

Shared and distinct genetic risk factors for childhood-onset and adult-onset asthma: genome-wide and transcriptome-wide studies



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Summary

Background Childhood-onset and adult-onset asthma differ with respect to severity and comorbidities. Whether they also differ with respect to genetic risk factors has not been previously investigated in large samples. The goals of this study were to identify shared and distinct genetic risk loci for childhood-onset and adult-onset asthma, and to identify the genes that might mediate the effects of associated variation.

Methods We did genome-wide and transcriptome-wide studies, using data from the UK Biobank, in individuals with asthma, including adults with childhood-onset asthma (onset before 12 years of age), adults with adult-onset asthma (onset between 26 and 65 years of age), and adults without asthma (controls; aged older than 38 years). We did genome-wide association studies (GWAS) for childhood-onset asthma and adult-onset asthma each compared with shared controls, and for age of asthma onset in all asthma cases, with a genome-wide significance threshold of $p < 5 \times 10^{-8}$. Enrichment studies determined the tissues in which genes at GWAS loci were most highly expressed, and PrediXcan, a transcriptome-wide gene-based test, was used to identify candidate risk genes.

Findings Of 376 358 British white individuals from the UK Biobank, we included 37 846 with self-reports of doctor-diagnosed asthma: 9433 adults with childhood-onset asthma; 21 564 adults with adult-onset asthma; and an additional 6849 young adults with asthma with onset between 12 and 25 years of age. For the first and second GWAS analyses, 318 237 individuals older than 38 years without asthma were used as controls. We detected 61 independent asthma loci: 23 were childhood-onset specific, one was adult-onset specific, and 37 were shared. 19 loci were associated with age of asthma onset. The most significant asthma-associated locus was at 17q12 (odds ratio 1·406, 95% CI 1·365–1·448; $p = 1·45 \times 10^{-111}$) in the childhood-onset GWAS. Genes at the childhood onset-specific loci were most highly expressed in skin, blood, and small intestine; genes at the adult onset-specific loci were most highly expressed in lung, blood, small intestine, and spleen. PrediXcan identified 113 unique candidate genes at 22 of the 61 GWAS loci. Single-nucleotide polymorphism-based heritability estimates were more than three times larger for childhood-onset asthma (0·327) than for adult-onset disease (0·098). The onset of disease in childhood was associated with additional genes with relatively large effect sizes, with the largest odds ratio observed at the *FLG* locus at 1q21·3 (1·970, 95% CI 1·823–2·129).

Interpretation Genetic risk factors for adult-onset asthma are largely a subset of the genetic risk for childhood-onset asthma but with overall smaller effects, suggesting a greater role for non-genetic risk factors in adult-onset asthma. Combined with gene expression and tissue enrichment patterns, we suggest that the establishment of disease in children is driven more by dysregulated allergy and epithelial barrier function genes, whereas the cause of adult-onset asthma is more lung-centred and environmentally determined, but with immune-mediated mechanisms driving disease progression in both children and adults.

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Introduction

Asthma is the most prevalent chronic respiratory disease worldwide.¹ The diagnosis of asthma is based on the presence of reversible airflow obstruction and clinical symptoms that include wheeze, cough, and shortness of breath. Despite these shared features, asthma probably comprises many different conditions. In particular, childhood-onset asthma and adult-onset asthma differ with respect to sex ratios, triggers of exacerbation, associated comorbidities, severity,^{2,3} and potentially

genetic risk factors.^{4,5} For example, a genome-wide association study (GWAS)⁶ showed that the most often replicated and most statistically significant single-nucleotide polymorphisms (SNPs) at the 17q12–21 locus are specific to asthma with onset of symptoms in early life. Only one asthma GWAS to date has been conducted on adult-onset asthma, and this was as a subanalysis of a larger sample that also included childhood-onset asthma and asthma with unknown age of onset. The GABRIEL Consortium included 1947 people with adult-onset

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Research in context

Evidence before this study

We searched PubMed for genome-wide association studies of childhood-onset asthma, adult-onset asthma, and age of asthma onset from database inception to July 1, 2018, using the terms "asthma", "GWAS", and "age of onset", and manually searched those papers for age of onset-specific studies of asthma. No language restriction was applied. We included studies with more than 1000 cases and 1000 controls and considered only loci that met genome-wide significance ($p < 5 \times 10^{-8}$). These previous studies reported five genome-wide significant loci for childhood-onset asthma, none for adult-onset asthma, and five for age to asthma onset. Genome-wide association studies in large samples that include both childhood-onset and adult-onset asthma identified many loci associated with asthma risk. However, little was known about the shared or distinct effects of those or other loci on age of asthma onset, or about the genes that might mediate the effects of loci associated with childhood-onset or adult-onset asthma.

Added value of this study

Leveraging the resources of the UK Biobank, we identified loci with both age of onset-specific effects and shared effects. We further showed a significantly greater contribution of genetic variation to childhood-onset asthma, implying a greater role for environmental risk factors in adult-onset asthma, and different biological pathways and tissue enrichments for genes at loci associated with childhood-onset versus adult-onset asthma.

Implications of all the available evidence

Our results suggest that childhood onset-specific loci and those associated with age of onset play a part in disease initiation, whereas the other associated loci reflect shared mechanisms of disease progression. The childhood onset-specific loci highlight skin as a primary target tissue for early-onset disease and support the idea that asthma in childhood is due to impaired barrier function in the skin and other epithelial surfaces.

asthma (defined as 16 years of age or older) and 3669 adult controls.⁷ Overall, genome-wide significant variants in the combined sample of 10 365 cases and 16 110 controls revealed larger odds ratios (ORs) in the childhood-onset group than in the adult-onset group,⁷ but no loci reached significance in the adult-onset cases, probably because of low power. Therefore, whether loci other than 17q12–21 contribute specifically to childhood-onset or adult-onset asthma remains unknown. Delineation of genetic risk factors that affect age of onset from those that are shared between childhood-onset and adult-onset asthma could provide insights into the molecular mechanisms contributing to different clinical manifestations of asthma that is diagnosed at different ages.

To address this question and directly compare genetic risk architectures of adult-onset and childhood-onset asthma, we used data from the UK Biobank, a large-scale prospective study collecting demographic, clinical, medical history, and genetic data for nearly 500 000 participants.⁸ Our goals were to identify shared and distinct genetic risk loci for childhood-onset and adult-onset asthma, and to identify genes that might mediate the effects of associations at age of onset-specific loci and those shared between childhood-onset and adult-onset asthma.

Methods

Study design and participants

We did GWAS and transcriptome-wide studies across three categories: childhood-onset cases (compared with controls without asthma), adult-onset cases (compared with controls without asthma), and asthma cases with onset in childhood, adolescence and young adulthood, or adulthood (to assess age of onset).

We used data for British white individuals from UK Biobank data release July 19, 2017.⁸ We extracted disease status (asthma, allergic rhinitis, atopic dermatitis, food allergy, chronic obstructive pulmonary disease (COPD), emphysema, and chronic bronchitis), age of onset of asthma, and sex from self-reported questionnaires and hospital records (International Classification of Diseases 10th revision [ICD-10] codes) by querying our in-house protected UK Biobank database server.⁹ For our main case analysis, we included individuals who self-reported that they had doctor-diagnosed asthma. Further details of our research approach are provided in the appendix (pp 4–7).

We defined childhood-onset and adult-onset asthma using strict age of onset criteria that would minimise the likelihood of misclassification; we considered asthma cases with onset at younger than 12 years as childhood-onset cases and those with onset between 26 years and 65 years of age as adult-onset cases. UK Biobank participants aged older than 38 years without an asthma diagnosis (ie, no self-reports and no ICD-10 codes) were included as controls. Individuals with COPD, emphysema, or chronic bronchitis (self-reports or ICD-10 codes) were excluded from adult-onset cases and controls. Additionally, for the age-of-onset GWAS, we included UK Biobank participants with asthma (according to the inclusion and exclusion criteria above) with onset between the ages of 12 and 25 years. Additional details on genotype quality control and phenotype definitions are provided in the appendix (pp 4–7).

Genome-wide association studies

We did a childhood-onset and an adult-onset GWAS by logistic regression and an age-of-onset GWAS by linear regression, all using the allele dosages under an additive genetic model, as implemented in Hail. We used the

See Online for appendix

For more on Hail see
<https://github.com/hail-is/hail>

Bionimbus Protected Data Cloud for all analyses.¹⁰ In all three GWAS, we included sex and the first ten genetic principal components as covariates (to adjust for ancestry) and used a genome-wide significance threshold of $p < 5 \times 10^{-8}$. We used FUMA,¹¹ an integrative post-GWAS annotation web-based tool, to define independent risk loci and identify enriched tissues. FUMA defines independent loci using linkage disequilibrium information from the 1000 Genomes Project.¹² We specified an r^2 threshold of more than 0.6 between genome-wide significant SNPs to represent a single locus. We calculated tissue enrichments in FUMA using a hypergeometric test to determine over-representation of genes mapped to risk loci (by physical distance) among highly expressed genes in each tissue in the Genotype-Tissue Expression project relative to all others.

Childhood-onset and adult-onset specific loci were defined as those that were genome-wide significant in either the childhood-onset or adult-onset GWAS but were not associated with asthma at $p < 0.05$ in the other group and the 95% CIs of the respective ORs did not overlap. Shared loci were defined as those that were genome-wide significant in at least one of the childhood-onset or adult-onset GWAS and had $p < 0.05$ in both GWAS and overlapping 95% CIs. For regions where the lead SNP differs between GWAS, the SNP with the lowest p value across all three GWAS is referenced. Colocalisation of variants associated with childhood-onset and adult-onset asthma were also tested using pairwise GWAS.¹³ For this analysis, adult-onset GWAS results were input as phenotype 1 and childhood-onset GWAS results were input as phenotype 2.

SNP-based heritability estimation

We used linkage disequilibrium score regression to estimate the SNP-based heritability from the childhood-onset, adult-onset, and age-of-onset GWAS summary statistics. For this analysis, we used SNPs identified as risk loci in this study, and selected those that overlapped with known HapMap3 variants (a database of SNP population frequency),¹⁴ with an estimate of population prevalence of 8.68% for childhood-onset asthma and 9.55% for adult-onset asthma.¹⁵ Heritability estimates for binary traits are reported in the liability scale.

Sensitivity analysis

We did two sets of post-hoc sensitivity analyses to assess the effects of potential poor recall of age of onset among individuals with adult-onset asthma, and the effects of misclassification of COPD as asthma among the adult-onset cases, even with exclusion of cases with a reported diagnosis of COPD, emphysema, or chronic bronchitis. First, to assure that the adult-onset cases did not include a significant proportion of childhood-onset asthma in which symptoms remitted in early life but then relapsed in adulthood, we replaced adult-onset cases with increasing proportions of randomly selected childhood-

onset cases, and then tested for association at the two most significant childhood onset-specific loci. This procedure was repeated 20 times for each proportion to quantify the sampling variability (appendix pp 7–8). Second, we did two analyses in which we removed either individuals with ages of asthma onset between 46 and 65 years or adult-onset cases and controls with FEV₁/FVC < 0.70 . For each, we compared p values and ORs with the GWAS including all adult-onset cases (appendix pp 8–9).

We also repeated the GWAS analyses while varying the numbers of principal components (10, 14, or 20; appendix p 12) and limiting the sample to cases with diagnoses based on ICD-10 codes (appendix pp 13–14). To test for potential effects of asthma diagnostic criteria on the GWAS results, we did a GWAS comparing individuals with asthma based on self-reported doctor diagnosis alone compared with those with self-reported doctor diagnosis plus ICD-10 codes.

Predicted transcriptome association test

We used the PrediXcan¹⁶ framework to identify genes that might mediate associations between genetic variants and asthma risk. PrediXcan is a software tool that estimates tissue-specific gene expression profiles from an individual's SNP genotype profile by use of prediction models trained in large reference databases of genotypes and tissue-specific gene expression profiles. With these genotype-imputed expression profiles, PrediXcan can perform gene-based association tests that correlate predicted expression levels with phenotypes (eg, asthma) to identify candidate causal genes from GWAS data. We used a summary version of PrediXcan, which has high concordance with the individual-level version ($r^2 > 0.99$).¹⁷ For predictions, we downloaded elastic net models trained with reference transcriptome data from the

For more on the **Genotype-Tissue Expression** project see <https://gtexportal.org/home/>

	Childhood onset (n=9433)	Adolescent or young adult onset (n=6849)	Adult onset (n=21 564)	Controls (n=318 237)
Age at recruitment, years	55 (8); 40–70	52 (8); 40–70	57 (8); 40–70	57 (8); 39–73
Age at asthma onset, years	6 (3); 0–11	19 (4); 12–25	44 (10); 26–65	NA
Sex				
Female	3840 (40.7%)	3934 (57.4%)	13 708 (63.6%)	170 144 (53.5%)
Male	5593 (59.3%)	2915 (42.6%)	7856 (36.4%)	148 093 (46.5%)
Asthma medication use in the past 12 months	1383 (14.7%)	1124 (16.4%)	4081 (18.9%)	NA
Current smokers	802 (8.5%)	688 (10.0%)	1379 (6.4%)	30 056 (9.4%)
Allergic diseases ever				
Allergic rhinitis*	2537 (26.9%)	2042 (29.8%)	4660 (21.6%)	27 289 (8.6%)
Atopic dermatitis*	1126 (11.9%)	473 (6.9%)	927 (4.3%)	7168 (2.3%)
Food allergy†	138 (1.5%)	63 (0.9%)	172 (0.8%)	1229 (0.4%)
Any allergic disease‡	3205 (34.0%)	2321 (33.9%)	5306 (24.6%)	33 808 (10.6%)

Data are mean (SD); range or n (%). NA=not applicable. *Based on self-reports and International Classification of Diseases 10th revision codes. †Based on self-reports. ‡Based on self-reports, International Classification of Diseases 10th revision codes, or both.

Table 1: Baseline characteristics

Genotype-Tissue Expression consortium¹⁸ for 49 tissues (appendix pp 9, 47).

PrediXcan was run separately in the childhood-onset and adult-onset cases, each with the same controls. For the transcriptome-wide analysis, we analysed genes that were expressed in the tissues determined by FUMA to be enriched, using a Bonferroni correction to determine significance ($p < 1.29 \times 10^{-6}$). We defined childhood onset-specific genes as those with predicted expression significantly associated with childhood-onset asthma and the variants that predicted their expression using the PrediXcan models were within childhood onset-specific loci in our GWAS. Adult onset-specific genes were similarly defined. Because SNPs at shared loci might predict the expression of genes that are associated only in childhood-onset or adult-onset cases, we also considered genes to be age of onset-specific if they were significantly associated with asthma at $p < 1.29 \times 10^{-6}$ in one age group and not associated with asthma at $p < 0.05$ in the other. All other genes were considered to be shared.

Role of the funding source

The funder of the study had no role in study design; collection, analysis, or interpretation of data; in writing of the manuscript; in the decision to submit the paper for publication; or in determining who had access to the raw data. The corresponding author had full access to all of

the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 376 358 British white individuals from the UK Biobank, we included 37846 with self-reports of doctor-diagnosed asthma: 9433 adults with childhood-onset asthma (3462 [36.7%] of whom also had hospital records with an asthma diagnosis [ICD-10 codes]); 21564 adults with adult-onset asthma (9260 [42.9%] with ICD-10 codes); and an additional 6849 young adults with asthma with onset between the ages of 12 and 25 years of age (2797 [40.8%] with ICD-10 codes). For the first and second GWAS analyses, 318 237 individuals older than 38 years without asthma were used as controls. 20 275 individuals from UK Biobank did not have asthma but were excluded as controls because they had been diagnosed with COPD, emphysema, or chronic bronchitis. Characteristics of the total sample ($n=37846$) are shown in table 1. After genotype quality control, 10 894 596 variants were available for analyses.

The GWAS of childhood-onset and adult-onset asthma revealed 61 independent loci associated with asthma. 56 were significant in the childhood-onset asthma GWAS, and 19 were significant in the adult-onset asthma GWAS ($p < 5 \times 10^{-8}$; figure 1). 28 of the 61 loci, in 27 chromosomal regions, were not previously reported in the GWAS catalogue,¹⁹ including one study also done in UK Biobank participants but focused on the phenotype

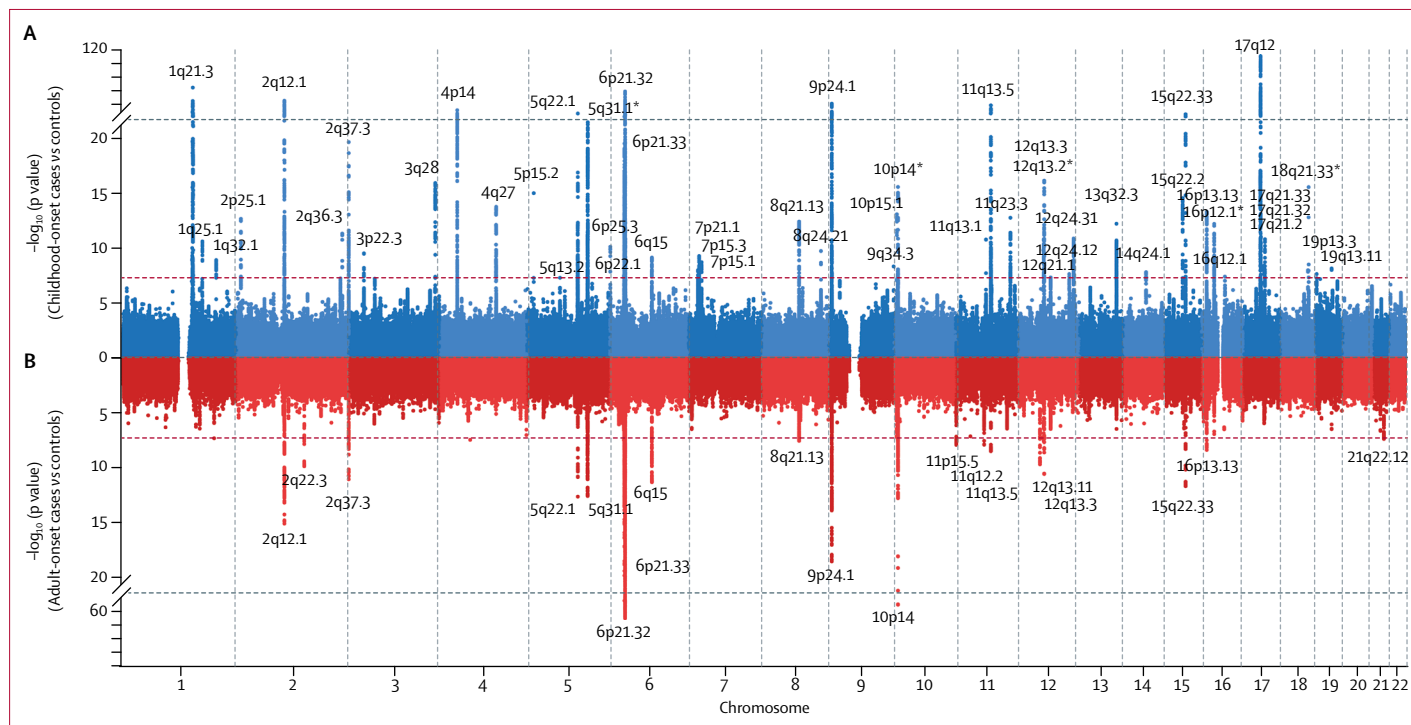


Figure 1: Miami plot of childhood-onset and adult-onset asthma GWAS

Miami plot showing results for the childhood-onset versus controls GWAS (A) and adult-onset versus controls GWAS (B). Each point corresponds to a SNP; the y-axes show the $-\log_{10}$ p values from the childhood-onset GWAS and adult-onset GWAS. The x-axis shows the position of each SNP along the 22 autosomes. The red dashed line indicates the genome-wide significance threshold (5×10^{-8}). See appendix p 41 for the age of asthma onset Manhattan plot. GWAS=genome-wide association study. SNP=single-nucleotide polymorphism. *Chromosomal bands with two independent loci.

asthma plus allergies.²⁰ Among the 28 new loci, 17 were significant in the childhood-onset GWAS, one was significant in the adult-onset GWAS, and ten were shared (table 2). Some of these loci contained genes that have been associated with asthma in candidate gene studies (eg, *FADS2*,²¹ *MUC5AC*,^{22,23} and *TBX21*²⁴). The lead SNP or a linkage disequilibrium surrogate SNP ($r^2 > 0.40$) was reported for 23 of the 28 new loci in the Transnational Asthma Genetics Consortium GWAS.²⁵ SNPs at 16 of the 23 loci were associated with asthma in the Transnational Asthma Genetics Consortium GWAS ($p < 0.05$) and had the same direction of effects as in the UK Biobank GWAS (appendix p 58).

As in previous GWAS comprising largely children, the most significant locus in the childhood-onset GWAS was at 17q12 (OR 1.406, 95% CI 1.365–1.448; $p = 1.45 \times 10^{-11}$), with the lead SNP in *GSDMB* (figure 1A, table 2).²⁶ However, the estimated ORs for the lead SNPs at three other loci were similar to or larger than the OR for the lead SNP at the 17q12 locus. The lead SNPs in *ILIR1* at 2q12.1 and in *EMSY* at 11q13.5, both of which were shared risk loci between adult-onset and childhood-onset asthma, had effect sizes on childhood-onset asthma similar to the lead SNP in *GSDMB* on 17q12 (table 2). Both loci have been prominent in previous asthma GWAS.^{7,25} The lead SNP at the 1q21.3 locus, corresponding to a nonsense mutation (Arg501X) in the filaggrin (*FLG*) gene at 1q21.3, had the largest OR overall and was specific to childhood-onset asthma (OR 1.970, 95% CI 1.823–2.129; $p = 1.88 \times 10^{-65}$; table 2). Variants in *FLG* have been robustly associated with food allergies^{27–29} and atopic dermatitis,^{30–32} but previous associations with asthma have been in the context of other allergic conditions.^{20,33} Whether variants in *FLG* are associated with risk for childhood-onset asthma independent of its effects on early life allergic disease is yet unknown. To address this possibility, we repeated the childhood-onset GWAS after excluding 3205 individuals with childhood-onset asthma and 5785 controls who reported having a history of allergic rhinitis, atopic dermatitis, or food allergy. As expected in a smaller sample, the p values were larger overall, but the ORs were strikingly similar (appendix pp 16, 59–60). Even though the OR at the *FLG* locus on 1q21.3 decreased from 1.970 (95% CI 1.823–2.129) to 1.612 (1.492–1.743), it remained both highly significant ($p = 2.45 \times 10^{-19}$) and the largest OR for childhood onset.

The most significant association in the adult-onset GWAS was in the HLA region, with independent associations at the HLA-C/B (6p21.33) and HLA-DR/DQ (6p21.32) loci, both of which were shared risk loci between adult-onset and childhood-onset asthma (figure 1B). Compared with the childhood-onset GWAS, effect sizes were quite small in adult-onset cases, with ORs reaching 1.1 at only six loci (2q12.1, 6p21.33, 6p21.32, 9p24.1, 10p14, and 19q13.11; table 2).

Among the 61 asthma loci, 23 were specific to childhood-onset asthma and one was specific to adult-onset asthma

(table 2). Regional association plots for the 24 loci with childhood onset-specific or adult onset-specific effects are shown in the appendix (pp 17–40). Among the remaining 37 shared loci (table 2), mean ORs were larger in the childhood-onset cases at all but six loci (permutation test $p < 10^{-4}$; appendix pp 8–9), indicating both that more loci contribute to childhood-onset asthma, and that even among shared loci the effect sizes are larger in childhood-onset asthma cases (figure 2). Colocalisation analyses using pairwise GWAS¹³ yielded results that supported our classification of age of onset-specific and shared loci (appendix pp 61–62).

To directly test for loci associated with asthma age of onset, we did a third GWAS of all individuals with asthma in the UK Biobank who met our inclusion criteria ($n = 37846$), including those with onset during adolescence or young adulthood ($n = 6849$). In this analysis, 19 loci were associated with age of onset ($p < 5 \times 10^{-8}$; appendix pp 41, 63). Age-of-onset loci overlapped with the childhood onset-specific, adult onset-specific, and shared loci, and asthma risk alleles at all but two loci were associated with earlier age of onset in the age-of-onset GWAS (11q12 in the *FADS2* gene and 12q13.11 near the *VDR* gene; table 2; figure 2). SNPs at the 1q21.3 locus (*FLG*) had the largest effect on age of onset, with an average 4.57 years (SE 0.43) earlier onset in individuals with a copy of the risk allele (rs61816761) than in individuals with the non-risk allele ($p = 8.15 \times 10^{-27}$). At the 17q12 locus (rs4795399), each copy of the risk allele was associated on average with 2.29 years (SE 0.13) earlier onset than individuals without the risk allele ($p = 6.76 \times 10^{-65}$), so individuals who were homozygous for the risk allele had on average 4.6 years earlier onset asthma than those who were homozygous for the non-risk allele. Examples of significant age-of-onset effects at these and other loci are shown in figure 3. Overall, both childhood onset-specific and shared asthma risk loci were associated with younger ages of onset than were adult onset-specific loci, and alleles at loci associated with younger ages of onset had larger effects than did alleles at loci associated with later ages of onset.

We used linkage disequilibrium score regression to estimate the heritabilities of childhood-onset asthma, adult-onset asthma, and age of asthma onset. Consistent with the number of associated SNPs and their effect sizes, estimated heritabilities were 0.327 for childhood-onset asthma, 0.098 for adult-onset asthma, and 0.136 for age of asthma onset. After excluding the significant SNPs (table 2), estimates were reduced to 0.213 for childhood-onset asthma, 0.082 for adult-onset asthma, and 0.087 for age of asthma onset, indicating that the associated SNPs account for 0.114 of the variance in childhood-onset asthma risk, 0.016 of the variance in adult-onset risk, and 0.049 of the variance in age of asthma onset risk.

We assessed whether the tissue-specific expression of genes that mapped to the 56 childhood-onset loci differed from the tissue-specific expression of genes that mapped to the 19 adult-onset loci. Genes at childhood-onset loci

	rsID	Position*	Nearby genes†	Allele‡	RAF§	Childhood-onset asthma GWAS			Adult-onset asthma GWAS			Age-of-onset GWAS		
						OR	95% CI	p value	OR	95% CI	p value	β value	SE	p value
Childhood-onset asthma-specific loci														
1q21.3	rs61816761	1:152285861	FLG, HRNR, FLG2	G/A	0.024	1.970	1.823–2.129	1.88 × 10 ⁻⁶⁵	1.016	0.948–1.088	6.56 × 10 ⁻⁹¹	-4.571	0.426	8.15 × 10 ⁻²⁷
1q25.1	rs7518129	1:173163568	TNFSF4, TNFSF18, PRDX6	A/G	0.310	1.111	1.077–1.146	2.21 × 10 ⁻¹¹	0.997	0.977–1.019	8.17 × 10 ⁻⁹¹	-0.849	0.145	4.89 × 10 ⁻⁹⁹
2q36.3¶	rs10175070	2:228670575	CCL20, SLC18A3	A/G	0.251	1.122	1.086–1.160	4.31 × 10 ⁻¹²	1.000	0.978–1.023	9.92 × 10 ⁻⁹¹	-0.862	0.154	2.24 × 10 ⁻⁹⁸
3q28	rs12634152	3:188121019	LPP, FLJ42393, LPP-AS1	C/T	0.547	1.133	1.100–1.166	1.08 × 10 ⁻¹⁶	1.007	0.987–1.027	4.98 × 10 ⁻⁹¹	-0.968	0.136	1.21 × 10 ⁻¹²
4p14	rs5743618	4:38798648	TLR1, TLR10, TLR6	A/C	0.774	1.249	1.203–1.295	3.19 × 10 ⁻³²	1.008	0.985–1.032	5.09 × 10 ⁻⁹¹	-1.578	0.163	4.53 × 10 ⁻²²
5q13.2¶	rs10036789	5:71695918	PTCD2, ZNF366	C/G	0.460	1.085	1.054–1.117	4.51 × 10 ⁻⁹⁸	1.016	0.996–1.036	1.12 × 10 ⁻⁹¹	-0.511	0.137	1.95 × 10 ⁻⁹⁴
5q31.1	rs2051809	5:132056874	KIF3A, IL4, CCNI2	C/A	0.247	1.175	1.137–1.214	3.24 × 10 ⁻²²	1.016	0.994–1.040	1.58 × 10 ⁻⁹¹	-0.933	0.155	1.59 × 10 ⁻⁹⁹
6p25.3¶	rs9391997	6:409119	IRF4, DUSP22, EXOC2	A/G	0.527	1.102	1.070–1.135	6.89 × 10 ⁻¹¹	0.995	0.976–1.015	6.35 × 10 ⁻⁹¹	-0.597	0.136	1.06 × 10 ⁻⁹⁵
7p15.3¶	rs34880821	7:22775450	IL6, TOMM7	G/A	0.283	1.106	1.071–1.141	4.73 × 10 ⁻¹⁰	1.000	0.979–1.022	9.88 × 10 ⁻⁹¹	-0.667	0.149	7.59 × 10 ⁻⁹⁶
8q24.21¶	rs13277355	8:128777719	MYC, TMEM75	G/A	0.274	1.110	1.075–1.146	1.65 × 10 ⁻¹⁰	1.013	0.991–1.036	2.46 × 10 ⁻⁹¹	-0.660	0.151	1.20 × 10 ⁻⁹⁵
9q34.3¶	rs117137535	9:140500443	ARRDC1, ZMYND19, EHMT1	G/A	0.026	1.307	1.195–1.429	4.16 × 10 ⁻⁹⁹	0.977	0.913–1.046	5.10 × 10 ⁻⁹¹	-2.464	0.446	3.42 × 10 ⁻⁹⁸
10p15.1¶	rs943451	10:6621773	PRKCQ, PFKFB3, SFMBT2	C/T	0.318	1.125	1.091–1.161	7.51 × 10 ⁻¹⁴	1.021	1.000–1.043	5.30 × 10 ⁻⁹²	-0.613	0.145	2.54 × 10 ⁻⁹⁵
11q13.1¶	rs479844	11:65551957	AP5B1, OVOL1	A/G	0.555	1.106	1.074–1.139	1.48 × 10 ⁻¹¹	1.015	0.995–1.035	1.41 × 10 ⁻⁹¹	-0.657	0.135	1.22 × 10 ⁻⁹⁶
11q23.3¶	rs12365699	11:118743286	CXCR5, DDX6	A/G	0.833	1.167	1.120–1.216	1.57 × 10 ⁻¹³	1.004	0.978–1.031	7.43 × 10 ⁻⁹¹	-1.396	0.185	4.42 × 10 ⁻¹⁴
12q13.2¶	rs62623446	12:55368291	TESPA1, MUC1, NEUROD4	C/T	0.072	1.188	1.127–1.252	1.40 × 10 ⁻¹⁰	1.038	0.999–1.077	5.32 × 10 ⁻⁹²	-1.079	0.253	1.95 × 10 ⁻⁹⁵
12q24.12¶	rs10774625	12:111910219	ATXN2, SH2B3, BRAP	A/G	0.504	1.087	1.056–1.119	2.07 × 10 ⁻⁹⁸	0.997	0.978–1.017	7.92 × 10 ⁻⁹¹	-0.713	0.135	1.43 × 10 ⁻⁹⁷
12q24.31¶	rs1696361	12:121363823	SPPL3, HNF1A	C/T	0.359	1.109	1.076–1.142	1.19 × 10 ⁻¹¹	1.019	0.998–1.040	6.96 × 10 ⁻⁹²	-0.696	0.140	6.84 × 10 ⁻⁹⁷
17q12	rs4795399	17:38061439	GSDMB, ZBP2, ORMDL3	C/T	0.529	1.406	1.365–1.448	1.45 × 10 ⁻¹¹¹	1.005	0.985–1.025	6.28 × 10 ⁻⁹¹	-2.286	0.134	6.76 × 10 ⁻⁶⁵
17q21.2¶	rs8066625	17:40390629	STAT5B, GHDC, STAT5A	G/A	0.100	1.151	1.098–1.206	4.90 × 10 ⁻⁹⁹	1.006	0.973–1.040	7.33 × 10 ⁻⁹¹	-0.846	0.227	1.88 × 10 ⁻⁹⁴
17q21.32¶	rs56308324	17:45819206	TBX21, TBKBP1, OSBPL7	A/T	0.132	1.132	1.086–1.180	3.47 × 10 ⁻⁹⁹	1.025	0.996–1.055	8.72 × 10 ⁻⁹²	-0.714	0.195	2.54 × 10 ⁻⁹⁴
18q21.33¶	rs4574025	18:60009814	TNFRSF11A, KIAA1468, ZCCHC2	C/T	0.535	1.090	1.058–1.122	9.25 × 10 ⁻⁹⁹	0.986	0.967–1.006	1.69 × 10 ⁻⁹¹	-0.871	0.136	1.61 × 10 ⁻¹⁰
18q21.33¶	rs12964116	18:61442619	SERPINB7, SERPINB11, SERPINB2	A/G	0.036	1.336	1.247–1.432	2.56 × 10 ⁻¹⁶	1.005	0.953–1.059	8.62 × 10 ⁻⁹¹	-1.916	0.351	4.87 × 10 ⁻⁹⁸
19p13.3¶	rs4807630	19:1170445	SBN02, GPX4, STK11	C/T	0.308	1.093	1.060–1.128	2.06 × 10 ⁻⁹⁸	1.013	0.992–1.035	2.32 × 10 ⁻⁹¹	-0.487	0.147	9.25 × 10 ⁻⁹⁴
Adult-onset asthma-specific loci														
2q22.3¶	rs12617922	2:146156679	TEX41, ACVR2A	A/G	0.518	0.983	0.955–1.012	2.36 × 10 ⁻⁹¹	1.066	1.045–1.087	1.59 × 10 ⁻¹⁰	0.478	0.136	4.46 × 10 ⁻⁹⁴
Shared asthma loci														
1q32.1	rs12023876	1:203093201	ADORA1, PPFIA4	T/G	0.668	1.102	1.068–1.137	1.11 × 10 ⁻⁹⁹	1.032	1.010–1.053	3.37 × 10 ⁻⁹³	-0.567	0.144	8.65 × 10 ⁻⁹⁵
2p25.1	rs13416555	2:8441735	RNF144A, ID2	G/C	0.705	1.130	1.094–1.167	1.94 × 10 ⁻¹³	1.040	1.018–1.063	3.50 × 10 ⁻⁹⁴	-0.715	0.150	1.91 × 10 ⁻⁹⁶
2q12.1	rs72823641	2:102936159	IL1RL1, IL1RL2, IL18R1	A/T	0.863	1.415	1.349–1.484	3.01 × 10 ⁻⁴⁶	1.109	1.077–1.142	3.72 × 10 ⁻¹²	-1.687	0.208	4.73 × 10 ⁻¹⁶
2q37.3	rs34290285	2:242698640	D2HGDH, ING5, GAL3ST2	A/G	0.745	1.177	1.137–1.219	2.06 × 10 ⁻²⁰	1.081	1.056–1.106	2.16 × 10 ⁻¹¹	-0.821	0.159	2.56 × 10 ⁻⁹⁷
3p22.3¶	rs35570272	3:33047662	GLB1, TRIM71, TMPE	G/T	0.396	1.100	1.068–1.133	2.68 × 10 ⁻¹⁰	1.046	1.025–1.067	9.84 × 10 ⁻⁹⁶	-0.454	0.138	1.03 × 10 ⁻⁹³
4q27	rs2069763	4:123377482	IL2, ADAD1, IL21	C/A	0.334	1.126	1.092–1.160	1.59 × 10 ⁻¹⁴	1.032	1.011–1.054	2.44 × 10 ⁻⁹³	-0.631	0.142	8.39 × 10 ⁻⁹⁶
5p15.2¶	rs16903574	5:14610309	FAM105A, TRIO, OTULIN	C/G	0.077	1.236	1.174–1.302	9.01 × 10 ⁻¹⁶	1.052	1.013–1.091	7.75 × 10 ⁻⁹³	-1.055	0.250	2.51 × 10 ⁻⁹⁵
5q22.1	rs1837253	5:110401872	SLC25A46, TSLP	T/C	0.740	1.211	1.169–1.253	2.33 × 10 ⁻²⁷	1.088	1.064–1.113	2.77 × 10 ⁻¹³	-0.733	0.158	3.72 × 10 ⁻⁹⁶
(Table 2 continues on next page)														

