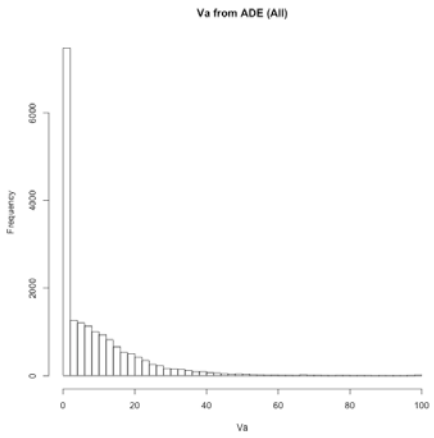
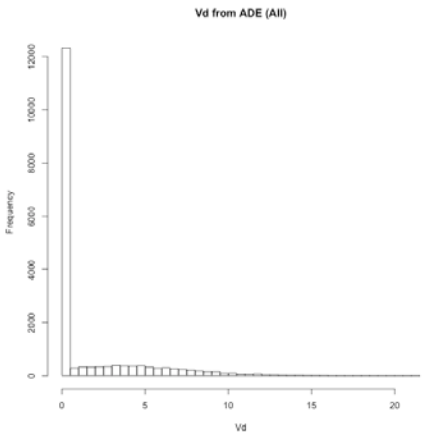
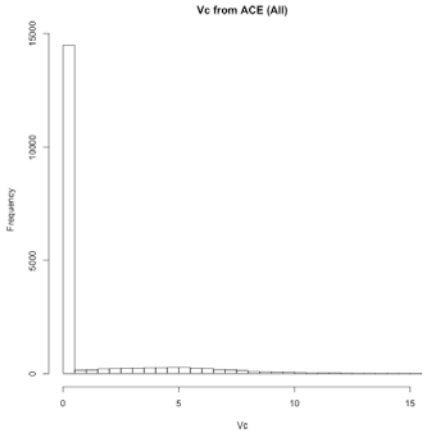
a)

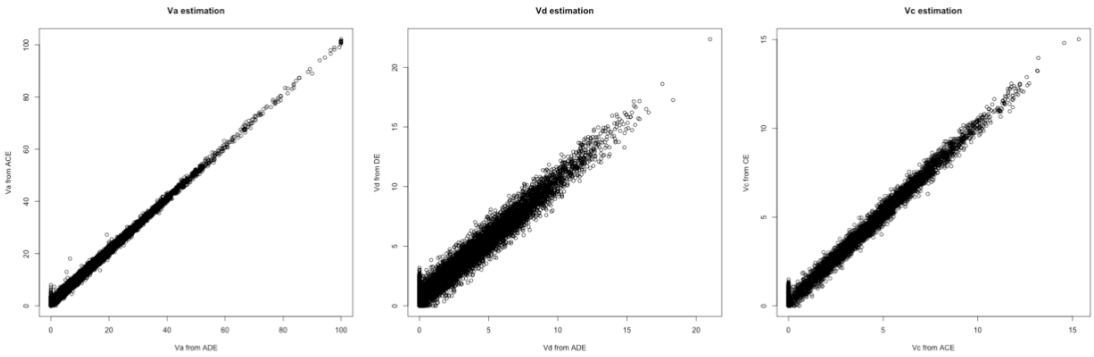

Va from ADE (All)
Frequency
0
2000
4000
6000
0
20
40
60
80
100
Va

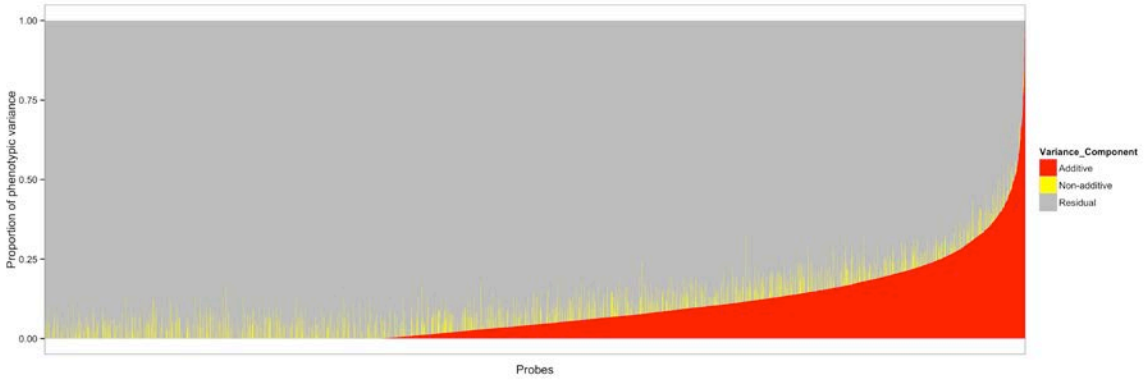
b)


