

A Genome-Wide Association Study of Total Serum and Mite-Specific IgEs in Asthma Patients

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Abstract

Immunoglobulin E (IgE) is one of the central players in asthma and allergic diseases. Although the serum IgE level, a useful endophenotype, is generally increased in patients with asthma, genetic factors influencing IgE regulation in asthma are still not fully understood. To identify the genetic variations associated with total serum and mite-specific IgEs in asthmatics, a genome-wide association study (GWAS) of 657,366 single nucleotide polymorphisms (SNPs) was performed in 877 Korean asthmatics. This study found that several new genes might be associated with total IgE in asthmatics, such as *CRIM1* (rs848512, $P = 1.18 \times 10^{-6}$; rs711254, $P = 6.73 \times 10^{-6}$), *ZNF71* (rs10404342, $P = 7.60 \times 10^{-6}$), *TLN1* (rs4879926, $P = 7.74 \times 10^{-6}$), and *SYNPO2* (rs1472066, $P = 8.36 \times 10^{-6}$; rs1038770, $P = 8.66 \times 10^{-6}$). Regarding the association of specific IgE to house dust mites, it was observed that intergenic SNPs nearby to *OPRK1* and *LOC730217* might be associated with *Dermatophagoides pteronyssinus* (D.p.) and *Dermatophagoides farinae* (D.f.) in asthmatics, respectively. In further pathway analysis, the phosphatidylinositol signaling system and adherens junction pathways were estimated to play a role in the regulation of total IgE levels in asthma. Although functional evaluations and replications of these results in other populations are needed, this GWAS of serum IgE in asthmatics could facilitate improved understanding of the role of the newly identified genetic variants in asthma and its related phenotypes.

Citation: Kim J-H, Cheong HS, Park JS, Jang A-S, Uh S-T, et al. (2013) A Genome-Wide Association Study of Total Serum and Mite-Specific IgEs in Asthma Patients. PLoS ONE 8(8): e71958. doi:10.1371/journal.pone.0071958

Editor: Michael B. Fessler, National Institute of Environmental Health Sciences, United States of America

Received: June 24, 2013; **Accepted:** July 8, 2013; **Published:** August 13, 2013

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Funding: This work was supported by a grant from the Korea Health 21 R&D Project (A010249 & A090548) and by a grant from the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0080157 & 2012-0006690). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: SNP Genetics, Inc. provided the iScan scanner instrument and GenomeStudio software used in the research. Co-authors HSC and HDS are employed by SNP Genetics, Inc. There are no patents, products in development or marketed products to declare. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

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Introduction

Asthma, a chronic inflammatory respiratory disease, is characterized by bronchial hyperresponsiveness. Asthma and its related illnesses are complex diseases resulting from interactions among multiple genetic factors as well as environmental components [1]. Despite recent advancements in our knowledge of asthma genetics, the need for a comprehensive etiology of asthma and its related phenotypes still remains. At the same time, it is generally known that patients with asthma show an increase in levels of serum immunoglobulin E (IgE), a closely related endophenotype of asthma [2,3]. Furthermore, several loci, such as the *CTLA4* and *C11orf30-LRR32* regions, have been shown to be associated with total serum IgE levels in patients with asthma [2,4]. Two genome-wide association studies (GWASs) on total IgE in four population-based cohorts [5] and in subjects combined with asthmatics and controls [6] have identified *FCER1A* as a novel susceptibility locus. Furthermore, two other recent GWASs have found additional

genes (such as *IL13* and *HLA-DQB1*) that are associated with the total serum IgE [7,8]. However, given that asthma is a complex disease and that the nature of the associations between genetic variations and levels of IgE in asthmatics is not yet fully understood, this study aims to identify additional risk loci for the elevation of total serum IgE in asthmatics.

IgE is a class of antibody that plays an essential role in immediate hypersensitivity response, which is the hallmark of allergic diseases including asthma [9,10]. Omalizumab, a humanized antibody drug against IgE, is clinically effective in patients with moderate to severe, persistent allergic asthma [11], indicating that IgE has an important role in the development of allergies and allergic responses. Several IgE-influencing genes that are significantly associated with asthma have been reported [4,5,12,13]. In the case of *interleukin 4* (*IL4*) and *IL13*, which stimulate B cells to produce IgE, genetic variants have been determined to be significantly associated with serum IgE in childhood asthma and atopy [12,14]. However, more recent studies have suggested that

new candidate genes, such as *DPP10* and the *C11orf30-LRRC32* region, may affect IgE levels in asthmatics [2,15]. Therefore, considering that asthma is a heterogeneous and very complex disease, a more specific investigation using a GWAS of IgE in asthma cohorts could increase understanding of the pathogenesis of the disease, and may provide a new strategy for its control.

It has been reported that asthma severity is positively correlated with serum concentration of both total IgE and specific IgE to *Dermatophagoides pteronyssinus* (D.p.) [16]. In addition, house dust mites (HDMs), D.p. and *Dermatophagoides farinae* (D.f.), are generally considered among the most implicated asthma triggers associated with blood allergen-specific IgEs [17]. Furthermore, levels of allergen-specific IgE against D.p. and D.f. in serum have been found to be significantly increased in the bronchial allergen challenge with HDM accompanied by enhanced Th2-cytokine production [18]. Therefore, based on these facts, this study has performed a GWAS for each of allergen-specific IgEs (D.p. and D.f.).

Subjects and Methods

Study Subjects

A total of 877 asthma patients were recruited from Soonchunhyang University, Chungbuk National University, Chonnam National University, Seoul National University, and Chung-Ang University in Korea. All subjects provided written informed consent. In the case of children patients, their parents provided written informed consent before the study commenced. The study protocols were approved by an Institutional Review Board of the Soonchunhyang University Bucheon Hospital, a member of the National Biobank of Korea (IRB No. SCHBC_IRB_05_02). All patients met the criteria for clinical symptoms in accordance with the definition of asthma in the Global Initiative for Asthma (GINA) guidelines. All patients had airway reversibility, as documented by a positive bronchodilator response of >15% increase in forced expiratory volume in one second (FEV₁) and/or airway hyperreactivity to <10 mg/mL of PC₂₀ methacholine. Twenty-four common inhalant allergens, including dust mites (D.p. and D.f.), car fur, dog fur, cockroaches, grass, tree, pollens, ragweed, and the aspergillus species (Bencard Co., Brentford, UK), were used for the skin-prick test. Atopy was defined as having a wheal reaction to an allergen that was equal to or greater than that to histamine (1 mg/ml), or that was 3 mm in diameter.

Total IgE and specific IgE to D.p. and D.f. were measured using the UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden). UniCAP-specific IgE calibrators were used for the determination of specific IgE antibodies. Specific IgE (D.p and D.f.) was classified as 0-6, based on the semi-quantitatively expressed concentrations (Table S1). For UniCAP allergen, 0.35 kU/l was used as a cut-off value (value <0.35 kU/l was a negative result, whereas value >0.35 kU/l was a positive result). A positive result indicates presence of specific IgE antibodies to one or more of the allergens coupled to UniCAP allergens [19].

Genome-wide Genotyping

Genome-wide SNP genotyping of asthma subjects was performed using approximately 200 ng of genomic DNA from the subjects' peripheral blood lymphocytes on Illumina's Human660W-Quad BeadChip® (Illumina, San Diego, CA, USA), according to the manufacturer's protocol. Quality controls of call rate (>98%) and high minor allele frequency (MAF >0.05) were measured. In addition, visual inspection of the genotype cluster image was performed for the SNPs with deviation from Hardy-Weinberg equilibrium (HWE) and with an association *P*-value

<0.001. SNPs in chromosome X of males were excluded from HWE analysis. Although there were significantly deviated SNPs from HWE (as measured by an asymptotic test) in asthmatics, these SNPs were included in the association analysis in order not to miss any SNPs underlying both asthma and total or specific IgEs (i.e., pleiotropy). X-chromosomal markers were also included in the association study. For the additive genetic model among males, genotypes of X chromosome were coded as "0" (homozygous for the major allele) or "2" (homozygous for the minor allele). A total of 70,601 SNPs were excluded, and 442,098 SNP markers were examined for further association analysis.

Statistics

All subjects were of Korean ethnicity. Using the principal component analysis (PCA) for population stratification [20], the genomic control inflation factor (λ , calculated by dividing median χ^2 statistics by 0.456) was computed as 1.003, indicating no significant deviation of the population stratification. For genome-wide evaluation, associations of genotype distributions were calculated using linear regression analysis for total IgE (IU/ml, log₁₀-transformed) association and logistic analysis for specific IgE association, adjusted for age (continuous value), sex (male = 0, female = 1), and smoking status (non-smoker = 0, ex-smoker = 1, current smoker = 2) as covariates, using HelixTree® software (Golden Helix, Bozeman, MT, USA). Statistical power analysis of linear regression for total IgE was obtained from a two-tailed *t*-test; case-control analysis for specific IgE was obtained from the CaTS power calculator [21], using heritability estimates for total IgE (0.49), specific IgE against D.p. (0.24), and specific IgE against D.f. (0.25) [22].

Statistical test used in the Pathway Express (<http://vortex.cs.wayne.edu/projects.htm>) is represented by the corrected gamma *P*-value, as the *P*-value provided by an impact analysis calculated as the sum of the statistically significant number of genes showing biological meanings in the given pathway [23]. In our pathway analysis, the list of gene symbols, which include top SNPs, has been inputted as instructed in the pathway analysis program.

Results

Demographic characteristics of study subjects are summarized in Table 1. A total of 877 Korean asthmatics were involved in the GWAS, including two subgroups for specific IgEs (D.p. and D.f.): 329 (37.5%) D.p.-positive vs. 548 (62.5%) D.p.-negative and 404 (46.1%) D.f.-positive vs. 473 (53.9%) D.f.-negative. Female-male ratio was ~1.8:1 for asthmatics, as was expected in light of general gender differences in adult asthma according to the Global Allergy and Asthma European Network (GA2LEN). Also as expected, atopy was more prevalent in specific IgE-positive groups compared to the negative groups. Specific IgE-positive asthmatics showed higher total IgE levels compared to those of specific IgE-negative patients (*P*<0.001, Table 1).

Total IgE Association in Asthmatics

A total of 442,117 SNPs were passed through strict quality-control measures (call rate >98%, MAF >0.05). First, we tested association with total serum IgE levels in asthmatics using linear regression analysis corrected for age, gender, and smoking status as covariates. In the case of genetic homogeneity of the study subjects, the measured genomic control inflation factor was λ =1.003, indicating no inflation of the type I error. The quantile-quantile (Q-Q) plot for the association test with total IgE showed that distributions between observed and expected *P*-values were deviated in the extreme tail (Figure S1A).

Table 1. Clinical profiles of study subjects.

Clinical profile	Asthmatics	Asthmatics for specific IgE (D.p.)		Asthmatics for specific IgE (D.f.)	
		Positive	Negative	Positive	Negative
Number of subjects (n)	877	329	548	404	473
Age [year, mean (range)]	45.3 (10.8–77.5)	39.0 (10.8–77.1)	49.1 (14.1–77.5)	41.1 (10.8–77.1)	49.0 (16.1–77.5)
Sex (n, male/female)	320/557	147/182	173/375	190/214	130/343
Smoking (n, No/Yes/Ex)	619/118/140	217/59/53	402/59/87	254/77/73	365/41/67
Atopy (n, No/Yes)	397/480	23/306	374/174	48/356	349/124
Log ₁₀ [Total IgE (IU/ml)]	2.18±0.65	2.50±0.51*	1.98±0.64*	2.47±0.56*	1.93±0.61*

Ex indicates ex-smoker.

D.p., Dermatophagoides pteronyssinus; D.f., Dermatophagoides farinae.

* $P < 0.001$.

doi:10.1371/journal.pone.0071958.t001

Although no individual SNPs reached a genome-wide significant level (Bonferroni-corrected significance), top signals ($P < 1.0 \times 10^{-5}$, Table 2 and Table S2) identified several new loci in the intronic region of genes, such as *CRIM1* (rs848512, $P = 1.18 \times 10^{-6}$; rs711254, $P = 6.73 \times 10^{-6}$), *ZNF71* (rs10404342, $P = 7.60 \times 10^{-6}$), *TLN1* (rs4879926, $P = 7.74 \times 10^{-6}$), and *SYNPO2* (rs1472066, $P = 8.36 \times 10^{-6}$; rs1038770, $P = 8.66 \times 10^{-6}$), as susceptibility markers for total IgE levels in asthmatics (Figure 1). In further regional association of each new locus associated with IgE, six SNPs of *SYNPO2* in the chromosome 4q26 (Figure 2) showed relatively strong association signals ($P = 8.36 \times 10^{-6}$ for rs1472066 to $P = 0.0056$ for rs1021377) when compared to other top signals (Figure S2, S3, S4). In the case of linkage disequilibrium (LD) analysis, it was revealed that *SYNPO2* or its SNPs that showed

significant associations with total IgE were likely to not be in LD with nearby genes ($r^2 \leq 0.243$, Figure 2).

Specific IgE (D.p. and D.f.) Associations in Asthmatics

In further association analyses with specific IgE to house dust mites (Figure S5), along with Q-Q plots for the association test with specific IgE against D.p. and D.f. (Figure S1B and S1C), intergenic SNPs nearby to *OPRK1* (rs1425902, $P = 1.44 \times 10^{-6}$, Table S3) and *LOC730217* (rs10142119, $P = 1.86 \times 10^{-7}$; rs1456988, $P = 1.11 \times 10^{-6}$; rs12590389, $P = 2.47 \times 10^{-6}$, Table S4, coefficient r^2 among these three SNPs = 0.515–0.757) were detected as the most significant polymorphisms associated with the specific IgEs of D.p. and D.f. in asthmatics, respectively.

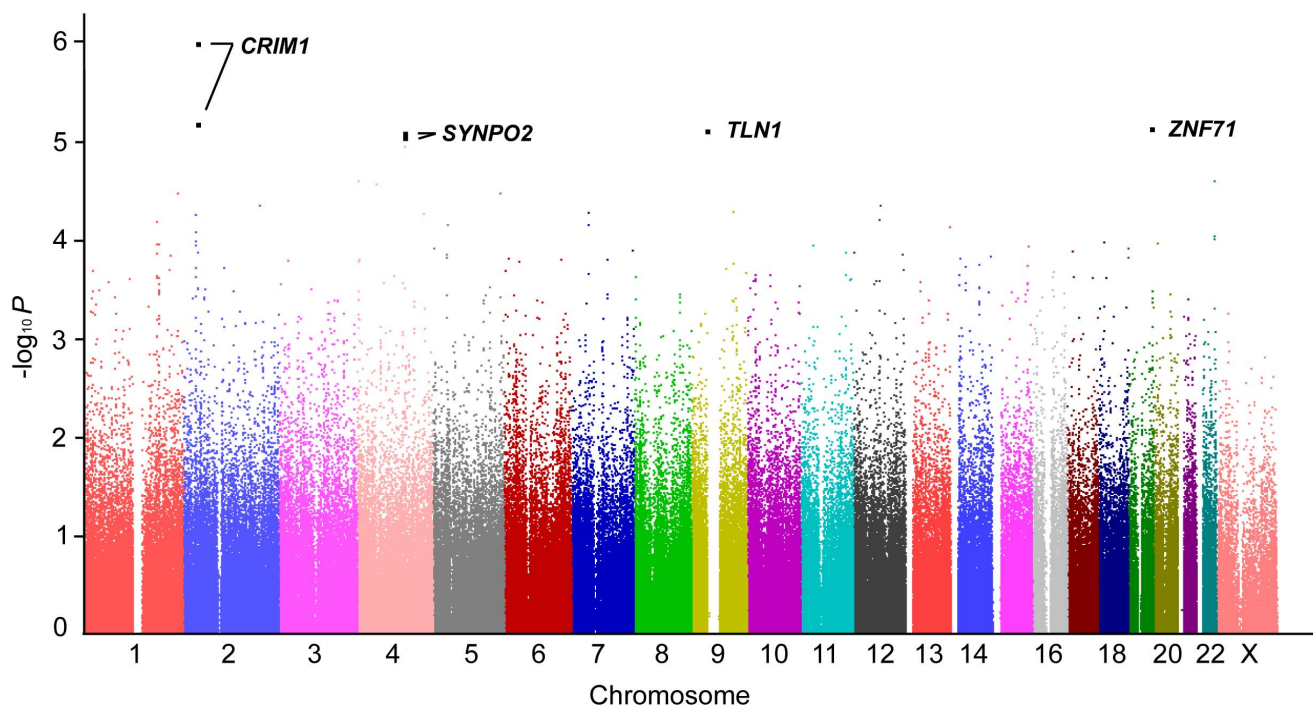


Figure 1. Graphical summary (Manhattan plot) presenting P -values for the association with total serum IgE in asthma patients. The y-axis represents $-\log_{10}P$ (linear regression analysis) from 442,117 SNPs in 877 patients with asthma, correcting for age, gender, and smoking status as covariates; the x-axis indicates its physical position on successive chromosomes.
doi:10.1371/journal.pone.0071958.g001

