

Letter to the Editor

Serum from Asian patients with atopic dermatitis is characterized by T_H2/T_H22 activation, which is highly correlated with nonlesional skin measures

To the Editor:

Assessment of atopic dermatitis (AD) severity is largely limited to clinical disease measures, but the nature of the disease is such that it cannot be quantified accurately through clinical scores alone. Biomarkers of disease activity in the skin or blood might be useful adjuncts in clinical trials to follow disease severity by using objective criteria.¹ However, the cytokine profile of Asian patients with AD differs from that of European American (EA) patients with AD in the skin, representing a blend between EA patients with AD and patients with psoriasis and showing increased epidermal hyperplasia, greater T_H17/T_H22 and lower T_H1 skewing, and comparable T_H2 activation.² Currently, it is unknown how these differences translate to circulating biomarkers. Peripheral biomarker profiling is essential for precision therapeutic approaches and for potentially minimizing the need for biopsies. Although skin and serum data exist for EA patients with AD,^{1,3} integrated skin-blood biomarkers are not yet available for Asian patients with AD. Thus we analyzed serum biomarkers of Asian patients with AD and control subjects, with comparisons to circulating measures in EA patients with AD,¹ as well as to clinical parameters and prior skin data.²

Under institutional review board–approved protocols, blood was obtained from 15 Asian patients with moderate-to-severe AD (13 male patients/2 female patients; age range, 19–33 years [mean, 25 years]; total SCORAD [assessing AD severity] score range, 23–71 [mean, 48.3]) and age-matched control subjects (for demographic data, see Table E1 in this article's Online Repository at www.jacionline.org). Electrochemiluminescence and Erenna immunoassays were used to quantify T_H1 -, T_H2 -, T_H17 -, and T_H22 -related inflammatory markers. Recently reported skin data from Asian patients with AD² and blood biomarkers from EA patients with AD from a cohort of patients with similar disease severity¹ were used for comparisons. The Student *t* test and Pearson correlation coefficients were used for analyses and correlations, respectively. A *P* value of less than .05 was considered significant (see Table E2 and the Methods section in this article's Online Repository at www.jacionline.org).

Although greater T_H1 -related measures (IFN- γ , CCL2, CCL3, and CCL4) were seen in patients with AD versus control subjects, levels were significantly greater in EA versus Asian patients with AD for most markers, except CXCL10 (Fig 1, A). Decreased T_H1 /IFN- γ skewing in blood from Asian patients with AD can be attributed to reciprocal downregulation of this axis by the T_H17 pathway that is increased in skin of Asian patients with AD.² Although CXCL10 is regulated by IFN- γ , it is also associated with innate immunity and IFN- α activation,^{2,4} possibly accounting for its relatively increased levels in Asian patients. In line with their cutaneous profiles,² both EA and Asian patients with AD showed significant increases in levels of T_H2 markers in serum versus respective control values (IL-13, CCL13, CCL17, CCL22, and CCL26; *P* < .05 for all; Fig 1, B), highlighting the T_H2 axis as the common denominator of AD across races, with

even stronger induction of key pathogenic T_H2 markers (IL-13 and CCL26; Fig 1, B) in Asian versus EA patients with AD. The significant CCL26 level increase in Asian patients with AD is in line with reports on increased circulating eosinophil counts in Asian compared with EA patients.⁵ Despite the greater skin expression and single-cell frequencies in Asian patients with AD,^{2,6} serum IL-17 levels were similar between races (Fig 1, C), possibly reflecting excessive migration to the skin, which was similar to prior reports in patients with psoriasis.⁷ Although both EA and Asian patients with AD showed significant IL-22 increases versus respective control subjects, IL-22 levels were significantly increased in Asian versus EA patients with AD (*P* < .01; Fig 1, D), which is concordant with T_H17/T_H22 upregulation and more prominent epidermal hyperplasia and parakeratosis in Asian patients with AD.² A summary waterfall fold change (FCH) comparison between Asian and EA patients with AD is shown in Fig 1, E, highlighting significant increases in T_H2 /IL-13, CCL26, and T_H22 /IL-22 axes, with decreases in T_H1 /IFN- γ levels in Asian patients.

We next correlated serum markers with total SCORAD scores and IgE levels (see Tables E3 and E4 in this article's Online Repository at www.jacionline.org). Correlations classified by immune axes are presented in Fig 2, A and B, and see Fig E1, A–D, in this article's Online Repository at www.jacionline.org. Contrary to EA patients with AD,¹ in Asian patients IFN- γ was the only T_H1 marker that correlated negatively with disease severity (*r* = −0.44, *P* = .09; Fig 2, A, and see Fig E1, A). Conversely, and in line with their increased serum levels, most T_H2 measures were correlated positively with SCORAD scores, similar to what is seen in EA patients with AD (*P* < .05 for CCL11 and CCL26; Fig 2, A, and see Fig E1, B).¹ Reflective of the high occurrence of extrinsic AD among the Asian AD cohort,² multiple T_H2 -related cytokines and chemokines, including eosinophil chemoattractants (IL-13, CCL26, and CCL13; Fig 2, B), also showed significant correlations with IgE levels. Nonsignificant positive correlations were observed between IL-22 and IL-17 levels and AD severity in Asian patients or IgE levels (see Fig E1, C and D).

Aiming at defining blood biomarkers that best reflect cutaneous involvement and clusters of serum markers that correlate with skin biomarkers, we correlated each serum marker with other serum markers and with expression of lesional/nonlesional biomarkers. We found that T_H2 serum biomarkers, including IL-13, CCL26, CCL11, CCL22, and CCL17, were not only highly correlated among themselves but also showed highly significant correlations with serum IL-17 and/or IL-22 levels (see Table E5 in this article's Online Repository at www.jacionline.org). The high correlations between serum levels of T_H2 -related CCL26 and CCL11 with serum IL-17A levels are also reflected by the high correlations between these T_H2 serum markers with IL-17A mRNA skin expression (see Table E5). Contrary to lesional skin measures that were mostly not correlated with serum markers (except CCL17; Fig 2, C), nonlesional levels of various T_H2 -attracting chemokine and T_H22 /IL-22 levels were significantly correlated with their corresponding serum markers. These markers included CCL13 (*r* = 0.51, *P* = .05), CCL22 (*r* = 0.68, *P* = .0051), CCL26 (*r* = 0.61, *P* = .016), and IL-22 (*r* = 0.58, *P* = .025; Fig 2, C and D). Although serum IL-13 levels showed a positive trend for

