

Supplementary Appendix

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Supplementary Appendix

Effect of 17q21 Variants and Smoking Exposure in Early-onset Asthma

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SUPPLEMENTARY INFORMATION

METHODS

Study Population and data collected

Subjects were enrolled between 1991 and 1995 in the EGEA study, a French epidemiological survey on the environmental and genetic factors of asthma, bronchial hyperresponsiveness and atopy. Written informed consent was obtained from all subjects participating to the study under an Institutional Review Board-approved protocol. A total of 388 nuclear families was ascertained through 217 adult and 171 pediatric asthmatic probands (age at time of study varying from 7 to 65 years) followed-up in seven chest clinics of five French cities (Grenoble, Lyon, Marseille, Montpellier, Paris).^{1,2} Inclusion criteria used to define asthma in probands were based on self-reported answers to four questions: Have you ever had attacks of breathlessness at rest with wheezing? Have you ever had asthma attacks? Was this diagnosis confirmed by a physician? Have you had an asthma attack in the last 12 months?.¹ A self-completed questionnaire was used to avoid discordances among medical practices. All probands and their two parents had to be Caucasian and born in France. Probands, their first-degree relatives and spouses (total of 1,621 family members) were examined with a standard protocol, based on international standardized tools. All family members answered a detailed questionnaire, by face-to-face interview, regarding upper and lower airway symptoms, allergic symptoms, medical history and treatment, and environmental exposures based on British Medical Research Council (BMRC)/European Coal and Steel Community (ECSC), American Thoracic Society, and European Community Respiratory Health Survey (ECRHS) questionnaires. Based on the BMRC/ECSC questionnaire, asthma status was defined by answers to the two questions: Have you ever had attacks of breathlessness at rest with wheezing? Have you ever had asthma attacks?. For individuals who developed asthma, information on asthma age-of-onset was obtained from

adult asthmatics or parents of asthmatic children who answered to the following question: How old were you when you had your first asthma attack? or How old was your child when he (or she) had his (her) first asthma attack?. Environmental tobacco smoke (ETS) exposure in early-life was defined as follows: 1) in adults, by a positive answer to the question: did your mother or your father smoke during your early-childhood? 2) for children by a positive answer to the question asked to the child's mother (or father): did you or the father (or the mother) of your child smoke when your child was less than 2 years of age?. We did not use information on *in-utero* exposure to tobacco-smoke since it did not add any additional information to ETS exposure in early life (all mothers who smoked during pregnancy continued to smoke during the early childhood of their offspring). The questionnaire is accessible through internet (http://www.splf.org/rmr/depotElectronique/2001-10_Kauffmann/Kauffmann2002.htm).

The four main associated-phenotypes that were examined included atopy, IgE levels, eosinophil counts and %FEV₁. Atopy was defined as a positive skin prick test response (corresponding to a wheal size minus the negative control ≥ 3 mm) to at least one of the 11 allergens tested (including moulds, indoors and outdoors allergens). Total serum IgE levels were measured by radioimmunoassay (Phadebas PRIST technique; Pharmacia diagnostics, AB, France) in one central laboratory (Pasteur Institute, Lyon). Total eosinophil count was performed using standard procedures. Spirometric measures were carried out for all subjects above 7 years of age according to the European Respiratory Health Survey protocol.³ The best of three FEV₁ measures was used to calculate a percentage of predicted FEV₁ values (%FEV₁) based on age, height and gender.^{4,5} We did not consider the bronchial hyper-responsiveness phenotype since the methacholine challenge test could not be conducted in 51% of asthmatics because of altered lung function and this could bias the results.

