

# 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 traits<sup>1</sup> and contributes to their variation<sup>2,3</sup> is a fundamental question in evolution and human genetics. Though epistasis has been demonstrated in artificial gene manipulation studies in model organisms,<sup>4,5</sup> and examples have been reported in other species,<sup>6</sup> few convincing examples with independent replication exist for epistasis amongst natural polymorphisms in human traits.<sup>7,8</sup> Its absence from empirical findings may simply be due to its low incidence in the genetic control of complex traits,<sup>2,3</sup> but an alternative view is that it has previously been too technically challenging to detect due to statistical power and computational issues.<sup>9</sup> Here we show that, using advanced computation techniques<sup>10</sup> 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<sup>11,12</sup> 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 interactions<sup>13</sup> ( $p = 1.8 \times 10^{-10}$ ). 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.<sup>14</sup> But to date, though its contribution to phenotypic variance is frequently the subject of debate,<sup>1-3</sup> there is little empirical exploration of the role that epistasis plays in the architecture of complex traits in humans.<sup>7,8</sup> Beyond the prism of human association studies there is evidence for epistasis, not only at the molecular scale from artificially induced mutations<sup>4</sup> but also at the evolutionary scale in fitness adaptation<sup>15</sup> and speciation.<sup>16</sup>

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,<sup>17,18</sup> increased model complexity in fitting interaction terms,<sup>19</sup> and more extreme significance thresholds to account for increased multiple testing<sup>9</sup> 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,<sup>14</sup> the power to detect epistasis diminishes rapidly. There are two simple ways to overcome this problem. One is by using extremely large sample sizes;<sup>20</sup> 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,<sup>21</sup> maximising the chance at detecting epistasis, should it exist.

In our discovery dataset (Brisbane Systems Genetics Study, BSGS<sup>22</sup>) 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, Fehrman<sup>12</sup> and the Estonian Genomics Centre University of Tartu (EGCUT),<sup>11</sup> 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). These significant interactions exhibited remarkable similarity in GP maps between all three 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 in the independent datasets (Methods). The most significant epistatic effect in the discovery sample was in the same direction in both replication datasets in 22 out of the 30 significantly replicated interactions ( $p = 3.76 \times 10^{-8}$ , Supplementary Table S3).

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,<sup>23</sup> 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.<sup>17,18</sup> 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,<sup>9</sup> 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 association<sup>21</sup> (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.<sup>24</sup>

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 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 splicing<sup>25</sup>) 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 previously<sup>21</sup> (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 types<sup>26</sup> (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 states<sup>27</sup> (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.<sup>13</sup> We cross-referenced our epistatic SNPs with a map of chromosome interacting regions ( $n = 96,139$ ) in K562 blood cell lines<sup>28</sup> (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.<sup>29,30</sup>

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,<sup>22</sup> 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.<sup>2</sup> Ideally one would approach this question from a whole genome perspective<sup>31</sup> 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.<sup>2,3</sup> 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,<sup>22</sup> 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 software<sup>10</sup> advances that use graphics processing units (GPUs) made it possible to perform the  $1.03 \times 10^{15}$  statistical tests to complete this analysis. We used permutation analysis<sup>32</sup> 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.<sup>18,19</sup> 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 dataset<sup>12</sup> ( $n = 1240$ ) and the Estonian Genome Centre University of the University of Tartu (EGCUT) dataset<sup>11</sup> ( $n = 891$ ). 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 <sup>2</sup>	Fehrmann <sup>3</sup>	EGCUT <sup>3</sup>	Meta <sup>4</sup>
1	ADK (10)	rs2395095 (10)	rs10824092 (10)	6.69 <sup>1</sup>	18.33 <sup>1</sup>	21.21 <sup>1</sup>	39.82 <sup>1</sup>
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

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

<sup>2</sup> Discovery dataset

<sup>3</sup> Independent replication dataset

<sup>4</sup> 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

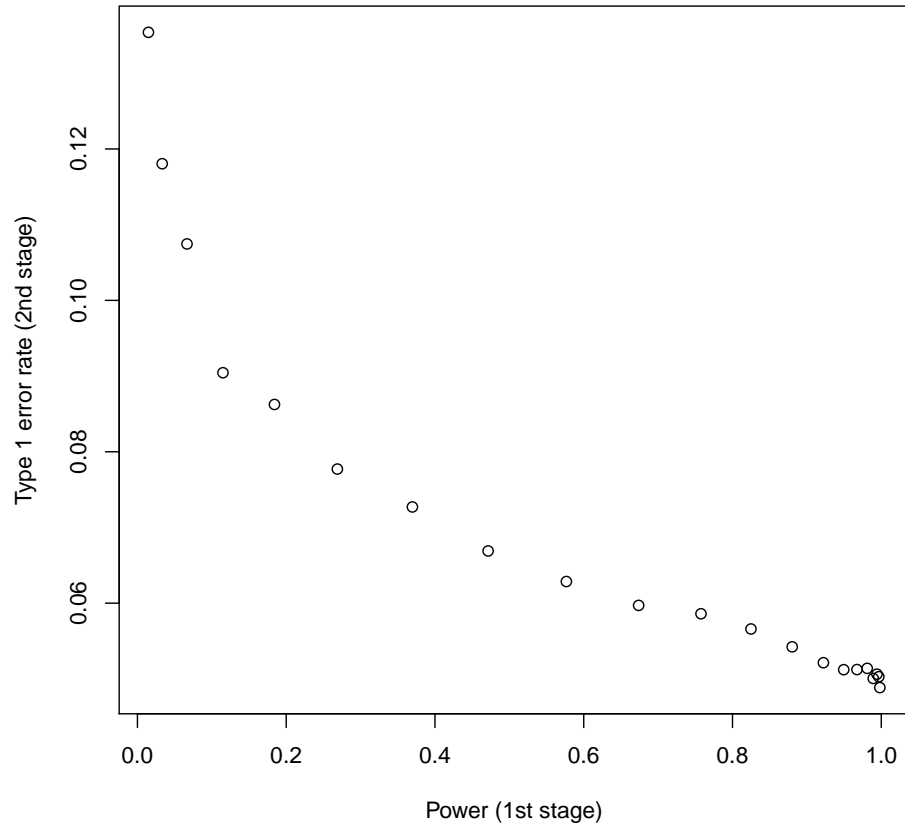


Figure S1: **Type 1 error rate of two stage design** In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These interaction  $p$ -values are then adjusted (Bonferroni) for the 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.

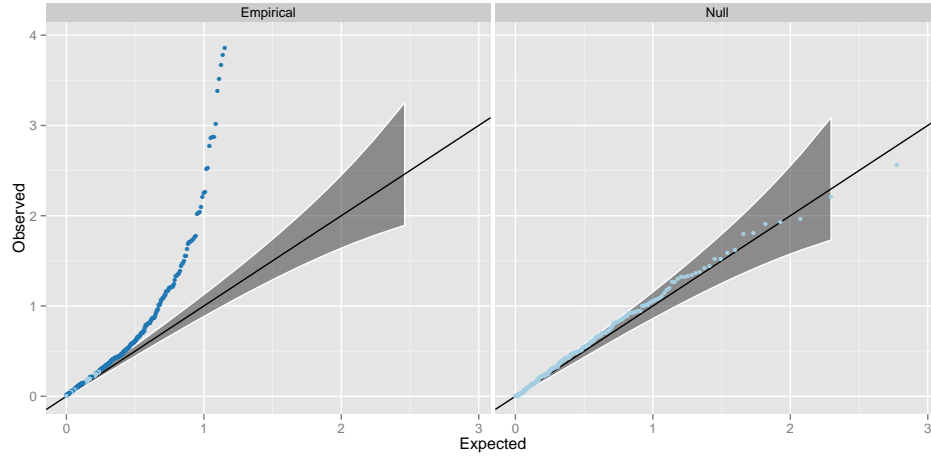


Figure S2: **Q-Q plots of interaction  $p$ -values from replication datasets, excluding the 30 points significant at the Bonferroni level** The right panel (Null) shows the interaction  $p$ -values from a meta analysis across two independent datasets on 434 randomly drawn SNP pairs. The left panel (Empirical)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