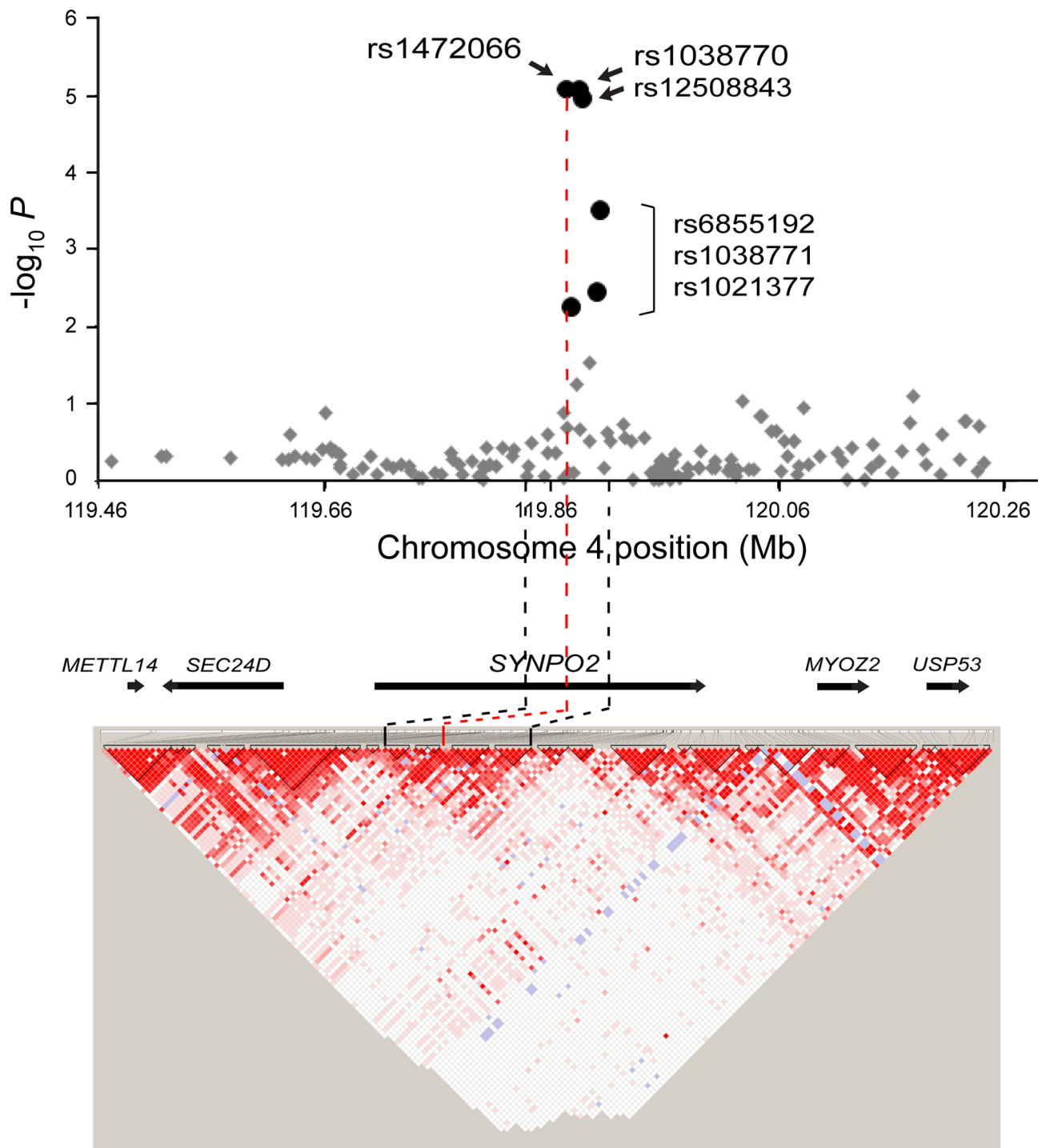


Figure 2. Regional association plot and LD of *SYNPO2* for the total IgE in asthmatics. GWAS associations ($-\log_{10}P$) of SNPs across approximately 768 kb region around *SYNPO2* in the chromosome 4q26 are shown. Relatively strong associations are shown as large black circles; relatively less significances as small gray diamonds.
doi:10.1371/journal.pone.0071958.g002

Pathway Analysis

To better understand the biological process and molecular function involved in total serum IgE in asthma, the signaling pathways were estimated using Pathway Express (<http://vortex.cs.wayne.edu/projects.htm>). Among the significantly associated SNPs with total IgE ($P < 0.001$), only the SNPs in the gene regions

were analyzed. The phosphatidylinositol signaling system ($P = 2.89 \times 10^{-18}$) and adherens junction ($P = 1.57 \times 10^{-13}$) pathways were estimated to play a role in the regulation of total IgE levels in asthmatics (Table S5).

Table 2. Top 6 SNPs ($P < 1.0 \times 10^{-5}$) associated with total IgE of asthmatics in the GWAS.

								Genotype**			
SNP ID	Chr	Gene	Location	Variation	MAF	LD (coefficient r^2)	HWE*	M/M [†]	M/m [†]	m/m [†]	P-value
rs848512	2	CRIM1	Intron	C>T	0.078	0.925 (rs848512- rs711254)	0.283	744 (2.22)	130 (1.93)	3 (1.89)	1.18×10^{-6}
rs711254	2	CRIM1	Intron	C>T	0.083		0.373	735 (2.22)	137 (1.97)	4 (1.76)	6.73×10^{-6}
rs10404342	19	ZNF71	Intron	A>C	0.399		0.748	315 (2.05)	425 (2.23)	137 (2.33)	7.60×10^{-6}
rs4879926	9	TLN1	Intron	T>C	0.072		0.070	751 (2.22)	125 (1.96)	1 (2.3)	7.74×10^{-6}
rs1472066	4	SYNPO2	Intron	A>G	0.107	0.581 (rs1472066–rs1038770)	0.744	700 (2.23)	166 (1.99)	11 (1.81)	8.36×10^{-6}
rs1038770	4	SYNPO2	Intron	G>A	0.116		0.805	685 (2.23)	181 (2.02)	11 (1.6)	8.66×10^{-6}

Association analyses were adjusted by age, sex, and smoking status as covariates.

*P-value of Hardy-Weinberg equilibrium (HWE).

**Genotype represents number of subjects (mean of log[Total IgE (IU/ml)]).

[†]M/M, M/m, and m/m indicate homozygote for common allele, heterozygote, and homozygote for rare allele, respectively.

Chr, chromosome; MAF, minor allele frequency.

doi:10.1371/journal.pone.0071958.t002

Discussion

IgE is considered an important target in the treatment of asthma. Furthermore, anti-IgE therapy, i.e., using a humanized antibody drug of Omalizumab against IgE, has been demonstrated to be efficacious for the management of asthma as well as allergic diseases [11,24]. Asthma susceptibility is generally classified into four main mechanisms as follows: (1) innate immunity and immunoregulation, (2) T_H2-cell differentiation and effector function, (3) epithelial cells, and (4) lung function. Although IgE and its binding to FcεRI (high-affinity Fc receptor for IgE) regulates the activation of mast cells and basophils mainly in the first and second mechanisms, IgE is associated with a more complicated network of proteins [10,25]. Therefore, together with the identification of new potential risk factors, our GWAS of total serum IgE and mite-specific IgE in asthmatics may provide additional supporting information about genetic associations related to IgE function in asthma and related diseases.

In this study, no individual SNPs reached a genome-wide significance level (Bonferroni-corrected significance), which is a limitation of this study. According to the power calculation, this failure to reach a genome-wide signal might be due to an underpowered study (in particular, statistical powers of 44.5% in total IgE analysis and 62.0% in specific IgE against D.f., Table S6), because of insufficient sample size and lack of replication. In order to address this limitation, further replications in larger cohorts are needed. On the other hand, being that asthma is a complex disease, we also cannot rule out the possibility that confounders with small to modest effects may contribute to the regulation of total IgE in asthma [26]. Our results identified new potential genes associated with total IgE in asthmatics, such as *CRIM1*, *ZNF71*, *TLN1*, and *SYNPO2*. Recently, *SYNPO2* has been reported to be significantly associated with airway hyperresponsiveness in patients with asthma [27]. In addition, in our further in silico analysis using the Human Splicing Finder (<http://www.umd.be/HSF/>) [28], rs4879926 of *TLN1*, rs1472066 and rs1038770 of *SYNPO2* were predicted as potential branch point (BP) sites for alternative splicing (Figure S6), revealing that these variations might have a possibility to produce an isoform of the gene. These results suggest that genetic variants of the newly discovered genes, in particular *SYNPO2*, could play a role in IgE regulation.

Recent results from GWASs on total serum IgE levels have identified associated genes, including *RAD50*, *STAT6*, *FCER1A*,

IL13, and *HLA-DQB1* [5–8]. When genetic associations of the identified SNPs from previous GWASs were compared with those from this GWAS, most were not replicated in our Korean asthmatic subjects (Table S7). Instead, this study identified additional candidate genes (*CRIM1*, *ZNF71*, *TLN1*, *SYNPO2*, etc.) for total serum IgE levels in asthma patients. Among the several well-known IgE-influencing genes (*IL4*, *IL13*, *CD28*, *C11orf30-LRRC32* region, etc.) [2,4,12,15,29], this study confirmed a significant association between *CD28* SNPs and total IgE in asthmatics (minimum $P = 0.001$, data not shown). Serum total IgE levels have been elucidated to be correlated with CD28, an important regulator of T-cell activation and subsequent IgE production [30,31]. In this study, differences in the results between present and previous GWASs might be attributed to population and/or ethnic differences, limitation and mismatch of the tested SNP markers (albeit only SNPs in the *C11orf30-LRRC32* region were matched with those of this GWAS), and a diversity of clinical phenotypes among asthma patients.

As other potential genes that are not as well-known but that potentially affect IgE levels, SNPs of *NPSR1* and *IRAK3* were also observed to be associated with total IgE among asthmatics in this study (Table S8). SNP-tagged haplotypes of *neuropeptide S receptor 1* (*NPSR1*; also known as G-protein-coupled receptor for asthma susceptibility, *GPRA* or *GPRA154*) have been found to be associated with increased serum IgE levels or asthma, and have been functionally evaluated to be distinctively distributed between protein isoforms in bronchial biopsies from healthy and asthmatic subjects [32]. However, since conflicting results in associations of *NPSR1* and its genetic variations with total IgE level and/or asthma have also been reported [33,34], further studies are required to determine their effect on the disease trait. In addition, *IRAK3* rs1821777, which showed a nominal signal (Table S8) in the present study, has also been reported to be related to asthma in North Americans ($P = 0.03$) and in Sardinians ($P = 0.001$) of Italy [35,36]. Two *IRAK3* SNPs (rs2701653 and rs1821777, Table S8) were also observed to be related to atopic asthma in a Spanish population ($P = 0.034$) and in a meta-analysis of Spanish and Sardinian populations ($P = 0.013$) [37]. In light of the potential association of the nonsynonymous variant rs1152888 of *IRAK3* with total IgE in asthmatics ($P = 0.003$, Table S8), further functional evaluations will be valuable in identifying whether *IRAK3* can serve as a new therapeutic target.

Given that a previous study showed the association between total serum IgE and asthma independently of specific IgE levels to mites [38], we performed further analyses to discover factors associated with specific IgE against two major house dust mites (D.p. and D.f.) in asthmatics. Similar to the previous study, totally different profiles of genetic variants between total IgE and mite-specific IgEs (possibly even between specific IgEs against D.p. and D.f.) in asthmatics were observed in the further analyses. These observations suggest that patients with asthma may have allergies to different environmental allergens such as cockroaches and pet allergens [39,40], as well as house dust mites.

To better understand the biological process and molecular function involved in total serum IgE in asthma, the signaling pathways were estimated using Pathway Express (<http://vortex.cs.wayne.edu/projects.htm>). The result showed that the phosphatidylinositol signaling system ($P=2.89 \times 10^{-18}$), as supported by previous strong evidence [41,42], and adherens junction ($P=1.57 \times 10^{-13}$) pathways might play a role in the regulation of total IgE levels in asthmatics (Table S5). In addition, in the Gene Relationships Across Implicated Loci (GRAIL) analysis based on PubMed articles published before December 2006, several genes (*KALRN*, *CNTN5*, *INPP4B*, etc.; $P \sim 0.01$) were shown to have functional connectivity (Table S9). Thus, despite study limitations (lacks of genome-wide significance, replication, and functional evaluation), our GWAS of IgE in asthmatics may provide an outline of the genetic implication for total serum and mite-specific IgEs in asthma and its related phenotypes.

Supporting Information

Figure S1 Q-Q plots of total IgE, specific IgE (D.p.), and specific IgE (D.f.). The observed P -value (y-axis) is compared with the expected P -value (x-axis, under null distribution) for (A) total IgE, (B) specific IgE (D.p.), and (C) specific IgE (D.f.). (DOC)

Figure S2 Regional association plot and LD of *CRIM1* for the total IgE in asthmatics. GWAS associations ($-\log_{10}P$) of SNPs across approximately 310 kb region around *CRIM1* in the chromosome 2p21 are shown. Relatively strong associations are shown as large black circles; relatively less significances as small gray diamonds. (DOC)

Figure S3 Regional association plot and LD of *ZNF71* for the total IgE in asthmatics. GWAS associations ($-\log_{10}P$) of SNPs across approximately 245 kb region around *ZNF71* in the chromosome 19q13.4 are shown. Relatively strong associations are shown as large black circles; relatively less significances as small gray diamonds. (DOC)

Figure S4 Regional association plot and LD of *TLN1* for the total IgE in asthmatics. GWAS associations ($-\log_{10}P$) of SNPs across approximately 126 kb region around *TLN1* in the chromosome 9p13 are shown. Relatively strong associations are shown as large black circles; relatively less significances as small gray diamonds. (DOC)

References

- Sengler C, Lau S, Wahn U, Nickel R (2002) Interactions between genes and environmental factors in asthma and atopy: new developments. *Respir Res* 3: 7.
- Li X, Ampleford EJ, Howard TD, Moore WC, Li H, et al. (2012) The C11orf30-LRRC32 region is associated with total serum IgE levels in asthmatic patients. *J Allergy Clin Immunol* 129: 575–78.
- Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, et al. (1991) Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 325: 1067–71.

Figure S5 Manhattan plots of specific IgE against house dust mites (D.p. and D.f.). Associations for the specific IgE against (A) D.p. and (B) D.f. in asthma patients are obtained by correcting for age, gender, and smoking status as covariates. (DOC)

Figure S6 In silico analysis of top 6 SNPs in intron regions. (A) Potential branch point (BP) sites are predicted by the change between major allele and minor allele using the Human Splicing Finder (<http://www.umd.be/HSF/>). (B) A schematic plot of alternative splicing by the predicted additional BP site. The picture of consensus sequence is modified from Desmet et al. *Nucleic Acids Research* 37(9): e67, 2009. (DOC)

Table S1 Classification of specific IgE. (DOC)

Table S2 Top 100 SNPs associated with total IgE of asthmatics in the GWAS. (DOC)

Table S3 Top 100 SNPs associated with specific IgE for D.p. in the GWAS. (DOC)

Table S4 Top 100 SNPs associated with specific IgE for D.f. in the GWAS. (DOC)

Table S5 Pathway analysis for significantly associated SNPs ($P < 0.001$), only in the gene regions from the results of GWAS, on total IgE in asthmatics. (DOC)

Table S6 Statistical power for the analysis in each subgroup of study subjects. (DOC)

Table S7 Genetic associations from this GWAS compared to the previously identified SNPs from other GWASs. (DOC)

Table S8 SNPs of other potential genes (but not well-known IgE-influencing genes) associated with total IgE in asthmatics ($P < 0.01$). (DOC)

Table S9 Genes based clustering from GRAIL. (DOC)

Acknowledgments

The DNA samples were generously provided by the Soonchunhyang University, Bucheon Hospital Biobank, a member of the National Biobank of Korea, supported by the Ministry of Health, Welfare and Family Affairs, Republic of Korea.

Author Contributions

Conceived and designed the experiments: CSP HDS. Performed the experiments: JHK JSB. Analyzed the data: JHK HSC. Contributed reagents/materials/analysis tools: JSP STU YHK MKK ISC SHC BWC CSP. Wrote the paper: JHK CSP HDS.

