

1 Detection and replication of epistasis influencing
2 transcription in humans

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Abstract

Epistasis is the phenomenon whereby a polymorphism's effect on a trait depends on other polymorphisms present in the genome. The extent to which epistasis influences complex traits¹ and contributes to their variation^{2,3} is a fundamental question in evolution and human genetics. Though epistasis has been demonstrated in artificial gene manipulation studies in model organisms,^{4,5} and examples have been reported in other species,⁶ few convincing examples with independent replication exist for epistasis amongst natural polymorphisms in human traits.^{7,8} Its absence from empirical findings may simply be due to its low incidence in the genetic control of complex traits,^{2,3} but an alternative view is that it has previously been too technically challenging to detect due to statistical power and computational issues.⁹ Here we show that, using advanced computation techniques¹⁰ and a gene expression study design, many instances of epistasis are found between common single nucleotide polymorphisms (SNPs). In a cohort of 846 individuals with data on 7339 gene expression levels in peripheral blood, we found 501 significant pairwise epistatic interactions between common SNPs acting on the expression levels of 238 genes ($p < 2.91 \times 10^{-16}$). Replication of these 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 $p < 0.05/501$. There was evidence of functional enrichment for the interacting SNPs, for instance 44 of the genetic interactions are located within 5Mb of regions of known physical chromosome interactions¹³ ($p = 1.8 \times 10^{-10}$). Epistatic networks of three SNPs or more influence the expression levels of 129 genes, whereby one *cis*-acting SNP is modulated by several *trans*-acting SNPs. For example MBNL1 is influenced by an additive effect at rs13069559 which itself is masked by *trans*-SNPs on 14 different chromosomes, with nearly identical genotype-phenotype (GP) maps for each *cis-trans* interaction. This study presents the first evidence for multiple instances of 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 associations.¹⁴ But to date, though its contribution to phenotypic variance is frequently the subject of debate,¹⁻³ there is little empirical exploration of the role that epistasis plays in the architecture of complex traits in humans.^{7,8} Beyond the prism of human association studies there is evidence for epistasis, not only at the molecular scale from artificially induced mutations⁴ but also at the evolutionary scale in fitness adaptation¹⁵ and speciation.¹⁶

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

duced statistical power. For example increased dependence on linkage disequilibrium (LD) between causal SNPs and observed SNPs,^{17,18} increased model complexity in fitting interaction terms,¹⁹ and more extreme significance thresholds to account for increased multiple testing⁹ all make it more difficult to detect epistasis in comparison to additive effects. Thus, when combined with small genetic effect sizes, as is expected in most complex traits of interest,¹⁴ the power to detect epistasis diminishes rapidly. There are two simple ways to overcome this problem. One is by using extremely large sample sizes;²⁰ another is by analysing traits that are likely to have large effect sizes among common variants. Because our focus was to ascertain the extent to which instances of epistasis 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 heritable.²¹ But unlike complex diseases, genetic associations with gene expression commonly have very large effect sizes that explain large proportions of the genetic variance,²² 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 (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 ($A1$, $A2$, $D1$, $D2$, $A \times A$, $A \times D$, $D \times A$, $D \times D$) and tested for concordance of the sign of the most significant effect (Supplementary Table S3, Methods). Sign concordance between the discovery and both replication datasets was observed in 22 out of the 30 significantly replicated interactions (expected value = 7.5 under the null hypothesis of no interactions, $p = 3.76 \times 10^{-8}$).

In addition, using the meta analysis from the replication samples only, we

113 observed that 316 of the remaining 404 discovery SNP pairs had replication
 114 interaction p -values more extreme than the 2.5% confidence interval of the
 115 quantile-quantile plot against the null hypothesis of no interactions where p -
 116 values are assumed to be uniformly distributed ($p \ll 1.0 \times 10^{-16}$, Figure 2 and
 117 Supplementary Figure S2). Concordance of the direction of the effect of the
 118 largest variance component was also highly significant ($p = 5.71 \times 10^{-31}$, Sup-
 119plementary Table S3). The congruence of the epistatic networks in discovery
 120 and replication datasets is shown in Figure 3, demonstrating that these com-
 121 plex genetic patterns are common even across independent datasets. A further
 122 replication was attempted using the Centre for Health Discovery and Wellbeing
 123 (CHDWB) dataset,²⁴ but only 20 of the SNP pairs passed filtering because the
 124 sample size was small ($n = 139$), and likely due to insufficient power we found
 125 no evidence for replication (Supplementary Figure S6).

126 It should be noted that although it is a necessary step to establish the
 127 veracity of the interactions from the discovery set, replication of epistasis is
 128 difficult in practice. For example, LD between causal variants and observed
 129 markers plays an important role. Not only is the dependence on LD much
 130 greater for epistatic effects than for additive effects (Supplementary Figure S7),
 131 but when estimating epistatic variance it is more sensitive to changes in LD
 132 between observed SNPs and causal variants between independent samples when
 133 compared to additive effects (Supplementary Figure S8). This has a direct effect
 134 on statistical power for replication. The sampling variance of LD r leads to the
 135 ascertainment of marker associations with higher sample r in the discovery stage
 136 in comparison to the replication stage. However, the average decrease in \hat{r}^x in
 137 replication samples becomes larger as x increases (Methods, Supplementary
 138 Figure S9). For example, the decrease in \hat{r}^8 (which is proportional to the power
 139 of detecting $D \times D$ effects), is on average three fold greater than the decrease in
 140 \hat{r}^2 (which is proportional to the power of detecting additive effects).

141 Though seldom the focus of association studies, SNPs with known main
 142 effects are often tested for additive \times additive genetic interactions,⁹ but our
 143 analysis shows that this is unlikely to be the most effective strategy for its
 144 detection. The majority of our discovery interactions comprised of one SNP
 145 that was significantly associated with the gene expression level in the discov-
 146 ery dataset, and one SNP that had no previous association²² (439 out of 501,
 147 Methods). Only nine interactions were between SNPs that both had known
 148 main effects while 64 were between SNPs that had no known main effects. Ad-
 149 ditionally, we observed that the largest epistatic variance component for the
 150 501 interactions was equally divided amongst additive \times additive, additive \times
 151 dominance, dominance \times additive and dominance \times dominance at the discovery
 152 stage ($p = 0.22$ for departure from expectation). This is not surprising because
 153 the patterns of epistasis used for statistical decomposition (*i.e.* $A \times A$, $A \times D$,
 154 $D \times A$, $D \times D$) are simply convenient orthogonal parameterisations of a two
 155 locus model, and are not intended to model biological function.²⁵

156 Of the discovery interactions, 26 were *cis-cis* acting (within 1Mb of the
 157 transcription start site, mean distance between SNPs was 0.53Mb), 462 were
 158 *cis-trans*-acting, and 13 were *trans-trans*-acting. We observed a wide range of

159 significant GP maps (Figure 1) but the most common pattern of epistasis that
 160 we detected involved a *trans*-SNP masking the effect of an additive *cis*-SNP. For
 161 example, MBNL1 (involved in RNA modification and regulation of splicing²⁶)
 162 has a *cis* effect at rs13069559 which in turn is controlled by 13 *trans*-SNPs and
 163 one *cis*-SNP that each exhibit a masking pattern, such that when the *trans*-
 164 SNP is homozygous for the masking allele the decreasing allele of the *cis*-SNP
 165 no longer has an effect (Supplementary Figure S10). Each of these interac-
 166 tions has evidence for replication in at least one dataset and six are significantly
 167 replicated at the Bonferroni level (Supplementary Figure S3). We see similar
 168 epistatic networks involving multiple (eight or more) *trans*-acting SNPs for other
 169 gene expression levels too, for example TMEM149 (Supplementary Figure S11),
 170 NAPRT1 (Supplementary Figure S12), TRAPPC5 (Supplementary Figure S13),
 171 and CAST (Supplementary Figure S14). We observed that from pedigree anal-
 172 ysis these five gene expression phenotypes had non-additive variance component
 173 estimates within the 95th percentile of the 17,994 gene expression phenotypes
 174 that were analysed previously²² (Supplementary Table S2, Methods).

175 In total the 501 interactions comprised 781 unique SNPs, which we analysed
 176 for functional enrichment (Methods). We tested the SNPs for cell-type specific
 177 overlap with transcriptionally active chromatin regions, tagged by histone-3-
 178 lysine-4,tri-methylation (H3K4me3) chromatin marks, in 34 cell types²⁷ (Sup-
 179 plementary Figure S5). There was significant enrichment for *cis*-acting SNPs
 180 in haematopoietic cell types only ($p < 1 \times 10^{-4}$ for the three tissues with the
 181 strongest enrichment after adjusting for multiple testing). However *trans*-acting
 182 SNPs did not show any tissue specific enrichment ($p > 0.1$ for all tissues). This
 183 difference between *cis* and *trans* SNPs suggests different roles in epistatic in-
 184 teractions where tissue specificity is provided by the *cis* SNPs. There is also
 185 enrichment for *cis*-SNPs to be localised in regions with regulatory genomic fea-
 186 tures as measured by chromatin states²⁸ (Supplementary Figure S4).

187 We also demonstrate physical organisation of interacting loci within the cell,
 188 suggesting a mechanism by which biological function can lead to epistatic ge-
 189 netic variance. It has been shown that different chromosomal regions spatially
 190 colocalise in the cell through chromatin interactions.¹³ We cross-referenced our
 191 epistatic SNPs with a map of chromosome interacting regions ($n = 96,139$)
 192 in K562 blood cell lines²⁹ (Methods) and found that 44 epistatic interactions
 193 mapped to within 5Mb ($p < 1.8 \times 10^{-10}$), (Supplementary Figure S15). Inter-
 194 action of distant loci may occur through physical proximity in transcriptional
 195 factories that organise across different chromosome regions and can regulate
 196 transcription of related genes.^{30,31}

197 Though we present many instances of epistasis, quantifying its relative im-
 198 portance to complex traits in humans remains an open question. In this study
 199 we are able to identify 238 gene expression traits with at least one significant
 200 interaction given our experiment-wide threshold, where the minimum estimated
 201 variance explained by the epistatic effects of any interaction was 2.1% of phe-
 202 notypic variance. Taking results from our previously published eQTL²³ we
 203 calculated that 1848 of the 7339 gene expression levels analysed were influenced
 204 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 explain.² Ideally one would approach this question from a whole genome perspective³² but this is intractable for non-additive variance components. Nevertheless, some inference can be made from the ascertained effects in these analyses and it is evident that estimated additive variance is overall a larger component than estimated epistatic variance, as has been argued previously.^{2,3} 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. 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. This is due to differences in the rate of decay of the estimate of the genetic variance of the causal SNPs as LD decreases with the observed SNPs. And forthly, the extent of winner’s curse in estimation of effect sizes may differ between the the two studies.