(Table 2 continues on next page)

	rsID	Position*	Nearby genest	Allele‡	RAF§	Childhood-onset asthma GWAS			Adult-onset asthma GWAS			Age-of-onset GWAS		
						OR	95% CI	p value	OR	95% CI	p value	β value	SE	p value
(Continued from previous page)														
5q31.1	rs17622378	5:131778452	C5orf56, SLC22A5, IRF1	G/A	0.573	1.103	1.071-1.136	8.52 × 10 ⁻¹¹	1.077	1.055-1.098	3.17 × 10 ⁻¹³	-0.044	0.137	7.46 × 10 ⁻⁰¹
6p22.1	rs1117490	6:30170510	TRIM26, TRIM15, TRIM39	T/C	0.234	1.100	1.063-1.137	2.78 × 10 ⁻⁰⁸	1.059	1.036-1.084	6.83 × 10 ⁻⁰⁷	-0.453	0.158	4.07 × 10 ⁻⁰³
6p21.33	rs2428494	6:31322197	HLA-B, HLA-C, MICA	T/A	0.477	1.157	1.124-1.191	7.94 × 10 ⁻²³	1.104	1.082-1.126	4.77 × 10 ⁻²³	-0.648	0.136	1.78 × 10 ⁻⁰⁶
6p21.32	rs28407950	6:32626348	HLA-DQA1, HLA-DQB	T/C	0.756	1.354	1.306-1.405	1.27 × 10 ⁻⁵⁹	1.148	1.121-1.175	7.67 × 10 ⁻³¹	-1.284	0.163	4.03 × 10 ⁻¹⁵
6q15	rs1321859	6:91011673	BACH2, MAP3K7	T/C	0.649	1.102	1.068-1.136	9.32 × 10 ⁻¹⁰	1.076	1.054-1.098	5.68 × 10 ⁻¹²	-0.268	0.144	6.28 × 10 ⁻⁰²
7p21.1¶	rs4473914	7:20426263	ITGB6, MACC1, ABCB5	C/T	0.604	1.092	1.060-1.125	9.02 × 10 ⁻⁰⁹	1.035	1.014-1.056	8.44 × 10 ⁻⁰⁴	-0.338	0.139	1.51 × 10 ⁻⁰²
7p15.1¶	rs917115	7:28172586	JAZF1, TAX1BP1, CREB5	T/C	0.208	1.112	1.074-1.152	1.73 × 10 ⁻⁰⁹	1.042	1.017-1.067	7.35 × 10 ⁻⁰⁴	-0.577	0.164	4.17 × 10 ⁻⁰⁴
8q21.13	rs4739738	8:81291645	TPD52, ZBTB10	A/G	0.359	1.117	1.084-1.151	3.45 × 10 ⁻¹³	1.057	1.036-1.079	8.63 × 10 ⁻⁰⁸	-0.450	0.140	1.27 × 10 ⁻⁰³
9p24.1	rs992969	9:6209697	RANBP6, IL33	G/A	0.252	1.248	1.209-1.289	6.76 × 10 ⁻⁴²	1.100	1.076-1.125	3.14 × 10 ⁻¹⁷	-1.026	0.152	1.35 × 10 ⁻¹¹
10p14¶	rs7894791	10:8591369	GATA3, CELF2	A/C	0.587	1.103	1.071-1.137	9.43 × 10 ⁻¹¹	1.024	1.004-1.045	1.94 × 10 ⁻⁰²	-0.494	0.137	3.24 × 10 ⁻⁰⁴
10p14	rs1775554	10:9054340	GATA3, CELF2	C/A	0.577	1.117	1.084-1.150	2.85 × 10 ⁻¹³	1.121	1.098-1.143	5.17 × 10 ⁻²⁹	-0.002	0.138	9.91 × 10 ⁻⁰¹
11p15.5¶	rs12788104	11:1123739	MUC6, MUC5AC	A/G	0.688	1.029	0.997-1.061	7.99 × 10 ⁻⁰²	1.064	1.041-1.087	1.41 × 10 ⁻⁰⁸	0.147	0.148	3.22 × 10 ⁻⁰¹
11q12.2¶	rs174621	11:61630104	FADS2, FADS1, FADS3	A/G	0.772	1.013	0.978-1.049	4.63 × 10 ⁻⁰¹	1.071	1.046-1.097	1.46 × 10 ⁻⁰⁸	0.508	0.163	1.87 × 10 ⁻⁰³
11q13.5	rs61894547	11:76248630	EMSY, THAP12, LRRC32	C/T	0.052	1.463	1.382-1.548	2.17 × 10 ⁻³⁹	1.093	1.047-1.141	5.46 × 10 ⁻⁰⁵	-2.227	0.284	4.42 × 10 ⁻¹⁵
11q13.5	rs7936312	11:76293726	EMSY, LRRC32	G/T	0.477	1.194	1.160-1.230	4.89 × 10 ⁻³³	1.060	1.040-1.081	4.10 × 10 ⁻⁰⁹	-0.978	0.134	3.49 × 10 ⁻¹³
12q13.11	rs56389811	12:48205358	HDAC7, SLC48A1, VDR	T/C	0.761	1.022	0.988-1.058	2.11 × 10 ⁻⁰¹	1.078	1.054-1.104	2.36 × 10 ⁻¹⁰	0.485	0.161	2.55 × 10 ⁻⁰³
12q13.2	rs705699	12:56384804	RAB5B, CDK2, SUOX	G/A	0.425	1.106	1.074-1.139	1.43 × 10 ⁻¹¹	1.052	1.031-1.072	6.10 × 10 ⁻⁰⁷	-0.481	0.136	4.20 × 10 ⁻⁰⁴
12q13.3	rs3122929	12:57509102	STAT6, NAB2, LRP1	C/T	0.404	1.134	1.101-1.167	6.59 × 10 ⁻¹⁷	1.061	1.040-1.082	5.73 × 10 ⁻⁰⁹	-0.564	0.138	4.07 × 10 ⁻⁰⁵
12q21.1¶	rs11178648	12:71533210	TSPAN8, PTPRR, LGR5	T/C	0.592	1.087	1.055-1.120	4.16 × 10 ⁻⁰⁸	1.052	1.031-1.073	6.62 × 10 ⁻⁰⁷	-0.183	0.138	1.86 × 10 ⁻⁰¹
13q32.3¶	rs1887704	13:99974492	UBAC2, DOCK9, TM9SF2	C/G	0.681	1.124	1.089-1.161	5.48 × 10 ⁻¹³	1.048	1.026-1.070	1.57 × 10 ⁻⁰⁵	-0.476	0.147	1.15 × 10 ⁻⁰³
14q24.1	rs1950897	14:68760141	RAD51B, ZFYVE26, ZFF36L1	T/C	0.287	1.096	1.062-1.131	1.38 × 10 ⁻⁰⁸	1.031	1.009-1.053	5.39 × 10 ⁻⁰³	-0.520	0.148	4.52 × 10 ⁻⁰⁴
15q22.2	rs11071559	15:61069988	RORA, ANXA2, VPS13C	T/C	0.872	1.205	1.151-1.262	2.57 × 10 ⁻¹⁵	1.069	1.037-1.101	1.22 × 10 ⁻⁰⁵	-0.958	0.210	5.11 × 10 ⁻⁰⁶
15q22.33	rs56062135	15:67455630	SMAD3, SMAD6, AAGAB	C/T	0.237	1.194	1.156-1.234	2.97 × 10 ⁻²⁶	1.083	1.058-1.108	6.27 × 10 ⁻¹²	-0.681	0.155	1.10 × 10 ⁻⁰⁵
16p13.13	rs35032408	16:11215424	CLEC16A, CIITA, RMI2	G/T	0.785	1.152	1.111-1.195	4.59 × 10 ⁻¹⁴	1.073	1.048-1.100	1.10 × 10 ⁻⁰⁸	-0.568	0.169	7.91 × 10 ⁻⁰⁴
16p12.1	rs3785356	16:27349168	IL4R, NSMCE, IL21R	C/T	0.297	1.122	1.087-1.157	5.69 × 10 ⁻¹³	1.036	1.014-1.058	1.24 × 10 ⁻⁰³	-0.641	0.147	1.30 × 10 ⁻⁰⁵
16q12.1	rs2066844	16:50745926	NOD2, SNX20, CYLD	C/T	0.048	1.194	1.121-1.272	3.52 × 10 ⁻⁰⁸	1.049	1.003-1.097	3.76 × 10 ⁻⁰²	-0.743	0.306	1.54 × 10 ⁻⁰²
17q21.33	rs28406364	17:47454507	ZNF652, PHB	C/T	0.377	1.108	1.076-1.142	1.39 × 10 ⁻¹¹	1.036	1.015-1.057	6.55 × 10 ⁻⁰⁴	-0.489	0.140	4.81 × 10 ⁻⁰⁴
19q13.11	rs10414065	19:33721455	LRP3, CEBPA	T/C	0.934	1.207	1.133-1.287	6.37 × 10 ⁻⁰⁹	1.108	1.064-1.155	1.01 × 10 ⁻⁰⁶	-1.078	0.291	2.12 × 10 ⁻⁰⁴
21q22.12¶	rs11088309	21:36464631	RUNX1, SETD4	C/G	0.143	1.039	0.997-1.083	6.82 × 10 ⁻⁰²	1.079	1.050-1.109	4.83 × 10 ⁻⁰⁸	0.063	0.189	7.38 × 10 ⁻⁰¹

Information for the SNP with smallest p value at each locus is shown. Summary statistics for the 19 significant SNPs in the age of asthma onset GWAS are shown in appendix p 63. GWAS=genome-wide association study. OR=odds ratio. RAF=risk allele frequency. SNP=single-nucleotide polymorphism. *SNP position according to Genome Reference Consortium Build 37 (hg19). †The gene in which the SNP is located is indicated first, followed by the previous gene and the next gene; for intergenic SNPs, only the previous and next genes are shown. ‡Alleles are shown as non-risk/risk alleles, where the risk allele is the allele associated with increased asthma risk. §RAF in the UK Biobank. ¶Not reported in previous GWAS. ||The SNP with the smallest p value differs in the childhood-onset GWAS and the adult-onset GWAS at the same locus; both SNPs are shown.

Table 2: Regions with SNPs that were genome-wide significant in the childhood-onset or adult-onset GWAS

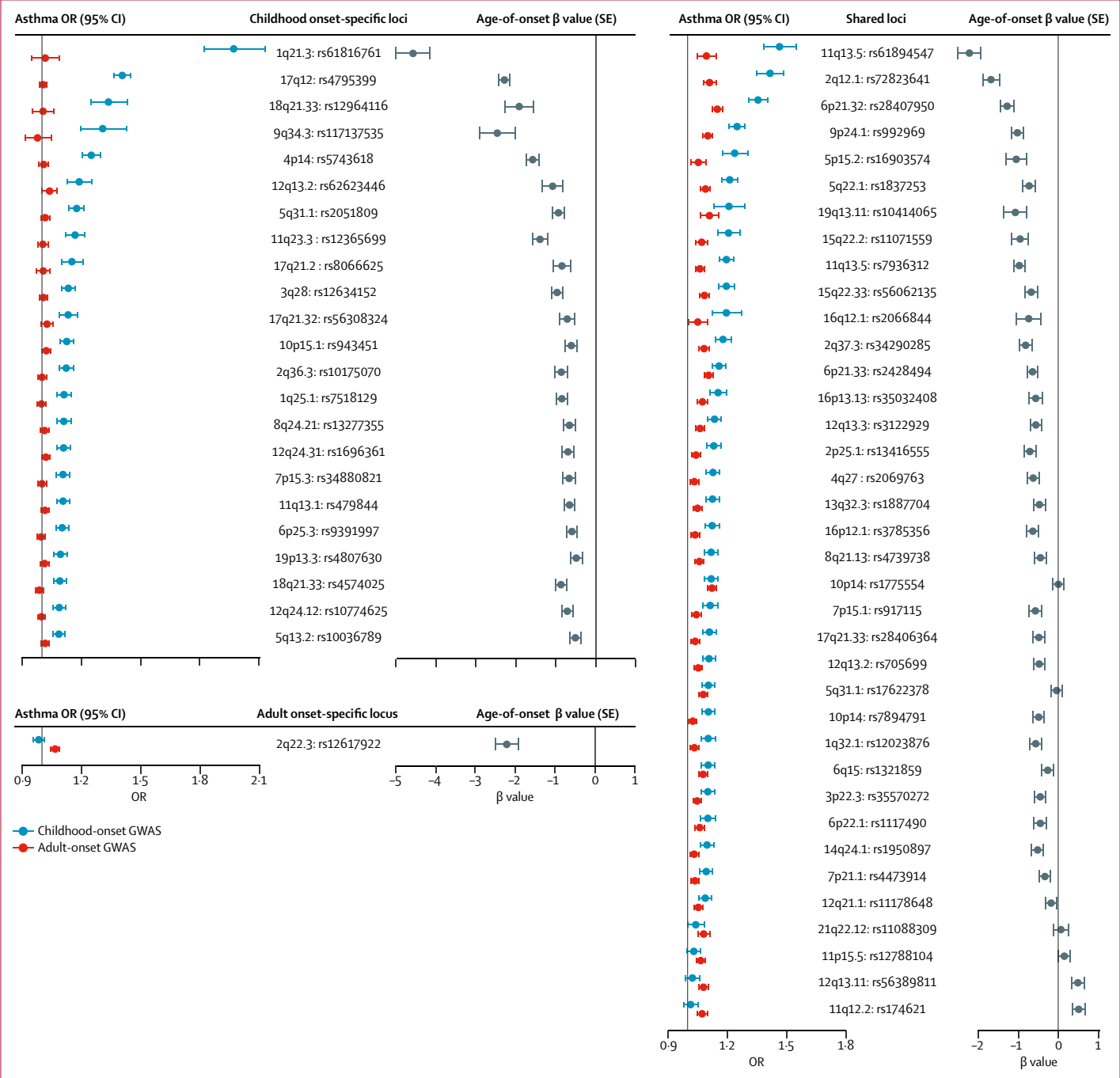


Figure 2: Forest plot of childhood-onset asthma, adult-onset asthma, and age-of-onset GWAS
Error bars show 95% CIs. GWAS=genome-wide association study. OR=odds ratio.

(figure 1A) were most highly expressed in skin, whole blood, and small intestine (lower ileum) compared with all other tissues, whereas genes at adult-onset loci (figure 1B) were most highly expressed in lung, whole blood, small intestine (lower ileum), and spleen (enrichment for higher expression, $p < 10 \times 10^{-3}$; appendix pp 42, 65).

To better understand molecular mechanisms and to narrow the list of candidate causal genes at associated loci, we focused on the five tissues that most highly expressed the genes at loci associated with childhood-onset asthma or those associated with adult-onset asthma: skin, lung, whole blood, small intestine, and spleen. We used PrediXcan¹⁶ to identify genes whose

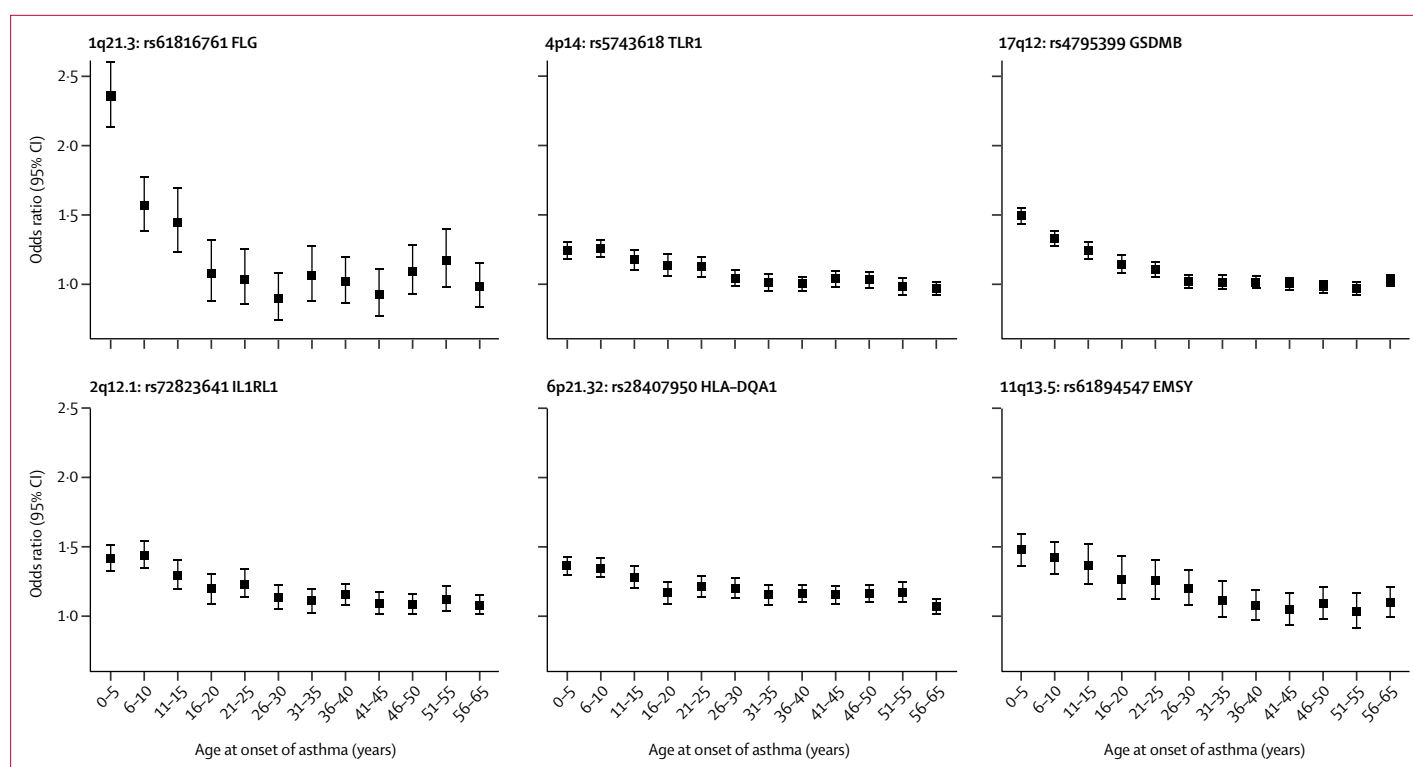


Figure 3: Examples of age-of-onset effect sizes

Age-of-onset effects for lead single-nucleotide polymorphisms at three genome-wide significant childhood onset-specific loci (1q21.3, 4p14 and 17q12), and three genome-wide significant shared loci (2q12.1, 6p21.32, and 11q13.5). The sample sizes for the age-of-onset bins are $n=4637$ for 0–5 years, $n=4255$ for 6–10 years, $n=2684$ for 11–15 years, $n=2128$ for 16–20 years, $n=2578$ for 21–25 years, $n=2923$ for 26–30 years, $n=2599$ for 31–35 years, $n=3571$ for 36–40 years, $n=2967$ for 41–45 years, $n=3266$ for 46–50 years, $n=2544$ for 51–55 years, and $n=3694$ for 56–65 years.

expression is predicted by variants associated with asthma in the childhood-onset or adult-onset GWAS and potentially mediate the effects of associated SNPs on asthma risk.

Of 38 608 genes in the five tissues of interest, the transcriptome-wide association analysis identified 113 unique, candidate causal genes at 22 of the 61 GWAS loci ($p < 1.4 \times 10^{-6}$; figures 4,5; appendix pp 43–44, 66). These included 39 genes associated with childhood-onset asthma at eight of the childhood onset-specific loci and 74 genes associated with childhood-onset or adult-onset asthma at 13 of the shared loci. Variants at the one adult onset-specific locus at 2q22.3 did not predict the expression of any genes in the five tissues.

The predicted genes most significantly associated with childhood-onset asthma were at the 17q12 locus (Z score >10 or <-10) in skin (*ORMDL3*, *ERBB2*, *PGAP3*, and *GSDMA*, as well as two long non-coding RNAs), lung (*ORMDL3*, *GSDMB*, *GSDMA*, *PGAP3*, and *PNMT*), blood (*ORMDL3*, *GSDMB*, *IKZF3*, and *MED24*), small intestine (*GSDMA*, *GSDMB*, and *PGAP3*), and spleen (*ORMDL3*, *GSDMB*, *ZBP2*, and *MED24*; figure 4; appendix p 43). Some genes were predicted to be highly expressed in individuals with asthma (eg, *ORMDL3*, *GSDMB*, *PGAP3*, and *ERBB2*), whereas others were predicted to have reduced expression in individuals with

asthma (eg, *GSDMA*, *MED24*, and *IKZF3*; figure 4). This pattern of expression reflects the broad regulatory effects of SNPs and tissue specificity of gene expression at this locus.²⁶ The childhood-onset asthma locus at 1q21.3 includes genes that are essential for epidermal differentiation and maintenance of essential barrier function. The predicted expression of nine genes at the 1q21.3 locus was associated with childhood-onset asthma: higher predicted expression of *CRNN*, *CRCT1*, and *THEM5* in skin, of *PSDM4* in lung and of *LINGO4* in skin, lung, and blood was associated with increased asthma risk, whereas lower predicted expression of *SPRR2D* in skin, of *S100A12* in lung, of *FLG* in skin, lung, and spleen, and of *TDRKH* in skin, lung, blood, and spleen was associated with increased asthma risk. *S100A12* has been previously implicated in asthma³⁴ and *FLG* variants have been associated with atopic dermatitis and food allergies, and asthma in the context of other allergic diseases.^{20,27–33} Other childhood onset-specific genes previously implicated in asthma but not previously reported in asthma GWAS are *CCL20*³⁵ at 2q36.3 and *TLR10*³⁶ at 4p14 in whole blood, and *TLR6*^{37,38} at 4p14, *AP5B1* at 11q13.1, and *SERPINEB*³⁹ at 18q21.33 in skin.

The 5q31.1 region had independent loci that were both childhood-onset specific and shared in the GWAS. Although the predicted expression of all eight asthma

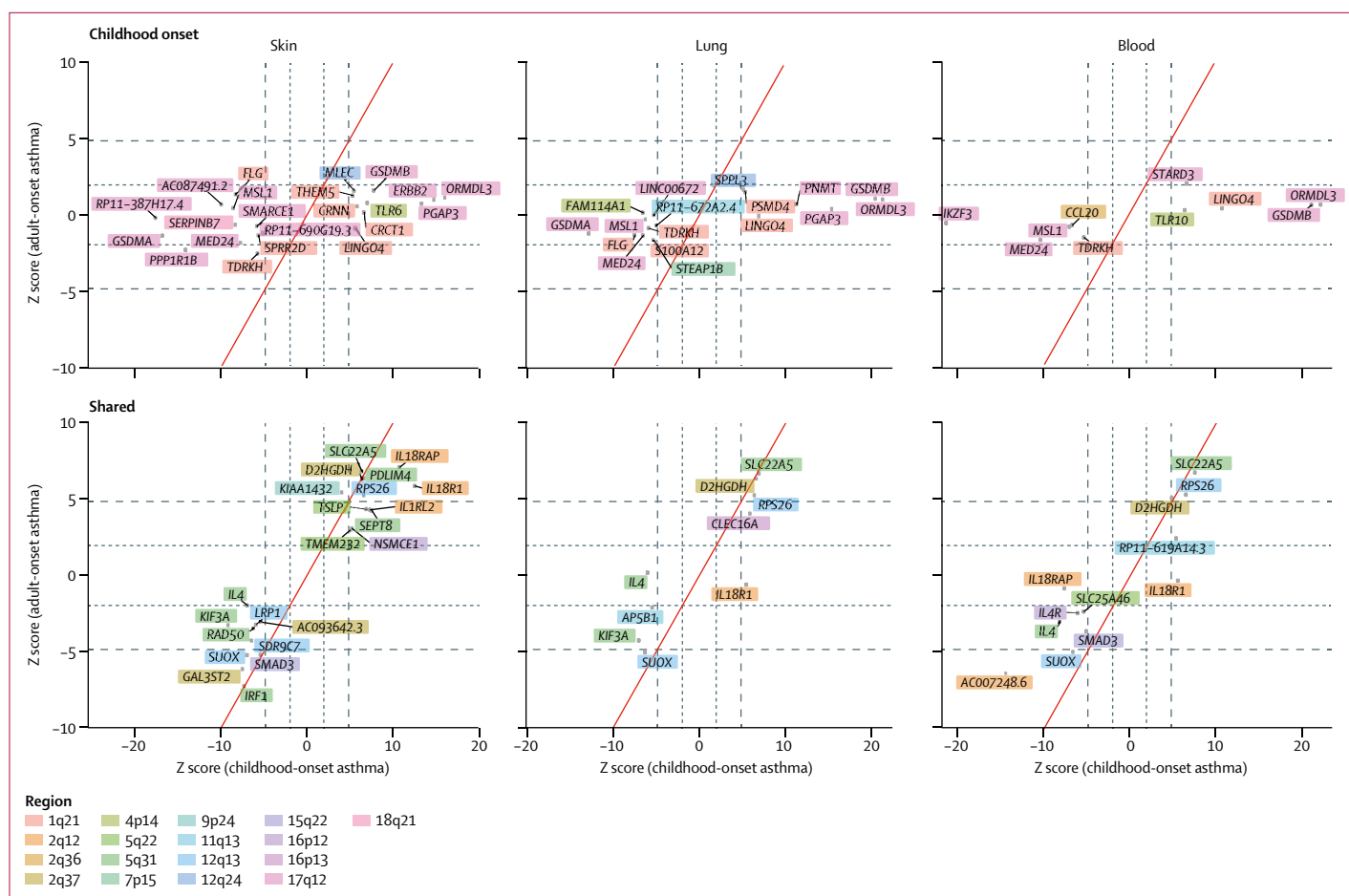


Figure 4: Results of PrediXcan studies at non-HLA region loci

Genes whose predicted expression was significantly associated with asthma in either the childhood-onset asthma cases or the adult-onset cases are shown. Values for skin combine both sun-exposed and non-sun-exposed skin, showing the most significant statistic of the two. Results using gene expression in spleen and small intestine are shown in appendix p 43. The Z scores on the x-axes and y-axes are from transcriptome-wide tests of association with asthma using single-nucleotide polymorphism sets that predict the expression of that gene. The diagonal lines show the expected values when associations are the same in the childhood-onset and adult-onset cases. The horizontal and vertical dashed lines correspond to Z scores ± 4.84 ($p=1.29 \times 10^{-6}$); the horizontal and vertical dotted lines correspond to Z scores ± 1.96 ($p=0.05$).

genes at this extended locus were shared, five genes were more significantly associated with childhood-onset asthma: higher predicted expression of *RAD50* in skin but lower predicted expression of *SEPT8* in skin and lung, *IL4* in skin, lung, and blood, and *AFF4* small intestine were associated with increased risk for asthma (figure 4). The remaining three genes had similar associations with childhood-onset and adult-onset asthma, with predicted lower expression of *IRF1* in skin and spleen and predicted higher expression of *PDLIM4* in skin and *SLC22A5* in all five tissues associated with increased asthma risk. *IL4*, *RAD50*, *SLC22A5*, and *PDLIM4* have been highlighted in previous asthma GWAS,^{25,40} and *KIF3A* was identified in a GWAS of the progression of allergic disease in childhood (ie, the atopic march)⁴¹ and associated with childhood-onset asthma in a candidate gene study.⁴²

Predicted expression of 44 genes at two independent shared loci in the HLA region (ie, 6p21.32 and 6p21.33) were associated with childhood-onset asthma only ($n=1$;

in skin and lung), adult-onset asthma only ($n=3$; in skin only), or both ($n=39$; in multiple tissues; figure 5).

Among the remaining 37 shared loci (figure 2B), SNPs at 12 predicted the expression of 23 unique genes, all of which were associated with both childhood-onset and adult-onset asthma. These include *IL18R1*, *IL18RAP*, and *ILRL2* at 2q12.1 in multiple tissues, *TSLP* at 5q22.1 in skin, *SMAD3* at 15q22.33 in skin and blood, *LRP1* at 12q13.3 in skin, *IL4R* at 16p12.1 in blood, and *CLEC16A* at 16p13.13 in lung. Loci associated with *IL18R1*, *IL18RAP*, *ILRL2*, *TSLP*, *SMAD3*, *LRP1*, *IL4R*, and *CLEC16A* were reported in previous asthma GWAS.^{13,20,25}

In sensitivity analyses, the GWAS results were robust to inclusion of varying numbers of principal components (10, 14, or 20; appendix p 12) and to limiting the sample to cases with diagnoses based on ICD-10 codes (appendix p 13).

In the GWAS comparing individuals with asthma based on self-reported doctor diagnosis alone compared

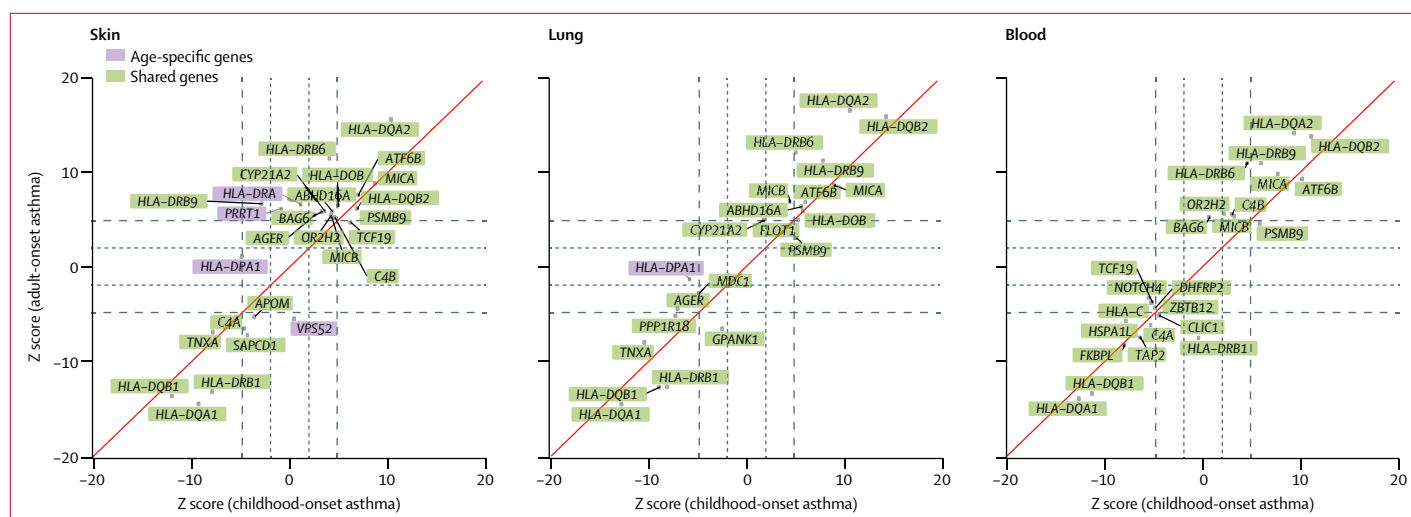


Figure 5: Results of PrediXcan studies of HLA region genes

Genes in the HLA region whose predicted expression was associated with childhood-onset or adult-onset asthma are shown. Results using gene expression in spleen and small intestine are shown in appendix p 44.

with those with self-reported doctor diagnosis plus ICD-10 codes, no differences in risk loci were detected between these two groups (appendix p 15), indicating that differences in identifying asthma cases between these groups did not affect the GWAS results. We also did a COPD GWAS using all cases and controls, and there was no overlap between regions identified in the COPD GWAS and any of the asthma groups, including the locus on chromosome 15q25.1 (appendix p 45).

Discussion

We report here the first large GWAS of both childhood-onset and adult-onset asthma cases. These GWAS revealed 61 independent asthma loci, 23 specific to childhood onset, one specific to adult onset, and 37 shared, with overall larger effect sizes for childhood-onset asthma at nearly all loci. Moreover, the predicted expression of 42 of the 113 implicated genes were associated specifically with childhood-onset asthma, compared with the predicted expression of three genes associated specifically with adult-onset asthma. Several newly discovered risk loci in this study contain genes (eg, *FADS2*,²¹ *MUC5AC*,^{22,23} and *TBX21*²⁴) that have been associated with asthma in candidate gene studies, which supports the external validity of our GWAS findings.

We found that childhood-specific or shared loci were associated with development of asthma at younger ages and with alleles with larger effects by comparison with adult-specific loci. These results are consistent with a previous GWAS of age of asthma onset in individuals with European ancestry that reported five genome-wide significant and three suggestive significant loci, all of which were associated with earlier age of onset;⁴³ six of those eight loci are also associated with age of onset in the UK Biobank GWAS (appendix p 64). Our findings are

particularly striking given that there were nearly 2.5 times more adult-onset than childhood-onset cases in this study.

Thus, despite having substantially less power to detect loci specific to childhood-onset asthma, our analyses revealed many more childhood-onset asthma loci. Similarly, the asthma risk alleles at 19 loci that were significant in the age-of-onset GWAS were all associated with younger age of onset. Finally, we showed that the SNP-based heritability of childhood-onset asthma is more than three times larger than that of adult-onset asthma, suggesting a more important role for genetic variation in risk for childhood-onset than in adult-onset asthma and, conversely, the larger role for environmental variation in risk for adult-onset than for childhood-onset asthma. Regardless, the loci with genome-wide significant SNPs in these GWAS accounted for only 32.7% of the heritability of childhood-onset asthma and 9.8% of the heritability of adult-onset asthma, suggesting that many more asthma loci remain to be discovered. These findings are consistent with previous studies showing decreased estimates of asthma heritability with increasing age of onset,⁴⁴ SNPs associated with earlier age of onset,⁴³ and an additive, unweighted genetic risk score comprising 15 SNPs at eight asthma-associated loci associated with earlier age of onset.⁴⁵ Our study further shows that genetic risk for adult-onset asthma is largely a subset of the genetic risk loci for childhood-onset asthma, but with overall smaller effect sizes, consistent with a larger role for environmental risk factors in adult-onset asthma.

Despite the overlap of adult-onset and childhood-onset loci, distinct mechanisms contributing to each were suggested by tissue enrichments: childhood-onset loci were enriched for genes with highest expression in skin, whereas adult-onset loci were enriched for genes with highest expression in lung and spleen; both were

enriched for genes highly expressed in whole blood and small intestine. These findings suggest both overlapping and distinct underlying mechanisms associated with asthma that begins in childhood and asthma with onset in adulthood. The highlighting of skin as a target tissue for childhood-onset asthma supports the widely held idea that asthma in childhood is due to impaired barrier function in the skin and other epithelial surfaces. This model proposes that compromised epithelial barriers promote sensitisation to food and airway allergens and to wheezing illnesses in early life.^{46,47} In fact, childhood onset-specific loci identified in this study have been associated with atopic dermatitis or food allergies, such as *FLG* on 1q21.3 with the atopic march,⁴¹ atopic dermatitis,^{30–32} and food allergies,^{27–29} *KIF3A* on 5q31.1 and *AP5B1/OVOL1* on 11q13.1 with the atopic march⁴¹ and atopic dermatitis,⁴⁸ *SERPINB7* on 18q21.33 with food allergies,³⁹ and *CRNN* (which encodes cornulin) on 1q21.3 with atopic dermatitis concomitant with asthma and reduced expression in atopic dermatitis-affected skin.⁴⁹ Variants at those loci were all associated with earlier age of asthma onset. We further showed that these loci are associated with childhood-onset asthma, even after exclusion of patients with a history of allergic diseases in prespecified analyses, suggesting both a crucial role for the allergic diathesis in the development of asthma in childhood and a shared architecture between allergic disease and childhood-onset asthma.^{33,46}

By contrast, the enrichment for genes highly expressed in lung and spleen at adult-onset loci suggests a more lung-centred, and potentially immune-mediated, cause for asthma with onset later in life. The prominent role of the HLA region in the adult-onset asthma GWAS further highlights a central role for immune processes driving asthma pathogenesis in adults. Our findings are consistent with previous research suggesting that the HLA region (6p21.32 and 6p21.33) is among the most significant loci in nearly all asthma GWAS, and was the most significant locus in a previous small GWAS of adult-onset asthma⁷ and in adults with asthma.^{40,50} The fact that both childhood-onset and adult-onset asthma loci were enriched for genes that are most highly expressed in whole blood cells and small intestine further indicate a shared immune cause, as suggested from a large GWAS that included both children and adults.²⁵

Combining GWAS with a transcriptome-wide association test that uses combinations of associated SNPs to predict gene expression in different tissues revealed significant complexity at the two most highly associated asthma loci. SNPs at the 17q12 locus predicted expression of 18 childhood-onset asthma genes and SNPs at the HLA region predicted expression of 42 genes: three were associated with adult-onset asthma and most were not HLA genes per se. These results strengthen the argument that multiple genes contribute to asthma risk at the HLA and 17q12 loci and probably account for the highly

significant GWAS p values observed at these loci in nearly all studies. It is also likely that these genes have both tissue-specific and broad effects in epithelium, lung, and immune tissues.

The new loci identified in our study include the first adult-onset asthma-specific association at 2q22.3. The lead SNP at 2q22.3 is intergenic between *TEX41* and *ACVR2A*. The predicted expression of *ACVR2A* was not associated with asthma in our study, despite it being expressed in lung, blood, small intestine, and spleen. *TEX41* was not expressed in any of the five tissues investigated. Interestingly, a GWAS also done in UK Biobank participants implicated variants near *TEX41* in heavy versus never smoking behaviour.⁵¹ However, even after removing adult-onset cases and controls with reported ever smoking, the p value for this SNP remained significant and the OR slightly increased (OR 1.077 [95% CI 1.05–1.1], $p=2.26 \times 10^{-8}$; $n=12\,132$ cases and 176\,704 controls).⁵¹ Variants in or near this gene, which encodes a long intergenic non-coding RNA, have been associated with cardiovascular and immune-mediated traits,⁵² making this a potentially interesting candidate gene for adult-onset asthma.

Our study had limitations. First, diagnoses of asthma and allergic disease in study participants were from self reported doctor diagnosis and medical records (ICD-10 codes). Thus, it is possible that diagnoses, age of onset, or both are misspecified in some participants. On the one hand, the large sample size and our ability to replicate nearly all previously reported asthma loci (appendix pp 58, 67) suggest that our analyses were robust to any inaccuracies in the data. On the other hand, it is possible that individuals with adult-onset asthma included people with poor recall of childhood-onset asthma in which symptoms remitted and then relapsed later in life⁵³ or misclassified cases of COPD among the older age groups. Our sensitivity analysis suggested that if even as few as 5% of the adult-onset cases were misclassified, we should have observed some signal of association at childhood-onset loci, which we did not. The fact that the ORs for asthma at shared loci are relatively similar from approximately 25 to 65 years of age (figure 3), and that we do not detect any association signal at the major COPD locus on chromosome 15q25.1 (appendix p 45), further suggests that there is negligible misclassification of cases in the older age groups. Second, although we used stringent criteria to classify loci as childhood-onset or adult-onset specific, we cannot exclude the possibility that in infinitely large sample sizes the effect sizes of some of these loci will have 95% CIs that overlap or the association p value will become smaller than 0.05. Conversely, some of the shared loci with modest p values in the adult-onset cases might not be true risk loci for asthma with onset at older ages. Third, the gene expression data used to predict candidate target genes included heterogeneous tissues and were collected mostly from adults. As a result, our study might have missed relevant genes with expression

that is developmentally regulated or environment specific. Our finding of candidate genes at only 22 of the 61 asthma loci might be due in part to the importance of both in asthma pathogenesis. Moreover, all inference based on gene expression is using imputed expression. It is possible, therefore, that some relevant genes were more difficult to impute and not included in our analysis, although a comparative study⁵⁴ showed that PrediXcan is a more robust method for prediction of gene expression than other related methods. Fourth, because of the ethnic composition of the UK Biobank, this study was limited to individuals of European ancestry only. As a result, we could not evaluate the genetic risk architecture or assess the effects of age of onset-specific loci in other populations. Finally, in our study sample, the proportion of self-reported, doctor-diagnosed asthma was 37846 of 318237 (11.9%) cases, lower than the UK lifetime prevalence of patient-reported, clinician-diagnosed asthma of 15.6%⁵⁵ and consistent with the known healthy volunteer bias in UK Biobank.⁵⁶

In the largest asthma GWAS so far, we show that genetic risk loci for adult-onset asthma are largely a subset of the loci associated with childhood-onset asthma, with overall smaller effect sizes for onset at later ages. These data suggest that childhood onset-specific loci and those associated with age of onset play a part in disease initiation, whereas the other associated loci reflect shared mechanisms of disease progression. The differences in the target tissues that most highly express the genes at associated loci and the predicted expression of genes at age-specific and shared loci provides additional genetic and molecular evidence for both shared and distinct pathogenic mechanisms in childhood-onset and adult-onset asthma. It is therefore possible that the most effective treatments will also differ between these two groups, and that strategies for precision medicine should be further personalised to account for age of asthma onset.

