

## Chromatin marks identify critical cell-types for fine-mapping complex trait variants

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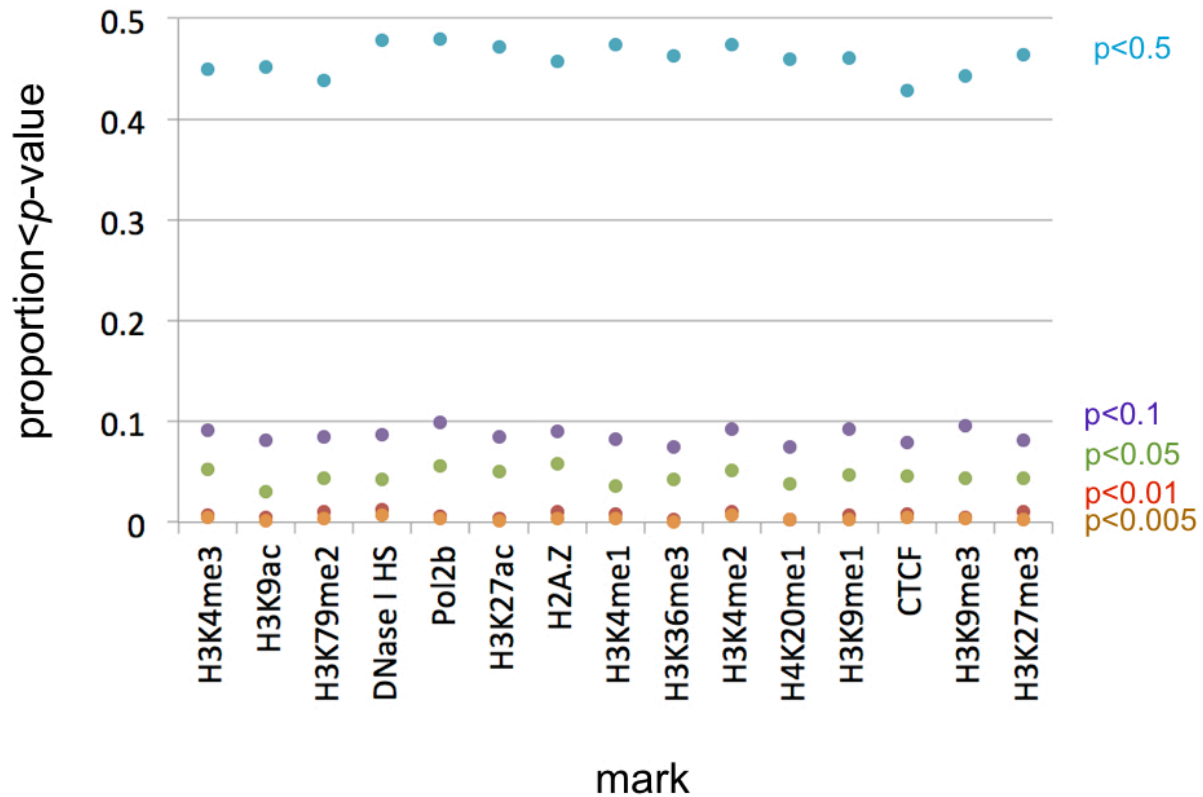
\*These authors contributed equally to this manuscript

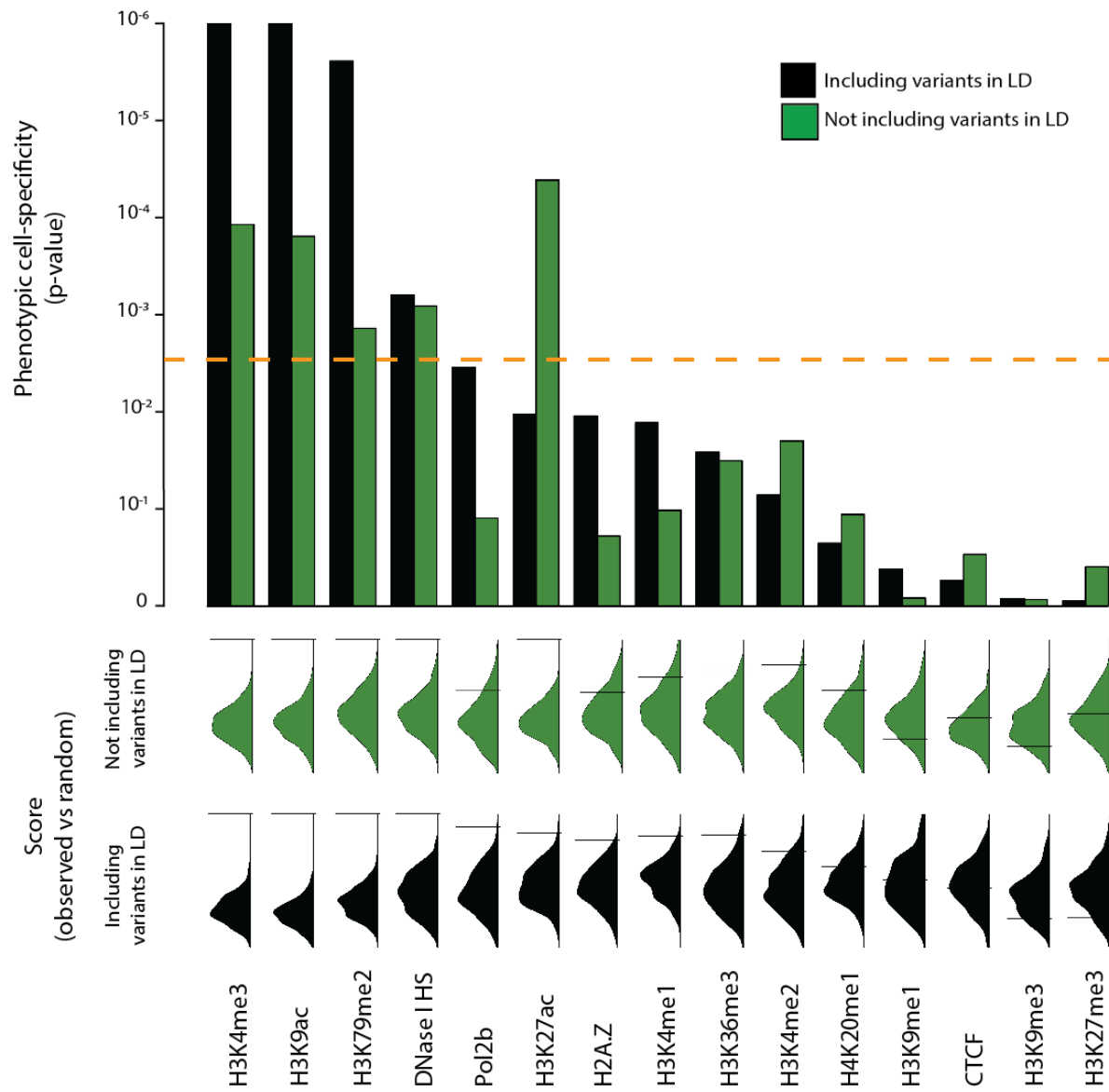
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## SUPPLEMENTARY MATERIALS

