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[1] 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 techniques[10] 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 interactions[13] ($p = 1.8 \times 10^{-10}$). 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 mutations[4] but also at the evolutionary scale in fitness adaptation[15] 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 testing[9] 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, BSGS[22]) 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, Fehrmann[12] 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 ($p \ll 1.0 \times 10^{-16}$, Figure 2 and Supplementary Figure S2). Concordance of the

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direction 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 for several reasons. For example, LD between causal variants and observed markers plays an important role. Not only is the dependence on LD much greater for epistatic effects than for additive effects (Supplementary Figure S7), but when estimating epistatic variance it is more sensitive to changes in LD between observed SNPs and causal variants between independent samples when compared to additive effects (Supplementary Figure S8), and this has a direct effect on statistical power for replication. Indeed, in addition to heterogeneity between populations, sampling variance of LD r alone leads to over three fold decrease in observed variance for the most extreme case of $D \times D$ effects when compared to the average decrease for additive variance on average (Methods, Supplementary Figure S9). 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 association[21] (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 splicing[25]) 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

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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 S10). 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 expresson levels too, for example TMEM149 (Supplementary Figure S11), NAPRT1 (Supplementary Figure S12), TRAPPC5 (Supplementary Figure S13), and CAST (Supplementary Figure S14). 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[21] (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[26] (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[27] (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 lines[28] (Methods) and found that 44 epistatic interactions mapped to within 5Mb ($p < 1.8 \times 10^{-10}$), (Supplementary Figure S15). 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, where the minimum variance explained by the epistatic effects of any interaction was 2.1% of phenotypic variance. Taking published results from a standard eQTL study[22] we calculated that 1848 of the 7339 gene expression levels analysed were influenced by additive effects where the additive variance of a locus was 2.1% or greater. Thus, we can infer that the number of instances of large additive effects is significantly greater than the number of instances of large epistatic effects.

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 perspective[31] 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) where the minimum additive variance was 2.1%, we calculated that the proportion of total phenotypic variance of all 7339 gene expression levels explained by additive effects alone was 2.16%. By contrast, the epistatic variance from the interacting SNPs detected in this study on average explain a total of 0.22% of phenotypic variance, approximately ten 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 minimum variance thresholds, 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 software[10] 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 analysis[32] 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 dataset[12] ($n = 1240$) and the Estonian Genome Centre University of the University of Tartu (EGCUT) dataset[11] ($n = 891$). 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.

Acknowledgements

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
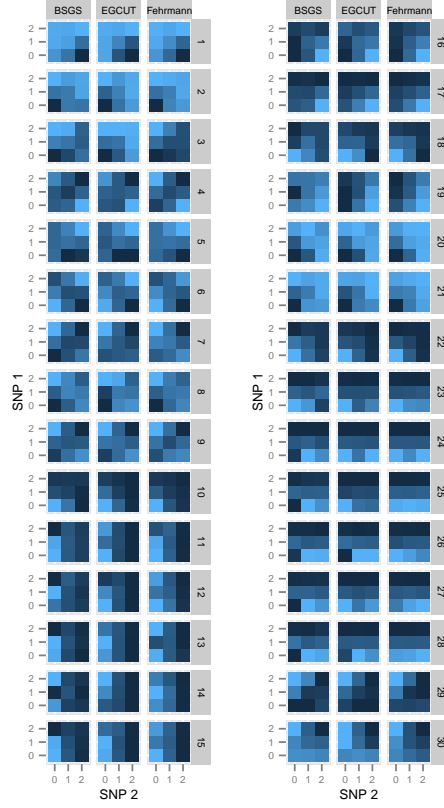
Figure 1: **Replication of GP maps in two independent populations** The GP maps for each epistatic interaction that is significant at the Bonferroni level in both replication datasets are shown. Each GP map consists of nine tiles where each tile represents the expression level for that two-locus genotype 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.
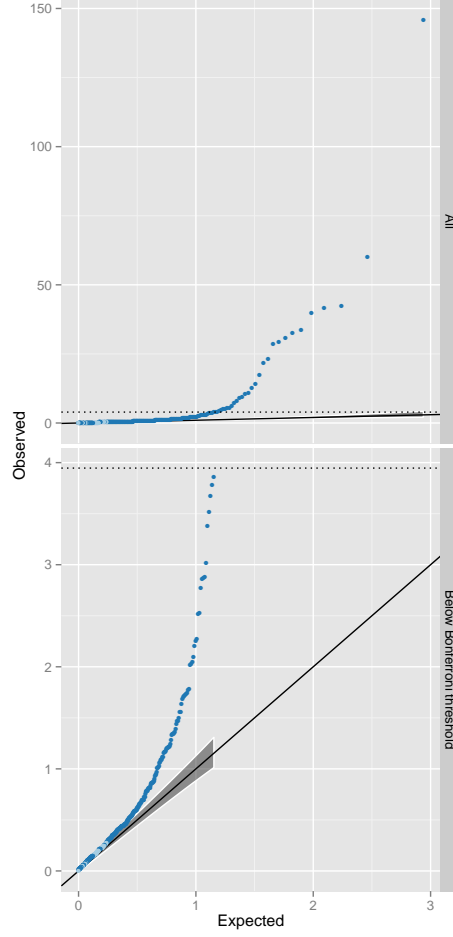
Figure 2: **Q-Q plots of interaction p-values from replication datasets**
The top panel shows all 434 discovery SNPs that were tested for interactions.
Observed p-values (y-axis, $-\log_{10}$ scale) are plotted against the expected p-values (x-axis, $-\log_{10}$ scale). The multiple testing correction 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.
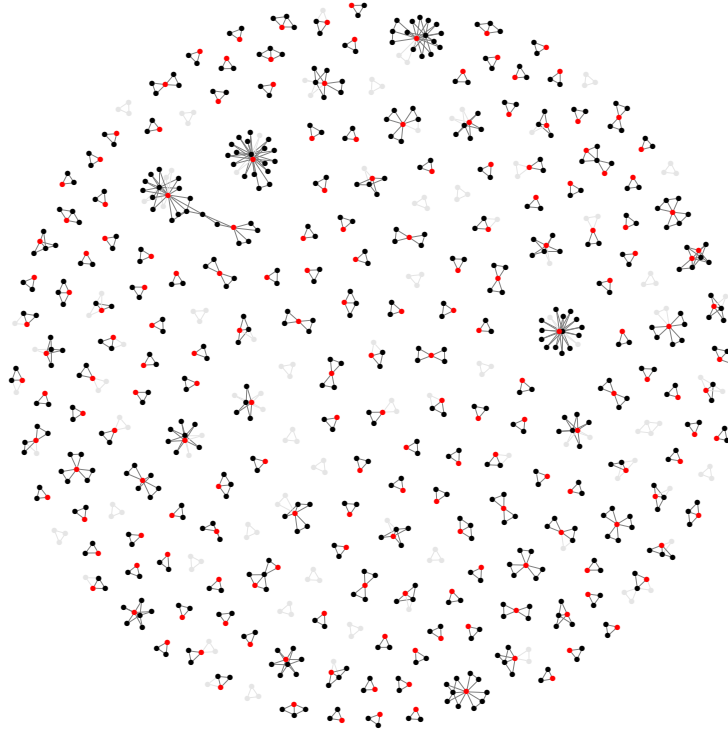
Figure 3: **Discovery and replication of epistatic networks** All 434 putative genetic interactions (edges) with data common to discovery and replication sets is shown, where black nodes represent SNPs and red nodes represent traits (gene expression probes). Three hundred and forty-five interactions 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
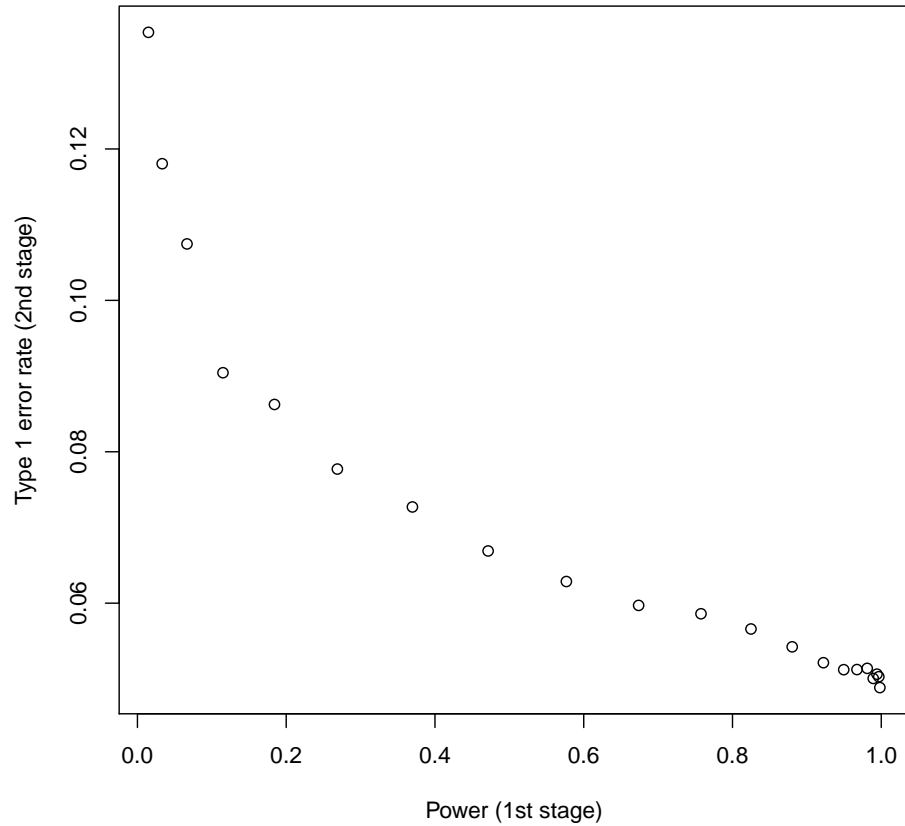
Figure S1: **Type 1 error rate of two stage design** In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These interaction p-values are then adjusted (Bonferroni) for the total 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.
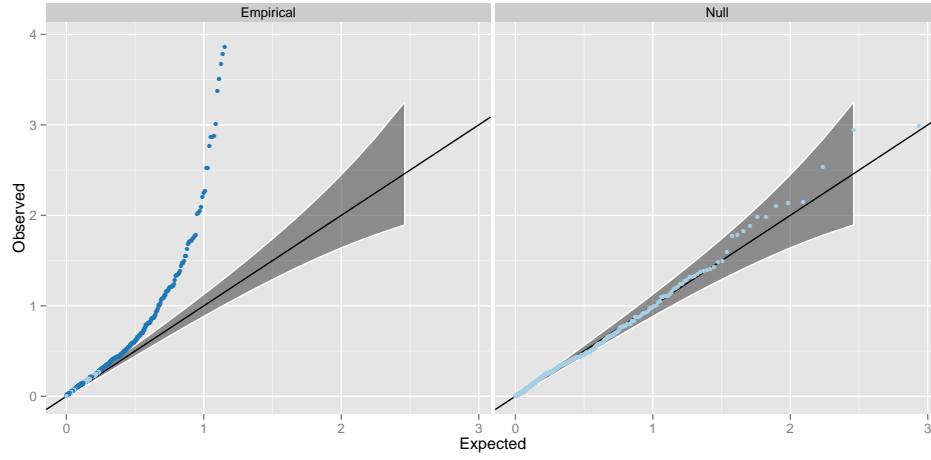
Figure S2: **Q-Q plots of interaction p-values from replication datasets, excluding the 30 points significant at the Bonferroni level** The right panel (Null) shows the interaction p-values from a meta analysis across two independent datasets on 434 randomly drawn SNP pairs. The left panel (Empirical) 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.

17
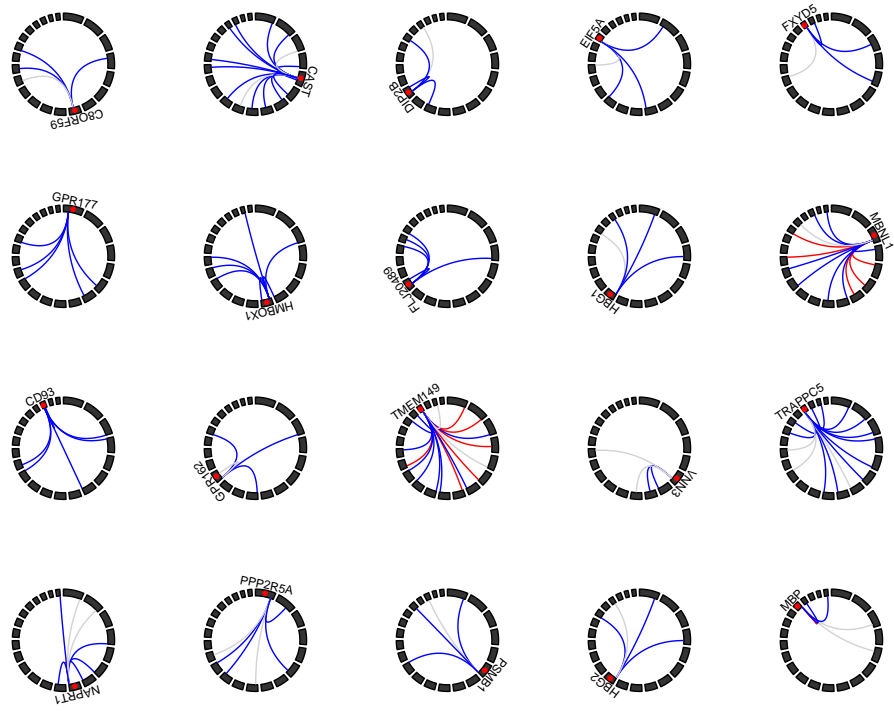
Figure S3: **Gene expression traits with four or more genetic interactions** Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent 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.