Contributors

All authors were involved in the conception and design of the study and in writing the manuscript. MP and NS did all analyses and prepared figures and tables, under the overall supervision of DLN, CO, and HKI.

Declaration of interests

HKI reports personal fees from AbbVie and GlaxoSmithKline. The other authors declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix

Shared and distinct genetic risk factors for childhood onset and adult onset asthma: genome- and transcriptome-wide studies

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Methods

Quality control of samples

We relied on quality control procedures performed centrally by the UK Biobank (UKB). We selected individuals from the White British Ancestry Set and filtered out those with poor-quality genotypes (high heterozygosity and missing rates)¹. In addition, we excluded individuals with ambiguous sex assignments using X and Y chromosome SNPs; for pairs of individuals who were related as first or second-degree relatives based on genotypes, only the individual with the smallest number of missing genotypes was included. This resulted in 376,358 unrelated individuals with high-quality genotype for our study.

Phenotype and Group definitions

We defined five different groups for this study: childhood onset asthma cases, childhood onset asthma cases excluding individuals with allergic disease, adult onset asthma cases, and two sets of controls (with and without allergic disease).

Childhood onset asthma cases consisted of individuals with onset prior to 12 years of age (n=9,433), using the UKB data field 22147 (*Age asthma diagnosed by doctor*, Online follow-up) and data field 3786 (*Age asthma diagnosed*, Touchscreen). A similar group was defined excluding allergic rhinitis, atopic dermatitis and food allergy (n=6,228), using self-reported data in data fields 20002 (*Non-cancer illness code*, Verbal interview), 22126 (*Doctor diagnosed hayfever or allergic rhinitis*, Online follow-up) and 22146 (*Age hayfever or allergic rhinitis diagnosed by doctor*, Online follow-up), as well as hospital-level data 41202/41204 (main and secondary diagnoses using ICD10 codes L208, L209, J301, J302, J303 and J304). The adult onset asthma cases group was defined as individuals with onset after 25 and before 66 years of age (n=21,564), excluding individuals with chronic obstructive airways disease (COPD) either self-reported using UKB data fields 20002, 22130 (*Doctor diagnosed COPD*, Online follow-up), 22150 (*Age COPD diagnosed by doctor*, Online follow-up), 22128 (*Doctor diagnosed emphysema*, Online follow-up), 22129 (*Doctor diagnosed chronic bronchitis*, Online follow-up), 22148 (*Age emphysema diagnosed by doctor*, Online follow-up), 22149 (*Age chronic bronchitis diagnosed by doctor*, Online follow-up) and 3992 (*Age emphysema/chronic bronchitis diagnosed*, Online follow-up), or with COPD diagnosed by a doctor (hospital-level data) using data fields 41202/41204 (ICD10 codes J43, J430, J431, J432, J438, J439, J44, J440, J441, J448 and J449).

The control group was defined as individuals not having neither asthma nor COPD (n=318,237) using self-reported and hospital-level data (ICD10 codes used to exclude individuals with an asthma diagnosis are J45, J450, J451, J458 and J459). A second controls group with no allergy (n=284,429) was also defined with the same exclusions described above.

For the GWAS of asthma age of onset, all asthma cases with onset before 66 years of age were included (n=37,846).

Reproducible research – Phenotype query file

In the previous section we provide a description of our quality control procedures for samples and the phenotypes definitions. To further improve the reproducibility of our study, we also provide here the query file used to retrieve exactly the same data employed in our analysis. The UK Biobank, as other biobanks, is composed of large amounts of highly heterogeneous data types, different sources, and structure. To address to many challenges posed by these characteristics, we developed a tool called ukbREST (<https://github.com/hakyimlab/ukbrest>)² that processes the UK Biobank data, creating a private and secure server for easy and quick access for authorized users within a protected cloud (to be clear, the data is NOT made publicly available). This resource allows streamlined updating and programmatic, simple, and reproducible phenotype extraction within the private cloud the investigator is using. As a REST API implementation, it allows researchers to efficiently access subsets of SNPs and phenotypic traits, leveraging a BGEN indexer and an SQL database. We have used this tool to efficiently retrieve data to distribute jobs performing phenome-wide gene level association with PrediXcan/MetaXcan to thousands of phenotypes, leveraging a secure biomedical cloud called Bionimbus Protected Data Cloud (PDC)³, which operates at FISMA moderate as IaaS with an NIH Trusted Partner status for analyzing protected datasets.

Our ukbREST tool allows us to write a descriptive query file in YAML that can be submitted to the private server for retrieval of the phenotype data requested. At the top of the file the user specifies the quality control criteria for samples (section “sample_filters” at the top), and then a series of sections that can be individually downloaded as separate files. The previous descriptions of the phenotypes are here shown as the precise SQL statements to get the exact set of data employed in this study.

ukbREST phenotype query file. This YAML file specifies the data to be pulled from the UK Biobank database stored in our in-house protected database server (Bionimbus)

```
samples_filters:
- cin_white_british_ancestry_subset_0_0 = 1
- eid not in (select eid from bad_related_samples_2nd_higher_and_high_missrate)
- chet_missing_outliers_0_0 = 0
- cputative_sex_chromosome_aneuploidy_0_0 = 0
- cexcess_relatives_0_0 = 0
- eid not in (select eid from withdrawals)
- eid > 0

extras:
sex: c31_0_0
age_recruitment: c21022_0_0
asthma_medication: c22167_0_0
smoking_status: coalesce(nullifneg(c20116_2_0::int), nullifneg(c20116_1_0::int), nullifneg(c20116_0_0::int))
fev1: array_avg(array[c3063_0_0, c3063_0_1, c3063_0_2])
fev1_pred: c20153_0_0
fev1_pred_perc: c20154_0_0
fvc: array_avg(array[c3062_0_0, c3062_0_1, c3062_0_2])
fev1_fvc_ratio: array_avg(array[c3063_0_0, c3063_0_1, c3063_0_2]) / array_avg(array[c3062_0_0, c3062_0_1, c3062_0_2])
fev1pred_fvc_ratio: c20153_0_0 / array_avg(array[c3062_0_0, c3062_0_1, c3062_0_2])
has_eczema:
sql:
1: |
(
  (
    eid in (
      select eid from events where field_id = 20002 and event in (values('I452'))
      union
      select eid from events where field_id in (values(41202), (41204)) and event in (values('L208'), ('L209'))
    )
  )
)
has_hayfever:
sql:
1: |
(
  (
    eid in (
      select eid from events where field_id = 20002 and event in (values('I387'))
      union
      select eid from events where field_id in (values(41202), (41204)) and event in (values('J301'), ('J302'), ('J303'), ('J304'))
    )
    or
    (c22126_0_0 = '1')
    or
    (c22146_0_0 is not null)
  )
)
has_food_allergy:
sql:
1: |
eid in (select eid from events where field_id = 20002 and event in (values('I385'))))

simple_covariates:
sex: c31_0_0
pc1: cpc1_0_0
pc2: cps2_0_0
pc3: cpc3_0_0
pc4: cpc4_0_0
pc5: cps5_0_0
pc6: cps6_0_0
pc7: cps7_0_0
pc8: cps8_0_0
pc9: cps9_0_0
pc10: cps10_0_0

data_aliases:
- &asthma_age_onset |
case when
  -- children
  (
    coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0)) < 12
  )
  or
  (
    coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0)) BETWEEN 12 and 25
  )
  or
  (
    coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0)) BETWEEN 26 and 65
  )
  and
  -- exclude copd
  eid not in (select eid from events where field_id = 20002 and event in (values('I112'))))
  and
  (c22130_0_0 is null or c22130_0_0::int = 0)
  and
  nullifneg(c22150_0_0) is null
  and
  eid not in (select eid from events where field_id in (values(41202), (41204)) and event in (values('J44'), ('J440'), ('J441'), ('J448'), ('J449'))))
  and
  -- emphysema/chronic bronchitis
  eid not in (select eid from events where field_id = 20002 and event in (values('I113'), ('I412'), ('I472'))))
  and
  (c22128_0_0 is null or c22128_0_0::int = 0) and (c22129_0_0 is null or c22129_0_0::int = 0)
  and
  nullifneg(c22148_0_0) is null and nullifneg(c22149_0_0) is null
  and
  coalesce(nullifneg(c3992_0_0), nullifneg(c3992_1_0), nullifneg(c3992_2_0)) is null
  and
  eid not in (select eid from events where field_id in (values(41202), (41204)) and event in (values('J43'), ('J430'), ('J431'), ('J432'), ('J438'), ('J439'))))
)
then
coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0))
else
NULL
```

```

end

- &asthma_children |
  coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0)) < 12

- &asthma_children_no_allergic |
  (
    coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0)) < 12
  )
  and
  (
    eid not in (select eid from events where field_id = 20002 and event in (values('1452'), ('1387'), ('1385')))
    and
    eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (
      values('L208'), ('L209'),
      ('J301'), ('J302'), ('J303'), ('J304')
    )
    and
    (c22126_0_0 = '0' or c22126_0_0 is null)
    and
    c22146_0_0 is null
  )

- &asthma_adults |
  (
    coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0)) BETWEEN 26 and 65
  )
  and
  (
    -- exclude copd
    eid not in (select eid from events where field_id = 20002 and event in (values('1112')))
    and
    (c22130_0_0 is null or c22130_0_0::int = 0)
    and
    nullifneg(c22150_0_0) is null
    and
    eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (values('J44'), ('J440'), ('J441'), ('J448'), ('J449')))
  )
  and

  -- emphysema/chronic bronchitis
  eid not in (select eid from events where field_id = 20002 and event in (values('1113'), ('1412'), ('1472')))
  and
  (c22128_0_0 is null or c22128_0_0::int = 0) and (c22129_0_0 is null or c22129_0_0::int = 0)
  and
  nullifneg(c22148_0_0) is null and nullifneg(c22149_0_0) is null
  and
  coalesce(nullifneg(c3992_0_0), nullifneg(c3992_1_0), nullifneg(c3992_2_0)) is null
  and
  eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (values('J43'), ('J430'), ('J431'), ('J432'), ('J438'), ('J439')))

- &controls |
  (
    coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0)) is null
    and
    eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (values('J45'), ('J450'), ('J451'), ('J458'), ('J459')))
  )
  and
  (
    -- copd
    eid not in (select eid from events where field_id = 20002 and event in (values('1112')))
    and
    (c22130_0_0 is null or c22130_0_0::int = 0)
    and
    nullifneg(c22150_0_0) is null
    and
    eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (values('J44'), ('J440'), ('J441'), ('J448'), ('J449')))
  )
  and

  -- emphysema/chronic bronchitis
  eid not in (select eid from events where field_id = 20002 and event in (values('1113'), ('1412'), ('1472')))
  and
  (c22128_0_0 is null or c22128_0_0::int = 0) and (c22129_0_0 is null or c22129_0_0::int = 0)
  and
  nullifneg(c22148_0_0) is null and nullifneg(c22149_0_0) is null
  and
  coalesce(nullifneg(c3992_0_0), nullifneg(c3992_1_0), nullifneg(c3992_2_0)) is null
  and
  eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (values('J43'), ('J430'), ('J431'), ('J432'), ('J438'), ('J439')))

- &controls_no_allergic |
  (
    coalesce(nullifneg(c22147_0_0), nullifneg(c3786_2_0), nullifneg(c3786_1_0), nullifneg(c3786_0_0)) is null
    and
    eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (values('J45'), ('J450'), ('J451'), ('J458'), ('J459')))
  )
  and
  (
    -- copd
    eid not in (select eid from events where field_id = 20002 and event in (values('1112')))
    and
    (c22130_0_0 is null or c22130_0_0::int = 0)
    and
    nullifneg(c22150_0_0) is null
    and
    eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (values('J44'), ('J440'), ('J441'), ('J448'), ('J449')))
  )
  and

  -- emphysema/chronic bronchitis
  eid not in (select eid from events where field_id = 20002 and event in (values('1113'), ('1412'), ('1472')))
  and
  (c22128_0_0 is null or c22128_0_0::int = 0) and (c22129_0_0 is null or c22129_0_0::int = 0)
  and
  nullifneg(c22148_0_0) is null and nullifneg(c22149_0_0) is null
  and
  coalesce(nullifneg(c3992_0_0), nullifneg(c3992_1_0), nullifneg(c3992_2_0)) is null
  and
  eid not in (select eid from events where field_id in (values(41202), (41204))) and event in (values('J43'), ('J430'), ('J431'), ('J432'), ('J438'), ('J439')))

```

```

)
and
(
  eid not in (select eid from events where field_id = 20002 and event in (values('1452'), ('1387'), ('1385')))
  and
  eid not in (select eid from events where field_id in (values(41202), (41204)) and event in (
    values('L208'), ('L209'),
    ('J301'), ('J302'), ('J303'), ('J304'))
  )
  and
  (c22126_0_0 = 'W' or c22126_0_0 is null)
  and
  c22146_0_0 is null
)

data:
asthma_age_onset: *asthma_age_onset

asthma_children:
sql:
  1: *asthma_children
  0: *controls

asthma_children_no_allergic:
sql:
  1: *asthma_children_no_allergic
  0: *controls_no_allergic

asthma_adults:
sql:
  1: *asthma_adults
  0: *controls

```

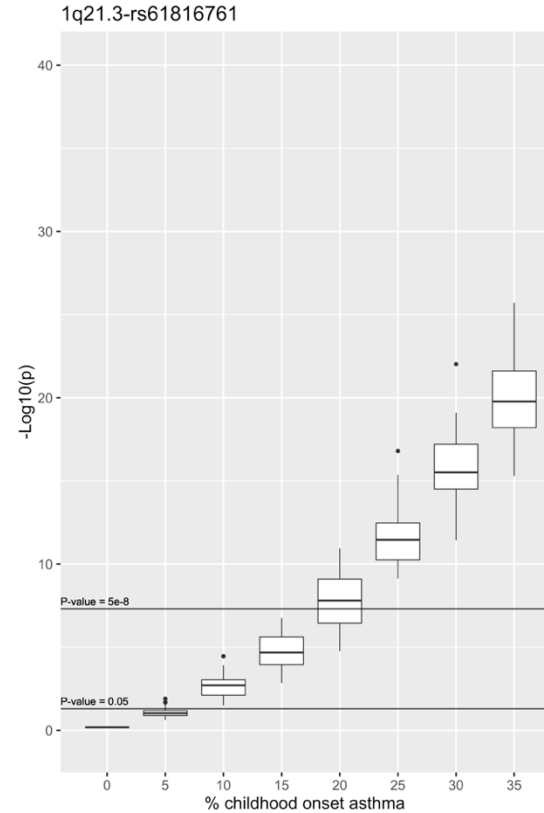
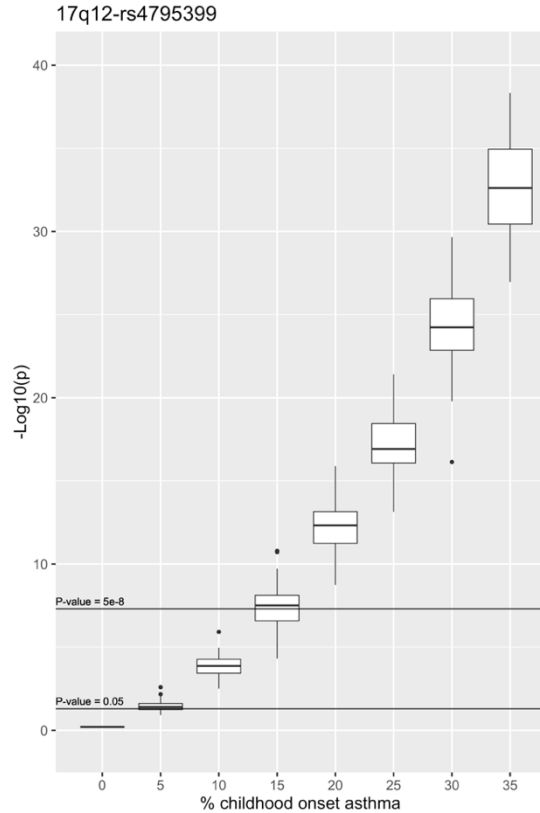
Quality control of genotype data

Details on genotyping, imputation and QC of UK Biobank genotype are described in Bycroft¹. Briefly, after sample and marker QC, a genotype dataset containing 488,377 samples and 803,426 markers from two arrays (UK BiLEVE Axiom Array and UK Biobank Axiom Array) was imputed using the Haplotype Reference Consortium (HRC) and UK10K haplotype resource increasing the total number of variants to 96 million.

We performed additional QC to ensure high quality genotypes by requiring variants to have an imputation quality score (INFO) > 80%, a minor allele frequency (MAF) > 0.1%, call rate > 95%, and a Hardy-Weinberg equilibrium P-value greater than 1×10^{-10} . This resulted in a final set of 10,894,596 variants for analyses.

Sensitivity analysis to adult onset misclassification

To assess the proportion of childhood onset cases among the adult onset cases needed to detect associations with SNPs at the childhood onset loci, we replaced adult onset cases with childhood onset cases in varying proportions and repeated analyses of association with the lead SNP at the most associated locus (rs4795399 in *GSDMB* on 17q12-21; left panel of figure below) and the lead SNP at the locus with the largest effect size (rs61816761 in *FLG* on 1q21-3; right panel). We considered proportions from 0% to 35% replacements with randomly sampled childhood onset cases (x-axis). For each proportion, we repeated the procedure 50 times to quantify the sampling variability; the median and 25th and 75th percentiles of the $-\log_{10}$ p-values are shown. The black horizontal lines show the genome-wide significance threshold (5×10^{-8}) and the nominally significant threshold (0.05). The p-value for each SNP in the UK Biobank adult onset asthma GWAS is shown as 0% contamination. At the 17q locus (left panel), the p-values (y-axis) become genome-wide significant when 15% or more of the sample is composed of childhood onset cases; at 5% contamination the median p-value for the 17q SNP in the “adult onset” sample is 0.039 (interquartile range [IQR] = 0.031), which is considerably more significant than the p-value in the adult onset cases in our study (0.628). At the 1q locus (right panel), the p-values (y-axis) become genome-wide significant when 20% or more of the sample is composed of childhood onset cases; at 5% contamination the median p-value for the 1q SNP in the “adult onset” sample is 0.094 (IQR = 0.065), which is considerably more significant than the p-value in the adult onset cases as defined in our study (0.656). These data indicate that relatively few (~5%) childhood onset cases would be sufficient to generate some signal of association at these two childhood onset loci in the adult onset cases. The fact that we did not suggests that the adult onset cases have little “contamination” with childhood asthma cases.



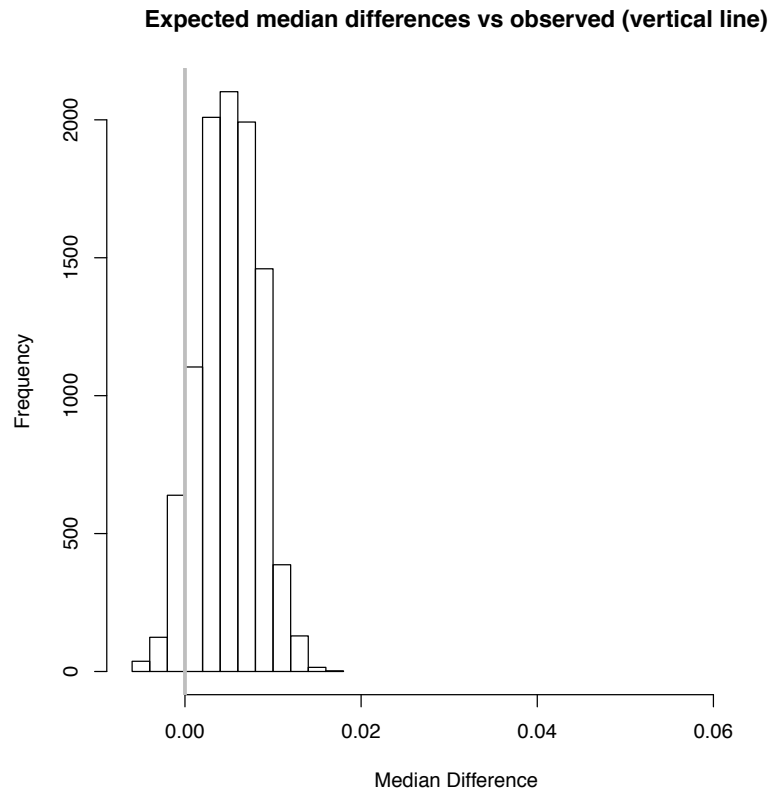
Permutation testing of shared risk loci

To compare the odds ratios (OR) between childhood onset and adult onset asthma GWAS we simulated shared variants under the null hypothesis of no difference in effect size between childhood and adult onset cases. To simulate effect sizes under the null hypothesis, we reshuffled (permuted) the childhood and adult onset cases.

We sampled 9,433 individuals from the combined pool of childhood and adult onset cases and labelled them as childhood onset cases. Similarly, we sampled 21,564 individuals and labelled them as adult onset cases. By sampling from the combined pool, we ensured the null hypothesis of no difference between the two classes. The sampling was done with replacement. We used the same 318,237 controls as for the main GWASs.

For the genotypes, we used the 39 shared SNPs from our main analysis (Table 2C in manuscript). We performed logistic regression of childhood onset cases vs controls against each of the 39 SNPs separately. The effect sizes were implicitly established by the true underlying effect sizes. We repeated this sampling 100 times resulting in 3900 representative SNPs. 739 SNPs were genome-wide significant ($P < 5 \times 10^{-8}$) in both the childhood onset and the adult onset permuted “cases” and therefore considered to be shared.

To generate the null distribution of median differences between childhood and adult onset loci, we further resampled 10,000 sets of 39 SNPs and computed the median difference of their log odds ratios. Finally, we compared the observed median difference between childhood onset and adult onset log odds ratios to this null distribution as plotted in the following figure. The P -value was calculated as the number of times the observed median exceeded the simulated median differences. The observed median value (0.074) is shown by the vertical black line on the figure below (permutation test $P < 10^{-4}$).



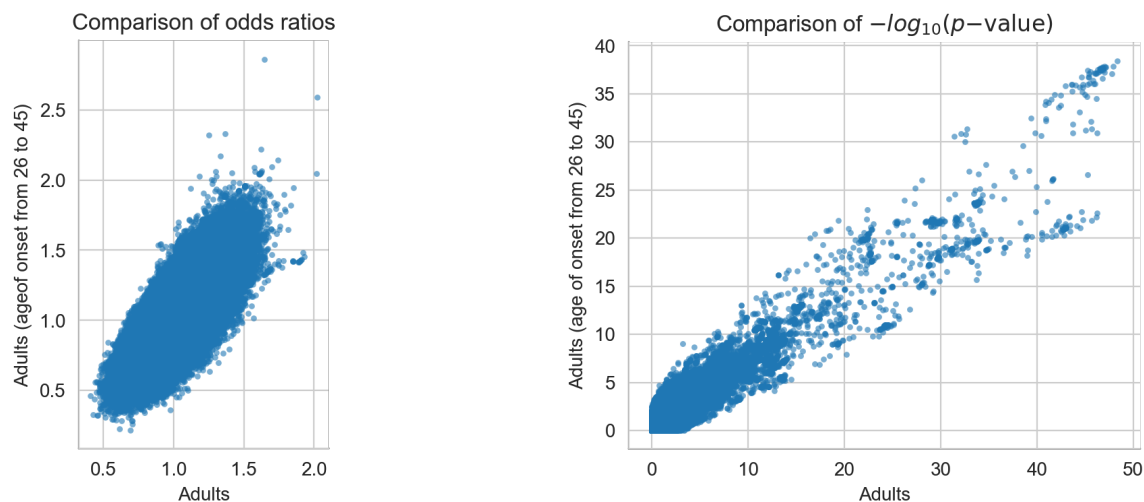
PrediXcan and S-PrediXcan

PrediXcan correlates predicted expression levels with phenotypes to find genes that may mediate the genotype-phenotype association. Here we use the summary statistic version, S-PrediXcan, which uses GWAS results and prediction weights to directly infer the gene-level association statistics. The weights were downloaded from our repository <http://predictdb.org>, which serves prediction models from GTEx and other reference transcriptome datasets. These are based on elastic net models with mixing parameter 0.5, which we have shown to produce sparse and robust prediction⁴.

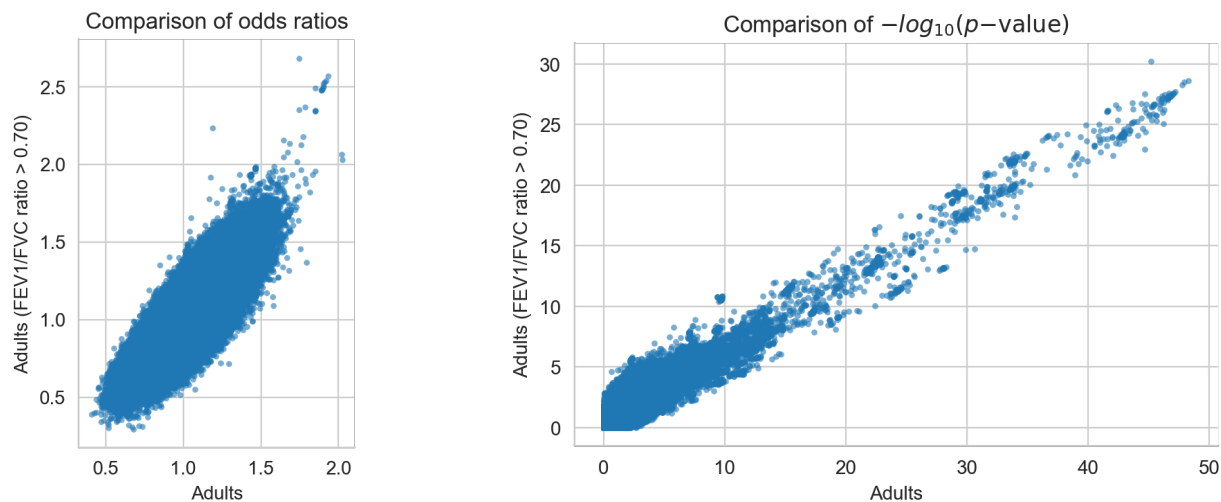
Sensitivity analysis of COPD and asthma age of onset

To further the potential misclassification of COPD as adult onset asthma, we performed two sensitivity analyses (GWAS): 1) we removed adults with ages of asthma onset between 46 to 65 years, and 2) we removed adult-onset cases and controls with FEV1/FVC <0.70. The first GWAS included 12,060 cases with onset between ages 25 and 45 years, who were compared to all controls. The second GWAS included 14,409 cases and 252,199 controls with FEV1/FVC ≥0.70 from among the 18,930 adult onset asthma cases and 294,043 controls with spirometry data (FEV1 and FVC). We then compared the results of these two GWASs with the GWAS using the full set of adult onset cases and controls. As shown in the figures below, the ORs and p-values from each GWAS are highly correlated ($r = 0.76$ for both ORs and p-values in sensitivity analysis #1, and $r = 0.82$ for both ORs and p-values in sensitivity analysis #2). However, both yielded ORs that were slightly larger in the subset analyses. This suggests some dilution of the genetic effect by both the older cases and those with FEV1/FVC <0.70 (who have a slightly later onset). This could be due to the decreasing heritability with age on onset or to contamination with COPD cases. However, the fact that significance increases overall when the excluded individuals are included, reassures us that most of these cases are likely to have asthma. Moreover, the fact that we do not see any evidence for association in the adult onset GWAS at the prominent COPD locus on chromosome 15q25.1 (see appendix Figure 9) further suggests that contamination with COPD cases is not a major issue in our analysis and that the lower ORs in the adult onset compared GWAS to childhood onset GWAS (see Figure 2) is not due to misdiagnosis in the adult onset cases. In fact, these differences would be even greater if we focused only on younger adults or excluded those with poor lung function.

Comparisons of the GWAS odds ratios (left) and p-values (right) from the complete adult onset group (x-axis) vs adult onset cases with age of onset from 26 to 45 years (y-axis). The correlations for both panels are 0.76.



Comparisons of GWAS odds ratios (left) and p-values (right) from the complete adult onset group (x-axis) vs adult onset cases with FEV1/FVC < 0.70 (y-axis). The correlations for both panels are 0.82.



Figures

Figure 1. Comparisons of odds ratios and p-values from childhood onset (top) and adult onset (bottom) GWAS using the top 10 principal components (x-axis) and the top 14 principal components (y-axis).

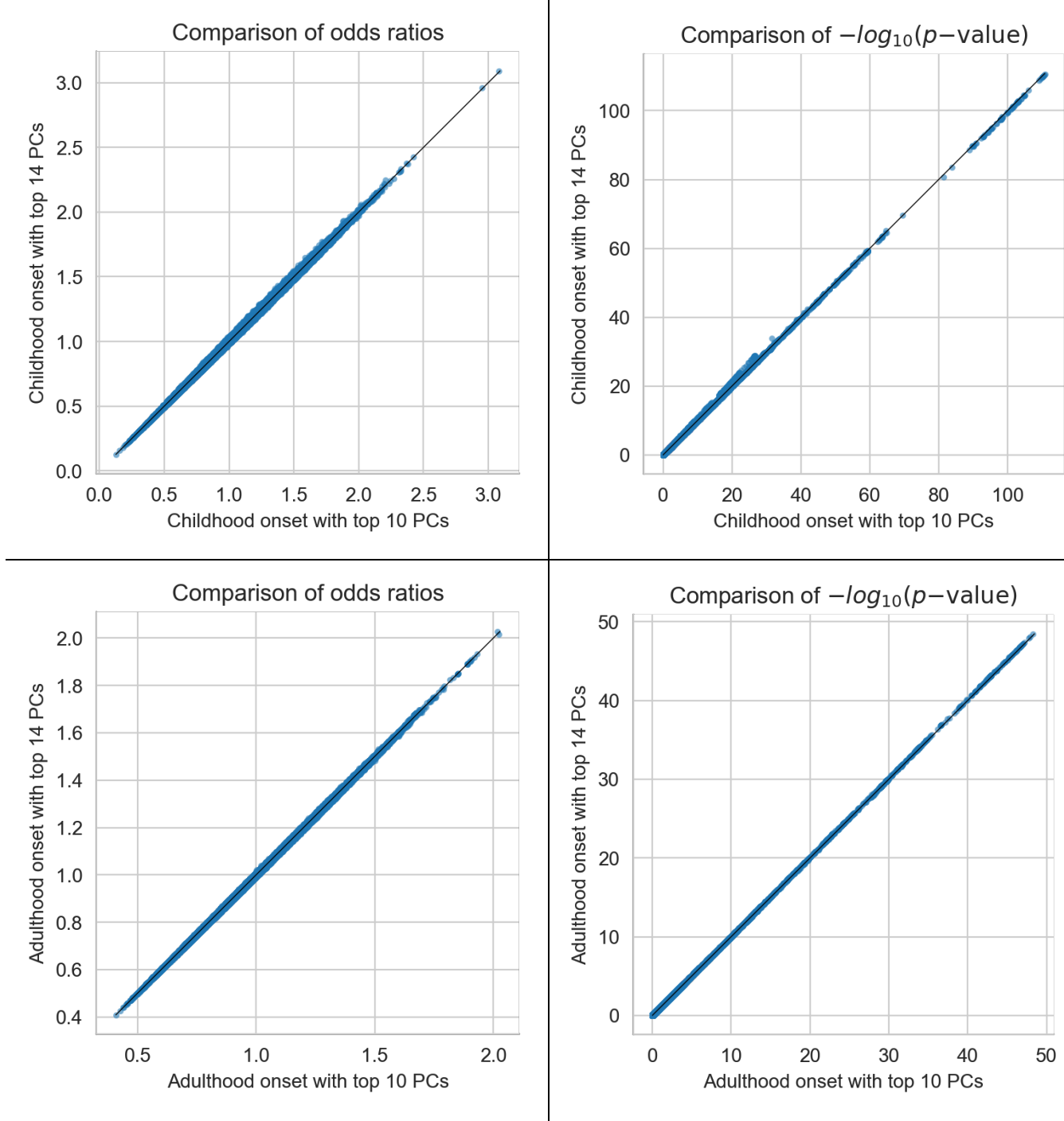
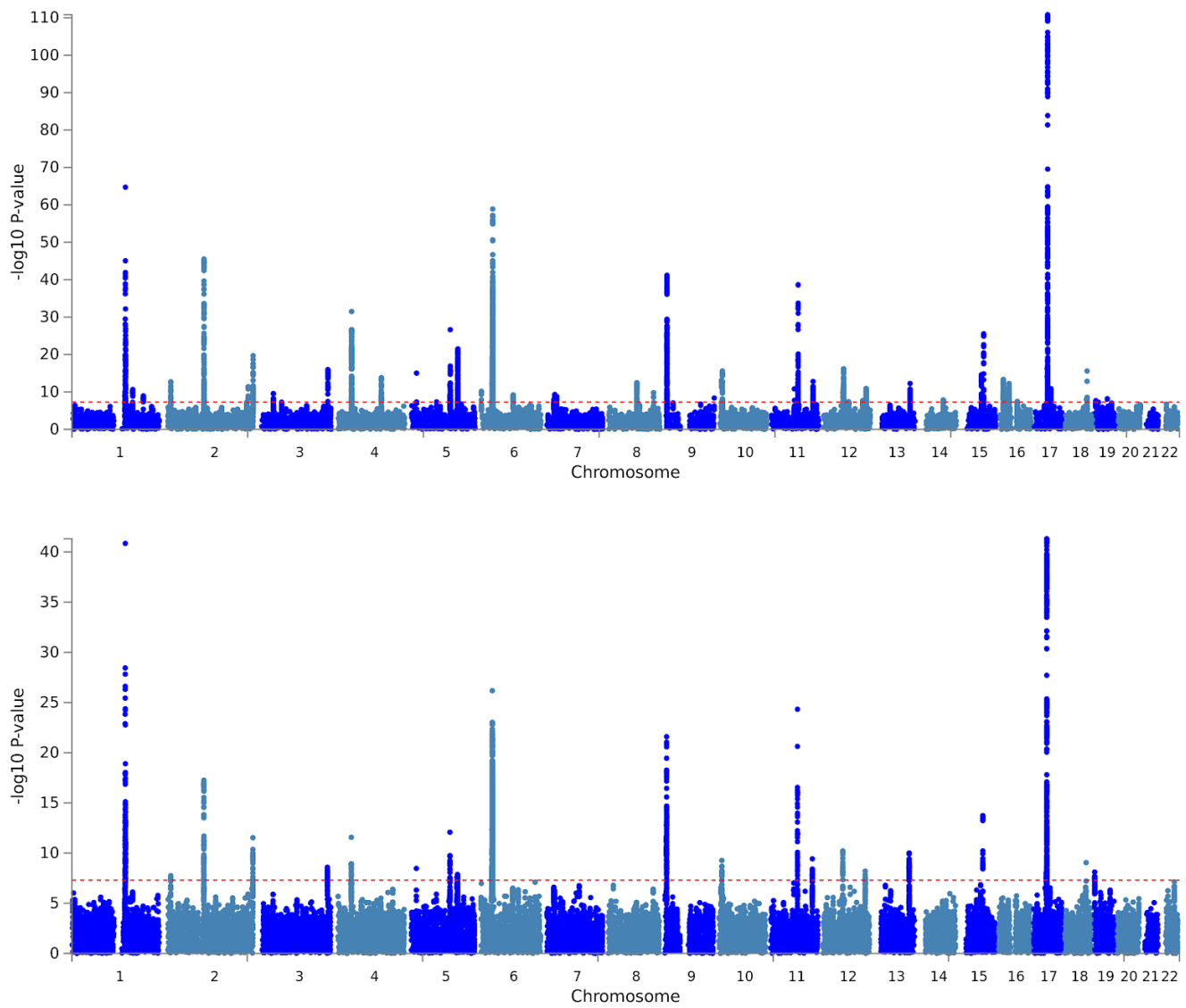


Figure 2. Manhattan plots showing GWAS results excluding self-reported asthma.

A. The GWAS results of childhood onset (full set including self-report + ICD10, 9,433 cases) at the top and the childhood onset (ICD10 only, 3,462 cases) at the bottom.



B. The GWAS results of adult onset (full set including self-report + ICD10, 21,564 cases) at the top and the adult onset (ICD10 only, 9,260 cases) at the bottom.

