Supplementary figures:

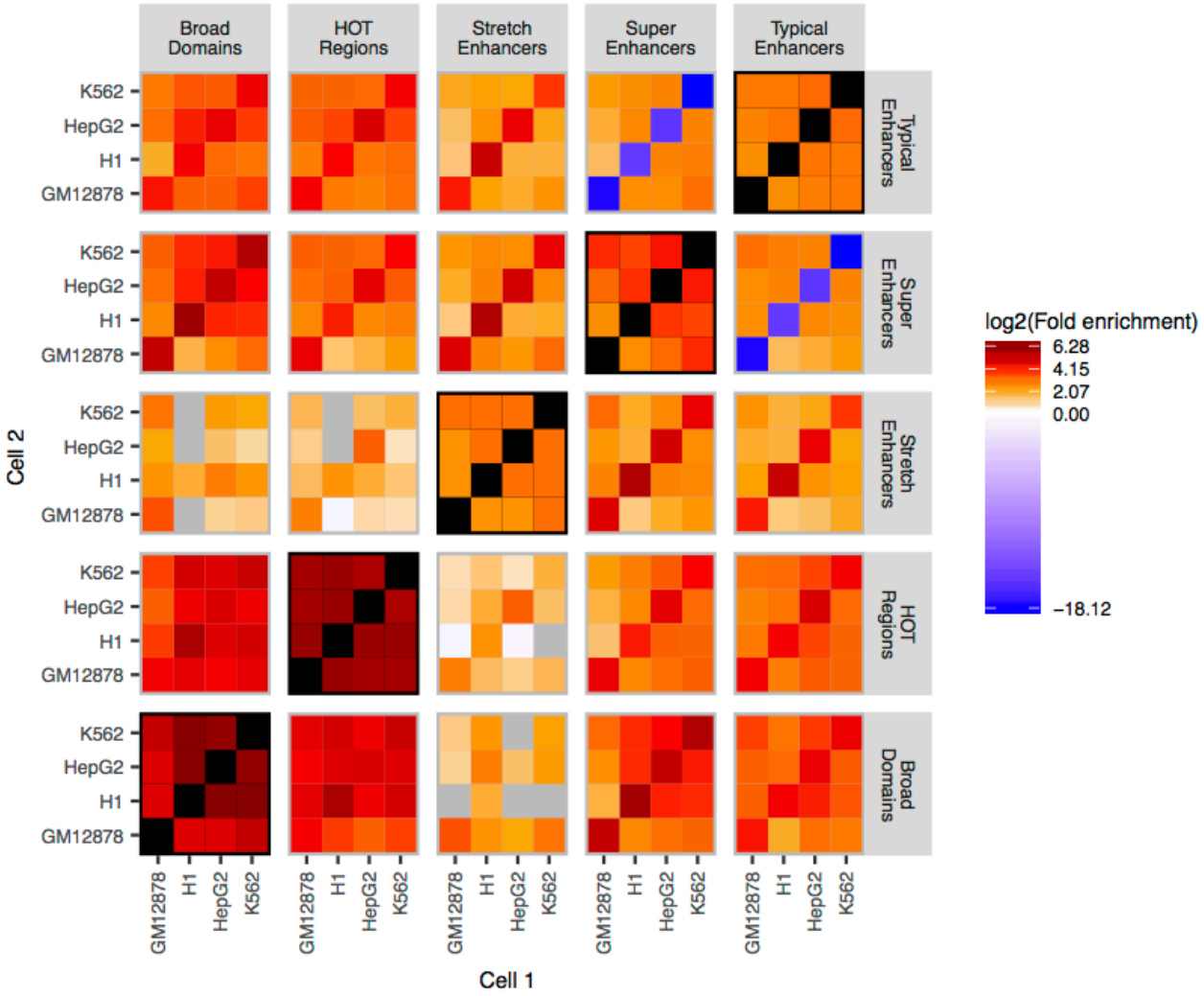

Figure S1: Log 2(Fold enrichment) for overlap between each pair of regulatory annotations is shown. Enrichments calculated using GAT [46]. Gray=Not significant after Bonferroni correction. Super and typical enhancers in the same cell type are strongly depleted for overlap since these are disjoint sets. Black tiles on the diagonal represent same cell type and regulatory annotation in the pair.