Vd from ADE (All)
Frequency
0
2000
4000
6000
8000
10000
12000
0
5
10
15
20
Vd

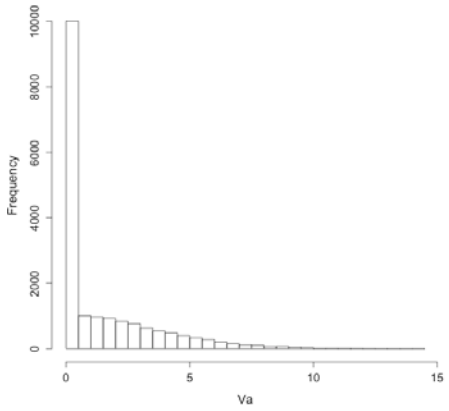
c)


Vc from ACE (All)
Frequency
0
5000
10000
15000
0
5
10
15
Vc

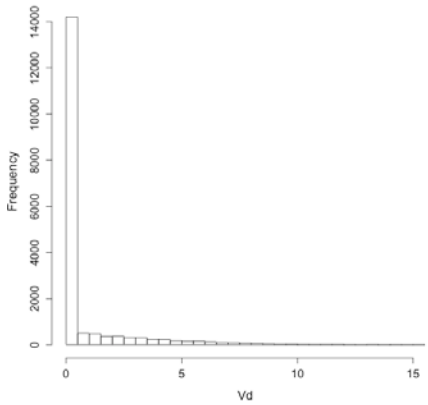

Va estimation
Va from ACE
Va from ADE
0
20
40
60
80
100
Vd estimation
Vd from DE
Vd from ADE
0
5
10
15
20
Vc estimation
Vc from CE
Vc from ACE
0
5
10
15


1.00
0.75
0.50
0.25
0.00
Proportion of phenotypic variance
Probes
Variance_Component
Additive
Non-additive
Residual

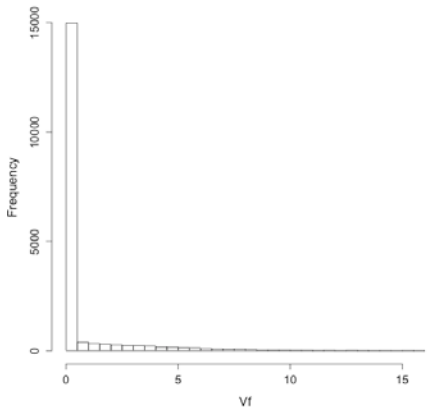
a)

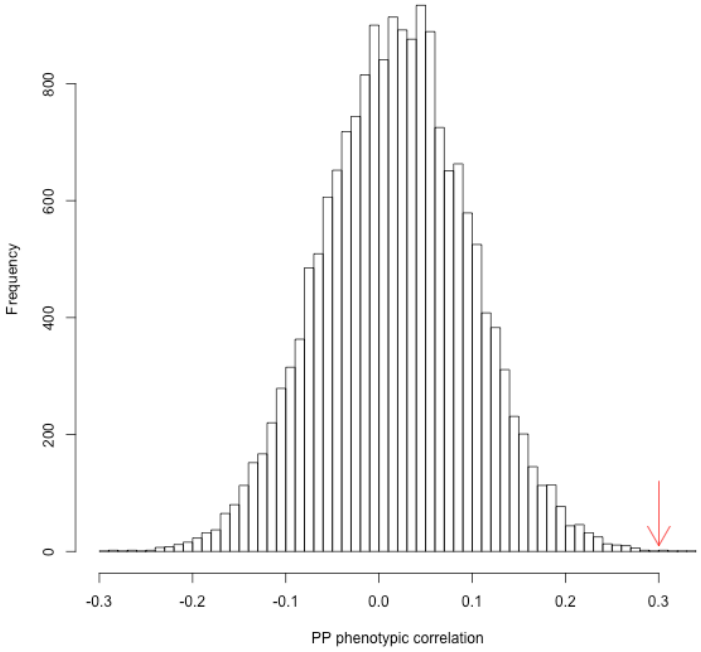

Frequency
0
2000
4000
6000
8000
10000
0
5
10
15
Va

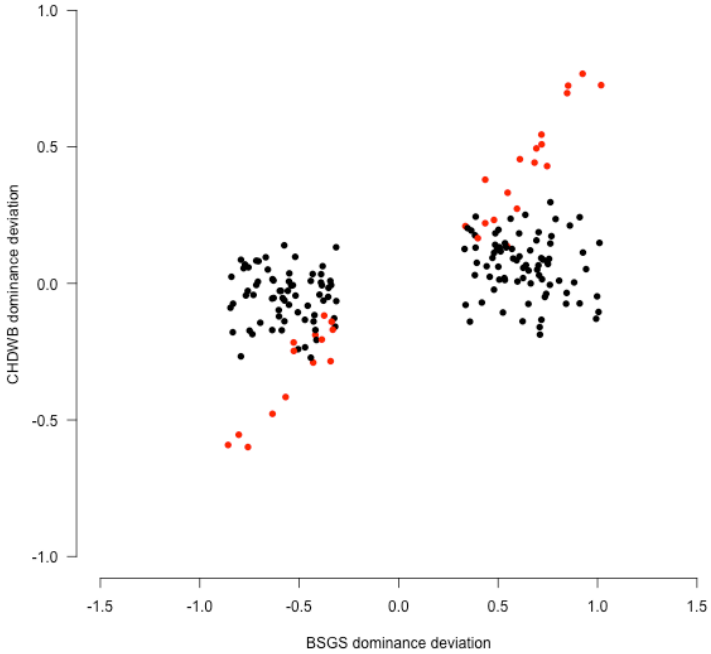
b)


