Detection and replication of epistasis influencing transcription in humans

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22 Abstract

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Epistasis is the phenomenon whereby a polymorphism's effect on a trait depends on other polymorphisms present in the genome. The extent to which epistasis influences complex traits¹ and contributes to their variation^{2,3} is a fundamental question in evolution and human genetics. Though epistasis has been demonstrated in artificial gene manipulation studies in model organisms, 4,5 and examples have been reported in other species, 6 few convincing examples with independent replication exist for epistasis amongst natural polymorphisms in human traits.^{7,8} Its absence from empirical findings may simply be due to its low incidence in the genetic control of complex traits, 2,3 but an alternative view is that it has previously been too technically challenging to detect due to statistical power and computational issues. Here we show that, using advanced computation techniques¹⁰ and a gene expression study design, many instances of epistasis are found between common single nucleotide polymorphisms (SNPs). In a cohort of 846 individuals with data on 7339 gene expression levels in peripheral blood, we found 501 significant pairwise epistatic interactions between common SNPs acting on the expression levels of 238 genes $(p < 2.91 \times 10^{-16})$. Replication of these interactions in two independent data sets^{11,12} showed both concordance of direction of epistatic effects $(p = 5.56 \times 10^{-31})$ and enrichment of interaction p-values, with 30 being significant at a conservative threshold of p < 0.05/501. There was evidence of functional enrichment for the interacting SNPs, for instance 44 of the genetic interactions are located within 5Mb of regions of known physical chromosome interactions¹³ ($p = 1.8 \times 10^{-10}$). Epistatic networks of three SNPs or more influence the expression levels of 129 genes, whereby one cis-acting SNP is modulated by several trans-acting SNPs. For example MBNL1 is influenced by an additive effect at rs13069559 which itself is masked by trans-SNPs on 14 different chromosomes, with nearly identical genotype-phenotype (GP) maps for each cis-trans interaction. This study presents the first evidence for multiple instances of segregating common polymorphisms interacting to influence human traits.

Main text

In the genetic analysis of complex traits it is usual for SNP effects to be estimated using an additive model where they are assumed to contribute independently and cumulatively to the mean of a trait. This framework has been successful in identifying thousands of associations. 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. Beyond the prism of human association studies there is evidence for epistasis, not only at the molecular scale from artificially induced mutations but also at the evolutionary scale in fitness adaptation. and speciation. The special sequence of the special special sequence of the special sequence of the special sequence of the sequence of the special sequence of the

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

duced statistical power. For example increased dependence on linkage disequilibrium (LD) between causal SNPs and observed SNPs, 17,18 increased model complexity in fitting interaction terms, ¹⁹ and more extreme significance thresholds to account for increased multiple testing⁹ all make it more difficult to detect epistasis in comparison to additive effects. Thus, when combined with small genetic effect sizes, as is expected in most complex traits of interest, ¹⁴ the power to detect epistasis diminishes rapidly. There are two simple ways to overcome this problem. One is by using extremely large sample sizes;²⁰ another is by analysing traits that are likely to have large effect sizes among common variants. Because our focus was to ascertain the extent to which instances of epistasis arises from natural genetic variation we designed a study around the latter approach and searched for epistatic genetic effects that influence gene expression levels. Transcription levels can be measured for thousands of genes and like most complex diseases, these expression traits are typically heritable.²¹ But unlike complex diseases, genetic associations with gene expression commonly have very large effect sizes that explain large proportions of the genetic variance, ²² making them good candidates to search for epistasis, should it exist.

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In our discovery dataset (Brisbane Systems Genetics Study, BSGS²³) of 846 individuals genotyped at 528,509 SNPs, we used a two stage approach to identify genetic interactions. First, we exhaustively test every pair of SNPs for pairwise effects against each of 7339 expression traits in peripheral blood (family-wise error rate of 5% corresponding to a significance threshold of $p < 2.91 \times 10^{-16}$, Methods). Second, we filtered the SNP pairs from stage 1 on LD and genotype class counts, and tested the remaining pairwise effects for significant interaction terms and used a Bonferroni correction for multiple testing (estimated type 1 error rate $0.05 < \alpha < 0.14$, Methods, Supplementary Figure S1). Using this design we identified 501 putative genetic interactions influencing the expression levels of 238 genes (Supplementary Table S1). We used strict quality control measures to avoid statistical associations being driven by technical artifacts (Methods). However it remains possible that unexplained technical artifacts may have led to the significant discovery interactions. Of the 501 discovery interactions, 434 had available data and passed filtering (Methods) in two independent replication datasets, Fehrmann¹² and the Estonian Genomics Centre University of Tartu (EGCUT),¹¹ in which we saw convincing evidence for replication. We used the summary statistics from the replication datasets to perform a meta analysis to obtain an independent p-value for the putative interactions, and 30 were significant after applying a Bonferroni correction for multiple testing (5% significance threshold p < 0.05/501, Table 1). To quantify the similarity of GP maps between the independent datasets (Figure 1) we decomposed the genetic effects of each of the SNP pairs into orthogonal additive, dominance and epistatic effects $(A1, A2, D1, D2, A \times A, A \times D, D \times A, D \times D)$ and tested for concordance of the sign of the most 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 = 7.5under 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) dataset, 24 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 epistasis is difficult in practice. For example, LD between causal variants and observed markers plays an important role. Not only is the dependence on LD much greater for epistatic effects than for additive effects (Supplementary Figure S7), but when estimating epistatic variance it is more sensitive to changes in LD between observed SNPs and causal variants between independent samples when compared to additive effects (Supplementary Figure S8). This has a direct effect on statistical power for replication. The sampling variance of LD r leads to the ascertainment of marker associations with higher sample r in the discovery stage in comparison to the replication stage. However, the average decrease in \hat{r}^x in replication samples becomes larger as x increases (Methods, Supplementary Figure S9). For example, the decrease in \hat{r}^8 (which is proportional to the power of detecting $D \times D$ effects), is on average three fold greater than the decrease in \hat{r}^2 (which is proportional to the power of detecting additive effects).

Though seldom the focus of association studies, SNPs with known main effects are often tested for additive \times additive genetic interactions, ⁹ but our analysis shows that this is unlikely to be the most effective strategy for its detection. The majority of our discovery interactions comprised of one SNP that was significantly associated with the gene expression level in the discovery dataset, and one SNP that had no previous 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 additive \times additive, additive \times dominance, dominance \times additive and dominance \times dominance at the discovery stage (p = 0.22 for departure from expectation). This is not surprising because the patterns of epistasis used for statistical decomposition (*i.e.* $A \times A$, $A \times D$, $D \times A$, $D \times D$) are simply convenient orthogonal parameterisations of a two locus model, and are not intended to model biological function.²⁵

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. We cross-referenced our epistatic SNPs with a map of chromosome interacting regions (n=96,139) in K562 blood cell lines (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. 30,31

Though we present many instances of epistasis, quantifying its relative importance to complex traits in humans remains an open question. In this study we are able to identify 238 gene expression traits with at least one significant interaction given our experiment-wide threshold, where the minimum 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 explain.² Ideally one would approach this question from a whole genome perspective³² but this is intractable for non-additive variance components. Nevertheless, some inference can be made from the ascertained effects in these analyses and it is evident that estimated additive variance is overall a larger component than estimated epistatic variance, as has been argued previously.^{2,3} Taking all additive effects detected in Powell et al (2012) that have additive variance explaining 2.1% or greater of phenotypic variance, we calculated that the proportion of total phenotypic variance of all 7339 gene expression levels explained by additive effects alone was 2.16%. By contrast, the estimated epistatic variance from the interacting SNPs detected in this study on average explain a total of 0.22% of phenotypic variance, approximately ten times lower than the estimated additive variance. There are several caveats to this comparison. Firstly, the ratio of additive to epistatic variance may differ at different minimum variance thresholds, and our estimate is determined by the threshold used. Secondly, the power of a 1 d.f. test exceeds that of an 8 d.f. test. Thirdly, the non-additive variance at causal variants is expected to be underestimated by observed SNPs in comparison to estimates for additive variance. This is due to differences in the rate of decay of the estimate of the genetic variance of the causal SNPs as LD decreases with the observed SNPs. And forthly, the extent of winner's curse in estimation of effect sizes may differ between the two studies.

Overall, we have demonstrated that it is possible to identify and replicate epistasis in complex traits amongst common human variants, despite the relative contribution of pairwise epistasis to phenotypic variation being small. The bioinformatic analysis of the significant epistatic loci suggests that there are a large number of possible mechanisms that can lead to non-additive genetic variation. Further research into such epistatic effects may provide a useful framework for understanding molecular mechanisms and complex trait variation in greater detail. With computational techniques and data now widely available the search for epistasis in larger datasets for traits of broader interest is warranted.

Methods Summary

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We searched for pairwise epistasis exhaustively in the BSGS discovery dataset, ²³ which comprises 846 individuals who are genotyped at 528,509 autosomal SNPs. Each individual had gene expression levels measured in peripheral blood at 47,323 probes. Only the probes that passed quality control and had significant expression in $\geq 90\%$ of individuals were used in the analysis (7,339 probes representing 6,158 RefSeq genes). Recent hardware and software ¹⁰ advances that use graphics processing units (GPUs) made it possible to perform the 1.03×10^{15} statistical tests to complete this analysis. We used permutation analysis ³³ to calculate an experiment-wide significance threshold of $T_e = 2.91 \times 10^{-16}$ at the 5% family-wise error rate (FWER). SNP pairs were modelled for

full genetic effects, including marginal additive and dominance at both SNPs plus four interaction terms. Though we could have used a less complex model to improve statistical efficiency, we deemed it important to be agnostic about the type of epistasis that might exist, and therefore chose not to over-parameterise the test. ^{18,19} Because there are many large marginal effects present in these data 253 it was necessary to perform several filtering steps to exclude SNP pairs that were significant due to marginal effects alone. All SNP pairs with LD $r^2 > 0.1$ and $D^{\prime 2} > 0.1$ 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, 259 a nested test contrasting the full genetic model against the marginal additive 260 and dominance model was performed for each remaining SNP pair (Methods), resulting in 501 significant interactions after Bonferroni correction for multiple 262 testing of the filtered SNPs. 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, the Fehrmann dataset (n = 1)1240) and the Estonian Genome Centre University of the University of Tartu 266 (EGCUT) dataset¹¹ (n = 891). Of these, 434 passed filtering in both replication datasets. A meta analysis on the interaction p-values from each replication 268 dataset was performed to provide an overall replication statistic for each putative interaction. 270

Acknowledgements

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Tables

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

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

 $^{^{1}}$ $-\log_{10} p$ -values for 4 d.f. interaction tests 2 Discovery dataset

 ³ Independent replication dataset
 ⁴ Meta analysis of interaction terms between replication datasets only

Figures 513

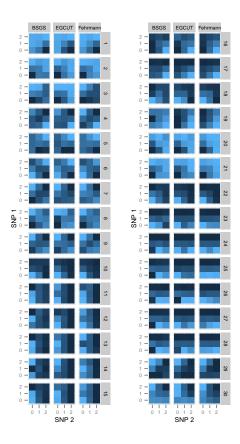


Figure 1: Replication of GP maps in two independent populations. The GP maps for each epistatic interaction that is significant at the Bonferroni level in both replication datasets are shown. Each GP map consists of nine tiles where each tile represents the expression level for that two-locus genotype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

