

Detection and replication of epistasis influencing transcription in humans

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Abstract

Epistasis is the phenomenon whereby one polymorphism's effect on a trait depends on other polymorphisms present in the genome. The extent to which epistasis influences complex traits¹ and contributes to their variation^{2,3} is a fundamental question in evolution and human genetics. Though epistasis has been demonstrated in artificial gene manipulation studies in model organisms,^{4,5} and some examples have been reported in other species,⁶ few convincing examples exist for epistasis amongst natural polymorphisms in human traits.^{7,8} Its absence from empirical findings may simply be due to its low incidence in the genetic control of complex traits,^{2,3} but an alternative view is that it has previously been too technically challenging to detect due to statistical power and computational issues.⁹ Here we show that, using advanced computation techniques¹⁰ and a gene expression study design, many instances of epistasis are found between common single nucleotide polymorphisms (SNPs). In a cohort of 846 individuals with data on 7339 gene expression levels in whole blood, we found 501 significant pairwise epistatic interactions between common SNPs acting on the expression levels of 238 genes ($p < 2.91 \times 10^{-16}$). We tested the discovery interactions for replication in two independent data sets.^{11,12} Three hundred and forty-five interactions had replication interaction p -values that were more extreme than the 2.5% confidence interval of the distribution under the null hypothesis of no epistasis, with 30 significant at a conservative $p < 0.05$ Bonferroni level. There was evidence of functional enrichment for the interacting SNPs, for instance 44 of the genetic interactions are located within 2Mb of regions of known intra-cellular chromosome interactions¹³ ($p = 1.8 \times 10^{-10}$). Epistatic networks of three SNPs or more influence the expression levels of 129 genes, whereby one *cis*-acting SNP is modulated by several *trans*-acting SNPs. For example MBNL1 is influenced by an additive effect at rs13069559 which itself is masked by *trans*-SNPs on 14 different chromosomes, with nearly identical genotype-phenotype (GP) maps for each *cis-trans* interaction. This study presents the first evidence for multiple instances of epistatic genetic effects emerging from natural genetic variation in humans.

1 Main text

In the genetic analysis of complex traits it is usual for SNP effects to be estimated using an additive model where they are assumed to contribute independently and cumulatively to the mean of a trait. This framework has been successful in identifying thousands of associations,¹⁴ but to date there is little empirical exploration of the role that epistasis plays in the architecture of complex traits in humans,^{7,8} though its contribution to phenotypic variance is frequently the subject of debate.¹⁻³ Outside the prism of human association studies there is evidence for epistasis, not only at the molecular scale from artificially induced mutations⁴ but also at the evolutionary scale in fitness adaptation¹⁵ and speciation.¹⁶

Methods are now available to overcome the computational problems involved in searching for epistasis, but its detection still remains problematic due to re-

duced statistical power. For example increased dependence on linkage disequilibrium (LD) between causal SNPs and observed SNPs,^{17,18} increased model complexity in fitting interaction terms,¹⁹ and more extreme significance thresholds to account for increased multiple testing⁹ all make it more difficult to detect epistasis in comparison to additive effects. When genetic effect sizes are small, as is expected in most complex traits of interest,¹⁴ the power to detect epistasis diminishes rapidly. There are two simple ways to overcome this problem. One is by using extremely large sample sizes;²⁰ another is by analysing traits that are likely to have large effect sizes. Because our focus was to ascertain the extent to which instances of epistasis occur amongst natural genetic variation we designed a study around the latter approach and searched for epistatic genetic effects that influence gene expression levels. Transcription levels can be measured for thousands of genes. These traits are largely heritable but on average less polygenic than high level phenotypes,²¹ thus it is expected that many genetic effects will be relatively large, maximising the chance at detecting epistasis, should it exist.

In our discovery dataset (Brisbane Systems Genetics Study, BSGS²²) of 846 individuals genotyped at 528,509 SNPs, we exhaustively tested every pair of SNPs for genetic interactions against each of 7339 expression traits in whole blood. After stringent filtering and multiple testing correction (Methods) we identified 501 putative genetic interactions influencing the expression levels of 238 genes. Of the 501 discovery interactions, 434 had available data and passed filtering (Methods) in two independent replication datasets, Fehrman¹² and the Estonian Genomics Centre University of Tartu (EGCUT),¹¹ in which we saw convincing evidence for replication. We used the summary statistics from the replication datasets to perform a meta analysis to obtain an independent p -value for the putative interactions, and 30 were significant after applying a Bonferroni correction for multiple testing (Table 1). These significant interactions exhibited remarkable similarity in GP maps between all three datasets (Figure 2).

In addition, we observed that 316 of the remaining 404 discovery SNPs had replication interaction p -values exceeding the one-tailed 2.5% confidence interval under the null distribution of no effects ($p \ll 1.0 \times 10^{-16}$, Figure 3 and Supplementary Figure S1). The congruence of the epistatic networks in discovery and replication datasets is shown in Figure 1, demonstrating that these complex genetic patterns are common even across independent datasets. A further replication was attempted using the Centre for Health Discovery and Wellbeing (CHDWB) dataset,²³ but only 185 of the SNP pairs passed filtering because the sample size was small ($n = 139$), and likely due to insufficient power we found no evidence for replication. It should be noted that although it is a necessary step to establish the veracity of the signals from the discovery set, replication of epistasis is theoretically difficult because the dependence on LD between observed SNPs and causal variants is up to four orders of magnitude higher than it is for independent additive effects.^{17,18} Therefore these results are encouraging with regards to the detection and replication of epistasis.

Though seldom the focus of association studies, SNPs with known main effects are often tested for additive \times additive genetic interactions,⁹ but our analysis shows that this is unlikely to be the most effective strategy for its detec-

tion. The majority of our discovery interactions comprised of one SNP that was significantly associated with the gene expression level in the discovery dataset, and one SNP that had no previous association²¹ (439 out of 501, Methods). Only nine interactions were between SNPs that both had known main effects while 64 were between SNPs that had no known main effects. Additionally, we observed that the largest epistatic variance component for the 501 interactions was equally divided amongst additive \times additive, additive \times dominance, dominance \times additive and dominance \times dominance ($p = 0.22$ for departure from expectation). This is not surprising because the patterns of epistasis used for statistical decomposition are not designed to resemble biological function.²⁴

Of the discovery interactions, 47 were *cis-cis* acting (both SNPs were on the same chromosome as the expression gene), 441 were *cis-trans*-acting, and 13 were *trans-trans*-acting. We observed a wide range of significant GP maps (Figure 2) but the most common pattern of epistasis that we detected involved a *trans*-SNP masking the effect of an additive *cis*-SNP. For example, MBNL1 (involved in RNA modification and regulation of splicing²⁵) has a *cis* effect at rs13069559 which in turn is controlled by 13 *trans*-SNPs and one *cis*-SNP that each exhibit a masking pattern, such that when the *trans*-SNP is homozygous for the masking allele the decreasing allele of the *cis*-SNP no longer has an effect (Supplementary Figure S5). Each of these interactions have evidence for replication in at least one dataset and six are significant at the Bonferroni level (Supplementary Figure S2). We see similar epistatic networks involving multiple *trans*-acting SNPs for other gene expression levels too, for example TMEM149 (Supplementary Figure S6), NAPRT1 (Supplementary Figure S7), TRAPPC5 (Supplementary Figure S8), and CAST (Supplementary Figure S9).

In total the 501 interactions comprised 781 unique SNPs, which we analysed for functional enrichment (Methods). We tested the SNPs for cell-type specific overlap with transcriptionally active chromatin regions, tagged by histone-3-lysine-4,3-methylation (H3K4me3) chromatin marks, in 34 cell types²⁶ (Supplementary Figure S4). There was significant enrichment for *cis*-acting SNPs in haematopoietic cell types only ($p < 1 \times 10^{-4}$ for the three tissues with the strongest enrichment after adjusting for multiple testing). However *trans*-acting SNPs did not show any tissue specific enrichment ($p > 0.1$ for all tissues). This difference between *cis* and *trans* SNPs suggests different roles in which epistasis might arise where the *cis*-SNPs provide tissue specificity in these interactions. There is also strong enrichment for SNPs to be localised in enhancer regions,²⁷ consistent for both *cis* and *trans* SNPs ($p < 1 \times 10^{-6}$).

We also demonstrate spacial organisation of interacting loci suggesting a mechanism by which biological function can lead to epistatic genetic variance. It has been shown that different chromosomal regions spatially colocalise in the cell through chromatin interactions.¹³ We cross-referenced our epistatic SNPs with a map of chromosome interacting regions ($n = 96, 139$) in K562 blood cell lines²⁸ (Methods) and found that 44 epistatic interactions mapped to within 2Mb ($p < 1.8 \times 10^{-10}$), (Supplementary Figure S10). Interaction of distant loci may occur through physical proximity in transcriptional factories that organise across different chromosome regions and can regulate transcription of related

genes.^{29,30}

Though we present many instances of epistasis, quantifying its relative importance to complex traits in humans remains an open question. In this study we are able to identify 238 gene expression traits with at least one significant interaction given our experiment-wide threshold. How does this compare to the number of traits influenced by additive effects? The BSGS dataset has been previously analysed for additive effects at all expression traits,²² and if we take all the additive eQTLs that were significant at the epistatic threshold of $p < 2.91 \times 10^{-16}$ we find that 453 gene expression levels out of the 7339 analysed had at least one significant expression quantitative trait locus (eQTL). Therefore it can be argued that the number of instances of detectable epistasis are substantial.

However in terms of their contribution to complex traits a more important metric might be the proportion of the variance that the epistatic loci explain.² Ideally one would approach this question from a whole genome perspective³¹ but this is intractable for non-additive variance components. Nevertheless, some inference can be made from the ascertained effects in these analyses and it is evident that additive variance is overall a larger component than epistatic variance, as has been argued previously.^{2,3} Taking the additive effects detected in Powell *et al* (2012) at the $p < 2.91 \times 10^{-16}$ threshold, we calculate that on average they explain 1.73% of the phenotypic variance of each of the 7339 probes. By contrast, the epistatic variance from the interacting SNPs detected in this study on average explain 0.25% of phenotypic variance, approximately seven times lower than the additive variance (Methods). There are several caveats to this comparison. Firstly, the ratio of additive to epistatic variance may differ at different effect sizes, and our estimate is determined by the threshold used. Secondly, the power of a 1 *d.f.* test exceeds that of an 8 *d.f.* test. And thirdly, the non-additive variance at causal variants is expected to be underestimated by observed SNPs in comparison to estimates for additive variance, due to differences in the rate of decay of the estimate of the genetic variance of the causal SNPs as LD decreases with the observed SNPs.

Overall, we have demonstrated that it is possible to identify and replicate epistasis in complex traits amongst common human variants. The functional analysis of the significant epistatic loci suggests that there are a large number of possible mechanisms that can lead to non-additive genetic variation. Further research into such epistatic effects may provide a useful portal to understanding molecular mechanisms and complex trait variation with greater clarity. With computational techniques and data now widely available the search for epistasis in larger datasets for traits of broader interest is warranted.

1.1 Methods Summary

We searched for pairwise epistasis exhaustively in the BSGS discovery dataset,²² which comprises 846 individuals who are genotyped at 528,509 autosomal SNPs and who have gene expression levels measured in whole blood samples for 7,339 probes representing 6,158 RefSeq genes. Recent hardware and software¹⁰ ad-

vances made it possible to perform the 1.03×10^{15} statistical tests to complete this analysis. We used permutation analysis³² to calculate an experiment-wide significance threshold of $T_e = 2.91 \times 10^{-16}$ at the 5% family-wise error rate (FWER). SNP pairs were modelled for full genetic effects, including marginal additive and dominance at both SNPs plus four interaction terms. Though we could have used a less complex model to improve statistical efficiency, we deemed it important to be agnostic about the type of epistasis that might exist, and therefore chose not to over-parameterise the test.^{18,19} Because there are many large marginal effects present in these data it was necessary to perform several filtering steps to exclude SNP pairs that were significant due to marginal effects alone. All SNP pairs with LD $r^2 > 0.1$ and $D'^2 > 0.1$ were removed to minimise the possibility of haplotype effects. All SNP pairs were required to have at least five data points in all nine genotype classes. If multiple SNP pairs were present on the same chromosomes for a particular expression trait then only the sentinel SNP pair was retained. Finally, a nested test contrasting the full genetic model against the marginal additive and dominance model was performed for each remaining SNP pair (Methods), resulting in 501 significant interactions after Bonferroni correction for multiple testing of the filtered SNPs. The significant SNP pairs were carried forward for replication in two independent datasets that used the same expression assays for analysing transcription in whole blood, the Fehrman dataset¹² ($n = 1240$) and the Estonian Genome Centre University of the University of Tartu (EGCUT) dataset¹¹ ($n = 891$). Of these, 434 passed filtering in both replication datasets. A meta analysis on the interaction p -values from each replication dataset was performed to provide an overall replication statistic for each putative interaction.