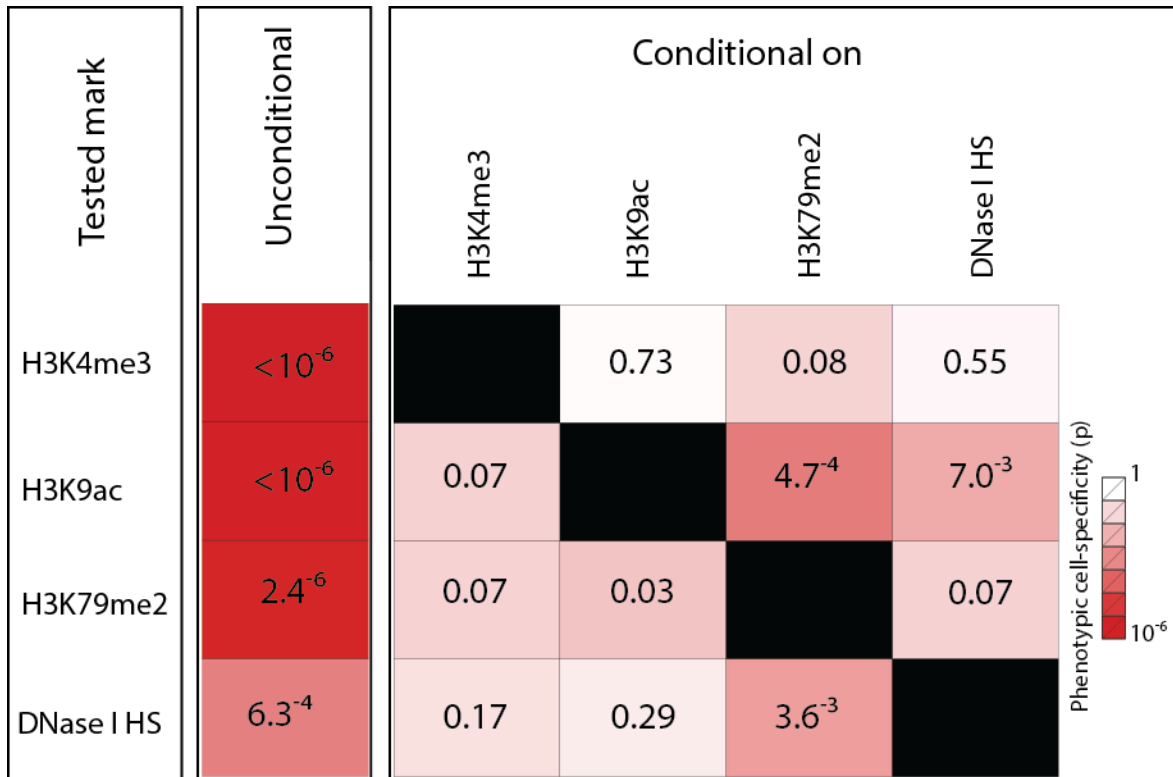
**Supplementary Figure 1: (A) Phenotypic cell-specificity p-values approximate type I error rate.** We tested 1,000 sets of 510 sampled SNPs where we replaced the 510 GWA catalog SNPs with SNPs sampled from throughout the genome where we matched on the total number of SNP in LD ( $r^2 > 0.8$ ) with them. We then tested marks for statistically significant phenotypic cell-specificity. We observed that in ~1% of instances marks obtained a  $p < 0.01$  significance threshold. **(B) Evaluating the phenotypic cell-specificity of different chromatin marks by including variants in LD with lead SNPs ( $r^2 > 0.8$ ) (black) and by using only the lead SNP of each region (green).** For each mark, we performed up to  $10^6$  permutations of SNPs and phenotypes to calculate the null distribution of phenotypic cell-specificity for comparison to the observed phenotypic cell-specificity. We display the distribution of phenotypic cell-specificity compared to the null (bottom) and the corresponding p-value (top). Yellow, dashed line indicates Bonferroni corrected p-value threshold.



