

Abbreviations used

AD:	Atopic dermatitis
DC:	Dendritic cell
DEG:	Differentially expressed gene
EDC:	Epidermal differentiation complex
FCH:	Fold change
hARP:	Human acidic ribosomal protein
IHC:	Immunohistochemistry
K16:	Keratin 16
LCN2:	Lipocalin 2
PI3:	Peptidase inhibitor 3
RT-PCR:	Real-time PCR

characterization of spontaneous acute AD lesions and comparison with chronic lesions from the same patient are warranted.

We sought to characterize the mechanisms underlying the onset and maintenance of AD based on paired comparisons between nonlesional skin and acute and chronic skin lesions from individual patients (Fig 1, A).

METHODS

Patient population

Intrapersonal acute, chronic (>72 hours duration), and nonlesional (≥ 10 cm from active lesions) skin biopsy specimens (Fig 1, A) and blood samples were collected from each of 17 patients with moderate-to-severe AD under an institutional review board–approved protocol. Biopsy specimens were not taken from skin that was clinically judged to be infected. No systemic or topical treatments were allowed for 4 or more weeks before biopsy. Ten patients (4 male and 6 female patients; age, 20–67 years; mean age, 44 years; see Table E1 in this article's Online Repository at www.jacionline.org) met the following criteria for distinguishing true acute from “acute on chronic” skin lesions: (1) new lesions of less than 72 hours' duration, as previously defined¹⁶; (2) lack of skin lichenification; and (3) lack of regenerative hyperplasia, as defined by an epidermal thickness of 150 μ m or less (hematoxylin and eosin staining; Fig 1, B), and basal or confluent suprabasal keratin 16 (K16) positivity (Fig 1, C). Serum IgE levels were increased in 7 of 10 patients (range, 27.9–3652 kU/L; mean, 1032 kU/L; reference range, 0–160 kU/L), and eosinophil counts were increased in 1 patient (reference range, 0% to 7%). The SCORAD index was used to evaluate disease severity (range, 40–63; mean, 50). No filaggrin gene mutations were found.

Skin biopsy specimens from healthy volunteers²⁵ and patients with psoriasis²⁶ ($n = 15$ in both groups) were used for comparisons (see the Methods section in this article's Online Repository at www.jacionline.org).

Biopsy specimens were frozen in OCT medium for immunohistochemistry (IHC) and liquid nitrogen for RNA extraction. Histologic and real-time PCR (RT-PCR) analyses were performed on nonlesional, acute, and chronic skin samples from all 10 patients. However, because of loss of tissue with laboratory processing, gene array analysis was performed on 8 patients.

IHC

IHC was performed on cryostat tissue sections by using purified mouse anti-human mAbs (see Table E2 and the Methods section in this article's Online Repository at www.jacionline.org). Epidermal thickness was quantified and positive cells per millimeter were counted manually by using computer-assisted image-analysis software (ImageJ 1.42; National Institutes of Health, Bethesda, Md).

Sample preparation for RT-PCR and gene chip analysis

RNA was extracted for RT-PCR, which was performed with EZ-PCR Core Reagents (Life Technologies, Grand Island, NY), and custom primers were generated, as previously described.²⁷ We used human HG133Plus2.0

GeneChip probe arrays (Affymetrix, Santa Clara, Calif). Total RNA was extracted by using the Qiagen RNeasy Mini Kit (Qiagen, Valencia, Calif), and DNA was removed with the Qiagen RNase-free DNase Set. Total RNA (50 ng) was reverse transcribed and amplified with Ovation Whole Blood Solution from NuGen (San Carlos, Calif). The labeled target was fragmented and hybridized to probe arrays by using the Encore Biotin Module from NuGen (see the Methods section in this article's Online Repository).

Statistical analyses

Analysis of gene array and RT-PCR data ($\log_2$ scale of normalized values) was through a linear mixed-effects model, and analysis of IHC cell counts was through paired Wilcoxon rank sum tests.

Affymetrix CEL files were scrutinized for spatial artifacts by using the Harshlight package.²⁸ Expression values were obtained with the frozen robust multiarray analysis algorithm.²⁹ Because samples were hybridized with different kits, the batch effect was removed with the R package COMBAT.³⁰ Raw data were deposited in the National Center for Biotechnology Information's Gene Expression Omnibus repository (accession no. GSE36842).

Expression values (in $\log_2$) were modeled by a linear mixed-effects model, with group as the fixed effect and a random intercept for each patient, in the framework of Bioconductor's limma package. The comparisons of interest were tested by using a moderated t test,³¹ and resultant P values were adjusted for multiple hypotheses by using the Benjamini-Hochberg procedure. Because typical false discovery rate cutoffs proved to be very stringent for the small sample size, genes with a fold change (FCH) of greater than 1.5 and a P value of less than .01 were considered differentially expressed genes (DEGs; see the Methods section and Table E3 in this article's Online Repository at www.jacionline.org).

RESULTS

To identify the key pathways associated with acute skin lesions, we characterized the global cellular, molecular, and gene expression alterations that appear with the onset of AD lesions.

Acute disease triggers increased hyperplasia

We compared epidermal thickness and protein expression of the proliferation markers K16 and Ki67 among nonlesional skin and acute and chronic AD skin lesions (Fig 1, B–D). A significant increase in epidermal thickness (52%, $P = .027$) and proliferation (153% increase in Ki67⁺ cells, $P = .004$) was observed from nonlesional skin to acute lesions, with additional respective increases of 141% ($P = .02$) and 110% ($P = .02$) from acute to chronic lesions (Fig 1, B and D). K16 mRNA expression was also significantly upregulated between nonlesional skin and acute lesions ($P = .02$; Fig 1, C), with a further significant increase in chronic lesions ($P = .016$; Fig 1, C). Although chronic lesions demonstrated continuous suprabasal K16 staining, acute lesions showed patchy K16 positivity (Fig 1, C).

Genomic expression differences between nonlesional and acute and chronic AD skin

Gene arrays were conducted to explore the characteristics of acute compared with chronic AD skin lesions and nonlesional skin by using the above criteria to define DEGs in acute compared with chronic and nonlesional AD (see Table E3).

Our study defined a set of intrapersonal transcriptomes from nonlesional skin and acute and chronic skin lesions of individual patients. Ninety probe sets (76 genes) were upregulated and 42 probe sets (26 genes) were downregulated in acute lesions compared with nonlesional AD skin (Fig 1, E). A higher number of DEGs was identified in chronic in comparison with nonlesional AD skin (411 probe sets [310 genes] upregulated and 141 probe

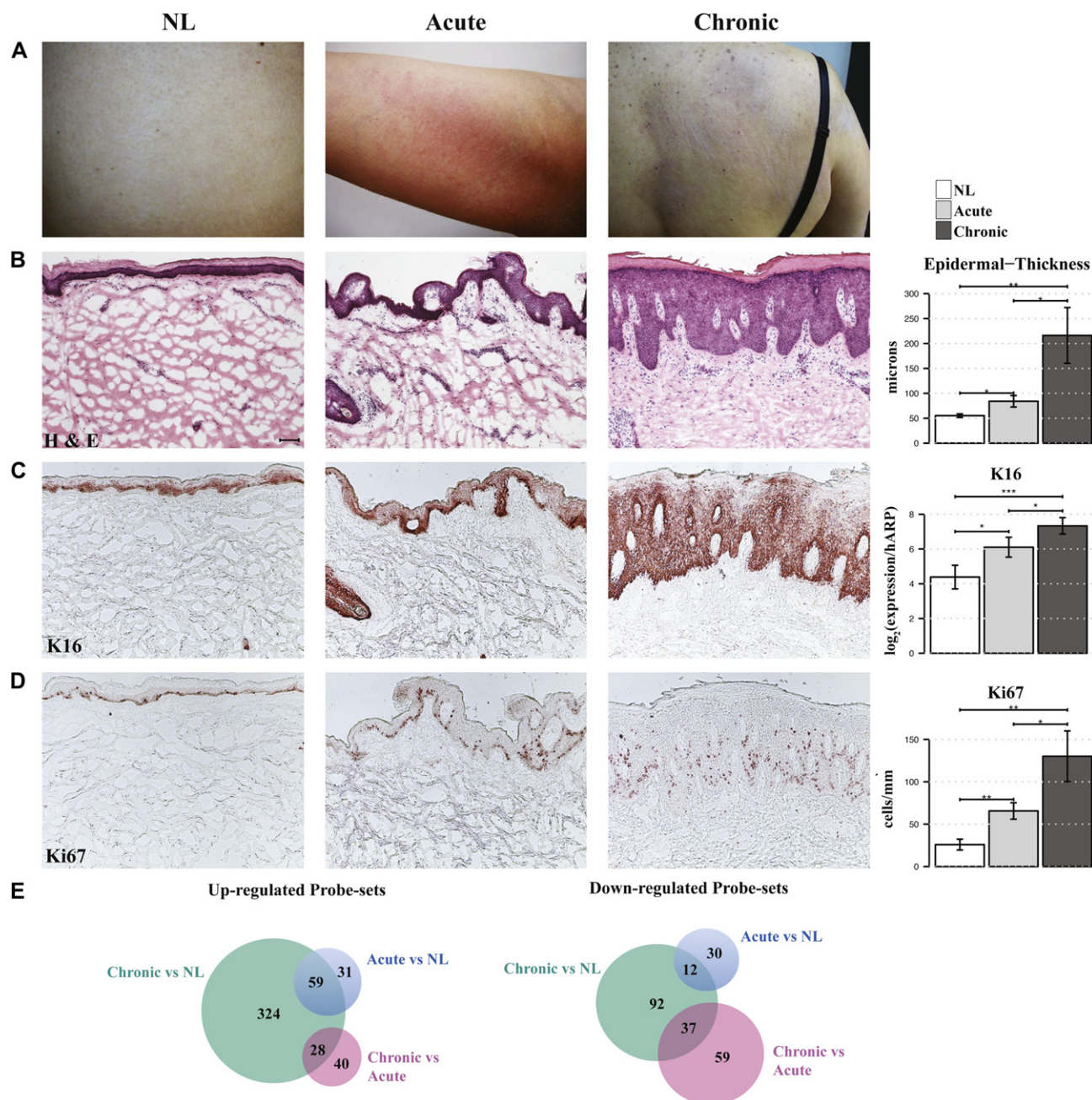


FIG 1. Clinical, histologic, and genomic differences among nonlesional (NL), acute, and chronic AD skin. **A**, Clinical images of NL, acute, and chronic AD skin demonstrate bright erythema of acute lesions and dullness and lichenification of chronic lesions. **B-D**, Representative IHC stainings of hematoxylin and eosin (H&E; Fig 1, B) and the proliferation markers K16 (Fig 1, C) and Ki67 (Fig 1, D) in tissue sections of nonlesional, acute, and chronic AD skin, as well as quantification of epidermal thickness (Fig 1, B); K16 determined by using real-time PCR (RT-PCR; Fig 1, C), represented in log₂ (log₂[expression/hARP]); and Ki67⁺ cell counts (Fig 1, D), showing significantly increased epidermal hyperplasia and abnormal proliferation in acute lesions, with further increases in chronic lesions. * $P < .05$, ** $P < .01$, and *** $P < .001$ ($n = 10$). Bar plots represent means $\pm$ SEMs. Scale bar = 100 μ m. **E**, Venn diagrams of upregulated and downregulated probe sets in acute and chronic skin lesions in comparison with nonlesional skin using criteria of an FCH of greater than 1.5 and a P value of less than .01 ($n = 8$).

sets [110 genes] downregulated). A relatively small set of DEGs distinguished chronic and acute AD (68 probe sets [47 genes] up-regulated and 96 probe sets [75 genes] downregulated; Fig 1, E, and see Table E3).

Acute AD is associated with an abrupt increased expression of epidermal S100 proteins

Because the top 50 DEGs between acute and nonlesional AD skin include many terminal differentiation genes (see Fig E1 in this

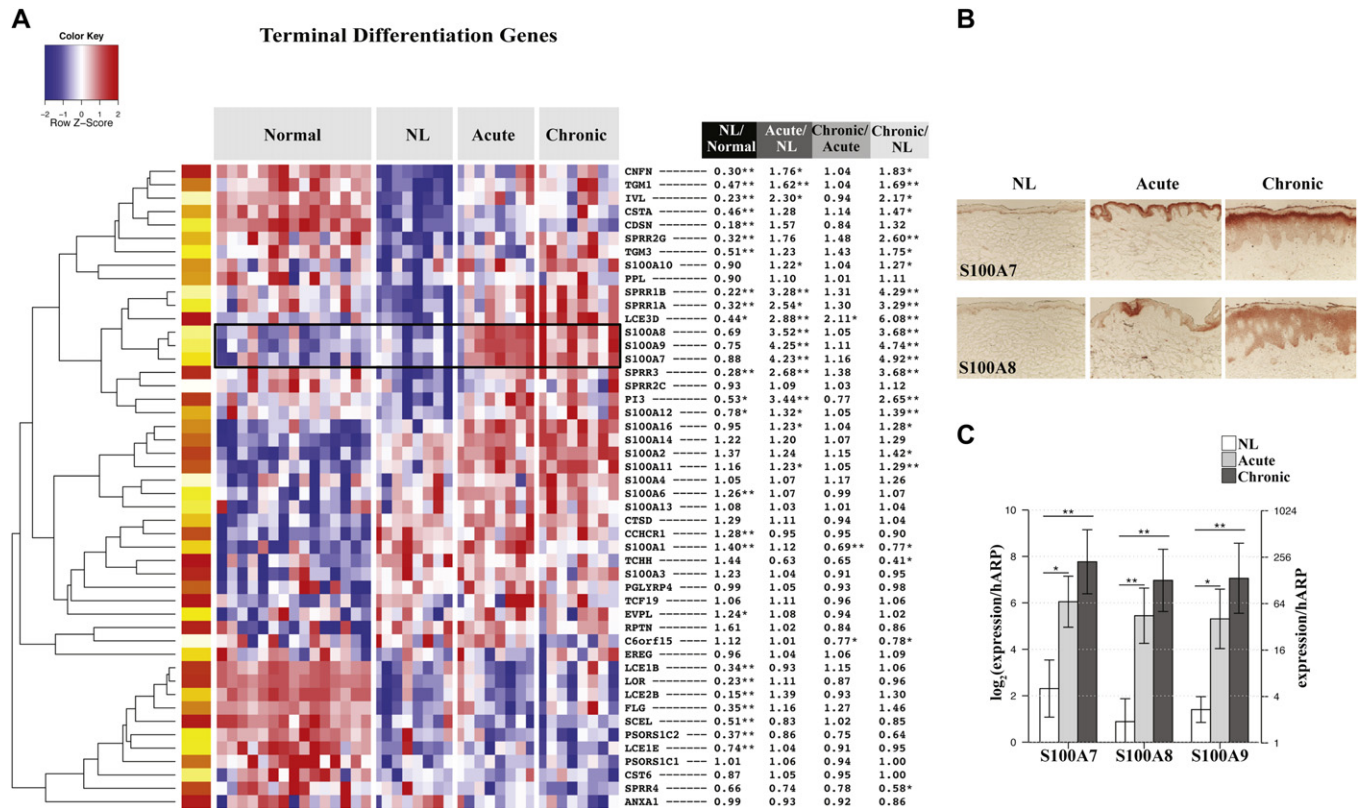


FIG 2. Onset of acute lesions is associated with coordinated increases in S100A7, S100A8, and S100A9 levels. **A**, Unsupervised hierarchic clustering of terminal differentiation genes across normal, nonlesional (NL), acute, and chronic AD skin samples (red, upregulated; blue, downregulated). In contrast to the uniform downregulation of well-characterized EDC genes, such as filaggrin and loricrin, throughout nonlesional skin and acute and chronic skin lesions, there is a steep increase in expression of S100A7, S100A8, and S100A9 with the onset of acute disease, with further induction in chronic lesions, as indicated by the black highlighting. Probes with the largest FCHs were chosen when several probes represented single genes. * $P < .05$, ** $P < .01$, and *** $P < .001$ ($n = 8$ for patients with AD and $n = 15$ for healthy subjects). **B** and **C**, The significant induction of these S100 proteins has been validated by increases in protein expression of S100A7 and S100A8 in representative IHC stainings of acute and chronic lesions compared with nonlesional skin (Fig 2, B) and mRNA gene expression levels by using real-time PCR (RT-PCR; Fig 2, C), represented in log₂[log₂(expression/hARP)] and natural scale (expression/hARP; approximate FCH of 8, $P < .02$). hARP, Human acidic ribosomal protein ($n = 10$).

article's Online Repository at www.jacionline.org), we further analyzed this gene group (Fig 2, A).

The transition from nonlesional to acute lesional skin was associated with a striking increase in the expression of a subset of epidermal differentiation complex (EDC) genes, including S100A7, S100A8, and S100A9 (approximate FCH of 4; Fig 2, A, and see Fig E1 and Table E3). These steep increases, detected by using gene arrays (approximate FCH of 4), were confirmed based on both strong protein expression of S100A7 and S100A8 in tissue sections of acute lesions, which localized to the upper spinous and granular layers of the epidermal keratinocytes (Fig 2, B), and comparatively large increases in gene expression levels determined by using RT-PCR (approximate FCH of 8; $P = .019$; Fig 2, C).

Compared with healthy control subjects, the expression of other well-characterized EDC genes (ie, filaggrin, loricrin, and late cornified envelope 2B [LCE2B]) showed large reductions in nonlesional AD skin and were unaltered with either acute or chronic disease (Fig 2, A). This was further confirmed by using RT-PCR, showing grossly similar mRNA expression of filaggrin

and corneodesmosin across nonlesional skin and skin of patients with active disease (Fig 3).

Acute AD is associated with T_H2 and T_H22 cytokine activation

One hypothesis for the abrupt activation of the S100A7, S100A8, and S100A9 genes is that they are induced by T cell–derived cytokines because these products were shown to be upregulated *in vitro* by IL-22, IL-17, or both cytokines.^{8,10,32,33} Thus we broadly measured changes in activation of major cytokines and chemokines that define T_H1, T_H2, T_H22, and T_H17 T-cell subsets, as well as representative genes shown to be upregulated in cytokine-treated keratinocytes,^{6,34–41} using both gene arrays and quantitative RT-PCR measures because transcripts of primary cytokines are not always measured on gene arrays (Fig 3 and see Fig E2 in this article's Online Repository at www.jacionline.org).