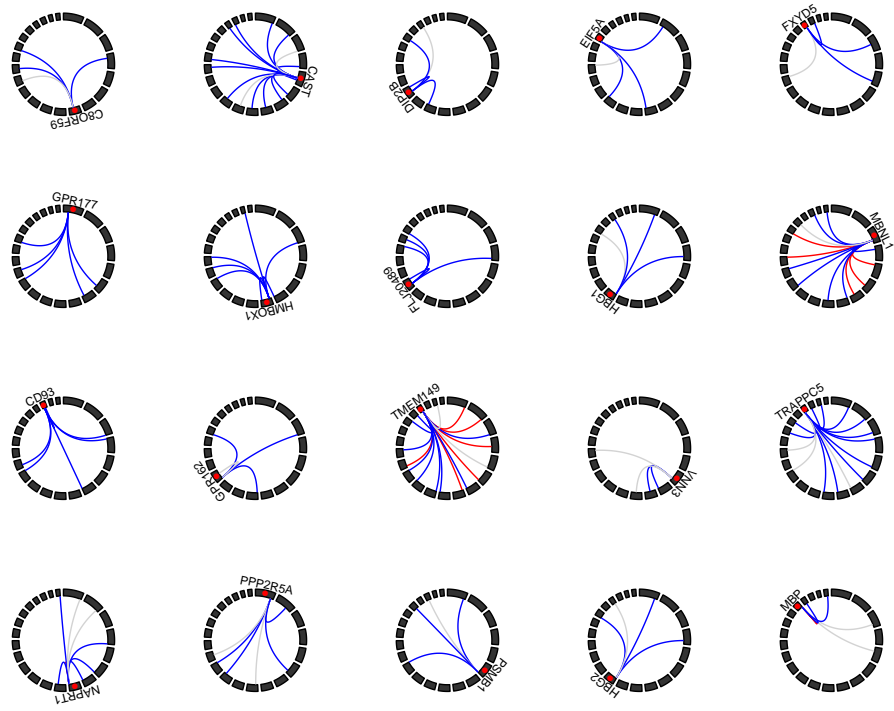


Figure S3: **Gene expression traits with four or more genetic interactions** Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent 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.



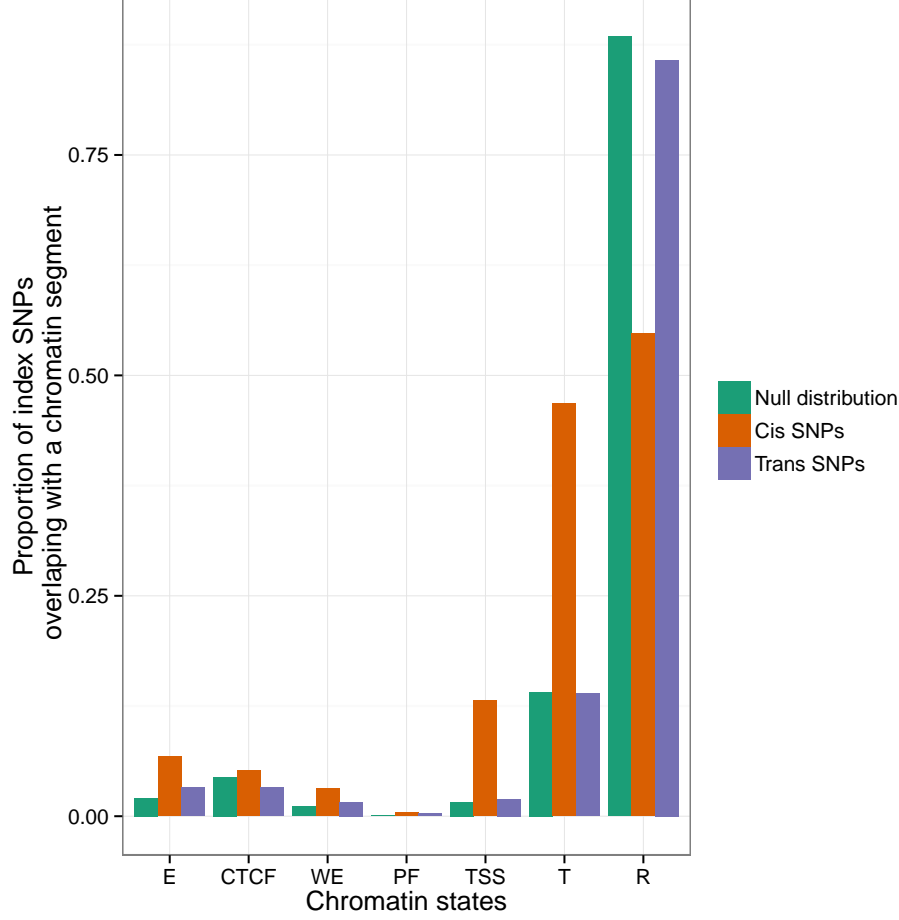
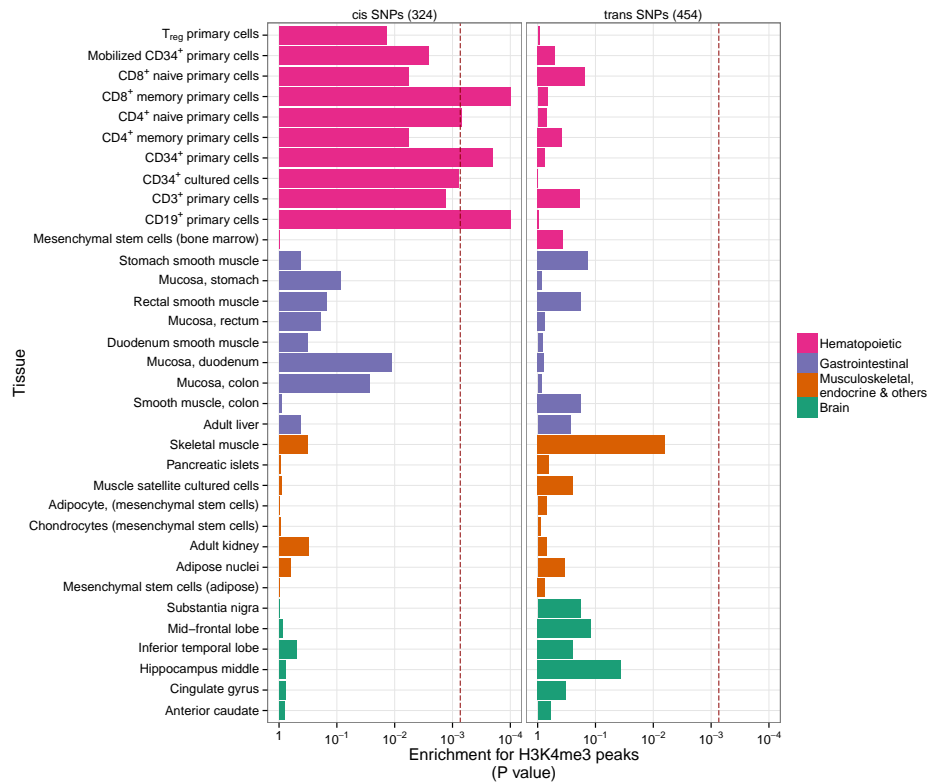


Figure S4: **Location of SNPs relative to genomic features** We used chromatin segmentation<sup>27</sup> as a method for labelling genomic features. All SNPs within 1Mb and  $r^2 > 0.8$  of each *cis*- and *trans*-SNP were taken to find which genomic features ( $x$ -axis) were covered by the SNPs that 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.<sup>26</sup> 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.

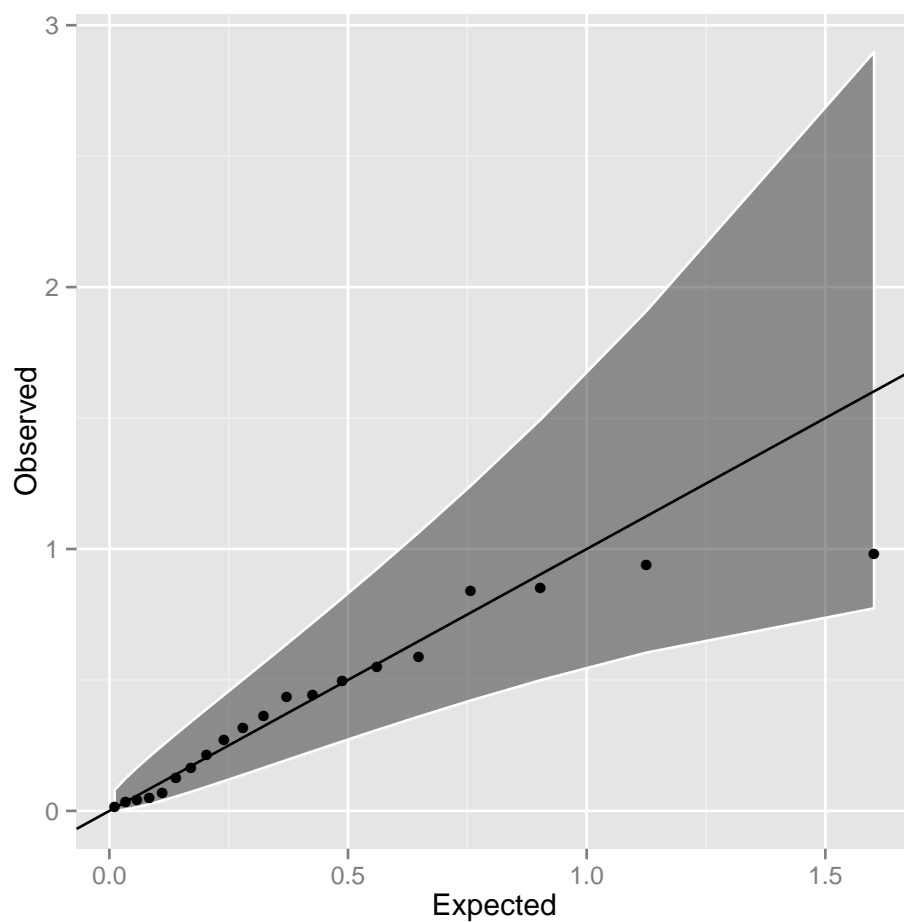


Figure S6: **Q-Q plot of interaction  $p$ -values in the CDHWB dataset**  
 Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset (mainly due to small sample size). There is no evidence for enrichment of interaction terms, most likely due to insufficient power given the limited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

