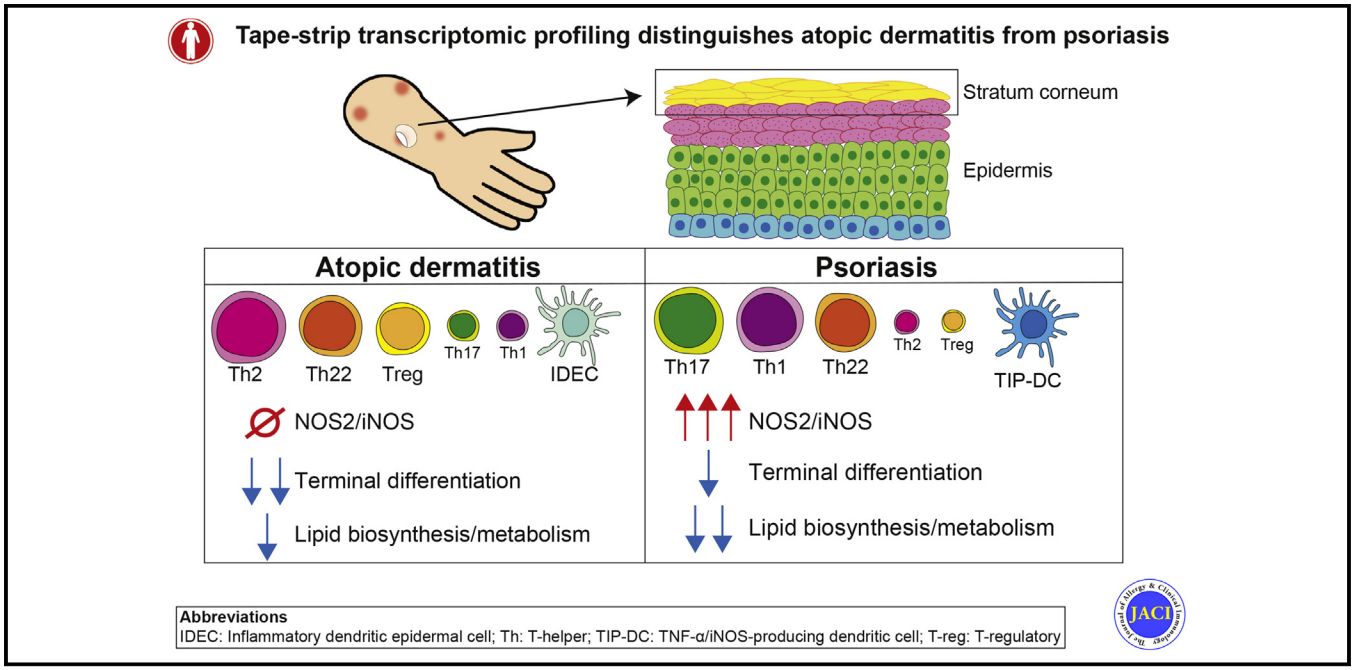
Tape strips detect distinct immune and barrier profiles in atopic dermatitis and psoriasis

Helen He, MD,[a,b]* Robert Bissonnette, MD,[c]* Jianni Wu, BS,[a,b,d]* Aisleen Diaz, MD,[a,e] Etienne Saint-Cyr Proulx, MD,[c] Catherine Maari, MD,[c] Carolyn Jack, MD, PhD,[c] Maudeline Louis, BS,[c] Yeriel Estrada, BS,[a] James G. Krueger, MD, PhD,[b] Ning Zhang, MD, PhD,[a] Ana B. Pavel, PhD,[a] and Emma Guttman-Yassky, MD, PhD[a,b] *New York, NY; Montreal, Quebec, Canada; and Ponce, Puerto Rico*

GRAPHICAL ABSTRACT



Background: Our current understanding of atopic dermatitis (AD) and psoriasis pathophysiology is largely derived from skin biopsy studies that cause scarring and may be impractical in large-scale clinical trials. Although tape strips show promise as a minimally invasive technique in these common diseases, a comprehensive molecular profiling characterizing and differentiating the 2 diseases in tape strips is unavailable. Objective: Our aim was to construct a global transcriptome of tape strips from lesional and nonlesional skin of adults with moderate-to-severe AD and psoriasis.

From [a]the Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York; [b]Laboratory of Investigative Dermatology, The Rockefeller University, New York; [c]Innovaderm Research, Montreal; [d]State University of New York Downstate Medical Center, College of Medicine, New York; and [e]Ponce Health Sciences University School of Medicine.

*These authors contributed equally to this work.

Disclosure of potential conflict of interest: J. G. Krueger is an employee of the Rockefeller University and has received research support (grants paid to his institution) and/or personal fees from Pfizer, Amgen, Janssen, Lilly, Merck, Novartis, Kadmon, Dermira, Boehringer, Innovaderm, Kyowa, BMS, Serono, BiogenIdec, Delenex, AbbVie, Sanofi, Baxter, Paraxel, Xenoport, and Kineta. E. Guttman-Yassky is an employee of Mount Sinai and has received research funds (grants paid to her institution) from AbbVie, Celgene, Eli Lilly, Janssen, Medimmune/AstraZeneca, Novartis, Pfizer, Regeneron, Vitae, Glenmark, Galderma, Asana, Innovaderm, Dermira, and UCB. E. Guttman-Yassky is also a consultant for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, Leo Pharma, AbbVie, Eli Lilly, Kyowa, Mitsubishi Tanabe, Asana Biosciences, and Promius. R. Bissonnette is an advisory board member, consultant, speaker, and/or investigator for and/or receives honoraria or grant from AbbVie, AntibioTx, Aquinox Pharma, Arcutis, Arena Pharma, Asana BioSciences, Bellus Health, Boehringer-Ingelheim, Brickell Biotech, Dermavant, Celgene, Dignity Sciences, Eli Lilly, EMD Serono, Galderma, Glenmark, GSK-Stiefel, Incyte, Kiniksa, Leo Pharma, Neokera, Novan, Pfizer, Ralexar, Regeneron Pharmaceuticals, Sanofi Genzyme, Sienna, and Vitae. R. Bissonnette is also an employee and shareholder of Innovaderm Research. E. Saint-Cyr Proulx is an advisory board member, consultant, speaker, and/or investigator for and/or receives honoraria or grant from AbbVie, AntibioTx, Arcutis, Asana BioSciences, Bellus Health, Boehringer-Ingelheim, Brickell Biotech, Dermavant, Celgene, Eli Lilly, Galderma, Glenmark, GSK-Stiefel, Incyte, Kiniksa, Leo Pharma, Neokera, Pfizer, Ralexar, Regeneron Pharmaceuticals, Sanofi Genzyme, Sienna, UCB, and Vitae. Y. Estrada, N. Zhang, and A. B. Pavel are employees of Mount Sinai. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 11, 2020; revised April 21, 2020; accepted for publication May 19, 2020.

Corresponding author: Emma Guttman-Yassky, MD, PhD, Department of Dermatology and the Laboratory of Inflammatory Skin Diseases, Icahn School of Medicine at Mount Sinai Medical Center, 5 E 98th Street, New York, NY 10029. E-mail: emma.guttman@mountsinai.org.

0091-6749/$36.00

© 2020 American Academy of Allergy, Asthma & Immunology

https://doi.org/10.1016/j.jaci.2020.05.048

Methods: A total of 20 tape strips were obtained from lesional and nonlesional skin of patients with AD and psoriasis and skin from controls (n = 20 each); the strips were subjected to RNA sequencing (RNA-seq), with quantitative RT-PCR validation of immune and barrier biomarkers.

Results: We detected RNA-seq profiles in 96 of 100 of samples (96%), with 4123 and 5390 genes differentially expressed in AD and psoriasis lesions versus in controls, respectively (fold change ≥ 2; false discovery rate [FDR] < 0.05). Nonlesional tape-stripped skin from patients with AD was more similar to lesional skin than to nonlesional skin of patients with psoriasis, which showed larger differentiation from lesions. AD and psoriasis tissues shared increases in levels of dendritic cell and T-cell markers (CD3, ITGAX/CD11c, and CD83), but AD tissues showed preferential T_H2 skewing (IL-13, CCL17/TARC, and CCL18), whereas psoriasis was characterized by higher levels of expression of T_H17-related (IL-17A/F and IL-36A/IL-36G), T_H1-related (IFN-γ and CXCL9/CXCL10), and innate immunity–related (nitric oxide synthase 2/inducible nitric oxide synthase and IL-17C) products (FDR < 0.05). Terminal differentiation (FLG2 and LCE5A), tight junction (CLDN8), and lipid biosynthesis and metabolism (FA2H and ALOXE3) products were significantly downregulated in both AD and psoriasis (FDR < 0.05). Nitric oxide synthase 2/inducible nitric oxide synthase expression (determined by quantitative PCR) differentiated AD and psoriasis with 100% accuracy.

Conclusion: RNA-seq tape strip profiling detected distinct immune and barrier signatures in lesional and nonlesional AD and psoriasis skin, suggesting their utility as a minimally invasive alternative to biopsies for detecting disease biomarkers. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

Key words: *Atopic dermatitis, psoriasis, tape strips, biomarker, skin, RNA sequencing, T_H1, T_H2, T_H17, immune, epidermal barrier*

Abbreviations used

AD:	Atopic dermatitis
AUC:	Area under the curve
CCL:	C-C motif chemokine ligand
CXCL:	C-X-C motif chemokine ligand
DC:	Dendritic cell
DEG:	Differentially expressed gene
FCH:	Fold change
FDR:	False discovery rate
IGA:	Investigator's Global Assessment
iNOS:	Inducible nitric oxide synthase
LCE:	Late cornified envelope
NOS:	Nitric oxide synthase
PGA:	Physician's Global Assessment
qRT-PCR:	Quantitative real-time polymerase chain reaction
RNA-seq:	RNA sequencing
TLSS:	Target Lesion Symptom Score
TSS:	Total Sign Score

Atopic dermatitis (AD) and psoriasis are chronic inflammatory skin disorders, affecting 7% to 10% and ~3% of adults in the United States, respectively.[1] Molecular studies of skin biopsy samples that utilized high-throughput analyses revealed immune and barrier abnormalities of both diseases, showing that AD is driven by T_H2/T_H22 inflammation with varying degrees of T_H1/T_H17 skewing,[2-5] whereas psoriasis is primarily T_H17/IL-23–polarized.[6-10] Although both diseases share some barrier abnormalities such as epidermal hyperplasia and impaired terminal differentiation, there are notable differences, including prominent parakeratosis only in psoriasis.[11,12] However, biopsies cause scarring and pain and carry a risk of infection, limiting their utility in large clinical trials and longitudinal studies, especially in children. Thus, a less invasive means to accurately detect disease profiles in skin is needed. Tape stripping is a minimally invasive, nonscarring approach utilizing serial adhesive films to capture the stratum corneum and the upper part of the granular layer.[13,14] Previously used to differentiate pigmented lesions from melanoma,[15] tape stripping has recently been used in relation to inflammatory skin diseases.[5,13,14,16-38]

We recently used quantitative real-time PCR (qRT-PCR) to study AD-related biomarkers in tape strips from toddlers (age <5 years) with moderate-to-severe AD,[38] with a high level of sample analysis (99% [70 of 71]) and gene detection (97 [77 of 79]), capturing an AD gene signature similar to that in prior biopsy studies in this age group.[39,40] We detected alterations in levels of expression of key T_H2 (IL-4, IL-13, C-C motif chemokine ligand 13 [CCL13], and CCL26), T_H17/T_H22 (IL-19 and S100As), and barrier (FLG and LOR) products, many of which were undetectable in other tape strip studies.[19,20,23,25-27,29,33,35,36,38] Earlier tape strip analyses evaluated a more limited panel of proteins in adult[23,25-27,29,33,35,36] or pediatric AD,[19,20] reporting protein detection rates of 46% to 70%.[19,20,23] Broader proteomic approaches, including with use of mass spectrometry, focused primarily on barrier products.[5,30,32,34,37] The tape strip studies in psoriasis include a few qRT-PCR[28,41] and proteomic studies[18,21,24,27] assessing limited numbers of analytes. Mass spectrometry studies in psoriasis have captured up to 543 markers but did not fully characterize its cutaneous profile.[22,31]

A few global RNA sequencing (RNA-seq) profiling studies using tape strips in AD have been reported.[14,16,17] Two tape strip RNA-seq analyses in patients with mild-to-severe AD focused on immune dysregulation in nonlesional skin.[14,16] Dyjack et al. identified 29 differentially expressed genes (DEGs) in nonlesional skin of adults with AD,[14] whereas Leung et al assessed children with AD (ages 4-17 years) with and without food allergies, associating food allergies with enrichment of T_H2 and dendritic cell (DC) pathways.[16] A third study, based on the same cohort as in the study reported by Dyjack et al,[14] described lipid alterations but did not evaluate other barrier measures.[17] In these studies, the detection rates in healthy skin, nonlesional skin of patients with AD, and lesional skin of patients with AD were 18% to 52%, 26% to 60%, and 57% to 89%, respectively.[14,16,17] A comprehensive tape strip molecular profile that accurately captures the global gene signatures of lesional and nonlesional skin in AD and psoriasis and differentiates them is lacking.

Here, we present the first global RNA-seq molecular profiling of tape strips from both lesional and nonlesional skin of adults with moderate-to-severe AD and psoriasis compared with the profile of the skin of healthy controls (n = 20 each), with additional validation of key immune and barrier biomarkers by qRT-PCR. We were able to quantify mRNA in 100% of samples by qRT-PCR (and 100% of evaluated genes) and in 96 of 100 of samples by RNA-seq (96%), capturing characteristic and distinct cutaneous gene signatures for AD and psoriasis.

TABLE I. Clinical demographics

Characteristic	Patients with AD (n = 20)	Patients with psoriasis (n = 20)	Controls (n = 20)
Age (y), mean ± SD	31.0 ± 13.8	42.6 ± 15.4	40.3 ± 15.7
Sex, no. (%)			
Female	15	8	11
Male	5	12	9
Race, no. (%)			
White	18	19	20
African American	2	0	0
Asian	0	1	0
Clinical severity			
TSS, mean ± SD (range)	7.6 ± 2.5 (4-15)	—	—
IGA, mean ± SD	2.6 ± 0.6	—	—
No. of patients with IGA score			
IGA 2 (mild)	8	—	—
IGA 3 (moderate)	11	—	—
IGA 4 (severe)	1	—	—
TLSS, mean ± SD (range)	—	8.9 ± 1.8 (5-12)	—
PGA, mean ± SD	—	3.1 ± 0.6	—
No. of patients with PGA score			
PGA 2 (mild)	—	3	—
PGA 3 (moderate)	—	12	—
PGA 4 (severe)	—	5	—

METHODS

Study population and characteristics

We enrolled 20 adults with moderate-to-severe AD (15 females and 5 males with a mean age of 31 years) and psoriasis (8 females and 12 males with a mean age of 42.6 years) and 20 healthy volunteers (11 females and 9 males with a mean age of 40.3 years) under institutional review board–approved protocols. Clinical severity scores, including a 5-grade AD Investigator's Global Assessment (IGA) score (mean score 2.6), Total Sign Score (TSS) (mean score 7.6), Physician's Global Assessment (PGA) score (mean score 3.1), and Target Lesion Severity Score (TLSS) (mean score 8.9), were measured for AD and psoriasis, respectively, before tape stripping (Table I).[42,43] The exclusion criteria included immunodeficiency; use of biologics within the previous 12 weeks; use of systemic steroids, use of immunosuppressants or phototherapy within the previous 4 weeks; and use of topical medication within the previous 2 weeks.

Tape strip collection, RNA extraction, qRT-PCR, and RNA-seq

A total of 20 consecutive large D-Squame tape strips (CuDerm, Dallas, Tex) were collected from representative lesions and nonlesional skin (in close proximity to but >10 cm away from lesions) in the extremities of all patients with AD and psoriasis, as well as from the skin of controls.[14,29,38] After cleansing with an alcohol pad, the tape strips were placed on the skin and pressure was applied with the fingers for approximately 5 seconds. The tapes were removed, placed on a D-Squame cardboard, and immediately frozen on dry ice. The pieces of cardboard were subsequently kept in a freezer at –80°C. All 20 tapes for lesional or nonlesional skin were placed on exactly the same skin area.

RNA was extracted by using an miRNAeasy Mini Kit (Qiagen, Hilden, Germany). The mean RNA yield across tape strip samples was 39.7 ± 56.6 ng. For qRT-PCR, 500 pg of RNA per sample was subjected to reverse transcription, preamplification, and qRT-PCR, as previously described.[2] The primers are listed in Table E1 (in this article's Online Repository at jacionline.org). RNA AmpliSeq libraries were constructed with the Ion AmpliSeq Transcriptome Human Gene Expression Kit by using 5 ng of RNA per sample and an amplification approach that screens more than 20,000 genes per reaction. RNA-seq libraries were pooled and sequenced on the Ion S5 XL system sequencer with Ion 550 Chips (Thermo Fisher, Waltham, Mass).

Statistical analysis

Statistical analyses were performed by using the statistical language R (www.R-project.org). Sample quality was assessed by using FastQC. Samples were aligned to the human reference genome by using STAR (open source aligner).[44] Mapped sequencing reads were assigned to genomic features by using the featureCounts function. Counts were transformed to log scale by voom transform[45] and fit in a linear model. Fold changes (FCHs) were estimated, and hypothesis testing was conducted by using contrasts under the general framework for linear models in the *limma* package. *P* values were adjusted for multiple hypotheses by using the Bejamini-Hochberg procedure, controlling for false discovery rate (FDR). Genes with an FCH of 2 or more and an FDR less than 0.05 were considered to be DEGs. qRT-PCR values were normalized to the housekeeping gene *Rplp0*. Values below the limit of detection were imputed as 20% of the minimal expression value. Because our primarily European American cohort included 2 African American patients with AD and 1 Asian patient with psoriasis, we performed a sensitivity analysis with only white patients, which did not alter the significance of our findings. Spearman correlation coefficients and 1-way ANOVA were used to evaluate correlations between biomarkers and TSS/TLSS and IGA/PGA score, respectively. To evaluate the performance of a molecular classifier that discriminates between AD and psoriasis, we used the area under the curve (AUC) of the receiver operating characteristic.

RESULTS

Tape strips were obtained from lesional and nonlesional skin of patients with AD, lesional and nonlesional skin of patients with psoriasis, and skin from healthy volunteers (n = 20 each) and profiled by using an RNA-seq approach that screens more than 20,000 transcripts,[46] followed by qRT-PCR analysis of disease-related immune and barrier biomarkers. For RNA-seq, the sample recovery rates were as follows: 20 of 20 (100%) and 19 of 20 (95%) for samples from patients with lesional and nonlesional psoriasis, respectively; 19 of 20 (95%) and 19 of 20 (95%) for samples from patients with lesional and nonlesional AD, respectively; and 19 of 20 (95%) for controls, with an overall 96% sample recovery rate (96 of 100 samples). mRNA was acquired from all 100 samples (100%) by qRT-PCR.

Tape-stripped skin showed T_H2 skewing in AD and T_H17 in psoriasis

We used an FCH of 2 or more and an FDR less than 0.05 to define DEGs. For AD versus control comparisons, we identified 4123 DEGs (2563 up and 1560 down) in lesional skin and 1498 DEGs (1176 up and 322 down) in nonlesional skin. For psoriasis versus control comparisons, 5390 genes (1578 up and 3812 down) were differentially expressed in lesional skin, whereas 1135 genes (915 up and 220 down) were differentially expressed in nonlesional skin (see Table E2 in this article's Online Repository at www.jacionline.org). When comparing lesional skin with normal skin, we detected 1752 DEGs unique to AD (1270 up and 482 down), 3019 unique to psoriasis (285 up and 2734 down), and 2371 shared by both diseases (1293 up and 1078 down) (Fig 1, *A*). For nonlesional versus healthy tissues, 1007 DEGs were unique to AD (727 up and 280 down), 644 were unique to psoriasis (466 up, and 178 down), and 491 were shared (449 up and 42 down) (Fig 1, *B*). We identified 4549 DEGs in lesional versus nonlesional skin of patients with psoriasis (371 up and 4178 down) (see Table E2). In contrast, most differences between lesional versus nonlesional skin from patients with AD were not significant enough to pass the FDR threshold (see Table E2).

A heatmap depicting a set of immune-related genes, which were also used in prior studies,[2,3,47,48] is shown in Fig 2. Although the lesional tape strips of both diseases displayed high levels of immune activation, an overall greater inflammatory tone characterized nonlesional AD skin than characterized skin from patients with psoriasis. Several genes were commonly upregulated in AD and psoriasis tissues versus in the controls, including markers of epidermal hyperplasia (SERPINB3/SERPINB4), general inflammation (MMP12), DCs/macrophages (FCER1G, ITGAX/CD11c, CD83, CD86, LAMP3/DC-LAMP, and CSF2), T-cell proliferation and migration (CD4, CD69, CD80, and CCR7), and JAK/STAT signaling (JAK3 and STAT4) (Fig 2 and see Table E2). Levels of ITGAM/CD11b, which is expressed on various leukocytes, including DCs, macrophages, eosinophils, and neutrophils, as well as FCER1A, the high-affinity IgE component expressed on mast cells and inflammatory dendritic epidermal cells, were increased in both diseases, but they showed preferential elevation in AD. Levels of ICOS (a marker of T-cell activation) and CD1A (which is expressed by DCs and Langerhans cells) were significantly increased only in AD and not in psoriasis. Negative regulators (IL-34, IL-37, and IL-1F10) were commonly downregulated in lesions of both diseases, similar to in biopsy studies (all FDRs < 0.05).[2,3,7,49,50]

Although AD and psoriasis shared increases in markers defining cellular infiltrates, distinct immune signatures separated the diseases. Psoriasis lesional and/or nonlesional tape strips were most notable for prominent T_H17 skewing, with significant increases in many T_H17 products (IL-17A/F, IL-36A/G, CCL20, VNN3, DEFB4A/B, and LCN2/lipocalin-2) that were either unchanged or showed more modest changes in AD (Fig 2 and see Table E2). IL-19, which is induced by both IL-17 and IL-4/IL-13,[51] was the only IL-17–induced cytokine with higher expression in AD than in psoriasis. Psoriasis tissues also demonstrated preferential significant upregulation of T_H1 (IFN-γ, C-X-C motif chemokine ligand 9 [CXCL9]/CXCL10/CXCL11, CCL2/CCL3/CCL4, and STAT1) and innate immunity (nitric oxide synthase 2 [NOS2]/inducible nitric oxide synthase [iNOS], IL-1B, and IL-17C) products compared with both control and AD tissues.

