

Detection and replication of epistasis influencing transcription in humans

Gibran Hemani^{1,2,*}, Konstantin Shakhbazov^{1,2}, Harm-Jan Westra³,
Tonu Esko^{4,5,6}, Anjali K Henders⁷, Allan F. McRae^{1,2}, Jian Yang²,
Greg Gibson⁸, Nick G Martin⁷, Andres Metspalu⁴, Lude Franke³,
Grant W Montgomery^{7,+}, Peter M Visscher^{1,2,+}, and Joseph E
Powell^{1,2,+}

¹University of Queensland Diamantina Institute, University of Queensland, Princess Alexandra Hospital, Brisbane, Queensland, Australia. ²Queensland Brain Institute, University of Queensland, Brisbane, QLD, Australia. ³Department of Genetics, University Medical Center Groningen, University of Groningen, Hanzeplein 1, Groningen, the Netherlands. ⁴Estonian Genome Center, University of Tartu, Tartu, 51010, Estonia. ⁵Medical and Population Genetics, Broad Institute, Cambridge, MA, 02142, US. ⁶Divisions of Endocrinology, Children's Hospital, Boston, MA, 02115, US. ⁷Queensland Institute of Medical Research, Brisbane, Queensland, Australia. ⁸School of Biology and Centre for Integrative Genomics, Georgia Institute of Technology, Atlanta, Georgia United States of America. ⁺These authors contributed equally. ^{*}Corresponding author: g.hemani@uq.edu.au

Abstract

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 epistasis has been demonstrated in artificial gene manipulation studies in model organisms,^{4,5} and some examples have been reported in other species,⁶ few convincing examples exist for epistasis amongst natural polymorphisms in human traits.^{7,8} Its absence from empirical findings may simply be due to its low incidence in the genetic control of complex traits,^{2,3} but an alternative view is that it has previously been too technically challenging to detect due to statistical power and computational issues.⁹ Here we show that, using advanced computation techniques¹⁰ and a gene expression study design, many instances of epistasis are found between common single nucleotide polymorphisms (SNPs). In a cohort of 846 individuals with data on 7339 gene expression levels in peripheral blood, we found 501 significant pairwise epistatic interactions between common SNPs acting on the expression levels of 238 genes ($p < 2.91 \times 10^{-16}$). We tested the discovery interactions for replication in two independent data sets.^{11,12} Three hundred and forty-five interactions had replication interaction p -values that were more extreme than the 2.5% confidence interval of the distribution under the null hypothesis of no epistasis, with 30 significant at a conservative $p < 0.05$ Bonferroni level. There was evidence of functional enrichment for the interacting SNPs, for instance 44 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 epistatic genetic effects emerging from natural genetic variation in humans.

Main text

In the genetic analysis of complex traits it is usual for SNP effects to be estimated using an additive model where they are assumed to contribute independently and cumulatively to the mean of a trait. This framework has been successful in identifying thousands of associations.¹⁴ But to date, though its contribution to phenotypic variance is frequently the subject of debate,¹⁻³ there is little empirical exploration of the role that epistasis plays in the architecture of complex traits in humans.^{7,8} Outside the prism of human association studies there is evidence for epistasis, not only at the molecular scale from artificially induced mutations⁴ but also at the evolutionary scale in fitness adaptation¹⁵ and speciation.¹⁶

Methods are now available to overcome the computational problems involved in searching for epistasis, but its detection still remains problematic due to 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 occur amongst 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. These traits are largely heritable but on average less polygenic than high level phenotypes,²¹ thus many genetic effects are relatively large, maximising the chance at detecting epistasis, should it exist.

In our discovery dataset (Brisbane Systems Genetics Study, BSGS²²) of 846 individuals genotyped at 528,509 SNPs, we exhaustively tested every pair of SNPs for genetic interactions against each of 7339 expression traits in peripheral blood. After stringent filtering and multiple testing correction (5% significance threshold $p < 2.91 \times 10^{-16}$, Methods) we identified 501 putative genetic interactions influencing the expression levels of 238 genes (Supplementary Table). Of the 501 discovery interactions, 434 had available data and passed filtering (Methods) in two independent replication datasets, Fehrman¹² 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 $p < 0.0001$, Table 1). These significant interactions exhibited remarkable similarity in GP maps between all three datasets (Figure 1).

In addition, using the meta analysis from the replication samples only, we observed that 316 of the remaining 404 discovery SNPs had replication interaction p -values more extreme than the 2.5% confidence interval of the distribution under the null distribution of no epistatic effects ($p < 1.0 \times 10^{-16}$, Figure 2 and Supplementary Figure S1). 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,²³ 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 S5). It should be noted that although it is a necessary step to establish the veracity of the signals from the discovery set, replication of epistasis is difficult in practice because

the dependence on LD between observed SNPs and causal variants is up to three orders of magnitude higher than it is for independent additive effects.^{17,18} Therefore these results are encouraging with regards to the detection and replication of epistasis.

Though seldom the focus of association studies, SNPs with known main effects are often tested for additive \times additive genetic interactions,⁹ but our analysis shows that this is unlikely to be the most effective strategy for its detection. The majority of our discovery interactions comprised of one SNP that was significantly associated with the gene expression level in the discovery dataset, and one SNP that had no previous association²¹ (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 are not designed to resemble biological function.²⁴

Of the discovery interactions, 47 were *cis-cis* acting (both SNPs were on the same chromosome as the expression gene), 441 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 splicing²⁵) 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 S6). Each of these interactions has evidence for replication in at least one dataset and six are significantly replicated at the Bonferroni level (Supplementary Figure S2). We see similar epistatic networks involving multiple (eight or more) *trans*-acting SNPs for other gene expression levels too, for example TMEM149 (Supplementary Figure S7), NAPRT1 (Supplementary Figure S8), TRAPPC5 (Supplementary Figure S9), and CAST (Supplementary Figure S10). 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 previously²¹ (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 types²⁶ (Supplementary Figure S4). 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 in-

teractions 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 states²⁷ (Supplementary Figure S3).

We also demonstrate physical organisation of interacting loci within the cell, suggesting a mechanism by which biological function can lead to epistatic genetic variance. It has been shown that different chromosomal regions spatially colocalise in the cell through chromatin interactions.¹³ We cross-referenced our epistatic SNPs with a map of chromosome interacting regions ($n = 96,139$) in K562 blood cell lines²⁸ (Methods) and found that 44 epistatic interactions mapped to within 2Mb ($p < 1.8 \times 10^{-10}$), (Supplementary Figure S11). 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.^{29,30}

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. How does this compare to the number of traits influenced by additive effects? The BSGS dataset has been previously analysed for additive effects at all expression traits,²² and if we take all the additive eQTLs that were significant at the epistatic threshold of $p < 2.91 \times 10^{-16}$ we find that 453 gene expression levels out of the 7339 analysed had at least one significant expression quantitative trait locus (eQTL). Therefore it can be argued that the number of instances of detectable epistasis are substantial.

However in terms of their contribution to complex traits a more important metric might be the proportion of the variance that the epistatic loci explain.² Ideally one would approach this question from a whole genome perspective³¹ but this is intractable for non-additive variance components. Nevertheless, some inference can be made from the ascertained effects in these analyses and it is evident that additive variance is overall a larger component than epistatic variance, as has been argued previously.^{2,3} Taking the additive effects detected in Powell *et al* (2012) at the $p < 2.91 \times 10^{-16}$ threshold, we calculate that on average they explain 1.73% of the phenotypic variance of each of the 7339 probes. By contrast, the epistatic variance from the interacting SNPs detected in this study on average explain 0.25% of phenotypic variance, approximately seven times lower than the additive variance. There are several caveats to this comparison. Firstly, the ratio of additive to epistatic variance may differ at different effect sizes, 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. And thirdly, the non-additive variance at causal variants is expected to be underestimated by observed SNPs in comparison to estimates for additive variance, due to differences in the rate of decay of the estimate of the genetic variance of the causal SNPs as LD decreases with the observed SNPs.

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 to understanding molecular mechanisms and complex trait variation in greater detail. With computational techniques and data now widely available the search for epistasis in larger datasets for traits of broader interest is warranted.

Methods Summary

We searched for pairwise epistasis exhaustively in the BSGS discovery dataset,²² which comprises 846 individuals who are genotyped at 528,509 autosomal SNPs. Each individual had gene expression levels measured in peripheral blood at 47,323 probes. Only the probes that passed quality control and had significant expression in $\geq 90\%$ of individuals were used in the analysis (7,339 probes representing 6,158 RefSeq genes). Recent hardware and software¹⁰ advances that use graphics processing units (GPUs) made it possible to perform the 1.03×10^{15} statistical tests to complete this analysis. We used permutation analysis³² to calculate an experiment-wide significance threshold of $T_e = 2.91 \times 10^{-16}$ at the 5% family-wise error rate (FWER). SNP pairs were modelled for full genetic effects, including marginal additive and dominance at both SNPs plus four interaction terms. Though we could have used a less complex model to improve statistical efficiency, we deemed it important to be agnostic about the type of epistasis that might exist, and therefore chose not to over-parameterise the test.^{18,19} Because there are many large marginal effects present in these data it was necessary to perform several filtering steps to exclude SNP pairs that were significant due to marginal effects alone. All SNP pairs with LD $r^2 > 0.1$ and $D'^2 > 0.1$ 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), resulting in 501 significant interactions after Bonferroni correction for multiple testing of the filtered SNPs. The significant SNP pairs were carried forward for replication in two independent datasets that used the same expression assays for analysing transcription in peripheral blood, the Fehrmann dataset¹² ($n = 1240$) and the Estonian Genome Centre University of the University of Tartu (EGCUT) dataset¹¹ ($n = 891$). 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.

Acknowledgements

We are grateful to the volunteers for their generous participation in these studies. We thank Bill Hill, Chris Haley and Lars Ronnegard for helpful discussions and

comments.

This work could not have been completed without access to high performance GPGPU compute clusters. We acknowledge iVEC for the use of advanced computing resources located at iVEC@UWA (www.ivec.org), and the Multimodal Australian ScienceS Imaging and Visualisation Environment (MASSIVE) (www.massive.org.au). We also thank Jake Carroll and Irek Porebski from the Queensland Brain Institute Information Technology Group for HPC support.

The University of Queensland group is supported by the Australian National Health and Medical Research Council (NHMRC) grants 389892, 496667, 613601, 1010374 and 1046880, the Australian Research Council (ARC) grant (DE130100691), and by National Institutes of Health (NIH) grants GM057091 and GM099568.

The QIMR researchers acknowledge funding from the Australian National Health and Medical Research Council (grants 241944, 389875, 389891, 389892, 389938, 442915, 442981, 496739, 496688 and 552485), the and the National Institutes of Health (grants AA07535, AA10248, AA014041, AA13320, AA13321, AA13326 and DA12854). We thank Anthony Caracella and Lisa Bowdler for technical assistance with the micro-array hybridisations.

