

A genome-wide cross-trait analysis from UK Biobank highlights the shared genetic architecture of asthma and allergic diseases

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Clinical and epidemiological data suggest that asthma and allergic diseases are associated and may share a common genetic etiology. We analyzed genome-wide SNP data for asthma and allergic diseases in 33,593 cases and 76,768 controls of European ancestry from UK Biobank. Two publicly available independent genome-wide association studies were used for replication. We have found a strong genome-wide genetic correlation between asthma and allergic diseases ($r_g = 0.75$, $P = 6.84 \times 10^{-62}$). Cross-trait analysis identified 38 genome-wide significant loci, including 7 novel shared loci. Computational analysis showed that shared genetic loci are enriched in immune/inflammatory systems and tissues with epithelium cells. Our work identifies common genetic architectures shared between asthma and allergy and will help to advance understanding of the molecular mechanisms underlying co-morbid asthma and allergic diseases.

Asthma is a chronic respiratory syndrome that is characterized by abnormal and inflamed mucosa of the airways, wheezing and shortness of breath. Allergic diseases are immune responses for allergies, such as allergic rhinitis and atopic dermatitis (eczema). Asthma is a heterogeneous disease that can be either allergic or non-allergic¹. Allergic asthma (including the immunoglobulin E (IgE)-mediated sub-type), allergic rhinitis and eczema can be viewed as an immune response to a foreign antigen and often associates with IgE-mediated inflammation^{2,3}. Genetic studies offer a structured means of understanding the causes of asthma and allergic diseases, as well as identifying targets that can be used to treat the syndrome^{4–8}.

Clinical and epidemiological studies suggest that asthma and allergy are associated^{9,10}. Several studies have identified allergic diseases, such as allergic rhinitis and eczema, with the prevalence of them in asthmatic patients being up to 90% (refs^{9,11}). These studies demonstrate that the coexistence of asthma and allergy is frequent, and that allergy usually precedes asthma. Our previous epigenetic study has identified methylation loci linked to asthma and allergy via the IgE pathway¹².

One hypothesis to account for the similarity in symptoms for these conditions is that they share a common genetic etiology. Nearly half of the loci in genome-wide association studies (GWASs) of an individual immune-related disease influence risk to at least two diseases, indicating the shared genetic architecture of immune-mediated inflammatory and autoimmune diseases¹³. As each of the shared or similar risk factors has strong genetic influences on disease risk, the observed clustering of multiple risk factors could be due to an overlap in the causal genes and pathways^{14–21}. In addition,

grouping variants by the traits they influence should provide insight into the specific biological processes underlying co-morbidity and disease risk. Clinical and epidemiological studies have found that asthma and allergic diseases can occur either in the same individual or in closely related family members^{22–25}, suggesting a potential pleiotropic effect. Heritability has been estimated at varying between 35% and 95% for asthma^{22,26} and 33% and 91% for allergic rhinitis, 71% and 84% for atopic dermatitis (eczema) and 34% and 84% for serum IgE levels, which suggests that the genetic contribution for each may be significant²². While a previous study investigated the shared genetic etiology for 38 allergic diseases including asthma²⁷, our understanding has been limited to only 16 genome-wide shared susceptibility loci that were based on a self-reported phenotype. Moreover, a recent larger study has identified a shared genetic origin among three allergic diseases using a mixed population of self-reported and doctor-diagnosed phenotypes; however, a standard fixed-effect meta-analysis model was applied without considering artificial inflation due to heterogeneous effects among different sub-studies and phenotype definitions²⁸.

To increase our knowledge of shared genetic determinants influencing doctor-diagnosed allergic diseases and asthma, and to potentially discover novel loci, we investigated the genetic commonality among asthma and allergic diseases (hay fever/allergic rhinitis or eczema). We conducted a large-scale GWAS analysis based on these traits to explore genetic correlations and shared genetic components among these diseases using data from UK Biobank, which is the largest and most complete European Biobank available at present. Replication was performed in two independent publicly available GWAS studies, the GABRIEL asthma GWAS study⁵ and the Early

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Genetics and Lifecourse Epidemiology (EAGLE) eczema consortium study²⁹.

Results

Genetic correlation among immune-related traits. There was a strong positive genetic correlation between asthma and allergic diseases ($r_g = 0.75$, $P = 6.84 \times 10^{-62}$). When extending our genetic correlation analysis to rheumatoid arthritis³⁰, Crohn's disease and ulcerative colitis³¹, we did not find a significant genetic correlation between asthma and these other immune traits and confirmed the high genetic correlation between Crohn's disease and ulcerative colitis ($r_g = 0.57$, $P = 7.98 \times 10^{-23}$) (Table 1). In a functional partitioned genetic correlation analysis, we observed significant genetic correlation in 11 of 12 functional categories with the only exception being repressed regions (Fig. 1 and Supplementary Table 1). This empirical evidence of a shared genetic etiology for asthma and allergic diseases encourages the investigation of a common pathophysiology, particularly in specific functional categories. Estimates of SNP-based heritability on the observed scale using GWAS summary statistics were 7.2% (s.e. 0.7%) for asthma and 7.5% (s.e. 0.7%) for allergic diseases (Supplementary Table 2).

Genome-wide association in UK Biobank. The phenotype-genotype association test was carried out on 110,361 samples and 7,488,535 SNPs from UK Biobank after quality control. The genomic control parameter λ was 1.13 for asthma and 1.14 for allergic diseases (Supplementary Figs. 1 and 2)^{32–34}. The intercept (s.e.) from linkage disequilibrium score regression (LDSC) for asthma and allergy was 1.0279 (0.0074) and 1.0242 (0.0054), respectively. We identified 32 genome-wide significant ($P < 5 \times 10^{-8}$) independent loci for asthma and 33 for allergic diseases (see Methods, Supplementary Tables 3 and 4 and Supplementary Figs. 3 and 4).

For asthma, we confirmed most of the previously reported association loci, including *IL1R1*, *IL1RL1*, *IL18R1*, *IL13*, *SLC25A46*, *HLA* regions, *SMAD3*, *GSDMB* and many others (Supplementary Table 3). Out of the 32 independent loci reported here, 6 are novel associations with asthma and 2 of these fall within protein-coding gene bodies. For allergic diseases, genes such as *HLA-DQB*, *C11orf30*, *FLG*, *SLC25A46*, *TMEM232*, *CAMK4*, *TSLP*, *WDR36*, *CLEC16A*, *DEXT*, *HLA* regions and many others were confirmed in our analysis (Supplementary Table 4). Out of the 33 independent loci identified for allergic diseases, 8 are novel, of which 7 were mapped to protein-coding genes. Six index SNPs were found to show genome-wide significance in both asthma and allergic diseases (rs34290285 on *D2HGDH* and *GAL3ST2*, rs7705653 on *SLC25A46* and *TMEM232*,

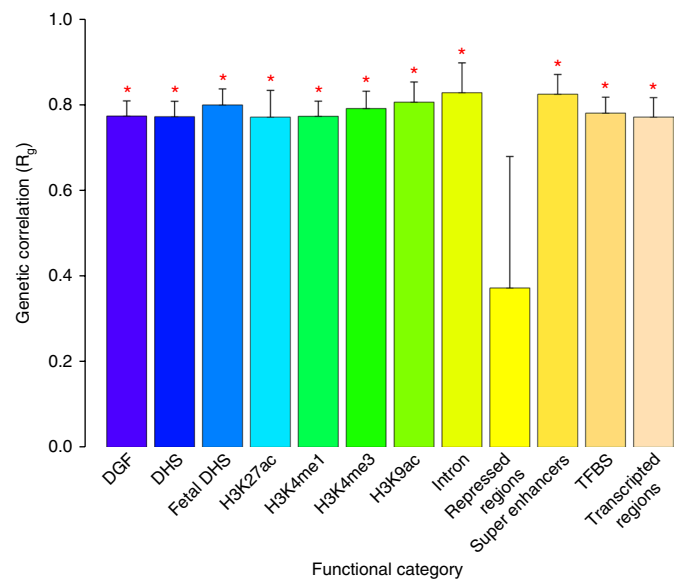


Fig. 1 | Partitioned genetic correlation between asthma and allergic diseases in UK Biobank. The vertical axis represents the genetic correlation estimate R_g ; the horizontal axis represents 12 functional categories. The asterisk represents significance ($P < 0.05$), error bars represent the standard error of genetic correlation estimates. DGF, DNase I digital genomic footprinting; DHS, DNase I hypersensitivity site; TFBS, transcription-factor binding sites.

rs12413578 near *HV745896*, rs7936070 on *C11orf30*, rs56062135 on *SMAD3* and rs10414065 near *SLC7A10*), and 22 loci contain the same protein-coding genes between asthma and allergic diseases, although they do not share the same peak SNP.

Among the six loci with overlapping index SNPs, four were mapped to protein-coding genes. *TMEM232* and *SLC25A46* (index SNP: rs7705653, Supplementary Figs. 5 and 6) encode transmembrane protein 232 that belongs to the tetraspanin family and a solute carrier protein involved in transport of metabolites, respectively. *C11orf30* (index SNP: rs7936070, Supplementary Figs. 7 and 8) is associated with total serum IgE levels in asthma³⁵; and the *C11orf30* locus increases susceptibility to poly-sensitization³⁶. *SMAD3* (index SNP: rs56062135, Supplementary Figs. 9 and 10) is involved in the development of asthmatic inflammation due to the response of immune cells, such as cytokines and T-helper 2 (Th2)

Table 1 | Genetic correlation between immune diseases

Phenotype	Asthma	Allergic diseases	Rheumatoid arthritis	Crohn's disease	Ulcerative colitis	Asthma (GABRIEL)	Eczema (EAGLE)
Asthma (N=90,853)	1	0.7455	0.0942	0.0428	−0.0514	0.6649	0.4138
Allergic diseases (N=102,453)	6.84×10^{-62}	1	0.0042	0.1415	0.0611	0.5008	0.5308
Rheumatoid arthritis (N=58,284)	0.0793	0.9259	1	0.067	0.1003	0.1001	−0.0463
Crohn's disease (N=69,268)	0.5925	0.0371	0.318	1	0.5711	0.0604	0.1190
Ulcerative colitis (N=72,647)	0.4942	0.3721	0.1032	7.98×10^{-23}	1	−0.0289	−0.0121
Asthma (GABRIEL) (N=26,475)	3.52×10^{-25}	3.24×10^{-15}	0.1312	0.5005	0.7338	1	0.5310
Eczema (EAGLE) (N=54,632)	1.29×10^{-9}	4.04×10^{-15}	0.5846	0.1982	0.9134	6.05×10^{-6}	1

The upper off-diagonal shows LD score regression estimates of the genetic correlation score (R_g , ranges from −1 to 1). The lower off-diagonal shows the corresponding genetic correlation P value.

cells, which are known to be important in generating an inflammation that characterizes asthma and allergic disease³⁷. A fourth variant, rs34290285, is the index SNP within a locus that contained two relatively new genes implicated in asthma and allergic diseases, *D2HGDH* and *GAL3ST2* (Supplementary Figs. 11 and 12), which are responsible for encoding the metabolism-related D-2-hydroxyglutarate dehydrogenase enzyme³⁸ and the tumor metastasis-related galactose-3-O-sulfotransferase 2 enzyme³⁹.

Cross-trait meta-analysis. Given the strong genetic correlation and similarity of SNP effect sizes for asthma and allergic diseases (Supplementary Fig. 13), we improved our power to detect shared loci between asthma and allergy by performing a cross-trait analysis. When doing so, we identified 38 loci that contained SNPs with $P < 5 \times 10^{-8}$ (Fig. 2 and Table 2). The genomic control parameter λ was 1.31 in the cross-trait meta-analysis (Supplementary Fig. 14) and Fig. 2 displays the Manhattan plot of these results.

The strongest association signal was observed on chromosome 6 at the *HLA-DQ* region (rs9273374, $P_{\text{meta}} = 7.87 \times 10^{-35}$), the first asthma-susceptibility locus identified⁴⁰, and extended haplotypes encompassing *HLA-DQ* and *HLA-DR* have been studied for their effects on specific allergen sensitization^{27,41}. The second strongest signal was mapped to *C11orf30* on chromosome 11q13 (rs7936070, $P_{\text{meta}} = 2.81 \times 10^{-28}$), a gene associated with total serum IgE levels and increased susceptibility to poly-sensitization. This SNP shows a significant association with both asthma and allergic diseases in each respective single-trait GWAS model. The third strongest signal was observed on *IL1R1* genes (rs72823641, $P_{\text{meta}} = 1.58 \times 10^{-27}$)⁴². Cytokine receptors have an impact on many cytokine-induced immune and inflammatory responses, such as asthma and allergy^{5,29,43}. The fourth strongest signal observed on *SMAD3* (rs56062135, $P_{\text{meta}} = 1.56 \times 10^{-22}$) is another loci found in both asthma and allergic diseases, which is known to have a role in immune cell response³⁷. We have also identified the *FLG* (Filaggrin) gene (rs61816766, $P_{\text{meta}} = 4.63 \times 10^{-12}$) to be associated with both asthma and allergic diseases, which is crucial for maintaining normal skin layer function⁴⁴. In general, our cross-trait results show that most identified loci are significant for both asthma and allergic disease, suggesting that it is these shared genetic loci driving the overall significant positive genetic correlation.

GTEX tissue enrichment analysis of asthma and allergic diseases' shared genes. To understand whether the 38 identified loci are enriched for expression in certain tissue types, we performed a tissue-specific expression analysis (TSEA) using the Genotype-Tissue Expression (GTEx) pilot data⁴⁵. We identified five independent tissues that demonstrated significantly enriched expression (after Benjamini–Hochberg correction) of cross-trait-associated genes (Fig. 3). The most strongly enriched tissue was part of the integumentary system (skin). The other significantly enriched tissues included esophagus, vagina, lung and whole blood. We also found that the identified shared genes between asthma and allergic diseases have significant cross-tissue heritability between each pair of tissues, with skin and lung showing notably high cross-tissue heritability (Supplementary Fig. 15).

Replication analysis in two independent asthma and eczema studies. In our replication analysis, we have confirmed a significant level of genetic correlation between asthma and eczema by using two independent GWAS data sets: the GABRIEL study⁵ and the EAGLE study²⁹. LDSC results showed that there was a strong positive genetic correlation between asthma (GABRIEL) and eczema (EAGLE) ($r_g = 0.53$, $P = 6.05 \times 10^{-6}$) (Table 1). We have then used cross-phenotype meta-analysis (CPMA) to identify genes with shared genetic signals between asthma and one allergic disease,

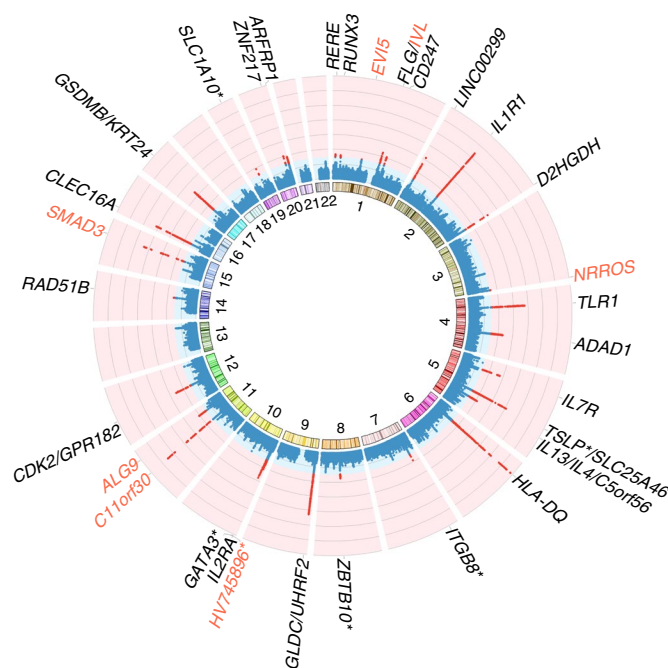


Fig. 2 | Circus Manhattan plot of cross-trait meta-analysis. The first layer of the plot illustrates the chromosome position and the second layer illustrates the representative genes of significant loci. Genes in red are novel shared genes between asthma and allergic diseases. The inside layer illustrates the significance level $-\log_{10}(P \text{ value})$ of asthma and allergic diseases' shared markers from cross-trait meta-analysis. The red dots indicate genome-wide significant ($P < 5 \times 10^{-8}$). A total of 38 independent loci were identified to be associated with both diseases. Genes at loci in close proximity were assigned one gene label separated by a slash. Asterisks represent the gene closest to index SNP. The sample size for asthma is 90,853, and that for allergic diseases is 102,453.

eczema. Twenty-two loci demonstrated genome-wide significance. Of these, the genes *HLA-DQB1*, *LCE5A*, *FLG*, *IL6R*, *IL1RL1*, *IL13*, *IL4*, *ACSL6*, *TSLP*, *IL33*, *C11orf30*, *GSDMB* and some others were replicated when comparing with the UK Biobank results (Supplementary Table 5 and Supplementary Fig. 16). Some genes were found as suggestive even though the association signal did not reach genome-wide significance. These include *RERE* (rs11581328, $P_{\text{meta}} = 4.47 \times 10^{-6}$), *SMAD3* (rs744910, $P_{\text{meta}} = 1.46 \times 10^{-7}$) and *CLEC16A* (rs2041733, $P_{\text{meta}} = 2.32 \times 10^{-6}$) (Supplementary Table 6). While the phenotypes in our replication phase are not exactly the same as those of UK Biobank, these results underscore the emerging overlap in genetic bases of asthma and allergy.

Over-representation enrichment analysis. Gene Ontology (GO) analysis highlighted several biological processes significantly enriched in the shared genes between asthma and allergic diseases, including epithelium development, keratinization, skin development and T-helper 1-type immune response (Supplementary Table 7). Additional analyses of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways found that shared association signals for asthma and allergic disease were significantly enriched in immune-related pathways (Supplementary Table 8), which is consistent with the findings of a recent study²⁸.

Fine-mapping and co-localization analysis identify shared causal variants. A list of a credible set of SNPs for each locus is shown in Supplementary Table 9. A co-localization analysis showed that 33 out of 38 loci share causal variants between asthma and allergic

Table 2 | Summary of the 38 genomic loci associated with asthma and allergic diseases in cross-trait meta-analysis

SNP	N	Chr.	Peak SNP position	Ref. allele	Alt. allele	Asthma		Allergy	UK Biobank meta-analysis		Replication	Genes within clumping range		
						P	P		OR	ASSET P		GABRIEL P	EAGLE P	CPMA P
rs9273374	65	6	32626614	A	G	1.31 × 10 ⁻³⁵	1.17 × 10 ⁻⁴	0.84	7.87 × 10 ⁻³⁵	9.27 × 10 ^{-3a}	0.0331	NA ^b	HLA-DQB1, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DRB1, HLA-DRB6, TAP2	
rs7936070	77	11	76293527	T	G	2.17 × 10 ⁻²¹	4.40 × 10 ⁻²²	1.08	2.81 × 10 ⁻²⁸	1.06 × 10 ⁻⁵	1.27 × 10 ⁻¹²	3.77 × 10 ⁻¹⁵	C11orf30, LOC100506127, PRKRIR	
rs72823641	151	2	102936159	A	T	7.43 × 10 ⁻¹⁸	4.27 × 10 ⁻²⁴	0.89	1.58 × 10 ⁻²⁷	1.86 × 10 ⁻⁹	1.50 × 10 ⁻³	4.67 × 10 ⁻¹⁰	IL1R1, IL1RL1, IL1RL2, IL18R1, IL18RAP, MIR4772, SLC9A2, SLC9A4	
rs56062135	25	15	67455630	T	C	2.62 × 10 ⁻²³	6.23 × 10 ⁻¹³	1.16	1.56 × 10 ⁻²²	7.46 × 10 ⁻⁷	0.2354	1.37 × 10 ⁻⁵	SMAD3	
rs9775039	109	9	6177453	A	G	7.41 × 10 ⁻²³	4.84 × 10 ⁻⁸	1.18	4.42 × 10 ⁻²²	2.38 × 10 ⁻¹²	0.1900	8.11 × 10 ⁻¹¹	GLDC, IL33, TPD52L3, UHRF2	
rs36045143	259	16	11224966	G	A	9.05 × 10 ⁻¹⁷	8.94 × 10 ⁻¹⁷	0.93	1.83 × 10 ⁻²¹	1.81 × 10 ⁻³	0.1057	6.90 × 10 ⁻³	CLEC16A, DEXI	
rs1837253	1	5	110401872	T	C	1.81 × 10 ⁻²⁰	1.07 × 10 ⁻¹³	0.93	4.38 × 10 ⁻²¹	3.03 × 10 ⁻¹⁰	0.5307	2.09 × 10 ⁻⁸	TSLP ^c	
rs7705653	349	5	110142816	G	A	4.58 × 10 ⁻¹⁰	1.88 × 10 ⁻²⁰	1.14	1.12 × 10 ⁻¹⁹	1.39 × 10 ⁻³	3.00 × 10 ⁻³	2.00 × 10 ⁻³	SLC25A46, TMEM232	
rs28393318	200	4	38784267	G	A	2.61 × 10 ⁻¹⁰	6.67 × 10 ⁻²⁰	0.92	2.14 × 10 ⁻¹⁹	3.92 × 10 ⁻³	0.0596	8.10 × 10 ⁻³	FAM114A1, MIR574, TLR1, TLR6, TLR10	
rs869402	225	17	38068043	C	T	7.02 × 10 ⁻¹⁸	6.70 × 10 ⁻⁴	1.12	4.15 × 10 ⁻¹⁷	1.14 × 10 ⁻¹⁶	0.0247	8.30 × 10 ⁻¹⁶	ERBB2, GRB7, GSDMA, GSDMB, IKZF3, LRRC3C, MIEN1, MIR4728, ORMDL3, PGAP3, PNMT, STARD3, TCAP, ZPBP2	
rs34290285	73	2	242698640	A	G	3.89 × 10 ⁻¹¹	1.54 × 10 ⁻¹⁵	0.93	5.17 × 10 ⁻¹⁷	0.0240 ^d	0.1619	0.082	D2HGDH, GAL3ST2	
rs10174949	59	2	8442248	A	G	6.08 × 10 ⁻¹⁰	5.72 × 10 ⁻¹⁶	0.94	1.70 × 10 ⁻¹⁶	5.77 × 10 ⁻³	6.91 × 10 ⁻⁶	3.53 × 10 ⁻⁶	LINC00299	
rs9911533	104	17	38775476	C	T	2.08 × 10 ⁻⁰⁷	1.65 × 10 ⁻¹⁶	0.92	9.70 × 10 ⁻¹⁶	0.8210	0.0302	0.3335	KRT24, KRT222, SMARCE1	
rs12413578	24	10	9049253	T	C	3.27 × 10 ⁻¹⁴	4.63 × 10 ⁻¹⁰	0.91	1.09 × 10 ⁻¹⁴	0.3080	0.0855	0.3470	HV745896 ^c	
rs6881270	71	5	35879095	T	C	7.87 × 10 ⁻⁶	2.61 × 10 ⁻¹⁵	0.91	1.53 × 10 ⁻¹⁴	0.2700	2.40 × 10 ⁻³	0.0195	CAPSL, IL7R, LOC100506406, SPEF2, UGT3A1	
rs10876864	61	12	56401085	G	A	1.43 × 10 ⁻¹²	8.49 × 10 ⁻¹⁰	1.05	1.41 × 10 ⁻¹³	0.1880	0.0407	0.1396	CDK2, ERBB3, IKZF4, PA2G4, RAB5B, RPL41, RPS26, SUOX, ZC3H10	
rs1059513	15	12	57489709	C	T	1.18 × 10 ⁻¹¹	1.62 × 10 ⁻⁰⁹	0.92	7.65 × 10 ⁻¹³	9.85 × 10 ⁻³	1.74 × 10 ⁻⁵	1.34 × 10 ⁻⁵	GPR182, MYO1A, NAB2, RDH16, SDR9C7, STAT6, TAC3, TMEM194A, ZBTB39	
rs56267605	196	4	123363109	C	A	3.29 × 10 ⁻¹⁰	6.59 × 10 ⁻¹⁰	1.05	2.56 × 10 ⁻¹²	9.02 × 10 ⁻³	1.64 × 10 ⁻⁵	1.17 × 10 ⁻⁵	ADAD1, IL2, IL21, IL21-AS1, KIAA1109	
rs61816766	10	1	152319572	C	T	3.10 × 10 ⁻⁸	3.07 × 10 ⁻¹¹	1.14	4.63 × 10 ⁻¹²	0.970 ^a	8.17 × 10 ⁻²¹	NA ^b	C1orf68, CRCT1, CRNN, FLG, FLG-AS1, FLG2, HRNR, LCE2A, LCE2B, LCE2C, LCE2D, LCE3A, LCE3B, LCE3C, LCE3D, LCE3E, LCE4A, LCE5A, NBPFI8P, RPTN, S100A11, TCHH, TCHHL1	
rs61839660	47	10	6094697	T	C	6.86 × 10 ⁻⁴	3.98 × 10 ⁻¹²	1.12	2.30 × 10 ⁻¹¹	0.2650	0.0226	0.1157	IL2RA, RBM17	
rs2706362	96	5	131925187	C	T	1.27 × 10 ⁻¹¹	1.73 × 10 ⁻⁷	1.06	3.75 × 10 ⁻¹¹	8.14 × 10 ⁻⁸	9.76 × 10 ⁻¹⁴	2.84 × 10 ⁻¹⁸	IL13, RAD50	
rs1214598	33	1	167426424	A	G	6.66 × 10 ⁻⁸	4.54 × 10 ⁻¹⁰	0.95	5.14 × 10 ⁻¹¹	4.04 × 10 ⁻⁴	0.194	3.19 × 10 ⁻³	CD247	
rs659529	192	11	111436896	T	A	3.45 × 10 ⁻⁷	1.20 × 10 ⁻¹⁰	0.95	6.03 × 10 ⁻¹¹	0.9940	0.9530	1.70 × 10 ⁻³	ALG9, BTG4, C11orf1, C11orf88, FDXACB1, LAYN, MIR34B, MIR34C, PPP2R1B, SIK2	
rs2766664	14	20	52171241	A	G	1.72 × 10 ⁻³	1.41 × 10 ⁻¹¹	1.08	8.07 × 10 ⁻¹¹	0.3540	2.25 × 10 ⁻⁵	4.00 × 10 ⁻³	LOC101927770, ZNF217	
rs2169282	42	9	6350235	A	G	3.13 × 10 ⁻¹¹	1.30 × 10 ⁻⁵	1.09	1.80 × 10 ⁻¹⁰	0.0172	0.7321	0.2030	GLDC, UHRF2	
rs10074523	132	5	132060583	C	A	4.15 × 10 ⁻¹¹	1.13 × 10 ⁻⁵	1.1	2.37 × 10 ⁻¹⁰	1.22 × 10 ⁻³	2.01 × 10 ⁻¹⁰	4.52 × 10 ⁻¹¹	CCNI2, IL4, KIF3A, SEPT8	
rs10414065	5	19	33721455	T	C	6.78 × 10 ⁻⁹	2.74 × 10 ⁻⁸	0.91	2.63 × 10 ⁻¹⁰	0.0740	0.249	0.2690	SLC7A10 ^c	
rs6461503	89	7	20560996	T	C	2.13 × 10 ⁻⁹	8.16 × 10 ⁻⁸	1.05	3.19 × 10 ⁻¹⁰	6.65 × 10 ⁻³	0.0133	3.60 × 10 ⁻³	ITGB8 ^c	
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Continued

Table 2 | Summary of the 38 genomic loci associated with asthma and allergic diseases in cross-trait meta-analysis (continued)

SNP	N	Chr.	Peak SNP position	Ref. allele	Alt. allele	Asthma		Allergy		UK Biobank meta-analysis		Replication		Genes within clumping range
						P	P	P	P	OR	ASET P	GABRIEL P	EAGLE P	
rs3208007	133	20	62322288	T	C	9.27 × 10 ⁻⁹	2.81 × 10 ⁻⁸	0.95	3.22 × 10 ⁻¹⁰	0.9310	7.40 × 10 ⁻⁶	4.00 × 10 ⁻³	ARFRP1, LIME1, RTEL1, RTEL1-TNFRSF6B, SLC2A4RG, STMN3, TNFRSF6B, ZBTB46, ZGPAT	
rs10795656	36	10	8595839	A	G	2.10 × 10 ⁻⁶	3.19 × 10 ⁻¹⁰	1.05	4.07 × 10 ⁻¹⁰	2.93 × 10 ⁻³	0.6890	0.0488	GATA3 ^c	
rs2548992	88	5	131808668	A	G	7.96 × 10 ⁻¹¹	5.40 × 10 ⁻⁴	1.1	4.54 × 10 ⁻¹⁰	3.68 × 10 ⁻⁶	0.5090	1.00 × 10 ⁻³	C5orf56, IRF1, LOC553103, MIR3936, P4HA2, PDLIM4, SLC22A4, SLC22A5	
rs2136016	95	8	81300681	G	A	3.72 × 10 ⁻¹⁰	3.57 × 10 ⁻⁴	1.09	2.11 × 10 ⁻⁹	5.03 × 10 ⁻³	9.40 × 10 ⁻⁶	4.13 × 10 ⁻⁶	ZBTB10 ^c	
rs61815704	24	1	152893891	G	C	4.08 × 10 ⁻⁷	5.51 × 10 ⁻⁸	1.14	5.16 × 10 ⁻⁹	0.2520 ^a	3.91 × 10 ⁻²⁰	NA ^b	IVL, LCE1A, LCE1B, LCE1C, LCE1D, LCE6A, SMCP, SPRR1A, SPRR1B, SPRR2A, SPRR2B, SPRR2D, SPRR2E, SPRR2F, SPRR3, SPRR4	
rs301805	31	1	8481016	T	G	6.01 × 10 ⁻⁸	3.36 × 10 ⁻⁷	0.96	6.43 × 10 ⁻⁹	0.0591	8.02 × 10 ⁻⁵	3.00 × 10 ⁻³	RERE	
rs742230	19	1	25251424	G	A	5.95 × 10 ⁻⁶	1.27 × 10 ⁻⁸	0.96	1.02 × 10 ⁻⁸	0.3030	0.0287	0.1538	RUNX3	
rs8008961	66	14	68752643	T	C	2.14 × 10 ⁻⁷	3.01 × 10 ⁻⁷	1.05	1.24 × 10 ⁻⁸	4.05 × 10 ⁻³	0.2360	0.0266	RAD51B	
rs4916533	9	3	196373582	T	C	2.79 × 10 ⁻⁷	3.62 × 10 ⁻⁷	0.93	1.66 × 10 ⁻⁸	0.6070	0.0667	0.4690	NRROS	
rs12743520	77	1	93037112	A	C	3.02 × 10 ⁻³	6.87 × 10 ⁻⁹	0.93	3.83 × 10 ⁻⁸	0.0460	0.7340	0.7340	EVIS	

^aThe index SNP is missing in the replication data set; thus, the best available proxy (highest LD) from the replication data within a distance of 500 kb of the index SNP was used. The best proxy SNPs, rs3135344 ($R^2 = 0.36$), rs61816766, rs9050 ($R^2 = 0.44$), rs61815704: rs6181907 ($R^2 = 0.77$), No common SNP between GABRIEL and EAGLE for CPMA analysis. ^cThe nearest gene to this locus. ^dThe imputation accuracy (r^2_{pred}) for rs34290285 from imPG is 0.54, lower than the imPG standard criterion $r^2_{pred} > 0.6$. N, number of SNPs clumped with the peak SNP; Chr., chromosome; Ref. allele, reference allele; Alt. allele, alternative allele; OR, odds ratio.

diseases, consistent with being driven by the same signal from the meta-analysis (Supplementary Table 10).

Discussion

In this study, we have shown a strong genetic correlation between asthma and allergic diseases (hay fever/allergic rhinitis or eczema), as well as identified specific loci that are shared between diseases. Furthermore, we have replicated our finding in two independent GWAS studies^{5,29}. Finally, we have found that genetic loci shared between asthma and allergic diseases were significantly enriched in several tissues, including skin, esophageal, vagina, lung and whole blood.

Most of our identified shared loci are consistent with the findings of two recently published studies^{17,28}. In total, seven novel loci were identified that are shared between asthma and allergic diseases (Fig. 2). Of these, six loci were mapped within a gene body. All of these loci have significant single-tissue expression quantitative trait loci (eQTL) mainly in the skin, lung, esophagus system, thyroid and whole blood (Supplementary Table 11). Given that GTEx eQTLs are pervasive at many loci, we have tried to determine whether our association signals co-localized with eQTL signals from eight relevant GTEx tissues. Several important genes showed strong evidence of co-localization ($H_4 > 0.5$), such as *RERE* and *GSDMB* in epithelium and immune-related tissues. On the other hand, even though the *HLA* regions were shown co-localize in all eight tissues, we note that the extended LD in the *HLA* region may not provide sufficient resolution to co-localize relevant eQTL results with the cross-disease associations. Further experiments are required to elucidate the association between asthma/allergy and expression of the *HLA* region.