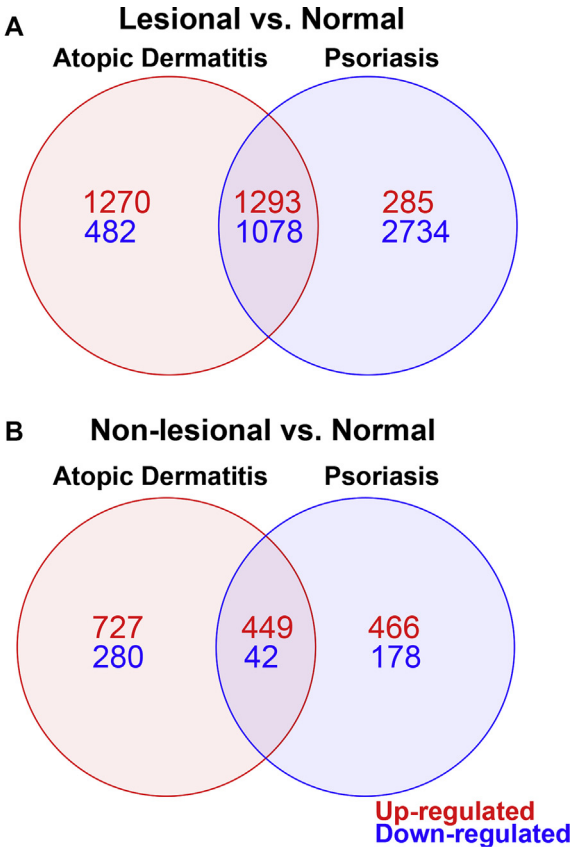
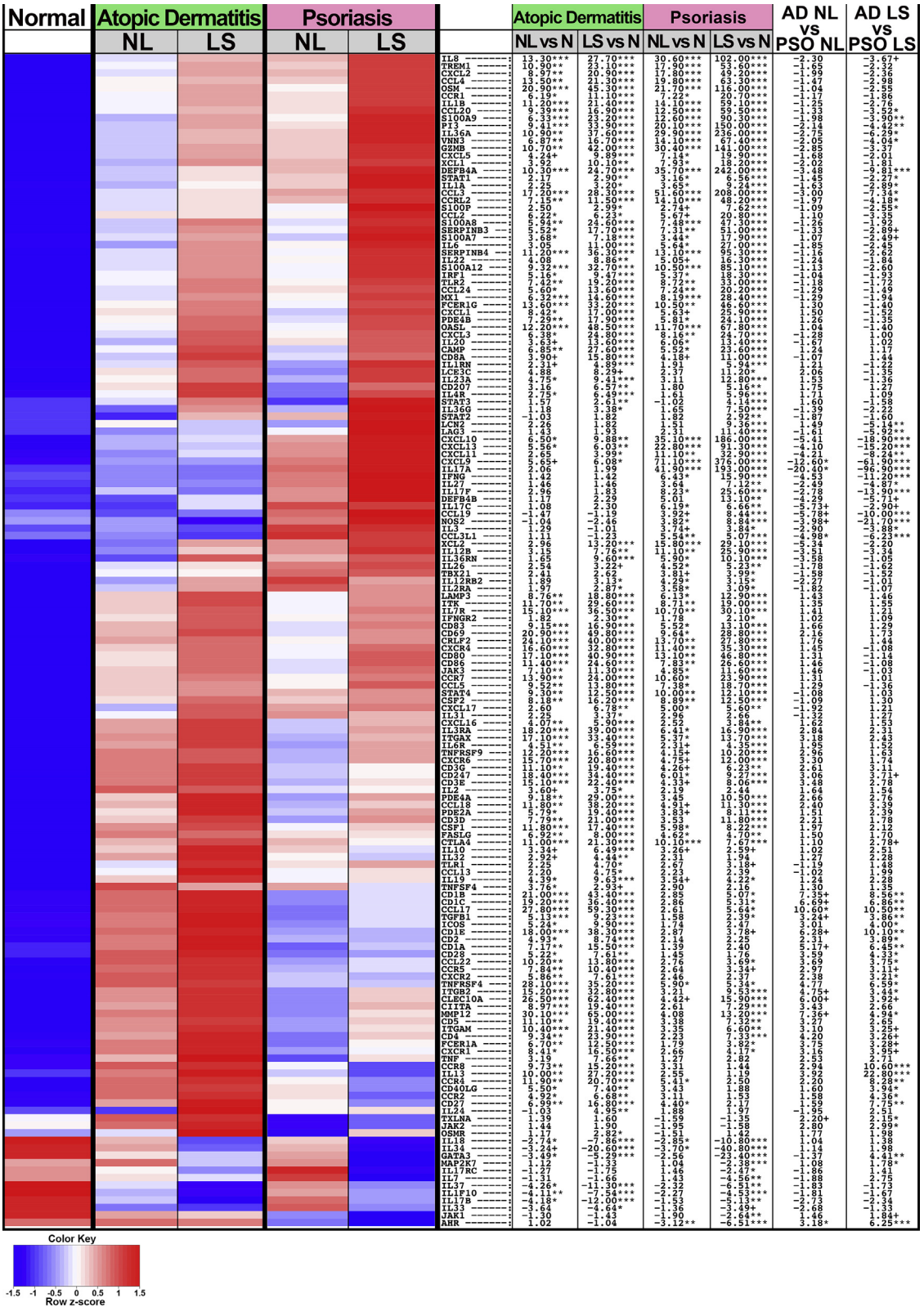


FIG 1. Venn diagram depicting DEGs using RNA-seq that are unique to either AD or psoriasis and DEGs common among both in lesional (LS) versus normal (N) tape-stripped skin. Red denotes upregulation; blue denotes downregulation.

In contrast, levels of expression of most T_H2-related products (IL-13, IL-10, IL-31, CCL13, CCL17/TARC, CCL22, CCL24/eotaxin-2, CCR4, and TNFRSF4/OX40) were significantly increased in patients with AD versus in controls and/or patients with psoriasis. Levels of most of these T_H2 products (eg, IL-13, CCL17/TARC, CCL24/eotaxin-2, and TNFRSF4/OX40) were significantly increased in both lesional and nonlesional AD, whereas the pruritus mediator IL-31 was uniquely upregulated in lesional AD. T_H22-related products (IL-22 and S100As) shared upregulation in both diseases (all FDRs < 0.05). When lesional versus nonlesional tape-stripped skin samples were compared, significant differences were not detected in AD, whereas in psoriasis, key biomarkers, including T_H17/T_H22-related products (IL36A, CCL20, VNN3, LCN2/lipocalin-2, and S100As) and T_H1-related products (CXCL9/CXCL10) were significantly increased in lesional skin (FDR < 0.05) (see Table E2).

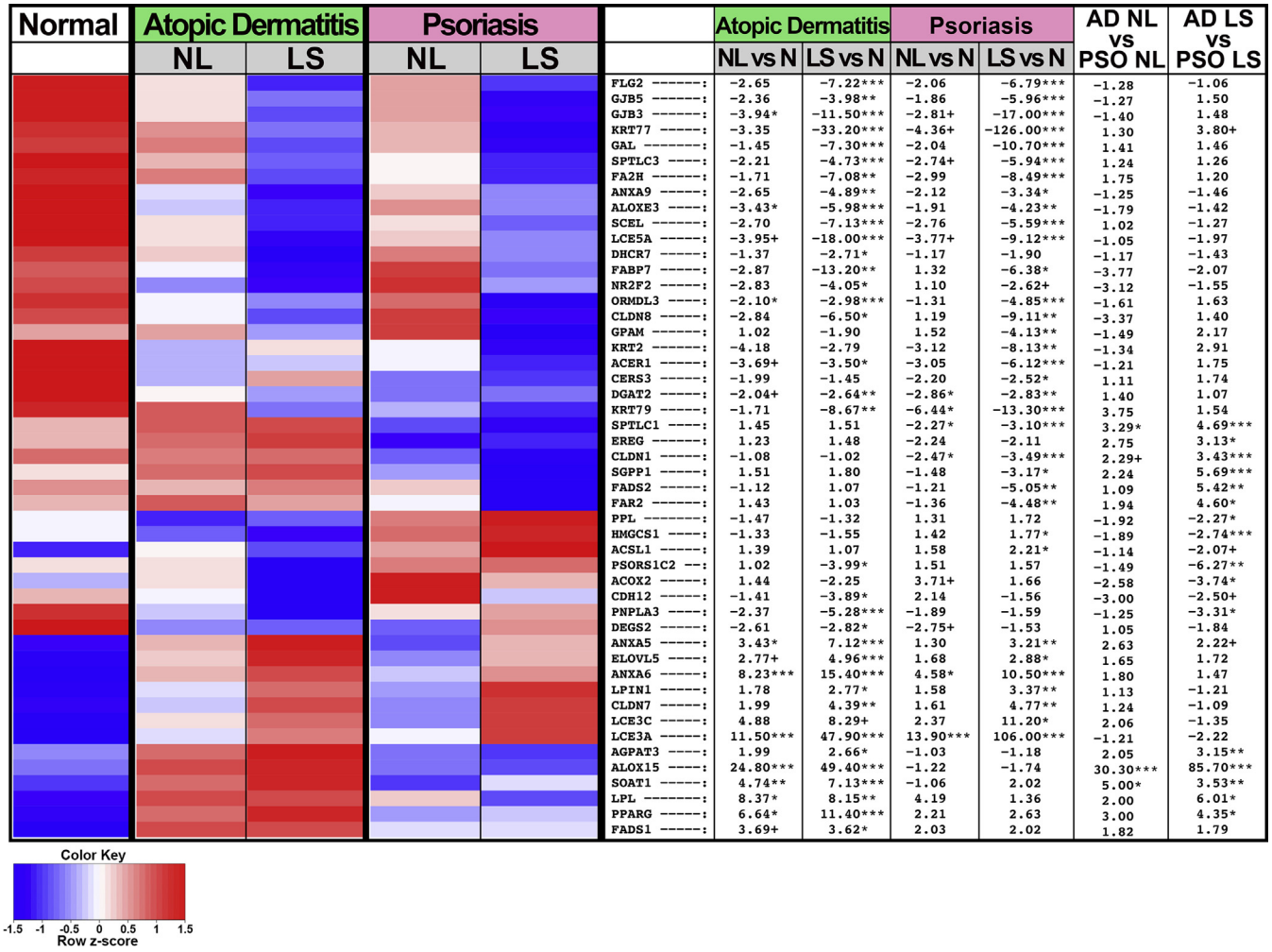
Distinct barrier alterations in AD and psoriasis

We also assessed a previously defined epidermal barrier gene subset (Fig 3).[2,38,48,52] Terminal differentiation (FLG2, ANXA9, LCE5A, and SCEL), gap/tight junction (GJB3/GJB5 and CLDN8), keratin (KRT77/KRT79), and lipid biosynthesis/metabolism (GAL, FABP7, FA2H, and ALOXE3) products were significantly downregulated in tape strips from both AD and psoriasis lesions versus in those from controls, whereas few



	Atopic Dermatitis		Psoriasis		AD NL vs PSO NL	AD LS vs PSO LS
	NL vs N	LS vs N	NL vs N	LS vs N		
IL8	13.30***	27.70***	30.60***	102.00***	-2.30	-3.67+
TREM1	10.90***	23.10***	17.90***	53.60***	-1.65	-2.32
CXCL2	8.97**	20.90***	17.80***	49.20***	-1.99	-2.36
CCL4	13.50**	21.30***	19.80***	63.30***	-1.47	-2.98
OSM	20.90**	45.30***	21.70***	116.00***	-1.04	-2.55
CCR1	6.19*	11.10***	7.22*	20.70***	-1.17	-1.86
IL1B	11.20***	21.40***	14.10***	59.10***	-1.25	-2.76
CCL20	9.39***	16.90***	12.50***	59.50***	-1.33	-1.52*
S100A9	6.33***	23.20***	12.60***	90.30***	-1.98	-3.90**
PI3	9.41***	33.90***	26.10***	150.00***	-2.14	-4.42**
IL36A	10.90**	37.60***	29.90***	236.00***	-2.75	-5.29**
VNN3	6.87**	16.70***	14.10***	67.40***	-2.05	-4.04*
GZMB	10.70**	42.00***	30.40***	141.00***	-2.85	-3.37
CXCL5	4.24+	9.89***	7.14*	19.90***	-1.68	-2.01
XCL1	3.92	10.10**	7.93*	18.20***	-2.02	-1.81
DEFB4A	10.30***	24.70***	35.70***	242.00***	-3.48	-9.81***
STAT1	2.17	2.90**	3.16*	6.56***	-1.45	-2.27*
IL1A	2.25	3.20*	3.65*	9.24***	-1.63	-2.89*
CCL3	17.30***	28.30***	51.60***	208.00***	-3.00	-7.34**
CCRL2	7.15**	11.50***	14.10***	48.20***	-1.97	-4.18*
S100P	2.50	2.99*	2.74+	7.62***	-1.09	-2.55*
CCL2	5.22*	6.23*	5.67+	20.80***	-1.10	-3.05
S100A8	5.94**	24.60***	7.48***	47.30***	-1.26	-1.92
SERPINB3	5.52*	17.70***	7.31**	51.00***	-1.33	-2.89+
S100A7	3.68*	7.18***	3.49+	17.90***	-1.07	-2.49+
IL6	3.05	11.00***	5.64*	27.00***	-1.85	-2.45
SERPINB4	11.20***	36.30***	13.10***	95.30***	-1.16	-2.62
IL22	8.08	8.86**	5.04+	16.30***	-1.24	-1.84
S100A12	9.32***	32.70***	10.50***	85.10***	-1.13	-2.60
IRF1	5.16*	9.47***	5.37*	18.30***	-1.04	-1.93
TLR2	7.42**	19.20***	8.72**	33.00***	-1.18	-1.72
CCL24	5.60*	13.60***	7.24**	20.20***	-1.29	-1.49
MX1	6.32***	14.60***	8.19***	28.40***	-1.29	-1.94
FCER1G	13.60***	33.20***	10.90**	96.60***	-1.90	-1.40
CXCL1	8.42*	17.00***	5.63+	25.90***	1.50	-1.52
PDE4B	7.29**	17.90***	5.81*	24.10***	1.26	-1.35
OASL	12.20***	48.50***	11.70***	67.80***	1.04	-1.40
CXCL3	6.38*	24.80***	8.16**	24.70***	-1.28	1.00
IL20	3.63+	13.60***	4.02+	13.40***	-1.67	1.02
CAMP	6.85**	27.60***	5.52*	23.60***	1.24	1.17
CD8A	3.90+	15.80***	4.18+	11.00***	-1.07	1.44
IL1RN	2.31+	4.89***	1.91	5.94***	1.21	-1.22
LCE3C	4.88	8.29+	2.37	11.20*	2.06	-1.35
IL23A	4.75*	9.41***	3.11	12.80***	1.53	-1.36
CD207	3.16	6.57**	1.80	5.16**	1.75	1.27
IL4R	2.75*	6.49***	1.61	5.96***	1.71	1.09
STAT3	1.57	2.61**	-1.02	4.14***	1.60	-1.58
IL36G	1.18	3.58*	1.65	7.50***	-1.59	-2.22
STAT2	-1.03	1.82	1.82	2.92**	-1.87	-1.60
LCN2	2.26	1.82	1.51	9.36***	-1.49	-8.14**
LAG3	1.43	1.93	1.51	11.40***	-1.61	-5.92**
CXCL10	6.50*	9.88**	35.10***	186.00***	-5.41	-18.90***
CXCL13	5.56*	6.03**	22.80***	91.30***	-4.10	-18.20***
CXCL11	2.65	3.99*	11.10***	32.90***	-4.21	-8.24**
CXCL9	5.65+	6.08*	71.10***	376.00***	-12.60*	-61.90***
IL17A	2.06	1.98	41.90***	193.00***	-20.40*	-96.90***
IFNG	1.42	1.42	6.43*	15.90***	-4.53	-11.20***
IL27	1.46	1.46	3.64	7.12**	-2.49	-4.87*
IL17F	2.96	1.83	8.23*	25.60***	-2.78	-13.90***
DEFB4B	1.17	2.29	5.01	13.10**	-4.29	-5.71+
IL17C	1.08	2.30	6.19*	6.66**	-5.73+	-2.90+
CCL19	-1.47	-1.19	3.92*	8.44***	-5.78+	-10.00***
NOS2	-1.04	-2.46	3.82*	8.84***	-3.98+	-21.70***
IL3	1.29	-1.01	3.74+	3.84*	-2.90	-3.88*
CCL3L1	1.11	-1.23	5.54**	5.07***	-4.98*	-6.33***
XCL2	2.96	13.20***	15.80***	29.10***	-5.34	-2.20
IL12B	3.15	7.76**	11.10**	25.90***	-3.51	-3.34
IL36RN	1.65	9.60***	5.90*	10.10***	-3.58	-1.05
IL26	2.54	3.22+	4.52*	5.23**	-1.78	-1.62
TBX21	2.41	2.62	3.81+	3.99*	-1.58	-1.52
IL12RB2	1.89	2.13*	4.29*	3.15*	-2.27	-1.91
IL2RA	1.97	2.87*	3.58*	3.09*	-1.82	-1.07
LAMP3	8.76**	18.80***	6.13*	12.90***	1.43	1.46
ITK	11.70**	29.60***	8.71**	19.00***	1.35	1.55
IL7R	15.10***	36.50***	10.70**	30.10***	1.41	1.21
IFNGR2	1.82	2.30**	1.78	2.10*	1.02	1.09
CD83	9.15***	16.90***	5.52*	13.10***	1.66	1.29
CD69	20.90***	49.80***	9.64*	28.80***	2.16	1.73
CRLF2	24.10***	40.00***	13.70**	37.80***	1.76	1.44
CXCR4	16.60***	32.80***	11.40**	35.30***	1.45	1.08
CD80	17.10***	40.90***	13.10**	46.80***	1.31	1.14
CD86	11.40***	24.60***	7.83**	26.60***	1.46	1.08
JAK3	7.10**	11.30***	4.95*	11.60***	1.43	1.03
CCR7	13.90**	24.00***	10.60*	23.90***	1.31	1.01
CCL5	9.52**	13.80***	7.36*	18.70***	1.29	1.03
STAT4	9.30**	12.50***	10.00**	12.10***	-1.08	1.03
CSF2	8.18**	16.20***	8.89**	12.50***	-1.09	1.30
CXCL17	2.60	6.78**	5.90*	5.60**	-2.27	1.21
IL31	2.25	3.37*	2.96	2.66	-1.32	1.27
CXCL16	4.07**	5.90***	2.52	3.84**	1.62	1.53
IL3RA	18.20***	39.00***	6.41*	16.90***	2.84	2.31
ITGAX	17.10***	33.40***	5.37*	13.70***	3.18	2.43
IL6R	4.51**	6.59***	2.31+	4.35***	1.95	1.52
TNFRSF9	12.20***	16.60***	4.15*	10.20***	2.96	1.63
CXCR6	15.70***	20.80***	4.75+	12.00***	3.30	1.74
CD3G	11.10**	19.40***	4.26+	6.23**	2.61	3.11
CD247	18.40***	34.40***	6.01*	9.27***	3.06	3.71+
CD3E	15.10***	22.40***	4.33+	8.06***	3.48	2.78
IL2	3.60+	3.75*	2.19	2.44	1.64	1.54
PDE4A	9.18**	29.00***	3.45	10.50***	2.66	2.76
CCL18	11.80**	38.20***	4.91+	11.30***	2.40	3.39
PDE2A	5.79*	19.40***	3.83+	8.11***	1.51	2.39
CD3D	7.79**	21.00***	3.53	11.80***	2.21	2.78
CSF1	11.80***	17.40***	5.98*	8.22***	1.97	2.12
FASLG	6.92**	8.00***	4.62+	4.70**	1.50	1.70
CTLA4	11.00***	21.30***	10.10***	7.67***	1.10	2.78+
IL10	3.34+	6.49***	3.26+	2.59+	1.02	2.51
IL32	2.92+	4.44**	2.17	1.91	1.27	2.28
TLR1	2.25	2.70*	2.67	3.18+	-1.19	1.48
CCL13	2.20	4.75*	2.23	2.39	-1.02	1.99
IL19	4.39*	9.63***	3.54+	4.22*	1.24	2.28
TNFSF4	3.76*	2.93+	2.90	2.16	1.30	1.35
CD1B	21.00***	43.40***	2.85	5.07*	7.35+	8.56**
CD1C	19.20***	36.40***	2.86	5.31*	6.69+	6.86**
CCL17	27.80***	59.30***	2.61	5.64*	10.60*	10.50**
TGFB1	5.13***	9.23***	1.58	2.39*	3.24+	3.86**
ICOS	5.24*	5.80***	1.74	2.47	3.58*	4.00**
CD1E	18.00***	38.30***	2.87	3.78+	6.28+	10.10**
CD2	4.93*	8.74***	2.14	2.25	2.31	3.89*
CD1A	7.17**	15.50***	1.39	2.40	2.97	6.45**
CD28	5.22*	7.61**	1.45	1.76	3.59	4.33*
CCL22	10.20**	13.80***	2.76	3.69*	3.69	3.75*
CCR5	11.84**	10.40***	2.71+	3.34+	2.97	3.11+
CXCR2	5.86**	7.61***	2.46	2.37	2.38	3.21*
TNFRSF4	28.10***	35.20***	5.90*	5.34*	4.77	6.59*
ITGB2	15.20***	32.80***	3.21*	11.53***	4.75+	3.44*
CLEC10A	26.50***	62.40***	4.42+	15.90***	6.00+	3.92+
CIITA	8.97***	19.40***	2.61	7.20***	3.43	2.66
MMP12	30.10***	65.00***	4.98	13.20***	7.36+	4.94*
CD5	11.10**	19.40***	3.38	7.32**	3.27	2.65
ITGAM	10.40***	21.40***	3.35	6.60**	3.10	3.25+
CD4	9.34**	23.90***	2.23	7.33***	4.20	3.26+
FCER1A	6.70**	12.50***	1.79	3.82*	3.75	3.28+
CXCR1	4.41*	16.50***	2.66	4.17*	3.16	3.95+
TNF	3.19	7.66**	1.27	2.82	2.53	2.71
CCR8	9.73**	15.20***	3.31	1.44	2.94	10.60***
IL13	10.00**	27.20***	2.55	1.19	3.92	22.80***
CCR4	11.90**	20.70***	5.41*	2.50	2.20	8.28**
CD40LG	5.50*	7.40**	3.43	1.88	1.60	3.94*
CCR2	5.92*	6.68**	3.11	1.53	1.08	4.36*
CD27	6.99**	16.80***	4.40*	2.17	1.59	7.75**
IL24	-1.03	4.95**	1.88	1.97	-1.95	2.51
TXLNA	1.39	1.60	-1.99	-1.35	2.20+	2.15*
JAK2	1.44	1.90	-1.95	-1.58	2.80	2.99*
OSMR	1.17	2.82*	-1.51	1.42	1.77	1.98
IL18	-2.74*	-7.60***	-2.85*	-10.80***	1.04	1.38
IL34	-3.24+	-20.60***	-3.70*	-40.80***	1.14	1.98
GATA3	-3.49*	-5.29***	-2.56	-23.40***	-1.37	4.41**
MAP2K7	1.12	-1.33	1.04	-2.38**	1.08	1.78+
IL17RC	-1.27	-1.75	1.46	-2.47*	-1.86	1.41
IL7	-4.31	-5.66	1.43	-4.56**	-1.88	2.75
IL37	-4.26*	-11.30***	-2.32	-6.51**	-1.83	-1.73
IL1F10	-4.11**	-7.54***	-2.27	-4.53***	-1.81	-1.67
IL17B	-4.18*	-12.00***	-1.53	-5.13**	-2.73	-2.34
IL33	-3.64	-4.64*	-1.36	-3.49+	-2.68	-1.33
JAK1	-1.30	-1.43	-1.90	-2.64**	1.46	1.84+
AHR	1.02	-1.04	-3.12**	-6.51***	3.18*	6.25***

FIG 2. Immune genes. Summary heatmap of immune genes from multiple pathways in tape-stripped skin of AD and psoriasis (PSO), and controls using RNA-seq with criteria of FCH greater than 2 and FDR less than 0.05. Table shows FCHs in nonlesional (NL) versus normal (N), lesional (LS) versus N, LS versus LS, and NL versus NL tape-stripped skin for AD and PSO. ***FDR < 0.001; **FDR < 0.01; *FDR < 0.05; $^{+}$FDR < 0.1.