Genotyping and quality-control filtering

From the total sample of 1,621 individuals, 1,543 subjects with DNA available were genotyped for 38 SNPs located between 35.23 and 35.38 Mb on chromosome 17q21. This SNP panel included the key SNPs reported to be associated with asthma in Moffatt et al.⁶ plus a set of SNPs from the region of strongest association reported in the supplementary data from Moffatt et al.⁶ to provide additional information for association and to examine linkage disequilibrium (LD) patterns. Genotyping was performed on an ABI7900HT Sequence Detection System using Taqman Probes (Applied Biosystems, Foster City, California) at the Centre National de Génotypage (CNG, Evry, France).

Consistency of the SNP data with Mendelian inheritance was evaluated using the PEDCHECK program.⁷ Test of Hardy-Weinberg equilibrium was performed using an exact test.⁸ No SNP showed Hardy-Weinberg disequilibrium (Supplementary Table 1). We eliminated two SNPs with minor allele frequency less than 5%. After quality control, the final sample for the present analysis included 36 SNPs genotyped in 1,511 subjects from 372 families comprising 708 genotyped parents and 803 genotyped offspring.

Statistical Methods

Association between each SNP and asthma was investigated using a recently proposed likelihood-based method^{9,10} that allows the joint analysis of parents and offspring's phenotypes and genotypes from families of arbitrary size, mode of selection and disease-status configuration and is thus well suited to the EGEA family data. The mode of ascertainment of the families is taken into account by conditioning the likelihood on affection status (retrospective likelihood). This retrospective likelihood provides unbiased parameter estimates and valid tests even if there are additional genetic or environmental factors inducing correlations between family members.¹⁰ Association between asthma and each marker is

evaluated by use of a likelihood-ratio statistic, $T = 2\ln(L_{LD}) - 2\ln(L_{UL})$, which compares the likelihood (L_{UL}) maximized under the null hypothesis of no linkage and no association between SNP and disease locus and the likelihood (L_{LD}) maximized under the alternative hypothesis of complete linkage and complete linkage disequilibrium. Under the null model, L_{UL} is a function of the SNP allele frequency (q) while, under the alternative, L_{LD} is a function of the SNP allele frequency and three penetrances (f_{dd} , f_{Dd} , f_{DD} for each disease locus/SNP genotype, D being the risk allele). The allele frequency and penetrances are constrained to fit a specified disease prevalence in order to have identifiable parameters (the prevalence of asthma was set at 5%). We checked that changing the disease prevalence led to similar outcomes of the test and to similar estimates of the allele frequency and ratios of penetrances of heterozygotes and homozygotes carrying respectively one and two copies of the risk allele with respect to the baseline penetrance (homozygotes with no copy of risk allele). The test statistic, T , follows asymptotically a chi-square with 2 degrees of freedom when considering a general codominant model for the SNP effect and a chi-square with 1 degree of freedom (df) when a specific (dominant, recessive or multiplicative) model is assumed. Each specific model can be tested against the general model by a likelihood-ratio test which, asymptotically, follows a chi-square with 1 df. The strength of the association (SNP effect) was estimated by the ratio of penetrance for genotype(s) with the risk allele to the penetrance for the other genotype(s), depending on the genetic model. Alternative tests of association in presence of linkage were also considered, these tests being based on likelihood-ratio tests.⁹ We used primarily the former tests rather than the latter ones since they require estimating a smaller number of parameters and are more appropriate for samples including a higher proportion of families with single affected offspring than with two or more affected offspring (31% of families having two or more asthmatic sibs). Anyhow, we verified that the two types

of tests led to similar results. This method is implemented in the LAMP program (<http://www.sph.umich.edu/csg/abecasis/lamp>).