Frequency
0
2000
4000
6000
8000
10000
12000
14000
0
5
10
15
Vd

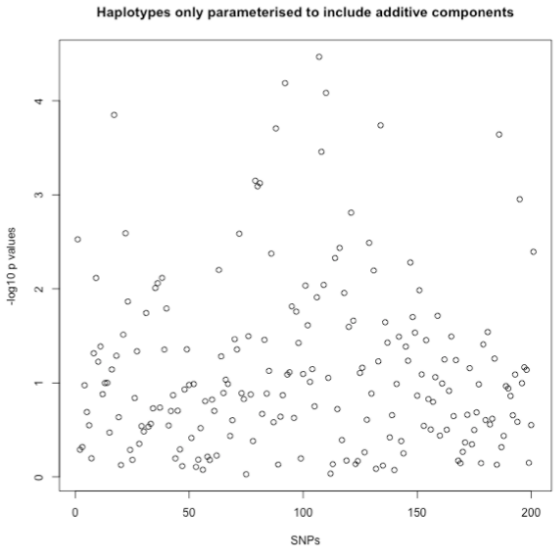
c)


Frequency
0
5000
10000
15000
0
5
10
15
Vf

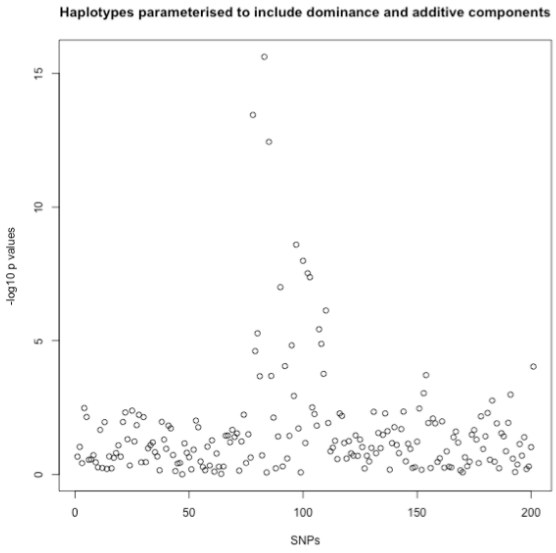

Frequency
0
200
400
600
800
-0.3
-0.2
-0.1
0.0
0.1
0.2
0.3
PP phenotypic correlation


1.0
0.5
0.0
-0.5
-1.0
CHDWB dominance deviation
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
BSGS dominance deviation

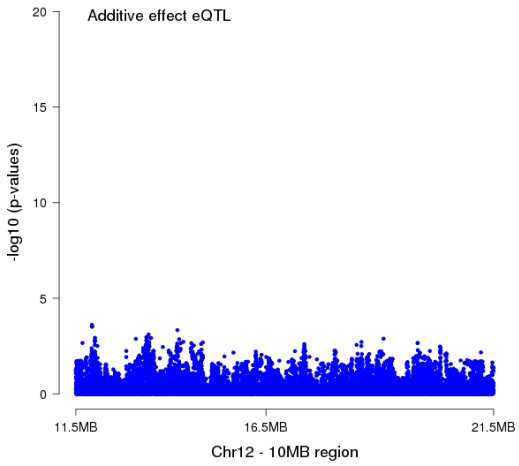
a)


Haplotypes only parameterised to include additive components
-log10 p values
SNPs
0
50
100
150
200
0
1
2
3
4

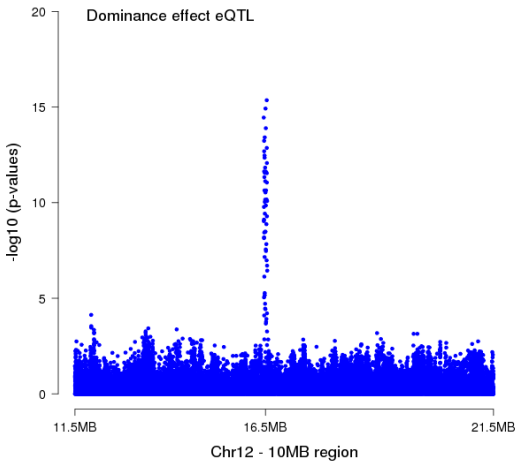
b)