	Atopic Dermatitis		Psoriasis		AD NL vs PSO NL	AD LS vs PSO LS
	NL vs N	LS vs N	NL vs N	LS vs N		
FLG2 ------:	-2.65	-7.22***	-2.06	-6.79***	-1.28	-1.06
GJB5 ------:	-2.36	-3.98**	-1.86	-5.96***	-1.27	1.50
GJB3 ------:	-3.94*	-11.50***	-2.81+	-17.00***	-1.40	1.48
KRT77 -----:	-3.35	-33.20***	-4.36+	-126.00***	1.30	3.80+
GAL -------:	-1.45	-7.30***	-2.04	-10.70***	1.41	1.46
SPTLC3 ----:	-2.21	-4.73***	-2.74+	-5.94***	1.24	1.26
FA2H ------:	-1.71	-7.08**	-2.99	-8.49***	1.75	1.20
ANXA9 -----:	-2.65	-4.89**	-2.12	-3.34*	-1.25	-1.46
ALOXE3 ----:	-3.43*	-5.98***	-1.91	-4.23**	-1.79	-1.42
SCEL ------:	-2.70	-7.13***	-2.76	-5.59***	1.02	-1.27
LCE5A -----:	-3.95+	-18.00***	-3.77+	-9.12***	-1.05	-1.97
DHCR7 -----:	-1.37	-2.71*	-1.17	-1.90	-1.17	-1.43
FABP7 -----:	-2.87	-13.20**	1.32	-6.38*	-3.77	-2.07
NR2F2 -----:	-2.83	-4.05*	1.10	-2.62+	-3.12	-1.55
ORMDL3 ----:	-2.10*	-2.98***	-1.31	-4.85***	-1.61	1.63
CLDN8 -----:	-2.84	-6.50*	1.19	-9.11**	-3.37	1.40
GPAM ------:	1.02	-1.90	1.52	-4.13**	-1.49	2.17
KRT2 ------:	-4.18	-2.79	-3.12	-8.13**	-1.34	2.91
ACER1 -----:	-3.69+	-3.50*	-3.05	-6.12***	-1.21	1.75
CERS3 -----:	-1.99	-1.45	-2.20	-2.52*	1.11	1.74
DGAT2 -----:	-2.04+	-2.64**	-2.86*	-2.83**	1.40	1.07
KRT79 -----:	-1.71	-8.67**	-6.44*	-13.30***	3.75	1.54
SPTLC1 ----:	1.45	1.51	-2.27*	-3.10***	3.29*	4.69***
EREG ------:	1.23	1.48	-2.24	-2.11	2.75	3.13*
CLDN1 -----:	-1.08	-1.02	-2.47*	-3.49***	2.29+	3.43***
SGPP1 -----:	1.51	1.80	-1.48	-3.17*	2.24	5.69***
FADS2 -----:	-1.12	1.07	-1.21	-5.05**	1.09	5.42**
FAR2 ------:	1.43	1.03	-1.36	-4.48**	1.94	4.60*
PPL -------:	-1.47	-1.32	1.31	1.72	-1.92	-2.27*
HMGCS1 ----:	-1.33	-1.55	1.42	1.77*	-1.89	-2.74***
ACSL1 -----:	1.39	1.07	1.58	2.21*	-1.14	-2.07+
PSORS1C2 --:	1.02	-3.99*	1.51	1.57	-1.49	-6.27**
ACOX2 -----:	1.44	-2.25	3.71+	1.66	-2.58	-3.74*
CDH12 -----:	-1.41	-3.89*	2.14	-1.56	-3.00	-2.50+
PNPLA3 ----:	-2.37	-5.28***	-1.89	-1.59	-1.25	-3.31*
DEGS2 -----:	-2.61	-2.82*	-2.75+	-1.53	1.05	-1.84
ANXA5 -----:	3.43*	7.12***	1.30	3.21**	2.63	2.22+
ELOVL5 ----:	2.77+	4.96***	1.68	2.88*	1.65	1.72
ANXA6 -----:	8.23***	15.40***	4.58*	10.50***	1.80	1.47
LPIN1 -----:	1.78	2.77*	1.58	3.37**	1.13	-1.21
CLDN7 -----:	1.99	4.39**	1.61	4.77**	1.24	-1.09
LCE3C -----:	4.88	8.29+	2.37	11.20*	2.06	-1.35
LCE3A -----:	11.50***	47.90***	13.90***	106.00***	-1.21	-2.22
AGPAT3 ----:	1.99	2.66*	-1.03	-1.18	2.05	3.15**
ALOX15 ----:	24.80***	49.40***	-1.22	-1.74	30.30***	85.70***
SOAT1 -----:	4.74**	7.13***	-1.06	2.02	5.00*	3.53**
LPL -------:	8.37*	8.15**	4.19	1.36	2.00	6.01*
PPARG -----:	6.64*	11.40***	2.21	2.63	3.00	4.35*
FADS1 -----:	3.69+	3.62*	2.03	2.02	1.82	1.79

FIG 3. Terminal differentiation and lipid biosynthesis/metabolism genes. Summary heatmap of barrier genes in tape-stripped skin of AD and psoriasis (PSO), as well as healthy skin using RNA-seq with criteria of FCH greater than 2 and FDR less than 0.05. Table shows FCHs in nonlesional (NL) versus normal (N), lesional (LS) versus N, LS versus LS, and NL versus NL in tape-stripped skin for the AD and PSO groups. ***FDR < 0.001; **FDR < 0.01; *FDR < 0.05; $^{+}$FDR < 0.1.

barrier-related products (ELOVL5, CLDN7, and ANXA5/6) were increased in both diseases. Lipid biosynthesis/metabolism-related abnormalities were overall more pronounced in psoriasis, and several products related to lipid processing were significantly downregulated only in psoriasis (FADS2, FAR2, SPTLC1, and GPAM). The levels of late cornified envelope (LCE) components (LCE3A/LCE3C) were preferentially upregulated in psoriasis, as described in biopsy studies.[12,53-55] In contrast, terminal differentiation (PSORS1C2) and cadherin (CDH12) markers were significantly decreased only in AD (all FDRs < 0.05).

Pathway analyses highlight enrichment of disease-specific axes

Gene set variation analysis was performed to evaluate enrichment of previously published immune and T_H pathway gene sets (Fig 4).[2,48] Although immune genes were significantly enriched in lesional and nonlesional tape-stripped skin from patients with both diseases ($P < .01$) (Fig 4, *A*), the T_H2 pathway was highest in AD ($P < .05$) (Fig 4, *B*), with lesser or no significant changes in psoriasis. Conversely, levels of T_H1/T_H17 axes were highest in psoriasis, with lesser but significant upregulations in AD versus in controls ($P < .05$) (Fig 4, *C* and *D*). The T_H22/IL-22 axis showed similar upregulation in both diseases ($P < .01$) (Fig 4, *E*). Downregulation of lipid-related genes was greatest in psoriasis lesions, with significant downregulation also seen in AD versus in controls ($P < .05$) (Fig 4, *F*).

Comparison of tape strips with biopsy specimens

We compared the tape strip transcriptome of AD and psoriasis with that of biopsy specimens from patients with similar disease severity, using the cohort published by Tsoi et al.[56] Overall, for both AD and psoriasis, the differences between diseased and healthy skin were highly correlated between tape strips and biopsy specimens (see Fig E1 in this article's Online Repository at www.jacionline.org).

Taking the intersection of 14,313 genes that were evaluated in both studies, lesional AD demonstrated 3,958 DEGs in tape strips and 1,307 DEGs in biopsy specimens, whereas lesional psoriasis

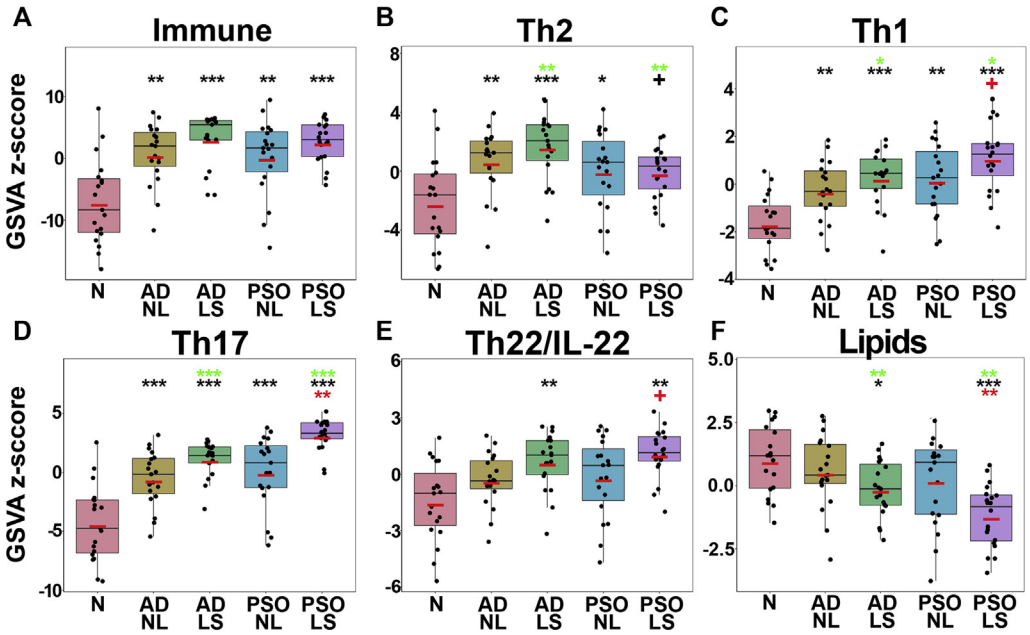


FIG 4. Immune gene signatures. Mean *z* scores of immune-related gene set variation analysis (GSVA) pathways in lesional (LS) and nonlesional (NL) tape-stripped skin of AD and psoriasis (PSO), as well as control tape-stripped skin. Black symbols indicate significance of comparison with normal (N) skin; red symbols indicate significance of comparison between LS and NL tape-stripped skin; colored symbols indicate significance of comparison between the respective groups. ***$P < .001$; **$P < .01$; *$P < .05$; $^{+}P < .1$.

showed 5,208 DEGs in tape strips and 2,706 DEGs in biopsy specimens. In AD and psoriasis lesions, respectively, 679 and 943 DEGs overlapped between tape strips and biopsy specimens. In both diseases, various DC/T-cell–related markers (FCER1A, ITGAX/CD11c, CD69, CD80, and CD86), negative regulators (IL-34 and IL-1F10), and barrier markers (GJB3, KRT79, and PSORS1C2) displayed greater FCHs in tape strips, whereas the S100As and some lipid-related gene products (FADS1/2 and AWAT1) conversely showed greater differences in biopsy specimens (see Fig E1, *A* and *B*). Furthermore, AD lesions showed greater FCHs for T_H2 chemokine CCL17/TARC in tape strips than did biopsy specimens (see Fig E1, *A*). In psoriasis, tape strips demonstrated greater FCHs for T_H1 chemokines (CXCL9/10, CCL3), although T_H17 markers (IL-36G, IL-19, and LCN2/lipocalin-2) were more dysregulated in biopsy specimens (see Fig E1, *B*).

Tape strips displayed markedly greater dysregulation in nonlesional skin than did biopsy specimens for both AD (1450 DEGs in tapes and 81 DEGs in biopsy specimens) and psoriasis (1071 DEGs in tapes and 43 DEGs in biopsy specimens) (Fig E1, *C* and *D*). Tape strips, but not biopsy specimens, showed significant upregulation of DC/T-cell markers (CD3D, CD69, CD80, CD86, and CCR7) for both diseases, T_H2 products (CCL17/TARC and TNFRSF4/OX40) for AD, and T_H1/T_H17 markers (CXCL9/10, CCL3, IL-17A, IL-36A, and PI3) for psoriasis.

qRT-PCR confirms and expands RNA-seq data

To validate the RNA-seq data and assess key immune and barrier markers that are often below detection even in RNA-seq,[3,56] we evaluated a large panel of 99 genes representing cellular, immune, and barrier markers by qRT-PCR. We were able to quantify 99 of 99 (100%) mRNA products in all samples (100% detection) (Figs 5-7 and see Figs E2-E4 in this article's Online Repository at www.jacionline.org).

Levels of cellular markers defining immune cell subsets, such as macrophages, T cells, and DCs/LCs, were increased in both lesional AD and psoriasis versus in controls (Figs 5, *A* and 7). The levels of these markers were mostly also significantly elevated in nonlesional AD but not in psoriasis ($P < .05$). Levels of the T-cell activation marker ICOS, CCR4 (which defines activated T_H2 cells), and the DC marker CD209/DC-SIGN were significantly higher in AD lesions than in psoriasis lesions ($P < .05$).

Levels of the innate immune markers (NOS2/iNOS, IL-17C, IL-1B, IL-6, and CXCL8/IL-8) were significantly higher in psoriasis lesions than in both the controls and AD lesions ($P < .01$), with NOS2/iNOS, IL-6, and CXCL8/IL-8 also harboring increases in nonlesional psoriasis ($P < .05$) (Figs 5, *B* and 7 and see Fig E2). In contrast, T_H2 cytokine genes were consistently significantly upregulated in lesional and/or nonlesional AD than in the controls and psoriasis tissues. These included markers that matched RNA-seq data (IL-13, IL-31, CCL17/TARC, and CCL22), as well as others that were below detection in RNA-seq, including the key T_H2 cytokine IL-4, and the mediators of eosinophil growth/recruitment IL-5 and CCL26/eotaxin-3 ($P < .05$) (Figs 5, *B* and 7 and see Fig E2 in this article's Online Repository at www.jacionline.org). Levels of IL-13, CCL17/TARC, CCL22, TNFRSF4/OX40, and IL-1RL1/ST2/IL-33R were also significantly higher in nonlesional AD than in both the control and nonlesional psoriasis ($P < .05$). T_H1 products (IFN-γ, CXCL9, CXCL10, and STAT1) were upregulated in lesional and/or nonlesional psoriasis than in both the controls and AD ($P < .05$) (Figs 5, *B* and 7 and see Figs E2 and E3). Levels of expression of T_H17-related genes were mostly significantly increased in lesional and/or nonlesional psoriasis versus in both the controls and AD tissues, which was

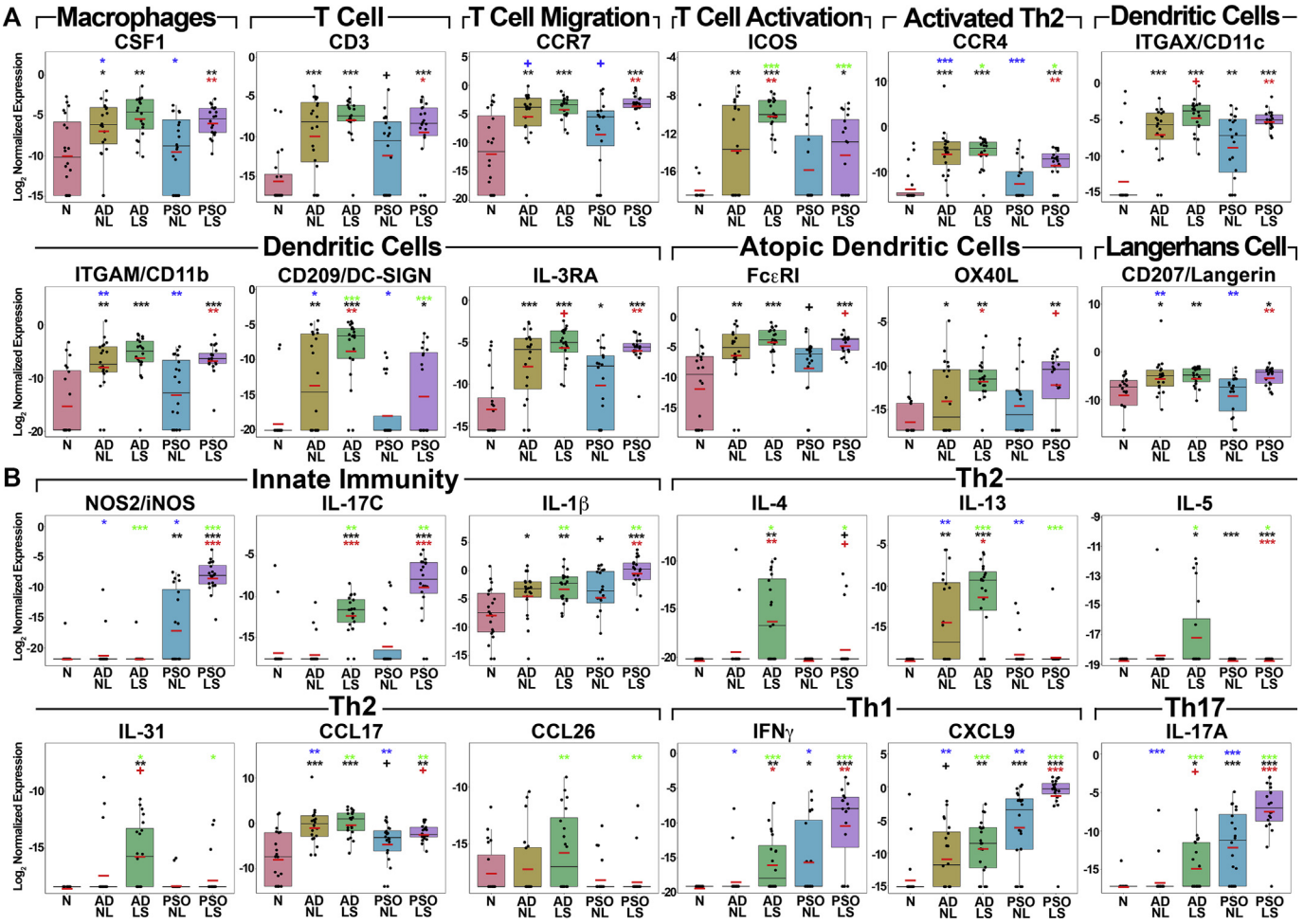


FIG 5. Cellular and immune biomarkers. FCHs of cellular and immune mediators detected in lesional (LS) and nonlesional (NL) tape-stripped skin of AD and psoriasis (PSO) and controls, as measured by quantitative real-time PCR. Black symbols indicate significance of comparison with normal (N) skin; red symbols indicate significance of comparison between LS and NL tape-stripped skin; colored symbols indicate significance of comparison between the respective groups. ***$P < .001$; **$P < .01$; *$P < .05$; $^{+}P < .1$.

similar to the results of RNA-seq (Figs 5B and 7 and see Fig E3 in this article's Online Repository at www.jacionline.org). IL-17A, IL-23p19, IL-36A, CCL20, DEFB4B, CXCL1/2, and PI3 were also overexpressed in nonlesional psoriasis versus in the controls ($P < .05$) (Figs 5, *B* to 7 and see E3). As in RNA-seq, the epidermal cytokine IL-19 was the only IL-17–related product with a higher level in AD than in psoriasis (Figs 6 and 7). Levels of expression of the T_H17/T_H22-related genes (IL-22 and most S100As) were elevated in both diseases, although the levels of S100As were significantly higher in psoriasis than in AD lesions ($P < .05$) (Figs 6 and 7 and see Fig E3). The levels of expression of the regulatory T-cell genes IL-10 and FOXP3 were higher in AD lesions than in both controls and psoriasis ($P < .05$), whereas the levels of negative regulators (IL-34, IL-37) were decreased in both diseases versus in the controls (Figs 6 and 7). The levels of epidermal hyperplasia markers (KRT16, SERPINB3, and Ki67) were significantly increased in both AD and psoriasis lesions ($P < .05$), although the levels of KRT16 and SERPINB3 were higher in psoriasis than in AD ($P < .01$) (Figs 6 and 7 and see Fig E4 in this article's Online Repository at www.jacionline.org). The terminal differentiation products (FLG, FLG2, and LOR) were downregulated in lesional AD versus in the controls ($P < .05$) (Figs 6 and 7). A summary heatmap of all evaluated markers is presented in Fig 7, highlighting predominantly the T_H2 (*yellow box*) and T_H1/T_H17 (*green box*) clusters of genes preferentially enhanced in AD and psoriasis, respectively.

We identified NOS2/iNOS as a single gene classifier able to discriminate lesional AD from lesional psoriasis with 100% accuracy (AUC = 1.0) by quantitative PCR and almost perfectly (AUC = 0.97) with use of the RNA-seq data (see Fig E5 in this article's Online Repository at www.jacionline.org).

