

Genes Involved in Interleukin-1 Receptor Type II Activities are Associated with Asthmatic Phenotypes

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Purpose: Interleukin-1 (IL-1) plays a key role in inflammation and immunity and its decoy receptor, IL-1R2, has been implicated in transcriptomic and genetic studies of asthma. **Methods:** Two large asthma family collections, the French-Canadian Saguenay—Lac-St-Jean (SLSJ) study and the French Epidemiological Study on the Genetics and Environment of Asthma (EGEA), were used to investigate the association of SNPs in 10 genes that modulate IL-1R2 activities with asthma, allergic asthma, and atopy. Gene-gene interactions were also tested. **Results:** One SNP in *BACE2* was associated with allergic asthma in the SLSJ study and replicated in the EGEA study before statistical correction for multiple testing. Additionally, two SNPs in the *MMP2* gene were replicated in both studies prior to statistical correction and reached significance in the combined analysis. Moreover, three gene-gene interactions also survived statistical correction in the combined analyses (*BACE1-IL1RAP* in asthma and allergic asthma and *IL1R1-IL1RAP* in atopy). **Conclusions:** Our results highlight the relevance of genes involved in the IL-1R2 activity in the context of asthma and asthma-related traits.

Key Words: Atopy; asthma; *IL1R1*; *IL1R2*; genetic; SNPxSNP

INTRODUCTION

Over 300 genes related to the asthma phenotype have been identified in genetic association studies.¹ However, some genes and *loci* have been associated, replicated numerous times, and are recognized as the “gold standard.” Several association studies have reported the 2q12 locus association with asthma.² Among the genes of this *locus*, interleukin 1 (*IL1*) receptor type 1 (*IL1R1*) has been associated with innate immunity and the *IL1* receptor type 2 (*IL1R2*) with atopy.^{3,4} *IL1R2* was also found to be overexpressed in bronchial biopsies of individuals with allergic asthma.⁵

IL-1 is a potent cytokine of innate immunity primarily involved in the initiation of inflammation, as well as Th17 and nonconventional Th1 (CD161+) responses. It has been shown that drugs neutralizing IL-1 lead to a reduction of airway hyper-reactivity, a decrease of inflammatory infiltration and less Th2 cytokines.⁶⁻⁸ IL-1 has two receptors: 1) IL-1R1 is expressed on virtually all cell types; and 2) IL-1R2 is principally expressed by neutrophils, B-cells, monocytes, and macrophages, as well as in

the plasma in its soluble form (sIL-1R2).⁹ IL-1R2 is involved in the negative regulation of IL-1 as it does not possess the Toll-like domain essential for signal transduction¹⁰ and sIL-1R2 can bind directly to IL-1 and sIL-1RAP.⁹ As the *IL1R1* and *IL1R2* genes have been implicated in asthma, we hypothesized that genes that modulate *IL1R2* activity could have a role in asthma and asthma-related phenotypes. To investigate this hypothesis, we selected single nucleotide polymorphisms (SNPs) of 10 genes involved in *IL1R2* activities and investigated their associations with asthma, allergic asthma, and atopy using 2 familial collections.

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MATERIALS AND METHODS

The French-Canadian Saguenay-Lac-St-Jean (SLSJ) asthma familial collection and the French Epidemiological Study on the Genetics and Environment of Asthma (EGEA) are both large collections that bring power to this study. The SLSJ familial collection is comprised of 1,284 individuals (253 unrelated asthmatic probands) native of SLSJ, a region of Québec (Canada) and was used in the discovery study.¹¹ This population of European origin is known for its founder effect and has a wide range of highly conserved chromosomal regions, facilitating the identification of disease-associated genes. A total of 789 individuals (235 probands) with European ancestry¹² from the EGEA family collection were included in this study and used for replication. All probands and their two parents were of European ancestry, born in France.¹² A description of the studies and a table describing the phenotypic features are available in the online supplement (Table E1). For SLSJ and EGEA independent studies, ethical approval was obtained from the appropriate institutional ethic committees and all individuals gave written informed consent.

The power to detect single SNP associations and SNP x SNP

interactions in the discovery collection was determined using the Quanto program (<http://biostats.usc.edu/Quanto.html>).^{13,14} The power was estimated under an additive genetic model with minor allele frequencies (maf) between 0.05 and 0.50 and main effect size (odds ratio) or interaction effect size (odds ratio in interaction analyses) ranging from 1.1 to 2.5. The study had sufficient power (>80%) to detect moderate to large effects (≥ 1.7) for SNPs with maf ≥ 0.05 and sufficient power to detect small to moderate effects (≥ 1.4) for SNPs with maf ≥ 0.20 in single SNP analyses. For the interaction analyses, the study had sufficient power to detect moderately large effects between common alleles (odds ratio ≥ 1.7 for maf ≥ 0.15 and an odds ratio ≥ 1.4 for maf ≥ 0.30). Full details of the power calculations are in Tables E2 and E3.

To identify genes involved in *IL1R2* function, a review of the literature was performed using PubMed by entering different combinations of the following keywords: *IL1R2*, interleukin 1 decoy receptor, expression, induce, regulate, decrease, and increase. A total of 10 genes were selected according to their direct effect on the *IL1R2* expression or protein level or for the direct impact on IL-1R2 binding activity. The genes are presented in Figure and Supplementary Table E4.

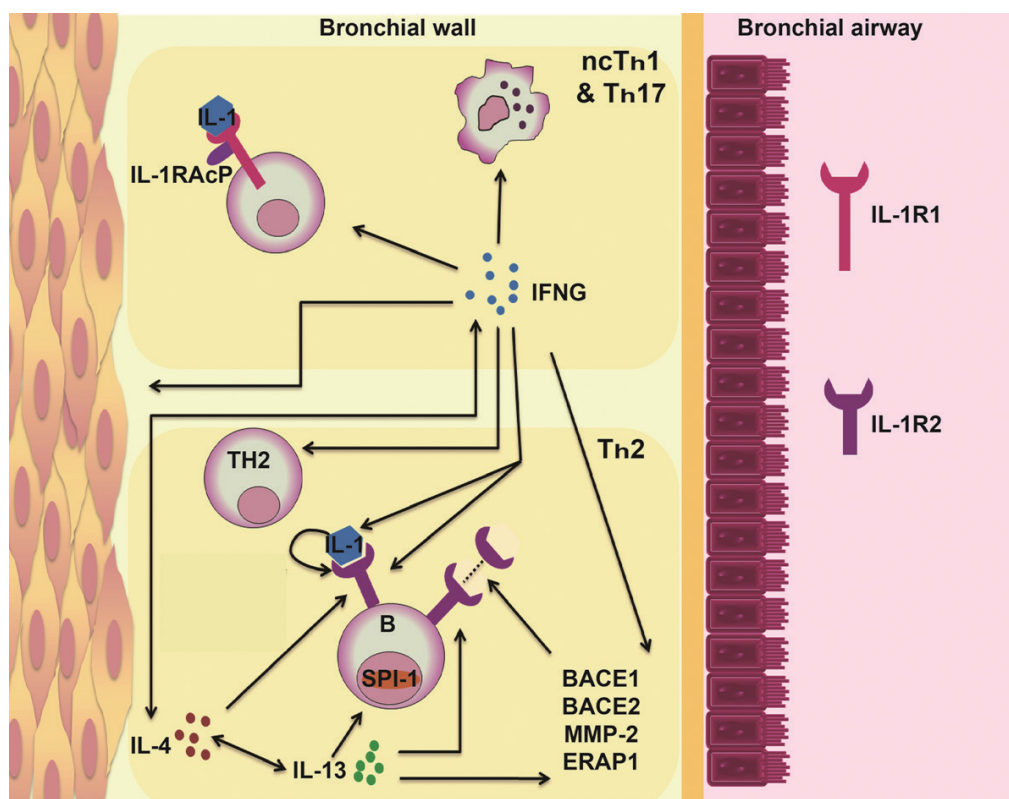


Figure. Schema of the genes involved in IL-1R2 activities analysed in this study. This figure represents the potential actions and interactions of genes involved in the *IL1R2* gene activities in the bronchus of an asthmatic individual. Arrows represent the interactions between genes selected. The upper panel shows the possible involvement of the receptor IL-1R1 in the Th1 and Th17 immune response. The bottom panel illustrates the actions of IL-1R2 in the Th2 immune response. The complete information about the genes selected are available in the Supplementary Table E4.

Genotypes were extracted from the genome-wide data obtained in the context of the European GABRIEL asthma consortium using the 610K Quad Array from Illumina (Illumina, San Diego, CA, USA). A single SNP analysis was performed using the Family-Based Association Test (FBAT; <http://www.hsph.harvard.edu/fbat/default.html>) under an additive genetic model. Analyses of gene-gene interactions including 17,040 SNP pairs were tested using UNPHASED software (v3.1.5) (<https://sites.google.com/site/fdudbridge/software/unphased-3-1>) with the «genotype tests» option. The most frequent haplotype for each pair of SNPs was used as the reference haplotype for the interactions. Moreover, only haplotypes with a frequency $\geq 1\%$ were examined. Analyses were first performed in the discovery SLSJ family dataset, and the most significant signals were used for replication in EGEA families ($P \leq 0.05$ for single SNPs and $P \leq 0.0005$ for interaction analyses (corrected p value considering the number of independent SNPs). Using the SNPSpD and the matSpD tools, the critical P -value thresholds for single SNP analysis was set to $P \leq 0.0003$. Using a Bonferroni correction, the statistical threshold was set to $P \leq 2.9 \times 10^{-6}$ for the SNPxSNP interactions (correcting for the number of SNP x SNP interactions and independent phenotypes).¹⁵ For the replication analysis, the statistical thresholds were obtained for each phenotype according to the number of SNPs tested and were set to $P \leq 0.0048$, $P \leq 0.0030$, and $P \leq 0.0056$ for asthma, allergic

asthma and atopy phenotypes, respectively in single SNP analyses. The thresholds were set to $P \leq 0.05$ for the SNP x SNP interaction analyses for all phenotypes as only one different association was tested for each. These statistical thresholds were also applied to the combined meta-analysis results of both the discovery and replication studies. SLSJ and EGEA results were combined using the Stouffer's method implemented in METAL (single SNP analyses; <http://www.sph.umich.edu/csg/abecasis/metal/>) and MetaP software (interaction analyses; <http://compute1.lsrc.duke.edu/software/MetaP/metap.php>).

