Heritability enrichment of regulatory elements is concentrated in elements with ancient sequence age and conserved function

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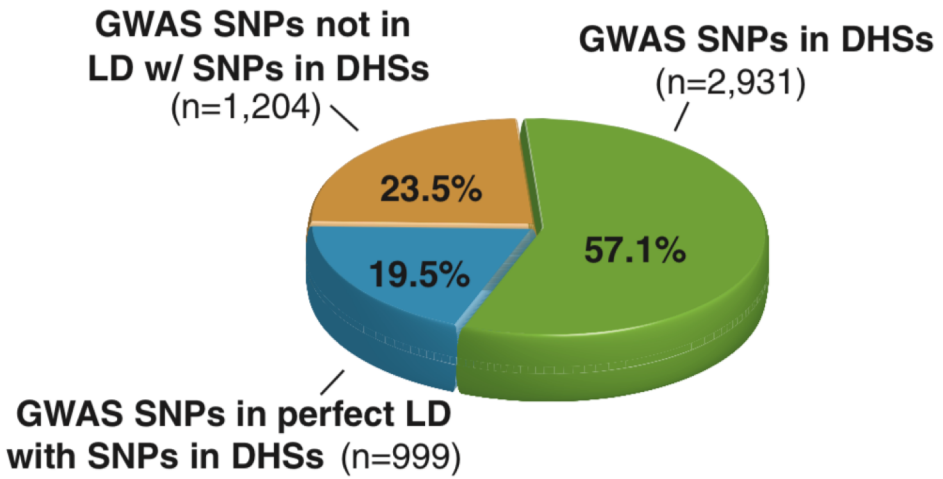
Enhancers and promoters impact disease

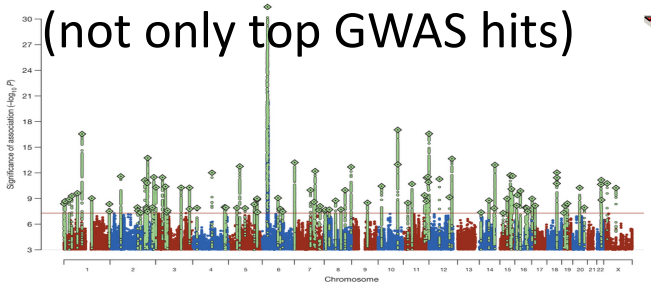
- Disease-associated variants and disease heritability are concentrated in regulatory elements, such as enhancer and promoters
- **Goal: to determine *which* enhancers and promoters are most important**



(Maurano et al. 2012 *Science*; Trynka et al. 2013 *Nat Genet*; Pickrell 2014 *AJHG*; Finucane et al. 2015 *Nat Genet*)

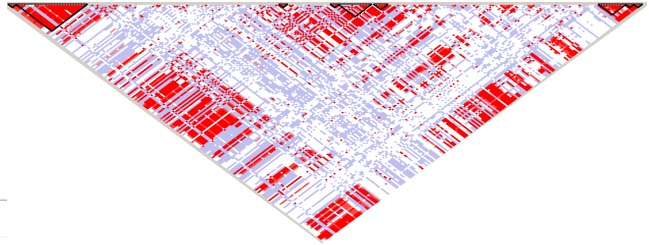
Stratified LD Score Regression (S-LDSC) is a method to partition disease heritability

GWAS summary statistics (not only top GWAS hits)

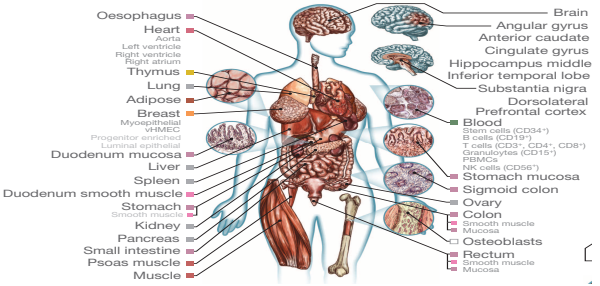


PGC-SCZ 2014 *Nature*

Reference panel (1000G)



