The American Journal of Human Genetics, Volume *104*

Supplemental Data

Disease Heritability Enrichment of Regulatory Elements Is Concentrated in Elements with Ancient Sequence Age and Conserved Function across Species

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Figure S1: **Correlation heat map.** Correlation of the annotations presented in this paper with all functional annotations in baseline-LD model (among common SNPs, MAF $\geq$ 0.05). Numerical values found in Table S1

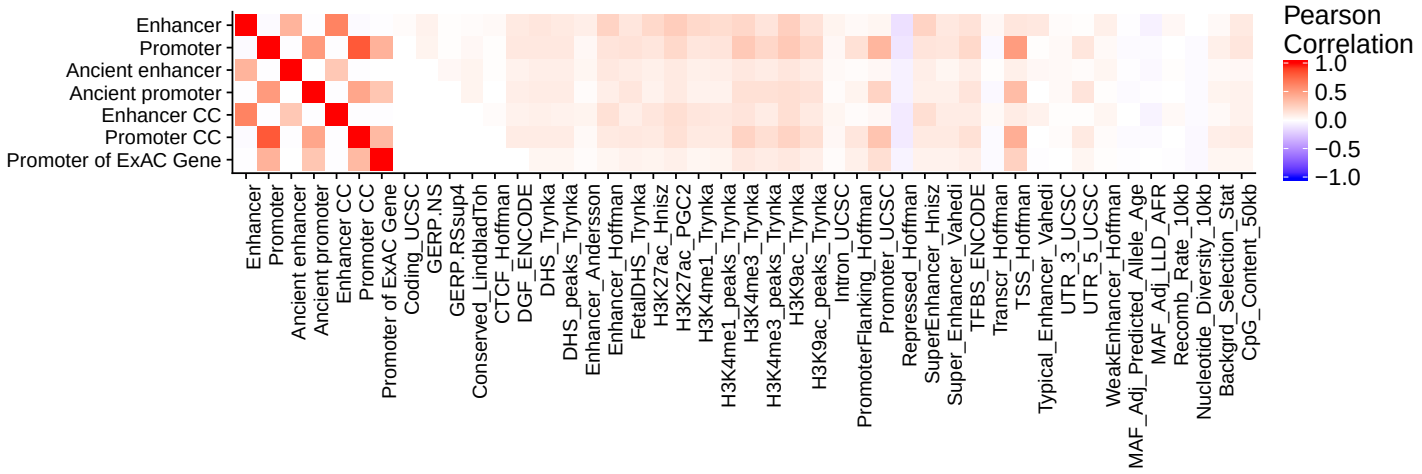

Table S1: **Correlation between main annotations and functional annotations of baseline-LD model.** We report correlation of annotations with all functional annotations in baseline-LD model (among common SNPs, MAF ≥ 0.05).

See attached Excel file

Annotation	Source	Model
All SNPs	Finucane et al.[1]	baseline/baseline-LD
Coding	UCSC Genome Browser[2], post-processed by Gusev et al.[3], Finucane et al.[1]	baseline/baseline-LD
3' UTR	UCSC Genome Browser[2], post-processed by Gusev et al.[3], Finucane et al.[1]	baseline/baseline-LD
5' UTR	UCSC Genome Browser[2], post-processed by Gusev et al.[3], Finucane et al.[1]	baseline/baseline-LD
Promoter	UCSC Genome Browser[2], post-processed by Gusev et al.[3], Finucane et al.[1]	baseline/baseline-LD
Intron	UCSC Genome Browser[2], post-processed by Gusev et al.[3], Finucane et al.[1]	baseline/baseline-LD
Transcription factor binding site	ENCODE[4], post-processed by Gusev et al.[3], Finucane et al.[1]	baseline/baseline-LD
Digital genomic footprint	ENCODE[4], post-processed by Gusev et al.[3], Finucane et al.[1]	baseline/baseline-LD
CTCF	Hoffman et al[5] and Finucane et al.[1]	baseline/baseline-LD
Promoter-Flanking	Hoffman et al[5] and Finucane et al.[1]	baseline/baseline-LD
Transcribed	Hoffman et al[5] and Finucane et al.[1]	baseline/baseline-LD
Transcription start site (TSS)	Hoffman et al[5] and Finucane et al.[1]	baseline/baseline-LD
Enhancer	Hoffman et al[5] and Finucane et al.[1]	baseline/baseline-LD
Weak enhancer	Hoffman et al[5] and Finucane et al.[1]	baseline/baseline-LD
Repressed	Hoffman et al[5] and Finucane et al.[1]	baseline/baseline-LD
DHS	ENCODE[4]/Roadmap[6] post-processed by Trynka et al[7] and Finucane et al.[1]	baseline/baseline-LD
Fetal DHS	ENCODE[4]/Roadmap[6] post-processed by Trynka et al[7] and Finucane et al.[1]	baseline/baseline-LD
H3K4me1	Roadmap Epigenomics[6], post-processed by Trynka et al[7], Finucane et al.[1]	baseline/baseline-LD
H3K4me3	Roadmap Epigenomics[6], post-processed by Trynka et al[7], Finucane et al.[1]	baseline/baseline-LD
H3K9ac	Roadmap Epigenomics[6], post-processed by Trynka et al[7], Finucane et al.[1]	baseline/baseline-LD
H3K27ac	Roadmap Epigenomics[6], post-processed[8], Finucane et al.[1]	baseline/baseline-LD
H3K27ac	Hnisz et al[9] and Finucane et al.[1]	baseline/baseline-LD
Super-enhancer	Hnisz et al[9] and Finucane et al.[1]	baseline/baseline-LD
Conserved	Lindblad-Toh et al.[10], post-processed by Ward and Kellis[11], Finucane et al.[1]	baseline/baseline-LD
FANTOM5 enhancer	Anderson et al.[12] and Finucane et al.[1]	baseline/baseline-LD
Super-enhancer	Vahedi et al.[13], Gazal et al.[14]	baseline/baseline-LD
Typical enhancer	Vahedi et al.[13], Gazal et al.[14]	baseline/baseline-LD
GERP[15] conserved	GERP++score[15] and Gazal et al.[14]	baseline/baseline-LD
10 MAF bins	Gazal et al.[14]	baseline-LD
Predicted Allele Age	Gazal et al.[14]	baseline-LD
LLD-AFR	Gazal et al.[14]	baseline-LD
Recombination Rate	Gazal et al.[14]	baseline-LD
Nucleotide Diversity	Gazal et al.[14]	baseline-LD
Background Selection Statistics	Gazal et al.[14]	baseline-LD
CpG-Content	Gazal et al.[14]	baseline-LD

Table S2: **75 functional annotations in baseline-LD model.** 59 annotations define the baseline model: 1 annotation for all SNPs, 27 binary functional annotations and one continuous annotation (there exist 2 GERP conserved annotations, one binary and one continuous)[1,14], for each binary annotation (excluding the binary GERP related annotation) a 500-bp window around the category is added; for DHS, H3K4me1, H3K4me3, and H3K9ac, a 100-bp window around the peaks is also added as an additional annotation. The baseline-LD model is the baseline model with 16 additional annotations (ten MAF bins and 6 LD-related annotations)[14].

