

1 Supplementary Tables

Table S1 - Additional details of the reported *cis-trans* interactions.

For each interaction, the adjusted r^2 of the models which fit the two main effects and the models incorporating the interaction effect, the p-value of the goodness of fit as measured from a likelihood ratio test comparing both models and the measures of linkage disequilibrium (r^2) between interacting SNPs are given.

Tissue	Cis-SNP	Cis Position	Trans-SNP	Trans Position	Probe I.D.	Transcript	Probe Position	Main Effects (Adj. r^2)	Interaction Effects (Adj. r^2)	P-Value (LRT)	LD
Liver	rs3129045	6:29652576	rs7761068	6:31333939	10025907254	HLA-G	6:29798725-29798785	0.18	0.23	9.35×10^{-07}	0.004
	rs2747442	6:29653186	rs7761068	6:31333939	10025907254	HLA-G	6:29798725-29798785	0.20	0.24	2.22×10^{-05}	0.005
	rs2747436	6:29651935	rs7761068	6:31333939	10025907254	HLA-G	6:29798725-29798785	0.18	0.22	2.54×10^{-05}	0.003
	rs9267873	6:32199352	rs2247056	6:31265490	10025904809	HLA-DRB5	6:32485162-32485222	0.10	0.15	2.19×10^{-08}	0.009
	rs9267873	6:32199352	rs6457374	6:31272261	10025904809	HLA-DRB5	6:32485162-32485222	0.10	0.15	2.74×10^{-08}	0.009
	rs507778	6:32209861	rs6457374	6:31272261	10025904809	HLA-DRB5	6:32485162-32485222	0.08	0.13	1.57×10^{-08}	0.002
	rs507778	6:32209861	rs2247056	6:31265490	10025904809	HLA-DRB5	6:32485162-32485222	0.08	0.12	2.32×10^{-07}	0.003
	rs2072633	6:31919578	rs3093998	6:31485174	10025904809	HLA-DRB5	6:32485162-32485222	0.09	0.13	1.05×10^{-07}	0.007
	rs592229	6:31930441	rs3093998	6:31485174	10025904809	HLA-DRB5	6:32485162-32485222	0.12	0.16	2.09×10^{-07}	0
	rs805262	6:31628733	rs2247056	6:31265490	10025904809	HLA-DRB5	6:32485162-32485222	0.07	0.12	2.34×10^{-06}	0
Pre-Frontal Cortex	rs805262	6:31628733	rs6457374	6:31272261	10025904809	HLA-DRB5	6:32485162-32485222	0.07	0.10	3.10×10^{-06}	0
	rs2858331	6:32681277	rs3093998	6:31485174	10025904809	HLA-DRB5	6:32485162-32485222	0.07	0.11	3.24×10^{-06}	0.008
	rs915664	6:30794617	rs3094212	6:31085770	10025907254	HLA-G	6:29798725-29798785	0.24	0.27	6.56×10^{-07}	0.004
	rs13201769	6:30756066	rs2524089	6:31266522	10025907254	HLA-G	6:29798725-29798785	0.31	0.34	7.48×10^{-07}	0.001
	rs13201769	6:30756066	rs2243868	6:31261276	10025907254	HLA-G	6:29798725-29798785	0.31	0.34	8.01×10^{-07}	0.001
	rs10947091	6:30747216	rs2524089	6:31266522	10025907254	HLA-G	6:29798725-29798785	0.30	0.33	9.66×10^{-07}	0.001
	rs10947091	6:30747216	rs2243868	6:31261276	10025907254	HLA-G	6:29798725-29798785	0.30	0.33	1.05×10^{-06}	0.001
	rs3869070	6:30023868	rs3093998	6:31485174	10025907254	HLA-G	6:29798725-29798785	0.13	0.17	1.86×10^{-06}	0.008
	rs11744596	5:68519291	rs13168712	5:70679626	10023810270	LOC100506658	5:68849630-68849690	0.21	0.25	1.52×10^{-06}	0.005
	rs2932777	5:68525027	rs13168712	5:70679626	10023810270	LOC100506658	5:68849630-68849690	0.21	0.25	1.52×10^{-06}	0.005
Cerebellum											

Table S2 - Multiple Regression Model of Main Effect and Interaction Terms Showing Independent Effects on HLA-DRB5 Expression in the Pre-Frontal Cortex.

Model Terms	Effect Size	P-Value
rs2072633	-55.675	0.001997
rs2858331	26.475	0.053860
rs592229	58.684	7.42×10^{-05}
rs9267873	4.250	
rs2247056	-26.552	
rs3093998	38.964	
rs9267873:rs2247056	56.654	0.000139
rs2072633:rs3093998	39.399	0.007252
rs2858331:rs3093998	-40.709	0.005094

Table S3 - Multiple Regression Model of Main Effect and Interaction Terms Showing Independent Effects on HLA-G Expression in the Pre-Frontal Cortex.