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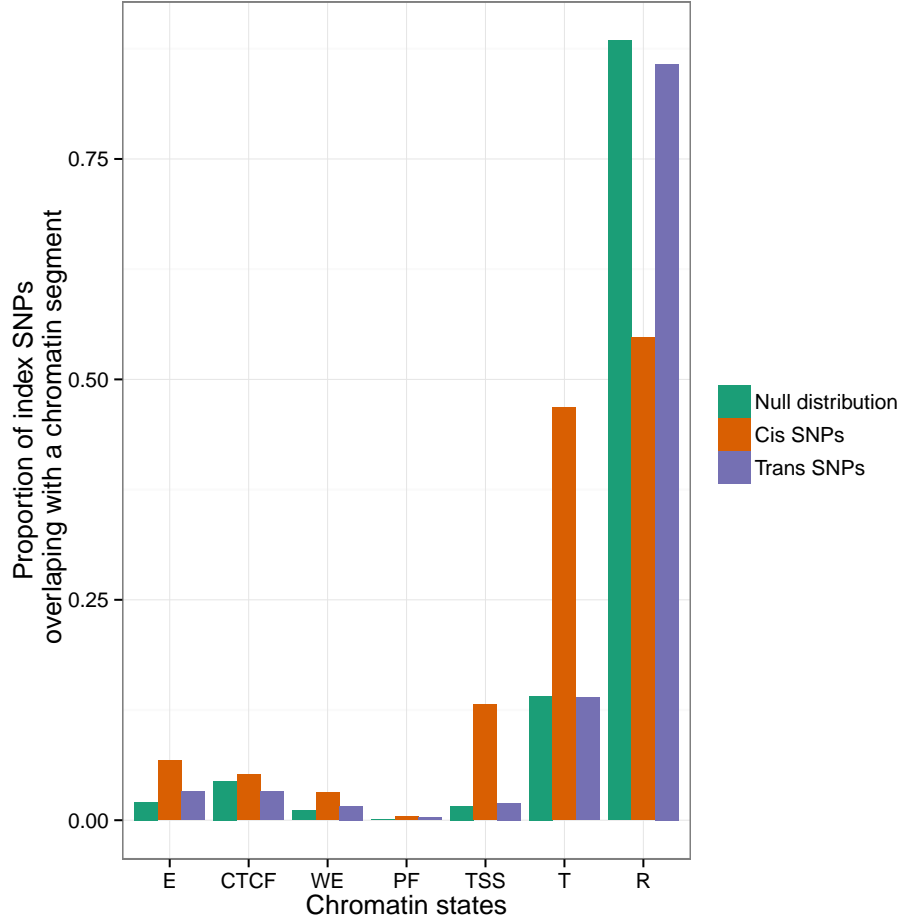
Figure S4: **Location of SNPs relative to genomic features** We used chromatin segmentation[27] as a method for labelling genomic features. All SNPs within 1Mb and $r^2 > 0.8$ of each *cis-* and *trans*-SNP were taken to find which genomic features (x-axis) were covered by the SNPs that compose the 501 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
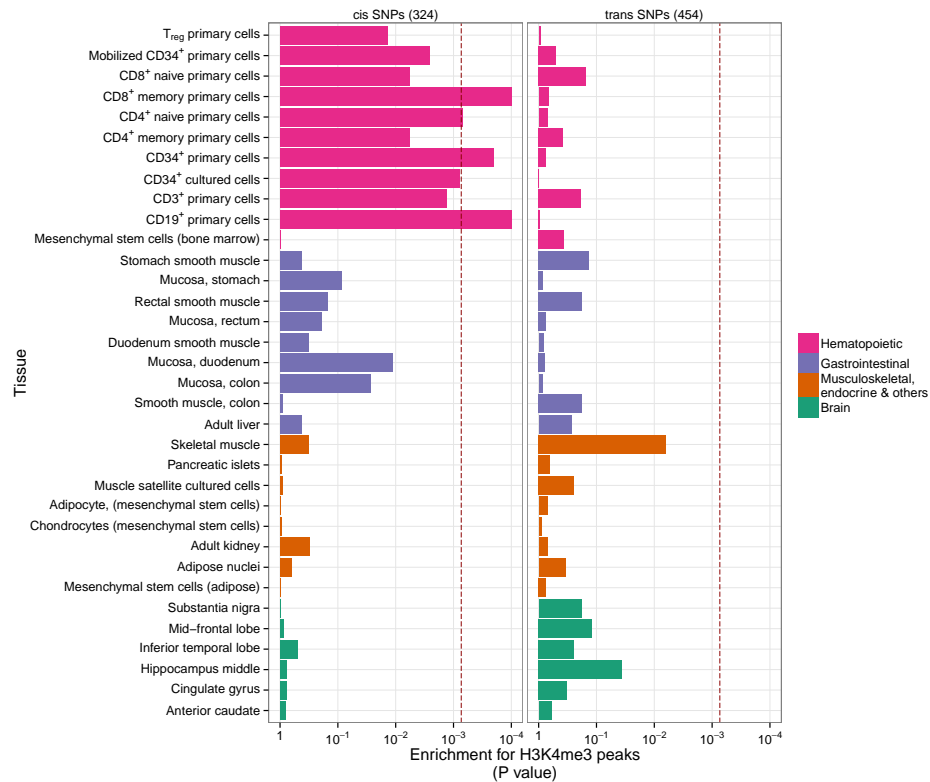
Figure S5: **Tissue specific enrichment of SNPs in transcriptionally active regions** The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3.[26] Enrichment *p*-values are calculated using permutation analysis for 34 different cell types (*y*-axis) in four tissue 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.
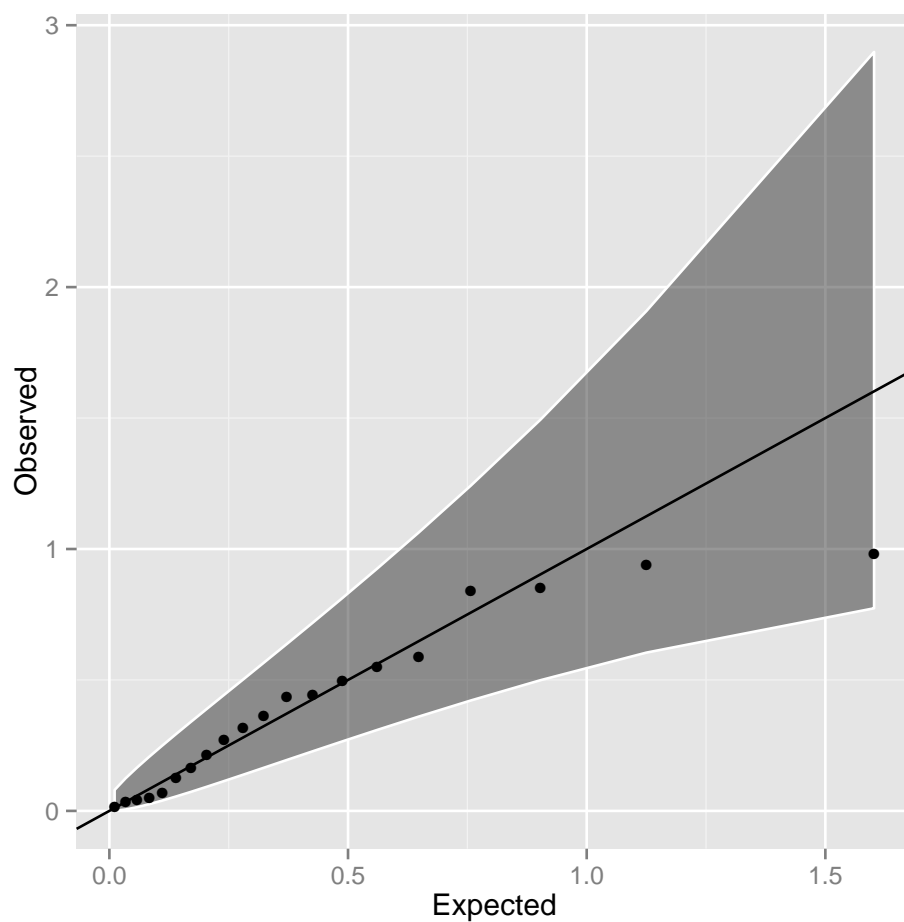
Figure S6: **Q-Q plot of interaction *p*-values in the CDHWB dataset**
Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset
(mainly due to small sample size). There is no evidence for enrichment of
interaction terms, most likely due to insufficient power given the limited sample
size.
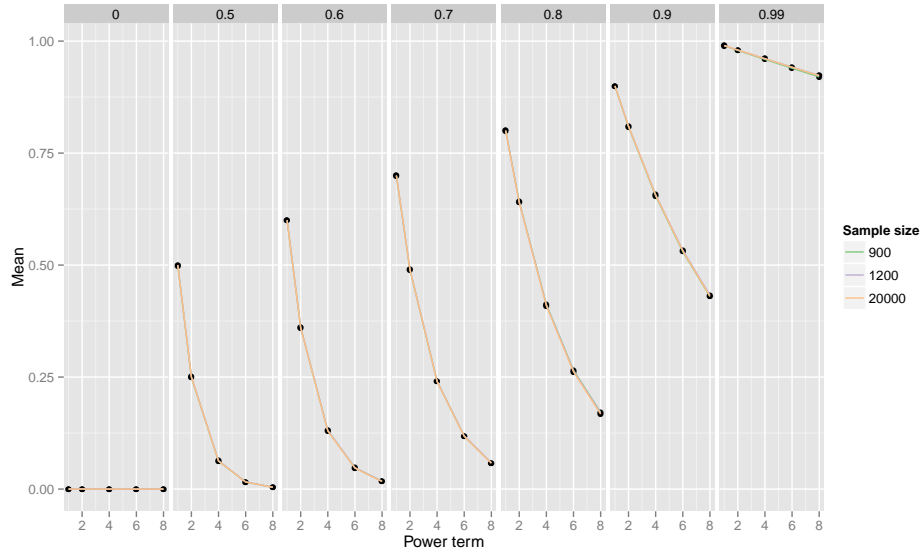
Figure S7: **Sampling mean for different power terms of population r values** Power of detection and replication of epistatic signals depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8. For a given a population value of LD r (columns of plots), plotted is the sample mean (y-axis) of $\hat{r}$, $\hat{r}^2$ (additive), $\hat{r}^4$ (dominance, A×A), $\hat{r}^6$ (A×D), $\hat{r}^8$ (D×D) (x-axis) for different sample sizes (coloured lines). As true r reduces the statistical power to detect epistatic variants drops dramatically under the assumption that statistical power is proportional to higher moments of r.
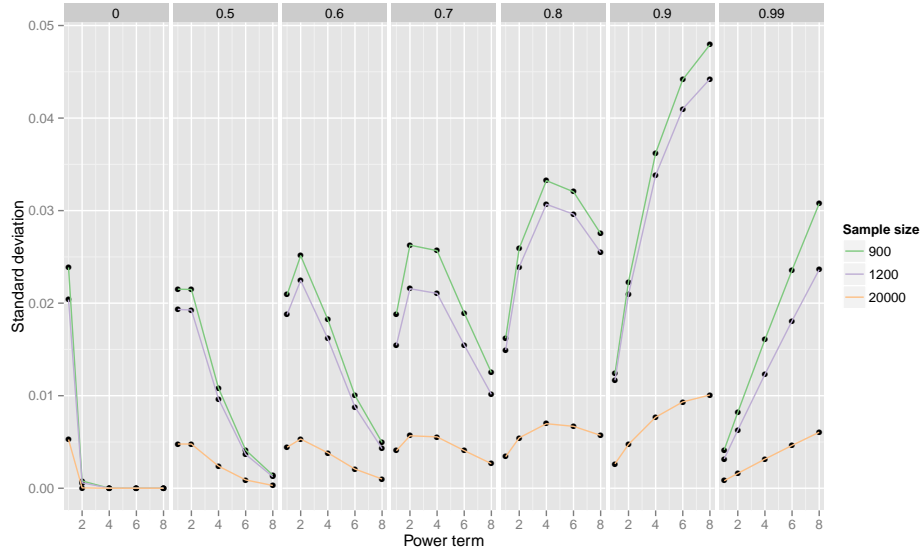
Figure S8: **Sampling standard deviation for different power terms of population r values** Power of detection and replication of epistatic signals depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8. For a given a population value of LD r (columns of plots), plotted is the sampling standard deviation (y-axis) of $\hat{r}$, $\hat{r}^2$ (additive), $\hat{r}^4$ (dominance, A×A), $\hat{r}^6$ (A×D), $\hat{r}^8$ (D×D) (x-axis) for different sample sizes (coloured lines). As the power term of r increases the sampling variance also increases. Supposing that there is sufficiently high r^x in the discovery sample for detection of epistasis, the replication sample is less likely to have similarly high r^x as x increases, leading to an expectation of reduced replication rates.
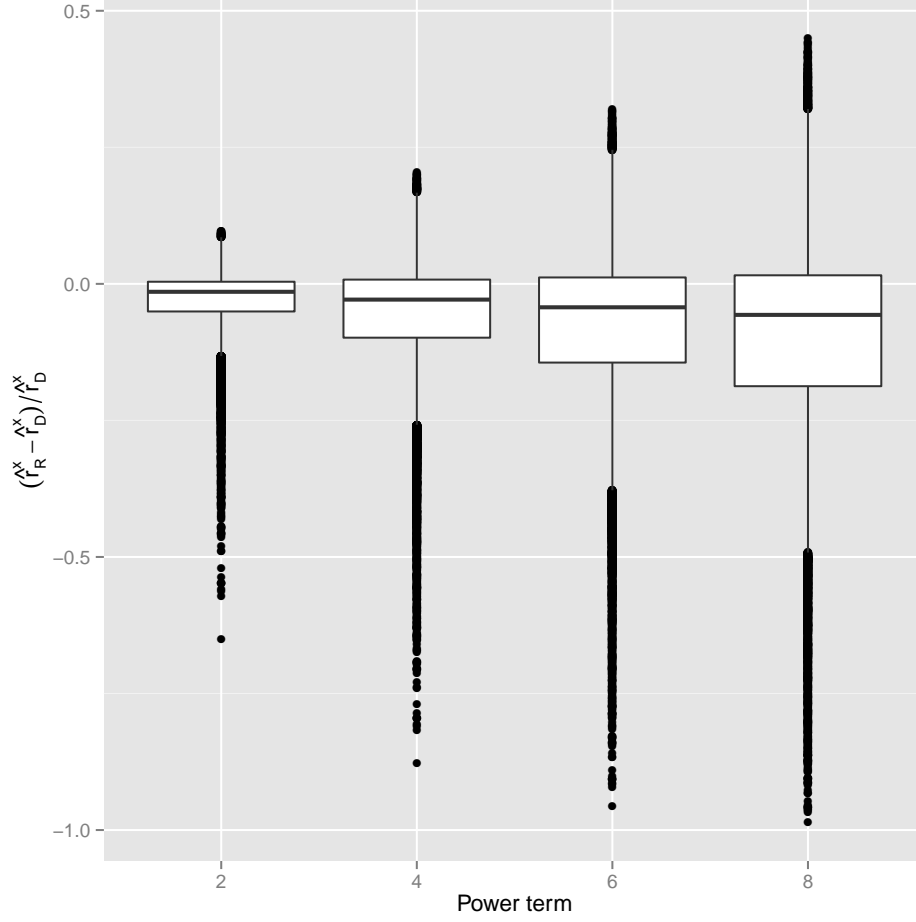
Figure S9: **Reduction in LD as estimated in replication data after ascertaining for high LD in discovery data** 100,000 "unobserved" causal variants (CVs) were tested for LD against a panel of 528,509 "observed" discovery markers (DMs). DM/CV pairs with LD $r^2 > 0.9$ were then tested in an independent sample. Simulation results of the proportional decrease between discovery and replication datasets in LD (y-axis) of $\hat{r}^2, \hat{r}^4, \hat{r}^6, \hat{r}^8$ (x-axis) are shown, where $\hat{r}_D^x$ and $\hat{r}_R^x$ are the sample LD measurements in the discovery and replication datasets, respectively. The average proportional decrease in the replication $\hat{r}_R^x$ was $2.8\%, 5.3\%, 7.4\%$ and 9.2% for $x = 2, 4, 6$ and 8, respectively.
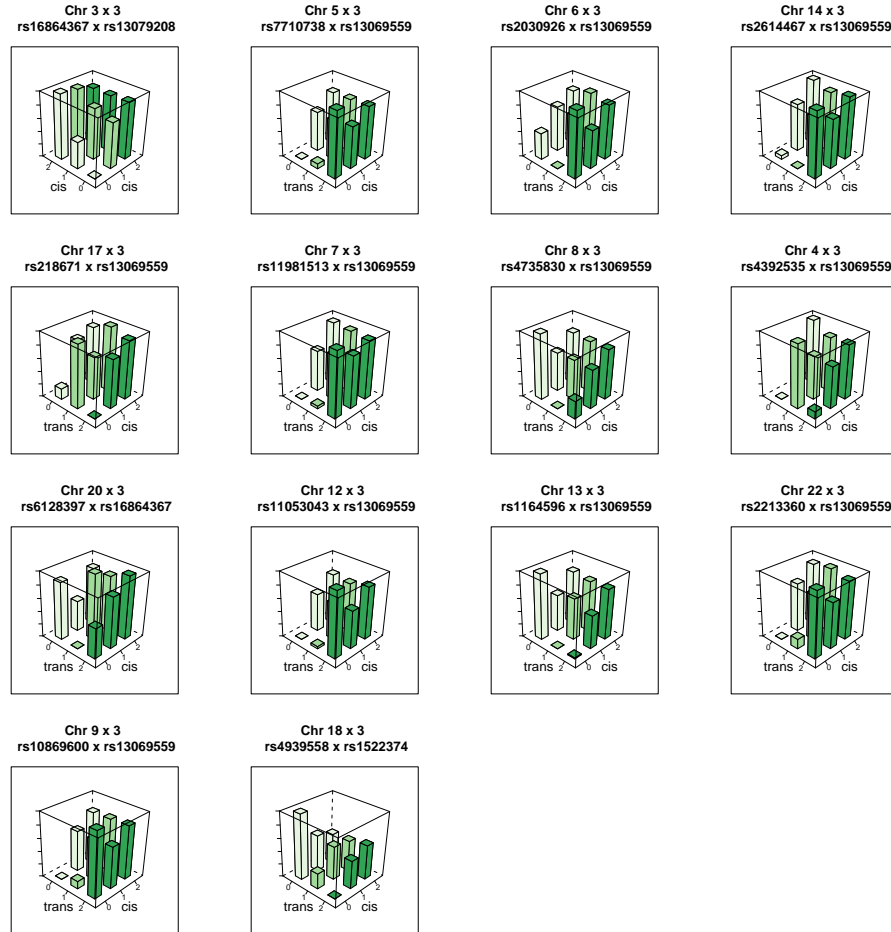
Figure S10: **Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous for the masking allele.
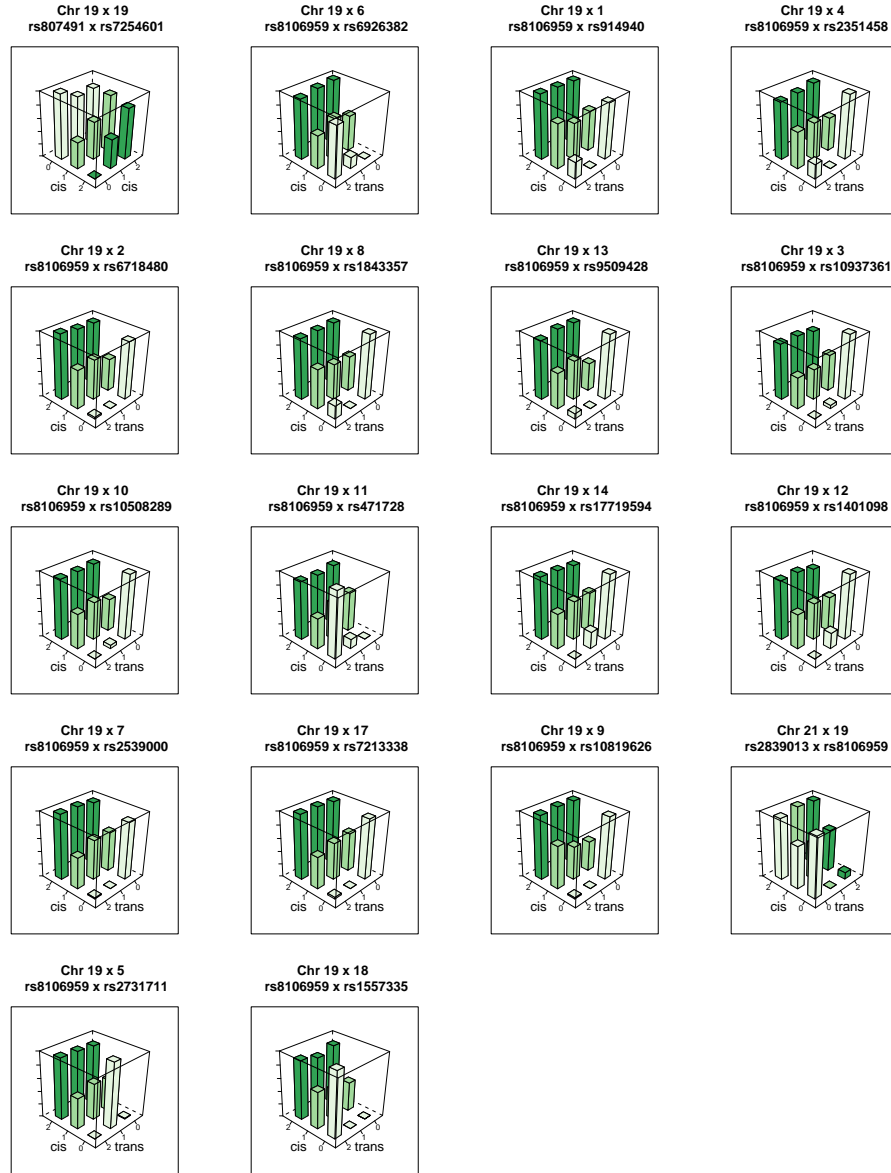
Figure S11: **Genotype-phenotype maps for 19 interactions influencing the expression of TMEM149** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of TMEM149, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous for the masking allele.