The CHDWB study funding support from the Georgia Institute of Technology Research Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

The Fehrmann study was supported by grants from the Celiac Disease Consortium (an innovative cluster approved by the Netherlands Genomics Initiative and partly funded by the Dutch Government (grant BSIK03009), the Netherlands Organization for Scientific Research (NWO-VICI grant 918.66.620, NWO-VENI grant 916.10.135 to L.F.), the Dutch Digestive Disease Foundation (MLDS WO11-30), and a Horizon Breakthrough grant from the Netherlands Genomics Initiative (grant 92519031 to L.F.). This project was supported by the Prinses Beatrix Fonds, VSB fonds, H. Kersten and M. Kersten (Kersten Foundation), The Netherlands ALS Foundation, and J.R. van Dijk and the Adessium Foundation. The research leading to these results has received funding from the European Communitys Health Seventh Framework Programme (FP7/2007-2013) under grant agreement 259867.

The EGCUT study received targeted financing from Estonian Government SF0180142s08, Center of Excellence in Genomics (EXCEGEN) and University of Tartu (SP1GVARENG). We acknowledge EGCUT technical personnel, especially Mr V. Soo and S. Smit. Data analyzes were carried out in part in the High Performance Computing Center of University of Tartu.

Tables

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

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

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

² Discovery dataset

³ Independent replication dataset

⁴ Meta analysis of interaction terms between replication datasets only

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: **Q-Q plots of interaction p -values from replication datasets**

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

Figure 3: **Discovery and replication of epistatic networks**

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

References

- ¹ Carlborg, O. & Haley, C. S. Epistasis: too often neglected in complex trait studies? *Nature Reviews Genetics* **5**, 618–25 (2004).
- ² Hill, W. G., Goddard, M. E. & Visscher, P. M. Data and Theory Point to Mainly Additive Genetic Variance for Complex Traits. *PLoS Genetics* **4** (2008).
- ³ Crow, J. F. On epistasis: why it is unimportant in polygenic directional selection. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* **365**, 1241–4 (2010).
- ⁴ Costanzo, M. *et al.* The genetic landscape of a cell. *Science (New York, N.Y.)* **327**, 425–31 (2010).
- ⁵ Bloom, J. S., Ehrenreich, I. M., Loo, W. T., Lite, T.-L. V. o. & Kruglyak, L. Finding the sources of missing heritability in a yeast cross. *Nature* 1–6 (2013).
- ⁶ Carlborg, O., Jacobsson, L., Ahgren, P., Siegel, P. & Andersson, L. Epistasis and the release of genetic variation during long-term selection. *Nature Genetics* **38**, 418–420 (2006).
- ⁷ Strange, A. *et al.* A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nature Genetics* **42**, 985–90 (2010).
- ⁸ Evans, D. M. *et al.* Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nature Genetics* **43** (2011).
- ⁹ Cordell, H. J. Detecting gene-gene interactions that underlie human diseases. *Nature Reviews Genetics* **10**, 392–404 (2009).
- ¹⁰ Hemani, G., Theocharidis, A., Wei, W. & Haley, C. EpiGPU: exhaustive pairwise epistasis scans parallelized on consumer level graphics cards. *Bioinformatics (Oxford, England)* **27**, 1462–5 (2011).
- ¹¹ Metspalu, A. The Estonian Genome Project. *Drug Development Research* **62**, 97–101 (2004).
- ¹² Fehrmann, R. S. N. *et al.* Trans-eQTLs reveal that independent genetic variants associated with a complex phenotype converge on intermediate genes, with a major role for the HLA. *PLoS genetics* **7**, e1002197 (2011).
- ¹³ Lieberman-Aiden, E. *et al.* Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science (New York, N.Y.)* **326**, 289–93 (2009).

- ¹⁴ Visscher, P. M., Brown, M. a., McCarthy, M. I. & Yang, J. Five years of GWAS discovery. *American journal of human genetics* **90**, 7–24 (2012).
- ¹⁵ Weinreich, D. M., Delaney, N. F., Depristo, M. a. & Hartl, D. L. Darwinian evolution can follow only very few mutational paths to fitter proteins. *Science (New York, N.Y.)* **312**, 111–4 (2006).
- ¹⁶ Breen, M. S., Kemena, C., Vlasov, P. K., Notredame, C. & Kondrashov, F. a. Epistasis as the primary factor in molecular evolution. *Nature* **490**, 535–538 (2012).
- ¹⁷ Weir, B. S. Linkage disequilibrium and association mapping. *Annual review of genomics and human genetics* **9**, 129–42 (2008).
- ¹⁸ Hemani, G., Knott, S. & Haley, C. An Evolutionary Perspective on Epistasis and the Missing Heritability. *PLoS Genetics* **9**, e1003295 (2013).
- ¹⁹ Marchini, J., Donnelly, P. & Cardon, L. R. Genome-wide strategies for detecting multiple loci that influence complex diseases. *Nature Genetics* **37**, 413–417 (2005).
- ²⁰ Lango Allen, H. *et al.* Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* **467**, 832–8 (2010).
- ²¹ Powell, J. E. *et al.* Congruence of Additive and Non-Additive Effects on Gene Expression Estimated from Pedigree and SNP Data. *PLoS Genetics* **9**, e1003502 (2013).
- ²² Powell, J. E. *et al.* The Brisbane Systems Genetics Study: genetical genomics meets complex trait genetics. *PloS one* **7**, e35430 (2012).
- ²³ Preiner, M. *et al.* Blood-informative transcripts define nine common axes of peripheral blood gene expression. *PLoS genetics* **9**, e1003362 (2013).
- ²⁴ Cockerham, C. C. An extension of the concept of partitioning hereditary variance for analysis of covariances among relatives when epistasis is present. *Genetics* **39**, 859–882 (1954).
- ²⁵ Ho, T. H. *et al.* Muscleblind proteins regulate alternative splicing. *The EMBO journal* **23**, 3103–12 (2004).
- ²⁶ Trynka, G. *et al.* Chromatin marks identify critical cell types for fine mapping complex trait variants. *Nature genetics* **45**, 124–30 (2013).
- ²⁷ Hoffman, M., Buske, O., Wang, J. & Weng, Z. Unsupervised pattern discovery in human chromatin structure through genomic segmentation. *Nature Methods* **9**, 473–476 (2012).
- ²⁸ Lan, X. *et al.* Integration of Hi-C and ChIP-seq data reveals distinct types of chromatin linkages. *Nucleic acids research* **40**, 7690–704 (2012).

- ²⁹ Osborne, C. S. *et al.* Active genes dynamically colocalize to shared sites of ongoing transcription. *Nature genetics* **36**, 1065–71 (2004).
- ³⁰ Rieder, D., Trajanoski, Z. & McNally, J. G. Transcription factories. *Frontiers in genetics* **3**, 221 (2012).
- ³¹ Visscher, P. M., Hill, W. G. & Wray, N. R. Heritability in the genomics era—concepts and misconceptions. *Nature Reviews Genetics* **9**, 255–66 (2008).
- ³² Churchill, G. A. & Doerge, R. W. Empirical threshold values for quantitative trait mapping. *Genetics* **138**, 963–71 (1994).

Supplementary Figures

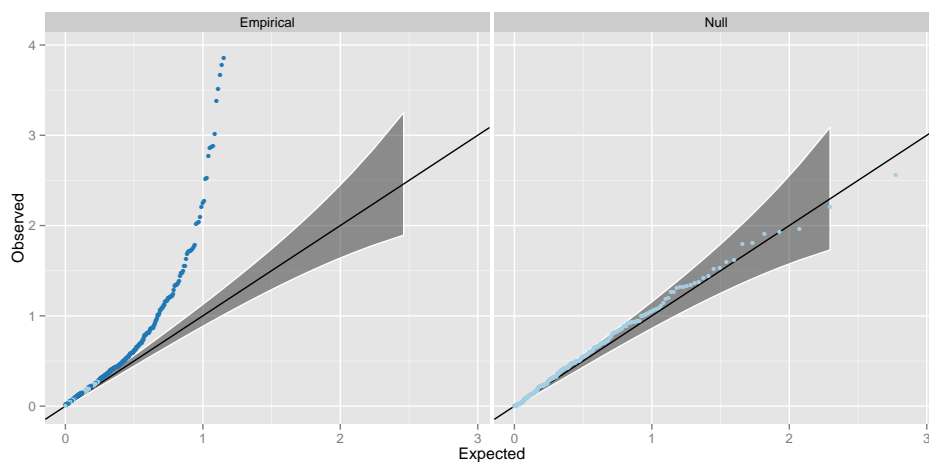


Figure S1: **Q-Q plots of interaction p -values from replication datasets, excluding the 30 points significant at the Bonferroni level** The right panel (Null) shows the interaction p -values from a meta analysis across two independent datasets on 434 randomly drawn SNP pairs. The left panel (Empirical) 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.

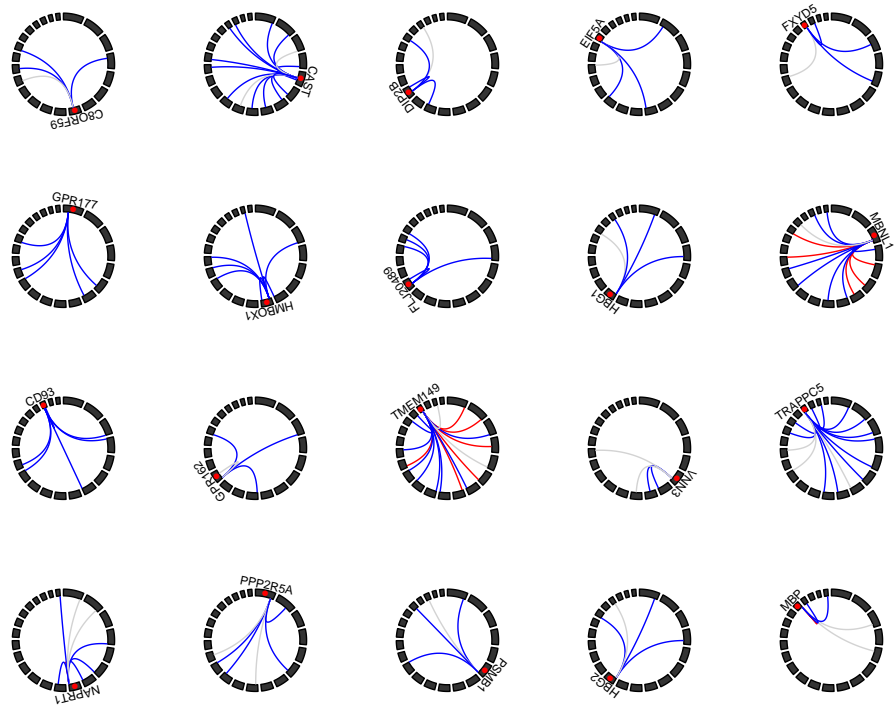


Figure S2: **Gene expression traits with four or more genetic interactions** Circle plots represent the genomic positions for SNPs (linking lines) and expression probes (red points). Chromosomes are represented by black blocks and ordered from 1 to 22 clockwise, starting from the top. Grey lines represent 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.