Functional annotations



Roadmap Epigenomics Consortium 2015 *Nature*

S-LDSC with baseline-LD model (75 functional annotations)

Annotation **Enrichment**

$$\text{Enrichment} = \frac{\text{Prop. h}^2}{\text{Prop. SNPs}}$$

Annotation **Effect Size** (τ_c^*)

Conditional on other annotations

(Finucane et al. 2015 *Nat Genet*, Gazal et al. 2017 *Nat Genet*)

Summary of datasets analyzed

We utilize summary statistics for 41 independent traits and diseases ($\overline{N}$=320K).

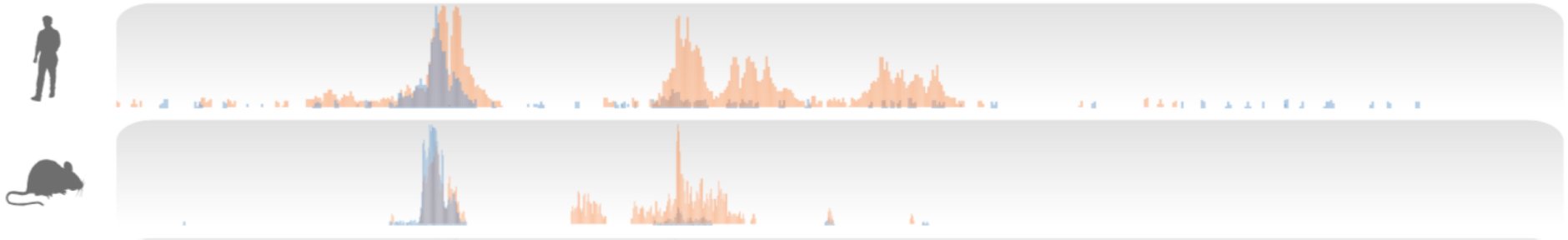
- UK Biobank summary statistics are publicly available
- Enrichment and τ* is meta-analyzed over 41 traits

Results are obtained by conditioning on the baseline-LD model (75 functional annotations) and enhancer and promoter annotations

(Gazal et al. 2017 *Nat Genet*; Loh et al. 2018 *Nat Genet*; Hormozdiari et al. 2018 *Nat Genet*)

Enhancer and promoter annotations

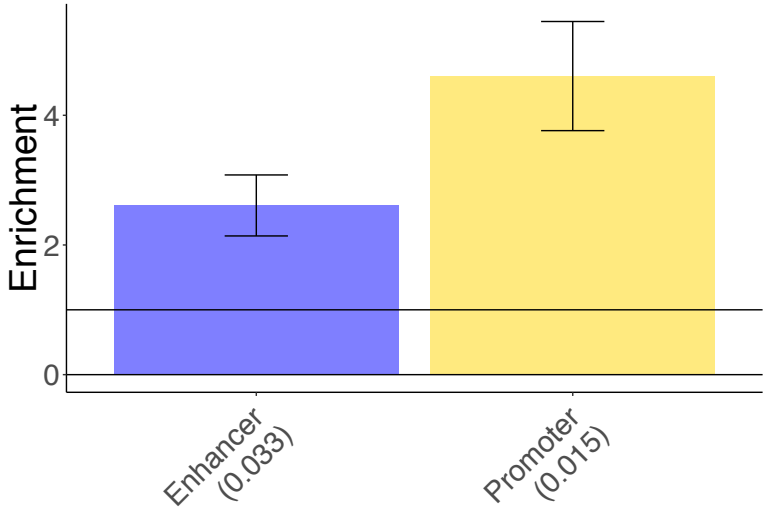
- Annotated enhancers and promoters using histone marks H3K27ac and H3K4me3
- 20 mammalian liver genomes
- Used only biologically reproducible peaks present in two or more replicates



(Villar et al. 2015 *Cell*)

Human enhancers and promoters are enriched for disease heritability

- Enhancers were 2.6x enriched (p=2.5e-12)
- Promoters were 4.6x enriched (p=3.2e-17)