Correlations between tape strip biomarkers and clinical severity

Levels of mRNA expression in lesional tape-stripped skin (by qRT-PCR) were correlated with clinical severity scores of the AD (according to TSS and IGA score) and psoriasis (according to TLSS and PGA score) tape-stripped lesions (see Table E3 in this article's Online Repository at www.jacionline.org). In AD, significant positive correlation (or trending toward significance) was observed between either TSS or IGA score and markers of general inflammation (MMP12), T-cell activation (ICOS), T_H2 (IL-13, CCL17/TARC, and CCL26/eotaxin-3), T_H22 (IL-22), T_H17 (IL-

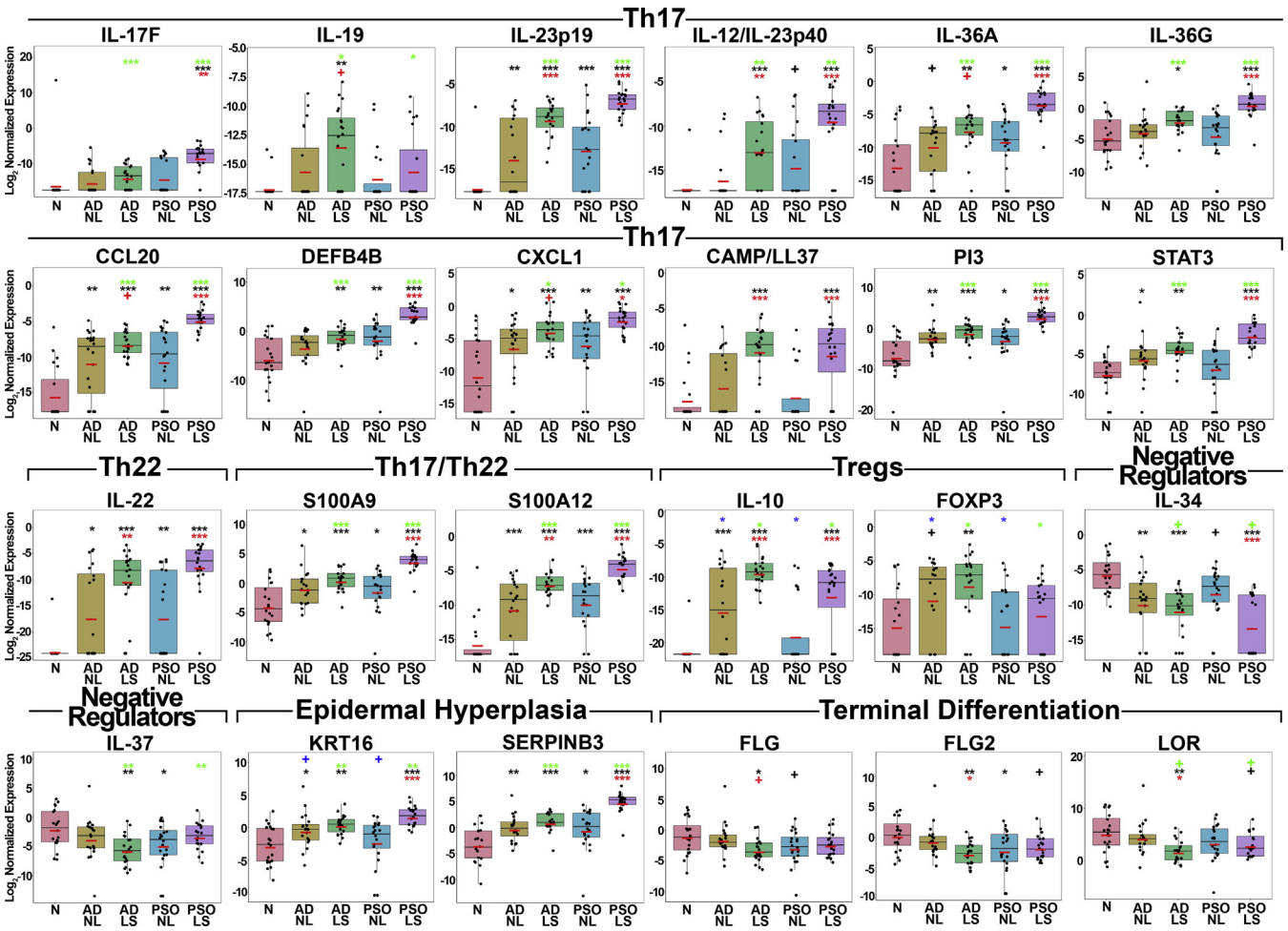


FIG 6. Immune and epidermal hyperplasia markers. FCHs of additional immune and barrier markers detected in lesional (LS) and nonlesional (NL) tape-stripped skin of AD and psoriasis (PSO) and controls, as measured by qRT-PCR. Black symbols indicate significance of comparison to normal (N); red symbols indicate significance of comparison between LS and NL tape-stripped skin; colored symbols indicate significance of comparison between the respective groups. ***$P < .001$; **$P < .01$; *$P < .05$; $^{+}P < .1$.

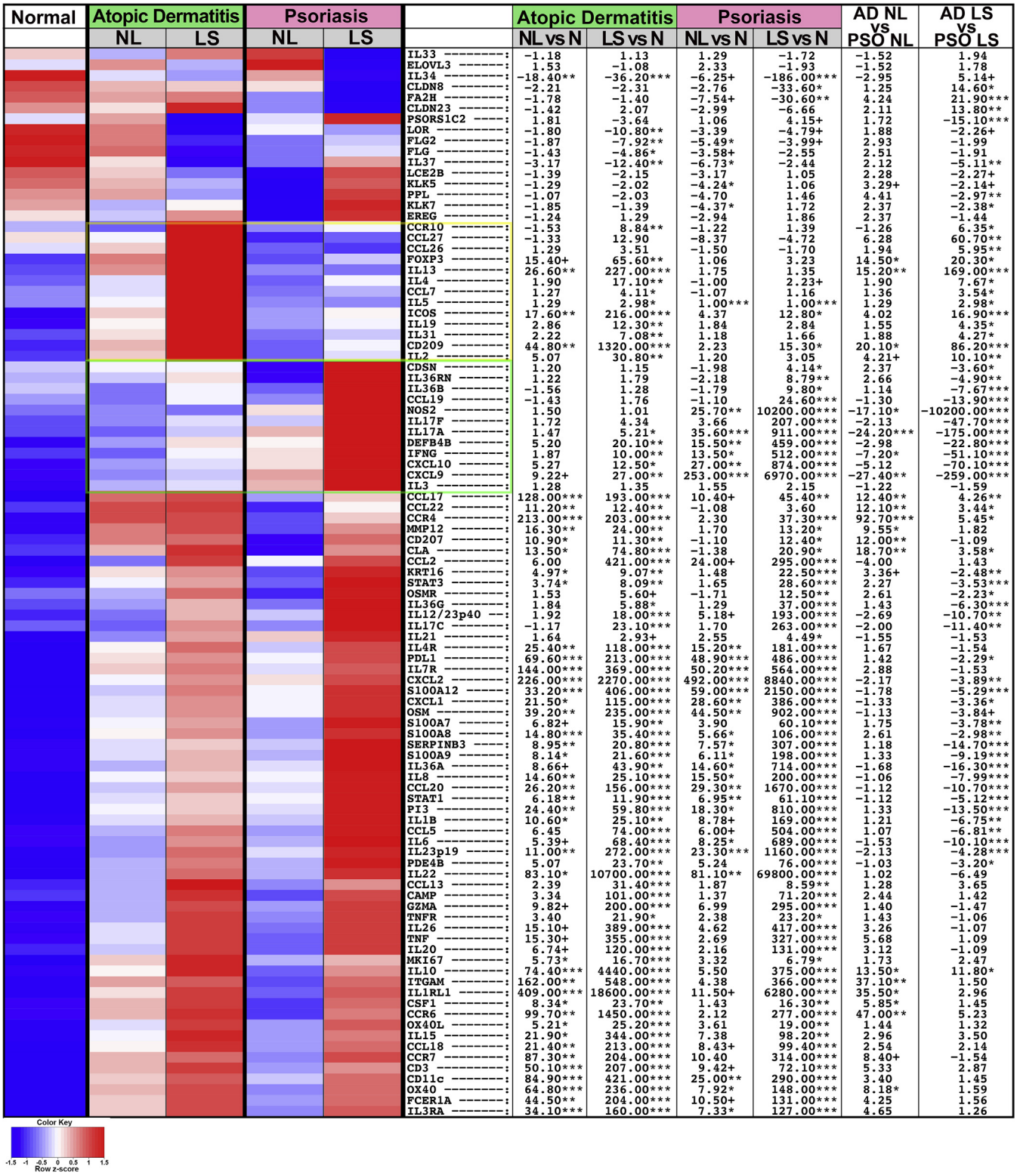
17F, IL-26, and CAMP/LL37), and T-regs (FOXP3) ($r > 0.4$; $P < .1$) (see Table E3). Significant (or trending toward significance) negative correlations with TSS were seen in AD lesions with negative regulators (IL-34) and barrier measures (FA2H and CLDN23) ($r < –0.4$; $P < .1$). In psoriasis, lesional PGA score and/or TLSS correlated positively with the T_H1/T_H17-related (IL-12/IL-23p40 and CCR6) and DC (ITGAX/CD11c) markers ($r > 0.3$; $P < .1$) (see Table E3).

DISCUSSION

We have presented what, to our knowledge, is the most comprehensive tape strip molecular profiling in any inflammatory skin disease to date and the first to fully characterize and compare AD to psoriasis. This was achieved via RNA-seq measuring of more than 20,000 transcripts and targeted qRT-PCR analysis of an extensive set of 99 cellular, immune, and barrier biomarkers, both validating the RNA-seq results and uncovering additional key disease-related measures, some of which were below detection by RNA-seq (eg, IL-4, IL-5, and CCL26/eotaxin-3). We successfully defined a cutaneous molecular phenotype of AD and psoriasis that is consistent with the results of previous biopsy studies,[2-4,6-10,12] identifying genes and pathways that both define and distinguish AD and psoriasis, as well as a single gene accurately classifying these diseases. In fact, as we demonstrated in our comparison of tape strips with the findings for a published biopsy cohort,[56] some biomarkers (eg, CCL17/TARC and FCER1A in AD, CXCL9/10 in psoriasis, and IL-34 in both diseases) showed even larger differentiation in diseased versus healthy tape-stripped skin than in biopsy specimens, likely because of increased synthesis in upper epidermis.

Most tape strip reports in AD and psoriasis have evaluated a limited panel of proteins,[18-21,23-27,29,35,36] with detection rates ranging from 46% to 70% of analytes.[19,20,23] Mass spectrometry, which allows broader protein screening, has also been used in tape strips.[5,16,22,30,31,34,37] Available mass spectrometry studies have primarily focused on barrier measures (keratins and lipids) in AD but have not fully captured the lesional and nonlesional cutaneous profiles of moderate-to-severe psoriasis.[5,22,30,31,34,37]

The increasing knowledge of pathogenic pathways and cytokines in AD and psoriasis derives from mRNA profiling studies in skin biopsy specimens.[2,3,7,8,39,40,48,55,57-66] Global transcriptomic profiling may allow for better detection of pathogenic



	Atopic Dermatitis		Psoriasis		AD NL vs PSO NL	AD LS vs PSO LS
	NL vs N	LS vs N	NL vs N	LS vs N		
IL33	-1.18	1.13	1.29	-1.72	-1.52	1.94
ELOVL3	1.53	-1.08	2.33	-1.93	-1.52	1.78
IL34	-18.40**	-36.20***	-6.25+	-186.00***	-2.95	5.14+
CLDN8	-2.21	-2.31	-2.76	-33.60*	1.25	14.60*
FA2H	-1.78	-1.40	-7.54+	-30.60**	4.24	21.90***
CLDN23	-1.42	2.07	-2.99	-6.66	2.11	13.80**
PSORS1C2	1.81	-3.64	1.06	4.15+	1.72	-15.10***
LOR	-1.80	-10.80**	-3.39	-4.79+	1.88	-2.26+
FLG2	-1.87	-7.92**	-5.49*	-3.99+	2.93	-1.99
FLG	-1.43	-4.86*	-3.58+	-2.55	2.51	-1.91
IL37	-3.17	-12.40**	-6.73*	-2.44	2.12	-5.11**
LCE2B	-1.39	-2.15	-3.17	1.05	2.28	-2.27+
KLK5	-1.29	-2.02	-4.24*	1.06	3.29+	-2.14+
PPL	-1.07	-2.03	-4.70	1.46	4.41	-2.97**
KLK7	-1.85	-1.39	-4.37*	1.72	2.37	-2.38*
EREG	-1.24	1.29	-2.94	1.86	2.37	-1.44
CCR10	-1.53	8.84**	-1.22	1.39	-1.26	6.35*
CCL27	-1.33	12.90	-8.37	-4.72	6.28	60.70**
CCL26	1.29	3.51	-1.50	-1.70	1.94	5.95**
FOXP3	15.40+	65.60**	1.06	3.23	14.50*	20.30*
IL13	26.60**	227.00***	1.75	1.35	15.20**	169.00***
IL4	1.90	17.10**	-1.00	2.23+	1.90	7.67*
CCL7	1.27	4.11*	-1.07	1.16	1.36	3.54*
IL5	1.29	2.98*	1.00***	1.00***	1.29	2.98*
ICOS	17.60**	216.00***	4.37	12.80*	4.02	16.90***
IL19	2.86	12.30**	1.84	2.84	1.55	4.35*
IL31	2.22	7.08**	1.18	1.66	1.88	4.27*
CD209	44.80**	1320.00***	2.23	15.30*	20.10*	86.20***
IL2	5.07	30.80**	1.20	3.05	4.21+	10.10**
CDSN	1.20	1.15	-1.98	4.14*	2.37	-3.60*
IL36RN	1.22	1.79	-2.18	8.79**	2.66	-4.90**
IL36B	-1.56	1.28	-1.79	9.80*	1.14	-7.67***
CCL19	-1.43	1.76	-1.10	24.60***	-1.30	-13.90***
NOS2	1.50	1.01	25.70**	10200.00***	-17.10*	-10200.00***
IL17F	1.72	4.34	3.66	207.00***	-2.13	-47.70***
IL17A	1.47	5.21*	35.60***	911.00***	-24.20***	-175.00***
DEFB4B	5.20	20.10**	15.50**	459.00***	-2.98	-22.80***
IFNG	1.87	10.00**	13.50*	512.00***	-7.20*	-51.10***
CXCL10	5.27	12.50*	27.00**	874.00***	-5.12	-70.10***
CXCL9	9.22+	27.00**	253.00***	6970.00***	-27.40**	-259.00***
IL3	1.28	1.35	1.55	2.15	-1.22	-1.59
CCL17	128.00***	193.00***	10.40+	45.40**	12.40**	4.26**
CCL22	11.20**	12.40**	-1.08	3.60	12.10**	3.44*
CCR4	213.00***	203.00***	2.30	37.30***	92.70***	5.45*
MMP12	16.30**	24.00**	1.70	13.20*	9.55*	1.82
CD207	10.90*	11.30**	-1.10	12.40*	12.00**	-1.09
CLA	13.50*	74.80***	-1.38	20.90*	18.70**	3.58*
CCL2	6.00	421.00***	24.00+	295.00***	-4.00	1.43
KRT16	4.97*	9.07**	1.48	22.50***	3.36+	-2.48**
STAT3	3.74*	8.09**	1.65	28.60***	2.27	-3.53***
OSMR	1.53	5.60+	-1.71	12.50**	2.61	-2.23*
IL36G	1.84	5.88*	1.29	37.00***	1.43	-6.30***
IL12/23p40	1.92	18.00***	5.18+	193.00***	-2.69	-10.70**
IL17C	-1.17	23.10***	1.70	263.00***	-2.00	-11.40**
IL21	1.64	2.93+	2.55	4.49*	-1.55	-1.53
IL4R	25.40**	118.00***	15.20**	181.00***	1.67	-1.54
PDL1	69.60***	213.00***	48.90***	486.00***	1.42	-2.29*
IL7R	144.00***	369.00***	50.20***	564.00***	2.88	-1.53
CXCL2	226.00***	2270.00***	492.00***	8840.00***	-2.17	-3.89**
S100A12	33.20***	406.00***	59.00***	2150.00***	-1.78	-5.29***
CXCL1	21.50*	115.00***	28.60**	386.00***	-1.33	-3.36*
OSM	39.20**	235.00***	44.50**	902.00***	-1.13	-3.84+
S100A7	6.82+	15.90**	3.90	60.10***	1.75	-3.78**
S100A8	14.80***	35.40***	5.66*	106.00***	2.61	-2.98**
SERPINB3	8.95**	20.80***	7.57*	307.00***	1.18	-14.70***
S100A9	8.14*	21.60***	6.11*	198.00***	1.33	-9.19***
IL36A	8.66+	43.90**	14.60*	714.00***	-1.68	-16.30***
IL8	14.60**	25.10***	15.50*	200.00***	-1.06	-7.99***
CCL20	26.20**	156.00***	29.30**	1670.00***	-1.12	-10.70***
STAT1	6.18**	11.90***	6.95**	61.10***	-1.12	-5.12***
PI3	24.40**	59.80***	18.30*	810.00***	1.33	-13.50***
IL1B	10.60*	25.10**	8.78+	169.00***	1.21	-6.75**
CCL5	6.45	74.00***	6.00+	504.00***	1.07	-6.81**
IL6	5.39+	68.40***	8.25*	689.00***	-1.53	-10.10***
IL23p19	11.00**	272.00***	23.30***	1160.00***	-2.13	-4.28***
PDE4B	5.07	23.70**	5.24	76.00***	-1.03	-3.20*
IL22	83.10*	10700.00***	81.10**	69800.00***	1.02	-6.49
CCL13	2.39	31.40***	1.87	8.59**	1.28	3.65
CAMP	3.34	101.00***	1.37	71.20***	2.44	1.42
GZMA	9.82+	200.00***	6.99	295.00***	1.40	-1.47
TNFR	3.40	21.90*	2.38	23.20*	1.43	-1.06
IL26	15.10+	389.00***	4.62	417.00***	3.26	-1.07
TNF	15.30+	355.00***	2.69	327.00***	5.68	1.09
IL20	6.74+	120.00***	2.16	131.00***	3.12	-1.09
MKI67	5.73*	16.70***	3.32	6.79*	1.73	2.47
IL10	74.40***	4440.00***	5.50	375.00***	13.50*	11.80*
ITGAM	162.00**	548.00***	4.38	366.00***	37.10**	1.50
IL1RL1	409.00***	18600.00***	11.50+	6280.00***	35.50*	2.96
CSF1	8.34*	23.70**	1.43	16.30**	5.85*	1.45
CCR6	99.70**	1450.00***	2.12	277.00***	47.00**	5.23
OX40L	5.21*	25.20***	3.61	19.00**	1.44	1.32
IL15	21.90*	344.00***	7.38	98.20**	2.96	3.50
CCL18	21.40**	213.00***	8.43+	99.40***	2.54	2.14
CCR7	87.30**	204.00***	10.40	314.00***	8.40+	-1.54
CD3	50.10***	207.00***	9.42+	72.10***	5.33	2.87
CD11c	84.90***	421.00***	25.00**	290.00***	3.40	1.45
OX40	64.80***	236.00***	7.92*	148.00***	8.18*	1.59
FCER1A	44.50**	204.00***	10.50+	131.00***	4.25	1.56
IL3RA	34.10***	160.00***	7.33*	127.00***	4.65	1.26

FIG 7. Summary heatmap of gene expressions measured by qRT-PCR of cellular, immune, and barrier biomarkers. Table shows FCHs in nonlesional (NL) versus (N), lesional (LS) versus N, LS versus LS, and NL vs NL tape-stripped skin for AD and psoriasis (PSO). The yellow box indicates a cluster of predominantly T_H2 biomarkers upregulated in AD lesional skin versus in N tape-stripped skin. The green box indicates a cluster of predominately T_H1/T_H17 biomarkers upregulated in PSO LS versus N skin. ***$P < .001$; **$P < .01$; *$P < .05$; $^{+}P < .1$.

mechanisms than in more focused studies.[2-4,7-10,52,56,66] To date, 2 mRNA tape strip studies have been reported in psoriasis, evaluating a limited number of analytes.[28,41] In AD, 3 RNA-seq studies have been published; 2 of them are based on the same cohort of adults with mild-to-severe AD.[14,16,17] Of these adult studies, 1 focused on nonlesional skin, reported 29 DEGs, and detected a T_H2-high endotype in a subset of patients with AD with greater inflammation,[14] and another reported abnormal expression of lipid enzymes (ELOVLs).[17] A pediatric RNA-seq study distinguished nonlesional skin from pediatric patients with AD (aged 4-17 years) with and without food allergies based on expression of T_H2-related markers; it reported 288 DEGs and an overall sample detection rate of 45%.[16] Our group recently evaluated the mRNA expression of an extended panel of key immune and barrier markers in children with moderate-to-severe AD by using qRT-PCR, recovering mRNA from 70 of 71 samples (99%) and quantifying 77 of 79 products (97%).[38]

The current genomic profiling study, which combines RNA-seq and qRT-PCR, provides a comprehensive tape strip–based molecular map of immune and barrier alterations in skin of adults with AD and psoriasis. We optimized the level of detection and mRNA recovery,[14,16,17,19,20,23] obtaining close to 100% ability to evaluate samples and genes, similar to in our previous study in children.[38] We also identified the highest numbers of DEGs of any tape strip study (4123 and 1498 for lesional and nonlesional AD and 5390 and 1135 for lesional and nonlesional psoriasis).

We show that although AD and psoriasis share markers of cellular infiltration and activation of T-cells (CD3 and CD69), mononuclear cells (CSF2), and DCs (FCER1G, ITGAX/CD11c, CD1a, and CD83) in the outer epidermis, they are distinguished by their cytokine polarization. Moreover, the presence of T-cell–derived cytokine mRNAs (IL-4, IL-13, IL-31, IL-5, IL-17A, IL-17F, and IFN-γ) without exogenous stimulation suggests superficial T-cell activation in both diseases, as previously shown by upper epidermal immunostaining.[14,38] These data support the general framework of AD as a T_H2/T_H22-driven disease.[2-4,60] Levels of T_H2 markers were preferentially higher in AD than in psoriasis, with key cytokines/receptors (IL-13, IL-31, CCL17/TARC, and CCR4) uniquely upregulated in AD. Levels of mediators of eosinophil growth or recruitment (IL-5, eotaxin-2/CCL24, and eotaxin-3/CCL26) also showed greater increases in AD. Dysregulation of the itch cytokine IL-31 was described in AD biopsy specimens,[40,48,59,65] but it has not been detected in tape strips.[14,16,17,19,20,23,38] Levels of additional T_H2 markers that are targeted by recently approved or currently tested treatments, including IL-4R, IL-13, and TNFRSF4/OX40,[67-70] were significantly increased in AD and correlated with disease severity. The level of CCL26/eotaxin-3, which is perhaps the best therapeutic response biomarker for dupilumab,[48] was also significantly upregulated in AD. It is critical that minimally invasive approaches be able to detect changes in either therapeutic targets or therapeutic response biomarkers in AD or psoriasis. This is also the first study to report significant upregulation of IL-22/T_H22, which has been pathogenically linked to AD and psoriasis,[71,72] in tape-stripped lesions.

