

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 examples have been reported in other species,⁶ few convincing examples with independent replication 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 peripheral blood, we found 501 significant pairwise epistatic interactions between common SNPs acting on the expression levels of 238 genes ($p < 2.91 \times 10^{-16}$). Replication of these signals in two independent data sets^{11,12} showed both concordance of direction of epistatic effects ($p = 5.56 \times 10^{-31}$) and enrichment of interaction p -values, with 30 being significant at a conservative threshold of $p < 0.05/434$. There was evidence of functional enrichment for the interacting SNPs, for instance 44 of the genetic interactions are located within 5Mb of regions of known physical 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 natural genetic polymorphisms interacting to influence human traits.

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, though its contribution to phenotypic variance is frequently the subject of debate,¹⁻³ there is little empirical exploration of the role that epistasis plays in the architecture of complex traits in humans.^{7,8} Beyond 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. Thus, when combined with small genetic effect sizes, 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 among common variants. 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, thus many genetic effects are relatively large,²¹ 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 used a two stage approach to identify genetic interactions. First, we exhaustively test every pair of SNPs for pairwise effects against each of 7339 expression traits in peripheral blood (5% significance threshold $p < 2.91 \times 10^{-16}$, Methods). Second, we filtered the SNP pairs from stage 1 on LD and genotype class counts, and tested the remaining pairwise effects for significant interaction terms and used a Bonferroni correction for multiple testing (estimated type 1 error rate $\alpha \approx 0.07$, Methods, Supplementary Figure S1). Using this design we identified 501 putative genetic interactions influencing the expression levels of 238 genes (Supplementary Table S1). 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 (5% significance threshold $p < 0.05/434$, Table 1). To quantify the similarity of GP maps between the independent datasets (Figure 1) we decomposed the genetic effects of each of the SNP pairs into orthogonal additive, dominance and epistatic effects ($A1$, $A2$, $D1$, $D2$, $A \times A$, $A \times D$, $D \times A$, $D \times D$) and tested for concordance of the sign of the most significant effect (Supplementary Table S3, Methods). Sign concordance between the discovery and both replication datasets was observed in 22 out of the 30 significantly replicated interactions (expected value = 7.5 under the null hypothesis of no interactions, $p = 3.76 \times 10^{-8}$).

In addition, using the meta analysis from the replication samples only, we observed that 316 of the remaining 404 discovery SNP pairs had replication interaction p -values more extreme than the 2.5% confidence interval of the quantile-quantile plot against the null hypothesis of no interactions ($p < 1.0 \times 10^{-16}$, Figure 2 and Supplementary Figure S2). Concordance of the direc-

tion of the effect of the largest variance component was also highly significant ($p = 5.71 \times 10^{-31}$, Supplementary Table S3). The congruence of the epistatic networks in discovery and replication datasets is shown in Figure 3, 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 20 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 (Supplementary Figure S6). 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 difficult in practice because the dependence on LD between observed SNPs and causal variants is up to three 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 detection. 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 at the discovery stage ($p = 0.22$ for departure from expectation). This is not surprising because the patterns of epistasis used for statistical decomposition (*i.e.* $A \times A$, $A \times D$, $D \times A$, $D \times D$) are simply convenient orthogonal parameterisations of a two locus model, and are not intended to model biological function.²⁴

Of the discovery interactions, 47 were *cis-cis* acting (both SNPs were on the same chromosome as the expression gene, median distance between interacting SNPs is 1.83Mb), 441 were *cis-trans*-acting, and 13 were *trans-trans*-acting. We observed a wide range of significant GP maps (Figure 1) 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 S7). Each of these interactions has evidence for replication in at least one dataset and six are significantly replicated at the Bonferroni level (Supplementary Figure S3). We see similar epistatic networks involving multiple (eight or more) *trans*-acting SNPs for other gene expression levels too, for example TMEM149 (Supplementary Figure S8), NAPRT1 (Supplementary Figure S9), TRAPPC5 (Supplementary Figure S10), and CAST (Supplementary Figure S11). We observed that from pedigree analysis these five gene expression phenotypes had non-additive

variance component estimates within the 95th percentile of the 17,994 gene expression phenotypes that were analysed previously²¹ (Supplementary Table S2, Methods).

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,tri-methylation (H3K4me3) chromatin marks, in 34 cell types²⁶ (Supplementary Figure S5). 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 epistatic interactions where tissue specificity is provided by the *cis* SNPs. There is also enrichment for *cis*-SNPs to be localised in regions with regulatory genomic features as measured by chromatin states²⁷ (Supplementary Figure S4).

We also demonstrate physical organisation of interacting loci within the cell, 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 5Mb ($p < 1.8 \times 10^{-10}$), (Supplementary Figure S12). 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 is 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. 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, despite the relative contribution of pairwise epistasis to phenotypic variation being small. The bioinformatic 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 framework to understanding molecular mechanisms and complex trait variation in greater detail. With computational techniques and data now widely available the search for epistasis in larger datasets for traits of broader interest is warranted.

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. Each individual had gene expression levels measured in peripheral blood at 47,323 probes. Only the probes that passed quality control and had significant expression in $\geq 90\%$ of individuals were used in the analysis (7,339 probes representing 6,158 RefSeq genes). Recent hardware and software¹⁰ advances that use graphics processing units (GPUs) 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 peripheral blood, the Fehrmann 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.

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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

Figures

Figure 1: **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 = high expression, light coloured tiles = low expression). Columns of GP maps are for each independent dataset. 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 2: **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.

Figure 3: **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. 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.

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Supplementary Figures

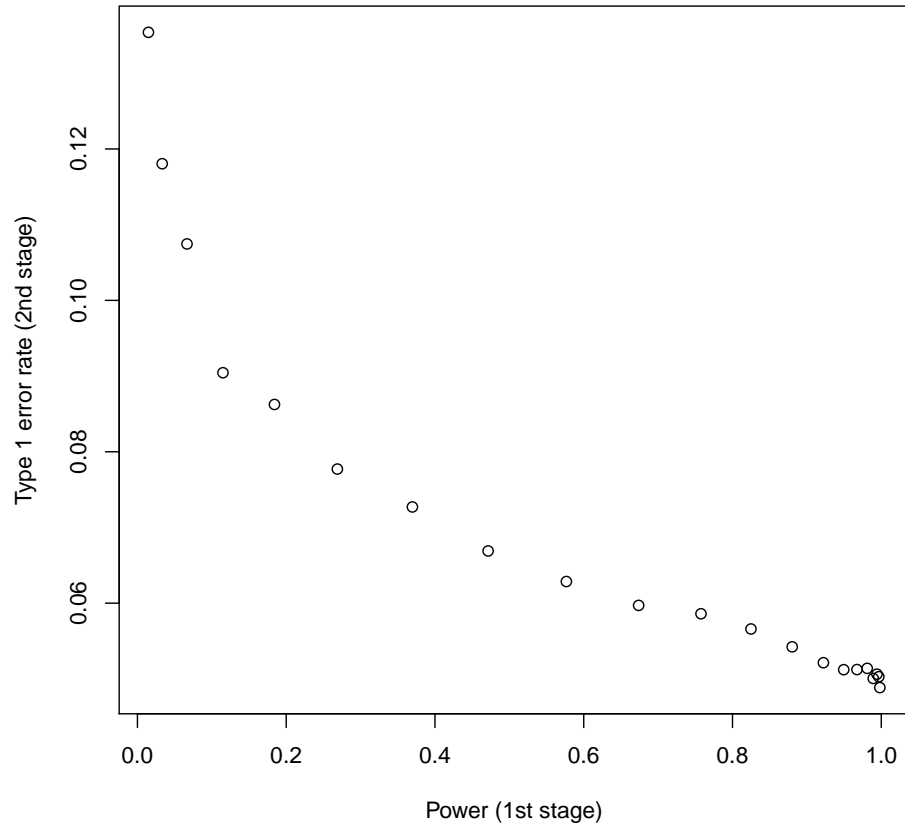


Figure S1: **Type 1 error rate of two stage design** In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These interaction p -values are then adjusted (Bonferroni) for the total number of tests that passed stage 1. The type 1 error rate of this two stage design is dependent on the power, which is not known empirically.

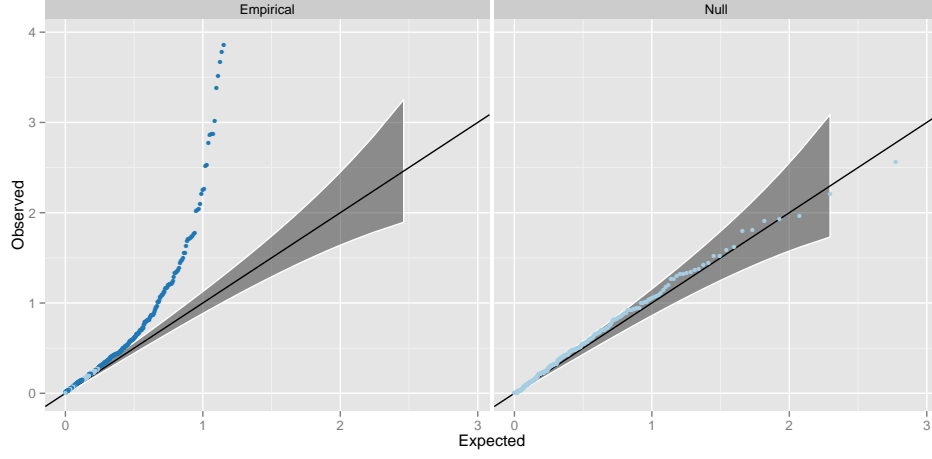


Figure S2: **Q-Q plots of interaction p -values from replication datasets, excluding the 30 points significant at the Bonferroni level** The right panel (Null) shows the interaction p -values from a meta analysis across two independent datasets on 434 randomly drawn SNP pairs. The left panel (Empirical) 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 2.