Overall, we have demonstrated that it is possible to identify and replicate epistasis in complex traits amongst common human variants, despite the relative contribution of pairwise epistasis to phenotypic variation being small. The bioinformatic analysis of the significant epistatic loci suggests that there are a large number of possible mechanisms that can lead to non-additive genetic variation. Further research into such epistatic effects may provide a useful framework 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 dataset,²³ which comprises 846 individuals who are genotyped at 528,509 autosomal SNPs. Each individual had gene expression levels measured in peripheral blood at 47,323 probes. Only the probes that passed quality control and had significant expression in $\geq 90\%$ of individuals were used in the analysis (7,339 probes representing 6,158 RefSeq genes). Recent hardware and software¹⁰ advances that use graphics processing units (GPUs) made it possible to perform the 1.03×10^{15} statistical tests to complete this analysis. We used permutation analysis³³ to calculate an experiment-wide significance threshold of $T_e = 2.91 \times 10^{-16}$ at the 5% family-wise error rate (FWER). SNP pairs were modelled for

249 full genetic effects, including marginal additive and dominance at both SNPs
 250 plus four interaction terms. Though we could have used a less complex model to
 251 improve statistical efficiency, we deemed it important to be agnostic about the
 252 type of epistasis that might exist, and therefore chose not to over-parameterise
 253 the test.^{18,19} Because there are many large marginal effects present in these data
 254 it was necessary to perform several filtering steps to exclude SNP pairs that were
 255 significant due to marginal effects alone. All SNP pairs with LD $r^2 > 0.1$ and
 256 $D'^2 > 0.1$ were removed to minimise the possibility of haplotype effects. All
 257 SNP pairs were required to have at least five data points in all nine genotype
 258 classes. If multiple SNP pairs were present on the same chromosomes for a
 259 particular expression trait then only the sentinel SNP pair was retained. Finally,
 260 a nested test contrasting the full genetic model against the marginal additive
 261 and dominance model was performed for each remaining SNP pair (Methods),
 262 resulting in 501 significant interactions after Bonferroni correction for multiple
 263 testing of the filtered SNPs. The 501 significant SNP pairs were carried forward
 264 for replication in two independent datasets that used the same expression assays
 265 for analysing transcription in peripheral blood, the Fehrmann dataset¹² ($n =$
 266 1240) and the Estonian Genome Centre University of the University of Tartu
 267 (EGCUT) dataset¹¹ ($n = 891$). Of these, 434 passed filtering in both replication
 268 datasets. A meta analysis on the interaction p -values from each replication
 269 dataset was performed to provide an overall replication statistic for each putative
 270 interaction.

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Tables

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

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

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

² Discovery dataset

³ Independent replication dataset

⁴ Meta analysis of interaction terms between replication datasets only

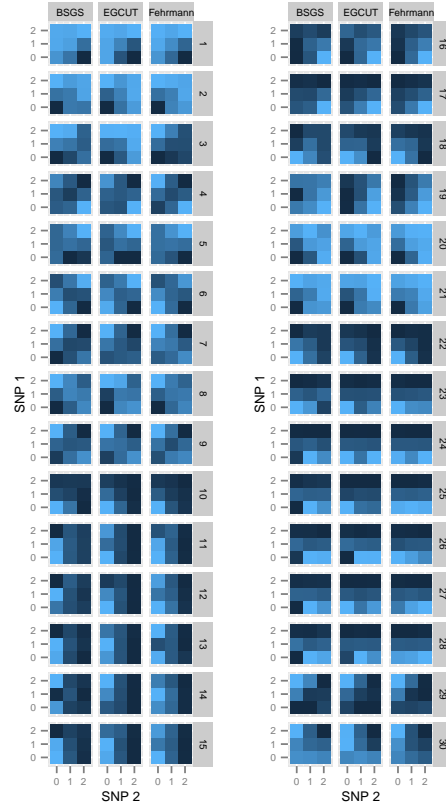


Figure 1: Replication of GP maps in two independent populations
 The GP maps for each epistatic interaction that is significant at the Bonferroni level in both replication datasets are shown. Each GP map consists of nine tiles where each tile represents the expression level for that two-locus genotype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

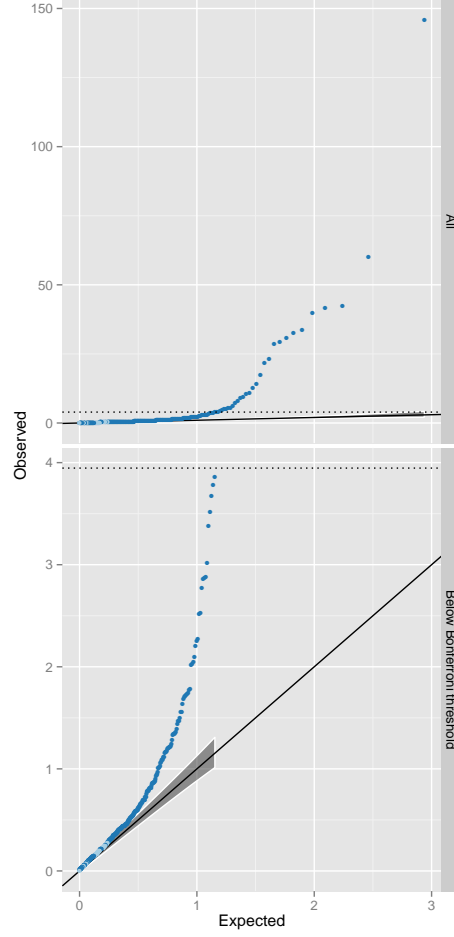


Figure 2: **Q-Q plots of interaction p -values from replication datasets** The top panel shows all 434 discovery SNPs that were tested for interactions. Observed p -values (y -axis, $-\log_{10}$ scale) are plotted against the expected p -values (x -axis, $-\log_{10}$ scale). The multiple testing correction threshold for significance following Bonferroni correction is denoted by a dotted line. The bottom panel shows the same data as the top panel but excluding the 30 interactions that were significant at the Bonferroni level in the replication datasets. The shaded grey area represents the 5% confidence interval for the expected distribution of p -values. Dark blue points represent p -values that exceed the confidence interval, light blue are within the confidence interval.

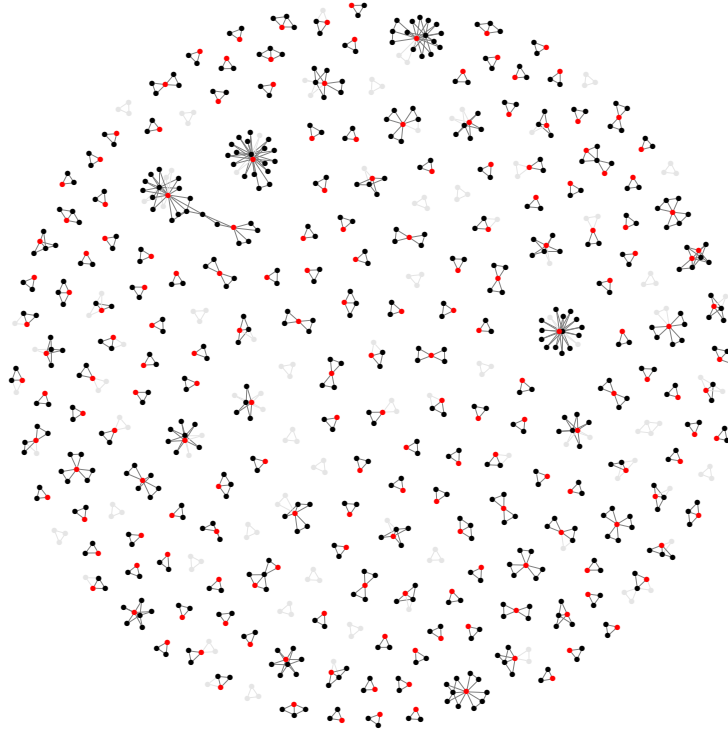


Figure 3: **Discovery and replication of epistatic networks** All 434 putative genetic interactions (edges) with data common to discovery and replication sets is shown, where black nodes represent SNPs and red nodes represent traits (gene expression probes). Three hundred and forty-five interactions had p -values exceeding the 2.5% confidence interval following meta analysis of the replication data. The remaining 89 interactions that did not replicate are depicted in grey. It is evident that a large proportion of the complex networks identified in the discovery set also exist in independent populations.

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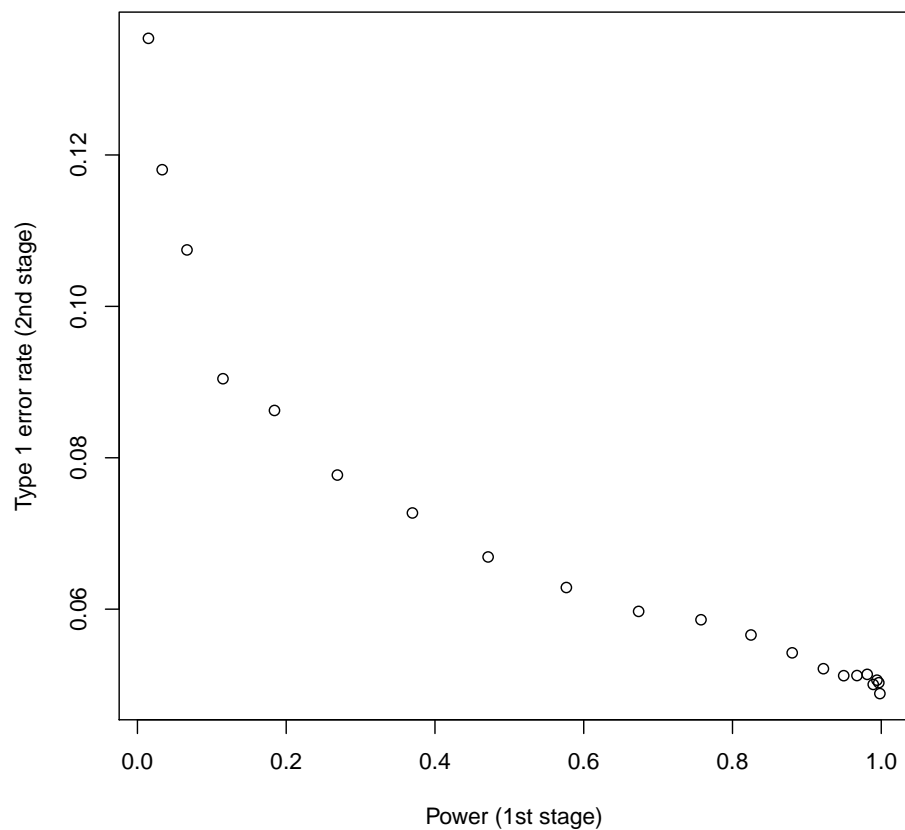


Figure S1: **Type 1 error rate of two stage design assuming a null model of one large additive effect and no epistasis** In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These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

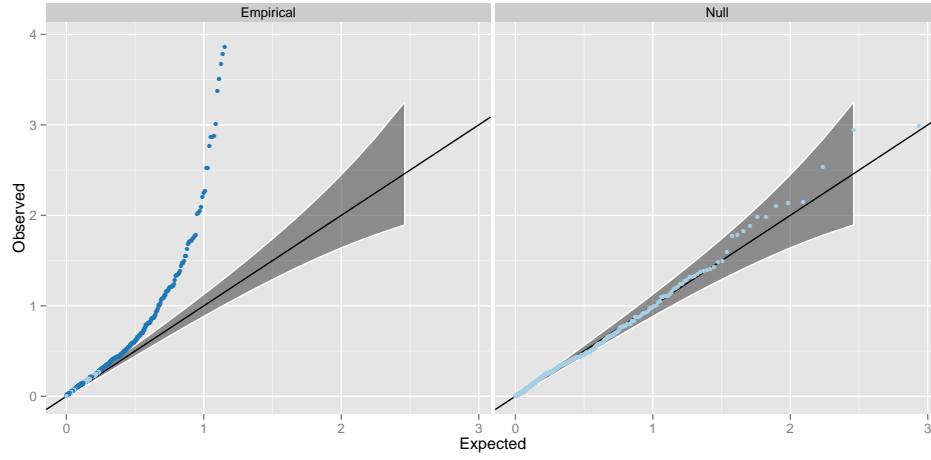


Figure S2: **Q-Q plots of interaction p -values from replication datasets, excluding the 30 points significant at the Bonferroni level** The right panel (Null) shows the interaction p -values from a meta analysis across two independent datasets on 434 randomly drawn SNP pairs. The left panel (Empirical) shows the interaction p -values from the 404 putative interactions that were not significant at the Bonferroni correction threshold. Dark blue points represent p -values that surpass the 2.5% FDR level, as in Figure 2.