Table S3: **List of 47 datasets analyzed in this study.** We meta-analyzed all results across a previously chosen collection of 47 datasets[16]. We obtained the summary statistics for each trait from previous published studies where the summary statistics are publicly available. In the case of UK Biobank traits, we computed the summary statistics using BOLT-LMM[17,18]. For some traits we have more than one dataset, thus we have 41 independent traits. However, we utilized all the 47 datasets in our meta-analyses as the number of samples that overlap is low. These traits have been selected based on a heritability z-score > 6.

See attached Excel file

Table S4: **List of all models analyzed in this study.** We report the set of annotations included in each model analyzed.

See attached Excel file

Table S5: **Enhancer and promoter results.** (A) Meta-analysis results from including the annotations for putative enhancer and promoter conditional on baseline-LD. Both putative enhancers and promoters are enriched for heritability, however only promoter provides unique information for trait heritability conditional on the baseline-LD model. (B) Meta-analysis results from including the annotations for highly reproducible putative enhancer and highly reproducible promoter conditional on baseline-LD. Results using highly reproducible elements are similar as those found using all putative enhancers and promoters.

A Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.61(0.24)	2.5e-12	0.008(0.032)	0.79
Promoter	0.015	4.605(0.429)	3.2e-17	0.114(0.043)	0.0074
B Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Highly reproducible enhancer	0.022	2.61(0.249)	3.8e-10	-0.004(0.026)	0.86
Highly reproducible promoter	0.013	4.655(0.444)	4.4e-16	0.118(0.041)	0.0044

Table S6: **Sequence age annotations.** Meta-analysis results from models with each sequence age annotation conditioned on the baseline-LD model and putative enhancer and promoter annotations.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^*	τ^* p-val
Enhancer	0.033	2.584(0.238)	5.6e-12	0.241(0.058)	3.4e-05
Promoter	0.015	4.653(0.432)	1.5e-17	0.127(0.043)	0.003
Young enhancer	0.014	-0.134(0.188)	1.6e-05	-0.333(0.06)	2.5e-08
Enhancer	0.033	2.581(0.239)	6e-12	0.013(0.032)	0.68
Promoter	0.015	4.709(0.436)	1.3e-17	0.462(0.07)	3.7e-11
Young promoter	0.005	-1.395(0.433)	0.0003	-0.484(0.058)	1e-16
Enhancer	0.033	2.61(0.239)	2e-12	0(0.041)	1
Promoter	0.015	4.612(0.43)	3.1e-17	0.114(0.043)	0.0073
Intermediate enhancer	0.013	2.256(0.36)	0.015	-0.094(0.034)	0.0058
Enhancer	0.033	2.613(0.24)	2.3e-12	0.01(0.032)	0.75
Promoter	0.015	4.632(0.43)	3.3e-17	0.228(0.061)	0.00017
Intermediate promoter	0.005	1.742(0.426)	0.26	-0.207(0.041)	3.6e-07
Enhancer	0.033	2.741(0.248)	1.3e-13	-0.184(0.029)	3e-10
Promoter	0.015	4.611(0.429)	2.5e-17	0.135(0.043)	0.0016
Ancient enhancer	0.005	10.102(0.9)	3.1e-19	0.483(0.06)	8.7e-16
Enhancer	0.033	2.57(0.238)	7.3e-12	0.021(0.032)	0.52
Promoter	0.015	4.923(0.446)	6.9e-19	-0.225(0.04)	1.4e-08
Ancient promoter	0.004	15.078(1.219)	4.3e-24	0.76(0.072)	3.6e-26

Table S7: **Joint sequence age model.** Meta-analysis results of joint model with sequence age annotations, the baseline-LD model and putative enhancer and promoter annotations. Only significant sequence age annotations (Bonferroni $p = 0.05/4 = 0.0125$) were retained in the model. (A) Enrichment for annotations as well as the difference of enrichments between annotations and the relevant element annotation (Δ). (B) τ^* value and significance. (C) Measures of negative selection on sequence age annotations. These measures (calculated on common SNPs within the annotation) include: the proportion of GERP RS≥ 4[14,15], the mean of the background selection statistic (BSS)[14,19], the proportion conserved[1,10], the mean of the MAF adjusted predicted allele age (age)[14], and the mean of nucleotide diversity (10kb) (Nuc. Div.)[14,20]. Standard error is calculated via block-jacknife.

A Category	Prop.	Enr (s.e.)	Enr p-val	Δ (s.e.)	Δ p-val
Enhancer	0.033	2.692(0.246)	4.9e-13		
Promoter	0.015	4.903(0.445)	8.3e-19		
Ancient enhancer	0.005	9.283(0.867)	3.4e-17	6.578(0.685)	4.3e-15
Ancient promoter	0.004	14.277(1.179)	1.2e-22	9.176(0.769)	2.1e-18
B Category	τ^* (s.e.)	τ^* p-val			
Enhancer	-0.156(0.03)	1.6e-07			
Promoter	-0.188(0.039)	1.1e-06			
Ancient enhancer	0.429(0.058)	1.2e-13			
Ancient promoter	0.704(0.068)	9e-25			
C Category	GERP RS ≥ 4	BSS	Conserved	Age	Nuc. Div.
Enhancer	0.012(1.0e-05)	0.21(1.7e-05)	0.039(2.5e-05)	-0.031(9.9e-05)	4.5(3.3e-04)
Promoter	0.014(2.7e-05)	0.3(5.5e-05)	0.071(5.5e-05)	-0.15(2.1e-04)	4.2(8.6e-04)
Ancient enhancer	0.058(1.8e-04)	0.24(1.4e-04)	0.16(2.3e-04)	-0.13(6.0e-04)	4.1(1.8e-03)
Ancient promoter	0.041(1.5e-04)	0.33(2.0e-04)	0.18(3.2e-04)	-0.29(8.4e-04)	3.9(2.9e-03)

Table S8: **Joint sequence age model enrichment per trait.** Enrichment (standard error) for putative enhancer, promoter, ancient putative enhancer, and ancient promoter for each trait from the joint model with sequence age annotations, the baseline-LD model and putative enhancer and promoter annotations.

See attached Excel file

Table S9: **Joint sequence age model in liver traits only.** Meta-analysis results across liver traits of joint model with sequence age annotations, the baseline-LD model and putative enhancer and promoter annotations. (A) Enrichment for annotations as well as the difference of enrichments between annotations and the relevant element annotation (Δ). (B) τ^* value and significance.