(Villar et al. 2015 *Cell*)

Results meta-analyzed across 41 traits

Outline

① Enhancers and promoters with ancient sequence age

② Functionally conserved enhancers and promoters

③ Promoters of loss-of-function intolerant genes

④ All of the above are informative in a joint model

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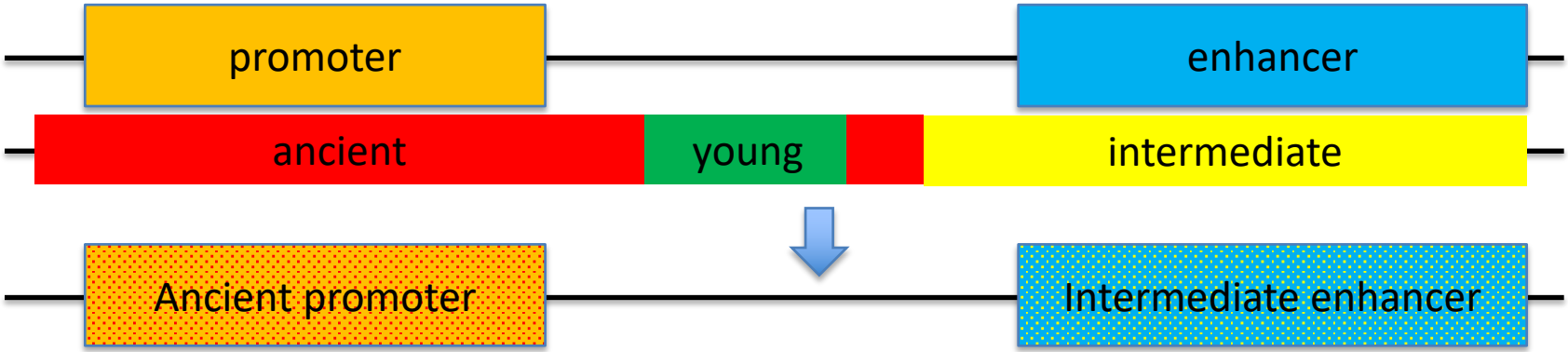
Underlying sequence age

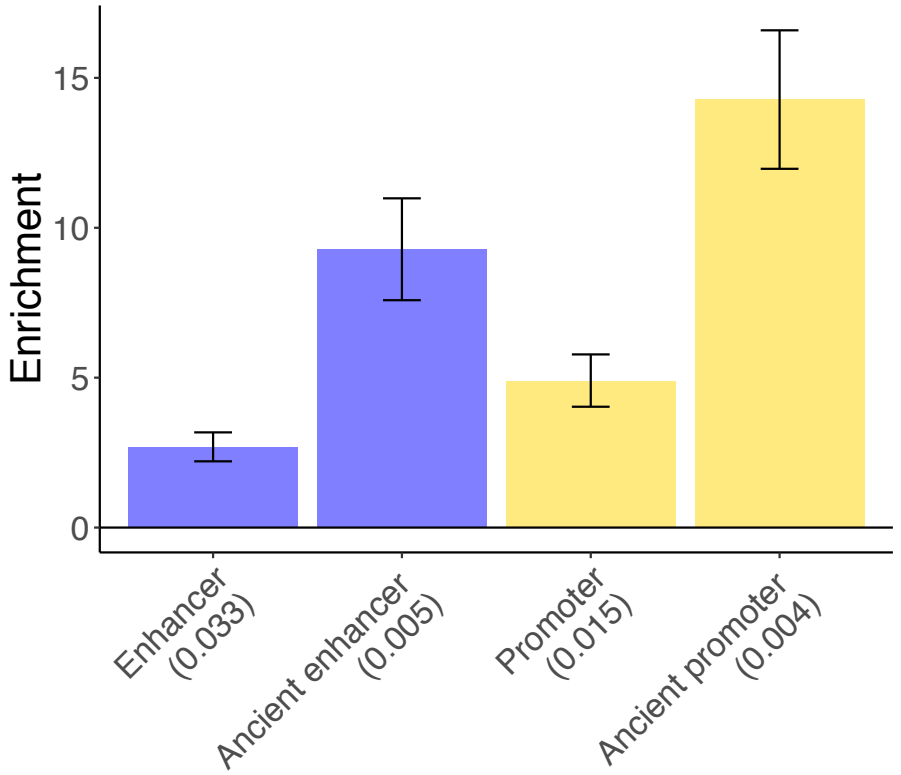
- Date the underlying sequence age of human enhancers and promoters
- Young (< 160 MYA), intermediate (~160 MYA), ancient (> 160 MYA)
- 16% of enhancers are ancient, 28% of promoters are ancient



