California Santa Cruz Build 36.1 assembly of the human genome. Genomic alignments of Affymetrix probe sets to the human genome were generated by using standalone BLAT v.34 application, as described previously,¹² with HG-U133_Plus_2 Target Sequences, FASTA, 8/20/08. Probe sets that aligned to the same exon were considered a combined statistical entity. A total of 27,115 probes were found to be sharing their targets, whereas 27,498 probes were unique for their corresponding genes.

Transcript profiling with Affymetrix oligonucleotide arrays

Affymetrix GeneChip profiling was performed at the Lowe Family Genomics Core. The total mRNA was isolated from sham-treated and VV-treated unaffected skin explants from patients with AD ($n = 12$), patients with psoriasis ($n = 12$), or healthy subjects ($n = 13$). The processed RNA (quality monitored on an Agilent 2100 Bioanalyzer) was hybridized to an Affymetrix GeneChip U133_Plus2 (54,613 probe sets for 38,500 genes), and hybridization signals were measured with the Agilent Gene Array Scanner. The resulting digitized matrix (CEL files) was processed, masked, and normalized, as described previously.^{10,11}

Computational identification of significant transcriptional changes

SAM 2.20¹³ was conducted with 500 permutations of 11 control samples and 10 AD or psoriatic samples without application of arbitrary restrictions.¹⁴ Gene candidates were selected in 2 analytic runs. During the first run, each probe set was treated as an individual gene. In the second run probes that were targeting 1 gene were analyzed together. The latter allowed us to detect moderate changes in gene expression that are still significant.¹² For the second run, we created 2 data sets wherein the first data set contained 4,246 detectable

probe sets that represent double targeting of a gene, and the second data set contained 1,995 triplets of probe sets that share 1 gene. For these data sets, the blocking feature of SAM was used, as described previously.¹⁵

FC cutoffs were calculated based on the number of analyzed probes per a given gene and power prediction analysis for minimum array requirements.¹⁶ Identified median of standard deviations of $\log_2$ expression values of all probe sets ($\square = 0.494$) was submitted to the microarray sample size–identifying formula¹⁷ using $n = 10$, $n = 20$, and $n = 30$ for the first, second, and third data sets, respectively, and imposing 95% of detecting power ($1 - \square$). The significance level ($\square$) was individually calculated for each data set and represented 5% of the highest false discovery rate for a given data set. The calculated cutoff values are presented in Table E1 and were used for identification of genes that are significantly affected by VV.

Selection of VV-specific gene candidates for AD

Identification of VV-specific genes in AD skin samples was conducted in 3 steps. First, AD-specific genes were selected. For this, we generated gene expression profiles for sham (media)–treated skin samples from healthy control subjects, patients with AD, and patients with psoriasis. Significant changes in gene expression of AD samples compared with either control or psoriatic samples were considered AD specific. Genes that were significant in both comparisons were selected as our first-line candidates. Second, we identified VV-specific genes using the same approach. Gene expression profiles for VV-treated skin samples from healthy control subjects, patients with AD, and patients with psoriasis were generated. VV-responsive genes in patients with AD but not in control subjects or patients with psoriasis were considered VV/AD specific. Those that have been called “significant” by both comparisons (patients with AD vs healthy subjects and patients with AD vs patients with psoriasis) become our first-line candidates. The AD-specific genes were subtracted from the VV/AD-specific genes to further narrow our candidate list, resulting in a VV-specific pool.

Gene ontology analysis

The MAPPFinder compatible files were prepared by using the GenMAPP converting tool, as described previously.¹⁸ Significant bioprocesses were selected by choosing GO terms containing greater than 5% of the total number of genes linked by MAPPFinder. A z score of greater than 2 and first GO node of greater than 0 were also applied as filtering criteria. Generalized terms, such as “development” and “signal transduction,” were not considered.

Real-time RT-PCR validation

Transcript levels of 10 selected candidate genes were measured ($n = 3$ per condition), as previously described.¹¹ Briefly, the 96-well microtiter plate setting of an ABI Prism 7700 Sequence Detector System (Perkin-Elmer/Applied Biosystems) was used with addition of multiple internal controls (huACTB, huGAPDH, and huPGK1). The mRNA expression levels were normalized to the average concentrations of 3 internal controls: huACTB, huGAPDH, and huPGK1. All experimental protocols were based on the manufacturers’ recommendations using the TaqMan Gold RT-PCR Core Reagents Kit (Perkin-Elmer/Applied Biosystems). The significance of the obtained differences was assessed by using t tests in which a P value of less than .05 was considered significant.

Biomarker-association analysis

Transcriptional signals of sham (media)–treated AD skin explants were used as basal gene expression and pairwise subtracted from corresponding VV-affected transcriptional signals. Resulting changes in expression were correlated with EASI scores of the population of patients with AD. To reduce the level of type II error,¹⁹ because of the small sample size, the symmetric trimming of the highest and the lowest EASI scores was conducted. Gene expression profiles were sorted by EASI scores and R (correlation coefficient) and P (2-tailed probability) values identified with the llinregress() function of the Python Statistical Module.¹⁰ EASI-associated changes in gene expression were evaluated as the FC difference among the 3 samples with the lowest and 3 samples with the highest EASI scores, as described previously.¹¹ Genes with R values of greater than 0.7 and FCs of greater than 2 or R values of less

than -0.7 and FCs of less than -2 were considered significantly associated with the EASI score, as defined by Beck et al.⁵ The full list of R and FC values is provided in [Table E4](#). Detailed GO analysis of AD severity-associated genes is combined in [Table E4](#).

PubMatrix analysis

VV-affected transcripts in AD samples were searched against “skin,” “dermatitis,” and “atopic dermatitis” terms in the PubMed database by using the PubMatrix automated literature search engine.²⁰

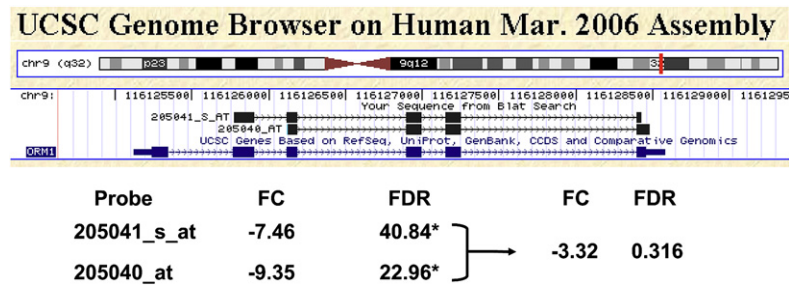


FIG E1. VV -induced transcriptional changes in psoriatic skin biopsy specimens from unaffected areas. **A**, Gene expression analysis was conducted with standard (*solid circles*) and clustering (*dashed circles*) approaches (see the Methods section). The *single* pool represents the number of significantly different genes that were detected by using information from individual probe sets per gene (generating >1 value per gene). The *doublets* and *triplets* pools represent the number of significantly different genes that are targeted by 2 or 3 probe sets, respectively, and were analyzed by using combined values of those probe sets (generating only 1 value per gene). **B**, Cross-referencing of VV effects in psoriatic (*dashed circles*) and AD (*solid circles*) skin.

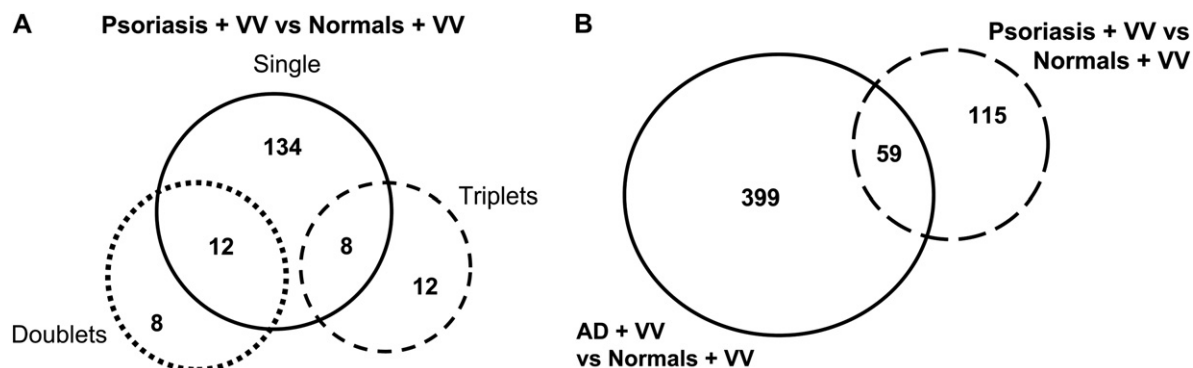


FIG E2. Genome alignment and hybridization pattern of *ORM1* probe sets in skin tissues detected by using the GeneChip array. The snapshot of the GoldenPath browser (Human genome March 2006 Build) of chromosomal alignments of *ORM1* gene and its corresponding probe sets. Each exon is shown as a *horizontal solid rectangle* where the narrow region of the last exon represents the 3' untranslated region. The intronic regions are represented by *solid lines*, with *arrows* showing the direction of transcription. The SAM-calculated FC and false discovery rate (*FDR*) values are reported below the genome alignment diagram. *Not significant (false discovery rate >5). *UCSC*, University of California Santa Cruz.

TABLE E1. Filtering values for identification of significant genes

Data set	Media treated				VV treated					
	AD vs normal skin		AD vs psoriatic skin		AD vs normal skin		AD vs psoriatic skin		Psoriatic vs normal skin	
	FC	FDR	FC	FDR	FC	FDR	FC	FDR	FC	FDR
Single	1.69	5.0	1.70	4.6	1.72	3.9	1.74	3.3	1.69	5.0
Doublets	1.46	4.6	1.44	4.7	1.46	3.2	1.44	4.7	1.51	3.9
Triplets	1.36	3.0	1.34	4.3	1.36	3.0	1.34	4.3	1.40	3.5

FDR, False discovery rate.