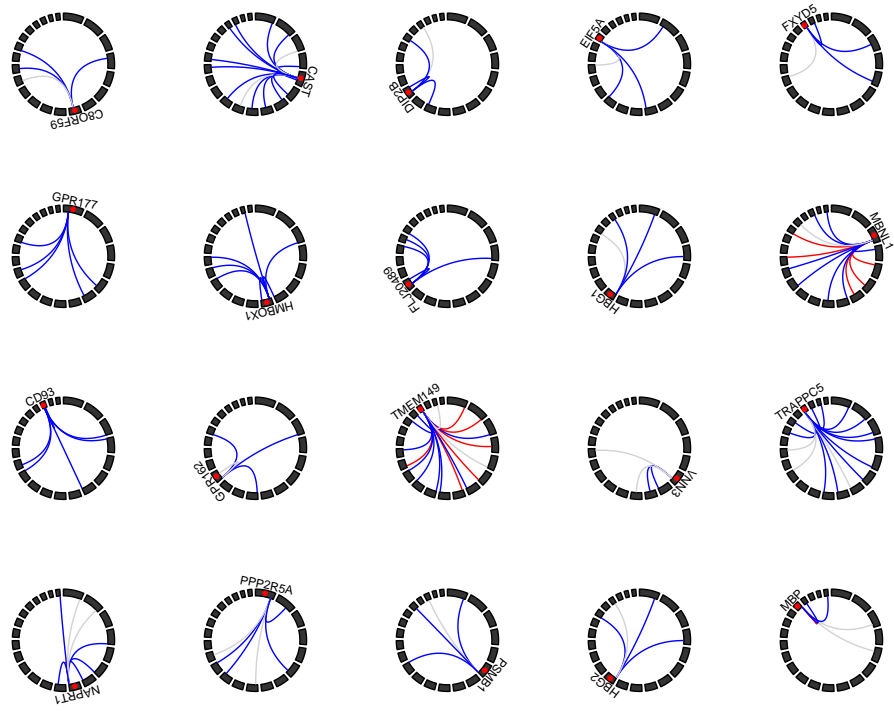


Figure S3: **Gene expression traits with four or more genetic interactions** Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent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

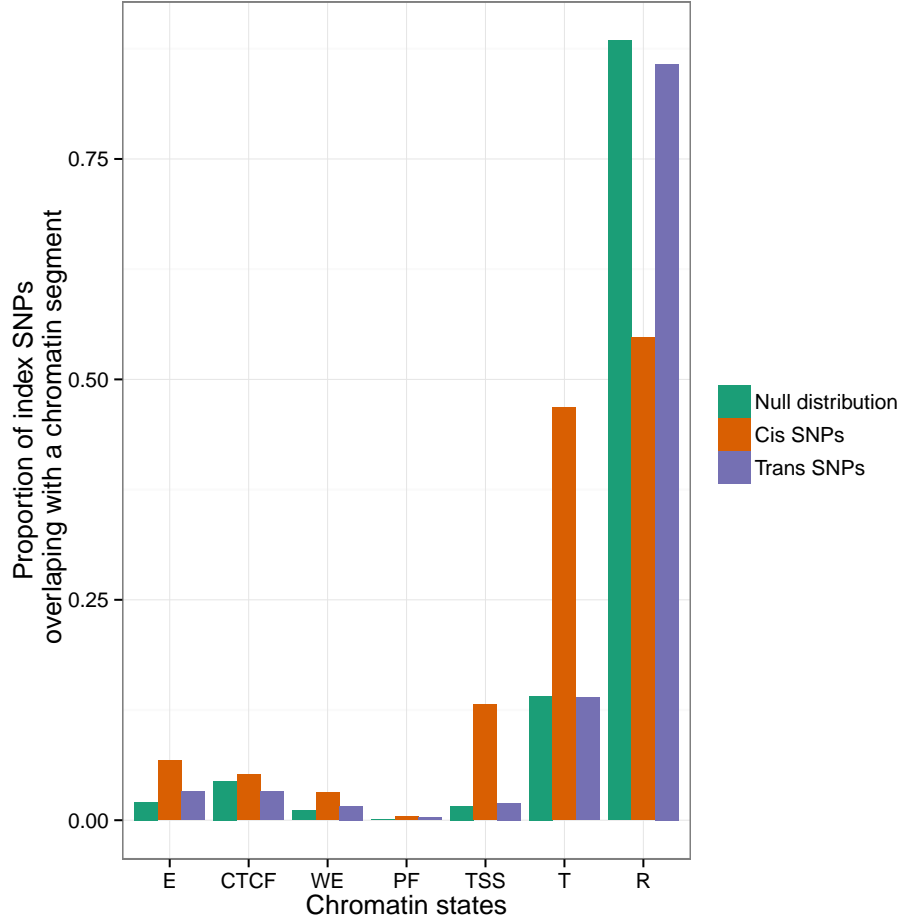


Figure S4: **Location of SNPs relative to genomic features** We used chromatin segmentation²⁸ as a method for labelling genomic features. All SNPs within 1Mb and $r^2 > 0.8$ of each *cis*- and *trans*-SNP were taken to find which genomic features (x -axis) were covered by the SNPs that compose the 501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

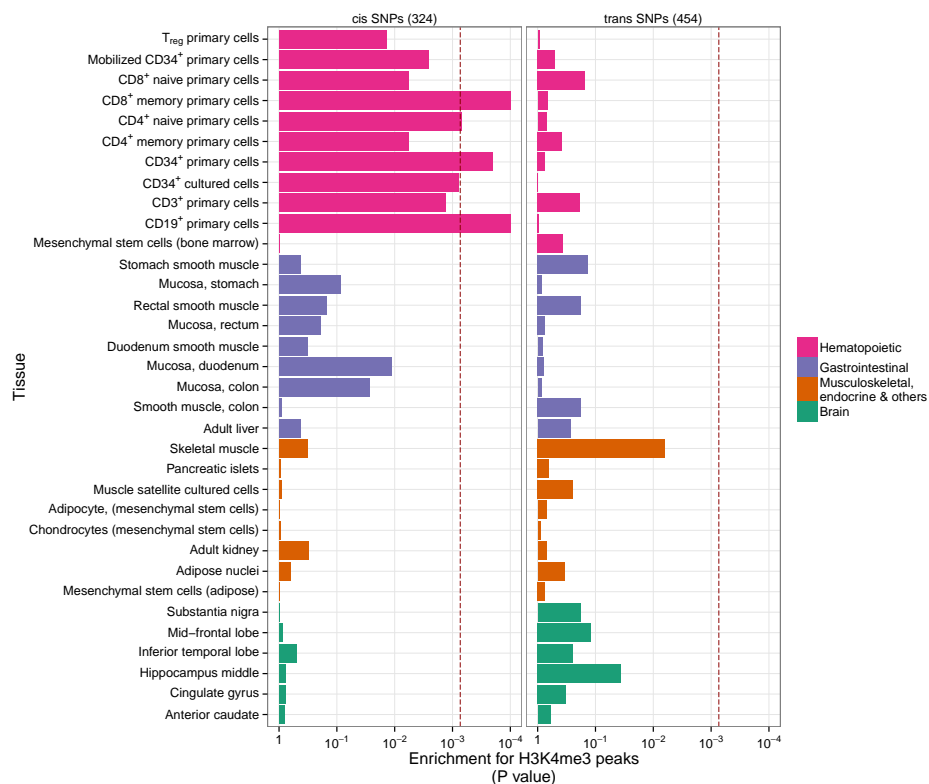


Figure S5: Tissue specific enrichment of SNPs in transcriptionally active regions The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3.²⁷ Enrichment p -values are calculated using permutation analysis for 34 different cell types (y -axis) in four tissue types (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.

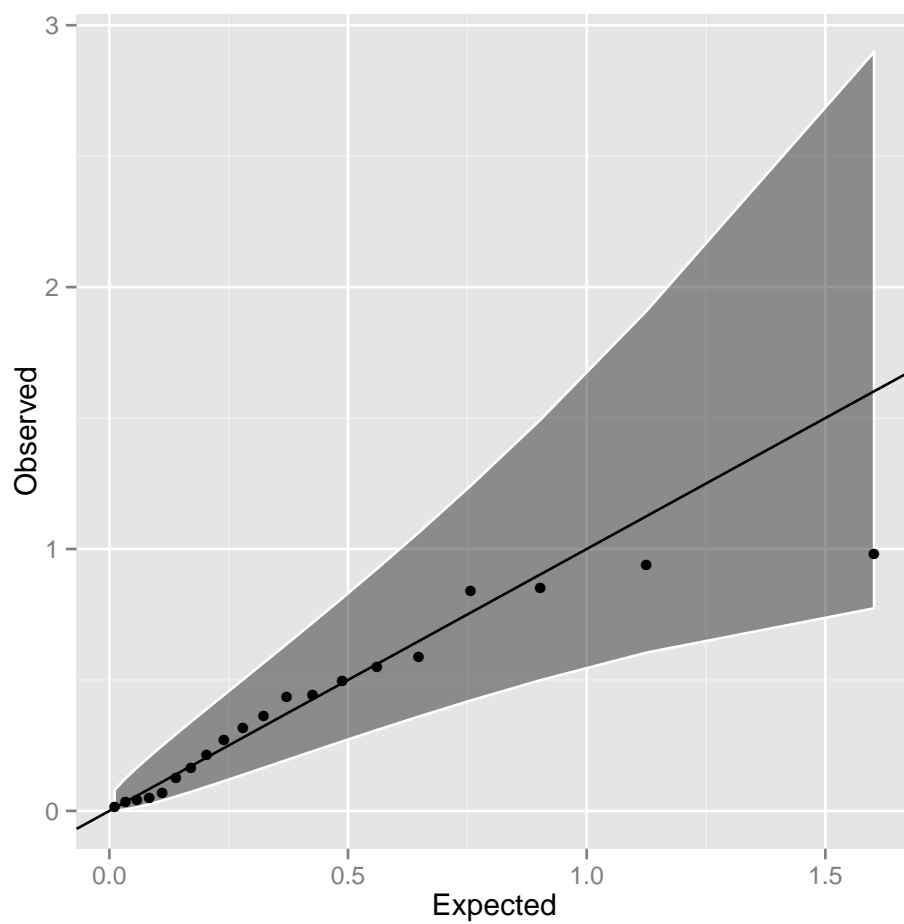


Figure S6: **Q-Q plot of interaction p -values in the CDHWB dataset**
 Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset (mainly due to small sample size). There is no evidence for enrichment of interaction terms, most likely due to insufficient power given the limited sample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

