

Examination of the relationship between variation at 17q21 and childhood wheeze phenotypes

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Background: Genome-wide association studies have identified associations of genetic variants at 17q21 near *ORMDL3* with childhood asthma.

Objectives: We sought to determine whether associations in this region are specific to particular asthma phenotypes and specific to *ORMDL3*.

Methods: We examined associations between 244 independent single nucleotide polymorphisms (SNPs) plus 13 previously identified asthma-related SNPs in the region between 34 and 36 Mb on chromosome 17 and early wheezing phenotypes, doctor-diagnosed asthma and atopy at 7½ years, and bronchial hyperresponsiveness and lung function at 8½ years in 7045 children from the Avon Longitudinal Study of Parents and Children birth cohort study. With this, *cis* expression quantitative trait loci signals for the same SNPs were assessed in 875 samples across genes in the same region.

Results: The strongest evidence for phenotypic association was seen for persistent wheezing (rs8076131 near *ORMDL3*: relative risk ratio [RRR], 1.60 [95% CI, 1.40-1.84], $P = 1.4 \times 10^{-11}$; rs2305480 near *GSDML*: RRR, 1.60 [95% CI, 1.39-1.83], $P = 1.5 \times 10^{-11}$; and rs9303277 near *IKZF3*: RRR, 1.57 [95% CI, 1.37-1.79], $P = 4.4 \times 10^{-11}$). Similar but less precisely estimated effects were seen for intermediate-onset wheeze, but there was little evidence of associations with other wheezing phenotypes. There was some evidence of associations with bronchial

hyperresponsiveness. SNPs across the whole region show strong evidence of association with differential levels of expression at *GSDML*, *IKZF3*, and *MED24*, as well as *ORMDL3*.

Conclusions: Associations of SNPs in the 17q21 locus are specific to asthma and specific wheezing phenotypes and are not explained by associations with intermediate phenotypes, such as atopy or lung function. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Avon Longitudinal Study of Parents and Children, wheezing phenotypes, chromosome 17, *ORMDL3*, gene expression

Asthma is a complex disorder resulting from interactions of genes and environmental factors.^{1,2} Associations of candidate genes with asthma have been reported, but few were replicated in independent studies.³ Lack of replication can be explained in part by difficulties in defining the asthma phenotype and by gene-environment interactions leading to variable genetic expression in differing settings.⁴ Recently, a genome-wide association study (GWAS) identified multiple single nucleotide polymorphisms (SNPs) on locus 17q21 that were associated with asthma in several populations of European descent.⁵ The association of SNPs in this region with asthma has been replicated in similar⁶⁻⁹ and ethnically diverse^{10,11} populations. Most,⁶⁻⁸ but not all,¹² studies found that associations were stronger in patients with asthma beginning in early childhood.

Heterogeneity in early childhood wheezing illness and its association with subsequent asthma^{13,14} led us to describe¹⁵ and replicate¹⁶ phenotypes of wheezing during the first 7 years of childhood based on data from population-based birth cohort studies. These phenotypes are differentially associated with physician-diagnosed asthma, atopy, lung function, and bronchial responsiveness.¹⁵ Investigation of the biological origins of well-characterized asthma-related phenotypes is crucial to the better understanding of this often ill-defined clinical entity. Evidence points to early childhood as a critical period in asthma development,¹⁷ and therefore we aimed to assess the association of asthma-related phenotypes with a comprehensive set of common independent variants within the previously identified asthma-associated region of chromosome 17 and to examine the association of these variants with gene expression in the same region.

METHODS

Subjects

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal, population-based birth cohort study that recruited pregnant women residing in Avon, United Kingdom, with expected dates of delivery

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Abbreviations used

ALSPAC: Avon Longitudinal Study of Parents and Children
 BHR: Bronchial hyperresponsiveness
 FEF₂₅₋₇₅: Forced expiratory flow at 25% to 75% of FVC
 FVC: Forced vital capacity
 GWAS: Genome-wide association study
 LD: Linkage disequilibrium
 OR: Odds ratio
 PARF: Population-attributable risk fraction
 Q-Q: Quantile-quantile
 RRR: Relative risk ratio
 SNP: Single nucleotide polymorphism

from April 1, 1991, to December 31, 1992. The study methodology has been described in detail previously.¹⁸ Ethical approval was obtained from the ALSPAC Law and Ethics Committee and local research ethics committees.

Asthma outcomes and wheezing phenotypes

Reports of physician-diagnosed asthma ever were obtained from questionnaires sent to the mother when the child was aged 7½ years. Skin prick tests were performed in all participants at a research clinic at age 7½ years.¹⁹ A positive response was defined as a mean wheal diameter of greater than 2 mm with no response to negative control solution, and atopy was defined as a positive response to 1 or more of house dust mite, cat, or mixed grass. Spirometric results in all participants and bronchial responsiveness to methacholine were measured in a research clinic at age 8½ years.²⁰ Forced vital capacity (FVC), FEV₁, and forced expiratory flow at 25% to 75% of FVC (FEF₂₅₋₇₅) were converted to sex-, age- and height-adjusted *z* scores. Bronchial hyperresponsiveness (BHR) was defined as being in the highest tertile of the dose-response slope. Responses to the question, "In the past 12 (6 for first questionnaire) months has (your child) had wheezing/wheezing with whistling on the chest?" at 6, 18, 30, 42, 54, 69, and 81 months after birth were used in a longitudinal latent class analysis to define phenotypes of childhood wheezing¹⁵ in children with at least 2 questionnaire responses. The best-fitting model resulted in 6 phenotypes: (1) *never/infrequent wheeze*, with approximately 10% prevalence of wheezing at 6 months and decreasing prevalence of sporadic wheeze thereafter, including children who never reported wheeze; (2) *transient early wheeze*, with 50% to 60% prevalence of wheeze up to 18 months and decreasing to low prevalence from 42 months; (3) *prolonged early wheeze*, with peak prevalence of wheeze around 65% at 30 months and decreasing to low prevalence from 69 months; (4) *intermediate-onset wheeze*, with low prevalence of wheeze up to 18 months and increasing rapidly to high prevalence from age 42 months; (5) *late-onset wheeze*, with approximately 20% prevalence of wheeze up to 42 months and increasing to greater than 50% prevalence thereafter; and (6) *persistent wheeze*, with 65% prevalence of wheeze at 6 months and approximately 90% prevalence thereafter. Trajectories of prevalence of wheeze for each phenotype are presented in Fig 1 of Henderson et al¹⁵ and Fig 1 of Savenije et al.¹⁶

Genetic data

Details on genotyping, quality control, and exclusions can be found in the Methods section in this article's Online Repository at www.jacionline.org.

Previously reported SNPs associated with childhood asthma are located in the region containing *ORMDL3* and 14 nearby genes (Fig 1 and see Table E1 in this article's Online Repository at www.jacionline.org)^{5,21,22} between 35.0 and 35.5 Mb on chromosome 17. SNPs within the region between 34.0 and 36.0 Mb were extracted in the form of allelic dosages to allow for associations outside this locus. Linkage disequilibrium (LD)-based data pruning was undertaken based on a pairwise tagging approach to avoid redundancy. Using the analysis software Haploview version 4.2²³ and after taking the best genotypes from the imputation process (best-guess genotypes were only used for

the variant-pruning process), we removed SNPs correlated with remaining tags at an *r*² value of 0.80 or greater. From an initial set of 749 SNPs across the region, pruning yielded a working data set of 257 variants, including 13 SNPs at the 17q21 locus (35.2-35.4 Mb) previously reported to be associated with asthma. As a sensitivity analysis and to further explore the patterns of association with gene expression, a further pruned SNP set was generated by using the more stringent threshold of an *r*² value of 0.20 or greater, yielding a set of 63 variants.

Expression data

mRNA-quantified expression data were collected for 947 unrelated ALSPAC participants from lymphoblastoid cell lines established from blood samples taken when the children were 9 years old. Of these, 875 also had genotypic data available, and 815 also had data on asthma status at 7½ years. For more technical details, see the Methods section in this article's Online Repository.

Children with expression data were selected on the basis of availability of cell lines and completeness of phenotypic data across a wide range of outcomes, neither of which was associated with asthma outcome.

Statistical analyses

Multinomial logistic regression was used to estimate relative risk ratios (RRRs), which are also known as "multinomial odds ratios," with 95% CIs and *P* values for associations of SNP dosages with wheezing phenotypes (never/infrequent wheeze was used as the reference group). Posterior probabilities of phenotype membership for each child were used as weights in the regression models to account for uncertainty in phenotype membership. Logistic, ordinal logistic, and linear regression models were used to estimate associations of SNP dosages with asthma, atopy, BHR, and lung function outcomes. We included terms for interaction with atopy in logistic regression models of the association of the top-ranked SNPs with asthma. The direction of association depends on the arbitrary assignment of one allele (that with greatest population frequency) as wild-type. RRRs and odds ratios (ORs) of less than 1 were inverted, and mean differences were coded as absolute values; therefore all associations are reported as positive, and reported risk alleles are swapped accordingly. Conditional analyses were performed by adjusting for the dosages of 13 SNPs previously reported as asthma related (see Table E1).^{5,21,22} Quantile-quantile (Q-Q) plots were used to assess the overall evidence for associations. The cumulative incidence of wheezing from 6 to 81 months was estimated by using life tables in a survival-time data framework. We estimated the population-attributable risk fraction (PARF) to quantify the reduction in prevalence of a wheezing phenotype if the genotype in all subjects was changed to "no risk alleles" as follows:

$$\text{PARF} = 1 - \frac{\text{Average probability of wheezing phenotype in the "no risk alleles" group}}{\text{Average probability of wheezing phenotype across all genotypes}}$$

Normalized and transformed expression levels at each of the 15 genes (*STARD3* to *MED24*) in the region from 35.0 to 35.5 Mb were regressed on SNP dosages in a linear regression model, assuming an additive genetic model as for other analyses. The variance in expression levels explained by genotypic variation (*r*²) was reported along with *P* values adjusted for 3855 independent tests (945 when the reduced SNP set based on an LD pruning threshold of an *r*² value of ≥0.8 was used) by using Bonferroni correction.

All analyses were performed with STATA version 11.0 software (Stata-Corp, College Station, Tex).

RESULTS

A total of 7045 children with central European ancestry had at least 2 questionnaire responses on wheezing between 6 and 81 months and data on SNP dosages. Of these children, 3595 (51.0%) were male, 1085 (19.7%) had asthma, 3140 (46.7%) had an asthmatic or allergic mother, 1516 (22.3%) were exposed to

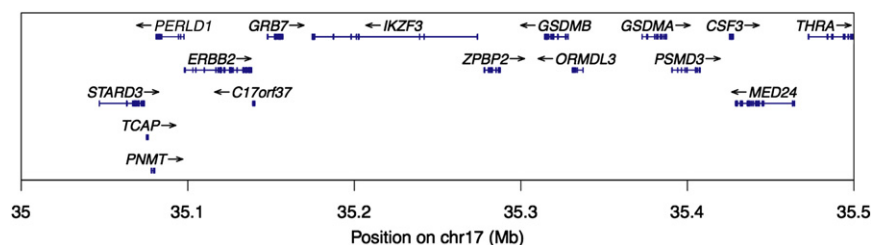


FIG 1. Schematic of chromosome 17 between 35.0 and 35.5 Mb.

TABLE I. Characteristics of children included in analyses

	No. of children with data available	No. (%) of children with characteristic*	Subsample with expression data (n = 947)	No. (%) with characteristic in subsample*
Male sex	7045	3595 (51.0)	875	413 (47.2)
Maternal history of asthma or allergy	6723	3140 (46.7)	855	423 (49.5)
Paternal history of asthma or allergy	4963	1994 (40.2)	671	267 (39.8)
Prenatal maternal smoking	6786	1516 (22.3)	857	136 (15.9)
Maternal lower education level†	6853	4012 (58.5)	864	445 (51.5)
Wheezing phenotype‡	7045		947	
Never/infrequent		4815 (68.4)		682 (72.0)
Transient early		715 (10.2)		81 (8.6)
Prolonged early		526 (7.5)		58 (6.1)
Intermediate onset		162 (2.3)		20 (2.1)
Late onset		335 (4.8)		48 (5.1)
Persistent		492 (7.0)		58 (6.1)
Doctor-diagnosed asthma ever by 7½ y	5497	1085 (19.7)	815	149 (18.3)
Skin prick test sensitivity at 7½ y	4710	948 (20.1)	728	123 (16.9)
Mean (IQR) FVC at 8½ y (L)	4831	0.02 (1.26)	833	0.03 (1.23)
Mean (IQR) FEV ₁ at 8½ y (L)	4758	0.02 (1.29)	821	0.04 (1.20)
Mean (IQR) FEF ₂₅₋₇₅ at 8½ y (L/s)	4831	0.02 (1.33)	833	0.02 (1.21)
BHR at 8½ y	3216		875	
No BHR (LSDRS < 0)		616 (19.2)		93 (15.5)
Positive BHR (first tertile)		869 (27.0)		152 (25.3)
Positive BHR (second tertile)		867 (27.0)		184 (30.7)
Positive BHR (third tertile)		864 (27.0)		171 (28.5)

FVC, FEV₁, FEF₂₅₋₇₅ adjusted z-scores. IQR, interquartile range; LSDRS, least-squares dose-response slope.

*Unless labeled as means (interquartile ranges).

†Educated to General Certificate of Education (GCE) level (school-leaving certificate) or less.

‡Estimated by using posterior probabilities.

maternal smoking during pregnancy, and 948 (20.1%) were atopic (Table I). The estimated numbers with each wheezing phenotype were as follows: never/infrequent, 4815 (68.4%); transient early, 715 (10.2%); prolonged early, 526 (7.5%); intermediate onset, 162 (2.3%); late onset, 335 (4.8%); and persistent wheezing, 492 (7.0%).