RESULTS

A total of 184 SNPs were located in a ± 10 kb region of the 10 selected genes and met the following quality control criteria (call rate $\geq 95\%$; maf $\geq 5\%$; Hardy-Weinberg equilibrium P value $\geq 5\%$; and Mendelian errors $\leq 1\%$) were analysed.

We found suggestive evidence of an association ($P \leq 0.05$) in the SLSJ families for 29 SNPs (see Table and Tables E5-E7 for the complete results). Of those, the *IL1R1* rs3732131 SNP was associated with asthma in both studies with a significant association after statistical correction in the EGEA study. However, it was not fully replicated as the risk allele was not the same ($p_{\text{SLSJ}}=0.04$, $p_{\text{EGEA}}=0.001$, and $p_{\text{combined}}=0.34$). The association between the *BACE2* rs9975388 SNP with allergic asthma was

Table. Main association results for single SNP and SNP x SNP interaction analyses

Gene	Marker Location*	Freq	Asthma			Allergic asthma			Atopy		
			SLSJ	EGEA	Comb.	SLSJ	EGEA	Comb.	SLSJ	EGEA	Comb.
			Pvalue (n)	Pvalue (n)	Pvalue (n)	Pvalue (n)	Pvalue (n)	Pvalue (n)	Pvalue (n)	Pvalue (n)	Pvalue (n)
Single SNP analysis											
IL1R1	rs3732131 3' UTR	0.08	0.0415 (64)	0.0012 (73)	0.3351 (137)						
BACE2	rs9975388 Intron	0.37				0.049 (124)	0.035 (113)	0.004 (237)			
MMP2	rs17301608 Intron	0.31				0.009 (107)	0.05 (138)	0.002 (245)			
	rs9302671 Intron	0.30				0.010 (112)	0.070 (140)	0.003 (252)			
SNP × SNP interaction analysis											
BACE1	rs551662 Intron		7.62 × 10 ⁻⁵	0.662	0.012						
IL1RAP	rs997534 Intron		(300)	(323)	(623)						
IL1R1	rs10208708 Intron-upstream variant 2KB								3.87 × 10 ⁻⁶ (254)	0.040 (400)	5.40 × 10 ⁻⁵ (654)
IL1RAP	rs2241343 Intron										
BACE1	rs676134 Intron					2.99 × 10 ⁻⁵ (222)	0.079 (659)	0.005 (881)			
IL1RAP	rs3773976 Intron										

Comb., Combination of both p values using the Stouffer's method; Freq., allele frequency of the minor allele in the SLSJ familial collection; n, number of families that contributed to the single SNP association tests and the number of individuals that contributed to the SNP x SNP interaction analysis; SNP, Single Nucleotide Polymorphism; UTR, Untranslated region.

Single SNP association with $P \leq 0.05$ and SNP x SNP interaction with $P \leq 0.0005$ in SLSJ were selected for replication in the EGEA asthma study.

*Locations according to the UCSC Genome Browser assembly ID hg38.

replicated in the EGEA study and reached statistical significance in the combined analysis ($p_{\text{SLSJ}}=0.05$, $p_{\text{EGEA}}=0.04$, and $p_{\text{combined}}=0.004$). Two SNPs in the *MMP2* gene were associated with asthma in the SLSJ study (rs17301608 [$p_{\text{SLSJ}}=0.009$] and rs9302671 [$p_{\text{SLSJ}}=0.01$]), showed a replication in EGEA near the significance threshold ($p_{\text{EGEA}}=0.05$ and $p_{\text{EGEA}}=0.07$), and reached statistical significance in the combined analysis. This was observed as the same risk allele was associated in both studies ($p_{\text{combined}}=0.002$ and $p_{\text{combined}}=0.003$).

Three SNP x SNP interactions met the threshold of 5×10^{-4} in SLSJ and were tested for replication in EGEA (Table). All three reached statistical significance in the combined analysis after correction for multiple testing, however, none could be replicated in the EGEA study. The interaction between *IL1R1**rs10208708 and *IL1RAP**rs2241343 was associated with atopy ($p_{\text{combined}}=5.4 \times 10^{-5}$), the interaction between *BACE1**rs551662 and *IL1RAP**rs997534 with asthma, and the interaction between *BACE1**rs676134 and *IL1RAP**rs3773976 with allergic asthma ($p_{\text{combined}}=0.01$ and $p_{\text{combined}}=0.005$, respectively).

DISCUSSION

The association between *IL1* and asthma has been inconsistent between studies.⁸ A meta-analysis revealed that there is no clear association between *IL1* and asthma but shows an association between the *IL1RA* (receptor antagonist) and an increased risk for the disease.⁸ The decoy receptor IL-1R2 has also been associated with asthma-related phenotypes^{3,4} and is involved in a decrease of inflammation in several complex diseases, such as arthritis, endometriosis, diabetes, atherosclerosis, Alzheimer's disease (AD), and ulcerative colitis.⁹ However, the distinct role of IL-1R2, especially in asthma and allergy remains unknown.

In this study, associations were found in the single SNP analyses for *IL1R1*, *BACE2*, *MMP2*, and two SNPs associated with the *MMP2* gene (which was associated with asthma in an Indian population)¹⁶ survived statistical correction in the combined analysis. As IL-1R2 is a negative regulator of the IL-1 signalisation, IL-1R1 is its direct competitor for the binding of IL-1.⁶ The two other associated genes, *BACE2* and *MMP2*, are known to modulate the quantity of sIL-1R2 via cleavage.^{6,17} Interestingly, sIL-1R2 seems to have a more durable interaction with IL-1 β compared to the membrane-bound IL-1R2 and can also bind pro-IL-1 β , being highly efficient in IL-1 sequestration.⁹ IL-1 is primarily involved in the initiation of the innate immune response, as well as Th17 and nonconventional Th1 cell responses. Therefore, mutations in the genes that encode its principal receptor and two enzymes that participate to the solubilisation of the decoy receptor (i.e., IL-1R2) may influence the immune response in asthma and atopy. As reported by Vasilyev and colleagues, SNPs in *IL1R1* and *IL1R2* modulate the level of the soluble form of these receptors on immunocompetent cells.¹⁸

Thus, it can be assumed that the associated SNPs in this study can also modulate the expression of these genes and subsequently affect the levels of IL-1R1 and IL-1R2.

The strongest gene-gene statistical interaction observed was between the *IL1RAP* and *IL1R1* genes, and has the most biological relevance. These genes encode proteins that are associated with the regulation of the IL-1 receptor and the functionality of IL-1.⁶ Indeed, IL-1R1 and IL-1RAP have been shown to form a protein complex with IL-1. Furthermore, the interplay between these proteins may serve to unbalance the interaction between IL-1 and its signaling receptor (IL-1R1 and IL-1RAP) and its decoy receptor complex (IL-1R2 and IL-1RAP). This imbalance may have an important impact on the multiple roles of IL-1 in inflammation and potentially in asthma and atopy.

The interactions found between *BACE1* and *IL1RAP* in asthma and allergic asthma is also of interest. *BACE1* is known for its role in AD¹⁹ and has not been reported in relation to asthma or allergy to date. As *BACE1* is involved in the inflammatory processes in AD through its modulation of IL-1B via a β -amyloid precursor protein,²⁰ the same type of interaction may occur in asthma between *BACE1* and IL-1B through IL-1RAP. Indeed, since *BACE1* cleaves IL-1R2¹⁷ and subsequently changes the proportion of membrane-bound and soluble forms of the receptor, the increase of sIL-1R2 may increase the competition with IL-1RAP for binding with IL-1 β .

The association between the genes involved in IL-1R2 activities and asthma phenotypes have been demonstrated in this work. The power of the present study was sufficient to detect associations with the threshold of $P \leq 0.05$ for SNPs with small to moderate effects and $\text{maf} \geq 0.2$ in the SLSJ discovery study. As the size effect of SNPs in complex traits is usually small, the power of the study surely impacts the results for the few SNPs with a lower maf (70% of the SNPs tested have $\text{maf} \geq 0.2$) and may lead to missing some other associations between these genes and asthma or atopy. However, genes involved in IL-1R2 activity were chosen based on strong evidence of its role in asthma and asthma-related phenotypes. Moreover, the investigation of candidate genes was selected on the basis of their biological interactions with IL-1R2 and should reduce the number of false-positive findings.²¹

In conclusion, we suggest for the first time, that associations exist between *BACE2* and *MMP2* with allergic asthma and a potentially important SNP x SNP interaction between *IL1RAP* and *IL1R1*. While this genetic study does not claim to demonstrate a direct effect of these genes and SNPs on the pathophysiology of asthma, it provides a strong basis for functional studies. It will certainly achieve further fine-mapping and sequencing approaches to fully characterize the molecular structure of the genes that were associated in this study and to identify any causal variants. Our study highlights the possible role of genes modulating IL-1R2 activities in the pathophysiology of asthma, as well as asthma-related phenotypes.

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Supplementary Table E1. Phenotypic features and distribution of families

	SLSJ		EGEA*	
	Probands [†]	Family members	Probands [†]	Family members
	n=253	n=1,031	n=235	n= 554
Male : Female ratio	1 : 1.1	1 : 1.2	1.6	1.0
Mean age, year (range)	18 (3-50)	44 (2-93)	15 (7-41)	17 (1-43)
Smoking status, n (%) [‡]				
Non smoker	211 (85)	473 (47)	46 (63)	156 (58)
Ex-smoker	12 (5)	342 (34)	10 (14)	28 (11)
Smoker	25 (10)	197 (19)	17 (23)	84 (31)
FEV ₁ , % predicted (SD) [§]	92.7 (15.7)	94.6 (20.3)	92.7 (14.0)	98.7 (13.0)
PC ₂₀ , mg/mL (SD)	2.53 (3.51)	10.10 (4.97)	1.82 (2.63)	6.31 (6.76)
PD ₂₀ < = 4 mg, n (SD) [¶]	NA	NA	121 (95.3)	194 (51.9)
Serum IgE, µg/L (SD)**	254.2 (4.9)	112.4 (4.4)	371.5 (3.2)	100.0 (5.0)
Subphenotypes, n (%)				
Asthma ^{††}	253 (100)	378 (37)	235 (100)	250 (42)
Atopy ^{‡‡}	200 (79)	509 (49)	207 (91)	289 (54)
Atopic asthma	200 (79)	257 (25)	207 (91)	131 (25)

*The EGEA (the French Epidemiological Study on the Genetics and Environment of Asthma) data shown in this table are for the offspring generation of the nuclear families; [†]Probands are first affected family member recruited in the familial collection and family members refer, in the SLSJ (Saguenay—Lac-Saint-Jean) asthma familial collection, to other family members who joined the study and correspond to sibs of probands in EGEA study; [‡]In EGEA study, smoking habits were only recorded for individuals ≥ 16 years of age; [§]FEV₁=The mean forced expiratory volume in 1 s (FEV₁) calculated as % of predicted value (% pred.); ^{||}PC₂₀=Geometric mean of provocative concentration of methacholine that induces a 20% fall in FEV₁; [¶]PD₂₀=Decrease of FEV₁ > =20% for a < =4 mg dose of methacholine; ^{**}IgE=Geometric mean of immunoglobulin E serum concentration; ^{††}Present asthma or past documented clinical history of asthma; ^{‡‡}Defined as at least one positive response on skin prick testing (wheal diameter >3 mm at 10 minutes).