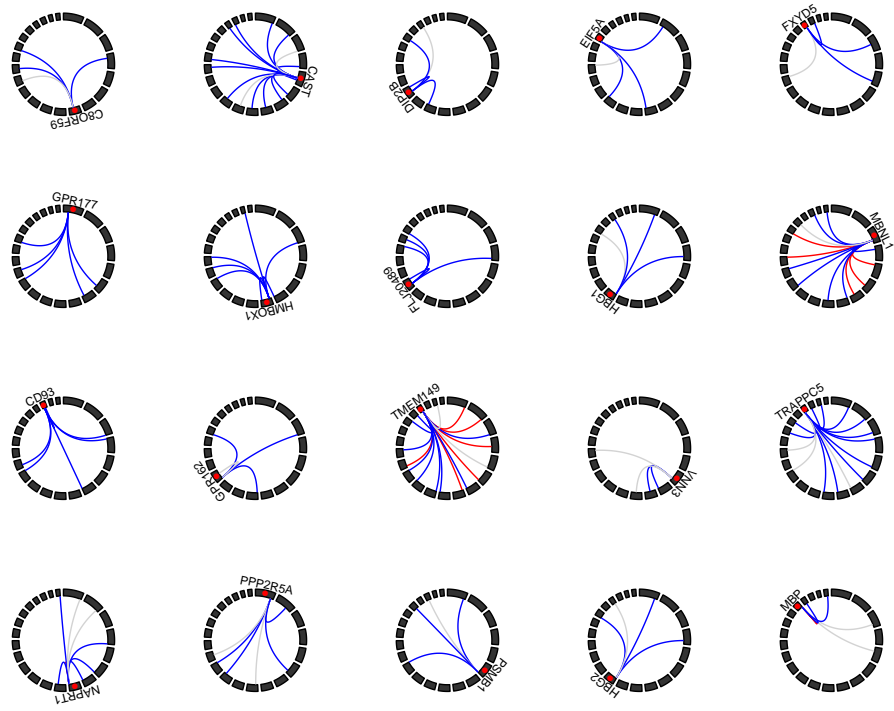


Figure S3: **Gene expression traits with four or more genetic interactions** Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent no evidence for replication, blue lines denote interactions that are outside the 97.5% confidence interval or the Q-Q plot (Figure 2), and red lines denote replication at the Bonferroni correction level. Most interactions are characterised as being *cis-trans* to the expression probe.

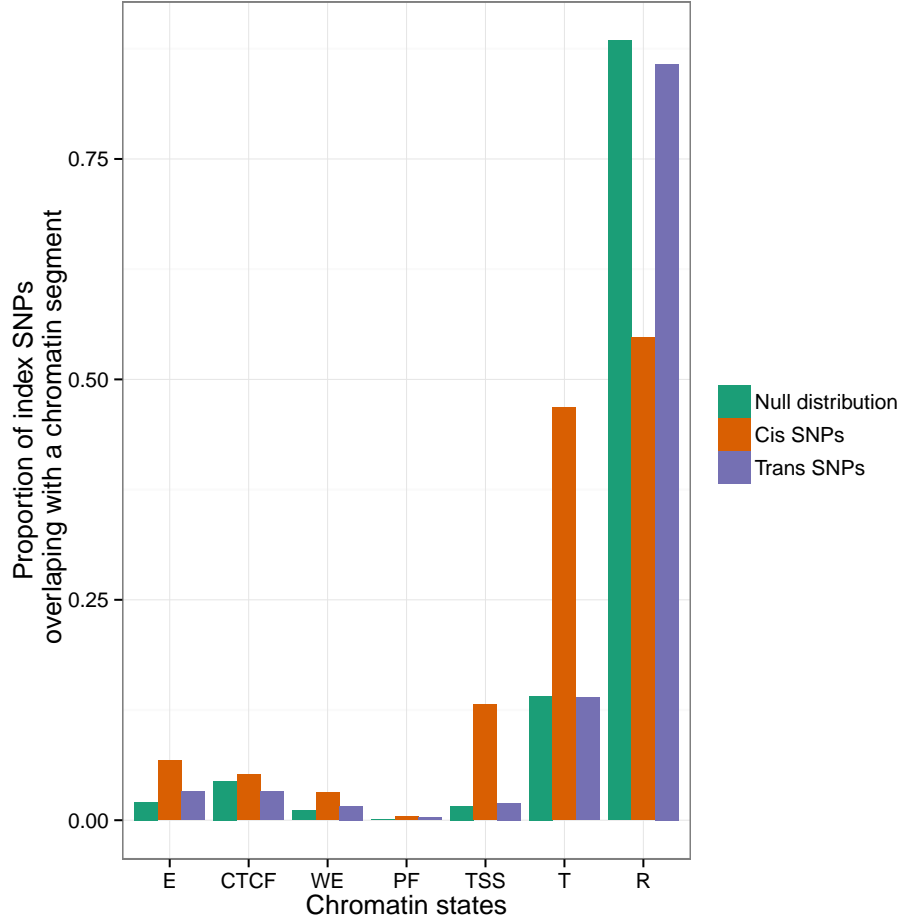


Figure S4: Location of SNPs relative to genomic features We used chromatin segmentation²⁷ as a method for labelling genomic features. All SNPs within 1Mb and $r^2 > 0.8$ of each *cis*- and *trans*-SNP were taken to find which genomic features (x -axis) were covered by the SNPs that compose the 501 significant 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. The labels on the x -axis are as follows: E = Predicted enhancer, CTCF = CTCF enriched element, WE = Predicted weak enhancer or open chromatin cis regulatory element, PF = Predicted promoter flanking region, TSS = Predicted promoter region including transcriptional start site, T = Predicted transcribed region, R = Predicted Repressed or Low Activity region

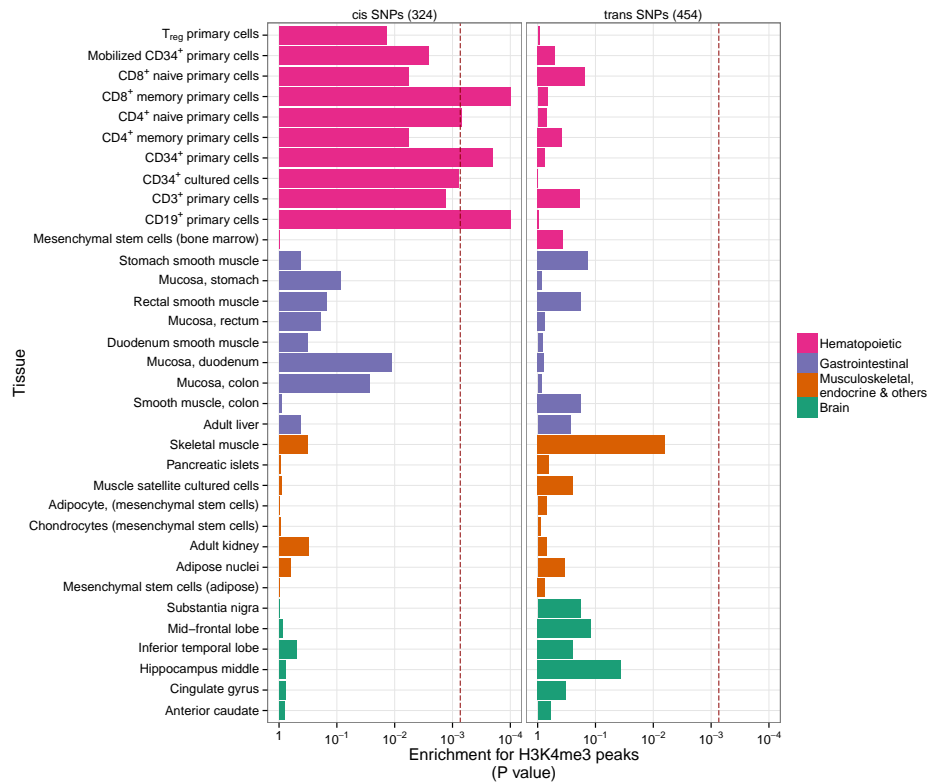


Figure S5: Tissue specific enrichment of SNPs in transcriptionally active regions The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3.²⁶ Enrichment *p*-values are calculated using permutation analysis for 34 different cell types (*y*-axis) in four tissue types (Rows of boxes). The dotted red line denotes significance (Bonferroni correction for 34 cell types, *x*-axis). There is enrichment for *cis*-acting SNPs in Haematopoietic tissue types only. *Trans*-acting SNPs have no tissue specificity.

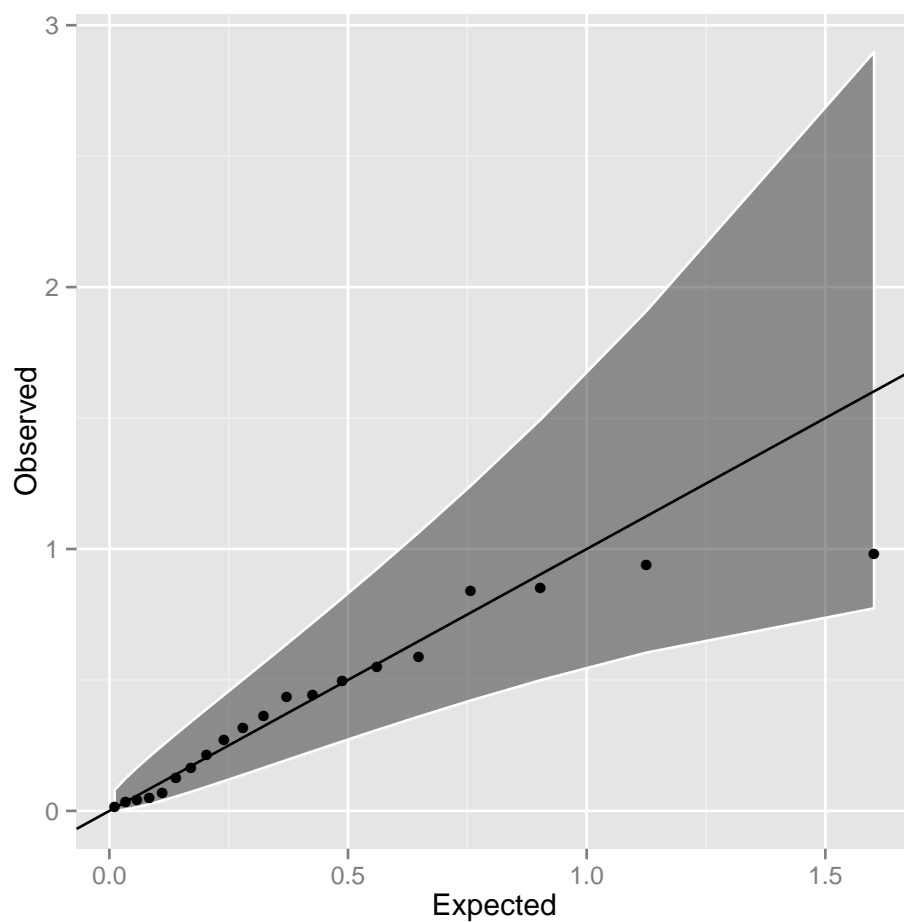


Figure S6: **Q-Q plot of interaction p -values in the CDHWB dataset**
 Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset (mainly due to small sample size). There is no evidence for enrichment of interaction terms, most likely due to insufficient power given the limited sample size.