Associations of *ORMDL3* region SNPs with doctor-diagnosed asthma, atopy, BHR, and lung function

Q-Q plots showed substantial deviation from expected values for doctor-diagnosed asthma ever at 7½ years and small deviation for BHR but not for the other phenotypes (see Fig E1 in this article's Online Repository at www.jacionline.org). Consistent with previously reported GWASs, the strongest evidence of association with doctor-diagnosed asthma was for variants in the region between 35.0 and 35.5 Mb (Fig 2).^{5,21,22} Corresponding conditional *P* values are plotted in Fig E2 in this article's Online

Repository at www.jacionline.org, which shows that the 13 previously asthma-related SNPs explain the majority of the observed associations. The strongest evidence for association with doctor-diagnosed asthma was for the previously asthma-related SNPs: rs9303277 near *IKZF3* (OR, 1.30; 95% CI, 1.19-1.43; *P* = 4.6×10^{-8}) and rs2290400 near *GSDML* (OR, 1.30; 95% CI, 1.18-1.43; *P* = 4.7×10^{-8} ; see Tables E2 and E3 in this article's Online Repository at www.jacionline.org). The strongest evidence of association with BHR was for rs1042658 near *CSF3* (OR, 1.20; 95% CI, 1.10-1.31; *P* = 7.5×10^{-5}) and for the previously asthma-related SNP rs3859192 near *GSDMI* (OR, 1.19; 95% CI, 1.09-1.30; *P* = 8.2×10^{-5} ; see Table E3). Corresponding figures for crude (see Fig E3 in this article's Online Repository at www.jacionline.org) and conditional (see Fig E4 in this article's Online Repository at www.jacionline.org) ORs and mean differences for the various asthma outcomes can be found in this article's Online Repository at www.jacionline.org. No evidence of effect

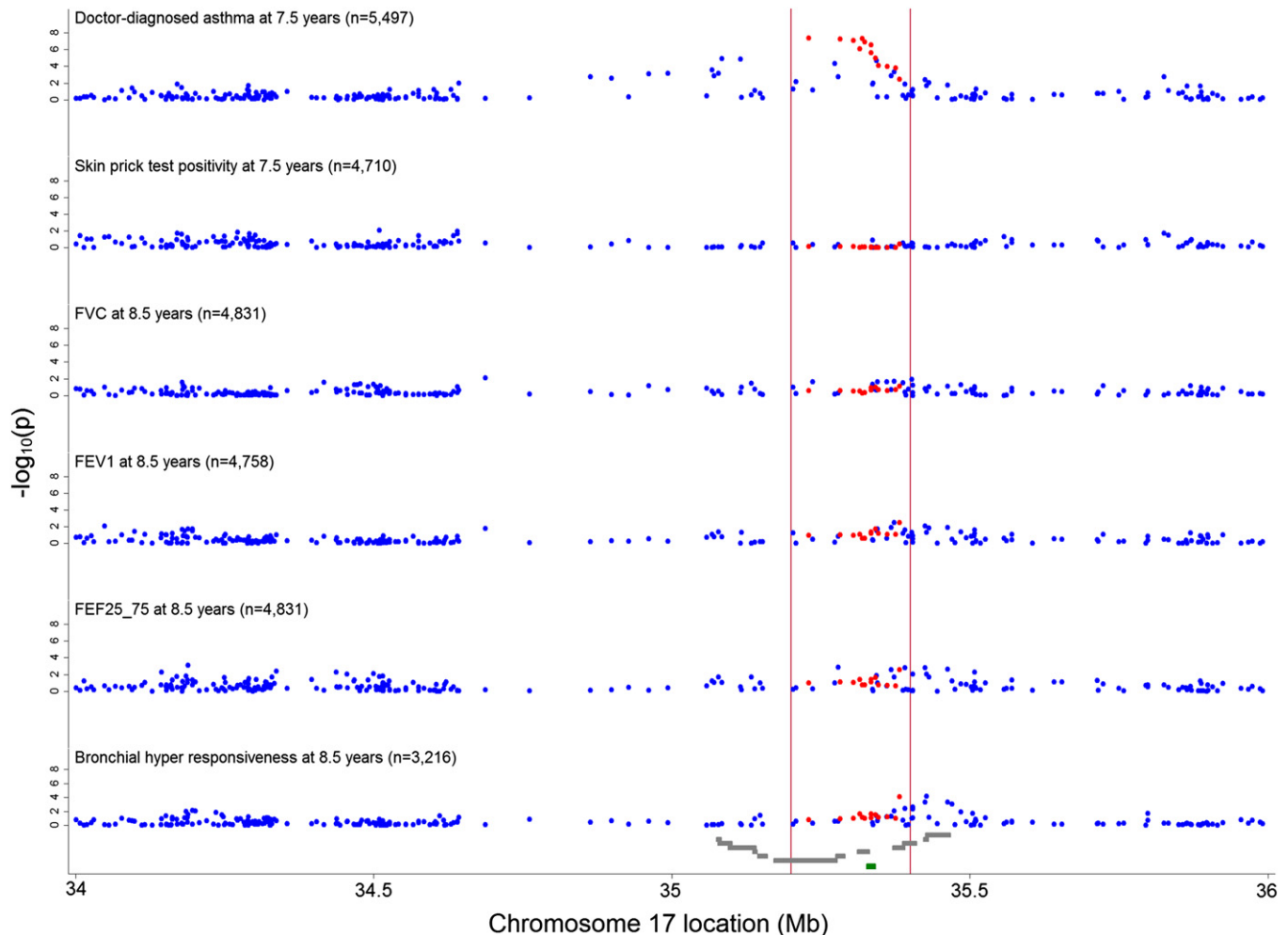


FIG 2. Inverse $\log_{10}$ transformed P values for crude associations of 257 independent SNPs between 34 and 36 Mb on chromosome 17 with doctor-diagnosed asthma ever, skin prick test response positivity, BHR, FVC, FEV₁, and FEF₂₅₋₇₅. Vertical red lines delineate the region between 35.2 and 35.4 Mb around *ORMDL3* (marked in green) containing 13 asthma-related SNPs (highlighted in red).^{5,21,22} Gray gene tracks show loci in the order *PNMT*, *PERLD1*, *ERBB2*, *C17orf37*, *GRB7*, *IKZF3*, *ZBP2*, *GSDML*, *GSDM1*, *PSMD3*, *CSF3*, and *MED24*.

modification by atopy was observed in the association between the top 10 ranked SNPs and asthma (see Table E4 in this article's Online Repository at www.jacionline.org). Conditioning on each of the top SNPs did not show evidence of independent associations with doctor-diagnosed asthma ever (see the Results section and Table E5 in this article's Online Repository at www.jacionline.org).

Associations of the *ORMDL3* region SNPs with wheezing phenotypes

For the intermediate-onset and persistent wheezing phenotypes, Q-Q plots showed substantial deviations from expected values (see Fig E5 in this article's Online Repository at www.jacionline.org). The strongest evidence of association was for SNPs in the region between 35.2 and 35.4 Mb with persistent wheezing, although there was some evidence of association for SNPs in the flanking regions between 35.0 and 35.2 and between 35.4 and 35.6 Mb (Fig 3).^{5,21,22} Similar but less precisely estimated

effects were seen for intermediate-onset wheeze, but there was little evidence of associations with other wheezing phenotypes.

SNPs near the *IKZF3*, *ZBP2*, *GSDML*, *ORMDL3*, and *GSDM1* genes were associated with intermediate-onset ($P \leq .001$) and persistent ($P \leq 1.5 \times 10^{-9}$) wheezing (Table II). The magnitude of associations appeared similar for these 2 phenotypes (RRR range, 1.46-1.60) and were generally larger than the corresponding ORs for association with doctor-diagnosed asthma (OR, <1.30). The strongest evidence of association was for persistent wheezing and rs8076131 near *ORMDL3* (RRR, 1.60; 95% CI, 1.40-1.84; $P = 1.4 \times 10^{-11}$), rs2305480 near *GSDML* (RRR, 1.60; 95% CI, 1.39-1.83; $P = 1.5 \times 10^{-11}$), and rs9303277 near *IKZF3* (RRR, 1.57; 95% CI, 1.37-1.79; $P = 4.4 \times 10^{-11}$; Table II). Respective associations for the less frequent (162 children, prevalence of 2.3%) intermediate-onset wheezing phenotype were as follows: RRRs of 1.60 (95% CI, 1.27-2.02; $P = 7.5 \times 10^{-5}$), 1.58 (95% CI, 1.25-1.99; $P = 1.1 \times 10^{-4}$), and 1.52 (95% CI, 1.21-1.91; $P = 2.8 \times 10^{-4}$). In contrast, associations with other wheezing

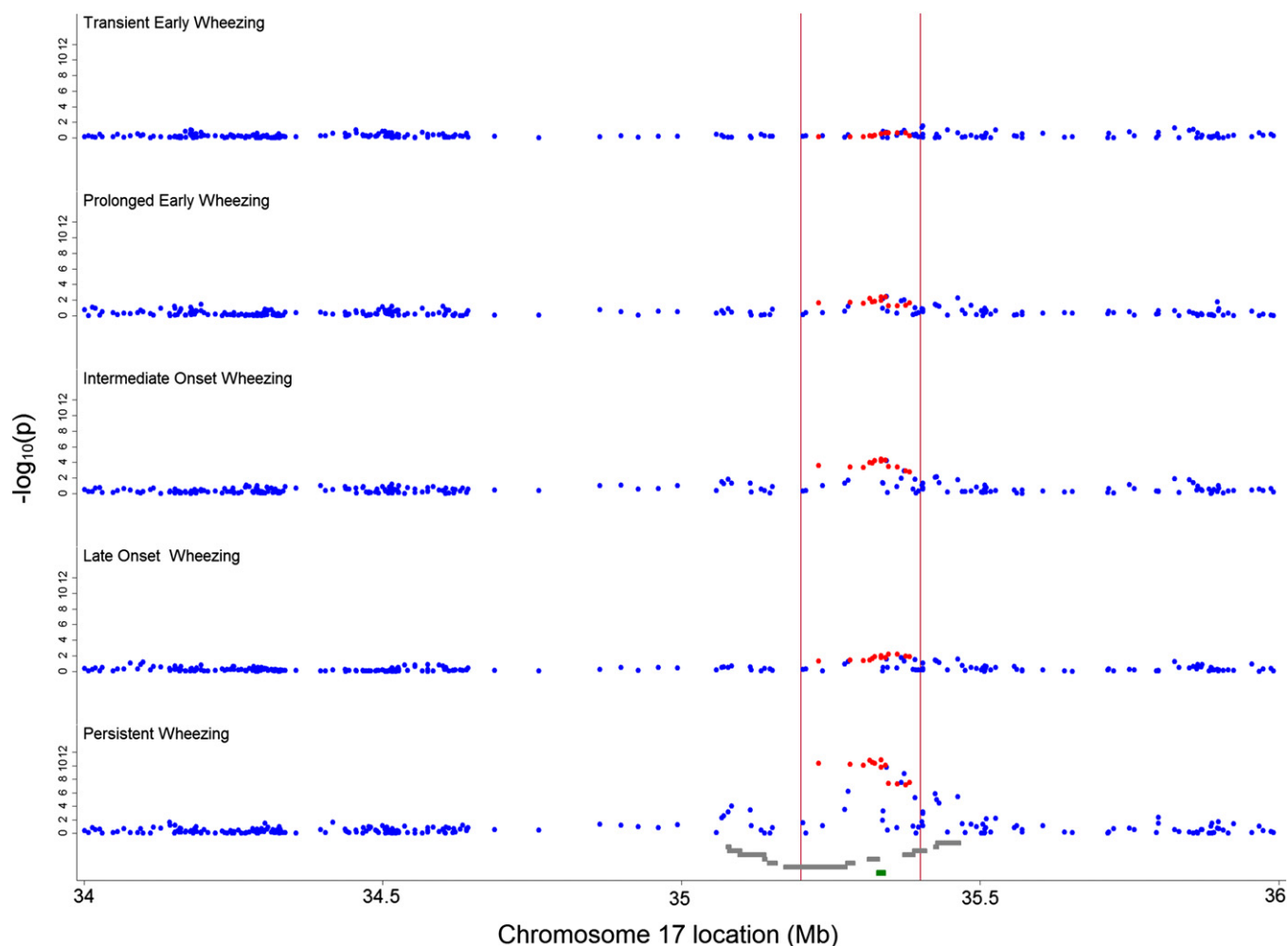


FIG 3. Inverse $\log_{10}$ transformed P values for crude associations of 257 independent SNPs between 34 and 36 Mb on chromosome 17 with wheezing phenotypes (compared with never/infrequent wheeze). Vertical red lines delineate the region between 35.2 and 35.4 Mb around *ORMDL3* (marked in green) containing 13 asthma-related SNPs (highlighted in red).^{5,21,22} Gray gene tracks show loci in the order *PNMT*, *PERLD1*, *ERBB2*, *C17orf37*, *GRB7*, *IKZF3*, *ZBP2*, *GSDML*, *GSDM1*, *PSMD3*, *CSF3*, and *MED24*.

phenotypes were smaller (RRR, <1.20; Table II). Similarly, genes in the flanking regions were only associated with intermediate-onset and persistent wheezing, but the magnitude of associations was smaller. A list of the top crude associations for intermediate-onset and persistent wheezing can be found in Table E3.

Conditional analyses, including the 13 previously asthma-related SNPs, essentially removed any evidence for association (see Fig E6 in this article's Online Repository at www.jacionline.org) and demonstrated that these original signals explain the majority of observed signals across the region. Corresponding figures for crude (see Fig E7 in this article's Online Repository at www.jacionline.org) and conditional (see Fig E8 in this article's Online Repository at www.jacionline.org) RRRs for the wheezing phenotypes can be found in this article's Online Repository.

Fig E9 in this article's Online Repository at www.jacionline.org shows a low cumulative incidence of wheezing up to approximately 6 months, with a large increment between 6 and 18 months. Stratification by the top SNPs rs8076131 near *ORMDL3* and rs2305480 near *GSDML* shows the lack of association with wheeze at 6 months and emergence of association from age 18

months together with possible departures from a per-allele genetic model (particularly for rs2305480). The estimated PARF for the top SNP rs8076131 near *ORMDL3* was 35% for intermediate-onset and 40% for persistent wheezing.

Associations of *ORMDL3* region SNPs with expression

Expression of *ORMDL3*, *GSDML*, *IKZF3*, and *MED24* genes showed evidence for association with genetic variation in the region between 35.0 and 35.5 Mb (Fig 4).^{5,21,22} Expression of other genes showed little evidence for association (see Fig E10 in this article's Online Repository at www.jacionline.org). Of those SNPs showing the strongest evidence for association with the wheezing phenotypes (as reported in Table II), the greatest evidence for association with gene specific expression levels was exhibited by the following SNPs: rs9303277 (in *IKZF3*) for *ORMDL3*, *IKZF3*, and *GSDML* expression ($r^2 = 0.20$, Bonferroni-corrected $P = 1.39 \times 10^{-44}$; $r^2 = 0.13$, $P = 2.53 \times 10^{-27}$; and $r^2 = 0.19$, $P = 6.09 \times 10^{-44}$, respectively);

TABLE II. Association of variants in the region of chromosome 17 between 35.0 and 35.5 Mb (around 17q21) with wheezing phenotypes in 7045 children

