

Detection and replication of epistasis influencing transcription in humans

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Abstract

Epistasis is the phenomenon whereby one polymorphism’s effect on a trait depends on other polymorphisms present in the genome. The extent to which epistasis influences complex traits¹ and contributes to their variation^{2,3} is a fundamental question in evolution and human genetics. Though often demonstrated in artificial gene manipulation studies in model organisms^{4,5}, and some examples have been reported in other species⁶, few examples exist for epistasis amongst natural polymorphisms in human traits^{7,8}. Its absence from empirical findings may simply be due to 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 and computational issues⁹. Here we show that, using advanced computation¹⁰ 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 7339 gene expression levels measured in peripheral blood, we found 501 significant pairwise interactions between common SNPs influencing the expression of 238 genes ($p < 2.91 \times 10^{-16}$). Replication of these interactions 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 $p < 0.05/501$. Forty-four of the genetic interactions are located within 2Mb of regions of known physical chromosome interactions¹³ ($p = 1.8 \times 10^{-10}$). Epistatic networks of three SNPs or more influence the expression levels of 129 genes, whereby one *cis*-acting SNP is modulated by several *trans*-acting SNPs. For example MBNL1 is influenced by an additive effect at rs13069559 which itself is masked by *trans*-SNPs on 14 different chromosomes, with nearly identical genotype-phenotype (GP) maps for each *cis-trans* interaction. This study presents the first evidence for multiple instances of segregating common 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 associations¹⁴. But to date, though its contribution to phenotypic variance is frequently the subject of debate¹⁻³, there is little empirical exploration of the role that epistasis plays in the architecture of complex traits in humans^{7,8}. Beyond the prism of human association studies there is evidence for epistasis, not only at the molecular scale from artificially induced mutations⁴ but also at the evolutionary scale in fitness adaptation¹⁵ and speciation¹⁶.

Methods are now available to overcome the computational problems involved in searching for epistasis, but its detection still remains problematic due to reduced statistical power. For example, increased dependence on linkage disequilibrium (LD) between causal SNPs and observed SNPs^{17,18}, increased model

complexity in fitting interaction terms¹⁹, and more extreme significance thresholds to account for increased multiple testing⁹ all make it more difficult to detect epistasis in comparison to additive effects. Thus, with small genetic effect sizes, as is expected in most complex traits of interest¹⁴, the power to detect epistasis diminishes rapidly. There are two simple ways to overcome this problem. One is by using extremely large sample sizes²⁰; 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 arises from 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 and like most complex diseases, these expression traits are typically heritable²¹. But unlike complex diseases, genetic associations with gene expression commonly have very large effect sizes that explain large proportions of the genetic variance²², making them good candidates to search for epistasis, should it exist.

In our discovery dataset (Brisbane Systems Genetics Study, BSGS²³) 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 (1.03×10^{15} statistical tests, family-wise error rate of 5% corresponding to a significance threshold of $p < 2.91 \times 10^{-16}$, 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 $0.05 \leq \alpha \leq 0.14$, Methods, Supplementary Figure S1). Using this design we identified 501 putative genetic interactions influencing the expression levels of 238 genes (Supplementary Table S1). We used strict quality control measures to avoid statistical associations being driven by technical artifacts (Methods). However it remains possible that unexplained technical artifacts may have led to the significant discovery interactions. Of the 501 discovery interactions, 434 had available data and passed filtering (Methods) in two independent replication datasets, Fehrmann¹² 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 $p < 0.05/501$, 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 ($A1$, $A2$, $D1$, $D2$, $A1 \times A2$, $A1 \times D2$, $D1 \times A2$, $D1 \times D2$) 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 where p -values are assumed to be uniformly distributed ($p \ll 1.0 \times 10^{-16}$, Figure 2 and Supplementary Figure S2). Concordance of the 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) dataset²⁴, 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 interactions from the discovery set, replication of epistatic effects in independent samples is difficult in practice due to LD (Methods).

Though seldom the focus of association studies, SNPs with known main effects are often tested for $A \times A$ genetic interactions⁹, but our analysis suggests this is unlikely to be the best 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 association²² (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 $A \times A$, $A \times D$, $D \times A$ and $D \times D$ at the discovery stage ($p = 0.22$ for departure from expectation). This is not surprising because these patterns of epistasis used for statistical decomposition are simply convenient orthogonal parameterisations of a two locus model, and are not intended to model biological function²⁵.

Of the discovery interactions, 26 were *cis-cis* acting (within 1Mb of the transcription start site, mean distance between SNPs was 0.53Mb), 462 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 splicing²⁶) 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 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 expression 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 previously²² (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 types²⁷ (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 states²⁸ (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 interactions¹³. We cross-referenced our epistatic SNPs with a map of chromosome interacting regions ($n = 96,139$) in K562 blood cell lines²⁹ (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 genes³⁰.

Quantifying the importance of epistasis in complex traits in humans remains an open question. Here we are able to identify 238 gene expression traits with at least one significant interaction given our experiment-wide threshold, where the minimum estimated variance explained by the epistatic effects of any interaction was 2.1% of phenotypic variance. Taking results from our previously published eQTL²³ we calculated that 1848 of the 7339 gene expression levels analysed were influenced by additive effects where the estimated 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 explain². Taking all additive effects detected in Powell *et al* (2012) that have additive variance explaining 2.1% or greater of phenotypic variance, 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 estimated 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 estimated additive variance. There are several caveats to this comparison which we discuss in the Methods.

Overall, we have demonstrated that it is possible to identify and replicate epistasis in complex traits amongst common human variants, despite the rela-

tive 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 for 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 dataset²³, which comprises 846 individuals who are genotyped at 528,509 autosomal SNPs. Each individual had gene expression levels measured in peripheral blood at 7,339 probes representing 6,158 RefSeq genes (significant expression in $\geq 90\%$ of individuals). SNP pairs were modelled for full genetic effects, including marginal additive and dominance at both SNPs plus four interaction terms. We used permutation analysis to calculate an experiment-wide significance threshold of $T_e = 2.91 \times 10^{-16}$ at the 5% family-wise error rate (FWER). 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. The 501 significant SNP pairs were carried forward for replication in two independent datasets that used the same expression assays for analysing transcription in peripheral blood Fehrmann¹², $n = 1240$; EGCUT¹¹, ($n = 891$). 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

We are grateful to the volunteers for their generous participation in these studies. We thank Bill Hill, Chris Haley and Lars Ronnegard for helpful discussions and comments.

This work could not have been completed without access to high performance GPGPU compute clusters. We acknowledge iVEC for the use of advanced computing resources located at iVEC@UWA (www.ivec.org), and the Multimodal Australian ScienceS Imaging and Visualisation Environment (MASSIVE) (www.massive.org.au). We also thank Jake Carroll and Irek Porebski from the Queensland Brain Institute Information Technology Group for HPC support.

The University of Queensland group is supported by the Australian National Health and Medical Research Council (NHMRC) grants 389892, 496667, 613601, 1010374 and 1046880, the Australian Research Council (ARC) grant

(DE130100691), and by National Institutes of Health (NIH) grants GM057091 and GM099568.

The QIMR researchers acknowledge funding from the Australian National Health and Medical Research Council (grants 241944, 389875, 389891, 389892, 389938, 442915, 442981, 496739, 496688 and 552485), the and the National Institutes of Health (grants AA07535, AA10248, AA014041, AA13320, AA13321, AA13326 and DA12854). We thank Anthony Caracella and Lisa Bowdler for technical assistance with the micro-array hybridisations.

The CHDWB study funding support from the Georgia Institute of Technology Research Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

The Fehrmann study was supported by grants from the Celiac Disease Consortium (an innovative cluster approved by the Netherlands Genomics Initiative and partly funded by the Dutch Government (grant BSIK03009), the Netherlands Organization for Scientific Research (NWO-VICI grant 918.66.620, NWO-VENI grant 916.10.135 to L.F.), the Dutch Digestive Disease Foundation (MLDS WO11-30), and a Horizon Breakthrough grant from the Netherlands Genomics Initiative (grant 92519031 to L.F.). This project was supported by the Prinses Beatrix Fonds, VSB fonds, H. Kersten and M. Kersten (Kersten Foundation), The Netherlands ALS Foundation, and J.R. van Dijk and the Adessium Foundation. The research leading to these results has received funding from the European Communitys Health Seventh Framework Programme (FP7/2007-2013) under grant agreement 259867.

The EGCUT study received targeted financing from Estonian Government SF0180142s08, Center of Excellence in Genomics (EXCEGEN) and University of Tartu (SP1GVARENG). We acknowledge EGCUT technical personnel, especially Mr V. Soo and S. Smit. Data analyzes were carried out in part in the High Performance Computing Center of University of Tartu.

Author contributions

G.H., J.E.P., P.M.V., and G.W.M. conceived and designed the study. G.H., J.E.P., K.S., H-J.W., and J.Y. performed the analysis. T.E. and A.M. provided the EGCUT data. A.K.H., A.F.M., G.W.M., N.G.M., and J.E.P. provided the BSGS data. G.G. provided the CHDWB data. H-J.W. and L.F. provided the Fehrmann data. G.H. and J.E.P. wrote the manuscript with the participation of all authors.

Author information

The authors declare no financial competing interests.

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

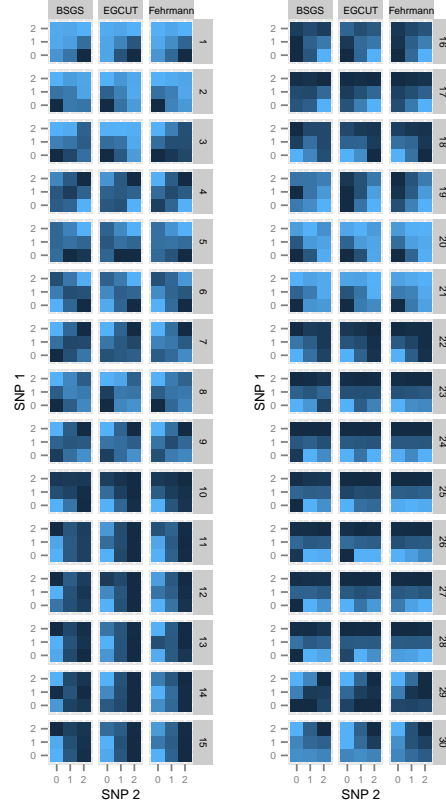


Figure 1: Replication of GP maps in two independent populations
The GP maps for each epistatic interaction that is significant at the Bonferroni level in both replication datasets are shown. Each GP map consists of nine tiles where each tile represents the expression level for that two-locus genotype 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.

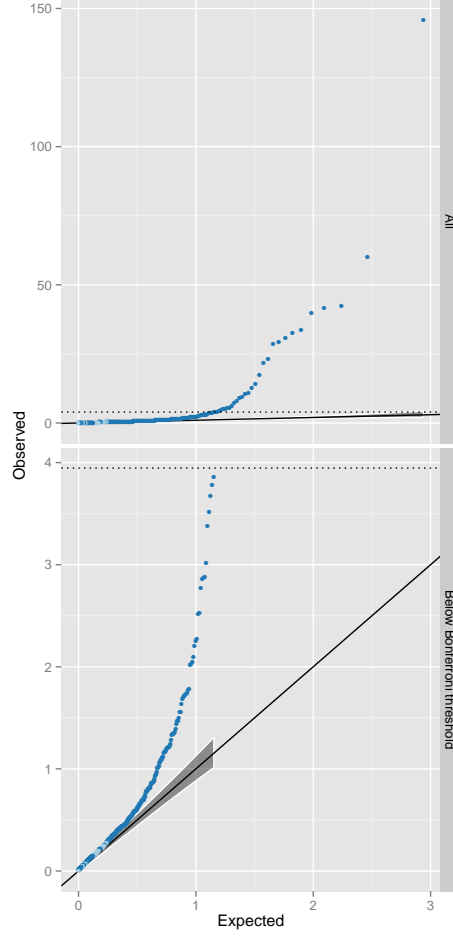


Figure 2: **Q-Q plots of interaction p -values from replication datasets** The top panel shows all 434 discovery SNPs that were tested for interactions. Observed p -values (y -axis, $-\log_{10}$ scale) are plotted against the expected p -values (x -axis, $-\log_{10}$ scale). The multiple testing correction 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.

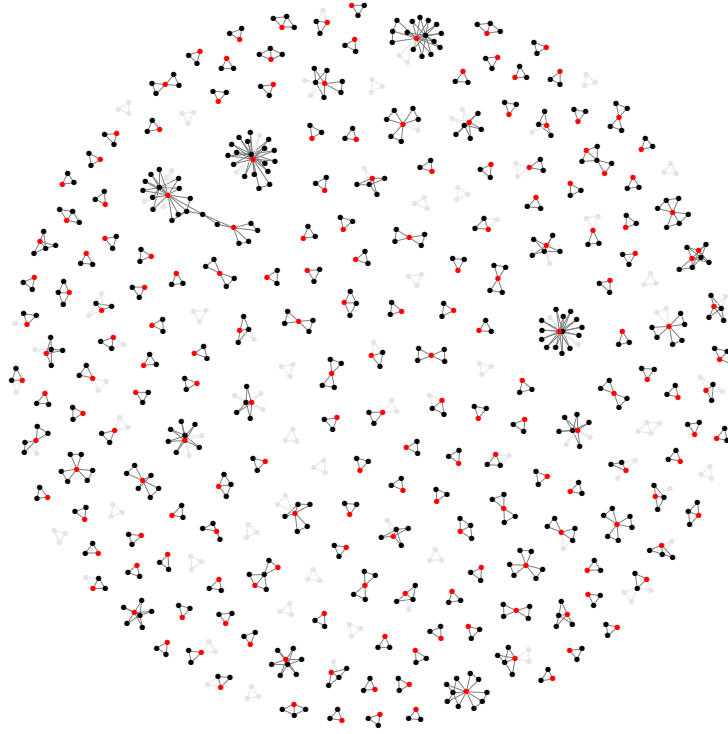


Figure 3: **Discovery and replication of epistatic networks** All 434 putative genetic interactions (edges) with data common to discovery and replication sets is shown, where black nodes represent SNPs and red nodes represent traits (gene expression probes). Three hundred and forty-five interactions 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. An interactive version of this graph can be found here: http://kn3in.github.io/detecting_epi/

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Online methods

1 Discovery data

1.1 Data description

The Brisbane Systems Genetics Study (BSGS) comprises 846 individuals of European descent from 274 independent families²³. DNA samples from each individual were genotyped on the Illumina 610-Quad Beadchip by the Scientific Services Division at deCODE Genetics Iceland. Full details of genotyping procedures are given in Medland et al.³¹ Standard quality control (QC) filters were applied and the remaining 528,509 autosomal SNPs were carried forward for further analysis.

Gene expression profiles were generated from peripheral blood collected with PAXgene TM tubes (QIAGEN, Valencia, CA) using Illumina HT12-v4.0 bead arrays. The Illumina HT-12 v4.0 chip contains 47,323 probes, although some probes are not assigned to RefSeq genes. We removed any probes that did not match the following criteria: contained a SNP within the probe sequence with MAF > 0.05 within 1000 genomes data; did not map to a listed RefSeq gene; were not significantly expressed (based on a detection p -value < 0.05) in at least 90% of samples. After this stringent QC 7339 probes remained for 2D-eQTL mapping. These data are accessible through GEO Series accession number GSE53195.