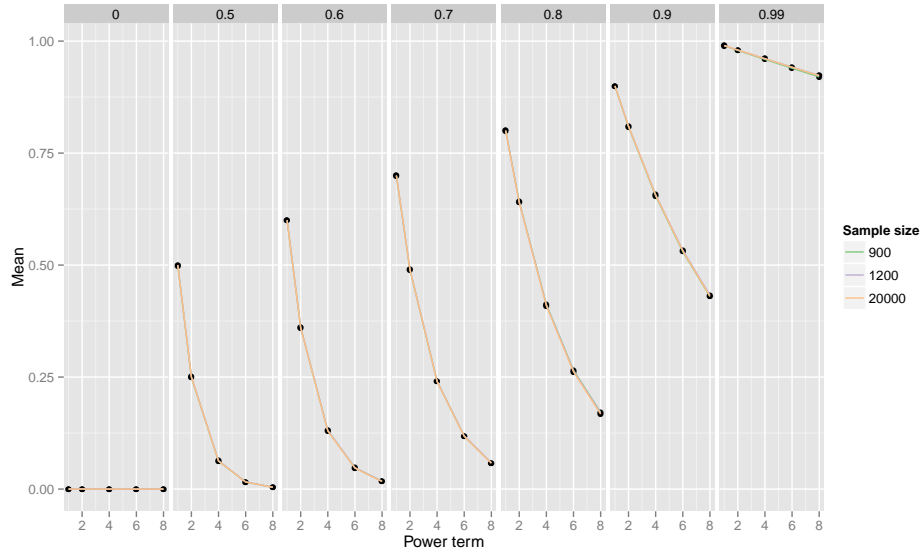


Figure S7: **Sampling mean for different power terms of population r values** Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8 . For a given population value of LD r (columns of plots), plotted is the sample 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 .

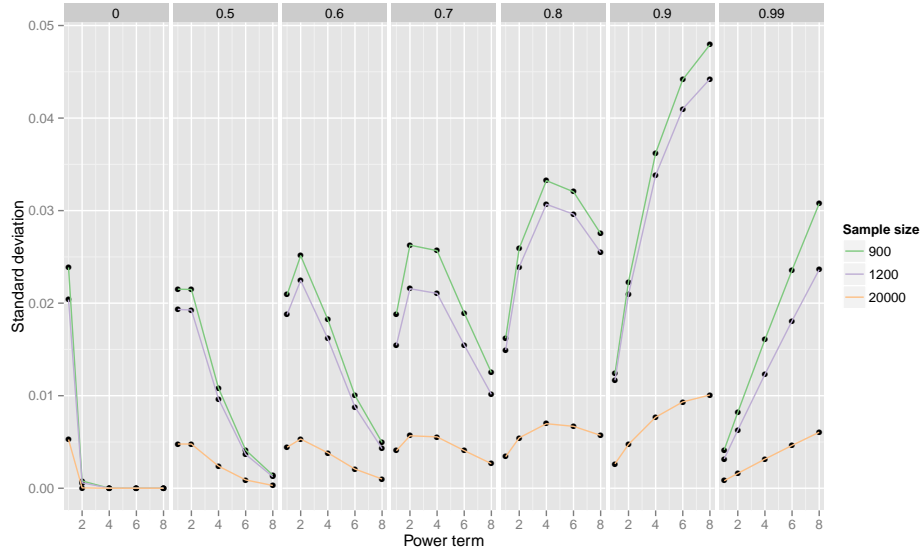


Figure S8: Sampling standard deviation for different power terms of population r values Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8 . For a given a population value of LD r (columns of plots), plotted 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.

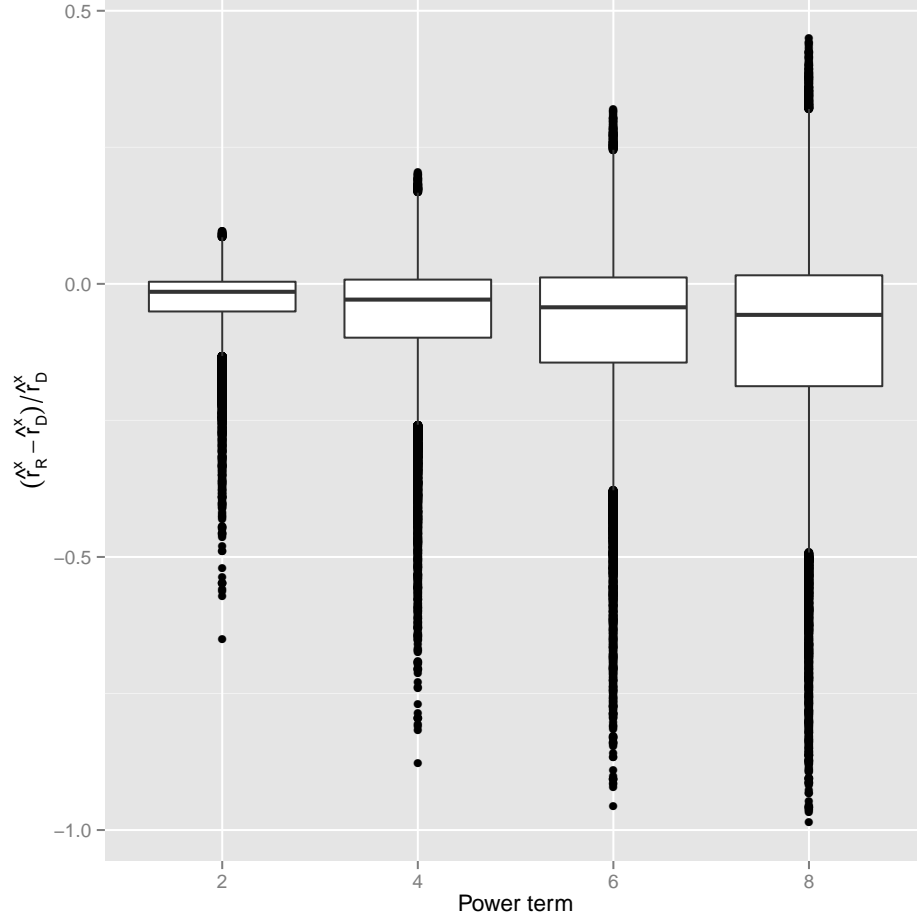


Figure S9: **Reduction in LD as estimated in replication data after ascertaining for high LD in discovery data** 100,000 “unobserved” causal variants (CVs) were tested for LD against a panel of 528,509 “observed” discovery markers (DMs). DM/CV pairs with LD $r^2 > 0.9$ were then tested in an independent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

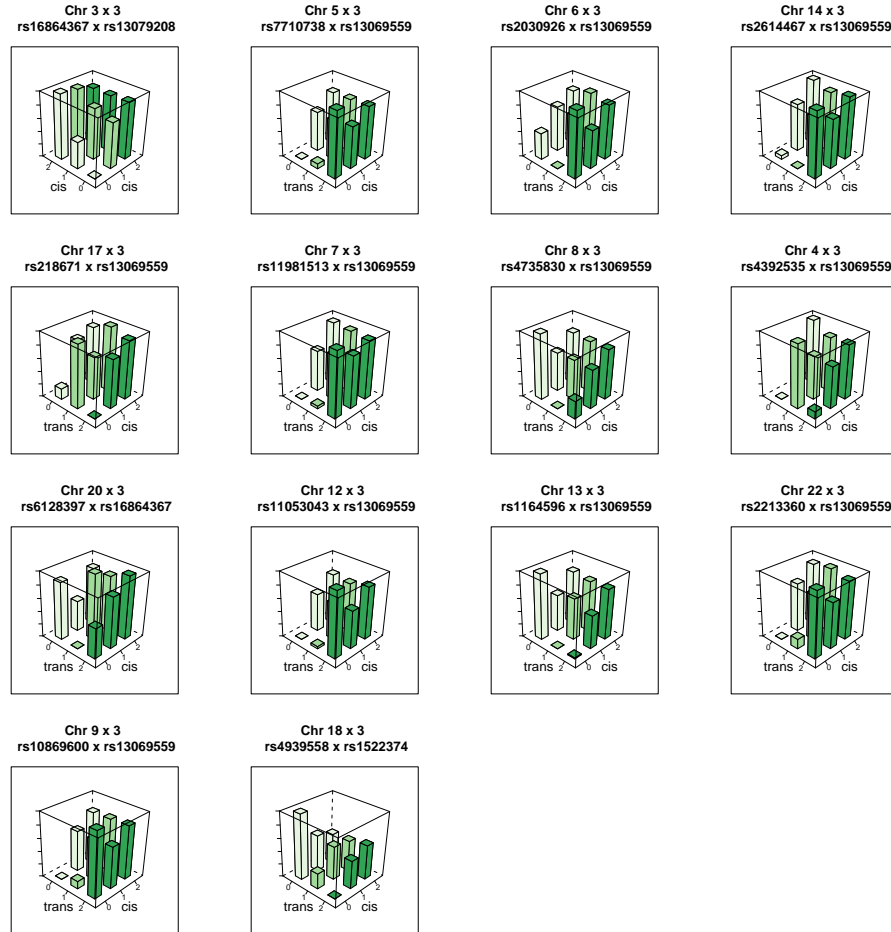


Figure S10: **Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions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

