

Letter to the Editor

Replication of genome-wide association study loci for allergic rhinitis and house dust mite sensitization in an Asian population of ethnic Chinese in Singapore

To the Editor:

We have read with interest the meta-analysis for allergic rhinitis (AR) and grass sensitization reported by Ramasamy et al.¹ in the November issue of the *Journal*. In this study we aim to replicate the association of the reported single nucleotide polymorphisms (SNPs) to AR and house dust mite (HDM) sensitization in our ethnic Chinese population recruited in Singapore. We performed a case-control study with 3743 subjects who were well defined for sensitization to HDMs and a medical history of allergic phenotypes. Sensitization to HDM species (*Dermatophagoides pteronyssinus* and *Blomia tropicalis*) was used instead of grass because HDMs are the major allergens in Southeast Asia and Singapore in particular (see Table E1 and the Methods section in this article's Online Repository at www.jacionline.org). We have used 2 AR definitions (1) based on self-reported history of AR to be consistent with the definition used in the meta-analysis and (2) based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines considering 2 criteria: (1) a positive HDM reaction and (2) 2 or more major AR symptoms (see the Methods section in this article's Online Repository).

Thirteen SNPs were successfully genotyped by using the Sequenom iPLEX assay (Sequenom, San Diego, Calif) in 3743 subjects. All SNPs considered for statistical analysis were in Hardy-Weinberg equilibrium (see Table E2 in this article's Online Repository at www.jacionline.org). For the AR phenotype (as defined based on the meta-analysis), only 1 SNP, rs2155219, was found to be significantly associated ($P = 4.3 \times 10^{-3}$; odds ratio [OR], 1.15) when using 2200 patients with AR and 1510 control subjects without AR (Table I). This SNP is located at locus 11q13.5, approximately 40 kb downstream of *C11orf30*

(chromosome 11, open reading frame 30) and approximately 70 kb downstream of *LRRC32* (leucine-rich repeat region containing 32). We then performed an association test on 1859 patients with AR (as defined by ARIA guidelines) and 662 nonatopic control subjects without AR. The same SNP, rs2155219, was associated with AR at a significant P value of 8.89×10^{-5} and an OR of 1.30, whereas another SNP, rs7617456, was close to association at a P value of .05 and an OR of 1.163 (Table II). When considering atopy, it could be observed that the OR for rs2155219 increased from 1.15 to 1.30 and the P value improved, suggesting that considering atopy could be crucial in defining patients with AR and control subjects.

We then performed association of the SNPs with sensitization for the HDMs *D pteronyssinus* and *B tropicalis*. The association with other common allergens could not be estimated because sensitization to these allergens, such as grass, cat, pollen, and cockroach, in our population has not been performed. A total of 3 SNPs, the AR-associated SNP rs2155219, along with rs7617456 (30 kb upstream of a transmembrane protein *TMEM108* gene) and rs1898671 (on the thymic stromal lymphopoietin gene [*TSLP*]) were associated ($P < .05$) with both HDMs (Table I). These 3 SNPs were also associated when tested for any HDM sensitization (see Table E3 in this article's Online Repository at www.jacionline.org). To our knowledge, there has been no report of association of *TMEM108* with allergy in other publications. However, *TSLP* has been reported to be vital in influencing the allergic response, and its SNPs are associated with atopic dermatitis.² Interestingly, the SNP rs1898671 occurs at a much lower frequency in the HapMap Asian populations (CHB and JPT) compared with the white population (CEU; for population definitions, see Table E4 in this article's Online Repository at www.jacionline.org). Hence fine mapping of this locus might potentially reveal more informative markers relevant for the Asian population that associate with disease predisposition.

In addition, there are 2 SNPs, rs6673480 and rs17513503, which were reported by Ramasamy et al.¹ These SNPs are extremely rare

TABLE I. Replication of GWAS signals, as reported by Ramasamy et al.,¹ for AR and HDM sensitization