1.2 Acknowledgements

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2 Tables

Table 1: Epistatic interactions significant at the Bonferroni level in two replication sets

	Gene (chr.)	SNP 1 (chr.)	SNP 2 (chr.)	BSGS ²	Fehrmann ³	EGCUT ³	Meta ⁴
1	ADK (10)	rs2395095 (10)	rs10824092 (10)	6.69 ¹	18.33 ¹	21.21 ¹	39.82 ¹
2	ATP13A1 (19)	rs4284750 (19)	rs873870 (19)	5.30	12.18	3.25	14.23
3	C21ORF57 (21)	rs9978658 (21)	rs11701361 (21)	9.42	6.08	16.36	21.67
4	CSTB (21)	rs9979356 (21)	rs3761385 (21)	11.99	25.20	16.72	42.27
5	CTSC (11)	rs7930237 (11)	rs556895 (11)	7.16	18.76	15.06	33.53
6	FN3KRP (17)	rs898095 (17)	rs9892064 (17)	16.16	28.24	29.39	59.95
7	GAA (17)	rs11150847 (17)	rs12602462 (17)	13.91	19.98	12.99	32.60
8	HNRPH1 (5)	rs6894268 (5)	rs4700810 (5)	15.38	8.55	3.01	10.37
9	LAX1 (1)	rs1891432 (1)	rs10900520 (1)	19.16	18.60	11.22	29.24
10	MBNL1 (3)	rs16864367 (3)	rs13079208 (3)	13.49	16.25	24.74	41.56
11	MBNL1 (3)	rs7710738 (5)	rs13069559 (3)	7.92	2.55	7.89	9.28
12	MBNL1 (3)	rs2030926 (6)	rs13069559 (3)	7.10	0.91	5.80	5.53
13	MBNL1 (3)	rs2614467 (14)	rs13069559 (3)	5.74	4.13	2.22	5.30
14	MBNL1 (3)	rs218671 (17)	rs13069559 (3)	7.63	0.62	5.82	5.23
15	MBNL1 (3)	rs11981513 (7)	rs13069559 (3)	7.71	0.43	5.36	4.58
16	MBP (18)	rs8092433 (18)	rs4890876 (18)	5.40	7.06	21.91	28.73
17	NAPRT1 (8)	rs2123758 (8)	rs3889129 (8)	8.45	15.12	16.08	30.77
18	NCL (2)	rs7563453 (2)	rs4973397 (2)	7.31	7.51	6.33	12.70
19	PRMT2 (21)	rs2839372 (21)	rs11701058 (21)	4.81	0.69	4.47	4.06
20	RPL13 (16)	rs352935 (16)	rs2965817 (16)	4.98	3.79	14.41	17.24
21	SNORD14A (11)	rs2634462 (11)	rs6486334 (11)	7.31	13.11	10.96	23.22
22	TMEM149 (19)	rs807491 (19)	rs7254601 (19)	12.16	81.55	45.78	145.78
23	TMEM149 (19)	rs8106959 (19)	rs6926382 (6)	5.80	3.06	8.80	10.72
24	TMEM149 (19)	rs8106959 (19)	rs914940 (1)	6.22	3.36	6.96	9.20
25	TMEM149 (19)	rs8106959 (19)	rs2351458 (4)	7.30	0.04	9.61	8.00
26	TMEM149 (19)	rs8106959 (19)	rs6718480 (2)	8.55	3.31	5.15	7.36
27	TMEM149 (19)	rs8106959 (19)	rs1843357 (8)	6.21	3.72	3.33	6.00
28	TMEM149 (19)	rs8106959 (19)	rs9509428 (13)	9.44	0.10	5.75	4.47
29	TRA2A (7)	rs7776572 (7)	rs11770192 (7)	8.23	3.19	1.89	4.09
30	VASP (19)	rs1264226 (19)	rs2276470 (19)	5.09	0.94	5.14	4.95

¹ $-\log_{10} p$ -values for 4 *d.f.* interaction tests

² Discovery dataset

³ Independent replication dataset

⁴ Meta analysis of interaction terms between replication datasets only

3 Figures

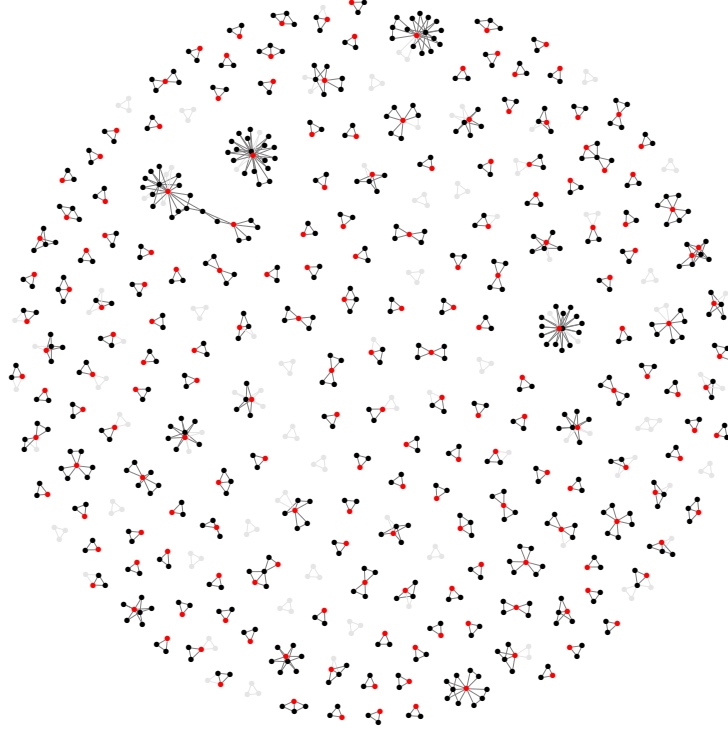


Figure 1: **Discovery and replication of epistatic networks** All 434 putative genetic interactions (edges) with data common to discovery and replication sets is shown, where black nodes represent SNPs and red nodes represent traits (gene expression probes). Three hundred and forty-five interactions had p -values exceeding the 2.5% confidence interval following meta analysis of the replication data, but the remaining 89 interactions that did not replicate are depicted in grey. It is evident that a large proportion of the complex networks identified in the discovery set also exist in independent populations.

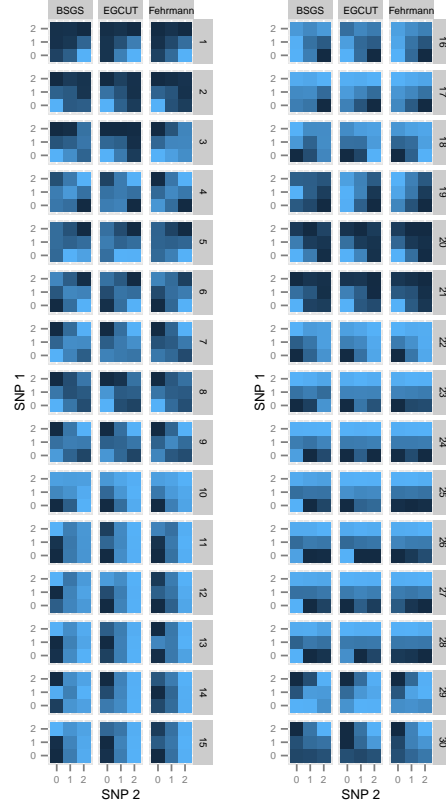


Figure 2: Replication of GP maps in two independent populations The GP maps for each epistatic interaction that is significant at the Bonferroni level in both replication datasets are shown. Each GP map consists of nine tiles where each tile represents the expression level for that two-locus genotype class. Phenotypes are for gene transcript levels (dark coloured tiles = low expression, light coloured tiles = high expression). Columns of GP maps are for each independent population. Rows of GP maps are for each of 30 significantly replicated interactions at the Bonferroni level, corresponding to the rows in Table 1. There is a clear trend of the GP maps replicating across all three datasets.

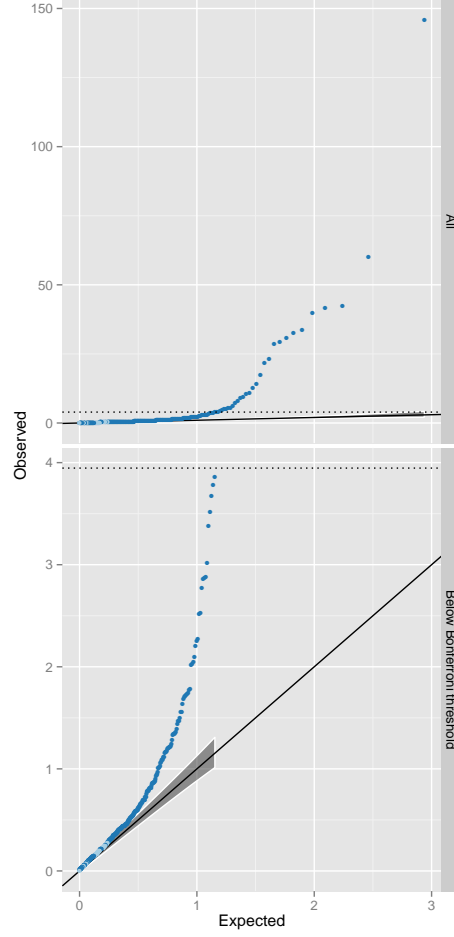


Figure 3: **Q-Q plots of interaction p -values from replication datasets** The top panel shows all 434 discovery SNPs that were tested for interactions. Observed p -values (y -axis, $-\log_{10}$ scale) are plotted against the expected p -values (x -axis, $-\log_{10}$ scale). The multiple testing correction threshold for significance following Bonferroni correction is denoted by a dotted line. The bottom panel shows the same data as the top panel but excluding the 30 interactions that were significant at the Bonferroni level in the replication datasets. The shaded grey area represents the 5% confidence interval for the expected distribution of p -values. Dark blue points represent p -values that exceed the confidence interval, light blue are within the confidence interval.

4 Supplementary Figures

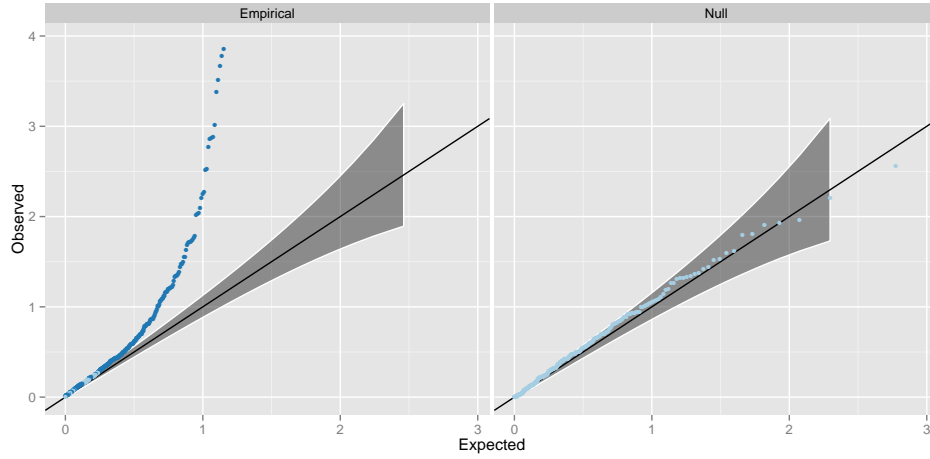


Figure S1: **Q-Q plots of interaction p -values from replication datasets, excluding the 30 points significant at the Bonferroni level** The right panel (Null) shows the interaction p -values from a meta analysis across two independent datasets on 434 randomly drawn SNP pairs. The left panel (Empirical) shows the interaction p -values from the 404 putative interactions that were not significant at the Bonferroni correction threshold. Dark blue points represent p -values that surpass the 2.5% FDR level, as in Figure 3.