TABLE E2. Effects of VV in patients with AD compared with healthy subjects

Probe ID	Gene symbol	FC	q Value (%)
205040_at/205041_s_at	<i>ORM1</i>	-8.41	2.272
205719_s_at	<i>PAH</i>	-8.35	0.100
206754_s_at	<i>CYP2B7P1</i>	-8.33	0.431
206505_at	<i>UGT2B4</i>	-7.81	1.233
230554_at	<i>ACSM2A</i>	-6.81	0.241
205650_s_at	<i>FGA</i>	-6.46	0.527
206651_s_at	<i>CPB2</i>	-5.98	0.947
206727_at	<i>C9</i>	-5.62	0.351
207218_at	<i>F9</i>	-5.61	0.736
214465_at	<i>ORM2</i>	-5.60	0.351
211429_s_at	<i>SERPINA1</i>	-5.59	0.106
205302_at	<i>IGFBP1</i>	-5.54	0.527
217683_at	<i>HBE1</i>	-5.40	<0.05
206697_s_at/208470_s_at	<i>HP</i>	-5.33	1.614
210929_s_at	<i>AHSG</i>	-5.22	3.153
210013_at	<i>HPX</i>	-5.18	3.153
202833_s_at/211429_s_at/230318_at	<i>AGT</i>	-5.14	<0.05
214063_s_at	<i>TF</i>	-5.09	1.233
206350_at	<i>APCS</i>	-4.80	0.736
220017_x_at	<i>CYP2C9</i>	-4.74	0.947
206293_at	<i>SULT2A1</i>	-4.68	1.233
204416_x_at	<i>APOC1</i>	-4.56	0.106
204705_x_at/211357_s_at/214423_x_at	<i>ALDOB</i>	-4.41	<0.05
205654_at	<i>C4BPA</i>	-4.28	3.784
37020_at	<i>CRP</i>	-3.99	3.784
230702_at	<i>C8orf16</i>	-3.89	<0.05
205700_at/37512_at	<i>HSD17B6</i>	-3.65	1.631
206054_at/217512_at	<i>KNG1</i>	-3.31	2.884
205477_s_at/214425_at	<i>AMBP</i>	-3.06	2.272
220626_at	<i>SERPINA10</i>	-2.81	3.153
217564_s_at	<i>CPS1</i>	-2.70	0.527
220786_s_at	<i>SLC38A4</i>	-2.64	0.100
227232_at	<i>EVL</i>	-2.58	<0.05
209728_at	<i>HLA-DRB4</i>	-2.58	2.354
202834_at	<i>TXNL4A</i>	-2.57	0.100
204607_at	<i>HMGCS2</i>	-2.53	<0.05
205999_x_at	<i>CYP3A4</i>	-2.52	0.106
229819_at	<i>AIBG</i>	-2.52	<0.05
226548_at	<i>SBK1</i>	-2.46	<0.05
214261_s_at	<i>ADH6</i>	-2.46	<0.05
209660_at	<i>TTR</i>	-2.39	0.241
222943_at	<i>GBA3</i>	-2.36	1.233
217022_s_at	<i>IGHA1</i>	-2.36	0.175
207861_at	<i>CCL22</i>	-2.35	<0.05
205221_at	<i>HGD</i>	-2.32	0.106
205871_at	<i>PLGLA1</i>	-2.30	2.354
217593_at	<i>ZSCAN18</i>	-2.29	<0.05
206345_s_at	<i>PON1</i>	-2.29	1.233
213592_at	<i>AGTRL1</i>	-2.27	<0.05
209138_x_at	<i>IGL@</i>	-2.27	<0.05
215271_at	<i>TNN</i>	-2.24	0.527
204339_s_at	<i>RGS4</i>	-2.24	<0.05
216388_s_at	<i>LTB4R</i>	-2.20	<0.05
201927_s_at	<i>PKP4</i>	-2.18	<0.05
225960_at	<i>ZNRF1</i>	-2.18	<0.05
202376_at	<i>SERPINA3</i>	-2.17	0.351
203854_at	<i>CFI</i>	-2.16	0.736
207407_x_at	<i>CYP4A11</i>	-2.15	<0.05
203989_x_at	<i>F2R</i>	-2.15	<0.05
210168_at	<i>C6</i>	-2.13	0.175
205924_at	<i>RAB3B</i>	-2.12	<0.05
208451_s_at	<i>C4A</i>	-2.11	<0.05

(Continued)

TABLE E2. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
238160_at	<i>ACOT12</i>	-2.11	<0.05
234980_at	<i>TMEM56</i>	-2.11	1.649
239704_at	<i>RNF144B</i>	-2.10	<0.05
205457_at	<i>C6orf106</i>	-2.10	<0.05
235540_at	<i>GNRH1</i>	-2.10	<0.05
226755_at	<i>LOC642587</i>	-2.10	<0.05
1553333_at	<i>C1orf161</i>	-2.07	<0.05
202549_at	<i>VAPB</i>	-2.07	<0.05
1559094_at/1559096_x_at/1566507_a_at	<i>FBXO9</i>	-2.06	<0.05
206354_at	<i>SLCO1B3</i>	-2.05	0.527
203803_at	<i>PCYOX1</i>	-2.05	<0.05
236140_at	<i>GCLM</i>	-2.03	<0.05
212671_s_at	<i>HLA-DQA1</i>	-2.03	0.100
216074_x_at	<i>WWC1</i>	-2.02	<0.05
201668_x_at	<i>MARCKS</i>	-2.02	<0.05
201596_x_at	<i>KRT18</i>	-2.01	<0.05
212113_at	<i>LOC552889</i>	-2.01	<0.05
210368_at	<i>PCDHGA8</i>	-2.01	0.241
214320_x_at	<i>CYP2A6</i>	-2.00	<0.05
209696_at	<i>FBP1</i>	-2.00	0.241
211743_s_at	<i>PRG2</i>	-1.99	<0.05
243543_at	<i>ADH1B</i>	-1.98	<0.05
221651_x_at	<i>IGKC</i>	-1.97	2.354
215101_s_at	<i>CXCL5</i>	-1.97	<0.05
213089_at	<i>GUSBP1</i>	-1.97	<0.05
1552563_a_at	<i>C8orf6</i>	-1.96	0.175
204734_at	<i>KRT15</i>	-1.96	<0.05
230630_at	<i>AK3L2</i>	-1.95	<0.05
239022_at	<i>SDHALP1</i>	-1.95	<0.05
224730_at	<i>WDR68</i>	-1.94	<0.05
206957_at	<i>AGXT</i>	-1.94	0.736
228844_at	<i>SLC13A5</i>	-1.94	0.100
204636_at	<i>COL17A1</i>	-1.94	<0.05
206979_at	<i>C8B</i>	-1.93	3.784
220801_s_at	<i>HAO2</i>	-1.92	0.100
226216_at	<i>INSR</i>	-1.92	<0.05
1552622_s_at	<i>LOC441259</i>	-1.92	<0.05
206133_at	<i>XAF1</i>	-1.92	0.100
204044_at	<i>QPRT</i>	-1.92	0.527
243292_at	<i>LOC220729</i>	-1.91	<0.05
219250_s_at	<i>FLRT3</i>	-1.91	3.153
1431_at/209975_at/209976_s_at	<i>CYP2E1</i>	-1.91	<0.05
232480_at	<i>FLJ27365</i>	-1.91	<0.05
31835_at	<i>HRG</i>	-1.90	0.175
218960_at	<i>TMPRSS4</i>	-1.90	<0.05
1558011_at/213089_at	<i>LOC340089</i>	-1.90	1.957
203757_s_at	<i>CEACAM6</i>	-1.90	<0.05
232079_s_at	<i>PVRL2</i>	-1.89	<0.05
232494_at	<i>CYP8B1</i>	-1.89	3.784
213336_at	<i>BAZ1B</i>	-1.87	<0.05
221882_s_at	<i>TMEM8</i>	-1.87	<0.05
221029_s_at	<i>WNT5B</i>	-1.87	<0.05
204858_s_at	<i>ECGF1</i>	-1.87	<0.05
1567014_s_at	<i>NFE2L2</i>	-1.87	<0.05
213577_at	<i>SQLE</i>	-1.87	<0.05
223525_at	<i>DLL4</i>	-1.86	<0.05
233882_s_at	<i>SEMA6D</i>	-1.86	<0.05
234284_at	<i>GNG8</i>	-1.86	<0.05
211668_s_at	<i>PLAU</i>	-1.86	<0.05
222439_s_at	<i>THRAP3</i>	-1.86	<0.05
209270_at	<i>LAMB3</i>	-1.86	<0.05
205325_at	<i>PHYHIP</i>	-1.85	<0.05

(Continued)

TABLE E2. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
203936_s_at	<i>MMP9</i>	-1.85	<0.05
230180_at	<i>DDX17</i>	-1.84	<0.05
1557953_at	<i>ZKSCAN1</i>	-1.84	<0.05
1558621_at	<i>CABLES1</i>	-1.84	<0.05
200835_s_at	<i>MAP4</i>	-1.84	0.241
224943_at	<i>BTBD7</i>	-1.84	<0.05
223916_s_at	<i>BCOR</i>	-1.84	<0.05
201884_at	<i>CEACAM5</i>	-1.84	<0.05
207491_at	<i>MOGAT2</i>	-1.83	<0.05
205731_s_at	<i>NCOA2</i>	-1.83	<0.05
1558378_a_at	<i>AHNAK2</i>	-1.83	0.527
214240_at	<i>GAL</i>	-1.83	0.736
206712_at	<i>GRTP1</i>	-1.83	0.106
208890_s_at	<i>PLXNB2</i>	-1.83	<0.05
203683_s_at	<i>VEGFB</i>	-1.83	<0.05
205031_at	<i>EFNB3</i>	-1.82	<0.05
212285_s_at	<i>AGRN</i>	-1.82	<0.05
214958_s_at	<i>TMC6</i>	-1.82	<0.05
230380_at	<i>THAP2</i>	-1.82	0.106
201508_at	<i>IGFBP4</i>	-1.82	<0.05
205844_at	<i>VNN1</i>	-1.81	0.106
228040_at	<i>LOC728903</i>	-1.81	<0.05
213605_s_at	<i>LOC728411</i>	-1.81	<0.05
225009_at	<i>CMTM4</i>	-1.81	<0.05
203056_s_at	<i>PRDM2</i>	-1.81	<0.05
219269_at	<i>HMBOX1</i>	-1.81	<0.05
212771_at	<i>C10orf38</i>	-1.81	<0.05
225115_at	<i>HIPK2</i>	-1.80	0.175
204421_s_at/204422_s_at/220183_s_at	<i>FGF2</i>	-1.80	<0.05
212073_at	<i>CSNK2A1</i>	-1.80	<0.05
1554821_a_at	<i>ZBED1</i>	-1.80	<0.05
238350_at	<i>FLJ25778</i>	-1.79	<0.05
1558220_at	<i>MUC20</i>	-1.79	0.175
204463_s_at	<i>EDNRA</i>	-1.79	<0.05
211081_s_at	<i>MAP4K5</i>	-1.79	0.431
222652_s_at	<i>N-PAC</i>	-1.79	<0.05
212107_s_at	<i>DHX9</i>	-1.79	<0.05
239213_at	<i>SERPINB1</i>	-1.79	<0.05
218272_at	<i>FLJ20699</i>	-1.79	<0.05
202067_s_at	<i>LDLR</i>	-1.79	0.100
203147_s_at	<i>TRIM14</i>	-1.79	<0.05
217538_at	<i>SGSM2</i>	-1.78	<0.05
1563228_x_at	<i>MGC15523</i>	-1.78	<0.05
1570388_a_at	<i>LOC440896</i>	-1.78	0.947
1564796_at	<i>EMP1</i>	-1.78	0.106
205208_at	<i>ALDH1L1</i>	-1.78	<0.05
201072_s_at	<i>SMARCC1</i>	-1.78	<0.05
212332_at	<i>RBL2</i>	-1.77	0.100
209241_x_at	<i>MINK1</i>	-1.77	<0.05
231235_at	<i>NKTR</i>	-1.77	<0.05
209616_s_at	<i>CES1</i>	-1.77	<0.05
213408_s_at	<i>PI4KA</i>	-1.77	<0.05
208893_s_at	<i>DUSP6</i>	-1.77	<0.05
239392_s_at	<i>POGK</i>	-1.77	<0.05
204933_s_at	<i>TNFRSF11B</i>	-1.77	<0.05
215355_at	<i>POU2F3</i>	-1.77	<0.05
209278_s_at	<i>TFPI2</i>	-1.77	<0.05
230645_at	<i>FRMD3</i>	-1.77	0.527
228068_at	<i>C10orf132</i>	-1.77	<0.05
213260_at	<i>FOXC1</i>	-1.77	<0.05
204029_at	<i>CELSR2</i>	-1.76	<0.05
202669_s_at	<i>EFNB2</i>	-1.76	0.100

(Continued)

