

**Figure S1: Type 1 error rate of two stage design assuming a null model of one large additive effect and no epistasis** In stage 1 SNPs are tested for full genetic effects (8 d.f.) and those that surpass a threshold for multiple testing are then tested for significant interaction terms in stage 2. These interaction  $p$ -values are then adjusted (Bonferroni) for the total number of tests that passed stage 1. The type 1 error rate of this two stage design is dependent on the power, which is not known empirically.

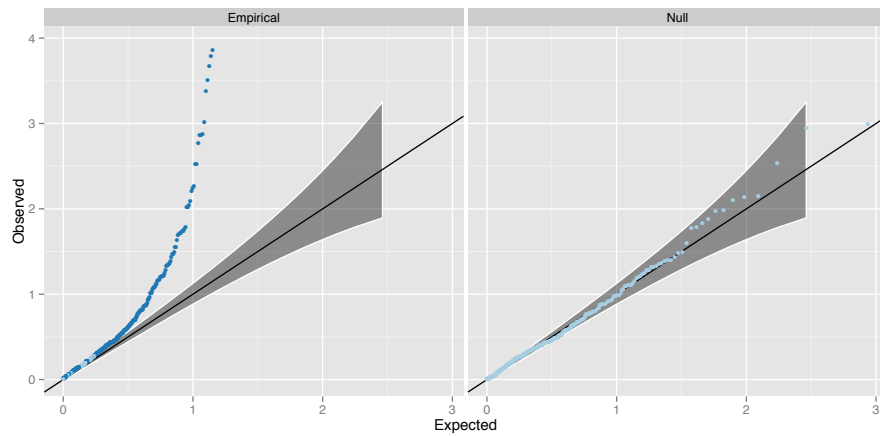


Figure S2: **Q-Q plots of interaction  $p$ -values from replication datasets, excluding the 30 points significant at the Bonferroni level** The right panel (Null) shows the interaction  $p$ -values from a meta analysis across two independent datasets on 434 SNP pairs where one SNP has a marginal effect.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

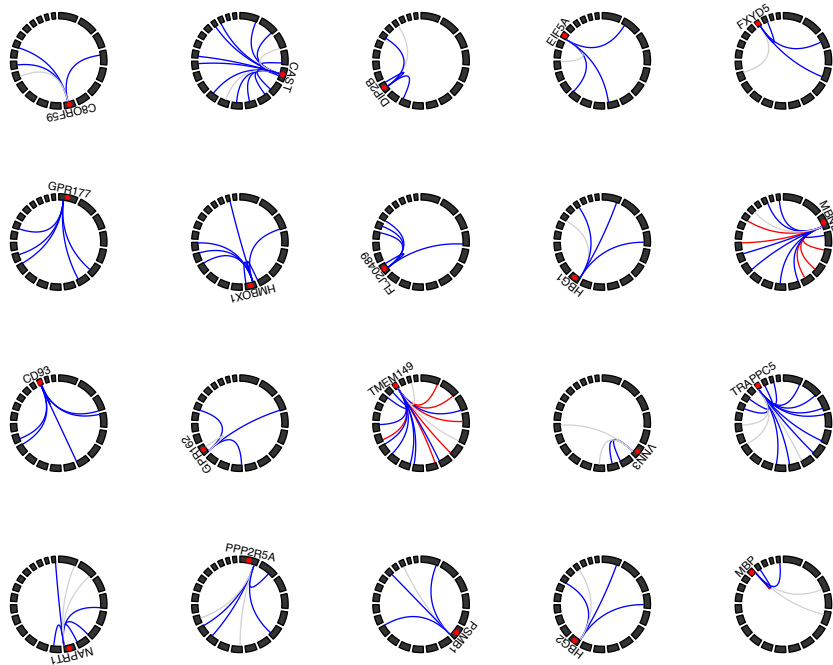
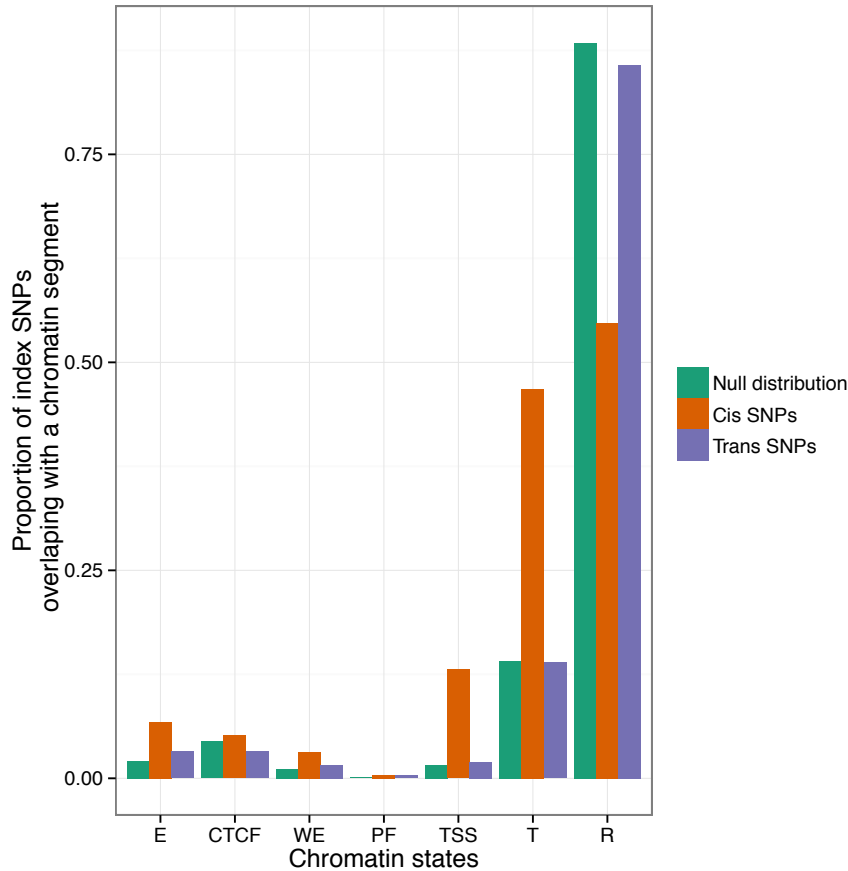
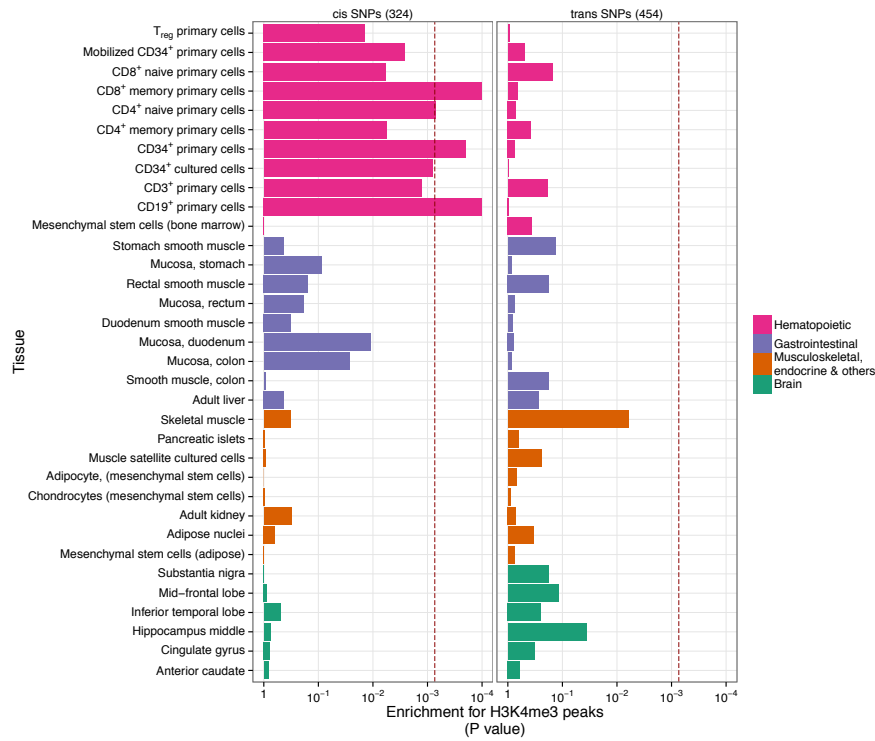