A relatively new region we identified as having an association signal with both asthma and allergic disease was 2q14.3 (index SNP: rs34290285), which contains the genes *D2HGDH* and *GAL3ST2*. Both of these genes have significant single-tissue eQTLs from multiple tissues including lung, esophagus mucosa and skin (Supplementary Tables 12 and 13). Notably, the lead variant in this locus, rs34290285, was found to co-localize with multiple tissues only through *GAL3ST2*, not through *D2HGDH* (Supplementary Table 14). *GAL3ST2* encodes the tumor metastasis-related galactose-3-O-sulfotransferase 2 enzyme³⁹ and is expressed in the human small airway epithelium⁴⁶.

We found that genes that are associated with IgE function can consist of another crucial pathway for atopic diseases, such as asthma and eczema. We have found that *C11orf30* on chromosome 11 (Supplementary Tables 3–5) falls in an association locus shared between asthma and allergic diseases. *C11orf30* was reported to be associated with total serum IgE levels and increases susceptibility to poly-sensitization³⁵. When individuals are exposed to an allergen, IgE is released from the immune system and travels to local organs or tissues to release type 2 cytokines such as *IL-4*, *IL-13* and other inflammatory mediators⁴⁷. These cytokines can further cause allergic diseases and asthma, such as reddish/dry skin and coughing, wheezing or shortness of breath^{48,49}.

Clinical and epidemiologic observations have shown that immune-mediated inflammatory and autoimmune diseases can be associated due to overlap of genes¹³. Indeed, our LDSC analysis showed high genome-wide genetic correlation between asthma and allergic diseases and identified shared genes between them. However, we did not find significant genetic correlation between asthma and three other immune-related diseases, rheumatoid arthritis, Crohn's disease and ulcerative colitis, suggesting that the patterns of genetic architecture among immune-related traits can still be distinct. IgE-mediated hypersensitivity may underlie allergic asthma and other allergic diseases. Rheumatoid arthritis belongs to immune complex-mediated hypersensitivity, whereas Crohn's disease and ulcerative colitis belong to delayed cell-mediated hypersensitivity. This may explain why we identified a strong genetic

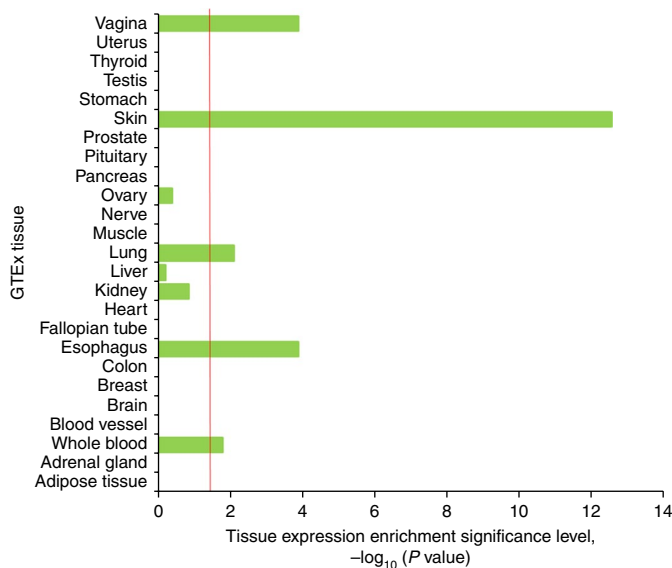


Fig. 3 | GTEx TSEA. The horizontal axis illustrates tissue expression enrichment P values after Benjamini–Hochberg correction. The vertical axis illustrates 25 independent tissue types from GTEx.

correlation for the traits within each hypersensitivity category. Different types of hypersensitivity are characterized by different types of gene set.

Although the association between respiratory diseases such as asthma and skin tissue diseases may, at first, seem counterintuitive, exploring the link between the two apparently distinct phenotypes from a gene function perspective reveals a noticeable overlap in underlying genetics and molecular pathways in their etiologies. We have confirmed that the *FLG* gene on chromosome 1 was associated with both allergic diseases and asthma. *FLG* is important for the formation of the stratum corneum and also for the hydration of this barrier layer⁴⁴. People who have mutations in the *FLG* gene can be sensitive to external allergens and produce dry and flaky skin⁴⁴. Meanwhile, it can activate a strong allergic immune response through peripheral blood to many organs, such as the lung, causing the inflammation in the lungs that results in shortness of breath⁴⁴.

Our finding of whole blood tissue enrichment indicated that these diseases were caused by some malfunction of the shared immune system. Genes such as *CD247* and *RUNX3* play important roles in T-helper cells, CD8⁺ T cells, natural killer cells and dendritic cells⁵⁰ and were previously reported as risk genes for many immune-related inflammatory diseases, such as asthma, Crohn's disease, ulcerative colitis and eczema^{50–53}. Moreover, whole blood is responsible for the production of anti-inflammatory cytokines and circulating them in the whole body⁵⁴.

Additional tissue enrichment in skin, esophagus, vagina and lung suggests that the shared pathway between asthma and allergic diseases might have significant functions extending beyond whole blood. Skin, esophagus, vagina and lung tissues are all characterized by various types of epithelium or mucosa^{55,56}, which share similarities in terms of functions and mechanisms. For example, the epithelial cells lining the airway, lungs and skin serve as the primary defense to inflammatory stimuli and antigens infiltrating these tissues through inducing cell signaling pathways in response to contact with the irritants. Indeed, a hallmark of asthma and allergic rhinitis is allergic sensitization by means of epithelial activation in the respiratory tract^{57,58}. Epithelial cells can also transdifferentiate into motile mesenchymal cells, which can behave like stem cells and differentiate into multiple cell lineages and migrate to damaged tissues to repair⁵⁹. Thus, the enrichment of asthma and

allergy genes expressed in epithelial components is not specific to a certain organ or tissue; rather, it seems to be generalizable across epithelium types.

It is worth noting that a recently published study²⁸ identified 136 independent risk variants spanning 73 novel loci that were shared between 3 allergic diseases. Some of their identified loci are consistent with ours, such as shared genes in the *HLA* region, *D2HGDH*, *IL1RL1*, *RERE*, *RUNX3* and many others. Moreover, they have noted enrichment of results in whole blood and lung tissue, as well as immune-related pathways. However, this study was based on a mixed population of self-reported and doctor-diagnosed allergic diseases, whereas our study was based only on doctor-diagnosed phenotypes. Such a complex phenotype background could introduce heterogeneity between studies. Moreover, a standard inverse-variance-weighted fixed-effects meta-analysis model was used to combine the association results from each sub-study, which has a limited ability to account for heterogeneous effects. In comparison with the above-mentioned study, our study has several strengths and presents additional novel results. First, we included an independent cohort to replicate our findings of shared loci between asthma and allergy. Second, we demonstrated both genome-wide LDSC and partitioned LDSC to assess the overall genetic correlation and functionally categorized genetic correlation between asthma and allergy. Third, we conducted cross-trait meta-analysis using ASSET, which is robust to heterogeneous effects and overlap samples between two phenotypes. Finally, we found skin to be one of the major tissues that was significantly enriched between asthma and allergy. We further showed significant cross-tissue heritability for identified genes among enriched tissues and found that this connection might be due to similar epithelial cell components.

We also acknowledge the limitations of our study. First, our allergic symptom phenotype contained both allergic rhinitis/hay fever and eczema. The allergy genes we found may not be associated with a specific type of allergy. However, since allergic rhinitis and eczema are both IgE-mediated hypersensitivities and characterized by epithelial cells, they might share a highly similar physiology^{60,61}. Moreover, one cannot exclude the potential for misclassification of allergy phenotypes since participants in UK Biobank may not report a condition they have. Second, our UK Biobank cohort traits are not independent. There are shared cases between asthma and allergic diseases and completely shared controls. However, our sensitivity analysis showed that LDSC analysis is robust to overlap samples under different scenarios (Supplementary Fig. 17 and Supplementary Table 15). In our meta-analysis, we have also applied methods that can account for overlapping samples and replicated our results in two independent studies to demonstrate the robustness of shared loci. We demonstrated that the effect estimates of 38 loci were not influenced after excluding asthma and allergic diseases overlapped subjects in the meta-analysis, although the significance levels were lowered due to the smaller sample size (Supplementary Figs. 18 and 19 and Supplementary Table 16). Given the high genetic correlation between asthma and allergy GWASs within the Caucasian population in UK Biobank, population heterogeneity among GABRIEL and UK Biobank Caucasian could give a slightly lower value for the cross-population genetic correlation for asthma. For example, cross-population r_g for the same disease (asthma) could be smaller than cross-disease r_g within the same population, especially when the two diseases share substantial genetic correlation such as asthma and allergy. Since the GABRIEL study was based on childhood asthma, and UK Biobank is based on adult asthma, the genetic effect between these two types of asthma may also lead to r_g differences. Finally, even after imputing the GABRIEL study summary statistics, there were still ~1 million fewer SNPs than the UK Biobank data set. A smaller number of SNPs from the GABRIEL asthma GWAS could also affect the r_g estimation and provide fewer overlapping SNPs for both traits in the replication data compared

to UK Biobank. This is also the reason that only a fraction of the shared genes was found in the replication analysis.

These shared genetic components can provide an opportunity to investigate asthma and allergy co-morbidity on molecular and functional levels (Supplementary Table 17). Drugs targeting shared genetic loci might benefit the treatment of both diseases. Our findings can also inspire patients and doctors to be more cautious about co-morbidity of asthma and allergic diseases in clinical practice.

Understanding the genetic overlap between asthma and allergic diseases can be beneficial to treat disease outcomes more efficiently. Our GWAS study has highlighted a shared genetic pathway in immune and inflammatory systems and epithelium tissues by asthma and allergic diseases. This work reinforces the idea that asthma and allergy share common biological processes and opens new avenues for treatment.

URLs. UK Biobank, <http://biobank.ctsu.ox.ac.uk/>; 1000 Genomes Project, <http://www.1000genomes.org/>; PLINK, <https://www.cog-genomics.org/plink2/>; ASSET, <https://bioconductor.org/packages/release/bioc/html/ASSET.html>; CPMA, <http://coruscant.itmat.upenn.edu/software.html>; GenABEL, <http://www.genabel.org/packages/GenABEL/>; FM-summary, <https://github.com/hailiang-huang/FM-summary>; Coloc tool, <https://github.com/chriswallace/coloc>; Roadmap Epigenomics, <http://www.roadmapepigenomics.org/>; GABRIEL consortium, <https://www.cng.fr/gabriel/index.html>; EAGLE consortium, <http://data.bris.ac.uk/data/>; LiftOver, <http://genome.sph.umich.edu/wiki/LiftOver>; ImpG, <https://github.com/huwenboshi/ImpG>; LDSC, <https://github.com/bulik/ldsc>; GCTA, <http://cns.genomics.com/software/gcta/>; GTEx, <http://www.gtexportal.org>; TSEA, <http://genetics.wustl.edu/jdlab/tsea/>; WebGestalt, <http://www.webgestalt.org/option.php>; GWAS catalog, <https://www.ebi.ac.uk/gwas/>; LocusZoom, <http://locuszoom.org>.

Methods

Methods, including statements of data availability and any associated accession codes and references, are available at <https://doi.org/10.1038/s41588-018-0121-0>.

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Author contributions

Z.Z., L.L., P.H.L., Q.L. and D.C.C. designed the study. Z.Z., M.D.C., W.C. and P.-R.L. performed the statistical analysis. Z.Z., M.D.C., L.L., W.C. and Q.L. wrote the manuscript. All authors helped interpret the data, reviewed and edited the final paper, and approved the submission.

Competing interests

The authors declare no competing interests.

Additional information

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Methods

Study population and design. Study participants were from the UK Biobank study, described in detail elsewhere^{62–64}. In brief, UK Biobank is a prospective study of >500,000 people living in the UK. All people in the National Health Service registry who were aged 40–69 years and living <25 miles from a study center were invited to participate from 2006–2010. In total, 503,325 participants were recruited from over 9.2 million mailed invitations. For the current analysis, individuals of non-white ethnicity were excluded to avoid confounding effects. All participants provided informed consent to UK Biobank.

To identify genetic variants that contribute to doctor-diagnosed asthma and allergic diseases (detailed phenotype information described in the Supplementary Note) and link them with other conditions, we performed GWASs using phenotype measures in UK Biobank participants ($N=487,409$). We removed 39,698 samples that are non-white, are related, withdrew from UK Biobank or are missing genotype information. Thus, a total of 110,361 European descendants with high-quality genotyping and complete phenotype/covariate data were used for these analyses, including 25,685 allergic diseases subjects (hay fever/allergic rhinitis or eczema, without doctor-diagnosed asthma), 14,085 asthma subjects and 76,768 controls for the analysis. Key demographic characteristics for each population are shown in Supplementary Table 18.

Furthermore, we have included summary statistics for a replication analysis from an independent asthma GWAS (GABRIEL study, 10,365 cases 16,110 controls)⁵ and an independent eczema GWAS (EAGLE eczema consortium, 13,287 cases and 41,345 controls)²⁹.

Data summary, quality control (QC) and imputation. Detailed genotyping and QC procedures of UK Biobank were described previously (<http://biobank.ctsu.ox.ac.uk/>) and are provided in the Supplementary Note. In summary, after QC procedures were applied, the current released UK Biobank data contains 806,466 SNPs that passed SNP QC in at least one batch. Post-imputation QC was performed as previously outlined (<http://biobank.ctsu.ox.ac.uk/>); and the genotype imputation procedure provided a total of 73,355,677 SNPs. In this study, we focused only on common variants for the analysis with minor allele frequency >1% due to higher imputation accuracy of common variants in UK Biobank⁶⁵. In addition, we performed stringent QC standards by PLINK 1.90⁶⁶. We selected variants that did not deviate from Hardy–Weinberg equilibrium ($P > 1 \times 10^{-12}$), per-variant missing call rates <5%, per-sample missing rate <40% and an imputation quality score (INFO) >0.8. Quantile–quantile plots were produced and checked for each phenotype. The R package GenABEL was used to compute genomic inflation values. A total of 7,488,535 SNPs passed QC on the whole genome and with complete information in both phenotypes, which were eligible for statistical association analyses.

Genome-wide association analysis. We performed additive logistic regression genetic association analysis adjusting for age, sex, genotyping array and ten ancestry principal components using PLINK 1.90⁶⁶ to assess the association between phenotype and genotype on each individual disease. After association analysis, we applied the PLINK clumping function (parameters: --clump-p1 5e-8 --clump-p2 1e-5 --clump-r2 0.2 --clump-kb 500) to determine top loci that are independent from each other; that is, variants with a P value less than 1×10^{-5} , R^2 more than 0.2 and less than 500 kb away from the peak will be assigned to that peak's clump). The top loci that were annotated to the same gene were then further combined as one independent loci for downstream analysis. We have used the GWAS catalog (<https://www.ebi.ac.uk/gwas>, search date: October 18, 2017) to identify previously reported genes by other GWAS studies.

LD score regression analysis. Post-GWAS genome-wide genetic correlation analysis by LD score regression (LDSC)⁶⁷ was conducted using UK Biobank summary statistics overlap with HapMap3 variants as recommended⁶⁸. LDSC estimates genetic correlation between the true causal effects of two traits (ranging from -1 to 1) from summary statistics using the fact that the GWAS effect size estimate for each SNP incorporates the effects of all SNPs in LD with that SNP. SNPs in a high-LD region would have higher χ^2 statistics than SNPs in a low-LD region, and a similar relationship is observed when single-study test statistics are replaced with the product of the z scores from two studies of traits with some correlation⁶⁷. LDSC applied a self-estimated intercept during the analysis to account for shared subjects between studies⁶⁷.

Partitioned genetic correlation. We estimated the genetic correlation between asthma and allergic diseases within functional categories using partitioned LDSC⁶⁹. Twelve functional categories were used including transcribed region, repressed region, intron, transcription factor-binding sites, super-enhancer, DNaseI digital genomic footprinting region, DNase I hypersensitivity sites (DHSs), fetalDHS, and histone marks H3K4me1, H3K27ac, H3K4me3 and H3K9ac from Roadmap Epigenomics Project⁷⁰. Recalculated LD scores for SNPs classified in each particular annotation were used for estimating the asthma–allergy genetic correlation within that functional group.

Cross-trait meta-analysis. After assessing genetic correlations among all traits, we applied cross-trait GWAS meta-analysis by using the R package Association

analysis based on SubSETs (ASSET) to combine the association evidence for asthma and allergic diseases at individual variants⁷¹. This method combines the effect estimate and standard error of the GWAS summary statistics to test the hypothesis of association between the SNP with any subset of studies. It can also account for the correlation among studies/subjects that might arise due to shared subjects across distinct studies or due to correlation among related traits in the same study by using case–control overlap matrices. We used one-sided ASSET assuming the same direction of association for asthma and allergic diseases.

Fine-mapping credible set analysis. We identified a credible set of causal variants at each of the 38 shared loci that met asthma–allergic disease cross-trait meta-analysis criteria using the Bayesian fine-mapping algorithm FM-summary (see the URLs section). For each locus, we extracted variants within 500 kb of the index SNP. The FM-summary program maps the primary signal and uses a flat prior with the steepest descent approximation. The details of this method are described elsewhere^{72–74}.

Co-localization analysis. We used the R package coloc⁷⁵ to determine whether asthma and allergic disease association signals co-localized at shared loci and whether shared loci co-localized with GTEx (version 7) eQTL in eight relevant tissues, including skin (not sun-exposed), skin (sun-exposed), esophagus mucosa, esophagus muscularis, esophagus gastroesophageal junction, lung, vagina and whole blood. We extracted summary association data for variants within 500 kb of the index SNP at each of the 38 shared loci and calculated the probability that the two traits share one common causal variant (H4). Loci with probability greater than 0.5 were considered to co-localize.

GTEx TSEA. To determine whether shared asthma and allergy genes are overly expressed in disease-relevant tissues, we conducted TSEA^{76,77}. Gene lists were generated from lists obtained from analyses for asthma, allergic diseases and cross-disease, and by including those that have a matching HUGO Gene Nomenclature Committee (HGNC) name. Genes identified in this way were analyzed for tissue enrichment using publicly available expression data from the pilot phase of the GTEx⁴⁵ project (www.gtexportal.org, January 31, 2013). In the GTEx project, post-mortem samples from a wide variety of tissues and donors have been used for bulk RNA sequencing according to a unified protocol. All samples were sequenced using Illumina 76 base-pair paired-end reads. The pilot phase of the GTEx project consists of 1,839 samples derived from 189 post-mortem subjects, including samples from 45 different tissues, with some tissues offering multiple 'sub-tissue' types. TSEA averaged collapsed reads per kilobase per million mapped reads (RPKM) values for the sub-tissue types (25 'whole-tissue' types). We filtered for unique HGNC IDs ($n=213$ shared genes mapped by identified loci from the meta-analysis result existing in the tissue expression data set). For each tissue, transcripts from the processed GTEx transcripts that are specifically expressed or enriched have been identified by using the TSEA pSI R package function to calculate the specificity index probability (pSI). The significance levels of shared genes between asthma and allergic diseases enriched in each tissue were identified by Fisher's exact test with Benjamini–Hochberg correction.

Replication analysis. To confirm our findings, we have further included two publicly available independent GWAS data sets: asthma GWAS, the GABRIEL consortium study⁵, and eczema GWAS, the EAGLE eczema consortium study²⁹, for LD score regression analysis, cross-trait analysis and GTEx tissue expression enrichment analysis. We have used the LiftOver tool (see the URLs section) to convert the asthma GWAS reference genome from hg18 to hg19. ImpG-Summary was used to impute asthma GWAS summary statistics to the 1000 Genomes Project variants (phase 3 release v5)⁷⁸. SNPs with imputation quality r^2 pred <0.6 were removed. Cross-trait analysis between two replication GWAS data sets was conducted using the R package CPMA, which tests for the hypothesis that each independent SNP has multiple phenotype associations and combines the empirical evidence based on their P values¹³.

Over-representation enrichment analysis. To understand the biological insights of the shared genes, we have used the WebGestalt tool⁷⁹ to assess over-represented enrichment of the identified shared gene set between asthma and allergic diseases in KEGG⁸⁰ pathways and GO biological processes^{81,82}.

Cross-tissue heritability of gene expression. The GTEx project⁴⁵ (phs000424.v6.p1) was also used to quantify the cis SNP cross-tissue heritability (h^2_{cis}) of gene expression across a range of tissues. All estimates were obtained using restricted maximum likelihood as implemented in genome-wide complex trait analysis (GCTA)⁸³. Only common variants that fall within 1 Mb of the transcription start site of a gene were considered in deriving these estimates. Enrichment of h^2_{cis} was determined by comparing average h^2_{cis} for a given gene list to 1,000,000 random gene lists of equal size in the same tissue pair. Detailed information of our method is provided in the Supplementary Note.

Sensitivity analysis. To estimate the effect of using non-allergic asthma individuals, we performed additive logistic regression analysis adjusting for the same covariates as the primary analysis to assess the association between

phenotype and genotype on each individual disease excluding allergic asthma ($N=6,177$). We carried out cross-disease heritability analysis and meta-analysis to identify the loci that are associated with both diseases. Due to the large reduction in sample size of asthma cases and allergic diseases cases, the power of detecting an association between phenotypes and SNPs is expected to decrease. Furthermore, to determine whether overlap samples can bias genetic correlation estimates, we performed additional sensitivity analysis. We randomly split controls into two equal sample size data sets ($N=38,384$ for each), and used real disease proportions of asthma and allergic diseases with two distinct control data sets. Details of the overlap sample sensitivity analysis design can be found in Supplementary Fig. 17. Using the same set of cases, we also compared the genetic correlation estimates via using disease-free controls versus using non-asthma or non-allergy controls (Supplementary Table 15).

Reporting Summary. Further information on experimental design is available in the Nature Research Reporting Summary linked to this article.

Data availability. Summary GWAS statistics are available at <http://lianglab.rc.fas.harvard.edu/AsthmaAllergyHeritability/>.

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► Experimental design

1. Sample size

Describe how sample size was determined.

The sample size was based on the availability of UK Biobank data field 6152 information on asthma, hay fever/allergic rhinitis or eczema status. Based on literature reports, with sample size more than 110,000, we expected sufficient power for the genetic correlation analysis and meta-analysis.

2. Data exclusions

Describe any data exclusions.

The exclusion criteria were described as part of standard GWAS quality control procedures, such as MAF<1%, HWE<10⁻¹², imputation INFO score<0.8, per variant missing call rates>5%, per-sample missing rate>40%, related individuals.

3. Replication

Describe whether the experimental findings were reliably reproduced.

Two public available GWAS summary statistics data (GABRIEL asthma and EAGLE eczema) were used for replication phase in this study. The findings were reliably reproduced in replication phase.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Case status for asthma, allergic diseases (hay fever/allergic rhinitis or eczema) were defined as if the individual has ever been told by a doctor if he/she have had any of the conditions. Participants who had never suffered from any of these conditions told by doctor were considered as controls.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

For UK Biobank blood collection, DNA extraction and genotyping procedures, researchers are blinded to phenotype information.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or the Methods section if additional space is needed).

n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
- ☐ ☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly.
- ☐ ☒ A statement indicating how many times each experiment was replicated
- ☐ ☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
- ☐ ☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
- ☐ ☒ The test results (e.g. p values) given as exact values whenever possible and with confidence intervals noted
- ☐ ☒ A summary of the descriptive statistics, including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
- ☐ ☒ Clearly defined error bars

See the web collection on [statistics for biologists](#) for further resources and guidance.

► Software

Policy information about [availability of computer code](#)

7. Software

Describe the software used to analyze the data in this study.

R statistical software programs 3.3, PLINK 1.9, LDSC, ImpG 1.0, LiftOver, GCTA, Coloc tool, SHAPEIT3, IMPUTE2, QCTOOL

For all studies, we encourage code deposition in a community repository (e.g. GitHub). Authors must make computer code available to editors and reviewers upon request. The *Nature Methods* [guidance for providing algorithms and software for publication](#) may be useful for any submission.

► Materials and reagents

Policy information about [availability of materials](#)

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

Summary statistic data for GWAS will be publicly available at the time of publication from UK Biobank with application

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

No antibodies were used

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

No cell lines were used

b. Describe the method of cell line authentication used.

No cell lines were used

c. Report whether the cell lines were tested for mycoplasma contamination.

No cell lines were used

d. If any of the cell lines used in the paper are listed in the database of commonly misidentified cell lines maintained by [ICLAC](#), provide a scientific rationale for their use.

No cell lines were used

► Animals and human research participants

Policy information about [studies involving animals](#); when reporting animal research, follow the [ARRIVE guidelines](#)

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

No animal were used

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

We used a UK population based biobank to perform a cross trait GWAS meta-analysis for asthma and allergic diseases, that both phenotypes were based on doctor diagnosis. Key demographic statistics appear in supplementary table 18 (age, gender). Individuals were genotyped using the UK Biobank array, and imputed using a 1000G/UK10K reference panel. Additive logistic regression genetic association analysis was performed adjusting for age, sex, genotyping array and ten ancestry principal components.

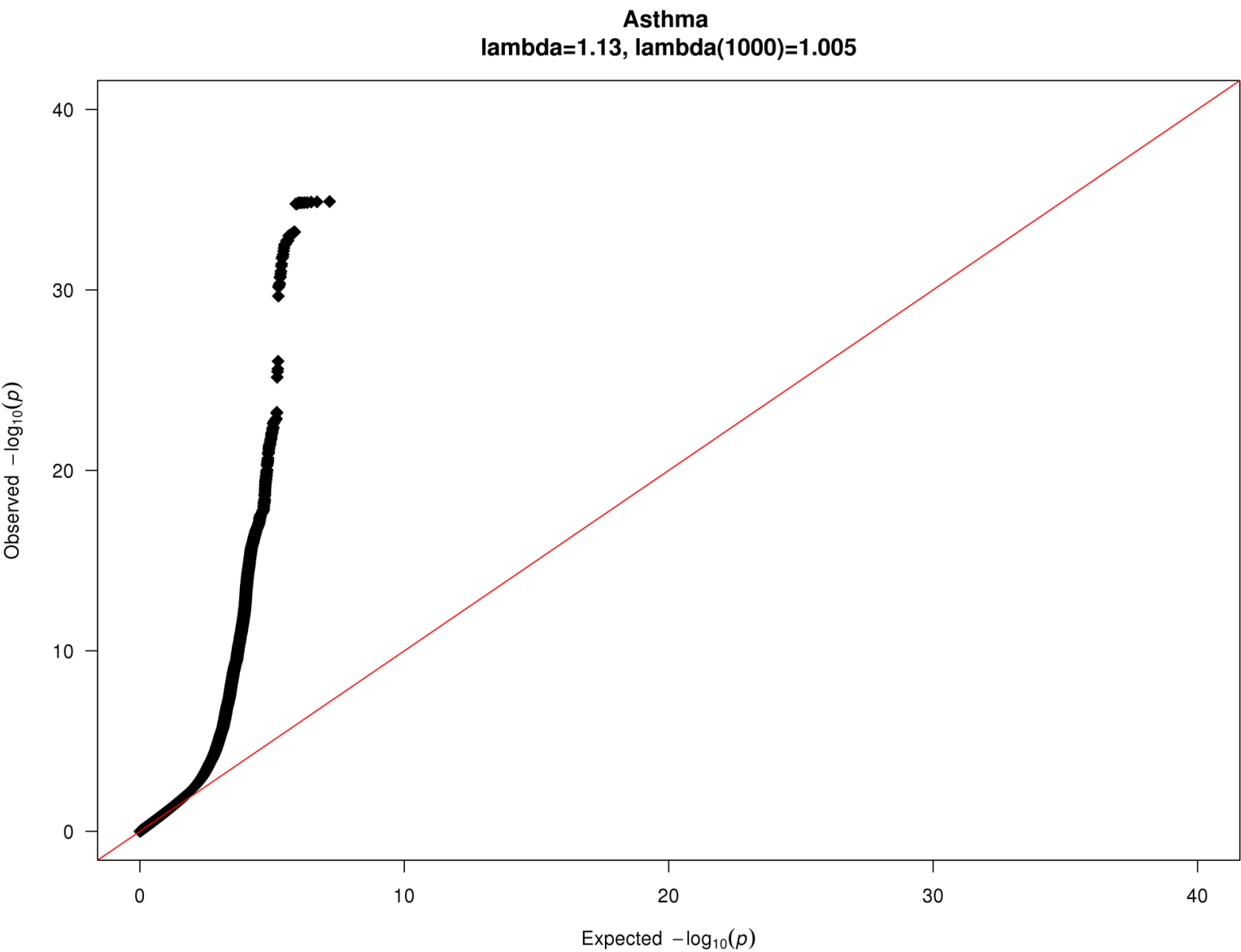
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A genome-wide cross-trait analysis from UK Biobank highlights the shared genetic architecture of asthma and allergic diseases

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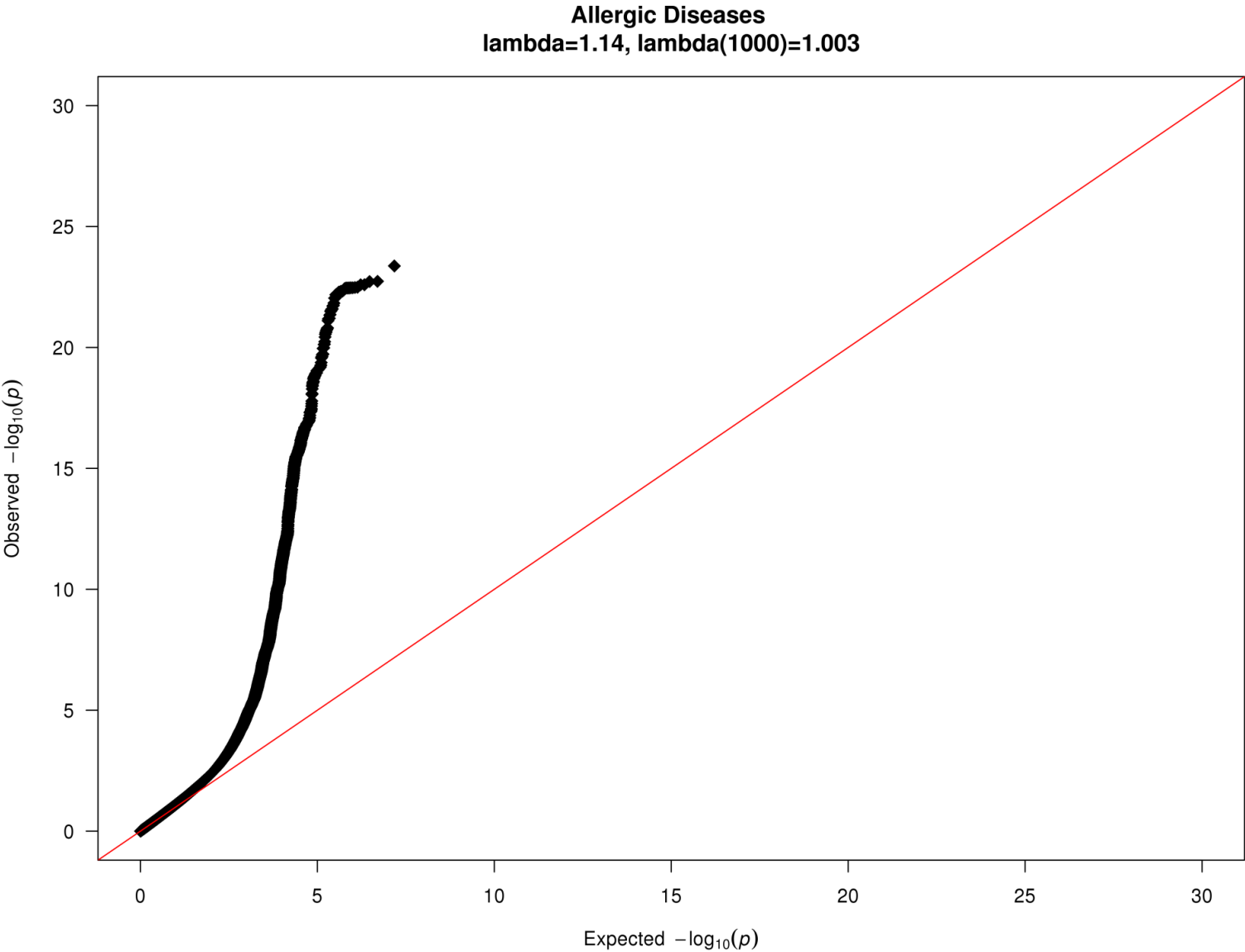
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Supplementary Figure 1. QQ plot of asthma GWAS in UK Biobank