A Category	Prop.	Enr (s.e.)	Enr. p-val	Δ (s.e.)	Δ p-val
Enhancer	0.033	6.561(0.977)	0.0015		
Promoter	0.015	17.779(2.833)	4e-06		
Ancient enhancer	0.005	8.441(4.118)	0.12	1.663(4.105)	0.79
Ancient promoter	0.004	38.264(6.649)	0.0029	20.414(5.706)	0.021
B Category	τ^* (s.e.)	τ^* p-val			
Enhancer	1.016(0.28)	0.00029			
Promoter	1.485(0.473)	0.0017			
Ancient enhancer	0.137(0.338)	0.68			
Ancient promoter	1.94(0.539)	0.00032			

Table S10: **Sequence age model with ancient sequence age annotation included.** Meta-analysis results from adding the annotation of ancient sequence age (irrespective of putative enhancer/promoter status) to the joint model with sequence age annotations. Regions with ancient sequence age are enriched for heritability, although a portion of this enrichment is explained by ancient putative enhancers and promoters there is still other genomic regions with ancient sequence age that contribute to this enrichment. However, we see that conditional on baseline-LD, putative enhancer, promoter, ancient putative enhancer, and ancient promoter the annotation for ancient sequence age does not provide novel information as quantified via τ^*.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.0330	2.695(0.246)	4.3e-13	-0.142(0.03)	1.9e-06
Promoter	0.0150	4.908(0.445)	7.2e-19	-0.177(0.038)	4.2e-06
Ancient enhancer	0.0050	9.256(0.869)	3.6e-17	0.425(0.06)	1.7e-12
Ancient promoter	0.0040	14.283(1.181)	1.2e-22	0.693(0.071)	2.6e-22
Ancient sequence	0.1040	3.375(0.153)	7.2e-25	0.062(0.051)	0.22

Table S11: **Ancient sequence age results in non-liver specific putative regulatory elements.** Meta-analysis results of the model with putative regulatory annotations restricted to regions with ancient sequence age from the baseline-LD model (not liver specific). We find the same main result that putative enhancers and promoters with ancient sequence age are enriched for trait heritability.

Category	Prop. SNPs	Enrichment (s.e.)	Enrichment_pval
CTCF_Hoffman	0.024	0.384(0.206)	0.035
CTCF_Hoffman.ancient	0.003	4.74(0.703)	0.0011
DGF_ENCODE	0.136	2.551(0.235)	8.8e-13
DGF_ENCODE.ancient	0.024	8.733(0.768)	4.1e-28
DHS_peaks_Trynka	0.111	2.233(0.228)	7.1e-09
DHS_peaks_Trynka.ancient	0.025	7.193(0.709)	8.7e-23
DHS_Trynka	0.166	1.942(0.172)	8.1e-09
DHS_Trynka.ancient	0.036	6.139(0.534)	1.9e-24
Enhancer_Andersson	0.004	3.209(0.873)	0.039
Enhancer_Andersson.ancient	0.001	21.732(2.903)	1.1e-10
Enhancer_Hoffman	0.042	3.029(0.226)	7.1e-14
Enhancer_Hoffman.ancient	0.008	12.197(0.921)	1.9e-26
FetalDHS_Trynka	0.084	2.718(0.215)	6e-13
FetalDHS_Trynka.ancient	0.023	7.203(0.61)	2.7e-23
H3K27ac_Hnisz	0.389	1.639(0.068)	5e-40
H3K27ac_Hnisz.ancient	0.051	5.707(0.29)	9.7e-36
H3K27ac_PGC2	0.269	1.918(0.1)	6.2e-25
H3K27ac_PGC2.ancient	0.041	6.81(0.386)	5.4e-36
H3K4me1_peaks_Trynka	0.170	2.274(0.102)	4.8e-16
H3K4me1_peaks_Trynka.ancient	0.030	7.75(0.466)	7.9e-30
H3K4me1_Trynka	0.424	1.755(0.069)	5.7e-29
H3K4me1_Trynka.ancient	0.066	5.13(0.252)	7.1e-33
H3K4me3_peaks_Trynka	0.042	2.991(0.237)	6.2e-09
H3K4me3_peaks_Trynka.ancient	0.010	12.926(0.849)	7.4e-27
H3K4me3_Trynka	0.133	2.571(0.158)	6.2e-24
H3K4me3_Trynka.ancient	0.026	8.987(0.535)	1.3e-37
H3K9ac_peaks_Trynka	0.038	3.708(0.281)	2.2e-10
H3K9ac_peaks_Trynka.ancient	0.009	13.217(0.851)	5e-26
H3K9ac_Trynka	0.125	2.62(0.201)	1.2e-22
H3K9ac_Trynka.ancient	0.027	8.384(0.539)	3.7e-36
PromoterFlanking_Hoffman	0.008	1.084(0.516)	1
PromoterFlanking_Hoffman.ancient	0.001	12.866(1.248)	2.9e-10
Promoter_UCSC	0.046	2.118(0.172)	5.4e-08
Promoter_UCSC.ancient	0.011	7.809(0.492)	8.2e-22
SuperEnhancer_Hnisz	0.167	2.047(0.098)	1.2e-45
SuperEnhancer_Hnisz.ancient	0.023	7.204(0.401)	1.4e-34
Super_Enhancer_Vahedi	0.021	3.122(0.228)	3.1e-21
Super_Enhancer_Vahedi.ancient	0.003	8.55(0.866)	1.6e-14
TFBS_ENCODE	0.131	2.65(0.199)	9.6e-18
TFBS_ENCODE.ancient	0.024	9.162(0.655)	5.9e-33
Transcr_Hoffman	0.346	1.166(0.033)	0.00015
Transcr_Hoffman.ancient	0.037	4.266(0.202)	9.4e-20
TSS_Hoffman	0.018	5.741(0.492)	6.2e-19
TSS_Hoffman.ancient	0.005	17.709(1.271)	9e-31
Typical_Enhancer_Vahedi	0.022	2.193(0.188)	1.4e-08
Typical_Enhancer_Vahedi.ancient	0.003	8.206(0.866)	1.1e-10
WeakEnhancer_Hoffman	0.021	2.307(0.23)	4.2e-06
WeakEnhancer_Hoffman.ancient	0.004	11.015(0.941)	1.9e-16

Table S12: **Roadmap H3K27ac and H3K4me3 annotations** Meta-analysis results of the model with H3K27ac and H3K4me3 annotations from Roadmap[6] based on marks present in 1/10/20 tissues/cell-types, respectively, as well as restrincting to regions with ancient sequence age.

Category	Prop. SNPs	Enrichment (s.e.)	Enrichment_pval
H3K4me3 $\geq$ 1 tissue-type	0.200	1.851(0.071)	1.6e-15
H3K4me3 $\geq$ 1 tissue-type $\cap$ ancient seq. age	0.033	7.695(0.425)	1.4e-35
H3K4me3 $\geq$ 10 tissue-types	0.029	4.883(0.312)	3e-23
H3K4me3 $\geq$ 10 tissue-types $\cap$ ancient seq. age	0.009	13.752(0.77)	3.2e-32
H3K4me3 $\geq$ 20 tissue-types	0.019	6.368(0.435)	1.1e-22
H3K4me3 $\geq$ 20 tissue-types $\cap$ ancient seq. age	0.007	16.261(0.915)	1.2e-31
H3K27ac $\geq$ 1 tissue-type	0.325	1.843(0.089)	1.2e-25
H3K27ac $\geq$ 1 tissue-type $\cap$ ancient seq. age	0.051	6.231(0.335)	1.9e-36
H3K27ac $\geq$ 10 tissue-types	0.058	3.631(0.277)	7.5e-26
H3K27ac $\geq$ 10 tissue-types $\cap$ ancient seq. age	0.014	11.52(0.834)	4.5e-35
H3K27ac $\geq$ 20 tissue-types	0.026	4.612(0.393)	2.3e-20
H3K27ac $\geq$ 20 tissue-types $\cap$ ancient seq. age	0.007	14.388(1.078)	7.2e-31