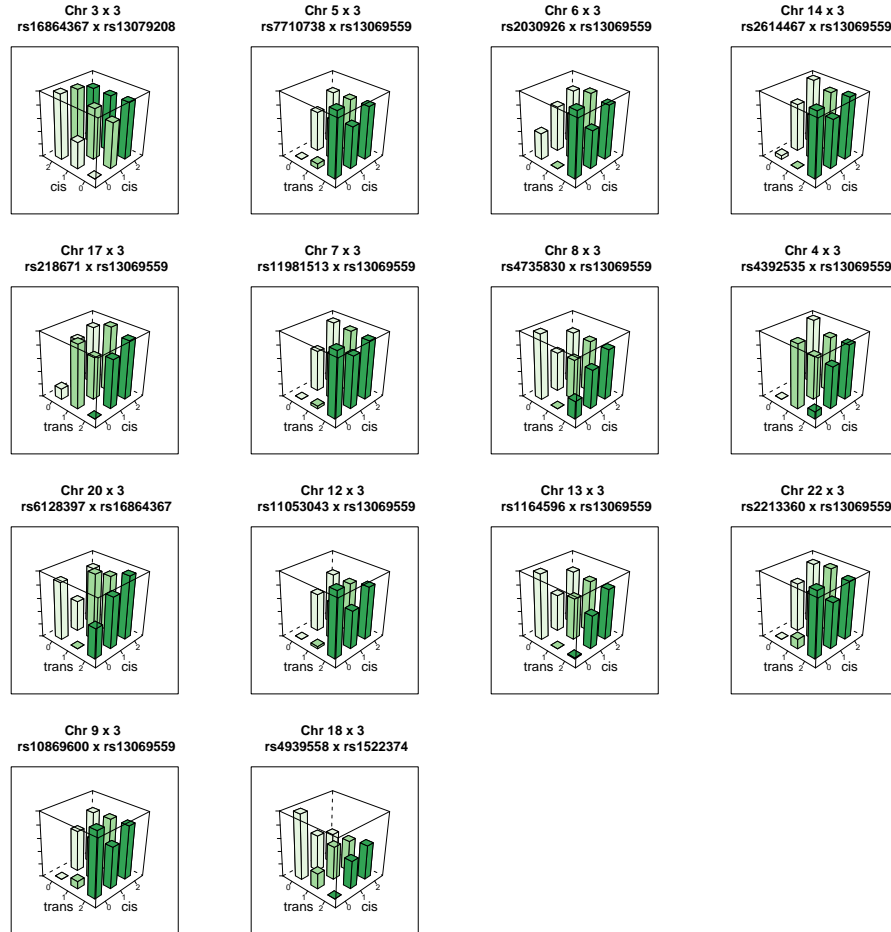


Figure S7: **Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous for the masking allele.

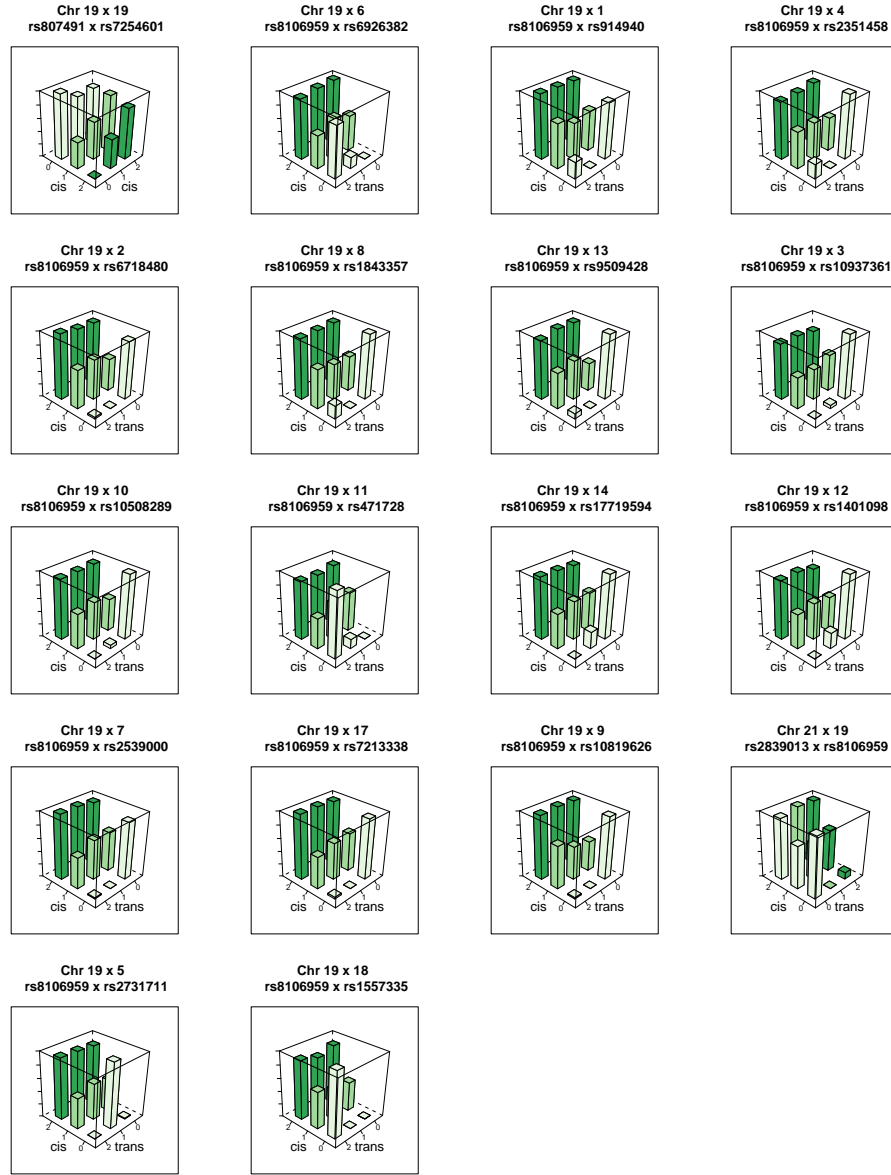


Figure S8: **Genotype-phenotype maps for 19 interactions influencing the expression of TMEM149** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of TMEM149, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous for the masking allele.

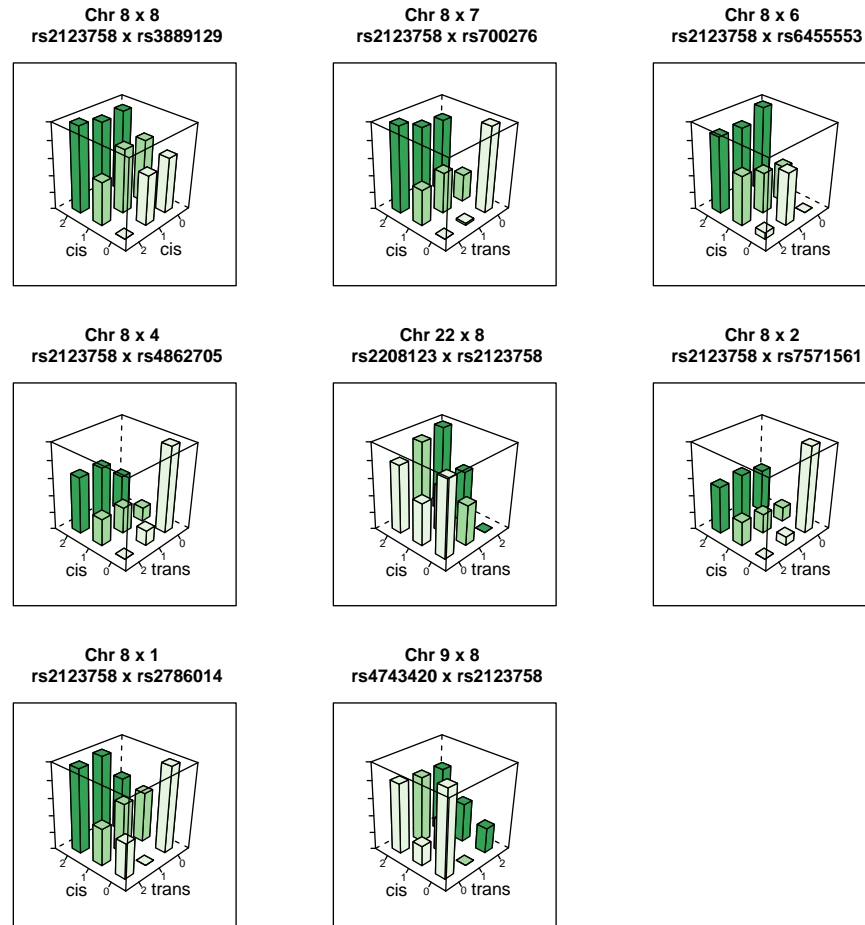


Figure S9: **Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1** Each bar represents the mean phenotypic value for individuals in that genotype class.

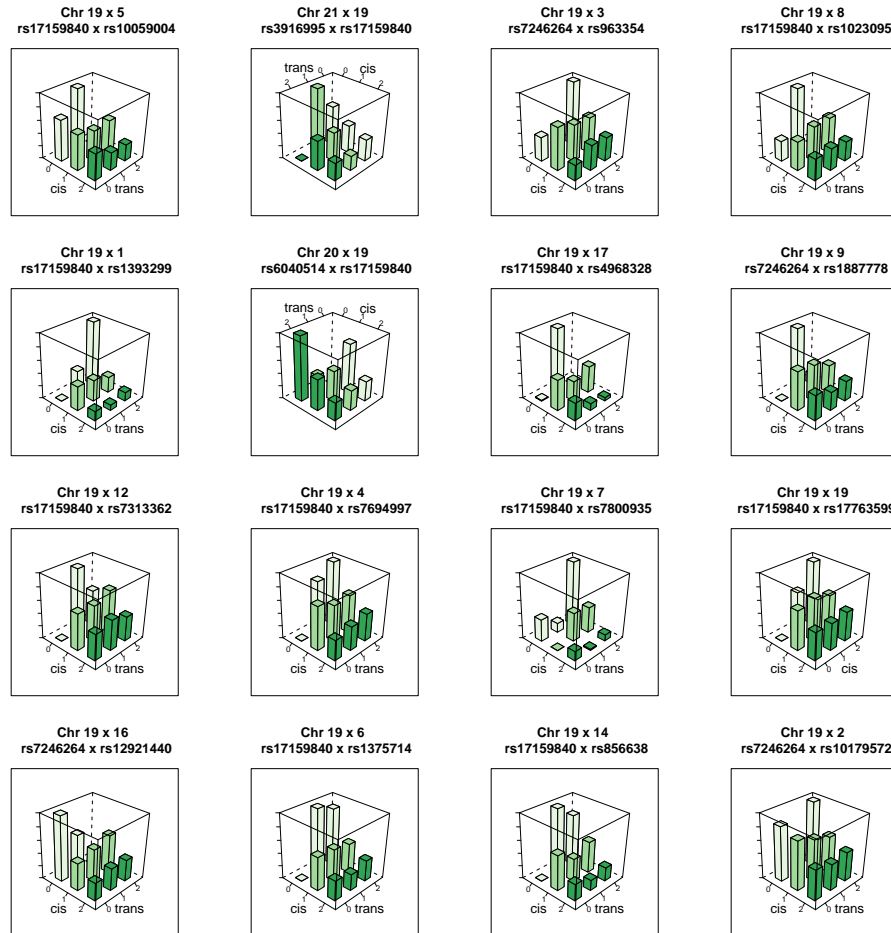


Figure S10: **Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5** Each bar represents the mean phenotypic value for individuals in that genotype class.