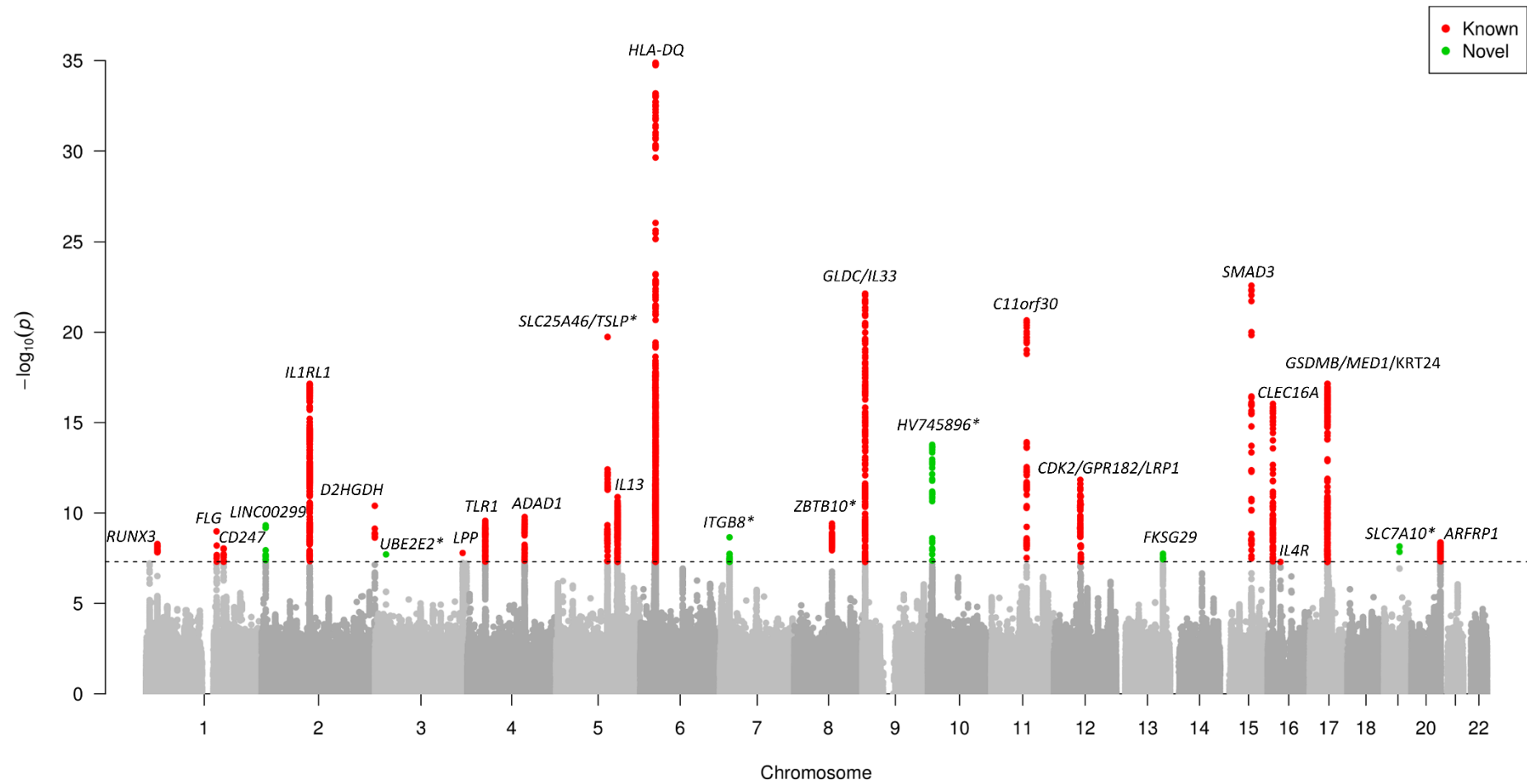
Sample size for asthma is 90,853

Supplementary Figure 2. QQ plot of allergic disease GWAS in UK Biobank



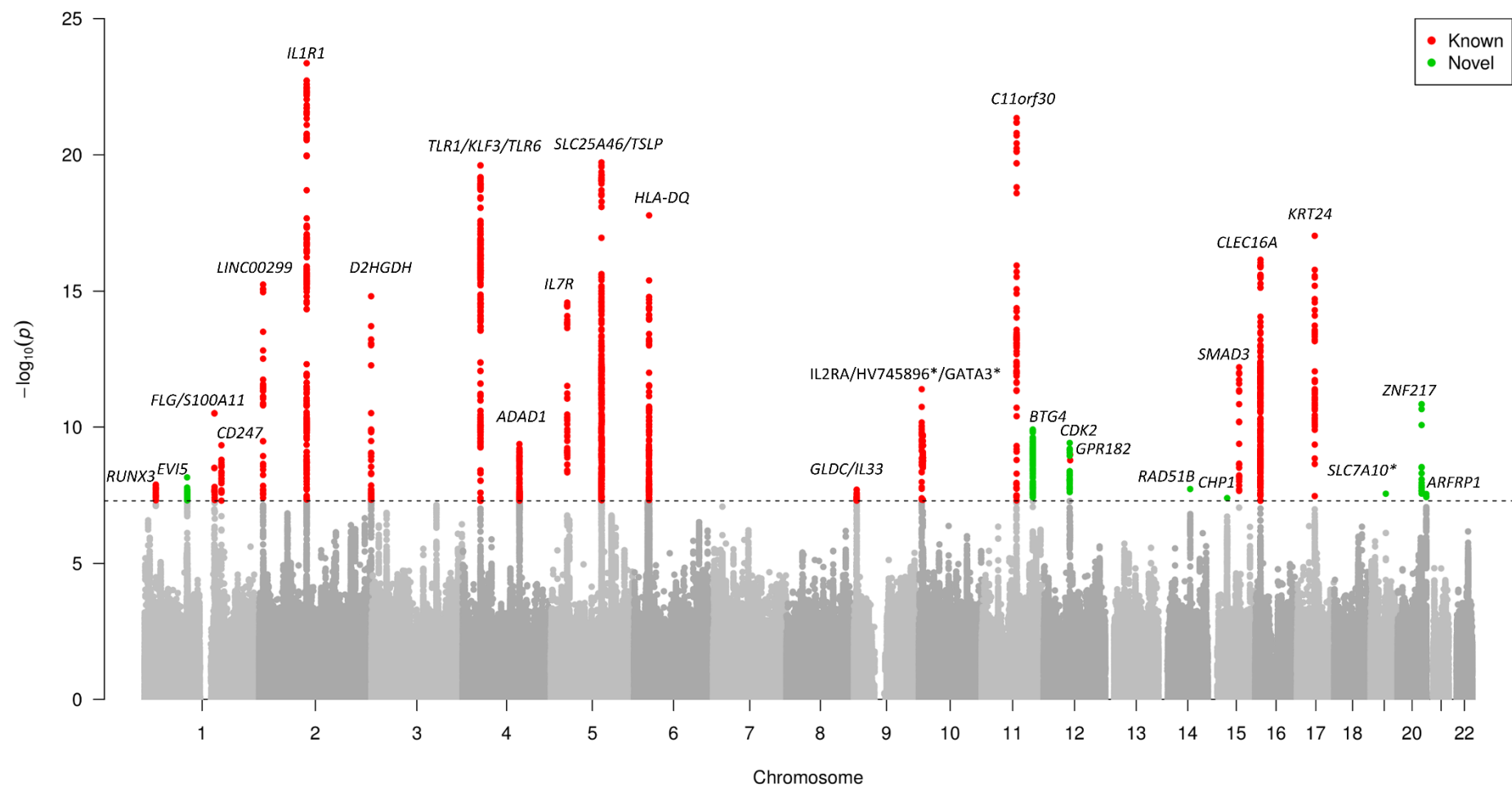
Sample size for allergic diseases is 102,453.

Supplementary Figure 3. Manhattan plot of asthma GWAS in UK Biobank



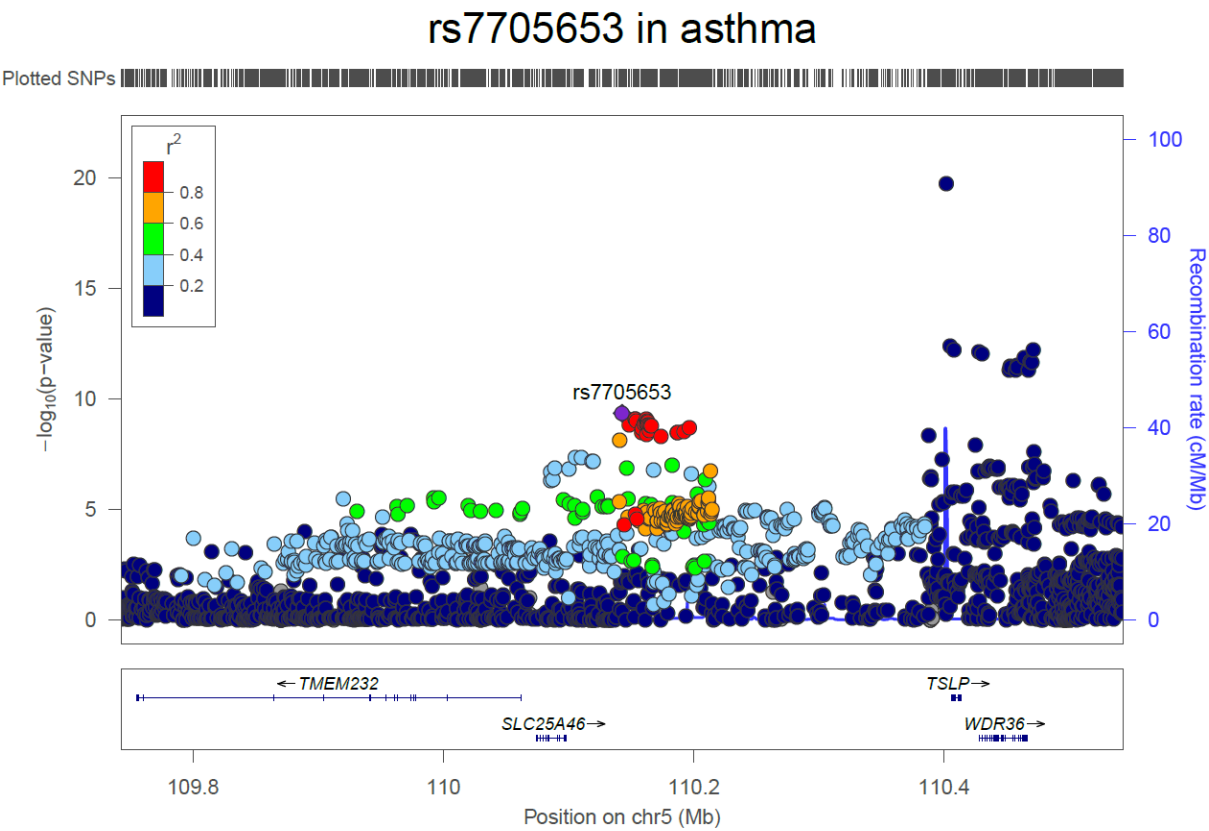
Sample size for asthma is 90,853.

Supplementary Figure 4. Manhattan plot of allergic diseases GWAS in UK Biobank

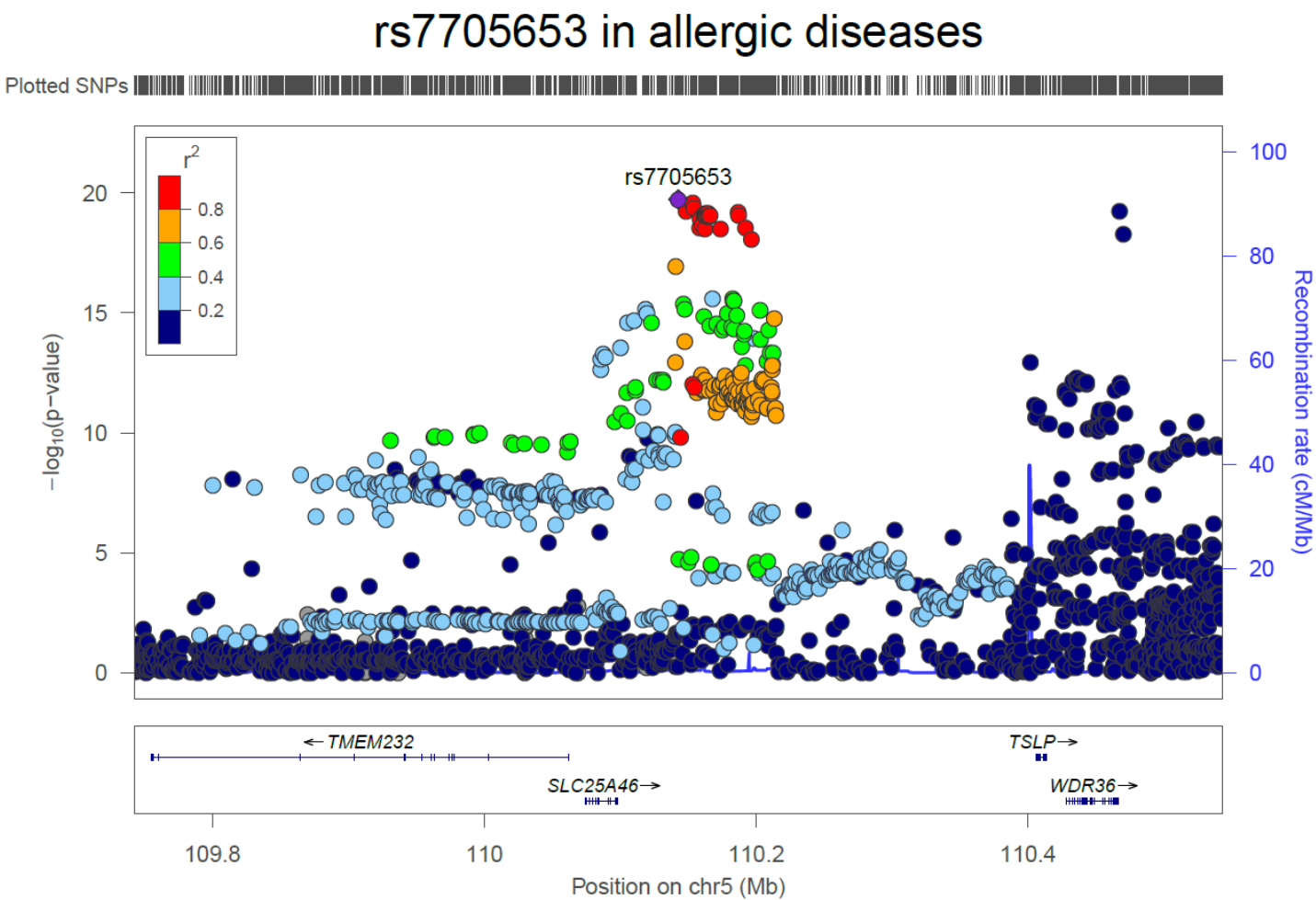


Sample size for allergic diseases is 102,453.

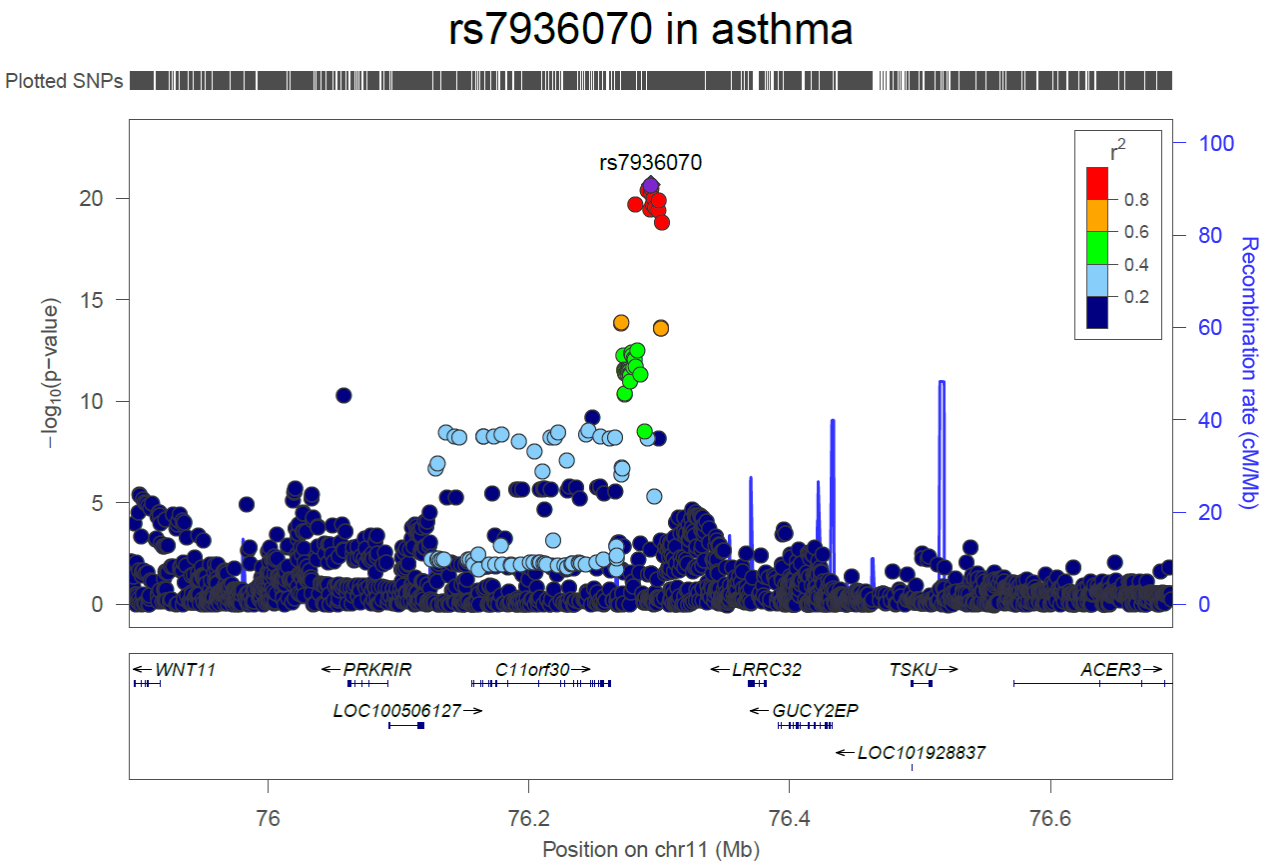
Supplementary Figure 5. Regional plot of rs7705653 (*TMEM232*) in asthma



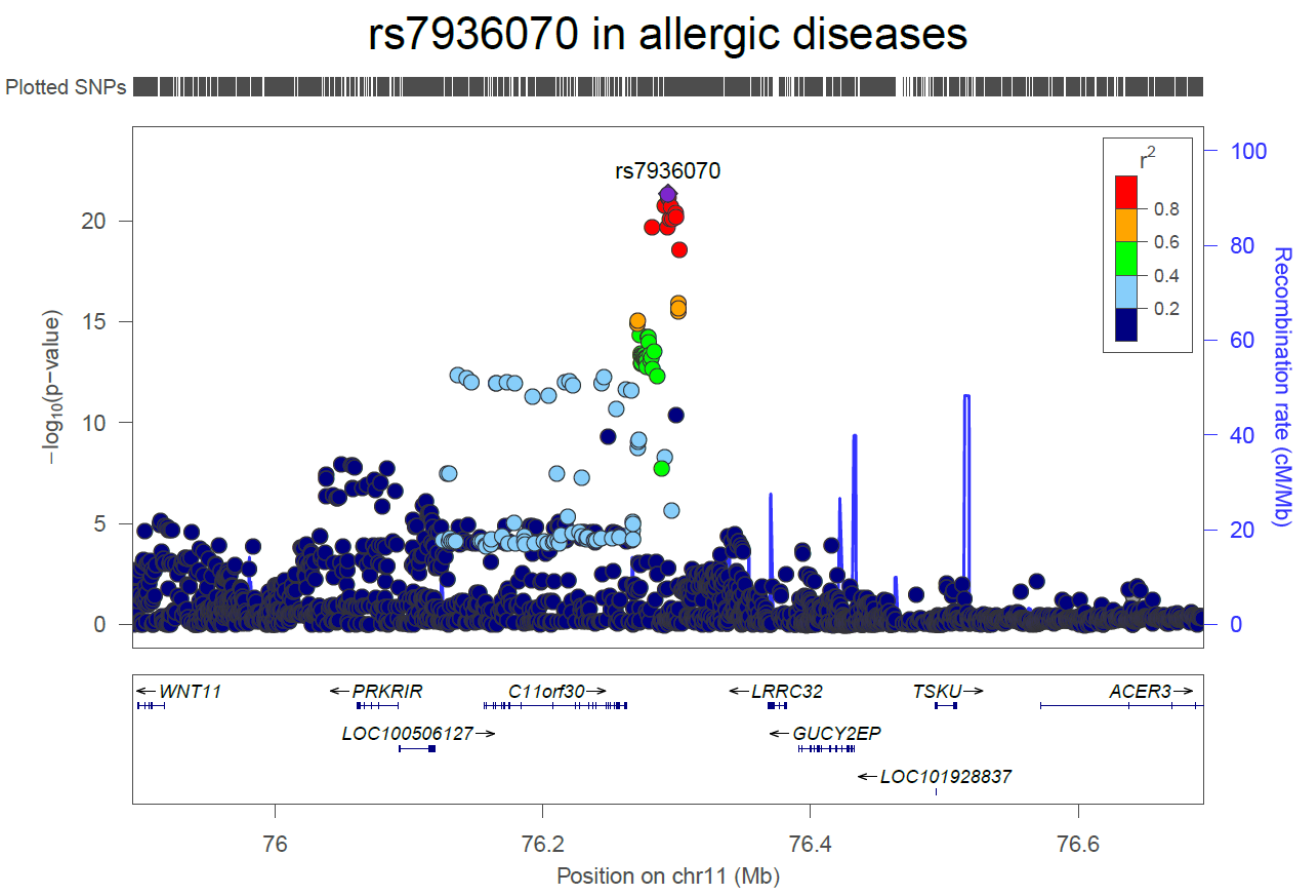
Supplementary Figure 6. Regional plot of rs7705653 (*TMEM232*) in allergic diseases



Supplementary Figure 7. Regional plot of rs7936070 (*C11orf30*) in asthma

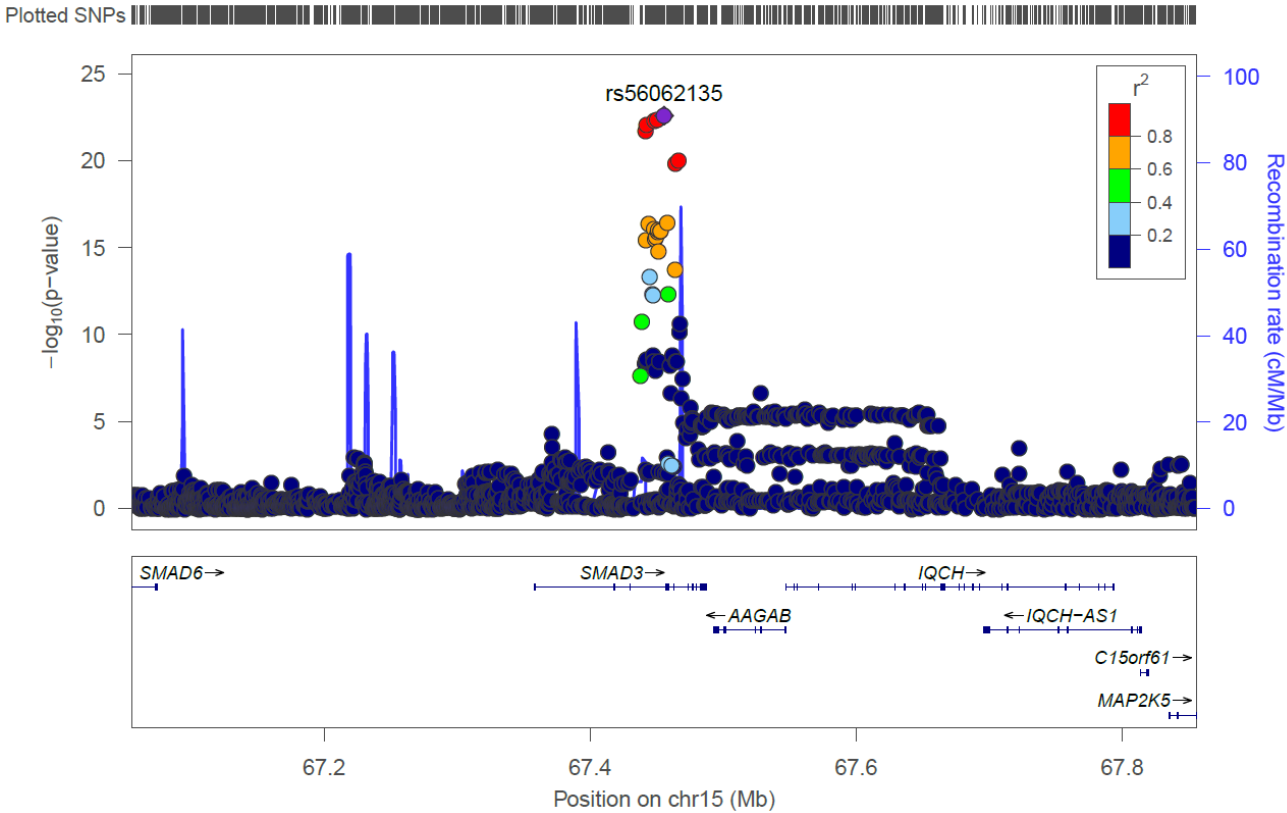


Supplementary Figure 8. Regional plot of rs7936070 (*C11orf30*) in allergic diseases

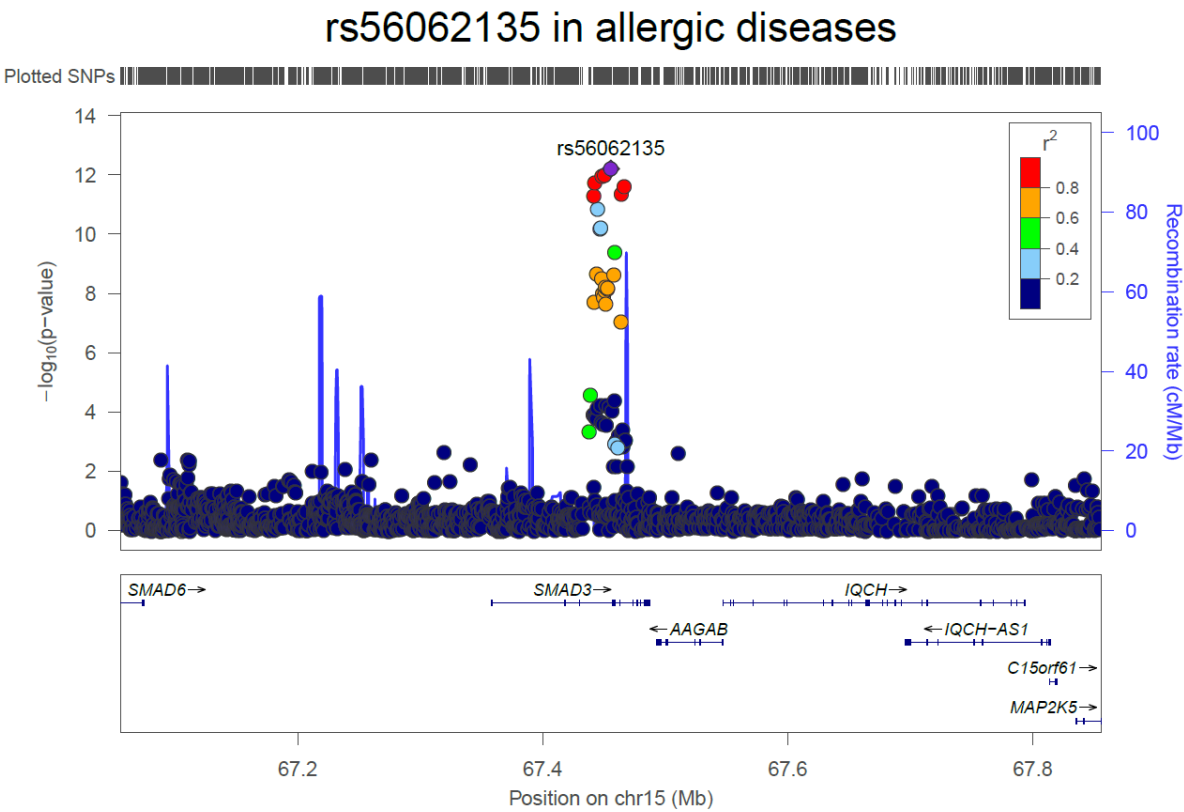


Supplementary Figure 9. Regional plot of rs56062135 (*SMAD3*) in asthma

rs56062135 in asthma

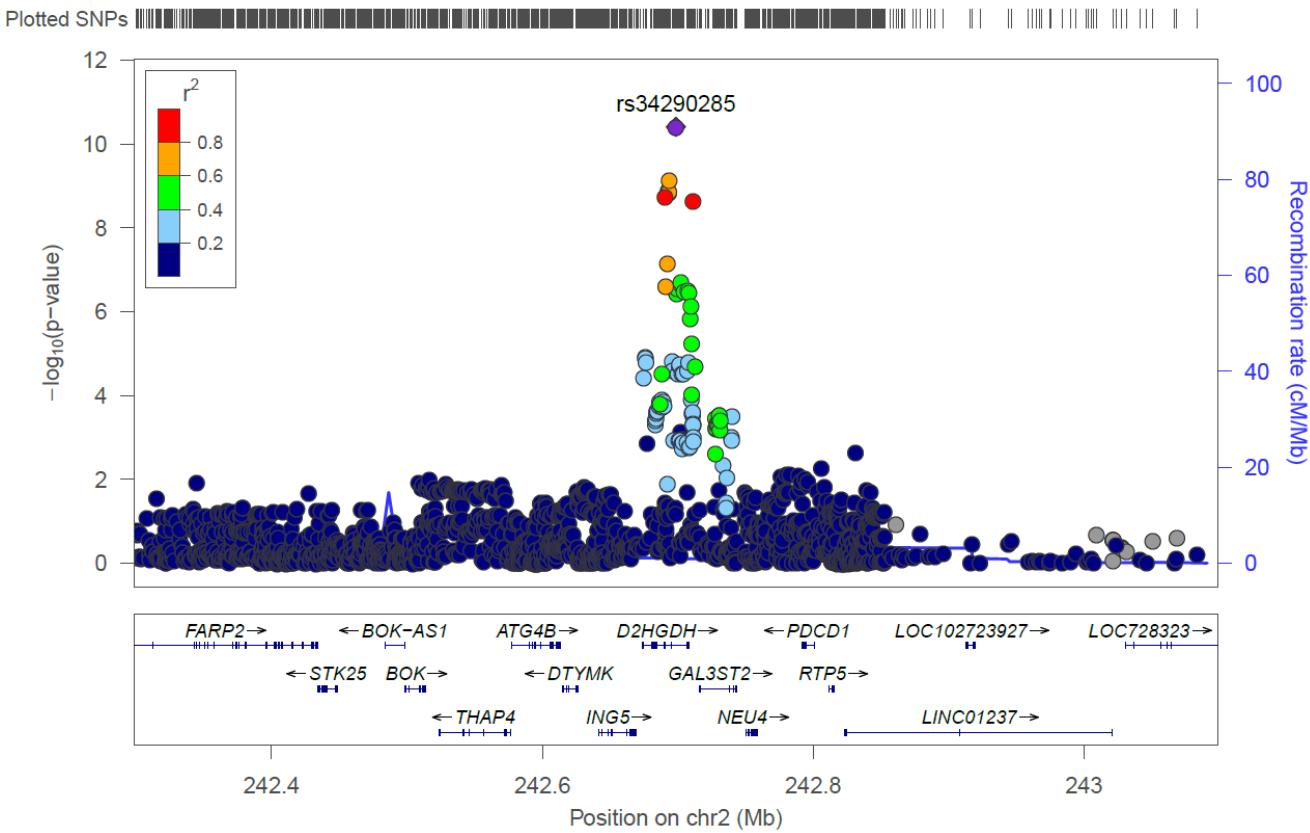


Supplementary Figure 10. Regional plot of rs56062135 (*SMAD3*) in allergic diseases

