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. 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 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 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 $0.05 \le \alpha \le 0.14$, 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 signicant 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 ($p << 1.0 \times 10^{-16}$, 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 expresson levels too, for example TMEM149 (Supplementary Figure S11), NAPRT1 (Supplementary Figure S12), TRAPPC5 (Supplementary Figure S13), and CAST (Supplementary Figure S14). We observed that from pedigree analysis these five gene expression phenotypes had non-additive variance component estimates within the 95th percentile of the 17,994 gene expression phenotypes that were analysed 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 interactions ¹³. We cross-referenced our epistatic SNPs with a map of chromosome interacting regions (n=96,139) in K562 blood cell lines ²⁹ (Methods) and found that 44 epistatic interactions mapped to within 5Mb ($p<1.8\times10^{-10}$), (Supplementary Figure S15). Interaction of distant loci may occur through physical proximity in transcriptional factories that organise across different chromosome regions and can regulate transcription of related genes ³⁰.

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.

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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

| Table 1. Epistatic interactions significant at the Bolherron level in two replication sets | | | | | | | |
|--|---------------|-----------------|-----------------|-------------------|-------------|-------------|-------------|
| | Gene (chr.) | SNP 1 (chr.) | SNP 2 (chr.) | BSGS^2 | | | $Meta^4$ |
| 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 |

 $^{^{1}}$ - log₁₀ 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

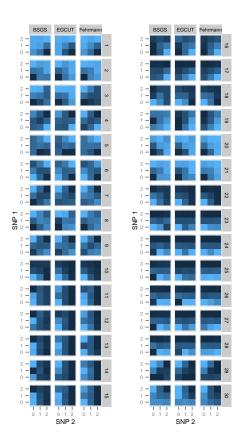


Figure 1: Replication of GP maps in two independent populations. The GP maps for each epistatic interaction that is significant at the Bonferroni level in both replication datasets are shown. Each GP map consists of nine tiles where each tile represents the expression level for that two-locus genotype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

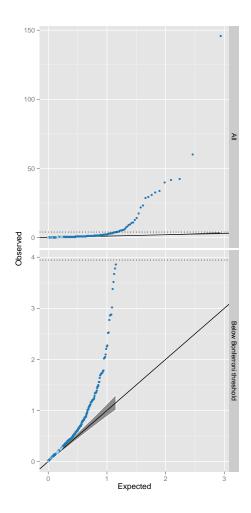


Figure 2: \mathbf{Q} - \mathbf{Q} plots of interaction p-values from replication datasets. The top panel shows all 434 discovery SNPs that were tested for interactions. Observed p-values (y-axis, $-\log_{10}$ scale) are plotted against the expected p-values (x-axis, $-\log_{10}$ scale). The multiple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

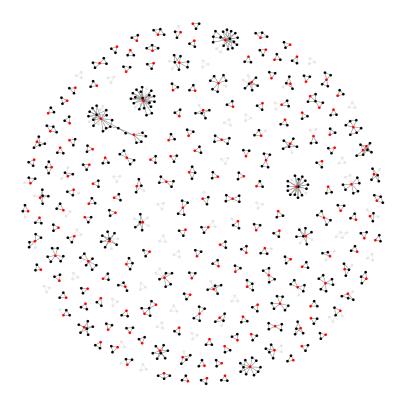


Figure 3: **Discovery and replication of epistatic networks** All 434 putative genetic interactions (edges) with data common to discovery and replication sets is shown, where black nodes represent SNPs and red nodes represent traits (gene expression probes). Three hundred and forty-five interactions 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

$$y = \mu + \beta_1 c + \beta_2 p + \beta_3 s + \beta_4 a + g + e \tag{1}$$

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

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

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

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

where μ is the mean expression level and 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 $1.03 \times 10^{15}~F$ -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 = $1/n_{\rm unrelated} = 0.0039$).

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 (CD-HWB) 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 $-2 \ln p_1 - 2 \ln p_2 \sim \chi_{4d.f.}^2$. 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 test 35 .

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 method 36 .

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 $0.9^8V_t=0.43V_t$. 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

$$h_{11} = r\sqrt{p_1q_1p_2q_2} + p_1q_1 \tag{5}$$

$$h_{12} = p_1 q_2 - r \sqrt{p_1 q_1 p_2 q_2} \tag{6}$$

$$h_{21} = p_2 q_1 - r \sqrt{p_1 q_1 p_2 q_2} \tag{7}$$

$$h_{22} = r\sqrt{p_1 q_1 p_2 q_2} + p_2 q_2 \tag{8}$$

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

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

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 hypothesis 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 frequence > 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 epistatis 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 genomewide 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 2012^{23} 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

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 $et\ al\ 2013^{22}$. 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, gastrointenstinal, 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 $10\mathrm{kb}.$

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

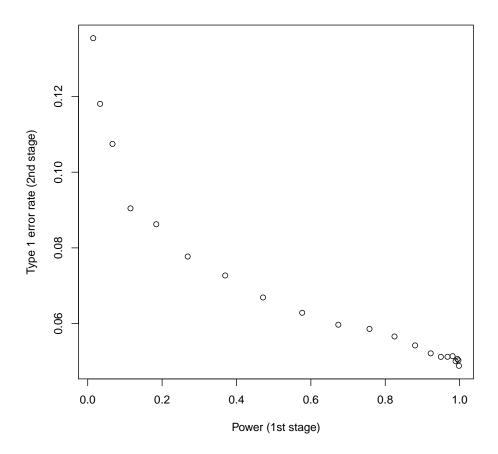


Figure S1: Type 1 error rate of two stage design assuming a null model of one large additive effect and no epistasis In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These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

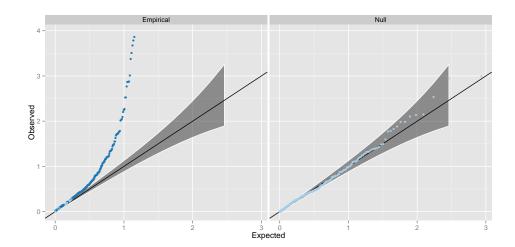


Figure S2: Q-Q plots of interaction p-values from replication datasets, excluding the 30 points significant at the Bonferroni level The right panel (Null) shows the interaction p-values from a meta analysis across two independent datasets on 434 SNP pairs where one SNP has a marginal effect. The left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

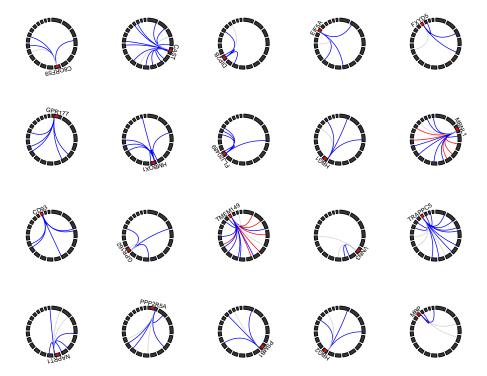


Figure S3: Gene expression traits with four or more genetic interactions Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent 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 segmentation 28 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, E CTCF enriched element, E Predicted weak enhancer or open chromatin cis regulatory element, E Predicted promoter flanking region, E Predicted promoter region including transcriptional start site, E Predicted transcribed region, E Predicted Repressed or Low Activity region

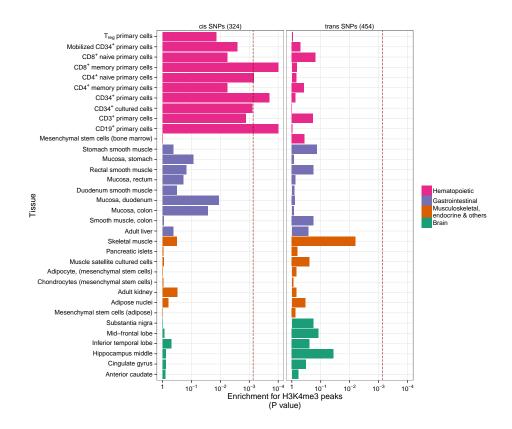


Figure S5: Tissue specific enrichment of SNPs in transcriptionally active regions The locations of transcriptional activity can be predicted by chromatin marks, assayed by $\rm H3K4me3^{27}$. Enrichment p-values are calculated using permutation analysis for 34 different cell types (y-axis) in four tissue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

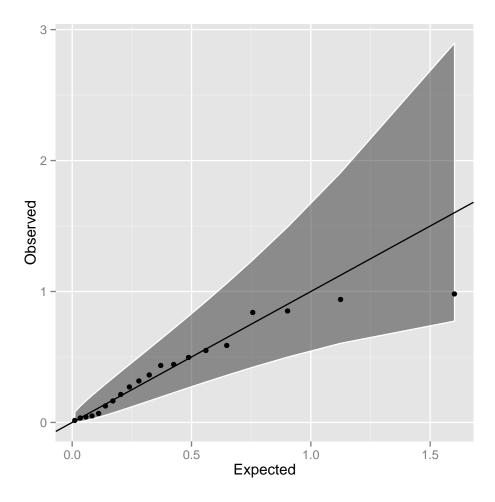


Figure S6: Q-Q plot of interaction p-values in the CDHWB dataset Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset (mainly due to small sample size). There is no evidence for enrichment of interaction terms, most likely due to insufficient power given the limited sample size.

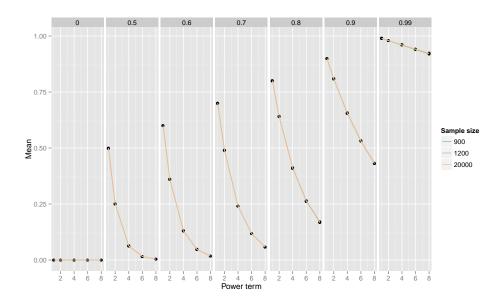


Figure S7: Sampling mean for different power terms of population r values Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8 . For a given population value of LD r (columns of plots), plotted is the sample mean (y-axis) of \hat{r} , \hat{r}^2 (additive), \hat{r}^4 (dominance, A×A), \hat{r}^6 (A×D), \hat{r}^8 (D×D) (x-axis) for different sample sizes (coloured lines). As true r reduces the statistical power to detect epistatic variants drops dramatically under the assumption that statistical power is proportional to higher moments of r.

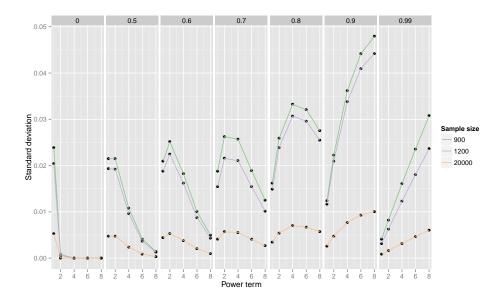


Figure S8: Sampling standard deviation for different power terms of population r values Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4 , r^6 , r^8 . For a given a population value of LD r (columns of plots), plotted is the sampling standard deviation (y-axis) of \hat{r} , \hat{r}^2 (additive), \hat{r}^4 (dominance, A×A), \hat{r}^6 (A×D), \hat{r}^8 (D×D) (x-axis) for different sample sizes (coloured lines). As the power term of r increases the sampling variance also increases. Supposing that there is sufficiently high r^x in the discovery sample for detection of epistasis, the replication sample is less likely to have similarly high r^x as x increases, leading to an expectation of reduced replication rates.

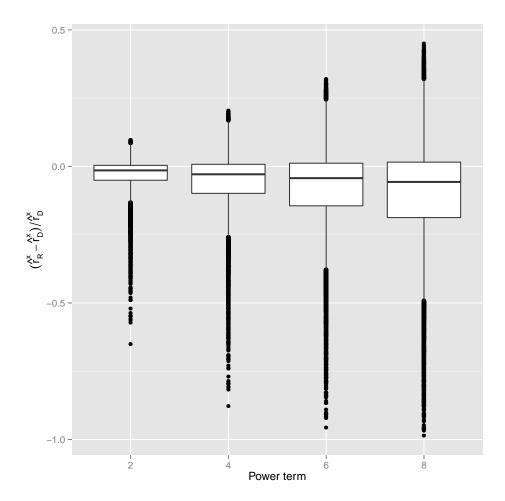


Figure S9: Reduction in LD as estimated in replication data after ascertaining for high LD in discovery data 100,000 "unobserved" causal variants (CVs) were tested for LD against a panel of 528,509 "observed" discovery markers (DMs). DM/CV pairs with LD $r^2 > 0.9$ were then tested in an independent sample. Simulation results of the proportional decrease between discovery and replication datasets in LD (y-axis) of $\hat{r}^2, \hat{r}^4, \hat{r}^6, \hat{r}^8$ (x-axis) are shown, where \hat{r}_D^x and \hat{r}_R^x are the sample LD measurements in the discovery and replication datasets, respectively. The average proportional decrease in the replication \hat{r}_R^x was 2.8%, 5.3%, 7.4% and 9.2% for x=2,4,6 and 8, respectively.

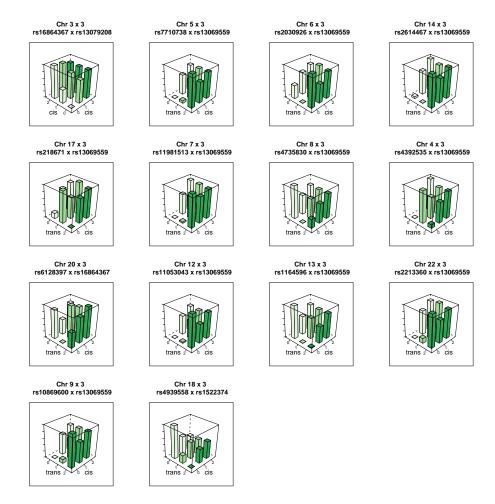


Figure S10: Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1 Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions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



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

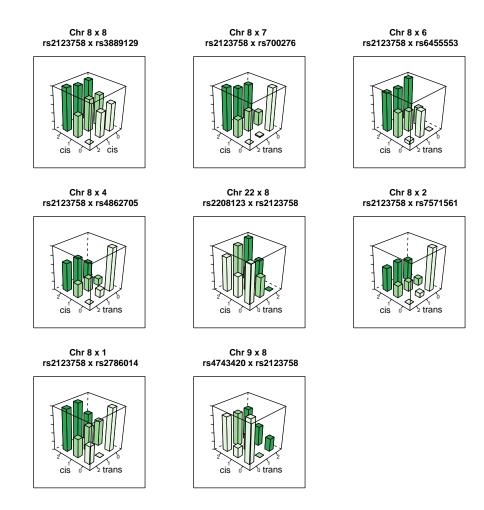


Figure S12: Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1 Each bar represents the mean phenotypic value for individuals in that genotype class.

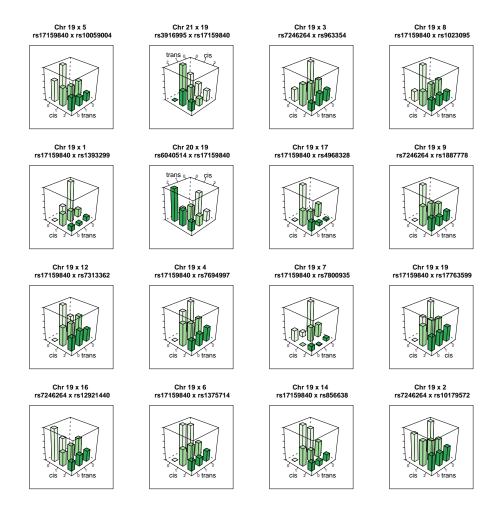


Figure S13: Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5 Each bar represents the mean phenotypic value for individuals in that genotype class.

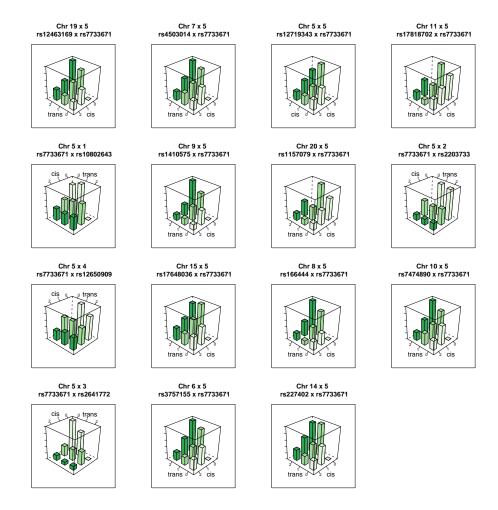


Figure S14: Genotype-phenotype maps for 15 interactions influencing the expression of CAST Each bar represents the mean phenotypic value for individuals in that genotype class.