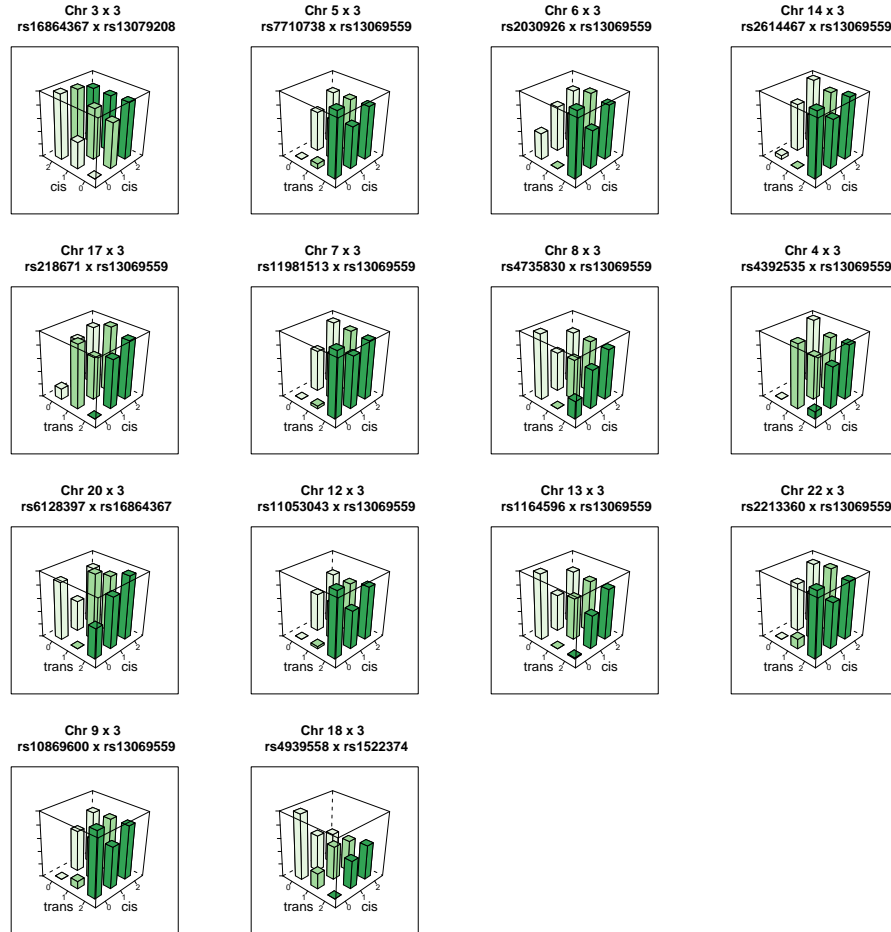


Figure S7: **Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions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

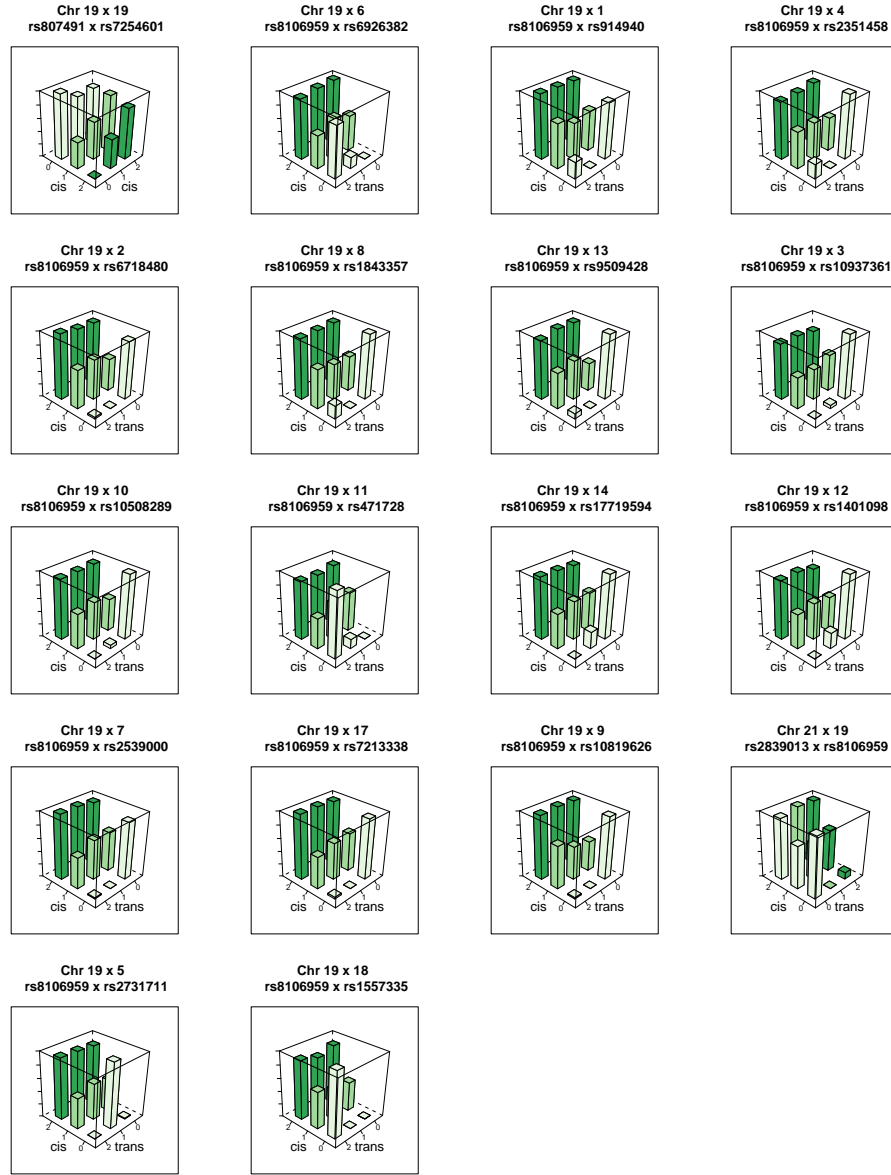


Figure S8: **Genotype-phenotype maps for 19 interactions influencing the expression of TMEM149** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of TMEM149, but in many of these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