Supplementary Table E2. Power calculation for specific allele frequencies and effect sizes (odd ratios)

Maf	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
OR	Power									
1.1	0.08	0.10	0.12	0.14	0.15	0.16	0.17	0.18	0.18	0.18
1.2	0.15	0.24	0.31	0.38	0.43	0.46	0.49	0.51	0.52	0.52
1.3	0.27	0.45	0.58	0.67	0.73	0.77	0.80	0.81	0.82	0.82
1.4	0.41	0.66	0.80	0.87	0.91	0.94	0.95	0.96	0.96	0.96
1.5	0.57	0.82	0.93	0.96	0.98	0.99	0.99	0.99	0.99	0.99
1.6	0.70	0.92	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00
1.7	0.81	0.97	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.8	0.89	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.9	0.94	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.0	0.97	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.1	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.2	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.4	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

maf, minor allele frequency; OR, odd ratio.

Supplementary Table E3. Power calculation for specific allele frequencies and effect sizes (odd ratios) for gene – gene interactions

SNP 1 maf	0.05										0.10										0.15									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.09	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
OR	Power																													
1.1	0.05	0.06	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.07	0.06	0.07	0.07	0.08	0.08	0.08	0.09	0.09	0.09	0.09	0.09	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
1.2	0.07	0.08	0.09	0.10	0.11	0.12	0.12	0.13	0.13	0.13	0.11	0.13	0.15	0.16	0.18	0.19	0.19	0.20	0.20	0.20	0.20	0.21	0.23	0.24	0.25	0.26	0.26	0.26	0.26	0.26
1.3	0.08	0.11	0.14	0.16	0.18	0.20	0.21	0.22	0.22	0.23	0.17	0.22	0.27	0.30	0.33	0.35	0.36	0.37	0.37	0.37	0.37	0.30	0.35	0.40	0.44	0.46	0.48	0.48	0.48	0.48
1.4	0.11	0.16	0.21	0.25	0.28	0.31	0.33	0.34	0.35	0.35	0.26	0.35	0.42	0.47	0.52	0.54	0.56	0.57	0.57	0.57	0.46	0.55	0.61	0.65	0.68	0.70	0.71	0.71	0.71	0.71
1.5	0.14	0.22	0.29	0.35	0.40	0.44	0.47	0.49	0.50	0.50	0.37	0.49	0.58	0.65	0.69	0.72	0.74	0.75	0.75	0.75	0.64	0.73	0.79	0.83	0.85	0.86	0.87	0.87	0.86	0.86
1.6	0.18	0.29	0.39	0.47	0.53	0.57	0.61	0.63	0.64	0.64	0.49	0.63	0.73	0.79	0.83	0.86	0.87	0.88	0.88	0.88	0.78	0.86	0.90	0.93	0.94	0.95	0.95	0.95	0.95	0.95
1.7	0.22	0.37	0.49	0.58	0.65	0.70	0.73	0.75	0.77	0.77	0.61	0.76	0.84	0.89	0.92	0.94	0.94	0.95	0.95	0.95	0.88	0.94	0.96	0.98	0.98	0.98	0.99	0.99	0.98	0.98
1.8	0.27	0.45	0.59	0.69	0.76	0.80	0.83	0.85	0.86	0.86	0.72	0.85	0.92	0.95	0.97	0.98	0.98	0.98	0.98	0.98	0.94	0.98	0.99	0.99	1.00	1.00	1.00	1.00	1.00	1.00
1.9	0.32	0.53	0.68	0.78	0.84	0.88	0.90	0.92	0.92	0.92	0.80	0.92	0.96	0.98	0.99	0.99	0.99	0.99	0.99	0.99	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.0	0.37	0.61	0.76	0.85	0.90	0.93	0.95	0.96	0.96	0.96	0.87	0.96	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.1	0.42	0.69	0.83	0.91	0.94	0.96	0.97	0.98	0.98	0.98	0.92	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.2	0.48	0.75	0.88	0.94	0.97	0.98	0.99	0.99	0.99	0.99	0.95	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.3	0.54	0.81	0.92	0.97	0.98	0.99	1.00	1.00	1.00	1.00	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.4	0.59	0.86	0.95	0.98	0.99	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.5	0.64	0.90	0.97	0.99	1.00	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

maf, minor allele frequency; OR, odd ratio; SNP, single nucleotide polymorphism.

(Continued to the next page)

Supplementary Table E3. Continued

SNP1 maf	0.20					0.25					0.30					0.35						
	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.25	0.30	0.35	0.40	0.45	0.50	0.30	0.35	0.40	0.45	0.50	0.35	0.40	0.45	0.50
SNP2 maf	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.25	0.30	0.35	0.40	0.45	0.50	0.30	0.35	0.40	0.45	0.50	0.35	0.40	0.45	0.50
OR	Power																					
1.1	0.09	0.10	0.11	0.11	0.11	0.12	0.12	0.11	0.12	0.12	0.12	0.13	0.13	0.12	0.13	0.13	0.13	0.13	0.13	0.14	0.14	0.14
1.2	0.22	0.25	0.27	0.29	0.30	0.30	0.30	0.29	0.31	0.33	0.34	0.34	0.34	0.34	0.36	0.37	0.37	0.37	0.37	0.39	0.39	0.39
1.3	0.43	0.48	0.52	0.54	0.56	0.56	0.56	0.54	0.58	0.60	0.62	0.62	0.62	0.62	0.64	0.66	0.66	0.65	0.66	0.68	0.69	0.68
1.4	0.64	0.70	0.74	0.77	0.78	0.79	0.78	0.76	0.80	0.82	0.83	0.84	0.83	0.84	0.85	0.86	0.86	0.86	0.87	0.88	0.88	0.88
1.5	0.82	0.87	0.89	0.91	0.92	0.92	0.92	0.91	0.93	0.94	0.95	0.95	0.94	0.95	0.96	0.96	0.96	0.95	0.96	0.97	0.97	0.96
1.6	0.92	0.95	0.97	0.97	0.98	0.98	0.97	0.97	0.98	0.98	0.99	0.99	0.98	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99
1.7	0.97	0.99	0.99	0.99	0.99	0.99	0.99	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.8	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.9	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.4	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

maf, minor allele frequency; OR, odd ratio; SNP, single nucleotid polymorphism.

Supplementary Table E4. Genes selected for their direct effect on IL1R2 expression or binding activity with IL-1

Gene	Function linked with IL1R2	Model/experimentation	Ref
<i>BACE1</i>	IL1R2 cleavage into soluble form.	Human embryonic kidney 293 cells (HEK293) were transiently transfected with IL-1R2 either with BACE1 or BACE2.	Kuhn et al. 2007 (17307738)
<i>BACE2</i>	IL1R2 cleavage into soluble form.	Human embryonic kidney 293 cells (HEK293) were transiently transfected with IL-1R2 either with BACE1 or BACE2.	Kuhn et al. 2007 (17307738)
<i>ERAP1</i>	Necessary for IL-1R2 ectodomain liberation when cleaved by metalloproteases.	Immunoprecipitation were done using NCI-H292 cells, a human pulmonary mucoepidermoid carcinoma cell line, stably transfected with full-length <i>ARTS1</i> gene or NCI-H292 knockout cell line (<i>arts-1^{-/-}</i>).	Cui et al. 2003 (14662887)
<i>IL13</i>	Increase soluble IL-1R2 (sIL-1R2) expression.	Human polymorphonuclear cells isolated from healthy donors treated with human recombinant IL-13 for 12-14 hours were incubated with decreasing concentrations of IL-1B./ Stimulation of human monocytes with IL-4, IL-13, and dexamethasone.	Colotta et al. 1994 (7909801)/Colotta et al. 1996 (8786316)
<i>IL1R1</i>	Signaling receptor of IL1A and IL1B. Direct competitor for the binding of their common ligands (IL1A and IL1B) and coreceptor (IL1RAP).	Binding affinity was measured for human IL-1 α , IL-1 β , and IL-1Ra on human and murine IL-R1 and IL-1R2./Monoclonal antibody that block binding of human and murine IL-1 was isolated in murine IL-1 receptor-bearing cells.	McMahan et al. 1991 (1833184)/Greenfeder et al 1995 (7775431)
<i>IL1RAP</i>	Coreceptor of IL-1R1 and IL-1R2 for the binding of IL1A and IL1B.	Monoclonal antibody that block binding of human and murine IL-1 was isolated in murine IL-1 receptor-bearing cells. /IL-1 β and IL-1 receptors were cloned from human and from rhesus and cynomolgus monkeys and human and monkey ligands (IL-1 α , IL-1 β , and IL-1Ra) were used with IL-1RAP.	Greenfeder et al. 1995 (7775431)/Smith et al. 2003 (12530978)
<i>IL4</i>	Increase soluble IL-1R2 (sIL-1R2) expression.	Stimulation of human monocytes with IL-4, IL-13, and dexamethasone.	Colotta et al. 1996 (8786316)
<i>IFNG</i>	Downregulate IL-1R2 gene expression.	cDNA microarray analysis of genes of interest in human uterine microvascular endothelial cells after treatment with IFN γ for 4 hours.	Kitaya et al. 2007 (17912462)
<i>MMP2</i>	Negatively correlated with IL1R2 level.	Endometrial adenocarcinoma cell line stably transfected with IL1R2 was used for stimulation with IL1B and MMP2 and IL1R2 levels were measured.	Gay and Akoum 2007 (17709570)
<i>SPI1</i>	Transcription factor involved in IL1R2 expression.	They used the Burkitt lymphoma Raji and Daudi cell lines and the myelomonocytic THP-1 cell line to compare expression of IL1R2 after transfection. The expression of IL1R2 in the Daudi cell line that do not express SPI1 was lower and increased after transfection with the SPI1 sequence.	Vanier et al. 1995 (abstract published in Cytokines 1995:7:596, 3rd Annual Conference International Cytokine Society)