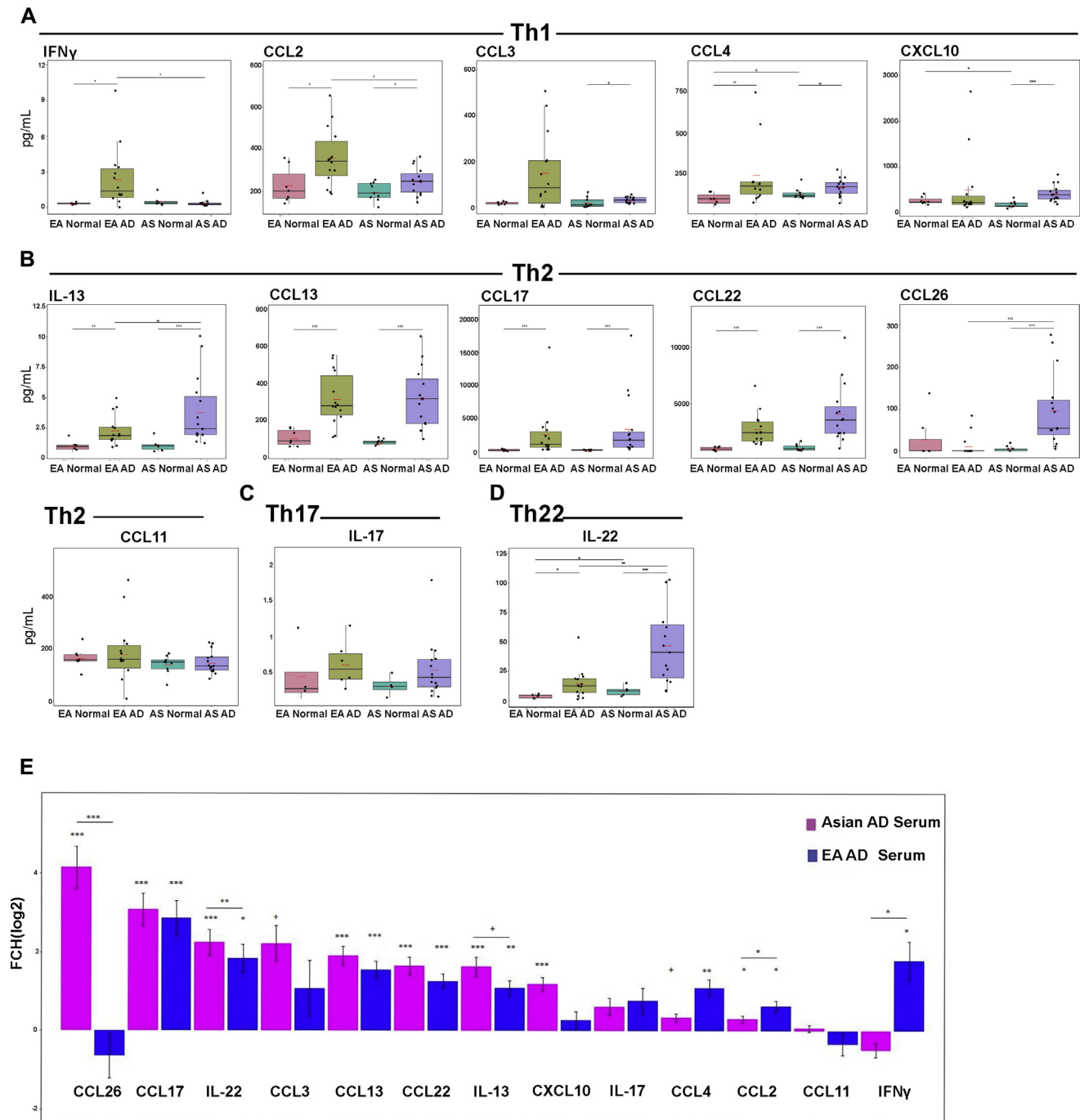


FIG 1. A-D, Box plots depicting serum chemokine/cytokine levels in EA and Asian patients with AD and their respective control subjects. Individual markers were grouped according to major inflammatory/regulatory pathways. Black horizontal lines in boxes indicate medians, red horizontal lines in boxes indicate means, and whiskers represent values within 1.5 times the interquartile range. Black points represent individual patients. Lines above boxes represent intergroup comparisons. **E,** Waterfall FCH comparison between sera from Asian (pink) and EA (blue) patients with AD versus respective control subjects. Significance at top is shown versus each respective control subjects. Significance above the lines compares Asian and EA patients with AD. + $P < .1$, * $P < .05$, ** $P < .01$, and *** $P < .001$.

correlation with nonlesional skin, it did not correlate with lesional values (see Fig E1, F). Levels of T_H1- and T_H17-related markers, which were relatively low in serum (Fig 1), did not correlate with either lesional or nonlesional skin measures (see Fig E1, E and G). Correlations with nonlesional skin suggest that implementing

serum cytokine measures in evaluation of AD severity might enable a more precise assessment of disease extent beyond overt skin lesions. In fact, most serum markers clustered with nonlesional markers in an unsupervised hierarchical clustering (black box and dendrogram; see Fig E2 in this article's Online