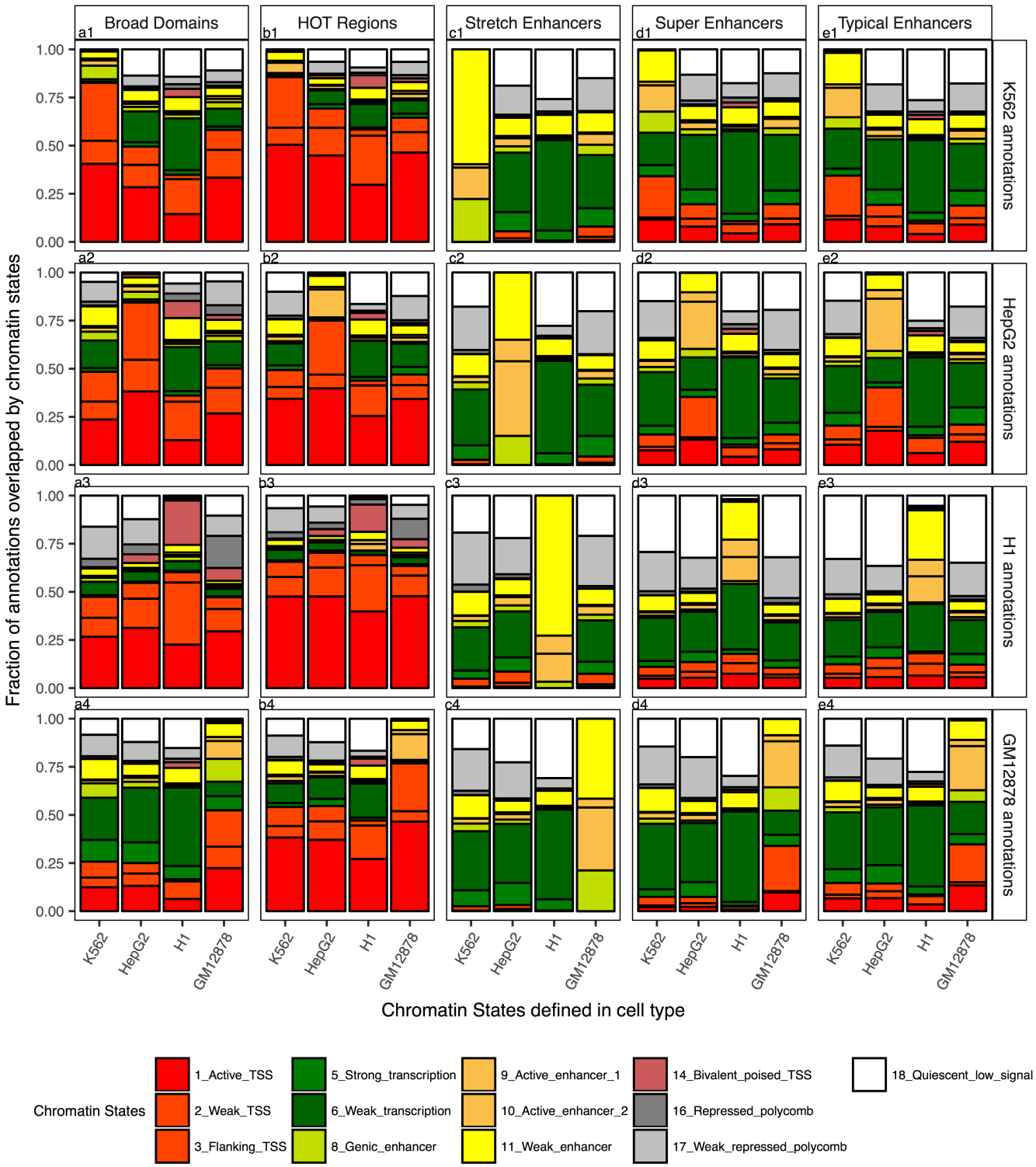

Figure S2: Fraction of annotations overlapped by chromatin states. Overlap fractions of each annotation (facet columns) defined in each cell type (facet rows) with chromatin states defined in each cell type (X-axis) is shown. Stretch enhancers were defined using the same chromatin state model for the corresponding cell types.

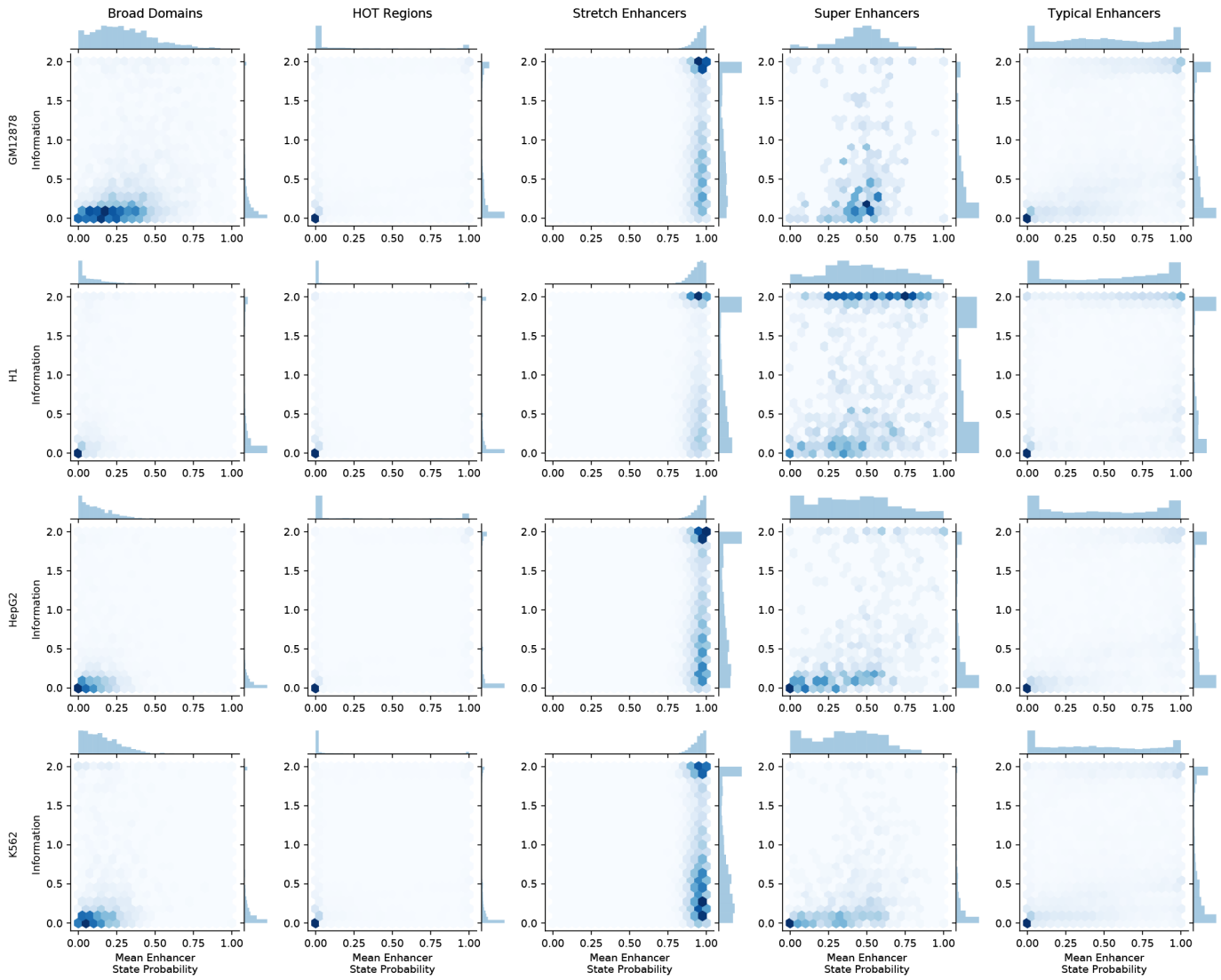

Figure S3: Enhancer chromatin state information content for annotations. Average posterior probability for an annotation segment to be called an enhancer chromatin state vs the information content of that feature in the each cell type (facet rows).