Chr 8 x 8
rs2123758 x rs3889129

Chr 8 x 7
rs2123758 x rs700276

Chr 8 x 6
rs2123758 x rs6455553

Chr 8 x 4
rs2123758 x rs4862705

Chr 22 x 8
rs2208123 x rs2123758

Chr 8 x 2
rs2123758 x rs7571561

Chr 8 x 1
rs2123758 x rs2786014

Chr 9 x 8
rs4743420 x rs2123758
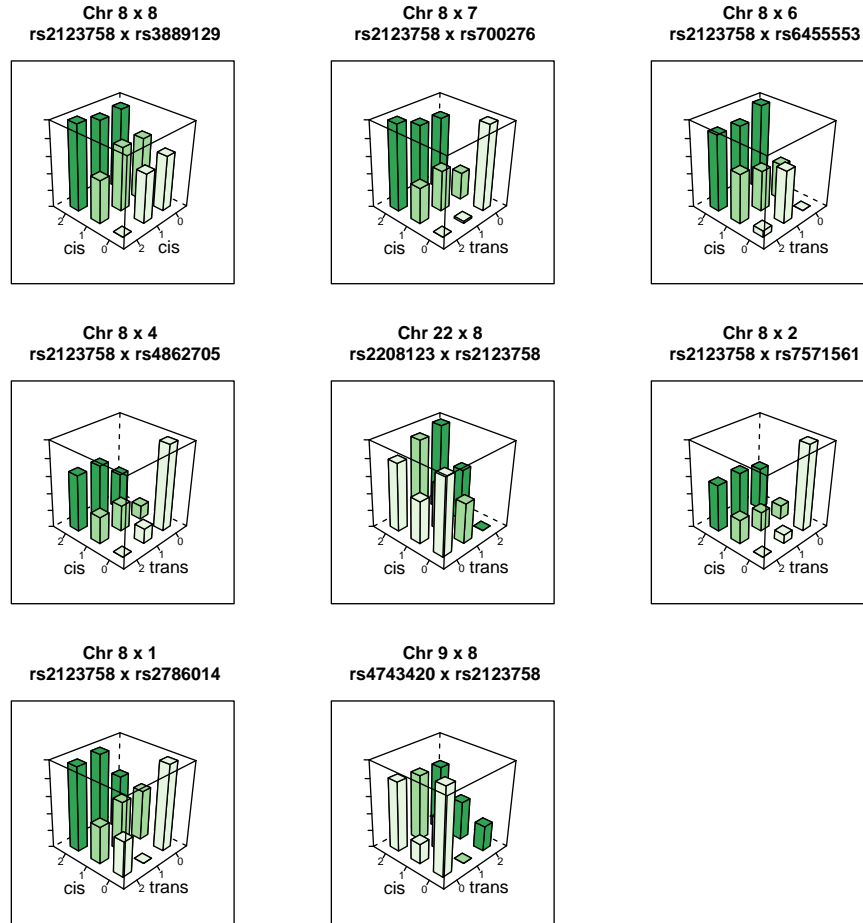
Figure S12: **Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1** Each bar represents the mean phenotypic value for individuals in that genotype class.
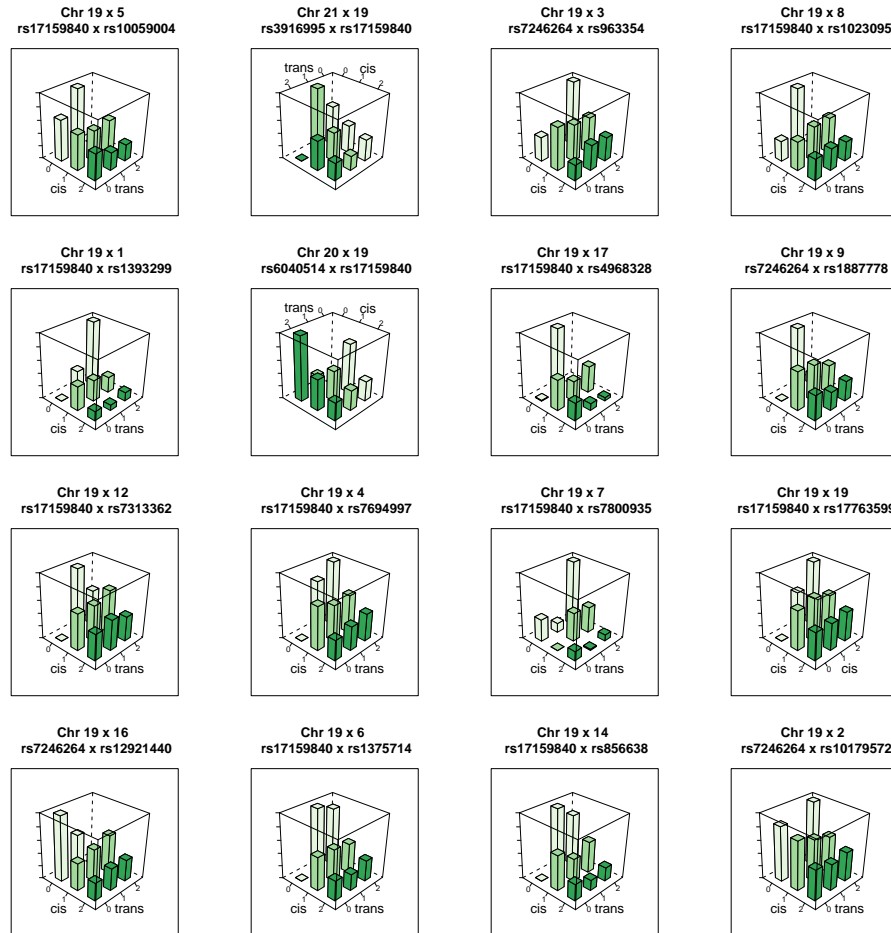
Figure S13: **Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5** Each bar represents the mean phenotypic value for individuals in that genotype class.
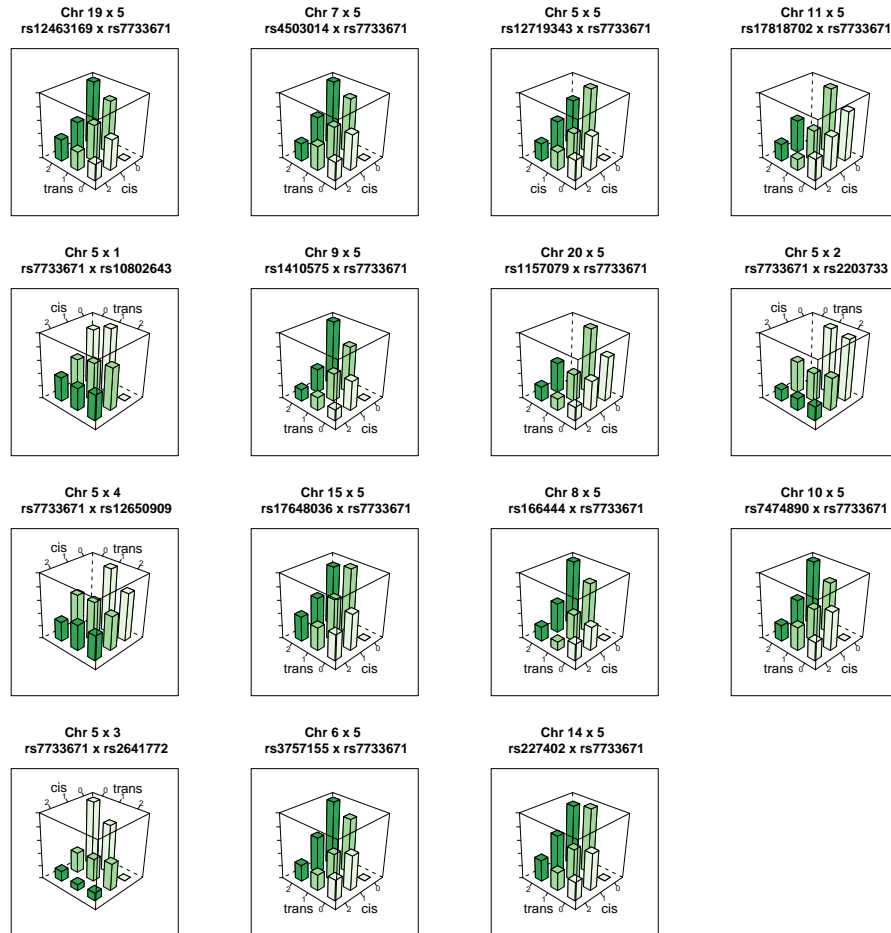
Figure S14: **Genotype-phenotype maps for 15 interactions influencing the expression of CAST** Each bar represents the mean phenotypic value for individuals in that genotype class.
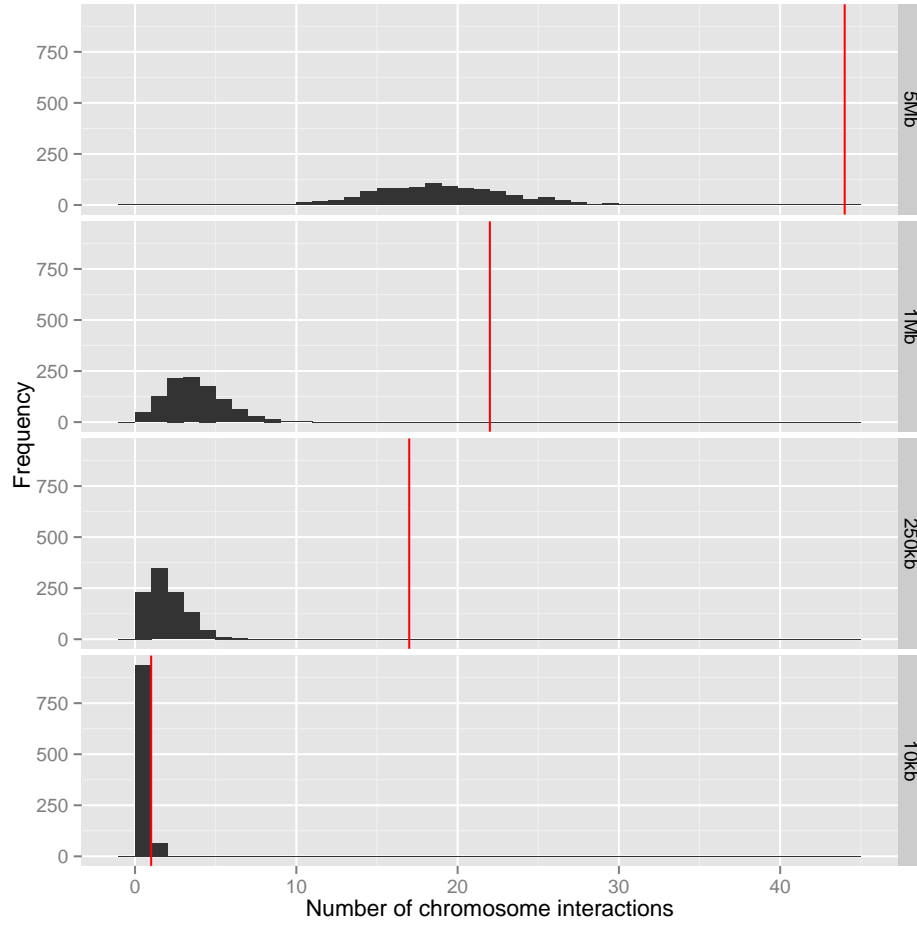
Figure S15: **Number of overlaps between chromosome interactions and epistatic interactions** Interacting chromosome regions may be a possible mechanism underlying epistatic interactions. The number of epistatic interactions within 20kb, 500kb, 2Mb and 10Mb of known chromosome interacting regions are shown by red vertical lines. The histograms represent the null distribution based on random sampling of 1,000 datasets for each window size.
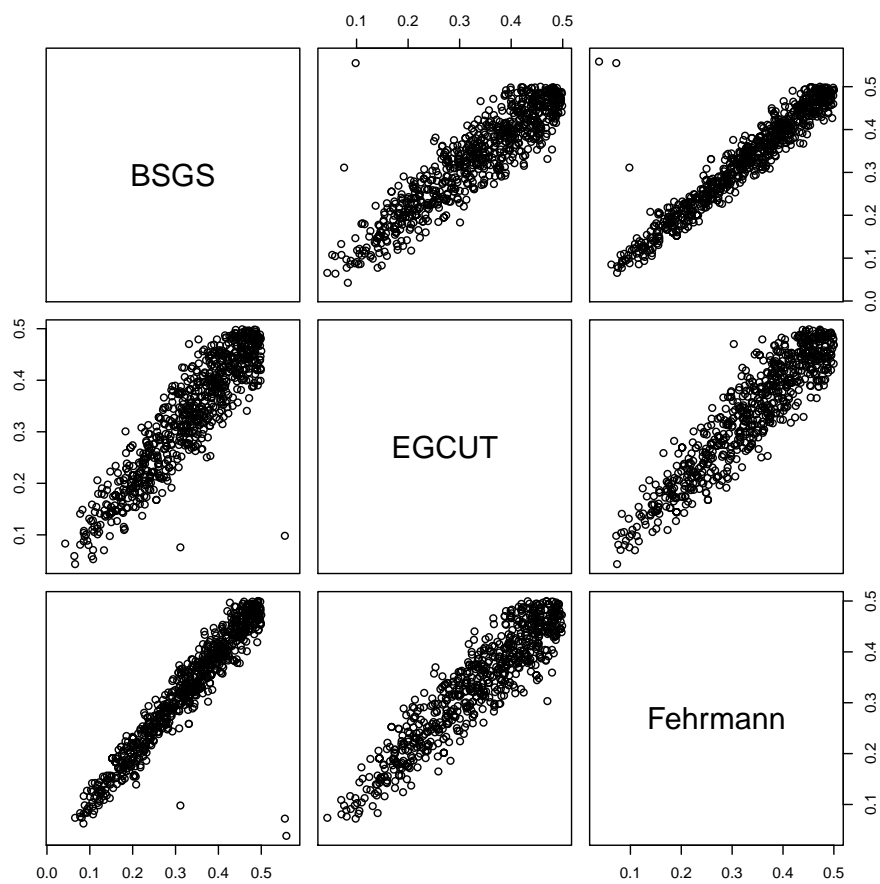
Figure S16: **Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations** Outliers were removed from the analysis as part of the filtering stage during replication.
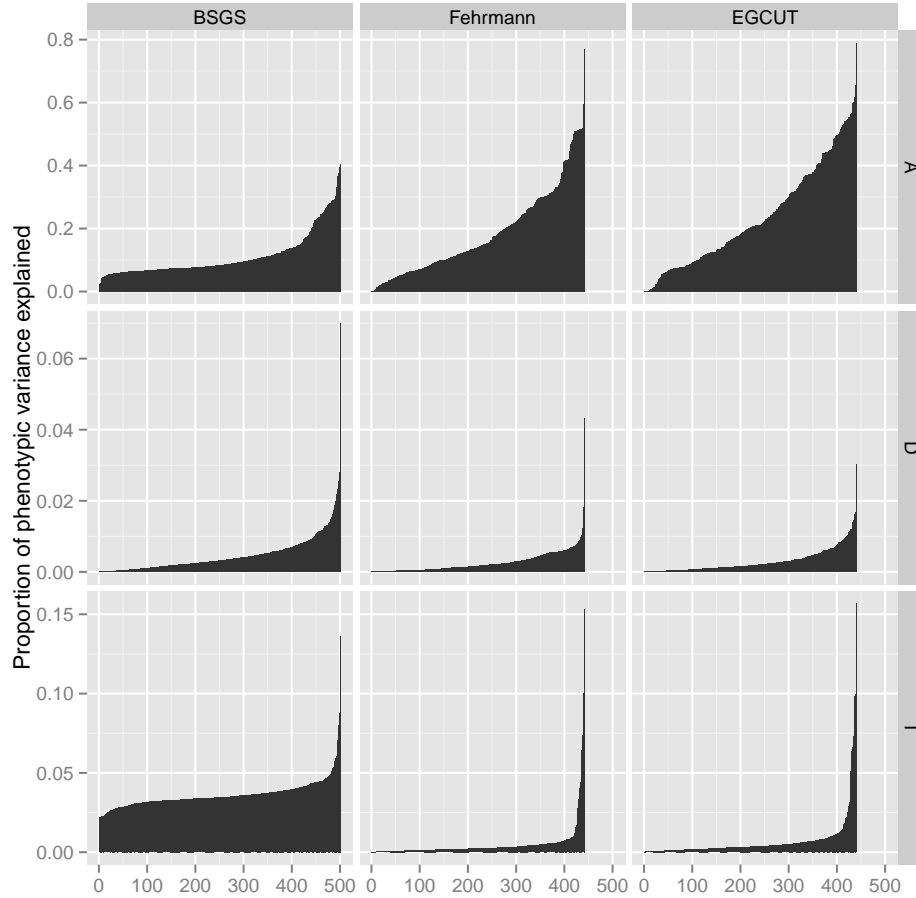
Figure S17: **Comparison of variance explained by additive, dominant and epistatic effects from different cohorts** How does the estimated variance decomposition change in different cohorts? The proportion of the phenotypic variance that is additive (A), dominant (D), or epistatic (I) for each putative 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$_{10}$ p-values				Distance / Mb[h]
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[i]	Meta[g]	
ABCA7	ILMN_1743205	19	rs3752237	19	1047161	ABCA7	rs596183	6	158100199		5.82	0.38[i]	0.02[i]	0.09[i]	
ABCA7	ILMN_1743205	19	rs3752237	19	1047161	ABCA7	rs914737	9	139522101		5.50	0.02	1.81	0.95	
ABCC3	ILMN_1677814	17	rs9455	17	48771135	ABCC3	rs47322202	7	136057883		6.10	1.04	1.78	2.02	
ACAT1	ILMN_1800008	11	rs227064	11	108207393	ACAT1	rs4744894	9	72001517		6.59	0.36	1.14	0.87	
ADCK1	ILMN_1698777	14	rs12431896	14	78088813	ADCK1	rs4833241	4	122933691		5.59	2.04	0.83	2.05	
ADCK1	ILMN_1698777	14	rs8058066	14	88462550	ADCK1	rs12431896	14	78088813	ADCK1	6.58	18.33	21.21	39.82	0.517
ADK	ILMN_2358626	10	rs2395095	10	76446305	ADK	rs10824092	10	75929517		6.69				
AGAP6	ILMN_3239130	10	rs2611512	10	51515534	AGAP8	rs2547996	5	95174319		6.22				
AHSA2	ILMN_1798308	9	rs10851585	2	137112421	HLA-G	rs842647	2	61119471	AHSA2	7.15	1.83	1.93	2.88	
AHSA2	ILMN_1798308	2	rs2523971	6	29938258		rs1177303	2	61388355	AKTIP	5.45	0.92	0.64	0.94	4.231
AKTIP	ILMN_1665982	16	rs2896940	16	57721127	AKTIP	rs13332406	16	53489705		6.91	0.16	0.99	0.57	
AKTIP	ILMN_1665982	16	rs7189819	16	53536345	AKTIP	rs1362032	7	125543391		5.93	0.71	0.20	0.42	
AKTIP	ILMN_1665982	16	rs7189819	16	53536345	AKTIP	rs1473017	4	179323762		6.18	0.27	0.30	0.23	
ALDH3A2	ILMN_2401641	14	rs3760489	17	19581009	ALDH3A2	rs11720112	3	161996349		6.26	0.33	1.37	1.01	