Phenotypes in 7545 children									
Nearby gene*	SNP†	Position (Mb)	MAF	Overall <i>P</i> value	Ph	Risk allele	RRR (95% CI)‡	<i>P</i> value for Ph	Other SNPs (overall <i>P</i> value)§
Region between 35.0 and 35.2 Mb									
<i>PNMT</i>	rs876493	35.078071	0.41	.002	TE	A (common)	1.02 (0.91-1.14)	.79	NA
					PE	G	1.10 (0.97-1.25)	.13	
					IO	G	1.35 (1.06-1.73)	.02	
					LO	G	1.08 (0.93-1.26)	.33	
					P	G	1.29 (1.11-1.48)	6.52×10^{-4}	
<i>PERLD1</i>	rs2941504	35.084426	0.31	.001	TE	G (common)	1.01 (0.91-1.13)	.81	NA
					PE	A	1.06 (0.94-1.20)	.36	
					IO	A	1.27 (1.00-1.60)	.05	
					LO	A	1.10 (0.95-1.28)	.21	
					P	A	1.31 (1.14-1.51)	9.98×10^{-5}	
<i>ERBB2</i>	rs2952155	35.229995	0.24	.004	TE	C (common)	1.03 (0.91-1.16)	.64	No signals
					PE	T	1.06 (0.93-1.22)	.39	
					IO	T	1.29 (1.00-1.67)	.05	
					LO	T	1.10 (0.93-1.29)	.27	
					P	T	1.31 (1.13-1.53)	3.68×10^{-4}	
Region between 35.2 and 35.4 Mb									
<i>IKZF3</i>	rs9303277	35.229995	0.48	2.24×10^{-11}	TE	T (common)	1.02 (0.92-1.12)	.77	rs9635726 (.004)
					PE	C	1.14 (1.02-1.28)	.024	
					IO	C	1.52 (1.21-1.91)	2.81×10^{-4}	
					LO	C	1.15 (1.00-1.32)	.05	
					P	C	1.57 (1.37-1.79)	4.43×10^{-11}	
<i>ZBPB2</i>	rs11557467	35.282160	0.48	3.52×10^{-11}	TE	T (common)	1.02 (0.92-1.13)	.73	rs8067378 (6.37×10^{-11}) rs12150079 (3.57×10^{-6})
					PE	G	1.14 (1.02-1.28)	.02	
					IO	G	1.50 (1.20-1.89)	4.11×10^{-4}	
					LO	G	1.16 (1.01-1.33)	.04	
					P	G	1.56 (1.37-1.78)	5.99×10^{-11}	
<i>GSDML</i>	rs2305480	35.323475	0.48	1.69×10^{-12}	TE	T (common)	1.03 (0.93-1.15)	.51	rs7216389 (4.82×10^{-12}) rs2290400 (6.66×10^{-12})
					PE	T (common)	1.17 (1.05-1.31)	.006	
					IO	T (common)	1.58 (1.25-1.99)	1.11×10^{-4}	
					LO	T (common)	1.16 (1.01-1.34)	.03	
					P	T (common)	1.60 (1.39-1.83)	1.5×10^{-11}	
Region between 35.2 and 35.4 Mb									
<i>ORMDL3</i>	rs8076131	35.334438	0.48	8.55×10^{-13}	TE	A (common)	1.05 (0.95-1.17)	.31	rs4795405 (3.08×10^{-12}) rs4378650 (6.76×10^{-12}) rs4794820 (7.04×10^{-12}) rs8079416 (1.06×10^{-8}) rs3744246 (5.57×10^{-4})
					PE	A (common)	1.18 (1.06-1.33)	.004	
					IO	A (common)	1.60 (1.27-2.02)	7.52×10^{-5}	
					LO	A (common)	1.19 (1.03-1.37)	.02	
					P	A (common)	1.60 (1.40-1.84)	1.41×10^{-11}	
<i>GSDM1</i>	rs3902025	35.372780	0.44	1.20×10^{-9}	TE	T (common)	1.09 (0.98-1.20)	.12	rs4795408 (1.38×10^{-8}) rs3859192 (2.23×10^{-8}) rs7219080 (5.34×10^{-8}) rs3894194 (6.36×10^{-8})
					PE	T (common)	1.17 (1.04-1.31)	.009	
					IO	T (common)	1.46 (1.16-1.85)	.001	
					LO	T (common)	1.15 (1.00-1.33)	.05	
					P	T (common)	1.53 (1.33-1.75)	1.46×10^{-9}	
Region between 35.4 and 35.5 Mb									
<i>PSMD3</i>	rs2227321	35.424820	0.37	1.60×10^{-6}	TE	G (common)	1.00 (0.90-1.11)	.95	rs8075668 (6.80×10^{-6}) rs2241245 (.003)
					PE	G (common)	1.14 (1.01-1.28)	.04	
					IO	G (common)	1.38 (1.09-1.76)	.009	
					LO	G (common)	1.17 (1.01-1.35)	.04	
					P	G (common)	1.42 (1.23-1.64)	1.36×10^{-6}	
<i>CSF3</i>	rs1042658	35.427428	0.38	3.45×10^{-5}	TE	T	1.05 (0.95-1.16)	.36	NA
					PE	T	1.12 (1.00-1.26)	.05	
					IO	T	1.36 (1.08-1.70)	.008	
					LO	T	1.15 (1.00-1.32)	.05	
					P	T	1.34 (1.18-1.53)	1.13×10^{-5}	

(Continued)

rs11557467 (in *ZBPB2*) for *ORMDL3*, *IKZF3*, and *GSDML* expression ($r^2 = 0.20$, $P = 6.75 \times 10^{-45}$; $r^2 = 0.13$, $P = 1.78 \times 10^{-26}$; and $r^2 = 0.20$, $P = 3.64 \times 10^{-45}$, respectively); rs2290400 (in *GSDML*) for *ORMDL3*, *IKZF3*, and *GSDML* expression ($r^2 = 0.20$, $P = 3.96 \times 10^{-45}$; $r^2 = 0.12$, $P = 2.43$

$\times 10^{-25}$; and $r^2 = 0.19$, $P = 4.17 \times 10^{-43}$, respectively); and rs4378650 (in *ORMDL3*) for *ORMDL3*, *IKZF3*, and *GSDML* expression ($r^2 = 0.18$, $P = 8.00 \times 10^{-41}$; $r^2 = 0.12$, $P = 3.39 \times 10^{-23}$, and $r^2 = 0.16$, $P = 8.39 \times 10^{-36}$, respectively) among other associations (Table III and Table E6 in this article's Online

TABLE II. (Continued)

Nearby gene*	SNP†	Position (Mb)	MAF	Overall <i>P</i> value	Ph	Risk allele	RRR (95% CI)‡	<i>P</i> value for Ph	Other SNPs (overall <i>P</i> value)§
<i>MED24</i>	rs8065443	35.462466	0.41	5.84×10^{-6}	TE	A	1.07 (0.96-1.18)	.22	rs2302776 (1.77×10^{-4})
					PE	A	1.18 (1.05-1.32)	.006	
					IO	A	1.31 (1.05-1.65)	.02	
					LO	A	1.17 (1.02-1.35)	.03	
					P	A	1.36 (1.2-1.56)	4.15×10^{-6}	

IO, Intermediate onset, LO, late onset; MAF, minor allele frequency; P, persistent; PE, prolonged early; Ph, phenotype; TE, transient early.

*From online database SNP Function Prediction (FuncPred): <http://manticore.niehs.nih.gov/snpfunc.htm>.

†SNP with the smallest overall *P* value only for genes for which there is evidence of association for at least 1 variant ($P < .001$). A complete list of results for all SNPs is available from the authors on request. SNPs highlighted in boldface are the 13 previously reported asthma-related SNPs.^{5,21,22}

‡The risk allele is a rare allele unless indicated otherwise.

§Overall *P* values for other SNPs within the same gene that are also associated with intermediate-onset and persistent wheezing only.

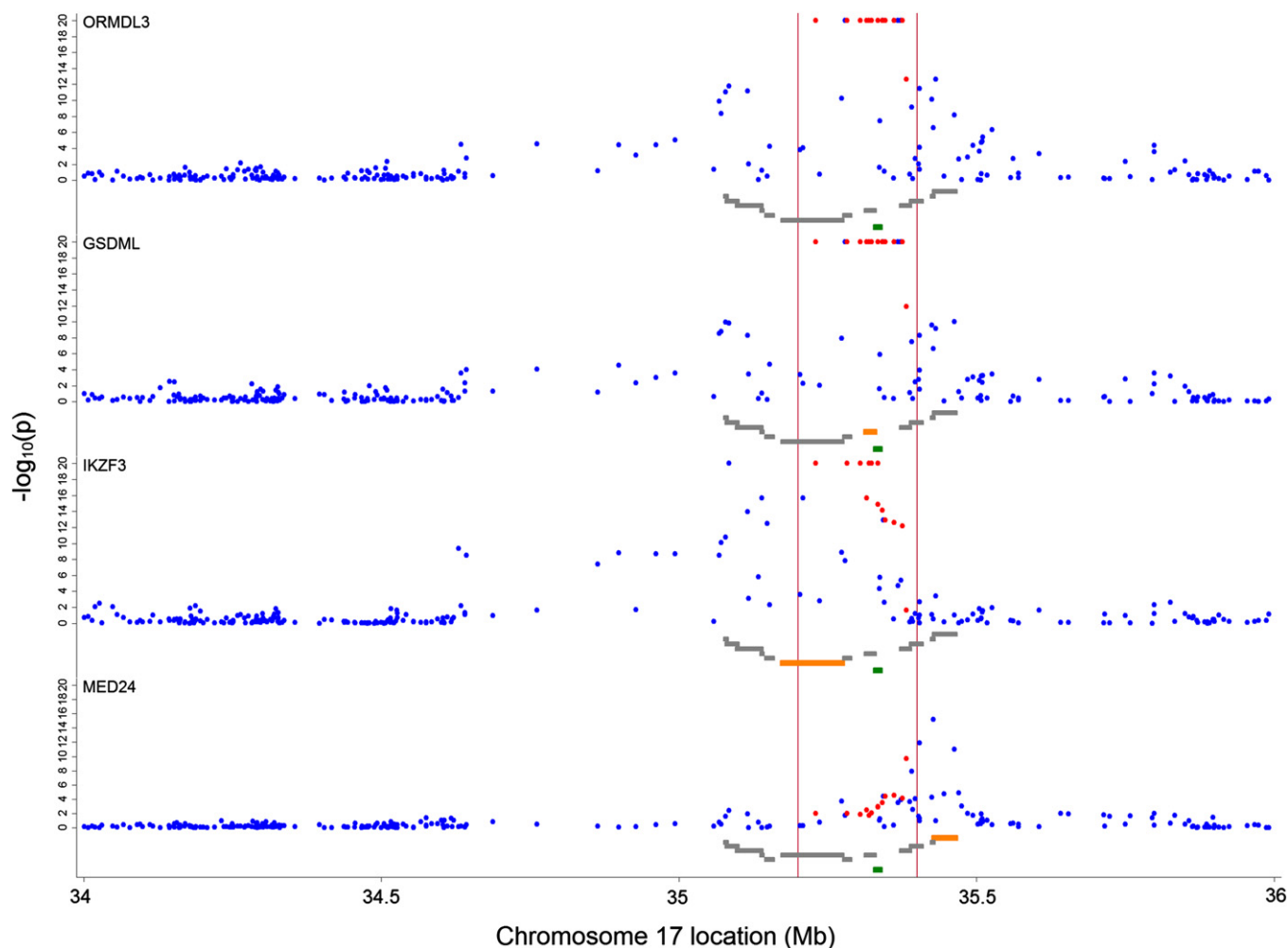


FIG 4. Inverse $\log_{10}$ transformed *P* values for crude associations of 257 independent SNPs between 34 and 36 Mb on chromosome 17 with gene specific expression levels. Vertical red lines delineate the region between 35.2 and 35.4 Mb around *ORMDL3* (marked in green) containing 13 asthma-related SNPs (highlighted in red).^{5,21,22} Gray gene tracks show loci in the order *PNMT*, *PERLD1*, *ERBB2*, *C17orf37*, *GRB7*, *IKZF3*, *ZBPB2*, *GSDML*, *GSDM1*, *PSMD3*, *CSF3*, and *MED24*, with the reported marker in orange. The figure shows results for *ORMDL3*, *GSDML*, *IKZF3*, and *MED24*.

Repository at www.jacionline.org). The strongest evidence for variable expression at *MED24* was seen for rs1042658 in *CSF3* ($r^2 = 0.07$, $P = 2.62 \times 10^{-12}$), which was the SNP showing the strongest association with BHR. A list of the top 10 crude associations for expression of *ORMDL3*, *GSDML*, *IKZF3*, and

MED24 genes can be found in Table E7 in this article's Online Repository at www.jacionline.org. In a reduced set of 63 SNPs based on a more stringent LD pruning threshold of an r^2 value of 0.2 or greater, associations with expression were still concentrated on the loci *IKZF3*, *GSDML*, *ORMDL3*, *MED24*, and *ZBPB2* (see

TABLE III. Association of variants in the region of chromosome 17 between 35.0 and 35.5 Mb (around 17q21) with expression of quantitative traits for local genes in 875 children

Nearby gene	SNP*	<i>ORMDL3</i> expression (r^2)†	<i>P</i> value‡	Other eQTL§	Expression (r^2)†	<i>P</i> value‡
Region between 35.0 and 35.2 Mb						
<i>PNMT</i>	rs876493	0.05	3.38×10^{-8}	<i>IKZF3</i>	0.05	6.28×10^{-8}
				<i>GSDML</i>	0.05	4.50×10^{-7}
<i>PERLD1</i>	rs2941504	0.05	6.10×10^{-9}	<i>IKZF3</i>	0.08	1.47×10^{-14}
				<i>GSDML</i>	0.05	5.37×10^{-7}
<i>ERBB2</i>	rs2952155	0.05	2.48×10^{-8}	<i>IKZF3</i>	0.43	4.08×10^{-11}
				<i>GSDML</i>	−0.33	1.93×10^{-5}
Region between 35.2 and 35.4 Mb						
<i>IKZF3</i>	rs9303277	0.20	1.39×10^{-44}	<i>IKZF3</i>	0.13	2.53×10^{-27}
				<i>ZBPB2</i>	0.02	.04
				<i>GSDML</i>	0.19	6.09×10^{-44}
<i>ZBPB2</i>	rs11557467	0.20	6.75×10^{-45}	<i>IKZF3</i>	0.13	1.78×10^{-26}
				<i>ZBPB2</i>	0.02	.09
				<i>GSDML</i>	0.20	3.64×10^{-45}
<i>GSDML</i>	rs2305480	0.16	1.78×10^{-35}	<i>IKZF3</i>	0.07	1.15×10^{-12}
				<i>GSDML</i>	0.17	6.33×10^{-36}
<i>ORMDL3</i>	rs8076131	0.16	4.05×10^{-34}	<i>IKZF3</i>	0.07	4.86×10^{-12}
				<i>GSDML</i>	0.16	4.03×10^{-33}
<i>GSDM1</i>	rs3902025	0.10	1.40×10^{-19}	<i>IKZF3</i>	0.02	.02
				<i>GSDML</i>	0.10	1.83×10^{-20}
				<i>MED24</i>	0.02	.46
Region between 35.4 and 35.5 Mb						
<i>PSMD3</i>	rs2227321	0.05	2.79×10^{-7}	<i>GSDML</i>	0.04	.001
				<i>MED24</i>	0.02	.20
<i>CSF3</i>	rs1042658	0.03	.001	<i>GSDML</i>	0.03	.001
				<i>MED24</i>	0.07	2.62×10^{-12}
<i>MED24</i>	rs8065443	0.04	2.59×10^{-5}	<i>GSDML</i>	0.05	3.77×10^{-7}
				<i>MED24</i>	0.05	3.84×10^{-8}

eQTL, Expression quantitative trait loci.

*SNPs near each gene with the smallest overall *P* values from primary analyses with wheeze phenotypes (Table II) and their relationships with expression quantitative traits for genes in the *ORMDL3* region of chromosome 17. Table E6 shows the complete list of expression quantitative traits for the SNPs reported in this table. A complete list of SNPs and their relationship with expression quantitative traits for all loci in this region is available from the authors.

†The r^2 value refers to variance in expression explained in expression levels by SNPs. For all results, 875 samples were available with both genotype and expression data.

‡Bonferroni-corrected *P* values (based on 3855 tests).

§Other eQTL results are shown where evidence for association exceeds a threshold when taking a Bonferroni-corrected *P* value for 3855 tests (257 independent loci * 15 expression quantitative traits). All raw *P* values are less than .0002.

Table E8 in this article's Online Repository at www.jacionline.org. We found no evidence of associations between expression and wheezing phenotypes (see the Results section and Table E9 in this article's Online Repository at www.jacionline.org).