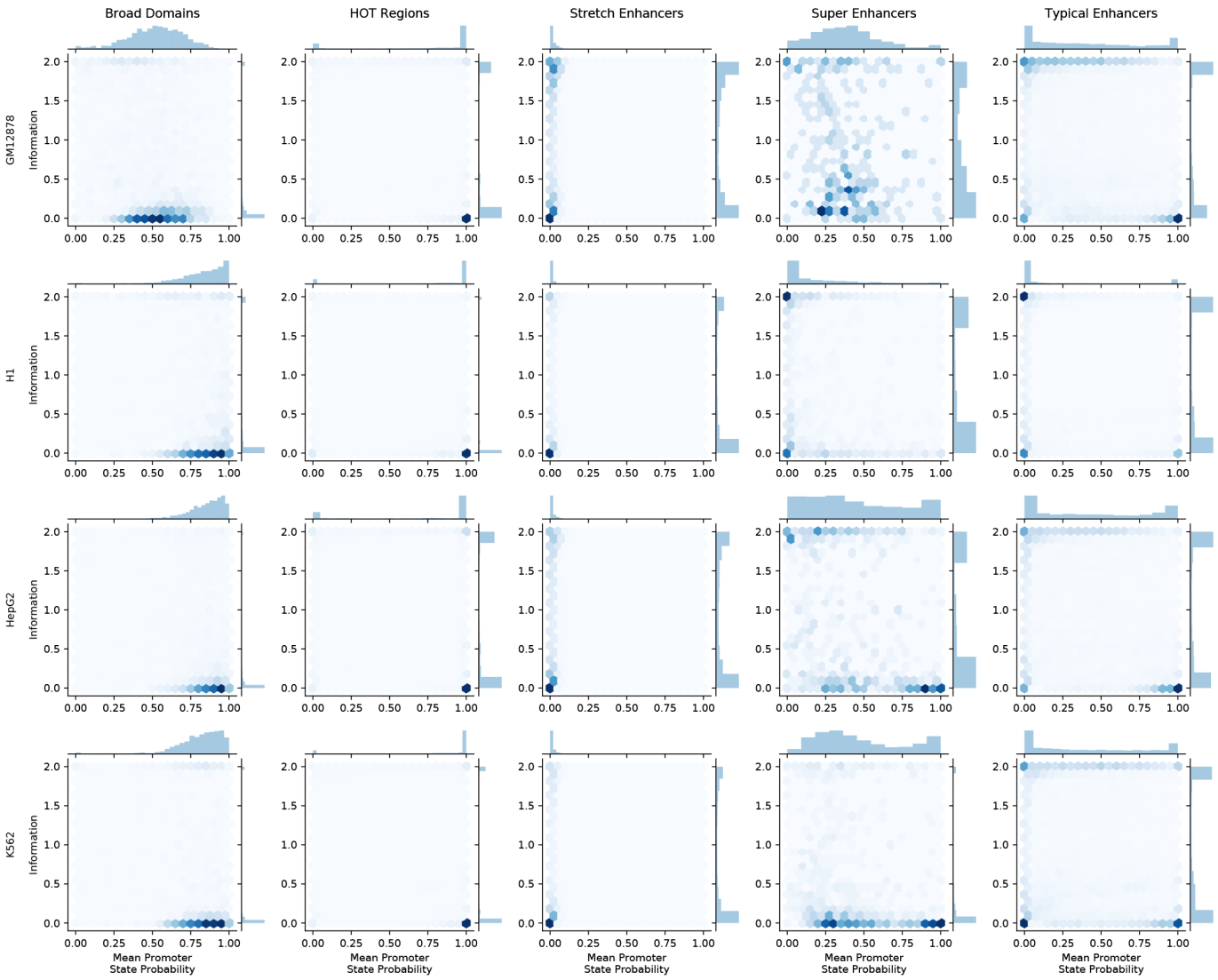

Figure S4: Promoter chromatin state information content for annotations. Average posterior probability for an annotation segment to be called an promoter chromatin state vs the information content of that feature in the each cell type (facet rows).

