The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased T_H17 polarization

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Background: Atopic dermatitis (AD) shows very high prevalence in Asia, with a large unmet need for effective therapeutics. Direct comparisons between European American (EA) and Asian patients with AD are unavailable, but earlier blood studies detected increased IL-17$^+$–producing cell counts in Asian patients with AD.

Objective: We sought to characterize the Asian AD skin phenotype and compare it with the EA AD skin phenotype.

Methods: We performed genomic profiling (real-time PCR) and immunohistochemistry on lesional and nonlesional biopsy specimens from 52 patients with AD (25 EAs and 27 Asians), 10 patients with psoriasis (all EAs), and 27 healthy subjects (12 EAs and 15 Asians).

Results: Although disease severity/SCORAD scores were similar between the AD groups (58.0 vs 56.7, $P = .77$), greater acanthosis, higher Ki67 counts, and frequent parakeratosis were characteristics of lesional epidermis from Asian patients with AD ($P < .05$). Most (24/27) Asian patients had high IgE levels. A principal component analysis using real-time PCR data clustered the Asian AD phenotype between the EA AD and psoriasis phenotypes. T_H2 skewing characterized both Asian and EA patients with AD but not patients with psoriasis. Significantly higher T_H17 and T_H22 (*IL17A*, *IL19*, and *S100A12* in lesional and IL-22 in nonlesional skin; $P < .05$) and lower T_H1/interferon (*CXCL9*, *CXCL10*, *MX1*, and *IFNG* in nonlesional skin; $P < .05$) gene induction typified AD skin in Asian patients.

Conclusion: The Asian AD phenotype presents (even in the presence of increased IgE levels) a blended phenotype between that of EA patients with AD and those with psoriasis, including increased hyperplasia, parakeratosis, higher T_H17 activation, and a strong T_H2 component. The relative pathogenic contributions of the T_H17 and T_H2 axes in creating the Asian AD phenotype need to be tested in future clinical trials with appropriate targeted therapeutics. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Atopic dermatitis, T_H1, T_H2, T_H17, T_H22, acanthosis, parakeratosis, psoriasis, Asian, European American*

Atopic dermatitis (AD) is the most common inflammatory skin disease,[1] with a prevalence of 3% to 10%[2-5] and a large unmet need for effective therapeutics.[6] Increased IgE levels are found in approximately 80% ("extrinsic") and normal IgE levels ("intrinsic") are detected in 20% of patients with AD.[7] AD and psoriasis, another common skin disease, are recognized as polar inflammatory skin diseases.[8] With evolving molecular phenotyping, psoriasis is emerging as an IL-23/T_H17–skewed disease, whereas AD is considered a T_H2-centered disease, both sharing a common T_H22 component.[9-12] These distinctions are highly relevant to emerging therapies because psoriasis responds remarkably well to IL-23/IL-17 antagonists,[13-16] whereas AD responds to T_H2 antagonists.[17,18]

To date, the characterization of AD in different populations has made the assumption that disease mechanisms are similar across different populations. However, some findings potentially negate a unified pathogenic model. We have shown distinct differences in patients with intrinsic versus extrinsic AD, as judged by skin profiling.[10] In patients with intrinsic AD, we detected significantly increased expression of *IL12B* (p40), *IL17A*, *IL22*, and respective keratinocyte-induced products (ie, S100As), whereas similar expression of T_H2-related products

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Supported by a research grant (EGY) from Leo Pharma. S.N., B.U., M.S.-F., and J.G.K. were supported by grant no. 5UL1RR024143-02 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research. S.N. was supported in part by grant no. UL1 TR000043 from the National Center for Advancing Translational Sciences (NCATS), NIH Clinical and Translational Science Award (CTSA) program.

Disclosure of potential conflict of interest: S. Noda has received research support from the CTSA program. C. de Guzman Strong has received research support from the National Institutes of Health (NIH; R01 AR065523). J. G. Krueger has received research support (grants paid to his institution) and personal fees from Novartis, Pfizer, Janssen, Lilly, Merck, Kadmon, Dermira, Boehringer, BMS, and Paraxel during the conduct of the study and has received research support (grants paid to his institution) from Amgen, Innovaderm, and Kyowa and personal fees from Serono, BiogenIdec, Delenex, AbbVie, Sanofi, Baxter, Xenoport, and Kineta. E. Guttman-Yassky is a board member for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, Medimmune, Celgene, Anacor, and Leo Pharma; has received consultancy fees from Regeneron, Sanofi Aventis, Medimmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, and Drais; and has received research support from Regeneron, Celgene, BMS, and Janssen. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 9, 2015; revised August 17, 2015; accepted for publication August 18, 2015.

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0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2015.08.015

Abbreviations used
AD: Atopic dermatitis
DC: Dendritic cell
EA: European American
FCH: Fold change
FLG: Filaggrin
IHC: Immunohistochemistry
LC: Langerhans cell
PCA: Principal component analysis
RT-PCR: Real-time PCR
STAT1: Signal transducer and activator of transcription 1

was observed in both patients with extrinsic and those with intrinsic AD[10]; indeed, these subtypes show similar responses to IL-4 receptor antagonism.[17,18]

Although a direct comparison is unavailable, a few findings suggest that Asian patients with AD might have different phenotypic characteristics. In Asia there is a much higher prevalence of AD in adults (7% to 10%),[19-21] and prominent T_H17 activation has been observed in blood and acute AD skin lesions.[22] In contrast, no increases were seen in IL-17 activation in European American (EA) patients with extrinsic AD.[10,11,23] Thus we sought to directly compare AD in EA and Asian (Japanese and Korean) AD populations, focusing mainly on extrinsic subsets and with a comparison with psoriasis vulgaris. Our report classifies the Asian AD phenotype as a mixed phenotype between the EA AD and psoriasis phenotypes, with highly atypical features for AD, including parakeratosis and a unique cytokine profile with coactivation of the T_H2 and T_H17 axes. The relative pathogenic contributions of the T_H2 versus T_H17 axes in Asian patients with AD will need to be established through clinical trials with pathway-selective antagonists.[17,18]

METHODS

Skin samples

We included several cohorts of EA patients with AD (n = 25) and psoriasis (n = 10) previously published by our group,[24-26] as well as 27 East Asian patients with AD (12 Japanese and 15 Korean), which we refer to as the Asian AD patients throughout the article. Fifteen Asian (7 Japanese and 8 Korean) and 12 EA healthy control subjects were included for comparison. Japanese and Korean AD samples were obtained from patients with AD living in their respective countries. Lesional and nonlesional (>10 cm from active lesions) AD skin biopsy specimens were collected for these studies from areas with representative AD lesions (example shown in Fig E1 in this article's Online Repository at www.jacionline.org) under institutional review board–approved protocols, according to the Declaration of Helsinki principles. Nonlesional samples were unavailable from 7 Japanese patients with AD. Patients were allowed to use emollients only and avoided using systemic immunomodulators and phototherapy within the prior 4 weeks and topical steroids or calcineurin inhibitors within the prior 8 days. Patients were stratified into extrinsic (24 in Asian patients with AD and 14 in EA patients with AD) and intrinsic AD categories, with IgE levels of greater than 200 kU/L defining extrinsic AD and values of less than 200 kU/L defining intrinsic AD. No heterozygous filaggrin (FLG) mutations (R501X and 2282del4 allele) were found in any Korean patients with AD (all with extrinsic AD) and 6 EA patients with AD (1 with extrinsic and 5 with intrinsic AD, see Table E1 in this article's Online Repository at www.jacionline.org). The FLG mutation status was unavailable for the rest of the patients and healthy control subjects. Patients' characteristics are summarized in Table I, and the whole patient list is available in Table E1.

Quantitative real-time PCR

RNA was extracted for real-time PCR (RT-PCR) with EZ-PCR Core Reagents (Life Technologies, Grand Island, NY). Reverse transcription to cDNA from RNA was carried out by using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, Calif). cDNA was amplified with TaqMan PreAmp Master Mix (Applied Biosystems), and the preamplified cDNA product was analyzed with TaqMan Gene Expression Master Mix. The primers used in this study are listed in Table E2 in this article's Online Repository at www.jacionline.org. Expression values were normalized to human acidic ribosomal protein *(hARP)*. Although data have been published on the EA AD cohort,[25] tissue samples from these patients were run together with all other samples for RT-PCR, eliminating a batch effect. RNA samples were unavailable from 1 EA patient and 2 Japanese patients with AD and 4 Korean, 3 Japanese, and 4 EA healthy subjects.