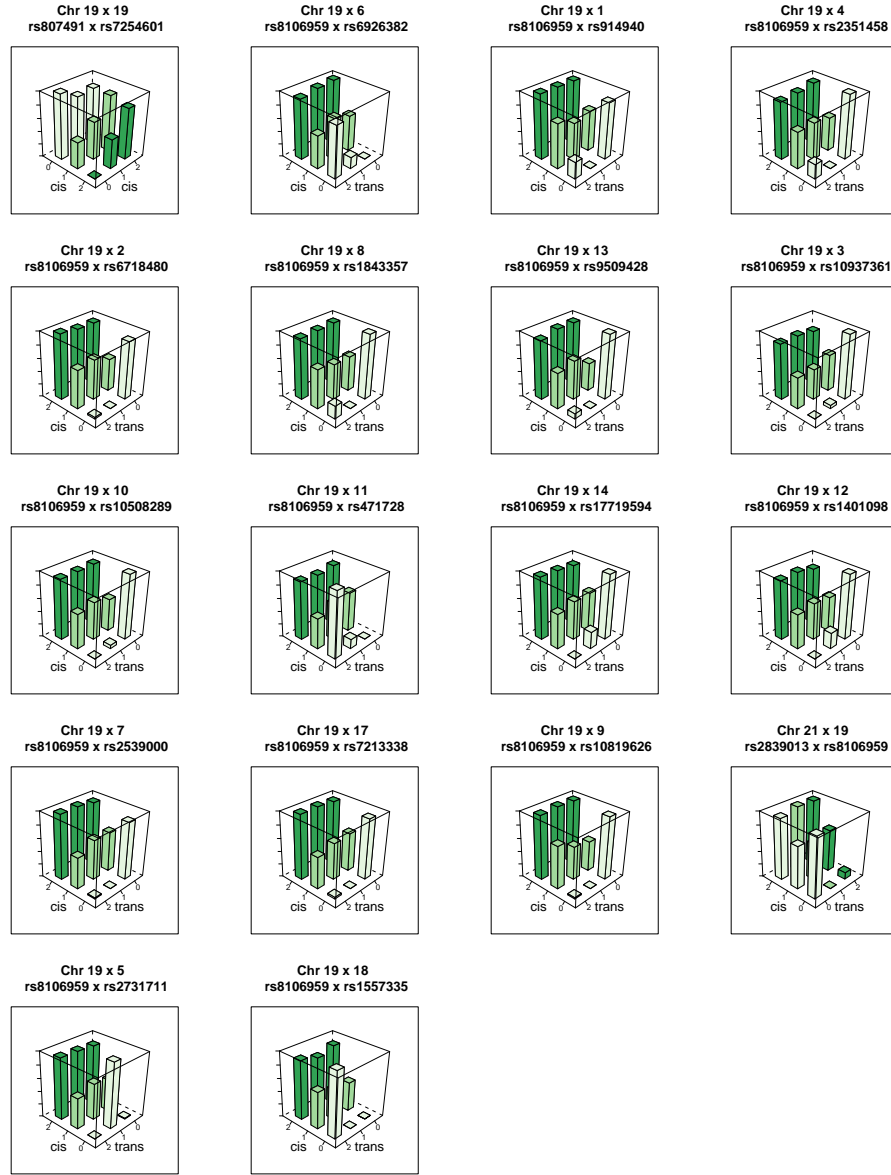


Figure S11: **Genotype-phenotype maps for 19 interactions influencing the expression of TMEM149** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of TMEM149, but in many of these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

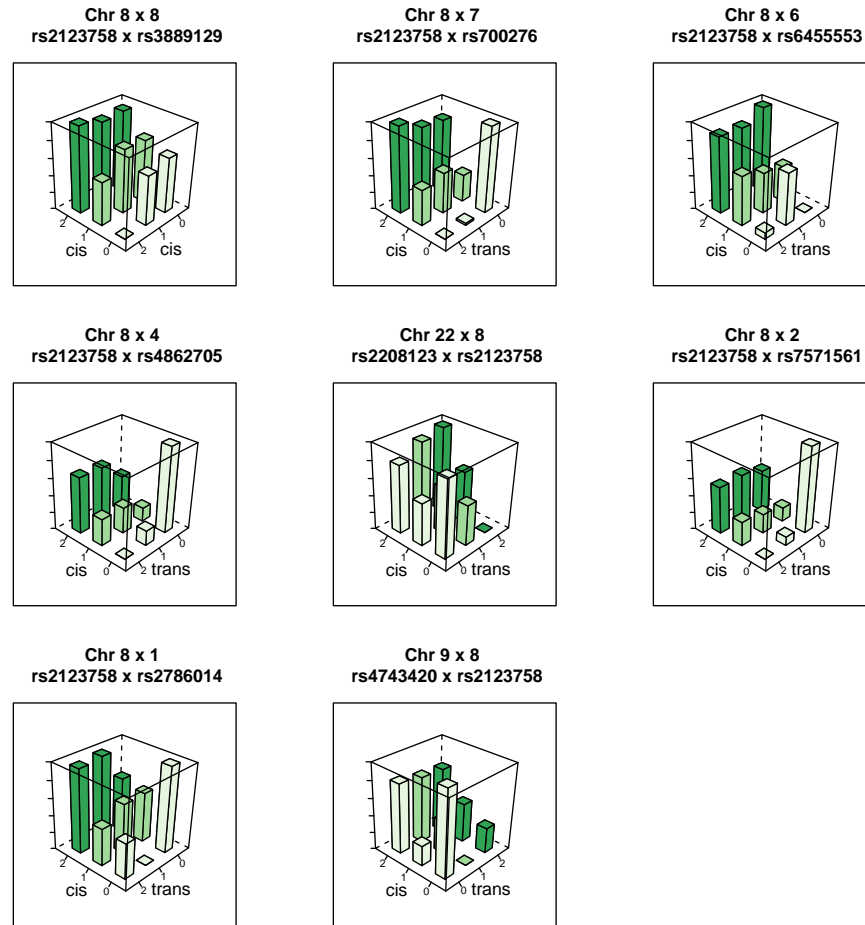


Figure S12: **Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1** Each bar represents the mean phenotypic value for individuals in that genotype class.

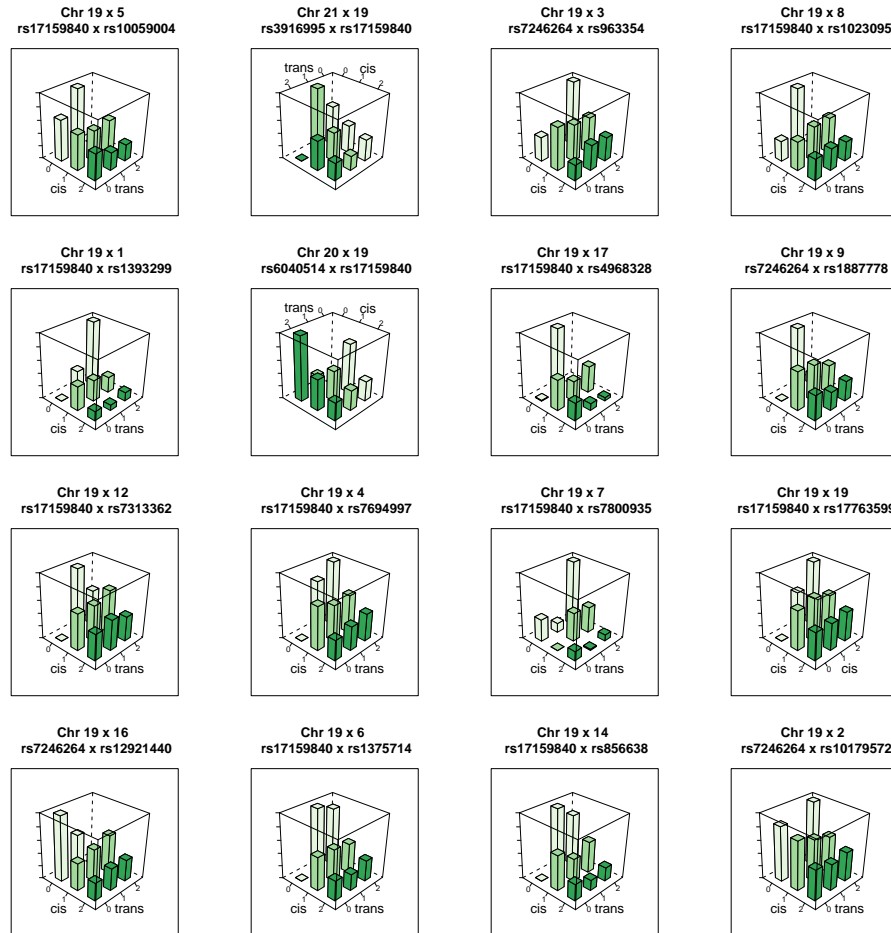


Figure S13: **Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5** Each bar represents the mean phenotypic value for individuals in that genotype class.

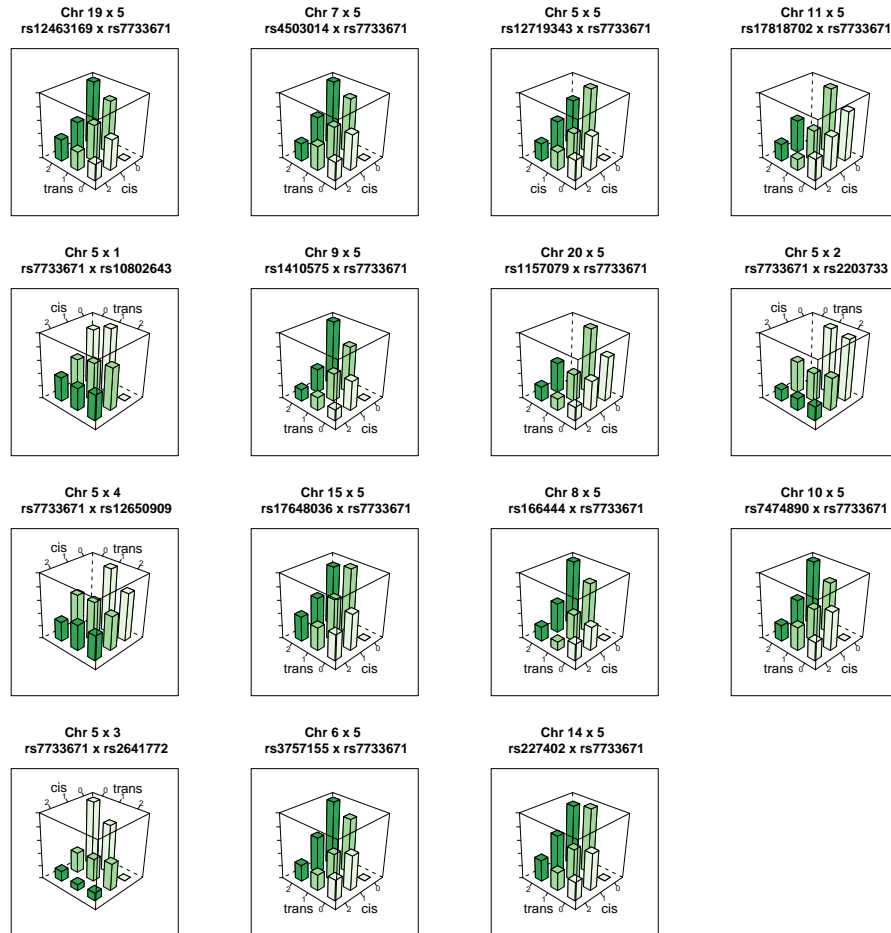


Figure S14: **Genotype-phenotype maps for 15 interactions influencing the expression of CAST** Each bar represents the mean phenotypic value for individuals in that genotype class.