TABLE E2. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
213695_at	PON3	-1.76	<0.05
203796_s_at	BCL7A	-1.76	<0.05
202935_s_at	SOX9	-1.76	0.100
205076_s_at	MTMR11	-1.75	<0.05
204836_at	GLDC	-1.75	1.233
226715_at	FOXK1	-1.75	<0.05
221753_at	SSH1	-1.75	<0.05
1557582_at	BIN3	-1.75	<0.05
219360_s_at	TRPM4	-1.75	<0.05
1568640_at	LOC400960	-1.75	<0.05
206503_x_at	PML	-1.75	<0.05
229164_s_at	ABTB1	-1.74	<0.05
1552621_at/1552622_s_at/1554182_at	POLR2J2	-1.74	<0.05
215513_at	HYMAI	-1.74	<0.05
202440_s_at	ST5	-1.74	<0.05
205552_s_at	OAS1	-1.74	0.106
206065_s_at	DPYS	-1.74	2.354
209727_at	GM2A	-1.74	<0.05
1570505_at	ABCB4	-1.74	0.175
205379_at	CBR3	-1.74	<0.05
209643_s_at	PLD2	-1.74	<0.05
204154_at	CDO1	-1.74	0.106
227405_s_at	FZD8	-1.73	<0.05
238168_at	TM4SF1	-1.73	<0.05
209848_s_at	SILV	-1.73	<0.05
200917_s_at	SRPR	-1.73	0.527
227996_at	FARP1	-1.73	<0.05
209823_x_at/211654_x_at/211656_x_at	HLA-DQB1	-1.68	<0.05
223019_at/233974_s_at	FAM129B	-1.67	0.378
1555997_s_at/203425_s_at/203426_s_at	IGFBP5	-1.65	<0.05
223781_x_at/231678_s_at	ADH4	-1.65	1.285
202855_s_at/202856_s_at	SLC16A3	-1.64	0.378
214234_s_at/214235_at	CYP3A5	-1.64	<0.05
221204_s_at/228068_at	CRTAC1	-1.63	0.378
206576_s_at/209498_at	CEACAM1	-1.63	<0.05
221756_at/221757_at	PIK3IP1	-1.62	<0.05
1565436_s_at/212078_s_at/212079_s_at	MLL	-1.62	<0.05
202340_x_at/211143_x_at	NR4A1	-1.62	<0.05
201867_s_at/201868_s_at	TBLIX	-1.61	<0.05
224784_at/225628_s_at	MLLT6	-1.61	<0.05
228195_at/232773_at	MGC13057	-1.60	1.614
206929_s_at/213298_at	NFIC	-1.58	<0.05
1552862_at/230256_at	C1orf104	-1.56	1.285
202315_s_at/217223_s_at	BCR	-1.56	<0.05
219723_x_at/223182_s_at/223183_at	AGPAT3	-1.56	<0.05
227740_at/235003_at	UHMK1	-1.55	0.922
204670_x_at/209312_x_at/209728_at	HLA-DRB1	-1.55	<0.05
200635_s_at/200636_s_at/200637_s_at	PTPRF	-1.54	<0.05
222162_s_at/222486_s_at	ADAMTS1	-1.54	<0.05
221562_s_at/221647_s_at/221913_at	SIRT3	-1.53	<0.05
205768_s_at/205769_at	SLC27A2	-1.53	1.776
218384_at/224910_at	CARHSP1	-1.53	<0.05
210778_s_at/212346_s_at/212347_x_at	MXD4	-1.52	<0.05
207966_s_at/214730_s_at	GLG1	-1.52	<0.05
205187_at/205188_s_at/225219_at	SMAD5	-1.52	1.881
200679_x_at/210985_s_at/216508_x_at	HMGB1	-1.51	1.237
202203_s_at/202204_s_at	AMFR	-1.51	1.285
200616_s_at/200617_at	KIAA0152	-1.50	<0.05
200678_x_at/211284_s_at/216041_x_at	GRN	-1.50	<0.05
1554916_a_at/1568605_at/214692_s_at	JRK	-1.50	<0.05
207522_s_at/213036_x_at	ATP2A3	-1.50	0.614
209528_s_at/34260_at	TELO2	-1.49	<0.05

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TABLE E2. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
227449_at/228948_at/229374_at	<i>EPHA4</i>	-1.49	<0.05
209008_x_at/216821_at	<i>KRT8</i>	-1.49	2.884
210094_s_at/221526_x_at	<i>PARD3</i>	-1.49	<0.05
1554600_s_at/203411_s_at/212086_x_at	<i>LMNA</i>	-1.48	<0.05
206061_s_at/212888_at/213229_at	<i>DICER1</i>	-1.47	<0.05
238460_at/242944_at	<i>FAM83A</i>	-1.47	1.614
1561355_at/1569453_a_at	<i>LOC692247</i>	-1.47	0.378
209436_at/209437_s_at/213993_at	<i>SPON1</i>	-1.47	<0.05
208455_at/225211_at	<i>PVRL1</i>	-1.47	2.272
1556359_at/224977_at/224987_at	<i>C6orf89</i>	-1.47	<0.05
204998_s_at/204999_s_at	<i>ATF5</i>	-1.47	1.312
203348_s_at/203349_s_at	<i>ETV5</i>	-1.47	0.614
213839_at/225759_x_at	<i>KIAA0500</i>	-1.47	0.614
203249_at/32259_at	<i>EZH1</i>	-1.47	<0.05
209297_at/209298_s_at/210713_at	<i>ITSN1</i>	-1.46	<0.05
201625_s_at/201626_at/201627_s_at	<i>INSIG1</i>	-1.46	<0.05
203445_s_at/208735_s_at	<i>CTDSP2</i>	-1.46	1.631
206543_at/225127_at	<i>SMARCA2</i>	-1.46	1.957
202940_at/39313_at	<i>WNK1</i>	-1.46	2.272
205614_x_at/213380_x_at/216320_x_at	<i>MST1</i>	-1.45	<0.05
202262_x_at/214909_s_at/215537_x_at	<i>DDAH2</i>	-1.45	<0.05
1555470_a_at/203063_at/37384_at	<i>PPM1F</i>	-1.44	<0.05
220454_s_at/223449_at/225660_at	<i>SEMA6A</i>	-1.43	<0.05
209465_x_at/209466_x_at/211737_x_at	<i>PTN</i>	-1.43	<0.05
203627_at/203628_at/225330_at	<i>IGF1R</i>	-1.43	<0.05
209370_s_at/209371_s_at/211250_s_at	<i>SH3BP2</i>	-1.43	<0.05
209372_x_at/213476_x_at/214023_x_at	<i>TUBB2A</i>	-1.42	<0.05
204875_s_at/214106_s_at/232779_at	<i>GMDS</i>	-1.42	<0.05
210847_x_at/211282_x_at/211841_s_at	<i>PLEKHG5</i>	-1.42	<0.05
221064_s_at/224887_at/229908_s_at	<i>C16orf28</i>	-1.41	<0.05
1552611_a_at/239695_at/240613_at	<i>JAK1</i>	-1.41	<0.05
220412_x_at/224008_s_at/224055_x_at	<i>KCNK7</i>	-1.41	<0.05
204060_s_at/204061_at/206279_at	<i>PRKX</i>	-1.41	<0.05
1557228_at/1557749_at/221755_at	<i>EHBP1L1</i>	-1.41	<0.05
212399_s_at/214004_s_at/222709_at	<i>VGLL4</i>	-1.40	<0.05
209499_x_at/209500_x_at/210314_x_at	<i>TNFSF12-TNFSF13</i>	-1.40	<0.05
204595_s_at/204596_s_at/204597_x_at	<i>STC1</i>	-1.40	<0.05
210854_x_at/213843_x_at/215812_s_at	<i>SLC6A8</i>	-1.40	<0.05
223005_s_at/223006_s_at/223007_s_at	<i>C9orf5</i>	-1.40	<0.05
1558117_s_at/226033_at/226035_at	<i>USP31</i>	-1.39	<0.05
205195_at/205196_s_at/209635_at	<i>AP1S1</i>	-1.39	1.549
209026_x_at/211714_x_at/212320_at	<i>TUBB</i>	-1.39	<0.05
203392_s_at/212863_x_at/213979_s_at	<i>CTBP1</i>	-1.38	1.012
224611_s_at/224612_s_at/224613_s_at	<i>DNAJC5</i>	-1.38	<0.05
204556_s_at/204557_s_at/205328_at	<i>DZIP1</i>	-1.37	<0.05
209163_at/209164_s_at/210816_s_at	<i>CYBS61</i>	-1.37	1.881
1559159_at/207971_s_at/239442_at	<i>CEP68</i>	-1.37	1.237
201536_at/201537_s_at/201538_s_at	<i>DUSP3</i>	-1.36	1.237
201874_at/201875_s_at/210087_s_at	<i>LOC644387</i>	-1.36	<0.05
210092_at/210093_s_at/217692_at	<i>MAGOH</i>	1.36	2.866
225783_at/225787_at/231948_s_at	<i>UBE2F</i>	1.37	1.750
205849_s_at/209065_at/209066_x_at	<i>UQCRB</i>	1.38	1.881
212857_x_at/214512_s_at/224586_x_at	<i>SUB1</i>	1.38	1.881
206288_at/235615_at/242844_at	<i>PGGT1B</i>	1.39	2.866
203465_at/216305_s_at/232071_at	<i>MRPL19</i>	1.40	2.866
207023_x_at/210633_x_at/213287_s_at	<i>KRT10</i>	1.40	0.899
205063_at/210779_x_at/211114_x_at	<i>SIP1</i>	1.41	0.899
1568955_at/1568957_x_at/229067_at	<i>SRGAP2P1</i>	1.42	0.899
218643_s_at/220682_s_at/222702_x_at	<i>CRIP1</i>	1.42	2.337
202141_s_at/202142_at/214260_at	<i>COPS8</i>	1.43	1.033
219657_s_at/222913_at/225133_at	<i>KLF3</i>	1.46	1.750
1568954_s_at/217682_at	<i>C16orf72</i>	1.46	2.272

(Continued)

