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

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Abstract

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.

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Conflicts of interest: none

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

Methods—Our study included 246 children with recalcitrant AD and 551 adult controls with a negative history of both allergic disease and allergic sensitization. DNA from these individuals was genotyped; sets of common 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 ($P < 2.0\times10^{-8}$). These associated SNPs are >1Mb from the closest gene, *PCDH9*. SNPs at four additional loci had $P < 1\times10^{-6}$, including SNPs at or near the *NBAS* (2p24.3), *THEMIS* (6q22.33), *GATA3* (10p14) and *SCAPER* (15q24.3) genes. Further analysis of total serum IgE levels suggested 13q21.31 may be primarily an IgE locus, and analyses of published data demonstrated SNPs at the 15q24.3 region are expression quantitative trait loci (eQTL) for two nearby genes, *ISL2* and *PSTPIP1*, in immune cells.

Conclusion—Our GWAS of recalcitrant AD identified new susceptibility regions containing genes involved in epithelial cell function and immune dysregulation, two key features of AD, and potentially extend our understanding of their role in pathogenesis.

Keywords

genome-wide association study; atopic dermatitis; allergic sensitization; IgE; severity; children

Introduction

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 healthcare costs.[2] Available treatment options for 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 AD.[6] In particular, low frequency and rare loss-of-function variants in the filaggrin (*FLG*) gene 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 (filaggrin, in particular) has been placed in the center of AD pathogenesis.

Three large genome-wide association studies (GWAS),[11–13] a meta-analysis of GWAS 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 phenotypic heterogeneity, and this is consistent with the finding susceptibility loci discovered to date, including *FLG*, account for only 14.4% of the heritability of AD in Europeans,[15] and suggest studies in additional populations and 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 focus on the distinct phenotype of recalcitrant AD, defined as moderate to severe AD with allergic sensitization. Moreover, we included as controls non-allergic adults without history of allergic diseases. We identified a novel region of chromosome 13q21.31 as likely to contain genes controlling risk to AD which was genome-wide significant and additional loci including the *NBAS*, *THEMIS*, *GATA3* and *SCAPER* genes 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 controls without 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 in the 246 case children and 108 healthy Korean children without allergic diseases or evidence of allergic sensitization where measured levels of total serum IgE as controls were available (Table S1). Children cases and controls were recruited from Severance children's hospital, Seoul, Korea, and adult controls were from the Ansung population-based cohort (N = 5,108), which was established as part of the KoGES by 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 the severity using the Severity SCOring Atopic Dermatitis (SCORAD) index[18] of 572 children, and then recruited 275 children cases with moderate to severe AD (SCORAD ≥ 30; mean ± SD, 59.9 ± 14.4) for our studies. Allergic sensitization was defined by specific IgE greater than 0.7 kUA/l to at least one of the following food or airborne allergens: egg white, milk, peanut, soybean, wheat, *Dermatophagoides pteronyssinus (Der p)*, *Dermatophagoides farina (Der f)*, Alternatia or *Blattella germanica*. Of the 275 children with moderate to severe AD, 246 had specific IgE to at least one of the allergens. We selected 551 adult controls with a negative history of both allergic diseases and allergic sensitization among 1,214 adults. Negative histories of allergic diseases, including asthma and AD, were based on a self-administered questionnaire; lack of sensitization was based on a negative skin prick test result to 12 common allergens (*Der p*, *Der f*, 2 tree pollen mixtures, grass pollen mixture, ragweed, mugwort, cockroach, Alternaria, Aspergillus, cat dander and dog dander). Additionally, 108 control children were recruited during routine

hospital visits and were included in our study if they had a negative history of allergic diseases based on interviews with their parents, were negative for serum specific IgE to 6 common allergens (egg white, milk, *Der p*, *Der f*, Alternatia or *Blattella germanica*) and had total serum IgE levels below 100 kU/l. All cases and controls were unrelated and either they or their parents provided written informed consent for themselves to participate 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 using the Affymetrix Axiom array in the AD and control children and the Affymetrix 5.0 chip (Affymetrix, Santa Clara, Calif) in the adult controls (Table S1). We excluded samples with call rates for autosomal SNPs less than 95%, and excluded SNPs with minor allele frequencies less than 5% or Hardy-Weinberg P values less than 10^{-4}. Quality control was performed using PLINK 1.07.[19] After quality control exclusions, 402,919 SNPs remained in the children and 287,622 SNPs in the adults. The common sets of SNPs were then used for imputation 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 ($r^2 > 0.9$) and minor allele frequency > 5%. As a final quality filter, SNPs were excluded if their allele frequencies differed ($P \geq 0.001$) between the adult and children control samples. In the end, 2,501,352 autosomal SNPs were used for the GWAS analysis.