(Marnetto et al. 2018 *AJHG*)

Heritability enrichment is concentrated in human elements with ancient sequence age

- Ancient human enhancers were 9.3x enriched, compared to 2.7x for all human enhancers (p=4e-15 for difference)
- Ancient human promoters were 14.3x enriched, compared to 4.9x for all human promoters (p=2e-18 for difference)



Results meta-analyzed across 41 traits (Hujoel et al. 2018 *bioRxiv*)

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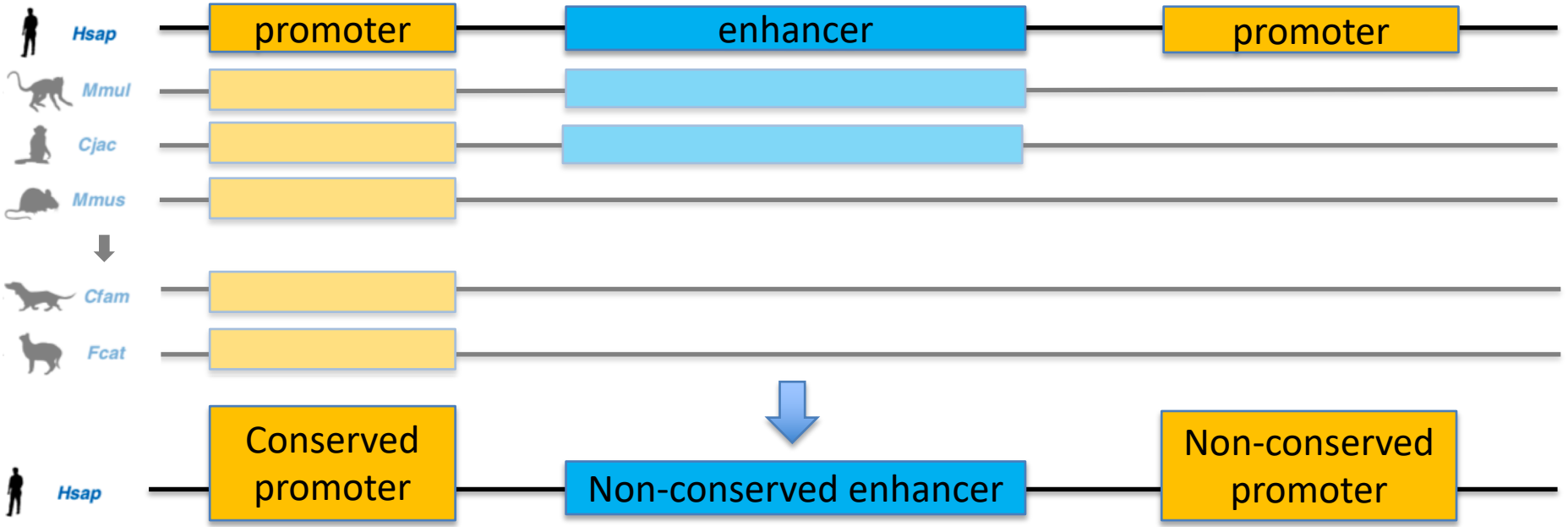
Conserved function across species

- Determine the number of mammalian species in which the human enhancer and promoter were also functional in
- conserved = conserved function in ≥ 5 of 9 other mammalian species
- Promoters tend to be more conserved (53% vs. 16%)