Supplementary Table E5. Association results for the 184 SNPs that fulfilled all quality criteria and asthma phenotype

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P [†]	Freq	Fam	Z	P [†]	Z	P [†]	Dir [‡]
2	<i>IL1R1</i>	rs7580384	102144258	G	A	0.43	153	-0.69	0.4883							
		rs11883987	102144780	C	T	0.38	152	-1.51	0.1307							
		rs11123911	102145078	T	C	0.17	104	1.33	0.1844							
		rs4851547	102145307	A	C	0.46	147	1.07	0.2845							
		rs10187031	102146734	C	T	0.16	108	-0.80	0.4216							
		rs13001315	102146750	A	G	0.16	105	0.92	0.3587							
		rs13035227	102147377	C	T	0.16	105	0.92	0.3587							
		rs1558642	102147500	T	G	0.19	125	-0.21	0.8340							
		rs2110727	102147834	A	G	0.16	106	-0.65	0.5159							
		rs6754776	102148318	G	C	0.16	106	1.07	0.2864							
		rs4851000	102148557	C	T	0.46	150	0.57	0.5659							
		rs10208708	102148981	G	C	0.16	104	-0.57	0.5698							
		rs10184523	102149040	A	G	0.16	108	-0.80	0.4216							
		rs1558641	102149405	A	G	0.16	108	-0.80	0.4216							
		rs1558640	102149418	A	G	0.16	108	-0.80	0.4216							
		rs35318065	102150172	A	C	0.16	101	-0.76	0.4466							
		rs3917225	102152842	G	A	0.46	149	0.46	0.6465							
		rs949963	102153326	T	C	0.16	108	-0.48	0.6322							
		rs871657	102154881	T	C	0.16	105	-0.41	0.6857							
		rs2287048	102157539	T	C	0.16	108	-0.80	0.4216							
		rs2287047	102157594	A	G	0.32	142	0.21	0.8376							
		rs3917254	102160058	A	G	0.07	60	2.36	0.0182	0.13	100	-1.48	0.1398	0.28	0.7803	+-
		rs3917265	102162001	T	C	0.40	121	-0.02	0.9828							
		rs3917289	102165451	T	G	0.08	66	-1.48	0.1381							
		rs2160227	102166895	T	G	0.27	146	0.21	0.8344							
		rs3917296	102168373	G	A	0.08	65	1.52	0.1282							
		rs3917304	102171665	T	G	0.27	144	0.36	0.7208							
		rs3771200	102172314	A	G	0.46	147	0.60	0.5486							
		rs3171845	102174921	A	G	0.08	66	-1.56	0.1194							
		rs3917318	102176300	G	A	0.27	144	0.36	0.7208							
		rs2110726	102177822	A	G	0.40	147	1.51	0.1309							
		rs3732131	102178143	G	A	0.08	64	2.04	0.0415	0.09	73	-3.23	0.0012	-0.96	0.3351	+-
		rs3917329	102179403	T	G	0.08	64	-1.57	0.1161							
		rs6744454	102182692	G	A	0.14	94	-1.03	0.3026							
		rs1030021	102185018	C	A	0.27	144	0.36	0.7208							
3	<i>IL1RAP</i>	rs766442	190505165	G	T	0.35	146	-0.48	0.6349							
		rs6800609	190516515	C	T	0.06	49	1.15	0.2513							
		rs9290935	190519562	C	T	0.25	137	1.01	0.3108							
		rs17196143	190520509	A	G	0.14	95	0.00	1.0000							
		rs9290936	190534846	T	G	0.12	90	-0.17	0.8618							
		rs3773992	190535876	A	C	0.07	61	0.00	1.0000							
		rs9876152	190537403	T	C	0.07	62	-0.22	0.8231							
		rs2361832	190542248	G	A	0.16	110	0.60	0.5488							
		rs997534	190542374	C	T	0.14	95	0.48	0.6287							
		rs3773990	190544263	A	G	0.07	65	-0.66	0.5102							

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Supplementary Table E5. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P [†]	Freq	Fam	Z	P [†]	Z	P [†]	Dir [‡]
3	<i>IL1RAP</i>	rs3773989	190547640	G	A	0.50	152	-0.87	0.3842							
		rs4686554	190556029	C	T	0.28	141	0.79	0.4271							
		rs16865597	190557756	C	T	0.12	92	0.20	0.8421							
		rs2885370	190559206	G	T	0.27	134	0.65	0.5179							
		rs3773986	190561126	A	G	0.08	62	-0.71	0.4772							
		rs3773982	190562263	A	G	0.17	108	0.77	0.4422							
		rs4687150	190563095	T	C	0.34	155	1.41	0.1575							
		rs2241343	190564925	G	T	0.12	91	-0.40	0.6893							
		rs9877268	190568033	A	G	0.33	148	1.17	0.2412							
		rs3773976	190569496	G	T	0.12	87	0.55	0.5794							
		rs10937439	190575766	G	A	0.38	158	1.41	0.1585							
		rs6801017	190577941	G	A	0.24	133	-0.91	0.3622							
		rs1559018	190579294	G	A	0.33	160	0.55	0.5839							
		rs1024940	190580192	G	A	0.34	159	0.55	0.5851							
		rs6444435	190586016	G	A	0.35	149	0.04	0.9693							
		rs3773967	190587229	T	C	0.21	116	0.60	0.5503							
		rs3773966	190587260	T	G	0.10	74	0.09	0.9304							
		rs10513854	190588085	T	C	0.19	108	-0.69	0.4887							
		rs7628250	190590738	G	A	0.28	130	0.05	0.9581							
		rs3773958	190591814	C	A	0.21	127	-2.40	0.0166	0.20	135	-0.48	0.6342	-2.01	0.0446	--
		rs2193874	190600737	G	A	0.39	148	1.43	0.1526							
		rs2193875	190603667	C	T	0.35	150	0.49	0.6210							
		rs6781037	190609732	G	A	0.36	154	0.47	0.6360							
		rs12636004	190611402	A	G	0.40	152	1.21	0.2252							
		rs9290939	190616087	A	G	0.08	66	-0.38	0.7079							
		rs4687161	190623503	C	T	0.39	149	0.71	0.4809							
		rs4687163	190623650	G	A	0.35	148	-0.11	0.9161							
		rs6444444	190628442	A	G	0.13	92	1.84	0.0664							
		rs2885373	190628679	T	C	0.13	92	1.84	0.0664							
		rs7626795	190632672	G	A	0.18	118	-1.56	0.1188							
		rs4320092	190643226	G	T	0.22	139	0.60	0.5516							
5	<i>ERAP1</i>	rs28096	96773540	A	G	0.33	153	0.32	0.7456							
		rs11135480	96774878	G	T	0.17	99	-0.25	0.7996							
		rs13160562	96775667	A	G	0.27	137	0.65	0.5144							
		rs10515247	96776022	A	G	0.17	106	-0.10	0.9214							
		rs10515248	96776301	T	C	0.17	106	-0.10	0.9214							
		rs149078	96779489	A	G	0.27	144	-1.28	0.2011							
		rs27042	96781236	A	G	0.33	146	-1.25	0.2122							
		rs42398	96784751	C	T	0.16	116	0.80	0.4212							
		rs469783	96785820	C	T	0.49	168	1.65	0.0993							
		rs10050860	96786506	T	C	0.22	121	-0.40	0.6924							
		rs13154629	96786754	T	C	0.21	116	-0.48	0.6324							
		rs30187	96788627	T	C	0.40	160	0.85	0.3975							
		rs27434	96793809	A	G	0.23	130	1.15	0.2515							
		rs26618	96795133	C	T	0.20	115	-2.02	0.0433	0.24	159	-0.43	0.6686	-1.64	0.1020	--

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Supplementary Table E5. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P [†]	Freq	Fam	Z	P [†]	Z	P [†]	Dir [‡]
		rs25866	96795334	A	C	0.27	142	0.12	0.9022							
		rs13173167	96795780	T	G	0.21	117	-0.33	0.7403							
		rs30333	96798532	A	G	0.10	73	0.40	0.6892							
		rs34753	96815208	C	T	0.27	132	1.52	0.1275							
	<i>IL13</i>	rs1295686	132660151	T	C	0.26	138	1.56	0.1179							
		rs20541	132660272	A	G	0.26	138	1.71	0.0883							
		rs2243204	132663802	T	C	0.10	81	2.22	0.0264	0.10	72	-0.62	0.5345	1.19	0.2343	+-
		rs2243300	132668394	T	G	0.09	69	1.52	0.1296							
11	<i>SPI1</i>	rs3729989	47348490	C	T	0.13	95	0.97	0.3334							
		rs2697920	47349056	T	C	0.32	138	-0.91	0.3635							
		rs3740689	47359042	G	A	0.47	165	2.38	0.0171	0.38	197	0.74	0.4591	2.16	0.0311	++
		rs10769258	47369488	C	T	0.32	149	0.03	0.9768							
		rs11606287	47385888	A	C	0.38	128	-1.66	0.0961							
	<i>BACE1</i>	rs505045	117281824	G	T	0.38	162	0.33	0.7444							
		rs7083	117285836	T	C	0.38	162	0.33	0.7444							
		rs522843	117305218	C	T	0.29	145	-2.87	0.0041	0.33	183	0.44	0.6598	-1.58	0.1143	-+
		rs687740	117306887	C	A	0.40	159	1.53	0.1268							
		rs473210	117307084	T	C	0.37	159	-3.11	0.0019	0.41	185	0.44	0.6615	-1.79	0.0732	-+
		rs551662	117308287	C	T	0.10	88	-1.69	0.0918							
		rs676134	117309175	T	C	0.39	170	-1.74	0.0822							
		rs560564	117324912	C	A	0.40	156	-2.42	0.0154	0.38	189	-0.04	0.9723	-1.66	0.0980	--
12	<i>IFNG</i>	rs2193045	68140740	A	G	0.29	163	-2.15	0.0313	0.27	172	1.51	0.1307	-0.42	0.6751	-+
		rs12369470	68151116	C	T	0.06	53	0.23	0.8162							
		rs2069727	68154443	C	T	0.40	168	1.28	0.2011							
		rs2069718	68156382	A	G	0.45	176	-1.94	0.0520							
16	<i>MMP2</i>	rs1005913	55470609	G	T	0.28	136	-0.90	0.3671							
		rs1347653	55471128	T	G	0.10	70	1.13	0.2568							
		rs16955194	55471416	A	G	0.06	59	-0.22	0.8292							
		rs17301608	55484698	T	C	0.31	128	1.77	0.0769							
		rs1053605	55485695	T	C	0.05	46	-1.10	0.2715							
		rs9302671	55487813	T	G	0.29	131	1.56	0.1189							
		rs243842	55493510	C	T	0.43	143	-1.09	0.2741							
		rs183112	55493770	A	G	0.16	112	-0.45	0.6518							
		rs1992116	55493979	A	G	0.39	141	0.82	0.4117							
		rs243840	55494247	G	A	0.18	118	-0.01	0.9907							
		rs243834	55502775	A	G	0.50	166	0.93	0.3518							
		rs1861320	55507128	T	G	0.45	164	1.01	0.3127							
		rs8054459	55510637	G	A	0.49	166	-1.26	0.2074							
21	<i>BACE2</i>	rs2410404	41157981	T	G	0.07	53	1.43	0.1536							
		rs2016240	41158333	T	C	0.21	134	0.55	0.5809							
		rs7276900	41160148	A	C	0.32	131	-0.09	0.9322							
		rs6517653	41162326	A	C	0.22	133	0.35	0.7282							
		rs766850	41174890	T	C	0.16	97	-0.54	0.5903							
		rs4818219	41175967	G	A	0.24	134	-0.12	0.9013							
		rs8130833	41184958	G	A	0.30	145	-0.43	0.6708							