1.2 Normalisation

Gene expression profiles were normalised and adjusted for batch and polygenic effects. Profiles were first adjusted for raw background expression in each sample. Expression levels were then adjusted using quantile and \log_2 transformation to standardise distributions between samples. Batch and polygenic effects were adjusted using the linear model

$$y = \mu + \beta_1 c + \beta_2 p + \beta_3 s + \beta_4 a + g + e \quad (1)$$

where μ is the population mean expression levels, c , p , s and a are vectors of chip, chip position, sex and generation respectively, fitted as fixed effects; and g is a random additive polygenic effect with a variance covariance matrix

$$G_{jk} = \begin{cases} \sigma_a^2 & j = k \\ 2\phi_{jk}\sigma_a^2 & j \neq k \end{cases} \quad (2)$$

The parameter σ_a^2 is the variance component for additive background genetic. Here, we are using family based pedigree information rather than SNP based IBD to account for relationships between individuals and so ϕ_{jk} is the kinship coefficient between individuals j and k . The residual, e , from equation 1 is assumed to follow a multivariate normal distribution with a mean of zero.

Residuals were normalised by rank transformation and used as the adjusted phenotype for the pairwise epistasis scan to remove any skewness and avoid results being driven by outliers. The GenABEL package for R was used to perform the normalisation³².

2 Exhaustive 2D-eQTL analysis

2.1 Two stage search

We used epiGPU¹⁰ software to perform an exhaustive scan for pairwise interactions, such that each SNP is tested against all other SNPs for statistical association with the expression values for each of the 7339 probes. This uses the massively parallel computational architecture of graphical processing units (GPUs) to speed up the exhaustive search. For each SNP pair there are 9 possible genotype classes. We treat each genotype class as a fixed effect and fit an 8 *d.f.* *F*-test to test the following hypotheses:

$$H_0 : \sum_{i=1}^3 \sum_{j=1}^3 (\bar{x}_{ij} - \mu)^2 = 0; \quad (3)$$

$$H_1 : \sum_{i=1}^3 \sum_{j=1}^3 (\bar{x}_{ij} - \mu)^2 > 0; \quad (4)$$

where μ is the mean expression level and \bar{x}_{ij} is the pairwise genotype class mean for genotype i at SNP 1 and genotype j at SNP 2. This type of test does not parameterize for specific types of epistasis, rather it tests for the joint genetic effects at two loci. This has been demonstrated to be statistically more efficient when searching for a wide range of epistatic patterns, although will also include any marginal effects of SNPs which must be dealt with post-hoc¹⁸.

2.1.1 Stage 1

The complete exhaustive scan for 7339 probes comprises 1.03×10^{15} *F*-tests. We used permutation analysis to estimate an appropriate significance threshold for the study. To do this we performed a further 1600 exhaustive 2D scans on permuted phenotypes to generate a null distribution of the extreme *p*-values expected to be obtained from this number of multiple tests given the correlation structure between the SNPs. We took the most extreme *p*-value from each of the 1600 scans and set the 5% FWER to be the 95% most extreme of these *p*-values, $T_* = 2.13 \times 10^{-12}$. The effective number of tests in one 2D scan being performed is therefore $N_* = 0.05/T_* \approx 2.33 \times 10^{10}$. To correct for the testing of multiple traits we established an experiment wide threshold of $T_e = 0.05/(N_* \times 7339) = 2.91 \times 10^{-16}$. This is likely to be conservative as it assumes independence between probes.

Filtering We used two approaches to filter SNPs from stage 1 to be tested for significant interaction effects in stage 2.

Filter 1 After keeping SNP pairs that surpassed the 2.91×10^{-16} threshold in stage 1 only SNP pairs with at least 5 data points in all 9 genotype classes were kept. We then calculated the LD between interacting SNPs (amongst unrelated individuals within the discovery sample and also from 1000 genomes data) and removed any pairs with $r^2 > 0.1$ or $D'^2 > 0.1$ to avoid the inclusion of haplotype effects and to increase the accuracy of genetic variance decomposition. If multiple SNP pairs were present on the same chromosomes for a particular expression trait then only the sentinel SNP pair was retained, *i.e.* if a probe had multiple SNP pairs that were on chromosomes one and two then only the SNP pair with the most significant p -value was retained. At this stage 6404 filtered SNP pairs remained.

Filter 2 We also performed a second filtering screen applied to the list of SNP pairs from stage 1 that was identical to filter 1 but an additional step was included where any SNPs that had previously been shown to have a significant additive or dominant effect ($p < 1.29 \times 10^{-11}$) were removed²², creating a second set of 4751 unique filtered SNP pairs.

2.1.2 Stage 2

To ensure that interacting SNPs were driven by epistasis and not marginal effects we performed a nested ANOVA on each pair in the filtered set to test if the interaction terms were significant. We did this by contrasting the full genetic model (8 *d.f.*) against the reduced marginal effects model which included the additive and dominance terms at both SNPs (4 *d.f.*). Thus, a 4 *d.f.* F -test was performed on the residual genetic variation, representing the contribution of epistatic variance. Significance of epistasis was determined using a Bonferroni threshold of $0.05/(6404 + 4751) = 4.48 \times 10^{-6}$. This resulted in 406 and 95 SNP pairs with significant interaction terms from filters 1 and 2, respectively.

2.2 Type 1 error rate

Using a Bonferroni correction of 0.05 in the second stage of the two stage discovery scan implies a type 1 error rate of $\alpha = 0.05$. However, this could be underestimated because the number tests performed in the second stage depends on the number of tests in the first stage, and this depends on statistical power and model choice. We performed simulations to estimate the type 1 error rate of this study design.

We assumed a null model where there was one true additive effect and 7 other terms with no effect. To simulate a test statistic we simulated 8 z-scores, $z_1 \sim N(\sqrt{NCP}, 1)$ and $z_{2..8} \sim N(0, 1)$. Thus $z_{full} = \sum_{i=1}^8 z_i \sim \chi_8^2$ (representing the 8 d.f. test) and $z_{int} = \sum_{i=5}^8 z_i \sim \chi_4^2$ (representing the 4 d.f. test where the null hypothesis of no epistasis is true). For a particular value of NCP we simulated

100,000 z values, and calculated the p_{full} -value for the z_{full} test statistic. The n_{int} test statistics with $p_{full} < 2.31 \times 10^{-16}$ were kept for the second stage, where the type 1 error rate of stage 2 was calculated as the proportion of $p_{int} < 0.05/n_{int}$. The power at stage 1 was calculated as $n_{int}/100,000$. This procedure was performed for a range of NCP parameters that represented power ranging from ~ 0 to ~ 1 .

2.3 Population stratification

We ruled out population stratification as a possible cause of inflated test statistics. To test for cryptic relatedness driving the interaction terms we tested for increased LD among the SNPs³³. We calculated the mean of the off-diagonal elements of the correlation matrix of all unique SNPs from the 501 interactions (731 SNPs) using only unrelated individuals, $\bar{r}^2 = 0.0039$. This is not significantly different from the null hypothesis of zero (sampling error $= 1/n_{unrelated} = 0.0039$).

2.4 Probe mapping

To avoid possibility that epistatic signals might arise due to expression probes hybridising in multiple locations we verified that probe sequences for genes with significant interactions mapped to only a single location. As an initial verification we performed a BLAST search of the full probe sequence against 1000 genomes phase 1 version 3 human genome reference and ensured that only one genomic location aligned significantly ($p < 0.05$). As a second step, to mitigate the possibility of weak hybridisation elsewhere in the genome we divided the probe sequence into three sections (1-25bp, 13-37bp, 26-50bp) and performed a BLAST search of these probe sequence fragments. No probe sequences or probe sequence fragments mapped to positions other than the single expected genomic target ($p < 0.05$).

3 Replication

3.1 Data description

We attempted replication of the 501 significant interactions from the discovery set using three independent cohorts; Fehrmann, EGCUT, and CHDWB. It was required that LD $r^2 < 0.1$ and $D'^2 < 0.1$ between interacting SNPs (as measured in the replication sample directly), and all nine genotype classes had at least 5 individuals present in order to proceed with statistical testing for replication in both datasets. We also excluded any putative SNPs that had discordant allele frequencies in any of the datasets. Details of the cohorts are as follows.

Fehrmann: $n = 1240$ The Fehrmann dataset¹² consists of peripheral blood samples of 1240 unrelated individuals from the United Kingdom and the Netherlands. Some of these individuals are patients, while others are healthy controls.

Individuals were genotyped using the Illumina HumanHap300, Illumina HumanHap370CNV, and Illumina 610 Quad platforms. RNA levels were quantified using the Illumina HT-12 V3.0 platform. These data are accessible through GEO Series accession numbers GSE20332 and GSE20142.

EGCUT: $n = 891$ The Estonian Genome Center of the University of Tartu (EGCUT) study¹¹ consists of peripheral blood samples of 891 unrelated individuals from Estonia. They were genotyped using the Illumina HumanHap370CNV platform. RNA levels were quantified using the Illumina HT-12 V3.0 platform. These data are accessible through GEO Series accession number GSE48348.

CDHWB: $n = 139$ The Center for Health Discovery and Well Being (CDHWB) Study²⁴ is a population based cohort consisting of 139 individuals of European descent collected in Atlanta USA. Gene expression profiles were generated with Illumina HT-12 V3.0 arrays from peripheral blood collected from Tempus tubes that preserve RNA. Whole genome genotypes were measured using Illumina OmniQuad arrays. Due to the small sample size, most SNP pairs did not pass filtering in this dataset (20 SNP pairs remained) and so we have excluded it from the rest of the analysis.

3.2 Meta Analysis

The 4 *d.f.* interaction p -values for each independent replication dataset were calculated using the same statistical test as was performed in the discovery dataset. We then took the interaction p -values from EGCUT and Fehrmann and calculated a joint p -value using Fisher’s method of combining p -values for a meta analysis as $-2 \ln p_1 - 2 \ln p_2 \sim \chi^2_{4d.f.}$. As in the discovery analysis, all gene expression levels were normalised using rank transformation to avoid skew or outliers in the distribution³⁴.

3.3 Concordance of direction of effects

We used four methods to calculate the concordance of the direction of effects between the discovery and replication datasets.

Test 1 Is the most significant epistatic effect in the discovery set in the same direction as the same epistatic effect in the replication sets? We decomposed the genetic variance into 8 orthogonal effects, four of which are epistatic ($A \times A$, $A \times D$, $D \times A$, $D \times D$). The sign of the epistatic effect that had the largest variance in the discovery was recorded, and then was compared to the same epistatic effect in the two replication datasets (regardless of whether or not the same epistatic effect was the largest in the replication datasets). The probability of the sign being the same in one dataset is 1/2. The probability of the sign being the same in two is 1/4.

Test 2 Is the most significant epistatic effect in the discovery the same as the largest epistatic effect in the replication set with the sign being concordant. As in Test 1, but this time we required that the largest effect was the same in the discovery and the replication, and that they had the same sign (*e.g.* if the largest effect in the discovery is $A \times A$, with a positive effect, then concordance is achieved if the same is true in the replication). The probability of one replication dataset being concordant by chance is $1/8$, and concordance in both is $1/64$.

Test 3 Do the epistatic effects that are significant at nominal $p < 0.05$ in the discovery have the same direction of effect as in the replication? Here we count all the epistatic variance components in the discovery that have $p < 0.05$ (1133 amongst the 434 discovery SNP pairs, *i.e.* each SNP pair has at least 1 and at most 4 significant epistatic variance components). Then we compare the direction of the effect in the replication dataset. The probability of the sign being the same in one dataset for any one significant effect is $1/2$. The probability of the sign being the same in two is $1/4$.

Test 4 If we count how many of the 4 epistatic effects are concordant between the discovery and replication data for each interaction then is this significant from what we expect by chance? There can be either 0, 1, 2, 3 or 4 concordant signs at each interaction, each with expectation of $p = 1/16, 4/16, 6/16, 4/16, 1/16$ under the null, respectively. Observed counts are multinomially distributed, and we tested if the observed proportions were statistically different from the expected proportions using an approximation of the multinomial test³⁵.

The probability of observing the number of concordant signs in tests 1-3 is calculated using a binomial test. All variance decompositions were calculated using the NOIA method³⁶.

4 Effects of LD on detection and replication

The power to detect genetic effects, when the observed markers are in LD with the causal variants, is proportional to r^x . For additive effects $x = 2$, but for non-additive effects x is larger, *i.e.* $x = 4$ for dominance or $A \times A$, $x = 6$ for $A \times D$ or $D \times A$, and $x = 8$ for $D \times D$. Many biologically realistic GP maps may be comprised of all 8 variance components¹⁸.

This is important for both detection and for replication of epistasis. For detection, if the epistatic effect includes the $D \times D$ term then if the two causal variants are tagged by observed markers that are each in LD $r = 0.9$, then if the true variance is V_t then the observed variance V_o at the markers will be $0.9^8 V_t = 0.43 V_t$. Therefore, it is important to consider the sampling variation of \hat{r}^x in a sample given some true population value of r .

4.1 Simulation 1

For some values of fixed population parameters, p_1 (minor allele frequency at observed marker), q_1 (minor allele frequency at causal variant), and r (LD between marker and causal variant), the expected haplotype frequencies are

$$h_{11} = r\sqrt{p_1q_1p_2q_2} + p_1q_1 \quad (5)$$

$$h_{12} = p_1q_2 - r\sqrt{p_1q_1p_2q_2} \quad (6)$$

$$h_{21} = p_2q_1 - r\sqrt{p_1q_1p_2q_2} \quad (7)$$

$$h_{22} = r\sqrt{p_1q_1p_2q_2} + p_2q_2 \quad (8)$$

where $p_2 = 1 - p_1$ and $q_2 = 1 - q_1$. For a range of population parameters we randomly sampled $2n$ haplotypes where the expected haplotype frequencies were $h_{11}, h_{12}, h_{21}, h_{22}$. From the sample haplotype frequencies we then calculated sample estimates of \hat{r} where

$$\hat{r} = \frac{\hat{h}_{11} - \hat{p}_1\hat{q}_1}{\sqrt{\hat{p}_1\hat{q}_1\hat{p}_2\hat{q}_2}} \quad (9)$$

For each value of combination of the parameters p_1, q_1, r, n 1000 simulations were performed and the sampling mean and sampling standard deviation of $\hat{r}, \hat{r}^2, \hat{r}^4, \hat{r}^6, \hat{r}^8$ were recorded. It was observed that sampling variance increases for increasing x in \hat{r}^x .

4.2 Simulation 2

We assume that the discovery SNP pairs are ascertained (from a very large number of tests) have high \hat{r} between observed SNPs and causal variants because otherwise power of detection would be low. We can hypothesize that the distribution of \hat{r} in this ascertained sample will be a mixture of r that is high and r that is lower but with ascertained higher values from sampling. Therefore, we would expect those with truly high r to have a higher replication rate in independent datasets, and those with ascertained high \hat{r} to have lower replication because resampling is unlikely to result in the same extreme ascertainment. To obtain empirical estimates of \hat{r} in discovery and replication datasets we conducted the following simulation.