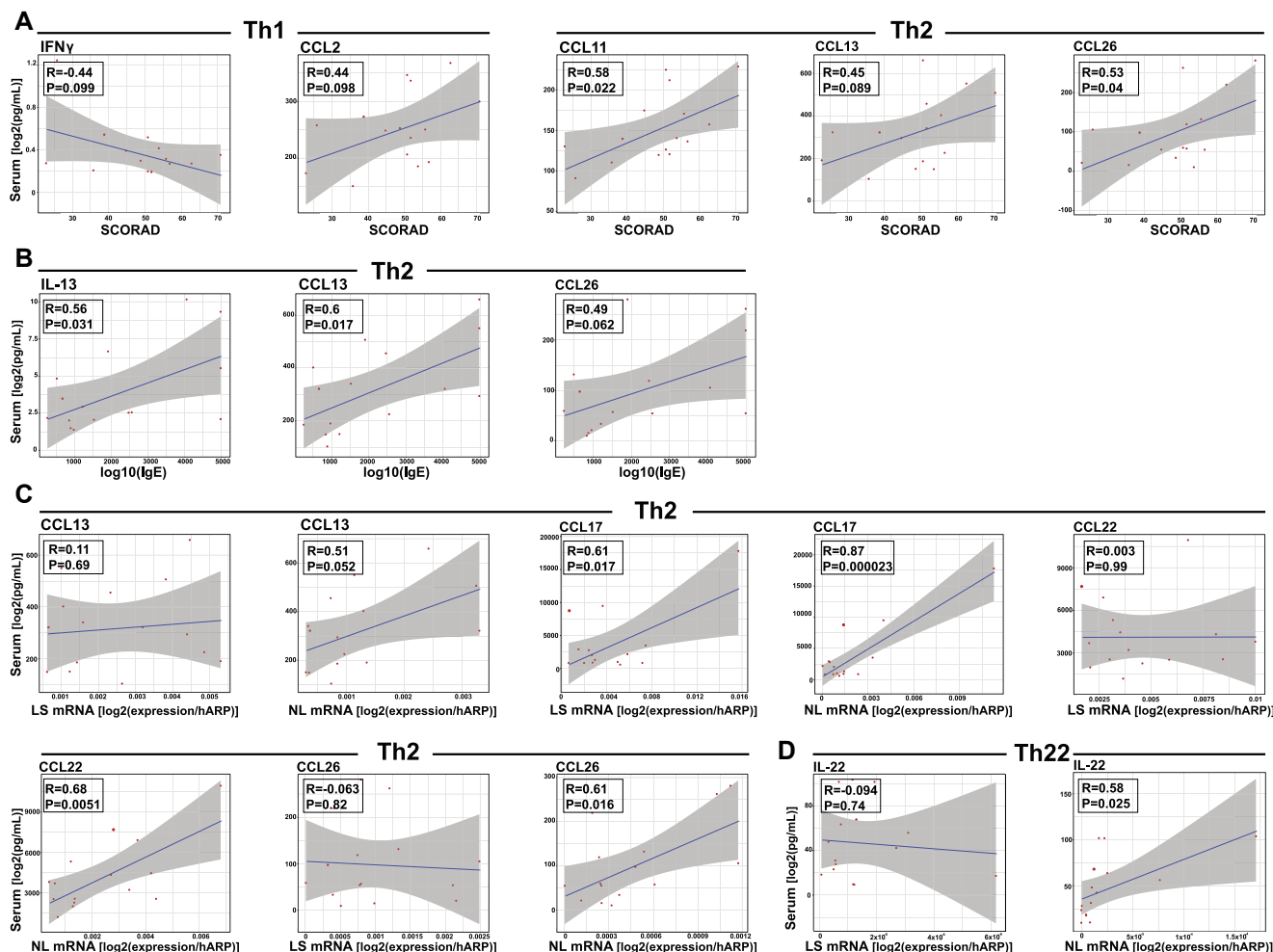


FIG 2. Pearson correlation scatterplots of serum chemokine/cytokine levels in Asian patients with AD, with SCORAD scores (A), IgE levels (B), and mRNA expression (C and D) in lesional (LS) and nonlesional (NL) skin. Red points represent individual patients. r , Pearson correlation coefficient with associated P value. Linear regressions are presented as blue lines with their CIs (shaded area). Data are grouped according to major inflammatory/regulatory pathways. hARP, Human acidic ribosomal protein.

Repository at www.jacionline.org), suggesting their collective reflection of the AD phenotype.

The significant correlations between nonlesional skin and serum markers in Asian patients with AD might be attributed to high circulatory levels of these markers or to induction of polar cytokines by local cutaneous T cells, further highlighting the importance of nonlesional skin in AD pathogenesis in Asian patients similar to that seen in EA patients with AD.¹ These data, together with excessive circulating T-cell activation in patients with AD,⁸ highlight the systemic nature of AD regardless of race and advocate for an integrated approach that includes nonlesional, lesional, and serum biomarkers to construct a precise AD profile.

Overall, sera from Asian patients with AD demonstrate a Th2/Th22 profile, with lower Th1 levels compared with EA patients with AD.² Selective therapeutic approaches against the Th2, Th22, and Th17 cytokine axes with circulating and skin biomarkers are still needed in Asian patients with AD to clarify the relative contribution of each axis to the Asian AD phenotype. This is particularly important because most targeted therapeutic

clinical trials with biomarker correlates were performed in EA patients with AD.

Although prior serum studies in Asian patients focused mostly on Th1/Th2 biomarkers⁹ without comparison across races, to the best of our knowledge, this is the first head-to-head comparison of serum profiles in Asian versus EA patients with AD, with respective lesional and nonlesional skin correlates.

The AD study population only included Asians from Korea and Japan with a primarily Asian diet, possibly affecting their microbiome and potentially influencing their AD phenotype. Future studies will need to determine whether Asian patients from the United States share a similar profile to those from Asia (or whether the primary influence is genetic or environmental).

In summary, integrating serum and skin biomarkers to build a disease profile can advance personalized therapeutics. The serum biomarker phenotyping can serve as a surrogate for assessing disease extent beyond disease severity as assessed by SCORAD score, which only evaluates visible skin lesions. Establishing blood biomarkers is particularly crucial in children, in whom skin

biopsies are challenging. Future studies across different age groups and races are required to develop such approaches.

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METHODS

Patients and samples

This study was conducted under institutional review board–approved protocols. Blood was collected from 15 Asian patients with moderate-to-severe AD (13 male patients/2 female patients; age, 19–33 years [mean, 25.2 years]; SCORAD score [which integrates disease severity and extent with subjective symptoms]^{E1} range, 23–71 [mean, 48.33]) for evaluation of serum chemokine levels. Additionally, blood from 7 healthy EA control subjects^{E2} and 9 healthy Asian control subjects^{E3} was also included from previously published cohorts. Univariate Pearson correlations were performed for lesional and nonlesional (>10 cm from active lesions) skin samples of 27 Asian patients with AD from a previously published cohort.^{E3} Extrinsic AD was defined as an IgE level of greater than 200 kU/L. Patients enrolled in this study were allowed to use only topical emollients, prohibited from using systemic immunomodulators and phototherapy within the prior 4 weeks of the study, and prohibited from using topical steroids or calcineurin inhibitors within the prior 8 days of the study. Table E1 lists patients' demographics.

Serum immunoassays

Electrochemiluminescence immunoassays, which have greater sensitivity than standard ELISAs,^{E4} were used in a multiplex format. Concentrations of 9 chemokines in each sample in sera from Asian and EA patients with AD were quantified through spotting at the bottom of a 96-well plate (Meso Scale Discovery, Rockville, Md). Chemokines assessed included CCL11/eotaxin, CCL26/eotaxin3, CXCL10/interferon-inducible protein 10, CCL2/monocyte chemoattractant protein 1, CCL13/monocyte chemoattractant protein 4, CCL22/macrophage-derived chemokine, CCL3/macrophage inflammatory protein 1 α , CCL4/macrophage inflammatory protein 1 β , and CCL17/thymus and activation-regulated chemokine. After blocking the plate well, serum was added, incubated for 2 hours, and subsequently read in the Sector Imager Reader (Meso Scale Discovery), which measures chemiluminescence. Because serum IFN- γ , IL-17A, IL-13, and IL-22 cytokine levels are very low, we used Erenna immunoassays (EMD Millipore, Burlington, Mass), which have a lower limit of quantification that is 10 to 100 times smaller than that for electrochemiluminescence.^{E2} Single molecule technology, which has the potential to quantify femtomole levels of biomarkers in a single-format assay (EMD Millipore), was used. This assay uses 2 sequential incubations with the target antibody and the fluorophore-labeled detection antibody. Samples were transferred and washed in 1 plates and subsequently read in the Erenna instrument, which measures fluorescence, to decrease background.

Quantitative real-time PCR

RNA was extracted for real-time PCR with EZ-PCR Core reagents (Life technologies, Grand Island, NY) from 27 skin samples from Asian patients with AD, as previously reported.^{E3} The High Capacity cDNA Reverse

Transcription Kit (Applied Biosystems, Foster City, Calif) was used for reverse transcription to cDNA, which was then amplified with TaqMan Pre-Amp Master Mix (Applied Biosystems). Primers used are listed in Table E2. Expression values were normalized to human acidic ribosomal protein, as previously described.^{E3,E5,E6}

Statistical methods

All analyses were carried out in the statistical language R (www.R-project.org). Quantification of chemokines, as measured in picograms per milliliter, were transformed to the log₂ scale, and a 2-sided *t* test on data was performed to assess for significant differences in sera from control subjects versus patients with AD. Intrarace and interracial comparisons were performed. For example, samples from healthy subjects with EA were compared with samples from EA patients with AD but were also compared with samples from healthy Asian subjects and Asian patients with AD. FCHs of each chemokine in the blood of EA and Asian patients with AD (vs respective healthy control subjects) were obtained by using a linear model, with serum levels as the response variable and race as the explanatory variable. FCHs for comparisons of interest were estimated by using contrasts. Univariate correlations with lesional and nonlesional skin data^{E3} were computed by using Pearson correlation coefficients. Correlations are summarized in Tables E3–E5.