Prominent, and more significant T_H17/T_H1 upregulation characterized lesional and nonlesional skin of patients with psoriasis but not tape-stripped skin of patients with AD, which is consistent with biopsy findings.[6-10] Tape stripping the skin of patients with psoriasis detected significant upregulation of previously defined IL-17–related biomarkers of psoriasis (IL-36A/G, VNN3, DEFB4A/B, and CXCL1)[73-77] compared with that in skin from healthy individuals and patients with AD. Because IL-36 cytokines have emerged as therapeutic targets in psoriasis, tape strip biomarkers may be valuable to track therapeutic improvement.[78] Of note, IL-19 is the sole IL-17–related gene with a level of expression that was higher in AD than in psoriasis, potentially reflecting its coregulation by IL-17A and IL-4/IL-13.[51] Likewise, although T_H22 activation was comparable in both diseases, levels of S100As were preferentially higher in psoriasis, likely owing to IL-17/IL-22 coregulation.[79] Although T_H1/T_H17 activation was still evident in AD, it was subtler than in psoriasis. This is consistent with the findings of prior skin biopsy and blood studies in populations of white individuals with AD, which associated T_H1 with disease chronicity rather than pathogenicity,[65,80-82] whereas T_H17 may be more prominent in other AD endotypes (eg, Asian and pediatric).[39,40,60,83]

Given that tape strips could define unique genes and pathways, we sought to define a biomarker that could accurately differentiate the diseases, identifying NOS2/iNOS as a perfect discriminator between psoriasis and AD. In biopsy specimens, a molecular classifier consisting of 2 genes (*NOS2/iNOS* and *CCL27*) rather than a single-gene classifier could differentiate these diseases.[84] NOS2/iNOS, which produces nitrous oxide subsequent to stimulation by proinflammatory cytokines, is an innate immunity marker associated with hypergranulosis.[85] The higher neutrophil activity in psoriasis is also suggested by increases in innate immunity markers that are either produced by neutrophils (NOS2/iNOS, IL-1B) or influence neutrophil trafficking (IL-6, IL-17C, and IL-8/CXCL8). The preferential enrichment of these products in psoriasis supports the critical role of innate immunity in directing T_H1/T_H17 differentiation and keratinocyte proliferation,[86,87] likely contributing to the higher epidermal hyperplasia (SERPINB3 and KRT16) in psoriasis versus AD. Quantification of NOS2/iNOS in tape strips can potentially help diagnose psoriasis in clinically ambiguous cases or to track treatment response.

AD and psoriasis are both increasingly recognized as systemic diseases, with inflammation extending beyond clinically affected skin.[2,3,14,16,38,47,48,52,60,65,88,89] Here, we have reported a highly abnormal gene signature in the nonlesional skin of both diseases as compared with in normal skin, particularly in AD. Nonlesional AD skin showed significant increases in numerous T_H2 products (IL-4R, IL-13, CCL17/TARC, and TNFRSF4/OX40).[67-70] Level of IL-1RL1/ST2/IL-33R, which is also increased in AD blood,[47] was also increased in nonlesional AD skin. IL-1RL1/ST2/IL-33R mediates allergic sensitization and T_H2 responses, and it has been linked to increased cardiovascular risk and mortality in large longitudinal studies.[90-92] Nonlesional psoriasis skin showed increases in T_H17-related psoriasis biomarkers (IL-17A/F, IL-36A, and VNN3). These data highlight the ability of tape strips to capture abnormalities in the uninvolved skin of patients with AD and psoriasis, further supporting their systemic nature. In fact, in our comparison of nonlesional skin obtained from tape strips versus from biopsy specimens,[56] tape strips captured a far greater number of DEGs than did biopsy specimens, including key disease biomarkers such as CCL17/TARC for AD and IL-17A for psoriasis.

AD and psoriasis also have characteristic barrier alterations.[3,5,12,49,52-55,93-96] Although we found that terminal differentiation (FLG2 and ANXA9), tight junction (CLDN8), and levels of LCE products were abnormal in both AD and psoriasis,

the nature of these abnormalities differs between the diseases. For example, the levels of expression LCE3 gene products (LCE3A/LCE3C), which function in barrier repair after injury (unlike other LCE members involved in barrier maintenance), were preferentially increased in psoriasis but not in AD lesions, which is consistent with biopsy data.[12,53-55] Although terminal differentiation was impaired in both diseases, decreases in levels of certain products such as PSORS1C2 were unique to AD, which is in line with our tape strip study in children and previous biopsy results.[38,55] Abnormalities that involve lipid synthesis and metabolism were seen in both conditions (FA2H, ALOXE3, and GAL), with higher dysregulation of some lipid-related products (FADS2 and FAR2) in psoriasis, primarily involving lipid biosynthetic genes. Decreased extracellular lipid synthesis and release may contribute to poor corneocyte adhesion and subsequent scaling seen in psoriasis.[11] Overall, the epidermal barrier defects characteristic for AD and psoriasis are reflected in tape-stripped skin, providing further insight into these distinct diseases.

Tape stripping has some limitations, including the time-consuming RNA isolation process and the potential differences in depth of tape stripping among various conditions, although prior studies have shown that use of more than 15 tapes reaches the stratum granulosum, regardless of tissue.[13,14] In particular, given the potential variation in depth of tape stripping among samples, it is important to interpret gene expression differences judiciously, as they may be confounded by the differentiation state of sampled keratinocytes. Additionally, clinical scores were limited to IGA score and TSS for AD and PGA score and TLSS for psoriasis, whereas more comprehensive scores that incorporate disease extent (eg, Scoring Atopic Dermatitis, Eczema Area and Severity Index, Psoriasis Area and Severity Index) were not obtained. Finally, very few genes were differentially expressed between lesional and nonlesional AD skin, although larger differences were observed in psoriasis. These findings suggest that nonlesional AD skin more closely resembles the lesional phenotype than in psoriasis. Furthermore, tape strips may better capture the disease activity in the superficial portions of nonlesional AD skin, whereas some gene expression levels (eg, terminal differentiation products) become diluted in whole skin biopsy specimens.[48,52]

In summary, this global transcriptomic profiling of lesional and nonlesional tape-stripped skin in patients with moderate-to-severe AD and psoriasis has nearly perfect sample recovery rates, showing preferential T_H2 and T_H17/T_H1 polarizations, respectively, and distinct barrier alterations. Tape strips provide complete discrimination between AD and psoriasis with accurate detection of disease-associated cytokines and pathways. This may provide a useful alternative to biopsies for tracking cutaneous disease activity in longitudinal studies and clinical trials.

Clinical implications: Tape strips may provide a minimally invasive alternative to skin biopsies for monitoring biomarkers of disease activity in skin of patients with AD and psoriasis, and beyond.

REFERENCES

1. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol 2013;132:1132-8.
2. Sanyal RD, Pavel AB, Glickman J, Chan TC, Zheng X, Zhang N, et al. Atopic dermatitis in African American patients is TH2/TH22-skewed with TH1/TH17 attenuation. Ann Allergy Asthma Immunol 2019;122:99-110.
3. Suarez-Farinas M, Ungar B, Correa da Rosa J, Ewald DA, Rozenblit M, Gonzalez J, et al. RNA sequencing atopic dermatitis transcriptome profiling provides insights into novel disease mechanisms with potential therapeutic implications. J Allergy Clin Immunol 2015;135:1218-27.
4. Nomura I, Gao B, Boguniewicz M, Darst MA, Travers JB, Leung DY. Distinct patterns of gene expression in the skin lesions of atopic dermatitis and psoriasis: a gene microarray analysis. J Allergy Clin Immunol 2003;112:1195-202.
5. Broccardo CJ, Mahaffey S, Schwarz J, Wruck L, David G, Schlievert PM, et al. Comparative proteomic profiling of patients with atopic dermatitis based on history of eczema herpeticum infection and Staphylococcus aureus colonization. J Allergy Clin Immunol 2011;127:186-93.
6. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol 2017;140:645-53.
7. Li B, Tsoi LC, Swindell WR, Gudjonsson JE, Tejasvi T, Johnston A, et al. Transcriptome analysis of psoriasis in a large case-control sample: RNA-seq provides insights into disease mechanisms. J Invest Dermatol 2014;134:1828-38.
8. Jabbari A, Suárez-Fariñas M, Dewell S, Krueger JG. Transcriptional profiling of psoriasis using RNA-seq reveals previously unidentified differentially expressed genes. J Invest Dermatol 2012;132:246-9.
9. Suarez-Farinas M, Lowes MA, Zaba LC, Krueger JG. Evaluation of the psoriasis transcriptome across different studies by gene set enrichment analysis (GSEA). PLoS One 2010;5:e10247.
10. Swindell WR, Johnston A, Voorhees JJ, Elder JT, Gudjonsson JE. Dissecting the psoriasis transcriptome: inflammatory- and cytokine-driven gene expression in lesions from 163 patients. BMC Genomics 2013;14:527.
11. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. Ann Rheum Dis 2005;64(suppl 2):ii30-6.
12. Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis—part I: clinical and pathologic concepts. J Allergy Clin Immunol 2011;127:1110-8.
13. Kim BE, Goleva E, Kim PS, Norquest K, Bronchick C, Taylor P, et al. Side-by-side comparison of skin biopsies and skin tape stripping highlights abnormal stratum corneum in atopic dermatitis. J Invest Dermatol 2019;139:2387.
14. Dyjack N, Goleva E, Rios C, Kim BE, Bin L, Taylor P, et al. Minimally invasive skin tape strip RNA sequencing identifies novel characteristics of the type 2-high atopic dermatitis disease endotype. J Allergy Clin Immunol 2018;141:1298-309.
15. Wachsman W, Morhenn V, Palmer T, Walls L, Hata T, Zalla J, et al. Noninvasive genomic detection of melanoma. Br J Dermatol 2011;164:797-806.
16. Leung DYM, Calatroni A, Zaramela LS, LeBeau PK, Dyjack N, Brar K, et al. The nonlesional skin surface distinguishes atopic dermatitis with food allergy as a unique endotype. Sci Transl Med 2019;11.
17. Berdyshev E, Goleva E, Bronova I, Dyjack N, Rios C, Jung J, et al. Lipid abnormalities in atopic skin are driven by type 2 cytokines. JCI insight 2018;3:e98006.
18. Berekméri A, Latzko A, Alase A, Macleod T, Ainscough JS, Laws P, et al. Detection of IL-36γ through noninvasive tape stripping reliably discriminates psoriasis from atopic eczema. J Allergy Clin Immunol 2018;142:988-91.
19. Hulshof L, Hack DP, Hasnoe QCJ, Dontje B, Jakasa I, Riethmuller C, et al. A minimally invasive tool to study immune response and skin barrier in children with atopic dermatitis. Br J Dermatol 2019;180:621-30.
20. McAleer MA, Jakasa I, Hurault G, Sarvari P, McLean W, Tanaka RJ, et al. Systemic and stratum corneum biomarkers of severity in infant atopic dermatitis include markers of innate and T helper cell-related immunity and angiogenesis. Br J Dermatol 2019;180:586-96.
21. Ainscough JS, Macleod T, McGonagle D, Brakefield R, Baron JM, Alase A, et al. Cathepsin S is the major activator of the psoriasis-associated proinflammatory cytokine IL-36γ. Proc Natl Acad Sci U S A 2017;114:E2748.
22. Mehul B, Laffet G, Seraidaris A, Russo L, Fogel P, Carlavan I, et al. Noninvasive proteome analysis of psoriatic stratum corneum reflects pathophysiological pathways and is useful for drug profiling. Br J Dermatol 2017;177:470-88.
23. Koppes SA, Brans R, Ljubojevic Hadzavdic S, Frings-Dresen MH, Rustemeyer T, Kezic S. Stratum corneum tape stripping: monitoring of inflammatory mediators in atopic dermatitis patients using topical therapy. Int Arch Allergy Immunol 2016;170:187-93.
24. Loesche C, Kolbinger F, Valentin M, Jarvis P, Ceci M, Wieczorek G, et al. Interleukin-17A blockade with secukinumab results in decreased neutrophil infiltration in psoriasis: minimally-invasive measurement by tape stripping. Adv Precis Med 2016;1:1-9.
25. Sano Y, Masuda K, Tamagawa-Mineoka R, Matsunaka H, Murakami Y, Yamashita R, et al. Thymic stromal lymphopoietin expression is increased in the horny layer of patients with atopic dermatitis. Clin Exp Immunol 2013;171:330-7.

26. Morita E, Takahashi H, Niihara H, Dekio I, Sumikawa Y, Murakami Y, et al. Stratum corneum TARC level is a new indicator of lesional skin inflammation in atopic dermatitis. Allergy 2010;65:1166-72.
27. Yamaguchi J, Aihara M, Kobayashi Y, Kambara T, Ikezawa Z. Quantitative analysis of nerve growth factor (NGF) in the atopic dermatitis and psoriasis horny layer and effect of treatment on NGF in atopic dermatitis. Journal of Dermatol Sci 2009; 53:48-54.
28. Benson NR, Papenfuss J, Wong R, Motaal A, Tran V, Panko J, et al. An analysis of select pathogenic messages in lesional and non-lesional psoriatic skin using non-invasive tape harvesting. J Invest Dermatol 2006;126:2234-41.
29. Clausen ML, Slotved HC, Krogfelt KA, Agner T. Measurements of AMPs in stratum corneum of atopic dermatitis and healthy skin-tape stripping technique. Sci Rep 2018;8:1666.
30. Winget JM, Finlay D, Mills KJ, Huggins T, Bascom C, Isfort RJ, et al. Quantitative proteomic analysis of stratum corneum dysfunction in adult chronic atopic dermatitis. J Invest Dermatol 2016;136:1732-5.
31. Emson CL, Fitzmaurice S, Lindwall G, Li KW, Hellerstein MK, Maibach HI, et al. A pilot study demonstrating a non-invasive method for the measurement of protein turnover in skin disorders: application to psoriasis. Clin Transl Med 2013;2:12.
32. Janssens M, van Smeden J, Gooris GS, Bras W, Portale G, Caspers PJ, et al. Increase in short-chain ceramides correlates with an altered lipid organization and decreased barrier function in atopic eczema patients. J Lipid Res 2012;53:2755-66.
33. Angelova-Fischer I, Mannheimer AC, Hinder A, Ruether A, Franke A, Neubert RH, et al. Distinct barrier integrity phenotypes in filaggrin-related atopic eczema following sequential tape stripping and lipid profiling. Exp Dermatol 2011;20: 351-6.
34. Broccardo CJ, Mahaffey SB, Strand M, Reisdorph NA, Leung DY. Peeling off the layers: skin taping and a novel proteomics approach to study atopic dermatitis. J Allergy Clin Immunol 2009;124:1113-5.
35. Voegeli R, Rawlings AV, Breternitz M, Doppler S, Schreier T, Fluhr JW. Increased stratum corneum serine protease activity in acute eczematous atopic skin. Br J Dermatol 2009;161:70-7.
36. Amarbayasgalan T, Takahashi H, Dekio I, Morita E. Interleukin-8 content in the stratum corneum as an indicator of the severity of inflammation in the lesions of atopic dermatitis. Int Arch Allergy Immunol 2013;160:63-74.
37. Sakabe J-I, Kamiya K, Yamaguchi H, Ikeya S, Suzuki T, Aoshima M, et al. Proteome analysis of stratum corneum from atopic dermatitis patients by hybrid quadrupole-orbitrap mass spectrometer. J Allergy Clin Immunol 2014; 134:957-60.
38. Guttman-Yassky E, Diaz A, Pavel AB, Fernandes M, Lefferdink R, Erickson T, et al. Use of tape strips to detect immune and barrier abnormalities in the skin of children with early-onset atopic dermatitis. JAMA Dermatol 2019;155:1358-70.
39. Brunner PM, Israel A, Zhang N, Leonard A, Wen HC, Huynh T, et al. Early-onset pediatric atopic dermatitis is characterized by TH2/TH17/TH22-centered inflammation and lipid alterations. J Allergy Clin Immunol 2018;141:2094-106.
40. Esaki H, Brunner PM, Renert-Yuval Y, Czarnowicki T, Huynh T, Tran G, et al. Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. J Allergy Clin Immunol 2016;138:1639-51.
41. Baerveldt EM, Onderdijk AJ, Kurek D, Kant M, Florencia EF, Ijpma AS, et al. Ustekinumab improves psoriasis-related gene expression in noninvolved psoriatic skin without inhibition of the antimicrobial response. Br J Dermatol 2013;168: 990-8.
42. Bissonnette R, Pavel AB, Diaz A, Werth JL, Zang C, Vranic I, et al. Crisaborole and atopic dermatitis skin biomarkers: an intrapatient randomized trial. J Allergy Clin Immunol 2019;144:1274-89.
43. Emer JJ, Frankel A, Sohn A, Lebwohl M. A bilateral comparison study of pimecrolimus cream 1% and a topical medical device cream in the treatment of patients with atopic dermatitis. J Drugs Dermatol 2011;10:735-43.
44. Dobin A, Davis CA, Schlesinger F, Drenkow J, Zaleski C, Jha S, et al. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 2013;29:15-21.
45. Law CW, Chen Y, Shi W, Smyth GK. voom: Precision weights unlock linear model analysis tools for RNA-seq read counts. Genome Biol 2014;15:R29.
46. Li W, Turner A, Aggarwal P, Matter A, Storvick E, Arnett DK, et al. Comprehensive evaluation of AmpliSeq transcriptome, a novel targeted whole transcriptome RNA sequencing methodology for global gene expression analysis. BMC Genomics 2015;16:1069.
47. He H, Li R, Choi S, Zhou L, Pavel A, Estrada YD, et al. Increased cardiovascular and atherosclerosis markers in blood of older patients with atopic dermatitis. Ann Allergy Asthma Immunol 2020;124:70-8.
48. Guttman-Yassky E, Bissonnette R, Ungar B, Suarez-Farinas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. J Allergy Clin Immunol 2019;143: 155-72.
49. Esaki H, Ewald DA, Ungar B, Rozenblit M, Zheng X, Xu H, et al. Identification of novel immune and barrier genes in atopic dermatitis by means of laser capture microdissection. J Allergy Clin Immunol 2015;135:153-63.
50. Keermann M, Koks S, Reimann E, Abram K, Erm T, Silm H, et al. Expression of IL-36 family cytokines and IL-37 but not IL-38 is altered in psoriatic skin. J Dermatol Sci 2015;80:150-2.
51. Huang F, Wachi S, Thai P, Loukoianov A, Tan KH, Forteza RM, et al. Potentiation of IL-19 expression in airway epithelia by IL-17A and IL-4/IL-13: important implications in asthma. J Allergy Clin Immunol 2008;121:1415-21.
52. Suarez-Farinas M, Tintle SJ, Shemer A, Chiricozzi A, Nograles K, Cardinale I, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. J Allergy Clin Immunol 2011;127:954-64.
53. Bergboer JG, Tjabringa GS, Kamsteeg M, van Vlijmen-Willems IM, Rodijk-Olthuis D, Jansen PA, et al. Psoriasis risk genes of the late cornified envelope-3 group are distinctly expressed compared with genes of other LCE groups. Am J Pathol 2011;178:1470-7.
54. Niehues H, Tsoi LC, van der Krieken DA, Jansen PAM, Oortveld MAW, Rodijk-Olthuis D, et al. Psoriasis-associated late cornified envelope (LCE) proteins have antibacterial activity. J Invest Dermatol 2017;137:2380-8.
55. Guttman-Yassky E, Suarez-Farinas M, Chiricozzi A, Nograles KE, Shemer A, Fuentes-Duculan J, et al. Broad defects in epidermal cornification in atopic dermatitis identified through genomic analysis. J Allergy Clin Immunol 2009;124: 1235-44.
56. Tsoi LC, Rodriguez E, Degenhardt F, Baurecht H, Wehkamp U, Volks N, et al. Atopic Dermatitis is an IL-13-dominant disease with greater molecular heterogeneity compared to psoriasis. J Invest Dermatol 2019;139:1480-9.
57. Nograles KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. J Allergy Clin Immunol 2009;123:1244-52.
58. Hamilton JD, Suarez-Farinas M, Dhingra N, Cardinale I, Li X, Kostic A, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol 2014;134:1293-300.
59. Suarez-Farinas M, Dhingra N, Gittler J, Shemer A, Cardinale I, de Guzman Strong C, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. J Allergy Clin Immunol 2013;132:361-70.
60. Noda S, Suarez-Farinas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. J Allergy Clin Immunol 2015; 136:1254-64.
61. Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis–part II: immune cell subsets and therapeutic concepts. J Allergy Clin Immunol 2011;127:1420-32.
62. Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suarez-Farinas M, Cardinale I, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol 2008;159: 1092-102.
63. Ewald DA, Malajian D, Krueger JG, Workman CT, Wang T, Tian S, et al. Meta-analysis derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature highlighting the involvement of atherosclerosis and lipid metabolism pathways. BMC Med Genomics 2015;8:60.
64. Ghosh D, Ding L, Sivaprasad U, Geh E, Biagini Myers J, Bernstein JA, et al. Multiple transcriptome data analysis reveals biologically relevant atopic dermatitis signature genes and pathways. PloS One 2015;10:e0144316.
65. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 2012;130:1344-54.
66. Gudjonsson JE, Ding J, Johnston A, Tejasvi T, Guzman AM, Nair RP, et al. Assessment of the psoriatic transcriptome in a large sample: additional regulated genes and comparisons with in vitro models. J Invest Dermatol 2010; 130:1829-40.
67. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-9.
68. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016;375:2335-48.
69. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. J Allergy Clin Immunol 2019;143:135-41.