SNP	Risk allele	AR symptoms				Sensitization to HDM allergens			
						<i>Dermatophagoides pteronyssinus</i> or <i>Blomia tropicalis</i>			
		F_A	F_U	P_{trend}	OR (95% CI)	F_A	F_U	P_{trend}	OR (95% CI)
rs2155219	T	0.59	0.554	.0043	1.15 (1.04-1.27)	0.5861	0.5336	.00051	1.24 (1.10-1.40)
rs6554809	C	0.89	0.88	.1456	1.11 (0.962-1.33)	0.893	0.8801	.1753	1.14 (0.94-1.41)
rs1325195	A	0.4851	0.502	.1595	0.93 (0.85-1.03)	0.4922	0.4925	.9852	0.99 (0.89-1.13)
rs6898653	G	0.156	0.1457	.2333	1.08 (0.95-1.24)	0.1522	0.1511	.9182	1.01 (0.85-1.19)
rs216518	A	0.0546	0.0608	.2607	0.89 (0.73-1.09)	0.05783	0.05547	.7382	1.05 (0.81-1.35)
rs7789045	T	0.4116	0.4244	.2811	0.95 (0.86-1.04)	0.4179	0.416	.902	1.01 (0.89-1.14)
rs7617456	G	0.77	0.78	.2984	0.94 (0.84-1.05)	0.7827	0.7553	.030	1.17 (1.02-1.33)
rs1898671	C	0.968	0.972	.3584	0.88 (0.67-1.16)	0.97192	0.96114	.037	1.40 (1.01-1.92)
rs6673480	T	0.0014	0.0007	.3642	2.07 (0.42-10.24)	0.001166	0.00075	.674	1.56 (0.19-12.7)
rs4724100	T	0.276	0.2681	.4617	1.04 (0.94-1.16)	0.2735	0.2704	.8179	1.02 (0.89-1.16)
rs17513503	G	0.0002	0.0003	.7911	0.69 (0.04-11.02)	0.000166	0.00075	.2446	0.22 (0.01-3.57)
rs887864	G	0.2028	0.198	.6192	1.03 (0.92-1.16)	0.2021	0.1917	.3906	1.07 (0.92-1.24)
rs2069772	C	0.132	0.1304	.8473	1.01 (0.88-1.16)	0.1341	0.1198	.1616	1.14 (0.94-1.37)

P_{trend} values were calculated by using the Cochran-Armitage trend test with PLINK software.

P_{trend} values of less than .05 are shown in boldface. AR symptoms are as defined by self-reported AR history of symptoms.

F_A, Risk allele frequency in affected subjects (cases); F_U, risk allele frequency in the unaffected subjects (controls).

TABLE II. Association for AR, as defined by ARIA guidelines

SNP	Risk allele	F_A	F_U	P _{trend}	OR (95% CI)
rs2155219	T	0.5963	0.5333	8.89E-05	1.30 (1.14-1.47)
rs7617456	G	0.7777	0.7512	.05	1.163 (1.0-1.35)
rs6554809	C	0.90	0.88	.1154	1.18 (0.962-1.43)
rs1898671	C	0.971	0.962	.125	1.3 (0.93-1.85)
rs2069772	C	0.1348	0.1227	.2691	1.11 (0.92-1.35)
rs887864	G	0.2047	0.1903	.2694	1.1 (0.93-1.29)
rs1325195	A	0.4891	0.4985	.5639	0.96 (0.85-1.09)
rs6673480	T	0.001354	0.000759	.5915	1.79 (0.21-15.3)
rs17513503	G	0.00027	0.00075	.4468	0.36 (0.02-5.712)
rs4724100	T	0.2754	0.2696	.6895	1.03 (0.89-1.19)
rs6898653	G	0.1557	0.1514	.7099	1.03 (0.87-1.23)
rs7789045	T	0.4123	0.4146	.8815	0.99 (0.87-1.13)
rs216518	A	0.05534	0.05488	.9499	1.01 (0.76-1.33)

P_{trend} values were calculated by using the Cochran-Armitage trend test with PLINK software.

P_{trend} values of less than .05 are shown in boldface. AR symptoms are as defined by self-reported AR history of symptoms.

F_A, Risk allele frequency in affected subjects (cases); F_U, risk allele frequency in the unaffected subjects (controls).

in the Singapore Chinese population, with minor allele frequencies of 0.001 and 0.00025, respectively. Similar prevalence was reported in the HapMap Asian population of Han Chinese (CHB) and Japanese (JPT) populations (see Table E4). The minor allele frequency of these SNPs in the white population is low but not rare (minor allele frequency > 0.05), but for the Asian populations, these SNPs are not good tag SNPs because of their very low allelic frequencies.

Finally, we also estimated the association *P* values of these SNPs on comparing control subjects with sensitized subjects with and without AR (see Tables E5 and E6 in this article's Online Repository at www.jacionline.org). Interestingly, only rs2155219 was significant in both comparisons. Two other SNPs, rs1325195 and rs6554809, were associated nominally on comparing atopic patients with AR versus atopic patients without AR; however, these results need to be validated by other studies.