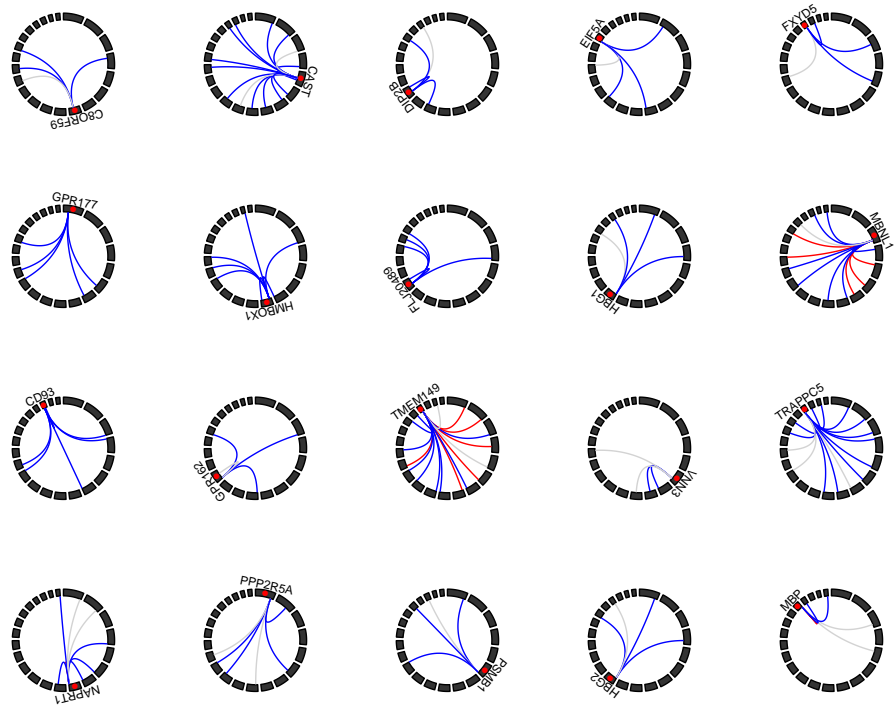


Figure S2: **Gene expression traits with four or more genetic interactions** Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent no evidence for replication, blue lines denote interactions that are outside the 97.5% confidence interval or the Q-Q plot (Figure 3), and red lines denote replication at the Bonferroni correction level. Most interactions are characterised as being *cis-trans* to the expression probe.

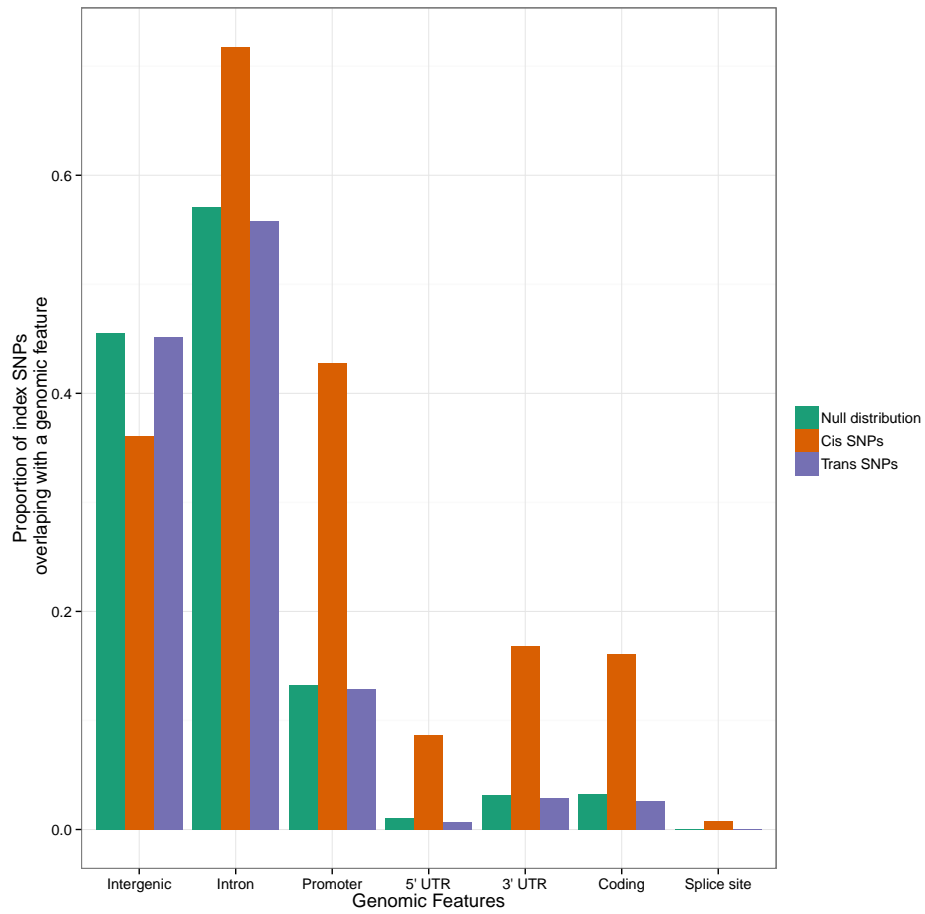


Figure S3: Location of SNPs relative to genomic features All SNPs within 1kb and $r^2 > 0.8$ of each *cis*- and *trans*-SNP were taken to find which genomic features (*x*-axis) were covered by the SNPs that compose the 501 significant interactions. Green bars represent the proportion (*y*-axis) of the 528,509 SNPs used in the analysis that fall within the range of the different genomic features. There is enrichment for *cis*-acting SNPs (red bars) in promotor regions, but *trans*-acting SNPs (blue bars) are not enriched for genomic features.

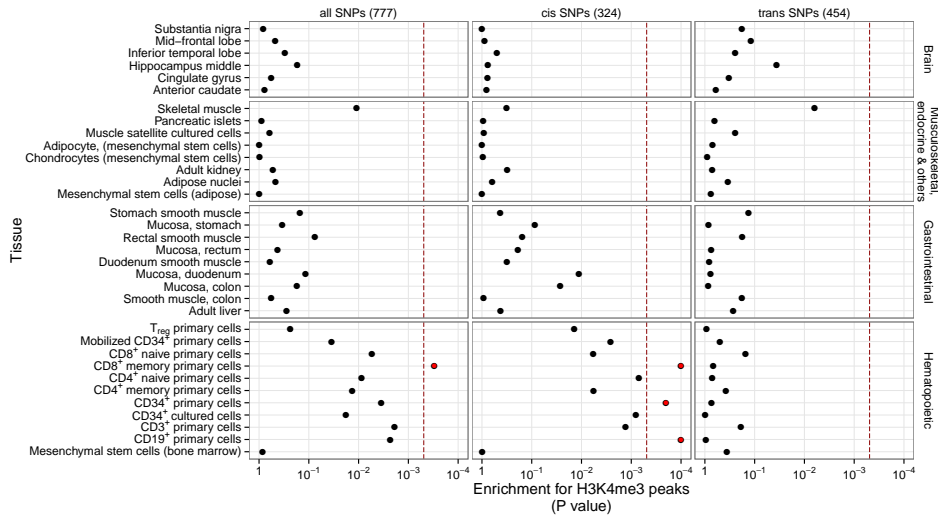


Figure S4: Tissue specific enrichment of SNPs in transcriptionally active regions The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3.²⁶ Enrichment p -values are calculated using permutation analysis for 34 different cell types (y -axis) in four tissue types (Rows of boxes). There is enrichment for *cis*-acting SNPs in Haematopoietic tissue types only. *Trans*-acting SNPs have no tissue specificity.

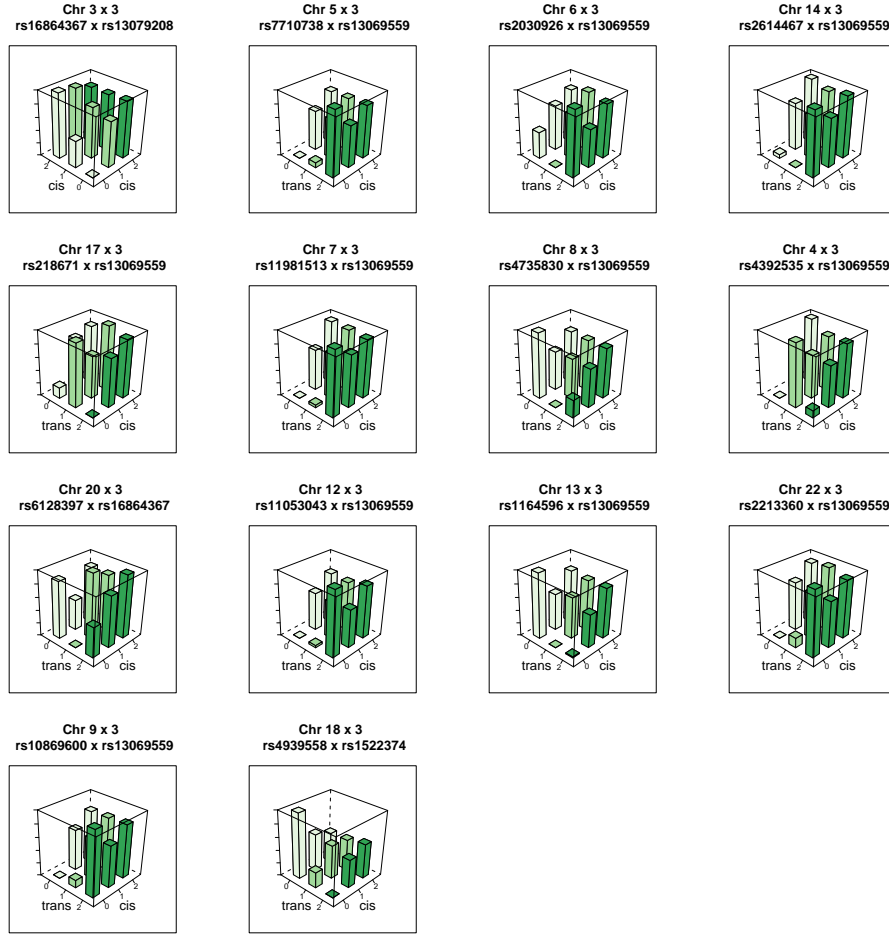


Figure S5: **Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous.

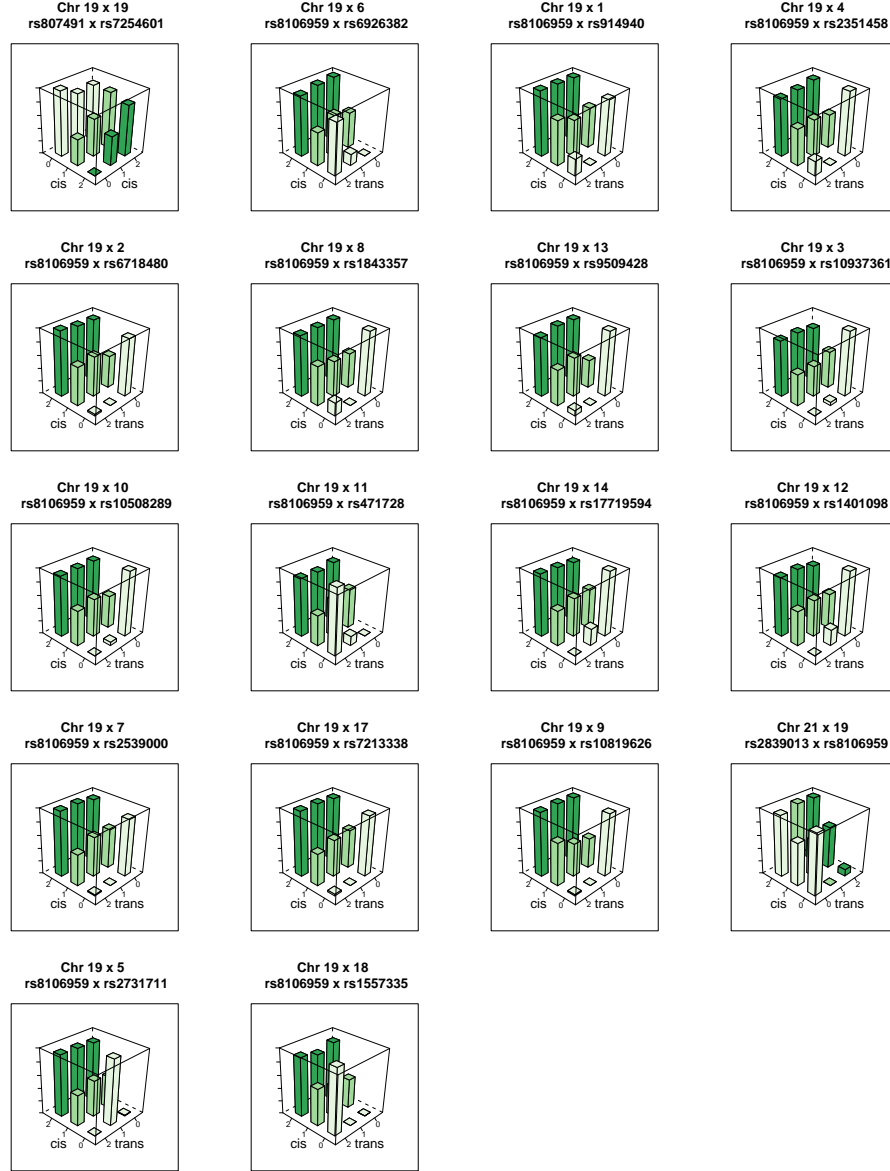


Figure S6: **Genotype-phenotype maps for 19 interactions influencing the expression of TMEM149** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of TMEM149, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous.