To investigate heterogeneity according to age-of-onset of asthma and to identify the cut-off point allowing us to classify patients into early-onset asthma and late-onset asthma for subsequent LAMP analysis, we conducted an ordered-subset regression analysis, based on the same principle as the ordered-subset analysis (OSA) proposed in the context of linkage analysis.¹¹ Asthmatic subjects were ranked according to their age at first asthma attack from less than 1 year to 57 years. Logistic regression analysis was carried out in ordered age-specific subsets, each subset including all unaffected subjects and affected subjects with age-of-onset less than or equal to the subset-specific age. A likelihood-ratio test (LRT) for association of asthma with SNP was computed in each subset. For each subset, we calculated Δ -LRT, defined as the difference between the LRT statistic obtained in that subset and the baseline LRT statistic obtained in the whole sample. We then identified the subset and corresponding age at which Δ -LRT was maximum (Δ -LRT_{max}). Significance of Δ -LRT_{max} was assessed by a permutation strategy where the affected subjects were randomly ordered. The P value was estimated by the proportion of 10,000 permutations giving Δ -LRT as large or larger than the one observed.

Since the ordered-subset regression analysis provided evidence for heterogeneity according to asthma age-of-onset, we applied two strategies to analyze and compare results in early-onset and late onset asthma by the LAMP-based approach. First, we examined disease in one age-of-onset category, all patients in the other category being assigned an unknown disease status. Second, we considered two independent family samples in which families were included only when all affected individuals in the offspring generation were in a single age-of-onset category to test formally for heterogeneity of SNP effect according to asthma age-of-onset. To test for heterogeneity of SNP effect between these two early and late-onset family

samples, we used a likelihood-ratio test which follows a chi-square with 3 df under a general codominant model for the SNP effect. Since there was significant evidence for genetic heterogeneity and SNPs were only significantly associated with early-onset asthma, specific models of SNP effect (recessive, multiplicative dominant) were only tested in the early-onset family sample. We found that the recessive model was the best fitting model.

To investigate genetic heterogeneity according to ETS exposure by the LAMP-based approach, we grouped families according to the exposure status of the offspring. Most families (91.2%) had either all their offspring exposed or unexposed, the remaining families being discarded from further analysis. Association analyses between early-onset asthma and 17q21 SNPs were performed, using LAMP, in the family sample with offspring concordant with respect to ETS exposure, in the families with ETS-exposed offspring and in the families with ETS-unexposed offspring. In these analyses, the parental affection status and early-life ETS exposure were assumed unknown. Tests of association of early-onset asthma with each variant were based on likelihood-ratio tests, as explained above. Significance for heterogeneity of association between exposed and unexposed families was assessed by a likelihood-ratio test. P-values were determined by a permutation strategy which randomly assigned exposure status of sibships among those having the same number of affected sibs; the sibship size distribution was similar between exposed and unexposed families. As the above analyses used phenotype and exposure information only from the offspring generation, we sought confirmation by testing for association between early-onset asthma and 17q21 SNPs in early-life ETS exposed and unexposed parents using Fisher's exact test.

Since several SNPs were associated with early-onset asthma, we used logistic regression to test for the effect of multiple markers on disease in a stepwise manner. Prior to conducting multiple regression analysis, we estimated linkage disequilibrium (LD) coefficients (D' and

r^2) among SNPs using Haploview.¹² We used the Tagger program¹³ within Haploview to select SNPs belonging to different LD groups (bins) to potentially enter the regression.

Association analysis of 17q21 markers with asthma associated-phenotypes was conducted in the offspring generation using logistic (binary phenotypes) or linear (quantitative phenotypes) regression models and taking into account familial clustering using Stata10.0. All regression models included the asthma affection status (unaffected, early-onset asthma and late-onset asthma) and other potential confounders such as gender and age.

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Supplementary Table 1. Minor allele frequency (MAF) and test of Hardy-Weinberg (HW) equilibrium (P value) for 36 SNPs at 17q21 locus investigated for association with asthma.