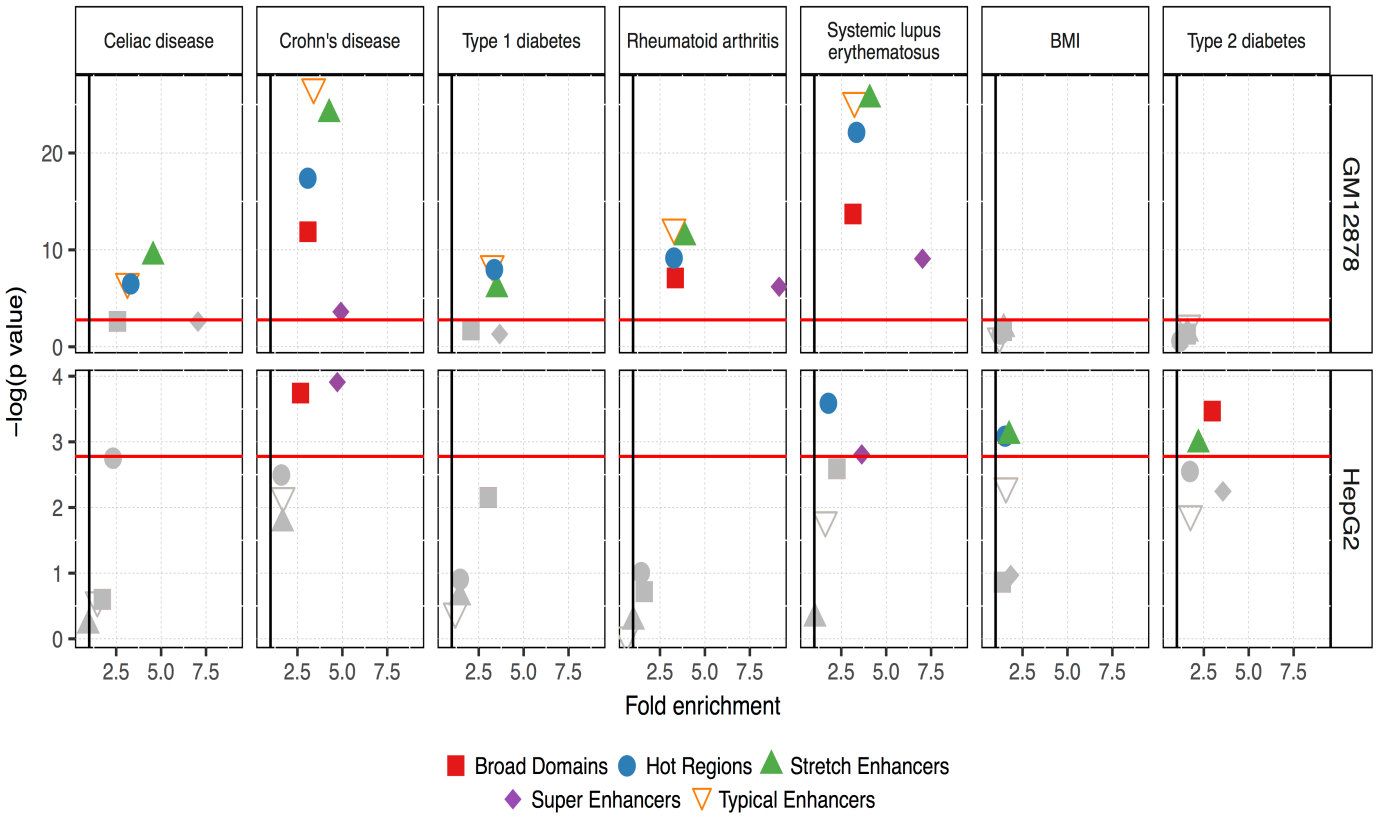

Figure S5: Enrichment for annotations in GM12878 and HepG2 to overlap GWAS loci for different traits. Red line = Bonferroni multiple testing correction threshold. Gray = not significant after Bonferroni correction. Annotations overlapping at least 3 GWAS loci for a trait are shown in each panel.

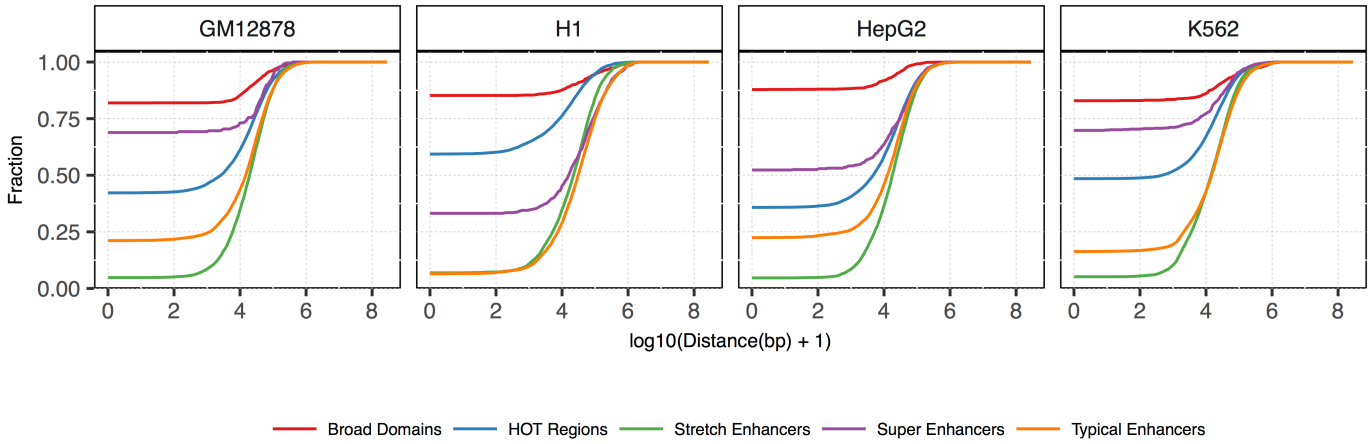

Figure S6: Cumulative distribution for distance to nearest TSS (all Gencode V19 protein coding genes) for segments in each regulatory annotation in each cell type.