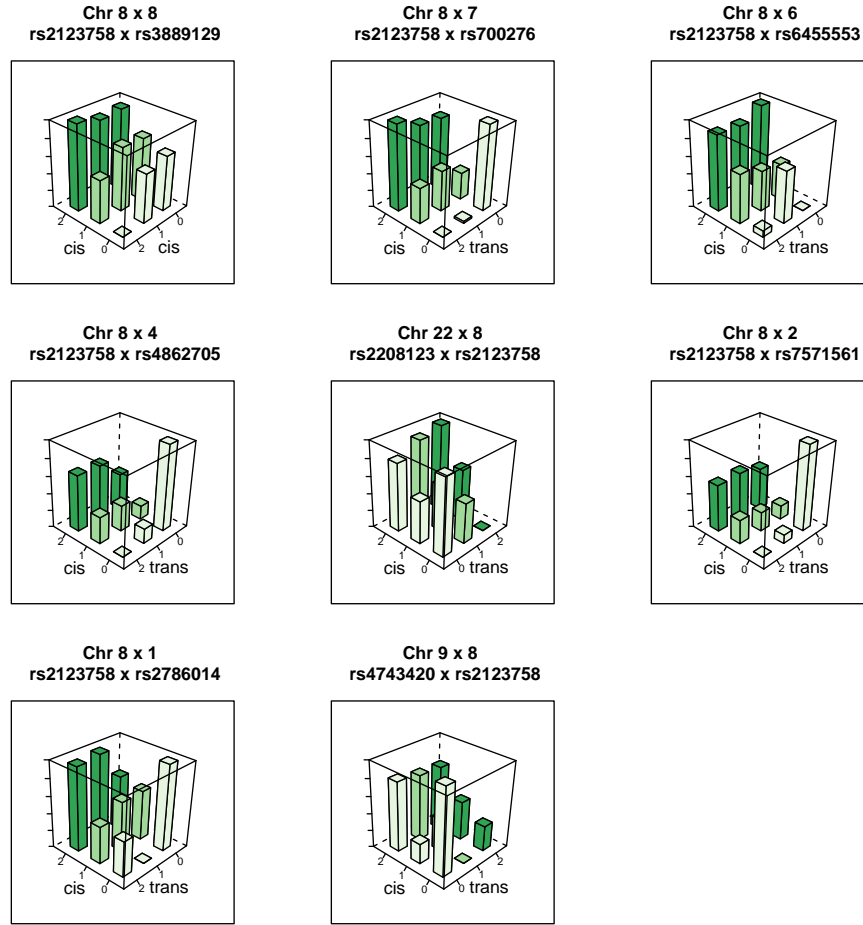


Figure S7: **Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1** Each bar represents the mean phenotypic value for individuals in that genotype class.

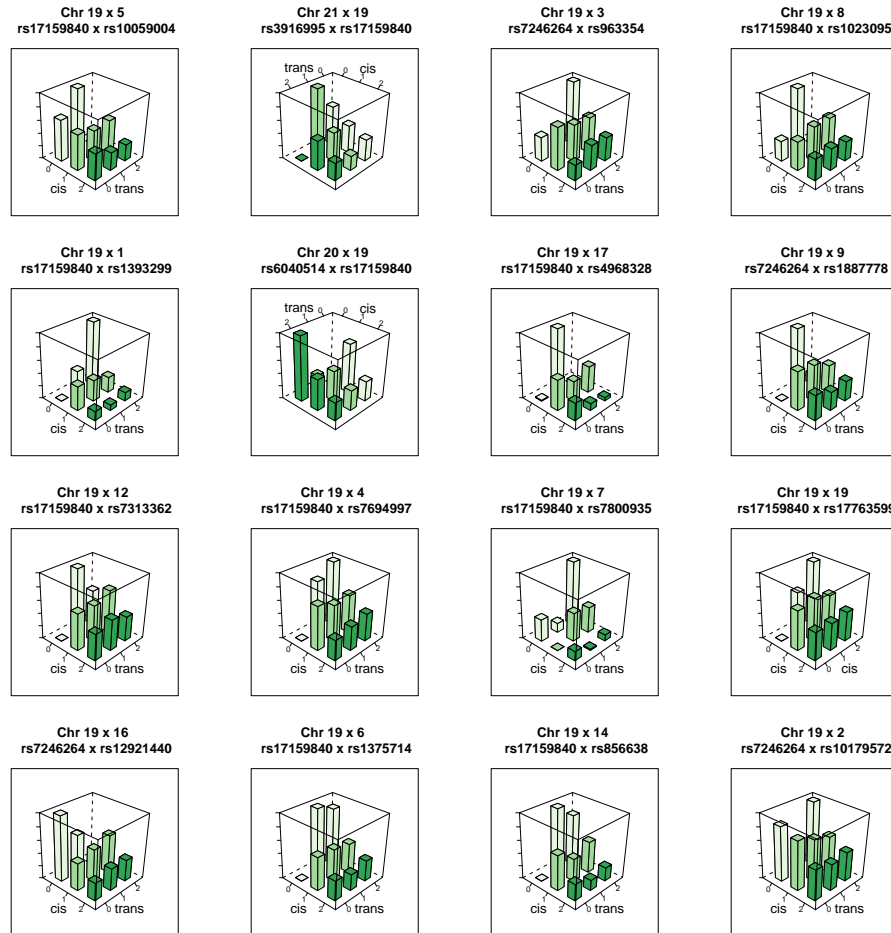


Figure S8: **Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5** Each bar represents the mean phenotypic value for individuals in that genotype class.

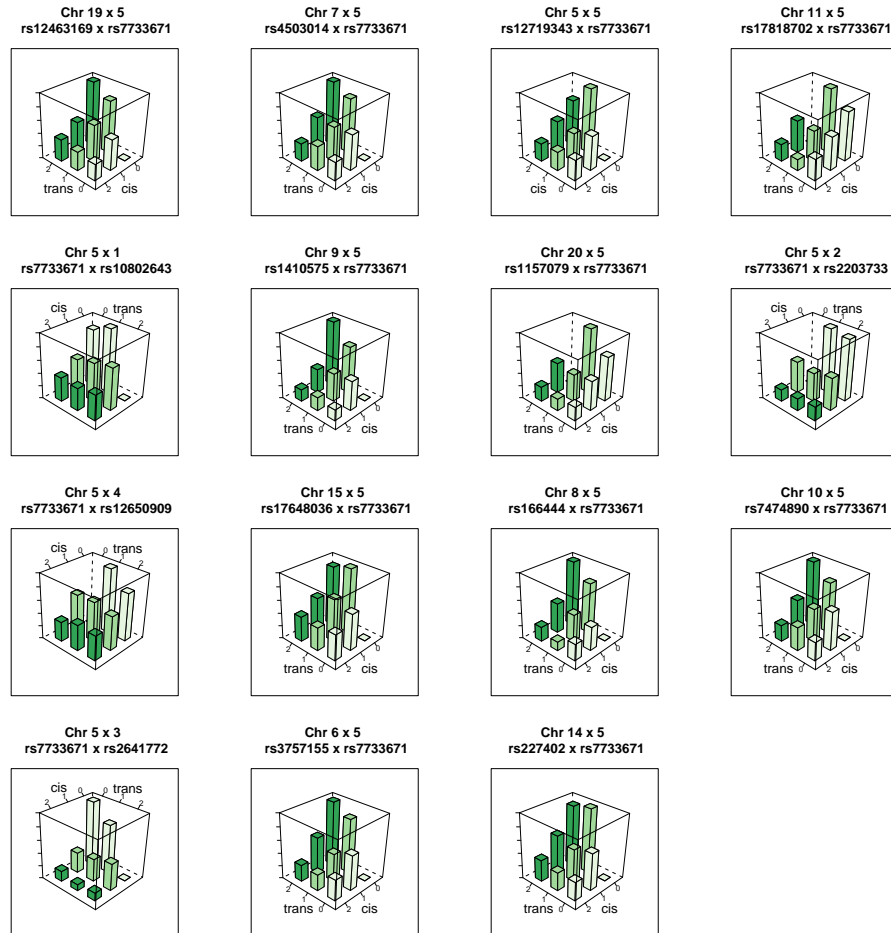


Figure S9: **Genotype-phenotype maps for 15 interactions influencing the expression of CAST** Each bar represents the mean phenotypic value for individuals in that genotype class.

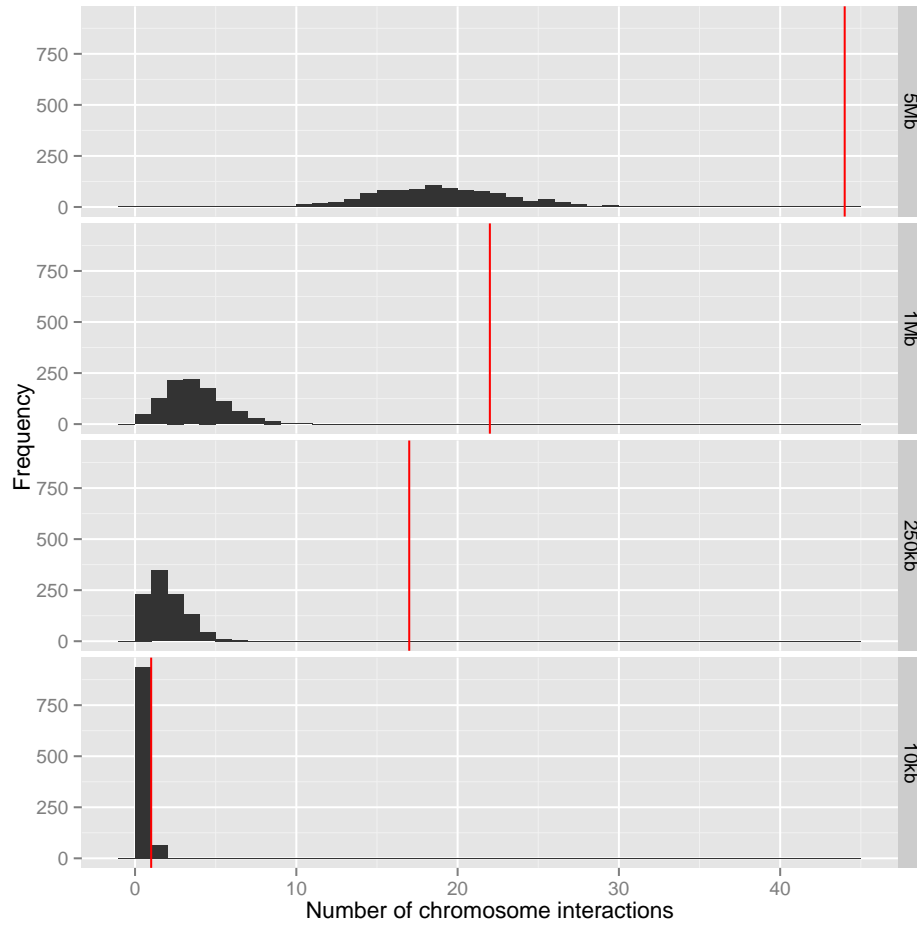


Figure S10: Number of overlaps between chromosome interactions and epistatic interactions Interacting chromosome regions may be a possible mechanism underlying epistatic interactions. The number of epistatic interactions within 20kb, 500kb, 2Mb and 10Mb of known chromosome interacting regions are shown by red vertical lines. The histograms represent the null distribution based on random sampling of 10,000 datasets for each window size.