DISCUSSION

Common SNPs in the 17q21 locus are associated with childhood asthma. On the basis of a birth cohort study with detailed information on phenotypes of asthma and allergic disease, we found that these SNPs were strongly associated with persistent and intermediate-onset childhood wheezing phenotypes characterized by onset before age 30 months.¹⁵ These SNPs were also strongly associated with a diagnosis of asthma in midchildhood, as previously reported^{5,21,22}; however, we found that the magnitude of these associations was smaller and the *P* values were weaker than for persistent wheeze. Little evidence of associations with early wheezing that resolved or with late-onset wheezing were found. We did not find evidence that SNPs in the 17q21 locus were associated with atopy or lung function in midchildhood but found some evidence of associations with BHR. SNPs in the 17q21 locus were associated with expression of the *ORMDL3*, *GSDML*, *IKZF3*, and *MED24* genes, but no associations

between asthma phenotypes and expression data were found. Our analyses were well powered to detect associations of modest strength within phenotype groups. We have previously shown that these phenotypes have face validity in their associations with other markers of asthma and its intermediate phenotypes and can be replicated in independent data.¹⁶ The phenotypes reported here have some consonance with those described by Stein and Martinez in the Tucson study.^{13,14} The transient early phenotype is similar in both studies: the ALSPAC prolonged early wheezing phenotype corresponds approximately to the Tucson "nonatopic wheezers," and our intermediate-onset, late-onset, and persistent wheezing phenotypes, all of which were associated with atopy and BHR, correspond approximately to the Tucson "IgE-associated wheeze/asthma" phenotype, although with earlier age of onset. Our study provides further evidence for the distinct nature of these phenotypes on the basis of their differential associations with genetic variants in the 17q21 region.

Studies reporting associations of SNPs in the 17q21 locus with early-onset asthma have used varying definitions of this outcome. Bouzigon et al⁷ used ordered subset regression to classify early-onset asthma (≤ 4 years), which was strongly associated with 4 SNPs in the 17q21 locus. Flory et al¹² reported that associations did not differ according to age of onset, whereas Bisgaard et al⁶

reported evidence of a stronger association of SNPs in the 17q12-21 region with asthma that began earlier than age 3 years and, consistent with our results, a lack of association with allergic sensitization. They suggested that these associations reflected increased susceptibility to nonatopic asthma. However, the situation might be more complicated than a simple dichotomy between atopic and nonatopic disease. Galanter et al¹⁰ reported stronger associations between *ORMDL3* SNPs and asthma when the latter was associated with increased serum IgE concentrations.

In the first report of the association of the 17q21 locus with asthma, Moffatt et al⁵ suggested *ORMDL3* as a promising candidate on the basis of gene expression studies in EBV-transformed lymphoblastoid cell lines. However, the function of *ORMDL3* remains to be fully elucidated, and it is possible that other genes in this region or more distant genes contain the true causal variants.²⁴ We confirmed that SNPs at the 17q21 locus were associated with expression of *ORMDL3* but also identified associations with *GSDML*, *IKZF3*, and *MED24*. *ORMDL3* encodes a member of a family of transmembrane proteins that are anchored in the endoplasmic reticulum and ubiquitously expressed in adult and fetal tissues and show evidence of functional conservation between species.²⁵ It has recently been reported to bind and inhibit sarco/endoplasmic reticulum Ca^{2+} ATPase activity, which might contribute to the airway remodeling seen in asthmatic patients,²⁶ and this provides a plausible mechanism whereby *ORMDL3* might contribute to nonallergic mechanisms of airway inflammatory responses.²⁷

Other than *ORMDL3*, the loci implicated in this study have a number of possible connections to the persistent wheeze phenotype and to measureable changes in gene expression. First, *GSDML*, *IKZF3*, and *ZBP2* (and *MED24/THRAP4* by way of regional association) have all been directly highlighted in GWASs for conditions that have an etiologic contribution from autoimmunity, including ulcerative colitis,²⁸ rheumatoid arthritis,²⁹ biliary cirrhosis,³⁰ and type 1 diabetes.³¹ Although not providing direct evidence that observed associations are underpinned by autoimmunity, this does confirm the likely importance of immunologic processes in the development of wheezing phenotypes.

Second, these loci have been shown to play roles in the action and control of transcription and gene expression. For example, *IKZF3* encodes a member of the IKAROS family of zinc finger proteins, which are hematopoiesis-specific transcription factors involved in the regulation of lymphocyte development.³²

Lastly, observed associations between the genetic variation seen here and expression patterns might be the result of more global patterns of transcriptional activity. Variation at *MED24/THRAP4* encodes a component of the mediator complex that is thought to be required for the expression of almost all genes,^{33,34} which might be related to nonspecific differential expression at multiple loci but has downstream effects that contribute to the overall risk of persistent wheeze. Taken together, these aspects make it entirely plausible that variation at multiple loci contributes to observed phenotypes, but considerable effort will be required to elucidate the precise mechanisms. Although associations of wheezing phenotype-related SNPs with expression data were found in this study, the absence of a direct association of expression profiles with asthma phenotypes is likely to be due to measurement error, confounding, and sample size limitation.

The results of this study suggest that associations of SNPs in the 17q21 locus with susceptibility to asthma in early childhood and midchildhood are specific to asthma and specific wheezing

phenotypes and are not explained by associations with intermediate phenotypes, such as atopy or lung function. Elucidation of causal mechanisms has the potential to facilitate disease prediction in children with wheezing in the preschool years, to contribute to the separation of discrete phenotypes of childhood asthma, and to identify risk factors that might be targets for primary or secondary disease prevention.

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

Key messages

- Asthma-related genetic variants are associated with intermediate-onset and persistent wheezing but not with early-onset wheezing.
- These associations are not explained by associations with intermediate phenotypes, such as atopy or lung function.
- Elucidation of causal mechanisms has the potential to identify risk factors that might be targets for primary or secondary disease prevention.

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1 ONLINE REPOSITORY MATERIALS

2 **Title: Examination of the relationship between variation at 17q21 and childhood wheeze**
3 **phenotypes**

4 METHODS

5 Genetic data

6 Genotyping was carried out at two different centres (The Wellcome Trust Sanger Centre, Cambridge,
7 UK and Laboratory Corporation of America, Burlington, NC, US) using the Illumina HumanHap 550
8 array (Illumina, Inc., San Diego, CA). Individuals were excluded on the basis of the following: sex
9 mismatches, minimal or excessive heterozygosity, disproportionate levels of individual missingness
10 ($>3\%$), cryptic relatedness measured as proportion of identity by descent ($IBD > 0.1$), and insufficient
11 sample replication ($IBD < 0.8$). The remaining individuals were assessed for evidence of population
12 stratification by multidimensional scaling analysis and compared with Hapmap II (release 22)
13 European descent (CEU), Han Chinese, Japanese and Yoruba reference populations; all individuals
14 with non-European ancestry were removed. SNPs with a minor allele frequency of $< 1\%$, a call rate of
15 $< 95\%$ or evidence for violations of Hardy-Weinberg equilibrium ($P < 5 \times 10^{-7}$) were removed.
16 Autosomal genotypic data were subsequently imputed using Markov Chain Haplotyping software
17 (MACH v.1.0.16, Li et al. 2010) and phased haplotype data from CEU individuals (Hapmap release
18 22, Phase II NCBI B36, dbSNP 126) based on a cleaned dataset of 8,365 individuals and 464,311
19 autosomal SNPs. After imputation, all SNPs with indication of poor imputation quality ($\hat{r}^2 < 0.30$) were
20 removed.

21 Expression data

22 All cell lines were from a first passage, cells were harvested when confluent, washed in phosphate
23 buffered saline and frozen in RNA Later (Ambion, Life Technologies, Grand Island, NY), RNA was

extracted using Qiagen's Rneasy extraction kit and amplified using Ambion's Illumina TotalPrep 96 RNA amplification kit. Expression was surveyed using the Illumina HG-12 bead arrays and each individual run with 2 replicates. Expression data was normalized by quantile normalization between replicates and then median normalization across individuals was taken forward for further analysis. 15 genes (STARD3 to MED24) in the region between 35.0 and 35.5Mb on chromosome 17 (genomic locations taken from HAPMAP, release 28, release III, build 126) had probe data available (Figure 1). For loci with more than one probe on this array, mean normalized expression was taken before an inverse rank transformation (to mean zero and standard deviation 1) was used to transform all expression data.

RESULTS

Conditional analyses among top-ranked SNPs

Online Table E5 shows the estimated associations of 11 selected SNPs, with doctor-diagnosed asthma ever at 7½ years, after conditioning on each of these SNPs in turn. The selected SNPs are 10 top-ranked SNPs (including rs2305480) together with rs3894194; rs2305480 and rs3894194 were identified as independently associated with asthma in the Gabriel study ¹. Clear evidence of association with at least some SNPS remained after conditioning on rs2305480, rs8076131, rs4795405, rs4794820 and rs3894194. Little evidence of association remained after conditioning on rs9303277, rs11557467, rs8067378, rs2290400, rs7216389 and rs4378650. Thus, although the effects of rs2305480 and rs3894194 did not completely explain the observed associations of other SNPs with doctor-diagnosed asthma at 7½ years, the effects of other top SNPs were not separable.

Lack of association between asthma phenotypes and expression data

Online Table E9 shows the lack of association between the expression data and the wheezing phenotypes. To test for Pleiotrophy (in this case trans effects) as a possible reason for this we run the

47 13 original SNPs against all 48,630 probes on the Illumina array. With all probes in, we got the
48 expected excess signal we found in the first analyses. However, when we removed the probes used in
49 our study (i.e. those cis) then the signal was effectively removed. Therefore, it is unlikely that trans
50 effects (or pleiotrophic effects) are responsible for the disparity in results that we are seeing.
51 Other possible explanations are - (a) the tissue is specific to cord blood not the lungs
52 (however if there was a tissue specific issue, why do we see an association between asthma-related
53 SNPs and expression?), (b) measurement error i.e. whilst we are good at
54 measuring genotype and to some extent expression, we are poor at measuring phenotypes.
55 Hence both the assessment of genotype/asthma and expression /asthma relationships are
56 challenging. In the former, we have sample size on our side and genotypes are largely free of
57 confounding which could influence any effects in either direction. In the latter, we have only
58 8-900 samples with expression and of course both expression and asthma data will be
59 subject to confounding. It is likely to be a mixture of measurement error, confounding and
60 sample size limitation what is yielding a failure to see a relationship between expression
61 and outcome.

62 **ONLINE REPOSITORY TABLES**

63 Table E1. List of previously reported asthma-related SNPs in the region 35.2 to 35.4 Mb in the 17q21
 64 locus

Reference	SNP	BP position (Kb)	Allele	Nearby gene ^a
Moffatt et al. Nature 2007 ²	rs9303277	35229995	C/T	<i>IKZF3</i>
	rs11557467	35282160	G/T	<i>ZPBP2</i>
	rs8067378	35304874	A/G	<i>ZPBP2</i> or <i>GSDML</i>
	rs2290400	35319766	T/C	<i>GSDMB</i> or <i>GSDML</i>
	rs7216389	35323475	C/T	<i>GSDMB</i> or <i>GSDML</i>
	rs4795405	35341943	C/T	<i>ORMDL3</i>
	rs8079416	35346239	C/T	<i>ORMDL3</i>
	rs4795408	35361153	A/G	<i>GSDM1</i> or <i>GSDMA</i>
	rs3894194	35375519	G/A	<i>GSDM1</i> or <i>GSDMA</i>
	rs3859192	35382174	C/T	<i>GSDM1</i> or <i>GSDMA</i>
Moffatt et al. Nature 2007 ² & Rogers et al. 2009 ³	rs4378650	35334391	A/G	<i>ORMDL3</i>
	rs8076131	35334438	A/G	<i>ORMDL3</i>
GABRIEL Nature Genetics 2010 ¹	rs2305480	35315722	G/A	<i>GSDMB</i> or <i>GSDML</i>

65 ^a From online database SNP Function Prediction (FuncPred): <http://manticore.niehs.nih.gov/snpfunc.htm>

Table E2. Crude associations of previously reported asthma-related SNPs in chromosome 17q21 with doctor-diagnosed asthma ever and skin prick test positivity at 7½ years, bronchial hyper responsiveness and FEV1 at 8½ years.

		Doctor-diagnosed asthma ever at 7½ years (n=5,497)	Skin prick test positivity at 7½ years (n=4,710)	FEV ₁ at 8½ years (n=4,758)	BHR at 8½ years (n=3,216)
SNP	Nearby Gene ^a	OR (95%CI) p-value	OR (95%CI) p-value	Mean Diff (95%CI) p-value	OR (95%CI) p-value
rs9303277	<i>IKZF3</i>	1.30 (1.19, 1.43) p=4.56×10 ⁻⁸	1.02 (0.92, 1.13) p=0.70	0.03 (-0.01, 0.07) p=0.11	1.07 (0.98, 1.16) p=0.15
rs11557467	<i>ZPBP2</i>	1.30 (1.18, 1.43) p=5.77×10 ⁻⁸	1.02 (0.92, 1.13) p=0.70	0.03 (-0.01, 0.07) p=0.10	1.07 (0.98, 1.17) p=0.12
rs8067378	<i>ZPBP2</i>	1.03 (1.18, 1.42) p=8.23×10 ⁻⁸	1.02 (0.92, 1.13) p=0.69	0.03 (-0.01, 0.07) p=0.11	1.07 (0.98, 1.17) p=0.11
rs2305480	<i>GSDML</i>	1.27 (1.16, 1.40) p=8.30×10 ⁻⁷	1.0 (0.91, 1.11) p=0.94	0.04 (0.00, 0.08) p=0.08	1.11 (1.01, 1.21) p=0.02
rs2290400	<i>GSDML</i>	1.30 (1.18, 1.43) p=4.65×10 ⁻⁸	1.01 (0.92, 1.12) p=0.79	0.02 (-0.02, 0.06) p=0.26	1.08 (0.99, 1.18) p=0.07
rs7216389	<i>GSDML</i>	1.29 (1.17, 1.42) p=1.36×10 ⁻⁷	1.01 (0.91, 1.12) p=0.84	0.02 (-0.02, 0.06) p=0.26	1.08 (0.99, 1.18) p=0.10
rs4378650	<i>ORMDL3</i>	1.28 (1.17, 1.41) p=3.01×10 ⁻⁷	1.01 (0.91, 1.12) p=0.83	0.04 (0.00, 0.08) p=0.04	1.08 (0.99, 1.18) p=0.08
rs8076131	<i>ORMDL3</i>	1.26 (1.14, 1.39) p=2.59×10 ⁻⁶	1.01 (0.91, 1.11) p=0.90	0.04 (0.00, 0.08) p=0.06	1.11 (1.01, 1.21) p=0.02
rs4795405	<i>ORMDL3</i>	1.24 (1.13, 1.37) p=1.02×10 ⁻⁵	1.01 (0.91, 1.11) p=0.92	0.05 (0.01, 0.09) p=0.02	1.10 (1.01, 1.20) p=0.03
rs8079416	<i>ORMDL3</i>	1.21 (1.10, 1.33) p=7.90×10 ⁻⁵	1.01 (0.91, 1.11) p=0.91	0.04 (0.00, 0.08) p=0.07	1.09 (0.99, 1.19) p=0.07
rs4795408	<i>GSDM1</i>	1.21 (1.01, 1.33) p=1.03×10 ⁻⁴	1.0 (0.91, 1.11) p=0.97	0.04 (-0.01, 0.08) p=0.09	1.09 (0.99, 1.19) p=0.07
rs3894194	<i>GSDM1</i>	1.20 (1.09, 1.32) p=1.69×10 ⁻⁴	1.0 (0.91, 1.11) p=0.93	0.04 (0.00, 0.08) p=0.08	1.08 (0.98, 1.17) p=0.11
rs3859192	<i>GSDM1</i>	1.15 (1.05, 1.26) p=0.003	1.05 (0.95, 1.16) p=0.35	0.06 (0.02, 0.10) p=0.003	1.19 (1.09, 1.30) p=8.23×10 ⁻⁵

^a From online database SNP Function Prediction (FuncPred): <http://manticore.niehs.nih.gov/snpfunc.htm>.

