Detection and replication of epistasis influencing transcription in humans

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22 Abstract

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Epistasis is the phenomenon whereby one polymorphism's effect on a trait depends on other polymorphisms present in the genome. The extent to which epistasis influences complex traits¹ and contributes to their variation^{2,3} is a fundamental question in evolution and human genetics. Though often demonstrated in artificial gene manipulation studies in model organisms, 4,5 and some examples have been reported in other species, ⁶ few examples exist for epistasis amongst natural polymorphisms in human traits.^{7,8} Its absence from empirical findings may simply be due to low incidence in the genetic control of complex traits, 2,3 but an alternative view is that it has previously been too technically challenging to detect due to statistical and computational issues.⁹ Here we show that, using advanced computation 10 and a gene expression study design, many instances of epistasis are found between common single nucleotide polymorphisms (SNPs). In a cohort of 846 individuals with 7339 gene expression levels measured in peripheral blood, we found 501 significant pairwise interactions between common SNPs influencing the expression of 238 genes ($p < 2.91 \times 10^{-16}$). Replication of these interactions in two independent data sets 11,12 showed both concordance of direction of epistatic effects $(p = 5.56 \times 10^{-31})$ and enrichment of interaction p-values, with 30 being significant at a conservative threshold of p < 0.05/501. Forty-four of the genetic interactions are located within 2Mb of regions of known physical chromosome interactions¹³ ($p = 1.8 \times 10^{-10}$). Epistatic networks of three SNPs or more influence the expression levels of 129 genes, whereby one cis-acting SNP is modulated by several trans-acting SNPs. For example MBNL1 is influenced by an additive effect at rs13069559 which itself is masked by trans-SNPs on 14 different chromosomes, with nearly identical genotype-phenotype (GP) maps for each *cis-trans* interaction. This study presents the first evidence for multiple instances of segregating common polymorphisms interacting to influence human traits.

52 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. He is to date, though its contribution to phenotypic variance is frequently the subject of debate, Here 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. In the subject of the su

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

complexity in fitting interaction 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 $0.05 \le \alpha \le 0.14$, Methods, Supplementary Figure S1). Using this design we identified 501 putative genetic interactions influencing the expression levels of 238 genes (Supplementary Table S1). We used strict quality control measures to avoid statistical associations being driven by technical artifacts (Methods). However it remains possible that unexplained technical artifacts may have led to the significant discovery interactions. Of the 501 discovery interactions, 434 had available data and passed filtering (Methods) in two independent replication datasets, Fehrmann¹² and the Estonian Genomics Centre University of Tartu (EGCUT), 11 in which we saw convincing evidence for replication. We used the summary statistics from the replication datasets to perform a meta analysis to obtain an independent p-value for the putative interactions, and 30 were significant after applying a Bonferroni correction for multiple testing (5% significance threshold p < 0.05/501, Table 1). To quantify the similarity of GP maps between the independent datasets (Figure 1) we decomposed the genetic effects of each of the SNP pairs into orthogonal additive, dominance and epistatic effects $(A1, A2, D1, D2, A \times A, A \times D, D \times A, D \times D)$ 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 due to LD (Methods).

Though seldom the focus of association studies, SNPs with known main effects are often tested for additive \times additive genetic interactions, but our analysis shows that this is unlikely to be the most effective strategy for its detection. The majority of our discovery interactions comprised of one SNP that was significantly associated with the gene expression level in the discovery dataset, and one SNP that had no previous association (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.

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. On the color of the c

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 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. And forthly, the extent of winner's curse in estimation of effect sizes may differ between the the two studies.

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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.

We searched for pairwise epistasis exhaustively $(1.03 \times 10^{15} \text{ statistical tests})$ 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). Permutation analysis was used 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 Several filtering steps were performed to exclude SNP pairs that were significant due to marginal effects alone. All SNP pairs with LD $r^2 > 0.1$ and $D'^2 > 0.1$ were removed to minimise the possibility of haplotype effects. All SNP pairs were required to have at least five data points in all nine genotype classes. If multiple SNP pairs were present on the same chromosomes for a particular expression trait then only the sentinel SNP pair was retained. Finally, a nested test contrasting the full genetic model against the marginal additive and dominance model was performed for each remaining SNP pair (Methods). 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 Fehrmann¹² (n = 1240)and the EGCUT¹¹ (n = 891) datasets. Of these, 434 passed filtering in both replication datasets. A meta analysis on the interaction p-values from each replication dataset was performed to provide an overall replication statistic for each putative interaction.

Tables

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

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

 $^{^{1}}$ – $\log_{10} p$ -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 Figures

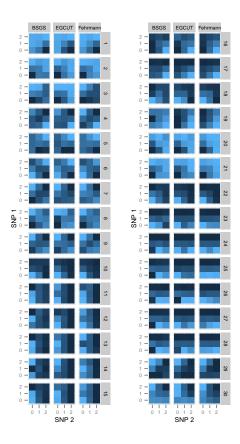


Figure 1: Replication of GP maps in two independent populations. The GP maps for each epistatic interaction that is significant at the Bonferroni level in both replication datasets are shown. Each GP map consists of nine tiles where each tile represents the expression level for that two-locus genotype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

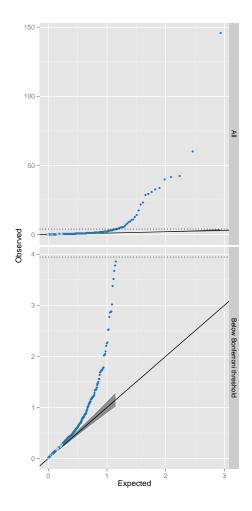


Figure 2: \mathbf{Q} - \mathbf{Q} plots of interaction p-values from replication datasets. The top panel shows all 434 discovery SNPs that were tested for interactions. Observed p-values (y-axis, $-\log_{10}$ scale) are plotted against the expected p-values (x-axis, $-\log_{10}$ scale). The multiple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

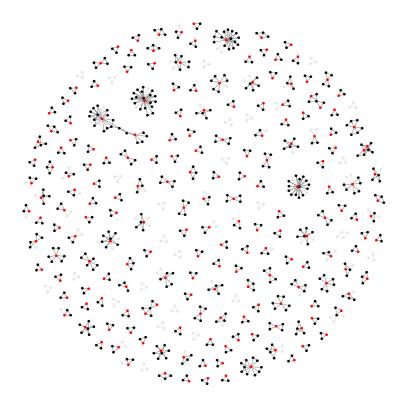


Figure 3: **Discovery and replication of epistatic networks** All 434 putative genetic interactions (edges) with data common to discovery and replication sets is shown, where black nodes represent SNPs and red nodes represent traits (gene expression probes). Three hundred and forty-five interactions had p-values exceeding the 2.5% confidence interval following meta analysis of the replication data The remaining 89 interactions that did not replicate are depicted in grey. It is evident that a large proportion of the complex networks identified in the discovery set also exist in independent populations. An interactive version of this graph can be found here: http://kn3in.github.io/detecting_epi/

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323 Supplementary Figures

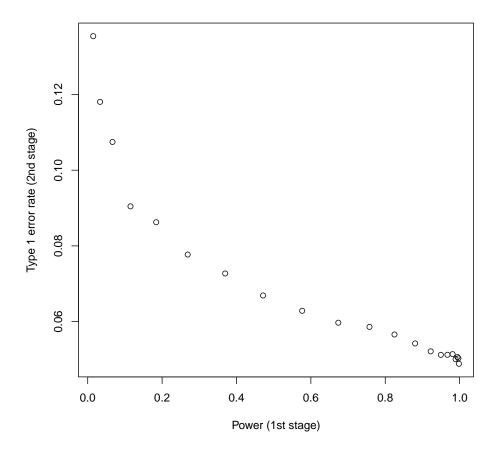


Figure S1: Type 1 error rate of two stage design assuming a null model of one large additive effect and no epistasis In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These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

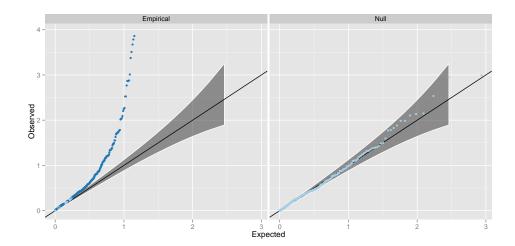


Figure S2: Q-Q plots of interaction p-values from replication datasets, excluding the 30 points significant at the Bonferroni level The right panel (Null) shows the interaction p-values from a meta analysis across two independent datasets on 434 randomly drawn SNP pairs. The left panel (Empirical) shows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

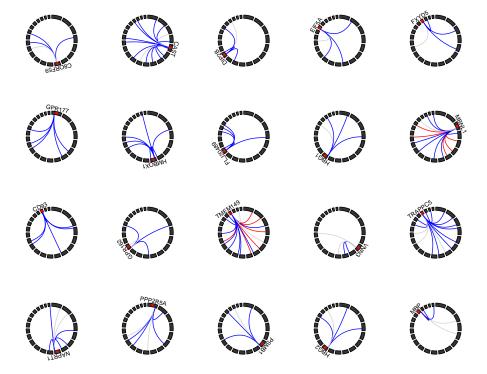


Figure S3: Gene expression traits with four or more genetic interactions Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent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



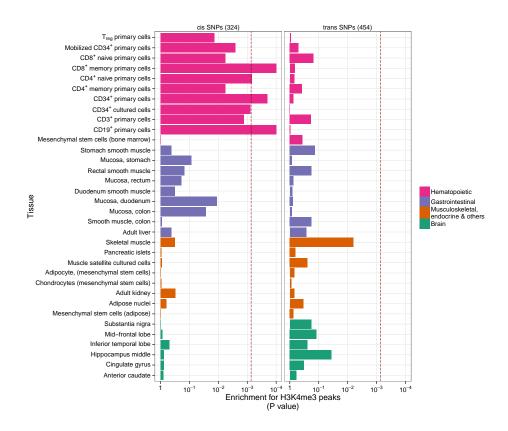


Figure S5: Tissue specific enrichment of SNPs in transcriptionally active regions The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3.²⁷ Enrichment *p*-values are calculated using permutation analysis for 34 different cell types (*y*-axis) in four tissue types (Rows of boxes). The dotted red line denotes significance (Bonferroni correction for 34 cell types, *x*-axis). There is enrichment for *cis*-acting SNPs in Haematopoietic tissue types only. *Trans*-acting SNPs have no tissue specificity.

