Genome-wide association study of recalcitrant atopic dermatitis in Korean children

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Background: Atopic dermatitis (AD) is a heterogeneous chronic inflammatory skin disease. Most AD during infancy resolves during childhood, but moderate-to-severe AD with allergic sensitization is more likely to persist into adulthood and more often occurs with other allergic diseases.

Objective: We sought to find susceptibility loci by performing the first genome-wide association study (GWAS) of AD in Korean children with recalcitrant AD, which was defined as moderate-to-severe AD with allergic sensitization.

Methods: Our study included 246 children with recalcitrant AD and 551 adult control subjects with a negative history of both allergic disease and allergic sensitization. DNA from these subjects was genotyped; sets of common single nucleotide polymorphisms (SNPs) were imputed and used in the GWAS after quality control checks.

Results: SNPs at a region on 13q21.31 were associated with recalcitrant AD at a genome-wide threshold of significance ($P < 2.0 \times 10^{-8}$). These associated SNPs are more than 1 Mb from the closest gene, protocadherin (*PCDH*)9. SNPs at 4 additional loci had P values of less than 1×10^{-6}, including SNPs at or near the neuroblastoma amplified sequence (*NBAS*; 2p24.3), thymus-expressed molecule involved in selection (*THEMIS*; 6q22.33), *GATA3* (10p14), and S-phase cyclin A-associated protein in the ER (*SCAPER*; 15q24.3) genes. Further analysis of total serum IgE levels suggested 13q21.31 might be primarily an IgE locus, and analyses of published data demonstrated that SNPs at the 15q24.3 region are expression quantitative trait loci for 2 nearby genes, *ISL2* and proline-serine-threonine phosphatase interacting protein 1 (*PSTPIP1*), in immune cells.

Conclusion: Our GWAS of recalcitrant AD identified new susceptibility regions containing genes involved in epithelial cell function and immune dysregulation, 2 key features of AD, and potentially extend our understanding of their role in pathogenesis. (J Allergy Clin Immunol 2015;136:678-84.)

Key words: *Genome-wide association study, atopic dermatitis, allergic sensitization, IgE, severity, children*

Atopic dermatitis (AD) is a complex chronic inflammatory skin disease that commonly presents during childhood, when it is strongly associated with allergic sensitization.[1] Although AD has a varied disease course, children with moderate-to-severe AD with allergic sensitization are more likely to have disease persisting to adulthood and more concomitant allergic diseases, such as asthma or allergic rhinitis, which result in significant health care costs.[2] Available treatment options for the prevention and treatment of this subtype of recalcitrant AD are still insufficient,[3] reflecting our poor understanding of disease pathogenesis.

AD is highly heritable, with heritability estimates of 72% in European twin pairs[4,5] and genetic studies supporting a significant role for aberrant gene expression in patients with AD.[6] In particular, low-frequency and rare loss-of-function variants in the filaggrin gene *(FLG)* are major predisposing factors for persistent AD, as well as for skin infections with AD and multiple allergic diseases.[7-9] Filaggrin deficiency results in skin barrier dysfunction, resulting in accelerated water loss, skin alkalinization, and colonization by microbial pathogens.[10] Based on these findings, epithelial barrier dysfunction (in particular filaggrin) has been placed at the center of AD pathogenesis.

Three large genome-wide association studies (GWASs),[11-13] a meta-analysis of GWASs from 16 population-based European cohorts,[14] and targeted studies using the immunochip[15] have identified several candidate AD genes in addition to *FLG*. However, none reached genome-wide significance in the discovery samples, and moreover, there were no shared loci among the top associations in studies of European and Han Chinese AD populations.[11,12] These combined results suggest genetic heterogeneity in AD between continental populations, particularly when broad case definitions are used. AD is characterized by genetic and

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Abbreviations used
AD: Atopic dermatitis
eQTL: Expression quantitative trait locus
FLG: Filaggrin gene
GWAS: Genome-wide association study
LD: Linkage disequilibrium
NBAS: Neuroblastoma amplified sequence
PCDH: Protocadherin
PSTPIP1: Proline-serine-threonine phosphatase interacting protein 1
SCAPER: S-phase cyclin A-associated protein in the ER
SNP: Single nucleotide polymorphism
THEMIS: Thymus-expressed molecule involved in selection

phenotypic heterogeneity, and this is consistent with the finding that susceptibility loci discovered to date, including *FLG*, account for only 14.4% of the heritability of AD in Europeans.[15] This also suggests that studies in additional populations and with narrower clinical definitions are needed to fully characterize the genetic architecture of AD.

Here we conducted the first GWAS of AD in Korean children and focused on the distinct phenotype of recalcitrant AD, which is defined as moderate-to-severe AD with allergic sensitization. Moreover, we included as control subjects nonallergic adults without a history of allergic diseases. We identified a novel region of chromosome 13q21.31 as likely to contain genes controlling AD risk, which was genome-wide significant, with additional loci, including neuroblastoma amplified sequence *(NBAS)*, thymus-expressed molecule involved in selection *(THEMIS)*, *GATA3*, and S-phase cyclin A-associated protein in the ER (*SCAPER*), as suggested genes for AD.

METHODS

Sample compositions

Our study included 246 Korean children with both moderate-to-severe AD and allergic sensitization and 551 Korean adult control subjects without a history of allergic diseases or evidence of allergic sensitization. In addition, because IgE levels vary with age, we performed association studies of selected single nucleotide polymorphisms (SNPs) with total serum IgE levels in the 246 case children and 108 healthy Korean children without allergic disease or evidence of allergic sensitization where measured levels of total serum IgE as controls were available (see Table E1 in this article's Online Repository at www.jacionline.org). Case and control children were recruited from Severance Children's Hospital, Seoul, Korea, and adult control subjects were from the Ansung population-based cohort (n = 5108), which was established as part of the KoGES by the Korea Center for Diseases Control and Prevention.[16]