70. Guttman-Yassky E, Pavel AB, Zhou L, Estrada YD, Zhang N, Xu H, et al. GBR 830, an anti-OX40, improves skin gene signatures and clinical scores in patients with atopic dermatitis. J Allergy Clin Immunol 2019;144:482-93.
71. Brunner PM, Pavel AB, Khattri S, Leonard A, Malik K, Rose S, et al. Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab. J Allergy Clin Immunol 2019;143:142-54.
72. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. J Am Acad Dermatol 2018; 78:872-81.
73. Kamsteeg M, Jansen PA, van Vlijmen-Willems IM, van Erp PE, Rodijk-Olthuis D, van der Valk PG, et al. Molecular diagnostics of psoriasis, atopic dermatitis, allergic contact dermatitis and irritant contact dermatitis. Br J Dermatol 2010; 162:568-78.
74. Jansen PA, Kamsteeg M, Rodijk-Olthuis D, van Vlijmen-Willems IM, de Jongh GJ, Bergers M, et al. Expression of the vanin gene family in normal and inflamed human skin: induction by proinflammatory cytokines. J Invest Dermatol 2009; 129:2167-74.
75. Dietrich D, Martin P, Flacher V, Sun Y, Jarrossay D, Brembilla N, et al. Interleukin-36 potently stimulates human M2 macrophages, Langerhans cells and keratinocytes to produce pro-inflammatory cytokines. Cytokine 2016;84:88-98.
76. Keermann M, Koks S, Reimann E, Prans E, Abram K, Kingo K. Transcriptional landscape of psoriasis identifies the involvement of IL36 and IL36RN. BMC Genomics 2015;16:322.
77. Yan J. Identifying biomarkers in human psoriasis: revealed by a systems metabolomics approach. Br J Dermatol 2017;176:555-7.
78. Todorovic V, Su Z, Putman CB, Kakavas SJ, Salte KM, McDonald HA, et al. Small molecule IL-36gamma antagonist as a novel therapeutic approach for plaque psoriasis. Sci Rep 2019;9:9089.
79. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. J Exp Med 2006;203:2271-9.
80. Grewe M, Walther S, Gyufko K, Czech W, Schopf E, Krutmann J. Analysis of the cytokine pattern expressed in situ in inhalant allergen patch test reactions of atopic dermatitis patients. J Invest Dermatol 1995;105:407-10.
81. Thepen T, Langeveld-Wildschut EG, Bihari IC, van Wichen DF, van Reijsen FC, Mudde GC, et al. Biphasic response against aeroallergen in atopic dermatitis showing a switch from an initial TH2 response to a TH1 response in situ: an immunocytochemical study. J Allergy Clin Immunol 1996;97:828-37.
82. Czarnowicki T, Esaki H, Gonzalez J, Malajian D, Shemer A, Noda S, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)(+) TH2/TH1 cell imbalance, whereas adults acquire CLA(+) TH22/TC22 cell subsets. J Allergy Clin Immunol 2015;136:941-51.
83. Brunner PM, He H, Pavel AB, Czarnowicki T, Lefferdink R, Erickson T, et al. The blood proteomic signature of early-onset pediatric atopic dermatitis shows systemic inflammation and is distinct from adult long-standing disease. J Am Acad Dermatol 2019;81:510-9.
84. Garzorz-Stark N, Krause L, Lauffer F, Atenhan A, Thomas J, Stark SP, et al. A novel molecular disease classifier for psoriasis and eczema. Exp Dermatol 2016; 25:767-74.
85. Kanwar JR, Kanwar RK, Burrow H, Baratchi S. Recent advances on the roles of NO in cancer and chronic inflammatory disorders. Curr Med Chem 2009;16: 2373-94.
86. Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS, et al. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. Immunity 2009;30:576-87.
87. Grossman RM, Krueger J, Yourish D, Granelli-Piperno A, Murphy DP, May LT, et al. Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. Proc Natl Acad Sci U S A 1989;86: 6367-71.
88. Brunner PM, Suarez-Farinas M, He H, Malik K, Wen HC, Gonzalez J, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. Sci Rep 2017;7:8707.
89. Czarnowicki T, Gonzalez J, Shemer A, Malajian D, Xu H, Zheng X, et al. Severe atopic dermatitis is characterized by selective expansion of circulating TH2/TC2 and TH22/TC22, but not TH17/TC17, cells within the skin-homing T-cell population. J Allergy Clin Immunol 2015;136:104-15.
90. Januzzi JL Jr. ST2 as a cardiovascular risk biomarker: from the bench to the bedside. J Cardiovasc Transl Res 2013;6:493-500.
91. Galand C, Leyva-Castillo JM, Yoon J, Han A, Lee MS, McKenzie ANJ, et al. IL-33 promotes food anaphylaxis in epicutaneously sensitized mice by targeting mast cells. J Allergy Clin Immunol 2016;138:1356-66.
92. Vocca L, Di Sano C, Uasuf CG, Sala A, Riccobono L, Gangemi S, et al. IL-33/ST2 axis controls Th2/IL-31 and Th17 immune response in allergic airway diseases. Immunobiology 2015;220:954-63.
93. Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. J Allergy Clin Immunol 2017;139:1723-34.
94. Kim BE, Leung DY. Significance of skin barrier dysfunction in atopic dermatitis. Allergy Asthma Immunol Res 2018;10:207-15.
95. Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. J Allergy Clin Immunol 2014; 134:769-79.
96. Cole C, Kroboth K, Schurch NJ, Sandilands A, Sherstnev A, O'Regan GM, et al. Filaggrin-stratified transcriptomic analysis of pediatric skin identifies mechanistic pathways in patients with atopic dermatitis. J Allergy Clin Immunol 2014;134: 82-91.

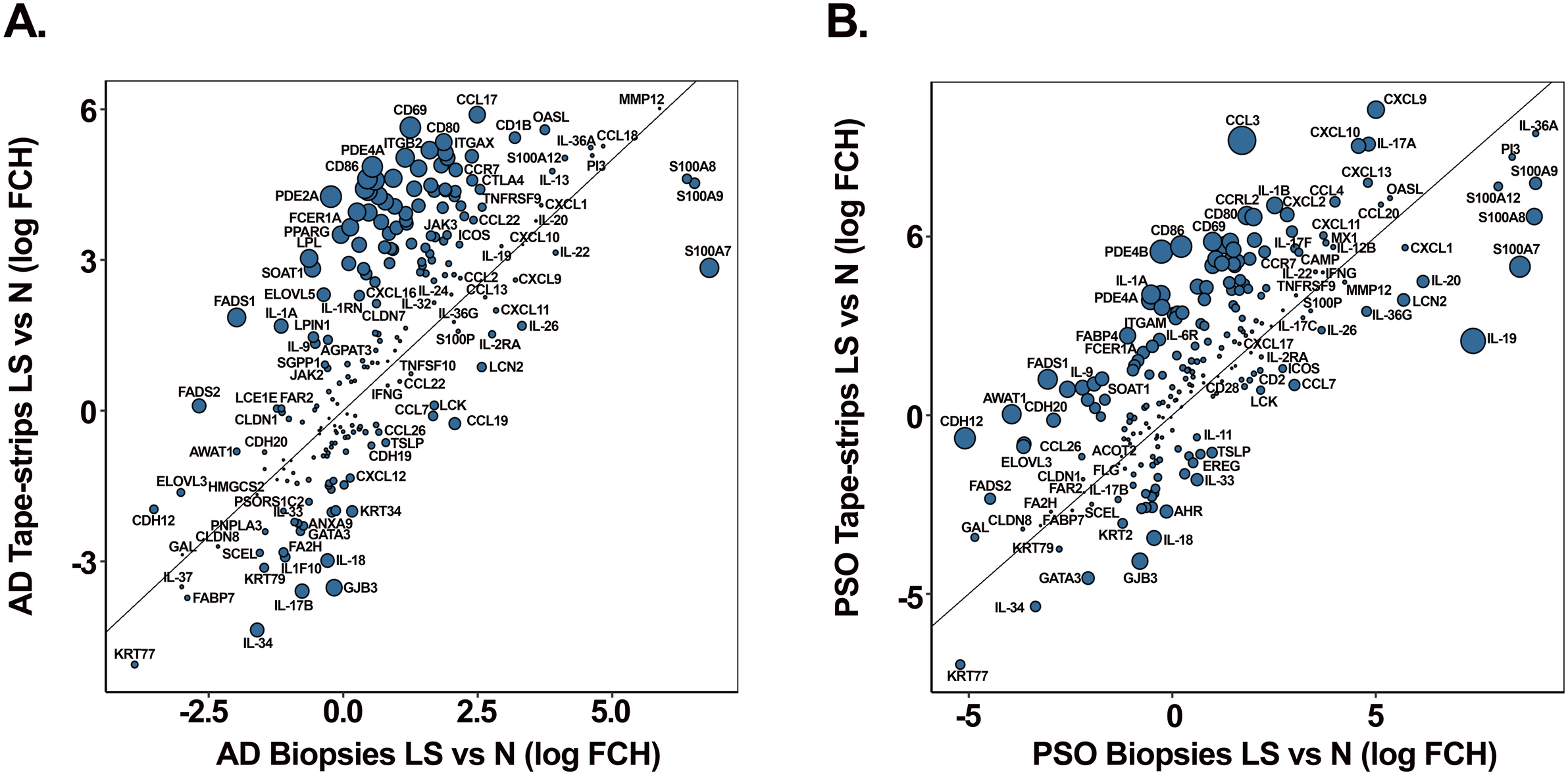
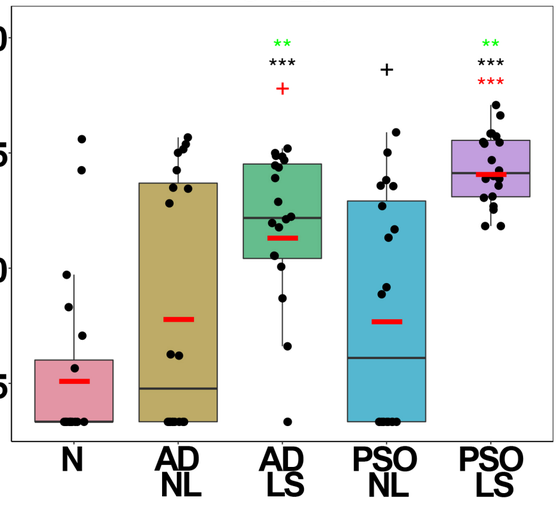

A.
AD Tape-strips LS vs N (log FCH)
AD Biopsies LS vs N (log FCH)
B.
PSO Tape-strips LS vs N (log FCH)
PSO Biopsies LS vs N (log FCH)
C.
AD Tape-strips NLvs N (log FCH)
AD Biopsies NL vs N (log FCH)
D.
PSO Tape-strips NLvs N (log FCH)
PSO Biopsies NL vs N (log FCH)