Table S13: **Sequence age model with flanking regions.** To guard against bias due to model misspecification[1], we repeated our sequence age analysis by including 500bp flanking regions around putative enhancer, promoter, and sequence age annotations. In order to facilitate the creation of 500 BP flanking regions we made bed files for the sequence age annotations which were not needed to make the annotations analyzed in the main analyses. The difference of the proportion of SNPs within main analysis annotations and those created using bed files was $\leq 2 * 10^{-6}$.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.266(0.211)	2.5e-08	-0.175(0.033)	1.3e-07
Enhancer flanking	0.010	2.012(0.551)	0.089	0.04(0.049)	0.42
Promoter	0.015	4.933(0.457)	3.2e-17	-0.298(0.041)	3.3e-13
Promoter flanking	0.004	0.175(0.862)	0.41	-0.126(0.053)	0.018
Ancient enhancer	0.005	8.814(0.795)	3.5e-15	0.416(0.055)	3e-14
Ancient enhancer flanking	0.009	1.251(0.351)	0.49	-0.007(0.033)	0.84
Ancient promoter	0.004	12.71(1.137)	6.6e-18	0.673(0.067)	7.4e-24
Ancient promoter flanking	0.005	3.877(0.502)	4.1e-05	0.265(0.043)	7.2e-10

Table S14: **Conserved function annotations.** Meta-analysis results from models with each conserved function annotation conditioned on the baseline-LD model and putative enhancer and promoter annotations. Conservation of regulatory function is assessed using 9 other mammalian species. Binary annotations for enhancers and promoters include highly conserved and human-specific reflecting 9 and 0 other species with function at the given regulatory element, respectively. Categorical annotations include conservation count (CC), mapped count (mappedC), and missing count (missingC) reflecting the number of other mammals for which the element is functionally conserved, the underlying sequence of the element aligns but its function is not conserved, and the underlying sequence of the element does not align (is missing), respectively.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.608(0.24)	2.6e-12	0.008(0.032)	0.81
Promoter	0.015	4.602(0.429)	3.6e-17	0.086(0.041)	0.038
Highly conserved promoter	0.002	5.051(0.637)	4.1e-07	0.017(0.02)	0.39
Enhancer	0.033	2.558(0.237)	8.1e-12	-0.018(0.031)	0.56
Promoter	0.015	4.59(0.428)	4e-17	0.112(0.043)	0.0087
Highly conserved enhancer	0.001	5.142(0.727)	7.8e-06	0.053(0.015)	0.0003
Enhancer	0.033	2.61(0.24)	2.6e-12	0.009(0.032)	0.78
Promoter	0.015	4.602(0.43)	3.6e-17	0.135(0.045)	0.0028
Human-specific promoter	0.003	3.024(0.448)	0.0002	-0.042(0.019)	0.029
Enhancer	0.033	2.55(0.236)	1.1e-11	0.107(0.041)	0.0095
Promoter	0.015	4.549(0.426)	6.9e-17	0.109(0.042)	0.01
Human-specific enhancer	0.013	0.91(0.184)	0.46	-0.186(0.033)	1.4e-08
Enhancer	0.033	2.608(0.24)	2.8e-12	0.009(0.032)	0.77
Promoter	0.015	4.599(0.43)	4.9e-17	-0.043(0.047)	0.35
Promoter CC	N/A	N/A	N/A	0.125(0.033)	0.00014
Enhancer	0.033	2.442(0.23)	1.7e-10	-0.182(0.027)	2.2e-11
Promoter	0.015	4.504(0.424)	1.3e-16	0.107(0.042)	0.011
Enhancer CC	N/A	N/A	N/A	0.212(0.032)	2.1e-11
Enhancer	0.033	2.608(0.24)	2.6e-12	0.008(0.032)	0.79
Promoter	0.015	4.604(0.43)	4e-17	0.112(0.047)	0.016
Promoter mappedC	N/A	N/A	N/A	-0.019(0.019)	0.32
Enhancer	0.033	2.584(0.239)	4.7e-12	0.034(0.045)	0.45
Promoter	0.015	4.585(0.424)	3.4e-17	0.113(0.042)	0.0076
Enhancer mappedC	N/A	N/A	N/A	-0.032(0.034)	0.35
Enhancer	0.033	2.61(0.24)	2.4e-12	0.009(0.032)	0.78
Promoter	0.015	4.575(0.429)	6.4e-17	0.188(0.048)	8.8e-05
Promoter missingC	N/A	N/A	N/A	-0.108(0.029)	0.00017
Enhancer	0.033	2.651(0.243)	1.3e-12	0.098(0.039)	0.011
Promoter	0.015	4.63(0.431)	2.1e-17	0.115(0.043)	0.0072
Enhancer missingC	N/A	N/A	N/A	-0.143(0.024)	5e-09

Table S15: **Joint conserved function model.** Meta-analysis results from joint model with functional count annotations, the baseline-LD model and putative enhancer and promoter annotations. Only significant functional count annotations (Bonferroni $p = 0.05/8 = 0.00625$) were retained in the model. (A) Enrichment for annotations as well as the difference of enrichments between annotations and the relevant element annotation (Δ). The enrichment for the categorical annotations enhancer conservation count (enhancer CC) and promoter conservation count (promoter CC) is shown for a subset of the annotation, namely conserved putative enhancers and promoters (CC ≥ 5), but is calculated using the model with conservation count variables. (B) τ^* value and significance. (C) Measures of negative selection on regulatory function annotations. These measures (calculated on common SNPs within the annotation) include: the proportion of GERP RS≥ 4[14,15], the mean of the background selection statistic (BSS)[14,19], the proportion conserved[1,10], the mean of the MAF adjusted predicted allele age (age)[14], and the mean of nucleotide diversity (10kb) (Nuc. Div.)[14,20]. Standard error is calculated via block-jacknife. For categorical annotations (enhancer CC and promoter CC) these measures are shown for conserved enhancers and promoters (CC ≥ 5).