Clinical evaluations

AD was diagnosed by pediatric allergists based on the revised Hanifin and Rajka criteria.[17] We first determined severity by using SCORAD indexes[18] of 572 children and then recruited 275 case children with moderate-to-severe AD (SCORAD score ≥30; mean ± SD, 59.9 ± 14.4) for our studies. Allergic sensitization was defined by specific IgE levels of greater than 0.7 kU_A/L to at least 1 of the following food or airborne allergens: egg white, milk, peanut, soybean, wheat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria* species, or *Blattella germanica*. Of the 275 children with moderate-to-severe AD, 246 had specific IgE to at least 1 of the allergens. We selected 551 adult control subjects with a negative history of both allergic diseases and allergic sensitization among 1214 adults. Negative histories of allergic diseases, including asthma and AD, were based on a self-administered questionnaires; lack of sensitization was based on a negative skin prick test response to 12 common allergens (*D pteronyssinus*, *D farinae*, 2 tree pollen mixtures, grass pollen mixture, ragweed, mugwort, cockroach, *Alternaria* species, *Aspergillus* species, cat dander, and dog dander). Additionally, 108 control children were recruited during routine hospital visits and included in our study if they had a negative history of allergic diseases based on interviews with their parents, had negative serum specific IgE levels to 6 common allergens (egg white, milk, *D pteronyssinus*, *D farinae*, *Alternaria* species, or *Blattella germanica*), and had total serum IgE levels of less than 100 kU/L. All cases and control subjects were unrelated, and either they or their parents provided written informed consent for participation in the study according to the hospital's institutional review board.

Genotyping, imputation, and quality control in the GWAS

Blood samples were collected from each participant, and the derived genomic DNA was genotyped with the Affymetrix Axiom array in the children with AD and control children and the Affymetrix 5.0 chip (Affymetrix, Santa Clara, Calif) in the adult control subjects (see Table E1). We excluded samples with call rates for autosomal SNPs of less than 95% and excluded SNPs with minor allele frequencies of less than 5% or Hardy-Weinberg P values of less than 10^{-4}. Quality control was performed with PLINK 1.07.[19] After quality control exclusions, 402,919 SNPs remained in the children, and 287,622 SNPs remained in the adults. The common sets of SNPs were then used for imputation by using minimac[20] and the 1000 Genomes Asian reference panel.[21] The resulting genotype data for 14,598,181 SNPs were subjected to further quality control checks and selected for high imputation accuracy ($r^2 > .9$) and minor allele frequency of greater than 5%. As a final quality filter, SNPs were excluded if their allele frequencies differed ($P \geq .001$) between the adult and child control samples. In all, 2,501,352 autosomal SNPs were used for the GWAS analysis.

Association of the most significant SNPs with total serum IgE levels

We tested 20 of the 53 SNPs with P values of less than 10^{-6} in the GWAS of AD after pruning for linkage disequilibrium (LD; $r^2 > 0.8$ in the Asian 1000 genomes data) for association with total serum IgE levels in 108 control children (see Table E1). These studies were performed in nonallergic control children to determine whether these variants were also associated with IgE levels independent of AD (see Fig E1 in this article's Online Repository at www.jacionline.org).

Replication studies

To examine the association of SNPs with P values of less than 10^{-6} in our GWAS, we obtained P values of those SNPs from a GWAS of AD in Japanese subjects (see Table E1). That study included 1472 cases with physician-diagnosed AD and 7966 control subjects, including 6042 subjects with one of 5 non-AD diseases (cerebral aneurysm, esophageal cancer, endometrial cancer, chronic obstructive pulmonary disease, and glaucoma) and 1929 healthy volunteers without a history of asthma or AD.[13]

Gene expression and expression quantitative trait loci analysis

To determine whether the SNPs associated with AD in our GWAS were expression quantitative trait loci (eQTLs), we used the eQTL browser (GTEx, http://www.gtexportal.org/)[22] and published reports from eQTL studies of different cell types, including skin,[15,23-25] B cells and monocytes,[26,27] and $CD14^+$ monocytes stimulated with IFN-γ or LPS.[28]

Statistical analysis

We performed logistic regression analysis for binary phenotypes (AD) and linear regression analysis for continuous phenotypes (total serum IgE) by using R software for an additive model. The statistical significance of the association with each SNP was assessed by using a 1-*df* Cochran-Armitage trend test. Regional association plots were generated with LocusZoom.[29]