1. Using 1000 genomes data (phase 1, version 3, 379 European samples) we selected the 528,509 “markers” used in the original discovery analysis, plus 100,000 randomly chosen “causal variants” (CVs) with minor allele frequency > 0.05 .
2. The 379 individuals were split into discovery (190) and replication (189) sets.
3. For each CV the marker with the maximum \hat{r}_D^2 from the marker panel was recorded in the discovery set. This marker was known as the “discovery marker” (DM).

4. The \hat{r}_R^2 for each CV/DM pair was then calculated in the replication set where the discovery LD was ascertained to be high, such that $\hat{r}_D^2 > 0.9$.

We observed that there was an average decrease in \hat{r}_R^x relative to \hat{r}_D^x , and that this decrease was larger with increasing x . We observed that $(\hat{r}_R^2 - \hat{r}_D^2)/\hat{r}_D^2 = 0.029$ whereas $(\hat{r}_R^8 - \hat{r}_D^8)/\hat{r}_D^8 = 0.092$. The average drop in in replication \hat{r}^8 was 3 times higher than the drop in \hat{r}^2 .

4.3 Interpretation

Simulation 1 shows that sampling variance of r^x increases as x increases. Detection of epistasis is highly dependent upon high \hat{r} . Amongst the discovery SNPs there will be a mixture of interactions where observed SNPs are either in true high LD with causal variants, or will have highly inflated sample \hat{r}^x compared to the population r^x . Simulation 2 shows that as x gets larger, the average decrease in \hat{r}^x between discovery and replication becomes larger, likely to be a result of ascertained high \hat{r} in the discovery and increased sampling variance with increasing x in the replication. These results demonstrate that if all else is equal, the impact of sampling variance of r alone will reduce the replication rate of epistatic effects compared to additive effects.

5 Additive and non-additive variance estimation

5.1 Fixed effects

To compare the relative contribution to the phenotypic variance of gene expression levels between additive and epistatic effects we are constrained by the problem that non-additive variance components for a phenotype cannot be calculated directly. Here, we only have SNP pairs that exceed a threshold of $p < 2.91 \times 10^{-16} = T_e$. A strong conclusion cannot be made about the genome-wide variance contribution, but we can compare the variance explained by SNP effects at this threshold for additive scans and epistatic scans.

In Powell *et al* 2012²³ an expression quantitative trait locus (eQTL) study was performed searching for additive effects in the same BSGS dataset as was used for the discovery here. Using the threshold T_e for the additive eQTL study, 453 of the 7339 probes analysed here had at least one significant additive effect. Assuming that the phenotypic variance for each of the probes is normalised to 1, the total phenotypic variance of all 7339 explained by the significant additive effects was 1.73%.

Following the same procedure, at the threshold T_e there were 238 gene expression probes with at least one significant pairwise epistatic interaction out of the 7339 tested. In total the proportion of the phenotypic variance explained by the epistatic effects at these SNP pairs was 0.25%.

5.2 Limitations of this type of comparison

Though it is useful to compare the relative variances of epistatic and additive effects, it must be stressed that our results here are approximations that are very limited by the study design. We estimate that additive effects explain approximately 10 times more variance than epistatic effects, but this could be an overestimate or an underestimate due to a number of different caveats. 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. Thirdly, the non-additive variance at causal variants is expected to be underestimated by observed SNPs in comparison to estimates for additive variance. And fourthly, the extent of winner’s curse in estimation of effect sizes may differ between the two studies.

5.3 Pedigree estimates

The gene expression levels for MBNL1, TMEM149, NAPRT1, TRAPPC5 and CAST are influenced by large *cis-trans* epistatic networks (eight interactions or more). Though it is not possible to orthogonally estimate the non-additive genetic variance for non-clonal populations, an approximation of a component of non-additive variance can be estimated using pedigree information. The BSGS data is comprised of some related individuals and standard quantitative genetic analysis was used to calculate the additive and dominance variance components for each gene expression phenotype in Powell *et al* 2013²². The dominance effect is likely to capture additive \times additive genetic variance plus some fraction of other epistatic variance components. We found that the aforementioned genes had dominance variance component estimates within the top 5% of all 17,994 gene expression probes that were analysed in Powell *et al* 2013.

6 Functional enrichment analysis

6.1 Tissue specific transcriptionally active regions

We employed a recently published method (<http://www.broadinstitute.org/mpg/epigwas/>)²⁷ that tests for cell-type-specific enrichment of active chromatin, measured through H3K4me3 chromatin marks³⁷ in regions surrounding the 731 SNPs that comprise the 501 discovery interactions. The exact method used to perform this analysis has been described previously³⁸. Briefly, we tested the hypothesis that the 731 SNPs were more likely to be in transcriptionally active regions (as measured by chromatin marks) than a random set of SNPs selected from the same SNP chip. This hypothesis was tested for 34 cell types across four broad tissue types (haematopoietic, gastrointestinal, musculoskeletal and endocrine, and brain).

6.2 Chromosome interactions

It has been shown¹³ that different regions on different chromosomes or within chromosomes spatially colocalise within the cell. We shall refer to the colocalisation of two chromosome regions as a chromosome interaction. A map of pairwise chromosome interactions for K562 blood cell lines was recently produced²⁹, and we hypothesised that part of the underlying biological mechanism behind some of the 501 epistatic interactions may arise from chromosome interactions. We found that 44 of the putative epistatic interactions were amongst SNPs that were within 5Mb of known chromosome interactions. This means that SNP A was no more than 2.5Mb from the focal point of the chromosome interaction on chromosome A, and SNP B was no more than 2.5Mb from the focal point on chromosome B.

We performed simulations to test how extreme the observation of 44 epistatic interactions overlapping with chromosome interactions is compared to chance. Chromosome interactions fall within functional genomic regions^{13,29}, and the SNPs in our epistatic interactions are enriched for functional genomic regions. Therefore, we designed the simulations to ensure that the null distribution was of chromosome interactions between SNPs enriched for functional genomic regions but with no known epistatic interactions. To do this we used the 731 SNPs that form the 501 putative epistatic interactions and randomly shuffled them to create new sets of 501 pairs, disallowing any SNP combinations that were in the original set. Therefore, each new random set was enriched for functional regions but had no genetic interactions. We scanned the map of chromosome interactions for overlaps with the new sets and then repeated the random shuffling process. We performed 1,000 such permutations to generate a null distribution of chromosome interaction overlaps.

We repeated this process, searching for overlaps within 1Mb, 250kb, and 10kb.

6.3 SNP colocalisation with genomic features

We tested for enrichment of genomic features for the 687 IndexSNPs that comprise the 434 epistatic interactions with data present in discovery and replication datasets. For each of the 687 IndexSNPs we calculated LD with all regional SNPs within a radius of 0.5Mb and kept all regional SNPs with LD $r^2 > 0.8$. We then cross-referenced the remaining regional SNPs with the annotated chromatin structure reference²⁸) querying whether the regional SNPs fell in Predicted promoter region including TSS (TSS), Predicted promoter flanking region (PF), Predicted enhancer (E), Predicted weak enhancer or open chromatin cis regulatory element (WE), CTCF enriched element (CTCF), Predicted transcribed region (T), or Predicted Repressed or Low Activity region (R) positions. Therefore a particular IndexSNP might cover multiple genomic features through LD.

We then performed the whole querying process for each of the 528,509 SNPs present in the SNP chip used in the scan, and used the results from this second

analysis to establish a null distribution for the expected proportion of SNPs for each genomic feature. We calculated p -values for enrichment of each of the seven genomic features independently, and for *cis*- and *trans*-SNPs separately, using a binomial test. For each genomic feature we used the expected proportion of SNPs as the expected probability of “success” (p). Here, a success is defined as an IndexSNP residing in a region that includes the genomic feature. The observed number of successes for each IndexSNP (k) out of the total count of IndexSNPs (n) was then modelled as $\Pr(X = k) = \binom{n}{k} p^k (1 - p)^{n-k}$.

6.4 Transcription factor enrichment

To test for enrichment of transcription factor binding sites (TFBS) we followed a procedure similar to that described in Section 6.3. For each of the 687 IndexSNPs we extracted regional SNPs as previously described. We then used the PWMEnrich package in Bioconductor (<http://www.bioconductor.org/packages/2.12/bioc/html/PWMEnrich.html>) to identify which TFBSs each of the regional SNPs for one IndexSNP falls in (within a radius of 250bp). Thus, the number of occurrences of a particular TFBS was counted for each IndexSNP. We used the “Threshold-free affinity” method for identifying TFBSs³⁹.

We constructed a null distribution of expected TFBS occurrences based on the same null hypothesis as described in Section 6.3 - the probability of an IndexSNP covering a particular TFBS is identical to any of the 528,509 SNPs in the discovery SNP chip. To do this, we performed the same procedure for each SNP in the discovery SNP chip as was performed for each IndexSNP to obtain an expected probability of covering a particular TFBS. We then tested the IndexSNPs for enrichment of each TFBS independently, and for *cis*- and *trans*-SNPs separately. p -values were obtained using Z-scores, calculated by using a normal approximation to the sum of binomial random variables representing motif hits along the sequence⁴⁰.

6.5 Defining previously identified SNP associations

The discovery dataset (BSGS) had previously been analysed for additive and dominant marginal effects for all gene expression levels^{22,23}. To define SNPs that had been previously detected to have effects for a particular gene expression level we used a significance threshold accounting for multiple testing across SNPs and expression probes, $T_m = 0.05/(528509 \times 7339) = 1.29 \times 10^{-11}$. From this, we found that only nine of the 501 discovery interactions had known main effects, 64 were between SNPs that had no known marginal effects, and 439 were between a SNP with a known marginal effect and a SNP with no known marginal effect.

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Supplementary Figures

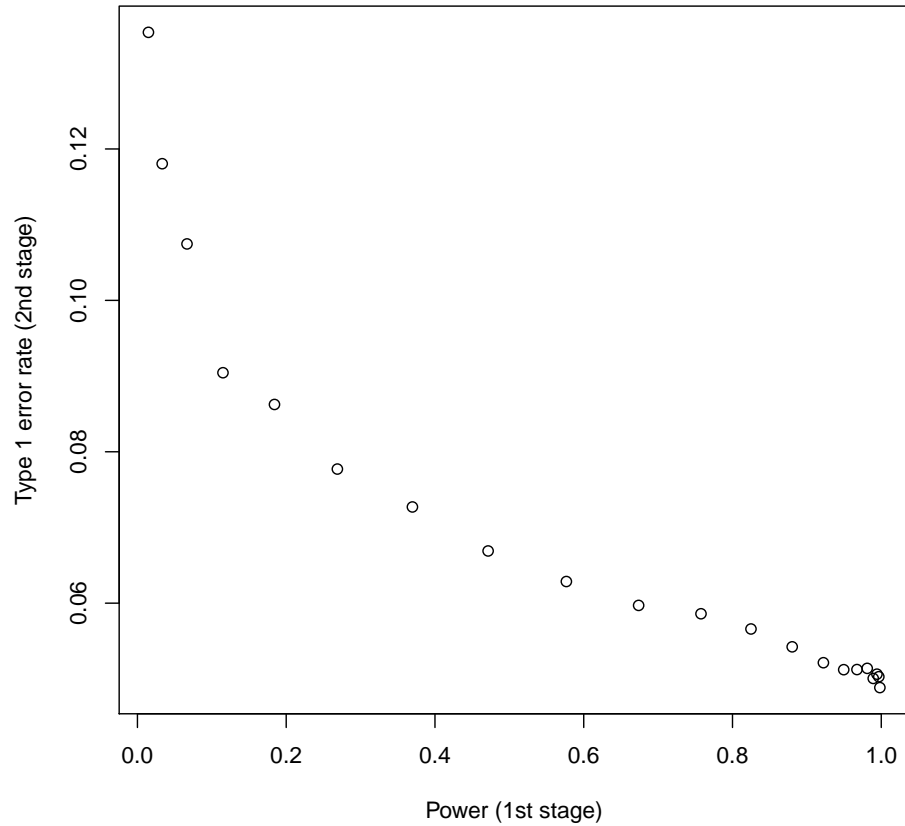


Figure S1: **Type 1 error rate of two stage design assuming a null model of one large additive effect and no epistasis** In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These 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.

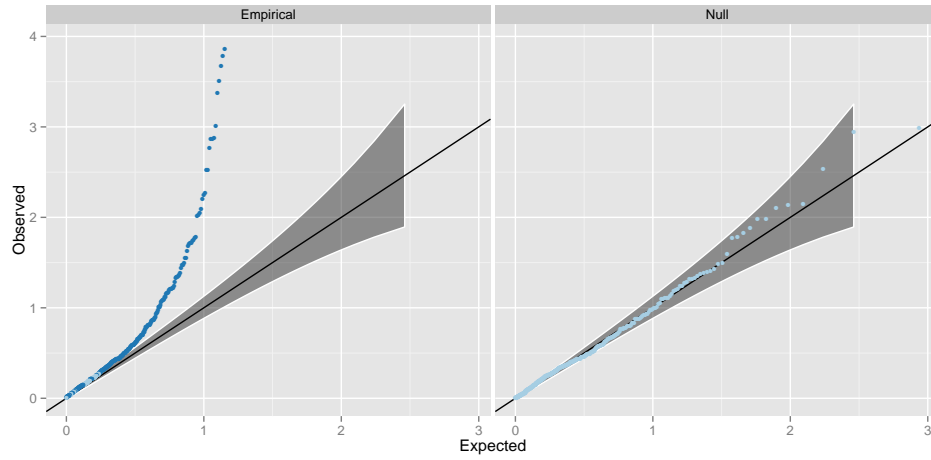


Figure S2: **Q-Q plots of interaction p -values from replication datasets, excluding the 30 points significant at the Bonferroni level** The right panel (Null) shows the interaction p -values from a meta analysis across two independent datasets on 434 SNP pairs where one SNP has a marginal effect. The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

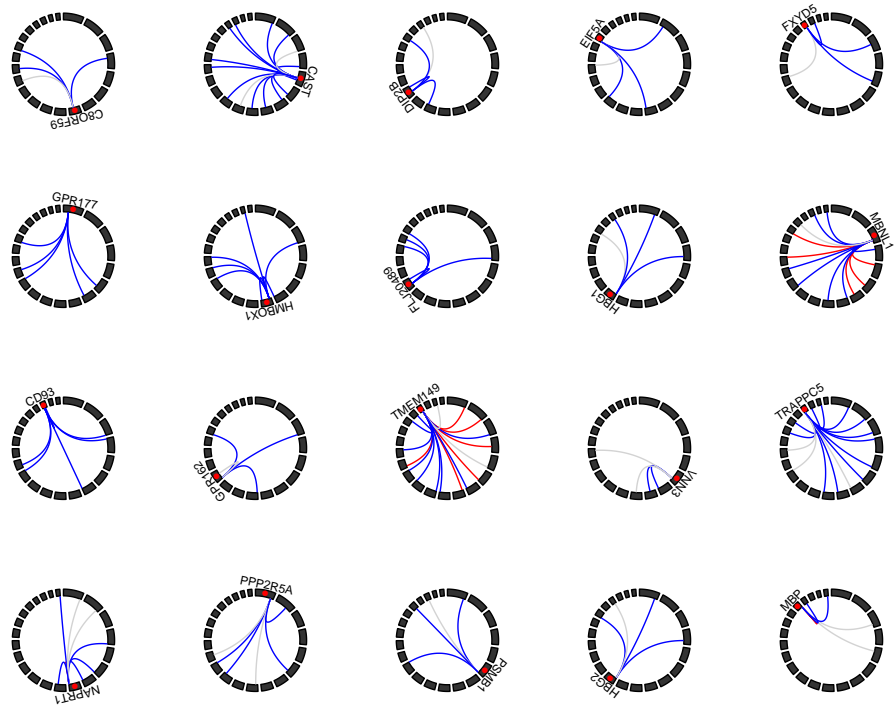


Figure S3: **Gene expression traits with four or more genetic interactions** Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent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