A Category	Prop.	Enr (s.e.)	Enr p-val	Δ (s.e.)	Δ p-val
Enhancer	0.033	2.448(0.23)	1.5e-10		
Promoter	0.015	4.508(0.425)	1.7e-16		
Conserved enhancer	0.005	4.572(0.429)	3.5e-17	2.054(0.243)	2.6e-12
Conserved promoter	0.008	5.065(0.474)	6.4e-16	0.559(0.133)	0.022
B Category	τ^*	τ^* p-val			
Enhancer	-0.176(0.027)	7.1e-11			
Promoter	-0.016(0.048)	0.73			
Enhancer CC	0.201(0.031)	6.6e-11			
Promoter CC	0.092(0.033)	0.005			
C Category	GERP RS ≥ 4	BSS	Conserved	Age	NucDiv
Enhancer	0.012(1.0e-05)	0.21(1.7e-05)	0.039(2.5e-05)	-0.031(9.9e-05)	4.5(3.3e-04)
Promoter	0.014(2.7e-05)	0.3(5.5e-05)	0.071(5.5e-05)	-0.15(2.1e-04)	4.2(8.6e-04)
Conserved enhancer	0.017(7.9e-05)	0.24(1.3e-04)	0.055(1.5e-04)	-0.047(5.1e-04)	4(7.6e-04)
Conserved promoter	0.017(5.4e-05)	0.34(1.0e-04)	0.084(1.2e-04)	-0.15(4.1e-04)	3.8(6.6e-04)

Table S16: **Joint conserved function model enrichment per trait.** Enrichment (standard error) for putative enhancer, promoter, conserved putative enhancer, and conserved promoter for each trait from the joint model with putative enhancer conservation count, promoter conservation count, the baseline-LD model and putative enhancer and promoter annotations.

See attached Excel file

Table S17: **Binary conserved function model.** (A) Meta-analysis results of enrichment and τ^* for putative enhancers and promoters shared in CC other mammals (CC$\in \{0, \ldots, 9\}$). (B) Measures of negative selection on common SNPs within the annotations: the proportion of GERP RS≥ 4[14,15], the mean of the background selection statistic (BSS)[14,19], the proportion conserved[1,10], the mean of the MAF adjusted predicted allele age (age)[14], and the mean of nucleotide diversity (10kb) (Nuc. Div.)[14,20]. Standard error is calculated via block-jacknife.

A Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enh CC=0	0.013(39.78%)	1.072(0.192)	0.98	-0.12(0.018)	5.2e-11
Enh CC=1	0.006(17.28%)	0.872(0.307)	0.47	-0.093(0.022)	2.6e-05
Enh CC=2	0.004(11.86%)	1.575(0.331)	0.22	-0.045(0.016)	0.005
Enh CC=3	0.003(8.55%)	2.446(0.438)	0.011	0.007(0.02)	0.7
Enh CC=4	0.002(6.03%)	1.684(0.362)	0.66	-0.03(0.016)	0.066
Enh CC=5	0.002(5.08%)	1.939(0.377)	0.073	-0.023(0.016)	0.14
Enh CC=6	0.001(3.48%)	4.15(0.701)	0.00024	0.047(0.022)	0.034
Enh CC=7	0.001(3.21%)	2.913(0.554)	0.029	0.002(0.016)	0.9
Enh CC=8	0.001(2.58%)	2.661(0.53)	0.015	-0.007(0.014)	0.58
Enh CC=9	0.001(2.15%)	4.388(0.676)	0.00016	0.031(0.016)	0.049
Pro CC=0	0.003(19.17%)	3.072(0.451)	0.00014	-0.001(0.023)	0.98
Pro CC=1	0.001(7.65%)	1.292(0.49)	0.62	-0.04(0.018)	0.028
Pro CC=2	0.001(6.75%)	1.336(0.603)	0.7	-0.048(0.019)	0.013
Pro CC=3	0.001(7.05%)	2.343(0.498)	0.015	-0.024(0.016)	0.14
Pro CC=4	0.001(6.88%)	3.845(0.908)	0.013	0.014(0.027)	0.62
Pro CC=5	0.001(7.48%)	2.372(0.507)	0.0012	-0.027(0.018)	0.13
Pro CC=6	0.001(8.11%)	4.084(0.617)	0.00032	0.023(0.019)	0.22
Pro CC=7	0.001(9.25%)	4.481(0.525)	1.2e-05	0.04(0.019)	0.04
Pro CC=8	0.002(12.95%)	3.95(0.617)	0.00012	0.027(0.027)	0.3
Pro CC=9	0.002(14.72%)	4.451(0.598)	6.9e-06	0.038(0.025)	0.13

B Category	GERP RS ≥ 4	BSS	Conserved	Age	NucDiv
Enh CC=0	0.011(2.8e-05)	0.19(4.9e-05)	0.036(5.7e-05)	-0.033(2.5e-04)	5(1.7e-03)
Enh CC=1	0.0096(7.6e-05)	0.21(1.2e-04)	0.033(1.0e-04)	-0.02(5.4e-04)	4.4(1.1e-03)
Enh CC=2	0.011(1.2e-04)	0.22(1.6e-04)	0.038(1.7e-04)	-0.02(8.2e-04)	4.3(1.4e-03)
Enh CC=3	0.012(1.5e-04)	0.22(2.4e-04)	0.038(2.3e-04)	-0.016(1.2e-03)	4.3(2.1e-03)
Enh CC=4	0.013(1.8e-04)	0.21(3.2e-04)	0.045(2.8e-04)	-0.043(1.4e-03)	4.3(2.4e-03)
Enh CC=5	0.013(1.4e-04)	0.23(3.7e-04)	0.043(3.7e-04)	-0.022(1.8e-03)	4.1(2.9e-03)
Enh CC=6	0.017(3.8e-04)	0.26(6.4e-04)	0.058(7.4e-04)	-0.054(2.7e-03)	4(3.9e-03)
Enh CC=7	0.015(3.8e-04)	0.25(7.3e-04)	0.053(4.6e-04)	-0.028(3.1e-03)	4.1(4.7e-03)
Enh CC=8	0.02(4.7e-04)	0.23(8.8e-04)	0.063(6.3e-04)	-0.056(4.2e-03)	4.1(6.5e-03)
Enh CC=9	0.024(7.6e-04)	0.25(1.1e-03)	0.07(1.2e-03)	-0.11(4.1e-03)	3.8(6.3e-03)
Pro CC=0	0.014(1.1e-04)	0.28(2.8e-04)	0.066(2.8e-04)	-0.11(1.2e-03)	5.1(8.5e-03)
Pro CC=1	0.0059(3.2e-04)	0.23(5.6e-04)	0.042(5.4e-04)	-0.11(2.7e-03)	5.7(2.7e-02)
Pro CC=2	0.0091(2.8e-04)	0.26(8.2e-04)	0.054(6.4e-04)	-0.16(3.4e-03)	4.5(1.4e-02)
Pro CC=3	0.012(3.4e-04)	0.27(7.7e-04)	0.06(5.8e-04)	-0.17(3.0e-03)	4(4.2e-03)
Pro CC=4	0.01(1.1e-17)	0.28(8.7e-04)	0.057(7.0e-04)	-0.19(2.9e-03)	3.9(4.3e-03)
Pro CC=5	0.011(5.2e-04)	0.27(6.8e-04)	0.067(8.1e-04)	-0.13(2.9e-03)	4.1(4.7e-03)
Pro CC=6	0.014(2.3e-04)	0.28(6.1e-04)	0.074(6.8e-04)	-0.14(2.3e-03)	3.9(3.8e-03)
Pro CC=7	0.015(3.5e-04)	0.32(5.7e-04)	0.08(6.3e-04)	-0.15(2.2e-03)	4(4.1e-03)
Pro CC=8	0.018(1.9e-04)	0.34(4.4e-04)	0.087(4.6e-04)	-0.17(1.6e-03)	3.6(2.6e-03)
Pro CC=9	0.023(2.4e-04)	0.4(4.1e-04)	0.097(4.1e-04)	-0.16(1.3e-03)	3.5(2.0e-03)

Table S18: **Binary conserved function model enrichment per trait.** Enrichment (standard error) for putative enhancers and promoters shared in CC other mammals (CC $\in \{0, \ldots, 9\}$) for each trait from the model with 20 binary annotations reflecting putative enhancers and promoters shared in CC other mammals and the baseline-LD model.