TABLE E2. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
208180_s_at/208181_at	<i>HIST1H4H</i>	1.46	2.272
209707_at/227639_at	<i>PIGK</i>	1.46	0.922
1554095_at/1554096_a_at/234753_x_at	<i>RBM33</i>	1.46	1.549
219975_x_at/233126_s_at	<i>OLAH</i>	1.47	1.614
205098_at/205099_s_at	<i>CCR1</i>	1.47	2.272
238762_at/239562_at	<i>MTHFD2L</i>	1.47	1.185
219573_at/230793_at	<i>LRRC16</i>	1.47	1.185
1554482_a_at/218254_s_at	<i>SAR1B</i>	1.47	1.776
1555471_a_at/223618_at	<i>FMN2</i>	1.48	1.631
219546_at/59644_at	<i>BMP2 K</i>	1.48	0.537
225922_at/225924_at	<i>KIAA1450</i>	1.48	2.272
207247_s_at/207920_x_at/214678_x_at	<i>ZFX</i>	1.49	0.899
1553338_at/244103_at	<i>C1orf55</i>	1.50	1.631
219810_at/234988_at	<i>VCPIP1</i>	1.50	0.922
207845_s_at/208446_s_at	<i>ANAPC10</i>	1.50	1.185
1554241_at/204496_at/215505_s_at	<i>COCH</i>	1.50	1.549
221803_s_at/223650_s_at	<i>NRBF2</i>	1.51	2.272
220285_at/227551_at	<i>FAM108B1</i>	1.51	1.185
205116_at/213519_s_at	<i>LAMA2</i>	1.52	0.922
235338_s_at/238731_at	<i>SETDB2</i>	1.53	1.776
220175_s_at/229804_x_at	<i>CBWD1</i>	1.53	1.185
217919_s_at/222466_s_at	<i>MRPL42</i>	1.53	0.537
205250_s_at/213701_at/228378_at	<i>CEP290</i>	1.54	0.899
216718_at/216935_at	<i>C1orf46</i>	1.55	2.884
227628_at/228141_at	<i>LOC493869</i>	1.55	0.537
202920_at/202921_s_at	<i>ANK2</i>	1.56	0.922
202634_at/202635_s_at	<i>POLR2K</i>	1.56	0.537
215150_at/224050_s_at/224051_at	<i>YOD1</i>	1.56	0.899
202291_s_at/238481_at	<i>MGP</i>	1.57	1.185
225036_at/228053_s_at	<i>C9orf105</i>	1.58	1.185
205361_s_at/205362_s_at	<i>PFDN4</i>	1.58	2.272
226145_s_at/231511_at	<i>FRAS1</i>	1.65	1.185
218330_s_at/222598_s_at/222599_s_at	<i>NAV2</i>	1.65	2.866
208118_x_at/210396_s_at	<i>IMAA</i>	1.65	0.922
1554915_a_at/231839_at	<i>2'-PDE</i>	1.69	0.537
238677_at	<i>WDR36</i>	1.72	<0.05
233504_at	<i>C9orf84</i>	1.72	0.084
227840_at	<i>LOC130355</i>	1.72	<0.05
206604_at/229396_at	<i>OVOL1</i>	1.72	2.272
208567_s_at	<i>KCNJ12</i>	1.73	3.784
234405_s_at	<i>RNUXA</i>	1.73	0.106
224315_at	<i>DDX20</i>	1.73	0.084
209335_at	<i>DCN</i>	1.73	<0.05
1554719_at	<i>NDUFA10</i>	1.73	0.947
204161_s_at	<i>ENPP4</i>	1.73	<0.05
36742_at	<i>TRIM15</i>	1.73	0.527
204351_at	<i>SI00P</i>	1.73	<0.05
228186_s_at	<i>RSPO3</i>	1.73	0.106
229444_at	<i>LOC729776</i>	1.73	0.084
227214_at	<i>GOPC</i>	1.74	<0.05
1553137_s_at	<i>KLF11</i>	1.74	0.084
222765_x_at	<i>ESF1</i>	1.74	<0.05
209451_at	<i>TANK</i>	1.74	<0.05
219949_at	<i>LRRC2</i>	1.74	0.351
244224_x_at	<i>LYNX1</i>	1.74	<0.05
239781_at	<i>hCG_1815504</i>	1.75	1.649
221634_at	<i>RPL23AP7</i>	1.75	<0.05
225686_at	<i>FAM33A</i>	1.75	<0.05
221156_x_at	<i>CCPG1</i>	1.75	<0.05
224723_x_at	<i>LOC401397</i>	1.76	<0.05
1553835_a_at	<i>FLJ35880</i>	1.76	0.947
219284_at	<i>HSPBAP1</i>	1.76	<0.05

(Continued)

TABLE E2. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
1554256_a_at	<i>PCNXL2</i>	1.77	<0.05
235535_x_at	<i>C20orf80</i>	1.77	1.649
224463_s_at	<i>C11orf70</i>	1.78	<0.05
238575_at	<i>OSBPL6</i>	1.78	<0.05
213566_at	<i>RNASE6</i>	1.78	<0.05
1553581_s_at	<i>P18SRP</i>	1.78	0.431
1554556_a_at	<i>ATP11B</i>	1.79	<0.05
222039_at	<i>LOC146909</i>	1.79	<0.05
1553286_at	<i>ZNF555</i>	1.79	<0.05
222438_at	<i>MED4</i>	1.80	<0.05
204162_at	<i>NDC80</i>	1.81	<0.05
1555513_at	<i>PIAS2</i>	1.81	<0.05
229390_at	<i>FAM26F</i>	1.81	0.947
204349_at	<i>MED7</i>	1.81	<0.05
1553133_at	<i>C9orf72</i>	1.81	1.649
207302_at	<i>SGCG</i>	1.82	0.175
202287_s_at	<i>TACSTD2</i>	1.82	0.106
1554014_at	<i>CHD2</i>	1.83	<0.05
231175_at	<i>C6orf65</i>	1.83	<0.05
218936_s_at	<i>CCDC59</i>	1.83	<0.05
218886_at	<i>PAK11P1</i>	1.83	0.084
209859_at	<i>TRIM9</i>	1.83	<0.05
238717_at	<i>LOC729137</i>	1.84	0.175
226218_at	<i>IL7R</i>	1.84	0.084
206643_at	<i>HAL</i>	1.85	<0.05
210861_s_at	<i>WISP3</i>	1.85	<0.05
219386_s_at	<i>SLAMF8</i>	1.86	0.084
226588_at	<i>KIAA1604</i>	1.86	0.241
239381_at	<i>KLK7</i>	1.87	0.175
205767_at	<i>EREG</i>	1.87	0.527
1552897_a_at	<i>KCNG3</i>	1.88	<0.05
219037_at	<i>RRP15</i>	1.88	<0.05
1554309_at	<i>EIF4G3</i>	1.88	<0.05
1554314_at	<i>C6orf141</i>	1.89	<0.05
205046_at	<i>CENPE</i>	1.89	<0.05
209363_s_at	<i>MED21</i>	1.89	<0.05
225762_x_at	<i>LOC284801</i>	1.89	3.784
1554047_at	<i>TXNDC9</i>	1.89	<0.05
239835_at	<i>KBTBD8</i>	1.90	0.084
227399_at	<i>VGLL3</i>	1.90	<0.05
227015_at	<i>ASPHD2</i>	1.90	<0.05
228796_at	<i>CPNE4</i>	1.90	<0.05
237968_at	<i>ARL6IP2</i>	1.90	<0.05
239878_at	<i>IPMK</i>	1.91	0.241
219607_s_at	<i>MS4A4A</i>	1.91	0.241
206373_at	<i>ZIC1</i>	1.92	1.233
224209_s_at	<i>GDA</i>	1.93	0.527
215779_s_at	<i>HIST1H2BG</i>	1.94	0.084
236341_at	<i>CTLA4</i>	1.94	0.106
237342_at	<i>TOLLIP</i>	1.95	<0.05
206584_at	<i>LY96</i>	1.95	<0.05
236119_s_at	<i>SPRR2G</i>	1.96	0.084
1558552_s_at/206157_at/224254_x_at	<i>C3orf55</i>	1.96	2.337
1557609_s_at	<i>TBC1D12</i>	1.98	3.153
1553697_at	<i>C1orf96</i>	1.98	0.175
1553736_at	<i>CCDC131</i>	1.98	0.175
206227_at	<i>CILP</i>	1.99	0.175
206023_at	<i>NMU</i>	1.99	0.106
223631_s_at	<i>C19orf33</i>	2.00	0.084
1555756_a_at	<i>CLEC7A</i>	2.02	0.084
1555019_at	<i>PCDH21</i>	2.04	3.784
228128_x_at	<i>PAPPA</i>	2.04	<0.05

(Continued)

TABLE E2. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
205433_at	<i>BCHE</i>	2.06	<0.05
207165_at	<i>HMMR</i>	2.10	<0.05
225195_at	<i>DPH3</i>	2.12	<0.05
206177_s_at	<i>ARG1</i>	2.12	<0.05
229566_at	<i>LOC645638</i>	2.15	<0.05
230193_at	<i>WDR66</i>	2.17	0.084
205819_at	<i>MARCO</i>	2.22	<0.05
206157_at	<i>PTX3</i>	2.23	<0.05
213764_s_at	<i>MFAP5</i>	2.26	0.106
227919_at	<i>UCA1</i>	2.26	0.175
224840_at	<i>FKBP5</i>	2.27	3.784
229290_at	<i>DAPL1</i>	2.27	<0.05
236937_at	<i>VPS8</i>	2.28	<0.05
211712_s_at	<i>ANXA9</i>	2.34	<0.05
206951_at	<i>HIST1H4E</i>	2.39	<0.05
230867_at	<i>COL6A6</i>	2.40	0.106
210809_s_at	<i>POSTN</i>	2.62	<0.05
209924_at	<i>CCL18</i>	2.62	<0.05
213436_at	<i>CNR1</i>	2.80	0.431
1554663_a_at	<i>NUMA1</i>	3.01	0.351
227736_at	<i>C10orf99</i>	3.15	<0.05
228501_at	<i>GALNTL2</i>	3.42	<0.05
215049_x_at	<i>CD163</i>	3.65	<0.05
214624_at	<i>UPK1A</i>	3.98	<0.05

TABLE E3. Effects of VV in patients with psoriasis compared with healthy subjects

Affymetrix	Gene symbol	FC	q Value (%)
217022_s_at	IGHA1	-7.25	<0.1
205001_s_at	DDX3X	-6.20	<0.1
221671_x_at	IGKC	-3.46	0.801
205229_s_at	COCH	-3.44	<0.1
205000_at	DDX3Y	-3.11	0.109
204410_at	EIF1AY	-3.08	<0.1
1552620_at	SPRR4	-3.07	2.302
200835_s_at	MAP4	-2.99	<0.1
214131_at	CYorf15B	-2.99	0.801
202765_s_at	FBN1	-2.81	<0.1
201650_at	KRT19	-2.80	<0.1
206624_at	USP9Y	-2.79	<0.1
230760_at	ZFY	-2.79	0.386
204607_at	HMGCS2	-2.54	<0.1
206700_s_at	JARID1D	-2.46	0.600
205457_at	C6orf106	-2.45	<0.1
211062_s_at	CPZ	-2.43	<0.1
202549_at	VAPB	-2.34	<0.1
203854_at	CFI	-2.33	0.160
200917_s_at	SRPR	-2.30	<0.1
229819_at	A1BG	-2.29	0.160
204154_at	CDO1	-2.24	<0.1
214320_x_at	CYP2A6	-2.23	<0.1
1558378_a_at	AHNAK2	-2.18	<0.1
201909_at	RPS4Y1	-2.18	1.192
235763_at	SLC44A5	-2.14	0.109
242918_at	NASP	-2.12	<0.1
214677_x_at	IGL@	-2.11	2.302
240809_at	C21orf121	-2.11	<0.1
235643_at	SAMD9L	-2.07	<0.1
206279_at	PRKY	-2.07	0.386
201008_s_at	TXNIP	-2.07	<0.1
210012_s_at	EWSR1	-2.05	<0.1
209660_at	TTR	-2.03	4.947
211081_s_at	MAP4K5	-2.02	<0.1
235765_at	TLE4	-2.02	<0.1
202773_s_at	SFRS8	-2.02	<0.1
201787_at	FBLN1	-2.02	<0.1
221491_x_at	hCG_1998957	-2.02	3.393
1560020_at	DNAJC13	-2.01	<0.1
241683_at	HECTD1	-2.01	<0.1
210322_x_at	UTY	-2.00	<0.1
214261_s_at	ADH6	-2.00	2.302
226211_at	MEG3	-1.98	<0.1
201615_x_at	CALD1	-1.98	<0.1
206133_at	XAF1	-1.97	<0.1
205221_at	HGD	-1.97	3.393
207063_at	CYorf14	-1.97	0.600
208451_s_at	C4A	-1.96	<0.1
229399_at	C10orf118	-1.96	0.160
209696_at	FBP1	-1.94	4.947
203824_at	TSPAN8	-1.94	<0.1
207703_at	NLGN4Y	-1.93	1.192
215271_at	TNN	-1.92	3.393
213286_at	ZFR	-1.90	<0.1
213446_s_at	IQGAP1	-1.89	<0.1
201058_s_at	MYL9	-1.89	0.307
202311_s_at	COL1A1	-1.89	<0.1
204734_at	KRT15	-1.88	<0.1
206239_s_at	SPINK1	-1.86	4.947
206730_at	GRIA3	-1.86	<0.1
232428_at	MOGAT2	-1.85	0.600

(Continued)

TABLE E3. (Continued)