4. Howard TD, Postma DS, Hawkins GA, Koppelman GH, Zheng SL, et al. (2002) Fine mapping of an IgE-controlling gene on chromosome 2q: Analysis of CTLA4 and CD28. *J Allergy Clin Immunol* 110: 743–51.
5. Weidinger S, Gieger C, Rodriguez E, Baurecht H, Mempel M, et al. (2008) Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus. *PLoS Genet* 4: e1000166.
6. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, et al. (2010) A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 363: 1211–21.
7. Granada M, Wilk JB, Tuzova M, Strachan DP, Weidinger S, et al. (2012) A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study. *J Allergy Clin Immunol* 129: 840–845 e21.
8. Levin AM, Mathias RA, Huang L, Roth LA, Daley D, et al. (2013) A meta-analysis of genome-wide association studies for serum total IgE in diverse study populations. *J Allergy Clin Immunol*. In press.
9. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG (1989) Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med*, 271–7.
10. Gould HJ, Sutton BJ (2008) IgE in allergy and asthma today. *Nat Rev Immunol* 8: 205–17.
11. Avila PC (2007) Does anti-IgE therapy help in asthma? Efficacy and controversies. *Annu Rev Med* 58: 185–203.
12. Kabesch M, Schedel M, Carr D, Woitsch B, Fritzsche C, et al. (2006) IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J Allergy Clin Immunol* 117: 269–74.
13. Xu J, Postma DS, Howard TD, Koppelman GH, Zheng SL, et al. (2000) Major genes regulating total serum immunoglobulin E levels in families with asthma. *Am J Hum Genet* 67: 1163–73.
14. Liu X, Beatty TH, Deindl P, Huang SK, Lau S, et al. (2004) Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol* 113: 489–95.
15. Gao J, Li W, Willis-Owen SA, Jiang L, Ma Y, et al. (2010) Polymorphisms of PHF11 and DPP10 are associated with asthma and related traits in a Chinese population. *Respiration* 79: 17–24.
16. Kovac K, Dodig S, Tjesic-Drinkovic D, Raos M (2007) Correlation between asthma severity and serum IgE in asthmatic children sensitized to Dermatophagoides pteronyssinus. *Arch Med Res* 38: 99–105.
17. Gaffin JM, Phipatanakul W (2009) The role of indoor allergens in the development of asthma. *Curr Opin Allergy Clin Immunol* 9: 128–35.
18. van de Pol MA, Lutter R, van Ree R, van der Zee JS (2012) Increase in allergen-specific IgE and ex vivo Th2 responses after a single bronchial challenge with house dust mite in allergic asthmatics. *Allergy* 67: 67–73.
19. Pastorello EA, Incorvaia C, Pravettoni V, Bonini S, Canonica GW, et al. (1991) A multicentric study on sensitivity and specificity of a new in vitro test for measurement of IgE antibodies. *Ann Allergy* 67: 365–70.
20. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, et al. (2006) Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 38: 904–9.
21. Skol AD, Scott LJ, Abecasis GR, Boehnke M (2006) Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. *Nat Genet* 38: 209–13.
22. Tsai HJ, Kumar R, Pongracic J, Liu X, Story R, et al. (2009) Familial aggregation of food allergy and sensitization to food allergens: a family-based study. *Clin Exp Allergy* 39: 101–9.
23. Draghici S, Khatri P, Tarca AL, Amin K, Done A, et al. (2007) A systems biology approach for pathway level analysis. *Genome Res* 17: 1537–45.
24. Holgate ST, Polosa R (2008) Treatment strategies for allergy and asthma. *Nat Rev Immunol* 8: 218–30.
25. Lee SH, Park JS, Park CS (2011) The search for genetic variants and epigenetics related to asthma. *Allergy Asthma Immunol Res* 3: 236–44.
26. Frazer KA, Murray SS, Schork NJ, Topol EJ (2009) Human genetic variation and its contribution to complex traits. *Nat Rev Genet* 10: 241–51.
27. Yick CY, Zwiderman AH, Kunst PW, Grunberg K, Mauad T, et al. (2013) Glucocorticoid-Induced Changes in Gene Expression of Airway Smooth Muscle in Patients with Asthma. *Am J Respir Crit Care Med*. In press.
28. Desmet FO, Hamroun D, Lalande M, Colod-Beroud G, Claustres M, et al. (2009) Human Splicing Finder: an online bioinformatics tool to predict splicing signals. *Nucleic Acids Res* 37: e67.
29. King CL, Gallin JI, Malech HL, Abramson SL, Nutman TB (1989) Regulation of immunoglobulin production in hyperimmunoglobulin E recurrent-infection syndrome by interferon gamma. *Proc Natl Acad Sci U S A* 86: 10085–9.
30. Bottema RW, Postma DS, Reijmerink NE, Thijs C, Stelma FF, et al. (2010) Interaction of T-cell and antigen presenting cell co-stimulatory genes in childhood IgE. *Eur Respir J* 35: 54–63.
31. Wong CK, Lun SW, Ko FW, Ip WK, Hui DS, et al. (2005) Increased expression of plasma and cell surface co-stimulatory molecules CTLA-4, CD28 and CD86 in adult patients with allergic asthma. *Clin Exp Immunol* 141: 122–9.
32. Laitinen T, Polvi A, Rydman P, Vendelin J, Pulkkinen V, et al. (2004) Characterization of a common susceptibility locus for asthma-related traits. *Science* 304: 300–4.
33. Vergara C, Jimenez S, Acevedo N, Martinez B, Mercado D, et al. (2009) Association of G-protein-coupled receptor 154 with asthma and total IgE in a population of the Caribbean coast of Colombia. *Clin Exp Allergy* 39: 1558–68.
34. Wu H, Romieu I, Sienra-Monge JJ, del Rio-Navarro BE, Burdett L, et al. (2008) Lack of association between genetic variation in G-protein-coupled receptor for asthma susceptibility and childhood asthma and atopy. *Genes Immun* 9: 224–30.
35. Balaci L, Spada MC, Olla N, Sole G, Loddo L, et al. (2007) IRAK-M is involved in the pathogenesis of early-onset persistent asthma. *Am J Hum Genet* 80: 1103–14.
36. Rogers AJ, Raby BA, Lasky-Su JA, Murphy A, Lazarus R, et al. (2009) Assessing the reproducibility of asthma candidate gene associations, using genome-wide data. *Am J Respir Crit Care Med* 179: 1084–90.
37. Pino-Yanes M, Sanchez-Machin I, Cumplido J, Figueroa J, Torres-Galvan MJ, et al. (2012) IL-1 receptor-associated kinase 3 gene (IRAK3) variants associate with asthma in a replication study in the Spanish population. *J Allergy Clin Immunol* 129: 573–5, 575 e1–10.
38. Sunyer J, Anto JM, Castellsague J, Soriano JB, Roca J (1996) Total serum IgE is associated with asthma independently of specific IgE levels. The Spanish Group of the European Study of Asthma. *Eur Respir J* 9: 1880–4.
39. Helm R, Cockrell G, Stanley JS, Brenner RJ, Burks W, et al. (1996) Isolation and characterization of a clone encoding a major allergen (Bla g Bd90K) involved in IgE-mediated cockroach hypersensitivity. *J Allergy Clin Immunol* 98: 172–80.
40. Kelly LA, Erwin EA, Platts-Mills TA (2012) The indoor air and asthma: the role of cat allergens. *Curr Opin Pulm Med* 18: 29–34.
41. Doi T, Obayashi K, Kadowaki T, Fujii H, Koyasu S (2008) PI3K is a negative regulator of IgE production. *Int Immunol* 20: 499–508.
42. Gilfillan AM, Tkaczuk C (2006) Integrated signalling pathways for mast-cell activation. *Nat Rev Immunol* 6: 218–30.