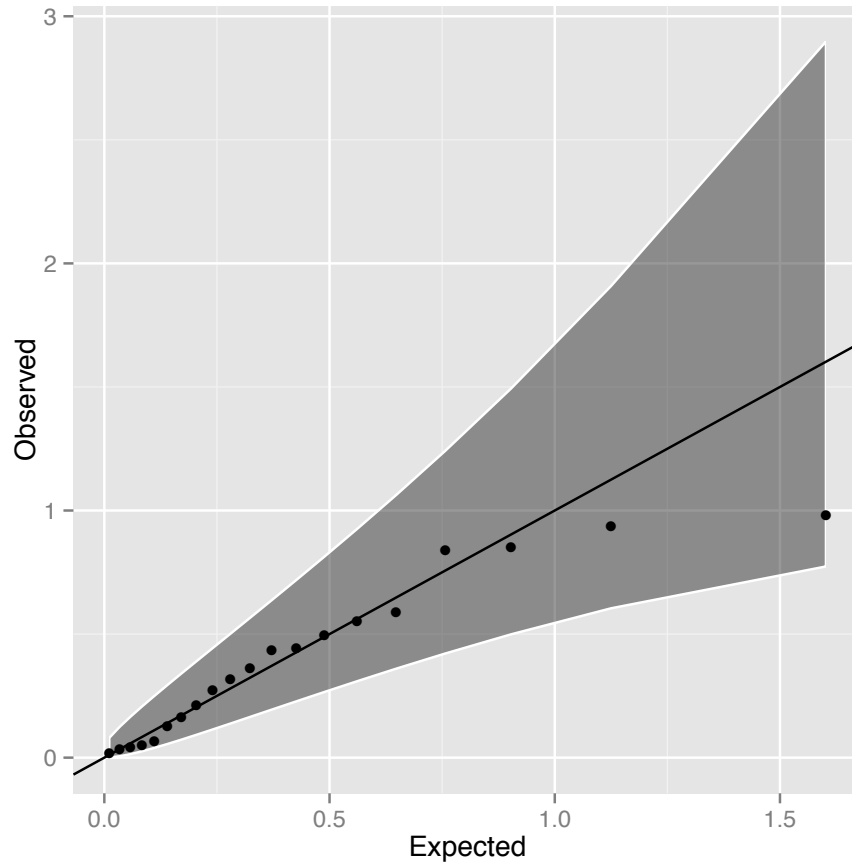
Figure S3: **Gene expression traits with four or more genetic interactions** Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent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