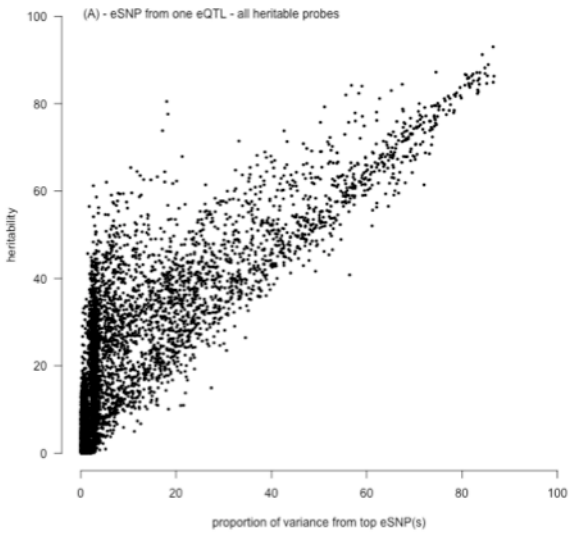

Haplotypes parameterised to include dominance and additive components
-log10 p values
SNPs
0
50
100
150
200
0
5
10
15

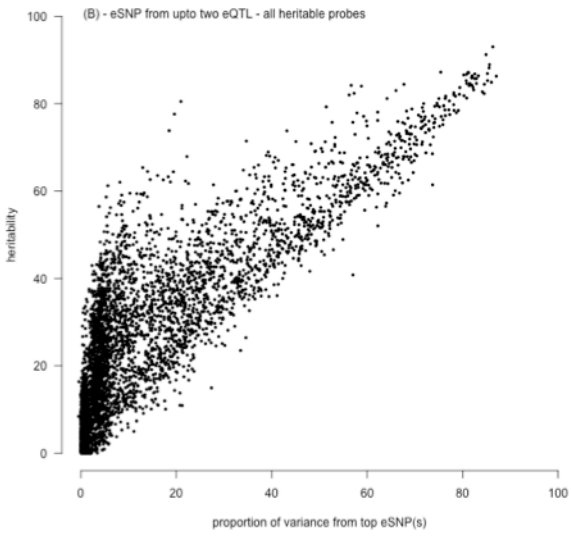
c)

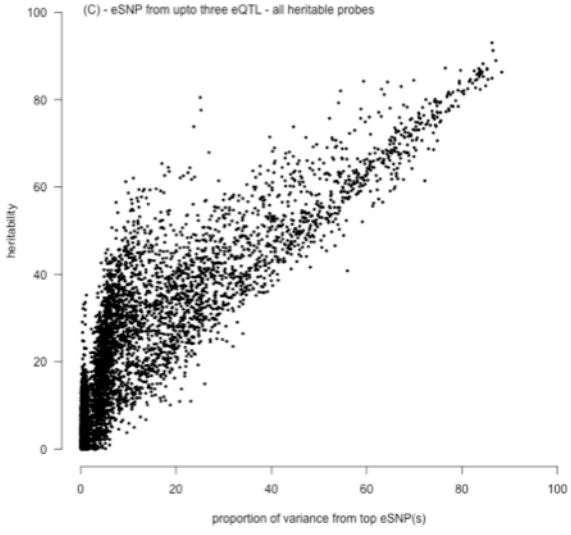

Additive effect eQTL
-log10 (p-values)
Chr12 - 10MB region
11.5MB
16.5MB
21.5MB
0
5
10
15
20

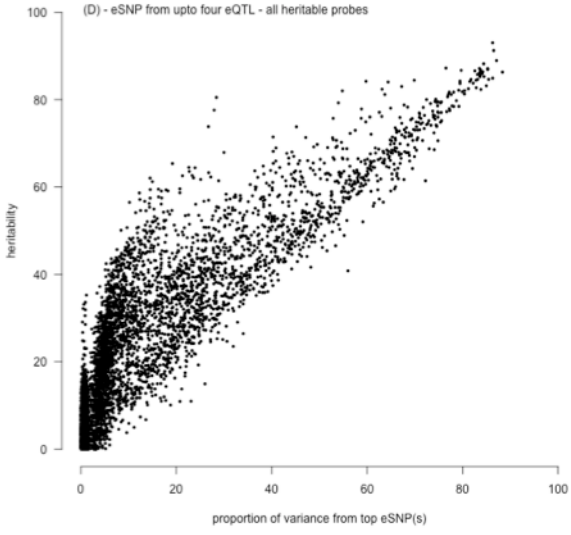
d)

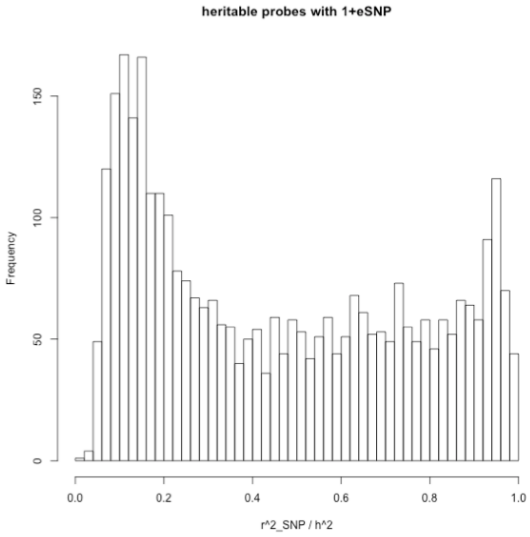

Dominance effect eQTL
-log10 (p-values)
Chr12 - 10MB region
11.5MB
16.5MB
21.5MB
0
5
10
15
20