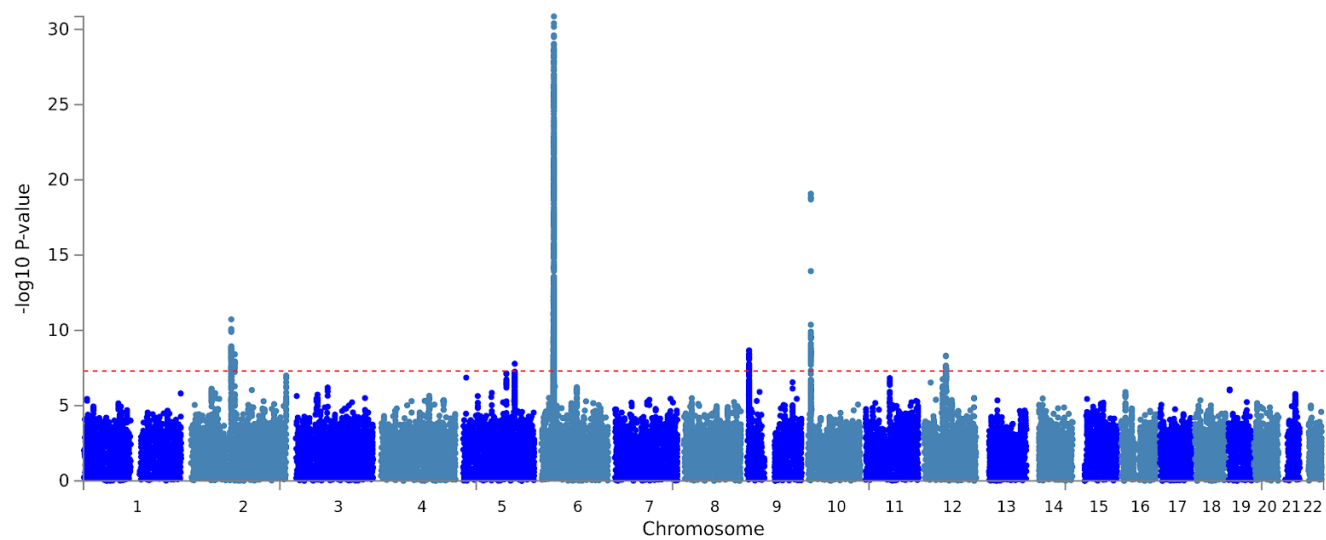
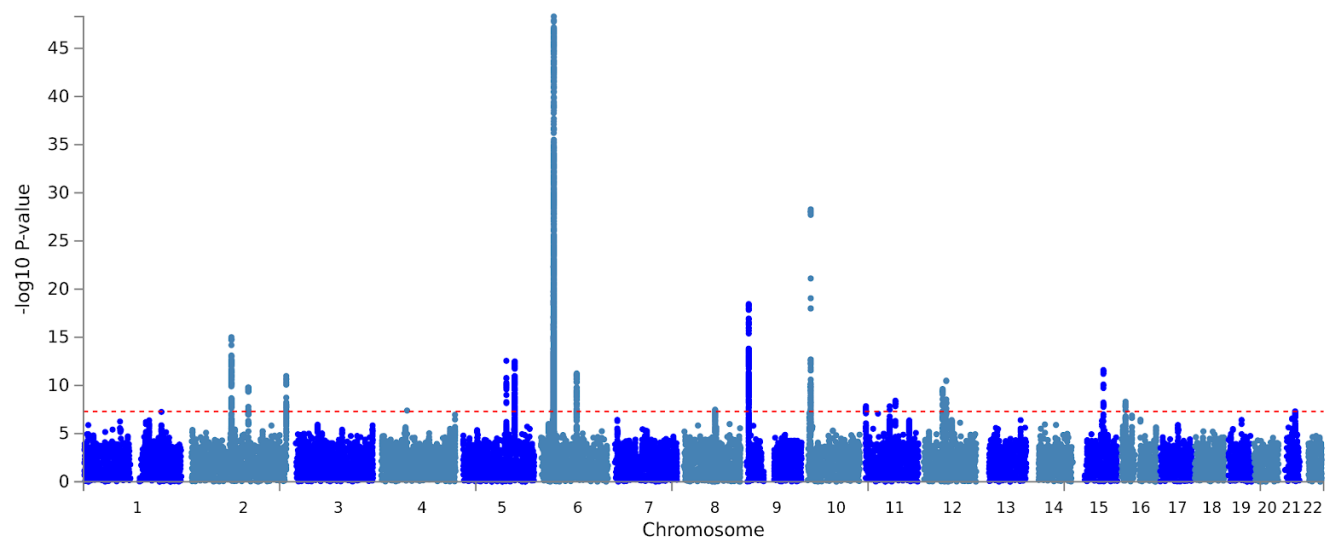


Figure 3. QQ-plot of p-values from a GWAS comparing patients with asthma with ICD10 + self-report to those with self-report only.

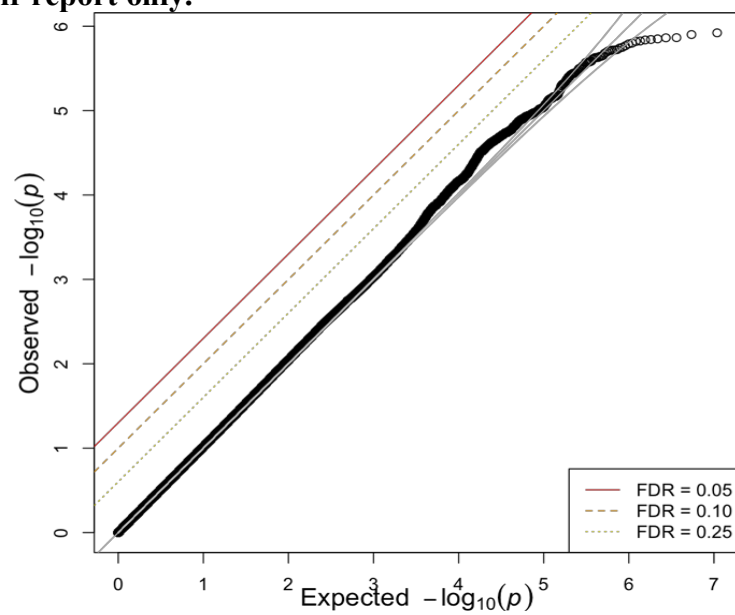


Figure 4. Forest plot comparing ORs from the GWASs for all childhood onset cases and childhood onset cases excluding those with allergy. ORs and 95% confidence intervals are shown for the 61 loci in Table 2 (blue, childhood onset asthma; green, childhood onset asthma excluding allergy), ordered by the OR in the childhood onset GWAS (largest to smallest).

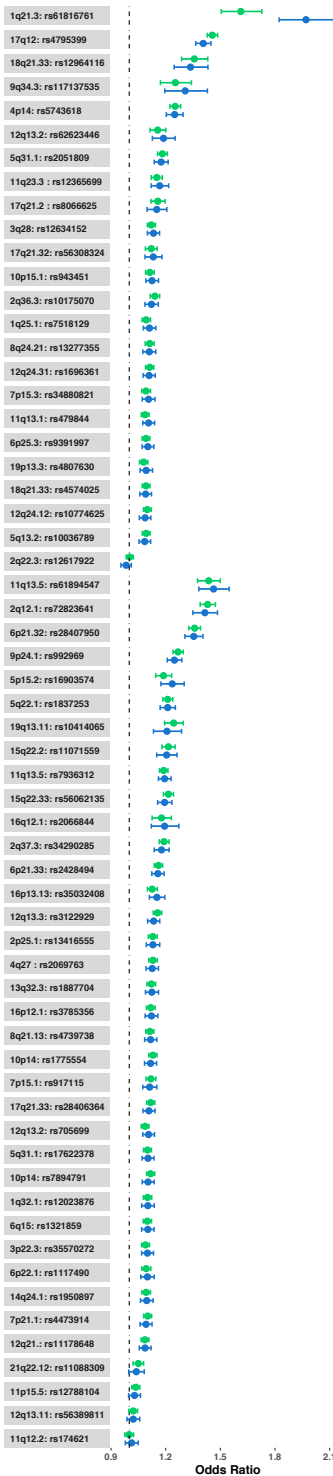
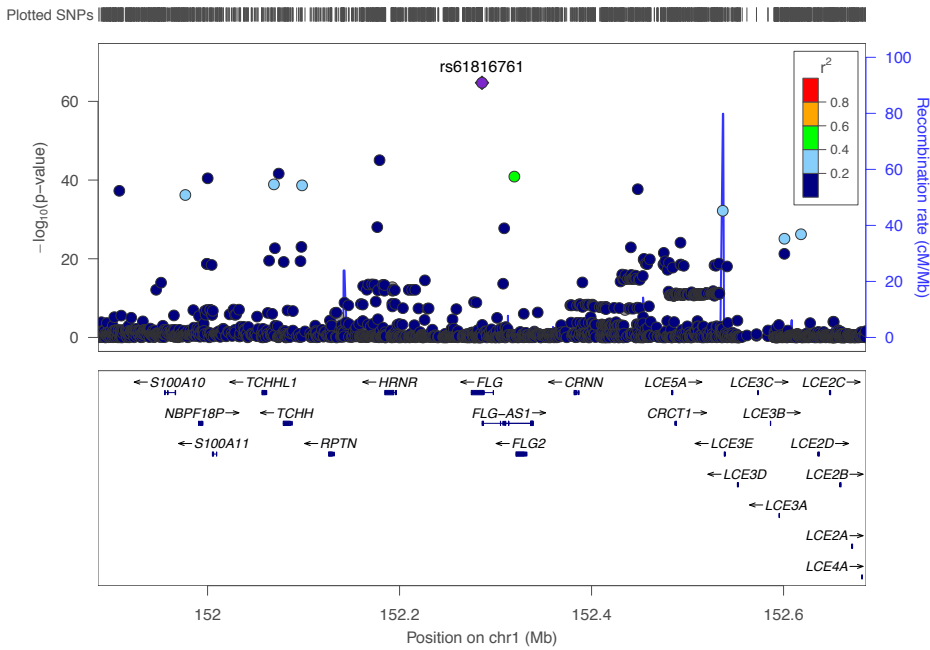


Figure 5. Regional association plots for 23 childhood and one adult onset asthma specific loci.

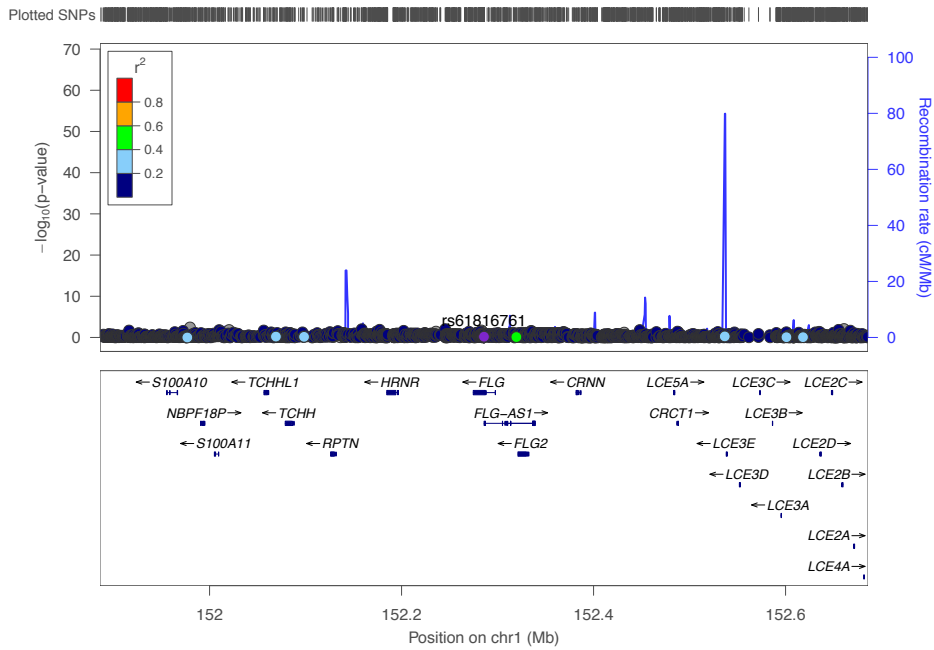
Loci Associated with Childhood Onset Asthma Only