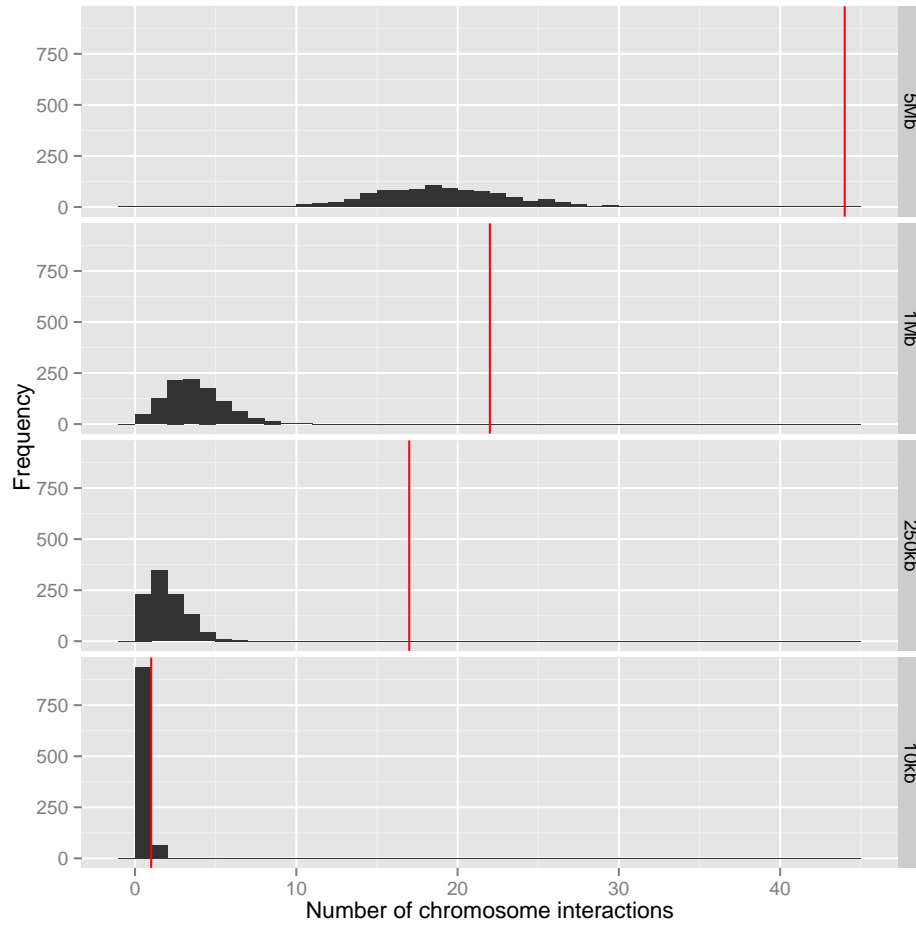


Figure S15: Number of overlaps between chromosome interactions and epistatic interactions Interacting chromosome regions may be a possible mechanism underlying epistatic interactions. The number of epistatic interactions within 20kb, 500kb, 2Mb and 10Mb of known chromosome interacting regions are shown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

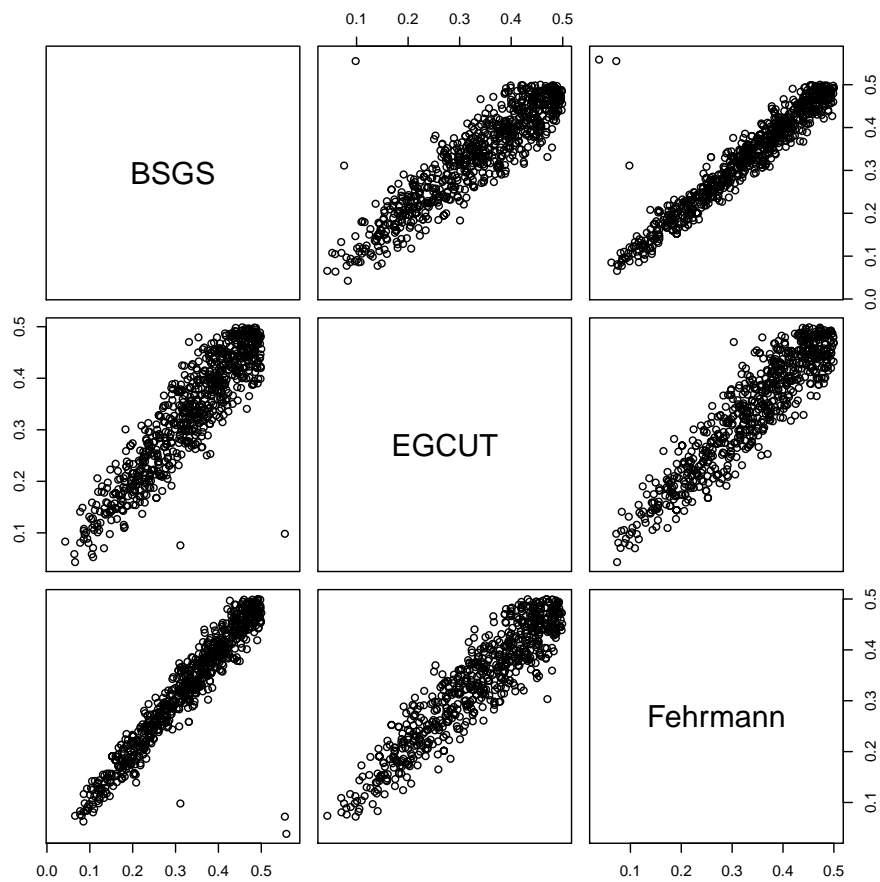


Figure S16: **Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations** Outliers were removed from the analysis as part of the filtering stage during replication.

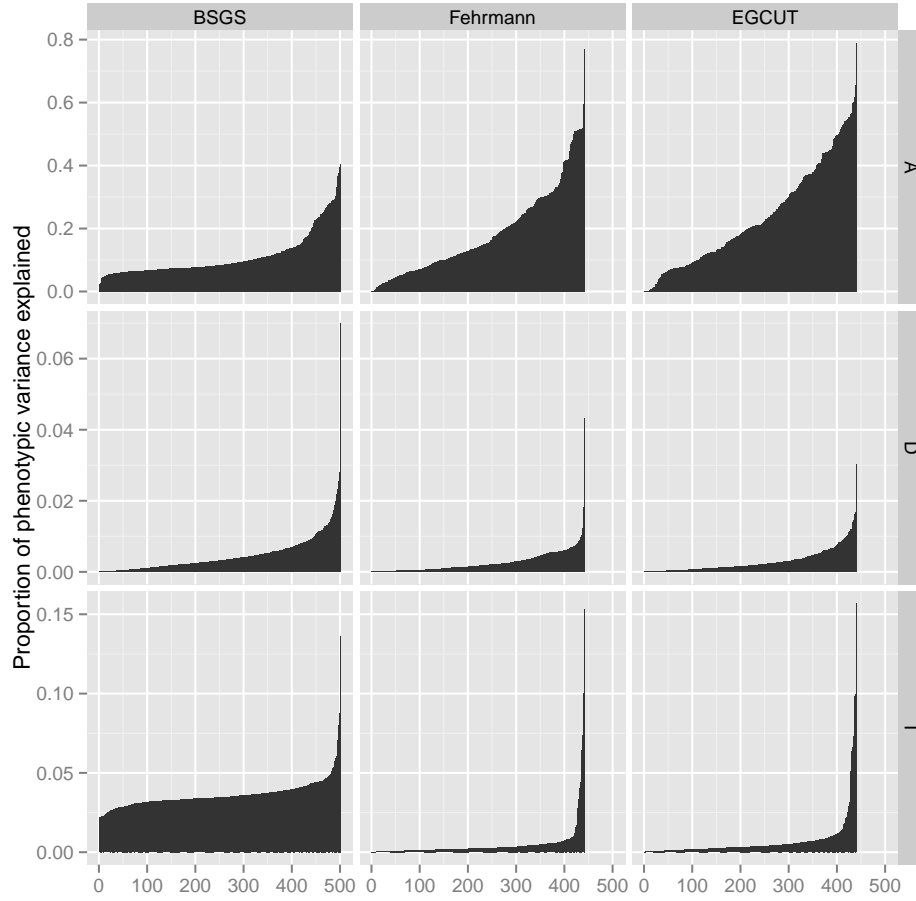


Figure S17: Comparison of variance explained by additive, dominant and epistatic effects from different cohorts How does the estimated variance decomposition change in different cohorts? The proportion of the phenotypic variance that is additive (A), dominant (D), or epistatic (I) for each putative interaction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