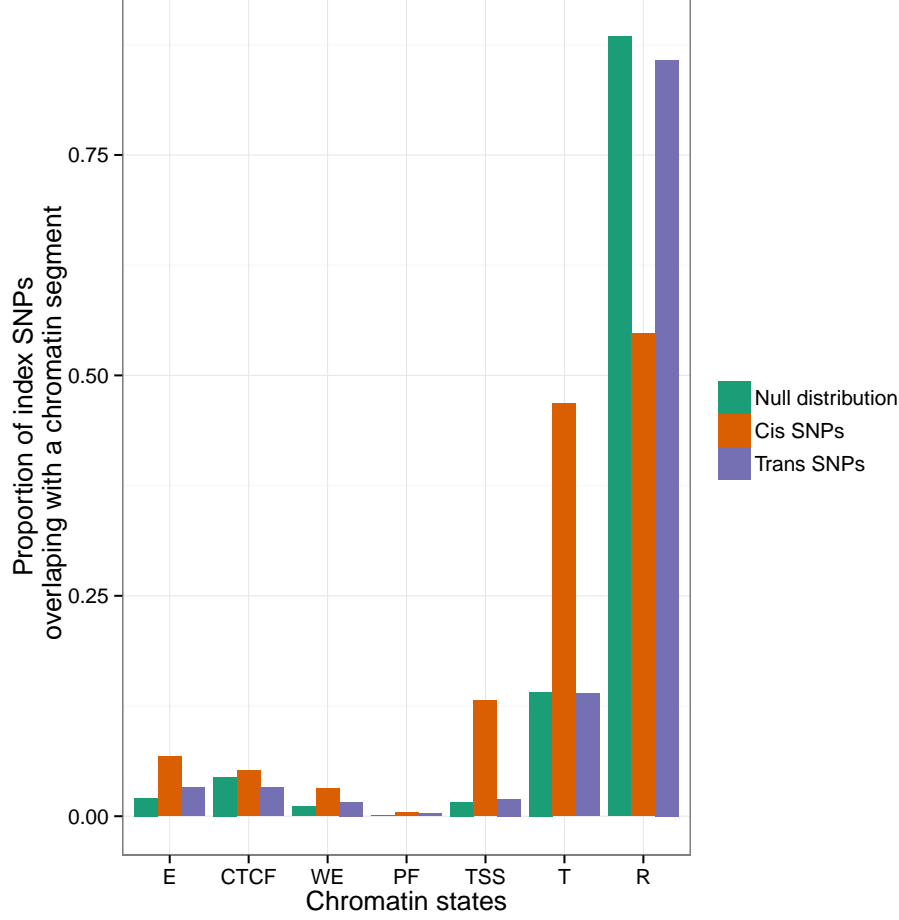


Figure S3: Location of SNPs relative to genomic features We used chromatin segmentation²⁷ as a method for labelling genomic features. All SNPs within 1Mb and $r^2 > 0.8$ of each *cis*- and *trans*-SNP were taken to find which genomic features (x -axis) were covered by the SNPs that compose the 501 significant interactions. Green bars represent the proportion (y -axis) of the 528,509 SNPs used in the analysis that fall within the range of the different genomic features. There is enrichment for *cis*-acting SNPs (red bars) in promotor regions, but *trans*-acting SNPs (blue bars) are not enriched for genomic features. The labels on the x -axis are as follows: E = Predicted enhancer, CTCF = CTCF enriched element, WE = Predicted weak enhancer or open chromatin cis regulatory element, PF = Predicted promoter flanking region, TSS = Predicted promoter region including transcriptional start site, T = Predicted transcribed region, R = Predicted Repressed or Low Activity region

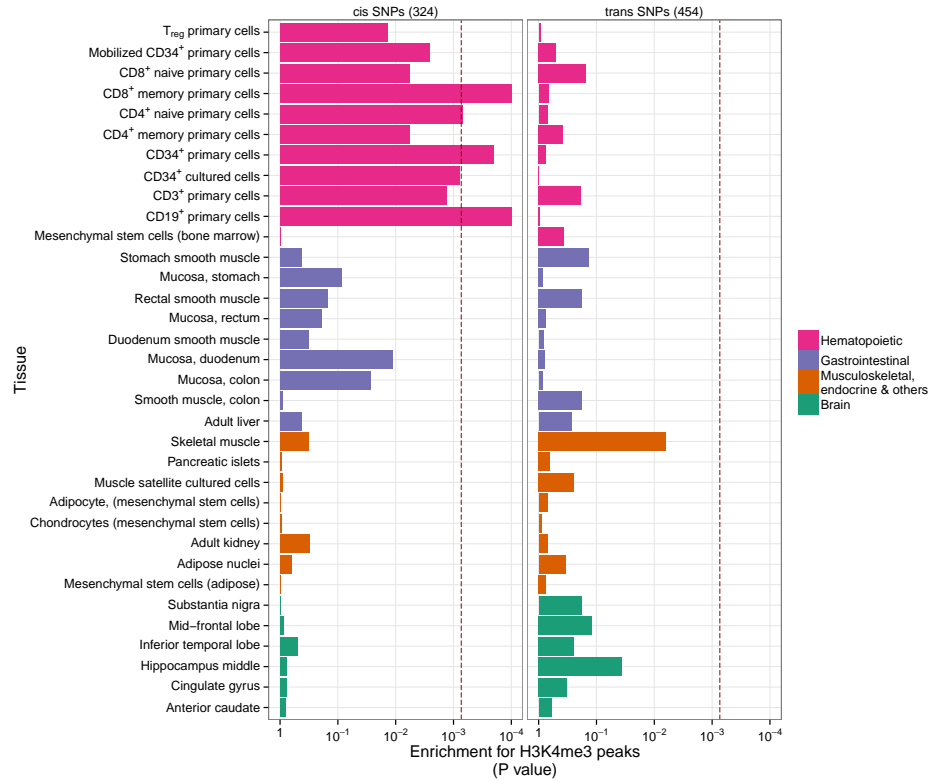


Figure S4: Tissue specific enrichment of SNPs in transcriptionally active regions The locations of transcriptional activity can be predicted by chromatin marks, assayed by H3K4me3.²⁶ Enrichment p -values are calculated using permutation analysis for 34 different cell types (y -axis) in four tissue types (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.

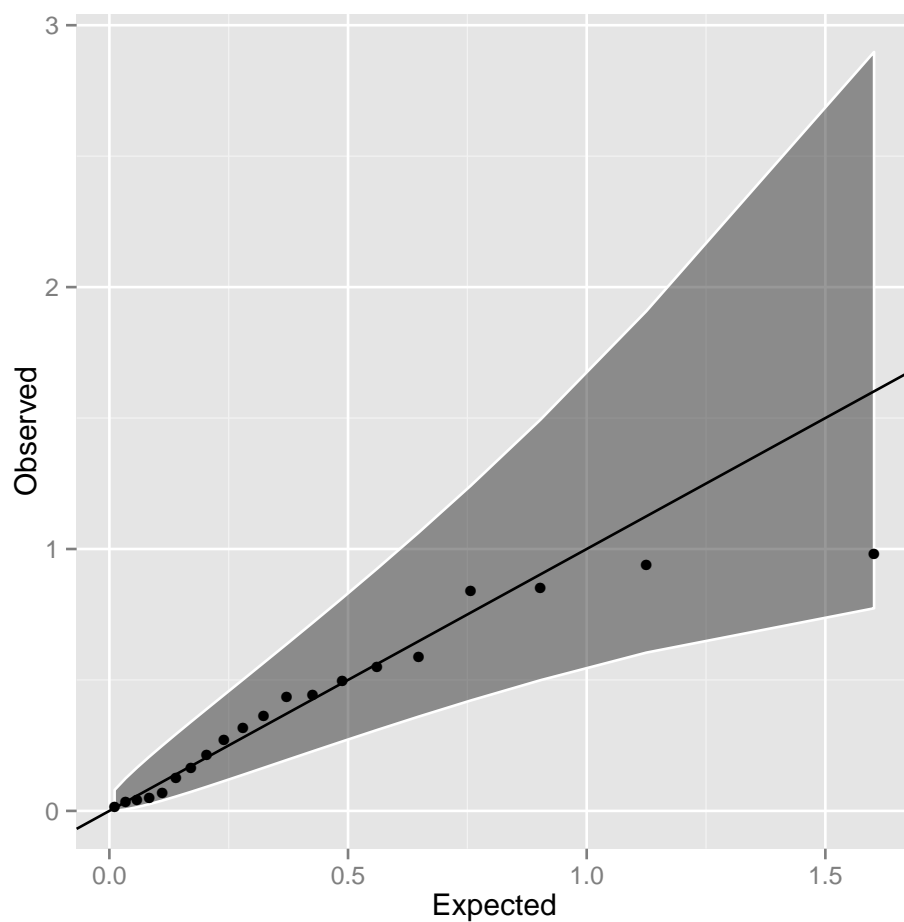


Figure S5: **Q-Q plot of interaction p -values in the CDHWB dataset**
 Twenty of the 501 discovery SNP pairs passed filtering in the CDHWB dataset (mainly due to small sample size). There is no evidence for enrichment of interaction terms, most likely due to insufficient power given the limited sample size.