Figure S1

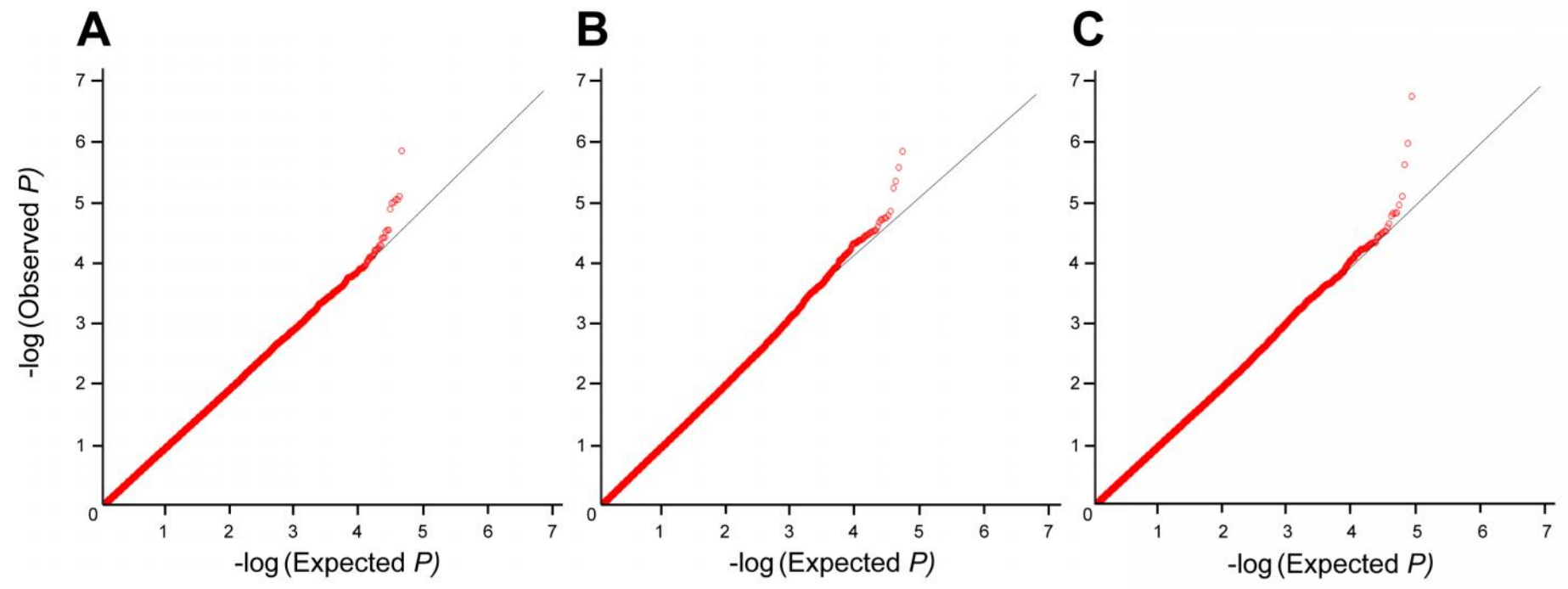


Figure S2

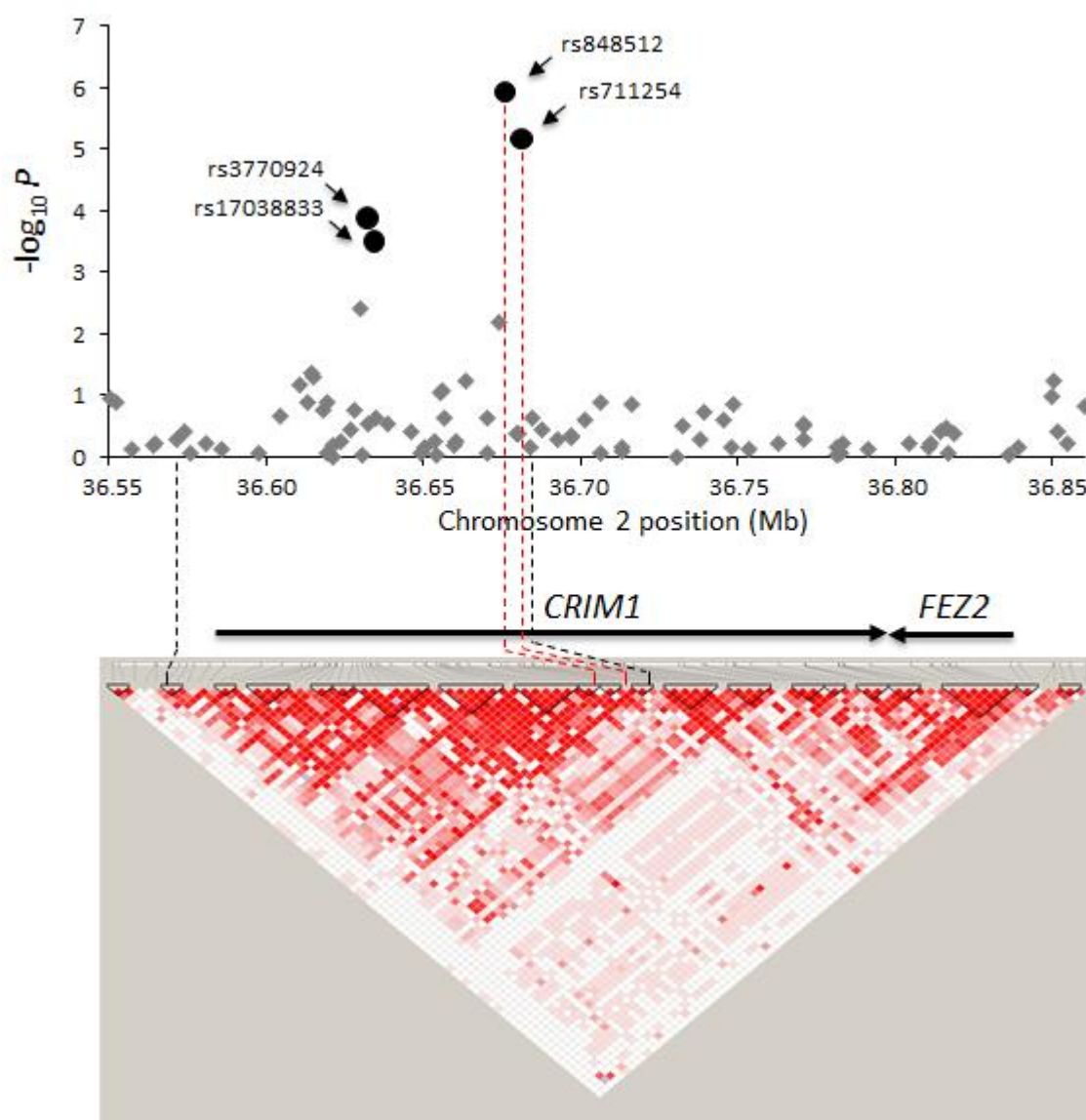


Figure S3

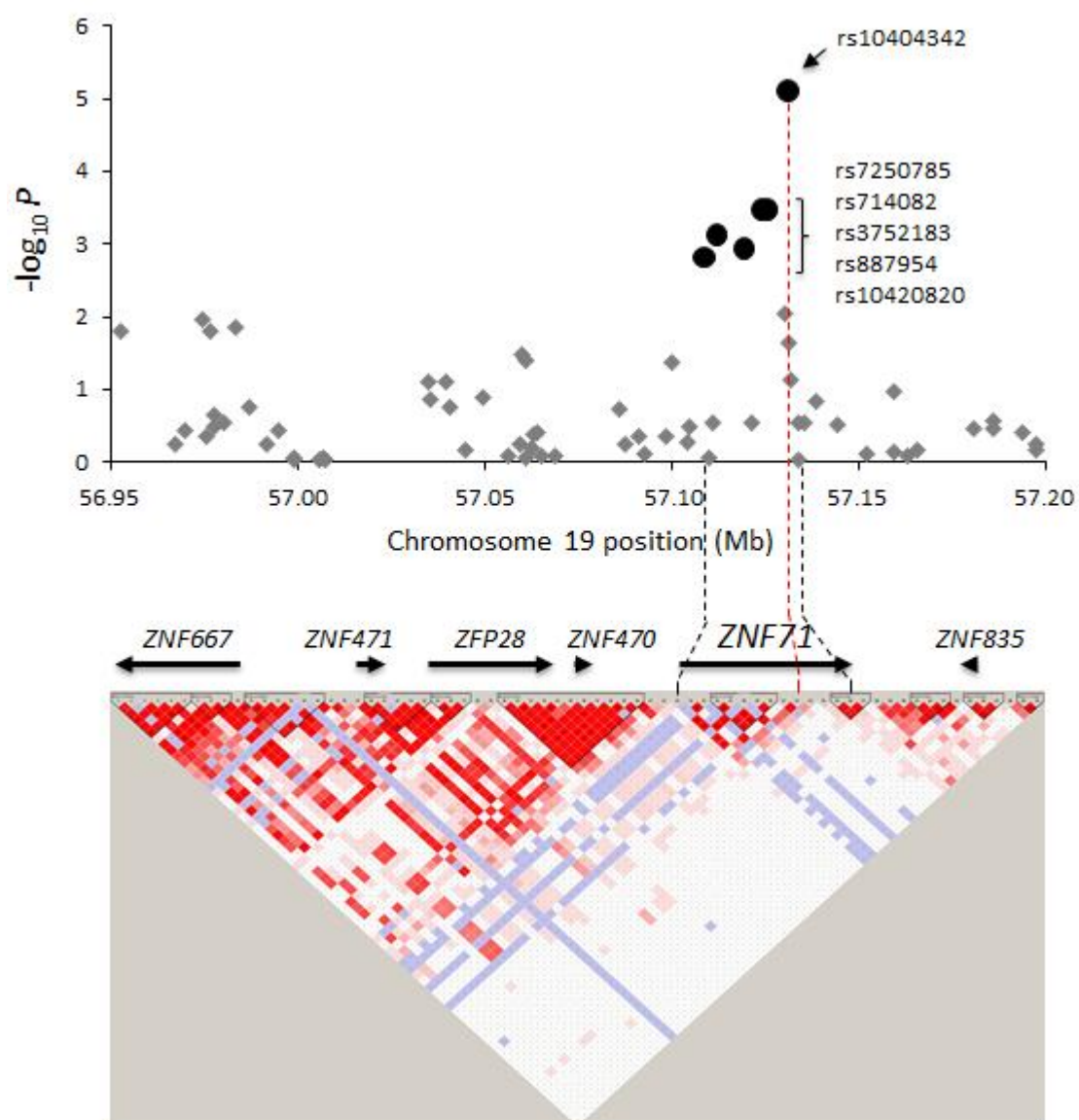


Figure S4

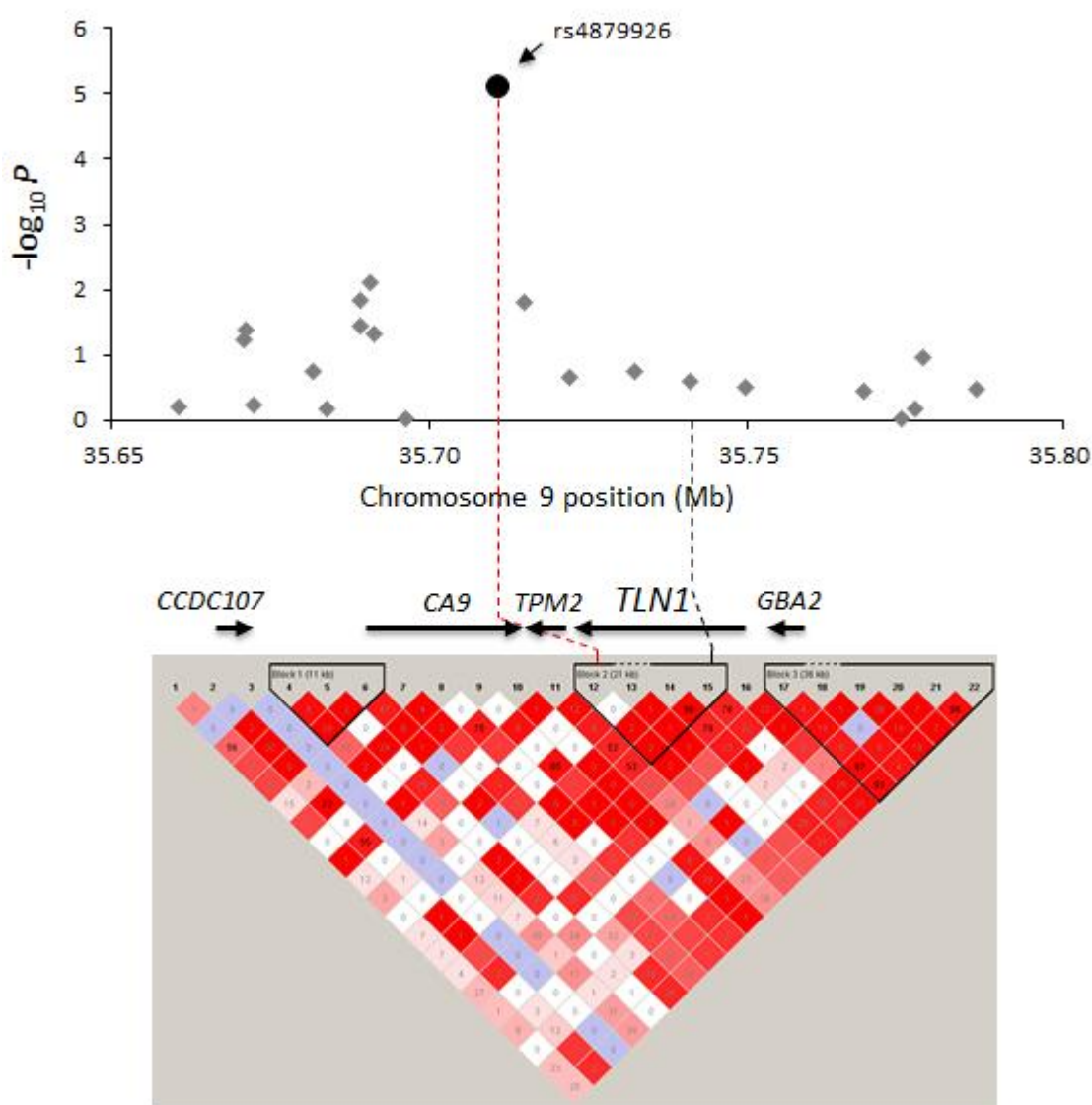


Figure S5

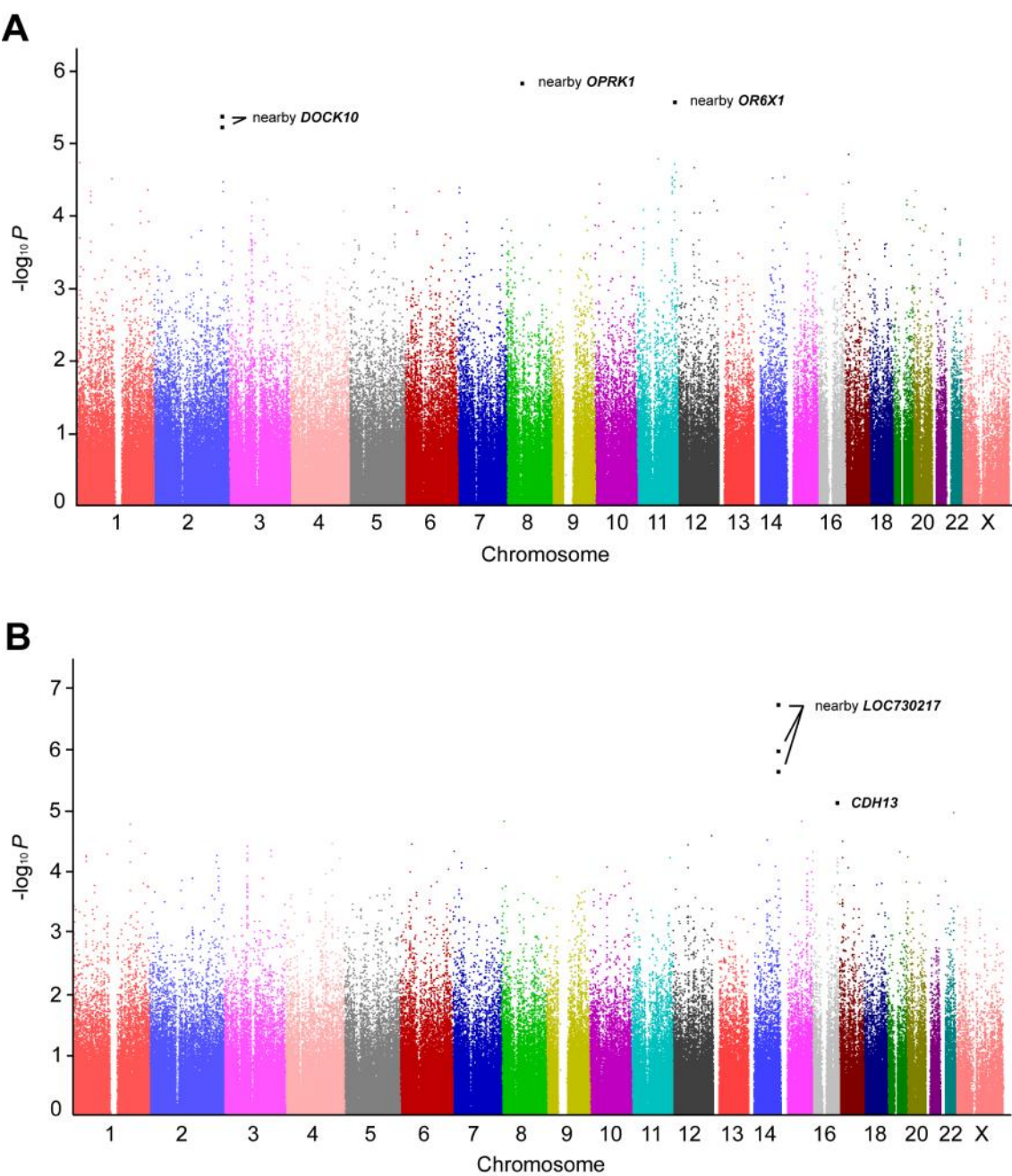


Figure S6

A

No	SNP ID	Gene	Location	Allele variation	Consensus value of BP site for alternative splicing	
					Major allele	Minor allele
1	rs848512	<i>CRIM1</i>	Intron	C>T	21.42	51.05
2	rs711254	<i>CRIM1</i>	Intron	C>T	8.34	37.97
3	rs10404342	<i>ZNF71</i>	Intron	A>C	62.32	32.70
4	rs4879926	<i>TLN1</i>	Intron	T>C	75.96	46.33
5	rs1472066	<i>SYNPO2</i>	Intron	A>G	71.15	41.52
6	rs1038770	<i>SYNPO2</i>	Intron	G>A	42.64	72.27

■ Motifs with high consensus values (> 67) are candidates of the branch point (BP) site as described in the program

B

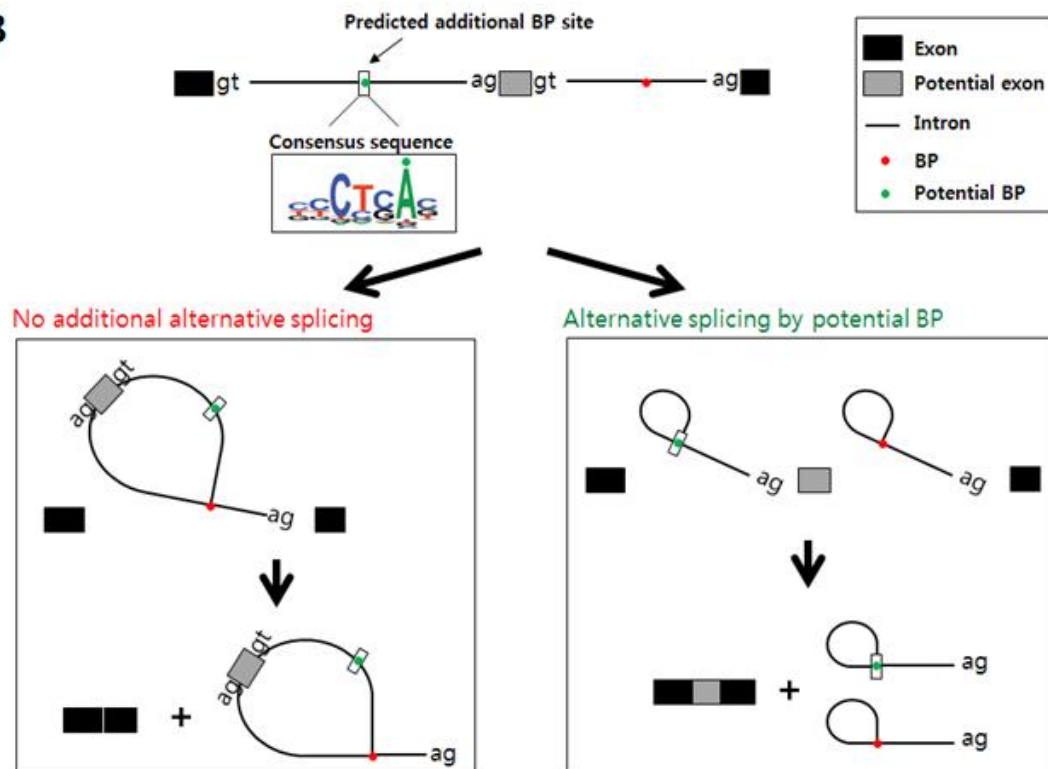


Table S1. Classification of specific IgE

Specific IgE class	ImmunoCAP specific IgE Units (kU/l)	Level of allergen specific IgE Ab
6	>100	Very high
5	50-100	Very high
4	17.5-50	Very high
3	3.5-17.5	High
2	0.7-3.5	Moderate
1	0.35-0.7	Low
0	0.35	Absent or undetectable

Ab, antibody.

Table S2. Top 100 SNPs associated with total IgE of asthmatics in the GWAS

SNP ID	Chr	(Nearby) gene	Location	Variation	MAF	HWE*	Genotype**			P-value
							M/M†	M/m†	m/m†	
rs848512	2	<i>CRIM1</i>	Intron	C>T	0.078	0.283	744 (2.22)	130 (1.93)	3 (1.89)	1.18E-06
rs711254	2	<i>CRIM1</i>	Intron	C>T	0.083	0.373	735 (2.22)	137 (1.97)	4 (1.76)	6.73E-06
rs10404342	19	<i>ZNF71</i>	Intron	A>C	0.399	0.748	315 (2.05)	425 (2.23)	137 (2.33)	7.60E-06
rs4879926	9	<i>TLN1</i>	Intron	T>C	0.072	0.070	751 (2.22)	125 (1.96)	1 (2.30)	7.74E-06
rs1472066	4	<i>SYNPO2</i>	Intron	A>G	0.107	0.744	700 (2.23)	166 (1.99)	11 (1.81)	8.36E-06
rs1038770	4	<i>SYNPO2</i>	Intron	G>A	0.116	0.805	685 (2.23)	181 (2.02)	11 (1.60)	8.66E-06
rs12508843	4	<i>SYNPO2</i>	Intron	G>T	0.193	0.597	574 (2.24)	268 (2.09)	35 (1.82)	1.10E-05
rs5766564	22	<i>C22orf9</i>	Intron	G>A	0.339	0.073	371 (2.26)	417 (2.16)	89 (1.95)	2.48E-05
rs7667661	4	<i>NOL14</i>	Intron	G>A	0.078	0.869	745 (2.21)	127 (2.02)	5 (1.62)	2.50E-05
rs1866990	4	<i>GABRB1</i>	Intron	G>A	0.270	0.858	466 (2.27)	348 (2.08)	63 (2.06)	2.68E-05
rs6683160	1	<i>RYR2</i>	Intron	A>C	0.348	0.638	376 (2.26)	391 (2.16)	109 (1.97)	3.31E-05
rs315782	5	(<i>LCP2</i>)	Intergenic	T>C	0.097	0.102	711 (2.14)	162 (2.36)	4 (2.34)	3.36E-05
rs777734	2	(<i>LOC391470</i>)	Intergenic	C>A	0.106	0.759	700 (2.22)	168 (2.04)	9 (1.61)	4.39E-05
rs1152937	12	<i>CPM</i>	Intron	C>T	0.145	0.337	637 (2.23)	225 (2.07)	15 (1.81)	4.45E-05
rs1990458	7	<i>GCK</i>	Intron	G>A	0.292	0.593	443 (2.10)	356 (2.23)	78 (2.38)	5.24E-05
rs17053323	4	(<i>SPOCK3</i>)	Intergenic	A>G	0.130	0.153	655 (2.23)	207 (2.04)	10 (1.96)	5.37E-05
rs10197865	2	<i>GALNT14</i>	Intron	T>C	0.380	0.003	358 (2.27)	372 (2.14)	147 (2.06)	5.48E-05
rs1168745	12	<i>TMBIM4</i>	Intron	T>C	0.186	0.608	579 (2.24)	270 (2.08)	28 (1.91)	6.21E-05
rs10911203	1	<i>LAMC1</i>	Intron	G>A	0.133	0.889	659 (2.23)	203 (2.06)	15 (1.87)	6.53E-05
rs395157	5	<i>OSMR</i>	Intron	G>A	0.265	0.558	471 (2.24)	348 (2.14)	58 (1.93)	6.94E-05
rs3757840	7	(<i>GCK</i>)	Intergenic	A>C	0.405	0.644	314 (2.07)	416 (2.21)	147 (2.32)	7.05E-05
rs9549433	13	(<i>LOC729095</i>)	Intergenic	C>A	0.251	0.271	484 (2.12)	341 (2.24)	49 (2.38)	7.40E-05
rs7608731	2	<i>GALNT14</i>	Intron	C>T	0.379	0.004	358 (2.27)	373 (2.14)	146 (2.07)	8.15E-05
rs5766584	22	(<i>C22orf9</i>)	Intergenic	G>T	0.460	0.046	241 (2.04)	465 (2.23)	171 (2.25)	9.05E-05
rs11090735	22	<i>C22orf9</i>	Intron	T>C	0.324	0.041	387 (2.25)	411 (2.16)	79 (1.95)	9.64E-05
rs9308914	2	<i>GALNT14</i>	Intron	A>C	0.388	0.010	347 (2.27)	380 (2.15)	150 (2.05)	0.00010
rs9955902	18	(<i>MC5R</i>)	Intergenic	T>G	0.396	0.065	307 (2.11)	445 (2.17)	124 (2.38)	0.00010
rs4610128	20	(<i>LOC441940</i>)	Intergenic	G>A	0.115	0.402	685 (2.22)	183 (2.04)	9 (1.75)	0.00011
rs996384	20	(<i>LOC441940</i>)	Intergenic	T>G	0.115	0.402	685 (2.22)	183 (2.04)	9 (1.75)	0.00011
rs12136061	1	(<i>LOC730175</i>)	Intergenic	C>T	0.151	0.121	627 (2.12)	236 (2.33)	14 (2.28)	0.00011
rs17479287	1	(<i>LAMC2</i>)	Intergenic	G>A	0.078	0.198	749 (2.21)	120 (2.01)	8 (1.76)	0.00011
rs10836063	11	(<i>HIPK3</i>)	Intergenic	C>T	0.210	0.970	547 (2.11)	291 (2.30)	39 (2.26)	0.00011
rs1862968	2	<i>GALNT14</i>	Intron	A>G	0.383	0.002	355 (2.27)	370 (2.14)	150 (2.07)	0.00011
rs7170834	15	(<i>LOC390641</i>)	Intergenic	G>T	0.179	0.113	598 (2.22)	244 (2.12)	35 (1.93)	0.00012
rs6875477	5	(<i>LOC728878</i>)	Intergenic	A>G	0.214	0.952	541 (2.11)	296 (2.29)	40 (2.32)	0.00012
rs2074920	19	<i>SBNO2</i>	Coding	C>T	0.320	0.790	404 (2.25)	385 (2.13)	88 (2.07)	0.00012
rs12536378	7	<i>NULL</i>	Intron	T>C	0.304	0.665	427 (2.23)	366 (2.19)	84 (1.87)	0.00013
rs7211689	17	(<i>FLJ45831</i>)	Intergenic	A>C	0.404	0.921	312 (2.08)	421 (2.21)	144 (2.30)	0.00013
rs1698157	11	(<i>LOC283143</i>)	Intergenic	C>A	0.477	0.072	253 (2.06)	411 (2.21)	213 (2.26)	0.00013
rs7298821	12	<i>CACNA1C</i>	Intron	C>T	0.302	0.084	417 (2.27)	391 (2.11)	69 (2.04)	0.00013
rs3770924	2	<i>CRIM1</i>	Intron	C>T	0.076	0.325	747 (2.21)	127 (2.00)	3 (1.89)	0.00013
rs10911180	1	(<i>KRT18P28</i>)	Intergenic	C>A	0.125	0.836	671 (2.22)	193 (2.05)	13 (1.87)	0.00014
rs2113097	5	<i>SLC45A2</i>	Intron	G>A	0.227	0.722	526 (2.11)	304 (2.27)	47 (2.35)	0.00014
rs2287949	5	<i>SLC45A2</i>	Coding	C>T	0.227	0.722	526 (2.11)	304 (2.27)	47 (2.35)	0.00014
rs7967521	12	<i>SCARB1</i>	Intron	T>C	0.321	0.715	402 (2.11)	387 (2.22)	88 (2.33)	0.00014
rs10495085	1	(<i>SPATA17</i>)	Intergenic	C>T	0.060	0.904	774 (2.15)	100 (2.36)	3 (3.22)	0.00014
rs7494167	14	(<i>DIO3OS</i>)	Intergenic	G>A	0.194	0.643	567 (2.24)	279 (2.10)	31 (1.90)	0.00015
rs2072280	19	<i>SBNO2</i>	Coding	G>A	0.319	0.842	404 (2.25)	383 (2.13)	88 (2.07)	0.00015
rs1010872	5	<i>SLC45A2</i>	Intron	C>A	0.226	0.622	526 (2.11)	300 (2.27)	47 (2.35)	0.00015
rs11159411	14	(<i>LOC401767</i>)	Intergenic	C>T	0.223	0.935	530 (2.12)	303 (2.25)	44 (2.41)	0.00015
rs994565	6	(<i>EDN1</i>)	Intergenic	C>T	0.457	0.648	255 (2.26)	442 (2.18)	180 (2.06)	0.00015
rs4689941	4	(<i>MSX1</i>)	Intergenic	C>A	0.327	0.794	395 (2.10)	389 (2.23)	92 (2.34)	0.00016
rs7787692	7	(<i>FZD1</i>)	Intergenic	C>A	0.124	0.429	670 (2.14)	196 (2.32)	11 (2.48)	0.00016
rs1531160	3	(<i>LOC728516</i>)	Intergenic	T>C	0.187	0.160	586 (2.12)	254 (2.29)	37 (2.32)	0.00016
rs1046279	6	<i>PI16</i>	3'UTR	T>C	0.489	0.799	231 (2.30)	434 (2.16)	211 (2.09)	0.00016
rs7694687	4	(<i>HTT</i>)	Intergenic	C>T	0.086	0.283	730 (2.21)	143 (2.05)	4 (1.45)	0.00017