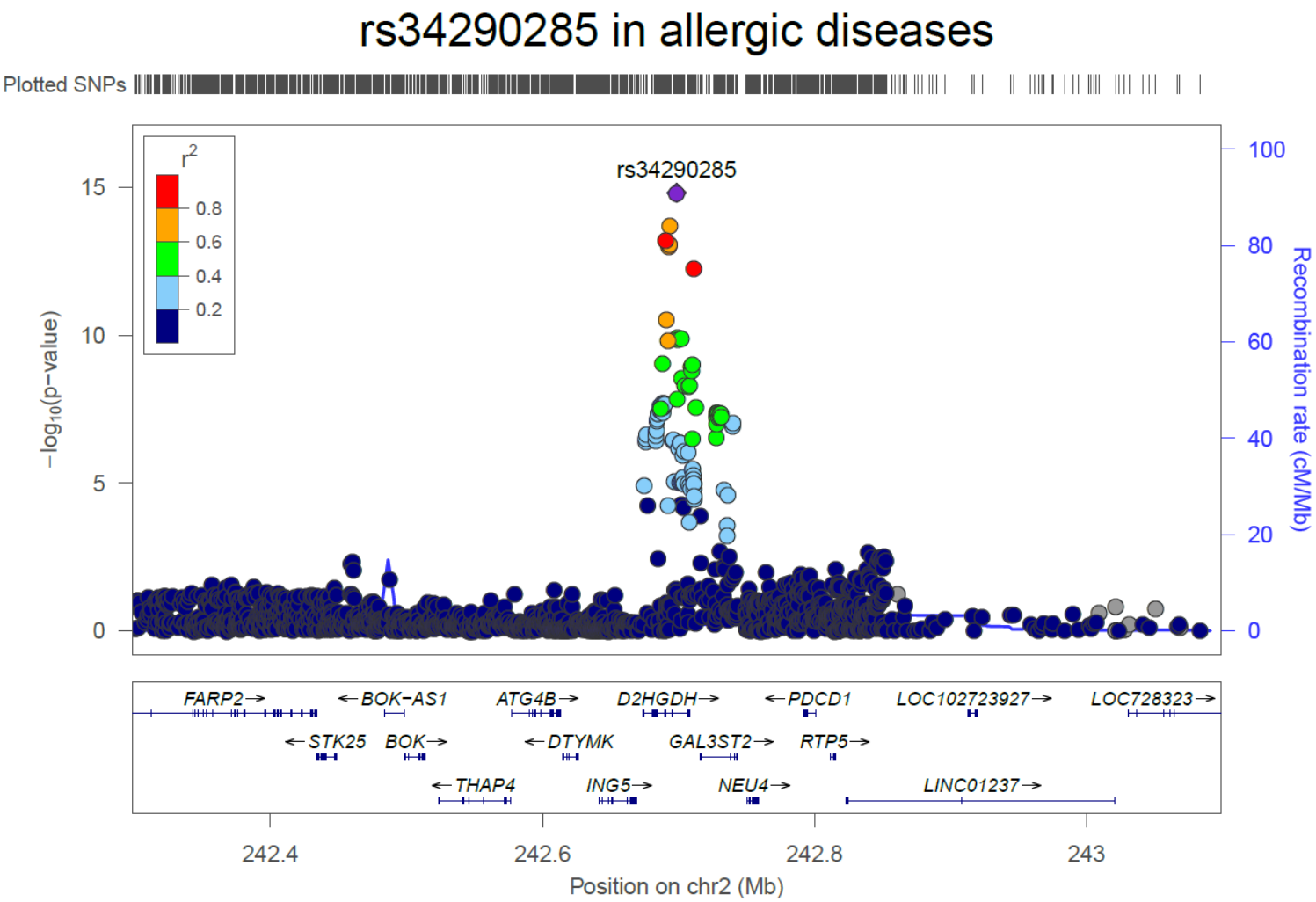


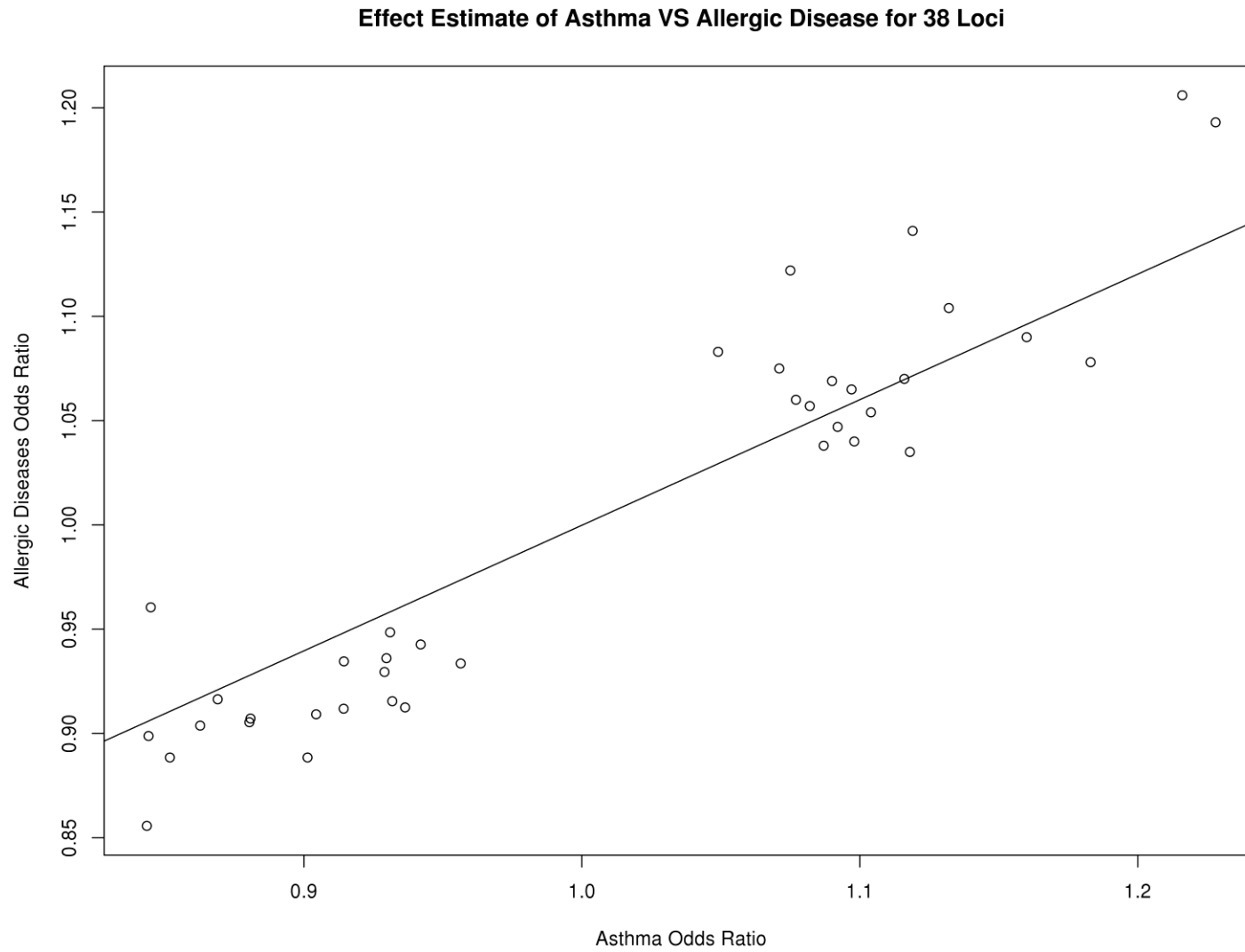
Supplementary Figure 11. Regional plot of rs34290285 (*D2HGDH*) in asthma

rs34290285 in asthma

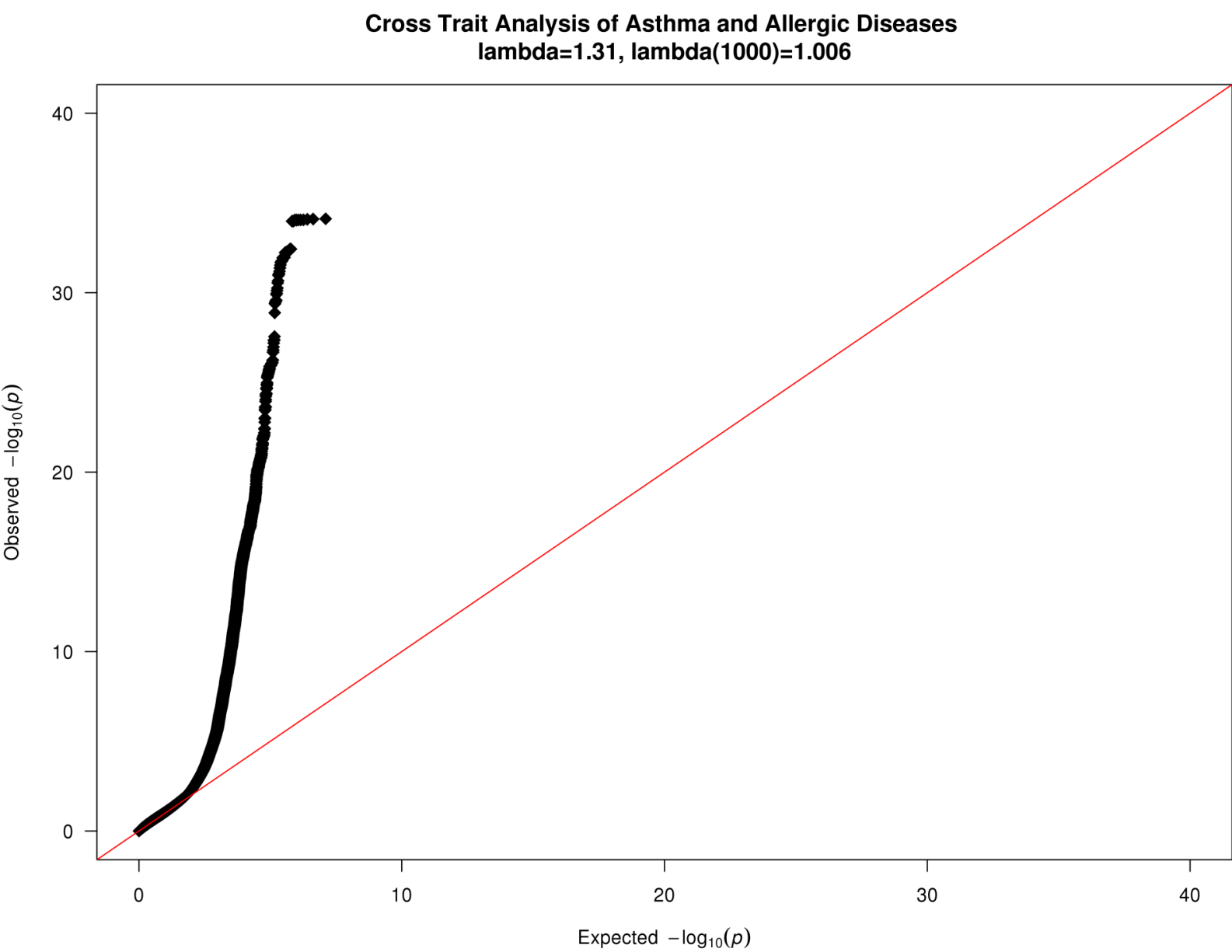


Supplementary Figure 12. Regional plot of rs34290285 (*D2HGDH*) in allergic diseases



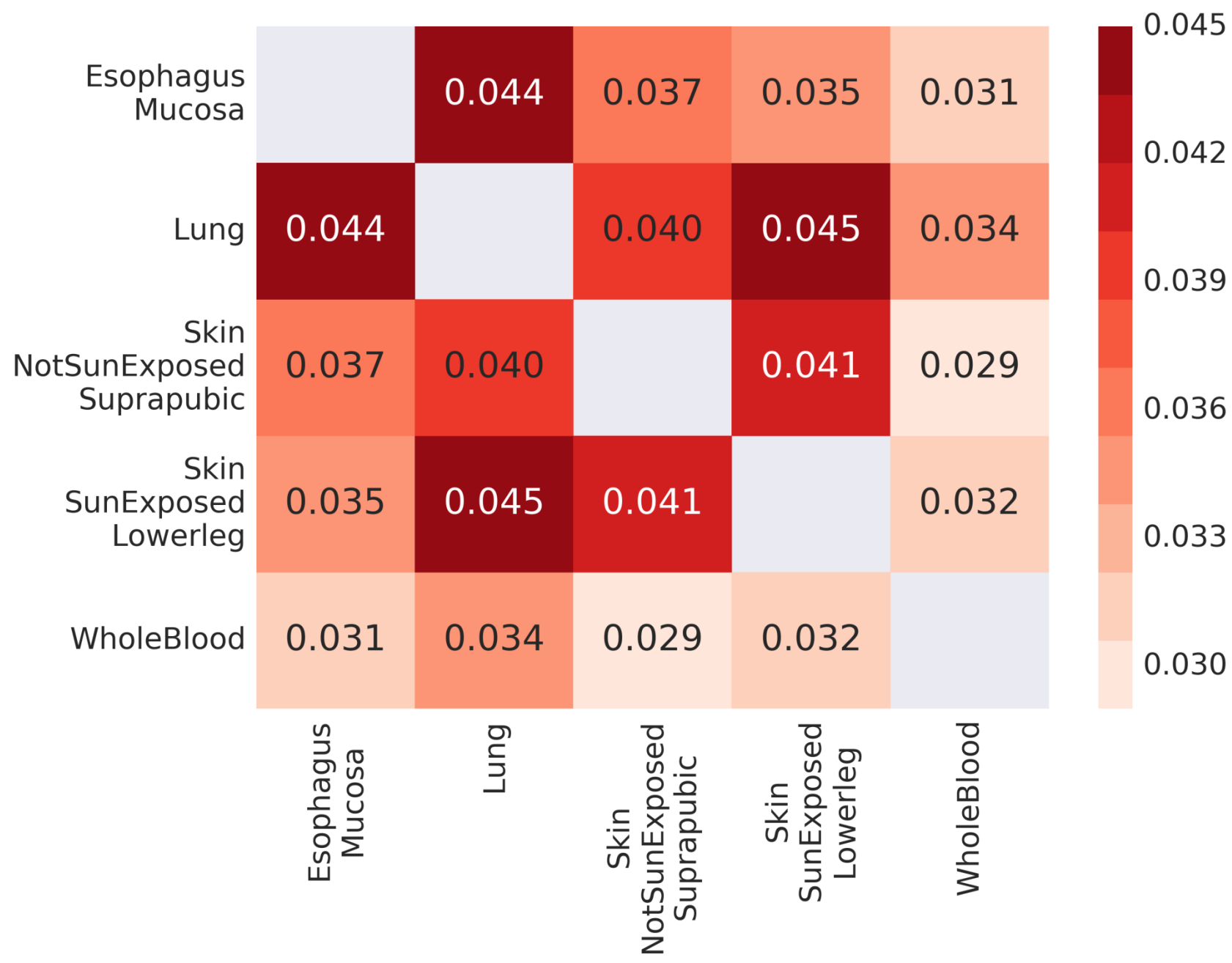


Supplementary Figure 14. QQ plot of cross trait meta-analysis in UK Biobank

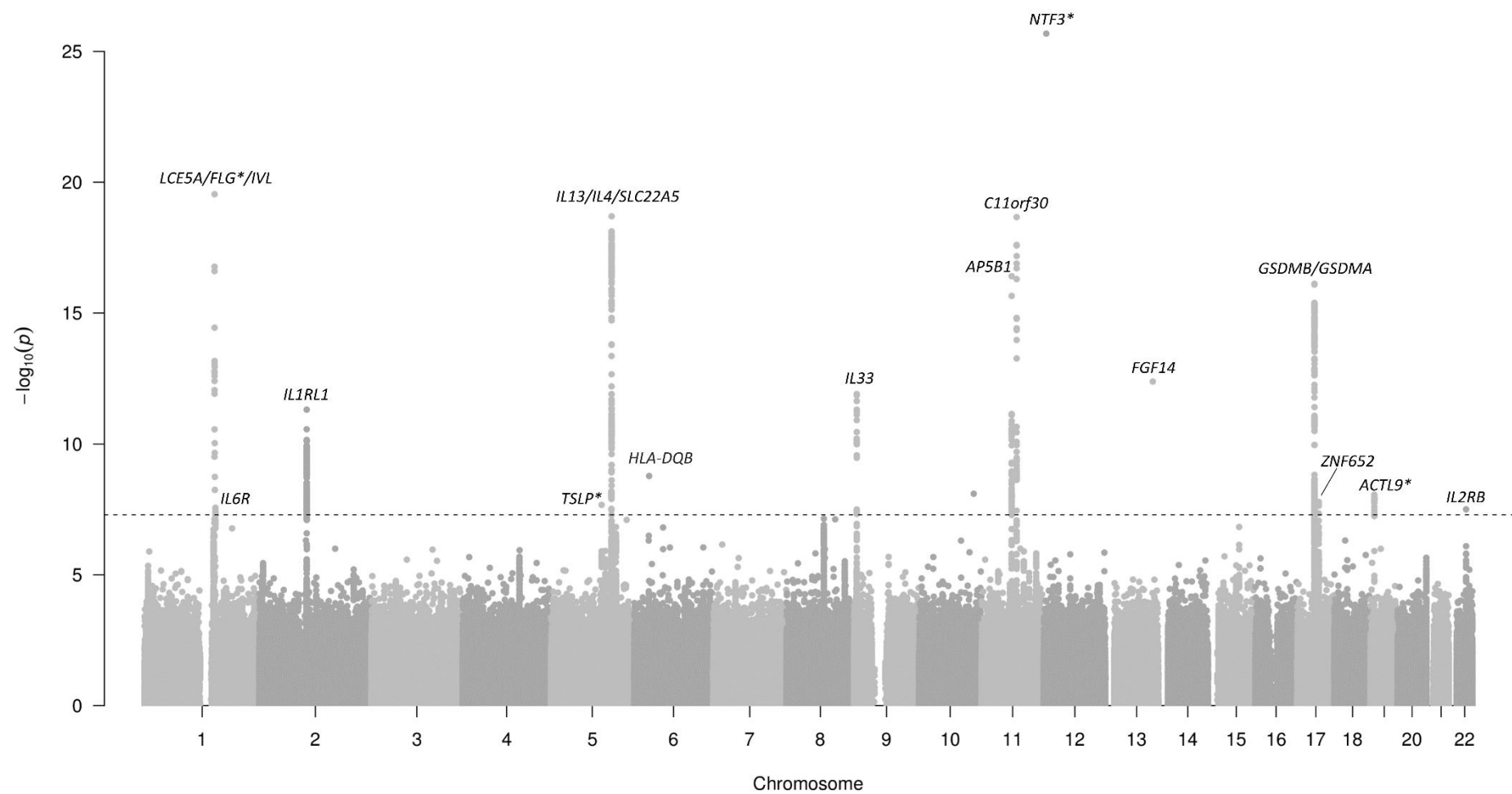


Sample size for asthma is 90,853, and for allergic diseases is 102,453.

Supplementary Figure 15. Average cross-tissue SNP-heritability ($h^2_{g1g2,cis}$) of gene expression for asthma and allergic diseases genes identified in meta-analysis shown for relevant tissues

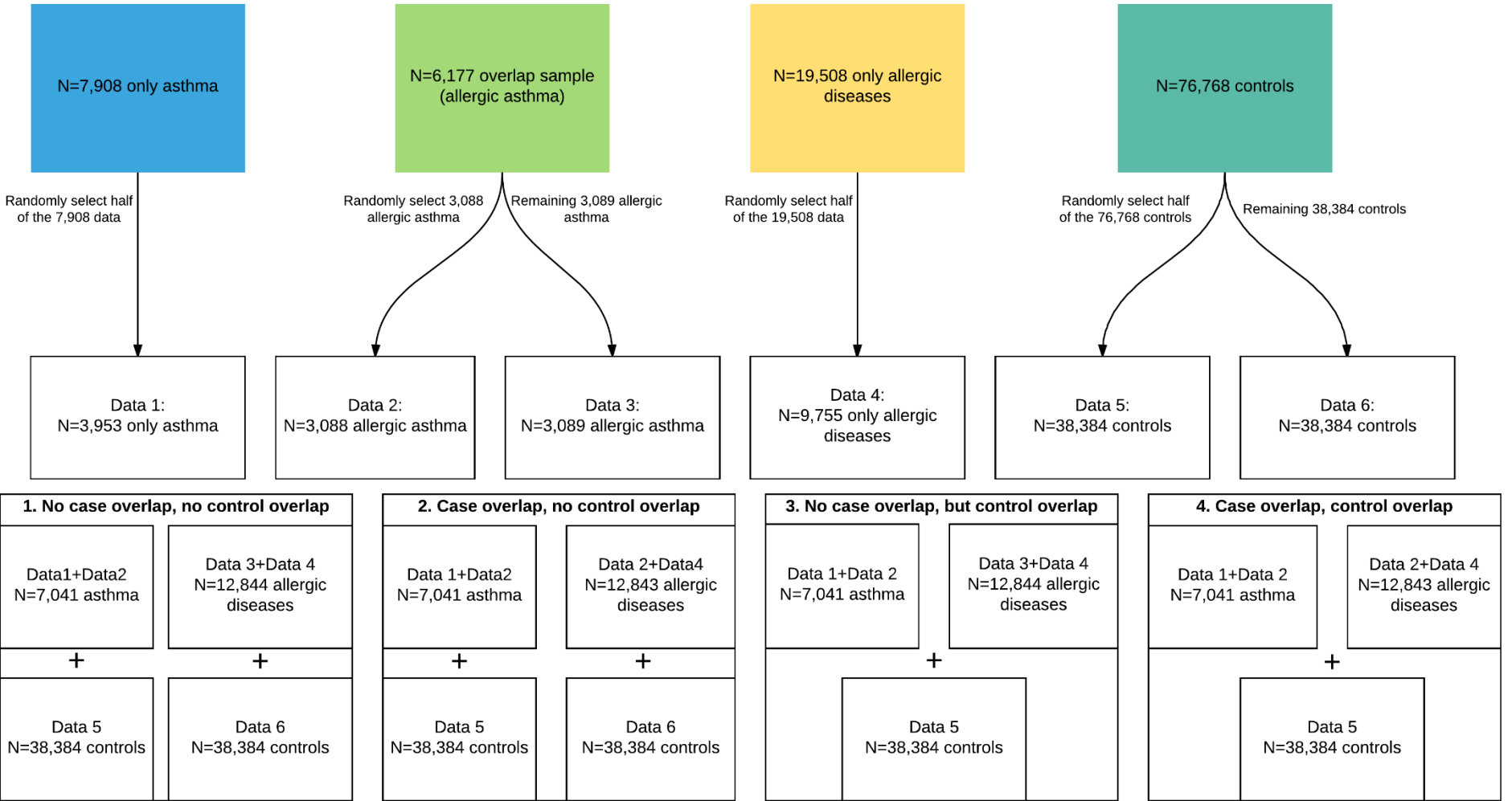


Supplementary Figure 16. Manhattan plot of cross trait meta-analysis in replication

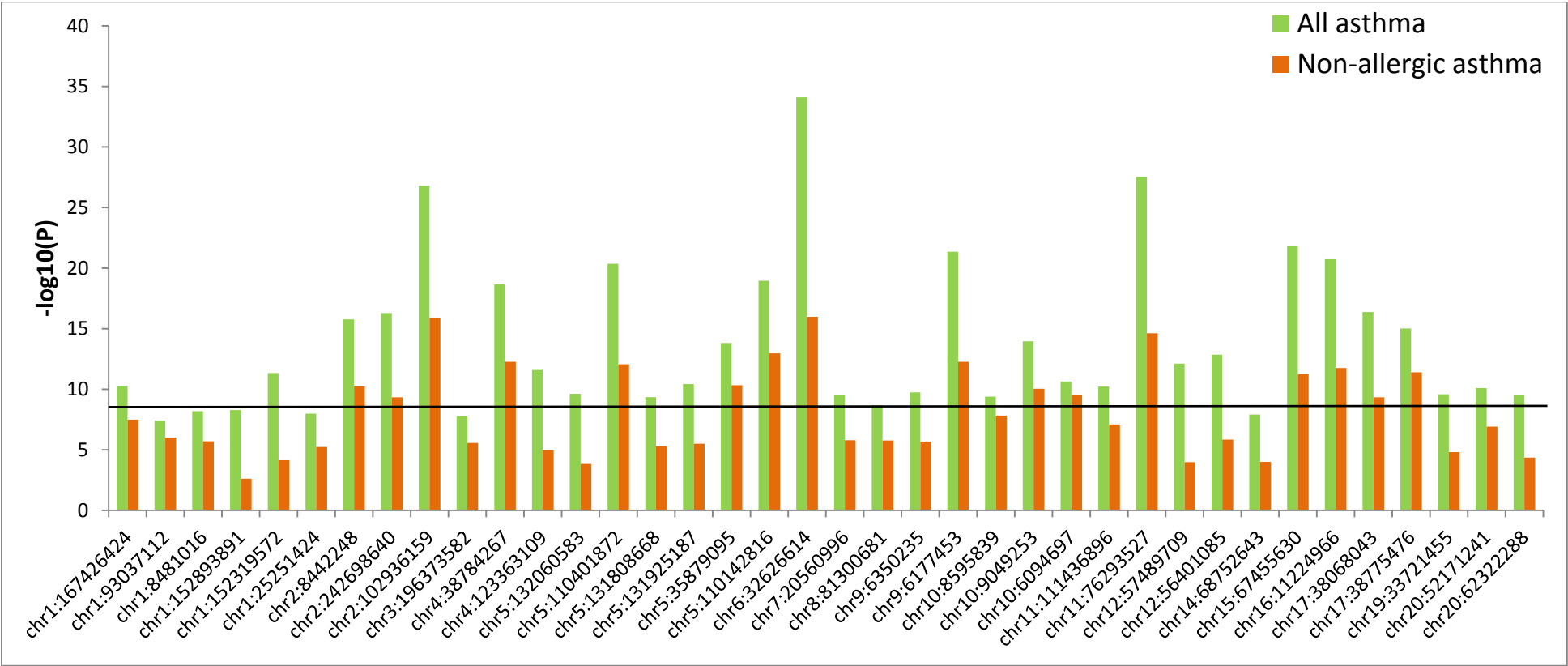


Sample size for asthma (GABRIEL) is 26,475, and for eczema (EAGLE) is 54,632.

Supplementary Figure 17. Sensitivity analysis design of 4 scenarios for non-overlap and overlap sample settings in UK Biobank cohort



Supplementary Figure 18. Comparing of $-\log_{10}(P)$ value in sensitivity analysis of excluding asthma and allergic diseases overlapped subjects (allergic asthma, $n = 6,177$) for top 38 shared loci between two traits



Supplementary Figure 19. Comparing of effect size (Beta) in sensitivity analysis of excluding asthma and allergic diseases overlapped subjects (allergic asthma, $n = 6,177$) for top 38 shared loci between two traits



Supplementary Table 1. Genetic correlation between asthma and allergy in different functional categories

Functional Category	Phenotype 1	Phenotype 2	R _g	SE	P
DNaseI Digital Genomic Footprinting	Asthma	Allergic diseases	0.7727	0.0353	2.09E-106
DNase I hypersensitivity Site	Asthma	Allergic diseases	0.7711	0.036	8.27E-102
Fetal DNase I Hypersensitivity Site	Asthma	Allergic diseases	0.7985	0.0376	2.46E-100
H3K27ac	Asthma	Allergic diseases	0.7701	0.0626	8.87E-35
H3K4me1	Asthma	Allergic diseases	0.7722	0.0353	7.72E-106
H3K4me3	Asthma	Allergic diseases	0.7901	0.0408	1.78E-83
H3K9ac	Asthma	Allergic diseases	0.8052	0.047	1.10E-65
Intron	Asthma	Allergic diseases	0.827	0.0699	2.90E-32
Repressed Regions	Asthma	Allergic diseases	0.3722	0.3066	0.2247
Super Enhancers	Asthma	Allergic diseases	0.8237	0.0462	3.90E-71
Transcription Factor Binding Sites	Asthma	Allergic diseases	0.7792	0.0375	4.11E-96
Transcribed Regions	Asthma	Allergic diseases	0.77	0.0456	4.25E-64

Partitioned LD score regression was used. Sample size for asthma is 90,853, for allergic diseases is 102,453.

Supplementary Table 2. SNP based heritability estimated by LDSC

Phenotype	Heritability (h ²)	Heritability SE
Asthma	0.0719	0.0074
Allergic diseases	0.0747	0.0071
Rheumatoid arthritis	0.1438	0.0293
Crohn's disease	0.103	0.0147
Ulcerative colitis	0.0644	0.01
Asthma (GABRIEL)	0.111	0.0213
Eczema (EAGLE)	0.0126	0.0045

Sample size for asthma is 90,853, for allergic diseases is 102,453, for rheumatoid arthritis is 58,284, for Crohn's disease is 69,268, for ulcerative colitis is 72,647, for asthma (GABRIEL) is 26,475, and for eczema (EAGLE) is 54,632.

Supplementary Table 3. UK Biobank asthma GWAS result.

SNP	<i>P</i>	<i>n</i>	Genome Position	kb span of clumped SNPs	Peak SNP position	Ref allele	Alt allele	OR (95% CI)	INFO	Report status	Genes within clumping range
rs6600246	5.04E-09	25	chr1:25226208..25305261	79.054	25299426	T	C	0.89 (0.86-0.93)	0.995649	Known	MIR6731,RUNX3
rs12123821	1.00E-09	7	chr1:151908055..152600854	692.8	152179152	T	C	1.19 (1.13-1.26)	1	Known	CRCT1,CRNN,FLG,FLG-AS1,FLG2,HRNR,LCE3A,LCE3B,LCE3C,LCE3D,LCE3E,LCE5A,NBPF18P,RP-TN,S100A10,S100A11,TCHHL1
rs2056626	8.80E-09	27	chr1:167405418..167436300	30.883	167420425	G	T	0.93 (0.9-0.95)	1	Known	CD247
rs891058	4.64E-10	46	chr2:8438693..8488143	49.451	8442547	A	G	0.91 (0.89-0.94)	0.988479	New	LINC00299
rs13020553	8.57E-18	155	chr2:102852802..103092503	239.702	102931826	G	C	1.12 (1.09-1.15)	0.995965	Known	IL1RL1,IL1RL2,IL18R1,IL18RAP,MIR4772,SLC9A4
rs34290285	3.89E-11	20	chr2:242690675..242711282	20.608	242698640	A	G	0.9 (0.88-0.93)	0.988732	Known	D2HGDH
rs115913567	1.89E-08	1	chr3:23653570..23653570	0.001	23653570	G	C	0.81 (0.75-0.87)	1	New	Intergenic,UBE2E2*
rs60946162	1.57E-08	35	chr3:188077586..188133336	55.751	188133336	T	C	1.08 (1.05-1.11)	0.968771	Known	LPP
rs28393318	2.61E-10	164	chr4:38736550..38906951	170.402	38784267	G	A	0.9 (0.87-0.93)	0.99633	Known	FAM114A1,MIR574,TLR1,TLR6,TLR10
rs4380538	1.61E-10	161	chr4:123024769..123502008	477.24	123448562	T	C	1.09 (1.06-1.12)	0.994943	Known	ADAD1,IL2,KIAA1109
rs7705653	4.58E-10	85	chr5:109920159..110304800	384.642	110142816	G	A	1.12 (1.08-1.16)	0.982238	Known	SLC25A46,TMEM232
rs1837253	1.81E-20	1	chr5:110401872..110401872	0.001	110401872	T	C	0.87 (0.84-0.9)	1	Known	Intergenic, TSLP*
rs2706362	1.27E-11	95	chr5:131881605..131996669	115.065	131925187	C	T	1.12 (1.08-1.15)	0.992934	Known	IL13,RAD50
rs9273374	1.31E-35	65	chr6:32522576..32804570	281.995	32626614	A	G	0.84 (0.82-0.87)	0.992338	Known	HLA-DOB,HLA-DQA1,HLA-DQA2,HLA-DQB1,HLA-DQB2,HLA-DRB1,HLA-DRB6,TAP2
rs6461503	2.13E-09	101	chr7:20501204..20628847	127.644	20560996	T	C	1.08 (1.05-1.11)	0.990695	New	Intergenic,ITGB8*
rs2136016	3.72E-10	101	chr8:81246659..81315490	68.832	81300681	G	A	1.09 (1.06-1.12)	0.99243	Known	Intergenic, ZBTB10*
rs343495	2.31E-12	146	chr9:6047765..6142948	95.184	6069445	C	T	0.89 (0.86-0.92)	0.993043	Known	Intergenic, IL33,RANBP6*
rs9775039	7.41E-23	113	chr9:6086913..6535500	448.588	6177453	A	G	1.18 (1.14-1.22)	0.989356	Known	GLDC,IL33,TPD52L3,UHRF2
rs12413578	3.27E-14	24	chr10:9043457..9153428	109.972	9049253	T	C	0.84 (0.81-0.88)	1	New	Intergenic,HV745896*

rs7936070	2.17E-21	78	chr11:76019014..76302073	283.06	76293527	T	G	1.13 (1.1-1.16)	0.997647	Known	C11orf30,LOC100506127,PRKRIR
rs10876864	1.43E-12	58	chr12:56364321..56518408	154.088	56401085	G	A	1.1 (1.07-1.13)	1	Known	CDK2,ERBB3,IKZF4,PA2G4,RAB5B,RPL41,RPS26,SUOX,ZC3H10
rs1059513	1.18E-11	10	chr12:57331370..57510785	179.416	57489709	C	T	0.86 (0.83-0.9)	1	Known	GPR182,MYO1A,NAB2,RDH16,STAT6,TAC3,TMEM194A,ZBTB39
rs167769	6.04E-09	22	chr12:57489828..57525756	35.929	57503775	T	C	1.08 (1.05-1.11)	1	Known	LRP1,STAT6
rs1319132	1.74E-08	64	chr13:99836033..100040979	204.947	99999601	G	C	0.92 (0.89-0.95)	0.990886	New	FKSG29,GPR18,GPR183,MIR548AN,MIR623,UBAC2,UBAC2-AS1
rs56062135	2.62E-23	25	chr15:67437863..67466599	28.737	67455630	T	C	1.16 (1.13-1.19)	0.995546	Known	SMAD3
rs36045143	9.05E-17	179	chr16:11031741..11267441	235.701	11224966	G	A	0.88 (0.85-0.91)	1	Known	CLEC16A,DEXI
rs3024655	4.89E-08	8	chr16:27369502..27386761	17.26	27369502	A	G	0.85 (0.81-0.91)	0.987019	Known	IL4R
rs146644295	9.43E-09	1	chr17:37574592..37574592	0.001	37574592	C	G	1.32 (1.2-1.45)	0.895391	Known	MED1
rs869402	7.02E-18	268	chr17:37810218..38215117	404.9	38068043	C	T	1.12 (1.09-1.15)	0.998675	Known	CSF3,ERBB2,GRB7,GSDMA,GSDMB,IKZF3,LRR3C,MED24,MIEN1,MIR4728,MIR6884,ORMDL3,PGAP3,PNMT,PSMD3,SNORD124,STARD3,TCAP,ZBP2
rs11658582	1.94E-08	60	chr17:38754800..38875684	120.885	38763200	C	G	0.93 (0.9-0.95)	0.991065	Known	KRT24,KRT222,SMARCE1
rs10414065	6.78E-09	4	chr19:33721455..33726578	5.124	33721455	T	C	0.85 (0.81-0.9)	0.983709	New	Intergenic,SLC7A10*
rs1623866	4.04E-09	116	chr20:62270637..62373079	102.443	62333022	A	G	0.91 (0.89-0.94)	0.994229	Known	ARFRP1,LIME1,RTEL1,RTEL1-TNFRSF6B,SLC2A4RG,STMN3,TNFRSF6B,ZGPAT

*No genes were found to be mapped by this loci, thus nearest gene within 500 kb were used

n, number of SNPs clumped with peak SNP; INFO, imputation quality score

Supplementary Table 4. UK Biobank allergic diseases GWAS result.