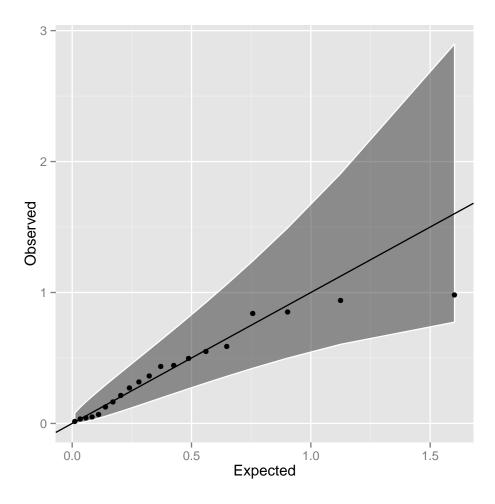


Figure S6: Q-Q plot of interaction p-values in the CDHWB dataset Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset (mainly due to small sample size). There is no evidence for enrichment of interaction terms, most likely due to insufficient power given the limited sample size.

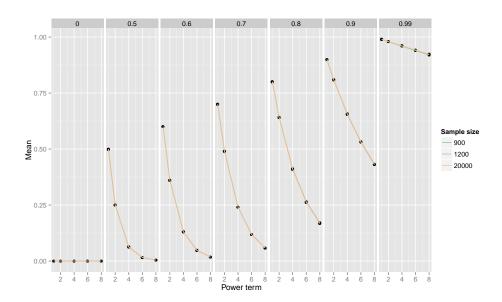


Figure S7: Sampling mean for different power terms of population r values Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4, r^6, r^8 . For a given population value of LD r (columns of plots), plotted is the sample mean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

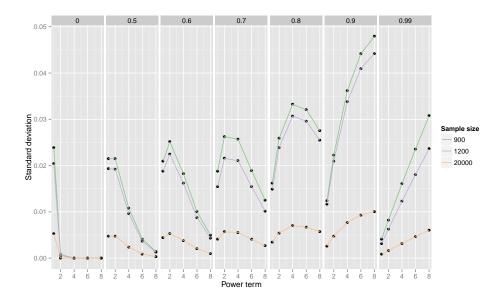


Figure S8: Sampling standard deviation for different power terms of population r values Power of detection and replication of epistatic interactions depends not on r^2 between causal variants and observed SNPs, but on r^4 , r^6 , r^8 . For a given a population value of LD r (columns of plots), plotted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

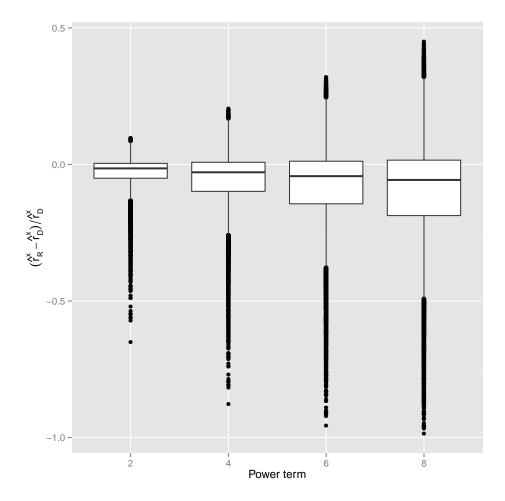


Figure S9: Reduction in LD as estimated in replication data after ascertaining for high LD in discovery data 100,000 "unobserved" causal variants (CVs) were tested for LD against a panel of 528,509 "observed" discovery markers (DMs). DM/CV pairs with LD $r^2 > 0.9$ were then tested in an independent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

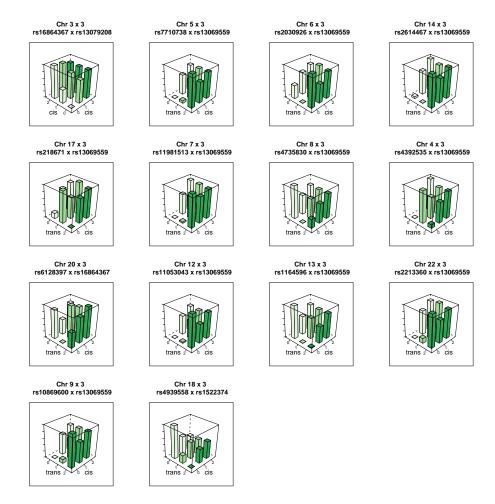


Figure S10: Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1 Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions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

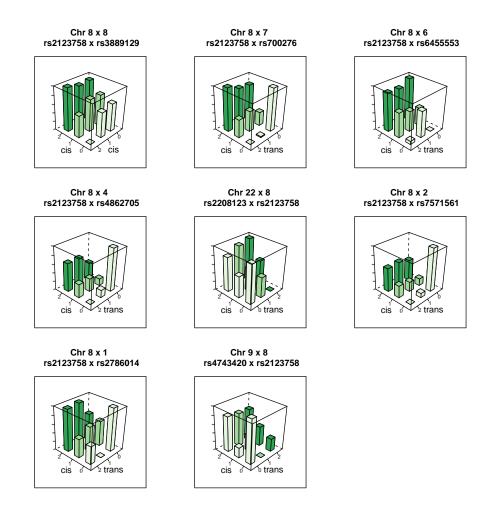


Figure S12: Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1 Each bar represents the mean phenotypic value for individuals in that genotype class.



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.

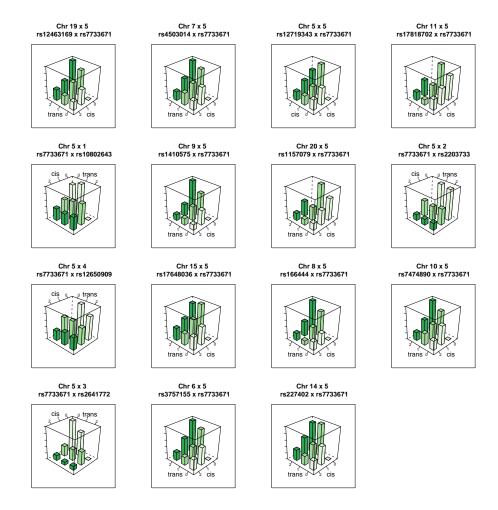


Figure S14: Genotype-phenotype maps for 15 interactions influencing the expression of CAST Each bar represents the mean phenotypic value for individuals in that genotype class.



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.

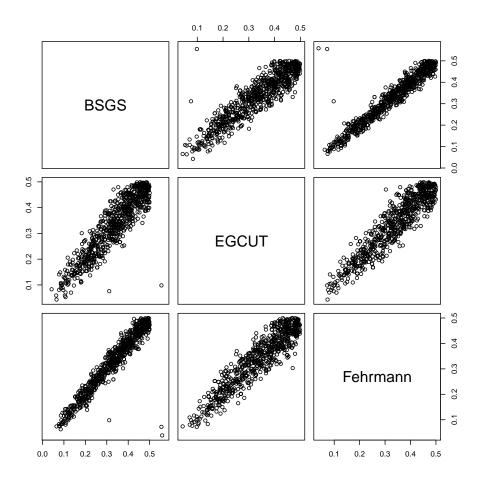


Figure S16: Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations Outliers were removed from the analysis as part of the filtering stage during replication.