Immunohistochemistry

Immunohistochemistry (IHC) was performed on frozen skin sections. The antibodies used in this study are listed in Table E3 in this article's Online Repository at www.jacionline.org. Epidermal thickness and positive cells per millimeter were quantified for IHC by using ImageJ V1.42 software (National Institutes of Health, Bethesda, Md). Skin tissue was unavailable for IHC from lesional samples of 2 Japanese patients with AD and samples of 2 Korean healthy subjects.

Statistical analysis

All analyses were carried out with the statistical language R (www.R-project.org).

The RT-PCR values normalized to human acidic ribosomal protein were transformed to the $\log_2$ scale. Both expression values (in $\log_2$) and cell counts were modeled by using a linear mixed-effects model with a fixed effect for tissue and ethnicity and patient as a random effect. Once the model was estimated, the comparisons of interests were tested by using contrast/*lsmeans*. Data are presented as (least squares) means and 95% CIs. Similar approaches were used in the subgroup analysis including only extrinsic patients.

For the RT-PCR data, principal component analysis (PCA) was carried out by using 25 variables and 129 lesional, nonlesional, and normal tissue samples. Because some of the values were missing, we used probabilistic PCA,[27] an iterative method that is tolerant to amounts of missing values between 10% to 15%, as in our case. Probabilistic PCA combines an expectation-maximization approach for PCA with a probabilistic model. The expectation-maximization approach is based on the assumption that the latent variables, as well as the noise, are normally distributed. We used the implementation available in the R package *pcaMethods*.[28,29]

Lesional versus nonlesional differences for all markers are represented by using heat maps. Unsupervised clustering of all lesional versus nonlesional $\log_2$ fold changes (FCHs) were carried out by using the Euclidean distance and average agglomeration criteria.

RESULTS

Patients' characteristics

This study included 27 Asian patients with AD (5 female and 22 male patients; age, 18-74 years [median, 27 years]) with SCORAD scores from 23 to 100 (mean, 58; SD, 20.2) and serum eosinophil counts of 2.3% to 33% (median, 8.2%); 25 EA patients with AD (9 female and 16 male patients; age, 23-73 years [median, 45 years]) with SCORAD scores from 33 to 77 (mean, 56.7; SD, 12.2) and serum eosinophil counts of 0.6% to 11.8% (median, 4.3%); 10 EA patients with psoriasis; and 15 Asian and 12 EA healthy control subjects. Among Asian patients with AD, 24 (89%) of 27 had extrinsic AD (serum IgE level,

TABLE I. Summary of clinical characteristics and demographics of patients with AD (mean ± SE if not specified)

Characteristic	Asian patients with AD (n = 27)	EA patients with AD (n = 25)	EA patients with psoriasis (n = 10)	Healthy Asian subjects (n = 15)	Healthy EA subjects (n = 12)	*P* value (Asian vs EA patients with AD)
Age (y), mean (SE)	29.6 (2.2)	45.7 (2.3)*	51.3 (4.9)	32.1 (3.0)	47.3 (3.3)	.0001
Sex (male/female), no.	22/5	16/9	6/4	8/7	9/3	.21
SCORAD index, mean (SE)	58.0 (3.2)	56.7 (3.4)				.77
IgE (kU/L), $\log_{10}$ (SE)	3.4* (0.17)	2.4 (0.17)				.0003
Eosinophils (% [SE])	9.9* (1.1)	4.9 (1.2)				.004
Extrinsic AD, no. (%)	24/27 (89)	14/25 (56)				.004

One Asian patient with AD did not have a serum IgE value recorded.
*$P < .05$.

269-31,000 kU/L; median, 4,185.5 kU/L), and among EA patients with AD, 14 (56%) of 25 had extrinsic AD (serum IgE level, 254-3,000 kU/L; median, 1,292.8 kU/L). Comparing groups (Table I), there was no difference in clinical severity (SCORAD), whereas the Asian patients with AD more frequently had extrinsic AD ($P = .004$), higher IgE and eosinophil levels ($P < .01$ for both), and lower mean age ($P < .001$). Ten patients with EA with moderate-to-severe psoriasis were also included for comparison (Psoriasis Area Severity Index, 8.4-59.5; mean, 20.3; SD, 14.5). A summary of patients' characteristics is presented in Table E1.

Prominent epidermal hyperplasia and frequent parakeratosis characterize the Asian AD phenotype

Although AD in both EA and Asian subjects was characterized by erythematous excoriated patches, Asian patients with AD often showed clearer demarcation of lesions, with more prominent scaling and lichenification (Fig 1, *A* and *B*). Histologic analyses identified significantly increased epidermal hyperplasia in Asian patients with AD, as measured based on greater thickness ($P < .001$; Fig 1, *C-E*) and a larger number of $Ki67^+$ cells in the basal layer of the epidermis ($P < .001$; Fig 1, *F-H*) compared with EA patients with AD. Asian patients with AD also demonstrated more frequent parakeratosis (46% vs 17%, $P = .035$), focal hypogranulosis, and more elongated rete ridges, although not as typically found in psoriasis lesions (Fig 1, *C-E*). Epidermal thickness measures of our cohort of Asian patients with AD were similar to those seen in several populations of patients with psoriasis.[26,30]

Increased dendritic cell counts and similar T-cell infiltrates occur in Asian patients with AD compared with EA patients with AD

Lesion from both Asian and EA patients with AD were characterized by marked increases in T-cell ($CD3^+$ and $CD8^+$ cells, $P < .001$ for both; Fig 2, *A-F*) and dendritic cell (DC; $CD11c^+$ and $Fc\varepsilon RI^+$ cells, $P < .01$ for both; Fig 2, *J-O*) numbers compared with respective nonlesional and normal skin. Although T-cell and langerin$^+$ Langerhans cell (LC) counts did not show significant differences between Asian and EA AD skin lesions (Fig 2, *A-I*), myeloid ($CD11c^+$) and $Fc\varepsilon RI^+$ DCs showed increased counts in Asian AD lesional (also nonlesional for $Fc\varepsilon RI^+$) skin ($P < .01$ for both; Fig 2, *J-O*) compared with those in EA patients with AD. Comparable T-cell and DC myeloid infiltrates were previously reported in EA patients with AD and patients with psoriasis.[31]

RT-PCR defines the Asian AD phenotype as a blended phenotype between EA AD and psoriasis with increased T_H17 and T_H22 induction

PCA based on RT-PCR data clustered both lesional and nonlesional skin of Asian patients with AD between EA patients with AD and those with psoriasis, suggesting that Asian patients with AD have a more psoriasiform phenotype compared with EA patients with AD (Fig 3, *A* and *B*). Also, the variation within each group was smaller in patients with psoriasis and Asian patients with AD compared with EA patients with AD. Further evaluation of the subsets with extrinsic AD showed that the extrinsic EA patient group is particularly distant from the Asian AD or psoriasis groups (Fig 3, *A* and *B*). Because most Asian patients were extrinsic (24/27 [89%]) compared with 56% (14/25) of EA patients with AD and because intrinsic and extrinsic AD have been shown to have different phenotypic characteristics (Table I),[10] we performed an extrinsic-only subgroup analysis to allow for appropriate comparisons of equivalent populations. The extrinsic AD–only analysis included 23 Asian patients with AD (23 lesional and 18 nonlesional), 13 EA patients with AD (13 lesional and 13 nonlesional), 8 Asian healthy subjects, and 8 EA healthy subjects. We also included lesional and nonlesional skin samples from 10 well-characterized patients with psoriasis for additional comparison.[26]