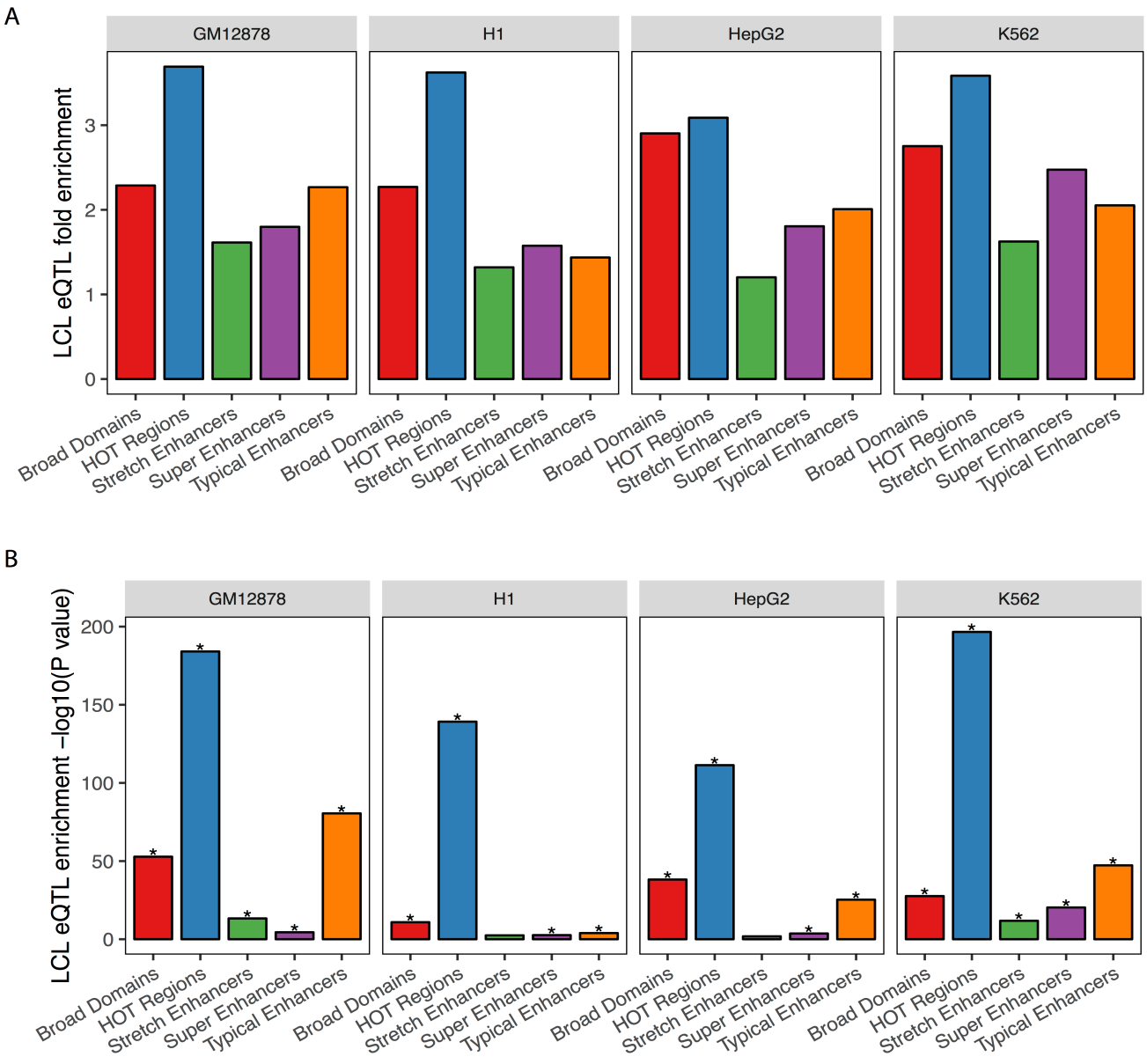

Figure S7: Enrichment of regulatory annotations in four cell types to overlap with LCL eQTL (GTEx v7). Fold enrichments are shown in A, -log10(p values) are shown in B. Enrichment p values significant after a Bonferroni correction for 20 tests are marked with '*'.

