

A genome-wide association meta-analysis of self-reported allergy identifies shared and allergy-specific susceptibility loci

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Allergic disease is very common and carries substantial public-health burdens. We conducted a meta-analysis of genome-wide associations with self-reported cat, dust-mite and pollen allergies in 53,862 individuals. We used generalized estimating equations to model shared and allergy-specific genetic effects. We identified 16 shared susceptibility loci with association $P < 5 \times 10^{-8}$, including 8 loci previously associated with asthma, as well as 4p14 near *TLR1*, *TLR6* and *TLR10* (rs2101521, $P = 5.3 \times 10^{-21}$); 6p21.33 near *HLA-C* and *MICA* (rs9266772, $P = 3.2 \times 10^{-12}$); 5p13.1 near *PTGER4* (rs7720838, $P = 8.2 \times 10^{-11}$); 2q33.1 in *PLCL1* (rs10497813, $P = 6.1 \times 10^{-10}$); 3q28 in *LPP* (rs9860547, $P = 1.2 \times 10^{-9}$); 20q13.2 in *NFATC2* (rs6021270, $P = 6.9 \times 10^{-9}$); 4q27 in *ADAD1* (rs17388568, $P = 3.9 \times 10^{-8}$); and 14q21.1 near *FOXA1* and *TTC6* (rs1998359, $P = 4.8 \times 10^{-8}$). We identified one locus with substantial evidence of differences in effects across allergies at 6p21.32 in the class II human leukocyte antigen (HLA) region (rs17533090, $P = 1.7 \times 10^{-12}$), which was strongly associated with cat allergy. Our study sheds new light on the shared etiology of immune and autoimmune disease.

Allergies and allergic asthma are among the most common diseases in the industrialized world. In the United States, a nationwide survey found that over half the population tested positive for sensitization to at least one common allergen, showing a considerable increase in prevalence compared to results collected approximately 10 years earlier¹. The cause of this apparent increase in prevalence is unknown, but the rapidity with which it has occurred implicates an environmental component². Still, estimates of the heritability of allergy are high^{3,4}, suggesting that understanding the genetic liability underlying these conditions is key to understanding disease.

A number of genes implicated in allergy and asthma through association and functional studies belong to pathways involved in immune and inflammatory processes, such as innate immunity, adaptive

immunity and allergic inflammation⁵. These genes belong to a range of gene families that encode Toll-like receptors, interleukins, chemokines and various other signaling molecules and transcription factors. Published genome-wide association studies (GWAS) on allergic conditions have focused on asthma and atopic dermatitis, resulting in the identification of a substantial number of loci associated with asthma (*HLA-DQB1*, *IL33*, *IL18R1*, *SMAD3*, *GSDMA*, *IL2RB*, *RORA*, *GSDMB*, *IL13*, *SLC22A5*, *DENND1B*, *PDE4D*, *ORMDL3*, *IL6R*, 5q22.1 and 11q13.5)^{6–11} and a smaller number associated with atopic dermatitis (*FLG*, *OVOL1*, *ACTL9*, 5q22.1, 11q13.5 and 20q13.33)^{12–14}. Studies using other measures of atopy have been less definitive, likely owing to limited sample sizes^{15–17}; the largest study, of allergic rhinitis and immunoglobulin E (IgE) sensitization to grass pollen, identified three regions with genome-wide significant association (the class II HLA region, 5q22.1 and 11q13.5).

We selected three common self-reported allergy phenotypes (pollen allergy, dust-mite allergy and cat allergy) for which comparable data were available in the 23andMe participant cohort¹⁸ and in a cohort of mothers from the Avon Longitudinal Study of Parents and Children (ALSPAC)¹⁹ (Table 1). We used generalized estimating equations (GEEs) to jointly model genetic effects across all three phenotypes. The GEE approach accounts for correlations between phenotypes and enabled us to estimate both shared and allergy-specific effects. We first performed a genome-wide meta-analysis of GEE tests for shared effects. Then, for a set of 3,725 markers with nominal evidence of association with at least one allergy, we performed GEE tests for allergy-specific effects (Supplementary Table 1).

In the GEE meta-analysis for shared effects across allergies, we identified 16 genome-wide significant loci with association $P < 5 \times 10^{-8}$ (Fig. 1, Table 2 and Supplementary Fig. 1). Of these, eight had association $P < 5 \times 10^{-8}$ in the 23andMe cohort and association $P < 0.05$ in the ALSPAC cohort (Supplementary Tables 2 and 3). We identified six loci with suggestive evidence of association ($5 \times 10^{-8} < P < 1 \times 10^{-6}$) (Supplementary Note). Many of these loci have

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Table 1 Demographic characteristics of cohorts

	23andMe		ALSPAC	
	<i>n</i>	Percent	<i>n</i>	Percent
Total	46,646	100.0	7,216	100.0
Sex				
Male	26,344	56.5	0	0.0
Female	20,302	43.5	7,216	100.0
Age				
≤30	4,300	14.6	4,829	67.0
>30 and ≤45	8,088	31.1	2,382	33.0
>45 and ≤60	6,282	25.6	0	0.0
>60	6,428	28.7	0	0.0
Allergy status				
Cat allergy	10,509	22.5	704	9.8
Dust-mite allergy	9,815	21.0	964	13.4
Pollen allergy	16,133	34.6	1,201	16.6
Number of allergies				
Three allergies	4,947	10.6	328	4.6
Any two allergies	6,228	13.3	536	7.4
Any one allergy	9,160	19.6	813	11.3
No allergy	26,311	56.4	5,539	76.8

previously been associated with other immunity-related phenotypes, and eight have been associated with asthma in previous GWAS (**Supplementary Note**). Although we describe loci in terms of their proximal genes, in most cases, we have no functional evidence for a specific target, and these variants may affect the regulation of more distant genes.

To ensure that the results were not confounded by age or differences between genotyping platforms, we tested the index SNPs for platform-specific effects and for interactions with age within the 23andMe cohort, but no tests yielded strong evidence of interaction after adjusting for multiple comparisons (**Supplementary Table 4**). We also tested for pairwise interactions between the 22 loci, but none of these interactions were significant after adjustment for multiple comparisons (**Supplementary Table 5**).

We assessed whether the identified associations were supported by data from a companion study of allergic sensitization²⁰ (**Table 3** and **Supplementary Table 6**). All 22 loci had effects in the same direction in the 2 studies, and 10 of our 16 genome-wide significant loci were supported with association $P < 0.05$ in the sensitization study. We also annotated our findings on the basis of linkage disequilibrium (LD) with results from published GWAS, coding variation, monocyte expression quantitative trait loci (eQTLs)²¹ and putative regulatory regions identified by the Encyclopedia of DNA Elements (ENCODE) Project (**Table 3** and **Supplementary Tables 7–10**).

We examined evidence of association in our meta-analysis at other loci previously associated with either asthma or atopic dermatitis

(**Supplementary Tables 11** and **12**). We found nominal support ($P < 0.05$, consistent risk allele) for seven additional asthma-relevant loci (*IL6R*, *GAB1*, *RAD50*, *IL13*, *IKZF4*, *RORA* and *IL2RB*), with a false discovery rate (FDR) of 0.04 across these variants. For atopic dermatitis, we found nominal support for associations at five additional loci (*IL13*, *KIF3A*, *CARD11*, *MIR1208* and *NCF4*), with an FDR of 0.07 for this group. These results indicate substantial overlap between these phenotypes, beyond that observed for the loci meeting our criteria for significant and suggestive associations.

To test for allergy-specific genetic effects, we included interaction terms for specific allergies in our GEE models (**Supplementary Table 1**). We found one locus with strong evidence of allergy-specific effects on chromosome 6 in the major histocompatibility complex (MHC) region, with the strongest signal 14 kb upstream of *HLA-DQA1* (**Fig. 2** and **Supplementary Fig. 2**). Index SNP rs17533090 had combined $P = 1.7 \times 10^{-12}$ for interaction with allergy type. Effects for the three allergies were consistent across cohorts and indicated that this locus was specifically associated with cat allergy (**Fig. 3**). Of the SNPs listed in **Table 2**, only rs2101521 showed evidence of a specific effect favoring cat allergy (unadjusted $P = 0.0011$), which was weak compared to the evidence for shared effect ($P = 5.3 \times 10^{-21}$).

We performed an exploratory analysis to assess the associations of allergy-associated loci with symptoms of allergic rhinitis, allergic contact dermatitis and allergic asthma in the 23andMe cohort. We reclassified cases on the basis of reported symptoms and used the GEE approach to jointly model genetic effects across symptoms (**Supplementary Tables 13** and **14**). All effects were in the same direction at all index SNPs. At most loci, we did not see evidence of differential effects across symptoms ($P > 0.05$ for interaction). One exception was found in *GSDMB*, where the rs9303280 SNP was most strongly associated with asthma ($P = 0.000035$ for interaction). Effect sizes for contact dermatitis symptoms tended to be smaller than those for asthma (20/23 loci; $P = 0.0004$) and rhinitis (18/23 loci; $P = 0.007$). Effect sizes for asthma tended to be larger than those for rhinitis, but not significantly so (14/23 loci; $P = 0.30$). However, in association tests, most loci showed more significant association with rhinitis than with asthma (18/23 loci; $P = 0.007$), with association P values often differing by several orders of magnitude. Thus, although asthma may be a slightly more specific atopy phenotype, rhinitis seems to be more powerful in the discovery of atopy-related loci in cohort studies because it is reported by a much higher proportion of individuals who report allergies.

Genes implicated in our GWAS highlight key pathways in the etiology of common allergy. In the 4p14 region near rs2101521, *TLR1* (Toll-like receptor 1) and *TLR6* (Toll-like receptor 6) encode pattern-recognition receptors whose roles in recognizing external pathogens and activating appropriate immune responses lie at the interface between innate immunity and immunoregulation. Candidate gene

Figure 1 Manhattan plot of meta-analysis results for shared effects. The plotted values represent the most significant scores from the meta-analyses of cat, pollen and dust-mite allergy, with all results with association $P < 1 \times 10^{-4}$ recomputed using GEEs to assess effects shared across allergens. The gray line corresponds to $P = 5 \times 10^{-8}$, and results above this threshold are shown in red. Gene labels are provided for cross-referencing with other results and are not intended to suggest that we have established a causal basis for the observed associations.

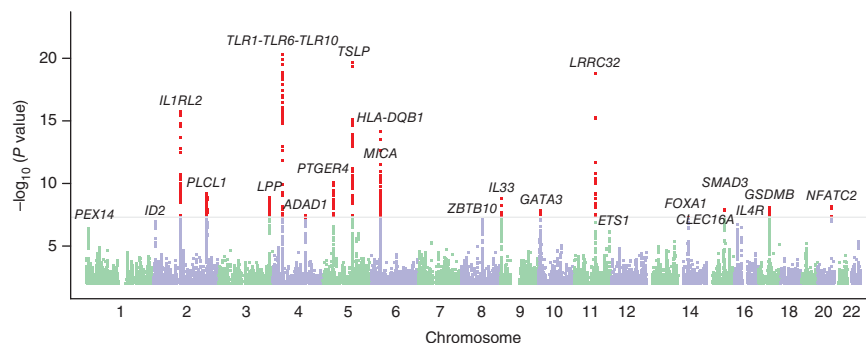


Table 2 Index SNPs from meta-analysis for shared effects

SNP	Region	Position	Alleles	RAF	OR (95% CI)	P	Gene context
rs2101521	4p14	38811551	A/G	0.766	1.15 (1.11–1.18)	5.3×10^{-21}	<i>TLR1</i> –[–] <i>TLR6</i>
rs1438673	5q22.1	110467499	T/C	0.498	1.12 (1.09–1.14)	2.3×10^{-20}	<i>WDR36</i> –[–] <i>CAMK4</i>
rs2155219	11q13.5	76299194	G/T	0.511	1.11 (1.09–1.14)	1.6×10^{-19}	<i>C11orf30</i> –[–] <i>LRR32</i>
rs10189629	2q12.1	102879464	A/C	0.857	1.16 (1.12–1.20)	1.8×10^{-16}	<i>IL1RL2</i> –[–] <i>IL1RL1</i>
rs6906021	6p21.32	32626311	T/C	0.475	1.10 (1.07–1.13)	7.1×10^{-15}	<i>HLA-DQA1</i> –[–] <i>HLA-DQB1</i>
rs9266772	6p21.33	31352113	T/C	0.193	1.11 (1.08–1.14)	3.2×10^{-12}	<i>HLA-C</i> –[–] <i>MICA</i>
rs7720838	5p13.1	40486896	G/T	0.580	1.08 (1.06–1.11)	8.2×10^{-11}	[–] <i>PTGER4</i>
rs10497813	2q33.1	198914072	T/G	0.483	1.08 (1.05–1.10)	6.1×10^{-10}	[–] <i>PLCL1</i>
rs9860547	3q28	188128979	G/A	0.462	1.08 (1.05–1.10)	1.2×10^{-9}	[–] <i>LPP</i>
rs7032572	9p24.1	6172380	A/G	0.167	1.12 (1.08–1.16)	1.7×10^{-9}	<i>RANBP6</i> –[–] <i>IL33</i>
rs6021270	20q13.2	50141264	C/T	0.939	1.16 (1.11–1.23)	6.9×10^{-9}	[–] <i>NFATC2</i>
rs9303280	17q12	38074031	T/C	0.517	1.07 (1.05–1.10)	8.9×10^{-9}	[–] <i>GSDMB</i>
rs17228058	15q22.33	67450305	A/G	0.240	1.08 (1.05–1.11)	1.2×10^{-8}	[–] <i>SMAD3</i>
rs962993	10p14	9053132	T/C	0.576	1.07 (1.05–1.10)	1.5×10^{-8}	<i>GATA3</i> –[–]
rs17388568	4q27	123329362	G/A	0.275	1.08 (1.05–1.10)	3.9×10^{-8}	[–] <i>ADAD1</i>
rs1998359	14q21.1	38077148	C/G	0.246	1.08 (1.05–1.12)	4.8×10^{-8}	<i>FOXA1</i> –[–] <i>TTC6</i>
rs6473223	8q21.13	81268155	C/T	0.358	1.07 (1.04–1.10)	7.7×10^{-8}	<i>TPD52</i> –[–] <i>ZBTB10</i>
rs10174949	2p25.1	8442248	A/G	0.724	1.07 (1.05–1.10)	1.0×10^{-7}	[–] <i>ID2</i>
rs7203459	16p13.13	11230703	C/T	0.734	1.07 (1.04–1.10)	2.0×10^{-7}	[–] <i>CLEC16A</i>
rs2107357	16p12.1	27410829	G/A	0.138	1.09 (1.06–1.13)	3.3×10^{-7}	<i>IL4R</i> –[–] <i>IL21R</i>
rs2056417	1p36.22	10581658	A/G	0.694	1.07 (1.04–1.10)	3.7×10^{-7}	[–] <i>PEX14</i>
rs10893845	11q24.3	128186882	T/G	0.493	1.06 (1.04–1.09)	6.4×10^{-7}	[–] <i>ETS1</i>

Region, cytogenetic band; position, build 37 map position of the SNP; alleles, low/high-risk alleles on genomic reference strand; RAF, risk allele frequency across all study participants; OR, meta-analysis odds ratio for the high-risk allele; CI, confidence interval; gene context, gene(s) spanning or flanking (<1 Mb away from) the index SNP; brackets indicate the position of the SNP, and dashes indicate distance to a flanking gene (–, >1 kb; –, >10 kb; —, >100 kb).

studies have identified associations of TLR genes with asthma^{22–24}, as well as with sensitization to grass and rhinitis¹⁷. However, this region has not been reported to show significant association in genome-wide analyses.

We see substantial overlap between loci associated with allergy and loci previously implicated in autoimmune disease. In the 5p13.1 region, index SNP rs7720838 is upstream of *PTGER4*, encoding prostaglandin E receptor 4, previously implicated as a candidate asthma locus²⁵. This SNP is in strong LD ($r^2 = 0.94$) with rs10440635, which has been associated with ankylosing spondylitis²⁶. Variants affecting *PTGER4* expression have also been associated with Crohn's disease²⁷, and mouse studies point to a role for *Ptger4* in the initiation of skin immune responses^{28,29}. In the 2q33.1 region, our eQTL analysis suggested that index SNP rs10497813 was associated with the expression of *PLCL1*, encoding phospholipase C-like 1, involved in inositol 1,4,5-triphosphate intracellular signaling³⁰. Variation in *PLCL1* (at rs6738825, $r^2 = 0.97$ with rs10497813) has also been associated with Crohn's disease³¹.

Several new allergy-associated loci are in or near genes involved in helper T cell differentiation. Index SNP rs9860547 in the 3q28 region falls in the *LPP* gene (lipoma-preferred partner). A nearby variant in *LPP* (rs1464510, $r^2 = 0.70$) has been associated with celiac disease^{32,33} and vitiligo³⁴. Our eQTL analysis suggested that our association may be mediated

by an effect on the expression of *BCL6* (B cell lymphoma 6), a transcription factor that represses the STAT6-mediated response to interleukin (IL)-4 and IL-13 and IgE class switching³⁵ and inhibits type 2 helper T cell (T_H2) differentiation in a mouse model³⁶. In the 20q13.2 region, index SNP rs6021270 is in the *NFATC2* gene, encoding a component of the NFAT (nuclear factor of activated T cells) transcription complex, which has an important role in regulating helper T cell differentiation³⁷. Variation in *NFATC2* has not been associated with any allergic or autoimmune phenotype; however, mice lacking *Nfatc2* show increased lung inflammation in experimentally induced allergic asthma^{38,39}. In the 4q27 region, index SNP rs17388568 falls in the *ADAD1* gene, but evidence for association spans the nearby *IL2* and *IL21* genes. This same SNP has been associated with the formation of autoantibodies in type 1 diabetes⁴⁰ and with ulcerative colitis⁴¹, and a nearby SNP in strong LD associated with the inhibition of IL-2 production (rs2069772, $r^2 = 0.91$) has been suggestively associated with allergic rhinitis¹⁷. The IL-2 and IL-21 cytokines are involved in the regulation of multiple helper T cell types: IL-21 is upregulated in T_H2 and T_H17 cells, and IL-2 is required for T_H1 differentiation and inhibits the differentiation of T_H17 cells⁴².

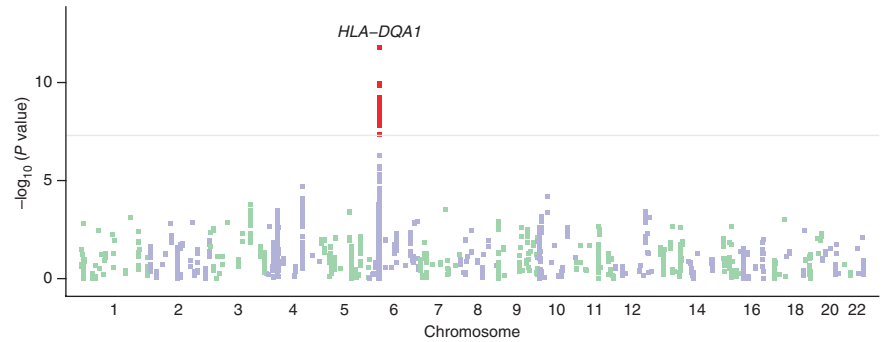
In the 14q21.1 region, index SNP rs1998359 is upstream of *FOXA1*, a member of the forkhead-box transcription factor family.

Table 3 Summary of supporting evidence for allergy-associated loci

SNP	Region	Replication ^a	Atopy ^b	Autoimmune disease ^c	Nonsynonymous SNP ^d	eQTL ^e	Gene context ^f
rs2101521	4p14	***			*	<i>TLR6</i>	<i>TLR1</i> –[–] <i>TLR6</i>
rs1438673	5q22.1	***	**				<i>WDR36</i> –[–] <i>CAMK4</i>
rs2155219	11q13.5	***	***	**			<i>C11orf30</i> –[–] <i>LRR32</i>
rs10189629	2q12.1	**	*				<i>IL1RL2</i> –[–] <i>IL1RL1</i>
rs6906021	6p21.32	***					<i>HLA-DQA1</i> –[–] <i>HLA-DQB1</i>
rs9266772	6p21.33	**					<i>HLA-C</i> –[–] <i>MICA</i>
rs7720838	5p13.1	*		*			[–] <i>PTGER4</i>
rs2117339	2q33.1			*		<i>PLCL1</i>	[–] <i>PLCL1</i>
rs9860547	3q28	***		***		<i>BCL6</i>	[–] <i>LPP</i>
rs7032572	9p24.1		**				<i>RANBP6</i> –[–] <i>IL33</i>
rs6021270	20q13.2						[–] <i>NFATC2</i>
rs9303280	17q12		***	***	*	<i>IKZF3</i>	[–] <i>GSDMB</i>
rs17293632	15q22.33			*			[–] <i>SMAD3</i>
rs962993	10p14	*					<i>GATA3</i> –[–]
rs17388568	4q27	***	*	***			[–] <i>ADAD1</i>
rs9671863	14q21.1						<i>FOXA1</i> –[–] <i>TTC6</i>
rs2202749	8q21.13	***					<i>TPD52</i> –[–] <i>ZBTB10</i>
rs13416555	2p25.1	***				<i>ID2</i>	[–] <i>ID2</i>
rs7203459	16p13.13		*	*			[–] <i>CLEC16A</i>
rs2107357	16p12.1						<i>IL4R</i> –[–] <i>IL21R</i>
rs2056417	1p36.22					<i>PEX14</i>	[–] <i>PEX14</i>
rs970924	11q24.3						[–] <i>ETS1</i>

^aStrength of replication for allergic sensitization²⁰; * $P < 0.05$, ** $P < 0.005$, *** $P < 0.0005$ (Supplementary Table 4). ^bNearby (<500 kb away, $r^2 > 0.5$) GWAS findings for atopy phenotypes (Supplementary Table 7). ^cNearby (<500 kb away, $r^2 > 0.5$) GWAS findings for autoimmune disease phenotypes (Supplementary Table 7). ^dNonsynonymous SNP: * $r^2 > 0.5$ with nonsynonymous SNP (Supplementary Table 8). ^eAssociation with the expression of the gene listed (Supplementary Table 9). ^fBrackets indicate the position of the SNP, and dashes indicate distance to a flanking gene (–, >1 kb; –, >10 kb; —, >100 kb).

Figure 2 Manhattan plot of meta-analysis results for interactions with allergen. The gray line corresponds to $P = 5 \times 10^{-8}$, and results above this threshold are shown in red. Interaction tests were performed for markers with $P < 1 \times 10^{-4}$ for association with at least one of cat, pollen or dust-mite allergy.



In mice, the closely related *Foxa1* and *Foxa2* transcription factors have roles in the regulation of T_H2 -mediated inflammation and mucous production in allergic airway disease⁴³; although a similar role for *Foxa1* has not been established, *Foxa1* and *Foxa2* are known to have overlapping patterns of expression in the respiratory epithelium⁴⁴.

In the 6p21.33 region, *HLA-B* and *HLA-C* encode major histocompatibility complex (MHC) class I molecules, which are expressed on most cell types and are responsible for the presentation of intracellular peptides to T cells. *MICA* encodes a protein that belongs to a family of non-classical MHC molecules that resemble the class I molecules and are thought to be involved in innate antitumor and antiviral surveillance⁴⁵. Alleles of *HLA-B* are associated with severe allergic reactions, such as abacavir hypersensitivity and Stevens-Johnson syndrome^{46,47}. SNPs in these three genes have been associated with a number of immune system-related phenotypes, such as psoriasis and HIV-1 control^{48,49}.

Previous studies have suggested associations between specific allergen sensitivities and HLA class II alleles⁵⁰. However, these studies have been small and have reported inconsistent results⁵¹. Our finding of a specific association with cat allergy is the first demonstration to our knowledge of allergen specificity in a GWAS context.

We assessed the directionality of effects in cases where our index SNPs were in strong LD ($r^2 > 0.5$) with SNPs previously associated with autoimmune disease (Supplementary Table 15). At some loci (*LRRC32*, *PTGER4*, *PLCL1*, *SMAD3*, *ADAD1* and *CLEC16A*), autoimmune disease and allergy were associated with the same risk alleles. At others (*GSDMB* and *LPP*), the risk allele for autoimmune disease seemed to be protective against allergy. Many autoimmune diseases are associated with increased activation of T_H1 responses, whereas allergy has been associated with T_H2 activity⁵². Our results may help to identify elements that influence the balance between T_H1 and T_H2 activity, as well as elements that contribute to both responses.

Self-reported allergy status can be unreliable⁵³, and the surveys we used were not standardized or validated. In the 23andMe cohort, the high proportion of allergy cases likely reflects responder bias in completing the allergy survey. The ALSPAC cohort was assessed during pregnancy, which can alter allergic disease status⁵⁴. These limitations

should not compromise the validity of our genetic associations, but they make functional interpretation more challenging.

Our results demonstrate that self-reported allergy can be used to identify disease susceptibility loci, with results consistent with studies of more narrowly defined allergy manifestations and allergic sensitization. Self-directed web-based data collection in the 23andMe cohort yielded results largely consistent with those obtained with the traditional survey methods used in the ALSPAC cohort. Our findings reinforce and extend evidence of a shared genetic etiology of allergic and autoimmune disease, with newly discovered susceptibility loci for allergy identified near *LPP-BCL6*, *HLA-C-MICA*, *PTGER4* and *PLCL1*, all of which were previously associated with autoimmune disease. Our findings also highlight the role of the T_H2 lineage in the pathogenesis of allergy, with associations identified in or near key T_H2 genes, including *ID2*, *BCL6*, *GATA3*, *IL13*, *IL33*, *TSLP* and *ILIR1*. An important next step will be to more carefully characterize the extent to which individual associations lead to a global predisposition to allergy compared to effects on specific target tissues, such as skin, lung or mucosa.

URLs. BEAGLE, <http://faculty.washington.edu/browning/beagle/beagle.html>; HapMap, <http://hapmap.ncbi.nlm.nih.gov/>; MaCH, <http://www.sph.umich.edu/csg/abecasis/MaCH/>; Minimac, <http://genome.sph.umich.edu/wiki/Minimac>; NCBI Gap Plus, http://www.ncbi.nlm.nih.gov/projects/gapplus/gap_plus.htm; 1000 Genomes Project, <http://www.1000genomes.org/>; UCSC Genome Browser, <http://genome.ucsc.edu/>.

METHODS

Methods and any associated references are available in the [online version of the paper](#).

Note: Supplementary information is available in the online version of the paper.

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This publication is the work of the authors, and D.A.H., N.J.T. and J.Y.T. will serve as guarantors for the contents of this paper.

AUTHOR CONTRIBUTIONS

D.A.H. and G.M. analyzed the data. A.K.K. designed the survey for 23andMe. G.M., D.M.E. and B.S.P. were part of the ALSPAC GWAS preparation team.

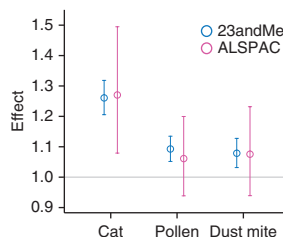


Figure 3 Marginal effect sizes and 95% confidence intervals for rs17533090 for cat, pollen and dust-mite allergy in the 23andMe and ALSPAC cohorts. Effects are odds ratios for the high-risk G allele of rs17533090.

S.M.R. was responsible for ALSPAC sample collection and preparation. C.B.D. and N.E. developed analytical tools. J.L.M., U.F. and G.D.-S. supervised the project. D.A.H., G.M., N.J.T. and J.Y.T. designed the study and wrote the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the [online version of the paper](#).

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ONLINE METHODS

23andMe cohort. Participants in the 23andMe cohort were customers of 23andMe, Inc., a personal genetics company, who had been genotyped as part of the 23andMe Personal Genome Service. Individuals included in the analysis were selected for having >97% European ancestry, as determined through an analysis of local ancestry via comparison to the CEU, YRI and JPT + CHB HapMap 2 populations⁵⁵. A maximal set of unrelated individuals was chosen for the analysis using a segmental identity-by-descent (IBD) estimation algorithm⁵⁶. Individuals were defined as related if they shared more than 700 cM of IBD, including regions where the two individuals shared either one or both genomic segments IBD. This level of relatedness (involving roughly 20% of the genome) corresponds approximately to the minimal expected sharing between first cousins in an outbred population. The study protocol and consent form were approved by the external Association for the Accreditation of Human Research Protection Programs (AAHRPP)-accredited Institutional Review Board, Ethical & Independent Review Services (E&I Review). For a small number of participants ($n = 167$) under the age of 18 years, consent was provided by a parent, guardian or legally authorized adult.

DNA extraction and genotyping were performed on saliva samples by the National Genetics Institute (NGI), a Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory and subsidiary of the Laboratory Corporation of America. Samples were genotyped on one of two platforms. About 35% of the participants were genotyped on the Illumina HumanHap550+ BeadChip platform, which included SNPs from the standard HumanHap550 panel augmented with a custom set of approximately 25,000 SNPs selected by 23andMe. Two slightly different versions of this platform were used, as previously described¹⁸. The remaining 65% of participants were genotyped on the Illumina HumanOmniExpress+ BeadChip. This platform has a base set of 730,000 SNPs augmented with approximately 250,000 SNPs to obtain a superset of the HumanHap550+ content, as well as a custom set of about 30,000 SNPs. Every sample that did not reach a 98.5% call rate for SNPs on the standard platforms was reanalyzed. Individuals whose analyses repeatedly failed were contacted by 23andMe customer service to provide additional samples.

Participant genotype data were imputed against the August 2010 release of the 1000 Genomes Project reference haplotypes⁵⁷. First, we used BEAGLE⁵⁸ (version 3.3.1) to phase batches of 8,000 to 9,000 individuals across chromosomal segments of no more than 10,000 genotyped SNPs, with overlaps of 200 SNPs. We excluded SNPs with minor allele frequency (MAF) < 0.001, Hardy-Weinberg equilibrium $P < 1 \times 10^{-20}$, call rate < 95% or large allele frequency discrepancies compared to the 1000 Genomes Project reference data. We then assembled fully phased chromosomes by matching the phase of haplotypes across the overlapping segments. We imputed each batch against the European subset of 1000 Genomes Project haplotypes using Minimac⁵⁹ (2011-10-27) with 5 rounds and 200 states for parameter estimation. Analyses were limited to 7.4 million SNPs with imputed $r^2 > 0.5$ averaged across all batches and $r^2 > 0.3$ in every batch.

23andMe participants were able to fill out web-based questionnaires whenever they logged into their 23andMe accounts. Allergy information was derived primarily from an Allergies and Asthma survey (**Supplementary Note**). The survey covers allergic reactions to 38 common allergens, including foods, plants, animals, molds, latex, dust mites, medicines and vaccines. Cases were defined as those who reported a positive allergy test, difficulty swallowing or speaking, hives, itchy mouth, itchy eyes, itchy nose or asthma in response to a particular allergen. Controls were defined as individuals who did not meet these criteria. For pollen allergy, we aggregated reports of allergies to grasses, trees or weeds. At the time of the analysis, 30% of 171,274 23andMe research participants had taken this allergy survey. We incorporated 7,635 additional controls who reported having neither seasonal nor environmental allergies in a medical history survey or who reported not currently having allergies in an asthma survey. The final analysis included 46,646 participants.

ALSPAC cohort. ALSPAC¹⁹ is a large birth cohort that recruited 14,541 pregnant women resident in Avon, UK, with dates of delivery between 1 April 1991 and 31 December 1992. Mothers enrolled in the study filled out a questionnaire at the end of the third month of pregnancy, which included questions on allergies. Mothers were asked whether they were allergic to cat, pollen or

dust, with the option each time of indicating yes or no. The questions did not specify whether an allergy was current or in the past.

The Centre National de Génotypage (CNG) carried out DNA genotyping on the Illumina Human660W-Quad array, and genotypes were called with Illumina GenomeStudio. PLINK⁶⁰ (v1.07) was used to carry out quality control measures on an initial set of 10,015 subjects and 557,124 directly genotyped SNPs. SNPs were removed if they had more than 5% missingness or Hardy-Weinberg equilibrium $P < 1 \times 10^{-6}$. Additionally, SNPs with MAF of less than 1% were removed. Samples were excluded if they had more than 5% missingness, indeterminate X-chromosome heterozygosity or extreme autosomal heterozygosity. We restricted the analysis to individuals with European ancestry; samples showing evidence of population stratification were identified by multidimensional scaling of genome-wide identity-by-state (IBS) pairwise distances using the CEU, YRI, JPT and CHB HapMap populations as a reference and were then excluded. Cryptic relatedness was defined as a π hat value of more than 0.125, which is expected to correspond to roughly 12.5% of alleles being shared IBD or relatedness at a first-cousin level.

A total of 8,340 subjects and 526,688 SNPs passed these quality control filters. We imputed autosomal SNPs against the HapMap⁶¹ CEU population (Utah residents of Northern and Western European ancestry; release 22) using MaCH⁶² (v1.0.16). A combination of MaCH and Minimac⁵⁹ (v4.4.3, 2010-12-13) was used to impute X-chromosome genotypes against the HapMap CEU population (release 21). Analyses were limited to 2.5 million SNPs with imputed $r^2 > 0.3$. Out of 8,340 subjects with genotype data, 7,216 had allergy phenotype data and were used in the GWAS.

Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees, and written informed consent was provided by all parents.

Single-phenotype GWAS. We performed traditional genome-wide tests for association with each of the three allergy phenotypes using logistic regression, assuming an additive model for genetic effects. The 23andMe analyses were adjusted for age, sex and the top five principal components of the genotype data matrix. The ALSPAC analyses were not adjusted for covariates. ALSPAC GWAS results were remapped to NCBI Build 37 using the liftOver tool⁶³. For each allergy phenotype, we used METAL⁶⁴ to perform an inverse variance-weighted fixed-effects meta-analysis across 2.4 million SNPs in the intersection of the 23andMe and ALSPAC results. We applied genomic control corrections to the individual GWAS result sets (23andMe: $\lambda = 1.06$ –1.08; ALSPAC: $\lambda = 1.00$ –1.02). The meta-analysis results showed no inflation ($\lambda = 1.001$ –1.004).

Multiple-phenotype GWAS. We jointly modeled association across the three allergens using GEEs⁶⁵. We used an unstructured correlation matrix for the three outcomes. In each cohort, we first fit GEE models with the same covariates used in the single-phenotype GWAS, with additional terms for interactions between each covariate and allergen and a single shared genotype effect, using a fast approximate method⁶⁶. Results were adjusted for genomic control (23andMe: $\lambda = 1.07$; ALSPAC: $\lambda = 1.02$). We performed an inverse variance-weighted fixed-effects meta-analysis of the shared effects across the 23andMe and ALSPAC cohorts. Then, for a subset of 3,725 SNPs with either single-phenotype association $P < 1 \times 10^{-4}$ with any allergy or with association $P < 1 \times 10^{-4}$ in the approximate GEE meta-analysis, we refit GEE models using the R package *geepack*⁶⁷. In addition to refitting the shared effects, we incorporated interactions between genotype and allergy type and used analysis of deviance to assess the significance of the interactions. We used Fisher's method⁶⁸ to compute combined P values from the 23andMe and ALSPAC interaction tests. This test combines interaction evidence in each cohort but does not assess the directional consistency of the interactions.