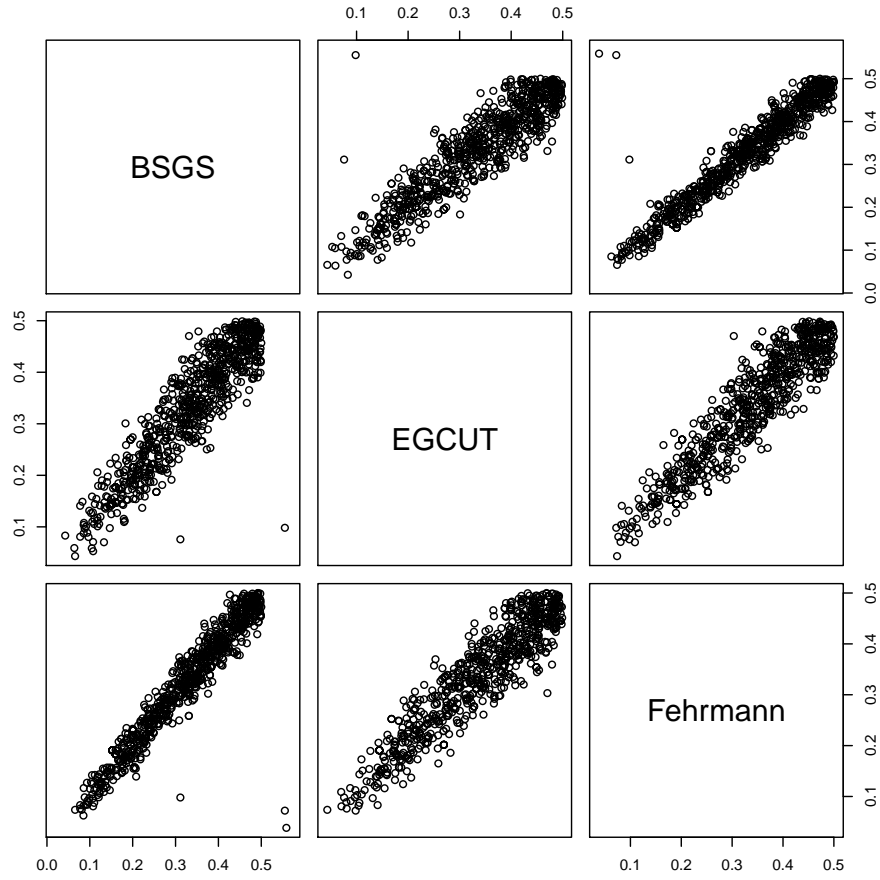


Figure S11: **Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations** Outliers were removed from the analysis as part of the filtering stage during replication.

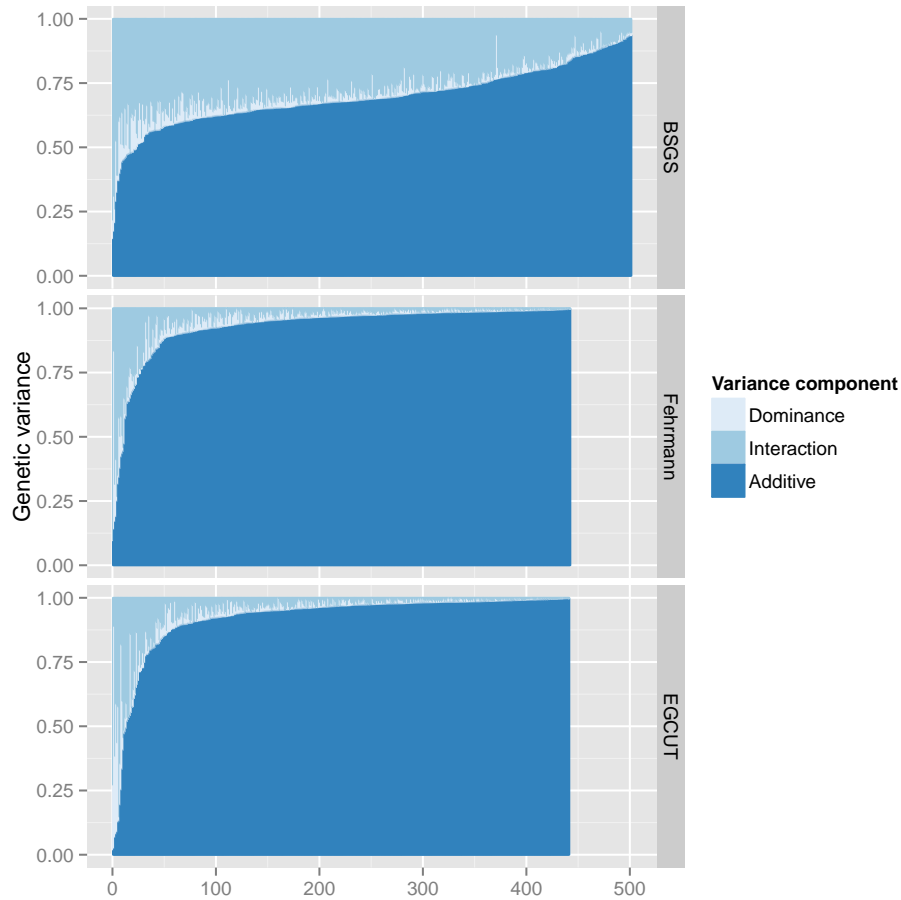


Figure S12: Comparison of variance distribution from different cohorts
How does the estimated variance decomposition change in different cohorts? The cumulative proportion of the genetic variance that is additive, dominant, or epistatic for each putative interaction is shown on the y -axis. BSGS has 501 interactions whereas Fehrmann and EGCUT have 434 (x -axis). The variance estimates are ordered from lowest additive to highest additive proportion. This is done independently for each cohort to depict the distribution of estimated effects.

5 Supplementary Tables

Table S1: Details on 501 interactions discovered in BSGS dataset

Expression trait			SNP 1			SNP 2			Interaction statistic / $-\log_{10} p$ -values				Distance / Mb		
Gene ID ^a	Probe ID ^b	Chr.	rs ID	Chr.	Pos / Mb ^c	Association ^d	rs ID	Chr.	SNP 2	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g	
ABCA7	ILMN-1743205	19	rs3752237	19	1047161	ABCA7	rs596183	6	158100199		5.50	0.38	0.02	0.09	
ABCA7	ILMN-1743205	19	rs3752237	19	1047161	ABCA7	rs914737	9	139522101		5.50				
ABCC3	ILMN-1677814	17	rs9455	17	48771135	ABCC3	rs4732202	7	136057883		6.10	0.02	1.81	0.95	
ACAT1	ILMN-1800008	11	rs227064	11	108207393	ACAT1	rs4744894	9	72001517		6.59	1.04	1.78	2.02	
ADCK1	ILMN-1698777	14	rs12431896	14	78088813	ADCK1	rs4833241	4	122933691		5.59	0.36	1.14	0.87	
ADCK1	ILMN-1698777	14	rs8058066	16	88462550	ADCK1	rs12431896	14	78088813	ADCK1	6.58	2.04	0.83	2.05	
ADK	ILMN-2358626	10	rs2395095	10	76446305	ADK	rs10824092	10	75929517		6.69	18.33	21.21	39.82	0.517
AGAP6	ILMN-3239130	10	rs2611512	10	51515534	AGAP8	rs25477996	5	95174319		6.22				
AHSA2	ILMN-1798308	2	rs10881585	9	137112421		rs842647	2	61119471		7.15	1.83	1.93	2.88	
AHSA2	ILMN-1798308	2	rs2523971	6	29938258	HLA-G	rs11773903	2	61388355	AHSA2	5.45	0.92	0.64	0.94	
AKTIP	ILMN-1665982	16	rs2896940	16	57721127	AKTIP	rs13332406	16	53489705	AKTIP	6.91	0.16	0.99	0.57	
AKTIP	ILMN-1665982	16	rs7189819	16	53536345	AKTIP	rs1362032	7	125543391		5.93	0.71	0.20	0.42	4.231
ADH3A2	ILMN-2401641	17	rs3760489	17	19581009	ADH3A2	rs1473017	4	179323762		6.18	0.27	0.30	0.23	
ANG	ILMN-1760727	14	rs9322855	14	21153299	ANG	rs11720112	3	161996349		6.26	0.33	1.37	1.01	
ANPEP	ILMN-1763837	15	rs11073891	15	90363995	ANPEP	rs4866516	5	3032625		5.75	0.02	0.20	0.04	
ANPEP	ILMN-1763837	15	rs11073891	15	90363995	ANPEP	rs3823523	7	154511163		5.85	0.44	1.09	0.90	
AP3B1	ILMN-1768867	5	rs6453374	5	77508159	AP3B1	rs6846031	4	178019148		6.31	0.47	0.17	0.26	
APPL2	ILMN-1765076	12	rs935251	12	105580918	APPL2	rs4684443	3	48187928		5.94	0.05			
ARL17B	ILMN-3231962	17	rs12947580	17	75768225		rs2769594	9	87918528	ARL17B	5.60	0.80	1.02	1.16	31.703
ARL17B	ILMN-3231962	17	rs2834541	21	35932619		rs8079215	17	44064851	ARL17B	6.65				
ARL17B	ILMN-3231962	17	rs8079215	17	44064851	ARL17B	rs1950646	14	94722497		7.04	0.15	0.04	0.54	
ARL17B	ILMN-3231962	17	rs8079215	17	44064851	ARL17B	rs2197777	12	125831219		6.26				
ARL17B	ILMN-3231962	17	rs8079215	17	44064851	ARL17B	rs2684789	15	99492045		5.98				
ATP13A1	ILMN-2134224	19	rs4284750	19	19810050		rs9834627	3	191203546		5.72				
BID	ILMN-1763386	22	rs8919	22	18213057	BID	rs9804943	12	129906275		5.70	12.18	3.25	14.23	0.071
BID	ILMN-1763386	22	rs181405	22	18233000		rs10888267	1	248059423		6.60	0.06	0.40	0.14	
C10ORF17	ILMN-1752988	11	rs2568061	11	8886260	C10ORF17	rs6553184	4	189150656		5.66	1.15	0.04	0.54	
C10ORF18	ILMN-2196550	13	rs2110603	16	6259852	C10ORF18	rs674754	13	46913416	C10ORF18	6.66	0.28	0.28	0.22	
C10ORF18	ILMN-2196550	13	rs674754	22	46913416	C10ORF18	rs6857876	4	153610164		3.87	0.38	0.50	0.43	
C10ORF173	ILMN-2393450	14	rs11089825	22	37575398	C10ORF173	rs4983382	14	105189504	C10ORF173	6.02	0.60	0.84	0.85	
C10ORF173	ILMN-2393450	14	rs3935344	15	92276674		rs4983382	14	105189504	C10ORF173	5.98	0.31	0.28	0.24	
C10ORF173	ILMN-2393450	14	rs4983382	14	105189504	C10ORF173	rs10754644	1	238724741		7.15	0.42	0.34	0.35	
C10ORF4	ILMN-1804396	14	rs1293455	18	13819673		rs2655991	14	77574438		4.87				
C10ORF4	ILMN-1804396	14	rs2655991	14	77574438		rs10972462	9	35427324		4.32				
C10ORF4	ILMN-1804396	14	rs2655991	14	77574438		rs6445340	3	63371601		4.40				
C10ORF4	ILMN-1804396	14	rs2655991	14	77574438		rs9787151	1	63179138		4.05				
C10ORF4	ILMN-1804396	14	rs4793445	17	70416307		rs2655991	14	77574438		3.85				
C10ORF4	ILMN-1804396	14	rs6010061	22	51151724		rs2655991	14	77574438		4.61				
C10ORF4	ILMN-1804396	14	rs7245800	19	52083552		rs7405659	14	77574438		4.69				
C10ORF60	ILMN-1747347	17	rs9907897	17	63502633		rs7405659	17	77574438		6.79	0.53	0.05	0.19	
C10ORF60	ILMN-1747347	17	rs2334323	6	110577257		rs2257182	1	2082566	C10ORF60	5.90	0.01	0.50	0.13	
C10ORF86	ILMN-2097790	1	rs2279474	18	46384412		rs2460002	1	2119833	C10ORF86	5.65	0.03	0.03	0.37	
C10ORF86	ILMN-2097790	1	rs7188668	16	25711358		rs2460002	1	2119833	C10ORF86	5.59	0.29	0.50	0.37	
C21ORF57	ILMN-1795836	21	rs4819271	21	48052838		rs901964	12	48676038	ZNF641	4.91	0.65	0.08	0.28	
C21ORF57	ILMN-1795836	21	rs9978658	21	48027084		rs11701361	21	47764477		9.42	6.08	16.36	21.67	0.263
C5ORF4	ILMN-1728742	5	rs1122762	18	45866512		rs286595	5	154348552	C5ORF4	5.55	0.72	0.04	0.27	
C5ORF59	ILMN-1653205	8	rs124529804	13	36577930		rs2896452	8	86102223	C5ORF59	5.49	0.29	0.02	0.07	
C5ORF59	ILMN-1653205	8	rs12454561	18	31272238		rs2896452	8	86102223	C5ORF59	5.45	0.31	0.02	0.07	
C5ORF59	ILMN-1653205	8	rs2896452	8	86102223	C5ORF59	rs1004564	4	55242625		7.62	0.38	0.18	0.21	
C5ORF59	ILMN-1653205	8	rs7152284	14	52273663	C5ORF59	rs2896452	8	86102223	C5ORF59	5.67	2.18	0.07	1.33	