69 Table E3. Top crude associations of SNPs in chromosome 17 with doctor-diagnosed asthma ever at 7.5 years,
 70 bronchial hyper responsiveness at 8.5 years, intermediate onset and persistent wheezing using the pruned dataset

SNP	Nearby gene ^a	BP position(Kb)	OR (95%CI)	P-value ^c
Doctor-diagnosed asthma ever at 7.5 years				
rs9303277 ^b	<i>IKZF3</i>	35229995	1.30 (1.19, 1.43)	4.56×10 ⁻⁸
rs2290400 ^b	<i>GSDML</i>	35319766	1.30 (1.18, 1.43)	4.65×10 ⁻⁸
rs11557467 ^b	<i>ZBPB2</i>	35282160	1.30 (1.18, 1.43)	5.77×10 ⁻⁸
rs8067378 ^b	<i>ZBPB2 GSDML</i>	35304874	1.30 (1.18, 1.42)	8.23×10 ⁻⁸
rs7216389 ^b	<i>GSDML</i>	35323475	1.29 (1.17, 1.42)	1.36×10 ⁻⁷
rs4378650 ^b	<i>ORMDL3</i>	35334391	1.28 (1.17, 1.41)	3.01×10 ⁻⁷
rs2305480 ^b	<i>GSDML</i>	35315722	1.27 (1.16, 1.40)	8.30×10 ⁻⁷
rs8076131 ^b	<i>ORMDL3</i>	35334438	1.26 (1.14, 1.39)	2.59×10 ⁻⁶
rs4795405 ^b	<i>ORMDL3</i>	35341943	1.24 (1.13, 1.37)	1.02×10 ⁻⁵
rs2941504	<i>PERLD1</i>	35084426	1.25 (1.13, 1.38)	1.32×10 ⁻⁵
rs2952155	<i>ERBB2</i>	35115244	1.27 (1.14, 1.42)	1.46×10 ⁻⁵
rs4794820	<i>ORMDL3</i>	35342870	1.23 (1.12, 1.36)	2.27×10 ⁻⁵
rs9635726	<i>IKZF3</i>	35273667	1.26 (1.13, 1.42)	4.99×10 ⁻⁵
rs8079416 ^b	<i>ORMDL3</i>	35346239	1.21 (1.10, 1.33)	7.90×10 ⁻⁵
rs4795408 ^b	<i>GSDM1</i>	35361153	1.21 (1.10, 1.33)	1.03×10 ⁻⁴
rs3894194 ^b	<i>GSDM1</i>	35375519	1.2 (1.09, 1.32)	1.69×10 ⁻⁴
rs11869286	<i>STARD3</i>	35067382	1.20 (1.09, 1.33)	2.75×10 ⁻⁴
rs3902025	<i>GSDM1</i>	35372780	1.19 (1.08, 1.30)	4.80×10 ⁻⁴
rs1877030	<i>CRKRS NEUROD2</i>	34993687	1.25 (1.10, 1.42)	7.20×10 ⁻⁴
rs876493	<i>PNMT</i>	35078071	1.20(1.08, 1.33)	7.33×10 ⁻⁴
rs12947506	<i>CRKRS NEUROD2</i>	34961118	1.24 (1.09, 1.41)	8.29×10 ⁻⁴
Bronchial hyper responsiveness at 8.5 years				
rs1042658	<i>CSF3</i>	35427428	1.20 (1.10, 1.31)	7.47×10 ⁻⁵
rs3859192 ^b	<i>GSDM1</i>	35382174	1.19 (1.09, 1.30)	8.23×10 ⁻⁵
rs2227321	<i>PSMD3 CSF3</i>	35424820	1.18 (1.07, 1.29)	4.95×10 ⁻⁴
rs8065443	<i>MED24</i>	35462466	1.17 (1.07, 1.28)	5.15×10 ⁻⁴
rs7502966	<i>SNORD124 THRA</i>	35470048	1.16 (1.06, 1.27)	9.90×10 ⁻⁴
SNP	Nearby gene ^a	BP position(Kb)	RRR (95%CI)	P-value ^c
Intermediate onset wheezing				
rs4378650 ^b	<i>ORMDL3</i>	35334391	1.63 (1.29, 2.05)	3.74×10 ⁻⁵
rs4795405 ^b	<i>ORMDL3</i>	35341943	1.62 (1.28, 2.05)	5.10×10 ⁻⁵
rs4794820	<i>ORMDL3</i>	35342870	1.63 (1.28, 2.06)	5.96×10 ⁻⁵
rs7216389 ^b	<i>GSDML</i>	35323475	1.59 (1.27, 2.00)	6.49×10 ⁻⁵
rs8076131 ^b	<i>ORMDL3</i>	35334438	1.60 (1.27, 2.02)	7.52×10 ⁻⁵
rs2305480 ^b	<i>GSDML</i>	35315722	1.58 (1.25, 1.99)	1.11×10 ⁻⁴
rs2290400 ^b	<i>GSDML</i>	35319766	1.56 (1.24, 1.96)	1.32×10 ⁻⁴
rs9303277 ^b	<i>IKZF3</i>	35229995	1.52 (1.21, 1.91)	2.81×10 ⁻⁴
rs8079416 ^b	<i>ORMDL3</i>	35346239	1.51 (1.20, 1.89)	3.47×10 ⁻⁴
rs11557467 ^b	<i>ZBPB2</i>	35282160	1.50 (1.20, 1.89)	4.11×10 ⁻⁴
rs4795408 ^b	<i>GSDM1</i>	35361153	1.50 (1.20, 1.88)	4.34×10 ⁻⁴

Persistent wheezing				
rs8076131	<i>ORMDL3</i>	35334438	1.60 (1.40, 1.84)	1.41×10^{-11}
rs2305480	<i>GSDML</i>	35315722	1.60 (1.39, 1.83)	1.50×10^{-11}
rs2290400	<i>GSDML</i>	35319766	1.57 (1.38, 1.80)	3.25×10^{-11}
rs9303277	<i>IKZF3</i>	35229995	1.57 (1.37, 1.79)	4.43×10^{-11}
rs7216389	<i>GSDML</i>	35323475	1.57 (1.37, 1.79)	4.70×10^{-11}
rs11557467	<i>ZPBP2</i>	35282160	1.56 (1.37, 1.78)	5.99×10^{-11}
rs8067378	<i>ZPBP2 GSDML</i>	35304874	1.56 (1.36, 1.78)	8.19×10^{-11}
rs4795405	<i>ORMDL3</i>	35341943	1.57 (1.37, 1.80)	8.62×10^{-11}
rs4378650	<i>ORMDL3</i>	35334391	1.55 (1.36, 1.78)	1.70×10^{-10}
rs4794820	<i>ORMDL3</i>	35342870	1.57 (1.37, 1.80)	1.78×10^{-10}
rs3902025	<i>GSDM1</i>	35372780	1.53 (1.33, 1.75)	1.46×10^{-9}
rs3859192	<i>GSDM1</i>	35382174	1.45 (1.27, 1.65)	3.00×10^{-8}
rs7219080	<i>GSDM1</i>	35368042	1.49 (1.30, 1.72)	3.06×10^{-8}
rs8079416	<i>ORMDL3</i>	35346239	1.45 (1.27, 1.65)	4.34×10^{-8}
rs4795408	<i>GSDM1</i>	35361153	1.45 (1.27, 1.65)	4.73×10^{-8}
rs3894194	<i>GSDM1</i>	35375519	1.44 (1.26, 1.64)	7.25×10^{-8}
rs12150079	<i>ZPBP2</i>	35278943	1.47 (1.27, 1.72)	6.31×10^{-7}
rs2227321	<i>PSMD3 CSF3</i>	35424820	1.42 (1.23, 1.64)	1.36×10^{-6}
rs8065443	<i>MED24</i>	35462466	1.36 (1.20, 1.56)	4.15×10^{-6}
rs8075668	<i>PSMD3</i>	35391149	1.36 (1.19, 1.56)	5.61×10^{-6}
rs1042658	<i>CSF3</i>	35427428	1.34 (1.18, 1.53)	1.13×10^{-5}
rs2302776	<i>MED24</i>	35431675	1.36 (1.17, 1.57)	3.30×10^{-5}
rs2941504	<i>PERLD1</i>	35084426	1.31 (1.14, 1.51)	9.98×10^{-5}
rs9635726	<i>IKZF3</i>	35273667	1.33 (1.14, 1.56)	2.97×10^{-4}
rs2952155	<i>ERBB2</i>	35115244	1.31 (1.13, 1.53)	3.68×10^{-4}
rs3744246	<i>ORMDL3</i>	35337876	1.35 (1.14, 1.60)	4.88×10^{-4}
rs876493	<i>PNMT</i>	35078071	1.29 (1.11, 1.48)	6.52×10^{-4}
rs2241245	<i>PSMD3</i>	35404540	1.26 (1.10, 1.43)	6.68×10^{-4}

^a From online database SNP Function Prediction (FuncPred): <http://manticore.niehs.nih.gov/snpfunc.htm>.. *GSDML* is equivalent to *GSDMB*; *GSDM1* is equivalent to *GSDMA*

^b This is a previously reported asthma-related SNP

^c Reported p-value are ≤ 0.001 . Complete list of associations for all SNPs is available from authors on request.

75 Table E4. Interaction with atopy, for the associations of the top 10 ranked SNPs with doctor-diagnosed asthma
 76 ever at 7½ years

Interaction term ^a	OR (95% CI) for DDA at 7½ years	P-value
atopy × rs9303277	1.06 (0.83, 1.35)	0.66
atopy × rs11557467	1.03 (0.81, 1.31)	0.81
atopy × rs8067378	1.05 (0.82, 1.33)	0.72
atopy × rs2305480	1.05 (0.83, 1.34)	0.67
atopy × rs2290400	1.07 (0.84, 1.37)	0.59
atopy × rs7216389	1.03 (0.81, 1.32)	0.80
atopy × rs4378650	1.10 (0.86, 1.41)	0.45
atopy × rs8076131	1.05 (0.82, 1.34)	0.72
atopy × rs4795405	1.09 (0.86, 1.40)	0.47
atopy × rs4794820	1.11 (0.87, 1.42)	0.42

77 ^a Interaction of skin prick test at 7.5 years and top 10 SNPs with smallest overall p-value in Table 2

78 Table E5. Conditional analysis among the 10 top-ranked SNPs plus rs3894194 for doctor-diagnosed asthma ever
 79 at 7½ years

		OR (95%CI) ^a for Doctor-diagnosed asthma ever at 7.5 years on					
		rs9303277	rs11557467	rs8067378	rs2305480	rs2290400	
Conditioned on	rs9303277	n/a	1.04 (0.56,1.95)	0.94 (0.52,1.68)	0.99 (0.79,1.23)	0.86 (0.59,1.26)	
	rs11557467	1.24 (0.66,2.32)	n/a	0.62 (0.17,2.26)	0.99 (0.79,1.25)	0.81 (0.51,1.29)	
	rs8067378	1.37 (0.77,2.46)	2.06 (0.57,7.47)	n/a	0.97 (0.77,1.22)	0.74 (0.46,1.20)	
	rs2305480	1.27 (1.02,1.58)	1.27 (1.01,1.60)	1.25 (0.99,1.57)	n/a	0.76 (0.60,0.97)	
	rs2290400	1.11 (0.76,1.62)	1.05 (0.66,1.66)	0.96 (0.59,1.55)	1.02 (0.80,1.30)	n/a	
	rs7216389	1.23 (0.91,1.67)	1.23 (0.87,1.73)	1.18 (0.83,1.67)	0.95 (0.76,1.18)	0.70 (0.44,1.10)	
	rs4378650	1.24 (0.99,1.54)	1.23 (0.97,1.56)	1.21 (0.95,1.53)	0.91 (0.75,1.09)	0.77 (0.59,1.01)	
	rs8076131	1.29 (1.06,1.55)	1.29 (1.06,1.57)	1.27 (1.04,1.54)	0.76 (0.53,1.09)	0.75 (0.61,0.93)	
	rs4795405	1.31 (1.10,1.55)	1.31 (1.10,1.56)	1.29 (1.08,1.54)	0.75 (0.58,0.97)	0.74 (0.62,0.90)	
	rs4794820	1.31 (1.12,1.54)	1.31 (1.11,1.54)	1.30 (1.10,1.53)	0.76 (0.61,0.94)	0.75 (0.63,0.89)	
	rs3894194	1.28 (1.13,1.46)	1.28 (1.13,1.46)	1.28 (1.12,1.45)	0.82 (0.72,0.92)	0.77 (0.68,0.88)	
			OR (95%CI) ^a for Doctor-diagnosed asthma ever at 7.5 years on				
		rs7216389	rs4378650	rs8076131	rs4795405	rs4794820	rs3894194
Conditioned on	rs9303277	0.96 (0.71,1.30)	0.96 (0.76,1.20)	1.00 (0.83,1.21)	0.98 (0.83,1.17)	1.02 (0.87,1.20)	1.00 (0.88,1.14)
	rs11557467	0.96 (0.68,1.35)	0.96 (0.75,1.21)	1.00 (0.82,1.22)	0.98 (0.82,1.17)	1.03 (0.87,1.21)	1.00 (0.88,1.14)
	rs8067378	0.92 (0.65,1.30)	0.94 (0.74,1.19)	1.01 (0.83,1.23)	0.99 (0.83,1.18)	1.02 (0.86,1.20)	1.01 (0.88,1.14)
	rs2305480	0.82 (0.66,1.02)	0.86 (0.71,1.04)	0.96 (0.67,1.37)	0.94 (0.72,1.21)	1.06 (0.85,1.32)	1.05 (0.93,1.18)
	rs2290400	1.12 (0.70,1.77)	1.00 (0.77,1.31)	0.96 (0.78,1.19)	0.95 (0.79,1.15)	1.05 (0.88,1.25)	0.99 (0.87,1.13)
	rs7216389	n/a	0.96 (0.70,1.32)	0.97 (0.77,1.24)	0.96 (0.78,1.17)	1.04 (0.87,1.26)	1.00 (0.87,1.14)
	rs4378650	0.81 (0.59,1.12)	n/a	1.02 (0.81,1.28)	0.88 (0.67,1.15)	1.11 (0.88,1.39)	0.99 (0.86,1.13)
	rs8076131	0.76 (0.60,0.97)	0.80 (0.64,1.01)	n/a	0.81 (0.50,1.29)	1.11 (0.82,1.51)	1.05 (0.92,1.19)
	rs4795405	0.75 (0.62,0.92)	0.70 (0.53,0.92)	1.54 (0.96,2.48)	n/a	1.04 (0.70,1.52)	1.06 (0.93,1.20)
	rs4794820	0.76 (0.63,0.91)	0.72 (0.58,0.90)	1.38 (1.02,1.86)	1.27 (0.87,1.85)	n/a	1.06 (0.92,1.22)
	rs3894194	0.78 (0.68,0.89)	0.78 (0.68,0.90)	1.21 (1.06,1.37)	1.18 (1.04,1.34)	0.86 (0.74,0.99)	n/a

80 ^a Highlighted in bold are estimates with confidence intervals excluding nullity.