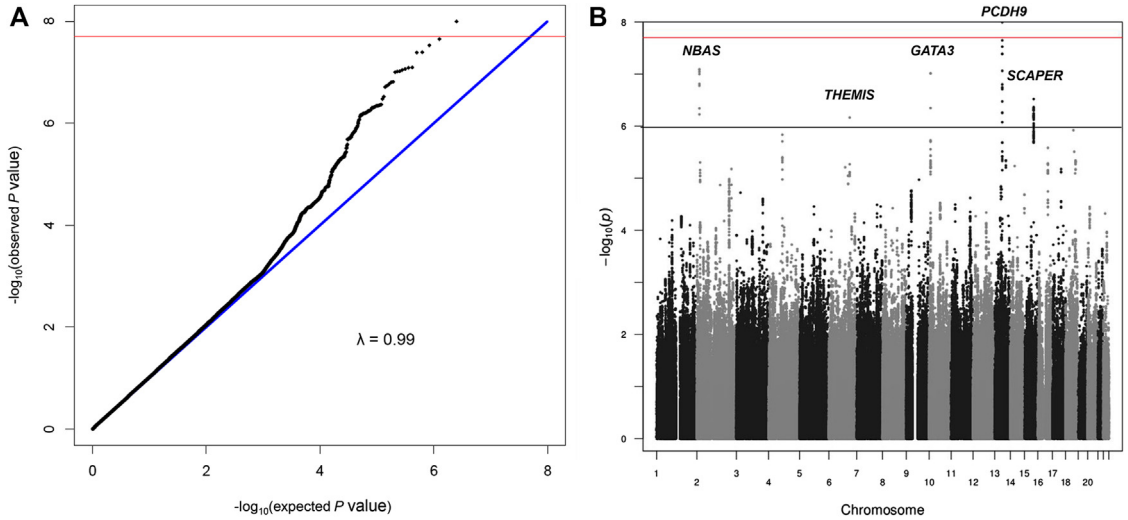

FIG 1. A, Quantile-quantile plot of *P* values for test statistics (Cochran-Armitage trend tests) in the GWAS. *Horizontal* and *vertical axes* show expected *P* values under a null distribution and observed *P* values, respectively. *Black data points* correspond to the *P* values of all SNPs in the GWAS. **B,** Manhattan plot showing the $-\log_{10}$ *P* values of 2,501,352 SNPs in the GWAS for 246 Korean children with recalcitrant AD and 551 Korean adult control subjects without a history of allergic diseases and allergic sensitization plotted against their respective positions on the autosomes. The *red line* shows the genome-wide significance threshold ($P = 2.0 \times 10^{-8}$). The *gray line* shows the threshold at a *P* value of 1×10^{-6}. Locations of *NBAS* (2p24.3), *THEMIS* (6q22.33), *GATA3* (10p14), *PCDH9* (13q21.31), and *SCAPER* (15q24.3) loci are indicated.

RESULTS

The GWAS of AD in 246 Korean children with moderate-to-severe AD and allergic sensitization and 551 Korean adults with a negative history of allergic diseases and no allergic sensitization showed an excess of small *P* values compared with those expected by chance (Fig 1, *A*). One SNP (rs9540294) at 13q21.31 passed the genome-wide threshold of significance (Bonferroni-corrected $P < 2.0 \times 10^{-8}$); 13 additional SNPs at this region, including protocadherin (*PCDH*)*20-PCDH9*, were associated with moderate-to-severe AD with allergic sensitization at a *P* value of less than 1×10^{-6} (Fig 1, *B*, and see Fig E2, *A*, in this article's Online Repository at www.jacionline.org). A total of 39 SNPs in 4 additional regions were also associated at a *P* value of less than 1×10^{-6}: *NBAS* at 2p24.3 (see Fig E2, *B*), *THEMIS* at 6q22.33 (see Fig E2, *C*), the *GATA3-CELF2* locus at 10p14 (see Fig E2, *D*), and *SCAPER* at 15q24.3 (Fig 2). The most significant SNP at each locus is shown in Table I; the results for SNPs at these 6 loci are shown in Table E2 in this article's Online Repository at www.jacionline.org.

Because all the cases had both AD and allergic sensitization and the adult control subjects had neither, we used a second control group of nonallergic children with measured levels of total serum IgE to disentangle associations primarily with AD from those that primarily with IgE levels (ie, allergic sensitization). SNPs at the 13q21.31 locus showed suggestive evidence for association with serum total IgE levels in 108 control children ($P < .05$, Table II). Thus it is likely that the association with AD at this region might be due to the significantly higher levels of IgE in the AD cases compared with those in the nonallergic control subjects and that the primary effects of this locus are on IgE production and not the risk of AD *per se*.

To attempt replication of the SNPs identified in our GWAS of patients with moderate-to-severe AD with allergic sensitization, we examined the results of the 53 SNPs yielding *P* values of less than 10^{-6} in our study compared with a published GWAS in another Asian study comprised of Japanese adults in which AD was diagnosed by physicians irrespective of severity or allergic sensitization population.[13] None of the associations in the Korean children in our study were replicated in the study of Japanese adults (see Table E2).

We next examined in our study subjects SNP loci associated with AD or IgE in previous GWASs. We detected modest associations ($P < .05$) with SNPs associated with AD at the *IL2-IL21*, *RAD50-IL13*, *TMEM232-SLC25A46*, *KIF3A*, and *ZNF365* loci and with total serum IgE levels at the *PTBP2*, *PEX14*, *IL2-ADAD1*, *PTGER4*, *TSLP*, *SLC25A46*, *RAD50*, *PCDH20*, *FOXA1-TTC6*, and *IL4R-IL21R* loci (Table III).[12,14,15,30-36] Among these associations, 4 regions (4q27, 5q13, 5q22.1, and 5q31) have been previously reported in GWASs of both AD and IgE phenotypes. In addition, an SNP near the *PCDH20* gene at the 13q21.31 region was previously associated with IgE in a Japanese population,[30] further suggesting the 13q21.31 region might contain a gene controlling IgE levels.

Finally, we investigated whether the 53 SNPs associated with AD at a *P* value of less than 10^{-6} in our study or SNPs in strong LD with these SNPs ($r^2 = 0.8$) were also associated with the expression of nearby (±1 Mb) genes (ie, are *cis*-eQTLs) in relevant tissues.[15,22-28] Five SNPs in strong LD at the 15q24.3 locus were *cis*-eQTLs for proline-serine-threonine phosphatase interacting protein 1 (*PSTPIP1*) in primary $CD14^+$ monocytes after LPS exposure ($P = 1.8 \times 10^{-5}$, Fig 2)[28] and were also *cis*-eQTLs for *ISL2* in whole blood ($P < 3.1 \times 10^{-6}$, GTEx). SNPs at the other 4 AD-associated loci in our study were not reported as eQTLs in any published studies in skin or blood cells.

DISCUSSION

AD is a heterogeneous disease[1] with respect to the presence of allergic sensitization, total serum IgE levels, predilection to skin lesions, and prognosis, which differ both between children and