The onset of acute lesions is associated with significant increases in gene expression levels of T_H2-defining (ie, IL-4,

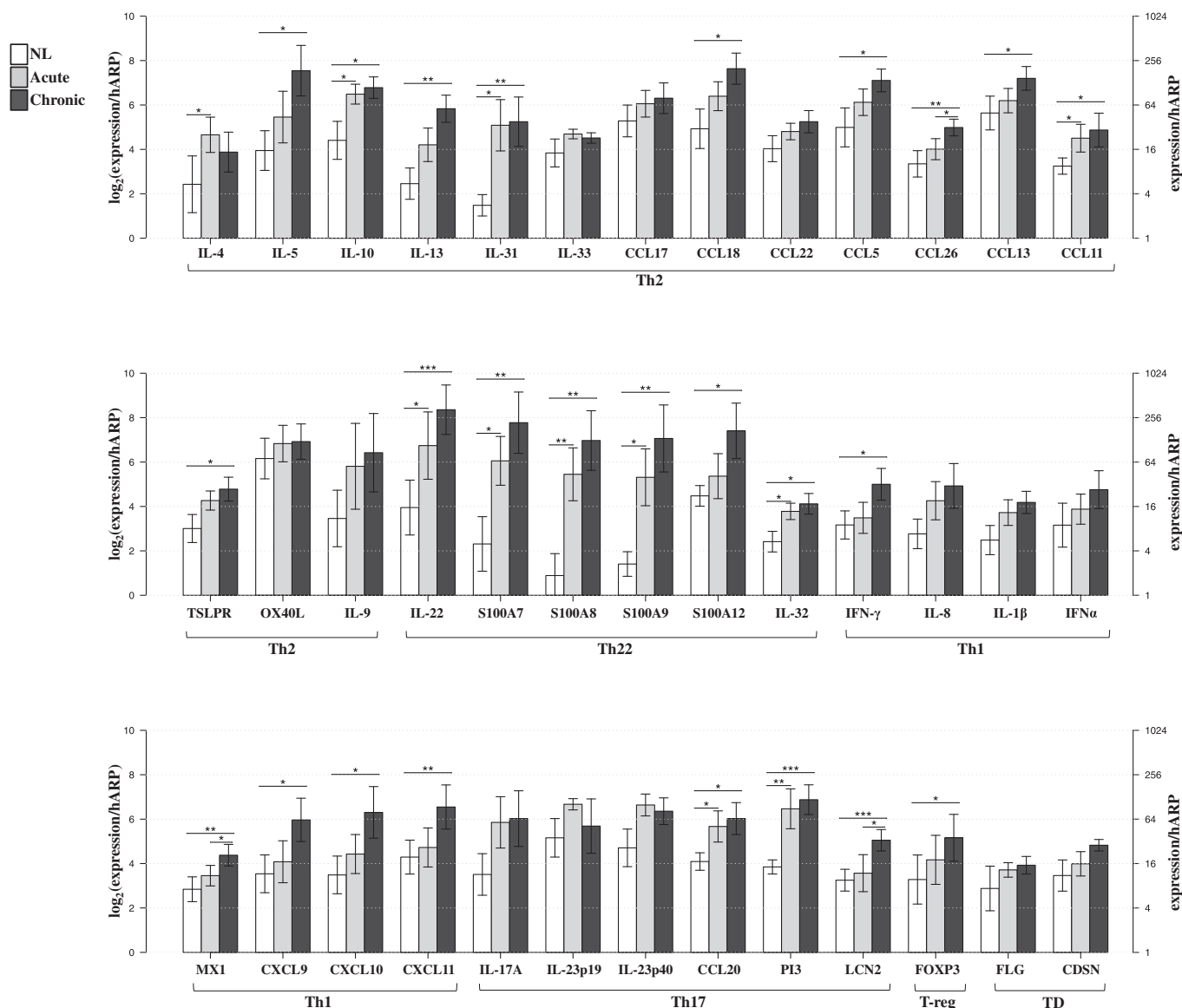


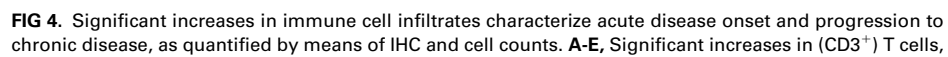
FIG 3. Marked activation of T_H2 and T_H22 immune pathways in acute disease, with progressive activation in chronic skin lesions by means of real-time PCR (RT-PCR). Mean expression estimates normalized to human acidic ribosomal protein (hARP) are represented in $\log_2$ ($\log_2$ (expression/hARP)) and natural scale (expression/hARP). The largest gene expression increases are associated with T_H2 - and T_H22 -associated products, including IL-31, IL-22, S100A7, S100A8, and S100A9. Small increases in T_H1 -related products are evident in both acute and chronic lesions. In contrast with the immune mediators, the mRNA expression levels of filaggrin (FLG) and corneodesmosin (CDSN) showed similarity across the disease. Bar plots represent means $\pm$ SEMs. * $P < .05$, ** $P < .01$, and *** $P < .001$ ($n = 10$). FOXP3, Forkhead box protein 3; MX1, myxovirus resistance 1; OX40L, OX40 ligand; TD, terminal differentiation; TSLPR, thymic stromal lymphopoietin receptor.

IL-13, and IL-31) and T_H22 -defining (ie, IL-22) cytokines (Fig 3 and see Fig E2, A and B). The largest quantitative gene expression increases are associated with IL-31, IL-22, S100A7, S100A8, and S100A9, as demonstrated by using both RT-PCR and gene arrays (Fig 3 and see Fig E2, B). Acute disease showed a positive correlation between the SCORAD index and IL-22 mRNA expression ($r = 0.55$, $P = .132$). A lesser induction of T_H1 /interferon-induced (ie, IFN- γ , myxovirus resistance 1 [MX1], IL-1 β , and CXCL9 to CXCL11) products was also evident in acute disease (Fig 3 and see Fig E2, C). Small increases in T_H17 axis cytokine

levels (IL-17, IL-23p19, and IL-23p40) were detected in acute disease accompanied by significant increases in IL-17-regulated products (CCL20, peptidase inhibitor 3 [PI3]/elafin, and lipocalin 2 [LCN2]; Fig 3 and see Fig E2, D).

Intensification of immune activation rather than an immune switch characterizes chronic disease

Progressive increases in levels of IL-22 mRNA and its associated products (S100A7, S100A8, S100A9, and IL-32)⁴²



were detected between acute and chronic lesions (Fig 3 and see Fig E2, B). Chronic lesions are also characterized by intensified T_H2 -related inflammation with significant increases in most associated products (ie, IL-5, IL-13, IL-10, IL-31, CCL5, CCL13, and CCL18), with the exception of IL-4 and its receptor, levels of which decreased from acute to chronic lesions (Fig 3 and see Fig E2, A). Nevertheless, in chronic disease changes in IL-4 mRNA expression correlate with the SCORAD index ($r = 0.833$, $P = .008$). Significant increases in T_H1 -related products (ie, IFN- γ , myxovirus resistance 1 [MX1], and CXCL9 to CXCL11) were detected only in chronic skin lesions, although small increases were evident in acute lesions. No significant differences were found in T_H17 -mediated products between acute and chronic disease (except for LCN2). Significant increases in the expression of several IL-17-regulated genes (CCL20, PI3, and LCN2) were detected in chronic lesions compared with nonlesional skin (Fig 3 and see Fig E2, D). A significant increase in the regulatory T-cell marker forkhead box protein 3 was found in chronic disease alone (Fig 3).

A multiple regression analysis identified the best set of SCORAD predictors in chronic AD as T_H2 -, T_H1 -, and T_H17 -associated products and T_H2 -derived CCL18 and CCL13 in acute AD (see Table E4 in this article's Online Repository at www.jacionline.org).

Increased immune cell infiltrates with disease onset determined by using IHC

Because these data associate the onset and chronicity of AD with progressive increases in cytokine and chemokine levels, we measured the infiltration of nonlesional skin and acute and chronic lesions by various inflammatory cells (Fig 4).

Significant increases in numbers of infiltrating T ($CD3^+$) cells (303%, $P = .004$), myeloid ($CD11c^+$) dendritic cells (DCs; 178%, $P = .004$), mature DCs ($CD83^+$, $P = .034$), and inflammatory dendritic epidermal cells (as quantified by $Fc\epsilon RI^+$ [$P = .038$] and $CD206^+$ [$P = .009$] cells) were observed between nonlesional skin and acute AD skin lesions (Fig 4). Increases in cell counts were also noted in Langerhans cells ($CD1a^+$) and other DC subsets, including "inflammatory" (TNF-related-apoptosis-inducing ligand-positive) DCs and "resident" ($CD1c^+$) DCs.⁴³ T-cell and DC infiltrates were further increased with disease chronicity ($P < .05$ for most subsets, Fig 4).

Although scant numbers of eosinophils, neutrophils, and mast cells were detected in skin lesions (as quantified by using major basic protein-positive, neutrophil elastase-positive, and tryptase-positive cell counts, respectively), we observed an increase in these infiltrates from nonlesional skin through chronic disease ($P = .036$ and $P = .022$ for eosinophils and neutrophils, respectively; see Fig E3 in this article's Online Repository at www.jacionline.org).

Compared with patients with psoriasis, expression of IL-17-induced genes is not highly increased in patients with AD

$T_H17/IL-17$ upregulates a large set of genes in keratinocytes that are coordinately upregulated in patients with psoriasis.^{10,44-46} Therefore we examined disease profiles of acute AD, chronic AD, and psoriasis (each compared with nonlesional skin) for genes induced by IL-17.¹⁰

In contrast to a strong upregulation of $T_H17/IL-17$ -induced genes in patients with psoriasis, this association is attenuated in both acute and chronic AD skin (Fig 5, A, B, and D). As visualized in Fig 5, A, B, and D, almost all of the IL-17-related genes (61/74 [82%] in acute AD skin and 63/74 [85%] in chronic AD skin) are within the psoriasis field, with few exceptions, including S100A7 and S100A8, which are synergistically induced by IL-17 and IL-22.^{8,10,33,43}

A similar magnitude of representation of IL-17-induced genes was found between acute and chronic AD lesions, demonstrating a lack of major differences in this immune axis between acute and chronic disease (Fig 5, C and D).

Thus although psoriasis has a strong $T_H17/IL-17$ molecular fingerprint, this signature is less evident in both acute and chronic AD.

DISCUSSION

The pathogenesis of AD has been attributed to alternate mechanisms, including (1) a defective formation of the epidermal barrier, with mutations in filaggrin that might contribute to this defect,⁵ or (2) effects of immune cytokines, such as IL-4, IL-13, and IL-31, that can suppress epidermal differentiation.^{2,8-11,47} In the first model immune activation might arise as a consequence of abnormal growth/differentiation of the epidermis, whereas in the second model disease-related barrier changes might be driven by underlying T-cell activation and cytokine production. Although early models of immune activation in patients with AD focused on the differential roles for T_H2 and T_H1 in disease initiation and maintenance, recently, roles for T_H17 and T_H22 T cells have also been proposed.^{7,12,44,48}

Within the context of alternate models of pathogenesis, it is extremely important to measure alterations in terminal epidermal differentiation and immune mediators that occur with the onset of acute skin lesions. However, it has been extremely difficult to perform studies on true acute AD lesions because most patients with AD present with only chronic lesions (defined as persisting for >72 hours).¹⁶ In turn, most studies of "acute" disease changes have examined skin inflammation induced by topical application of environmental allergens that is assumed to parallel immune changes in acute skin lesions.²¹⁻²⁴ Measures made in these patch reactions have suggested the biphasic model, in which initiation of inflammation is associated with T_H2 activation, and chronic disease is associated with a T_H1 switch.²¹⁻²³ The biphasic model is in marked contrast to the progressive cytokine activation that occurs in

myeloid ($CD11c^+$) DCs, mature ($CD83^+$) DCs, Langerhans ($CD1a^+$) cells, and inflammatory dendritic epidermal cells ($Fc\epsilon RI^+$) characterize acute disease. **F**, Cell counts of plasmacytoid (blood dendritic cell antigen 2 [$BDCA2^+$]) DCs, mature (dendritic cell lysosome-associated membrane glycoprotein [$DC-LAMP^+$]) DCs, resident ($CD1c^+$) DCs, inflammatory (TNF-related-apoptosis-inducing ligand [$TRAIL^+$]) DCs, inflammatory dendritic epidermal cells ($CD206^+$), and atopic (OX40 ligand [$OX40L^+$]) DCs increase from nonlesional (NL) through chronic AD skin. * $P < .05$, ** $P < .01$, and *** $P < .001$ ($n = 10$). Bar plots represent means $\pm$ SEMs. Scale bar = 100 μm .

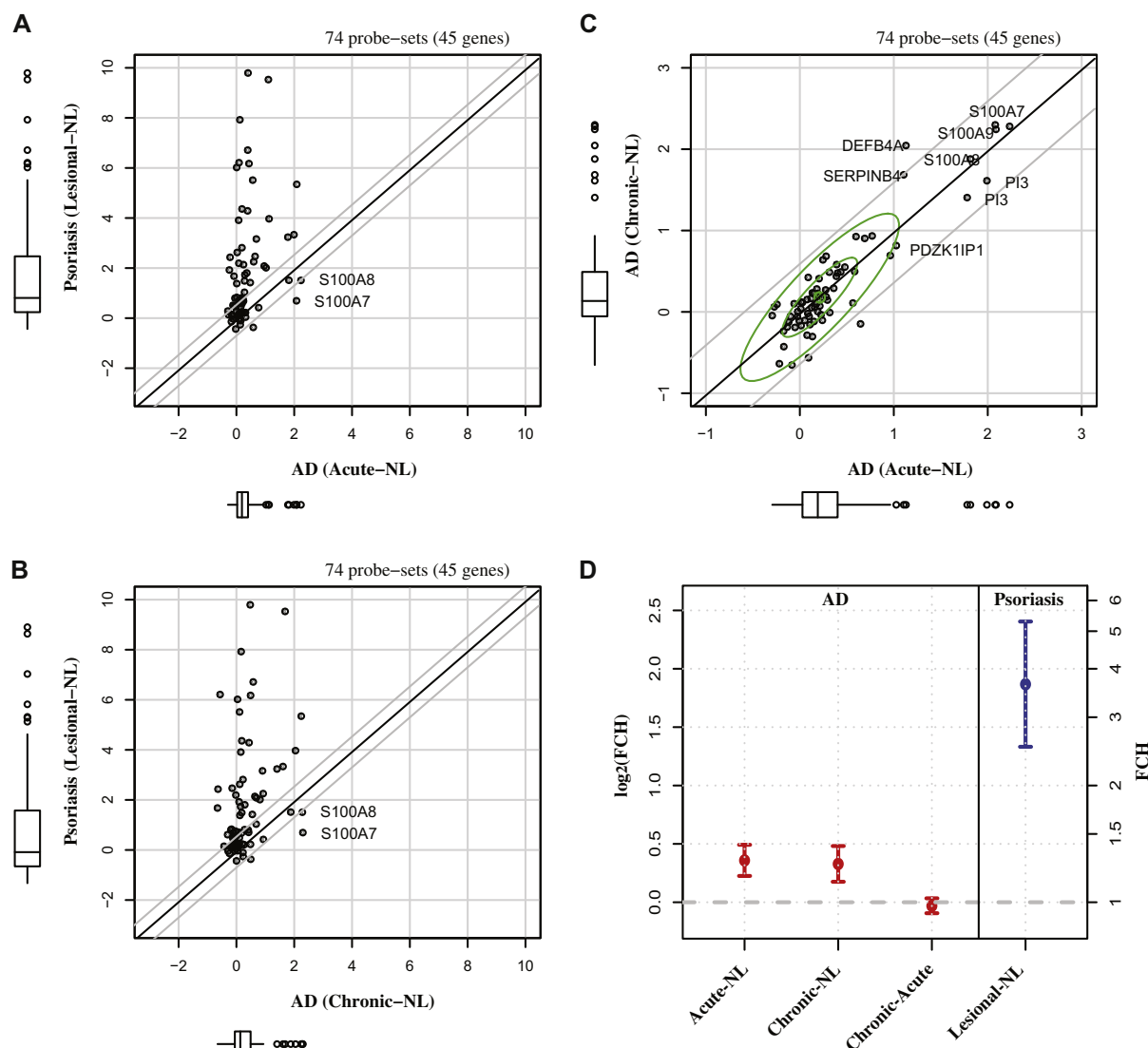


FIG 5. Disease profiles of IL-17-induced genes in patients with acute and chronic AD compared with those in patients with psoriasis. **A** and **B**, A scatter plot of FCHs between lesional and nonlesional (NL) skin for each disease (in log₂ scale) demonstrates that although these genes are well associated with the genomic differences between nonlesional and lesional skin in patients with psoriasis, no such association was found for either acute or chronic AD. **C**, There is a similar distribution of the T_H17-regulated genes between acute and chronic AD skin compared with nonlesional skin. **D**, Means and 95% CIs of the log₂(FCH) among IL-17 genes in psoriasis and AD transcriptomes (n = 8 for patients with AD and n = 15 for patients with psoriasis).

an IL-4 transgenic murine model resembling AD-related inflammation.³⁵

Our study represents the first comprehensive genomic and molecular comparison of intrapersonal nonlesional skin and acute and chronic skin lesions. With analysis of well-defined acute AD lesions in comparison with chronic and clinically uninvolved AD skin, we have established detailed changes in epidermal growth/differentiation and immune activation that occur with both onset of new lesions and persistence of disease.