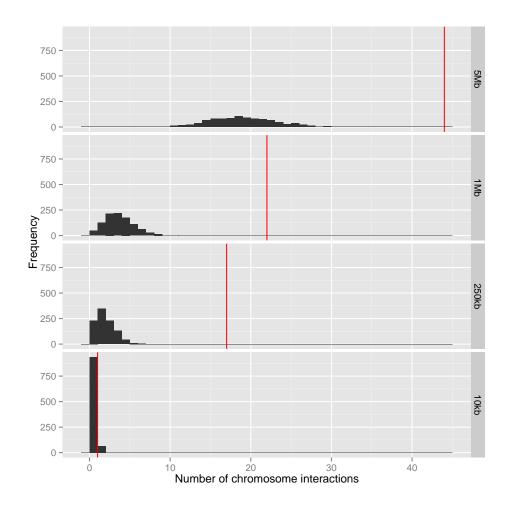


Figure S15: Number of overlaps between chromosome interactions and epistatic interactions Interacting chromosome regions may be a possible mechanism underlying epistatic interactions. The number of epistatic interactions within 20kb, 500kb, 2Mb and 10Mb of known chromosome interacting regions are shown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

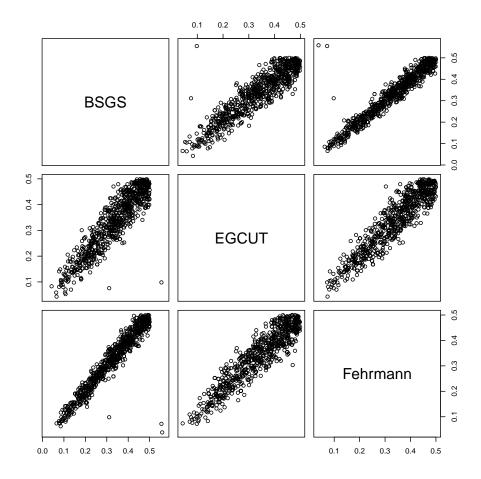


Figure S16: Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations Outliers were removed from the analysis as part of the filtering stage during replication.

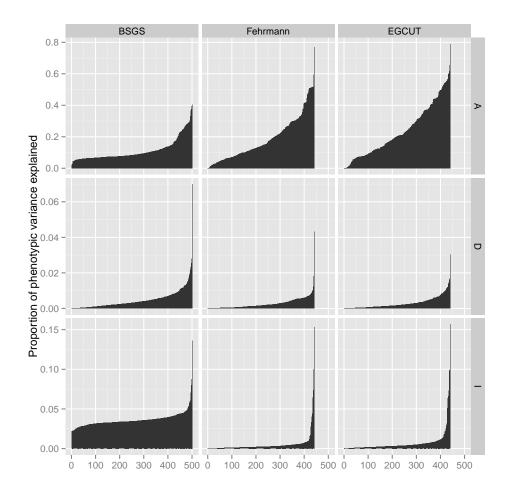


Figure S17: Comparison of variance explained by additive, dominant and epistatic effects from different cohorts How does the estimated variance decomposition change in different cohorts? The proportion of the phenotypic variance that is additive (A), dominant (D), or epistatic (I) for each putative interaction is shown on the y-axis (Note: different scales for each row). BSGS has 501 interactions whereas Fehrmann and EGCUT have 434 (x-axis). The variance estimates in each plot are ordered from lowest additive to highest. This is done independently for each cohort to depict the distribution of estimated effects.

Supplementary Tables

Table S1: Details on 501 interactions discovered in BSGS dataset

| Probe ID D Other ID | rs ID rs3752237 rs3752237 rs9455 rs227664 rs12431896 rs8058066 rs8058066 rs2395095 rs23151512 rs10881585 | Chr. 19 | Pos/Mpc | Association | | , | | - | | | | | |
|---|--|---------|-----------|-------------|------------|--------|-----------|-------------|-------|-----------------------|------------|-------|---------------|
| | | 19 | | ***** | rs ID | CITY: | Pos/Mbc | Association | BSGSe | Fehrmann ¹ | EGCUT. | Metag | Distance / Mb |
| | | | 1047161 | ABCA7 | rs596183 | 9 | 158100199 | | 5.82 | 0.38^{1} | 0.02^{1} | 0.09j | |
| | | 1 2 | 1047161 | ABCA7 | rs914737 | 10 | 139522101 | | 5.50 | 0 | | 1 | |
| | | 11 | 108207303 | A D C C S | rs4/32202 | - 0 | 72001517 | | 6.10 | 1.02 | 1.01 | 0.83 | |
| | | 14 | 7808813 | ADCK1 | rs4833241 | 0 4 | 122933691 | | 2.50 | 0.36 | 1.14 | 0.87 | |
| | | 16 | 88462550 | | rs12431896 | 14 | 78088813 | ADCK1 | 6.58 | 2.04 | 0.83 | 2.05 | |
| | | 10 | 76446305 | ADK | rs10824092 | 10 | 75929517 | | 69.9 | 18.33 | 21.21 | 39.82 | 0.517 |
| | | 10 | 51515534 | AGAP8 | rs2547996 | Ю | 95174319 | | 6.22 | | | | |
| | _ | 6 | 137112421 | | rs842647 | 2 | 61119471 | | 7.15 | 1.83 | 1.93 | 2.88 | |
| | | 9 | 29938258 | HLA-G | rs1177303 | 2 | 61388355 | AHSA2 | 5.45 | 0.92 | 0.64 | 0.94 | |
| | | 16 | 57721127 | | rs13332406 | 16 | 53489705 | AKTIP | 6.91 | 0.16 | 0.99 | 0.57 | 4.231 |
| | _ | 16 | 53536345 | AKTIP | rs1362032 | 7 | 125543391 | | 5.93 | 0.71 | 0.20 | 0.42 | |
| | | 16 | 53536345 | AKTIP | rs1473017 | 4 | 179323762 | | 6.18 | 0.27 | 0.30 | 0.23 | |
| | rs3760489 | 17 | 19581009 | ALDH3A2 | rs11720112 | က | 161996349 | | 6.26 | 0.33 | 1.37 | 1.01 | |
| | rs9322855 | 14 | 21153299 | ANG | rs4866516 | IJ | 3032625 | | 5.75 | 0.02 | 0.20 | 0.04 | |
| | rs11073891 | 15 | 90363995 | ANPEP | rs3823523 | - | 154511163 | | 5.85 | 0.44 | 1.09 | 06.0 | |
| ILMN_1763837 15 | rs11073891 | 15 | 90363995 | ANPEP | rs6846031 | 4 | 178019148 | | 6.31 | 0.47 | 0.17 | 0.26 | |
| ILMN_1768867 5 | rs6453374 | ю | 77508159 | AP3B1 | rs4684443 | က | 4818792 | | 5.94 | 0.05 | | | |
| _ | | 12 | 105580918 | APPL2 | rs2769594 | 6 | 87918528 | | 5.60 | 0.80 | 1.02 | 1.16 | |
| ILMN_3231952 17 | rs12947580 | 17 | 75768225 | | rs8079215 | 17 | 44064851 | ARL17B | 5.96 | | | | 31.703 |
| ILMN_3231952 17 | rs2834541 | 21 | 35932619 | | rs8079215 | 17 | 44064851 | ARL17B | 6.65 | | | | |
| ILMN_3231952 17 | _ | 17 | 44064851 | ARL17B | rs1950646 | 14 | 94722497 | | 7.64 | | | | |
| ILMN_3231952 17 | rs8079215 | 17 | 44064851 | ARL17B | rs2197777 | 12 | 125831219 | | 6.26 | | | | |
| ILMN_3231952 17 | rs8079215 | 17 | 44064851 | ARL17B | rs2684789 | 15 | 99492045 | | 5.98 | | | | |
| | _ | 17 | 44064851 | ARL17B | rs9834627 | က | 191203546 | | 5.72 | | | | |
| | _ | 19 | 19810050 | | rs873870 | 19 | 19738554 | | 5.30 | 12.18 | 3.25 | 14.23 | 0.071 |
| | _ | 22 | 18213057 | BID | rs9804943 | 12 | 129906275 | | 5.84 | 90.0 | 0.40 | 0.14 | |
| ••• | _ | 22 | 18233000 | | rs10888267 | - | 248059423 | | 09.9 | 0.87 | 0.16 | 0.20 | |
| | _ | 11 | 8886260 | C11ORF17 | rs6553184 | 4 | 189150656 | | 5.66 | 1.15 | 0.04 | 0.54 | |
| | _ | 16 | 6259852 | 0 | rs674754 | 13 | 46913416 | C13ORF18 | 6.66 | 0.28 | 0.28 | 0.22 | |
| | _ | 13 | 46913416 | C13ORF18 | rs6857876 | 4 ; | 153610164 | | 3.80 | 0.38 | 0.50 | 0.43 | |
| | _ | 55 | 37575398 | | rs4983382 | 14 | 105189504 | C140RF173 | 6.02 | 09.0 | 0.84 | 0.85 | |
| | _ | 15 | 92276674 | 0.10 | rs4983382 | 14 | 105189504 | C14ORF173 | 10.08 | 0.31 | 0.28 | 0.24 | |
| ILMIN_2393450 14 | TS4900001 | 10 | 19810679 | CI4ORF1/3 | FSIU/54644 | 1. | 77574400 | | 7.10 | 0.47 | 0.34 | 0.33 | |
| | _ | 14 | 77574438 | | rs10972462 | * G | 35427324 | | 4.32 | | | | |
| | _ | 14 | 77574438 | | rs6445340 | n | 63371601 | | 4.40 | | | | |
| ILMN_1804396 14 | rs2655991 | 14 | 77574438 | | rs9787151 | -1 | 63179138 | | 4.05 | | | | |
| ILMN_1804396 14 | rs4793445 | 17 | 70416307 | | rs2655991 | 14 | 77574438 | | 3.85 | | | | |
| | _ | 22 | 51151724 | | rs2655991 | 14 | 77574438 | | 4.61 | | | | |
| | | 61 | 52083552 | | rs2655991 | 41. | 77574438 | 0 | 4.69 | 0 | i c | | |
| ILMIN_1/4/34/ 1/ | rs9907897 | 17 | 110577053 | | rs/405659 | 1, | 00000 | CIORFO | 0.0 | 0.03 | 0.00 | 91.0 | |
| TI MAN 20027200 | F82004020 | 0 9 | 10011201 | | FS223/102 | ٠, | 2002300 | CIORFOR | 0.90 | 0.01 | 0.00 | 0.13 | |
| 0077200 NW:II | 1044-04-4 | 16 | 25711258 | | 18240002 | - | 2119833 | CIOBES | . r | 06.0 | 0.00 | 0.37 | |
| 11.MN 1795836 21 | _ | 2.5 | 48052838 | | rs901964 | 12 | 48676038 | ZNF641 | 4 91 | 0.00 | 80.0 | 80.0 | |
| | _ | 212 | 48027084 | | rs11701361 | 21 | 47764477 | | 9.42 | 6.08 | 16.36 | 21.67 | 0.263 |
| | | 18 | 45866512 | | rs286595 | ı D | 154348552 | C5ORF4 | 5.55 | 0.72 | 0.04 | 0.27 | |
| | | 13 | 36577930 | | rs2896452 | 00 | 86102223 | CSORF59 | 5.49 | 0.29 | 0.02 | 0.07 | |
| ILMN_1653205 | 8 rs12454561 | 18 | 31272238 | | rs2896452 | œ | 86102223 | CSORF59 | 5.45 | 0.31 | | | |
| | _ | œ | 86102223 | CSORF59 | rs1004564 | 4 | 55242625 | | 7.62 | 0.38 | 0.18 | 0.21 | |
| ILMN_1653205 8 | rs7152284 | 14 | 52273663 | | rs2896452 | œ | 86102223 | CSORF59 | 5.67 | 2.18 | 0.07 | 1.33 | |

| | цq | | | | | | | 6 | | | | | | | | | | | | | | | | | | | | | | | ۲- | | | | | - | | | | | | | | | | | | - |
|-------------------------|----------------------------|--------------|--------------|--------------|--------------|-------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|---------------|--|---|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|--------------|--------------|--------------|--------------|---------------|---------------|----------------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|-------------|
| | Distance / Mb ^h | | | | | | | 29.369 | | | | | | | | | | | | | | | | | | | | | | | 14.697 | | | | | 15.781 | | | | | | | | | | | | |
| values | Metag | 0.87 | 0.34 | | 0.42 | 1 75 | | 1.20 | 0.78 | 0.37 | 0.41 | 1.09 | 0.01 | | 0.12 | 1.72 | 0.23 | 0.03 | 0.50 | 0.54 | 0.15 | 0.22 | 0.31 | 0.02 | 0.02 | 1.20 | 0.42 | 80.0 | 1.16 | 0.45 | 0.81 | | | | 0.11 | 0.45 | 0.48 | 1.44 | 0.12 | 0.0 | 0.44 | 0.36 | 0.67 | 0.73 | | 0.02 | 1.39 | |
| $-\log_{10} p$ -values | \mathtt{EGCUT}^{f} | 0.18 | 0.00 | | 0.86 | 0.96 | | 1.57 | 1.34 | 0.52 | 0.03 | 0.59 | 0.01 | | 0.33 | 1.56 | 0.12 | 0.78 | 0.78 | 0.87 | 0.26 | 0.30 | 0.57 | 0.10 | 0.03 | 0.24 | 0.80 | 0.27 | 1.67 | 0.22 | 0.75 | | | | 0.14 | 0.07 | 0.12 | 0.16 | 0.24 | 0.10 | 0.20 | 0.02 | 1.28 | 0.36 | 0.27 | 0.07 | 0.28 | |
| Interaction statistic / | $Fehrmann^{f}$ | 1.39 | 0.94 | | 0.09 | 0.23 | | 0.36 | 0.13 | 0.27 | 0.97 | 1.15 | 0.11 | | 0.07 | 0.92 | 0.49 | 0.75 | 0.23 | 0.22 | 0.19 | 0.26 | 0.00 | 0.23 | 0.08 | 1.74 | 0.13 | 0.04 | 0.24 | 0.71 | 0.64 | | | | 0.21 | 0.95 | 0.90 | 2.16 | 0.15 | 07:0 | 0.72 | 0.92 | 0.07 | 0.95 | | 0.07 | 1.92 | 0.0 |
| Interactic | BSGS ^e F | 5.79 | 6.36 | 5.81 | 6.61 | 7.07 | 7.00 | 7.68 | 6.55 | 7.01 | 7.81 | 6.62 | 6.12 | 6.87 | 7.24 | 5.88 | 6.74 | 7.42 | 7.42 | 6.07 | 6.93 | 0.4I | 00.00 | 0.00 | 5.09 | 6.06 | 5.71 | 5.56 | 6.31 | 7.88 | 5.71 | 7.43 | 6.13 | 6.08 | 5.46 | 5.47 | 6.15 | 6.67 | 5.75 | 0 .0 0 .0 0 .0 | 5.74 | 4.75 | 5.55 | 7.54 | 5.55 | 7.56 | 6.33 | |
| | Associationd | C8ORF59 | CABCI | | INPPSE | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | | | | E | CAT | CCDCssb | VAMPS | CD55 | | | | | | CD93 | | | | CDC16 | CDK5R1 | CEACAM21 | | 0120474 | ANALCIO | CHPT1 | | CLEC12A | | CLTB | | | |
| SNP 2 | Pos/Mb ^c | 86102223 | 227174210 | 82128660 | 139266496 | 96000269 | _ | _ | _ | 96000269 | | 96000269 | _ | | | _ | _ | 238120177 | 170192890 | 224093101 | | 34447586 | 04125142 | 85816334 | 207502534 | 157182040 | 7992632 | 196721395 | 125145394 | | _ | 238899903 | 74439542 | 77264482 | 115008038 | | 42066556 | 158943044 | 180265266 | 13424//00 | 102087844 | 81937002 | 10132283 | 134236688 | 175595960 | 63121080 | 67713633 | 1000001 |
| SIS | Chr. | ∞ - | | 1 | 6 6 | υĸ | ı.c | 10 | ю | ю | ю | ю | ю | ю | ю | ro: | ıo ' | .,, | 4.0 | . 7 . | n - | 1: | 110 | 70 | - 1 | . 1 | 4 | 3 | | 13 | 50 | - · · | , , , | 17 | | 1.7 | 19 | 0.4 | 4.0 | 00 | 10 | | 12 | 10 1 | | 16 | 13 | , |
| | rs ID | rs2896452 | rs3738725 | rs684040 | rs4077515 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs10802643 | rs12650909 | rs2203733 | rs2641772 | rs11032695 | rs541207 | rs1254900 | rs6700168 | rs10255470 | rs4696726 | rs7622580 | rs838875 | rs9576388 | rs1884655 | rs10925747 | rs4328531 | rs4789981 | rs7324744 | rs11655031 | rs4803481 | rs2421050 | rs13132719 | rs15079012 | rs2695290 | rs867578 | rs7313235 | rs3903088 | rs6863172 | rs169130 | rs7336017 | 0000111 |
| | Associationd | COORE72 | | INPP5E | | | | | | | | | | | | | | CAST | CAST | CAST | CAST | | 0000000 | T C C C C C C C C C C C C C C C C C C C | | CD93 | CD93 | CD93 | CD93 | CD93 | | CD93 | CD93 | CD93 | | HOXB2 | | CEACAM21 | CEFISZ | CESI | CEST | | | | | ABCA7 | ABCA7 | |
| SNP 1 | Pos/Mb^{c} | 7188323 | 4353908 | 139289825 | 6026661 | 17321669 | 81840122 | 125369113 | 78255630 | 78392770 | 27311111 | 86107920 | 70496867 | 15166804 | 136458593 | 31149140 | 59590078 | 96000269 | 96000269 | 96000269 | 96000269 | 1700000 | 64007333 | 80280117 | 76033374 | 23074375 | 23074375 | 23074375 | 23074375 | 23074375 | 37771578 | 23076914 | 23076914 | 23076914 | 104162263 | 46614102 | 51956250 | 42066556 | 13069782 | | | 102277782 | 84471642 | 10156646 | 96929337 | 1047161 | 1047161 | 1010011 |
| S | Chr. | 16 | 10 | 6 | Ξ; | 07- | 16 | 10 | 6 | œ | 12 | 11 | 14 | 21 | 9 | - | 10 | ı, n | ı, n | ລາ | 0 0 | 0 0 | S - | 11 | 11 | 20 | 20 | 20 | 20 | 20 | 20 | 0.70 | 20 | 20 | 14 | 17 | 20 | 5. | × - | 14 | 13 | 17 | 16 | 12 | 11 | 19 | 19 | (|
| | rs ID | rs8051751 | rs12765847 | rs4266763 | rs4573661 | rs1157079 | rs12599264 | rs12719343 | rs1410575 | rs166444 | rs17648036 | rs17818702 | rs227402 | rs2822124 | rs3757155 | rs4503014 | rs7474890 | rs7733671 | rs7733671 | rs7733671 | rs7733671 | rs872311 | rs2555205 | rs3211834 | rs750801 | rs1884655 | rs1884655 | rs1884655 | rs1884655 | rs1884655 | rs2868504 | rs4813479 | rs4813479 | rs4813479 | rs861544 | rs9905940 | rs200609 | rs4803481 | rs6505780 | rs3825569 | rs591967 | rs6539014 | rs429790 | rs7305054 | rs17129799 | rs3752237 | rs3752237 | 400001 |
| | Chr. | ∞ o | o | 6 | 6 | οıc | , rü | 10 | r0 | r0 | 10 | ю | r0 | ю | 10 | ın. | ıņ i | io i | ıo ı | ه ۵ | o : | 1: | 1: | 11 | - | 20 | 20 | 20 | 20 | 20 | 50 | 0.70 | 20 | 20 | 13 | 17 | 19 | 10 | | o 1 | 15 | 17 | 12 | 12 | r0 | 19 | 16 | • |
| Expression trait | Probe ID ^b | ILMN_1653205 | ILMN_1731064 | ILMN_1712532 | ILMN_1712532 | ILMN-1717234 II.MN 1717234 | ILMN_1717234 | ILMN-1717234 | ILMN_1717234 | ILMN-1717234 | ILMN-1717234 | ILMN-1717234 | ILMIN-1717234 | ILMIN_1651705 | ILMIN_1772208 | II.MN 1784863 | ILMN_1800540 | ILMN_1704730 | ILMN_1704730 | ILMN_1704730 | ILMN_1704730 | ILMN_1704730 | ILMN-1704730 | ILMN-1704730 | II.MN 1704730 | ILMN_1704730 | ILMN_2339796 | ILMN_1730928 | ILMN_1745949 | ILMIN_1745949 | ILMIN_1703754 | ILMN-1787808 | II.MN 2202940 | ILMN_2202940 | ILMN_1663142 | ILMN_2403228 | ILMN_1674609 | ILMN_1770290 | ILMN_1770290 | TINGS TOTAL |
| Exp | Gene ID ^a | CSORF59 | CABC1 | CARD9 | CARD9 | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CAST | CASI | CAI | 10000000000000000000000000000000000000 | CD36 | CD55 | CD93 | CD93 | CDC16 | CDK5R1 | CEACAM21 | CEACAM21 | CEFISZ | CEFES | CHPT1 | CHPT1 | CLEC12A | CLEC12A | CLTB | CNN2 | CNNZ | ינוכנכ |