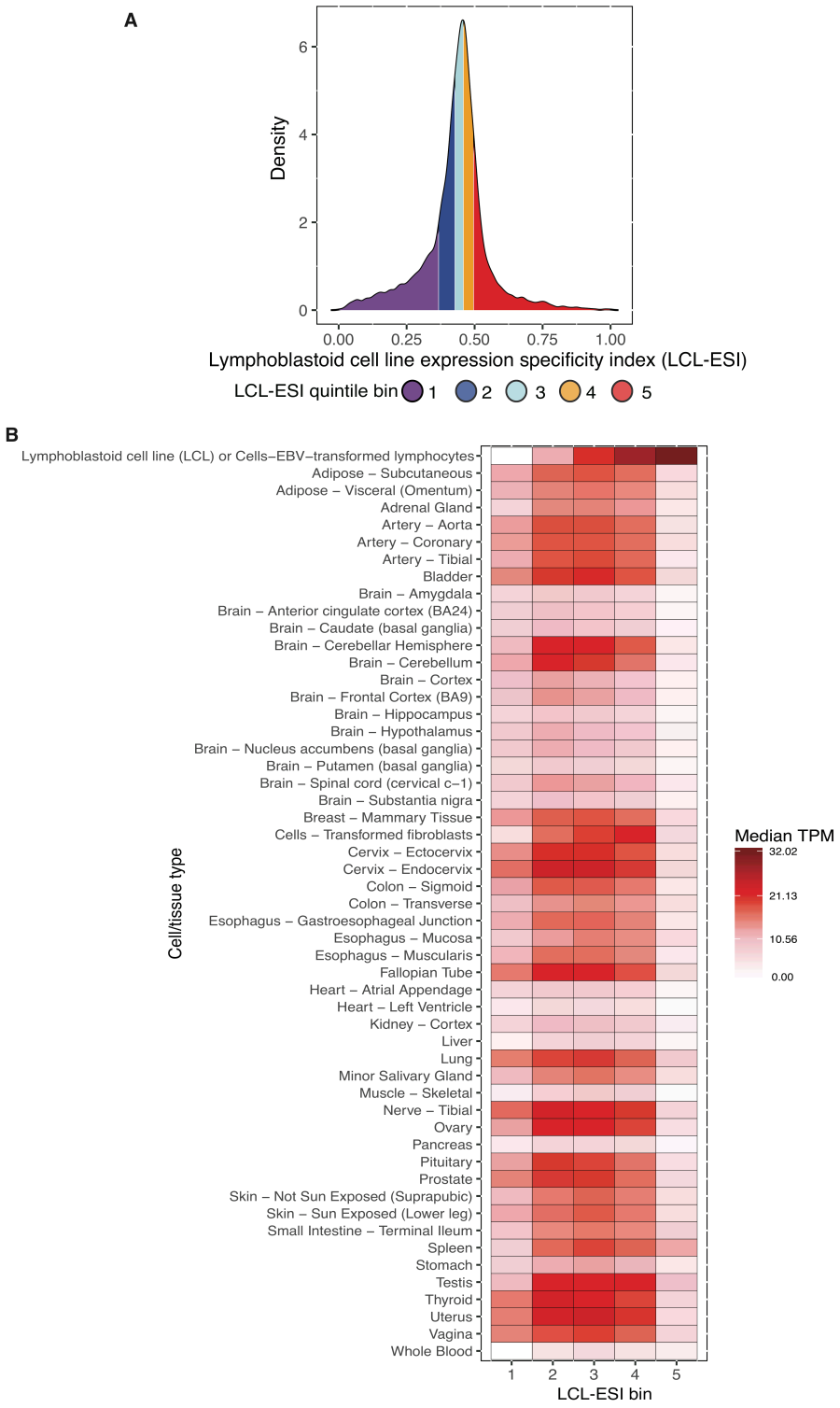

Fig S8: Gene expression specificity index in lymphoblastoid cell line (LCL-ESI). A: Distribution of LCL-ESI for protein coding genes with median transcripts per million (TPM) >= 0.15 in LCL. Colors indicate equal sized binning of the genes into quintiles by LCL-ESI. Each bin contained 2753 protein coding genes. B: Median TPM for genes in each LCL-ESI quintile bin across the 50 GTEx tissues analyzed. Lymphoblastoid cell line (LCL) is named as 'Cells-EBV-transformed lymphocytes' in the GTEx dataset.

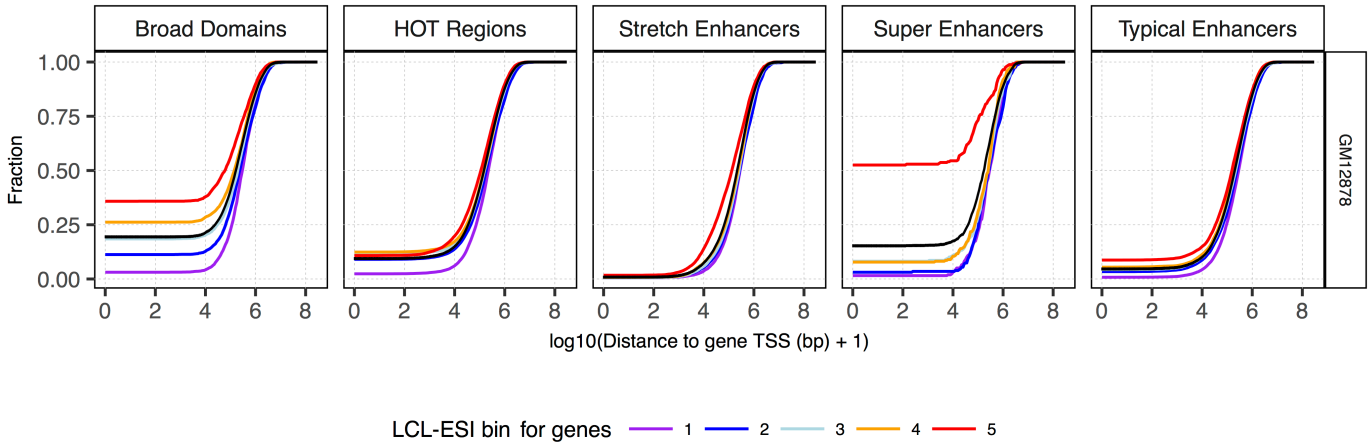

Figure S9: Cumulative distribution for distance to nearest TSS (Gencode V19 protein coding genes binned by LCL-ESI, 2753 genes in each bin) for regulatory annotations in GM12878. Black curves represent 10,000 random sub-samplings of 2753 genes from across the five bins.