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Table S1 – continued from previous page

Gene ID ^a	Expression trait	Chr.	SNP 1			SNP 2			Interaction statistic / -log ₁₀ p-values			Distance / Mb ^h		
			rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	BSGS ^e		Fehrmann ^f	EGCUT ^g
CBORF59	ILMN_1653205	8	rs8051751	16	7188323		rs2890452	8	86102233	CBORF59	5.79	1.39	0.18	0.87
CBORF72	ILMN_1741881	9	rs10122902	9	27556780	C9ORF72	rs24202910	1	24202910	C9ORF72	6.36	0.96	0.01	0.37
CAC1	ILMN_1731064	1	rs12765847	10	4353908		rs3738725	1	227174210	CAC1	6.36	0.94	0.00	0.34
CARD9	ILMN_1712532	9	rs4260763	9	139289825	INPP5E	rs684040	1	82128600		5.81			
CARD9	ILMN_1712532	9	rs4573661	11	6026661		rs4077515	9	139266496	INPP5E	6.61	0.09	0.86	0.42
CAST	ILMN_1717234	5	rs1157079	9	6778978		rs7733671	5	96000269	CAST	7.07	0.23	0.96	0.62
CAST	ILMN_1717234	5	rs12463169	19	17321669		rs7733671	5	96000269	CAST	5.73	0.02	2.85	1.75
CAST	ILMN_1717234	5	rs12599264	16	81840122		rs7733671	5	96000269	CAST	7.00			
CAST	ILMN_1717234	5	rs12719343	5	125369113		rs7733671	5	96000269	CAST	7.68	0.36	1.57	1.20
CAST	ILMN_1717234	5	rs1410575	9	78255630		rs7733671	5	96000269	CAST	6.55	0.13	1.34	0.78
CAST	ILMN_1717234	5	rs166444	8	78392770		rs7733671	5	96000269	CAST	7.01	0.27	0.52	0.37
CAST	ILMN_1717234	5	rs17648036	15	27311111		rs7733671	5	96000269	CAST	7.81	0.97	0.03	0.41
CAST	ILMN_1717234	5	rs17818702	11	86107920		rs7733671	5	96000269	CAST	6.62	1.15	0.59	1.09
CAST	ILMN_1717234	5	rs227402	14	70496807		rs7733671	5	96000269	CAST	6.12	0.11	0.01	0.01
CAST	ILMN_1717234	5	rs2822124	21	15166804		rs7733671	5	96000269	CAST	6.87			
CAST	ILMN_1717234	5	rs3757155	6	136458593		rs7733671	5	96000269	CAST	7.24	0.07	0.33	0.12
CAST	ILMN_1717234	5	rs4503014	7	31149140		rs7733671	5	96000269	CAST	5.88	0.92	1.56	1.72
CAST	ILMN_1717234	5	rs474890	10	59590078		rs7733671	5	96000269	CAST	6.74	0.49	0.12	0.23
CAST	ILMN_1717234	5	rs747890	10	59590078		rs7733671	5	96000269	CAST	7.42	0.75	0.78	0.93
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs12650909	4	170129890		7.42	0.23	0.78	0.50
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs2203733	2	224093101		6.07	0.22	0.87	0.54
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs2641772	3	195531841		6.93	0.19	0.26	0.15
CAT	ILMN_1651705	11	rs872311	18	66175386		rs541207	11	34447582	CAT	6.41	0.26	0.30	0.22
CCDC88B	ILMN_1772208	11	rs23532303	19	17099980		rs127171349	10	64125142	CCDC88B	5.68	0.33	0.37	0.31
CCDC88B	ILMN_1772208	11	rs694739	11	64097233	CCDC88B	rs1254900	2	85816334	VAMP8	5.62	0.15	0.01	0.02
CD36	ILMN_1784863	7	rs3211834	7	80280117		rs6700168	7	157182040	CD55	6.06	1.74	0.24	1.20
CD55	ILMN_1800540	1	rs750801	11	76033374		rs10255470	7	207502534		5.09	0.08	0.03	0.02
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs4696726	4	7992632		6.06	0.13	0.20	0.42
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs7623520	3	196721395		5.71	0.13	0.80	0.42
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs838875	12	125145394		5.56	0.04	0.27	0.08
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs8576388	13	38434472		6.31	0.24	1.67	1.16
CD93	ILMN_1704730	20	rs2865804	20	37771578		rs1864655	20	23074375	CD93	5.71	0.71	0.22	0.45
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs10925247	1	238890903		7.43	0.64	0.75	0.81
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs2873430	8	138500554		7.02			
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs4295531	18	77264432		6.13			
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs7294744	13	115080398		6.08			
CDK16	ILMN_2230796	13	rs901544	14	104162263		rs11655031	17	3083182	CDK16	5.46	0.21	0.14	0.11
CDK5R1	ILMN_1730928	17	rs200690	17	46614102	HOXB2	rs2421050	5	158043044	CDK5R1	5.47	0.95	0.07	0.45
CEACAM21	ILMN_1745949	19	rs4803481	19	42068556		rs4803481	19	42068556	CEACAM21	6.15	0.90	0.12	0.48
CEACAM21	ILMN_1707554	18	rs6505780	18	13069782	CEACAM21	rs13132719	3	180265266		6.67	2.16	0.16	1.44
CEP192	ILMN_1787808	14	rs3825569	14	101350298	CEP192	rs13079012	3	134247706	ANAPC13	5.75	0.15	0.24	0.12
CEP63	ILMN_2259945	3	rs81992935	16	55861794	CES1	rs2695290	2	235248562		6.36	0.23	0.10	0.09
CHPT1	ILMN_2209240	16	rs501967	13	38831724		rs2695290	12	102087804	CHPT1	5.65	0.72	0.20	0.44
CHPT1	ILMN_2209240	12	rs501967	13	38831724		rs67578	12	102087804	CHPT1	4.75	0.92	0.02	0.36
CHPT1	ILMN_2209240	12	rs501967	13	38831724		rs7313235	11	81937002	CHPT1	4.75	0.92	0.02	0.36
CLEC12A	ILMN_1663142	12	rs429790	16	84471642		rs7313235	12	10132283	CLEC12A	5.55	0.07	1.28	0.67
CLEC12A	ILMN_2403228	12	rs7305054	16	10156646		rs3903088	10	134236688		7.54	0.95	0.36	0.73
CLEC12A	ILMN_1674609	5	rs17129799	11	96929337		rs6863172	5	173595960	CLTB	5.55			
CNN2	ILMN_1770290	19	rs3752237	19	1047161	ABCA7	rs169130	16	63121080		7.56	0.07	0.02	0.02
CNN2	ILMN_1770290	19	rs3752237	19	1047161	ABCA7	rs7336017	13	67713633		6.33	1.92	0.28	1.39
CP5F1	ILMN_1654545	8	rs4333645	8	145569535		rs1455268	4	61738094		6.34	0.10	0.01	0.01
CPVL	ILMN_1682928	7	rs12596791	16	26115562		rs2455884	7	29188475	CPVL	5.74	0.06	0.57	0.23

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Table S1 – continued from previous page

Gene ID ^a	Expression trait		SNP 1				SNP 2				Interaction statistic ^f / -log ₁₀ p-values				Distance / Mb ^h
	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g	
CPVL	ILMN-1682928	7	rs2835998	21	39202070		rs245884	7	29188475	CPVL	5.55	0.19	0.03	0.04	
	ILMN-1813256	2	rs2131290	4	18859908		rs1531133	7	46843631	CPVL	5.47	0.28	0.10	0.12	
CRLP1	ILMN-1737685	20	rs6139887	20	5986234	CRLS1	rs1473927	5	62406408	CRLP1	6.18	0.10	0.36	0.15	
	ILMN-1761797	21	rs9979356	21	43230974		rs3761385	21	45198355		11.99	25.20	16.72	42.27	0.033
CTNNA1	ILMN-1804854	5	rs924943	18	69000505		rs176382	5	138226707	CTNNA1	5.74	0.02	0.41	0.11	
	ILMN-1696347	11	rs2457684	11	88139983	CTSC	rs7079264	10	10679892		5.67	0.92	0.74	1.03	
CTSC	ILMN-1696347	11	rs7532236	22	26250645		rs1728352	11	88087357	CTSC	5.84	0.49	0.80	0.73	
	ILMN-2242463	11	rs7930237	11	88117962		rs12784396	11	88077479		7.16	18.76	15.06	33.53	0.040
CWFI9L1	ILMN-1651886	10	rs7108734	11	11456027		rs12784396	10	102027407	CWFI9L1	5.42	0.21	0.01	0.03	
	ILMN-1712305	4	rs2592948	4	129994690		rs888427	2	172368120	CYBRD1	5.89	0.23	0.53	0.34	
CYBRD1	ILMN-1712305	2	rs7852475	9	140698856		rs888427	2	172368120	CYBRD1	5.68	0.20	0.02	0.04	
	ILMN-2087692	2	rs11257679	10	12318284		rs888427	2	172368120	CYBRD1	5.81	0.39	1.87	1.47	
CYBRD1	ILMN-2087692	2	rs6137908	20	23344590		rs888427	2	172368120	CYBRD1	5.53	0.05	0.83	0.36	
	ILMN-2087692	2	rs888427	2	172368120	CYBRD1	rs7591849	2	160112881		5.85	0.87	0.10	0.44	12.255
CYP27A1	ILMN-1704985	2	rs6021982	20	36571928		rs933994	2	219650616	CYP27A1	5.42	0.29	0.86	0.60	
	ILMN-2128428	5	rs7778910	17	110451383		rs835223	5	39381357	DAB2	5.44	0.48	0.40	0.14	
DCAKD	ILMN-1811648	17	rs9900173	17	133111688		rs1343244	6	82076988		9.12	0.00	0.58	0.14	
	ILMN-1690982	22	rs9760102	22	24248761	DDT	rs2378341	3	187475208		5.62	0.64	0.25	0.42	
DDX58	ILMN-1797001	9	rs4937097	11	125962645		rs7042042	9	32451144		5.31	0.61	0.29	0.44	
	ILMN-1783996	1	rs10120023	9	137810259	COQ10A	rs2519515	7	88204888		5.47	0.08	0.41	0.16	
DEN1	ILMN-1733998	1	rs12363827	13	106703727		rs10120023	9	137810259	COQ10A	6.39	0.77	0.02	0.29	
	ILMN-1733998	2	rs1519956	12	89468283		rs7566044	2	169960422	DHRS9	6.00	0.06	1.17	0.58	
DHRS9	ILMN-2384181	2	rs1528529	7	147132505		rs7566044	2	169960422	DHRS9	6.48	0.37	0.34	0.32	
	ILMN-2384181	2	rs2831914	21	29959453		rs2161037	2	169893419	DHRS9	5.51	0.88	0.04	0.37	
DHRS9	ILMN-1755589	12	rs7661304	4	187776431		rs2161037	2	169893419	DHRS9	7.64	0.05	0.11	0.03	
	ILMN-1755589	12	rs11080134	17	59161503	LASS5	rs1169322	12	50610976	LASS5	4.65	0.32	0.05	0.10	
DIP2B	ILMN-1755589	12	rs1166935	12	50636364		rs2872008	7	153134888	LASS5	4.87	0.30	0.58	0.19	
	ILMN-1755589	12	rs3383855	19	41711815	LASS5	rs1734595	12	50730458	LASS5	5.31	0.37	0.02	0.22	
DIP2B	ILMN-1755589	12	rs7319252	12	50730458	LASS5	rs1808634	8	61971140		4.40	0.09	0.02	0.01	66.920
	ILMN-1755589	12	rs7319252	12	50730458	LASS5	rs4532958	10	115214154	LASS5	5.03	0.48	0.00	0.11	
DNAB1B6	ILMN-1793770	7	rs2288842	15	93400954		rs7044171	7	51074199	LASS5	5.92	0.23	1.45	0.97	0.052
	ILMN-2109708	3	rs12252308	15	117994348		rs3775539	7	157163614	DNAB1B6	5.79	0.23	0.27	1.12	
EGCF1	ILMN-2349610	22	rs4324091	22	50971269		rs1566972	3	16320360	DNAB1B6	6.17	1.58	0.18	0.70	
	ILMN-1671568	1	rs5092637	22	241911027	ECGF1	rs4891884	18	64004670	DNAB1B6	4.81	0.15	1.18	0.70	
EGHDC2	ILMN-1720083	15	rs50403312	19	53244938		rs11206043	1	53402552	EGHDC2	6.19	0.22	0.35	0.22	
	ILMN-1713380	14	rs6567288	18	60218334		rs1048166	1	53402552	EGHDC2	5.58	0.64	0.16	0.35	
EIF2B2	ILMN-1745522	17	rs7216490	17	7221707	EIF5A	rs1048166	15	42192040	EGHDC2	6.98	0.90	0.47	0.79	
	ILMN-1794522	17	rs7216490	17	7221707	EIF5A	rs1269096	14	75503040	EIF2B2	5.56	0.23	0.11	0.10	
EIF5A	ILMN-1794522	17	rs7216490	17	7221707	EIF5A	rs1754556	14	99603119	EIF2B2	5.44	0.56	0.08	0.24	
	ILMN-1794522	17	rs7216490	17	7221707	EIF5A	rs1553474	2	49359676	EIF2B2	5.55	0.28	0.05	0.02	
EIF5A	ILMN-1794522	17	rs7216490	17	7221707	EIF5A	rs2197210	8	129624067	EIF2B2	6.36	0.08	0.05	0.02	
	ILMN-2353633	19	rs2827076	21	23196249	EIF5A	rs4471434	11	126387391	EIF2B2	5.52	0.05	1.12	0.53	
EMR2	ILMN-2353633	19	rs6132112	20	18761714		rs9305048	19	14879034	EMR2	6.51	0.36	0.04	0.11	
	ILMN-2353633	19	rs9405048	19	14879034	EMR2	rs9305048	19	14879034	EMR2	5.56	0.40	0.40	0.41	
EPHX2	ILMN-1709237	8	rs1107764	11	12790396		rs3007765	13	102480759	EMR2	6.03	0.20	0.58	0.35	
	ILMN-1731001	8	rs10894861	11	13461176		rs13269963	8	27400604	EPHX2	5.70	0.25	1.20	0.81	
ERICH1	ILMN-1731001	8	rs5766218	22	45337329		rs12115088	8	578742	ERICH1	5.43	0.20	0.11	0.09	
	ILMN-1731001	8	rs726145	18	31187910		rs12115088	8	578742	ERICH1	6.11	0.20	0.11	0.09	
ERICH1	ILMN-2104696	5	rs4735895	8	600729	ERICH1	rs1517297	4	182786760	ERICH1	5.65	0.29	0.04	0.08	
	ILMN-1789419	5	rs187076	10	55228462		rs12188164	5	428236	EXOC3	6.83	0.67	1.03	1.06	
FAHD1	ILMN-2246661	16	rs1560104	16	12708208		rs344363	16	1972548	FAHD1	5.63	0.74	0.19	0.44	
	ILMN-1668063	9	rs12580388	12	129591144		rs10120023	9	137810259	COQ10A	6.33	0.27	0.30	0.23	10.736