| | Distance / Mb ^h | | | 0.033 | | | 0.040 | | | | | | 12.255 | | | | | | | | | | | | | | | | 66,920 | 0.052 | | | | | | | | | | | | | | | | | | 10.736 | 0.23 |
|-----------------------|----------------------------|------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|---------------|--------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|-----------------------|--------------|--------------|
| alues | Metag | 0.04 | 0.15 | 42.27 | 0.11 | 1.03 | 33.53 | 0.03 | 0.34 | 0.04 | 1.47 | 0.36 | 0.44 | 09.0 | 0.44 | 0.14 | 0.42 | 0.44 | 0.16 | 0.29 | 0.58 | 0.32 | 0.37 | 0.03 | 0.10 | 01 | 0.13 | 0.01 | 0.11 | 0.97 | 1.12 | 0.70 | 0.22 | 0.35 | 0.79 | 0.10 | 0.41 | 0.02 | 0.53 | 0.11 | 0.41 | | 0.35 | 0.81 | 0.09 | 0.08 | 0.44 | F | 0.23 |
| - log10 p-values | $EGCUT^{f}$ | 0.03 | 0.36 | 16.72 | 0.41 | 0.74 | 15.06 | 0.01 | 0.53 | 0.02 | 1.87 | 0.83 | 0.10 | 98.0 | 0.41 | 0.58 | 0.25 | 0.29 | 0.41 | 0.02 | 1.17 | 0.34 | 0.04 | 0.11 | 0.00 | 0.00 | 0.52 | 0.02 | 0.00 | 1.45 | 0.27 | 1.18 | 0.35 | 0.16 | 0.47 | 0.11 | 0.59 | 0.05 | 1.12 | 0.04 | 0.40 | | 0.58 | 1.20 | 0.11 | 0.04 | 0.19 | 1.38 | 0.30 |
| | Fehrmann ^f] | 0.19 | 0.10 | 25.20 | 0.02 | 0.92 | 18.76 | 0.21 | 0.23 | 0.20 | 0.39 | 0.05 | 0.87 | 0.29 | 0.48 | 0.00 | 0.64 | 0.61 | 80.0 | 0.77 | 90.0 | 0.37 | 88.0 | 0.05 | 0.32 | 0.80 | 0.30 | 60:0 | 0.48 | 0.23 | 1.58 | 0.15 | 0.22 | 0.64 | 0.90 | 0.43 | 0.28 | 0.08 | 0.05 | 0.36 | 0.45 | | 0.20 | 0.25 | 0.20 | 0.23 | 0.74 | H - | 0.27 |
| Interaction statistic | BSGS ^e Fel | 5.55 | 6.18 | 11.99 | 5.74 | 79.0 84 | 7.16 | 5.42 | 5.89 | 5.68 | 5.81 | 5.53 | 5.85 | 5.42 | 5.44 | 9.12 | 5.62 | 5.31 | 5.47 | 6.39 | 0.00 | 6.48 | 5.51 | 7.64 | 4.00 | 4. n | 4.40 | 5.03 | 5.92 | 5.79 | 6.17 | 4.81 | 6.19 | 22.28 | 5.50 | 5.30 7.44 | 5.55 | 6.36 | 5.52 | 6.51 | 5.56 | 6.03 | 5.70 | 5.43 | 6.11 | 0.00 | 0.00 | 5.61 | 6.33 |
| | Associationd | CPVL | | | CTNNA1 | Carc | | CWF19L1 | CYBRD1 | CYBRD1 | CYBRD1 | CYBRD1 | | CYP27A1 | DAB2 | | | | | COQ10A | DHRS9 | DHRS9 | DHRS9 | L A SSE | LASSS | A O O A | LASSS | | LASS5 | DNAJB6 | DPH3 | | ECHDC2 | ECHDC2 | EHD4 | DIF 2D2 | | | | EMR2 | EMR2 | | EPHX2 | ERICH1 | ERICH1 | ERICHI | EXOC3 | FAHD1 | COQ10A |
| SNP 2 | Pos/Mb ^c | 29188475 46843631 | 62406408 | 45198355 | 138226767 | 108679892 | 88077479 | 102027407 | 172368120 | 172368120 | 172368120 | 172368120 | 160112881 | 219650616 | 39381357 | 82076988 | 187475208 | 32451144 | 88204888 | 137810259 | 169960422 | 169960422 | 169893419 | 169893419 | 153134888 | 50730458 | 61971140 | 115214154 | 51074199 | 157163614 | 16320360 | 64004670 | 53402552 | 53402552 | 42192040 | 0.0590540 | 49359676 | 129624067 | 126387391 | 14879034 | 14879034 | 102480759 | 27400604 | 578742 | 607161 | 5,000,000,000 | 428236 | 1972548 | 137810259 |
| | Chr. | r c | ıю | 21 | 10 | 10 | 11 | 10 | 7 | 7 | 61 | 61 | 7 | 73 | 10 | 9 | က | 6 | 7 | 6 | 7 | 01 (| 01 (| 2 5 | 1 17 | - 61 | 1 oc | 0 - | 12 | 7 | 8 | 18 | | Η; | 1.5 1.4 | 1.4 | 7 7 | 00 | 11 | 19 | 19 | 13 | œ | ∞ 0 | x 0 0 | x0 = | # LC | 16 | 6 |
| | rs ID | rs245884 rs1531133 | rs1473927 | rs3761385 | rs176382 | rs7079264 | rs556895 | rs12784396 | rs888427 | rs888427 | rs888427 | rs888427 | rs7591849 | rs933994 | rs835223 | rs1343244 | rs2378341 | rs7042042 | rs2519515 | rs10120023 | rs7566044 | rs7566044 | rs2161037 | rs2161037 | 1811109322 | rsz8/2008 | rs1808634 | rs4532958 | rs12427378 | rs3779589 | rs1566972 | rs4891884 | rs11206043 | rs11206043 | rs1048166 | rs1769096 | rs1553474 | rs2197210 | rs4471434 | rs9305048 | rs9305048 | rs3007765 | rs13269963 | rs12115088 | rs4735900 | rs12115088 | rs12188164 | rs344363 | rs10120023 |
| | Associationd | | CRLS1 | | i i | CISC | | | | | | | CYBRD1 | | | | DDT | | COQ10A | | | | | | A 0.0 A | LASSS | LASSE | LASSE | | | | ECGF1 | | | | FIFEA | EIF5A | EIF5A | EIF5A | | | EMR2 | | | | 11171 | PRICEI | | |
| SNP 1 | Pos/Mb ^c | 39202070 188859908 | 5986234 | 45230974 | 69500505 | 26250645 | 88117962 | 11456027 | 129994690 | 140698856 | 12318284 | 23344590 | 172368120 | 36571928 | 110451383 | 43111688 | 24248761 | 125962645 | 137810259 | 106703727 | 89468283 | 147132505 | 29959453 | 187776431 | 50636364 | 71711815 | 50730458 | 50744171 | 117994348 | 157216093 | 93409054 | 50971266 | 241911027 | 17675900 | 53244938 | 70212034 | 7221707 | 7221707 | 7221707 | 23196249 | 18761714 | 14879034 | 127909396 | 134611176 | 45337329 | 31187910 | 55228462 | 12708208 | 129591144 |
| 01 | Chr. | 21 | 20 | 21 | 18 | 116 | 11 | 11 | 4 | 6 | 10 | 20 | 73 | 20 | 7 | 17 | 22 | 11 | 6 | 11 | 12 | 7 | 21 | 4 5 | 13 | 7 0 | 12 | 2 5 | 12 | 1 | 15 | 22 | 7 | 55 | 19 | 1 0 | 17 | 17 | 17 | 21 | 20 | 19 | 11 | 11 | 5 5 | × 0 | ° 0 | 16 | 12 |
| | rs ID | rs2835998 | rs6139887 | rs9979356 | rs924943 | rs2457684 | rs7930237 | rs7108734 | rs2592948 | rs7852475 | rs11257679 | rs6137908 | rs888427 | rs6021982 | rs7778910 | rs9900173 | rs5760102 | rs4937097 | rs10120023 | rs12363827 | rs1519956 | rs1528529 | rs2831914 | rs7661304 | rs11160325 | rsillosco | rs7134595 | rs7312252 | rs871257 | rs2286842 | rs12232308 | rs140522 | rs4234091 | rs5992637 | rs10403312 | rs030724 | rs7216490 | rs7216490 | rs7216490 | rs2827076 | rs6132112 | rs9305048 | rs1107764 | rs10894861 | rs5766218 | rs/20145 | rs4755855 rs187076 | rs1560104 | rs12580388 |
| | Chr. | r- 0 | 20 | 21 | ю; | I : | 111 | 10 | 73 | 7 | 61 | 61 | 7 | 61 | 10 | 17 | 22 | 6 | | - | 7 | 01 (| 01 (| 21 5 | 7 5 | 7 5 | 2 6 | 1 0 | 12 | 1- | 8 | 22 | - | - ; | 1.5 | 7 1 | 17 | 17 | 17 | 19 | 19 | 19 | œ | oo 0 | 20 0 | x 0 0 | 0 10 | 16 | 6 |
| Expression trait | Probe ID ^b | ILMN_1682928 ILMN_1813256 | ILMN_1737685 | ILMN_1761797 | ILMN_1804854 | ILMN-1696347 | ILMN_2242463 | ILMN_1651886 | ILMN_1712305 | ILMN_1712305 | ILMN_2087692 | ILMN_2087692 | ILMN_2087692 | ILMN_1704985 | ILMN_2128428 | ILMN_1811648 | ILMN_1690982 | ILMN_1797001 | ILMN_1783996 | ILMN_1783996 | ILMN_1733998 | ILMN_1733998 | ILMN_2384181 | ILMN-2384181 | ILMIN-1755559 | ILMIN_1755559 | ILMN 1755589 | II.MN 1755589 | ILMN_1755589 | ILMN_1793770 | ILMN_2349610 | ILMN_2109708 | ILMN_1671568 | ILMN_1671568 | ILMIN_1720083 | ILMN 1794599 | ILMN 1794522 | ILMN_1794522 | ILMN_1794522 | ILMN_2353633 | ILMN_2353633 | ILMN_2353633 | ILMN_1709237 | ILMN_1731001 | ILMN_1731001 | ILMIN-1731001 | ILMN 1789419 | ILMN_2246661 | ILMN_1668063 |
| Ex | Gene IDa | CPVL | CRLS1 | CSTB | CTNNA1 | CIRC | CISC | CWF19L1 | CYBRD1 | CYBRD1 | CYBRD1 | CYBRD1 | CYBRD1 | CYP27A1 | DAB2 | DCAKD | DDT | DDX58 | DEM1 | DEM1 | DHRS9 | DHRS9 | DHRS9 | DHRS9 | DIFZE | DIFZB | DIP2B | DIP2B | DIP2B | DNAJB6 | DPH3 | ECGF1 | ECHDC2 | ECHDC2 | EHD4 | EIF 2D2 | EIF5A | EIF5A | EIF5A | EMR2 | EMR2 | EMR2 | EPHX2 | ERICH1 | ERICHI | ERICHI | EXOCA | FAHD1 | FCN1 |