Heterogeneity assessment. In the 23andMe cohort, we assessed effects from the genotyping platforms by logistic regression of an indicator variable representing the genotyping platform against five principal components and the imputed allele dosage, performing a likelihood ratio test to assess the significance of the allele dosage term. We assessed the index SNPs for age-related effects in the 23andMe cohort by fitting a GEE model with an

age-by-dosage interaction term and testing the significance of the interaction term with a Wald test. We tested index SNPs for heterogeneity across cohorts using Cochran's Q statistic, and we used I^2 to measure the extent of heterogeneity⁶⁹. We determined confidence intervals for I^2 using the non-central χ^2 method (**Supplementary Table 4**). Although several SNPs had large I^2 values, confidence intervals were very wide and remained consistent with the null hypothesis of no heterogeneity.

Assessment of SNP interactions. In the 23andMe cohort, we fit GEE models assuming shared effects across allergy types with allele dosages and interaction terms for all pairwise combinations of the 22 shared-effect index SNPs and rs17533090 (**Supplementary Table 5**). We used Wald tests to assess the significance of the interaction terms. Given a conditioning SNP₁ and tested SNP₂, we also computed a joint test of both the main effect of SNP₂ and the interaction SNP₁ $\times$ SNP₂ being equal to zero.

Functional annotation. We used publicly available bioinformatics resources to annotate putative associations. In general, we required that an annotated variant be within 500 kb of our index SNP with $r^2 > 0.5$, based on the European subset of 1000 Genomes Project haplotypes. We used the NCBI Gap Plus resource to identify nearby GWAS findings (**Supplementary Table 7**). We used tables from the UCSC Genome Browser to identify nearby coding SNPs (**Supplementary Table 8**). We identified nearby eQTLs from a study of monocytes²¹ (**Supplementary Table 9**). We also used HaploReg⁷⁰ to identify nearby annotations from the ENCODE Project⁷¹ (**Supplementary Table 10**). Finally, we took all reported associations with asthma or atopic dermatitis from the National Human Genome Research Institute (NHGRI) GWAS Catalog⁷² and looked up the corresponding results for these loci in our meta-analysis (**Supplementary Tables 11 and 12**).

Assessment of SNP effects on allergy symptoms. In the 23andMe cohort, we reclassified cases on the basis of self-reported allergic symptoms representing allergic rhinitis, allergic asthma and/or allergic contact dermatitis (**Supplementary Note**). We performed a GEE analysis across these multiple outcomes, including the same controls used in the GWAS (**Supplementary Tables 13 and 14**). The model included the same covariates used in the GWAS

(age, sex and five principal components), as well as interactions between these covariates and symptom type.

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A genome-wide association meta-analysis of self-reported allergy identifies shared and allergy-specific susceptibility loci

Supplementary Tables, Figures and Note

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Supplementary Table 2. Detailed results for allergy loci in the 23andMe cohort.

SNP	region	position	alleles	RAF	r ²	typed	OR	95% CI	<i>P</i> _{main}	<i>P</i> _{int}	<i>P</i> _{total}
rs2101521	4p14	38811551	A/G	0.762	0.982	I	1.138	[1.105,1.172]	2.4e-17	0.00015	1.5e-19
rs1438673	5q22.1	110467499	T/C	0.495	0.988	I	1.116	[1.089,1.144]	2.3e-18	0.0062	3.6e-19
rs2155219	11q13.5	76299194	G/T	0.515	0.990	P	1.108	[1.081,1.136]	2.5e-16	0.63	3.2e-15
rs10189629	2q12.1	102879464	A/C	0.855	0.995	P	1.152	[1.111,1.194]	1.2e-14	0.058	2.0e-14
rs6906021	6p21.32	32626311	T/C	0.475	0.951	P	1.097	[1.070,1.125]	3.4e-13	0.10	7.4e-13
rs9266772	6p21.33	31352113	T/C	0.188	0.995	P	1.101	[1.068,1.135]	9.2e-10	0.79	1.4e-08
rs7720838	5p13.1	40486896	G/T	0.575	0.997	G	1.086	[1.060,1.113]	6.6e-11	0.060	9.2e-11
rs10497813	2q33.1	198914072	T/G	0.482	0.999	I	1.075	[1.050,1.102]	5.5e-09	0.54	5.7e-08
rs9860547	3q28	188128979	G/A	0.463	0.948	I	1.073	[1.047,1.100]	2.8e-08	0.14	7.9e-08
rs7032572	9p24.1	6172380	A/G	0.166	0.668	I	1.129	[1.085,1.175]	2.0e-09	0.95	3.6e-08
rs6021270	20q13.2	50141264	C/T	0.942	0.968	I	1.173	[1.111,1.238]	9.5e-09	0.12	2.8e-08
rs9303280	17q12	38074031	T/C	0.520	0.980	I	1.067	[1.041,1.094]	2.0e-07	0.059	2.3e-07
rs17228058	15q22.33	67450305	A/G	0.235	0.991	I	1.084	[1.053,1.116]	3.5e-08	0.45	2.8e-07
rs962993	10p14	9053132	T/C	0.571	0.931	I	1.073	[1.045,1.100]	7.9e-08	0.54	7.9e-07
rs17388568	4q27	123329362	G/A	0.275	1.000	G	1.074	[1.045,1.103]	2.9e-07	0.040	2.1e-07
rs1998359	14q21.1	38077148	C/G	0.249	0.839	I	1.080	[1.047,1.113]	9.6e-07	0.86	1.3e-05
rs6473223	8q21.13	81268155	C/T	0.360	0.980	I	1.061	[1.034,1.088]	6.7e-06	0.18	2.1e-05
rs10174949	2p25.1	8442248	A/G	0.727	1.000	G	1.070	[1.041,1.099]	1.3e-06	0.016	4.0e-07
rs7203459	16p13.13	11230703	C/T	0.733	0.989	P	1.074	[1.044,1.104]	5.0e-07	0.020	2.3e-07
rs2107357	16p12.1	27410829	G/A	0.138	0.967	I	1.091	[1.054,1.131]	1.2e-06	0.63	1.2e-05
rs2056417	1p36.22	10581658	A/G	0.697	1.000	G	1.058	[1.030,1.086]	3.2e-05	0.55	0.00025
rs10893845	11q24.3	128186882	T/G	0.493	0.999	G	1.063	[1.038,1.089]	8.2e-07	0.44	6.2e-06
rs17533090	6p21.32	32590722	G/T	0.840	0.998	G	1.130	[1.093,1.169]	9.6e-13	8.4e-13	2.1e-22

Region, cytogenetic band; position, build 37 map position of SNP; alleles, low/high risk alleles on genomic reference strand; RAF, risk allele frequency; r², imputation quality estimated from variance in imputed allele dosages; typed: I=imputed, G=genotyped, P=partial (genotyped in ~65% of individuals); OR, odds ratio per copy of the risk allele, for the main effect across allergy types; CI, confidence interval; *P*_{main}, test of main effect across allergens; *P*_{int}, test for interaction with allergy type; *P*_{total}, joint test including main effect and interaction.

Supplementary Table 3. Detailed results for allergy loci in the ALSPAC cohort.

SNP	region	position	alleles	RAF	r ²	typed	OR	95% CI	<i>P</i> _{main}	<i>P</i> _{int}	<i>P</i> _{total}
rs2101521	4p14	38811551	A/G	0.791	0.956	I	1.262	[1.139,1.398]	8.2e-06	0.75	0.00013
rs1438673	5q22.1	110467499	T/C	0.518	0.995	I	1.124	[1.041,1.214]	0.0028	0.60	0.019
rs2155219	11q13.5	76299194	G/T	0.489	0.946	I	1.177	[1.089,1.273]	4.2e-05	0.16	0.00015
rs10189629	2q12.1	102879464	A/C	0.870	0.997	I	1.200	[1.062,1.355]	0.0033	0.90	0.030
rs6906021	6p21.32	32626311	T/C	0.475	0.982	I	1.117	[1.032,1.208]	0.0060	0.56	0.031
rs9266772	6p21.33	31352113	T/C	0.222	0.995	I	1.188	[1.084,1.303]	0.00023	0.034	0.00011
rs7720838	5p13.1	40486896	G/T	0.616	0.999	G	1.035	[0.954,1.123]	0.41	0.29	0.37
rs10497813	2q33.1	198914072	T/G	0.489	0.999	I	1.084	[1.002,1.172]	0.043	0.97	0.24
rs9860547	3q28	188128979	G/A	0.455	0.947	I	1.118	[1.030,1.213]	0.0077	0.44	0.032
rs7032572	9p24.1	6172380	A/G	0.171	0.975	I	1.063	[0.960,1.177]	0.24	0.40	0.35
rs6021270	20q13.2	50141264	C/T	0.918	0.945	I	1.094	[0.937,1.277]	0.25	0.41	0.38
rs9303280	17q12	38074031	T/C	0.501	0.986	I	1.111	[1.028,1.200]	0.0082	0.54	0.040
rs17228058	15q22.33	67450305	A/G	0.269	0.971	I	1.065	[0.977,1.161]	0.15	0.71	0.42
rs962993	10p14	9053132	T/C	0.612	0.893	I	1.082	[0.994,1.178]	0.069	0.68	0.25
rs17388568	4q27	123329362	G/A	0.272	0.996	G	1.095	[1.004,1.193]	0.040	0.46	0.12
rs1998359	14q21.1	38077148	C/G	0.229	0.928	I	1.128	[1.029,1.236]	0.010	0.60	0.053
rs6473223	8q21.13	81268155	C/T	0.346	0.995	I	1.156	[1.067,1.252]	0.00041	0.77	0.0043
rs10174949	2p25.1	8442248	A/G	0.706	1.000	G	1.101	[1.013,1.198]	0.024	0.99	0.16
rs7203459	16p13.13	11230703	C/T	0.741	0.969	I	1.065	[0.971,1.168]	0.18	0.25	0.21
rs2107357	16p12.1	27410829	G/A	0.136	0.961	I	1.096	[0.978,1.227]	0.11	0.83	0.40
rs2056417	1p36.22	10581658	A/G	0.671	1.000	G	1.175	[1.080,1.278]	0.00017	0.89	0.0022
rs10893845	11q24.3	128186882	T/G	0.493	0.997	G	1.038	[0.961,1.121]	0.35	0.99	0.82
rs17533090	6p21.32	32590722	G/T	0.830	0.897	G	1.104	[0.989,1.232]	0.077	0.063	0.038

Region, cytogenetic band; position, build 37 map position of SNP; alleles, low/high risk alleles on genomic reference strand; RAF, risk allele frequency; r², imputation quality estimated from variance in imputed allele dosages; typed: I=imputed, G=genotyped; OR, odds ratio per copy of the risk allele for the main effect across allergy types; CI, confidence interval; *P*_{main}, P value for test of main effect across allergy types; *P*_{int}, test for interaction with allergy type; *P*_{total}, overall test including main effect and interaction.

Supplementary Table 4. Tests for platform effects, age effects, and study heterogeneity

SNP	P_{gt}	P_{age}	P_Q	I^2	95% CI	gene context
rs2101521	0.46	0.057	0.06	0.72	[0.00,0.92]	TLR1-[]--TLR6
rs1438673	0.33	0.57	0.86	0.00	[0.00,0.80]	WDR36-[]--CAMK4
rs2155219	0.69	0.56	0.15	0.53	[0.00,0.89]	C11orf30-[]--LRRC32
rs10189629	0.15	0.16	0.53	0.00	[0.00,0.80]	IL1RL2-[]--IL1RL1
rs6906021	0.17	0.41	0.68	0.00	[0.00,0.80]	HLA-DQA1-[]--HLA-DQB1
rs9266772	0.64	0.98	0.12	0.58	[0.00,0.90]	HLA-C-[]--MICA
rs7720838	0.91	0.89	0.27	0.19	[0.00,0.84]	[]---PTGER4
rs10497813	0.96	0.83	0.85	0.00	[0.00,0.80]	[PLCL1]
rs9860547	0.31	0.56	0.35	0.00	[0.00,0.80]	[LPP]
rs7032572	0.098	0.99	0.28	0.15	[0.00,0.83]	RANBP6-[]--IL33
rs6021270	0.39	0.24	0.41	0.00	[0.00,0.80]	[NFATC2]
rs9303280	0.67	0.59	0.34	0.00	[0.00,0.80]	[GSDMB]
rs17228058	0.94	0.37	0.70	0.00	[0.00,0.80]	[SMAD3]
rs962993	0.34	0.66	0.85	0.00	[0.00,0.80]	GATA3-[]
rs17388568	0.26	0.052	0.68	0.00	[0.00,0.80]	[ADAD1]
rs1998359	0.96	0.79	0.37	0.00	[0.00,0.80]	FOXA1-[]---TTC6
rs6473223	0.43	0.15	0.05	0.75	[0.00,0.93]	TPD52-[]---ZBTB10
rs10174949	0.20	0.42	0.52	0.00	[0.00,0.80]	[]---ID2
rs7203459	0.26	0.27	0.86	0.00	[0.00,0.80]	[CLEC16A]
rs2107357	0.041	0.67	0.95	0.00	[0.00,0.80]	IL4R-[]--IL21R
rs2056417	0.24	0.42	0.02	0.82	[0.00,0.94]	[PEX14]
rs10893845	0.51	0.40	0.56	0.00	[0.00,0.80]	[]---ETS1

P_{gt} , result of test for a genotyping platform effect between Illumina HumanHap 550-based results and OmniExpress-based results in the 23andMe cohort; P_{age} , test of interaction between genotype and age in the 23andMe cohort; P_Q , P value for test of heterogeneity based on Cochran's Q statistic; I^2 , proportion of variance in effects attributable to study heterogeneity; 95% CI, confidence interval for I^2 ; gene context, as in Table 2.

Supplementary Table 6. Replication of allergy loci in analysis of allergic sensitization²⁰.

SNP	OR	95% CI	match	<i>P</i>	<i>P</i> _{fisher}	gene context
rs2101521	1.234	[1.155,1.319]	Yes	6.3e-10	3.7e-30	TLR1-[]--TLR6
rs1438673	1.114	[1.060,1.170]	Yes	2.2e-05	5.0e-25	WDR36-[]--CAMK4
rs2155219	1.202	[1.142,1.265]	Yes	1.8e-12	2.6e-31	C11orf30-[]--LRRC32
rs10189629	1.146	[1.059,1.241]	Yes	0.00072	1.3e-19	IL1RL2-[]--IL1RL1
rs6906021	1.158	[1.101,1.219]	Yes	1.3e-08	9.6e-23	HLA-DQA1-[]--HLA-DQB1
rs9266772	1.120	[1.043,1.203]	Yes	0.0019	5.5e-15	HLA-C-[]--MICA
rs7720838	1.056	[1.004,1.110]	Yes	0.033	2.7e-12	[]---PTGER4
rs2117339	1.032	[0.983,1.084]	Yes	0.21	1.4e-10	[PLCL1]
rs9860547	1.121	[1.063,1.181]	Yes	2.3e-05	2.7e-14	[LPP]
rs7032572	1.028	[0.962,1.099]	Yes	0.41	7.7e-10	RANBP6-[]--IL33
rs6021270	1.041	[0.940,1.153]	Yes	0.45	3.1e-09	[NFATC2]
rs9303280	1.044	[0.988,1.102]	Yes	0.13	1.0e-09	[GSDMB]
rs962993	1.069	[1.009,1.132]	Yes	0.024	3.3e-10	GATA3-[]
rs17293632	1.039	[0.982,1.099]	Yes	0.18	2.5e-09	[SMAD3]
rs2202749	1.108	[1.051,1.167]	Yes	0.00014	3.4e-12	TPD52-[]---ZBTB10
rs17388568	1.116	[1.058,1.177]	Yes	5.6e-05	2.0e-12	[ADAD1]
rs9671863	1.015	[0.960,1.074]	Yes	0.60	3.1e-08	FOXA1-[]---TTC6
rs13416555	1.121	[1.062,1.183]	Yes	3.3e-05	3.6e-12	[]---ID2
rs7203459	1.033	[0.970,1.101]	Yes	0.31	6.4e-08	[CLEC16A]
rs2107357	1.079	[0.992,1.174]	Yes	0.077	2.4e-08	IL4R-[]--IL21R
rs2056417	1.031	[0.978,1.087]	Yes	0.27	1.4e-07	[PEX14]
rs970924	1.050	[0.993,1.110]	Yes	0.085	5.2e-08	[]---ETS1

OR, odds ratio for the risk allele defined in Table 2; CI, confidence interval; match, agreement of risk alleles across allergy and allergic sensitization studies; *P*, *P* value for allergic sensitization; *P*_{fisher}, combined *P* value across allergy (Table 2) and allergic sensitization meta-analyses using Fisher's method⁶⁹; gene context, as in Table 2.

Supplementary Table 7. NCBI Gap Plus annotations near allergy index SNPs.

allergy association				relationship		Gap Plus annotation				
region	position	SNP	P	distance	r ²	SNP	P	study ID	MeSH term	genes
5q22.1	110467499	rs1438673	2.3e-20	-61824	0.771	rs3806932	3.0e-09	20208534	Esophagitis	TSLP
5q22.1	110467499	rs1438673	2.3e-20	-59497	0.564	rs1898671	5.0e-06	22036096	Rhinitis, Allergic, Seasonal	TSLP
11q13.5	76299194	rs2155219	1.4e-19	-28511	0.513	rs7130588	2.0e-08	21907864	Asthma	C11orf30 - LRRC32
11q13.5	76299194	rs2155219	1.4e-19	0	1.000	rs2155219	5.0e-16	21297633	Colitis, Ulcerative	C11orf30 - LRRC32
11q13.5	76299194	rs2155219	1.4e-19	0	1.000	rs2155219	1.0e-08	22036096	Rhinitis, Allergic, Seasonal	C11orf30 - LRRC32
11q13.5	76299194	rs2155219	1.4e-19	2122	0.583	rs7927894	1.0e-09	18587394	Crohn Disease	C11orf30 - LRRC32
11q13.5	76299194	rs2155219	1.4e-19	2122	0.583	rs7927894	8.0e-10	19349984	Dermatitis, Atopic	C11orf30 - LRRC32
2q12.1	102879464	rs10189629	1.9e-16	74153	0.775	rs3771180	2.0e-15	21804549	Asthma	IL1RL1
5p13.1	40486896	rs7720838	8.3e-11	3894	0.936	rs10440635	3.0e-07	21743469	Spondylitis, Ankylosing	DAB2 - PTGER4
2q33.1	198914072	rs10497813	6.1e-10	-17177	0.972	rs6738825	4.0e-09	21102463	Crohn Disease	PLCL1
3q28	188128979	rs9860547	1.2e-09	-16425	0.698	rs1464510	3.0e-40	20190752	Celiac Disease	LPP
3q28	188128979	rs9860547	1.2e-09	-16425	0.698	rs1464510	5.0e-09	18311140	Celiac Disease	LPP
3q28	188128979	rs9860547	1.2e-09	-16425	0.698	rs1464510	1.0e-11	20410501	Vitiligo	LPP
9p24.1	6172380	rs7032572	1.9e-09	17696	0.949	rs1342326	9.0e-10	20860503	Asthma	RANBP6 - IL33
9p24.1	6172380	rs7032572	1.9e-09	21075	0.537	rs2381416	2.0e-12	21804549	Asthma	RANBP6 - IL33
17q12	38074031	rs9303280	8.3e-09	-151772	0.681	rs907092	8.0e-06	19458352	Liver Cirrhosis, Biliary	IKZF3
17q12	38074031	rs9303280	8.3e-09	-97562	0.781	rs9303277	2.0e-09	20639880	Liver Cirrhosis, Biliary	IKZF3
17q12	38074031	rs9303280	8.3e-09	-33268	0.745	rs2872507	9.0e-07	20453842	Arthritis, Rheumatoid	ZBP2 - GSDMB
17q12	38074031	rs9303280	8.3e-09	-33268	0.745	rs2872507	5.0e-11	21297633	Colitis, Ulcerative	ZBP2 - GSDMB
17q12	38074031	rs9303280	8.3e-09	-33268	0.745	rs2872507	5.0e-09	18587394	Crohn Disease	ZBP2 - GSDMB
17q12	38074031	rs9303280	8.3e-09	-33268	0.745	rs2872507	2.0e-06	21829393	Diabetes Mellitus, Type 1	ZBP2 - GSDMB
17q12	38074031	rs9303280	8.3e-09	-11835	0.752	rs2305480	1.0e-07	20860503	Asthma	GSDMB
17q12	38074031	rs9303280	8.3e-09	-11835	0.752	rs2305480	3.0e-08	20228799	Colitis, Ulcerative	GSDMB
17q12	38074031	rs9303280	8.3e-09	-9626	0.760	rs11078927	2.0e-16	21804549	Asthma	GSDMB
17q12	38074031	rs9303280	8.3e-09	-7791	0.855	rs2290400	6.0e-13	19430480	Diabetes Mellitus, Type 1	GSDMB
17q12	38074031	rs9303280	8.3e-09	-4082	0.924	rs7216389	9.0e-11	17611496	Asthma	GSDMB
17q12	38074031	rs9303280	8.3e-09	21143	0.559	rs6503525	5.0e-07	21150878	Asthma	ORMDL3 - GSDMA
15q22.33	67450305	rs17228058	1.2e-08	-7709	0.989	rs17293632	3.0e-19	21102463	Crohn Disease	SMAD3
4q27	123329362	rs17388568	3.6e-08	-196870	0.706	rs4505848	5.0e-13	19430480	Diabetes Mellitus, Type 1	KIAA1109
4q27	123329362	rs17388568	3.6e-08	-130927	0.617	rs6534347	2.0e-06	17554300	Diabetes Mellitus, Type 1	KIAA1109
4q27	123329362	rs17388568	3.6e-08	0	1.000	rs17388568	9.0e-07	21297633	Colitis, Ulcerative	ADAD1
4q27	123329362	rs17388568	3.6e-08	0	1.000	rs17388568	6.0e-06	21829393	Diabetes Mellitus, Type 1	ADAD1
4q27	123329362	rs17388568	3.6e-08	43771	0.909	rs2069772	1.0e-06	22036096	Rhinitis, Allergic, Seasonal	IL2
8q21.13	81268155	rs6473223	7.7e-08	-449	0.970	rs6992476	9.1e-05	pha002864	Diabetic Nephropathies	RPS5P5 - ZBTB10
16p13.13	11230703	rs7203459	2.1e-07	-71818	0.508	rs887864	1.0e-06	22036096	Rhinitis, Allergic, Seasonal	CLEC16A
16p13.13	11230703	rs7203459	2.1e-07	8080	0.596	rs2903692	7.0e-11	17632545	Diabetes Mellitus, Type 1	CLEC16A

Allergy association, an index SNP from table 2; relationship, the distance and r² between the allergy index SNP and the annotation. The Gap Plus annotation includes the reported SNP identifier and P value; a study ID, either a PubMed ID for the reporting study, or a dbGAP “pha” accession number; a MeSH term, or medical subject heading; and associated genes as reported in the original study.

Supplementary Table 8. Nonsynonymous SNPs near allergy index SNPs.

allergy association				relationship		nsSNP annotation		
region	position	SNP	<i>P</i>	distance	<i>r</i> ²	SNP	gene	mutation
4p14	38811551	rs2101521	5.9e-21	-36662	0.550	rs4129009	TLR10	I775V
4p14	38811551	rs2101521	5.9e-21	-12903	0.676	rs5743618	TLR1	S602I
4p14	38811551	rs2101521	5.9e-21	-11841	0.806	rs4833095	TLR1	N248S
17q12	38074031	rs9303280	8.3e-09	-45397	0.821	rs11557467	ZBPB2	S173I
17q12	38074031	rs9303280	8.3e-09	-11835	0.752	rs2305480	GSDMB	P298S
17q12	38074031	rs9303280	8.3e-09	-11814	0.848	rs2305479	GSDMB	G291R

Allergy association, an index SNP from Table 2; relationship, distance and *r*² between the allergy index SNP and the annotation. The nsSNP annotation includes the SNP identifier, affected gene, and amino acid change associated with this SNP.

Supplementary Table 9. Monocyte expression QTLs near allergy index SNPs.

allergy association				relationship		eQTL annotation				
region	position	SNP	<i>P</i>	distance	<i>r</i> ²	SNP	distance	gene	<i>P</i>	<i>r</i> ²
4p14	38811551	rs2101521	5.9e-21	-8488	0.711	rs5743592	25160	TLR6	1.4e-08	0.024
2q33.1	198914072	rs10497813	6.1e-10	-33591	0.897	rs1318867	67998	PLCL1	3.0e-28	0.083
3q28	188128979	rs9860547	1.2e-09	-23923	0.872	rs9864529	641581	BCL6	5.2e-10	0.028
17q12	38074031	rs9303280	8.9e-09	-5988	0.924	rs869402	47602	IKZF3	3.0e-07	0.020
2p25.1	8442248	rs10174949	1.0e-07	-1216	0.687	rs6734135	377943	ID2	9.0e-10	0.028
1p36.22	10581658	rs2056417	5.3e-07	-37111	0.861	rs668805	0	PEX14	1.2e-19	0.057

Allergy association, an index SNP from Table 2; relationship, distance and *r*² between the index SNP and the annotation. The eQTL annotation includes the associated SNP; the absolute distance in base pairs between that SNP and the associated gene; the associated gene; the reported *P* value; and *r*², the proportion of variance in expression explained by the association.

Supplementary Table 11. Replication of reported associations with asthma

region	pubmed.id	first author	pub date	GWAS Catalog result				Allergy result		
				risk allele	P	OR	genes	P	OR	agree
1q21.3	21804549	Torgerson DG	2011-07-31	rs4845783-G	6.0e-06		CRCT1	0.13	1.02	
1q21.3	21907864	Ferreira MA	2011-09-10	rs4129267-T	2.0e-08	1.09	IL6R	0.034	1.03	+
1q31.3	20032318	Sleiman PM	2009-12-23	rs2786098-C	2.0e-13	1.43	DENND1B, CRB1	0.64	0.99	
2q12.1	21804549	Torgerson DG	2011-07-31	rs3771180-G	2.0e-15		IL1RL1	1.6e-13	1.15	+++
2q12.1	23028483	Ramasamy A	2012-09-28	rs13408661-G	1.0e-09	1.23	IL1RL1, IL18R1	1.9e-15	1.15	+++
2q12.1	20860503	Moffatt MF	2010-09-23	rs3771166-G	3.0e-09	1.15	IL18R1	3.8e-07	1.06	+++
4q31.21	21804548	Hirota T	2011-07-31	rs7686660-T	2.0e-12	1.16	LOC729675	0.099	0.98	
4q31.21	21804548	Hirota T	2011-07-31	rs3805236-G	7.0e-08	1.12	GAB1	0.00031	1.06	+++
5q12.1	19426955	Himes BE	2009-05-07	rs1588265-C	3.0e-08	1.18	PDE4D	0.26	1.01	
5q22.1	21804549	Torgerson DG	2011-07-31	rs1837253-C	1.0e-14		TSLP	2.3e-10	1.09	+++
5q22.1	21804548	Hirota T	2011-07-31	rs1837253-C	1.0e-16	1.17	TSLP	2.3e-10	1.09	+++
5q31.1	20860503	Moffatt MF	2010-09-23	rs2073643-T	2.0e-07	1.11	SLC22A5	0.090	1.02	
5q31.1	20159242	Li X	2010-02-01	rs2244012-C	3.0e-07	1.64	RAD50	0.00056	1.05	++
5q31.1	20860503	Moffatt MF	2010-09-23	rs1295686-T	1.0e-07	1.15	IL13	1.7e-06	1.07	+++
6p21.32	21804548	Hirota T	2011-07-31	rs204993-A	2.0e-15	1.17	PBX2	7.3e-07	0.94	---
6p21.32	21804548	Hirota T	2011-07-31	rs404860-A	4.0e-23	1.21	NOTCH4	0.61	1.01	
6p21.32	21804548	Hirota T	2011-07-31	rs3129943-T	3.0e-15	1.17	C6orf10	0.20	1.02	
6p21.32	21804548	Hirota T	2011-07-31	rs3117098-G	5.0e-12	1.16	BTNL2	0.45	1.01	
6p21.32	23028483	Ramasamy A	2012-09-28	rs9268516-T	1.0e-08	1.15	BTNL2, HLA-DRA	4.2e-05	1.06	+++
6p21.32	21804548	Hirota T	2011-07-31	rs3129890-T	5.0e-13	1.15	HLA-DRA	0.56	1.01	
6p21.32	21804548	Hirota T	2011-07-31	rs7775228-A	5.0e-15	1.17	HLA-DQB1	0.00012	0.94	---
6p21.32	21804548	Hirota T	2011-07-31	rs9275698-T	5.0e-12	1.18	HLA-DQA2	0.68	1.01	
6p21.32	21804548	Hirota T	2011-07-31	rs9500927-T	4.0e-09	1.13	HLA-DOA	0.0062	1.05	+
6p21.32	21814517	Noguchi E	2011-07-21	rs987870-C	2.0e-10	1.40	HLA, DPB1	9.2e-05	1.07	+++
8q24.11	21814517	Noguchi E	2011-07-21	rs3019885-G	5.0e-13	1.34	SLC30A8	0.068	0.98	
9p24.1	20860503	Moffatt MF	2010-09-23	rs1342326-C	9.0e-10	1.20	IL33	6.0e-09	1.10	+++
9p24.1	21804549	Torgerson DG	2011-07-31	rs2381416-C	2.0e-12		IL33	1.2e-07	1.07	+++
10p14	21804548	Hirota T	2011-07-31	rs10508372-C	2.0e-15	1.16	LOC338591	0.00019	1.09	+++
10q21.1	21907864	Ferreira MA	2011-09-10	rs7922491-A	5.0e-07	1.13	PRKG1	0.46	1.01	
11q13.5	21907864	Ferreira MA	2011-09-10	rs7130588-G	2.0e-08	1.09	LRRRC32	2.2e-12	1.09	+++
12q13.2	21804548	Hirota T	2011-07-31	rs2069408-C	1.0e-10	1.15	CDK2	0.060	1.02	
12q13.2	21804548	Hirota T	2011-07-31	rs1701704-G	2.0e-13	1.19	IKZF4	0.012	1.03	+
15q22.2	20860503	Moffatt MF	2010-09-23	rs11071559-C	1.0e-07	1.18	RORA	9.2e-05	1.07	+++
15q22.33	20860503	Moffatt MF	2010-09-23	rs744910-G	4.0e-09	1.12	SMAD3	4.2e-06	1.06	+++
17q12	20860503	Moffatt MF	2010-09-23	rs2305480-G	1.0e-07	1.18	GSDMB	4.4e-08	1.07	+++
17q12	21804549	Torgerson DG	2011-07-31	rs11078927-C	2.0e-16		GSDMB	3.9e-08	0.94	+++
17q12	17611496	Moffatt MF	2007-07-26	rs7216389-T	9.0e-11	1.45	ORMDL3	3.2e-08	1.07	+++
17q12	21150878	Ferreira MA	2010-12-08	rs6503525-C	5.0e-07	1.33	ORMDL3	5.9e-06	1.06	+++
17q21.1	20860503	Moffatt MF	2010-09-23	rs3894194-A	5.0e-09	1.17	GSDMA	7.9e-06	1.05	+++
22q12.3	20860503	Moffatt MF	2010-09-23	rs2284033-G	1.0e-08	1.12	IL2RB	0.016	1.03	+

Results are shown for all asthma reports in the NHGRI GWAS Catalog for which the risk allele was available or could be inferred from the original study, and the reported SNP was tested in our allergy analysis. Entries in gray italics overlap a region identified in Table 2. Allergy result: P, P value from shared-effect meta-analysis; OR, odds ratio for the previously reported risk allele; agree, '+' P<0.05, '++' P<0.005, '+++ ' P<0.0005 with the same risk allele; dashes indicate the same levels of significance but with inconsistent risk alleles.

Supplementary Table 12. Replication of reported associations with atopic dermatitis.

GWAS Catalog result								Allergy result		
region	pubmed.id	first author	pubdate	riskallele	P	OR	genes	P	OR	agree
1q21.3	21666691	Sun LD	2011-06-13	rs3126085-A	6.0e-12	1.22	FLG	0.068	0.97	
2q12.1	23042114	Hirota T	2012-10-07	rs13015714-G	8.0e-18	1.27	IL1RL1, IL18R1, IL18RAP	0.18	0.98	
2q13	23042114	Hirota T	2012-10-07	rs2271404-G	3.0e-07	1.17	LOC100505634	0.58	0.99	
3p22.3	23042114	Hirota T	2012-10-07	rs7613051-A	6.0e-21	1.29	GLB1	0.19	1.02	
3q13.2	23042114	Hirota T	2012-10-07	rs12634229-G	2.0e-19	1.29	CCDC80, LOC100630917	0.49	1.02	
5q31.1	23042114	Hirota T	2012-10-07	rs1295686-T	2.0e-06	1.22	KIF3A, IL13	1.7e-06	1.07	+++
5q31.1	22197932	Paternoster L	2011-12-25	rs2897442-C	4.0e-08	1.11	KIF3A	0.024	1.03	+
6p21.33	23042114	Hirota T	2012-10-07	rs9368677-G	1.0e-17	1.36	HLA-C	0.12	0.96	
6p21.33	22197932	Paternoster L	2011-12-25	rs3853601-G	2.0e-06	1.13	BAT1	0.92	1.00	
6p21.32	23042114	Hirota T	2012-10-07	rs176095-T	8.0e-20	1.40	GPSM3	9.6e-07	0.93	---
6p21.32	23042114	Hirota T	2012-10-07	rs9469099-G	5.0e-19	1.61	C6orf10	0.35	1.04	
7p22.2	23042114	Hirota T	2012-10-07	rs4722404-G	8.0e-09	1.18	CARD11	0.0069	1.03	+
8q24.21	23042114	Hirota T	2012-10-07	rs7815944-A	4.0e-07	1.16	MIR1208	0.0033	1.10	++
10q21.2	23042114	Hirota T	2012-10-07	rs10995251-C	6.0e-20	1.28	ZNF365	0.090	1.02	
11p15.4	23042114	Hirota T	2012-10-07	rs878860-G	2.0e-22	1.31	OR10A3, NLRP10	0.082	0.98	
11q13.1	23042114	Hirota T	2012-10-07	rs593982-C	6.0e-07	1.23	OVOL1	0.47	0.99	
11q13.1	22197932	Paternoster L	2011-12-25	rs479844-G	1.0e-13	1.14	OVOL1	0.15	1.02	
11q13.5	19349984	Esparza-Gordillo J	2009-04-06	rs7927894-A	8.0e-10	1.22	C11orf30	6.2e-16	1.10	+++
11q13.5	23042114	Hirota T	2012-10-07	rs11236809-G	3.0e-06	1.24	C11orf30	0.20	1.03	
16p13.13	23042114	Hirota T	2012-10-07	rs9923856-A	6.0e-06	1.17	CLEC16A	4.4e-05	1.05	+++
19p13.2	22197932	Paternoster L	2011-12-25	rs2164983-A	7.0e-09	1.16	ACTL9	0.20	1.02	
20q13.2	23042114	Hirota T	2012-10-07	rs16999165-T	2.0e-08	1.19	CYP24A1, PFDN4	0.24	1.04	
22q12.3	22197932	Paternoster L	2011-12-25	rs4821544-C	6.0e-06	1.09	NCF4	0.0064	1.04	+

Results are shown for all atopic dermatitis reports in the NHGRI GWAS Catalog for which the risk allele was available or could be inferred from the original study, and the reported SNP was tested in our allergy analysis. Entries in gray italics overlap a region identified in Table 2. Allergy result: P, P value from shared-effect meta-analysis; OR, odds ratio for the previously reported risk allele; agree, '+' P<0.05, '++' P<0.005, '+++ 'P<0.0005 with the same risk allele; dashes indicate the same levels of significance but with inconsistent risk alleles.

