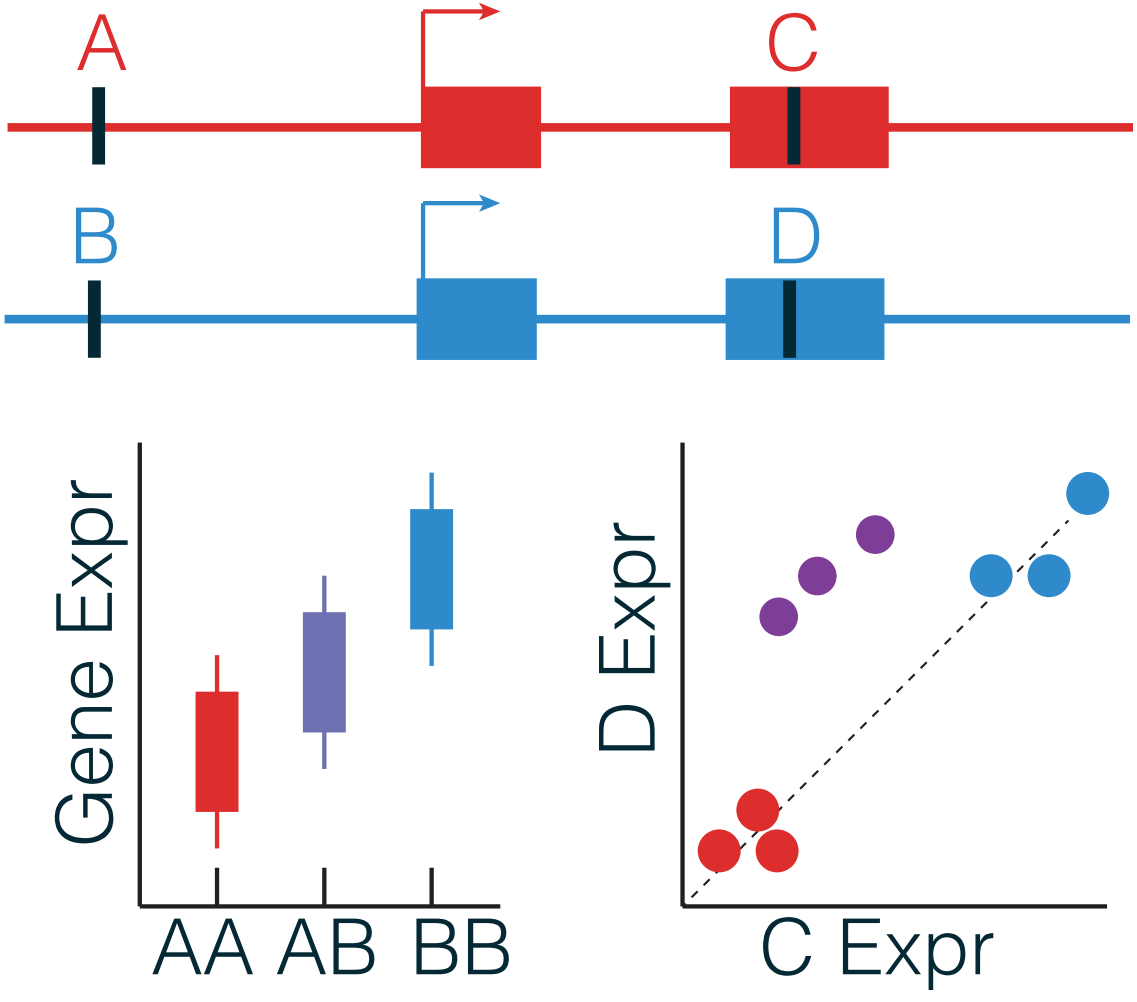
Genetics of gene expression: from rare to common, from ubiquitous to cell specific

Christopher Brown (@casey6r0wn)

The GWAS era has been an incredible success

- Observation: Majority of complex trait h^2 is explained by common, non-coding variation
- Hypothesis: Most GWAS variants function by modifying gene expression
- Problem: Regulatory elements act across large distances, making target gene identification difficult

The search for regulatory variation



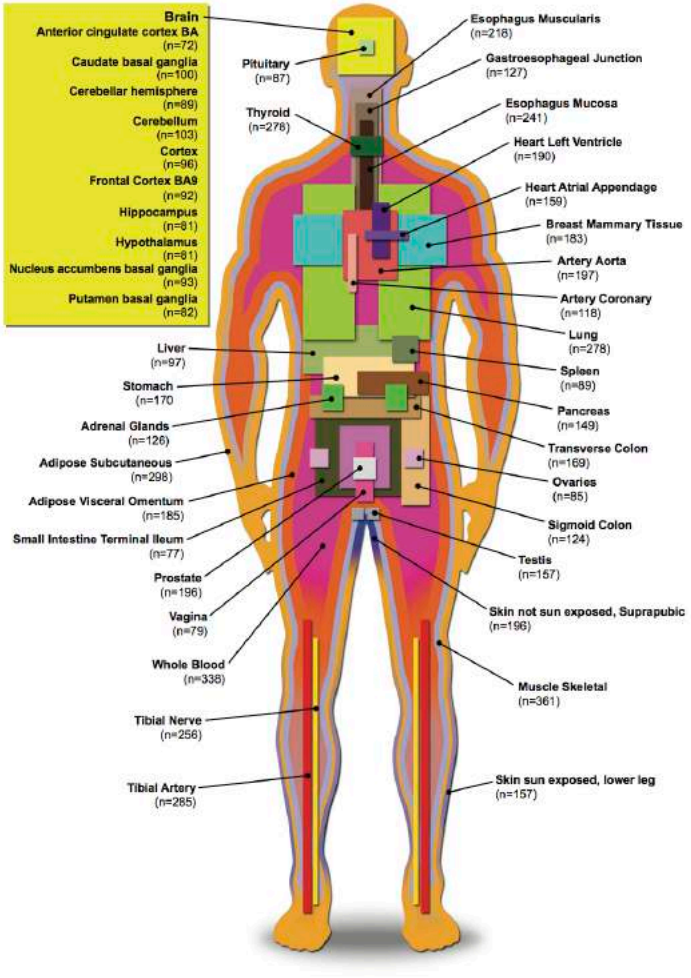
eQTL complications

- Many eQTLs have cell-type restricted functions
- Power to detect rare eQTLs is limited

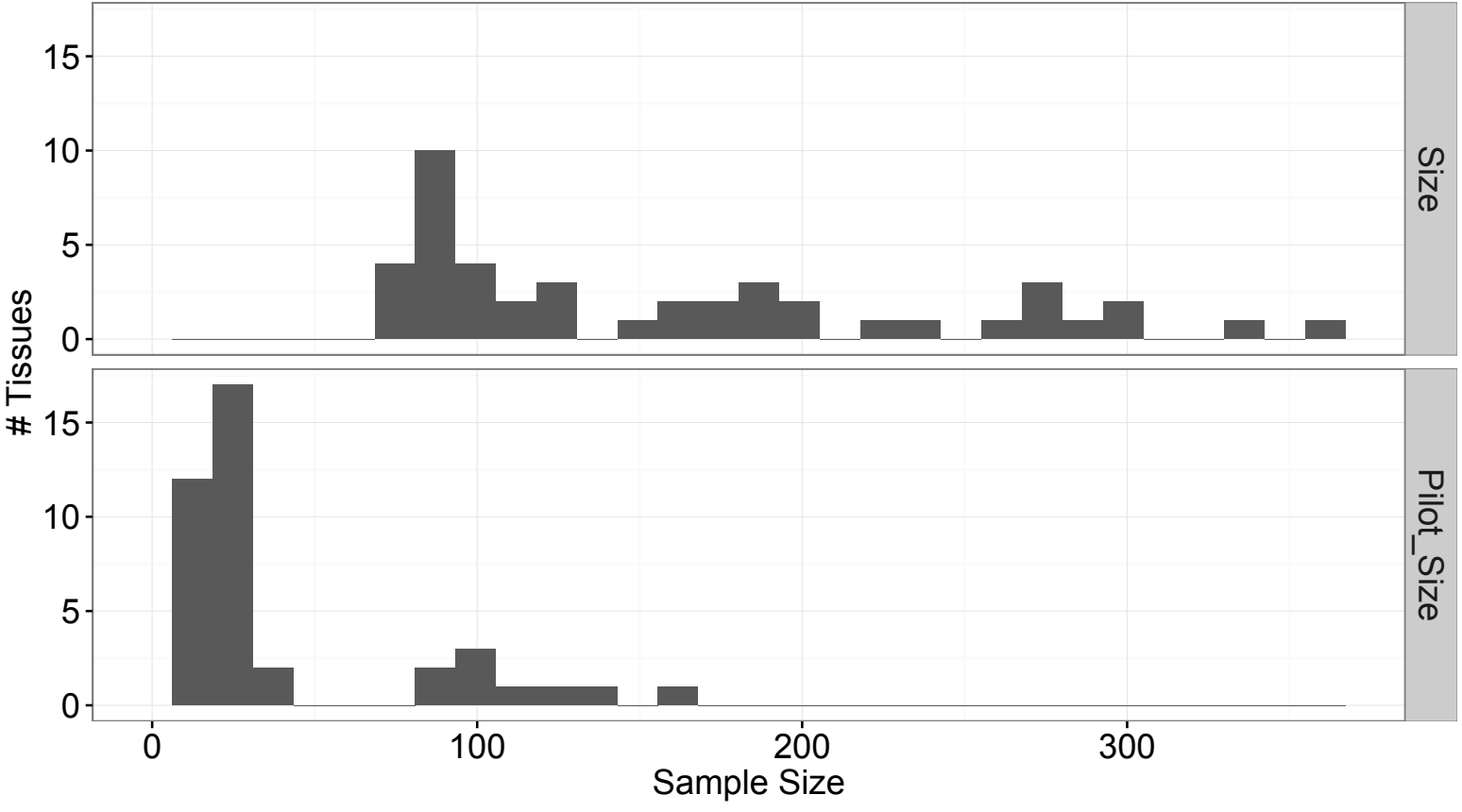
GTEx: Genotype Tissue Expression

GTEx v6 eQTL analysis:

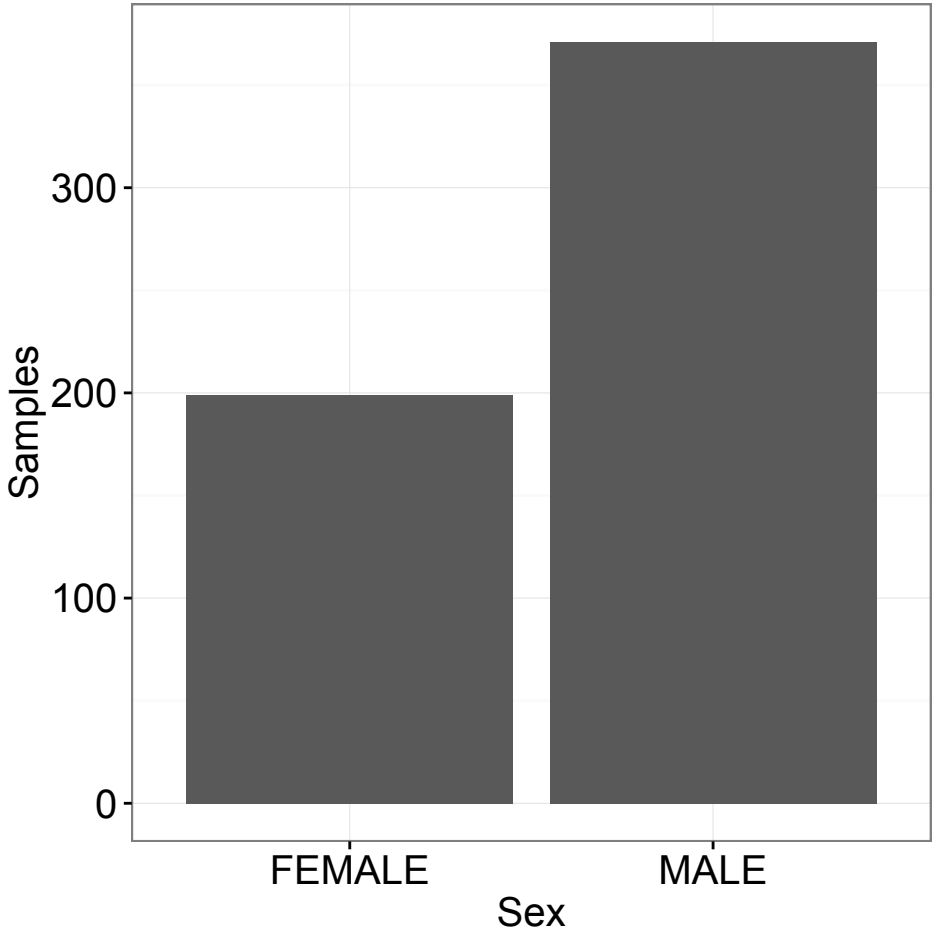
- 7051 transcriptomes
- 44 tissues
- 449 individuals