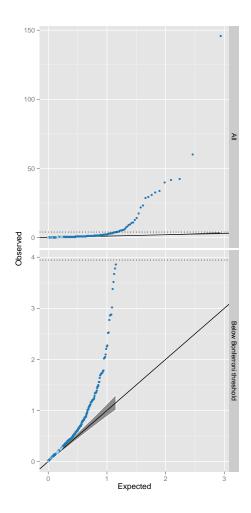


Figure 2: \mathbf{Q} - \mathbf{Q} plots of interaction p-values from replication datasets. The top panel shows all 434 discovery SNPs that were tested for interactions. Observed p-values (y-axis, $-\log_{10}$ scale) are plotted against the expected p-values (x-axis, $-\log_{10}$ scale). The multiple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

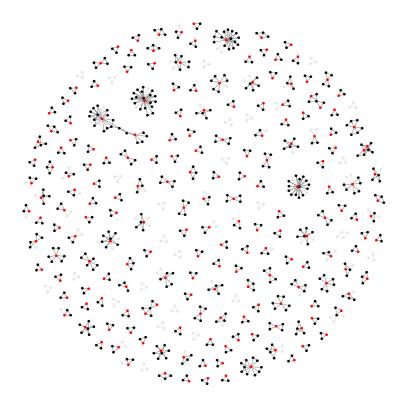


Figure 3: Discovery and replication of epistatic networks All 434 putative genetic interactions (edges) with data common to discovery and replication sets is shown, where black nodes represent SNPs and red nodes represent traits (gene expression probes). Three hundred and forty-five interactions had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

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396 Supplementary Figures

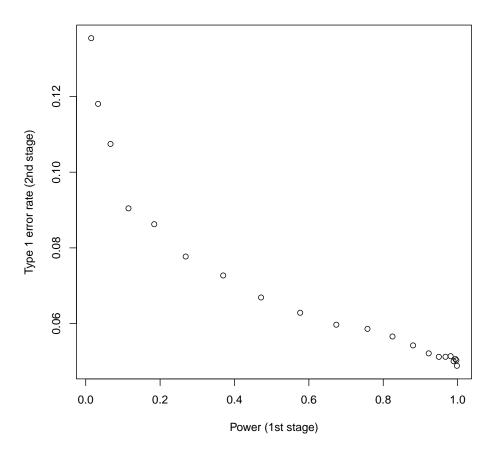


Figure S1: Type 1 error rate of two stage design assuming a null model of one large additive effect and no epistasis In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These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

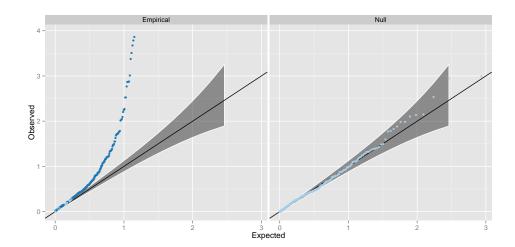


Figure S2: Q-Q plots of interaction p-values from replication datasets, excluding the 30 points significant at the Bonferroni level The right panel (Null) shows the interaction p-values from a meta analysis across two independent datasets on 434 randomly drawn SNP pairs. The left panel (Empirical) shows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

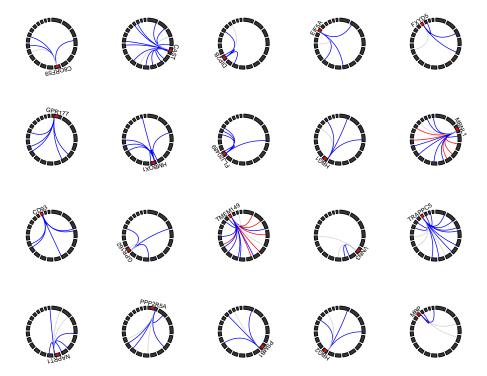


Figure S3: Gene expression traits with four or more genetic interactions Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent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



Figure S4: Location of SNPs relative to genomic features We used chromatin segmentation 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

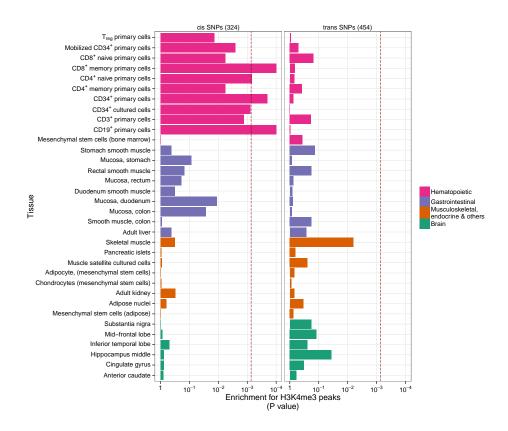


Figure S5: Tissue specific enrichment of SNPs in transcriptionally active regions The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3. Enrichment p-values are calculated using permutation analysis for 34 different cell types (y-axis) in four tissue types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

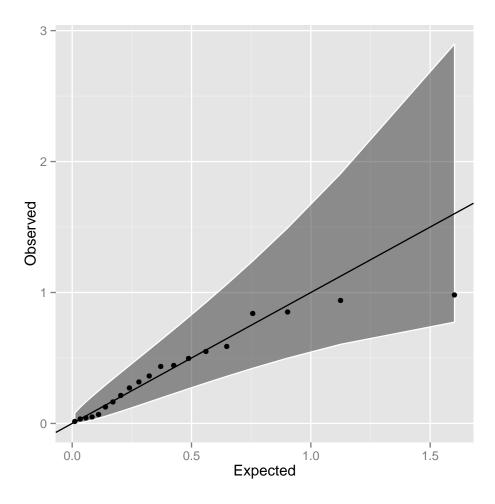


Figure S6: Q-Q plot of interaction p-values in the CDHWB dataset Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset (mainly due to small sample size). There is no evidence for enrichment of interaction terms, most likely due to insufficient power given the limited sample size.

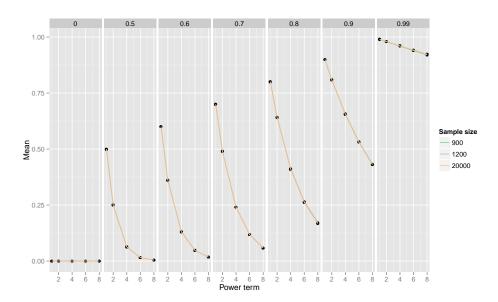


Figure S7: Sampling mean for different power terms of population r values Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8 . For a given population value of LD r (columns of plots), plotted is the sample mean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

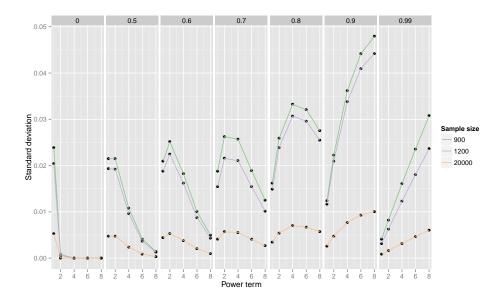


Figure S8: Sampling standard deviation for different power terms of population r values Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4 , r^6 , r^8 . For a given a population value of LD r (columns of plots), plotted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

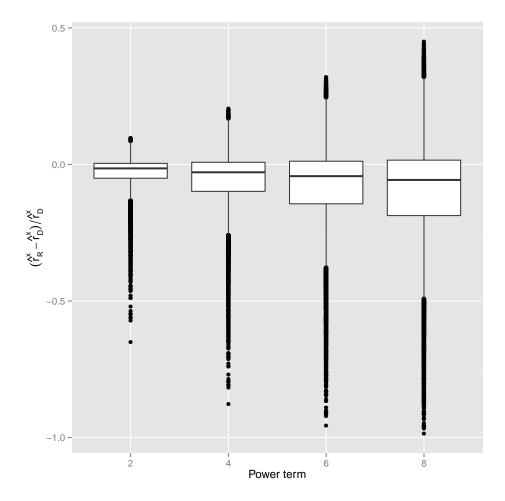


Figure S9: Reduction in LD as estimated in replication data after ascertaining for high LD in discovery data 100,000 "unobserved" causal variants (CVs) were tested for LD against a panel of 528,509 "observed" discovery markers (DMs). DM/CV pairs with LD $r^2 > 0.9$ were then tested in an independent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

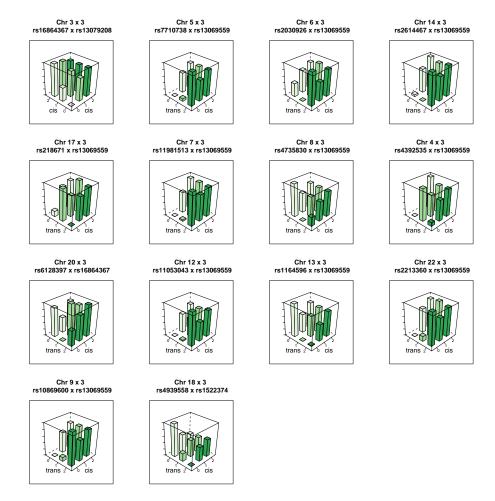


Figure S10: Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1 Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions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

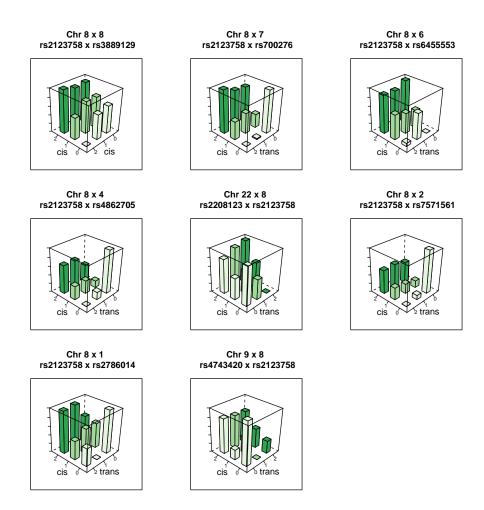


Figure S12: Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1 Each bar represents the mean phenotypic value for individuals in that genotype class.



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.

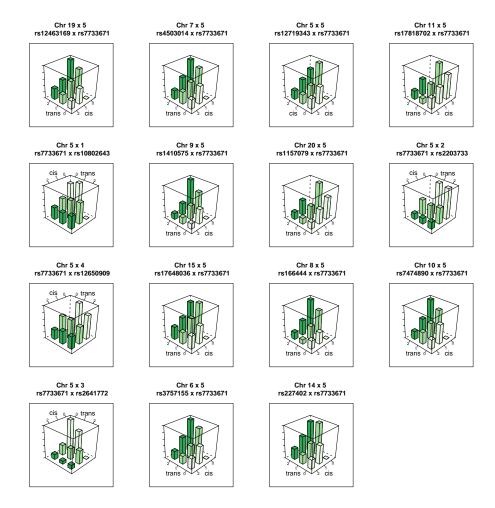


Figure S14: Genotype-phenotype maps for 15 interactions influencing the expression of CAST Each bar represents the mean phenotypic value for individuals in that genotype class.