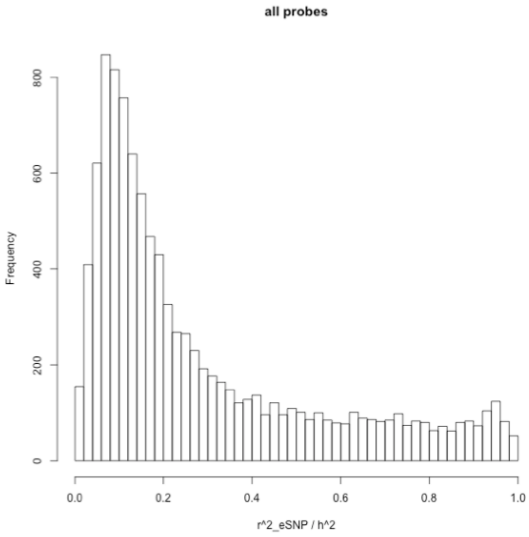

(A) - eSNP from one eQTL - all heritable probes
heritability
proportion of variance from top eSNP(s)
0
20
40
60
80
100

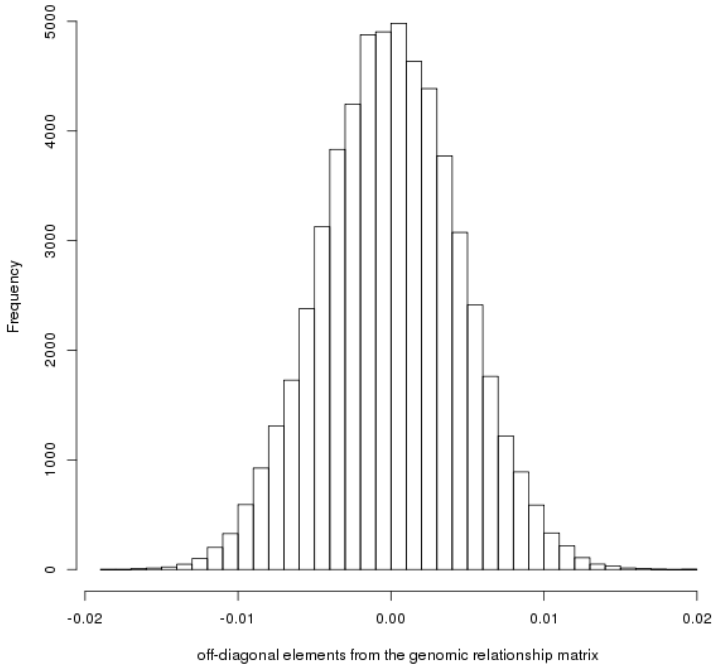

(B) - eSNP from upto two eQTL - all heritable probes
heritability
proportion of variance from top eSNP(s)
0
20
40
60
80
100


(C) - eSNP from upto three eQTL - all heritable probes
heritability
proportion of variance from top eSNP(s)
0
20
40
60
80
100


(D) - eSNP from upto four eQTL - all heritable probes
heritability
proportion of variance from top eSNP(s)
0
20
40
60
80
100


heritable probes with 1+eSNP
Frequency
0
50
100
150
0.0
0.2
0.4
0.6
0.8
1.0
r^2_SNP / h^2


all probes
Frequency
0
200
400
600
800
0.0
0.2
0.4
0.6
0.8
1.0
r^2_eSNP / h^2


Frequency
0
1000
2000
3000
4000
5000
-0.02
-0.01
0.00
0.01
0.02
off-diagonal elements from the genomic relationship matrix

Supplementary Table 1 | Information on the 17 probes that have a significant (p < 1e-4) common family effect. Variance components h^2 and d^2 were estimated using equation [1] (main text) and f^2 using model [3] (main text).