Affymetrix	Gene symbol	FC	q Value (%)
207754_at	<i>RASSF8</i>	−1.85	1.192
238166_s_at	<i>C17orf51</i>	−1.85	<0.1
208719_s_at	<i>DDX17</i>	−1.84	<0.1
238160_at	<i>ACOT12</i>	−1.84	<0.1
219250_s_at	<i>FLRT3</i>	−1.84	3.393
212107_s_at	<i>DHX9</i>	−1.84	<0.1
220356_at	<i>CORIN</i>	−1.84	0.900
219360_s_at	<i>TRPM4</i>	−1.84	<0.1
211966_at	<i>COL4A2</i>	−1.83	<0.1
226248_s_at	<i>KIAA1324</i>	−1.83	<0.1
219679_s_at	<i>WAC</i>	−1.82	<0.1
205018_s_at	<i>MBNL2</i>	−1.82	0.386
202269_x_at	<i>GBP1</i>	−1.81	<0.1
231671_at	<i>FGA</i>	−1.81	1.525
230478_at	<i>OIT3</i>	−1.80	<0.1
1558093_s_at	<i>LOC727839</i>	−1.80	<0.1
216392_s_at	<i>SEC23IP</i>	−1.79	<0.1
209136_s_at	<i>USP10</i>	−1.79	0.801
222508_s_at	<i>FLJ10154</i>	−1.79	<0.1
210875_s_at	<i>ZEB1</i>	−1.79	<0.1
203056_s_at	<i>PRDM2</i>	−1.79	<0.1
224828_at	<i>CPEB4</i>	−1.78	<0.1
217593_at	<i>ZSCAN18</i>	−1.78	<0.1
234701_at	<i>ANKRD11</i>	−1.78	<0.1
218457_s_at	<i>DNMT3A</i>	−1.77	<0.1
216508_x_at	<i>CTCFL</i>	−1.77	<0.1
214235_at	<i>CYP3A5</i>	−1.77	<0.1
1560705_at	<i>SLC25A28</i>	−1.77	<0.1
202718_at	<i>IGFBP2</i>	−1.77	<0.1
238224_at	<i>CLASP2</i>	−1.77	<0.1
1556551_s_at	<i>SLC39A6</i>	−1.76	<0.1
1553224_at	<i>LUZP1</i>	−1.76	<0.1
244165_at	<i>C10orf18</i>	−1.76	0.386
226548_at	<i>SBK1</i>	−1.75	<0.1
218892_at	<i>DCHS1</i>	−1.75	<0.1
208621_s_at	<i>VIL2</i>	−1.74	<0.1
235645_at	<i>ESCO1</i>	−1.74	3.393
202036_s_at	<i>SFRP1</i>	−1.74	0.801
210057_at	<i>SMG1</i>	−1.74	<0.1
224853_at	<i>SLAIN2</i>	−1.74	<0.1
238811_at	<i>ATP11B</i>	−1.74	0.386
1559129_a_at	<i>LOC158257</i>	−1.73	<0.1
201085_s_at	<i>SON</i>	−1.73	<0.1
205200_at	<i>CLEC3B</i>	−1.73	0.600
202855_s_at	<i>SLC16A3</i>	−1.73	0.900
225241_at	<i>CCDC80</i>	−1.73	<0.1
1569472_s_at	<i>TTC3</i>	−1.73	<0.1
215646_s_at	<i>VCAN</i>	−1.72	<0.1
205620_at	<i>F10</i>	−1.72	<0.1
239397_at	<i>ARHGEF7</i>	−1.72	<0.1
212240_s_at	<i>PIK3R1</i>	−1.72	<0.1
211813_x_at	<i>DCN</i>	−1.72	<0.1
201641_at	<i>BST2</i>	−1.72	0.109
209540_at	<i>IGF1</i>	−1.72	<0.1
1565436_s_at	<i>MLL</i>	−1.72	<0.1
202273_at	<i>PDGFRB</i>	−1.72	<0.1
201708_s_at	<i>NIPSNAP1</i>	−1.72	<0.1
212113_at	<i>LOC552889</i>	−1.71	<0.1
205997_at	<i>ADAM28</i>	−1.71	<0.1
225491_at	<i>SLC1A2</i>	−1.71	<0.1
217602_at	<i>PPIA</i>	−1.71	<0.1

(Continued)

TABLE E3. (Continued)

Affymetrix	Gene symbol	FC	q Value (%)
209616_s_at	<i>CES1</i>	−1.71	<0.1
227860_at	<i>CPXM1</i>	−1.71	2.302
223888_s_at	<i>LARS</i>	−1.71	<0.1
205127_at	<i>PTGS1</i>	−1.70	0.801
1559094_at	<i>FBXO9</i>	−1.70	0.139
1567014_s_at	<i>NFE2L2</i>	−1.70	<0.1
203215_s_at	<i>MYO6</i>	−1.70	<0.1
244508_at	<i>7-Sep</i>	−1.70	0.900
240528_s_at	<i>EXOC4</i>	−1.70	<0.1
240573_at	<i>LOC374443</i>	−1.70	3.393
1568658_at	<i>LOC339804</i>	1.69	<0.1
1568646_x_at	<i>ZNF208</i>	1.70	0.900
237563_s_at	<i>LOC440731</i>	1.70	<0.1
215510_at	<i>ETV2</i>	1.71	<0.1
229007_at	<i>LOC283788</i>	1.72	<0.1
231821_x_at	<i>FLJ14186</i>	1.73	<0.1
217962_at	<i>NOLA3</i>	1.77	0.109
227735_s_at	<i>C10orf99</i>	1.78	<0.1
241784_x_at	<i>HEL308</i>	1.79	<0.1
1558688_at	<i>LOC441461</i>	1.79	<0.1
206951_at	<i>HIST1H4E</i>	1.80	<0.1
229290_at	<i>DAPL1</i>	1.80	<0.1
205749_at	<i>CYP1A1</i>	1.84	0.109
207165_at	<i>HMMR</i>	1.89	<0.1
1559950_at	<i>FAM66C</i>	2.00	<0.1
1556457_s_at	<i>FLJ39739</i>	2.01	0.386
232602_at	<i>WFDC3</i>	2.04	<0.1
223631_s_at	<i>C19orf33</i>	2.23	0.386
224209_s_at	<i>GDA</i>	2.40	<0.1
229152_at	<i>C4orf7</i>	2.53	<0.1
214624_at	<i>UPK1A</i>	3.18	<0.1
230417_at/ 230418_s_at	<i>GALNTL1</i>	−1.52	1.246
204834_at/ 227265_at	<i>FGL2</i>	−1.52	<0.1
202905_x_at/ 217299_s_at	<i>NBN</i>	−1.52	<0.1
1553466_at/ 200679_x_at	<i>CXorf59</i>	−1.54	3.156
241620_at/ 241621_at	<i>SMCHD1</i>	−1.55	<0.1
204998_s_at/ 204999_s_at	<i>ATF5</i>	−1.56	<0.1
207981_s_at/ 209966_x_at	<i>ESRRG</i>	−1.65	<0.1
206344_at/ 206345_s_at	<i>PON1</i>	−1.76	2.340
208178_x_at/ 209011_at/ 209013_x_at	<i>TRIO</i>	−1.41	<0.1
1554600_s_at/ 203411_s_at/ 212086_x_at	<i>LMNA</i>	−1.43	<0.1
206093_x_at/ 208609_s_at/ 213451_x_at	<i>TNXB</i>	−1.44	<0.1
203325_s_at/ 212488_at/ 212489_at	<i>COL5A1</i>	−1.46	<0.1

(Continued)

TABLE E3. (Continued)

Affymetrix	Gene symbol	FC	q Value (%)
213575_at/ 213593_s_at/ 227939_s_at	<i>TRA2A</i>	−1.47	<0.1
209465_x_at/ 209466_x_at/ 211737_x_at	<i>PTN</i>	−1.50	<0.1
1552611_a_at/ 239695_at/ 240613_at	<i>JAK1</i>	−1.52	<0.1
200679_x_at/ 210985_s_at/ 216508_x_at	<i>HMGB1</i>	−1.64	<0.1
1555997_s_at/ 203425_s_at/ 203426_s_at	<i>IGFBP5</i>	−1.68	<0.1
1431_at/ 209975_at/ 209976_s_at	<i>CYP2E1</i>	−1.75	0.387
202833_s_at/ 211429_s_at/ 230318_at	<i>AGT</i>	−2.75	0.670
204705_x_at/ 211357_s_at/ 214423_x_at	<i>ALDOB</i>	−2.83	0.670

TABLE E4. Effects of VV in patients with AD compared with patients with psoriasis

Probe ID	Gene symbol	FC	q Value (%)
209728_at	<i>HLA-DRB4</i>	-4.54	<0.01
233681_at	<i>KRTAP3-3</i>	-4.12	2.198
204409_s_at/204410_at/244482_at	<i>EIF1AY</i>	-3.99	<0.01
206697_s_at	<i>HP</i>	-3.45	<0.01
205041_s_at	<i>ORM1</i>	-3.30	0.316
233533_at	<i>KRTAP1-5</i>	-3.19	0.316
209116_x_at	<i>HBB</i>	-3.03	<0.01
205216_s_at	<i>APOH</i>	-3.02	1.147
230702_at	<i>C8orf16</i>	-3.00	<0.01
211298_s_at	<i>ALB</i>	-2.98	0.316
216810_at	<i>KRTAP4-7</i>	-2.94	0.028
220976_s_at	<i>KRTAP1-1</i>	-2.93	1.147
211743_s_at	<i>PRG2</i>	-2.90	<0.01
219466_s_at	<i>APOA2</i>	-2.84	<0.01
204988_at	<i>FGB</i>	-2.76	1.654
219612_s_at	<i>FGG</i>	-2.55	0.622
227232_at	<i>EVL</i>	-2.55	<0.01
206777_s_at	<i>CRYBB2</i>	-2.54	<0.01
233534_at	<i>KRTAP3-2</i>	-2.52	0.316
211429_s_at	<i>SERPINA1</i>	-2.51	<0.01
214974_x_at	<i>CXCL5</i>	-2.46	<0.01
205649_s_at	<i>FGA</i>	-2.41	0.028
228501_at/236361_at	<i>GALNTL2</i>	-2.40	<0.01
1555778_a_at/210809_s_at	<i>POSTN</i>	-2.40	<0.01
205820_s_at	<i>APOC3</i>	-2.33	0.622
207247_s_at/230760_at	<i>ZFX</i>	-2.29	<0.01
227671_at	<i>XIST</i>	-2.29	<0.01
206754_s_at	<i>CYP2B7P1</i>	-2.29	0.921
207861_at	<i>CCL22</i>	-2.29	<0.01
217683_at	<i>HBE1</i>	-2.26	<0.01
204965_at	<i>GC</i>	-2.25	<0.01
1564796_at	<i>EMP1</i>	-2.24	<0.01
205719_s_at	<i>PAH</i>	-2.24	<0.01
209371_s_at	<i>SH3BP2</i>	-2.21	<0.01
211357_s_at	<i>ALDOB</i>	-2.21	<0.01
41469_at	<i>PI3</i>	-2.19	<0.01
212531_at	<i>LCN2</i>	-2.16	<0.01
204416_x_at	<i>APOC1</i>	-2.15	<0.01
228040_at	<i>LOC728903</i>	-2.13	<0.01
228245_s_at	<i>LOC728715</i>	-2.13	<0.01
207955_at	<i>CCL27</i>	-2.12	<0.01
1559827_at	<i>LOC401074</i>	-2.11	<0.01
206727_at	<i>C9</i>	-2.10	<0.01
205477_s_at	<i>AMBP</i>	-2.10	<0.01
201668_x_at	<i>MARCKS</i>	-2.08	<0.01
207356_at	<i>DEFB4</i>	-2.08	<0.01
205979_at	<i>SCGB2A1</i>	-2.07	<0.01
204007_at	<i>FCGR3B</i>	-2.05	<0.01
216388_s_at	<i>LTB4R</i>	-2.04	<0.01
234685_x_at	<i>KRTAP4-9</i>	-2.02	1.147
206505_at	<i>UGT2B4</i>	-2.01	<0.01
230645_at	<i>FRMD3</i>	-2.01	<0.01
205067_at	<i>IL1B</i>	-2.00	<0.01
205305_at	<i>FGL1</i>	-2.00	0.316
205031_at	<i>EFNB3</i>	-1.99	<0.01
223949_at	<i>TMPRSS3</i>	-1.99	<0.01
220412_x_at	<i>KCNK7</i>	-1.98	<0.01
234994_at	<i>KIAA1913</i>	-1.98	<0.01
209241_x_at	<i>MINK1</i>	-1.97	<0.01
229957_at	<i>TMEM91</i>	-1.97	<0.01
213089_at	<i>GUSBP1</i>	-1.97	<0.01
202833_s_at	<i>AGT</i>	-1.97	0.316