ANG	ILMN_1760727	14	rs9322855	14	21153299	ANG	rs4866516	5	30326625		5.75	0.02	0.20	0.04	
ANPEP	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs3823523	7	154511163		5.85	0.44	1.09	0.90	
ANPEP	ILMN_1763837	15	rs11073891	15	90363995	ANPEP	rs6846031	4	178019148		6.31	0.47	0.17	0.26	
AP3B1	ILMN_1768867	5	rs6453374	5	77508159	AP3B1	rs4684443	3	4818792		5.94	0.05			
APPL2	ILMN_1765076	12	rs935251	12	105580918	APPL2	rs2769594	9	87918528		5.60	0.80	1.02	1.16	31.703
ARL17B	ILMN_3231952	17	rs12947580	17	75768225	ARL17B	rs8079215	17	44064851	ARL17B	5.96				
ARL17B	ILMN_3231952	17	rs28334541	21	35932619	ARL17B	rs8079215	17	44064851	ARL17B	6.65				
ARL17B	ILMN_3231952	17	rs8079215	17	44064851	ARL17B	rs1950646	14	94722497		7.64				
ARL17B	ILMN_3231952	17	rs8079215	17	44064851	ARL17B	rs2197777	12	125831219		6.26				
ARL17B	ILMN_3231952	17	rs8079215	17	44064851	ARL17B	rs26847789	15	99492045		5.98				
ARL17B	ILMN_3231952	17	rs8079215	17	44064851	ARL17B	rs9834627	3	191203546		5.72				
ATP13A1	ILMN_2134224	19	rs4284750	19	19810050		rs873870	19	19738554		5.30				
BID	ILMN_1763386	22	rs8919	22	18213057	BID	rs9804943	12	129906275		5.84	12.18	3.25	14.23	0.071
BID	ILMN_2372413	22	rs1811405	22	18233000		rs10888267	1	248059423		6.60	0.06	0.40	0.14	
C11ORF17	ILMN_1752988	11	rs2568061	11	8866260	C11ORF17	rs6553184	4	189150656		5.66	0.87	0.16	0.50	
C13ORF18	ILMN_2196550	13	rs2110603	16	6259852		rs674754	13	46913416	C13ORF18	6.66	1.15	0.04	0.54	
C13ORF18	ILMN_2196550	13	rs674754	13	46913416	C13ORF18	rs6857876	4	153610164		3.87	0.28	0.28	0.22	
C14ORF173	ILMN_2393450	14	rs110859825	22	37557539		rs4983382	14	105189504	C14ORF173	6.02	0.38	0.50	0.43	
C14ORF173	ILMN_2393450	15	rs3935344	15	92276674		rs4983382	14	105189504	C14ORF173	5.98	0.60	0.84	0.85	
C14ORF173	ILMN_2393450	14	rs4983382	14	105189504	C14ORF173	rs10754644	1	238724741		7.15	0.31	0.28	0.24	
C14ORF4	ILMN_1804396	14	rs1293455	18	138196673		rs2655991	14	77574438		4.87				
C14ORF4	ILMN_1804396	14	rs2655991	14	77574438		rs10972462	9	35427324		4.32				
C14ORF4	ILMN_1804396	14	rs2655991	14	77574438		rs6445340	3	63371601		4.40				
C14ORF4	ILMN_1804396	14	rs2655991	14	77574438		rs9787151	1	63179138		4.05				
C14ORF4	ILMN_1804396	14	rs47933445	17	70416307		rs2655991	14	77574438		3.85				
C14ORF4	ILMN_1804396	14	rs6010061	22	51151724		rs2655991	14	77574438		4.61				
C17ORF60	ILMN_1747347	17	rs7245800	19	52083552		rs74405659	17	77574438	C17ORF60	4.69	0.42	0.05	0.35	
C1ORF86	ILMN_1726989	1	rs9907897	17	63502633		rs2257182	1	2082566	C1ORF86	6.79	0.53	0.50	0.19	
C1ORF86	ILMN_2097790	1	rs2334323	18	110577257		rs2460002	1	2119833	C1ORF86	5.90				
C1ORF86	ILMN_2097790	1	rs2279474	18	46384412		rs2460002	1	2119833	C1ORF86	5.65	0.01	0.03	0.13	
C21ORF57	ILMN_1795836	21	rs7188668	16	25771358		rs901964	12	48676038	ZNF641	5.59	0.29	0.50	0.37	0.263
C21ORF57	ILMN_1795836	21	rs48819271	21	48052838		rs11701361	21	47764477		4.91				
C5ORF4	ILMN_1728742	5	rs1122762	5	45866512	C5ORF4	rs286595	5	154348552	C5ORF4	9.42	6.08	16.36	21.67	
C8ORF59	ILMN_1653205	8	rs12429804	13	36577930		rs2896452	8	86102223	C8ORF59	5.55	0.72	0.04	0.27	
C8ORF59	ILMN_1653205	8	rs12454561	18	312772238		rs2896452	8	86102223	C8ORF59	5.49	0.29	0.02	0.07	
C8ORF59	ILMN_1653205	8	rs2896452	8	86102223	C8ORF59	rs1004564	4	55242625		5.45	0.31	0.18	0.21	
C8ORF59	ILMN_1653205	8	rs1004564	4	86102223		rs2896452	8	86102223	C8ORF59	7.62	0.38	0.07		
C8ORF59	ILMN_1653205	14	rs7152284	14	52273663		rs2896452	8	86102223	C8ORF59	5.67	2.18		1.33	