³⁹⁷ **Supplementary Tables**

Table S1 – continued from previous page

Gene ID ^a	Expression trait	SNP 1			SNP 2			Interaction statistic / -log ₁₀ p-values		
		rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	Distance / Mb ^h
CBORF69	ILMN_1633205	rs8051751	16	7188323		rs2890452	8	86102223	CBORF59	5.79
CBORF72	ILMN_1741881	rs10122902	9	27550780	C9ORF72	rs24202910	1	24202910	CABC1	0.18
CAC1	ILMN_1731064	rs12765847	10	4353908		rs3738725	1	221714210		0.96
CARD9	ILMN_1712532	rs4260763	9	139289825	INPP5E	rs654040	1	82128600		0.01
CARD9	ILMN_1712532	rs4573069	11	6026601		rs4077515	9	139266486	INPP5E	3.81
CAST	ILMN_1717234	rs112463169	20	6778978		rs7733671	5	96000269	CAST	0.61
CAST	ILMN_1717234	rs12463169	19	17321669		rs7733671	5	96000269	CAST	0.09
CAST	ILMN_1717234	rs12599264	16	81840122		rs7733671	5	96000269	CAST	0.23
CAST	ILMN_1717234	rs12719343	5	125369113		rs7733671	5	96000269	CAST	0.02
CAST	ILMN_1717234	rs1410575	9	78255630		rs7733671	5	96000269	CAST	0.73
CAST	ILMN_1717234	rs160444	8	78392770		rs7733671	5	96000269	CAST	7.00
CAST	ILMN_1717234	rs17048036	15	27311111		rs7733671	5	96000269	CAST	7.68
CAST	ILMN_1717234	rs17818702	11	86107920		rs7733671	5	96000269	CAST	0.36
CAST	ILMN_1717234	rs227402	14	70496867		rs7733671	5	96000269	CAST	0.13
CAST	ILMN_1717234	rs2822124	21	13160804		rs7733671	5	96000269	CAST	0.27
CAST	ILMN_1717234	rs3757155	6	136458593		rs7733671	5	96000269	CAST	0.37
CAST	ILMN_1717234	rs4003014	7	31149140		rs7733671	5	96000269	CAST	0.41
CAST	ILMN_1717234	rs4747890	10	39590078		rs7733671	5	96000269	CAST	0.59
CAST	ILMN_1717234	rs7733671	5	96000269	CAST	rs10802643	1	238120177	CAST	0.01
CAST	ILMN_1717234	rs7733671	5	96000269	CAST	rs12630909	2	17012880	CAST	0.33
CAST	ILMN_1717234	rs7733671	5	96000269	CAST	rs2203753	2	224095101	CAST	0.92
CAST	ILMN_1717234	rs7733671	5	96000269	CAST	rs2641772	3	195531841	CAST	1.72
CAST	ILMN_1717234	rs8723203	11	66175386		rs41152695	11	34115386	CAST	0.37
CAST	ILMN_1692705	rs2352303	18	66175386		rs41152695	11	34115386	CAST	0.37
CCDC88B	ILMN_172208	rs694739	19	1709390		rs1271549	10	6415142	CCDC88B	0.11
CCDC88B	ILMN_1784663	rs5211834	7	80283117	CCDC88B	rs1254900	1	8698193	YAMP8	0.22
CD86	ILMN_1800940	rs7508015	11	76053374		rs670105	7	20755354	CD55	0.18
CD86	ILMN_1704730	rs1884655	20	23074375	CD93	rs4607740	7	15782340		0.13
CD93	ILMN_1704730	rs1884655	20	23074375	CD93	rs7623520	4	7692632		0.01
CD93	ILMN_1704730	rs1884655	20	23074375	CD93	rs8388750	3	196721305		0.03
CD93	ILMN_1704730	rs1884655	20	23074375	CD93	rs8388750	12	125145394		0.24
CD93	ILMN_1704730	rs1884655	20	23074375	CD93	rs8576388	13	38434372		0.82
CD93	ILMN_1704730	rs2889504	20	37771578		rs186858	20	38434372		0.27
CD93	ILMN_1704730	rs4813479	20	23076914		rs10925247	1	238890903		1.67
CD93	ILMN_1704730	rs4813479	20	23076914		rs2873430	8	138500554		0.71
CD93	ILMN_1704730	rs4813479	20	23076914		rs4295531	17	77264432		0.64
CD93	ILMN_1704730	rs4813479	20	23076914		rs7294744	13	115080398		0.18
CD93	ILMN_2309796	rs9015940	14	104162263		rs11655031	17	3083182	CDK16	0.21
CEACAM21	ILMN_1730928	rs200690	20	46614102	HOXB2	rs2421050	5	158043044	CEACAM21	0.95
CEACAM21	ILMN_1745949	rs4803481	19	51956256		rs4803481	19	43066556		0.07
CEACAM21	ILMN_1707554	rs6505780	18	42068556	CEACAM21	rs13132719	3	180265266		0.12
CEACAM21	ILMN_1707554	rs6505780	18	42068556	CEP102	rs13079012	3	134247706	ANAPC13	0.24
CEP63	ILMN_1787808	rs3825569	14	101350298		rs2692290	12	235248562		0.09
CEP63	ILMN_2359945	rs81992935	16	55861794	CES1	rs2692290	12	235248562		0.72
CHPT1	ILMN_2209240	rs501967	13	38838122		rs867578	11	102087844	CHPT1	0.44
CHPT1	ILMN_2209240	rs501967	13	38838122		rs7313235	12	81937002		0.20
CHPT1	ILMN_1663142	rs429790	12	102277782		rs7313235	12	10132283	CLEC12A	0.92
CLEC12A	ILMN_2403228	rs7405054	16	84471642		rs3903088	10	134236688	CLEC12A	0.36
CLEC12A	ILMN_1674609	rs17129799	11	96922937		rs6863172	5	173595960	CLTB	0.73
CNN2	ILMN_1770290	rs3752237	19	1047161	ABCA7	rs169130	16	63121080		0.27
CNN2	ILMN_1770290	rs3752237	19	1047161	ABCA7	rs7713633	13	67713633		0.02
CPSF1	ILMN_1654545	rs4333645	8	145569535		rs1455268	4	61738094		1.39
CPVL	ILMN_1682928	rs12596791	16	26115562		rs2455884	7	29188475	CPVL	0.01
										0.57

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Table S1 – continued from previous page

Gene ID ^a	Expression trait	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-value	MetaSig	Distance / Mb ^g
HBG2	ILMN_2084825	11	rs12975066	19	35723301	11	HBG2	rs2855039	11	5271671	21	HBG2	5.77	0.08	0.13	0.05	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs12042181	11	213068494	1	LQN1	6.84	0.06	0.54	0.21	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs12033379	4	141533832	4	LQN1	5.98	0.00	0.46	0.10	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs47060636	12	48173352	12	HBG2	5.75	0.00	0.46	0.10	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
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HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
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HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
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HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
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HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
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HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671	11	HBG2	rs17086655	17	133220622	17	HBG2	5.98	0.15	0.59	0.32	
HBG2	ILMN_2084825	11	rs2855039	11	5271671												

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Table S1 – continued from previous page

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Expression trait			SNP 1			SNP 2			Interaction statistic / -log ₁₀ p-values			Distance / Mb
Gene ID ^a	rs ID	Chr.	Pos/Mb/c	Association ^d	rs ID	Chr.	Pos/Mb/c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	MetaSig ^h
NRRF2	rs6025645	20	56157341		rs7923609	10	65133822	NRRF2	5.45			
NRRF2	rs6517815	21	19819016		rs7923609	10	65133822	NRRF2	6.11			
NDR1	rs4852124	2	240680022		rs6588415	1	52334047	NDR1	6.13	0.47	0.05	0.17
OAS1	rs5017851	12	24543482		rs1005901	8	21964378	NUDT18	5.44	0.03	0.46	0.15
OAS1	rs11613438	12	113480510		rs1047944	6	163997467		8.19	1.27	1.55	2.03
ILMN_1658247	rs13311	12	11348652		rs2072133	12	113409260		4.13	4.12	0.81	3.86
ILMN_1675640	rs1892233	12	19160255		rs3741981	12		OAS1	4.38	0.87	0.46	0.76
ILMN_2381899	rs7192613	16	74286646		rs17512962	10	13169066	OPN1	5.64	0.42	0.06	0.14
ILMN_2307032	rs2829679	19	26662143		rs998639	11	3149249	OSBPL5	5.00	0.36	0.00	0.07
ILMN_1742456	rs17780195	17	70624189		rs2273770	9	77755469	OSTF1	5.42	0.16	0.87	0.40
ILMN_1734546	rs2273770	9	77755469	OSTF1	rs7718088	5	179590952		5.42	1.20	0.08	0.62
ILMN_1734542	rs10802822	1	240132968		rs11969283	5	111992823	OVGP1	5.43	0.13	1.48	0.88
PAM	rs347331	3	140148107		rs1264894	1	119697919	OVGP1	6.04	0.25	1.21	0.82
ILMN_2313901	rs28092	5	102149795	PAM	rs784600	1	40139553	HPCAL4	5.59	0.66	0.44	0.59
ILMN_1815951	rs2438490	5	148726162	PCYOX1L	rs2731939	3	2395989		6.20	0.19	0.26	0.16
ILMN_1660232	rs10444467	12	128052636		rs4329748	12	7364442	PEX5	5.85	0.09	0.71	0.32
PEX5	rs131969	15	27246462		rs4329748	12	7364442	PEX5	5.74	0.34	0.09	0.13
PPAAP5	rs7328733	13	49151303		rs7328733	13	33126737	PPAAP5	5.64	0.87	0.36	0.67
PGLYRP1	rs12829353	19	46529456		rs1263806	14	21982957		5.51	0.03	0.65	0.24
PIK3IP1	rs493642	11	123097386	PGLYRP1	rs10736812	11	76708086	PHCA	6.51	0.36	0.90	0.70
PIK3IP1	rs14141404	22	31675185		rs2065841	1	61728597		5.60	0.20	0.01	0.03
PISD	rs470072	22	32263131	PISD	rs10498313	14	30398876		5.23	0.02	0.87	0.33
PISD	rs6518752	22	31999127	PISD	rs954627	1	18236681		7.11	0.00	1.19	0.48
PISD	rs3234931	22	332434931		rs6518754	22	32097775	PISD	4.12	0.05	0.42	0.15
PNKD	rs6869411	5	158781604		rs928046	9	149482481	PNKD	6.35	0.16	0.04	0.04
PNKD	rs11639998	16	4527109		rs11568001	11	7559930	PNFLA7	5.15	0.31	0.78	0.56
PNFLA7	rs911019	20	49668255		rs1156875	14	35619816	PFHPBP2	4.44	0.29	0.33	0.26
PFHPBP2	rs12914603	15	163308696		rs12120009	1	212447167	PPP2R3C	5.81	0.12	0.42	0.19
PPP2R3C	rs10930170	12	123393067		rs12120009	1	212447167	PPP2R3C	5.63	0.72	0.48	0.66
PPP2R5A	rs124232355	12	163395064		rs12120009	1	212447167	PPP2R5A	5.72	0.08	0.95	0.46
PPP2R5A	rs1880895	13	66222691		rs12120009	1	212447167					

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Table S1 – continued from previous page

Gene ID ^a			Expression trait			SNP 1			SNP 2			Interaction statistic ^f			BSCS ^e			-log ₁₀ p-values			Distance / Mb ^b		
Gene	ID ^a	Chr.	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	F _{max}	F _{max} p	Meta ^g	Meta ^g	Meta ^g	Meta ^g	Meta ^g	Meta ^g		
RENE	ILMN_18020380	1	rs4982958	14	24987865		rs301819	1	8501786	RENE	rs301819	1	8501786	5.66	0.61	1.23	1.17						
RENE	ILMN_18020380	1	rs7697290	4	135248366		rs301819	1	8501786	RENE	rs301819	1	8501786	5.74	0.14	0.10	0.06						
RENE	ILMN_18020380	1	rs11085629	19	13174312		rs301819	1	8501786	RENE	rs301819	1	8501786	5.12	0.21	0.33	0.21						
RENE	ILMN_2347795	14	rs38520111	3	12844086	RNASE6	rs301819	1	8501786	RENE	rs301819	1	8501786	5.71	0.08	0.60	0.26						
RENE	ILMN_2347795	14	rs10218598	14	21182850		rs75234365	13	100601327	RNASE6	rs75234365	13	100601327	5.48	0.42	0.21	0.26						
RENE	ILMN_2347795	14	rs38520111	3	12844086		rs485857	13	51685192	RNASE6	rs485857	13	51685192	4.37	0.09	0.82	0.08						
RENE	ILMN_17047296	17	rs9382927	17	4875521		rs11706900	1	36348968		rs11706900	1	36348968	5.59	0.71	0.46	0.64						
RENE	ILMN_17047296	17	rs4006888	17	4839930	RNF167	rs11706900	1	36348968		rs11706900	1	36348968	5.59	0.71	0.46	0.64						
RENE	ILMN_1738347	1	rs1071621	21	67127549		rs2819365	1	201983242		rs2819365	1	201983242	6.27	0.11	0.30	0.13						
RENE	ILMN_1738347	1	rs8071711	21	67153386		rs2819365	1	201983242		rs2819365	1	201983242	6.27	0.11	0.30	0.13						
RENE	ILMN_24413278	16	rs3529385	16	89648580		rs29685817	16	89513934		rs29685817	16	89513934	4.98	3.79	14.41	17.24						
RENE	ILMN_24413278	16	rs1401202	16	89620056		rs48492617	2	114450028		rs48492617	2	114450028	5.55	0.13	0.73	0.38						
RENE	ILMN_2189933	14	rs4007033	14	50103816	RPL36AL	rs17495030	9	138038093		rs17495030	9	138038093	5.46	0.09	0.06	0.02						
RENE	ILMN_2189933	14	rs4009028	14	50020817	RPL36AL	rs1502991	6	66137260		rs1502991	6	66137260	5.86	0.32	0.20	0.19						
RENE	ILMN_1764721	8	rs2958482	8	145984615	RPL8	rs2958482	8	145984615		rs2958482	8	145984615	4.59	0.10	0.37	0.15						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						
RENE	ILMN_1764721	8	rs143674	20	4741304		rs2958482	8	145984615		rs2958482	8	145984615	4.33	0.13	0.45	0.22						