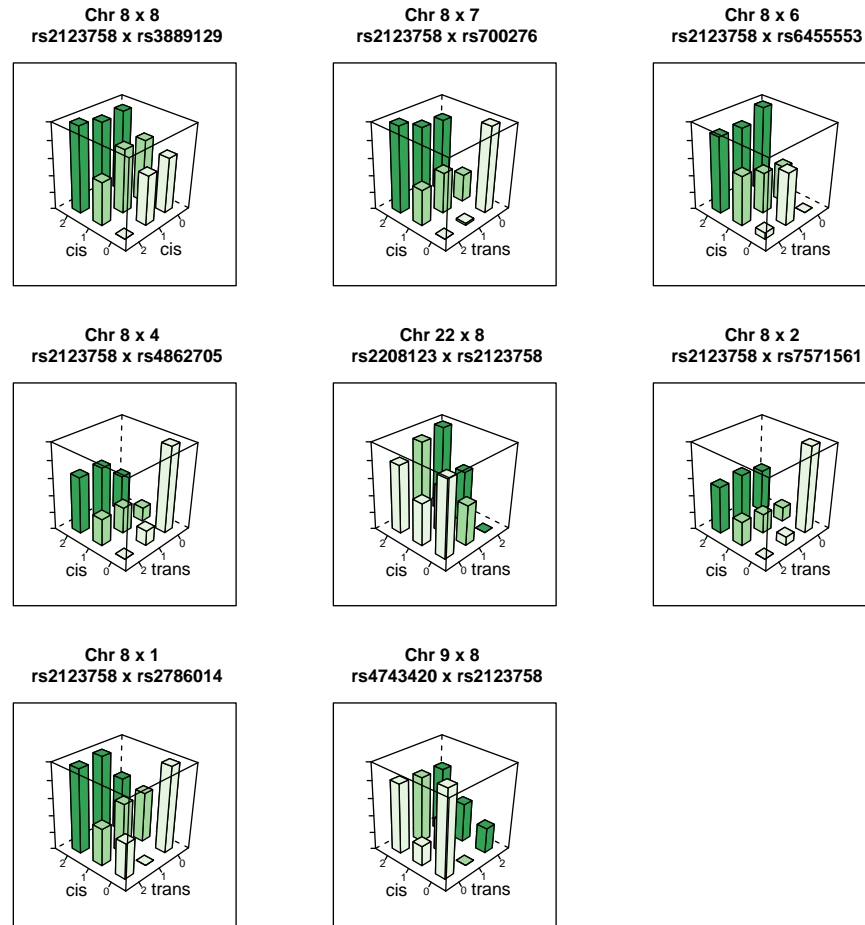


Figure S9: **Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1** Each bar represents the mean phenotypic value for individuals in that genotype class.

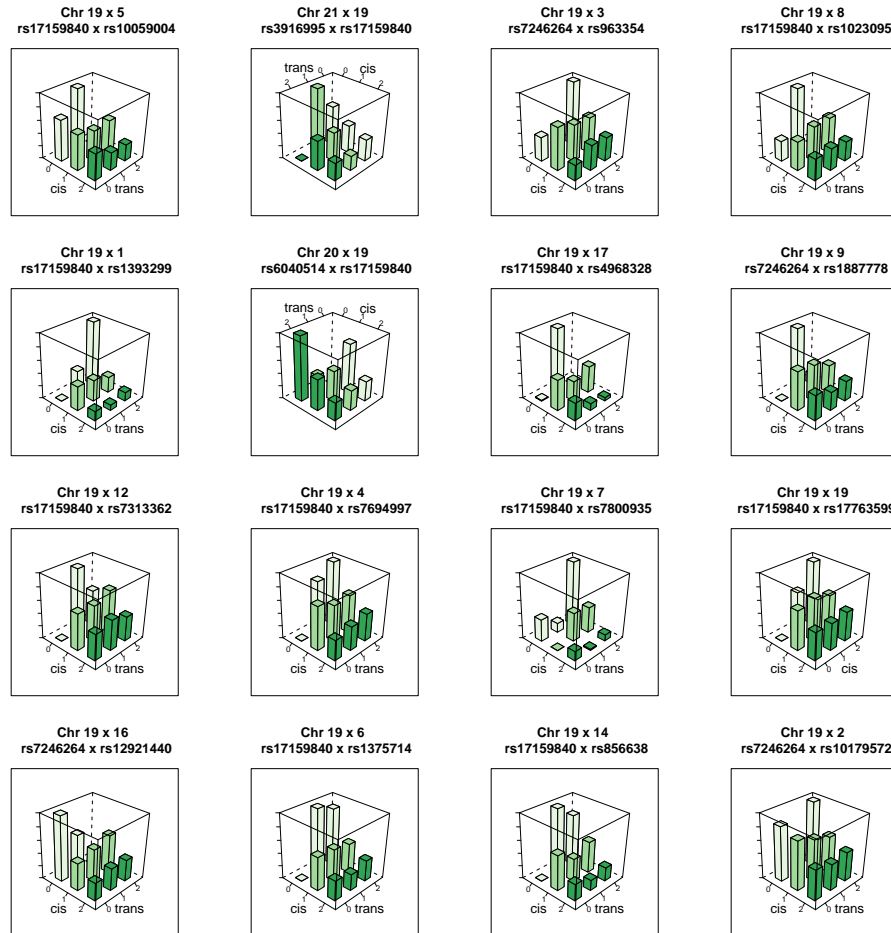


Figure S10: **Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5** Each bar represents the mean phenotypic value for individuals in that genotype class.

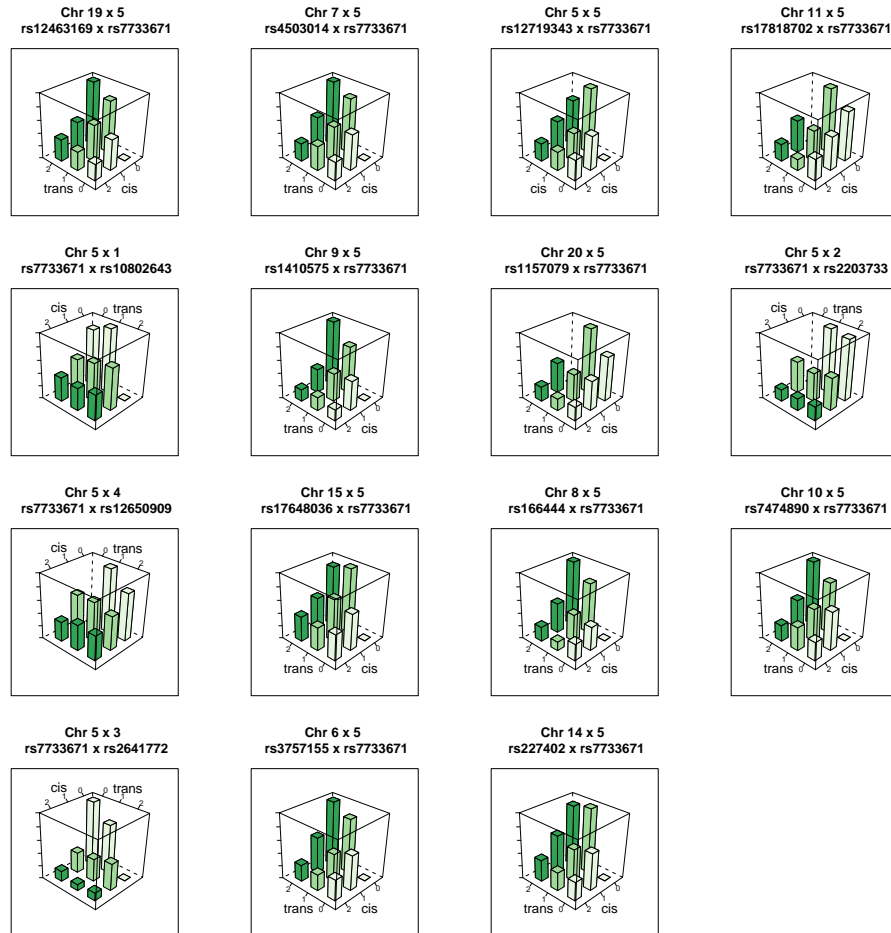
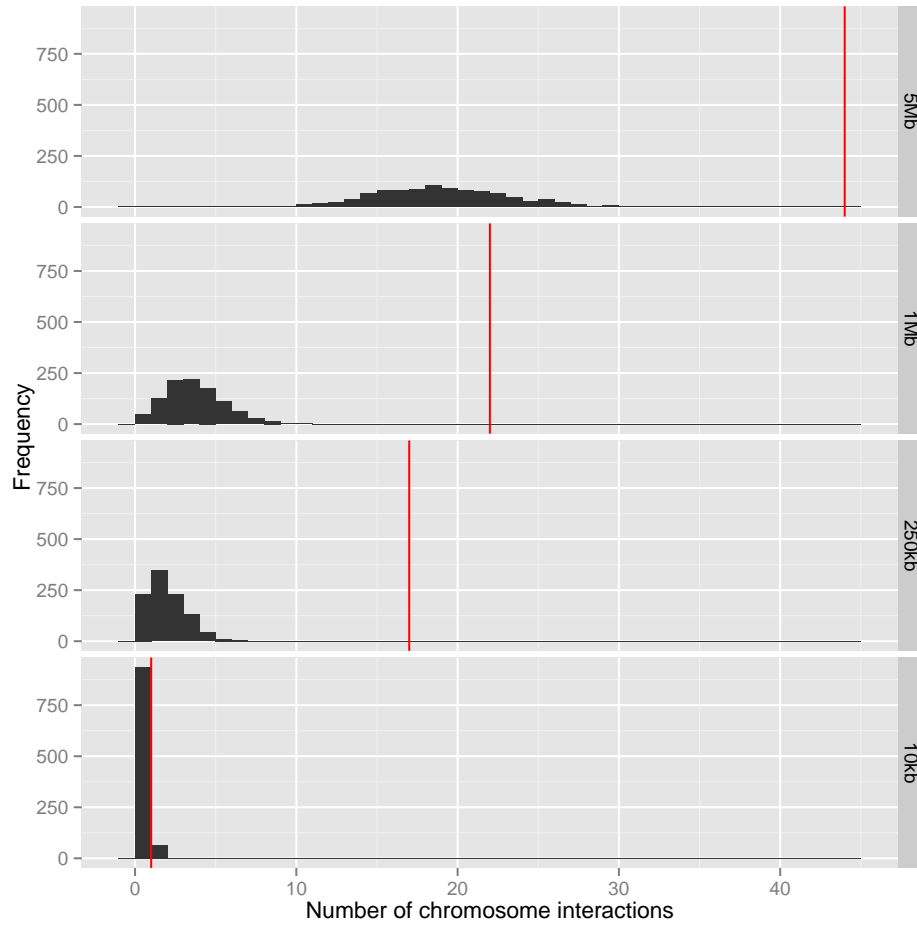


Figure S11: **Genotype-phenotype maps for 15 interactions influencing the expression of CAST** Each bar represents the mean phenotypic value for individuals in that genotype class.