81 Table E6. Association of variants in the region of chromosome 17 between 35.0 and 35.5 Mb (around 17q21)
 82 with expression of quantitative traits for local genes in 875 children

Nearby gene	SNP ^a	Expression quantitative trait ^d	r ² ^b	P-value ^b	Bonferroni P-value ^c
<i>PNMT</i>	rs876493	<i>TCAP</i>	<0.01	0.48	1.00
	rs876493	<i>PERLD1</i>	<0.01	0.12	1.00
	rs876493	<i>STARD3</i>	<0.01	0.27	1.00
	rs876493	<i>c17orf3</i>	<0.01	0.81	1.00
	rs876493	<i>IKZF3</i>	0.05	1.63×10 ⁻¹¹	6.28×10 ⁻⁸
	rs876493	<i>PSMD3</i>	<0.01	0.21	1.00
	rs876493	<i>CSF3</i>	<0.01	0.83	1.00
	rs876493	<i>ZPBP2</i>	0.01	0.02	1.00
	rs876493	<i>GSDM1</i>	<0.01	0.34	1.00
	rs876493	<i>ERBB2</i>	0.01	0.01	1.00
	rs876493	<i>MED24 (THRAP4)</i>	0.01	0.02	1.00
	rs876493	<i>GRB7</i>	<0.01	0.53	1.00
	rs876493	<i>ORMDL3</i>	0.05	8.78×10 ⁻¹²	3.38×10 ⁻⁸
	rs876493	<i>PNMT</i>	<0.01	0.63	1.00
	rs876493	<i>GSDML</i>	0.05	1.17×10 ⁻¹⁰	4.50×10 ⁻⁷
<i>PERLD1</i>	rs2941504	<i>ZPBP2</i>	0.01	0.01	1.00
	rs2941504	<i>PSMD3</i>	<0.01	0.39	1.00
	rs2941504	<i>MED24 (THRAP4)</i>	0.01	3.74×10 ⁻³	1.00
	rs2941504	<i>IKZF3</i>	0.08	3.82×10 ⁻¹⁸	1.47×10 ⁻¹⁴
	rs2941504	<i>GSDM1</i>	<0.01	0.16	1.00
	rs2941504	<i>PNMT</i>	<0.01	0.80	1.00
	rs2941504	<i>STARD3</i>	<0.01	0.17	1.00
	rs2941504	<i>GSDML</i>	0.05	1.39×10 ⁻¹⁰	5.37×10 ⁻⁷
	rs2941504	<i>ERBB2</i>	0.01	0.02	1.00
	rs2941504	<i>CSF3</i>	<0.01	0.88	1.00
	rs2941504	<i>TCAP</i>	<0.01	0.62	1.00
	rs2941504	<i>PERLD1</i>	0.01	0.02	1.00
	rs2941504	<i>GRB7</i>	<0.01	0.98	1.00
	rs2941504	<i>ORMDL3</i>	0.05	1.58×10 ⁻¹²	6.10×10 ⁻⁹
	rs2941504	<i>c17orf3</i>	<0.01	0.26	1.00
<i>ERBB2</i>	rs2952155	<i>ZPBP2</i>	0.01	1.65×10 ⁻³	1.00
	rs2952155	<i>GRB7</i>	<0.01	0.53	1.00
	rs2952155	<i>PNMT</i>	<0.01	0.95	1.00
	rs2952155	<i>STARD3</i>	<0.01	0.40	1.00
	rs2952155	<i>ERBB2</i>	0.01	0.01	1.00
	rs2952155	<i>c17orf3</i>	<0.01	0.26	1.00
	rs2952155	<i>PERLD1</i>	<0.01	0.07	1.00

	rs2952155	<i>GSDM1</i>	<0.01	0.33	1.00
	rs2952155	<i>CSF3</i>	<0.01	0.74	1.00
	rs2952155	<i>MED24 (THRAP4)</i>	0.01	0.01	1.00
	rs2952155	<i>GSDML</i>	0.04	5.01×10^{-9}	1.93×10^{-5}
	rs2952155	<i>ORMDL3</i>	0.05	6.43×10^{-12}	2.48×10^{-8}
	rs2952155	<i>IKZF3</i>	0.06	1.06×10^{-14}	4.08×10^{-11}
	rs2952155	<i>PSMD3</i>	<0.01	0.53	1.00
	rs2952155	<i>TCAP</i>	<0.01	0.74	1.00
<i>IKZF3</i>	rs9303277	<i>CSF3</i>	<0.01	0.96	1.00
	rs9303277	<i>GSDML</i>	0.19	1.58×10^{-47}	6.09×10^{-44}
	rs9303277	<i>PSMD3</i>	<0.01	0.23	1.00
	rs9303277	<i>MED24 (THRAP4)</i>	0.01	0.01	1.00
	rs9303277	<i>c17orf3</i>	<0.01	0.88	1.00
	rs9303277	<i>ORMDL3</i>	0.20	3.61×10^{-48}	1.39×10^{-44}
	rs9303277	<i>GSDM1</i>	<0.01	0.08	1.00
	rs9303277	<i>ZPBP2</i>	0.02	1.14×10^{-5}	0.04
	rs9303277	<i>PERLD1</i>	0.01	7.59×10^{-4}	1.00
	rs9303277	<i>TCAP</i>	<0.01	0.10	1.00
	rs9303277	<i>STARD3</i>	<0.01	0.27	1.00
	rs9303277	<i>IKZF3</i>	0.13	6.56×10^{-31}	2.53×10^{-27}
	rs9303277	<i>ERBB2</i>	<0.01	0.04	1.00
	rs9303277	<i>PNMT</i>	<0.01	0.16	1.00
	rs9303277	<i>GRB7</i>	<0.01	0.99	1.00
<i>IKZF3</i>	rs9635726	<i>STARD3</i>	<0.01	0.91	1.00
	rs9635726	<i>ZPBP2</i>	0.01	2.34×10^{-3}	1.00
	rs9635726	<i>GRB7</i>	<0.01	0.61	1.00
	rs9635726	<i>ERBB2</i>	<0.01	0.05	1.00
	rs9635726	<i>PERLD1</i>	<0.01	0.21	1.00
	rs9635726	<i>c17orf3</i>	<0.01	0.26	1.00
	rs9635726	<i>CSF3</i>	<0.01	0.41	1.00
	rs9635726	<i>GSDML</i>	0.04	1.21×10^{-8}	4.68×10^{-5}
	rs9635726	<i>MED24 (THRAP4)</i>	0.02	1.78×10^{-4}	0.69
	rs9635726	<i>PNMT</i>	<0.01	0.60	1.00
	rs9635726	<i>PSMD3</i>	<0.01	0.52	1.00
	rs9635726	<i>GSDM1</i>	<0.01	0.54	1.00
	rs9635726	<i>TCAP</i>	<0.01	0.31	1.00
	rs9635726	<i>IKZF3</i>	0.04	1.41×10^{-9}	5.43×10^{-6}
	rs9635726	<i>ORMDL3</i>	0.05	5.89×10^{-11}	2.27×10^{-7}
<i>ZPBP2</i>	rs12150079	<i>ORMDL3</i>	0.14	3.92×10^{-33}	1.51×10^{-29}
	rs12150079	<i>GRB7</i>	<0.01	0.33	1.00
	rs12150079	<i>PERLD1</i>	0.01	0.01	1.00
	rs12150079	<i>STARD3</i>	0.01	0.03	1.00
	rs12150079	<i>c17orf3</i>	<0.01	0.20	1.00

	rs12150079	<i>GSDM1</i>	<0.01	0.33	1.00
	rs12150079	<i>PNMT</i>	<0.01	0.24	1.00
	rs12150079	<i>ZPBP2</i>	<0.01	0.30	1.00
	rs12150079	<i>ERBB2</i>	0.01	0.02	1.00
	rs12150079	<i>CSF3</i>	0.01	0.03	1.00
	rs12150079	<i>PSMD3</i>	<0.01	0.21	1.00
	rs12150079	<i>IKZF3</i>	0.04	1.56×10^{-8}	5.99×10^{-5}
	rs12150079	<i>MED24 (THRAP4)</i>	0.01	0.02	1.00
	rs12150079	<i>GSDML</i>	0.13	1.79×10^{-31}	6.88×10^{-28}
	rs12150079	<i>TCAP</i>	<0.01	0.09	1.00
<i>ZPBP2</i>	rs11557467	<i>PERLD1</i>	0.01	9.29×10^{-4}	1.00
	rs11557467	<i>GSDM1</i>	<0.01	0.10	1.00
	rs11557467	<i>MED24 (THRAP4)</i>	0.01	0.01	1.00
	rs11557467	<i>ERBB2</i>	<0.01	0.04	1.00
	rs11557467	<i>ORMDL3</i>	0.20	1.75×10^{-48}	6.75×10^{-45}
	rs11557467	<i>c17orf3</i>	<0.01	0.83	1.00
	rs11557467	<i>GSDML</i>	0.20	9.44×10^{-49}	3.64×10^{-45}
	rs11557467	<i>CSF3</i>	<0.01	0.73	1.00
	rs11557467	<i>ZPBP2</i>	0.02	2.27×10^{-5}	0.09
	rs11557467	<i>IKZF3</i>	0.13	4.61×10^{-30}	1.78×10^{-26}
	rs11557467	<i>STARD3</i>	<0.01	0.26	1.00
	rs11557467	<i>GRB7</i>	<0.01	0.98	1.00
	rs11557467	<i>PSMD3</i>	<0.01	0.18	1.00
	rs11557467	<i>TCAP</i>	<0.01	0.06	1.00
	rs11557467	<i>PNMT</i>	<0.01	0.15	1.00
<i>ZPBP2</i>	rs8067378	<i>IKZF3</i>	0.13	7.22×10^{-30}	2.78×10^{-26}
	rs8067378	<i>STARD3</i>	<0.01	0.25	1.00
	rs8067378	<i>GRB7</i>	<0.01	0.81	1.00
	rs8067378	<i>ERBB2</i>	<0.01	0.05	1.00
	rs8067378	<i>TCAP</i>	<0.01	0.07	1.00
	rs8067378	<i>MED24 (THRAP4)</i>	0.01	0.01	1.00
	rs8067378	<i>PERLD1</i>	0.01	7.28×10^{-4}	1.00
	rs8067378	<i>GSDML</i>	0.20	3.00×10^{-49}	1.16×10^{-45}
	rs8067378	<i>PSMD3</i>	<0.01	0.17	1.00
	rs8067378	<i>GSDM1</i>	<0.01	0.11	1.00
	rs8067378	<i>c17orf3</i>	<0.01	0.82	1.00
	rs8067378	<i>PNMT</i>	<0.01	0.11	1.00
	rs8067378	<i>CSF3</i>	<0.01	0.78	1.00
	rs8067378	<i>ORMDL3</i>	0.20	5.60×10^{-49}	2.16×10^{-45}
	rs8067378	<i>ZPBP2</i>	0.02	2.24×10^{-5}	0.09
<i>GSDML</i>	rs2305480	<i>IKZF3</i>	0.07	2.99×10^{-16}	1.15×10^{-12}
	rs2305480	<i>TCAP</i>	<0.01	0.05	1.00
	rs2305480	<i>ORMDL3</i>	0.16	4.63×10^{-39}	1.78×10^{-35}

	rs2305480	<i>c17orf3</i>	<0.01	0.76	1.00
	rs2305480	<i>PSMD3</i>	<0.01	0.59	1.00
	rs2305480	<i>ERBB2</i>	0.01	0.03	1.00
	rs2305480	<i>PNMT</i>	<0.01	0.05	1.00
	rs2305480	<i>STARD3</i>	<0.01	0.17	1.00
	rs2305480	<i>GRB7</i>	<0.01	0.92	1.00
	rs2305480	<i>MED24 (THRAP4)</i>	0.01	3.13×10^{-3}	1.00
	rs2305480	<i>CSF3</i>	<0.01	0.95	1.00
	rs2305480	<i>GSDM1</i>	<0.01	0.16	1.00
	rs2305480	<i>ZPBP2</i>	0.01	0.02	1.00
	rs2305480	<i>GSDML</i>	0.17	1.64×10^{-39}	6.33×10^{-36}
	rs2305480	<i>PERLD1</i>	0.01	1.26×10^{-3}	1.00
<i>GSDML</i>	rs2290400	<i>GRB7</i>	<0.01	1.00	1.00
	rs2290400	<i>c17orf3</i>	<0.01	0.68	1.00
	rs2290400	<i>IKZF3</i>	0.12	6.31×10^{-29}	2.43×10^{-25}
	rs2290400	<i>PERLD1</i>	0.01	9.02×10^{-4}	1.00
	rs2290400	<i>STARD3</i>	<0.01	0.22	1.00
	rs2290400	<i>PNMT</i>	<0.01	0.14	1.00
	rs2290400	<i>ERBB2</i>	<0.01	0.05	1.00
	rs2290400	<i>TCAP</i>	<0.01	0.12	1.00
	rs2290400	<i>MED24 (THRAP4)</i>	0.01	0.02	1.00
	rs2290400	<i>GSDML</i>	0.19	1.08×10^{-46}	4.17×10^{-43}
	rs2290400	<i>ORMDL3</i>	0.20	1.03×10^{-48}	3.96×10^{-45}
	rs2290400	<i>GSDM1</i>	<0.01	0.22	1.00
	rs2290400	<i>ZPBP2</i>	0.02	4.30×10^{-5}	0.17
	rs2290400	<i>PSMD3</i>	<0.01	0.28	1.00
	rs2290400	<i>CSF3</i>	<0.01	0.94	1.00
<i>GSDML</i>	rs7216389	<i>PERLD1</i>	0.01	1.00×10^{-3}	1.00
	rs7216389	<i>TCAP</i>	<0.01	0.13	1.00
	rs7216389	<i>STARD3</i>	<0.01	0.26	1.00
	rs7216389	<i>CSF3</i>	<0.01	0.89	1.00
	rs7216389	<i>GSDM1</i>	<0.01	0.23	1.00
	rs7216389	<i>PSMD3</i>	<0.01	0.41	1.00
	rs7216389	<i>ZPBP2</i>	0.02	1.39×10^{-5}	0.05
	rs7216389	<i>GRB7</i>	<0.01	0.80	1.00
	rs7216389	<i>ERBB2</i>	<0.01	0.07	1.00
	rs7216389	<i>c17orf3</i>	<0.01	0.62	1.00
	rs7216389	<i>PNMT</i>	<0.01	0.18	1.00
	rs7216389	<i>ORMDL3</i>	0.19	1.03×10^{-46}	3.96×10^{-43}
	rs7216389	<i>GSDML</i>	0.18	1.08×10^{-44}	4.17×10^{-41}
	rs7216389	<i>MED24 (THRAP4)</i>	0.01	0.01	1.00
	rs7216389	<i>IKZF3</i>	0.13	1.63×10^{-29}	6.27×10^{-26}
<i>ORMDL3</i>	rs4378650	<i>GSDML</i>	0.16	2.18×10^{-39}	8.39×10^{-36}