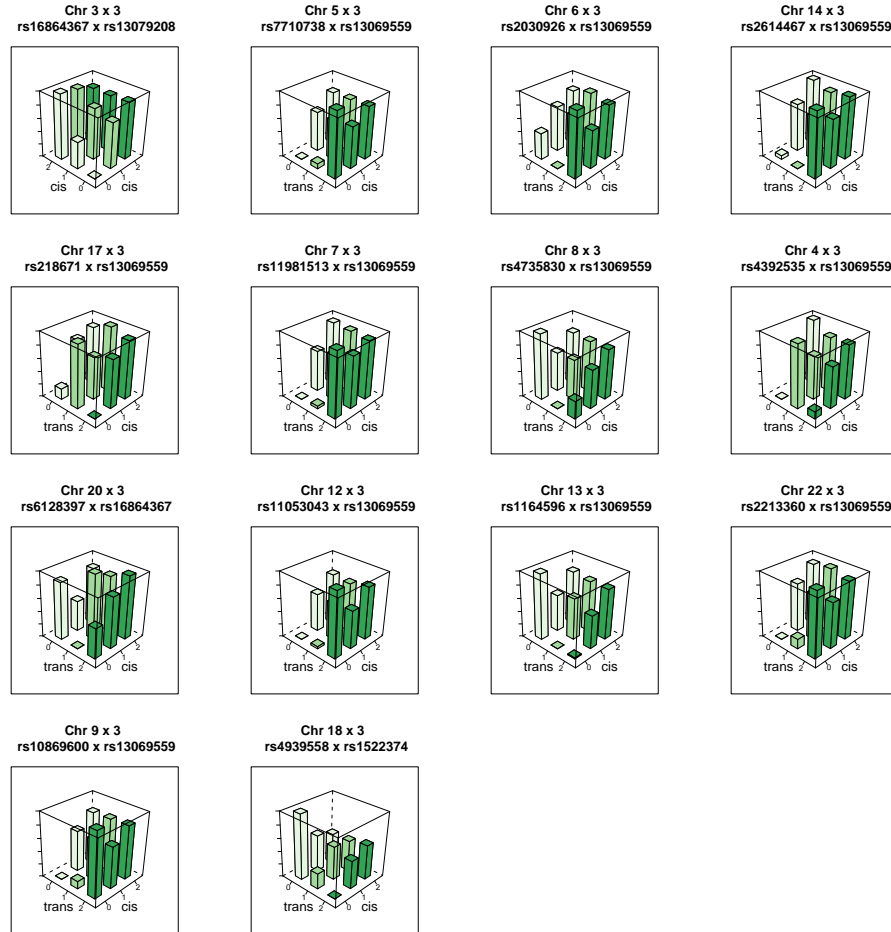


Figure S6: **Genotype-phenotype maps for 14 interactions influencing the expression of MBNL1** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of MBNL1, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous for the masking allele.

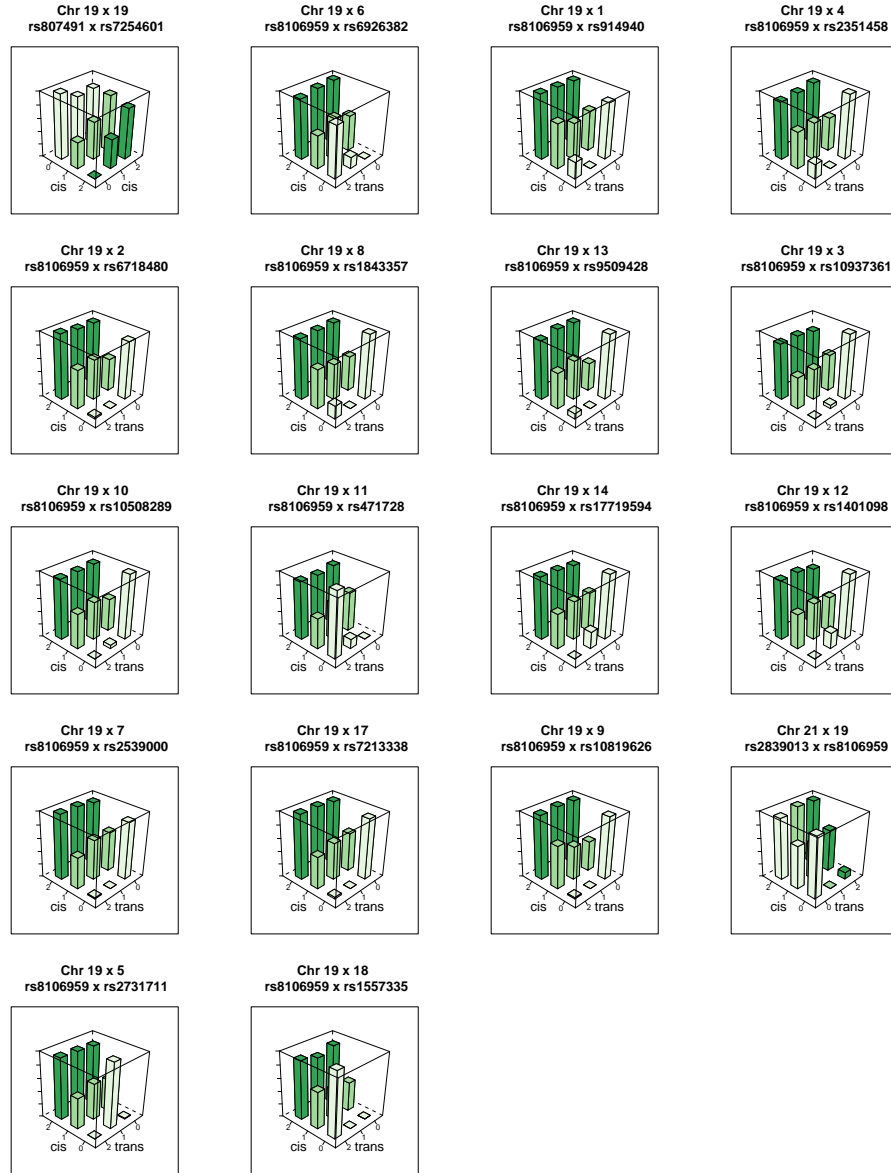


Figure S7: **Genotype-phenotype maps for 19 interactions influencing the expression of TMEM149** Each bar represents the mean phenotypic value for individuals in that genotype class. The rs13069559 SNP typically has a *cis*-additive decreasing effect on the expression of TMEM149, but in many of these interactions the *cis* effect is masked when the *trans* SNP is homozygous for the masking allele.

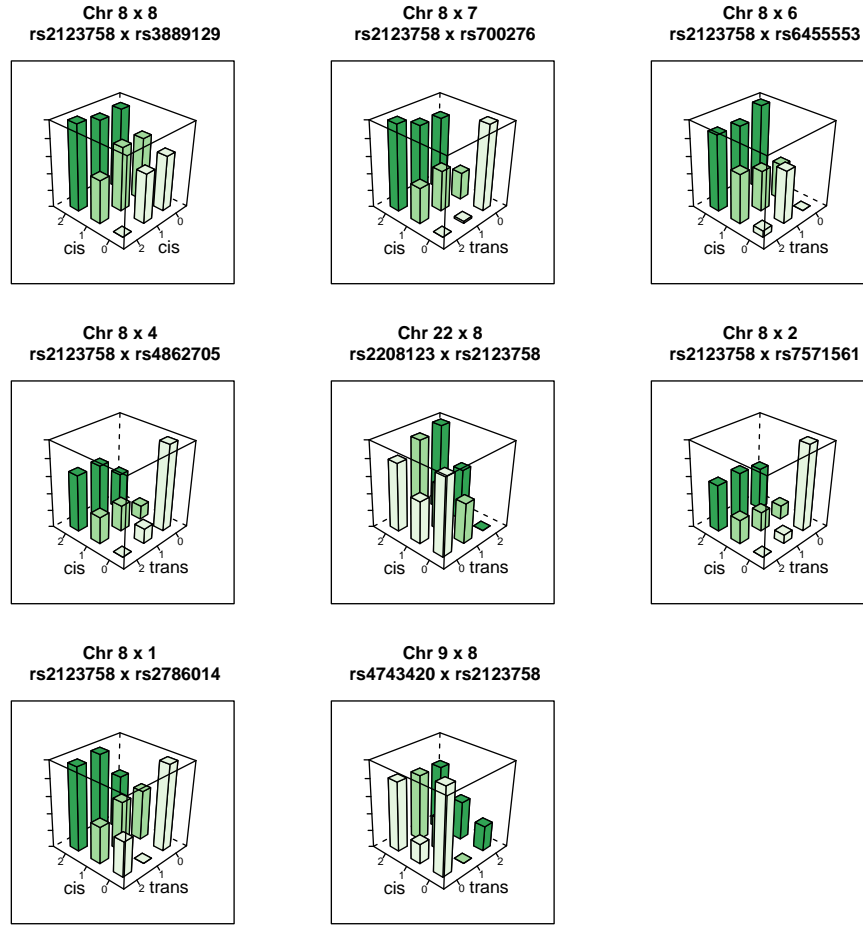


Figure S8: **Genotype-phenotype maps for 8 interactions influencing the expression of NAPRT1** Each bar represents the mean phenotypic value for individuals in that genotype class.

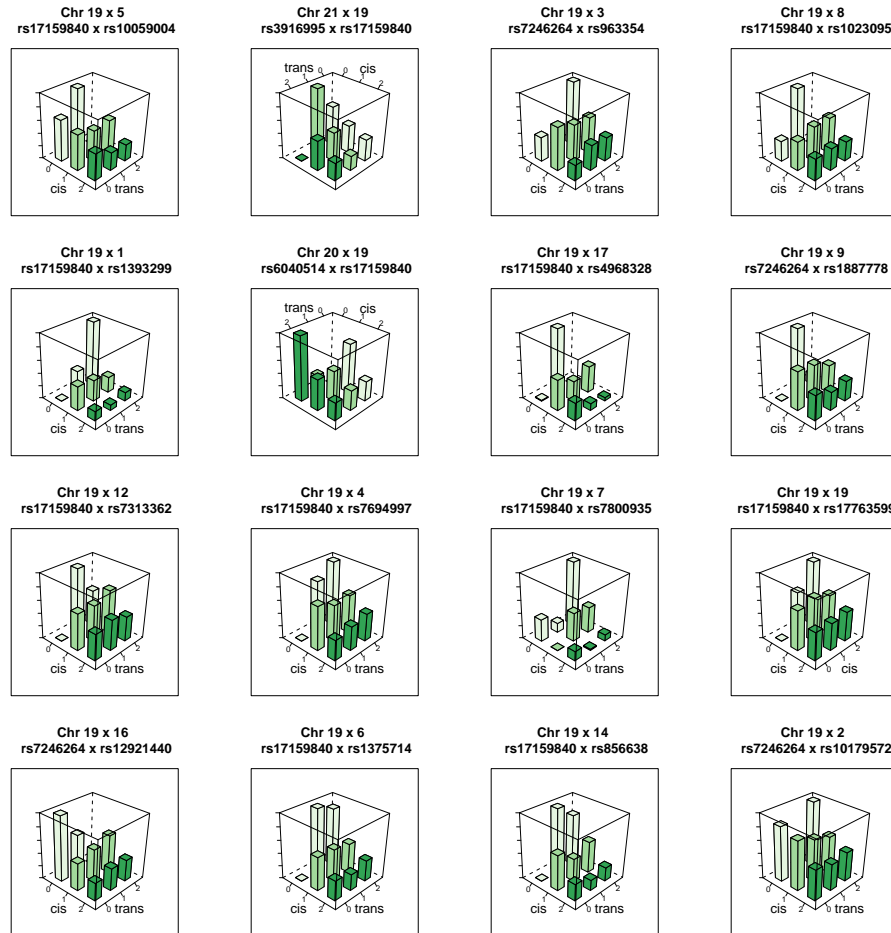


Figure S9: **Genotype-phenotype maps for 16 interactions influencing the expression of TRAPPC5** Each bar represents the mean phenotypic value for individuals in that genotype class.