**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.

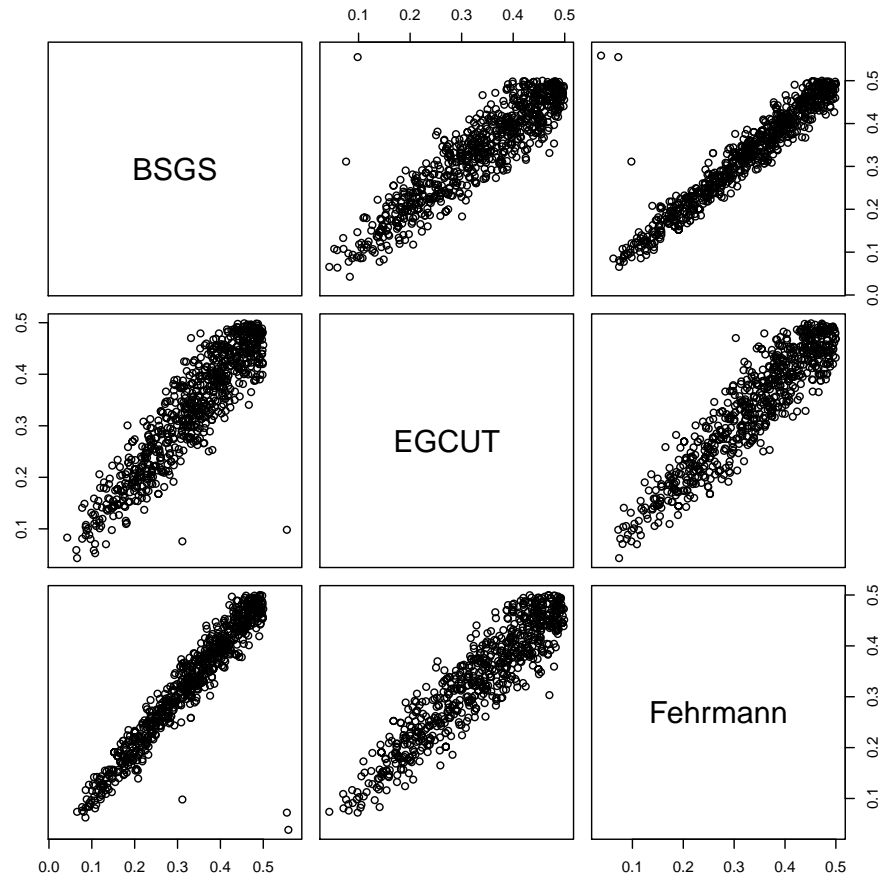
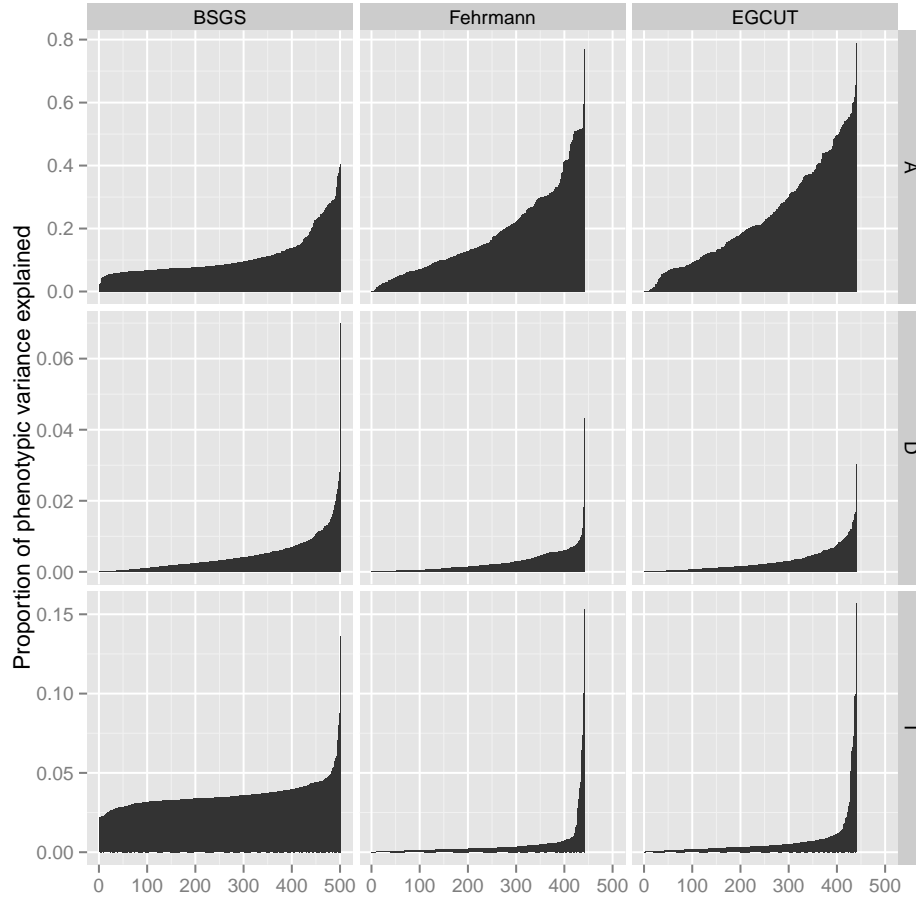


Figure S13: **Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations** Outliers were removed from the analysis as part of the filtering stage during replication.



**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: Details on 501 interactions discovered in BSGS dataset

Expression trait			SNP 1			SNP 2			Interaction statistic / -log <sub>10</sub> p-values			Distance / Mb		
Gene ID <sup>a</sup>	Probe ID <sup>b</sup>	Chr.	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	BSGS <sup>e</sup>		Fehrmann <sup>f</sup>	EGCUT <sup>g</sup>
ABCA7	ILMN_1743205	19	rs3752237	19	1047161	ABCA7	rs596183	6	158100199	6	158100199	5.82	0.38 <sup>1</sup>	0.09
	ILMN_1743205	19	rs3752237	19	1047161	ABCA7	rs1473737	7	139522101	7	139522101	5.50		
	ILMN_1677814	17	rs9455	17	48771135	ABCC3	rs4732202	7	136057883	7	136057883	6.10	0.02	1.81
	ILMN_1800008	11	rs2270664	11	108207393	ACAT1	rs4744894	9	72001517	9	72001517	6.59	1.04	1.78
	ILMN_1698777	14	rs12431896	14	78088813	ADCK1	rs4833241	4	122933691	4	122933691	5.59	0.36	1.14
	ILMN_2358626	16	rs8058066	16	88462550	ADCK1	rs12431896	14	78088813	14	78088813	6.58	2.04	0.83
	ILMN_1698777	14	rs2395095	10	7646305	ADK	rs10824092	10	7529517	10	7529517	6.69	18.33	21.21
	ILMN_339130	10	rs2611512	10	5151534	AGAP8	rs2547996	5	95174319	5	95174319	6.22		39.82
	ILMN_1798308	2	rs10881585	9	137112421	AGAP8	rs2547996	5	95174319	5	95174319	6.22		
	ILMN_1798308	2	rs10881585	9	137112421	AGAP8	rs2547996	5	95174319	5	95174319	6.22		
AHSA2	ILMN_1798308	2	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
	ILMN_1665982	16	rs2523971	6	29938258	HLA-G	rs842647	7	61119471	7	61119471	7.15	1.83	2.88
ALDH3A2	ILMN_2401641	17	rs3760489	17	19581009	AKTIP	rs13332406	16	53488355	16	53488355	5.45	0.92	0.64
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	ILMN_1760727	14	rs9322855	14	21153299	AKTIP	rs13332406	16	53488355	16	53488355	5.45	0.92	0.64
	ILMN_1760727	14	rs9322855	14	21153299	AKTIP	rs13332406	16	53488355	16	53488355	5.45	0.92	0.64
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	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs8466516	2	3032625	2	3032625	6.26	0.33	1.37
	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs8466516	2	3032625	2	3032625	6.26	0.33	1.37
	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs8466516	2	3032625	2	3032625	6.26	0.33	1.37
	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs8466516	2	3032625	2	3032625	6.26	0.33	1.37
	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs8466516	2	3032625	2	3032625	6.26	0.33	1.37
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	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs8466516	2	3032625	2	3032625	6.26	0.33	1.37
	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs8466516	2	3032625	2	3032625	6.26	0.33	1.37
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	ILMN_1768067	12	rs6453374	5	10558019	AP3B1	rs6846031	4	178019148	4	178019148	5.85	0.47	0.17
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	ILMN_3331952	17	rs12947580	17	35932225	APPL2	rs2769594	9	87918528	9	87918528	5.94	0.80	1.16
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	ILMN_1763386	22	rs4284750	19	19810050	BID	rs373870	19	19738554	19	19738554	5.72		
	ILMN_1763386	22	rs4284750	19	19810050	BID	rs373870	19	19738554	19	19738554	5.72		