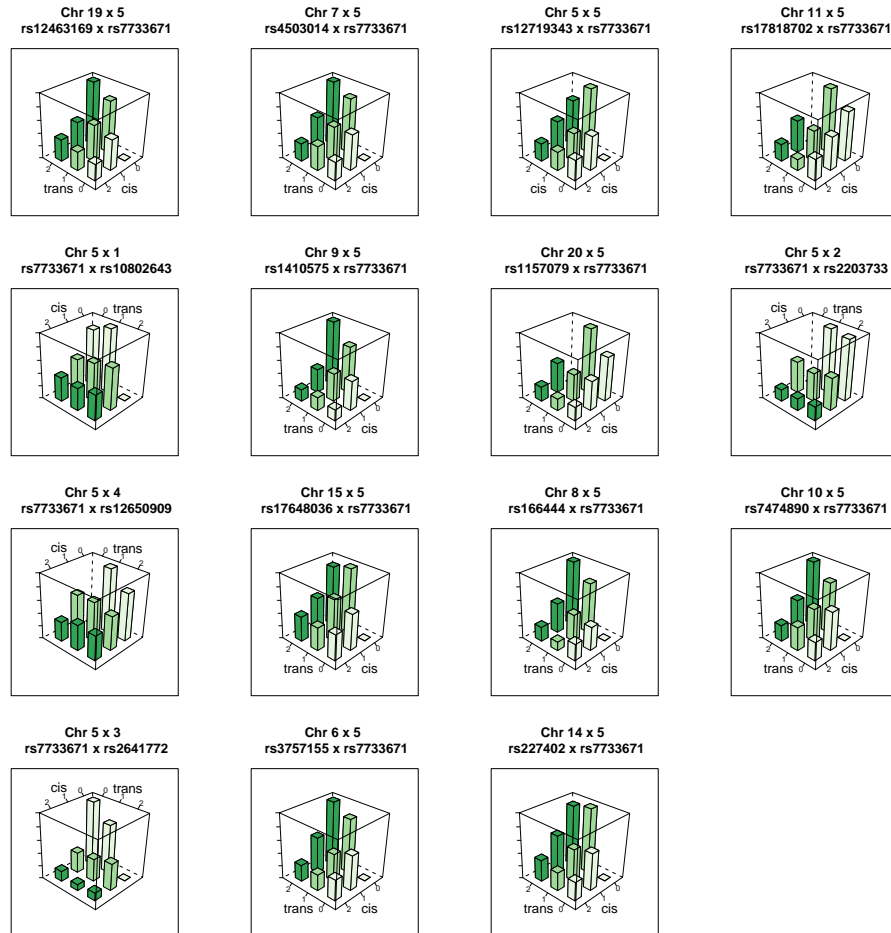


Figure S11: **Genotype-phenotype maps for 15 interactions influencing the expression of CAST** Each bar represents the mean phenotypic value for individuals in that genotype class.

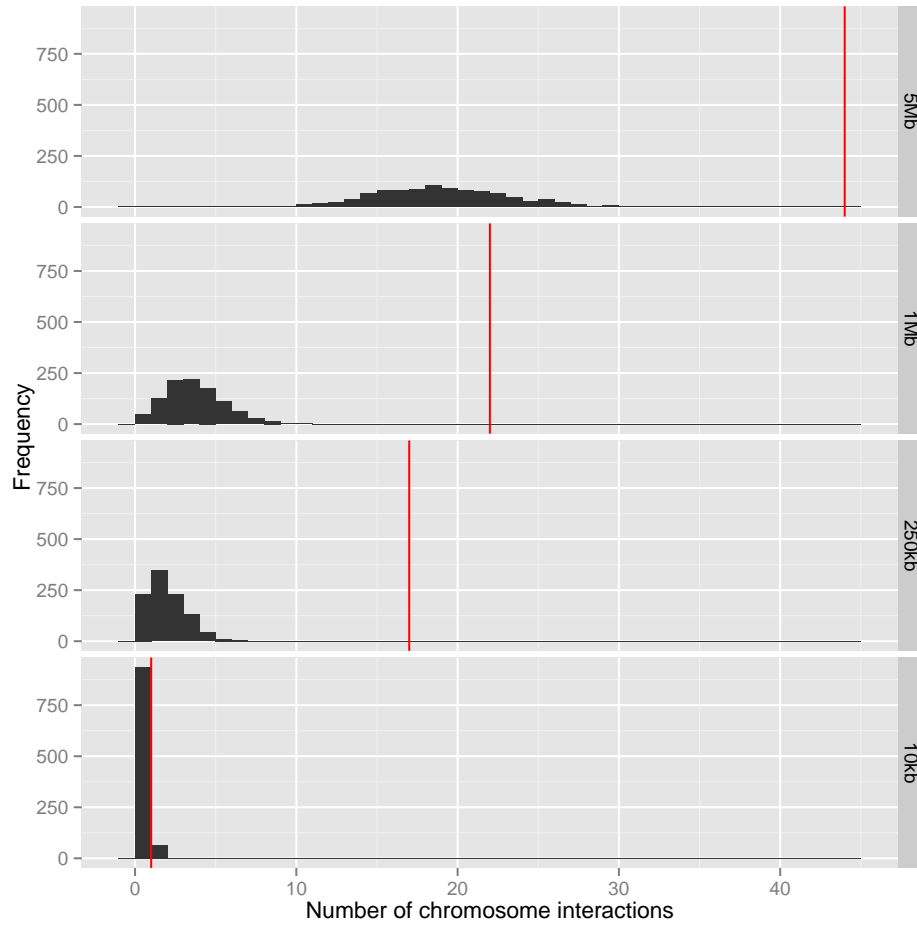


Figure S12: Number of overlaps between chromosome interactions and epistatic interactions Interacting chromosome regions may be a possible mechanism underlying epistatic interactions. The number of epistatic interactions within 20kb, 500kb, 2Mb and 10Mb of known chromosome interacting regions are shown by red vertical lines. The histograms represent the null distribution based on random sampling of 1,000 datasets for each window size.

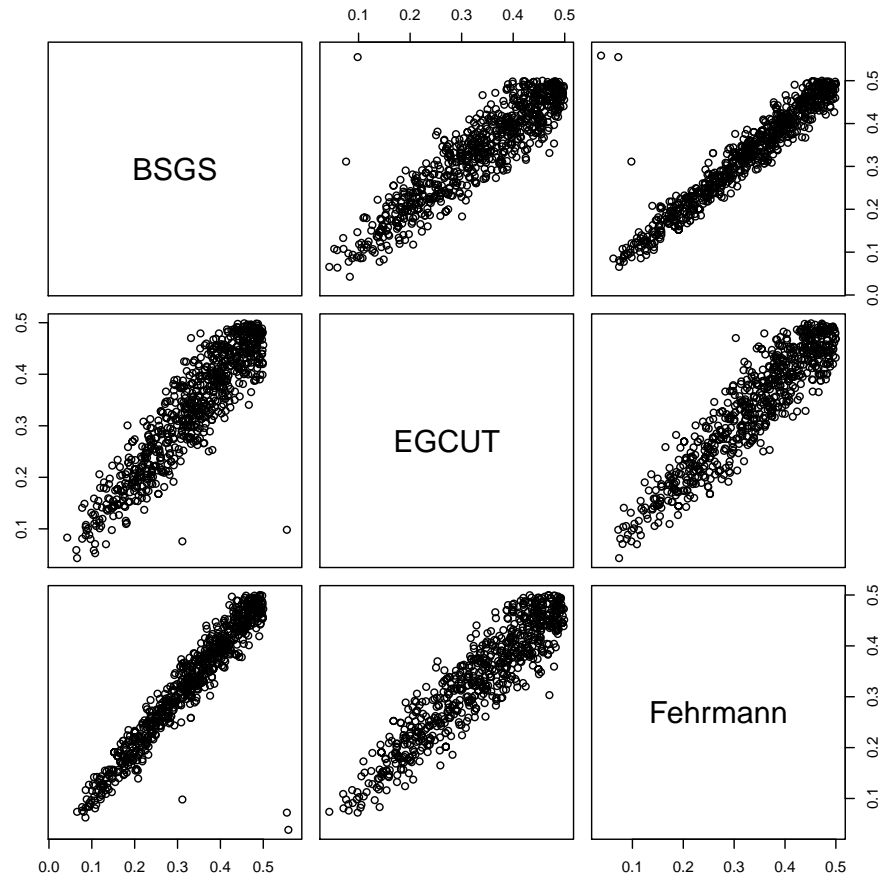


Figure S13: **Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations** Outliers were removed from the analysis as part of the filtering stage during replication.

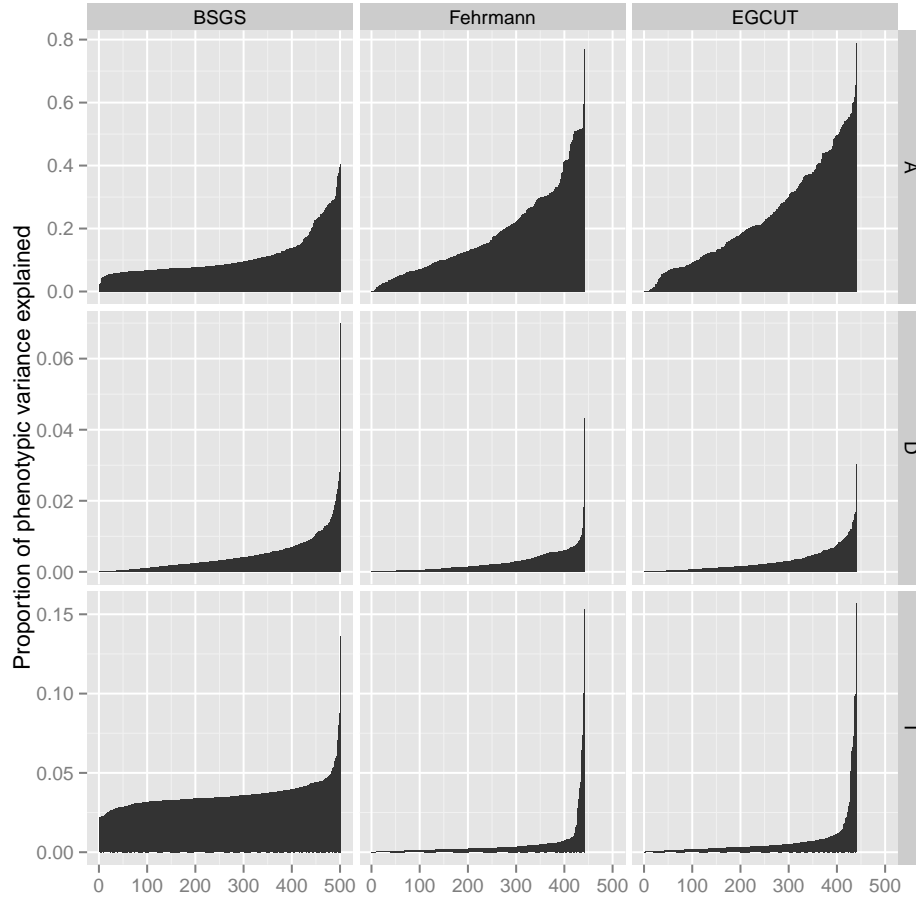


Figure S14: Comparison of variance explained by additive, dominant and epistatic effects from different cohorts How does the estimated variance decomposition change in different cohorts? The proportion of the phenotypic variance that is additive (A), dominant (D), or epistatic (I) for each putative interaction is shown on the y -axis (Note: different scales for each row). BSGS has 501 interactions whereas Fehrmann and EGCUT have 434 (x -axis). The variance estimates in each plot are ordered from lowest additive to highest. This is done independently for each cohort to depict the distribution of estimated effects.