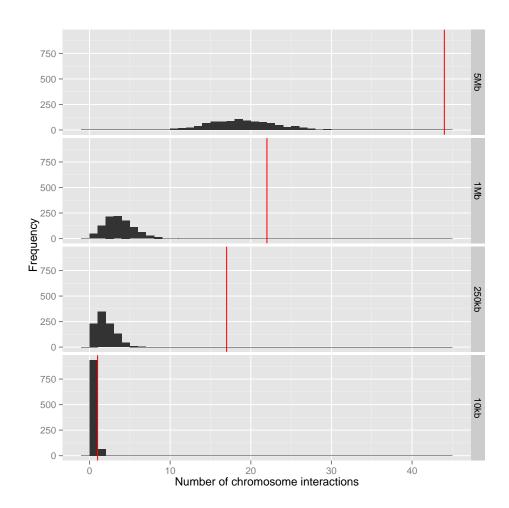


Figure S15: Number of overlaps between chromosome interactions and epistatic interactions Interacting chromosome regions may be a possible mechanism underlying epistatic interactions. The number of epistatic interactions within 20kb, 500kb, 2Mb and 10Mb of known chromosome interacting regions are shown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

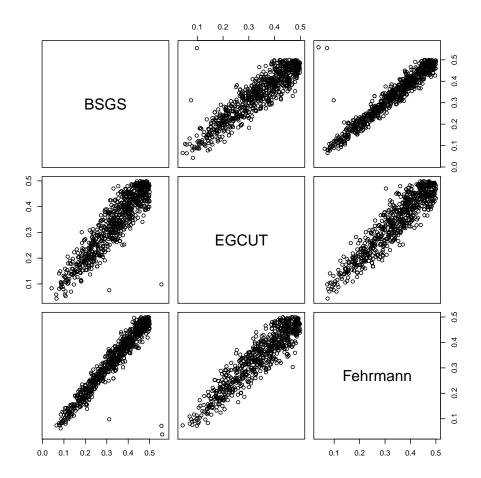


Figure S16: Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations Outliers were removed from the analysis as part of the filtering stage during replication.

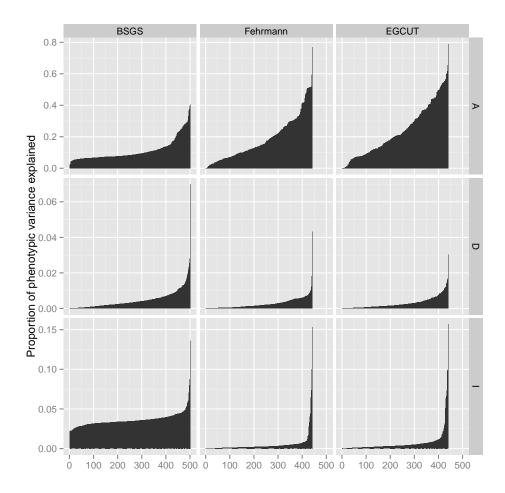


Figure S17: Comparison of variance explained by additive, dominant and epistatic effects from different cohorts How does the estimated variance decomposition change in different cohorts? The proportion of the phenotypic variance that is additive (A), dominant (D), or epistatic (I) for each putative interaction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

397 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/Mbc	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	78088813	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		3.82	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	

Exi	Expression trait				SNP 1			01	SNP 2		Interact	Interaction statistic /	- log10 p-values	values	
Gene ID ^a	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
CSORF59	ILMN_1653205	œ	rs8051751	16	7188323		rs2896452	œ	86102223	CSORF59	5.79	1.39	0.18	0.87	
C9ORF72	ILMN_1741881	o -	rs10122902	o ;	27556780	C9ORF72	rs2526698		242029101	5	6.36	0.96	0.01	0.37	
CABCI	ILMN-1731064	٦ ٥	rs12765847	01	4353908	TNDDR	rs3738725		227174210	CABCI	6.35 01	0.94	0.00	0.34	
CARDS	II.MN 1712532	0	rs4573661	- E	6026661	TIVE FOR	rs4077515	- σ	139266496	INPPSE	6.61	0.09	980	0.42	
CAST	II.MN 1717234	o ro	rs1157079	20	6778978		rs7733671	o rc	96000269	CAST	7.07	0.23	0.96	0.62	
CAST	ILMN_1717234	ю	rs12463169	19	17321669		rs7733671	ю	96000269	CAST	5.73	0.02	2.85	1.75	
CAST	ILMN_1717234	ю	rs12599264	16	81840122		rs7733671	Ŋ	96000269	CAST	7.00				
CAST	ILMN_1717234	ro	rs12719343	Ю	125369113		rs7733671	rO.	96000269	CAST	7.68	0.36	1.57	1.20	29.369
CAST	ILMN_1717234	io:	rs1410575	6	78255630		rs7733671	ıo:	96000269	CAST	6.55	0.13	1.34	0.78	
CAST	ILMN_1717234	iO:	rs166444	œ ;	78392770		rs7733671	ın ı	96000269	CAST	7.01	0.27	0.52	0.37	
CAST	ILMN_1717234	n	rs17648036	15	27311111		rs7733671	ı,	96000269	CAST	7.81	0.97	0.03	0.41	
CAST	ILMN_1717234	n	rs17818702	11	86107920		rs7733671	ı,	96000269	CAST	6.62	1.15	0.59	1.09	
CAST	ILMN_1717234	ıo ı	rs227402	14	70496867		rs7733671	iO i	96000269	CAST	6.12	0.11	0.01	0.01	
CASI	ILMIN-LITIOSE	OF	182022124	77	1000004		TS/ 1000/ I	O E	96000269	CASI	100	1	0	0	
CASI	TOWN THE STATE OF	0 1	185757155	0 1	1304393		1200011	0 1	96000269	CANI	# 0	0.0	0.00	0.12	
CASI	ILMIN-1/1/234	Ои	rs45005014		51149140		rs//550/1	OR	96000269	CASI	0.00	0.92	1.30	1.0	
Esec	II MN 1717394	o m	151414630	H L	08000080	For	151133011 201000649	o -	99000203	1000	10.7	0.10	0.15	24.0	
Esec	II MN 1717394	o m	157753671	o m	90000209	Toy C	1210802043		17010260		4.1	00	0.10	0.00	
Esec	II MN 1717394	o m	157753671	o m	90000209	E S C	1512030303	# C	224002101		2 1 2	22.0	0.70	0.00	
Esec	II MN 1717394	o m	157753671	o m	90000209	Fort	154203133	40	10559101		0.0	44.0	0.00	, - , -	
1 1 1	II MN 1651705	. [100011	0 0	66175386	1000	15204112 ve11030605		24447586	E	0.00	0.08	0.50	0.10	
מאטעטט	II.MN 1772208	1 :	re2353203	010	17099980		re541207		64125142	140 140 140 140 140 140 140 140 140 140	. r	03.0	0.30	2 5	
CCCCC B88CCCCC	II.MN 1772208	11	rs694739	11	64097233	CCDCSSB	rs12771349	10	96998193		5.62	0.23	80.0	0.14	
CD36	ILMN_1784863	2	rs3211834	7	80280117		rs1254900	2 2	85816334	VAMP8	6.93	0.15	0.01	0.02	
CD55	ILMN 1800540	-	rs750801	-	76033374		rs6700168	-	207502534	CD55	5.09	0.08	0.03	0.02	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs10255470	-	157182040		6.06	1.74	0.24	1.20	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs4696726	4	7992632		5.71	0.13	0.80	0.42	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs7622580	8	196721395		5.56	0.04	0.27	0.08	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs838875	12	125145394		6.31	0.24	1.67	1.16	
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs9576388	13	38434472		7.88	0.71	0.22	0.45	
CD93	ILMN_1704730	20	rs2868504	20	37771578		rs1884655	20	23074375	CD93	5.71	0.64	0.75	0.81	14.697
CD93	ILMN-1704730	20	rs4813479	20	23076914	CD93	rs10925747	П	238899903		7.43				
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs2873420	œ	136500554		7.02				
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs4328531	χ I	74439542		6.13				
CD93	ILMIN_I704730	200	rs4813479	02.	23076914	CD93	rs4789981	7.7	7.7264482	0.00	6.08				
CDCI6	ILMN-2339796	1 13	rs861544	14	104162263	00000	rs/324/44	1 1	115008038	CDCI6	5.46	0.21	0.14	0.11	11
CDASAL	ILMIN-1730926	101	rs9903940	7.7	40014102 F1056950	HOAB2	rs11033031	- 0	42066556	CEACAMET	0.47	0.90	0.07	0.45	1001
CEACAM21	ILMN_1745949	19	rs4803481	6	42066556	CEACAM21	rs2421050	1 10	158943044		6.67	2.16	0.16	1.44	
CEP192	ILMN_1703754	18	rs6505780	18	13069782	CEP192	rs13132719	4	180265266		5.75	0.15	0.24	0.12	
CEP63	ILMN_1787808	8	rs3825569	14	101350298		rs13079012	8	134247706	ANAPC13	6.36	0.23	0.10	0.09	
CES1	ILMN_2359945	16	rs8192935	16	55861794	CES1	rs772788	7	235248562		5.65				
CHPT1	ILMN_2202940	12	rs591967	13	38838122		rs2695290	12	102087844	CHPT1	5.74	0.72	0.20	0.44	
CHPT1	ILMN_2202940	12	rs6539014	12	102277782		rs867578	11	81937002		4.75	0.92	0.02	0.36	
CLEC12A	ILMN_1663142	12	rs429790	16	84471642		rs7313235	12	10132283	CLEC12A	5.55	0.07	1.28	0.67	
CLECI2A	ILMN_2403228	12	rs7305054	12	10156646		rs3903088	10	134236688		7.54	0.95	0.36	0.73	
CLFB	ILMN_1674609	ω,	rs17129799	11	96929337	1	rs6863172	Ω,	175595960	CLTB	5.52	1	0.27	0	
CNNS	ILMN-1770290	61	rs3752237	50	1047161	ABCA7	rs169130	91	63121080		7.56	0.07	0.07	0.02	
CDSE1	ILMN-1770290	G 06	FS3132231	n or	145569535	ADCA	rs/33001/	51	61738094		6.33	1.92	0.20	1.09	
CPVL	ILMN_1682928	۰.	rs12596791	16	26115562		rs245884	# L-	29188475	CPVL	5.74	0.06	0.57	0.23	
						1								Continue	Continued on next page