Model Terms	Effect Size	P-Value
rs10947091	87.249	0.028331
rs13201769	-109.688	0.004251
rs3869070	-11.171	0.336558
rs915664	20.560	0.166855
rs2524089	88.493	1.22e-11
rs3093998	-6.221	0.660640
rs3094212	74.164	5.85e-10
rs915664:rs3094212	-39.636	0.000911
rs10947091:rs2524089	-29.304	0.018983
rs3869070:rs3093998	33.367	0.005853

Table S4 - RNA-Seq derived expression data from Brawand *et al* (2011). The RNA-Seq data is given as the log₂ transformed reads per kilobase of transcript per million mapped reads (RPKM). The tissues of relevance for this study are the liver, pre-frontal cortex and cerebellum. RNA-Seq data for 26 of the 32 transcripts reported to be under epistatic control in this study. Values in bold indicate the tissue in which a gene is reported to be regulated by epistasis. Where expression data was not available, this is indicated by a dash (-)

Gene	Liver	Pre-Frontal Cortex	Cerebellum	Frontal Lobe	Temporal Lobe	Heart	Kidney	Testis
MICB	-	-	4	0.7	0.6	1	1	3
KLRC2	-	0.9	-	-	0.9	-	-	-
HSD17B13	132	-	-	-	-	-	-	-
THAP5	3	5	3	2	-	1	2	6
IL33	2	3	0.9	1	-	4	-	3
KCNIP4	-	27	10	13	3	-	3	-
CCDC103	-	-	-	-	-	-	-	44
N4BP2	-	-	-	-	-	-	-	0.9
QRSL1	4	3	1	2	1	3	3	4
TRIM4	3	3	6	2	2	3	7	8
NR1D2	5	21	39	16	12	3	7	4
HLA-DRB5	6	2	1	6	1	6	13	70
USP34	7	22	11	8	4	6	6	17
USP31	5	12	13	12	10	9	9	24
FCER1A	2	-	-	-	-	-	-	0.8
NCR-00292	0.8	2	0.8	2	2	-	0.9	2
TSPAN15	6	11	48	78	79	11	19	40
TMPRSS5	-	3	2	4	7	-	-	2
PRPH2	-	7	0.7	2	4	-	0.6	2
HPR	-	1	4	1	6	47	14	2
HLA-G	1	0.9	-	0.7	1	-	5	7
IFT172	3	25	23	14	19	11	17	76
PSORS1C1	-	-	-	2	-	0.6	-	82
KDM4B	16	6	18	10	52	9	6	35
SLC27A6	-	-	-	1	0.6	4	-	2
HCG4	-	0.9	1	0.8	-	-	1	0.9
GBP3	2	2	1	1	0.8	4	7	2
ATP8A1	-	25	8	35	7	2	0.7	0.6
DSCC1	0.6	0.7	2	1	2	-	-	3

2 Supplementary Figures

Figure S1 - Interaction between rs507778 (A) and rs6457374 (B) and its affect on HLA-DRB5 expression in the pre-frontal cortex.

(a) Summary of the parameters for the interaction model. (b) Distribution of HLA-DRB5 expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked HLA-DRB5 expression for each genotype. The mean value is denoted $\bar{x}$. The mean rank expression for the double homozygote (aabb) is less than would be expected if no interaction were present and both SNPs had independent effects on the expression of HLA-DRB5.

(a)

SNP	Estimate	Std. Error	P-Value
rs507778 (cis)	6.49	12.85	0.61
rs6457374 (trans)	124.89	16.09	4×10^{-14}
Interaction	-80.99	15.25	1.57×10^{-7}

(b)

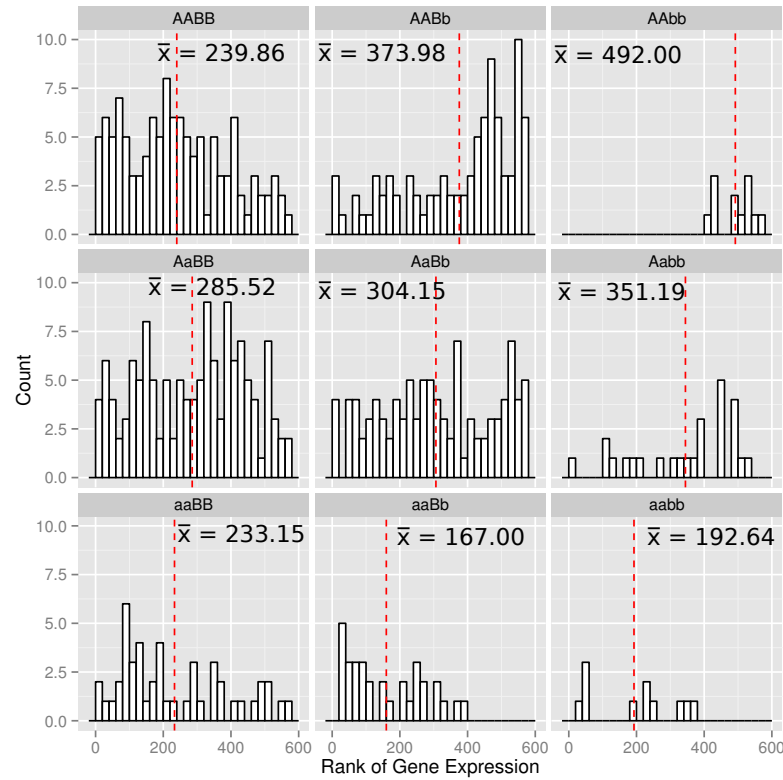


Figure S2 - Interaction between rs2072633 (A) and rs3093998 (B) and its affect on HLA-DRB5 expression in the pre-frontal cortex.

(a) Summary of the parameters for the interaction model. (b) Distribution of HLA-DRB5 expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked HLA-DRB5 expression for each genotype. The mean value is denoted $\bar{x}$. The mean rank expression for the double homozygote (aabb) is greater than would be expected if no interaction were present and both SNPs had independent effects on the expression of HLA-DRB5.