SNP*	Position (Mb)	Minor Allele Frequency	H-W Test P value
rs9303277	35.230	0.460	0.81
rs11557467	35.282	0.448	0.44
rs8069176	35.311	0.411	0.21
rs2305480	35.316	0.408	0.21
rs2305479	35.316	0.439	0.31
rs4795400	35.321	0.408	0.29
rs7216389	35.323	0.456	0.76
rs9303281	35.328	0.463	0.98
rs7219923	35.328	0.463	0.89
rs4378650	35.334	0.448	1.00
rs8076131	35.334	0.421	0.35
rs3744246	35.338	0.205	0.28
rs4795402	35.339	0.233	0.50
rs4795403	35.339	0.203	0.33
rs4795404	35.339	0.205	0.24
rs4795405	35.342	0.404	0.68
rs4794820	35.343	0.409	0.71
rs7207600	35.345	0.344	0.28
rs8079416	35.346	0.489	0.36
rs6503525	35.349	0.491	0.55
rs8065126	35.353	0.336	0.87
rs3893044	35.357	0.417	0.70
rs4795408	35.361	0.489	0.89
rs7209742	35.362	0.342	0.68
rs8076474	35.365	0.340	0.55
rs1007654	35.365	0.340	0.81
rs1007655	35.365	0.345	0.66
rs2313640	35.365	0.341	0.49
rs7218742	35.368	0.342	0.79
rs7218321	35.368	0.342	0.60
rs7219080	35.368	0.344	0.52
rs6503526	35.368	0.486	0.70
rs6503527	35.368	0.341	0.53
rs3894194	35.376	0.491	0.50
rs7212938	35.376	0.454	0.99
rs3859192	35.382	0.478	0.47

* Two SNPs from the panel of 38 genotyped SNPs had MAF < 5% and were eliminated from the analysis.

Supplementary Table 2. Tests of association of asthma with 36 SNPs at 17q21 locus using a likelihood-based method implemented in the LAMP program⁹

SNP	Position (Mb)	Test of association *
		P value
rs9303277	35.230	0.002
rs11557467	35.282	0.004
rs8069176	35.311	2.1x10 ⁻⁴
rs2305480	35.316	1.4x10 ⁻⁴
rs2305479	35.316	0.005
rs4795400	35.321	9.4x10 ⁻⁴
rs7216389	35.323	0.03
rs9303281	35.328	0.005
rs7219923	35.328	0.009
rs4378650	35.334	0.02
rs8076131	35.334	0.003
rs3744246	35.338	0.05
rs4795402	35.339	0.10
rs4795403	35.339	0.07
rs4795404	35.339	0.06
rs4795405	35.342	0.002
rs4794820	35.343	0.002
rs7207600	35.345	0.12
rs8079416	35.346	0.19
rs6503525	35.349	0.27
rs8065126	35.353	0.07
rs3893044	35.357	0.10
rs4795408	35.361	0.10
rs7209742	35.362	0.08
rs8076474	35.365	0.04
rs1007654	35.365	0.11
rs1007655	35.365	0.05
rs2313640	35.365	0.04
rs7218742	35.368	0.13
rs7218321	35.368	0.08
rs7219080	35.368	0.03
rs6503526	35.368	0.07
rs6503527	35.368	0.07
rs3894194	35.376	0.28
rs7212938	35.376	0.56
rs3859192	35.382	0.08

* P values are based on 2-degrees-of-freedom (df) likelihood-ratio tests under a general codominant model for SNP effect.

Supplementary Table 3. Tests of mode of inheritance of SNP effect on early-onset asthma against a general model in ETS-exposed families.

SNP*	Position (Mb)	Tested Models [†]		
		Recessive P-value	Multiplicative P-value	Dominant P-value
rs9303277	35.230	1.00	0.08	3.5x10 ⁻⁴
rs11557467	35.282	0.83	0.05	8.4x10 ⁻⁵
rs8069176	35.311	0.67	0.02	5.2x10 ⁻⁶
rs2305480	35.316	1.00	0.06	2.1x10 ⁻⁵
rs2305479	35.316	1.00	0.08	6.9x10 ⁻⁵
rs4795400	35.321	0.67	0.04	7.8x10 ⁻⁵
rs9303281	35.328	0.76	0.05	2.0x10 ⁻⁴
rs7219923	35.328	0.83	0.07	5.8x10 ⁻⁴
rs8076131	35.334	0.36	0.48	9.3x10 ⁻⁴
rs4795405	35.342	0.67	0.21	1.2x10 ⁻⁴
rs4794820	35.343	0.83	0.08	2.5x10 ⁻⁴

* The 11 SNPs shown in this table are those showing originally association with asthma at P<0.01.