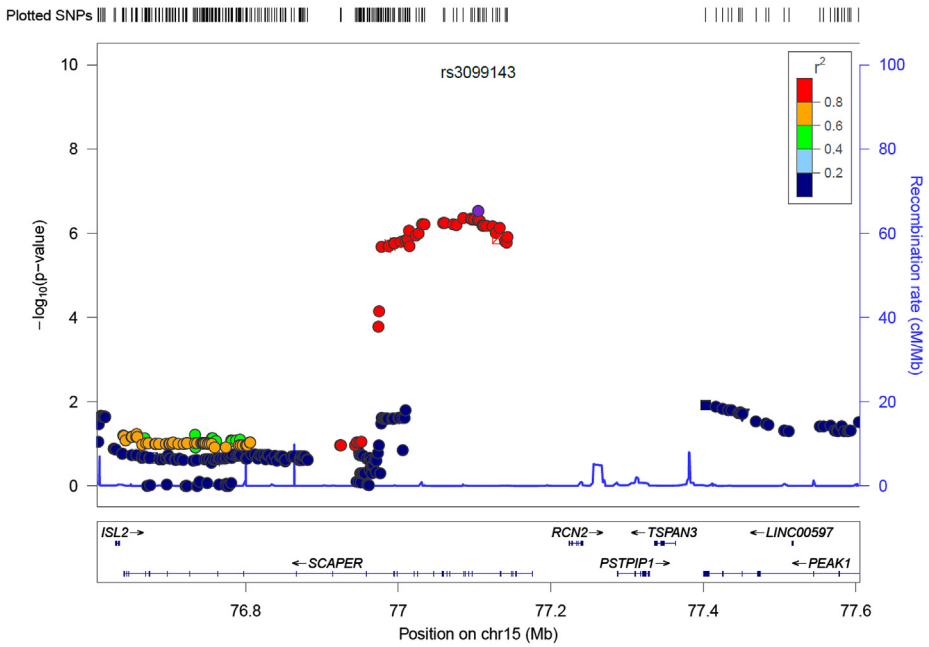

FIG 2. Regional association plots at the 15q24.3 locus for recalcitrant AD. Significant SNPs are located within *SCAPER* and include *cis*-eQTLs for *ISL2* in whole blood and for *PSTPIP1* in CD14$^+$ monocytes after treatment with LPS for 24 hours. The $-\log_{10}$ *P* value *(left y-axis)* of each SNP is shown according to its chromosomal position *(x-axis)*. Genetic recombination rates are shown by the *blue line*, and *horizontal arrows* indicate locations of genes and direction of transcription. The most associated SNP (labeled by rs number) is shown as a purple circle, and its LD *(r^2)* with all other SNPs is indicated by color.

TABLE I. Summary of GWASs of AD at *P* values of less than 10^{-6} in Korean children

Genes or nearby genes	Location	SNP	Position	Alleles (risk/alt)	RAF (cases)	RAF (control subjects)	*P* value	OR	95% CI
NBAS	2p24.3	rs13403179	15482752	C/G	0.131	0.054	8.07E-08	2.947	1.989-4.386
THEMIS	6q22.33	rs675531	128040839	C/T	0.205	0.113	6.82E-07	2.193	1.610-2.994
GATA3	10p14	rs35766269	9023815	A/T	0.717	0.580	9.61E-08	1.946	1.529-2.494
PCDH9	13q21.31	rs9540294	65564031	G/T	0.181	0.083	1.01E-08*	2.655	1.904-3.717
SCAPER	15q24.3	rs3099143	77104856	C/A	0.239	0.137	3.02E-07	2.126	1.594-2.841

The most significant SNPs at each locus are shown and ordered by genomic location.
OR, Odds ratio; *RAF*, risk allele frequency.
*P value exceeded the threshold for Bonferroni-corrected genome-wide significance ($P < 2.0 \times 10^{-8}$).

adults and among children and adults separately.[2] It is likely that the genetic architecture also differs between phenotypic subtypes of AD. Yet this heterogeneity was not considered in previous GWASs that included cases with physician-diagnosed AD without regard to severity or sensitization and relied on population control subjects who were not screened for AD or allergic sensitization.[11-13] We hypothesized that focusing on more severe AD in sensitized children would identify additional genes and pathways. To this end, we focused on an extreme phenotype by including only children with moderate-to-severe AD and allergic sensitization and considered as control subjects adults without a current or prior history of allergic disease and lack of allergic sensitization. The stringent criteria resulted in a smaller sample than in previous GWASs of AD,[11-14] yet we identified a new AD locus at genome-wide levels of significance on chromosome 13q, and a second locus at 15q24.3 included SNPs that are eQTLs for 2 nearby genes in relevant cell types. Although associations with variants in the *FLG* gene have robust associations with AD, the low frequency and rare pathogenic mutations in *FLG* were not imputed in our study, and therefore we could not directly assess the effects of those variants or their interactions with genotypes at other associated AD loci in our study.

The most significant association in our GWAS was with SNPs on 13q21.31 (smallest $P = 1.01 \times 10^{-8}$). In previous studies SNPs in this region were associated with asthma,[37] rheumatoid arthritis,[38] and total serum IgE levels.[30] In fact, some of the most significant SNPs ($P < 10^{-6}$) were also associated with serum total IgE levels in nonallergic control subjects (Table II). The associated SNPs reside in a gene desert, including 6 long intergenic non–protein-coding RNAs and predicted regulatory elements (DNaseI hypersensitivity sites) in skin tissue from patients with malignant melanoma or lymphoblast.[39] The closest protein-coding gene, *PCDH9*, is approximately 1.3 Mb and encodes a member of the nonclustered protocadherin family, a subgroup of the cadherin superfamily of cell adhesion proteins.[40] Another member of the protocadherin family of genes, *PCDH1*, has been implicated in susceptibility to both AD[41,42] and asthma.[41,43,44] Nonetheless, our results extend earlier findings

TABLE II. Summary of results for the most significant AD-associated SNPs with total serum IgE levels in Korean child control subjects

Genes or nearby genes	Location	SNP	Position	Alleles (risk/alt)	*P* value	OR	95% CI
NBAS	2p24.3	rs13398948	15481147	A/G	.346	0.726	0.371-1.421
		rs75790198	15481366	T/C	.351	0.729	0.372-1.423
		rs16862519	15481752	T/C	.350	0.729	0.374-1.422
		rs13428288	15482611	G/A	.354	0.731	0.375-1.424
		rs13403179	15482752	C/G	.354	0.731	0.375-1.424
		rs147759857	15485351	A/T	.354	0.731	0.375-1.424
		rs114663129	15486515	T/C	.351	0.730	0.375-1.422
THEMIS	6q22.33	rs675531	128040839	C/T	.510	0.828	0.471-1.458
GATA3	10p14	rs35766269	9023815	A/T	.569	1.100	0.790-1.532
PCDH9	13q21.31	rs7987130	65557327	T/C	.005	2.433	1.314-4.505
		rs9540294	65564031	G/T	.005	2.431	1.313-4.498
		rs9528865	65564293	A/G	.305	1.256	0.810-1.948
		rs9540298	65567319	T/C	.005	2.435	1.315-4.510
SCAPER	15q24.3	rs141545456	77014367	T/C	.422	1.215	0.752-1.963
		rs111406539	77076517	C/T	.429	1.211	0.750-1.955
		rs1114717	77086078	A/G	.424	1.213	0.753-1.953
		rs3099143	77104856	C/A	.464	1.193	0.741-1.922
		rs3099140	77111012	A/G	.423	1.211	0.756-1.939
		rs3099139	77112291	G/A	.423	1.211	0.756-1.939
		rs3099138	77115524	A/G	.423	1.210	0.756-1.937