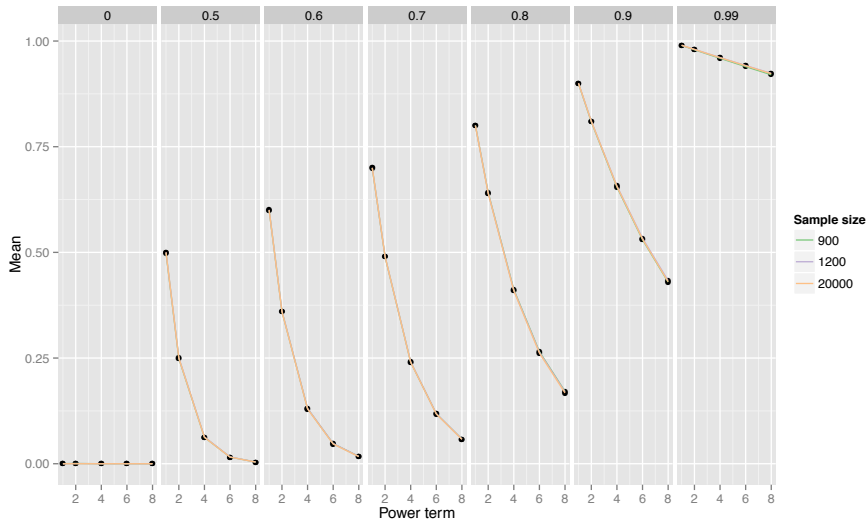
**Figure S4: Location of SNPs relative to genomic features** We used chromatin segmentation<sup>28</sup> as a method for labelling genomic features. All SNPs within 1Mb and  $r^2 > 0.8$  of each *cis*- and *trans*-SNP were taken to find which genomic features (*x*-axis) were covered by the SNPs that compose the 501 significant interactions. Green bars represent the proportion (*y*-axis) of the 528,509 SNPs used in the analysis that fall within the range of the different genomic features. There is enrichment for *cis*-acting SNPs (red bars) in promoter regions, but *trans*-acting SNPs (blue bars) are not enriched for genomic features. The labels on the *x*-axis are as follows: E = Predicted enhancer, CTCF = CTCF enriched element, WE = Predicted weak enhancer or open chromatin cis regulatory element, PF = Predicted promoter flanking region, TSS = Predicted promoter region including transcriptional start site, T = Predicted transcribed region, R = Predicted Repressed or Low Activity region



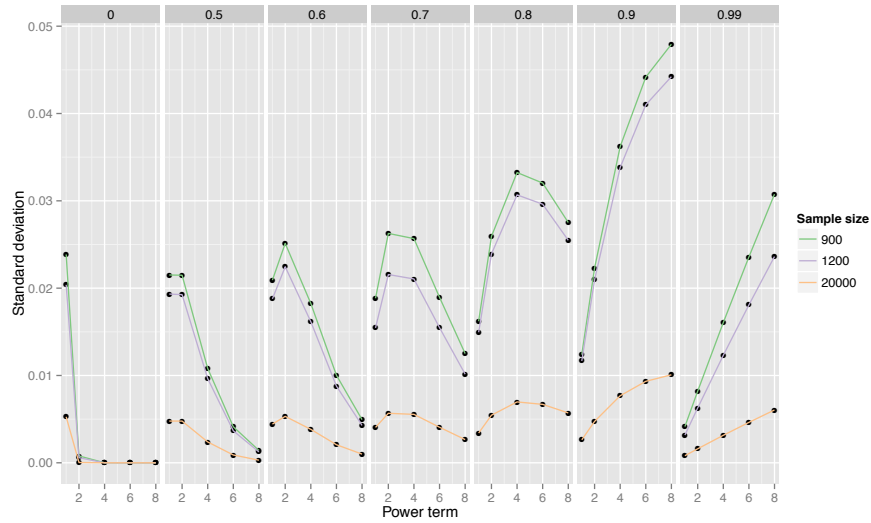
**Figure S5: Tissue specific enrichment of SNPs in transcriptionally active regions** The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3.<sup>27</sup> Enrichment *p*-values are calculated using permutation analysis for 34 different cell types (*y*-axis)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