Although the expression of some epidermal differentiation gene products, such as filaggrin and loricrin, is largely reduced in nonlesional AD skin, further downregulation does not occur with acute or chronic lesions. Thus onset of clinically significant disease is not accompanied by decreases in epidermal differentiation genes but is instead associated with marked

activation of an EDC gene cluster on chromosome 1q, with the largest increases in the expression of S100A7, S100A8, and S100A9. The increase in these gene products corresponds with the abrupt increased synthesis of S100 proteins in epidermal keratinocytes in acute and chronic AD skin lesions. Increased S100A7 levels in acute AD lesions have been detected in only one past study, in which both a specific definition of acute AD and a comparison with chronic lesions from the same patients were lacking.⁴⁹ The S100A7, S100A8, and S100A9 proteins were shown to be highly expressed in chronic hyperproliferative epithelium and have been associated with an alternative differentiation pathway.⁵⁰⁻⁵² They have important functions in inflammation, such as chemotaxis of T cells, monocytes, and neutrophils, as well as proinflammatory functions in patients with many inflammatory diseases.^{8,53-55} The particular

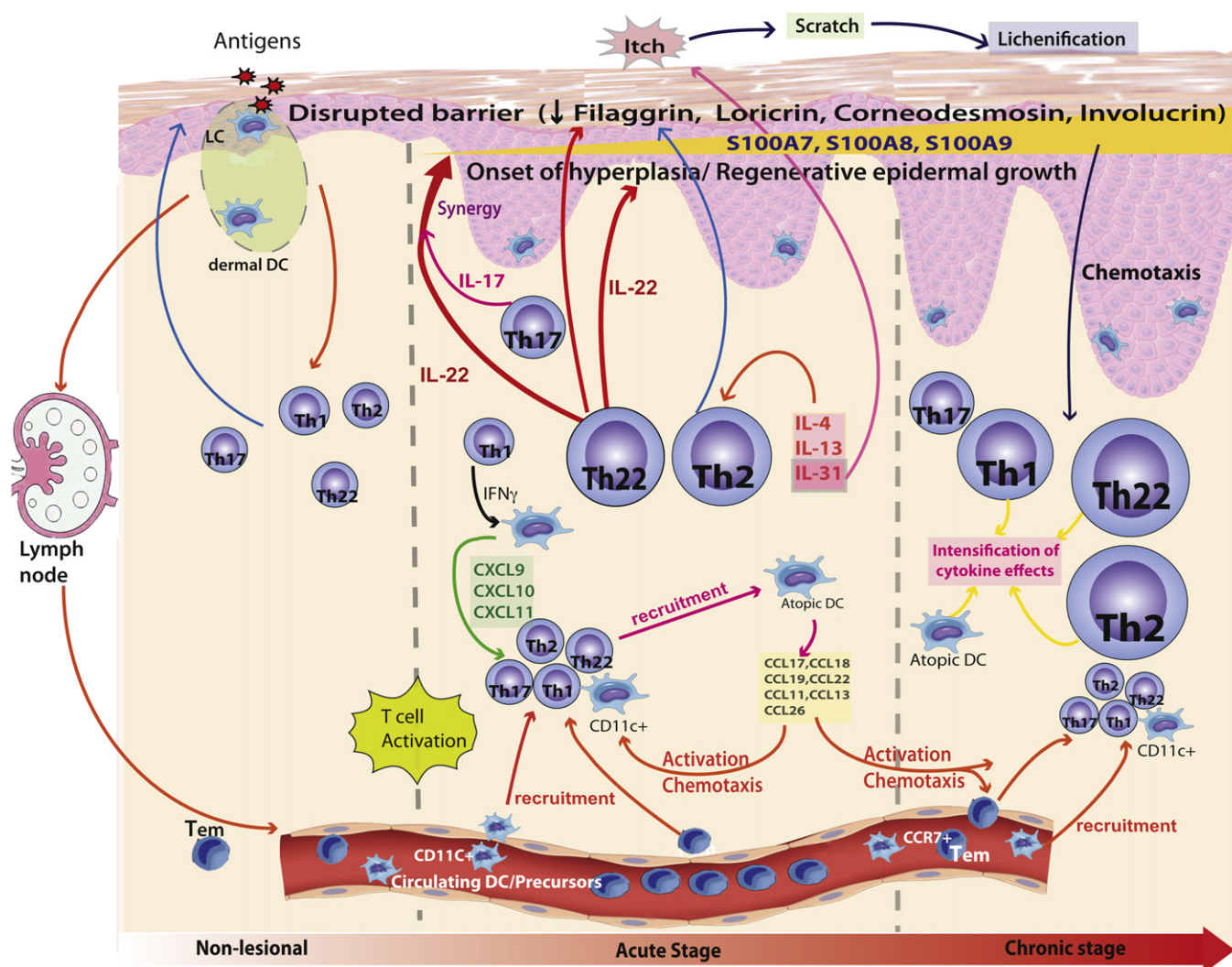


FIG 6. A schematic illustration of initiation of acute AD and progression to chronic skin lesions. Nonlesional AD skin lesions show some immune infiltrates that produce inflammatory mediators, which might contribute to a defective epidermal barrier. Barrier defects lead to penetration by epicutaneous antigens that encounter Langerhans cells in the epidermis and dermal DCs in the dermis, inducing marked immune activation and recruitment of inflammatory cells in acute AD lesions. Marked activation of T_H2 and T_H22 axes occurs in acute disease onset. Smaller increases in T_H1 and T_H17 immune axes were found in acute lesions. A progressive activation of T_H2 and T_H22 , as well as T_H1 , pathways is characteristic of the chronic stage of AD. The relative induction of each T-cell subset according to disease stage is represented pictorially by their size relative to the other T-cell subsets. Cytokines (ie, IL-4 and IL-13) and chemokines (ie, CCL17, CCL18, CCL19, CXCL9, CXCL10, and CXCL11) produced by various T cells and DCs induce further activation and recruitment of additional immune cells. With the onset of acute disease, T_H22 cells release IL-22, which induces epidermal hyperplasia and, synergistically with the T_H17 cytokine IL-17, drives an abrupt increase in a subset of terminal differentiation genes, specifically S100A7, S100A8, and S100A9 proteins. The increases in these barrier proteins contrast with the uniformly disrupted epidermal differentiation gene products (eg, filaggrin, loricrin, and corneodesmosin) throughout nonlesional, acute, and chronic AD skin. The T_H2 and T_H22 cytokines contribute to inhibition of the terminal differentiation proteins. IL-31 is abruptly upregulated in acute disease, potentially reflecting its role as an itch mediator in patients with AD.

relevance of these proteins for inflammation was underlined with the identification of a new inflammatory disorder, the hallmark of which is an abundance of S100A8 and S100A9.⁵⁶ This disorder is characterized by recurrent skin infections and systemic inflammation, bearing similarities to AD.⁵⁶ Yet these proteins were also suggested to have antimicrobial activities, particularly against gram-negative bacteria, such as *Escherichia coli*. Indeed, AD skin is rarely infected with *E coli*.^{51,57} However, because AD skin is characterized by an increased rate of

Staphylococcus aureus skin infections, even in the presence of upregulated S100A7, S100A8, and S100A9 expression, these molecules might be more important as proinflammatory mediators in the pathogenesis of the disease. In acute AD these proteins might contribute to chemotaxis of immune cells and particularly T cells, numbers of which are highly increased in patients with acute disease.

The onset of acute AD skin lesions is also linked to increased skin infiltration by T cells and DCs, along with significantly

increased synthesis of cytokines that define activation of T_H2 and T_H22 T-cell subsets, as well as increased IL-17–related products (ie, CCL20, PI3/elfafin, and LCN2). S100A7, S100A8, and S100A9 were demonstrated to be regulated by IL-22 and IL-17 cytokines alone and in synergy.^{8,10,33,43} Thus the marked induction of S100 genes in the epidermis could be explained by inductive effects of IL-22, IL-17, or both cytokines on these gene products in epidermal keratinocytes, whereas the induction of epidermal hyperplasia at the onset of acute AD might result from a direct response of keratinocytes to IL-22.⁷ Although increased expression of IL-4, IL-13, and IL-31 has been hypothesized to decrease keratinocyte differentiation,^{9,47} we did not identify corresponding decreases in the expression of filaggrin, loricrin, or other terminal differentiation genes from nonlesional skin through chronic skin lesions. A particularly dramatic induction of the itch-associated T_H2 cytokine IL-31 was measured in acute AD lesions, corresponding to the marked pruritus experienced during development of new lesions.^{58,59}

The sum of these observations suggests a new hypothesis, namely that onset of clinically evident acute AD lesions is linked to activation of a subset of epidermal differentiation genes instead of a further suppression of terminal differentiation (Fig 6). This could be driven by a set of established activators of the S100 epidermal differentiation proteins,^{8,10,33,43} specifically IL-22 and IL-17, levels of which are increased in acute lesions. Although these cytokines are typically derived from T_H17 and T_H22 T-cell subsets and corresponding increases in T-cell infiltrates are evident in acute lesions, further studies should still establish T cells as the source of these cytokines. Furthermore, the S100 proteins could be modulated by additional factors, such as IL-1 α , IL-6, oncostatin M, and TNF- α .⁶⁰⁻⁶⁵ We did not detect altered expression of these markers in our study but cannot exclude the possibility that factors beyond increased expression of IL-22, IL-17, or both contribute to modulation of S100 proteins in acute disease.

Chronic AD lesions are characterized by further increases in epidermal proliferation, skin infiltration by T cells and DCs, and mRNA levels of IL-22 and S100 proteins, further supporting a probable link between expression of these transcriptional axes. The increase in T_H1 /IFN- γ –related products in chronic lesions could either represent a proinflammatory stimulus for activation of T_H17 / T_H22 T cells⁶⁶ or a counterregulatory signal to T_H2 ⁶⁷ or T_H17 ⁶⁸ activation. Our findings indicate that progression to chronic disease is associated with intensification of the immune axes that are upregulated in acute lesions, particularly T_H22 and T_H2 , as well as significant increases in levels of T_H1 –related products. Although less significant increases were detected in IL-17 cytokine expression ($P = .13$), levels of several IL-17–regulated products were also significantly increased in acute or chronic AD lesions (Fig 3 and see Fig E2, D). Furthermore, IL-17–related genes were among the set of best predictors of the SCORAD index in chronic disease. Thus IL-17 might still be biologically important in initiation and progression of AD lesions and could activate or synergize with IL-22 for induction of S100A7, S100A8, and S100A9. However, the increases in IL-17–associated products in patients with both acute and chronic versus nonlesional AD are much lower than in patients with psoriasis (Fig 5, A, B, and D).⁴⁶ The more modest contribution of the T_H17 axis in patients with AD might result from inhibition of this pathway by activated T_H2 cytokines in both acute and chronic AD skin.⁴²

Our data expand the prevailing view of pathogenic pathways¹⁶ and have important implications for the treatment of acute and chronic AD. One implication of these data is that potential antagonism of the T_H2 and T_H22 inflammatory pathways might not only reverse chronic AD lesions but could also prevent the onset of new skin lesions.

Clinical implications: Targeting T_H2 and T_H22 pathways in patients with AD can be an effective therapeutic strategy, regardless of disease stage.

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Table E1. Characteristics of atopic dermatitis study patients

Patient	Age (y)	Family history of atopy^a	SCORAD^b	IgE^c	Eosinophil count^d	Filaggrin mutation^e
1 (P110)	67	No	54	48	3.90%	Negative
2 (P111)	33	No	50	39	1.20%	Negative
3 (P112)	45	No	63	3,652	0.30%	Negative
4 (P113)	52	No	40	374	4.70%	Negative
5 (P114)	20	No	49	28	1.2%	Negative
6 (P115)	33	Yes	43	663	5.30%	Negative
7 (P116)	26	Yes	59	750	6.90%	Negative
8 (P10)	41	No	62	>2000	4.8%	Negative
9	60	No	51	2238	7.5%	Negative
10	58	No	31	531	4.9%	Negative

^a Family history defined as history of allergic rhinitis and/or hay fever, atopic dermatitis, and/or asthma in parent and/or sibling of patient.

^b SCORing of Atopic Dermatitis index (see Methods).

^c Reference range, 0-160 kU/L.

^d Reference range, 0-7% serum eosinophil count.

^e DNA samples from all patients were sequenced for detection of either a R501X or 2282del4 mutation of the filaggrin gene.

Table E2. Antibodies used for immunohistochemical analysis

Antibody	Vendor	Clone	Isotype	Dilution
Keratin 16 (K16)	Sigma Aldrich	K8.12	IgG1	1:40
Ki67	Santa Cruz	MIB-1	IgG1	1:100
CD3	BD Biosciences	SK7	IgG1	1:100
CD8	Abcam	144B	IgG1	1:25
CD11c	BD Biosciences	B-ly6	IgG1	1:100
CD1c/BDCA-1	Miltenyi Biotec	AD5-8E7	IgG2a	1:100
CD1a	Abcam	CD1a007	IgG1	1:25
FcεRI	Thermo Scientific	CRA1 (AER37)	IgG2b	1:100
TRAIL	R&D Systems	75402.11	IgG1	1:50
OX40L	R&D Systems	159403	IgG1	1:50
BDCA-2	Miltenyi Biotec	AC144	IgG1	1:5
CD206	Genetex	15-2	IgG1	1:100
CD83	BD Biosciences	HB15e	IgG2	1:20
S100A7	Abcam	47C1068	IgG1	1:500
S100A8	LifeSpan	MAC387	IgG1	1:100

	Biosciences			
DC-LAMP	Fisher Scientific	104.G4	IgG1	1:50
Major Basic Protein	Thermo Scientific	BMK13	IgG1	1:15
Neutrophil Elastase	Dako	NP57	IgG1	1:200
Tryptase	Abcam	AA1	IgG1	1:100

Table E3. Differentially expressed genes (DEGs) in acute (ALS) vs chronic (CLS) vs non-lesional (NL) atopic dermatitis, organized by fold change (FCH) of ALS vs NL. DEGs were determined using criteria of FCH>1.5 and p-value<0.01. Status columns indicate if the gene is up-regulated (1), down-regulated (-1), or not differentially expressed (0).

Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	5.31	0.00	1	1.28	0.48	0	6.82	0.00	1
SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	4.78	0.00	1	1.41	0.37	0			
S100A8	S100 calcium binding protein A8	4.70	0.00	1	1.03	0.91	0	4.86	0.00	1
S100A9	S100 calcium binding protein A9	4.25	0.00	1	1.11	0.80	0	4.74	0.00	1
S100A7	S100 calcium binding protein A7	4.23	0.00	1	1.16	0.65	0	4.92	0.00	1
PI3	peptidase inhibitor 3, skin-derived	3.98	0.00	1	0.77	0.42	0	3.06	0.00	1
MMP12	matrix metalloproteinase 12 (macrophage elastase)	3.83	0.00	1	1.21	0.65	0	4.64	0.00	1
S100A8	S100 calcium binding protein A8	3.52	0.00	1	1.05	0.86	0	3.68	0.00	1
PI3	peptidase inhibitor 3, skin-derived	3.44	0.00	1	0.77	0.39	0	2.65	0.00	1
SPRR1B	small proline-rich protein 1B	3.28	0.01	1	1.31	0.51	0	4.29	0.00	1
LCE3D	late cornified envelope 3D	2.88	0.01	1	2.11	0.04	0	6.08	0.00	1
COL6A5	collagen, type VI, alpha 5	2.86	0.00	1	1.23	0.41	0	3.52	0.00	1
C10orf99	chromosome 10 open reading frame 99	2.78	0.01	0	2.03	0.07	0	5.65	0.00	1
MMP1	matrix metalloproteinase 1 (interstitial collagenase)	2.76	0.01	1	1.33	0.44	0	3.68	0.00	1
FOSL1	FOS-like antigen 1	2.70	0.00	1	0.74	0.22	0	2.00	0.01	1
SPRR3	small proline-rich protein 3	2.68	0.01	1	1.38	0.33	0	3.68	0.00	1
SPRR1A	small proline-rich protein 1A	2.65	0.02	0	1.43	0.39	0	3.79	0.00	1
SPRR1A	small proline-rich protein 1A	2.54	0.01	0	1.30	0.47	0	3.30	0.00	1
COL6A6	collagen, type VI, alpha 6	2.39	0.01	1	1.60	0.14	0	3.83	0.00	1
COL6A5	collagen, type VI, alpha 5	2.26	0.00	1	1.30	0.28	0	2.95	0.00	1
AKR1B10	aldo-keto reductase family 1, member B10 (aldose reductase)	2.21	0.01	1	1.53	0.13	0	3.39	0.00	1
DEFB4A	defensin, beta 4A	2.19	0.04	0	1.89	0.10	0	4.13	0.00	1
SERPINB4	serpin peptidase inhibitor, clade B (ovalbumin), member 4	2.15	0.05	0	1.50	0.29	0	3.22	0.00	1
SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	2.10	0.00	1	0.77	0.26	0	1.63	0.04	0
ZG16B	zymogen granule protein 16 homolog B (rat)	2.04	0.01	1	0.55	0.02	0	1.13	0.63	0
PDZK1IP1	PDZK1 interacting protein 1	2.04	0.00	1	0.86	0.51	0	1.76	0.02	0
TPRSS4	transmembrane protease, serine 4	1.99	0.00	1	1.00	0.98	0	1.98	0.00	1
CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	1.97	0.10	0	2.42	0.04	0	4.77	0.00	1
RGS1	regulator of G-protein signaling 1	1.96	0.01	1	1.21	0.43	0	2.38	0.00	1
NR4A3	nuclear receptor subfamily 4, group A, member 3	1.95	0.01	1	0.84	0.44	0	1.64	0.03	0
PDZK1IP1	PDZK1 interacting protein 1	1.95	0.00	1	0.83	0.37	0	1.62	0.03	0
KRT16	keratin 16	1.90	0.03	0	1.43	0.22	0	2.71	0.00	1
SOCS3	suppressor of cytokine signaling 3	1.90	0.00	1	1.01	0.97	0	1.91	0.00	1
OGN	osteonectin	1.88	0.00	1	0.79	0.24	0	1.49	0.05	0
GALNT6	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylglucosaminyltransferase 6 (GalNAc-T6)	1.86	0.00	1	1.10	0.45	0	2.05	0.00	1
HAL	histidine ammonia-lyase	1.83	0.04	0	1.29	0.37	0	2.36	0.01	1
FGL2	fibrinogen-like 2	1.82	0.00	1	0.92	0.57	0	1.67	0.00	1
ZNF557	zinc finger protein 557	1.82	0.00	1	0.88	0.30	0	1.59	0.00	1
F5	coagulation factor V (proaccelerin, labile factor)	1.81	0.00	1	0.62	0.01	-1	1.12	0.51	0
AQP3	aquaporin 3 (Gill blood group)	1.80	0.02	0	1.12	0.64	0	2.01	0.01	1
CCL22	chemokine (C-C motif) ligand 22	1.79	0.03	0	1.13	0.64	0	2.01	0.01	1
AQP3	aquaporin 3 (Gill blood group)	1.79	0.03	0	1.17	0.54	0	2.09	0.01	1
CYP4F22	cytochrome P450, family 4, subfamily F, polypeptide 22	1.79	0.00	1	0.81	0.23	0	1.44	0.05	0
CCL2	chemokine (C-C motif) ligand 2	1.77	0.02	0	1.26	0.32	0	2.23	0.00	1