-	Distance / Mb=			0.033			0.040					10 044	000													66 920	0.052																
ь	0.	0.04	0.15	42.27	0.11	1.03	33.53	0.03	0.34	0.04	1.47	0.36	0.60	0.44	0.14	0.42	0.44	0.29	0.58	0.32	0.37	0.03		0.19	10 0	0.01	0.97	1.12	0.70	0.22	0.79	0.10	0.24	0.02	0.53	0.11	0.41	0.35	0.81	0.09	0.08		0.44
4	,	0.03			0.41	0.74			0.53	0.02	1.87	0.83	0.86	0.41	0.58	0.25	0.29	0.02	1.17	0.34	0.04	0.05	0.58	0.22	000	0.02	1.45	0.27	1.18	0.35	0.47	0.11	80.0	0.05	1.12	0.04	0.40	0.58	1.20	0.11	0.04		0.19
-	.	0.19	0.10	25.20	0.02	0.92	18.76	0.21	0.23	0.20	0.39	0.05	0.29	0.48	00.00	0.64	19.0	0.77	90.0	0.37	88.0	0.32		0.30	0.37	0.03	0.23	1.58	0.15	0.22	06.0	0.23	0.56	80.0	0.05	0.36	0.45	0.20	0.25	0.20	0.29		0.74
	,	5.55	6.18	11.99	5.74	50.0 82	7.16	5.42	5.89	5.68	1.81	o r o o o r	5.42	5.44	9.12	5.62	5.31	6.39	6.00	6.48	5.51	4.65	4.87	5.31	4.40	0.00	5.79	6.17	4.81	5 75 1 15 20 00	86.98	5.56	5.44 7.77	6.36	5.52	6.51	5.56	5.70	5.43	6.11	5.65 7.63	0.0	6.83
	Association	CPVL			CTNNA1	Deti		CWF19L1	CYBRD1	CYBRD1	CYBRD1	CYBRDI	CYP27A1	DAB2				COOTOA	DHRS9	DHRS9	DHRS9	LASSE		LASS5		7. A. S. S. A.	DNAJB6	ррн3	000	ECHDC2	EHD4	EIF2B2				EMR2	EMRZ	EPHX2	ERICH1	ERICH1	ERICH1		EXOC3
O TATO	Pos/Mb	29188475 46843631	62406408	45198355	138226767	880873892	88077479	102027407	172368120	172368120	172368120	172368120	219650616	39381357	82076988	187475208	32451144	137810259	169960422	169960422	169893419	50610976	153134888	50730458	61971140	51074199	157163614	16320360	64004670	53402552 53402552	42192040	75590340	99603119	129624067	126387391	14879034	14879034	27400604	578742	607161	578742		428236
	Chr.	r- 6	Ю	21	ro (0 -	11	10	27	73	01 0	71 0	1 01	ю			10	- თ	. 61	7	C1 C			12	∞ <u>-</u>			က	18		12	14	14	1 00	17	19	5 - 1		œ	œ	∞ <	,	ıÇ
	rs 1D	rs245884 rs1531133	rs1473927	rs3761385	rs176382	rs7U79264	rs556895	rs12784396	rs888427	rs888427	rs888427	rs888427	rs933994	rs835223	rs1343244	rs2378341	rs7042042	rs10120023	rs7566044	rs7566044	rs2161037	rs11169322	rs2872008	rs7134595	rs1808634	rs12427378	rs3779589	rs1566972	rs4891884	rs11206043	rs1048166	rs175450	rs1269096	rs2197210	rs4471434	rs9305048	rs9305048	rs13269963	rs12115088	rs4735900	rs12115088	010101	rs12188164
	Association		CRLS1		C C	CIRC						CVBBD1				DDT	V 01.00	401300					LASS5		LASS5				ECGF1				EIF5A	EIF5A	EIF5A		EMB2				EPICH1	1110111	
7 117	Fos/Mb	39202070 188859908	5986234	45230974	69500505	88139983 26250645	88117962	11456027	129994690	140698856	12318284	23344590	36571928	110451383	43111688	24248761	125962645	106703727	89468283	147132505	29959453	29161503	50636364		50730458	. ~	157216093	93409054	50971266	241911027 17675900	53244938	60218334	7221707	7221707	7221707	23196249	18761714	127909396	134611176	45337329	31187910		55228462
	Chr.	21	20	21	8:	11	1 :	11	4	6	10	0.70	20	2	17	22	Ξ.	. =	12	7	21	14	12	19	12	2 -	- 1	12	55	2 6	19	18	17	17	17	21	07.	1 1	11	22	χ. α)	10
ţ	rs 1D	rs2835998	rs6139887	rs9979356	rs924943	rs2457684	rs7930237	rs7108734	rs2592948	rs7852475	rs11257679	rs0137908	rs6021982	rs7778910	rs9900173	rs5760102	rs4937097	rs12363827	rs1519956	rs1528529	rs2831914	rs11080134	rs11169335	rs338585	rs7134595	rs871257	rs2286842	rs12232308	rs140522	rs4234091	rs10403312	rs6567288	rs7216490	rs7216490	rs7216490	rs2827076	rs6132112	rs1107764	rs10894861	rs5766218	rs726145	00001111	rs187076
	Chr.	r- c	20	21	ω ;	I :	1 ::	10	7	67	01 0	21 0	1 (1	10	17	22	n -		7	7	01 0	7 2	12	12	2 2	7 0	1 1-	က	55		15	14	17	17	17	19	61	2 00	œ		00 00)	ıÇ
Table man	Frobe ID	ILMN_1682928 II.MN_1813256	ILMN_1737685	ILMN_1761797	ILMN_1804854	ILMN-1696347	ILMN_2242463	ILMN_1651886	ILMN_1712305	ILMN_1712305	ILMN_2087692	ILMN-2087692	ILMN-1704985	ILMN_2128428	ILMN_1811648	ILMN_1690982	ILMN_1797001	ILMN 1783996	ILMN_1733998	ILMN_1733998	ILMN_2384181	ILMN_1755589	ILMN_1755589	ILMN_1755589	ILMN_1755589	II.MN 1755589	ILMN_1793770	ILMN_2349610	ILMN_2109708	ILMN-1671568	ILMN_1720083	ILMN_1713380	ILMN_1794522	ILMN_1794522	ILMN_1794522	ILMN_2353633	ILMN_2353633	ILMN_1709237	ILMN_1731001	ILMN_1731001	ILMN_1731001		II.MN 1789419
1	Gene ID	CPVL	CRLS1	CSTB	CTNNA1	CERC	CTSC	CWF19L1	CYBRD1	CYBRD1	CYBRD1	CYBRDI	CYP27A1	DAB2	DCAKD	DDT	DDX58	DEM1	DHRS9	DHRS9	DHRS9	DIP2B	DIP2B	DIP2B	DIP2B	DIF 2B	DNAJB6	DPH3	ECGF1	ECHDC2	EHD4	EIF2B2	EIF5A FIF5A	EIF5A	EIF5A	EMR2	EMR2 EMB2	EPHX2	ERICH1	ERICH1	ERICH1	1110	EXOC3

Ex	Expression trait				SNP 1				SNP 2		Interacti	Interaction statistic /	- log10 p-values	ralues	
Gene IDa	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb ^c	Associationd	rs ID	Chr.	Pos/Mb ^c	Associationd	BSGS _e I	Fehrmann ^f	EGCUT	Metag	Distance / Mbh
FEZ2	ILMN_1739586	61.6	rs2356400	19	44321776		rs13406184	61.6	36791226	FEZ2	5.78	0.14	0.33	0.16	
FE22	ILMN-1739586 ILMN-2115005	9 19	rs969010	4 6	159963132		rs11691600 rs831486	71 92	37001267	FE22	0.00	0.14	0.25	0.14	
FGD2	ILMN_2115005	9	rs902634	10	133943951		rs831489	9	36999682	FGD2	5.49	1.20	0.11	99.0	
FLJ20489	ILMN_1778144	12	rs17615703	12	117036766		rs3782908	12	48169526	FLJ20489	5.81	0.06	0.70	0.29	68.867
FLJ20489	ILMN-1778144	7 7	rs3782908	1 5	48169526	FLJ20489	rs897511	4 6	167695661	ET. 120.480	5.53	0.03	0.11	0.00	
FLJ20489	ILMN_1778144	12	rs4984440	12	97033129		rs3782908	121	48169526	FLJ20489	6.49	0.31	0.47	0.36	
FLJ20489	ILMN_1778144	12	rs7204135	16	50626195		rs3782908	12	48169526	FLJ20489	6.90	0.38	0.17	0.21	
FLJ20718	ILMN_1763663	16	rs9325634	21	43818790		rs2287197	16	50106594	FLJ20718	6.04	0.14	0.95	0.53	
FLJ43093	ILMN_2123450	9	rs17112712	14	107276627		rs6906101	9	36667610	FLJ43093	5.48	0.39	90.0	0.13	
FLJ43093	ILMN_2123450	9	rs6906101	9	36667610	FLJ43093	rs13214069	9	32705248		5.44	0.00	0.64	0.18	3.962
FN3KRP	ILMN_1652333	17	rs898095	17	80890638		rs9892064	17	80827903		16.16	28.24	29.39	59.95	0.063
FUCAL	ILMN_1752728	- o	rs4971478	24 6	1346063		rs12744386	- č	24168019	FUCAL	6.41	0.01	0.30	0.06	
FXYD5	ILMN_2309848	19	rs17398183	20	55609148		rs2285515	1.0	35660450	FXYD5	6.58	0.03	0.48	0.15	
FXYD5	ILMN_2309848	19	rs2285515	19	35660450	FXYD5	rs11739594	10	141709563		5.70	0.07	0.17	0.02	
FXYD5	ILMN_2309848	19	rs2285515	19	35660450	FXYD5	rs13067700	က	95331048		6.00	0.09	0.51	0.22	
FXYD5	ILMN_2309848	19	rs2285515	19	35660450	FXYD5	rs17036504	5	47567329		6.10	0.28			
G3BP2	ILMN_2381758	4	rs10230232	4	29390239		rs1553985	4	76554604		5.19	0.08	0.37	0.14	
GAA	ILMN_2410783	17	rs11150847	17	78153130		rs12602462	17	78146016		13.91	19.98	12.99	32.60	0.007
GAA	ILMN_2410783	17	rs8068856	17	78100731	GAA	rs10902506	12	132678089		5.65	0.11	0.39	0.17	
GAPT	ILMN_1675191	ı, ı	rs10070522	ı,	57786110	GAPT	rs7605821	71	235695228		10.18 10.18	0.01	0.78	0.28	
GAPT	ILMN_1675191	ıo ı	rs7082031	10	128038717		rs10070522	ıo ı	57786110	GAPT	5.72	0.26	0.11	0.11	
GATS	ILMN_1699631	- 1	rs1147447	14	66460742		rs2950520	1 ~	99827148	GAIS	5.47	0.83	0.63	0.87	
GAIS	ILMIN-1099051	7 -	rs2425256	071	201026012	, רם ר	rs2950520		9902/140	GAIS	0.72	000	0.42	000	
GDFDS	ILMIN_1774901	16	rs3809624	16	30102802	GULUS STATUS	rsz197405	41	485/2052		0.07	0.0	0.33	0.00	
GULDS	ILMN 1790692	01	rs4145072	13 1	11089955	50105	rs7577293	4 0	85935282	CINIC	20.00	0.00	0.03	4 6 6	
GPN3	ILMN_3239426	175	rs7198646	16	26084476		rs7960552	12	111164237	GPN3	5.72)	
GPR162	ILMN_1730816	12	rs1860563	16	6478898		rs2707210	12	6902002	GPR162	5.49	0.36	0.46	0.39	
GPR162	ILMN_1730816	12	rs2272500	12	79685913		rs2707210	12	6902002	GPR162	5.07	0.25	0.03	90.0	72.784
GPR162	ILMN_1730816	12	rs2707210	12	6902002	GPR162	rs4740848	6	6554558		5.47	0.25	90.0	0.07	
GPR162	ILMN-1730816	12	rs2707210	12	6902002	GPR162	rs9827054	က	188880113		6.21	0.96	0.06	0.44	
GPR177	ILMN_1660549		rs11057383	12	124369421		rs12065581		68732819	GPR177	5.45	0.72	0.67	0.81	
GPR177	ILMN_1660549		rs12527241	: O	120468039		rs12065581		68732819	GPR177	5.76	0.17	0.40	0.22	
GFR177	ILMIN-1660549		rs12032999	- 9	11160699		rs12005551		66793619	GFR177	0.00	0.70	L.43	1.30	
GPR177	ILMN 1660549		rs9575097	2 5	82986268		rs12065581		68732819	GPR177	6.04	10.0	0.21	09.0	
GPR177	ILMN_2283325	-	rs6566669	18	70506011		rs12065581	-	68732819	GPR177	5.86	0.24	0.34	0.23	
GPR177	ILMN_2283325	1	rs9290426	ო	171399321		rs12065581	1	68732819	GPR177	6.50	0.01	0.24	0.04	
GSDMB	ILMN_2347193	17	rs11557467	17	38028634	GSDMB	rs4965745	15	101508261		5.88	0.68	0.20	0.41	
GSTM1	ILMN_2391861	1	rs12248673	10	53192833		rs11101992	1	110266754	GSTM1	6.11	0.27	0.19	0.16	
GSTM1	ILMN_2391861	1	rs1547574	13	85344527		rs11101992	-	110266754	GSTM1	5.91	0.27	1.14	0.79	
GSTM2	ILMN_2201580	1	rs6492807	13	96159560		rs3754446		110253241	GSTM1	6.77				
HIFO	ILMN_1757467	5 5	rs139898	5 5	38399979		rs4853333	C1 ±	77919015		6.36	0.52	0.66	0.65	
11150	ILMIN-11/5/46/	7 0	1S159090	7 0	000000000		rso497007	0 -	00001011		100	7 0 0	0.51	0.23	
HBC1	ILMIN_1796678	77 -	rs159696	1 17	4598167		159905949	7 -	5971671	HBG9	0.70 74	0.23	0.40	0.02	
HBG1	II.MN 1796678	: =	rs12975066	- 61	35723501		rs2855039	: :	5271671	HBG2	00 00 10	0.00	0.24	21.0	
HBG1	ILMN_1796678	11	rs2855039	11	5271671	HBG2	rs12042181	-	213088494	LQK1	6.78	0.08	0.52	0.21	
HBG1	ILMN_1796678	11	rs2855039	11	5271671	HBG2	rs12503379	4	141533832	,	6.42	0.01	0.46	0.11	
HBG2	ILMN_2084825	11	rs11078523	17	4523167		rs16912979	11	5309695	HBG2	90.9	0.01	0.41	0.10	
														Continu	Continued on next page