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Supplementary Table E5. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P ^t	Freq	Fam	Z	P ^t	Z	P ^t	Dir ^t
21	<i>BACE2</i>	rs914185	41195210	T	C	0.20	116	-1.45	0.1472							
		rs2837965	41195710	T	G	0.31	145	-0.83	0.4096							
		rs16998096	41195981	G	T	0.08	57	-0.46	0.6468							
		rs750445	41200417	C	A	0.15	108	0.97	0.3338							
		rs4816713	41202257	T	C	0.14	94	-0.21	0.8307							
		rs2837967	41205037	A	G	0.21	141	-0.74	0.4573							
		rs746064	41209521	A	G	0.33	146	-1.70	0.0899							
		rs7510366	41210000	T	C	0.05	34	0.13	0.8946							
		rs914178	41210260	A	G	0.27	146	-1.04	0.3004							
		rs6517656	41211811	A	G	0.15	119	-0.15	0.8802							
		rs9983496	41214203	C	T	0.38	143	-1.45	0.1484							
		rs914183	41214568	G	A	0.11	96	0.71	0.4760							
		rs17175402	41215505	T	C	0.11	68	2.80	0.0051	0.07	70	0.66	0.5074	2.44	0.0147	++
		rs2837970	41219684	A	G	0.32	146	-1.47	0.1414							
		rs7280770	41223963	A	G	0.13	95	-0.66	0.5108							
		rs7278856	41226960	G	T	0.24	132	-1.13	0.2592							
		rs2837974	41230808	G	A	0.11	69	-0.55	0.5839							
		rs2009135	41236304	G	A	0.33	149	-0.43	0.6672							
		rs1541103	41241417	G	A	0.38	163	-1.33	0.1851							
		rs2252576	41243366	T	C	0.24	133	0.17	0.8638							
		rs2837981	41244078	C	T	0.24	124	0.67	0.5059							
		rs2837983	41244830	A	G	0.21	125	-1.45	0.1483							
		rs2837985	41245829	G	A	0.10	84	-0.48	0.6317							
		rs3827211	41247327	A	G	0.49	164	-0.93	0.3501							
		rs2837988	41247617	A	C	0.35	151	-0.57	0.5702							
		rs914187	41247822	T	C	0.37	154	0.09	0.9317							
		rs2837990	41248222	A	G	0.17	109	-1.50	0.1347							
		rs2837992	41248593	T	C	0.37	154	1.47	0.1407							
		rs960230	41250552	A	G	0.24	130	1.56	0.1192							
		rs1046210	41250859	T	C	0.41	153	-0.37	0.7099							
		rs9975388	41254435	C	A	0.37	150	1.43	0.1522							
		rs2837997	41257725	T	C	0.08	67	-0.77	0.4440							
		rs3787944	41257817	T	G	0.06	53	-1.40	0.1630							
		rs4818225	41257968	A	G	0.33	147	0.65	0.5155							
		rs2837998	41258166	G	A	0.40	165	0.88	0.3790							
		rs4818226	41261138	A	G	0.31	146	0.48	0.6286							
		rs726980	41263749	A	G	0.13	87	-0.83	0.4047							
		rs7277420	41265288	T	C	0.11	90	-0.17	0.8648							
		rs2410415	41269475	C	T	0.19	122	0.23	0.8180							
		rs6517659	41270055	T	C	0.16	108	-0.12	0.9029							
		rs8133778	41270111	A	G	0.27	139	0.14	0.8864							
		rs12483323	41271918	T	C	0.15	101	0.39	0.7005							
		rs2838000	41274591	A	G	0.21	129	0.41	0.6819							
		rs2838002	41276840	C	T	0.27	141	0.14	0.8885							
		rs8126886	41280790	T	C	0.12	79	-0.08	0.9329							

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Supplementary Table E5. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	<i>P</i> [†]	Freq	Fam	Z	<i>P</i> [†]	Z	<i>P</i> [†]	Dir [‡]
		rs1964927	41281310	A	G	0.37	163	0.73	0.4642							
		rs2838006	41281640	T	C	0.36	161	0.90	0.3662							
		rs2297277	41282721	A	G	0.48	158	-0.61	0.5405							
		rs1072869	41285621	C	A	0.32	160	-0.31	0.7541							

Abbreviations used: A1=minor allele; A2=major allele; Chr=chromosome; EGEA=the French Epidemiological Study on the Genetics and Environment of Asthma; Fam=number of trios involved in the analysis; Freq=frequency of the minor allele; SLSJ=the French Canadian Saguenay—Lac-Saint-Jean asthma familial collection. *Chromosomes, gene names and locations according to the UCSC Genome Browser assembly ID hg38; [†]*P* values in italics are those below 0.05 and *P* values in italics and bold are those below the statistical threshold for the discovery study ($P \leq 0.0003$) or the replication study and the combined analysis ($P \leq 0.0048$); [‡]A positive direction “+” indicates an over transmission of the minor allele to asthmatic individuals and negative effect “-” an under transmission of the minor allele to asthmatic individuals.

Supplementary Table E6. Association results for the 184 SNPs that fulfilled all quality criteria and allergic asthma phenotype

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P [†]	Freq	Fam	Z	P [†]	Z	P [†]	Dir [‡]
2	<i>IL1R1</i>	rs7580384	102144258	G	A	0.43	128	-0.59	0.5540							
		rs11883987	102144780	C	T	0.38	126	-2.16	0.0312	0.41	133	1.70	0.0900	-0.29	0.7734	- +
		rs11123911	102145078	T	C	0.17	88	2.19	0.0285	0.16	73	-1.56	0.1199	0.57	0.5674	+ -
		rs4851547	102145307	A	C	0.46	119	0.71	0.4750							
		rs10187031	102146734	C	T	0.16	87	-0.52	0.6061							
		rs13001315	102146750	A	G	0.16	88	1.83	0.0672							
		rs13035227	102147377	C	T	0.16	87	1.93	0.0539							
		rs1558642	102147500	T	G	0.19	99	-0.74	0.4609							
		rs2110727	102147834	A	G	0.16	85	-0.34	0.7365							
		rs6754776	102148318	G	C	0.16	89	1.98	0.0479	0.15	70	-1.88	0.0602	0.23	0.8158	+ -
		rs4851000	102148557	C	T	0.46	121	0.32	0.7477							
		rs10208708	102148981	G	C	0.16	83	-0.24	0.8075							
		rs10184523	102149040	A	G	0.16	87	-0.52	0.6061							
		rs1558641	102149405	A	G	0.16	87	-0.52	0.6061							
		rs1558640	102149418	A	G	0.16	87	-0.52	0.6061							
		rs35318065	102150172	A	C	0.16	82	-0.45	0.6560							
		rs3917225	102152842	G	A	0.46	120	0.19	0.8528							
		rs949963	102153326	T	C	0.16	86	-0.24	0.8121							
		rs871657	102154881	T	C	0.16	84	-0.24	0.8106							
		rs2287048	102157539	T	C	0.16	87	-0.52	0.6061							
		rs2287047	102157594	A	G	0.32	113	1.14	0.2525							
		rs3917254	102160058	A	G	0.07	48	2.02	0.0435	0.13	69	-1.23	0.2204	0.35	0.7247	+ -
		rs3917265	102162001	T	C	0.40	103	-0.07	0.9433							
		rs3917289	102165451	T	G	0.08	57	-0.91	0.3650							
		rs2160227	102166895	T	G	0.27	121	0.71	0.4771							
		rs3917296	102168373	G	A	0.08	61	1.34	0.1804							
		rs3917304	102171665	T	G	0.27	120	0.81	0.4202							
		rs3771200	102172314	A	G	0.46	126	0.23	0.8149							
		rs3171845	102174921	A	G	0.08	57	-0.91	0.3650							
		rs3917318	102176300	G	A	0.27	120	0.81	0.4202							
		rs2110726	102177822	A	G	0.40	122	0.92	0.3562							
		rs3732131	102178143	G	A	0.08	52	1.96	0.0503							
		rs3917329	102179403	T	G	0.08	56	-0.80	0.4250							
		rs6744454	102182692	G	A	0.14	73	-2.01	0.0446	0.18	90	-0.14	0.8876	-1.45	0.1473	--
		rs1030021	102185018	C	A	0.27	120	0.81	0.4202							
3	<i>IL1RAP</i>	rs766442	190505165	G	T	0.35	125	-0.02	0.9812							
		rs6800609	190516515	C	T	0.06	45	1.23	0.2184							
		rs9290935	190519562	C	T	0.25	114	1.04	0.2968							
		rs17196143	190520509	A	G	0.14	74	0.62	0.5345							
		rs9290936	190534846	T	G	0.12	71	0.65	0.5176							
		rs3773992	190535876	A	C	0.07	50	0.13	0.8964							
		rs9876152	190537403	T	C	0.07	51	0.00	1.0000							
		rs2361832	190542248	G	A	0.16	92	0.73	0.4669							
		rs997534	190542374	C	T	0.14	75	0.62	0.5345							
		rs3773990	190544263	A	G	0.07	55	0.11	0.9136							