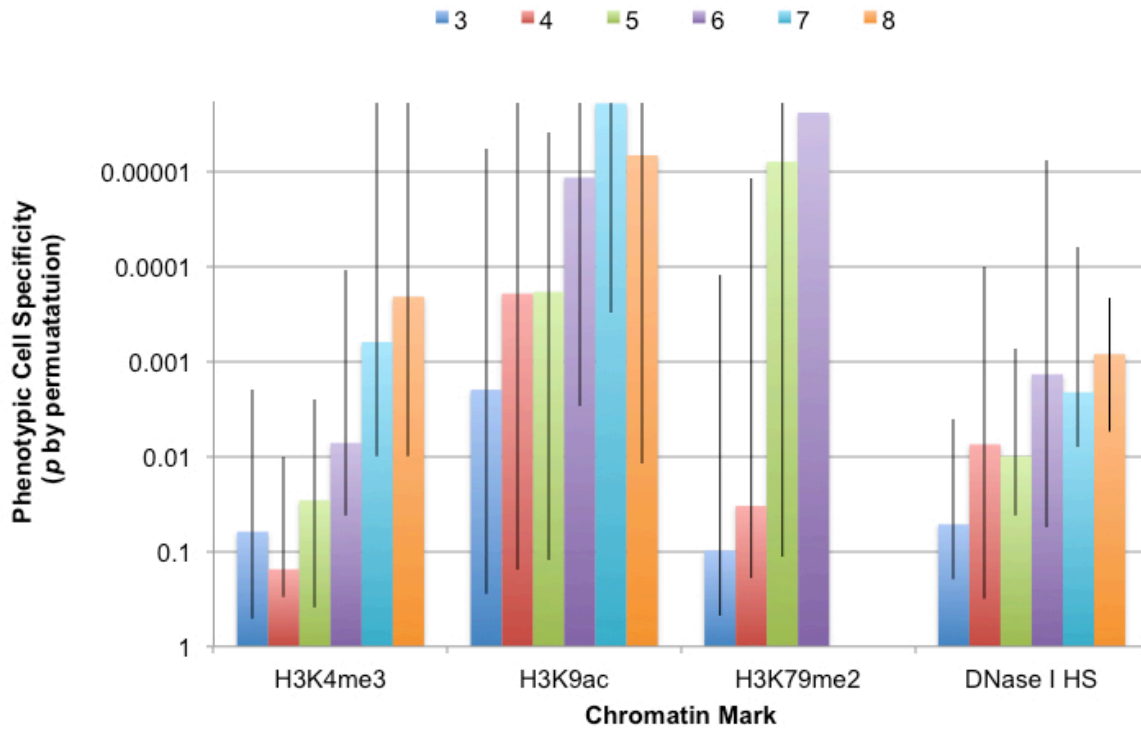




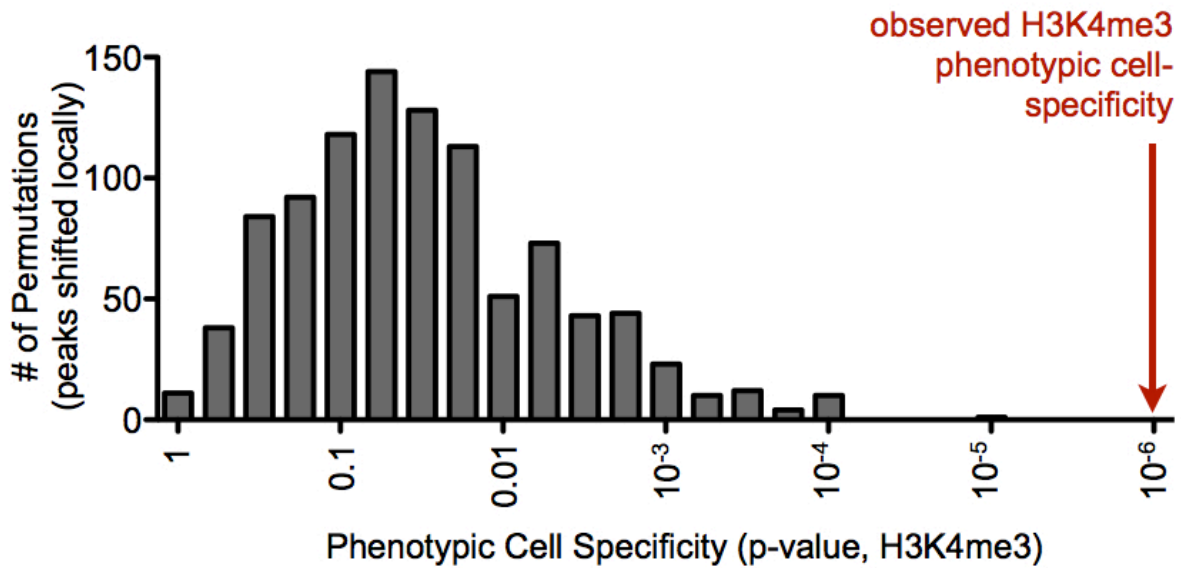
**Figure 3: Evaluation of the conditional phenotypic cell-specificity of five chromatin marks.** For the four most informative chromatin marks (see **Figure 2**) we estimated their significance for phenotypic cell-specificity before and after conditioning on other chromatin marks (listed across the top). To condition on marks we removed peaks overlapping with those of a second mark that we were conditioning on and reassessed phenotypic cell-specificity. We computed the significance based on permutation, using only those cell-types where data for both common chromatin marks was available.



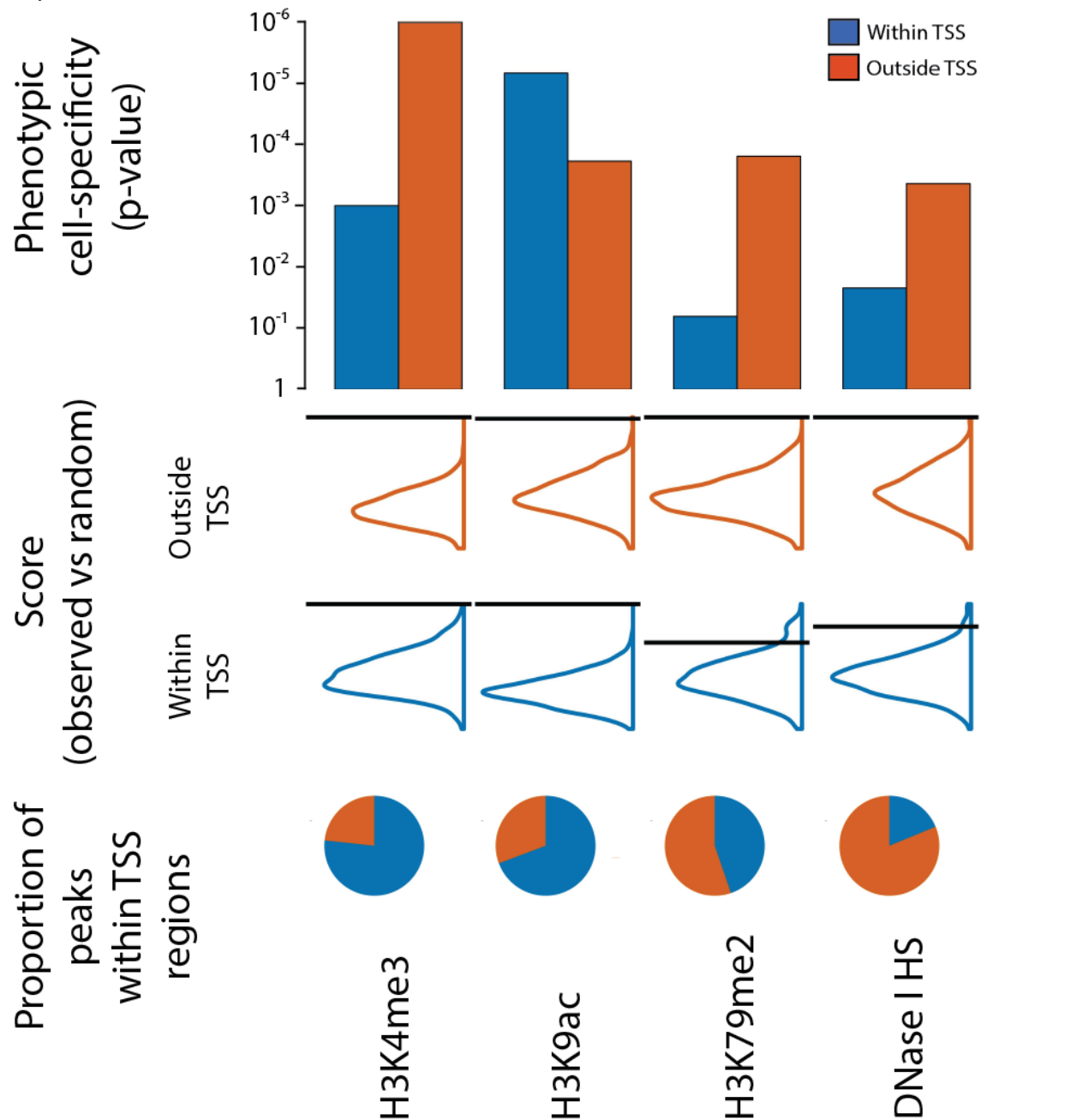
**Supplementary Figure 4: Number of tissues assayed for different ENCODE chromatin marks increases the power to detect phenotypic cell-specificity.** Among the variable number of tissues assayed for chromatin modification, we sampled a data from a fixed number, (3-8), and estimated the phenotypic cell-specificity and its significance with this subset. We reported for each chromatin modification the median p-value and 80% range.