In conclusion, we performed the first independent replication of the genome-wide association study (GWAS) meta-analysis for AR and sensitization. We identified 3 SNPs (rs2155219, rs7617456, and rs1898671) associated with HDM sensitization (both *D pteronyssinus* and *B tropicalis*), of which 1 SNP, rs2155219, was also significantly associated with AR. This agrees with the findings of the meta-analysis in which only rs2155219 reached genome-wide significance for both grass sensitization and AR and provides an interesting observation in which a single SNP is associated with AR, as well as 2 diverse allergens, grass and HDM. The SNP rs2155219 is present at an intergenic noncoding locus, 11q13.5, where there have been previous reports of associations of SNPs with other allergic diseases. A recent GWAS identified a different SNP, rs7130588, at this intergenic locus to be associated with asthma in an Australian cohort,³ whereas an earlier GWAS in 2009 identified rs7927894 to be associated with atopic dermatitis.⁴ Fig E1 (in this article's Online Repository at www.jacionline.org) represents 35 kb of the intergenic locus 11q13.5, which describes this reported GWAS's SNPs. Hence this SNP at *C11orf30-LRRC32*, which is now associated in the white and Chinese populations for both allergen sensitizations, is unlikely to be spurious and hence warrants further functional characterization.

Common GWAS noncoding variations have recently been shown to contribute directly to clinical phenotypes, such as the risk for chronic obstructive pulmonary disease.⁵ We thus probed this locus for possible noncoding effects by using the UCSC

genome browser. Enhancers and the promoter-associated histone marks H3K27ac and H3K4me1 were identified at this locus (see Fig E1), which identifies active enhancers and predicts a cell's developmental state.⁶ Interestingly, histone modifications, particularly H3K27ac, are involved in controlling gene expression.⁷ The locus surrounding rs2155219, which is conserved in the mammalian genome, also contains DNase hypersensitivity sites, which are developed during lineage commitment, which coincides with regions for DNA demethylation, histone acetylation, and thereby control of the transcriptional activity of genes.⁸ A recent article in the *Journal* provides evidence that epigenetic regulation in T cells affects asthma development and suggests that this could provide an avenue for pharmacologic intervention.⁹ Taken together, this 11q13.5 locus containing rs2155219 identified in the meta-analysis in Europeans and now replicated in Singapore Chinese would probably be involved in disease pathogenesis through epigenetic mechanisms that have not been widely explored in the context of allergic phenotypes.

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METHODS

Ethics statement

This study was performed with the approval of the Institutional Review Board of National University of Singapore (references NUS07-023 and NUS10-343) and is in compliance with the Declaration of Helsinki. DNA samples used in this study were collected from ethnic Chinese participants according to standard protocols of informed consent. The consent obtained was “written consent” collected by using a participant information sheet, which had information about the study.

Samples

Study subjects were recruited at the National University of Singapore through multiple volunteer recruitment drives, as described previously.^{E1}

Disease definition

Atopy is defined by a positive skin prick test (SPT) response to one of the common inhalant allergens (particularly dust mite allergens in our study).^{E1-E3} In the current study atopy was defined by a positive SPT response to one of the common inhalant allergen (particularly dust mite allergens).

AR is diagnosed based on the presence of atopic status and typical AR symptoms, as defined by the ARIA guidelines^{E2,E3}: 2 or more AR symptoms (nasal congestion, rhinorrhea, nasal itching, and sneezing) persisting for 4 or more days a week during the past year.

Healthy nonallergic control subjects were identified as subjects with negative results to both the HDM species tested with SPTs and also no history of any of the allergic conditions of asthma, atopic dermatitis, and AR.

Genotyping

Genotyping of the case-control samples for SNPs selected for replication from the meta-analysis was performed by using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry for the determination of allele-specific primer extension products by using Sequenom's MassARRAY system and iPLEX technology. The design of oligonucleotides was carried out according to the Sequenom guidelines and performed by using MassARRAY Assay Design software. Of the total of 18 SNPs from the meta-analysis attempted for SNP assay design, 3 SNPs (rs7775228, rs631208, and rs3860069) failed the assay design. Thus multiplex PCR amplification of amplicons containing the 15 SNPs of interest was performed by using Qiagen HotStart Taq Polymerase (Qiagen, Hilden, Germany) with 5 ng of genomic DNA. Primer extension reactions were carried out according to the manufacturer's instructions for iPLEX chemistry. Assay data were analyzed by using the Sequenom TYPHER software. Clustering of genotype calls was evaluated to determine that the clustering was sufficient for inclusion in the statistical analysis. Two SNPs (rs1044573 and rs6586513) failed quality control for

genotyping success and hence were not included for further statistical analysis. All the other SNPs were in Hardy-Weinberg equilibrium and hence were taken forward for further statistical analysis.