See attached Excel file

Table S19: **Joint conserved function model in liver traits only.** Meta-analysis results across liver traits from joint model with functional count annotations, the baseline-LD model and putative enhancer and promoter annotations. (A) Enrichment for annotations as well as the difference of enrichments between annotations and the relevant element annotation (Δ). The enrichment for the categorical annotations enhancer conservation count (enhancer CC) and promoter conservation count (promoter CC) is shown for a subset of the annotation, namely conserved putative enhancers and promoters (CC ≥ 5), but is calculated using the model with conservation count variables. (B) τ^* value and significance.

A Category	Prop.	Enr (s.e.)	Enr. p-val	Δ (s.e.)	Δ p-val
Enhancer	0.033	6.268(0.959)	0.0023		
Promoter	0.015	16.327(2.796)	3.8e-07		
Conserved enhancer	0.005	11.846(2.236)	0.00044	5.827(1.777)	0.0017
Conserved promoter	0.008	19.652(3.802)	5.2e-05	2.119(1.765)	0.38
B Category	τ^* (s.e.)	τ^* p-val			
Enhancer	0.506(0.208)	0.015			
Promoter	1.758(0.526)	0.00083			
Enhancer CC	0.733(0.226)	0.0012			
Promoter CC	0.549(0.43)	0.2			

Table S20: **Joint conserved function model with binary conserved annotations.** Meta-analysis results of conserved function model with putative enhancer and promoter conservation counts coded as binary annotations reflecting conserved function.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.474(0.232)	8.8e-11	-0.097(0.028)	0.00049
Promoter	0.015	4.503(0.426)	1.8e-16	0.019(0.049)	0.7
Conserved enhancer	0.005	4.483(0.435)	2.9e-14	0.134(0.022)	8e-10
Conserved promoter	0.008	4.981(0.454)	2.3e-15	0.083(0.028)	0.0027

Table S21: **Conserved function model with flanking regions** To guard against bias due to model misspecification[1], we repeated our conserved function analysis with binary conserved function annotations (Table S20) by including 500bp flanking regions around putative enhancer, promoter, conserved putative enhancer, and conserved promoter annotations.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	1.876(0.189)	8.1e-05	-0.137(0.025)	8.1e-08
Enhancer flanking	0.010	2.818(0.606)	0.0056	0.045(0.046)	0.33
Promoter	0.015	4.417(0.431)	1.4e-14	0.054(0.049)	0.26
Promoter flanking	0.004	0.488(0.853)	0.58	-0.136(0.066)	0.041
Conserved enhancer	0.005	3.393(0.352)	6.2e-08	0.1(0.02)	7e-07
Conserved enhancer flanking	0.001	5.037(1.565)	0.063	0.06(0.041)	0.15
Conserved promoter	0.008	4.703(0.47)	2.9e-12	0.049(0.032)	0.12
Conserved promoter flanking	0.002	1.452(1.263)	0.57	0.1(0.071)	0.16

Table S22: **Conserved function model with human-specific promoter annotation added.** Meta-analysis results of adding an annotation for human-specific promoters to our regulatory function model. The value of τ^* for the promoter conservation count annotation became larger and more statistically significant.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.447(0.23)	1.5e-10	-0.176(0.027)	7.8e-11
Promoter	0.015	4.505(0.425)	2e-16	-0.088(0.057)	0.12
Enhancer CC	N/A	N/A	N/A	0.203(0.031)	7.9e-11
Promoter CC	N/A	N/A	N/A	0.138(0.043)	0.0014
Human-specific promoter	0.003	3.113(0.451)	0.00011	0.043(0.026)	0.095

Table S23: **Gene function annotations.** Meta-analysis results from models with each gene function annotation conditioned on the baseline-LD model and putative enhancer and promoter annotations.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.599(0.24)	3.6e-12	0.008(0.032)	0.79
Promoter	0.015	4.779(0.439)	1.3e-17	-0.027(0.042)	0.53
Promoter of ancient gene	0.011	5.24(0.494)	8.2e-16	0.148(0.039)	0.00012
Enhancer	0.033	2.579(0.24)	6.6e-12	0.01(0.032)	0.75
Promoter	0.015	5.076(0.448)	8.7e-20	0.013(0.04)	0.74
Promoter of ExAC gene	0.002	12.365(0.894)	9.3e-22	0.371(0.031)	1.5e-32
Enhancer	0.033	2.598(0.239)	3.4e-12	0.009(0.032)	0.78
Promoter	0.015	4.747(0.437)	1.9e-17	-0.042(0.041)	0.31
Promoter of gene with mouse ortholog	0.011	5.132(0.486)	1.5e-15	0.168(0.041)	4e-05

Table S24: **Joint gene function model.** Meta-analysis results of joint model with gene function annotations, the baseline-LD model and putative enhancer and promoter annotations. Only significant gene functions annotations (Bonferroni $p = 0.05/3 = 0.0167$) were retained in the model. (A) Enrichment for annotations as well as the difference of enrichments between promoter of ExAC gene and (all) promoter annotation (Δ). (B) τ^* value and significance. (C) Measures of negative selection on gene function annotations. These measures (calculated on common SNPs within the annotation) include: the proportion of GERP RS≥ 4[14,15], the mean of the background selection statistic (BSS)[14,19], the proportion conserved[1,10], the mean of the MAF adjusted predicted allele age (age)[14], and the mean of nucleotide diversity (10kb) (Nuc. Div.)[14,20]. Standard error is calculated via block-jacknife.

A Category	Prop.	Enr (s.e.)	Enr p-val	Δ (s.e.)	Δ p-val
Enhancer	0.033	2.579(0.24)	6.6e-12		
Promoter	0.015	5.076(0.448)	8.7e-20		
Promoter of ExAC gene	0.002	12.365(0.894)	9.3e-22	6.805(0.491)	9.1e-16
B Category	τ^* (s.e.)	τ^* p-val			
Enhancer	0.01(0.032)	0.75			
Promoter	0.013(0.04)	0.74			
Promoter of ExAC gene	0.371(0.031)	1.5e-32			
C Category	GERP RS ≥ 4	BSS	Conserved	Age	Nuc. Div.
Enhancer	0.012(1.0e-05)	0.21(1.7e-05)	0.039(2.5e-05)	-0.031(9.9e-05)	4.5(3.3e-04)
Promoter	0.014(2.7e-05)	0.3(5.5e-05)	0.071(5.5e-05)	-0.15(2.1e-04)	4.2(8.6e-04)
Promoter of ExAC gene	0.024(1.9e-04)	0.38(3.4e-04)	0.12(4.0e-04)	-0.25(1.3e-03)	3.4(1.6e-03)

Table S25: **Joint gene function model enrichment per trait.** Enrichment (standard error) for putative enhancer, promoter, and promoter of ExAC gene for each trait from the joint model with promoter of ExAC gene, the baseline-LD model and putative enhancer and promoter annotations.