Association of most significant SNPs with total serum IgE levels

We tested 20 of the 53 SNPs with $P < 10^{-6}$ in the GWAS of AD after pruning for LD ($r^2 > 0.8$ in the Asian 1000 genomes data) for association with total serum IgE in 108 control children (Table S1). These studies were performed in non-allergic control children to determine if these variants were also associated with IgE independent of AD (Fig. S2).

Replication studies

To examine the association of SNPs with P value $< 10^{-6}$ in our GWAS, we obtained P-values of those SNPs from a GWAS of AD in Japanese individuals (Table S1). That study included 1,472 cases with physician-diagnosed AD, and 7,966 controls including 6,042 subjects with one of five non-AD diseases (cerebral aneurysm, esophageal cancer, endometrial cancer, chronic obstructive pulmonary disease and glaucoma) and 1,929 healthy volunteers without history of asthma or AD.[13]

Gene expression and eQTL 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 of $CD14^+$ monocytes stimulated with interferon-γ or lipopolysaccharide (LPS).[28]

Statistical Analysis

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

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 to those expected by chance (Fig. 1a). One SNP (rs9540294) at 13q21.31 passed genome-wide threshold of significance (Bonferroni corrected $P < 2.0 \times 10^{-8}$); 13 additional SNPs at this region including *PCDH20-PCDH9* were associated with moderate to severe AD with allergic sensitization at $P < 1 \times 10^{-6}$ (Fig. 1b, Fig. S1a). A total of 39 SNPs in four additional regions were also associated at $P < 1 \times 10^{-6}$: the *NBAS* gene at 2p24.3 (Fig. S1b), the *THEMIS* gene at 6q22.33 (Fig. S1c), the *GATA3- CELF2* locus at 10p14 (Fig. S1d), and the *SCAPER* gene at 15q24.3 (Fig. 2). The most significant SNP at each locus is shown in Table 1; the results for SNPs at these six loci are shown in Table S2.

Because all the cases had both AD and allergic sensitization and the adult controls had neither, we utilized a second control group of non-allergic children with measured levels of total serum IgE to disentangle associations primarily with AD from those that are primarily with IgE levels (i.e., allergic sensitization). SNPs at the 13q21.31 locus showed suggestive evidence for association with serum total IgE in 108 control children ($P < 0.05$, Table 2). Thus, it is likely the association with AD at this region may be due to the significantly higher levels of IgE in the AD cases compared to non-allergic controls, and that the primary effects of this locus are on IgE production and not risk of AD *per se*.

To attempt replication of the SNPs identified in our GWAS of moderate to severe AD with allergic sensitization, we examined the results of the 53 SNPs yielding $P < 10^{-6}$ in our study to 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 replicated in the study of Japanese adults (Table S2).

We next examined in our study subjects SNPs loci associated with AD or IgE in previous GWAS. We detected modest associations ($P < 0.05$) with SNPs associated with AD at the *IL2-IL21, RAD50-IL13, TMEM232-SLC25A46, KIF3A* and *ZNF365* loci, and with total serum IgE at the *PTBP2, PEX14, IL2-ADAD1, PTGER4, TSLP, SLC25A46, RAD50, PCDH20, FOXA1-TTC6* and *IL4R-IL21R* loci (Table 3). Among these associations, four regions (4q27, 5q13, 5q22.1 and 5q31) have been previously reported in GWAS of both AD and IgE phenotypes. In addition, a SNP nearby *PCDH20* gene at the 13q21.31 region was previously associated with IgE in a Japanese population,[30] further suggesting 13q21.31 region might contain a gene controlling IgE levels.