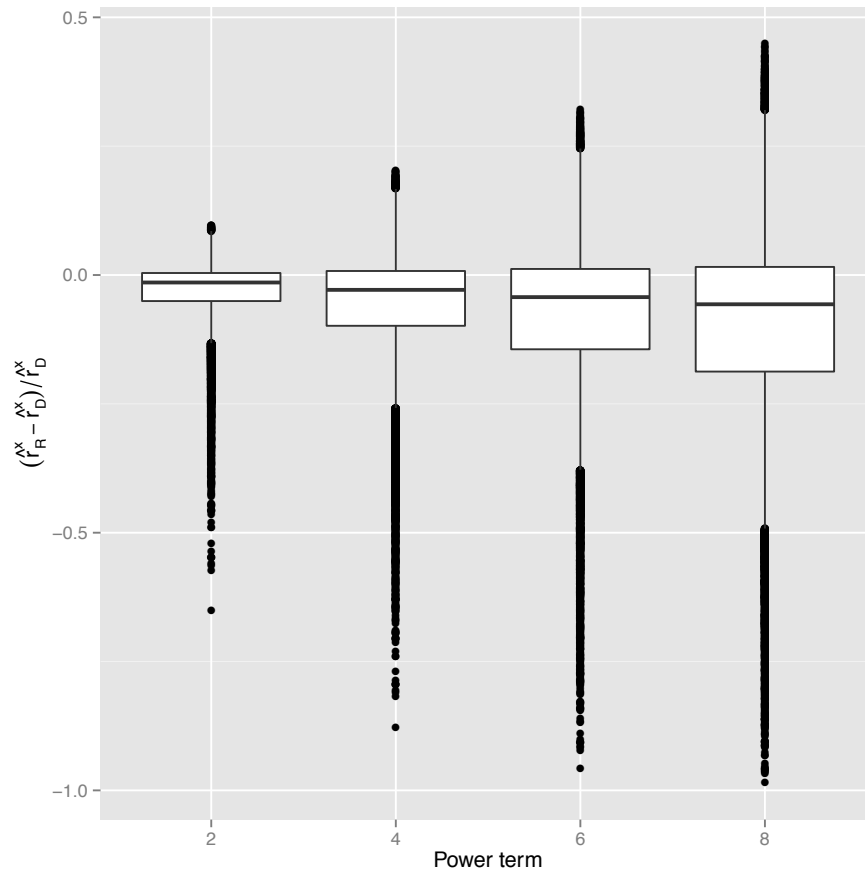


**Figure S7: Sampling mean for different power terms of population  $r$  values** Power of detection and replication of epistatic interactions depends not on  $r^2$  between causal variants and observed SNPs, but on  $r^4, r^6, r^8$ . For a given population value of LD  $r$  (columns of plots), plotted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

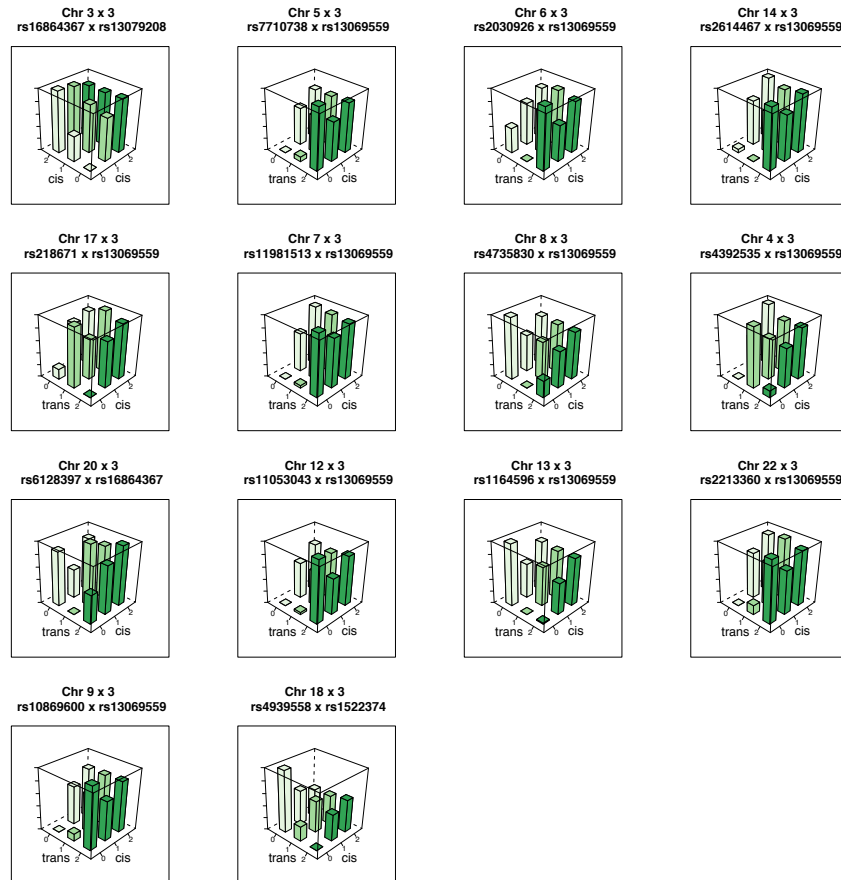


Figure S10: **Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions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