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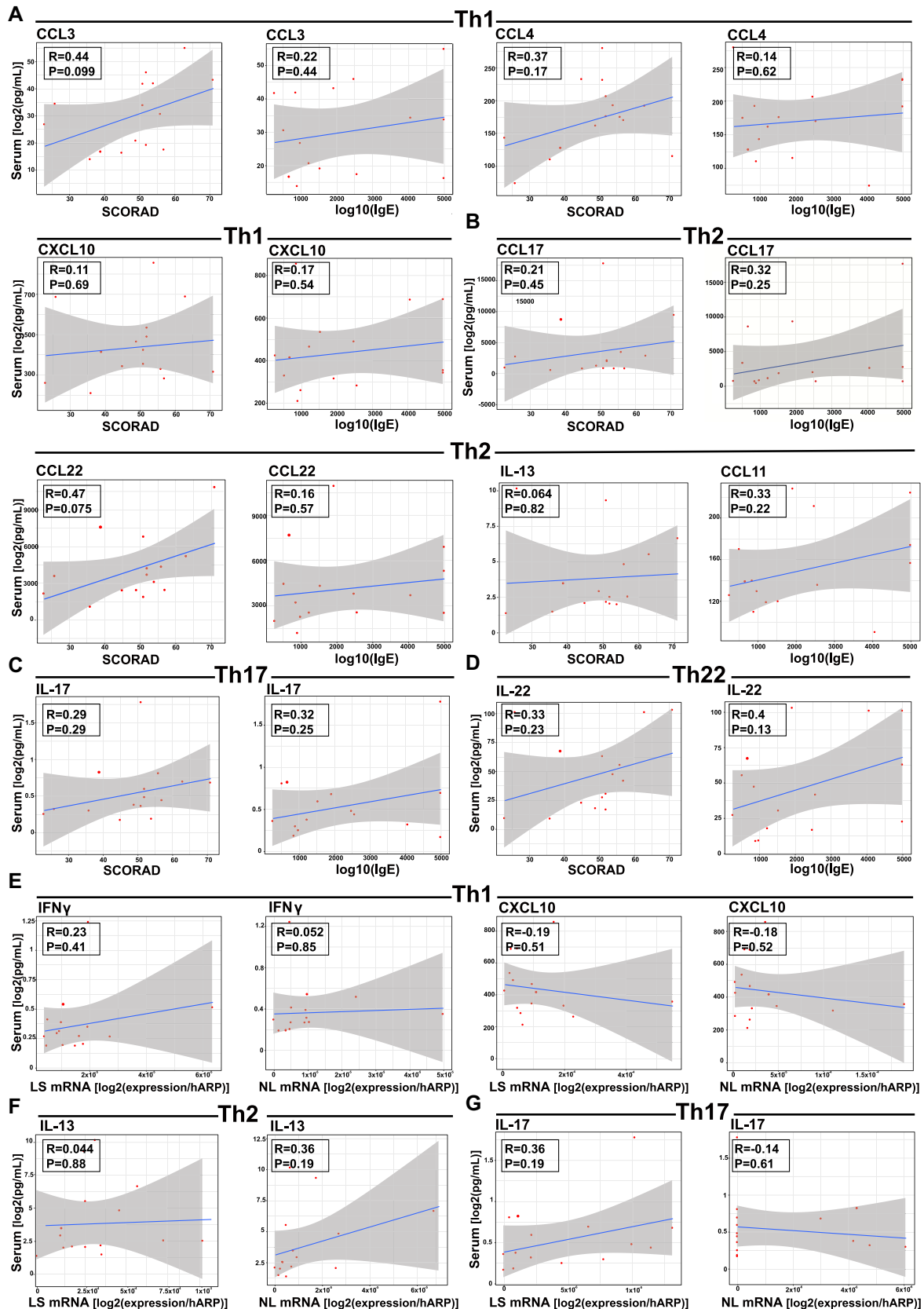


FIG E1. Pearson correlation scatterplots of serum chemokine/cytokine levels in Asian patients with AD, with SCORAD scores and IgE levels (A-D) and mRNA expression in lesional (LS) and nonlesional (NL) skin (E-G) shown. Red points represent individual patients. r , Pearson correlation coefficient with associated P values; Linear regression (blue line) with its CI (shaded area). Data are grouped according to major inflammatory/regulatory pathways. hARP, Human acidic ribosomal protein.