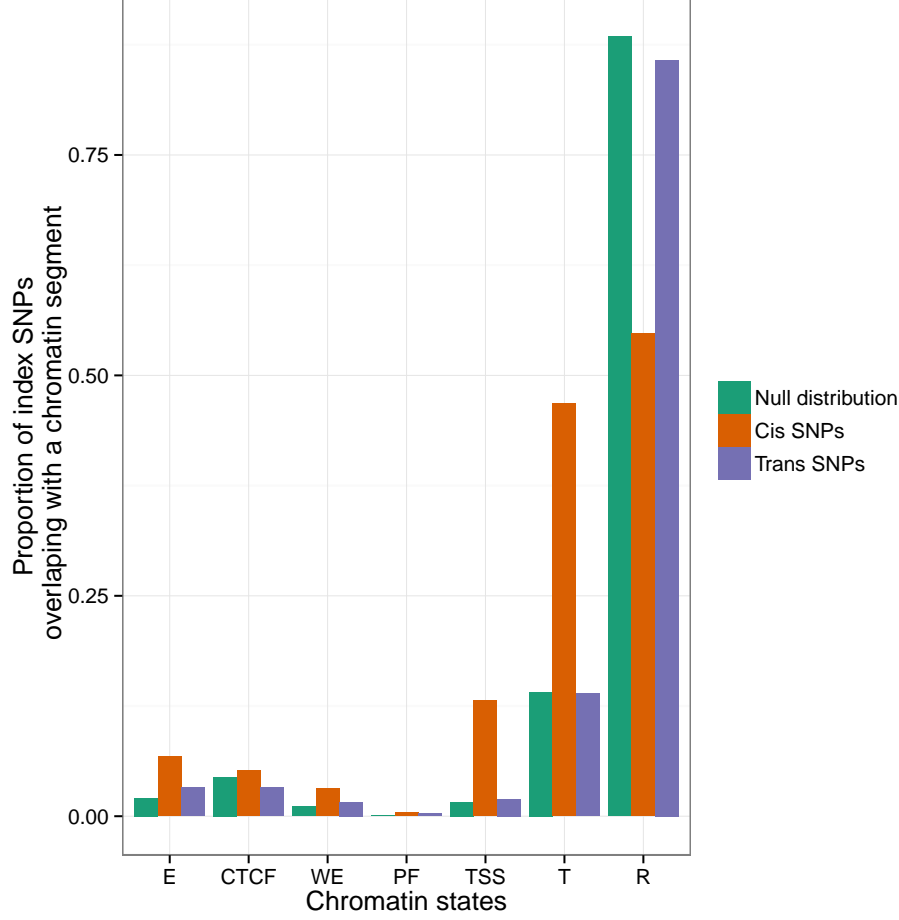


Figure S4: Location of SNPs relative to genomic features We used chromatin segmentation²⁸ as a method for labelling genomic features. All SNPs within 1Mb and $r^2 > 0.8$ of each *cis*- and *trans*-SNP were taken to find which genomic features (x -axis) were covered by the SNPs that compose the 501 significant 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

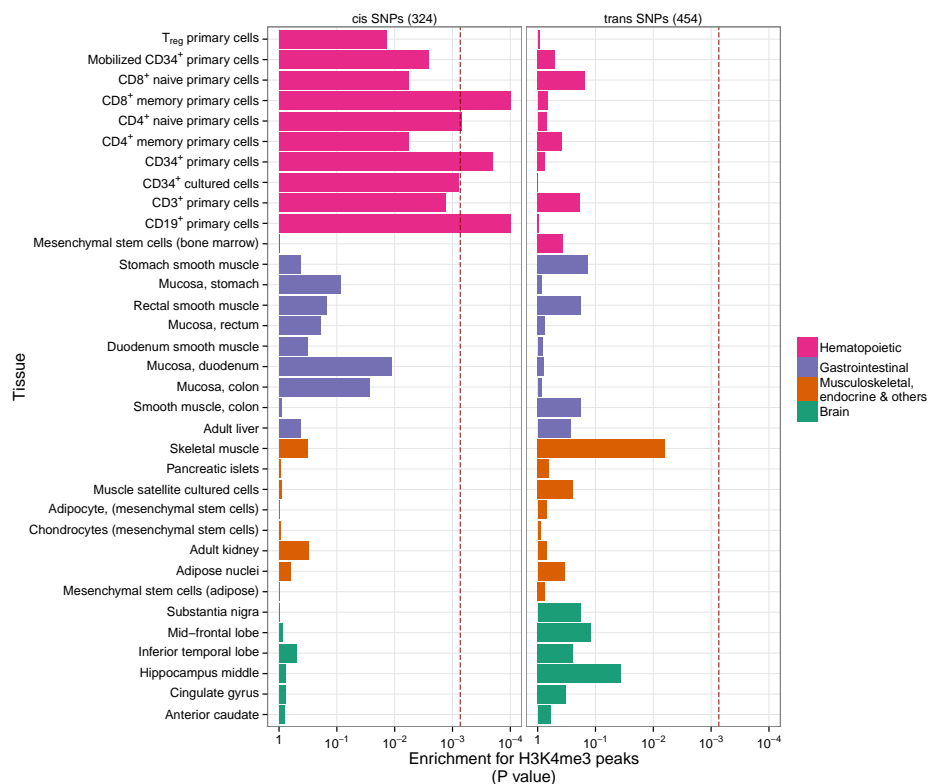


Figure S5: Tissue specific enrichment of SNPs in transcriptionally active regions The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3²⁷. Enrichment p -values are calculated using permutation analysis for 34 different cell types (y -axis) in four tissue types (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.

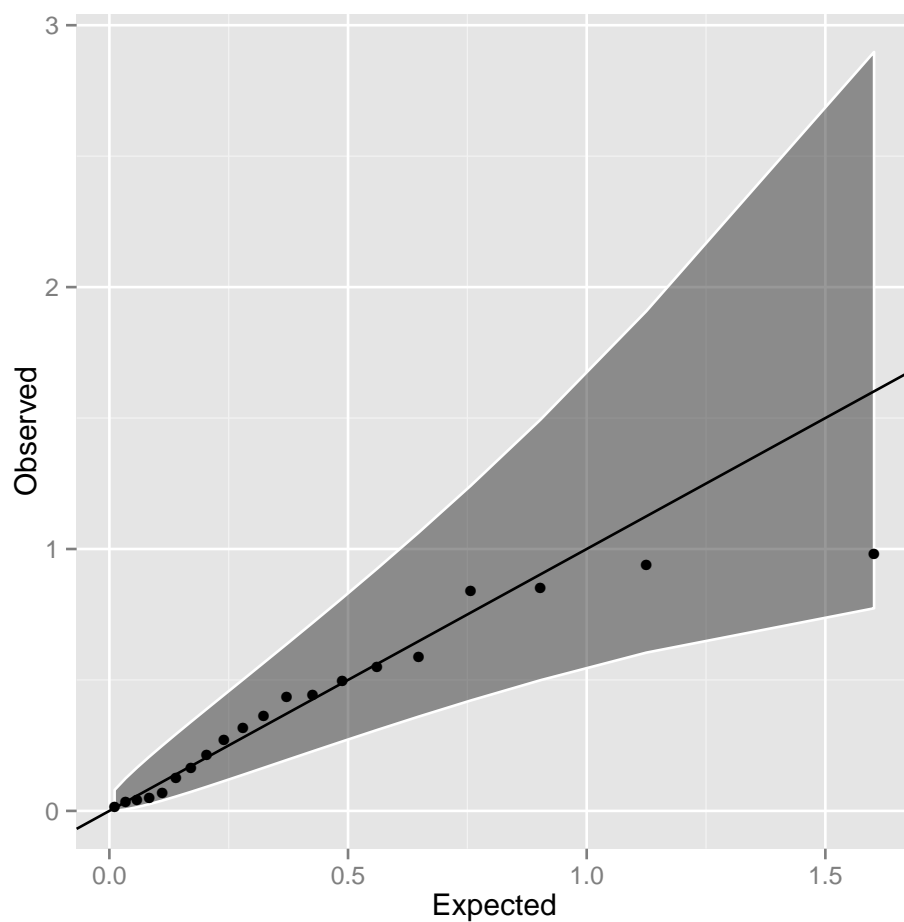


Figure S6: **Q-Q plot of interaction p -values in the CDHWB dataset**
 Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset (mainly due to small sample size). There is no evidence for enrichment of interaction terms, most likely due to insufficient power given the limited sample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

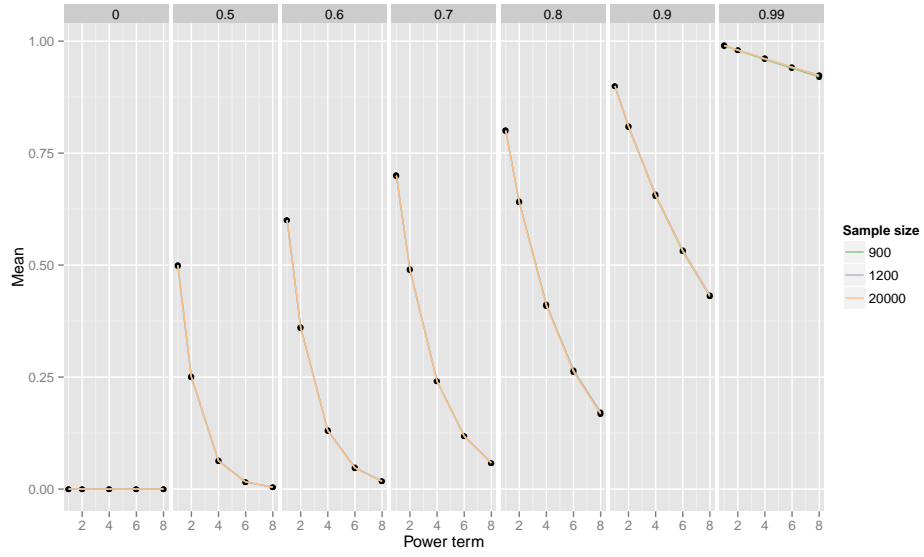


Figure S7: **Sampling mean for different power terms of population r values** Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8 . For a given population value of LD r (columns of plots), plotted is the sample mean (y -axis) of \hat{r} , \hat{r}^2 (additive), \hat{r}^4 (dominance, $A \times A$), \hat{r}^6 ($A \times D$), \hat{r}^8 ($D \times D$) (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 .

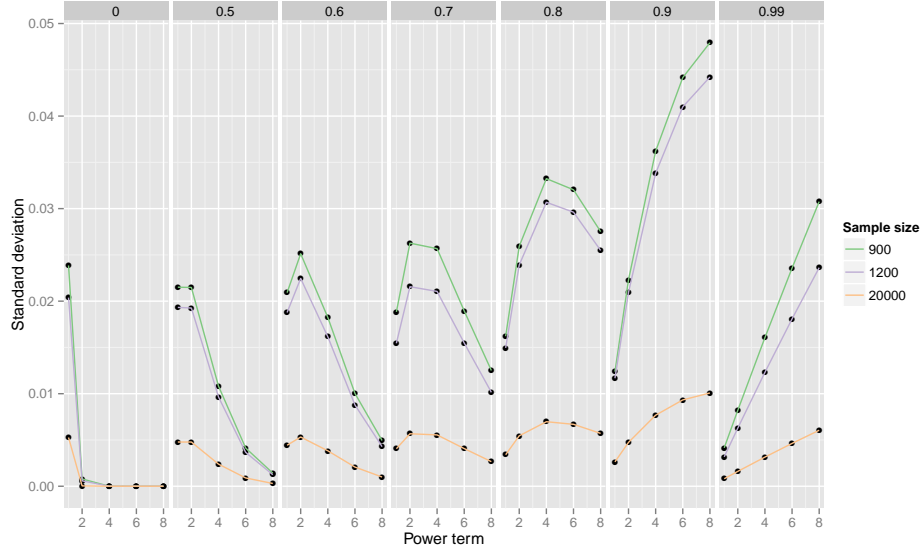


Figure S8: Sampling standard deviation for different power terms of population r values Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8 . For a given a population value of LD r (columns of plots), plotted is the sampling standard deviation (y -axis) of \hat{r} , \hat{r}^2 (additive), \hat{r}^4 (dominance, $A \times A$), \hat{r}^6 ($A \times D$), \hat{r}^8 ($D \times D$) (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.

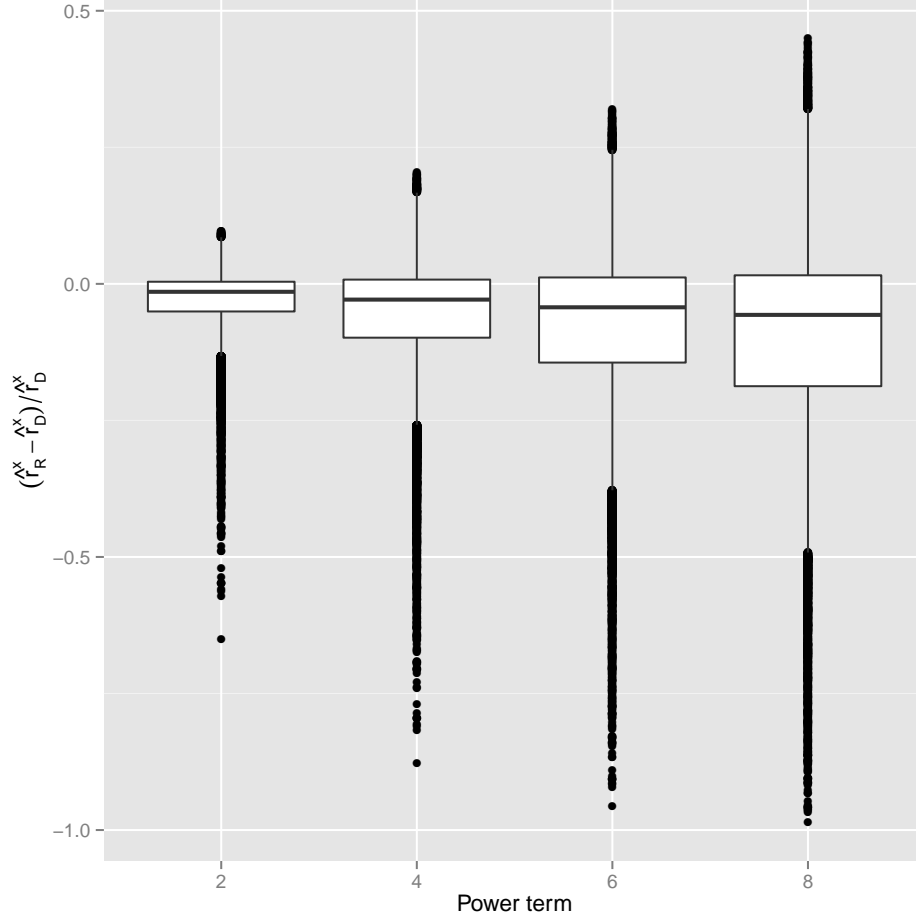


Figure S9: **Reduction in LD as estimated in replication data after ascertaining for high LD in discovery data** 100,000 “unobserved” causal variants (CVs) were tested for LD against a panel of 528,509 “observed” discovery markers (DMs). DM/CV pairs with LD $r^2 > 0.9$ were then tested in an independent 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.