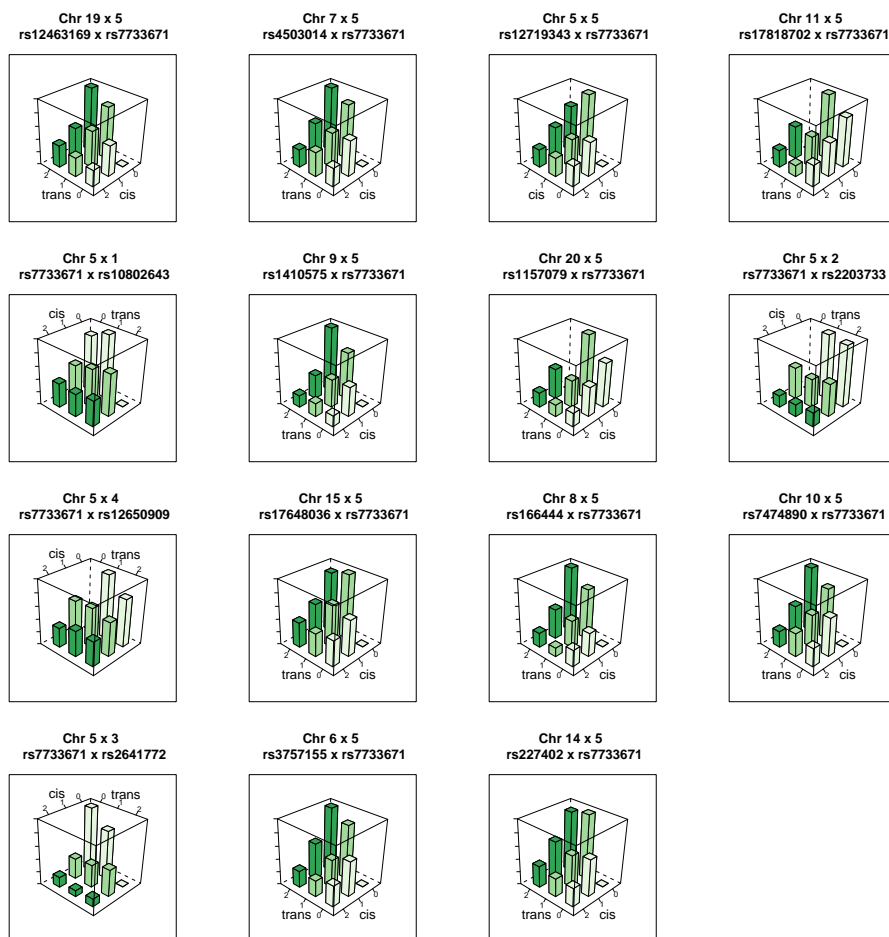


Figure S10: **Genotype-phenotype maps for 15 interactions influencing the expression of CAST** Each bar represents the mean phenotypic value for individuals in that genotype class.

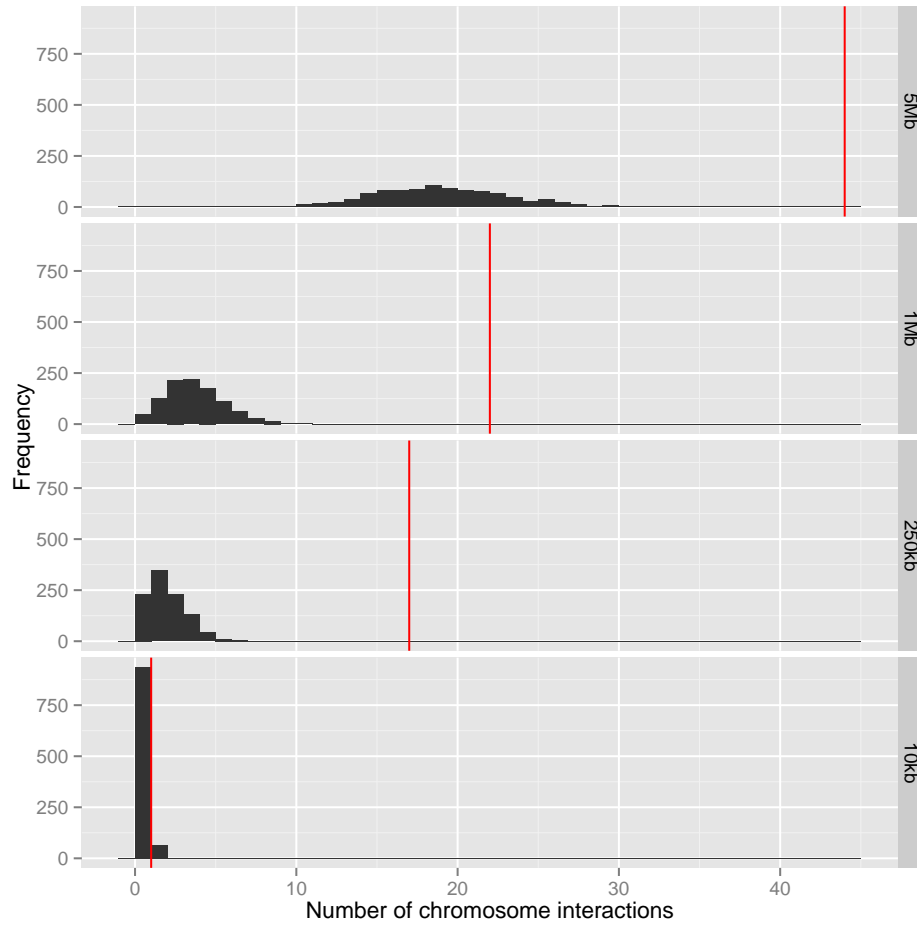


Figure S11: Number of overlaps between chromosome interactions and epistatic interactions Interacting chromosome regions may be a possible mechanism underlying epistatic interactions. The number of epistatic interactions within 20kb, 500kb, 2Mb and 10Mb of known chromosome interacting regions are shown by red vertical lines. The histograms represent the null distribution based on random sampling of 1,000 datasets for each window size.

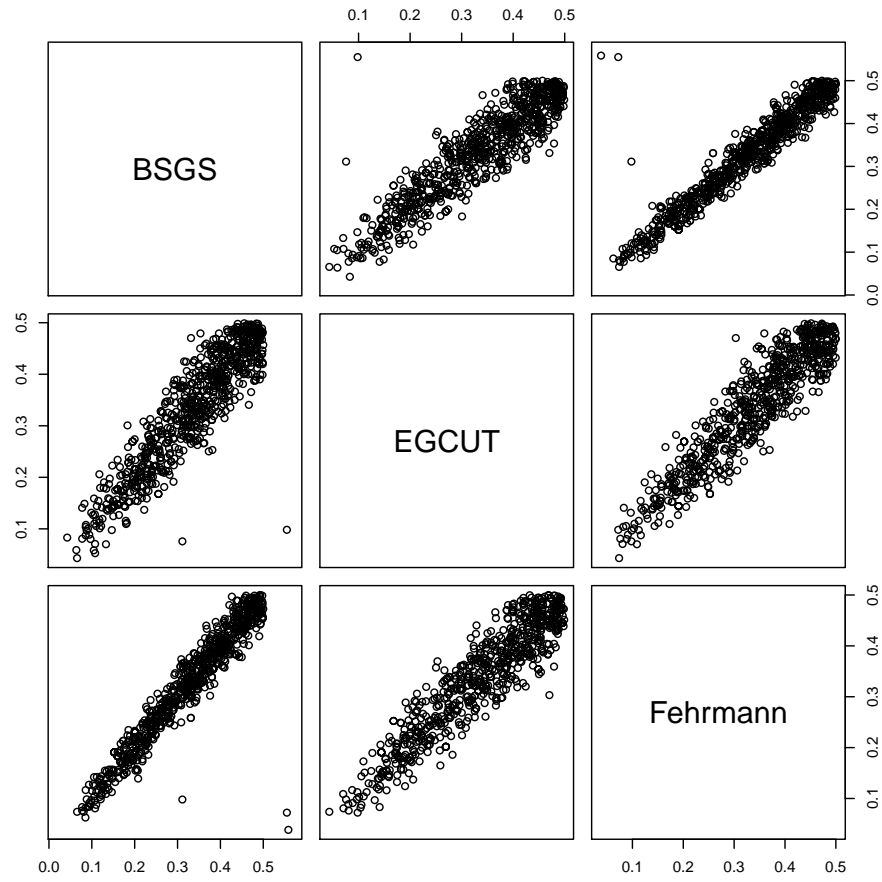


Figure S12: **Comparison of allele frequencies for 781 SNPs involved in genetic interactions across independent populations** Outliers were removed from the analysis as part of the filtering stage during replication.

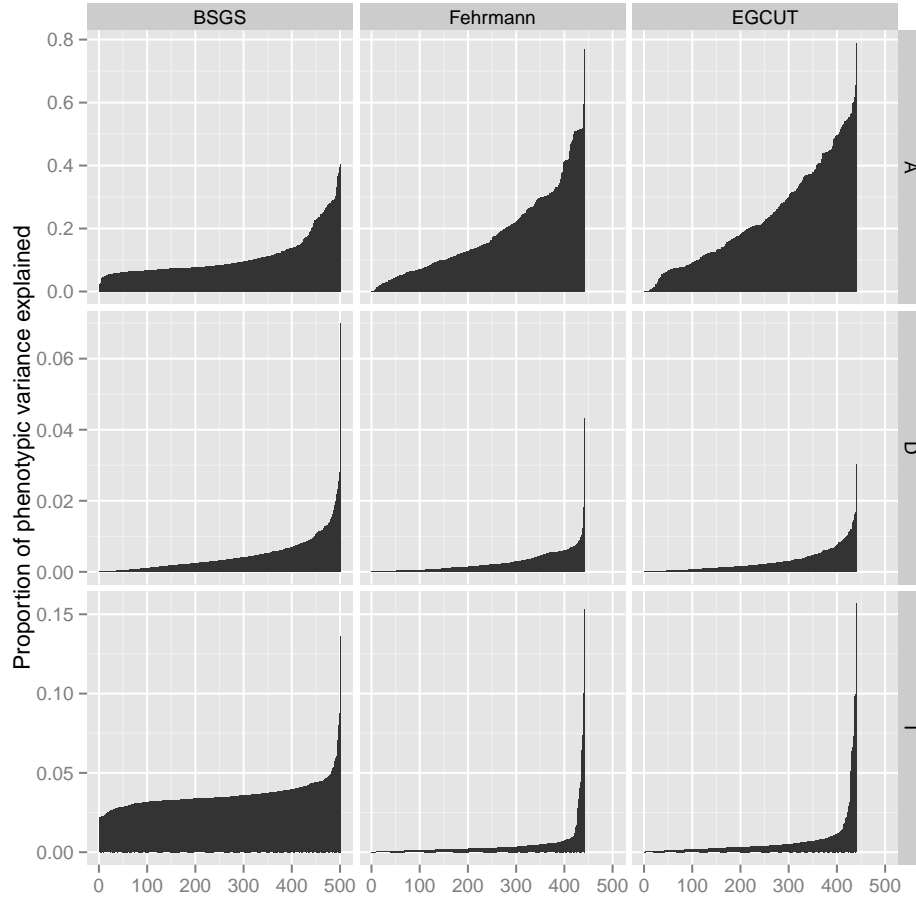


Figure S13: Comparison of variance explained by additive, dominant and epistatic effects from different cohorts How does the estimated variance decomposition change in different cohorts? The proportion of the phenotypic variance that is additive (A), dominant (D), or epistatic (I) for each putative interaction is shown on the y -axis (Note: different scales for each row). BSGS has 501 interactions whereas Fehrmann and EGCUT have 434 (x -axis). The variance estimates in each plot are ordered from lowest additive to highest. This is done independently for each cohort to depict the distribution of estimated effects.