		Page 2 of 12								
Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
CCL13	chemokine (C-C motif) ligand 13	1.77	0.03	0	1.72	0.04	0	3.04	0.00	1
IL7R	interleukin 7 receptor	1.77	0.02	0	1.21	0.41	0	2.13	0.00	1
SPRR2G	small proline-rich protein 2G	1.76	0.06	0	1.48	0.18	0	2.60	0.00	1
CST7	cystatin F (leukocystatin)	1.76	0.01	0	1.23	0.35	0	2.15	0.00	1
ARNTL2	aryl hydrocarbon receptor nuclear translocator-like 2	1.75	0.01	1	1.30	0.18	0	2.28	0.00	1
FBN1	fibrillin 1	1.74	0.00	1	1.03	0.86	0	1.79	0.00	1
DPP4	dipeptidyl-peptidase 4	1.74	0.00	1	1.06	0.71	0	1.84	0.00	1
EPHX3	epoxide hydrolase 3	1.72	0.00	1	0.92	0.60	0	1.57	0.01	0
CCL26	chemokine (C-C motif) ligand 26	1.71	0.03	0	1.33	0.23	0	2.28	0.00	1
HSD3B1	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1	1.71	0.20	0	0.32	0.01	-1	0.54	0.14	0
TYMP	thymidine phosphorylase	1.71	0.00	1	1.12	0.47	0	1.91	0.00	1
TTC39A	tetratricopeptide repeat domain 39A	1.70	0.00	1	1.03	0.81	0	1.75	0.00	1
DNASE1L3	deoxyribonuclease I-like 3	1.70	0.00	1	1.10	0.51	0	1.86	0.00	1
PHLDA2	pleckstrin homology-like domain, family A, member 2	1.70	0.01	1	0.68	0.04	0	1.16	0.42	0
TMEM176B	transmembrane protein 176B	1.70	0.00	1	0.99	0.92	0	1.67	0.00	1
TMEM45B	transmembrane protein 45B	1.69	0.00	1	0.87	0.32	0	1.47	0.01	0
RGS1	regulator of G-protein signaling 1	1.69	0.02	0	1.28	0.26	0	2.17	0.00	1
CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	1.69	0.12	0	2.09	0.03	0	3.52	0.00	1
CTLA4	cytotoxic T-lymphocyte-associated protein 4	1.67	0.05	0	1.44	0.15	0	2.41	0.00	1
KRT7	keratin 7	1.67	0.01	1	0.62	0.01	-1	1.03	0.87	0
SLC5A1	solute carrier family 5 (sodium/glucose cotransporter), member 1	1.67	0.00	1	0.83	0.17	0	1.38	0.02	0
IL1F5	interleukin 1 family, member 5 (delta)	1.67	0.05	0	1.26	0.37	0	2.10	0.01	1
NAPSB	napsin B aspartic peptidase pseudogene	1.67	0.02	0	1.13	0.55	0	1.88	0.00	1
F5	coagulation factor V (proaccelerin, labile factor)	1.66	0.02	0	0.51	0.00	-1	0.85	0.43	0
NAPSB	napsin B aspartic peptidase pseudogene	1.65	0.01	0	1.02	0.90	0	1.69	0.01	1
CH25H	cholesterol 25-hydroxylase	1.64	0.00	1	1.07	0.66	0	1.75	0.00	1
LYZ	lysozyme	1.64	0.07	0	1.49	0.14	0	2.44	0.00	1
CD274	CD274 molecule	1.63	0.02	0	1.31	0.19	0	2.14	0.00	1
SLAMF7	SLAM family member 7	1.63	0.02	0	1.11	0.60	0	1.81	0.01	1
GPR171	G protein-coupled receptor 171	1.63	0.03	0	1.51	0.06	0	2.46	0.00	1
SCO2	SCO cytochrome oxidase deficient homolog 2 (yeast)	1.63	0.02	0	1.06	0.77	0	1.72	0.01	1
TGM1	transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase)	1.62	0.01	1	1.05	0.80	0	1.69	0.01	1
TYMP	thymidine phosphorylase	1.61	0.02	0	1.16	0.46	0	1.87	0.00	1
APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	1.61	0.06	0	1.26	0.34	0	2.04	0.01	1
CD24	CD24 molecule	1.61	0.01	1	0.77	0.13	0	1.24	0.22	0
SBNO2	strawberry notch homolog 2 (Drosophila)	1.61	0.00	1	0.98	0.88	0	1.58	0.00	1
MMP19	matrix metalloproteinase 19	1.60	0.00	1	0.87	0.27	0	1.39	0.01	0
PTGS1	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)	1.59	0.00	1	1.01	0.92	0	1.61	0.00	1
SYNCRIP	synaptotagmin binding, cytoplasmic RNA interacting protein	1.59	0.00	1	0.88	0.37	0	1.41	0.02	0
NFE2L3	nuclear factor (erythroid-derived 2)-like 3	1.59	0.01	1	1.08	0.64	0	1.71	0.00	1
KIAA1644	KIAA1644	1.59	0.00	1	1.07	0.61	0	1.70	0.00	1
LASS3	LAG1 homolog, ceramide synthase 3	1.58	0.01	1	0.95	0.77	0	1.51	0.02	0
DPT	dermatopontin	1.58	0.01	1	1.01	0.98	0	1.59	0.01	1
IGFL1	IGF-like family member 1	1.58	0.10	0	1.56	0.11	0	2.47	0.00	1
LYPD3	LY6/PLAUR domain containing 3	1.58	0.01	1	0.82	0.20	0	1.30	0.10	0
TMEM49	transmembrane protein 49	1.57	0.00	1	1.10	0.51	0	1.73	0.00	1
DPT	dermatopontin	1.57	0.01	1	0.85	0.28	0	1.33	0.07	0
LRG1	leucine-rich alpha-2-glycoprotein 1	1.57	0.03	0	0.56	0.00	-1	0.87	0.47	0
SAMD9	sterile alpha motif domain containing 9	1.56	0.01	1	1.25	0.16	0	1.96	0.00	1
IRF1	interferon regulatory factor 1	1.55	0.01	0	1.12	0.52	0	1.73	0.00	1
ELANE	elastase, neutrophil expressed	1.55	0.00	1	0.76	0.04	0	1.17	0.23	0
NFASC	neurofascin	1.55	0.00	1	1.04	0.74	0	1.61	0.00	1

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Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
AGPAT9	1-acylglycerol-3-phosphate O-acyltransferase 9	1.55	0.00	1	0.95	0.63	0	1.46	0.00	0
PSTPIP1	proline-serine-threonine phosphatase interacting protein 1	1.55	0.00	1	0.96	0.79	0	1.49	0.01	0
FAM110C	family with sequence similarity 110, member C	1.55	0.00	1	1.02	0.88	0	1.58	0.00	1
IL2RG	interleukin 2 receptor, gamma	1.55	0.05	0	1.28	0.25	0	1.97	0.00	1
SLC16A3	solute carrier family 16, member 3 (monocarboxylic acid transporter 4)	1.55	0.00	1	0.86	0.24	0	1.33	0.03	0
IL13RA2	interleukin 13 receptor, alpha 2	1.54	0.01	0	1.16	0.37	0	1.79	0.00	1
TRBC1	T cell receptor beta constant 1	1.54	0.10	0	1.39	0.20	0	2.15	0.01	1
CD83	CD83 molecule	1.54	0.00	1	0.90	0.44	0	1.39	0.02	0
GNA15	guanine nucleotide binding protein (G protein), alpha 15 (Gq class)	1.54	0.00	1	1.01	0.91	0	1.56	0.00	1
ISG20	interferon stimulated exonuclease gene 20kDa	1.54	0.01	1	0.99	0.95	0	1.52	0.01	0
IL1R2	interleukin 1 receptor, type II	1.54	0.01	1	1.06	0.69	0	1.63	0.00	1
LY6D	lymphocyte antigen 6 complex, locus D	1.54	0.01	0	1.33	0.09	0	2.04	0.00	1
NNMT	nicotinamide N-methyltransferase	1.53	0.01	1	0.86	0.28	0	1.31	0.06	0
CCL13	chemokine (C-C motif) ligand 13	1.53	0.08	0	1.66	0.04	0	2.54	0.00	1
LAMP3	lysosomal-associated membrane protein 3	1.53	0.04	0	1.29	0.20	0	1.97	0.00	1
DHRS9	dehydrogenase/reductase (SDR family) member 9	1.53	0.02	0	0.59	0.01	-1	0.90	0.55	0
ICAM1	intercellular adhesion molecule 1	1.53	0.00	1	1.01	0.92	0	1.55	0.00	1
PPIF	peptidylprolyl isomerase F	1.52	0.00	1	0.79	0.06	0	1.20	0.16	0
DHRS9	dehydrogenase/reductase (SDR family) member 9	1.52	0.02	0	0.58	0.00	-1	0.88	0.45	0
KRT6A	keratin 6A	1.52	0.12	0	1.40	0.21	0	2.13	0.01	1
AMD1	adenosylmethionine decarboxylase 1	1.52	0.00	1	1.04	0.75	0	1.58	0.00	1
PPIF	peptidylprolyl isomerase F	1.52	0.00	1	0.80	0.06	0	1.21	0.12	0
MOXD1	monooxygenase, DBH-like 1	1.51	0.00	1	1.24	0.08	0	1.87	0.00	1
NOD2	nucleotide-binding oligomerization domain containing 2	1.51	0.00	1	1.26	0.08	0	1.90	0.00	1
HBEGF	heparin-binding EGF-like growth factor	1.51	0.01	1	0.85	0.23	0	1.28	0.08	0
SELL	selectin L	1.51	0.06	0	1.36	0.15	0	2.06	0.00	1
KLK7	kallikrein-related peptidase 7	1.51	0.02	0	1.09	0.61	0	1.64	0.01	1
CA2	carbonic anhydrase II	1.51	0.06	0	1.30	0.22	0	1.96	0.00	1
IL1R2	interleukin 1 receptor, type II	1.51	0.01	1	0.98	0.90	0	1.48	0.01	0
PTGS1	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)	1.50	0.01	1	1.00	0.98	0	1.51	0.01	1
PLAU	plasminogen activator, urokinase	1.50	0.01	1	1.04	0.80	0	1.55	0.00	1
DPYSL3	dihydropyrimidinase-like 3	1.50	0.00	1	0.88	0.31	0	1.32	0.04	0
MFHAS1	malignant fibrous histiocytoma amplified sequence 1	1.50	0.00	1	1.16	0.24	0	1.75	0.00	1
CBLC	Cas-Br-M (murine) ecotropic retroviral transforming sequence c	1.50	0.01	0	1.08	0.63	0	1.61	0.00	1
KRT7	keratin 7	1.50	0.04	0	0.52	0.00	-1	0.79	0.22	0
C1R	complement component 1, r subcomponent	1.50	0.02	0	1.16	0.35	0	1.74	0.00	1
RRM2	ribonucleotide reductase M2	1.49	0.07	0	1.36	0.16	0	2.03	0.00	1
FOX11	forkhead box I1	1.49	0.03	0	0.57	0.00	-1	0.85	0.36	0
ACPP	acid phosphatase, prostate	1.49	0.02	0	1.10	0.59	0	1.63	0.01	1
LOC100288860	hypothetical LOC100288860	1.49	0.00	0	1.04	0.74	0	1.55	0.00	1
PRDM1	PR domain containing 1, with ZNF domain	1.48	0.05	0	1.18	0.40	0	1.75	0.01	1
JUNB	jun B proto-oncogene	1.48	0.01	0	1.02	0.89	0	1.51	0.00	1
CD53	CD53 molecule	1.48	0.04	0	1.32	0.14	0	1.96	0.00	1
HPSE	heparanase	1.48	0.07	0	1.21	0.37	0	1.79	0.01	1
IL32	interleukin 32	1.48	0.06	0	1.29	0.20	0	1.91	0.00	1
GALNT6	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylglucosaminyltransferase 6 (GalNAc-T6)	1.47	0.11	0	1.30	0.26	0	1.91	0.01	1
MIR155HG	MIR155 host gene (non-protein coding)	1.47	0.07	0	1.44	0.09	0	2.11	0.00	1
CD1B	CD1b molecule	1.47	0.05	0	1.40	0.09	0	2.05	0.00	1
EPSTI1	epithelial stromal interaction 1 (breast)	1.46	0.05	0	1.16	0.43	0	1.70	0.01	1
ARHGAP9	Rho GTPase activating protein 9	1.46	0.01	0	1.18	0.23	0	1.72	0.00	1
OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa	1.46	0.09	0	1.65	0.03	0	2.41	0.00	1

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Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
TIFAB	TRAF-interacting protein with forkhead-associated domain, family member B	1.46	0.03	0	1.18	0.34	0	1.72	0.00	1
DPP4	dipeptidyl-peptidase 4	1.46	0.02	0	1.23	0.17	0	1.80	0.00	1
F2RL2	coagulation factor II (thrombin) receptor-like 2	1.45	0.03	0	1.12	0.49	0	1.63	0.01	1
NMU	neuromedin U	1.45	0.05	0	1.21	0.30	0	1.76	0.01	1
CD47	CD47 molecule	1.45	0.01	0	1.15	0.26	0	1.67	0.00	1
TRIM14	tripartite motif-containing 14	1.45	0.01	0	1.12	0.42	0	1.62	0.00	1
F12	coagulation factor XII (Hageman factor)	1.45	0.01	0	1.18	0.19	0	1.70	0.00	1
SFRP2	secreted frizzled-related protein 2	1.44	0.19	0	1.58	0.11	0	2.28	0.01	1
GPR55	G protein-coupled receptor 55	1.44	0.02	0	1.11	0.49	0	1.60	0.00	1
IRF1	interferon regulatory factor 1	1.44	0.03	0	1.23	0.21	0	1.77	0.00	1
PYCARD	PYD and CARD domain containing	1.44	0.02	0	1.15	0.36	0	1.65	0.00	1
SERPINB13	serpin peptidase inhibitor, clade B (ovalbumin), member 13	1.44	0.24	0	1.94	0.04	0	2.80	0.00	1
GLIPR1	GLI pathogenesis-related 1	1.44	0.02	0	1.14	0.38	0	1.64	0.00	1
PAPPA	pregnancy-associated plasma protein A, pappalysin 1	1.44	0.00	0	1.11	0.24	0	1.59	0.00	1
C5orf27	chromosome 5 open reading frame 27	1.43	0.12	0	0.49	0.00	-1	0.70	0.13	0
RAB27A	RAB27A, member RAS oncogene family	1.43	0.02	0	1.07	0.64	0	1.53	0.01	1
SFRP2	secreted frizzled-related protein 2	1.43	0.10	0	1.75	0.01	0	2.51	0.00	1
BEND6	BEN domain containing 6	1.43	0.02	0	1.08	0.63	0	1.54	0.01	1
SLAMF8	SLAM family member 8	1.42	0.09	0	1.31	0.19	0	1.87	0.00	1
CYTIP	cytohesin 1 interacting protein	1.42	0.06	0	1.43	0.06	0	2.03	0.00	1
TDRD12	tudor domain containing 12	1.42	0.05	0	0.50	0.00	-1	0.70	0.05	0
PRSS53	protease, serine, 53	1.42	0.03	0	1.16	0.35	0	1.64	0.00	1
ARNTL2	aryl hydrocarbon receptor nuclear translocator-like 2	1.42	0.04	0	1.30	0.12	0	1.84	0.00	1
CD1C	CD1c molecule	1.42	0.07	0	1.31	0.15	0	1.86	0.00	1
SECTM1	secreted and transmembrane 1	1.41	0.02	0	1.08	0.58	0	1.52	0.00	1
SFN	stratifin	1.41	0.03	0	1.10	0.54	0	1.55	0.01	1
NMI	N-myc (and STAT) interactor	1.41	0.02	0	1.16	0.31	0	1.63	0.00	1
C16orf89	chromosome 16 open reading frame 89	1.41	0.03	0	0.65	0.01	-1	0.92	0.58	0
ADAM19	ADAM metallopeptidase domain 19	1.41	0.04	0	1.14	0.42	0	1.61	0.01	1
BCAT1	branched chain amino-acid transaminase 1, cytosolic	1.41	0.10	0	1.33	0.18	0	1.87	0.01	1
IFIH1	interferon induced with helicase C domain 1	1.41	0.03	0	1.16	0.33	0	1.63	0.00	1
JAK3	Janus kinase 3	1.41	0.06	0	1.15	0.41	0	1.62	0.01	1
PTPRC	protein tyrosine phosphatase, receptor type, C	1.40	0.18	0	1.52	0.10	0	2.14	0.00	1
FAP	fibroblast activation protein, alpha	1.40	0.03	0	1.16	0.30	0	1.63	0.00	1
GGH	gamma-glutamyl hydrolase (conjugase, folypolygammaglutamyl hydrolase)	1.40	0.02	0	1.16	0.29	0	1.63	0.00	1
TAGAP	T-cell activation RhoGTPase activating protein	1.40	0.14	0	1.42	0.12	0	1.99	0.00	1
SLAMF1	signaling lymphocytic activation molecule family member 1	1.40	0.10	0	1.31	0.19	0	1.83	0.01	1
SLC16A14	solute carrier family 16, member 14 (monocarboxylic acid transporter 14)	1.40	0.04	0	1.43	0.03	0	2.00	0.00	1
SERHL2	serine hydrolase-like 2	1.40	0.12	0	0.53	0.01	-1	0.74	0.17	0
CD3D	CD3d molecule, delta (CD3-TCR complex)	1.40	0.14	0	1.33	0.21	0	1.86	0.01	1
SLC31A1	solute carrier family 31 (copper transporters), member 1	1.40	0.02	0	0.66	0.00	-1	0.92	0.51	0
TNFRSF21	tumor necrosis factor receptor superfamily, member 21	1.39	0.01	0	1.15	0.27	0	1.61	0.00	1
CSF2RB	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	1.39	0.12	0	1.28	0.23	0	1.79	0.01	1
NCALD	neurocalcin delta	1.39	0.05	0	0.61	0.01	-1	0.85	0.31	0
CD86	CD86 molecule	1.39	0.04	0	1.35	0.05	0	1.88	0.00	1
CTSC	cathepsin C	1.39	0.06	0	1.22	0.26	0	1.69	0.01	1
LGALS2	lectin, galactoside-binding, soluble, 2	1.39	0.08	0	1.27	0.19	0	1.76	0.00	1
C1S	complement component 1, s subcomponent	1.39	0.02	0	1.18	0.20	0	1.64	0.00	1
ITGAL	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	1.39	0.13	0	1.34	0.18	0	1.85	0.01	1
EGLN3	egl nine homolog 3 (C. elegans)	1.38	0.10	0	1.23	0.27	0	1.71	0.01	1

Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
LAD1	ladinin 1	1.38	0.03	0	1.16	0.30	0	1.61	0.00	1
IFI27	interferon, alpha-inducible protein 27	1.38	0.16	0	1.39	0.15	0	1.92	0.01	1
CEACAM1	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	1.38	0.11	0	0.58	0.01	-1	0.80	0.27	0
CXCL10	chemokine (C-X-C motif) ligand 10	1.38	0.42	0	2.45	0.03	0	3.38	0.00	1
CD2	CD2 molecule	1.38	0.16	0	1.37	0.17	0	1.89	0.01	1
F13A1	coagulation factor XIII, A1 polypeptide	1.38	0.03	0	1.25	0.13	0	1.72	0.00	1
ADCY8	adenylate cyclase 8 (brain)	1.38	0.05	0	0.63	0.01	-1	0.87	0.38	0
HS3ST3B1	heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1	1.38	0.07	0	1.24	0.21	0	1.70	0.00	1
CD69	CD69 molecule	1.37	0.15	0	1.60	0.04	0	2.20	0.00	1
COTL1	coactosin-like 1 (Dictyostelium)	1.37	0.11	0	1.27	0.21	0	1.75	0.01	1
MPEG1	macrophage expressed 1	1.37	0.07	0	1.31	0.11	0	1.79	0.00	1
DTX3L	deltex 3-like (Drosophila)	1.36	0.02	0	1.22	0.12	0	1.66	0.00	1
VCAM1	vascular cell adhesion molecule 1	1.36	0.05	0	1.25	0.15	0	1.71	0.00	1
CCR7	chemokine (C-C motif) receptor 7	1.36	0.06	0	1.20	0.25	0	1.63	0.00	1
KCNK1	potassium channel, subfamily K, member 1	1.36	0.05	0	1.14	0.37	0	1.55	0.01	1
AQP5	aquaporin 5	1.36	0.10	0	0.55	0.00	-1	0.75	0.12	0
LCP1	lymphocyte cytosolic protein 1 (L-plastin)	1.36	0.14	0	1.41	0.10	0	1.91	0.00	1
UNC5C	unc-5 homolog C (C. elegans)	1.35	0.03	0	0.64	0.00	-1	0.86	0.29	0
PIK3R5	phosphoinositide-3-kinase, regulatory subunit 5	1.35	0.04	0	1.11	0.46	0	1.50	0.01	1
KCNK6	potassium channel, subfamily K, member 6	1.35	0.03	0	1.16	0.25	0	1.57	0.00	1
MIAT	myocardial infarction associated transcript (non-protein coding)	1.35	0.14	0	1.44	0.07	0	1.95	0.00	1
CACNB4	calcium channel, voltage-dependent, beta 4 subunit	1.35	0.06	0	1.40	0.04	0	1.89	0.00	1
PPY	pancreatic polypeptide	1.35	0.03	0	1.14	0.34	0	1.54	0.00	1
ADORA1	adenosine A1 receptor	1.35	0.03	0	0.66	0.00	-1	0.89	0.36	0
EMP3	epithelial membrane protein 3	1.35	0.04	0	1.22	0.17	0	1.64	0.00	1
RNASE6	ribonuclease, RNase A family, k6	1.35	0.13	0	1.39	0.10	0	1.88	0.00	1
CLEC7A	C-type lectin domain family 7, member A	1.35	0.27	0	2.09	0.01	1	2.82	0.00	1
AKT1S1	AKT1 substrate 1 (proline-rich)	1.35	0.06	0	1.13	0.41	0	1.53	0.01	1
GPR183	G protein-coupled receptor 183	1.35	0.13	0	1.30	0.17	0	1.76	0.01	1
OASL	2'-5'-oligoadenylate synthetase-like	1.35	0.21	0	1.65	0.04	0	2.22	0.00	1
SLA	Src-like adaptor	1.35	0.07	0	1.22	0.21	0	1.65	0.00	1
CD44	CD44 molecule (Indian blood group)	1.35	0.06	0	1.17	0.30	0	1.58	0.01	1
PLA2R1	phospholipase A2 receptor 1, 180kDa	1.35	0.04	0	0.65	0.00	-1	0.88	0.35	0
GBP1	guanylate binding protein 1, interferon-inducible, 67kDa	1.34	0.15	0	1.44	0.08	0	1.93	0.00	1
SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 2	1.34	0.06	0	1.19	0.25	0	1.59	0.00	1
CTSK	cathepsin K	1.34	0.08	0	1.22	0.23	0	1.63	0.01	1
TNC	tenascin C	1.33	0.07	0	1.19	0.27	0	1.59	0.01	1
GSDMC	gasdermin C	1.33	0.07	0	1.18	0.30	0	1.57	0.01	1
IGFBP3	insulin-like growth factor binding protein 3	1.33	0.08	0	1.16	0.35	0	1.55	0.01	1
LAPTM5	lysosomal protein transmembrane 5	1.33	0.18	0	1.42	0.11	0	1.89	0.01	1
AMMECR1	Alport syndrome, mental retardation, midface hypoplasia and elliptocytosis chromosomal region gene 1	1.33	0.04	0	1.18	0.23	0	1.56	0.00	1
EMB	embigin	1.33	0.11	0	1.36	0.09	0	1.80	0.00	1
FMNL1	formin-like 1	1.33	0.04	0	1.19	0.20	0	1.59	0.00	1
CORO1A	coronin, actin binding protein, 1A	1.33	0.12	0	1.27	0.19	0	1.68	0.01	1
NUF2	NUF2, NDC80 kinetochore complex component, homolog (S. cerevisiae)	1.33	0.08	0	1.34	0.07	0	1.78	0.00	1
OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa	1.33	0.10	0	1.47	0.03	0	1.95	0.00	1
FCHSD1	FCH and double SH3 domains 1	1.33	0.09	0	1.22	0.24	0	1.61	0.01	1
METTL7B	methyltransferase like 7B	1.32	0.24	0	0.45	0.00	-1	0.60	0.03	0
CD52	CD52 molecule	1.32	0.24	0	1.60	0.05	0	2.11	0.00	1
P2RY8	purinergic receptor P2Y, G-protein coupled, 8	1.32	0.11	0	1.22	0.25	0	1.61	0.01	1
ZBED2	zinc finger, BED-type containing 2	1.32	0.05	0	1.31	0.06	0	1.72	0.00	1

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Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL		FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
PIK3R5	phosphoinositide-3-kinase, regulatory subunit 5	1.32	0.06	0		1.24	0.13	0	1.64	0.00	1
SELPLG	selectin P ligand	1.32	0.10	0		1.28	0.15	0	1.68	0.00	1
NT5E	5'-nucleotidase, ecto (CD73)	1.32	0.05	0		1.23	0.13	0	1.62	0.00	1
C21orf91	chromosome 21 open reading frame 91	1.31	0.04	0		1.17	0.24	0	1.53	0.00	1
COL14A1	collagen, type XIV, alpha 1	1.31	0.08	0		1.34	0.07	0	1.75	0.00	1
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	1.31	0.18	0		1.32	0.17	0	1.73	0.01	1
IRF8	interferon regulatory factor 8	1.31	0.18	0		1.33	0.16	0	1.74	0.01	1
VEGFA	vascular endothelial growth factor A	1.31	0.00	0		1.15	0.13	0	1.50	0.00	1
PKIA	protein kinase (cAMP-dependent, catalytic) inhibitor alpha	1.31	0.06	0		1.25	0.12	0	1.63	0.00	1
SFRP4	secreted frizzled-related protein 4	1.31	0.13	0		1.24	0.23	0	1.61	0.01	1
CTSC	cathepsin C	1.30	0.08	0		1.18	0.28	0	1.53	0.01	1
CD3G	CD3g molecule, gamma (CD3-TCR complex)	1.30	0.20	0		1.42	0.09	0	1.85	0.01	1
SHROOM3	shroom family member 3	1.30	0.12	0		0.61	0.01	-1	0.79	0.17	0
AWAT1	acyl-CoA wax alcohol acyltransferase 1	1.30	0.19	0		0.51	0.00	-1	0.66	0.04	0
FUT9	fucosyltransferase 9 (alpha (1,3) fucosyltransferase)	1.30	0.08	0		0.63	0.00	-1	0.82	0.18	0
RASSF2	Ras association (RalGDS/AF-6) domain family member 2	1.29	0.04	0		1.26	0.06	0	1.64	0.00	1
ARHGAP9	Rho GTPase activating protein 9	1.29	0.10	0		1.30	0.09	0	1.68	0.00	1
DUOXA1	dual oxidase maturation factor 1	1.29	0.02	0		1.20	0.09	0	1.56	0.00	1
PARP9	poly (ADP-ribose) polymerase family, member 9	1.29	0.11	0		1.32	0.08	0	1.71	0.00	1
TNFAIP3	tumor necrosis factor, alpha-induced protein 3	1.29	0.11	0		1.27	0.13	0	1.63	0.00	1
1-Mar	membrane-associated ring finger (C3HC4) 1	1.29	0.10	0		1.33	0.07	0	1.72	0.00	1
DUOX1	dual oxidase 1	1.29	0.10	0		1.23	0.17	0	1.58	0.00	1
MFI2	antigen p97 (melanoma associated) identified by monoclonal antibodies 133.2 and 96.5	1.29	0.14	0		0.60	0.00	-1	0.77	0.12	0
SAMS1	SAM domain, SH3 domain and nuclear localization signals 1	1.28	0.25	0		1.86	0.01	1	2.39	0.00	1
CCR2	chemokine (C-C motif) receptor 2	1.28	0.08	0		1.35	0.04	0	1.73	0.00	1
CPVL	carboxypeptidase, vitellogenic-like	1.28	0.22	0		1.55	0.04	0	1.99	0.00	1
KIF20A	kinesin family member 20A	1.28	0.12	0		1.23	0.19	0	1.58	0.01	1
MAPK1	mitogen-activated protein kinase 1	1.28	0.05	0		1.18	0.19	0	1.51	0.00	1
HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	1.28	0.21	0		0.55	0.00	-1	0.70	0.07	0
SC4MOL	sterol-C4-methyl oxidase-like	1.28	0.26	0		0.54	0.01	-1	0.69	0.09	0
TGFB1	transforming growth factor, beta 1	1.28	0.14	0		1.31	0.10	0	1.67	0.00	1
KRT7	keratin 7	1.28	0.07	0		0.66	0.00	-1	0.84	0.19	0
HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	1.28	0.22	0		0.50	0.00	-1	0.64	0.03	0
PCDH7	protocadherin 7	1.28	0.12	0		1.39	0.04	0	1.77	0.00	1
KPNA2	karyopherin alpha 2 (RAG cohort 1, importin alpha 1)	1.27	0.02	0		1.21	0.06	0	1.54	0.00	1
IL1F9	interleukin 1 family, member 9	1.27	0.27	0		1.68	0.02	0	2.13	0.00	1
POLR3G	polymerase (RNA) III (DNA directed) polypeptide G (32kD)	1.27	0.07	0		1.24	0.10	0	1.57	0.00	1
DPP4	dipeptidyl-peptidase 4	1.27	0.07	0		1.29	0.05	0	1.63	0.00	1
FAS	Fas (TNF receptor superfamily, member 6)	1.27	0.07	0		1.32	0.04	0	1.67	0.00	1
PTPRC	protein tyrosine phosphatase, receptor type, C	1.26	0.31	0		1.62	0.04	0	2.05	0.00	1
SH3RF2	SH3 domain containing ring finger 2	1.26	0.14	0		1.21	0.22	0	1.53	0.01	1
CKS2	CDC28 protein kinase regulatory subunit 2	1.26	0.06	0		1.30	0.04	0	1.64	0.00	1
SLA2	Src-like-adaptor 2	1.26	0.17	0		1.28	0.13	0	1.61	0.01	1
TAPBP	TAP binding protein (tapasin)	1.26	0.08	0		1.29	0.05	0	1.62	0.00	1
FCER1G	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	1.26	0.27	0		1.42	0.10	0	1.78	0.01	1
WNT3	wingless-type MMTV integration site family, member 3	1.26	0.23	0		1.33	0.14	0	1.66	0.01	1
FAM26F	family with sequence similarity 26, member F	1.25	0.18	0		1.37	0.07	0	1.72	0.00	1
RAB31	RAB31, member RAS oncogene family	1.25	0.04	0		1.21	0.09	0	1.51	0.00	1
KRT18	keratin 18	1.25	0.26	0		0.58	0.01	-1	0.72	0.10	0
TPX2	TPX2, microtubule-associated, homolog (Xenopus laevis)	1.25	0.12	0		1.43	0.02	0	1.79	0.00	1
COL4A4	collagen, type IV, alpha 4	1.25	0.13	0		1.58	0.00	1	1.97	0.00	1

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Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL	
FABP7	fatty acid binding protein 7, brain	1.25	0.46	0	0.31	0.00	-1	0.38	0.00	-1	
LCP2	lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)	1.25	0.18	0	1.36	0.07	0	1.70	0.00	1	
CD96	CD96 molecule	1.25	0.11	0	1.27	0.09	0	1.58	0.00	1	
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	1.25	0.16	0	1.34	0.07	0	1.67	0.00	1	
HCK	hemopoietic cell kinase	1.25	0.12	0	1.30	0.07	0	1.62	0.00	1	
IL10RA	interleukin 10 receptor, alpha	1.25	0.13	0	1.24	0.14	0	1.55	0.01	1	
CD52	CD52 molecule	1.25	0.34	0	1.62	0.04	0	2.02	0.00	1	
ELOVL3	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 3	1.25	0.45	0	0.36	0.00	-1	0.44	0.01	-1	
FAM65C	family with sequence similarity 65, member C	1.25	0.14	0	1.44	0.02	0	1.80	0.00	1	
CCRL1	chemokine (C-C motif) receptor-like 1	1.24	0.25	0	1.42	0.07	0	1.76	0.01	1	
MPZL2	myelin protein zero-like 2	1.24	0.27	0	1.43	0.07	0	1.76	0.01	1	
SP100	SP100 nuclear antigen	1.24	0.11	0	1.21	0.15	0	1.50	0.00	1	
HLA-DRA	major histocompatibility complex, class II, DR alpha	1.24	0.31	0	1.45	0.08	0	1.79	0.01	1	
APOC1	apolipoprotein C-I	1.23	0.44	0	0.37	0.00	-1	0.46	0.01	-1	
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	1.23	0.24	0	1.36	0.09	0	1.68	0.01	1	
MPEG1	macrophage expressed 1	1.23	0.34	0	1.76	0.01	0	2.16	0.00	1	
TRERF1	transcriptional regulating factor 1	1.23	0.17	0	1.33	0.07	0	1.64	0.00	1	
CLECT7A	C-type lectin domain family 7, member A	1.23	0.26	0	1.56	0.02	0	1.91	0.00	1	
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	1.23	0.18	0	1.26	0.13	0	1.54	0.01	1	
FADS1	fatty acid desaturase 1	1.23	0.50	0	0.44	0.01	-1	0.54	0.05	0	
CD53	CD53 molecule	1.22	0.31	0	1.48	0.05	0	1.80	0.01	1	
CTSS	cathepsin S	1.22	0.16	0	1.24	0.13	0	1.52	0.01	1	
TNFAIP8L2	tumor necrosis factor, alpha-induced protein 8-like 2	1.22	0.15	0	1.27	0.09	0	1.55	0.00	1	
CCNB1	cyclin B1	1.22	0.21	0	1.27	0.14	0	1.56	0.01	1	
FAM26F	family with sequence similarity 26, member F	1.22	0.31	0	1.43	0.07	0	1.74	0.01	1	
CD86	CD86 molecule	1.21	0.23	0	1.55	0.01	1	1.88	0.00	1	
ARHGAP9	Rho GTPase activating protein 9	1.21	0.16	0	1.25	0.11	0	1.52	0.00	1	
CENPW	centromere protein W	1.21	0.09	0	1.24	0.06	0	1.51	0.00	1	
TRAC	T cell receptor alpha constant	1.21	0.27	0	1.43	0.04	0	1.74	0.00	1	
GPR12	G protein-coupled receptor 12	1.21	0.16	0	0.66	0.00	-1	0.80	0.09	0	
FASN	fatty acid synthase	1.21	0.24	0	0.47	0.00	-1	0.57	0.00	-1	
HLA-DRA	major histocompatibility complex, class II, DR alpha	1.21	0.36	0	1.47	0.07	0	1.77	0.01	1	
CSF2RA	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	1.20	0.26	0	1.31	0.11	0	1.57	0.01	1	
HCLS1	hematopoietic cell-specific Lyn substrate 1	1.20	0.28	0	1.36	0.08	0	1.63	0.01	1	
C16orf54	chromosome 16 open reading frame 54	1.20	0.41	0	1.53	0.06	0	1.83	0.01	1	
UHRF1	ubiquitin-like with PHD and ring finger domains 1	1.20	0.25	0	1.28	0.12	0	1.54	0.01	1	
ULK4	unc-51-like kinase 4 (C. elegans)	1.20	0.24	0	0.61	0.00	-1	0.73	0.05	0	
DEGS2	degenerative spermatocyte homolog 2, lipid desaturase (Drosophila)	1.19	0.23	0	0.65	0.01	-1	0.78	0.09	0	
INSIG1	insulin induced gene 1	1.19	0.41	0	0.44	0.00	-1	0.52	0.00	-1	
ALOX5AP	arachidonate 5-lipoxygenase-activating protein	1.19	0.26	0	1.44	0.02	0	1.72	0.00	1	
FANCA	Fanconi anemia, complementation group A	1.19	0.19	0	1.29	0.06	0	1.53	0.00	1	
CIDEA	cell death-inducing DFFA-like effector a	1.19	0.25	0	0.42	0.00	-1	0.50	0.00	-1	
FGD2	FYVE, RhoGEF and PH domain containing 2	1.19	0.22	0	1.30	0.06	0	1.54	0.00	1	
IFIT3	interferon-induced protein with tetratricopeptide repeats 3	1.19	0.33	0	1.38	0.07	0	1.64	0.01	1	
NAMPT	nicotinamide phosphoribosyltransferase	1.19	0.27	0	1.32	0.08	0	1.56	0.01	1	
SLC2A1	solute carrier family 2 (facilitated glucose transporter), member 1	1.19	0.21	0	1.31	0.05	0	1.55	0.00	1	
ACAT2	acetyl-CoA acetyltransferase 2	1.18	0.41	0	0.57	0.01	-1	0.68	0.06	0	
APOL6	apolipoprotein L, 6	1.18	0.29	0	1.43	0.03	0	1.70	0.00	1	
SERPINB13	serpin peptidase inhibitor, clade B (ovalbumin), member 13	1.18	0.42	0	1.60	0.03	0	1.90	0.00	1	
MFAP3L	microfibrillar-associated protein 3-like	1.18	0.16	0	0.63	0.00	-1	0.75	0.02	0	
NEK2	NIMA (never in mitosis gene a)-related kinase 2	1.18	0.27	0	1.41	0.03	0	1.66	0.00	1	
RHOF	ras homolog gene family, member F (in filopodia)	1.18	0.28	0	1.31	0.09	0	1.54	0.01	1	