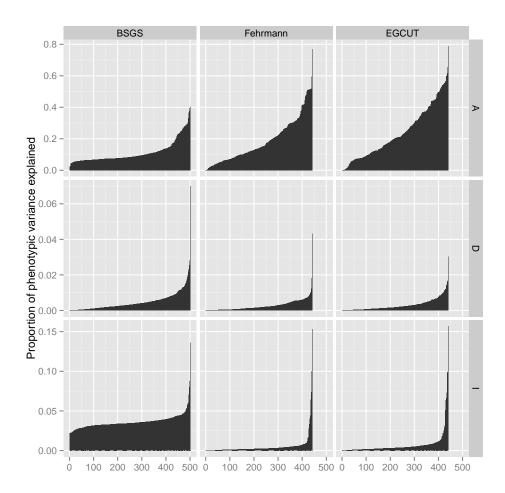


Figure S17: Comparison of variance explained by additive, dominant and epistatic effects from different cohorts How does the estimated variance decomposition change in different cohorts? The proportion of the phenotypic variance that is additive (A), dominant (D), or epistatic (I) for each putative interaction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

324 Supplementary Tables

Table S1: Details on 501 interactions discovered in BSGS dataset

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17 rs9455 11 rs227064 14 rs12431896 14 rs8058066 10 rs3305006
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19	rs13067700 3	95331048			0.09 0.51	0.22	
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16 First	rs2950520 7	99827148	GATS	6.22	0.42		
16 16 174504270 16 301689955 18 187198445 16 20084475 18 110899955 18 187198445 16 20084475 18 187198465 19 20084475 19 1871980563 16 6478898 12 872872500 12 6478898 13 872707210 12 6902002 GPR162 19 872707210 12 6902002 GPR162 19 872707210 12 124369421 1872557241 6 124369421 1872557241 6 124369421 1872557241 6 1169683 11 8725613 16 1169683 11 87256669 18 70560611 1892590426 17 82988268 187399321 1873924873 10 53195760 13 53195760 13 53195760 13 8614577 13 8614577 13 8614577 13 8614577 13 8614576 13 8614576 14 86445888 22 83399979 18139888 22 83399979 18139888 22 83399979 18139888 22 83399979 18139888 22 83399979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18139888 24 83339979 18138888 24	rs2197465 14	48572632					
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1 rse556669 18 70506011 1 rse9290426 3 71399321 1 rse11557467 17 38028634 1 rse11557467 17 38028634 1 rse1547574 13 85344527 1 rse6422807 13 9615560 22 rse138898 22 38399979 22 rse139888 22 38399979 1 rse11078523 17 4523167 1 rse129666 19 35728501 1 rse2550399 11 5571671 HBG2	065581 1	68732819	GPR177				
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	rs12042181 1	213088494	LQK1				
11 rs2855039 11 5271671 HBG2	rs12503379 4	141533832	000	6.42	0.01 0.46		
17 4523167	rs16912979 11	2309092	HBGZ		0.01 0.41		0.10