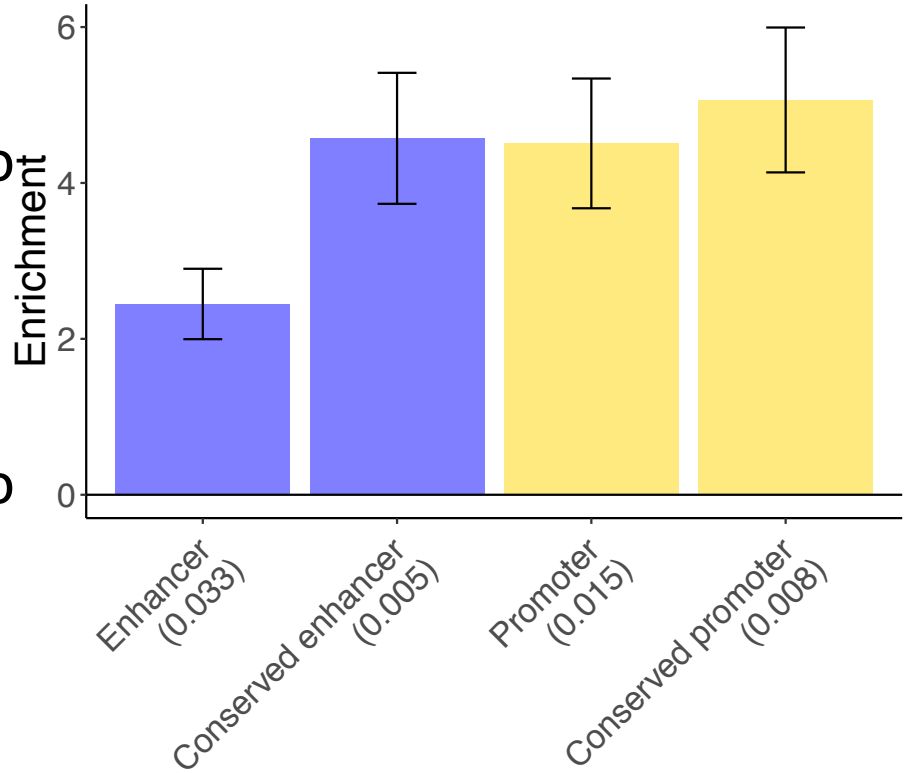


(Villar et al. 2015 *Cell;* Vermunt et al. 2016 *Nat Neuro*; Trizzino et al. 2017 *Genome Res*)

Heritability enrichment is concentrated in functionally conserved enhancers and promoters

- Conserved human enhancers were 4.6x enriched, compared to 2.4x for all human enhancers (p=3e-12 for difference)
- Conserved human promoters were 5.1x enriched, compared to 4.5x for all human promoters (p=0.022 for difference)

Results meta-analyzed across 41 traits



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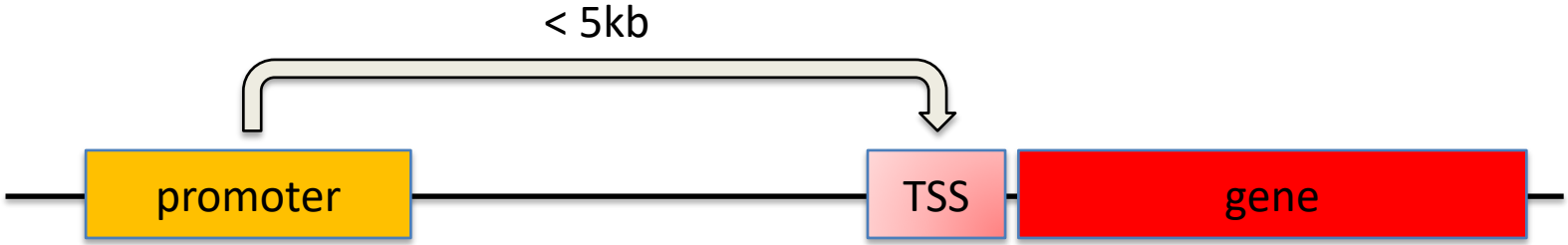
Target gene