Supplementary Table 13. Association of index SNPs with symptoms in the 23andMe cohort.

SNP	OR	95% CI	P_{main}	P_{int}	P_{total}	gene context
rs2101521	1.143	[1.109,1.178]	2.6e-18	0.62	1.2e-16	TLR1-[]--TLR6
rs1438673	1.124	[1.097,1.152]	1.8e-20	0.34	5.7e-19	WDR36-[]--CAMK4
rs2155219	1.106	[1.079,1.133]	1.1e-15	0.17	1.3e-14	C11orf30-[]--LRRC32
rs10189629	1.170	[1.128,1.213]	1.6e-17	0.20	2.6e-16	IL1RL2-[]--IL1RL1
rs6906021	1.105	[1.078,1.133]	4.5e-15	0.064	1.8e-14	HLA-DQA1-[]--HLA-DQB1
rs9266772	1.109	[1.075,1.143]	6.4e-11	0.91	2.6e-09	HLA-C-[]--MICA
rs7720838	1.076	[1.050,1.103]	7.9e-09	0.96	2.7e-07	[]--PTGER4
rs10497813	1.067	[1.041,1.093]	2.2e-07	0.0078	5.5e-08	[PLCL1]
rs9860547	1.080	[1.053,1.107]	2.0e-09	0.54	4.3e-08	[LPP]
rs7032572	1.142	[1.097,1.188]	6.4e-11	0.043	1.3e-10	RANBP6-[]--IL33
rs6021270	1.167	[1.105,1.234]	3.6e-08	0.69	8.5e-07	[NFATC2]
rs9303280	1.064	[1.038,1.090]	1.0e-06	3.5e-05	1.2e-09	[GSDMB]
rs17228058	1.096	[1.065,1.128]	3.2e-10	0.13	1.8e-09	[SMAD3]
rs962993	1.068	[1.041,1.096]	4.5e-07	0.32	3.8e-06	GATA3-[]--
rs17388568	1.077	[1.048,1.107]	8.2e-08	0.30	7.2e-07	[ADAD1]
rs1998359	1.079	[1.046,1.112]	1.2e-06	0.024	7.8e-07	FOXA1-[]--TTC6
rs6473223	1.070	[1.042,1.097]	2.7e-07	0.55	4.2e-06	TPD52-[]--ZBTB10
rs10174949	1.058	[1.030,1.088]	5.1e-05	0.65	0.00063	[]--ID2
rs7203459	1.079	[1.049,1.110]	1.0e-07	0.081	2.7e-07	[CLEC16A]
rs2107357	1.078	[1.040,1.116]	3.2e-05	0.76	0.00046	IL4R-[]--IL21R
rs2056417	1.064	[1.036,1.092]	5.5e-06	0.22	2.9e-05	[PEX14]
rs10893845	1.064	[1.038,1.090]	7.2e-07	0.20	3.7e-06	[]--ETS1
rs17533090	1.122	[1.085,1.161]	2.7e-11	0.32	4.1e-10	

OR, odds ratio per copy of the risk allele, for the main effect across allergy types; CI, confidence interval; P_{main} , test of main effect across symptoms; P_{int} , test for interaction with symptom; P_{total} , joint test including main effect and interaction. The across-symptom test

Supplementary Table 14. SNP effects on individual symptoms in the 23andMe cohort.

SNP	Rhinitis			Asthma			Contact Dermatitis		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
rs2101521	1.149	[1.112,1.188]	6.0e-17	1.140	[1.089,1.192]	1.1e-08	1.125	[1.076,1.177]	1.8e-07
rs1438673	1.131	[1.101,1.162]	3.7e-19	1.126	[1.084,1.169]	3.1e-10	1.102	[1.063,1.143]	1.2e-07
rs2155219	1.103	[1.073,1.133]	9.7e-13	1.133	[1.092,1.175]	2.1e-11	1.091	[1.052,1.131]	1.9e-06
rs10189629	1.167	[1.122,1.214]	9.9e-15	1.210	[1.144,1.279]	1.0e-11	1.145	[1.084,1.209]	9.2e-07
rs6906021	1.110	[1.080,1.141]	7.1e-14	1.124	[1.083,1.167]	4.3e-10	1.073	[1.034,1.113]	0.00015
rs9266772	1.111	[1.074,1.150]	1.2e-09	1.109	[1.059,1.162]	8.6e-06	1.101	[1.052,1.152]	2.8e-05
rs7720838	1.078	[1.048,1.108]	6.9e-08	1.074	[1.035,1.115]	0.00015	1.073	[1.034,1.113]	0.00016
rs10497813	1.081	[1.052,1.110]	1.6e-08	1.072	[1.033,1.112]	0.00017	1.023	[0.986,1.061]	0.21
rs9860547	1.080	[1.051,1.111]	3.5e-08	1.065	[1.026,1.106]	0.00077	1.090	[1.051,1.132]	3.8e-06
rs7032572	1.140	[1.091,1.192]	4.1e-09	1.196	[1.127,1.268]	1.5e-09	1.100	[1.037,1.166]	0.0014
rs6021270	1.167	[1.100,1.239]	2.8e-07	1.193	[1.096,1.298]	3.5e-05	1.146	[1.056,1.245]	0.0010
rs9303280	1.046	[1.018,1.075]	0.0011	1.133	[1.091,1.176]	3.3e-11	1.056	[1.018,1.096]	0.0032
rs17228058	1.096	[1.062,1.132]	1.1e-08	1.125	[1.078,1.174]	3.9e-08	1.072	[1.027,1.119]	0.0012
rs962993	1.067	[1.038,1.098]	4.9e-06	1.088	[1.047,1.130]	1.3e-05	1.053	[1.014,1.094]	0.0071
rs17388568	1.069	[1.037,1.102]	1.2e-05	1.101	[1.058,1.146]	1.8e-06	1.079	[1.036,1.123]	0.00018
rs1998359	1.074	[1.038,1.111]	3.6e-05	1.126	[1.076,1.178]	2.2e-07	1.053	[1.006,1.102]	0.025
rs6473223	1.065	[1.036,1.096]	9.8e-06	1.086	[1.046,1.129]	1.7e-05	1.067	[1.027,1.108]	0.00070
rs10174949	1.056	[1.024,1.088]	0.00041	1.074	[1.030,1.119]	0.00070	1.054	[1.013,1.098]	0.0095
rs7203459	1.073	[1.041,1.107]	5.4e-06	1.117	[1.070,1.165]	2.5e-07	1.064	[1.020,1.109]	0.0032
rs2107357	1.071	[1.030,1.114]	0.00050	1.086	[1.030,1.144]	0.0018	1.089	[1.035,1.147]	0.00097
rs2056417	1.070	[1.039,1.102]	4.9e-06	1.037	[0.996,1.079]	0.072	1.068	[1.027,1.111]	0.00089
rs10893845	1.072	[1.043,1.101]	3.7e-07	1.066	[1.028,1.106]	0.00051	1.039	[1.001,1.077]	0.039
rs17533090	1.131	[1.089,1.174]	7.3e-11	1.129	[1.072,1.189]	2.9e-06	1.091	[1.037,1.147]	0.00064

OR, odds ratio per copy of the risk allele, for specific self reported allergy symptom; CI, confidence interval; *P*, Wald test for significance of the effect for this particular symptom.

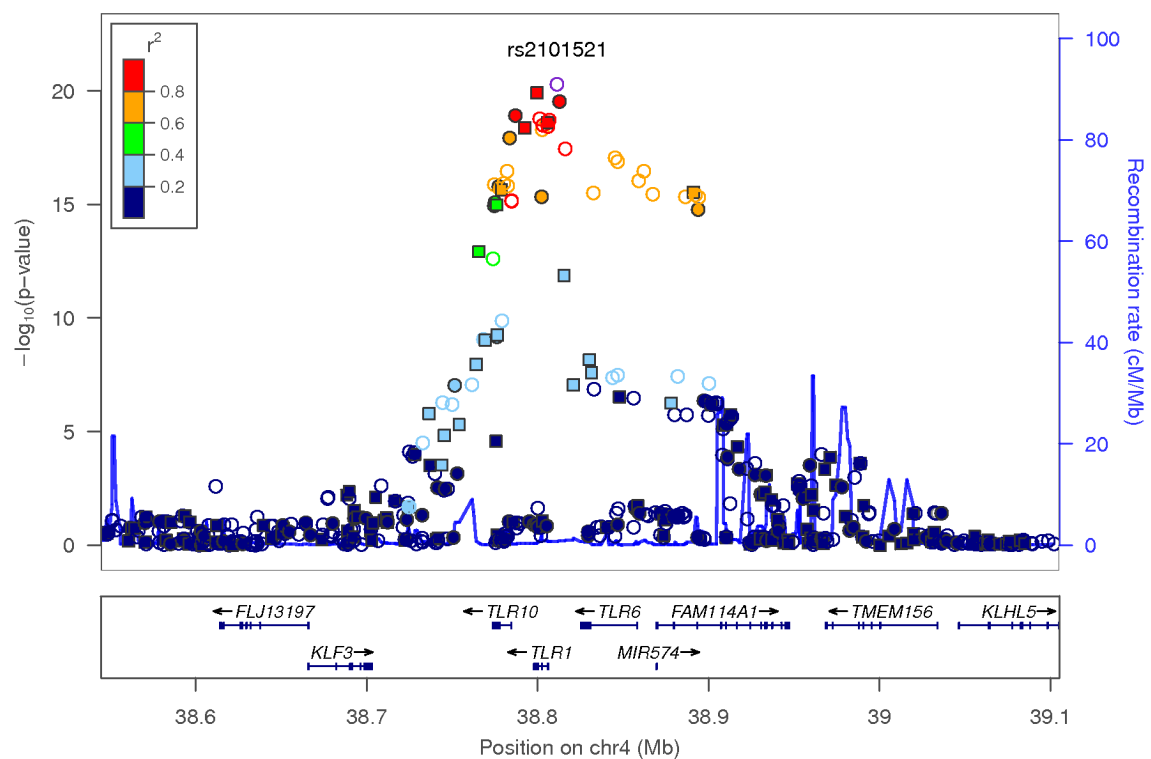
Supplementary Table 15. Consistency of effects at shared allergy and autoimmune loci

region	gene	diseases	match
11q13.5	<i>LRRC32</i>	CD, UC	yes
5p13.1	<i>PTGER4</i>	AS	yes
2q33.1	<i>PLCL1</i>	CD	yes
3q28	<i>LPP</i>	CE, VI	no
17q12	<i>GSDMB</i>	BC, CD, UC, RA, T1D	no
15q22.33	<i>SMAD3</i>	CD	yes
4q27	<i>ADAD1</i>	UC, T1D	yes
16p13.13	<i>CLEC16A</i>	T1D	yes

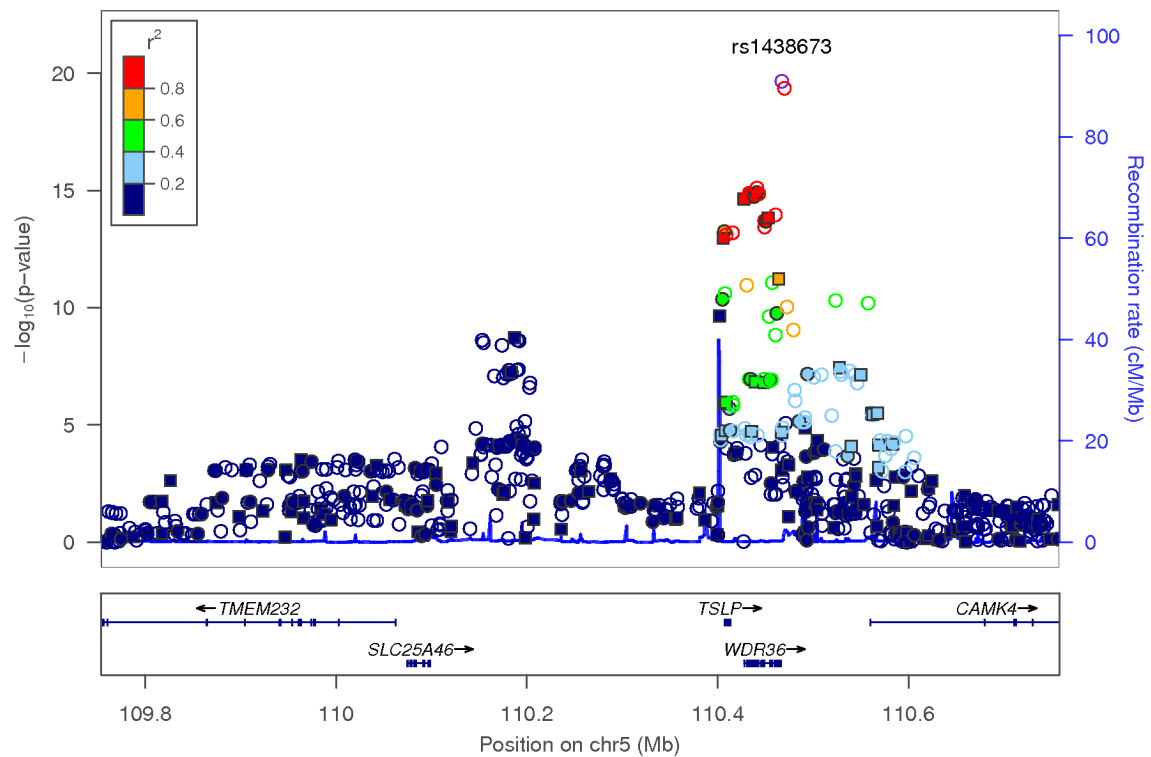
Diseases: CD, Crohn's disease; UC, ulcerative colitis; BC, primary biliary cirrhosis; RA, rheumatoid arthritis; T1D, type 1 diabetes; CE, celiac disease; VI, vitiligo; AS, ankylosing spondylitis. Match, indicates whether allergy risk allele matches risk allele(s) for autoimmune disease.

Supplementary Figure 1. Regional plots of allergy associations. Symbol colors indicate linkage disequilibrium with the index SNP, which is labeled and colored purple. Open circles indicate imputed variants, filled circles indicate partially genotyped variants, and filled squares indicate fully genotyped variants. Plots were generated using LocusZoom⁷³. Results are in NCBI Build 37 coordinates.