(Continued)

TABLE E4. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
213909_at	<i>LRRC15</i>	-1.96	<0.01
205132_at	<i>ACTC1</i>	-1.96	<0.01
234284_at	<i>GNG8</i>	-1.96	<0.01
1553834_at/1553835_a_at	<i>FLJ35880</i>	-1.96	<0.01
230380_at	<i>THAP2</i>	-1.95	<0.01
222062_at	<i>IL27RA</i>	-1.95	<0.01
230554_at	<i>ACSM2A</i>	-1.94	<0.01
210013_at	<i>HPX</i>	-1.93	0.028
217466_x_at	<i>LOC400963</i>	-1.92	<0.01
220065_at	<i>TNMD</i>	-1.92	0.622
210929_s_at	<i>AHSG</i>	-1.92	<0.01
37020_at	<i>CRP</i>	-1.92	<0.01
214240_at	<i>GAL</i>	-1.92	<0.01
213577_at	<i>SQLE</i>	-1.91	<0.01
221491_x_at/238900_at	<i>hCG_1998957</i>	-1.91	<0.01
203936_s_at	<i>MMP9</i>	-1.90	<0.01
207218_at	<i>F9</i>	-1.90	<0.01
223274_at	<i>TCF19</i>	-1.89	<0.01
211748_x_at	<i>PTGDS</i>	-1.88	<0.01
1558220_at	<i>MUC20</i>	-1.88	<0.01
204834_at/227265_at	<i>FGL2</i>	-1.88	<0.01
219260_s_at	<i>C17orf81</i>	-1.87	<0.01
202938_x_at	<i>CTA-126B4.3</i>	-1.86	<0.01
1553333_at	<i>C1orf161</i>	-1.86	<0.01
242372_s_at	<i>MFSD4</i>	-1.86	<0.01
209540_at/209541_at/209542_x_at	<i>IGF1</i>	-1.85	<0.01
239213_at	<i>SERPINB1</i>	-1.85	<0.01
239153_at	<i>FLJ41747</i>	-1.84	<0.01
216074_x_at	<i>WWC1</i>	-1.84	<0.01
205749_at	<i>CYP11A1</i>	-1.84	<0.01
212671_s_at	<i>HLA-DQA1</i>	-1.84	<0.01
220017_x_at	<i>CYP2C9</i>	-1.84	<0.01
203989_x_at	<i>F2R</i>	-1.84	<0.01
204818_at	<i>HSD17B2</i>	-1.83	<0.01
239260_at/239261_s_at	<i>CORIN</i>	-1.83	<0.01
229770_at	<i>GLT1D1</i>	-1.83	<0.01
200635_s_at	<i>PTPRF</i>	-1.83	<0.01
1556457_s_at	<i>FLJ39739</i>	-1.83	<0.01
1558688_at	<i>LOC441461</i>	-1.83	<0.01
205199_at	<i>CA9</i>	-1.81	<0.01
208147_s_at	<i>CYP2C8</i>	-1.81	1.654
206651_s_at	<i>CPB2</i>	-1.80	0.316
239831_at	<i>TMEM106C</i>	-1.80	<0.01
212770_at	<i>TLE3</i>	-1.80	<0.01
1566324_a_at	<i>MAF</i>	-1.80	<0.01
213605_s_at	<i>LOC728411</i>	-1.80	<0.01
206048_at	<i>OVOL2</i>	-1.80	<0.01
241742_at	<i>PRAM1</i>	-1.79	<0.01
203815_at	<i>GSTT1</i>	-1.79	<0.01
214319_at	<i>FRY</i>	-1.79	<0.01
219949_at/231781_s_at	<i>LRRC2</i>	-1.79	<0.01
221470_s_at	<i>IL1F7</i>	-1.79	<0.01
205208_at	<i>ALDH1L1</i>	-1.79	<0.01
227405_s_at	<i>FZD8</i>	-1.78	<0.01
1559096_x_at	<i>FBXO9</i>	-1.78	0.921
214461_at	<i>LBP</i>	-1.78	0.432
221064_s_at	<i>C16orf28</i>	-1.77	<0.01
206293_at	<i>SULT2A1</i>	-1.76	0.028
207110_at/208567_s_at	<i>KCNJ12</i>	-1.76	<0.01
219498_s_at	<i>BCL11A</i>	-1.76	<0.01
232480_at	<i>FLJ27365</i>	-1.76	<0.01
204415_at	<i>IFI6</i>	-1.76	<0.01

(Continued)

TABLE E4. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
217564_s_at	<i>CPS1</i>	-1.76	<0.01
219271_at	<i>GALNT14</i>	-1.76	<0.01
205325_at	<i>PHYHIP</i>	-1.76	<0.01
205479_s_at	<i>PLAU</i>	-1.76	<0.01
1557131_at	<i>LOC254100</i>	-1.76	<0.01
234954_at	<i>LOC442262</i>	-1.75	<0.01
35820_at	<i>GM2A</i>	-1.75	<0.01
220428_at	<i>CD207</i>	-1.75	<0.01
212955_s_at	<i>POLR2I</i>	-1.75	<0.01
217538_at	<i>SGSM2</i>	-1.75	<0.01
1556986_at	<i>OR2H1</i>	-1.75	<0.01
204750_s_at	<i>DSC2</i>	-1.75	0.316
235540_at	<i>GNRH1</i>	-1.75	<0.01
206350_at	<i>APCS</i>	-1.74	0.622
225191_at	<i>CIRBP</i>	-1.74	<0.01
221905_at	<i>CYLD</i>	-1.74	<0.01
224489_at/224490_s_at	<i>KIAA1267</i>	-1.67	3.729
205116_at/213519_s_at	<i>LAMA2</i>	-1.64	<0.01
1552798_a_at/224341_x_at	<i>TLR4</i>	-1.64	<0.01
216997_x_at/233575_s_at/235765_at	<i>TLE4</i>	-1.60	<0.01
208118_x_at/210396_s_at	<i>IMAA</i>	-1.60	3.585
1556113_at/1556114_a_at	<i>DKFZp451A211</i>	-1.60	3.585
1554095_at/1554096_a_at/234753_x_at	<i>RBM33</i>	-1.59	<0.01
206744_s_at/215948_x_at	<i>ZMYM5</i>	-1.58	3.585
212781_at/212783_at	<i>RBBP6</i>	-1.56	3.729
202920_at/202921_s_at	<i>ANK2</i>	-1.56	3.585
204160_s_at/204161_s_at	<i>ENPP4</i>	-1.55	3.729
219934_s_at/222940_at	<i>SULT1E1</i>	-1.54	<0.01
203760_s_at/203761_at	<i>SLA</i>	-1.54	<0.01
207605_x_at/235408_x_at	<i>ZNF117</i>	-1.52	3.585
209736_at/38918_at	<i>SOX13</i>	-1.51	3.585
201893_x_at/209335_at/211813_x_at	<i>DCN</i>	-1.51	<0.01
1555728_a_at/219607_s_at	<i>MS4A4A</i>	-1.51	3.585
241620_at/241621_at	<i>SMCHD1</i>	-1.50	<0.01
230417_at/230418_s_at	<i>GALNTL1</i>	-1.47	3.585
214336_s_at/214337_at	<i>COPA</i>	-1.47	3.585
209924_at/32128_at	<i>CCL18</i>	-1.46	3.585
1557080_s_at/214927_at	<i>ITGBL1</i>	-1.46	3.729
1554036_at/1554037_a_at	<i>ZBTB24</i>	-1.45	3.729
213316_at/231841_s_at/231842_at	<i>KIAA1462</i>	-1.43	<0.01
202269_x_at/202270_at/231577_s_at	<i>GBP1</i>	-1.41	<0.01
202717_s_at/209658_at/209659_s_at	<i>CDC16</i>	1.34	2.533
208929_x_at/212191_x_at/212734_x_at	<i>RPL13</i>	1.35	2.533
217740_x_at/224930_x_at/234873_x_at	<i>RPL7A</i>	1.35	2.533
205712_at/213362_at/214043_at	<i>PTPRD</i>	1.35	2.533
1554916_a_at/1568605_at/214692_s_at	<i>JRK</i>	1.35	3.588
229209_at/238691_at/244786_at	<i>SNHG10</i>	1.35	3.250
1559159_at/207971_s_at/239442_at	<i>CEP68</i>	1.37	2.533
214579_at/225875_s_at/225876_at	<i>NPAL3</i>	1.37	3.250
209823_x_at/211654_x_at/211656_x_at	<i>HLA-DQB1</i>	1.38	2.533
223382_s_at/225959_s_at/225960_at	<i>ZNRF1</i>	1.40	3.250
1555470_a_at/203063_at/37384_at	<i>PPM1F</i>	1.42	2.533
204670_x_at/209312_x_at/209728_at	<i>HLA-DRB1</i>	1.43	<0.01
202219_at/210854_x_at/213843_x_at	<i>SLC6A8</i>	1.44	<0.01
1553589_a_at/219630_at	<i>PDZK1IP1</i>	1.45	<0.01
221562_s_at/221647_s_at/221913_at	<i>SIRT3</i>	1.46	2.533
200678_x_at/211284_s_at/216041_x_at	<i>GRN</i>	1.48	<0.01
213667_at/38766_at	<i>SRCAP</i>	1.50	2.168
212285_s_at/217419_x_at	<i>AGRN</i>	1.50	2.168
209693_at/215407_s_at	<i>ASTN2</i>	1.52	2.168
226571_s_at/229465_s_at	<i>PTPRS</i>	1.54	2.168
218650_at/64474_g_at	<i>DGCR8</i>	1.59	<0.01

(Continued)

TABLE E4. (Continued)

Probe ID	Gene symbol	FC	q Value (%)
219759_at	<i>LRAP</i>	1.77	0.316
206675_s_at	<i>SKIL</i>	1.94	0.432
205810_s_at	<i>WASL</i>	2.00	1.147
206177_s_at	<i>ARG1</i>	2.27	0.316
215049_x_at	<i>CD163</i>	2.55	0.921
214131_at	<i>CYorf15B</i>	2.80	2.853