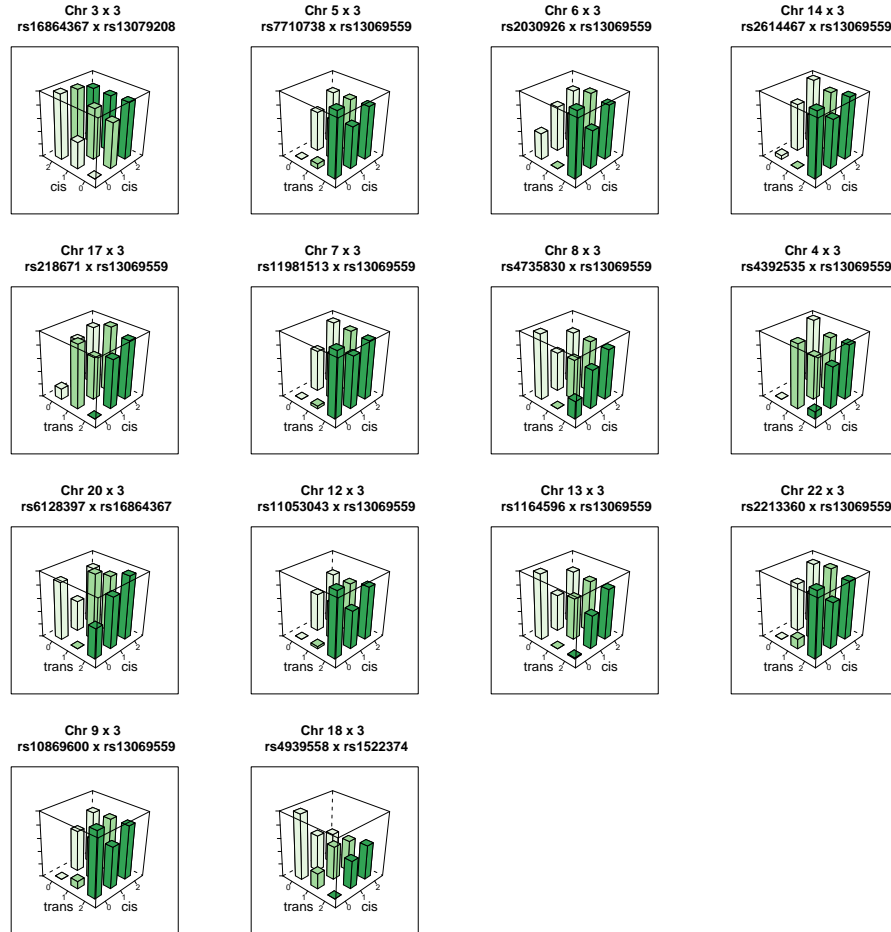


Figure S10: **Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous for the masking allele.

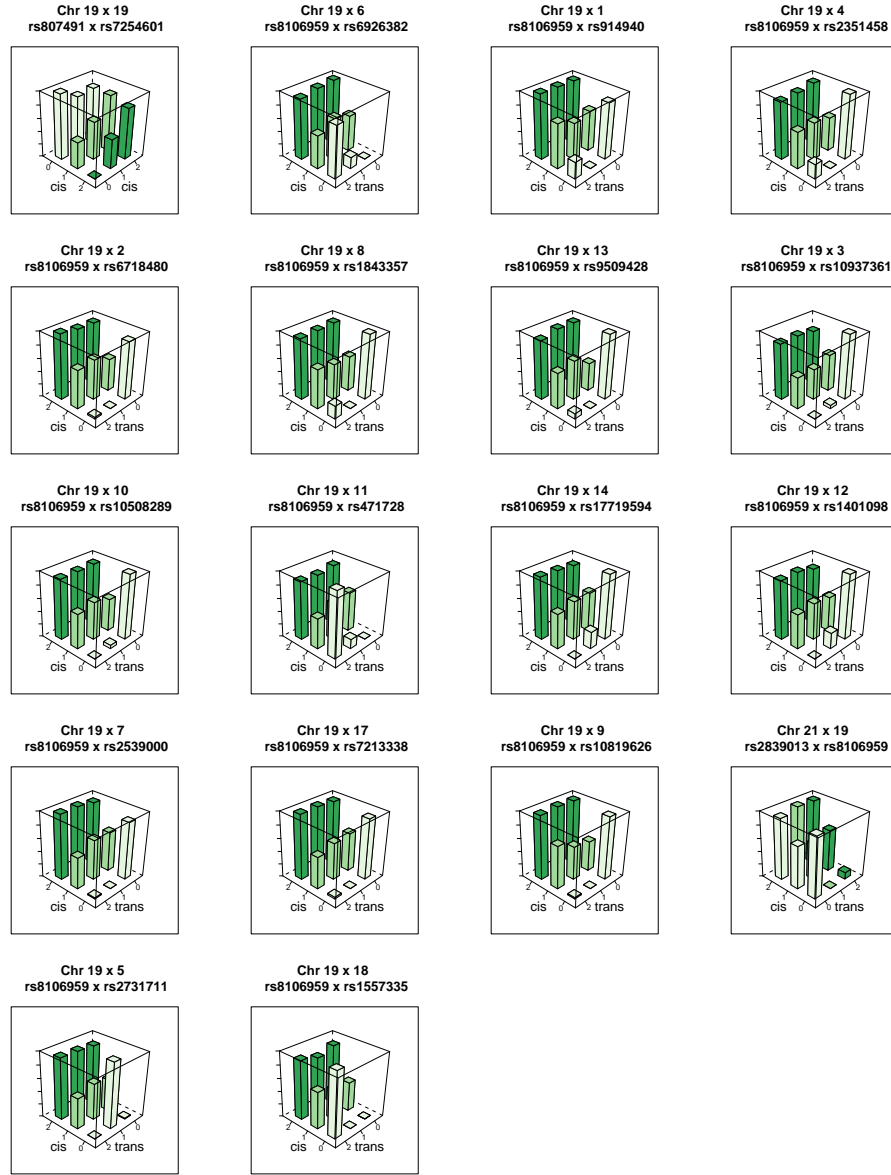


Figure S11: **Genotype-phenotype maps for 19 interactions influencing the expression of TMEM149** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of TMEM149, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous for the masking allele.

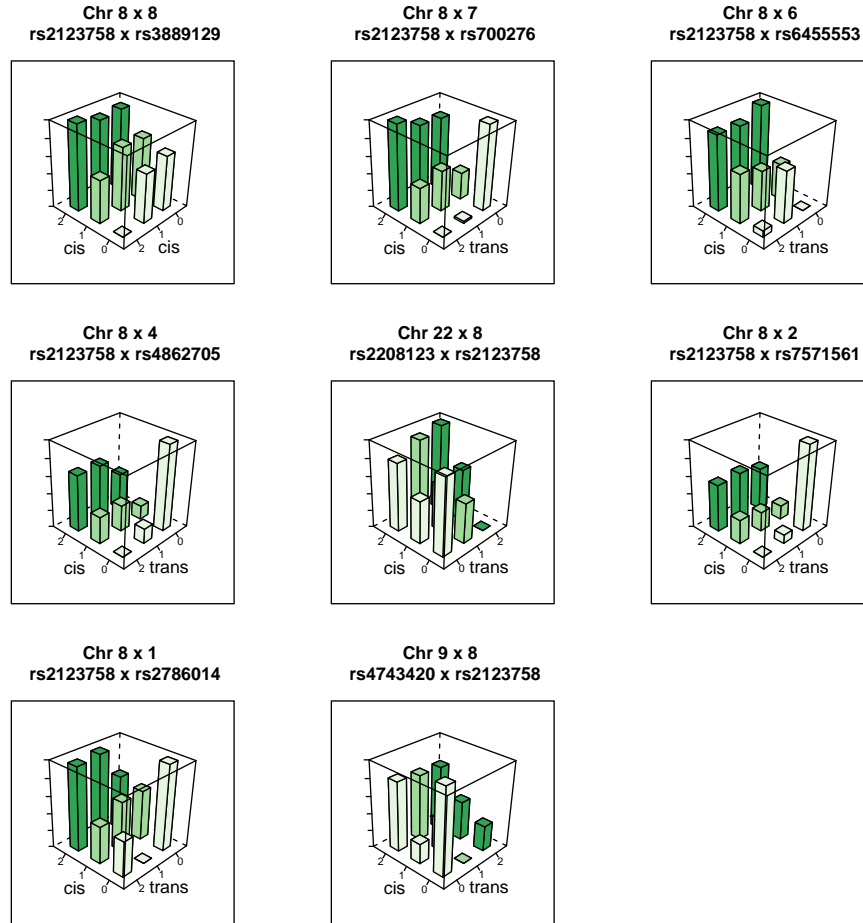


Figure S12: **Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1** Each bar represents the mean phenotypic value for individuals in that genotype class.

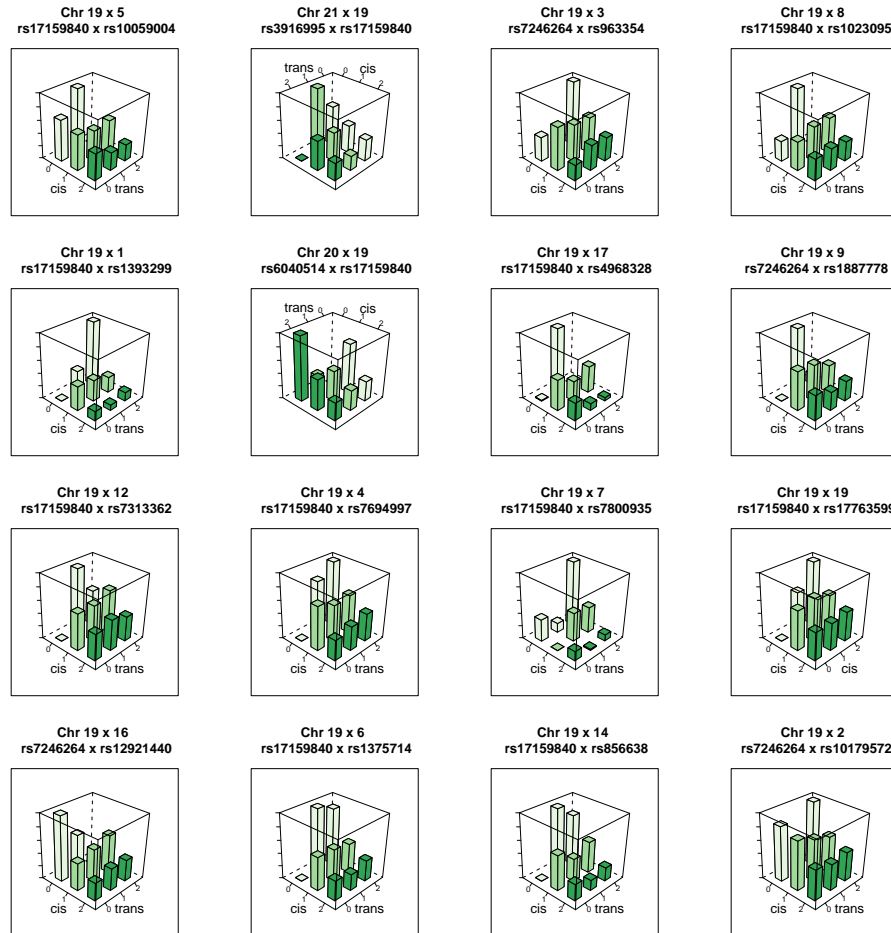


Figure S13: **Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5** Each bar represents the mean phenotypic value for individuals in that genotype class.

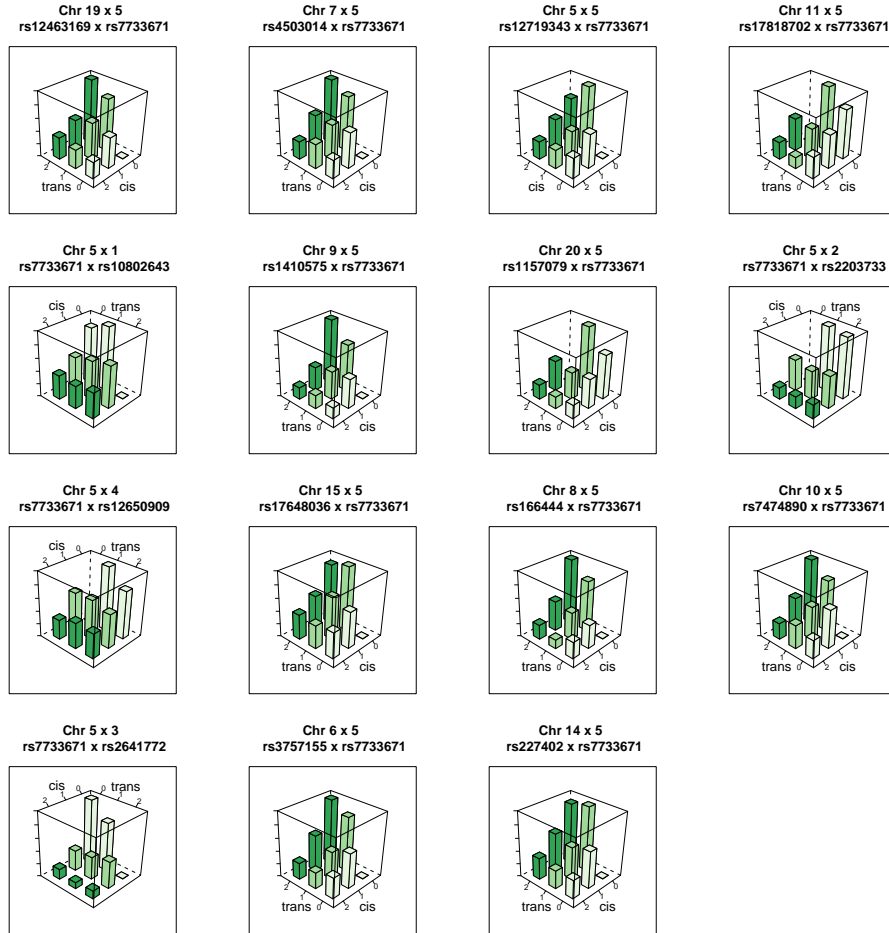


Figure S14: **Genotype-phenotype maps for 15 interactions influencing the expression of CAST** Each bar represents the mean phenotypic value for individuals in that genotype class.