Gene	Probe	Chr	Position (bb)	h^2	d^2	f^2	Function
ATRN	ILMN_2355586	20	3529623	4.2	1.2	16.4	Proteins involved in the initial immune cell clustering during inflammatory responses that may regulate the chemotactic activity of chemokines.
C11ORF63	ILMN_1709050	11	122280189	3.2	0.9	15.9	Uncharacterized protein C11orf63
C16ORF73	ILMN_1754241	16	1824080	6.8	2.3	15.7	Uncharacterized protein C11orf63
CCDC33	ILMN_1681136	15	72415460	4.7	2.7	15.6	
CNTN5	ILMN_1710289	11	98932098	6.5	0.2	14.5	Protein encoded by this gene is a member of the immunoglobulin superfamily, and contactin family, which mediate cell surface interactions during nervous system development
DNAL1	ILMN_1730464	14	73232375	0.0	0.0	14.2	Gene encodes an axonemal dynein light chain which functions as a component of the outer dynein arms complex. This complex acts as the molecular motor that provides the force to move cilia in an ATP-dependent manner
FAM26E	ILMN_3236080	6	116839628	2.4	1.5	13.8	
GKN2	ILMN_1813688	2	69172515	1.6	3.6	13.8	
GRASP	ILMN_1705210	12	50695586	0.7	0.7	13.7	Plays a role in intracellular trafficking and contributes to the macromolecular organization of group 1 metabotropic glutamate receptors at synapses
ITIH1	ILMN_1755251	3	52800872	0.0	2.6	13.6	The protein encoded by this gene is the heavy chain of a serine protease inhibitor that may serve to carry hyaluronan in plasma
OTC	ILMN_1749114	23	38156192	2.4	4.8	13.1	Gene encodes a mitochondrial matrix enzyme
RGPD5	ILMN_2246256	2	109951178	0.0	0.9	13.0	Small GTP-binding protein of the RAS superfamily that is associated with the nuclear membrane and is thought to control a variety of cellular functions through its interactions with other proteins
SLC6A1	ILMN_1744191	3	11055330	0.2	1.7	12.8	Gene encodes a gamma-aminobutyric acid (GABA) transporter, which removes GABA from the synaptic cleft
TCP10L	ILMN_1754656	21	32870965	0.0	2.2	12.7	T-complex protein 10
TFAP2A	ILMN_1765574	6	10506312	8.4	3.5	12.7	Gene is a transcription factor that binds the consensus sequence 5'-GCCNNNGGC-3'. The encoded protein functions as either a homodimer or as a heterodimer with similar family members. This protein activates the transcription of some genes while inhibiting the transcription of others.
TMPRSS13	ILMN_1671154	11	117276857	2.7	0.6	12.5	Gene encodes a member of the type II transmembrane serine protease family
TPX2	ILMN_1796949	20	29852491	6.4	2.4	12.1	Spindle assembly factor. Required for normal assembly of mitotic spindles

Supplementary Table 3 | Primary and their conditionally correlated probes. is the variance explained by the eSNP. P-values from the association of the eSNP with conditionally correlated probes are given, with significant associations (multiple testing corrected for using a Bonferroni adjustment) denoted with *. To further demonstrate a genetic causal link between probes, the eSNP from the primary probe was included as a linear covariate in the family based analysis (model [1]). Heritability estimated from this model is conditional on the eSNP genotypes; is the difference in compared to the model not including the eSNP represents the proportion of accounted for by the eSNP for the conditionally correlated probes.

Primary Probes			**Conditionally correlated probes**					
Gene	Probe	eSNP	Gene	Probe	Conditional Correlation	*p* value of the eSNP	*100	
HLA-DRB1	ILMN_1715169	rs9271170						
			HLA-DRB3	ILMN_1717261	0.64	2.78e-13*	7.29	-5.91
			TMEM154	ILMN_2088124	0.16	5.05e-4*	1.56	-2.42
			NR4A2	ILMN_1782305	0.09	1.10e-3*	1.32	-4.33
			ZNF436	ILMN_2357781	0.37	7.72e-4*	3.44	-1.65
			LST1	ILMN_1718936	0.22	9.27e-6*	4.27	-4.62
			ZNF385C	ILMN_1770400	0.07	2.95e-2	2.68	0.00
			C12ORF73	ILMN_3241041	0.11	1.98e-1	1.74	0.01
ERAP2	ILMN_1743145	rs10051637						
			ANKRD47	ILMN_1755588	0.33	5.27e-4*	5.91	-1.91
			ERAP1	ILMN_2336220	0.49	1.03e-5*	3.66	-2.01
			MRPS30	ILMN_1726743	0.07	1.24e-1	0.51	0.00
			PPM1A	ILMN_1727127	0.31	1.25e-1	0.51	0.00
			SDR42E1	ILMN_1798817	0.10	1.04e-1	1.03	0.00
MED4	ILMN_1664641	rs943067						
			ABHD14B	ILMN_2227533	0.16	1.22e-4*	2.07	-2.36
			BRMS1L	ILMN_1775943	0.17	9.39e-5*	4.81	-3.66
			TOP1MT	ILMN_2405628	0.28	5.87e-4*	1.69	-4.45
			JAG1	ILMN_1691376	0.34	4.97e-4*	12.8	-4.18
			DOK1	ILMN_1700086	0.09	4.03e-4*	11.7	-0.28
			RAP1GDS1	ILMN_1687724	0.14	5.42e-5*	4.64	-1.13
			PIGM	ILMN_1799860	0.18	3.62e-4*	1.74	-0.91
			TIMM23	ILMN_1679555	0.25	1.23e-1	0.32	-0.03
			RORA	ILMN_2322498	0.03	1.21e-1	0.43	-0.03
			EIF4E3	ILMN_2225144	0.16	1.27e-1	0.36	0.02
			FBXO5	ILMN_1710676	0.27	1.08e-1	0.39	0.00
RPS26	ILMN_2209027	rs10876864						
			RPS26L	ILMN_2310703	0.81	1.24e-98*	60.8	-28.6
			FBXO11	ILMN_1678404	0.07	1.14e-3*	8.65	-8.21
			C3ORF59	ILMN_1700967	0.16	1.8e-3*	1.95	-4.02
			MSL2	ILMN_1766859	0.08	1.3e-3*	1.72	-2.90
			SDCCAG3	ILMN_1803997	0.06	1.84e-1	0.21	0.00
			NUP88	ILMN_1734826	0.03	3.26e-1	0.11	-0.04
GSTM1	ILMN_1762255	rs11101992						
			GSTM2	ILMN_2201580	0.65	1.17e-14*	8.26	-7.45
			C18ORF2	ILMN_3250066	0.34	2.16e-3*	9.61	-1.31
			MESP2	ILMN_1751911	0.04	6.40e-4*	9.38	-2.36
			FLJ23152	ILMN_1696243	0.26	3.25e-3*	10.2	-3.43