- Identify the target gene of human promoters

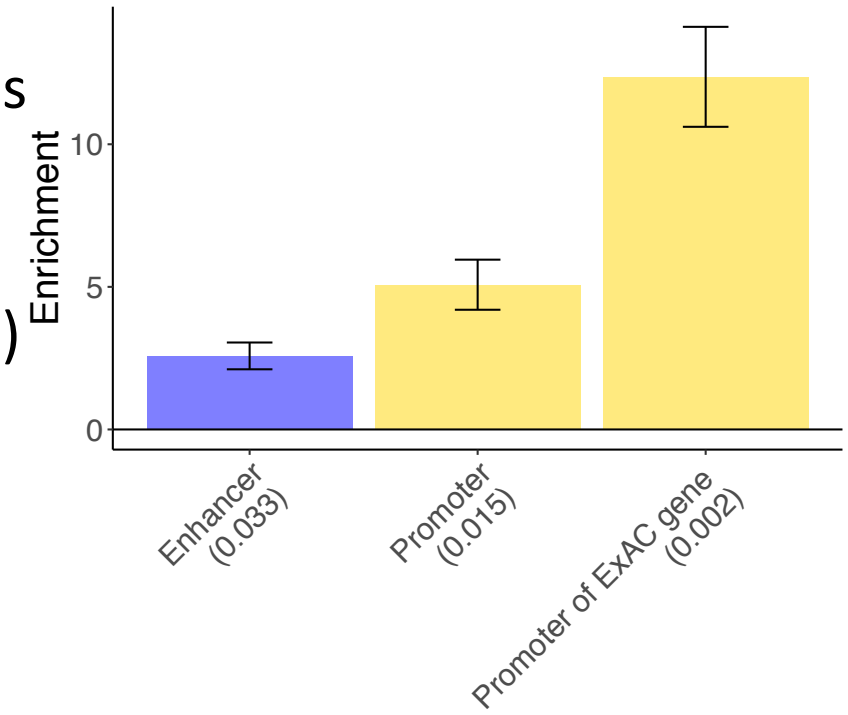


- Genes looked at:
  - ExAC loss-of-function (LoF) intolerant genes
  - Ancient genes (emerged before the vertebrates split; ~500 MYA)
  - Genes with a mouse ortholog

(Domazet-Loso and Tautz 2008 *Mol. Biol. Evol*;
Neme and Tautz 2013 *BMC Genomics*; Gao et al. 2018 *Cell*; Lek et al. 2016 *Nature*)

Heritability enrichment is concentrated in human promoters of ExAC LoF intolerant genes

- 16% of human promoters are promoters of ExAC Lof intolerant genes
- Promoters of ExAC genes were 12.4x enriched, compared to 5.1x for all promoters (p=9e-16 for the difference)
- Annotations for promoters of ancient genes or genes with a mouse ortholog were not conditionally significant



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Obtaining final joint model

Included annotations relating to:

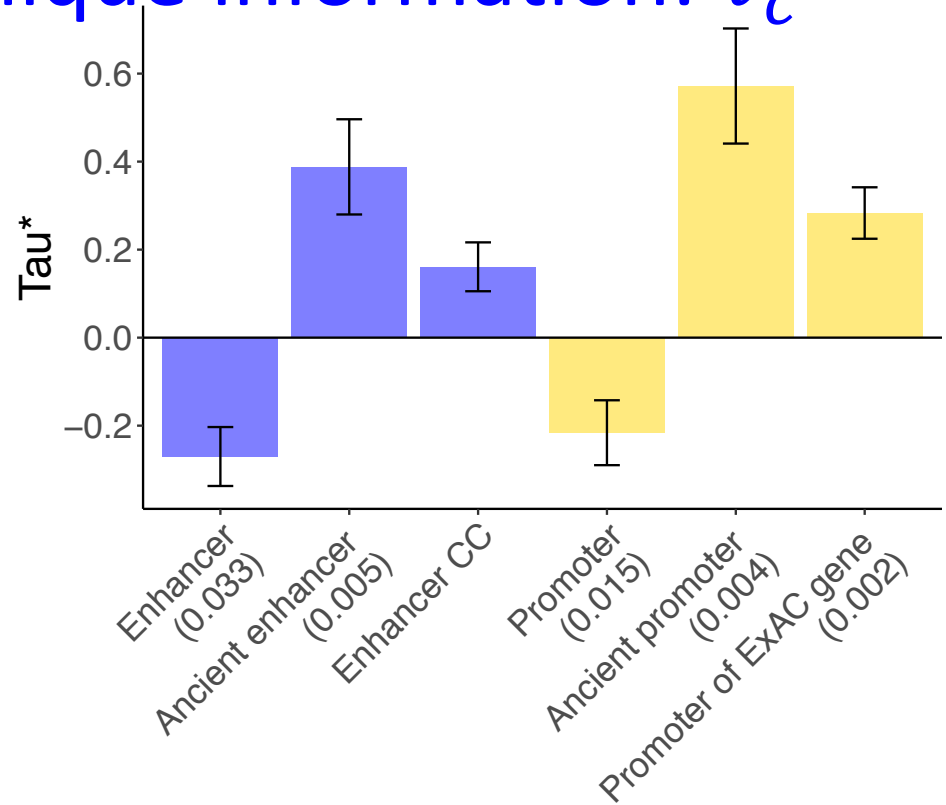
- Sequence age: enhancer/promoter w/ ancient sequence age
- Conserved function: enhancer/promoter conservation count
- Target gene: promoter of ExAC LoF intolerant genes

Iteratively removed annotations that were not conditionally significant (adjusting for multiple testing; based on τ_c^* p-value)

Sequence age, conserved function, and target gene each provide unique information: τ_c^*

Final model included

- Ancient enhancer
- Enhancer conservation count
- Ancient promoter
- Promoter of ExAC LoF intolerant gene

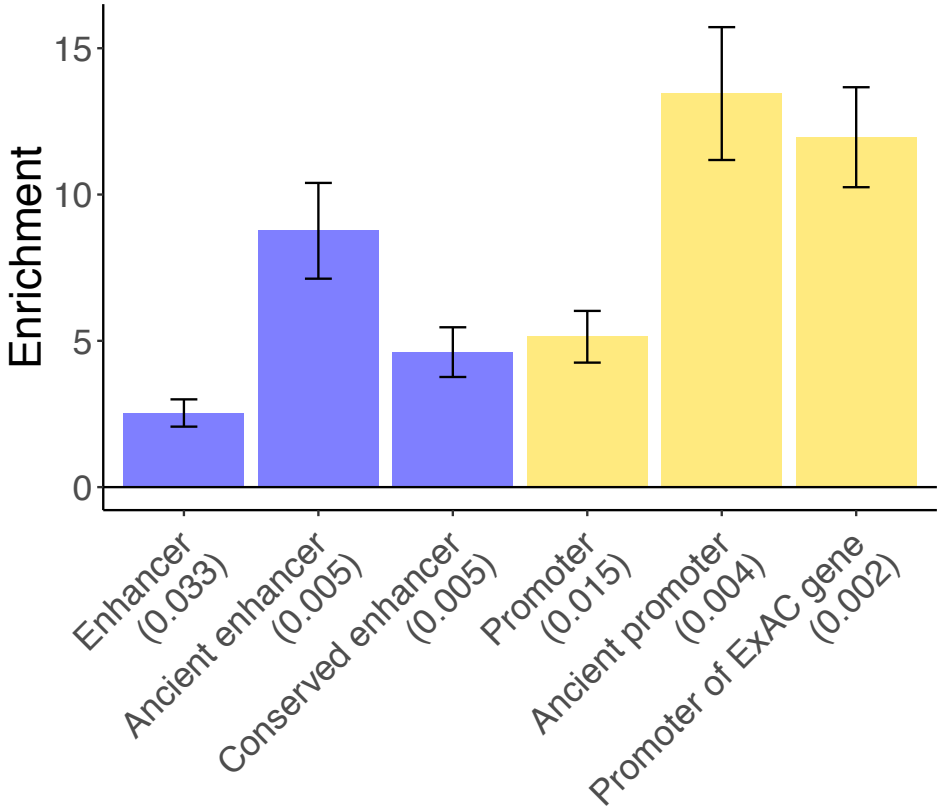


Results meta-analyzed across 41 traits

τ_c^*: the proportionate change in per-SNP h^2 per one s.d. increase in the value of the annotation