(a)

SNP	Estimate	Std. Error	P-Value
rs2072633 (cis)	-12.53	13.90	0.37
rs3093998 (trans)	-5.96	14.94	0.69
Interaction	74.74	13.87	1.05×10^{-7}

(b)

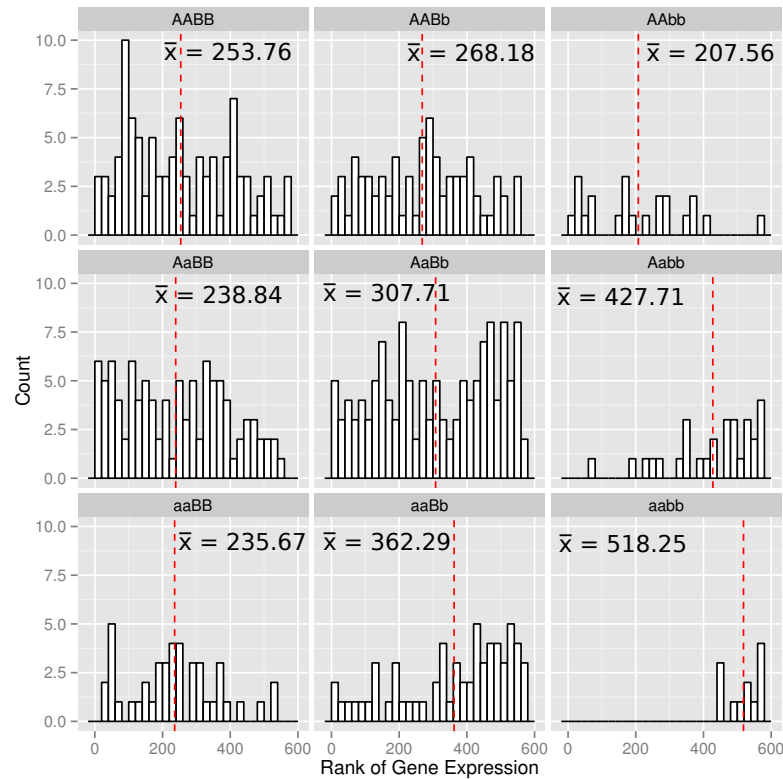


Figure S3 - Interaction between rs805262 (A) and rs2247056 (B) and its affect on HLA-DRB5 expression in the pre-frontal cortex.

(a) Summary of the parameters for the interaction model. (b) Distribution of HLA-DRB5 expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked HLA-DRB5 expression for each genotype. The mean value is denoted $\bar{x}$. The mean rank expression for the double homozygote (aabb) is less than would be expected if no interaction were present and both SNPs had independent effects on the expression of HLA-DRB5.

(a)

SNP	Estimate	Std. Error	P-Value
rs805262 (cis)	11.41	12.42	0.36
rs2247056 (trans)	122.28	17.07	2.55×10^{-12}
Interaction	72.20	14.83	2.34×10^{-6}

(b)

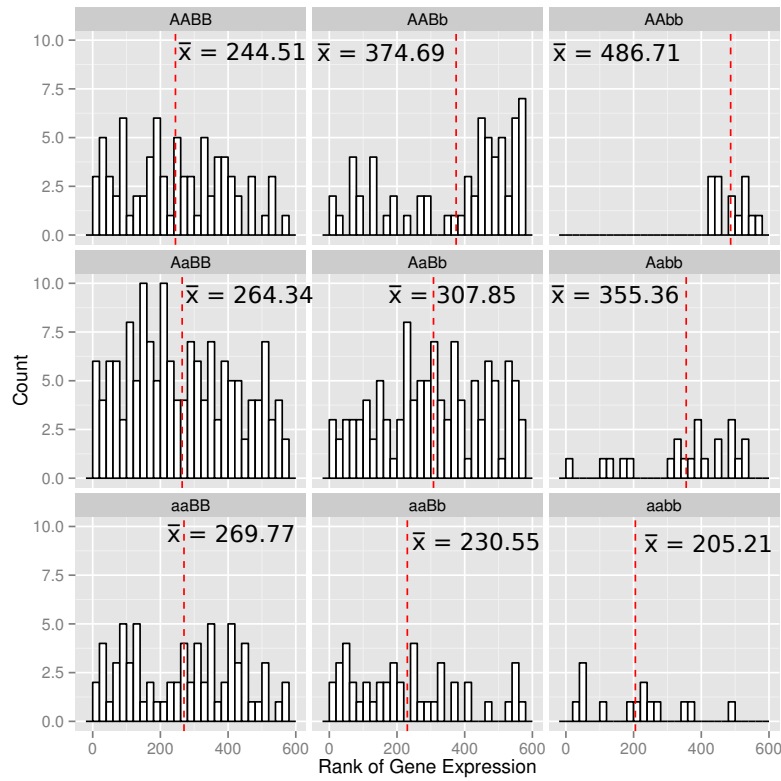


Figure S4 - Interaction between rs2858331 (A) and rs3093998 (B) and its affect on HLA-DRB5 expression in the pre-frontal cortex.

(a) Summary of the parameters for the interaction model. (b) Distribution of HLA-DRB5 expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked HLA-DRB5 expression for each genotype. The mean value is denoted $\bar{x}$. The mean rank expression for the double homozygote (aabb) is less than would be expected if no interaction were present and both SNPs had independent effects on the expression of HLA-DRB5.