			OPRM1	ILMN_1803261	0.16	3.50e-3*	5.34	-1.92
			FCRL4	ILMN_1738517	0.05	1.24e-1	2.03	-0.02
			ARHGAP24	ILMN_1775441	0.02	1.27e-1	0.98	0.00
IRF5	ILMN_2312606	rs6965542						
			TNPO3	ILMN_1683811	0.43	1.55e-10*	5.78	-9.96
			PHF20	ILMN_1813657	0.17	1.24e-3*	1.29	-2.91
			FABP5L3	ILMN_2217574	0.32	2.51e-3*	11.7	-3.64
			QTRT1	ILMN_1780153	0.25	3.95e-3*	1.02	-0.72
			RAB20	ILMN_1708881	0.19	1.08e-1	0.74	-0.18
			IFITM4P	ILMN_1770071	0.04	1.01e-1	1.41	0.00
PAM	ILMN_2313901	rs28092						
			RAB23	ILMN_2346997	0.08	4.98e-4*	3.48	-7.95
			SLCO4C1	ILMN_1686464	0.18	1.44e-3*	1.53	-4.86
			OR10H3	ILMN_1731314	0.29	1.22e-3*	8.73	-11.3
			HELT	ILMN_1693843	0.10	2.33e-3*	9.45	-8.14
			MAPK8IP3	ILMN_1811574	0.13	1.16e-1	0.52	-0.17
			NCOA1	ILMN_2335198	0.26	1.26e-1	0.36	-0.34
ATP13A1	ILMN_2134224	rs2304130						
			C11ORF35	ILMN_1652602	0.07	7.99e-4*	4.95	-6.82
			CLCN5	ILMN_1690327	0.20	1.88e-3*	3.69	-7.34
			CRLF2	ILMN_1767573	0.24	1.44e-3*	1.72	-2.86
			LAD1	ILMN_1728215	0.08	2.81e-4*	6.92	-7.31
			NCSTN	ILMN_1735180	0.02	2.43e-4*	1.09	-1.98
			HRB	ILMN_2196734	0.34	5.39e-4*	5.39	-4.87
			MLXIP	ILMN_1693987	0.21	4.41e-4*	9.04	-12.3
			RC1P8	ILMN_2342068	0.14	4.12e-3*	5.10	-5.12
			NCSTN	ILMN_1735180	0.10	2.43e-3*	1.07	-1.01
			SLC25A19	ILMN_1666553	0.16	1.04e-1	0.28	-0.05
			IRF1	ILMN_1708375	0.06	2.41e-2	0.63	0.00
			KRT8P9	ILMN_3191922	0.03	2.26e-2	4.41	-2.14
ZSWIM7	ILMN_3298167	rs1045599						
			SARM1	ILMN_1746265	0.38	7.08e-5*	2.07	-6.76
			CECR4	ILMN_3177532	0.25	4.53e-4*	10.6	-16.7
			HSPD1	ILMN_1784367	0.14	2.39e-6*	2.88	-4.51
			MTR	ILMN_1670801	0.03	3.52e-4*	1.56	-3.46
			C22ORF32	ILMN_1706859	0.16	5.22e-5*	2.31	-4.82
			AMY2B	ILMN_2073157	0.18	3.38e-4*	1.64	-2.47
			RALGPS1	ILMN_1674135	0.06	5.03e-4*	1.55	-3.61
			ZSWIM3	ILMN_2283196	0.14	1.02e-1	0.33	-1.98
			MIF	ILMN_1807074	0.12	1.98e-2	0.71	-0.18
			NELL2	ILMN_1725417	0.05	1.12e-1	0.34	-2.45
			PPP2R1A	ILMN_1810467	0.31	1.05e-1	0.33	-0.36
HBG2	ILMN_2084825	rs766432						
			SIAH1	ILMN_2380566	0.13	4.7e-10*	4.78	-6.81
			PKDREJ	ILMN_1673234	0.19	2.24e-3*	9.06	-12.8
			DYNC1H1	ILMN_1780302	0.20	3.70e-4*	1.49	-2.36
			ARCN1	ILMN_1699703	0.14	9.51e-4*	1.32	-3.64
			RIPK1	ILMN_2119535	0.31	8.16e-5*	1.91	-2.47
			ZNFX1	ILMN_1745148	0.04	4.48e-4*	1.48	-3.67
			WDR68	ILMN_1706706	0.11	6.29e-4*	1.48	-2.98
			EHD1	ILMN_1651832	0.16	3.43e-4*	1.53	-2.71
			PTPN6	ILMN_1738675	0.22	3.66e-4*	1.51	-3.78
			NCOR2	ILMN_2340052	0.19	2.13e-4*	1.42	-4.94
			CA1	ILMN_1652431	0.25	7.73e-2	0.23	-0.27