Table S1 – continued from previous page

Expression trait			SNP 1				SNP 2				Interaction statistic / −log$_{10}$ p-values				Distance / Mb[h]
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[f]	Meta[g]	
C8ORF59	ILMN_1653205	8	rs8051751	16	7188323		rs2896452	8	86102223	C8ORF59	5.79	1.39	0.18	0.87	
C9ORF72	ILMN_1741881	9	rs10122902	9	27556780	C9ORF72	rs2526698	1	242029101		6.36	0.96	0.01	0.37	
CABC1	ILMN_1731064	1	rs12765847	10	4353908		rs3738725	1	227174210	CABC1	6.36	0.94	0.00	0.34	
CARD9	ILMN_1712532	9	rs4266763	9	139289825	INPP5E	rs684040	1	82128660		5.81	0.09	0.86	0.42	
CARD9	ILMN_1712532	9	rs4573661	9	6026661		rs4077515	9	139266496	INPP5E	6.61	0.23	0.96	0.62	
CAST	ILMN_1717234	5	rs1157079	20	6778978		rs7733671	5	96000269	CAST	7.07	0.02	2.85	1.75	
CAST	ILMN_1717234	5	rs12463169	16	17321669		rs7733671	5	96000269	CAST	5.73	0.36	1.57	1.20	
CAST	ILMN_1717234	5	rs12599264	5	81840122		rs7733671	5	96000269	CAST	7.00	0.13	1.34	0.78	
CAST	ILMN_1717234	5	rs12719343	5	125369113		rs7733671	5	96000269	CAST	7.68	0.27	0.52	0.37	29.369
CAST	ILMN_1717234	5	rs1410575	5	78255630		rs7733671	5	96000269	CAST	6.55	0.97	0.03	0.41	
CAST	ILMN_1717234	5	rs160444	8	78392770		rs7733671	5	96000269	CAST	7.01	1.15	0.59	1.09	
CAST	ILMN_1717234	5	rs17648036	5	27311111		rs7733671	5	96000269	CAST	7.81	0.11	0.01	0.01	
CAST	ILMN_1717234	5	rs17818702	11	86107920		rs7733671	5	96000269	CAST	6.62	0.07	0.33	0.12	
CAST	ILMN_1717234	5	rs2274402	14	70496867		rs7733671	5	96000269	CAST	6.12	0.92	1.56	1.72	
CAST	ILMN_1717234	5	rs2822124	5	15166804		rs7733671	5	96000269	CAST	6.87	0.49	0.12	0.23	
CAST	ILMN_1717234	5	rs3757155	6	136458593		rs7733671	5	96000269	CAST	7.24	0.75	0.78	0.93	
CAST	ILMN_1717234	5	rs4503014	5	31149140		rs7733671	5	96000269	CAST	5.88	0.23	0.78	0.50	
CAST	ILMN_1717234	5	rs7474890	10	59590078		rs7733671	5	96000269	CAST	6.74	0.22	0.87	0.54	
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs10802643	1	238120177		7.42	0.19	0.26	0.15	
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs12650909	4	170192890		7.42	0.26	0.30	0.22	
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs2203733	2	224093101		6.07	0.33	0.37	0.31	
CAT	ILMN_1651705	11	rs872311	18	66175386		rs2641772	3	195531841	CAT	6.93	0.23	0.18	0.14	
CCDC88B	ILMN_1772208	11	rs2353203	19	17099980	CCDC88B	rs11032695	11	34447586		6.41	0.15	0.01	0.02	
CCDC88B	ILMN_1772208	11	rs6947339	7	64097233		rs541207	11	64125142	CCDC88B	5.68	0.08	0.03	0.02	
CD36	ILMN_1784863	7	rs3211834	7	80280117		rs12771349	10	96998193	VAMP8	5.62	1.74	0.24	1.20	
CD55	ILMN_1800540	1	rs750801	11	76033374		rs1254900	2	85816334	CD55	6.93	0.13	0.80	0.42	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs6700168	1	207502534		5.09	0.04	0.27	0.08	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs10255470	7	157182040		6.06	0.24	1.67	1.16	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs4696726	4	7992632		5.71	0.71	0.22	0.45	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs7622580	3	196721395		5.56	0.64	0.75	0.81	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs838875	12	125145394		6.31	0.21	0.14	0.11	
CD93	ILMN_1704730	20	rs2868504	20	37771578		rs1884655	20	23074375	CD93	7.88	0.95	0.07	0.45	14.697
CD93	ILMN_1704730	20	rs48113479	20	23076914	CD93	rs9576388	13	38434472		5.71	0.90	0.12	0.48	
CD93	ILMN_1704730	20	rs48113479	20	23076914		rs10925747	1	238899903		7.43	2.16	0.16	1.44	
CD93	ILMN_1704730	20	rs48113479	20	23076914		rs2873420	8	136500554		7.02	0.15	0.24	0.12	
CD93	ILMN_1704730	20	rs48113479	20	23076914		rs4328531	18	74439542		6.13	0.23	0.10	0.09	
CDC16	ILMN_2339796	13	rs8615544	14	104162063		rs7324744	13	115008038	CDC16	6.08	0.72	0.20	0.44	
CDK5R1	ILMN_1730928	17	rs9905940	17	46614102	HOXB2	rs11655031	17	30833162	CDK5R1	5.46	0.92	0.02	0.36	15.781
CEACAM21	ILMN_1745949	19	rs2006609	20	51956250		rs4803481	19	42066556	CEACAM21	5.47	0.07	1.28	0.67	
CEACAM21	ILMN_1745949	19	rs4803481	19	42066556	CEACAM21	rs2421050	5	158943044		6.15	0.95	0.36	0.73	
CEP192	ILMN_1703754	18	rs6505780	18	13069782	CEP192	rs13132719	4	180265266		6.67	0.07	0.27	0.02	
CEP63	ILMN_1787808	3	rs3825569	14	101350298		rs13079012	3	134247706	ANAPC13	5.75	1.92	0.28	1.39	
CES1	ILMN_2359945	16	rs8192935	16	55861794	CES1	rs5772788	2	235248562		6.36	0.10	0.01	0.01	
CHPT1	ILMN_2202940	12	rs591967	13	38838122		rs2695290	12	102087844	CHPT1	5.65	0.06	0.57	0.23	
CHPT1	ILMN_2202940	12	rs6539014	12	102277782		rs867578	11	81937002		5.74	0.92	0.20	0.44	
CLEC12A	ILMN_1663142	12	rs429790	16	84471642		rs7313235	12	10132283	CLEC12A	4.75	0.95	0.36	0.36	
CLEC12A	ILMN_2403228	12	rs7305054	12	10156646		rs3903088	10	134236688		5.55	0.07	0.27	0.67	
CLTB	ILMN_1674609	5	rs17129799	11	96929337		rs6863172	5	175595960	CLTB	7.54	0.95	0.28	0.73	
CNN2	ILMN_1770290	19	rs3752237	19	1047161	ABCA7	rs169130	5	63121080		5.55	0.07	0.01	0.02	
CNN2	ILMN_1770290	19	rs3752237	19	1047161	ABCA7	rs7336017	16	67713633		7.56	1.92	0.07	1.39	
CPSF1	ILMN_1654545	8	rs4336645	8	145569535		rs1455268	13	61738094		6.33	0.10	0.01	0.01	
CPVL	ILMN_1082928	7	rs12596791	16	26115562		rs245884	7	29188475	CPVL	6.34	0.06	0.57	0.23	

Table S1 – continued from previous page

Gene ID[a]	Probe ID[b]	Chr.	rs ID	Pos/Mb[c]	Association[d]	rs ID	Chr.	Pos/Mb[c]	Association[d]	BSGS[e]	Fehrmann[f]	EGCUT[f]	Meta[g]	Distance / Mb[h]
				SNP 1				SNP 2		Interaction statistic / −log₁₀ p-values				
CPVL	ILMN_1682928	7	rs2835998	39202070		rs245884	7	29188475	CPVL	5.55	0.19	0.03	0.04	
CRIPT	ILMN_1813256	2	rs2131290	188859908		rs1531133	2	46843631	CRIPT	5.47	0.28	0.10	0.12	
CRLS1	ILMN_1737685	20	rs6139887	5986234	CRLS1	rs1473927	5	62406408		6.18	0.10	0.36	0.15	0.033
CSTB	ILMN_1761797	21	rs9979356	45230974		rs37613385	21	45198355		11.99	25.20	16.72	42.27	
CTNNA1	ILMN_1804854	5	rs924943	69500505		rs176382	5	135226767	CTNNA1	5.74	0.02	0.41	0.11	
CTSC	ILMN_1696347	11	rs2457684	88139983	CTSC	rs7079264	10	108679892		5.67	0.92	0.74	1.03	
CTSC	ILMN_1696347	11	rs5752236	26250645		rs7128352	11	88087357	CTSC	5.84	0.49	0.80	0.73	
CTSC	ILMN_2242463	11	rs7930237	88117962		rs556895	11	88077479	CTSC	7.16	18.76	15.06	33.53	0.040
CWF19L1	ILMN_1651886	10	rs7108734	11456027		rs12784396	10	102027407	CWF19L1	5.42	0.21	0.01	0.03	
CYBRD1	ILMN_1712305	2	rs2592948	129994690		rs888427	2	172368120	CYBRD1	5.89	0.23	0.53	0.34	
CYBRD1	ILMN_1712305	2	rs7852475	140698856		rs888427	2	172368120	CYBRD1	5.68	0.20	0.02	0.04	
CYBRD1	ILMN_2087692	2	rs11257679	12318284		rs888427	2	172368120	CYBRD1	5.81	0.39	1.87	1.47	
CYBRD1	ILMN_2087692	2	rs6137908	23344590		rs888427	2	172368120	CYBRD1	5.53	0.05	0.83	0.36	
CYBRD1	ILMN_2087692	2	rs888427	172368120	CYBRD1	rs7591849	2	160112881		5.85	0.87	0.10	0.44	12.255
CYP27A1	ILMN_1704985	2	rs6021982	36571928		rs933994	2	219650616	CYP27A1	5.42	0.29	0.86	0.60	
DAB2	ILMN_2128428	5	rs7778910	110451383		rs835223	5	39381357	DAB2	5.44	0.48	0.41	0.44	
DCAKD	ILMN_1811648	17	rs9900173	43111688		rs1343244	6	82076988		9.12	0.00	0.58	0.14	
DDT	ILMN_1690982	22	rs5760102	24248761	DDT	rs2378341	3	187475208		5.62	0.64	0.25	0.42	
DDX58	ILMN_1797001	9	rs4937097	125962645		rs7042042	9	32451144		5.31	0.61	0.29	0.44	
DEM1	ILMN_1783996	1	rs10120023	137810259	COQ10A	rs25195515	7	88204888		5.47	0.08	0.41	0.16	
DEM1	ILMN_1783996	1	rs12363827	106703727		rs10120023	9	137810259	COQ10A	6.39	0.77	0.02	0.29	
DHRS9	ILMN_1733998	2	rs1519956	89468283		rs7566044	2	169960422	DHRS9	6.00	0.06	1.17	0.58	
DHRS9	ILMN_1733998	2	rs1528529	147132505		rs7566044	2	169960422	DHRS9	6.48	0.37	0.34	0.32	
DHRS9	ILMN_2384181	2	rs2831914	29959453		rs2161037	2	169893419	DHRS9	5.51	0.88	0.04	0.37	
DHRS9	ILMN_2384181	2	rs7661304	187776431		rs2161037	2	169893419	DHRS9	7.64	0.05	0.11	0.03	
DIP2B	ILMN_1755589	12	rs11080134	29161503		rs11169322	12	50610976	LASS5	4.65	0.32	0.05	0.10	
DIP2B	ILMN_1755589	12	rs11169335	50636364	LASS5	rs2872008	7	153134888		4.87	0.58	0.58	0.19	
DIP2B	ILMN_1755589	12	rs3385585	41711815		rs7134595	12	50730458		5.31	0.30	0.22		
DIP2B	ILMN_1755589	12	rs7134595	50730458	LASS5	rs1808634	8	61971140		4.40	0.37	0.02	0.01	
DIP2B	ILMN_1755589	12	rs7312252	117994348	LASS5	rs4532958	10	115214154	LASS5	5.03	0.09	0.00	0.11	
DNAJB6	ILMN_1793770	7	rs2286842	157216093		rs12427378	12	51074199	LASS5	5.92	0.23	1.45	0.97	66.920
DPH3	ILMN_2349610	3	rs12232308	93409054		rs3779589	7	157163614	DNAJB6	5.79	1.58	1.18	1.12	0.052
ECGF1	ILMN_2109708	22	rs1405222	509712266	ECGF1	rs1566972	3	16320360	DPH3	6.17	0.15	0.27	0.70	
ECHDC2	ILMN_1671568	1	rs4234091	241911027		rs4891884	18	64004670		4.81	0.22	0.35	0.22	
ECHDC2	ILMN_1671568	1	rs5992637	176675900		rs11206043	1	534002552	ECHDC2	6.19	0.64	0.16	0.35	
EHD4	ILMN_1720083	15	rs10403312	53244938		rs11206043	1	534002552	ECHDC2	5.58	0.90	0.47	0.79	
EIF2B2	ILMN_1713380	14	rs6567288	60218334		rs1048166	15	421192040	EHD4	6.98	0.23	0.11	0.10	
EIF5A	ILMN_1794522	17	rs7216490	7221707	EIF5A	rs175450	14	75590340	EIF2B2	5.56	0.56	0.08	0.24	
EIF5A	ILMN_1794522	17	rs7216490	7221707	EIF5A	rs1269096	14	96003119		5.44	0.28	0.59	0.41	
EIF5A	ILMN_1794522	17	rs7216490	7221707	EIF5A	rs1553474	2	49359676		5.55	0.08	0.05	0.02	
EIF5A	ILMN_1794522	17	rs7216490	7221707	EIF5A	rs2197210	8	129624067		6.36	0.05	1.12	0.53	
EMR2	ILMN_2827076	19	rs61132112	23196249	EMR2	rs4471434	11	126387391		5.52	0.36	0.04	0.11	
EMR2	ILMN_2353633	19	rs9305048	18761714		rs9305048	19	14879034	EMR2	6.51	0.45	0.40	0.41	
EMR2	ILMN_2353633	19	rs9305048	14879034		rs30007765	13	102480759		6.03	0.20	0.58	0.35	
EPHX2	ILMN_1709237	11	rs1107764	127909396		rs13269963	8	27400604	EPHX2	5.70	0.20	0.58	0.35	
ERICH1	ILMN_1731001	8	rs10894861	134611176		rs12115088	8	578742	ERICH1	5.43	0.25	1.20	0.81	
ERICH1	ILMN_1731001	8	rs5766218	453337329		rs4735900	8	607161	ERICH1	6.11	0.20	0.09	0.09	
ERICH1	ILMN_1731001	8	rs726145	31187910		rs12115088	8	578742	ERICH1	5.65	0.29	0.04	0.08	
ERICH1	ILMN_1731001	8	rs4735895	600729	ERICH1	rs12188164	4	182786760		5.63	0.29	0.19	1.06	
EXOC3	ILMN_2104696	5	rs1870076	55228462		rs1517297	5	428236	EXOC3	6.83	0.67	1.03	0.44	
FAHD1	ILMN_1789419	16	rs1560104	12708208		rs344363	16	1972548	FAHD1	5.61	0.74	1.38	0.44	10.736
FCN1	ILMN_1668063	9	rs12580388	129591144		rs10120023	9	137810259	COQ10A	6.33	0.27	0.30	0.23	