(a)

SNP	Estimate	Std. Error	P-Value
rs2858331 (cis)	24.51	13.96	0.08
rs3093998 (trans)	108.09	14.96	1.64×10^{-12}
Interaction	-67.31	14.31	3.24×10^{-6}

(b)

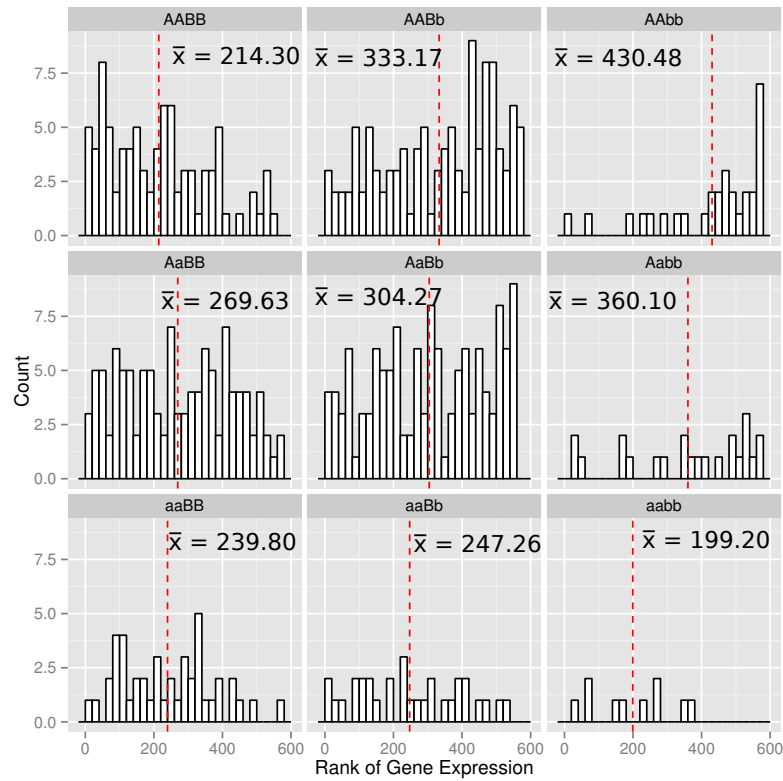


Figure S5 - Interaction between rs915664 (A) and rs3094212 (B) and its affect on HLA-G expression in the pre-frontal cortex.

(a) Summary of the parameters for the interaction model. (b) Distribution of HLA-G expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked HLA-G expression for each genotype. The mean value is denoted $\bar{x}$. The mean rank expression for the double homozygote (aabb) is less than would be expected if no interaction were present and both SNPs had independent effects on the expression of HLA-G.

(a)

SNP	Estimate	Std. Error	P-Value
rs915664 (cis)	22.83	16.34	0.16
rs3094212 (trans)	127.49	11.51	6.27×10^{-26}
Interaction	-63.73	12.67	6.56×10^{-7}

(b)

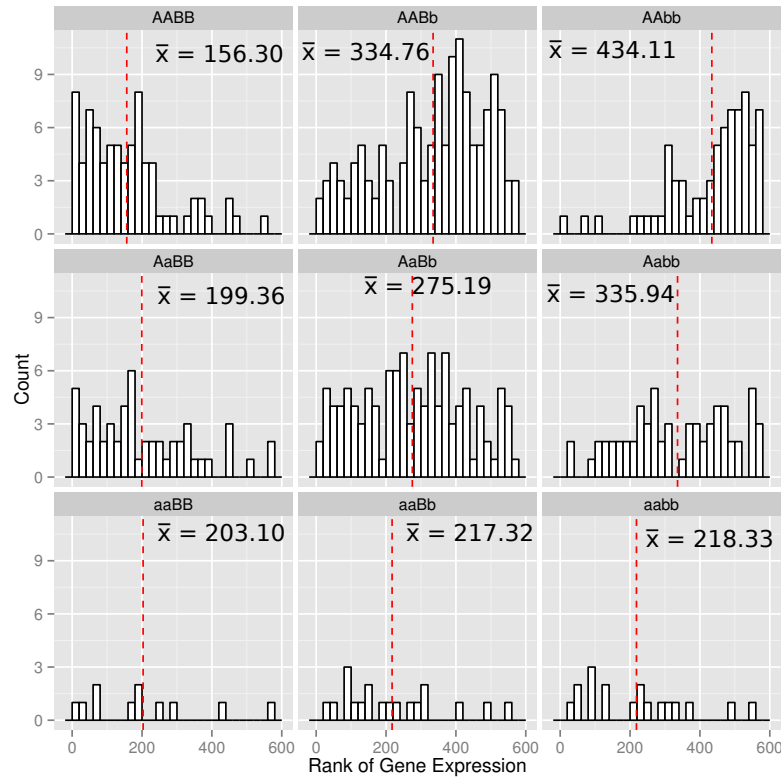


Figure S6 - Interaction between rs13201769 (A) and rs2524089 (B) and its affect on HLA-G expression in the pre-frontal cortex.

(a) Summary of the parameters for the interaction model. (b) Distribution of HLA-G expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked HLA-G expression for each genotype. The mean value is denoted $\bar{x}$. The mean rank expression for the double homozygote (aabb) is less than would be expected if no interaction were present and both SNPs had independent effects on the expression of HLA-G.