SNPs are ordered by genomic location. SNPs were selected after LD pruning ($r^2 > 0.8$) by using Asian 1000 Genomes genotypes from the 53 SNPs with *P* values of less than 10^{-6} in GWAS results. No *P* value exceeded the threshold for Bonferroni-corrected significance ($P < 2.5 \times 10^{-3}$, 0.05/20).
OR, Odds ratio.

TABLE III. Evidence of associations with AD or IgE phenotype in the Korean children for the previously reported loci

			Previous report				Current study		
Phenotype	Location	Gene	SNP	*P* value	Population	Reference	SNP	HapMap r^2	*P* value
AD	4q27	*IL2-IL21*	rs17389644	1.16E-06	European	Ellinghaus et al[15]	rs17454584	1	.038
	5q22.1	*TMEM232-SLC25A46*	rs7701890	4.33E-08	Chinese	Sun et al[12]	rs10038233	0.863	.025
	5q22.1	*TMEM232-SLC25A46*	rs10067777	6.32E-08	Chinese	Sun et al[12]	rs10035754	0.846	.039
	5q22.1	*TMEM232-SLC25A46*	rs13361382	2.09E-07	Chinese	Sun et al[12]	rs10038233	0.863	.025
	5q22.1	*TMEM232-SLC25A46*	rs13360927	2.80E-07	Chinese	Sun et al[12]	rs13360927	—	.046
	5q31	*KIF3A*	rs2897442	3.80E-08	European	Paternoster et al[14]	rs2897442	—	.002
	5q31.1	*RAD50*	rs2897443	8.95E-13	European	Weidinger et al[32]	rs2897443	—	.029
	5q31.1	*RAD50*	rs6871536	2.11E-15	European	Weidinger et al[32]	rs6871536	—	.028
	5q31.1	*RAD50-IL13*	rs2158177	5.90E-11	European	Weidinger et al[32]	rs2706338	0.92	.022
	10q21.2	*ZNF365*	rs2393903	1.05E-07	Chinese	Sun et al[12]	rs2393903	—	.033
IgE phenotype	1p21.3	*PTBP2*	rs321588	2.05E-06	Admixture	Levin et al[33]	rs321588	—	.003
	1p36.22	*PEX14*	rs2056417	3.70E-07	European	Hinds et al[31]	rs2056417	—	.029
	4q27	*IL2*	rs2069772	1.10E-06	European	Ramasamy et al[34]	rs2069772	—	.042
	4q27	*IL2-ADAD1*	rs17454584	5.50E-10	European	Bonnelykke et al[35]	rs17454584	—	.038
	4q27	*ADAD1*	rs17388568	3.90E-08	European	Hinds et al[31]	rs17388568	—	.043
	5p13.1	*PTGER4*	rs7720838	8.20E-11	European	Hinds et al[31]	rs7720838	—	.016
	5q22.1	*TSLP*	rs1898671	9.00E-03	European	Ramasamy et al[34]	rs1898671	—	.006
	5q22.1	*SLC25A46*	rs10056340	5.20E-14	European	Bonnelykke et al[35]	rs4259213	1	.001
	5q31.1	*RAD50*	rs2706347	6.28E-07	European	Weidinger et al[36]	rs2706347	—	.026
	5q31.1	*RAD50*	rs3798135	6.69E-08	European	Weidinger et al[36]	rs3798135	—	.027
	5q31.1	*RAD50*	rs2040704	4.46E-08	European	Weidinger et al[36]	rs2040704	—	.030
	5q31.1	*RAD50*	rs7737470	3.35E-07	European	Weidinger et al[36]	rs7737470	—	.033
	13q21.31	*PCDH20*	rs1399315	6.40E-07	Japanese	Yatagai et al[30]	rs1399315	—	.033
	14q21.1	*FOXA1-TTC6*	rs1998359	4.80E-08	European	Hinds et al[31]	rs9671863	1	.042
	16p12.1	*IL4R-IL21R*	rs2107357	3.30E-07	European	Hinds et al[31]	rs2107357	—	.026

SNPs are shown with *P* values of less than .05 and ordered by phenotype and genomic location. If the reported SNP was not imputed in our data, a surrogate SNP with the strongest LD to the reported SNP and the amount of LD in Japanese HapMap (r^2) are shown.

by potentially implicating other genes in the protocadherin family in AD pathogenesis.