Table S1 - continued from previous page

	Expression trait			-4	SNP 1			•1	SNP 2	•	Interact	Interaction statistic /	- log10 p-values	values	•
Gene ID ^a	Probe ID ^D	Chr.	rs ID	Chr.	Pos/Mb^{c}	Associationd	rs ID	Chr.	Pos/Mb^{c}	Association	$BSGS_e$	$Fehrmann^{I}$	$EGCUT^{t}$	Metag	Distance / Mb ⁿ
HBG2	ILMN_2084825	11	rs12975066	19	35723501	нвсэ	rs2855039	11	5271671	HBG2	5.77	0.08	0.13	0.05	
HBG2	ILMN_2084825	11	rs2855039	: :	5271671	HBG2	rs12503379	4 4	141533832	7.17	86.0	00:00	0.46	0.10	
HDAC7	ILMN_3266186	12	rs2109029	16	6036851		rs4760636	12	48173352	HDAC7	5.75				
HEBP1	ILMN_1802557	12	rs3782567	12	13145613	HEBP1	rs17686635	οο į	135220622		5.98	0.15	0.59	0.32	
HEXDC HI A DBA	ILMN-1741180	17	rs1942719	20 5	71237270		rs7213057	17	80378939	HEXDC HI A DEDE	5.81	1.61	0.34	1.22	
HLA-F	ILMN_1762861	9	rs11660982	f 00	75467313		rs2523404	9	29695713	HLA-H	5.69	1.00	0.47	0.86	
HMBOX1	ILMN_1720059	oo	rs12435486	14	98670849		rs7837237	00	28876221	HMBOX1	6.54	0.92	1.11	1.34	
HMBOX1	ILMN_1720059	œ	rs2837803	21	42112794		rs4732890	œ	28751381	HMBOX1	6.62	0.05	1.01	0.46	
HMBOX1	ILMN_1720059	œ	rs4765451	12	127237464		rs8180944	œ	28904086	HMBOX1	5.80	0.39	3.13	2.52	
HMBOX1	ILMN_1720059	œ	rs587639	œ	132725731		rs7837237	œ	28876221	HMBOX1	6.58	0.55	0.34	0.44	103.850
HMBOX1	ILMN_1720059	œ	rs8180944	00	28904086	HMBOX1	rs4553956	က	189533772		6.88	3.38	0.03	2.20	
HMBOX1	ILMN_1720059	x	rs8180944	00 0	28904086	HMBOX1	rs7810884	- 0	158276926	130000	6.12	0.34	0.66	0.52	
HMBOAL	ILMIN_1720059	XO 1	rs9521666	υ,	170030466		rs8180944	ю 1	28904086	HMBOAI	0.40	0.0	0.20	0.45	0 0 0
HODO153	ILMIN-2101920	0 -	150094200	0 -	119052400		184700010	0 -	110881184	10001117	10.02 0.03 10.00	0.00	9.01	10.01	0.041
HSPC157	ILMN 3194087	-	rs6063164	30	46486900		rs4654783		22439520	HSPC157	5.0				
HSPC157	II.MN 3194087		rs662739	0 -	121229893		rs4654783	-	22439520	HSPC157	6.61				
HSPC157	ILMN 3194087	-	rs7088558	0	101884937	CWF19L1	rs4654783		22439520	HSPC157	6.48				
IL32	ILMN_1778010	16	rs1554999	16	3115628	IL32	rs4759890	12	131757163		6.90	0.19	0.50	0.29	
IL32	ILMN_2368530	16	rs765044	19	2560423	!	rs1554999	16	3115628	IL32	5.53	69.0	0.23	0.44	
INPP5E	ILMN_1811301	6	rs8044524	16	81603771		rs1127152	6	139335599	INPP5E	5.58	1.46	0.84	1.55	
JAZF1	ILMN_1682727	7	rs757355	12	47970693		rs849341	4	28288174		8.16	0.03	0.26	0.05	
KCNJ15	ILMN_1675756	21	rs2186344	21	39606769	KCNJ15	rs424299	11	5570771		5.64	0.65	0.13	0.33	
KIR2DS5	ILMN_1691803	19	rs649216	19	55324635	KIR2DL1	rs6419960	4	189055298		4.74	0.46	0.89	0.77	
KTELC1	ILMN_1811104	က	rs4349034	13	84597119		rs727905	က	119119433	KTELC1	5.53	80.0	08.0	0.37	
KTELC1	ILMN_1811104	က	rs6815953	4	183109012		rs6414283	က	119195913	KTELC1	5.45	0.64	80.0	0.28	
L3MBTL2	ILMN_2336109	55	rs4822006	22	41519362	L3MBTL2	rs1294338	-	233438952		5.88	0.33	0.04	60.0	
LAP3	ILMN_1683792	4	rs7042087	6	132602868		rs7658240	4	17588950	LAP3	5.72	0.24	0.47	0.31	
LAXI	ILMN_1769782	н,	rs1891432	٠,	203877662		rs10900520	н,	203780591		19.16	18.60	11.22	29.24	0.097
LDLKAPI	ILMN_1809040	- ţ	rs1552032	10	59971635		1171070	⊣ 1	25889632	LDLKAFI	6.00	1	9		
LGALSS	ILMIN-2412214	7.7	rs12450521	10	20083392	111 D A E	rs11/49/2/	υ ō	71561407		0.TO	0.35	0.40	0.34	
LINSI	ILMN 2338197	2 12	rs3639332	9 12	101120963	LINSI	rs/1278387	0 0	127804531		0.00	0.43	0.03	0.03	
LRRC25	ILMN 2150196	61	rs6009951	22	51151350		rs8101804	61	18496107	LBRC25	2.68	0.11	0.35	0.15	
LY86	ILMN_1807825	9	rs977785	9	6588881	LY86	rs1543675	н	78946879		5.61	0.13	0.15	0.07	
LYZ	ILMN_1815205	12	rs2168029	12	69734641	LYZ	rs11981725	-1	154137150		5.95	0.15	0.03	0.03	
$_{\rm LYZ}$	ILMN_2162972	12	rs177820	18	77276964		rs2168029	12	69734641	LYZ	5.71	0.49	0.03	0.16	
LYZ	ILMN_2162972	12	rs2168029	12	69734641	LYZ	rs2253135	6	130319560		6.31	0.61	0.36	0.49	
MADILI	ILMN_2358069	,	rs//83/15	, ,	1923385	MADILI	rs6414306	n	127011798	200	5.62	0.25	0.88	0.59	
MADZLIBP	ILMN_1694711	9 6	rs7983718	13	103203146		rs1096699	9 0	43528441	MADZLIBP	5.93	0.63	1.11	1.09	
MAPILCSA	ILMIN_I776188	20	rs974607	77	700010		rsb0b0034	0.7	33351864	MAPILC3A	10.0	1.18	0	п 2	
MBNLI	ILMIN-2313138	00	rs10869600	. c	0202201		rs13069559	9 0	152187451	MBNLI	6.70	67.0 00.0	0.27	0.04	
MBNL1	ILMN_2313158	0 00	rs1164596	13	97100681		rs13069559		152187431	MBNL1	7.38	1.43	0.63	1.34	
MBNL1	ILMN_2313158	8	rs11981513	7	94648239		rs13069559	က	152187431	MBNL1	7.71	0.43	5.36	4.58	
MBNL1	ILMN_2313158	3	rs16864367	8	152234166		rs13079208	8	152116652		13.49	16.25	24.74	41.56	0.118
MBNL1	ILMN_2313158	3	rs2030926	9	114067127		rs13069559	က	152187431	MBNL1	7.10	0.91	5.80	5.53	
MBNL1	ILMN_2313158	8	rs218671	17	6604708		rs13069559	က	152187431	MBNL1	7.63	0.62	5.82	5.23	
MBNL1	ILMN_2313158	no	rs2213360	525	34291750		rs13069559	ကင	152187431	MBNL1	6.05	0.52	0.72	0.70	
MBNLI	ILMN_2313158 ILMN_2313158	0 00	rs2305802 rs2614467	1. 1.4	16038535 99770138		rs13069559 rs13069559	ာ က	152187431	MBNL1	6.94 5.74	1.67	2.22	5.30	
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lues	po es		0.17	0.15	2.03	3.86	0.76	0.14	0.07	0.49	0.62	0.88	0.82	0.50	0.10	20.0	0.67	0.24	0.70	0.03	0.33	0.48	0.15	0.04	0.56	0.26	0.19	0.66	0.46	0.17	1.21	91.0	0.44	0.25	0.04	4.06	200	0.04	1.78	0.86	0.15	0.38	0.11	1.55	0.00	0.59	0.08	
- log10 p-values	EGCUT		0.02	0.46	1.55	0.81	0.46	0.00	0.00	0.00	0.08	1.48	1.21	0.44	0.70	500	0.36	0.65	06.0	0.01	0.87	1.19	0.42	0.04	0.78	0.33	0.42	0.48	0.95	0.13	0.28	0.30	0.14	0.11	0.03	4.47	0.44	0.20	0.64	0.32	0.48	0.08	0.40	1.25	0.08	0.84	0.31	
┡	Fehrmann ^f E		0.47	0.03	1.27	4.12	0.87	0.42	0.36	1.00	1.20	0.13	0.25	0.66	0.19	0.00	0.87	0.03	0.36	0.20	0.02	0.00	0.05	0.16	0.31	0.29	0.12	0.72	0.08	0.36	1.00 3.7	0.16	0.81	0.53	0.19	69.0	0	0.00	1.95	1.18	0.03	0.80	0.02	1.03	0.25	0.28	0.03	
Interaction statistic	BSGS ^e Feb	5.45	6.13	5.44	8.59	4.13	4.38	5.64	5.00	27.42	5.42	5.43	6.04	0.00	0.40 E 0 E	27.50	5.64	6.51	5.51	5.60	5.23	7.11	4.12	6.35	5.15	4.44	5.81	5.63	5.72	5.61	00.00	5.72	6.43	7.34	5.60	4.81	5.79	5.44	82.78	5.42	5.00	5.90	5.70	5.75	6.55	6.42	6.38	
	Associationd	NRBF2 NRBF3	AICDE 2	NUDT18			CASI	NITAO	OSBPL5	Colri		OVGPI	CVGFI	TPCAL4	D V R	EX.E	PFAAP5)	PHCA				PISD	PNKD	PNPLA7	PPFIBP2	PPP2R3C	PP2R5A	PPP2R5A	PPZK5A	PPPRA	PP2R5A	PRDX5			C21ORF57	SMB1	SMB1		SMB1	PTDSS1	PTDSS1	PTDSS1	2DPR			INCO	
SNP 2	Pos/Mb ^c /	65133822 N		21964378 N	163997467	113409260								40139553 F					76708086 F		30398876	18236681	32097775 F	_							21244/16/ F			12639800		Ο,	170877444 F			_				•	70235726	120161117	26938488	
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	Associationd									E	CSTFI			FAM	LOIONE			PGLYRP1		PIK3IP1	PISD	PISD													C21ORF57				PSMB1							RABACI	AKTIF	
SNP 1	Pos/Mb^{C}	56157341	240680022	25453482	113480510	113448652	49160255	74286646	26662543	10024109	77755469	240132968	140148107	148795	10001000	27246462	49151303	46529456	123097386	31675185	32263131	31999127	33234931	158781604	4527109	49668255	58350896	166399467	123595064	169277991	135030045	27148475	95040482	23867776	47931653	48063862	121774705	30347832	170890384	131727816	95478823	76598123	126852438	106348246	33375704	42462788	53526551	44 / / /
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Expression trait	Probe ID ^b	ILMN_3237385	ILMN_1800897	ILMN_1787885	ILMN_1658247	ILMN_1658247	ILMN_1675640	ILMN-2381899	ILMN-2307032	ILMIN_1/42456	ILMIN-1742456	ILMIN_1734542	ILMIN_1734542	ILMN-2313901	ILMIN-1815951	ILMN 1660232	ILMN 1797893	ILMN_1704870	ILMN_1812552	ILMN_1719986	ILMN_1793934	ILMN_1793934	ILMN_1793934	ILMN_1774604	ILMN_1662587	ILMN_1675656	ILMN_1662617	ILMN_1738784	ILMN_1738784	ILMIN-1738784	ILMN-1738784	II.MN 1738784	ILMN_1711606	ILMN_1713603	ILMN_1675038	ILMN_1675038	ILMN-1789176	II.MN 1789176	ILMN 1789176	ILMN_1789176	ILMN_1743049	ILMN_1743049	ILMN_1743049	ILMN_1672443	ILMN_1803197	ILMN_2207363	ILMN_1756999	
Ext	Gene IDa	NRBF2 NRBF2	NRD1	NUDT18	OAS1	OAS1	OASI	NITAO	OSBPL5	Colri	OSTFI	OVGPI	OVGFI	PAM	PEVE	DEX.	PFAAP5	PGLYRP1	PHCA	PIK3IP1	PISD	PISD	PISD	PNKD	PNPLA7	PPFIBP2	PPP2R3C	PPP2R5A	PPP2R5A	PPP2R5A	PPP2R5A	PPP2R5A	PRDX5	PRKCB1	PRMT2	PRMT2	PSMB1	PSMB1	PSMB1	PSMB1	PWP1	PWP1	PWP1	QDPR	RAB3IP	RABACI	RBL2	