Table S2. Continued

rs7865631	9	(<i>CYLC2</i>)	Intergenic	A>G	0.060	0.904	774 (2.21)	100 (1.97)	3 (2.09)	0.00017
rs7141155	14	(<i>SIPA1L1</i>)	Intron	G>A	0.190	0.630	577 (2.24)	266 (2.08)	34 (1.99)	0.00018
rs8042861	15	(<i>IQGAP1</i>)	Intron	T>G	0.142	0.455	642 (2.23)	219 (2.04)	15 (2.06)	0.00018
rs1956967	14	(<i>SFTPH</i>)	Intron	C>A	0.074	0.283	754 (2.22)	116 (1.95)	7 (2.18)	0.00018
rs1914748	2	(<i>FHL2</i>)	Intron	T>C	0.404	0.066	325 (2.27)	396 (2.16)	156 (2.04)	0.00019
rs11140441	9	(<i>SLC28A3</i>)	Intergenic	A>G	0.117	0.509	686 (2.21)	177 (2.12)	14 (1.55)	0.00020
rs6540844	1	(<i>LOC643454</i>)	Intergenic	T>C	0.461	0.100	243 (2.09)	460 (2.18)	174 (2.29)	0.00020
rs3924902	12	(<i>TMEM132C</i>)	Intergenic	T>C	0.318	0.704	406 (2.09)	385 (2.23)	86 (2.34)	0.00020
rs17436172	1	(<i>IGSF21</i>)	Intron	A>G	0.441	0.157	264 (2.26)	453 (2.17)	160 (2.06)	0.00020
rs12197082	6	(<i>FAM50B</i>)	Intergenic	G>A	0.103	0.393	703 (2.15)	167 (2.31)	7 (2.58)	0.00021
rs1566652	16	(<i>SLC6A2</i>)	Intron	G>T	0.334	0.408	395 (2.09)	379 (2.22)	103 (2.36)	0.00021
rs10858366	9	(<i>OLFM1</i>)	Intergenic	A>C	0.105	0.930	702 (2.21)	165 (2.04)	10 (2.00)	0.00021
rs1127065	7	(<i>CAMK2B</i>)	Coding	G>A	0.310	0.796	419 (2.10)	372 (2.24)	86 (2.33)	0.00022
rs12263637	10	(<i>ZWINT</i>)	Intergenic	A>G	0.137	0.194	648 (2.22)	217 (2.08)	12 (1.80)	0.00022
rs2358866	10	(<i>PLXDC2</i>)	Intron	G>A	0.432	0.078	270 (2.31)	456 (2.13)	151 (2.09)	0.00022
rs2884567	10	(<i>PLXDC2</i>)	Intron	G>A	0.432	0.078	270 (2.31)	456 (2.13)	151 (2.09)	0.00022
rs1698193	11	(<i>LOC283143</i>)	Intergenic	G>T	0.417	0.252	306 (2.08)	410 (2.23)	161 (2.25)	0.00022
rs1040303	14	(<i>TRDV2</i>)	Intergenic	G>A	0.154	0.215	623 (2.14)	238 (2.27)	16 (2.52)	0.00022
rs714795	14	(<i>TRDV2</i>)	Intergenic	G>A	0.154	0.215	623 (2.14)	238 (2.27)	16 (2.52)	0.00022
rs4629410	4	(<i>GRID2</i>)	Intron	A>G	0.071	0.221	755 (2.21)	120 (1.99)	2 (1.57)	0.00023
rs12565776	1	(<i>LAMC1</i>)	Intergenic	A>G	0.116	0.964	685 (2.22)	180 (2.06)	12 (1.81)	0.00023
rs6543594	2	(<i>GALNT14</i>)	Intron	C>A	0.376	0.004	361 (2.26)	372 (2.14)	144 (2.07)	0.00023
rs571877	17	(<i>C17orf76</i>)	Intergenic	T>C	0.493	0.402	232 (2.08)	426 (2.18)	219 (2.29)	0.00023
rs2449215	8	(<i>CSMD1</i>)	Intron	C>T	0.386	0.633	334 (2.25)	409 (2.16)	134 (2.05)	0.00023
rs11075997	16	(<i>FTO</i>)	Intron	C>T	0.161	0.770	618 (2.23)	235 (2.08)	24 (1.95)	0.00024
rs2120663	18	(<i>OSBPL1A</i>)	Intron	C>T	0.275	0.554	464 (2.12)	343 (2.23)	70 (2.34)	0.00024
rs1489259	1	(<i>LOC730175</i>)	Intergenic	A>G	0.168	0.261	603 (2.11)	254 (2.34)	20 (2.17)	0.00024
rs2072268	17	(<i>ARSG</i>)	Intergenic	T>C	0.326	0.764	400 (2.28)	381 (2.10)	95 (2.10)	0.00024
rs10911167	1	(<i>KRT18P28</i>)	Intergenic	T>C	0.124	0.865	672 (2.22)	192 (2.06)	13 (1.87)	0.00024
rs4518993	10	(<i>PLXDC2</i>)	Intron	G>A	0.477	0.328	233 (2.30)	452 (2.16)	192 (2.07)	0.00025
rs1338078	1	(<i>LOC643329</i>)	Intergenic	G>T	0.432	0.150	292 (2.06)	407 (2.23)	173 (2.25)	0.00025
rs471728	11	(<i>LOC729717</i>)	Intergenic	G>A	0.475	0.914	241 (2.27)	439 (2.20)	197 (2.03)	0.00025
rs2322732	11	(<i>PRR10</i>)	Intergenic	G>A	0.121	0.983	677 (2.22)	187 (2.07)	13 (1.87)	0.00025
rs7299020	12	(<i>LRIG3</i>)	Intergenic	A>G	0.278	0.627	454 (2.26)	358 (2.12)	65 (1.96)	0.00026
rs11177048	12	(<i>LOC341333</i>)	Intron	G>A	0.081	0.212	738 (2.15)	136 (2.36)	3 (2.43)	0.00026
rs780827	10	(<i>CUBN</i>)	Intron	C>T	0.417	0.754	300 (2.12)	422 (2.17)	155 (2.34)	0.00026
rs11011827	10	(<i>PLXDC2</i>)	Intron	C>A	0.481	0.260	228 (2.31)	454 (2.16)	194 (2.07)	0.00026
rs8002916	13	(<i>POSTN</i>)	Intergenic	A>G	0.429	0.000	328 (2.28)	340 (2.13)	204 (2.10)	0.00026
rs480836	1	(<i>DAB1</i>)	Intron	C>T	0.273	0.434	468 (2.23)	339 (2.16)	70 (1.94)	0.00027
rs9307398	4	(<i>ARSJ</i>)	Intergenic	A>G	0.456	0.449	265 (2.29)	424 (2.15)	188 (2.08)	0.00027
rs9972327	15	(<i>IDH2</i>)	Intron	C>A	0.245	0.318	495 (2.24)	335 (2.13)	47 (1.95)	0.00027
rs11625806	14	(<i>LOC729042</i>)	Intergenic	G>A	0.079	0.506	743 (2.21)	130 (2.03)	4 (1.66)	0.00027
rs2350064	4	(<i>EPHA5</i>)	Intergenic	C>T	0.161	0.836	616 (2.22)	239 (2.09)	22 (1.96)	0.00027
rs17288177	3	(<i>GRM7</i>)	Intergenic	T>C	0.358	0.602	357 (2.25)	410 (2.16)	109 (2.03)	0.00027

Association analyses were adjusted by age, sex, and smoking status as covariates.

*P-value of Hardy-Weinberg equilibrium (HWE).

**Genotype represents number of subjects (mean of log[Total IgE (IU/ml)]).

†M/M, M/m, and m/m indicate homozygote for common allele, heterozygote, and homozygote for rare allele, respectively.

Chr, chromosome; MAF, minor allele frequency.

Table S3. Top 100 SNPs associated with specific IgE for D.p. in the GWAS

SNP ID	Chr	(Nearby) gene	Location	Variation	HWE*	MAF		OR (95% CI)	P-value
						Positive	Negative		
rs1425902	8	(OPRK1)	Intergenic	A>G	0.069	0.373	0.262	2.14 (1.56-2.94)	1.44E-06
rs17744026	11	(OR6X1)	Intergenic	T>G	0.866	0.035	0.095	0.25 (0.13-0.48)	2.66E-06
rs1843834	2	(DOCK10)	Intergenic	G>A	0.858	0.286	0.183	2.14 (1.54-2.96)	4.38E-06
rs10197382	2	(DOCK10)	Intergenic	C>T	0.063	0.332	0.229	2.09 (1.52-2.89)	5.72E-06
rs12952334	17	MYH2	Intron	G>A	0.478	0.182	0.111	2.38 (1.61-3.51)	1.40E-05
rs7105655	11	(FGF4)	Intergenic	C>A	0.340	0.159	0.255	0.47 (0.33-0.67)	1.61E-05
rs11219307	11	(OR6M1)	Intergenic	G>T	0.550	0.113	0.203	0.43 (0.29-0.65)	1.90E-05
rs2155362	11	(OR6M1)	Intergenic	G>A	0.550	0.113	0.203	0.43 (0.29-0.65)	1.90E-05
rs1566869	12	(ANKRD33)	Intergenic	A>G	0.315	0.428	0.314	1.83 (1.38-2.43)	2.12E-05
rs10791006	11	BARX2	Intron	T>C	0.192	0.575	0.474	1.78 (1.35-2.33)	2.45E-05
rs10142119	14	(LOC730217)	Intergenic	G>A	0.527	0.344	0.471	0.55 (0.42-0.73)	2.86E-05
rs2155633	11	(CADM1)	Intergenic	G>A	0.094	0.535	0.427	1.76 (1.35-2.31)	2.91E-05
rs2846895	11	(CADM1)	Intergenic	G>A	0.518	0.477	0.372	1.80 (1.36-2.37)	2.93E-05
rs2273623	14	(PPM1A)	Intergenic	A>G	0.614	0.145	0.076	2.59 (1.66-4.02)	2.98E-05
rs12273131	11	(PMP22CD)	Intergenic	C>T	0.708	0.118	0.210	0.45 (0.30-0.67)	3.14E-05
rs1565073	2	DOCK10	Intron	G>T	0.007	0.298	0.208	2.05 (1.46-2.88)	3.31E-05
rs2108606	17	MYH4	Intron	T>C	0.346	0.176	0.109	2.29 (1.55-3.39)	3.37E-05
rs2613468	11	(CADM1)	Intergenic	G>A	0.024	0.532	0.424	1.74 (1.34-2.28)	3.39E-05
rs7900357	10	FRMD4A	Intron	G>A	0.859	0.225	0.327	0.53 (0.38-0.72)	3.58E-05
rs6563898	16	CDH13	Intron	G>A	0.211	0.384	0.480	0.55 (0.41-0.74)	3.60E-05
rs1785016	11	(LOC283143)	Intergenic	G>A	0.256	0.434	0.343	1.79 (1.35-2.36)	3.64E-05
rs12283877	11	(PMP22CD)	Intergenic	C>T	0.694	0.116	0.201	0.45 (0.30-0.67)	3.88E-05
rs987651	5	STK32A	Intron	C>T	0.186	0.572	0.460	1.79 (1.35-2.38)	4.14E-05
rs446924	1	ABCB10	Intron	C>T	0.013	0.055	0.126	0.37 (0.22-0.62)	4.32E-05
rs4813955	20	(hCG_2045828)	Intergenic	A>C	0.196	0.341	0.253	1.85 (1.38-2.50)	4.44E-05
rs1698157	11	(LOC283143)	Intergenic	C>A	0.028	0.549	0.447	1.73 (1.32-2.26)	4.49E-05
rs6717059	2	DOCK10	Intron	T>C	0.011	0.269	0.184	2.08 (1.46-2.95)	4.54E-05
rs3799852	6	FIG4	Intron	G>A	0.923	0.358	0.252	1.85 (1.37-2.49)	4.55E-05
rs12024772	1	HIVEP3	Intron	G>A	0.960	0.410	0.514	0.56 (0.42-0.74)	4.55E-05
rs2155631	11	(LOC283143)	Intergenic	T>G	0.115	0.561	0.461	1.73 (1.32-2.27)	4.89E-05
rs4776381	15	(LBXCOR1)	Intergenic	G>A	0.120	0.179	0.089	2.23 (1.52-3.28)	4.92E-05
rs2993120	1	HIVEP3	Intron	A>C	0.880	0.419	0.520	0.56 (0.42-0.75)	5.17E-05
rs3736388	3	(KALRN)	Intergenic	T>C	0.181	0.237	0.374	0.55 (0.41-0.74)	5.87E-05
rs3810385	19	(DYRK1B)	Intergenic	A>G	0.217	0.023	0.078	0.24 (0.11-0.53)	6.00E-05
rs2195003	12	(MED13L)	Intergenic	A>G	0.218	0.283	0.402	0.55 (0.41-0.74)	6.11E-05
rs11210537	1	HIVEP3	Intron	A>G	0.910	0.422	0.520	0.57 (0.43-0.75)	6.39E-05
rs12630469	3	(CNTN3)	Intergenic	A>G	0.978	0.266	0.389	0.55 (0.40-0.74)	6.41E-05
rs7905868	10	(FAM107B)	Intergenic	T>C	0.255	0.338	0.240	1.83 (1.36-2.46)	6.64E-05
rs2247470	16	NECAB2	Intron	A>G	0.690	0.079	0.144	0.40 (0.25-0.65)	6.73E-05
rs3810384	19	(DYRK1B)	Intergenic	G>A	0.227	0.023	0.077	0.24 (0.11-0.54)	6.86E-05
rs13170855	5	STK32A	Intron	T>C	0.601	0.529	0.418	1.74 (1.32-2.30)	7.10E-05
rs1887104	14	PPM1A	Intron	A>C	0.922	0.116	0.059	2.71 (1.67-4.42)	7.34E-05
rs2423011	20	(RASSF2)	Intergenic	A>G	0.319	0.413	0.515	0.58 (0.45-0.77)	7.38E-05
rs1549881	5	STK32A	Intron	G>A	0.411	0.500	0.384	1.74 (1.32-2.30)	7.60E-05
rs763727	16	CDH13	Intron	A>G	0.792	0.564	0.474	1.75 (1.32-2.32)	7.61E-05
rs11263535	11	(FGF19)	Intergenic	A>G	0.668	0.214	0.131	2.07 (1.44-2.97)	8.04E-05
rs12283302	11	SLC6A5	Intron	T>G	0.959	0.237	0.319	0.54 (0.39-0.74)	8.15E-05
rs10773370	12	(LOC121296)	Intergenic	C>T	0.577	0.590	0.468	1.74 (1.31-2.30)	8.26E-05
rs7515178	1	RBBP5	Intron	G>A	0.494	0.104	0.054	2.85 (1.70-4.80)	8.51E-05
rs9502039	6	(C6orf145)	Intergenic	C>T	0.165	0.373	0.272	1.76 (1.32-2.33)	8.71E-05
rs1939915	11	(PMP22CD)	Intergenic	T>C	0.650	0.171	0.265	0.51 (0.36-0.72)	8.80E-05
rs2155363	11	(PMP22CD)	Intergenic	T>C	0.650	0.171	0.265	0.51 (0.36-0.72)	8.80E-05
rs609704	12	(KRT71)	Intergenic	T>C	0.805	0.552	0.453	1.73 (1.31-2.28)	8.96E-05
rs4294640	12	PTPRR	Intron	G>T	0.824	0.439	0.315	1.75 (1.32-2.32)	9.00E-05
rs7194029	16	CDH13	Intron	C>T	0.500	0.549	0.459	1.74 (1.31-2.32)	9.19E-05
rs9828201	3	(LOC728135)	Intergenic	T>C	0.790	0.286	0.424	0.56 (0.42-0.76)	9.86E-05