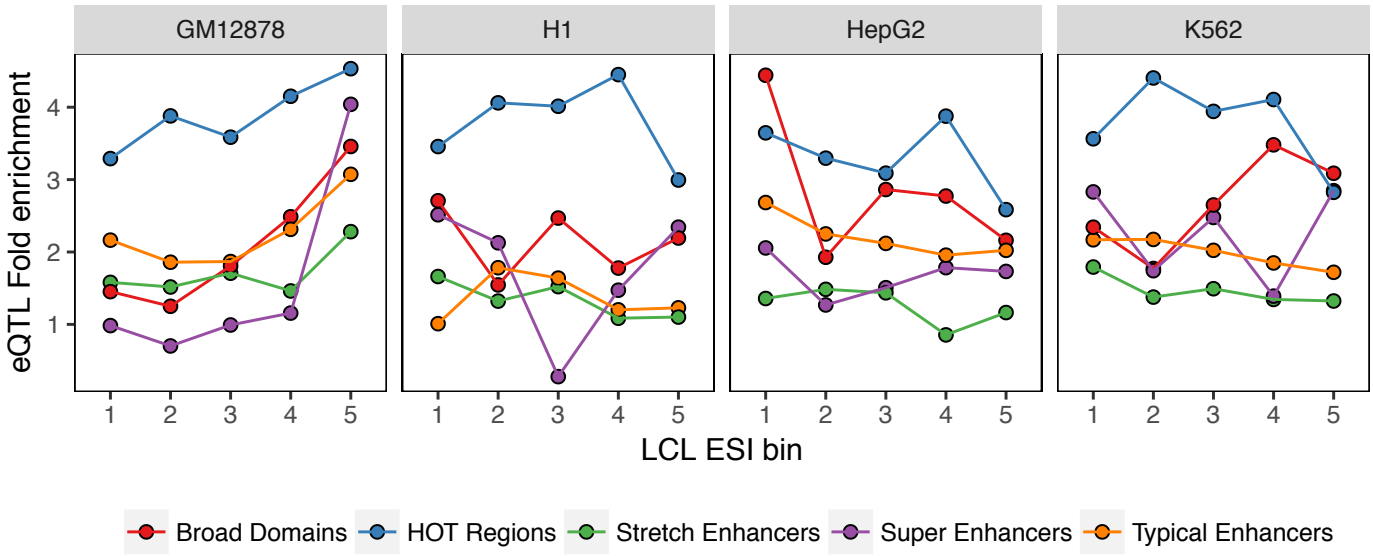

Figure S10: Enrichment for regulatory annotations to overlap LCL eQTL (GTEx v7, 10% FDR) binned by LCL-ESI or the eQTL eGene.

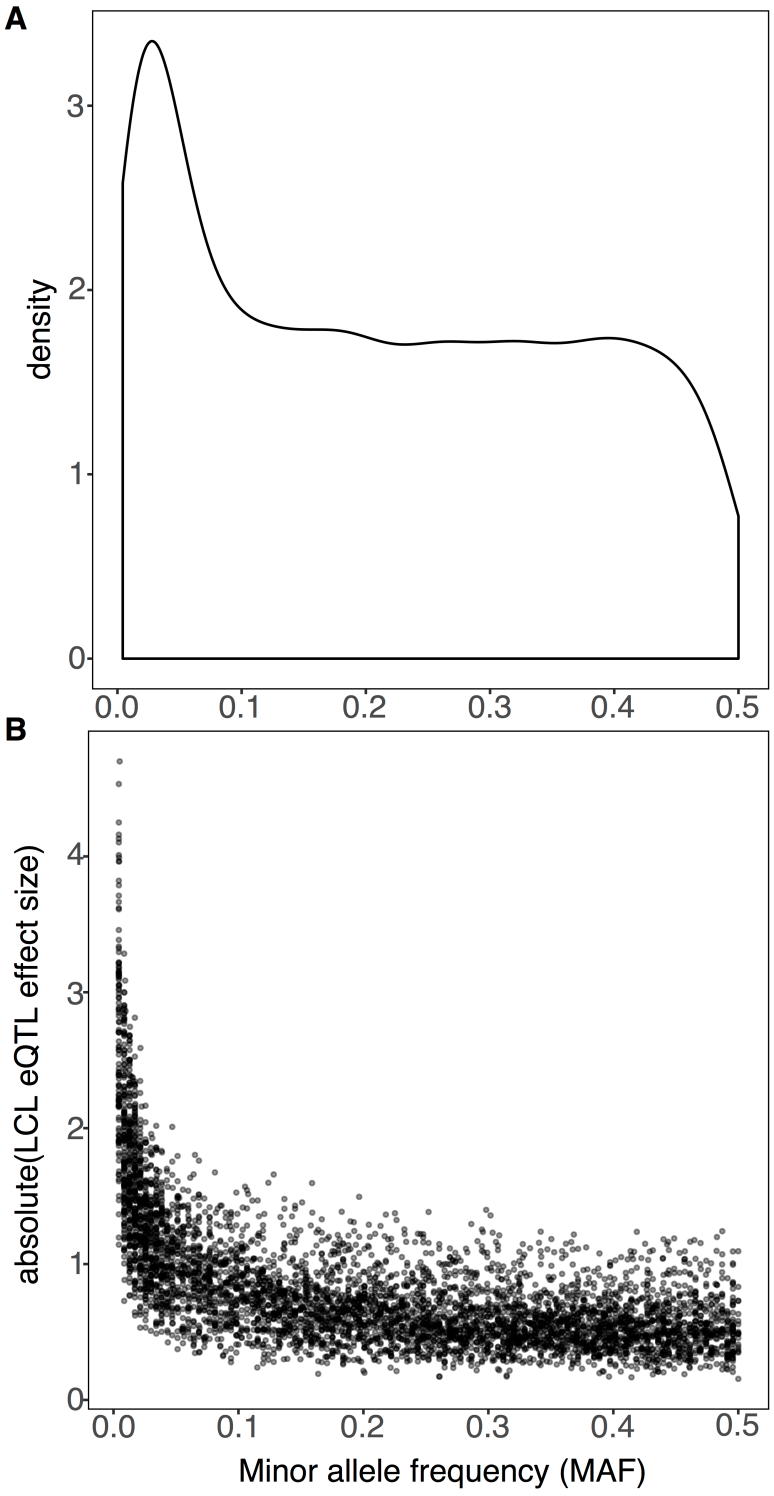

Fig S11: Lower minor allele frequency (MAF) variants have higher eQTL effect sizes. A: Distribution of MAF for LCL eQTL (GTEx v7, 10% FDR). B: LCL eQTL absolute effect size (slope of the linear regression) vs minor allele frequency (MAF).