Finally, we asked whether the 53 SNPs associated with AD at $P < 10^{-6}$ 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 (i.e., are *cis*-eQTLs) in relevant tissues.[15,22–28] Five SNPs in strong LD at the 15q24.3 locus were *cis*-eQTLs for *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 four 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, levels of total serum IgE, predilection to skin lesions, and prognosis, which differ both between children and 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 GWAS that included cases with physician-diagnosed AD without regard to severity or sensitization, and relied on population controls 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 controls 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 GWAS 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 two 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 so we could not directly assess the effects of those variants or their interactions with genotypes at other associated loci AD 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,[31] rheumatoid arthritis,[32] and total serum IgE.[30] In fact, some of the most significant SNPs ($P < 10^{-6}$) were also associated with serum total IgE in non-allergic controls (Table 2). The associated SNPs reside in a gene desert including six long intergenic non-protein coding (linc) RNAs and predicted regulatory elements (DNaseI hypersensitivity sites) in skin tissue from patients with malignant melamona or lymphoblast.[33] The closest protein coding genes, *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.[34] Another member of the protocadherin family of genes, *PCDH1*, has been implicated in susceptibility to both AD[35,36] and asthma.[35,37,38] Nonetheless, our results extend earlier findings by potentially implicating other genes in the protocadherin family in AD pathogenesis.

We also observed associations with AD at suggestive levels of significance at four additional loci at 2p24.3, 6q22.33, 10p14 and 15q24.3. The *NBAS* gene at 2p24.3 encodes neuroblastoma amplified sequence (NBAS) whose expression has been associated with poor outcome in patients with neuroblastoma.[39] NBAS protein is expressed in epidermal skin

cell, although it has not previously been implicated in chronic skin inflammatory diseases.[40] In contrast, genes at the 6q22.33, 10p14 and 15q24.3 locus 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's disease[41] and multiple sclerosis.[42] The *THEMIS* (thymus-expressed molecule involved in selection) gene at this locus encodes a molecule that "fine-tunes" positive and negative T-cell selection in the thymus,[43] and its mutation has been reported to yield impaired function of regulatory T cells and skewed cytokine profile toward Th2 phenotypes in inflammatory bowel disease animal model.[44] The associated locus at 10p14 resides between *GATA3* and *CELF2*. SNPs at this locus were previously associated with rheumatoid arthritis,[45] self-reported allergy,[46] or asthma.[47] *GATA3* is the closest protein coding gene (approximately 900 Kb), which an important regulator of T cell development and promotes the secretion of IL-4, IL-5 and IL-13 from Th2 cells, which lead to allergic sensitization.[48] This locus also includes predicted DNaseI hypersensitivity sites for *GATA3* in various tissues or cell types including skin or Th2 cell.[33] Of potential relevance is that allergen-specific GATA3 expression precedes clinical allergic sensitization,[49] which might suggest GATA3 plays a role at the beginning of allergic inflammation. Moreover, our GWAS replicated the previous reported association with SNPs at the Th2 cytokine (*RAD50-IL13-IL4*) locus on 5q31.1 (Table 3). Taken together, we suggest these Th2 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.[50] 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 if the eQTL is present in all leukocytes or just in a subset. Mutations in *PSTPIP1* gene cause PAPA syndrome (Pyogenic Arthritis, Pyodermagangrenosum, and Acne), which is an autosomal dominant auto-inflammatory disease.[51] In PAPA, *PSTPIP1* induces the activation of the inflammasome involved in interleukin-1 production resulting in aberrant innate immune responses in the skin and joints.[51] 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 individuals as controls. 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 may 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, two key features of AD. Further studies of these genes are required to both replicate the association with the distinct phenotype of recalcitrant AD and to better understand their role in pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations used

AD	Atopic dermatitis
GWAS	Genome-wide association study
SNP	Single nucleotide polymorphism
SCORAD	Severity SCOring Atopic Dermatitis
Der p	Dermatophagoides pteronyssinus
Der f	Dermatophagoides farina
eQTLs	expression quantitative trait loci
LPS	lipopolysaccharide
Linc	long intergenic non-protein coding

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Key Messages

- We report 5 new AD candidate genes through this GWAS in Korean children.
- SNPs at the13q21.31 locus were associated with recalcitrant AD at genome-wide levels of significance, but this may be a primarily IgE locus.
- GWAS of extreme phenotypes may reveal additional genes for AD.