Sequence age, conserved function, and target gene provide unique information: enrichment

- Enrichment remains consistent with previous models
- Within both enhancers and promoters, heritability is particularly concentrated within elements with ancient sequence age

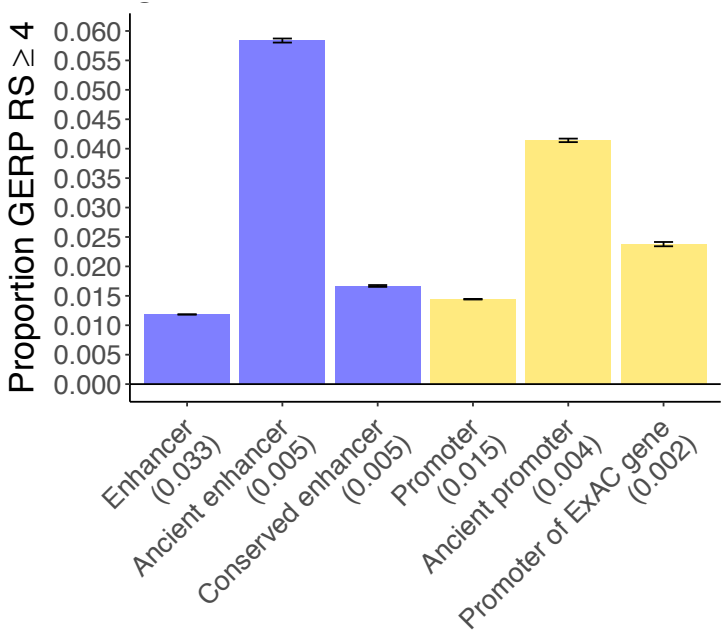


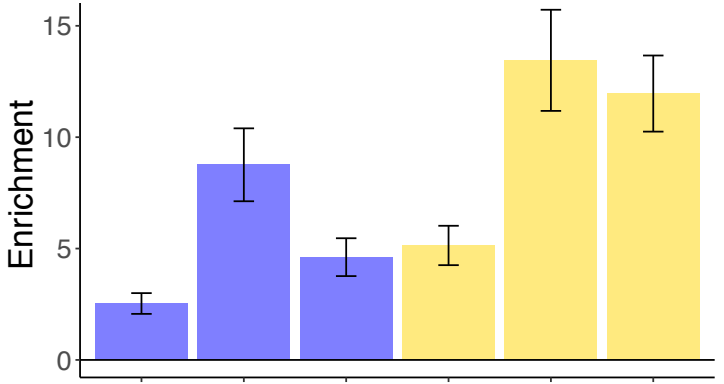
Results meta-analyzed across 41 traits

Negative selection metrics mirror these findings

- GERP RS score: a larger score is indicative of stronger negative selection
- Larger proportion of SNPs under stronger negative selection within elements that are more enriched
- Similar results for other measures of negative selection

(Gazal et al. 2017 *Nat Genet;*
Davydov et al. 2010 *PLoS Comput Biol*)





Conclusions

- Heritability enrichment within human enhancers and promoters is concentrated:
  - In elements with ancient sequence age
  - In elements with conserved function across many species
  - In promoters of ExAC LoF intolerant genes

- The mean value of several measures of negative selection within these genomic annotations mirrored all of these findings.

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Disease heritability enrichment of regulatory elements is concentrated in elements with ancient sequence age and conserved function across species
Hujoel *et al.* 2018 **bioRxiv:420166**