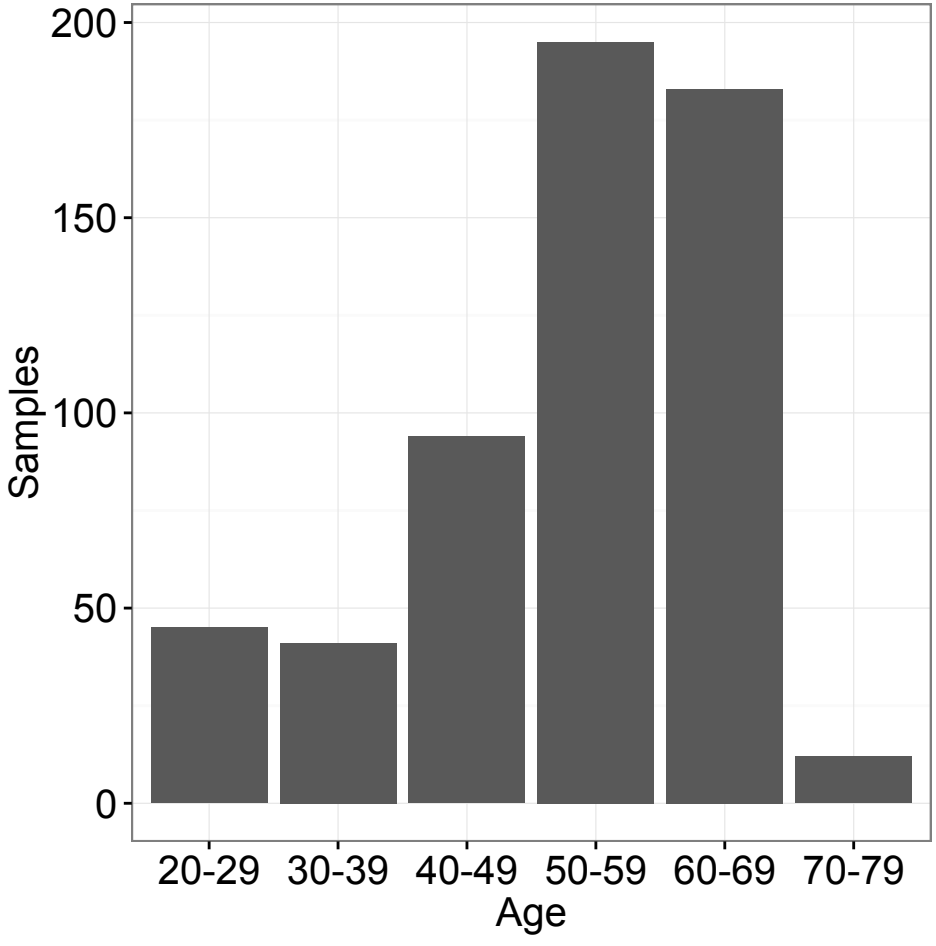


Latest GTEx release has added 5410 samples

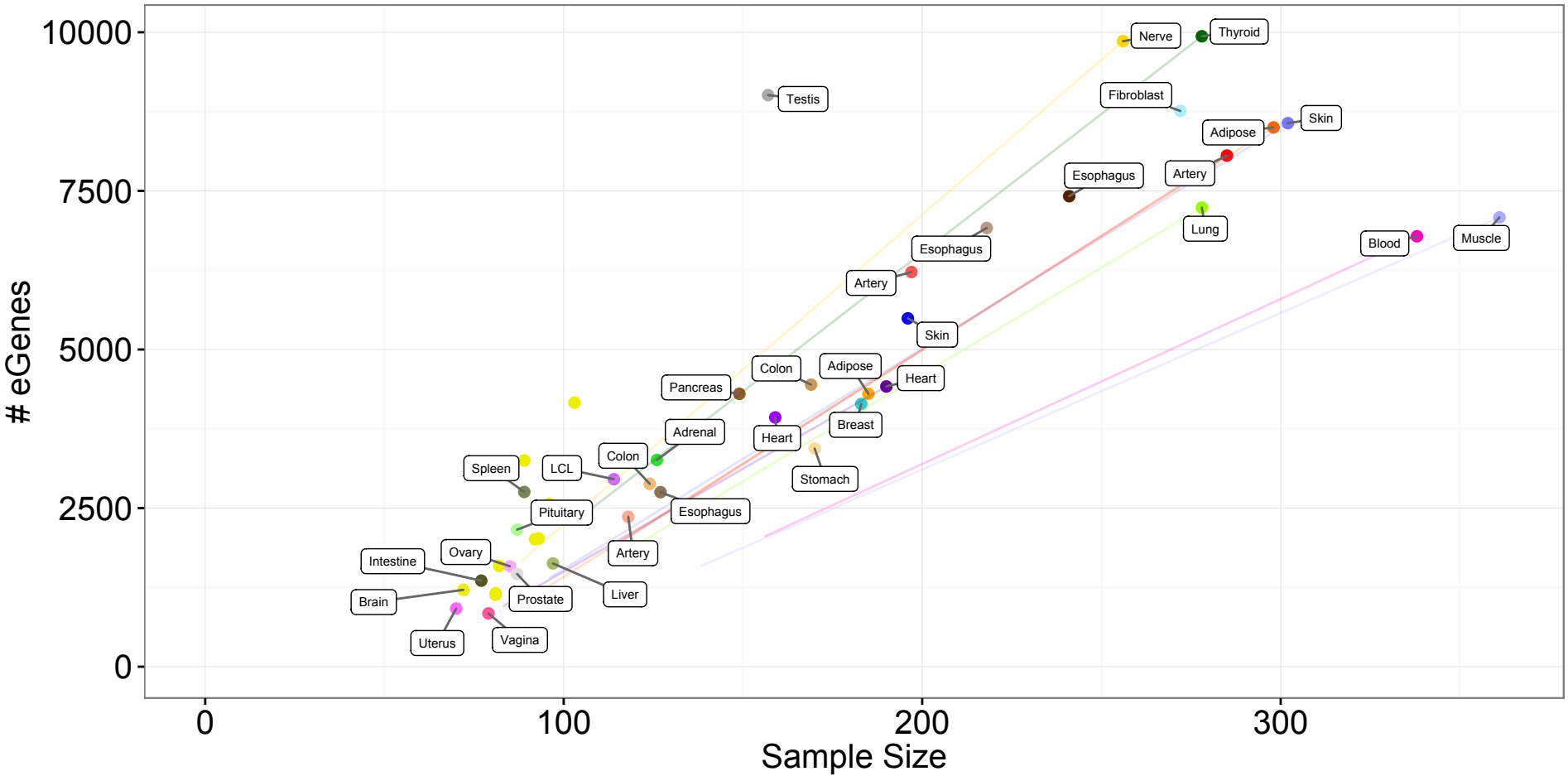


Sample demographics

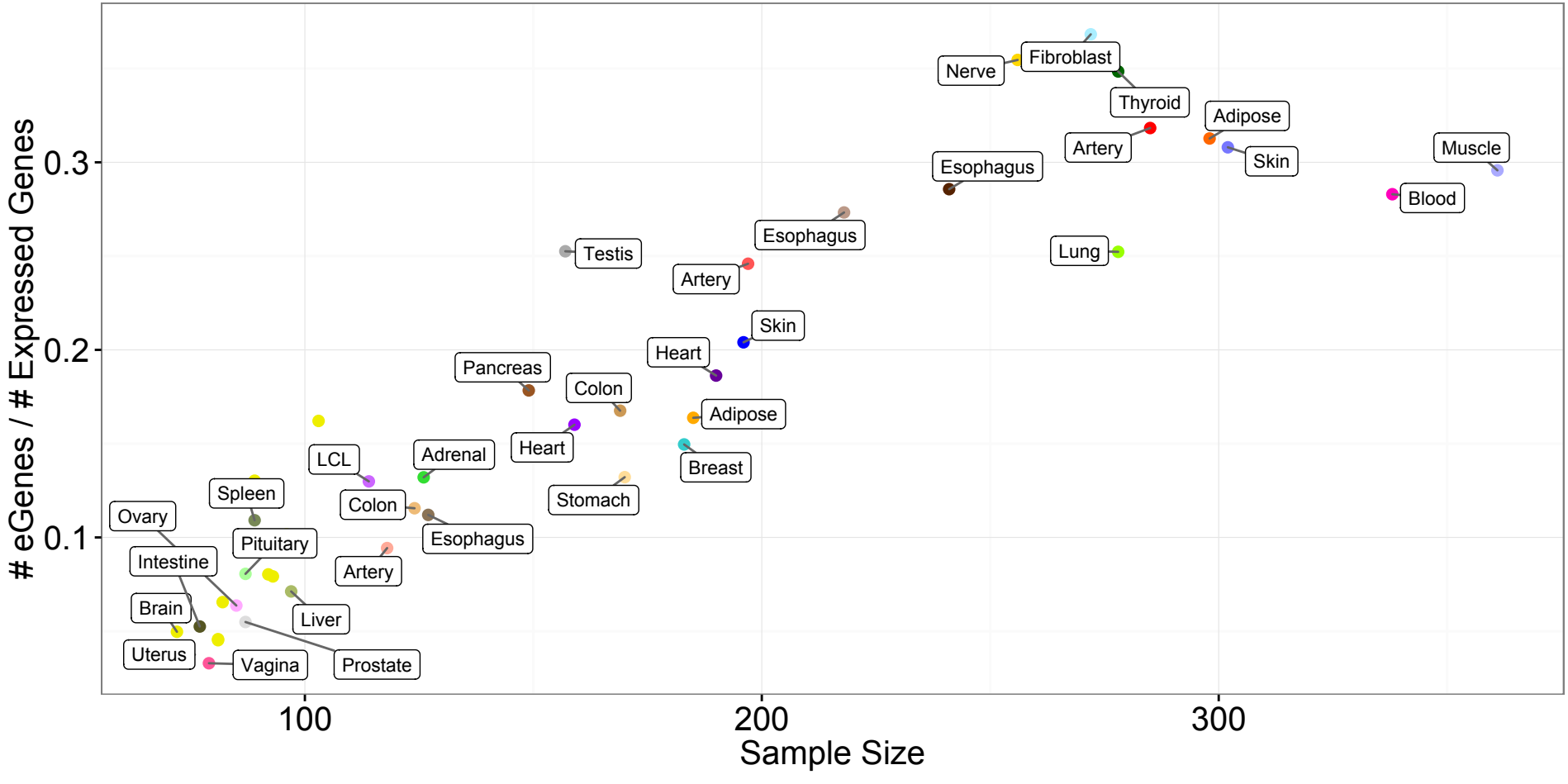




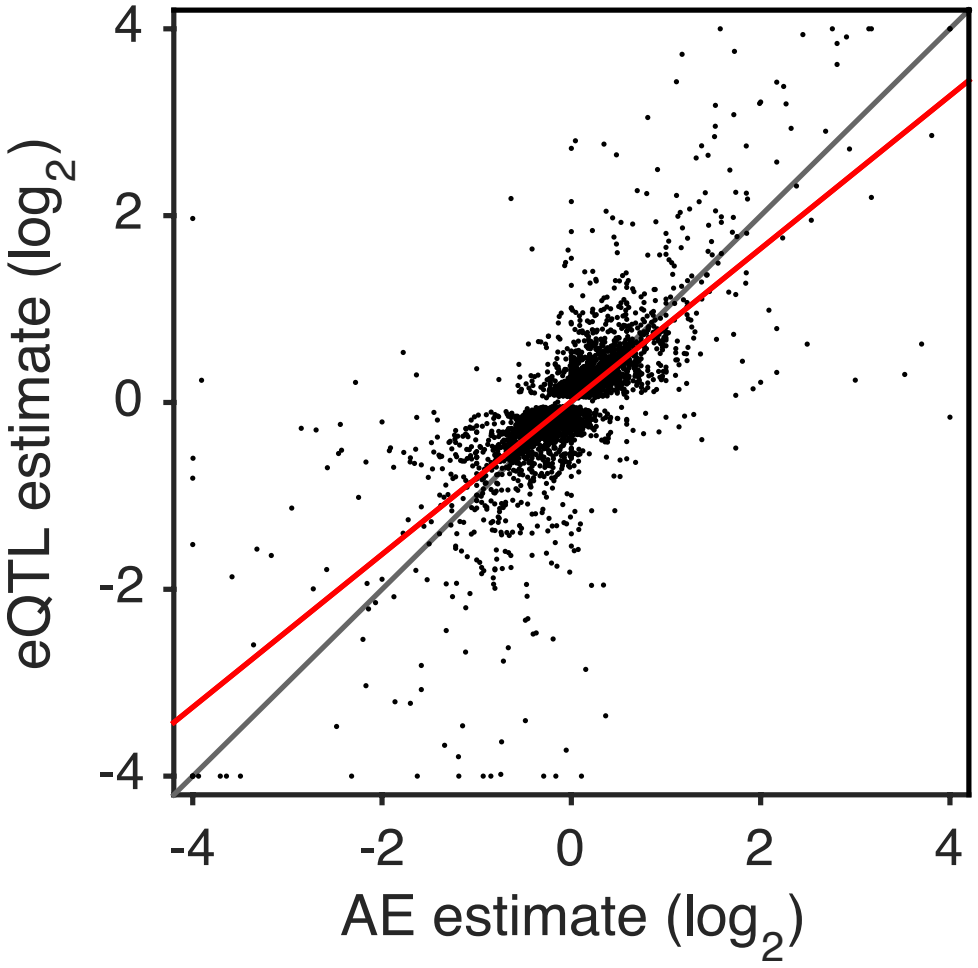
GTEx V6 eQTL discovery



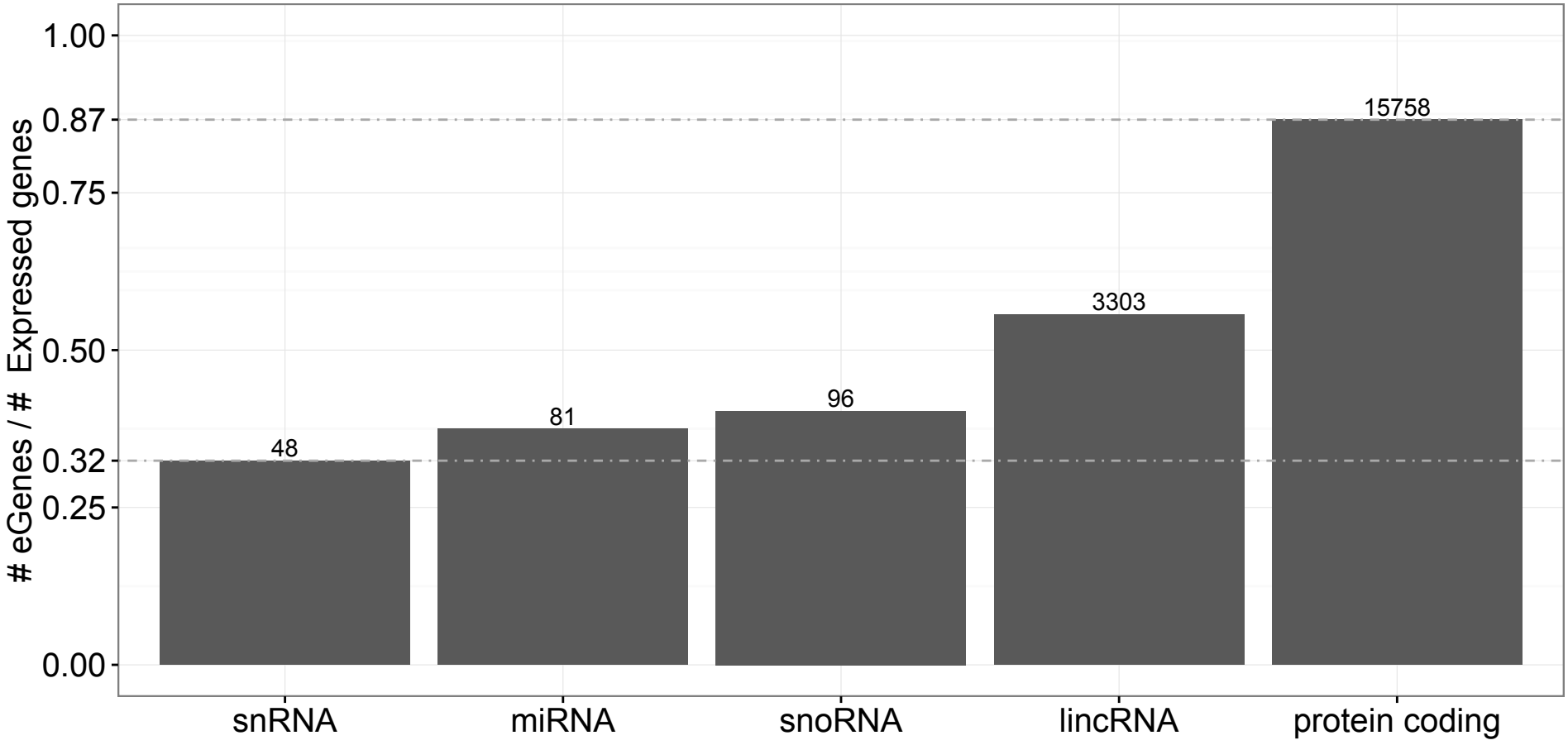