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Supplementary Table E6. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P [†]	Freq	Fam	Z	P [†]	Z	P [†]	Dir [‡]
3	<i>IL1RAP</i>	rs3773989	190547640	G	A	0.50	120	0.13	0.8989							
		rs4686554	190556029	C	T	0.28	122	0.12	0.9061							
		rs16865597	190557756	C	T	0.12	67	1.12	0.2630							
		rs2885370	190559206	G	T	0.27	108	0.59	0.5571							
		rs3773986	190561126	A	G	0.08	53	-0.98	0.3264							
		rs3773982	190562263	A	G	0.17	92	0.24	0.8071							
		rs4687150	190563095	T	C	0.34	123	1.44	0.1504							
		rs2241343	190564925	G	T	0.12	68	0.23	0.8184							
		rs9877268	190568033	A	G	0.33	117	1.51	0.1319							
		rs3773976	190569496	G	T	0.12	78	-0.24	0.8125							
		rs10937439	190575766	G	A	0.38	125	1.82	0.0683							
		rs6801017	190577941	G	A	0.24	109	-1.28	0.1992							
		rs1559018	190579294	G	A	0.33	131	0.61	0.5453							
		rs1024940	190580192	G	A	0.34	128	0.54	0.5898							
		rs6444435	190586016	G	A	0.35	120	0.25	0.8033							
		rs3773967	190587229	T	C	0.21	101	1.05	0.2940							
		rs3773966	190587260	T	G	0.10	61	0.52	0.6002							
		rs10513854	190588085	T	C	0.19	92	-1.65	0.0996							
		rs7628250	190590738	G	A	0.28	110	0.67	0.5000							
		rs3773958	190591814	C	A	0.21	100	-2.49	0.0127	0.20	96	-0.59	0.5534	-2.20	0.0281	--
		rs2193874	190600737	G	A	0.39	128	1.74	0.0822							
		rs2193875	190603667	C	T	0.35	129	0.61	0.5421							
		rs6781037	190609732	G	A	0.36	132	0.72	0.4743							
		rs12636004	190611402	A	G	0.40	132	1.69	0.0907							
		rs9290939	190616087	A	G	0.08	52	0.00	1.0000							
		rs4687161	190623503	C	T	0.39	127	1.72	0.0864							
		rs4687163	190623650	G	A	0.35	124	0.78	0.4367							
		rs6444444	190628442	A	G	0.13	77	2.75	0.0060	0.15	88	-0.68	0.4995	1.38	0.1668	+-
		rs2885373	190628679	T	C	0.13	77	2.75	0.0060	0.15	88	-0.68	0.4995	1.38	0.1668	+-
		rs7626795	190632672	G	A	0.18	98	-1.65	0.0996							
		rs4320092	190643226	G	T	0.22	116	0.56	0.5754							
5	<i>ERAP1</i>	rs28096	96773540	A	G	0.33	133	-0.35	0.7261							
		rs11135480	96774878	G	T	0.17	89	-0.20	0.8445							
		rs13160562	96775667	A	G	0.27	118	-0.30	0.7643							
		rs10515247	96776022	A	G	0.17	93	-0.19	0.8466							
		rs10515248	96776301	T	C	0.17	93	-0.19	0.8466							
		rs149078	96779489	A	G	0.27	119	0.05	0.9632							
		rs27042	96781236	A	G	0.33	122	0.04	0.9656							
		rs42398	96784751	C	T	0.16	102	0.16	0.8759							
		rs469783	96785820	C	T	0.49	140	2.01	0.0450	0.45	122	-0.81	0.4154	0.91	0.3629	+-
		rs10050860	96786506	T	C	0.22	101	-1.58	0.1132							
		rs13154629	96786754	T	C	0.21	97	-1.70	0.0894							
		rs30187	96788627	T	C	0.40	142	0.86	0.3888							
		rs27434	96793809	A	G	0.23	116	1.28	0.2009							
		rs26618	96795133	C	T	0.20	99	-1.48	0.1386							

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Supplementary Table E6. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P [†]	Freq	Fam	Z	P [†]	Z	P [†]	Dir [‡]
5	<i>ERAP1</i>	rs25866	96795334	A	C	0.27	122	0.32	0.7522							
		rs13173167	96795780	T	G	0.21	99	-1.69	0.0915							
		rs30333	96798532	A	G	0.10	64	0.73	0.4679							
		rs34753	96815208	C	T	0.27	114	1.69	0.0908							
	<i>IL13</i>	rs1295686	132660151	T	C	0.26	111	1.07	0.2827							
		rs20541	132660272	A	G	0.26	111	1.24	0.2162							
		rs2243204	132663802	T	C	0.10	70	2.35	0.0190	0.10	73	-0.47	0.6381	1.31	0.1920	+-
		rs2243300	132668394	T	G	0.09	60	1.65	0.0990							
11	<i>SPI1</i>	rs3729989	47348490	C	T	0.13	74	0.54	0.5880							
		rs2697920	47349056	T	C	0.32	111	-0.15	0.8815							
		rs3740689	47359042	G	A	0.47	132	3.00	0.0027	0.38	153	0.40	0.6868	2.34	0.0195	++
		rs10769258	47369488	C	T	0.32	119	-0.74	0.4593							
	<i>BACE1</i>	rs11606287	47385888	A	C	0.38	116	-1.70	0.0900							
		rs505045	117281824	G	T	0.38	138	0.83	0.4068							
		rs7083	117285836	T	C	0.38	138	0.83	0.4068							
		rs522843	117305218	C	T	0.29	118	-2.65	0.0081	0.33	122	-0.52	0.6036	-2.23	0.0260	--
	<i>IFNG</i>	rs687740	117306887	C	A	0.40	137	1.90	0.0573							
		rs473210	117307084	T	C	0.37	126	-3.33	0.0009	0.41	119	-0.46	0.6482	-2.71	0.0068	--
		rs551662	117308287	C	T	0.10	70	-0.60	0.5485							
		rs676134	117309175	T	C	0.39	144	-1.13	0.2588							
12	<i>IFNG</i>	rs560564	117324912	C	A	0.40	128	-2.04	0.0414	0.38	123	-0.80	0.4224	-2.02	0.0436	--
		rs2193045	68140740	A	G	0.29	129	-2.14	0.0320	0.27	129	0.19	0.8522	-1.38	0.1663	+-
		rs12369470	68151116	C	T	0.06	48	0.63	0.5287							
		rs2069727	68154443	C	T	0.40	137	1.87	0.0611							
	<i>MMP2</i>	rs2069718	68156382	A	G	0.45	143	-2.15	0.0316	0.38	132	0.19	0.8502	-1.42	0.1559	+-
		rs1005913	55470609	G	T	0.28	118	-1.15	0.2506							
		rs1347653	55471128	T	G	0.10	59	0.86	0.3883							
		rs16955194	55471416	A	G	0.06	47	-0.62	0.5351							
16	<i>MMP2</i>	rs17301608	55484698	T	C	0.31	107	2.59	0.0095	0.37	138	1.92	0.0547	3.16	0.0016	++
		rs1053605	55485695	T	C	0.05	41	-1.87	0.0614							
		rs9302671	55487813	T	G	0.29	112	2.48	0.0131	0.35	140	1.79	0.0731	2.99	0.0028	++
		rs243842	55493510	C	T	0.43	120	-0.79	0.4294							
	<i>BACE2</i>	rs183112	55493770	A	G	0.16	89	-1.25	0.2126							
		rs1992116	55493979	A	G	0.39	120	1.33	0.1847							
		rs243840	55494247	G	A	0.18	92	-1.17	0.2410							
		rs243834	55502775	A	G	0.50	135	1.49	0.1365							
21	<i>BACE2</i>	rs1861320	55507128	T	G	0.45	133	1.78	0.0744							
		rs8054459	55510637	G	A	0.49	135	-1.80	0.0715							
		rs2410404	41157981	T	G	0.07	42	1.55	0.1213							
		rs2016240	41158333	T	C	0.21	114	0.47	0.6394							
	<i>BACE2</i>	rs7276900	41160148	A	C	0.32	113	-0.39	0.7001							
		rs6517653	41162326	A	C	0.22	114	0.31	0.7533							
		rs766850	41174890	T	C	0.16	77	-0.28	0.7833							
		rs4818219	41175967	G	A	0.24	110	-0.14	0.8858							
	<i>BACE2</i>	rs8130833	41184958	G	A	0.30	119	-0.32	0.7473							