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Gene ID[a]	Expression trait Probe ID[b]	Chr.	SNP 1 rs ID	Chr.	Pos/Mb[c]	Association[d]	SNP 2 rs ID	Chr.	Pos/Mb[c]	Association[d]	Interaction statistic BSGS[e]	Fehrmann[f]	$-\log_{10}$ p-values EGCUT[f]	Meta[g]	Distance / Mb[h]
FEZ2	ILMN_1739586	2	rs2356400	19	44321776		rs13406184	2	36791226	FEZ2	5.78	0.14	0.33	0.16	
FEZ2	ILMN_1739586	2	rs969010	4	159963132		rs11691600	2	36810133	FEZ2	6.59	0.14	0.28	0.14	
FGD2	ILMN_2115005	6	rs4803848	19	46205050		rs831486	6	37001267	FGD2	5.69	0.12	0.25	0.11	
FGD2	ILMN_2115005	6	rs902634	10	133943951		rs831489	6	36999682	FGD2	5.49	1.20	0.11	0.66	
FLJ20489	ILMN_1778144	12	rs17615703	12	117036766		rs3782908	12	48169526	FLJ20489	5.81	0.06	0.70	0.29	68.867
FLJ20489	ILMN_1778144	12	rs3782908	12	48169526	FLJ20489	rs897511	4	167695661	FLJ20489	5.53	0.03	0.11	0.02	
FLJ20489	ILMN_1778144	12	rs4792199	17	7992118		rs3782908	12	48169526	FLJ20489	5.74	0.19	0.02	0.04	
FLJ20489	ILMN_1778144	12	rs4984440	15	97033129		rs3782908	12	48169526	FLJ20489	6.49	0.31	0.47	0.36	
FLJ20489	ILMN_1778144	12	rs7204135	16	50626195		rs3782908	12	48169526	FLJ20489	6.90	0.38	0.17	0.21	
FLJ20718	ILMN_1763063	16	rs9325634	21	43818790		rs2287197	16	50106594	FLJ20718	6.04	0.14	0.95	0.53	
FLJ43093	ILMN_2123450	6	rs17112712	14	107276627		rs6906101	6	36667610	FLJ20718	5.48	0.39	0.06	0.13	
FLJ43093	ILMN_2123450	6	rs6906101	6	36667610	FLJ43093	rs13214069	6	32705248	FLJ43093	5.44	0.00	0.64	0.18	3.962
FN3KRP	ILMN_1652333	17	rs898095	17	80890638		rs9892064	17	80827903		16.16	28.24	29.39	59.95	0.063
FUCA1	ILMN_1752728	1	rs4971478	2	1346063		rs12744386	1	24168019	FUCA1	6.41	0.01	0.30	0.06	
FXYD5	ILMN_2309848	19	rs1633921	19	35695200		rs788178	13	98328559		3.70	0.09	0.41	0.17	
FXYD5	ILMN_2309848	19	rs17398183	20	55609148		rs2285515	19	35660450	FXYD5	6.58	0.03	0.48	0.15	
FXYD5	ILMN_2309848	19	rs2285515	19	35660450	FXYD5	rs11739594	5	141709563		5.70	0.07	0.17	0.05	
FXYD5	ILMN_2309848	19	rs2285515	19	35660450	FXYD5	rs13067700	3	95331048		6.00	0.09	0.09	0.22	
FXYD5	ILMN_2309848	19	rs2285515	19	35660450	FXYD5	rs17036504	4	47567329		6.10	0.28	0.51	0.14	
G3BP2	ILMN_2381758	4	rs10230232	17	29390239		rs1553985	4	76554604		5.19	0.08	0.37	0.14	
GAA	ILMN_2410783	17	rs11115847	17	78153130	GAA	rs12602462	17	78146016		13.91	19.98	12.99	32.60	0.007
GAA	ILMN_2410783	17	rs8068856	17	78100731		rs10902506	12	132678089		5.65	0.11	0.39	0.17	
GAPT	ILMN_1675191	5	rs10070522	5	57786110	GAPT	rs7605821	2	235695228	GAPT	5.85	0.01	0.78	0.28	
GAPT	ILMN_1675191	5	rs7082031	10	128038717		rs10070522	5	57786110	GATS	5.72	0.26	0.11	0.11	
GATS	ILMN_1699631	7	rs1147447	14	66460742		rs9950520	7	99827148	GATS	5.47	0.83	0.63	0.87	
GATS	ILMN_1699631	7	rs2425256	20	35056572		rs2950520	7	99827148		6.22	0.38	0.42	0.33	
GDPD3	ILMN_1774901	16	rs3809624	16	30102802	GDPD3	rs2197465	14	48572632		6.57	0.55	0.35	0.24	
GDPD3	ILMN_1774901	16	rs7204270	16	30156963	GDPD3	rs1015111	4	128972357		5.86	0.02	0.09	0.13	
GNLY	ILMN_1790692	2	rs4145072	2	110899955		rs7577293	12	85935282	GNLY	5.78	0.36	0.45	0.39	
GPN3	ILMN_3239426	12	rs7198646	16	26084476		rs7960552	12	111164237	GPN3	5.72	0.25	0.39	0.06	
GPR162	ILMN_1730816	12	rs1860563	16	6478898		rs2707210	12	6902002	GPR162	5.49	0.36	0.46	0.39	
GPR162	ILMN_1730816	12	rs2272500	12	79685913		rs2707210	12	6902002	GPR162	5.07	0.25	0.03	0.06	72.784
GPR162	ILMN_1730816	12	rs2707210	12	6902002	GPR162	rs440848	9	6554558		5.47	0.25	0.06	0.07	
GPR162	ILMN_1730816	12	rs2707210	12	6902002	GPR162	rs9827054	3	188880113		6.21	0.96	0.44	0.44	
GPR177	ILMN_1660549	1	rs11057383	1	124369421		rs12065581	1	68732819	GPR177	5.45	0.72	0.67	0.81	
GPR177	ILMN_1660549	1	rs12527241	6	120468039		rs12065581	1	68732819	GPR177	5.76	0.17	0.40	0.22	
GPR177	ILMN_1660549	1	rs12532999	7	127939793		rs12065581	1	68732819	GPR177	6.50	0.79	1.43	1.50	
GPR177	ILMN_1660549	1	rs7256013	16	11169683		rs12065581	1	68732819	GPR177	5.43	0.31	0.11	0.13	
GPR177	ILMN_1660549	1	rs9575097	13	82986268		rs12065581	1	68732819	GPR177	6.04	0.95	0.21	0.60	
GPR177	ILMN_2283325	1	rs6566669	18	70506011		rs12065581	1	68732819	GPR177	5.86	0.24	0.34	0.23	
GPR177	ILMN_2283325	1	rs9290426	3	171399321		rs12065581	1	68732819	GPR177	6.50	0.01	0.24	0.04	
GSDMB	ILMN_2347193	17	rs11557467	17	38028634	GSDMB	rs4965745	15	101508261		5.88	0.68	0.20	0.41	
GSTM1	ILMN_2391861	1	rs12248673	10	53192833		rs11101992	1	110266754	GSTM1	6.11	0.27	0.19	0.16	
GSTM1	ILMN_2391861	1	rs1547574	13	85344527		rs11101992	1	110266754	GSTM1	5.91	0.27	1.14	0.79	
GSTM2	ILMN_2201580	1	rs64492807	1	96159560		rs3754446	1	110253241	GSTM1	6.77	0.52	0.66	0.65	
H1F0	ILMN_1757467	22	rs139898	22	38399979		rs4853333	2	77919015		6.36	0.27	0.31	0.23	
H1F0	ILMN_1757467	22	rs139898	22	38399979		rs6497007	15	85877017		6.52	0.25	0.48	0.32	
H1F0	ILMN_1757467	22	rs139898	22	38399979		rs9983949	21	19532546		5.70	0.00	0.66	0.19	
HBG1	ILMN_1796678	11	rs11078523	17	45231047		rs2855039	11	5271671	HBG2	5.47	0.15	0.24	0.12	
HBG1	ILMN_1796678	11	rs12975066	19	35723501		rs2855039	11	5271671	HBG2	5.98	0.08	0.52	0.21	
HBG1	ILMN_1796678	11	rs2855039	11	5271671	HBG2	rs12042181	4	213088494	LQK1	6.78	0.01	0.46	0.11	
HBG1	ILMN_1796678	11	rs2855039	11	5271671	HBG2	rs12503379	4	141533832		6.42	0.01	0.41	0.11	
HBG2	ILMN_2084825	11	rs11078523	17	45231047		rs16912979	11	5309695	HBG2	6.06	0.01	0.41	0.10	

Table S1 – continued from previous page

Expression trait			SNP 1				SNP 2				Interaction statistic / $-\log_{10}$ p-values				Distance / Mb[h]
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[f]	Meta[g]	
HBG2	ILMN_2084825	11	rs12975066	19	35723501		rs2855039	11	5271671	HBG2	5.77	0.08	0.13	0.05	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	HBG2	rs12042181	1	213088494	LQK1	6.84	0.06	0.54	0.21	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	HBG2	rs12503379	4	141533832		5.98	0.00	0.46	0.10	
HDAC7	ILMN_3266186	12	rs21009029	16	6036851		rs4760636	12	48173352	HDAC7	5.75				
HEBP1	ILMN_1802557	12	rs3782567	12	13145613	HEBP1	rs17686635	8	135220622		5.98	0.15	0.59	0.32	
HEXDC	ILMN_1741180	17	rs1942719	18	71237270		rs7213057	17	80378939	HEXDC	5.81	1.61	0.34	1.22	
HLA-DRA	ILMN_2157441	6	rs4899635	14	77532672		rs7192	6	32411646	HLA-DRB6	5.94	0.90	0.16	0.52	
HLA-F	ILMN_1762861	6	rs11660982	18	75467313		rs2523404	6	29695713	HLA-H	5.69	1.00	0.47	0.86	
HMBOX1	ILMN_1720059	8	rs12435486	14	98670849		rs7837237	8	28876221	HMBOX1	6.54	0.92	1.11	1.34	
HMBOX1	ILMN_1720059	8	rs2837803	21	42112794		rs4732890	8	28751381	HMBOX1	6.62	0.05	1.01	0.46	
HMBOX1	ILMN_1720059	8	rs4765451	12	127237464		rs8180944	8	28904086	HMBOX1	5.80	0.39	3.13	2.52	
HMBOX1	ILMN_1720059	8	rs587639	8	132725731		rs7837237	8	28876221	HMBOX1	6.58	0.55	0.34	0.44	103.850
HMBOX1	ILMN_1720059	8	rs8180944	8	28904086	HMBOX1	rs4553956	3	189533772		6.88	3.38	0.03	2.20	
HMBOX1	ILMN_1720059	8	rs8180944	8	28904086	HMBOX1	rs7810884	7	158276926		6.12	0.34	0.66	0.52	
HMBOX1	ILMN_1720059	8	rs9521666	13	110897444		rs8180944	8	28904086	HMBOX1	5.45	0.67	0.26	0.45	
HNRPH1	ILMN_2101920	5	rs6894268	5	179032488	CWF19L1	rs4700810	5	178991794		15.38	8.55	3.01	10.37	0.041
HSPC157	ILMN_3194087	1	rs558812	16	88882257	IL32	rs4654783	1	22439520	HSPC157	5.51	0.19	0.50	0.29	
HSPC157	ILMN_3194087	1	rs6063164	20	46486900		rs4654783	1	22439520	HSPC157	6.51	0.69	0.23	0.44	
HSPC157	ILMN_3194087	1	rs662739	12	121229893		rs4654783	1	22439520	HSPC157	6.61	1.46	0.84	1.55	
HSPC157	ILMN_3194087	1	rs7088558	10	101884937		rs4654783	1	22439520	HSPC157	6.48	0.02	0.26	0.05	
IL32	ILMN_1778010	16	rs1554999	16	3115628		rs4759890	12	131757163	IL32	6.90	0.69	0.89	0.77	
IL32	ILMN_2368530	16	rs765044	19	2560423		rs1554999	16	3115628		5.53	0.46	0.80	0.37	
INPP5E	ILMN_1811301	9	rs8044524	16	81603771		rs1127152	9	139335599	INPP5E	5.58	0.08	0.33	0.28	
JAZF1	ILMN_1675756	7	rs7573355	12	47970693		rs849341	7	28288174		8.16	0.64	0.08	0.09	
KCNJ15	ILMN_1691803	21	rs21863344	19	39606769	KCNJ15	rs424299	11	5570771		4.74	0.33	0.13	0.31	
KIR2DS5	ILMN_1811104	19	rs649216	13	55324635	KIR2DL1	rs6419960	4	189055298		5.53	0.24	0.09	0.09	
KTELC1	ILMN_1811104	3	rs4349034	3	84597119		rs727905	3	119119433	KTELC1	5.45	0.08	0.47	0.31	
L3MBTL2	ILMN_2336109	22	rs6815953	4	41519362	L3MBTL2	rs6414283	3	119195913	KTELC1	5.88	0.33	0.08	0.09	
LAP3	ILMN_1683792	4	rs4822006	22	132602868		rs1294338	1	234438952	LAP3	5.72	0.24	0.04	0.31	
LAX1	ILMN_1769782	1	rs7042087	9	132602868		rs7658240	4	175589050		19.16	18.60	11.22	29.24	
LDLRAP1	ILMN_1809040	1	rs1891432	1	203877662		rs10900520	1	203780591	LDLRAP1	6.00	0.35	0.40	0.34	0.097
LGALS9	ILMN_2412214	17	rs1552032	15	59971635		rs6687605	1	25889632		5.16	0.23	0.13	0.05	
LILRA5	ILMN_2357419	19	rs12450521	17	26083392	LILRA5	rs11749727	5	179608360		6.13	0.13	0.13	0.33	
LINS1	ILMN_2338197	15	rs3859532	19	54827248	LINS1	rs714789	18	71561497		5.89	0.23	0.23	0.05	
LRRC25	ILMN_2150196	19	rs11247226	15	101120963		rs1278387	10	127804531	LRRC25	5.68	0.11	0.35	0.15	
LY86	ILMN_1807825	6	rs6009951	19	51151350		rs8101804	19	18496107		5.61	0.13	0.15	0.07	
LYZ	ILMN_1815205	12	rs977785	6	6588881	LY86	rs1543675	1	78946879		5.95	0.15	0.03	0.03	
LYZ	ILMN_2162972	18	rs2168029	12	69734641		rs11981725	7	154137150		5.71	0.49	0.03	0.16	
LYZ	ILMN_2162972	12	rs1778620	18	77276964		rs2168029	12	69734641	LYZ	5.62	0.61	0.36	0.49	
MAD1L1	ILMN_2358069	7	rs2168029	12	69734641	LYZ	rs22531335	9	130319560		5.93	0.25	0.88	0.59	
MAD2L1BP	ILMN_1694711	6	rs7983718	13	103203146	MAD1L1	rs6414306	6	33351864		5.78	1.18	1.11	1.09	
MAP1LC3A	ILMN_1776188	20	rs974607	21	29435869		rs1096699	20	43528441	MAP1LC3A	5.62	0.63	0.27	0.54	
MBNL1	ILMN_2313158	3	rs10869600	9	78225815		rs13069559	3	152187431	MBNL1	7.96	0.79	0.27	0.54	
MBNL1	ILMN_2313158	3	rs11053043	12	99320070		rs13069559	3	152187431	MBNL1	6.70	0.08	2.21	1.37	
MBNL1	ILMN_2313158	3	rs1164596	13	97100681		rs13069559	3	152187431	MBNL1	7.38	1.43	0.63	1.34	
MBNL1	ILMN_2313158	3	rs11981513	7	94648239		rs13069559	3	152187431	MBNL1	7.71	0.43	5.36	4.58	
MBNL1	ILMN_2313158	3	rs16864367	3	152234166	MBNL1	rs13079208	3	152116652	MBNL1	13.49	16.25	24.74	41.56	0.118
MBNL1	ILMN_2313158	3	rs2030926	6	114067127		rs13069559	3	152187431	MBNL1	7.10	0.91	5.80	5.53	
MBNL1	ILMN_2313158	3	rs2186671	17	6604708		rs13069559	3	152187431	MBNL1	7.63	0.62	5.82	5.23	
MBNL1	ILMN_2313158	3	rs2213360	22	34291750		rs13069559	3	152187431	MBNL1	6.05	0.52	0.72	0.70	
MBNL1	ILMN_2313158	3	rs2305802	19	16038535		rs13069559	3	152187431	MBNL1	6.94	1.67			
MBNL1	ILMN_2313158	3	rs2614467	14	99770138		rs13069559	3	152187431	MBNL1	5.74	4.13	2.22	5.30	