IL13 expression in both lesional and nonlesional skin was comparable between Asian and EA patients with AD, with significantly lower levels in patients with psoriasis (Fig 4, *A*, and see Table E4 in this article's Online Repository at www.jacionline.org). The T_H2-related chemokines (*CCL17* and *CCL22*) showed significantly higher expression in extrinsic EA AD lesions compared with extrinsic Asian AD lesions (Fig 4, *B* and *C*, and Table E4). Several T_H1 markers (*IFNG, CXCL9, CXCL10, MX1*, and signal transducer and activator of transcription 1 [*STAT1*]) were significantly increased in lesional and nonlesional skin of EA patients with extrinsic AD compared with those in lesional and nonlesional skin of Asian patients with extrinsic AD ($P < .05$ for all but *IFNG* [$P = .53$] in lesional skin and *STAT1* [$P = .08$] in nonlesional skin; Fig 4, *D-H*, and see Table E4). Significantly higher induction of T_H17-related cytokines (*IL17A* and *IL19*, $P < .05$) and IL-17–induced markers (*CCL20*, $P = .09$) was shown in lesional and/or nonlesional skin of Asian patients with extrinsic AD compared with that in EA patients with extrinsic AD (Fig 4, *I-K*, and see Table E4). Higher upregulation of the T_H22 cytokine *IL22* was seen in both lesional and nonlesional skin of Asian patients with extrinsic AD compared with lesional and nonlesional skin of EA patients with AD (nonlesional skin, $P < .01$; lesional skin, $P = .06$), as well as the IL-17/IL-22–induced *S100A12* (Fig 4, *L* and *M*, and see

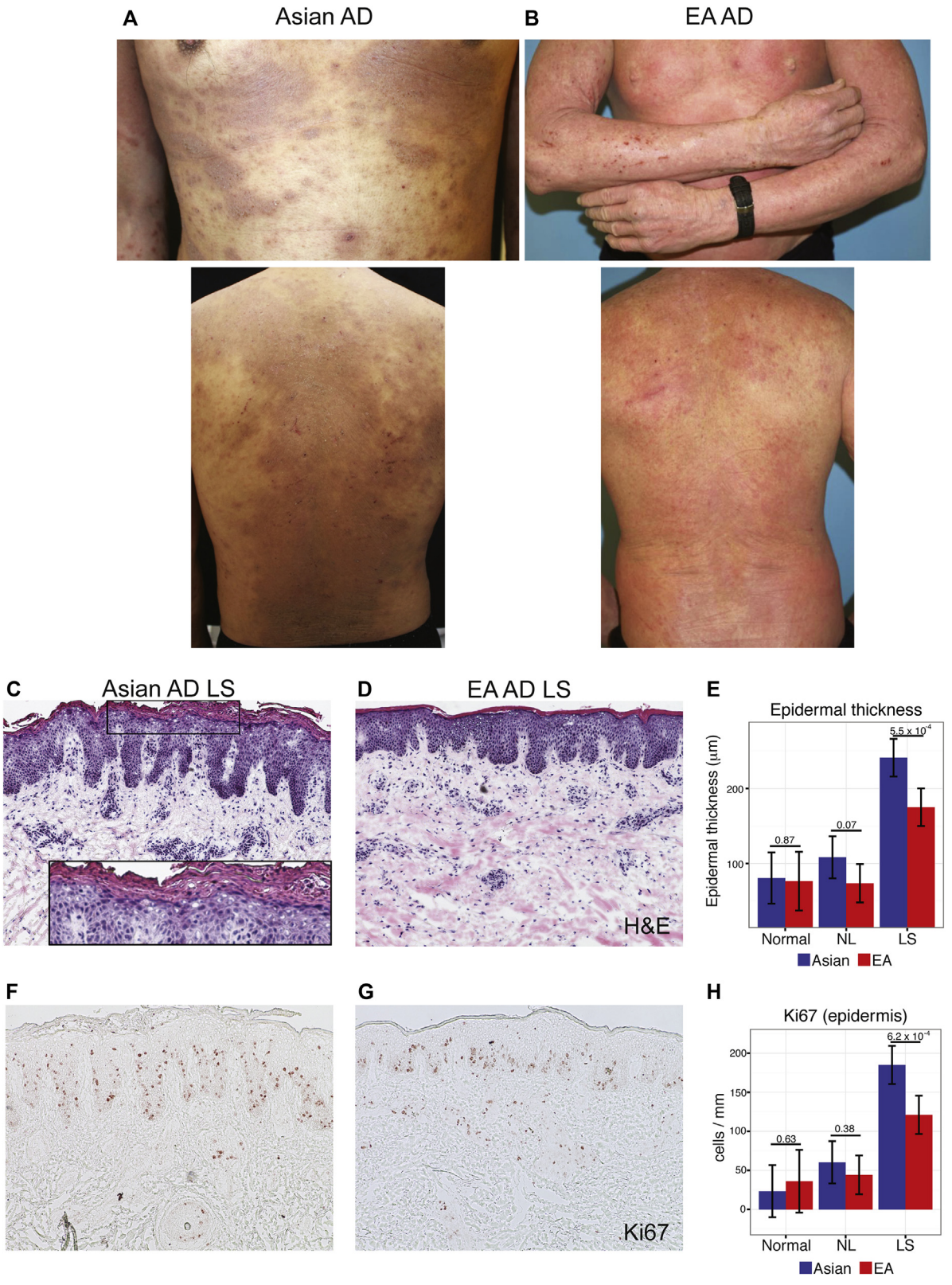


FIG 1. **A** and **B,** Representative clinical images of Asian (Fig 1, *A*) and EA (Fig 1, *B*) patients with AD. **C** and **D,** Representative hematoxylin and eosin staining for lesional skin of an Asian patient with AD (Fig 1, *C*) and a patient with EA AD (Fig 1, *D*). **E,** Epidermal thickness in Asian and EA patients with AD. **F** and **G,** Representative Ki67 staining for lesional skin of an Asian patient with AD (Fig 1, *F*) and an EA patient with AD (Fig 1, *G*). **H,** Ki67^{+} cell counts in Asian and EA patients with AD. *LS,* Lesional; *NL,* nonlesional. Least squares means and 95% CIs are shown.