**Supplementary Figure 5: Phenotypic cell-specificity of H3K4me3 is dependent on genomic position of peaks.** In order to assess the dependence of phenotypic cell-specificity on the specific location of ENCODE peaks, we conducted 1000 experiments where we re-assessed phenotypic cell-specificity by moving all epigenetic peaks within the region in LD with each of the 510 associated SNPs ( $r^2 > 0.8$ ). We moved peaks a fixed distance within the LD region that was defined based on a random distribution ( $\pm 10$  kb mean, 2.5 kb standard deviation). This approach maintained local peak structure across assayed cell-types. A histogram of significance p-values of phenotypic cell-specificity for the trials is presented; the red arrow indicates the observed phenotypic cell-specificity in the actual data ( $p < 10^{-6}$ ).

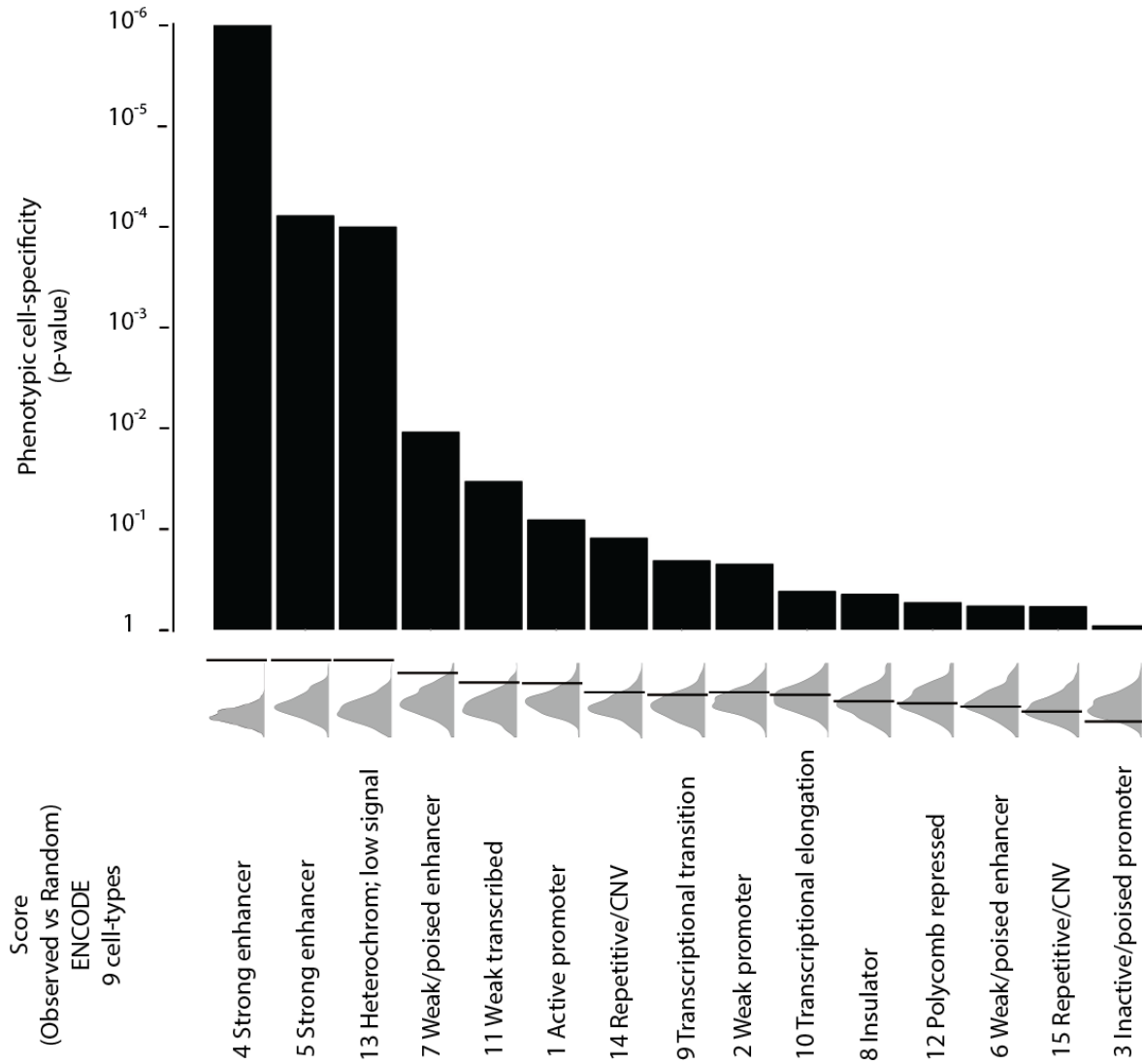


**Supplementary Figure 6: Evaluating the phenotypic cell-specificity of different chromatin marks within TSS regions (TSS +/- 2kbp) and outside the TSS regions.** We estimated the phenotypic cell-specificity with 510 SNPs associated with 31 phenotypes. We used chromatin profiles assayed on 14 ENCODE cell lines by classifying the peaks located within (blue) and outside of TSS regions (red). We then permuted SNPs to calculate significance (see **Methods, Figure 1**). We plot the p-values on the top. We used the null distribution to compute significance scores on the bottom. Scores within TSS are depicted in blue, while scores outside TSS are depicted in red.