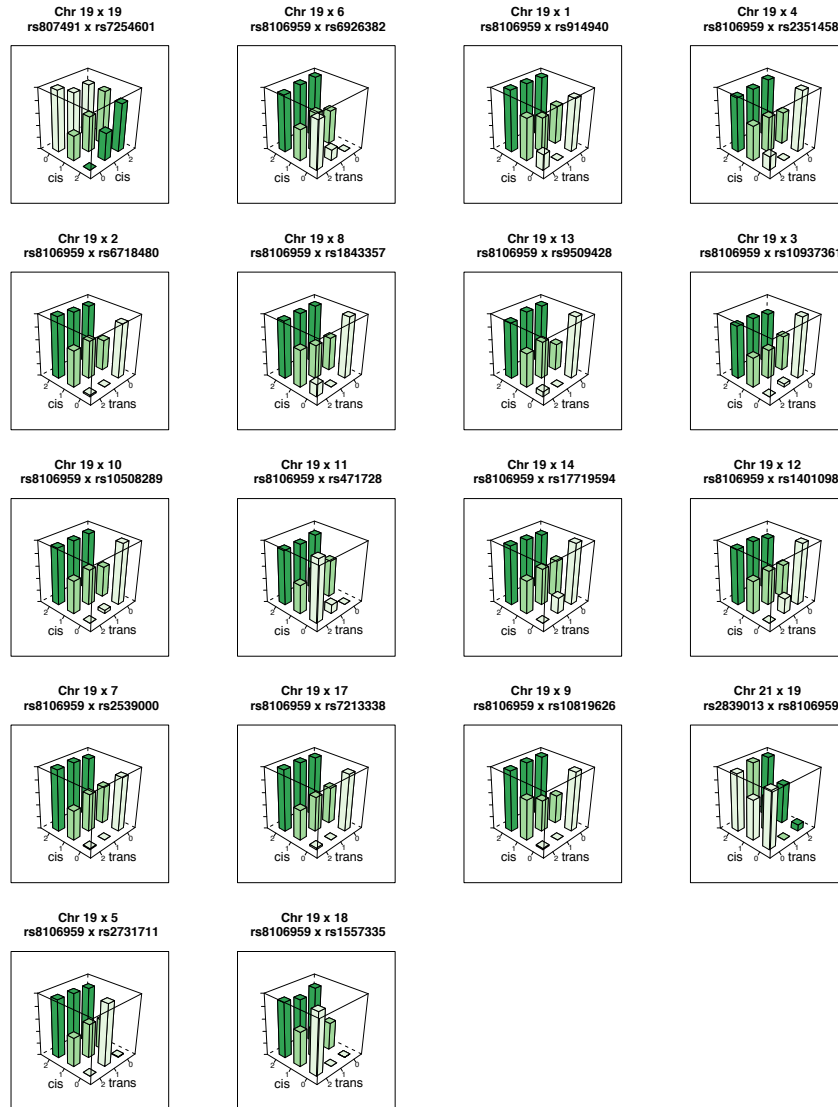


Figure S11: **Genotype-phenotype maps for 19 interactions influencing the expression of TMEM149** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of TMEM149, but in many of these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

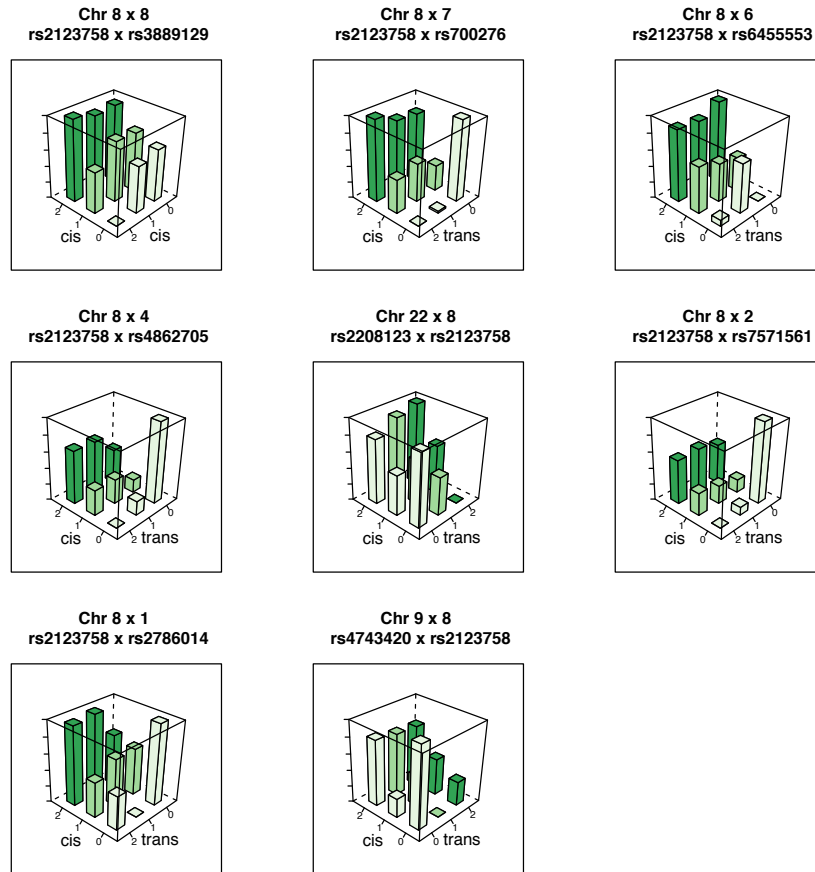


Figure S12: **Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1** Each bar represents the mean phenotypic value for individuals in that genotype class.