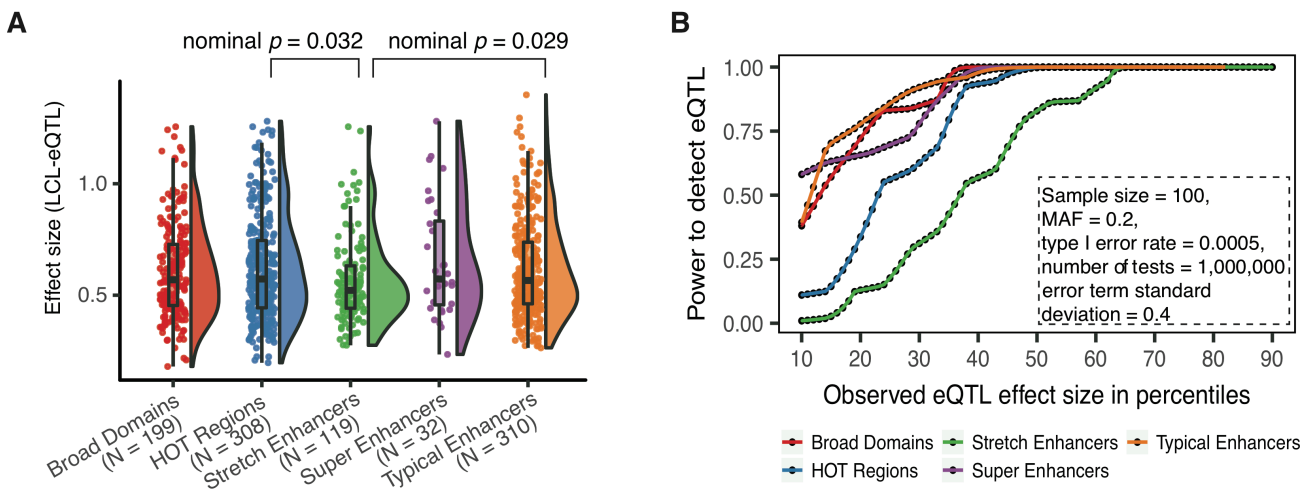

Figure S12: Gene expression and chromatin QTL effect size differences in regulatory annotations suggest regulatory buffering. A: Distribution of eQTL effect sizes for LCL eQTL (GTEx v7, 10% FDR) in GM12878 regulatory annotations are shown. Nominal P values < 0.05 are shown. B: Power to detect eQTL after Bonferroni correction at effect sizes corresponding the 10th through 90th percentiles observed for each annotation (shown in A). Other constant parameters for the power calculation are shown in box.

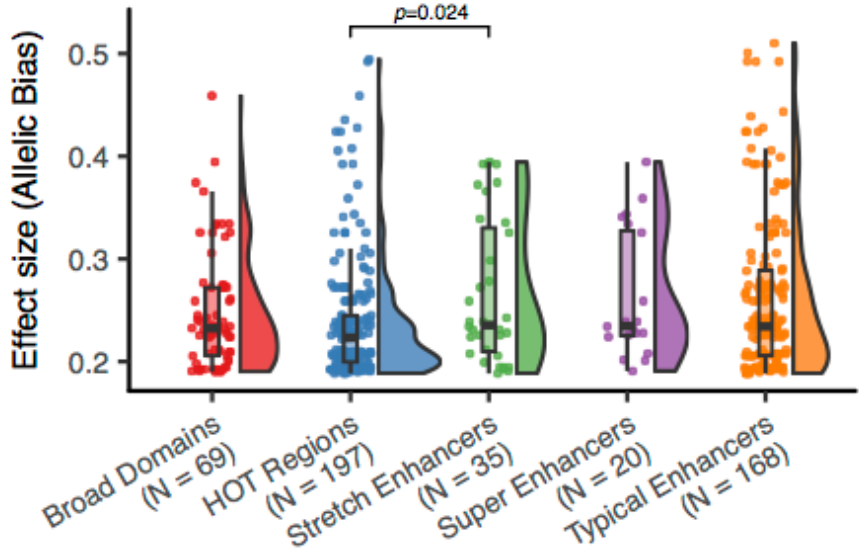

Figure S13: Effect sizes for Allelic Bias in GM12878 ATAC-seq after removing low MAF SNPs (consistent with eQTL and dsQTL effect size analyses). SNPs with MAF>0.2 and allelic bias *p* value < 0.05 were included for this analysis.

Supplementary tables:

Table S1: Ordinary least squares regression results modeling blood eQTL absolute effect size dependent on K562 HOT regions or stretch enhancer annotation, distance of the eQTL to eGene TSS and number of SNPs in LD r2>0.99

OLS Regression Results

Dependent Variable:	absolute eQTL effect size	R-squared:	0.027	Prob (F-statistic):	0.000172
Model:	OLS	Adj. R-squared:	0.023	Log-Likelihood:	153.18
Method:	Least Squares	F-statistic:	6.748		
No. Observations:	723	AIC:	-298.4		
Df Residuals:	719	BIC:	-280		
Df Model:	3				

	coef	standard error	t	P>|t|	[0.025	0.975]
Intercept	0.3211	0.009	34.394	0	0.303	0.339
absolute eQTL distance from eGene TSS	-0.1638	0.072	-2.281	0.023	-0.305	-0.023
Regulatory annotation binary variable HOT regions = 0; Stretch enhancer = 1	-0.0521	0.019	-2.795	0.005	-0.089	-0.015
Number of SNPs in LD r2>0.99	0.114	0.056	2.021	0.044	0.003	0.225

Omnibus:	210.562	Durbin-Watson:	1.999
Prob(Omnibus):	0	Jarque-Bera (JB):	483.62
Skew:	1.563	Prob(JB):	9.62E-106
Kurtosis:	5.505	Cond. No.	10.2

Table S2: See file gwas_reference.xlsx

Table S3: GM12878 ATAC-seq sample information

geo_accession	run_accession	cell_type	cell_count	replicate
GSM1155957	SRR891268	GM12878	50000	rep1
GSM1155958	SRR891269	GM12878	50000	rep2
GSM1155959	SRR891270	GM12878	50000	rep3
GSM1155960	SRR891271	GM12878	50000	rep4
GSM1155961	SRR891272	GM12878	500	rep1
GSM1155962	SRR891273	GM12878	500	rep2
GSM1155963	SRR891274	GM12878	500	rep3