We also observed associations with AD at suggestive levels of significance at 4 additional loci at 2p24.3, 6q22.33, 10p14, and 15q24.3. The *NBAS* gene at 2p24.3 encodes NBAS, the expression of which has been associated with poor outcome in patients with neuroblastoma.[45] NBAS protein is expressed in epidermal skin cell, although it has not previously been

implicated in chronic skin inflammatory diseases.[46] In contrast, genes at the 6q22.33, 10p14, and 15q24.3 loci are involved in immune dysregulation, which is a key pathogenic pathway in AD. The 6q22.33 and 10p14 loci include genes involved in adaptive immune responses, particularly in T-cell differentiation. SNPs at the 6q22.33 locus were associated with autoimmune diseases, such as Crohn disease[47] and multiple sclerosis.[48] The *THEMIS* gene at this locus encodes a molecule that "fine tunes" positive and negative T-cell selection in the thymus,[49] and its mutation has been reported to yield impaired function of regulatory T cells and a skewed cytokine profile toward T_H2 phenotypes in an inflammatory bowel disease animal model.[50] The associated locus at 10p14 resides between *GATA3* and *CELF2*. SNPs at this locus were previously associated with rheumatoid arthritis,[51] self-reported allergy,[31] or asthma.[52] *GATA3* is the closest protein-coding gene (approximately 900 Kb) and an important regulator of T-cell development and promotes the secretion of IL-4, IL-5, and IL-13 from T_H2 cells, which lead to allergic sensitization.[53] This locus also includes predicted DNaseI hypersensitivity sites for *GATA3* in various tissues or cell types, including skin or T_H2 cells.[39] Of potential relevance is that allergen-specific GATA3 expression precedes clinical allergic sensitization,[54] which might suggest that GATA3 plays a role at the beginning of allergic inflammation. Moreover, our GWAS replicated the previous reported association with SNPs at the T_H2 cytokine (*RAD50-IL13-IL4*) locus on 5q31.1 (Table III). Taken together, we suggest these T_H2-related loci represent excellent candidate regions for the inflammatory network of AD.

Finally, the associated SNPs at 15q24.3 are located within the *SCAPER* gene, which regulates cell-cycle progression.[55] Some of these SNPs are also *cis*-eQTLs for *PSTPIP1* in $CD14^+$ monocytes after treatment with LPS and for the *ISL2* gene in whole blood.[28] Because the latter results are from studies of mixed cells, we do not know whether the eQTL is present in all leukocytes or just in a subset. Mutations in the *PSTPIP1* gene cause pyogenic arthritis, pyoderma gangrenosum, and acne syndrome, which is an autosomal dominant autoinflammatory disease.[56] In patients with pyogenic arthritis, pyoderma gangrenosum, and acne syndrome, *PSTPIP1* induces the activation of the inflammasome involved in IL-1 production, resulting in aberrant innate immune responses in the skin and joints.[56] A primary feature of AD is skin inflammation, making this gene on 15q24.3 a logical functional candidate for moderate-to-severe AD in children.

To our knowledge, this is the first GWAS of AD in Koreans and the first GWAS of AD using extreme phenotypes in cases and unaffected subjects as control subjects. As a result, there are no available replication samples with the same phenotype or ethnicity as that used in our study. The lack of replication of our most significant SNPs might be due to different case definitions, differences between childhood and adult AD, different ancestries, or some combination of these factors. Regardless, this GWAS in Korean children with moderate-to-severe AD and allergic sensitization identified new AD candidate genes related to epithelial cell function and immune dysregulation, 2 key features of AD. Further studies of these genes are required both to replicate the association with the distinct phenotype of recalcitrant AD and to better understand their role in pathogenesis.

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Key messages

- **We report 5 new AD candidate genes through this GWAS in Korean children.**
- **SNPs at the 13q21.31 locus were associated with recalcitrant AD at genome-wide levels of significance, but this might be a primarily IgE locus.**
- **A GWAS of extreme phenotypes might reveal additional genes for AD.**

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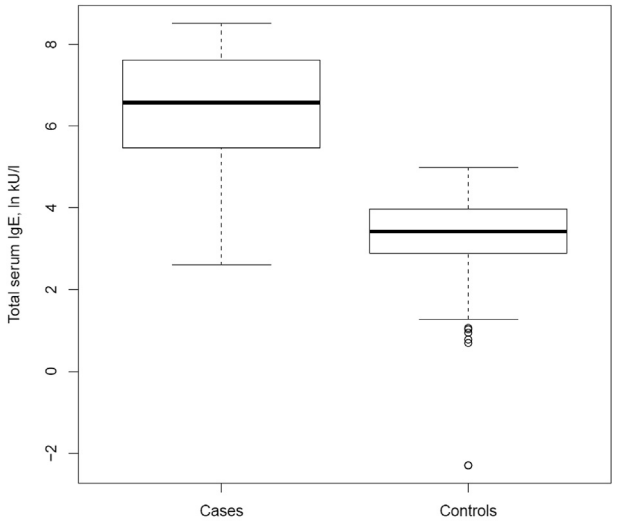

FIG E1. Box plots comparing total serum IgE levels between cases and control subjects among children. Total serum IgE levels are higher in cases than in control subjects (6.443 ± 1.449 vs 3.260 ± 0.941 ln kU/L, respectively; $P = 2.2 \times 10^{-16}$).