(a)

SNP	Estimate	Std. Error	P-Value
rs13201769 (cis)	-14.42	13.17	0.27
rs2524089 (trans)	139.07	11.59	1.17×10^{-29}
Interaction	-60.37	12.06	7.48×10^{-7}

(b)

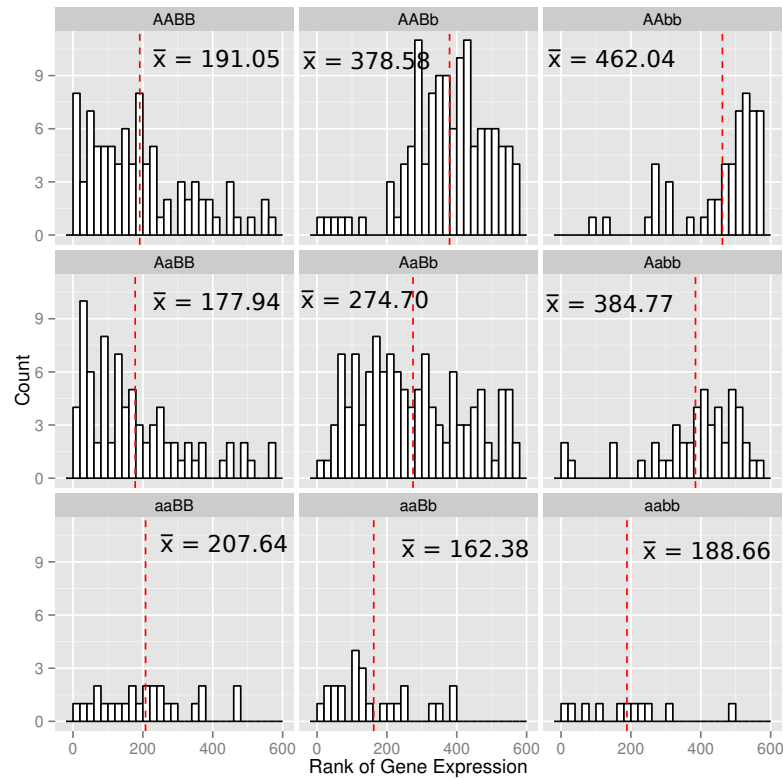


Figure S7 - Interaction between rs3129045 (A) and rs7761068 (B) and its affect on HLA-G expression in the liver.

(a) Summary of the parameters for the interaction model. (b) Distribution of *HLA-G* expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked *HLA-G* expression for each genotype. The mean value is denoted $\bar{x}$. Both main effects, A and B cause a decrease in *HLA-G* expression as seen by the shift in means of *HLA-G* for genotypes AABB, AaBB, and aaBB and ABbb, AABb and AAbb. In the absence of interaction, mean *HLA-G* expression for the aabb genotype is expected to be less than that for the aaBB and AAbb genotypes. Consistent with the parameterisation of the model, epistasis is visible by the increase in *HLA-G* gene expression for the aabb genotype.

(a)

SNP	Estimate	Std. Error	P-Value
rs3129045 (cis)	-97.48	13.63	5.36×10^{-12}
rs7761068 (trans)	-98.47	11.30	1.32×10^{-16}
Interaction	54.67	10.94	9.35×10^{-7}

(b)

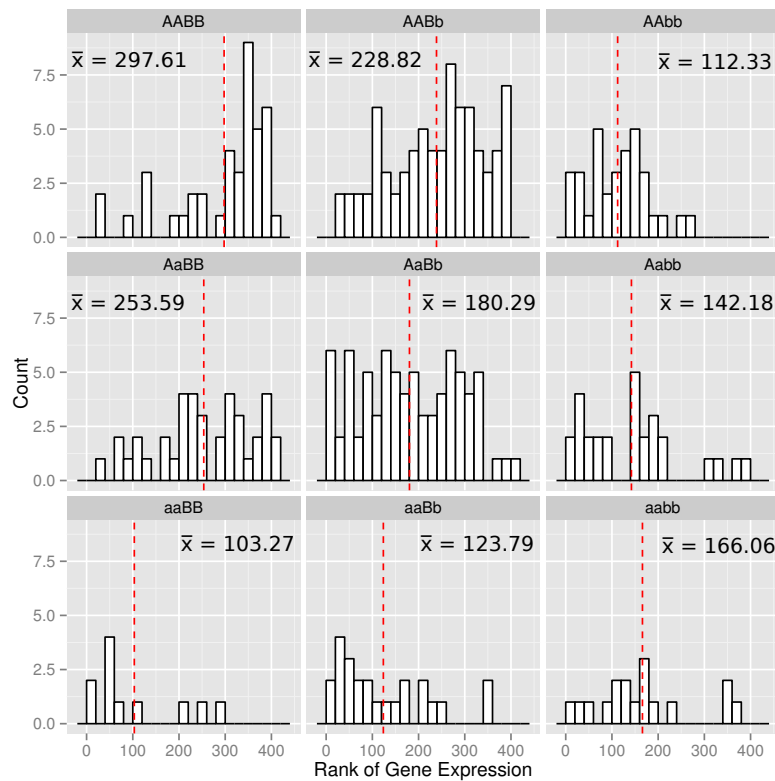


Figure S8 - Interaction between rs3869070 (A) and rs3093998 (B) and its affect on HLA-G expression in the pre-frontal cortex.

(a) Summary of the parameters for the interaction model. (b) Distribution of HLA-G expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked HLA-G expression for each genotype. The mean value is denoted $\bar{x}$. The mean rank expression for the double homozygote (aabb) is greater than would be expected if no interaction were present and both SNPs had independent effects on the expression of HLA-G.