TABLE E6. VV-specific gene ontologies

GOID	GO name	FC	R	Symbol	Gene	No. changed	No. measured	Percentage changed	z Score
6952	Defense response	0.45	-0.74163	CLEC4C	C-type lectin domain family 4 member C	17	590	2.88	2.859
6952	Defense response	0.29	-0.82615	GBP6	Guanylate-binding protein family member 6	17	590	2.88	2.859
6952	Defense response	0.37	-0.82582	NLRP1	NLR family pyrin domain containing 1	17	590	2.88	2.859
6952	Defense response	0.33	-0.73718	ORM1	Orosomucoid 1	17	590	2.88	2.859
6952	Defense response	0.36	-0.80508	TCF7	Transcription factor 7 (T cell-specific HMG box)	17	590	2.88	2.859
6952	Defense response	0.34	-0.76692	GNLY	Granulysin	17	590	2.88	2.859
6952	Defense response	0.16	-0.73015	PSG7	Pregnancy-specific β -1-glycoprotein 7	17	590	2.88	2.859
6952	Defense response	0.46	-0.87766	CCR2	Chemokine (C-C motif) receptor 2	17	590	2.88	2.859
6952	Defense response	0.31	-0.74713	TACR1	Tachykinin receptor 1	17	590	2.88	2.859
6952	Defense response	0.37	-0.86318	DMBT1	Deleted in malignant brain tumors 1	17	590	2.88	2.859
6952	Defense response	0.42	-0.74985	—	Transcribed locus	17	590	2.88	2.859
6952	Defense response	0.38	-0.74289	TLR4	Toll-like receptor 4	17	590	2.88	2.859
6952	Defense response	0.46	-0.78206	SERPINA1	Serpin peptidase inhibitor clade A (α -1 antipr	17	590	2.88	2.859
6952	Defense response	0.45	-0.82048	CTLA4	Cytotoxic T lymphocyte-associated protein 4	17	590	2.88	2.859
6952	Defense response	0.47	-0.74666	—	CDNA clone IMAGE:5270500	17	590	2.88	2.859
6952	Defense response	0.48	-0.83917	—	Transcribed locus	17	590	2.88	2.859
6952	Defense response	0.37	-0.74816	—	—	17	590	2.88	2.859
6955	Immune response	0.45	-0.74163	CLEC4C	C-type lectin domain family 4 member C	15	540	2.78	2.525
6955	Immune response	0.29	-0.82615	GBP6	Guanylate-binding protein family member 6	15	540	2.78	2.525
6955	Immune response	0.33	-0.73718	ORM1	Orosomucoid 1	15	540	2.78	2.525
6955	Immune response	0.36	-0.80508	TCF7	Transcription factor 7 (T cell-specific HMG box)	15	540	2.78	2.525
6955	Immune response	0.34	-0.76692	GNLY	Granulysin	15	540	2.78	2.525
6955	Immune response	0.46	-0.87766	CCR2	Chemokine (C-C motif) receptor 2	15	540	2.78	2.525
6955	Immune response	0.31	-0.74713	TACR1	Tachykinin receptor 1	15	540	2.78	2.525
6955	Immune response	0.37	-0.86318	DMBT1	Deleted in malignant brain tumors 1	15	540	2.78	2.525
6955	Immune response	0.42	-0.74985	—	Transcribed locus	15	540	2.78	2.525
6955	Immune response	0.38	-0.74289	TLR4	Toll-like receptor 4	15	540	2.78	2.525
6955	Immune response	0.46	-0.78206	SERPINA1	Serpin peptidase inhibitor clade A (α -1 antipr	15	540	2.78	2.525
6955	Immune response	0.45	-0.82048	CTLA4	cytotoxic T lymphocyte-associated protein 4	15	540	2.78	2.525
6955	Immune response	0.47	-0.74666	—	CDNA clone IMAGE:5270500	15	540	2.78	2.525
6955	Immune response	0.48	-0.83917	—	Transcribed locus	15	540	2.78	2.525
6955	Immune response	0.37	-0.74816	—	—	15	540	2.78	2.525
30154	Cell differentiation	0.43	-0.70922	—	CDNA FLJ12064 fis clone HEMBB1002232	9	308	2.92	2.099
30154	Cell differentiation	0.37	-0.86318	DMBT1	Deleted in malignant brain tumors 1	9	308	2.92	2.099
30154	Cell differentiation	0.32	-0.70230	POU4F1	POU class 4 homeobox 1	9	308	2.92	2.099
30154	Cell differentiation	0.42	-0.72326	TWIST1	Twist homolog 1 (acrocephalosyndactyly 3; Saethre-	9	308	2.92	2.099
30154	Cell differentiation	0.38	-0.74289	TLR4	Toll-like receptor 4	9	308	2.92	2.099
30154	Cell differentiation	0.47	-0.76672	—	CDNA: FLJ23454 fis clone HSI06959	9	308	2.92	2.099

(Continued)

TABLE E6. (Continued)

GOID	GO name	FC	R	Symbol	Gene	No. changed	No. measured	Percentage changed	z Score
30154	Cell differentiation	0.23	-0.79876	<i>MBNL1</i>	Muscleblind-like (Drosophila)	9	308	2.92	2.099
30154	Cell differentiation	0.46	-0.73830	<i>PTGS1</i>	Prostaglandin-endoperoxide synthase 1 (prostagland	9	308	2.92	2.099
30154	Cell differentiation	0.42	-0.77219	—	Full-length insert cDNA YI30F01	9	308	2.92	2.099
6954	Inflammatory response	0.33	-0.73718	<i>ORM1</i>	Orosomucoid 1	6	160	3.75	2.372
6954	Inflammatory response	0.46	-0.87766	<i>CCR2</i>	Chemokine (C-C motif) receptor 2	6	160	3.75	2.372
6954	Inflammatory response	0.31	-0.74713	<i>TACR1</i>	Tachykinin receptor 1	6	160	3.75	2.372
6954	Inflammatory response	0.38	-0.74289	<i>TLR4</i>	Toll-like receptor 4	6	160	3.75	2.372
6954	Inflammatory response	0.47	-0.74666	—	CDNA clone IMAGE:5270500	6	160	3.75	2.372
6954	Inflammatory response	0.37	-0.74816	—	—	6	160	3.75	2.372
15980	Energy derivation by oxidation of organic compounds	0.49	-0.76701	—	Full-length insert cDNA clone ZD43B07	5	117	4.27	2.494
15980	Energy derivation by oxidation of organic compounds	0.30	-0.86752	—	CDNA FLJ30250 fis clone BRACE2002304	5	117	4.27	2.494
15980	Energy derivation by oxidation of organic compounds	0.50	-0.72406	<i>PPP1CB</i>	Protein phosphatase 1 catalytic subunit β isofo	5	117	4.27	2.494
15980	Energy derivation by oxidation of organic compounds	0.16	-0.74365	<i>LEP</i>	Leptin (obesity homolog mouse)	5	117	4.27	2.494
15980	Energy derivation by oxidation of organic compounds	0.34	-0.78664	—	CDNA: FLJ21798 fis clone HEP00573	5	117	4.27	2.494

TABLE E7. Comparison of sham-treated AD samples versus sham-treated healthy skin

Affymetrix ID	Gene symbol	FC	q Value (%)
230867_at	<i>COL6A6</i>	3.45	0.122
210809_s_at	<i>POSTN</i>	3.44	<0.1
1554663_a_at	<i>NUMA1</i>	3.32	<0.1
227736_at	<i>C10orf99</i>	3.09	<0.1
228501_at	<i>GALNTL2</i>	2.79	<0.1
214624_at	<i>UPK1A</i>	2.53	1.221
205883_at	<i>ZBTB16</i>	2.50	1.221
213436_at	<i>CNR1</i>	2.49	<0.1
213764_s_at	<i>MFAP5</i>	2.48	0.432
205819_at	<i>MARCO</i>	2.45	<0.1
205476_at	<i>CCL20</i>	2.43	<0.1
220414_at	<i>CALML5</i>	2.41	<0.1
206007_at	<i>PRG4</i>	2.40	<0.1
206373_at	<i>ZIC1</i>	2.40	<0.1
205547_s_at	<i>TAGLN</i>	2.39	<0.1
215049_x_at	<i>CD163</i>	2.36	<0.1
215382_x_at	<i>TPSAB1</i>	2.35	2.755
233504_at	<i>C9orf84</i>	2.29	<0.1
202274_at	<i>ACTG2</i>	2.28	<0.1
212940_at	<i>COL6A1</i>	2.27	<0.1
235942_at	<i>LOC401629</i>	2.25	4.470
206157_at	<i>PTX3</i>	2.25	<0.1
209924_at	<i>CCL18</i>	2.23	<0.1
205683_x_at/207134_x_at/207741_x_at	<i>TPSAB1</i>	2.22	<0.1
226145_s_at	<i>FRAS1</i>	2.22	<0.1
206243_at	<i>TIMP4</i>	2.20	2.220
217546_at	<i>MT1M</i>	2.20	<0.1
218876_at	<i>TPPP3</i>	2.18	<0.1
238900_at	<i>HLA-DRB1</i>	2.18	<0.1
36742_at	<i>TRIM15</i>	2.16	2.220
219607_s_at	<i>MS4A4A</i>	2.14	<0.1
204438_at	<i>MRC1</i>	2.14	<0.1
242767_at	<i>LMCD1</i>	2.14	1.221
206023_at	<i>NMU</i>	2.13	<0.1
204298_s_at	<i>LOX</i>	2.06	<0.1
227265_at	<i>FGL2</i>	2.05	0.122
232602_at	<i>WFDC3</i>	2.05	<0.1
206637_at	<i>P2RY14</i>	2.04	<0.1
204083_s_at	<i>TPM2</i>	2.03	<0.1
1553835_a_at	<i>FLJ35880</i>	2.02	<0.1
1558552_s_at/206157_at/224254_x_at	<i>C3orf55</i>	2.00	2.691
212781_at	<i>RBBP6</i>	1.97	0.122
207110_at/208567_s_at	<i>KCNJ12</i>	1.95	2.895
1558834_s_at	<i>C1orf62</i>	1.93	<0.1
209156_s_at	<i>COL6A2</i>	1.92	<0.1
202628_s_at	<i>SERPINE1</i>	1.91	0.690
213247_at	<i>SVEP1</i>	1.90	<0.1
212935_at	<i>MCF2L</i>	1.87	<0.1
204938_s_at	<i>PLN</i>	1.85	<0.1
213519_s_at	<i>LAMA2</i>	1.85	<0.1
200648_s_at	<i>GLUL</i>	1.85	<0.1
227662_at	<i>SYNPO2</i>	1.83	1.602
201785_at	<i>RNASE1</i>	1.81	<0.1
206509_at	<i>PIP</i>	1.81	0.432
229152_at	<i>C4orf7</i>	1.80	4.470
213369_at	<i>PCDH21</i>	1.80	<0.1
220756_s_at	<i>GPR172B</i>	1.80	<0.1
205713_s_at	<i>COMP</i>	1.80	<0.1
203305_at	<i>F13A1</i>	1.78	<0.1
217466_x_at	<i>LOC400963</i>	1.77	<0.1
219304_s_at	<i>PDGFD</i>	1.76	<0.1
205046_at	<i>CENPE</i>	1.75	<0.1

(Continued)

TABLE E7. (Continued)