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Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
CEP55	centrosomal protein 55kDa	1.18	0.37	0	1.52	0.03	0	1.79	0.00	1
TFEC	transcription factor EC	1.18	0.37	0	1.45	0.05	0	1.71	0.01	1
FADS2	fatty acid desaturase 2	1.18	0.63	0	0.37	0.01	-1	0.44	0.02	0
ASF1B	ASF1 anti-silencing function 1 homolog B (S. cerevisiae)	1.18	0.20	0	1.30	0.04	0	1.53	0.00	1
DAPP1	dual adaptor of phosphotyrosine and 3-phosphoinositides	1.17	0.36	0	1.47	0.03	0	1.73	0.00	1
FAS	Fas (TNF receptor superfamily, member 6)	1.17	0.31	0	1.52	0.01	0	1.78	0.00	1
HAO2	hydroxyacid oxidase 2 (long chain)	1.17	0.67	0	0.35	0.01	-1	0.40	0.02	0
SYT11	synaptotagmin XI	1.17	0.15	0	1.32	0.02	0	1.55	0.00	1
ITK	IL2-inducible T-cell kinase	1.17	0.38	0	1.58	0.02	0	1.85	0.00	1
AURKB	aurora kinase B	1.17	0.18	0	1.30	0.03	0	1.53	0.00	1
BUB1	budding uninhibited by benzimidazoles 1 homolog (yeast)	1.17	0.25	0	1.55	0.00	1	1.81	0.00	1
CD48	CD48 molecule	1.17	0.20	0	1.29	0.04	0	1.51	0.00	1
FABP7	fatty acid binding protein 7, brain	1.17	0.67	0	0.29	0.00	-1	0.34	0.01	-1
TPBG	trophoblast glycoprotein	1.17	0.22	0	1.41	0.01	0	1.64	0.00	1
GLIPR1	GLI pathogenesis-related 1	1.17	0.25	0	1.29	0.06	0	1.50	0.00	1
PARP14	poly (ADP-ribose) polymerase family, member 14	1.17	0.33	0	1.37	0.06	0	1.59	0.01	1
1-Mar	membrane-associated ring finger (C3HC4) 1	1.17	0.38	0	1.43	0.05	0	1.66	0.01	1
KIAA0101	KIAA0101	1.16	0.40	0	1.40	0.06	0	1.63	0.01	1
SMC4	structural maintenance of chromosomes 4	1.16	0.22	0	1.33	0.02	0	1.55	0.00	1
TM7SF2	transmembrane 7 superfamily member 2	1.16	0.32	0	0.65	0.01	-1	0.76	0.07	0
ARNTL2	aryl hydrocarbon receptor nuclear translocator-like 2	1.16	0.29	0	1.39	0.03	0	1.61	0.00	1
SERPINB13	serpin peptidase inhibitor, clade B (ovalbumin), member 13	1.16	0.45	0	2.05	0.00	1	2.38	0.00	1
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	1.16	0.33	0	1.33	0.07	0	1.54	0.01	1
CLEC7A	C-type lectin domain family 7, member A	1.16	0.40	0	1.44	0.04	0	1.66	0.01	1
CD1E	CD1e molecule	1.15	0.34	0	1.39	0.03	0	1.61	0.00	1
NCF2	neutrophil cytosolic factor 2	1.15	0.35	0	1.38	0.04	0	1.58	0.00	1
RCSD1	RCSD domain containing 1	1.15	0.39	0	1.46	0.02	0	1.68	0.00	1
CD84	CD84 molecule	1.15	0.40	0	1.51	0.02	0	1.74	0.00	1
PTTG1	pituitary tumor-transforming 1	1.15	0.24	0	1.41	0.01	0	1.61	0.00	1
ROPN1	ropporin, rhophilin associated protein 1	1.15	0.44	0	0.56	0.00	-1	0.64	0.02	0
SERPINB13	serpin peptidase inhibitor, clade B (ovalbumin), member 13	1.15	0.42	0	1.54	0.02	0	1.77	0.00	1
TEX101	testis expressed 101	1.15	0.29	0	1.31	0.04	0	1.51	0.00	1
STIL	SCL/TAL1 interrupting locus	1.15	0.22	0	1.31	0.02	0	1.50	0.00	1
RASGRP1	RAS guanyl releasing protein 1 (calcium and DAG-regulated)	1.15	0.44	0	1.79	0.00	1	2.05	0.00	1
FADS1	fatty acid desaturase 1	1.14	0.64	0	0.43	0.01	-1	0.49	0.02	0
ASPM	asp (abnormal spindle) homolog, microcephaly associated (Drosophila)	1.14	0.43	0	1.75	0.00	1	2.00	0.00	1
DOCK2	dedicator of cytokinesis 2	1.14	0.22	0	1.35	0.01	0	1.55	0.00	1
COL1A2	collagen, type I, alpha 2	1.14	0.39	0	1.43	0.03	0	1.63	0.00	1
FAS	Fas (TNF receptor superfamily, member 6)	1.14	0.31	0	1.45	0.01	0	1.65	0.00	1
C20orf3	chromosome 20 open reading frame 3	1.14	0.32	0	0.63	0.00	-1	0.71	0.02	0
FNDC5	fibronectin type III domain containing 5	1.14	0.37	0	0.65	0.01	-1	0.74	0.04	0
FAM26F	family with sequence similarity 26, member F	1.14	0.46	0	1.45	0.04	0	1.66	0.01	1
HMMR	hyaluronan-mediated motility receptor (RHAMM)	1.14	0.39	0	1.44	0.02	0	1.64	0.00	1
ARAP2	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 2	1.14	0.23	0	1.34	0.01	0	1.52	0.00	1
FADS1	fatty acid desaturase 1	1.14	0.70	0	0.34	0.00	-1	0.39	0.01	-1
CCDC102B	coiled-coil domain containing 102B	1.14	0.33	0	1.37	0.02	0	1.56	0.00	1
PLEK	pleckstrin	1.14	0.37	0	1.40	0.02	0	1.59	0.00	1
HLA-DPB1	major histocompatibility complex, class II, DP beta 1	1.13	0.43	0	1.37	0.05	0	1.55	0.01	1
ALOX15B	arachidonate 15-lipoxygenase, type B	1.13	0.69	0	0.40	0.01	-1	0.46	0.02	0
SERPINB13	serpin peptidase inhibitor, clade B (ovalbumin), member 13	1.13	0.40	0	1.39	0.03	0	1.57	0.01	1

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Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
SEMA4D	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	1.13	0.30	0	1.33	0.02	0	1.51	0.00	1
FAS	Fas (TNF receptor superfamily, member 6)	1.13	0.19	0	1.36	0.00	0	1.54	0.00	1
SAMD9	sterile alpha motif domain containing 9	1.13	0.25	0	1.37	0.01	0	1.54	0.00	1
CHRM1	cholinergic receptor, muscarinic 1	1.12	0.41	0	0.62	0.00	-1	0.70	0.02	0
MNDA	myeloid cell nuclear differentiation antigen	1.12	0.35	0	1.41	0.01	0	1.58	0.00	1
GCH1	GTP cyclohydrolase 1	1.12	0.58	0	1.68	0.02	0	1.89	0.01	1
NDC80	NDC80 homolog, kinetochore complex component (S. cerevisiae)	1.12	0.48	0	1.39	0.05	0	1.56	0.01	1
COL1A1	collagen, type I, alpha 1	1.12	0.44	0	1.38	0.03	0	1.54	0.01	1
FBP1	fructose-1,6-bisphosphatase 1	1.12	0.57	0	0.50	0.00	-1	0.56	0.01	-1
MXD1	MAX dimerization protein 1	1.12	0.42	0	1.39	0.02	0	1.55	0.00	1
EPSTI1	epithelial stromal interaction 1 (breast)	1.12	0.61	0	1.69	0.02	0	1.88	0.01	1
SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	1.12	0.54	0	1.50	0.03	0	1.67	0.01	1
HSD11B1	hydroxysteroid (11-beta) dehydrogenase 1	1.11	0.69	0	0.40	0.00	-1	0.45	0.01	-1
CCR6	chemokine (C-C motif) receptor 6	1.11	0.47	0	1.50	0.01	1	1.67	0.00	1
MKI67	antigen identified by monoclonal antibody Ki-67	1.11	0.46	0	1.37	0.03	0	1.52	0.01	1
TRIP13	thyroid hormone receptor interactor 13	1.11	0.37	0	1.41	0.01	0	1.57	0.00	1
MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	1.11	0.50	0	1.48	0.01	0	1.63	0.00	1
KLRB1	killer cell lectin-like receptor subfamily B, member 1	1.10	0.52	0	1.41	0.03	0	1.56	0.01	1
TMEM56	transmembrane protein 56	1.10	0.74	0	0.41	0.00	-1	0.45	0.01	-1
APOC1	apolipoprotein C-I	1.10	0.66	0	0.47	0.00	-1	0.52	0.01	-1
STK17B	serine/threonine kinase 17b	1.10	0.47	0	1.57	0.00	1	1.73	0.00	1
ATP6V1B1	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B1	1.10	0.48	0	0.66	0.00	-1	0.73	0.02	0
KIF18B	kinesin family member 18B	1.10	0.52	0	1.52	0.01	1	1.67	0.00	1
KRT23	keratin 23 (histone deacetylase inducible)	1.10	0.59	0	0.63	0.01	-1	0.69	0.04	0
RNF213	ring finger protein 213	1.09	0.49	0	1.41	0.01	0	1.55	0.00	1
ROPN1	ropporin, rhophilin associated protein 1	1.09	0.55	0	0.62	0.00	-1	0.68	0.01	0
RRM2	ribonucleotide reductase M2	1.09	0.59	0	1.55	0.01	0	1.69	0.00	1
MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	1.09	0.60	0	1.50	0.02	0	1.63	0.01	1
CLEC2B	C-type lectin domain family 2, member B	1.09	0.52	0	1.42	0.01	0	1.54	0.00	1
MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	1.09	0.64	0	1.55	0.02	0	1.68	0.01	1
CDK1	cyclin-dependent kinase 1	1.08	0.63	0	1.43	0.03	0	1.55	0.01	1
DHCR7	7-dehydrocholesterol reductase	1.08	0.68	0	0.53	0.00	-1	0.57	0.00	-1
ME1	malic enzyme 1, NADP(+)-dependent, cytosolic	1.08	0.66	0	0.62	0.01	-1	0.66	0.02	0
PLIN5	perilipin 5	1.08	0.74	0	0.51	0.01	-1	0.55	0.01	0
FYB	FYN binding protein	1.08	0.71	0	1.67	0.02	0	1.79	0.01	1
C20orf3	chromosome 20 open reading frame 3	1.07	0.62	0	0.67	0.01	-1	0.72	0.03	0
RHCG	Rh family, C glycoprotein	1.07	0.62	0	0.64	0.00	-1	0.68	0.01	0
ALOX15B	arachidonate 15-lipoxygenase, type B	1.06	0.84	0	0.36	0.00	-1	0.38	0.00	-1
MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	1.06	0.71	0	1.49	0.02	0	1.58	0.01	1
KIF11	kinesin family member 11	1.06	0.73	0	1.53	0.02	0	1.62	0.01	1
DHCR7	7-dehydrocholesterol reductase	1.06	0.74	0	0.54	0.00	-1	0.57	0.00	-1
EVI2A	ecotropic viral integration site 2A	1.06	0.71	0	1.65	0.00	1	1.75	0.00	1
MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	1.06	0.74	0	1.54	0.01	0	1.62	0.01	1
CX3CR1	chemokine (C-X3-C motif) receptor 1	1.05	0.76	0	1.54	0.01	0	1.61	0.01	1
PPP1R1B	protein phosphatase 1, regulatory (inhibitor) subunit 1B	1.05	0.74	0	0.63	0.00	-1	0.67	0.01	-1
SGK2	serum/glucocorticoid regulated kinase 2	1.05	0.82	0	0.53	0.00	-1	0.55	0.01	-1
SLC14A1	solute carrier family 14 (urea transporter), member 1 (Kidd blood group)	1.04	0.86	0	0.49	0.00	-1	0.51	0.01	-1

Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
TMEM56	transmembrane protein 56	1.04	0.87	0	0.51	0.00	-1	0.53	0.01	-1
CENPA	centromere protein A	1.03	0.81	0	1.62	0.00	1	1.68	0.00	1
PC	pyruvate carboxylase	1.03	0.81	0	0.65	0.00	-1	0.67	0.00	-1
ALDH1L1	aldehyde dehydrogenase 1 family, member L1	1.03	0.85	0	0.62	0.00	-1	0.64	0.01	-1
CRAT	carnitine O-acetyltransferase	1.03	0.83	0	0.64	0.00	-1	0.66	0.00	-1
FOLR1	folate receptor 1 (adult)	1.03	0.84	0	0.63	0.00	-1	0.64	0.00	-1
PECR	peroxisomal trans-2-enoyl-CoA reductase	1.03	0.78	0	0.64	0.00	-1	0.66	0.00	-1
ACAA2	acetyl-CoA acyltransferase 2	1.03	0.89	0	0.60	0.01	-1	0.61	0.01	0
MS4A14	membrane-spanning 4-domains, subfamily A, member 14	1.02	0.91	0	1.56	0.01	1	1.59	0.01	1
WNT5A	wingless-type MMTV integration site family, member 5A	1.02	0.91	0	1.58	0.00	1	1.60	0.00	1
DGAT2	diacylglycerol O-acyltransferase 2	1.01	0.94	0	0.47	0.00	-1	0.48	0.00	-1
DGAT2	diacylglycerol O-acyltransferase 2	1.01	0.98	0	0.42	0.00	-1	0.42	0.00	-1
ELOVL5	ELOVL family member 5, elongation of long chain fatty acids (FEN1/Elo2, SUR4/Elo3-like, yeast)	1.01	0.98	0	0.60	0.01	-1	0.61	0.01	-1
MOGAT1	monoacylglycerol O-acyltransferase 1	1.00	0.98	0	0.57	0.01	-1	0.58	0.01	-1
CENPE	centromere protein E, 312kDa	1.00	0.97	0	1.50	0.00	1	1.49	0.00	0
PRC1	protein regulator of cytokinesis 1	0.99	0.96	0	1.51	0.01	1	1.50	0.01	0
TOP2A	topoisomerase (DNA) II alpha 170kDa	0.99	0.95	0	1.59	0.01	1	1.58	0.01	1
TF	transferrin	0.98	0.94	0	0.44	0.00	-1	0.43	0.00	-1
TOP2A	topoisomerase (DNA) II alpha 170kDa	0.97	0.87	0	1.63	0.01	1	1.59	0.01	1
BUB1B	budding uninhibited by benzimidazoles 1 homolog beta (yeast)	0.97	0.80	0	1.66	0.00	1	1.60	0.00	1
TOX3	TOX high mobility group box family member 3	0.97	0.82	0	0.61	0.00	-1	0.59	0.00	-1
TMPRSS11E	transmembrane protease, serine 11E	0.97	0.83	0	0.65	0.01	0	0.63	0.01	-1
KRT77	keratin 77	0.97	0.80	0	0.68	0.01	0	0.65	0.01	-1
CENPV	centromere protein V	0.96	0.79	0	0.66	0.01	-1	0.64	0.00	-1
TOX3	TOX high mobility group box family member 3	0.96	0.81	0	0.64	0.02	0	0.61	0.01	-1
WNT5A	wingless-type MMTV integration site family, member 5A	0.96	0.78	0	1.67	0.00	1	1.60	0.01	1
SLC25A18	solute carrier family 25 (mitochondrial carrier), member 18	0.95	0.85	0	0.51	0.01	0	0.49	0.01	-1
ASAP1	ArfGAP with SH3 domain, ankyrin repeat and PH domain 1	0.95	0.74	0	1.65	0.00	1	1.57	0.00	1
CDK1	cyclin-dependent kinase 1	0.95	0.69	0	1.56	0.00	1	1.49	0.00	0
POLQ	polymerase (DNA directed), theta	0.95	0.65	0	1.57	0.00	1	1.49	0.00	0
CENPV	centromere protein V	0.95	0.69	0	0.69	0.01	0	0.65	0.00	-1
SPC25	SPC25, NDC80 kinetochore complex component, homolog (S. cerevisiae)	0.94	0.74	0	1.87	0.00	1	1.77	0.00	1
C1orf115	chromosome 1 open reading frame 115	0.94	0.65	0	0.70	0.02	0	0.66	0.01	-1
KRT79	keratin 79	0.94	0.88	0	0.33	0.01	0	0.31	0.01	-1
CHRNA3	cholinergic receptor, nicotinic, alpha 3	0.94	0.61	0	1.54	0.00	1	1.44	0.01	0
PPP2R2B	protein phosphatase 2, regulatory subunit B, beta	0.93	0.55	0	0.71	0.01	0	0.66	0.00	-1
TF	transferrin	0.93	0.77	0	0.50	0.01	-1	0.46	0.00	-1
ASAM	adipocyte-specific adhesion molecule	0.93	0.64	0	0.67	0.02	0	0.62	0.01	-1
ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	0.93	0.58	0	1.51	0.01	1	1.40	0.02	0
MAOA	monoamine oxidase A	0.92	0.54	0	0.68	0.01	0	0.62	0.00	-1
PON3	paraoxonase 3	0.92	0.66	0	0.59	0.01	-1	0.54	0.00	-1
SEMA3G	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3G	0.91	0.46	0	0.71	0.01	0	0.65	0.00	-1
FOXC1	forkhead box C1	0.91	0.50	0	0.72	0.03	0	0.66	0.01	-1
ADRB1	adrenergic, beta-1-, receptor	0.90	0.58	0	0.62	0.01	0	0.56	0.00	-1
LOC728723	hypothetical LOC728723	0.90	0.45	0	0.69	0.01	0	0.63	0.00	-1
MAF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	0.90	0.47	0	1.59	0.00	1	1.43	0.02	0
CLCNKB	chloride channel Kb	0.90	0.48	0	0.69	0.02	0	0.62	0.00	-1
MACROD2	MACRO domain containing 2	0.90	0.47	0	0.74	0.05	0	0.66	0.01	-1