The role of transcriptome diversity



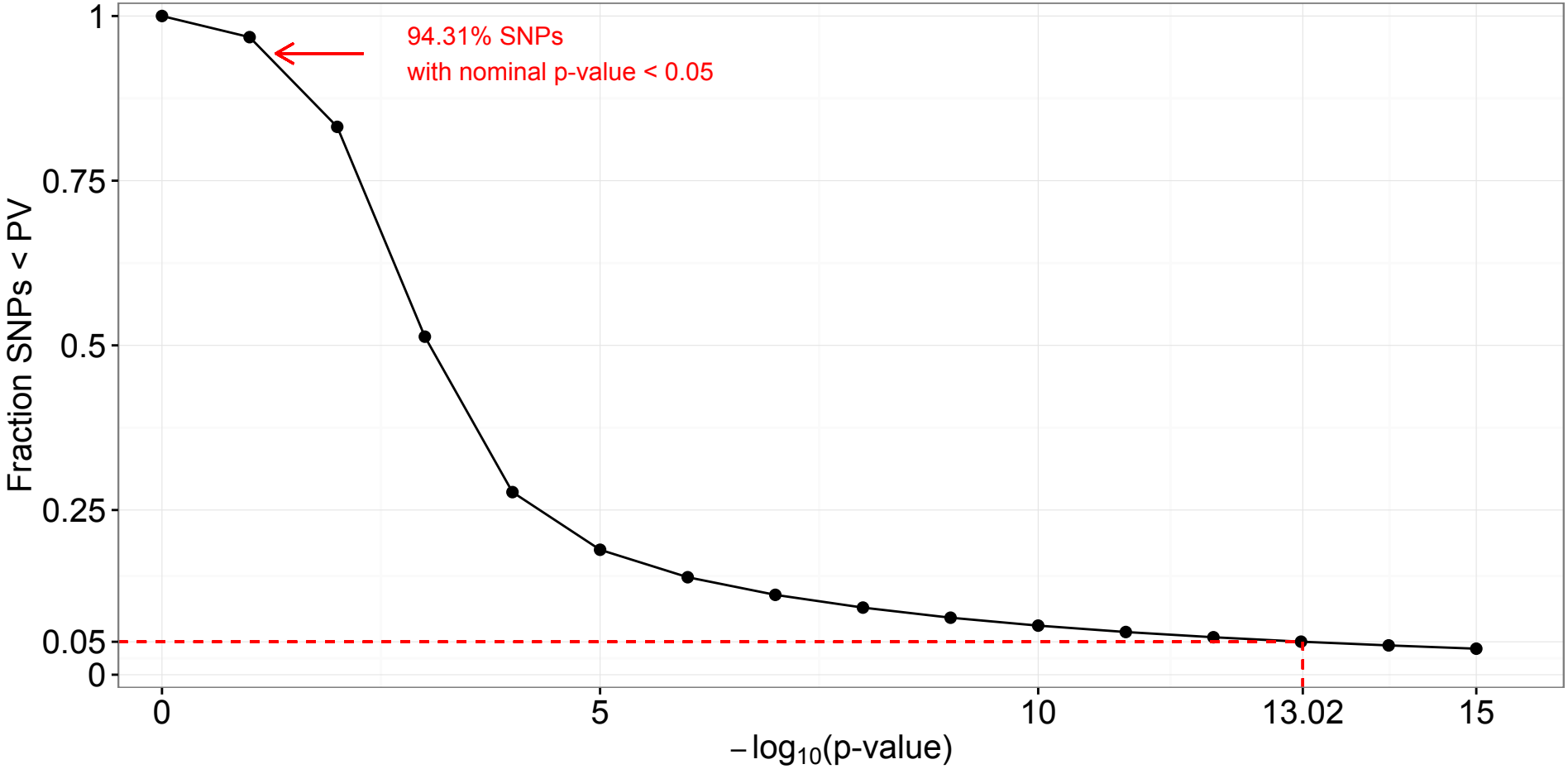
Consistency of eQTL-ASE effects



Majority of genes now have eQTLs

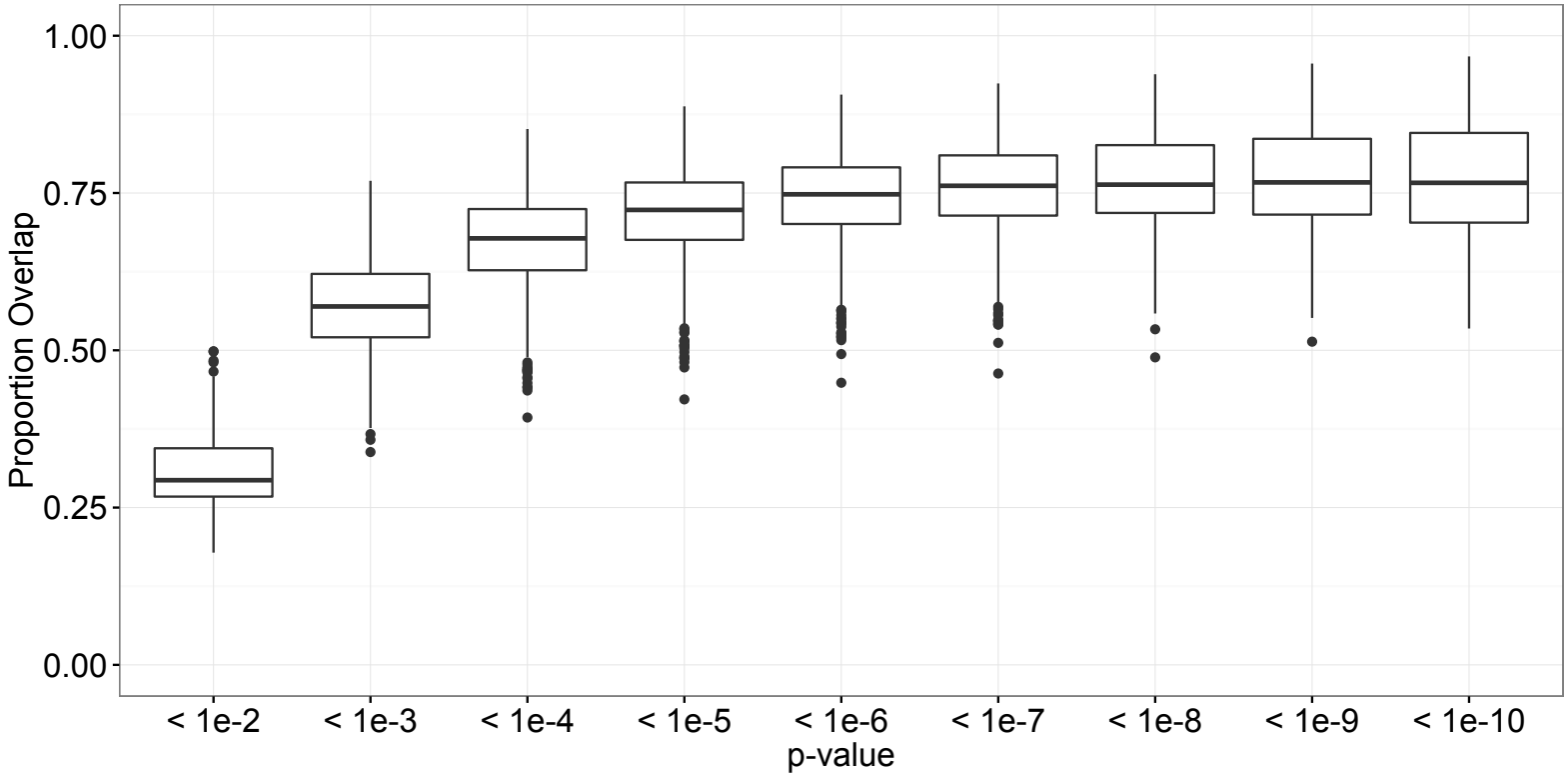


Your favorite SNP is likely an eQTL

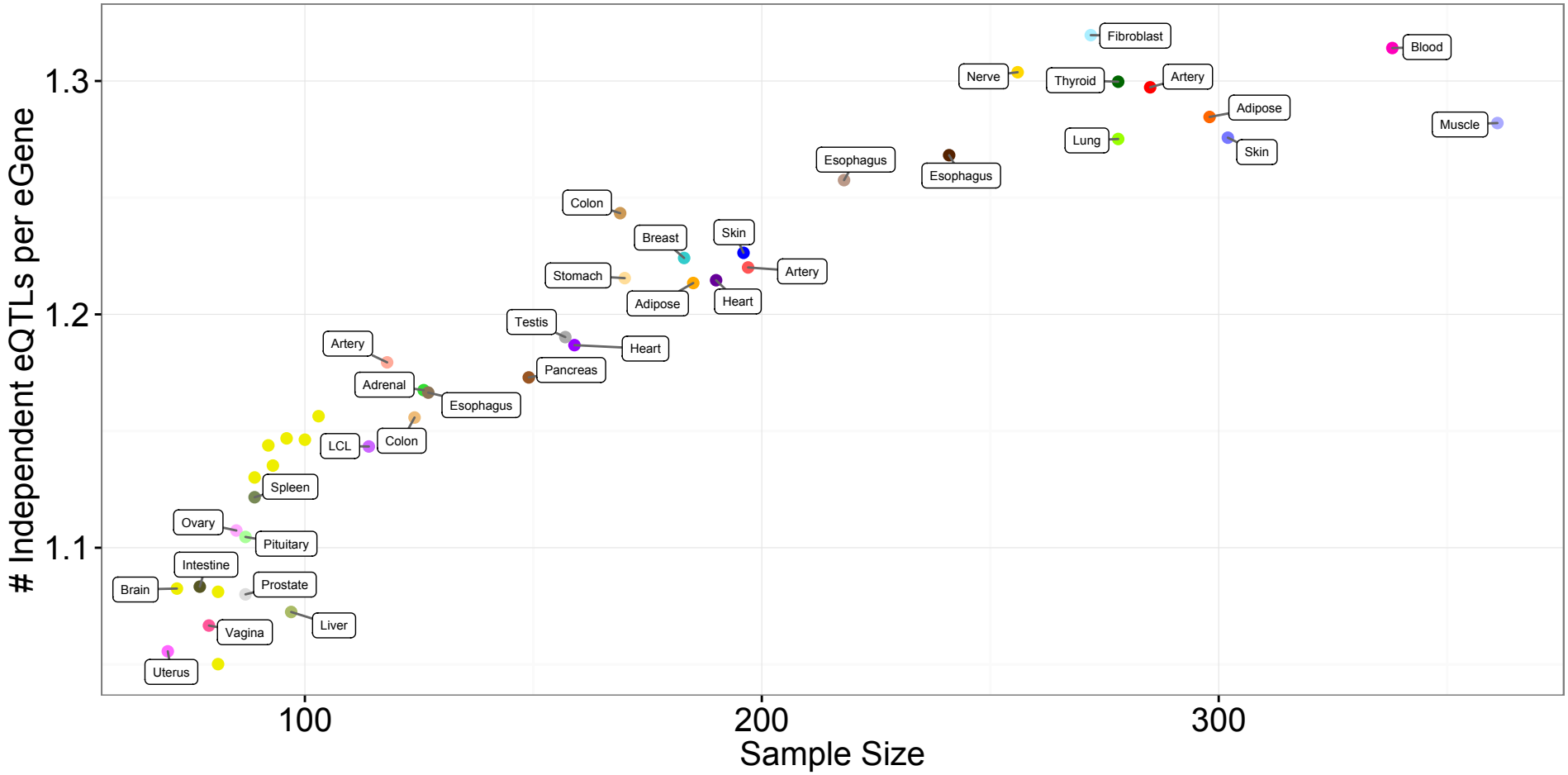