Supplementary Tables

Table S1 – continued from previous page

Gene ID ^a	Expression trait	Probe ID ^b	Chr.	rs ID	Chr.	SNP 1	Pos/Mb ^c	Association ^d	rs ID	Chr.	SNP 2	Pos/Mb ^c	Association ^d	BSGS ^e	Interaction statistic ^f	EGCUT ^g	Distance / Mb ^h
C8ORF59	ILMN-1653205	8	rs8051751	16	7188323				rs2890452	8	86102223			5.79	1.39	0.18	0.87
C9ORF72	ILMN-1741881	9	rs10122902	9	27556780	C9ORF72			rs2526068	1	242019101			6.36	0.96	0.01	0.37
CABC1	ILMN-1731064	1	rs121675847	10	4353808	CABC1			rs37538725	1	221714210	CABC1		6.36	0.94	0.00	0.34
CAD9	ILMN-1712532	9	rs4266763	9	139289825	INPP5E			rs6540410	1	82128660			5.81	0.81	0.00	0.37
CAD9	ILMN-1712532	9	rs4266763	9	139289825	INPP5E			rs4077315	1	139266496	INPP5E		7.61	0.09	0.86	0.42
CAD9	ILMN-1712532	9	rs4266763	9	139289825	INPP5E			rs12677315	1	139266496	INPP5E		7.61	0.09	0.86	0.42
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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				Distance / Mb ^b			
	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
CPVL	ILMN-1682928	7	rs2835998	21	39202070		rs245884	7	29185475	CPVL	5.55	0.19	0.03	0.04
CRPT	ILMN-1813256	2	rs2131290	4	188539908		rs1531133	7	46843651	CRPT	5.47	0.28	0.10	0.12
CRUS1	ILMN-1737685	20	rs6139887	20	5986234	CRUS1	rs1473927	5	42406408		6.18	0.10	0.36	0.15
CS1B	ILMN-1761797	21	rs6979356	21	43230974		rs3761385	21	45196355		11.99	25.20	16.72	42.27
CTNNA1	ILMN-1804854	5	rs924943	18	69000505		rs176382	5	138226707	CTNNA1	5.74	0.02	0.41	0.11
CTSC	ILMN-1696347	11	rs2457684	11	88139983	CTSC	rs7079264	10	10679892		5.67	0.92	0.74	0.03
CTSC	ILMN-1696347	11	rs7532236	22	26250645		rs1728352	11	88077457	CTSC	5.84	0.49	0.73	0.73
CTSC	ILMN-2242463	11	rs7930237	11	88117962		rs1258595	11	88077457		7.16	18.76	15.06	33.53
CWF19L1	ILMN-1651886	10	rs7108734	11	11450027		rs12784396	10	102027407	CWF19L1	5.42	0.21	0.01	0.03
CYBRD1	ILMN-1712305	4	rs2592948	4	129994690		rs888427	2	172366120	CYBRD1	5.89	0.23	0.53	0.34
CYBRD1	ILMN-1712305	2	rs7852475	9	140698856		rs888427	2	172366120	CYBRD1	5.68	0.20	0.02	0.04
CYBRD1	ILMN-2087692	2	rs11257679	10	12318284		rs888427	2	172366120	CYBRD1	5.81	0.39	1.87	1.47
CYBRD1	ILMN-2087692	2	rs6137908	20	23344590		rs888427	2	172366120	CYBRD1	5.53	0.05	0.83	0.36
CYP27A1	ILMN-1704985	2	rs888427	2	172366120	CYBRD1	rs7591849	2	160112881	CYP27A1	5.85	0.87	0.10	0.44
CYP27A1	ILMN-1704985	2	rs6021982	20	36571928		rs933994	2	219650616	CYP27A1	5.42	0.29	0.86	0.60
DAB2	ILMN-2128428	5	rs7778910	17	110451383		rs933994	2	219650616	DAB2	5.44	0.48	0.41	0.44
DDCAKD	ILMN-1811648	17	rs9900173	17	43111688	DDT	rs1343244	9	82076988		9.12	0.00	0.58	0.14
DDT	ILMN-1690982	22	rs9760102	22	24248761		rs275341	3	1847475208		5.62	0.64	0.25	0.42
DDX58	ILMN-1797001	9	rs4837097	11	125962645		rs7042042	7	32451144		5.31	0.61	0.29	0.44
DEM1	ILMN-1783996	1	rs10120023	9	137810259	COQ10A	rs10120023	9	137810259	COQ10A	5.37	0.08	0.41	0.16
DEM1	ILMN-1783996	1	rs12363827	13	106703727		rs7566044	2	169960422	DHRS9	6.39	0.77	0.02	0.29
DHRS9	ILMN-1733998	2	rs1511956	12	39468283		rs7566044	2	169960422	DHRS9	6.00	0.06	1.17	0.58
DHRS9	ILMN-1733998	2	rs1328529	12	39468283		rs2161037	2	169893419	DHRS9	6.48	0.37	0.34	0.32
DHRS9	ILMN-2384181	2	rs2831914	21	29959453		rs2161037	2	169893419	DHRS9	5.51	0.88	0.04	0.37
DHRS9	ILMN-2384181	4	rs77661304	4	187776431		rs11669322	12	50610976	LASS5	7.64	0.05	0.11	0.10
DIP2B	ILMN-1755589	12	rs11080134	17	29161503	LASS5	rs11669322	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
DIP2B	ILMN-1755589	12	rs3383853	19	41711815	LASS5	rs7134595	12	50730458	LASS5	5.31	0.38	0.22	0.19
DIP2B	ILMN-1755589	12	rs7312552	12	50730458	LASS5	rs1808634	8	61971140	LASS5	4.40	0.37	0.09	0.02
DIP2B	ILMN-1755589	12	rs7312552	12	50730458	LASS5	rs4532958	10	115214154	LASS5	5.03	0.48	0.00	0.11
DIP2B	ILMN-1755589	12	rs7312552	12	50744171	LASS5	rs12427378	12	51074199	DNAB1B6	5.92	0.23	1.45	0.97
DNAB1B6	ILMN-1793770	7	rs2288842	17	171994348		rs3775539	7	157163614	DNAB1B6	5.79	0.79	0.27	1.12
DPH3	ILMN-2140610	3	rs12252308	15	93409054	ECGF1	rs1566972	3	16320360	DPH3	6.17	1.58	0.27	1.12
ECGF1	ILMN-2109708	22	rs14323491	22	50971266		rs4891884	18	64004670	DPH3	4.81	0.15	1.18	0.70
ECGF1	ILMN-1671568	1	rs4324091	22	241911027		rs11206043	1	53402552	ECGF1	6.19	0.22	0.35	0.22
ECGF1	ILMN-1671568	1	rs5092637	22	17675900		rs11206043	1	53402552	ECGF1	5.58	0.64	0.16	0.35
ECGF1	ILMN-1720083	15	rs0403312	19	53244938		rs1048166	15	42192040	ECGF1	6.98	0.90	0.47	0.79
EIF2B2	ILMN-1713380	14	rs6567288	18	60218334		rs1754556	14	75503430	EIF2B2	5.56	0.23	0.11	0.10
EIF5A	ILMN-1794522	17	rs7216490	17	7221707	EIF5A	rs1269096	14	99603119	EIF2B2	5.44	0.56	0.08	0.24
EIF5A	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	rs1553474	2	49359676	EIF2B2	5.55	0.28	0.05	0.02
EIF5A	ILMN-1794522	17	rs7216490	17	7221707	EIF5A	rs44771434	11	126387391	EIF2B2	6.36	0.08	0.05	0.02
EMR2	ILMN-2353633	19	rs2827076	21	23196249		rs9305048	19	14879034	EMR2	5.52	0.05	1.12	0.53
EMR2	ILMN-2353633	19	rs6132112	20	18761714		rs9305048	19	14879034	EMR2	5.51	0.36	0.04	0.11
EMR2	ILMN-2353633	19	rs9405048	19	14879034		rs3007765	13	102480759	EMR2	6.56	0.45	0.40	0.41
EMR2	ILMN-1709237	8	rs1107764	11	12790396	EMR2	rs3007765	13	102480759	EMR2	5.70	0.20	0.58	0.35
EPHX2	ILMN-1731001	8	rs10894861	11	14879034		rs12115088	8	5787462	EPHX2	5.43	0.25	1.20	0.81
EPHX2	ILMN-1731001	8	rs5766218	22	45337329		rs12115088	8	5787462	EPHX2	6.11	0.20	0.11	0.09
EPHX2	ILMN-1731001	8	rs726145	18	31187910		rs12115088	8	5787462	EPHX2	5.63	0.29	0.04	0.08
ERICH1	ILMN-2104696	5	rs4735895	8	600729	ERICH1	rs1517297	4	182786760	ERICH1	5.63	0.67	1.03	1.06
ERICH1	ILMN-2104696	5	rs187076	10	55228462		rs12188164	5	4928236	ERICH1	6.83	0.74	0.19	0.44
EXOC3	ILMN-1789419	5	rs187076	10	55228462		rs12188164	5	4928236	EXOC3	6.83	0.74	0.19	0.44
FAHD1	ILMN-2246661	16	rs1560104	16	12708208		rs344363	16	1972548	FAHD1	5.61	1.38	0.30	0.23
FCN1	ILMN-1668063	9	rs12580388	12	129591144		rs10120023	9	137810259	COQ10A	6.33	0.27	0.30	0.23