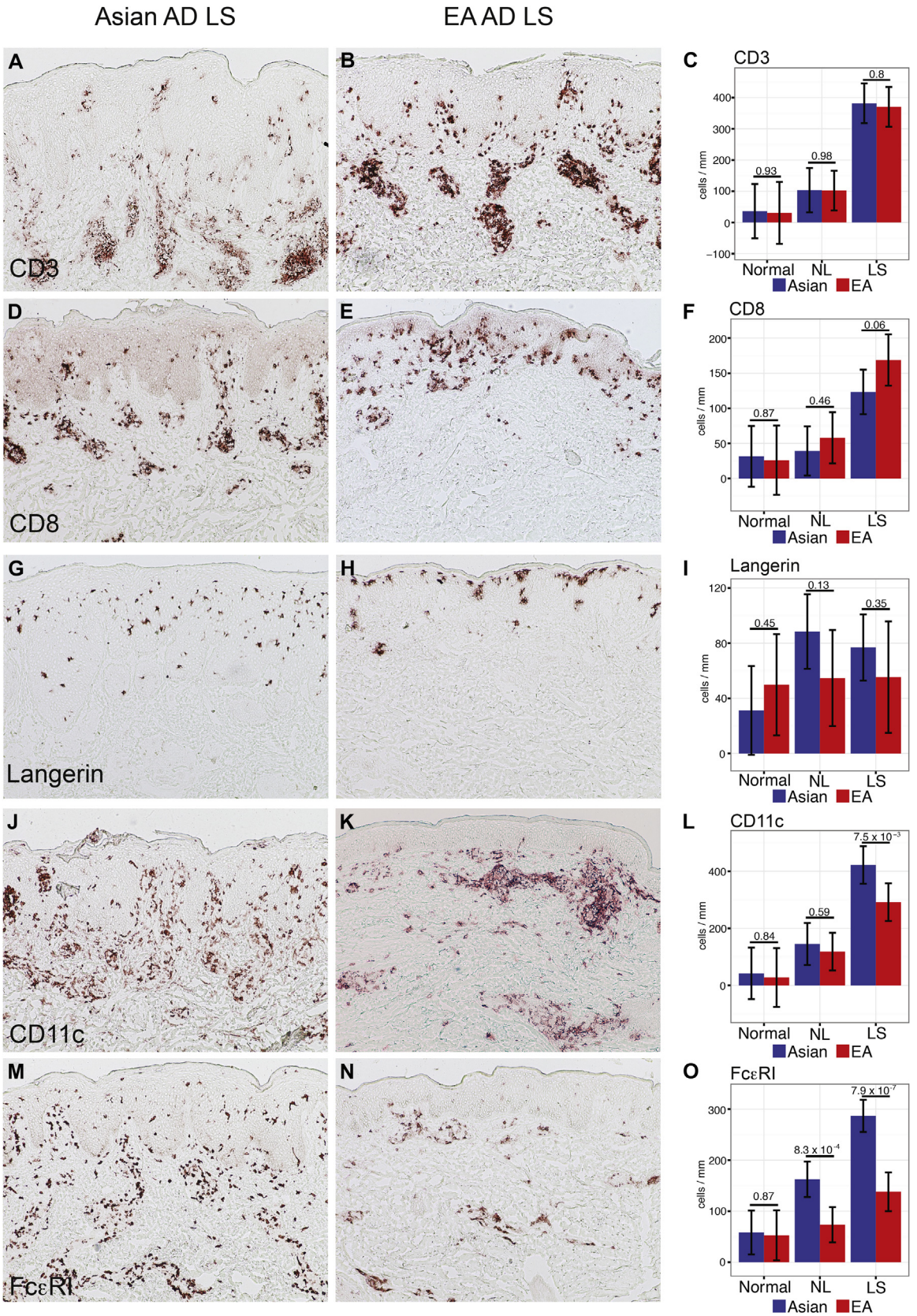


FIG 2. Representative images with IHC for Asian and EA patients with AD. Cell counts are also shown. **A-C,** CD3. **D-F,** CD8. **G-I,** Langerin. **J-L,** CD11c. **M-O,** FcεRI. *LS*, Lesional; *NL*, nonlesional. Least squares means and 95% CIs are shown.

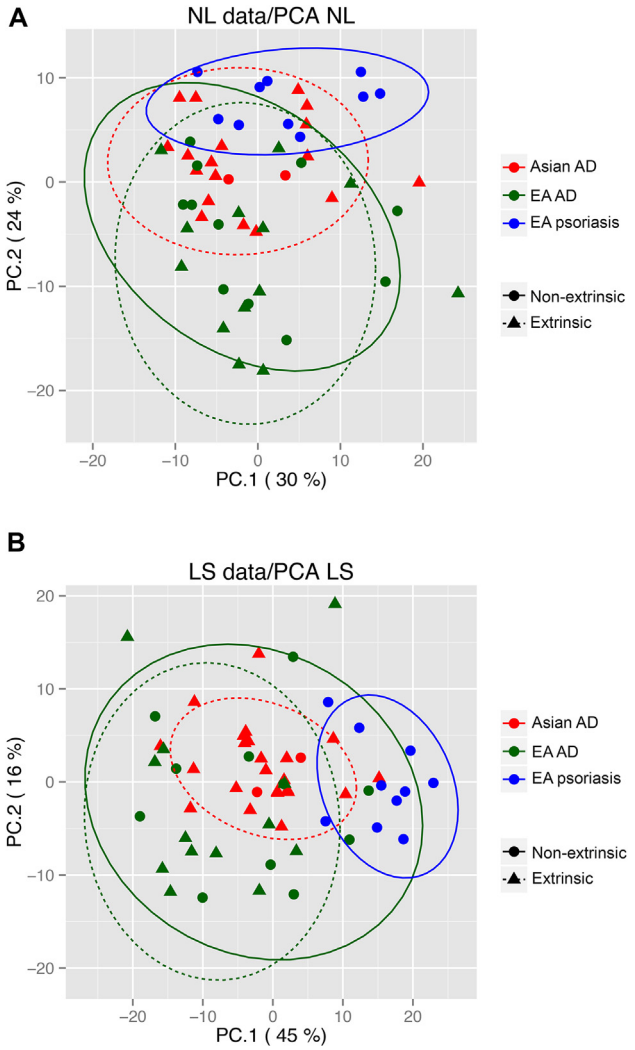


FIG 3. PCAs based on RT-PCR data with skin samples from Asian patients with AD, EA patients with AD, and EA patients with psoriasis. **A,** Nonlesional *(NL)* skin samples. **B,** Lesional *(LS)* skin samples.

Table E4). Of note, most IL-17–related markers still showed significantly higher levels in patients with psoriasis compared with those in Asian patients with extrinsic AD (Fig 4, *I* and *J*, and see Table E4), whereas *IL22* levels were comparable between patients with psoriasis and Asian patients with extrinsic AD (Fig 4, *L*, and see Table E4). Similarly *IFNG* expression was highest in lesional psoriasis (Fig 4, *D*, and see Table E4). *LOR* expression was remarkably diminished in both lesional and nonlesional skin of EA patients with extrinsic AD compared with their Asian counterparts, with a similar trend of decreased *FLG* expression in lesional skin of EA patients with AD (Fig 4, *N* and *O*, and see Table E4). This suggests more severe epidermal differentiation abnormalities in EA patients with AD, possibly derived from higher T_H2 induction.[32] In line with this observation, loricrin and, less evidently, filaggrin showed defective and discontinuous immunostaining in the granular layers of both lesional and nonlesional skin of EA patients with AD, and S100A8/9 showed stronger staining throughout the epidermis in Asian patients with AD (see Fig E2 in this article's Online Repository at www.jacionline.org).

Not only are expression patterns different when comparing respective lesional and nonlesional skin of Asian and EA patients with AD, but also significant differences were detected when comparing relative lesional versus nonlesional expression (previously defined as disease phenotype)[10,33,34] between AD groups and patients with psoriasis. Fig 5 illustrates a heat map showing expression differences (in FCHs) between lesional versus nonlesional skin of Asian and EA patients with extrinsic AD, as well as patients with psoriasis. The Asian AD skin transcriptome shows much larger induction of T_H17/IL-23 axis genes compared with the EA AD skin transcriptome, including *IL19* (FCH, 33.3), *S100A12* (FCH, 34.2), *IL17A* (FCH, 12.7), *IL12B* (p40, FCH, 9.0), peptidase inhibitor 3 (FCH, 6.7), and *IL20* (FCH, 4.7; all $P < .01$). However, the psoriasis profile consistently demonstrated the highest T_H17/IL-23 skewing (Fig 5). High induction of *IL22* and T_H17/T_H22-induced S100As was found in both AD groups.

Similar trends were also found when analyzing the whole populations of EA and Asian patients with AD, including both those with intrinsic and those with extrinsic AD (see Fig E3 and Table E5 in this article's Online Repository at www.jacionline.org), although expression differences between lesional skin of Asian and EA patients with AD were less significant (*IL17A*, $P = .09$; *IL19*, $P = .12$; and *S100A12*, $P = .05$; see Fig E3, *I*, *J*, and *M*, and Table E5). *CCL20* mRNA expression was significantly higher in nonlesional skin of Asian patients with AD compared with that in EA patients with AD (see Fig E3, *K*, and Table E5). The whole-group AD transcriptome (lesional vs nonlesional) analyses again showed trends similar to those of the extrinsic AD and psoriasis analyses (see Fig E4 and Table E5 in this article's Online Repository at www.jacionline.org).

DISCUSSION

Recent findings suggest that AD is more heterogeneous than psoriasis, which is now established as a T_H17/IL-23–centered disease.[8] Several subsets of AD have been recognized over time based on prevalence,[19,35] clinical characteristics,[36] IgE levels,[10] concomitant atopic disorders,[37,38] and *FLG* mutations,[39,40] for example. These endotypes include intrinsic and extrinsic AD, pediatric and adult AD,[41] and subcategories based on race (eg, Asian, EA, and African American).[42] We have shown distinct differences in skin cytokine profiles between patients with intrinsic and those with extrinsic AD.[10] Despite high IgE levels, similar T_H2 expression was detected, whereas significantly increased expression of T_H17/IL-23 and T_H22 pathway genes was detected in patients with intrinsic AD.[10] It is important to determine differences and similarities between various AD phenotypes because these have major therapeutic implications for specific cytokine-targeting strategies.