Part	Expression trait				SNP 1				SNP 2		Interac	Interaction statistic	$-\log_{10} p$ -values	/alues	
ILAN 1803280	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb^{c}	Associationd	rs ID	Chr.	Pos/Mb^{c}	Associationd	$BSGS_{e}$	Fehrmann ^f	$\mathtt{EGCUT}^{\mathrm{f}}$	Metag	Distance / Mb ^h
ILAN 2027706	ILMN_1802380		rs4982958	14	24987865		rs301819	1	8501786	RERE	5.66	0.61	1.23	1.17	
ILANI 1786-329 1 medical size medical size 1 medical size medical si	ILMN_2327795		rs11085829	19	13174312		rs301819		8501786	RERE	5.12	0.21	0.10	0.00	
ILANI 1780533 14 midoli24896 14 21102800 ILANI 1780536 13 midoli245 14 midoli24896 14 midoli2489 15 midoli2489 17 midoli2489 18 midoli2489	ILMN_2327795	-	rs3852011	က	112844086		rs301819	1	8501786	RERE	5.71	0.08	09.0	0.26	
ILANN 1785457 1 miltoria 1 miltoria miltori	ILMN_1780533	14	rs11628398	14	21182800	RNASE6	rs7324365	13	100601327		5.48	0.42	0.21	0.26	
LANK 17975 1	ILMN-1780533	14	rs6603134	19	8106521 4875566		rs11628398	13	54668512	KN ASE6	5.11	0.09	0.22	0.08	
ILINK 1778347 1 mit 1772 1 mit 172 1 mit	ILMN_1794726	17	rs400688	17	4839930	RNF167	rs11706900	9 00	36348968		5.59	0.71	0.46	0.64	
ILANY 2183287 1	ILMN_1738347	1	rs1107121	21	46127549		rs2819365	1	201983242		6.27	0.11	0.30	0.13	
LINK 176721 16 R8051234 16 80502035 16	ILMN_1738347	1	rs8071611	17	67153386		rs2819365	1	201983242		4.32	1.48	0.52	1.28	
ILMN 21207570 1	_	16	rs352935	16	89648580		rs2965817	16	89513234		4.98	3.79	14.41	17.24	0.135
ILMN 1289938		61	rs1401202	16	80320056		rs4849261	61	114450028	RPL23AP7	5.55	0.13	0.73	0.38	
ILMN 1209369 14 \$10002022 14 \$10002021 RPL86AL RF150299 0 60137200 0 60132 0	_	14	rs3007033	14	50103816	RPL36AL	rs17495030	6	138038093		5.46	0.09	90.0	0.02	
ILMN 1704771 St. 192084454 St. 194019446 ILMN 1704778 ILMN 1704771 St. 19404471 St	_	14	rs4900928	14	50020817	RPL36AL	rs1502991	9	66137260		5.86	0.32	0.20	0.19	
ILMN.1764721 8 malaboral mathematical mathe	ILMN_1764721	œ	rs2958482	œ	145984615	RPL8	rs1619856	П	234585790		4.59	0.10	0.37	0.15	
ILMN.17095478 11 mil.17085428 1 mil.048.0221 1 mil.04.220788 1 mil.04.22078 1 mil.	ILMN_1764721	00	rs4143674	20	4741304		rs2958482	œ	145984615	RPL8	4.33	0.13	0.45	0.22	
ILMN.1002677 ILMN.100267 ILMN.1	ILMN_3297880	3	rs4889214	16	80913946		rs696221	6	10342876	SEC13	6.48				
ILMN.1090.027 11 rig.1474-00 14 104412137 rig.848.66 11 94900111 SESN3 5.50 0.02 0.01 ILMN.1090.027 11 rig.955.89 15 94900111 SESN3 5.50 0.02 0.01 ILMN.1090.027 11 rig.955.89 14 49490511 14 49490511 5.50 0.02 0.01 0.01 0.02 0.01	ILMN_1702787	-1	rs17085428	ю	95388015		rs7695	1	156147326	SEMA4A	5.70	0.22	1.73	1.17	
ILMN.10694027 11 res684596 15 46691793 SESSA9 1 res685456 11 46691793 SESSA9 1 res684564 1 46691793 SESSA93 1 res684564 1 46691793 SESSA9343 1 43898365 1 43898363 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43898373 1 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 4 43893734 43893734 43893734 43893734 438937344 43893734 438937344 43893734 <	ILMN_1694027	111	rs12147460	14	104412137		rs684856	11	94906111	SESN3	5.50	0.03	0.51	0.15	
ILMN.10620427 11 reseased 11 14906041 res70494 8 134006424 0.02 0.01 0.02 0.01 ILMN.1062046 6 res2645386 1 43808056 res1344034 3 56840749 PPBP 5.52 0.07 0.01 ILMN.1072046 6 res2645386 5 6688397 7 6.02 0.02 0.01 ILMN.2172050 0 res104310 2.1 18196925 1.0 0.22 0.18 ILMN.2282006 11 res107320 12 2202826 1.0 0.22 0.18 ILMN.2382006 11 res07036 11 2202826 1.0 0.0 0.0 0.0 ILMN.2382006 11 res07036 12 2202826 1.0 0.0 0.0 0.0 ILMN.2382006 11 res07030 12 2202826 1.0 0.0 0.0 0.0 ILMN.2382006 12 res07030 12 res04034	ILMN_1694027	111	rs355391	15	46591793		rs684856	11	94906111	SESNS	5.67	0.31	90.0	0.10	
ILMN.1762764 6 reg2465284 6 reg2465864 7 reg246586 7 reg246586 7 reg248586 7 reg248586 7 reg248586 7 reg248705 7	ILMN_1694027	111	rs684856	11	94906111	SESN3	rs7004947	œ	134606425		5.60	0.21	0.51	0.31	
Image: 1.5 Image: 1.5 Image: 2.5 Ima	SH3BGRL2 ILMN_1762764	9	rs10838191	11	43893658		rs1354034	c	56849749	PPBP	5.52	0.70	0.12	0.35	
ILMN 238256 6 rest645394 4 8826652 Rest2734 5 13778566 5 123 0.22 0.18 ILMN 217881 2 rest04128 2 rest04128 3 rest04251 4 60498510 57.4 0.02 0.18 ILMN 2382565 11 rest0736 12 rest0736 11 2923826 SLC22A18 rest0705 5 7.7 0.09 0.13 ILMN 2382505 11 rest0705 11 2923826 SLC22A18 rest10074 7 21676724 5.7 0.09 0.13 ILMN 2382005 11 rest070705 12 rest08006 SLC22A18 rest100146 7 21676744 5.7 0.09 0.13 ILMN 1282016 13 rest0800 12 rest0800 12 1.00 0.09 0.13 ILMN 1282016 14 rest0800 12 rest0800 12 1.00 0.09 0.13 ILMN 1282016 14	Н	9	rs2545385	ro	66383979		rs1354034	n	56849749	PPBP	5.97	0.20	0.51	0.30	
ILMN 1771801 20 se1034120 21 18108622 2 se1034120 21 se108622 2 se1034120 20 se1034005 se103400	-	9	rs6845304	4	88280502		rs1354034	07	56849749	PPBP	5.23	0.32	0.71	0.53	
IMANIATION 20 rel55883 20 161891 SIRPG res62759 4 6048651 5.74 0.29 0.13 ILMN 238506 11 res67736 11 2928856 11 2928856 SLC22A18 res677104 2 20.28 C.0.2 0.19 0.13 ILMN 238506 11 res677036 11 292886 SLC22A18 res771064 2 5.20 0.19 0.13 ILMN 238506 11 res698506 12 2622862 SLC22A18 res771064 2 5.20 0.10 0.13 ILMN 147878 18 res698506 17 5.50 0.10 0.13 0.10 ILMN 147880 1 res03040 1 res030504 1 res030504 1 res030504 1 res04086 0.10 0.10 0.00 ILMN 147880 1 res04086 1 1.7530429 Res04086 N.CABA res10416 1 1.050420 1 1.00 <td< td=""><td></td><td>6</td><td>rs1034120</td><td>21</td><td>18196922</td><td></td><td>rs17455517</td><td>6</td><td>131785369</td><td>SH3GLB2</td><td>7.40</td><td>0.22</td><td>0.18</td><td>0.13</td><td></td></td<>		6	rs1034120	21	18196922		rs17455517	6	131785369	SH3GLB2	7.40	0.22	0.18	0.13	
LMN 2382505 11 res167326 12 2923826 SLC22A18 res110874 7 212324779 5.47 0.09 0.24 ILMN 2382506 11 res67735 11 2923826 SLC22A18 res110874 7 24167828 6.15 0.39 0.10 ILMN 2382506 11 res667035 11 24046744 SLC2A18 res11087818 6.15 0.39 0.10 ILMN 2382506 13 res69806 17 44357744 SLC46A3 SLC46A3 5.28 0.10 0.09 ILMN 145778 18 res64806 17 44357744 SLC46A4 5.28 0.09 0.09 0.08 ILMN 145778 18 res64806 17 4461500 SMOX res10494 SLC46A3 SLC46A3 <td< td=""><td></td><td>20</td><td>rs1535883</td><td>20</td><td>1612819</td><td>SIRPG</td><td>rs6842739</td><td>4</td><td>60489510</td><td></td><td>5.74</td><td>0.29</td><td>0.18</td><td>0.17</td><td></td></td<>		20	rs1535883	20	1612819	SIRPG	rs6842739	4	60489510		5.74	0.29	0.18	0.17	
ILMN 238505 11 res6f7035 11 2993886 SLC22A18 re371064 7 15324179 5.70 0.15 0.15 0.13 ILMN 238505 11 res6f734 SLC22A18 re3772034 2 2.68 0.13 0.13 ILMN 1255011 3 res693508 8 12433774 SLC45A4 re771703 3 125801067 5.88 0.13 0.13 ILMN 1256511 3 res693525 1 54020348 3 125801067 5.88 0.09 0.38 ILMN 1705853 1 res603325 1 res61825 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 13306023 1 1 10.9 1 1 13306023 1 1 13306023 1 <t< td=""><td>SLC22A18 ILMN_2382505</td><td>11</td><td>rs11673260</td><td>19</td><td>52181798</td><td></td><td>rs367035</td><td>11</td><td>2923826</td><td>SLC22A18</td><td>5.47</td><td>0.00</td><td>0.24</td><td>0.09</td><td></td></t<>	SLC22A18 ILMN_2382505	11	rs11673260	19	52181798		rs367035	11	2923826	SLC22A18	5.47	0.00	0.24	0.09	