Bosh Liu, Stephen Montgomery

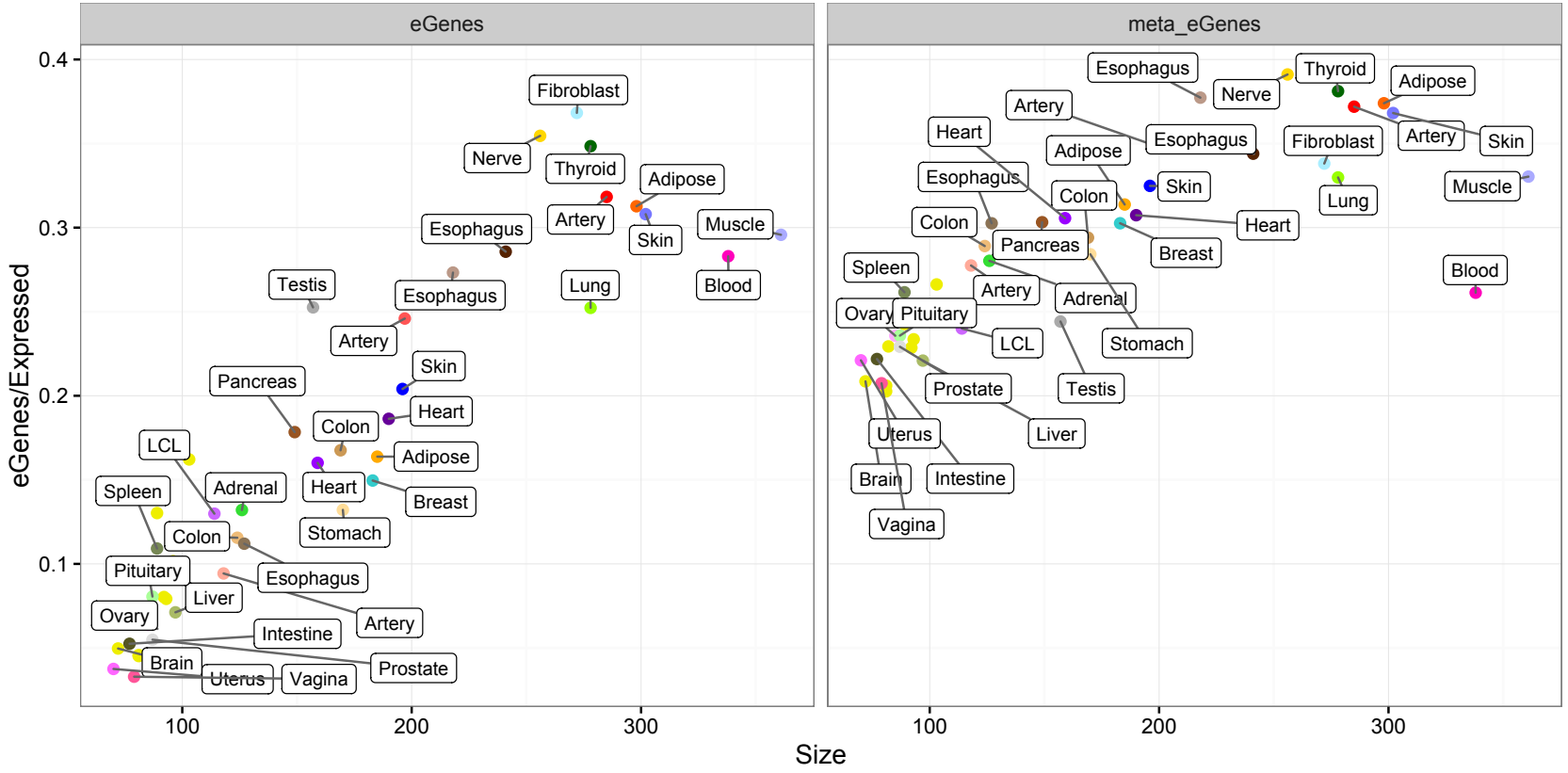
SNPs often associate with different genes across tissues



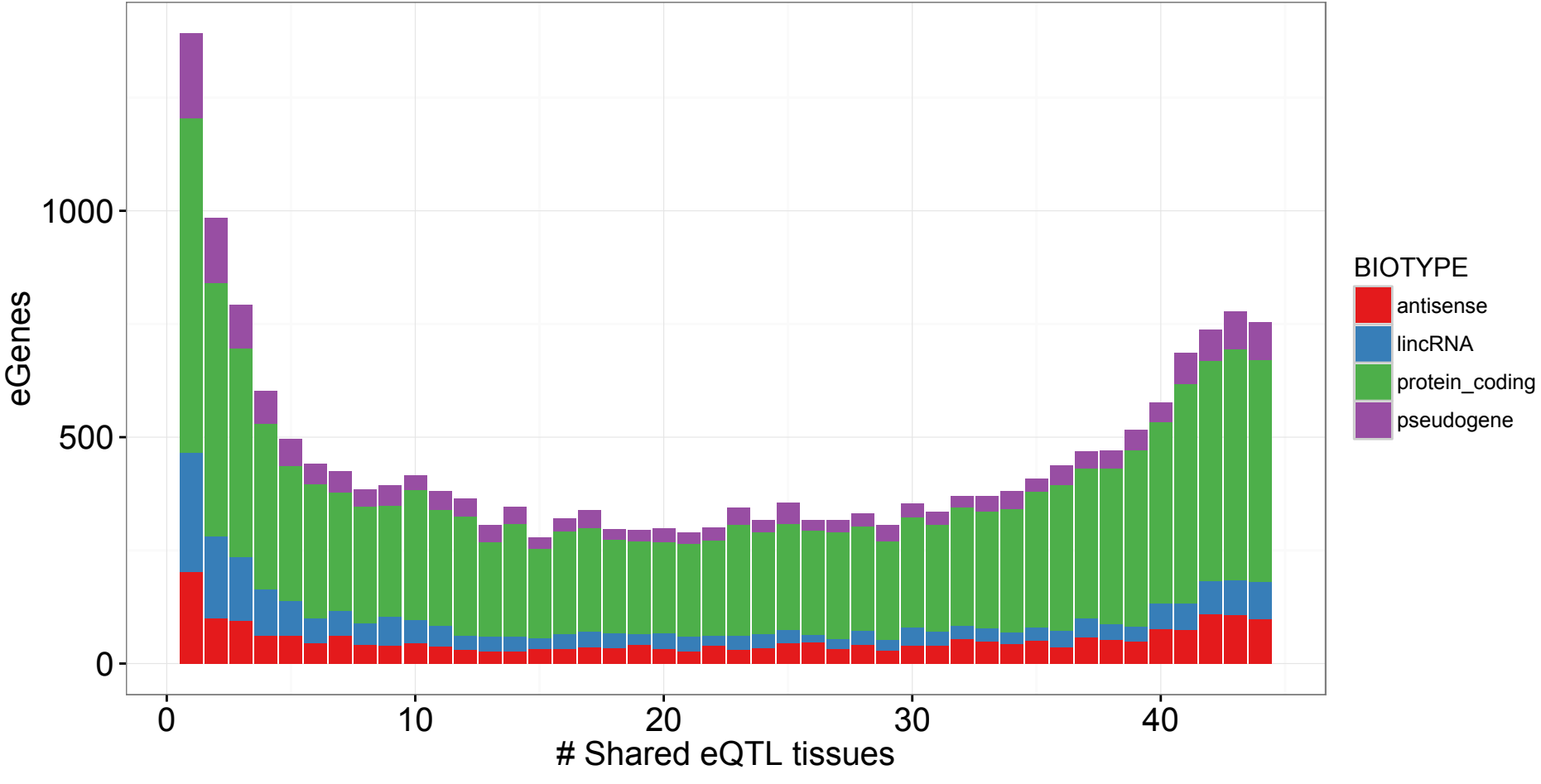
Allelic heterogeneity is pervasive



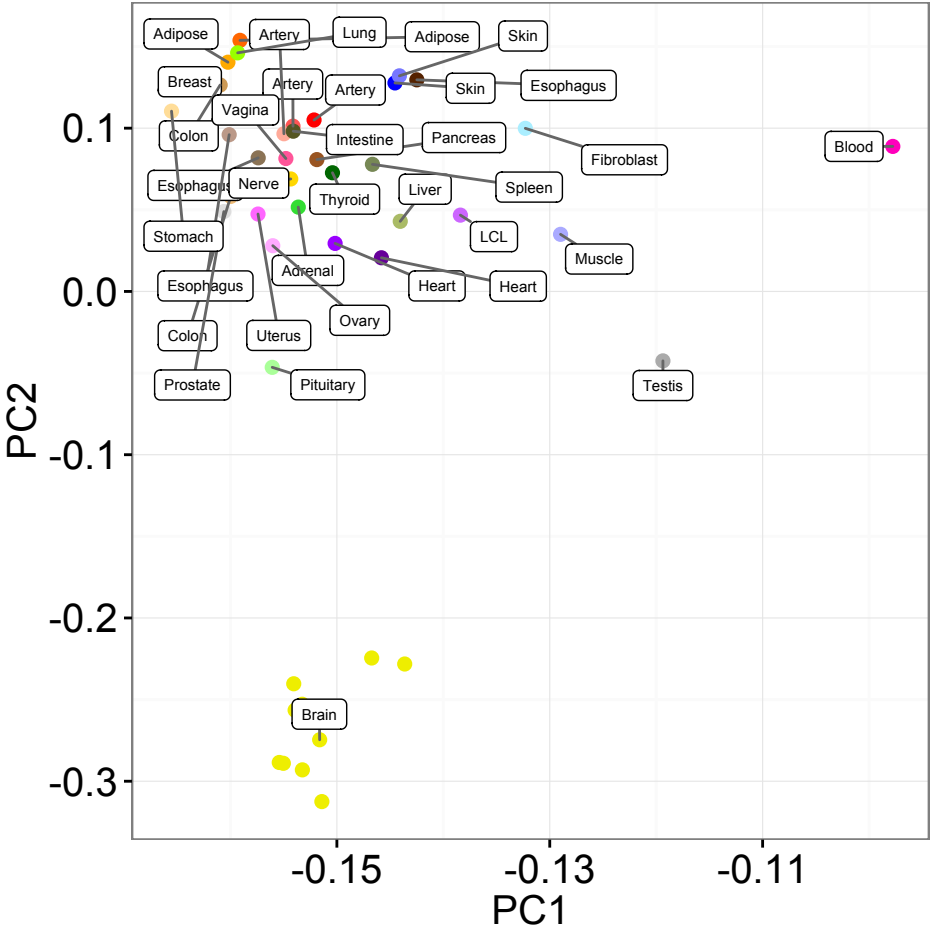
Multi tissue analysis improves discovery power