Expression trait				SNP 1				SNP 2		Interacti	Interaction statistic	/ - log10 p-values	values	
Probe ID ^D	Chr.	rs ID	Chr.	Pos/Mb^{c}	Association	rs ID	Chr.	Pos/Mb^{c}	Association ^d	BSGS _e 1	$Fehrmann^{I}$	$EGCUT^{I}$	Metag	Distance / Mb ^r
ILMN_2084825	11:	rs12975066	19	35723501	000	rs2855039	11	5271671	HBG2	5.77	0.08	0.13	0.05	
ILMIN-2084825	: :	rs2855039	11	5271671	HBG2	rs12042161		1.11533839	LQN.	0.0 r	0.00	0.34	0.21	
ILMN 3266186	12	rs2109029	16	6036851	75011	rs4760636	15	48173352	HDAC7	27.75	0.00	0.40	0.10	
ILMN_1802557	12	rs3782567	12	13145613	HEBP1	rs17686635	, oo	135220622		5.98	0.15	0.59	0.32	
ILMN_1741180	17	rs1942719	18	71237270		rs7213057	17	80378939	HEXDC	5.81	1.61	0.34	1.22	
ILMN_2157441	9	rs4899635	14	77532672		rs7192	9	32411646	HLA-DRB6	5.94	06.0	0.16	0.52	
ILMN_1762861	9	rs11660982	18	75467313		rs2523404	9	29695713	HLA-H	5.69	1.00	0.47	98.0	
ILMN_1720059	œ	rs12435486	14	98670849		rs7837237	œ	28876221	HMBOX1	6.54	0.92	1.11	1.34	
ILMN_1720059	00	rs2837803	21	42112794		rs4732890	œ	28751381	HMBOX1	6.62	0.02	1.01	0.46	
ILMN_1720059	00	rs4765451	12	127237464		rs8180944	00	28904086	HMBOX1	5.80	0.39	3.13	2.52	
ILMN_1720059	∞	rs587639	o o (132725731		rs7837237	œ o	28876221	HMBOX1	6.58	0.55	0.34	0.44	103.850
LMN_1720059	x0 0	rs8180944	x 0 0	28904086	HMBOXI	rs4553956	nı	189533772		0.00 0.00	83.38	0.03	2.20	
ILMN_1720059	00	rs8180944	œ j	28904086	HMBOX1	rs7810884	7	158276926		6.12	0.34	0.66	0.52	
ILMN_1720059	00	rs9521666	13	110897444		rs8180944	00	28904086	HMBOX1	5.45	0.67	0.26	0.45	
ILMN_2101920	n	rs6894268	n	179032488		rs4700810	n	178991794		15.38	8.55	3.01	10.37	0.041
ILMN-3194087	-	rs555812	16	88882257		rs4654783	1	22439520	HSPC157	5.51				
ILMN_3194087	-	rs6063164	20	46486900		rs4654783	1	22439520	HSPC157	6.51				
ILMN_3194087	1	rs662739	12	121229893		rs4654783	1	22439520	HSPC157	6.61				
ILMN_3194087	1	rs7088558	10	101884937	CWF19L1	rs4654783	1	22439520	HSPC157	6.48				
ILMN_1778010	16	rs1554999	16	3115628	IL32	rs4759890	12	131757163		06.90	0.19	0.50	0.29	
ILMN_2368530	16	rs765044	19	2560423		rs1554999	16	3115628	IL32	5.53	69.0	0.23	0.44	
ILMN_1811301	6	rs8044524	16	81603771		rs1127152	6	139335599	INPP5E	5.58	1.46	0.84	1.55	
ILMN_1682727	7	rs757355	12	47970693		rs849341	-1	28288174		8.16	0.05	0.26	0.02	
ILMN_1675756	21	rs2186344	21	39606769	KCNJ15	rs424299	11	5570771		5.64	0.65	0.13	0.33	
ILMN_1691803	19	rs649216	19	55324635	KIR2DL1	rs6419960	4	189055298		4.74	0.46	0.89	0.77	
ILMN_1811104	8	rs4349034	13	84597119		rs727905	8	119119433	KTELC1	5.53	0.08	0.80	0.37	
ILMN_1811104	e	rs6815953	4	183109012		rs6414283	თ	119195913	KTELC1	5.45	0.64	80.0	0.28	
LMN_2336109	22	rs4822006	22	41519362	L3MBTL2	rs1294338	П	233438952		5.88	0.33	0.04	0.09	
ILMN_1683792	4	rs7042087	6	132602868		rs7658240	4	17588950	LAP3	5.72	0.24	0.47	0.31	
LMN_1769782	-	rs1891432	П	203877662		rs10900520	1	203780591		19.16	18.60	11.22	29.24	0.097
ILMN_1809040	-	rs1552032	12	59971635		rs6687605	П	25889632	LDLRAP1	00.9				
ILMN_2412214	17	rs12450521	17	26083392		rs11749727	ю	179608360		5.16	0.35	0.40	0.34	
ILMN_2357419	19	rs3859532	19	54827248	LILRA5	rs714789	18	71561497		6.13	0.23	0.03	0.02	
ILMN_2338197	12	rs11247226	15	101120963	LINS1	rs1278387	10	127804531		5.89		0.13		
ILMN_2150196	19	rs6009951	22	51151350		rs8101804	19	18496107	LRRC25	2.68	0.11	0.35	0.15	
ILMN_1807825	9	rs977785	9	6588881	LY86	rs1543675	1	78946879		5.61	0.13	0.15	0.07	
ILMIN_1815205	77	rs2168029	77	69734641	LYZ	rs11981725		154137150		5.95	0.15	0.03	0.03	
LMN-2162972	7.	rsI77820	20 0	77276964		rs2168029	77	6973464I	LYZ	5.71	0.49	0.03	0.16	
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II.MN 1776188	000	re974607	21	29435869		rs6060034	000	33351864	MAP11.C3A	20.00	0.00	11:1	F.03	
II.MN 2313158	o	rs10869600	i o	78225815		rs13069559	o on	152187431	MBNL1	2.96	0.79	0.27	0.54	
ILMN_2313158	m	rs11053043	12	9932070		rs13069559	n	152187431	MBNL1	6.70	0.08	2.21	1.37	
ILMN_2313158	3	rs1164596	13	97100681		rs13069559	က	152187431	MBNL1	7.38	1.43	0.63	1.34	
ILMN_2313158	8	rs11981513	7	94648239		rs13069559	8	152187431	MBNL1	7.71	0.43	5.36	4.58	
ILMN_2313158	3	rs16864367	ဂ	152234166		rs13079208	က	152116652		13.49	16.25	24.74	41.56	0.118
ILMN_2313158	3	rs2030926	9	114067127		rs13069559	က	152187431	MBNL1	7.10	0.91	5.80	5.53	
ILMN_2313158	8	rs218671	17	6604708		rs13069559	က	152187431	MBNL1	7.63	0.62	5.82	5.23	
LMN_2313158	က	rs2213360	22	34291750		rs13069559	က	152187431	MBNL1	6.05	0.52	0.72	0.70	
ILMN_2313158	က	rs2305802	19	16038535		rs13069559	က	152187431	MBNL1	6.94	1.67			
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Probe Prop. Prop	Expression trait				SNP 1				SNP 2		Interact	Interaction statistic /	- log10 p-values	values	
10 reduction decided 4	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb^{c}	Associationd	rs ID	Chr.	Pos/Mb^{c}	Associationd		Fehrmann ^f	$EGCUT^{t}$	Metag	Distance / Mb ^h
1 10,000	ILMN_3237385	10	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2 NRBF2	5.45				
8 minoson mino	ILMN_1800897	1	rs4852124	- 61	240680022		rs6588415	1	52334047	MINDE	6.13	0.47	0.02	0.17	
12 nillididadi ilitatis 11 11486050 nillididadi ilitatis 11 11486050 nillididadi ilitatis 11 11486050 0AST 413 0.55 0.00 0AST 0.00 <td< td=""><td>ILMN_1787885</td><td>œ</td><td>rs5017351</td><td>11</td><td>25453482</td><td></td><td>rs1005901</td><td>œ</td><td>21964378</td><td>NUDT18</td><td>5.44</td><td>0.03</td><td>0.46</td><td>0.15</td><td></td></td<>	ILMN_1787885	œ	rs5017351	11	25453482		rs1005901	œ	21964378	NUDT18	5.44	0.03	0.46	0.15	
12 mistages m	ILMN_1658247	12	rs11613438	12	113480510		rs1047944	9	163997467		8.59	1.27	1.55	2.03	
10. 1.00 1	ILMN_1658247	12	rs13311	12	113448652		rs2072133	12	113409260		4.13	4.12	0.81	3.86	0.039
1 17,8555507 2 17,755469 CSPP1 CSP	ILMN_1675640	77.	rs2892233	61	49160255		rs3741981	7.	00000	OASI	4.38	0.87	0.46	0.76	
11 17,220,079 2.1 2.00,024.23 2.00,024.24 2.00	ILMN-2381899	01	rs7192613	16	74286646		rs17512962	01	13169066	OFTN	5.64	0.42	0.06	0.14	
9 FATABOLIS DE CONTRILIS PATABOLIS DE CONTRILICATION FATABOLIS DE CONTRILICATION </td <td>ILMN_2307032</td> <td>11</td> <td>rs2829679</td> <td>21</td> <td>26662543</td> <td></td> <td>rs998639</td> <td>11</td> <td>3149249</td> <td>OSBPL5</td> <td>5.00</td> <td>0.36</td> <td>0.00</td> <td>0.07</td> <td></td>	ILMN_2307032	11	rs2829679	21	26662543		rs998639	11	3149249	OSBPL5	5.00	0.36	0.00	0.07	
1 FAZZASTO 1 CONDENS CONDENS 1 CALL CALL <td>ILMIN_1742456</td> <td>n 0</td> <td>rs17780195</td> <td>1.7</td> <td>70624189</td> <td></td> <td>rs22/37/0</td> <td>ומ</td> <td>77755469</td> <td>CSTFI</td> <td>5.42</td> <td>0.16</td> <td>0.87</td> <td>0.49</td> <td></td>	ILMIN_1742456	n 0	rs17780195	1.7	70624189		rs22/37/0	ומ	77755469	CSTFI	5.42	0.16	0.87	0.49	
1 0.00000000 1.00000000 1.00000000 1.000000000 1.0000000000	ILMN-1742456	n ,	rs2273770	n ,	77755469	OSTFI	rs7718088	Ω,	179590952		5.42	1.20	80.0	0.62	000
1 1	ILMN_1734542	-	rs10802822	-	240132968		rs1264898	-	111992823	OVGP1	5.43	0.13	1.48	0.88	128.140
5 ##3248340 5 ##324840 6 ##324840 6 ##324840 7 ##324840 7 ##324840 7 ##324840 8 ##324840 9 PAM ##32440 PAM ##324840 PAM PAM PAM PAM <t< td=""><td>ILMN_1734542</td><td>- 1</td><td>rs347331</td><td>n :</td><td>140148107</td><td></td><td>rs1264894</td><td>-</td><td>111969719</td><td>CVGFI</td><td>6.04</td><td>0.25</td><td>1.21</td><td>0.82</td><td></td></t<>	ILMN_1734542	- 1	rs347331	n :	140148107		rs1264894	-	111969719	CVGFI	6.04	0.25	1.21	0.82	
15 FRANKSHOUND 1 JARY 2019 PEX.D A.18 A.18 <td>ILMN_2313901</td> <td>ı n</td> <td>rs28092</td> <td>io i</td> <td>102149795</td> <td>PAM</td> <td>rs784600</td> <td>- 0</td> <td>40139553</td> <td>HPCAL4</td> <td>5.59</td> <td>0.66</td> <td>0.44</td> <td>0.59</td> <td></td>	ILMN_2313901	ı n	rs28092	io i	102149795	PAM	rs784600	- 0	40139553	HPCAL4	5.59	0.66	0.44	0.59	
12 12 12 12 12 12 12 12	ILMN_1815951	o	rs2438490	o	148726162	PCYOXIL	rs2731939	n	21395989		6.20	0.19	0.26	0.16	
12 Fig405797 15 74,246,642 Fig4328748 12 7364442 PEX 5 5.74 0.34 0.09 11 rest208233 12 49151303 PGLYRP1 rest208237 14 7784444 6.54 0.54 0.05 22 rest208233 19 40151309 PEX 5 6.64 0.57 0.05 22 rest40444 22 31075185 PIK31P1 rest2082341 1 7788697 PKA 6.54 0.03 0.05 22 rest40444 22 32203131 PIK31P1 rest2082841 1 7788697 1 0.03 0.05 22 rest688411 15 16102848 2 310877884 2 31087788 0.03 0.05 22 rest688411 15 161028466 rest7884 2 31087886 1 0.05 0.05 0.05 11 rest868841 15 16103884 1 2.144767 PPP2RRA 6.54	ILMN_1660232	12	rs10444467	12	128052636		rs4329748	12	7364442	PEX5	5.85	0.09	0.71	0.32	120.688
13 18131090 22 401511030 PGTAPRA 5.64 0.87 0.36 21 18131090 22 140151030 PGCS9467 1.4 2195267 PGAPA 6.51 0.65 0.65 22 1847072 22 3167518 PHKZH 1778808 PHCA 6.51 0.69 0.60 22 1847072 22 3167518 PHKZH 18208887 PKZH 0.50 0.00 0.00 22 1867672 22 3199917 PHKZH 18208687 0.00 0.00 0.00 22 1867672 22 3199917 PHKZH 18208687 0.00 0.00 0.00 22 1867672 22 3199917 PHKZH 18208787 0.00 <td>ILMN_1660232</td> <td>12</td> <td>rs7495797</td> <td>15</td> <td>27246462</td> <td></td> <td>rs4329748</td> <td>12</td> <td>7364442</td> <td>PEX5</td> <td>5.74</td> <td>0.34</td> <td>0.00</td> <td>0.13</td> <td></td>	ILMN_1660232	12	rs7495797	15	27246462		rs4329748	12	7364442	PEX5	5.74	0.34	0.00	0.13	
11 pt.12982333 19 46.52466 PCLYRP1 rs12082367 14 212982367 6.51 0.03 0.05 22 rs4414404 22 3157156 PRINT rs40049831 1 76708086 PHCA 5.51 0.03 0.09 22 rs440440 22 3157156 PHSD rs506531 1 7785697 PHCA 5.60 0.20 0.09 22 rs470876 2 31926313 PHSD rs565847 1 11286689 1 0.00	ILMN_1797893	13	rs131969	22	49151303		rs7328733	13	33126737	PFAAP5	5.64	0.87	0.36	0.67	
21 residand 2 11 12007368 PHK3IP1 residand 2 11 12007368 PHKAB 11 12007368 PHKAB 11 12007368 PHKAB 11 12007368 PHKAB 12 120073775 12 120073775 12 120073775 12 120073775 12 120073777 12 120073777 12 120073777 12	ILMN_1704870	19	rs12982353	19	46529456	PGLYRP1	rs1263806	14	21982957		6.51	0.03	0.65	0.24	
2.2 ried/14/14/40 2. 314/75/18/2 products 1 61728/67 1 61728/67 1 61728/67 1 61728/67 1 61728/67 1 1 61728/67 1 1 61728/67 1 1 61728/67 1 <	II.MN 1812552	-	rs493642	=	123097386		rs10736812	-	76708086	PHCA	10	0.36	0 0	0.70	46 389
2.2 ind/10072 2. 2026333 PISD ind/100833 14 30368867 5.2 0.62 0.87 0.87 2.2 ind/10072 2. 32364031 PISD ind/10072 2. 3036918 PISD ind/10072 2. 3036040 0.0 1.0 0.0 <	11.MN 1719986	66	ro4141404	000	31675185	PIK3ID1	200000000000000000000000000000000000000	-	61798507		100	00.0	0.00	0 03	
2.2 Fight 10.2 2.2 STATION 2.2 2.2 </td <td>11 Men 1703034</td> <td>1 0</td> <td>10111111</td> <td>1 0</td> <td>99969191</td> <td>T TOTAL</td> <td>12000041</td> <td></td> <td>000000000000000000000000000000000000000</td> <td></td> <td>00.0</td> <td>000</td> <td>0.00</td> <td>0000</td> <td></td>	11 Men 1703034	1 0	10111111	1 0	99969191	T TOTAL	12000041		000000000000000000000000000000000000000		00.0	000	0.00	0000	
2.2 F. 180.1877.2 2.2 3.199.117 F. 1.5 F. 1.5 F. 1.1 O. 0.0 0.1.9 2.2 1.875.187.2 2.2 3.139.187 F. 1.5 1.1 1.1 1.1 1.1 1.1 1.1 0.00 0.1.2 0.04 2. 1.875.10.10 4.05.20.10 4.05.20.10 4.04.20.10 0.31 0.04 0.04 1.1 1.891.10.10 2. 3.32.34.34.3 1.1 7.55.30.0 0.04 0.04 0.04 1.1 1.891.10.10 2. 3.05.30.0 1.1 7.55.30.0 0.04 <	ILMIN_1,93934	7 0	2100153	7 0	10100270	LISD	FSIO490313	# ·	0.000000		0.70	0.02	0.0	0.00	
2 ref.15572 2 3524834 ref.15573 FIRD 4.12 0.05 0.42 9 ref.15572 2 18082447 P.B. 0.16 0.04 0.04 9 ref.15572 2 4527109 ref.288046 9 140847108 PPERD 6.15 0.05 0.04 1 ref.1231403 15 18578064 ref.28006 1 21244767 PPERD 5.15 0.05 0.04 1 ref.1232366 12 1858064 ref.1210009 1 21244767 PPERD 6.72 0.08 0.03 1 ref.1242326 12 18580644 ref.1210009 1 21244767 PPERD 6.72 0.08 0.03 1 ref.1242326 12 185080044 ref.1210009 1 21244767 PPERD 6.72 0.08 0.03 1 ref.124238 13 6622691 1 21244767 PPERDRA 5.72 0.08 0.03	ILMIN_I 793934	7.7	rsp518752	7.7	31999127	FISD	rs954627	-	18236681		7.11	0.00	1.19	0.48	
2 res6869411 5 ISSERSIGO4 res407884 2 219182481 PNKD 6:35 0.16 0.704 1 res1163998 6 4527100 res428064 9 14487108 0.31 0.73 0.73 14 res1163998 6 4527109 res22664 res1116887 1 755990 PPPPRRA 5.53 0.72 0.43 14 res129365 1 2659664 res12120009 1 212447167 PPPPRRA 5.63 0.72 0.43 1 res122355 13 6522669 res12120009 1 212447167 PPPPRRA 5.61 0.03 0.13 1 res86234 1 107417238 res12120009 1 212447167 PPPPRRA 5.61 0.03 0.13 1 res862269 1 107417238 res1120009 1 212447167 PPPPRRA 5.61 0.03 0.14 1 res6928641 121247167 PPPPRRA	ILMN_1793934	7.7	rs715572	7.7	33234931		rs6518754	7.7	32097775	PISD	4.12	0.05	0.42	0.15	1.137
9 res163998 16 4557109 res92804 9 140487108 PPFIBP2 4.44 0.31 0.37 14 res1291019 20 49668256 res92864 19 140487108 6.15 5.15 0.33 0.33 14 res12910109 20 5836086 res1120000 1 212447167 PPPRR5A 5.63 0.72 0.48 1 res1280367 13 66222691 res12120009 1 212447167 PPPRR5A 5.67 0.08 0.95 1 res188352 13 66222691 res12120009 1 212447167 PPPRR5A 5.67 0.08 0.30 1 res1082037 14 9504042 res12120009 1 212447167 PPPRR5A 5.65 0.30 0.30 1 res1082031 14 9504042 res1120009 1 212447167 PPPRR5A 5.65 0.30 0.30 1 res1082020 16 1522447167	ILMN_1774604	7	rs6869411	so.	158781604		rs4672884	7	219182481	PNKD	6.35	0.16	0.04	0.04	
11 re9911019 20 49688255 res475840 PFPRBP2 444 0.29 0.33 14 re9104409 2 49688255 res47864 5.830880 6.836886 1.1 755994609 1.2 21447167 PPPRBA 5.61 0.029 0.42 1 res10390170 2 1.65399647 res12120009 1.21447167 PPPPRBA 5.61 0.05 0.05 1 res622334 1.1 10747238 res12120009 1.21447167 PPPPRBA 5.61 0.05 0.13 1 res622091 1.21247167 PPPPRBA 5.65 0.13 0.05 1 res622093 1.2 1.2447167 PPPPRBA 5.65 0.13 0.06 1 res622093 1.2 1.2447167 PPPPRBA 5.65 0.13 0.06 1 res62200 1.2 1.2447167 PPPPRBA 5.72 0.06 0.13 1 res1212000 1.2 1.2447167 PPPPRBA	ILMN_1662587	6	rs11639998	16	4527109		rs928046	6	140487108	PNPLA7	5.15	0.31	0.78	0.56	
14 rs12914603 15 58350896 rs11168875 14 36198146 PPP2RAG 5.81 0.12 0.44 1 rs12914603 15 5835064 rs11156875 14 36198146 PPP2RAG 5.63 0.72 0.48 1 rs12422255 12 125596064 rs12120009 1 21447167 PPP2RAG 5.63 0.05 0.95 1 rs682334 11 107417238 rs12120009 1 21447167 PPP2RAG 5.63 0.05 0.36 1 rs682334 11 107417238 rs12120009 1 212447167 PPP2RAG 5.63 0.05 0.36 1 rs76757871 6 135030045 rs12120009 1 212447167 PPP2RAG 5.63 0.05 0.30 1 rs7675787 15 2500009 1 212447167 PPP2RAG 5.63 0.05 0.30 1 rs28019823 14 5600886 1 121447	ILMN_1675656	11	rs911019	20	49668255		rs4758001	11	7559930	PPFIBP2	4.44	0.29	0.33	0.26	