[†] Tests are based on 1-df likelihood-ratio tests of each specific model against the general model.

Supplementary Table 4. Test of association of early-onset asthma with 17q21 SNPs in parents exposed and unexposed to ETS in early-life

SNP*	Position (Mb)	Parents exposed to ETS in early-life (N=345) [†]	Parents unexposed to ETS in early-life (N=144) [†]
		P-value [§]	P-value [§]
rs9303277	35.230	0.01	0.60
rs11557467	35.282	0.01	0.62
rs8069176	35.311	0.01	0.21
rs2305480	35.316	0.01	0.27
rs2305479	35.316	0.02	0.40
rs4795400	35.321	0.03	0.28
rs9303281	35.328	0.08	0.36
rs7219923	35.328	0.08	0.34
rs8076131	35.334	0.06	0.21
rs4795405	35.342	0.05	0.11
rs4794820	35.343	0.03	0.15

* The 11 SNPs shown in this table are those showing originally association with asthma at $P < 0.01$.

[†] N is the total number of parents (early-onset asthmatics and unaffected) in either the ETS-exposed or unexposed group.

[§] P-values are based on Fisher's exact test

Supplementary Table 5. Outcomes of tests of association of early-onset asthma and 36 SNPs at 17q21 locus in families with offspring concordant with respect to ETS exposure and in families with ETS-exposed offspring

SNP	Position (Mb)	Family sample with offspring concordant with respect to ETS exposure	Family sample with ETS exposed offspring
		P value*	P value*
rs9303277	35.230	1.8x10 ⁻⁵	1.6x10 ⁻⁴
rs11557467	35.282	4.0x10 ⁻⁵	3.9x10 ⁻⁵
rs8069176	35.311	2.0x10 ⁻⁵	2.8x10 ⁻⁶
rs2305480	35.316	5.4x10 ⁻⁵	8.7x10 ⁻⁶
rs2305479	35.316	2.6x10 ⁻⁵	2.4x10 ⁻⁵
rs4795400	35.321	3.4x10 ⁻⁴	5.3x10 ⁻⁵
rs7216389	35.323	2.6x10 ⁻⁴	3.3x10 ⁻⁴
rs9303281	35.328	7.1x10 ⁻⁵	1.1x10 ⁻⁴
rs7219923	35.328	1.4x10 ⁻⁴	3.3x10 ⁻⁴
rs4378650	35.334	8.4x10 ⁻⁴	2.1x10 ⁻⁴
rs8076131	35.334	5.1x10 ⁻⁴	1.7x10 ⁻⁴
rs3744246	35.338	0.03	0.017
rs4795402	35.339	0.033	0.073
rs4795403	35.339	0.029	0.017
rs4795404	35.339	0.035	0.017
rs4795405	35.342	3.8x10 ⁻⁴	2.9x10 ⁻⁵
rs4794820	35.343	5.4x10 ⁻⁴	1.3x10 ⁻⁴
rs7207600	35.345	0.006	0.0014
rs8079416	35.346	0.013	0.0015
rs6503525	35.349	0.013	0.028
rs8065126	35.353	0.007	0.0015
rs3893044	35.357	0.033	0.003
rs4795408	35.361	0.0094	0.036
rs7209742	35.362	0.0075	9.6x10 ⁻⁴
rs8076474	35.365	0.005	4.7x10 ⁻⁴
rs1007654	35.365	0.0083	0.0045
rs1007655	35.365	0.003	6.4x10 ⁻⁴
rs2313640	35.365	0.0042	8.2x10 ⁻⁴
rs7218742	35.368	0.0062	9.0x10 ⁻⁴
rs7218321	35.368	0.011	0.003
rs7219080	35.368	0.0028	6.4x10 ⁻⁴
rs6503526	35.368	0.0076	0.019
rs6503527	35.368	0.008	6.7x10 ⁻⁴
rs3894194	35.376	0.0083	0.02
rs7212938	35.376	0.13	0.0053
rs3859192	35.382	0.04	0.22