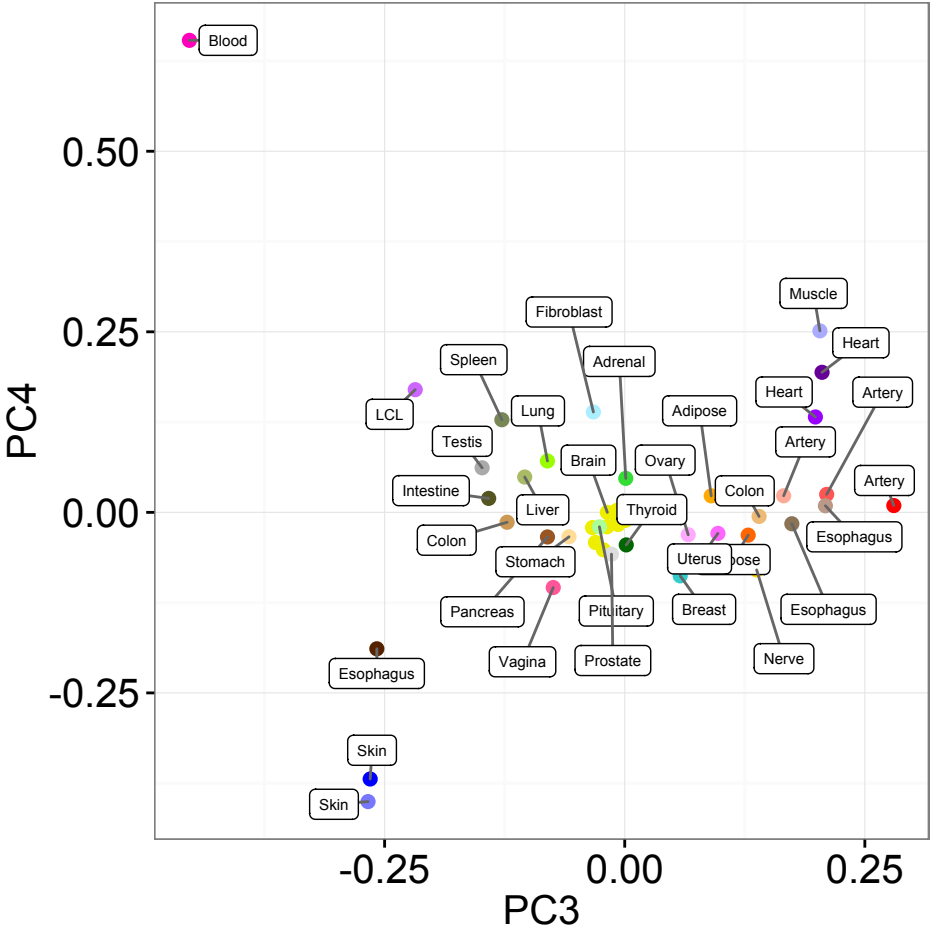


Tissue specificity of eQTLs

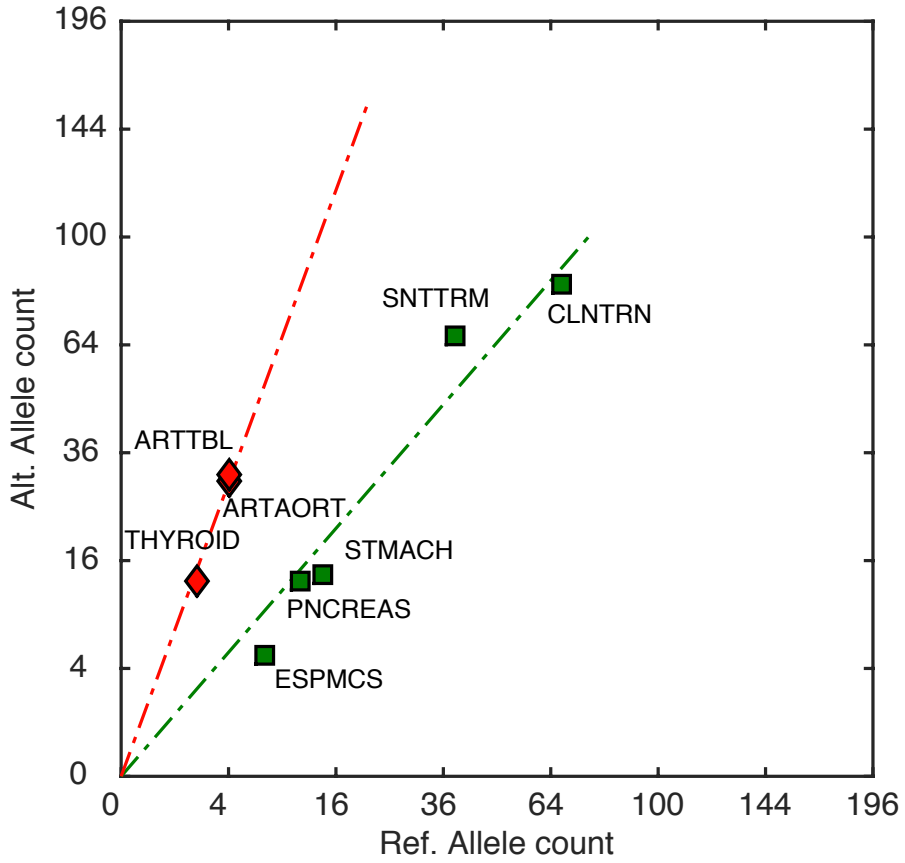


Patterns of eQTL sharing

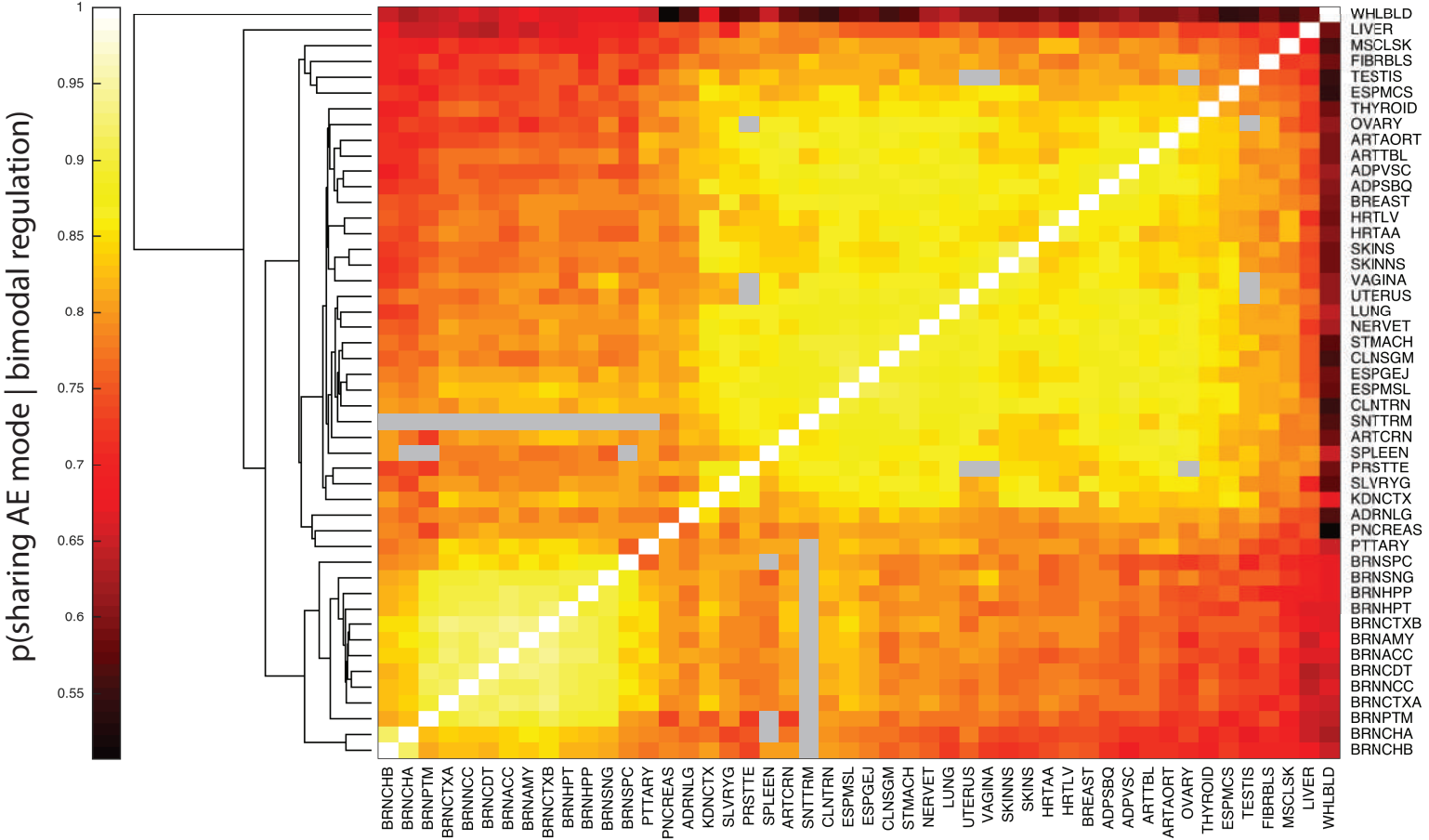




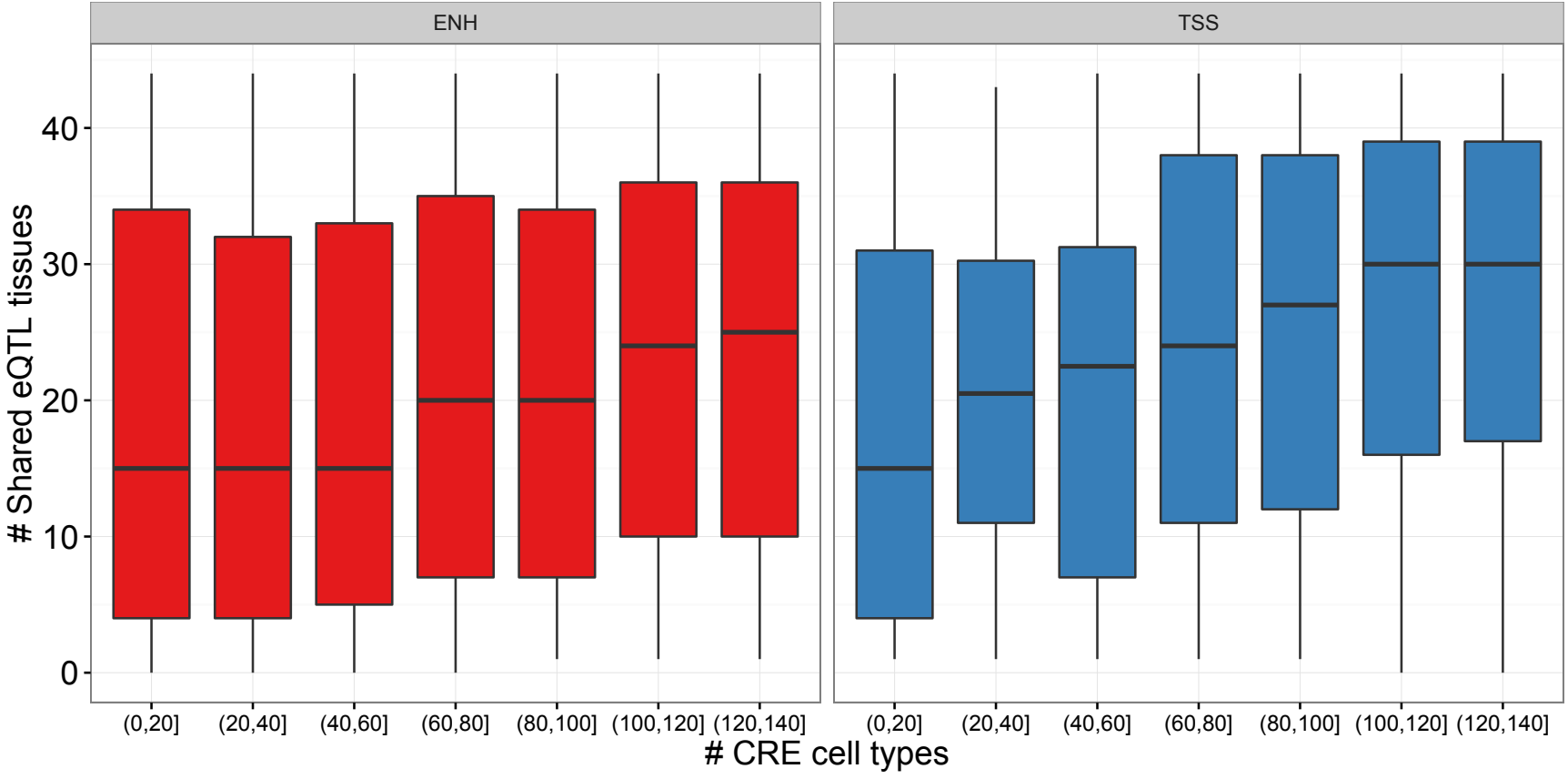
Patterns of ASE sharing