The high prevalence of AD in Asia[19,35] and increased IL-17^+ T cell expansion[22] in Asian patients with AD have suggested that the Asian AD phenotype might have different immune and barrier characteristics than the more studied EA AD phenotype.[10,23,25,33,34,43] To assess distinct features of the Asian AD phenotype, we conducted the first head-to-head comparison between Asian patients with AD and EA patients with AD using psoriasis as a point of reference and using skin samples obtained from each racial group.

Although some characteristics were commonly seen in both AD groups, such as increased epidermal hyperplasia, large T-cell and DC infiltrates, and T_H2 polarization, key differences were

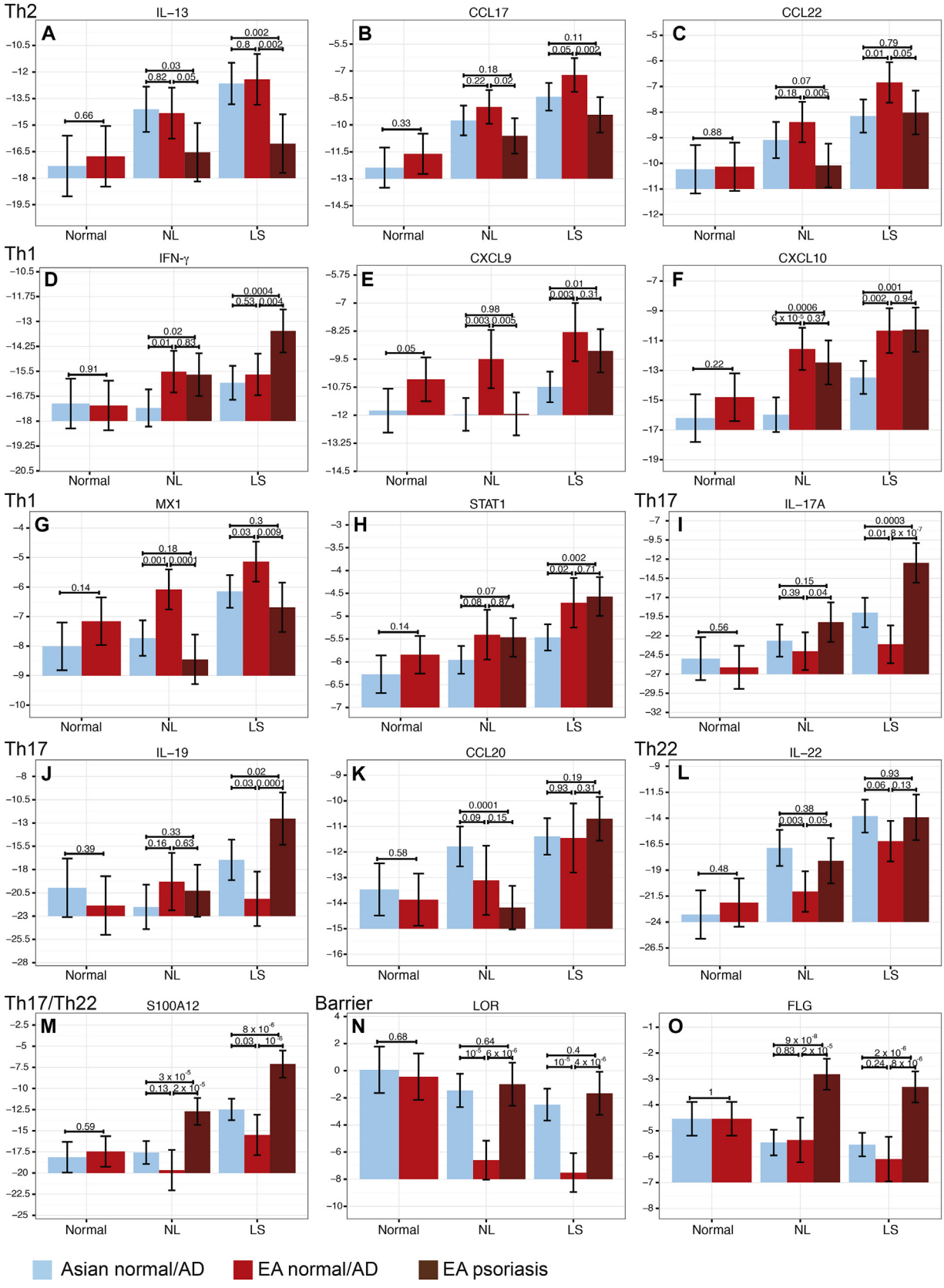


FIG 4. A-O, RT-PCR comparisons of inflammatory and epidermal barrier markers in respective lesional *(LS)*, nonlesional *(NL)*, and normal skin samples from patients with extrinsic AD, patients with psoriasis, and healthy subjects. T_H2 **(A-C)**, T_H1 **(D-H)**, T_H17 **(I-K)**, T_H22 **(L)**, T_H17/T_H22 **(M)**, and epidermal barrier (**N** and **O**) markers are listed. Values were adjusted to human acidic ribosomal protein *(hARP)* expression levels. Least squares means (log_2 expression/hARP) and 95% CIs are shown.

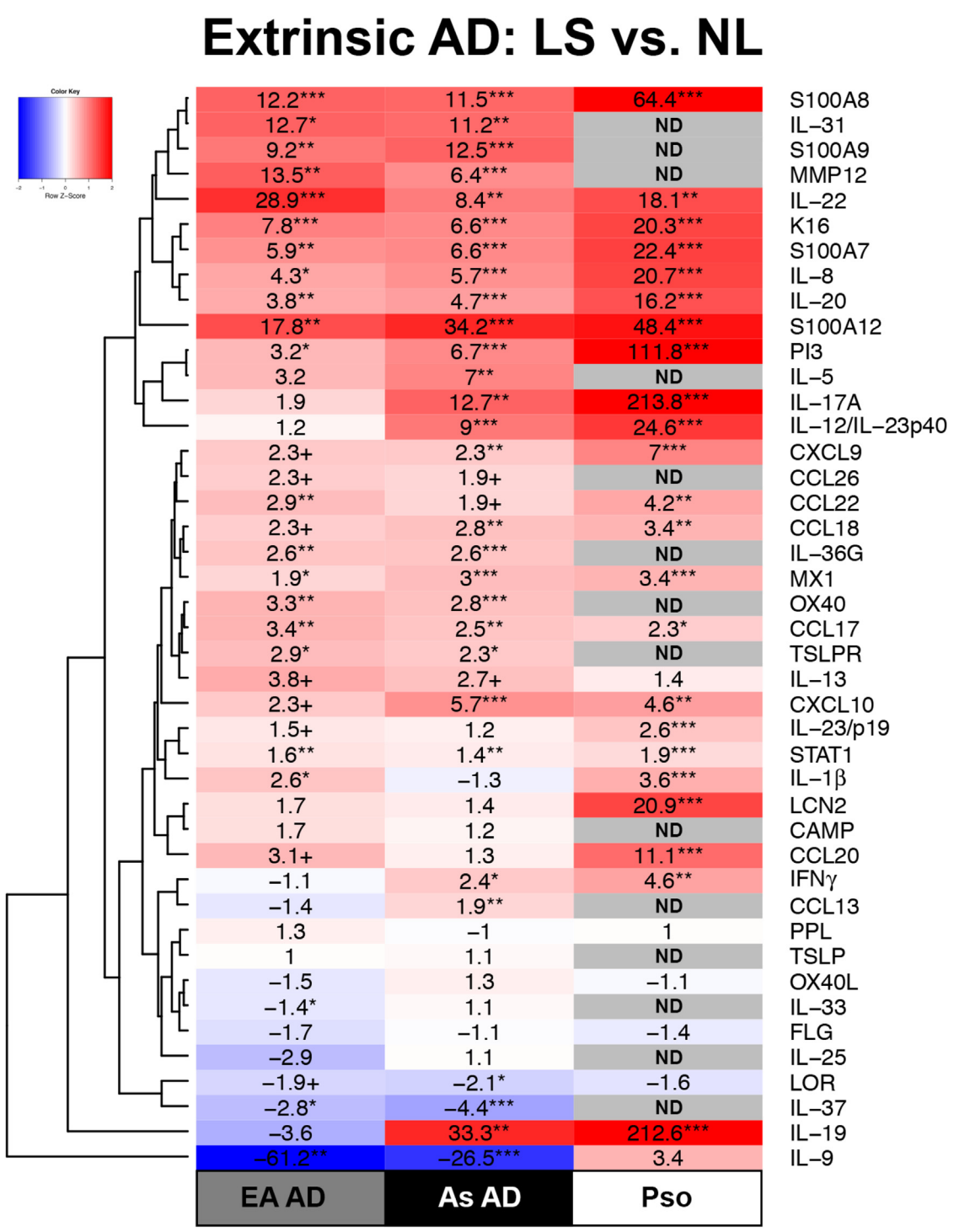


FIG 5. A, RT-PCR heat map of mRNA expression differences between lesional *(LS)* and nonlesional *(NL)* skin. Data obtained from the skin of EA patients with extrinsic AD, Asian *(As)* patients with extrinsic AD, and patients with psoriasis *(Pso)* were included. +$P < .1$, *$P < .05$, **$P < .01$, and ***$P < .001$. Expression of several genes for psoriasis was not determined *(ND)*, as indicated by *gray boxes*.