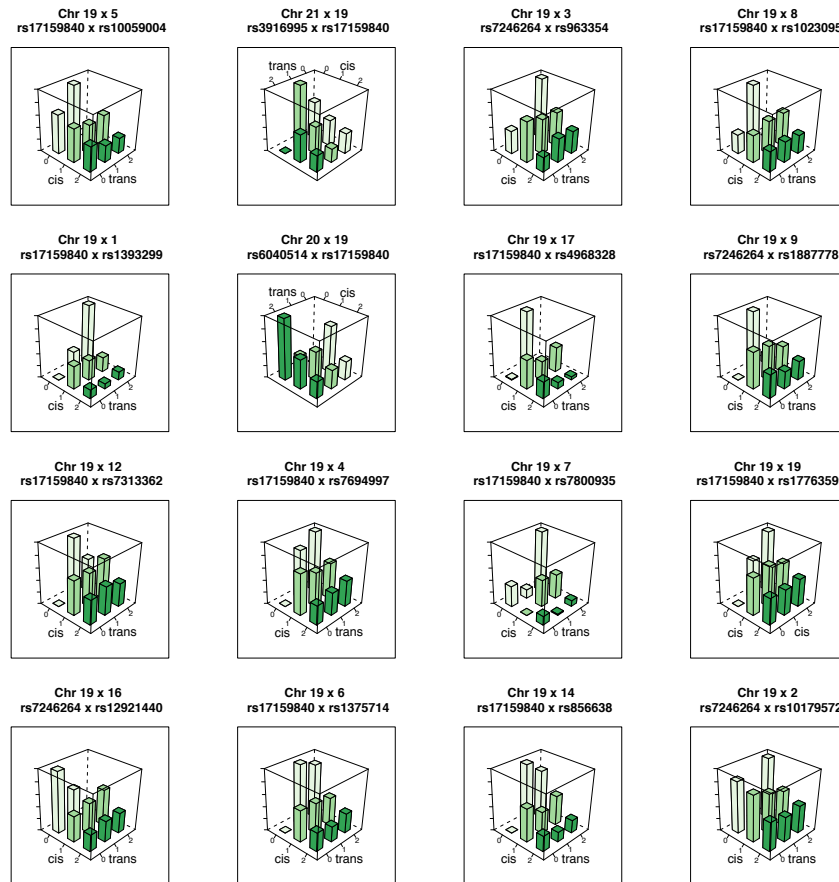


Figure S13: **Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5** Each bar represents the mean phenotypic value for individuals in that genotype class.

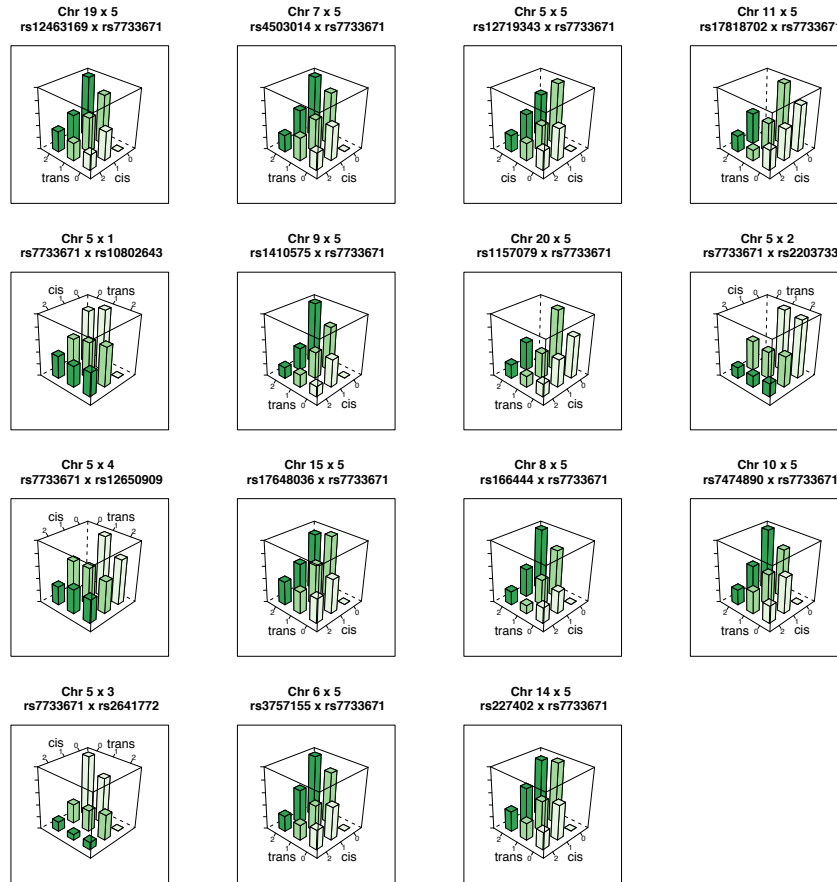
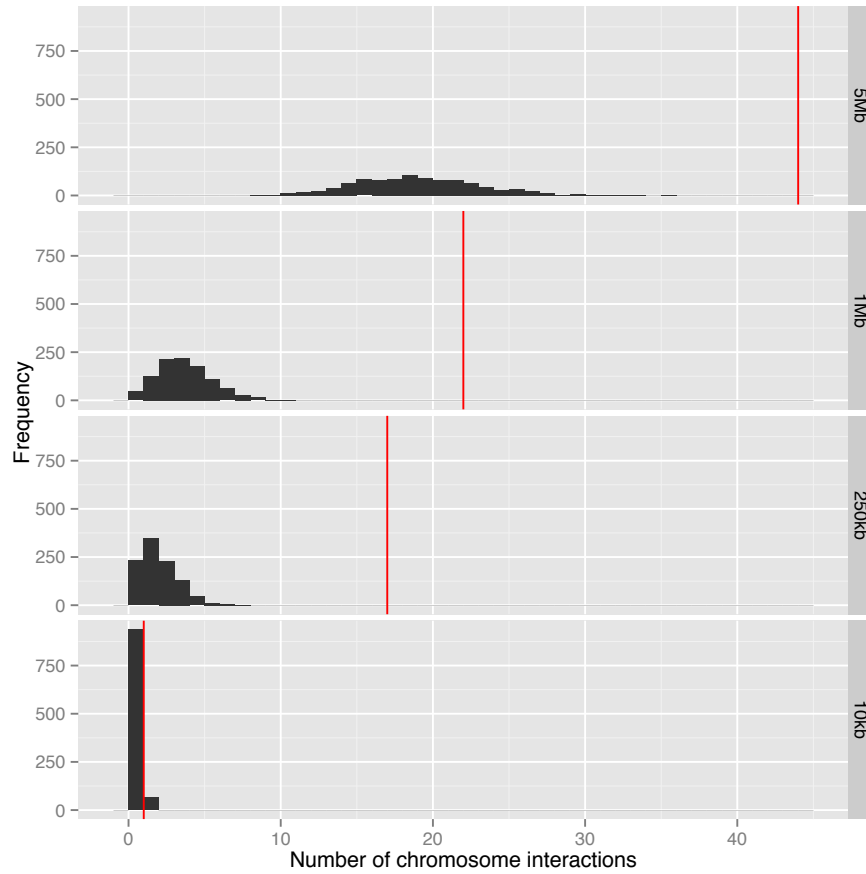


Figure S14: **Genotype-phenotype maps for 15 interactions influencing the expression of CAST** Each bar represents the mean phenotypic value for individuals in that genotype class.