Table S3. Continued

rs7863292	9	(<i>LOC644723</i>)	Intergenic	G>A	0.707	0.017	0.071	0.23 (0.10-0.56)	0.00010
rs1017078	19	(<i>DYRK1B</i>)	Intergenic	G>A	0.188	0.026	0.079	0.26 (0.12-0.57)	0.00011
rs2957086	8	(<i>DLGAP2</i>)	Intron	A>G	0.648	0.338	0.456	0.57 (0.43-0.77)	0.00011
rs1398748	3	(<i>CD96</i>)	Intron	T>C	0.249	0.416	0.521	0.59 (0.45-0.78)	0.00011
rs1275054	11	(<i>ZNF202</i>)	Intergenic	G>A	0.391	0.038	0.090	0.32 (0.17-0.61)	0.00011
rs1029709	19	(<i>ZFP28</i>)	Intergenic	C>T	0.173	0.185	0.277	0.52 (0.37-0.73)	0.00011
rs7629942	3	(<i>CNTN3</i>)	Intergenic	G>A	0.766	0.272	0.391	0.56 (0.41-0.76)	0.00012
rs4420916	3	(<i>CNTN3</i>)	Intergenic	G>A	0.766	0.272	0.391	0.56 (0.41-0.76)	0.00012
rs6795835	3	(<i>LOC728135</i>)	Intergenic	C>T	0.766	0.272	0.391	0.56 (0.41-0.76)	0.00012
rs16854967	1	(<i>DISC1</i>)	Intron	A>G	0.403	0.038	0.118	0.33 (0.18-0.62)	0.00012
rs3098360	10	(<i>ZWINT</i>)	Intergenic	T>C	0.326	0.098	0.046	2.87 (1.69-4.86)	0.00012
rs2244811	17	(<i>NXN</i>)	Intergenic	A>G	0.198	0.153	0.082	2.39 (1.54-3.72)	0.00012
rs2286992	7	(<i>CPVL</i>)	Intron	C>T	0.186	0.257	0.379	0.56 (0.41-0.76)	0.00012
rs4980684	11	(<i>FGF19</i>)	Intergenic	C>T	0.994	0.257	0.169	1.92 (1.38-2.68)	0.00012
rs1456988	14	(<i>LOC730217</i>)	Intergenic	T>G	0.692	0.572	0.463	1.70 (1.29-2.24)	0.00012
rs6593920	1	(<i>CNTN2</i>)	Intron	T>G	0.543	0.147	0.088	2.30 (1.51-3.51)	0.00012
rs1035569	16	(<i>CDH13</i>)	Intron	G>A	0.496	0.546	0.458	1.73 (1.30-2.29)	0.00013
rs723919	16	(<i>CDH13</i>)	Intron	A>G	0.628	0.566	0.477	1.72 (1.30-2.29)	0.00013
rs1343817	1	(<i>CD53</i>)	Intron	A>C	0.933	0.556	0.438	1.70 (1.29-2.23)	0.00013
rs2255522	8	(<i>KHDRBS3</i>)	Intergenic	C>T	0.355	0.419	0.516	1.70 (1.29-2.24)	0.00013
rs4881399	10	(<i>DIP2C</i>)	Intergenic	G>A	0.841	0.049	0.119	0.36 (0.20-0.64)	0.00013
rs4812609	20	(<i>PTPRT</i>)	Intron	G>A	0.737	0.419	0.524	1.71 (1.29-2.26)	0.00013
rs4750112	10	(<i>ECHDC3</i>)	Intergenic	G>A	0.211	0.220	0.307	0.54 (0.39-0.75)	0.00014
rs10498606	14	(<i>LOC283585</i>)	Intergenic	C>A	0.598	0.546	0.421	1.69 (1.28-2.22)	0.00014
rs6731785	2	(<i>CUL3</i>)	Intergenic	G>A	0.712	0.263	0.183	1.89 (1.36-2.62)	0.00014
rs6948622	7	(<i>LOC728466</i>)	Intergenic	G>A	0.493	0.301	0.194	1.83 (1.34-2.51)	0.00015
rs17663304	10	(<i>BUB3</i>)	Intergenic	T>C	0.299	0.040	0.099	0.32 (0.17-0.61)	0.00015
rs10902907	10	(<i>BUB3</i>)	Intergenic	C>T	0.299	0.040	0.099	0.32 (0.17-0.61)	0.00015
rs4813479	20	(<i>CD93</i>)	Intergenic	C>T	0.684	0.292	0.180	1.86 (1.35-2.57)	0.00015
rs10741848	11	(<i>SLC6A5</i>)	Intron	C>T	0.653	0.240	0.327	0.56 (0.41-0.76)	0.00015
rs2173318	3	(<i>CD96</i>)	Intron	T>C	0.220	0.416	0.520	0.60 (0.46-0.78)	0.00015
rs12929441	16	(<i>LOC643358</i>)	Intergenic	T>C	0.805	0.191	0.108	2.10 (1.43-3.09)	0.00016
rs784932	9	(<i>RGS3</i>)	Intergenic	G>A	0.861	0.176	0.254	0.52 (0.36-0.74)	0.00016
rs11203582	8	(<i>SGCZ</i>)	Intron	G>A	0.698	0.286	0.383	0.57 (0.42-0.77)	0.00016
rs2053273	2	(<i>RPRM</i>)	Intergenic	G>A	0.554	0.390	0.512	0.59 (0.45-0.78)	0.00016
rs2815124	6	(<i>KCNK5</i>)	Intron	C>T	0.631	0.098	0.050	2.83 (1.66-4.83)	0.00016
rs12670165	7	(<i>CPVL</i>)	Intron	C>T	0.226	0.257	0.377	0.57 (0.42-0.77)	0.00016
rs1569907	20	(<i>C20orf77</i>)	Intron	A>G	0.254	0.188	0.106	2.14 (1.45-3.16)	0.00016
rs2268251	21	(<i>ITSN1</i>)	Intron	G>T	0.283	0.289	0.400	0.58 (0.43-0.77)	0.00017
rs4677048	3	(<i>PROK2</i>)	Intergenic	A>G	0.818	0.237	0.145	1.96 (1.38-2.79)	0.00018
rs12452392	17	(<i>MYH2</i>)	Intergenic	G>A	0.450	0.153	0.099	2.21 (1.47-3.32)	0.00018
rs2041127	17	(<i>MYH3</i>)	Intergenic	G>A	0.450	0.153	0.099	2.21 (1.47-3.32)	0.00018
rs7185024	16	(<i>CDH11</i>)	Intergenic	A>C	0.696	0.052	0.102	0.37 (0.21-0.65)	0.00018
rs995361	17	(<i>MYH2</i>)	Intergenic	T>C	0.581	0.208	0.142	1.99 (1.39-2.84)	0.00018

Association analyses were adjusted by age, sex, and smoking status as covariates.

*P-value of Hardy-Weinberg equilibrium (HWE).

Positive-specific IgE (D.p.) includes asthmatics showing the semi-quantitatively expressed concentration as class 3-6 ($n = 173$); negative as class 0 ($n = 548$).

Chr, chromosome; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval.

Table S4. Top 100 SNPs associated with specific IgE for D.f. in the GWAS

SNP ID	Chr	(Nearby) gene	Location	Variation	HWE*	MAF		OR (95% CI)	P-value
						Positive	Negative		
rs10142119	14	(LOC730217)	Intergenic	G>A	0.394	0.336	0.484	0.51 (0.39-0.66)	1.86E-07
rs1456988	14	(LOC730217)	Intergenic	T>G	0.475	0.580	0.450	1.86 (1.44-2.40)	1.11E-06
rs12590389	14	(LOC730217)	Intergenic	T>C	0.969	0.491	0.368	1.85 (1.43-2.40)	2.47E-06
rs6563898	16	CDH13	Intron	G>A	0.147	0.384	0.477	0.55 (0.42-0.72)	8.19E-06
rs132470	22	ARHGAP8	Intron	T>C	0.364	0.283	0.179	1.93 (1.44-2.61)	1.13E-05
rs4776381	15	(LBXCOR1)	Intergenic	G>A	0.140	0.168	0.081	2.26 (1.56-3.28)	1.54E-05
rs13274039	8	(LOC729478)	Intergenic	G>A	0.316	0.525	0.415	1.72 (1.34-2.21)	1.56E-05
rs2383513	1	(PTGS2)	Intergenic	T>C	0.744	0.550	0.442	1.75 (1.35-2.27)	1.73E-05
rs4761051	12	(TMEM132C)	Intergenic	G>A	0.756	0.475	0.378	1.73 (1.34-2.25)	2.68E-05
rs2273623	14	(PPM1A)	Intergenic	A>G	0.545	0.141	0.075	2.41 (1.59-3.65)	3.16E-05
rs12952334	17	MYH2	Intron	G>A	0.693	0.180	0.108	2.15 (1.49-3.09)	3.29E-05
rs10489397	1	(PTGS2)	Intergenic	C>A	0.885	0.541	0.434	1.72 (1.32-2.22)	3.31E-05
rs7434739	4	(PET112L)	Intergenic	G>A	0.705	0.252	0.348	0.56 (0.42-0.74)	3.54E-05
rs2852474	12	(KRT7)	Intergenic	G>A	0.861	0.093	0.190	0.46 (0.31-0.68)	3.80E-05
rs9810161	3	(LOC728135)	Intergenic	G>A	0.838	0.227	0.333	0.55 (0.41-0.74)	3.94E-05
rs1218762	16	OR2C1	Coding	G>A	0.422	0.123	0.185	0.48 (0.33-0.69)	4.95E-05
rs2305744	19	HPN	Intron	A>G	0.328	0.318	0.207	1.84 (1.37-2.47)	4.97E-05
rs7188903	16	(OR2C1)	Intergenic	G>A	0.562	0.123	0.186	0.48 (0.33-0.69)	5.01E-05
rs10926189	1	(GNG4)	Intergenic	C>T	0.234	0.216	0.137	2.00 (1.43-2.81)	5.20E-05
rs9310315	3	(LOC728135)	Intergenic	T>C	0.847	0.239	0.341	0.56 (0.42-0.75)	5.26E-05
rs12024772	1	HIVEP3	Intron	G>A	0.980	0.425	0.519	0.59 (0.46-0.77)	5.73E-05
rs6720449	2	(ARPC2)	Intergenic	G>A	0.821	0.218	0.304	0.55 (0.41-0.75)	5.73E-05
rs6052862	20	(RASSF2)	Intergenic	T>G	0.497	0.288	0.177	1.83 (1.36-2.46)	5.91E-05
rs2993120	1	HIVEP3	Intron	A>C	0.999	0.434	0.526	0.59 (0.46-0.77)	6.00E-05
rs2322732	11	(PRR10)	Intergenic	G>A	0.292	0.077	0.141	0.44 (0.29-0.67)	6.07E-05
rs2108606	17	MYH4	Intron	T>C	0.563	0.175	0.106	2.10 (1.46-3.02)	6.18E-05
rs941304	3	(CNTN3)	Intergenic	A>G	0.148	0.236	0.335	0.57 (0.43-0.76)	6.24E-05
rs7194029	16	CDH13	Intron	C>T	0.207	0.548	0.465	1.70 (1.30-2.21)	6.25E-05
rs2333166	4	(LOC391718)	Intergenic	T>C	0.719	0.061	0.128	0.41 (0.25-0.65)	6.37E-05
rs6496137	15	AKAP13	Intron	A>C	0.063	0.284	0.392	0.59 (0.45-0.77)	6.39E-05
rs4677485	3	(LOC728135)	Intergenic	T>C	0.645	0.218	0.321	0.56 (0.42-0.75)	6.86E-05
rs7196196	16	(OR2C1)	Intergenic	A>C	0.662	0.216	0.296	0.56 (0.41-0.75)	6.92E-05
rs11210537	1	HIVEP3	Intron	A>G	0.970	0.436	0.526	0.60 (0.46-0.77)	6.99E-05
rs763727	16	CDH13	Intron	G>A	0.423	0.439	0.520	1.68 (1.30-2.19)	7.15E-05
rs4140432	1	(PTGS2)	Intergenic	T>G	0.967	0.523	0.422	1.68 (1.29-2.17)	7.28E-05
rs4674267	2	(IL8RA)	Intergenic	C>T	0.615	0.234	0.314	0.56 (0.42-0.75)	7.29E-05
rs1035569	16	CDH13	Intron	G>A	0.206	0.545	0.464	1.69 (1.30-2.20)	7.34E-05
rs2286992	7	CPVL	Intron	C>T	0.394	0.268	0.376	0.58 (0.44-0.76)	7.39E-05
rs6571636	14	(C14orf147)	Intergenic	G>A	0.505	0.255	0.345	0.58 (0.43-0.76)	8.05E-05
rs1424169	16	CDH13	Intron	G>A	0.629	0.098	0.039	2.71 (1.65-4.47)	8.42E-05
rs10498606	14	(LOC283585)	Intergenic	C>A	0.504	0.543	0.414	1.64 (1.28-2.11)	8.56E-05
rs1930149	10	PCDH15	Intron	A>G	0.394	0.416	0.334	1.67 (1.29-2.17)	8.75E-05
rs1021891	17	(ACCN1)	Intergenic	G>A	0.011	0.282	0.191	1.86 (1.36-2.54)	8.94E-05
rs12670165	7	CPVL	Intron	C>T	0.426	0.268	0.375	0.58 (0.44-0.77)	8.94E-05
rs1566869	12	(ANKRD33)	Intergenic	A>G	0.615	0.409	0.308	1.68 (1.29-2.19)	9.05E-05
rs10261639	7	(EIF3IP1)	Intergenic	T>G	0.735	0.234	0.142	1.90 (1.38-2.63)	9.26E-05
rs1843834	2	(DOCK10)	Intergenic	G>A	0.478	0.266	0.181	1.81 (1.34-2.43)	9.31E-05
rs2820406	6	(ARID1B)	Intergenic	G>A	0.623	0.559	0.465	0.61 (0.47-0.78)	9.53E-05
rs17028407	4	(PET112L)	Intergenic	C>A	0.111	0.098	0.162	0.48 (0.32-0.71)	9.59E-05
rs2497708	10	ABLIM1	Intron	C>A	0.607	0.395	0.301	1.68 (1.29-2.18)	0.00010
rs8039009	15	LRRC28	Intron	C>T	0.861	0.127	0.070	2.30 (1.51-3.50)	0.00010
rs723919	16	CDH13	Intron	G>A	0.337	0.434	0.516	1.66 (1.28-2.16)	0.00011
rs7774434	6	(HLA-DQB1)	Intergenic	T>C	0.039	0.391	0.483	0.59 (0.45-0.78)	0.00011
rs6563897	16	CDH13	Intron	G>A	0.196	0.414	0.493	0.60 (0.46-0.78)	0.00011
rs628527	4	(LOC729265)	Intergenic	A>G	0.738	0.534	0.414	1.63 (1.27-2.09)	0.00011
rs338544	15	AKAP13	Intron	T>C	0.068	0.275	0.379	0.60 (0.46-0.78)	0.00011