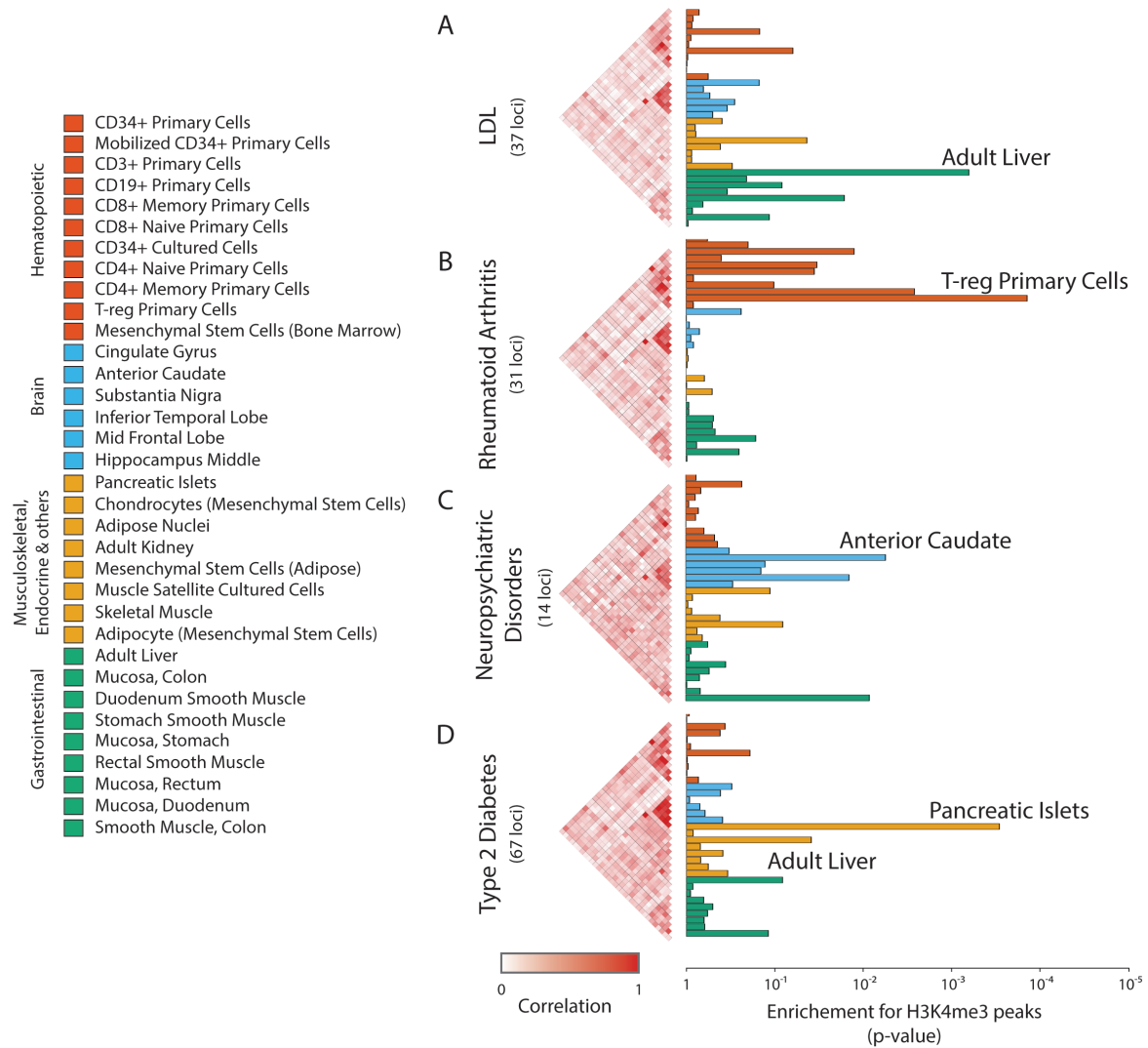




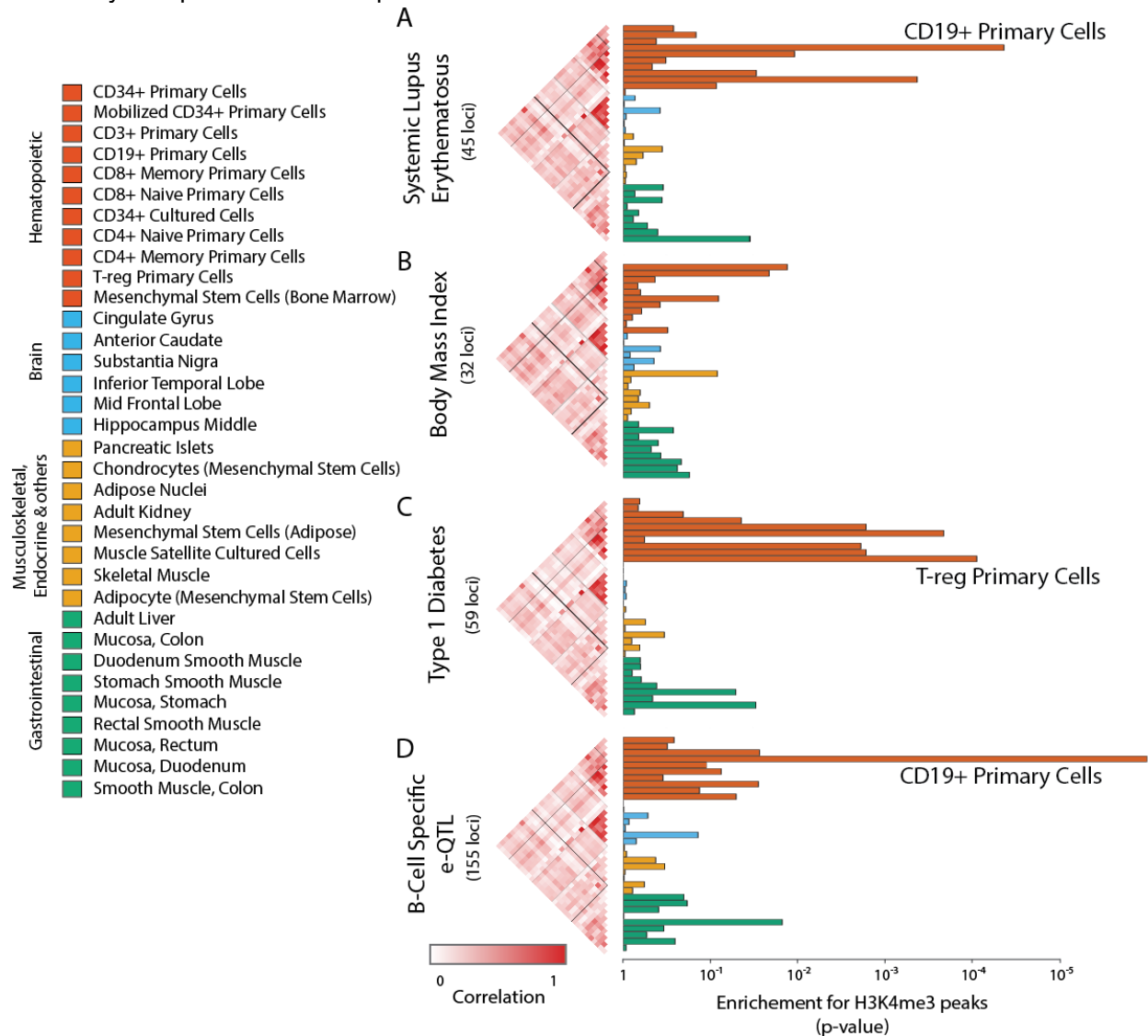
**Supplementary Figure 7: Evaluating the phenotypic cell-specificity for 15 functional annotations derived by clustering nine chromatin modifications into hidden Markov model states** (Ernst *et al. Nature* 2011). We computed the phenotypic cell-specificity of the different functional annotations using the same set of 510 SNPs and 31 different phenotypes. We then permuted SNPs and phenotypes to calculate a null distribution of phenotypic cell-specificity scores ( $n=10^6$ ); those results are plotted on the top panel. We used the null distribution to compute significance scores (bottom panel).