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Table S1 – continued from previous page

Gene ID ^a	Expression trait		SNP 1			SNP 2			Interaction statistic / -log ₁₀ p-values						
	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g	Distance / Mb ^h
TMEMD4	ILMN-1804148	7	rs1940400	11	132389627		rs17725246	7	44581986	TMEMD4	3.70	0.06	1.34	0.70	
TMEM149	ILMN-1780426	19	rs28390113	21	47248981		rs8106939	19	36219525	TMEM149	8.11	0.16	0.48	0.26	
TMEM149	ILMN-1780426	19	rs7562235	22	27923288		rs8106939	19	36219525	TMEM149	6.79				
TMEM149	ILMN-1780426	19	rs6090518	20	43207005		rs8106939	19	36219525	TMEM149	11.09				
TMEM149	ILMN-1780426	19	rs807491	19	36268923	SNX26	rs7254601	19	36147315	TMEM149	12.16	0.76	45.78	145.78	0.122
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs10916259	0	133025736	TMEM149	8.12	81.55	3.09	3.07	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs10937361	3	188395436	TMEM149	8.39	0.40	0.99	0.80	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs1401098	12	128884559	TMEM149	7.37	2.41	1.00	2.52	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs15572935	18	64268976	TMEM149	6.95	0.08	0.07	0.02	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs17719594	14	90932398	TMEM149	6.93	3.06	0.77	2.87	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs1843357	8	13822381	TMEM149	6.21	3.72	3.33	6.00	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs2531458	4	113317583	TMEM149	7.30	0.04	9.61	8.00	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs2539000	7	147619772	TMEM149	6.70	1.57	1.52	2.27	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs2731711	5	171792273	TMEM149	5.92	0.19	0.33	0.19	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs471728	11	129595460	TMEM149	8.89	0.90	3.62	3.51	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs6718480	2	233879066	TMEM149	8.55	3.31	5.15	7.36	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs6926382	2	161683974	TMEM149	5.80	3.06	8.80	10.72	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs7213338	17	80357420	TMEM149	5.49	0.07	3.14	2.10	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs914940	1	242889492	TMEM149	6.22	3.36	6.96	9.20	
TMEM149	ILMN-1780426	19	rs8106939	19	36219525	TMEM149	rs9509428	13	214739352	TMEM149	5.44	0.10	5.75	4.47	
TMEM63A	ILMN-1719649	1	rs1254086	13	72890603		rs4149226	1	226027323	TMEM63A	5.60				
TMEM80	ILMN-1708482	11	rs1548475	9	58058246		rs4963126	11	656845	TMEM80	5.79	0.12	0.15	0.32	
TNP03	ILMN-1683811	7	rs1537146	9	4859303		rs10488630	7	128593948	IRF5	5.61	0.11	0.15	0.07	
TNP03	ILMN-1683811	7	rs199793	20	22827303		rs10488630	7	128593948	IRF5	5.52	1.03	0.17	0.62	
TRA2A	ILMN-1710143	7	rs7776572	13	75258927		rs11770192	7	23493358		8.23	3.19	1.89	4.09	0.031
TRAPPC4	ILMN-1814650	11	rs1793823	13	113531675		rs3916581	11	118887887	TRAPPC4	5.61	0.28	0.40	0.29	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs10059004	1	166970604		5.52	0.93	0.01	0.36	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs1023095	8	132022957		6.92	0.37	1.60	1.07	12.131
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs1375714	6	156404902		7.79	0.21	0.18	0.08	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs1393299	1	242329791		6.43	0.63	0.47	0.59	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs17763599	19	23694315		6.38	0.21	0.24	0.16	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs4968328	17	57495457		6.51	0.50	0.38	0.44	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs7313362	12	129644342		7.08	0.04	0.65	0.25	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs7694997	4	9947811		5.86	0.20	0.36	0.22	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs800935	7	146690926		6.27	0.15	0.33	0.16	
TRAPPC5	ILMN-2372639	19	rs17159840	19	7758194	TRAPPC5	rs856638	14	85439550		6.73	0.24	0.07	0.08	
TRAPPC5	ILMN-2372639	19	rs380708	22	22740855		rs17159840	19	7758194	TRAPPC5	7.58				
TRAPPC5	ILMN-2372639	19	rs3916995	19	45128454		rs17159840	19	7758194	TRAPPC5	7.73	0.85	0.78	1.01	
TRAPPC5	ILMN-2372639	19	rs6040514	20	11272861		rs10179572	2	228504503	TRAPPC5	8.10	0.51	0.55	0.56	
TRAPPC5	ILMN-2372639	19	rs7246264	19	7762978		rs10179572	2	228504503	TRAPPC5	6.71	0.14	0.02	0.02	
TRAPPC5	ILMN-2372639	19	rs7246264	19	7762978		rs12921440	16	30408795		7.34	0.14	0.26	0.13	
TRAPPC5	ILMN-2372639	19	rs7246264	19	7762978		rs1887778	3	134635088	RAPGEF1	7.05	0.08	0.86	0.40	
TRAPPC5	ILMN-2372639	19	rs7246264	19	7762978		rs963354	3	157393770		7.41	0.36	0.90	0.69	
TREM1	ILMN-168231	6	rs10862975	12	85749398		rs2395771	6	41264577	TREM1	5.42	0.11	0.25	0.11	
TREM1	ILMN-168231	6	rs12412964	10	108256422		rs2395771	6	41264577	TREM1	5.92	1.20	1.23	1.69	
TREM1	ILMN-1697971	6	rs2527180	7	138808416		rs2395771	6	41264577	TREM1	6.46	0.04	0.91	0.39	
TSPAN3	ILMN-1780600	11	rs968726	17	17194634	MYBPC3	rs10748526	10	82273079	TSPAN3	5.01				
TSPAN3	ILMN-1718621	11	rs10383738	11	47603049	TSPAN3	rs12800098	11	2317951	TSPAN3	5.01				
TSPAN3	ILMN-2389970	11	rs12800998	11	5371951	TSPAN3	rs620607	6	137947208	TSPAN3	5.51				
TSPAN3	ILMN-2323126	22	rs140322	22	20971266	ECGF1	rs1198819	2	238746880	TSPAN3	6.34				
TSPAN3	ILMN-2323126	22	rs140322	22	20971266	ECGF1	rs4783126	16	85147633	TSPAN3	6.13				

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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 ^h		
Gene ID ^a	Probe ID ^b	Chr.	rs ID	Chr.	Pos / Mb ^c	Association ^d	rs ID	Chr.	SNP-2	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g
UBASH3A	LMN-2338348	21	rs1893592	21	43855067	UBASH3A	rs7201194	16	83600397		5.91	0.59	0.42	0.52
UBASH3A	LMN-2338348	21	rs1893592	21	43855067	UBASH3A	rs7201194	16	83600397		6.01	0.48	1.29	1.10
USP36	LMN-1697227	17	rs2279308	17	76794981	USP36	rs7225546	17	75151717		5.71	0.03	0.14	0.03
VASP	LMN-1743646	19	rs1264226	19	40063167		rs2276470	19	45974668		5.09	0.94	5.14	4.95
VNN2	LMN-1678939	6	rs10435352	7	103252718		rs1883613	6	133077063	VNN2	5.64	0.84	0.15	0.46
VNN2	LMN-1678939	6	rs10435352	7	103252718		rs1883613	6	133077063	VNN2	5.44	0.39	0.69	0.57
VNN2	LMN-1678939	6	rs134447	22	49927332		rs1883617	6	133072650	VNN2	5.72			
VNN2	LMN-1678939	6	rs134447	22	49927332		rs1883617	6	133072650	VNN2	5.77	0.33	0.19	0.19
VNN3	LMN-1678939	6	rs216495	11	16834510		rs1883617	6	133072650	VNN2	6.44	0.16	0.74	0.41
VNN3	LMN-1678939	6	rs10278073	7	151662184		rs2267952	6	133067782	VNN3	5.74	0.23	0.48	0.31
VNN3	LMN-1804935	6	rs1443946	8	73006453		rs2267952	6	133067782	VNN3	6.44	0.31	0.17	0.17
VNN3	LMN-1804935	6	rs348462	9	75547169		rs2267952	6	133067782	VNN3	5.82	0.03	0.19	0.04
VNN3	LMN-1804935	6	rs7157055	14	83262064		rs2267952	6	133067782	VNN3	6.12	0.73	1.15	1.21
VNN3	LMN-2387680	6	rs2823165	21	5694253		rs2267952	6	133067782	VNN3	4.83	0.46	0.05	0.16
VNN3	LMN-2387680	6	rs9596457	13	51692548		rs2267952	6	133067782	VNN3	5.60	0.53	0.54	0.57
VSTM1	LMN-1763455	19	rs9596457	19	54553697	VSTM1	rs4532100	18	71024750		5.71	0.48	0.17	0.26
VSTM1	LMN-1763455	19	rs10500316	19	54553697	VSTM1	rs7895870	10	123098249		5.88	0.81	1.38	1.47
VSTM1	LMN-1763455	19	rs10500316	19	54553697	VSTM1	rs7895870	10	123098249	VSTM1	5.71	0.48	0.17	0.26
VSTM1	LMN-1763455	19	rs9628570	22	30261219		rs10500316	19	54553697	VSTM1	5.88	0.19	1.38	1.47
WDR48	LMN-1762103	3	rs1388935	3	188927822		rs6778963	3	39091812	WDR48	5.88	0.19	1.38	1.47
WDR48	LMN-1762103	3	rs1887778	9	134635088		rs883349	3	39067925	WDR48	6.34	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	123371708		rs7619193	3	39044116	WDR6	4.86	1.64	1.43	2.25
XAF1	LMN-2330573	17	rs1535031	17	6073170	XAF1	rs11715581	3	49194331		5.86	2.38	0.17	1.63
ZNF90	LMN-1684628	16	rs906446	21	37040648		rs12591171	15	93179799		5.48	0.09	0.36	0.15
ZNF500	LMN-1700258	16	rs4829793	22	48283177		rs182968	16	68753945	ZFP P90	5.79	0.67	0.27	0.46
ZNF500	LMN-1700258	16	rs4829793	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