Affymetrix ID	Gene symbol	FC	q Value (%)
230193_at	WDR66	1.75	<0.1
214012_at	ARTS-1	1.74	<0.1
205612_at	MMRN1	1.74	0.122
232074_at	PRSS27	1.73	<0.1
206864_s_at	HRK	1.72	<0.1
227253_at	CP	1.72	0.690
209990_s_at	GABBR2	1.71	0.924
200974_at	ACTA2	1.70	<0.1
214770_at	MSR1	1.70	<0.1
204567_s_at/211113_s_at	ABCG1	1.67	1.986
216550_x_at/216563_at	ANKRD12	1.57	<0.1
219317_at/238992_at	POLI	1.52	1.986
203716_s_at/203717_at/211478_s_at	DPP4	1.51	<0.1
213371_at/216887_s_at	LDB3	1.47	1.986
227529_s_at/227530_at/231067_s_at	AKAP12	1.47	2.691
211361_s_at/211362_s_at/217272_s_at	SERPINB13	1.39	2.691
213316_at/231841_s_at/231842_at	KIAA1462	1.38	<0.1
210495_x_at/211719_x_at/212464_s_at	FN1	1.38	<0.1
208669_s_at/208670_s_at/211698_at	EID1	1.37	2.691
204675_at/210959_s_at/211056_s_at	SRD5A1	-1.44	<0.1
219901_at/226799_at	FGD6	-1.46	3.754
1553153_at/1553155_x_at	ATP6V0D2	-1.47	4.448
203757_s_at/211657_at	CEACAM6	-1.47	<0.1
210315_at/229039_at	SYN2	-1.48	3.634
204018_x_at/209458_x_at/211699_x_at	HBA1	-1.49	<0.1
213307_at/213308_at/243681_at	SHANK2	-1.51	<0.1
205712_at/213362_at/214043_at	PTPRD	-1.52	<0.1
202735_at/213787_s_at/213789_at	EBP	-1.53	<0.1
223551_at/231120_x_at	PK1B	-1.54	<0.1
207843_x_at/209366_x_at/215726_s_at	CYB5A	-1.58	<0.1
214318_s_at/214319_at	FRY	-1.60	2.945
204337_at/204339_s_at	RGS4	-1.60	<0.1
219429_at	FA2H	-1.70	0.141
203440_at	CDH2	-1.70	0.141
206938_at	SRD5A2	-1.70	<0.1
204987_at	ITIH2	-1.70	1.602
214038_at	CCL8	-1.70	0.141
243543_at	ADH1B	-1.70	0.141
208067_x_at	UTY	-1.71	<0.1
213909_at	LRRC15	-1.71	<0.1
213456_at	SOSTDC1	-1.71	<0.1
211726_s_at	FMO2	-1.72	<0.1
215649_s_at	MVK	-1.72	<0.1
202003_s_at	ACAA2	-1.72	<0.1
211295_x_at	CYP2A6	-1.73	2.755
230498_at	MCHR1	-1.73	<0.1
241683_at	HECTD1	-1.73	<0.1
226649_at	PANK1	-1.73	<0.1
224480_s_at	MAG1	-1.73	<0.1
209727_at	GM2A	-1.73	<0.1
207718_x_at	CYP2A13	-1.73	0.141
207367_at	ATP12A	-1.73	<0.1
215082_at	ELOVL5	-1.74	2.755
209605_at	TST	-1.75	<0.1
203147_s_at	TRIM14	-1.76	<0.1
238689_at	GPR110	-1.76	<0.1
222722_at	OGN	-1.76	<0.1
205552_s_at	OAS1	-1.76	<0.1
203595_s_at	IFIT5	-1.77	<0.1
208075_s_at	CCL7	-1.77	<0.1
227342_s_at	MYEOV	-1.78	<0.1
205844_at	VNN1	-1.78	0.924

(Continued)

TABLE E7. (Continued)

Affymetrix ID	Gene symbol	FC	q Value (%)
210002_at	<i>GATA6</i>	−1.78	0.296
205242_at	<i>CXCL13</i>	−1.78	0.924
210368_at	<i>PCDHGA8</i>	−1.78	4.470
206085_s_at/217127_at	<i>CTH</i>	−1.79	3.660
205799_s_at	<i>SLC3A1</i>	−1.79	<0.1
204533_at	<i>CXCL10</i>	−1.79	0.432
205899_at	<i>CCNA1</i>	−1.80	<0.1
213789_at	<i>TBC1D25</i>	−1.80	<0.1
216074_x_at	<i>WWC1</i>	−1.80	<0.1
205602_x_at	<i>PSG7</i>	−1.81	<0.1
207986_x_at	<i>CYB561</i>	−1.81	<0.1
221872_at	<i>RARRES1</i>	−1.81	<0.1
237120_at	<i>KRT77</i>	−1.81	<0.1
1556929_at	<i>PAPOLG</i>	−1.82	<0.1
207192_at	<i>DNASE1L2</i>	−1.83	<0.1
211883_x_at	<i>CEACAM1</i>	−1.84	<0.1
205998_x_at	<i>CYP3A4</i>	−1.84	4.470
219723_x_at	<i>AGPAT3</i>	−1.84	<0.1
229957_at	<i>TMEM91</i>	−1.85	<0.1
244276_at	<i>KLB</i>	−1.85	<0.1
1555713_at	<i>PNKD</i>	−1.85	<0.1
206214_at	<i>PLA2G7</i>	−1.86	0.924
230702_at	<i>C8orf16</i>	−1.86	<0.1
202935_s_at	<i>SOX9</i>	−1.86	0.924
213418_at	<i>HSPA6</i>	−1.87	<0.1
205924_at	<i>RAB3B</i>	−1.87	0.296
1564475_s_at	<i>LOC728723</i>	−1.87	<0.1
203180_at	<i>ALDH1A3</i>	−1.90	<0.1
238167_at	<i>C17orf51</i>	−1.91	<0.1
205927_s_at	<i>CTSE</i>	−1.91	<0.1
219076_s_at	<i>PXMP2</i>	−1.92	<0.1
226597_at	<i>REEP6</i>	−1.92	<0.1
207820_at	<i>ADH1A</i>	−1.93	0.690
210233_at	<i>IL1RAP</i>	−1.94	2.755
227794_at	<i>GLYATL1</i>	−1.96	2.220
230782_at	<i>LOC653381</i>	−1.97	<0.1
207485_x_at	<i>BTN3A1</i>	−1.97	<0.1
204934_s_at	<i>HPN</i>	−1.97	0.141
206010_at	<i>HABP2</i>	−2.00	0.141
210366_at	<i>SLCO1B1</i>	−2.02	1.602
219270_at	<i>CHAC1</i>	−2.02	<0.1
205208_at	<i>ALDH1L1</i>	−2.03	<0.1
31835_at	<i>HRG</i>	−2.04	2.220
214414_x_at	<i>HBA2</i>	−2.06	<0.1
210074_at	<i>CTSL2</i>	−2.06	0.432
219975_x_at	<i>OLAH</i>	−2.06	0.432
201625_s_at	<i>INSIG1</i>	−2.07	<0.1
214842_s_at	<i>ALB</i>	−2.07	<0.1
223605_at	<i>SLC25A18</i>	−2.08	<0.1
229160_at	<i>MUM1L1</i>	−2.10	3.566
202376_at	<i>SERPINA3</i>	−2.11	2.755
209116_x_at	<i>HBB</i>	−2.11	<0.1
208962_s_at	<i>FADS1</i>	−2.13	0.141
205695_at	<i>SDS</i>	−2.14	2.755
1553613_s_at	<i>FOXC1</i>	−2.16	<0.1
231583_at	<i>KRT74</i>	−2.18	1.602
213695_at	<i>PON3</i>	−2.19	<0.1
219954_s_at/222943_at	<i>GBA3</i>	−2.19	2.945
213920_at	<i>CUTL2</i>	−2.20	<0.1
205029_s_at	<i>FABP7</i>	−2.23	1.602
221142_s_at	<i>PECR</i>	−2.25	<0.1
230493_at	<i>TMEM46</i>	−2.26	<0.1

(Continued)

TABLE E7. (Continued)

Affymetrix ID	Gene symbol	FC	q Value (%)
230573_at	<i>SGK2</i>	-2.29	3.566
210576_at	<i>CYP4F8</i>	-2.29	<0.1
206957_at	<i>AGXT</i>	-2.32	<0.1
204607_at	<i>HMGCS2</i>	-2.32	0.141
239492_at	<i>SEC14L4</i>	-2.35	<0.1
205871_at/214415_at	<i>PLGLA1</i>	-2.36	4.448
1552620_at	<i>SPRR4</i>	-2.36	1.602
227055_at	<i>METTL7B</i>	-2.37	<0.1
202218_s_at	<i>FADS2</i>	-2.39	<0.1
243953_at	<i>LOC285286</i>	-2.40	<0.1
205769_at	<i>SLC27A2</i>	-2.41	<0.1
244187_at	<i>APOOL</i>	-2.42	<0.1
207065_at	<i>KRT75</i>	-2.45	<0.1
242625_at	<i>RSAD2</i>	-2.46	<0.1
231461_at	<i>KRT71</i>	-2.48	0.296
210168_at	<i>C6</i>	-2.48	0.924
236140_at	<i>GCLM</i>	-2.50	<0.1
206632_s_at	<i>APOBEC3B</i>	-2.51	<0.1
234671_at	<i>KRTAP4-2</i>	-2.52	0.296
210377_at	<i>ACSM3</i>	-2.54	0.141
1555673_at	<i>LOC728285</i>	-2.54	0.141
206677_at	<i>KRT31</i>	-2.55	0.924
206386_at	<i>SERPINA7</i>	-2.55	1.602
220431_at	<i>TMPRSS11E</i>	-2.56	<0.1
219799_s_at	<i>DHRS9</i>	-2.56	<0.1
205871_at	<i>PLGLA1</i>	-2.61	1.221
1564414_a_at	<i>PNLDC1</i>	-2.62	0.690
232428_at	<i>MOGAT2</i>	-2.70	<0.1
234678_at	<i>KRTAP4-3</i>	-2.72	0.141
216661_x_at	<i>CYP2C9</i>	-2.72	<0.1
214079_at	<i>DHRS2</i>	-2.78	<0.1
202834_at	<i>TXNL4A</i>	-2.87	3.566
205229_s_at	<i>COCH</i>	-2.87	2.220
212279_at	<i>TMEM97</i>	-2.90	<0.1
220507_s_at	<i>UPB1</i>	-2.96	<0.1
209696_at	<i>FBP1</i>	-2.97	<0.1
217564_s_at	<i>CPS1</i>	-3.04	2.755
205221_at	<i>HGD</i>	-3.06	<0.1
1553062_at	<i>MOGAT1</i>	-3.07	0.924
209522_s_at	<i>CRAT</i>	-3.11	4.470
1569909_at	<i>KRT79</i>	-3.19	1.221
206979_at	<i>C8B</i>	-3.28	0.296
205311_at	<i>DDC</i>	-3.79	<0.1
217683_at	<i>HBE1</i>	-3.87	<0.1
215189_at	<i>KRT86</i>	-4.05	0.296
205380_at	<i>PDZK1</i>	-4.12	<0.1
220801_s_at	<i>HAO2</i>	-4.23	<0.1
204836_at	<i>GLDC</i>	-4.46	<0.1
233534_at	<i>KRTAP3-2</i>	-4.46	1.602
234685_x_at	<i>KRTAP4-9</i>	-4.89	<0.1
206054_at/217512_at	<i>KNG1</i>	-4.95	2.945
220626_at	<i>SERPINA10</i>	-5.22	0.432
229476_s_at	<i>THRSP</i>	-5.33	0.141
211429_s_at	<i>SERPINA1</i>	-5.69	3.566
203400_s_at	<i>TF</i>	-5.92	<0.1
202833_s_at/211429_s_at/230318_at	<i>AGT</i>	-5.99	<0.1
213553_x_at	<i>APOC1</i>	-6.07	<0.1
234980_at	<i>TMEM56</i>	-6.15	<0.1
205649_s_at/231671_at	<i>FGA</i>	-6.37	<0.1
206293_at	<i>SULT2A1</i>	-6.37	0.432
207218_at	<i>F9</i>	-6.88	1.221
220976_s_at	<i>KRTAP1-1</i>	-7.19	<0.1

(Continued)

TABLE E7. (Continued)

Affymetrix ID	Gene symbol	FC	q Value (%)
210013_at	<i>HPX</i>	−7.44	2.755
233533_at	<i>KRTAP1-5</i>	−7.86	<0.1
216810_at	<i>KRTAP4-7</i>	−8.33	<0.1
205719_s_at	<i>PAH</i>	−10.71	1.221
204705_x_at	<i>ALDOB</i>	−10.77	2.755
206754_s_at	<i>CYP2B7P1</i>	−11.15	<0.1
233681_at	<i>KRTAP3-3</i>	−14.68	0.924