Figure 1a

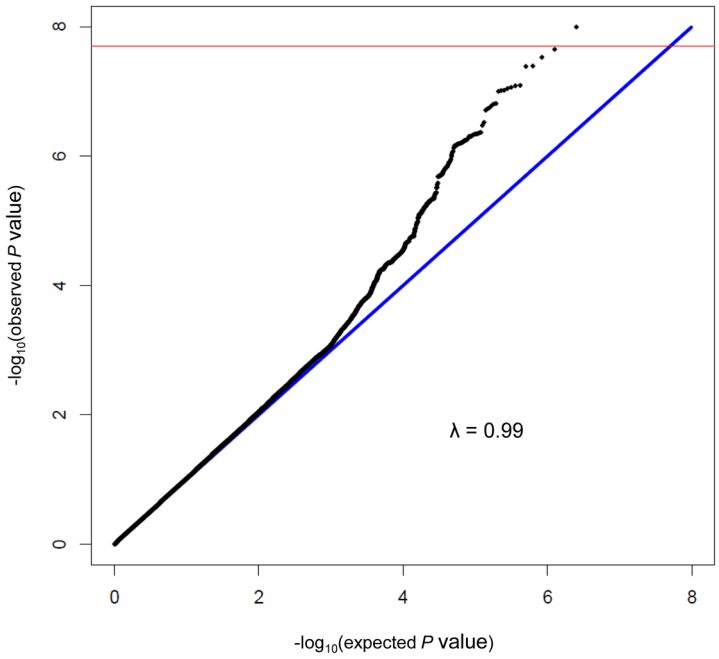

Figure 1b

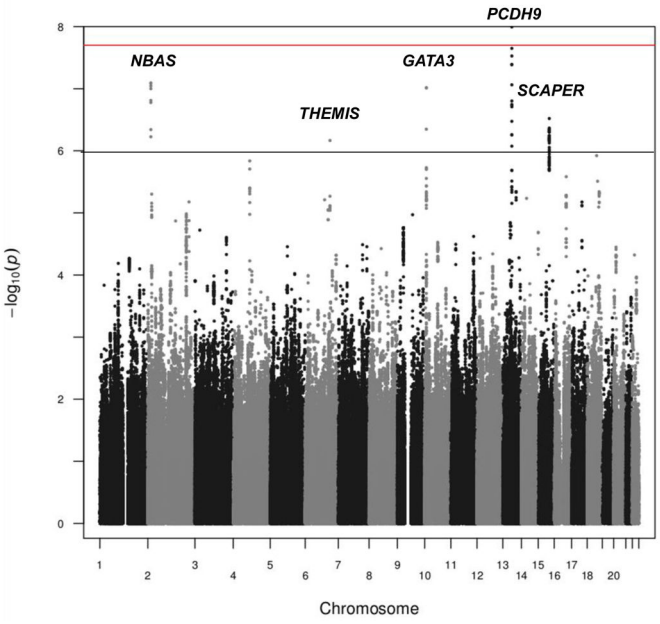

Figure 1.

(a) Quantile-quantile plot of *P* values for the 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 atopic dermatitis and 551 Korean adult controls 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 $P = 1 \times 10^{-6}$. Locations of the *NBAS* (2p24.3), *THEMIS* (6q22.33), *GATA3* (10p14), *PCDH9* (13q21.31), *SCAPER* (15q24.3) loci are indicated.