Statistical analyses

All statistical analyses for the SNPs genotyped in this study were performed with R program version 2.10.1 and PLINK version 1.07 software. All *P* values from this replication analysis were reported without correction for multiple testing.

Fisher test for comparing atopic control subjects without rhinitis and atopic patients with rhinitis

We wanted to study the effect of SNP genotypes on different subgroups considering their atopy and AR status. In this regard we defined 3 groups in the cohort, namely (1) atopic and having AR symptomatology (atopic rhinitis), (2) no atopy and no AR symptomatology (no atopy with rhinitis), and (3) negative results for both atopy and AR symptomatology. Pairwise comparisons were then made by using the Fisher exact test to determine whether there were any associations between the genotypes and the above-defined groups. The 2 pairwise comparisons made were (1) atopic rhinitis versus no atopy and no rhinitis and (2) atopy and no rhinitis versus no atopy and no rhinitis. *P* values of less than .05 were considered significant. All comparisons were done with the R statistical language, processed with the Accelrys Pipeline Pilot (Accelrys, San Diego, Calif).

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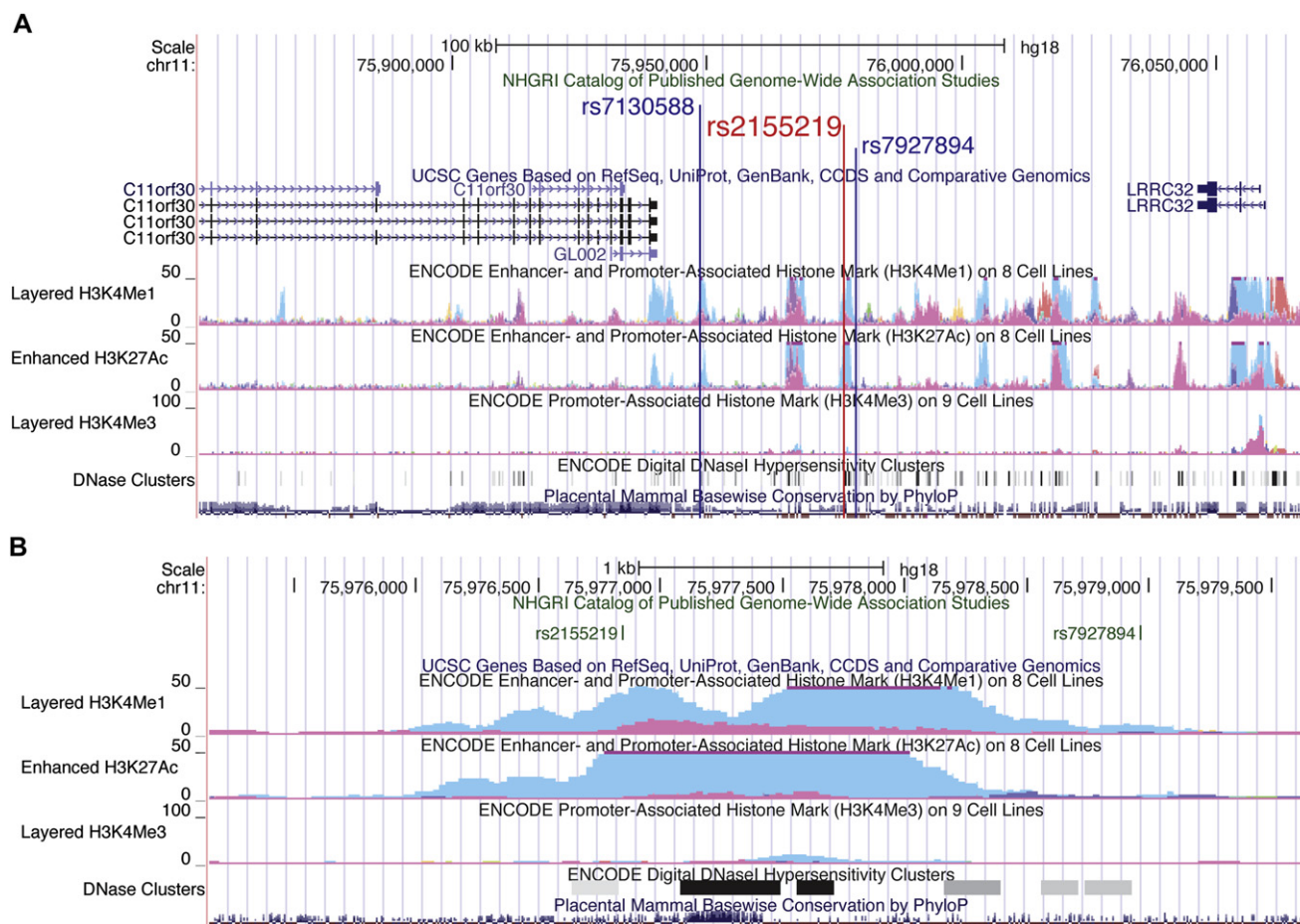