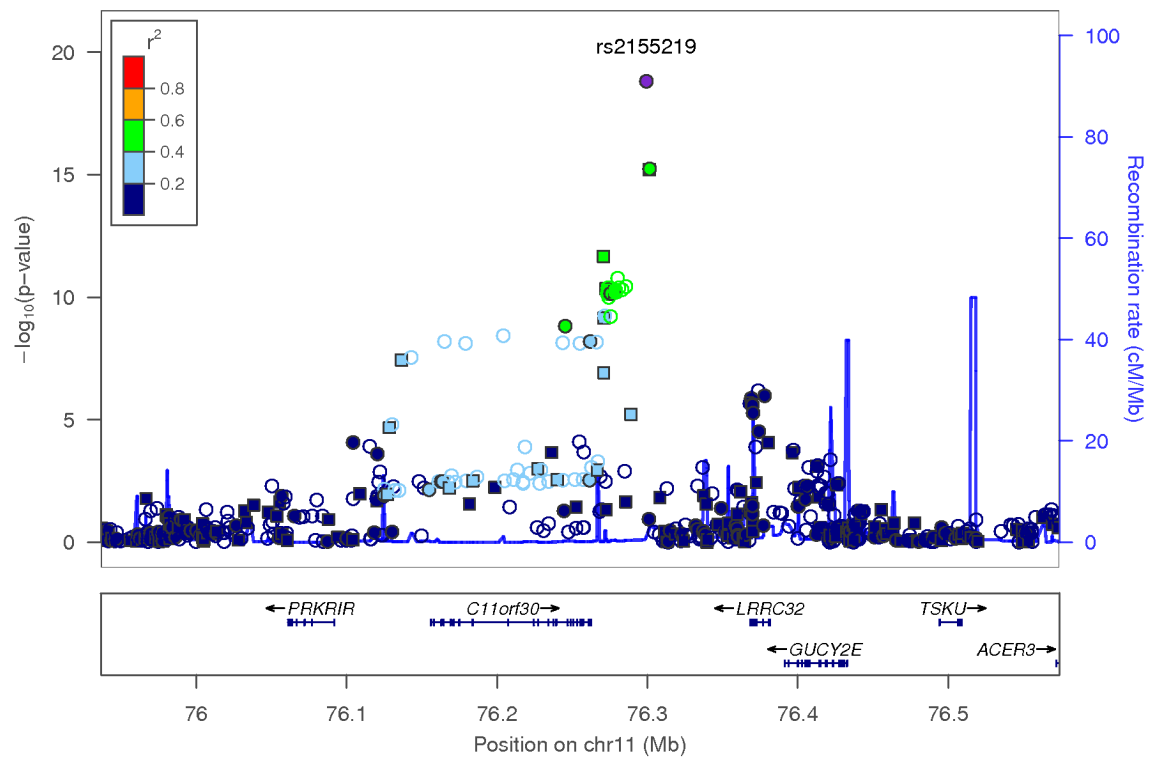
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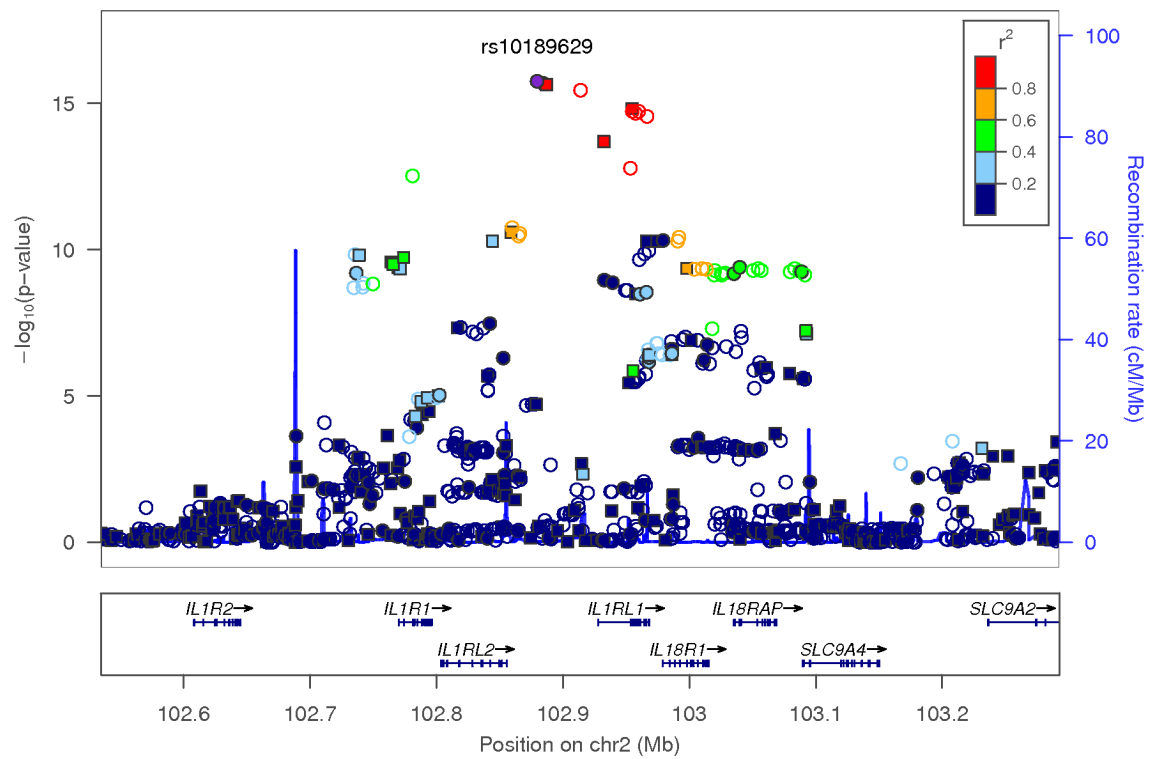
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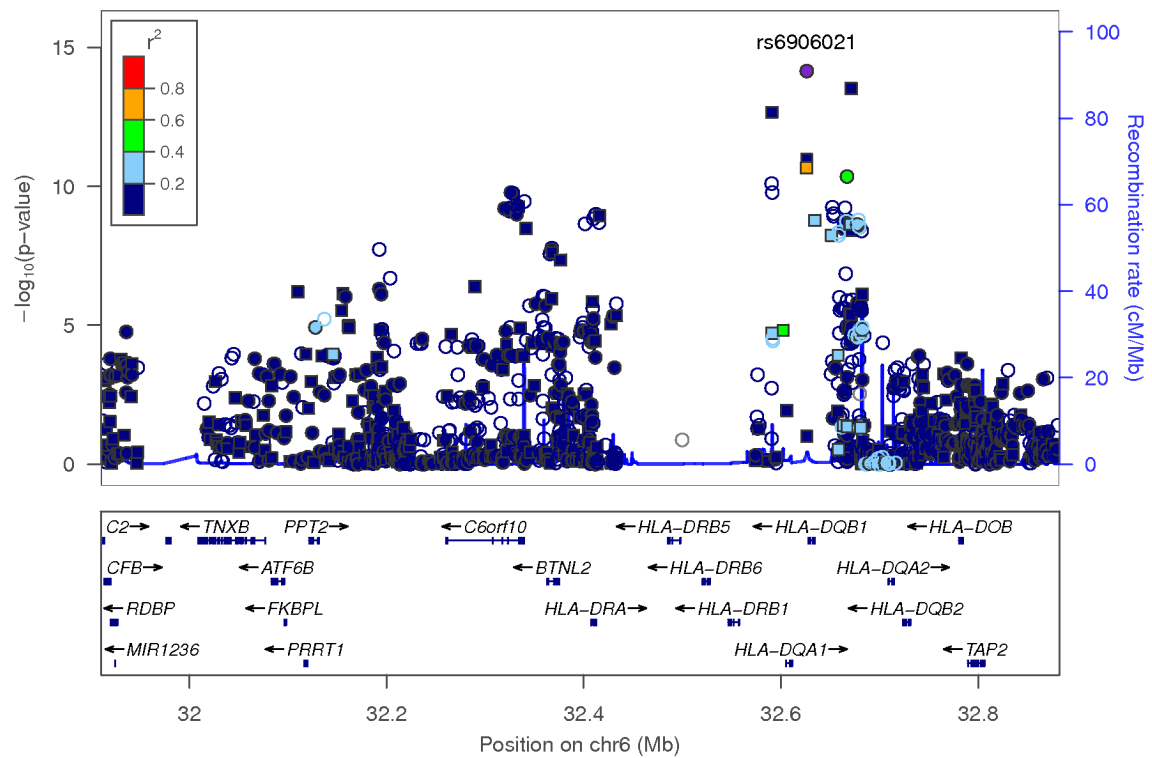
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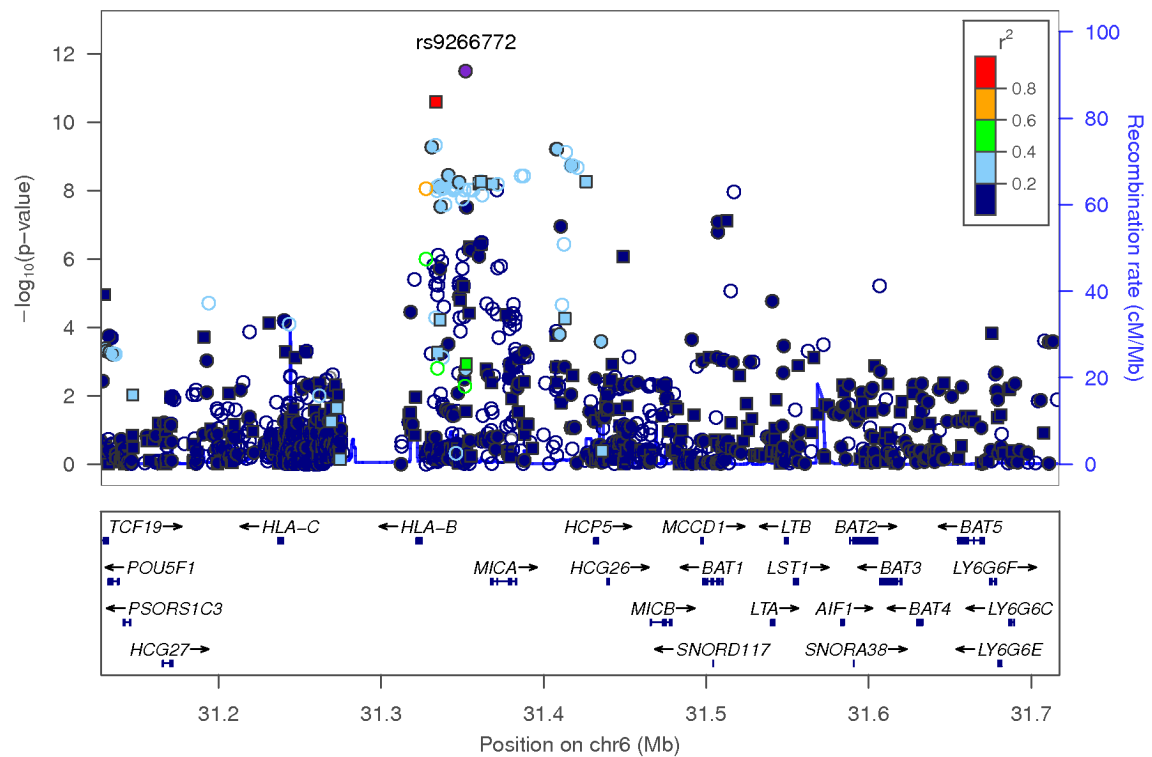
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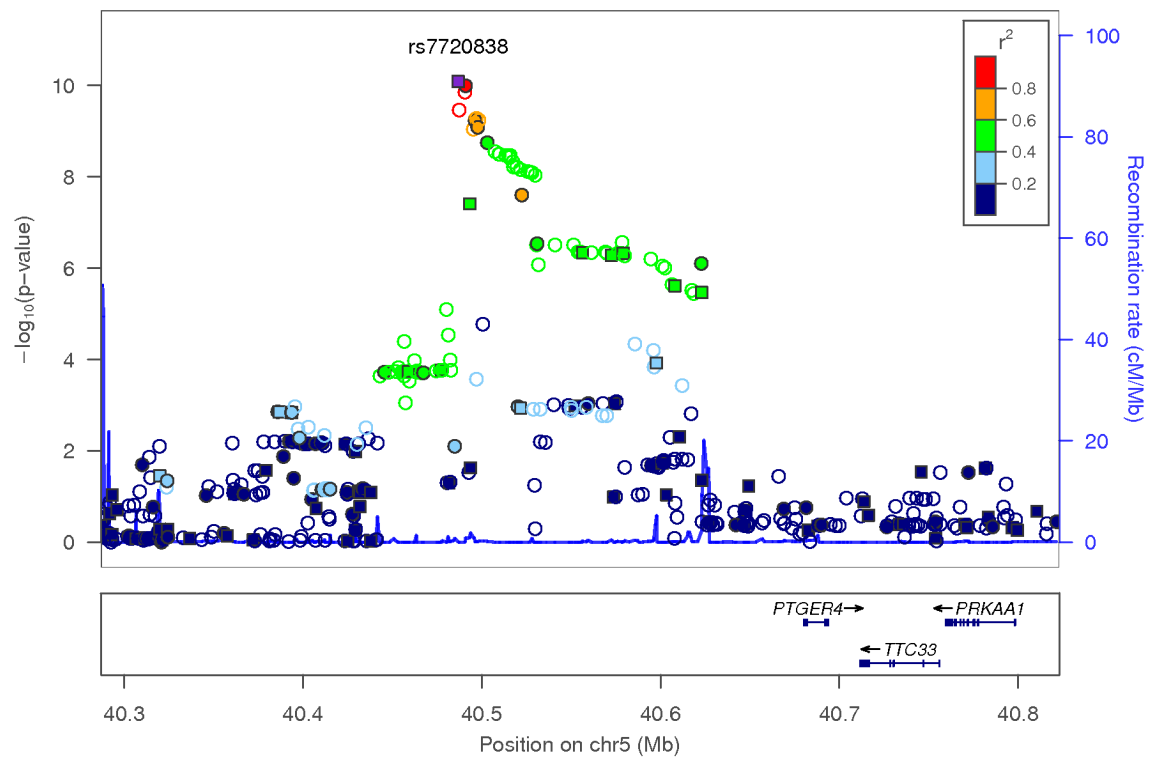
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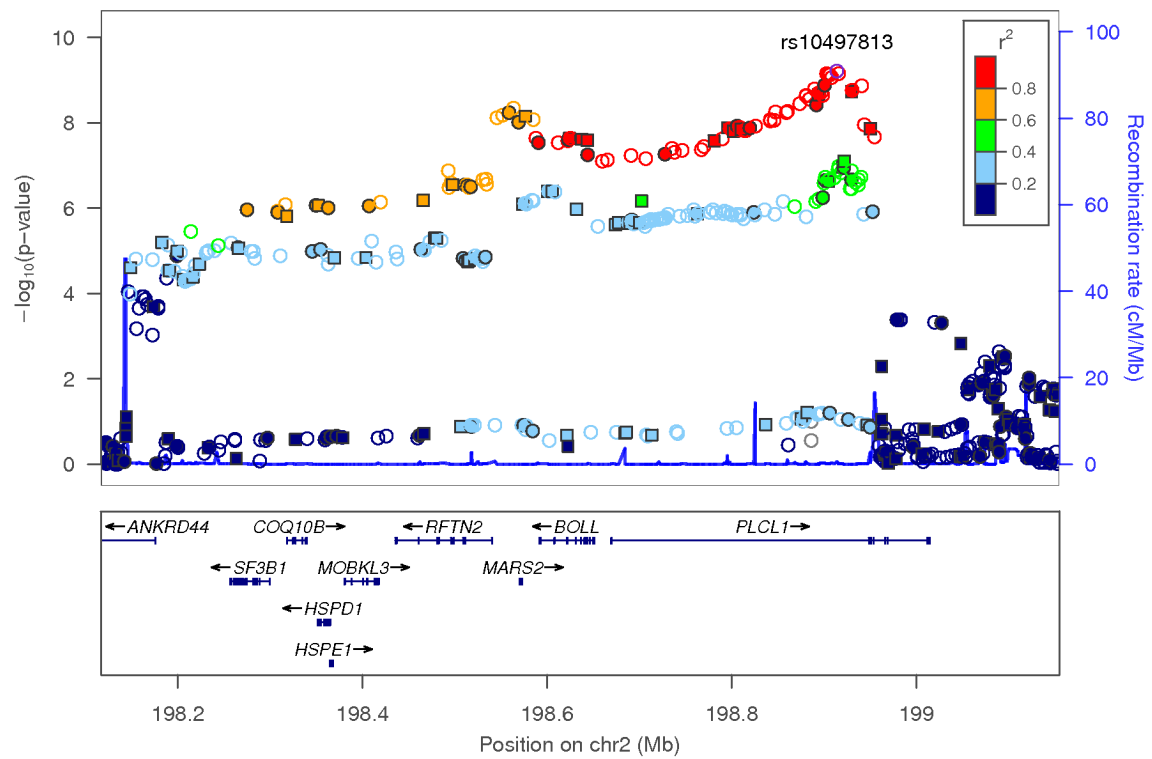
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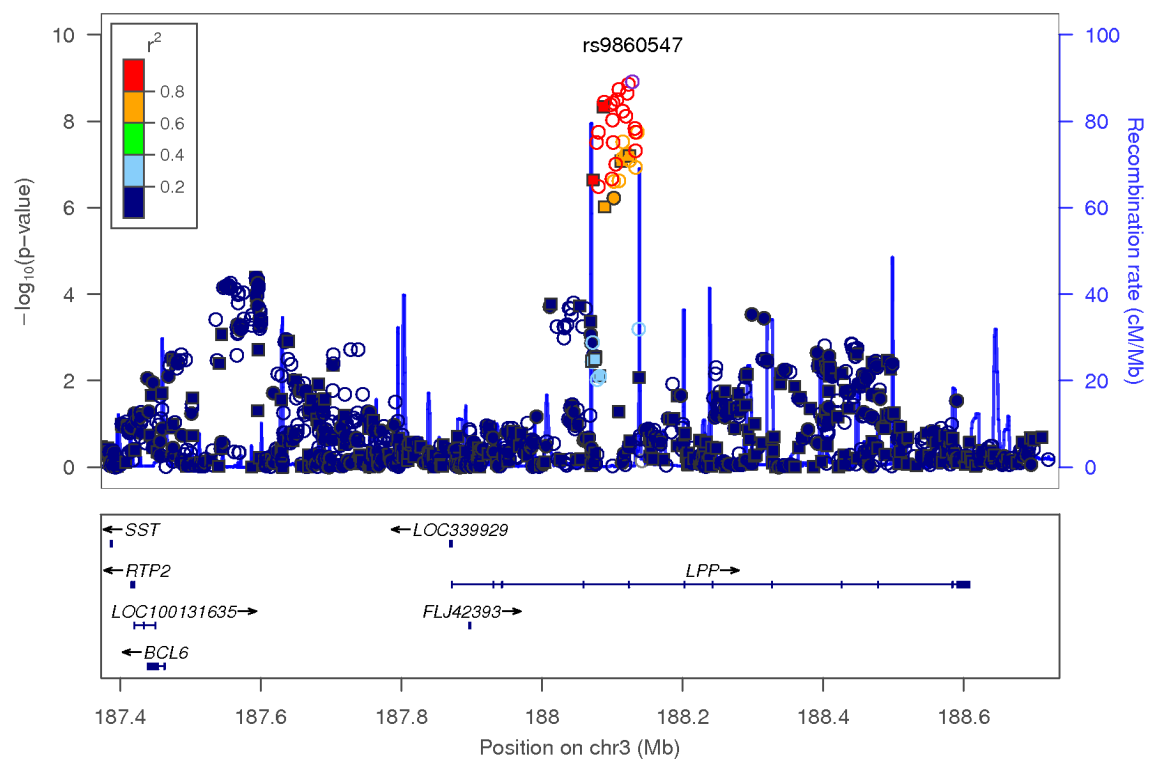
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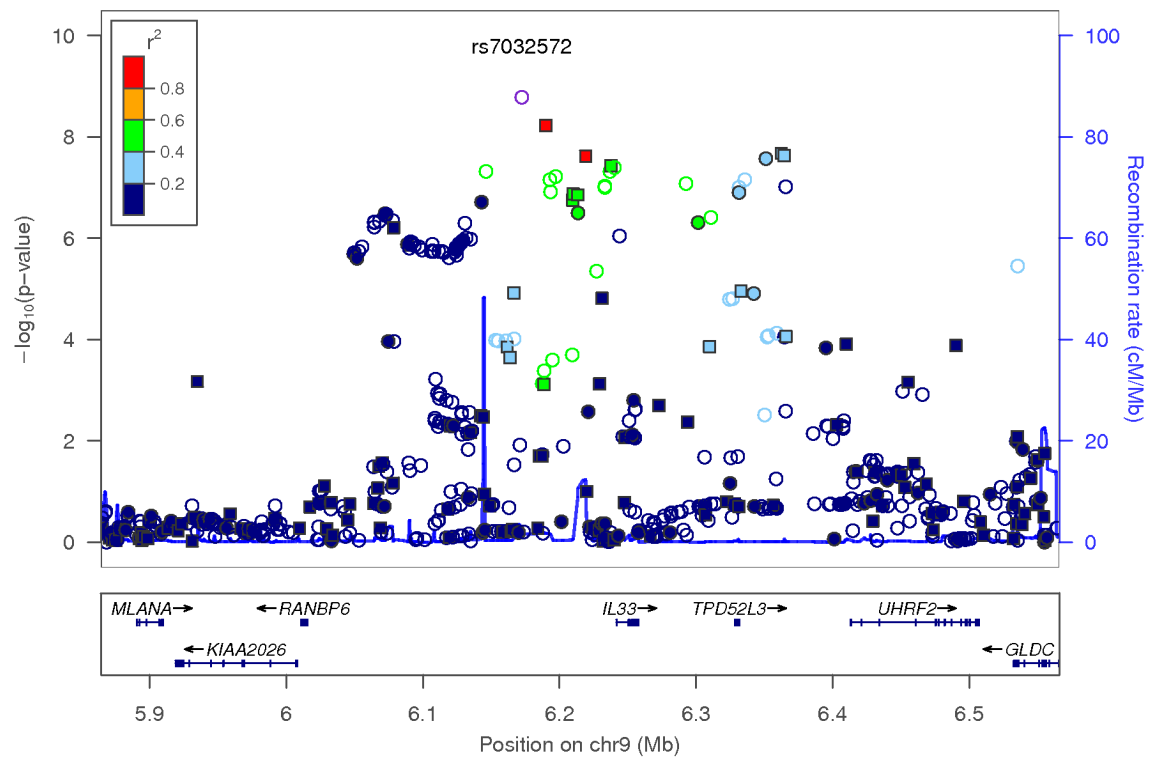
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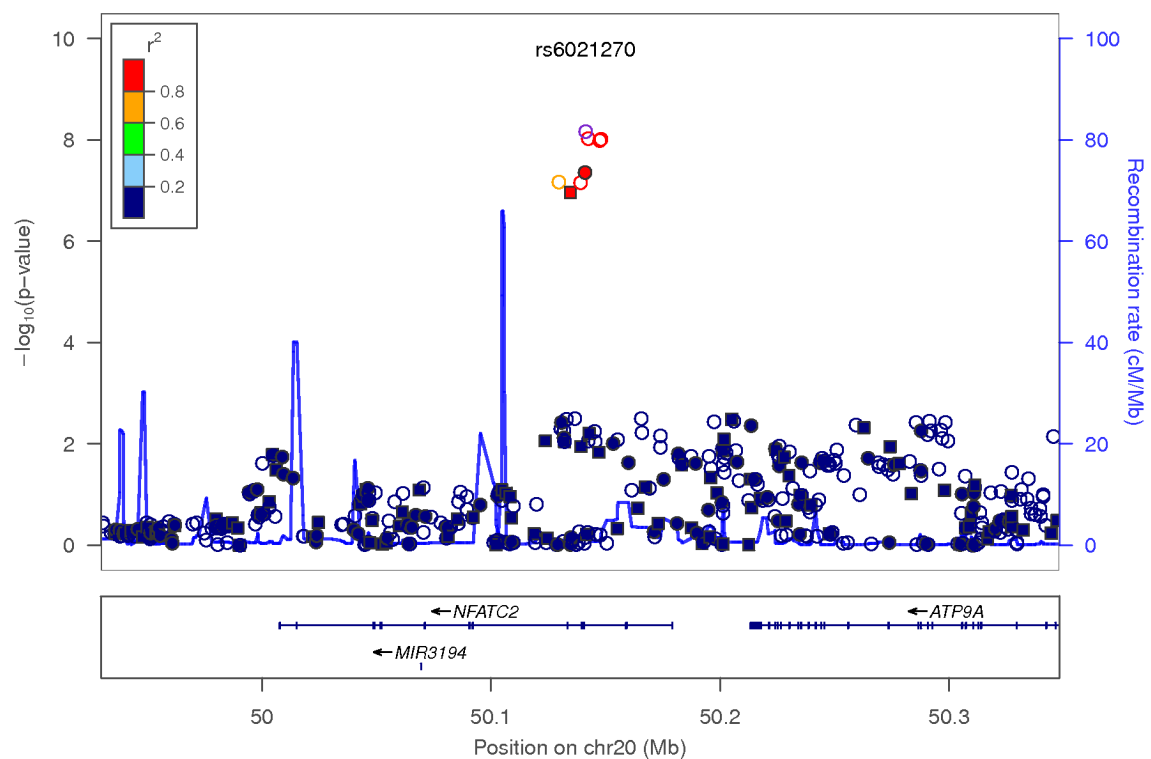
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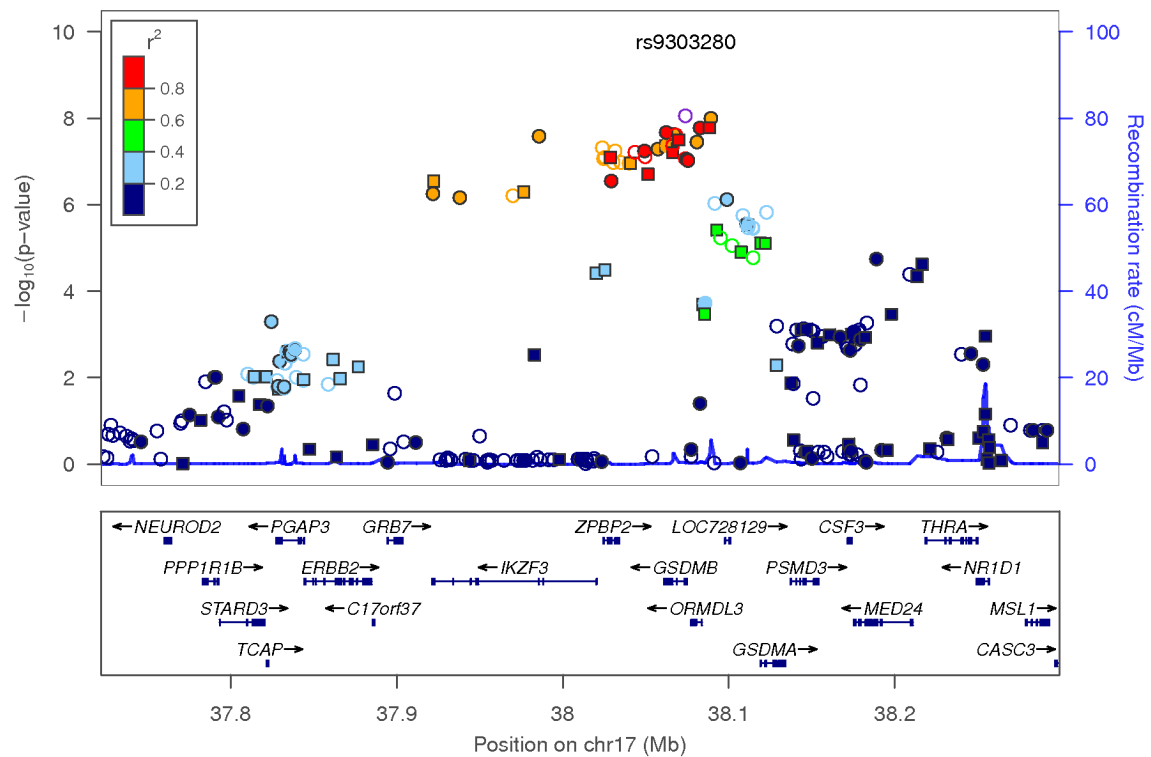
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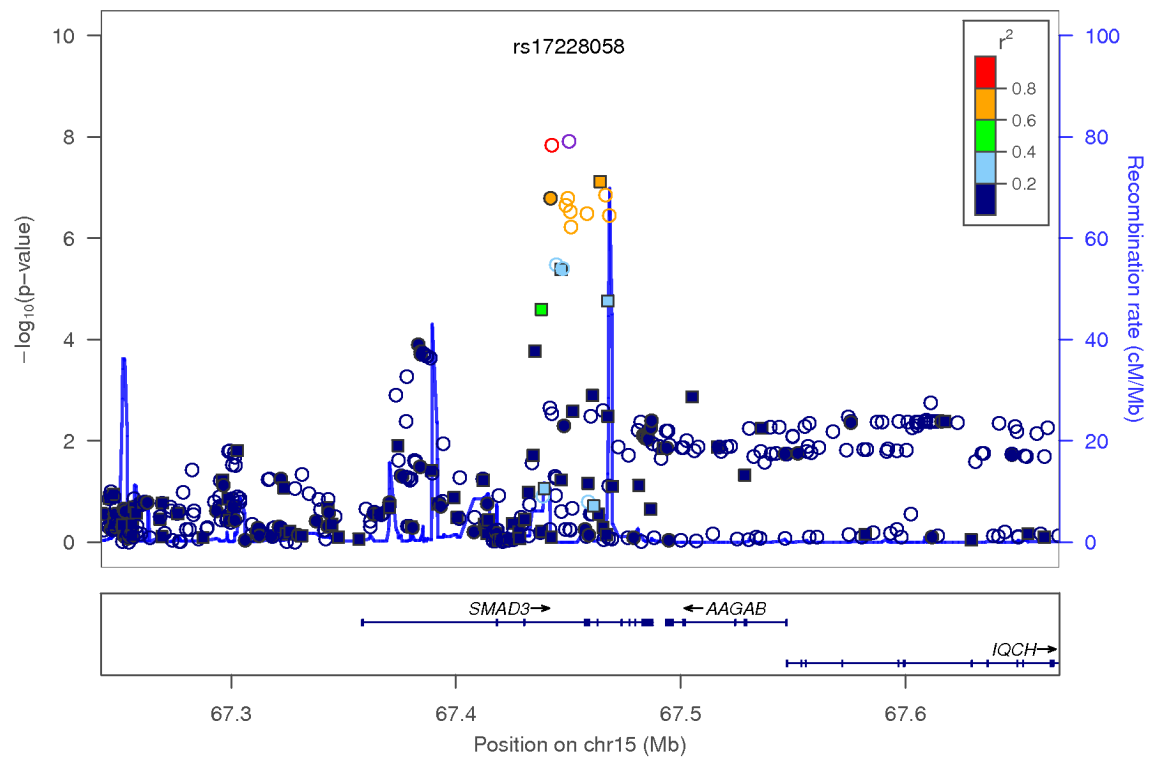
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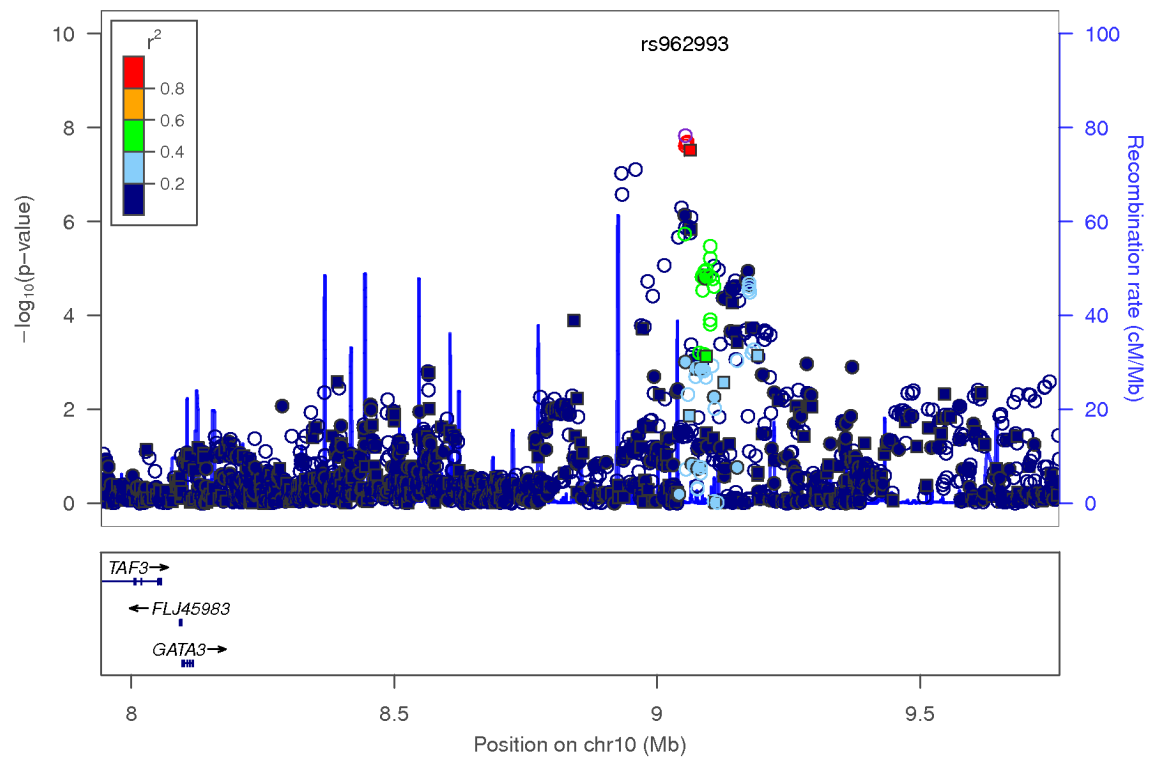
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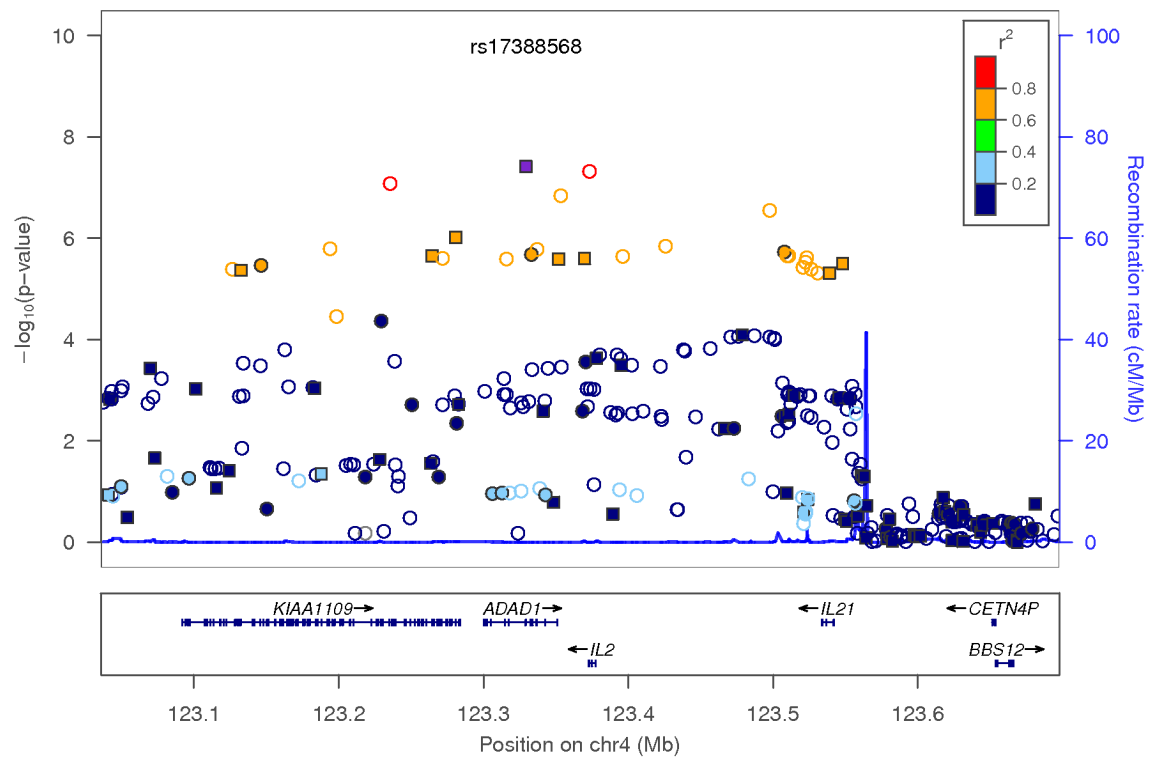
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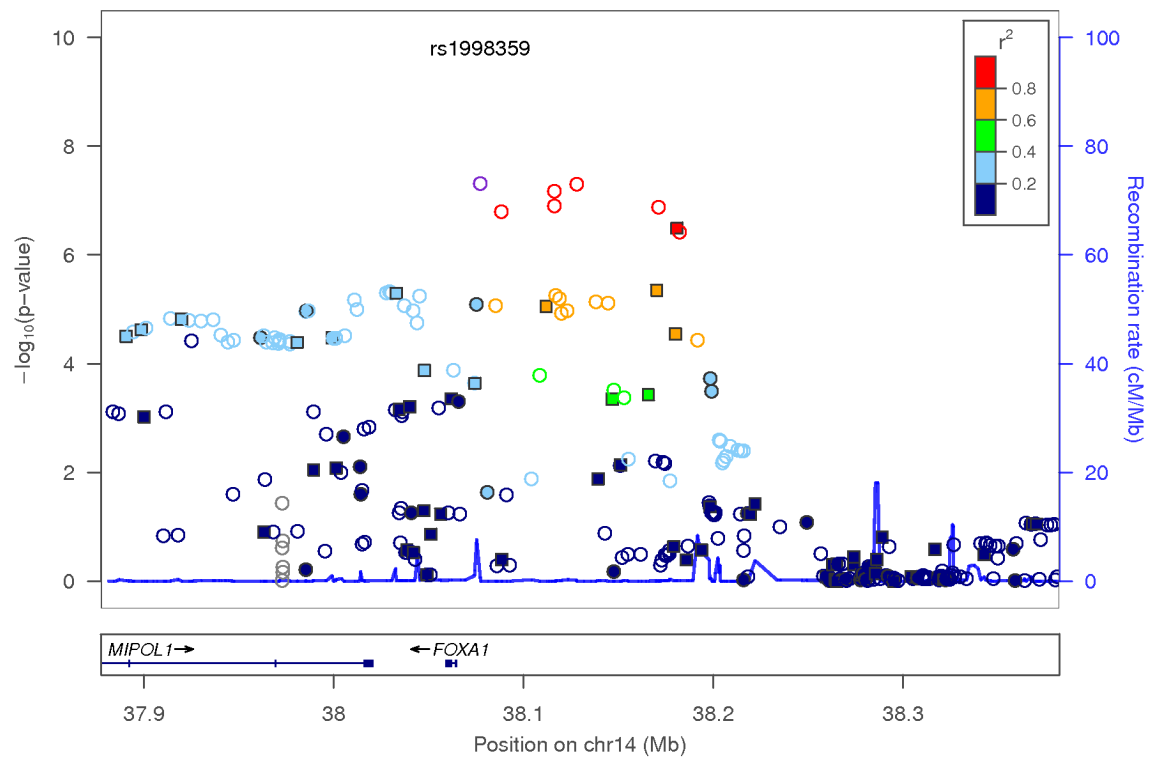
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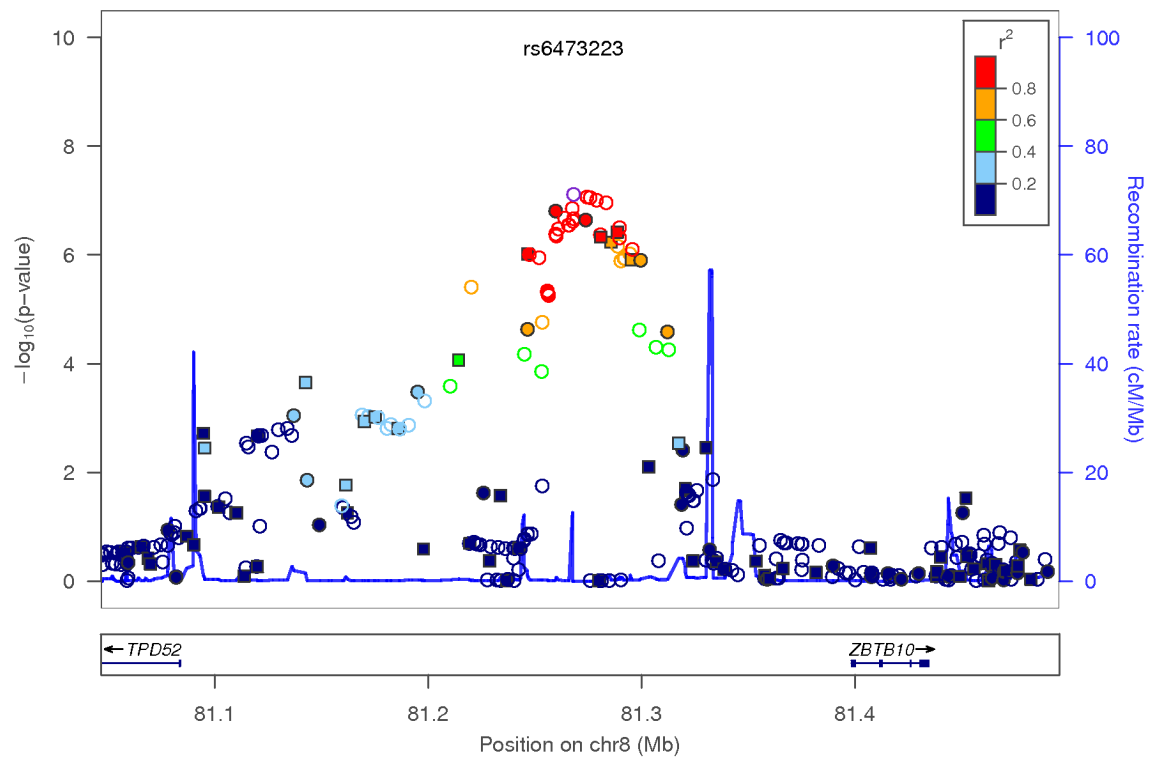
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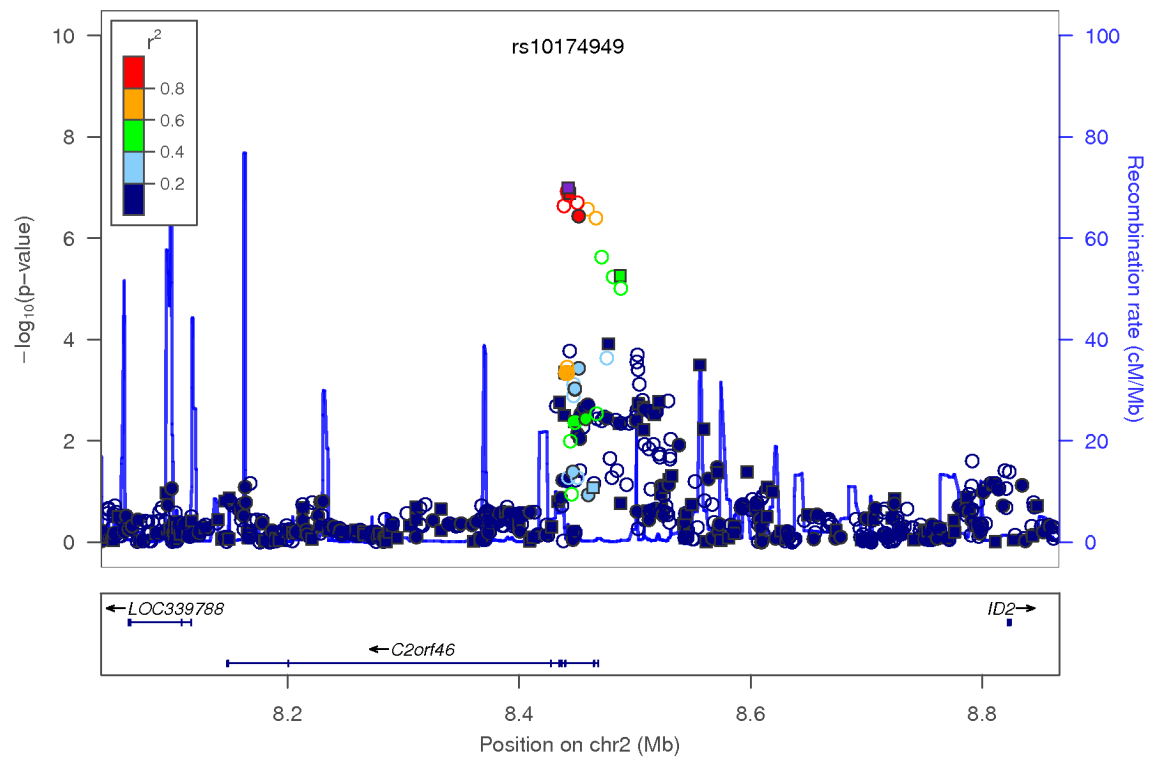
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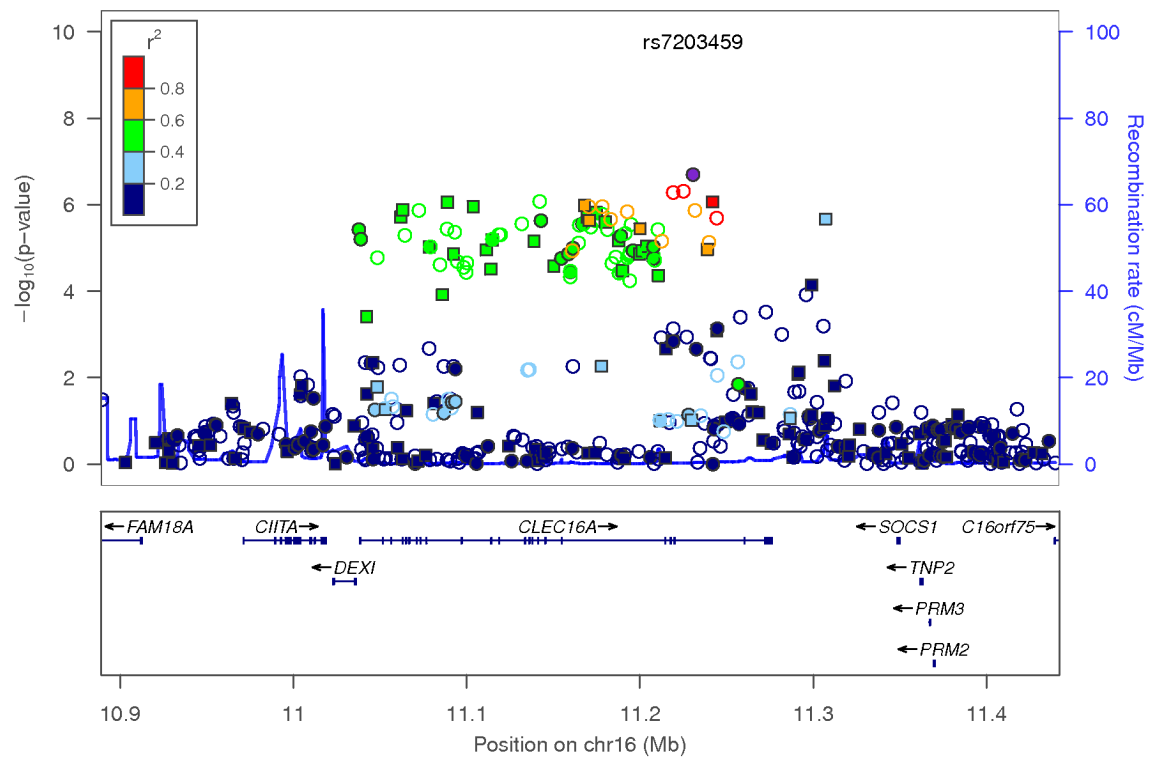
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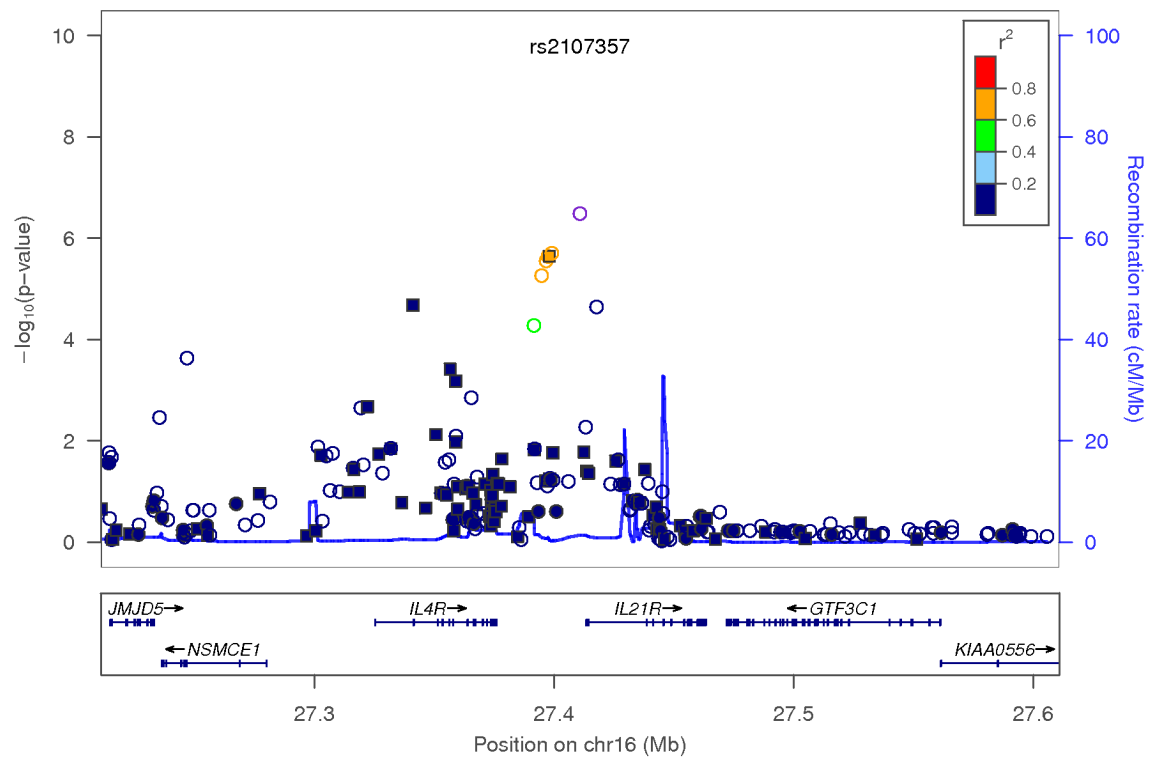
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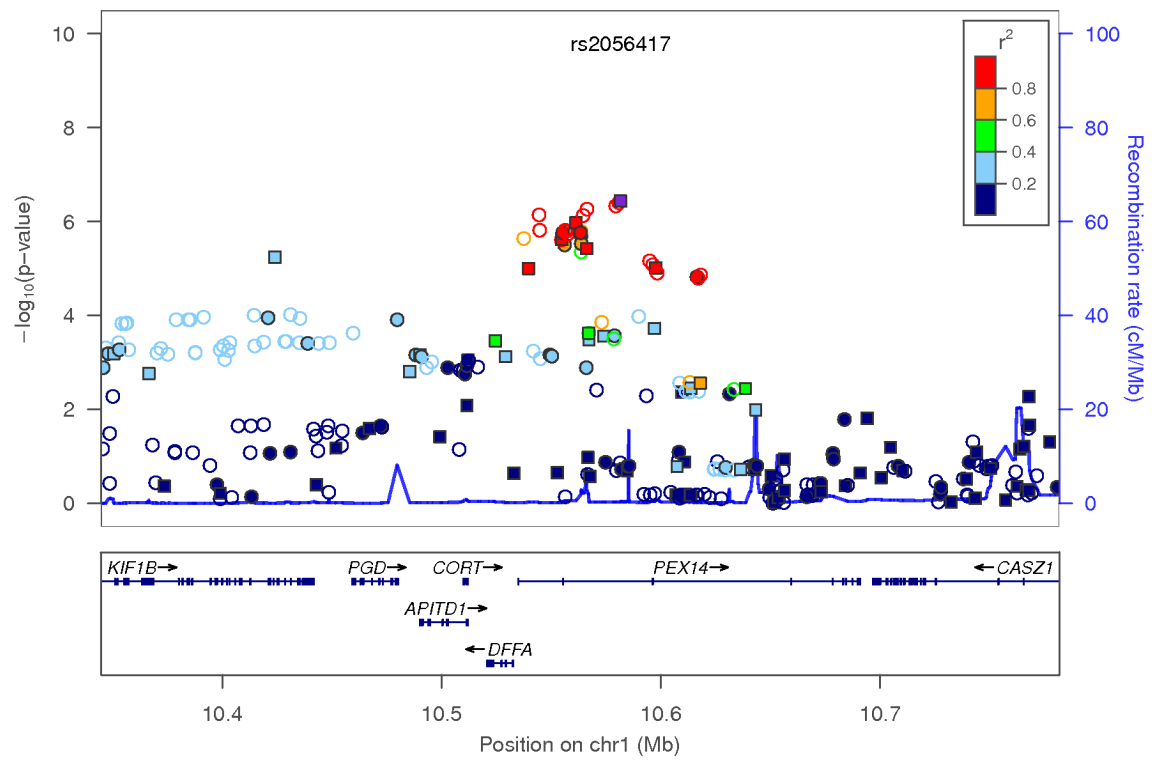
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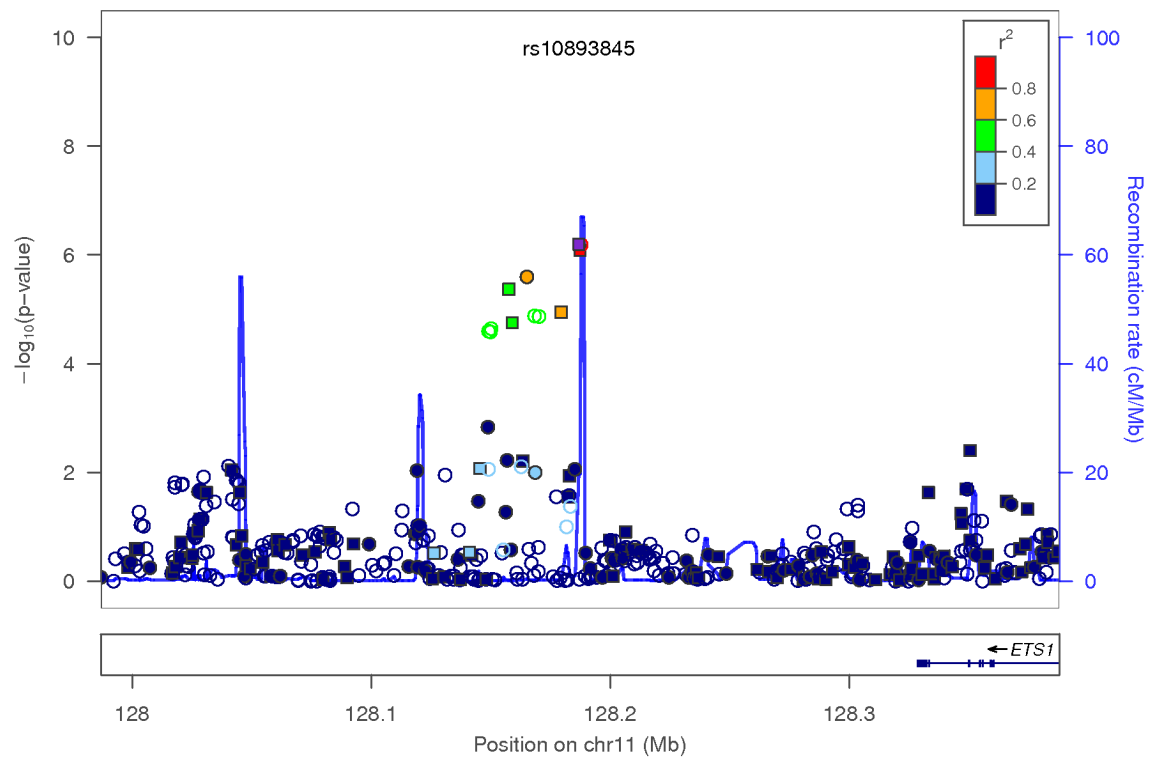
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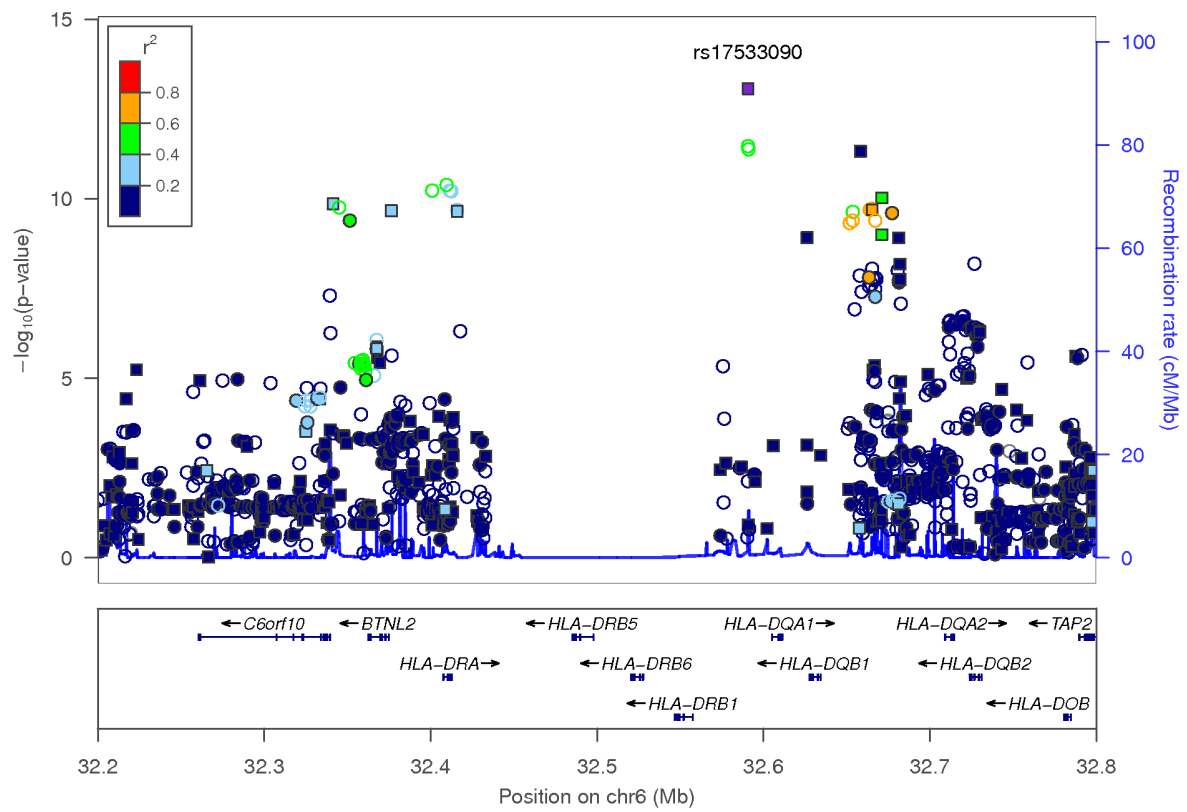
U