Supplementary Tables

Table S1 – continued from previous page

Expression trait			SNP 1			SNP 2			Interaction statistic ^f / -log ₁₀ p-values			Distance / Mb ^h		
Gene ID ^a	Probe ID ^b	Chr.	rs ID	Chr.	Pos / Mb ^c	Association ^d	rs ID	Chr.	Pos / Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g
CBORF59	ILMN_1633205	8	rs8051751	16	7188323		rs2896452	8	86102223	CBORF59	5.79	1.39	0.18	0.87
CBORF72	ILMN_1741881	9	rs10122902	9	27556780	C9ORF72	rs2526698	1	227029101		6.36	0.96	0.01	0.37
CACB1	ILMN_1731064	10	rs12765847	10	4353908		rs3738725	1	227174210	CACB1	6.36	0.94	0.00	0.34
CARD9	ILMN_1712532	9	rs4266763	9	139289825	INPP5E	rs684040	1	82128660		5.81			
CAST	ILMN_1712532	11	rs4573661	11	6026661		rs4077515	9	139266496	INPP5E	6.61	0.09	0.86	0.42
CAST	ILMN_1717234	19	rs1157079	20	6778978		rs7733671	5	96000269	CAST	7.07	0.23	0.96	0.62
CAST	ILMN_1717234	5	rs12463169	19	17321669		rs7733671	5	96000269	CAST	5.73	0.02	2.85	1.75
CAST	ILMN_1717234	5	rs12599264	16	81840122		rs7733671	5	96000269	CAST	7.00			
CAST	ILMN_1717234	5	rs12719343	5	125369113		rs7733671	5	96000269	CAST	7.68	0.36	1.57	29.369
CAST	ILMN_1717234	5	rs1410575	9	78255630		rs7733671	5	96000269	CAST	6.55	0.13	1.34	0.78
CAST	ILMN_1717234	5	rs166444	8	78392770		rs7733671	5	96000269	CAST	7.01	0.27	0.52	0.37
CAST	ILMN_1717234	5	rs17648036	15	27311111		rs7733671	5	96000269	CAST	7.81	0.97	0.03	0.41
CAST	ILMN_1717234	5	rs17818702	11	86107920		rs7733671	5	96000269	CAST	6.62	1.15	0.59	1.09
CAST	ILMN_1717234	5	rs227402	14	70496867		rs7733671	5	96000269	CAST	6.12	0.11	0.01	0.01
CAST	ILMN_1717234	5	rs2822124	21	15166804		rs7733671	5	96000269	CAST	6.87			
CAST	ILMN_1717234	5	rs3757155	6	136458593		rs7733671	5	96000269	CAST	7.24	0.07	0.33	0.12
CAST	ILMN_1717234	5	rs4503014	7	31149140		rs7733671	5	96000269	CAST	5.88	1.56	1.72	0.92
CAST	ILMN_1717234	5	rs7474890	10	59590078		rs7733671	5	96000269	CAST	6.74	0.49	0.12	0.23
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs10802643	1	238120177		7.42	0.75	0.78	0.93
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs12650909	4	170192890		7.42	0.23	0.87	0.50
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs2203733	2	224093101		6.07	0.22	0.30	0.22
CAST	ILMN_1717234	5	rs7733671	5	96000269	CAST	rs2641772	3	195531841	CAT	6.93	0.19	0.26	0.15
CAT	ILMN_1651705	11	rs872311	18	66175386		rs11032695	11	34447586	CAT	6.31	0.26	0.30	0.22
CCDC88B	ILMN_1722208	11	rs23532303	19	17099980		rs541207	11	64125142	CCDC88B	5.68	0.33	0.37	0.31
CCDC88B	ILMN_1722208	11	rs694739	11	64097233	CCDC88B	rs12771349	10	96998193		5.62	0.23	0.18	0.14
CD36	ILMN_1784863	7	rs3211834	7	80280117		rs1254900	2	85516334	CD36	6.93	0.15	0.01	0.02
CD55	ILMN_1800540	11	rs7508015	11	76033374		rs10255470	7	157182030	CD55	5.09	0.08	0.03	0.02
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs4696726	4	7992632	VAMP8	6.06	1.74	0.24	1.20
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs7622580	3	196721395		5.71	0.13	0.80	0.42
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs838875	12	125145394		5.56	0.04	0.27	0.08
CD93	ILMN_1704730	20	rs1884655	20	23074375	CD93	rs8576388	13	38434472	CD93	6.31	0.24	1.67	1.16
CD93	ILMN_1704730	20	rs2868504	20	37771578		rs1884655	20	23074375		5.71	0.71	0.22	0.45
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs10925747	1	238899903		7.43			
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs2873420	8	136500554		7.02			
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs4328531	18	74439542		6.13			
CD93	ILMN_1704730	20	rs4813479	20	23076914	CD93	rs4789981	17	77264482		6.08			
CD93	ILMN_1704730	20	rs861544	14	104162263		rs7324744	13	115008038	CDK16	5.46	0.21	0.17	0.11
CDK5R1	ILMN_1730928	13	rs5905940	17	46614102	HOXB2	rs11655031	17	30831362	CDK5R1	5.47	0.95	0.07	0.45
CEACAM21	ILMN_1745949	19	rs200690	19	51956250		rs4803481	19	42066556	CEACAM21	6.15	0.90	0.12	0.48
CEACAM21	ILMN_1745949	19	rs4803481	19	42066556	CEACAM21	rs2421050	5	158943044	CEACAM21	6.67	2.16	0.16	1.44
CEP192	ILMN_1703754	18	rs6505780	18	13069782	CEP192	rs13132719	3	180265266		5.75	0.15	0.24	0.12
CEP63	ILMN_1787808	3	rs32825569	14	101350298		rs13079012	3	134247706	ANAPC13	6.36	0.23	0.10	0.09
CES1	ILMN_2259945	16	rs8192935	16	58681794	CES1	rs772788	2	235248562		5.65			
CHPT1	ILMN_2209240	12	rs591967	13	38838122		rs2695290	12	102087844	CHPT1	5.74	0.72	0.20	0.44
CHPT1	ILMN_2209240	12	rs6539014	12	102277782		rs867578	11	102087844		4.75	0.92	0.02	0.36
CLEC12A	ILMN_1663142	12	rs429790	16	84471642		rs7313235	12	10132283	CLEC12A	5.55	0.07	1.28	0.67
CLEC12A	ILMN_2403228	12	rs7305054	12	10156646		rs3903088	10	134236688		7.54	0.95	0.36	0.73
CLTB	ILMN_1674609	5	rs17129799	11	96929337		rs6863172	5	175595960	CLTB	5.55	0.27	0.07	0.02
CNN2	ILMN_1770290	19	rs3752237	19	1047161	ABCA7	rs169130	16	63121080		7.56	0.07	0.28	1.39
CNN2	ILMN_1770290	19	rs3752237	19	1047161	ABCA7	rs7336017	13	67713633		6.33	1.92	0.01	0.01
CP5F1	ILMN_1654545	8	rs4333645	8	145569535		rs1455268	4	61738094		5.74	0.10	0.01	0.01
CPVL	ILMN_1682928	7	rs12596791	16	26115562		rs2455884	7	29188475	CPVL		0.06	0.57	0.23