1 rss1020009 1 212447167 PPP2R5A 5.63 0.72 0.48 1 rss1032055 2 166399467 rss12120009 1 212447167 PPP2R5A 5.63 0.72 0.95 1 rs1689083 13 162526691 rs12120009 1 212447167 PPP2R5A 5.65 0.13 0.05 1 rs682334 11 107417238 rs12120009 1 212447167 PPP2R5A 5.65 0.13 0.05 1 rs7871178 9 271444775 rs1000099 1 212447167 PPP2R5A 5.65 0.13 0.05 1 rs7871178 9 271444775 rs1000990 1 212447167 PPP2R5A 5.65 0.13 0.14 1 rs7871177 rs1000990 1 212447167 PPP2R5A 5.72 0.16 0.13 1 rs20188555 16 2386774 rs11049773 16 12633869 7.34 4.77	ILMN_1662617	14	rs12914603	15	58350896		rs11156875	14	35619816	PPP2R3C	5.81	0.12	0.42	0.19	
1 rest8492835 12 12555664 res12120009 1 212447167 PPP2R5A 5.72 0.08 0.05 1 res682334 11 10741228 res12120009 1 212447167 PPP2R5A 5.61 0.08 0.03 1 res682334 11 10741238 res12120009 1 212447167 PPP2R5A 5.62 0.08 0.03 1 res682334 11 10741238 res12120009 1 212447167 PPP2R5A 5.62 0.08 0.37 1 res682834 16 28867776 res1200099 11 212447167 PPP2R5A 5.73 0.05 0.11 2 res1209231 23 24867776 res1200099 11 21244767 PPP2R5A 5.73 0.01 0.14 2 res1209231 23 24867776 res1200099 11 21244767 PPPRA 5.73 0.01 0.14 2 res1209231 21 4793468	ILMN_1738784	1	rs10930170	73	166399467		rs12120009	-	212447167	PPP2R5A	5.63	0.72	0.48	99.0	
1 res6889083 13 66222691 res121200009 1 212447167 PPP2R5A 5.61 0.36 0.28 1 res6829083 13 66222691 res121200009 1 212447167 PPP2R5A 5.65 1.60 0.28 1 res7757871 6 135030045 res12120009 1 212447167 PPP2R5A 5.65 1.60 0.38 1 res7757871 6 135030045 res121200099 1 212447167 PPP2R5A 5.65 0.36 0.36 1 res1282355 16 42867776 res11000990 1 212447167 PPP2R5A 5.65 0.36 0.36 1 res1282355 16 42867776 res11701058 21 47776382 C210RF57 5.60 0.03 0.03 6 res28805648 18 43808354 FSMB1 res1220714 6 17087444 PSMB1 5.14 0.06 0.04 6 res6060390 2	ILMN_1738784	1	rs12423255	12	123595064		rs12120009	-	212447167	PPP2R5A	5.72	0.08	0.95	0.46	
1 rs652334 1 107417238 rs12120009 1 212447167 PPP2R5A 5.65 1.69 0.28 1 rs7571778 9 27144475 rs12120009 1 212447167 PPP2R5A 5.95 0.16 0.06 1 rs7571778 9 27144475 rs12120009 1 212447167 PPP2R5A 5.95 0.16 0.06 1 rs28019823 14 95040482 rs1100099 1 212447167 PPP2R5A 5.72 0.16 0.03 1 rs28019823 2 2887776 rs1000990 1 212447167 PPP2R5A 5.73 0.06 0.11 2 rs2801923 2 47931653 C210RF57 rs1107058 2 4777782 6 7.34 0.05 0.14 2 rs2802951 1 1776832 C210RF57 4.81 0.44 0.21 4 rs602883 2 17775382 177682379 PSMB1 5.74	ILMN_1738784	1	rs1889083	13	66222691		rs12120009	-	212447167	PPP2R5A	5.61	0.36	0.13	0.17	
1 res7757871 6 135030045 res12120009 1 212447167 PPP2R5A 5.95 0.37 0.06 11 res7757871 6 271444475 res12120009 11 212447167 PPP2R5A 5.95 0.37 0.08 11 res8019823 14 95040482 res11600990 11 64082807 PRDX5 6.43 0.81 0.14 15 res288372 21 47931653 C210RF57 res16407346 6.43 0.63 0.03 2 res28839372 21 47031653 C210RF57 res1600934 PSMB1 5.60 0.19 0.03 2 res28839372 21 42062843 6 17080084 PSMB1 5.14 0.00 0.03 6 res6060830 18 43983354 PSMB1 res282643 6 17080084 PSMB1 5.14 0.00 0.20 6 res6060830 20 30347824 PSMB1 res2826415 6	ILMN_1738784	1	rs682334	11	107417238		rs12120009	Т	212447167	PPP2R5A	5.65	1.69	0.28	1.21	
1 resp8719278 9 27144475 res12120009 1 210442867 PPP2R5A 5.72 0.16 0.30 16 res2188355 16 23867776 res1060990 1 6442887 PRDX5 6.43 0.14 0.14 21 res2188355 16 23867776 res10609279 16 12639800 7.34 0.15 0.13 21 res2188355 16 23867776 res1049273 16 12639800 7.34 0.55 0.11 21 res3862607 21 47931653 C210RF57 res1207114 6 17687744 PSMB1 5.79 0.05 0.14 6 res6060330 20 31347842 res12207114 6 17682379 PSMB1 5.14 0.04 0.21 6 res6060330 20 31347744 PSMB1 5.44 0.24 0.21 6 res6082843 6 17685423 1 77628275 PSMB1 5.44 0.24<	ILMN_1738784	Т	rs7757871	9	135030045		rs12120009	Т	212447167	PPP2R5A	5.95	0.37	90.0	0.12	
11 res6019823 14 95040482 res11600990 11 64082807 PRDX5 6.43 0.81 0.14 16 res1029231 21 473467776 res0402739 16 1263900 7.34 0.53 0.01 0.03 21 res283972 21 47931653 C21ORF57 res928437 21 4777340 5.60 0.19 0.03 21 res2839372 21 45068862 C21ORF57 res1207114 PARBH 5.79 0.03 0.044 6 res4890648 18 43983954 res13207114 FSMBH 5.79 0.00 0.04 6 res608030 20 30047822 pre608089 1 2777444 PSMBH 5.74 0.00 0.26 6 res608080 20 30047823 res12207144 PSMBH 5.74 0.04 0.26 1 res7299449 12 137287957 res1220714 1702877957 4.58 0.08 0.08	ILMN_1738784	1	rs7871178	6	27148475		rs12120009	1	212447167	PPP2R5A	5.72	0.16	0.30	0.16	
16 res188355 16 22867776 res10492793 16 12639800 7.34 0.53 0.11 21 res108355 21 42038653 C210RF57 res049377 18 34934653 C210RF57 6.60 0.19 0.45 21 res283972 21 48063862 res048362 1.81777638 21 4777638 6.79 0.09 0.44 7 6 res3802648 18 438938544 res0383843 6 17080334 PSMB1 5.14 0.00 0.26 6 res060830 20 3034782 res030415 6 170823379 PSMB1 5.14 0.04 0.26 6 res060830 20 30347824 res10320714 6 17087744 PSMB1 5.14 0.04 0.05 12 res060830 20 3034782 res10320714 6 170877444 PSMB1 5.14 0.04 0.05 12 res031562 1 7521825<	ILMN_1711606	11	rs8019823	14	95040482		rs11600990	11	64082807	PRDX5	6.43	0.81	0.14	0.44	
21 res1029321 21 47931653 C21ORF57 18 31497346 5.60 0.19 0.03 6 res280923 21 47931653 C21ORF57 18 41777344 PSMB1 5.76 0.19 0.04 6 res380507 11 121774705 res928843 6 170877444 PSMB1 5.74 0.00 0.26 6 res4800648 18 43983854 res928433 6 17089784 PSMB1 5.14 0.00 0.21 6 res6028843 6 res6028843 6 17089784 PSMB1 5.14 0.00 0.21 6 res6028843 6 res6028843 6 17089034 PSMB1 5.14 0.00 0.21 12 res6028846 13 res10207114 6 170879744 PSMB1 1.05 0.03 0.03 12 res615622 14 172877444 PSMB1 1.28579767 0.00 0.00 0.02	ILMN_1713603	16	rs2188355	16	23867776		rs10492793	16	12639800		7.34	0.53	0.11	0.25	11.228
21 res2839372 21 48068862 res11701058 21 4775382 C210RF57 4.81 0.69 4.47 6 res386057 11 121774705 res1220714 6 17087744 PSMB1 5.79 0.04 6 res3860568 13 43883854 res9295415 6 17082379 PSMB1 5.14 0.00 0.26 6 res6080830 20 3034782 res6080843 6 17082379 7.44 0.04 0.02 6 res6080830 20 3034782 res618089 1 27082379 7.45 0.04 0.02 12 res6080830 20 3034782 res1080384 PSMB1 res208044 6 1.08 4.47 12 res638567 14 31 221825 PTDSS1 5.00 0.03 0.08 12 res631562 1 17087444 PSMB1 5.21825 PTDSS1 5.00 0.03 0.08 <	ILMN_1675038	21	rs1029231	21	47931653	C21ORF57	rs958127	18	31497346		5.60	0.19	0.03	0.04	
6 res862667 11 12177476 res13207114 6 170877444 PSMB1 5.79 0.44 0.24 6 res60936 20 30347832 res0295415 6 170823379 PSMB1 5.14 0.04 0.26 6 res60936 20 30347832 res295415 6 170823379 PSMB1 5.14 0.04 0.21 6 res60936 20 30347832 res276964 1 22579797 5.44 0.44 0.21 12 res635367 14 9478823 res1030714 6 170823379 PSMB1 5.42 0.32 12 res631562 17 7658423 res1030714 1 5221825 PTDSS1 5.00 0.03 0.43 12 res631562 17 765842348 res10020773 4 17526853 QDPR 5.75 0.02 0.03 13 res631562 1 762854548 RABACI res7656537 1	ILMN_1675038	21	rs2839372	21	48063862		rs11701058	21	47776382	C21ORF57	4.81	0.69	4.47	4.06	0.287
6 re4890648 18 43983644 PSMB1 FSMB1 5.14 0.00 0.26 6 re5028643 6 170890384 PSMB1 FSMB1 FS.14 0.00 0.26 6 re5028643 6 170829384 6 170829384 6 170829384 6 170829384 6 170829384 6 6.45 1.35 0.02 1 re3729346 1.2 1.3727816 re31207114 6 17087744 PSMB1 5.42 1.35 0.64 0.02 1.2 re3253467 1.4 9478823 re31036212 1.1 521825 PTDSS1 5.00 0.03 0.48 1.2 re431562 1.7 76598123 re11036212 1.1 5221825 PTDSS1 5.00 0.08 0.08 1.2 re431562 1.2 1.2 7023872 QDPR 5.70 0.03 0.04 1.2 re431730 2.2 33345704 re1036342 1.2<	ILMN_1789176	9	rs3862607	11	121774705		rs13207114	9	170877444	PSMB1	5.79		0.44		
6 res0060830 20 3034783 PSMB1 5.44 0.44 0.1 6 res0608330 20 3034783 PSMB1 res99545 6 17087344 PSMB1 4.58 1.38 0.54 0.64 0.64 6 res7299749 12 137727816 res12307114 6 17087744 PSMB1 5.45 1.18 0.32 12 res2383567 14 5658123 res10320711 1 5221825 PTDSS1 5.00 0.03 0.08 0.08 12 res631562 17 7658123 res1036212 11 5221825 PTDSS1 5.00 0.03 0.08 12 res631562 1 7658123 res1036312 1 5221825 PTDSS1 5.70 0.02 0.03 12 res241730 2 33375704 res705037 12 70233726 QDPR 5.75 0.03 0.03 18 res047702 1 4 752682 <td>ILMN_1789176</td> <td>9</td> <td>rs4890648</td> <td>18</td> <td>43983954</td> <td></td> <td>rs6928843</td> <td>9</td> <td>170890384</td> <td>PSMB1</td> <td>5.14</td> <td>00.0</td> <td>0.26</td> <td>0.04</td> <td></td>	ILMN_1789176	9	rs4890648	18	43983954		rs6928843	9	170890384	PSMB1	5.14	00.0	0.26	0.04	
6 rs6928843 6 170890384 PSMB1 rs2769959 1 22579957 4.58 1.95 0.64 12 rs7239674 12 131727816 rs12207114 6 17087744 5.42 1.18 0.32 12 rs2353677 14 9.6478823 rs1038212 11 5221825 PTDSS1 5.00 0.03 0.48 12 rs4669205 17 76584246 rs1008212 11 5221825 PTDSS1 5.70 0.03 0.48 12 rs4669205 17 76584246 rs100820773 4 17526682 QDPR 5.70 0.03 0.48 12 rs2417728 6 106348246 rs10020773 4 17526682 QDPR 5.70 0.03 0.48 12 rs2440778 18 rs467786 RARACI rs78051628 11 12017417 6.42 0.25 0.08 11 rs9931702 16 55526551 AKTIP rs1492379 </td <td>ILMN_1789176</td> <td>9</td> <td>rs6060930</td> <td>20</td> <td>30347832</td> <td></td> <td>rs9295415</td> <td>9</td> <td>170823379</td> <td>PSMB1</td> <td>5.44</td> <td>0.44</td> <td>0.21</td> <td>0.27</td> <td></td>	ILMN_1789176	9	rs6060930	20	30347832		rs9295415	9	170823379	PSMB1	5.44	0.44	0.21	0.27	
6 res7299749 12 137727816 res13207114 6 170877444 PSMB1 5.42 1.18 0.32 12 res2396774 1 1.2085243 res1036212 11 5221825 PTDSS1 5.90 0.08 0.08 12 res631602 1 76598123 res11036212 11 5221825 PTDSS1 5.90 0.08 0.08 12 res631602 1 76598138 res11036212 11 5221825 PTDSS1 5.90 0.08 0.08 4 res631602 1 765982438 res11036212 11 5221825 PTDSS1 5.70 0.08 0.08 1 res041730 2 33375704 res10020773 12 7023726 QDPR 6.55 0.25 0.08 1 res042279 1 20161117 2 20237404 4.32 0.34 1 res0422579 1 32136436 RCNI res1417408 8 1.1074448 <td>ILMN_1789176</td> <td>9</td> <td>rs6928843</td> <td>9</td> <td>170890384</td> <td>PSMB1</td> <td>rs2769689</td> <td>1</td> <td>225797957</td> <td></td> <td>4.58</td> <td>1.95</td> <td>0.64</td> <td>1.78</td> <td></td>	ILMN_1789176	9	rs6928843	9	170890384	PSMB1	rs2769689	1	225797957		4.58	1.95	0.64	1.78	
12 res255367 14 99478823 res1036212 11 5221825 PTDSS1 5.00 0.03 0.48 12 res631562 11 12685423 res11036212 11 5221825 PTDSS1 5.70 0.02 0.03 12 res631562 11 126854248 res11036212 11 5221825 PTDSS1 5.70 0.02 0.03 12 res404676 6 1063428246 res10020773 4 17526682 QDPR 5.75 1.03 0.05 19 res1075728 12 33377504 1 70263177 0.02 0.05 0.05 16 res2087702 16 5526551 AKTIP res492279 11 32136436 RCNI 6.32 0.03 0.31 11 res4922579 11 22136436 RCNI res140836 RCNI 6.32 0.04 0.04 0.06	ILMN_1789176	9	rs7299749	12	131727816		rs13207114	9	170877444	PSMB1	5.42	1.18	0.32	98.0	
12 res4669205 17 76598123 res11036212 11 5221825 PTDSS1 5.90 0.08 0.08 12 res431562 11 126852438 res1036212 11 5221825 PTDSS1 5.70 0.02 0.04 14 res4946705 6 105348246 res10020773 4 17526882 QDPR 5.77 0.02 0.40 12 res247704 12 res246882 QDPR 6.55 0.25 0.05 16 res931702 16 53526551 AKTIP res1863464 15 26938488 RCNI 6.32 0.03 0.31 11 res9931702 16 53526551 AKTIP res492379 11 32136436 RCNI 8 0.13 0.31 11 res925779 11 32136436 RCNI res141899 1 102740645 5.40 0.04 0.04	ILMN_1743049	12	rs2353567	14	95478823		rs11036212	11	5221825	PTDSS1	5.00	0.03	0.48	0.15	
12 re631562 11 122656438 re11036212 11 5221825 FTDSS1 5.70 0.02 0.02 0.04 12 re3401730 22 33375704 re7305307 12 70235726 6.55 0.25 0.08 0.08 19 re1075728 19 42462788 RABACI re7305307 12 70235726 6.55 0.25 0.08 19 re1075728 19 42462788 RAFILP re1863344 15 20433488 6.38 0.03 0.31 11 re10877913 12 4114715 RFMIL re18633448 15 2043488 RCNI 6.38 0.03 0.31 11 re4922579 11 32136436 RCNI re11047468 RCNI 4.32 0.41 0.09 11 re4922579 11 22136436 RCNI re110474045 0.04 0.04 0.26	ILMN_1743049	12	rs4969205	17	76598123		rs11036212	11	5221825	PTDSS1	5.90	08.0	80.0	0.38	
4 res4946705 6 106348246 res10020773 4 17526682 QDPR 5.75 1.03 1.25 12 res421730 22 33375704 res736507 12 70235726 6.55 0.28 0.28 0.084 19 res045788 19 45462788 RABACI res1863464 15 226938488 6.38 0.03 0.31 11 res0831702 16 55526551 AKTIP res1863464 15 226938488 6.38 0.03 0.31 11 res10875911 12 213343486 RCNI res192579 11 32136436 RCNI 8 141174488 0.58 0.03 0.03 11 res4922579 11 32136436 RCNI res11417468 RCNI 6.38 0.04 0.04 0.06	ILMN_1743049	12	rs631562	11	126852438		rs11036212	11	5221825	PTDSS1	5.70	0.05	0.40	0.11	
12 rs241730 22 33375704 rs7305307 12 70235726 6.55 0.25 0.08 19 rs1075728 16 43262788 RAFAP rs765344 15 26938488 6.38 0.03 0.31 11 rs1087702 16 5352651 AKTIP rs4892879 11 32136436 RCNI 6.38 0.03 0.31 11 rs4922579 11 32136436 RCNI rs11416997 8 11177468 4.32 0.41 0.09 11 rs4922579 11 32136436 RCNI rs1341899 1 102740645 5.40 0.04 0.26	ILMN_1672443	4	rs4946705	9	106348246		rs10020773	4	17526682	QDPR	5.75	1.03	1.25	1.55	
19 rs1075728 19 42467788 RABACI rs7951628 11 120161117 6.42 0.28 0.84 16 rs9931702 16 53526551 AKTIP rs1863364 15 26938488 6.42 0.28 0.31 11 rs1927313 12 41147155 rs1427557 11 32136436 RCN1 rs11177468 4.32 0.41 0.09 11 rs4922579 11 32136436 RCN1 rs1341899 1 102740645 5.40 0.04 0.26	ILMN_1803197	12	rs241730	22	33375704		rs7305307	12	70235726		6.55	0.25	0.08	0.09	
16 re9931702 16 5552555 AKTIP rs1863464 15 296934488 6.38 0.03 0.31 11 rs102879131 12 41147155 RCN1 rs19292579 11 32136436 RCN1 5.23 0.58 0.37 11 rs4922579 11 32136436 RCN1 rs11166957 8 14177468 4.32 0.41 0.09 11 rs4922579 11 32136436 RCN1 rs1341899 1 102740645 5.40 0.04 0.26	ILMN_2207363	19	rs1075728	19	42462788	RABACI	rs7951628	11	120161117		6.42	0.28	0.84	0.59	
11 rs1087931 12 41147155 RCM1 rs4922579 11 32136436 RCM1 6.23 0.58 0.37 11 rs4922579 11 32136436 RCM1 rs1166957 8 14177468 4.32 0.41 0.09 11 rs4922579 11 32136436 RCM1 rs1341899 1 102740645 5.40 0.04 0.26	ILMN_1756999	16	rs9931702	16	53526551	AKTIP	rs1863464	15	26938488		6.38	0.03	0.31	0.08	
11 rs4922579 11 32136436 RCN1 rs11166957 8 141177468 4.32 0.41 0.09 11 rs4922579 11 32136436 RCN1 rs1341899 1 102740645 5.40 0.04 0.26	ILMN_1800276	11	rs10879131	12	41147155		rs4922579	11	32136436	RCN1	5.23	0.58	0.37	0.47	
11 rs4922579 11 32136436 RCN1 rs1341899 1 102740645 5.40 0.04 0.26	ILMN_1800276	11	rs4922579	11	32136436	RCN1	rs11166957	œ	141177468		4.32	0.41	0.09	0.17	
	ILMN_1800276	11	rs4922579	11	32136436	RCN1	rs1341899	1	102740645		5.40	0.04	0.26	0.02	