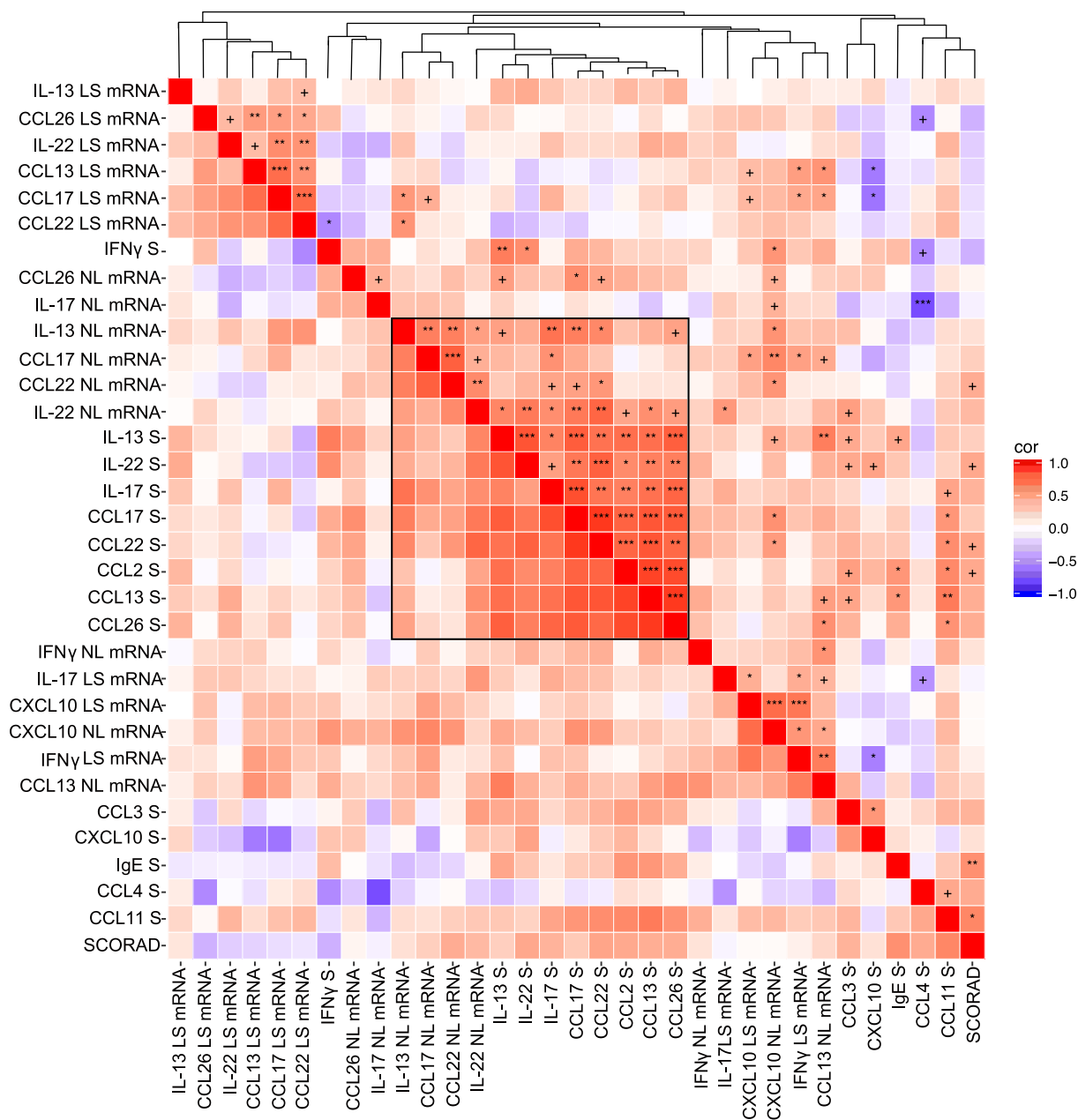


FIG E2. Pearson heat map summarizing correlations between serum chemokine/cytokine levels and mRNA levels of chemokines/cytokines in lesional (LS) and nonlesional (NL) skin of Asian patients with AD and clinical parameters, including IgE levels and SCORAD scores. The *black box* clusters highly correlating serum and nonlesional skin biomarkers. + $P < .1$, * $P < .05$, ** $P < .01$, and *** $P < .001$.

TABLE E1. Patients' demographics

Parameter	Asian patients with AD (n = 15)	Healthy Asian subjects (n = 9)	P value
Age (y), mean (SD)	25.2 (4.35)	28.3 (9.2)	.23
Sex (male/female), no.	13/2	7/2	.61
SCORAD index, mean (SD)	48.3 (12.6)	—	—
IgE (IU/mL), mean (SD)*	2204 (1741)	—	—
Eosinophils, mean (SD)†	8.6 (2.2)	—	—
Extrinsic AD, no. (%)	15/15 (100)	—	—

*Reference range, 0 to 200 kU/L for adults and 0 to 100 kU/L for children.

†Reference range, 0 to 0.8 K/ μ L (absolute eosinophil count).

TABLE E2. RT-PCR primers and probes for skin

Gene symbol	Sequence
<i>hARP</i>	
Forward	CGCTGCTGAACATGCTCAA
Reverse	TGTCGAACACCTGCTGGATG
Probe	6-FAM-TCCCCCTTCTCCTTTGGGCTGG-2TAMRA
	Assay ID
<i>CCL13</i>	Hs00234646_m1
<i>CCL17</i>	Hs00171074_m1
<i>CCL22</i>	Hs01574247_m1
<i>CCL26</i>	Hs00171146_m1
<i>CXCL10</i>	Hs01124251_g1
<i>IFNG</i>	Hs00989291_m1
<i>IL13</i>	Hs00174379_m1
<i>IL17A</i>	Hs00174383_m1
<i>IL22</i>	Hs01574154_m1

hARP, Human acidic ribosomal protein.

TABLE E3. Pearson correlations of serum and skin markers with SCORAD scores

	Correlation	P value
SCORAD score	1	0
IgE levels	0.728985942	2.40E-05
IL17A_NL	0.637566445	.123464126
Serum CCL11	0.583583497	.022379119
Serum CCL26	0.534137518	.040263904
IL13_NL	0.527047856	.020411368
IL17A_LS	0.525759553	.014369456
CCL22_NL	0.50386407	.023504458
Serum CCL22	0.473393019	.074688146
Serum CCL13	0.45366399	.089412329
Serum CCL2	0.443278804	.097936364
Serum CCL3	0.441996115	.099027332
IL22_NL	0.42396857	.079530131
Serum CCL4	0.371197634	.173137954
IFNG_NL	0.354878234	.135990908
Serum IL22	0.330389424	.229082763
CCL17_NL	0.316147122	.174479409
CCL13_NL	0.303488589	.193331211
Serum IL17	0.291750246	.29138301
Serum CCL17	0.213320686	.445246388
CCL26_NL	0.189229558	.424273818
Serum CXCL10	0.112565321	.689587086
CXCL10_NL	0.067259346	.778139875
Serum IL13	0.063986145	.82077442
IFNG_LS	0.050761412	.809579818
IL13_LS	0.031902839	.882354474
CCL17_LS	0.030353769	.885475493
CCL22_LS	0.016227478	.938632878
IL22_LS	−0.134743564	.520766163
CXCL10_LS	−0.146467515	.484785407
CCL13_LS	−0.187234378	.370142842
CCL26_LS	−0.406911636	.043517037
Serum IFNG	−0.442214947	.098840609

LS, Lesional; NL, nonlesional.

TABLE E4. Pearson correlations of serum markers with IgE levels

	Correlation	P value
IgE	1	0
IL17A_NL	0.867502361	.011413793
SCORAD	0.728985942	2.40E-05
Serum CCL2	0.608532756	.016070888
Serum CCL13	0.602571604	.017434913
Serum IL13	0.556655263	.031139663
Serum CCL26	0.493098009	.061804017
IL17A_LS	0.488146391	.028989089
CCL13_NL	0.438707845	.06024261
Serum IL22	0.404551097	.134730756
Serum IFNG	0.367670794	.177578626
Serum CCL11	0.333812079	.224003559
CCL26_NL	0.331615127	.165452562
Serum CCL17	0.31826237	.247654481
Serum IL17	0.315295398	.252334951
CCL17_NL	0.24008577	.322152745
Serum CCL3	0.215123534	.441317086
Serum CXCL10	0.172811405	.537964639
Serum CCL22	0.160588986	.567502943
IFNG_LS	0.154889958	.469880085
Serum CCL4	0.138497773	.622543799
IL13_NL	0.091677462	.717505714
IFNG_NL	0.085837692	.734866217
CXCL10_NL	0.051914069	.832834763
IL13_LS	0.02846596	.897412654
CCL17_LS	0.006725428	.975118738
IL22_NL	−0.045989856	.860868009
CCL22_LS	−0.046514195	.829125068
CCL13_LS	−0.08171614	.704249269
CXCL10_LS	−0.110343932	.607750629
CCL22_NL	−0.118633726	.628584259
CCL26_LS	−0.120997215	.573302117
IL22_LS	−0.253005487	.232936103

LS, Lesional; NL, nonlesional.