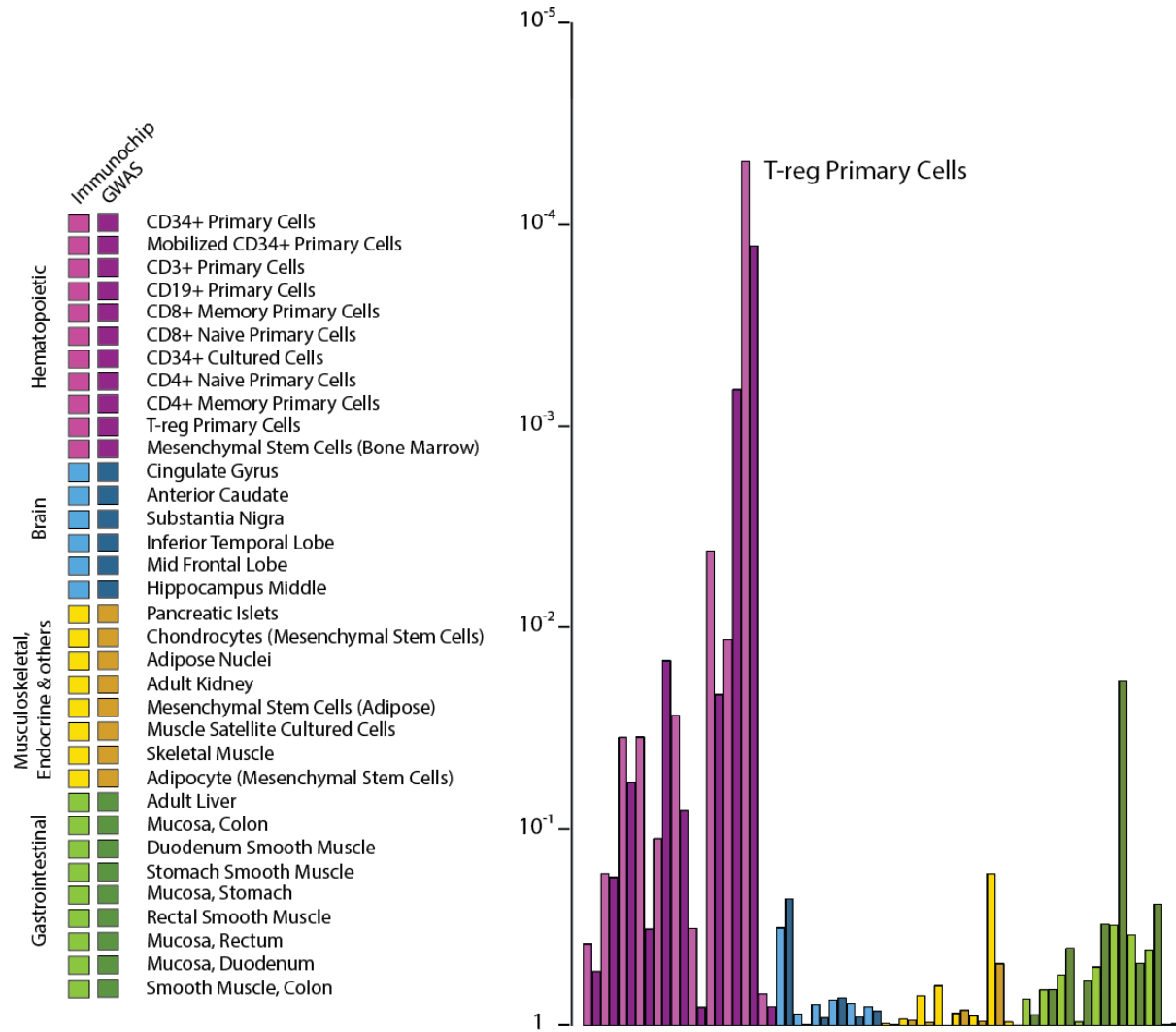
**Supplementary Figure 8: Calculating significance of H3K4me3 overlap with alleles from four complex traits using associated SNPs from the GWAS catalog.** We examined four phenotypes: **(A)** LDL cholesterol plasma concentration, **(B)** rheumatoid arthritis, **(C)** neuropsychiatric disorders (schizophrenia and bipolar disease) and **(D)** type 2 diabetes. For each phenotype we calculated the cell-specific overlap with H3K4me3 histone modification peaks in 34 tissues (listed on the left). In **Figure 3** we conducted a similar analysis, estimating significance from SNPs sampled throughout the genome, matching for the number of marks present locally for each SNP. Here, as a more stringent test, we restricted our matching to SNPs that had been associated with other phenotypes as reported in the GWAS catalog. The bars on the right represent the calculated significance of the overlap for each tissue with alleles from each of the phenotypes using sampled sets from the GWAS catalog. Adjacent to each bar plot, we present correlation coefficients between two tissues based on scores computed from randomly sampled sets of independent loci.



**Supplementary Figure 9: Overlap of SNPs for SLE, BMI, T1D and B-cell specific e-QTL with H3K4me3 marks in specific cell-types.** In addition to LDL, RA, neuropsychiatric disorders and type 2 diabetes, we examined further four, complex phenotypes: **(A)** SLE, **(B)** BMI, **(C)** T1D and **(D)** B-cell specific gene expression QTL. For each phenotype we calculated the cell-specific overlap with H3K4me3 histone modification peaks in 34 tissues (listed on the left). The bars on the right represent the significance of the overlap for each tissue with variants from each of the phenotypes, estimated by sampling sets of SNPs matched so that the total number of peaks overlapping SNPs in LD was the same as in the test set. Adjacent to each bar plots, we present correlation coefficients between two tissues based on scores computed from randomly sampled sets of independent loci.



**Supplementary Figure 10: Fine-mapping increases phenotypic-cell specificity signal.** In addition to 31 RA SNPs reported from GWAS studies, we tested the same loci but with recent results from fine-mapping study using dense genotyping platform, Immunochip (Eyre *et al* in review). The bars on the right represent the significance of the overlap for each tissue with variants from GWAS (darker shade) and Immunochip (lighter shade) studies.







**Supplementary Table 3: Individual SNPs for four phenotypes, and their proximity to cell-type specific peaks.**

**3A Rheumatoid Arthritis**

	Lead SNP	T-reg Primary Cells		
		best h/d SNP	distance	h/d score
Rheumatoid arthritis	rs4750316	rs947474	804	0.02
	rs874040	rs7441808	27	0.71
	rs548234	NA		
	rs3218253	rs3218251	166	0.21
	rs540386	rs4755453	269	0.22
	rs3890745	rs60733400	652	0.01
	rs3087243	rs12990970	621	0.38
	rs934734	rs268132	417	0.01
	rs1980422	rs6728441	76	0.23
	rs6920220	rs6927172	121	0.29
	rs13119723	rs13140464	116	0.63
	rs10865035	NA		
	rs13031237	rs67574266	493	0.04
	rs2104286	10:6102726	1065	0.79
	rs3093023	rs968334	368	0.07
	rs394581	rs169858	1091	0.13
	rs2476601	rs2476601	1193	0.03
	rs1678542	NA		
	rs7574865	rs10174238	571	0.15
	rs26232	rs28158	13	0.76
	rs2736340	rs998683	140	0.18
	rs951005	rs1928577	239	0.18
	rs12746613	NA		
	rs4810485	rs1883832	224	0.08
	rs6859219	rs10065637	5	0.80
	rs10488631	NA		
	rs3761847	rs11794516	17	0.41
	rs2812378	NA		
	rs11586238	NA		
	rs10892279	11:118660641	184	0.06
rs10919563	rs6683595	47	0.99	

**3B LDL cholesterol**

	Lead SNP	Adult Liver		
		best h/d SNP	distance	h/d score
	rs12027135	rs9438904	127	0.13
	rs7225700	rs11079772	8	0.06
	rs2000999	rs3794695	298	0.75