also observed. Although epidermal hyperplasia characterizes both AD subtypes, Asian patients show a more psoriasiform phenotype with more prominent epidermal hyperplasia and elongated rete ridges, parakeratosis, and hypogranulosis, typical features in patients with psoriasis.[44] Consistent with the similar disease activity (SCORAD) in both racial groups, T-cell and LC infiltrates were similarly increased in lesional skin. However, more significant increases in $CD11c^+$ myeloid DC and $Fc\varepsilon RI^+$ DC counts were seen in Asian patients with AD compared with those in EA patients with AD. FcεRI marks inflammatory dendritic epidermal cells that characterize AD.[45,46] Given that LC numbers are similar between the 2 groups, alterations in DC

counts and their activation status might contribute to the differential Asian AD skin phenotype.

Both AD groups show strong T_H2 polarization. However, even in the presence of high IgE status, Asian AD shows significantly higher induction of T_H17- and T_H22-related cytokines (*IL17A, IL19*, and *IL22*) and IL-17/IL-22–induced keratinocyte markers (*S100A12*) in lesional and/or nonlesional skin compared with those seen in EA patients with AD. Psoriasis is primarily a T_H17-driven disease with a T_H22 component.[8,47] IL-22 is known to induce epidermal hyperplasia, loss of the granular layer, and parakeratosis.[48] Another cytokine reported to induce hyperplasia is IL-19,[49] which showed robust significant increases in the Asian AD phenotype. Interestingly, IL-19 is induced by both IL-17 and IL-4/IL-13.[50,51] IL-19 also amplifies many IL-17A effects on keratinocytes and increases the production of S100As.[50] Thus the psoriasis-like histologic features in the skin of Asian patients with AD might be attributed to the increased T_H17/T_H22 polarization and IL-19 induction. Although strong increases in both lesional and nonlesional skin were seen in both AD groups compared with the patients with psoriasis, T_H2-associated chemokine levels showed larger increases in EA patients with AD compared with those in Asian patients with AD. Because T_H2 cytokines inhibit epidermal differentiation proteins, such as filaggrin and loricrin,[52] the higher T_H2 activation in EA patients with AD might explain the decreases in loricrin and filaggrin expression in this patient population compared with those seen in Asian patients with AD. T_H1/interferon-associated markers (*IFNG, CXCL9, CXCL10, MX1*, and *STAT1*) showed large reductions in Asian patients with AD versus those in EA patients with AD. Because IL-17 and interferon were reported to have reciprocal negative regulation capacities,[53-56] the decreases in T_H1 pathway genes in Asian patients with AD might be attributed to a negative regulatory effect of IL-17 on the interferon/T_H1 pathway.

Differential immune polarization in Asian patients has also been observed in another "allergic" disease, namely nasal polyps. Although patients with EA show a strong T_H2 bias, a more dominant T_H17 phenotype with lower T_H2 expression has been demonstrated in Asian patients.[57] Additionally, enhanced T_H17 responses in Chinese patients with nasal polyps have been shown regardless of coexisting eosinophilic inflammation.[58] Together with our data, this suggests a higher likelihood of T_H17 skewing in Asian patients with atopic/"allergic" diseases. This immune tendency might cause histologic and clinical differences between the races, such as a more hyperplastic epidermis in Asian patients with AD and less eosinophil-dominant inflammation with nasal polyps in Asian patients.[59]

Based on advances in pathogenic understanding, agents targeting polar T-cell subsets are being tested for in clinical trials for AD. These include biologics or small molecules against the T_H2 (anti–IL-4 receptor α/dupilumab, clinicaltrials.gov: NCT01949311; anti–IL-13/lebrikizumab, NCT02340234; a chemoattractant receptor–homologous molecule expressed on T_H2 lymphocytes (CRTH2) antagonist, NCT02002208; and anti–thymic stromal lymphopoietin receptor, NCT01732510), T_H22 (anti–IL-22/ILV-094, NCT01941537), and T_H17/IL-23 (anti–IL-23p40/ustekinumab, NCT01806662 and NCT01945086) axes.[1,8,60] Recent phase I and II studies with dupilumab showed major improvement (approximately 70%) in disease activity, with the highest dose coupled with large improvement in the genomic phenotype and reversal of epidermal hyperplasia, supporting the pathogenic role of the T_H2 axis in patients with AD.[17,18] A strong induction of IL-13 cytokine in both Asian patients with AD and EA patients with AD, together with similar activation of T_H2 cytokines in intrinsic/extrinsic and pediatric/adult subtypes, indicates that T_H2 expansion is a common feature of AD, regardless of race or phenotype.[10,41] However, other polar immune activation varies depending on individual phenotypes and racial groups. The Asian AD phenotype is characterized by higher induction of the T_H17 and T_H22 axes. This increased T_H17 induction is particularly noteworthy given that we have previously shown that patients with intrinsic AD have higher T_H17 expression than patients with extrinsic AD,[10] and almost all Asian patients with AD in our study had extrinsic AD. Additionally, the Asian AD cohort was younger than the EA cohort, and T_H17 activation has been reported to increase with age.[61,62] Thus our results might actually underestimate the increased T_H17 activation seen in Asian patients with AD. Future studies should address the effect of age on the differences we observed. Trials with anti–IL-22/ILV-094 and anti–IL-23p40/ustekinumab are still ongoing, and case reports for the use of ustekinumab in patients with AD have demonstrated controversial results.[63-66] Nevertheless, the present study, as well as our intrinsic versus extrinsic study,[10] suggest that the efficacy of these IL-22– and IL-23–targeted therapies can vary across phenotypes and racial groups, warranting subgroup analyses for differential subgroups. T_H17 blockers, which are now approved or being tested for psoriasis,[14,67,68] are candidates for future trials in patients with AD, especially for the Asian and intrinsic AD phenotypes, given the strong T_H17 skewing seen in these populations.[10] Human studies with selective antagonists against the T_H1, T_H2, T_H17, and T_H22 pathways will continue to dissect disease mechanisms in different AD categories.

AD and psoriasis are viewed as polar inflammatory skin conditions.[8] These diseases are usually seen in different patients, although unusual patients simultaneously displaying both diseases have been reported.[69,70] As phenotyping of these diseases has evolved, AD is now considered T_H2 centered, whereas psoriasis is a primarily T_H17/IL-23–skewed disease. These distinctions are highly relevant to emerging therapies because AD responds remarkably well to blockade of T_H2 cytokine signaling,[17,18] whereas psoriasis shows great response to IL-17 and IL-23 antagonism. Similar frequencies of AD (approximately 4%) and psoriasis (approximately 1% to 3% of adults) are observed in Western patients,[71,72] making these the most common human inflammatory diseases. Interestingly, psoriasis has a very low frequency in Asia, whereas AD presents a much higher frequency (approximately 0.5% vs 7% to 10% of adults).[19-21,73] In terms of molecular immunology, the T_H17 axis appears to be "missing" in Asia as we currently classify these polar diseases. Our report classifies Asian AD as a mixed phenotype between AD and psoriasis, harboring an intermediate cytokine profile of both diseases. Although the Asian AD phenotype is clinically closer to the EA AD phenotype (including high serum IgE levels and increased eosinophils), it actually shows a blended phenotype between EA patients with AD and patients with psoriasis on the cellular and molecular levels.