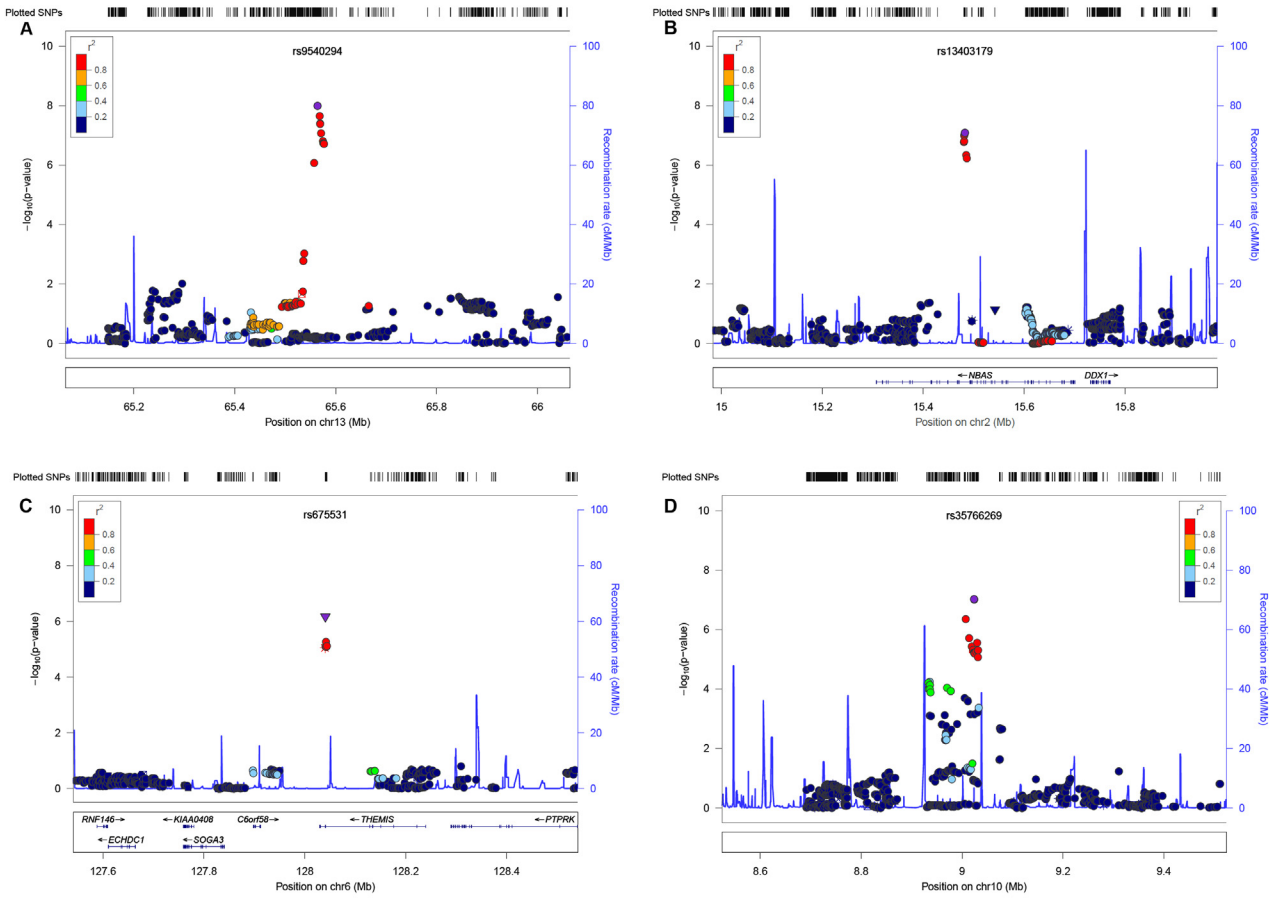

FIG E2. Regional association plots at the 13q21.31 **(A)**, 2p24.3 **(B)**, 6q22.33 **(C)**, and 10p14 **(D)** loci for recalcitrant AD. For each plot, the $-\log_{10}$ *P* value *(left y-axis)* of each SNP is shown according to its chromosomal position *(x-axis)*. Genetic recombination rates are shown by the *blue line*, and *horizontal arrows* indicate locations of genes and direction of transcription. The most associated SNP (labeled by rs number) is shown as a *purple circle*, and its LD *(r^2)* with all other SNPs is indicated by color

TABLE E1. Age and sex composition of the GWAS and replication studies

Study population	Cases*			Control subjects†			Ethnicity	Genotyping platform
	Sample size	Age (mean ± SD)	Sex ratio (M/F)	Sample size	Age (mean ± SD)	Sex ratio (M/F)		
GWAS groups								
Children	246	4.4 ± 4.1	169/77	108	9.5 ± 3.1	49/59	Korean	Axiom
Adults	NA	NA	NA	551	65.0 ± 8.4	211/340	Korean	5.0
Replication group[13]								
Adults	1472	28.6 ± 9.2	807/665	7966	49.1 ± 17.6	4588/3378	Japanese	Illumina Human OmniExpress-12

Child cases and adult control subjects were used for the GWAS analysis. Child control subjects were used for the association studies of selected SNPs with total serum IgE levels.
F, Female; *M*, male; *NA*, not applicable.
*Cases included children with both moderate-to-severe AD (SCORAD score ≥ 30; mean ± SD, 59.9 ± 14.4) and allergic sensitization (positive specific IgE level to ≥1 food or airborne allergen).
†Control subjects included subjects without a history of allergic disease or evidence of allergic sensitization (negative skin prick test responses or negative specific IgE levels to common allergens).

TABLE E2. Summary of association results from the discovery GWAS and replication stage