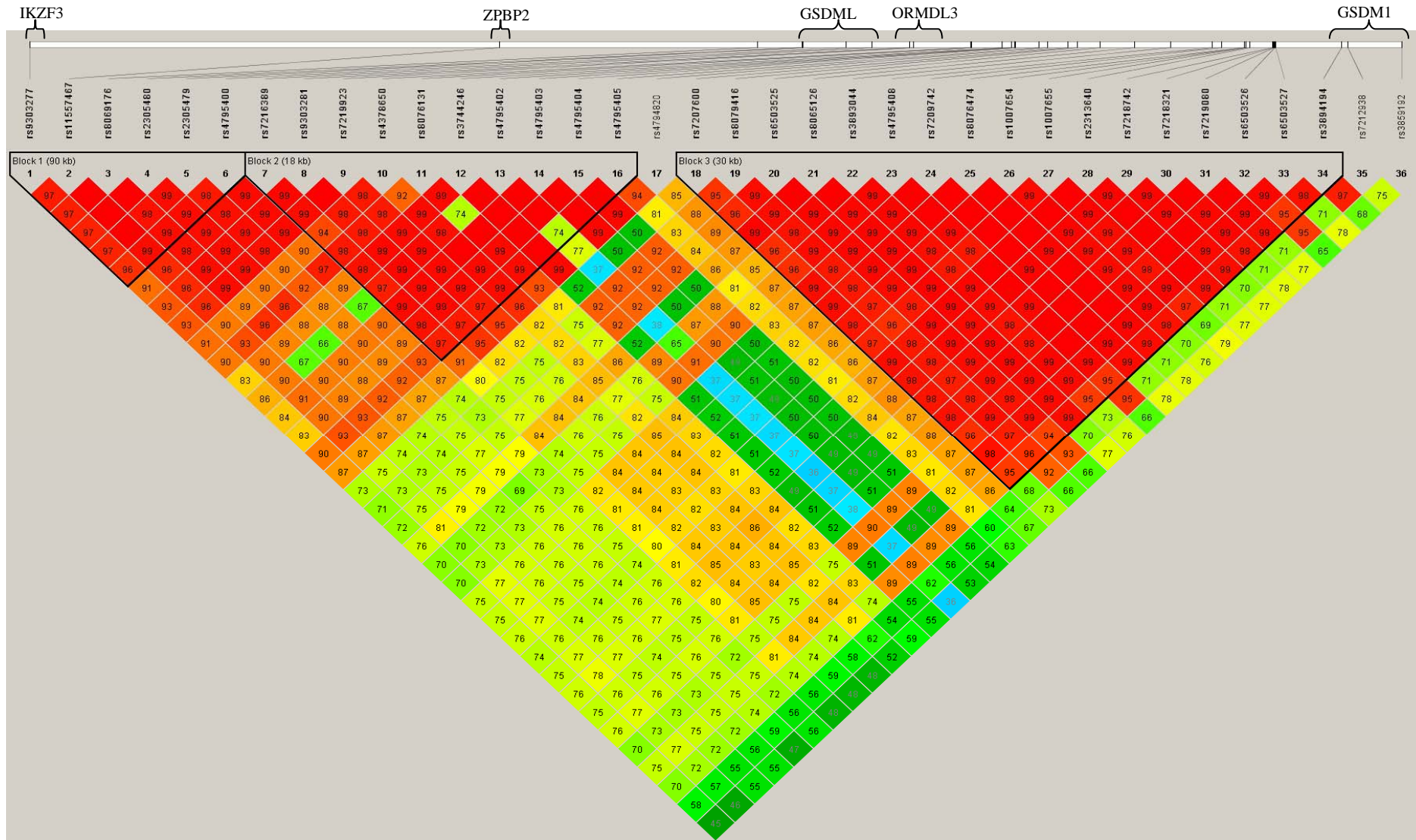
* P values are based on 1-df likelihood-ratio tests (using LAMP) under the best fitting recessive model for SNP effect