Table S1 – continued from previous page

Expression trait			SNP 1			SNP 2				Interaction statistic / $-\log_{10}$ p-values				Distance / Mb[h]
Gene ID[a]	Probe ID[b]	Chr.	rs ID	Pos/Mb[c]	Association[d]	Chr.	rs ID	Pos/Mb[c]	Association[d]	BSGS[e]	Fehrmann[f]	EGCUT[f]	Meta[g]	
MBNL1	ILMN_2313158	4	rs4392535	41513423		3	rs13069559	152187431	MBNL1	8.39	0.02	4.33	3.02	
MBNL1	ILMN_2313158	8	rs4735830	895841		3	rs13069559	152187431	MBNL1	6.74	0.32	4.21	3.38	
MBNL1	ILMN_2313158	18	rs4939558	46278591		3	rs1522374	152235530		7.72	0.03	0.27	0.07	
MBNL1	ILMN_2313158	20	rs6128397	57253132		3	rs16864367	152234166		7.22	1.34	1.15	1.73	
MBNL1	ILMN_2313158	5	rs7710738	22101322		3	rs13069559	152187431	MBNL1	7.92	2.55	7.89	9.28	
MBP	ILMN_2331544	20	rs6079849	15462661		18	rs2051344	74715653	MBP	6.26	0.10	0.03	0.02	
MBP	ILMN_2398939	22	rs1395568	42210985	MBP	18	rs2051344	74715653	MBP	5.56	0.03	0.23	0.05	
MBP	ILMN_2398939	18	rs2051344	74715653	MBP	3	rs1125539	155204939	MBP	5.79	0.02	0.76	0.27	
MBP	ILMN_2398939	18	rs2051344	74715653		5	rs2619046	55097534		6.03	0.15	0.50	0.26	
MBP	ILMN_2398939	19	rs4805021	33436367		18	rs2051344	74715653	MBP	5.82	0.03	0.47	0.14	
MBP	ILMN_2398939	18	rs8092433	74747424		18	rs4890876	74732087	MBP	5.40	7.06	21.91	28.73	0.015
MEGF9	ILMN_2290118	9	rs13039689	51922071		9	rs966396	123453281	MEGF9	4.63	1.13	1.33	1.71	
MFN2	ILMN_1651385	1	rs7989895	109401737		1	rs4846085	12050634	MFN2	5.76	0.61	0.25	0.41	
MGC13057	ILMN_1787526	7	rs12718598	50428445	MGC13057	4	rs11725347	171860973		5.81	0.13	0.30	0.14	
MGC13057	ILMN_1787526	18	rs674608	69070772		7	rs12718598	50428445	MGC13057	5.57	0.07	1.03	0.50	
MGC13057	ILMN_1787526	16	rs8058318	82628245		7	rs12718598	50428445	MGC13057	7.05	0.11	0.12	0.05	
MGC72104	ILMN_1688318	20	rs845787	26197931	MGC72104	8	rs2660665	137526799		4.17	0.05	0.08	0.02	
MGST3	ILMN_1751956	17	rs740441	55779644		1	rs4147592	165600146	MGST3	5.45	0.57	0.27	0.40	
MPZL2	ILMN_1752932	11	rs1805	118076069	MPZL2	7	rs11771552	154708716	MPZL2	5.90	0.01	0.23	0.04	
MPZL2	ILMN_1752932	11	rs7316716	19953193		11	rs1805	118076069		5.64	0.97	1.08	1.35	
MRPL36	ILMN_1800197	5	rs17469061	84364432		5	rs750495	1782046	MRPL36	6.89	0.34	0.18	0.19	
MRPL43	ILMN_2258774	10	rs6564769	80641040		10	rs2863095	102746503	MRPL43	5.71	0.26	0.18	0.22	
MRPL52	ILMN_1713966	14	rs1950857	26710271		14	rs3811188	42194916	MRPL52	6.56	0.14	0.44	0.64	
MRPS10	ILMN_1663664	8	rs10955512	102202230		6	rs722269	42158596	MRPS10	7.48	0.46	0.70	0.46	
MRPS10	ILMN_1663664	20	rs11698155	15063214		6	rs2395803	42164401	MRPS10	6.85	0.31	0.63	0.28	
MRPS10	ILMN_1663664	6	rs1420537	52453567		6	rs13217993	42068689	MRPS10	6.21	0.41	0.25	2.86	
MTMR15	ILMN_2152178	15	rs7178375	31215935	MTMR10	14	rs12431444	95514596		5.18	1.87	1.87	0.50	
MX1	ILMN_1662358	21	rs459498	42795027		3	rs11160227	26706382		6.31	0.46	0.52	0.23	
MX1	ILMN_1662358	21	rs459498	42795027		21	rs4973801	29363604		5.83	0.11	0.50	0.65	
MX1	ILMN_1662358	21	rs459498	42795027		21	rs8130120	47486885		6.78	0.29	0.92	0.23	13.431
MYBPC3	ILMN_1781184	11	rs101343030	61593110		11	rs1317149	47529947	MYBPC3	5.56	0.13	0.46	0.02	
MYBPC3	ILMN_1781184	13	rs7322768	109550561		11	rs7124681	134485237	MYBPC3	5.70	0.04	0.08	0.40	
MYOM1	ILMN_1680344	18	rs4798075	3247256	MYOM1	8	rs2737422	48632478		6.02	0.74	0.15	1.77	38.948
N4BP1	ILMN_2201966	16	rs12444224	87580855		16	rs11649236	76870229	N4BP1	5.54	2.00	0.59	0.04	
NAAA	ILMN_1668605	7	rs2707575	147638723	NAPRT1	4	rs6826085	76870229	NAAA	5.65	0.20	0.03	0.30	
NAAA	ILMN_2391512	22	rs2071856	37770630	NAPRT1	1	rs2786014	234897243	NAAA	5.46	0.27	0.43	0.18	
NAPRT1	ILMN_1710752	8	rs2123758	144663661	NAPRT1	1	rs3889129	144613680		6.08	0.07	0.48	0.18	
NAPRT1	ILMN_1710752	8	rs2123758	144663661	NAPRT1	8	rs4862705	187445552		8.45	15.12	16.08	30.77	0.050
NAPRT1	ILMN_1710752	8	rs2123758	144663661	NAPRT1	4	rs6455553	167811764		5.62	1.27	0.19	0.81	
NAPRT1	ILMN_1710752	8	rs2123758	144663661	NAPRT1	6	rs700276	146189057		6.12	0.87	0.76	1.01	
NAPRT1	ILMN_1710752	8	rs2123758	144663661	NAPRT1	2	rs7571561	213386267		6.86	1.10	2.58	2.77	
NAPRT1	ILMN_1710752	8	rs2208123	48214812		8	rs2123758	144663661		6.03	0.13	0.47	0.23	
NAPSA	ILMN_1784040	9	rs4743420	103488089		9	rs9302802	98391111	NAPRT1	6.60	0.29	0.88	0.63	
NAPSB	ILMN_2109416	19	rs1405655	50882619	NAPSB	10	rs10882406	95976932	NAPRT1	5.50	0.82	0.19	0.08	
NAPSB	ILMN_2109416	19	rs1405655	50882619	NAPSB	2	rs7577137	234721287		5.58	0.67	0.76	0.40	
NCL	ILMN_2121437	2	rs7563453	232301670		2	rs4973397	232291471		7.31	2.11	6.33	12.70	0.010
NDUFA12	ILMN_1737738	12	rs2746971	37101890	NMT2	12	rs11107847	95386791	NDUFA12	3.88	0.39	0.18	0.22	
NMT2	ILMN_1656378	10	rs10906857	15239498		3	rs12490878	50719103		6.84	0.42	0.34	0.35	
NOD2	ILMN_1762594	16	rs2967636	70677773		16	rs9302752	183114008	NOD2	5.90	0.42	0.34	0.35	
NRBF2	ILMN_3237385	12	rs11063498	52090048		10	rs7923609	65133822	NRBF2	5.45	0.34	0.35	0.35	
NRBF2	ILMN_3237385	11	rs2375269	69876894		10	rs7923609	65133822	NRBF2	5.53	0.24	0.04	0.06	

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Expression trait			SNP 1				SNP 2				Interaction statistic / −log₁₀ p-values				Distance / Mb[h]
Gene ID[a]	Probe ID[b]	Chr.	rs ID	Pos/Mb[c]	Chr.	Association[d]	rs ID	Chr.	Pos/Mb[c]	Association[d]	BSGS[e]	Fehrmann[f]	EGCUT[f]	Meta[g]	
NRBF2	ILMN_3237385	10	rs6025645	56157341	20		rs7923609	10	65133822	NRBF2	5.45			0.17	
NRBF2	ILMN_3237385	10	rs6517815	19819016	21		rs7923609	10	65133822	NRBF2	6.11			0.15	
NRD1	ILMN_1800897	1	rs4852124	240080022	2		rs6588415	1	52334047		6.13	0.47	0.05	0.17	
NUDT18	ILMN_1787885	8	rs5017351	254534482	11		rs1005901	8	21964378	NUDT18	5.44	0.03	0.46	2.03	0.039
OAS1	ILMN_1658247	12	rs11613438	113480510	12		rs1047944	6	163997467		8.59	1.27	1.55	3.86	
OAS1	ILMN_1658247	12	rs13311	113448652	12		rs2072133	12	113409260	OAS1	4.13	4.12	0.81	0.76	
OAS1	ILMN_1675640	12	rs2892233	49160255	19		rs3741981	12	13169066	OAS1	4.38	0.87	0.46	0.07	
OPTN	ILMN_2381899	10	rs7192613	742866646	16		rs17512962	10	13169066	OPTN	5.64	0.42	0.06	0.14	
OSBPL5	ILMN_2307032	11	rs2829679	26662543	21		rs998639	11	3149249	OSBPL5	5.00	0.36	0.00	0.07	
OSTF1	ILMN_1742456	9	rs17780195	70624189	17	OSTF1	rs2273770	9	777755469	OSTF1	5.42	0.16	0.87	0.49	
OSTF1	ILMN_1742456	9	rs2273770	777755469	9		rs7718088	5	179590952		5.42	1.20	0.08	0.62	
OVGP1	ILMN_1734542	1	rs10802822	240132968	1		rs1264898	1	111992823	OVGP1	5.43	0.13	1.48	0.88	128.140
OVGP1	ILMN_1734542	1	rs347331	140148107	3	PAM	rs1264894	1	111969719	OVGP1	6.04	0.25	1.21	0.82	
PAM	ILMN_2313901	5	rs28092	102149795	5	PCYOX1L	rs784600	1	40139553	HPCAL4	5.59	0.66	0.44	0.59	
PCYOX1L	ILMN_1815951	5	rs2438490	148726162	5		rs2731939	3	213395989		6.20	0.19	0.26	0.16	
PEX5	ILMN_1660232	12	rs10444467	128052636	12		rs4329748	12	7364442	PEX5	5.85	0.09	0.71	0.32	120.688
PEX5	ILMN_1660232	12	rs7495797	27246462	15		rs4329748	12	7364442	PEX5	5.74	0.34	0.09	0.13	
PFAAP5	ILMN_1797893	13	rs131969	49151303	22		rs7328733	13	33126737	PFAAP5	5.64	0.87	0.36	0.67	
PGLYRP1	ILMN_1704870	19	rs12982353	46529456	19	PGLYRP1	rs1263806	14	21982957		6.51	0.03	0.65	0.24	
PHCA	ILMN_1812552	11	rs493642	123097386	11		rs10736812	11	76708086	PHCA	5.51	0.36	0.90	0.70	46.389
PIK3IP1	ILMN_1719986	22	rs4141404	316751185	11	PIK3IP1	rs2065841	1	617728597		5.60	0.20	0.01	0.03	
PISD	ILMN_1793934	22	rs470072	332263131	22	PISD	rs10498313	14	30398876		5.23	0.02	0.87	0.33	
PISD	ILMN_1793934	22	rs6518752	31999127	22	PISD	rs954627	1	18236681	PISD	7.11	0.00	1.19	0.48	
PISD	ILMN_1793934	22	rs715572	33234931	22		rs6518754	22	32097775	PISD	4.12	0.05	0.42	0.15	1.137
PNKD	ILMN_1774604	2	rs6869411	158781604	5		rs4672884	2	219182481	PNKD	6.35	0.16	0.04	0.04	
PNPLA7	ILMN_1662587	9	rs11639998	4527109	16		rs928046	9	140487108	PNPLA7	4.44	0.29	0.78	0.26	
PPFIBP2	ILMN_1675656	11	rs911019	49668255	20		rs4758001	11	7559930	PPFIB3P2	5.15	0.31	0.33	0.19	
PPP2R3C	ILMN_1662617	14	rs12914603	58350896	15		rs11156875	14	35619816	PPP2R3C	5.81	0.12	0.42	0.66	
PPP2R5A	ILMN_1738784	1	rs10930170	166399467	2		rs12120009	1	212447167	PPP2R5A	5.63	0.72	0.48	0.46	
PPP2R5A	ILMN_1738784	1	rs12423255	123595064	12		rs12120009	1	212447167	PPP2R5A	5.72	0.08	0.95	0.17	
PPP2R5A	ILMN_1738784	1	rs1889083	66222691	13		rs12120009	1	212447167	PPP2R5A	5.61	0.36	0.13	1.21	
PPP2R5A	ILMN_1738784	1	rs682334	107417238	11		rs12120009	1	212447167	PPP2R5A	5.65	1.69	0.28	0.12	
PPP2R5A	ILMN_1738784	1	rs7757871	135030045	6		rs12120009	1	212447167	PPP2R5A	5.95	0.37	0.06	0.16	
PPP2R5A	ILMN_1738784	1	rs7871178	271484475	9		rs12120009	1	212447167	PPP2R5A	5.72	0.16	0.30	0.16	
PRDX5	ILMN_1711606	11	rs8019823	95040482	14		rs11600990	11	64082807	PRDX5	6.43	0.81	0.14	0.44	11.228
PRKCB1	ILMN_1713603	16	rs2188355	238677776	16		rs10492793	16	12639800		7.34	0.53	0.11	0.25	
PRMT2	ILMN_1675038	21	rs1029231	47931653	21	C21ORF57	rs958127	18	314497346	C21ORF57	5.60	0.19	0.03	0.04	0.287
PSMB1	ILMN_1675038	21	rs2839372	48063862	21		rs11701058	21	47776382	PSMB1	4.81	0.69	4.47	4.06	
PSMB1	ILMN_1789176	6	rs3862607	121774705	11		rs13307114	6	170890384	PSMB1	5.79	0.00	0.44	0.04	
PSMB1	ILMN_1789176	6	rs4890648	43983954	18	PSMB1	rs6928843	6	170823379	PSMB1	5.44	0.44	0.26	0.27	
PSMB1	ILMN_1789176	6	rs6000930	30347832	20		rs9295415	6	225797957		4.58	0.21	0.21	1.78	
PWP1	ILMN_1743049	12	rs6928843	170890384	6		rs2769689	6	170877444	PSMB1	5.42	1.95	0.64	0.86	
PWP1	ILMN_1743049	12	rs2353567	131727816	14		rs13207114	11	5221825	PTDSS1	5.00	1.18	0.32	0.15	
PWP1	ILMN_1743049	12	rs4969205	95478823	17		rs11036212	11	5221825	PTDSS1	5.90	0.03	0.48	0.38	
QDPR	ILMN_1672443	4	rs631562	126852438	11		rs10020773	4	175266682	QDPR	5.70	0.02	0.08	0.11	
RAB3IP	ILMN_1803197	12	rs4946705	106348246	6	RABAC1	rs7305307	12	70235726		5.75	1.03	0.40	1.55	
RBL2	ILMN_2207363	19	rs1075728	33375704	22	AKTIP	rs7951628	11	120161117		6.55	0.25	1.25	0.09	
RCN1	ILMN_1800276	16	rs9931702	42462788	19		rs1863464	15	26938488		6.42	0.28	0.84	0.59	
RCN1	ILMN_1800276	11	rs10879131	53526551	16	RCN1	rs4922579	11	32136436	RCN1	6.38	0.03	0.31	0.08	
RCN1	ILMN_1800276	11	rs4922579	32136436	11	RCN1	rs11166957	8	141177468		5.23	0.58	0.37	0.47	
RCN1	ILMN_1800276	11	rs4922579	32136436	11	RCN1	rs1341899	1	102740645		5.40	0.04	0.26	0.07	

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Table S1 – continued from previous page