| 313.001546 2 36701326 FEEZZ 6.78 0.14 0.33 0.16 313.001546 6 3 36701326 FEEZZ 6.78 0.14 0.23 0.16 313.001546 6 3 3670132 FEEZZ 6.58 0.14 0.23 0.11 313.001546 6 5 3670132 FEEZZ 6.59 0.13 0.02 0.01 313.001546 6 1000561 FLIZOMAS 6.54 0.01 0.02 0.01 315.00252 FLIZOMAS 6.44 0.03 0.01 0.02 0.01 315.0025 FLIZOMAS 6.44 0.03 0.04 0.03 0.04 315.0025 FLIZOMAS 6.44 0.03 0.04 0.03 0.04 315.0025 FLIZOMAS FLIZOMAS 6.44 0.03 0.04 0.03 0.04 315.0025 FLIZOMAS 6.44 0.03 0.04 0.03 0.04 0.03 315.0025 FLIZOMAS 6.44 0.03 0.04 0.03 | SNP 1 Pos/Mb ^c |
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| 2 30810133 FE222 6.59 0.14 0.28 0.14 1 37001033 FE224 6.69 0.14 0.28 0.11 1 37001035 FGD2 5.69 0.13 0.05 0.01 1 48169526 FL204489 6.49 0.03 0.01 0.05 1 24166026 FL2120489 6.49 0.03 0.01 0.05 1 24166026 FL2120489 6.49 0.03 0.01 0.05 1 481662 FL2120489 6.49 0.03 0.01 0.05 1 48167 0.03 0.04 | |
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| 14 48572632 0.35 0.35 4 128972852 GNLX 5.86 0.35 0.35 12 11104237 GPN3 5.78 0.05 0.46 12 11104237 GPN3 5.77 0.25 0.03 12 6902002 GPR162 5.47 0.25 0.03 1 68732819 GPR162 5.47 0.25 0.03 1 68732819 GPR177 5.45 0.17 0.40 1 68732819 GPR177 5.48 0.21 0.11 1 68732819 GPR177 5.48 0.24 0.21 1 68732819 GPR177 5.48 0.24 0.21 1 68732819 GPR177 | 85056572 rs2950520 |
| 4 128972357 5.86 0.55 0.09 2 85935287 GPN3 5.78 0.05 0.045 12 11116237 GPN3 5.77 0.25 0.045 12 6902002 GPR162 5.07 0.25 0.03 1 6972020 GPR162 5.47 0.25 0.05 3 18888013 GPR162 5.47 0.25 0.06 1 68723819 GPR177 5.45 0.72 0.67 1 68732819 GPR177 6.50 0.77 0.67 1 68732819 GPR177 6.50 0.77 0.67 1 68732819 GPR177 6.50 0.01 0.24 1 68732819 GPR177 5.86 0.24 0.24 1 68732819 GPR177 5.86 0.24 0.24 1 1010266754 GSTM1 6.10 0.01 0.24 1 110266754 <td< td=""><td>GDPD3</td></td<> | GDPD3 |
| 2 85935282 GNLY 5.78 0.02 0.45 112 6902002 GPR162 5.77 0.25 0.06 12 6902002 GPR162 5.49 0.36 0.06 12 6902002 GPR162 5.47 0.25 0.06 3 188880113 6.21 0.96 0.06 1 68732819 GPR177 5.45 0.17 0.40 1 68732819 GPR177 5.46 0.17 0.40 1 68732819 GPR177 5.43 0.31 0.11 1 68732819 GPR177 5.46 0.24 0.34 1 68732819 GPR177 5.86 0.21 0.11 1 68732819 GPR177 5.86 0.05 0.21 1 10266754 GSTM1 6.11 0.27 0.19 1 110266754 GSTM1 6.75 0.27 0.19 1 110266774 | GDPD3 |
| 12 111164237 GPN3 5.72 0.46 12 6902002 GPR162 5.49 0.36 0.46 12 6902002 GPR162 5.07 0.25 0.03 3 18860138 GPR177 6.21 0.96 0.06 1 68723819 GPR177 5.76 0.77 0.40 1 68723819 GPR177 6.50 0.79 1.43 1 68723819 GPR177 6.04 0.96 0.21 1 68723819 GPR177 6.04 0.36 0.21 1 68723819 GPR177 6.04 0.36 0.21 1 68723819 GPR177 6.50 0.21 0.21 1 101026574 GSTM1 6.11 0.24 0.25 1 110266754 GSTM1 6.11 0.27 1.14 1 11026574 GSTM1 6.36 0.25 0.48 1 11026574 <td< td=""><td>10899955 rs7577293</td></td<> | 10899955 rs7577293 |
| 12 6902002 GPR162 5.49 0.36 0.46 9 655458 5.77 0.25 0.03 1 68723819 GPR177 5.47 0.25 0.06 1 68723819 GPR177 5.47 0.25 0.06 1 68723819 GPR177 6.50 0.17 0.40 1 68723819 GPR177 6.50 0.17 0.41 1 68723819 GPR177 6.50 0.01 0.24 1 68723819 GPR177 6.50 0.01 0.24 1 168723819 GPR177 6.50 0.01 0.24 1 10266754 GSTM1 6.50 0.01 0.24 1 110266754 GSTM1 6.11 0.27 0.19 1 110266754 GSTM1 6.77 0.25 0.66 1 110266754 GSTM1 6.36 0.52 0.66 1 1532346 HBG | 26084476 rs7960552 |
| 12 6902002 GPR162 5.07 0.25 0.06 3 188880113 6.21 0.25 0.06 1 08732819 GPR177 5.46 0.72 0.06 1 08732819 GPR177 5.76 0.77 0.40 1 08732819 GPR177 5.43 0.31 0.11 1 08732819 GPR177 5.43 0.31 0.11 1 08732819 GPR177 5.46 0.05 0.11 1 08732819 GPR177 5.86 0.01 0.24 1 10266274 GSTM1 6.50 0.01 0.24 1 110266754 GSTM1 6.11 0.27 0.19 1 110266754 GSTM1 6.77 0.19 0.25 2 77919015 6.36 0.52 0.66 1 58877017 6.36 0.25 0.48 1 5871671 HBG2 5.70 0.25< | |
| 9 655458 5.47 0.25 0.06 1 1 8872819 GPR177 6.21 0.05 0.06 1 68722819 GPR177 5.76 0.77 0.40 1 68732819 GPR177 5.74 0.77 0.40 1 68732819 GPR177 5.43 0.79 1.43 1 68732819 GPR177 6.50 0.79 1.43 1 68732819 GPR177 6.50 0.21 0.21 1 68732819 GPR177 6.50 0.24 0.24 1 11026674 GSTM1 6.11 0.24 0.24 1 11026674 GSTM1 6.11 0.27 0.19 1 11026674 GSTM1 6.11 0.27 0.14 1 11026674 GSTM1 6.77 0.24 1 1252541 GSTM1 6.77 0.25 0.48 1 15271671 HBG2 5.96 <td>_</td> | _ |
| 3 18888011 G67232819 GPR177 5.45 0.96 0.06 1 68722819 GPR177 5.76 0.17 0.40 1 68722819 GPR177 6.50 0.17 0.40 1 68722819 GPR177 6.04 0.31 0.11 1 68722819 GPR177 6.50 0.01 0.24 1 68722819 GPR177 6.50 0.01 0.24 1 110266754 GSTM1 6.11 0.27 0.19 1 110266754 GSTM1 6.11 0.27 0.19 1 110266754 GSTM1 6.77 0.27 0.19 2 77919015 GSTM1 6.77 0.27 0.14 2 77919015 G.52 0.66 0.25 0.48 1 5271671 HBG2 5.94 0.05 0.64 1 5271671 HBG2 5.98 0.15 0.24 1 </td <td>GPR162</td> | GPR162 |
| 08732819 GPR177 5.45 0.77 0.67 08732819 GPR177 5.76 0.77 0.40 08732819 GPR177 5.76 0.17 0.40 08732819 GPR177 5.43 0.17 0.40 1 08732819 GPR177 5.43 0.13 0.11 1 08732819 GPR177 6.04 0.95 0.21 1 101026674 GSTM1 6.11 0.27 0.19 1 110266754 GSTM1 6.11 0.27 0.19 1 11026374 GSTM1 6.11 0.27 1.14 1 1 110254 GSTM1 6.11 0.27 0.19 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 | 2 GPR162 |
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| 1 0.8732819 GPR177 5.43 0.14 1 0.8732819 GPR177 5.43 0.31 0.11 1 0.8732819 GPR177 5.64 0.95 0.21 1 0.8732819 GPR177 5.86 0.01 0.24 1 1.01608261 GSTM1 6.51 0.27 0.19 1 1.10266754 GSTM1 6.11 0.27 0.19 1 1.10266754 GSTM1 6.77 0.29 0.66 1 1.10266754 GSTM1 6.36 0.27 0.19 2 77919015 6.36 0.27 0.14 2 1.953244 GSTM1 6.36 0.25 0.66 1.1 5271671 HBG2 5.70 0.05 0.48 1.1 5271671 HBG2 5.98 0.15 0.24 1 21308494 LQK1 6.78 0.06 0.66 1 414533835 HBG2 | _ |
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| 1 08732819 GPR177 | 11169683 rs1206 |
| 1 68732819 GPR177 6.50 0.21 0.24 15 101508261 GSTM1 6.11 0.27 0.29 1 10266754 GSTM1 6.11 0.27 0.19 1 10266754 GSTM1 6.11 0.27 0.19 1 10263241 GSTM1 6.77 0.27 0.19 1 10253241 GSTM1 6.77 0.27 0.19 1 10253246 GSTM1 6.77 0.27 0.31 1 1 5271671 HBG2 5.70 0.25 0.48 1 1 5271671 HBG2 5.98 0.15 0.24 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 | |
| 15 101508261 5.88 0.68 0.20 1 110266754 GSTM1 6.71 0.27 0.19 1 110253241 GSTM1 6.77 0.27 0.19 2 77919015 6.36 0.27 0.31 3 58777017 6.52 0.27 0.31 1 5271671 HBG2 5.47 0.00 0.66 1 5271671 HBG2 5.98 0.15 0.24 1 13088494 LQK1 6.78 0.01 0.46 1 5309695 HBG2 6.06 0.01 0.41 1 5309695 5309695 1.00 0.00 0.00 1 5309695 5309695 0.00 0.00 1 5309695 0.00 0.00 0.00 1 5309695 0.00 0.00 0.00 1 5309695 0.00 0.00 0.00 1 5309695 0.00 0.00 0.00 1 5309695 0.00 0.00 0.00 1 5309695 0.00 0.00 0.00 1 5309695 0.00 0.00 0.00 1 5309695 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 1 5305605 0.00 0.00 0.00 0 | |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | 38028634 GSDMB rs4965745 |
| 110266754 GSTMI 6.77 1.14 1102263741 GSTMI 6.77 0.27 1.14 177919015 6.36 0.52 0.27 0.31 15 8877017 6.52 0.25 0.48 11 5271671 HBG2 5.47 0.00 0.66 11 5271671 HBG2 5.98 0.15 0.24 1 13088494 LQKI 6.78 0.08 0.52 1 141333832 HBG2 6.06 0.01 0.46 | 53192833 rs11101992 |
| 1 110253241 GSTM1 6.77 0.66 15 8771017 6.52 0.27 0.31 21 19522546 5.70 0.25 0.48 11 5271671 HBG2 5.47 0.00 0.66 11 5271671 HBG2 5.98 0.15 0.24 1 121308849 LQK1 6.78 0.08 0.52 1 5309695 HBG2 6.06 0.01 0.46 | 85344527 rs11101992 |
| 2 77919015 6.36 0.52 0.66 15 5887707 6.52 0.27 0.31 21 19532546 5.70 0.25 0.48 11 5271671 HBG2 5.47 0.00 0.66 11 5271671 HBG2 5.98 0.15 0.24 1 213088494 LQK1 6.78 0.08 0.52 4 141533835 HBG2 6.78 0.01 0.41 11 5306955 HBG2 6.06 0.01 0.41 | 96159560 rs3754446 |
| 15 85877017 6.52 0.27 0.31 21 1953246 6.52 0.27 0.31 11 5271671 HBG2 5.47 0.06 0.66 11 5271671 HBG2 5.98 0.15 0.24 1 213088494 LQK1 6.78 0.08 0.52 4 1415383322 6.42 0.01 0.46 11 5309695 HBG2 6.06 0.01 0.41 | 38399979 rs4853333 |
| 21 1952246 5.70 0.25 0.48 11 5271671 HBG2 5.47 0.00 0.66 11 5271671 HBG2 5.98 0.15 0.24 1 21308849 LQK1 6.78 0.08 0.52 4 1415383832 6.42 0.01 0.46 11 5309695 HBG2 6.06 0.01 0.41 | 38399979 rs6497007 |
| 11 5271671 HBG2 5.47 0.00 0.66 11 5271671 HBG2 5.98 0.15 0.24 1 21308849 LQK1 6.78 0.08 0.52 4 141538342 6.42 0.01 0.46 11 5309695 HBG2 6.06 0.01 0.41 | 38399979 rs9983949 |
| 11 5271671 HBG2 5.98 0.15 0.24 1 1213088494 LQK1 6.78 0.05 0.52 4 1415383323 6.42 0.01 0.46 11 5309695 HBG2 6.06 0.01 0.41 | 4523167 rs2855039 |
| 1 213088494 LQK1 6.78 0.08 0.52 4 141533832 6.42 0.01 0.46 11 5309695 HBG2 6.06 0.01 0.41 | 35723501 rs2855039 |
| 4 141533832 6.42 0.01 0.46 11 5309695 HBG2 6.06 0.01 0.41 | 5271671 HBG2 rs1204218; |
| 11 5309695 HBG2 6.06 0.01 0.41 | HBG2 |
| | 4523167 rs169 |