Table S1 – continued from previous page

Gene ID <sup>a</sup>	Expression trait <sup>b</sup>	SNP 1			SNP 2			Interaction statistic / -log <sub>10</sub> p-values		
		rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	Metag <sup>e</sup>
CBORF69	ILMN_1653205	rs8051751	16	7188323		rs2890452	8	86102223	CBORF59	5.79
CBORF72	ILMN_1741881	rs10122902	9	27556780	C9ORF72	rs24202910	1	24202910	C9ORF72	0.18
CAC1	ILMN_1731064	rs12765847	10	4353908		rs3738725	1	22174210	CAC1	0.96
CARD9	ILMN_1712532	rs4260763	9	139289825	INPP5E	rs654040	1	82128600		0.01
CARD9	ILMN_1712532	rs4573661	11	6026661		rs4077515	9	139266486	INPP5E	0.86
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CAST	ILMN_1717234	rs4003014	7	31149140		rs7733671	5	96000269	CAST	0.01
CAST	ILMN_1717234	rs4747890	10	39590078		rs7733671	5	96000269	CAST	0.07
CAST	ILMN_1717234	rs7733671	5	96000269	GAST	rs10802643	1	238120177		0.33
CAST	ILMN_1717234	rs7733671	5	96000269	CAST	rs12630909	1	17012880		1.34
CAST	ILMN_1717234	rs7733671	5	96000269	CAST	rs2203753	2	224095101		0.78
CAST	ILMN_1717234	rs7733671	5	96000269	CAST	rs2641772	3	195531841		0.30
CAST	ILMN_1717234	rs8723203	18	69175886		rs41152695	11	34115386	CAT	0.94
CAST	ILMN_1692705	rs2352303	19	17093980		rs41152695	11	34115386	CAT	0.26
CCDC88B	ILMN_1722268	rs694739	17	6097235	CCDC88B	rs13771549	10	6415142	CCDC88B	0.22
CD86	ILMN_1784863	rs5211834	7	80283117		rs1254900	1	8498183	YAMP8	0.37
CD86	ILMN_1800940	rs7508015	11	76053374		rs1254900	1	8498183	YAMP8	0.18
CD86	ILMN_1704730	rs1884655	20	23074375	CD93	rs670105	7	20750534	CD55	0.13
CD86	ILMN_1704730	rs1884655	20	23074375	CD93	rs4607740	4	15782632		0.02
CD86	ILMN_1704730	rs1884655	20	23074375	CD93	rs7623520	3	196721395		1.34
CD86	ILMN_1704730	rs1884655	20	23074375	CD93	rs8388750	12	125145394		0.92
CD86	ILMN_1704730	rs1884655	20	23074375	CD93	rs8576388	13	38434372		0.49
CD86	ILMN_1704730	rs2889504	20	37771578	CD93	rs186858	20	23074375		0.27
CD86	ILMN_1704730	rs4813479	20	23076914	CD93	rs10925247	1	238890903	CD93	1.67
CD86	ILMN_1704730	rs4813479	20	23076914	CD93	rs2873430	8	138500554		0.22
CD86	ILMN_1704730	rs4813479	20	23076914	CD93	rs4295531	18	77264432		0.51
CD86	ILMN_1704730	rs4813479	20	23076914	CD93	rs7294744	17	77264432		0.14
CD86	ILMN_2309796	rs901544	14	104162263		rs11655031	13	115080398	CDK16	0.21
CEACAM21	ILMN_1730928	rs200690	17	46614102	HOXB2	rs11655031	17	3083182	CDK5R1	0.95
CEACAM21	ILMN_1745949	rs4803481	20	51956356		rs4803481	19	43066556	CEACAM21	0.15
CEACAM21	ILMN_1707554	rs6505780	18	42068556	CEACAM21	rs2421050	5	158043044		0.12
CEACAM21	ILMN_1707554	rs6505780	18	42068556	CEACAM21	rs13132719	3	180265266		0.16
CEACAM21	ILMN_1707554	rs6505780	18	42068556	CEACAM21	rs13132719	3	180265266	ANAPC13	0.24
CEACAM21	ILMN_1707554	rs6505780	18	42068556	CEACAM21	rs13132719	3	180265266	ANAPC13	0.09
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.72
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.44
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.20
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.36
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.67
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		1.28
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.73
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.27
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.02
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.07
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.28
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.01
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.06
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.57
CEACAM21	ILMN_2359945	rs81992935	16	55861794	CES1	rs2695290	3	235248562		0.23
CEACAM21										



Table S1 – continued from previous page

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Table S1 – continued from previous page

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Table S1 – continued from previous page