TABLE E5. Pearson correlations of serum markers with each other, with skin markers, and with clinical parameters

	A. Serum CXCL10	
	Correlation	P value
Serum CXCL10	1	0
Serum CCL3	0.528455899	.042851094
Serum IL22	0.380106245	.162247869
Serum IFNG	0.363549071	.182861924
Serum CCL2	0.234539196	.400128408
Serum IL13	0.198493996	.478215175
IgE	0.172811405	.537964639
CCL26_NL	0.123547294	.66089896
SCORAD score	0.112565321	.689587086
Serum CCL13	0.052873154	.851550011
Serum CCL4	0.044927664	.873678811
Serum CCL22	−3.48E-05	.999901849
Serum CCL26	−0.022736086	.935897892
CCL22_NL	−0.058174471	.836841417
CCL13_NL	−0.067051245	.812326784
IL22_LS	−0.126070703	.654366848
IL17A_NL	−0.143814085	.817523387
Serum IL17	−0.160289512	.568235156
Serum CCL17	−0.16139579	.565532291
CCL22_LS	−0.165399377	.555796418
CXCL10_NL	−0.181714637	.516885924
CXCL10_LS	−0.186224117	.506355405
IL13_NL	−0.206040241	.461290776
CCL26_LS	−0.20606573	.461234114
Serum CCL11	−0.211529507	.449167544
IL13_LS	−0.294346361	.307006877
CCL17_NL	−0.305609049	.267989765
IL22_NL	−0.315354942	.293925786
IFNG_NL	−0.335646305	.240710595
IFNG_LS	−0.351841842	.198422322
IL17A_LS	−0.438851327	.133559544
CCL17_LS	−0.463554489	.081795142
CCL13_LS	−0.551288798	.033156683

	B. Serum CCL3	
	Correlation	P value
Serum CCL3	1	0
Serum CCL2	0.550739872	.033368396
Serum CCL26	0.544539777	.035830725
Serum CXCL10	0.528455899	.042851094
Serum CCL13	0.498470683	.058590782
Serum IL22	0.492780424	.061997878
SCORAD score	0.441996115	.099027332
Serum CCL11	0.407463222	.131679295
Serum IL13	0.361397395	.185660201
CCL13_NL	0.337592677	.218476078
Serum CCL22	0.312484771	.256818389
IL22_LS	0.286924763	.299802254
IL13_LS	0.262743144	.364126736
Serum CCL4	0.259116689	.3510482
IL17A_LS	0.239290127	.431058451
IL22_NL	0.221002346	.46808796
IgE	0.215123534	.441317086
IL13_NL	0.204961177	.463692653
CCL26_NL	0.171383615	.541379856
IFNG_NL	0.151585975	.604940918
Serum IL17	0.145853981	.603989911
Serum CCL17	0.140739418	.61686689
CXCL10_NL	0.108817807	.699469458

(Continued)

TABLE E5. (Continued)

	B. Serum CCL3	
	Correlation	P value
CCL22_NL	0.105258323	.708897644
CCL17_NL	0.054680185	.846531033
Serum IFNG	0.029825035	.915968699
CXCL10_LS	−0.021843788	.938409147
CCL22_LS	−0.02707221	.923702827
CCL17_LS	−0.032371607	.908820255
IFNG_LS	−0.037814167	.893564909
CCL26_LS	−0.218154014	.43475172
CCL13_LS	−0.23148892	.406460703
IL17A_NL	−0.703331908	.185097733

	C. Serum CCL4	
	Correlation	P value
Serum CCL4	1	0
SCORAD score	0.371197634	.173137954
Serum CCL11	0.332397737	.226093782
Serum CCL3	0.259116689	.3510482
CXCL10_LS	0.21783214	.435446678
CCL17_LS	0.212789471	.446407502
CCL17_NL	0.189109712	.499669492
Serum CCL2	0.177421643	.527002564
Serum IL17	0.174853923	.53309562
Serum CCL13	0.148275982	.597929344
IL17A_LS	0.13934193	.649823112
IgE	0.138497773	.622543799
CXCL10_NL	0.099271748	.724842769
CCL22_LS	0.087752578	.75581593
IFNG_LS	0.084736546	.763984935
IL22_LS	0.075421989	.789356494
Serum CXCL10	0.044927664	.873678811
Serum CCL17	0.01832729	.948310902
Serum CCL26	0.016960429	.95216168
IL13_LS	0.011217977	.969638954
CCL13_LS	−0.089698939	.750556819
CCL22_NL	−0.141250055	.61557651
IFNG_NL	−0.201609512	.489457123
Serum CCL22	−0.214246761	.443225825
IL13_NL	−0.232877179	.403572223
IL17A_NL	−0.255709685	.678004094
Serum IL13	−0.260815925	.347784735
Serum IL22	−0.32978762	.229983218
IL22_NL	−0.357616306	.23026764
CCL26_NL	−0.363904349	.182402539
CCL13_NL	−0.371094798	.173266392
Serum IFNG	−0.480176188	.070053597
CCL26_LS	−0.492377265	.06224461

	D. Serum IL-13	
	Correlation	P value
Serum IL13	1	0
CCL13_NL	0.840302059	8.79E-05
CCL26_NL	0.836048305	.000103162
Serum IL22	0.791890258	.000433958
Serum CCL26	0.737212231	.001712475
Serum IFNG	0.726699801	.002148792
Serum CCL13	0.672421145	.006024757
Serum CCL17	0.662695593	.007095227
Serum IL17	0.592909934	.019832663
Serum CCL2	0.59157961	.020181626
CXCL10_NL	0.588014356	.021140024

(Continued)

TABLE E5. (Continued)

	D. Serum IL-13	
	Correlation	P value
CCL17_NL	0.562668837	.028990721
IgE	0.556655263	.031139663
IFNG_LS	0.549951903	.033674076
Serum CCL22	0.549105736	.034004668
IFNG_NL	0.428468115	.1263753
IL22_NL	0.379869419	.200444281
CCL17_LS	0.377651218	.165202402
Serum CCL3	0.361397395	.185660201
CXCL10_LS	0.359236621	.188498152
IL13_NL	0.357208954	.191186708
CCL26_LS	0.328789706	.231481223
Serum CCL11	0.281333993	.309732878
CCL22_NL	0.266976646	.336095814
Serum CXCL10	0.198493996	.478215175
IL17A_LS	0.166670773	.58628995
CCL13_LS	0.158477437	.572674118
SCORAD	0.063986145	.82077442
IL13_LS	−0.04695984	.873344231
IL22_LS	−0.091769247	.744973967
Serum CCL4	−0.260815925	.347784735
CCL22_LS	−0.336802926	.219623561
IL17A_NL	−0.365845157	.544801608