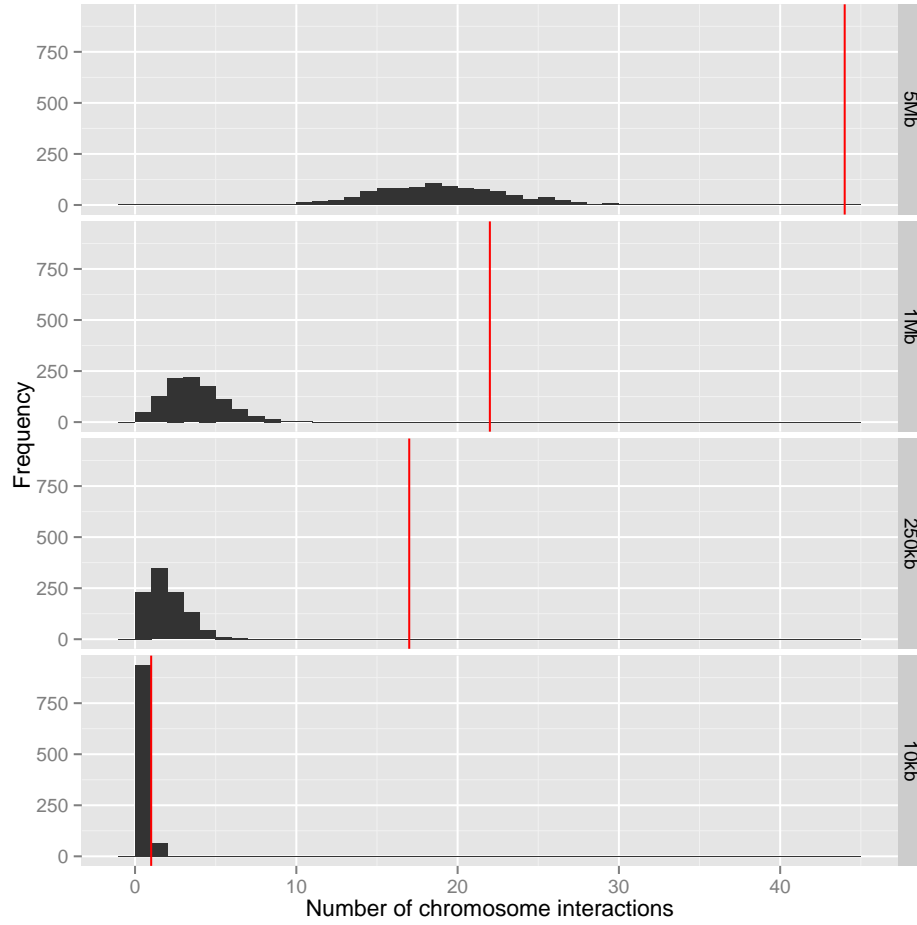


Figure S15: Number of overlaps between chromosome interactions and epistatic interactions Interacting chromosome regions may be a possible mechanism underlying epistatic interactions. The number of epistatic interactions within 20kb, 500kb, 2Mb and 10Mb of known chromosome interacting regions are shown by red vertical lines. The histograms represent the null distribution based on random sampling of 1,000 datasets for each window size.

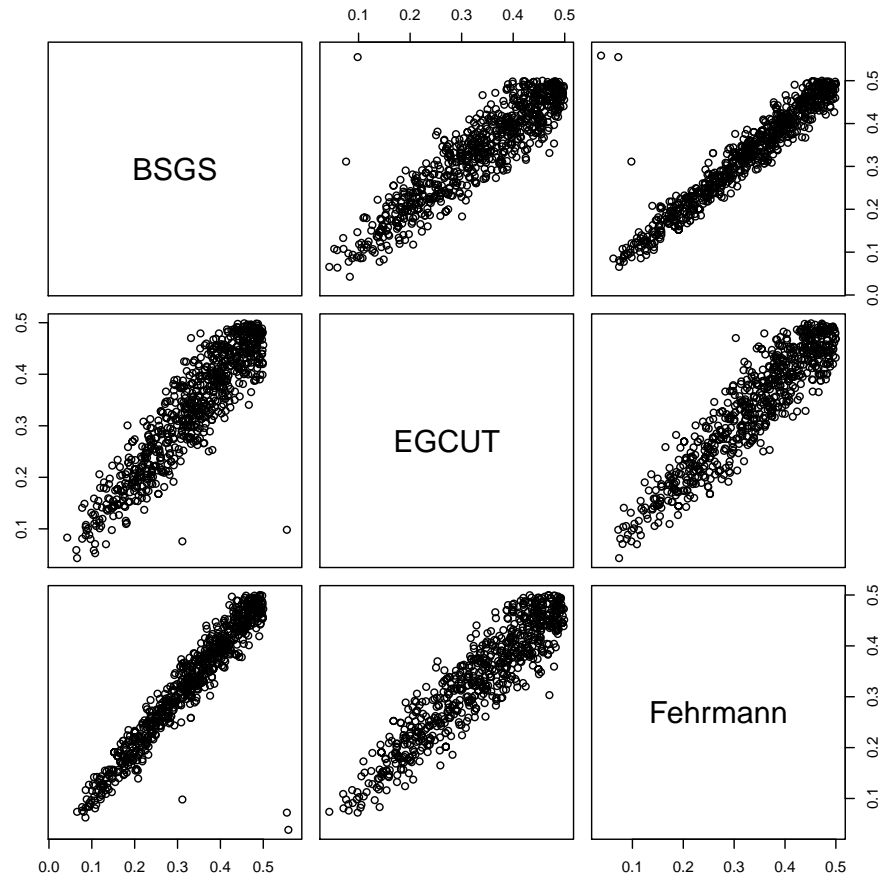


Figure S16: **Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations** Outliers were removed from the analysis as part of the filtering stage during replication.

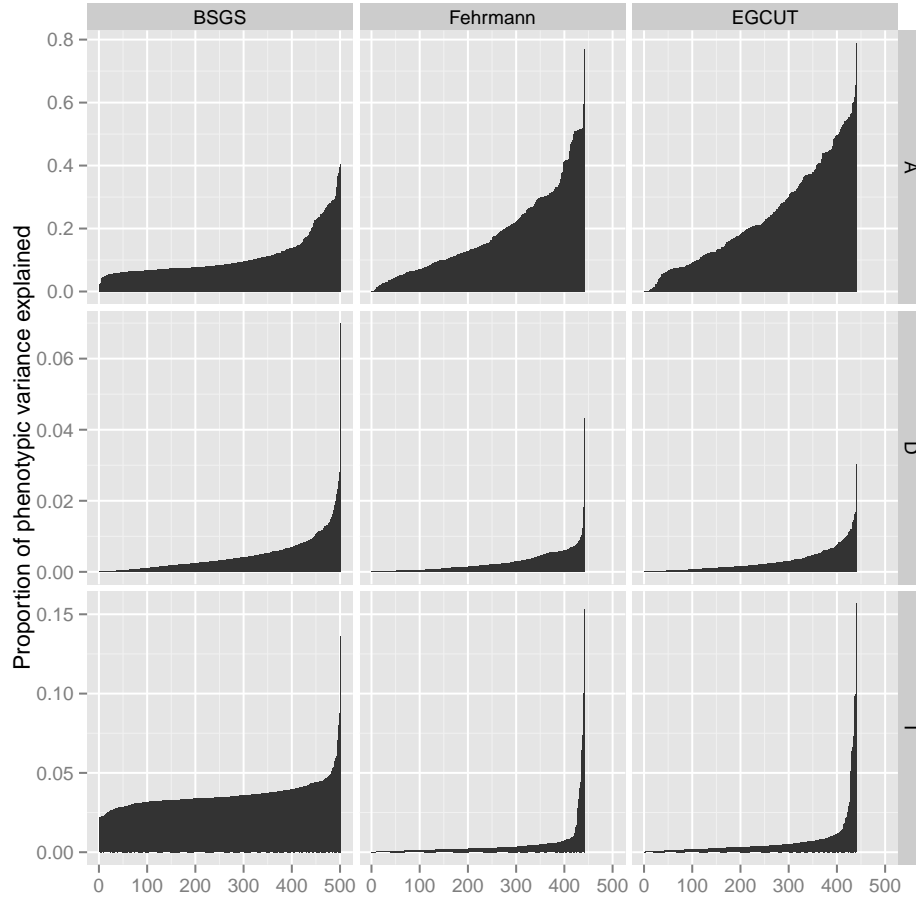


Figure S17: Comparison of variance explained by additive, dominant and epistatic effects from different cohorts How does the estimated variance decomposition change in different cohorts? The proportion of the phenotypic variance that is additive (A), dominant (D), or epistatic (I) for each putative interaction 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 – continued from previous page

Gene ID ^a	Expression trait	Probe ID ^b	Chr.	rs ID	Chr.	SNP 1	Pos/Mb ^c	Association ^d	rs ID	Chr.	SNP 2	Pos/Mb ^c	Association ^d	BSGS ^e	Interaction statistic ^f	-log ₁₀ p-values	EGCUT ^g	Meta ^g	Distance / Mb ^h
C8ORF59	ILMN-1653205	8	rs8051751	16	7188323		7188323		rs2890452	8	86102223		C8ORF59	5.79	1.39	0.18	0.87		
C9ORF72	ILMN-1741881	9	rs10122902	9	27556780		C9ORF72		rs2526068	1	242029101		CABC1	6.36	0.96	0.01	0.37		
CABC1	ILMN-1731064	1	rs12765847	10	4353808				rs3738725	1	227174210		CABC1	6.36	0.94	0.00	0.34		
CARD9	ILMN-1712532	9	rs42666703	9	139289825		INPP5E		rs684040	1	82128660		INPP5E	5.81	0.81	0.09	0.86	0.42	
CARD9	ILMN-1712532	9	rs45673661	1	6026661				rs4707315	9	139266496		INPP5E	4.61	0.09	0.86	0.42		
CARD9	ILMN-1712532	20	rs1573671	8	8187808				rs7733671	8	96000269		CABC1	5.77	0.23	0.96	0.62		
CARD9	ILMN-1712532	5	rs1319169	18	1732466				rs7733671	5	96000269		CABC1	5.77	0.23	0.96	0.62		
CARD9	ILMN-1712532	5	rs1269264	18	81840122				rs7733671	5	96000269		CABC1	7.06	0.02	2.85	1.75		
CARD9	ILMN-1712532	5	rs12719343	5	125369113				rs7733671	5	96000269		CABC1	7.68	0.36	1.57	1.20	29.369	
CARD9	ILMN-1712532	5	rs1410575	9	78925630				rs7733671	5	96000269		CABC1	6.55	0.13	1.34	0.78		
CARD9	ILMN-1712532	5	rs166644	8	78392770				rs7733671	5	96000269		CABC1	7.01	0.27	0.52	0.37		
CARD9	ILMN-1712532	5	rs17648036	15	2731111				rs7733671	5	96000269		CABC1	7.81	0.97	0.03	0.41		
CARD9	ILMN-1712532	5	rs17818702	11	86107920				rs7733671	5	96000269		CABC1	6.62	1.15	0.59	1.09		
CARD9	ILMN-1712532	5	rs227402	14	70496867				rs7733671	5	96000269		CABC1	6.12	0.11	0.01	0.01		
CARD9	ILMN-1712532	5	rs2822124	21	15166804				rs7733671	5	96000269		CABC1	6.87	0.07	0.33	0.12		
CARD9	ILMN-1712532	5	rs4503014	7	33149140				rs7733671	5	96000269		CABC1	7.24	0.74	0.07	0.33	0.12	
CARD9	ILMN-1712532	5	rs7474890	10	59199078				rs7733671	5	96000269		CABC1	5.88	0.92	1.56	1.72		
CARD9	ILMN-1712532	5	rs7733671	5	96000269		CABC1		rs10802643	1	238120177		CABC1	6.74	0.49	0.12	0.23		
CARD9	ILMN-1712532	5	rs7733671	5	96000269		CABC1		rs12650909	4	170192890		CABC1	7.42	0.75	0.78	0.93		
CARD9	ILMN-1712532	5	rs7733671	5	96000269		CABC1		rs2203733	2	224093101		CABC1	7.42	0.23	0.78	0.50		
CARD9	ILMN-1712532	5	rs7733671	5	96000269		CABC1		rs2641772	3	195531841		CABC1	6.97	0.22	0.87	0.54		
CARD9	ILMN-1712532	11	rs823311	18	66175386				rs541202	11	34447586		CABC1	6.41	0.26	0.26	0.21		
CARD9	ILMN-1712532	11	rs2353203	17	17099980		CDC88B		rs541202	11	64125142		CDC88B	5.68	0.33	0.37	0.32		
CDC88B	ILMN-1772208	11	rs694739	11	64097233				rs12771349	10	96989193		VAMP8	5.62	0.23	0.18	0.14		
CDC88B	ILMN-1772208	7	rs3211834	17	80280117				rs1254900	2	85816334		VAMP8	6.93	0.15	0.01	0.02		
CD36	ILMN-1800540	1	rs1750801	11	76033374		CD93		rs6700168	1	207502534		CD55	5.09	0.08	0.03	0.02		
CD93	ILMN-1704730	20	rs1884655	20	23074375		CD93		rs10255470	7	157182040		CD55	6.06	1.74	0.24	1.20		
CD93	ILMN-1704730	20	rs1884655	20	23074375		CD93		rs4696726	4	7992632		CD55	5.71	0.13	0.80	0.42		
CD93	ILMN-1704730	20	rs1884655	20	23074375		CD93		rs1884655	3	196721395		CD55	5.71	0.04	0.27	0.08		
CD93	ILMN-1704730	20	rs1884655	20	23074375		CD93		rs838875	12	125145394		CD55	5.56	0.04	0.24	1.67	1.16	
CD93	ILMN-1704730	20	rs1884655	20	23074375		CD93		rs9576388	13	38434472		CD55	7.88	0.71	0.22	0.45		
CD93	ILMN-1704730	20	rs268504	20	37771578		CD93		rs1884655	20	23074375		CD93	5.71	0.64	0.75	0.81	14.697	
CD93	ILMN-1704730	20	rs4813479	20	23076914		CD93		rs10925747	1	238899903		CD93	7.43					
CD93	ILMN-1704730	20	rs4813479	20	23076914		CD93		rs2873420	18	136500554		CD93	7.02					
CD93	ILMN-1704730	20	rs4813479	20	23076914		CD93		rs4328531	18	77439542		CD93	6.13					
CD93	ILMN-1704730	20	rs4813479	20	23076914		CD93		rs4789981	17	77264482		CD93	6.08					
CD93	ILMN-1704730	14	rs861544	14	104162263		HOXB2		rs7324744	13	115008038		CD93	5.46	0.21	0.14	0.11		
CD93	ILMN-2339796	13	rs9005940	17	46614102				rs11655031	17	30833162		CD93	5.47	0.95	0.07	0.45		
CD93	ILMN-1730928	19	rs200609	20	51956250				rs4803481	19	42066556		CD93	6.15	0.90	0.12	0.48		
CEACAM21	ILMN-1745949	19	rs8503781	19	142066556		CEACAM21		rs2421050	5	158943044		CEACAM21	6.67	2.16	0.16	1.44		
CEACAM21	ILMN-1703754	18	rs6050480	18	13069782		CEACAM21		rs13132719	4	180265266		CEACAM21	5.75	0.15	0.24	0.12		
CEACAM21	ILMN-1703754	18	rs6050480	18	13069782		CEACAM21		rs13790112	3	134247706		CEACAM21	6.36	0.23	0.10	0.09		
CEACAM21	ILMN-1703754	3	rs3825569	14	101350298		CEACAM21		rs13079012	3	235248562		CEACAM21	5.65	0.72	0.20	0.44		
CEACAM21	ILMN-1703754	16	rs182935	16	55861794		CEACAM21		rs2695290	12	102087844		CEACAM21	5.74	0.92	0.02	0.36		
CEACAM21	ILMN-2202940	12	rs691967	13	38838122		CEACAM21		rs6057578	11	81937002		CEACAM21	4.75	0.92	0.02	0.36		
CEACAM21	ILMN-2202940	12	rs6539014	12	102277782		CEACAM21		rs1313235	12	101322853		CEACAM21	5.55	0.07	1.28	0.67		
CEACAM21	ILMN-1663142	12	rs429790	16	84471642		CEACAM21		rs3903088	10	134266588		CEACAM21	7.54	0.95	0.36	0.73		
CEACAM21	ILMN-2403228	12	rs7305054	16	10156646		CEACAM21		rs6863172	5	175595960		CEACAM21	5.55	0.27	0.07	0.02		
CEACAM21	ILMN-1674609	5	rs17129799	11	96929537		CEACAM21		rs109130	16	631210580		CEACAM21	7.56	0.07	0.07	0.02		
CEACAM21	ILMN-1702890	19	rs3725237	19	1047161		CEACAM21		rs1453208	13	677136633		CEACAM21	6.33	1.92	0.28	1.39		
CEACAM21	ILMN-1694345	8	rs3752327	18	4747161		CEACAM21		rs1453208	13	677136633		CEACAM21	6.33	1.92	0.28	1.39		
CEACAM21	ILMN-1694345	8	rs3752327	18	4747161		CEACAM21		rs1453208	13	677136633		CEACAM21	6.33	1.92	0.28	1.39		
CEACAM21	ILMN-1694345	8	rs3752327	18	4747161		CEACAM21		rs1453208	13	677136633		CEACAM21	6.33	1.92	0.28	1.39		
CEACAM21	ILMN-1694345	8	rs3752327	18	4747161		CEACAM21		rs1453208	13	677136633		CEACAM21	6.33	1.92	0.28	1.39		