	rs4378650	TCAP	<0.01	0.10	1.00
	rs4378650	CSF3	<0.01	0.87	1.00
	rs4378650	PSMD3	<0.01	0.48	1.00
	rs4378650	GSDM1	<0.01	0.18	1.00
	rs4378650	GRB7	<0.01	0.85	1.00
	rs4378650	PERLD1	0.01	6.03×10^{-4}	1.00
	rs4378650	ORMDL3	0.18	2.08×10^{-44}	8.00×10^{-41}
	rs4378650	PNMT	<0.01	0.30	1.00
	rs4378650	STARD3	<0.01	0.32	1.00
	rs4378650	IKZF3	0.12	8.79×10^{-27}	3.39×10^{-23}
	rs4378650	ERBB2	<0.01	0.07	1.00
	rs4378650	ZPBP2	0.02	1.68×10^{-5}	0.06
	rs4378650	MED24 (THRAP4)	0.01	1.05×10^{-3}	1.00
	rs4378650	c17orf3	<0.01	0.60	1.00
ORMDL3	rs8076131	GRB7	<0.01	0.85	1.00
	rs8076131	ORMDL3	0.16	1.05×10^{-37}	4.05×10^{-34}
	rs8076131	ZPBP2	0.01	0.01	1.00
	rs8076131	IKZF3	0.07	1.26×10^{-15}	4.86×10^{-12}
	rs8076131	PSMD3	<0.01	0.84	1.00
	rs8076131	STARD3	<0.01	0.10	1.00
	rs8076131	PNMT	<0.01	0.07	1.00
	rs8076131	GSDML	0.16	1.05×10^{-36}	4.03×10^{-33}
	rs8076131	PERLD1	0.01	9.90×10^{-4}	1.00
	rs8076131	GSDM1	<0.01	0.16	1.00
	rs8076131	CSF3	<0.01	0.94	1.00
	rs8076131	ERBB2	<0.01	0.07	1.00
	rs8076131	c17orf3	<0.01	0.79	1.00
	rs8076131	MED24 (THRAP4)	0.01	1.18×10^{-3}	1.00
	rs8076131	TCAP	<0.01	0.06	1.00
ORMDL3	rs4795405	IKZF3	0.06	6.99×10^{-15}	2.70×10^{-11}
	rs4795405	PSMD3	<0.01	0.77	1.00
	rs4795405	GSDML	0.14	1.45×10^{-33}	5.59×10^{-30}
	rs4795405	c17orf3	<0.01	0.94	1.00
	rs4795405	ERBB2	<0.01	0.06	1.00
	rs4795405	CSF3	<0.01	0.96	1.00
	rs4795405	PNMT	<0.01	0.14	1.00
	rs4795405	TCAP	<0.01	0.05	1.00
	rs4795405	PERLD1	0.01	6.27×10^{-4}	1.00
	rs4795405	STARD3	<0.01	0.17	1.00
	rs4795405	ORMDL3	0.16	2.00×10^{-37}	7.72×10^{-34}
	rs4795405	ZPBP2	0.01	0.01	1.00
	rs4795405	GSDM1	<0.01	0.18	1.00
	rs4795405	MED24 (THRAP4)	0.01	3.11×10^{-4}	1.00

	rs4795405	GRB7	<0.01	0.95	1.00
ORMDL3	rs4794820	PSMD3	<0.01	0.84	1.00
	rs4794820	ERBB2	<0.01	0.04	1.00
	rs4794820	PNMT	<0.01	0.15	1.00
	rs4794820	GSDM1	<0.01	0.14	1.00
	rs4794820	PERLD1	0.01	8.39×10^{-4}	1.00
	rs4794820	ZPBP2	0.01	0.01	1.00
	rs4794820	IKZF3	0.06	1.15×10^{-13}	4.43×10^{-10}
	rs4794820	GRB7	<0.01	0.80	1.00
	rs4794820	ORMDL3	0.15	8.71×10^{-36}	3.36×10^{-32}
	rs4794820	MED24 (THRAP4)	0.02	4.09×10^{-5}	0.16
	rs4794820	GSDML	0.14	7.45×10^{-32}	2.87×10^{-28}
	rs4794820	CSF3	<0.01	0.94	1.00
	rs4794820	STARD3	<0.01	0.32	1.00
	rs4794820	TCAP	<0.01	0.05	1.00
	rs4794820	c17orf3	<0.01	0.90	1.00
ORMDL3	rs8079416	ORMDL3	0.14	7.13×10^{-32}	2.75×10^{-28}
	rs8079416	PERLD1	0.01	5.37×10^{-4}	1.00
	rs8079416	TCAP	<0.01	0.05	1.00
	rs8079416	IKZF3	0.06	1.12×10^{-13}	4.33×10^{-10}
	rs8079416	ERBB2	<0.01	0.07	1.00
	rs8079416	MED24 (THRAP4)	0.02	3.83×10^{-5}	0.15
	rs8079416	ZPBP2	0.02	1.34×10^{-4}	0.52
	rs8079416	PSMD3	<0.01	0.36	1.00
	rs8079416	c17orf3	<0.01	0.55	1.00
	rs8079416	GSDM1	<0.01	0.18	1.00
	rs8079416	GSDML	0.10	3.11×10^{-23}	1.20×10^{-19}
	rs8079416	STARD3	<0.01	0.49	1.00
	rs8079416	PNMT	<0.01	0.05	1.00
	rs8079416	GRB7	<0.01	0.09	1.00
	rs8079416	CSF3	<0.01	0.87	1.00
GSDM1	rs4795408	STARD3	<0.01	0.45	1.00
	rs4795408	GRB7	<0.01	0.11	1.00
	rs4795408	PERLD1	0.01	8.13×10^{-4}	1.00
	rs4795408	IKZF3	0.06	2.36×10^{-13}	9.10×10^{-10}
	rs4795408	MED24 (THRAP4)	0.02	2.66×10^{-5}	0.10
	rs4795408	PNMT	<0.01	0.06	1.00
	rs4795408	ERBB2	<0.01	0.06	1.00
	rs4795408	PSMD3	<0.01	0.35	1.00
	rs4795408	GSDML	0.10	2.66×10^{-23}	1.02×10^{-19}
	rs4795408	GSDM1	<0.01	0.16	1.00
	rs4795408	CSF3	<0.01	0.85	1.00
	rs4795408	ZPBP2	0.02	8.53×10^{-5}	0.33

	rs4795408	ORMDL3	0.14	5.64×10^{-32}	2.17×10^{-28}
	rs4795408	TCAP	<0.01	0.04	1.00
	rs4795408	c17orf3	<0.01	0.49	1.00
GSDM1	rs7219080	CSF3	<0.01	0.13	1.00
	rs7219080	STARD3	<0.01	0.11	1.00
	rs7219080	PSMD3	<0.01	0.87	1.00
	rs7219080	MED24 (THRAP4)	0.01	2.82×10^{-4}	1.00
	rs7219080	IKZF3	0.02	2.03×10^{-5}	0.08
	rs7219080	GSDML	0.10	3.65×10^{-23}	1.41×10^{-19}
	rs7219080	GSDM1	<0.01	0.21	1.00
	rs7219080	ERBB2	<0.01	0.04	1.00
	rs7219080	TCAP	<0.01	0.06	1.00
	rs7219080	PERLD1	0.01	0.01	1.00
	rs7219080	GRB7	<0.01	0.98	1.00
	rs7219080	ORMDL3	0.10	2.59×10^{-23}	9.97×10^{-20}
	rs7219080	PNMT	0.01	0.01	1.00
	rs7219080	ZPBP2	<0.01	0.38	1.00
	rs7219080	c17orf3	<0.01	0.50	1.00
GSDM1	rs3902025	PERLD1	0.01	3.78×10^{-4}	1.00
	rs3902025	c17orf3	<0.01	0.79	1.00
	rs3902025	MED24 (THRAP4)	0.02	1.18×10^{-4}	0.46
	rs3902025	ZPBP2	<0.01	0.11	1.00
	rs3902025	GRB7	<0.01	0.48	1.00
	rs3902025	GSDML	0.10	4.74×10^{-24}	1.83×10^{-20}
	rs3902025	STARD3	<0.01	0.08	1.00
	rs3902025	PNMT	0.01	1.84×10^{-3}	1.00
	rs3902025	GSDM1	<0.01	0.04	1.00
	rs3902025	ERBB2	<0.01	0.22	1.00
	rs3902025	PSMD3	<0.01	0.59	1.00
	rs3902025	TCAP	0.01	0.03	1.00
	rs3902025	IKZF3	0.02	4.42×10^{-6}	0.02
	rs3902025	CSF3	<0.01	0.82	1.00
	rs3902025	ORMDL3	0.10	3.62×10^{-23}	1.40×10^{-19}
GSDM1	rs3894194	STARD3	<0.01	0.60	1.00
	rs3894194	ZPBP2	0.02	5.16×10^{-5}	0.20
	rs3894194	ERBB2	<0.01	0.09	1.00
	rs3894194	c17orf3	<0.01	0.38	1.00
	rs3894194	GRB7	<0.01	0.31	1.00
	rs3894194	PERLD1	0.01	1.16×10^{-3}	1.00
	rs3894194	GSDML	0.10	5.31×10^{-24}	2.05×10^{-20}
	rs3894194	IKZF3	0.06	6.54×10^{-13}	2.52×10^{-9}
	rs3894194	GSDM1	<0.01	0.11	1.00
	rs3894194	MED24 (THRAP4)	0.02	6.80×10^{-5}	0.26

	rs3894194	<i>ORMDL3</i>	0.13	1.32×10^{-30}	5.08×10^{-27}
	rs3894194	<i>PNMT</i>	<0.01	0.10	1.00
	rs3894194	<i>PSMD3</i>	<0.01	0.58	1.00
	rs3894194	<i>CSF3</i>	<0.01	0.89	1.00
	rs3894194	<i>TCAP</i>	<0.01	0.07	1.00
<i>GSDM1</i>	rs3859192	<i>ERBB2</i>	<0.01	0.22	1.00
	rs3859192	<i>ZPBP2</i>	<0.01	0.32	1.00
	rs3859192	<i>GSDML</i>	0.05	1.22×10^{-12}	4.70×10^{-9}
	rs3859192	<i>GRB7</i>	<0.01	0.79	1.00
	rs3859192	<i>CSF3</i>	<0.01	0.96	1.00
	rs3859192	<i>MED24 (THRAP4)</i>	0.04	2.02×10^{-10}	7.79×10^{-7}
	rs3859192	<i>PERLD1</i>	<0.01	0.13	1.00
	rs3859192	<i>STARD3</i>	<0.01	0.08	1.00
	rs3859192	<i>ORMDL3</i>	0.06	2.30×10^{-13}	8.88×10^{-10}
	rs3859192	<i>IKZF3</i>	0.01	0.02	1.00
	rs3859192	<i>PSMD3</i>	<0.01	0.04	1.00
	rs3859192	<i>TCAP</i>	<0.01	0.07	1.00
	rs3859192	<i>PNMT</i>	<0.01	0.19	1.00
	rs3859192	<i>GSDM1</i>	<0.01	0.37	1.00
	rs3859192	<i>c17orf3</i>	<0.01	0.67	1.00
<i>PSMD3</i>	rs8075668	<i>ORMDL3</i>	0.04	6.76×10^{-10}	2.61×10^{-6}
	rs8075668	<i>ZPBP2</i>	<0.01	0.63	1.00
	rs8075668	<i>TCAP</i>	0.01	0.03	1.00
	rs8075668	<i>MED24 (THRAP4)</i>	0.04	1.13×10^{-8}	4.35×10^{-5}
	rs8075668	<i>PNMT</i>	<0.01	0.51	1.00
	rs8075668	<i>STARD3</i>	<0.01	0.08	1.00
	rs8075668	<i>PSMD3</i>	<0.01	0.07	1.00
	rs8075668	<i>CSF3</i>	<0.01	0.78	1.00
	rs8075668	<i>c17orf3</i>	<0.01	0.81	1.00
	rs8075668	<i>IKZF3</i>	<0.01	0.27	1.00
	rs8075668	<i>PERLD1</i>	<0.01	0.98	1.00
	rs8075668	<i>GSDM1</i>	<0.01	0.63	1.00
	rs8075668	<i>ERBB2</i>	<0.01	0.04	1.00
	rs8075668	<i>GRB7</i>	<0.01	0.65	1.00
	rs8075668	<i>GSDML</i>	0.03	3.30×10^{-8}	1.27×10^{-4}
<i>PSMD3</i>	rs2241245	<i>MED24 (THRAP4)</i>	0.05	1.21×10^{-12}	4.68×10^{-9}
	rs2241245	<i>STARD3</i>	<0.01	0.04	1.00
	rs2241245	<i>PNMT</i>	<0.01	0.43	1.00
	rs2241245	<i>PSMD3</i>	0.01	1.43×10^{-3}	1.00
	rs2241245	<i>GSDM1</i>	<0.01	0.22	1.00
	rs2241245	<i>TCAP</i>	0.01	0.02	1.00
	rs2241245	<i>ORMDL3</i>	0.02	7.73×10^{-5}	0.30
	rs2241245	<i>IKZF3</i>	<0.01	0.93	1.00

	rs2241245	ZPBP2	<0.01	0.55	1.00
	rs2241245	CSF3	<0.01	0.63	1.00
	rs2241245	GRB7	<0.01	0.57	1.00
	rs2241245	ERBB2	<0.01	0.06	1.00
	rs2241245	PERLD1	<0.01	0.79	1.00
	rs2241245	c17orf3	<0.01	0.84	1.00
	rs2241245	GSDML	0.02	1.16×10^{-4}	0.45
PSMD3	rs2227321	PSMD3	<0.01	0.64	1.00
	rs2227321	GRB7	<0.01	0.90	1.00
	rs2227321	ORMDL3	0.05	7.24×10^{-11}	2.79×10^{-7}
	rs2227321	IKZF3	<0.01	0.09	1.00
	rs2227321	ERBB2	<0.01	0.11	1.00
	rs2227321	PNMT	<0.01	0.14	1.00
	rs2227321	CSF3	<0.01	0.54	1.00
	rs2227321	TCAP	<0.01	0.04	1.00
	rs2227321	MED24 (THRAP4)	0.02	5.10×10^{-5}	0.20
	rs2227321	ZPBP2	<0.01	0.89	1.00
	rs2227321	STARD3	<0.01	0.05	1.00
	rs2227321	c17orf3	<0.01	0.57	1.00
	rs2227321	PERLD1	<0.01	0.60	1.00
	rs2227321	GSDM1	<0.01	0.80	1.00
	rs2227321	GSDML	0.04	2.41×10^{-10}	9.31×10^{-7}
CSF3	rs1042658	ORMDL3	0.03	2.55×10^{-7}	9.81×10^{-4}
	rs1042658	MED24 (THRAP4)	0.07	6.79×10^{-16}	2.62×10^{-12}
	rs1042658	PNMT	<0.01	0.09	1.00
	rs1042658	TCAP	0.01	0.02	1.00
	rs1042658	ERBB2	<0.01	0.26	1.00
	rs1042658	PSMD3	0.01	4.75×10^{-4}	1.00
	rs1042658	GRB7	<0.01	0.71	1.00
	rs1042658	GSDML	0.03	2.35×10^{-7}	9.05×10^{-4}
	rs1042658	IKZF3	<0.01	0.29	1.00
	rs1042658	STARD3	0.01	0.02	1.00
	rs1042658	c17orf3	<0.01	0.82	1.00
	rs1042658	PERLD1	<0.01	0.26	1.00
	rs1042658	GSDM1	<0.01	0.96	1.00
	rs1042658	CSF3	<0.01	0.29	1.00
	rs1042658	ZPBP2	<0.01	0.92	1.00
MED24	rs8065443	GSDML	0.05	9.78×10^{-11}	3.77×10^{-7}
	rs8065443	ERBB2	<0.01	0.83	1.00
	rs8065443	ORMDL3	0.04	6.73×10^{-9}	2.59×10^{-5}
	rs8065443	ZPBP2	<0.01	0.77	1.00
	rs8065443	GSDM1	<0.01	0.78	1.00
	rs8065443	PNMT	0.01	3.12×10^{-3}	1.00