ILMN 1285205 11 res272225 SLC22A18 res7777064 2 241678528 G.15 0.39 0.13 ILMN 2385106 3 res101216 1 24816743 SLC2A18 res777703 5 14168073 5.28 1.08 0.08 ILMN 174477 3 res103133 1 res071036 5 17680073 5.08 0.06 0.07 0.08 ILMN 174477 3 res03253 1 res03253 1 res0325349 5.08 0.06 0.07 0.05 ILMN 1775380 2 res03253 1 res032542 1 7.31 1.08 0.05 0.		11	rs367035	11	2923826	SLC22A18	rs3110874	7	153224179		5.70	0.15	0.10	0.06	
ILMN.12556111 3 resp92136 11 24616743 EAST EAST <td></td> <td>111</td> <td>rs367035</td> <td>11</td> <td>2923826</td> <td>SLC22A18</td> <td>rs3772054</td> <td>61</td> <td>241678528</td> <td></td> <td>6.15</td> <td>0.39</td> <td>0.13</td> <td>0.19</td> <td></td>		111	rs367035	11	2923826	SLC22A18	rs3772054	61	241678528		6.15	0.39	0.13	0.19	
ILMN.1705653 13 194987734 S.C45A4 Fr9701916 5 17458073 5.95 0.86 0.07 ILMN.1705653 13 156908506 15 97403923 SLC45A4 Fr97011916 5 17458073 SLC46A3 5.55 0.06 0.07 ILMN.1705653 13 158036259 15 97403923 SMOX 4161500 SMOX 17403923 SMC7 6.52 0.09 0.05 ILMN.170653 11 15204249 15 47403923 SMOX 1741 1759149 SNORD14A 6.50 0.07 0.05 ILMN.1709381 11 15204249 15 46259108 Fred466334 11 1759149 SNORD14A 7.31 1.03 ILMN.1709381 11 1529241 1739149 SNORD18A 6.50 0.07 0.05 ILMN.2328662 2 171789 1 1729149 SNORD18A 6.73 0.07 0.03 ILMN.2328662 1 15292634 1		3	rs1912136	11	24616743		rs6771703	က	125801067	SLC41A3	5.88	1.10	0.82	1.24	
ILMN.1766539 13 re9032054 17 556020991 SLC46A3 5.5.2 0.09 0.58 ILMN.1766539 1 re9032059 17 55602091 SMACT 6.52 0.17 0.09 ILMN.176380 2 re8118315 2 4161500 SMOX re11677815 2 6560082 SNHCR 6.52 0.09 0.58 ILMN.176380 2 re8118651 2 4 re116502 SMOX re1167815 2 6560082 SNHCR 6.01 0.29 0.09 0.58 ILMN.176380 1 re1166783 1 17221499 SNHCR 6.01 0.29 0.09 0.58 ILMN.1769381 1 re2034492 1 172604783 2 10188906 SNORDAS 6.01 0.29 0.103 ILMN.228662 2 re1160582 3 1 1726943 1 17260418 1.03 ILMN.238662 15 res11466 21 46376528 SNUPN		œ	rs6985508	œ	142337734	SLC45A4	rs7701916	ю	174598073		5.95	0.86	0.07	0.40	
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ILMN 1775380 20 restlistifs 20 4161500 SMOX restlistifs 2 4161500 SMOX restlistifs 2 4161500 SMOX restlistifs 2 65600837 4 11929499 SNHCB 6.11 0.39 0.62 ILMN 1799381 11 restlistifs 2 115292224 1 1733127 4 1929499 SNORD144 6.00 0.29 1.03 ILMN 1799381 11 restlistifs 2 11529224 1 1733132 1.03 0.02 ILMN 1738862 2 restlistifs 2 11529224 1 1753149 SNORD89 6.38 0.03 ILMN 1738862 2 restlistifs 2 101889306 SNORD89 6.35 0.03 ILMN 1730179 15 restlistifs 2 101889306 SNORD89 6.38 0.01 ILMN 1730179 15 restlistifs 3 101889306 SNORD89 6.38 0.01 ILMN 1770179		-1	rs8035259	15	97403923		rs10911353	1	183489203	SMG7	6.52	0.17	0.09	0.06	
ILMN.1399349 4 rs1105621 9 133050233 rs705837 4 119225940 SNHGS 6.11 0.03 1.03 ILMN.1799381 11 rs1264622 11 17339127 rs6486334 11 17291499 SNORD14A 6.66 0.09 1.03 ILMN.1799381 11 rs2664462 11 17339127 rs6486334 11 17291499 SNORD14A 6.60 0.09 1.03 ILMN.328862 2 rs1046863 2 11 15296326 SNORD189 5.96 6.08 0.09 1.03 ILMN.328662 2 rs1046863 21 46376528 SNUPN rs718536 2 101889306 SNORD89 6.33 0.03 ILMN.328662 15 rs8134646 21 46376528 SNUPN rs4774078 1 756033 SNORD89 6.33 0.03 1.11 1 1 1 1 1 1 1 1 1 1 1 1	ILMN_1775380	20	rs8118315	20	4161500	SMOX	rs11677815	61	65800982		5.68	0.39	0.62	0.52	
ILMN_1799381 11 res154042 15 46259108 res14607 11 17291499 NNRD14A 6.60 0.29 1.03 ILMN_1799381 11 res1524462 15 46259108 res4466334 11 1715557 7.31 13.11 10.96 ILMN_1238662 2 res1045863 2 115929241 res750783 2 101889306 SNORD89 6.60 0.29 1.03 ILMN_2328862 2 res160682 11 122988306 SNORD89 6.58 6.08 0.00 ILMN_2328862 1 res160683 11 res160683 10 8.188806 5.96 6.33 0.00 ILMN_2328862 15 res176063 2 101889306 SNORD89 6.38 0.00 ILMN_234646 2 46374520 SNUPN res176585 SNUPN res176586 SNORD89 6.08 0.03 0.00 ILMN_234614 2 14 1444751 144 1444751 144 <td>_</td> <td>4</td> <td>rs1105621</td> <td>6</td> <td>133050233</td> <td></td> <td>rs705837</td> <td>4</td> <td>119225940</td> <td>SNHG8</td> <td>6.11</td> <td></td> <td></td> <td></td> <td></td>	_	4	rs1105621	6	133050233		rs705837	4	119225940	SNHG8	6.11				
A ILMN.3238662 1 1733912	Ī.	111	rs1520429	15	46259108		rs214097	11	17291499	SNORD14A	09.9	0.29	1.03	0.72	
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ILMN 23238662	_	2	rs10445863	7	115929241		rs750783	7	101889306	SNORD89	80.9				14.040
ILMN 1236862		010	rs11605822	11	122986326		rs750783	01 (101889306	SNORD89	5.96				
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16 rs1463965 18 74332954 rs3785354 16 28550667 TUFM 7.05 0.01 0.05 16 rs2886657 21 40119768 rs378534 16 28550667 TUFM 5.83 0.01 0.05 9 rs6099026 20 56013994 rs485485 13 10410782 rs485485 11 85495269 SYTL2 5.47 0.28 0.31 1 rs1375719 13 10410782 rs4072037 1 155162067 THBS3 5.55 0.03 0.31 1 rs804955 11 155162067 THBS3 5.55 0.03 0.15 1 rs804956 12 15419480 THBS3 5.55 0.03 0.15 1 rs804956 2 1614583 1 15149480 THPR3 5.55 0.07 0.40	ILMN_2345142	20	rs11700063	20	46153148	SULF2	rs939294	. 4	180439236		5.51	0.46	0.24	0:30	
16 rs2886657 21 40119768 rs3785554 16 28550667 TUFM 5.83 0.26 0.16 1 rs609966 20 56013994 rs485485 1 8.43 6.14 0.26 0.16 1 rs18099875 11 96422867 rs486485 1 1.55162067 7HBS3 6.55 0.03 0.31 1 rs8104967 14 20688978 14 20688978 1.5146898 1.158163087 1.18833 5.65 0.07 0.40 1 rs2823245 21 16745523 1.168154599 TIPRL 5.22 0.07 0.40	ILMN_2336133	16	rs1463965	18	74332954		rs3785354	16	28550667	TUFM	7.05	0.01	0.05	0.00	
9 rs6099626 20 56013994 rs3118663 9 136281753 SURF6 6.14 0.26 0.16 11 rs1375719 13 103410782 rs48585 11 8549269 SYTL2 5.47 0.28 0.31 1 rs1987779 11 9422867 14 20687978 15.55 0.03 0.15 1 rs2823245 21 16745523 165154980 THPRS 5.55 0.07 0.40	ILMN_2336133	16	rs2836657	21	40119768		rs3785354	16	28550667	TUFM	5.83				
11 rs1375719 13 103410782 rs485485 11 84495269 SYTL2 5.47 0.28 0.31 1 rs1939875 11 95422867 1 155162067 THBS3 5.55 0.03 0.15 1 rs20404966 14 20687978 rs1320993 1 156154869 THPR.3 5.65 0.31 0.76 1 rs2223245 21 16745523 rs1320993 1 168154599 TIPRL 5.22 0.07 0.40	ILMN_1778032	6	rs6099626	20	56013994		rs3118663	6	136281753	SURF6	6.14	0.26	0.16	0.14	
1 res1898875 11 99422846 res204867 1 #55162067 THBS3 5.55 0.03 0.15 1 res20823245 21 16746523 res1220993 1 168154599 TIPRL 5.22 0.07 0.40	ILMN_2336609	111	rs1375719	13	103410782		rs485485	11	85495269	SYTL2	5.47	0.28	0.31	0.24	
1 rs204956 14 20687978 rs2049805 1 155194980 THBS3 5.65 0.31 0.76 1 rs2823245 21 16745523 rs1320993 1 168154599 TIPRL 5.22 0.07 0.40	ILMN_1804663	П	rs1939875	11	95422867		rs4072037	1	155162067	THBS3	5.55	0.03	0.15	0.03	
1 182823245 21 16/49523 181320993 1 168154599 11FKL 5.22 0.07 0.40	ILMN_1804663		rs8014956	14	20687978		rs2049805	п,	155194980	THBS3	5.65	0.31	0.76	0.55	
	ILMN-1781457	1	rs2823245	21	16745523		rs1320993	1	168154599	TIPRE	5.22	0.07	0.40	0.15	