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Gene ID ^a	Expression trait ^b		SNP 1			SNP 2			Interaction statistic ^c		Distance / Mb	
	rs ID	Chr.	Pos/Mb/c	Association ^d	rs ID	Chr.	Pos/Mb/c	Association ^d	BSGS ^e	Fehrmann ^f		EGCUT ^g
MBNL1	rs43925535	4	41513423		rs13069559	3	152187431	MBNL1	8.39	0.02	4.33	3.02
	rs47358380	8	895841		rs13069559	3	152187431	MBNL1	6.74	0.32	4.21	3.38
	rs4939558	18	46278591		rs1522374	3	152235530		7.72	0.03	0.27	0.07
	rs6128397	3	57253132		rs16864367	3	152234166		7.22	1.34	1.15	1.73
	rs7701738	5	22101322		rs13069559	3	152187431	MBNL1	7.92	2.55	7.89	9.28
	rs6079849	20	15462611		rs2051344	18	74715653	MBP	6.26	0.10	0.03	0.02
	rs139568	22	42210985		rs2051344	18	74715653	MBP	5.56	0.03	0.23	0.05
	rs2051344	18	74715653	MBP	rs1125539	3	155204939		5.79	0.02	0.76	0.27
	rs2051344	18	74715653	MBP	rs2619046	6	55097534		6.03	0.15	0.50	0.26
	rs4805021	19	33436367		rs2051344	18	74715653	MBP	5.82	0.03	0.47	0.14
MEGF9	rs8092433	18	74747424		rs4980876	18	74732087		7.06	7.06	21.91	28.73
	rs13039689	20	51922071		rs4846085	9	123453281	MEGF9	4.43	1.13	1.33	1.71
	rs7989895	13	109401737		rs4846085	1	12050634	MFN2	5.76	0.61	0.25	0.41
	rs12718598	7	50428445	MGC13057	rs11725347	4	171860973		5.81	0.13	0.30	0.14
	rs674608	18	89607072		rs12718598	7	50428445	MGC13057	5.07	0.07	1.03	0.50
	rs8058318	16	62828245		rs12718598	7	50428445	MGC13057	7.05	0.11	0.12	0.05
	rs484787	20	51977931		rs2660665	8	137526799		4.17	0.05	0.08	0.02
	rs405441	17	25977964		rs4147592	5	165600146	MGST3	5.45	0.57	0.27	0.40
	rs1805	11	118076069	MPZL2	rs11771552	7	154708716		5.90	0.01	0.23	0.04
	rs7316716	12	19953193		rs1805	11	118076069	MPZL2	5.64	0.97	1.08	1.35
MBNL1	rs4736176	12	19953193		rs2630095	5	1782046	MRPL36	6.89	0.34	0.18	0.19
	rs654769	16	80641040		rs2630095	5	1782046	MRPL36	6.89	0.34	0.18	0.19
	rs1950857	14	26710237		rs3811188	14		MRPL52	5.71	0.26	0.14	0.22
	rs10955512	8	110202230		rs722269	6	42194916		6.56	0.44	0.70	0.64
	rs11698155	20	5363214		rs2395803	6	42158596	MRPS10	7.48	0.46	0.70	0.64
	rs1420537	16	5453567		rs13217993	6	42164401	MRPS10	6.85	0.31	0.63	0.46
	rs178375	15	31215935	MTNR10	rs12431444	14	42068689		6.21	0.41	0.25	0.28
	rs459498	21	42795027		rs1160227	14	95514596		5.18	1.87	2.86	3.61
	rs459498	21	42795027		rs4973801	21	29363604		6.31	0.46	0.52	0.50
	rs10134030	14	61593110		rs130120	21	29363604		5.83	0.11	0.50	0.23
MBNL1	rs7322708	13	109530661		rs1317149	11	47486885	MYBPC3	6.78	0.29	0.92	0.65
	rs1958073	18	8247256		rs2734722	11	134483237	MYBPC3	5.56	0.13	0.46	0.23
	rs732754	17	8762968	MYOM1	rs2734722	11	134483237	MYBPC3	5.70	0.04	0	

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Gene ID ^a	Expression trait		SNP 1		Pos/Mb ^c	Association ^d	SNP 2		Chr.	Pos/Mb ^c	Association ^d	Interaction statistic / -log ₁₀ p-values		Distance / Mb ^b	
	Probe ID ^b	Chr.	rs ID	Chr.			rs ID	Chr.				BSGS ^e	Fehrmann ^f		EGCUT ^g
REBE	ILMN-1802380	1	rs4982958	14	24987865		rs301819	1	8501786	REBE	5.66	0.61	1.23	1.17	
REBE	ILMN-1802380	1	rs7697290	4	135248366		rs301819	1	8501786	REBE	5.74	0.14	0.10	0.06	
REBE	ILMN-2327795	1	rs11085829	19	13174312		rs301819	1	8501786	REBE	5.12	0.21	0.33	0.21	
REBE	ILMN-2327795	1	rs3852011	3	112844086		rs301819	1	8501786	REBE	5.71	0.08	0.60	0.26	
RNASE6	ILMN-1780533	14	rs11628398	14	8106521	RNASE6	rs7324365	13	100601327		5.48	0.42	0.21	0.26	
RNASE6	ILMN-1780533	14	rs6603134	19	8106521		rs11628398	14	21182800	RNASE6	5.11	0.09	0.22	0.08	
RNF167	ILMN-1794726	17	rs2382330	17	4875566		rs4848457	13	54668512		4.37				
RNF167	ILMN-1794726	17	rs400668	17	4839930		rs11706900	3	36348968		5.59	0.71	0.46	0.64	
RNFEP	ILMN-1738347	1	rs1107121	17	46127549		rs2819365	1	201983242		6.27	0.11	0.30	0.13	
RNFEP	ILMN-1738347	1	rs8071611	17	67153386		rs2819365	1	201983242		4.32	1.48	0.52	1.28	
RPL13	ILMN-2413278	16	rs352935	16	89648580		rs2965817	16	89513234		4.98	3.79	14.41	17.24	
RPL23AP7	ILMN-2222750	2	rs1401202	16	80320056		rs4849261	2	114450028	RPL23AP7	5.55	0.13	0.73	0.38	
RPL36AL	ILMN-2189933	14	rs3007033	14	50103816	RPL36AL	rs17495030	9	138035083		5.46	0.09	0.66	0.02	
RPL36AL	ILMN-2189936	14	rs4900928	14	50020817	RPL36AL	rs1502991	6	66137260		5.86	0.32	0.20	0.19	
RPL8	ILMN-1764721	8	rs2958452	8	145984615	RPL8	rs1619856	1	234585790		4.59	0.10	0.37	0.15	
RPL8	ILMN-1764721	8	rs4143674	20	4741304		rs2958452	8	145984615	RPL8	4.33	0.13	0.45	0.22	
SEC13	ILMN-3297880	3	rs4889214	16	80913946		rs696221	3	10342876	SEC13	6.48	0.22	1.73	1.17	
SEMA4A	ILMN-1702787	1	rs17085428	5	95388015		rs7695	1	156147326	SEMA4A	5.70	0.02	0.51	0.15	
SEMA3	ILMN-1694027	11	rs12147460	14	104412137		rs684856	11	94906111	SEMA3	5.50	0.31	0.06	0.10	
SEMA3	ILMN-1694027	11	rs355391	15	46391793		rs684856	11	94906111	SEMA3	5.67	0.31	0.06	0.10	
SEMA3	ILMN-1694027	11	rs684856	15	46391793	SEMA3	rs7004947	8	134606425		5.60	0.21	0.51	0.31	
SH3BGL2	ILMN-176764	6	rs10838191	11	43893658		rs1354034	3	56849749	PPBP	5.52	0.70	0.12	0.35	
SH3BGL2	ILMN-176764	6	rs2545385	5	66383979		rs1354034	3	56849749	PPBP	5.97	0.20	0.51	0.30	
SH3BGL2	ILMN-176764	6	rs6845304	4	88280592		rs1354034	3	56849749	PPBP	5.23	0.32	0.71	0.53	
SH3BGL2	ILMN-2158336	9	rs1034210	21	18196922		rs17455517	9	131785369	SH3BGL2	7.40	0.22	0.18	0.13	
SIRPG	ILMN-1771801	20	rs1535883	20	1612819	SIRPG	rs6842739	4	60489510		5.74	0.29	0.18	0.17	
SLC22A18	ILMN-2382505	11	rs11673260	19	52181798		rs367035	11	2923826	SLC22A18	5.47	0.09	0.24	0.09	
SLC22A18	ILMN-2382505	11	rs367035	11	2923826	SLC22A18	rs3110874	7	153224179		5.70	0.15	0.10	0.06	
SLC22A18	ILMN-2382505	11	rs367035	11	2923826		rs772054	2	241678528		6.15	0.39	0.13	0.19	
SLC41A3	ILMN-236111	3	rs012136	11	24616743		rs6771703	3	125801067	SLC41A3	5.88	1.10	0.82	1.24	
SLC45A4	ILMN-2157778	8	rs6985508	8	142337734	SLC45A4	rs7701916	5	174598073		5.95	0.86	0.07	0.40	
SLC46A3	ILMN-1658639	13	rs09805	17	5502091		rs7981190	13	29259349	SLC46A3	5.52	0.09	0.58	0.26	
SMG7	ILMN-1706553	1	rs803259	15	97403923		rs10911353	1	183489203	SMG7	6.52	0.17	0.09	0.06	
SMOX	ILMN-1775380	20	rs118315	20	4161500	SMOX	rs11677815	2	65800982		5.68	0.39	0.62	0.52	
SNHG8	ILMN-3309349	4	rs1105621	9	133050233		rs705837	4	119225940	SNHG8	6.11	0.29	1.03	0.72	
SNORD14A	ILMN-1799381	11	rs1520429	15	46259108		rs214097	11	17291499	SNORD14A	6.60	0.29	1.06	0.96	
SNORD14A	ILMN-1799381	11	rs2634462	11	17339127		rs6486334	11	17015557	SNORD14A	7.31	13.11	10.93	23.22	
SNORD89	ILMN-3238662	2	rs10445863	2	115929241		rs750783	2	101889306	SNORD89	6.08	0.31	0.17	0.31	
SNORD89	ILMN-3238662	2	rs11605822	11	122986326		rs750783	2	101889306	SNORD89	5.96	0.18	0.93	0.60	
SNORD89	ILMN-3238662	2	rs2135064	5	26778066		rs750783	2	101889306	SNORD89	6.33	0.01	0.05	0.00	
SNUPN	ILMN-1733932	15	rs1346466	21	46376528	SNUPN	rs17185362	16	81889005		6.45	0.13	1.41	0.83	
SNUPN	ILMN-2364535	15	rs1346466	21	46376528	SNUPN	rs1472075	3	193706323		5.59	0.34	0.00	0.06	
SPATA5L1	ILMN-1729179	15	rs1316320	19	41117869		rs4774580	15	45652086	SPATA5L1	5.44	0.67	0.12	0.33	
STARD10	ILMN-2210752	7	rs4073164	14	104947517		rs1006620	15	72509713	STARD10	5.88	0.57	0.17	0.31	
STYXL1	ILMN-2345142	20	rs2221406	13	104947517		rs17685	7	75616105	STYXL1	5.88	0.46	0.24	0.30	
SULT1A4	ILMN-2336133	16	rs1463965	18	74332954	SULF2	rs932994	4	180439236		7.05	0.01	0.05	0.00	
SULT1A4	ILMN-2336133	16	rs2436657	20	40119768		rs3785354	16	28550667	TUFM	5.83	0.26	0.16	0.14	
SURF6	ILMN-1778032	9	rs2609626	21	56013994		rs3785354	16	28550667	TUFM	5.83	0.26	0.16	0.14	
SYTL2	ILMN-2336609	11	rs1375719	13	103410782		rs485485	11	85495269	SYTL2	6.14	0.28	0.31	0.24	
THBS3	ILMN-1804663	1	rs1939875	14	95422867		rs4072037	1	155162087	THBS3	5.47	0.03	0.15	0.03	
THBS3	ILMN-1804663	1	rs8014956	14	20687978		rs2049805	1	155194980	THBS3	5.65	0.31	0.76	0.55	
TIPRL	ILMN-1781457	1	rs2823245	21	168154523		rs3204905	1	168154599	TIPRL	5.22	0.07	0.40	0.15	