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Supplementary Table E6. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P [†]	Freq	Fam	Z	P [†]	Z	P [†]	Dir [‡]
21	BACE2	rs914185	41195210	T	C	0.20	90	-1.82	0.0691							
		rs2837965	41195710	T	G	0.31	115	-1.16	0.2475							
		rs16998096	41195981	G	T	0.08	51	-0.31	0.7593							
		rs750445	41200417	C	A	0.15	90	0.67	0.5058							
		rs4816713	41202257	T	C	0.14	84	0.14	0.8875							
		rs2837967	41205037	A	G	0.21	116	-1.29	0.1962							
		rs746064	41209521	A	G	0.33	123	-2.42	0.0157	0.39	134	-0.73	0.4642	-2.20	0.0278	--
		rs7510366	41210000	T	C	0.05	26	0.32	0.7456							
		rs914178	41210260	A	G	0.27	120	-1.75	0.0797							
		rs6517656	41211811	A	G	0.15	95	-1.31	0.1904							
		rs9983496	41214203	C	T	0.38	122	-2.10	0.0358	0.44	139	-1.10	0.2712	-2.24	0.0252	--
		rs914183	41214568	G	A	0.11	72	-0.75	0.4530							
		rs17175402	41215505	T	C	0.11	60	2.40	0.0164	0.07	50	1.17	0.2436	2.56	0.0105	++
		rs2837970	41219684	A	G	0.32	121	-1.65	0.0988							
		rs7280770	41223963	A	G	0.13	85	-0.55	0.5807							
		rs7278856	41226960	G	T	0.24	114	-0.88	0.3789							
		rs2837974	41230808	G	A	0.11	56	-0.32	0.7505							
		rs2009135	41236304	G	A	0.33	127	0.56	0.5754							
		rs1541103	41241417	G	A	0.38	137	-0.50	0.6157							
		rs2252576	41243366	T	C	0.24	110	0.59	0.5574							
		rs2837981	41244078	C	T	0.24	104	1.55	0.1206							
		rs2837983	41244830	A	G	0.21	100	-1.31	0.1910							
		rs2837985	41245829	G	A	0.10	72	-0.55	0.5818							
		rs3827211	41247327	A	G	0.49	136	-0.13	0.9008							
		rs2837988	41247617	A	C	0.35	126	0.18	0.8572							
		rs914187	41247822	T	C	0.37	128	1.25	0.2132							
		rs2837990	41248222	A	G	0.17	98	-1.21	0.2270							
		rs2837992	41248593	T	C	0.37	126	1.77	0.0763							
		rs960230	41250552	A	G	0.24	106	1.76	0.0781							
		rs1046210	41250859	T	C	0.41	128	-1.16	0.2472							
		rs9975388	41254435	C	A	0.37	124	1.96	0.0496	0.35	113	2.11	0.0350	2.88	0.0040	++
		rs2837997	41257725	T	C	0.08	54	-0.51	0.6115							
		rs3787944	41257817	T	G	0.06	45	-0.78	0.4386							
		rs4818225	41257968	A	G	0.33	118	1.19	0.2355							
		rs2837998	41258166	G	A	0.40	131	1.38	0.1683							
		rs4818226	41261138	A	G	0.31	117	0.82	0.4148							
		rs726980	41263749	A	G	0.13	75	-0.19	0.8514							
		rs7277420	41265288	T	C	0.11	74	0.39	0.6949							
		rs2410415	41269475	C	T	0.19	101	1.09	0.2743							
		rs6517659	41270055	T	C	0.16	93	0.67	0.5050							
		rs8133778	41270111	A	G	0.27	118	0.44	0.6581							
		rs12483323	41271918	T	C	0.15	79	1.00	0.3173							
		rs2838000	41274591	A	G	0.21	105	0.48	0.6338							
		rs2838002	41276840	C	T	0.27	118	0.37	0.7127							
		rs8126886	41280790	T	C	0.12	64	0.10	0.9215							

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Supplementary Table E6. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	<i>P</i> [†]	Freq	Fam	Z	<i>P</i> [†]	Z	<i>P</i> [†]	Dir [‡]
21	<i>BACE2</i>	rs1964927	41281310	A	G	0.37	130	1.03	0.3024							
		rs2838006	41281640	T	C	0.36	128	1.16	0.2451							
		rs2297277	41282721	A	G	0.48	126	-1.62	0.1056							
		rs1072869	41285621	C	A	0.32	126	-0.14	0.8886							

Abbreviations used: A1=minor allele; A2=major allele; Chr=chromosome; EGEA=the French Epidemiological Study on the Genetics and Environment of Asthma; Fam=number of trios involved in the analysis; Freq=frequency of the minor allele; SLSJ=the French Canadian Saguenay—Lac-Saint-Jean asthma familial collection. *Chromosomes, gene names and location according to the UCSC Genome Browser assembly ID hg38; [†]*P*values in italics are those below 0.05 and *P*values in italics and bold are those below the statistical threshold for the discovery study ($P \leq 0.0003$) or the replication study and the combined analysis ($P \leq 0.0030$); [‡]A positive direction "+" indicates an over transmission of the minor allele to asthmatic individuals and negative effect "-" an under transmission of the minor allele to asthmatic individuals.

Supplementary Table E7. Association results for the 184 SNPs that fulfilled all quality criteria and atopy phenotype

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P ^t	Freq	Fam	Z	P ^t	Z	P ^t	Dir [†]
2	<i>IL1R1</i>	rs7580384	102144258	G	A	0.43	126	1.10	0.2697							
		rs11883987	102144780	C	T	0.38	128	-1.07	0.2871							
		rs11123911	102145078	T	C	0.17	94	2.79	0.0052	0.16	112	-1.11	0.2652	1.07	0.2867	+-
		rs4851547	102145307	A	C	0.46	117	-0.86	0.3906							
		rs10187031	102146734	C	T	0.16	91	-0.57	0.5715							
		rs13001315	102146750	A	G	0.16	95	2.39	0.0170	0.15	110	-1.40	0.1614	0.60	0.5493	+-
		rs13035227	102147377	C	T	0.16	94	2.47	0.0134	0.15	111	-1.53	0.1263	0.55	0.5821	+-
		rs1558642	102147500	T	G	0.19	100	0.31	0.7604							
		rs2110727	102147834	A	G	0.16	89	-0.41	0.6821							
		rs6754776	102148318	G	C	0.16	96	2.51	0.0119	0.15	111	-1.53	0.1263	0.59	0.5535	+-
		rs4851000	102148557	C	T	0.46	120	-1.19	0.2359							
		rs10208708	102148981	G	C	0.16	87	-0.25	0.8059							
		rs10184523	102149040	A	G	0.16	91	-0.57	0.5715							
		rs1558641	102149405	A	G	0.16	91	-0.57	0.5715							
		rs1558640	102149418	A	G	0.16	91	-0.57	0.5715							
		rs35318065	102150172	A	C	0.16	85	-0.34	0.7316							
		rs3917225	102152842	G	A	0.46	119	-1.32	0.1867							
		rs949963	102153326	T	C	0.16	91	-0.24	0.8119							
		rs871657	102154881	T	C	0.16	88	-0.16	0.8728							
		rs2287048	102157539	T	C	0.16	91	-0.57	0.5715							
		rs2287047	102157594	A	G	0.32	120	1.52	0.1275							
		rs3917254	102160058	A	G	0.07	50	2.09	0.0370	0.13	104	-1.04	0.2996	0.34	0.7370	+-
		rs3917265	102162001	T	C	0.40	104	-0.64	0.5254							
		rs3917289	102165451	T	G	0.08	62	-0.76	0.4497							
		rs2160227	102166895	T	G	0.27	117	0.06	0.9514							
		rs3917296	102168373	G	A	0.08	65	0.65	0.5139							
		rs3917304	102171665	T	G	0.27	116	0.18	0.8538							
		rs3771200	102172314	A	G	0.46	124	0.00	1.0000							
		rs3171845	102174921	A	G	0.08	62	-0.84	0.4013							
		rs3917318	102176300	G	A	0.27	116	0.18	0.8538							
		rs2110726	102177822	A	G	0.40	124	-0.06	0.9529							
		rs3732131	102178143	G	A	0.08	52	1.68	0.0939							
		rs3917329	102179403	T	G	0.08	61	-0.75	0.4537							
		rs6744454	102182692	G	A	0.14	77	-0.91	0.3610							
		rs1030021	102185018	C	A	0.27	116	0.18	0.8538							
3	<i>IL1RAP</i>	rs766442	190505165	G	T	0.35	125	0.12	0.9035							
		rs6800609	190516515	C	T	0.06	45	1.50	0.1333							
		rs9290935	190519562	C	T	0.25	119	0.68	0.4959							
		rs17196143	190520509	A	G	0.14	75	-0.42	0.6759							
		rs9290936	190534846	T	G	0.12	71	0.00	1.0000							
		rs3773992	190535876	A	C	0.07	48	-0.70	0.4855							
		rs9876152	190537403	T	C	0.07	49	-0.81	0.4189							
		rs2361832	190542248	G	A	0.16	90	0.45	0.6565							
		rs997534	190542374	C	T	0.14	72	0.34	0.7371							
		rs3773990	190544263	A	G	0.07	52	-1.07	0.2864							

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Supplementary Table E7. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P†	Freq	Fam	Z	P†	Z	P†	Dir†
3	<i>IL1RAP</i>	rs3773989	190547640	G	A	0.50	126	-0.79	0.4280							
		rs4686554	190556029	C	T	0.28	123	0.00	1.0000							
		rs16865597	190557756	C	T	0.12	64	1.20	0.2294							
		rs2885370	190559206	G	T	0.27	113	0.19	0.8510							
		rs3773986	190561126	A	G	0.08	51	-1.10	0.2737							
		rs3773982	190562263	A	G	0.17	105	0.34	0.7319							
		rs4687150	190563095	T	C	0.34	133	0.99	0.3203							
		rs2241343	190564925	G	T	0.12	73	0.00	1.0000							
		rs9877268	190568033	A	G	0.33	121	1.19	0.2353							
		rs3773976	190569496	G	T	0.12	70	-1.13	0.2568							
		rs10937439	190575766	G	A	0.38	129	1.17	0.2441							
		rs6801017	190577941	G	A	0.24	113	-1.69	0.0902							
		rs1559018	190579294	G	A	0.33	133	1.11	0.2680							
		rs1024940	190580192	G	A	0.34	129	0.94	0.3457							
		rs6444435	190586016	G	A	0.35	126	0.86	0.3924							
		rs3773967	190587229	T	C	0.21	101	1.55	0.1213							
		rs3773966	190587260	T	G	0.10	57	0.40	0.6862							
		rs10513854	190588085	T	C	0.19	91	-1.66	0.0961							
		rs7628250	190590738	G	A	0.28	113	0.12	0.9052							
		rs3773958	190591814	C	A	0.21	113	-1.36	0.1741							
		rs2193874	190600737	G	A	0.39	130	0.88	0.3770							
		rs2193875	190603667	C	T	0.35	133	0.06	0.9560							
		rs6781037	190609732	G	A	0.36	136	0.48	0.6294							
		rs12636004	190611402	A	G	0.40	135	1.13	0.2606							
		rs9290939	190616087	A	G	0.08	48	-0.32	0.7477							
		rs4687161	190623503	C	T	0.39	132	0.46	0.6469							
		rs4687163	190623650	G	A	0.35	130	-0.11	0.9123							
		rs6444444	190628442	A	G	0.13	81	2.59	0.0096	0.15	119	0.02	0.9826	1.67	0.0957	++
		rs2885373	190628679	T	C	0.13	81	2.65	0.0081	0.15	119	0.02	0.9826	1.70	0.0887	++
		rs7626795	190632672	G	A	0.18	100	-2.06	0.0394	0.14	123	1.19	0.2342	-0.50	0.6197	-+
		rs4320092	190643226	G	T	0.22	118	0.50	0.6143							
5	<i>ERAP1</i>	rs28096	96773540	A	G	0.33	137	-0.37	0.7109							
		rs11135480	96774878	G	T	0.17	93	-0.15	0.8774							
		rs13160562	96775667	A	G	0.27	118	-0.76	0.4479							
		rs10515247	96776022	A	G	0.17	95	-0.31	0.7590							
		rs10515248	96776301	T	C	0.17	96	-0.23	0.8185							
		rs149078	96779489	A	G	0.27	129	-0.31	0.7551							
		rs27042	96781236	A	G	0.33	127	-0.12	0.9028							
		rs42398	96784751	C	T	0.16	104	0.14	0.8886							
		rs469783	96785820	C	T	0.49	136	1.48	0.1386							
		rs10050860	96786506	T	C	0.22	100	-1.37	0.1714							
		rs13154629	96786754	T	C	0.21	96	-1.47	0.1425							
		rs30187	96788627	T	C	0.40	142	0.78	0.4380							
		rs27434	96793809	A	G	0.23	116	1.13	0.2576							
		rs26618	96795133	C	T	0.20	100	-1.83	0.0675							