(a)

SNP	Estimate	Std. Error	P-Value
rs3869070 (cis)	-26.46	13.54	0.05
rs3093998 (trans)	-7.20	15.86	0.65
Interaction	66.69	13.84	6.56×10^{-7}

(b)

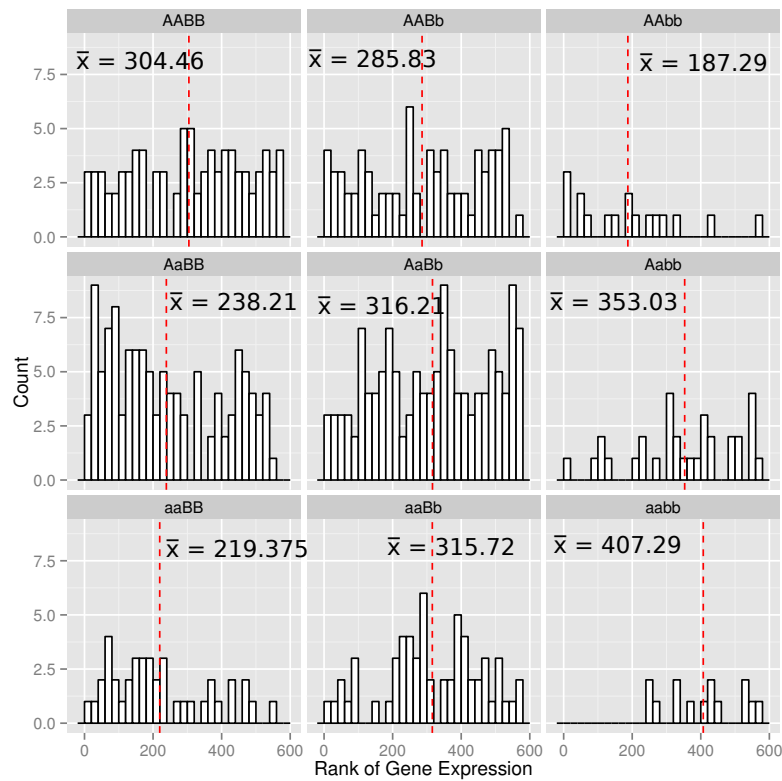


Figure S9 - Interaction between rs11744596 (A) and rs13168712 (B) and its affect on LOC100506658 expression in the cerebellum.

(a) Summary of the parameters for the interaction model. (b) Distribution of LOC100506658 expression stratified by pairwise genotypic combinations. The red line denotes the mean of the ranked LOC100506658 expression for each genotype. The mean value is denoted $\bar{x}$. The mean rank expression for the double homozygote (aabb) is less than would be expected if no interaction were present and both SNPs had independent effects on the expression of LOC100506658.

(a)

SNP	Estimate	Std. Error	P-Value
rs11744596 (cis)	74.81	11.52	2.11×10^{-10}
rs13168712 (trans)	130.94	12.81	2.67×10^{-22}
Interaction	-56.61	11.62	1.52×10^{-6}

(b)

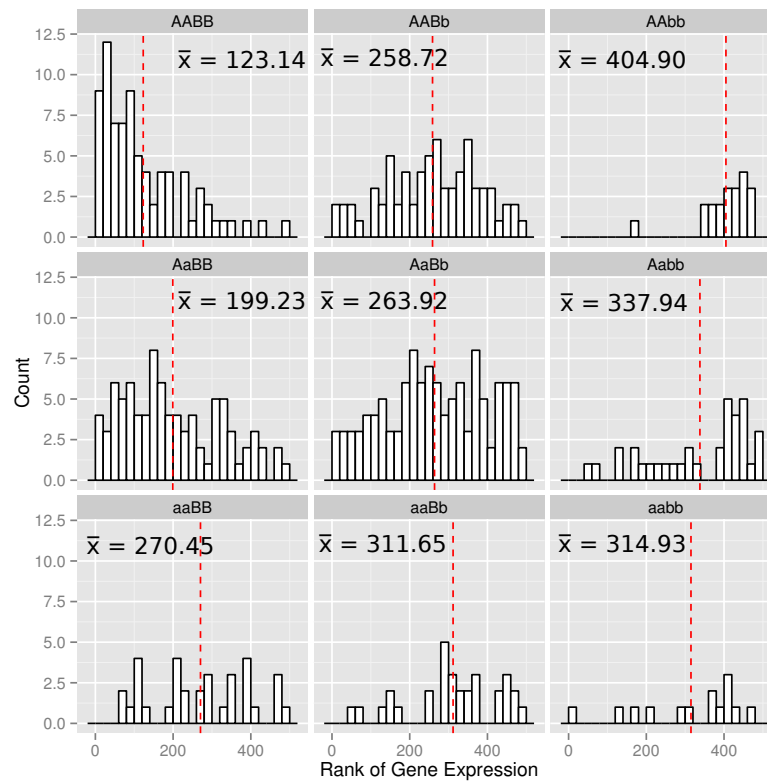


Figure S10 - Empirical cumulative distribution of the distances between SNPs in significant interactions (red) and all SNPs tested for interaction (black) in the liver.

The distributions of distances between SNPs involved in interaction versus the entire set of interactions tested are different from each other ($p = 1.89 \times 10^{-15}$).