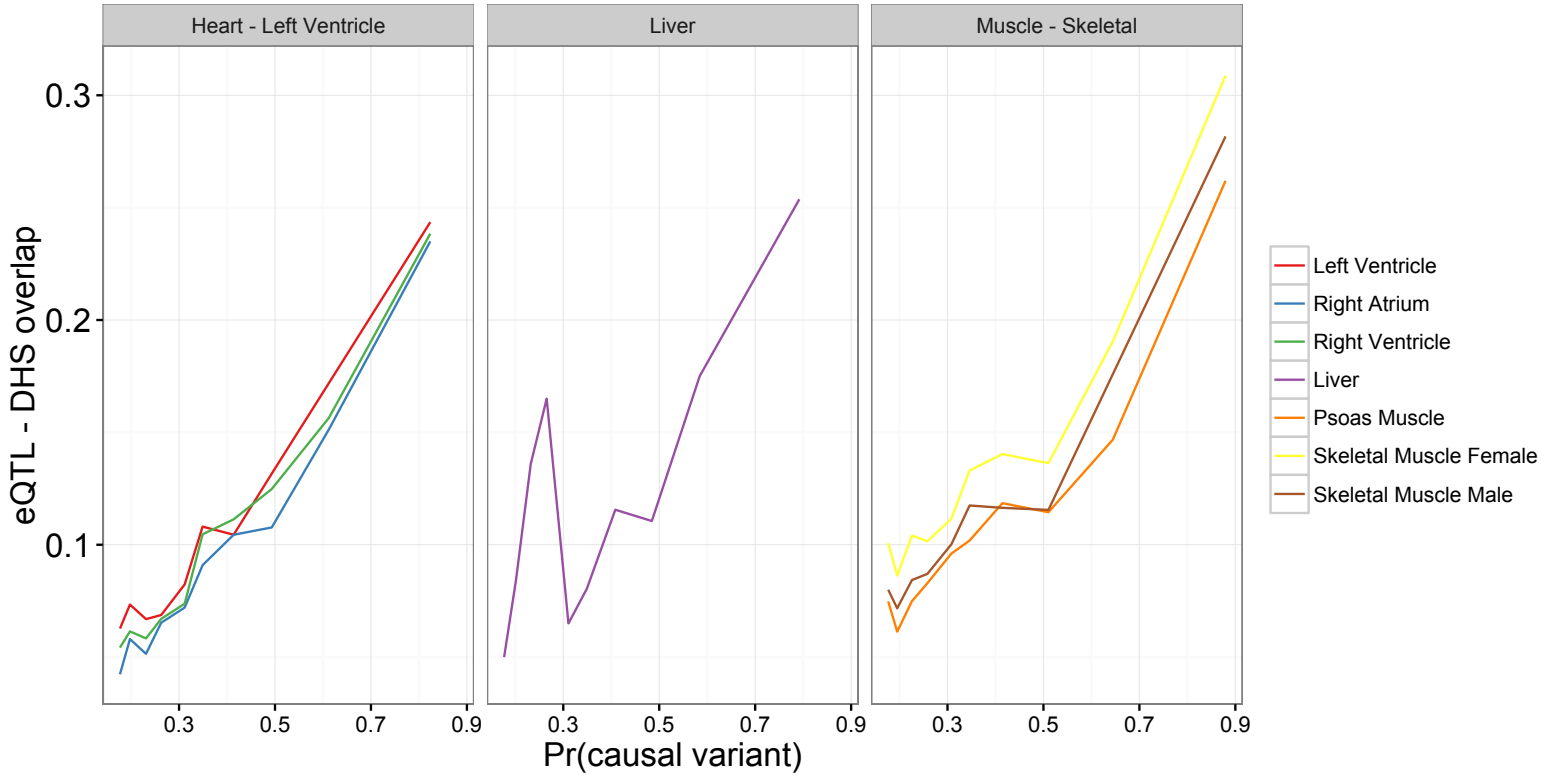
ASE sharing across tissues



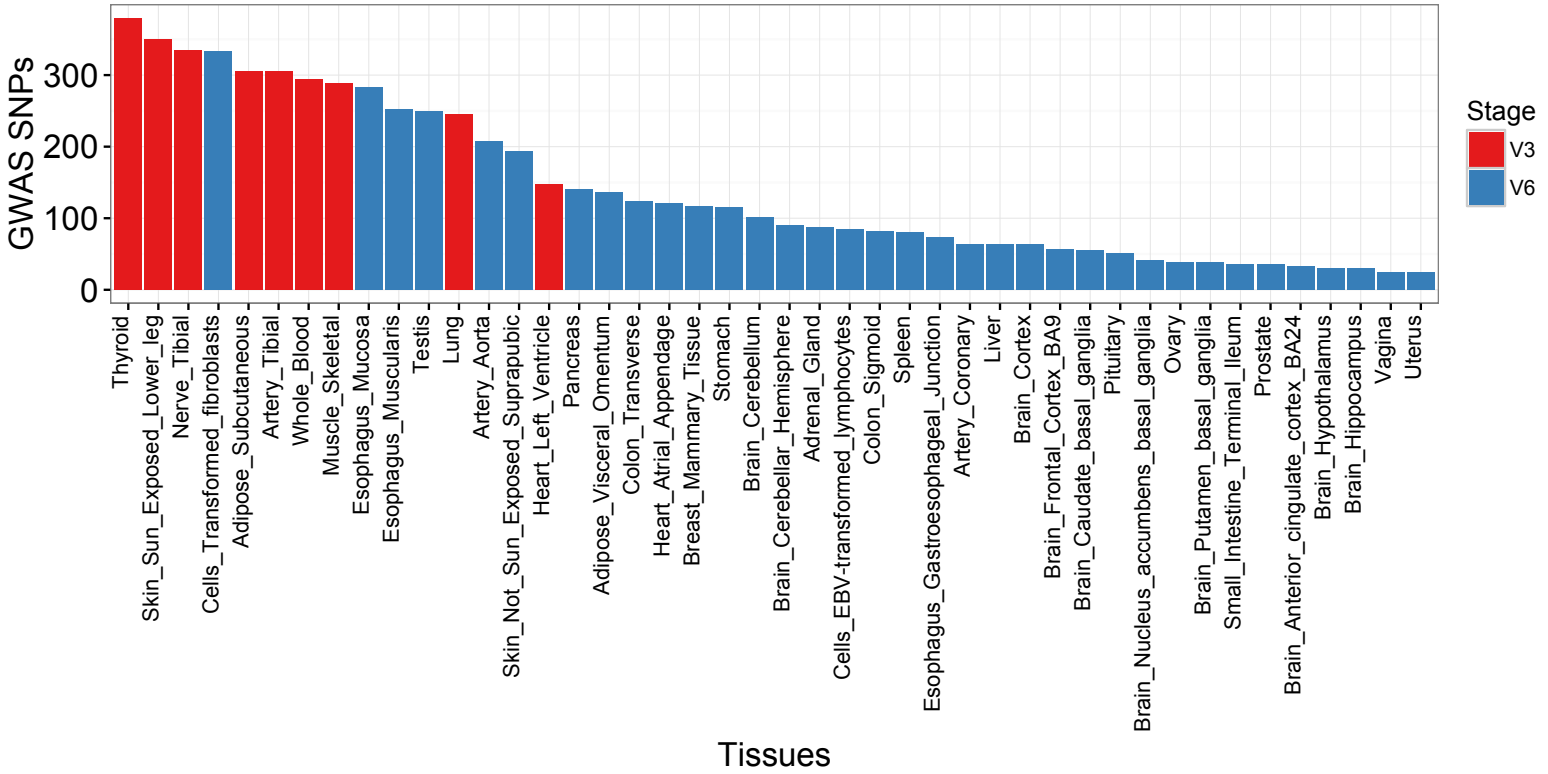
Regulatory element overlap is predictive of eQTL specificity



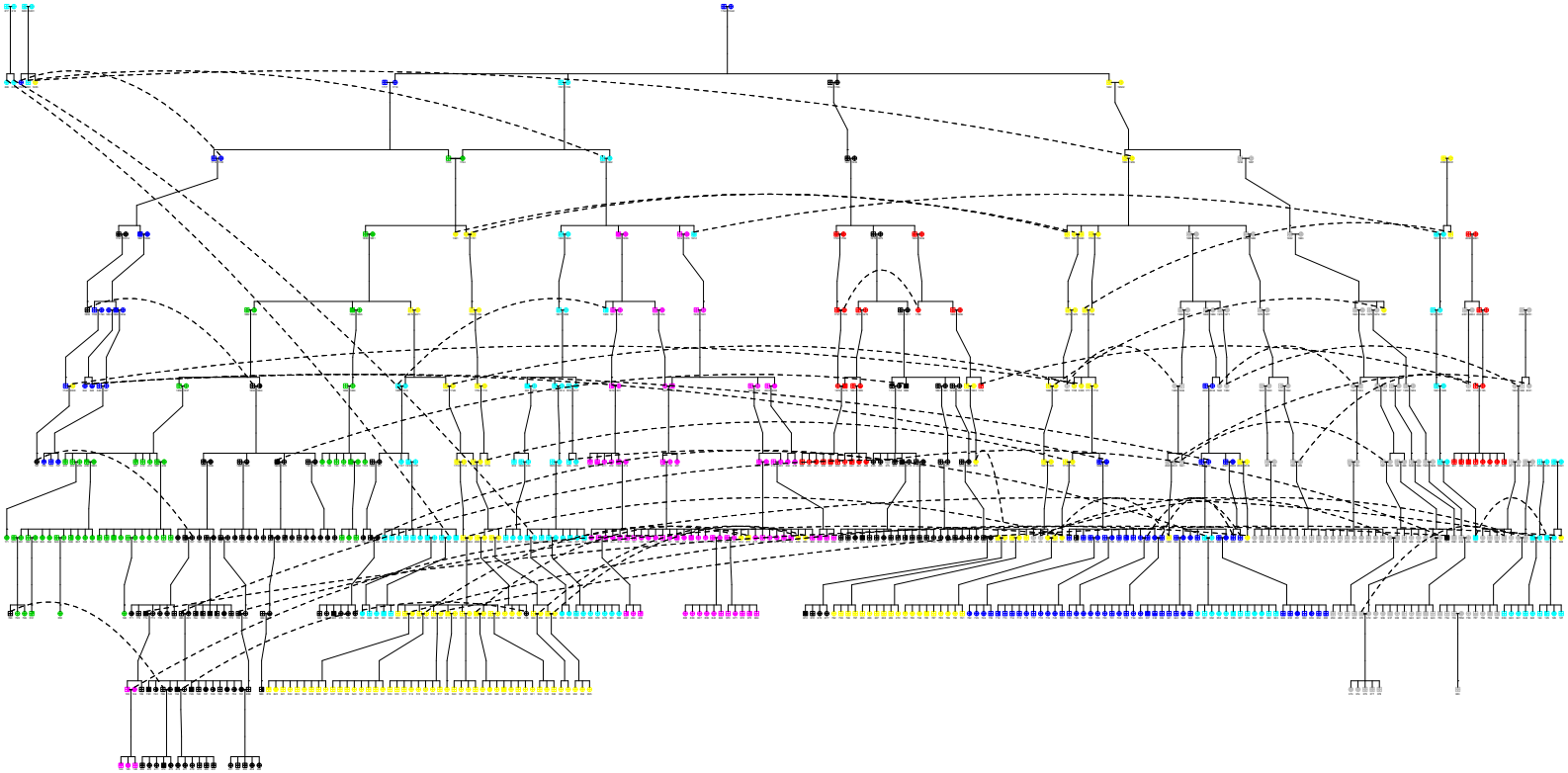
Greater regulatory element enrichment at likely causal SNPs