1q21.3 – rs61816761

Childhood Onset

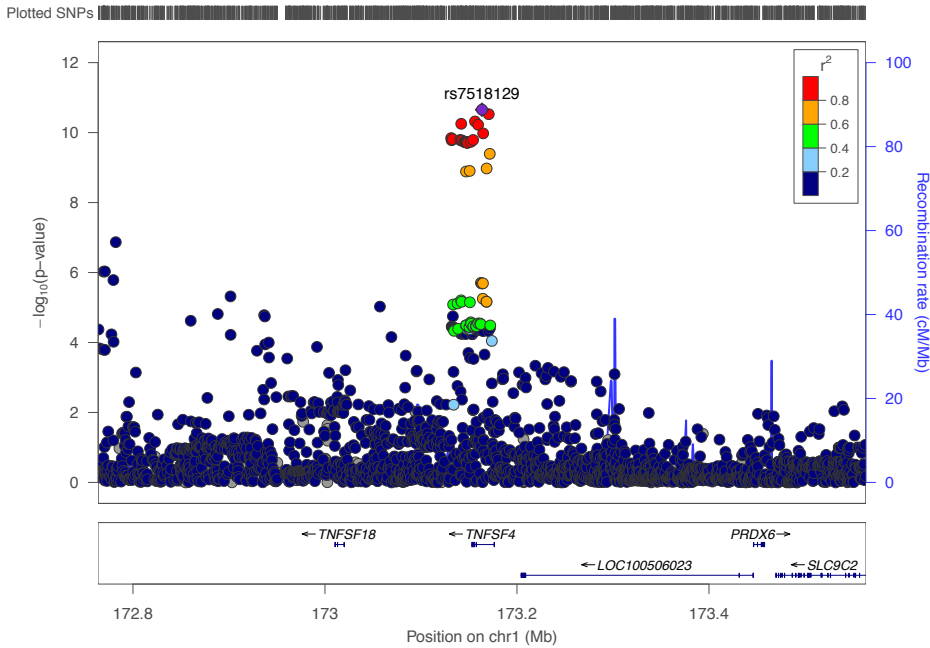


Adult Onset

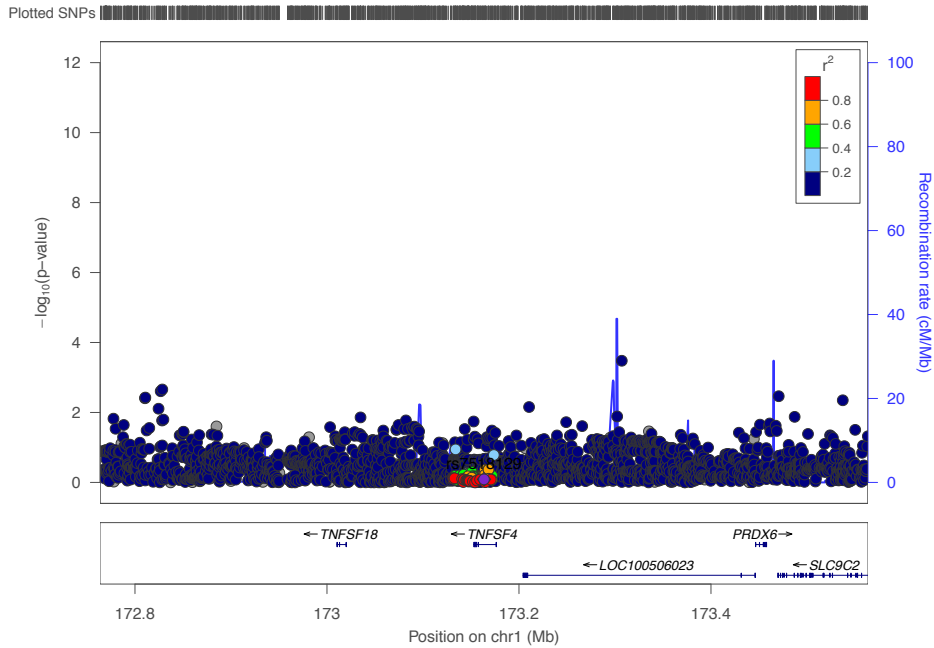


1q25.1 – rs7518129

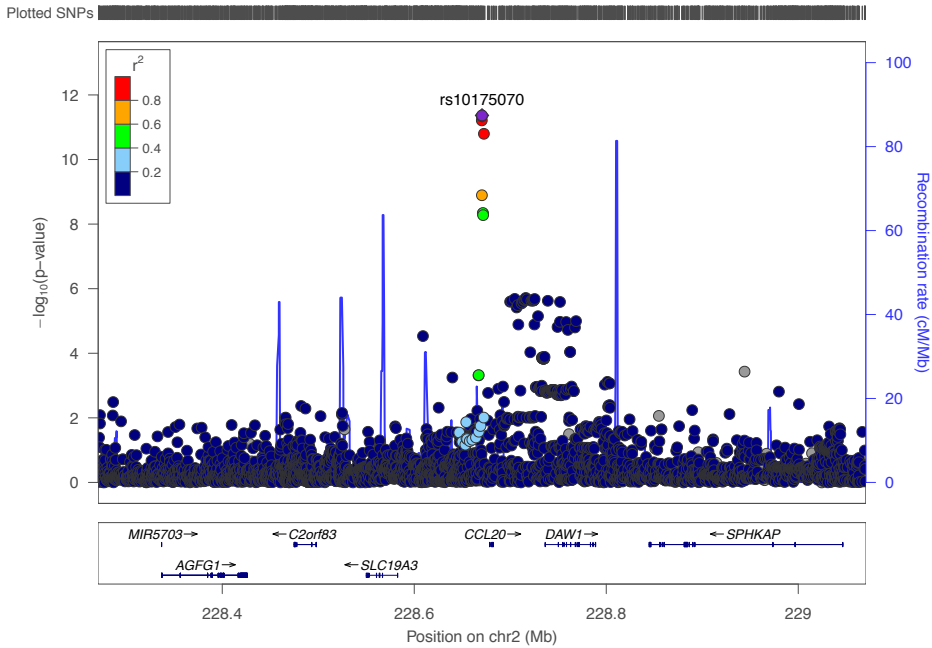
Childhood Onset



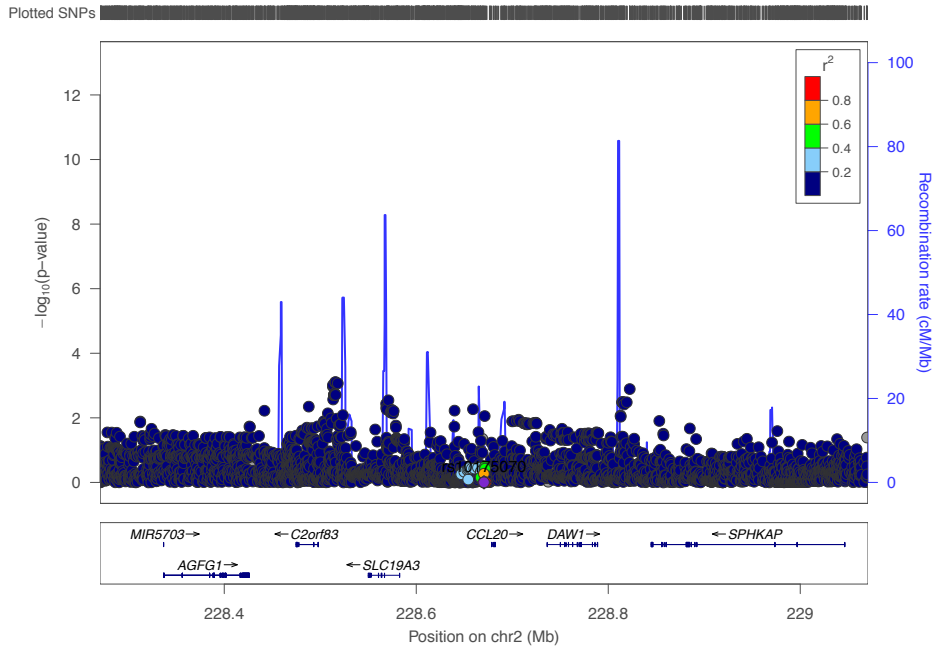
Adult Onset



Childhood Onset

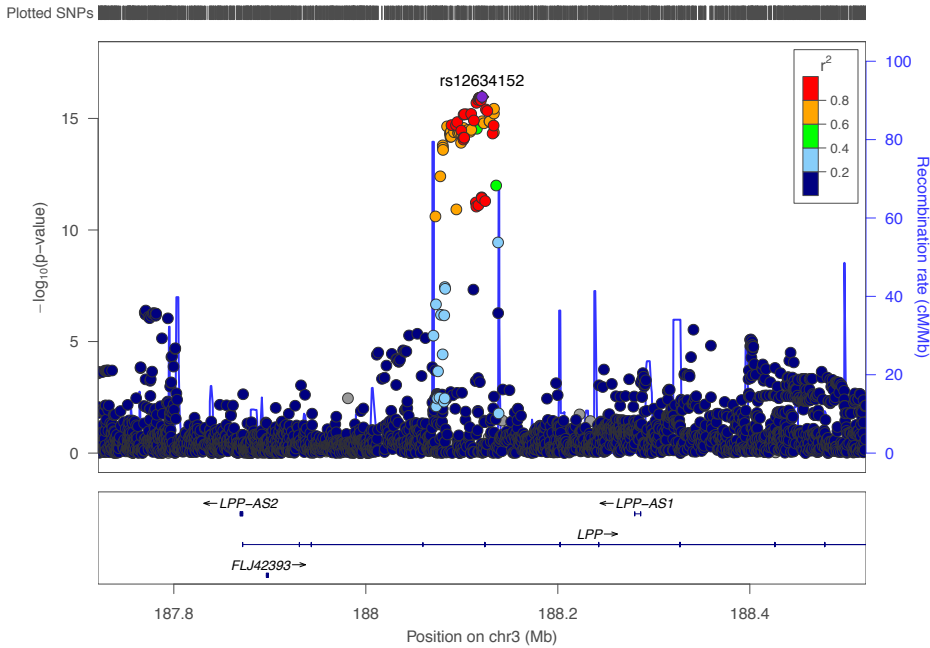


Adult Onset

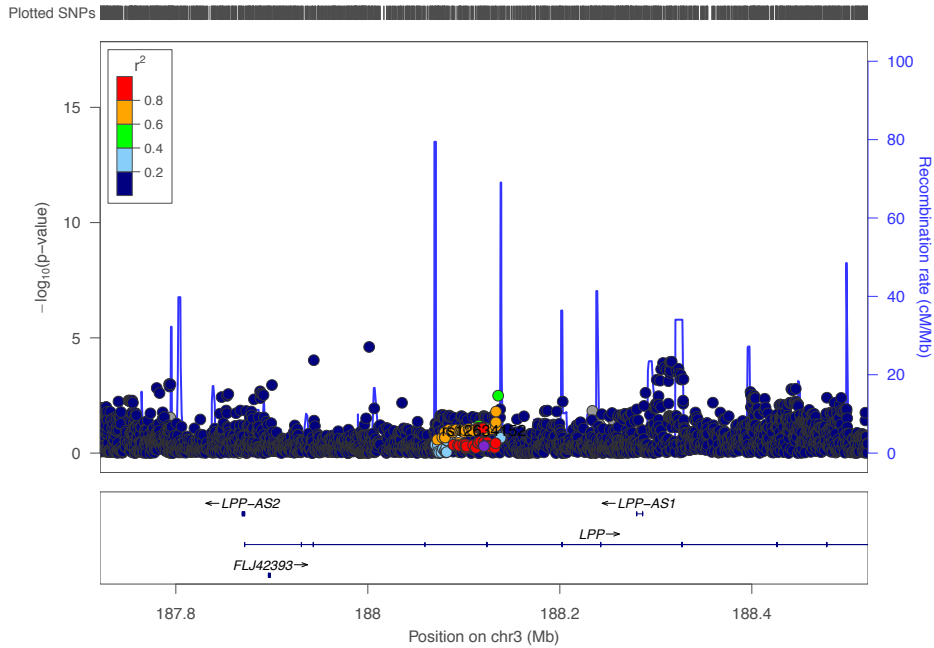


3q28 – rs12634152

Childhood Onset

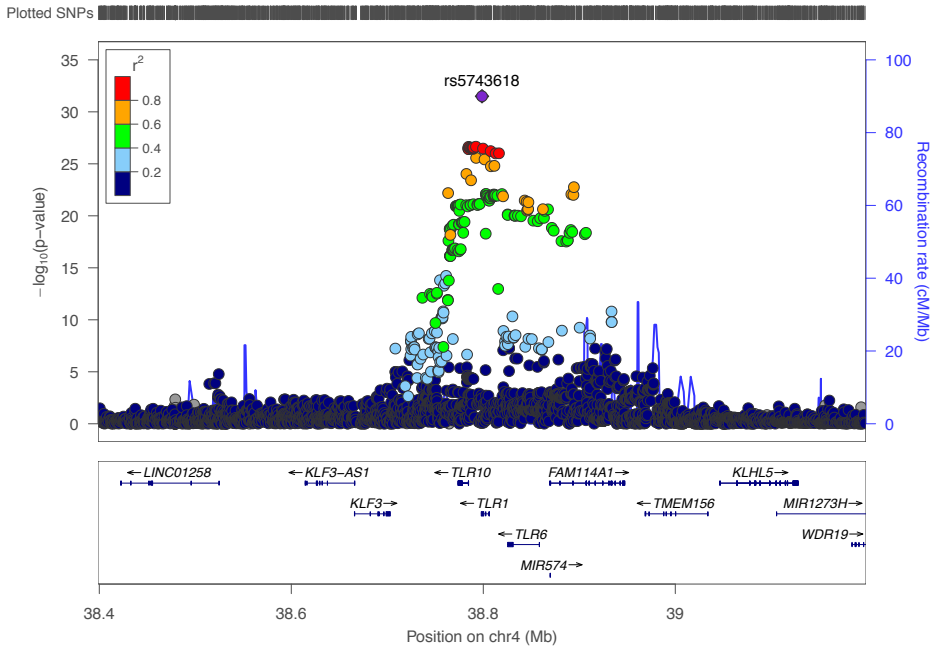


Adult Onset

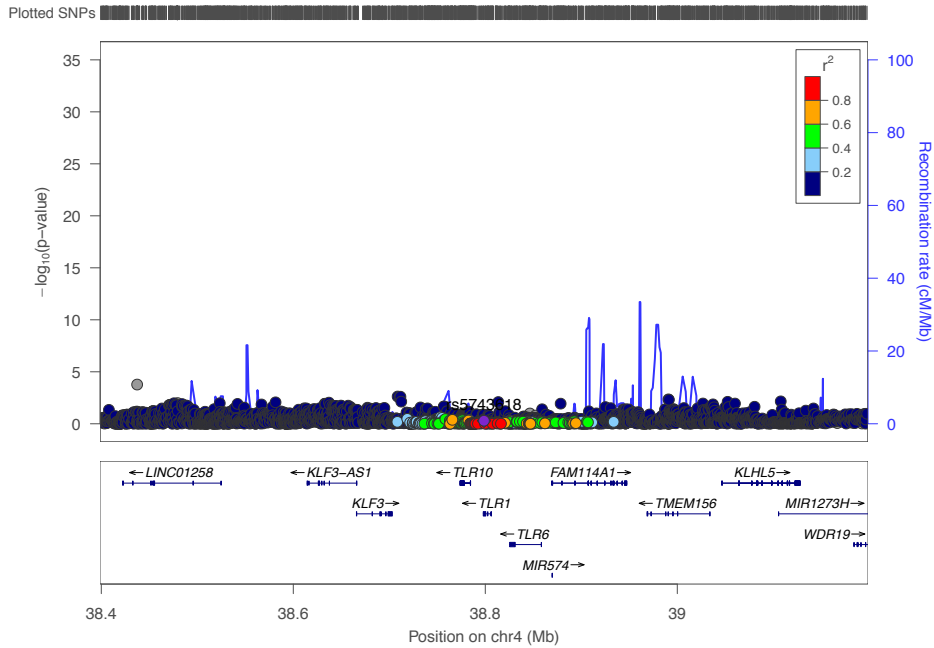


4p14 – rs5743618

Childhood Onset

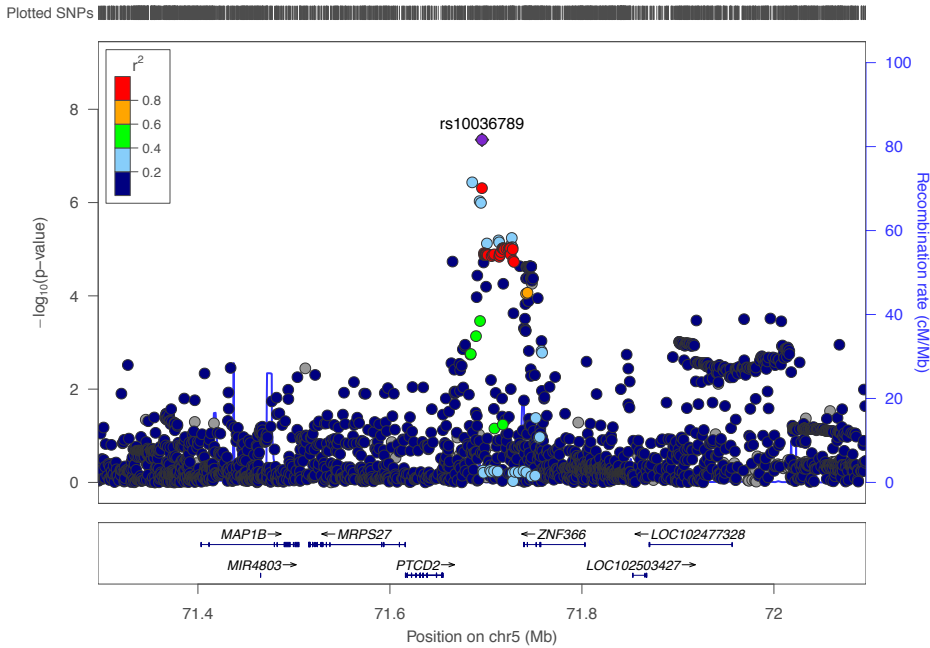


Adult Onset

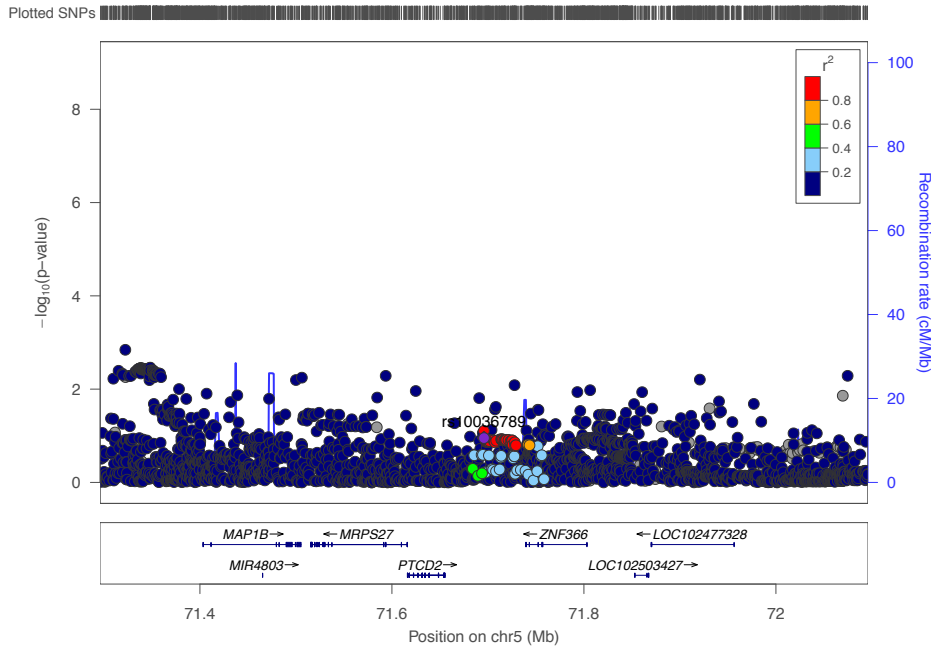


5q13.2 – rs10036789

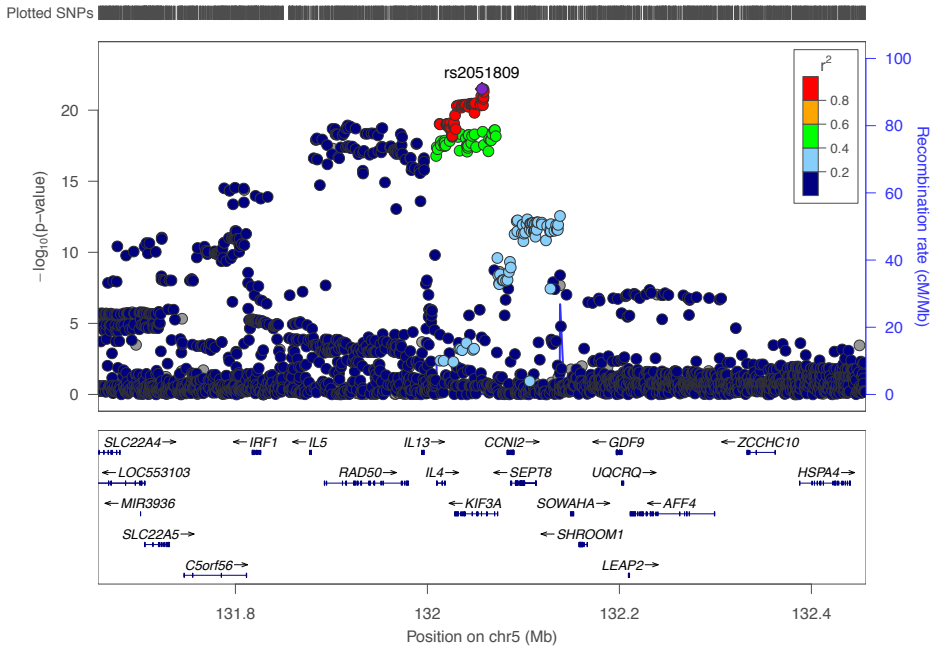
Childhood Onset



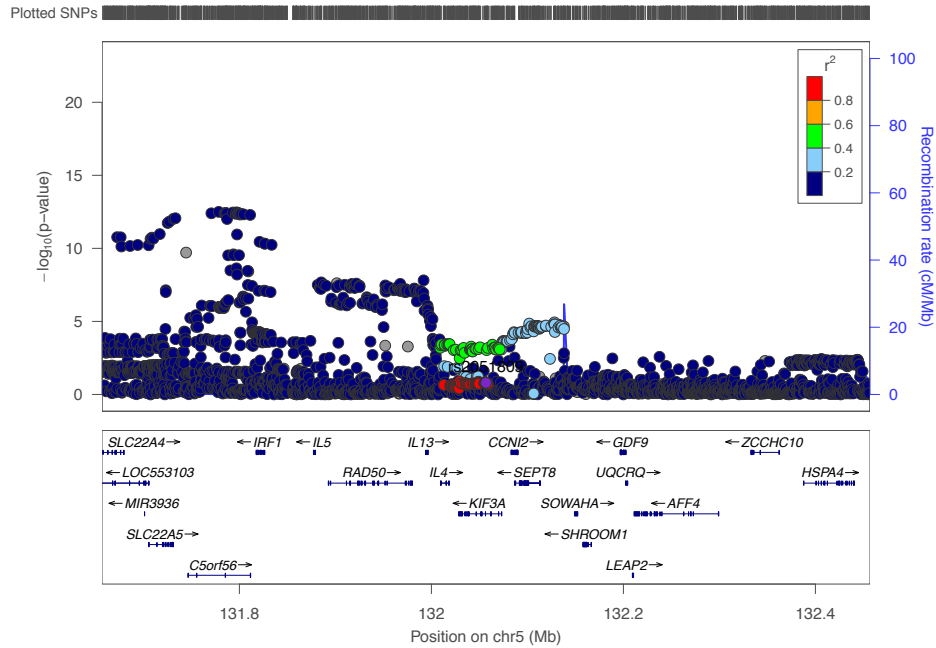
Adult Onset



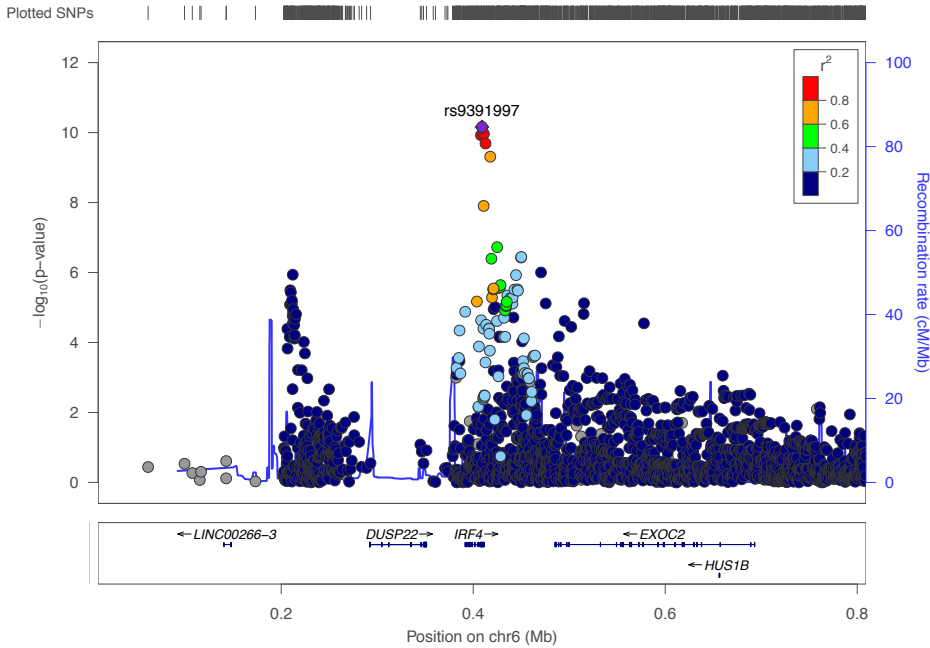
Childhood Onset



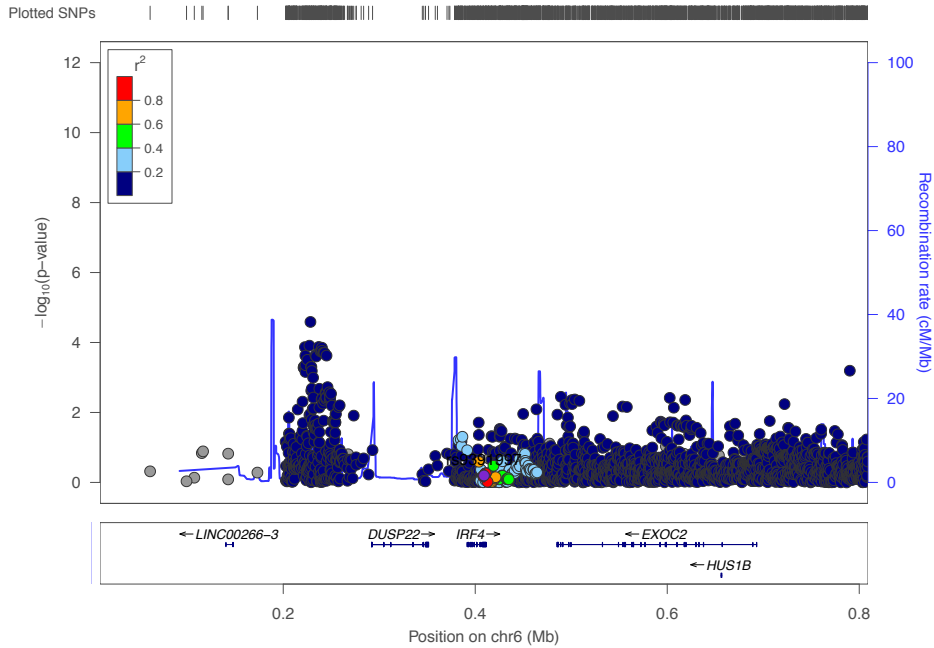
Adult Onset



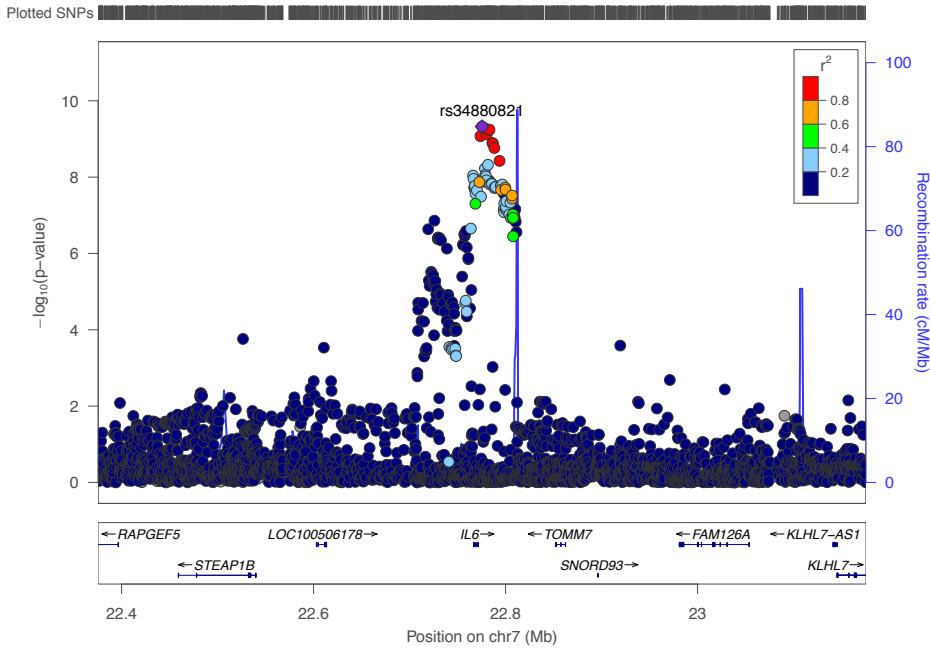
Childhood Onset



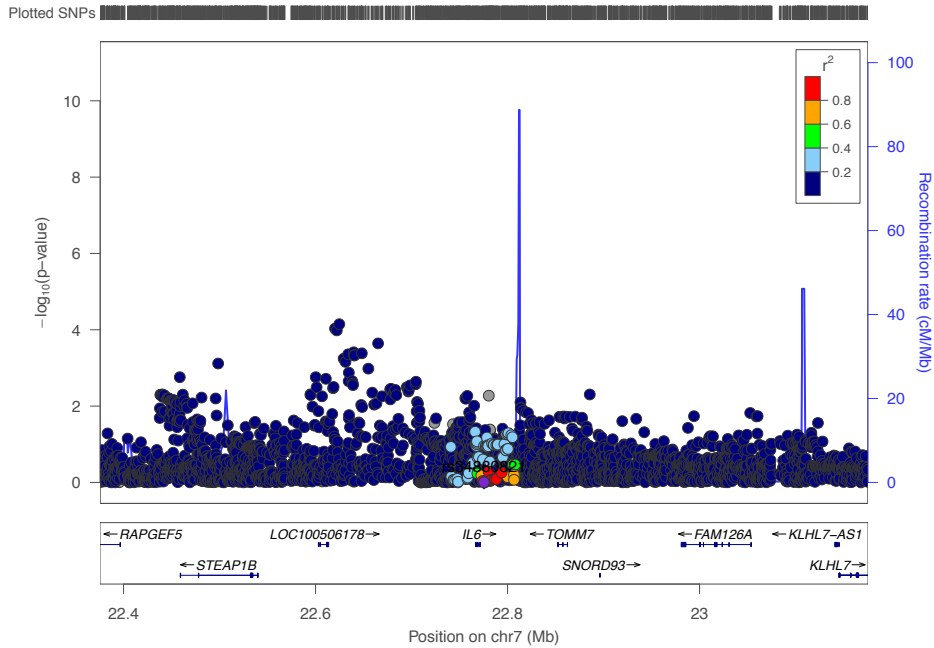
Adult Onset



Childhood Onset

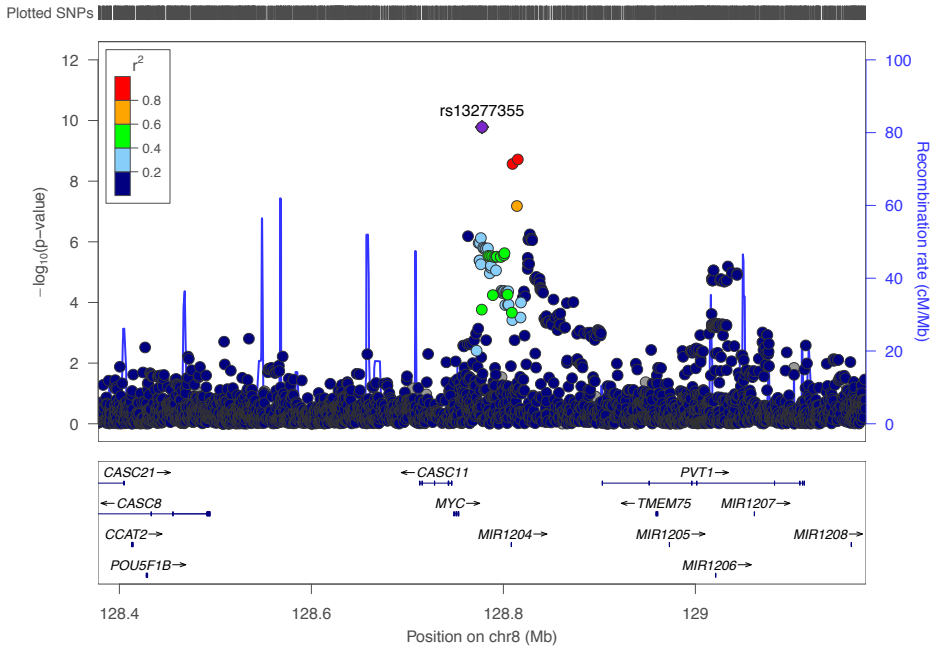


Adult Onset

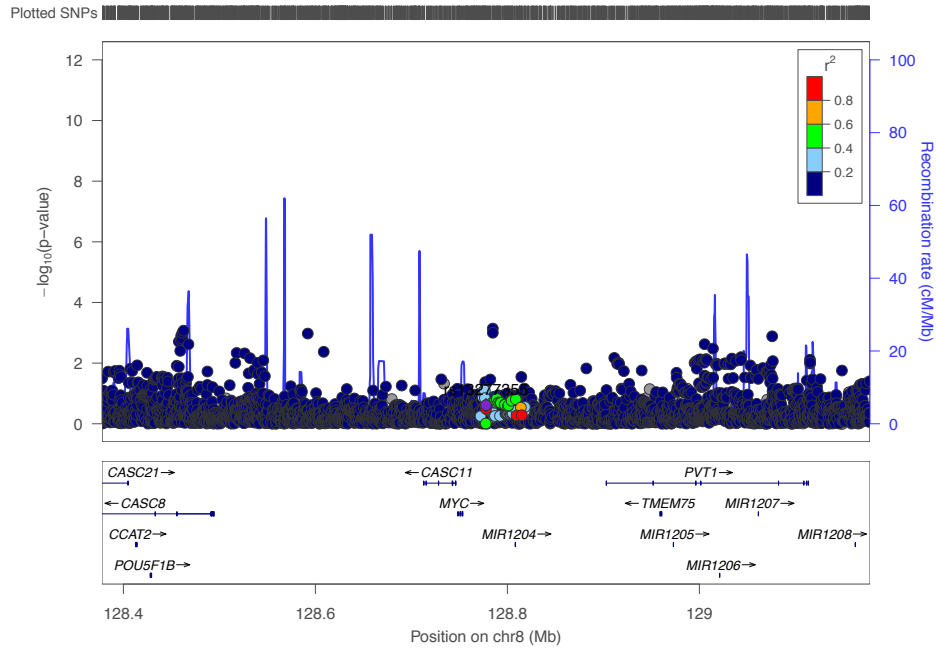


8q24.21 – rs13277355

Childhood Onset

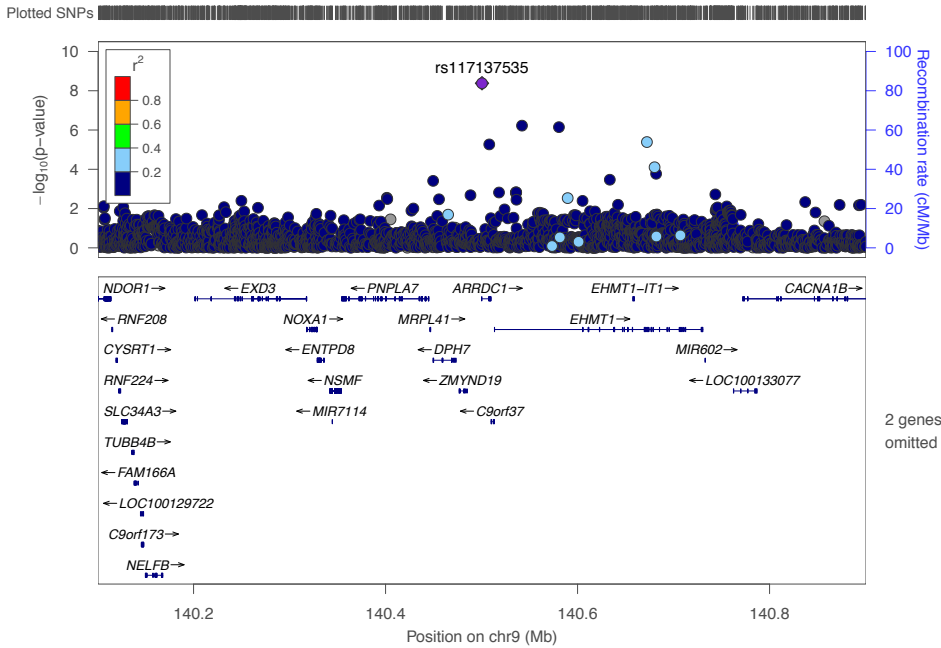


Adult Onset

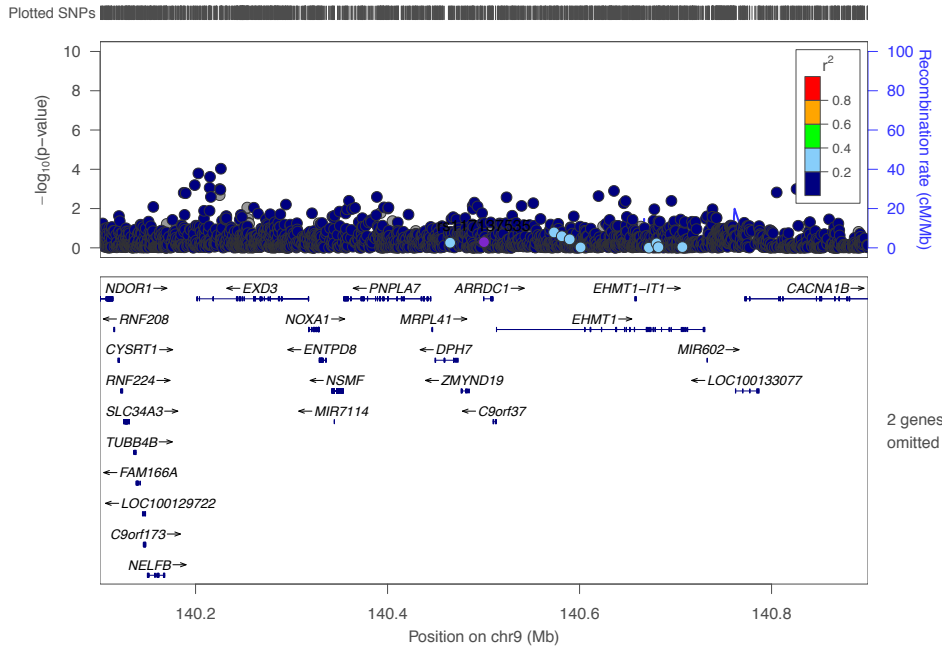


9q34.3 – rs117137535

Childhood Onset

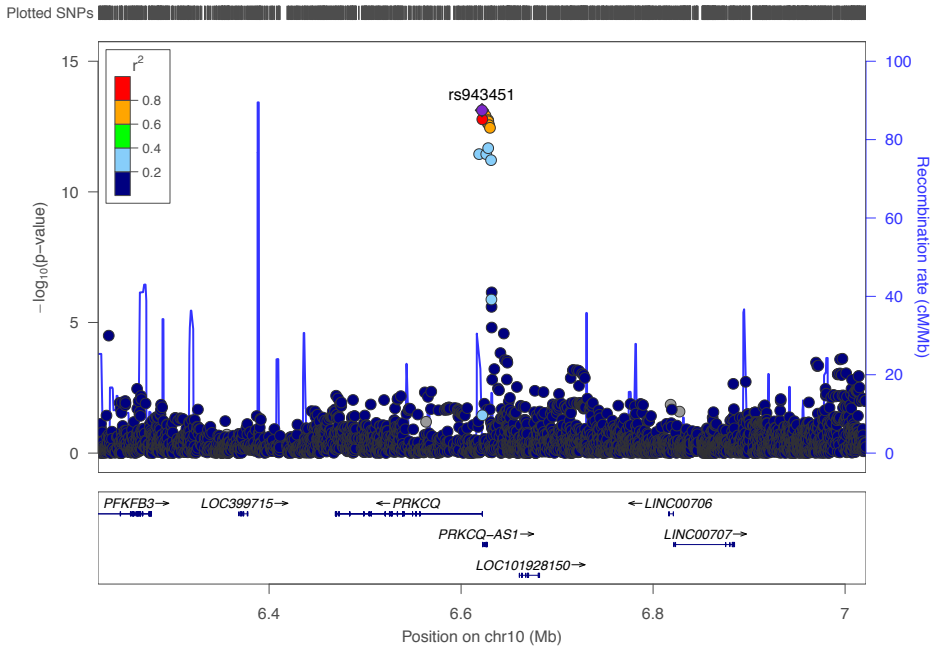


Adult Onset

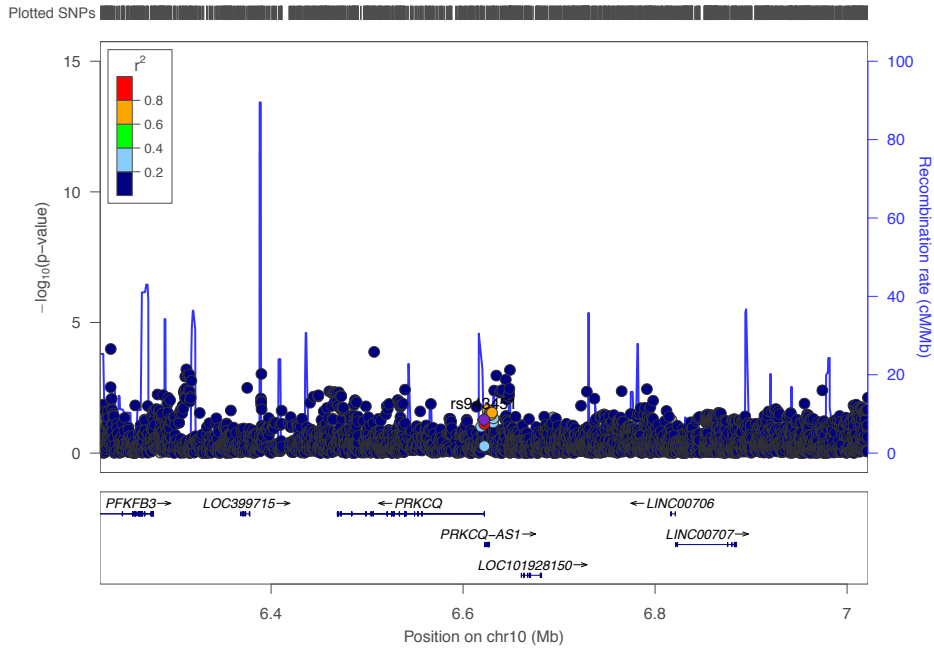


10p15.1 – rs943451

Childhood Onset

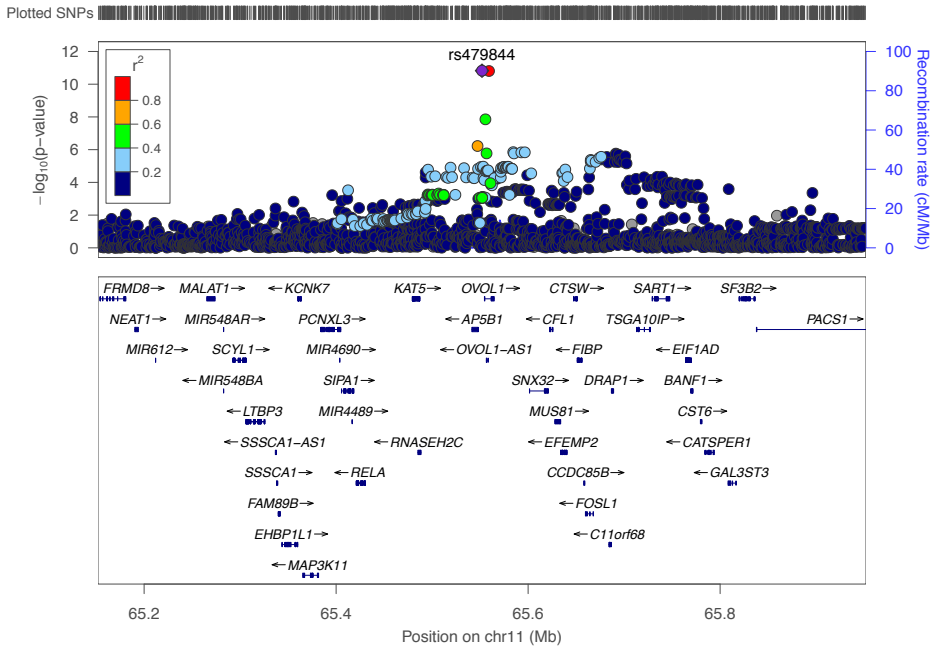


Adult Onset

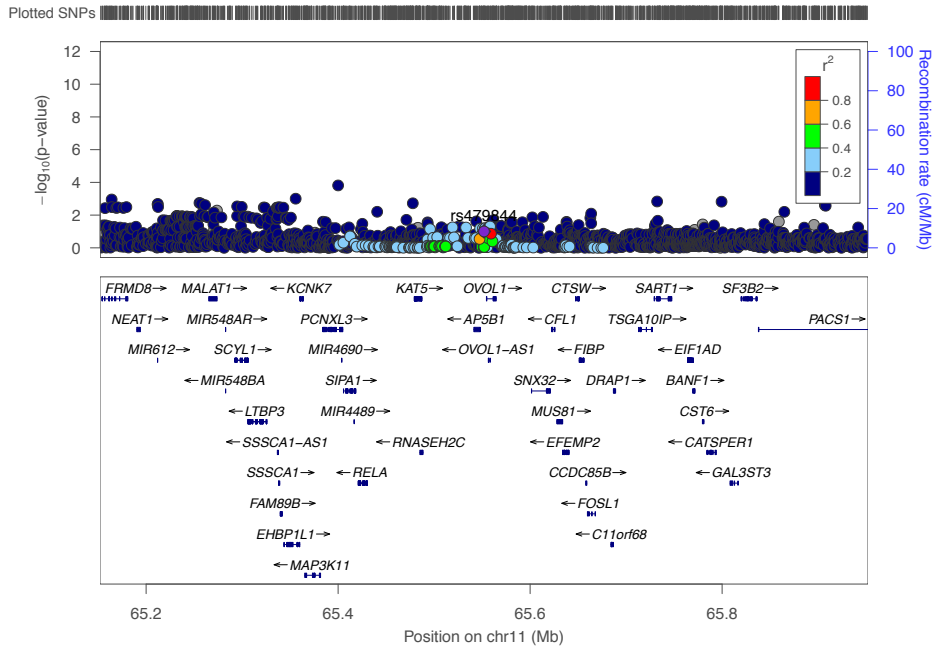


11q13.1 – rs479744

Childhood Onset

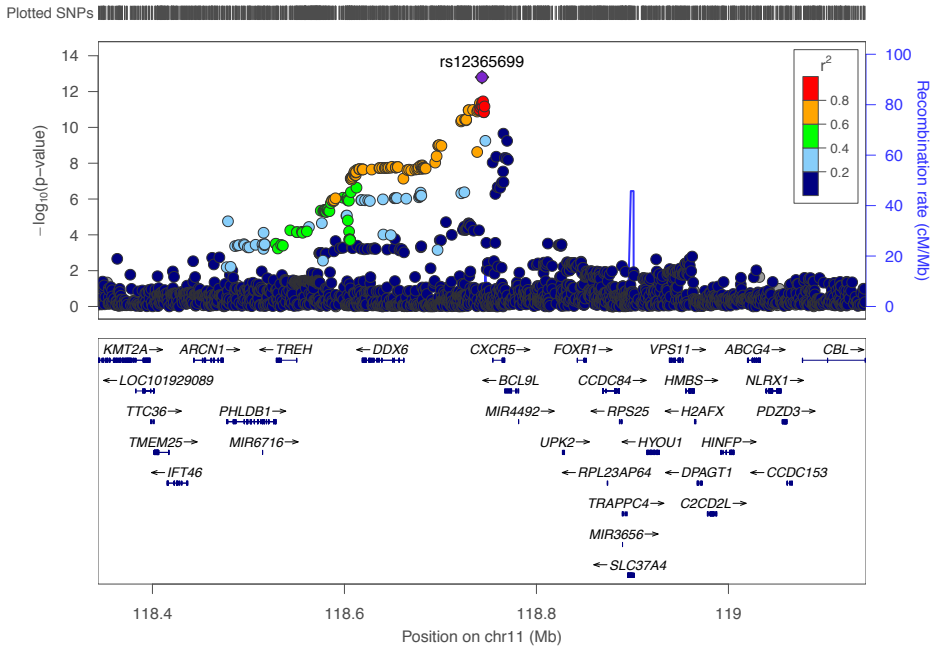


Adult Onset

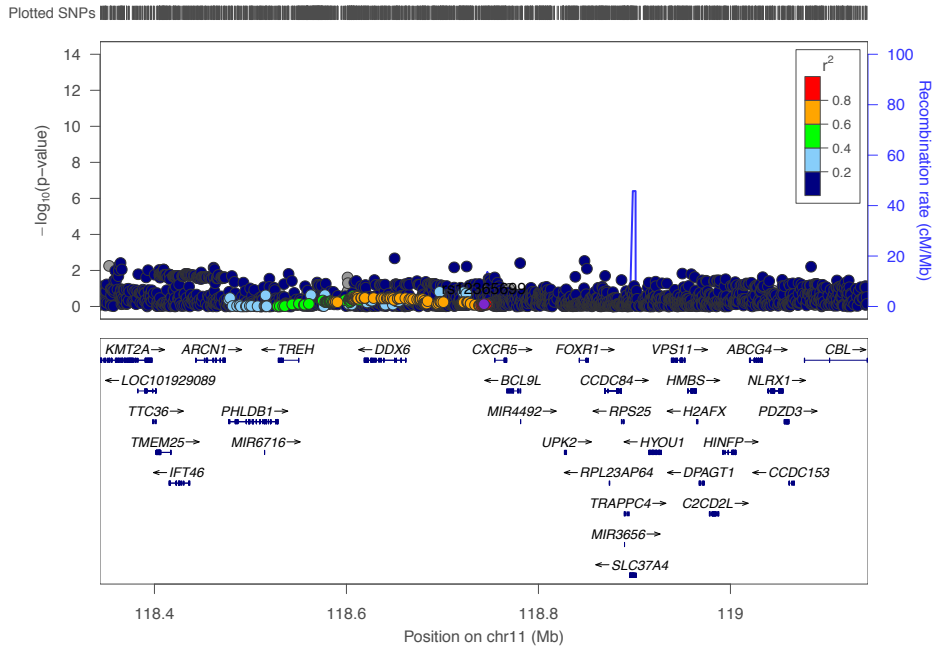


11q23.3 – rs12365699

Childhood Onset

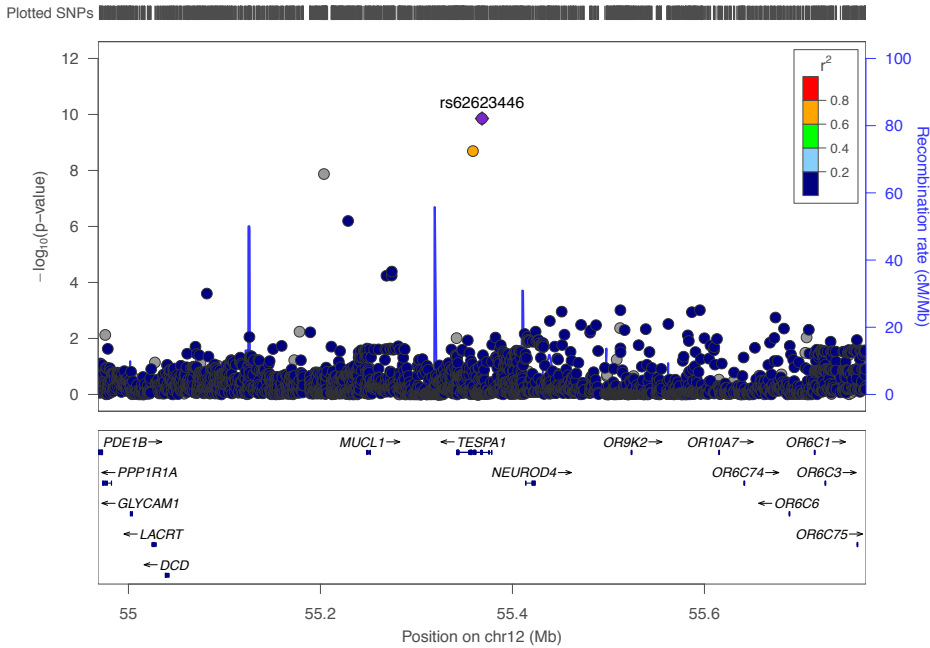


Adult Onset

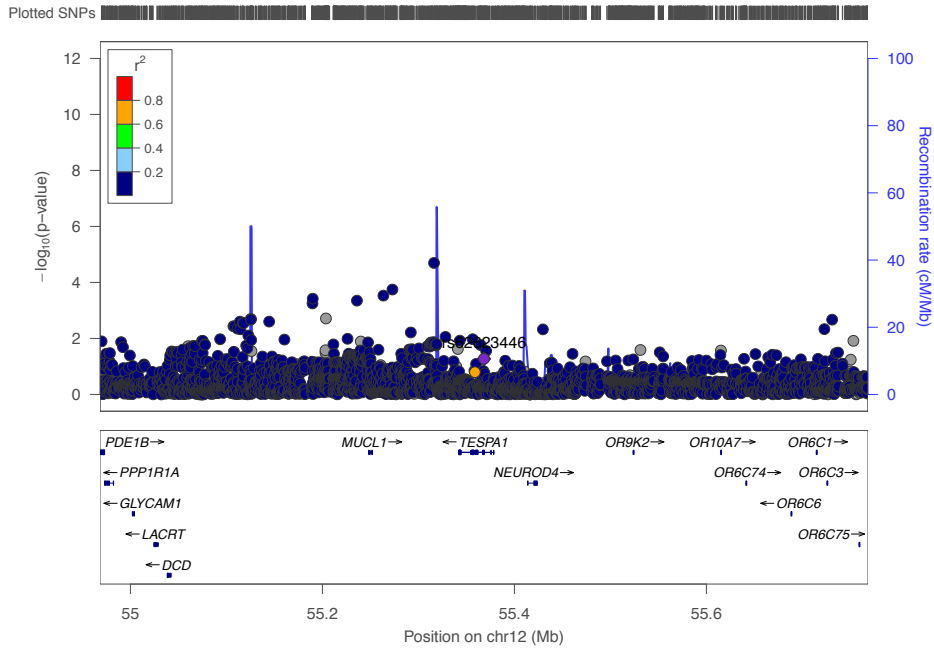


12q13.2 – rs62623446

Childhood Onset

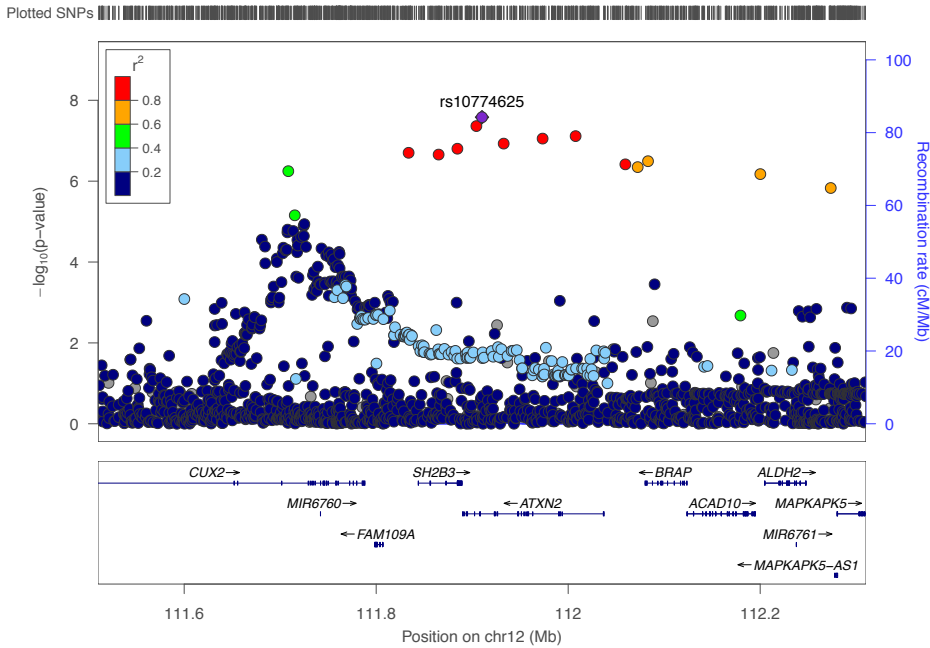


Adult Onset

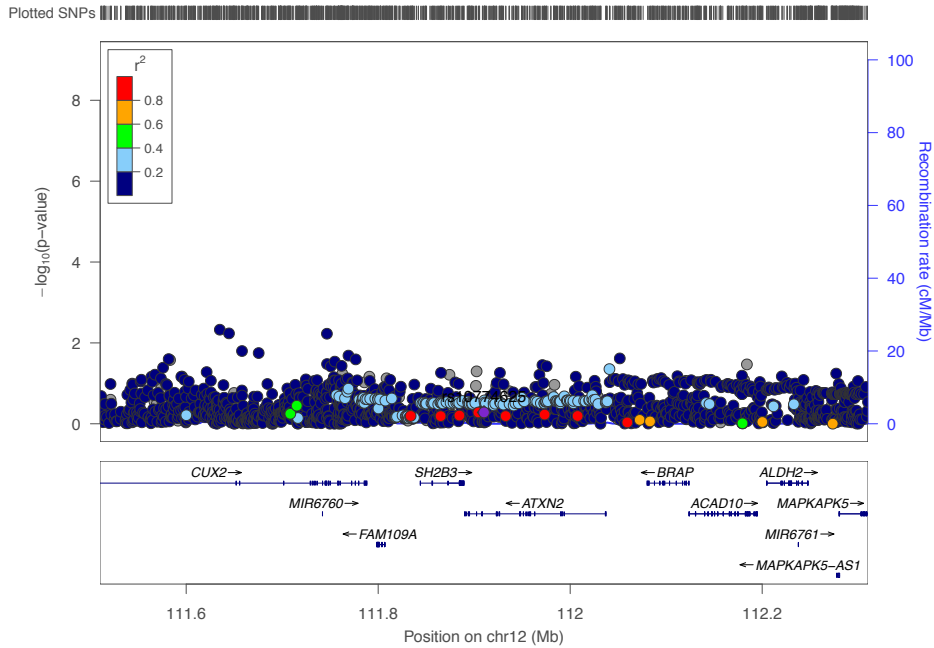


12p24.12 – rs10774625

Childhood Onset

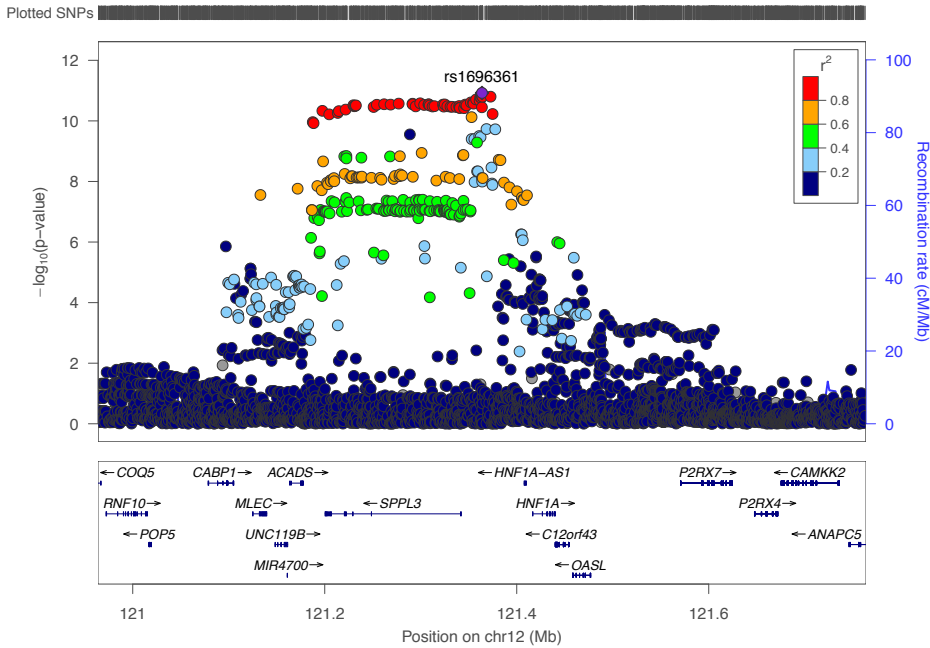


Adult Onset

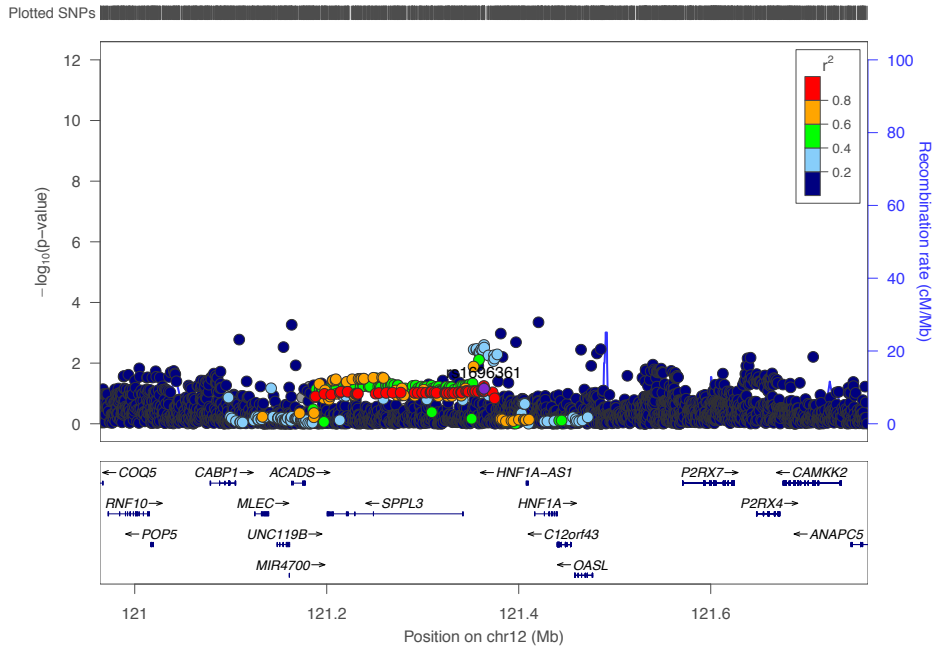


12q24.31 – rs1696361

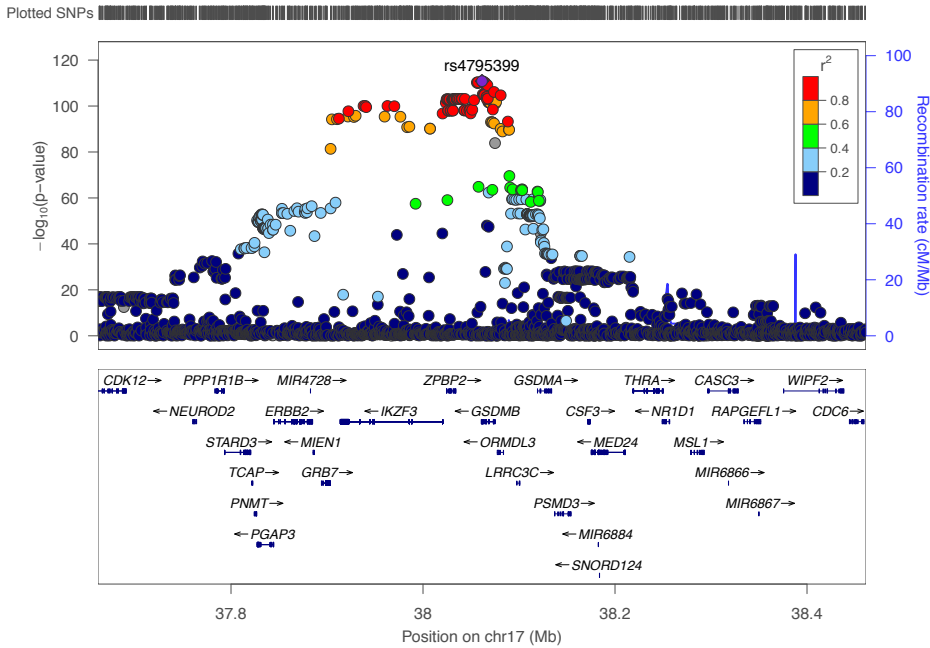