SNP	<i>P</i>	<i>n</i>	Genome position	kb span of clumped SNPs	Peak SNP position	Ref allele	Alt allele	OR (95% CI)	INFO	Report status	Genes within clumping range
rs12743520	6.87E-09	124	chr1:92941357..93320869	379.513	93037112	A	C	0.93 (0.91-0.96)	0.991654	New	EVI5,FAM69A,GFI1,RPL5,SNORA66,SNORD21
rs742230	1.27E-08	19	chr1:25249252..25262022	12.771	25251424	G	A	0.94 (0.92-0.96)	0.994418	Known	RUNX3
rs115288876	2.25E-08	2	chr1:152000117..152074116	74	152000117	A	G	1.15 (1.09-1.21)	1	Known	S100A11,TCHHL1
rs1214598	4.54E-10	33	chr1:167408670..167437953	29.284	167426424	A	G	0.94 (0.92-0.96)	0.990872	Known	CD247
rs61816766	3.07E-11	10	chr1:151976836..152729815	752.98	152319572	C	T	1.21 (1.14-1.28)	0.922487	Known	C1orf68,CRCT1,CRNN,FLG,FLG-AS1,FLG2,HRNR,LCE2A,LCE2B,LCE2C,LCE2D,LCE3A,LCE3B,LCE3C,LCE3D,LCE3E,LCE4A,LCE5A,NBPF18P,RP-TN,S100A11,TCHH,TCHHL1
rs34290285	1.54E-15	80	chr2:242676142..242740090	63.949	242698640	A	G	0.91 (0.89-0.93)	0.988732	Known	D2HGDH,GAL3ST2
rs10174949	5.72E-16	61	chr2:8438693..8488143	49.451	8442248	A	G	0.91 (0.89-0.93)	0.987595	Known	LINC00299
rs72823641	4.27E-24	149	chr2:102734551..103277862	543.312	102936159	A	T	0.86 (0.83-0.88)	0.993969	Known	IL1R1,IL1RL1,IL1RL2,IL18R1,IL18RAP,MIR4772,SLC9A2,SLC9A4
rs10008032	2.47E-10	5	chr4:38698924..38745482	46.559	38745482	C	T	0.94 (0.92-0.96)	0.985341	Known	KLF3
rs148906978	1.25E-16	1	chr4:38854369..38854369	0.001	38854369	T	C	0.89 (0.87-0.92)	0.997316	Known	TLR6
rs45605540	4.11E-10	64	chr4:123026869..123502008	475.14	123141054	C	T	1.07 (1.05-1.1)	0.998116	Known	ADAD1,IL2,KIAA1109
rs4833093	6.58E-20	197	chr4:38708403..38906951	198.549	38789740	T	G	0.89 (0.86-0.91)	0.991291	Known	FAM114A1,MIR574,TLR1,TLR6,TLR10
rs1438673	5.42E-20	170	chr5:110404999..110606055	201.057	110467499	T	C	0.91 (0.89-0.93)	0.995082	Known	CAMK4,TSLP,WD R36
rs6881270	2.61E-15	88	chr5:35803577..36029754	226.178	35879095	T	C	0.91 (0.89-0.93)	0.998096	Known	CAPSL,IL7R,LOC100506406,SPEF2,UGT3A1
rs7705653	1.88E-20	333	chr5:109800443..110263457	463.015	110142816	G	A	1.14 (1.11-1.17)	0.982238	Known	SLC25A46,TMEM232
rs146668528	5.01E-12	24	chr6:32587425..32626007	38.583	32598028	T	C	0.84 (0.8-0.89)	0.982018	Known	HLA-DQA1

rs12339348	1.96E-08	71	chr9:6172380..6535500	363.121	6233082	T	A	1.07 (1.05-1.1)	0.981758	Known	GLDC,IL33,TPD52L3,UHRF2
rs76962799	4.41E-08	7	chr9:5936490..6336033	399.544	6187132	A	C	1.15 (1.09-1.21)	1	Known	IL33,KIAA2026,MIR4665,RANBP6,TPD52L3
rs12413578	4.63E-10	3	chr10:9043457..9049253	5.797	9049253	T	C	0.9 (0.87-0.93)	1	Known	Intergenic, HV745896*
rs1409123	1.93E-10	40	chr10:8558388..8605553	47.166	8582317	A	T	0.94 (0.92-0.96)	0.992659	Known	Intergenic, GATA3*
rs61839660	3.98E-12	48	chr10:6061479..6185344	123.866	6094697	T	C	1.12 (1.09-1.16)	1	Known	IL2RA,RBM17
rs659529	1.20E-10	172	chr11:111366844..111647084	280.241	111436896	T	A	0.93 (0.91-0.95)	0.995178	New	BTG4,C11orf88,LAYN,MIR34B,MIR34C,PPP2R1B,SIK2
rs7936070	4.40E-22	79	chr11:76136482..76302073	165.592	76293527	T	G	1.1 (1.08-1.13)	0.997647	Known	C11orf30
rs11171739	3.73E-10	61	chr12:56364321..56518408	154.088	56470625	C	T	1.07 (1.04-1.09)	1	New	CDK2,ERBB3,IKZF4,PA2G4,RAB5B,RPL41,RPS26,SUOX,ZC3H10
rs3024971	1.01E-09	13	chr12:57331370..57493727	162.358	57493727	G	T	0.9 (0.87-0.93)	0.987576	Known	GPR182,MYO1A,NAB2,RDH16,STAT6,TAC3,TMEM194A,ZBTB39
rs56267624	1.84E-08	1	chr14:68662359..68662359	0.001	68662359	T	C	1.14 (1.09-1.2)	0.944026	New	RAD51B
rs8043253	3.96E-08	105	chr15:41255153..41774423	519.271	41503730	T	C	1.06 (1.04-1.08)	0.9953	New	CHP1,EXD1,INO80,NDUFAF1,NUSAP1,OIP5,OIP5-AS1,RTF1
rs56062135	6.23E-13	23	chr15:67441750..67466599	24.85	67455630	T	C	1.09 (1.06-1.12)	0.995546	Known	SMAD3
rs11645657	7.03E-17	141	chr16:11034959..11300216	265.258	11223454	C	G	1.09 (1.07-1.11)	0.989093	Known	CLEC16A,DEXI
rs9911533	1.65E-16	117	chr17:38729588..38876409	146.822	38775476	C	T	0.92 (0.9-0.94)	0.997149	Known	KRT24,KRT222,SMARCE1
rs10414065	2.74E-08	5	chr19:33721455..33726578	5.124	33721455	T	C	0.89 (0.85-0.93)	0.983709	New	Intergenic, SLC7A10*
rs2766664	1.41E-11	19	chr20:52167836..52186784	18.949	52171241	A	G	1.08 (1.06-1.11)	0.989024	New	LOC101927770,ZNF217
rs3208007	2.81E-08	93	chr20:62260636..62400021	139.386	62322288	T	C	0.93 (0.91-0.96)	0.985259	New	ARFRP1,LIME1,RTTEL1,RTEL1-TNFRSF6B,SLC2A4RG,STMN3,TNFRSF6B,ZBTB46,ZGPAT

*No genes were found to be mapped by this loci, thus nearest gene within 500 kb were used

n, number of SNPs clumped with peak SNP; INFO, imputation quality score

Supplementary Table 5. Genome-wide significant loci identified in replication analysis

SNP	CHR	Genomic position	kb	<i>n</i>	<i>P</i>	Genes within clumping region
rs4845779	1	chr1:152388138..152530510	142.373	12	2.85E-20	CRCT1,LCE5A
rs6700998	1	chr1:152393263..152434009	40.747	5	1.67E-17	Intergenic region, LCE5A, CRNN, FLG*
rs12565568	1	chr1:152823380..153070024	246.645	5	1.10E-13	IVL,SMCP,SPRR1A,SPRR1B,SPRR2A,SPRR2B,SPRR2D,SPRR2E,SPRR3,SPRR4
rs4129267	1	chr1:154395212..154428283	33.072	27	2.70E-08	IL6R
rs10208293	2	chr2:102858490..103091618	233.129	213	4.82E-12	IL1RL1,IL18R1,IL18RAP,MIR4772,SLC9A4
rs6419573	2	chr2:102927726..103188785	261.06	95	1.43E-09	IL1RL1,IL18R1,IL18RAP,MIR4772,SLC9A4
rs1041973	2	chr2:102955468..103092584	137.117	4	2.13E-08	IL1RL1,IL18R1,IL18RAP,MIR4772,SLC9A4
rs12188917	5	chr5:131840082..132002125	162.044	121	1.98E-19	IL5,IL13,RAD50
rs11747814	5	chr5:132009154..132071212	62.059	78	2.33E-12	IL4,KIF3A
rs2073643	5	chr5:131336287..131833599	497.313	166	1.20E-09	ACSL6,C5orf56,CSF2,IL3,IRF1,LOC553103,MIR3936,MIR6830,P4HA2,P4HA2-AS1,PDLIM4,SLC22A4,SLC22A5
rs1837253	5	chr5:110401872..110401872	0.001	1	2.09E-08	Intergenic region, TSLP*
rs17843604	6	chr6: 32570839..32620283	49.444	2	1.65E-09	HLA-DQB
rs992969	9	chr9:6146121..6237547	91.427	50	1.22E-12	IL33
rs2212434	11	chr11:76136482..76302073	165.592	71	2.13E-19	C11orf30
rs479844	11	chr11:65401336..65562257	160.922	81	3.87E-17	AP5B1,KAT5,MIR4489,MIR4690,OVOL1,OVOL1-AS1,PCNXL3,RELA,RNASEH2C,SIPA1
rs4766366	12	chr12:5516442..5516442	0.001	1	2.08E-26	Intergenic region, NTF3*
rs491260	13	chr13:102746223.. 102746223	0.001	1	4.09E-13	FGF14
rs7216389	17	chr17:37770481..38215117	444.637	288	7.53E-17	CSF3,ERBB2,GRB7,GSDMA,GSDMB,IKZF3,LRR3C,MED24,MIEN1,MIR4728,MIR6884,ORMDL3,PGAP3,PNMT,PPP1R1B,PSMD3,SNORD124,STAR3,TCAP,ZBP2
rs12953014	17	chr17:47341580..47474529	132.95	65	1.63E-08	LOC102724596,MIR6129,ZNF652
rs3859189	17	chr17:38128765..38216933	88.169	87	4.62E-08	CSF3,GSDMA,MED24,MIR6884,PSMD3,SNORD124
rs2918299	19	chr19:8785744..8796160	10.417	22	8.61E-09	Intergenic region, ACTL9*
rs2284033	22	chr22:37531436..37537514	6.079	7	3.10E-08	IL2RB

*No genes were found to be mapped by this loci, thus nearest gene within 500 kb were used

CHR, chromosome; kb, kb span of the clump; *n*, number of SNPs clumped with peak SNP

Supplementary Table 6. Suggestive loci ($P < 1 \times 10^{-5}$) identified in replication analysis

SNP	CHR	Genomic Position	kb	<i>n</i>	<i>P</i>	Genes within clumping region
rs4845779	1	chr1:152388138..152530510	142.373	13	2.85E-20	CRCT1,LCE5A
rs6700998	1	chr1:152393263..152434009	40.747	7	1.67E-17	Intergenic region
rs12565568	1	chr1:152823380..153070024	246.645	5	1.10E-13	IVL,SMCP,SPRR1A,SPRR1B,SPRR2A,SPRR2B,SPRR2D,SPRR2E,SPRR3,SPRR4
rs4129267	1	chr1:154395125..154518610	123.486	98	2.70E-08	IL6R,SHE,TDRD10
rs941934	1	chr1:152219679..152390452	170.774	2	7.30E-08	CRNN,FLG,FLG-AS1,FLG2
rs9050	1	chr1:152022989..152431931	408.943	3	1.02E-07	CRNN,FLG,FLG-AS1,FLG2,HRNR,RPTN,TCHH,TCHHL1
rs755805	1	chr1:190385714..190574068	188.355	31	1.66E-07	BRINP3,LOC101929120
rs7512552	1	chr1:150165849..150522242	356.394	342	1.81E-07	ADAMTSL4,ANP32E,APH1A,C1orf54,CA14,CIART,ECM1,LINC00568,MIR6878,MRPS21,PRPF3,RPRD2,TARS2
rs2387417	1	chr1:10847158..10854575	7.418	3	1.27E-06	CASZ1
rs3120745	1	chr1:152890470..153083539	193.07	188	2.08E-06	SPRR1A,SPRR1B,SPRR2A,SPRR2B,SPRR2D,SPRR2E,SPRR3,SPRR4
rs12130219	1	chr1:152159773..152213112	53.34	4	2.26E-06	HRNR
rs11576296	1	chr1:153168627..153177852	9.226	12	2.79E-06	LELP1
rs11581328	1	chr1:8389894..8879610	489.717	130	4.47E-06	REER,SLC45A1
rs75859940	1	chr1:36359669..36518627	158.959	7	6.76E-06	AGO1,AGO3
rs12122335	1	chr1:80121672..80450337	328.666	70	7.08E-06	Intergenic region
rs12035497	1	chr1:68100413..68108496	8.084	8	8.92E-06	Intergenic region
rs10208293	2	chr2:102858490..103091618	233.129	254	4.82E-12	IL1RL1,IL18R1,IL18RAP,MIR4772,SLC9A4
rs6419573	2	chr2:102880806..103208610	327.805	329	1.43E-09	IL1RL1,IL18R1,IL18RAP,MIR4772,SLC9A4
rs1041973	2	chr2:102734551..103210544	475.994	80	2.13E-08	IL1R1,IL1RL1,IL1RL2,IL18R1,IL18RAP,MIR4772,SLC9A4
rs80104165	2	chr2:101327847..101327847	0.001	1	4.78E-07	Intergenic region
rs6750731	2	chr2:164611976..164697894	85.919	8	9.89E-07	Intergenic region
rs13019081	2	chr2:102844249..103194558	350.31	90	3.19E-06	IL1RL1,IL1RL2,IL18R1,IL18RAP,MIR4772,SLC9A4
rs10174949	2	chr2:8438693..8496062	57.37	70	3.53E-06	LINC00299
rs7629891	3	chr3:132652701..132680540	27.84	15	1.07E-06	Intergenic region
rs115355628	3	chr3:76924551..76939755	15.205	6	2.60E-06	Intergenic region

rs181046608	3	chr3:142169115..142441124	272.01	116	2.88E-06	ATR,PLS1
rs852228	3	chr3:130564406..130916798	352.393	39	8.74E-06	ASTE1,ATP2C1,NEK11
rs62324212	4	chr4:123073009..123563078	490.07	52	1.13E-06	ADAD1,IL2,IL21,IL21-AS1,KIAA1109
rs58591947	4	chr4:14218347..14250959	32.613	3	2.08E-06	Intergenic region
rs13152362	4	chr4:122984633..123564119	579.487	91	2.53E-06	ADAD1,IL2,IL21,IL21-AS1,KIAA1109
rs9994725	4	chr4:160498966..160527249	28.284	9	3.47E-06	Intergenic region
rs10517435	4	chr4:58943081..59001255	58.175	22	5.31E-06	Intergenic region
rs6827756	4	chr4:122999452..123557236	557.785	64	5.48E-06	ADAD1,IL2,IL21,IL21-AS1,KIAA1109
rs10155071	4	chr4:108104369..108104369	0.001	1	8.56E-06	
rs12188917	5	chr5:131810619..132002844	192.226	130	1.98E-19	C5orf56,IL5,IL13,IRF1,RAD50
rs11747814	5	chr5:132009154..132128218	119.065	142	2.33E-12	CCNI2,IL4,KIF3A,SEPT8
rs2073643	5	chr5:131247790..131833599	585.81	448	1.20E-09	ACSL6,C5orf56,CSF2,IL3,IRF1,LOC553103,LOC728637, MIR3936,MIR6830,P4HA2,P4HA2- AS1,PDLIM4,SLC22A4,SLC22A5
rs1837253	5	chr5:110401872..110401872	0.001	1	2.09E-08	Intergenic region
rs7720663	5	chr5:164470161..164679036	208.876	91	7.82E-08	Intergenic region
rs7700687	5	chr5:141418770..141567415	148.646	185	1.47E-07	NDFIP1
rs11738721	5	chr5:118385691..118608427	222.737	75	1.20E-06	DMXL1,TNFAIP8
rs12186767	5	chr5:110387762..110558882	171.121	109	1.24E-06	TSLP,WDR36
rs17772583	5	chr5:131843465..131953510	110.046	11	3.34E-06	IL5,RAD50
rs6594882	5	chr5:114541887..114666669	124.783	13	3.85E-06	CCDC112,PGGT1B
rs12513723	5	chr5:135136818..135201164	64.347	53	4.19E-06	SLC25A48
rs76465214	5	chr5:27729608..27807161	77.554	35	6.65E-06	Intergenic region
rs328622	5	chr5:32050289..32051339	1.051	3	6.81E-06	PDZD2
rs111850488	6	chr6:62715469..63078491	363.023	23	1.53E-07	KHDRBS2
rs12212415	6	chr6:149831902..150249365	417.464	384	8.85E-07	GINM1,KATNA1,LATS1,LRP11,NUP43,PCMT1,PPIL4,R AET1E,RAET1E-AS1,RAET1G,RPS18P9
rs1739624	6	chr6:38461036..38605180	144.145	8	3.81E-06	BTBD9
rs13207327	6	chr6:168707167..168714147	6.981	5	7.38E-06	DACT2
rs13223709	7	chr7:20041985..20111347	69.363	7	6.87E-07	LOC101927668
rs11983418	7	chr7:55793345..56192051	398.707	66	2.26E-06	CCT6A,CHCHD2,GBAS,MRPS17,NUPR1L,PHKG1,PSPH ,SEPT14,SNORA15,SUMF2,ZNF713
rs2194651	7	chr7:53475388..53641514	166.127	123	4.93E-06	Intergenic region
rs12111836	7	chr7:123769135..123819567	50.433	154	7.04E-06	Intergenic region
rs10229197	7	chr7:154141223..154157327	16.105	13	7.85E-06	DPP6

rs13275449	8	chr8:81135504..81329123	193.62	199	7.04E-08	MIR5708
rs1460247	8	chr8:105780272..105874609	94.338	27	7.46E-08	Intergenic region
rs55895966	8	chr8:83431557..83566712	135.156	45	1.04E-06	Intergenic region
rs60258053	8	chr8:62845516..63014103	168.588	102	1.50E-06	Intergenic region
rs12334935	8	chr8:126574447..126620703	46.257	68	2.98E-06	Intergenic region
rs148746829	8	chr8:102177807..102198442	20.636	3	5.88E-06	Intergenic region
rs992969	9	chr9:6146121..6331610	185.49	82	1.22E-12	IL33,TPD52L3
rs340908	9	chr9:5934967..6144333	209.367	149	1.18E-06	KIAA2026,MIR4665,RANBP6
rs34064673	9	chr9:75232278..75286511	54.234	19	2.04E-06	TMC1
rs13298681	9	chr9:111544183..111796753	252.571	31	7.86E-06	ACTL7A,ACTL7B,CTNNAL1,FAM206A,IKBKAP,TMEM245
rs10971620	9	chr9:33602307..33655528	53.222	22	8.40E-06	ANXA2P2
rs111472375	9	chr9:15810989..15812405	1.417	2	9.80E-06	CCDC171
rs7922914	10	chr10:91289276..91290668	1.393	2	4.88E-07	SLC16A12
rs2773207	10	chr10:109601892..109605520	3.629	2	1.35E-06	Intergenic region
rs17229657	10	chr10:31112105..31344962	232.858	54	2.06E-06	ZNF438
rs4433484	10	chr10:19576622..19699871	123.25	26	4.83E-06	MALRD1
rs10826811	10	chr10:30840142..30850797	10.656	15	5.78E-06	Intergenic region
rs79295898	10	chr10:133960969..133972959	11.991	14	7.35E-06	JAKMIP3
rs2212434	11	chr11:76128490..76302073	173.584	80	2.13E-19	C11orf30
rs479844	11	chr11:65355650..65676137	320.488	130	3.87E-17	AP5B1,CCDC85B,CFL1,CTSW,EFEMP2,EHBP1L1,FIBP,FOSL1,KAT5,KCNK7,MAP3K11,MIR4489,MIR4690,MUS81,OVOL1,OVOL1-AS1,PCNXL3,RELA,RNASEH2C,SIPA1,SNX32
rs10896044	11	chr11:65395860..65600913	205.054	72	7.12E-07	AP5B1,KAT5,MIR4489,MIR4690,OVOL1,OVOL1-AS1,PCNXL3,RELA,RNASEH2C,SIPA1
rs1496701	11	chr11:91699343..91796007	96.665	74	1.24E-06	Intergenic region
rs10790275	11	chr11:118486110..118746769	260.66	184	1.50E-06	DDX6,MIR6716,PHLDB1,TREH
rs10743043	11	chr11:7937615..8001398	63.784	10	2.60E-06	NLRP10,OR10A3,OR10A6
rs3758716	11	chr11:76043831..76332210	288.38	75	3.19E-06	C11orf30,LOC100506127,PRKRIR
rs12290239	11	chr11:74452658..74743894	291.237	57	3.25E-06	NEU3,RNF169,SPCS2,XRRA1
rs7130129	11	chr11:65349063..65549606	200.544	46	5.68E-06	AP5B1,EHBP1L1,KAT5,KCNK7,MAP3K11,MIR4489,MIR4690,PCNXL3,RELA,RNASEH2C,SIPA1
rs2433192	11	chr11:36291717..36396678	104.962	59	7.26E-06	COMMD9,PRR5L
rs2408749	11	chr11:103499163..103542664	43.502	92	8.41E-06	Intergenic region

rs4756496	11	chr11:39183371..39329123	145.753	47	9.48E-06	Intergenic region
rs4766366	12	chr12:5516442..5516442	0.001	1	2.08E-26	Intergenic region
rs12312121	12	chr12:131482237..131490145	7.909	10	1.40E-06	GPR133
rs703817	12	chr12:57244168..57526646	282.479	45	1.62E-06	GPR182,LRP1,MYO1A,NAB2,RDH16,SDR9C7,STAT6,TAC3,TMEM194A,ZBTB39
rs75761974	12	chr12:25229982..25229982	0.001	1	2.77E-06	LRMP
rs11056396	12	chr12:15320385..15352051	31.667	17	4.06E-06	RERG
rs76660521	12	chr12:32187419..32211894	24.476	17	7.02E-06	Intergenic region
rs4906027	14	chr14:101375425..101469262	93.838	55	2.79E-06	LOC101929369,SNORD113-1,SNORD113-2,SNORD113-4,SNORD113-5,SNORD113-6,SNORD113-7,SNORD113-9,SNORD114-1,SNORD114-2,SNORD114-3,SNORD114-4,SNORD114-5,SNORD114-6,SNORD114-7,SNORD114-8,SNORD114-9,SNORD114-10,SNORD114-11,SNORD114-12,SNORD114-13,SNORD114-14,SNORD114-15,SNORD114-16,SNORD114-17,SNORD114-18,SNORD114-19,SNORD114-20,SNORD114-21,SNORD114-22,SNORD114-23,SNORD114-24,SNORD114-25,SNORD114-26,SNORD114-27,SNORD114-28,SNORD114-29,SNORD114-30,SNORD114-31
rs1874052	14	chr14:43460115..44047173	587.059	105	4.15E-06	Intergenic region
rs11622416	14	chr14:90228940..90280170	51.231	15	6.63E-06	EFCAB11
rs744910	15	chr15:67435075..67467830	32.756	35	1.46E-07	SMAD3
rs10468076	15	chr15:35530985..35726306	195.322	147	1.94E-06	DPH6,MIR3942
rs11071559	15	chr15:61032054..61123862	91.809	45	4.29E-06	RORA
rs961288	15	chr15:89890182..89944190	54.009	12	4.30E-06	LINC00925,MIR9-3
rs12906403	15	chr15:79973634..79991075	17.442	21	6.89E-06	Intergenic region
rs2041733	16	chr16:11034959..11306732	271.774	82	2.32E-06	CLEC16A,DEXI
rs6498113	16	chr16:10957681..10988396	30.716	3	5.60E-06	CIITA
rs12445760	16	chr16:65471927..65529316	57.39	4	8.78E-06	LINC00922
rs7216389	17	chr17:37770481..38215117	444.637	303	7.53E-17	CSF3,ERBB2,GRB7,GSDMA,GSDMB,IKZF3,LRR3C,MED24,MIEN1,MIR4728,MIR6884,ORMDL3,PGAP3,PNMT,PPP1R1B,PSMD3,SNORD124,STARD3,TCAP,ZBP2
rs12953014	17	chr17:47260130..47481374	221.245	111	1.63E-08	ABI3,FLJ40194,GNGT2,LOC102724596,MIR6129,PHOSPHO1,ZNF652

rs3859189	17	chr17:38128765..38219005	90.241	131	4.62E-08	CSF3,GSDMA,MED24,MIR6884,PSMD3,SNORD124,THRA
rs12951971	17	chr17:40338292..40594622	256.331	56	4.77E-06	GHDC,PTRF,STAT3,STAT5A,STAT5B
rs72876345	18	chr18:23532796..23756481	223.686	31	4.81E-07	PSMA8,SS18
rs17240853	18	chr18:68101639..68129703	28.065	21	1.73E-06	Intergenic region
rs1600201	18	chr18:28117230..28234745	117.516	25	2.69E-06	Intergenic region
rs1274285	18	chr18:362857..368215	5.359	3	9.59E-06	COLEC12
rs2918299	19	chr19:8776880..8814367	37.488	34	8.61E-09	ACTL9
rs2074333	19	chr19:22670328..22671333	1.006	2	1.00E-06	Intergenic region
rs10410331	19	chr19:3912165..3930323	18.159	8	3.44E-06	ATCAY
rs6062486	20	chr20:62199126..62400021	200.896	168	2.20E-06	ARFRP1,GMEB2,HELZ2,LIME1,RTEL1,RTEL1-TNFRSF6B,SLC2A4RG,STMN3,TNFRSF6B,ZBTB46,ZGPAT
rs2284033	22	chr22:37526529..37542762	16.234	29	3.10E-08	IL2RB
rs932380	22	chr22:44585958..44634708	48.751	8	6.28E-06	PARVG

CHR, chromosome; kb, kb span of the clump; *n*, number of SNPs clumped with peak SNP

Supplementary Table 7. Biological process of the shared gene set between asthma and allergic diseases in Gene Ontology (GO) terms

Geneset	Description	Link	# genes	FDR	Overlap genes
GO:0008544	epidermis development	http://amigo.geneontology.org/amigo/term/GO:0008544	21	<1E-10	C1orf68;LCE4A;FLG;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;HRNR;NAB2;CRCT1;TCHH;LCE3D
GO:0009913	epidermal cell differentiation	http://amigo.geneontology.org/amigo/term/GO:0009913	20	<1E-10	C1orf68;LCE4A;FLG;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;HRNR;CRCT1;TCHH;LCE3D
GO:0018149	peptide cross-linking	http://amigo.geneontology.org/amigo/term/GO:0018149	17	<1E-10	C1orf68;LCE4A;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;CRCT1;LCE3D
GO:0030216	keratinocyte differentiation	http://amigo.geneontology.org/amigo/term/GO:0030216	20	<1E-10	C1orf68;LCE4A;FLG;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;HRNR;CRCT1;TCHH;LCE3D
GO:0030855	epithelial cell differentiation	http://amigo.geneontology.org/amigo/term/GO:0030855	23	<1E-10	C1orf68;LCE4A;FLG;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;HRNR;SLC9A4;SMAD3;CRCT1;TCHH;KIAA1109;LCE3D
GO:0031424	keratinization	http://amigo.geneontology.org/amigo/term/GO:0031424	17	<1E-10	LCE4A;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;HRNR;TCHH;LCE3D

GO:0043588	skin development	http://amigo.geneontology.org/amigo/term/GO:0043588	21	<1E-10	C1orf68;LCE4A;FLG;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;HRNR;FLG2;CRCT1;TCHH;LCE3D
GO:0060429	epithelium development	http://amigo.geneontology.org/amigo/term/GO:0060429	24	1.73E-09	C1orf68;LCE4A;FLG;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;HRNR;SLC9A4;SMAD3;CRCT1;STAT6;TCHH;KIAA1109;LCE3D
GO:0009888	tissue development	http://amigo.geneontology.org/amigo/term/GO:0009888	27	2.59E-07	C1orf68;LCE4A;ERBB3;FLG;LCE5A;LCE2B;LCE1C;LCE1D;LCE1E;LCE1F;LCE2A;LCE2C;LCE2D;LCE3A;LCE3B;LCE3C;LCE3E;HRNR;SLC9A4;SMAD3;NAB2;CRCT1;STAT6;TCHH;KIAA1109;LCE3D;RUNX3
GO:0042088	T-helper 1 type immune response	http://amigo.geneontology.org/amigo/term/GO:0042088	5	0.000394	TLR6;STAT6;IL18R1;IL33;IL1RL1

Supplementary Table 8. Pathway analysis of the shared gene set between asthma and allergic diseases in KEGG pathways

Geneset	Description	Link	# genes	FDR	Overlap genes
hsa05321	Inflammatory bowel disease (IBD) - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa05321	10	1.26E-11	HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;IL2;SMAD3;STAT6;IL18RAP;IL18R1
hsa04659	Th17 cell differentiation - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa04659	10	1.12E-09	HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;IL1R1;IL2;SMAD3;STAT6;CD247
hsa04658	Th1 and Th2 cell differentiation - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa04658	9	6.58E-09	HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;IL2;STAT6;RUNX3;CD247
hsa05330	Allograft rejection - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa05330	7	8.58E-09	HLA-B;HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;IL2
hsa05332	Graft-versus-host disease - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa05332	7	1.21E-08	HLA-B;HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;IL2
hsa04940	Type I diabetes mellitus - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa04940	7	1.44E-08	HLA-B;HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;IL2
hsa05320	Autoimmune thyroid disease - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa05320	7	5.75E-08	HLA-B;HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;IL2
hsa04672	Intestinal immune network for IgA production - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa04672	6	1.39E-06	HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;IL2
hsa05416	Viral myocarditis - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa05416	6	3.74E-06	HLA-B;HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5
hsa04145	Phagosome - Homo sapiens (human)	http://www.kegg.jp/kegg-bin/show_pathway?hsa04145	8	3.74E-06	TLR6;HLA-B;HLA-DQA1;HLA-DQB1;HLA-DRA;HLA-DRB1;HLA-DRB5;RAB5B

Supplementary Table 9. List of credible set SNPs in each locus from fine mapping. For each of the 38 asthma and allergic diseases shared loci, the table lists all SNPs within 500 kb of 38 variants in the 99% credible sets that were calculated.