	rs8065443	<i>STARD3</i>	0.01	0.01	1.00
	rs8065443	<i>GRB7</i>	<0.01	0.32	1.00
	rs8065443	<i>IKZF3</i>	<0.01	0.10	1.00
	rs8065443	<i>PERLD1</i>	<0.01	0.23	1.00
	rs8065443	<i>MED24 (THRAP4)</i>	0.05	9.96×10^{-12}	3.84×10^{-8}
	rs8065443	<i>PSMD3</i>	0.01	0.01	1.00
	rs8065443	<i>c17orf3</i>	<0.01	0.87	1.00
	rs8065443	<i>TCAP</i>	0.01	0.02	1.00
	rs8065443	<i>CSF3</i>	<0.01	0.35	1.00
<i>MED24</i>	rs2302776	<i>MED24 (THRAP4)</i>	<0.01	0.10	1.00
	rs2302776	<i>ZPBP2</i>	<0.01	0.51	1.00
	rs2302776	<i>GRB7</i>	<0.01	0.57	1.00
	rs2302776	<i>PNMT</i>	<0.01	0.10	1.00
	rs2302776	<i>c17orf3</i>	<0.01	0.83	1.00
	rs2302776	<i>TCAP</i>	<0.01	0.07	1.00
	rs2302776	<i>ORMDL3</i>	0.06	2.19×10^{-13}	8.45×10^{-10}
	rs2302776	<i>IKZF3</i>	0.01	4.03×10^{-4}	1.00
	rs2302776	<i>GSDM1</i>	<0.01	0.78	1.00
	rs2302776	<i>CSF3</i>	<0.01	0.34	1.00
	rs2302776	<i>PSMD3</i>	<0.01	0.08	1.00
	rs2302776	<i>ERBB2</i>	<0.01	0.26	1.00
	rs2302776	<i>STARD3</i>	<0.01	0.18	1.00
	rs2302776	<i>PERLD1</i>	<0.01	0.54	1.00
	rs2302776	<i>GSDML</i>	0.04	7.29×10^{-10}	2.81×10^{-6}

83 ^a Results are shown for all SNPs appearing in Table 2 and for which there is evidence of association with asthma related phenotypes. A
84 non-pruned list of all associations between SNPs and expression levels is available on request.

85 ^b P-value and r^2 from a regression of inverse rank transformed, normalized expression on allelic dosage at each SNP.

86 ^c Bonferroni corrected p-value based on the undertaking of 257 independent tests across 15 expression quantitative traits

87 ^d *GSDML* is equivalent to *GSDMB*; *GSDM1* is equivalent to *GSDMA*

88 Table E7. Top 10 crude associations of SNPs in chromosome 17 with expression of *ORMDL3*, *GSDML*, *IKZF3*
 89 and *MED24* genes

	SNP	Nearby gene ^a	BP position(Kb)	P-value ^c
<i>ORMDL3</i> expression	rs8067378	<i>ZPBP2</i> <i>GSDML</i>	35304874	5.60×10^{-49}
	rs2290400	<i>GSDML</i>	35319766	1.03×10^{-48}
	rs11557467	<i>ZPBP2</i>	35282160	1.75×10^{-48}
	rs9303277	<i>IKZF3</i>	35229995	3.61×10^{-48}
	rs2305480	<i>GSDML</i>	35315722	3.61×10^{-48}
	rs7216389	<i>GSDML</i>	35323475	1.03×10^{-46}
	rs4378650	<i>ORMDL3</i>	35334391	2.08×10^{-44}
	rs8076131	<i>ORMDL3</i>	35334438	1.05×10^{-37}
	rs4795405	<i>ORMDL3</i>	35341943	2.00×10^{-37}
	rs4794820	<i>ORMDL3</i>	35342870	8.71×10^{-36}
<i>GSDML</i> expression	rs8067378	<i>ZPBP2</i> <i>GSDML</i>	35304874	3.00×10^{-49}
	rs11557467	<i>ZPBP2</i>	35282160	9.44×10^{-49}
	rs2290400	<i>GSDML</i>	35319766	1.08×10^{-46}
	rs7216389	<i>GSDML</i>	35323475	1.08×10^{-44}
	rs2305480	<i>GSDML</i>	35315722	1.64×10^{-39}
	rs4378650	<i>ORMDL3</i>	35334391	2.18×10^{-39}
	rs9303277	<i>IKZF3</i>	35229995	4.63×10^{-39}
	rs8076131	<i>ORMDL3</i>	35334438	1.05×10^{-36}
	rs4795405	<i>ORMDL3</i>	35341943	1.45×10^{-33}
	rs4794820	<i>ORMDL3</i>	35342870	7.45×10^{-32}
<i>IKZF3</i> expression	rs9303277	<i>IKZF3</i>	35229995	6.56×10^{-31}
	rs11557467	<i>ZPBP2</i>	35282160	4.61×10^{-30}
	rs8067378	<i>ZPBP2</i> <i>GSDML</i>	35304874	7.22×10^{-30}
	rs7216389	<i>GSDML</i>	35323475	1.63×10^{-29}
	rs2290400	<i>GSDML</i>	35319766	6.31×10^{-29}
	rs4378650	<i>ORMDL3</i>	35334391	8.79×10^{-27}
	rs2941504	<i>PERLD1</i>	35084426	3.82×10^{-18}
	rs9899345	<i>IKZF3</i>	35208284	2.22×10^{-16}
	rs4252665	<i>ERBB2</i> <i>C17orf37</i>	35138909	2.22×10^{-16}
	rs2305480	<i>GSDML</i>	35315722	2.22×10^{-16}
<i>MED24</i> expression	rs1042658	<i>CSF3</i>	35427428	6.66×10^{-16}
	rs2241245	<i>PSMD3</i>	35404540	1.21×10^{-12}
	rs8065443	<i>MED24</i>	35462466	9.96×10^{-12}
	rs3859192	<i>GSDML</i>	35382174	2.02×10^{-10}
	rs8075668	<i>PSMD3</i>	35391149	1.13×10^{-8}

rs7502966	<i>SNORD124 THRA</i>	35470048	1.36×10^{-5}
rs6503534	<i>MED24</i>	35445450	1.73×10^{-5}
rs4795408	<i>GSDM1</i>	35361153	2.66×10^{-5}
rs8079416	<i>ORMDL3</i>	35346239	3.83×10^{-5}
rs4794820	<i>ORMDL3</i>	35342870	4.09×10^{-5}

- 90 ^a From online database SNP Function Prediction (FuncPred): <http://manticore.niehs.nih.gov/snpfunc.htm>. *GSDML* is equivalent to
91 *GSDMB*; *GSDM1* is equivalent to *GSDMA*
92 ^b This is a previously reported asthma-related SNP
93 ^c Complete list of associations for all SNPs is available from authors on request.

94 Table E8. Association of variants in the region of chromosome 17 between 35.0 and 35.5 Mb with expression
 95 quantitative traits for local genes based on a LD pruning threshold of $r^2 \geq 0.2$.

Nearby gene	SNP ^a	Expression quantitative Trait	n	r^2 ^b	p1 ^b	p2 ^c
<i>PERDL1</i>	rs14050	<i>IKZF3</i>	875	0.08	3.43×10^{-18}	3.24×10^{-15}
<i>PERDL1</i>	rs14050	<i>ORMDL3</i>	875	0.05	1.64×10^{-12}	1.55×10^{-9}
<i>PERDL1</i>	rs14050	<i>GSDML</i> ^d	875	0.05	1.18×10^{-10}	1.11×10^{-7}
<i>STAC2</i>	rs4795354	<i>IKZF3</i>	875	0.04	4.26×10^{-10}	4.02×10^{-7}
<i>CSF3</i>	rs25645	<i>ORMDL3</i>	875	0.04	5.72×10^{-10}	5.40×10^{-7}
<i>CRKRS NEUROD2</i>	rs11654018	<i>IKZF3</i>	875	0.04	1.17×10^{-9}	1.11×10^{-6}
<i>CSF3</i>	rs25645	<i>GSDML</i> ^d	875	0.04	2.35×10^{-9}	2.22×10^{-6}
<i>MED24</i>	rs7503939	<i>MED24</i>	875	0.02	1.1×10^{-5}	0.01
<i>NR1D1</i>	rs2269457	<i>ORMDL3</i>	875	0.02	1.7×10^{-5}	0.02
<i>CRKRS NEUROD2</i>	rs11654018	<i>ORMDL3</i>	875	0.02	2.7×10^{-5}	0.03
<i>STAC2</i>	rs1106769	<i>ORMDL3</i>	875	0.02	3.2×10^{-5}	0.03
<i>STAC2</i>	rs4795354	<i>ZPBP2</i>	875	0.02	3.4×10^{-5}	0.03
<i>CRKRS NEUROD2</i>	rs11654018	<i>GSDML</i> ^d	875	0.02	3.6×10^{-5}	0.03
<i>THRA</i>	rs12939700	<i>ORMDL3</i>	875	0.02	4.3×10^{-5}	0.04
<i>ORMDL3</i>	rs17608925	<i>IKZF3</i>	875	0.02	4.6×10^{-5}	0.04

96 ^a Results are shown where evidence for association exceeds a threshold when taking a Bonferroni corrected p value for 945 tests (63
 97 independent loci*15 expression quantitative traits). Thus all raw p values are <0.0002.

98 ^b p1 and r^2 indicates p value and r^2 from a regression of inverse rank transformed, normalized expression on allelic dosage at each
 99 SNP.

100 ^c Bonferroni corrected p values (based on 945 tests)

101 ^d *GSDML* is equivalent to *GSDMB*;

102 Table E9. Crude association of expression quantitative traits with wheezing phenotypes

Expression quantitative trait	r^2 ^a	Overall p ^a
<i>STARD3</i>	<0.01	0.69
<i>TCAP</i>	<0.01	0.85
<i>PNMT</i>	<0.01	0.20
<i>PERLD1</i>	<0.01	0.60
<i>ERBB2</i>	<0.01	0.91
<i>C17orf37</i>	<0.01	0.64
<i>GRB7</i>	<0.01	0.93
<i>IKZF3</i>	<0.01	0.81
<i>ZBP2</i>	<0.01	0.61
<i>GSDML</i>	<0.01	0.06
<i>ORMDL3</i>	<0.01	0.65
<i>GSDM1</i>	<0.01	0.62
<i>PSMD3</i>	<0.01	0.08
<i>CSF3</i>	<0.01	0.57
<i>MED24</i>	<0.01	0.91

103 ^a r^2 and overall p are from a linear regression of wheezing phenotypes on inverse rank transformed normalized expression
 104 ^b *GSDML* is equivalent to *GSDMB*; *GSDM1* is equivalent to *GSDMA*
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ONLINE REPOSITORY

Examination of the relationship between variation at 17q21 and childhood wheeze phenotypes

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ONLINE REPOSITORY FIGURES

Figure A1 Quantile-quantile plots of 257 SNPs in the region of chromosome 17 between 34 and 36 Mb for associations with doctor-diagnosed asthma ever, skin prick test positivity, bronchial hyper responsiveness, FVC, FEV₁ and FEF₂₅₋₇₅. Observed p-values to those expected for a null distribution. 13 previously reported asthma-related SNPs are highlighted in red. Dashed lines correspond to the 95% confidence intervals.

Figure A2 P-values for conditional associations of 244 SNPs between 34 and 36 Mb on chromosome 17 with doctor-diagnosed asthma ever, skin prick test positivity, bronchial hyper responsiveness, FVC, FEV₁ and FEF₂₅₋₇₅. The vertical red lines delineate the region of 17q21 between 35.2 and 35.4 Mb, around *ORMDL3*.

Figure A3 Crude odds ratios and mean differences for associations of 257 SNPs between 34 and 36 Mb on chromosome 17 with doctor-diagnosed asthma ever, skin prick test positivity, bronchial hyper responsiveness, FVC, FEV₁ and FEF₂₅₋₇₅. The vertical red lines delineate the region of 17q21 between 35.2 and 35.4 Mb, around *ORMDL3* containing 13 previously reported asthma-related SNPs (highlighted in red). OR=Odds ratios; SD=Standard deviations (Z-scores).

Figure A4 Conditional odds ratios and mean differences for associations of 244 SNPs between 34 and 36 Mb on chromosome 17 with doctor-diagnosed asthma ever, skin prick test positivity, bronchial hyper responsiveness, FVC, FEV₁ and FEF₂₅₋₇₅. The vertical red lines delineate the region of 17q21 between 35.2 and 35.4 Mb, around *ORMDL3*. OR=Odds ratios; SD=Standard deviations (Z-scores).

Figure A5 Quantile-quantile plots of 257 SNPs in the region of chromosome 17 between 34 and 36 Mb for association to wheezing phenotypes. Observed p-values to those expected for

a null distribution. 13 previously reported asthma-related SNPs are highlighted in red.

Dashed lines correspond to the 95% confidence intervals.

Figure A6 P-values for conditional associations of 244 SNPs between 34 and 36 Mb on chromosome 17 with wheezing phenotypes. The vertical red lines delineate the region of 17q21 between 35.2 and 35.4 Mb, around *ORMDL3*.

Figure A7 Crude relative risk ratios for conditional associations of 257 SNPs between 34 and 36 Mb on chromosome 17 with wheezing phenotypes. The vertical red lines delineate the region of 17q21 between 35.2 and 35.4 Mb, around *ORMDL3* containing 13 previously reported asthma-related SNPs (highlighted in red). RRR= relative risk ratios

Figure A8 Conditional relative risk ratios for conditional associations of 244 SNPs between 34 and 36 Mb on chromosome 17. The vertical red lines delineate the region of 17q21 between 35.2 and 35.4 Mb, around *ORMDL3*. RRR= relative risk ratios.

Figure A9 Cumulative incidence of wheezing between 0 and 81 months stratified by rs8076131 and rs2305480 genotypes.

Figure A10 Inverse log10 transformed P-values for crude associations of 257 independent SNPs between 34 and 36 Mb on chromosome 17 with gene specific expression levels. The vertical red lines delineate the region of 17q21 between 35.2 and 35.4 Mb, around *ORMDL3* containing 13 previously reported asthma-related SNPs (highlighted in red). Grey gene tracks show loci in the order *PNMT*, *PERLD1*, *ERBB2*, *GRB7*, *C17ORF37*, *IKZF3*, *ZBP2*, *GSDML*, *GSDM1*, *PSMD3*, *CSF3*, *MED24* with *ORMDL3* marked in green and the locus with reported expression result marker in orange.