| Expression trait Probe ID ^b Chr. | Chr. | \vdash | rs ID | Chr. | SNP 1 Pos/Mb ^c | Associationd | rs ID | Chr. | SNP 2 Pos/Mb ^c | Associationd | Interact | Interaction statistic / | $-\log_{10} p$ -values | values Metag | Distance / Mbh |
|--|--|--|---------------------|-----------|------------------------------|--------------|------------|-------|------------------------------|----------------|------------------------------|-------------------------|------------------------|-----------------|------------------------|
| CIII. IS ID CIII. FOS/MD | IS ID CITIC LOS/MD | The contract of the contract o | r Os/ MID | | 1 | Association | 15 11 | | r Os/ MID | Tipos | | Lemmann | 10051 | Meta | Distance / MD |
| LLMIN_2084825 11 rs12975066 19 35723501 ILMN_2084825 11 rs2855039 11 5271671 HB | 19 35723501 | 19 35723501 | 35723501 5271671 | | Н | HBG2 | rs2855039 | 11 | 5271671 213088494 | HBG2 LOK1 | 5.77 | 80.0 0.0 0.0 | 0.13 | 0.05 | |
| 11 rs2855039 11 5271671 | rs2855039 11 5271671 | 11 5271671 | 5271671 | | HBG | 1 21 | rs12503379 | 4 | 141533832 | | 5.98 | 0.00 | 0.46 | 0.10 | |
| ILMN-3266186 12 rs2109029 16 6036851 | rs2109029 16 6036851 | 16 6036851 | 6036851 | | 1001 | - | rs4760636 | 12 | 48173352 | HDAC7 | 5.75 0.75 | 5 | O L | 0 | |
| 17 rs1942719 18 71237270 | rs1942719 18 71237270 | 12 13143613 | 71237270 | | D D | | rs7213057 | 17 | 80378939 | HEXDC | 5.81 | 1.61 | 0.34 | 1.22 | |
| 6 rs4899635 | rs4899635 14 | 14 | | 77532672 | | | rs7192 | 9 | 32411646 | HLA-DRB6 | 5.94 | 0.90 | 0.16 | 0.52 | |
| rs12435486 14 | rs12435486 14 | 0 4 | | 98670849 | | | rs2525404 | οœ | 28876221 | HMBOX1 | 6.54 | 0.92 | 1.11 | 1.34 | |
| 8 rs2837803 21 | rs2837803 21 | 21 | | 42112794 | | | rs4732890 | 000 | 28751381 | HMBOX1 | 6.62 | 0.05 | 1.01 | 0.46 | |
| 8 rs4765451 12 1 | rs4765451 12 1 | 12 1 | _ | 127237464 | | | rs8180944 | œ | 28904086 | HMBOX1 | 5.80 | 0.39 | 3.13 | 2.52 | |
| 8 rs587639 8 132725731 | 8 132725731 | 8 132725731 | 132725731 | | | | rs7837237 | oo i | 28876221 | HMBOX1 | 6.58 | 0.55 | 0.34 | 0.44 | 103.850 |
| 8 rs8180944 8 28904086 | 8 28904086 | 8 28904086 | 28904086 | | Ц; | HMBOXI | rs4553956 | 1 m | 189533772 | | | | 0.03 | 2.20 | |
| 28904086 13 110897444 | 28904086 13 110897444 | 28904086 13 110897444 | 110897444 | | - | HMBOAL | rs/810884 | ~ oc | 28904086 | HMBOX1 | 5.45 | 0.67 | 0.26 | 0.52 | |
| 5 rs6894268 5 1 | 52 | 52 | . – | 179032488 | | | rs4700810 | n | 178991794 | | 15.38 | 8.55 | 3.01 | 10.37 | 0.041 |
| 1 rs555812 16 | 16 | 16 | | 88882257 | | | rs4654783 | 1 | 22439520 | HSPC157 | 5.51 | | | | |
| 1 rs6063164 20 | 20 | 20 | | 46486900 | | | rs4654783 | -1 | 22439520 | HSPC157 | 6.51 | | | | |
| 1 rs662739 12 121229893 | 12 121229893 | 12 121229893 | 121229893 | | (| | rs4654783 | | 22439520 | HSPC157 | 6.61 | | | | |
| ILMN_3394087 1 rs7088558 10 101884937 C | 10 101884937 | 10 101884937 | 101884937 | | ב כ | CWF19L1 | rs4654783 | 1.5 | 22439520 | HSPC157 | 6.48 | 01.0 | 0 | 000 | |
| 16 rs765044 19 2560423 | rs765044 19 2560423 | 19 2560423 | 2560423 | | 3 | 4 | rs1554999 | 1 1 1 | 3115628 | 11.32 | . r. . r. . r. . r. | 0.69 | 0.23 | 0.43 | |
| 9 rs8044524 16 8 | rs8044524 16 8 | 4 16 8 | œ | 81603771 | | | rs1127152 | 6 | 139335599 | INPP5E | 5.58 | 1.46 | 0.84 | 1.55 | |
| 7 rs757355 12 47970693 | rs757355 12 47970693 | 12 47970693 | 47970693 | | | | rs849341 | -1 | 28288174 | | 8.16 | 0.02 | 0.26 | 0.05 | |
| 21 rs2186344 21 39606769 | rs2186344 21 39606769 | 21 39606769 | 39606769 | | X | KCNJ15 | rs424299 | 11 | 5570771 | | 5.64 | 0.65 | 0.13 | 0.33 | |
| 19 rs649216 19 55324635 | rs649216 19 55324635 | 19 55324635 | 55324635 | | Σ, | KIR2DL1 | rs6419960 | 4 0 | 189055298 | .0 | 4.74 | 0.46 | 0.89 | 0.77 | |
| 1LMN-1811104 3 rs4349034 13 84597119 | rs4349034 13 | 13 | - | 84597119 | | | rs727905 | n m | 119119433 | KTELCI | 5.53 8.53 | 0.08 | 08.0 | 0.37 | |
| 22 rs4822006 22 41519362 | rs4822006 22 41519362 | 22 41519362 | 41519362 | | Н | L3MBTL2 | rs1294338 | · | 233438952 | IVI EFFO | 80.10 | 0.33 | 0.04 | 0.00 | |
| 4 rs7042087 9 | 9 | 9 | _ | 132602868 | | | rs7658240 | 4 | 17588950 | LAP3 | 5.72 | 0.24 | 0.47 | 0.31 | |
| 1 rs1891432 1 2 | | | CI | 203877662 | | | rs10900520 | | 203780591 | | 19.16 | 18.60 | 11.22 | 29.24 | 0.097 |
| TEMN 9419914 17 "=1945052 19 989/1059 | 120 | 120 | | 2897 T022 | | | rs000/003 | чĸ | 170608360 | LULUALI | 6.00 | и 6 | 0.40 | 0 37 | |
| 19 rs3859532 19 | rs3859532 19 | 19 | | 54827248 | | LILRAS | rs714789 | 18 | 71561497 | | 6.13 | 0.23 | 0.03 | 0.02 | |
| 15 rs11247226 15 1 | rs11247226 15 1 | 15 1 | 1 | 101120963 | | LINS1 | rs1278387 | 10 | 127804531 | | 5.89 | | 0.13 | | |
| 19 rs6009951 22 5 | rs6009951 22 | 1 22 | | 51151350 | | | rs8101804 | 19 | 18496107 | LRRC25 | 5.68 | 0.11 | 0.35 | 0.15 | |
| 6 rs977785 6 | rs977785 6 | 9 ; | | 6588881 | | LY86 | rs1543675 | I | 78946879 | | 5.61 | 0.13 | 0.15 | 0.07 | |
| ILMN_1815205 12 rs2168029 12 69734641 | rs2168029 12 69734641 | 12 69734641 | 69734641 | | | LYZ | rs11981725 | ٠. | 154137150 | 1377 | 5.95 | 0.15 | 0.03 | 0.03 | |
| 12 EST/1820 10 (72/0904 19 rs9168099 19 69734641 | EST(1020 10 (1210904 12 co.2168090 12 60734641 | 19 69734641 | 69734641 | | | 1.7.2 | rs2105029 | 7 0 | 130319560 | 717 | 6.71 | 0.43 | 0.03 | 0.10 | |
| 7 187783715 7 | rs7783715 7 | 1 1- | , | 1923385 | | MADILI | rs6414306 | . m | 127011798 | | 5.62 | 0.25 | 0.88 | 0.59 | |
| 6 rs7983718 13 1 | rs7983718 13 | 13 | | 103203146 | | | rs1096699 | 9 | 43528441 | MAD2L1BP | 5.93 | 0.63 | 1.11 | 1.09 | |
| 20 rs974607 21 | rs974607 21 | 21 | • | 29435869 | | | rs6060034 | 20 | 33351864 | MAP1LC3A | 5.78 | 1.18 | | | |
| 3 rs10869600 9 7 | rs10869600 9 | 6 | | 78225815 | | | rs13069559 | က | 152187431 | MBNL1 | 7.96 | 0.79 | 0.27 | 0.54 | |
| 3 rs11053043 12 | 3 12 | 3 12 | | 9932070 | | | rs13069559 | က | 152187431 | MBNL1 | 6.70 | 0.08 | 2.21 | 1.37 | |
| 3 rs1164596 13 | rs1164596 13 | 13 | | 97100681 | | | rs13069559 | က | 152187431 | MBNL1 | 7.38 | 1.43 | 0.63 | 1.34 | |
| 3 rs11981513 7 | rs11981513 7 | 7 | 7 94648239 | 94648239 | | | rs13069559 | က | 152187431 | MBNL1 | 7.71 | 0.43 | 5.36 | 4.58 | |
| 3 rs16864367 3 1 | rs16864367 3 1 | . 3 | 3 152234166 | 152234166 | | | rs13079208 | က | 152116652 | | 13.49 | 16.25 | 24.74 | 41.56 | 0.118 |
| 3 rs2030926 6 11 | rs2030926 6 11 | 6 11 | 11 | 114067127 | | | rs13069559 | က | 152187431 | MBNL1 | 7.10 | 0.91 | 5.80 | 5.53 | |
| 3 rs218671 17 | 17 | 17 | | 6604708 | | | rs13069559 | က | 152187431 | MBNL1 | 7.63 | 0.62 | 5.82 | 5.23 | |
| ILMN_2313158 3 rs2213360 22 34291750 ILMN_2313158 3 rc2305802 10 16038535 | 252 | 252 | | 34291750 | | | rs13069559 | ကက | 152187431 | MBNL1 MBNL1 | 6.05 | 0.52 | 0.72 | 0.70 | |
| 3 rs2614467 14 | 14 | 14 | | 99770138 | | | rs13069559 | ာက | 152187431 | MBNL1 | 5.74 | 4.13 | 2.22 | 5.30 | |
| | | | | | | | | | | • | | | | Continu | Continued on next page |

| Ex | Expression trait | | | | SNP 1 | | | | SNP 2 | | Interact | Interaction statistic / | $-\log_{10} p$ -values | alues | |
|----------------------|-----------------------|-------|------------|------|--------------|--------------|------------|-------|--------------|--------------|---|-------------------------|-------------------------------|-------|----------------|
| Gene ID ^a | Probe ID ^b | Chr. | rs ID | Chr. | Pos/Mb^{c} | Associationd | rs ID | Chr. | Pos/Mb^{c} | Associationd | BSGSe | Fehrmann ^f | $\mathtt{EGCUT}^{\mathrm{f}}$ | Metag | Distance / Mbh |
| MBNL1 | ILMN_2313158 | 3 | rs4392535 | 4 | 41513423 | | rs13069559 | 3 | 152187431 | MBNL1 | 8.39 | 0.02 | 4.33 | 3.02 | |
| MBNL1 | ILMN_2313158 | 33 | rs4735830 | œ | 895841 | | rs13069559 | 3 | 152187431 | MBNL1 | 6.74 | 0.32 | 4.21 | 3.38 | |
| MBNL1 | ILMN_2313158 | က | rs4939558 | 18 | 46278591 | | rs1522374 | က | 152235530 | | 7.72 | 0.03 | 0.27 | 0.07 | |
| MBNL1 | ILMN_2313158 | က | rs6128397 | 20 | 57253132 | | rs16864367 | က | 152234166 | | 7.22 | 1.34 | 1.15 | 1.73 | |
| MBNL1 | ILMN_2313158 | က | rs7710738 | IJ | 22101322 | | rs13069559 | 33 | 152187431 | MBNL1 | 7.92 | 2.55 | 7.89 | 9.28 | |
| MBP | ILMN_2331544 | 18 | rs6079849 | 20 | 15462611 | | rs2051344 | 18 | 74715653 | MBP | 6.26 | 0.10 | 0.03 | 0.02 | |
| MBP | ILMN_2398939 | 18 | rs139568 | 22 | 42210985 | | rs2051344 | 18 | 74715653 | MBP | 5.56 | 0.03 | 0.23 | 0.02 | |
| MBP | ILMN_2398939 | 18 | rs2051344 | 18 | 74715653 | MBP | rs1125539 | n | 155204939 | | 5.79 | 0.05 | 0.76 | 0.27 | |
| MBP | ILMN_2398939 | 18 | rs2051344 | 18 | 74715653 | MBP | rs2619046 | ្ន | 55097534 | | 6.03 | 0.15 | 0.50 | 0.26 | |
| MBP | ILMN_2398939 | 18 | rs4805021 | 19 | 33436367 | | rs2051344 | 18 | 74715653 | MBP | 5.82 | 0.03 | 0.47 | 0.14 | |
| MBP | ILMN_2398939 | 18 | rs8092433 | 18 | 74747424 | | rs4890876 | 18 | 74732087 | | 5.40 | 2.06 | 21.91 | 28.73 | 0.015 |
| MEGF9 | ILMN_2290118 | 6 | rs13039689 | 20 | 51922071 | | rs966396 | 6 | 123453281 | MEGF9 | 4.63 | 1.13 | 1.33 | 1.71 | |
| MFN2 | ILMN_1651385 | | rs7989895 | 13 | 109401737 | | rs4846085 | | 12050634 | MFN2 | 5.76 | 0.61 | 0.25 | 0.41 | |
| MGC13057 | ILMN_1787526 | 61 | rs12718598 | -1 | 50428445 | MGC13057 | rs11725347 | 4 | 171860973 | | 5.81 | 0.13 | 0:30 | 0.14 | |
| MGC13057 | ILMN_1787526 | 61 | rs674608 | 18 | 69070772 | | rs12718598 | -1 | 50428445 | MGC13057 | 5.57 | 0.02 | 1.03 | 0.20 | |
| MGC13057 | ILMN_1787526 | 61 | rs8058318 | 16 | 82628245 | | rs12718598 | - | 50428445 | MGC13057 | 7.05 | 0.11 | 0.12 | 0.02 | |
| MGC72104 | ILMN_1688318 | 20 | rs845787 | 20 | 26197931 | MGC72104 | rs2660665 | œ | 137526799 | | 4.17 | 0.02 | 80.0 | 0.05 | |
| MGST3 | ILMN_1751956 | - | rs740441 | 17 | 55779644 | | rs4147592 | - | 165600146 | MGST3 | 5.45 | 0.57 | 0.27 | 0.40 | |
| MPZL2 | ILMN_1752932 | 11 | rs1805 | 11 | 118076069 | MPZL2 | rs11771552 | 7 | 154708716 | | 5.90 | 0.01 | 0.23 | 0.04 | |
| MPZL2 | ILMN_1752932 | 11 | rs7316716 | 12 | 19953193 | | rs1805 | 11 | 118076069 | MPZL2 | 5.64 | 0.97 | 1.08 | 1.35 | |
| MRPL36 | ILMN_1800197 | rO | rs17469061 | 10 | 8436432 | | rs750495 | IJ | 1782046 | MRPL36 | 68.9 | 0.34 | 0.18 | 0.19 | |
| MRPL43 | ILMN_2258774 | 10 | rs6564769 | 16 | 80641040 | | rs2863095 | 10 | 102746503 | MRPL43 | 5.71 | 0.26 | | | |
| MRPL52 | ILMN_1713966 | 14 | rs1950857 | 14 | 26710271 | | rs3811188 | 14 | | MRPL52 | 6.56 | 0.14 | 0.44 | 0.22 | |
| MRPS10 | ILMN_1663664 | 9 | rs10955512 | œ | 110202230 | | rs722269 | 9 | 42194916 | MRPS10 | 7.48 | 0.46 | 0.70 | 0.64 | |
| MRPS10 | ILMN_1663664 | 9 | rs11698155 | 20 | 15063214 | | rs2395803 | 9 | 42158596 | MRPS10 | 6.85 | 0.31 | 0.63 | 0.46 | |
| MRPS10 | ILMN_1663664 | 9 | rs1420537 | 16 | 52453567 | | rs13217993 | 9 | 42164401 | MRPS10 | 6.21 | 0.41 | 0.25 | 0.28 | |
| MTMR15 | ILMN_2152178 | 12 | rs7178375 | 15 | 31215935 | MTMR10 | rs12431444 | 14 | 42068689 | | 5.18 | 1.87 | 1.87 | 2.86 | |
| MX1 | ILMN_1662358 | 21 | rs459498 | 21 | 42795027 | | rs11160227 | 14 | 95514596 | | 6.31 | 0.46 | 0.52 | 0.50 | |
| MX1 | ILMN_1662358 | 21 | rs459498 | 21 | 42795027 | | rs4973801 | 3 | 26706382 | | 5.83 | 0.11 | 0.50 | 0.23 | |
| MX1 | ILMN_1662358 | 21 | rs459498 | 21 | 42795027 | | rs8130120 | 21 | 29363604 | | 6.78 | 0.29 | 0.92 | 0.65 | 13.431 |
| MYBPC3 | ILMN_1781184 | 11 | rs10134030 | 14 | 61593110 | | rs1317149 | 11 | 47486885 | MYBPC3 | 5.56 | 0.13 | 0.46 | 0.23 | |
| MYBPC3 | ILMN_1781184 | 11 | rs7322768 | 13 | 109550561 | | rs7124681 | 11 | 47529947 | MYBPC3 | 5.70 | 0.04 | 0.08 | 0.02 | |
| MYOM1 | ILMN_1680344 | 18 | rs4798075 | 18 | 3247256 | MYOM1 | rs2737422 | œ | 134485237 | | 6.02 | 0.74 | 0.15 | 0.40 | |
| N4BP1 | ILMN_2201966 | 16 | rs12444224 | 16 | 87580855 | | rs11649236 | 16 | 48632478 | N4BP1 | 5.54 | 2.00 | 0.59 | 1.77 | 38.948 |
| NAAA | ILMIN_1668605 | 4 - | rs2/0/5/5 | - 0 | 14/038/23 | | rs0820085 | 4 - | 108/0229 | NAAA | 0.00 | 0.20 | 0.03 | 0.04 | |
| NAAA | ILMIN_2391512 | 4 ox | rs20/1856 | N 00 | 144663661 | NAPRT1 | rs0826085 | 4 - | 78870229 | NAAA | 5.40 | 0.27 | 0.43 | 0.00 | |
| NAPRTI | II.MN 1710752 | 0 00 | rs2123758 | o oc | 144663661 | NAPRTI | rs3889129 | + ox | 144613680 | | 0.00 | 15.12 | 16.08 | 30.10 | 0.050 |
| NAPRT1 | ILMN_1710752 | 000 | rs2123758 | 000 | 144663661 | NAPRTI | rs4862705 | 4 | 187445552 | | 5.62 | 1.27 | 0.19 | 0.81 | |
| NAPRT1 | ILMN_1710752 | 00 | rs2123758 | 00 | 144663661 | NAPRT1 | rs6455553 | 9 | 167811764 | | 6.12 | 0.87 | 0.76 | 1.01 | |
| NAPRT1 | ILMN_1710752 | 00 | rs2123758 | œ | 144663661 | NAPRT1 | rs700276 | 7 | 146189057 | | 6.86 | 1.10 | 2.58 | 2.77 | |
| NAPRT1 | ILMN_1710752 | œ | rs2123758 | œ | 144663661 | NAPRT1 | rs7571561 | 2 | 213386267 | | 6.03 | 0.13 | 0.47 | 0.23 | |
| NAPRT1 | ILMN_1710752 | œ | rs2208123 | 22 | 48214812 | | rs2123758 | œ | 144663661 | NAPRT1 | 6.60 | 0.29 | 0.88 | 0.63 | |
| NAPRT1 | ILMN_1710752 | œ | rs4743420 | 6 | 103488089 | | rs2123758 | œ | 144663661 | NAPRT1 | 5.50 | 0.12 | 0.17 | 80.0 | |
| NAPSA | ILMN_1784040 | 19 | rs1405655 | 19 | 50882619 | NAPSB | rs930280 | 6 | 98391111 | | 5.58 | 0.82 | 0.10 | 0.40 | |
| NAPSB | ILMN_2109416 | 61 | rs1405655 | 61 | 50882619 | NAPSB | rs10882406 | 10 | 95976932 | | 10.1 10.1 10.1 | 0.67 | 1.10 | 1.12 | |
| NAPSB | ILMIN_2109416 | 61 | rs1405655 | 61 | 50882619 | NAPSB | rs7577137 | 201.0 | 234721287 | | 0.08 | 1.2.1 | 0.44 | 17.1 | 0 |
| NCL | ILMIN-2121437 | 201.5 | rs7563453 | 21 6 | 232301670 | | 11102012 | 71 7 | 232291471 | 0.4011016 | 7.31 | 7.51 | 6.33 | 12.70 | 0.010 |
| NDOFAIZ | TIMIN_1737738 | 7 5 | rs2/469/1 | 77 - | 37101890 | NIMETO | rs11107847 | 21 0 | 163114006 | NDOFAIZ | 50 50 50 50 50 50 50 50 50 50 50 50 50 5 | 0.39 | 0.18 | 0.77 | |
| NMIZ | ILMIN-1030378 | 1 91 | rs10906557 | 0,0 | 10259490 | Z I IVI VI | 1S12490976 | ٥ ۾ | 50710109 | SCON | 0.04 0.04 | 24.0 | 40.0 | 0.55 | |
| NRRES | ILMN 3237385 | 10 | re11063498 | 1.0 | 5200078 | | 20120261 | 2 0 | 65133800 | NBBE | 0. v | # 4 | * 0.0 | 00.0 | |
| NEBF2 | ILMN_3237385 | 10 | rs2375269 | 1 : | 69876894 | | rs7923609 | 10 | 65133822 | NRBF2 | 5.53 | | | | |
| | | | | | | | | | | | 11111 | | | | 4 |