V



Supplementary Figure 2. Regional plot of allergy interaction meta-analysis results. Symbol colors indicate linkage disequilibrium with the lead SNP. Open circles indicate imputed variants, filled circles indicate partially genotyped variants, and filled squares indicate fully genotyped variants. Results are in NCBI Build 37 coordinates.



Supplementary Note

23andMe Surveys and Scoring Logic

The following section shows excerpts from the surveys used to define cases and controls for each allergy phenotype in the 23andMe cohort.

Survey: Allergies and Asthma

[Q1] Have you had an allergic reaction to any of the following items?

	Yes	No	I'm not sure
Foods	☐	☐	☐
[Q1a] Plants (including pollen)	☐	☐	☐
[Q1b] Animals (mammals, birds, or insects)	☐	☐	☐
[Q1c] Dust mites	☐	☐	☐
Molds	☐	☐	☐
Latex	☐	☐	☐
Medicines	☐	☐	☐
Vaccines	☐	☐	☐
Something else	☐	☐	☐

[Q2: conditional on Q1a] Have you had an *allergic reaction* to any of the following types of plants?

	Yes	No	I'm not sure
[Q2a] Grasses	☐	☐	☐
[Q2b] Trees	☐	☐	☐
[Q2c] Weeds	☐	☐	☐
Another plant	☐	☐	☐

[Q3: conditional on Q1a] Have you had an allergy test administered by a medical professional which indicated that you are allergic to the following types of plants?

	Yes	No	I'm not sure
[Q3a] Grasses	☐	☐	☐
[Q3b] Trees	☐	☐	☐
[Q3c] Weeds	☐	☐	☐
Another plant	☐	☐	☐

[Q4] Have you had an *allergic reaction* to any of the following types of animals?

	Yes	No	I'm not sure
[Q4a] Cats	☐	☐	☐
Dogs	☐	☐	☐
Honeybees	☐	☐	☐
Red ants	☐	☐	☐
Yellow jackets	☐	☐	☐
Wasps	☐	☐	☐
Another animal	☐	☐	☐

[Q5: conditional on Q4] Have you had an allergy test administered by a medical professional which indicated that you are allergic to the following types of animals?

	Yes	No	I'm not sure
[Q5a] Cats	☐	☐	☐
Dogs	☐	☐	☐
Honeybees	☐	☐	☐
Red ants	☐	☐	☐
Yellow jackets	☐	☐	☐
Wasps	☐	☐	☐
Another animal	☐	☐	☐

[Q6: conditional on Q1c] Have you had an allergy test administered by a medical professional which indicated that you are allergic to the following?

	Yes	No	I'm not sure
Dust mites	☐	☐	☐
Molds	☐	☐	☐
Latex	☐	☐	☐
Medicines	☐	☐	☐
Vaccines	☐	☐	☐
Something else	☐	☐	☐

[Q7: asked separately for each allergen conditional on Q1, Q2, and Q4] What type of reaction did you have after being exposed to [allergen]? Please check all that apply.

- ☐ Abdominal pain or vomiting
- ☐ Diarrhea
- ☐ [Q7a] Difficulty swallowing or difficulty speaking
- ☐ Drop of blood pressure or passing out
- ☐ [Q7b] Hives (red, itchy, or swollen skin)
- ☐ [Q7c] Itching in your mouth
- ☐ [Q7d] Itchy or runny nose
- ☐ Nausea
- ☐ [Q7e] Wheezing or asthma
- ☐ None of the above

Survey: Your Medical History

[Q8] Have you ever been diagnosed by a doctor with one of the following types of *allergies*?

	Yes	No	I'm not sure
[Q8a] Seasonal allergies	☐	☐	☐
Asthma	☐	☐	☐
[Q8b] Environmental (but not seasonal) allergy	☐	☐	☐
Food allergy	☐	☐	☐
Drug allergy	☐	☐	☐

Survey: Asthma

[Q9] Do you currently have allergies?

- ☐ Yes
- ☐ No
- ☐ I'm not sure

Logic for Selecting 23andMe Cases and Controls

Pollen allergy

- Cases were defined by a 'Yes' answer to [Q1a] and one or more of [Q2a], [Q2b] or [Q2c], as well as either a 'Yes' answer to the corresponding [Q3a], [Q3b] or [Q3c], or one or more of [Q7a], [Q7b], [Q7c], [Q7d], or [Q7e].
- Controls were defined by a 'No' answer to [Q1a], or to all of [Q2a], [Q2b], and [Q2c].

Cat allergy

- Cases were defined by a 'Yes' answer to [Q1b] and [Q4a], as well as either a 'Yes' answer to either [Q5a], or one or more of [Q7a], [Q7b], [Q7c], [Q7d], or [Q7e].
- Controls were defined by a 'No' answer to [Q1a], or to all of [Q2a], [Q2b], and [Q2c].

Dust mite allergy

- Cases were defined by a 'Yes' answer to [Q1c], as well as either a 'Yes' answer to [Q6], or one or more of [Q7a], [Q7b], [Q7c], [Q7d], or [Q7e].
- Controls were defined by a 'No' answer to [Q1c].

Additional shared controls for all three allergy phenotypes were then identified, who (1) did not qualify as cases for any allergy phenotype; (2) either responded 'No' to both of [Q8a] and [Q8b], or to [Q9]; and (3) had not responded 'Yes' to any of these questions.

Finally, individuals who were classified as a case for at least one allergy phenotype were classified as controls for other allergy phenotypes for which they were not already classified as cases or controls.

Allergy Symptom Analysis

In this analysis, we reclassified allergy cases and controls based on their responses to symptom question [Q7]. We defined allergic contact dermatitis cases by a positive response to [Q7b]; allergic rhinitis cases by a positive response to [Q7d]; and allergic asthma cases by a positive response to [Q7e], for any allergy type. Controls gave only negative responses for the corresponding symptom.

Suggestive Associations with Allergy

Two of our suggestive associations, in the 8q21.13 and 2p25.1 regions, were strongly replicated in the companion study (Table 4). In the 8q21.13 region, our index SNP rs13275219 falls between *TPD52*, or tumor protein D52, and *ZBTB10*, or zinc finger and BTB domain containing 10. An association in this region (rs7000782, $r^2=0.51$) was tentatively identified in a discovery GWAS for eczema¹⁴ but failed to replicate in that study. In the 2p25.1 region, our index SNP rs10174949 is 350 kb upstream of *ID2*, or inhibitor of DNA binding protein 2, a transcription factor with roles in the differentiation of lymphoid tissue inducer cells, natural killer cells, and other innate lymphoid cell lineages⁷⁴. In a mouse model, *ID2* knockouts show substantially reduced allergic symptoms in a model of allergic rhinitis⁷⁵.

In the 16p13.13 region, variants in strong LD with our index SNP rs725613 have been widely associated with autoimmune disease in genome-wide association studies, including type 1 diabetes⁷⁶, multiple sclerosis⁷⁷, celiac disease³³ and primary biliary cirrhosis⁷⁸. A recent report suggests that the variants identified in these studies modify expression of the nearby *DEXI* gene⁷⁹, which is differentially expressed in lung epithelia in emphysema⁸⁰. An association has also been reported with allergic rhinitis but did not reach genome-wide significance¹⁷.

Among the remaining suggestive associations, in the 16p12.1 region, index SNP rs2107357 falls between T helper cytokine receptor genes *IL4R* and *IL21R*. IL-4 and IL-21 cytokines are associated with differentiation of Th2 and Th17 cell lineages, respectively^{81,82}. In the 11q24.3 region, index SNP rs10893845 is 150 kb downstream of the *ETS1* gene. *ETS1* is a transcription factor known to contribute to Th2 cytokine regulation⁸³, and inhibits differentiation of Th17 cells⁸⁴. Variation in or near *ETS1* has been associated with autoimmune diseases including celiac disease³³, rheumatoid arthritis⁸⁵, and systemic lupus erythematosus⁸⁶ but these variants are not in strong LD with our index SNP. In the 1p36.22 region, our association with rs2056417 in *PEX14*, or peroxisomal biogenesis factor 14, does not have an obvious connection with immune function.

Allergy Loci Previously Associated with Asthma

The 5q22.1 region spanning index SNP rs1438673 includes the *TSLP* (Thymic Stromal Lymphopoietin) gene, which has been described as a master switch for allergic inflammation⁸⁷ responsible for promoting differentiation of pro-inflammatory Th2 cells⁸⁸. In humans, variants in this region are strongly associated with asthma across multiple ethnic groups^{9,10,89}; while our index SNP is in low LD with rs1837253 reported in these studies ($r^2=0.05$), we also see good evidence of association with rs1837253 (meta-analysis $P=2.3\times 10^{-10}$). We see evidence for a secondary peak near *SLC25A46* (rs12659961: meta-analysis $P=1.9\times 10^{-9}$), which is not in LD with rs1438673 ($r^2<0.01$), but is in moderate LD with rs17513503 ($r^2=0.3$), reported to be associated with grass sensitization¹⁷.

In the 11q13.5 region spanning index SNP rs2155219, *LRRC32* (also known as GARP), encodes a protein that mediates the suppressive effects of regulatory T (Treg) cells⁹⁰. Regulatory T cells help suppress responses of Th2 cells to maintain functional tolerance. Patients with IPEX syndrome, which interferes with development of the Treg lineage, develop exaggerated IgE responses and atopic dermatitis⁹¹. This region has been associated with atopic dermatitis¹², asthma¹¹, allergic rhinitis¹⁷, hay fever⁹², ulcerative colitis⁹³ and Crohn's disease⁹⁴.

The 2q12.1 region around rs10189629 includes a cluster of cytokine genes. The *IL1RL1* gene encodes the ST2 receptor, which binds to IL-33, and is thought to be involved in stimulating production of Th2 cell cytokines such as IL-13 that ultimately promote allergic inflammation⁹⁵. SNPs in this region are also significantly associated with both atopic and autoimmune phenotypes, including celiac disease^{25,26}, plasma eosinophil count⁹⁶, asthma^{8,10} and Crohn's disease²⁷.

Near index SNP rs7032572 in the 9p24.1 region, *IL33* encodes a cytokine required for differentiation of Th2 cells, and is an important activator of Th2 and mast cells in response to inflammation⁹⁷. Its receptor, *IL1RL1*, is also a key asthma gene. Variation near *IL33* (rs1342326, $r^2=0.95$) has been previously associated with asthma⁸.

In the 17q12 region near index SNP rs9303280, *GSDMA* (gasdermin) is known to induce apoptosis in gastric pit cells in the stomach⁹⁸, but has also been associated with asthma and

total number of white blood cells in genome-wide association studies^{8,99}. *GSDMA* is also about 40kb away from *ORMDL3*, a gene that has been implicated strongly in asthma¹⁰⁰ and with a number of autoimmune diseases^{91,101,102}. The *ORMDL3* gene product may be involved in intracellular Ca²⁺ signaling¹⁰³. Our index SNP is in moderately strong LD ($r^2 > 0.5$) with the variants previously reported to be associated with asthma in this region^{8,10,100}.

The role of HLA class II genes is to present mainly exogenous peptides primarily to helper T cells, so it is unsurprising that they have frequently been associated with different allergic responses¹⁰⁴. SNPs in this region have been identified in a number of GWAS of immune-system related disorders, including asthma^{8,9}, celiac disease³³, vitiligo³⁴, ulcerative colitis¹⁰⁵, systemic sclerosis¹⁰⁶, multiple sclerosis¹⁰⁷, rheumatoid arthritis¹⁰⁸, systemic lupus erythematosus¹⁰⁹, and selective IgA deficiency¹¹⁰. Our index SNP rs6906021 is in moderate LD ($r^2 = 0.43$) with rs9273349, the lead SNP in the asthma studies^{8,9}.

The *SMAD3* gene encodes a key mediator of transforming growth factor beta (TGF- β) signaling. Variation in *SMAD3* has previously been associated with asthma⁸ and with Crohn's disease³¹. A mouse *SMAD3* knockout leads to an exaggerated asthma phenotype¹¹¹, as well as altered skin sensitization¹¹². Our index SNP rs17228058 is only moderate LD ($r^2 = 0.3$) with asthma association rs744910, but is in nearly complete LD ($r^2 = 0.99$) with the Crohn's association.

Index SNP rs962993 in the 10p14 region is in a gene poor region about 1 mb downstream of *GATA3*, or GATA-binding protein 3. *GATA3* was originally identified as a T cell specific transcription factor and is thought to be a master regulator of Th2 cell differentiation^{113,114}. This region has been associated with asthma in a Japanese cohort⁹; our rs962993 is about 80 kb from the reported SNP, rs10508372, but the two are not in linkage disequilibrium in either Europeans or Asians ($r^2 < 0.01$).

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A genome-wide association meta-analysis of self-reported allergy identifies shared and allergy-specific susceptibility loci

Supplementary Tables, Figures and Note

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Supplementary Table 2. Detailed results for allergy loci in the 23andMe cohort.

SNP	region	position	alleles	RAF	r ²	typed	OR	95% CI	<i>P</i> _{main}	<i>P</i> _{int}	<i>P</i> _{total}
rs2101521	4p14	38811551	A/G	0.762	0.982	I	1.138	[1.105,1.172]	2.4e-17	0.00015	1.5e-19
rs1438673	5q22.1	110467499	T/C	0.495	0.988	I	1.116	[1.089,1.144]	2.3e-18	0.0062	3.6e-19
rs2155219	11q13.5	76299194	G/T	0.515	0.990	P	1.108	[1.081,1.136]	2.5e-16	0.63	3.2e-15
rs10189629	2q12.1	102879464	A/C	0.855	0.995	P	1.152	[1.111,1.194]	1.2e-14	0.058	2.0e-14
rs6906021	6p21.32	32626311	T/C	0.475	0.951	P	1.097	[1.070,1.125]	3.4e-13	0.10	7.4e-13
rs9266772	6p21.33	31352113	T/C	0.188	0.995	P	1.101	[1.068,1.135]	9.2e-10	0.79	1.4e-08
rs7720838	5p13.1	40486896	G/T	0.575	0.997	G	1.086	[1.060,1.113]	6.6e-11	0.060	9.2e-11
rs10497813	2q33.1	198914072	T/G	0.482	0.999	I	1.075	[1.050,1.102]	5.5e-09	0.54	5.7e-08
rs9860547	3q28	188128979	G/A	0.463	0.948	I	1.073	[1.047,1.100]	2.8e-08	0.14	7.9e-08
rs7032572	9p24.1	6172380	A/G	0.166	0.668	I	1.129	[1.085,1.175]	2.0e-09	0.95	3.6e-08
rs6021270	20q13.2	50141264	C/T	0.942	0.968	I	1.173	[1.111,1.238]	9.5e-09	0.12	2.8e-08
rs9303280	17q12	38074031	T/C	0.520	0.980	I	1.067	[1.041,1.094]	2.0e-07	0.059	2.3e-07
rs17228058	15q22.33	67450305	A/G	0.235	0.991	I	1.084	[1.053,1.116]	3.5e-08	0.45	2.8e-07
rs962993	10p14	9053132	T/C	0.571	0.931	I	1.073	[1.045,1.100]	7.9e-08	0.54	7.9e-07
rs17388568	4q27	123329362	G/A	0.275	1.000	G	1.074	[1.045,1.103]	2.9e-07	0.040	2.1e-07
rs1998359	14q21.1	38077148	C/G	0.249	0.839	I	1.080	[1.047,1.113]	9.6e-07	0.86	1.3e-05
rs6473223	8q21.13	81268155	C/T	0.360	0.980	I	1.061	[1.034,1.088]	6.7e-06	0.18	2.1e-05
rs10174949	2p25.1	8442248	A/G	0.727	1.000	G	1.070	[1.041,1.099]	1.3e-06	0.016	4.0e-07
rs7203459	16p13.13	11230703	C/T	0.733	0.989	P	1.074	[1.044,1.104]	5.0e-07	0.020	2.3e-07
rs2107357	16p12.1	27410829	G/A	0.138	0.967	I	1.091	[1.054,1.131]	1.2e-06	0.63	1.2e-05
rs2056417	1p36.22	10581658	A/G	0.697	1.000	G	1.058	[1.030,1.086]	3.2e-05	0.55	0.00025
rs10893845	11q24.3	128186882	T/G	0.493	0.999	G	1.063	[1.038,1.089]	8.2e-07	0.44	6.2e-06
rs17533090	6p21.32	32590722	G/T	0.840	0.998	G	1.130	[1.093,1.169]	9.6e-13	8.4e-13	2.1e-22

Region, cytogenetic band; position, build 37 map position of SNP; alleles, low/high risk alleles on genomic reference strand; RAF, risk allele frequency; r², imputation quality estimated from variance in imputed allele dosages; typed: I=imputed, G=genotyped, P=partial (genotyped in ~65% of individuals); OR, odds ratio per copy of the risk allele, for the main effect across allergy types; CI, confidence interval; *P*_{main}, test of main effect across allergens; *P*_{int}, test for interaction with allergy type; *P*_{total}, joint test including main effect and interaction.

Supplementary Table 3. Detailed results for allergy loci in the ALSPAC cohort.

SNP	region	position	alleles	RAF	r ²	typed	OR	95% CI	<i>P</i> _{main}	<i>P</i> _{int}	<i>P</i> _{total}
rs2101521	4p14	38811551	A/G	0.791	0.956	I	1.262	[1.139,1.398]	8.2e-06	0.75	0.00013
rs1438673	5q22.1	110467499	T/C	0.518	0.995	I	1.124	[1.041,1.214]	0.0028	0.60	0.019
rs2155219	11q13.5	76299194	G/T	0.489	0.946	I	1.177	[1.089,1.273]	4.2e-05	0.16	0.00015
rs10189629	2q12.1	102879464	A/C	0.870	0.997	I	1.200	[1.062,1.355]	0.0033	0.90	0.030
rs6906021	6p21.32	32626311	T/C	0.475	0.982	I	1.117	[1.032,1.208]	0.0060	0.56	0.031
rs9266772	6p21.33	31352113	T/C	0.222	0.995	I	1.188	[1.084,1.303]	0.00023	0.034	0.00011
rs7720838	5p13.1	40486896	G/T	0.616	0.999	G	1.035	[0.954,1.123]	0.41	0.29	0.37
rs10497813	2q33.1	198914072	T/G	0.489	0.999	I	1.084	[1.002,1.172]	0.043	0.97	0.24
rs9860547	3q28	188128979	G/A	0.455	0.947	I	1.118	[1.030,1.213]	0.0077	0.44	0.032
rs7032572	9p24.1	6172380	A/G	0.171	0.975	I	1.063	[0.960,1.177]	0.24	0.40	0.35
rs6021270	20q13.2	50141264	C/T	0.918	0.945	I	1.094	[0.937,1.277]	0.25	0.41	0.38
rs9303280	17q12	38074031	T/C	0.501	0.986	I	1.111	[1.028,1.200]	0.0082	0.54	0.040
rs17228058	15q22.33	67450305	A/G	0.269	0.971	I	1.065	[0.977,1.161]	0.15	0.71	0.42
rs962993	10p14	9053132	T/C	0.612	0.893	I	1.082	[0.994,1.178]	0.069	0.68	0.25
rs17388568	4q27	123329362	G/A	0.272	0.996	G	1.095	[1.004,1.193]	0.040	0.46	0.12
rs1998359	14q21.1	38077148	C/G	0.229	0.928	I	1.128	[1.029,1.236]	0.010	0.60	0.053
rs6473223	8q21.13	81268155	C/T	0.346	0.995	I	1.156	[1.067,1.252]	0.00041	0.77	0.0043
rs10174949	2p25.1	8442248	A/G	0.706	1.000	G	1.101	[1.013,1.198]	0.024	0.99	0.16
rs7203459	16p13.13	11230703	C/T	0.741	0.969	I	1.065	[0.971,1.168]	0.18	0.25	0.21
rs2107357	16p12.1	27410829	G/A	0.136	0.961	I	1.096	[0.978,1.227]	0.11	0.83	0.40
rs2056417	1p36.22	10581658	A/G	0.671	1.000	G	1.175	[1.080,1.278]	0.00017	0.89	0.0022
rs10893845	11q24.3	128186882	T/G	0.493	0.997	G	1.038	[0.961,1.121]	0.35	0.99	0.82
rs17533090	6p21.32	32590722	G/T	0.830	0.897	G	1.104	[0.989,1.232]	0.077	0.063	0.038

Region, cytogenetic band; position, build 37 map position of SNP; alleles, low/high risk alleles on genomic reference strand; RAF, risk allele frequency; r², imputation quality estimated from variance in imputed allele dosages; typed: I=imputed, G=genotyped; OR, odds ratio per copy of the risk allele for the main effect across allergy types; CI, confidence interval; *P*_{main}, P value for test of main effect across allergy types; *P*_{int}, test for interaction with allergy type; *P*_{total}, overall test including main effect and interaction.

Supplementary Table 4. Tests for platform effects, age effects, and study heterogeneity

SNP	P_{gt}	P_{age}	P_Q	I^2	95% CI	gene context
rs2101521	0.46	0.057	0.06	0.72	[0.00,0.92]	TLR1-[]--TLR6
rs1438673	0.33	0.57	0.86	0.00	[0.00,0.80]	WDR36-[]--CAMK4
rs2155219	0.69	0.56	0.15	0.53	[0.00,0.89]	C11orf30-[]--LRRC32
rs10189629	0.15	0.16	0.53	0.00	[0.00,0.80]	IL1RL2-[]--IL1RL1
rs6906021	0.17	0.41	0.68	0.00	[0.00,0.80]	HLA-DQA1-[]--HLA-DQB1
rs9266772	0.64	0.98	0.12	0.58	[0.00,0.90]	HLA-C-[]--MICA
rs7720838	0.91	0.89	0.27	0.19	[0.00,0.84]	[]---PTGER4
rs10497813	0.96	0.83	0.85	0.00	[0.00,0.80]	[PLCL1]
rs9860547	0.31	0.56	0.35	0.00	[0.00,0.80]	[LPP]
rs7032572	0.098	0.99	0.28	0.15	[0.00,0.83]	RANBP6-[]--IL33
rs6021270	0.39	0.24	0.41	0.00	[0.00,0.80]	[NFATC2]
rs9303280	0.67	0.59	0.34	0.00	[0.00,0.80]	[GSDMB]
rs17228058	0.94	0.37	0.70	0.00	[0.00,0.80]	[SMAD3]
rs962993	0.34	0.66	0.85	0.00	[0.00,0.80]	GATA3-[]
rs17388568	0.26	0.052	0.68	0.00	[0.00,0.80]	[ADAD1]
rs1998359	0.96	0.79	0.37	0.00	[0.00,0.80]	FOXA1-[]---TTC6
rs6473223	0.43	0.15	0.05	0.75	[0.00,0.93]	TPD52-[]---ZBTB10
rs10174949	0.20	0.42	0.52	0.00	[0.00,0.80]	[]---ID2
rs7203459	0.26	0.27	0.86	0.00	[0.00,0.80]	[CLEC16A]
rs2107357	0.041	0.67	0.95	0.00	[0.00,0.80]	IL4R-[]--IL21R
rs2056417	0.24	0.42	0.02	0.82	[0.00,0.94]	[PEX14]
rs10893845	0.51	0.40	0.56	0.00	[0.00,0.80]	[]---ETS1

P_{gt} , result of test for a genotyping platform effect between Illumina HumanHap 550-based results and OmniExpress-based results in the 23andMe cohort; P_{age} , test of interaction between genotype and age in the 23andMe cohort; P_Q , P value for test of heterogeneity based on Cochran's Q statistic; I^2 , proportion of variance in effects attributable to study heterogeneity; 95% CI, confidence interval for I^2 ; gene context, as in Table 2.

Supplementary Table 6. Replication of allergy loci in analysis of allergic sensitization²⁰.

SNP	OR	95% CI	match	<i>P</i>	<i>P</i> _{fisher}	gene context
rs2101521	1.234	[1.155,1.319]	Yes	6.3e-10	3.7e-30	TLR1-[]--TLR6
rs1438673	1.114	[1.060,1.170]	Yes	2.2e-05	5.0e-25	WDR36-[]--CAMK4
rs2155219	1.202	[1.142,1.265]	Yes	1.8e-12	2.6e-31	C11orf30-[]--LRRC32
rs10189629	1.146	[1.059,1.241]	Yes	0.00072	1.3e-19	IL1RL2-[]--IL1RL1
rs6906021	1.158	[1.101,1.219]	Yes	1.3e-08	9.6e-23	HLA-DQA1-[]--HLA-DQB1
rs9266772	1.120	[1.043,1.203]	Yes	0.0019	5.5e-15	HLA-C-[]--MICA
rs7720838	1.056	[1.004,1.110]	Yes	0.033	2.7e-12	[]---PTGER4
rs2117339	1.032	[0.983,1.084]	Yes	0.21	1.4e-10	[PLCL1]
rs9860547	1.121	[1.063,1.181]	Yes	2.3e-05	2.7e-14	[LPP]
rs7032572	1.028	[0.962,1.099]	Yes	0.41	7.7e-10	RANBP6-[]--IL33
rs6021270	1.041	[0.940,1.153]	Yes	0.45	3.1e-09	[NFATC2]
rs9303280	1.044	[0.988,1.102]	Yes	0.13	1.0e-09	[GSDMB]
rs962993	1.069	[1.009,1.132]	Yes	0.024	3.3e-10	GATA3-[]
rs17293632	1.039	[0.982,1.099]	Yes	0.18	2.5e-09	[SMAD3]
rs2202749	1.108	[1.051,1.167]	Yes	0.00014	3.4e-12	TPD52-[]--ZBTB10
rs17388568	1.116	[1.058,1.177]	Yes	5.6e-05	2.0e-12	[ADAD1]
rs9671863	1.015	[0.960,1.074]	Yes	0.60	3.1e-08	FOXA1-[]--TTC6
rs13416555	1.121	[1.062,1.183]	Yes	3.3e-05	3.6e-12	[]---ID2
rs7203459	1.033	[0.970,1.101]	Yes	0.31	6.4e-08	[CLEC16A]
rs2107357	1.079	[0.992,1.174]	Yes	0.077	2.4e-08	IL4R-[]--IL21R
rs2056417	1.031	[0.978,1.087]	Yes	0.27	1.4e-07	[PEX14]
rs970924	1.050	[0.993,1.110]	Yes	0.085	5.2e-08	[]---ETS1

OR, odds ratio for the risk allele defined in Table 2; CI, confidence interval; match, agreement of risk alleles across allergy and allergic sensitization studies; *P*, *P* value for allergic sensitization; *P*_{fisher}, combined *P* value across allergy (Table 2) and allergic sensitization meta-analyses using Fisher's method⁶⁹; gene context, as in Table 2.