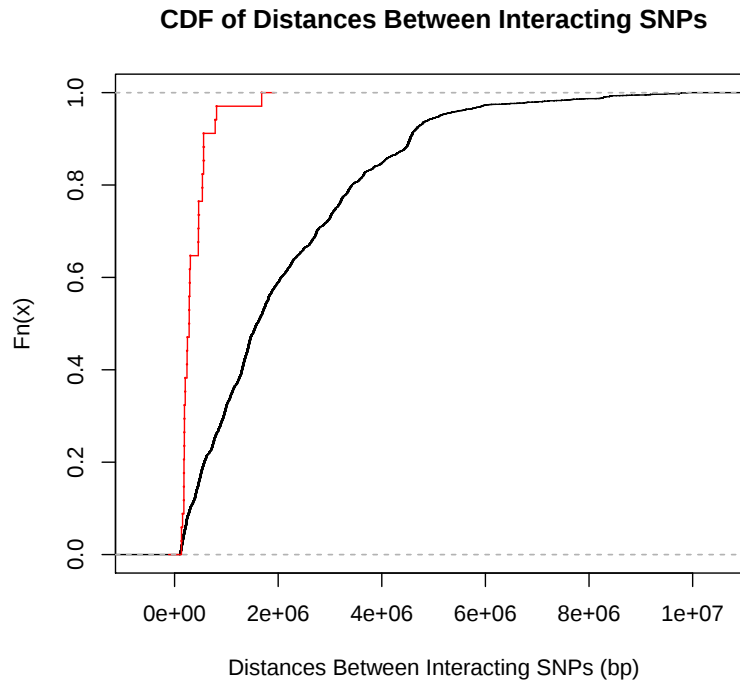


Figure S11 - Empirical cumulative distribution of the distances between SNPs in significant interactions (red) and all SNPs tested for interaction (black) in the pre-frontal cortex.

The distributions of distances between SNPs involved in interaction versus the entire set of interactions tested are different from each other ($p < 1 \times 10^{-16}$)

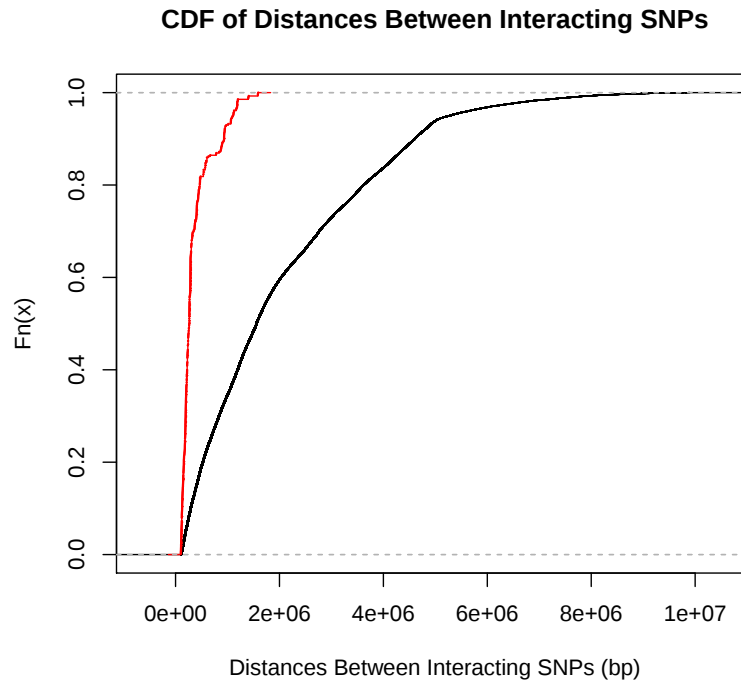


Figure S12 - Empirical cumulative distribution of the distances between SNPs in significant interactions (red) and all SNPs tested for interaction (black) in the cerebellum.

The distributions of distances between SNPs involved in interaction versus the entire set of interactions tested are different from each other ($p < 1 \times 10^{-16}$)

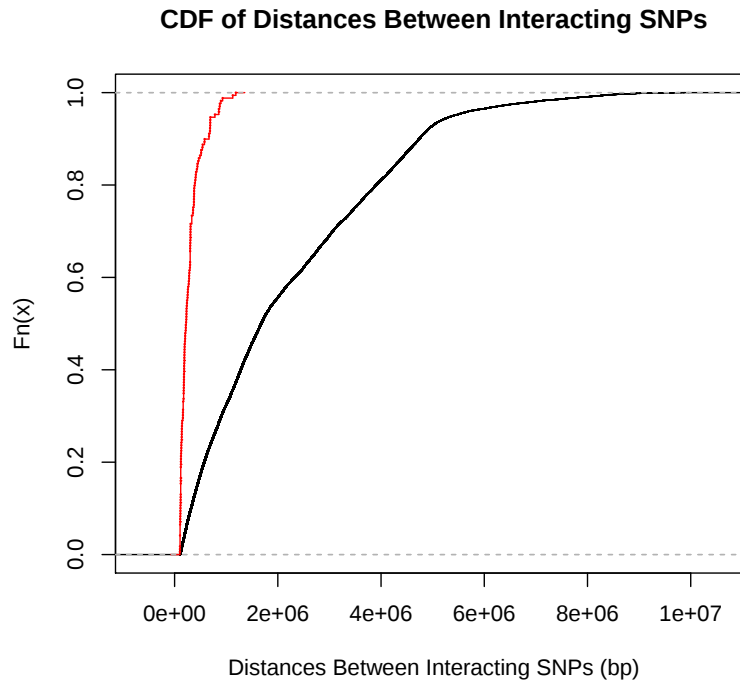


Figure S13 - Empirical cumulative distribution of the distances between SNPs in significant interactions (red) and all SNPs tested for interaction (black) in the visual cortex.