<b>LDL cholesterol plasma concentration</b>	rs3177928	NA		
	rs12916	NA		
	rs649129	NA		
	rs174583	11:61596322	1	1.00
	rs1564348	NA		
	rs3757354	rs760633	654	0.15
	rs2902941	NA		
	rs1129555	rs2419604	766	0.07
	rs2126259	rs2126259	186	0.99
	rs11065987	NA		
	rs1800562	rs115740542	1414	0.13
	rs2332328	NA		
	rs3850634	rs631106	56	0.01
	rs11153594	rs1999929	355	0.07
	rs1367117	2:21266774	1406	0.20
	rs964184	NA		
	rs4299376	NA		
	rs6882076	NA		
	rs10401969	19:19432290	1161	0.00
	rs2479409	rs2479409	900	0.45
	rs11220462	NA		
	rs1169288	rs1169288	143	0.43
	rs6511720	19:11201987	292	0.17
	rs247616	NA		
	rs1030431	NA		
	rs217386	rs217371	262	0.01
	rs629301	rs12740374	87	0.20
	rs514230	rs508293	2	1.00
rs4420638	rs56131196	17	1.00	
rs12670798	rs7809080	132	1.00	
rs909802	rs6072336	185	0.15	
rs11136341	rs11787335	41	0.10	
rs2807834	NA			
rs2954022	rs6999569	139	0.81	

### 3C Neuropsychiatric Diseases

	<b>Lead SNP</b>	<b>Anterior Caudate</b>		
		<b>best h/d SNP</b>	<b>distance</b>	<b>h/d score</b>
<b>iseases</b>	rs12576775	NA		
	rs10896135	rs7570	699	0.03
	rs17512836	NA		
	rs7296288	rs7296288	2377	0.24
	rs12807809	NA		



<b>Neuropsychiatric D</b>	rs7004633	NA		
	rs1625579	1:98513675	1327	0.08
	rs17662626	NA		
	rs4765913	NA		
	rs7914558	rs2275271	124	0.05
	rs10503253	NA		
	rs11191580	rs79780963	35	0.30
	rs10994397	rs1938540	4	0.97
	rs12966547	rs4128242	252	0.69

### 3D Type 2 Diabetes

Lead SNP	Pancreatic Islets			Adult Liver		
	best h/d SNP	distance	h/d score	best h/d SNP	distance	h/d score
rs2028299	NA			rs12594808	195	0.03
rs13292136	NA			NA		
rs12970134	NA			NA		
rs459193	rs30351	1977	0.05	NA		
rs4689388	4:6275294	16	0.04	rs6830765	15	0.18
rs12454712	NA			NA		
rs2334499	NA			rs4417225	163	1.00
rs4402960	rs6769511	24	1.00	NA		
rs1387153	rs10765572	12	1.00	rs10765572	355	0.03
rs1802295	NA			NA		
rs11708067	NA			NA		
rs163184	NA			NA		
rs7578326	rs7578326	1076	0.17	2:227025121	114	0.88
rs780094	NA			rs1260326	140	1.00
rs5215	rs1002226	1288	0.02	rs10832778	112	0.39
rs7961581	NA			NA		
rs1531343	NA			NA		
rs972283	NA			NA		
rs8090011	NA			NA		
rs11634397	rs1357336	85	0.53	rs2866367	587	0.13
rs4457053	rs7732130	5	1.00	NA		
rs231362	NA			NA		
rs3794991	NA			rs73002956	432	0.07
rs8108269	rs11670462	671	0.01	NA		
rs516946	NA			NA		
rs7041847	rs10814915	84	0.94	rs10814917	2021	0.06
rs831571	NA			NA		
rs10946398	NA			NA		
rs13266634	rs35859536	2428	1.00	NA		
rs6017317	rs12480669	1409	0.04	rs6031507	1986	0.19

Type 2 Diabetes						
rs10923931	NA			rs2934381	447	0.06
rs17584499	NA			NA		
rs896854	rs896854	46	0.04	rs1320164	14	0.33
rs243021	rs243018	297	0.24	NA		
rs7901695	rs7903146	345	0.07	NA		
rs12571751	NA			rs703976	340	0.04
rs9470794	6:38078250	12	0.28	6:38131851	4	0.84
rs16861329	NA			NA		
rs2191349	rs10228796	12	0.47	rs7798124	24	0.54
rs8050136	rs28567725	146	0.53	rs8047587	2207	0.02
rs7178572	rs62007299	292	0.09	rs34591043	200	0.18
rs864745	rs849142	1191	0.05	rs1635852	128	0.28
rs3786897	NA			rs3786898	2	1.00
rs2796441	rs2796441	161	0.93	NA		
rs5015480	NA			rs10882101	23	0.82
rs7202877	rs60879082	938	0.01	rs73605139	507	0.05
rs340874	rs340874	1301	0.06	rs340874	2456	0.06
rs10811661	NA			NA		
rs1552224	rs1552224	98	0.01	rs1552224	48	0.07
rs7612463	3:23243837	307	0.03	3:23243837	483	0.14
rs4523957	rs4523957	1333	0.05	17:2213409	68	0.73
rs8042680	rs6496747	253	0.17	rs6496747	1091	0.09
rs7957197	rs12425790	1442	0.07	rs12425790	1639	0.15
rs7593730	NA			NA		
rs1535500	NA			rs10947804	964	0.00
rs4607517	rs2908289	36	0.12	rs1004558	423	0.18
rs7172432	rs7163757	54	0.28	NA		
rs4607103	NA			NA		
rs1359790	rs11616380	18	0.16	rs11616380	87	0.03
rs10842994	rs10842991	2	1.00	NA		
rs6467136	rs4551267	1562	0.25	rs4551267	1932	0.18
rs1801282	rs17036160	774	0.01	rs7649970	181	0.12
rs3923113	NA			NA		
rs7578597	rs74382177	26	0.62	rs76282560	623	0.02
rs6815464	rs55875205	80	0.03	rs73069965	74	0.03
rs11063069	rs4238013	1941	0.11	NA		
rs12779790	NA			NA		