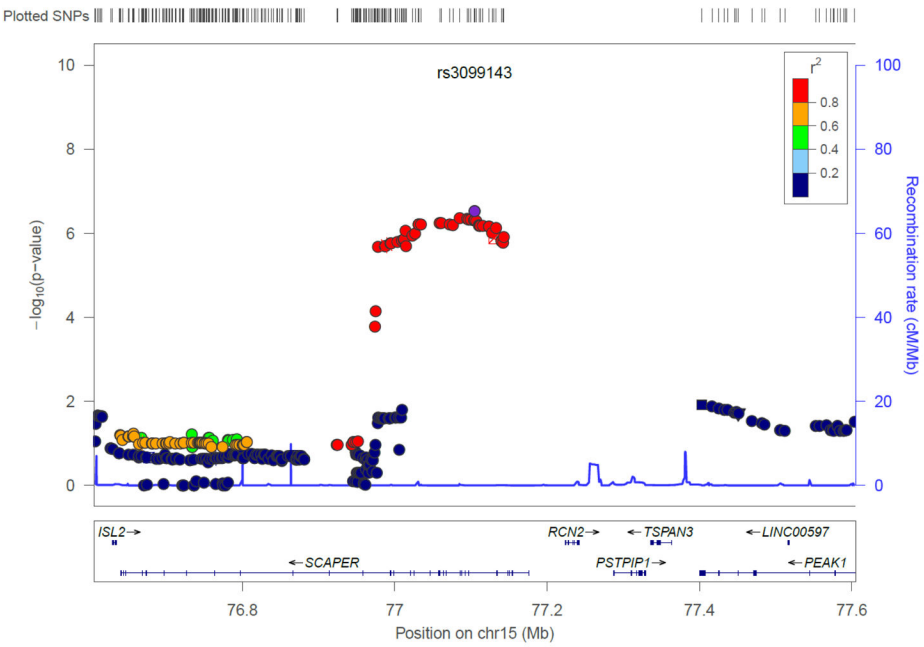

Figure 2.

Regional association plots at the 15q24.3 locus for recalcitrant atopic dermatitis. Significant SNPs are located within the *SCAPER* gene and include *cis*-eQTLs for the *ISL2* gene 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 the 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 1

Summary of GWAS of atopic dermatitis at P < 10^{-6} in Korean Children

Genes or nearby genes	Location	SNP	Position	Alleles (risk/alt)	RAF (Case)	RAF (Control)	*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)

RAF, risk allele frequency; OR, odds ratio; CI, confidence interval.

The most significant SNPs at each locus are shown and ordered by genomic location.

* *P* value exceeded the threshold for Bonferroni-corrected genome-wide significance ($P < 2.0 \times 10^{-8}$)

Table 2

Summary of results for most significant AD-associated SNPs with total serum IgE in Korean children controls

Genes or nearby genes	Location	SNP	Position	Alleles (risk/alt)	*P* value	OR	95% CI
NBAS	2p24.3	rs13398948	15481147	A/G	0.346	0.726	(0.371–1.421)
		rs75790198	15481366	T/C	0.351	0.729	(0.372–1.423)
		rs16862519	15481752	T/C	0.350	0.729	(0.374–1.422)
		rs13428288	15482611	G/A	0.354	0.731	(0.375–1.424)
		rs13403179	15482752	C/G	0.354	0.731	(0.375–1.424)
		rs147759857	15485351	A/T	0.354	0.731	(0.375–1.424)
		rs114663129	15486515	T/C	0.351	0.730	(0.375–1.422)
THEMIS	6q22.33	rs675531	128040839	C/T	0.510	0.828	(0.471–1.458)
GATA3	10p14	rs35766269	9023815	A/T	0.569	1.100	(0.790–1.532)
PCDH9	13q21.31	rs7987130	65557327	T/C	0.005	2.433	(1.314–4.505)
		rs9540294	65564031	G/T	0.005	2.431	(1.313–4.498)
		rs9528865	65564293	A/G	0.305	1.256	(0.810–1.948)
		rs9540298	65567319	T/C	0.005	2.435	(1.315–4.510)
SCAPER	15q24.3	rs141545456	77014367	T/C	0.422	1.215	(0.752–1.963)
		rs111406539	77076517	C/T	0.429	1.211	(0.750–1.955)
		rs1114717	77086078	A/G	0.424	1.213	(0.753–1.953)
		rs3099143	77104856	C/A	0.464	1.193	(0.741–1.922)
		rs3099140	77111012	A/G	0.423	1.211	(0.756–1.939)
		rs3099139	77112291	G/A	0.423	1.211	(0.756–1.939)
		rs3099138	77115524	A/G	0.423	1.210	(0.756–1.937)

OR, odds ratio; CI, confidence interval.