Continued on next page

Gene ID ^a	Expression trait	Chr.	rs ID	Chr.	SNP 1	Pos/Mb ^c	Association ^d	rs ID	Chr.	SNP 2	Pos/Mb ^c	Association ^d	BSGS ^e	Interaction statistic ^f – Fehrmann ^g	– log ₁₀ p-values	Metag ^h	Distance / Mb
CPV1	ILMN.1682928	7	rs2835998	21	39202070	4	188859080	rs245884	7	29188475	CPV1	5.55	0.19	0.03	0.04		
CPV1	ILMN.1813256	2	rs2131290	4	188859080	4	188859080	rs1531133	7	46843631	CPV1	5.47	0.28	0.10	0.12		
CRLS1	ILMN.1737685	20	rs16139887	20	5986234	20	5986234	rs14773927	25	62406408	CRLS1	6.18	0.10	0.36	0.15		
CS1B	ILMN.1761797	21	rs9979356	21	45230974	21	45230974	rs3761385	25	45198355	CS1B	11.99	25.20	16.72	42.27	0.033	
CTNNA1	ILMN.1804854	5	rs2494943	18	69500505	18	69500505	rs176382	5	138226767	CTNNA1	5.74	0.02	0.41	0.11		
CTSC	ILMN.1866347	11	rs9457684	11	88139983	11	88139983	rs7079264	10	108679892	CTSC	5.67	0.92	0.74	1.03		
CTSC	ILMN.2242463	11	rs7572236	22	26250645	22	26250645	rs7128352	11	88073757	CTSC	5.84	0.49	0.80	0.73		
CTSC	ILMN.2242463	11	rs7930237	11	88117962	11	88117962	rs556895	7	16	18.76	15.06	33.53	0.040			
CTSC	ILMN.1651886	10	rs7108734	11	11456027	11	11456027	rs12784396	10	102027407	CTSC	5.42	0.21	0.01	0.03		
CYBRD1	ILMN.1712305	4	rs2592948	4	129994690	4	129994690	rs88427	2	172368120	CYBRD1	5.89	0.23	0.53	0.34		
CYBRD1	ILMN.1712305	4	rs7852475	9	140698856	9	140698856	rs88427	2	172368120	CYBRD1	5.68	0.20	0.02	0.04		
CYBRD1	ILMN.2087692	2	rs11257679	10	12318284	10	12318284	rs88427	2	172368120	CYBRD1	5.81	0.39	1.87	1.47		
CYBRD1	ILMN.2087692	2	rs36137908	20	23344590	20	23344590	rs88427	2	172368120	CYBRD1	5.53	0.05	0.83	0.36		
CYBRD1	ILMN.2087692	2	rs88427	20	172368120	20	172368120	rs88427	2	160112881	CYBRD1	5.85	0.87	0.10	0.44		
CYBRD1	ILMN.1704985	3	rs6021982	20	36571928	20	36571928	rs7591849	2	219650616	CYBRD1	5.42	0.29	0.86	0.60		
DAB2	ILMN.2128428	5	rs7778910	7	10451383	7	10451383	rs835223	5	39381357	DAB2	5.44	0.48	0.41	0.44		
DAB2	ILMN.1811648	17	rs9600173	17	42481761	17	42481761	rs1343244	6	82076988	DAB2	9.12	0.00	0.58	0.12		
DDT	ILMN.1690982	22	rs5760102	22	2428761	22	2428761	rs2378341	3	187475208	DDT	5.62	0.64	0.25	0.42		
DDT	ILMN.1779001	9	rs4937097	13	125962645	13	125962645	rs7042042	7	32451144	DDT	5.31	0.61	0.29	0.41		
DDT	ILMN.1779001	9	rs4937097	13	125962645	13	125962645	rs219515	7	88204888	DDT	5.47	0.08	0.41	0.16		
DDT	ILMN.1783996	1	rs10120023	9	137810259	9	137810259	rs10120023	9	137810259	DDT	6.39	0.77	0.02	0.29		
DDT	ILMN.1783996	1	rs123633827	11	109703727	11	109703727	rs7566044	2	169960422	DDT	6.00	0.06	1.17	0.58		
DRH1	ILMN.1733998	12	rs1519956	12	89468283	12	89468283	rs7566044	2	169960422	DRH1	6.48	0.37	0			

Continued on next page

Table S1 – continued from previous page

Gene ID ^a	Expression trait	Chr.	SNP 1			SNP 2			Association ^d	Pos/Mb ^c	Chr.	Pos/Mb ^c	Association ^d	Interaction statistic / -log ₁₀ p-values			Distance / Mb ^h
			rs ID	Chr.	Pos/Mb ^c	rs ID	Chr.	Pos/Mb ^c						BSGS ^e	Fehrmann ^f	EGCUT ^g	
FEZ2	ILMN-1739586	2	rs2356400	19	44321776	rs13406184	2	36791226	FEZ2	5.78	0.14	0.33	0.16				
FEZ2	ILMN-1739586	2	rs969010	4	139963132	rs8310133	2	36810133	FEZ2	6.59	0.14	0.28	0.14				
FGD2	ILMN-2115005	6	rs4803848	6	46205050	rs831486	6	37001267	FGD2	5.69	0.12	0.25	0.11				
FGD2	ILMN-2115005	12	rs902634	10	133943951	rs831489	6	36999652	FGD2	5.49	1.20	0.11	0.66				
FLJ20489	ILMN-1778144	12	rs17615703	12	117036766	rs83782908	12	4169526	FLJ20489	5.81	0.06	0.70	0.29			68.867	
FLJ20489	ILMN-1778144	12	rs3782908	12	48169526	rs875111	4	167695601	FLJ20489	5.53	0.03	0.11	0.02				
FLJ20489	ILMN-1778144	12	rs4792199	17	7392118	rs3782908	12	48169526	FLJ20489	5.74	0.19	0.02	0.04				
FLJ20489	ILMN-1778144	12	rs4984440	15	97033129	rs3782908	12	48169526	FLJ20489	6.49	0.31	0.47	0.36				
FLJ20489	ILMN-1778144	12	rs7204135	16	50626195	rs3782908	12	48169526	FLJ20489	6.90	0.38	0.17	0.21				
FLJ20718	ILMN-1763663	16	rs9325634	21	43818790	rs2287197	16	50106594	FLJ20718	6.04	0.14	0.95	0.53				
FLJ43093	ILMN-2123450	6	rs17112712	14	10727627	rs6906101	6	36667610	FLJ43093	5.48	0.39	0.06	0.13			3.962	
FLJ43093	ILMN-2123450	6	rs6906101	6	36667610	rs13214069	6	32705248	FLJ43093	5.44	0.00	0.64	0.18			0.063	
FN3KBP	ILMN-1652333	17	rs898095	17	80890638	rs9892064	17	80827903		16.16	28.24	29.39	59.95				
FUCA1	ILMN-1752728	1	rs4971478	2	1346063	rs12744386	1	24168019	FUCA1	6.41	0.01	0.30	0.06				
FXD5	ILMN-2309848	19	rs1633921	19	35695200	rs98328515	13	98328559		3.70	0.09	0.41	0.17				
FXD5	ILMN-2309848	19	rs2285515	19	356609148	rs2285515	19	35660450	FXD5	6.58	0.03	0.48	0.15				
FXD5	ILMN-2309848	19	rs2285515	19	35660450	rs11739594	5	141709563		5.70	0.07	0.17	0.25				
FXD5	ILMN-2309848	19	rs2285515	19	35660450	FXD5	3	95331048		6.00	0.09	0.51	0.02				
G3BP2	ILMN-2309848	4	rs2285515	19	35660450	FXD5	2	47567329		6.10	0.28	0.08	0.37				
G3BP2	ILMN-2381758	4	rs10230232	7	29390239	rs1553985	4	76554604		5.19	0.08	0.40	0.14				
GAA	ILMN-2410783	17	rs1159847	17	78153130	rs12602462	17	78146016		13.91	19.98	12.99	32.60			0.007	
GAA	ILMN-2410783	17	rs8068856	17	75100731	rs1092506	12	132678089		5.95	0.11	0.39	0.17				
GAPT	ILMN-1675191	5	rs10070322	5	57786110	rs7605821	2	235695238		5.85	0.01	0.78	0.28				
GAPT	ILMN-1675191	7	rs7082031	10	128038717	rs10070522	5	57786110	GAPT	5.72	0.26	0.11	0.11				
GATS	ILMN-1696631	7	rs1147447	14	6640742	rs2950520	7	99827148	GATS	5.47	0.83	0.63	0.87				
GATS	ILMN-1696631	7	rs2423256	14	35056572	rs2950520	7	99827148	GATS	6.22	0.42	0.35	0.33				
GDPD3	ILMN-1774901	16	rs3809624	16	30102802	rs2197465	14	48972632		6.57	0.38	0.35	0.24				
GDPD3	ILMN-1774901	16	rs7204270	16	30156963	rs1015111	4	128972357		5.86	0.55	0.09	0.24				
GNLY	ILMN-1790692	13	rs4145072	13	110899955	rs7577293	2	85935282	GNLY	5.78	0.02	0.45	0.13				
GNLY	ILMN-3239426	12	rs7198646	16	26084476	rs7577293	2	85935282	GNLY	5.72	0.36	0.46	0.39				
GPR162	ILMN-1730816	12	rs1860563	16	6478898	rs2707210	12	6902002	GPR162	5.49	0.03	0.06	0.06			72.784	
GPR162	ILMN-1730816	12	rs2272500	12	79685913	rs2707210	12	6902002	GPR162	5.07	0.25	0.03	0.06				
GPR162	ILMN-1730816	12	rs2707210	12	6902002	rs4740848	9	6554558		5.47	0.25	0.06	0.07				
GPR162	ILMN-1730816	12	rs2707210	12	6902002	rs9827054	3	188880113		5.47	0.96	0.66	0.44				
GPR177	ILMN-1660549	1	rs11057383	12	124368421	rs12065581	1	68732819	GPR177	5.45	0.72	0.67	0.81				
GPR177	ILMN-1660549	1	rs12572741	6	120408039	rs12065581	1	68732819	GPR177	5.76	0.17	0.40	0.22				
GPR177	ILMN-1660549	1	rs12532999	7	127939793	rs12065581	1	68732819	GPR177	5.43	0.79	1.43	1.50				
GPR177	ILMN-1660549	1	rs725613	16	11169683	rs12065581	1	68732819	GPR177	6.50	0.31	0.11	0.13				
GPR177	ILMN-1660549	1	rs9575097	13	82986268	rs12065581	1	68732819	GPR177	6.04	0.95	0.21	0.60				
GPR177	ILMN-2283325	1	rs6566669	18	70506011	rs12065581	1	68732819	GPR177	5.86	0.24	0.34	0.23				
GPR177	ILMN-2283325	1	rs9290426	3	171399321	rs12065581	1	68732819	GPR177	6.50	0.01	0.24	0.04				
GSDMB	ILMN-2347193	17	rs11557467	17	38028634	rs4965745	15	101508261		5.88	0.68	0.20	0.41				
GSTM1	ILMN-2391861	1	rs12248673	10	8534527	rs11101992	1	110266754	GSTM1	6.11	0.27	0.19	0.16				
GSTM1	ILMN-2391861	1	rs1547574	13	96150560	rs3754446	1	110253241	GSTM1	5.91	0.27	1.14	0.79				
GSTM2	ILMN-2201580	22	rs6492807	22	38399979	rs453333	2	77919015		6.77	0.52	0.66	0.65				
H1FO	ILMN-1757467	22	rs139898	22	38399979	rs6497007	15	85877017		6.36	0.27	0.31	0.23				
H1FO	ILMN-1757467	22	rs139898	22	38399979	rs9893949	21	19532546		6.52	0.25	0.48	0.32				
H1FO	ILMN-1757467	22	rs139898	22	38399979	rs2855039	11	5271671	HBC2	5.47	0.00	0.66	0.19				
HBC1	ILMN-1796678	11	rs11078523	17	4523167	rs2855039	11	5271671	HBC2	5.98	0.15	0.24	0.12				
HBC1	ILMN-1796678	11	rs12975066	11	32723501	rs12042181	1	213088494	LQK1	6.78	0.08	0.32	0.21				
HBC1	ILMN-1796678	11	rs2855039	11	5271671	rs12503379	4	141533832		6.42	0.01	0.46	0.11				
HBC1	ILMN-1796678	11	rs2855039	11	5271671	HBC2	1	213088494		6.06	0.01	0.41	0.10				

Continued on next page

Table S1 – continued from previous page

[illegible]