FIG E1. Regulatory activity in the chromosome 11q13.5 locus containing the GWAS-reported SNPs rs2155219,^{E4} rs7130588,^{E5} and rs7927894.^{E6} From the UCSC genome browser, we could identify regulatory elements in this 35-kb locus with high reported enhancer activity, as shown by active histone marks, such as H3K27ac and H3K4me1, although not for H3KMe3, which marks for poised enhancer sites. The locus conserved in the mammalian genome also contains DNaseI hyperactivity clusters, which are crucial for transcription factor binding, which initiates and regulates gene expression.

TABLE E1. Demographics and medical history of the study population

Total	Total (count)	Female (count)	Male (count)	Female (count)	Male (count)
No. of subjects	3743	1927	1768	52.15%	47.85%
Age (y), mean (range)	21.37 (18-64)	21.03 (18-59)	21.75 (18-64)		
SPT response					
Positive response to <i>Blomia tropicalis</i> or <i>Dermatophagoides pteronyssinus</i>					
No. of subjects	3005	1460	1545	48.59%	51.41%
Age (y), mean (range)	21.25 (18-64)	20.88 (18-56)	21.6 (18-64)		
Positive response to <i>Dermatophagoides pteronyssinus</i>					
No. of subjects	2330	1078	1252	46.27%	53.73%
Age (y), mean (range)	21.21 (18-64)	20.88 (18-57)	21.49 (18-64)		
Positive result to <i>Blomia tropicalis</i>					
No. of subjects	2707	1293	1414	47.77%	52.23%
Age (y), mean (range)	21.32 (18-57)	20.92 (18-57)	21.68 (18-53)		
Negative result to <i>Blomia tropicalis</i> and <i>Dermatophagoides pteronyssinus</i>					
No. of subjects	668	454	214	67.96%	32.04%
Age (y), mean (range)	21.93 (18-59)	21.52 (18-59)	22.8 (18-56)		
AR					
AR cases, as defined by Ramasamy et al ¹					
No. of subjects	2180	1151	1029	52.80%	47.20%
Age (y), mean (range)	21.2 (18-57)	21 (18-57)	21.43 (18-45)		
Control subjects, as defined by Ramasamy et al ¹					
No. of subjects	1510	730	758	52.80%	47.20%
Age (y), mean (range)	21.2 (18-64)	22.2 (18-64)	21.08 (18-59)		
AR cases, as defined based on ARIA guidelines					
No. of subjects	1858	941	917	50.65%	49.35%
Age (y), mean (range)	21.05 (18-57)	20.85 (18-57)	21.25 (18-42)		
Control subjects, as defined based on ARIA guidelines					
No. of subjects	668	454	214	67.96%	32.04%
Age (y), mean (range)	21.93 (18-59)	21.52 (18-59)	22.8 (18-56)		

A positive SPT response was identified by a wheal diameter of 3 mm or greater in response to the allergens tested. A positive control of histamine and a negative control of saline were always used. SPTs were performed on the volunteers only if they have not taken any antiallergic drugs, especially antihistamines, for at least 3 days before the test. AR was classified based on 2 or more major symptoms, which include (nasal congestion, rhinorrhea, nasal itching, and sneezing) and a positive SPT response to 1 of the allergens tested (based on 2008 guidelines set by the ARIA consortium). Healthy control subjects are subjects classified based on no symptoms or history of allergic disease and who are nonatopic (negative SPT response to all of the allergens). Note: All samples have been age category matched.