	Distance / Mb ⁿ				0.122																				100	0.031	19 181	101.01				5.389														45 945	25,0.05	
values	Metag	0.70	0.20		145.78	3.67	0.80	3.78	2.52	0.03	2.87	00.9	8.00	2.27	0.19	3.51	7.36	10.72	2.10	9.20	4.47	0	0.32	0.07	70.0	4.09	0.29	1.07	0.68	0.08	0.59	0.16	0.44	0.23	0.16	80.0		1.01	0.50	0.07	0.40	0.69	0.11	1.69	0.39	90.0		
$-\log_{10} p$ -values	$EGCUT^{I}$	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	1.00	1.89	0.40	1.60	0.87	0.18	0.47	0.24	0.38	0.36	0.33	0.07		0.78	0.55	0.02	0.86	06:0	0.25	1.23	0.91	0.18		
interaction statistic /	$Fehrmann^{I}$	0.06	0.10	0.76	2.1.2	1.55	0.40	3.61	2.41	80.0	3.06	3.72	0.04	1.57	0.19	06.0	3.31	3.06	0.02	3.36	0.10		0.64	0.11	1.03	3.19	0.28	0.21	0.37	0.12	0.63	0.21	0.50	0.20	0.15	0.24		0.85	0.51	0.14 0.14	0.08	0.36	0.11	1.20	0.04	0.07		
Interaction	BSGS ^e F	5.70	8.11	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	20.0	8.72 8.73	0.01 0.01	5.02	6.92	7.79	6.43	6.38	6.51	0 00	6.27	6.73	7.58	7.73	8.10	7.34	7.05	7.41	5.42	5.92	6.46	6.00	5.51	
7	Association	TMED4	TMEM149	TMEM149	TMEM149																	TMEM63A	TMEMSO	IRF5	0 771	L Dag v at	TRAFFC4	* O I IVII									TRAPPC5	TRAPPOS	TRAFFCS		RAPGEF1		TREM1	TREM1	TRIM38	TSPANIA	101 CH	
7 JAIC	Pos/Mb^{c}	44581986	36219525	36219525	36147315	4799159	133025756	188359436	128884559	64268976	90932598	13822381	113317583	147619772	171792273	129595460	233879066	161683974	80357420	242889492	21473952	226027323	656845	128593948	128595948	23498358	110001001	166970604	132022957	156404902	242329791	2369415	57495457	9947811	146690926	85439550	7758194	7758194	7.758194	30408765	134635088	157393770	41264577	41264577	26044369	82273079	137947208	000000000000000000000000000000000000000
	Chr.	7	n -	61	6.	10	6	8	12	18	14	œ	4	7	ю	11	61	9	17	1	13	;	11	1 -1	1 -		1 :	1 10	00	9	1	19	- 1	4	-4	14	19	61	67	71 (9	5	m	9	9	9	10	9) (
	rs ID	rs17725246	rs&106959	rs8106959	rs7254601	rs10508289	rs10819626	rs10937361	rs1401098	rs1557335	rs17719594	rs1843357	rs2351458	rs2539000	rs2731711	rs471728	rs6718480	rs6926382	rs7213338	rs914940	rs9509428	rs4149226	rs4963126	rs10488630	rs10488650	rs11770192	rs5916581	rs10059004	rs1023095	rs1375714	rs1393299	rs17763599	rs4968328	rs7694997	rs7800935	rs856638	rs17159840	rs17159840	rs17159840	rs101/95/2	rs1887778	rs963354	rs2395771	rs2395771	rs2032447	rs10748526	rs620607	
	Association				SNX26	TMEM149							TRAPPCS	TRAPPCS	TRAPPC5	TRAPPC5	TRAPPC5	TRAPPOS	TRAPPCS	TRAPPCS	TRAPPC5										MyppCo	TSPAN32																
T JAIC	Pos/Mb^{c}	132389627	2702E381	45207005	36268923	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	36219525	72890603	58058246	4859303	2228/303	119591675	113531675	7758194	7758194	7758194	7758194	7758194	7758194	7758194	7758194	7758194	22740855	45128454	7763078	7762978	7762978	7762978	85749398	108256422	158808416	27194634	2317951	1
1	Chr.	11	17.0	200	6-1	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	13	19	5 0	1 0	- 0	1.5	10	19	19	19	19	57 -	61	19	19	22	77	07.	5 0	13	19	12	10	-	11	1 11	1 1
	rs ID	rs1940400	182839013	rs6090518	rs807491	rs8106959	rs1254086	rs1548475	rs1537146	18189785	rs///65/2	rs12/8/60	rs17159840	rs380708	rs3916995	rs6040514	rs/246264	rs7246264	rs7246264	rs10862975	rs12412964	rs2527180	rs968726	rs12800998	000000000000000000000000000000000000000																							
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Expression trait	Probe ID ^D	ILMN_1804148	ILMIN_1786426	ILMN 1786426	ILMN 1786426	ILMN_1786426	ILMN_1719649	ILMN_1708482	ILMN_1683811	ILMIN-1683811	ILMIN_1731043	ILMN-1814650	ILMN 2372639	ILMN_2372639	ILMN_2372639	ILMN_2372639	ILMN_2372639	ILMN-2372639	ILMN 2372639	ILMN_2372639	ILMN_2372639	ILMN_2372639	ILMN_2372639	ILMIN_2372639	ILMN-2372639	ILMN_2372639	ILMN_2372639	ILMN_1688231	ILMN_1688231	ILMN_1697971	ILMIN_1785060	ILMN_2389970																
	Gene ID ^a	TMED4	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM149	TMEM63A	TMEMSO	TNPOS	TNFOS	TRAZA TPAPPC4	TRAFFC4	TRAPPCS	TRAPPCS	TRAPPC5	TRAPPC5	TRAPPC5	TRAPPOS	TRAPPCS	TRAPPC5	TRAPPC5	TRAPPC5	TRAPPC5	TRAPPCS	TRAPPOS	TRAPPCS	TRAPPC5	TREM1	TREM1	TRIM38	TSPAN14	TSPAN32	

$\overline{}$	·	_											_	_									_	_	_	_
	ce / Mb ^h			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
$-\log_{10} p$	$\mathtt{EGCUT}^{\mathrm{f}}$	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 / $-\log_{10} p$ -values	$Fehrmann^{f}$	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	BSGSe	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	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
02	Chr.	16	1	17	19	9	9	9	9	9	9	9	9	9	9	18	10	19	က	ო	ო	ო	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
	Associationd	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
01	Chr.	21	21	17	19	7	20	22	11	7	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	က	က	က	က	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
Exi	Gene ID ^a	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

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

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

^b Number of tests for concordance

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

^d Observed number of concordant cases

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

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

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

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

Interactions ^a	Dataset	n^{b}	0^{c}	1 ^c	2^{c}	3^{c}	$4^{\rm c}$	\overline{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