Childhood Onset



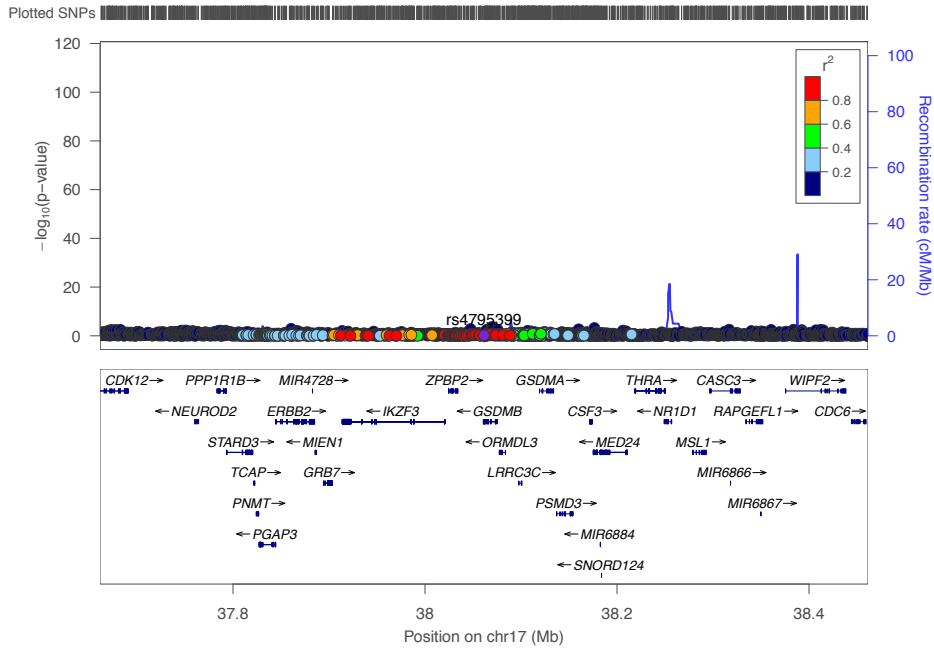
Adult Onset



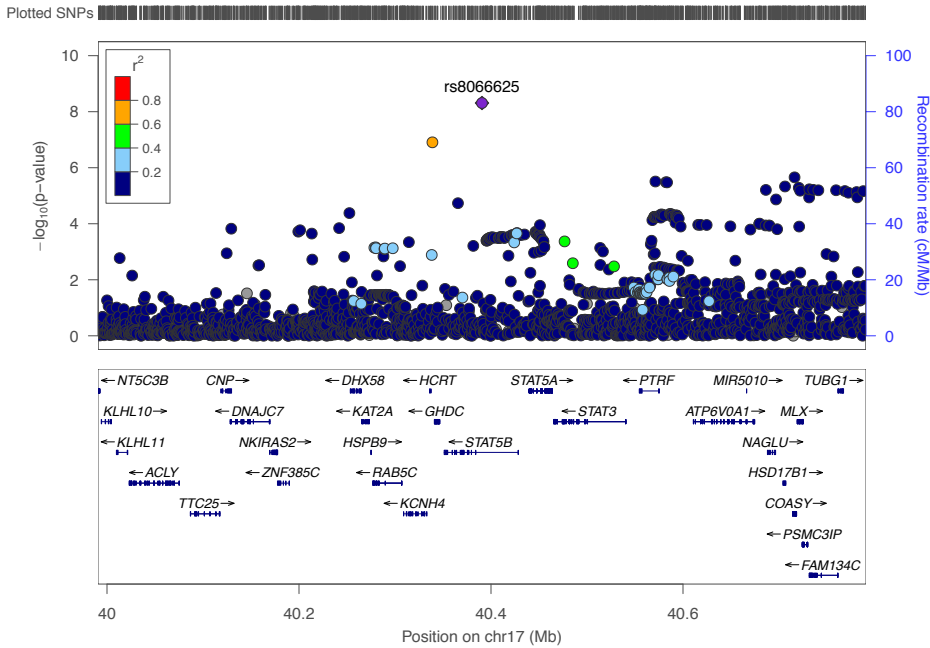
Childhood Onset



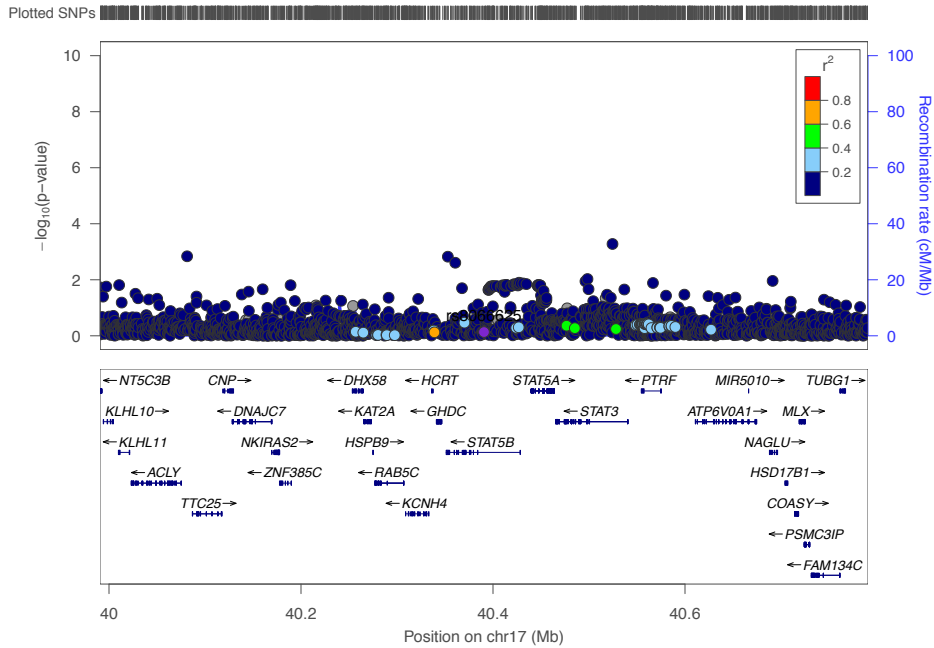
Adult Onset



Childhood Onset

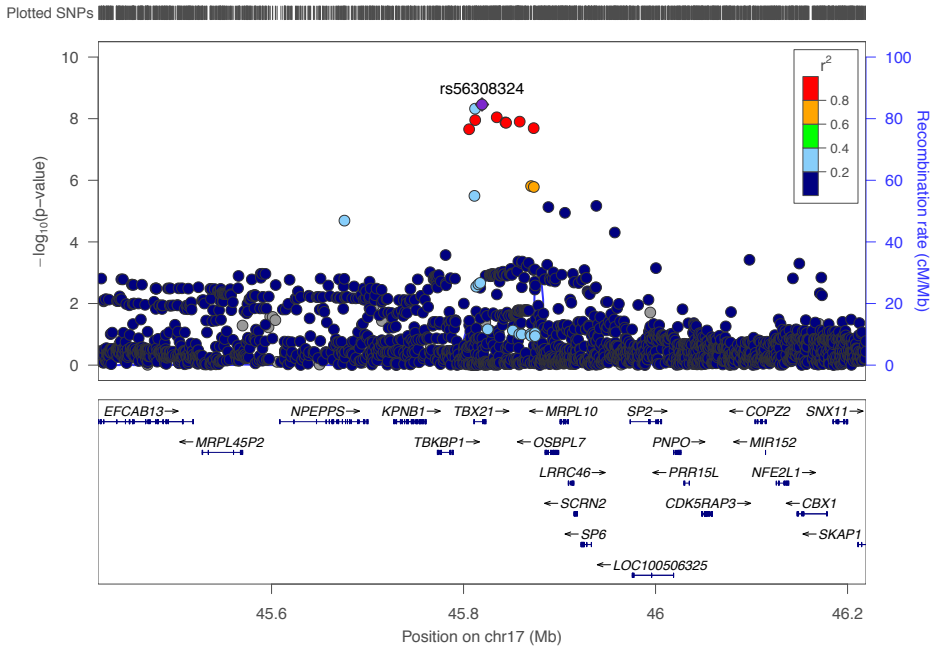


Adult Onset

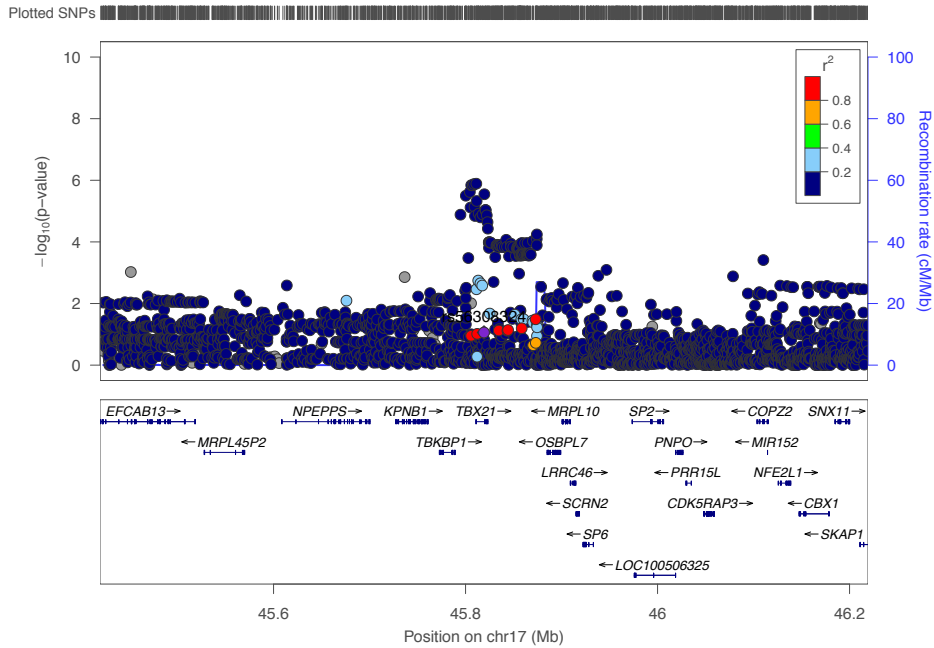


17q21·32 – rs56308324

Childhood Onset

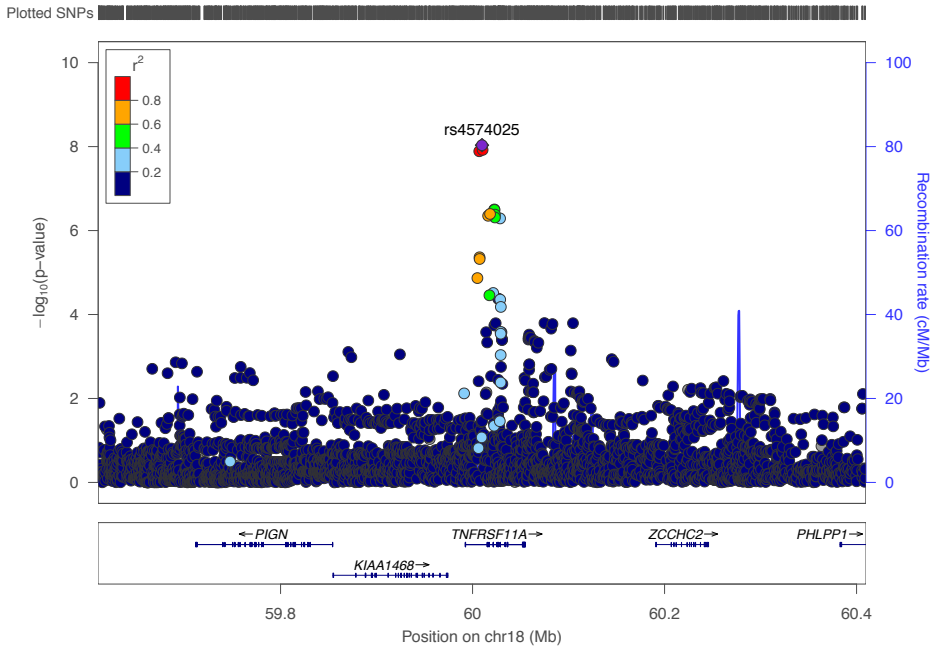


Adult Onset

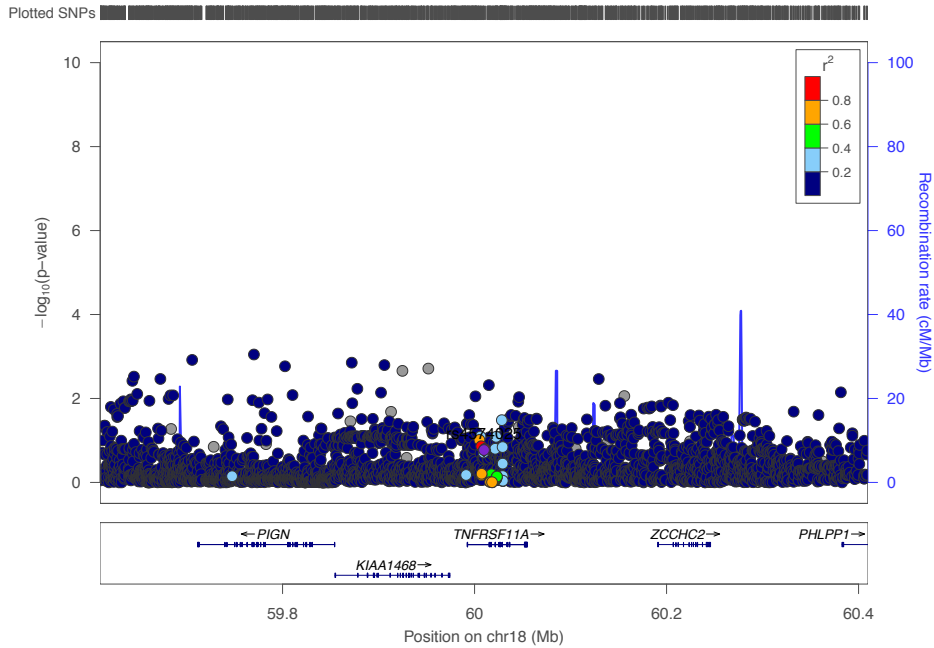


18q21.33 – rs4574025

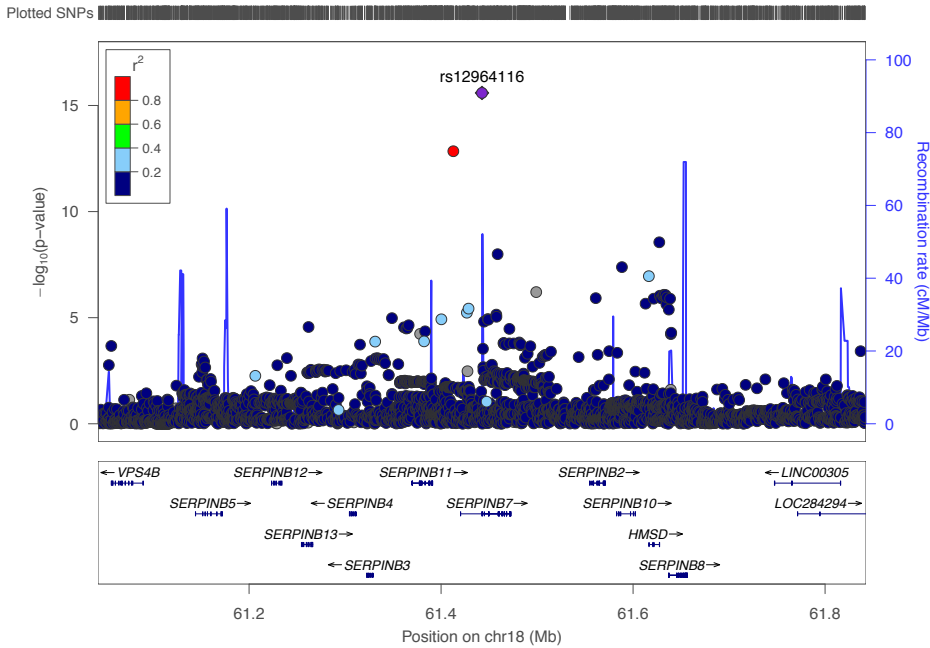
Childhood Onset



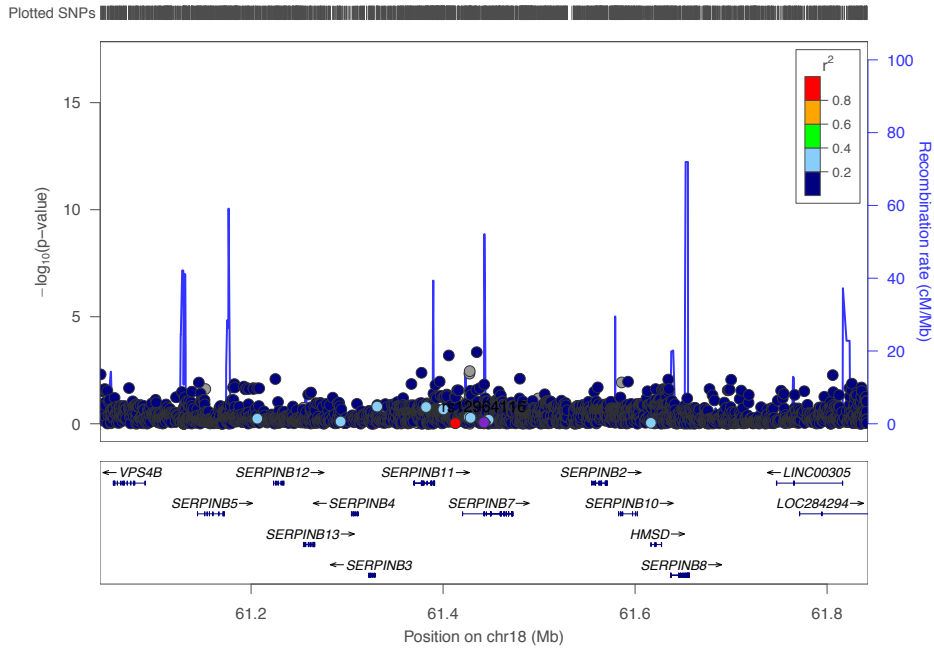
Adult Onset



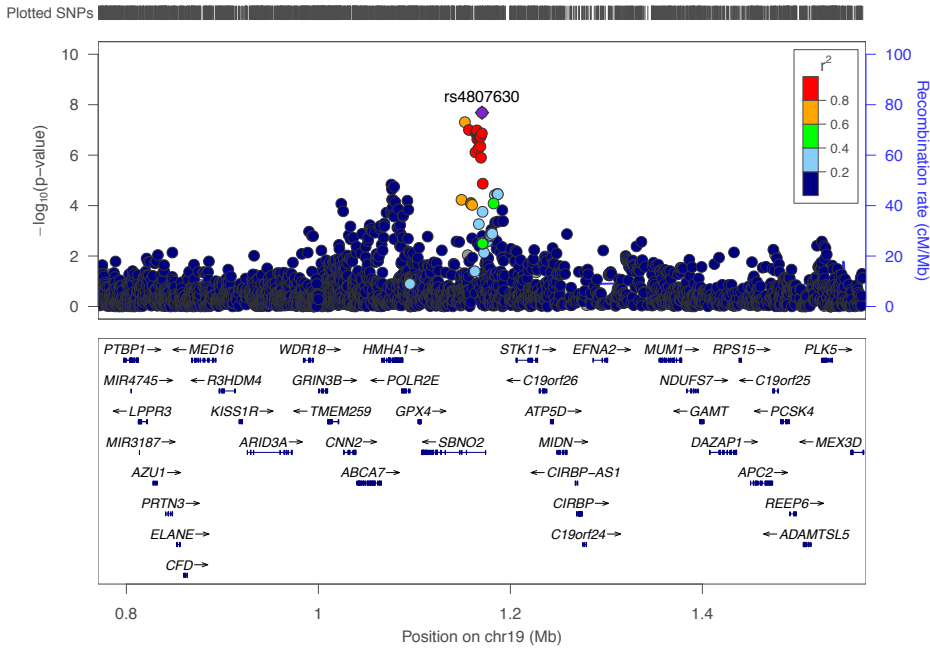
Childhood Onset



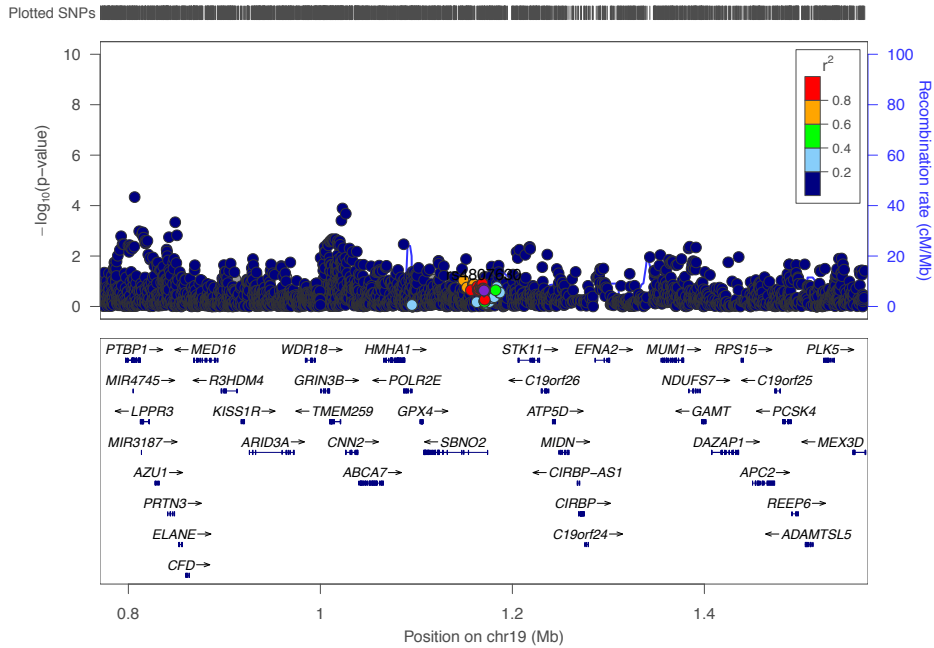
Adult Onset



Childhood Onset



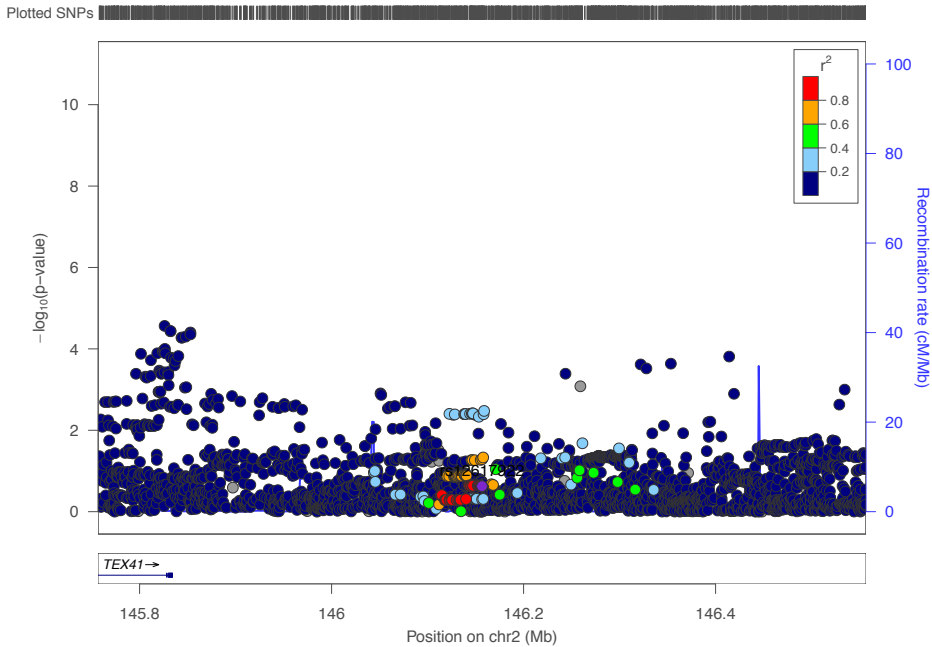
Adult Onset



Locus Associated with Adult Onset Asthma Only

2q22.3 – rs12617922

Childhood Onset



Adult Onset

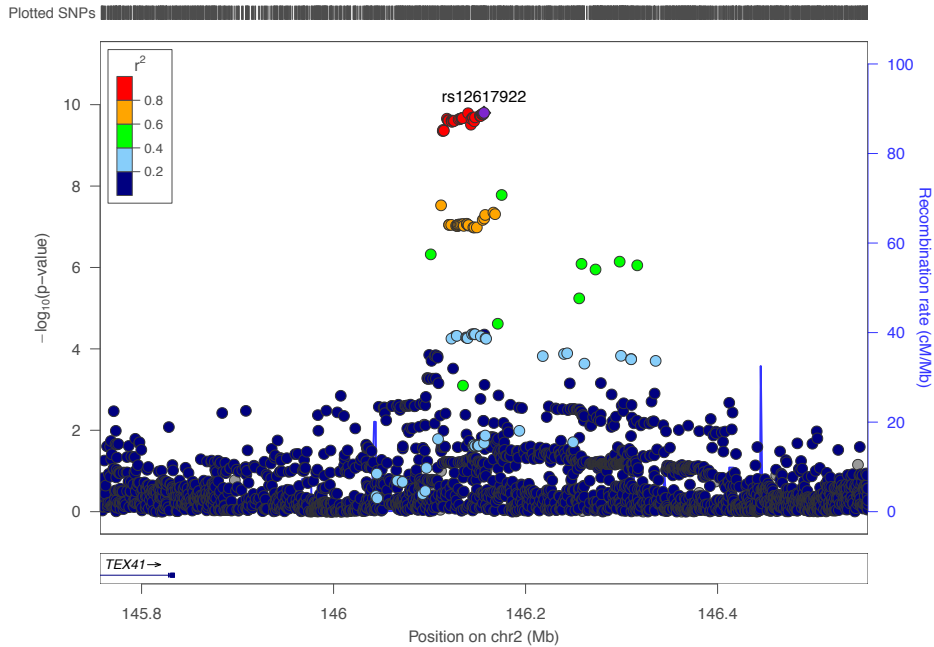


Figure 6. Manhattan plot showing results for the asthma age of onset GWAS. Each point corresponds to a SNP; the y-axis shows the $-\log_{10}$ p-value; the x-axis shows the position of each SNP along the 22 autosomes. The dashed red line shows genome-wide significance ($p=5 \times 10^{-8}$). Note two separate loci are present at chromosomal bands 18q21.33 and 6p21.33.

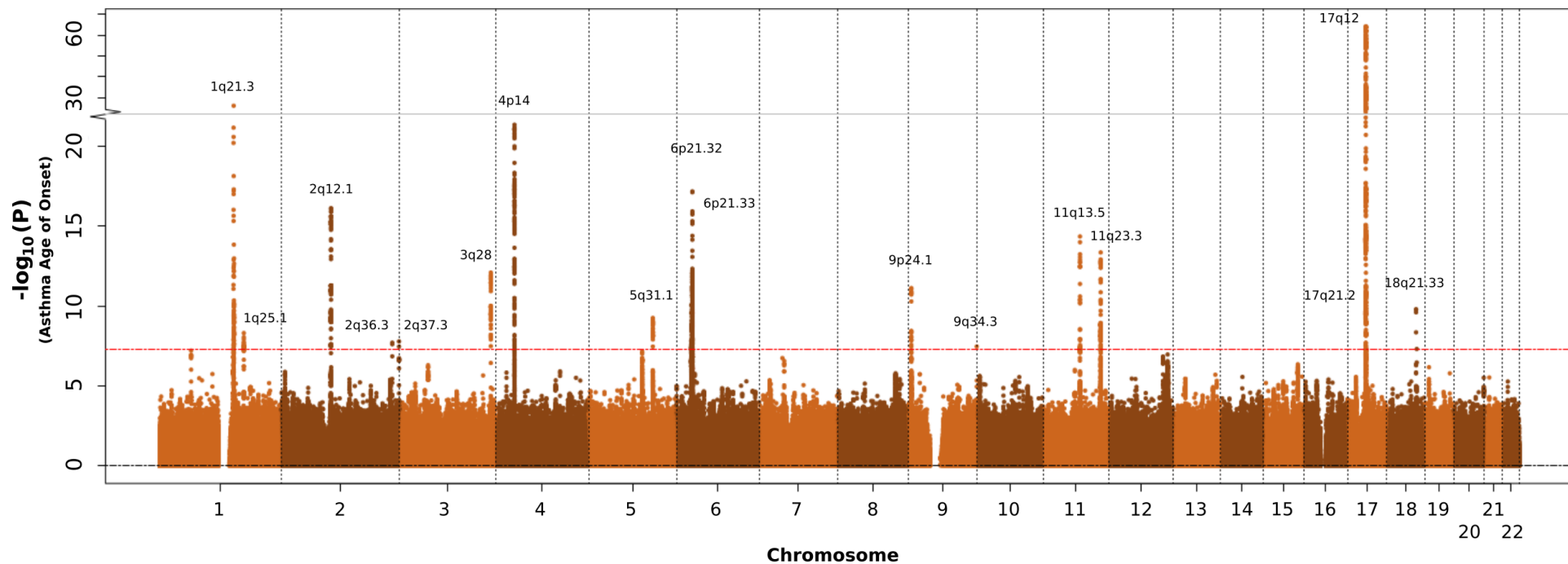


Figure 7. Tissue-specific enrichment of genes mapped to GWAS significant loci (from FUMA⁵). Asthma associated locus enrichment for differentially expressed genes in specific tissues (only more highly expressed genes are shown). A, childhood onset enrichment (at 54 loci); B, adult onset enrichment (19 loci). Tissues with $P_{\text{Bon}} < 0.05$ are shown in red. See Table 4 below for p-values.

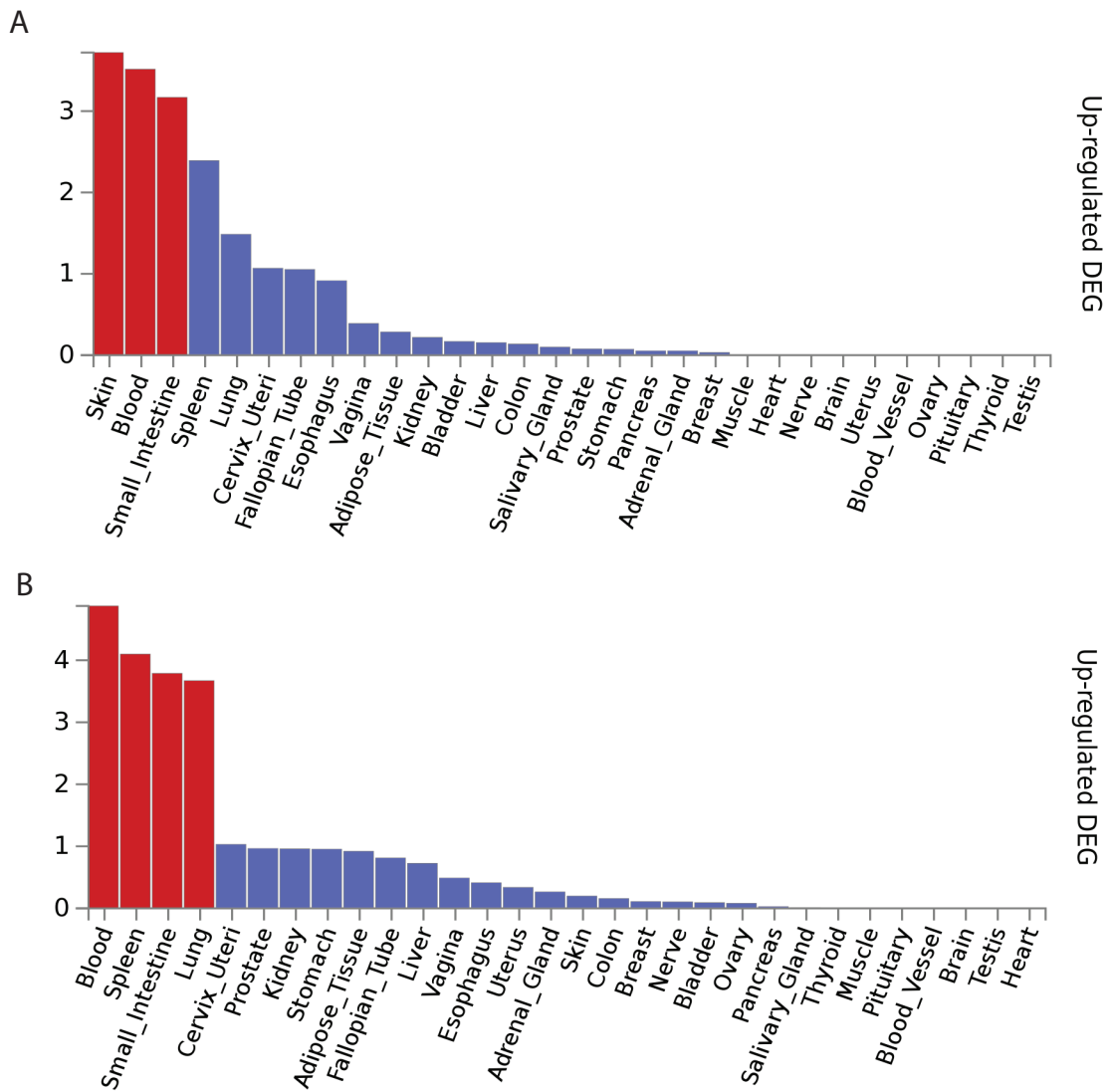


Figure 8. PrediXcan genes in non-HLA regions associated with childhood onset and/or adult onset asthma in spleen and small intestine. See Figure 4 in manuscript for additional details.

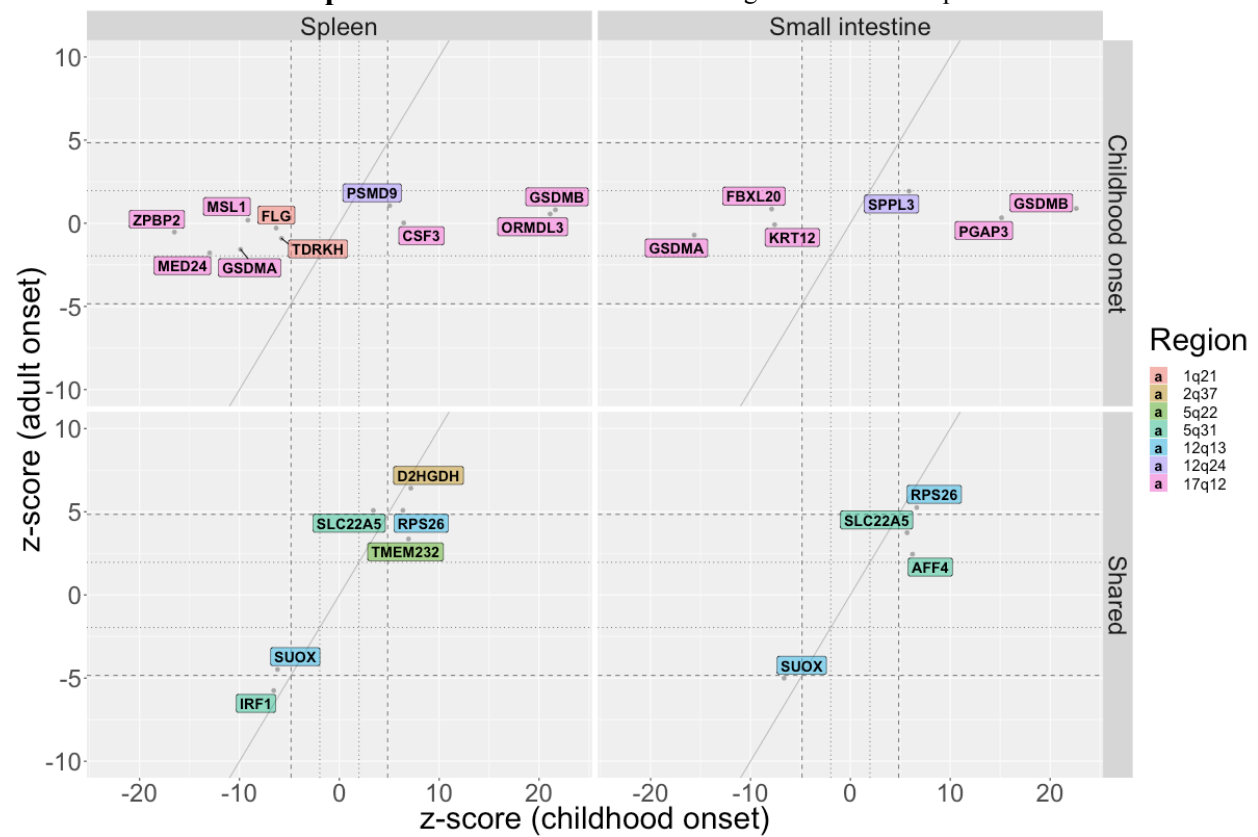


Figure 9. PrediXcan genes in the HLA region associated in childhood onset and adult onset asthma in spleen and small intestine. See Figure 5 in manuscript for additional details.