TABLE E2. Hardy-Weinberg equilibrium calculation

SNP	Allele 1	Allele 2	Genotype counts	O (Het)	O (Het)	HWE <i>P</i> value
rs1325195	A	G	383/716/377	0.4851	0.5	.2524
rs17513503	G	C	0/1/1504	0.0006645	0.0006642	1
rs1898671	T	C	3/77/1416	0.05147	0.05394	.1022
rs2069772	C	T	30/330/1135	0.2207	0.2268	.3041
rs2155219	G	T	290/723/456	0.4922	0.4936	.9158
rs216518	A	C	5/172/1320	0.1149	0.1142	1
rs4724100	T	C	101/591/787	0.3996	0.3924	.508
rs6554809	T	C	20/304/1156	0.2054	0.2054	1
rs6673480	T	C	0/2/1501	0.001331	0.00133	1
rs6898653	G	A	20/391/1068	0.2644	0.249	.01617
rs7617456	A	G	69/502/907	0.3396	0.3393	1
rs7789045	T	A	257/738/480	0.5003	0.4886	.3654
rs887864	G	A	55/473/944	0.3213	0.3176	.7426

HWE, Hardy-Weinberg equilibrium; *O (Het)*, observed heterozygosity.

TABLE E3. Replication of GWAS signals, as reported by Ramasamy et al,¹ for AR and HDM sensitization

SNP	Risk allele	AR symptoms				Sensitization to HDM allergens							
						<i>Dermatophagoides pteronyssinus</i>				<i>Blomia tropicalis</i>			
		F_A	F_U	P _{trend}	OR (95% CI)	F_A	F_U	P _{trend}	OR (95% CI)	F_A	F_U	P _{trend}	OR (95% CI)
rs2155219	T	0.59	0.554	.0043	1.15 (1.04-1.27)	0.587	0.534	.0006	1.25 (1.10-1.41)	0.585	0.534	.00076	1.24 (1.09-1.39)
rs6554809	C	0.89	0.88	.1456	1.11 (0.962-1.33)	0.9	0.88	.1001	1.18 (0.97-1.43)	0.89	0.88	.24	1.12 (0.93-1.35)
rs1325195	A	0.4851	0.502	.1595	0.93 (0.85-1.03)	0.4948	0.4985	.8141	0.99 (0.87-1.11)	0.492	0.495	.6765	0.97 (0.86-1.1)
rs6898653	G	0.156	0.1457	.2333	1.08 (0.95-1.24)	0.1549	0.1505	.6992	1.03 (0.87-1.23)	0.152	0.151	.9004	1.01 (0.85-1.2)
rs216518	A	0.0546	0.0608	.2607	0.89 (0.73-1.09)	0.0559	0.0543	.823	1.03 (0.79-1.35)	0.057	0.054	.6857	1.06 (0.81-1.38)
rs7789045	T	0.4116	0.4244	.2811	0.95 (0.86-1.04)	0.4135	0.4155	.8968	0.99 (0.88-1.12)	0.418	0.416	.8595	1.01 (0.89-1.14)
rs7617456	G	0.77	0.78	.2984	0.94 (0.84-1.05)	0.78	0.75	.0174	1.19 (1.03-1.37)	0.785	0.753	.012	1.20 (1.042-1.39)
rs1898671	C	0.968	0.972	.3584	0.88 (0.67-1.16)	0.973	0.96	.032	1.43 (1.03-2.0)	0.973	0.962	.022	1.47 (1.05-2.04)
rs6673480	T	0.0014	0.0007	.3642	2.07 (0.42-10.24)	0.001	0.0008	.6084	1.73 (0.21-14.3)	0.001	0.0008	.7134	1.48 (0.18-12.33)
rs4724100	T	0.276	0.2681	.4617	1.04 (0.94-1.16)	0.2707	0.269	.9054	1.01 (0.88-1.16)	0.275	0.269	.6784	1.03 (0.9-1.18)
rs17513503	G	0.0002	0.0003	.7911	0.69 (0.04-11.02)	0.0002	0.0007	.347	0.29 (0.02-4.6)	0.0002	0.0007	.284	0.25 (0.02-3.95)
rs887864	G	0.2028	0.198	.6192	1.03 (0.92-1.16)	0.2082	0.1898	.1465	1.12 (0.96-1.31)	0.205	0.190	.2359	1.1 (0.94-1.28)
rs2069772	C	0.132	0.1304	.8473	1.01 (0.88-1.16)	0.1355	0.1229	.2358	1.12 (0.93-1.35)	0.134	0.123	.2902	1.1 (0.92-1.32)

P_{trend} values were calculated by using the Cochran-Armitage trend test with PLINK software.

P_{trend} values of less than .05 are shown in boldface. AR symptoms are as defined by self-reported AR history of symptoms.

F_A, Risk allele frequency in affected subjects (cases); F_U, Risk allele frequency in the unaffected subjects (controls).