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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			Distance / Mb ^b			
		rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	BSGS ^e		Fehrmann ^f	EGCUT ^g	Meta ^g
NRBF2	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
NRBF2	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11	0.47	0.05	0.17
NRBF2	ILMN-1800897	1	rs4852124	2	240680022		rs6588415	1	52334047	NRBF2	6.13	0.03	0.46	0.15
NRDI	ILMN-1787885	8	rs5017351	11	25453442		rs1005901	8	21964378	NUDT18	5.44	1.27	1.35	2.03
NUDT18	ILMN-1658247	12	rs11613438	12	113480510		rs1047944	6	16399740		4.13	4.12	0.81	3.86
OAS1	ILMN-1658247	12	rs113311	12	113480510		rs2072133	12	113409260		4.38	0.87	0.46	0.76
OAS1	ILMN-1675640	19	rs2892233	19	49160255		rs3741981	12	13169066	OAS1	5.64	0.42	0.06	0.14
OPTN	ILMN-2381899	10	rs7192613	16	74286646		rs17312962	10	13169066	OPTN	5.00	0.36	0.00	0.07
OSBPL5	ILMN-2307032	11	rs2829679	21	26625433		rs998639	11	3149249	OSBPL5	5.00	0.16	0.87	0.49
OSTF1	ILMN-1742456	9	rs17780195	17	70624189		rs2273770	9	77755469	OSTF1	5.42	1.20	0.08	0.62
OSTF1	ILMN-1742456	9	rs2273770	9	77755469	OSTF1	rs7775469	9	77755469	OSTF1	5.42	1.20	0.08	0.62
OVGP1	ILMN-1734542	1	rs10802822	1	240132968		rs1264898	5	111992853	OVGP1	5.43	0.13	1.48	0.88
OVGP1	ILMN-1734542	1	rs347351	3	140148107		rs1264894	1	111992853	OVGP1	6.04	0.25	1.21	0.82
PAM	ILMN-2313901	5	rs28092	5	102149795	PAM	rs7846000	1	40139553	HPCAL4	5.59	0.66	0.44	0.59
PCYOX1L	ILMN-1815951	5	rs2438490	5	14826162	PCYOX1L	rs2731939	3	21395989		6.20	0.19	0.26	0.16
PEX5	ILMN-1602332	12	rs10444467	12	128052636		rs4329748	12	7364442	PEX5	5.85	0.09	0.71	0.32
PEX5	ILMN-1602332	12	rs7495797	15	27240462		rs4329748	12	7364442	PEX5	5.74	0.34	0.09	0.13
PFAAP5	ILMN-1797893	13	rs131969	22	49151303		rs7328733	13	33126737	PFAAP5	5.64	0.87	0.36	0.67
PGLYRP1	ILMN-1704870	19	rs12982353	19	46529456		rs1263806	14	21982957		6.51	0.03	0.65	0.24
PHCA	ILMN-1812552	11	rs493642	11	123097386	PGLYRP1	rs10736812	11	76708086	PHCA	5.51	0.36	0.90	0.70
PIK3P1	ILMN-1719986	22	rs4141404	22	31675185	PIK3P1	rs10498313	14	30398876		6.17	0.28	0.91	0.93
PISD	ILMN-1793934	22	rs470072	22	32263151	PISD	rs1465754	11	8209571		5.23	0.02	0.87	0.33
PISD	ILMN-1739934	22	rs615752	22	332334931	PISD	rs715572	22	332334931		7.11	0.00	1.19	0.48
PISD	ILMN-1793934	22	rs715572	22	332334931		rs58781604	2	219182481	PNL7	4.12	0.05	0.42	0.15
PNKD	ILMN-1774604	22	rs6869411	16	155781604		rs498046	9	140487108	PNL7	6.35	0.16	0.04	0.04
PNL7	ILMN-1662587	9	rs11639998	16	45271109		rs4735001	11	140487108	PNL7	5.15	0.31	0.78	0.56
PPFIP2	ILMN-1675656	11	rs911019	20	49668255		rs1156875	14	35619816	PPFIP2	4.44	0.29	0.33	0.26
PPFIP2	ILMN-1662617	14	rs12914603	15	58350896		rs12100009	1	212447167	PPFIP2	5.81	0.12	0.42	0.19
PPFIP2	ILMN-1738784	1	rs10930170	2	16339967		rs12100009	1	212447167	PPFIP2	5.63	0.72	0.48	0.66
PPFIP2	ILMN-1738784	1	rs12433255	12	123595064		rs12100009	1	212447167	PPFIP2	5.72	0.08	0.95	0.46
PPFIP2	ILMN-1738784	1	rs1889083	13	66222691		rs12100009	1	212447167	PPFIP2	5.61	0.36	0.13	0.17
PPFIP2	ILMN-1738784	1	rs682334	11	107417238		rs12100009	1	212447167	PPFIP2	5.65	1.69	0.28	1.21
PPFIP2	ILMN-1738784	1	rs7575781	1	135030045		rs12100009	1	212447167	PPFIP2	5.95	0.37	0.06	0.12
PPFIP2	ILMN-1738784	1	rs7575781	9	271040482		rs12100009	1	212447167	PPFIP2	5.72	0.16	0.30	0.16
PRDX5	ILMN-1711606	11	rs8019823	16	95040482		rs11600990	11	64082807	PRDX5	6.43	0.81	0.14	0.44
PRDX5	ILMN-1711606	11	rs2188355	16	23867776		rs10492793	16	12639800		7.34	0.53	0.11	0.25
PRDX5	ILMN-1711606	16	rs1028231	21	47931653	C21ORF57	rs958127	18	31497346		5.60	0.19	0.03	0.04
PRMT2	ILMN-1675038	21	rs2839372	21	48063862		rs11701058	21	47776382	C21ORF57	4.81	0.69	4.47	4.06
PSMB1	ILMN-1789176	6	rs38962607	17	121774705		rs13207114	6	170877444	PSMB1	5.79	0.00	0.26	0.04
PSMB1	ILMN-1789176	6	rs48906648	18	43983954		rs9295415	6	170890384	PSMB1	5.14	0.44	0.21	0.27
PSMB1	ILMN-1789176	6	rs6060930	20	30347832		rs9295415	6	170823379	PSMB1	5.44	1.95	0.64	1.78
PSMB1	ILMN-1789176	6	rs6928843	6	170890384	PSMB1	rs2769689	1	225797957	PSMB1	5.42	1.18	0.32	0.86
PSMB1	ILMN-1789176	6	rs7299749	12	131727816		rs13207114	6	170877444	PSMB1	5.00	0.03	0.48	0.15
PWP1	ILMN-1743049	12	rs2353567	14	95478823		rs11036212	11	5221825	PTDSS1	5.90	0.80	0.08	0.38
PWP1	ILMN-1743049	12	rs4969205	17	76598123		rs11036212	11	5221825	PTDSS1	5.70	1.02	0.40	0.11
PWP1	ILMN-1743049	12	rs631562	11	126852438		rs11036212	11	5221825	PTDSS1	5.75	1.03	1.25	1.55
QDPR	ILMN-1672443	4	rs4946705	6	106348246		rs10020773	4	17526682	QDPR	6.55	0.25	0.08	0.09
RAB3IP	ILMN-1803197	12	rs241730	22	33375704		rs7305307	12	70235726		6.42	0.28	0.84	0.59
RABAC1	ILMN-2207363	19	rs1075728	19	42462788	RABAC1	rs7951028	11	12016117		6.38	0.31	0.08	0.31
RBL2	ILMN-1796999	16	rs9931702	16	53526551	AKTIP	rs1863464	15	26998488	RCN1	5.23	0.58	0.37	0.47
RCN1	ILMN-1800276	11	rs10879131	12	41147155		rs4922579	11	32136436		4.32	0.41	0.09	0.17
RCN1	ILMN-1800276	11	rs4922579	11	32136436	RCN1	rs11166957	8	141177468		5.40	0.04	0.26	0.07
RCN1	ILMN-1800276	11	rs4922579	11	32136436	RCN1								