**Supplementary Table 4:** Significance (p) of the overlap for each tissue with alleles from each of the phenotypes.

		Chondrocytes from Bone Marrow Derived Mesenchymal Stem Cell Cultured Cells	Adipose Derived Mesenchymal Stem Cell	Mesenchymal Stem Cell Derived Adipocyte Cultured Cells	CD34 Primary Cells	Skeletal Muscle	Brain Cingulate Gyrus	Mobilized CD34 Primary Cells	Colon Smooth Muscle	Rectal Mucosa	Adipose Nuclei	CD19 Primary Cells	Adult Kidney	Bone Marrow Derived Mesenchymal Stem Cell Cultured Cells	Brain Anterior Caudate	Pancreatic Islets	Brain Substantia Nigra	Fetal Heart	Brain Inferior Temporal Lobe	Treg Primary Cells	Colonic Mucosa	CD4 Naive Primary Cells	Stomach Smooth Muscle	Brain Mid Frontal Lobe	Th17 Primary Cells	Muscle Satellite Cultured Cells	Duodenum Mucosa	CD3 Primary Cells	Rectal Smooth Muscle	Fetal Lung	CD34 Cultured Cells	CD8 Naive Primary Cells	Brain Hippocampus Middle	CD4 Memory Primary Cells	Fetal Brain	Adult Liver	CD8 Memory Primary Cells	Stomach Mucosa	Duodenum Smooth Muscle				
Serum Low Density Lipoprotein	H3K4me3	0.84	0.90	0.53	0.30	0.66	0.84	0.23	0.74	0.96	0.85	0.84	0.035	0.023	0.66	0.75	0.64	0.49	NA	0.20	0.97	0.19	0.95	0.29	0.53	0.91	0.077	0.91	0.37	NA	0.035	0.94	0.98	NA	NA	0.90	0.011	0.90	0.20				
	H3K27me3	0.90	0.60	0.36	0.30	0.038	NA	0.32	0.012	0.48	0.96	NA	NA	0.98	0.36	0.79	0.88	0.13	0.56	0.038	0.30	0.75	0.35	NA	NA	0.83	0.25	0.011	0.040	0.27	NA	0.039	0.54	0.43	NA	1.00	0.85	0.90	0.64	0.20			
	H3K36me3	0.55	0.24	0.72	0.36	0.60	0.55	0.94	0.31	0.47	0.84	0.87	0.086	0.20	0.67	0.069	0.64	0.29	0.37	0.66	0.72	0.88	0.78	0.73	NA	0.44	0.0085	0.13	0.040	0.81	0.87	0.49	0.17	0.051	NA	0.0050	0.72	0.41	0.38	0.64	0.20		
	H3K4me1	0.94	0.91	0.96	0.36	NA	0.20	0.064	0.22	0.30	0.27	0.84	NA	0.20	0.19	0.65	0.77	NA	0.19	0.76	NA	0.075	0.92	0.48	0.20	NA	0.76	0.024	0.64	0.79	0.32	0.11	0.019	0.27	0.023	0.84	0.21	0.17	0.41	0.64	0.20		
	H3K9ac	0.83	1.0	0.39	0.96	NA	0.94	0.56	NA	0.18	0.10	0.0025	NA	0.33	0.94	0.089	0.55	0.42	NA	0.76	NA	0.20	NA	0.50	0.89	0.97	0.09	0.75	0.28	0.79	NA	0.23	NA	0.038	0.028	0.66	0.21	0.17	0.41	0.64	0.20		
	H3K9me3	0.48	0.34	0.057	0.36	NA	0.093	0.69	0.99	0.26	0.48	0.77	NA	0.63	0.35	NA	0.42	0.0094	0.78	0.98	0.79	0.68	0.47	0.35	0.34	0.95	0.91	0.50	0.83	0.57	0.08	0.92	NA	NA	0.86	0.66	0.0018	0.21	0.17	0.41	0.64	0.20	
Neuropsychiatric Diseases	H3K4me3	0.90	0.36	0.63	0.63	0.63	0.72	0.14	0.026	0.95	0.87	0.47	0.86	0.54	0.0076	0.18	0.22	NA	0.36	0.33	0.63	0.97	0.41	0.044	NA	0.13	0.63	0.38	0.63	0.67	0.46	0.31	0.29	NA	0.58	0.80	0.52	0.18	0.82	0.18	0.82	0.18	0.82
	H3K27me3	0.69	0.99	0.99	0.63	0.81	0.44	0.44	0.088	0.54	0.47	NA	NA	0.24	0.88	0.76	0.17	7.0E-05	0.84	0.69	0.48	0.27	0.10	NA	NA	0.054	0.38	0.93	NA	0.23	0.59	0.39	0.52	0.91	0.49	0.91	0.49	0.80	0.57	0.52	0.18	0.82	
	H3K36me3	0.87	0.78	0.074	0.99	0.82	0.33	0.22	0.054	0.73	0.18	0.18	0.54	0.16	0.52	0.15	0.84	0.12	0.31	0.63	0.82	0.49	0.91	0.40	NA	0.90	0.79	0.68	0.31	0.68	0.23	0.63	0.46	0.60	0.15	0.89	0.89	0.68	0.87	0.18	0.82	0.18	0.82
	H3K4me1	0.50	0.08	0.029	0.074	NA	0.79	0.55	0.29	0.58	0.028	0.54	0.43	0.54	0.43	0.35	0.84	NA	0.71	0.69	0.15	0.82	0.91	0.31	0.40	NA	0.88	0.68	0.12	0.31	0.51	0.59	0.46	0.60	0.30	0.97	0.15	0.89	0.89	0.68	0.87	0.18	0.82
	H3K9ac	0.69	0.45	0.11	0.029	NA	0.075	0.55	0.44	1.0	0.88	0.96	NA	0.95	0.48	0.62	0.52	NA	NA	0.89	NA	0.90	0.13	0.07	0.07	0.44	0.94	0.95	0.95	0.12	0.51	0.83	0.60	0.30	0.83	0.97	0.15	0.89	0.89	0.68	0.87	0.18	0.82
	H3K9me3	0.59	0.64	0.64	0.63	NA	0.62	0.055	0.68	0.058	0.68	0.052	NA	0.10	0.94	0.26	0.17	0.30	NA	0.14	0.83	0.83	0.87	1.00	0.13	0.21	0.56	0.62	0.85	0.56	1.0	0.95	0.92	0.46	0.83	0.97	0.15	0.89	0.89	0.68	0.87	0.18	0.82

Type 2 Diabetes		Rheumatoid Arthritis	
H3K9me3	0.46	0.32	0.031
H3K4me1	0.14	0.73	0.37
H3K36me3	0.031	0.47	0.30
H3K27me3	NA	NA	NA
H3K4me3	0.44	0.99	0.13
H3K9ac	0.065	0.67	0.91
H3K36me3	0.32	NA	0.42
H3K27me3	0.0069	0.90	0.52
H3K4me1	0.61	0.42	0.25
H3K4me3	0.67	0.22	0.40
H3K9ac	NA	NA	NA
H3K36me3	0.27	0.23	0.21
H3K27me3	0.93	0.99	0.53
H3K4me1	0.61	0.66	0.65
H3K4me3	NA	0.0063	0.16
H3K9ac	0.015	0.87	0.89
H3K36me3	0.49	NA	NA
H3K27me3	0.68	0.37	0.38
H3K4me1	0.61	NA	NA
H3K4me3	0.024	0.95	0.13
H3K9ac	0.43	NA	0.94
H3K36me3	0.012	0.049	0.41
H3K27me3	0.60	0.99	0.84
H3K4me1	0.26	NA	NA
H3K4me3	0.83	0.77	0.74
H3K9ac	0.91	0.99	0.63
H3K36me3	NA	NA	0.08
H3K27me3	0.37	0.92	0.73
H3K4me1	0.52	0.34	0.68
H3K4me3	0.011	NA	0.21
H3K9ac	0.82	NA	0.77
H3K36me3	0.73	0.10	0.29
H3K27me3	0.81	NA	0.94
H3K4me1	NA	NA	0.08
H3K4me3	0.48	0.34	0.31
H3K9ac	0.72	NA	0.34
H3K36me3	0.63	0.26	0.65
H3K27me3	0.047	NA	0.10
H3K4me1			
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