TABLE E4. Summary of allele and genotype frequencies of SNPs in HapMap populations

Population	Allele 1 with frequency	Allele 2 with frequency	Genotype 1 with frequency	Genotype 2 with frequency	Genotype 3 with frequency
rs17513503					
Utah residents with Northern and Western European ancestry from the CEPH collection (CEU)	C (0.933)	G (0.067)	CC (0.865)	CG (0.135)	GG (0)
Han Chinese in Beijing, China (CHB)	C (0.978)	G (0.022)	CC (0.956)	CG (0.044)	GG (0)
Japanese in Tokyo, Japan (JPT)	C (1)	G (0)	CC (1)	CG (0)	GG (0)
Yoruba in Ibadan, Nigeria (YRI)	C (0.927)	G (0.073)	CC (0.855)	CG (0.145)	GG (0)
rs6673480					
Utah residents with Northern and Western European ancestry from the CEPH collection (CEU)	C (0.915)	T (0.085)	CC (0.83)	CT (0.17)	TT (0)
Han Chinese in Beijing, China (CHB)	C (1)	T (0)	CC (1)	CT (0)	TT (0)
Japanese in Tokyo, Japan (JPT)	C (0.988)	T (0.012)	CC (0.977)	CT (0.023)	TT (0)
Yoruba in Ibadan, Nigeria (YRI)	C (0.959)	T (0.041)	CC (0.919)	CT (0.081)	TT (0)
rs1898671					
Utah residents with Northern and Western European ancestry from the CEPH collection (CEU)	C (0.683)	T (0.317)	CC (0.483)	CT (0.4)	TT (0.117)
Han Chinese in Beijing, China (CHB)	C (0.933)	T (0.067)	CC (0.867)	CT (0.133)	TT (0)
Japanese in Tokyo, Japan (JPT)	C (0.967)	T (0.033)	CC (0.977)	CT (0.067)	TT (0)
Yoruba in Ibadan, Nigeria (YRI)	C (0.992)	T (0.008)	CC (0.919)	CT (0.107)	TT (0)

TABLE E5. Comparison of healthy control subjects (no atopy and no AR) versus patients with AR

SNP rs ID	SNP genotype	Expected count	Observed count	log ₂ (observed/expected)	Observed count	Expected count	log ₂ (Observed/expected)	P value	Total no.
rs1325195	AA	85.06	89	0.07	403	410.98	−0.03	.1265	2089
	AG	173.51	185	0.09	901	907.17	−0.01		
	GG	85.43	70	−0.29	441	426.85	0.05		
rs17513503	CC	347.72	347	0	1844	1843.32	0	.2923	2193
	GC	0.28	1	1.85	1	1.68	−0.75		
rs1898671	CC	327.52	325	−0.01	1701	1699.47	0	.7548	2153
	CT	19.05	22	0.21	104	105.69	−0.02		
	TT	0.44	0	NA	1	0.84	0.25		
rs2069772	CC	6.48	8	0.3	31	32.67	−0.08	.4159	2139
	CT	77.94	72	−0.11	421	413.02	0.03		
	TT	262.58	267	0.02	1340	1346.3	−0.01		
rs2155219	GG	63.36	81	0.35	277	299.16	−0.11	.00035	2081
	GT	167.41	170	0.02	850	852.37	0		
	TT	111.23	91	−0.29	612	587.47	0.06		
rs216518	AA	1.24	1	−0.31	7	6.71	0.06	1	2154
	CA	37.79	36	−0.07	186	186.24	0		
	CC	307.97	310	0.01	1614	1614.05	0		
rs4724100	CC	181.74	193	0.09	899	911.23	−0.02	.1872	2078
	TC	138.32	124	−0.16	715	700.11	0.03		
	TT	23.94	27	0.17	120	122.67	−0.03		
rs6554809	CC	271.3	271	0	1451	1447.35	0	.07375	2138
	CT	64.79	60	−0.11	324	322.75	0.01		
	TT	4.91	10	1.03	22	26.9	−0.29		
rs6673480	CC	347.37	348	0	1841	1841.79	0	1	2194
	CT	0.63	0	NA	5	4.21	0.25		
rs6898653	AA	247.95	252	0.02	1247	1252.5	−0.01	.5943	2098
	GA	90.97	88	−0.05	466	462.9	0.01		
	GG	6.08	5	−0.28	40	37.6	0.09		
rs7617456	AA	16.46	18	0.13	86	87.08	−0.02	.3945	2120
	GA	119.2	132	0.15	617	627.11	−0.02		
	GG	209.34	195	−0.1	1072	1060.81	0.02		
rs7789045	AA	112.76	120	0.09	562	568.77	−0.02	.1003	2084
	TA	177.04	163	−0.12	919	902.36	0.03		
	TT	56.2	63	0.16	257	266.87	−0.05		
rs887864	AA	218.02	223	0.03	1098	1105.44	−0.01	.3928	2102
	AG	113.4	113	−0.01	602	598.33	0.01		
	GG	11.58	7	−0.73	59	55.23	0.1		