	E. Serum IL-22	
	Correlation	P value
Serum IL22	1	0
Serum IL13	0.791890258	.000433958
Serum CCL26	0.731308699	.001947688
Serum CCL22	0.715635977	.002700019
CCL13_NL	0.669798137	.006299985
CCL26_NL	0.640047175	.010169528
Serum CCL13	0.604540862	.016974828
Serum IFNG	0.566787388	.027584914
Serum CCL2	0.558994692	.030289889
IL22_NL	0.544799334	.054197923
Serum CCL3	0.492780424	.061997878
Serum CCL17	0.475001994	.073569483
IFNG_NL	0.467621181	.091778302
IL13_NL	0.463303216	.081982731
IgE	0.404551097	.134730756
Serum CXCL10	0.380106245	.162247869
Serum IL17	0.37604869	.167150047
CCL22_NL	0.352207036	.197924494
CXCL10_NL	0.35212374	.198037971
SCORAD score	0.330389424	.229082763
CCL17_NL	0.241509268	.385856326
Serum CCL11	0.225554707	.41892918
IFNG_LS	0.127263559	.651287061
IL17A_LS	0.115279707	.707645391
CCL26_LS	0.098458972	.727015854
CXCL10_LS	0.00618338	.982551279
CCL17_LS	−0.070749394	.802160003
IL13_LS	−0.09201396	.75439466
IL22_LS	−0.093701618	.739773679
CCL13_LS	−0.103139743	.714528001
CCL22_LS	−0.274410413	.32229186

(Continued)

TABLE E5. (Continued)

	E. Serum IL-22	
	Correlation	P value
Serum CCL4	−0.32978762	.229983218
IL17A_NL	−0.613513404	.271080563

	F. Serum IFN- γ	
	Correlation	P value
Serum IFNG	1	0
Serum IL13	0.726699801	.002148792
CCL26_NL	0.645295725	.009378743
CCL13_NL	0.609687072	.015816547
Serum IL22	0.566787388	.027584914
CCL26_LS	0.482320119	.068632865
IgE	0.367670794	.177578626
Serum CXCL10	0.363549071	.182861924
Serum CCL17	0.240155586	.388606523
IFNG_LS	0.227590743	.414629131
CXCL10_NL	0.194452911	.48739918
Serum CCL22	0.171030033	.542227076
Serum CCL26	0.149400998	.595122508
Serum CCL2	0.138569074	.622362925
Serum CCL13	0.127449519	.650807408
CCL13_LS	0.111097028	.693453599
CXCL10_LS	0.089617675	.750776193
CCL17_NL	0.079093266	.779331526
Serum IL17	0.069549356	.805455944
IFNG_NL	0.034176084	.907664119
Serum CCL3	0.029825035	.915968699
IL22_NL	0.025697226	.933589662
IL17A_NL	0.013715785	.982537068
IL13_NL	−0.050539539	.858039369
CCL17_LS	−0.05851681	.835893262
CCL22_NL	−0.075493041	.789162179
Serum CCL11	−0.228678855	.412340514
IL13_LS	−0.248916076	.390808997
IL17A_LS	−0.254862961	.400718003
IL22_LS	−0.261865346	.345777773
CCL22_LS	−0.431750972	.10804823
SCORAD score	−0.442214947	.098840609
Serum CCL4	−0.480176188	.070053597

	G. Serum CCL22	
	Correlation	P value
Serum CCL22	1	0
Serum CCL26	0.824355024	.000156685
IFNG_NL	0.7937341	.000701366
IL13_NL	0.769555863	.000794197
Serum CCL17	0.761973582	.000960888
IL22_NL	0.749021283	.003212656
Serum IL22	0.715635977	.002700019
Serum CCL13	0.715228583	.002722286
CCL22_NL	0.681704548	.005125973
CCL26_NL	0.649702606	.008752626
CXCL10_NL	0.632535187	.011390763
Serum CCL11	0.63083236	.011682812
Serum CCL2	0.624638299	.012794545
Serum IL17	0.601587156	.017668476
Serum IL13	0.549105736	.034004668

(Continued)

TABLE E5. (Continued)

G. Serum CCL22		
	Correlation	P value
CCL13_NL	0.511135096	.051500563
SCORAD score	0.473393019	.074688146
CCL17_NL	0.465947934	.0800236
IL17A_LS	0.314251103	.295711154
Serum CCL3	0.312484771	.256818389
IFNG_LS	0.256359326	.356379979
CXCL10_LS	0.200272332	.47420017
Serum IFNG	0.171030033	.542227076
IgE	0.160588986	.567502943
CCL17_LS	0.11638812	.679553933
IL13_LS	0.03336023	.909860096
IL22_LS	0.017892985	.949534333
CCL22_LS	0.002972313	.991612055
Serum CXCL10	−3.48E-05	.999901849
CCL13_LS	−0.019668224	.944534199
CCL26_LS	−0.16623652	.553769804
Serum CCL4	−0.214246761	.443225825
IL17A_NL	−0.838776613	.075802589

H. Serum CCL26		
	Correlation	P value
Serum CCL26	1	0
Serum CCL13	0.923685151	8.91E-07
Serum CCL22	0.824355024	.000156685
Serum CCL2	0.819815088	.000182815
Serum CCL17	0.769759178	.000790074
Serum CCL11	0.737954542	.001684594
Serum IL13	0.737212231	.001712475
Serum IL17	0.733475516	.001858521
Serum IL22	0.731308699	.001947688
IFNG_NL	0.696038868	.005693879
CXCL10_NL	0.679485024	.005330508
CCL13_NL	0.66147287	.00723975
IL22_NL	0.639572727	.018576329
IL13_NL	0.627908187	.012197881
CCL17_NL	0.618345342	.014006337
CCL26_NL	0.610659428	.015604717
Serum CCL3	0.544539777	.035830725
SCORAD score	0.534137518	.040263904
IL17A_LS	0.52184282	.067375331
IgE	0.493098009	.061804017
IFNG_LS	0.468307693	.078303957
CCL22_NL	0.45861076	.085542411
CCL17_LS	0.41017411	.128881293
CXCL10_LS	0.324692661	.237695127
IL13_LS	0.195008008	.504079231
IL22_LS	0.16910636	.54684656
Serum IFNG	0.149400998	.595122508
CCL13_LS	0.121631771	.66587273
Serum CCL4	0.016960429	.95216168
CCL22_LS	−0.018291886	.94841063
Serum CXCL10	−0.022736086	.935897892
CCL26_LS	−0.062504422	.824864779
IL17A_NL	−0.815218628	.092662011

I. Serum CCL13		
	Correlation	P value
Serum CCL13	1	0
Serum CCL26	0.923685151	8.91E-07
Serum CCL2	0.897084916	5.83E-06

(Continued)

TABLE E5. (Continued)

I. Serum CCL13		
	Correlation	P value
Serum IL17	0.777479259	.000645894
Serum CCL11	0.751634591	.001232741
Serum CCL17	0.734254891	.001827263
Serum CCL22	0.715228583	.002722286
Serum IL13	0.672421145	.006024757
CXCL10_NL	0.614976497	.014690527
Serum IL22	0.604540862	.016974828
IgE	0.602571604	.017434913
CCL17_NL	0.575407441	.024810051
CCL26_NL	0.518219023	.047820948
CCL13_NL	0.510327211	.051933037
Serum CCL3	0.498470683	.058590782
IFNG_NL	0.471294828	.08891426
CCL17_LS	0.468513755	.078155056
IFNG_LS	0.462665523	.08246018
SCORAD score	0.45366399	.089412329
IL13_NL	0.447885889	.094087432
IL17A_LS	0.425753604	.146915628
IL22_NL	0.411687843	.16219937
CXCL10_LS	0.394689618	.145419475
IL22_LS	0.311030742	.259156761
CCL22_NL	0.273388363	.324170164
IL13_LS	0.227170836	.434777413
Serum CCL4	0.148275982	.597929344
Serum IFNG	0.127449519	.650807408
CCL22_LS	0.11225684	.690398833
CCL13_LS	0.110874179	.694041051
Serum CXCL10	0.052873154	.851550011
CCL26_LS	−0.024993847	.929546276
IL17A_NL	−0.804207257	.10088903