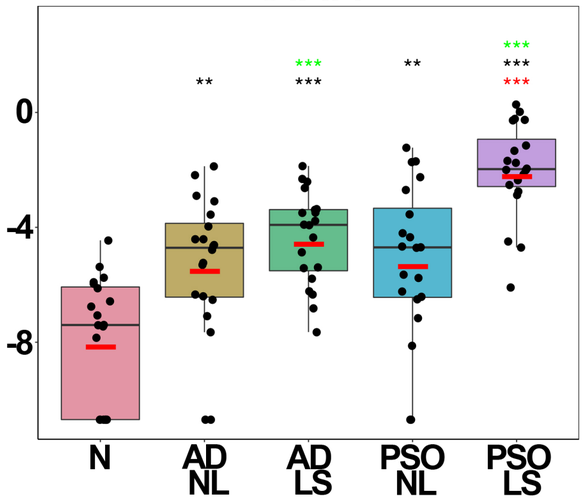
Figure E1

Th1

CCL5

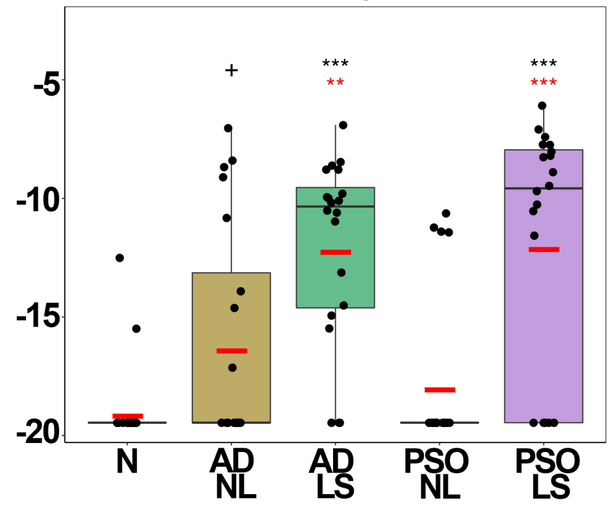


STAT1

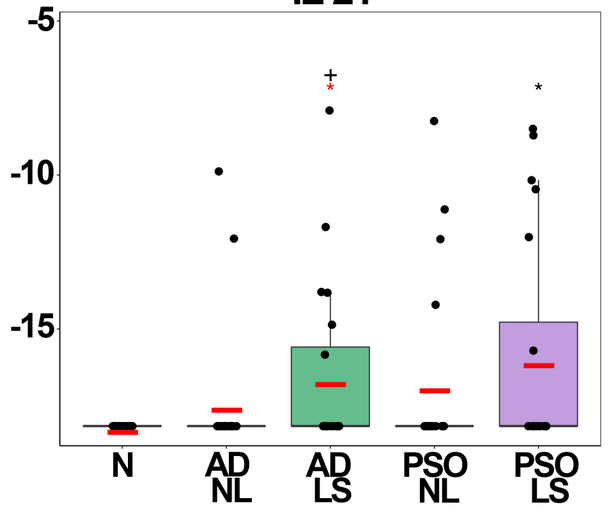


Th17

IL-20

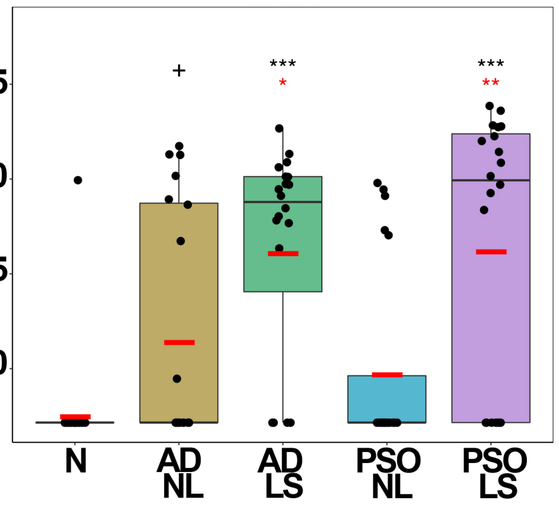


IL-21

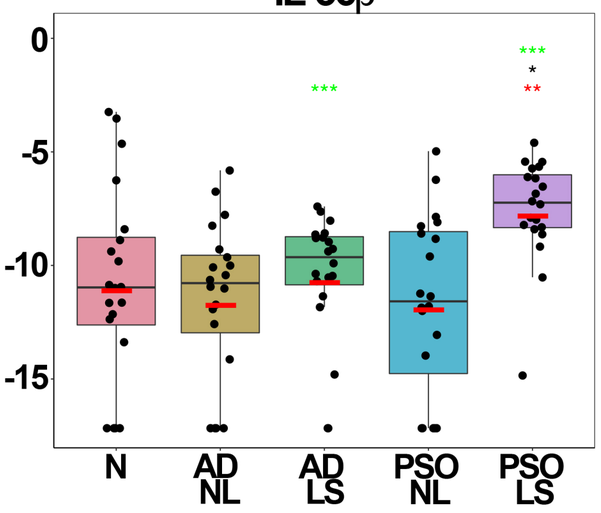


Th17

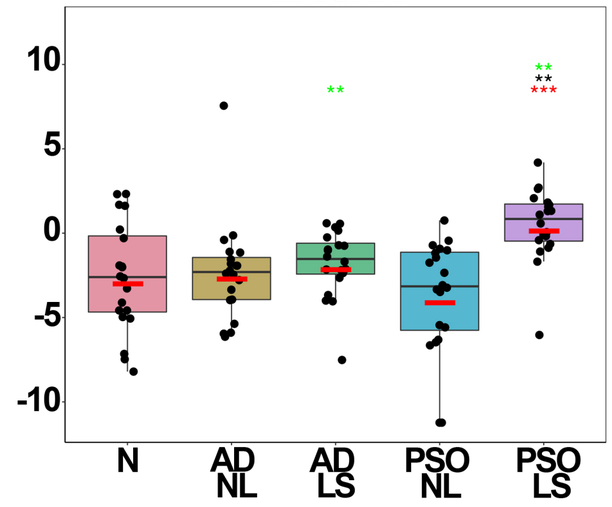
IL-26



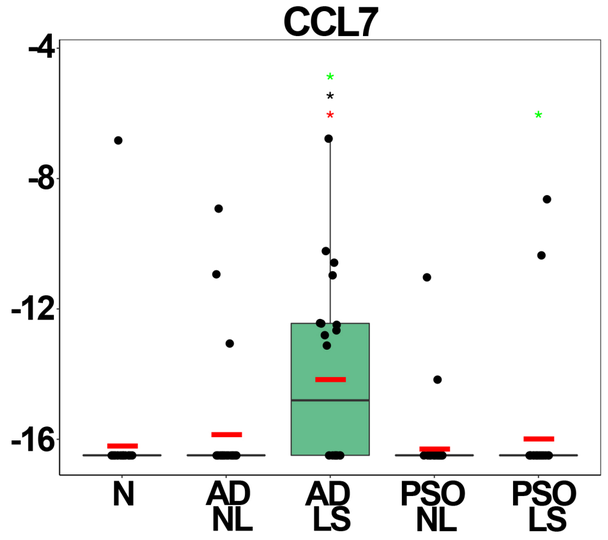
IL-36β



IL-36RN

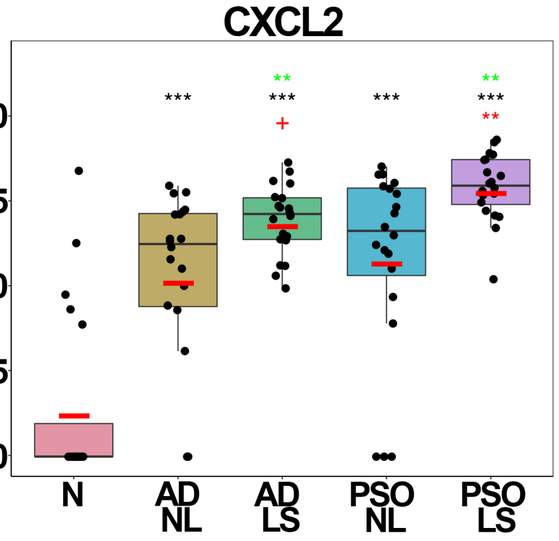


CCL7

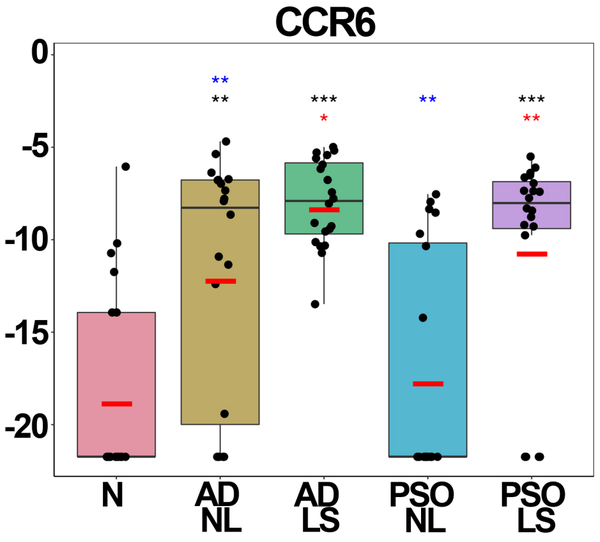


Th17

CXCL2

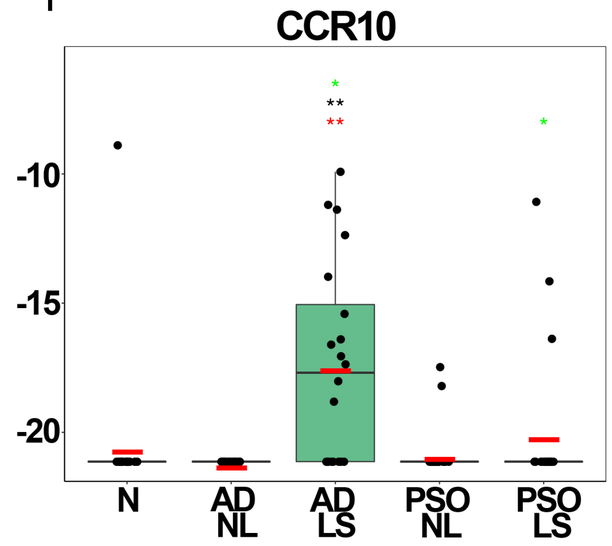


CCR6



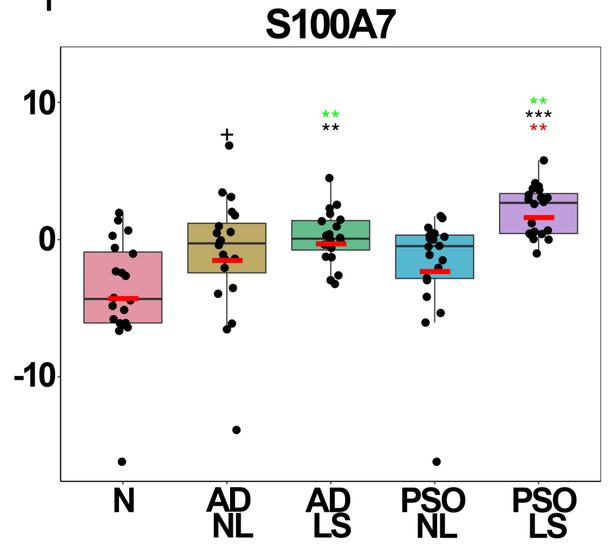
Th22

CCR10



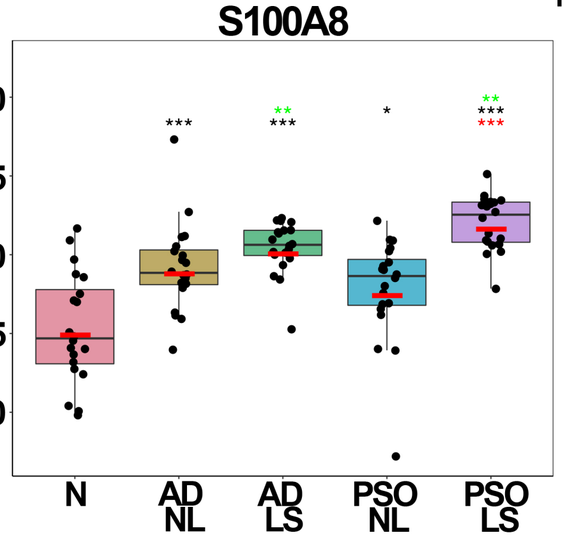
Th17/Th22

S100A7



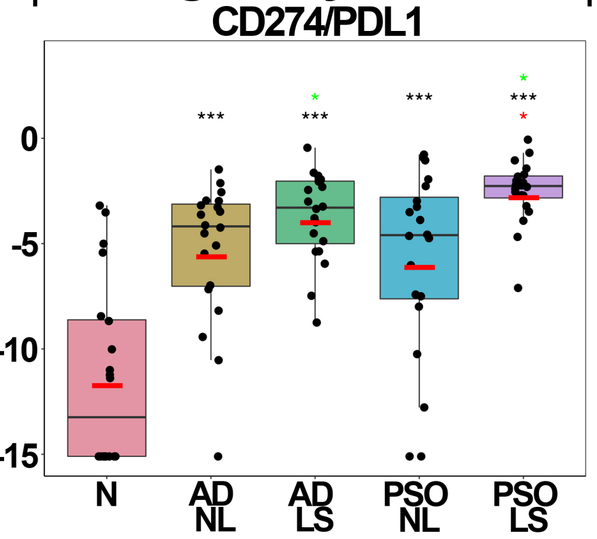
Th17/Th22

S100A8



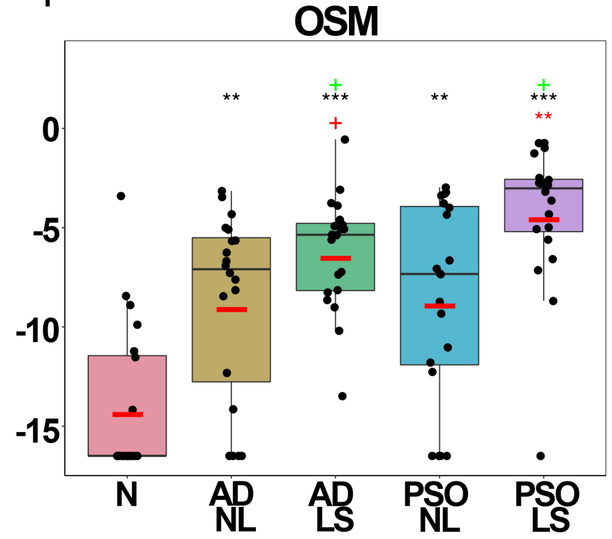
Regulatory Marker

CD274/PDL1

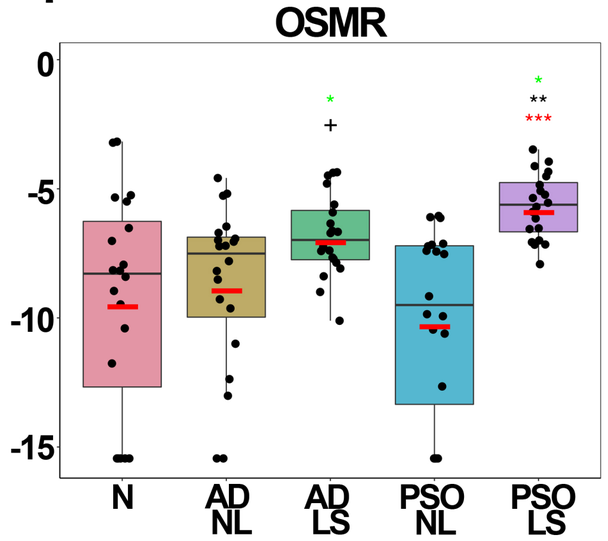


Markers of pruritus

OSM

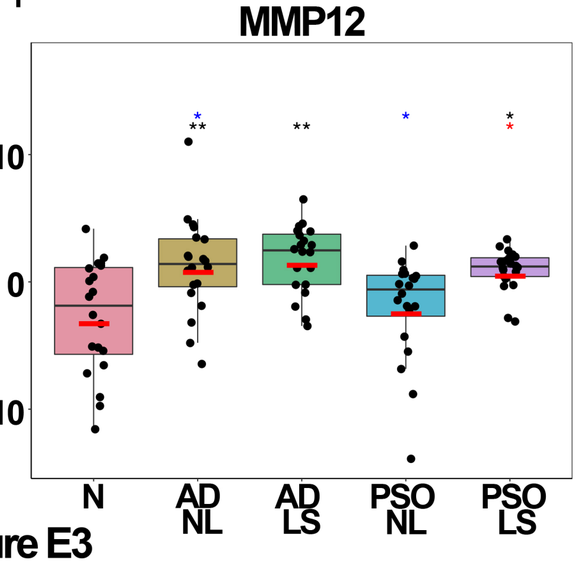


OSMR



General Inflammation

MMP12



PDE4B

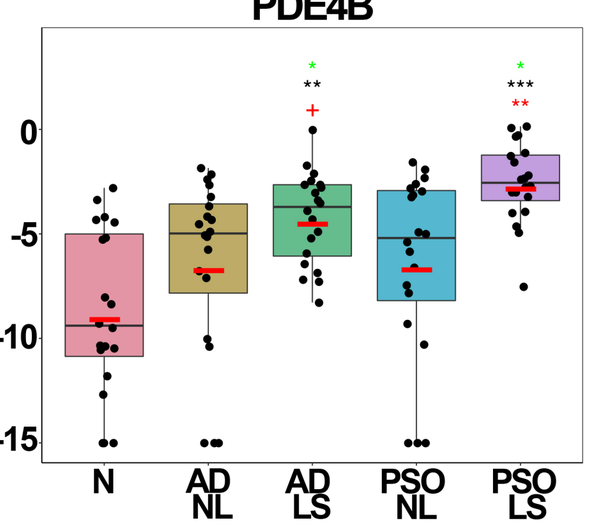
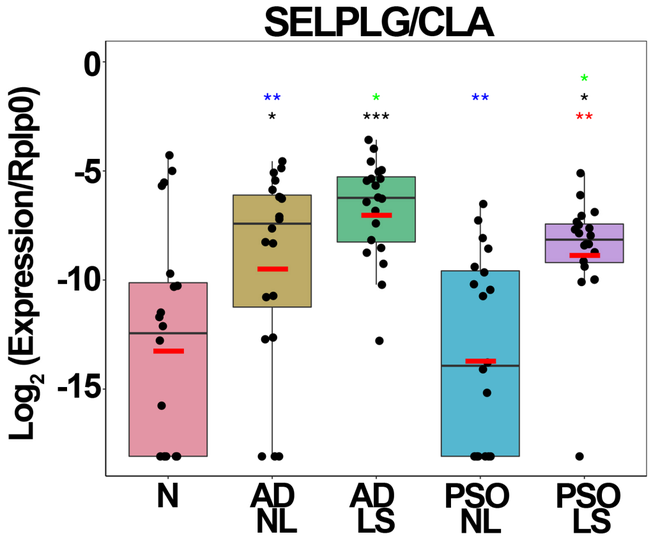