| Ex | Expression trait | | | | SNP 1 | | | | SNP 2 | | Interacti | Interaction statistic / | - log10 p-values | values | |
|----------------|------------------------------|------------|------------|----------------|---------------------|--------------|------------|----------------|---------------------|-------------------|----------------------|-------------------------|------------------|---------|----------------------------|
| Gene IDa | Probe ID ^b | Chr. | rs ID | Chr. | Pos/Mb ^c | Associationd | rs ID | Chr. | Pos/Mb ^c | Associationd | BSGS _e | Fehrmann ^f | $EGCUT^{f}$ | Metag | Distance / Mb ^h |
| NRBF2 NRBF2 | ILMN_3237385 ILMN 3237385 | 10 | rs6025645 | 20 | 56157341 | | rs7923609 | 10 | 65133822 | NRBF2 NRBF2 | 5.45 | | | | |
| NRD1 | ILMN_1800897 | 1 | rs4852124 | - 61 | 240680022 | | rs6588415 | 1 | 52334047 | MILLE | 6.13 | 0.47 | 0.02 | 0.17 | |
| NUDT18 | ILMN_1787885 | œ | rs5017351 | 11 | 25453482 | | rs1005901 | œ | 21964378 | NUDT18 | 5.44 | 0.03 | 0.46 | 0.15 | |
| OAS1 | ILMN_1658247 | 12 | rs11613438 | 12 | 113480510 | | rs1047944 | 9 | 163997467 | | 8.59 | 1.27 | 1.55 | 2.03 | |
| OASI | ILMN_1658247 | 7 7 | rs13311 | 7 7 | 113448652 | | rs2072133 | 7 7 | 113409260 | 200 | 4.13 | 4.12 | 0.81 | 3.86 | 0.039 |
| OPTN | ILMN 2381899 | 101 | rs7192613 | 16 | 74286646 | | rs17512962 | 7 0 | 13169066 | OPTN | 5.64 | 0.42 | 0.06 | 0.10 | |
| OSBPL5 | ILMN_2307032 | 11 | rs2829679 | 21 | 26662543 | | rs998639 | 11 | 3149249 | OSBPL5 | 5.00 | 0.36 | 0.00 | 0.07 | |
| OSTF1 | ILMN_1742456 | 6 | rs17780195 | 17 | 70624189 | | rs2273770 | 6 | 77755469 | OSTF1 | 5.42 | 0.16 | 0.87 | 0.49 | |
| OSTF1 | ILMN_1742456 | 6 | rs2273770 | 6 | 77755469 | OSTF1 | rs7718088 | 10 | 179590952 | | 5.42 | 1.20 | 80.0 | 0.62 | |
| OVGP1 | ILMN_1734542 | | rs10802822 | - | 240132968 | | rs1264898 | | 111992823 | OVGP1 | 5.43 | 0.13 | 1.48 | 0.88 | 128.140 |
| OVGP1 | ILMN_1734542 | ⊣ 1 | rs347331 | က၊ | 140148107 | | rs1264894 | ٠, | 111969719 | OVGP1 | 6.04 | 0.25 | 1.21 | 0.82 | |
| PAM | ILMN-2313901 | οĸ | rs28092 | οĸ | 102149795 | PAM | rs784600 | - 6 | 2139553 | HPCAL4 | 5.59 | 0.66 | 0.44 | 0.59 | |
| PEX5 | ILMN_1660232 | 12 | rs10444467 | 17 | 128052636 | | rs4329748 | 17 | 7364442 | PEX5 | 0.00 | 0.09 | 0.71 | 0.32 | 120,688 |
| PEX5 | ILMN_1660232 | 12 | rs7495797 | 12 | 27246462 | | rs4329748 | 12 | 7364442 | PEX5 | 5.74 | 0.34 | 0.00 | 0.13 | |
| PFAAP5 | ILMN_1797893 | 13 | rs131969 | 22 | 49151303 | | rs7328733 | 13 | 33126737 | PFAAP5 | 5.64 | 0.87 | 0.36 | 0.67 | |
| PGLYRP1 | ILMN_1704870 | 19 | rs12982353 | 19 | 46529456 | PGLYRP1 | rs1263806 | 14 | 21982957 | | 6.51 | 0.03 | 0.65 | 0.24 | |
| PHCA | ILMN_1812552 | 11 | rs493642 | 11 | 123097386 | | rs10736812 | 11 | 76708086 | PHCA | 5.51 | 0.36 | 0.90 | 0.70 | 46.389 |
| PIK3IP1 | ILMN_1719986 | 55 | rs4141404 | 55 | 31675185 | PIK3IP1 | rs2065841 | ; | 61728597 | | 5.60 | 0.20 | 0.01 | 0.03 | |
| PISD | ILMN-1793934 | 55 | rs470072 | 7.7 | 32263131 | PISD | rs10498313 | 14 | 30398876 | | 5.23 | 0.02 | 0.87 | 0.33 | |
| PISD | ILMN_1793934 | 55 | rs6518752 | 7.7.5 | 31999127 | PISD | rs954627 | - 0 | 18236681 | 400 | 7.11 | 0.00 | 1.19 | 84.0 | |
| PISD | ILMN_1793934 | 7.7 | rs715572 | 77. | 33234931 | | rs6518754 | 77 0 | 32097775 | PISD | 4.12 | 0.05 | 0.42 | 0.15 | 1.137 |
| PNRD | ILMIN_1/4504 | N C | rs0809411 | o 1 | 158/81604 | | rs4012004 | NI C | 140467106 | PINED PINED A7 | 0.50 0.50 0.50 | 0.10 | 0.04 | 0.04 | |
| PPFIRD2 | ILMN 1675656 | n = | rs011019 | 30 | 432/109 | | rs4758001 | . . | 7559930 | PDFIRDS | 0.10 | 0.01 | 0.70 | 0.00 | |
| PPP9R3C | II.MN 1662617 | 17 | re12914603 | 4 - | 58350896 | | re11156875 | 14 | 35619816 | PPP9R3C | + - x | 0.13 | 0.00 | 07:0 | |
| PPP2R5A | ILMN 1738784 | <u> </u> | rs10930170 | 27 67 | 166399467 | | rs12120009 | | 212447167 | PPP2R5A | 5.63 | 0.72 | 0.48 | 0.66 | |
| PPP2R5A | ILMN_1738784 | - | rs12423255 | 12 | 123595064 | | rs12120009 | - | 212447167 | PPP2R5A | 5.72 | 0.08 | 0.95 | 0.46 | |
| PPP2R5A | ILMN_1738784 | 1 | rs1889083 | 13 | 66222691 | | rs12120009 | Т | 212447167 | PPP2R5A | 5.61 | 0.36 | 0.13 | 0.17 | |
| PPP2R5A | ILMN_1738784 | 1 | rs682334 | 11 | 107417238 | | rs12120009 | | 212447167 | PPP2R5A | 5.65 | 1.69 | 0.28 | 1.21 | |
| PPP2R5A | ILMN-1738784 | 1 | rs7757871 | 9 | 135030045 | | rs12120009 | | 212447167 | PPP2R5A | 5.95 | 0.37 | 90.0 | 0.12 | |
| PPP2R5A | ILMN_1738784 | - ; | rs7871178 | 6 | 27148475 | | rs12120009 | ; | 212447167 | PPP2R5A | 5.72 | 0.16 | 0.30 | 0.16 | |
| PRDX5 | ILMN_1711606 | Ι. | rs8019823 | 14 | 95040482 | | rs11600990 | | 64082807 | PRDX5 | 6.43 | 0.81 | 0.14 | 0.44 | |
| PRKCBI | ILMIN_1713603 | 16 | rs2188355 | 16 | 23867776 | 10000 | rs10492793 | 16 | 12639800 | | 7.34 | 0.53 | 0.11 | 0.25 | 11.228 |
| PRMT2 | ILMN 1675038 | 21. | rs2839372 | 21 | 48063862 | CTIONE OF | rs11701058 | 21 | 47776382 | C21ORF57 | 2.00 | 0.69 | 4.47 | 4.06 | 0.287 |
| PSMB1 | ILMN_1789176 | 9 | rs3862607 | 11 | 121774705 | | rs13207114 | 9 | 170877444 | PSMB1 | 5.79 | | 0.44 | | |
| PSMB1 | ILMN_1789176 | 9 | rs4890648 | 18 | 43983954 | | rs6928843 | 9 | 170890384 | PSMB1 | 5.14 | 0.00 | 0.26 | 0.04 | |
| PSMB1 | ILMN_1789176 | 9 | rs6060930 | 50 | 30347832 | | rs9295415 | 9 | 170823379 | PSMB1 | 5.44 | 0.44 | 0.21 | 0.27 | |
| PSMB1 | ILMN_1789176 | 9 | rs6928843 | 9 | 170890384 | PSMB1 | rs2769689 | | 225797957 | | 4.58 | 1.95 | 0.64 | 1.78 | |
| PSMB1 | ILMN_1789176 | 9 9 | rs7299749 | 15 | 131727816 | | rs13207114 | 9 ; | 170877444 | PSMB1 | 5.42 | 1.18 | 0.32 | 0.86 | |
| PWP1 | ILMN_1743049 | 12 | rs2353567 | 14 | 95478823 | | rs11036212 | Ξ; | 5221825 | PTDSS1 | 5.00 | 0.03 | 0.48 | 0.15 | |
| PWP1 | ILMN-1743049 | 7 7 | rs4969205 | 17 | 76598123 | | rs11036212 | 11 | 5221825 | PTDSSI | 5.90 | 0.80 | 0.08 | 85.0 | |
| 1 W 7 I | ILMN 1679443 | 7 7 | 18031302 | 1 9 | 106348946 | | re10000212 | | 17596689 | ODDB | 7 C | 0.02 | | | |
| RABSIP | ILMN 1803197 | 13 | rs241730 | 2.5 | 33375704 | | rs7305307 | 15 | 70235726 | 11 17 | | 0.25 | 80.0 | 50.0 | |
| RABAC1 | ILMN_2207363 | 13 | rs1075728 | 19 | 42462788 | RABAC1 | rs7951628 | 11 | 120161117 | | 6.42 | 0.28 | 0.84 | 0.59 | |
| RBL2 | ILMN_1756999 | 16 | rs9931702 | 16 | 53526551 | AKTIP | rs1863464 | 15 | 26938488 | | 6.38 | 0.03 | 0.31 | 80.0 | |
| RCN1 | ILMN_1800276 | 11 | rs10879131 | 12 | 41147155 | | rs4922579 | 11 | 32136436 | RCN1 | 5.23 | 0.58 | 0.37 | 0.47 | |
| RCN1 | ILMN_1800276 | 11 | rs4922579 | 11 | 32136436 | RCN1 | rs11166957 | ∞ - | 141177468 | | 4.32 | 0.41 | 0.09 | 0.17 | |
| 1 | | | | : | | | | | | | | | 1 | Continu | Continued on next page |