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Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
THRSP	thyroid hormone responsive	0.89	0.41	0	0.71	0.02	0	0.64	0.00	-1
ACSS2	acyl-CoA synthetase short-chain family member 2	0.89	0.47	0	0.69	0.02	0	0.62	0.00	-1
FLJ37644	hypothetical LOC400618	0.89	0.45	0	0.68	0.02	0	0.61	0.00	-1
RBP7	retinol binding protein 7, cellular	0.89	0.49	0	0.70	0.05	0	0.62	0.01	-1
GBP4	guanylate binding protein 4	0.88	0.46	0	1.63	0.01	1	1.44	0.04	0
DNAH8	dynein, axonemal, heavy chain 8	0.88	0.44	0	0.67	0.02	0	0.59	0.00	-1
LOC401052	hypothetical LOC401052	0.87	0.32	0	0.76	0.07	0	0.66	0.01	-1
WFDC10B	WAP four-disulfide core domain 10B	0.87	0.32	0	0.75	0.05	0	0.65	0.00	-1
FGD6	FYVE, RhoGEF and PH domain containing 6	0.87	0.25	0	1.55	0.00	1	1.34	0.03	0
PCP4	Purkinje cell protein 4	0.86	0.46	0	0.65	0.04	0	0.56	0.01	-1
SOS1	son of sevenless homolog 1 (Drosophila)	0.86	0.32	0	1.60	0.01	1	1.38	0.05	0
CASC5	cancer susceptibility candidate 5	0.85	0.31	0	1.61	0.00	1	1.37	0.05	0
FOXC1	forkhead box C1	0.85	0.37	0	0.65	0.02	0	0.56	0.00	-1
HSD11B2	hydroxysteroid (11-beta) dehydrogenase 2	0.85	0.25	0	0.78	0.08	0	0.66	0.01	-1
PYGM	phosphorylase, glycogen, muscle	0.85	0.24	0	0.78	0.09	0	0.67	0.01	-1
FAH	fumarylacetoacetate hydrolase (fumarylacetoacetase)	0.85	0.31	0	0.75	0.09	0	0.64	0.01	-1
ALDOC	aldolase C, fructose-bisphosphate	0.84	0.25	0	0.78	0.10	0	0.65	0.01	-1
DIAPH3	diaphanous homolog 3 (Drosophila)	0.84	0.15	0	1.51	0.00	1	1.27	0.05	0
CRYAB	crystallin, alpha B	0.84	0.26	0	0.77	0.10	0	0.65	0.01	-1
PHYHIPL	phytanoyl-CoA 2-hydroxylase interacting protein-like	0.84	0.09	0	0.78	0.02	0	0.65	0.00	-1
ACACB	acetyl-CoA carboxylase beta	0.83	0.20	0	0.77	0.08	0	0.65	0.00	-1
SYN2	synapsin II	0.83	0.31	0	0.62	0.01	0	0.51	0.00	-1
THRSP	thyroid hormone responsive	0.83	0.55	0	0.39	0.00	-1	0.33	0.00	-1
RAD51AP1	RAD51 associated protein 1	0.83	0.27	0	1.59	0.01	1	1.33	0.10	0
TPM1	tropomyosin 1 (alpha)	0.83	0.11	0	0.78	0.03	0	0.65	0.00	-1
SRSF4	serine/arginine-rich splicing factor 4	0.83	0.24	0	1.56	0.01	1	1.30	0.10	0
ALDH6A1	aldehyde dehydrogenase 6 family, member A1	0.83	0.13	0	0.80	0.08	0	0.67	0.00	-1
COMP	cartilage oligomeric matrix protein	0.83	0.32	0	1.69	0.01	1	1.39	0.09	0
ACTA1	actin, alpha 1, skeletal muscle	0.82	0.36	0	0.61	0.02	0	0.50	0.00	-1
FBXO40	F-box protein 40	0.82	0.16	0	0.75	0.05	0	0.62	0.00	-1
MND1	meiotic nuclear divisions 1 homolog (S. cerevisiae)	0.82	0.14	0	1.56	0.00	1	1.28	0.06	0
ALDH1A2	aldehyde dehydrogenase 1 family, member A2	0.82	0.19	0	0.81	0.16	0	0.67	0.01	-1
CADM2	cell adhesion molecule 2	0.82	0.21	0	0.79	0.14	0	0.65	0.01	-1
LOC283392	hypothetical LOC283392	0.82	0.31	0	0.68	0.06	0	0.56	0.01	-1
ACACB	acetyl-CoA carboxylase beta	0.82	0.19	0	0.80	0.14	0	0.65	0.01	-1
GPD1	glycerol-3-phosphate dehydrogenase 1 (soluble)	0.82	0.49	0	0.53	0.04	0	0.43	0.01	-1
FGF1	fibroblast growth factor 1 (acidic)	0.81	0.09	0	0.80	0.08	0	0.64	0.00	-1
MAD2L1	MAD2 mitotic arrest deficient-like 1 (yeast)	0.81	0.15	0	1.52	0.01	1	1.23	0.18	0
MYH11	myosin, heavy chain 11, smooth muscle	0.81	0.16	0	0.78	0.11	0	0.63	0.00	-1
MAOA	monoamine oxidase A	0.80	0.12	0	0.77	0.07	0	0.62	0.00	-1
ABCD3	ATP-binding cassette, sub-family D (ALD), member 3	0.80	0.20	0	1.62	0.01	1	1.30	0.14	0
ACACB	acetyl-CoA carboxylase beta	0.80	0.16	0	0.79	0.13	0	0.63	0.01	-1
PPARG	peroxisome proliferator-activated receptor gamma	0.80	0.24	0	0.73	0.10	0	0.58	0.01	-1
RGL3	ral guanine nucleotide dissociation stimulator-like 3	0.80	0.04	0	0.80	0.05	0	0.64	0.00	-1
TACR2	tachykinin receptor 2	0.79	0.07	0	0.80	0.09	0	0.63	0.00	-1
DES	desmin	0.78	0.22	0	0.74	0.13	0	0.58	0.01	-1
RORC	RAR-related orphan receptor C	0.78	0.10	0	0.85	0.27	0	0.66	0.01	-1
RNF213	ring finger protein 213	0.78	0.12	0	1.72	0.00	1	1.34	0.07	0
ATP1A2	ATPase, Na+/K+ transporting, alpha 2 polypeptide	0.78	0.14	0	0.74	0.08	0	0.58	0.00	-1
RAPGEF3	Rap guanine nucleotide exchange factor (GEF) 3	0.78	0.05	0	0.80	0.09	0	0.62	0.00	-1
COL11A1	collagen, type XI, alpha 1	0.77	0.13	0	0.78	0.15	0	0.60	0.01	-1
HEATR4	HEAT repeat containing 4	0.77	0.14	0	0.75	0.11	0	0.58	0.00	-1
SORBS1	sorbin and SH3 domain containing 1	0.77	0.11	0	0.82	0.23	0	0.63	0.01	-1
HEATR5B	HEAT repeat containing 5B	0.76	0.08	0	1.52	0.01	1	1.16	0.34	0
MS4A7	membrane-spanning 4-domains, subfamily A, member 7	0.76	0.22	0	2.07	0.00	1	1.58	0.04	0
TBRG1	transforming growth factor beta regulator 1	0.76	0.06	0	1.63	0.00	1	1.23	0.15	0
HHATL	hedgehog acyltransferase-like	0.75	0.12	0	0.78	0.17	0	0.58	0.01	-1
THRSP	thyroid hormone responsive	0.75	0.34	0	0.39	0.00	-1	0.29	0.00	-1

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Symbol	Description	FCH-ALS-NL	P-ALS-NL	Status-ALS-NL	FCH-CLS-ALS	P-CLS-ALS	Status-CLS-ALS	FCH-CLS-NL	P-CLS-NL	Status-CLS-NL
FAT3	FAT tumor suppressor homolog 3 (Drosophila)	0.75	0.09	0	0.80	0.20	0	0.60	0.01	-1
PNPLA3	patatin-like phospholipase domain containing 3	0.74	0.17	0	0.75	0.18	0	0.56	0.01	-1
DEFB132	defensin, beta 132	0.74	0.10	0	0.80	0.20	0	0.59	0.01	-1
SNX32	sorting nexin 32	0.73	0.01	0	0.85	0.15	0	0.62	0.00	-1
BTNL9	butyrophilin-like 9	0.73	0.08	0	0.82	0.27	0	0.60	0.01	-1
LYG2	lysozyme G-like 2	0.73	0.03	0	0.91	0.51	0	0.67	0.01	-1
AKT3	v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)	0.72	0.02	0	1.62	0.00	1	1.17	0.24	0
CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	0.72	0.03	0	0.83	0.19	0	0.59	0.00	-1
COL11A1	collagen, type XI, alpha 1	0.72	0.09	0	0.72	0.09	0	0.52	0.00	-1
FGF18	fibroblast growth factor 18	0.72	0.03	0	0.89	0.40	0	0.64	0.00	-1
KRT82	keratin 82	0.72	0.09	0	0.81	0.29	0	0.58	0.01	-1
CTNND2	catenin (cadherin-associated protein), delta 2 (neural plakophilin-related arm-repeat protein)	0.71	0.05	0	0.84	0.29	0	0.59	0.00	-1
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	0.70	0.01	0	0.83	0.13	0	0.58	0.00	-1
PGAP1	post-GPI attachment to proteins 1	0.69	0.03	0	1.73	0.00	1	1.20	0.28	0
SEZ6L	seizure related 6 homolog (mouse)-like	0.69	0.01	0	0.94	0.67	0	0.65	0.00	-1
POSTN	periostin, osteoblast specific factor	0.69	0.05	0	1.73	0.01	1	1.20	0.33	0
CSMD1	CUB and Sushi multiple domains 1	0.69	0.08	0	0.60	0.02	0	0.41	0.00	-1
KANK4	KN motif and ankyrin repeat domains 4	0.69	0.06	0	0.74	0.12	0	0.51	0.00	-1
BTNL9	butyrophilin-like 9	0.67	0.01	0	0.95	0.71	0	0.63	0.01	-1
LINGO2	leucine rich repeat and Ig domain containing 2	0.67	0.00	0	0.95	0.62	0	0.64	0.00	-1
ZBTB16	zinc finger and BTB domain containing 16	0.67	0.04	0	0.80	0.24	0	0.53	0.00	-1
KCNH8	potassium voltage-gated channel, subfamily H (eag-related), member 8	0.67	0.00	0	1.00	0.96	0	0.66	0.00	-1
RUNDC3B	RUN domain containing 3B	0.66	0.00	-1	1.18	0.20	0	0.78	0.06	0
ACADL	acyl-CoA dehydrogenase, long chain	0.66	0.03	0	0.81	0.27	0	0.54	0.00	-1
TPH1	tryptophan hydroxylase 1	0.66	0.01	-1	1.18	0.27	0	0.78	0.10	0
RGS5	regulator of G-protein signaling 5	0.65	0.01	-1	1.25	0.13	0	0.82	0.17	0
ATP8B4	ATPase, class I, type 8B, member 4	0.65	0.01	-1	1.27	0.10	0	0.83	0.20	0
ATP8A2	ATPase, aminophospholipid transporter, class I, type 8A, member 2	0.65	0.00	-1	1.00	0.99	0	0.65	0.00	-1
C6orf162	chromosome 6 open reading frame 162	0.65	0.01	-1	1.33	0.06	0	0.86	0.32	0
PIRT	phosphoinositide-interacting regulator of transient receptor potential channels	0.64	0.01	-1	1.01	0.95	0	0.65	0.01	-1
FGF18	fibroblast growth factor 18	0.64	0.01	-1	0.90	0.49	0	0.58	0.00	-1
SMTNL2	smoothelin-like 2	0.63	0.00	-1	0.99	0.96	0	0.62	0.00	-1
COL6A4P1	collagen, type VI, alpha 4 pseudogene 1	0.63	0.01	-1	1.24	0.19	0	0.77	0.11	0
LY6G6D	lymphocyte antigen 6 complex, locus G6D	0.62	0.08	0	0.76	0.30	0	0.47	0.01	-1
GRP	gastrin-releasing peptide	0.62	0.01	-1	1.05	0.74	0	0.66	0.01	0
LAMB4	laminin, beta 4	0.62	0.00	-1	1.27	0.13	0	0.79	0.13	0
LOH3CR2A	loss of heterozygosity, 3, chromosomal region 2, gene A	0.61	0.00	-1	1.20	0.10	0	0.73	0.01	0
FGF18	fibroblast growth factor 18	0.61	0.01	-1	1.02	0.91	0	0.62	0.01	-1
CAPN14	calpain 14	0.60	0.00	-1	1.26	0.10	0	0.75	0.05	0
KRTAP17-1	keratin associated protein 17-1	0.59	0.02	0	0.87	0.53	0	0.52	0.01	-1
HIF3A	hypoxia inducible factor 3, alpha subunit	0.59	0.01	-1	1.09	0.64	0	0.64	0.02	0
SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	0.58	0.00	-1	1.30	0.04	0	0.76	0.03	0
BTBD18	BTB (POZ) domain containing 18	0.58	0.00	-1	1.47	0.00	0	0.85	0.17	0
WNK4	WNK lysine deficient protein kinase 4	0.56	0.01	-1	0.90	0.58	0	0.50	0.00	-1
KRT32	keratin 32	0.55	0.01	-1	0.93	0.73	0	0.52	0.00	-1
LHX2	LIM homeobox 2	0.55	0.01	-1	0.95	0.79	0	0.52	0.00	-1
FREM2	FRAS1 related extracellular matrix protein 2	0.52	0.01	-1	0.97	0.89	0	0.51	0.01	-1
ANGPTL7	angiopoietin-like 7	0.47	0.00	-1	1.04	0.86	0	0.49	0.00	-1
KRTAP11-1	keratin associated protein 11-1	0.40	0.02	0	0.85	0.66	0	0.34	0.01	-1
CBLN2	cerebellin 2 precursor	0.36	0.00	-1	1.13	0.65	0	0.41	0.00	-1

Table E4. Output of Multiple Regression Analysis for acute vs non-lesional and chronic vs non-lesional in $\log_2(\text{FCH})$ per patient and SCORAD. Variables showing a correlation with SCORAD larger than 0.5 were included in the regression. The best model was chosen in an exhaustive search as the one with higher adjusted R² which in both cases also show the smaller Bayesian information criterion (BIC).

Acute vs non-lesional^a				
Initial independent variables: CCL18, CCL13, S100A12, IFNg, CXCL9, CXCL10, p40, TRAIL				
	Estimate	Standard Error	t-value	p-value
Intercept	24.281	7.224	3.361	0.028
CCL18	18.905	5.979	3.162	0.034
CCL13	-16.347	5.645	-2.896	0.044
S100A12	-7.007	2.448	-2.862	0.046
TRAIL	0.178	0.054	3.318	0.029
Chronic vs non-lesional^b				
Initial independent variables: IL-5, IL-31, OX40L, IL-9, IL-22, S100A12, IFNg, CXCL9, IL-17A, p40, PI3				
Intercept	39.305	2.026	19.405	4.16e-05
IL-31	1.237	0.334	3.699	0.021
IFNg	-6.077	1.232	-4.935	0.008
IL-17A	2.439	0.399	6.114	0.004
PI3	3.911	0.894	4.375	0.012

^a Residual standard error: 5.5 on 4 degrees of freedom (DF)

Multiple R-squared: 0.84, Adjusted R-squared: 0.679

F-statistic: 5.24 on 4 and 4 DF

p-value: 0.0688

^b Residual standard error: 3.048 on 4 degrees of freedom (DF)

Multiple R-squared: 0.9516, Adjusted R-squared: 0.9031

F-statistic: 19.64 on 4 and 4 DF

p-value: 0.006813

METHODS

Patients' characteristics and skin samples

Three 4- to 6-mm biopsy specimens, one each of non-lesional (area clear of disease, $\geq$ 10 cm from any active lesion, and has never been diseased according to patient history), acute atopic dermatitis (AD) and chronic AD skin (> 72 hrs duration), and blood samples, were obtained from 17 patients with moderate-to-severe AD under an Institutional Review Board-approved protocol. Ten patients (4 males and 6 females, age: 20-67 years; mean age: 44 years) (Table E1) met our histologic criteria, as 7 patients were excluded. Histologic analysis and real-time PCR (RT-PCR) were performed on 10 patients (nonlesional, acute, and chronic), but because of loss of tissue with laboratory processing and analysis, gene microarray analysis was performed on 8 patients. One patient's (P10) non-lesional (series accession no. GSM815426) and chronic lesional (series accession no. GSM815427) data was obtained from a prior publication.^{E1} For some analyses we also used skin samples from 15 normal volunteers^{E2} (7 males and 8 females, age: 26-74 years; mean age: 50), as well as data from 15 lesional and non-lesional psoriasis samples.^{E3}

Venous blood samples were taken from patients for measurement of serum IgE levels (reference range: 0-160 kU/L), serum eosinophil counts (reference range: 0% to 7%) and DNA sequencing (see below). Serum IgE levels were increased in 7 of 10 patients (range: 27.9-3652 kU/L; mean: 1032 kU/L) and serum eosinophil counts were increased in 1 of 10 patients.

The severity of AD was evaluated in all patients by using the Scoring of AD

(SCORAD) index, as previously described,^{E4} and the SCORAD score was used to classify AD in each patient as mild (<25), moderate (25-50) or severe (>50) (maximum SCORAD score, 103), as previously defined.^{E5} The SCORAD index formula is as follows: $A/5 + 7B/2 + C$. In this formula A is defined as the extent of disease (percentage of BSA involvement, arrived at by application of the “rule of nines” applied to a front/back drawing of the patient), B is defined as the intensity (erythema, edema/papulation, excoriations, lichenification, oozing/crusts, and dryness), and C is defined as the subjective symptoms (daily pruritus and sleeplessness).^{E4} SCORAD index scores ranged from 40 to 63 (mean, 50).

Immunohistochemistry

Cryostat tissue sections of all patients were stained with hematoxylin (Fisher, Fair Lawn, NJ) and eosin (Shandon, Pittsburgh, PA). Immunohistochemistry (IHC) was performed by using purified mouse anti-human monoclonal antibodies (Table E2).

Biotin-labeled horse anti-mouse antibodies (Vector Laboratories, Burlingame, Calif) were amplified with avidin-biotin complex (Vector Laboratories) and developed with chromogen 3-amino-9-ethylcarbazole (Sigma-Aldrich, St Louis, MO). All immunostained sections were photographed and analyzed with ImageJ software to measure epidermal thickness and cell counts per millimeter (ImageJ 1.42; National Institutes of Health, Bethesda, MD).

Genotyping of Filaggrin Variants

Genomic DNA samples were isolated from whole blood from all patients included in the study and genotyped for two of the most common filaggrin null mutations, R501X and 2282del4, using TaqMan allelic discrimination assays as previously described,^{E6, E7} with minor modifications. Briefly, TaqMan assays using Universal PCR Master Mix in 10-ml reaction volumes were run under standard TaqMan conditions on a ViiA7 Real-Time PCR System (Life Technologies, Grand Island, NY). For R501X, primers were used at 300 nM, probes at 200 nM, and template DNA at 0.625 ng.^{E6} For 2282del4, the forward-1 and reverse primers were used at 1000 nM, the forward-2 primer at 200 nM, probes at 300 nM, and template DNA at 5 ng.^{E8}

Sample preparation for gene chip analysis

We used human HGU133Plus2.0 GeneChip probe arrays (Affymetrix Inc, Santa Clara, Calif) containing approximately 54,000 probe sets to assess expression of more than 47,000 transcripts, including approximately 38,500 genes and unigenes. Total RNA was extracted from tissues frozen in liquid nitrogen by the Qiagen RNeasy Mini Kit (Valencia, Calif). DNA was removed with on-column DNase digestion by the Qiagen RNase-free DNase Set. Total RNA (50 ng) was reverse transcribed and amplified with Ovation Whole Blood Solution from NuGen (San Carlos, Calif). The labeled target was fragmented and hybridized to probe arrays, using Encore Biotin Module from NuGen (San Carlos, Calif). The chips were washed, stained with streptavidin-phycoerythrin, and scanned (HP GeneArray Scanner; Hewlett-Packard Company, Palo Alto, Calif). On each chip, the human housekeeping genes β -actin and glyceraldehyde-3-phosphate

dehydrogenase (GAPDH) served as controls. Suite 5.0 software normalized the expression level values using these controls.