Continued on next page

Table S1 – continued from previous page

Gene ID ^a	Expression trait		SNP 1		SNP 2		Interaction statistic ^f / -log ₁₀ p-values		Distance / Mb ^b
	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	
NRBF2	rs6025645	20	56157341		rs7923609	10	65133822	NRBF2	5.45
ILMN-3237385	rs6517815	1	19819016		rs7923609	10	65133822	NRBF2	6.11
ILMN-1800987	rs4852124	21	240680022		rs6586415	1	52343047		6.13
ILMN-1767885	rs1017351	11	23453482		rs1005901	8	21964378	NUDT18	0.47
ILMN-1668247	rs11613438	12	113486081		rs1047944	1	163907467		0.03
ILMN-1767640	rs10051414	11	161909252		rs37411981	12	113490260	OAS1	1.27
ILMN-2381899	rs1802233	10	161909252		rs37411981	12	113490260	OAS1	0.81
ILMN-2381899	rs1026163	16	74286646		rs17512962	11	13169066	OPN1	3.56
ILMN-2307032	rs192613	16	74286646		rs9884639	11	3149249	OSBPL5	0.46
ILMN-1742456	rs2829679	19	26662543		rs9884639	11	3149249	OSBPL5	0.14
ILMN-1742456	rs17780195	17	70624189		rs2273770	9	77755469	OSTF1	0.00
ILMN-1742456	rs2273770	9	77755469	OSTF1	rs2273770	9	77755469	OSTF1	0.07
ILMN-1734542	rs10802822	1	240132968		rs7718088	5	179509052		0.87
ILMN-2313901	rs347331	3	140148107		rs1264898	1	111992823	OVGP1	1.20
ILMN-2313901	rs28092	5	102149795	PAM	rs1264898	1	111992823	OVGP1	0.08
ILMN-1815951	rs2438490	5	148726162	PCYOX1L	rs784600	1	40139553	HVPCAL4	1.48
ILMN-1660232	rs10444467	12	128052636		rs2731939	3	21395989		0.25
ILMN-1660232	rs7495797	15	27464642		rs4329748	12	7364442	PEX5	0.26
ILMN-1797893	rs131969	22	49151303		rs4329748	12	7364442	PEX5	0.19
ILMN-1704870	rs12982353	19	46529456	PGLYRP1	rs7328733	13	33126737	PFAAP5	0.34
ILMN-1812552	rs1493642	11	123097386		rs1263806	14	21982957		0.87
ILMN-1719986	rs4141404	22	31675185	PIK3P1	rs10736812	11	76708086	PHCA	0.03
ILMN-1793934	rs470072	22	32263131		rs2065841	11	60738597		0.65
ILMN-1793934	rs6518752	22	31999127	PISD	rs10498313	14	30398876		0.20
ILMN-1793934	rs115572	22	33234931		rs954627	1	18236681		0.01
ILMN-1774604	rs6869411	15	158781604		rs618754	22	32097775		0.00
ILMN-1662587	rs91163998	16	4527109		rs4672884	2	219182481	PISD	0.05
ILMN-16765656	rs911019	20	49668255		rs928046	9	140487108	PNPLA7	0.42
ILMN-1662617	rs12914603	15	58350896		rs11156875	11	7559989	PNPLA7	0.16
ILMN-1738784	rs10930170	12	123595064		rs12120009	1	212447167	PPFBP2	0.31
ILMN-1738784	rs12423255	12	123595064		rs12120009	1	212447167	PPFBP2	0.29
ILMN-1738784	rs6822691	11	66222691		rs12120009	1	212447167	PPFBP2	0.44
ILMN-1738784	rs1889083	13	107471238		rs12120009	1	212447167	PPFBP2	0.19
ILMN-1738784	rs7757871	1	60401945		rs12120009	1	212447167	PPFBP2	0.08
ILMN-1738784	rs7871178	9	27148475		rs12120009	1	212447167	PPFBP2	0.13
ILMN-1738784	rs8019823	16	93504082		rs12120009	1	212447167	PPFBP2	0.28
ILMN-1713603	rs1288355	14	25867776		rs11600990	11	64682807	PPFBP2	0.06

Continued on next page

Table S1 – continued from previous page

Gene ID ^a				Expression trait				SNP 1				SNP 2				Interaction statistic ^f				BGS ^g				-log ₁₀ p-values				Distance / Mb ^b	
Gene	ID ^a	Chr.	Probe ID ^b	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	BGS ^g	Fehrmann ^f	EGCUT ^e	Meta ^g	EGCUT ^e	Meta ^g	Distance	Mb ^b						
RENE	ILMN_1802830	1	rs4982958	14	24987865			rs301819	1	8501786	RENE	1	8501786	RENE	1	8501786	5.66	0.61	1.23	1.17									
RENE	ILMN_1802838	1	rs7697290	4	135248366			rs301819	1	8501786	RENE	1	8501786	RENE	1	8501786	5.74	0.14	0.10	0.06									
RENE	ILMN_1802840	1	rs11085629	19	13174312			rs301819	1	8501786	RENE	1	8501786	RENE	1	8501786	5.12	0.21	0.33	0.21									
RENE	ILMN_2327795	14	rs38520111	3	12844086		RNASE6	rs301819	1	8501786	RENE	1	8501786	RENE	1	8501786	5.71	0.08	0.60	0.26									
RENE	ILMN_2327795	14	rs10218598	14	21182850			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795	14	rs38520111	3	12844086			rs75234365	13	100601327	RNASE6	13	100601327	RNASE6	13	100601327	5.48	0.42	0.21	0.26									
RENE	ILMN_2327795																												

Continued on next page

Table S1 – continued from previous page

[illegible]

Continued on next page

Table S1 – continued from previous page

Expression trait			SNP 1			SNP 2			Interaction statistic / $-\log_{10}$ p-values						
Gene ID ^a	Probe ID ^b	Chr.	rs ID	Chr.	Pos/Mb ^c	Association ^d	rs ID	Chr.	Pos/Mb ^c	Association ^d	BSGS ^e	Fehrmann ^f	EGCUT ^g	Meta ^g	Distance / Mb ^h
UBASH3A	LMN-2338348	21	rs1893592	21	43855067	UBASH3A	rs7201194	16	83600397		5.91	0.59	0.42	0.52	
UBASH3A	LMN-2338348	21	rs1893592	21	43855067	UBASH3A	rs7512594	1	214517361		6.01	0.48	1.29	1.10	
USP36	LMN-1697227	17	rs2279308	17	76794981	USP36	rs7225546	17	75151717		5.71	0.03	0.14	0.03	1.643
VASP	LMN-1743646	19	rs1264226	19	40663167		rs2276470	19	45974668	VNN2	5.09	0.94	5.14	4.95	0.088
VNN2	LMN-1678939	6	rs10435352	7	103252718		rs1883613	6	133077063	VNN2	5.64	0.84	0.15	0.46	
VNN2	LMN-1678939	6	rs13044386	20	9116155		rs1883617	6	133072650	VNN2	5.44	0.39	0.69	0.57	
VNN2	LMN-1678939	6	rs134447	22	49927332		rs1883617	6	133072650	VNN2	5.72				
VNN3	LMN-1678939	6	rs216495	11	16834510		rs1883617	6	133072650	VNN2	5.77	0.33	0.19	0.19	
VNN3	LMN-1678939	6	rs10278073	7	151662184		rs2267932	6	133067782	VNN3	6.44	0.16	0.74	0.41	
VNN3	LMN-1804935	6	rs1443946	8	73006453		rs2267952	6	133067782	VNN3	5.74	0.23	0.48	0.31	
VNN3	LMN-1804935	6	rs348462	9	75547169		rs2267952	6	133067782	VNN3	6.44	0.31	0.17	0.17	
VNN3	LMN-1804935	6	rs7157055	14	83262064		rs2267952	6	133067782	VNN3	5.82	0.03	0.19	0.04	
VNN3	LMN-2387680	6	rs2823165	21	5694253		rs2267952	6	133067782	VNN3	6.12	0.73	1.15	1.21	
VNN3	LMN-2387680	6	rs9596457	13	51692548		rs2267952	6	133067782	VNN3	4.83	0.46	0.05	0.16	
VSTM1	LMN-1763455	19	rs10500316	19	54553697	VSTM1	rs4552100	18	71024750		5.60	0.53	0.54	0.57	
VSTM1	LMN-1763455	19	rs10500316	19	54553697	VSTM1	rs7895870	10	123095249		5.71	0.48	0.17	0.26	
VSTM1	LMN-1763455	19	rs9628570	22	30261219		rs10500316	19	54553697	VSTM1	5.88	0.81	1.38	1.47	
WDR48	LMN-1762103	3	rs1388935	4	18827822		rs6778963	3	39091812	WDR48	5.88	0.19	0.13	0.09	
WDR48	LMN-1762103	3	rs1887778	9	134635088		rs833349	3	39067925	WDR48	6.34	0.57	1.35	1.22	
WDR6	LMN-1762103	3	rs9554833	13	102624790		rs7619193	3	39044116	WDR6	5.85	0.18	0.61	0.35	
WDR6	LMN-1669484	3	rs12362253	11	123571708		rs7619193	3	39044116	WDR6	5.85	0.18	0.61	0.35	
XAF1	LMN-2330573	17	rs1535031	21	6673170	XAF1	rs11715581	3	49194331		4.86	1.64	1.43	2.25	
XAF1	LMN-2330573	17	rs9064476	17	39064068		rs12591171	15	93119799		5.48	2.38	0.17	1.63	
ZFP90	LMN-1684628	16	rs182968	16	37040648		rs1182968	16	68573945	ZFP90	5.79	0.09	0.36	0.15	
ZNF500	LMN-1700238	16	rs4823723	22	48283177		rs2290560	16	4799041	ZNF500	5.29	0.67	0.27	0.46	
ZNF500	LMN-1700238	16	rs4823723	22	48283177		rs2242601	7	143093824	ZYX	6.04	0.26	0.01	0.05	
ZYX	LMN-1701875	7	rs6056281	20	8953512		rs2242601	7	143093824	ZYX					

^a Phenotypes are expression levels of RefSeq Genes^b Illumina probe ID used to measure gene expression^c Physical SNP position in base pairs (HG19)^d RefSeq Gene ID of gene expression level that is influenced by the SNP (BSGS discovery dataset, significance threshold = 1.29 × 10⁻¹¹)^e Interaction – log₁₀ p -value from discovery dataset^f Interaction – log₁₀ p -value from replication dataset^g Interaction – log₁₀ p -value from meta analysis of replication datasets only^h Distance in Mb between interacting SNPs for *cis-cis* acting SNP pairsⁱ p -values are absent if the interaction did not pass the QC filtering in the replication dataset^j Meta analysis p -values are absent if the interaction did not pass the QC filtering in either replication dataset

Table S2: **Estimation of additive and non-additive variance components from pedigree information** Taken from previous analysis in Powell et al 2013²¹

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