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Expression trait			SNP 1			SNP 2			Interaction statistic / -log10 p-values			Distance / Mb		
Gene ID ^a	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
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	132424366		rs301819	1	8501786	REBE	5.74	0.14	0.10	0.06
REBE	ILMN-2327795	1	rs11085829	19	13174312		rs301819	1	8501786	REBE	5.74	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		rs4848487	13	54665512		4.37			
RNF167	ILMN-1794726	17	rs400668	17	4839930	RNF167	rs11706900	3	36348908		5.59	0.71	0.46	0.64
RNPEP	ILMN-1738347	1	rs1107121	17	46127549		rs2819365	1	201983242		6.27	0.11	0.30	0.13
RNPEP	ILMN-1738347	1	rs8071611	17	67153386		rs2819365	1	201983242		4.32	1.48	0.32	1.28
RPL13	ILMN-2413278	16	rs352935	16	89648580		rs2965817	16	89513234		4.98	3.79	14.41	17.24
RPL23AP7	ILMN-2222750	12	rs1401202	16	80320056		rs4849261	2	114450028	RPL23AP7	5.55	0.13	0.73	0.38
RPL36AL	ILMN-2186933	14	rs3007033	14	50103816	RPL36AL	rs17495030	9	138038093		5.46	0.09	0.06	0.02
RPL36AL	ILMN-2186936	14	rs4009028	14	50020817		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		rs2958482	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
SEC13	ILMN-3297880	3	rs17085428	5	95388015		rs7695	1	156147326	SEC13	5.70	0.02	0.51	0.15
SES3	ILMN-1694027	11	rs12147460	14	104412137		rs684856	11	94906111	SES3	5.50	0.31	0.06	0.10
SES3	ILMN-1694027	11	rs355391	15	46591793	SES3	rs684856	11	94906111	SES3	5.67	0.21	0.51	0.31
SES3	ILMN-1694027	11	rs684856	11	49406111		rs7004947	8	134606425	PPBP	5.60	0.32	0.70	0.35
SH3BGLR2	ILMN-1762764	6	rs10838191	11	43893658		rs1354034	3	56849749	PPBP	5.52	0.70	0.12	0.35
SH3BGLR2	ILMN-1762764	6	rs2545385	5	6683979		rs1354034	3	56849749	PPBP	5.97	0.32	0.71	0.30
SH3BGLR2	ILMN-1762764	6	rs6845304	4	88280502		rs1354034	3	56849749	PPBP	5.23	0.32	0.71	0.33
SH3BGLR2	ILMN-2158336	9	rs1034120	21	18196922		rs1745517	9	131785369	SH3BGLR2	7.40	0.22	0.18	0.13
SIRPG	ILMN-1771801	20	rs1535883	20	1612819	SIRPG	rs6842739	14	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	19	2923826	SLC22A18	rs3110874	7	153224179		5.70	0.15	0.10	0.06
SLC22A18	ILMN-2382505	11	rs367035	11	2923826	SLC22A18	rs7772054	2	241678528		6.15	0.39	0.13	0.19
SLC41A3	ILMN-236111	3	rs1912136	11	24616743		rs6771703	3	125801067	SLC41A3	5.88	1.10	0.82	1.24
SLC45A4	ILMN-1747578	8	rs698508	8	142337734	SLC45A4	rs70701916	5	174598073		5.95	0.86	0.07	0.40
SLC46A3	ILMN-1658639	13	rs198305	17	5502091		rs7981190	13	29259349	SLC46A3	5.52	0.09	0.38	0.26
SMG7	ILMN-1775553	1	rs803259	15	97403923		rs10911353	1	183489203	SMG7	6.52	0.17	0.09	0.06
SMOX	ILMN-3309349	20	rs1183515	9	4161500	SMOX	rs116777815	2	65800982		5.68	0.39	0.62	0.32
SNHG8	ILMN-3309349	19	rs1504220	9	1336050253		rs7080837	4	119225940	SNHG8	6.11	0.29	1.03	0.72
SNHG8	ILMN-3309349	19	rs3634462	15	46250108		rs214097	11	17291499	SNHG8	7.31	13.11	10.96	23.22
SNORD14A	ILMN-1709381	4	rs2634462	11	17339127		rs6486334	11	17015557	SNORD14A	6.08			
SNORD89	ILMN-3238663	2	rs10445863	2	115929241		rs750783	2	101889306	SNORD89	5.96			
SNORD89	ILMN-3238663	2	rs11605822	11	122986326		rs750783	2	101889306	SNORD89	6.33			
SNORD89	ILMN-3238663	2	rs2135064	5	26778066		rs750783	2	101889306	SNORD89	6.33			
SNUPN	ILMN-1733932	15	rs1346466	21	46376528	SNUPN	rs17185362	16	81888905		6.45			
SNUPN	ILMN-2364535	15	rs1346466	21	46376528		rs1472075	3	193706323		5.59	0.34	0.00	0.06
SPATA5L1	ILMN-1729179	15	rs131620	19	41117869		rs4774580	15	45652086	SPATA5L1	5.44			
STARD10	ILMN-2210752	11	rs2221406	13	90174526		rs1006620	11	72509713		5.65	0.67	0.12	0.33
STYXL1	ILMN-2345142	7	rs4073164	14	104947517	SULF2	rs1006620	11	72509713	STYXL1	5.85	0.57	0.17	0.31
SULF2	ILMN-2345142	20	rs11700063	18	74332954		rs932994	4	180439236	STYXL1	5.51	0.46	0.24	0.30
SULF2	ILMN-2336133	16	rs1463965	18	74332954		rs932994	4	180439236	TUFM	7.05	0.01	0.05	0.00
SURF6	ILMN-1778032	9	rs2436657	20	40119768		rs3785354	16	28550667	TUFM	5.83			
SURF6	ILMN-2336609	11	rs6099626	20	56013994		rs3785354	16	28550667	TUFM	5.83			
SYTL2	ILMN-1778032	9	rs1375719	13	103410782		rs3118663	9	136281753	SURF6	6.14	0.26	0.16	0.14
THBS3	ILMN-1804663	1	rs1939875	11	95422867		rs485485	11	85495269	SYTL2	5.47	0.28	0.31	0.24
THBS3	ILMN-1804663	1	rs1939875	11	95422867		rs4072037	1	155162067	THBS3	5.55	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	16745523		rs1320993	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			Distance / Mb ^b
	rs ID	Chr.	rs ID	Chr.	Pos/Mb/c	Association ^d	rs ID	Chr.	Pos/Mb/c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	
TNME14	rs1940400	11	rs1940400	11	132839627	TNME14	rs1775246	7	41581986	TNME14	5.71	0.06	1.34	0.70
TNME14	rs2839013	19	rs2839013	19	47238981	TNME14	rs106959	19	36210525	TNME14	8.11	0.16	0.48	0.26
TNME14	rs5762235	20	rs5762235	20	27925988	TNME14	rs106959	19	36210525	TNME14	6.79			
TNME14	rs6090518	20	rs6090518	20	45207005	TNME14	rs106959	19	36210525	TNME14	11.09	0.76		
TNME14	rs807491	19	rs807491	19	36268923	SNX26	rs7254601	19	36147315		12.16	81.55	45.78	145.78
TNME14	rs106959	19	rs106959	19	36210525	TNME14	rs10508289	10	47909159	TNME14	8.12	1.55	3.09	3.67
TNME14	rs8106959	19	rs8106959	19	36210525	TNME14	rs10819628	9	133025756		8.02	0.40	0.99	0.80
TNME14	rs106959	19	rs106959	19	36210525	TNME14	rs10937361	3	188359436		8.39	3.61	1.18	3.78
TNME14	rs8106959	19	rs8106959	19	36210525	TNME14	rs1401098	12	128884559		7.37	2.41	1.00	2.52
TNME14	rs106959	19	rs106959	19	36210525	TNME14	rs1557335	18	64268976		6.95	0.08	0.07	0.03
TNME14	rs8106959	19	rs8106959	19	36210525	TNME14	rs17719594	14	90932598		6.23	3.06	0.77	2.87
TNME14	rs106959	19	rs106959	19	36210525	TNME14	rs1843357	8	13822381		6.21	3.72	3.33	6.00
TNME14	rs8106959	19	rs8106959	19	36210525	TNME14	rs2551458	4	113317583		7.30	0.04	0.91	8.00
TNME14	rs106959	19	rs106959	19	36210525	TNME14	rs2539000	7	147619772		6.70	1.57	1.52	2.27
TNME14	rs8106959	19	rs8106959	19	36210525	TNME14	rs2731711	5	171792273		5.92	0.19	0.33	0.19
TNME14	rs106959	19	rs106959	19	36210525	TNME14	rs471728	11	129595460		8.89	0.90	3.62	3.51
TNME14	rs8106959	19	rs8106959	19	36210525	TNME14	rs6718480	2	233879066		8.55	3.31	5.15	7.36
TNME14	rs106959	19	rs106959	19	36210525	TNME14	rs6926382	6	161683974		5.80	3.06	8.80	10.72
TNME14	rs8106959	19	rs8106959	19	36210525	TNME14	rs7213338	17	80357420		5.49	0.07	3.14	2.10
TNME14	rs106959	19	rs106959	19	36210525	TNME14	rs914940	1	242889492		6.22	3.36	6.96	9.20
TNME14	rs1254086	13	rs1254086	13	72890603	TNME14	rs9090428	13	21473952		9.44	0.10	5.75	4.47
TNME63A	rs1548475	9	rs1548475	9	58058246		rs1449226	1	226027323	TNME63A	5.60			
TNME80	rs1537146	9	rs1537146	9	4859303		rs4963126	11	656845	TNME80	5.79	0.64	0.12	0.32
TNPO3	rs199793	20	rs199793	20	225287303		rs10488630	7	128593948	IRF5	5.52	1.03	0.17	0.62
TNPO3	rs7776572	13	rs7776572	13	113531675		rs10488630	7	128593948	IRF5	8.23	3.19	1.89	4.09
TNPO3	rs1793823	11	rs1793823	11	131018917		rs3916581	11	11888787	TRAPPC4	5.61	0.28	0.40	0.29
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs3916581	11	11888787	TRAPPC4	5.52	0.93	0.01	0.36
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs10059004	5	166970604		5.97	0.21	1.60	1.01
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs10230095	8	132022937		6.92	0.37	0.67	0.68
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs1375714	6	156404902		7.79	0.12	0.18	0.09
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs13932299	1	242329791		6.43	0.63	0.47	0.59
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs17633599	19	2369415		6.38	0.21	0.24	0.16
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs4968328	17	57495457		6.51	0.50	0.38	0.44
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs7313362	12	129644342		7.08	0.04	0.65	0.25
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs7694997	4	9947811		5.86	0.20	0.36	0.22
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs7800935	7	146690926		6.27	0.15	0.33	0.16
TNPO3	rs17159840	19	rs17159840	19	7758194	TRAPPC5	rs856638	14	85439550		6.73	0.24	0.07	0.08
TNPO3	rs380708	22	rs380708	22	24740855		rs17159840	19	7758194	TRAPPC5	7.58	0.85	0.78	1.01
TNPO3	rs3916995	21	rs3916995	21	45128454		rs17159840	19	7758194	TRAPPC5	7.73	0.51	0.55	0.56
TNPO3	rs6040514	20	rs6040514	20	11272861		rs17159840	19	7758194	TRAPPC5	8.10	0.02	0.02	0.02
TNPO3	rs7246204	19	rs7246204	19	7762978		rs10179572	2	228504503		6.71	0.14	0.26	0.13
TNPO3	rs7246204	19	rs7246204	19	7762978		rs12921440	16	30485765		7.34	0.08	0.86	0.40
TNPO3	rs7246204	19	rs7246204	19	7762978		rs1887778	3	15393377	RAPGEF1	7.05	0.36	0.90	0.69
TNPO3	rs7246204	19	rs7246204	19	7762978		rs963354	3	15739370		7.41	0.06	0.90	0.69
TNPO3	rs10862075	12	rs10862075	12	8749398		rs2395771	6	41264377	TREM1	5.42	0.11	0.25	0.11
TNPO3	rs1242864	6	rs1242864	6	106266422		rs2395771	6	41264377	TREM1	3.92	1.20	1.23	1.69
TNPO3	rs1242864	6	rs1242864	6	106266422		rs2027647	10	22979147	TRIM38	6.46	0.04	0.91	0.39
TNPO3	rs1242864	6	rs1242864	6	106266422		rs1848526	10	82792929	TSPAN14	6.06	0.07	0.18	0.06
TNPO3	rs1242864	6	rs1242864	6	106266422		rs12840098	1	5012317951	TSPAN32	5.01			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs2800998	6	137947208	TSPAN32	5.51			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs620807	2	238746880		6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs1783126	16	85147633		6.13			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422		rs470119	22	50966914	ECGF1	6.34			
TNPO3	rs1242864	6	rs1242864	6	106266422									

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Table S1 – continued from previous page