RT-PCR analysis

The TaqMan RT-PCR reaction was performed with EZ-PCR Core Reagents (Life Technologies), according to the manufacturer's directions. The primers and probes for K16 (assay ID Hs00955088_g1), IL-31 (assay ID Hs01098710_m1), IL-32 (assay ID Hs01098710_m1), IL-33 (assay ID Hs00369211_m1), IL-17A (assay ID Hs00174383_m1), IL-9 (assay ID Hs00914237_m1) IL23(p19) (assay ID Hs00372324_m1), IL23(p40) (assay ID Hs0001011518_m1), IL22 (assay ID Hs01574154_m1), IL-4 (assay ID Hs00174122_m1), IL13 (assay ID assay ID Hs99999038_m1), IL-10 (assay ID Hs00961622_m1), IL-5 (assay ID Hs00174200_m1), CCL5 (assay ID Hs00174575_m1), CCL26 (assay ID Hs00171146_m1), CCL17 (assay ID Hs00171074_m1), CCL18 (assay ID Hs00268113_m1), CCL22 (assay ID Hs01574247_m1), CCL2 (assay ID Hs00234140_m1), CCL13 (assay ID Hs00234646_m1), CCL11 (assay ID Hs99999025_m1), IFN γ (assay ID Hs00989291_m1), IFN α 1 (assay ID Hs00256882_m1), MX1 (assay ID Hs00895608_m1), IL-8 (assay ID Hs00174103_m1), IL-1 β (assay ID Hs01555413_m1), Foxp3 (assay ID Hs00203958_m1), CXCL9 (assay ID Hs00171065_m1), CXCL10 (assay ID Hs00171042_m1), CXCL11 (assay ID Hs00171138_m1), CCL20 (assay ID Hs01011368_m1), OX40L (assay ID Hs00182411_m1), TRAIL (assay ID Hs00234356_m1), TSLPR (assay ID Hs00845692_m1), PI3/Elafin (assay ID Hs00160066_m1), LCN2 (assay ID

Hs00856927_m1), FLG (assay ID Hs00856927_g1), LOR (assay ID Hs01894962_s1), CDSN (assay ID Hs00169911_m1), S100A7 (assay ID Hs00161488_m1), S100A8 (assay ID Hs00374263_m1), S100A9 (assay ID Hs00171086_m1), and S100A12 (assay ID Hs00942835_m1) were designed by Life Technologies.

The human acidic ribosomal protein (hARP) gene, a housekeeping gene, was used to normalize each sample and each gene. The primer sequences used were generated with the Primer Express algorithm (Applied Biosystems, Foster City, Calif), version 1.0, by using published genetic sequences (National Center for Biotechnology Information–PubMed), as follows: hARP forward CGCTGCTGAACATGCTCAA, hARP reverse TGTCGAACACCTGCTGGATG, and hARP probe 6-FAM-TCCCCCTTCTCCTTTGGGCTGG-TAMRA (Gene Bank accession no. NM-001002).

The data were analyzed and quantified by using the software provided with the Applied Biosystems PRISM 7700 (Sequence Detection Systems, version 1.7).

Statistical methods

All statistical analysis was carried out with open source R language (www.R-project.org) and packages from Bioconductor (www.bioconductor.org). Analysis of RT-PCR data ($\log_2$ scale of the normalized values) was carried out by a linear mixed-effects model and IHC cell counts through the paired Wilcoxon Rank Sum Tests. Spearman rank correlations were determined for all variables evaluated by means of IHC and RT-PCR with SCORAD index scores.

Quality control, preprocessing, normalization and filtering

Affymetrix CEL files for the HGU133Plus2.0 chips were scrutinized for spatial artifacts using the Harshlight package.^{E9} Classic microarray quality control was obtained by the Bioconductor's array Quality Metrics package.

In this study, we included 22 AD samples prepared using NuGen single amplification kit, 2 AD (series accession no. GSM815426-GSM815427) and 9 normals from previous publications,^{E1,E10,E11} (series accession no. GSM902824-GSM902832) prepared using Affymetrix single amplification kit and 6 normals prepared using Affymetrix double amplification kit (series accession no. GSM902833-GSM902838). Since different amplification strategies were used, in order to eliminate a possible bias, we included additional AD samples from a previous publication that were prepared using Affymetrix single amplification methods to have a total of 38 NuGen samples and 34 Affymetrix samples. The kit bias and amplification bias were estimated and removed using COMBAT program^{E12} by comparing the AD NuGen single amplified samples to the AD Affymetrix single amplified samples and by comparing the normal Affymetrix single amplified samples to the normal double amplified samples. Data were then limited to that of the 10 AD study patients, as well as the 15 added normals. Expression values were obtained with the frozen robust multi-array analysis (fRMA) algorithm.^{E13}

To confirm the normalization, we compared the chronic versus non-lesional differences with those obtained in a prior publication.^{E11} No significant differences were found between the fold changes estimated by both analyses, with a correlation of 0.75 ($p < 10^{-16}$).

Probe sets with more than 5 samples with expressions of greater than 3 and

standard deviations of larger than 0.2 were kept for further analysis; analysis included 37,845 probe-sets representing 16,184 unique genes with a known ENTREZ identifier.

Model and hypothesis testing

Expression values in $\log_2$ scale were modeled by a linear mixed-effects model, with Group as the fixed effect and a random intercept for each patient, in the framework of Bioconductors' limma package. The comparisons of interest (acute vs non-lesional skin, chronic vs acute skin, chronic vs non-lesional skin, and non-lesional vs normal skin) were tested using the moderated t test,^{E14} and resultant p values were adjusted for multiples hypothesis by the Benjamini-Hochberg procedure. Since typical FDR cutoffs proved to be very stringent for the small sample size, we considered genes to be differentially expressed if the unadjusted p-value was less than 0.01 and the FCH was greater than 1.5.

The sample size largely limited our analyses. While planning the experiments, it was contemplated that acute and chronic AD might represent different disease phenotypes with distinct pathways, and therefore expected a larger effect size. However, this was not the case, and a larger sample size would be needed in order to detect differences that may or may not exist, after adjustment for multiple hypotheses. Thus we consider the gene array analysis as exploratory, describing general trends and serving as a basis for future studies. Using the data generated in these experiments and the estimations of gene variances through the mixed effect model, we can calculate the sample size that would be needed to detect 1.5 differences at $FDR < 0.05$ levels. Setting the proportion of non-DEGs to above 0.997 (as observed in our data), the required

sample size as calculated by function *ssize.oneSampVary* from R package *ssize.fdr* is 18-20 patients (Figure E4), which was not possible to obtain in this study, given the difficulty in obtaining intrapersonal non-lesional, acute and chronic lesions and the stringent criteria utilized to ensure that acute lesions are not actually acute on chronic lesions.

For the comparisons between each group and normals, we used a fixed effect model. For this analysis, adjustment for multiple hypotheses was considered using Benjamini and Hochberg approach and cut-offs were set as $FDR < 0.05$ and $FCH > 2$.

Derivation of heat maps

Genes with similar patterns of expression were grouped together as hierarchical clusters and presented as color-coded heat maps. McQuitty linkage was used as an agglomeration method with Pearson correlation distance.

Heatmaps of representative genes associated with particular Th pathways as well as cytokine-regulated genes in keratinocytes are provided. These genes were selected based on past studies with cytokine-treated keratinocytes,^{E15} as well as an extensive review of the literature, which defined the major Th pathway/cytokine genes.^{E16-E23} However, these heat maps show only representative genes and are not inclusive of all genes that are regulated by the associated Th pathway/cytokines. Furthermore, some genes are regulated by more than one Th pathway/cytokine.

Multiple regression analysis

We conducted multiple regression analyses for acute vs non-lesional and chronic vs non-lesional and SCORAD. Variables showing a correlation with the SCORAD of above 0.5 were included in the analysis. The best model was chosen in an exhaustive search as the model with higher adjusted R^2 , which in both cases also show the smaller Bayesian information criterion (BIC). This analysis was conducted with the R package *leaps*. Due to the small sample size, these results should be cautiously interpreted.

Analysis of IL-17-regulated genes across psoriasis and AD transcriptomes

We compared the changes in IL-17 induced genes as previously described^{E15} in the psoriasis transcriptome^{E3} with the acute and chronic AD transcriptomes, as defined here. Patterns of dysregulation of IL-17-regulated genes across each transcriptome are illustrated in scatterplots and magnitudes of the FCHs are summarized in Figure 5.

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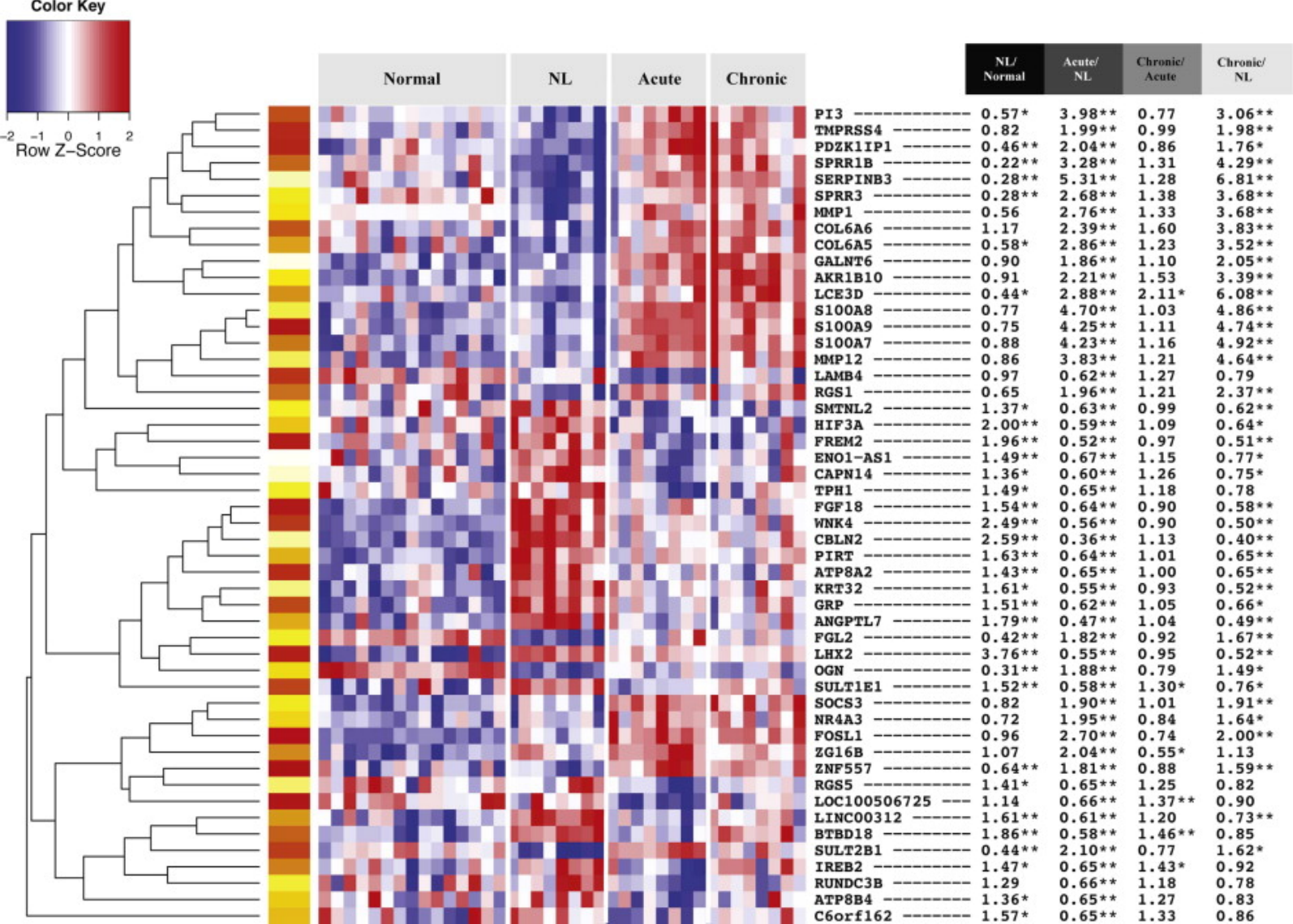
Figure E1. The 50 differentially expressed genes (DEGs) between acute and non-lesional atopic dermatitis (AD) include a large representation of terminal differentiation genes. Number of DEGs between acute, compared to non-lesional and chronic lesions, determined using the criteria of fold change (FCH)>1.5 and p-value<0.1. (red, upregulated; blue, downregulated) *P < .05,

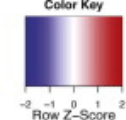
P < .01, and *P < .001, (n=8). NL, non-lesional.

Figure E2. Progressive activation of representative inflammatory mediators associated with Th1, Th2, Th17 and Th22 T-cell subsets from non-lesional (NL), through acute and chronic atopic dermatitis (AD) skin lesions, by genomic expression. A-D, Representative heatmaps of A, Th2 and IL-4/IL-13, B, Th22/IL-22, C, Th1 and IFN- γ , and D, Th17/IL-17 induced genes, respectively. (red, up-regulated; blue, down-regulated). *P < .05, **P < .01, and *P < .001, (n=8 for AD; n=15 for normals).**

Figure E3. Cell counts of eosinophils, neutrophils and mast cells in non-lesional (NL), acute and chronic AD skin lesions. Cell counts of eosinophils (major basic protein+ cells) and neutrophils (neutrophil elastase+ cells) increased from non-lesional through chronic disease (P<0.04, and P<0.02, respectively). *P < .05, **P < .01, and ***P < .001, (n=10). Bar plots represent mean $\pm$ SEM.

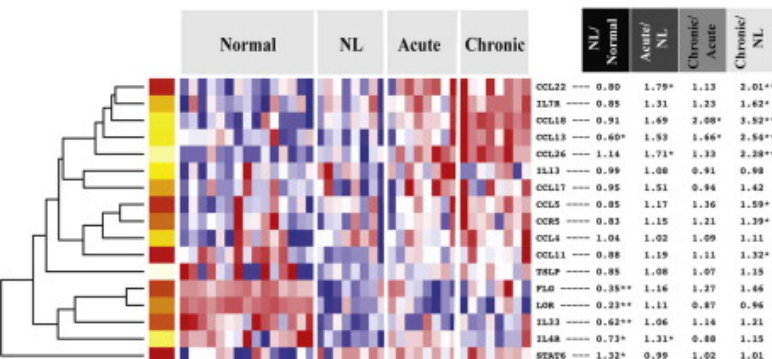
Figure E4. Average power vs. sample size needed to detect differences of 1.5 fold change at 0.05 FDR significance level.





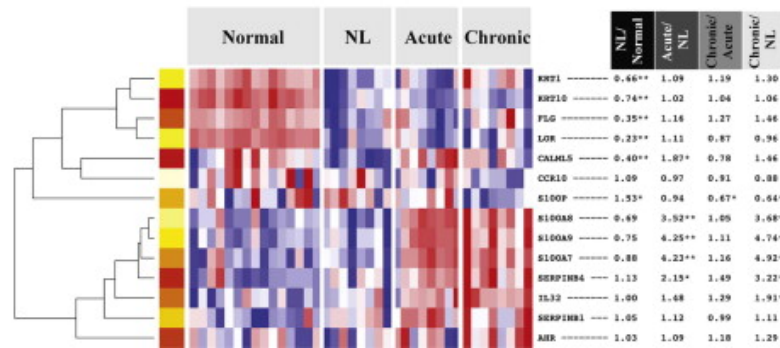
A

Th2 and IL-4/IL-13 induced genes



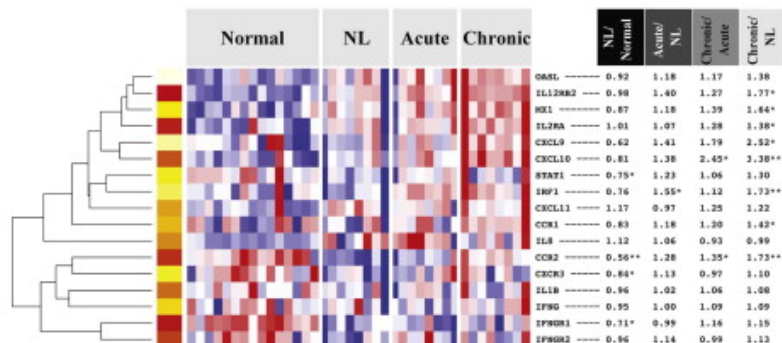
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Th22/IL-22 induced genes



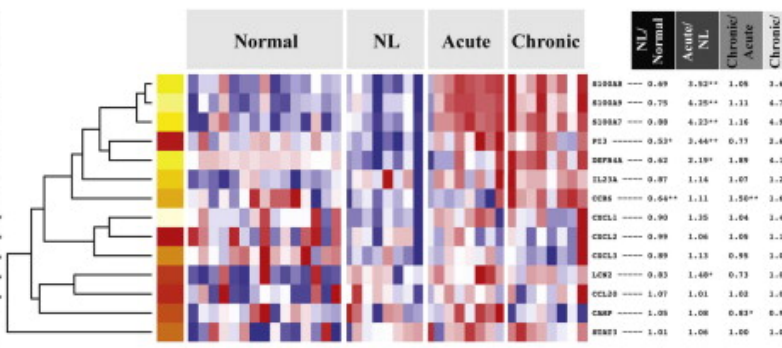
C

Th1 and IFN-γ induced genes

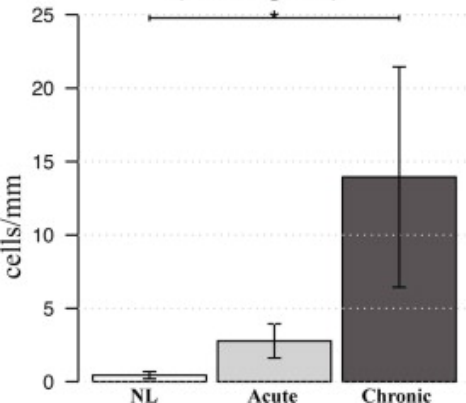


D

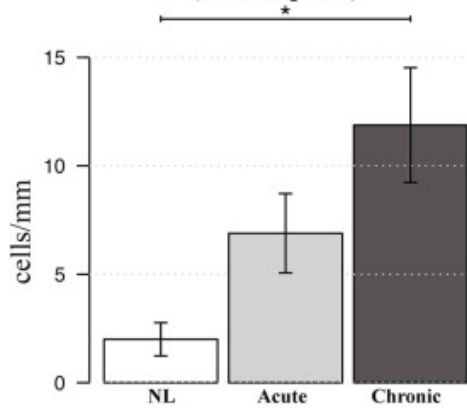
Th17/IL-17 induced genes



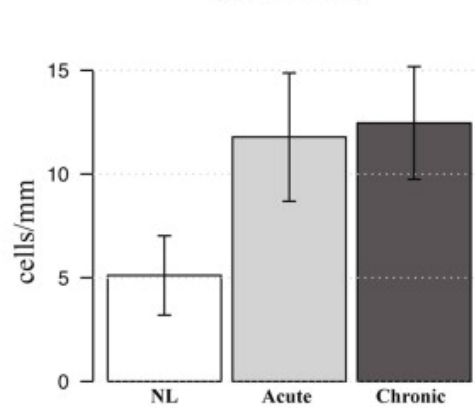
**Major Basic Protein
(Eosinophils)**



**Neutrophil Elastase
(Neutrophils)**



**Tryptase
(Mast Cells)**



Average power vs sample size with $\text{fdr}=0.05$,
 $\Delta_g \sim N(0.585, 0)$ and $\sigma_g^2 \sim \text{IG}(2.9865, 0.3263)$