Because the skin samples of Asian patients with AD were obtained from Japanese and Korean subjects living in their respective countries, it is unknown to what extent these phenotypic differences are genetic,[74-76] environmental,[77,78] and/or microbiome related.[79,80] Further studies will be necessary to determine whether there are phenotypic differences in members

of the same ethnic group living in different geographic locations (ie, Asian subjects vs Asian American AD populations). These results will also need to be verified in other Asian populations, including West Asian, Southeast Asian, and Chinese populations. Additionally, because the FLG mutation status is not known for the entire cohort (including patients and control subjects), future studies will be necessary to determine the association between FLG status and our data.

Our data establish Asian AD as a unique immune phenotype, combining characteristics of AD and psoriasis and demanding new clinical trials with specific cytokine antagonists to establish relative pathogenic contributions of T_H2 versus T_H17 in Asian patients with AD.

Clinical implications: The more "psoriasis-like" phenotype of Asian AD provides a rationale for testing of IL-17/IL-23–targeted strategies that are successfully tested in patients with psoriasis in addition to T_H2-specific therapeutics.

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Figure E1



Figure E2

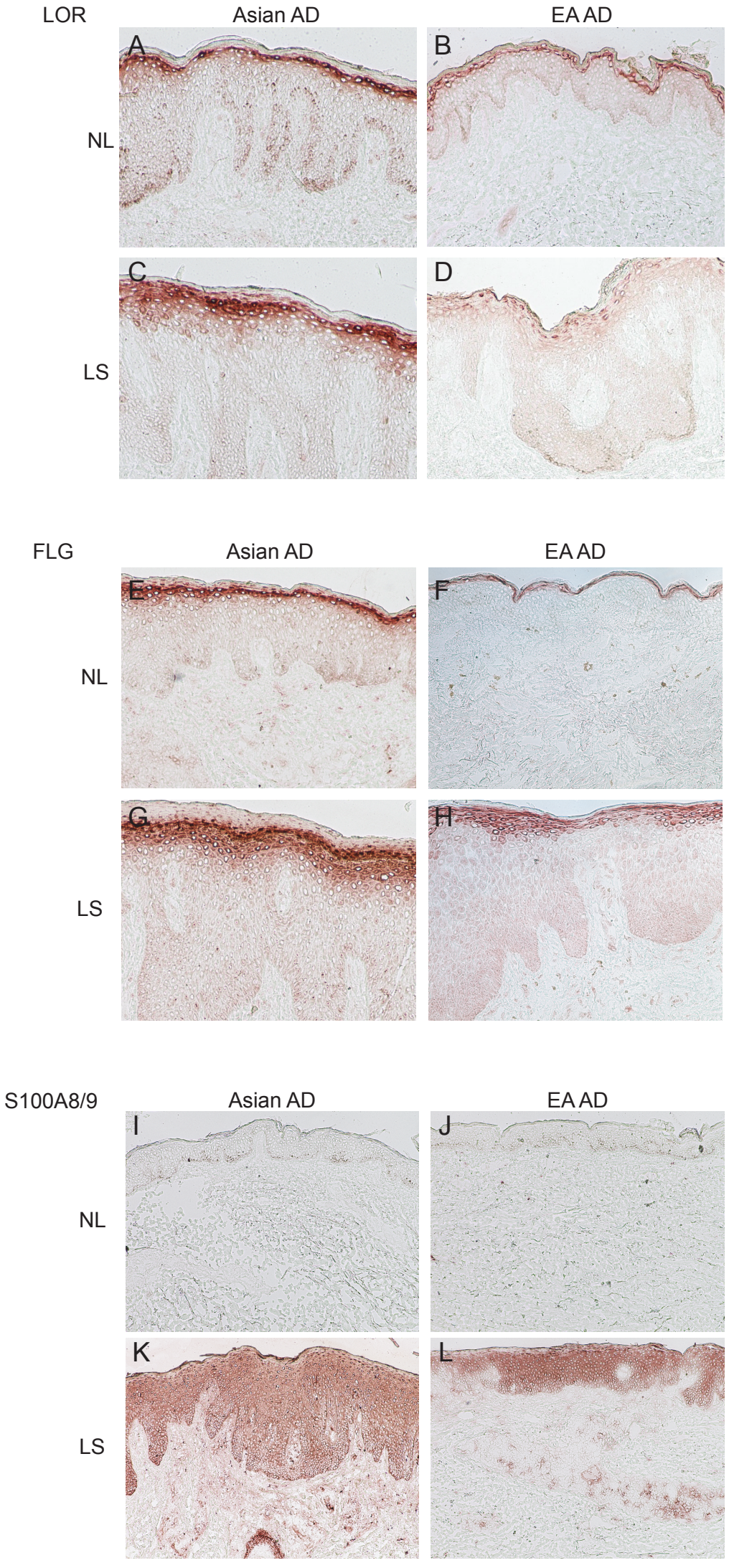

LOR
Asian AD
EA AD
A
B
NL
C
D
LS
FLG
Asian AD
EA AD
E
F
NL
G
H
LS
S100A8/9
Asian AD
EA AD
I
J
NL
K
L
LS

Figure E3 Whole AD log2 (expression/hARP)