Gene ID <sup>a</sup>	Expression trait		SNP 1		SNP 2		Interaction statistic / -log <sub>10</sub> p-values			
	Probe ID <sup>b</sup>	Chr.	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>
REBE	ILMN-1802380	1	rs4982958	14	24987865		rs301819	1	8501786	REBE
REBE	ILMN-1802380	1	rs7697290	4	132424366		rs301819	1	8501786	REBE
REBE	ILMN-2327795	1	rs11085829	19	13174312		rs301819	1	8501786	REBE
REBE	ILMN-2327795	1	rs3852011	3	112844086	RNASE6	rs301819	1	8501786	REBE
RNASE6	ILMN-1780533	14	rs11628398	14	8106521		rs7324365	13	100601327	RNASE6
RNASE6	ILMN-1780533	14	rs6003134	19	8106521		rs11628398	14	21182800	RNASE6
RNASE6	ILMN-1794726	17	rs238230	17	4875566		rs484857	13	34665512	
RNF167	ILMN-1794726	17	rs400658	17	4839930	RNF167	rs11706900	3	36348908	
RNFEP	ILMN-1738347	1	rs1107121	17	46127349		rs2819365	1	201983242	
RNFEP	ILMN-1738347	1	rs8071611	17	67153586		rs2819365	1	201983242	
RPL13	ILMN-2413278	16	rs352935	16	89045580		rs2965817	16	89513234	
RPL23AP7	ILMN-2222730	12	rs1401202	14	50320056		rs4848261	2	114450028	RPL23AP7
RPL36AL	ILMN-2186933	14	rs3007033	14	5003816	RPL36AL	rs17450530	9	138035083	
RPL36AL	ILMN-2186933	14	rs4009028	14	50020817	RPL36AL	rs1502991	6	66137260	
RPL8	ILMN-1764721	8	rs2958452	8	143984615	RPL8	rs1619856	1	234585790	
RPL8	ILMN-1764721	8	rs4143674	20	4741304		rs2958452	8	143984615	
SEC13	ILMN-3297880	3	rs4889214	16	80913946		rs696221	3	10342876	SEC13
SEC13	ILMN-3297880	3	rs17085428	3	93388015		rs7695	1	136147326	SEC13
SES3	ILMN-1702787	11	rs12147460	14	104412137		rs684856	11	949061111	SES3
SES3	ILMN-1694027	11	rs355391	15	46391793	SES3	rs684856	11	949061111	SES3
SES3	ILMN-1694027	11	rs684856	15	46391793		rs7004947	8	134606423	PPBP
SH3BGL2	ILMN-1694027	11	rs10838191	11	43893658		rs1354034	3	56849749	PPBP
SH3BGL2	ILMN-1767664	6	rs2345385	5	4683899		rs1354034	3	56849749	PPBP
SH3BGL2	ILMN-1767664	6	rs6645364	4	88280592		rs1354034	3	56849749	PPBP
SH3BGL2	ILMN-1767664	6	rs1034290	21	18196922	SIRPG	rs17455517	9	131785369	SH3BGL2
SIRPG	ILMN-2158336	9	rs1034290	21	18196922		rs6842739	14	60429380	SH3BGL2
SIRPG	ILMN-2158336	9	rs1355883	20	1512549		rs367035	17	15233826	SLC22A18
SLC22A18	ILMN-2382605	20	rs11673260	19	5215198	SLC22A18	rs1355883	20	1512549	SLC22A18
SLC22A18	ILMN-2382605	20	rs367035	17	15233826	SLC22A18	rs1355883	20	1512549	SLC22A18
SLC22A18	ILMN-2382605	20	rs367035	17	15233826	SLC22A18	rs367035	17	15233826	SLC22A18
SLC41A3	ILMN-236111	3	rs1912136	11	292363	SLC41A3	rs367035	17	15233826	SLC41A3
SLC41A3	ILMN-236111	3	rs698508	8	14233774	SLC41A3	rs7701916	5	174598073	SLC41A3
SLC46A3	ILMN-1658639	13	rs198005	17	5502091		rs7701916	5	174598073	SLC46A3
SLC46A3	ILMN-1658639	13	rs803259	15	97030923		rs10911353	1	18249303	SLC46A3
SMG7	ILMN-1775380	20	rs11677215	20	4161500	SMOX	rs11677215	2	65800982	SMG7
SMOX	ILMN-1775380	20	rs11677215	20	4161500		rs11677215	2	65800982	SMOX
SNHG8	ILMN-3309380	4	rs1105621	9	133050233		rs214097	11	19225940	SNHG8
SNHG8	ILMN-3309380	4	rs1105621	9	133050233		rs214097	11	19225940	SNHG8
SNORD14A	ILMN-1799381	11	rs1504220	15	46250108		rs6148334	11	1701499	SNORD14A
SNORD14A	ILMN-1799381	11	rs2634462	11	17339197		rs6148334	11	1701499	SNORD14A
SNORD89	ILMN-3238663	2	rs1605863	2	115929241		rs750783	2	101889306	SNORD89
SNORD89	ILMN-3238663	2	rs1605863	2	115929241		rs750783	2	101889306	SNORD89
SNORD89	ILMN-3238663	2	rs1605863	2	115929241		rs750783	2	101889306	SNORD89
SNUPN	ILMN-1739932	15	rs2135064	5	26778066	SNUPN	rs7185362	16	81888905	SNUPN
SNUPN	ILMN-1739932	15	rs2135064	5	26778066		rs1472075	3	193706323	SNUPN
SPATA5L1	ILMN-2364535	15	rs1346466	21	46376528		rs1472075	3	193706323	SPATA5L1
SPATA5L1	ILMN-2364535	15	rs1346466	21	46376528		rs1472075	3	193706323	SPATA5L1
STARD10	ILMN-1729179	15	rs2231406	19	41117869		rs1006620	15	45652086	STARD10
STARD10	ILMN-1729179	15	rs2231406	19	41117869		rs1006620	15	45652086	STARD10
STYXL1	ILMN-2210752	7	rs4073164	14	104947517		rs17685	7	75616105	STYXL1
STYXL1	ILMN-2210752	7	rs4073164	14	104947517		rs17685	7	75616105	STYXL1
SULT1A4	ILMN-2345142	20	rs11700063	18	74332954	SULF2	rs392994	4	180439236	SULT1A4
SULT1A4	ILMN-2345142	20	rs11700063	18	74332954		rs392994	4	180439236	SULT1A4
SULT1A4	ILMN-2345142	20	rs11700063	18	74332954		rs392994	4	180439236	SULT1A4
SURF6	ILMN-2336133	16	rs2436657	20	40119768		rs3785354	16	28550667	SURF6
SURF6	ILMN-2336133	16	rs2436657	20	40119768		rs3785354	16	28550667	SURF6
SYTL2	ILMN-1778032	9	rs6099626	20	56013994		rs3118663	9	136281753	SYTL2
SYTL2	ILMN-1778032	9	rs6099626	20	56013994		rs3118663	9	136281753	SYTL2
THBS3	ILMN-2336609	11	rs1375719	13	10341078		rs485485	11	85495269	THBS3
THBS3	ILMN-2336609	11	rs1375719	13	10341078		rs485485	11	85495269	THBS3
THBS3	ILMN-1804663	1	rs1939875	11	95422867		rs4072037	1	155194980	THBS3
THBS3	ILMN-1804663	1	rs1939875	11	95422867		rs4072037	1	155194980	THBS3
TIPRL	ILMN-1781457	1	rs8014956	14	20687978		rs2049805	1	168154599	TIPRL
TIPRL	ILMN-1781457	1	rs2823245	21	16745523		rs1320993	1	168154599	TIPRL

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Table S1 – continued from previous page

Gene ID <sup>a</sup>	Probe ID <sup>b</sup>		Expression trait		SNP 1		SNP 2		Interaction statistic <sup>c</sup> / -log <sub>10</sub> p-values			Distance / Mb <sup>b</sup>		
	rs ID	Chr.	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	BSGS <sup>e</sup>		Fehrmann <sup>f</sup>	EGCUT <sup>g</sup>
TNME14	rs1940013	11	rs1940013	11	192839627	TNME14	rs17795246	7	41581986	TNME14	5.71	0.06	1.34	0.70
TNME14	rs2839013	19	rs2839013	19	47238981	TNME14	rs11069559	19	36210525	TNME14	8.11	0.16	0.48	0.26
TNME14	rs5762235	22	rs5762235	22	27925988	TNME14	rs11069559	19	36210525	TNME14	6.79			
TNME14	rs6090518	20	rs6090518	20	45207005	TNME14	rs17795246	7	41581986	TNME14	11.09	0.76		
TNME14	rs807491	19	rs807491	19	36268923	SNX26	rs72546011	19	36147315	TNME14	12.16	81.55	45.78	145.78
TNME14	rs10810659	19	rs10810659	19	362106925	TNME14	rs105082826	10	47909119	TNME14	8.12	1.55	3.09	3.67
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs108196286	9	133025756	TNME14	8.02	0.40	0.99	0.80
TNME14	rs10810659	19	rs10810659	19	362106925	TNME14	rs10937361	3	188359436	TNME14	8.39	3.61	1.18	3.78
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs14010098	12	128884559	TNME14	7.37	2.41	1.00	2.52
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs1557335	18	642668976	TNME14	6.95	0.08	0.07	0.03
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs17719594	14	90932598	TNME14	6.23	3.06	0.77	2.87
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs1843357	8	13822381	TNME14	6.21	3.72	3.33	6.00
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs2551458	4	113317583	TNME14	7.30	0.04	0.91	8.00
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs2539000	7	147619772	TNME14	6.70	1.57	1.52	2.27
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs2731711	5	171792273	TNME14	5.92	0.19	0.33	0.19
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs471728	11	129595460	TNME14	8.89	0.90	3.62	3.51
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs6718480	2	233879066	TNME14	8.55	3.31	5.15	7.36
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs6926382	6	161683974	TNME14	5.80	3.06	8.80	10.72
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs7213338	17	80357420	TNME14	5.49	0.07	3.14	2.10
TNME14	rs8106959	19	rs8106959	19	362106925	TNME14	rs914940	1	242889492	TNME14	6.22	3.36	6.96	9.20
TNME14	rs1254086	13	rs1254086	13	72890603	TNME14	rs9090428	13	21473952	TNME14	9.44	0.10	5.75	4.47
TNME63A	rs1548475	9	rs1548475	9	58058246	TNME63A	rs1449226	1	226027323	TNME63A	5.60			
TNME80	rs1537146	9	rs1537146	9	4859303	TNME80	rs4963126	11	656845	TNME80	5.79	0.64	0.12	0.32
TNPO3	rs199793	20	rs22827903	20	22827903	IRF5	rs10488630	7	128593948	IRF5	5.52	1.03	0.17	0.62
TNPO3	rs7776572	13	rs13531675	13	113051917	IRF5	rs10488630	7	128593948	IRF5	8.23	3.19	1.89	4.09
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.61	0.28	0.40	0.29
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.52	0.93	0.01	0.36
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887	TRAPPC4	5.97	0.21	1.60	1.01
TNPO3	rs1793823	11	rs131018917	11	131018917	TRAPPC4	rs3916581	11	118887887					