Index SNP	CHR	No. credible set SNPs	List of credible set SNPs (posterior probability in brackets)
rs10074523	5	206	rs6897429 (0.99),rs2706336 (0.99),rs2548993 (0.989),rs2188962 (0.989),rs2243293 (0.989),rs2406539 (0.988),rs35081016 (0.988),rs72797306 (0.988),rs60156285 (0.987),rs10066662 (0.987),rs60168940 (0.987),rs11242124 (0.986),rs2706403 (0.986),rs12521868 (0.985),rs6879672 (0.985),rs2158177 (0.984),rs2522052 (0.984),rs3798130 (0.984),rs2299011 (0.983),rs9784675 (0.983),rs7732667 (0.982),rs2237057 (0.982),rs11242109 (0.981),rs17166203 (0.981),rs3798131 (0.98),rs11242125 (0.98),rs11747814 (0.979),rs10463516 (0.979),rs115911400 (0.978),rs2243267 (0.978),rs17622208 (0.977),rs4330455 (0.977),rs74863864 (0.976),rs17510339 (0.976),rs10060615 (0.975),rs3763112 (0.975),rs2073643 (0.974),rs2243266 (0.973),rs2706401 (0.973),rs17166215 (0.972),rs1468215 (0.972),rs10066660 (0.971),rs12514685 (0.97),rs10588133 (0.97),rs11242115 (0.969),rs6871350 (0.968),rs10900809 (0.968),rs4425499 (0.967),rs28472559 (0.966),rs62383710 (0.965),rs334902 (0.965),rs10068370 (0.964),rs6890009 (0.963),rs6863548 (0.963),rs2243268 (0.962),rs4705929 (0.961),rs10477742 (0.96),rs11242126 (0.959),rs2243290 (0.959),rs10463894 (0.958),rs2078387 (0.957),rs1859138 (0.956),rs736801 (0.955),rs58760622 (0.954),rs2243289 (0.953),rs2237059 (0.952),rs4705931 (0.951),rs56668723 (0.951),rs11242123 (0.95),rs77143352 (0.949),rs6865485 (0.947),rs11952099 (0.946),rs10463893 (0.945),rs2897443 (0.944),rs3798132 (0.943),rs1588263 (0.942),rs2227282 (0.941),rs2227284 (0.94),rs2522051 (0.939),rs3213639 (0.938),rs10520114 (0.937),rs9784600 (0.936),rs11749376 (0.934),rs2136188 (0.933),rs162908 (0.932),rs2136186 (0.931),rs59568225 (0.93),rs2706370 (0.929),rs112300250 (0.928),rs17690965 (0.926),rs2245460 (0.925),rs6885996 (0.924),rs2171247 (0.923),rs6867282 (0.921),rs4705927 (0.92),rs12514976 (0.919),rs2285700 (0.918),rs7735429 (0.916),rs7734673 (0.915),rs4426908 (0.913),rs200838 (0.912),rs2631360 (0.91),rs1800925 (0.909),rs2706347 (0.907),rs2136187 (0.906),rs2078386 (0.904),rs7737031 (0.903),rs12187537 (0.901),rs12186803 (0.9),rs10062446 (0.898),rs4266392 (0.897),rs2299005 (0.895),rs12652920 (0.893),rs11741255 (0.892),rs1080001 (0.89),rs2023823 (0.888),rs2299003 (0.886),rs2706348 (0.885),rs7736284 (0.883),rs2243677 (0.881),rs2706349 (0.879),rs6864396 (0.878),rs2706374 (0.876),rs2299009 (0.874),rs60632435 (0.872),rs2299004 (0.87),rs2522394 (0.868),rs2522414 (0.866),rs2522392 (0.863),rs2706372 (0.861),rs2522411 (0.859),rs10073911 (0.856),rs3798129 (0.854),rs6864565 (0.851),rs10036532 (0.848),rs4705964 (0.845),rs11740584 (0.843),rs7737470 (0.84),rs2706334 (0.837),rs1468217 (0.833),rs2299010 (0.83),rs2299007 (0.827),rs1295685 (0.823),rs62385261 (0.82),rs4705965 (0.816),rs11242127 (0.812),rs6873897 (0.808),rs17622656 (0.804),rs4705963 (0.8),rs847 (0.796),rs7717027 (0.791),rs10455052 (0.787),rs55982201 (0.782),rs6872131 (0.778),rs12188917 (0.773),rs2051809 (0.768),rs2706353 (0.764),rs2299013 (0.758),rs2897442 (0.753),rs2548992 (0.748),rs6874184 (0.742),rs1295686 (0.736),rs6896296 (0.73),rs848 (0.724),rs6873732 (0.717),rs62383758 (0.71),rs62383757 (0.703),rs3798134 (0.696),rs2240032 (0.689),rs12332204 (0.681),rs60490216 (0.672),rs12653750 (0.664),rs56798121 (0.655),rs6894017 (0.645),rs2074529 (0.635),rs2040704 (0.625),rs2299012 (0.615),rs6866095 (0.605),rs10074523 (0.595),rs62383715 (0.574),rs6596087 (0.563),rs62383714 (0.552),rs56183820 (0.54),rs2252775 (0.528),rs62385260 (0.515),rs6871536 (0.502),rs6596090 (0.489),rs17166050 (0.475),rs3091308 (0.461),rs3798135 (0.445),rs2246176 (0.43),rs10052993 (0.415),rs20541 (0.399),rs2074369 (0.381),rs3091307 (0.363),rs7449456 (0.344),rs2040703 (0.324),rs2706345 (0.298),rs2106984

			(0.271),rs2244012 (0.243),rs6596086 (0.212),rs2522403 (0.18),rs2301713 (0.142),rs6898898 (0.105),rs2706362 (0.064)
rs10174949	2	5	rs10178845 (0.998),rs13416555 (0.827),rs891058 (0.649),rs10174949 (0.467)
rs10414065	19	4	rs118013485 (0.996),rs117710327 (0.987),rs10414065 (0.49)
rs1059513	12	3	rs3024971 (1),rs1059513 (0.709)
rs10795656	10	13	rs1775553 (0.992),rs61840192 (0.986),rs962992 (0.976),rs1663680 (0.953),rs962993 (0.919),rs1775555 (0.876),rs1663687 (0.832),rs1031163 (0.786),rs1444782 (0.736),rs186856025 (0.677),rs144536148 (0.608),rs12413578 (0.508)
rs10876864	12	27	rs1873914 (0.992),rs1701704 (0.989),rs705704 (0.985),rs2640564 (0.98),rs7955865 (0.975),rs2456973 (0.971),rs61938963 (0.966),rs61938962 (0.961),rs34415530 (0.955),rs10876866 (0.95),rs1081975 (0.943),rs772921 (0.937),rs705705 (0.928),rs2640562 (0.92),rs7302200 (0.911),rs1702877 (0.903),rs705700 (0.894),rs1689510 (0.882),rs705699 (0.87),rs7971751 (0.852),rs2271194 (0.831),rs10876870 (0.799),rs7297175 (0.764),rs11171739 (0.679),rs1131017 (0.584),rs10876864 (0.224)
rs1214598	1	22	rs1617988 (0.999),rs1617333 (0.989),rs2988277 (0.979),rs1773561 (0.963),rs2056625 (0.946),rs34276574 (0.926),rs35014055 (0.903),rs2056626 (0.88),rs1773560 (0.854),rs3108155 (0.829),rs2988279 (0.801),rs1214595 (0.773),rs1214596 (0.742),rs2995089 (0.712),rs2949669 (0.681),rs2949661 (0.643),rs2995091 (0.604),rs1723016 (0.556),rs1723018 (0.475),rs1773542 (0.385),rs1214598 (0.138)
rs12413578	10	12	rs61840192 (0.991),rs962992 (0.984),rs1663680 (0.969),rs962993 (0.946),rs1775555 (0.918),rs1663687 (0.889),rs1031163 (0.858),rs1444782 (0.825),rs186856025 (0.786),rs144536148 (0.74),rs12413578 (0.337)
rs12743520	1	82	rs71652507 (0.99),rs11583778 (0.99),rs35705463 (0.989),rs34843292 (0.987),rs114225281 (0.984),rs150394053 (0.981),rs11585590 (0.978),rs35038369 (0.975),rs11581705 (0.972),rs11164814 (0.969),rs11164816 (0.965),rs11164801 (0.962),rs11809700 (0.958),rs11805698 (0.954),rs59864761 (0.95),rs71652503 (0.944),rs35901796 (0.938),rs11588545 (0.932),rs11803097 (0.925),rs72724586 (0.917),rs34288890 (0.909),rs111281067 (0.901),rs34250288 (0.893),rs11808092 (0.885),rs72724587 (0.876),rs1415296 (0.867),rs34202284 (0.858),rs12756698 (0.848),rs35311203 (0.839),rs12749480 (0.829),rs12743005 (0.82),rs36114576 (0.81),rs56044027 (0.8),rs11805007 (0.79),rs34221961 (0.78),rs11810217 (0.769),rs35241270 (0.759),rs11809055 (0.748),rs3790450 (0.737),rs35612297 (0.726),rs11589122 (0.715),rs11800409 (0.704),rs11807962 (0.692),rs34305407 (0.681),rs2051841 (0.669),rs11578004 (0.657),rs12749786 (0.645),rs76383441 (0.632),rs12733238 (0.62),rs34231012 (0.608),rs34734076 (0.595),rs68160001 (0.583),rs111807611 (0.57),rs11577426 (0.557),rs12746893 (0.544),rs11164803 (0.531),rs34761380 (0.517),rs11805229 (0.504),rs72724574 (0.49),rs12731107 (0.476),rs1333743 (0.461),rs12756786 (0.447),rs11800771 (0.432),rs35435370 (0.417),rs111805004 (0.401),rs72724515 (0.385),rs67876779 (0.369),rs150878650 (0.353),rs72724555 (0.336),rs67646822 (0.32),rs34812295 (0.303),rs11578098 (0.285),rs35526187 (0.267),rs12738833 (0.249),rs35699160 (0.23),rs11800848 (0.211),rs67026262 (0.192),rs11591094 (0.172),rs11589660 (0.152),rs112597199 (0.132),rs12743520 (0.108)
rs1837253	5	21	rs28874883 (0.992),rs7728612 (0.989),rs6885792 (0.986),rs10065671 (0.983),rs4280918 (0.98),rs6869502 (0.976),rs12657787 (0.973),rs7700507 (0.97),rs60557452 (0.966),rs10073425 (0.963),rs7710963 (0.959),rs12659961 (0.955),rs7728912 (0.951),rs3853750 (0.946),rs7735355 (0.939),rs7735519 (0.93),rs7705653 (0.919),rs6594499 (0.904),rs1438673 (0.848),rs1837253 (0.35)

rs2136016	8	80	rs3913969 (0.993),rs6996407 (0.99),rs12542061 (0.986),rs11786685 (0.982),rs6473222 (0.978),rs13274782 (0.974),rs7012968 (0.97),rs11784337 (0.965),rs13273143 (0.961),rs2202749 (0.956),rs1911714 (0.952),rs1911713 (0.947),rs13276888 (0.943),rs13258616 (0.938),rs10957977 (0.934),rs6473224 (0.929),rs13252706 (0.924),rs6473227 (0.92),rs3913968 (0.915),rs13253385 (0.91),rs4739735 (0.905),rs6987042 (0.9),rs6473225 (0.894),rs6473226 (0.889),rs952558 (0.883),rs13251923 (0.878),rs13270496 (0.872),rs13274471 (0.866),rs6473223 (0.86),rs10957975 (0.854),rs7826521 (0.848),rs11994858 (0.842),rs11776367 (0.836),rs13282260 (0.829),rs10957978 (0.822),rs13275449 (0.815),rs1911715 (0.808),rs55839241 (0.801),rs13263709 (0.794),rs2370615 (0.786),rs12543811 (0.779),rs13275219 (0.771),rs13274067 (0.763),rs6992476 (0.754),rs6991991 (0.746),rs7462675 (0.738),rs7824993 (0.729),rs11783496 (0.72),rs7837219 (0.711),rs4739736 (0.701),rs62517193 (0.692),rs13282455 (0.682),rs13253128 (0.671),rs62517192 (0.661),rs7837153 (0.65),rs6989309 (0.64),rs62517191 (0.629),rs1543857 (0.618),rs952559 (0.606),rs952557 (0.594),rs7009110 (0.582),rs10957979 (0.568),rs13272328 (0.554),rs4739737 (0.539),rs2202750 (0.524),rs13274426 (0.509),rs13267000 (0.492),rs13272105 (0.474),rs7824278 (0.457),rs6473228 (0.439),rs2221641 (0.421),rs7823800 (0.402),rs7824246 (0.382),rs7003011 (0.361),rs2001628 (0.323),rs2102418 (0.28),rs7824394 (0.232),rs4739738 (0.183),rs2136016 (0.067)
rs2169282	9	17	rs10975479 (0.993),rs928413 (0.989),rs3939286 (0.985),rs1929995 (0.98),rs7032572 (0.969),rs1342326 (0.955),rs72699191 (0.941),rs11521485 (0.917),rs10975468 (0.884),rs72699186 (0.826),rs144829310 (0.759),rs12349858 (0.688),rs10975471 (0.614),rs72699188 (0.527),rs9775039 (0.377),rs12376324 (0.189)

rs2548992	5	206	rs6897429 (0.99),rs2706336 (0.99),rs2548993 (0.989),rs2188962 (0.989),rs2243293 (0.989),rs2406539 (0.988),rs35081016 (0.988),rs72797306 (0.988),rs60156285 (0.987),rs10066662 (0.987),rs60168940 (0.986),rs11242124 (0.986),rs2706403 (0.986),rs12521868 (0.985),rs6879672 (0.985),rs2158177 (0.984),rs2522052 (0.984),rs3798130 (0.983),rs2299011 (0.983),rs9784675 (0.983),rs7732667 (0.982),rs2237057 (0.982),rs11242109 (0.981),rs17166203 (0.981),rs3798131 (0.98),rs11242125 (0.98),rs11747814 (0.979),rs10463516 (0.979),rs115911400 (0.978),rs2243267 (0.978),rs17622208 (0.977),rs4330455 (0.977),rs74863864 (0.976),rs17510339 (0.976),rs10060615 (0.975),rs3763112 (0.974),rs2073643 (0.974),rs2243266 (0.973),rs2706401 (0.973),rs17166215 (0.972),rs1468215 (0.971),rs10066660 (0.971),rs12514685 (0.97),rs10588133 (0.97),rs11242115 (0.969),rs6871350 (0.968),rs10900809 (0.968),rs4425499 (0.967),rs28472559 (0.966),rs62383710 (0.965),rs334902 (0.965),rs10068370 (0.964),rs6890009 (0.963),rs6863548 (0.962),rs2243268 (0.962),rs4705929 (0.961),rs10477742 (0.96),rs11242126 (0.959),rs2243290 (0.958),rs10463894 (0.958),rs2078387 (0.957),rs1859138 (0.956),rs736801 (0.955),rs58760622 (0.954),rs2243289 (0.953),rs2237059 (0.952),rs4705931 (0.951),rs56668723 (0.95),rs11242123 (0.949),rs77143352 (0.948),rs6865485 (0.947),rs11952099 (0.946),rs10463893 (0.945),rs2897443 (0.944),rs3798132 (0.943),rs1588263 (0.942),rs2227282 (0.941),rs2227284 (0.94),rs2522051 (0.939),rs3213639 (0.937),rs10520114 (0.936),rs9784600 (0.935),rs11749376 (0.934),rs2136188 (0.933),rs162908 (0.932),rs2136186 (0.931),rs59568225 (0.93),rs2706370 (0.928),rs112300250 (0.927),rs17690965 (0.926),rs2245460 (0.925),rs6885996 (0.924),rs2171247 (0.922),rs6867282 (0.921),rs4705927 (0.92),rs12514976 (0.918),rs2285700 (0.917),rs7735429 (0.916),rs7734673 (0.914),rs4426908 (0.913),rs200838 (0.911),rs2631360 (0.91),rs1800925 (0.908),rs2706347 (0.907),rs2136187 (0.905),rs2078386 (0.904),rs7737031 (0.902),rs12187537 (0.901),rs12186803 (0.899),rs10062446 (0.898),rs4266392 (0.896),rs2299005 (0.894),rs12652920 (0.893),rs11741255 (0.891),rs1080001 (0.889),rs2023823 (0.888),rs2299003 (0.886),rs2706348 (0.884),rs7736284 (0.882),rs2243677 (0.881),rs2706349 (0.879),rs6864396 (0.877),rs2706374 (0.875),rs2299009 (0.873),rs60632435 (0.871),rs2299004 (0.869),rs2522394 (0.867),rs2522414 (0.865),rs2522392 (0.863),rs2706372 (0.86),rs2522411 (0.858),rs10073911 (0.856),rs3798129 (0.853),rs6864565 (0.85),rs10036532 (0.847),rs4705964 (0.845),rs11740584 (0.842),rs7737470 (0.839),rs2706334 (0.836),rs1468217 (0.833),rs2299007 (0.829),rs2299010 (0.826),rs1295685 (0.822),rs62385261 (0.819),rs11242127 (0.815),rs4705965 (0.811),rs6873897 (0.807),rs17622656 (0.803),rs4705963 (0.799),rs847 (0.795),rs7717027 (0.79),rs10455052 (0.786),rs55982201 (0.781),rs6872131 (0.777),rs12188917 (0.772),rs2051809 (0.767),rs2706353 (0.762),rs2299013 (0.757),rs2897442 (0.752),rs2548992 (0.746),rs6874184 (0.735),rs1295686 (0.729),rs6896296 (0.723),rs848 (0.717),rs6873732 (0.71),rs62383758 (0.703),rs62383757 (0.696),rs3798134 (0.689),rs2240032 (0.682),rs12332204 (0.674),rs60490216 (0.665),rs12653750 (0.656),rs56798121 (0.647),rs6894017 (0.638),rs2074529 (0.628),rs2040704 (0.618),rs2299012 (0.608),rs6866095 (0.598),rs10074523 (0.587),rs62383715 (0.577),rs6596087 (0.566),rs62383714 (0.554),rs56183820 (0.543),rs2252775 (0.53),rs62385260 (0.517),rs6871536 (0.505),rs6596090 (0.491),rs17166050 (0.477),rs3091308 (0.463),rs3798135 (0.448),rs2246176 (0.432),rs10052993 (0.417),rs20541 (0.401),rs2074369 (0.383),rs3091307 (0.364),rs7449456 (0.346),rs2040703 (0.326),rs2706345 (0.3),rs2106984 (0.272),rs2244012 (0.244),rs6596086 (0.213),rs2522403 (0.18),rs2301713 (0.143),rs6898898 (0.106),rs2706362 (0.064)
rs2706362	5	204	rs2548993 (0.99),rs2188962 (0.99),rs2243293 (0.989),rs2406539 (0.989),rs35081016 (0.989),rs72797306 (0.988),rs60156285 (0.988),rs10066662 (0.988),rs60168940 (0.987),rs11242124 (0.987),rs2706403 (0.986),rs12521868 (0.986),rs6879672 (0.986),rs2158177 (0.985),rs2522052 (0.985),rs3798130 (0.984),rs2299011 (0.984),rs9784675 (0.984),rs7732667 (0.983),rs2237057 (0.983),rs11242109 (0.982),rs17166203 (0.982),rs3798131 (0.981),rs11242125 (0.981),rs11747814 (0.98),rs10463516 (0.98),rs115911400 (0.979),rs2243267 (0.979),rs17622208 (0.978),rs4330455 (0.978),rs74863864 (0.977),rs17510339 (0.977),rs10060615 (0.976),rs3763112 (0.976),rs2073643 (0.975),rs2243266

			(0.975),rs2706401 (0.974),rs17166215 (0.974),rs1468215 (0.973),rs10066660 (0.972),rs12514685 (0.972),rs10588133 (0.971),rs11242115 (0.971),rs6871350 (0.97),rs10900809 (0.969),rs4425499 (0.969),rs28472559 (0.968),rs62383710 (0.967),rs334902 (0.967),rs10068370 (0.966),rs6890009 (0.965),rs6863548 (0.964),rs2243268 (0.964),rs4705929 (0.963),rs10477742 (0.962),rs11242126 (0.961),rs2243290 (0.961),rs10463894 (0.96),rs2078387 (0.959),rs1859138 (0.958),rs736801 (0.957),rs58760622 (0.957),rs2243289 (0.956),rs2237059 (0.955),rs4705931 (0.954),rs56668723 (0.953),rs11242123 (0.952),rs77143352 (0.951),rs6865485 (0.95),rs11952099 (0.949),rs10463893 (0.948),rs2897443 (0.947),rs3798132 (0.946),rs1588263 (0.945),rs2227282 (0.944),rs2227284 (0.943),rs2522051 (0.942),rs3213639 (0.941),rs10520114 (0.94),rs9784600 (0.939),rs11749376 (0.938),rs2136188 (0.937),rs162908 (0.936),rs2136186 (0.935),rs59568225 (0.933),rs2706370 (0.932),rs112300250 (0.931),rs17690965 (0.93),rs2245460 (0.929),rs6885996 (0.928),rs2171247 (0.927),rs6867282 (0.925),rs4705927 (0.924),rs12514976 (0.923),rs2285700 (0.922),rs7735429 (0.92),rs7734673 (0.919),rs4426908 (0.918),rs200838 (0.916),rs2631360 (0.915),rs1800925 (0.914),rs2706347 (0.912),rs2136187 (0.911),rs2078386 (0.909),rs7737031 (0.908),rs12187537 (0.906),rs12186803 (0.905),rs10062446 (0.903),rs4266392 (0.902),rs2299005 (0.9),rs12652920 (0.899),rs11741255 (0.897),rs1080001 (0.895),rs2023823 (0.894),rs2299003 (0.892),rs2706348 (0.89),rs7736284 (0.889),rs2243677 (0.887),rs2706349 (0.885),rs6864396 (0.884),rs2706374 (0.882),rs2299009 (0.88),rs60632435 (0.878),rs2299004 (0.876),rs2522394 (0.874),rs2522414 (0.872),rs2522392 (0.87),rs2706372 (0.868),rs2522411 (0.866),rs10073911 (0.863),rs3798129 (0.861),rs6864565 (0.858),rs10036532 (0.856),rs4705964 (0.853),rs11740584 (0.851),rs7737470 (0.848),rs2706334 (0.845),rs1468217 (0.842),rs2299010 (0.839),rs2299007 (0.835),rs1295685 (0.832),rs62385261 (0.829),rs4705965 (0.825),rs11242127 (0.822),rs6873897 (0.818),rs17622656 (0.814),rs4705963 (0.81),rs847 (0.806),rs7717027 (0.802),rs10455052 (0.798),rs55982201 (0.793),rs6872131 (0.789),rs12188917 (0.785),rs2051809 (0.78),rs2706353 (0.775),rs2299013 (0.77),rs2897442 (0.765),rs2548992 (0.76),rs6874184 (0.755),rs1295686 (0.75),rs6896296 (0.744),rs848 (0.738),rs6873732 (0.731),rs62383758 (0.725),rs62383757 (0.718),rs3798134 (0.712),rs2240032 (0.704),rs12332204 (0.697),rs60490216 (0.689),rs12653750 (0.681),rs56798121 (0.672),rs6894017 (0.663),rs2074529 (0.654),rs2040704 (0.644),rs2299012 (0.635),rs6866095 (0.625),rs10074523 (0.615),rs62383715 (0.605),rs6596087 (0.595),rs62383714 (0.584),rs56183820 (0.573),rs2252775 (0.561),rs62385260 (0.549),rs6871536 (0.537),rs6596090 (0.524),rs17166050 (0.511),rs3091308 (0.498),rs3798135 (0.483),rs2246176 (0.469),rs10052993 (0.454),rs20541 (0.439),rs2074369 (0.422),rs3091307 (0.405),rs7449456 (0.387),rs2040703 (0.368),rs2706345 (0.344),rs2106984 (0.318),rs2244012 (0.291),rs6596086 (0.262),rs2522403 (0.231),rs2301713 (0.196),rs6898898 (0.16),rs2706362 (0.06)
rs2766664	20	5	rs13043901 (0.994),rs2766666 (0.947),rs2766667 (0.775),rs2766664 (0.52)
rs28393318	4	62	rs5743565 (0.99),rs5743585 (0.99),rs56357984 (0.989),rs11727978 (0.989),rs56289835 (0.988),rs11725779 (0.988),rs73236625 (0.987),rs5743563 (0.986),rs11722889 (0.986),rs11722813 (0.985),rs11722788 (0.984),rs5743593 (0.984),rs5743557 (0.983),rs5743556 (0.982),rs5743580 (0.982),rs5743571 (0.981),rs45588337 (0.98),rs55830619 (0.979),rs11722836 (0.979),rs200805729 (0.978),rs114719937 (0.977),rs5743592 (0.976),rs112318878 (0.975),rs2101521 (0.974),rs113558549 (0.973),rs200921532 (0.972),rs113465719 (0.971),rs7378375 (0.969),rs56408159 (0.968),rs67206233 (0.967),rs4833096 (0.966),rs9306967 (0.964),rs5743595 (0.963),rs199704972 (0.961),rs66922907 (0.96),rs73236629 (0.957),rs6815814 (0.953),rs73236628 (0.95),rs4543123 (0.946),rs10004195 (0.938),rs5743614 (0.925),rs4833095 (0.904),rs12233670 (0.878),rs73142654 (0.852),rs17616434 (0.825),rs10034903 (0.798),rs4833100 (0.771),rs6531663 (0.743),rs7664239 (0.716),rs10012017 (0.687),rs6834581 (0.658),rs4833097 (0.625),rs28690449 (0.591),rs1135430 (0.556),rs11936050 (0.519),rs5743604 (0.479),rs5743551 (0.439),rs4833093 (0.396),rs7658651 (0.35),rs28393318

			(0.209),rs5743618 (0.125)
rs301805	1	10	rs159960 (0.99),rs159963 (0.968),rs301816 (0.935),rs301819 (0.898),rs301799 (0.842),rs301802 (0.769),rs301807 (0.658),rs301806 (0.506),rs301805 (0.347)
rs3208007	20	85	rs3787088 (0.99),rs6089961 (0.99),rs6122157 (0.989),rs1758205 (0.988),rs2253829 (0.987),rs2738758 (0.986),rs2263805 (0.985),rs2427532 (0.984),rs914559 (0.982),rs6122159 (0.981),rs2315009 (0.98),rs34251386 (0.979),rs2427529 (0.977),rs7262150 (0.976),rs67616625 (0.975),rs71325464 (0.973),rs2427534 (0.972),rs2253823 (0.971),rs2750483 (0.969),rs2427530 (0.968),rs6122154 (0.966),rs1151624 (0.965),rs2263806 (0.963),rs2750482 (0.962),rs35046559 (0.96),rs1151622 (0.959),rs2750480 (0.957),rs2750481 (0.956),rs1275330 (0.954),rs35201382 (0.953),rs2872881 (0.951),rs2236510 (0.949),rs6122158 (0.948),rs2259858 (0.946),rs1741708 (0.944),rs1295810 (0.942),rs2257440 (0.941),rs67468102 (0.939),rs1151623 (0.937),rs2427531 (0.935),rs2257885 (0.933),rs1291209 (0.931),rs1291213 (0.928),rs1048665 (0.926),rs2297441 (0.924),rs1291210 (0.921),rs3208008 (0.918),rs4809219 (0.915),rs1291207 (0.912),rs1291205 (0.909),rs2236508 (0.906),rs2258056 (0.903),rs909341 (0.9),rs1291206 (0.897),rs2257818 (0.893),rs1623866 (0.889),rs2738778 (0.885),rs6010620 (0.881),rs4809321 (0.877),rs3761124 (0.873),rs6062301 (0.868),rs6011018 (0.864),rs6010994 (0.859),rs2297433 (0.855),rs3848669 (0.85),rs2297438 (0.845),rs6089953 (0.84),rs6010998 (0.835),rs6011016 (0.829),rs6010621 (0.823),rs3787100 (0.815),rs2297440 (0.807),rs7361098 (0.795),rs4809323 (0.781),rs6062302 (0.768),rs2738785 (0.742),rs6062490 (0.711),rs2777941 (0.679),rs3787090 (0.648),rs3787092 (0.614),rs3787091 (0.556),rs2236506 (0.484),rs6011033 (0.384),rs3208007 (0.256)
rs34290285	2	4	rs1106639 (0.991),rs77062581 (0.988),rs34290285 (0.488)
rs36045143	16	14	rs7203459 (0.995),rs34720006 (0.99),rs17673553 (0.981),rs34540843 (0.972),rs62026377 (0.947),rs62026379 (0.915),rs62026376 (0.883),rs35441874 (0.843),rs12919828 (0.801),rs12935657 (0.754),rs2241099 (0.662),rs12919732 (0.552),rs36045143 (0.214)
rs4916533	3	28	rs74394036 (0.99),rs74507992 (0.99),rs111699786 (0.989),rs113962850 (0.988),rs115113317 (0.987),rs75149776 (0.987),rs113929878 (0.986),rs4916527 (0.985),rs4916529 (0.984),rs4916528 (0.982),rs111261380 (0.981),rs112336433 (0.978),rs112232968 (0.973),rs112904080 (0.967),rs12152278 (0.96),rs112823631 (0.953),rs75366683 (0.945),rs7349483 (0.935),rs4916514 (0.923),rs113048054 (0.911),rs12152276 (0.897),rs4916534 (0.87),rs4916535 (0.814),rs112669193 (0.756),rs74626344 (0.693),rs80064395 (0.573),rs4916533 (0.193)
rs56062135	15	6	rs72743461 (0.998),rs17293632 (0.959),rs56375023 (0.875),rs17228058 (0.729),rs56062135 (0.563)
rs56267605	4	72	rs72669161 (0.99),rs113022969 (0.99),rs17005728 (0.99),rs72669153 (0.99),rs45515895 (0.989),rs45463791 (0.989),rs4833248 (0.989),rs7681161 (0.989),rs9790402 (0.989),rs6814233 (0.988),rs972425 (0.988),rs17454584 (0.988),rs7658100 (0.988),rs6827756 (0.988),rs10857090 (0.987),rs72669125 (0.987),rs4416491 (0.987),rs2086346 (0.987),rs6534347 (0.987),rs72669119 (0.986),rs7675731 (0.986),rs7699809 (0.986),rs936607 (0.985),rs7688384 (0.985),rs11727369 (0.984),rs146583707 (0.983),rs11729811 (0.983),rs112481526 (0.982),rs72669165 (0.98),rs72669172 (0.979),rs45485691 (0.977),rs45454992 (0.975),rs35914000 (0.973),rs59867199 (0.97),rs28454948 (0.968),rs2069772 (0.964),rs56035021 (0.96),rs45605540 (0.956),rs17388568 (0.951),rs7693745 (0.947),rs62323898 (0.942),rs7664452 (0.932),rs28854492 (0.919),rs55904957 (0.906),rs45599938 (0.892),rs11722421 (0.877),rs55969942 (0.861),rs4505848 (0.845),rs13147049 (0.829),rs7699742 (0.812),rs7671357 (0.796),rs4438772 (0.777),rs62322711 (0.755),rs75925700 (0.732),rs716501 (0.709),rs148505069 (0.683),rs72669154 (0.657),rs2069763 (0.629),rs58939053 (0.599),rs11098659 (0.567),rs72687044 (0.534),rs55896948 (0.501),rs56360035 (0.467),rs1904522 (0.431),rs11725823 (0.393),rs12499753 (0.352),rs3136534 (0.31),rs62322747 (0.267),rs4145717 (0.221),rs4380538 (0.168),rs56267605 (0.113)