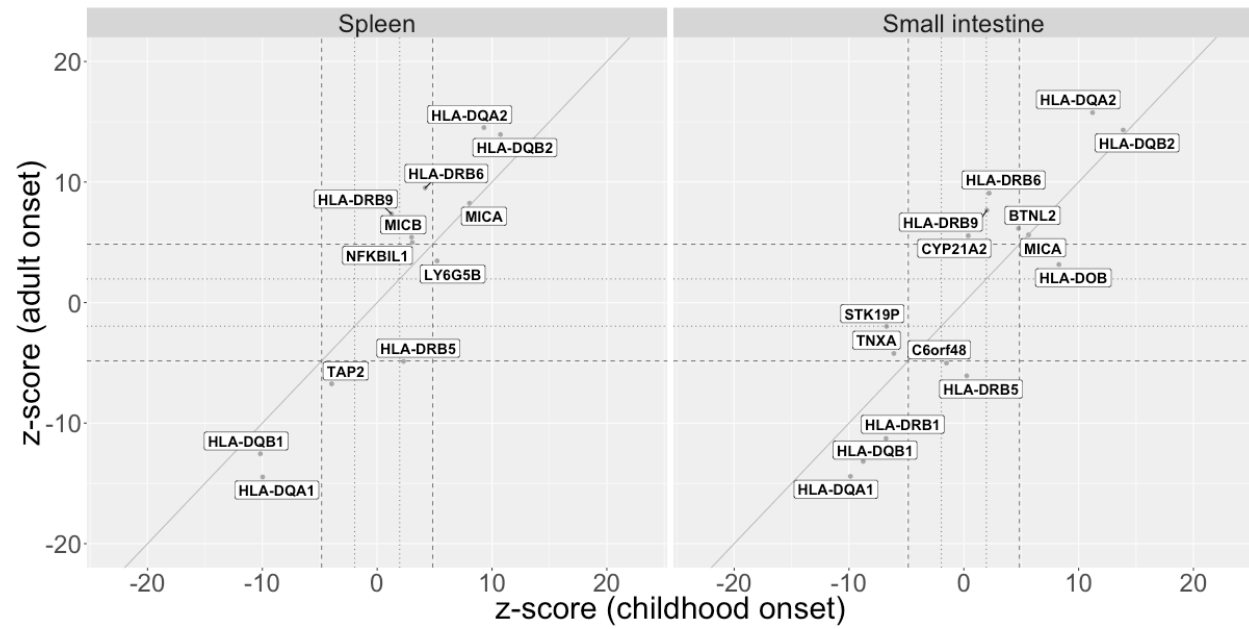
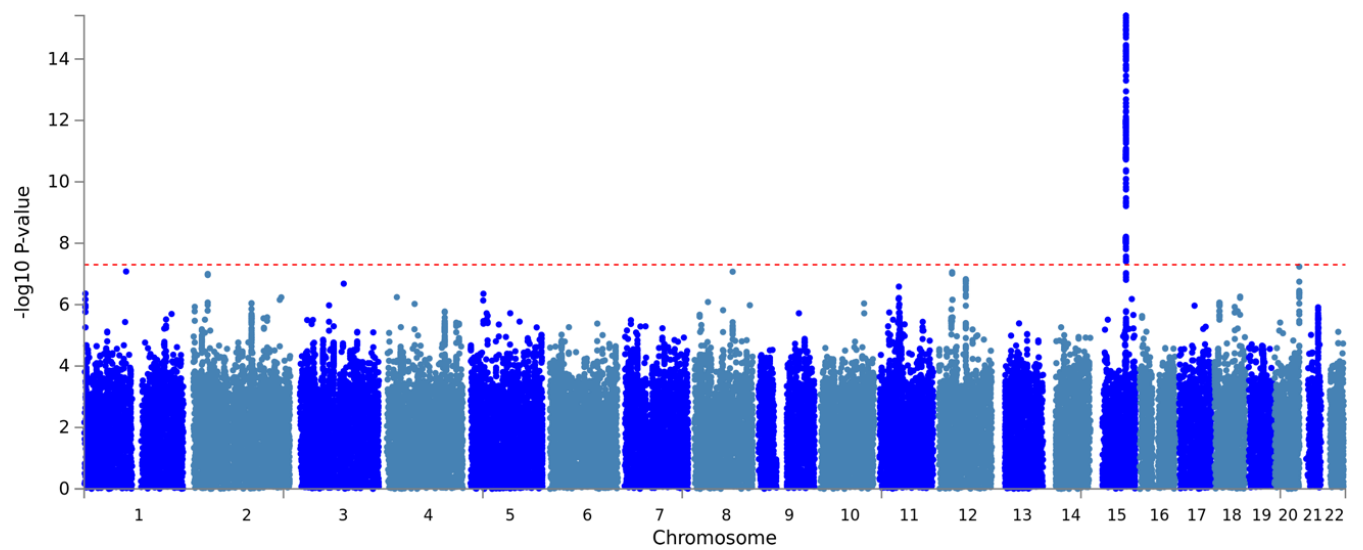


Figure 10. Manhattan plot of COPD GWAS in the UKB (9,876 cases and 318,237 controls).



Tables

Table 1. PrediXcan prediction performance p-values.

Tissue	Gene Ensembl ID	Gene Symbol	Prediction performance		Number of SNPs used
			R2	P-value	
Lung	ENSG00000172057.5	<i>ORMDL3</i>	0.143	2.539E-13	8
Lung	ENSG00000166949.11	<i>SMAD3</i>	0.024	5.450E-03	20
Lung	ENSG00000169442.4	<i>CD52</i>	0.136	1.938E-12	64
Lung	ENSG00000154252.11	<i>GAL3ST2</i>	0.096	9.324E-09	22
Lung	ENSG00000073584.14	<i>SMARCE1</i>	0.165	1.117E-14	39
Lung	ENSG00000204650.9	<i>CRHR1-IT1</i>	0.650	1.648E-88	142
Lung	ENSG00000204516.5	<i>MICB</i>	0.329	1.391E-31	56
Lung	ENSG00000115607.5	<i>IL18RAP</i>	0.090	2.061E-08	21
Lung	ENSG00000204525.10	<i>HLA-C</i>	0.423	1.224E-44	44
Lung	ENSG00000163221.7	<i>SI00A12</i>	0.014	3.155E-02	40
Lung	ENSG00000137337.10	<i>MDC1</i>	0.012	4.301E-02	57
Lung	ENSG00000100412.11	<i>ACO2</i>	0.085	3.947E-08	19
Lung	ENSG00000254810.1	<i>RP11-672A2.4</i>	0.084	5.383E-08	26
Lung	ENSG00000132394.6	<i>EEFSEC</i>	0.046	8.542E-05	43
Lung	ENSG00000229391.3	<i>HLA-DRB6</i>	0.671	2.219E-94	51
Lung	ENSG00000240065.3	<i>PSMB9</i>	0.236	1.404E-21	71
Lung	ENSG00000240053.8	<i>LY6G5B</i>	0.261	2.999E-24	54
Lung	ENSG00000264070.1	<i>DND1P1</i>	0.537	5.558E-63	51
Lung	ENSG00000137310.7	<i>TCF19</i>	0.064	3.562E-06	23
Lung	ENSG00000244731.3	<i>C4A</i>	0.328	6.631E-32	51
Lung	ENSG00000224389.4	<i>C4B</i>	0.112	2.231E-10	50
Lung	ENSG00000204463.8	<i>BAG6</i>	0.049	4.966E-05	18
Lung	ENSG00000164209.12	<i>SLC25A46</i>	0.012	4.585E-02	16
Lung	ENSG00000134824.9	<i>FADS2</i>	0.093	1.332E-08	5
Lung	ENSG00000204267.9	<i>TAP2</i>	0.130	3.480E-12	20
Lung	ENSG00000213760.6	<i>ATP6V1G2</i>	0.131	6.280E-12	11
Lung	ENSG00000108342.8	<i>CSF3</i>	0.017	2.039E-02	8
Lung	ENSG00000204301.5	<i>NOTCH4</i>	0.235	1.234E-21	62
Lung	ENSG00000237940.3	<i>AC093642.3</i>	0.093	1.563E-08	20

Lung	ENSG00000198502·5	<i>HLA-DRB5</i>	0·627	3·574E-82	44
Lung	ENSG00000186952·10	<i>TMEM232</i>	0·055	1·890E-05	51
Lung	ENSG00000223501·4	<i>VPS52</i>	0·037	5·237E-04	4
Lung	ENSG00000231852·2	<i>CYP21A2</i>	0·067	1·627E-06	28
Lung	ENSG00000204438·6	<i>GPANK1</i>	0·033	9·513E-04	18
Lung	ENSG00000113522·9	<i>RAD50</i>	0·176	7·418E-16	30
Lung	ENSG00000077238·9	<i>IL4R</i>	0·107	8·294E-10	40
Lung	ENSG00000263874·1	<i>LINC00672</i>	0·017	1·699E-02	13
Lung	ENSG00000204444·6	<i>APOM</i>	0·012	4·893E-02	3
Lung	ENSG00000105889·10	<i>STEAP1B</i>	0·130	1·283E-11	9
Lung	ENSG00000197375·8	<i>SLC22A5</i>	0·126	2·378E-11	11
Lung	ENSG00000146112·7	<i>PPP1R18</i>	0·056	1·534E-05	17
Lung	ENSG00000143631·10	<i>FLG</i>	0·220	9·150E-20	17
Lung	ENSG00000196301·3	<i>HLA-DRB9</i>	0·294	1·773E-27	134
Lung	ENSG00000196126·6	<i>HLA-DRB1</i>	0·360	2·730E-35	29
Lung	ENSG00000157837·11	<i>SPPL3</i>	0·124	3·508E-11	12
Lung	ENSG00000204520·8	<i>MICA</i>	0·505	1·171E-57	50
Lung	ENSG00000248290·1	<i>TNXA</i>	0·150	2·142E-13	131
Lung	ENSG00000237541·3	<i>HLA-DQA2</i>	0·648	1·746E-88	46
Lung	ENSG00000141744·3	<i>PNMT</i>	0·058	9·917E-06	15
Lung	ENSG00000167914·6	<i>GSDMA</i>	0·375	6·415E-38	41
Lung	ENSG00000196735·7	<i>HLA-DQA1</i>	0·519	8·282E-60	29
Lung	ENSG00000232629·4	<i>HLA-DQB2</i>	0·524	1·731E-60	37
Lung	ENSG00000161395·8	<i>PGAP3</i>	0·101	2·722E-09	9
Lung	ENSG00000073605·14	<i>GSDMB</i>	0·131	9·445E-12	26
Lung	ENSG00000204305·9	<i>AGER</i>	0·063	3·371E-06	18
Lung	ENSG00000131437·11	<i>KIF3A</i>	0·016	2·055E-02	8
Lung	ENSG00000179344·12	<i>HLA-DQB1</i>	0·634	2·591E-86	35
Lung	ENSG00000180902·12	<i>D2HGDH</i>	0·366	1·267E-36	8
Lung	ENSG00000137312·10	<i>FLOT1</i>	0·145	3·666E-13	34
Lung	ENSG00000213171·2	<i>LINGO4</i>	0·080	1·363E-07	43
Lung	ENSG00000159352·11	<i>PSMD4</i>	0·014	2·954E-02	48
Lung	ENSG00000254470·2	<i>AP5B1</i>	0·112	3·379E-10	22

Lung	ENSG00000115604·6	<i>IL18R1</i>	0·182	2·262E-16	123
Lung	ENSG00000241106·2	<i>HLA-DOB</i>	0·527	1·356E-60	44
Lung	ENSG00000231389·3	<i>HLA-DPA1</i>	0·050	4·911E-05	36
Lung	ENSG00000182134·11	<i>TDRKH</i>	0·104	1·686E-09	17
Lung	ENSG00000204427·7	<i>ABHD16A</i>	0·031	1·433E-03	53
Lung	ENSG00000038532·10	<i>CLEC16A</i>	0·050	4·444E-05	8
Lung	ENSG00000213676·6	<i>ATF6B</i>	0·153	1·521E-13	26
Lung	ENSG00000188895·7	<i>MSL1</i>	0·113	3·577E-10	29
Lung	ENSG00000139531·8	<i>SUOX</i>	0·286	1·589E-26	36
Lung	ENSG00000197728·5	<i>RPS26</i>	0·675	7·725E-96	29
Lung	ENSG00000008838·13	<i>MED24</i>	0·093	1·627E-08	25
Lung	ENSG00000197712·7	<i>FAM114A1</i>	0·031	1·413E-03	55
Lung	ENSG00000113520·6	<i>IL4</i>	0·021	8·424E-03	18
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204657·2	<i>OR2H2</i>	0·033	2·372E-03	6
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000213171·2	<i>LINGO4</i>	0·263	9·100E-21	24
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000226644·1	<i>RP11-128M1·1</i>	0·126	7·065E-10	44
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000240053·8	<i>LY6G5B</i>	0·145	1·077E-11	17
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000113520·6	<i>IL4</i>	0·045	2·834E-04	40
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000231389·3	<i>HLA-DPA1</i>	0·131	2·989E-10	22
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204650·9	<i>CRHR1-IT1</i>	0·707	1·301E-90	83
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000172057·5	<i>ORMDL3</i>	0·015	3·829E-02	37
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000131771·9	<i>PPP1R1B</i>	0·036	1·197E-03	9
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000161395·8	<i>PGAP3</i>	0·096	9·753E-08	15
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Skin_Not_Sun_Exposed_Suprapubic	ENSG00000264968·1	<i>RP11-387H17·4</i>	0·027	6·630E-03	3
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000179344·12	<i>HLA-DQB1</i>	0·709	3·446E-91	29
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000237541·3	<i>HLA-DQA2</i>	0·522	1·853E-52	41
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000141736·9	<i>ERBB2</i>	0·044	3·935E-04	33
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000229391·3	<i>HLA-DRB6</i>	0·595	4·320E-65	54
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204267·9	<i>TAP2</i>	0·121	1·404E-09	58
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000231852·2	<i>CYP21A2</i>	0·150	1·561E-11	39
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000214546·3	<i>AC087491·2</i>	0·077	1·950E-06	21
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000213760·6	<i>ATP6V1G2</i>	0·162	2·174E-12	34

Skin_Not_Sun_Exposed_Suprapubic	ENSG00000073605·14	<i>GSDMB</i>	0·028	5·239E-03	6
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000134824·9	<i>FADS2</i>	0·033	2·634E-03	4
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000232629·4	<i>HLA-DQB2</i>	0·038	1·111E-03	95
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000166949·11	<i>SMAD3</i>	0·034	2·005E-03	36
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000197712·7	<i>FAM114A1</i>	0·244	2·350E-19	46
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000198502·5	<i>HLA-DRB5</i>	0·698	1·943E-88	52
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204438·6	<i>GPANK1</i>	0·136	1·686E-10	76
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000132394·6	<i>EEFSEC</i>	0·041	6·077E-04	13
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000137310·7	<i>TCF19</i>	0·081	8·387E-07	16
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000196301·3	<i>HLA-DRB9</i>	0·191	9·649E-15	65
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204315·3	<i>FKBP1</i>	0·014	4·951E-02	7
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204525·10	<i>HLA-C</i>	0·469	2·620E-43	40
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000244731·3	<i>C4A</i>	0·391	1·092E-34	55
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000224389·4	<i>C4B</i>	0·194	3·474E-15	34
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000196735·7	<i>HLA-DQA1</i>	0·409	8·522E-36	41
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000170426·1	<i>SDR9C7</i>	0·061	1·985E-05	7
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000188895·7	<i>MSL1</i>	0·100	4·158E-08	25
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000143536·7	<i>CRNN</i>	0·077	1·062E-06	30
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000073584·14	<i>SMARCE1</i>	0·163	6·187E-13	10
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000182134·11	<i>TDRKH</i>	0·085	7·084E-07	15
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000163216·6	<i>SPRR2D</i>	0·028	4·100E-03	12
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000196407·7	<i>THEM5</i>	0·021	1·616E-02	14
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000237940·3	<i>AC093642·3</i>	0·169	2·887E-13	22
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204520·8	<i>MICA</i>	0·482	1·465E-45	62
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000266753·2	<i>FBXL20</i>	0·042	5·887E-04	7
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000254852·4	<i>NPIA2</i>	0·088	2·067E-07	14
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000110917·3	<i>MLEC</i>	0·116	2·992E-09	70
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000186952·10	<i>TMEM232</i>	0·094	1·279E-07	16
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000264070·1	<i>DND1P1</i>	0·650	3·194E-76	28
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204516·5	<i>MICB</i>	0·502	1·471E-49	92
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204314·6	<i>PRRT1</i>	0·217	8·503E-17	70
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000241782·1	<i>RP11-91P24·1</i>	0·041	6·355E-04	7
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000180902·12	<i>D2HGDH</i>	0·439	7·217E-40	34

Skin_Not_Sun_Exposed_Suprapubic	ENSG00000240065·3	<i>PSMB9</i>	0·088	3·054E-07	70
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000145777·10	<i>TSLP</i>	0·261	1·366E-20	20
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000166396·8	<i>SERPINB7</i>	0·132	1·146E-10	9
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000143631·10	<i>FLG</i>	0·029	3·948E-03	22
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000196126·6	<i>HLA-DRB1</i>	0·296	5·786E-24	29
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000248290·1	<i>TNXA</i>	0·088	3·842E-07	75
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000008838·13	<i>MED24</i>	0·136	8·432E-11	18
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000164402·9	<i>SEPT8</i>	0·173	1·255E-13	16
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000154252·11	<i>GAL3ST2</i>	0·053	9·932E-05	5
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000115598·5	<i>IL1RL2</i>	0·085	6·599E-07	46
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000174130·8	<i>TLR6</i>	0·210	3·392E-16	21
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000213676·6	<i>ATF6B</i>	0·138	1·241E-10	54
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000131435·8	<i>PDLIM4</i>	0·066	1·452E-05	14
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000197728·5	<i>RPS26</i>	0·759	1·092E-109	30
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000169509·5	<i>CRCT1</i>	0·060	3·740E-05	29
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000139531·8	<i>SUOX</i>	0·233	6·339E-19	11
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000197375·8	<i>SLC22A5</i>	0·287	2·716E-23	14
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000115607·5	<i>IL18RAP</i>	0·066	1·399E-05	42
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204301·5	<i>NOTCH4</i>	0·283	2·760E-23	30
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000204427·7	<i>ABHD16A</i>	0·040	7·840E-04	11
Skin_Not_Sun_Exposed_Suprapubic	ENSG00000241106·2	<i>HLA-DOB</i>	0·495	2·183E-48	50
Skin_Sun_Exposed_Lower_leg	ENSG00000204444·6	<i>APOM</i>	0·021	6·705E-03	25
Skin_Sun_Exposed_Lower_leg	ENSG00000163216·6	<i>SPRR2D</i>	0·099	1·369E-09	49
Skin_Sun_Exposed_Lower_leg	ENSG00000204427·7	<i>ABHD16A</i>	0·012	4·062E-02	27
Skin_Sun_Exposed_Lower_leg	ENSG00000204525·10	<i>HLA-C</i>	0·577	7·147E-78	98
Skin_Sun_Exposed_Lower_leg	ENSG00000105889·10	<i>STEAP1B</i>	0·016	1·775E-02	16
Skin_Sun_Exposed_Lower_leg	ENSG00000254852·4	<i>NPIPA2</i>	0·017	1·574E-02	7
Skin_Sun_Exposed_Lower_leg	ENSG00000204315·3	<i>FKBP1</i>	0·028	1·635E-03	15
Skin_Sun_Exposed_Lower_leg	ENSG00000229391·3	<i>HLA-DRB6</i>	0·617	1·272E-86	43
Skin_Sun_Exposed_Lower_leg	ENSG00000231852·2	<i>CYP21A2</i>	0·193	1·526E-18	32
Skin_Sun_Exposed_Lower_leg	ENSG00000248290·1	<i>TNXA</i>	0·071	3·603E-07	30
Skin_Sun_Exposed_Lower_leg	ENSG00000240053·8	<i>LY6G5B</i>	0·225	6·757E-22	28
Skin_Sun_Exposed_Lower_leg	ENSG00000228727·4	<i>SAPCD1</i>	0·042	8·167E-05	31

Skin_Sun_Exposed_Lower_leg	ENSG00000204516·5	<i>MICB</i>	0·445	8·909E-52	43
Skin_Sun_Exposed_Lower_leg	ENSG00000264070·1	<i>DND1P1</i>	0·623	5·574E-90	29
Skin_Sun_Exposed_Lower_leg	ENSG00000132394·6	<i>EEFSEC</i>	0·080	5·593E-08	16
Skin_Sun_Exposed_Lower_leg	ENSG00000244731·3	<i>C4A</i>	0·282	9·421E-29	64
Skin_Sun_Exposed_Lower_leg	ENSG00000164209·12	<i>SLC25A46</i>	0·066	8·972E-07	34
Skin_Sun_Exposed_Lower_leg	ENSG00000224389·4	<i>C4B</i>	0·198	6·450E-19	51
Skin_Sun_Exposed_Lower_leg	ENSG00000204650·9	<i>CRHRI-IT1</i>	0·721	4·585E-120	222
Skin_Sun_Exposed_Lower_leg	ENSG00000204463·8	<i>BAG6</i>	0·099	5·211E-10	37
Skin_Sun_Exposed_Lower_leg	ENSG00000073605·14	<i>GSDMB</i>	0·061	2·487E-06	26
Skin_Sun_Exposed_Lower_leg	ENSG00000263874·1	<i>LINC00672</i>	0·071	3·581E-07	39
Skin_Sun_Exposed_Lower_leg	ENSG00000204314·6	<i>PRRT1</i>	0·284	1·660E-29	36
Skin_Sun_Exposed_Lower_leg	ENSG00000134824·9	<i>FADS2</i>	0·032	7·800E-04	13
Skin_Sun_Exposed_Lower_leg	ENSG00000254470·2	<i>AP5B1</i>	0·022	5·141E-03	36
Skin_Sun_Exposed_Lower_leg	ENSG00000223501·4	<i>VPS52</i>	0·013	3·579E-02	27
Skin_Sun_Exposed_Lower_leg	ENSG00000213760·6	<i>ATP6V1G2</i>	0·114	4·153E-11	18
Skin_Sun_Exposed_Lower_leg	ENSG00000110801·9	<i>PSMD9</i>	0·043	9·339E-05	11
Skin_Sun_Exposed_Lower_leg	ENSG00000196407·7	<i>THEM5</i>	0·028	1·715E-03	21
Skin_Sun_Exposed_Lower_leg	ENSG00000204267·9	<i>TAP2</i>	0·215	6·009E-21	80
Skin_Sun_Exposed_Lower_leg	ENSG00000204287·9	<i>HLA-DRA</i>	0·090	5·285E-09	27
Skin_Sun_Exposed_Lower_leg	ENSG00000204420·4	<i>C6orf25</i>	0·032	7·022E-04	7
Skin_Sun_Exposed_Lower_leg	ENSG00000204301·5	<i>NOTCH4</i>	0·225	9·104E-22	45
Skin_Sun_Exposed_Lower_leg	ENSG00000143631·10	<i>FLG</i>	0·071	2·348E-07	33
Skin_Sun_Exposed_Lower_leg	ENSG00000204657·2	<i>OR2H2</i>	0·014	2·583E-02	39
Skin_Sun_Exposed_Lower_leg	ENSG00000137312·10	<i>FLOT1</i>	0·061	1·587E-06	16
Skin_Sun_Exposed_Lower_leg	ENSG00000197712·7	<i>FAM114A1</i>	0·402	1·334E-45	23
Skin_Sun_Exposed_Lower_leg	ENSG00000169442·4	<i>CD52</i>	0·051	1·314E-05	29
Skin_Sun_Exposed_Lower_leg	ENSG00000198502·5	<i>HLA-DRB5</i>	0·701	3·765E-113	46
Skin_Sun_Exposed_Lower_leg	ENSG00000204305·9	<i>AGER</i>	0·057	5·332E-06	22
Skin_Sun_Exposed_Lower_leg	ENSG00000174130·8	<i>TLR6</i>	0·214	9·039E-21	19
Skin_Sun_Exposed_Lower_leg	ENSG00000237940·3	<i>AC093642·3</i>	0·123	7·301E-12	14
Skin_Sun_Exposed_Lower_leg	ENSG00000143536·7	<i>CRNN</i>	0·219	3·501E-21	63
Skin_Sun_Exposed_Lower_leg	ENSG00000231389·3	<i>HLA-DPA1</i>	0·266	1·940E-26	16
Skin_Sun_Exposed_Lower_leg	ENSG00000241106·2	<i>HLA-DOB</i>	0·523	3·981E-65	63

Skin_Sun_Exposed_Lower_leg	ENSG00000145777·10	<i>TSLP</i>	0·247	6·762E-25	28
Skin_Sun_Exposed_Lower_leg	ENSG00000232629·4	<i>HLA-DQB2</i>	0·045	5·052E-05	66
Skin_Sun_Exposed_Lower_leg	ENSG00000008838·13	<i>MED24</i>	0·212	7·541E-21	40
Skin_Sun_Exposed_Lower_leg	ENSG00000125347·9	<i>IRF1</i>	0·013	2·967E-02	8
Skin_Sun_Exposed_Lower_leg	ENSG00000264968·1	<i>RP11-387H17·4</i>	0·071	3·630E-07	18
Skin_Sun_Exposed_Lower_leg	ENSG00000167914·6	<i>GSDMA</i>	0·056	7·190E-06	9
Skin_Sun_Exposed_Lower_leg	ENSG00000172057·5	<i>ORMDL3</i>	0·018	1·111E-02	21
Skin_Sun_Exposed_Lower_leg	ENSG00000141736·9	<i>ERBB2</i>	0·043	7·548E-05	20
Skin_Sun_Exposed_Lower_leg	ENSG00000240065·3	<i>PSMB9</i>	0·100	1·360E-09	45
Skin_Sun_Exposed_Lower_leg	ENSG00000131771·9	<i>PPP1R1B</i>	0·041	1·418E-04	17
Skin_Sun_Exposed_Lower_leg	ENSG00000179344·12	<i>HLA-DQB1</i>	0·668	1·291E-101	29
Skin_Sun_Exposed_Lower_leg	ENSG00000115604·6	<i>IL18R1</i>	0·086	1·491E-08	41
Skin_Sun_Exposed_Lower_leg	ENSG00000115607·5	<i>IL18RAP</i>	0·044	5·443E-05	41
Skin_Sun_Exposed_Lower_leg	ENSG00000237541·3	<i>HLA-DQA2</i>	0·660	9·621E-100	56
Skin_Sun_Exposed_Lower_leg	ENSG00000196735·7	<i>HLA-DQA1</i>	0·382	1·226E-41	49
Skin_Sun_Exposed_Lower_leg	ENSG00000131437·11	<i>KIF3A</i>	0·037	2·450E-04	13
Skin_Sun_Exposed_Lower_leg	ENSG00000204520·8	<i>MICA</i>	0·461	1·002E-53	88
Skin_Sun_Exposed_Lower_leg	ENSG00000188895·7	<i>MSL1</i>	0·143	1·197E-13	41
Skin_Sun_Exposed_Lower_leg	ENSG00000161395·8	<i>PGAP3</i>	0·091	6·666E-09	41
Skin_Sun_Exposed_Lower_leg	ENSG00000113520·6	<i>IL4</i>	0·039	1·481E-04	22
Skin_Sun_Exposed_Lower_leg	ENSG00000139531·8	<i>SUOX</i>	0·369	2·817E-40	14
Skin_Sun_Exposed_Lower_leg	ENSG00000196126·6	<i>HLA-DRB1</i>	0·321	2·123E-33	46
Skin_Sun_Exposed_Lower_leg	ENSG00000186952·10	<i>TMEM232</i>	0·059	3·198E-06	17
Skin_Sun_Exposed_Lower_leg	ENSG00000119408·12	<i>NEK6</i>	0·034	4·919E-04	31
Skin_Sun_Exposed_Lower_leg	ENSG00000169189·12	<i>NSMCE1</i>	0·025	2·689E-03	6
Skin_Sun_Exposed_Lower_leg	ENSG00000182134·11	<i>TDRKH</i>	0·084	2·944E-08	15
Skin_Sun_Exposed_Lower_leg	ENSG00000226644·1	<i>RP11-128M1·1</i>	0·029	1·086E-03	19
Skin_Sun_Exposed_Lower_leg	ENSG00000166949·11	<i>SMAD3</i>	0·054	6·257E-06	16
Skin_Sun_Exposed_Lower_leg	ENSG00000170426·1	<i>SDR9C7</i>	0·027	1·919E-03	17
Skin_Sun_Exposed_Lower_leg	ENSG00000110917·3	<i>MLEC</i>	0·143	5·962E-14	35
Skin_Sun_Exposed_Lower_leg	ENSG00000213171·2	<i>LINGO4</i>	0·335	1·283E-34	70
Skin_Sun_Exposed_Lower_leg	ENSG00000123384·9	<i>LRP1</i>	0·046	4·747E-05	17
Skin_Sun_Exposed_Lower_leg	ENSG00000166396·8	<i>SERPINB7</i>	0·028	1·675E-03	24

Skin_Sun_Exposed_Lower_leg	ENSG00000131435·8	<i>PDLIM4</i>	0·187	5·720E-18	19
Skin_Sun_Exposed_Lower_leg	ENSG00000113522·9	<i>RAD50</i>	0·018	1·156E-02	44
Skin_Sun_Exposed_Lower_leg	ENSG00000137310·7	<i>TCF19</i>	0·150	1·529E-14	38
Skin_Sun_Exposed_Lower_leg	ENSG00000115598·5	<i>IL1RL2</i>	0·137	5·314E-13	66
Skin_Sun_Exposed_Lower_leg	ENSG00000197375·8	<i>SLC22A5</i>	0·303	1·258E-30	28
Skin_Sun_Exposed_Lower_leg	ENSG00000197728·5	<i>RPS26</i>	0·698	2·508E-113	43
Skin_Sun_Exposed_Lower_leg	ENSG00000180902·12	<i>D2HGDH</i>	0·459	2·611E-53	18
Skin_Sun_Exposed_Lower_leg	ENSG00000154252·11	<i>GAL3ST2</i>	0·058	3·330E-06	4
Skin_Sun_Exposed_Lower_leg	ENSG00000164402·9	<i>SEPT8</i>	0·342	6·760E-36	22
Skin_Sun_Exposed_Lower_leg	ENSG00000213676·6	<i>ATF6B</i>	0·153	1·580E-14	108
Skin_Sun_Exposed_Lower_leg	ENSG00000073584·14	<i>SMARCE1</i>	0·237	3·980E-23	113
Skin_Sun_Exposed_Lower_leg	ENSG00000196301·3	<i>HLA-DRB9</i>	0·033	5·479E-04	66
Spleen	ENSG00000240053·8	<i>LY6G5B</i>	0·052	1·387E-02	10
Spleen	ENSG00000182134·11	<i>TDRKH</i>	0·242	1·911E-08	15
Spleen	ENSG00000139531·8	<i>SUOX</i>	0·389	6·252E-16	12
Spleen	ENSG00000143631·10	<i>FLG</i>	0·126	1·290E-04	16
Spleen	ENSG00000197728·5	<i>RPS26</i>	0·725	5·830E-41	18
Spleen	ENSG00000108342·8	<i>CSF3</i>	0·153	2·322E-05	36
Spleen	ENSG00000125347·9	<i>IRF1</i>	0·059	7·257E-03	4
Spleen	ENSG00000186952·10	<i>TMEM232</i>	0·062	6·144E-03	49
Spleen	ENSG00000180902·12	<i>D2HGDH</i>	0·347	1·006E-12	8
Spleen	ENSG00000204520·8	<i>MICA</i>	0·686	1·035E-34	29
Spleen	ENSG00000221946·3	<i>FXYD7</i>	0·072	2·165E-03	5
Spleen	ENSG00000137337·10	<i>MDC1</i>	0·099	5·640E-04	67
Spleen	ENSG00000237541·3	<i>HLA-DQA2</i>	0·632	3·549E-30	27
Spleen	ENSG00000167914·6	<i>GSDMA</i>	0·213	1·482E-07	4
Spleen	ENSG00000196735·7	<i>HLA-DQA1</i>	0·345	3·359E-12	59
Spleen	ENSG00000179344·12	<i>HLA-DQB1</i>	0·688	1·406E-35	61
Spleen	ENSG00000232629·4	<i>HLA-DQB2</i>	0·625	3·325E-36	39
Spleen	ENSG00000008838·13	<i>MED24</i>	0·082	1·610E-03	20
Spleen	ENSG00000186075·8	<i>ZBP2</i>	0·105	2·889E-04	12
Spleen	ENSG00000172057·5	<i>ORMDL3</i>	0·474	5·820E-20	46
Spleen	ENSG00000073605·14	<i>GSDMB</i>	0·490	3·154E-19	12

Spleen	ENSG00000164402·9	<i>SEPT8</i>	0·043	2·889E-02	11
Spleen	ENSG00000188895·7	<i>MSL1</i>	0·182	1·104E-06	7
Spleen	ENSG00000110801·9	<i>PSMD9</i>	0·071	4·123E-03	27
Spleen	ENSG00000244731·3	<i>C4A</i>	0·196	1·001E-07	79
Spleen	ENSG00000213719·4	<i>CLIC1</i>	0·105	5·656E-04	10
Spleen	ENSG00000240065·3	<i>PSMB9</i>	0·131	4·269E-05	20
Spleen	ENSG00000204650·9	<i>CRHRI-IT1</i>	0·583	8·850E-25	24
Spleen	ENSG00000134824·9	<i>FADS2</i>	0·523	1·962E-21	26
Spleen	ENSG00000237940·3	<i>AC093642·3</i>	0·120	5·348E-05	67
Spleen	ENSG00000163216·6	<i>SPRR2D</i>	0·061	9·541E-03	8
Spleen	ENSG00000204301·5	<i>NOTCH4</i>	0·159	1·474E-05	4
Spleen	ENSG00000196301·3	<i>HLA-DRB9</i>	0·297	6·692E-11	130
Spleen	ENSG00000197712·7	<i>FAM114A1</i>	0·144	3·654E-05	53
Spleen	ENSG00000254810·1	<i>RP11-672A2·4</i>	0·054	1·327E-02	17
Spleen	ENSG00000198502·5	<i>HLA-DRB5</i>	0·535	1·000E-22	13
Spleen	ENSG00000241106·2	<i>HLA-DOB</i>	0·419	7·045E-16	77
Spleen	ENSG00000204516·5	<i>MICB</i>	0·263	2·624E-10	41
Spleen	ENSG00000204498·6	<i>NFKBIL1</i>	0·125	5·668E-05	47
Spleen	ENSG00000196126·6	<i>HLA-DRB1</i>	0·300	1·488E-10	26
Spleen	ENSG00000073584·14	<i>SMARCE1</i>	0·100	5·344E-04	13
Spleen	ENSG00000197375·8	<i>SLC22A5</i>	0·115	1·439E-04	88
Spleen	ENSG00000204267·9	<i>TAP2</i>	0·291	3·257E-10	48
Spleen	ENSG00000229391·3	<i>HLA-DRB6</i>	0·620	1·822E-28	117
Spleen	ENSG00000137310·7	<i>TCF19</i>	0·278	1·706E-11	31
Spleen	ENSG00000264070·1	<i>DND1P1</i>	0·413	5·303E-15	166
Spleen	ENSG00000145777·10	<i>TSLP</i>	0·485	6·884E-21	15
Spleen	ENSG00000204525·10	<i>HLA-C</i>	0·298	3·360E-12	86
Whole_Blood	ENSG00000131748·11	<i>STARD3</i>	0·079	5·283E-07	29
Whole_Blood	ENSG00000115009·7	<i>CCL20</i>	0·136	9·696E-12	3
Whole_Blood	ENSG00000197728·5	<i>RPS26</i>	0·587	4·336E-70	25
Whole_Blood	ENSG00000139531·8	<i>SUOX</i>	0·142	4·811E-12	11
Whole_Blood	ENSG00000174123·6	<i>TLR10</i>	0·033	1·334E-03	42
Whole_Blood	ENSG00000240065·3	<i>PSMB9</i>	0·325	1·044E-29	66

Whole_Blood	ENSG00000196301·3	<i>HLA-DRB9</i>	0·151	5·090E-13	27
Whole_Blood	ENSG00000077238·9	<i>IL4R</i>	0·089	5·858E-08	9
Whole_Blood	ENSG00000115604·6	<i>IL18R1</i>	0·039	4·249E-04	46
Whole_Blood	ENSG00000204301·5	<i>NOTCH4</i>	0·436	3·812E-43	59
Whole_Blood	ENSG00000255362·1	<i>RP11-619A14·3</i>	0·029	2·659E-03	9
Whole_Blood	ENSG00000188895·7	<i>MSL1</i>	0·039	4·846E-04	28
Whole_Blood	ENSG00000204267·9	<i>TAP2</i>	0·158	1·359E-13	35
Whole_Blood	ENSG00000115607·5	<i>IL18RAP</i>	0·404	7·052E-39	90
Whole_Blood	ENSG00000232629·4	<i>HLA-DQB2</i>	0·558	1·608E-63	46
Whole_Blood	ENSG00000197375·8	<i>SLC22A5</i>	0·167	4·289E-14	46
Whole_Blood	ENSG00000172057·5	<i>ORMDL3</i>	0·279	5·693E-25	30
Whole_Blood	ENSG00000264198·1	<i>IKZF3</i>	0·023	6·740E-03	3
Whole_Blood	ENSG00000073605·14	<i>GSDMB</i>	0·302	2·135E-27	20
Whole_Blood	ENSG00000205716·4	<i>AC007248·6</i>	0·025	5·414E-03	8
Whole_Blood	ENSG00000196735·7	<i>HLA-DQA1</i>	0·226	1·294E-19	8
Whole_Blood	ENSG00000179344·12	<i>HLA-DQB1</i>	0·571	5·188E-66	42
Whole_Blood	ENSG00000204520·8	<i>MICA</i>	0·189	1·583E-16	43
Whole_Blood	ENSG00000244731·3	<i>C4A</i>	0·168	1·321E-14	13
Whole_Blood	ENSG00000213676·6	<i>ATF6B</i>	0·025	5·859E-03	13
Whole_Blood	ENSG00000008838·13	<i>MED24</i>	0·052	4·423E-05	8
Whole_Blood	ENSG00000237541·3	<i>HLA-DQA2</i>	0·650	3·498E-84	105
Whole_Blood	ENSG00000113520·6	<i>IL4</i>	0·019	1·475E-02	4
Whole_Blood	ENSG00000204315·3	<i>FKBP1</i>	0·036	7·876E-04	88
Whole_Blood	ENSG00000204390·8	<i>HSPA1L</i>	0·019	1·585E-02	5
Whole_Blood	ENSG00000213171·2	<i>LINGO4</i>	0·059	1·395E-05	23
Whole_Blood	ENSG00000164209·12	<i>SLC25A46</i>	0·065	5·360E-06	29
Whole_Blood	ENSG00000204366·3	<i>ZBTB12</i>	0·291	7·007E-27	15
Whole_Blood	ENSG00000204525·10	<i>HLA-C</i>	0·315	3·614E-29	19
Whole_Blood	ENSG00000163221·7	<i>SI00A12</i>	0·174	7·580E-15	37
Whole_Blood	ENSG00000241106·2	<i>HLA-DOB</i>	0·480	1·752E-50	36
Whole_Blood	ENSG00000196126·6	<i>HLA-DRB1</i>	0·159	7·772E-14	20
Whole_Blood	ENSG00000204305·9	<i>AGER</i>	0·067	4·282E-06	26
Whole_Blood	ENSG00000134824·9	<i>FADS2</i>	0·528	1·480E-57	25

Whole_Blood	ENSG00000204463·8	<i>BAG6</i>	0·034	1·136E-03	29
Whole_Blood	ENSG00000226644·1	<i>RP11-128M1·1</i>	0·059	8·861E-06	5
Whole_Blood	ENSG00000119408·12	<i>NEK6</i>	0·121	2·158E-10	8
Whole_Blood	ENSG00000263874·1	<i>LINC00672</i>	0·038	6·672E-04	33
Whole_Blood	ENSG00000159352·11	<i>PSMD4</i>	0·014	3·904E-02	14
Whole_Blood	ENSG00000110917·3	<i>MLEC</i>	0·038	4·668E-04	9
Whole_Blood	ENSG00000213760·6	<i>ATP6V1G2</i>	0·018	2·002E-02	19
Whole_Blood	ENSG00000204657·2	<i>OR2H2</i>	0·031	1·764E-03	15
Whole_Blood	ENSG00000157837·11	<i>SPPL3</i>	0·020	1·290E-02	40
Whole_Blood	ENSG00000254810·1	<i>RP11-672A2·4</i>	0·056	2·302E-05	31
Whole_Blood	ENSG00000198502·5	<i>HLA-DRB5</i>	0·606	3·017E-74	50
Whole_Blood	ENSG00000224389·4	<i>C4B</i>	0·222	1·305E-19	41
Whole_Blood	ENSG00000137310·7	<i>TCF19</i>	0·072	1·815E-06	18
Whole_Blood	ENSG00000254852·4	<i>NPIPA2</i>	0·024	6·332E-03	8
Whole_Blood	ENSG00000166949·11	<i>SMAD3</i>	0·032	1·649E-03	54
Whole_Blood	ENSG00000180902·12	<i>D2HGDH</i>	0·245	1·608E-21	14
Whole_Blood	ENSG00000204650·9	<i>CRHR1-IT1</i>	0·455	1·385E-46	23
Whole_Blood	ENSG00000169442·4	<i>CD52</i>	0·237	1·130E-20	41
Whole_Blood	ENSG00000182134·11	<i>TDRKH</i>	0·086	1·691E-07	11
Whole_Blood	ENSG00000264070·1	<i>DND1P1</i>	0·540	7·495E-60	21
Whole_Blood	ENSG00000213719·4	<i>CLIC1</i>	0·026	4·221E-03	9
Whole_Blood	ENSG00000137312·10	<i>FLOT1</i>	0·135	1·835E-11	40
Whole_Blood	ENSG00000240053·8	<i>LY6G5B</i>	0·071	2·126E-06	37
Whole_Blood	ENSG00000167914·6	<i>GSDMA</i>	0·122	6·011E-11	20
Whole_Blood	ENSG00000204516·5	<i>MICB</i>	0·339	4·070E-31	45
Whole_Blood	ENSG00000231852·2	<i>CYP21A2</i>	0·046	1·189E-04	19
Whole_Blood	ENSG00000229391·3	<i>HLA-DRB6</i>	0·561	7·405E-65	77
Whole_Blood	ENSG00000131435·8	<i>PDLIM4</i>	0·024	5·908E-03	10

Table 2. Comparison of new loci in UKB asthma GWAS and Demenais et al⁶ meta-analysis of asthma GWASs.