The distributions of distances between SNPs involved in interaction versus the entire set of interactions tested are different from each other ($p < 1 \times 10^{-16}$)

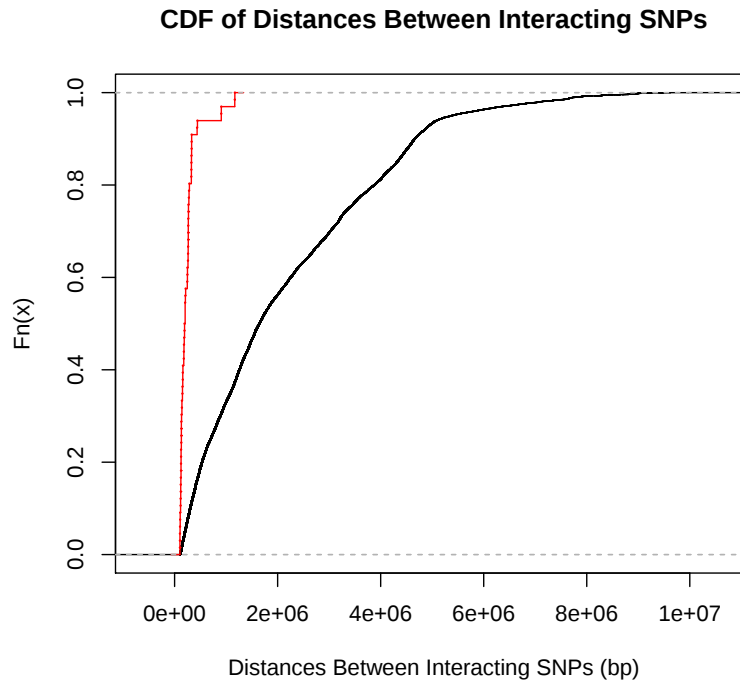


Figure S14 - HLA-G, PSORS1C1 and HLA-DRB5 share common interactors in the pre-frontal cortex.

SNPs involved in interactions affecting the expression of any of *HLA-G*, *PSORS1C1* or *HLA-DRB5* are denoted by a black rectangle. Where multiple rectangles exist for a single SNP, that SNP is a common interactor, i.e., rs2240064 is involved in interactions affecting the expression of *HLA-G* and *PSORS1C1*. SNPs are ordered from left to right in increasing order of their position on chromosome 6. The common interactors of the three transcripts span ≈ 1.6 Mb from rs2240064 (chr6:31114573) to rs2858331 (chr6:32681277). The schematic (bottom) shows the relative position of the three genes and the common interactors on chromosome 6.

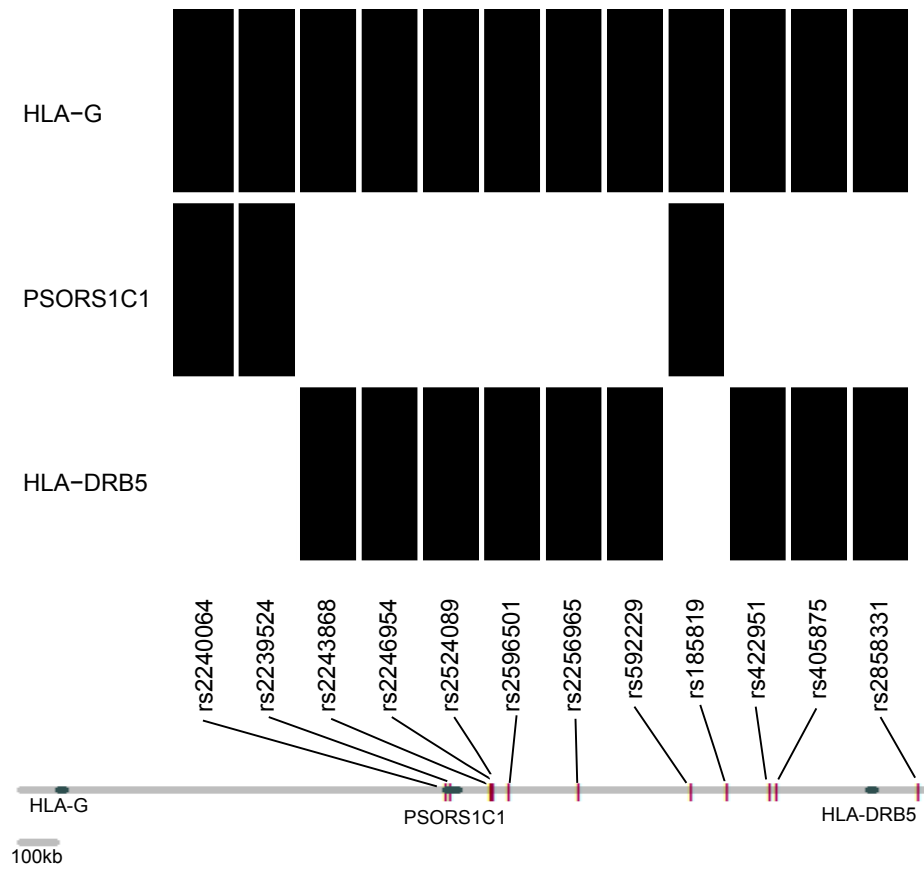


Figure S15 - Correlated expression of genes under epistatic regulation in the pre-frontal cortex

The expression of three transcripts, namely, *HLA-G*, *PSORS1C1* and *HLA-DRB5* on chromosome 6 are correlated. *PSORS1C1* expression is negatively correlated with *HLA-G* expression ($\rho = -0.21$, $p = 4.21 \times 10^{-7}$) and *HLA-DRB5* expression is positively correlated with *HLA-G* expression ($\rho = 0.18$, $p = 1.83 \times 10^{-5}$). The presence of multiples of the same gene is due to there being multiple expression probes for a single gene.