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Table S1 – continued from previous page

Gene ID ^a			Probe ID ^b			Expression trait			SNP 1			SNP 2			Interaction statistic ^c / -log ₁₀ p-values			Meta ^g			Distance / Mb
Gene ID	Probe ID	Chr.	rs ID	Chr.	Pos / Mb ^c	Association ^d	rs ID	Chr.	Pos / Mb ^c	Association ^d	BSGS ^e	F _{DR} ^f	EGCUP ^h	Meta ^g							
TMEM149	ILMN_1804148	7	rs1904000	11	192389629	TMEM149	rs17925246	7	41581986	TMEM149	3.70	0.06	1.34	0.76	0.122						
TMEM149	ILMN_1784266	19	rs2830914	22	47248981	TMEM149	rs8106959	19	36210525	TMEM149	8.11	0.16	0.48	0.26							
TMEM149	ILMN_1786426	19	rs76792235	22	47207988	TMEM149	rs8106959	19	36210525	TMEM149	6.70	0.16	0.48	0.26							
TMEM149	ILMN_1786426	19	rs6904519	20	425027005	SNX26	rs17254601	19	36147315	TMEM149	11.09	0.76	45.78	145.78							
TMEM149	ILMN_1786426	19	rs807491	19	36288923	TMEM149	rs10508289	10	4790159	TMEM149	12.16	81.55	45.78	145.78							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs10819626	9	133025756	TMEM149	8.02	0.40	0.99	0.80							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs10819626	9	133025756	TMEM149	8.39	3.61	1.18	3.78							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs1401098	12	128884559	TMEM149	7.37	2.41	1.00	2.52							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs15575335	18	64268976	TMEM149	6.95	0.08	0.07	0.03							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs17719594	14	9032598	TMEM149	6.93	3.06	0.77	2.87							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs1843357	8	13822381	TMEM149	6.21	3.72	3.33	6.00							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs2351458	4	113317583	TMEM149	7.30	0.04	9.61	8.00							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs2539000	7	14761972	TMEM149	6.70	1.57	1.52	2.27							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs2731711	5	171792273	TMEM149	5.92	0.19	0.33	0.19							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs471728	11	12959460	TMEM149	8.89	0.90	3.62	3.51							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs6718480	2	233879066	TMEM149	8.55	3.31	5.15	7.36							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs6926382	6	161683974	TMEM149	5.80	3.06	8.80	10.72							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs7213338	17	80357420	TMEM149	5.49	0.07	3.14	2.10							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs814940	1	242889492	TMEM149	6.22	3.36	6.96	9.20							
TMEM149	ILMN_1786426	19	rs8106959	19	36210525	TMEM149	rs9509428	13	21473952	TMEM149	9.44	0.10	5.75	4.47							
TMEM63A	ILMN_1719649	1	rs1254086	13	72890603	TMEM63A	rs4149226	1	226027323	TMEM63A	5.60	0.64	0.12	0.32							
TMEM80	ILMN_1708482	11	rs1548475	9	58058246	TMEM80	rs4963126	11	656845	TMEM80	5.79	0.11	0.15	0.07							
TNPO3	ILMN_1683811	7	rs1537146	9	4859303	TRAPP5	rs10488630	7	128593948	TRAPP5	5.61	1.03	0.17	0.62							
TNPO3	ILMN_1683811	7	rs199793	20	22827303	TRAPP5	rs10488630	7	128593948	TRAPP5	5.52	3.19	1.89	4.09							
TRA2A	ILMN_1731043	7	rs7776572	7	23528927	TRAPP5	rs3916581	11	118887887	TRAPP5	8.23	0.28	0.40	0.29							
TRAPP4	ILMN_1814650	11	rs1793283	13	133531675	TRAPP5	rs10059004	4	166970604	TRAPP4	5.61	0.93	0.01	0.36							
TRAPP5	ILMN_1814650	11	rs1793283	13	133531675	TRAPP5	rs10059004	4	166970604	TRAPP5	5.52	0.21	1.60	1.07							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs1023095	8	132022957	TRAPP5	6.92	0.37	0.87	0.68							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs1375714	6	156404902	TRAPP5	7.79	0.12	0.18	0.08							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs1393299	1	242329791	TRAPP5	6.43	0.63	0.47	0.59							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs17763599	19	2369415	TRAPP5	6.38	0.21	0.24	0.16							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs4968328	17	57495457	TRAPP5	6.51	0.50	0.38	0.40							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs7313362	12	129644342	TRAPP5	7.08	0.04	0.65	0.25							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs7694997	4	9947811	TRAPP5	5.86	0.20	0.36	0.22							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs7800935	7	146690926	TRAPP5	6.27	0.15	0.33	0.16							
TRAPP5	ILMN_2372639	19	rs17159840	19	7758194	TRAPP5	rs856638	14	85439550	TRAPP5	6.73	0.24	0.07	0.08							
TRAPP5	ILMN_2372639	19	rs80708	22	22740855	TRAPP5	rs17159840	19	7758194	TRAPP5	7.58	0.85	0.78	1.01							
TRAPP5	ILMN_2372639	19	rs6401695	21	45128454	TRAPP5	rs17159840	19	7758194	TRAPP5	8.10	0.51	0.55	0.56							
TRAPP5	ILMN_2372639	19	rs6040514	20	11272861	TRAPP5	rs10179572	2	228504503	TRAPP5	6.71	0.14	0.02	0.02							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs12921440	16	30408765	TRAPP5	7.34	0.14	0.26	0.13							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs1887778	9	134635088	TRAPP5	7.05	0.08	0.86	0.40							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs693354	3	15739377	TRAPP5	7.41	0.36	0.90	0.69							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.42	0.11	0.25	0.11							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.92	1.20	0.23	0.69							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	6.46	0.07	0.91	0.39							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	8.27	0.04	0.04	0.04							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	9.01	0.07	0.18	0.06							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
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TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
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TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
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TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
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TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
TRAPP5	ILMN_2372639	19	rs7246264	19	7762978	TRAPP5	rs2395771	6	41264577	TRAPP5	5.01	0.07	0.18	0.06							
TRAPP5	ILMN_2372639																				

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Table S1 – continued from previous page

Gene ID ^a	Expression trait		SNP 1		SNP 2		Interaction statistic / -log ₁₀ p-values			
	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d
UBASH3A	ILMN-2338348	21	rs1893592	21	43855067	UBASH3A	rs7201194	16	83600397	
UBASH3A	ILMN-2338348	21	rs1893592	21	43855067	UBASH3A	rs7512594	1	214514361	
USP36	ILMN-1697227	17	rs2279308	17	76794981	USP36	rs22725546	17	75151717	
VASP	ILMN-1743646	19	rs1204226	19	40063167		rs1883613	6	1330774668	VNN2
VNN2	ILMN-1678939	6	rs10435352	7	103252718		rs1883617	6	133077063	VNN2
VNN2	ILMN-1678939	6	rs13044386	20	9116155		rs1883617	6	133072650	VNN2
VNN2	ILMN-1678939	6	rs134447	22	49927332		rs1883617	6	133072650	VNN2
VNN3	ILMN-1678939	6	rs216495	11	16834510		rs2267932	6	133067782	VNN3
VNN3	ILMN-1804935	6	rs10278073	7	151662184		rs2267932	6	133067782	VNN3
VNN3	ILMN-1804935	6	rs1443946	8	73006453		rs2267932	6	133067782	VNN3
VNN3	ILMN-1804935	6	rs348462	9	73547169		rs2267932	6	133067782	VNN3
VNN3	ILMN-1804935	6	rs7137055	14	83262064		rs2267932	6	133067782	VNN3
VNN3	ILMN-2387680	6	rs2823165	21	5694253		rs2267932	6	133067782	VNN3
VNN3	ILMN-2387680	6	rs9596457	13	51692548		rs4532100	18	71024750	
VSTM1	ILMN-1763455	19	rs10500316	19	54553697	VSTM1	rs7895870	10	123095249	
VSTM1	ILMN-1763455	19	rs10500316	19	54553697	VSTM1	rs10500316	19	54553697	VSTM1
WDR48	ILMN-1763455	19	rs9628570	22	30261219		rs6778963	3	39091812	WDR48
WDR48	ILMN-1762103	3	rs1388935	4	138927822		rs853549	3	39067925	WDR48
WDR48	ILMN-1762103	3	rs1887778	9	134635088	RAPGEF1	rs7619193	3	39044116	WDR48
WDR6	ILMN-1762103	3	rs9554833	13	102624790		rs7715581	3	49194351	WDR6
XAF1	ILMN-1669484	3	rs12362253	11	123571708		rs12891171	15	9317379	
XAF1	ILMN-233053	17	rs1535031	21	9673170	XAF1	rs182968	16	68175945	ZEP00
ZEP00	ILMN-1680528	16	rs9064476	17	3070648		rs2242601	7	143693824	ZEP00
ZNF500	ILMN-1700228	16	rs4282793	22	4828377		rs2242601	7	143693824	ZNF500
ZYX	ILMN-1701873	7	rs6056281	20	8953312					ZYX

^a Phenotypes are expression levels of RefSeq Genes^b Illumina probe ID used to measure gene expression^c Physical SNP position in base pairs (HG19)^d RefSeq Gene ID of gene expression level that is influenced by the SNP (BSGS discovery dataset, significance threshold = 1.29 × 10⁻¹¹)^e Interaction - log₁₀ p-value from discovery dataset^f Interaction - log₁₀ p-value from replication dataset^g Interaction - log₁₀ p-value from meta analysis of replication datasets only^h Distance in Mb between interacting SNPs for *cis-cis* acting SNP pairs

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