Locus ^a	rsID	Position ^b	Nearby Genes ^c	Allele ^d	RAF ^e	UKB Childhood Onset Asthma GWAS			UKB Adult Onset Asthma GWAS			UKB Age of Onset GWAS			Demenais et al (TAGC) ^f									
						OR	95% CI	p-value	OR	95% CI	p-value	Beta	SE	p-value	TAGC SNP	SNP position	r ² between UKB and TAGC SNPs	Reference allele	Alternate allele	MAF	Multi-ancestry GWAS		European GWAS	
																						Beta ^g	p-value	Beta ^h
Childhood Onset Specific																								
2q36.3	rs10175070	2,228,705,75	CCL20, SLC18A3	A/G	0.251	1.122	1.086-1.16	4.31E-12	1.000	0.978-1.023	9.92E-01	-0.862	0.154	2.24E-08	rs13034664 [†]	228672579	0.89	A	G	0.247	-0.0143	4.27E-01	-0.0104	5.78E-01
5q13.2	rs10036789	5,716,959,18	PTCD2, ZNF366	C/G	0.460	1.085	1.054-1.117	4.51E-08	1.016	0.996-1.036	1.12E-01	-0.511	0.137	1.95E-04	rs10040192 [†]	71695880	0.94	T	C	0.478	0.0107	3.87E-01	0.0175	1.74E-01
6p25.3	rs9391997	6,409,119	IRF4, DUSP22, EXOC2	A/G	0.527	1.102	1.070-1.135	6.89E-11	0.995	0.976-1.015	6.35E-01	-0.597	0.136	1.06E-05	rs9391997	409119	1.00	A	G	0.325	0.0388	5.11E-03	0.0342	1.47E-02
7p15.3	rs34880821	7,227,7545	IL6, TOMM7	G/A	0.283	1.106	1.071-1.141	4.73E-10	1.000	0.979-1.022	9.88E-01	-0.667	0.149	7.59E-06	N.A.									
8q24.21	rs13277719	8,128,777,19	MYC, TMEM75	G/A	0.274	1.110	1.075-1.146	1.65E-10	1.013	0.991-1.036	2.46E-01	-0.660	0.151	1.20E-05	rs6990534 [†]	128814091	0.88	A	G	0.313	-0.0351	6.29E-03	-0.0301	3.00E-02
9q34.3 [†]	rs117137535	9,140,500,443	ABRD1, ZMIND19, EHM1	G/A	0.026	1.307	1.195-1.429	4.16E-09	0.977	0.913-1.046	5.10E-01	-2.464	0.446	3.42E-08	N.A.									
10p15.1	rs943451	10,662,1773	PRKCE, PFKFB3, SEMB2	C/T	0.318	1.125	1.091-1.161	7.51E-14	1.021	1.000-1.043	5.30E-02	-0.613	0.145	2.54E-05	rs943451	6621773	1.00	T	C	0.280	-0.0356	1.41E-02	-0.0502	1.19E-03
11q13.1	rs479844	11,655,51957	AP5B1, OVOL1	A/G	0.555	1.106	1.074-1.139	1.48E-11	1.015	0.995-1.035	1.41E-01	-0.657	0.135	1.22E-06	rs479844	65551957	1.00	A	G	0.379	0.0532	2.98E-05	0.0546	2.74E-05
11q23.3	rs12365699	11,118,743,286	CXCR3, DDX6	A/G	0.833	1.167	1.120-1.216	1.57E-13	1.004	0.978-1.031	7.43E-01	-1.396	0.185	4.42E-14	rs12365699	118743286	1.00	G	A	0.203	-0.0494	4.69E-03	-0.0430	1.60E-02
12q13.2 [†]	rs62623446	12,553,682,91	TESPA1, MUC11, NEUROD4	C/T	0.072	1.188	1.127-1.252	1.40E-10	1.038	0.999-1.077	5.32E-02	-1.079	0.253	1.95E-05	N.A.									
12q24.12	rs10774625	12,111,910,219	ATXN2, SH2B3, BRAP	A/G	0.504	1.087	1.056-1.119	2.07E-08	0.997	0.978-1.017	7.92E-01	-0.713	0.135	1.43E-07	rs10774625	111910219	1.00	A	G	0.498	0.0450	3.52E-04	0.0494	1.20E-04
12q24.31	rs1696361	12,121,363,823	SPPL3, HNF1A	C/T	0.359	1.109	1.076-1.142	1.19E-11	1.019	0.998-1.040	6.96E-02	-0.696	0.140	6.84E-07	rs558275 [†]	121196891	0.87	A	G	0.390	-0.0462	1.39E-04	-0.0496	8.25E-05
17q21.2	rs8066625	17,403,906,29	STAT3B, GHDC, STAT3A	G/A	0.100	1.151	1.098-1.206	4.90E-09	1.006	0.973-1.040	7.33E-01	-0.846	0.227	1.88E-04	rs4796770 [†]	40264896	0.44	C	A	0.077	-0.0240	5.20E-01	-0.0568	1.82E-01
17q21.32	rs56308324	17,458,192,06	TBC1, TBKBP1, OSBP1	A/T	0.132	1.132	1.086-1.180	3.47E-09	1.025	0.996-1.055	8.72E-02	-0.714	0.195	2.54E-04	rs10514934 [†]	45812124	1.00	T	C	0.143	0.0357	5.72E-02	0.0489	1.25E-02
18q21.33	rs4574025	18,600,988,14	TNFRSF11A, KIAA1468, ZCCHC2	C/T	0.535	1.090	1.058-1.122	9.25E-09	0.986	0.967-1.006	1.69E-01	-0.871	0.136	1.61E-10	rs4369774 [†]	60010448	1.00	A	C	0.456	0.0256	3.98E-02	0.0217	1.07E-01
18q21.33	rs12964116	18,614,426,19	SERPINE7, SERPINB1, SERPINB2	A/G	0.036	1.336	1.247-1.432	2.56E-16	1.005	0.953-1.059	8.62E-01	-1.916	0.351	4.87E-08	N.A.									
19p13.3	rs4807630	19,117,044,5	SNO2, GPX4, STK11	C/T	0.308	1.093	1.060-1.128	2.06E-08	1.013	0.992-1.035	2.32E-01	-0.487	0.147	9.25E-04	rs4807630	1170445	1.00	C	T	0.258	0.0498	2.21E-03	0.0447	1.05E-02
Adult Onset Specific																								
2q22.3	rs12617922	2,146,156,679	TEX11, ACVR2A	A/G	0.518	0.983	0.955-1.012	2.36E-01	1.066	1.045-1.087	1.59E-10	0.478	0.136	4.46E-04	rs6721116 [†]	146156197	1.00	G	A	0.500	0.0131	2.68E-01	0.0083	5.14E-01
Shared																								
3p22.3	rs35570272	3,330,476,62	GLB1, TRIM71, TMPE	G/T	0.396	1.100	1.068-1.133	2.68E-10	1.046	1.025-1.067	9.84E-06	-0.454	0.138	1.03E-03	rs9828592 [†]	33044339	0.65	T	C	0.418	0.0372	1.93E-03	0.0364	4.30E-03
5p15.2	rs16903574	5,146,103,09	FAM105A, TRIO, OTULIN	C/G	0.077	1.236	1.174-1.302	9.01E-16	1.052	1.013-1.091	7.75E-03	-1.055	0.250	2.51E-05	N.A.									
7p21.1	rs4473914	7,204,262,63	ITGB6, MACC1, ABCB3	C/T	0.604	1.092	1.060-1.125	9.02E-09	1.035	1.014-1.056	8.44E-04	-0.338	0.139	1.51E-02	rs4473914	20426263	1.00	T	C	0.478	-0.0118	3.20E-01	-0.0155	2.23E-01
7p15.1	rs917115	7,281,725,86	JAZF1, TAX1BP1, CREB5	T/C	0.208	1.112	1.074-1.152	1.73E-09	1.042	1.017-1.067	7.35E-04	-0.577	0.164	4.17E-04	rs917115	28172586	1.00	T	C	0.231	0.0478	7.08E-04	0.0457	2.21E-03
10p1.4	rs7894791	10,859,136,9	GATA3, CELF2	A/C	0.587	1.103	1.071-1.137	9.43E-11	1.024	1.004-1.045	1.94E-02	-0.494	0.137	3.24E-04	rs7894791	8591369	1.00	C	A	0.352	-0.0488	7.00E-05	-0.0435	8.03E-04
11p15.5	rs12788104	11,112,373,9	MUC6, MUC5AC	A/G	0.688	1.029	0.997-1.061	7.99E-02	1.064	1.041-1.087	1.41E-08	0.147	0.148	3.22E-01	rs11245962 [†]	1111164	0.95	C	T (G)	0.363	0.0596 ^b	8.00E-05	0.0566 ^c	7.19E-04
11q12.2	rs174621	11,616,301,04	FADS2, FADS1, FADS3	A/G	0.772	1.013	0.978-1.049	4.63E-01	1.071	1.046-1.097	1.46E-08	0.508	0.163	1.87E-03	rs174621 [†]	61637466	0.62	G	A	0.165	-0.0866	1.67E-06	-0.0927	4.86E-07
12q21.1	rs11178648	12,715,332,10	TSPAN8, PTPRR, LGB5	T/C	0.592	1.087	1.055-1.120	4.16E-08	1.052	1.031-1.073	6.62E-07	-0.183	0.138	1.86E-01	rs11178648	71533210	1.00	C	T	0.374	-0.0454	1.76E-04	-0.0429	6.61E-04
13q32.3	rs1887704	13,999,744,92	UBAC2, DOCK9, TMPSF2	C/G	0.681	1.124	1.089-1.161	5.48E-13	1.048	1.026-1.070	1.57E-05	-0.476	0.147	1.15E-03	rs9517642 [†]	99845912	0.89	G	A	0.264	0.0419	1.28E-03	0.0419	3.09E-03
21q22.12	rs11088309	21,364,646,31	RUNX1, SETD4	C/G	0.143	1.039	0.997-1.083	6.82E-02	1.079	1.050-1.109	4.83E-08	0.063	0.189	7.38E-01	rs17812917 [†]	36459698	1.00	G	A	0.099	0.0630	3.57E-04	0.0693	1.20E-04

^aCytogenetic band. ^bSNP position, Genome Reference Consortium Build 37 (hg19). ^cThe gene in which the SNP is located is indicated first, followed by the previous gene and the next gene; for intergenic SNPs, only the previous and next genes are shown. ^dAlleles are shown as non-risk/non-risk alleles, where the risk allele is the allele associated with increased asthma risk. ^eRAF, risk allele frequency in the UK Biobank. ^fThe lead SNP in the UKB GWAS locus was not present and the TAGC SNP in highest LD with the lead SNP. ^gBeta values have not been adjusted for non-risk/risk allele effects. ^hBeta value direction is discordant with UKB results. N/A: Not available; there was no SNP in the TAGC summary data with r² > 0.40

^aCytogenetic band. ^bSNP position, Genome Reference Consortium Build 37 (hg19). ^cThe gene in which the SNP is located is indicated first, followed by the previous gene and the next gene; for intergenic SNPs, only the previous and next genes are shown. ^dAlleles are shown as non-risk/risk alleles, where the risk allele is the allele associated with increased asthma risk. ^eRAF, risk allele frequency in the UK Biobank. ^fThe lead SNP in the UKB GWAS locus was not present and the TAGC SNP in highest LD is reported. [†]Beta values have not been adjusted for not-risk/risk allele effects. ^bBeta value direction is discordant with UKB results. N.A. Not available; there was no SNP in the TAGC summary data with r² > 0.40

Table 3. Summary statistics for childhood onset GWASs with and without individuals with allergic disease. Childhood onset asthma GWAS columns are also shown in Table 2 of the manuscript.

Locus	rsID	Position	Alleles	RAF	Childhood Onset Asthma GWAS			Childhood Onset Asthma GWAS (no allergies)		
					OR	95% CI	P-value	OR	95% CI	P-value
1q21.3	rs61816761	1:152285861	G/A	0.024	1.970	1.823-2.129	1.88E-65	1.612	1.492-1.743	2.45E-19
1q25.1	rs7518129	1:173163568	A/G	0.310	1.111	1.077-1.146	2.21E-11	1.093	1.06-1.128	4.22E-06
2q36.3	rs10175070	2:228670575	A/G	0.251	1.122	1.086-1.160	4.31E-12	1.141	1.104-1.179	1.00E-10
3q28	rs12634152	3:188121019	C/T	0.547	1.133	1.100-1.166	1.08E-16	1.121	1.089-1.155	4.33E-10
4p14	rs5743618	4:38798648	A/C	0.774	1.249	1.203-1.295	3.19E-32	1.252	1.207-1.299	1.67E-22
5q31.1	rs2051809	5:132056874	C/A	0.247	1.175	1.137-1.214	3.24E-22	1.182	1.144-1.221	1.92E-16
5q13.2	rs10036789	5:71695918	C/G	0.460	1.085	1.054-1.117	4.51E-08	1.093	1.061-1.125	1.23E-06
6p25.3	rs9391997	6:409119	A/G	0.527	1.102	1.070-1.135	6.89E-11	1.092	1.06-1.124	1.68E-06
7p15.3	rs34880821	7:2277545	G/A	0.283	1.106	1.071-1.141	4.73E-10	1.092	1.058-1.128	8.39E-06
8q24.21	rs13277355	8:128777719	G/A	0.274	1.110	1.075-1.146	1.65E-10	1.112	1.077-1.148	1.10E-07
9q34.3	rs117137535	9:140500443	G/A	0.026	1.307	1.195-1.429	4.16E-09	1.253	1.146-1.37	7.44E-05
10p15.1	rs943451	10:6621773	C/T	0.318	1.125	1.091-1.161	7.51E-14	1.113	1.079-1.148	3.36E-08
11q23.3	rs12365699	11:118743286	A/G	0.833	1.167	1.120-1.216	1.57E-13	1.151	1.104-1.199	3.83E-08
12q13.2	rs62623446	12:55368291	C/T	0.072	1.188	1.127-1.252	1.40E-10	1.156	1.097-1.219	1.24E-05
12q24.12	rs10774625	12:111910219	A/G	0.504	1.087	1.056-1.119	2.07E-08	1.099	1.068-1.132	1.84E-07
12q24.31	rs1696361	12:121363823	C/T	0.359	1.109	1.076-1.142	1.19E-11	1.112	1.079-1.145	1.50E-08
17q12	rs4795399	17:38061439	C/T	0.529	1.406	1.365-1.448	1.45E-111	1.456	1.414-1.5	5.64E-90
17q21.2	rs8066625	17:40390629	G/A	0.100	1.151	1.098-1.206	4.90E-09	1.157	1.104-1.213	6.82E-07
17q21.32	rs56308324	17:45819206	A/T	0.132	1.132	1.086-1.180	3.47E-09	1.121	1.075-1.168	1.03E-05
18q21.33	rs4574025	18:60009814	C/T	0.535	1.090	1.058-1.122	9.25E-09	1.092	1.061-1.125	1.46E-06
18q21.33	rs12964116	18:61442619	A/G	0.036	1.336	1.247-1.432	2.56E-16	1.357	1.266-1.455	1.16E-12
19p13.3	rs4807630	19:1170445	C/T	0.308	1.093	1.060-1.128	2.06E-08	1.079	1.046-1.113	9.83E-05
2q22.3	rs12617922	2:146156679	A/G	0.518	0.983	0.955-1.012	2.36E-01	1.003	0.974-1.032	8.86E-01
1q32.1	rs12023876	1:203093201	T/G	0.668	1.102	1.068-1.137	1.11E-09	1.100	1.066-1.135	1.05E-06
2p25.1	rs13416555	2:8441735	G/C	0.705	1.130	1.094-1.167	1.94E-13	1.129	1.092-1.166	2.72E-09
2q12.1	rs72823641	2:102936159	A/T	0.863	1.415	1.349-1.484	3.01E-46	1.430	1.364-1.5	3.33E-33
2q37.3	rs34290285	2:242698640	A/G	0.745	1.177	1.137-1.219	2.06E-20	1.191	1.151-1.233	5.65E-16
3p22.3	rs33570272	3:33047662	G/T	0.396	1.100	1.068-1.133	2.68E-10	1.089	1.058-1.122	3.86E-06
4q27	rs2069763	4:123377482	C/A	0.334	1.126	1.092-1.160	1.59E-14	1.130	1.097-1.165	9.67E-11
5p15.2	rs16903574	5:14610309	C/G	0.077	1.236	1.174-1.302	9.01E-16	1.188	1.128-1.251	1.52E-07
5q22.1	rs1837253	5:110401872	T/C	0.740	1.211	1.169-1.253	2.33E-27	1.211	1.17-1.254	7.01E-19
5q31.1	rs17622378	5:131778452	G/A	0.573	1.103	1.071-1.136	8.52E-11	1.100	1.068-1.133	2.77E-07
6p22.1	rs1117490	6:30170510	T/C	0.234	1.100	1.063-1.137	2.78E-08	1.093	1.057-1.131	2.15E-05
6p21.33	rs2428494	6:31322197	T/A	0.477	1.157	1.124-1.191	7.94E-23	1.160	1.127-1.194	3.59E-16
6p21.32	rs28407950	6:32626348	T/C	0.756	1.354	1.306-1.405	1.27E-59	1.359	1.31-1.409	5.11E-41
6q15	rs1321859	6:91011673	T/C	0.649	1.102	1.068-1.136	9.32E-10	1.099	1.066-1.134	9.91E-07
7p21.1	rs4473914	7:20426263	C/T	0.604	1.092	1.060-1.125	9.02E-09	1.101	1.068-1.134	3.09E-07
7p15.1	rs917115	7:28172586	T/C	0.208	1.112	1.074-1.152	1.73E-09	1.119	1.081-1.158	2.14E-07
8q21.13	rs4739738	8:81291645	A/G	0.359	1.117	1.084-1.151	3.45E-13	1.113	1.08-1.147	1.02E-08
9p24.1	rs992969	9:6209697	G/A	0.252	1.248	1.209-1.289	6.76E-42	1.268	1.228-1.309	1.46E-32
10p14	rs7894791	10:8591369	A/C	0.587	1.103	1.071-1.137	9.43E-11	1.117	1.084-1.151	2.76E-09
10p14	rs1775554	10:9054340	C/A	0.577	1.117	1.084-1.150	2.85E-13	1.130	1.097-1.164	4.83E-11
11p15.5	rs12788104	11:1123739	A/G	0.688	1.029	0.997-1.061	7.99E-02	1.036	1.004-1.069	7.34E-02
11q12.2	rs174621	11:61630104	A/G	0.772	1.013	0.978-1.049	4.63E-01	0.999	0.965-1.035	9.80E-01
11q13.1	rs479844	11:65551957	A/G	0.555	1.106	1.074-1.139	1.48E-11	1.087	1.056-1.12	4.95E-06
11q13.5	rs61894547	11:76248630	C/T	0.052	1.463	1.382-1.548	2.17E-39	1.436	1.357-1.52	6.29E-24
11q13.5	rs7936312	11:76293726	G/T	0.477	1.194	1.160-1.230	4.89E-33	1.189	1.155-1.224	1.61E-21

12q13.11	rs56389811	12:48205358	T/C	0.761	1.022	0.988-1.058	2.11E-01	1.022	0.987-1.057	3.18E-01
12q13.2	rs705699	12:56384804	G/A	0.425	1.106	1.074-1.139	1.43E-11	1.087	1.055-1.119	5.53E-06
12q13.3	rs3122929	12:57509102	C/T	0.404	1.134	1.101-1.167	6.59E-17	1.155	1.121-1.189	5.34E-15
12q21.1	rs11178648	12:71533210	T/C	0.592	1.087	1.055-1.120	4.16E-08	1.086	1.054-1.119	8.63E-06
13q32.3	rs1887704	13:99974492	C/G	0.681	1.124	1.089-1.161	5.48E-13	1.121	1.086-1.157	1.02E-08
14q24.1	rs1950897	14:68760141	T/C	0.287	1.096	1.062-1.131	1.38E-08	1.093	1.059-1.128	7.44E-06
15q22.2	rs11071559	15:61069988	T/C	0.872	1.205	1.151-1.262	2.57E-15	1.215	1.16-1.273	1.66E-11

Table 4. Results of GWAS-PW to test for co-localization of variants associated with childhood onset and adult onset asthma. The childhood onset GWAS results were input for phenotype 1 and the adult onset GWAS results were input for phenotype 2. The childhood onset specific loci and adult onset specific locus did not colocalize (high probabilities of P1 for childhood onset, low probabilities of P2 for adult onset, and zero to very low probabilities of P3 for colocalization). The only exceptions are the childhood onset loci at 5q31.1, which has a P1 = 0 and a P4 = 1, and at 17q21.32, which has a P1 = 0.05 and a P4 = 0.95. P4 indicates that the locus is shared but different variants are associated with risk in the childhood onset and adult onset GWASs. This is evident in the locus zoom plots of these two regions (appendix pages 23 and 34, respectively) where it is clear that the variants that are genome-wide significant in the childhood onset GWAS (over *KIF3A* at the 5q31.1 locus and over *TBX21* at the 17q21.32 locus) are not significant in the adult onset GWAS (lead SNP shown as a blue diamond and SNPs in high LD with the lead SNPs shown as red dots). At the 17q21.32 locus, the lead genome-wide significant variant in the childhood onset GWAS had a p=0.08 in the adult onset GWAS, although other variants in this region that were not in LD with the lead childhood onset variant had p-values $\sim 10^{-6}$ in the adult onset GWAS. Because those variants did not reach genome-wide significance, a second 17q21.32 locus was not included as a shared or adult onset specific locus in our analysis. In contrast, the 5q31.1 locus was listed as both childhood onset specific and shared because a second peak over *IRF1* was significant in both GWAS. Among the shared loci, nearly all have high probabilities for P3 (indicating co-localization) except for a few, such as 5q31.1 that have low probabilities of P3 and high probabilities of P4 as discussed above, or have similar P3 and P4 probabilities. This indicates that these are complex regions that likely harbor multiple independent susceptibility variants, not all of which reached genome wide significance in our GWASs. Notably, we do not find high probabilities of P1 or P2 for the shared loci, indicating that the shared loci are not misclassified.

Locus	rsID	Position	P1	P2	P3	P4
Childhood onset loci						
1q21.3	rs61816761	1:152285861	0.954	0.000	0.000	0.046
1q25.1	rs7518129	1:173163568	0.961	0.000	0.000	0.039
2q36.3	rs10175070	2:228670575	0.941	0.000	0.000	0.059
3q28	rs12634152	3:188121019	0.951	0.000	0.000	0.048
4p14	rs5743618	4:38798648	0.965	0.000	0.000	0.035
5q13.2	rs10036789	5:71695918	0.954	0.000	0.000	0.045
5q31.1	rs2051809	5:132056874	0.000	0.000	0.000	1.000
6p25.3	rs9391997	6:409119	0.974	0.000	0.000	0.026
7p15.3	rs34880821	7:22775450	0.958	0.000	0.000	0.042
8q24.21	rs13277355	8:128777719	0.898	0.000	0.000	0.102
9q34.3	rs117137535	9:140500443	1.000	0.000	0.000	0.000
10p15.1	rs943451	10:6621773	0.939	0.000	0.001	0.060
11q13.1	rs479844	11:65551957	0.972	0.000	0.000	0.028
11q23.3	rs12365699	11:118743286	0.959	0.000	0.000	0.041
12q13.2	rs62623446	12:55368291	0.963	0.000	0.001	0.036
12q24.12	rs10774625	12:111910219	0.957	0.000	0.000	0.042
12q24.31	rs1696361	12:121363823	0.956	0.000	0.000	0.044
17q12	rs4795399	17:38061439	0.929	0.000	0.000	0.071
17q21.2	rs8066625	17:40390629	0.920	0.000	0.000	0.080
17q21.32	rs56308324	17:45819206	0.051	0.000	0.000	0.949
18q21.33	rs4574025	18:60009814	0.951	0.000	0.000	0.049
18q21.33	rs12964116	18:61442619	0.953	0.000	0.000	0.047
19p13.3	rs4807630	19:1170445	0.964	0.000	0.000	0.036
Adult onset locus						
2q22.3	rs12617922	2:146156679	0.000	0.984	0.003	0.013
Shared loci						
1q32.1	rs12023876	1:203093201	0.000	0.000	0.938	0.062
2p25.1	rs13416555	2:8441735	0.000	0.000	0.988	0.012
2q12.1	rs72823641	2:102936159	0.000	0.000	0.183	0.817
2q37.3	rs34290285	2:242698640	0.000	0.000	0.994	0.006
3p22.3	rs35570272	3:33047662	0.000	0.000	0.999	0.001
4q27	rs2069763	4:123377482	0.000	0.000	0.648	0.352

5p15.2	rs16903574	5:14610309	0.000	0.000	0.961	0.038
5q22.1	rs1837253	5:110401872	0.000	0.000	1.000	0.000
5q31.1	rs17622378	5:131778452	0.000	0.000	0.000	1.000
6p22.1	rs1117490	6:30170510	0.000	0.000	0.995	0.005
6p21.33	rs2428494	6:31322197	0.000	0.000	1.000	0.000
6p21.32	rs28407950	6:32626348	0.000	0.000	0.000	1.000
6q15	rs1321859	6:91011673	0.000	0.000	0.978	0.022
7p21.1	rs4473914	7:20426263	0.000	0.000	0.952	0.048
7p15.1	rs917115	7:28172586	0.000	0.000	0.965	0.034
8q21.13	rs4739738	8:81291645	0.000	0.000	0.964	0.036
9p24.1	rs992969	9:6209697	0.000	0.000	0.958	0.042
10p14	rs7894791	10:8591369	0.000	0.000	0.602	0.398
10p14	rs1775554	10:9054340	0.000	0.000	0.879	0.121
11p15.5	rs12788104	11:1123739	0.000	0.001	0.441	0.588
11q12.2	rs174621	11:61630104	0.000	0.003	0.659	0.338
11q13.5	rs61894547	11:76248630	0.000	0.000	0.984	0.016
11q13.5	rs7936312	11:76293726	0.000	0.000	0.063	0.937
12q13.11	rs56389811	12:48205358	0.000	0.001	0.275	0.724
12q13.2	rs705699	12:56384804	0.000	0.000	0.973	0.027
12q13.3	rs3122929	12:57509102	0.000	0.000	0.880	0.120
12q21.1	rs11178648	12:71533210	0.000	0.000	0.969	0.031
13q32.3	rs1887704	13:99974492	0.000	0.000	0.987	0.013
14q24.1	rs1950897	14:68760141	0.000	0.000	0.918	0.082
15q22.2	rs11071559	15:61069988	0.000	0.000	0.992	0.008
15q22.33	rs56062135	15:67455630	0.000	0.000	0.992	0.008
16p13.13	rs35032408	16:11215424	0.000	0.000	0.997	0.003
16p12.1	rs3785356	16:27349168	0.000	0.000	0.090	0.910
16q12.1	rs2066844	16:50745926	0.001	0.000	0.925	0.075
17q21.33	rs28406364	17:47454507	0.000	0.000	0.982	0.018
19q13.11	rs10414065	19:33721455	0.000	0.000	0.981	0.019
21q22.12	rs11088309	21:36464631	0.000	0.001	0.831	0.168

Table 5. Summary statistics for the age of asthma onset GWAS and the childhood and adult onset GWAS. Information for the most significant SNP at each of 19 independent loci in the age of onset GWAS is shown.

Locus	rsID	Position	Alleles	MAF	Age of Asthma Onset GWAS			Childhood Onset Asthma GWAS			Adult Onset Asthma GWAS		
					Beta	SE	p-value	OR	95% CI	p-value	OR	95% CI	p-value
1q21.3	rs61816761	rs61816761	G/A	0.024	-4.571	0.426	8.145E-27	1.970	1.823-2.129	1.879E-65	1.016	0.948-1.088	6.563E-01
1q25.1	rs7518129	rs7518129	A/G	0.310	-0.849	0.145	4.887E-09	1.111	1.077-1.146	2.213E-11	0.997	0.977-1.019	8.168E-01
2q12.1	rs3771175	rs3771175	A/T	0.863	-1.726	0.207	7.661E-17	1.410	1.344-1.478	1.529E-45	1.104	1.072-1.137	2.810E-11
2q36.3	rs10187276	rs10187276	C/T	0.251	-0.865	0.154	1.976E-08	1.122	1.086-1.159	4.543E-12	1.000	0.977-1.023	9.853E-01
2q37.3	rs78147778	rs78147778	C/T	0.748	-0.914	0.162	1.638E-08	1.168	1.128-1.210	3.464E-18	1.070	1.045-1.095	9.790E-09
3q28	rs2889896	rs2889896	T/C	0.547	-0.975	0.136	8.066E-13	1.129	1.096-1.162	6.485E-16	1.007	0.987-1.027	5.076E-01
4p14	rs5743618	rs5743618	A/C	0.774	-1.578	0.163	4.526E-22	1.249	1.203-1.295	3.188E-32	1.008	0.985-1.032	5.090E-01
5q31.1	rs4705962	rs4705962	C/T	0.229	-0.985	0.159	5.571E-10	1.170	1.132-1.210	2.238E-20	1.010	0.987-1.034	3.814E-01
6p21.33	rs12207974	rs12207974	G/C	0.776	-1.066	0.164	8.862E-11	1.100	1.062-1.141	1.614E-07	0.978	0.956-1.002	6.758E-02
6p21.33	rs1093	rs1093	A/G	0.212	-0.994	0.162	8.405E-10	1.138	1.100-1.178	1.459E-13	1.036	1.012-1.061	3.152E-03
6p21.32	rs9274659	rs9274659	T/A	0.670	-1.249	0.145	6.707E-18	1.175	1.138-1.213	2.512E-23	1.004	0.983-1.025	7.226E-01
9p24.1	rs7848215	rs7848215	C/T	0.261	-1.031	0.151	7.510E-12	1.246	1.207-1.287	7.805E-42	1.098	1.074-1.122	1.157E-16
9q34.3	rs117137535	rs117137535	G/A	0.026	-2.464	0.446	3.419E-08	1.307	1.195-1.429	4.160E-09	0.977	0.913-1.046	5.097E-01
11q13.5	rs61894547	rs61894547	C/T	0.052	-2.227	0.284	4.421E-15	1.463	1.382-1.548	2.167E-39	1.093	1.047-1.141	5.462E-05
11q23.3	rs12365699	rs12365699	A/G	0.833	-1.396	0.185	4.423E-14	1.167	1.120-1.216	1.575E-13	1.004	0.978-1.031	7.434E-01
17q12	rs4795399	rs4795399	C/T	0.529	-2.286	0.134	6.760E-65	1.406	1.365-1.448	1.448E-111	1.005	0.985-1.025	6.279E-01
17q21.2	rs11658582	rs11658582	C/G	0.626	-0.905	0.141	1.373E-10	1.106	1.073-1.140	7.912E-11	1.012	0.992-1.033	2.358E-01
18q21.33	rs4574025	rs4574025	C/T	0.535	-0.871	0.136	1.605E-10	1.090	1.058-1.122	9.251E-09	0.986	0.967-1.006	1.690E-01
18q21.33	rs12964116	rs12964116	A/G	0.036	-1.916	0.351	4.866E-08	1.336	1.247-1.432	2.561E-16	1.005	0.953-1.059	8.623E-01

Table 6. Asthma age of onset GWAS comparison. The lead SNPs reported by Sarnowski et al⁷ are shown with their p values in the three UKB asthma GWASs.

Sarnowski et al						UKB		
Reported SNP	Locus	Effect/reference alleles	Effect frequency	Hazard ratio	P value	Childhood onset GWAS p value	Adult onset GWAS p value	Age of onset GWAS p value
GWS								
rs10208293	2q12	G/A	0.73	1.14	3.10E-08	3.68E-38	3.11E-06	1.36E-15
rs9272346	6p21	A/G	0.59	1.13	1.60E-08	4.17E-37	2.48E-47	7.18E-08
rs928413	9p24	G/A	0.25	1.19	6.50E-16	2.01E-40	4.61E-17	5.13E-11
rs1861760	16q22	A/C	0.04	1.28	4.20E-08	5.68E-01	2.96E-01	8.80E-01
rs9901146	17q12-q21	G/A	0.51	1.18	1.90E-16	8.14E-99	4.43E-01	4.46E-57
Suggestive loci								
rs12468899	2q11-q12	G/A	0.69	1.12	1.70E-07	4.45E-03	8.83E-01	4.08E-02
rs11071559	15q22	C/T	0.85	1.16	8.30E-07	2.57E-15	1.22E-05	5.11E-06
rs1805013	16p12-p11	T/C	0.05	1.22	8.00E-07	9.62E-01	3.76E-01	5.75E-01

Table 7. Tissue enrichment p-values of GWAS loci. Bonferroni adjusted 1-sided p-values for higher expression from FUMA⁵ are shown.

	Childhood onset p-value	Adult onset p-value
Skin	5.72E-03	1.00E+00
Lung	9.79E-01	6.39E-03
Blood	9.13E-03	4.00E-04
Spleen	1.22E-01	2.38E-03
Small intestine	2.03E-02	4.87E-03

Table 8. Results of PrediXcan analysis in 5 tissues. Results sorted by locus category and chromosomal band within each category. Only predicted genes with significant associations with asthma ($<1.29 \times 10^{-6}$) in at least one tissue are shown. Gene categories: A, adult onset; C, childhood onset; S, shared (see above Methods for details).

[illegible]

Table 9. Loci that were genome-wide significant in three previous large GWASs^{6,8,9} that were not genome-wide significant in the childhood onset or adult onset GWASs. For regions in which multiple SNPs were reported in previous GWAS, the SNP with the smallest p-value is shown.

Locus	Position	rsID	UK Biobank		Zhu et al ⁷	Pickrell et al ⁶	Demenais et al ⁵
			Childhood Onset Asthma <i>P</i> -value	Adult Onset Asthma <i>P</i> -value	<i>P</i> -value	<i>P</i> -value	<i>P</i> -value
1p36.22	1:10557251	rs662064	3.538e-5	9.393e-3	n.r.	3.2e-8	n.r.
1p36.11	1:25299426	rs6600246	1.105e-4	8.870e-3	5.04e-9	n.r.	n.r.
1q23.3	1:161159147	rs4233366	1.717e-5	2.959e-1	n.r.	4.8e-15	n.r.
1q24.2	1:167433420	rs1723018	8.302e-6	7.141e-6	n.r.	1.4e-8	n.r.
	1:167420425	rs2056626	1.048e-4	1.547e-7	8.80e-9	n.r.	n.r.
3p24.3	3:23653570	rs115913567	1.846e-1	3.748e-1	1.89e-8	n.r.	n.r.
5q31.3	5:141492419	rs7705042	3.814e-7	6.530e-4	n.r.	2.5e-8 ^a	7.9e-9 ^a
6p22.1	6:28712247	rs1233578	5.013e-5	3.224e-5	n.r.	n.r.	5.9e-7
7p21.1	7:20560996	rs6461503	9.210e-8	1.570e-1	2.13e-9	n.r.	n.r.
7q22.3	7:105676505	rs6959584	4.581e-4	6.970e-1	n.r.	2.0e-8	n.r.
20q13.33	20:62333022	rs1623866	8.822e-6	4.930e-2	4.04e-9	n.r.	n.r.
n.r., not reported as genome-wide significant. ^a The lead SNP reported in this region (rs200634877 at 5:141529512) in Zhu <i>et al.</i> is not present in the 1000 genomes database or the imputed UK Biobank data; instead we show the nearest lead SNP at 5q31.3 in Pickrell <i>et al.</i> and Demenais <i>et al.</i>							

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