Table S4. Continued

rs6717059	2	<i>DOCK10</i>	Intron	T>C	0.048	0.259	0.182	1.87 (1.36-2.58)	0.00012
rs12630469	3	<i>(CNTN3)</i>	Intergenic	A>G	0.642	0.280	0.392	0.59 (0.45-0.78)	0.00012
rs4590517	9	<i>C9orf25</i>	Intron	C>T	0.363	0.175	0.098	2.02 (1.41-2.89)	0.00013
rs3736388	3	<i>(KALRN)</i>	Intergenic	T>C	0.113	0.255	0.375	0.60 (0.46-0.78)	0.00013
rs40222	16	<i>ZNF597</i>	Intron	T>C	0.696	0.125	0.182	0.51 (0.36-0.73)	0.00014
rs1350279	14	<i>(LOC730217)</i>	Intergenic	T>C	0.160	0.325	0.420	0.61 (0.47-0.79)	0.00014
rs338540	15	<i>AKAP13</i>	Intron	T>C	0.077	0.277	0.379	0.60 (0.46-0.79)	0.00015
rs6713364	2	<i>(LOC284998)</i>	Intergenic	T>C	0.648	0.405	0.309	1.67 (1.28-2.17)	0.00015
rs10197382	2	<i>(DOCK10)</i>	Intergenic	C>T	0.137	0.314	0.229	1.76 (1.31-2.35)	0.00015
rs9604967	22	<i>psiTPTE22</i>	Intron	C>T	0.136	0.086	0.137	0.45 (0.29-0.70)	0.00015
rs9490054	6	<i>(C6orf170)</i>	Intergenic	G>T	0.782	0.166	0.106	2.02 (1.40-2.91)	0.00015
rs10410631	19	<i>ZNF550</i>	Coding	C>T	0.898	0.373	0.464	0.61 (0.48-0.79)	0.00015
rs4812609	20	<i>PTPRT</i>	Intron	A>G	0.680	0.559	0.462	1.61 (1.25-2.07)	0.00016
rs2156208	18	<i>(LOC390861)</i>	Intergenic	T>C	0.942	0.102	0.051	2.51 (1.56-4.04)	0.00016
rs446924	1	<i>ABCB10</i>	Intron	C>T	0.028	0.064	0.124	0.44 (0.28-0.70)	0.00016
rs2489382	10	<i>C10orf141</i>	Intron	G>A	0.855	0.423	0.524	0.62 (0.48-0.80)	0.00016
rs13099862	3	<i>(CNTN3)</i>	Intergenic	T>C	0.273	0.220	0.311	0.59 (0.44-0.78)	0.00017
rs9828201	3	<i>(LOC728135)</i>	Intergenic	T>C	0.898	0.305	0.429	0.61 (0.46-0.79)	0.00017
rs2244811	17	<i>(NXN)</i>	Intergenic	A>G	0.224	0.141	0.080	2.22 (1.46-3.37)	0.00017
rs12458013	18	<i>(SMAD2)</i>	Intergenic	A>G	0.907	0.100	0.173	0.49 (0.33-0.72)	0.00017
rs8035496	15	<i>AKAP13</i>	Intron	T>C	0.070	0.280	0.381	0.61 (0.47-0.79)	0.00018
rs11209099	1	<i>(SERBP1)</i>	Intergenic	G>A	0.007	0.270	0.354	0.61 (0.47-0.79)	0.00018
rs2428684	17	<i>ACSF2</i>	Intron	C>A	0.660	0.368	0.268	1.67 (1.28-2.19)	0.00018
rs6585041	10	<i>(ADRA2A)</i>	Intergenic	T>C	0.810	0.386	0.478	0.62 (0.48-0.80)	0.00018
rs40633	16	<i>(ZNF434)</i>	Intergenic	A>G	0.997	0.118	0.174	0.50 (0.34-0.73)	0.00018
rs12046472	1	<i>(PLD5)</i>	Intergenic	G>A	0.266	0.130	0.061	2.25 (1.47-3.44)	0.00018
rs11203582	8	<i>SGCZ</i>	Intron	G>A	0.657	0.293	0.384	0.60 (0.46-0.79)	0.00018
rs17609347	16	<i>(LOC645478)</i>	Intergenic	C>A	0.669	0.126	0.068	2.26 (1.48-3.44)	0.00018
rs1925227	6	<i>GRIK2</i>	Intron	C>T	0.269	0.105	0.182	0.51 (0.35-0.74)	0.00018
rs6790277	3	<i>(CNTN3)</i>	Intergenic	G>T	0.256	0.220	0.310	0.59 (0.44-0.78)	0.00019
rs956706	1	<i>SMYD3</i>	Intron	C>T	0.597	0.281	0.192	1.73 (1.30-2.32)	0.00019
rs4420916	3	<i>(CNTN3)</i>	Intergenic	G>A	0.497	0.284	0.393	0.60 (0.46-0.79)	0.00019
rs6795835	3	<i>(LOC728135)</i>	Intergenic	C>T	0.497	0.284	0.393	0.60 (0.46-0.79)	0.00019
rs7629942	3	<i>(CNTN3)</i>	Intergenic	G>A	0.497	0.284	0.393	0.60 (0.46-0.79)	0.00019
rs12469757	2	<i>(DOCK10)</i>	Intergenic	G>A	0.125	0.298	0.220	1.76 (1.30-2.37)	0.00019
rs987651	5	<i>STK32A</i>	Intron	C>T	0.302	0.552	0.464	1.62 (1.25-2.10)	0.00019
rs17065935	8	<i>CSMD1</i>	Intron	A>G	0.073	0.136	0.228	0.54 (0.39-0.76)	0.00019
rs7144501	14	<i>(LOC730217)</i>	Intergenic	G>A	0.838	0.239	0.328	0.59 (0.44-0.78)	0.00020
rs10014970	4	<i>(ANTXR2)</i>	Intergenic	G>A	0.426	0.339	0.248	1.70 (1.28-2.25)	0.00020
rs7905868	10	<i>(FAM107B)</i>	Intergenic	T>C	0.260	0.323	0.233	1.68 (1.28-2.21)	0.00021
rs7793513	7	<i>(RAPGEF5)</i>	Intergenic	T>C	0.888	0.534	0.433	1.60 (1.25-2.06)	0.00021
rs10204762	2	<i>(LOC284998)</i>	Intergenic	G>A	0.544	0.220	0.148	1.85 (1.34-2.56)	0.00021
rs2383477	1	<i>C1orf27</i>	Intron	C>T	0.128	0.032	0.088	0.34 (0.18-0.64)	0.00021
rs1565073	2	<i>DOCK10</i>	Intron	G>T	0.037	0.284	0.206	1.79 (1.31-2.44)	0.00022

Association analyses were adjusted by age, sex, and smoking status as covariates.

*P-value of Hardy-Weinberg equilibrium (HWE).

Positive-specific IgE (D.f.) includes asthmatics showing the semi-quantitatively expressed concentration as class 3-6 (n = 220); negative as class 0 (n = 473).

Chr, chromosome; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval.

Table S5. Pathway analysis for significantly associated SNPs ($P < 0.001$), only in the gene regions from the results of GWAS, on total IgE in asthmatics

Pathway Name	Impact Factor	#Genes in Pathway	#Input Genes in Pathway	#Pathway Genes on Chip	Corrected gamma P -value
Phosphatidylinositol signaling system	44.198	76	2	76	2.89E-18
Adherens junction	33.006	78	2	75	1.57E-13
Focal adhesion	8.87	203	5	199	0.001
Glioma	8.406	65	3	65	0.002
MAPK signaling pathway	7.516	272	1	266	0.005
Type II diabetes mellitus	7.436	45	1	43	0.005
Insulin signaling pathway	6.6	138	1	137	0.01
Melanoma	6.37	71	1	71	0.01
Long-term depression	6.066	75	2	73	0.02
Long-term potentiation	5.919	73	2	72	0.02
Natural killer cell mediated cytotoxicity	5.853	135	2	130	0.02
Regulation of actin cytoskeleton	5.839	217	3	207	0.02
Calcium signaling pathway	5.48	182	3	176	0.03
Prostate cancer	5.353	90	1	89	0.03
ErbB signaling pathway	4.825	87	2	86	0.05
Jak-STAT signaling pathway	4.587	155	1	153	0.06
Maturity onset diabetes of the young	4.448	24	1	23	0.06
Cardiac muscle contraction	4.332	87	2	73	0.07
Axon guidance	4.209	129	1	128	0.08
GnRH signaling pathway	3.751	103	2	100	0.11
ECM-receptor interaction	3.197	84	1	82	0.17
Vibrio cholerae infection	3.058	62	1	59	0.19
Type I diabetes mellitus	2.863	44	1	40	0.22
Pathways in cancer	2.543	330	2	328	0.28
Olfactory transduction	2.505	382	1	374	0.29
Neuroactive ligand-receptor interaction	2.415	256	2	250	0.31
Chronic myeloid leukemia	2.319	75	1	74	0.33
Colorectal cancer	2.305	84	1	83	0.33
Cytokine-cytokine receptor interaction	2.258	263	2	259	0.34
Small cell lung cancer	2.198	86	1	85	0.36
TGF-beta signaling pathway	2.198	87	1	85	0.36
Melanogenesis	2.053	102	1	102	0.39
Leukocyte transendothelial migration	1.987	119	1	115	0.41
Cell adhesion molecules (CAMs)	1.898	134	1	129	0.43
Wnt signaling pathway	1.756	152	1	150	0.48
Alzheimer's disease	1.719	178	1	159	0.49

Associated pathway with total IgE in asthmatics is estimated using Pathway Express (<http://vortex.cs.wayne.edu/projects.htm>).

Table S6. Statistical power for the analysis in each subgroup of study subjects

Analysis group	Total IgE	Specific IgE (D.p.)	Specific IgE (D.f.)
Sample size	n = 877	Positive (n = 173) vs. Negative (n = 548)	Positive (n = 220) vs. Negative (n = 473)
Statistical power	44.5%	92.0%	62.0%

Statistical power of linear regression analysis for total IgE is obtained from two-tailed *t*-test.

Statistical power of case-control analysis for specific IgE is obtained using the CaTS power calculator (Skol et al., 2006).

Table S7. Genetic associations from this GWAS compared to the previously identified SNPs from other GWASs

Gene	SNP ID	Chr	This study		Previous GWASs
			MAF	P-value	P-value
<i>FCER1A</i>	rs2511211	1	0.000**	N/A	9.28×10 ⁻⁸ [ref. 5]
<i>FCER1A</i>	rs10489854	1	0.460	0.51	0.029 [ref. 5]
<i>FCER1A</i>	rs2494262	1	-	N/A	1.67×10 ⁻⁴ [ref. 5]
<i>FCER1A</i>	rs2427837*	1	0.035	0.62	3.23×10 ⁻⁹ [ref. 5]
<i>FCER1A</i>	rs12565775*	1	0.425	0.36	0.025 [ref. 5]
<i>FCER1A</i>	rs2427824	1	0.160	0.46	0.025 [ref. 5]
<i>FCER1A</i>	rs2427827*	1	0.190	0.29	2.45×10 ⁻⁴ [ref. 5]
<i>FCER1A</i>	rs2251746	1	0.035	0.62	6.07×10 ⁻¹⁰ [ref. 5]; 2.11×10 ⁻¹² [ref. 7]; 0.0072 [ref. 8]
<i>FCER1A</i>	rs2252226	1	0.190	0.29	6.60×10 ⁻⁵ [ref. 6]
<i>FCER1A</i>	rs2494264	1	-	N/A	1.37×10 ⁻⁹ [ref. 7]; 0.235 [ref. 8]
<i>FCER1A</i>	rs2252226	1	0.190	0.29	0.0060 [ref. 8]
<i>RAD50</i>	rs2706347*	5	0.204	0.16	2.26×10 ⁻⁴ [ref. 5]; 0.0064 [ref. 8]
<i>RAD50</i>	rs3798135*	5	0.205	0.17	2.32×10 ⁻⁴ [ref. 5]; 8.38×10 ⁻⁵ [ref. 8]
<i>RAD50</i>	rs2040704*	5	0.205	0.17	2.47×10 ⁻⁴ [ref. 5]; 0.0007 [ref. 8]
<i>RAD50</i>	rs7737470*	5	0.205	0.17	2.27×10 ⁻⁴ [ref. 5]; 0.021 [ref. 8]
<i>RAD50</i>	rs2240032	5	0.205	0.17	4.01×10 ⁻⁴ [ref. 5]
<i>IL13</i>	rs20541	5	0.312	0.34	1.00×10 ⁻⁶ [ref. 6]; 3.55×10 ⁻⁸ [ref. 7] ; 0.025 [ref. 8]
<i>HLA-DRB1</i>	rs9271300	6	-	N/A	8.30×10 ⁻¹⁵ [ref. 6]
<i>STAT6</i>	rs12368672	12	-	N/A	2.03×10 ⁻⁶ [ref. 5]; 0.0022 [ref. 8]
<i>STAT6</i>	rs167769	12	0.259	0.82	8.50×10 ⁻⁷ [ref. 6]; 5.18×10 ⁻⁶ [ref. 7]; 2.48×10 ⁻⁵ [ref. 8]
<i>STAT6</i>	rs1059513	12	0.067	0.077	2.87×10 ⁻⁸ [ref. 7]
<i>IL4R/IL21R</i>	rs1859308	16	0.288	0.59	8.20×10 ⁻⁶ [ref. 6]; 0.22 [ref. 8]

*Imputed SNP based on nearby SNPs with absolute LD ($|D'| = 1$ and $r^2 = 1$).

**MAF of Asians from dbSNP of the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/snp>).

N/A, not available due to no nearby SNPs with tight LD ($r^2 > 0.8$) or monomorphic allele.

Chr, chromosome; MAF, minor allele frequency; LD, linkage disequilibrium.

Table S8. SNPs of other potential genes (but not well-known IgE-influencing genes) associated with total IgE in asthmatics ($P < 0.01$)

SNP ID	Chr	Gene	Location	AA change	Variation	MAF	HWE*	Genotype**			P-value†	P-value††
								M/M	M/m	m/m		
rs1006393	7	NPSR1	Flanking_5'UTR		T>C	0.298	0.052	444 (2.21)	343 (2.13)	90 (2.21)	0.37	0.59
rs376825	7	NPSR1	Flanking_5'UTR		A>C	0.297	0.043	445 (2.21)	341 (2.13)	90 (2.21)	0.40	0.64
rs1458550	7	NPSR1	Flanking_5'UTR		G>A	0.152	0.336	634 (2.17)	219 (2.20)	24 (2.17)	0.98	0.96
rs1023556	7	NPSR1	Flanking_5'UTR		C>T	0.454	0.579	257 (2.19)	443 (2.17)	177 (2.18)	0.71	0.69
rs2530545	7	NPSR1	Flanking_5'UTR		C>T	0.177	0.086	601 (2.21)	241 (2.08)	35 (2.40)	0.54	0.91
rs887020	7	NPSR1	5'UTR		G>A	0.225	0.386	522 (2.19)	315 (2.19)	40 (1.99)	0.40	0.51
rs2530548	7	NPSR1	Intron		A>G	0.136	0.415	657 (2.21)	200 (2.08)	19 (2.11)	0.03	0.008
rs2530552	7	NPSR1	Intron		A>G	0.136	0.436	657 (2.21)	201 (2.08)	19 (2.11)	0.02	0.007
rs11761197	7	NPSR1	Intron		A>G	0.117	0.995	684 (2.16)	181 (2.25)	12 (2.09)	0.11	0.05
rs1379928	7	NPSR1	Intron		T>C	0.205	0.326	550 (2.19)	295 (2.15)	32 (2.26)	0.85	1.00
rs411323	7	NPSR1	Intron		C>T	0.198	0.358	560 (2.16)	287 (2.22)	30 (2.19)	0.33	0.25
rs425990	7	NPSR1	Intron		T>C	0.251	0.991	487 (2.19)	327 (2.17)	55 (2.11)	0.64	0.54
rs2530561	7	NPSR1	Intron		C>T	0.088	0.456	727 (2.20)	144 (2.07)	5 (2.45)	0.12	0.02
rs2609224	7	NPSR1	Intron		T>G	0.202	0.749	554 (2.18)	284 (2.17)	34 (2.24)	0.66	0.77
rs2609220	7	NPSR1	Intron		G>A	0.196	0.710	565 (2.18)	280 (2.17)	32 (2.26)	0.60	0.68
rs2530571	7	NPSR1	Intron		G>A	0.237	0.264	515 (2.19)	304 (2.19)	55 (2.11)	0.84	0.73
rs10486653	7	NPSR1	Intron		C>T	0.049	0.937	793 (2.19)	82 (2.11)	2 (1.62)	0.17	0.19
rs1458536	7	NPSR1	Intron		G>A	0.080	0.787	742 (2.19)	130 (2.09)	5 (2.45)	0.27	0.09
rs2609215	7	NPSR1	Intron		A>G	0.080	0.787	742 (2.19)	130 (2.09)	5 (2.45)	0.27	0.09
rs10255979	7	NPSR1	Intron		C>T	0.450	0.315	270 (2.13)	415 (2.22)	183 (2.15)	0.48	0.45
rs2531840	7	NPSR1	Intron		G>A	0.129	0.182	670 (2.20)	188 (2.10)	19 (2.11)	0.09	0.03
rs2531841	7	NPSR1	Intron		T>C	0.245	0.532	502 (2.19)	317 (2.18)	56 (2.10)	0.78	0.73
rs10274146	7	NPSR1	Intron		A>G	0.049	0.937	793 (2.19)	82 (2.11)	2 (1.62)	0.17	0.19
rs1419837	7	NPSR1	Flanking_3'UTR		C>T	0.116	0.964	685 (2.16)	180 (2.25)	12 (2.09)	0.12	0.05
rs1436849	12	IRAK3	Flanking_5'UTR	I147V	T>C	0.226	0.710	523 (2.23)	311 (2.14)	43 (1.93)	0.004	0.01
rs2701653	12	IRAK3	Flanking_5'UTR		C>T	0.420	0.763	293 (2.09)	431 (2.22)	152 (2.24)	0.02	0.02
rs1732877	12	IRAK3	Intron		C>T	0.452	0.434	269 (2.19)	423 (2.22)	185 (2.08)	0.13	0.27
rs1152888	12	IRAK3	Coding		G>A	0.404	0.644	308 (2.10)	429 (2.20)	140 (2.28)	0.003	0.007
rs1821777	12	IRAK3	Intron		C>T	0.142	0.643	644 (2.20)	217 (2.14)	16 (1.94)	0.05	0.03
rs1623665	12	IRAK3	Intron		T>G	0.450	0.303	273 (2.18)	419 (2.23)	185 (2.08)	0.26	0.44
rs17826057	12	IRAK3	Intron		G>A	0.052	0.804	788 (2.18)	87 (2.17)	2 (1.98)	0.77	0.67
rs1152912	12	IRAK3	Intron		G>A	0.355	0.958	365 (2.19)	401 (2.16)	111 (2.20)	0.65	0.64
rs1152918	12	IRAK3	Intron		C>T	0.405	0.604	307 (2.14)	430 (2.22)	140 (2.13)	0.83	0.64
rs3782348	12	IRAK3	Intron		C>T	0.405	0.664	307 (2.14)	429 (2.22)	141 (2.13)	0.88	0.69
rs12307857	12	IRAK3	Flanking_3'UTR		T>C	0.270	0.613	470 (2.18)	340 (2.18)	67 (2.18)	0.47	0.40

*P-value of Hardy-Weinberg equilibrium (HWE).