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Supplementary Table E7. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P†	Freq	Fam	Z	P†	Z	P†	Dir†
5	ERAP1	rs25866	96795334	A	C	0.27	117	0.74	0.4619							
		rs13173167	96795780	T	G	0.21	98	-1.54	0.1226							
		rs30333	96798532	A	G	0.10	65	2.07	0.0385	0.08	74	-0.96	0.3349	0.71	0.4769	+ -
		rs34753	96815208	C	T	0.27	117	1.95	0.0508							
	IL13	rs1295686	132660151	T	C	0.26	108	0.92	0.3601							
		rs20541	132660272	A	G	0.26	107	1.13	0.2592							
		rs2243204	132663802	T	C	0.10	70	1.69	0.0918							
		rs2243300	132668394	T	G	0.09	60	1.21	0.2254							
11	SPI1	rs3729989	47348490	C	T	0.13	74	0.94	0.3484							
		rs2697920	47349056	T	C	0.32	119	-1.06	0.2889							
		rs3740689	47359042	G	A	0.47	148	2.52	0.0119	0.38	211	0.41	0.6827	1.93	0.0538	++
		rs10769258	47369488	C	T	0.32	135	-0.45	0.6517							
	BACE1	rs11606287	47385888	A	C	0.38	125	-1.68	0.0928							
		rs505045	117281824	G	T	0.38	158	-0.22	0.8297							
		rs7083	117285836	T	C	0.38	158	-0.22	0.8297							
		rs522843	117305218	C	T	0.29	131	-1.83	0.0673							
		rs687740	117306887	C	A	0.40	154	0.62	0.5338							
		rs473210	117307084	T	C	0.37	142	-2.36	0.0182	0.41	192	-0.26	0.7977	-1.73	0.0829	--
		rs551662	117308287	C	T	0.10	78	-0.08	0.9360							
		rs676134	117309175	T	C	0.39	155	-0.71	0.4750							
12	IFNG	rs560564	117324912	C	A	0.40	138	-0.99	0.3247							
		rs2193045	68140740	A	G	0.29	132	-1.93	0.0542							
		rs12369470	68151116	C	T	0.06	48	1.57	0.1159							
		rs2069727	68154443	C	T	0.40	148	1.86	0.0633							
		rs2069718	68156382	A	G	0.45	147	-2.06	0.0396	0.38	205	0.80	0.4234	-0.72	0.4722	- +
16	MMP2	rs1005913	55470609	G	T	0.28	120	-0.98	0.3266							
		rs1347653	55471128	T	G	0.10	60	0.89	0.3752							
		rs16955194	55471416	A	G	0.06	45	-0.76	0.4477							
		rs17301608	55484698	T	C	0.31	114	1.92	0.0555							
		rs1053605	55485695	T	C	0.05	38	-0.51	0.6115							
		rs9302671	55487813	T	G	0.29	121	1.82	0.0682							
		rs243842	55493510	C	T	0.43	127	-1.13	0.2596							
		rs183112	55493770	A	G	0.16	86	-1.04	0.2971							
		rs1992116	55493979	A	G	0.39	126	1.43	0.1542							
		rs243840	55494247	G	A	0.18	94	-0.92	0.3559							
		rs243834	55502775	A	G	0.50	138	1.52	0.1278							
		rs1861320	55507128	T	G	0.45	135	1.72	0.0851							
		rs8054459	55510637	G	A	0.49	136	-2.06	0.0396	0.43	204	0.38	0.7052	-1.01	0.3133	- +
21	BACE2	rs2410404	41157981	T	G	0.07	45	1.04	0.2987							
		rs2016240	41158333	T	C	0.21	119	0.21	0.8324							
		rs7276900	41160148	A	C	0.32	119	0.19	0.8527							
		rs6517653	41162326	A	C	0.22	119	0.00	1.0000							
		rs766850	41174890	T	C	0.16	86	-1.19	0.2356							
		rs4818219	41175967	G	A	0.24	112	-1.04	0.2963							
		rs8130833	41184958	G	A	0.30	125	-0.74	0.4590							

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Supplementary Table E7. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	P [†]	Freq	Fam	Z	P [†]	Z	P [†]	Dir [‡]
21	<i>BACE2</i>	rs914185	41195210	T	C	0.20	97	-1.43	0.1533							
		rs2837965	41195710	T	G	0.31	115	-1.29	0.1971							
		rs16998096	41195981	G	T	0.08	57	-0.97	0.3317							
		rs750445	41200417	C	A	0.15	90	0.49	0.6265							
		rs4816713	41202257	T	C	0.14	89	-0.45	0.6529							
		rs2837967	41205037	A	G	0.21	116	-0.70	0.4817							
		rs746064	41209521	A	G	0.33	119	-1.41	0.1573							
		rs7510366	41210000	T	C	0.05	29	-0.51	0.6115							
		rs914178	41210260	A	G	0.27	120	-0.73	0.4634							
		rs6517656	41211811	A	G	0.15	94	-0.66	0.5101							
		rs9983496	41214203	C	T	0.38	118	-1.29	0.1968							
		rs914183	41214568	G	A	0.11	77	-0.30	0.7653							
		rs17175402	41215505	T	C	0.11	65	1.77	0.0776							
		rs2837970	41219684	A	G	0.32	125	-1.30	0.1930							
		rs7280770	41223963	A	G	0.13	85	-0.57	0.5715							
		rs7278856	41226960	G	T	0.24	120	-0.58	0.5605							
		rs2837974	41230808	G	A	0.11	57	0.19	0.8514							
		rs2009135	41236304	G	A	0.33	136	-0.43	0.6684							
		rs1541103	41241417	G	A	0.38	147	-0.96	0.3381							
		rs2252576	41243366	T	C	0.24	115	-0.27	0.7883							
		rs2837981	41244078	C	T	0.24	110	0.14	0.8897							
		rs2837983	41244830	A	G	0.21	108	-1.19	0.2328							
		rs2837985	41245829	G	A	0.10	75	-0.47	0.6381							
		rs3827211	41247327	A	G	0.49	141	-1.22	0.2230							
		rs2837988	41247617	A	C	0.35	129	-0.43	0.6684							
		rs914187	41247822	T	C	0.37	133	-0.12	0.9071							
		rs2837990	41248222	A	G	0.17	100	-1.21	0.2278							
		rs2837992	41248593	T	C	0.37	133	0.89	0.3743							
		rs960230	41250552	A	G	0.24	109	0.87	0.3829							
		rs1046210	41250859	T	C	0.41	138	-0.11	0.9090							
		rs9975388	41254435	C	A	0.37	133	1.00	0.3190							
		rs2837997	41257725	T	C	0.08	60	0.00	1.0000							
		rs3787944	41257817	T	G	0.06	52	-0.78	0.4367							
		rs4818225	41257968	A	G	0.33	127	0.29	0.7717							
		rs2837998	41258166	G	A	0.40	139	0.30	0.7647							
		rs4818226	41261138	A	G	0.31	126	-0.12	0.9065							
		rs726980	41263749	A	G	0.13	84	0.00	1.0000							
		rs7277420	41265288	T	C	0.11	76	0.44	0.6622							
		rs2410415	41269475	C	T	0.19	101	0.76	0.4467							
		rs6517659	41270055	T	C	0.16	99	0.65	0.5192							
		rs8133778	41270111	A	G	0.27	125	-0.07	0.9484							
		rs12483323	41271918	T	C	0.15	84	0.24	0.8119							
		rs2838000	41274591	A	G	0.21	106	-0.21	0.8307							
		rs2838002	41276840	C	T	0.27	126	-0.06	0.9491							
		rs8126886	41280790	T	C	0.12	74	-0.66	0.5079							

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Supplementary Table E7. Continued

Chr*	Gene*	Marker	Location*	A1	A2	SLSJ				EGEA				Combined		
						Freq	Fam	Z	<i>P</i> [†]	Freq	Fam	Z	<i>P</i> [†]	Z	<i>P</i> [†]	Dir [‡]
21	<i>BACE2</i>	rs1964927	41281310	A	G	0.37	134	-0.29	0.7732							
		rs2838006	41281640	T	C	0.36	132	-0.17	0.8623							
		rs2297277	41282721	A	G	0.48	131	-0.45	0.6547							
		rs1072869	41285621	C	A	0.32	133	-0.81	0.4210							

Abbreviations used: A1=minor allele; A2=major allele; Chr=chromosome; EGEA=the French Epidemiological Study on the Genetics and Environment of Asthma; Fam=number of trios involved in the analysis; Freq=frequency of the minor allele; SLSJ=the French Canadian Saguenay—Lac-Saint-Jean asthma familial collection. *Chromosomes, gene names and location according to the UCSC Genome Browser assembly ID hg38; [†]*P*values in italics are those below 0.05 and *P*values in italics and bold are those below the statistical threshold for the discovery study ($P \leq 0.0003$) or the replication study and the combined analysis ($P \leq 0.0056$); [‡]A positive direction "+" indicates an over transmission of the minor allele to asthmatic individuals and negative effect "-" an under transmission of the minor allele to asthmatic individuals.