Figure E3

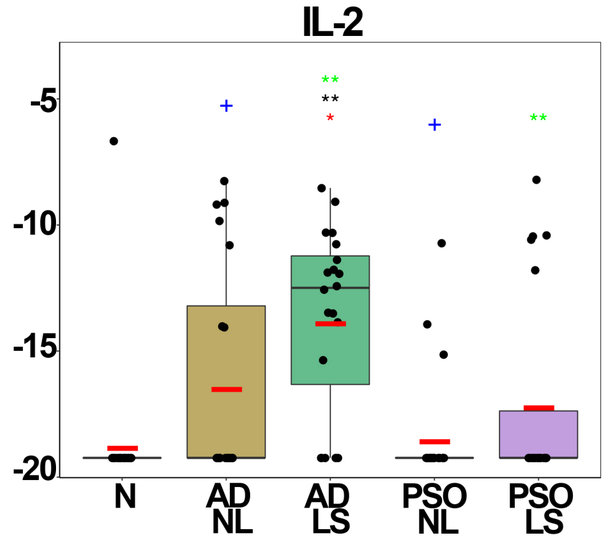
Skin Homing

SELPLG/CLA

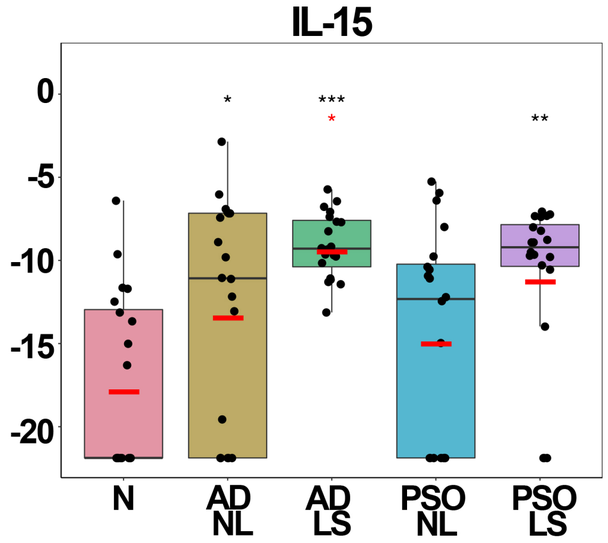


T-Cell/NK/T-Cell Activation

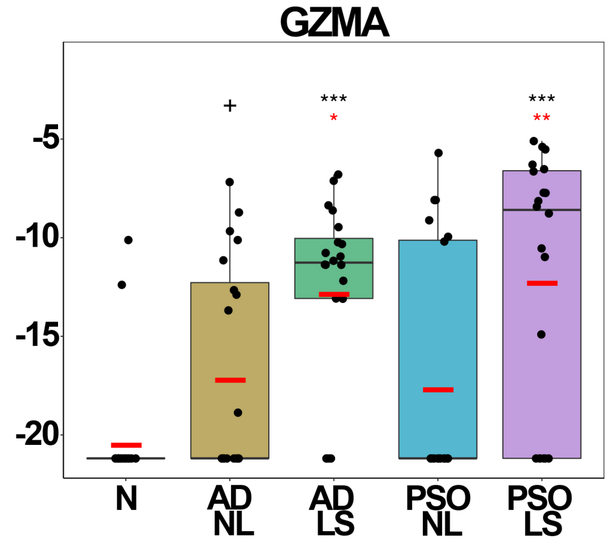
IL-2



IL-15

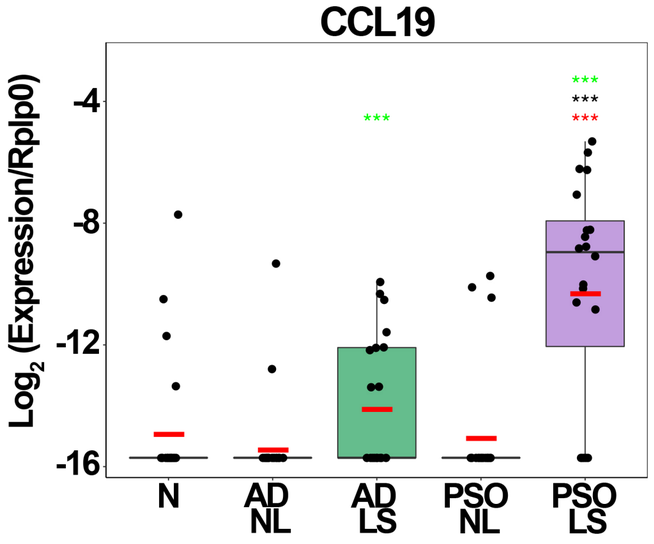


GZMA



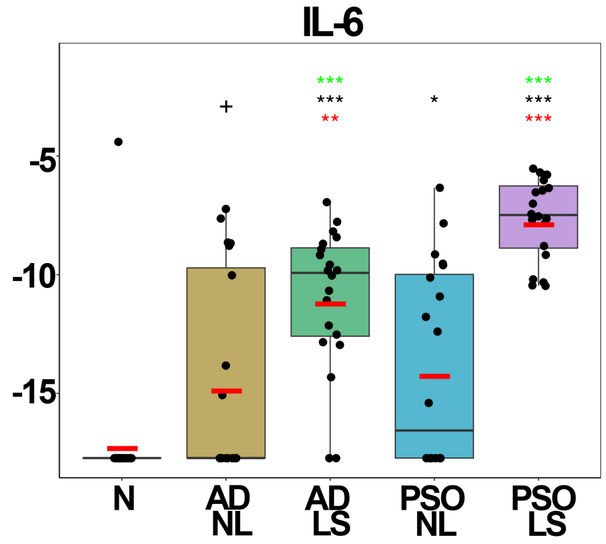
T cell migration

CCL19

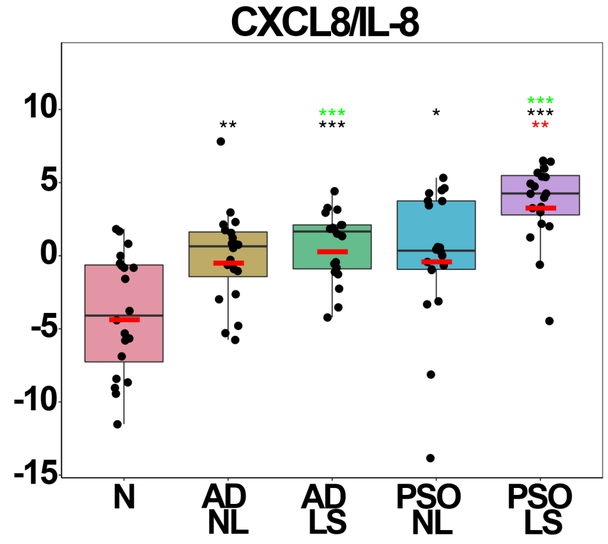


Innate Immunity

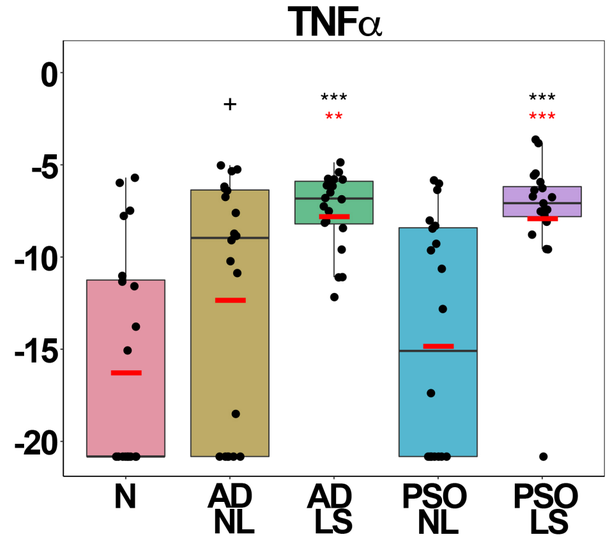
IL-6



CXCL8/IL-8

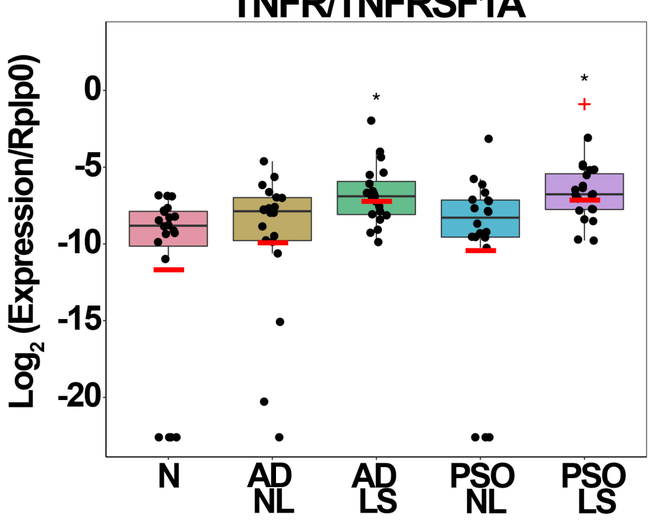


TNFα



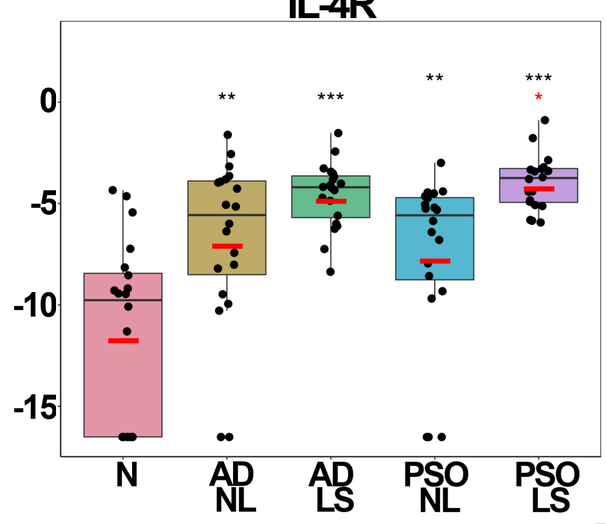
Innate Immunity

TNFR/TNFRSF1A

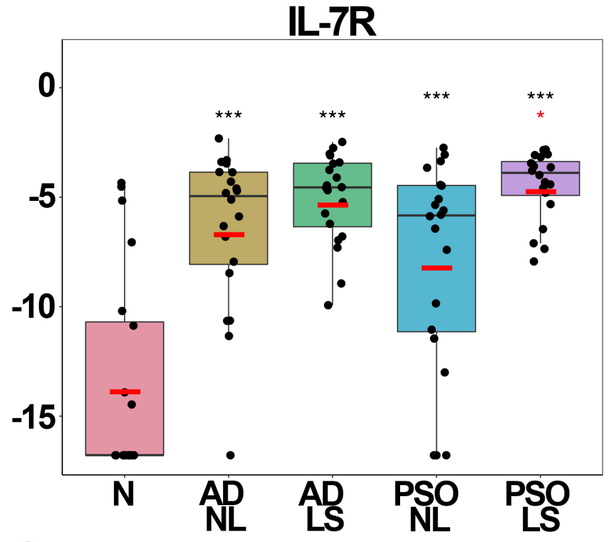


Th2

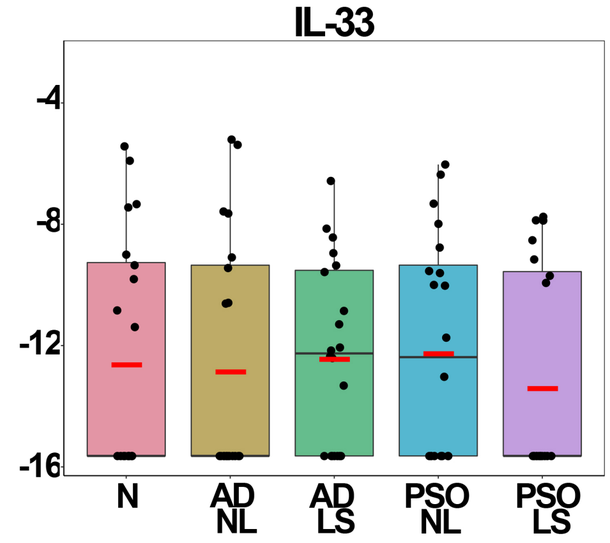
IL-4R



IL-7R

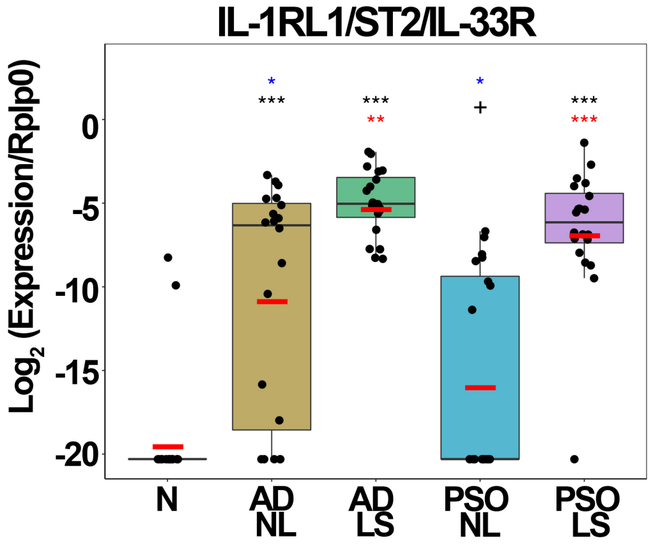


IL-33

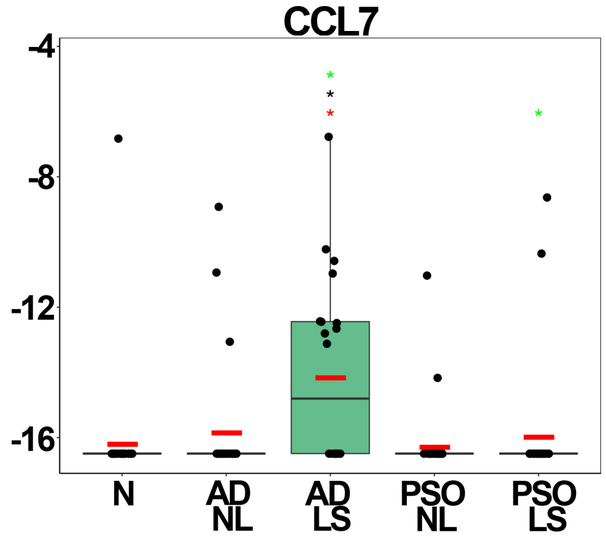


Th2

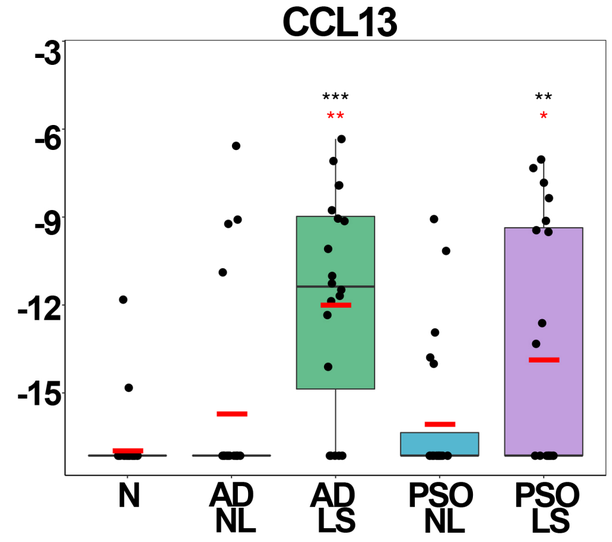
IL-1RL1/ST2/IL-33R



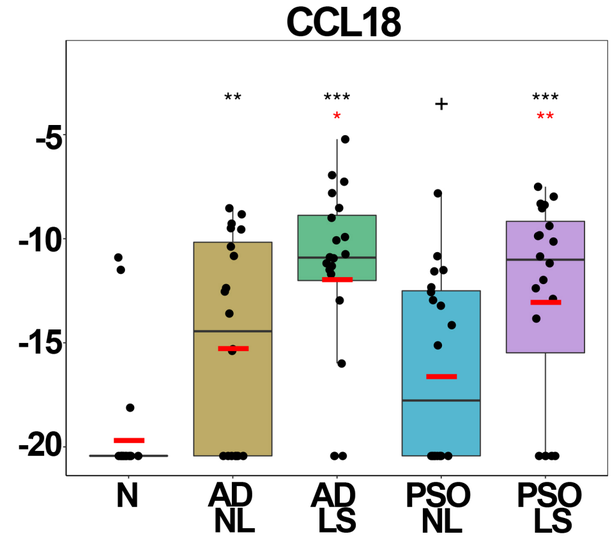
CCL7



CCL13

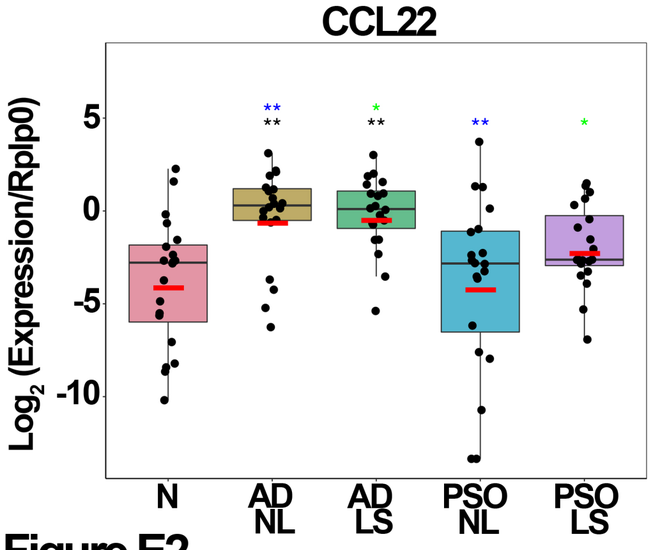


CCL18

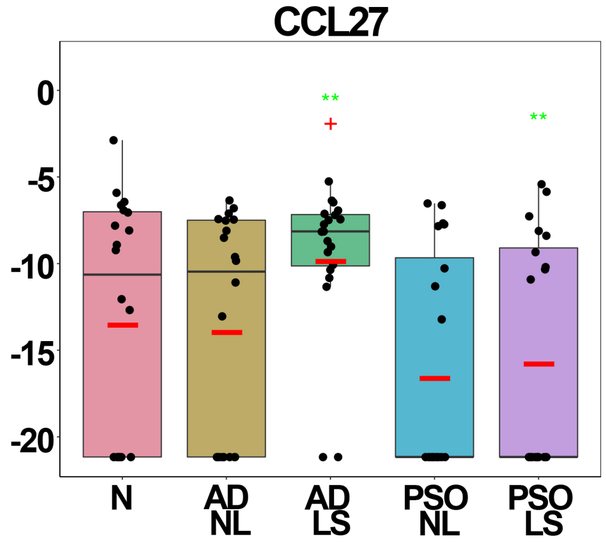


Th2

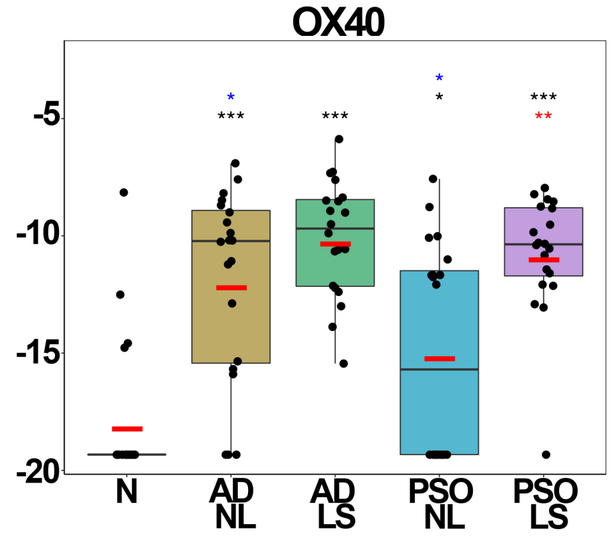
CCL22



CCL27



OX40



Th1

CXCL10

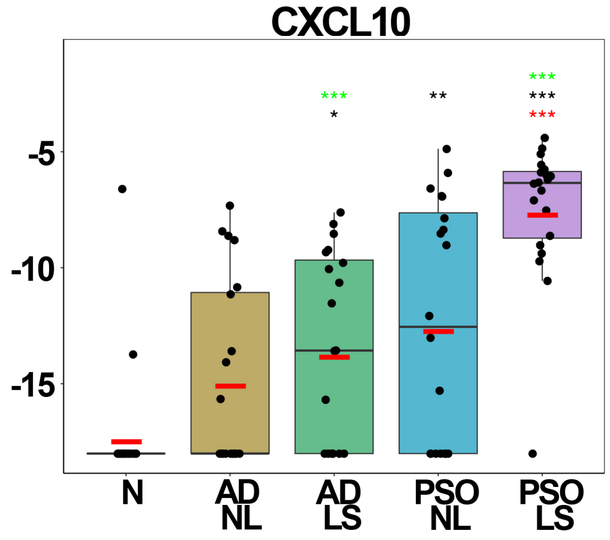


Figure E2

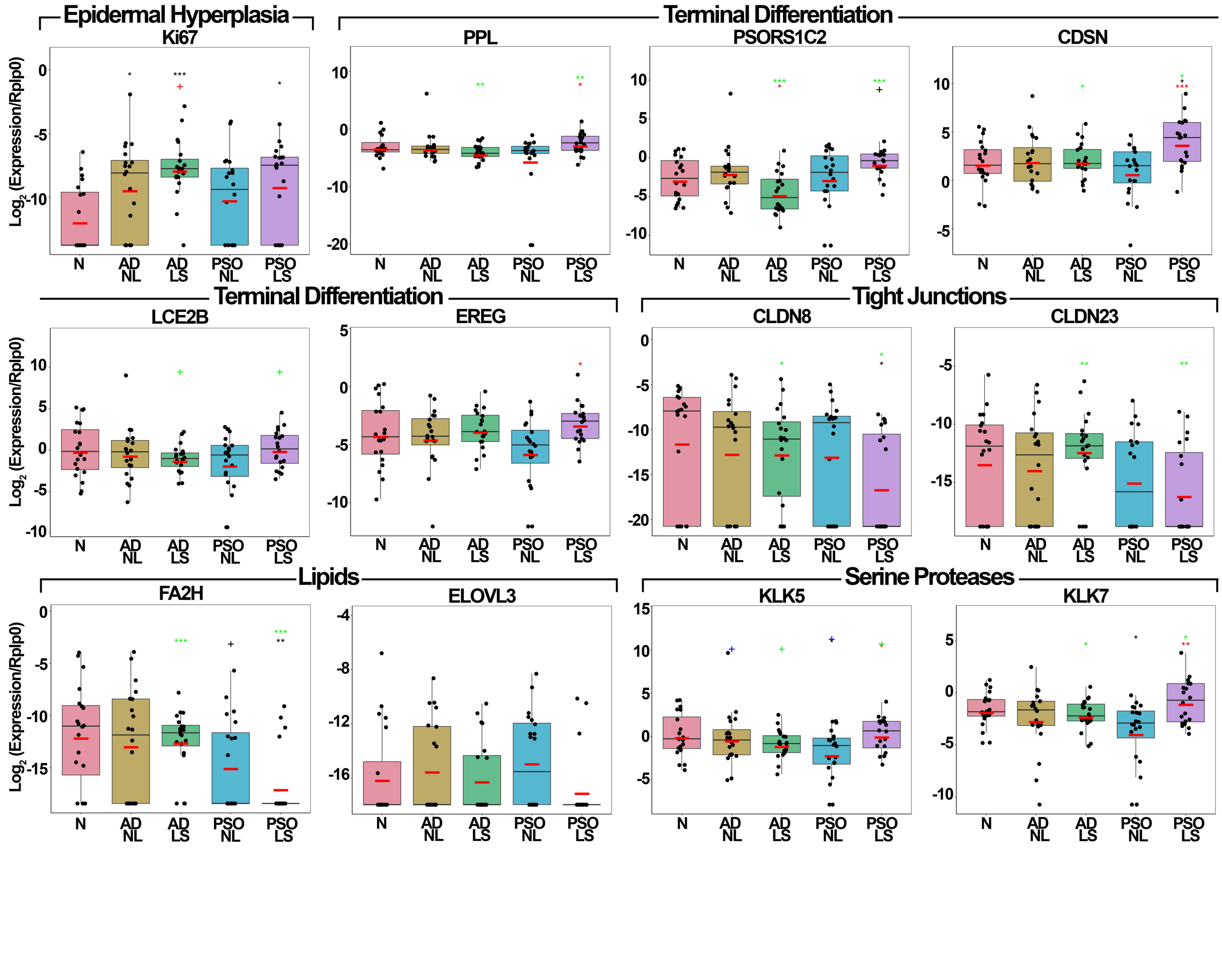

Epidermal Hyperplasia
Ki67
Terminal Differentiation
PPL
PSORS1C2
CDSN
Terminal Differentiation
LCE2B
EREG
Tight Junctions
CLDN8
CLDN23
Lipids
FA2H
ELOVL3
Serine Proteases
KLK5
KLK7
Log2 (Expression/Rplp0)
N
AD NL
AD LS
PSO NL
PSO LS

Figure E4

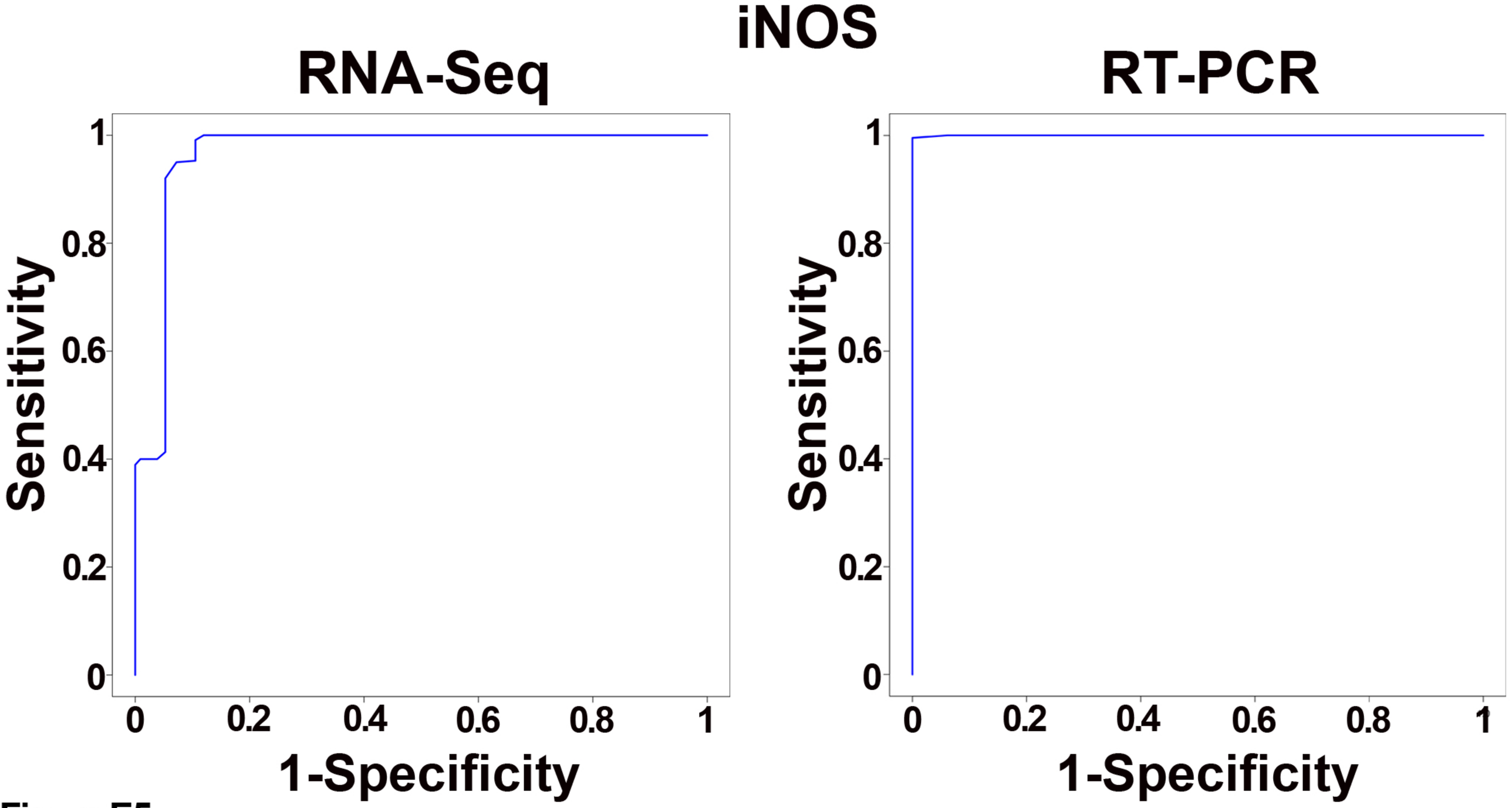


Figure E5

SUPPLEMENTARY TEXT

Tape-strip collection, RNA extraction, qRT-PCR and RNA-sequencing

Twenty consecutive large D-Squame (CuDerm, Dallas, TX) were collected from lesional and non-lesional skin. Each large D-Squame (D102) tape-strip was applied for a few seconds to the antecubital fossa when possible for lesional skin, and nearby skin that was at least 10 cm away was collected for non-lesional skin. Tape-strips were applied with pressure with the Cu-derm pressurizer device (D500), utilizing the plunger mechanism to ensure even and consistent pressure application to each tape-strip. After pressure is applied and released, tape-strips were transported by gloved hands, and stuck onto the D-Squame Standard storage cards (D120). Using a pen, small marks were made on the skin after placement of the first tape-strip to ensure consistent placement of each subsequent tape-strip. Cards were immediately stored on dry ice in biohazard specimen bags and then transferred to an -80□C freezer until time for shipment. The tapes were pooled together and thoroughly washed with QIAzol for RNA extraction using miRNAeasy Mini Kit.

Table E1. 99 immune and barrier primers used for qRT-PCR.

Gene	Assay ID	Gene	Assay ID
CAMP/LL37	Hs00189038_m1	IL-10	Hs00961622_m1
CCL2	Hs00234140_m1	IL-12/IL-23p40	Hs01011518_m1
CCL5	Hs00174575_m1	IL-13	Hs00174379_m1
CCL7	Hs00171147_m1	IL-15	Hs01003716_m1
CCL13	Hs00234646_m1	IL-17A	Hs00174383_m1
CCL17	Hs00171074_m1	IL-17C	Hs00171163_m1
CCL18	Hs00268113_m1	IL-17F	Hs00369400_m1
CCL19	Hs00171149_m1	IL-19	Hs00604657_m1
CCL20	Hs00355476_m1	IL-20	Hs00218888_m1
CCL22	Hs01574247_m1	IL-21	Hs00222327_m1
CCL26	Hs00171146_m1	IL-22	Hs01574154_m1
CCL27	Hs04399123_g1	IL-23p19	Hs00900828_g1
CCR4	Hs99999919_m1	IL-26	Hs00218189_m1
CCR6	Hs01890706_s1	IL-31	Hs01098710_m1
CCR7	Hs01013469_m1	IL-33	Hs04931857_m1
CCR10	Hs00706455_s1	IL-34	Hs01050926_m1
CD3	Hs00174158_m1	IL-36A	Hs00205367_m1
CD207/Langerin	Hs00210453_m1	IL-36B	Hs00758166_m1
CD209/DC-SIGN	Hs01588349_m1	IL-36G	Hs00219742_m1
CDSN	Hs00169911_m1	IL-36RN	Hs01104220_g1
CLA/CD162	Hs05033974_s1	IL-37	Hs00367201_m1
CLDN8	Hs04186769_s1	ITGAM/CD11b	Hs00167304_m1
CLDN23	Hs01013638_s1	ITGAX/CD11c	Hs00174217_m1
CSF1/M-CSF	Hs00174164_m1	Ki67	Hs04260396_g1
CXCL1	Hs00236937_m1	KLK5	Hs01548153_m1
CXCL2	Hs00601975_m1	KLK7	Hs00192503_m1
CXCL9	Hs00171065_m1	KRT16	Hs00955082_g1
CXCL10	Hs01124252_g1	LCE2B	Hs04194422_s1
DEFB4B	Hs00823638_m1	LOR	Hs01894962_s1
ELOVL3	Hs00537016_m1	MMP12	Hs00159178_m1
EREG	Hs00914313_m1	iNOS (NOS2)	Hs01075529_m1
FA2H	Hs00757813_m1	OSM	Hs00171165_m1
FceR1A	Hs00175408_m1	OSMR	Hs00384276_m1
FLG	Hs00856927_g1	OX40 (TNFRSF4)	Hs00937194_g1
FLG2	Hs00418578_m1	OX40L (TNFSF4)	Hs04400731_m1
FOXP3	Hs01085834_m1	PDE4B	Hs00963643_m1
GZMA	Hs00989184_m1	PDL1 (CD274)	Hs00204257_m1

ICOS	Hs00359999_m1	PI3	Hs00160066_m1
IFN-γ	Hs00989291_m1	PPL	Hs00160312_m1
IL-1β	Hs00174097_m1	PSORS1C2	Hs00204152_m1
IL-1RL1/IL-33R/ST2	Hs00249384_m1	S100A7	Hs01923188_u1
IL-2	Hs00174114_m1	S100A8	Hs00374264_g1
IL-3	Hs00174117_m1	S100A9	Hs00610058_m1
IL-3RA/CD123	Hs00608141_m1	S100A12	Hs00942835_g1
IL-4	Hs00174122_m1	SERPINB3	Hs00199468_m1
IL-4R	Hs00965056_m1	STAT1	Hs01013996_m1
IL-5	Hs01548712_g1	STAT3	Hs00374280_m1
IL-6	Hs00985639_m1	TNF	Hs01113624_g1
IL-7R	Hs00233682_m1	TNFR	Hs01042313_m1
IL-8	Hs00174103_m1		

qRT-PCR, quantitative real-time polymerase chain reaction

Table E3. Clinical correlations of biomarkers in lesional tape-stripped skin.

Atopic Dermatitis					
Investigator's Global Assessment			**Total Sign Score**		
Markers	***r***	***P* value**	**Markers**	***r***	***P* value**
IL-26	0.621	0.003	IL-17F	0.614	0.004
IL-13	0.607	0.005	IL-13	0.569	0.009
CCL5	0.511	0.021	CAMP/LL37	0.568	0.009
IL-22	0.495	0.026	IL-26	0.545	0.013
FOXP3	0.481	0.032	IL-20	0.536	0.015
IL-20	0.456	0.043	FOXP3	0.490	0.028
CD209/DC-SIGN	0.452	0.045	CD209/DC-SIGN	0.484	0.031
IL-6	0.429	0.059	IL-19	0.482	0.031
IL-17F	0.419	0.066	CCL26	0.437	0.045
CAMP/LL37	0.413	0.071	CXCL1	0.434	0.047
S100A7	0.389	0.090	IL-6	0.421	0.054
CXCL1	0.377	0.101	IL-1B	0.420	0.056
TNF	0.377	0.101	ICOS	0.416	0.057
IL-12/IL-23p40	0.360	0.119	IL-22	0.410	0.064
			MMP12	0.403	0.065
			CCL17	0.403	0.066
			CCL5	0.378	0.068
			FCER1A	0.377	0.073
			TNFR	0.369	0.078
			IL-7R	0.364	0.078
			OSM	0.359	0.100
			ITGAX/CD11c	0.354	0.101
			CSF1/M-CSF	0.346	0.109
			OX40	0.338	0.115
			CLDN23	-0.419	0.066
			FA2H	-0.432	0.057
			IL-34	-0.449	0.047
Psoriasis					
Physician's Global Assessment			**Target Lesion Severity Score**		
Markers	***r***	***P* value**	**Markers**	***r***	***P* value**
IL-12/IL-23p40	0.576	0.008	FOXP3	0.443	0.023
FCER1A	0.454	0.044	ITGAX/CD11c	0.341	0.037
FOXP3	0.336	0.147	CCR6	0.339	0.051
			OX40L	0.331	0.078
			CCL7	0.315	0.111
			IL-21	0.290	0.121

r correlation coefficient

SUPPLEMENTARY FIGURE LEGENDS

FIG E1. Tape-strips versus biopsies. Scatter plots depict RNA-seq log2 fold-changes (log FCH) for lesional skin versus controls (LS vs N) for (A) atopic dermatitis (AD) and (B) psoriasis (PSO), and non-lesional skin versus controls (NL vs N) for (C) atopic dermatitis (AD) and (D) psoriasis (PSO), between tape-strips from this study and biopsies from a previously published similarly severe cohort. The size of the circle represents the absolute difference (in log2 fold-change) for each diseased group versus controls.

FIG E2. Immune biomarkers. Fold changes of immune mediators from multiple pathways detected in lesional (LS) and non-lesional (NL) tape stripped skin of atopic dermatitis (AD) and psoriasis (PSO); as well as healthy tape-stripped skin as measured by quantitative real-time PCR. *Black symbols*: significance of comparison to normal (N)*; red symbols:* significance of comparison between lesional and non-lesional tape stripped skin; *colored symbols*: significance of comparison between respective groups. ***P<0.001, **P<0.01, *P<0.05, ^{+}P<0.1

FIG E3. Additional inflammatory markers. Fold changes of immune mediators from multiple pathways detected in lesional (LS) and non-lesional (NL) tape stripped skin of atopic dermatitis (AD) and psoriasis (PSO); as well as healthy tape-stripped skin as measured by quantitative real-time PCR. *Black symbols*: significance of comparison to normal (N)*; red symbols:* significance of comparison between lesional and non-lesional

tape stripped skin; *colored symbols*: significance of comparison between respective groups. ***P<0.001, **P<0.01, *P<0.05, ^{+}P<0.1

FIG E4. Epidermal barrier markers. Fold changes of barrier markers detected in lesional (LS) and non-lesional (NL) tape stripped skin of atopic dermatitis (AD) and psoriasis (PSO); as well as healthy tape-stripped skin as measured by quantitative real-time PCR. *Black symbols*: significance of comparison to normal (N)*; red symbols:* significance of comparison between lesional and non-lesional tape stripped skin; *colored symbols*: significance of comparison between respective groups. ***P<0.001, **P<0.01, *P<0.05, ^{+}P<0.1

FIG E5. Area under the receiver operating characteristic curve (ROC AUC) in tape strips. We identified iNOS (NOS2) as a molecular classifier that accurately discriminates between AD and psoriasis using RNA Sequencing (AUC = 0.97) and real-time PCR (AUC = 1) platforms. *RNA-seq*, RNA-sequencing; *RT-PCR*, real-time polymerase chain reaction; *AD*, atopic dermatitis.