0.23 Continued on next page

Expression trait			SNP 1			SNP 2			Interaction statistic / $-\log_{10}$ p-values			Distance / Mb		
Gene ID ^a	Chr.	rs ID	Chr.	Pos / Mb ^c	Association ^d	rs ID	Chr.	Pos / Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^h	
ILMN.1682928	7	rs2353598	21	39202070		rs245884	2	29188475	GPVL	5.55	0.19	0.03	0.04	
ILMN.1813256	2	rs2131290	4	18858908		rs1531133	7	6843631	CRPT	5.47	0.28	0.10	0.12	
ILMN.1737685	20	rs6139887	20	5986234	CRLS1	rs61473927	21	62406408	CRPT	6.18	0.10	0.36	0.15	
ILMN.1767197	21	rs9979356	21	4523074		rs3761385	5	45198355		11.99	25.20	16.72	42.27	
ILMN.1804854	5	rs294943	18	69500505		rs176382	5	138226767	CTNNA1	5.74	0.02	0.41	0.11	
ILMN.1696347	11	rs92457	11	88139983	CTSC	rs7079264	10	108679892		5.74	0.92	0.74	1.03	
ILMN.1696347	11	rs5752236	22	26250645		rs7128352	11	88087357	CTSC	5.84	0.49	0.80	0.73	
ILMN.2242463	11	rs7930237	22	26250645		rs556895	11	88077479		7.16	18.76	15.06	33.53	
ILMN.1651886	4	rs7108734	11	11456027		rs12784396	10	102027407	CWF19L1	5.42	0.21	0.01	0.03	
ILMN.1712305	4	rs2592948	4	129994690		rs888427	2	172368120	CYBRD1	5.89	0.23	0.53	0.34	
ILMN.1712305	9	rs7852475	9	140698856		rs888427	2	172368120	CYBRD1	5.68	0.20	0.02	0.04	
ILMN.2087692	2	rs11257679	2	12318284		rs888427	2	172368120	CYBRD1	5.81	0.39	1.87	1.47	
ILMN.2087692	2	rs6137908	2	23344590		rs888427	2	172368120	CYBRD1	5.53	0.05	0.83	0.36	
ILMN.2087692	2	rs888427	2	172368120	CYBRD1	rs5791849	2	160112881		5.85	0.87	0.10	0.44	
ILMN.1704985	2	rs6021982	2	36571928		rs933994	2	219650616	CYP27A1	5.42	0.29	0.86	0.60	
ILMN.2128428	5	rs7775910	7	110451383		rs835223	5	39381357	DAB2	5.44	0.48	0.41	0.44	
ILMN.1811648	5	rs9900173	17	44111088		rs1343244	6	82076988		9.12	0.60	0.58	0.42	
ILMN.1690982	22	rs5760102	22	24248761	DDT	rs2378341	3	187475208		5.62	0.64	0.05	0.14	
ILMN.1779091	9	rs4937097	9	125962645		rs7042042	9	32451144		5.31	0.61	0.29	0.40	
ILMN.1783906	1	rs140120023	9	137810259	COQ10A	rs2519515	7	88204888		5.47	0.08	0.41	0.16	
ILMN.1783906	1	rs123633827	11	106703727		rs10120023	9	137810259	COQ10A	6.39	0.77	0.02	0.29	
ILMN.1733998	2	rs1519956	12	89482823		rs7566044	2	169960422	DHRS9	6.00	0.06	1.17	0.58	
ILMN.1733998	2	rs1528529	7	147132505		rs7566044	2	169960422	DHRS9	6.48	0.37	0.34	0.32	
ILMN.2384181	2	rs2831914	21	29959453		rs2161037	2	169893419	DHRS9	5.51	0.88	0.04	0.37	
ILMN.2384181	2	rs7661304	4	187776431		rs2161037	2	169893419	DHRS9					

Table S1 – continued from previous page

Gene ID ^a	Expression trait ^b	Chr.	rs ID	Chr.	SNP 1	Pos/Mb ^c	Association ^d	rs ID	Chr.	SNP 2	Pos/Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g	Distance / Mb ^h
HGB2	ILMN-2084825	11	rs12975066	19	35723501		HGB2	rs2855039	11	3271671		HGB2	5.77	0.08	0.13	0.05	
HGB2	ILMN-2084825	11	rs2855039	11	35723501		HGB2	rs2855039	11	3271671		HGB2	5.77	0.08	0.13	0.05	
HGB2	ILMN-2084825	11	rs2855039	11	35723501		HGB2	rs2855039	11	3271671		HGB2	5.77	0.08	0.13	0.05	
HDBA7	ILMN-206186	12	rs2109029	16	6036851		HDBA7	rs4760636	12	48173352		HDBA7	5.98	0.00	0.46	0.10	
HEBP1	ILMN-1802567	12	rs1942719	18	71345613		HEBP1	rs17680635	8	133220622		HEBP1	5.98	0.15	0.59	0.32	
HEXDC	ILMN-1741180	17	rs1942719	18	71345613		HEXDC	rs17680635	8	133220622		HEXDC	5.98	0.15	0.59	0.32	
HLA-DRA	ILMN-2157441	6	rs4896635	14	75346732		HLA-DRA	rs17192	6	32411646		HLA-DRA	5.81	1.61	0.34	1.22	
HLA-F	ILMN-1762861	6	rs11660982	18	75346732		HLA-F	rs2223404	6	32411646		HLA-F	5.94	0.90	0.16	0.52	
HMBX1	ILMN-1720059	8	rs12435486	14	98070849		HMBX1	rs4732890	8	28576221		HMBX1	3.69	1.00	0.47	0.86	
HMBX1	ILMN-1720059	8	rs2837803	21	42112794		HMBX1	rs4732890	8	28576221		HMBX1	6.54	0.92	1.11	1.34	
HMBX1	ILMN-1720059	8	rs4760451	12	127237464		HMBX1	rs8180944	8	28576221		HMBX1	6.62	0.05	0.05	1.01	
HMBX1	ILMN-1720059	8	rs576639	8	132723731		HMBX1	rs8180944	8	28576221		HMBX1	3.80	0.39	3.13	2.52	
HMBX1	ILMN-1720059	8	rs8180944	8	28576639		HMBX1	rs4553956	2	189535772		HMBX1	6.88	3.38	0.33	0.44	
HMBX1	ILMN-1720059	8	rs9321666	13	110897444		HMBX1	rs7810854	7	158276926		HMBX1	5.12	0.34	0.66	0.32	
HMBX1	ILMN-2101920	5	rs6894268	8	179032488		HMBX1	rs4700810	5	178904856		HMBX1	13.38	5.45	0.67	0.37	
HMBX1	ILMN-3194087	1	rs505812	16	88882257		HMBX1	rs4634783	1	22439520		HMBX1	3.51				
HMBX1	ILMN-3194087	1	rs6063164	20	164869000		HMBX1	rs4634783	1	22439520		HMBX1	6.51				
HMBX1	ILMN-3194087	1	rs6062759	12	121228953		HMBX1	rs4634783	1	22439520		HMBX1	6.61				
HMBX1	ILMN-3194087	1	rs7088538	10	101884937		HMBX1	rs4634783	1	22439520		HMBX1	6.48				
IL32	ILMN-1778010	16	rs1354999	16	3115628		IL32	rs4739890	12	131757163		IL32	5.40	0.19	0.50	0.29	
IL32	ILMN-2368530	16	rs7050444	19	2604243		IL32	rs1534999	16	3115628		IL32	5.53	0.69	0.23	0.44	
IL32	ILMN-1815721	7	rs8004124	19	8063771		IL32	rs1271152	7	139383599		IL32	5.58	1.46	0.24	1.35	
IL32	ILMN-1815721	7	rs778355	12	47970693		IL32	rs8180944	8	28576639		IL32	5.64	0.65	0.23	0.33	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644	21	37970693		IL32	rs4242390	11	189655298		IL32	4.74	0.46	0.89	0.77	
IL32	ILMN-1657227	21	rs2186644</														

Table S1 – continued from previous page

[illegible]

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Table S1 – continued from previous page

Expression trait			SNP 1			SNP 2			Interaction statistic ^f / -log ₁₀ p-values			Distance / Mb ^g		
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
NRBF2	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45			
	ILMN-3237385	10	rs6517815	21	19819016		rs7923609	10	65133822	NRBF2	6.11			
	ILMN-1800897	1	rs4852124	2	240680022		rs6585415	1	52343047		6.13			
	ILMN-1767885	18	rs11613438	11	23453482		rs1005901	8	21964378	NUDT18	3.44	0.47	0.05	0.17
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.03	0.46	0.15
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	1.27	1.35	2.03
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.81	3.56	4.13
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.46	0.16	0.14
	ILMN-1668247	12	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.42	0.06	0.14
	ILMN-1767885	18	rs11348608	12	11348608		rs1047944	8	163907467		8.59	0.36	0.00	0.07
OAS1	ILMN-3237385	10	rs6025645</											

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Table S1 – continued from previous page

Gene ID ^a	Expression trait		SNP 1		Pos/Mb ^c	Association ^d	SNP 2		Pos/Mb ^c	Association ^d	Interaction statistic / -log ₁₀ p-values				Distance / Mb ^h
	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g	
REBE	ILMN-1802380	1	rs4982958	14	24987865		rs301819	1	8501786	REBE	5.66	0.61	1.23	1.17	
REBE	ILMN-1802380	1	rs7697290	4	135248366		rs301819	1	8501786	REBE	5.74	0.14	0.10	0.06	
REBE	ILMN-2327795	1	rs11085829	19	13174312		rs301819	1	8501786	REBE	5.12	0.21	0.33	0.21	
REBE	ILMN-2327795	1	rs3852011	3	112844086		rs301819	1	8501786	REBE	5.71	0.08	0.60	0.26	
RNASE6	ILMN-1780533	14	rs11628398	14	8106521	RNASE6	rs7324365	13	100601327		5.48	0.42	0.21	0.26	
RNASE6	ILMN-1780533	14	rs6603134	19	8106521		rs11628398	14	21182800	RNASE6	5.11	0.09	0.22	0.08	
RNPF167	ILMN-1794726	17	rs2382330	17	4875566		rs4848457	13	54668512		4.37				
RNPF167	ILMN-1794726	17	rs400688	17	4839930		rs11706900	3	36348968		5.59				
RNPFEP	ILMN-1738347	1	rs1107121	17	46127549		rs2819365	1	201983242		6.27	0.11	0.30	0.13	
RNPFEP	ILMN-1738347	1	rs8071611	17	67153386		rs2819365	1	201983242		4.32	1.48	0.52	1.28	
RPL13	ILMN-2413278	16	rs352935	16	89648580		rs2965817	16	89513234		4.98	3.79	14.41	17.24	
RPL23AP7	ILMN-2222730	2	rs1401202	16	80320056		rs4849261	2	114450028	RPL23AP7	5.55	0.13	0.73	0.38	
RPL36AL	ILMN-2186933	14	rs3007033	14	50103816		rs17495030	9	138035083		5.46	0.09	0.06	0.02	
RPL36AL	ILMN-2186936	14	rs4900928	14	50020817		rs1502991	6	66137260		5.86	0.32	0.20	0.19	
RPL8	ILMN-1764721	8	rs2958482	8	145984615		rs1619856	1	234585790		4.59	0.10	0.37	0.15	
RPL8	ILMN-1764721	8	rs4143674	20	4741304		rs2958482	8	145984615	RPL8	4.33	0.13	0.45	0.22	
SEC13	ILMN-3297880	3	rs4889214	16	80913946		rs696221	3	10342876	SEC13	6.48				
SEMA4A	ILMN-1702787	1	rs17085428	5	95388015		rs7695	1	156147326	SEMA4A	5.70	0.22	1.73	1.17	
SESN3	ILMN-1694027	11	rs12147460	15	46391793		rs684856	11	94906111	SESN3	5.50	0.02	0.51	0.15	
SESN3	ILMN-1694027	11	rs353591	15	46391793		rs684856	11	94906111	SESN3	5.67	0.31	0.06	0.10	
SESN3	ILMN-1694027	11	rs684856	15	46391793	SESN3	rs7004947	8	134606425		5.60	0.21	0.51	0.31	
SH3BGL2	ILMN-1762764	6	rs10838191	11	43893658		rs1354034	3	56849749	PPBP	5.52	0.70	0.12	0.35	
SH3BGL2	ILMN-1762764	6	rs2545385	5	66383979		rs1354034	3	56849749	PPBP	5.97	0.20	0.51	0.30	
SH3BGL2	ILMN-1762764	6	rs6845304	4	88280592		rs1354034	3	56849749	PPBP	5.23	0.32	0.71	0.53	
SH3BGL2	ILMN-2158336	9	rs1034210	21	18196922		rs17455517	9	131785369	SH3BGL2	7.40	0.22	0.18	0.13	
SIRPG	ILMN-1771801	20	rs1535883	20	1612819	SIRPG	rs6842739	14	60489510		5.74	0.29	0.18	0.17	
SLC22A18	ILMN-2382505	11	rs11673260	19	52181798		rs367035	11	2923826	SLC22A18	5.47	0.09	0.24	0.09	
SLC22A18	ILMN-2382505	11	rs367035	19	52181798	SLC22A18	rs3110874	7	153224179		5.70	0.15	0.10	0.06	
SLC22A18	ILMN-2382505	11	rs367035	11	2923826		rs772054	2	241678528		6.15	0.39	0.13	0.19	
SLC41A3	ILMN-236111	3	rs1912136	11	24616743		rs6771703	3	125801067	SLC41A3	5.88	1.10	0.82	1.24	
SLC45A4	ILMN-1747778	8	rs6985508	8	142337734	SLC45A4	rs7701916	5	174598073		5.95	0.07	0.40	0.40	
SLC46A3	ILMN-1658639	13	rs198005	17	5502091		rs7981190	13	29259349	SLC46A3	5.52	0.09	0.58	0.26	
SMG7	ILMN-1706553	1	rs803259	15	97403923		rs10911353	1	183489203	SMG7	6.52	0.17	0.09	0.06	
SMOX	ILMN-175380	20	rs118315	20	4161500	SMOX	rs11677815	2	65800982		5.68	0.39	0.62	0.52	
SNHG8	ILMN-3309349	4	rs1105321	9	133050233		rs705837	4	119225940	SNHG8	6.11				
SNORD14A	ILMN-1799381	11	rs1520429	15	46259108		rs214097	11	17291499	SNORD14A	6.60	0.29	1.03	0.72	
SNORD14A	ILMN-1799381	11	rs2634462	11	17339127		rs6486334	11	17015557		7.31	10.96	10.96	23.22	
SNORD89	ILMN-3238662	2	rs10445863	2	115929241		rs750783	2	101889306	SNORD89	6.08				
SNORD89	ILMN-3238662	2	rs11605822	11	122986326		rs750783	2	101889306	SNORD89	5.96				
SNORD89	ILMN-3238662	2	rs2135064	5	26778066		rs750783	2	101889306	SNORD89	6.33				
SNUPN	ILMN-1733932	15	rs1346466	21	46376528	SNUPN	rs7185362	16	81888905		6.45				
SNUPN	ILMN-2364535	15	rs1346466	21	46376528		rs1472075	3	193706323		5.59	0.34	0.00	0.06	
SPATA5L1	ILMN-1729179	15	rs1316320	19	41117869		rs1472075	3	193706323	SPATA5L1	5.44				
STARD10	ILMN-1717052	11	rs2221406	13	90174526		rs1006620	15	45652086		5.44				
STYXL1	ILMN-2345142	7	rs4073164	14	104947517		rs17685	7	75616105	STYXL1	5.85	0.67	0.12	0.33	
SULT1A4	ILMN-2336133	16	rs1463965	18	74332954	SULF2	rs392994	4	180439236		5.51	0.46	0.24	0.30	
SULT1A4	ILMN-2336133	16	rs1463965	18	74332954		rs3785354	16	28550667	TUFM	7.05	0.01	0.05	0.00	
SURF6	ILMN-1778032	9	rs2609626	21	40119768		rs3785354	16	28550667	TUFM	7.05				
SURF6	ILMN-1778032	9	rs2609626	21	40119768		rs3118663	9	136281753	SURF6	6.14	0.26	0.16	0.14	
SYTL2	ILMN-2336609	11	rs1375719	13	103410782		rs485485	11	85495269	SYTL2	5.47	0.28	0.31	0.24	
THBS3	ILMN-1804663	1	rs1939875	11	95422867		rs4072037	1	155162087	THBS3	5.55	0.03	0.15	0.03	
THBS3	ILMN-1804663	1	rs8014956	14	20687978		rs2049805	1	155194980	THBS3	5.65	0.31	0.76	0.55	
TIPRL	ILMN-1781457	1	rs2823245	21	16745523		rs1320993	1	168154599	TIPRL	5.22	0.07	0.40	0.15	