Supplementary Table 7. NCBI Gap Plus annotations near allergy index SNPs.

allergy association				relationship		Gap Plus annotation				
region	position	SNP	P	distance	r ²	SNP	P	study ID	MeSH term	genes
5q22.1	110467499	rs1438673	2.3e-20	-61824	0.771	rs3806932	3.0e-09	20208534	Esophagitis	TSLP
5q22.1	110467499	rs1438673	2.3e-20	-59497	0.564	rs1898671	5.0e-06	22036096	Rhinitis, Allergic, Seasonal	TSLP
11q13.5	76299194	rs2155219	1.4e-19	-28511	0.513	rs7130588	2.0e-08	21907864	Asthma	C11orf30 - LRRC32
11q13.5	76299194	rs2155219	1.4e-19	0	1.000	rs2155219	5.0e-16	21297633	Colitis, Ulcerative	C11orf30 - LRRC32
11q13.5	76299194	rs2155219	1.4e-19	0	1.000	rs2155219	1.0e-08	22036096	Rhinitis, Allergic, Seasonal	C11orf30 - LRRC32
11q13.5	76299194	rs2155219	1.4e-19	2122	0.583	rs7927894	1.0e-09	18587394	Crohn Disease	C11orf30 - LRRC32
11q13.5	76299194	rs2155219	1.4e-19	2122	0.583	rs7927894	8.0e-10	19349984	Dermatitis, Atopic	C11orf30 - LRRC32
2q12.1	102879464	rs10189629	1.9e-16	74153	0.775	rs3771180	2.0e-15	21804549	Asthma	IL1RL1
5p13.1	40486896	rs7720838	8.3e-11	3894	0.936	rs10440635	3.0e-07	21743469	Spondylitis, Ankylosing	DAB2 - PTGER4
2q33.1	198914072	rs10497813	6.1e-10	-17177	0.972	rs6738825	4.0e-09	21102463	Crohn Disease	PLCL1
3q28	188128979	rs9860547	1.2e-09	-16425	0.698	rs1464510	3.0e-40	20190752	Celiac Disease	LPP
3q28	188128979	rs9860547	1.2e-09	-16425	0.698	rs1464510	5.0e-09	18311140	Celiac Disease	LPP
3q28	188128979	rs9860547	1.2e-09	-16425	0.698	rs1464510	1.0e-11	20410501	Vitiligo	LPP
9p24.1	6172380	rs7032572	1.9e-09	17696	0.949	rs1342326	9.0e-10	20860503	Asthma	RANBP6 - IL33
9p24.1	6172380	rs7032572	1.9e-09	21075	0.537	rs2381416	2.0e-12	21804549	Asthma	RANBP6 - IL33
17q12	38074031	rs9303280	8.3e-09	-151772	0.681	rs907092	8.0e-06	19458352	Liver Cirrhosis, Biliary	IKZF3
17q12	38074031	rs9303280	8.3e-09	-97562	0.781	rs9303277	2.0e-09	20639880	Liver Cirrhosis, Biliary	IKZF3
17q12	38074031	rs9303280	8.3e-09	-33268	0.745	rs2872507	9.0e-07	20453842	Arthritis, Rheumatoid	ZBP2 - GSDMB
17q12	38074031	rs9303280	8.3e-09	-33268	0.745	rs2872507	5.0e-11	21297633	Colitis, Ulcerative	ZBP2 - GSDMB
17q12	38074031	rs9303280	8.3e-09	-33268	0.745	rs2872507	5.0e-09	18587394	Crohn Disease	ZBP2 - GSDMB
17q12	38074031	rs9303280	8.3e-09	-33268	0.745	rs2872507	2.0e-06	21829393	Diabetes Mellitus, Type 1	ZBP2 - GSDMB
17q12	38074031	rs9303280	8.3e-09	-11835	0.752	rs2305480	1.0e-07	20860503	Asthma	GSDMB
17q12	38074031	rs9303280	8.3e-09	-11835	0.752	rs2305480	3.0e-08	20228799	Colitis, Ulcerative	GSDMB
17q12	38074031	rs9303280	8.3e-09	-9626	0.760	rs11078927	2.0e-16	21804549	Asthma	GSDMB
17q12	38074031	rs9303280	8.3e-09	-7791	0.855	rs2290400	6.0e-13	19430480	Diabetes Mellitus, Type 1	GSDMB
17q12	38074031	rs9303280	8.3e-09	-4082	0.924	rs7216389	9.0e-11	17611496	Asthma	GSDMB
17q12	38074031	rs9303280	8.3e-09	21143	0.559	rs6503525	5.0e-07	21150878	Asthma	ORMDL3 - GSDMA
15q22.33	67450305	rs17228058	1.2e-08	-7709	0.989	rs17293632	3.0e-19	21102463	Crohn Disease	SMAD3
4q27	123329362	rs17388568	3.6e-08	-196870	0.706	rs4505848	5.0e-13	19430480	Diabetes Mellitus, Type 1	KIAA1109
4q27	123329362	rs17388568	3.6e-08	-130927	0.617	rs6534347	2.0e-06	17554300	Diabetes Mellitus, Type 1	KIAA1109
4q27	123329362	rs17388568	3.6e-08	0	1.000	rs17388568	9.0e-07	21297633	Colitis, Ulcerative	ADAD1
4q27	123329362	rs17388568	3.6e-08	0	1.000	rs17388568	6.0e-06	21829393	Diabetes Mellitus, Type 1	ADAD1
4q27	123329362	rs17388568	3.6e-08	43771	0.909	rs2069772	1.0e-06	22036096	Rhinitis, Allergic, Seasonal	IL2
8q21.13	81268155	rs6473223	7.7e-08	-449	0.970	rs6992476	9.1e-05	pha002864	Diabetic Nephropathies	RPS5P5 - ZBTB10
16p13.13	11230703	rs7203459	2.1e-07	-71818	0.508	rs887864	1.0e-06	22036096	Rhinitis, Allergic, Seasonal	CLEC16A
16p13.13	11230703	rs7203459	2.1e-07	8080	0.596	rs2903692	7.0e-11	17632545	Diabetes Mellitus, Type 1	CLEC16A

Allergy association, an index SNP from table 2; relationship, the distance and r² between the allergy index SNP and the annotation. The Gap Plus annotation includes the reported SNP identifier and P value; a study ID, either a PubMed ID for the reporting study, or a dbGAP “pha” accession number; a MeSH term, or medical subject heading; and associated genes as reported in the original study.

Supplementary Table 8. Nonsynonymous SNPs near allergy index SNPs.

allergy association				relationship		nsSNP annotation		
region	position	SNP	<i>P</i>	distance	<i>r</i> ²	SNP	gene	mutation
4p14	38811551	rs2101521	5.9e-21	-36662	0.550	rs4129009	TLR10	I775V
4p14	38811551	rs2101521	5.9e-21	-12903	0.676	rs5743618	TLR1	S602I
4p14	38811551	rs2101521	5.9e-21	-11841	0.806	rs4833095	TLR1	N248S
17q12	38074031	rs9303280	8.3e-09	-45397	0.821	rs11557467	ZBPB2	S173I
17q12	38074031	rs9303280	8.3e-09	-11835	0.752	rs2305480	GSDMB	P298S
17q12	38074031	rs9303280	8.3e-09	-11814	0.848	rs2305479	GSDMB	G291R

Allergy association, an index SNP from Table 2; relationship, distance and *r*² between the allergy index SNP and the annotation. The nsSNP annotation includes the SNP identifier, affected gene, and amino acid change associated with this SNP.

Supplementary Table 9. Monocyte expression QTLs near allergy index SNPs.

allergy association				relationship		eQTL annotation				
region	position	SNP	<i>P</i>	distance	<i>r</i> ²	SNP	distance	gene	<i>P</i>	<i>r</i> ²
4p14	38811551	rs2101521	5.9e-21	-8488	0.711	rs5743592	25160	TLR6	1.4e-08	0.024
2q33.1	198914072	rs10497813	6.1e-10	-33591	0.897	rs1318867	67998	PLCL1	3.0e-28	0.083
3q28	188128979	rs9860547	1.2e-09	-23923	0.872	rs9864529	641581	BCL6	5.2e-10	0.028
17q12	38074031	rs9303280	8.9e-09	-5988	0.924	rs869402	47602	IKZF3	3.0e-07	0.020
2p25.1	8442248	rs10174949	1.0e-07	-1216	0.687	rs6734135	377943	ID2	9.0e-10	0.028
1p36.22	10581658	rs2056417	5.3e-07	-37111	0.861	rs668805	0	PEX14	1.2e-19	0.057

Allergy association, an index SNP from Table 2; relationship, distance and *r*² between the index SNP and the annotation. The eQTL annotation includes the associated SNP; the absolute distance in base pairs between that SNP and the associated gene; the associated gene; the reported *P* value; and *r*², the proportion of variance in expression explained by the association.

Supplementary Table 11. Replication of reported associations with asthma

region	pubmed.id	first author	pub date	risk allele	GWAS Catalog result			Allergy result		
					P	OR	genes	P	OR	agree
1q21.3	21804549	Torgerson DG	2011-07-31	rs4845783-G	6.0e-06		CRCT1	0.13	1.02	
1q21.3	21907864	Ferreira MA	2011-09-10	rs4129267-T	2.0e-08	1.09	IL6R	0.034	1.03	+
1q31.3	20032318	Sleiman PM	2009-12-23	rs2786098-C	2.0e-13	1.43	DENND1B, CRB1	0.64	0.99	
2q12.1	21804549	Torgerson DG	2011-07-31	rs3771180-G	2.0e-15		IL1RL1	1.6e-13	1.15	+++
2q12.1	23028483	Ramasamy A	2012-09-28	rs13408661-G	1.0e-09	1.23	IL1RL1, IL18R1	1.9e-15	1.15	+++
2q12.1	20860503	Moffatt MF	2010-09-23	rs3771166-G	3.0e-09	1.15	IL18R1	3.8e-07	1.06	+++
4q31.21	21804548	Hirota T	2011-07-31	rs7686660-T	2.0e-12	1.16	LOC729675	0.099	0.98	
4q31.21	21804548	Hirota T	2011-07-31	rs3805236-G	7.0e-08	1.12	GAB1	0.00031	1.06	+++
5q12.1	19426955	Himes BE	2009-05-07	rs1588265-C	3.0e-08	1.18	PDE4D	0.26	1.01	
5q22.1	21804549	Torgerson DG	2011-07-31	rs1837253-C	1.0e-14		TSLP	2.3e-10	1.09	+++
5q22.1	21804548	Hirota T	2011-07-31	rs1837253-C	1.0e-16	1.17	TSLP	2.3e-10	1.09	+++
5q31.1	20860503	Moffatt MF	2010-09-23	rs2073643-T	2.0e-07	1.11	SLC22A5	0.090	1.02	
5q31.1	20159242	Li X	2010-02-01	rs2244012-C	3.0e-07	1.64	RAD50	0.00056	1.05	++
5q31.1	20860503	Moffatt MF	2010-09-23	rs1295686-T	1.0e-07	1.15	IL13	1.7e-06	1.07	+++
6p21.32	21804548	Hirota T	2011-07-31	rs204993-A	2.0e-15	1.17	PBX2	7.3e-07	0.94	---
6p21.32	21804548	Hirota T	2011-07-31	rs404860-A	4.0e-23	1.21	NOTCH4	0.61	1.01	
6p21.32	21804548	Hirota T	2011-07-31	rs3129943-T	3.0e-15	1.17	C6orf10	0.20	1.02	
6p21.32	21804548	Hirota T	2011-07-31	rs3117098-G	5.0e-12	1.16	BTNL2	0.45	1.01	
6p21.32	23028483	Ramasamy A	2012-09-28	rs9268516-T	1.0e-08	1.15	BTNL2, HLA-DRA	4.2e-05	1.06	+++
6p21.32	21804548	Hirota T	2011-07-31	rs3129890-T	5.0e-13	1.15	HLA-DRA	0.56	1.01	
6p21.32	21804548	Hirota T	2011-07-31	rs7775228-A	5.0e-15	1.17	HLA-DQB1	0.00012	0.94	---
6p21.32	21804548	Hirota T	2011-07-31	rs9275698-T	5.0e-12	1.18	HLA-DQA2	0.68	1.01	
6p21.32	21804548	Hirota T	2011-07-31	rs9500927-T	4.0e-09	1.13	HLA-DOA	0.0062	1.05	+
6p21.32	21814517	Noguchi E	2011-07-21	rs987870-C	2.0e-10	1.40	HLA, DPB1	9.2e-05	1.07	+++
8q24.11	21814517	Noguchi E	2011-07-21	rs3019885-G	5.0e-13	1.34	SLC30A8	0.068	0.98	
9p24.1	20860503	Moffatt MF	2010-09-23	rs1342326-C	9.0e-10	1.20	IL33	6.0e-09	1.10	+++
9p24.1	21804549	Torgerson DG	2011-07-31	rs2381416-C	2.0e-12		IL33	1.2e-07	1.07	+++
10p14	21804548	Hirota T	2011-07-31	rs10508372-C	2.0e-15	1.16	LOC338591	0.00019	1.09	+++
10q21.1	21907864	Ferreira MA	2011-09-10	rs7922491-A	5.0e-07	1.13	PRKG1	0.46	1.01	
11q13.5	21907864	Ferreira MA	2011-09-10	rs7130588-G	2.0e-08	1.09	LRRC32	2.2e-12	1.09	+++
12q13.2	21804548	Hirota T	2011-07-31	rs2069408-C	1.0e-10	1.15	CDK2	0.060	1.02	
12q13.2	21804548	Hirota T	2011-07-31	rs1701704-G	2.0e-13	1.19	IKZF4	0.012	1.03	+
15q22.2	20860503	Moffatt MF	2010-09-23	rs11071559-C	1.0e-07	1.18	RORA	9.2e-05	1.07	+++
15q22.33	20860503	Moffatt MF	2010-09-23	rs744910-G	4.0e-09	1.12	SMAD3	4.2e-06	1.06	+++
17q12	20860503	Moffatt MF	2010-09-23	rs2305480-G	1.0e-07	1.18	GSDMB	4.4e-08	1.07	+++
17q12	21804549	Torgerson DG	2011-07-31	rs11078927-C	2.0e-16		GSDMB	3.9e-08	0.94	+++
17q12	17611496	Moffatt MF	2007-07-26	rs7216389-T	9.0e-11	1.45	ORMDL3	3.2e-08	1.07	+++
17q12	21150878	Ferreira MA	2010-12-08	rs6503525-C	5.0e-07	1.33	ORMDL3	5.9e-06	1.06	+++
17q21.1	20860503	Moffatt MF	2010-09-23	rs3894194-A	5.0e-09	1.17	GSDMA	7.9e-06	1.05	+++
22q12.3	20860503	Moffatt MF	2010-09-23	rs2284033-G	1.0e-08	1.12	IL2RB	0.016	1.03	+

Results are shown for all asthma reports in the NHGRI GWAS Catalog for which the risk allele was available or could be inferred from the original study, and the reported SNP was tested in our allergy analysis. Entries in gray italics overlap a region identified in Table 2. Allergy result: P, P value from shared-effect meta-analysis; OR, odds ratio for the previously reported risk allele; agree, '+' P<0.05, '++' P<0.005, '+++ ' P<0.0005 with the same risk allele; dashes indicate the same levels of significance but with inconsistent risk alleles.

Supplementary Table 12. Replication of reported associations with atopic dermatitis.

GWAS Catalog result								Allergy result		
region	pubmed.id	first author	pubdate	riskallele	P	OR	genes	P	OR	agree
1q21.3	21666691	Sun LD	2011-06-13	rs3126085-A	6.0e-12	1.22	FLG	0.068	0.97	
2q12.1	23042114	Hirota T	2012-10-07	rs13015714-G	8.0e-18	1.27	IL1RL1, IL18R1, IL18RAP	0.18	0.98	
2q13	23042114	Hirota T	2012-10-07	rs2271404-G	3.0e-07	1.17	LOC100505634	0.58	0.99	
3p22.3	23042114	Hirota T	2012-10-07	rs7613051-A	6.0e-21	1.29	GLB1	0.19	1.02	
3q13.2	23042114	Hirota T	2012-10-07	rs12634229-G	2.0e-19	1.29	CCDC80, LOC100630917	0.49	1.02	
5q31.1	23042114	Hirota T	2012-10-07	rs1295686-T	2.0e-06	1.22	KIF3A, IL13	1.7e-06	1.07	+++
5q31.1	22197932	Paternoster L	2011-12-25	rs2897442-C	4.0e-08	1.11	KIF3A	0.024	1.03	+
6p21.33	23042114	Hirota T	2012-10-07	rs9368677-G	1.0e-17	1.36	HLA-C	0.12	0.96	
6p21.33	22197932	Paternoster L	2011-12-25	rs3853601-G	2.0e-06	1.13	BAT1	0.92	1.00	
6p21.32	23042114	Hirota T	2012-10-07	rs176095-T	8.0e-20	1.40	GPSM3	9.6e-07	0.93	---
6p21.32	23042114	Hirota T	2012-10-07	rs9469099-G	5.0e-19	1.61	C6orf10	0.35	1.04	
7p22.2	23042114	Hirota T	2012-10-07	rs4722404-G	8.0e-09	1.18	CARD11	0.0069	1.03	+
8q24.21	23042114	Hirota T	2012-10-07	rs7815944-A	4.0e-07	1.16	MIR1208	0.0033	1.10	++
10q21.2	23042114	Hirota T	2012-10-07	rs10995251-C	6.0e-20	1.28	ZNF365	0.090	1.02	
11p15.4	23042114	Hirota T	2012-10-07	rs878860-G	2.0e-22	1.31	OR10A3, NLRP10	0.082	0.98	
11q13.1	23042114	Hirota T	2012-10-07	rs593982-C	6.0e-07	1.23	OVOL1	0.47	0.99	
11q13.1	22197932	Paternoster L	2011-12-25	rs479844-G	1.0e-13	1.14	OVOL1	0.15	1.02	
11q13.5	19349984	Esparza-Gordillo J	2009-04-06	rs7927894-A	8.0e-10	1.22	C11orf30	6.2e-16	1.10	+++
11q13.5	23042114	Hirota T	2012-10-07	rs11236809-G	3.0e-06	1.24	C11orf30	0.20	1.03	
16p13.13	23042114	Hirota T	2012-10-07	rs9923856-A	6.0e-06	1.17	CLEC16A	4.4e-05	1.05	+++
19p13.2	22197932	Paternoster L	2011-12-25	rs2164983-A	7.0e-09	1.16	ACTL9	0.20	1.02	
20q13.2	23042114	Hirota T	2012-10-07	rs16999165-T	2.0e-08	1.19	CYP24A1, PFDN4	0.24	1.04	
22q12.3	22197932	Paternoster L	2011-12-25	rs4821544-C	6.0e-06	1.09	NCF4	0.0064	1.04	+

Results are shown for all atopic dermatitis reports in the NHGRI GWAS Catalog for which the risk allele was available or could be inferred from the original study, and the reported SNP was tested in our allergy analysis. Entries in gray italics overlap a region identified in Table 2. Allergy result: P, P value from shared-effect meta-analysis; OR, odds ratio for the previously reported risk allele; agree, '+' P<0.05, '++' P<0.005, '+++ 'P<0.0005 with the same risk allele; dashes indicate the same levels of significance but with inconsistent risk alleles.

Supplementary Table 13. Association of index SNPs with symptoms in the 23andMe cohort.

SNP	OR	95% CI	P_{main}	P_{int}	P_{total}	gene context
rs2101521	1.143	[1.109,1.178]	2.6e-18	0.62	1.2e-16	TLR1-[]--TLR6
rs1438673	1.124	[1.097,1.152]	1.8e-20	0.34	5.7e-19	WDR36-[]--CAMK4
rs2155219	1.106	[1.079,1.133]	1.1e-15	0.17	1.3e-14	C11orf30-[]--LRRC32
rs10189629	1.170	[1.128,1.213]	1.6e-17	0.20	2.6e-16	IL1RL2-[]--IL1RL1
rs6906021	1.105	[1.078,1.133]	4.5e-15	0.064	1.8e-14	HLA-DQA1-[]--HLA-DQB1
rs9266772	1.109	[1.075,1.143]	6.4e-11	0.91	2.6e-09	HLA-C-[]--MICA
rs7720838	1.076	[1.050,1.103]	7.9e-09	0.96	2.7e-07	[]--PTGER4
rs10497813	1.067	[1.041,1.093]	2.2e-07	0.0078	5.5e-08	[PLCL1]
rs9860547	1.080	[1.053,1.107]	2.0e-09	0.54	4.3e-08	[LPP]
rs7032572	1.142	[1.097,1.188]	6.4e-11	0.043	1.3e-10	RANBP6-[]--IL33
rs6021270	1.167	[1.105,1.234]	3.6e-08	0.69	8.5e-07	[NFATC2]
rs9303280	1.064	[1.038,1.090]	1.0e-06	3.5e-05	1.2e-09	[GSDMB]
rs17228058	1.096	[1.065,1.128]	3.2e-10	0.13	1.8e-09	[SMAD3]
rs962993	1.068	[1.041,1.096]	4.5e-07	0.32	3.8e-06	GATA3-[]
rs17388568	1.077	[1.048,1.107]	8.2e-08	0.30	7.2e-07	[ADAD1]
rs1998359	1.079	[1.046,1.112]	1.2e-06	0.024	7.8e-07	FOXA1-[]--TTC6
rs6473223	1.070	[1.042,1.097]	2.7e-07	0.55	4.2e-06	TPD52-[]--ZBTB10
rs10174949	1.058	[1.030,1.088]	5.1e-05	0.65	0.00063	[]--ID2
rs7203459	1.079	[1.049,1.110]	1.0e-07	0.081	2.7e-07	[CLEC16A]
rs2107357	1.078	[1.040,1.116]	3.2e-05	0.76	0.00046	IL4R-[]--IL21R
rs2056417	1.064	[1.036,1.092]	5.5e-06	0.22	2.9e-05	[PEX14]
rs10893845	1.064	[1.038,1.090]	7.2e-07	0.20	3.7e-06	[]--ETS1
rs17533090	1.122	[1.085,1.161]	2.7e-11	0.32	4.1e-10	

OR, odds ratio per copy of the risk allele, for the main effect across allergy types; CI, confidence interval; P_{main} , test of main effect across symptoms; P_{int} , test for interaction with symptom; P_{total} , joint test including main effect and interaction. The across-symptom test

Supplementary Table 14. SNP effects on individual symptoms in the 23andMe cohort.

SNP	Rhinitis			Asthma			Contact Dermatitis		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
rs2101521	1.149	[1.112,1.188]	6.0e-17	1.140	[1.089,1.192]	1.1e-08	1.125	[1.076,1.177]	1.8e-07
rs1438673	1.131	[1.101,1.162]	3.7e-19	1.126	[1.084,1.169]	3.1e-10	1.102	[1.063,1.143]	1.2e-07
rs2155219	1.103	[1.073,1.133]	9.7e-13	1.133	[1.092,1.175]	2.1e-11	1.091	[1.052,1.131]	1.9e-06
rs10189629	1.167	[1.122,1.214]	9.9e-15	1.210	[1.144,1.279]	1.0e-11	1.145	[1.084,1.209]	9.2e-07
rs6906021	1.110	[1.080,1.141]	7.1e-14	1.124	[1.083,1.167]	4.3e-10	1.073	[1.034,1.113]	0.00015
rs9266772	1.111	[1.074,1.150]	1.2e-09	1.109	[1.059,1.162]	8.6e-06	1.101	[1.052,1.152]	2.8e-05
rs7720838	1.078	[1.048,1.108]	6.9e-08	1.074	[1.035,1.115]	0.00015	1.073	[1.034,1.113]	0.00016
rs10497813	1.081	[1.052,1.110]	1.6e-08	1.072	[1.033,1.112]	0.00017	1.023	[0.986,1.061]	0.21
rs9860547	1.080	[1.051,1.111]	3.5e-08	1.065	[1.026,1.106]	0.00077	1.090	[1.051,1.132]	3.8e-06
rs7032572	1.140	[1.091,1.192]	4.1e-09	1.196	[1.127,1.268]	1.5e-09	1.100	[1.037,1.166]	0.0014
rs6021270	1.167	[1.100,1.239]	2.8e-07	1.193	[1.096,1.298]	3.5e-05	1.146	[1.056,1.245]	0.0010
rs9303280	1.046	[1.018,1.075]	0.0011	1.133	[1.091,1.176]	3.3e-11	1.056	[1.018,1.096]	0.0032
rs17228058	1.096	[1.062,1.132]	1.1e-08	1.125	[1.078,1.174]	3.9e-08	1.072	[1.027,1.119]	0.0012
rs962993	1.067	[1.038,1.098]	4.9e-06	1.088	[1.047,1.130]	1.3e-05	1.053	[1.014,1.094]	0.0071
rs17388568	1.069	[1.037,1.102]	1.2e-05	1.101	[1.058,1.146]	1.8e-06	1.079	[1.036,1.123]	0.00018
rs1998359	1.074	[1.038,1.111]	3.6e-05	1.126	[1.076,1.178]	2.2e-07	1.053	[1.006,1.102]	0.025
rs6473223	1.065	[1.036,1.096]	9.8e-06	1.086	[1.046,1.129]	1.7e-05	1.067	[1.027,1.108]	0.00070
rs10174949	1.056	[1.024,1.088]	0.00041	1.074	[1.030,1.119]	0.00070	1.054	[1.013,1.098]	0.0095
rs7203459	1.073	[1.041,1.107]	5.4e-06	1.117	[1.070,1.165]	2.5e-07	1.064	[1.020,1.109]	0.0032
rs2107357	1.071	[1.030,1.114]	0.00050	1.086	[1.030,1.144]	0.0018	1.089	[1.035,1.147]	0.00097
rs2056417	1.070	[1.039,1.102]	4.9e-06	1.037	[0.996,1.079]	0.072	1.068	[1.027,1.111]	0.00089
rs10893845	1.072	[1.043,1.101]	3.7e-07	1.066	[1.028,1.106]	0.00051	1.039	[1.001,1.077]	0.039
rs17533090	1.131	[1.089,1.174]	7.3e-11	1.129	[1.072,1.189]	2.9e-06	1.091	[1.037,1.147]	0.00064

OR, odds ratio per copy of the risk allele, for specific self reported allergy symptom; CI, confidence interval; *P*, Wald test for significance of the effect for this particular symptom.

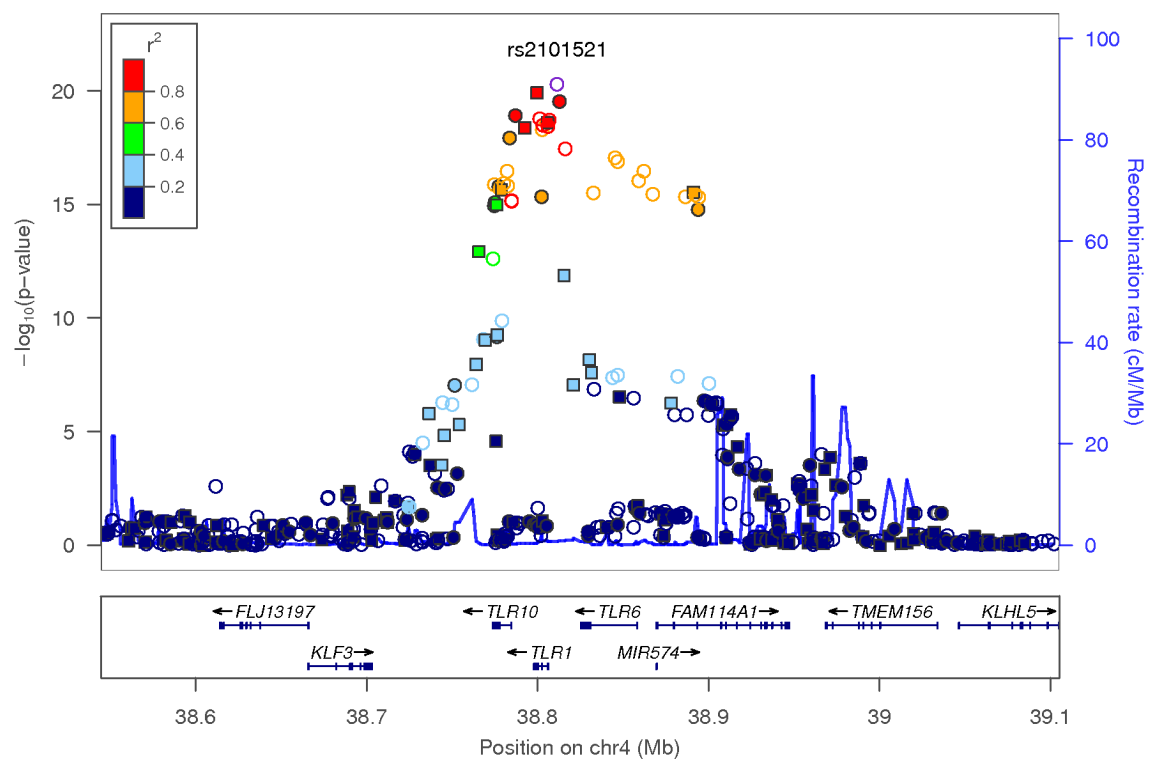
Supplementary Table 15. Consistency of effects at shared allergy and autoimmune loci

region	gene	diseases	match
11q13.5	<i>LRR32</i>	CD, UC	yes
5p13.1	<i>PTGER4</i>	AS	yes
2q33.1	<i>PLCL1</i>	CD	yes
3q28	<i>LPP</i>	CE, VI	no
17q12	<i>GSDMB</i>	BC, CD, UC, RA, T1D	no
15q22.33	<i>SMAD3</i>	CD	yes
4q27	<i>ADAD1</i>	UC, T1D	yes
16p13.13	<i>CLEC16A</i>	T1D	yes

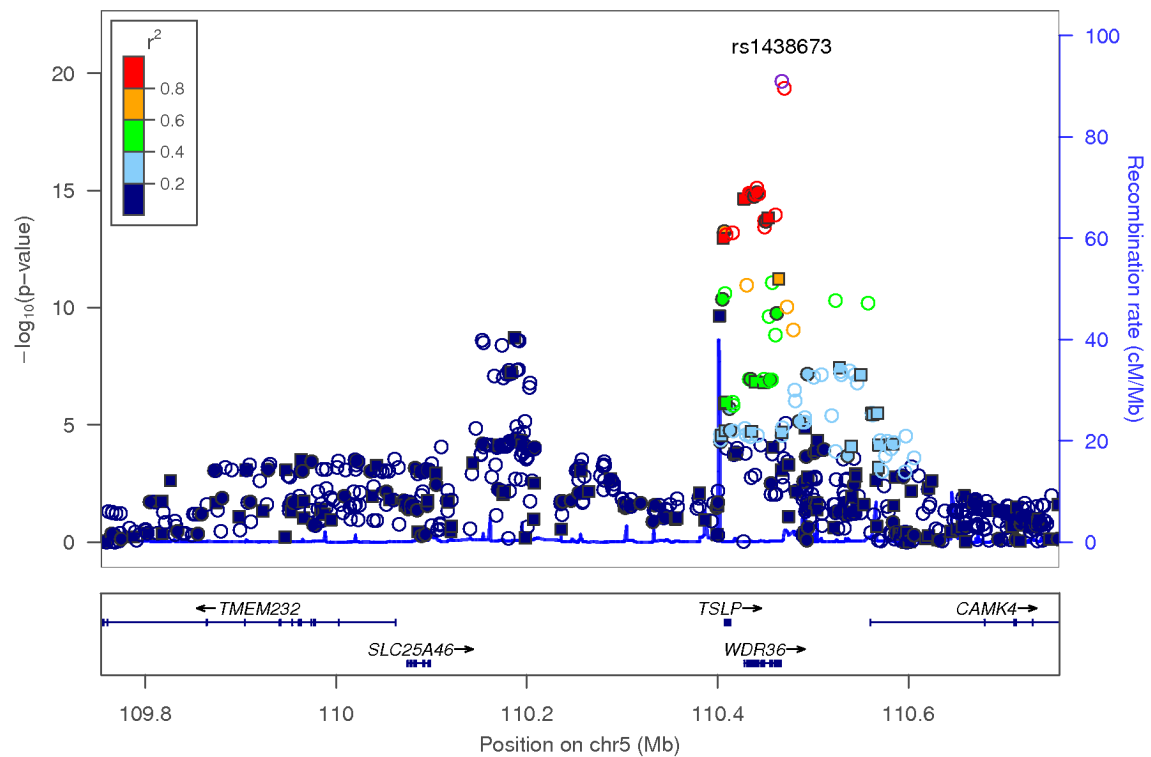
Diseases: CD, Crohn's disease; UC, ulcerative colitis; BC, primary biliary cirrhosis; RA, rheumatoid arthritis; T1D, type 1 diabetes; CE, celiac disease; VI, vitiligo; AS, ankylosing spondylitis. Match, indicates whether allergy risk allele matches risk allele(s) for autoimmune disease.

Supplementary Figure 1. Regional plots of allergy associations. Symbol colors indicate linkage disequilibrium with the index SNP, which is labeled and colored purple. Open circles indicate imputed variants, filled circles indicate partially genotyped variants, and filled squares indicate fully genotyped variants. Plots were generated using LocusZoom⁷³. Results are in NCBI Build 37 coordinates.