Expression trait			SNP 1			SNP 2			Interaction statistic / -log ₁₀ p-values						
Gene ID ^a	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	Distance / Mb ^h
UBASH3A	LMN-2338348	21	rs1893592	21	43855067	UBASH3A	rs7201194	16	83600397		5.91	0.59	0.42	0.52	
UBASH3A	LMN-2338348	21	rs1893592	21	43855067	UBASH3A	rs7512594	1	214517361		6.01	0.48	1.29	1.10	
USP36	LMN-1697227	17	rs2279308	17	76794981	USP36	rs7225546	17	75151717		5.71	0.03	0.14	0.03	1.643
VASP	LMN-1743646	19	rs1264226	19	40663167		rs2276470	19	45974668	VNN2	5.09	0.94	5.14	4.95	0.088
VNN2	LMN-1678939	6	rs10435352	7	103252718		rs1883613	6	133077063	VNN2	5.64	0.84	0.15	0.46	
VNN2	LMN-1678939	6	rs13044386	20	9116155		rs1883617	6	133072650	VNN2	5.44	0.39	0.69	0.57	
VNN2	LMN-1678939	6	rs134447	22	49927332		rs1883617	6	133072650	VNN2	5.72				
VNN3	LMN-1678939	6	rs216495	11	16834510		rs1883617	6	133072650	VNN2	5.77	0.33	0.19	0.19	
VNN3	LMN-1678939	6	rs10278073	7	151662184		rs2267932	6	133067782	VNN3	6.44	0.16	0.74	0.41	
VNN3	LMN-1804935	6	rs1443946	8	73006453		rs2267932	6	133067782	VNN3	5.74	0.23	0.48	0.31	
VNN3	LMN-1804935	6	rs348462	9	75547169		rs2267952	6	133067782	VNN3	6.44	0.31	0.17	0.17	
VNN3	LMN-1804935	6	rs7157055	14	83262064		rs2267952	6	133067782	VNN3	5.82	0.03	0.19	0.04	
VNN3	LMN-2387680	6	rs2823165	21	5694253		rs2267952	6	133067782	VNN3	6.12	0.73	1.15	1.21	
VNN3	LMN-2387680	6	rs9596457	13	51692548		rs2267952	6	133067782	VNN3	4.83	0.46	0.05	0.16	
VSTM1	LMN-1763455	19	rs9596457	19	54553697	VSTM1	rs4552100	18	71024750		5.60	0.53	0.54	0.57	
VSTM1	LMN-1763455	19	rs10500316	19	54553697	VSTM1	rs7895870	10	123095249		5.71	0.48	0.17	0.26	
VSTM1	LMN-1763455	19	rs10500316	19	54553697	VSTM1	rs10500316	19	54553697	VSTM1	5.88	0.81	1.38	1.47	
WDR48	LMN-1762103	3	rs9628570	22	30261219		rs6778963	3	39091812	WDR48	5.88	0.09	0.33	0.09	
WDR48	LMN-1762103	3	rs1388935	4	18827822	RAPGEF1	rs853349	3	39067325	WDR48	5.34	0.57	1.35	1.22	
WDR48	LMN-1762103	3	rs1887778	9	134635088		rs7619193	3	39044116	WDR48	5.85	0.18	0.61	0.35	
WDR6	LMN-1669484	3	rs9554833	13	102624790		rs7619193	3	39044116	WDR6	4.86	1.64	1.43	2.25	
XAF1	LMN-2330573	17	rs12362253	11	123571708		rs11715581	3	49194331	XAF1	4.86	2.38	0.17	1.63	
XAF1	LMN-2330573	17	rs1535031	21	36773170	XAF1	rs12591171	15	68119799	XAF1	5.79	0.09	0.36	0.15	
ZEP00	LMN-1680928	16	rs906446	21	37040648		rs1182968	16	68573945	ZEP00	5.79	0.67	0.27	0.46	
ZNF500	LMN-1700238	16	rs4283723	22	48283177		rs2290560	16	4799041	ZNF500	5.29	0.67	0.27	0.46	
ZYX	LMN-1701875	7	rs6056281	20	8935312		rs2242601	7	143093824	ZYX	6.04	0.26	0.01	0.05	

^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 pairsⁱ p-values are absent if the interaction did not pass the QC filtering in the replication dataset^j Meta analysis p-values are absent if the interaction did not pass the QC filtering in either replication dataset

Table S2: **Estimation of additive and non-additive variance components from pedigree information** Taken from previous analysis in Powell et al 2013²¹

Gene	Probe	Additive		Non-additive	
		Variance	s.e.	Variance	s.e.
NAPRT1	ILMN_1710752	0.37	0.03	0.14	0.05
TMEM149	ILMN_1786426	0.41	0.04	0.09	0.04
MBNL1	ILMN_2313158	0.18	0.03	0.11	0.04
TRAPPC5	ILMN_2372639	0.32	0.04	0.13	0.05
CAST	ILMN_1717234	0.31	0.03	0.10	0.04

Table S3: **Concordance of sign of epistatic variance components between discovery and replication datasets**

Test	Interactions ^a	Dataset	n^b	Expected ^c	Observed ^d	p -value
1 ^e	All	EGCUT	434	217.00	306	6.69×10^{-18}
		Fehrmann	434	217.00	278	5.04×10^{-9}
		Both	434	108.50	221	5.56×10^{-31}
	Significant	EGCUT	30	15.00	25	3.25×10^{-4}
		Fehrmann	30	15.00	24	1.43×10^{-3}
		Both	30	7.50	22	3.76×10^{-8}
2 ^f	All	EGCUT	434	54.25	92	4.22×10^{-7}
		Fehrmann	434	54.25	79	6.18×10^{-4}
		Both	434	6.78	30	2.55×10^{-11}
	Significant	EGCUT	30	3.75	19	9.46×10^{-11}
		Fehrmann	30	3.75	19	9.46×10^{-11}
		Both	30	0.47	18	2.23×10^{-25}
3 ^g	All	EGCUT	1133	566.50	775	7.10×10^{-36}
		Fehrmann	1133	566.50	726	1.90×10^{-21}
		Both	1133	283.25	562	1.39×10^{-70}
	Significant	EGCUT	73	36.50	55	1.69×10^{-5}
		Fehrmann	73	36.50	55	1.69×10^{-5}
		Both	73	18.25	46	7.86×10^{-12}

^a “All” denotes 434 discovery interactions and “Significant” denotes 30 interactions with significant replication p -values

^b Number of tests for concordance

^c Expected number of concordant cases under the null hypothesis of no interactions

^d Observed number of concordant cases

^e The sign of the most significant epistatic variance component in discovery is the same as the corresponding variance component in the replication data.

^f The largest epistatic variance component in the discovery is the same as in the replication with the same sign in both.

^g The sign of all epistatic variance components in the discovery with $p < 0.05$ are the same as the corresponding variance components in the replication data.

Table S4: **Concordance of sign of epistatic variance components between discovery and replication datasets using test 4**

Interactions ^a	Dataset	n^b	0 ^c	1 ^c	2 ^c	3 ^c	4 ^c	p
Expected ^d	-	-	0.06	0.25	0.38	0.25	0.06	-
All	EGCUT	434	0.06	0.22	0.41	0.23	0.08	0.194
All	Fehrman	434	0.07	0.22	0.39	0.24	0.08	0.385
All	Combined	868	0.07	0.22	0.40	0.23	0.08	0.0448
Significant	EGCUT	30	0.07	0.03	0.30	0.33	0.27	4.72×10^{-4}
Significant	Fehrman	30	0.03	0.07	0.33	0.27	0.30	6.69×10^{-4}
Significant	Combined	60	0.05	0.05	0.32	0.30	0.28	5.49×10^{-8}

^a “All” denotes 434 discovery interactions and “Significant” denotes 30 interactions with significant replication p -values.

^b Number of tests for concordance.

^c Proportion of tests that have 0, 1, 2, 3 or 4 concordant signs between discovery and replication.

^d Expected proportion of concordant signs under the null hypothesis of no epistasis.

Table S5: Details on linkage disequilibrium and relative positions of all discovery *cis-cis* interactions

Chr	Gene	SNP 1	SNP 2	Position 1	Position 2	Distance / Mb	R^2	D'
19	TMEM149	rs807491	rs7254601	36268923	36147315	0.122	0.000	0.001
17	FN3KRP	rs898095	rs9892064	80890638	80827903	0.063	0.063	0.088
21	CSTB	rs9979356	rs3761385	45230974	45198355	0.033	0.041	0.066
3	MBNL1	rs16864367	rs13079208	152234166	152116652	0.118	0.041	0.117
10	ADK	rs2395095	rs10824092	76446305	75929517	0.517	0.013	0.020
11	CTSC	rs7930237	rs556895	88117962	88077479	0.040	0.012	0.045
17	GAA	rs11150847	rs12602462	78153130	78146016	0.007	0.000	0.001
8	NAPRT1	rs2123758	rs3889129	144663661	144613680	0.050	0.053	0.060
1	LAX1	rs1891432	rs10900520	203877662	203780591	0.097	0.065	0.106
18	MBP	rs8092433	rs4890876	74747424	74732087	0.015	0.035	0.053
11	SNORD14A	rs2634462	rs6486334	17339127	17015557	0.324	0.008	0.012
21	C21ORF57	rs9978658	rs11701361	48027084	47764477	0.263	0.032	0.065
16	RPL13	rs352935	rs2965817	89648580	89513234	0.135	0.054	0.060
19	ATP13A1	rs4284750	rs873870	19810050	19738554	0.071	0.008	0.015
2	NCL	rs7563453	rs4973397	232301670	232291471	0.010	0.027	0.029
5	HNRPH1	rs6894268	rs4700810	179032488	178991794	0.041	0.000	0.001
19	VASP	rs1264226	rs2276470	46063167	45974668	0.088	0.018	0.022
7	TRA2A	rs7776572	rs11770192	23528927	23498358	0.031	0.064	0.064
21	PRMT2	rs2839372	rs11701058	48063862	47776382	0.287	0.100	0.122
12	OAS1	rs13311	rs2072133	113448652	113409260	0.039	0.002	0.016
16	N4BP1	rs12444224	rs11649236	87580855	48632478	38.948	0.007	0.021
5	CAST	rs12719343	rs7733671	125369113	96000269	29.369	0.001	0.001
7	DNAJB6	rs2286842	rs3779589	157216093	157163614	0.052	0.005	0.006
1	OVGP1	rs10802822	rs1264898	240132968	111992823	128.140	0.008	0.030
20	CD93	rs2868504	rs1884655	37771578	23074375	14.697	0.000	0.002
11	PHCA	rs493642	rs10736812	123097386	76708086	46.389	0.002	0.008
21	MX1	rs459498	rs8130120	42795027	29363604	13.431	0.000	0.000
16	AKTIP	rs2896940	rs13332406	57721127	53489705	4.231	0.000	0.001
17	CDK5R1	rs9905940	rs11655031	46614102	30833162	15.781	0.000	0.000
2	CYBRD1	rs888427	rs7591849	172368120	160112881	12.255	0.000	0.000
8	HMBX1	rs587639	rs7837237	132725731	28876221	103.850	0.001	0.001
11	TRAPPC4	rs1793823	rs3916581	131018917	118887887	12.131	0.001	0.002
12	PEX5	rs10444467	rs4329748	128052636	7364442	120.688	0.000	0.000
12	FLJ20489	rs17615703	rs3782908	117036766	48169526	68.867	0.001	0.002
16	PRKCB1	rs2188355	rs10492793	23867776	12639800	11.228	0.000	0.000
14	MRPL52	rs1950857	rs3811188	26710271	23299135	3.411	0.002	0.004
17	C17ORF60	rs9907897	rs7405659	63502633	59874129	3.629	0.004	0.011
6	FLJ43093	rs6906101	rs13214069	36667610	32705248	3.962	0.000	0.000
19	TRAPPC5	rs17159840	rs17763599	7758194	2369415	5.389	0.000	0.000
22	PISD	rs715572	rs6518754	33234931	32097775	1.137	0.001	0.003
12	DIP2B	rs871257	rs12427378	117994348	51074199	66.920	0.001	0.001
12	GPR162	rs2272500	rs2707210	79685913	6902002	72.784	0.003	0.005
17	USP36	rs2279308	rs7225546	76794981	75151717	1.643	0.000	0.000