Genes or nearby genes	Location	SNP ID	Position	Alleles (risk/alt)	Discovery GWAS					Replication stage (Japanese group)			
					RAF (cases)	RAF (control subjects)	*P* value	OR	95% CI	RAF	β	SE	*P* value
NBAS	2p24.3	rs13403179	15482752	C/G	0.131	0.054	8.07E-08	2.947	1.989-4.386	0.032	0.043	0.113	.705
		rs13428288	15482611	G/A	0.131	0.054	8.20E-08	2.946	1.988-4.385	0.032	0.043	0.113	.704
		rs16862519	15481752	T/C	0.131	0.054	9.03E-08	2.943	1.984-4.384	0.032	0.043	0.113	.704
		rs75790198	15481366	T/C	0.130	0.054	1.00E-07	2.936	1.978-4.375	0.032	0.043	0.113	.703
		rs13398948	15481147	A/G	0.129	0.055	1.54E-07	2.903	1.952-4.334	0.032	0.044	0.114	.701
		rs13409223	15480569	C/T	0.129	0.055	1.67E-07	2.898	1.948-4.328	0.032	0.044	0.114	.701
		rs147759857	15485351	A/T	0.125	0.054	4.55E-07	2.826	1.890-4.243	0.032	0.043	0.113	.705
		rs114663129	15486515	T/C	0.124	0.054	5.94E-07	2.810	1.875-4.226	0.032	0.043	0.113	.705
THEMIS	6q22.33	rs675531	128040839	C/T	0.205	0.113	6.82E-07	2.193	1.610-2.994	0.164	−0.017	0.054	.755
GATA3	10p14	rs35766269	9023815	A/T	0.717	0.580	9.61E-08	1.946	1.529-2.494	0.654	−0.013	0.043	.767
		rs12253258	9024290	T/C	0.717	0.580	9.72E-08	1.946	1.529-2.494	0.654	−0.012	0.043	.778
		rs34385685	9007216	T/A	0.689	0.557	4.49E-07	1.843	1.458-2.342	0.630	−0.022	0.042	.604
PCDH9	13q21.31	rs9540294	65564031	G/T	0.181	0.083	1.01E-08	2.655	1.904-3.717	0.117	−0.047	0.064	.454
		rs9540299	65568331	T/C	0.178	0.083	2.24E-08	2.614	1.869-3.669	0.117	−0.048	0.064	.453
		rs9540298	65567319	T/C	0.186	0.088	2.97E-08	2.515	1.818-3.493	0.122	−0.058	0.063	.354
		rs9598920	65569199	T/G	0.184	0.088	4.06E-08	2.499	1.804-3.474	0.122	−0.058	0.063	.353
		rs9598921	65569216	T/C	0.184	0.088	4.12E-08	2.498	1.804-3.473	0.122	−0.058	0.063	.353
		rs9540302	65571257	G/A	0.172	0.083	8.66E-08	2.536	1.806-3.573	0.117	−0.048	0.064	.451
		rs4600354	65574724	G/A	0.170	0.083	1.58E-07	2.498	1.776-3.525	0.117	−0.048	0.064	.452
		rs7993759	65575511	G/A	0.178	0.088	1.79E-07	2.415	1.736-3.370	0.122	−0.058	0.063	.353
		rs9540309	65575966	C/T	0.178	0.088	1.86E-07	2.413	1.735-3.368	0.122	−0.058	0.063	.352
		rs9598922	65577047	G/C	0.169	0.083	1.96E-07	2.484	1.765-3.507	0.117	−0.048	0.063	.451
		rs9528865	65564293	A/G	0.267	0.160	3.35E-07	2.044	1.555-2.695	0.214	−0.023	0.049	.629
		rs4293255	65562307	T/C	0.265	0.160	5.49E-07	2.022	1.536-2.667	0.214	−0.022	0.049	.653
		rs9564212	65566594	C/T	0.265	0.160	5.56E-07	2.020	1.535-2.665	0.214	−0.024	0.049	.626
		rs7987130	65557327	T/C	0.164	0.083	8.42E-07	2.380	1.687-3.368	0.117	−0.047	0.064	.456
SCAPER	15q24.3	rs3099143	77104856	C/A	0.239	0.137	3.02E-07	2.126	1.594-2.841	0.123	−0.072	0.063	.252
		rs2046415	77085253	G/A	0.235	0.134	4.31E-07	2.096	1.575-2.798	0.122	−0.066	0.063	.291
		rs1114717	77086078	A/G	0.235	0.134	4.36E-07	2.096	1.574-2.797	0.121	−0.066	0.063	.291
		rs3110379	77095175	G/A	0.235	0.135	4.56E-07	2.094	1.573-2.795	0.121	−0.067	0.063	.288
		rs901008	77097018	A/C	0.235	0.135	4.64E-07	2.093	1.572-2.794	0.121	−0.067	0.063	.288
		rs3110381	77099665	T/A	0.235	0.135	4.70E-07	2.092	1.571-2.793	0.121	−0.067	0.063	.287
		rs3106380	77104377	A/G	0.235	0.135	4.84E-07	2.091	1.570-2.792	0.121	−0.067	0.063	.287
		rs3099142	77104909	T/C	0.235	0.135	4.95E-07	2.090	1.570-2.791	0.121	−0.067	0.063	.287
		rs4886831	77106801	T/C	0.235	0.135	4.98E-07	2.090	1.569-2.791	0.121	−0.067	0.063	.286
		rs78020233	77107050	G/T	0.235	0.135	5.00E-07	2.090	1.569-2.790	0.121	−0.067	0.063	.286
		rs3102712	77058926	A/G	0.235	0.136	5.68E-07	2.097	1.570-2.807	0.122	−0.063	0.063	.312
		rs3102710	77061148	C/T	0.235	0.136	5.69E-07	2.097	1.570-2.807	0.122	−0.064	0.063	.311
		rs280024	77034518	C/A	0.235	0.136	6.03E-07	2.096	1.569-2.808	0.122	−0.060	0.062	.337
		rs280028	77031466	G/A	0.235	0.136	6.14E-07	2.096	1.568-2.807	0.122	−0.059	0.062	.338
		rs280029	77031235	G/A	0.235	0.136	6.16E-07	2.095	1.568-2.807	0.122	−0.059	0.062	.338
		rs3102709	77072260	T/C	0.235	0.136	6.24E-07	2.088	1.564-2.793	0.122	−0.065	0.063	.303
		rs3106378	77110524	C/A	0.235	0.136	6.39E-07	2.077	1.559-2.774	0.121	−0.070	0.064	.272
		rs111406539	77076517	C/T	0.235	0.136	6.45E-07	2.084	1.562-2.787	0.122	−0.065	0.063	.302
		rs3099140	77111012	A/G	0.235	0.136	6.53E-07	2.076	1.558-2.773	0.121	−0.070	0.064	.272
		rs3099139	77112291	G/A	0.235	0.136	6.54E-07	2.076	1.558-2.773	0.121	−0.070	0.064	.272
		rs3099138	77115524	A/G	0.235	0.136	6.68E-07	2.075	1.557-2.772	0.121	−0.070	0.064	.268
		rs4886832	77121196	G/A	0.235	0.136	6.89E-07	2.074	1.556-2.770	0.121	−0.071	0.064	.263
		rs3099137	77123626	A/G	0.235	0.137	6.92E-07	2.073	1.556-2.769	0.121	−0.071	0.064	.263
		rs111908804	77123773	G/C	0.235	0.137	6.94E-07	2.073	1.556-2.769	0.121	−0.071	0.064	.263
		rs3099134	77133168	G/T	0.235	0.137	7.48E-07	2.069	1.553-2.764	0.121	−0.071	0.064	.261
		rs141545456	77014367	T/C	0.228	0.132	8.82E-07	2.078	1.554-2.787	0.118	−0.066	0.065	.307
		rs3110378	77127983	A/G	0.234	0.137	9.57E-07	2.059	1.544-2.753	0.121	−0.071	0.064	.263

OR, Odds ratio; *RAF*, risk allele frequency.