J. Serum CCL2		
	Correlation	P value
Serum CCL2	1	0
Serum CCL13	0.897084916	5.83E-06
Serum CCL26	0.819815088	.000182815
Serum CCL11	0.647929466	.009000485
Serum CCL22	0.624638299	.012794545
Serum IL17	0.619695392	.013739179
IgE	0.608532756	.016070888
Serum IL13	0.59157961	.020181626
Serum CCL17	0.585007266	.021975078
Serum IL22	0.558994692	.030289889
Serum CCL3	0.550739872	.033368396
SCORAD score	0.443278804	.097936364
CXCL10_NL	0.433726503	.106265939
CCL26_NL	0.39376462	.146450448
CCL17_NL	0.349229783	.202006493
IL22_LS	0.330972194	.228212892
CCL13_NL	0.328809937	.231450793
IFNG_NL	0.292330149	.310487427
IL17A_LS	0.282487447	.349716129
IL13_NL	0.271084797	.32842652
IFNG_LS	0.254527686	.359946376
Serum CXCL10	0.234539196	.400128408
CCL17_LS	0.23001088	.409547866
IL22_NL	0.222432053	.465140059
CXCL10_LS	0.200523413	.473634611
CCL22_NL	0.194200806	.487974886
Serum CCL4	0.177421643	.527002564
IL13_LS	0.158550167	.588249114

(Continued)

TABLE E5. (Continued)

J. Serum CCL2		
	Correlation	P value
Serum IFNG	0.138569074	.622362925
CCL22_LS	0.045948056	.870831741
CCL13_LS	−0.108980706	.699038942
CCL26_LS	−0.240510232	.387884998
IL17A_NL	−0.930632291	.021701944

K. Serum CCL11		
	Correlation	P value
Serum CCL11	1	0
Serum CCL13	0.751634591	.001232741
Serum CCL26	0.737954542	.001684594
CXCL10_NL	0.666272221	.006685466
Serum CCL2	0.647929466	.009000485
IFNG_NL	0.645093282	.01273197
Serum CCL22	0.63083236	.011682812
Serum CCL17	0.627842567	.012209638
IL17A_LS	0.615212271	.025219522
SCORAD score	0.583583497	.022379119
Serum IL17	0.570725861	.026289406
CCL17_NL	0.561871123	.029269147
IL22_NL	0.559905764	.046599537
IL13_NL	0.502614207	.056197164
CCL17_LS	0.492720852	.062034291
IFNG_LS	0.438349733	.102175161
CXCL10_LS	0.422020765	.117130206
CCL22_NL	0.417488532	.121534965
IL22_LS	0.409145019	.129938632
Serum CCL3	0.407463222	.131679295
IL13_LS	0.406166263	.149570885
CCL22_LS	0.351482946	.198912348
IgE	0.333812079	.224003559
Serum CCL4	0.332397737	.226093782
CCL13_NL	0.320799032	.243695488
Serum IL13	0.281333993	.309732878
CCL26_NL	0.269993999	.33045307
CCL13_LS	0.244770182	.379274406
Serum IL22	0.225554707	.41892918
CCL26_LS	−0.197828625	.47972159
Serum CXCL10	−0.211529507	.449167544
Serum IFNG	−0.228678855	.412340514
IL17A_NL	−0.783234892	.117129711

L. Serum CCL17		
	Correlation	P value
Serum CCL17	1	0
Serum IL17	0.912992361	2.04E-06
CXCL10_NL	0.907081547	3.08E-06
CCL17_NL	0.871356219	2.33E-05
Serum CCL26	0.769759178	.000790074
Serum CCL22	0.761973582	.000960888
IFNG_LS	0.750030943	.001279973
Serum CCL13	0.734254891	.001827263
CXCL10_LS	0.697643272	.003832884
Serum IL13	0.662695593	.007095227
CCL26_NL	0.658580793	.007590804
IFNG_NL	0.641155244	.01347112
Serum CCL11	0.627842567	.012209638
CCL17_LS	0.606243188	.016584686
Serum CCL2	0.585007266	.021975078
CCL22_NL	0.505479931	.054584041

(Continued)

TABLE E5. (Continued)

L. Serum CCL17		
	Correlation	P value
CCL13_NL	0.502461287	.056284211
Serum IL22	0.475001994	.073569483
IL13_NL	0.457865937	.086117352
IL22_NL	0.374895329	.206889471
IL17A_LS	0.338084453	.258547066
IgE	0.31826237	.247654481
Serum IFNG	0.240155586	.388606523
SCORAD score	0.213320686	.445246388
CCL13_LS	0.181245189	.517987875
Serum CCL3	0.140739418	.61686689
Serum CCL4	0.01832729	.948310902
CCL26_LS	−0.040168528	.886976116
IL22_LS	−0.081546101	.772651536
IL13_LS	−0.095134187	.746311514
Serum CXCL10	−0.16139579	.565322291
CCL22_LS	−0.219884644	.431024784
IL17A_NL	−0.740396652	.152447185

M. Serum IL-17		
	Correlation	P value
Serum IL17	1	0
Serum CCL17	0.912992361	2.04E-06
CCL17_NL	0.882675826	1.32E-05
Serum CCL13	0.777479259	.000645894
CXCL10_NL	0.763417961	.000927127
Serum CCL26	0.733475516	.001858521
CCL17_LS	0.730439939	.00198439
IFNG_LS	0.72372694	.002287113
CXCL10_LS	0.722600882	.002341332
Serum CCL2	0.619695392	.013739179
Serum CCL22	0.601587156	.017668476
Serum IL13	0.592909934	.019832663
Serum CCL11	0.570725861	.026289406
CCL26_NL	0.492330719	.062273143
IFNG_NL	0.412257409	.142975541
CCL22_NL	0.40421867	.135082113
Serum IL22	0.37604869	.167150047
IL13_NL	0.336218684	.220474885
CCL13_NL	0.327428928	.233533726
IgE	0.315295398	.252334951
SCORAD score	0.291750246	.29138301
IL17A_LS	0.277974661	.357795721
IL22_NL	0.202364696	.507310441
Serum CCL4	0.174853923	.53309562
Serum CCL3	0.145853981	.603989911
Serum IFNG	0.069549356	.805455944
IL22_LS	0.062827632	.823972182
CCL13_LS	0.061254615	.82831818
IL13_LS	−0.03350276	.909476415
CCL26_LS	−0.049622375	.860592165
Serum CXCL10	−0.160289512	.568235156
CCL22_LS	−0.178954832	.523379365
IL17A_NL	−0.627993938	.256626037

LS, Lesional; NL, nonlesional.