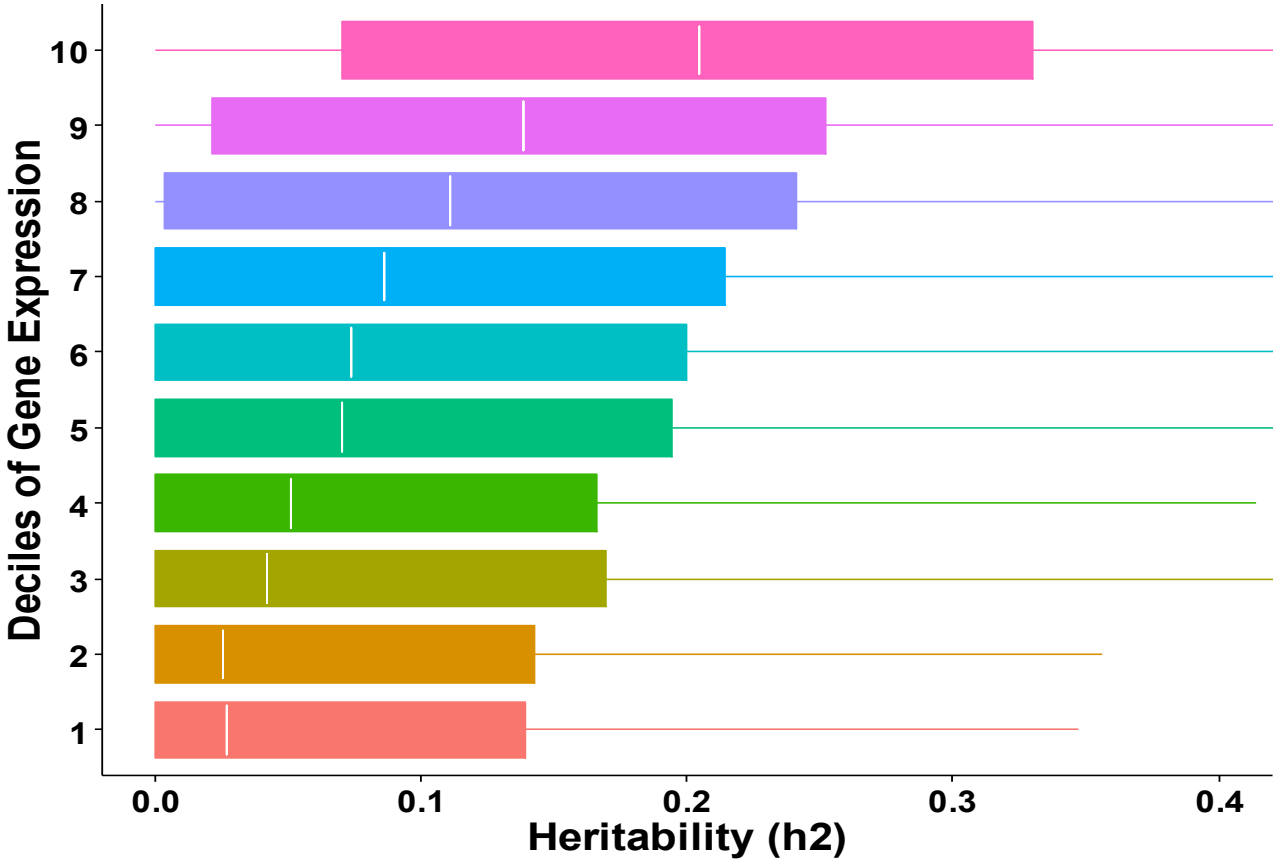
Multi tissue eQTL discovery explains additional GWAS SNPs



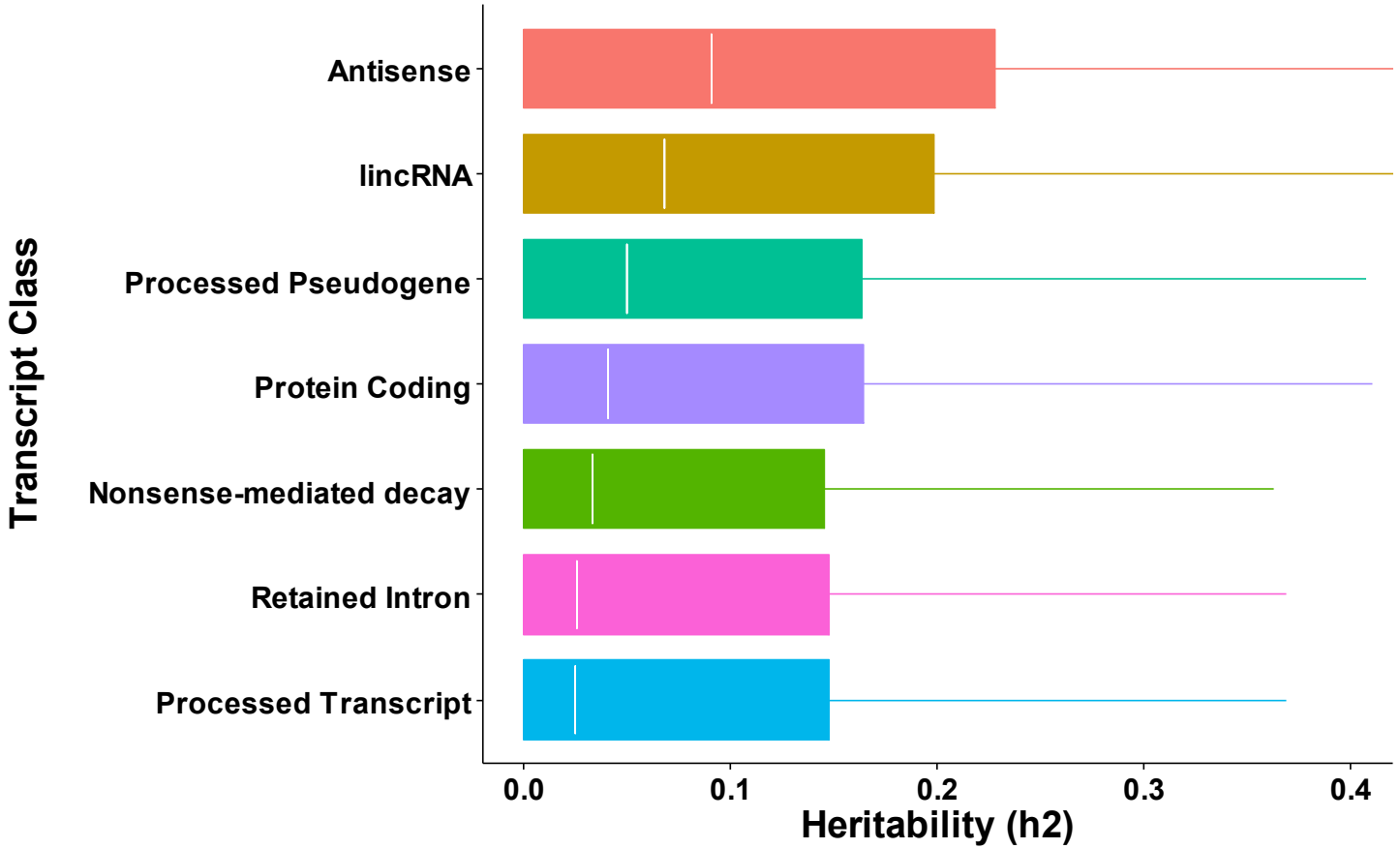
Regulatory variation in a large pedigree from a founder population