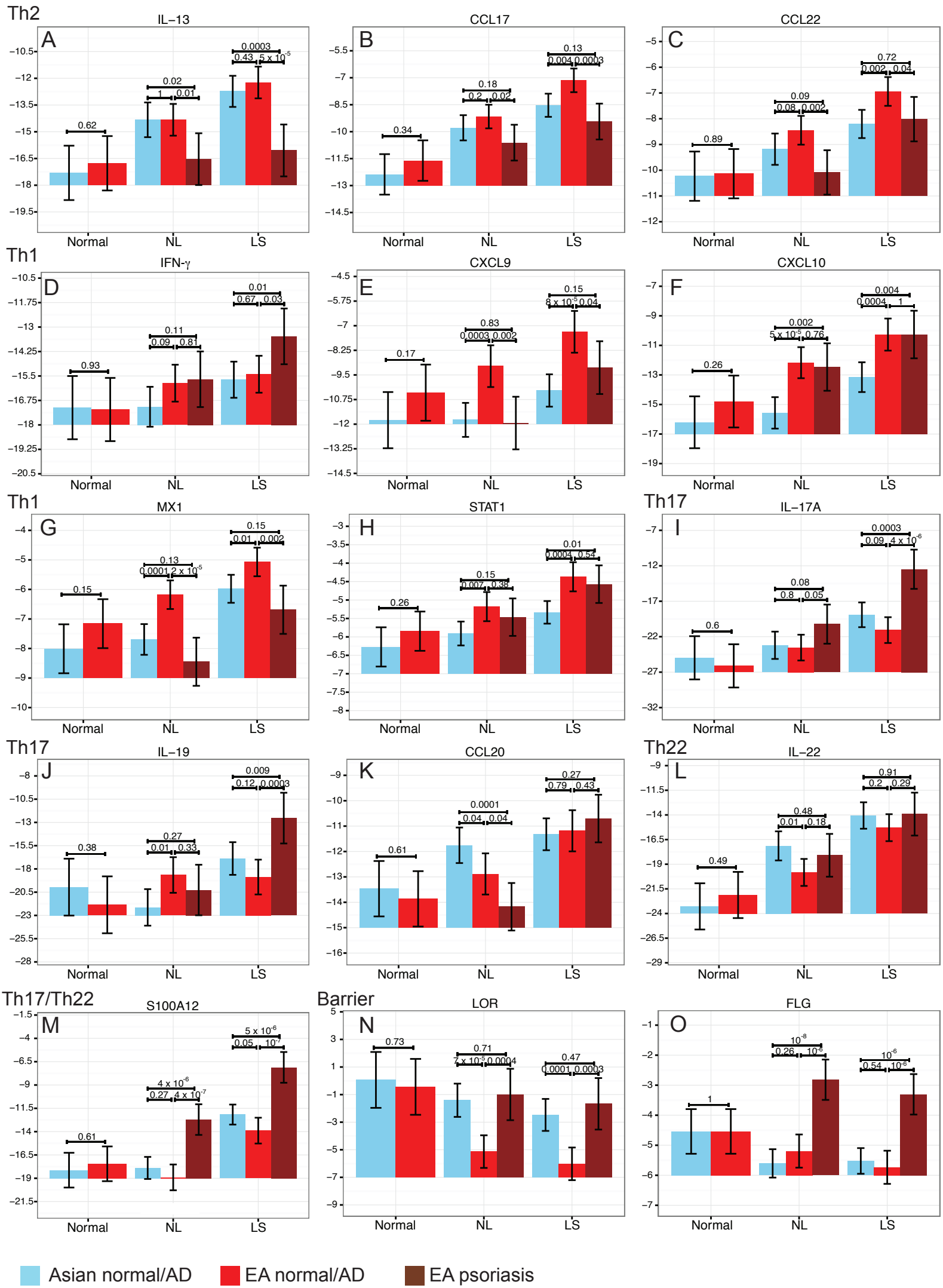
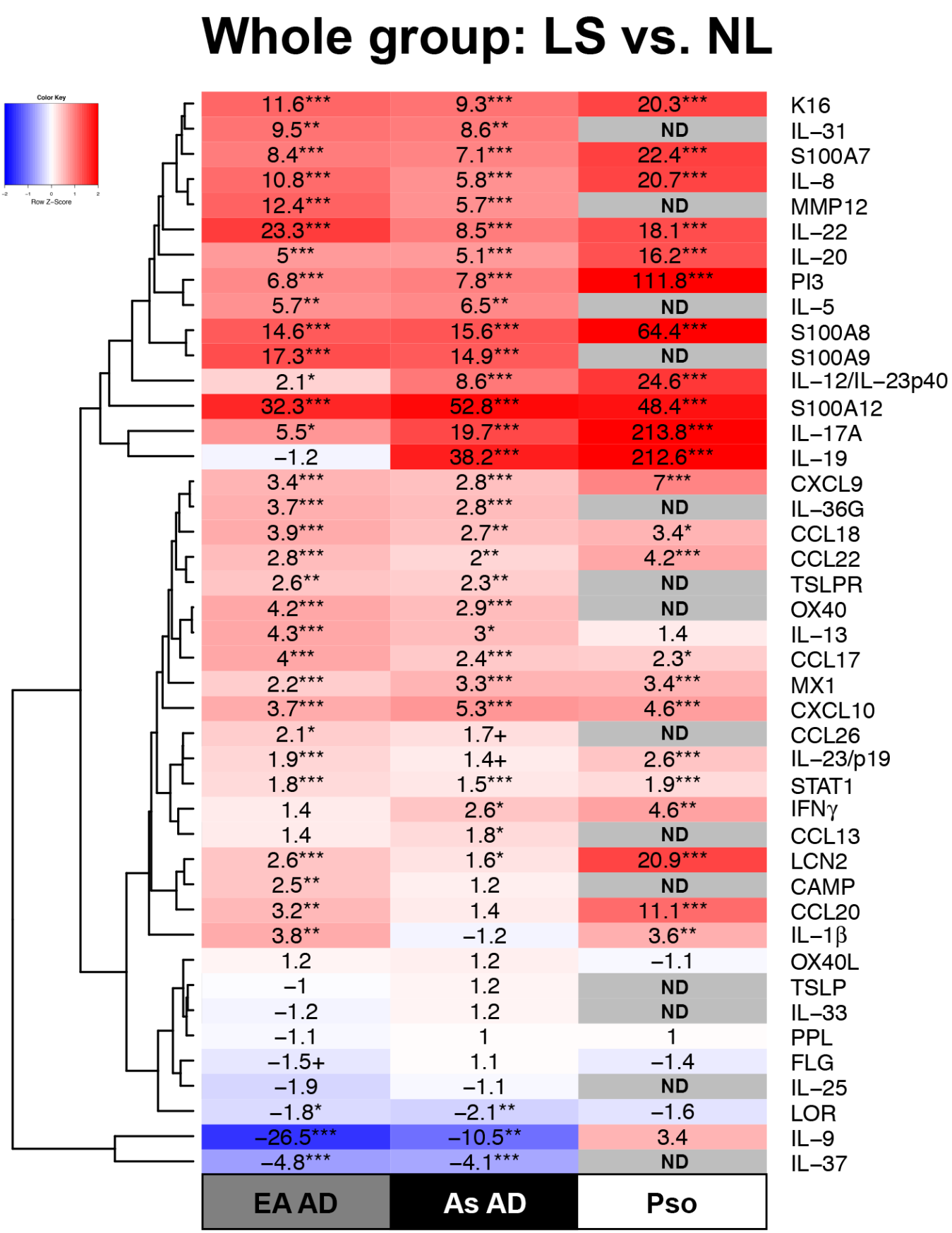


Figure E4


Whole group: LS vs. NL
Color Key
Row Z-Score
11.6*** 9.3*** 20.3*** K16
9.5** 8.6** ND IL–31
8.4*** 7.1*** 22.4*** S100A7
10.8*** 5.8*** 20.7*** IL–8
12.4*** 5.7*** ND MMP12
23.3*** 8.5*** 18.1*** IL–22
5*** 5.1*** 16.2*** IL–20
6.8*** 7.8*** 111.8*** PI3
5.7** 6.5** ND IL–5
14.6*** 15.6*** 64.4*** S100A8
17.3*** 14.9*** ND S100A9
2.1* 8.6*** 24.6*** IL–12/IL–23p40
32.3*** 52.8*** 48.4*** S100A12
5.5* 19.7*** 213.8*** IL–17A
–1.2 38.2*** 212.6*** IL–19
3.4*** 2.8*** 7*** CXCL9
3.7*** 2.8*** ND IL–36G
3.9*** 2.7** 3.4* CCL18
2.8*** 2** 4.2*** CCL22
2.6** 2.3** ND TSLPR
4.2*** 2.9*** ND OX40
4.3*** 3* 1.4 IL–13
4*** 2.4*** 2.3* CCL17
2.2*** 3.3*** 3.4*** MX1
3.7*** 5.3*** 4.6*** CXCL10
2.1* 1.7+ ND CCL26
1.9*** 1.4+ 2.6*** IL–23/p19
1.8*** 1.5*** 1.9*** STAT1
1.4 2.6* 4.6** IFNγ
1.4 1.8* ND CCL13
2.6*** 1.6* 20.9*** LCN2
2.5** 1.2 ND CAMP
3.2** 1.4 11.1*** CCL20
3.8** –1.2 3.6** IL–1β
1.2 1.2 –1.1 OX40L
–1 1.2 ND TSLP
–1.2 1.2 ND IL–33
–1.1 1 1 PPL
–1.5+ 1.1 –1.4 FLG
–1.9 –1.1 ND IL–25
–1.8* –2.1** –1.6 LOR
–26.5*** –10.5** 3.4 IL–9
–4.8*** –4.1*** ND IL–37
EA AD
As AD
Pso

Supplementary Figure Legends

EFig. 1. Representative clinical image of a biopsy site (with white rectangle) from an Asian AD patient.

EFig. 2. Representative images with immunohistochemistry for Asian atopic dermatitis (AD) and European American (EA) AD. **A-D,** LOR. **E-H,** FLG. **I-L,** S100A8/9. LS, lesional. NL, non-lesional.

EFig. 3. A-O, Real-time PCR comparisons of inflammatory and epidermal barrier markers in respective lesional (LS), non-lesional (NL), and normal skin samples from atopic dermatitis (AD), psoriasis, and normal individuals. Values were adjusted to human acidic ribosomal protein (hARP) expression levels. Least squares means (log_2 expression/hARP) **±** 95% confidence intervals. EA, European American.

EFig. 4. An RT-PCR heatmap of mRNA expression differences between lesional (LS) and non-lesional (NL). The data obtained from the skin of European American (EA) atopic dermatitis (AD), Asian (As) AD, and psoriasis (Pso) patients were included. +p-value<0.1; *p<0.05; **p<0.01; ***p<0.001. Several gene expressions for psoriasis were not determined (ND), showing gray boxes.