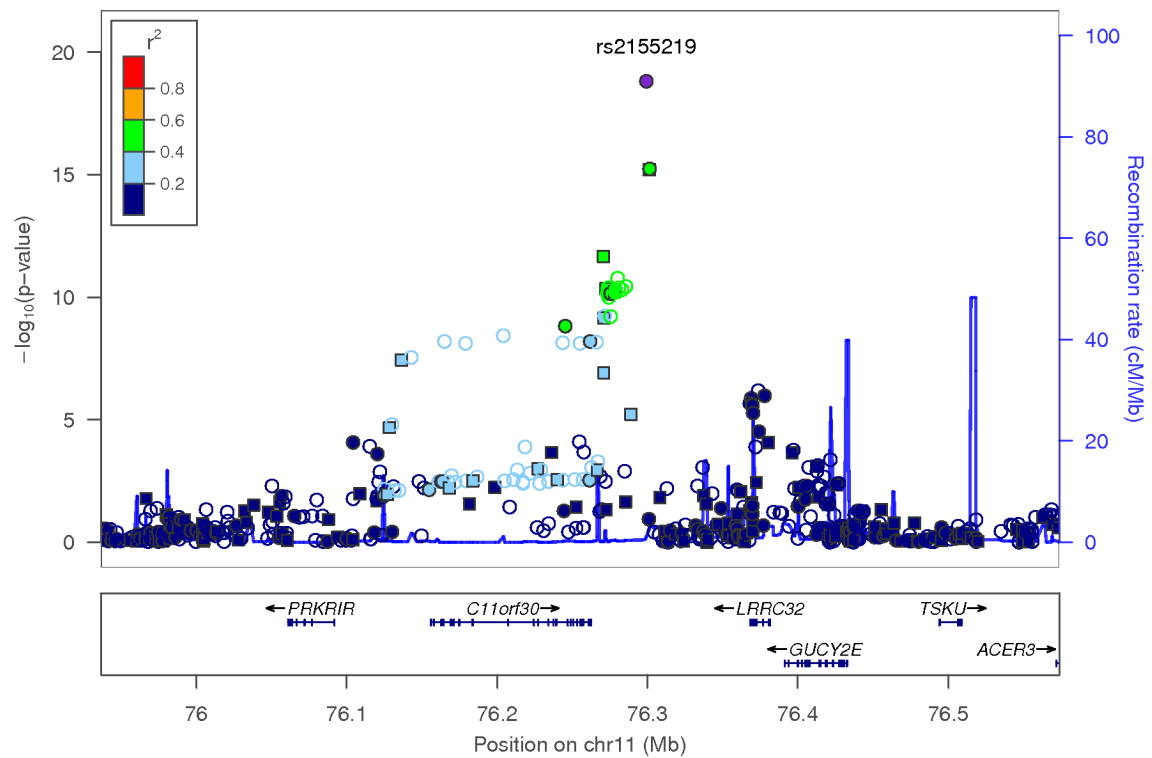
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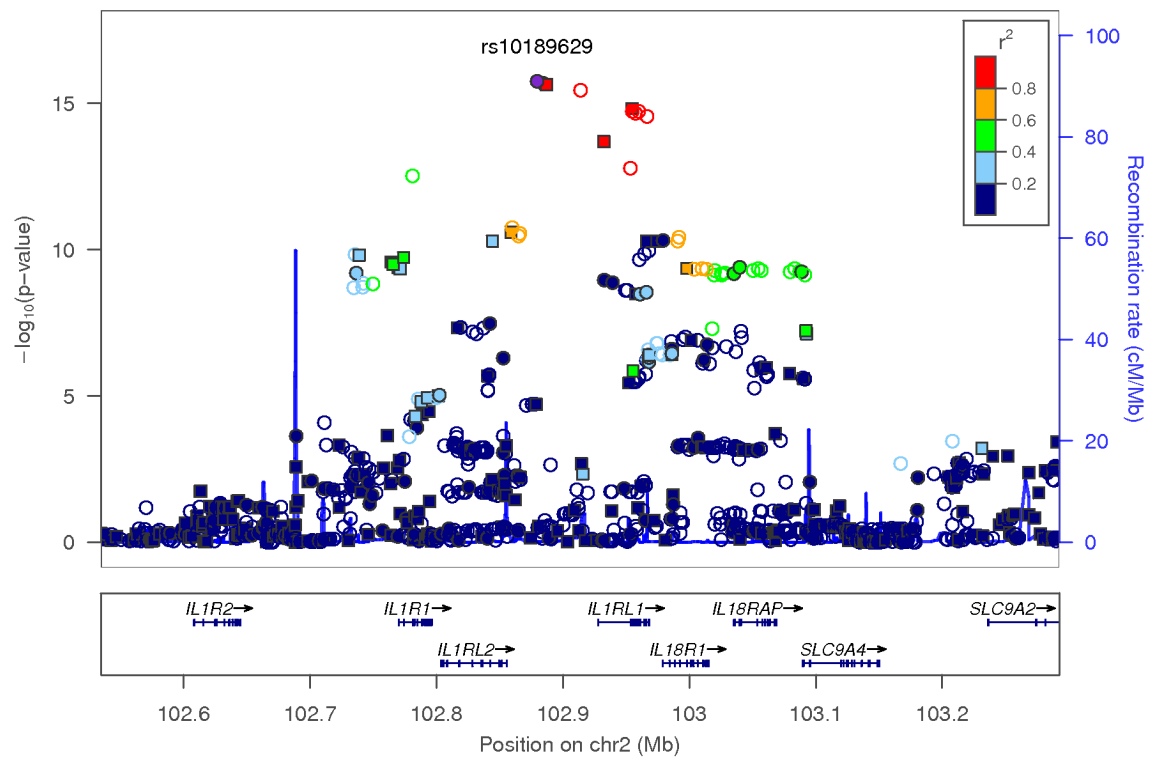
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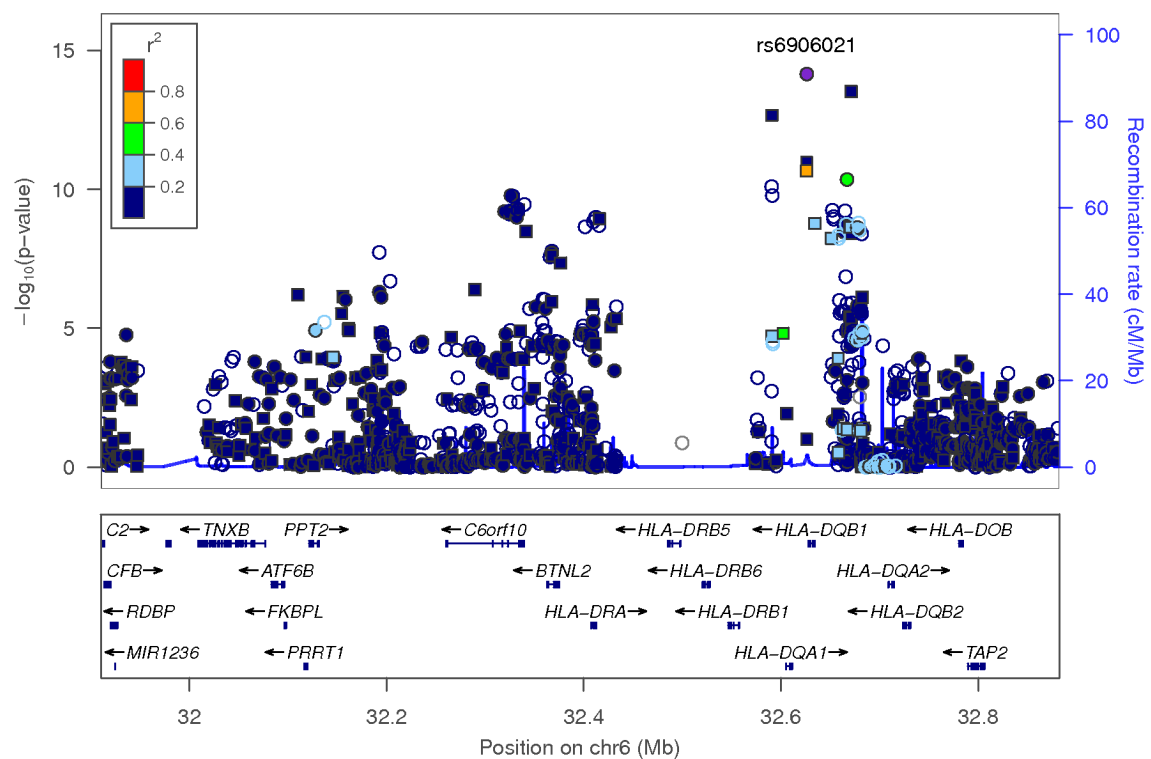
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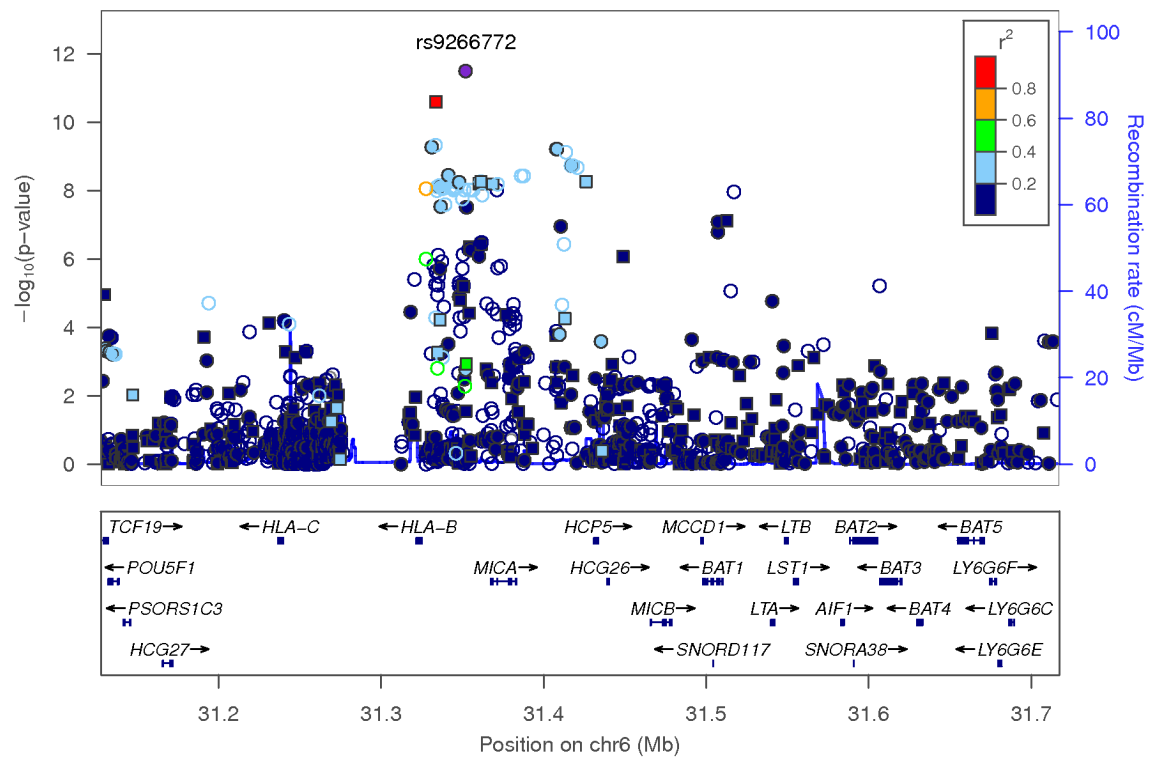
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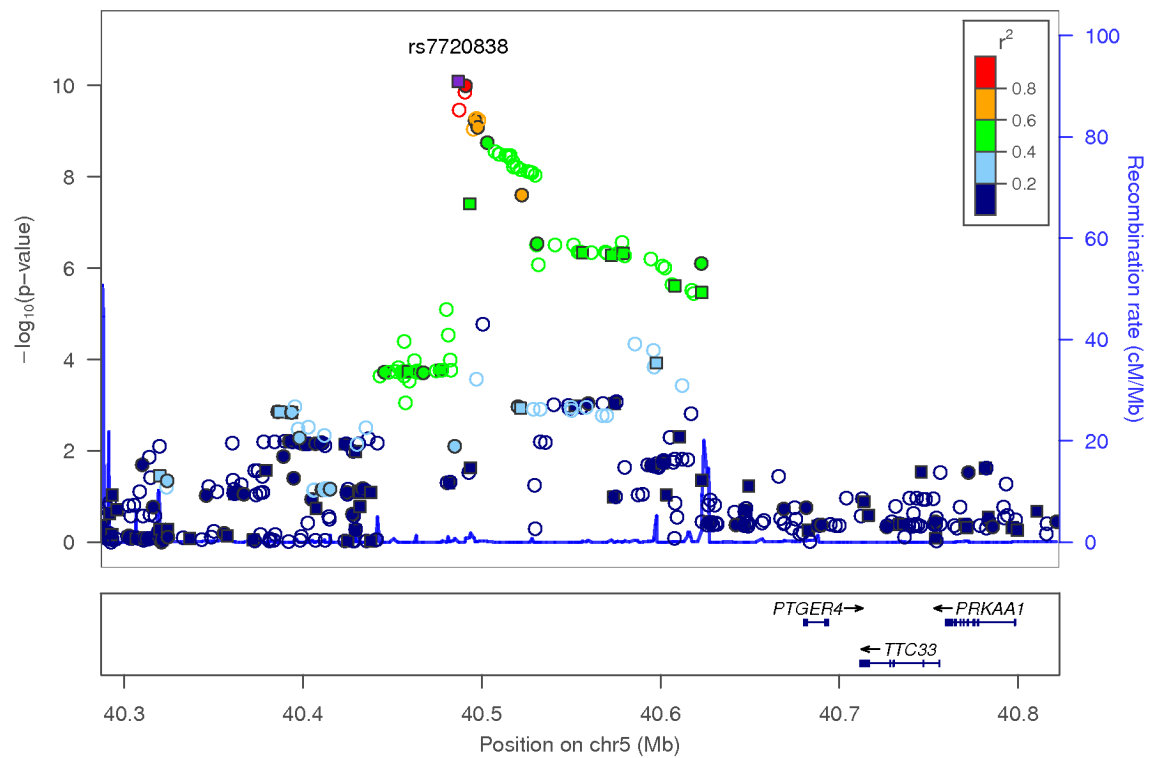
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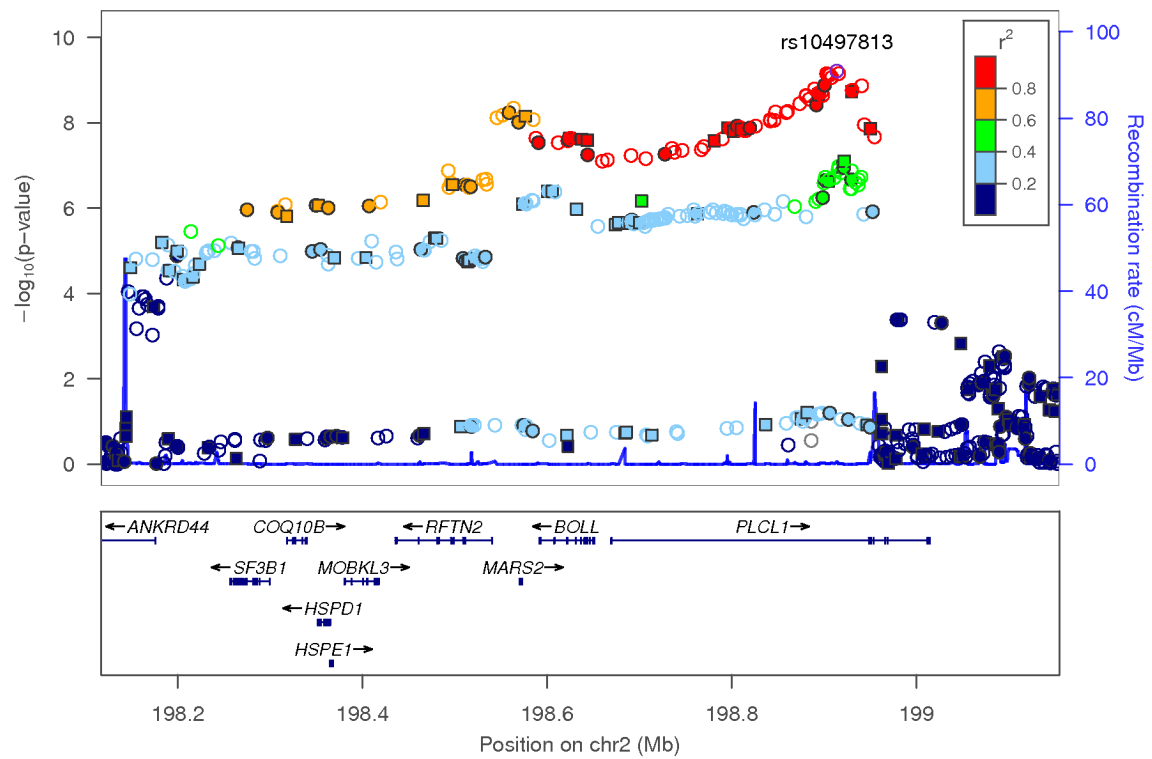
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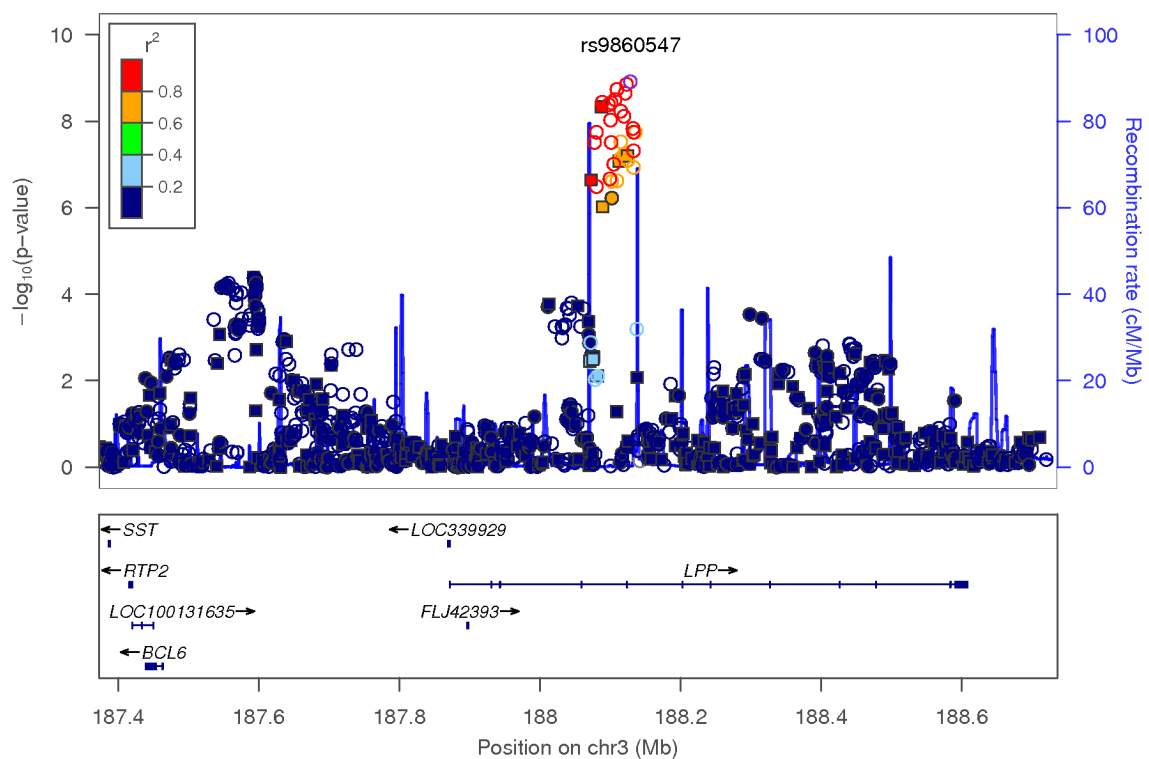
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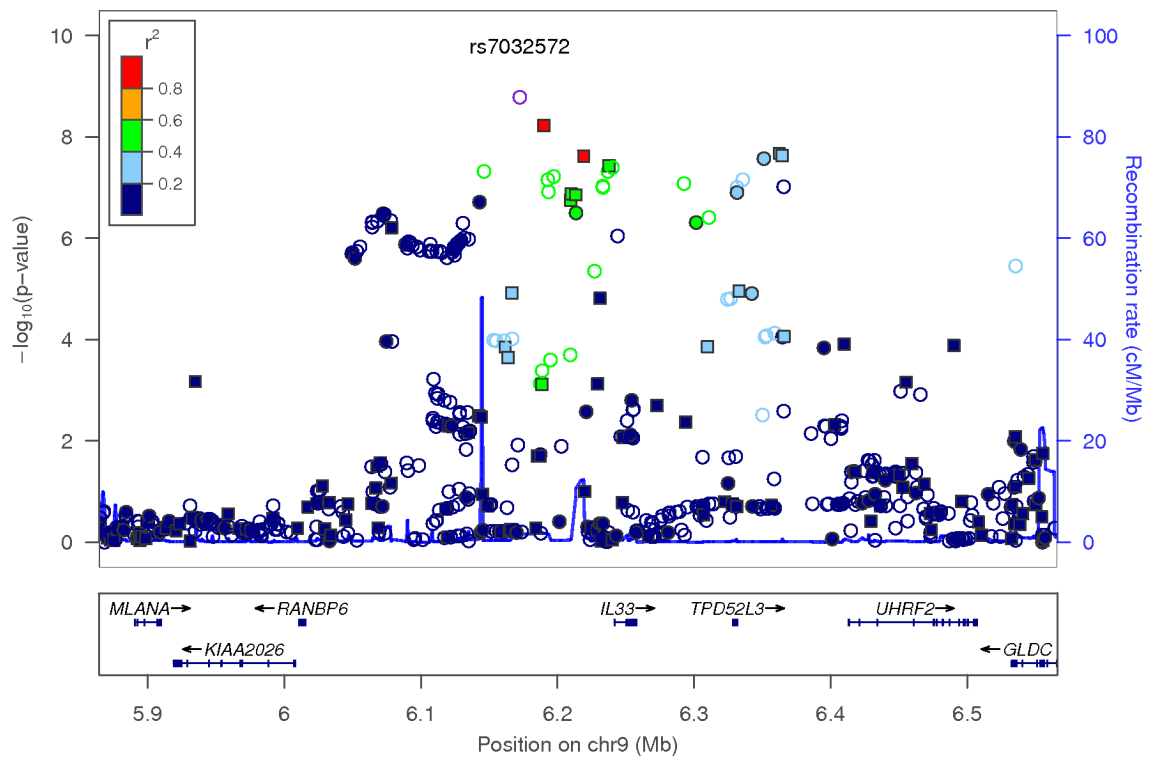
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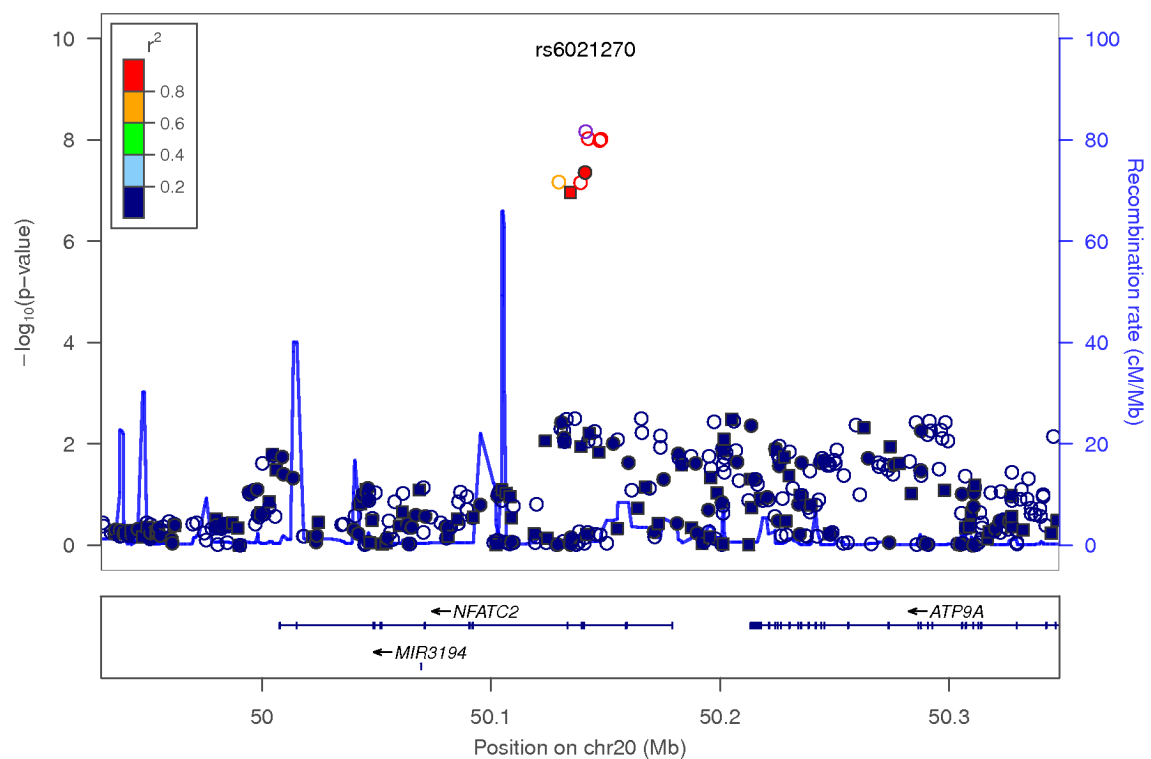
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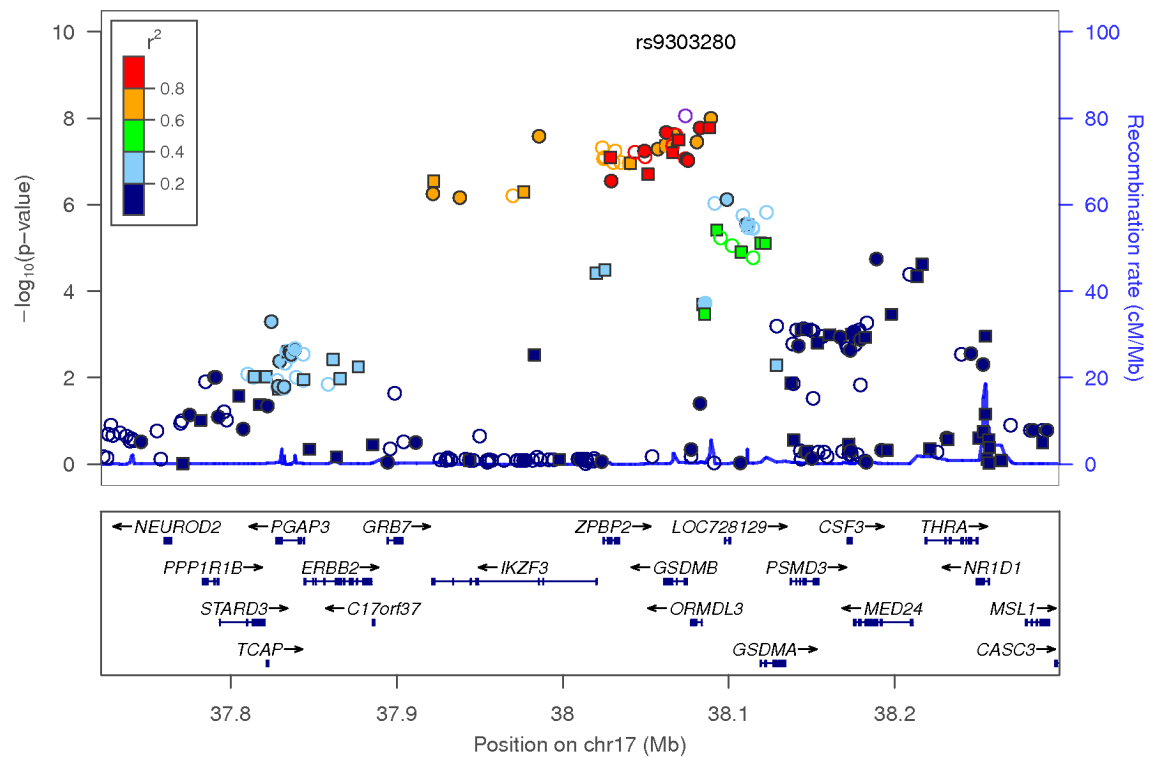
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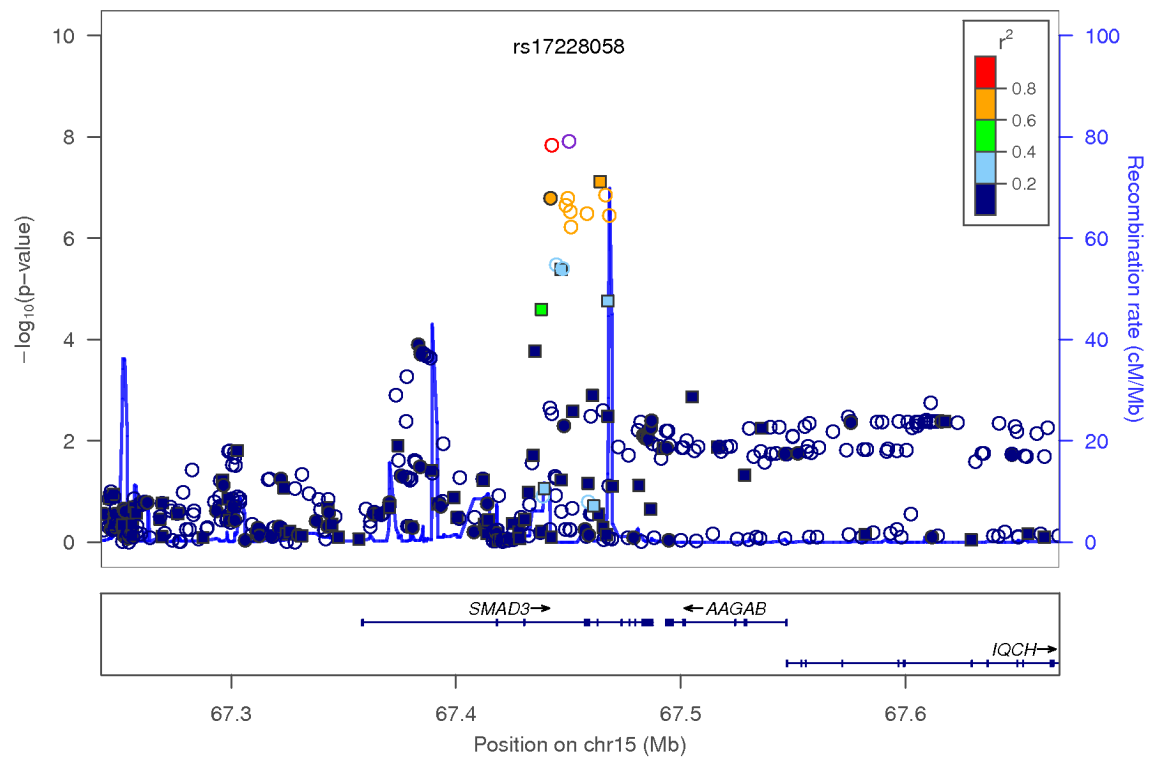
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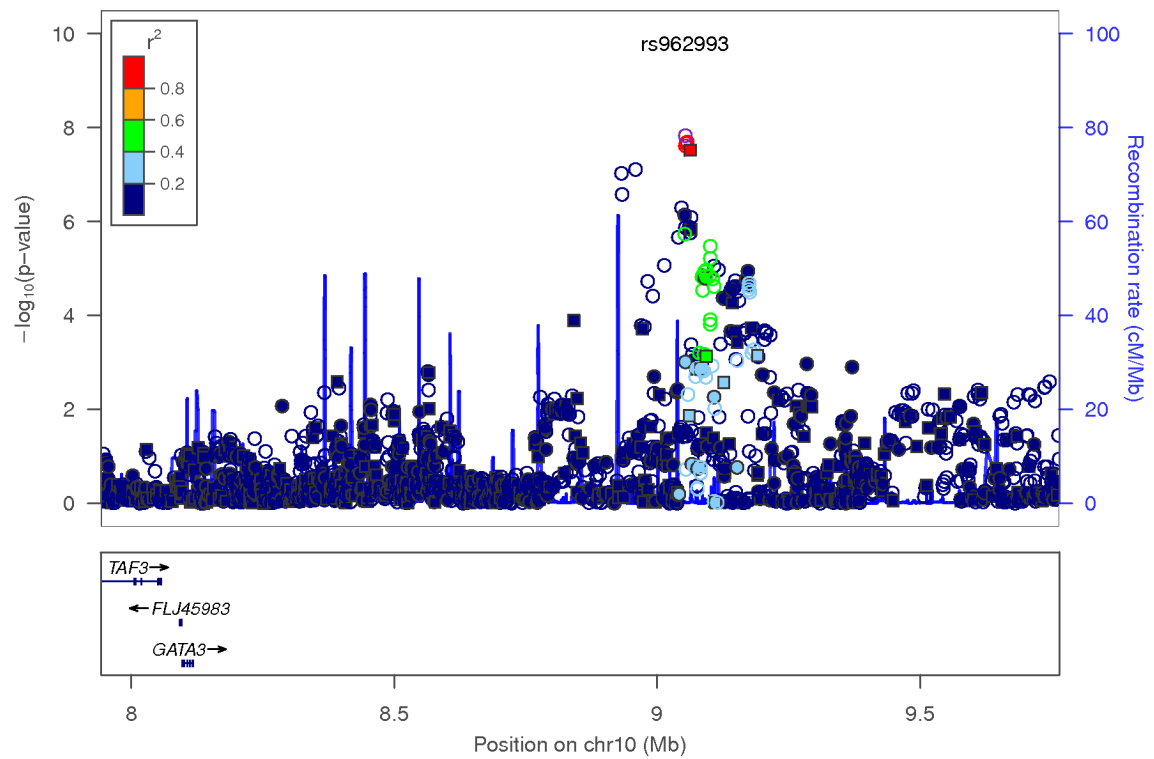
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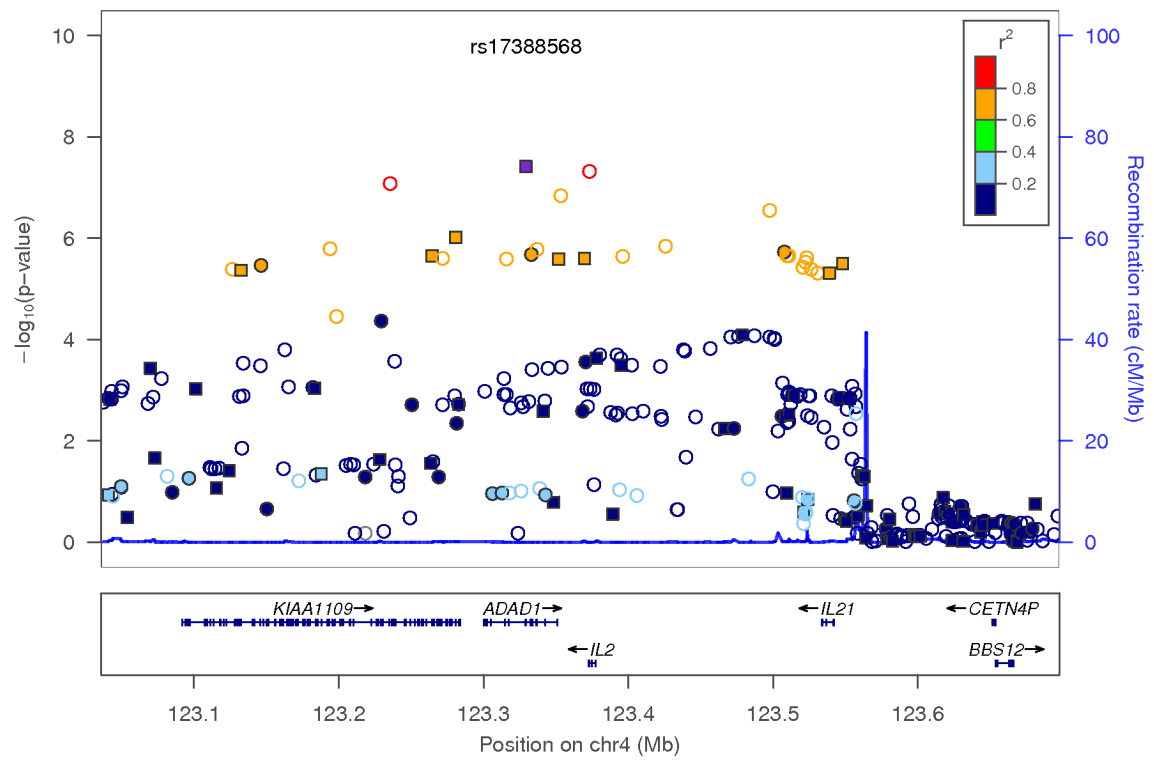
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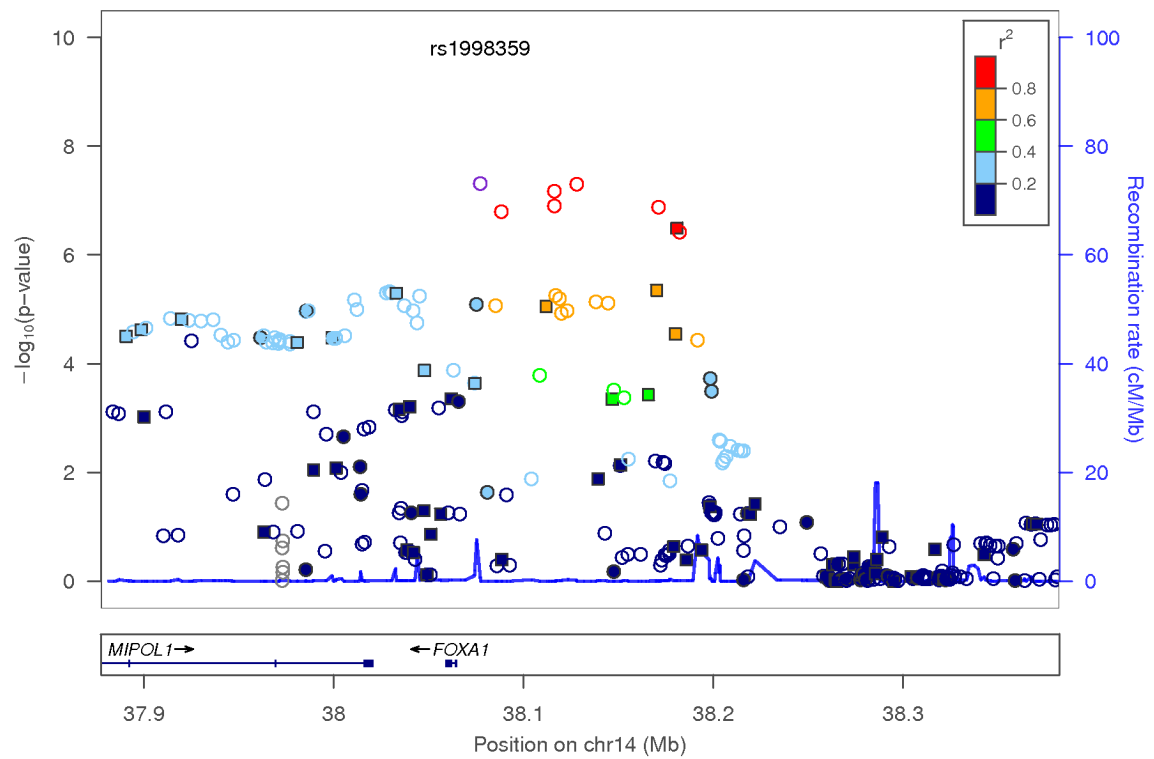
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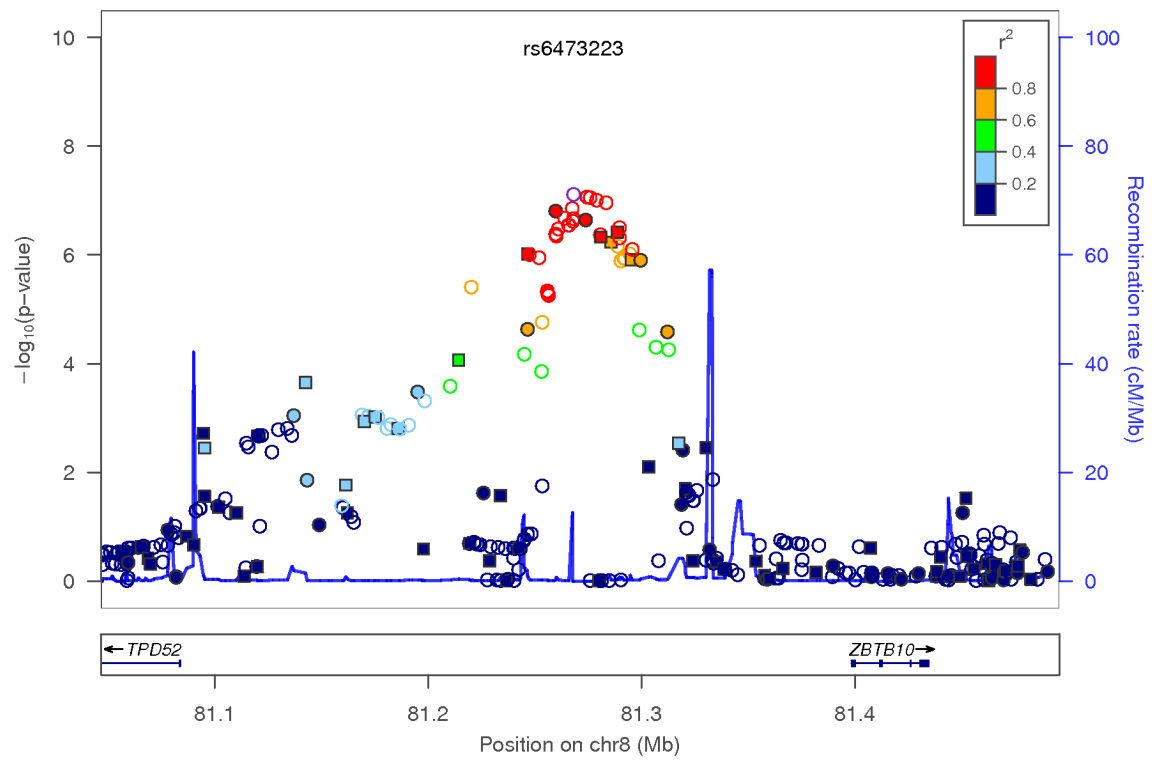
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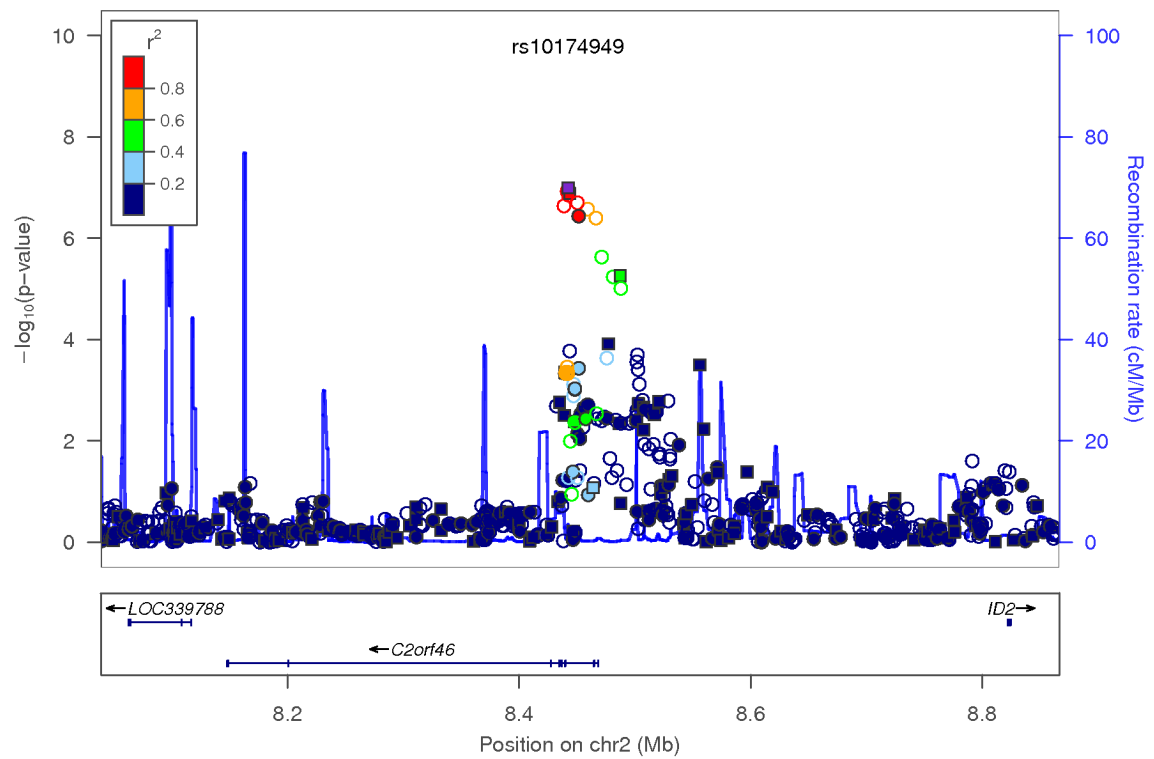
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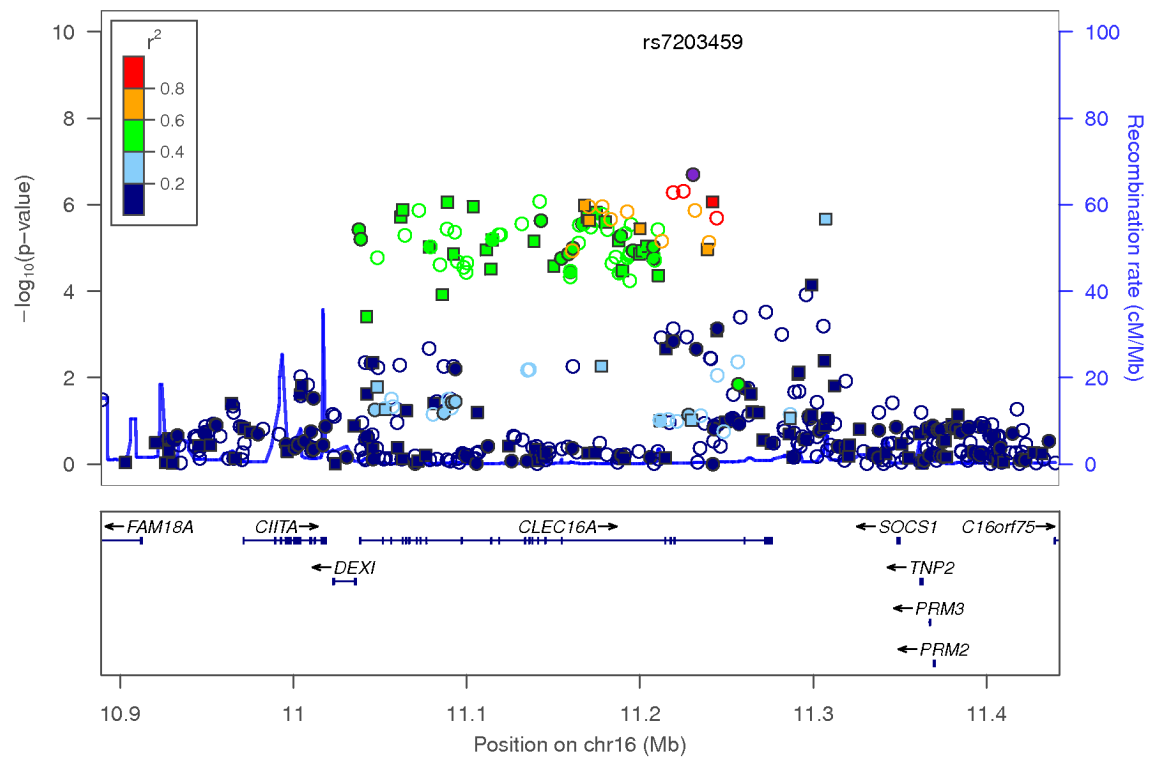
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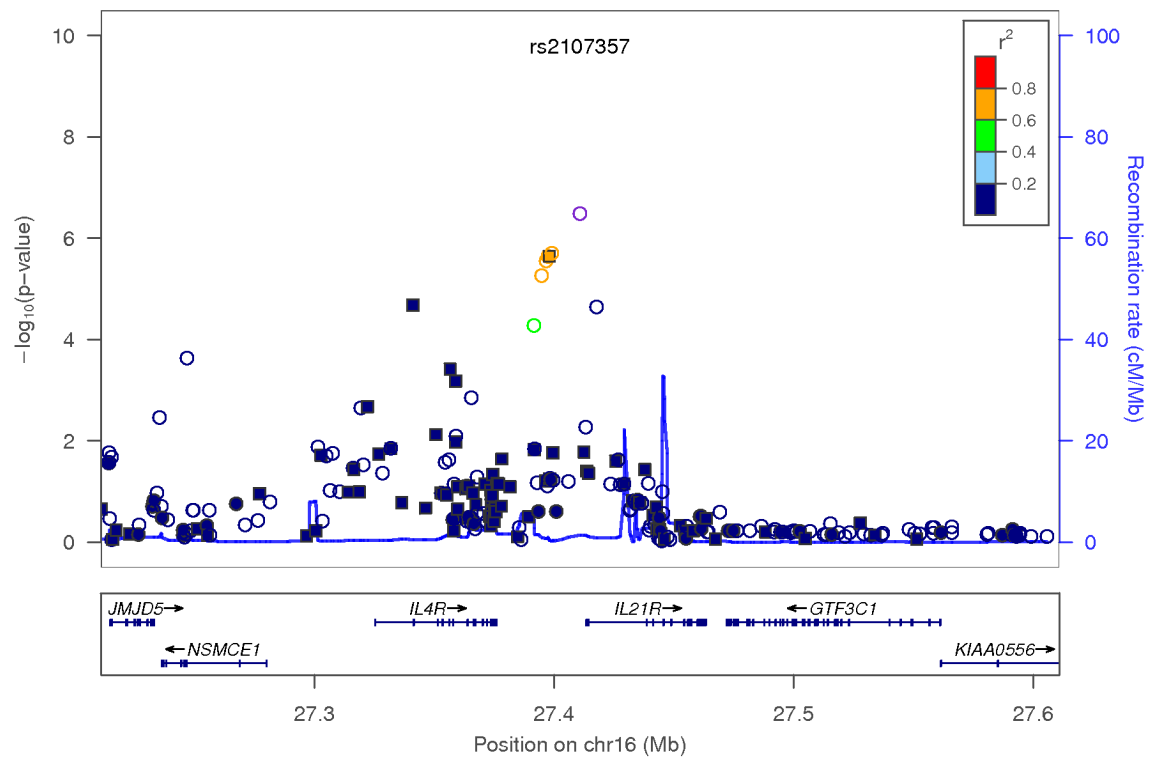
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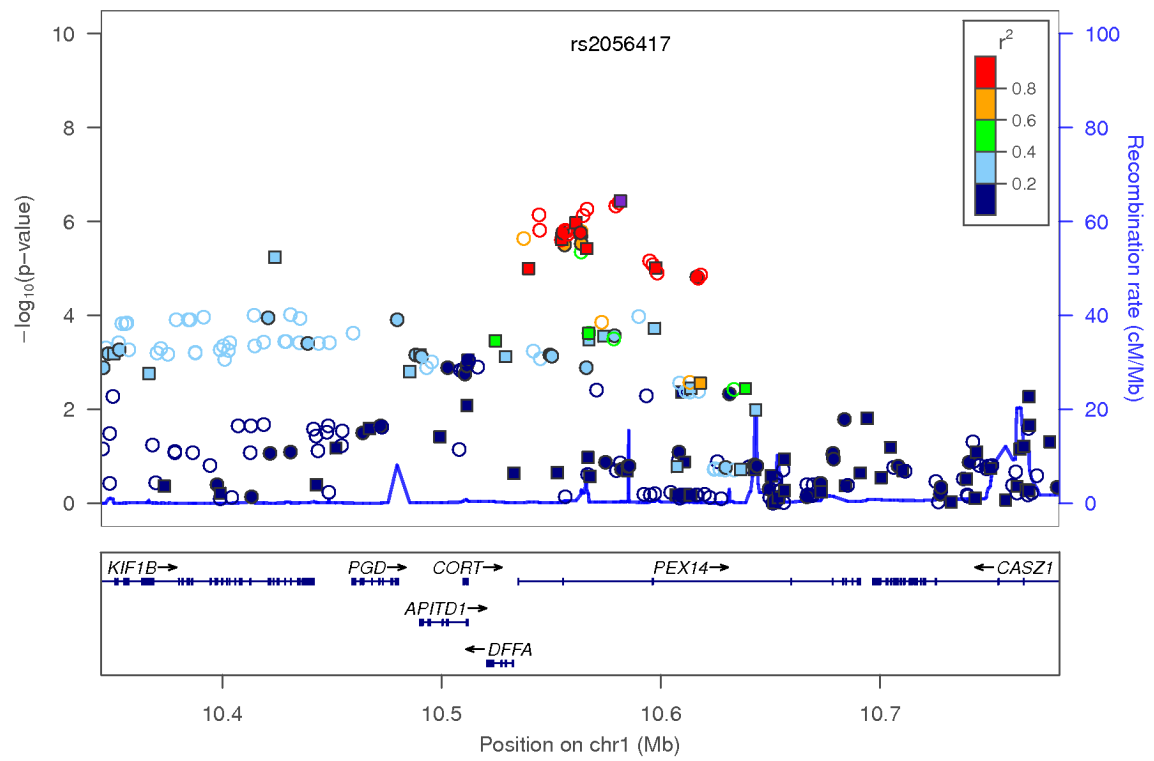
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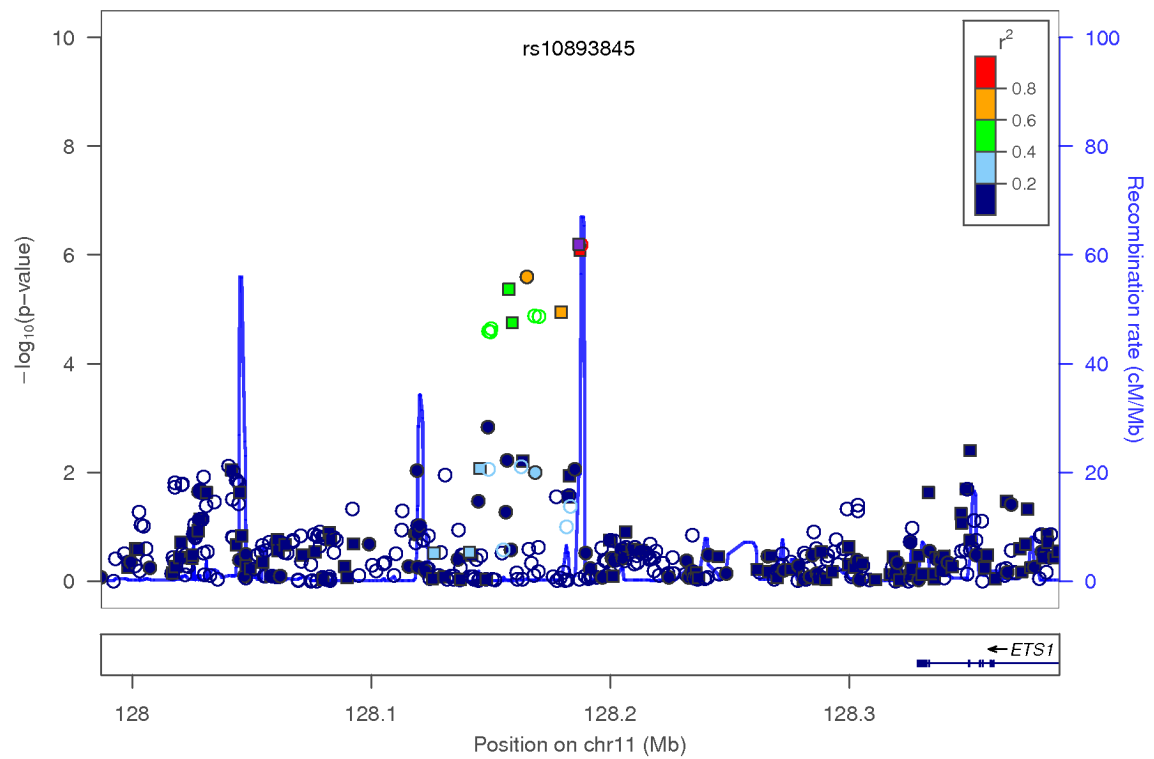
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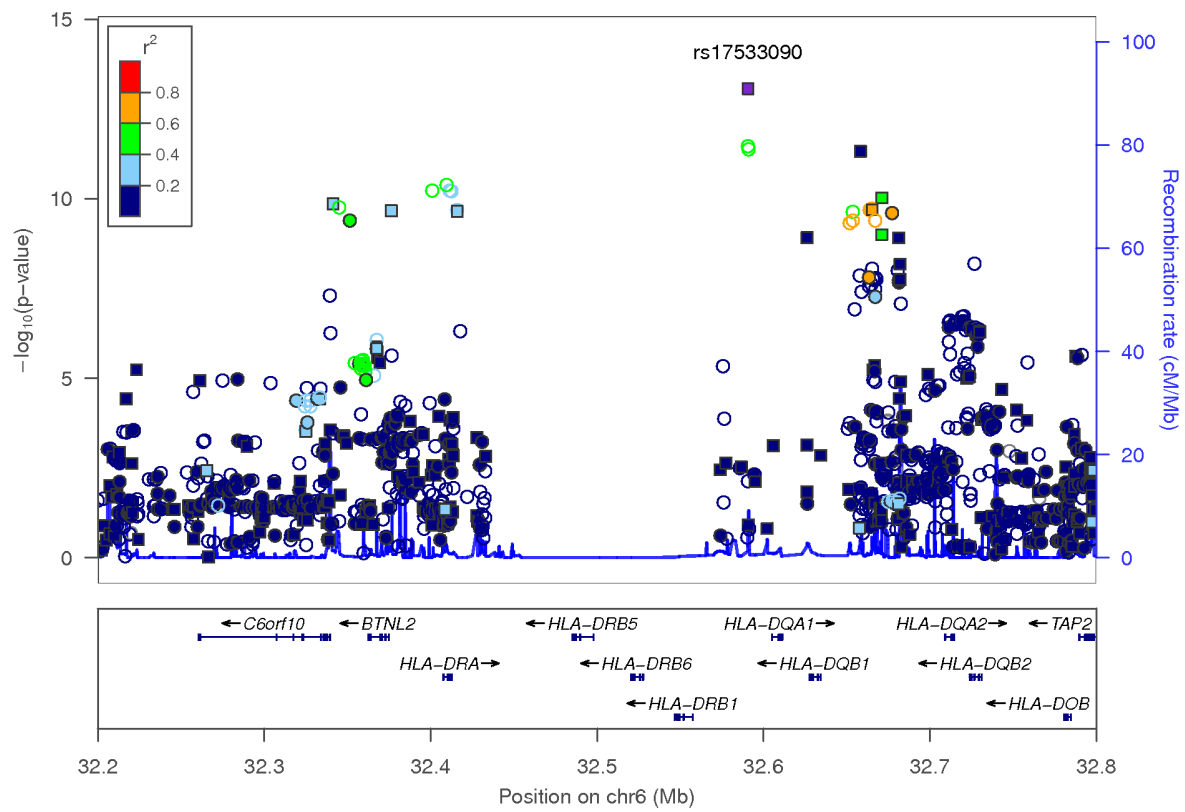
U