			ACTN4	ILMN_1725534	0.03	2.39e-2	0.61	-1.01
			FAM178A	ILMN_3233135	0.03	1.06e-1	0.33	-1.27
			KDELR1	ILMN_2130411	0.15	1.04e-1	0.34	0.00
			HIST1H3B	ILMN_2222163	0.17	1.04e-1	4.23	-3.87
			MRPL38	ILMN_1719656	0.01	1.14e-1	0.54	-0.41

Supplementary Table 2 | Summary statistics for the 832 individuals in BSGS. Phenotypic correlations were calculated between pairs of individuals for normalised expression levels in each of the 17,994 probes.

			Shared coefficients			Mean phenotypic correlation for 17,994 probes (sd)
Relationship pair	**Code**	**N pairs**	**A**	**D**	**F**	
Monozygotic twins	MZ	78	1	1	1	0.182 (0.089)
Dizygotic twins	DZ	206	0.5	0.25	1	0.097 (0.082)
Siblings	SIB	343	0.5	0.25	1	0.089 (0.084)
Parent – Offspring	PO	425	0.5	0	1	0.092 (0.081)
Parent – Parent	PP	71	0	0	1	0.017 (0.075)

Supplementary Table 4 | Full and reduced models for variance components

Variance component	Full model	Reduced model
A		
D		
F		

Supplementary Note 1

Confounding between variance component estimates

One potential problem when estimating variance component , and is that estimates may be confounded due to correlation in the off-diagonals of the relationship matrices **A**, **D**, and **F**. We attempted to evaluate the potential levels of confounding by running a series of full and reduced models and comparing the estimates of the variance components (supplementary figure 2). The following series of models were run;

1. Comparison of in the presence and absence of a non-additive component.
Full:
Reduced:

2. Comparison of in the presence and absence of an additive component.
Full:
Reduced

3. Comparison of in the presence and absence of an additive component.
Full:
Reduced:

Supplementary Note 2

Sampling variance of variance components

Here we have estimated variance components for 17,994 transcripts using models [1] and [3] (online methods). The sampling variance of these variance estimates provides information on the expected distributions of estimates under assumptions of known population parameters. Knowledge of the expected sampling variance of each parameter is useful as it allows us to compare the observed distribution of estimates against the expected distribution under assumptions of the true population values being equal to 0. Calculating the expected sampling variances of genetic (and) and non-genetic ( ) variances estimated from related individuals is relatively straightforward when estimates are made from simple relationship pairings (i.e. MZ-DZ, Sibling pairs, Parent-Offspring)[1,2]. However, in more complex pedigrees, such as BSGS, algebraic methods are not available to calculate the expected sampling variance. To explore the expected sampling variance of the parameter estimates in our data we conducted a series of simulation studies to calculate the expected distribution of estimates under the assumption that the true value of the variance component equals 0, whilst the remaining model parameters equal their empirical mean. For example, to estimate the sampling variance of , which is estimated using equation [1] (online methods), matrices from the right side of equation [2] were sampled from an appropriate Wishart distribution (see below), with a sampled from a random normal distribution, and and sampled from the empirical estimates for the 17,994 probes. Variance components for the simulated data were obtained by REML[3]. This process was repeated 100,000 times and the sampling variance calculated from the estimates of . A similar approach was used to calculate the sampling variance of and , but with *a* sampled from the empirical values and model [1] and [3] used respectively.

Simulating matrices using the Wishart distribution

Here we simulated matrices from a Wishart distribution resulting in an *n x n* matrix, where *n* is the number of individuals, and the off diagonals have a built in correlation structure pertaining to the relationship matrix[4], hereon denoted **U**, that is being simulated (either **A**, **D** or **F**). The resulting matrix is positive definite.

Observed relationship matrix

To generate a matrix having a Wishart distribution, we start with the relationship matrix **U** equal a matrix with *n* rows and *n* columns. From **U** we calculate **W** as, **W=U'U**. Next we perform a Cholesky decomposition of **W**, so that **W=TT'**, where **T** is the lower triangular matrix.

Wishart distribution

First an n by n matrix, **M** is formed with elements populated by random normal deviates generated by the *rnorm* function in R . A vector **I**, of length n is generated with elements drawn from a Chi-squared distribution (*rchisq* function in R) with $n - i$ degrees of freedom where i is the element in the vector; i.e. element 1 has $n - 1$ degrees of freedom, element 2 has $n - 2$ degrees of freedom and so on. Element n has 1 degree of freedom.

Next an n by n matrix **Z** is formed. When $i = 1$ the diagonal element is calculated by;

when $i > 1$ diagonal elements are calculated by;

When $i = 1$ off diagonal elements of **Z** are calculated by;

and when $i > 1$ off diagonal elements are calculated by;

A final matrix, **X**, is the simulated random Wishart matrix based on the relationships contained within **U**, and is calculated by;

$$\mathbf{X = TZT'}$$

References

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