rs61815704	1	15	rs150107843 (0.995),rs17670505 (0.99),rs61811860 (0.984),rs147320119 (0.975),rs61815704 (0.965),rs61812715 (0.927),rs80337964 (0.897),rs61813875 (0.856),rs61813914 (0.813),rs76321446 (0.762),rs12731336 (0.687),rs72702900 (0.578),rs72702813 (0.447),rs61813920 (0.284)
rs61816766	1	9	rs12731336 (0.991),rs61814899 (0.989),rs72702900 (0.986),rs72702813 (0.983),rs61813920 (0.98),rs12123821 (0.974),rs61815559 (0.945),rs61816766 (0.394)
rs61839660	10	20	rs61839660 (0.36),rs61839672 (0.803),rs41295065 (0.827),rs7893324 (0.846),rs41295049 (0.863),rs41295071 (0.881),rs41295061 (0.898),rs41295081 (0.911),rs76996808 (0.924),rs12244238 (0.936),rs41295063 (0.947),rs12722522 (0.957),rs41295113 (0.966),rs7909519 (0.971),rs12254050 (0.977),rs12722496 (0.982),rs12722495 (0.985),rs61839702 (0.989),rs12722490 (0.992)
rs6461503	7	67	rs13236052 (0.991),rs2390341 (0.99),rs2390342 (0.989),rs13223048 (0.989),rs2214245 (0.988),rs12531500 (0.987),rs7779912 (0.986),rs7783149 (0.985),rs4721916 (0.984),rs916788 (0.983),rs2893003 (0.983),rs10260049 (0.982),rs7801672 (0.981),rs10272302 (0.98),rs10261154 (0.979),rs2390343 (0.978),rs2214244 (0.976),rs929220 (0.975),rs6947837 (0.974),rs7780222 (0.973),rs6969222 (0.972),rs4721917 (0.971),rs17142961 (0.97),rs10950814 (0.969),rs916787 (0.967),rs10273717 (0.966),rs10950813 (0.965),rs10278826 (0.963),rs7811804 (0.962),rs10260836 (0.961),rs2106759 (0.96),rs6965263 (0.958),rs12700213 (0.957),rs10271322 (0.955),rs7799620 (0.954),rs2188874 (0.953),rs10259919 (0.951),rs2214243 (0.95),rs7786951 (0.948),rs7802450 (0.947),rs10232906 (0.945),rs916789 (0.943),rs13221999 (0.942),rs7801605 (0.94),rs7798883 (0.938),rs10950815 (0.937),rs28712631 (0.935),rs7793850 (0.933),rs28506099 (0.931),rs71526332 (0.929),rs112721447 (0.926),rs4141371 (0.924),rs6947194 (0.922),rs7797370 (0.919),rs916790 (0.917),rs12700214 (0.914),rs2023789 (0.912),rs13247229 (0.909),rs7793679 (0.906),rs28650131 (0.904),rs11982540 (0.901),rs13225539 (0.898),rs4335039 (0.894),rs2023791 (0.89),rs10244416 (0.886),rs6461503 (0.865)
rs659529	11	102	rs10891283 (0.99),rs7128353 (0.99),rs4630327 (0.989),rs663763 (0.989),rs11213973 (0.989),rs11213968 (0.988),rs11213971 (0.988),rs542424 (0.988),rs875258 (0.987),rs6589244 (0.987),rs7938360 (0.986),rs7130753 (0.986),rs518294 (0.985),rs542275 (0.985),rs679032 (0.984),rs682239 (0.983),rs587010 (0.982),rs539524 (0.981),rs539553 (0.98),rs527078 (0.979),rs1784788 (0.977),rs10789841 (0.976),rs1784787 (0.974),rs490897 (0.972),rs490199 (0.97),rs61896951 (0.967),rs11213945 (0.964),rs539693 (0.961),rs1784776 (0.958),rs1784775 (0.954),rs1789359 (0.951),rs479667 (0.947),rs12806479 (0.942),rs1784784 (0.937),rs516263 (0.932),rs541198 (0.927),rs521155 (0.922),rs571462 (0.917),rs1784786 (0.911),rs34584980 (0.906),rs1789360 (0.901),rs521947 (0.895),rs567859 (0.889),rs1789361 (0.884),rs560821 (0.878),rs1619652 (0.872),rs1784785 (0.866),rs542831 (0.86),rs510866 (0.853),rs4534611 (0.847),rs1789358 (0.84),rs484013 (0.833),rs4938814 (0.826),rs1613778 (0.819),rs1612013 (0.812),rs493865 (0.805),rs1789351 (0.797),rs568506 (0.79),rs472465 (0.783),rs1611989 (0.775),rs11213948 (0.768),rs566647 (0.76),rs480293 (0.753),rs486038 (0.745),rs484834 (0.737),rs549143 (0.729),rs490492 (0.721),rs631490 (0.714),rs512669 (0.706),rs553632 (0.698),rs500163 (0.689),rs491937 (0.681),rs517982 (0.673),rs529529 (0.665),rs1784777 (0.656),rs11213940 (0.648),rs10749985 (0.639),rs7119893 (0.63),rs59921976 (0.622),rs576195 (0.613),rs578022 (0.604),rs493810 (0.595),rs1784778 (0.587),rs551825 (0.578),rs510388 (0.569),rs688354 (0.56),rs552387 (0.55),rs577044 (0.541),rs10891280 (0.532),rs2212520 (0.521),rs10749984 (0.509),rs11828343 (0.496),rs1944119 (0.483),rs12804962 (0.469),rs4616071 (0.453),rs12366001 (0.433),rs583032 (0.392),rs674230 (0.35),rs568038 (0.286),rs11213941 (0.218),rs659529 (0.148)
rs6881270	5	16	rs13188960 (1),rs34463936 (0.984),rs10214237 (0.963),rs11567705 (0.942),rs6890853 (0.919),rs10214273 (0.895),rs6871748 (0.869),rs11742270 (0.844),rs11742240 (0.813),rs7717955 (0.77),rs6897932 (0.677),rs10213865

			(0.58),rs11567694 (0.477),rs6881706 (0.374),rs6881270 (0.131)
rs72823641	2	29	rs11690644 (0.993),rs11465723 (0.99),rs10197862 (0.983),rs13408661 (0.976),rs13408569 (0.968),rs72823619 (0.959),rs3771180 (0.95),rs13418548 (0.94),rs72823621 (0.931),rs11465702 (0.92),rs72825916 (0.908),rs13431828 (0.893),rs72823646 (0.878),rs10179458 (0.86),rs3771175 (0.84),rs58815545 (0.815),rs12053429 (0.788),rs950881 (0.761),rs59185885 (0.733),rs10189154 (0.706),rs10189526 (0.677),rs10865050 (0.649),rs573943987 (0.62),rs10173081 (0.583),rs72823635 (0.545),rs11679893 (0.507),rs72823628 (0.465),rs72823641 (0.205)
rs742230	1	40	rs11805920 (0.99),rs11805484 (0.981),rs11805904 (0.972),rs1005733 (0.963),rs11803573 (0.953),rs66880507 (0.943),rs11249209 (0.933),rs11249217 (0.922),rs11803594 (0.91),rs7536175 (0.899),rs4648884 (0.887),rs11249216 (0.875),rs74060619 (0.863),rs4648883 (0.848),rs1005734 (0.834),rs11802714 (0.818),rs11249204 (0.803),rs6695069 (0.786),rs11249210 (0.768),rs12131497 (0.749),rs4644442 (0.73),rs67823079 (0.711),rs60097574 (0.692),rs10903115 (0.672),rs3845302 (0.652),rs71514255 (0.632),rs12128982 (0.609),rs6600246 (0.585),rs10794666 (0.56),rs1507101 (0.536),rs760805 (0.505),rs61774728 (0.471),rs7517302 (0.434),rs4649037 (0.394),rs11249203 (0.351),rs742232 (0.303),rs742231 (0.255),rs7518125 (0.194),rs742230 (0.13)
rs7705653	5	22	rs7734635 (0.991),rs28874883 (0.988),rs7728612 (0.983),rs6885792 (0.979),rs10065671 (0.974),rs4280918 (0.969),rs6869502 (0.964),rs12657787 (0.96),rs7700507 (0.955),rs60557452 (0.949),rs10073425 (0.944),rs7710963 (0.938),rs12659961 (0.932),rs7728912 (0.926),rs3853750 (0.918),rs7735355 (0.909),rs7735519 (0.894),rs7705653 (0.877),rs6594499 (0.834),rs1438673 (0.75),rs1837253 (0.528)
rs7936070	11	11	rs10160518 (0.994),rs4494327 (0.987),rs2155219 (0.98),rs11236797 (0.972),rs11236791 (0.96),rs61893460 (0.928),rs7936312 (0.866),rs7936434 (0.764),rs7936323 (0.622),rs7936070 (0.234)
rs8008961	14	68	rs2145423 (0.993),rs7155473 (0.989),rs7147852 (0.984),rs2180769 (0.98),rs12890124 (0.975),rs8017304 (0.97),rs7148416 (0.965),rs12890109 (0.96),rs2145422 (0.954),rs11626138 (0.949),rs60593979 (0.943),rs12878627 (0.937),rs7150988 (0.932),rs12890110 (0.926),rs11628825 (0.92),rs2180770 (0.914),rs11626195 (0.908),rs3784104 (0.902),rs7146850 (0.896),rs1956528 (0.889),rs12884901 (0.883),rs8015139 (0.876),rs12880842 (0.87),rs10131490 (0.863),rs1956526 (0.857),rs11628954 (0.85),rs1956529 (0.843),rs1956532 (0.836),rs11628890 (0.829),rs3784108 (0.821),rs1108590 (0.813),rs61985136 (0.805),rs3825730 (0.797),rs61985135 (0.789),rs7148073 (0.78),rs11627646 (0.771),rs3784109 (0.762),rs12881502 (0.753),rs2877455 (0.744),rs2064912 (0.735),rs10141370 (0.725),rs12889949 (0.715),rs11158729 (0.705),rs12878858 (0.694),rs12883719 (0.684),rs1956524 (0.673),rs7158493 (0.663),rs2064911 (0.652),rs12896939 (0.64),rs12885750 (0.628),rs3825729 (0.616),rs1956525 (0.603),rs2013413 (0.589),rs911254 (0.574),rs56267624 (0.56),rs12892777 (0.545),rs10483807 (0.531),rs12886238 (0.516),rs12880109 (0.5),rs11158730 (0.48),rs1950897 (0.454),rs3784099 (0.427),rs2104047 (0.398),rs1885013 (0.368),rs911263 (0.338),rs2208397 (0.28),rs8008961 (0.189)
rs869402	17	87	rs11658993 (0.991),rs4065275 (0.99),rs35569035 (0.988),rs11557466 (0.987),rs11078925 (0.985),rs9910826 (0.984),rs9907088 (0.982),rs12946510 (0.98),rs34120102 (0.979),rs2952140 (0.977),rs34189114 (0.975),rs12232497 (0.973),rs4795398 (0.971),rs13380815 (0.968),rs9904624 (0.966),rs9905959 (0.964),rs907091 (0.962),rs11870965 (0.959),rs12939566 (0.957),rs12941333 (0.955),rs4795397 (0.952),rs1054609 (0.95),rs2941522 (0.947),rs12936409 (0.944),rs12709365 (0.941),rs35736272 (0.938),rs2872507 (0.935),rs12939457 (0.932),rs10852936 (0.929),rs8069176 (0.925),rs2313430 (0.92),rs10852935 (0.916),rs36095411 (0.912),rs1453559 (0.907),rs9891174 (0.903),rs11557467 (0.898),rs9903250 (0.893),rs12949100 (0.888),rs11658278 (0.882),rs2952144 (0.875),rs12936231 (0.869),rs12939565 (0.862),rs11650661 (0.855),rs12950209 (0.848),rs11655198 (0.841),rs9916765 (0.834),rs9908132 (0.827),rs12103884 (0.819),rs12950743 (0.812),rs9303279 (0.804),rs11651596 (0.796),rs8067378 (0.788),rs9901146 (0.779),rs9906951

			(0.77),rs9303277 (0.761),rs11655292 (0.752),rs2305480 (0.742),rs4795400 (0.732),rs4795399 (0.721),rs56750287 (0.71),rs11078928 (0.698),rs7359623 (0.686),rs62067034 (0.674),rs8076131 (0.661),rs11078926 (0.647),rs9747973 (0.633),rs11078927 (0.619),rs36000226 (0.603),rs7224129 (0.585),rs2290400 (0.565),rs9303281 (0.545),rs1011082 (0.524),rs4795401 (0.503),rs2305479 (0.481),rs7219923 (0.46),rs883770 (0.438),rs7216558 (0.415),rs8074437 (0.392),rs1008723 (0.365),rs56380902 (0.338),rs7216389 (0.307),rs921650 (0.276),rs6503524 (0.243),rs921649 (0.206),rs12453507 (0.169),rs869402 (0.057)
rs9273374	6	16	rs3828791 (0.99),rs28675927 (0.989),rs1063355 (0.987),rs9274660 (0.985),rs3828798 (0.983),rs9273372 (0.981),rs9273373 (0.906),rs9273444 (0.831),rs9273445 (0.744),rs17205191 (0.657),rs9273376 (0.57),rs9273443 (0.482),rs9273356 (0.393),rs9273374 (0.298),rs28407950 (0.102)
rs9775039	9	16	rs928413 (0.991),rs3939286 (0.987),rs1929995 (0.983),rs7032572 (0.974),rs1342326 (0.962),rs72699191 (0.95),rs11521485 (0.93),rs10975468 (0.902),rs72699186 (0.854),rs144829310 (0.797),rs12349858 (0.738),rs10975471 (0.676),rs72699188 (0.602),rs9775039 (0.318),rs12376324 (0.159)
rs9911533	17	8	rs7226035 (0.993),rs7223136 (0.99),rs11658582 (0.984),rs7221109 (0.962),rs757411 (0.937),rs9911533 (0.908),rs112401631 (0.812)

Supplementary Table 10. Co-localization analysis of both asthma and allergic diseases are associated and share a single causal variant

SNP	CHR	Position	Asthma Beta	Asthma SE	Asthma <i>P</i>	Allergy Beta	Allergy SE	Allergy <i>P</i>	ASSET <i>P</i>	Representative gene	Coloc H4 Prob
rs10074523	5	132060583	0.0989399	0.015233021	4.15E-11	0.0525925	0.0124082	1.13E-05	2.37E-10	<i>IL4</i>	0.921
rs10174949	2	8442248	-0.0895965	0.014740511	6.08E-10	-0.0922249	0.0115132	5.72E-16	1.7E-16	<i>LINC00299</i>	0.995
rs10414065	19	33721455	-0.160404	0.028246005	6.78E-09	-0.118221	0.021751	2.74E-08	2.63E-10	<i>SLC7A10*</i>	0.998
rs1059513	12	57489709	-0.147688	0.022102605	1.18E-11	-0.101147	0.017089	1.62E-09	7.65E-13	<i>GPR182</i>	0.998
rs10795656	10	8595839	0.0685928	0.014907806	2.10E-06	0.0723207	0.0117006	3.19E-10	4.07E-10	<i>GATA3*</i>	0.907
rs10876864	12	56401085	0.0925792	0.013255067	1.43E-12	0.0629748	0.0104535	8.49E-10	1.41E-13	<i>CDK2</i>	0.982
rs1214598	1	167426424	-0.0728933	0.013820532	6.66E-08	-0.066033	0.0107813	4.54E-10	5.14E-11	<i>CD247</i>	0.962
rs12413578	10	9049253	-0.169484	0.022607707	3.27E-14	-0.106695	0.0174287	4.63E-10	1.09E-14	<i>HV745896*</i>	0.944
rs12743520	1	93037112	-0.044579	0.016236528	3.02E-03	-0.0687072	0.0121034	6.87E-09	3.83E-08	<i>EVIS</i>	0.219
rs1837253	5	110401872	-0.140412	0.015264394	1.81E-20	-0.0873023	0.0118953	1.07E-13	4.38E-21	<i>TSLP*</i>	0.000
rs2136016	8	81300681	0.0834216	0.013550589	3.72E-10	0.0372958	0.0110197	3.57E-04	2.11E-09	<i>ZBTB10*</i>	0.666
rs2169282	9	6350235	0.0880109	0.013463079	3.13E-11	0.0459289	0.0109209	1.30E-05	1.8E-10	<i>GLDC</i>	0.959
rs2548992	5	131808668	0.0934903	0.014616344	7.96E-11	0.0392207	0.0119985	5.40E-04	4.54E-10	<i>C5orf56</i>	0.922
rs2706362	5	131925187	0.109751	0.016451271	1.27E-11	0.0676586	0.0132761	1.73E-07	3.75E-11	<i>IL13</i>	0.927
rs2766664	20	52171241	0.0478373	0.016347276	1.72E-03	0.079735	0.0119791	1.41E-11	8.07E-11	<i>LOC101927770</i>	0.416
rs28393318	4	38784267	-0.103917	0.016727359	2.61E-10	-0.118221	0.0130521	6.67E-20	2.14E-19	<i>TLR1</i>	0.940
rs301805	1	8481016	-0.071496	0.013507164	6.01E-08	-0.0528735	0.0106398	3.36E-07	6.43E-09	<i>RERE</i>	0.990
rs3208007	20	62322288	-0.0894872	0.015908335	9.27E-09	-0.0676366	0.0124544	2.81E-08	3.22E-10	<i>ARFRP1</i>	0.904
rs34290285	2	242698640	-0.100484	0.01544798	3.89E-11	-0.0951902	0.0120684	1.54E-15	5.17E-17	<i>D2HGDH</i>	0.999
rs36045143	16	11224966	-0.127379	0.015469744	9.05E-17	-0.0993784	0.012067	8.94E-17	1.83E-21	<i>CLEC16A</i>	0.987
rs4916533	3	196373582	-0.126925	0.025359194	2.79E-07	-0.0973923	0.0196559	3.62E-07	1.66E-08	<i>NRROS</i>	0.983
rs56062135	15	67455630	0.14842	0.015026954	2.62E-23	0.0861777	0.0121372	6.23E-13	1.56E-22	<i>SMAD3</i>	0.996
rs56267605	4	123363109	0.0861777	0.01395361	3.29E-10	0.0667236	0.011001	6.59E-10	2.56E-12	<i>ADAD1</i>	0.940
rs61815704	1	152893891	0.205387	0.041647527	4.08E-07	0.176471	0.0332405	5.51E-08	5.16E-09	<i>LCE1A</i>	0.985
rs61816766	1	152319572	0.195567	0.036128756	3.10E-08	0.187309	0.0286397	3.07E-11	4.63E-12	<i>FLG</i>	0.952
rs61839660	10	6094697	0.0723207	0.02259624	6.86E-04	0.115113	0.0168313	3.98E-12	2.3E-11	<i>IL2RA</i>	0.751
rs6461503	7	20560996	0.0788112	0.013416772	2.13E-09	0.0554347	0.0105852	8.16E-08	3.19E-10	<i>ITGB8*</i>	0.993
rs659529	11	111436896	-0.0736465	0.014835826	3.45E-07	-0.0731085	0.0115445	1.20E-10	6.03E-11	<i>ALG9</i>	0.940
rs6881270	5	35879095	-0.0657125	0.015218137	7.87E-06	-0.0915672	0.0117073	2.61E-15	1.53E-14	<i>IL7R</i>	0.941
rs72823641	2	102936159	-0.170195	0.019956772	7.43E-18	-0.155835	0.0154948	4.27E-24	1.58E-27	<i>IL1R1</i>	0.975
rs742230	1	25251424	-0.05975	0.013643157	5.95E-06	-0.0590072	0.0105915	1.27E-08	1.02E-08	<i>RUNX3</i>	0.082
rs7705653	5	110142816	0.112435	0.018361605	4.58E-10	0.131905	0.0143456	1.88E-20	1.12E-19	<i>SLC25A46</i>	0.000

rs7936070	11	76293527	0.123986	0.013156332	2.17E-21	0.0989399	0.010317	4.40E-22	2.81E-28	<i>C11orf30</i>	0.994
rs8008961	14	68752643	0.0741794	0.014671117	2.14E-07	0.0582689	0.0116761	3.01E-07	1.24E-08	<i>RAD51B</i>	0.910
rs869402	17	38068043	0.111541	0.013068885	7.02E-18	0.0344014	0.0107262	6.70E-04	4.15E-17	<i>GSDMA</i>	0.379
rs9273374	6	32626614	-0.168537	0.013592122	1.31E-35	-0.0403013	0.0109526	1.17E-04	7.87E-35	<i>HLA-DOB</i>	0.991
rs9775039	9	6177453	0.168054	0.017197038	7.41E-23	0.0751075	0.0140845	4.84E-08	4.42E-22	<i>IL33</i>	0.961
rs9911533	17	38775476	-0.0706371	0.013955291	2.08E-07	-0.0882849	0.0108164	1.65E-16	9.7E-16	<i>KRT24</i>	0.982

Co-localization test was used. Coloc H4 Prob: The probability of both traits are associated and share a single causal variant. Sample size for asthma is 90,853, and for allergic diseases is 102,453.

Supplementary Table 11. Significant single-tissue expression quantitative trait loci (eQTL) from GTEx for 22 representative genes

Gene symbol	Chromosome	P-value	Effect size	Tissue
<i>CD247</i>	1	6.20E-07	0.24	Muscle - Skeletal
<i>CD247</i>	1	3.2E-06	0.15	Lung
<i>CD247</i>	1	5.9E-06	-0.54	Brain - Cerebellum
<i>CD247</i>	1	0.000013	-0.33	Brain - Cerebellar Hemisphere
<i>CD247</i>	1	0.000014	0.53	Esophagus - Gastroesophageal Junction
<i>CD247</i>	1	0.000034	-0.29	Nerve - Tibial
<i>RERE</i>	1	3.00E-26	0.32	Esophagus - Mucosa
<i>RERE</i>	1	9.20E-22	0.19	Whole Blood
<i>RERE</i>	1	3.00E-20	-0.3	Adipose - Subcutaneous
<i>RERE</i>	1	2.30E-15	-0.17	Skin - Sun Exposed (Lower leg)
<i>RERE</i>	1	2.90E-15	-0.29	Adipose - Visceral (Omentum)
<i>RERE</i>	1	8.80E-12	-0.2	Nerve - Tibial
<i>RERE</i>	1	2.30E-11	0.16	Skin - Not Sun Exposed (Suprapubic)
<i>RERE</i>	1	1.60E-09	0.24	Breast - Mammary Tissue
<i>RERE</i>	1	1.60E-09	0.23	Cells - Transformed fibroblasts
<i>RERE</i>	1	8.20E-09	0.23	Thyroid
<i>RERE</i>	1	3.60E-08	0.15	Lung
<i>RERE</i>	1	3.30E-07	-0.38	Brain - Nucleus accumbens (basal ganglia)
<i>RERE</i>	1	6.30E-07	-0.3	Spleen
<i>RERE</i>	1	6.70E-07	0.28	Pancreas
<i>RERE</i>	1	3.7E-06	-0.11	Muscle - Skeletal
<i>RERE</i>	1	3.8E-06	0.29	Brain - Cortex
<i>RERE</i>	1	5.7E-06	-0.34	Brain - Caudate (basal ganglia)
<i>RERE</i>	1	0.000011	0.68	Artery - Aorta
<i>RUNX3</i>	1	1.00E-07	0.42	Testis
<i>RUNX3</i>	1	2.7E-06	-0.26	Cells - Transformed fibroblasts
<i>RUNX3</i>	1	0.00001	-1.1	Pituitary
<i>IL13</i>	5	1.60E-10	0.25	Testis
<i>IL13</i>	5	0.000013	-1.1	Artery - Tibial
<i>IL4</i>	5	9.40E-13	0.7	Pituitary
<i>IL4</i>	5	1.90E-07	0.56	Prostate
<i>IL4</i>	5	3.4E-06	0.29	Lung

<i>IL4</i>	5	6.5E-06	0.45	Ovary
<i>IL4</i>	5	0.000021	0.89	Testis
<i>C11orf30</i>	11	1.90E-07	-0.15	Thyroid
<i>C11orf30</i>	11	5.60E-07	3	Brain - Nucleus accumbens (basal ganglia)
<i>C11orf30</i>	11	1.9E-06	0.96	Spleen
<i>C11orf30</i>	11	2.7E-06	0.39	Esophagus - Mucosa
<i>C11orf30</i>	11	0.000011	0.21	Skin - Not Sun Exposed (Suprapubic)
<i>C1orf68</i>	12	4.40E-18	-0.29	Skin - Not Sun Exposed (Suprapubic)
<i>C1orf68</i>	12	4.70E-09	-0.15	Skin - Sun Exposed (Lower leg)
<i>C1orf68</i>	12	0.000011	1.7	Adipose - Visceral (Omentum)
<i>SMAD3</i>	15	1.60E-25	-0.42	Esophagus - Mucosa
<i>SMAD3</i>	15	1.20E-21	-0.5	Thyroid
<i>SMAD3</i>	15	4.20E-15	0.3	Muscle - Skeletal
<i>SMAD3</i>	15	2.10E-10	0.22	Testis
<i>SMAD3</i>	15	1.60E-08	-0.22	Adipose - Subcutaneous
<i>SMAD3</i>	15	7.30E-08	1.1	Skin - Not Sun Exposed (Suprapubic)
<i>SMAD3</i>	15	6.50E-07	-0.21	Cells - Transformed fibroblasts
<i>SMAD3</i>	15	9.80E-07	-0.16	Skin - Sun Exposed (Lower leg)
<i>SMAD3</i>	15	2.5E-06	0.22	Brain - Cerebellum
<i>SMAD3</i>	15	3.6E-06	-0.23	Adipose - Visceral (Omentum)
<i>SMAD3</i>	15	4.8E-06	-4.4	Brain - Amygdala
<i>CLEC16A</i>	16	4.40E-08	0.26	Testis
<i>CLEC16A</i>	16	6.70E-08	-0.2	Lung
<i>CLEC16A</i>	16	1.50E-07	0.14	Nerve - Tibial
<i>CLEC16A</i>	16	2.20E-07	0.19	Adipose - Subcutaneous
<i>CLEC16A</i>	16	4.40E-07	0.19	Skin - Not Sun Exposed (Suprapubic)
<i>CLEC16A</i>	16	5.60E-07	-0.2	Thyroid
<i>CLEC16A</i>	16	0.000013	-0.27	Muscle - Skeletal
<i>CLEC16A</i>	16	0.000014	0.25	Artery - Tibial

Supplementary Table 12. rs34290285 on *D2HGDH* gene single-tissue eQTL from GTEx

Gene symbol	SNP	P-value	Effect size	Tissue
<i>D2HGDH</i>	rs34290285	5.20E-17	-0.44	Thyroid
<i>D2HGDH</i>	rs34290285	1.90E-14	-0.41	Cells - Transformed fibroblasts
<i>D2HGDH</i>	rs34290285	1.70E-13	-0.42	Esophagus - Mucosa
<i>D2HGDH</i>	rs34290285	4.20E-12	-0.25	Muscle - Skeletal
<i>D2HGDH</i>	rs34290285	1.40E-11	-0.43	Adipose - Subcutaneous
<i>D2HGDH</i>	rs34290285	2.40E-11	-0.34	Artery - Tibial
<i>D2HGDH</i>	rs34290285	1.30E-10	-0.36	Lung
<i>D2HGDH</i>	rs34290285	1.70E-10	-0.37	Nerve - Tibial
<i>D2HGDH</i>	rs34290285	3.20E-10	-0.35	Skin - Sun Exposed (Lower leg)
<i>D2HGDH</i>	rs34290285	1.10E-09	-0.39	Esophagus - Muscularis
<i>D2HGDH</i>	rs34290285	2.00E-09	-0.37	Heart - Left Ventricle
<i>D2HGDH</i>	rs34290285	1.50E-08	-0.5	Testis
<i>D2HGDH</i>	rs34290285	1.90E-08	-0.53	Adrenal Gland
<i>D2HGDH</i>	rs34290285	5.10E-08	-0.39	Heart - Atrial Appendage
<i>D2HGDH</i>	rs34290285	1.10E-07	-0.47	Pancreas
<i>D2HGDH</i>	rs34290285	2.00E-07	-0.35	Stomach
<i>D2HGDH</i>	rs34290285	5.00E-07	-0.3	Breast - Mammary Tissue
<i>D2HGDH</i>	rs34290285	6.70E-07	-0.54	Brain - Cortex
<i>D2HGDH</i>	rs34290285	7.00E-07	-0.29	Artery - Aorta
<i>D2HGDH</i>	rs34290285	0.000001	-0.3	Colon - Transverse
<i>D2HGDH</i>	rs34290285	5.2E-06	-0.27	Skin - Not Sun Exposed (Suprapubic)
<i>D2HGDH</i>	rs34290285	0.000011	-0.51	Brain - Putamen (basal ganglia)
<i>D2HGDH</i>	rs34290285	0.000011	-0.52	Spleen
<i>D2HGDH</i>	rs34290285	0.000017	-0.46	Brain - Frontal Cortex (BA9)
<i>D2HGDH</i>	rs34290285	0.000032	-0.43	Brain - Caudate (basal ganglia)
<i>D2HGDH</i>	rs34290285	0.000033	-0.47	Cells - EBV-transformed lymphocytes

Supplementary Table 13. rs34290285 on *GAL3ST2* gene single-tissue eQTL from GTEx

Gene symbol	SNP	P-value	Effect size	Tissue
<i>GAL3ST2</i>	rs34290285	3.20E-08	0.46	Muscle - Skeletal
<i>GAL3ST2</i>	rs34290285	3.90E-08	0.57	Esophagus - Muscularis
<i>GAL3ST2</i>	rs34290285	1.90E-07	0.56	Artery - Aorta
<i>GAL3ST2</i>	rs34290285	3.30E-07	0.46	Thyroid
<i>GAL3ST2</i>	rs34290285	8.80E-07	0.57	Skin - Not Sun Exposed (Suprapubic)
<i>GAL3ST2</i>	rs34290285	2.3E-06	0.46	Cells - Transformed fibroblasts
<i>GAL3ST2</i>	rs34290285	0.00001	0.63	Esophagus - Gastroesophageal Junction
<i>GAL3ST2</i>	rs34290285	0.000014	0.59	Liver
<i>GAL3ST2</i>	rs34290285	0.000034	0.37	Skin - Sun Exposed (Lower leg)

Supplementary Table 14. Co-localization using 8 tissues from GTEx (H4>0.5)

ensembleID	Gene	CHR	SNP	Tissue	Coloc H4 Prob
ENSG00000142599.13	RERE	1	rs301805	Skin_Not_Sun_Exposed_Suprapubic	0.99361188
ENSG00000142599.13	RERE	1	rs301805	Esophagus_Mucosa	0.993492322
ENSG00000232912.1	RP5-1115A15.1	1	rs301805	Skin_Not_Sun_Exposed_Suprapubic	0.992012148
ENSG00000142599.13	RERE	1	rs301805	Whole_Blood	0.991210364
ENSG00000213171.2	LINGO4	1	rs61815704	Skin_Sun_Exposed_Lower_leg	0.98523104
ENSG00000232912.1	RP5-1115A15.1	1	rs301805	Esophagus_Mucosa	0.984730329
ENSG00000232912.1	RP5-1115A15.1	1	rs301805	Lung	0.977220751
ENSG00000232912.1	RP5-1115A15.1	1	rs301805	Esophagus_Muscularis	0.923077427
ENSG00000232912.1	RP5-1115A15.1	1	rs301805	Whole_Blood	0.921447774
ENSG00000232912.1	RP5-1115A15.1	1	rs301805	Skin_Sun_Exposed_Lower_leg	0.906407192
ENSG00000142599.13	RERE	1	rs301805	Lung	0.9033932
ENSG00000213171.2	LINGO4	1	rs61816766	Skin_Sun_Exposed_Lower_leg	0.849816464
ENSG00000273160.1	RP11-104L21.3	1	rs1214598	Esophagus_Muscularis	0.836954489
ENSG00000142599.13	RERE	1	rs301805	Skin_Sun_Exposed_Lower_leg	0.81360367
ENSG00000232912.1	RP5-1115A15.1	1	rs301805	Esophagus_Gastroesophageal_Junction	0.804126648
ENSG00000269978.1	RP11-338N10.3	1	rs301805	Esophagus_Muscularis	0.583929699
ENSG00000162676.7	GFI1	1	rs12743520	Lung	0.567067399
ENSG00000176720.3	BOK	2	rs34290285	Lung	0.962055436
ENSG00000154252.11	GAL3ST2	2	rs34290285	Esophagus_Muscularis	0.927348619
ENSG00000205716.4	AC007248.6	2	rs72823641	Whole_Blood	0.888185229
ENSG00000188011.5	CXXC11	2	rs34290285	Whole_Blood	0.829179052
ENSG00000234235.1	BOK-AS1	2	rs34290285	Lung	0.805372576
ENSG00000154252.11	GAL3ST2	2	rs34290285	Skin_Not_Sun_Exposed_Suprapubic	0.778788182
ENSG00000188389.6	PDCD1	2	rs34290285	Whole_Blood	0.662632657
ENSG00000154252.11	GAL3ST2	2	rs34290285	Skin_Sun_Exposed_Lower_leg	0.645666526
ENSG00000174004.5	NRROS	3	rs4916533	Skin_Sun_Exposed_Lower_leg	0.905554089
ENSG00000061938.12	TNK2	3	rs4916533	Lung	0.538806761
ENSG00000174123.6	TLR10	4	rs28393318	Skin_Not_Sun_Exposed_Suprapubic	0.766079872
ENSG00000197712.7	FAM114A1	4	rs28393318	Lung	0.694576592
ENSG00000145386.5	CCNA2	4	rs56267605	Esophagus_Gastroesophageal_Junction	0.624076338
ENSG00000158985.9	CDC42SE2	5	rs10074523	Whole_Blood	0.779905873
ENSG00000158985.9	CDC42SE2	5	rs2706362	Whole_Blood	0.761736723