SNPs are ordered by genomic location.

SNPs were selected after LD pruning ($r^2 > 0.8$) using Asian 1000Genome genotypes from the 53 SNPs with $P < 10^{-6}$ in GWAS results. No *P* value exceeded the threshold for Bonferroni-corrected significance ($P < 2.5\times10^{-3}$, 0.05/20).

Table 3

Evidence of associations with atopic dermatitis or IgE phenotype in the Korean children for the previously reported loci

Phenotype	Location	Gene	Previous report				Current study		
			SNP	*P* value	Population	Reference	SNP	HapMap r^2	*P* value
Atopic dermatitis	4q27	*IL2-IL21*	rs17389644	1.16E-06	European	Ellinghaus D[15]	rs17454584	1	0.038
	5q22.1	*TMEM232-SLC25A46*	rs7701890	4.33E-08	Chinese	Sun LD[12]	rs10038233	0.863	0.025
	5q22.1	*TMEM232-SLC25A46*	rs10067777	6.32E-08	Chinese	Sun LD[12]	rs10035754	0.846	0.039
	5q22.1	*TMEM232-SLC25A46*	rs13361382	2.09E-07	Chinese	Sun LD[12]	rs10038233	0.863	0.025
	5q22.1	*TMEM232-SLC25A46*	rs13360927	2.80E-07	Chinese	Sun LD[12]	rs13360927	-	0.046
	5q31	*KIF3A*	rs2897442	3.80E-08	European	Paternoster L[14]	rs2897442	-	0.002
	5q31.1	*RAD50*	rs2897443	8.95E-13	European	Weidinger S[52]	rs2897443	-	0.029
	5q31.1	*RAD50*	rs6871536	2.11E-15	European	Weidinger S[52]	rs6871536	-	0.028
	5q31.1	*RAD50-IL13*	rs2158177	5.90E-11	European	Weidinger S[52]	rs2706338	0.92	0.022
	10q21.2	*ZNF365*	rs2393903	1.05E-07	Chinese	Sun LD[12]	rs2393903	-	0.033
IgE phenotype	1p21.3	*PTBP2*	rs321588	2.05E-06	Admixture	Levin AM[53]	rs321588	-	0.003
	1p36.22	*PEX14*	rs2056417	3.70E-07	European	Hinds DA[46]	rs2056417	-	0.029
	4q27	*IL2*	rs2069772	1.10E-06	European	Ramasamy A[54]	rs2069772	-	0.042
	4q27	*IL2-ADAD1*	rs17454584	5.50E-10	European	Bonnelykke K[55]	rs17454584	-	0.038
	4q27	*ADAD1*	rs17388568	3.90E-08	European	Hinds DA[46]	rs17388568	-	0.043
	5p13.1	*PTGER4*	rs7720838	8.20E-11	European	Hinds DA[46]	rs7720838	-	0.016
	5q22.1	*TSLP*	rs1898671	9.00E-03	European	Ramasamy A[54]	rs1898671	-	0.006
	5q22.1	*SLC25A46*	rs10056340	5.20E-14	European	Bonnelykke K[55]	rs4259213	1	0.001
	5q31.1	*RAD50*	rs2706347	6.28E-07	European	Weidinger S[56]	rs2706347	-	0.026
	5q31.1	*RAD50*	rs3798135	6.69E-08	European	Weidinger S[56]	rs3798135	-	0.027
	5q31.1	*RAD50*	rs2040704	4.46E-08	European	Weidinger S[56]	rs2040704	-	0.030
	5q31.1	*RAD50*	rs7737470	3.35E-07	European	Weidinger S[56]	rs7737470	-	0.033
	13q21.31	*PCDH20*	rs1399315	6.40E-07	Japanese	Yatagai Y[30]	rs1399315	-	0.033
	14q21.1	*FOXA1-TTC6*	rs1998359	4.80E-08	European	Hinds DA[46]	rs9671863	1	0.042
	16p12.1	*IL4R-IL21R*	rs2107357	3.30E-07	European	Hinds DA[46]	rs2107357	-	0.026

SNPs are shown with *P* value < 0.05 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.