Darit in D	-	9		SNP 1	D	9	- 1	SNP 2	p : - : v	Interac	Interaction statistic	\sim	values	`
0000	Chr.	rs ID	Chr.	Pos/Mb	Association	rs ID	Chr.	Pos/Mb	Association	BSGS	Fehrmann	EGCO.I.	Metas	Distance / Mb
ILMN_1802380		rs4982958	14	24987865 135248366		rs301819		8501786	RERE	5.66	0.61	1.23	1.17	
LMN 2327795		rs11085829	19	13174312		rs301819		8501786	RERE	21.2	0.21	0.33	0.21	
LMN_2327795		rs3852011	'n	112844086		rs301819		8501786	RERE	5.71	0.08	0.60	0.26	
ILMN_1780533	14	rs11628398	14	21182800	RNASE6	rs7324365	13	100601327		5.48	0.42	0.21	0.26	
LMN_1780533	14	rs6603134	19	8106521		rs11628398	14	21182800	RN ASE6	5.11	0.09	0.22	80.0	
LMN_1794726	17	rs238230	17	4875566		rs4884857	13	54668512		4.37				
LMN_1794726	17	rs400688	17	4839930	RNF167	rs11706900	n	36348968		5.59	0.71	0.46	0.64	
LMN_1738347		rs1107121	21	46127549		rs2819365	1	201983242		6.27	0.11	0.30	0.13	
LMN_1738347	- ;	rs8071611	17	67153386		rs2819365	Τ,	201983242		4.32	1.48	0.52	1.28	9
LMN_2413278	91	rs352935	16	89648580		rs2965817	16	89513234		4.98	3.79	14.41	17.24	0.135
LMN-2222750		rs1401202	16	80320056	1400100	rs4849261	N C	114450028	RPL23AP7	5.55	0.13	0.73	0.38	
LMN_2189933	4.	rs3007033	14	50103816	RPL36AL	rs17495030	n c	138038093		5.46	60.0	0.06	0.02	
LMIN_2189936	4.	rs4900928	14	50020817	RFL30AL	rs1502991	٥٠	00137200		0.80	0.32	0.20	0.19	
LMN-1764721	x 0 0	rs2958482	00 0	145984615	KPL8	rs1619856	- 0	234585790	-	4.59	0.10	0.37	0.15	
LMN-1764721	x 0	rs4143674	50	4741304		rs2958482	00	145984615	KPLS	4.33	0.13	0.45	0.22	
LMN-3297880	က	rs4889214	16	80913946		rs696221	က	10342876	SEC13	6.48				
LMN_1702787	-	rs17085428	no ;	95388015		rs7695	-	156147326	SEMA4A	5.70	0.22	1.73	1.17	
LMN_1694027	11	rs12147460	14	104412137		rs684856	11	94906111	SESN3	5.50	0.02	0.51	0.15	
LMN_1694027	11	rs355391	15	46591793		rs684856	11	94906111	SESN3	5.67	0.31	90.0	0.10	
LMN_1694027	11	rs684856	11	94906111	SESN3	rs7004947	œ	134606425		5.60	0.21	0.51	0.31	
LMN_1762764	9	rs10838191	11	43893658		rs1354034	8	56849749	PPBP	5.52	0.70	0.12	0.35	
LMN_1762764	9	rs2545385	Ŋ	66383979		rs1354034	n	56849749	PPBP	5.97	0.20	0.51	0.30	
LMN_1762764	9	rs6845304	4	88280502		rs1354034	n	56849749	PPBP	5.23	0.32	0.71	0.53	
LMN_2158336	6	rs1034120	21	18196922		rs17455517	6	131785369	SH3GLB2	7.40	0.22	0.18	0.13	
LMN_1771801	50	rs1535883	20	1612819	SIRPG	rs6842739	4	60489510		5.74	0.29	0.18	0.17	
LMN_2382505		rs11673260	19	52181798		rs367035	11	2923826	SLC22A18	5.47	0.09	0.24	0.09	
LMN_2382505	= ;	rs367035	11;	2923826	SLC22A18	rs3110874	٠ - ا	153224179		5.70	0.15	0.10	0.06	
LMN_2382505	Ξ.	rs367035	11	2923826	SLCZZAIS	rs3772054	201.0	241678528	04.70	6.15	0.39	0.13	0.19	
LMN_2356111	n 0	rs1912136	11	140007734	2 4 1 7 7	rs6771703	n	125801067	SLC41A3	0 F	01.10	0.87	42.1	
745778	o ç	rs0985508	o į	142337734	SLC45A4	rs7701916	0 0	174598073		0.80	0.86	0.07	0.40	
LMN_1058039	η -	rs949805	11.	55602091		rs/981190	1.3	100460000	SEC40A3	0.02	0.08	80.0	0.70	
LMN 1775380	1 00	18800003	200	4161500	SMOX	rs10911505	٠, د	65800983	DIVID	0.0	0.10	0.03	0.00	
L.M.N. 3309349	0 4	re1105691	0	133050233	NO WIG	1911011010	1 <	119995940	SUHUS	5.0	0:0	20.0		
1799381	' =	rs1520429	<u>.</u>	46259108		rs214097	' =	17291499	SNORD14A	6.60	0.29	1.03	0.72	
LMN_1799381	11	rs2634462	11	17339127		rs6486334	11	17015557		7.31	13.11	10.96	23.22	0.324
LMN_3238662	7	rs10445863	7	115929241		rs750783	7	101889306	SNORD89	80.9				14.040
LMN_3238662	7	rs11605822	11	122986326		rs750783	63	101889306	SNORD89	5.96				
LMN_3238662	67	rs2135064	Ŋ	26778066		rs750783	7	101889306	SNORD89	6.33				
LMN_1733932	12	rs8134646	21	46376528	SNUPN	rs7185362	16	81888905		6.45	0.13	1.41	0.83	
LMN_2364535	12	rs8134646	21	46376528	SNOPN	rs1472075	ن ده	193706323		5.59	0.34	0.00	90.0	
T MM 17170E9	2 -	rs1131620	5 -	41117869		rs4774580	1.0	45052080	PEALABEL	5.44	0	0.0	000	
LMN 2210729	1 2	rs4073164	1.5	104947517		rs17685	1 1	75616105	STYXL	0 00	0.0	0.17		
LMN_2345142	20	rs11700063	20	46153148	SULF2	rs939294	4	180439236		5.51	0.46	0.24	0.30	
LMN_2336133	16	rs1463965	18	74332954		rs3785354	16	28550667	TUFM	7.05	0.01	0.05	0.00	
LMN_2336133	16	rs2836657	21	40119768		rs3785354	16	28550667	TUFM	5.83				
LMN_1778032	6	rs6099626	20	56013994		rs3118663	6	136281753	SURF6	6.14	0.26	0.16	0.14	
LMN_2336609	11	rs1375719	13	103410782		rs485485	11	85495269	SYTL2	5.47	0.28	0.31	0.24	
LMN_1804663	1	rs1939875	11	95422867		rs4072037	1	155162067	THBS3	5.55	0.03	0.15	0.03	
LMN_1804663		rs8014956	14	20687978		rs2049805	1	155194980	THBS3	5.65	0.31	0.76	0.55	
1781457		1 C C C C C C C C C C C C C C C C C C C												