V



Supplementary Figure 2. Regional plot of allergy interaction meta-analysis results. Symbol colors indicate linkage disequilibrium with the lead SNP. Open circles indicate imputed variants, filled circles indicate partially genotyped variants, and filled squares indicate fully genotyped variants. Results are in NCBI Build 37 coordinates.



Supplementary Note

23andMe Surveys and Scoring Logic

The following section shows excerpts from the surveys used to define cases and controls for each allergy phenotype in the 23andMe cohort.

Survey: Allergies and Asthma

[Q1] Have you had an allergic reaction to any of the following items?

	Yes	No	I'm not sure
Foods	☐	☐	☐
[Q1a] Plants (including pollen)	☐	☐	☐
[Q1b] Animals (mammals, birds, or insects)	☐	☐	☐
[Q1c] Dust mites	☐	☐	☐
Molds	☐	☐	☐
Latex	☐	☐	☐
Medicines	☐	☐	☐
Vaccines	☐	☐	☐
Something else	☐	☐	☐

[Q2: conditional on Q1a] Have you had an *allergic reaction* to any of the following types of plants?

	Yes	No	I'm not sure
[Q2a] Grasses	☐	☐	☐
[Q2b] Trees	☐	☐	☐
[Q2c] Weeds	☐	☐	☐
Another plant	☐	☐	☐

[Q3: conditional on Q1a] Have you had an allergy test administered by a medical professional which indicated that you are allergic to the following types of plants?

	Yes	No	I'm not sure
[Q3a] Grasses	☐	☐	☐
[Q3b] Trees	☐	☐	☐
[Q3c] Weeds	☐	☐	☐
Another plant	☐	☐	☐

[Q4] Have you had an *allergic reaction* to any of the following types of animals?

	Yes	No	I'm not sure
[Q4a] Cats	☐	☐	☐
Dogs	☐	☐	☐
Honeybees	☐	☐	☐
Red ants	☐	☐	☐
Yellow jackets	☐	☐	☐
Wasps	☐	☐	☐
Another animal	☐	☐	☐

[Q5: conditional on Q4] Have you had an allergy test administered by a medical professional which indicated that you are allergic to the following types of animals?

	Yes	No	I'm not sure
[Q5a] Cats	☐	☐	☐
Dogs	☐	☐	☐
Honeybees	☐	☐	☐
Red ants	☐	☐	☐
Yellow jackets	☐	☐	☐
Wasps	☐	☐	☐
Another animal	☐	☐	☐

[Q6: conditional on Q1c] Have you had an allergy test administered by a medical professional which indicated that you are allergic to the following?

	Yes	No	I'm not sure
Dust mites	☐	☐	☐
Molds	☐	☐	☐
Latex	☐	☐	☐
Medicines	☐	☐	☐
Vaccines	☐	☐	☐
Something else	☐	☐	☐

[Q7: asked separately for each allergen conditional on Q1, Q2, and Q4] What type of reaction did you have after being exposed to [allergen]? Please check all that apply.

- ☐ Abdominal pain or vomiting
- ☐ Diarrhea
- ☐ [Q7a] Difficulty swallowing or difficulty speaking
- ☐ Drop of blood pressure or passing out
- ☐ [Q7b] Hives (red, itchy, or swollen skin)
- ☐ [Q7c] Itching in your mouth
- ☐ [Q7d] Itchy or runny nose
- ☐ Nausea
- ☐ [Q7e] Wheezing or asthma
- ☐ None of the above

Survey: Your Medical History

[Q8] Have you ever been diagnosed by a doctor with one of the following types of *allergies*?

	Yes	No	I'm not sure
[Q8a] Seasonal allergies	☐	☐	☐
Asthma	☐	☐	☐
[Q8b] Environmental (but not seasonal) allergy	☐	☐	☐
Food allergy	☐	☐	☐
Drug allergy	☐	☐	☐

Survey: Asthma

[Q9] Do you currently have allergies?

- ☐ Yes
- ☐ No
- ☐ I'm not sure

Logic for Selecting 23andMe Cases and Controls

Pollen allergy

- Cases were defined by a 'Yes' answer to [Q1a] and one or more of [Q2a], [Q2b] or [Q2c], as well as either a 'Yes' answer to the corresponding [Q3a], [Q3b] or [Q3c], or one or more of [Q7a], [Q7b], [Q7c], [Q7d], or [Q7e].
- Controls were defined by a 'No' answer to [Q1a], or to all of [Q2a], [Q2b], and [Q2c].

Cat allergy

- Cases were defined by a 'Yes' answer to [Q1b] and [Q4a], as well as either a 'Yes' answer to either [Q5a], or one or more of [Q7a], [Q7b], [Q7c], [Q7d], or [Q7e].
- Controls were defined by a 'No' answer to [Q1a], or to all of [Q2a], [Q2b], and [Q2c].

Dust mite allergy

- Cases were defined by a 'Yes' answer to [Q1c], as well as either a 'Yes' answer to [Q6], or one or more of [Q7a], [Q7b], [Q7c], [Q7d], or [Q7e].
- Controls were defined by a 'No' answer to [Q1c].

Additional shared controls for all three allergy phenotypes were then identified, who (1) did not qualify as cases for any allergy phenotype; (2) either responded 'No' to both of [Q8a] and [Q8b], or to [Q9]; and (3) had not responded 'Yes' to any of these questions.

Finally, individuals who were classified as a case for at least one allergy phenotype were classified as controls for other allergy phenotypes for which they were not already classified as cases or controls.

Allergy Symptom Analysis

In this analysis, we reclassified allergy cases and controls based on their responses to symptom question [Q7]. We defined allergic contact dermatitis cases by a positive response to [Q7b]; allergic rhinitis cases by a positive response to [Q7d]; and allergic asthma cases by a positive response to [Q7e], for any allergy type. Controls gave only negative responses for the corresponding symptom.

Suggestive Associations with Allergy

Two of our suggestive associations, in the 8q21.13 and 2p25.1 regions, were strongly replicated in the companion study (Table 4). In the 8q21.13 region, our index SNP rs13275219 falls between *TPD52*, or tumor protein D52, and *ZBTB10*, or zinc finger and BTB domain containing 10. An association in this region (rs7000782, $r^2=0.51$) was tentatively identified in a discovery GWAS for eczema¹⁴ but failed to replicate in that study. In the 2p25.1 region, our index SNP rs10174949 is 350 kb upstream of *ID2*, or inhibitor of DNA binding protein 2, a transcription factor with roles in the differentiation of lymphoid tissue inducer cells, natural killer cells, and other innate lymphoid cell lineages⁷⁴. In a mouse model, *ID2* knockouts show substantially reduced allergic symptoms in a model of allergic rhinitis⁷⁵.

In the 16p13.13 region, variants in strong LD with our index SNP rs725613 have been widely associated with autoimmune disease in genome-wide association studies, including type 1 diabetes⁷⁶, multiple sclerosis⁷⁷, celiac disease³³ and primary biliary cirrhosis⁷⁸. A recent report suggests that the variants identified in these studies modify expression of the nearby *DEXI* gene⁷⁹, which is differentially expressed in lung epithelia in emphysema⁸⁰. An association has also been reported with allergic rhinitis but did not reach genome-wide significance¹⁷.

Among the remaining suggestive associations, in the 16p12.1 region, index SNP rs2107357 falls between T helper cytokine receptor genes *IL4R* and *IL21R*. IL-4 and IL-21 cytokines are associated with differentiation of Th2 and Th17 cell lineages, respectively^{81,82}. In the 11q24.3 region, index SNP rs10893845 is 150 kb downstream of the *ETS1* gene. *ETS1* is a transcription factor known to contribute to Th2 cytokine regulation⁸³, and inhibits differentiation of Th17 cells⁸⁴. Variation in or near *ETS1* has been associated with autoimmune diseases including celiac disease³³, rheumatoid arthritis⁸⁵, and systemic lupus erythematosus⁸⁶ but these variants are not in strong LD with our index SNP. In the 1p36.22 region, our association with rs2056417 in *PEX14*, or peroxisomal biogenesis factor 14, does not have an obvious connection with immune function.

Allergy Loci Previously Associated with Asthma

The 5q22.1 region spanning index SNP rs1438673 includes the *TSLP* (Thymic Stromal Lymphopoietin) gene, which has been described as a master switch for allergic inflammation⁸⁷ responsible for promoting differentiation of pro-inflammatory Th2 cells⁸⁸. In humans, variants in this region are strongly associated with asthma across multiple ethnic groups^{9,10,89}; while our index SNP is in low LD with rs1837253 reported in these studies ($r^2=0.05$), we also see good evidence of association with rs1837253 (meta-analysis $P=2.3\times 10^{-10}$). We see evidence for a secondary peak near *SLC25A46* (rs12659961: meta-analysis $P=1.9\times 10^{-9}$), which is not in LD with rs1438673 ($r^2<0.01$), but is in moderate LD with rs17513503 ($r^2=0.3$), reported to be associated with grass sensitization¹⁷.

In the 11q13.5 region spanning index SNP rs2155219, *LRRC32* (also known as GARP), encodes a protein that mediates the suppressive effects of regulatory T (Treg) cells⁹⁰. Regulatory T cells help suppress responses of Th2 cells to maintain functional tolerance. Patients with IPEX syndrome, which interferes with development of the Treg lineage, develop exaggerated IgE responses and atopic dermatitis⁹¹. This region has been associated with atopic dermatitis¹², asthma¹¹, allergic rhinitis¹⁷, hay fever⁹², ulcerative colitis⁹³ and Crohn's disease⁹⁴.

The 2q12.1 region around rs10189629 includes a cluster of cytokine genes. The *IL1RL1* gene encodes the ST2 receptor, which binds to IL-33, and is thought to be involved in stimulating production of Th2 cell cytokines such as IL-13 that ultimately promote allergic inflammation⁹⁵. SNPs in this region are also significantly associated with both atopic and autoimmune phenotypes, including celiac disease^{25,26}, plasma eosinophil count⁹⁶, asthma^{8,10} and Crohn's disease²⁷.

Near index SNP rs7032572 in the 9p24.1 region, *IL33* encodes a cytokine required for differentiation of Th2 cells, and is an important activator of Th2 and mast cells in response to inflammation⁹⁷. Its receptor, *IL1RL1*, is also a key asthma gene. Variation near *IL33* (rs1342326, $r^2=0.95$) has been previously associated with asthma⁸.

In the 17q12 region near index SNP rs9303280, *GSDMA* (gasdermin) is known to induce apoptosis in gastric pit cells in the stomach⁹⁸, but has also been associated with asthma and

total number of white blood cells in genome-wide association studies^{8,99}. *GSDMA* is also about 40kb away from *ORMDL3*, a gene that has been implicated strongly in asthma¹⁰⁰ and with a number of autoimmune diseases^{91,101,102}. The *ORMDL3* gene product may be involved in intracellular Ca²⁺ signaling¹⁰³. Our index SNP is in moderately strong LD ($r^2 > 0.5$) with the variants previously reported to be associated with asthma in this region^{8,10,100}.

The role of HLA class II genes is to present mainly exogenous peptides primarily to helper T cells, so it is unsurprising that they have frequently been associated with different allergic responses¹⁰⁴. SNPs in this region have been identified in a number of GWAS of immune-system related disorders, including asthma^{8,9}, celiac disease³³, vitiligo³⁴, ulcerative colitis¹⁰⁵, systemic sclerosis¹⁰⁶, multiple sclerosis¹⁰⁷, rheumatoid arthritis¹⁰⁸, systemic lupus erythematosus¹⁰⁹, and selective IgA deficiency¹¹⁰. Our index SNP rs6906021 is in moderate LD ($r^2 = 0.43$) with rs9273349, the lead SNP in the asthma studies^{8,9}.

The *SMAD3* gene encodes a key mediator of transforming growth factor beta (TGF- β) signaling. Variation in *SMAD3* has previously been associated with asthma⁸ and with Crohn's disease³¹. A mouse *SMAD3* knockout leads to an exaggerated asthma phenotype¹¹¹, as well as altered skin sensitization¹¹². Our index SNP rs17228058 is only moderate LD ($r^2 = 0.3$) with asthma association rs744910, but is in nearly complete LD ($r^2 = 0.99$) with the Crohn's association.

Index SNP rs962993 in the 10p14 region is in a gene poor region about 1 mb downstream of *GATA3*, or GATA-binding protein 3. *GATA3* was originally identified as a T cell specific transcription factor and is thought to be a master regulator of Th2 cell differentiation^{113,114}. This region has been associated with asthma in a Japanese cohort⁹; our rs962993 is about 80 kb from the reported SNP, rs10508372, but the two are not in linkage disequilibrium in either Europeans or Asians ($r^2 < 0.01$).

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