Table S1 - continued from previous page

| Exp | Expression trait | | | | SNP 1 | | | | SNP 2 | | Interac | Interaction statistic / | $-\log_{10} p$ -values | ralues | |
|----------------------|-----------------------|--------|------------|------|--------------|--------------|-----------------------|-------|--------------|-----------------------------|---|-------------------------|-------------------------------|--------|----------------------------|
| Gene ID ^a | Probe ID ^b | Chr. | rs ID | Chr. | Pos/Mb^{c} | Associationd | rs ID | Chr. | Pos/Mb^{c} | Associationd | BSGSe | Fehrmann ^f | $\mathtt{EGCUT}^{\mathrm{f}}$ | Metag | Distance / Mb ^h |
| RERE | ILMN_1802380 | 1 | rs4982958 | 14 | 24987865 | | rs301819 | -1 | 8501786 | RERE | 5.66 | 0.61 | 1.23 | 1.17 | |
| RERE | ILMN_1802380 | | rs7697290 | 4. | 135248366 | | rs301819 | · | 8501786 | RERE | 5.74 | 0.14 | 0.10 | 0.06 | |
| KEKE | ILMIN-2327795 | | rs11085829 | 61 | 113874312 | | rs301819 | | 8501786 | 7,57,57 7,07,0 7,07,0 | 5.12 | 0.21 | 0.33 | 0.21 | |
| RNASE6 | ILMN 1780533 | 141 | rs11628398 | . 4 | 21182800 | BNASE6 | rs7324365 | - 2 | 100601327 | TOTAL | 4 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 | 0.08 | 0.20 | 0.26 | |
| RNASE6 | ILMN_1780533 | 14 | rs6603134 | 19 | 8106521 | | rs11628398 | 14 | 21182800 | RN ASE6 | 5.11 | 60.0 | 0.22 | 0.08 | |
| RNF167 | ILMN_1794726 | 17 | rs238230 | 17 | 4875566 | | rs4884857 | 13 | 54668512 | | 4.37 | | | | |
| RNF167 | ILMN_1794726 | 17 | rs400688 | 17 | 4839930 | RNF167 | rs11706900 | က | 36348968 | | 5.59 | 0.71 | 0.46 | 0.64 | |
| RNPEP | ILMN_1738347 | 1 | rs1107121 | 21 | 46127549 | | rs2819365 | 1 | 201983242 | | 6.27 | 0.11 | 0.30 | 0.13 | |
| RNPEP | ILMN_1738347 | 1 | rs8071611 | 17 | 67153386 | | rs2819365 | 1 | 201983242 | | 4.32 | 1.48 | 0.52 | 1.28 | |
| RPL13 | ILMN_2413278 | 16 | rs352935 | 16 | 89648580 | | rs2965817 | 16 | 89513234 | | 4.98 | 3.79 | 14.41 | 17.24 | 0.135 |
| RPL23AP7 | ILMN_22222750 | 61 | rs1401202 | 16 | 80320056 | | rs4849261 | 73 | 114450028 | RPL23AP7 | 5.55 | 0.13 | 0.73 | 0.38 | |
| RPL36AL | ILMN_2189933 | 14 | rs3007033 | 14 | 50103816 | RPL36AL | rs17495030 | 6 | 138038093 | | 5.46 | 0.09 | 90.0 | 0.02 | |
| RPL36AL | ILMN_2189936 | 14 | rs4900928 | 14 | 50020817 | RPL36AL | rs1502991 | 9 | 66137260 | | 5.86 | 0.32 | 0.20 | 0.19 | |
| RPL8 | ILMN_1764721 | ∞ ∞ | rs2958482 | œ | 145984615 | RPL8 | rs1619856 | 1 | 234585790 | | 4.59 | 0.10 | 0.37 | 0.15 | |
| RPL8 | ILMN-1764721 | œ | rs4143674 | 20 | 4741304 | | rs2958482 | œ | 145984615 | RPL8 | 4.33 | 0.13 | 0.45 | 0.22 | |
| SEC13 | ILMN-3297880 | 8 | rs4889214 | 16 | 80913946 | | rs696221 | 3 | 10342876 | SEC13 | 6.48 | | | | |
| SEMA4A | ILMN_1702787 | - | rs17085428 | n | 95388015 | | rs7695 | 1 | 156147326 | SEMA4A | 5.70 | 0.22 | 1.73 | 1.17 | |
| SESN3 | ILMN_1694027 | 111 | rs12147460 | 14 | 104412137 | | rs684856 | 11 | 94906111 | SESN3 | 5.50 | 0.02 | 0.51 | 0.15 | |
| SESN3 | ILMN_1694027 | 11 | rs355391 | 15 | 46591793 | | rs684856 | 11 | 94906111 | SESN3 | 5.67 | 0.31 | 90.0 | 0.10 | |
| SESN3 | ILMN_1694027 | 11 | rs684856 | 11 | 94906111 | NENN3 | rs7004947 | 00 | 134606425 | | 5.60 | 0.21 | 0.51 | 0.31 | |
| SH3BGRL2 | ILMN_1762764 | 9 0 | rs10838191 | Ξ, | 43893658 | | rs1354034 | က | 56849749 | PPBP | 5.52 | 0.70 | 0.12 | 0.35 | |
| SHSBGRL2 | ILMN_1762764 | 9 | rs2545385 | ٠. | 66383979 | | rs1354034 | n | 56849749 | PPBP | 5.97 | 0.20 | 0.51 | 0.30 | |
| SHSBGRLZ | ILMIN_1762764 | ۰ ۵ | rsb845304 | 4.0 | 88280502 | | rs1354034 | n | 56849749 | PFBF | 5.23 | 0.32 | 0.71 | 0.53 | |
| SH3GLB2 | ILMIN_2158336 | 5 6 | rs1034120 | 17.0 | 18196922 | Segre | rsI/4555I/ | D 4 | 131785369 | SH3GLB2 | 7.40 | 0.22 | 0.18 | 0.13 | |
| 01 A 20 A 10 | ILMIN-LITTOOL | 0 - | 181000000 | 07 | 1012013 | PIRE | 150042139 1196709E | * : | 01060#00 | OT 600 10 | H C. | 00.0 | 0.10 | 100 | |
| SLC22A18 | ILMIN-2382505 | 1 : | rs116/3260 | E - | 2023826 | ST.C22 A 18 | rs56/055 | 11 | 153224179 | SUCZZAIS | 0.4 7.0 | 0.09 | 0.24 | 0.00 | |
| SI.C22A18 | II.MN 2382505 | | re367035 | 1: | 2023826 | ST.C22A18 | rs3772054 | ۰. | 241678528 | | | 0.39 | 0.10 | 00:0 | |
| SLC41A3 | ILMN_2356111 | - 60 | rs1912136 | 11 | 24616743 | | rs6771703 | 1 00 | 125801067 | SLC41A3 | 8 8 8 | 1.10 | 0.82 | 1.24 | |
| SLC45A4 | ILMN_1745778 | 00 | rs6985508 | œ | 142337734 | SLC45A4 | rs7701916 | n | 174598073 | | 5.95 | 0.86 | 0.07 | 0.40 | |
| SLC46A3 | ILMN_1658639 | 13 | rs949805 | 17 | 55602091 | | rs7981190 | 13 | 29259349 | SLC46A3 | 5.52 | 0.09 | 0.58 | 0.26 | |
| SMG7 | ILMN_1706553 | - | rs8035259 | 15 | 97403923 | | rs10911353 | 1 | 183489203 | SMG7 | 6.52 | 0.17 | 0.09 | 90.0 | |
| SMOX | ILMN_1775380 | 20 | rs8118315 | 20 | 4161500 | SMOX | rs11677815 | 2 | 65800982 | | 5.68 | 0.39 | 0.62 | 0.52 | |
| SNHG8 | ILMN_3309349 | 4 | rs1105621 | 6 | 133050233 | | rs705837 | 4 | 119225940 | SNHG8 | 6.11 | | , | 1 | |
| SNORD14A | ILMN_1799381 | === | rs1520429 | 12 | 46259108 | | rs214097 | 11 | 17291499 | SNORD14A | 6.60 | 0.29 | 10.08 | 0.72 | 7660 |
| SNORD89 | II.MN 3238662 | 7.7 | rs10445863 | 7.7 | 115929241 | | rs750783 | 7.7 | 101889306 | SNOBD89 | 20.9 | 11.01 | 10.30 | 9 | 14 040 |
| SNORD89 | ILMN_3238662 | 1 (7) | rs11605822 | 11 | 122986326 | | rs750783 | 1 (7) | 101889306 | SNORD89 | 5.96 | | | | |
| SNORD89 | ILMN_3238662 | 2 | rs2135064 | ъ | 26778066 | | rs750783 | 2 | 101889306 | SNORD89 | 6.33 | | | | |
| SNUPN | ILMN_1733932 | 12 | rs8134646 | 21 | 46376528 | SNUPN | rs7185362 | 16 | 81888905 | | 6.45 | 0.13 | 1.41 | 0.83 | |
| SNUPN | ILMN_2364535 | 12 | rs8134646 | 21 | 46376528 | SNUPN | rs1472075 | က | 193706323 | | 5.59 | 0.34 | 0.00 | 90.0 | |
| SPATA5L1 | ILMN_1729179 | 12 | rs1131620 | 13 | 41117869 | | rs4774580 | 12 | 45652086 | SPATA5L1 | 5.44 | 1 | | 0 | |
| STARDIO | ILMIN_I717052 | 1 1 | rs2221406 | 27 - | 901/4526 | | rs1000620 | 1 1 | 72509713 | 1127 | 0.00 0.00 | 0.67 | 0.12 | 0.33 | |
| SIIALI SIII.F2 | ILMIN-2210/29 | 06 | rs40/3164 | 20 | 46153148 | SIII.F2 | rs1/685 | - 4 | 180439236 | SITALI | 0 10 0 10 0 10 | 0.57 | 0.17 | 0.30 | |
| SULT1A4 | ILMN_2336133 | 1 91 | rs1463965 | 8 | 74332954 | 1 | rs3785354 | 16 | 28550667 | TUFM | 7.05 | 0.01 | 0.05 | 00.00 | |
| SULT1A4 | ILMN_2336133 | 16 | rs2836657 | 21 | 40119768 | | rs3785354 | 16 | 28550667 | TUFM | 5.83 | | | | |
| SURF6 | ILMN_1778032 | 6 | rs6099626 | 20 | 56013994 | | rs3118663 | 6 | 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 | - | rs1939875 | 11 | 95422867 | | rs4072037 | - | 155162067 | THBS3 | 5.55 | 0.03 | 0.15 | 0.03 | |
| THBS3 | ILMN_1804663 | | rs8014956 | 14 | 20687978 | | rs2049805 | · | 155194980 | THBS3 | 5.65 | 0.31 | 0.76 | 0.55 | |
| ILUT | TEIMIN-1.101407 | - | LSZ0Z0Z40 | 17 | 10/40020 | | rs1520995 | 7 | 100104033 | IIFND | 0.22 | 0.07 | 0.40 | 01.0 | |

| | Distance / Mb ^{II} | | | | | 0.122 | | | | | | | | | | | | | | | | | | | | 0 | 0.031 | 12.131 | | | | 1 | 5.389 | | | | | | | | | | | | | | 45.345 | | |
|------|-----------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|------------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 8 | Meta ⁸ Dist | 0.70 | 0.26 | | | - 28 | 3.67 | 08.0 | 78 | 2.52 | 0.03 | 87 | 00.9 | 00 | 27 | 19 | .51 | 7.36 | 10.72 | 2.10 | 9.20 | 4.47 | | 0.32 | 0.07 | 0.62 | 4.09 | 0.29 | 1.07 | 0.68 | 0.08 | 0.59 | 0.16 | 0.44 | 0.22 | 0.16 | 80.0 | | 1.01 | 0.02 | 0.13 | 0.40 | 0.69 | 0.11 | 1.69 0.30 | 0.06 | | | |
| | | | | | | 14 | | | | | | | | | | | | | _ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Test | EGCUT | 1.34 | 0.48 | | | 45.78 | 3.09 | 0.99 | 1.18 | 1.00 | 0.07 | 0.77 | 3.33 | 9.61 | 1.52 | 0.33 | 3.62 | 5.15 | 8.80 | 3.14 | 96.9 | 5.75 | | 0.12 | 0.15 | 0.17 | 1.89 | 0.40 | 1.60 | 0.87 | 0.18 | 0.47 | 0.24 | 0.38 | 0.36 | 0.33 | 0.07 | i | 0.78 | 0.02 | 0.26 | 0.86 | 06.0 | 0.25 | 1.23 | 0.18 | | | |
| 3 | Fehrmann ¹ | 90.0 | 0.16 | | 0.76 | 81.55 | 1.55 | 0.40 | 3.61 | 2.41 | 0.08 | 3.06 | 3.72 | 0.04 | 1.57 | 0.19 | 0.90 | 3.31 | 3.06 | 0.07 | 3.36 | 0.10 | | 0.64 | 0.11 | 1.03 | 3.19 | 0.50 | 0.21 | 0.37 | 0.12 | 0.63 | 0.21 | 0.50 | 0.20 | 0.15 | 0.24 | 0 | 0.85 | 0.14 | 0.14 | 80.0 | 0.36 | 0.11 | 1.20 | 0.07 | | | |
| | BSGSc | 5.70 | 8.11 | 6.79 | 11.09 | 12.16 | 8.12 | 8.02 | 8.39 | 7.37 | 6.95 | 6.93 | 6.21 | 7.30 | 6.70 | 5.92 | 8.89 | 8.55 | 5.80 | 5.49 | 6.22 | 9.44 | 5.60 | 5.79 | 5.61 | 5.52 | 80 E | 5.52 | 5.97 | 6.92 | 7.79 | 6.43 | 6.38 | 6.51 | 5.86 | 6.27 | 6.73 | 7.58 | 5.73 10 | 6.71 | 7.34 | 7.05 | 7.41 | 5.42 | 0.92 | 00.9 | 5.01 | 5.51 | 6.34 |
| 7 | Association | TMED4 | TMEM149 | TMEM149 | TMEM149 | TMEM149 | | | | | | | | | | | | | | | | | TMEM63A | TMEM80 | IRF5 | IRF5 | TD A DDCA | TRAPPC4 | | | | | | | | | | TRAPPC5 | TRAPPCS | CO I IVIII | | RAPGEF1 | | TREMI | TRIMIS | TSPAN14 | TSPAN32 | | |
| | Pos/Mb^{c} | 44581986 | 36219525 | 36219525 | 36219525 | 36147315 | 4799159 | 133025756 | 188359436 | 128884559 | 64268976 | 90932598 | 13822381 | 113317583 | 147619772 | 171792273 | 129595460 | 233879066 | 161683974 | 80357420 | 242889492 | 21473952 | 226027323 | 656845 | 128593948 | 128593948 | 23498358 | 118887887 | 166970604 | 132022957 | 156404902 | 242329791 | 2369415 | 57495457 | 9947811 | 146690926 | 85439550 | 7758194 | 7758194 | 228504503 | 30408765 | 134635088 | 157393770 | 41264577 | 26044369 | 82273079 | 2317951 | 137947208 | 238746880 |
| | Chr. | 2 | 19 | 19 | 19 | 19 | 10 | 6 | က | 12 | 18 | 14 | œ | 4 | 7 | 10 | 11 | 7 | 9 | 17 | 1 | 13 | 1 | 11 | 7 | ⊳ 1 | - 1- | 1 [| 10 | œ | 9 | - ! | 19 | 12 | 4 | - | 14 | 19 | S 1 C | 2 | 16 | 6 | en 1 | 9 9 | 0 9 | 10 | 11 | 9 | 7 |
| | rs ID | rs17725246 | rs8106959 | rs8106959 | rs8106959 | rs7254601 | rs10508289 | rs10819626 | rs10937361 | rs1401098 | rs1557335 | rs17719594 | rs1843357 | rs2351458 | rs2539000 | rs2731711 | rs471728 | rs6718480 | rs6926382 | rs7213338 | rs914940 | rs9509428 | rs4149226 | rs4963126 | rs10488630 | rs10488630 | rs11770192 | rs3916581 | rs10059004 | rs1023095 | rs1375714 | rs1393299 | rs17763599 | rs4968328 | rs7694997 | rs7800935 | rs856638 | rs17159840 | rs17159840 | rs10179572 | rs12921440 | rs1887778 | rs963354 | rs2395771 | rs2393771 | rs10748526 | rs12800998 | rs620607 | rs1198819 |
| | Association | | | | | SNX26 | TMEM149 | | | | | | | TRAPPC5 | TRAPPC5 | TRAPPC5 | TRAPPC5 | TRAPPC5 | TRAPPCS | TRAPPC5 | TRAPPC5 | TRAPPC5 | | | | | | | | | | MYBPC3 | TSPAN32 | ECGF1 |
| 0 | Pos/Mb^{c} | 132389627 | 47248981 | 27925288 | 45207005 | 36268923 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 36219525 | 72890603 | 58058246 | 4859303 | 22287303 | 112521675 | 131018917 | 7758194 | 7758194 | 7758194 | 7758194 | 7758194 | 7758194 | 7758194 | 7758194 | 7758194 | 22740855 | 45128454 | 7762978 | 7762978 | 7762978 | 7762978 | 85749398 | 158808416 | 27194634 | 47663049 | 2317951 | 50971266 |
| | Chr. | 11 | 21 | 22 | 20 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 13 | 19 | 6 | 50 | - 2 | 3 = | 19 | 19 | 19 | 19 | 13 | 61 | 19 | 19 | 19 | 5 5 | 27 | 61 | 19 | 19 | 19 | 12 | 10 | 17 | 11 | 11 | 22 |
| | rs ID | rs1940400 | rs2839013 | rs5762235 | rs6090518 | rs807491 | rs8106959 | rs1254086 | rs1548475 | rs1537146 | rs199793 | rs7776572 | rs1793823 | rs17159840 | rs380708 | rs3916995 | rs7246264 | rs7246264 | rs7246264 | rs7246264 | rs10862975 | rs12412964 | rs968726 | rs10838738 | rs12800998 | rs140522 |
| 1 | Chr. | 7 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 1 | 11 | 7 | r- 1 | 11 | | 19 | 19 | 19 | 19 | 10 | 51 51 | 13 | 19 | 19 | 19 | 61 C | 61 | 19 | 19 | 19 | 9 9 | - u | 01 | 11 | 11 | 22 |
| 4 | Probe ID | ILMN_1804148 | ILMN_1786426 | ILMN_1719649 | ILMN_1708482 | ILMN_1683811 | ILMN_1683811 | ILMN_1731043 | II.MN 1814650 | ILMN_2372639 | ILMN_2372639 | ILMN_2372639 | ILMN_2372639 | ILMN_2372639 | ILMN-2372639 | ILMN_2372639 | ILMN_2372639 | ILMN_2372639 | ILMN_2372639 | ILMN-2372639 | ILMN 2372639 | ILMN_2372639 | ILMN_2372639 | ILMN_2372639 | ILMN_1688231 | ILMN-1695651 | ILMN_1785060 | ILMN_1718621 | ILMN_2389970 | ILMN_3223126 |
| ı | Gene ID ^a | TMED4 | TMEM149 | TMEM63A | TMEM80 | TNP03 | TNPO3 | TRAZA TPAPPCA | TRAPPC4 | TRAPPC5 | TRAPPC5 | TRAPPC5 | TRAPPC5 | TRAPPC5 | TRAPPCS | TRAPPC5 | TRAPPC5 | TRAPPC5 | TRAPPC5 | TRAFFC5 | TRAPPCS | TRAPPC5 | TRAPPC5 | TRAPPC5 | TREMI | TRIMIS | TSPAN14 | TSPAN32 | TSPAN32 | TYMP |