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Table S1 – continued from previous page

Gene ID ^a	Expression trait		SNP 1			SNP 2			Interaction statistic / -log ₁₀ p-values				Distance / Mb ^h		
	Probe ID ^b	Chr.	rs ID	Chr.	Pos / Mb ^c	Association ^d	rs ID	Chr.	Pos / Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f		EGCUT ^g	Meta ^g
TMED4	ILMN-1804148	7	rs1940400	11	132389627		rs17725246	7	44581986	TMED4	3.70	0.06	1.34	0.70	
TMEM149	ILMN-1786426	19	rs2839013	21	47248981		rs8106939	19	36219525	TMEM149	8.11	0.16	0.48	0.26	
TMEM149	ILMN-1786426	19	rs7562235	22	27923288		rs8106939	19	36219525	TMEM149	6.79				
TMEM149	ILMN-1786426	19	rs6090518	20	43207005		rs8106939	19	36219525	TMEM149	11.09	0.76			
TMEM149	ILMN-1786426	19	rs807491	19	36268923	SNX26	rs7254601	19	36147315	TMEM149	12.16	81.55	45.78	145.78	0.122
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs10916259	3	13491599	TMEM149	8.12	1.55	3.09	3.07	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs10916259	3	13491599	TMEM149	8.02	0.40	0.99	0.80	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs10916259	3	13491599	TMEM149	8.39	3.61	1.18	3.78	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs1401098	12	128850436	TMEM149	7.37	2.41	1.00	2.52	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs1401098	12	128850436	TMEM149	6.95	0.08	0.07	0.03	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs1557935	18	64268976	TMEM149	6.93	3.06	0.77	2.87	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs17719594	14	90932598	TMEM149	6.21	3.72	3.33	6.00	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs1843357	8	13822381	TMEM149	6.21	3.72	3.33	6.00	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs2351458	4	113317583	TMEM149	7.30	1.57	1.52	2.27	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs2539000	7	147610772	TMEM149	6.70	0.90	0.33	0.19	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs2731711	5	171792273	TMEM149	5.92	0.19	0.33	0.19	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs471728	11	129595460	TMEM149	8.59	0.90	3.62	3.51	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs6718480	2	233790066	TMEM149	8.55	3.31	5.15	7.36	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs6926382	2	161683974	TMEM149	5.80	3.06	8.80	10.72	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs7213338	17	80357420	TMEM149	5.49	0.07	3.14	2.10	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs7914940	1	242889492	TMEM149	6.22	3.36	6.96	9.20	
TMEM149	ILMN-1786426	19	rs8106939	19	36219525	TMEM149	rs9509428	13	214739352	TMEM149	9.44	0.10	5.75	4.47	
TMEM63A	ILMN-1796426	1	rs1254086	13	72890603		rs4149226	13	226027323	TMEM63A	5.60	0.64	0.12	0.32	
TMEM80	ILMN-1708482	11	rs1548475	19	58058246		rs4963126	11	656845	TMEM80	5.79	0.11	0.15	0.07	
TNP03	ILMN-1683811	7	rs1537146	9	4859303		rs10488630	7	128593948	IRF5	5.51	1.03	0.17	0.62	
TNP03	ILMN-1683811	7	rs199793	20	22827303		rs10488630	7	128593948	IRF5	5.52	3.19	1.89	4.09	
TRAZA	ILMN-1731043	7	rs7776572	13	113531675		rs1776572	7	23498358	TRAPPC4	8.23	0.28	0.40	0.29	
TRAPPC4	ILMN-1814650	11	rs1793823	11	7758194		rs3916581	11	118887887	TRAPPC4	5.51	0.93	0.01	0.36	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs10059004	4	166970604	TRAPPC5	5.52	0.31	1.60	1.07	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs1023095	8	132022957	TRAPPC5	6.92	0.37	0.87	0.68	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs1375714	6	156404902	TRAPPC5	7.79	0.12	0.18	0.08	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs1393299	1	242329791	TRAPPC5	6.43	0.63	0.47	0.59	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs17763599	19	23694415	TRAPPC5	6.38	0.21	0.24	0.16	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs17763599	19	23694415	TRAPPC5	6.51	0.50	0.34	0.44	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs4968328	17	57495457	TRAPPC5	6.51	0.28	0.40	0.25	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs7313362	12	129644342	TRAPPC5	7.08	0.04	0.65	0.25	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs7694997	4	9947811	TRAPPC5	5.86	0.20	0.36	0.22	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs8600935	7	146690926	TRAPPC5	6.27	0.15	0.33	0.16	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs856638	14	85439550	TRAPPC5	6.73	0.24	0.07	0.08	
TRAPPC5	ILMN-2372639	19	rs380708	22	22740855		rs17159840	19	7758194	TRAPPC5	7.58	0.85	0.78	1.01	
TRAPPC5	ILMN-2372639	19	rs3916995	19	45128454		rs17159840	19	7758194	TRAPPC5	7.73	0.51	0.55	0.56	
TRAPPC5	ILMN-2372639	19	rs6040514	20	11272861		rs10179572	19	7758194	TRAPPC5	8.10	0.14	0.02	0.02	
TRAPPC5	ILMN-2372639	19	rs7246264	19	7762978		rs10179572	19	7758194	TRAPPC5	6.71	0.14	0.26	0.13	
TRAPPC5	ILMN-2372639	19	rs7246264	19	7762978		rs12921440	16	30408705	TRAPPC5	7.34	0.06	0.86	0.40	
TRAPPC5	ILMN-2372639	19	rs7246264	19	7762978		rs963354	3	157393770	TRAPPC5	7.05	0.08	0.90	0.69	
TREM1	ILMN-1688231	6	rs10862975	12	85749398		rs963354	3	157393770	TREM1	5.42	0.11	0.25	0.11	
TREM1	ILMN-1688231	6	rs10862975	12	85749398		rs2395771	6	41264577	TREM1	5.42	0.11	0.25	0.11	
TREM1	ILMN-1688231	6	rs12412964	10	108256422		rs2395771	6	41264577	TREM1	5.92	1.20	1.23	1.69	
TSPAN32	ILMN-1785060	10	rs2527180	7	158808416		rs10748526	10	82274369	TSPAN32	6.46	0.04	0.91	0.39	
TSPAN32	ILMN-1785060	10	rs968726	17	17194634	MYBPC3	rs10748526	10	82274369	TSPAN32	5.01	0.07	0.18	0.06	
TSPAN32	ILMN-1785060	10	rs968726	17	17194634	MYBPC3	rs10748526	10	82274369	TSPAN32	5.01	0.07	0.18	0.06	
TSPAN32	ILMN-1785060	10	rs10838738	11	47663049	TSPAN32	rs12800098	11	2317951	TSPAN32	5.51				
TSPAN32	ILMN-2389070	11	rs12800098	11	2317951	TSPAN32	rs12800098	11	2317951	TSPAN32	5.51				
TYP	ILMN-323126	22	rs140522	22	50971266	ECGF1	rs1198819	2	238746880	TYP	6.34				
TYP	ILMN-323126	22	rs470119	22	50966914	ECGF1	rs4783126	16	85147633	TYP	6.13				

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Table S1 – continued from previous page

Expression trait			SNP 1			SNP 2			Interaction statistic / -log ₁₀ p-values						
Gene ID ^a	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g	Distance / Mb ^h
UBASH3A	LMN-2338348	21	rs1893592	21	4385067	UBASH3A	rs7201194	16	83600397		5.91	0.59	0.42	0.52	
UBASH3A	LMN-2338348	21	rs1893592	21	4385067	UBASH3A	rs7512594	1	214514361		6.01	0.48	1.29	1.10	
USP36	LMN-1697227	17	rs2279308	17	76794981	USP36	rs22725546	17	75151717		5.71	0.03	0.14	0.03	1.643
VASP	LMN-1743646	19	rs1264226	19	40063167		rs2276470	19	45974668	VNN2	5.09	0.94	5.14	4.95	0.088
VNN2	LMN-1678939	6	rs10435352	7	103252718		rs1883613	6	133077063	VNN2	5.64	0.84	0.15	0.46	
VNN2	LMN-1678939	6	rs13044386	20	9116155		rs1883617	6	133072650	VNN2	5.44	0.39	0.69	0.57	
VNN2	LMN-1678939	6	rs134447	22	49927332		rs1883617	6	133072650	VNN2	5.72				
VNN3	LMN-1678939	6	rs216495	11	16834510		rs1883617	6	133072650	VNN2	5.77	0.33	0.19	0.19	
VNN3	LMN-1678939	6	rs10278073	7	151662184		rs2267932	6	133067782	VNN3	6.44	0.16	0.74	0.41	
VNN3	LMN-1804935	6	rs1443946	8	73006453		rs2267932	6	133067782	VNN3	5.74	0.23	0.48	0.31	
VNN3	LMN-1804935	6	rs348462	9	73547169		rs2267952	6	133067782	VNN3	6.44	0.31	0.17	0.17	
VNN3	LMN-1804935	6	rs7157055	14	83262064		rs2267952	6	133067782	VNN3	5.82	0.03	0.19	0.04	
VNN3	LMN-2387680	6	rs2823165	21	5694253		rs2267952	6	133067782	VNN3	6.12	0.73	1.15	1.21	
VNN3	LMN-2387680	6	rs9596457	13	51692548		rs2267952	6	133067782	VNN3	4.83	0.46	0.05	0.16	
VSTM1	LMN-1763455	19	rs10500316	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	rs9625870	19	34553697		rs10500316	19	54553697	VSTM1	5.88	0.81	1.38	1.47	
WDR48	LMN-1762103	3	rs1388935	4	18827822		rs6778963	3	39091812	WDR48	5.88	0.09	0.33	0.09	
WDR48	LMN-1762103	3	rs1887778	4	134635088	RAPGEF1	rs853349	3	39067325	WDR48	5.34	0.57	1.35	1.22	
WDR48	LMN-1762103	3	rs9554833	13	102624790		rs7619193	3	39044116	WDR48	5.85	0.18	0.61	0.35	
WDR6	LMN-1669484	3	rs12362253	11	123571708		rs17715581	3	49194351	WDR6	4.86	1.64	1.43	2.25	
XAF1	LMN-2330573	17	rs1535031	21	9673170	XAF1	rs12591171	15	93119799		5.48	2.38	0.17	1.63	
ZFP90	LMN-1684628	16	rs909446	17	37040648		rs182968	16	68573945	ZFP90	5.79	0.09	0.36	0.15	
ZNF500	LMN-1700238	16	rs4282723	22	48283177		rs2290560	16	4799041	ZNF500	5.29	0.67	0.27	0.46	
ZYX	LMN-1701875	7	rs6056281	20	8935312		rs2242601	7	143093824	ZYX	6.04	0.26	0.01	0.05	

^a Phenotypes are expression levels of RefSeq Genes^b Illumina probe ID used to measure gene expression^c Physical SNP position in base pairs (HG19)^d RefSeq Gene ID of gene expression level that is influenced by the SNP (BSGS discovery dataset, significance threshold = 1.29 × 10⁻¹¹)^e Interaction - log₁₀ p-value from discovery dataset^f Interaction - log₁₀ p-value from replication dataset^g Interaction - log₁₀ p-value from meta analysis of replication datasets only^h Distance in Mb between interacting SNPs for *cis-cis* acting SNP pairsⁱ p-values are absent if the interaction did not pass the QC filtering in the replication dataset^j Meta analysis p-values are absent if the interaction did not pass the QC filtering in either replication dataset

Table S2: **Estimation of additive and non-additive variance components from pedigree information** Taken from previous analysis in Powell et al 2013²²

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

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

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

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

^b Number of tests for concordance

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

^d Observed number of concordant cases

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

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

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

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

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

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

^b Number of tests for concordance.

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

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

Table S5: Details on linkage disequilibrium and relative positions of all discovery interactions with SNPs on the same chromosome

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