See attached Excel file

Table S26: **Joint gene function model in liver traits only.** Meta-analysis results across liver traits of joint model with gene function annotations, the baseline-LD model and putative enhancer and promoter annotations. (A) Enrichment for annotations as well as the difference of enrichments between promoter of ExAC gene and (all) promoter annotation (Δ). (B) τ^* value and significance.

A Category	Prop.	Enr (s.e.)	Enr. p-val	Δ (s.e.)	Δ p-val
Enhancer	0.033	6.653(1.003)	0.0015		
Promoter	0.015	17.585(2.789)	2.1e-06		
Promoter of ExAC gene	0.002	26.947(4.795)	0.0056	7.285(4.132)	0.18
B Category	τ^* (s.e.)	τ^* p-val			
Enhancer	1.03(0.225)	4.5e-06			
Promoter	2.189(0.471)	3.4e-06			
Promoter of ExAC gene	0.481(0.243)	0.048			

Table S27: **Gene function model with flanking regions.** To guard against bias due to model misspecification[1], we repeated our gene function analysis by including 500bp flanking regions around putative enhancer, promoter, and promoter of ExAC gene annotations.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.124(0.202)	4.8e-07	-0.043(0.028)	0.12
Enhancer flanking	0.010	2.19(0.568)	0.056	0.057(0.05)	0.26
Promoter	0.015	4.963(0.453)	2.1e-17	0.02(0.039)	0.61
Promoter flanking	0.004	0.614(0.886)	0.68	-0.099(0.055)	0.072
Promoter of ExAC gene	0.002	11.174(0.879)	7.4e-17	0.32(0.035)	9.3e-20
Promoter of ExAC gene flanking	0.001	4.045(2.031)	0.09	0.09(0.051)	0.075

Table S28: **Gene function model with functional annotations based on molecular quantitative trait loci.** Meta-analysis results when including the annotations for Max CPP (allGenes) and MaxCPP (ExAC), where these latter two annotations are found with a fixed effect meta-analysis (FE-Meta-Tissue) of GTEx data[16,21] to the gene function model. Even conditional on both Max CPP and MaxCPP of ExAC Genes we find that promoter of an ExAC LoF gene is still conditionally significant although the τ^* value is slightly smaller than when we exclude these two annotations.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.6(0.24)	3.9e-12	0.017(0.032)	0.59
Promoter	0.015	4.605(0.434)	1.2e-16	0.002(0.039)	0.96
Promoter of ExAC gene	0.002	10.971(0.848)	7.1e-19	0.313(0.029)	3.7e-27
MaxCPP (allGenes)	N/A	N/A	N/A	0.406(0.047)	4.3e-18
MaxCPP (ExAC)	N/A	N/A	N/A	0.352(0.041)	1.3e-17

Table S29: **Final joint model.** Meta-analysis results of final model with regulatory and sequence conservation as well as gene function annotations, the baseline-LD model and putative enhancer and promoter annotations. (A) Enrichment for annotations and the difference of enrichments between annotations and (all) putative enhancer and (all) promoter annotations (Δ). The enrichment for putative enhancer conservation count (CC) is shown for a subset of the annotation, namely conserved putative enhancers (CC ≥ 5), but is calculated using the model with putative enhancer conservation count annotation. (B) τ^* value and significance. (C) Measures of negative selection on annotations within final joint model. These measures (calculated on common SNPs within the annotation) include: the proportion of GERP RS≥ 4[14,15], the mean of the background selection statistic (BSS)[14,19], the proportion conserved[1,10], the mean of the MAF adjusted predicted allele age (age)[14], and the mean of nucleotide diversity (10kb) (Nuc. Div.)[14,20]. Standard error is calculated via block-jacknife. For the categorical annotation enhancer CC these measures are shown for conserved enhancers (CC ≥ 5).

A Category	Prop.	Enr (s.e.)	Enr p-val	Δ (s.e.)	Δ p-val
Enhancer	0.033	2.534(0.238)	3.1e-11		
Promoter	0.015	5.139(0.451)	5.1e-20		
Ancient enhancer	0.005	8.761(0.835)	4.9e-16	6.243(0.662)	2.7e-14
Ancient promoter	0.004	13.451(1.158)	5.1e-21	8.201(0.755)	5.2e-16
Conserved enhancer	0.005	4.614(0.433)	2.7e-17	2.012(0.244)	5.2e-12
Promoter of ExAC gene	0.002	11.958(0.872)	4.5e-21	6.39(0.481)	8.3e-15
B Category		τ^* (s.e.)	τ^* p-val		
Enhancer		-0.27(0.034)	2.6e-15		
Promoter		-0.216(0.038)	9.3e-09		
Ancient enhancer		0.388(0.055)	2.1e-12		
Ancient promoter		0.572(0.067)	1e-17		
Enhancer CC		0.161(0.028)	1.3e-08		
Promoter of ExAC gene		0.283(0.03)	2.3e-21		
C Category	GERP RS ≥ 4	BSS	Conserved	Age	Nuc. Div.
Enhancer	0.012(1.0e-05)	0.21(1.7e-05)	0.039(2.5e-05)	-0.031(9.9e-05)	4.5(3.3e-04)
Promoter	0.014(2.7e-05)	0.3(5.5e-05)	0.071(5.5e-05)	-0.15(2.1e-04)	4.2(8.6e-04)
Ancient enhancer	0.058(1.8e-04)	0.24(1.4e-04)	0.16(2.3e-04)	-0.13(6.0e-04)	4.1(1.8e-03)
Ancient promoter	0.041(1.5e-04)	0.33(2.0e-04)	0.18(3.2e-04)	-0.29(8.4e-04)	3.9(2.9e-03)
Conserved enhancer	0.017(7.9e-05)	0.24(1.3e-04)	0.055(1.5e-04)	-0.047(5.1e-04)	4(7.6e-04)
Promoter of ExAC gene	0.024(1.9e-04)	0.38(3.4e-04)	0.12(4.0e-04)	-0.25(1.3e-03)	3.4(1.6e-03)

Table S30: **Final joint model enrichment per trait.** Enrichment (standard error) for putative enhancer, promoter, conserved putative enhancer, ancient putative enhancer, ancient promoter, and promoter of ExAC gene for each trait from the joint model with ancient putative enhancer, putative enhancer conservation count, ancient promoter, promoter of ExAC gene, the baseline-LD model and putative enhancer and promoter annotations.

See attached Excel file

Table S31: **Final joint model in liver traits only.** Meta-analysis results across liver traits of final model with regulatory and sequence conservation as well as gene function annotations, the baseline-LD model and putative enhancer and promoter annotations. Only significant annotations (Bonferroni $p = 0.05/15 = 0.0033$) were retained in the model. (A) Enrichment for annotations and the difference of enrichments between annotations and (all) enhancer and (all) promoter annotations (Δ). The enrichment for putative enhancer conservation count (CC) is shown for a subset of the annotation, namely conserved putative enhancers (CC ≥ 5), but is calculated using the model with putative enhancer conservation count annotation. (B) τ^* value and significance.