**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.

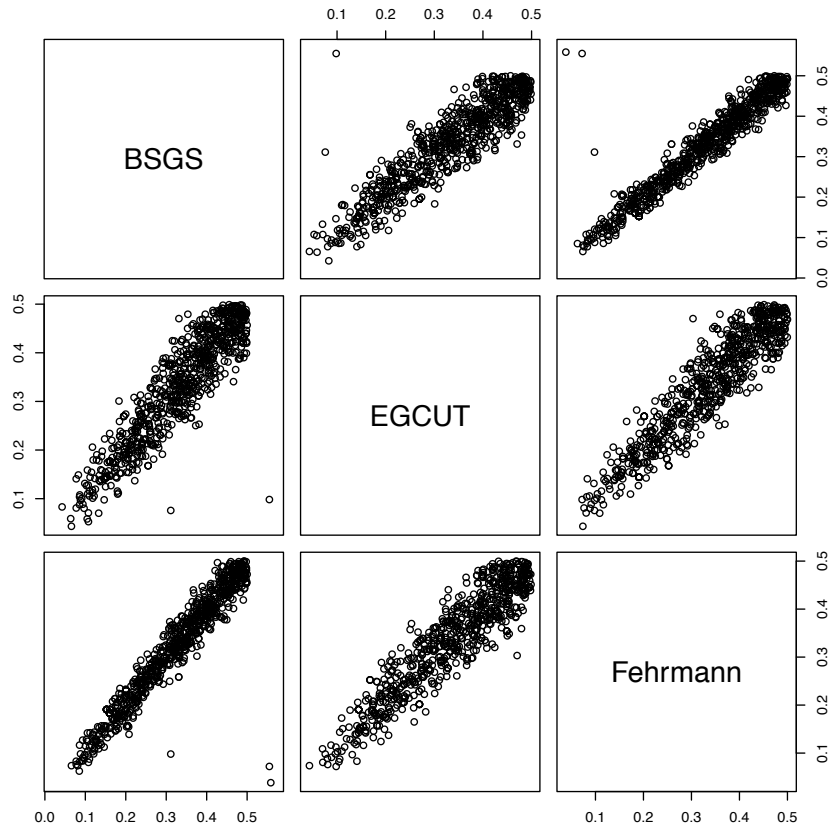
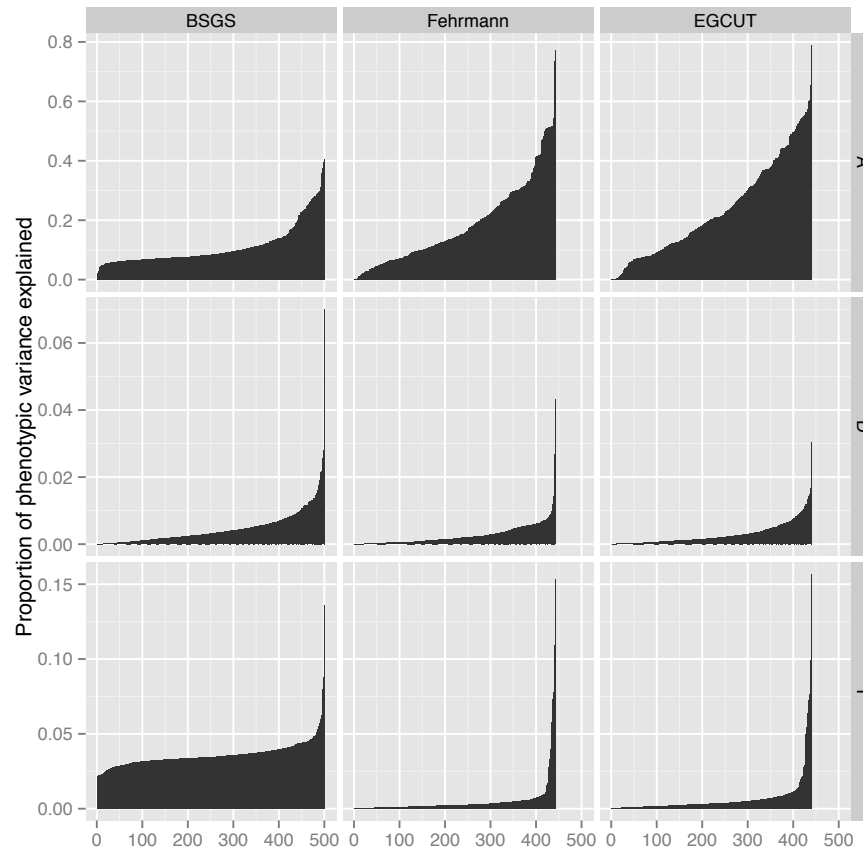


Figure S16: Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations. Outliers were removed from the analysis as part of the filtering stage during replication.





**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.













Table S2: **Estimation of additive and non-additive variance components from pedigree information** Taken from previous analysis in Powell et al 2013<sup>22</sup>

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

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

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

<sup>a</sup> “All” denotes 434 discovery interactions and “Significant” denotes 30 interactions with significant replication  $p$ -values

<sup>b</sup> Number of tests for concordance

<sup>c</sup> Expected number of concordant cases under the null hypothesis of no interactions

<sup>d</sup> Observed number of concordant cases

<sup>e</sup> The sign of the most significant epistatic variance component in discovery is the same as the corresponding variance component in the replication data.