ENSG00000134987.7	WDR36	5	rs7705653	Skin_Not_Sun_Exposed_Suprapubic	0.723752912
ENSG00000113522.9	RAD50	5	rs2706362	Skin_Not_Sun_Exposed_Suprapubic	0.711880646
ENSG00000113522.9	RAD50	5	rs10074523	Skin_Not_Sun_Exposed_Suprapubic	0.683466563
ENSG00000131437.11	KIF3A	5	rs10074523	Skin_Sun_Exposed_Lower_leg	0.682976802
ENSG00000131437.11	KIF3A	5	rs2548992	Skin_Sun_Exposed_Lower_leg	0.681788089
ENSG00000131437.11	KIF3A	5	rs2706362	Skin_Sun_Exposed_Lower_leg	0.668508645
ENSG00000131437.11	KIF3A	5	rs10074523	Esophagus_Gastroesophageal_Junction	0.651335824
ENSG00000131437.11	KIF3A	5	rs2548992	Esophagus_Gastroesophageal_Junction	0.65011701
ENSG00000131437.11	KIF3A	5	rs10074523	Skin_Not_Sun_Exposed_Suprapubic	0.647954655
ENSG00000113522.9	RAD50	5	rs2548992	Skin_Not_Sun_Exposed_Suprapubic	0.646262645
ENSG00000131437.11	KIF3A	5	rs2548992	Skin_Not_Sun_Exposed_Suprapubic	0.645793092
ENSG00000131437.11	KIF3A	5	rs2706362	Esophagus_Gastroesophageal_Junction	0.636198666
ENSG00000134987.7	WDR36	5	rs1837253	Skin_Not_Sun_Exposed_Suprapubic	0.635401793
ENSG00000131437.11	KIF3A	5	rs2706362	Skin_Not_Sun_Exposed_Suprapubic	0.632436159
ENSG00000197208.5	SLC22A4	5	rs2548992	Esophagus_Muscularis	0.609754695
ENSG00000197208.5	SLC22A4	5	rs10074523	Esophagus_Muscularis	0.608133678
ENSG00000197208.5	SLC22A4	5	rs2706362	Esophagus_Muscularis	0.605463646
ENSG00000113522.9	RAD50	5	rs10074523	Skin_Sun_Exposed_Lower_leg	0.576148077
ENSG00000113522.9	RAD50	5	rs2548992	Skin_Sun_Exposed_Lower_leg	0.568634074
ENSG00000113522.9	RAD50	5	rs2706362	Skin_Sun_Exposed_Lower_leg	0.568358722
ENSG00000113520.6	IL4	5	rs10074523	Lung	0.563019731
ENSG00000113520.6	IL4	5	rs2548992	Lung	0.562853986
ENSG00000113520.6	IL4	5	rs2706362	Lung	0.548084044
ENSG00000158985.9	CDC42SE2	5	rs2548992	Whole_Blood	0.52523777
ENSG00000131437.11	KIF3A	5	rs10074523	Esophagus_Mucosa	0.523096635
ENSG00000131437.11	KIF3A	5	rs2548992	Esophagus_Mucosa	0.521716175
ENSG00000131437.11	KIF3A	5	rs2706362	Esophagus_Mucosa	0.506597927
ENSG00000232629.4	HLA-DQB2	6	rs9273374	Esophagus_Mucosa	0.987978452
ENSG00000223534.1	HLA-DQB1-AS1	6	rs9273374	Whole_Blood	0.987915412
ENSG00000232629.4	HLA-DQB2	6	rs9273374	Esophagus_Muscularis	0.987810607
ENSG00000223534.1	HLA-DQB1-AS1	6	rs9273374	Esophagus_Mucosa	0.987797454
ENSG00000196735.7	HLA-DQA1	6	rs9273374	Whole_Blood	0.987720196
ENSG00000196735.7	HLA-DQA1	6	rs9273374	Esophagus_Gastroesophageal_Junction	0.987705617
ENSG00000232629.4	HLA-DQB2	6	rs9273374	Lung	0.987401991

ENSG00000196735.7	HLA-DQA1	6	rs9273374	Lung	0.987388132
ENSG00000179344.12	HLA-DQB1	6	rs9273374	Lung	0.987296387
ENSG00000232629.4	HLA-DQB2	6	rs9273374	Whole_Blood	0.987237731
ENSG00000179344.12	HLA-DQB1	6	rs9273374	Esophagus_Gastroesophageal_Junction	0.987054648
ENSG00000232629.4	HLA-DQB2	6	rs9273374	Esophagus_Gastroesophageal_Junction	0.987020329
ENSG00000196735.7	HLA-DQA1	6	rs9273374	Esophagus_Mucosa	0.986890186
ENSG00000179344.12	HLA-DQB1	6	rs9273374	Vagina	0.986443668
ENSG00000179344.12	HLA-DQB1	6	rs9273374	Esophagus_Mucosa	0.985435242
ENSG00000196735.7	HLA-DQA1	6	rs9273374	Esophagus_Muscularis	0.984671484
ENSG00000179344.12	HLA-DQB1	6	rs9273374	Skin_Not_Sun_Exposed_Suprapubic	0.969448289
ENSG00000179344.12	HLA-DQB1	6	rs9273374	Skin_Sun_Exposed_Lower_leg	0.968200869
ENSG00000223534.1	HLA-DQB1-AS1	6	rs9273374	Vagina	0.945039753
ENSG00000232629.4	HLA-DQB2	6	rs9273374	Vagina	0.815109307
ENSG00000204525.10	HLA-C	6	rs9273374	Esophagus_Gastroesophageal_Junction	0.78394351
ENSG00000196735.7	HLA-DQA1	6	rs9273374	Vagina	0.717062116
ENSG00000196126.6	HLA-DRB1	6	rs9273374	Esophagus_Gastroesophageal_Junction	0.709112807
ENSG00000204444.6	APOM	6	rs9273374	Esophagus_Muscularis	0.673812437
ENSG00000204525.10	HLA-C	6	rs9273374	Skin_Sun_Exposed_Lower_leg	0.648370994
ENSG00000204520.8	MICA	6	rs9273374	Esophagus_Muscularis	0.627012481
ENSG00000204528.3	PSORS1C3	6	rs9273374	Lung	0.622582863
ENSG00000179344.12	HLA-DQB1	6	rs9273374	Esophagus_Muscularis	0.581272823
ENSG00000179344.12	HLA-DQB1	6	rs9273374	Whole_Blood	0.523772923
ENSG00000137033.7	IL33	9	rs9775039	Esophagus_Muscularis	0.765571245
ENSG00000137033.7	IL33	9	rs2169282	Esophagus_Muscularis	0.760696914
ENSG00000204381.7	LAYN	11	rs659529	Lung	0.906534163
ENSG00000170145.4	SIK2	11	rs659529	Esophagus_Mucosa	0.824896081
ENSG00000170145.4	SIK2	11	rs659529	Skin_Sun_Exposed_Lower_leg	0.785986904
ENSG00000204381.7	LAYN	11	rs659529	Esophagus_Muscularis	0.76400939
ENSG00000255561.2	FDXACB1	11	rs659529	Esophagus_Mucosa	0.718480693
ENSG00000170145.4	SIK2	11	rs659529	Skin_Not_Sun_Exposed_Suprapubic	0.62846992
ENSG00000170145.4	SIK2	11	rs659529	Whole_Blood	0.613964012
ENSG00000268472.1	AP002884.2	11	rs659529	Skin_Sun_Exposed_Lower_leg	0.562160217
ENSG00000137720.3	C11orf1	11	rs659529	Skin_Sun_Exposed_Lower_leg	0.541311394
ENSG00000086848.10	ALG9	11	rs659529	Esophagus_Mucosa	0.516576386

ENSG00000139531.8	SUOX	12	rs10876864	Skin_Not_Sun_Exposed_Suprapubic	0.995664168
ENSG00000197728.5	RPS26	12	rs10876864	Vagina	0.994315736
ENSG00000197728.5	RPS26	12	rs10876864	Whole_Blood	0.993887155
ENSG00000197728.5	RPS26	12	rs10876864	Esophagus_Gastroesophageal_Junction	0.993887141
ENSG00000197728.5	RPS26	12	rs10876864	Skin_Not_Sun_Exposed_Suprapubic	0.993887141
ENSG00000197728.5	RPS26	12	rs10876864	Skin_Sun_Exposed_Lower_leg	0.993887141
ENSG00000197728.5	RPS26	12	rs10876864	Esophagus_Mucosa	0.993887141
ENSG00000197728.5	RPS26	12	rs10876864	Esophagus_Muscularis	0.993887141
ENSG00000197728.5	RPS26	12	rs10876864	Lung	0.993887141
ENSG00000123411.10	IKZF4	12	rs10876864	Esophagus_Mucosa	0.988632038
ENSG00000139531.8	SUOX	12	rs10876864	Esophagus_Gastroesophageal_Junction	0.985222517
ENSG00000139531.8	SUOX	12	rs10876864	Whole_Blood	0.970885756
ENSG00000139531.8	SUOX	12	rs10876864	Esophagus_Muscularis	0.963598038
ENSG00000123411.10	IKZF4	12	rs10876864	Skin_Not_Sun_Exposed_Suprapubic	0.951233741
ENSG00000139531.8	SUOX	12	rs10876864	Lung	0.897997037
ENSG00000139531.8	SUOX	12	rs10876864	Esophagus_Mucosa	0.887389785
ENSG00000135482.2	ZC3H10	12	rs10876864	Skin_Sun_Exposed_Lower_leg	0.8670497
ENSG00000139531.8	SUOX	12	rs10876864	Skin_Sun_Exposed_Lower_leg	0.77435892
ENSG00000237493.3	RP11-603J24.7	12	rs1059513	Whole_Blood	0.696956543
ENSG00000123411.10	IKZF4	12	rs10876864	Skin_Sun_Exposed_Lower_leg	0.677889395
ENSG00000170426.1	SDR9C7	12	rs1059513	Skin_Not_Sun_Exposed_Suprapubic	0.649305289
ENSG00000111602.7	TIMELESS	12	rs10876864	Esophagus_Mucosa	0.621079218
ENSG00000139531.8	SUOX	12	rs10876864	Vagina	0.510547317
ENSG00000062485.14	CS	12	rs10876864	Esophagus_Mucosa	0.509190258
ENSG00000257303.1	RP11-977G19.11	12	rs10876864	Vagina	0.503579906
ENSG00000166949.11	SMAD3	15	rs56062135	Whole_Blood	0.902316685
ENSG00000103591.8	AAGAB	15	rs56062135	Esophagus_Mucosa	0.867937918
ENSG00000038532.10	CLEC16A	16	rs36045143	Lung	0.560326296
ENSG00000263179.1	HNRNPCP4	16	rs36045143	Esophagus_Gastroesophageal_Junction	0.505570741
ENSG00000172057.5	ORMDL3	17	rs869402	Whole_Blood	0.954998104
ENSG00000073605.14	GSDMB	17	rs869402	Lung	0.954962091
ENSG00000172057.5	ORMDL3	17	rs869402	Skin_Sun_Exposed_Lower_leg	0.947964282
ENSG00000172057.5	ORMDL3	17	rs869402	Esophagus_Mucosa	0.947204897
ENSG00000172057.5	ORMDL3	17	rs869402	Lung	0.946325248

ENSG00000172057.5	ORMDL3	17	rs869402	Esophagus_Muscularis	0.927470077
ENSG00000264968.1	RP11-387H17.4	17	rs869402	Skin_Sun_Exposed_Lower_leg	0.909271886
ENSG00000073605.14	GSDMB	17	rs869402	Skin_Sun_Exposed_Lower_leg	0.901160249
ENSG00000073605.14	GSDMB	17	rs869402	Whole_Blood	0.883185798
ENSG00000073605.14	GSDMB	17	rs869402	Esophagus_Mucosa	0.859863783
ENSG00000073584.14	SMARCE1	17	rs9911533	Esophagus_Gastroesophageal_Junction	0.856519095
ENSG00000172057.5	ORMDL3	17	rs869402	Skin_Not_Sun_Exposed_Suprapubic	0.848285377
ENSG00000264198.1	RP11-94L15.2	17	rs869402	Whole_Blood	0.806296568
ENSG00000073584.14	SMARCE1	17	rs9911533	Vagina	0.787172234
ENSG00000264968.1	RP11-387H17.4	17	rs869402	Esophagus_Gastroesophageal_Junction	0.666747389
ENSG00000141736.9	ERBB2	17	rs869402	Skin_Not_Sun_Exposed_Suprapubic	0.656466803
ENSG00000073605.14	GSDMB	17	rs869402	Esophagus_Muscularis	0.629825793
ENSG00000263818.1	CTD-2206N4.4	17	rs869402	Esophagus_Gastroesophageal_Junction	0.625590078
ENSG00000073584.14	SMARCE1	17	rs9911533	Skin_Sun_Exposed_Lower_leg	0.584425601
ENSG00000264968.1	RP11-387H17.4	17	rs869402	Esophagus_Mucosa	0.52260171
ENSG00000258366.3	RTEL1	20	rs3208007	Esophagus_Gastroesophageal_Junction	0.932578447
ENSG00000258366.3	RTEL1	20	rs3208007	Esophagus_Muscularis	0.876301413
ENSG00000197457.5	STMN3	20	rs3208007	Whole_Blood	0.818390743
ENSG00000101246.15	ARFRP1	20	rs3208007	Whole_Blood	0.701172825
ENSG00000130589.12	HELZ2	20	rs3208007	Lung	0.631134016
ENSG00000197114.7	ZGPAT	20	rs3208007	Whole_Blood	0.557234737

Supplementary Table 15. Sensitivity analysis of genetic correlation between asthma and allergic disease for assessing effect of overlap sample and control sample definition

Scenario	Phenotype	Case <i>n</i>	Control <i>n</i>	Total <i>n</i>	R _g	SE	<i>P</i>	Gcov_obs	h ² _obs	Gcov_int
Case non-overlap, control-non-overlap	Asthma	7,041	38,384	45,425	0.8751	0.0943	1.71E-20	0.0781	0.0958	0.0054
	Allergic diseases	12,844	38,384	51,228					0.0831	
Case overlap, no control overlap	Asthma	7,041	38,384	45,425	0.832	0.0722	9.75E-31	0.0771	0.0963	0.264
	Allergic diseases	12,843	38,384	51,227					0.0891	
No case overlap, but control overlap	Asthma	7,041	38,384	45,425	0.8144	0.0844	5.19E-22	0.0742	0.0956	0.2061
	Allergic diseases	12,844		51,228					0.0869	
Case overlap, control overlap	Asthma	7,041	38,384	45,425	0.7561	0.0556	4.60E-42	0.0741	0.096	0.465
	Allergic diseases	12,843		51,227					0.1001	
Case: individuals who reported disease Control: individuals who did not report disease	Asthma	7,041	48,139	55,180	0.7381	0.1266	5.51E-09	0.0505	0.0688	0.221
	Allergic diseases	12,843	42,337	55,180					0.0680	

Gcov_obs: genetic covariance estimate on the observed scale; h²_obs: heritability estimate on the observed scale; Gcov_int: genetic covariance intercept

Supplementary Table 16. Comparing of effect size (Beta) and *P*-value in sensitivity analysis of excluding asthma and allergic diseases overlapped subjects (allergic asthma, *n* = 6,177) for top 38 shared loci between two traits

SNP	All asthma		Non-allergic asthma		Region	Representative gene
	Beta	<i>P</i>	Beta	<i>P</i>		
rs1214598	-0.0476	5.14E-11	-0.05433	3.21E-08	chr1:167426424	<i>CD247</i>
rs12743520	-0.06871	3.83E-08	-0.06903	9.52E-07	chr1:93037112	<i>EVI5</i>
rs301805	-0.04159	6.43E-09	-0.0466	1.96E-06	chr1:8481016	<i>RERE</i>
rs61815704	0.129983	5.16E-09	0.105854	0.002443	chr1:152893891	<i>IVL</i>
rs61816766	0.131965	4.63E-12	0.138021	7.21E-05	chr1:152319572	<i>C1orf68</i>
rs742230	-0.04113	1.02E-08	-0.04512	5.81E-06	chr1:25251424	<i>RUNX3</i>
rs10174949	-0.06327	1.7E-16	-0.06826	5.8E-11	chr2:8442248	<i>LINC00299</i>
rs34290285	-0.0674	5.17E-17	-0.06824	4.58E-10	chr2:242698640	<i>D2HGDH</i>
rs72823641	-0.11186	1.58E-27	-0.11379	1.21E-16	chr2:102936159	<i>IL1R1</i>
rs4916533	-0.07527	1.66E-08	-0.08516	2.71E-06	chr3:196373582	<i>NRROS</i>
rs28393318	-0.07824	2.14E-19	-0.10725	5.46E-13	chr4:38784267	<i>FAM114A1</i>
rs56267605	0.051408	2.56E-12	0.045615	1.04E-05	chr4:123363109	<i>ADAD1</i>
rs10074523	0.09894	2.37E-10	0.08158	0.000145	chr5:132060583	<i>IL4</i>
rs1837253	-0.07447	4.38E-21	-0.07614	8.7E-13	chr5:110401872	<i>TSLP*</i>
rs2548992	0.09349	4.54E-10	0.091667	5.01E-06	chr5:131808668	<i>C5orf56</i>
rs2706362	0.0583	3.75E-11	0.057591	3.11E-06	chr5:131925187	<i>IL13</i>
rs6881270	-0.09157	1.53E-14	-0.08818	4.68E-11	chr5:35879095	<i>CAPSL</i>
rs7705653	0.131905	1.12E-19	0.121332	1.09E-13	chr5:110142816	<i>SLC25A46</i>
rs9273374	-0.16854	7.87E-35	-0.14827	1.04E-16	chr6:32626614	<i>HLA-DOB</i>
rs6461503	0.04463	3.19E-10	0.047085	1.6E-06	chr7:20560996	<i>ITGB8*</i>
rs2136016	0.083422	2.11E-09	0.088011	1.71E-06	chr8:81300681	<i>ZBTB10*</i>
rs2169282	0.088011	1.8E-10	0.087095	2.05E-06	chr9:6350235	<i>GLDC</i>
rs9775039	0.168054	4.42E-22	0.163818	5.41E-13	chr9:6177453	<i>GLDC</i>
rs10795656	0.04915	4.07E-10	0.06032	1.51E-08	chr10:8595839	<i>GATA3*</i>
rs12413578	-0.09031	1.09E-14	-0.10185	9.07E-11	chr10:9049253	<i>HV745896*</i>
rs61839660	0.115113	2.3E-11	0.121332	3.13E-10	chr10:6094697	<i>IL2RA</i>
rs659529	-0.05085	6.03E-11	-0.05692	7.91E-08	chr11:111436896	<i>ALG9</i>
rs7936070	0.075205	2.81E-28	0.072649	2.38E-15	chr11:76293527	<i>C11orf30</i>
rs1059513	-0.08228	7.65E-13	-0.06314	0.000103	chr12:57489709	<i>GPR182</i>

rs10876864	0.051508	1.41E-13	0.046895	1.44E-06	chr12:56401085	<i>CDK2</i>
rs8008961	0.044627	1.24E-08	0.042767	0.000098	chr14:68752643	<i>RAD51B</i>
rs56062135	0.14842	1.56E-22	0.075501	5.53E-12	chr15:67455630	<i>SMAD3</i>
rs36045143	-0.07627	1.83E-21	-0.07606	1.77E-12	chr16:11224966	<i>CLEC16A</i>
rs869402	0.111541	4.15E-17	0.108854	4.59E-10	chr17:38068043	<i>ERBB2</i>
rs9911533	-0.08828	9.7E-16	-0.08567	3.95E-12	chr17:38775476	<i>KRT24</i>
rs10414065	-0.09297	2.63E-10	-0.08779	1.58E-05	chr19:33721455	<i>SLC7A10*</i>
rs2766664	0.079735	8.07E-11	0.074179	1.21E-07	chr20:52171241	<i>ZNF217</i>
rs3208007	-0.05265	3.22E-10	-0.04803	4.44E-05	chr20:62322288	<i>ARFRP1</i>

Supplementary Table 17. Functional categories of 38 shared loci

SNP	CHR	Position	Conserved regions	DNaseI digital genomic footprinting	DNase I hypersensitivity site	Fetal DNase I hypersensitivity site	H3K27ac	H3K4me1	H3K4me3	H3K9ac	Intron	Repressed regions	Super enhancers	Transcription factor binding sites	Transcribed regions
rs301805	1	8481016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
rs742230	1	25251424	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
rs12743520	1	93037112	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes
rs61816766	1	152319572	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	No
rs61815704	1	152893891	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No	Yes
rs1214598	1	167426424	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
rs10174949	2	8442248	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
rs72823641	2	102936159	No	No	No	No	No	No	No	No	Yes	Yes	No	No	Yes
rs34290285	2	242698640	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes
rs4916533	3	196373582	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
rs28393318	4	38784267	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
rs56267605	4	123363109	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes
rs6881270	5	35879095	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes
rs7705653	5	110142816	No	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No
rs1837253	5	110401872	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes
rs2548992	5	131808668	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
rs2706362	5	131925187	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	Yes
rs10074523	5	132060583	Yes	No	No	No	No	No	No	No	Yes	No	No	No	Yes
rs9273374	6	32626614	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
rs6461503	7	20560996	No	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes
rs2136016	8	81300681	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes
rs9775039	9	6177453	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes
rs2169282	9	6350235	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No	Yes
rs61839660	10	6094697	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
rs10795656	10	8595839	Yes	No	No	No	No	Yes	No	No	No	Yes	No	No	Yes
rs12413578	10	9049253	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes
rs7936070	11	76293527	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes
rs659529	11	111436896	No	Yes	Yes	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes
rs10876864	12	56401085	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
rs1059513	12	57489709	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
rs8008961	14	68752643	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

rs56062135	15	67455630	No	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
rs36045143	16	11224966	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
rs869402	17	38068043	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	Yes
rs9911533	17	38775476	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
rs10414065	19	33721455	No	Yes	Yes	No	Yes	Yes	No	No	No	Yes	No	No	Yes
rs2766664	20	52171241	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes
rs3208007	20	62322288	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

Supplementary Table 18. Age and sex characteristics of UK Biobank subjects with complete information for asthma or allergic diseases (*n* = 110,361)

Phenotypes	<i>n</i>	Male (<i>n</i> , %)	Age, years (Mean, SD)
All asthma	14085	6191 (44.0%)	56.27 (8.10)
All allergic diseases	25685	10987 (42.8%)	55.43 (8.01)
Non-allergic asthma	7908	3697 (46.8%)	57.20 (7.98)
Allergic asthma	6177	6175 (40.4%)	55.07 (8.09)
Only allergic diseases	19508	8493 (43.5%)	55.54 (7.99)
Controls	76768	37400 (48.7%)	57.23 (7.86)

A genome-wide cross trait analysis from UK Biobank highlights the shared genetic architecture of asthma and allergic diseases

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Supplementary Note

UK Biobank data set

We have summarized the key points of the UK Biobank data. All detailed genotyping, quality control and imputation procedures are described at the UK Biobank website (<http://biobank.ctsu.ox.ac.uk/>). Out of 500,000 subjects in UK Biobank, currently around 153,000 individuals are genotyped for around 800,000 SNPs using Affymetrix facilities. Population structure was captured by principal-component analysis (PCA) on ~150,000 UK Biobank samples using ~100,000 SNPs. QC filters were applied before phasing. Data were prephased using SHAPEIT3¹. Phase 3 1000 Genomes Project was used as reference panel for imputation. Imputation was carried out using IMPUTE3 program, which has the same algorithm as is implemented in the IMPUTE2². In total, 73,355,667 variants were imputed 152,249 individuals. QCTOOL (<http://www.well.ox.ac.uk/~gav/qctool>) was used to calculate the minor allele frequency (MAF) and imputation information score of each imputed variant. We used data field 6152 as our doctor diagnosed asthma and allergic disease (hay fever, allergic rhinitis or eczema) phenotypes. Data field 6152 contains a question from touchscreen for the participants to answer: “has a doctor ever told you that you have had any of the following conditions? (You can select more than one answer): Blood clot in the leg (DVT); blood clot in the lung;

emphysema/chronic bronchitis; asthma; hayfever, allergic rhinitis or eczema; none of the above; prefer not to answer. If the participant chose either “none of the above” or “prefer not to answer”, then they could not choose other answers. We therefore followed the UK Biobank description to define individuals who chose these conditions or diseases as doctor diagnosed even though it is a touchscreen question for participant to report by themselves. There are 6,177 samples overlap between allergic diseases and asthma. All participants used in this study was based on UK Biobank acquired informed consent and answered surveys for the participants according to the UK Biobank protocol, we have complied with all ethical regulations according to UK Biobank policy. This research has been approved and conducted using the UK Biobank Resource under application number 16549.

GABRIEL data set

We retrieved asthma genome-wide association study (GWAS) summary statistics from the GABRIEL consortium study³ (<https://www.cng.fr/gabriel/index.html>). The GABRIEL study contains childhood asthma subjects of European descent from Canadian, Australian, and U.S. The childhood-onset asthma is defined as the presence of the disease in a person younger than 16 years of age and later-onset asthma is defined as disease that developed at 16 years of age or older. This data contains asthma GWAS meta-analysis result from 26 studies with genotype on 582,892 SNPs on 10,365 cases and 16,110 controls after quality control and filtering³. We filtered out SNPs with P-value equal to 0 and fixed effect OR equal to 0 in the original GABRIEL dataset due to uninterpretable information. The genome position in this data set is based on build 36. We converted it to build 37 using LiftOver tool (<http://genome.sph.umich.edu/wiki/LiftOver>). In addition, we imputed the summary statistics to 1000 Genome⁴. The ImpG procedure filtered SNPs with ambiguous strand information from original GABRIEL data for imputation. Thus in order to keep them in the final analysis, we included those filtered SNPs back after imputation. And SNPs with imputation quality $r^2_{\text{pred}} < 0.6$ were removed, thus finally leaving 6,303,505 SNPs.

EAGLE data set

We retrieved eczema GWAS summary statistics from the EAGLE consortium study⁵ (<http://data.bris.ac.uk/data>). This data contains eczema GWAS meta-analysis result for the discovery cohorts (excluding 23andMe) with 11,296,420 SNPs on 13,287 cases and 41,345 controls.

Association analysis based on subsets (ASSET)

ASSET is a generalized fixed-effects meta-analysis model that combines effect estimate and standard error of the GWASs of related but distinct traits to identify promising directions for the discovery of loci with small but common pleiotropic effects. The ASSET method explores subsets of studies for the presence of true association signals that are in either the same direction or possibly opposite directions⁶.

When S represents a set of study traits selected from K studies, meta-analysis statistics of the one-sided test ASSET is defined as:

$$Z_{\max-\text{ASSET}} = \max_{S \in \mathcal{S}} |Z(S)| = \max_{S \in \mathcal{S}} \left| \sum_{k \in S} \sqrt{\pi_k(S)} Z_k \right|$$

Where S is all possible $2^K - 1$ subsets of the K studies, $\pi_k(T) = n_k / \sum_{k \in T} n_k$ represents the sample size of the study k relative to the total sample size of the given subset S .

An advantage of using ASSET is that it can account for the correlation among studies/subjects that might arise due to shared subjects across distinct studies or due to correlation among related traits in the same study by using case-control overlap matrices. If $Z(A)$ and $Z(B)$ denote the Z statistics for the association test for a SNP from case-control studies A and B with an arbitrary amount of overlap between subjects, then, under the null hypothesis of no association and the assumption that there is no covariate adjustment, the correlation between the statistics is given by

$$\text{Corr}\{Z(A), Z(B)\} = \sqrt{\frac{n_A^{(1)} n_A^{(0)}}{N_A}} \sqrt{\frac{n_B^{(1)} n_B^{(0)}}{N_B}} \left[\frac{n_{AB}^{(11)}}{n_A^{(1)} n_B^{(1)}} - \frac{n_{AB}^{(10)}}{n_A^{(1)} n_B^{(0)}} - \frac{n_{AB}^{(01)}}{n_A^{(0)} n_B^{(1)}} + \frac{n_{AB}^{(00)}}{n_A^{(0)} n_B^{(0)}} \right]$$

Where $n_A^{(1)}$ and $n_A^{(0)}$ are the number of cases, controls and subjects respectively, in study A ; and $n_B^{(1)}$ and $n_B^{(0)}$ are the number of cases, controls and subjects respectively, in study B ; and $n_{AB}^{(ij)}$ represents the number of subjects with different phenotype categories $(i, j) \in (0, 1)$ who overlap between studies A and B . For example, $n_{AB}^{(11)}$ denotes the number of shared cases between studies A and B , which is 6,177 in our study; $n_{AB}^{(10)}$ denotes the number of individuals who are treated as cases in study A but as controls in study B , which is 0 in our study; $n_{AB}^{(01)}$ denotes the number of individuals who are treated as controls in study A but as cases in study B , which is 0 in our study; $n_{AB}^{(00)}$ denotes the number of shared controls between studies A and B , which is 76,768 in our study⁶.

Cross tissue heritability of gene expression

RNA-seq and genotype data from the Genotype-Tissue Expression (GTEx)⁷ project (phs000424.v6.p1) was used to quantify the cross-tissue heritability ($h_{g1g2, cis}^2$) of gene expression across a range of tissues. Genotype data for the 450 samples was imputed to the 1000 Genomes reference. Only variants with high imputation quality ($\text{INFO} > 0.4$), Hardy-Weinberg Equilibrium ($p > 1 \times 10^{-6}$), minor allele frequency > 0.05 , and genotype missing rate < 0.02 were considered. Gene transcripts were annotated by GENCODE v19 and quantified by reads per kilobase per million mapped reads (RPKM). Only transcripts with RPKM > 0.1 in at least 10 samples were retained for analysis. Expression data was quantile normalized across samples, by

tissue. To protect against a strong outlier effect, we applied an inverse normal transformation to normalize the distribution of expression.

To estimate *cis* cross-tissue SNP-heritability ($h_{g1g2,cis}^2$) of gene expression in each tissue, we employed restricted maximum likelihood (REML) implemented in Genome-wide Complex Trait Analysis (GCTA)⁸. In brief, for each tissue pair considered, a bivariate linear mixed model was fit for the expression of each gene transcript based on all *cis* variants with MAF > 0.05, adjusting for PC 1 to 3, genotyping array, and sex (with the exception of sex specific tissues). We defined *cis* as within 1 MB of the transcription start site of a gene based on the GENCODE v19 annotations. For each gene, in each tissue and tissue pair, the following two quantities were estimated:

$$\text{cis cross-tissue heritability } (h_{g1g2,cis}^2) = \sigma_{g1g2,cis}^2 / \sqrt{\sigma_{p1}^2 \sigma_{p2}^2}$$

Where $\sigma_{g1g2,cis}^2$ indicates *cis* genetic variance between 2 tissues, σ_{p1}^2 indicates gene expression variance in tissue 1, σ_{p2}^2 indicates gene expression variance in tissue 2, and $\sigma_{g1g2,cis}^2$ indicates the genetic covariance of gene expression between 2 tissues. Only tissues with more than 100 samples were considered for subsequent analyses.

To determine whether a particular subset of genes was enriched or depleted in $h_{g1g2,cis}^2$, a permutation test was applied. For a given gene set, average $h_{g1g2,cis}^2$ were calculated and compared to average $h_{g1g2,cis}^2$ of 1,000,000 random gene sets of the same size, for the same tissue or pair of tissues. Permutation p-values were calculated by comparing observed average $h_{g1g2,cis}^2$ for a given gene set to the empirically derived distribution.

Sensitivity analysis

To assess heterogeneity of significant loci potentially attributable to the overlap samples in UK Biobank, we performed a sensitivity analysis by excluding overlap case samples. When analyzing the 7,908 asthma only and 19,508 allergic diseases only subjects with 76,768 control subjects, in meta-analysis, most of the loci still showed robust genome wide shared associations between both traits, such as *HLA-DQ*, *IL1R1*, *C11orf30*, *SLC25A46*, *D2HGDH* and many others (Supplementary Table 18 and Supplementary Fig. 18). Although the significance level was reduced, this was mainly due to the loss of sample size for 6,177 individuals. In our sensitivity analysis for effect estimate, which should not be biased by sample size, we observed highly similar results between including and excluding allergic asthma subjects (Supplementary Table 18 and Supplementary Fig. 19).

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