A Category	Prop.	Enr (s.e.)	Enr. p-val	Δ (s.e.)	Δ p-val
Enhancer	0.033	6.065(0.939)	0.0024		
Promoter	0.015	17.823(2.791)	6e-06		
Ancient enhancer	0.005	6.403(4.166)	0.3	0.16(4.179)	0.93
Ancient promoter	0.004	36.732(6.644)	0.0028	19.001(5.745)	0.022
Conserved enhancer	0.005	11.584(2.177)	0.00065	5.785(1.751)	0.0016
Promoter of ExAC gene	0.002	26.32(4.812)	0.0061	6.389(4.107)	0.23
B Category	τ^* (s.e.)	τ^* p-val			
Enhancer	0.538(0.257)	0.037			
Promoter	1.442(0.471)	0.0022			
Ancient enhancer	-0.03(0.344)	0.93			
Ancient promoter	1.772(0.55)	0.0013			
Enhancer CC	0.748(0.227)	0.00098			
Promoter of ExAC gene	0.264(0.261)	0.31			

Table S32: **Final joint model with binary regulatory function annotations.** Meta-analysis results of final model with putative enhancer conservation count coded as a binary annotation reflecting conserved function.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.563(0.24)	2e-11	-0.212(0.031)	9.1e-12
Promoter	0.015	5.159(0.453)	4e-20	-0.215(0.038)	1.1e-08
Ancient enhancer	0.005	8.811(0.84)	5.8e-16	0.392(0.056)	1.7e-12
Ancient promoter	0.004	13.503(1.165)	4.2e-21	0.574(0.067)	1.2e-17
Conserved enhancer	0.005	4.398(0.432)	7.8e-14	0.092(0.018)	5.9e-07
Promoter of ExAC gene	0.002	11.991(0.875)	3.9e-21	0.283(0.03)	2.4e-21

Table S33: **Final joint model with flanking regions.** To guard against bias due to model misspecification[1], we repeated our final joint with binary conserved putative enhancer rather than putative enhancer conservation count including 500bp flanking regions around all introduced binary annotations (Table S32).

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.036(0.198)	4.2e-06	-0.219(0.034)	1.3e-10
Enhancer flanking	0.010	2.37(0.579)	0.029	0.017(0.044)	0.7
Promoter	0.015	5.085(0.458)	6.8e-18	-0.3(0.041)	4.5e-13
Promoter flanking	0.004	0.47(0.878)	0.6	-0.163(0.056)	0.0038
Ancient enhancer	0.005	8.38(0.753)	2.1e-14	0.385(0.052)	1.2e-13
Ancient enhancer flanking	0.009	1.06(0.348)	0.75	-0.027(0.034)	0.42
Ancient promoter	0.004	12.001(1.12)	1.3e-16	0.55(0.065)	4.4e-17
Ancient promoter flanking	0.005	4.192(0.501)	7e-06	0.232(0.043)	9.4e-08
Conserved enhancer	0.005	3.456(0.358)	3e-08	0.076(0.02)	0.00014
Conserved enhancer flanking	0.001	3.772(1.466)	0.17	0.04(0.041)	0.33
Promoter of ExAC gene	0.002	10.749(0.855)	3.5e-16	0.227(0.035)	8.6e-11
Promoter of ExAC gene flanking	0.001	4.378(2.029)	0.069	0.097(0.051)	0.056

Table S34: **Final joint model with additional promoter annotations.** Meta-analysis results are shown for the final joint model incorporating both promoter conservation count (CC) and human specific promoter annotations.

Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.535(0.238)	3e-11	-0.27(0.034)	2e-15
Promoter	0.015	5.148(0.453)	6.4e-20	-0.232(0.052)	6.4e-06
Ancient enhancer	0.005	8.782(0.834)	4e-16	0.39(0.055)	1.5e-12
Ancient promoter	0.004	13.452(1.16)	5.4e-21	0.576(0.067)	6.9e-18
Enhancer CC	N/A	N/A	N/A	0.161(0.028)	1.3e-08
Promoter CC	N/A	N/A	N/A	0.004(0.042)	0.93
Promoter of ExAC gene	0.002	11.971(0.874)	4.6e-21	0.286(0.03)	3.4e-21
Human-specific promoter	0.003	3.749(0.489)	3.9e-06	-0.007(0.026)	0.78

Table S35: **Final joint model with functional annotations based on molecular quantitative trait loci.** (A) Meta-analysis results when including the annotations for Max CPP (allGenes) and MaxCPP (ExAC), where these latter two annotations are found with a fixed effect meta-analysis (FE-Meta-Tissue) of GTEx data[16,21] to the final joint model. Even conditional on both Max CPP and MaxCPP of ExAC Genes we find that all our annotations remain conditionally significant. (B) Meta-analysis results when including the annotations for Max CPP (allGenes), MaxCPP (ExAC), as well as Max CPP (allGenes) restricted to regions with ancient sequence age to the final joint model. Conditional on these 3 additional annotations, we find that all our annotations remain conditionally significant. The conditional eQTL signal is concentrated in MaxCPP (allGenes) intersected with ancient sequence age.

A Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.547(0.238)	2.3e-11	-0.267(0.034)	7.8e-15
Promoter	0.015	4.666(0.437)	7.2e-17	-0.218(0.037)	5.2e-09
Ancient Enhancer	0.005	8.632(0.831)	1.2e-15	0.377(0.055)	6.7e-12
Ancient Promoter	0.004	12.536(1.128)	3.5e-19	0.547(0.066)	1.1e-16
Enhancer CC	N/A	N/A	N/A	0.169(0.029)	4.3e-09
Promoter of ExAC Gene	0.002	10.596(0.826)	3.2e-18	0.231(0.028)	5.1e-16
MaxCPP (allGenes)	N/A	N/A	N/A	0.393(0.046)	1.8e-17
MaxCPP (ExAC)	N/A	N/A	N/A	0.347(0.041)	2.2e-17
B Category	Prop.	Enr (s.e.)	Enr p-val	τ^* (s.e.)	τ^* p-val
Enhancer	0.033	2.55(0.238)	2.2e-11	-0.255(0.034)	9.5e-14
Promoter	0.015	4.668(0.437)	6.9e-17	-0.194(0.037)	1.3e-07
Ancient Enhancer	0.005	8.53(0.827)	2.4e-15	0.336(0.053)	1.9e-10
Ancient Promoter	0.004	12.37(1.128)	7.9e-19	0.479(0.066)	2.6e-13
Enhancer CC	N/A	N/A	N/A	0.17(0.029)	3.5e-09
Promoter of ExAC Gene	0.002	10.553(0.824)	4.1e-18	0.234(0.028)	1.4e-16
MaxCPP (allGenes)	N/A	N/A	N/A	0.17(0.044)	0.0001
MaxCPP (ExAC)	N/A	N/A	N/A	0.329(0.04)	4.1e-16
MaxCPP (allGenes) $\cap$ ancient sequence age	N/A	N/A	N/A	0.484(0.066)	1.5e-13

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