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

<sup>g</sup> 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 <sup>a</sup>	Dataset	<i>n</i> <sup>b</sup>	0 <sup>c</sup>	1 <sup>c</sup>	2 <sup>c</sup>	3 <sup>c</sup>	4 <sup>c</sup>	<i>p</i>
Expected <sup>d</sup>	-	-	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	$4.72 \times 10^{-4}$
Significant	Fehrmann	30	0.03	0.07	0.33	0.27	0.30	$6.69 \times 10^{-4}$
Significant	Combined	60	0.05	0.05	0.32	0.30	0.28	$5.49 \times 10^{-8}$

<sup>a</sup> “All” denotes 434 discovery interactions and “Significant” denotes 30 interactions with significant replication *p*-values.

<sup>b</sup> Number of tests for concordance.

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

<sup>d</sup> Expected proportion of concordant signs under the null hypothesis of no epistasis.

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

Chr	Gene	SNP 1	SNP 2	Position 1	Position 2	Distance / Mb	$R^2$	$D'$
19	TMEM149	rs807491	rs7254601	36268923	36147315	0.122	0.000	0.001
17	FN3KRP	rs898095	rs9892064	80890638	80827903	0.063	0.063	0.088
21	CSTB	rs9979356	rs3761385	45230974	45198355	0.033	0.041	0.066
3	MBNL1	rs16864367	rs13079208	152234166	152116652	0.118	0.041	0.117
10	ADK	rs2395095	rs10824092	76446305	75929517	0.517	0.013	0.020
11	CTSC	rs7930237	rs556895	88117962	88077479	0.040	0.012	0.045
17	GAA	rs11150847	rs12602462	78153130	78146016	0.007	0.000	0.001
8	NAPRT1	rs2123758	rs3889129	144663661	144613680	0.050	0.053	0.060
1	LAX1	rs1891432	rs10900520	203877662	203780591	0.097	0.065	0.106
18	MBP	rs8092433	rs4890876	74747424	74732087	0.015	0.035	0.053
11	SNORD14A	rs2634462	rs6486334	17339127	17015557	0.324	0.008	0.012
21	C21ORF57	rs9978658	rs11701361	48027084	47764477	0.263	0.032	0.065
16	RPL13	rs352935	rs2965817	89648580	89513234	0.135	0.054	0.060
19	ATP13A1	rs4284750	rs873870	19810050	19738554	0.071	0.008	0.015
2	NCL	rs7563453	rs4973397	232301670	232291471	0.010	0.027	0.029
5	HNRPH1	rs6894268	rs4700810	179032488	178991794	0.041	0.000	0.001
19	VASP	rs1264226	rs2276470	46063167	45974668	0.088	0.018	0.022
7	TRA2A	rs7776572	rs11770192	23528927	23498358	0.031	0.064	0.064
21	PRMT2	rs2839372	rs11701058	48063862	47776382	0.287	0.100	0.122
12	OAS1	rs13311	rs2072133	113448652	113409260	0.039	0.002	0.016
16	N4BP1	rs12444224	rs11649236	87580855	48632478	38.948	0.007	0.021
5	CAST	rs12719343	rs7733671	125369113	96000269	29.369	0.001	0.001
7	DNAJB6	rs2286842	rs3779589	157216093	157163614	0.052	0.005	0.006
1	OVGP1	rs10802822	rs1264898	240132968	111992823	128.140	0.008	0.030
20	CD93	rs2868504	rs1884655	37771578	23074375	14.697	0.000	0.002
11	PHCA	rs493642	rs10736812	123097386	76708086	46.389	0.002	0.008
21	MX1	rs459498	rs8130120	42795027	29363604	13.431	0.000	0.000
16	AKTIP	rs2896940	rs13332406	57721127	53489705	4.231	0.000	0.001
17	CDK5R1	rs9905940	rs11655031	46614102	30833162	15.781	0.000	0.000
2	CYBRD1	rs888427	rs7591849	172368120	160112881	12.255	0.000	0.000
8	HMBX1	rs587639	rs7837237	132725731	28876221	103.850	0.001	0.001
11	TRAPPC4	rs1793823	rs3916581	131018917	118887887	12.131	0.001	0.002
12	PEX5	rs10444467	rs4329748	128052636	7364442	120.688	0.000	0.000
12	FLJ20489	rs17615703	rs3782908	117036766	48169526	68.867	0.001	0.002
16	PRKCB1	rs2188355	rs10492793	23867776	12639800	11.228	0.000	0.000
14	MRPL52	rs1950857	rs3811188	26710271	23299135	3.411	0.002	0.004
17	C17ORF60	rs9907897	rs7405659	63502633	59874129	3.629	0.004	0.011
6	FLJ43093	rs6906101	rs13214069	36667610	32705248	3.962	0.000	0.000
19	TRAPPC5	rs17159840	rs17763599	7758194	2369415	5.389	0.000	0.000
22	PISD	rs715572	rs6518754	33234931	32097775	1.137	0.001	0.003
12	DIP2B	rs871257	rs12427378	117994348	51074199	66.920	0.001	0.001
12	GPR162	rs2272500	rs2707210	79685913	6902002	72.784	0.003	0.005
17	USP36	rs2279308	rs7225546	76794981	75151717	1.643	0.000	0.000