| | / Mp _p | | | 1.643 | 0.088 | | | | | | | | | | | | | | | | | | | | | |
|-------------------------|-------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| | Distance | | | | | | | | | | | | | | | | | | | | | | | | | |
| values | Metag | 0.52 | 1.10 | 0.03 | 4.95 | 0.46 | 0.57 | | 0.19 | 0.41 | 0.31 | 0.17 | 0.04 | 1.21 | 0.16 | 0.57 | 0.26 | 1.47 | 0.09 | 1.22 | 0.35 | 2.25 | 1.63 | 0.15 | 0.46 | 0.05 |
| $-\log_{10} p$ -values | $\mathtt{EGCUT}^{\mathrm{f}}$ | 0.42 | 1.29 | 0.14 | 5.14 | 0.15 | 0.69 | | 0.19 | 0.74 | 0.48 | 0.17 | 0.19 | 1.15 | 0.05 | 0.54 | 0.17 | 1.38 | 0.13 | 1.35 | 0.61 | 1.43 | 0.17 | 0.36 | 0.27 | 0.01 |
| Interaction statistic / | $Fehrmann^{f}$ | 0.59 | 0.48 | 0.03 | 0.94 | 0.84 | 0.39 | | 0.33 | 0.16 | 0.23 | 0.31 | 0.03 | 0.73 | 0.46 | 0.53 | 0.48 | 0.81 | 0.19 | 0.57 | 0.18 | 1.64 | 2.38 | 0.09 | 0.67 | 0.26 |
| Interact | $BSGS^{e}$ | 5.91 | 6.01 | 5.71 | 5.09 | 5.64 | 5.44 | 5.72 | 5.77 | 6.44 | 5.74 | 6.44 | 5.82 | 6.12 | 4.83 | 5.60 | 5.71 | 5.88 | 5.88 | 6.34 | 5.85 | 4.86 | 5.48 | 5.79 | 5.29 | 6.04 |
| | Associationd | | | | | VNN2 | VNN2 | VNN2 | VNN2 | VNN3 | VNN3 | VNN3 | VNN3 | VNN3 | VNN3 | | | VSTM1 | WDR48 | WDR48 | WDR48 | WDR6 | | ZFP90 | ZNF500 | ZYX |
| SNP 2 | $^{ m Pos/Mb^c}$ | 83600397 | 214514361 | 75151717 | 45974668 | 133077063 | 133072650 | 133072650 | 133072650 | 133067782 | 133067782 | 133067782 | 133067782 | 133067782 | 133067782 | 71024750 | 123098249 | 54553697 | 39091812 | 39067925 | 39044116 | 49194331 | 93119799 | 68573945 | 4799041 | 143093824 |
| | Chr. | 16 | 1 | 17 | 19 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 18 | 10 | 19 | က | က | က | က | 15 | 16 | 16 | 7 |
| | rs ID | rs7201194 | rs7512594 | rs7225546 | rs2276470 | rs1883613 | rs1883617 | rs1883617 | rs1883617 | rs2267952 | rs2267952 | rs2267952 | rs2267952 | rs2267952 | rs2267952 | rs4552100 | rs7895870 | rs10500316 | rs6778963 | rs883349 | rs7619193 | rs11715581 | rs12591171 | rs1182968 | rs2290560 | rs2242601 |
| | Association ^d | UBASH3A | UBASH3A | USP36 | | | | | | | | | | | | VSTM1 | VSTM1 | | | RAPGEF1 | | | XAF1 | | | |
| SNP 1 | Pos/Mb^{c} | 43855067 | 43855067 | 76794981 | 46063167 | 105252718 | 9116155 | 49927332 | 16834510 | 151662184 | 73006453 | 75547169 | 83262064 | 16594253 | 51692548 | 54553697 | 54553697 | 30261219 | 188927822 | 134635088 | 102624790 | 123371708 | 6673170 | 37040648 | 48283177 | 8935312 |
| 0. | Chr. | 21 | 21 | 17 | 19 | -1 | 20 | 22 | 11 | -1 | œ | 6 | 14 | 21 | 13 | 19 | 19 | 22 | 4 | 6 | 13 | 11 | 17 | 21 | 22 | 20 |
| | rs ID | rs1893592 | rs1893592 | rs2279308 | rs1264226 | rs10435352 | rs13044386 | rs134447 | rs216495 | rs10278073 | rs1443946 | rs348462 | rs7157055 | rs2823165 | rs9596457 | rs10500316 | rs10500316 | rs9625870 | rs1388935 | rs1887778 | rs9554833 | rs12362253 | rs1533031 | rs909446 | rs4823723 | rs6056281 |
| | Chr. | 21 | 21 | 17 | 19 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 19 | 19 | 19 | n | n | n | n | 17 | 16 | 16 | 7 |
| Expression trait | Probe ID ^b | ILMN_2338348 | ILMN_2338348 | ILMN_1697227 | ILMN_1743646 | ILMN_1678939 | ILMN_1678939 | ILMN_1678939 | ILMN_1678939 | ILMN_1804935 | ILMN_1804935 | ILMN_1804935 | ILMN_1804935 | ILMN_2387680 | ILMN_2387680 | ILMN_1763455 | ILMN_1763455 | ILMN_1763455 | ILMN_1762103 | ILMN_1762103 | ILMN_1762103 | ILMN_1669484 | ILMN_2370573 | ILMN_1684628 | ILMN_1700238 | ILMN_1701875 |
| Ex | Gene IDa | UBASH3A | UBASH3A | USP36 | VASP | VNN2 | VNN2 | VNN2 | VNN2 | VNN3 | VNN3 | VNN3 | VNN3 | VNN3 | VNN3 | VSTM1 | VSTM1 | VSTM1 | WDR48 | WDR48 | WDR48 | WDR6 | XAF1 | ZFP90 | ZNF500 | ZYX |

Table S1 - continued from previous page

a Phenotypes are expression levels of RefSeq Genes
Dilumina probe ID used to measure gene expression
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)
Interaction - log₁₀ p-value from discovery dataset
Interaction - log₁₀ p-value from meta analysis of replication datasets on the statement of the

Table S2: Estimation of additive and non-additive variance components from pedigree information Taken from previous analysis in Powell et al 2013^{22}

| | | Additi | ve | Non-add | itive |
|---------|-----------------|----------|------|----------|-------|
| Gene | Probe | 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

| | T | D | b | D + 10 | 01 1d | |
|-----------------------------|---------------------------|-----------------------|------------------|-----------------------|-----------------------|------------------------|
| Test | Interactions ^a | Dataset | n^{b} | Expected ^c | Observed ^d | <i>p</i> -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} |
| $\overline{3^{\mathrm{g}}}$ | 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} |

 $^{^{\}rm a}$ "All" denotes 434 discovery interactions and "Significant" denotes 30 interactions with significant replication $p\text{-}{\rm values}$

^b Number of tests for concordance

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

 $^{^{\}rm a}$ "All" denotes 434 discovery interactions and "Significant" denotes 30 interactions with significant replication $p\text{-}{\rm values}.$

^b Number of tests for concordance.

 $^{^{\}rm c}$ 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.

 ${\it Table~S5:~} \textbf{Details~on~linkage~disequilibrium~and~relative~positions~of~all~discovery~interactions~with~SNPs~on~the~same~chromosome$

| TMEMI49 | Chr | Gene | SNP 1 | SNP 2 | Position 1 | Position 2 | Distance / Mb | R^2 | D' |
|--|-----|----------|------------|------------|------------|------------|---------------|-------|-------|
| CSTB | | | | | | | | | |
| MBNL1 | | | rs898095 | rs9892064 | 80890638 | 80827903 | | 0.063 | |
| 10 | 21 | | rs9979356 | rs3761385 | 45230974 | 45198355 | 0.033 | 0.041 | 0.066 |
| Transfer | 3 | MBNL1 | rs16864367 | rs13079208 | 152234166 | 152116652 | 0.118 | 0.041 | 0.117 |
| 17 | 10 | | rs2395095 | rs10824092 | 76446305 | 75929517 | 0.517 | 0.013 | |
| NAPRT1 | 11 | CTSC | rs7930237 | rs556895 | 88117962 | 88077479 | 0.040 | 0.012 | 0.045 |
| LAX1 | 17 | GAA | rs11150847 | rs12602462 | 78153130 | 78146016 | 0.007 | 0.000 | 0.001 |
| MBP | 8 | NAPRT1 | rs2123758 | rs3889129 | 144663661 | 144613680 | 0.050 | 0.053 | 0.060 |
| SNORD14A | 1 | LAX1 | rs1891432 | rs10900520 | 203877662 | 203780591 | 0.097 | 0.065 | 0.106 |
| 21 C210RF57 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 rs776572 rs11701058 48063862 47776382 0.287 0.100 0.122 12 OAS1 rs13311 rs2072133 113448652 113409260 0.039 0.002 0.016 16 N4BP1 rs1244224 rs11649236 8758055 48 | 18 | MBP | rs8092433 | rs4890876 | 74747424 | 74732087 | 0.015 | 0.035 | 0.053 |
| 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 232201670 232291471 0.010 0.027 0.029 5 HNRPHI 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 rs1177101058 48663862 47776882 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 rs773589 157216093 1 | 11 | SNORD14A | rs2634462 | rs6486334 | 17339127 | 17015557 | 0.324 | 0.008 | 0.012 |
| NCL | 21 | C21ORF57 | rs9978658 | rs11701361 | 48027084 | 47764477 | 0.263 | 0.032 | 0.065 |
| 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 rs7775672 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 rs12749343 rs7733671 125369113 96000269 29.369 0.001 0.001 7 DNAJB6 rs2286842 rs3779589 157216093 <td< td=""><td>16</td><td>RPL13</td><td>rs352935</td><td>rs2965817</td><td>89648580</td><td>89513234</td><td>0.135</td><td>0.054</td><td>0.060</td></td<> | 16 | RPL13 | rs352935 | rs2965817 | 89648580 | 89513234 | 0.135 | 0.054 | 0.060 |
| 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 157166014 0.052 0.005 0.006 1 OVGP1 rs10802822 rs184655 37771578 <t< td=""><td>19</td><td>ATP13A1</td><td>rs4284750</td><td>rs873870</td><td>19810050</td><td>19738554</td><td>0.071</td><td>0.008</td><td>0.015</td></t<> | 19 | ATP13A1 | rs4284750 | rs873870 | 19810050 | 19738554 | 0.071 | 0.008 | 0.015 |
| 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 0.005 0.006 1 OVGP1 rs10802822 rs1264898 240132968 111992823 128.140 0.00 0.00 11 PHCA rs493642 rs10736812 1 | 2 | NCL | rs7563453 | rs4973397 | 232301670 | 232291471 | 0.010 | 0.027 | 0.029 |
| 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 rs28668504 rs1884655 37771578 23074375 14.697 0.000 0.002 11 PHCA rs493642 rs10736812 123097386 | 5 | HNRPH1 | rs6894268 | rs4700810 | 179032488 | 178991794 | 0.041 | 0.000 | 0.001 |
| 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 rs286842 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 rs2896940 rs13332406 57721127 | 19 | | rs1264226 | rs2276470 | 46063167 | 45974668 | 0.088 | 0.018 | 0.022 |
| 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 0.001 16 AKTIP rs2886940 rs13332406 57721127 | 7 | TRA2A | rs7776572 | rs11770192 | 23528927 | 23498358 | 0.031 | 0.064 | 0.064 |
| 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 rs1655031 46614102 | 21 | PRMT2 | rs2839372 | rs11701058 | 48063862 | 47776382 | 0.287 | 0.100 | 0.122 |
| 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 rs1655031 46614102 30833162 15.781 0.000 0.000 2 CYBRD1 rs888427 rs7591849 172368120 | 12 | OAS1 | rs13311 | rs2072133 | 113448652 | 113409260 | 0.039 | 0.002 | 0.016 |
| 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 | 16 | N4BP1 | rs12444224 | rs11649236 | 87580855 | 48632478 | 38.948 | 0.007 | 0.021 |
| 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 rs1655031 46614102 30833162 15.781 0.000 0.001 2 CYBRD1 rs88427 rs7591849 172368120 160112881 12.255 0.000 0.000 2 CYBRD1 rs88427 rs7591849 172368120 160112881 12.255 0.000 0.001 11 TRAPPC4 rs1793823 rs3916581 131018917 | 5 | CAST | rs12719343 | rs7733671 | 125369113 | 96000269 | 29.369 | 0.001 | 0.001 |
| 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 | 7 | DNAJB6 | rs2286842 | rs3779589 | 157216093 | 157163614 | 0.052 | 0.005 | 0.006 |
| 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 rs88427 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 <td>1</td> <td>OVGP1</td> <td>rs10802822</td> <td>rs1264898</td> <td>240132968</td> <td>111992823</td> <td>128.140</td> <td>0.008</td> <td>0.030</td> | 1 | OVGP1 | rs10802822 | rs1264898 | 240132968 | 111992823 | 128.140 | 0.008 | 0.030 |
| 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< | 20 | CD93 | rs2868504 | rs1884655 | 37771578 | 23074375 | 14.697 | 0.000 | 0.002 |
| 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 rs3411188 26710 | 11 | PHCA | rs493642 | rs10736812 | 123097386 | 76708086 | 46.389 | 0.002 | 0.008 |
| 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 635 | 21 | MX1 | rs459498 | rs8130120 | 42795027 | 29363604 | 13.431 | 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 C170RF60 rs9907897 rs7405659 63502633 59874129 3.629 0.004 0.011 19 TRAPPC5 rs17159840 rs17763599 77 | 16 | AKTIP | rs2896940 | rs13332406 | 57721127 | 53489705 | 4.231 | 0.000 | 0.001 |
| 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 C170RF60 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 7 | 17 | CDK5R1 | rs9905940 | rs11655031 | 46614102 | 30833162 | 15.781 | 0.000 | 0.000 |
| 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 3323493 | 2 | CYBRD1 | rs888427 | rs7591849 | 172368120 | 160112881 | 12.255 | 0.000 | 0.000 |
| 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 0.003 22 PISD rs715572 rs6518754 33234931 32097775 1.137 0.001 0.003 12 GPR162 rs27272500 rs2707210 79685913 </td <td>8</td> <td>HMBOX1</td> <td>rs587639</td> <td>rs7837237</td> <td>132725731</td> <td>28876221</td> <td>103.850</td> <td>0.001</td> <td>0.001</td> | 8 | HMBOX1 | rs587639 | rs7837237 | 132725731 | 28876221 | 103.850 | 0.001 | 0.001 |
| 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 C170RF60 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 <td>11</td> <td>TRAPPC4</td> <td>rs1793823</td> <td>rs3916581</td> <td>131018917</td> <td>118887887</td> <td>12.131</td> <td>0.001</td> <td>0.002</td> | 11 | TRAPPC4 | rs1793823 | rs3916581 | 131018917 | 118887887 | 12.131 | 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 | 12 | PEX5 | rs10444467 | rs4329748 | 128052636 | 7364442 | 120.688 | 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 | 12 | FLJ20489 | rs17615703 | rs3782908 | 117036766 | 48169526 | 68.867 | 0.001 | 0.002 |
| 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 | 16 | PRKCB1 | rs2188355 | rs10492793 | 23867776 | 12639800 | 11.228 | 0.000 | 0.000 |
| 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 | 14 | MRPL52 | rs1950857 | rs3811188 | 26710271 | 23299135 | 3.411 | 0.002 | 0.004 |
| 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 | C17ORF60 | rs9907897 | rs7405659 | 63502633 | 59874129 | 3.629 | 0.004 | 0.011 |
| 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 | 6 | FLJ43093 | rs6906101 | rs13214069 | 36667610 | 32705248 | 3.962 | 0.000 | 0.000 |
| 12 DIP2B rs871257 rs12427378 117994348 51074199 66.920 0.001 0.001 12 GPR162 rs2272500 rs2707210 79685913 6902002 72.784 0.003 0.005 | 19 | TRAPPC5 | rs17159840 | | 7758194 | | 5.389 | 0.000 | 0.000 |
| 12 GPR162 rs2272500 rs2707210 79685913 6902002 72.784 0.003 0.005 | 22 | PISD | rs715572 | rs6518754 | 33234931 | 32097775 | 1.137 | 0.001 | 0.003 |
| | 12 | DIP2B | rs871257 | rs12427378 | 117994348 | 51074199 | 66.920 | 0.001 | 0.001 |
| 17 USP36 rs2279308 rs7225546 76794981 75151717 1.643 0.000 0.000 | 12 | GPR162 | rs2272500 | rs2707210 | 79685913 | 6902002 | 72.784 | 0.003 | 0.005 |
| | 17 | USP36 | rs2279308 | rs7225546 | 76794981 | 75151717 | 1.643 | 0.000 | 0.000 |