**Genotype represents number of subjects (mean of Log[Total IgE (IU/ml)]).

M/M, M/m, and m/m indicate homozygote for common allele, heterozygote, and homozygote for rare allele, respectively.

†Association analyses were adjusted by age, sex, and smoking status as covariates.

††Association analyses were adjusted by age, sex, smoking status, and atopy as covariates

Chr, chromosome; AA, amino acid; MAF, minor allele frequency.

Table S9. Genes based clustering from GRAIL

Gene	GRAIL P-value	Selected similar genes (Rank in parentheses)													
KALRN	0.011	SIP1L1(14)	VAV2(150)	ARHGDB16(163)	RIN3(455)	PLXDC2(610)	CRIM1(806)	LSAMP(879)	A2BP1(1178)	BRD3(1210)	PIP3-E(1498)	IGF1R(1714)	UNC13C(1729)	NOL10(1816)	
CNTN5	0.011	PLXDC2(82)	LSAMP(99)	CRIM1(270)	KALRN(323)	A2BP1(443)	UNC13C(580)	CACNA1C(862)	CSMD1(1037)	SVOP(1545)	BRD3(1783)	NOL10(1923)			
INPP4B	0.015	PIB5PA(15)	IHPK2(71)	IGF1R(332)	PTPRN2(356)	CSMD1(381)	PIP3-E(496)	PLXDC2(753)	SYNPO2(791)	CCDC85A(1572)	BRD3(1936)				
SLC6A2	0.016	ADRA1A(76)	SLC45A2(248)	CACNA1C(355)	PLXDC2(423)	A2BP1(450)	SEC24D(682)	OPRM1(966)	LSAMP(999)	KALRN(1031)	BRD3(1099)	CSMD1(1141)	CRIM1(1343)	IGF1R(1373)	
		SVOP(1542)	IHPK2(1770)	DGKH(1845)											
UNC13C	0.018	KALRN(109)	SVOP(142)	SIP1L1(163)	PLXDC2(504)	CRIM1(574)	LSAMP(829)	CNTN5(894)	CACNA1C(1112)	A2BP1(1119)	FAM62B(1211)	PTPRN2(1533)			
LSAMP	0.021	PLXDC2(28)	CSMD1(89)	KALRN(166)	SVOP(492)	BRD3(717)	CRIM1(825)	NOL10(1091)	A2BP1(1266)	CNTN5(1730)					
HPSE2	0.025	CSMD1(14)	PLXDC2(206)	C1orf21(260)	ZEB2(304)	SYNPO2(401)	LSAMP(1192)	VPS13B(1194)	BRD3(1310)	SLC45A2(1519)	IGF1R(1822)	NOL10(1847)			
ADRA1A	0.027	CACNA1C(22)	SLC6A2(98)	IGF1R(305)	LAMA1(459)	OPRM1(554)	PLXDC2(1223)	KALRN(1395)	IHPK2(1669)	LSAMP(1831)	SYNPO2(1945)				
OPRM1	0.030	ADRA1A(119)	SLC6A2(222)	IGF1R(295)	CACNA1C(447)	PLXDC2(643)	LSAMP(664)	KALRN(773)	A2BP1(1210)	BRD3(1233)	CRIM1(1690)	SLC45A2(1876)	CSMD1(1956)		
VAV2	0.037	KALRN(19)	ARHGDB16(56)	IGF1R(508)	PIP3-E(754)	IGGAP1(832)	RIN3(1169)	CRIM1(1344)	BRD3(1353)	LAMA1(1652)					
ARHGDB16	0.058	KALRN(44)	VAV2(75)	SYNPO2(261)	CSMD1(658)	IGF1R(785)	IGGAP1(1053)	PIP3-E(1090)	PLXDC2(1508)	BRD3(1635)	CRIM1(1780)				
VPS13B	0.059	ZEB2(18)	SLC45A2(181)	CSMD1(381)	NOL10(410)	PLXDC2(742)	HPSE2(1315)	TMEM180(1692)	C1orf21(1776)	A2BP1(1841)	SVOP(1878)				
IHPK2	0.084	PIB5PA(16)	INPP4B(47)	PLXDC2(818)	NOL10(887)	BRD3(1022)	SVOP(1212)	SHISA5(1273)	NUDCD3(1580)	IGF1R(1816)	GTDC1(1969)				
IGGAP1	0.088	KALRN(138)	ARHGDB16(195)	VAV2(290)	SYNPO2(349)	TLN1(817)	SIP1L1(1099)	CACNA1C(1297)	IGF1R(1466)	LRRC16A(1472)	BRD3(1524)	PIP3-E(1591)			
COL7A1	0.098	LAMA1(103)	SLC45A2(115)	BRD3(551)	CSMD1(607)	ZEB2(741)	NOL10(672)	VPS13B(1094)	PLXDC2(1168)	CACNA1C(1833)					
GALNT14	0.120	IGF1R(37)	CSMD1(340)	SHISA5(544)	SYNPO2(563)	PLXDC2(877)	C1orf21(1572)	CRIM1(1678)	IHPK2(1720)	TMEM180(1989)					
ADAM12	0.123	IGF1R(108)	PLXDC2(351)	LAMA1(498)	CRIM1(634)	BRD3(771)	CSMD1(820)	KALRN(1398)	SYNPO2(1473)	CACNA1C(1521)	NOL10(1684)				
ZEB2	0.123	VPS13B(125)	CSMD1(178)	CRIM1(242)	PLXDC2(655)	BRD3(744)	NOL10(1481)	SLC45A2(1537)							
PIB5PA	0.142	INPP4B(9)	IHPK2(512)	NOL10(705)	PLXDC2(907)	GTDC1(956)	SVOP(1069)	BRD3(1143)	NUDCD3(1343)	FAM62B(1887)					
RIN3	0.191	KALRN(27)	VAV2(425)	PIP3-E(735)	NOL10(762)	PLXDC2(821)	ARHGDB16(1057)	SIP1L1(1229)	PIB5PA(1662)						
NPCL1	0.198	OSBPL1A(162)	SLC6A2(488)	IGF1R(505)	IHPK2(724)	PLXDC2(1286)	CACNA1C(1421)	ADRA1A(1491)	SLC45A2(1566)	KALRN(1882)	FAM62B(1955)				
ATP6V1C2	0.200	SYT17(90)	CACNA1C(102)	BRD3(495)	FAM62B(1116)	LAMA1(1164)	PLXDC2(1458)	NOL10(1802)	CRIM1(1958)						
SIP1L1	0.226	KALRN(14)	NOL10(576)	PLXDC2(804)	BRD3(873)	SVOP(1300)	UNC13C(1497)								
CSMD1	0.233	PLXDC2(112)	SYNPO2(223)	NOL10(287)	A2BP1(665)	LSAMP(1266)	BRD3(1284)	TMEM180(1948)							
PTPRN2	0.238	IGF1R(126)	PLXDC2(340)	KALRN(894)	PIB5PA(913)	INPP4B(936)	SVOP(1242)	CACNA1C(1543)	SYT17(1615)	BRD3(1845)					
SLC45A2	0.260	PLXDC2(294)	CSMD1(356)	NOL10(385)	BRD3(471)	SLC6A2(591)	A2BP1(1536)	VPS13B(1908)							
CRIM1	0.305	PLXDC2(43)	IGF1R(421)	BRD3(951)	TMEM180(1256)	KALRN(1262)	NOL10(1401)	SHISA5(1977)							
PLA2G3	0.313	CACNA1C(409)	PLXDC2(518)	CRIM1(595)	KALRN(818)	SHISA5(1051)	IGF1R(1224)	BRD3(1486)	PIB5PA(1716)	IHPK2(1757)	PLSCR1(1981)				
A2BP1	0.329	PLXDC2(141)	CSMD1(355)	NOL10(632)	CACNA1C(1234)	DGKH(1285)	BRD3(1373)	KALRN(1543)	TMEM180(1789)						
TLN1	0.340	LAMA1(199)	SYNPO2(384)	KALRN(481)	LRRC16A(810)	BRD3(1090)	PIB5PA(1301)	SIP1L1(1365)	NOL10(1773)	IGGAP1(1922)	VAV2(1936)	CACNA1C(1950)			
SYT17	0.355	ATP6V1C2(104)	FAM62B(220)	KALRN(722)	CRIM1(1051)	CACNA1C(1100)	BRD3(1124)	PLXDC2(1534)	PTPRN2(1584)	PIB5PA(1713)					
OSMR	0.361	IGF1R(160)	NLRP2(767)	PLXDC2(835)	CRIM1(1177)	LAMA1(1448)	BRD3(1518)	CPM(1599)	CACNA1C(1601)	CSMD1(1676)	ADRA1A(1996)				
IGF1R	0.368	GALNT14(212)	CRIM1(253)	PTPRN2(982)	BRD3(1205)	PLXDC2(1236)	ADRA1A(1357)	KALRN(1420)	IHPK2(1697)	CACNA1C(1817)					
PI16	0.445	NOL10(239)	TMEM180(279)	PLXDC2(860)	BRD3(1057)	SVOP(1134)	IGF1R(1624)	CRIM1(1835)							
LAMA1	0.452	PLXDC2(241)	CRIM1(448)	BRD3(887)	ADRA1A(1046)	KALRN(1414)	CACNA1C(1608)	TLN1(1842)							
PIP3-E	0.457	CCDC85A(192)	KALRN(650)	PLXDC2(781)	C1orf21(1113)	NOL10(1271)	BRD3(1871)	SYNPO2(1922)	CSMD1(1955)						
SYNPO2	0.463	CSMD1(93)	C1orf21(509)	BRD3(1175)	NOL10(1201)	PLXDC2(1204)	SHISA5(1944)								
SBNO2	0.490	PLXDC2(239)	BRD3(524)	CCDC85A(648)	CRIM1(1208)	NOL10(1345)	TMEM180(1425)								
FAM62B	0.519	NOL10(479)	SVOP(585)	PLXDC2(706)	TMEM180(923)	NUDCD3(1081)	GTDC1(1085)	CCDC85A(1251)	C1orf21(1550)	BRD3(1820)					
CACNA1C	0.542	ADRA1A(238)	A2BP1(708)	ATP6V1C2(1045)	PLXDC2(1362)	IGF1R(1410)	KALRN(1524)	SLC6A2(1691)	BRD3(1825)						
PLSCR1	0.546	CACNA1C(618)	PIB5PA(905)	BRD3(1022)	IHPK2(1034)	IGF1R(1052)	CRIM1(1138)	SHISA5(1147)	PLXDC2(1159)	LAMA1(1947)	SYNPO2(1967)				
SEC24D	0.557	SLC6A2(335)	NOL10(742)	CCDC85A(966)	SVOP(1241)	PLXDC2(1460)	OSBPL1A(1480)	SHISA5(1485)	BRD3(1567)	NUDCD3(1570)					
NLRP2	0.599	PLXDC2(666)	BRD3(698)	KALRN(960)	NOL10(1006)	CSMD1(1016)	SHISA5(1173)	A2BP1(1603)	IGF1R(1666)	OSBPL1A(1930)	CRIM1(1972)				
NUDCD3	0.616	NOL10(638)	TMEM180(686)	SVOP(801)	GTDC1(934)	PLXDC2(1188)	CCDC85A(1276)	C1orf21(1534)							
PLXDC2	0.622	NOL10(540)	SVOP(611)	GTDC1(927)	TMEM180(931)	NUDCD3(1172)	CRIM1(1198)	CCDC85A(1466)	C1orf21(1585)	FAM62B(1695)	BRD3(1896)				
SVOP	0.623	NOL10(627)	PLXDC2(754)	TMEM180(764)	GTDC1(840)	NUDCD3(883)	C1orf21(1120)	CCDC85A(1171)	FAM62B(1347)						
DGKH	0.633	PLXDC2(395)	NOL10(529)	GTDC1(834)	BRD3(1148)	A2BP1(1293)	SVOP(1356)	NUDCD3(1453)	CCDC85A(1561)	PIB5PA(1610)	TMEM180(1795)				
OSBPL1A	0.636	SVOP(290)	NOL10(501)	PLXDC2(728)	NUDCD3(933)	BRD3(1062)	PIB5PA(1336)	GTDC1(1490)							
NCAPG2	0.660	TMEM180(297)	NUDCD3(384)	NOL10(513)	BRD3(978)	PLXDC2(1547)									
GTDC1	0.678	SVOP(647)	NOL10(696)	NUDCD3(757)	PLXDC2(771)	CCDC85A(1239)	PIB5PA(1499)	C1orf21(1505)	BRD3(1550)	FAM62B(1621)	TMEM180(1819)				
CCDC85A	0.705	C1orf21(360)	TMEM180(749)	SVOP(1474)	NUDCD3(1627)	PLXDC2(1760)	NOL10(1902)								
LRRC16A	0.728	NOL10(522)	PLXDC2(576)	NUDCD3(1127)	SVOP(1145)	GTDC1(1285)	CCDC85A(1354)	BRD3(1810)	C1orf21(1827)	SYNPO2(1912)					
C1orf21	0.751	TMEM180(502)	CCDC85A(595)	SVOP(1658)	NOL10(1941)										
SUFU	0.753	BRD3(313)	NOL10(821)	PLXDC2(845)	SYNPO2(1143)	CRIM1(1203)	PIB5PA(1811)								
CPM	0.792	PLXDC2(244)	PIB5PA(857)	NOL10(1038)	BRD3(1373)	LAMA1(1677)									
GPR179	0.808	hCG_18290(482)	TMEM180(553)	NOL10(801)	SVOP(1278)										
BRD3	0.816	NOL10(150)	PLXDC2(1389)	NUDCD3(1850)	GTDC1(1952)										
SHISA5	0.819	TMEM180(583)	PLXDC2(895)	NOL10(1161)	NUDCD3(1183)	BRD3(1186)	C1orf21(1648)								
TMEM180	0.829	C1orf21(583)	NOL10(1123)	CCDC85A(1240)	SVOP(1386)	NUDCD3(1408)	PLXDC2(1864)								
hCG_18290	0.831	hCG_18290(5)	NOL10(656)	NUDCD3(707)	TMEM180(968)	SVOP(1214)	PLXDC2(1595)	GPR179(1688)	CCDC85A(1877)						
DNAJA1	0.849	BRD3(445)	NOL10(728)	PLXDC2(1234)	SHISA5(1685)	TMEM180(1831)	CRIM1(1881)								
NOL10	0.882	SVOP(1106)	TMEM180(1149)	PLXDC2(1194)	BRD3(1257)	NUDCD3(1292)	GTDC1(1581)	FAM62B(1897)							
ZNF71	0.926	C1orf21(976)	NOL10(1286)	TMEM180(1427)	PLXDC2(1734)										

Ten clusters of related genes with GRAIL *P*-values < 0.05 are generated out of the 63 gene clusters using the GRAIL package.