Continued on next page

Table S1 – continued from previous page

Expression trait			SNP 1			SNP 2			Interaction statistic / -log <sub>10</sub> p-values						
Gene ID <sup>a</sup>	Probe ID <sup>b</sup>	Chr.	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	rs ID	Chr.	Pos/Mb <sup>c</sup>	Association <sup>d</sup>	BSGS <sup>e</sup>	Fehrmann <sup>f</sup>	EGCUT <sup>g</sup>	Meta <sup>g</sup>	Distance / Mb <sup>h</sup>
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	214514361		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	40063167		rs2276470	19	45974668		5.09	0.94	5.14	4.95	0.088
VNN2	LMN-1678939	6	rs10435352	7	103252718		rs1883613	6	133077603	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		rs2267952	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	rs9596437	13	51692548		rs2267952	6	133067782	VNN3	4.83	0.46	0.05	0.16	
VSTM1	LMN-1763455	19	rs9596437	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	1.17	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		rs833349	3	39067325	WDR48	6.34	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	5.86	1.64	1.43	2.25	
XAF1	LMN-2330573	17	rs12362253	11	123571708		rs17715581	15	49194351		4.86	2.38	0.17	1.63	
XAF1	LMN-2330573	17	rs1535031	21	6073170	XAF1	rs12591171	15	93119799		5.79	0.09	0.36	0.15	
ZFP90	LMN-1684628	16	rs909446	21	39064048		rs182968	16	68573945	ZFP90	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	8953512		rs2242601	7	143093824	ZYX	6.04	0.26	0.01	0.05	

<sup>a</sup> Phenotypes are expression levels of RefSeq Genes<sup>b</sup> Illumina probe ID used to measure gene expression<sup>c</sup> Physical SNP position in base pairs (HG19)<sup>d</sup> RefSeq Gene ID of gene expression level that is influenced by the SNP (BSGS discovery dataset, significance threshold = 1.29 × 10<sup>-11</sup>)<sup>e</sup> Interaction - log<sub>10</sub> p-value from discovery dataset<sup>f</sup> Interaction - log<sub>10</sub> p-value from replication dataset<sup>g</sup> Interaction - log<sub>10</sub> p-value from meta analysis of replication datasets only<sup>h</sup> Distance in Mb between interacting SNPs for *cis-cis* acting SNP pairs<sup>i</sup> p-values are absent if the interaction did not pass the QC filtering in the replication dataset<sup>j</sup> 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 2013<sup>21</sup>

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	Dataset	$n$	Expected	Observed	$p$ -value
1 <sup>a</sup>	All	EGCUT	434	217.00	306	$6.69 \times 10^{18}$
		Fehrmann	434	217.00	278	$5.04 \times 10^{09}$
		Both	434	108.50	221	$5.56 \times 10^{31}$
	Significant	EGCUT	30	15.00	25	$3.25 \times 10^{04}$
		Fehrmann	30	15.00	24	$1.43 \times 10^{03}$
		Both	30	7.50	22	$3.76 \times 10^{08}$
2 <sup>b</sup>	All	EGCUT	434	54.25	92	$4.22 \times 10^{07}$
		Fehrmann	434	54.25	79	$6.18 \times 10^{04}$
		Both	434	6.78	30	$2.55 \times 10^{11}$
	Significant	EGCUT	30	3.75	19	$9.46 \times 10^{11}$
		Fehrmann	30	3.75	19	$9.46 \times 10^{11}$
		Both	30	0.47	18	$2.23 \times 10^{25}$
3 <sup>c</sup>	All	EGCUT	434	27.12	34	$1.65 \times 10^{01}$
		Fehrmann	434	27.12	35	$1.35 \times 10^{01}$
		Both	434	1.70	2	$6.89 \times 10^{01}$
	Significant	EGCUT	30	1.88	8	$3.92 \times 10^{04}$
		Fehrmann	30	1.88	9	$6.22 \times 10^{05}$
		Both	30	0.12	1	$1.11 \times 10^{01}$
4 <sup>d</sup>	All	EGCUT	1133	566.50	775	$7.10 \times 10^{36}$
		Fehrmann	1133	566.50	726	$1.90 \times 10^{21}$
		Both	1133	283.25	562	$1.39 \times 10^{70}$
	Significant	EGCUT	73	36.50	55	$1.69 \times 10^{05}$
		Fehrmann	73	36.50	55	$1.69 \times 10^{05}$
		Both	73	18.25	46	$7.86 \times 10^{12}$

<sup>a</sup> The sign of the most significant epistatic variance component in discovery is the same as the corresponding variance component in the replication data.

<sup>b</sup> The largest epistatic variance component in the discovery is the same as in the replication with the same sign in both.

<sup>c</sup> The sign of all four epistatic variance components are identical in the discovery and the replication.

<sup>d</sup> 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: 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	0.122	0.000	0.001
17	FN3KRP	rs898095	rs9892064	80890638	80827903.0	0.063	0.063	0.088
21	CSTB	rs9979356	rs3761385	45230974	45198355.0	0.033	0.041	0.066
3	MBNL1	rs16864367	rs13079208	152234166	152116652.0	0.118	0.041	0.117
10	ADK	rs2395095	rs10824092	76446305	75929517.0	0.517	0.013	0.020
11	CTSC	rs7930237	rs556895	88117962	88077479.0	0.040	0.012	0.045
17	GAA	rs11150847	rs12602462	78153130	78146016.0	0.007	0.000	0.001
8	NAPRT1	rs2123758	rs3889129	144663661	144613680.0	0.050	0.053	0.060
1	LAX1	rs1891432	rs10900520	203877662	203780591.0	0.097	0.065	0.106
18	MBP	rs8092433	rs4890876	74747424	74732087.0	0.015	0.035	0.053
11	SNORD14A	rs2634462	rs6486334	17339127	17015557.0	0.324	0.008	0.012
21	C21ORF57	rs9978658	rs11701361	48027084	47764477.0	0.263	0.032	0.065
16	RPL13	rs352935	rs2965817	89648580	89513234.0	0.135	0.054	0.060
19	ATP13A1	rs4284750	rs873870	19810050	19738554.0	0.071	0.008	0.015
2	NCL	rs7563453	rs4973397	232301670	232291471.0	0.010	0.027	0.029
5	HNRPH1	rs6894268	rs4700810	179032488	178991794.0	0.041	0.000	0.001
19	VASP	rs1264226	rs2276470	46063167	45974668.0	0.088	0.018	0.022
7	TRA2A	rs7776572	rs11770192	23528927	23498358.0	0.031	0.064	0.064
21	PRMT2	rs2839372	rs11701058	48063862	47776382.0	0.287	0.100	0.122
12	OAS1	rs13311	rs2072133	113448652	113409260.0	0.039	0.002	0.016
16	N4BP1	rs12444224	rs11649236	87580855	48632478.0	38.948	0.007	0.021
5	CAST	rs12719343	rs7733671	125369113	96000269.0	29.369	0.001	0.001
7	DNAJB6	rs2286842	rs3779589	157216093	157163614.0	0.052	0.005	0.006
1	OVGP1	rs10802822	rs1264898	240132968	111992823.0	128.140	0.008	0.030
20	CD93	rs2868504	rs1884655	37771578	23074375.0	14.697	0.000	0.002
11	PHCA	rs493642	rs10736812	123097386	76708086.0	46.389	0.002	0.008
21	MX1	rs459498	rs8130120	42795027	29363604.0	13.431	0.000	0.000
16	AKTIP	rs2896940	rs13332406	57721127	53489705.0	4.231	0.000	0.001
17	CDK5R1	rs9905940	rs11655031	46614102	30833162.0	15.781	0.000	0.000
2	CYBRD1	rs888427	rs7591849	172368120	160112881.0	12.255	0.000	0.000
8	HMBOX1	rs587639	rs7837237	132725731	28876221.0	103.850	0.001	0.001
11	TRAPPC4	rs1793823	rs3916581	131018917	118887887.0	12.131	0.001	0.002
12	PEX5	rs10444467	rs4329748	128052636	7364442.0	120.688	0.000	0.000
12	FLJ20489	rs17615703	rs3782908	117036766	48169526.0	68.867	0.001	0.002
16	PRKCB1	rs2188355	rs10492793	23867776	12639800.0	11.228	0.000	0.000
14	MRPL52	rs1950857	rs3811188	26710271	23299135.0	3.411	0.002	0.004
17	C17ORF60	rs9907897	rs7405659	63502633	59874129.0	3.629	0.004	0.011
6	FLJ43093	rs6906101	rs13214069	36667610	32705248.0	3.962	0.000	0.000
19	TRAPPC5	rs17159840	rs17763599	7758194	2369415.0	5.389	0.000	0.000
22	PISD	rs715572	rs6518754	33234931	32097775.0	1.137	0.001	0.003
12	DIP2B	rs871257	rs12427378	117994348	51074199.0	66.920	0.001	0.001
12	GPR162	rs2272500	rs2707210	79685913	6902002.0	72.784	0.003	0.005
17	USP36	rs2279308	rs7225546	76794981	75151717.0	1.643	0.000	0.000