Supplement Table 6. Results of association analysis of 17q21 variants with asthma-related phenotypes

SNP	Position (Mb)	Atopy P value*	IgE P value*	Eosinophils P value*	%FEV₁ P value*
rs9303277	35.230	0.69	0.66	0.61	0.69
rs11557467	35.282	0.49	0.54	0.49	0.78
rs8069176	35.311	0.48	0.84	0.37	0.91
rs2305480	35.316	0.43	0.67	0.53	0.88
rs2305479	35.316	0.69	0.57	0.73	0.79
rs4795400	35.321	0.08	0.66	0.55	0.82
rs7216389	35.323	0.45	0.56	0.45	0.93
rs9303281	35.328	0.58	0.74	0.83	0.99
rs7219923	35.328	0.46	0.84	0.96	0.99
rs4378650	35.334	0.75	0.88	0.80	0.95
rs8076131	35.334	0.16	0.51	0.63	0.88
rs3744246	35.338	0.87	0.63	0.28	0.77
rs4795402	35.339	0.83	0.36	0.12	0.48
rs4795403	35.339	0.86	0.40	0.30	0.58
rs4795404	35.339	0.83	0.53	0.30	0.76
rs4795405	35.342	0.16	0.65	0.70	0.94
rs4794820	35.343	0.49	0.50	0.74	0.67
rs7207600	35.345	0.85	0.25	0.16	0.35
rs8079416	35.346	0.95	0.52	0.98	0.48
rs6503525	35.349	0.99	0.53	0.94	0.55
rs8065126	35.353	0.66	0.21	0.41	0.26
rs3893044	35.357	0.66	0.56	0.87	0.70
rs4795408	35.361	0.99	0.66	0.87	0.64
rs7209742	35.362	0.60	0.39	0.41	0.44
rs8076474	35.365	0.75	0.39	0.34	0.44
rs1007654	35.365	0.50	0.36	0.17	0.43
rs1007655	35.365	0.72	0.51	0.39	0.58
rs2313640	35.365	0.71	0.43	0.41	0.54
rs7218742	35.368	0.86	0.37	0.22	0.43
rs7218321	35.368	0.78	0.43	0.21	0.44
rs7219080	35.368	0.76	0.33	0.31	0.40
rs6503526	35.368	0.99	0.88	0.94	0.89
rs6503527	35.368	0.56	0.38	0.31	0.44
rs3894194	35.376	0.85	0.70	0.79	0.67
rs7212938	35.376	0.74	0.74	0.74	0.70
rs3859192	35.382	0.89	0.83	0.69	0.99

* P values are based on Wald-tests using logistic regression for atopy and linear regression for the other phenotypes (regression models are adjusted for asthma affection status, age and sex)

Supplementary Figure 1. Linkage disequilibrium between 36 SNPs at 17q21 locus (using Haploview¹²)



Genes are indicated on the white bar at their respective positions; SNPs positions are connected to SNP IDs by black lines
IKZF3: IKAROS family zinc finger 3, *ZPBP2*: zona pellucida binding protein 2, *GSDML* (also called *GSDMB*): gasdermin B,
ORMDL3: ORM1-like 3 (*S. cerevisiae*), *GSDM1*: gasdermin 1.