Expression trait			SNP 1				SNP 2				Interaction statistic / −log₁₀ p-values				Distance / Mb[h]
Gene ID[a]	Probe ID[b]	Chr.	rs ID	Pos/Mb[c]	Association[d]	Chr.	Chr.	rs ID	Pos/Mb[c]	Association[d]	BSGS[e]	Fehrmann[f]	EGCUT[f]	Meta[g]	
RERE	ILMN_1802380	1	rs4982958	24987865		14	1	rs301819	8501786	RERE	5.66	0.61	1.23	1.17	
RERE	ILMN_1802380	1	rs7697290	135248366		4	1	rs301819	8501786	RERE	5.74	0.14	0.10	0.06	
RERE	ILMN_2327795	1	rs11085829	13174312		19	1	rs301819	8501786	RERE	5.12	0.21	0.33	0.21	
RERE	ILMN_2327795	1	rs3852011	112844086		3	1	rs301819	8501786	RERE	5.71	0.08	0.60	0.26	
RNASE6	ILMN_1780533	14	rs11628398	21182800	RNASE6	14	13	rs7324365	100601327		5.48	0.42	0.21	0.26	
RNASE6	ILMN_1780533	14	rs6603134	81106521		14	14	rs11628398	21182800	RNASE6	5.11	0.09	0.22	0.08	
RNF167	ILMN_1794726	17	rs2382230	4875566		17	13	rs4884857	54668512		4.37				
RNF167	ILMN_1794726	17	rs400688	4839930	RNF167	17	3	rs11706900	36348968		5.59	0.71	0.46	0.64	
RNPEP	ILMN_1738347	1	rs1107121	46127549		21	1	rs2819365	201983242		6.27	0.11	0.30	0.13	
RNPEP	ILMN_1738347	1	rs8071611	67153386		17	1	rs2819365	201983242		4.32	1.48	0.52	1.28	
RPL13	ILMN_2413278	16	rs352935	89648580		16	16	rs2965817	89513234		4.98	3.79	14.41	17.24	0.135
RPL23AP7	ILMN_2222750	2	rs1401202	80320056		16	2	rs4849261	114450028	RPL23AP7	5.55	0.13	0.73	0.38	
RPL36AL	ILMN_2189933	14	rs3007033	50103816	RPL36AL	14	16	rs17495030	138038093		5.46	0.09	0.06	0.02	
RPL36AL	ILMN_2189936	14	rs4900928	50020817	RPL36AL	14	6	rs1502991	66137260		5.86	0.32	0.20	0.19	
RPL8	ILMN_1764721	8	rs2958482	145984615	RPL8	8	1	rs1619856	234585790		4.59	0.10	0.37	0.15	
RPL8	ILMN_1764721	8	rs4143674	4741304		20	8	rs2958482	145984615	RPL8	4.33	0.13	0.45	0.22	
SEC13	ILMN_3297880	3	rs4889214	80913946		16	3	rs696221	10342876	SEC13	6.48	0.22	1.73	1.17	
SEMA4A	ILMN_1702787	1	rs17085428	95388015		5	1	rs7695	156147326	SEMA4A	5.70	0.02	0.51	0.15	
SESN3	ILMN_1694027	11	rs12147460	104412137		14	11	rs684856	94906111	SESN3	5.50	0.31	0.06	0.10	
SESN3	ILMN_1694027	11	rs355391	46591793		15	11	rs684856	94906111	SESN3	5.67	0.31	0.51	0.31	
SESN3	ILMN_1694027	11	rs684856	94906111	SESN3	11	8	rs7004947	134606425		5.60	0.21	0.12	0.35	
SH3BGRL2	ILMN_1762764	6	rs10838191	43936658		11	3	rs1354034	56849749	PPBP	5.52	0.70	0.12	0.30	
SH3BGRL2	ILMN_1762764	6	rs2545385	66383979		5	3	rs1354034	56849749	PPBP	5.97	0.20	0.51	0.53	
SH3BGRL2	ILMN_1762764	6	rs6845304	88280502		4	3	rs1354034	56849749	PPBP	5.23	0.32	0.71	0.13	
SH3GLB2	ILMN_2158336	9	rs1034120	18196922		21	9	rs17455517	131785369	SH3GLB2	7.40	0.22	0.18	0.17	
SIRPG	ILMN_1771801	20	rs1535883	52181798	SIRPG	20	4	rs6842739	60489510		5.74	0.29	0.18	0.09	
SLC22A18	ILMN_2382505	11	rs11673260	2923826	SLC22A18	11	11	rs367035	2923826		5.47	0.09	0.24	0.06	
SLC22A18	ILMN_2382505	11	rs367035	2923826	SLC22A18	11	7	rs3110874	153224179	SLC22A18	5.70	0.15	0.10	0.19	
SLC22A18	ILMN_2382505	11	rs3670035	2923826		11	2	rs3772054	241678528		6.15	0.39	0.13	0.24	
SLC41A3	ILMN_2356111	3	rs1912136	24616743		11	3	rs6771703	125801067	SLC41A3	5.88	1.10	0.82	1.24	
SLC45A4	ILMN_1745778	8	rs6985508	142337734	SLC45A4	8	5	rs7701916	174598073		5.95	0.86	0.07	0.40	
SLC46A3	ILMN_1706553	13	rs949805	55602091		13	13	rs7981190	292593349	SLC46A3	5.52	0.09	0.58	0.26	
SMG7	ILMN_3309349	1	rs8035259	97403923		20	1	rs109113353	183489203	SMG7	6.52	0.17	0.09	0.06	
SNHG8	ILMN_1775380	4	rs8118315	4161500	SMOX	20	4	rs11677815	65800982		5.68	0.39	0.62	0.52	
SNORD14A	ILMN_1799381	11	rs1105621	130050233		9	11	rs705837	119225940	SNORD14A	6.11	0.29	1.03	0.72	
SNORD89	ILMN_3238662	2	rs1520429	46259108		11	11	rs214097	17291499		6.60	13.11	10.96	23.22	
SNORD89	ILMN_3238662	2	rs2634462	17339127		2	11	rs6486334	17015557	SNORD89	7.31				0.324
SNORD89	ILMN_3238662	2	rs104455863	115929241		2	2	rs750783	101889306	SNORD89	6.08				14.040
SNUPN	ILMN_2364535	15	rs11605822	129986326		2	2	rs750783	101889306		5.96	0.13	1.41	0.83	
SNUPN	ILMN_1131620	15	rs2135064	267778066	SNUPN	2	16	rs7185362	81888905		6.33	0.34	0.00	0.06	
SPATA5L1	ILMN_1729179	15	rs8134646	46376528	SNUPN	21	15	rs4774580	45652086	SPATA5L1	6.45				
STARD10	ILMN_1717052	11	rs8134646	46376528		21	3	rs1472075	193706323		5.59	0.67	0.12	0.33	
STYXL1	ILMN_2210729	7	rs1131620	41117869		19	4	rs176685	75616105	STYXL1	5.44	0.57	0.17	0.31	
SULF2	ILMN_2345142	20	rs2221406	90174526	SULF2	14	4	rs939294	180439236		5.65	0.46	0.24	0.30	
SULT1A4	ILMN_2336133	16	rs1463965	74332954		18	16	rs3785354	28550667	TUFM	7.05	0.01	0.05	0.00	
SULT1A4	ILMN_2336133	16	rs117000063	46153148		20	16	rs3785354	28550667	TUFM	5.83				
SURF6	ILMN_1778032	9	rs6099626	56013994		20	9	rs3118663	136281753	SURF6	6.14	0.26	0.16	0.14	
SYTL2	ILMN_2336609	11	rs1375719	103410782		13	11	rs485485	84495269	SYTL2	5.47	0.28	0.31	0.24	
THBS3	ILMN_1804663	1	rs1939875	95422867		1	1	rs4072037	155162067	THBS3	5.55	0.03	0.15	0.03	
THBS3	ILMN_1804663	14	rs8014956	20687978		14	1	rs2049805	155194980	THBS3	5.65	0.31	0.76	0.55	
TIPRL	ILMN_1781457	1	rs2823245	16745523		21	1	rs1320993	168154599	TIPRL	5.22	0.07	0.40	0.15	

Table S1 – continued from previous page

Gene ID[a]	Probe ID[b]	Chr.	rs ID	Pos/Mb[c]	Association[d]	Chr.	rs ID	Pos/Mb[c]	Association[d]	BSGS[e]	Fehrmann[f]	EGCUT[f]	Meta[g]	Distance / Mb[h]
											Interaction statistic / $-\log_{10}$ p-values			
	Expression trait		SNP 1			SNP 2								
TMED4	ILMN_1804148	7	rs1940400	132389627		7	rs17725246	44581986	TMED4	5.70	0.06	1.34	0.70	
TMEM149	ILMN_1786426	19	rs2839013	47248981		19	rs8106959	36219525	TMEM149	8.11	0.16	0.48	0.26	
TMEM149	ILMN_1786426	19	rs57622235	27925288		19	rs8106959	36219525	TMEM149	6.79				
TMEM149	ILMN_1786426	19	rs6090518	45207005		19	rs8106959	36219525	TMEM149	11.09	0.76			
TMEM149	ILMN_1786426	19	rs8074491	36268923	SNX26	19	rs7254601	36147315	TMEM149	12.16	81.55	45.78	145.78	0.122
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	10	rs10508289	4799159		8.12	1.55	3.09	3.67	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	9	rs10819626	133025756		8.02	0.40	0.99	0.80	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	3	rs10937361	183359436		8.39	3.61	1.18	3.78	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	12	rs1401098	128884559		7.37	2.41	1.00	2.52	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	18	rs1557335	64268976		6.95	0.08	0.07	0.03	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	14	rs17719594	90932598		6.93	3.06	0.77	2.87	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	8	rs1843357	13822381		6.21	3.72	3.33	6.00	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	4	rs2351458	113317583		7.30	0.04	9.61	8.00	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	7	rs2539000	147619772		6.70	1.57	1.52	2.27	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	5	rs2731711	171792273		5.92	0.19	0.33	0.19	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	11	rs471728	129595460		8.89	0.90	3.62	3.51	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	2	rs6718480	233879066		8.55	3.31	5.15	7.36	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	6	rs6926382	161683974		5.80	3.06	8.80	10.72	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	17	rs7213338	80357420		5.49	0.07	3.14	2.10	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	1	rs914940	242889492		6.22	3.36	6.96	9.20	
TMEM149	ILMN_1786426	19	rs8106959	36219525	TMEM149	13	rs9509428	21473952		9.44	0.10	5.75	4.47	
TMEM63A	ILMN_1719649	13	rs12254086	72900603		1	rs4149226	226027323	TMEM63A	5.60				
TMEM80	ILMN_1708482	11	rs1548475	58058246		11	rs4963126	656845	TMEM80	5.79	0.64	0.12	0.32	
TNPO3	ILMN_1683811	7	rs1537146	4859303		7	rs10488630	128593948	IRF5	5.61	0.11	0.15	0.07	
TNPO3	ILMN_1683811	7	rs197793	22287303		7	rs10488630	128593948	IRF5	5.52	1.03	0.17	0.62	
TRA2A	ILMN_1731043	7	rs7776572	23528927		7	rs11770192	23498358		8.23	3.19	1.89	4.09	0.031
TRAPPC4	ILMN_1814650	11	rs1278760	135531675	TRAPPC5	11	rs3916581	118887887	TRAPPC4	5.61	0.28	0.40	0.29	
TRAPPC4	ILMN_1814650	11	rs1793823	131018917	TRAPPC5	11	rs3916581	118887887	TRAPPC4	5.52	0.93	0.01	0.36	12.131
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	5	rs10059004	166970604		5.97	0.21	1.60	1.07	
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	8	rs1023095	132022957		6.92	0.37	0.87	0.68	
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	6	rs1375714	156404902		7.79	0.12	0.18	0.08	
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	1	rs1393299	242329791		6.43	0.63	0.47	0.59	
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	19	rs17763599	2369415		6.38	0.21	0.24	0.16	5.389
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	17	rs4968328	574995457		6.51	0.50	0.38	0.44	
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	12	rs7313362	129644342		7.08	0.04	0.65	0.25	
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	4	rs7694997	99478111		5.86	0.20	0.36	0.22	
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	7	rs7800935	146690926		6.27	0.15	0.33	0.16	
TRAPPC5	ILMN_2372639	19	rs17159840	7758194	TRAPPC5	14	rs856638	85439550		6.73	0.24	0.07	0.08	
TRAPPC5	ILMN_2372639	19	rs380708	227740885		19	rs17159840	7758194	TRAPPC5	7.58	0.85	0.78	1.01	
TRAPPC5	ILMN_2372639	19	rs39916995	45128454		19	rs17159840	7758194	TRAPPC5	7.73	0.51	0.55	0.56	
TRAPPC5	ILMN_2372639	19	rs6040514	112728611		19	rs17159840	7758194	TRAPPC5	8.10	0.14	0.02	0.02	
TRAPPC5	ILMN_2372639	19	rs7246264	7762978		2	rs10179572	228504503		6.71	0.14	0.26	0.13	
TRAPPC5	ILMN_2372639	19	rs7246264	7762978		16	rs12921440	30408765		7.34	0.14	0.86	0.40	
TRAPPC5	ILMN_2372639	19	rs7246264	7762978		9	rs1887778	134635088	RAPGEF1	7.05	0.08	0.90	0.69	
TRAPPC5	ILMN_2372639	19	rs7246264	7762978		3	rs963354	157339377		7.41	0.36	0.25	0.11	
TREM1	ILMN_1688231	6	rs10862975	85749398		6	rs2395771	41264577	TREM1	5.42	0.11	0.25	0.11	
TREM1	ILMN_1688231	6	rs12412964	108256422		6	rs2395771	41264577	TREM1	5.92	1.20	1.23	1.69	
TRIM38	ILMN_1697971	6	rs2527180	158808416		6	rs2032447	26043369	TRIM38	6.46	0.04	0.91	0.39	
TSPAN14	ILMN_1785060	10	rs968726	27194634		10	rs10748526	82273079	TSPAN14	6.00	0.07	0.18	0.06	
TSPAN32	ILMN_1718621	11	rs10838738	47663049	MYBPC3	11	rs12800998	2317951	TSPAN32	5.01				45.345
TSPAN32	ILMN_2389970	11	rs12800998	2317951	TSPAN32	6	rs620607	137947208	TSPAN32	5.51				
TYMP	ILMN_3223126	22	rs1405522	50971266	ECGF1	2	rs1198819	238746880	TSPAN32	6.34				
TYMP	ILMN_3223126	22	rs470119	50966914	ECGF1	16	rs4783126	85147633	TSPAN32	6.13				

Table S1 – continued from previous page

Expression trait			SNP 1				SNP 2				Interaction statistic / −log10 p-values				Distance / Mb[h]
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[f]	Meta[g]	
UBASH3A	ILMN_2338348	21	rs1893592	21	43855067	UBASH3A	rs7201194	16	83600397		5.91	0.59	0.42	0.52	
UBASH3A	ILMN_2338348	21	rs1893592	21	43855067	UBASH3A	rs7512594	1	214514361		6.01	0.48	1.29	1.10	
USP36	ILMN_1697227	17	rs2279308	17	76794981	USP36	rs7225546	17	75151717		5.71	0.03	0.14	0.03	1.643
VASP	ILMN_1743646	19	rs1264226	19	46063167		rs2276470	19	45974668		5.09	0.94	5.14	4.95	0.088
VNN2	ILMN_1678939	6	rs10435352	7	105252718		rs1883613	6	133077063	VNN2	5.64	0.84	0.15	0.46	
VNN2	ILMN_1678939	6	rs13044386	20	9116155		rs1883617	6	133072650	VNN2	5.44	0.39	0.69	0.57	
VNN2	ILMN_1678939	6	rs1344447	22	49927332		rs1883617	6	133072650	VNN2	5.72				
VNN2	ILMN_1678939	6	rs216495	11	16345510		rs1883617	6	133072650	VNN2	5.77	0.33	0.19	0.41	
VNN3	ILMN_1804935	6	rs10278073	7	151662184		rs2267952	6	133067782	VNN3	6.44	0.16	0.74	0.31	
VNN3	ILMN_1804935	6	rs1443946	8	73006453		rs2267952	6	133067782	VNN3	6.44	0.23	0.48	0.17	
VNN3	ILMN_1804935	6	rs348462	9	75547169		rs2267952	6	133067782	VNN3	5.74	0.31	0.17	0.17	
VNN3	ILMN_1804935	6	rs7157055	14	83262064		rs2267952	6	133067782	VNN3	5.82	0.03	0.19	0.04	
VNN3	ILMN_2387680	6	rs2823165	21	16594253		rs2267952	6	133067782	VNN3	6.12	0.73	1.15	1.21	
VNN3	ILMN_2387680	6	rs9596457	13	51692548		rs2267952	6	133067782	VNN3	4.83	0.46	0.05	0.16	
VSTM1	ILMN_1763455	19	rs105000316	19	54553697	VSTM1	rs4552100	18	71024750		5.60	0.53	0.54	0.57	
VSTM1	ILMN_1763455	19	rs10500316	19	54553697	VSTM1	rs7895870	10	123098249		5.71	0.48	0.17	0.26	
VSTM1	ILMN_1763455	19	rs9625870	22	30261219		rs10500316	19	54533697	VSTM1	5.88	0.81	1.38	1.47	
WDR48	ILMN_1762103	3	rs1388935	4	188927822		rs6778963	3	39091812	WDR48	5.88	0.19	0.13	0.09	
WDR48	ILMN_1762103	3	rs1887778	9	134635088	RAPGEF1	rs883349	3	39067925	WDR48	6.34	0.57	1.35	1.22	
WDR48	ILMN_1762103	3	rs9554833	13	102624790		rs7619193	3	39044116	WDR48	5.85	0.18	0.61	0.35	
WDR6	ILMN_1669484	3	rs12362253	11	123371708		rs11715581	3	49194331	WDR6	4.86	1.64	1.43	2.25	
XAF1	ILMN_2370573	17	rs1533031	17	6673170	XAF1	rs12591171	15	93119799		5.48	2.38	0.17	1.63	
ZFP90	ILMN_1684628	16	rs909446	21	37040648		rs1182968	16	68573945	ZFP90	5.79	0.09	0.36	0.15	
ZNF500	ILMN_1700238	16	rs4823723	22	48283177		rs2290560	16	4799041	ZNF500	5.29	0.67	0.27	0.46	
ZYX	ILMN_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 $-\log_{10}$ p-value from discovery dataset

[f] Interaction $-\log_{10}$ p-value from replication dataset

[g] Interaction $-\log_{10}$ p-value from meta analysis of replication datasets only

[h] Distance in Mb between interacting SNPs for cis-cis acting SNP pairs

[i] 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 2013[21]

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	Fehrmann	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	Fehrmann	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	HMBOX1	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