Combined contingency table showing the genotypes for the various SNPs as the rows and the various disease groups as the columns. Each combination of genotype and disease group contains 3 cells, the first being the observed occurrences of the genotype and disease group combination, the second being the expected occurrences, and the last being the log₂ ratio of observed over expected occurrences. The log₂ ratios are positive if there is an enrichment of the particular genotype in the disease group and zero if there is no difference and negative otherwise. *P* values of less than .05 are shown in boldface.

NA, Not applicable.

TABLE E6. Comparison of healthy control subjects versus patients with atopy but no AR

SNP rs ID	SNP genotype	Expected count	Observed count	$\log_2(\text{Observed}/\text{expected})$	Observed count	Expected count	$\log_2(\text{Observed}/\text{expected})$	P value	Total no.
rs1325195	AA	85.06	89	0.07	285	284.9	0	.0391	1444
	AG	173.51	185	0.09	521	537.81	-0.05		
	GG	85.43	70	-0.29	294	277.29	0.08		
rs17513503	CC	347.72	347	0	1124	1123.24	0	.2364	1472
	GC	0.28	1	1.85	0	0.76	NA		
rs1898671	CC	327.52	325	-0.01	1060	1056.5	0	.3689	1463
	CT	19.05	22	0.21	53	57.21	-0.11		
	TT	0.44	0	NA	3	2.29	0.39		
rs2069772	CC	6.48	8	0.3	20	21.36	-0.09	.6827	1463
	CT	77.94	72	-0.11	248	244.1	0.02		
	TT	262.58	267	0.02	848	850.54	0		
rs2155219	GG	63.36	81	0.35	204	217.12	-0.09	.03852	1436
	GT	167.41	170	0.02	532	534.81	-0.01		
	TT	111.23	91	-0.29	358	342.07	0.07		
rs216518	AA	1.24	1	-0.31	4	3.81	0.07	.7991	1464
	CA	37.79	36	-0.07	132	128.18	0.04		
	CC	307.97	310	0.01	981	985	-0.01		
rs4724100	CC	181.74	193	0.09	575	585.29	-0.03	.1951	1446
	TC	138.32	124	-0.16	455	441.26	0.04		
	TT	23.94	27	0.17	72	75.45	-0.07		
rs6554809	CC	271.3	271	0	866	869.05	-0.01	.01503	1447
	CT	64.79	60	-0.11	230	221.66	0.05		
	TT	4.91	10	1.03	10	15.29	-0.61		
rs6673480	CC	347.37	348	0	1120	1120.47	0	1	1470
	CT	0.63	0	NA	2	1.53	0.39		
rs6898653	AA	247.95	252	0.02	794	796.61	0	.8893	1447
	GA	90.97	88	-0.05	293	290.16	0.01		
	GG	6.08	5	-0.28	15	15.23	-0.02		
rs7617456	AA	16.46	18	0.13	49	51	-0.06	.08106	1445
	GA	119.2	132	0.15	356	371.49	-0.06		
	GG	209.34	195	-0.1	695	677.51	0.04		
rs7789045	AA	112.76	120	0.09	348	355.71	-0.03	.364	1442
	TA	177.04	163	-0.12	564	552.56	0.03		
	TT	56.2	63	0.16	184	187.73	-0.03		
rs887864	AA	218.02	223	0.03	702	704.52	-0.01	.2017	1439
	AG	113.4	113	-0.01	349	351.88	-0.01		
	GG	11.58	7	-0.73	45	39.61	0.18		

Combined contingency table showing the genotypes for the various SNPs as the rows and the various disease groups as the columns. Each combination of genotype and disease group contains 3 cells, the first being the observed occurrences of the genotype and disease group combination, the second being the expected occurrences, and the last being the $\log_2$ ratio of observed over expected occurrences. The $\log_2$ ratios are positive if there is an enrichment of the particular genotype in the disease group and zero if there is no difference and negative otherwise. P values of less than .05 are shown in boldface.

NA, Not applicable.