	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	90.4	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	8.23	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 7 71	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	TRAPPCS	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																							
	Chr.	7	61.0	10	61	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	- ;	11	1 -1	- 1		1 :	11	19	19	19	19	61	61	19	19	19	61	61	61	61	19	9	9	9	2 :	11	1 1
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 TP A PPC 4	TRAFFC4	TRAPPCS	TRAPPCS	TRAPPC5	TRAPPC5	TRAPPC5	TRAPPOS	TRAPPCS	TRAPPC5	TRAPPC5	TRAPPC5	TRAPPC5	TRAPPCS	TRAPPOS	TRAPPCS	TRAPPC5	TREM1	TREM1	TRIM38	TSPAN14	TSPAN32	

	, MP			1.643	0.088																					
	Distance /			1	0																					
values	Metag	0.52	1.10	0.03	4.95	0.46	0.57		0.19	0.41	0.31	0.17	0.04	1.21	0.16	0.57	0.26	1.47	0.09	1.22	0.35	2.25	1.63	0.15	0.46	0.05
$-\log_{10} p$ -values	\mathtt{EGCUT}^{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 /	$\operatorname{Fehrmann}^{\mathrm{f}}$	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
Interacti	BSGS _e I	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
	Chr.	16	1	17	19	9	9	9	9	9	9	9	9	9	9	18	10	19	က	က	က	က	15	16	16	7
	rs ID	rs7201194	rs7512594	rs7225546	rs2276470	rs1883613	rs1883617	rs1883617	rs1883617	rs2267952	rs2267952	rs2267952	rs2267952	rs2267952	rs2267952	rs4552100	rs7895870	rs10500316	rs6778963	rs883349	rs7619193	rs11715581	rs12591171	rs1182968	rs2290560	rs2242601
	Associationd	UBASH3A	UBASH3A	USP36												VSTM1	VSTM1			RAPGEF1			XAF1			
SNP 1	$^{ m Pos/Mb^c}$	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	۲-	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	n	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
Ex	Gene IDa	UBASH3A	UBASH3A	USP36	VASP	VNN2	VNN2	VNN2	VNN2	VNN3	VNN3	VNN3	VNN3	VNN3	VNN3	VSTM1	VSTM1	VSTM1	WDR48	WDR48	WDR48	WDR6	XAF1	ZFP90	ZNF500	ZYX

Table S1 - continued from previous page

a Phenotypes are expression levels of RefSeq Genes
Dilumina probe ID used to measure gene expression
Physical SNP position in base pairs (HG19)
d RefSeq Gene ID of gene expression level that is influenced by the SNP (BSGS discovery dataset, significance threshold = 1.29 × 10⁻¹¹)
Interaction - log₁₀ p-value from discovery dataset
Interaction - log₁₀ p-value from meta analysis of replication datasets on the statement of the

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

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

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

Test	Interactions ^a	Dataset	n^{b}	Expected ^c	Observed ^d	<i>p</i> -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}
$\overline{3^{\mathrm{g}}}$	All	EGCUT	1133	566.50	775	7.10×10^{-36}
		Fehrmann	1133	566.50	726	1.90×10^{-21}
		Both	1133	283.25	562	1.39×10^{-70}
	Significant	EGCUT	73	36.50	55	1.69×10^{-5}
		Fehrmann	73	36.50	55	1.69×10^{-5}
		Both	73	18.25	46	7.86×10^{-12}

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

^b Number of tests for concordance

 $^{^{\}rm c}$ Expected number of concordant cases under the null hypothesis of no interactions

^d Observed number of concordant cases

 $^{^{}m e}$ 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°	1 ^c	2 ^c	3 ^c	4 ^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 DIP2B rs871257 rs12427378 117994348 <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