h^2 of gene expression

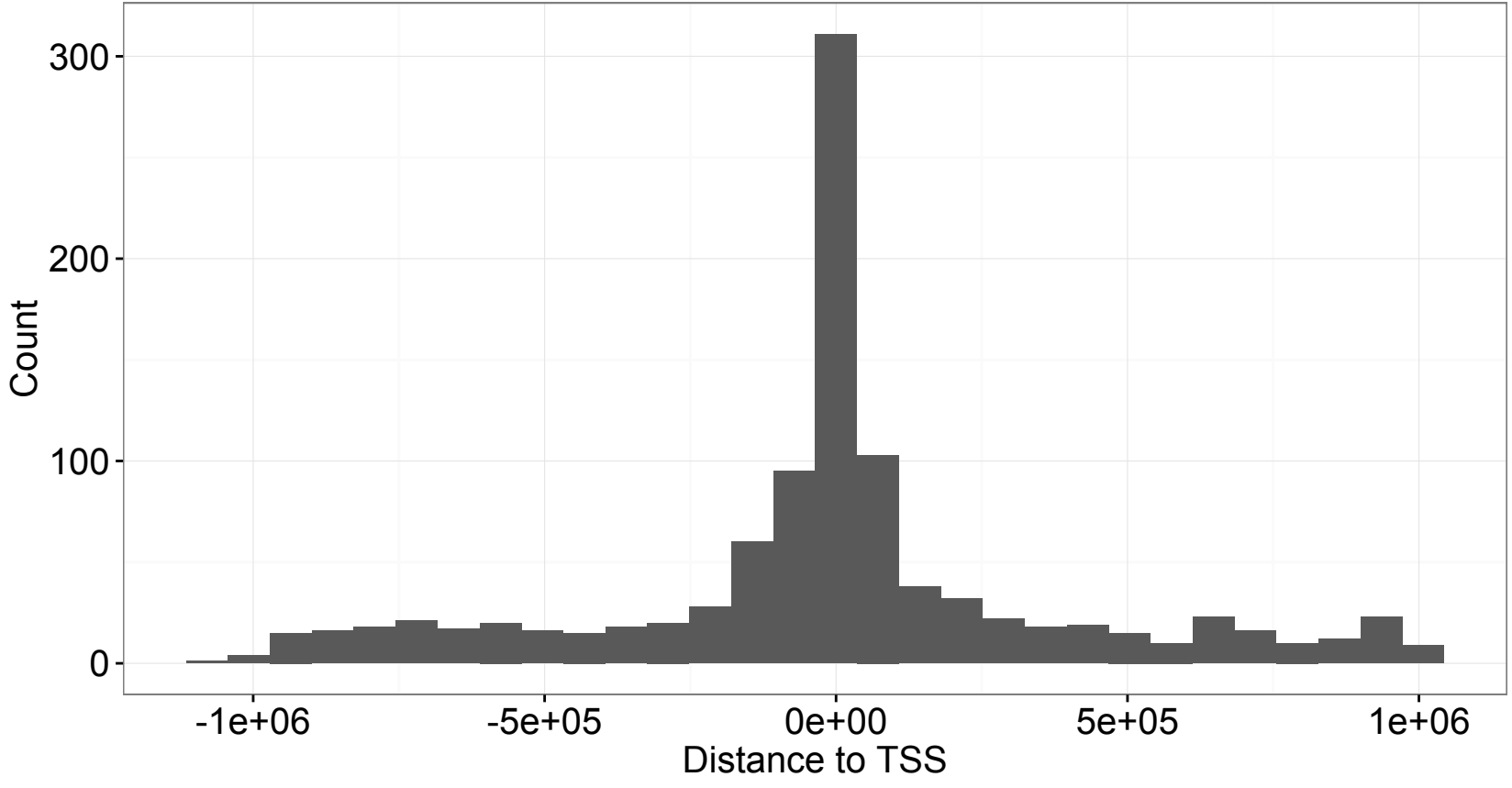


h^2 of transcript classes

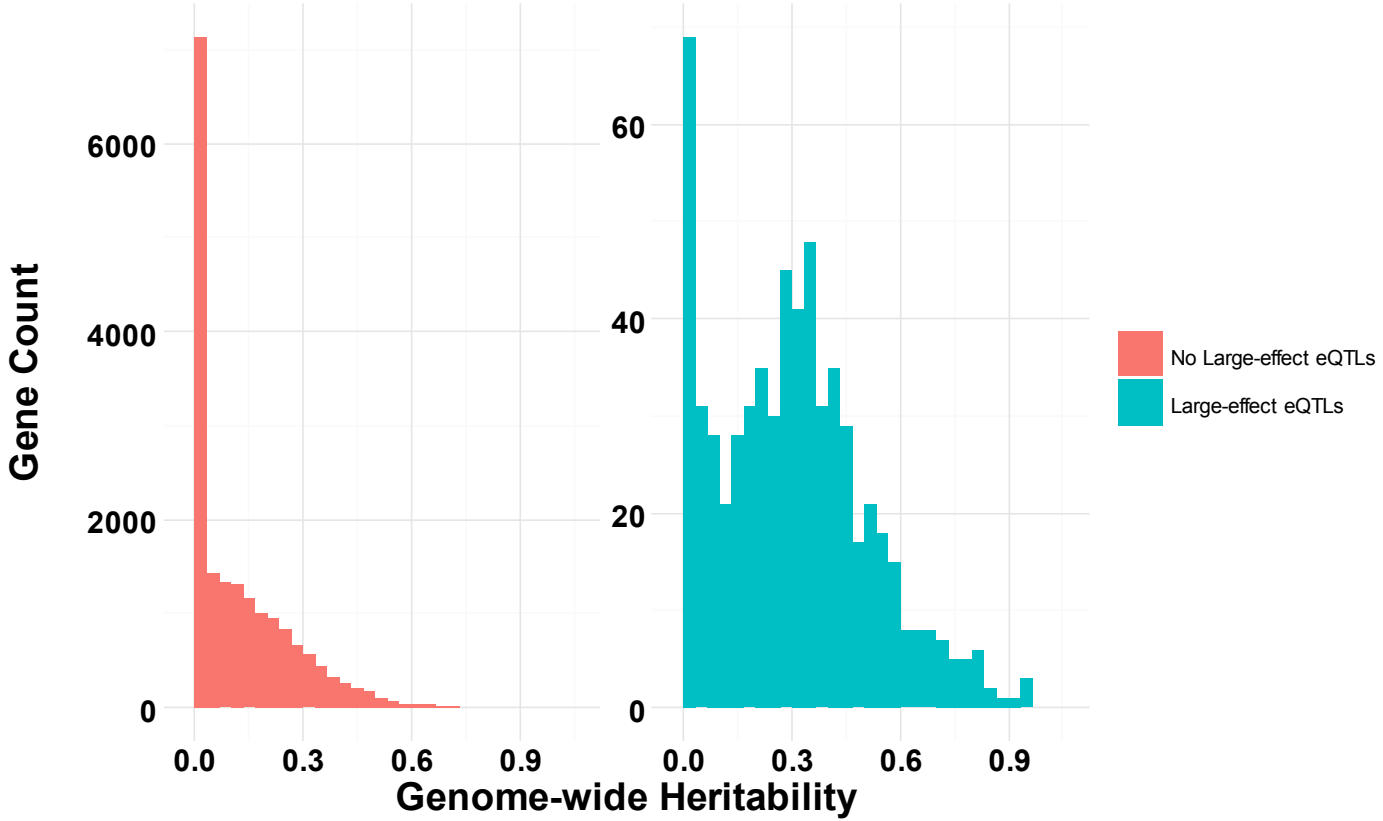


Family based association mapping

- 1025 eGenes identified at 5% FDR

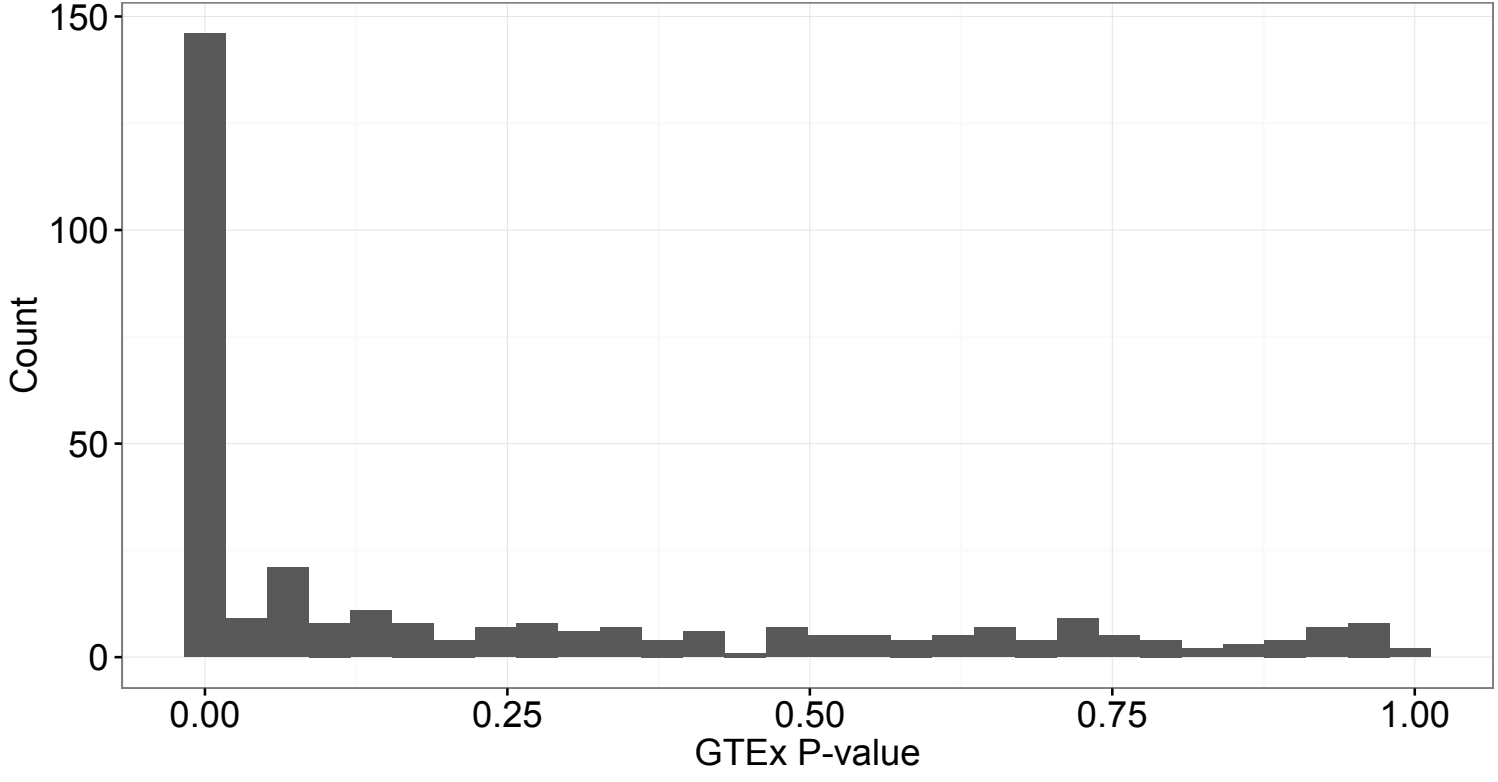


eQTL identification at heritable genes

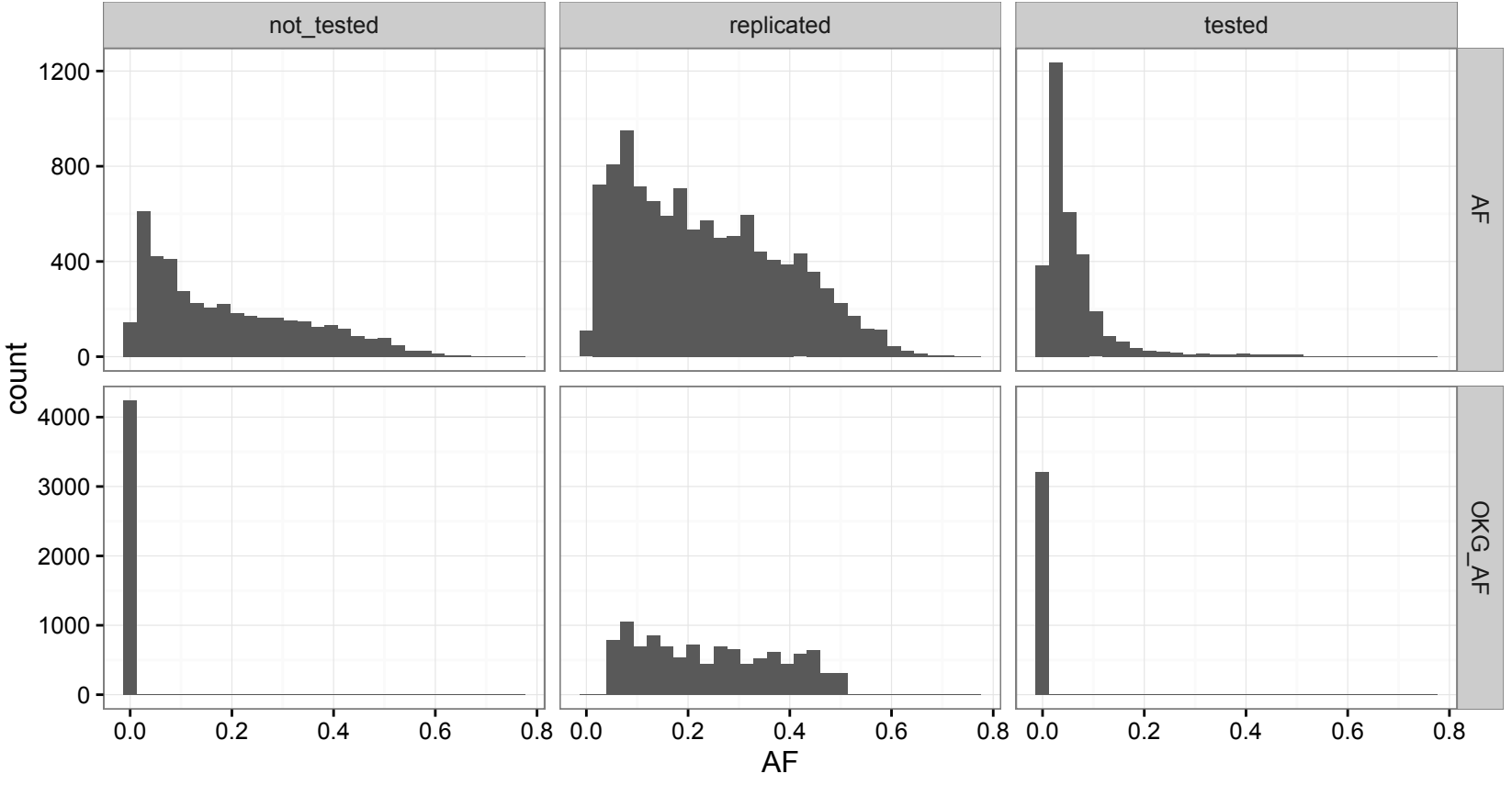


Replication of Amish eQTLs in GTEx

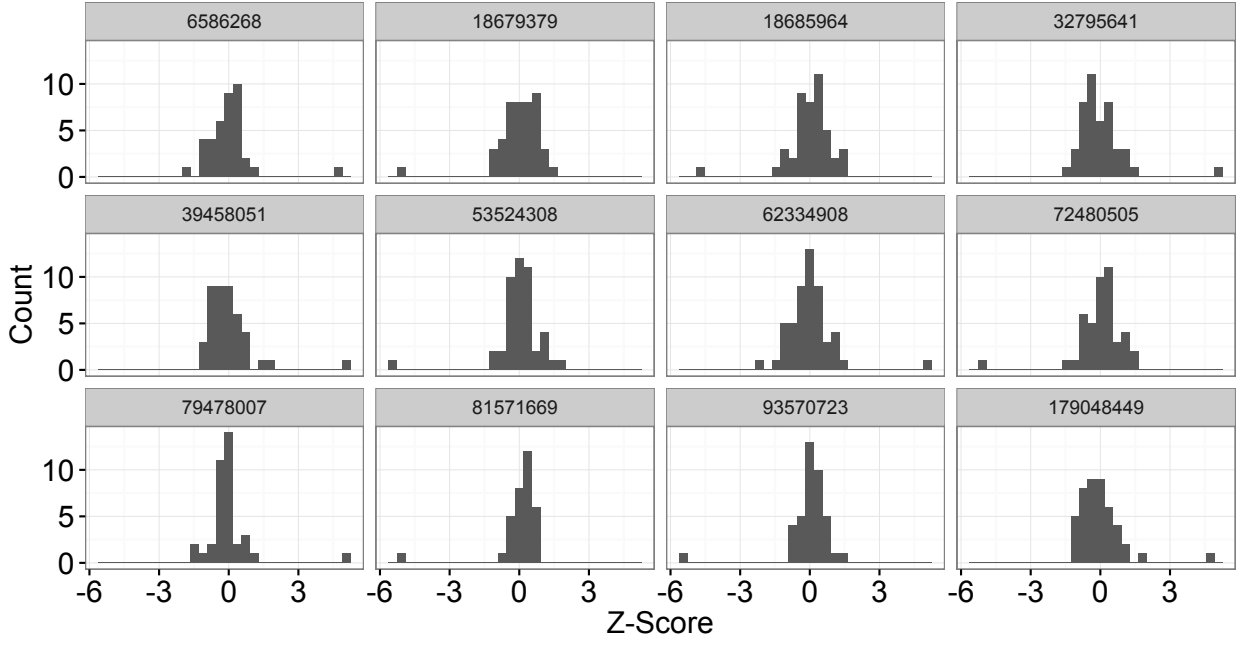
>75% replicate



Replication of Amish eQTLs in GTEx



Deleterious variants associated with expression outliers



15k outliers, ~2x enriched for novel vars w/ CADD>20

Summary & Conclusions

- Majority of genes now have detectable eQTLs
- Tissue restricted and ubiquitous eQTLs are common
- Regulatory element overlap can predict eQTL activity
- Expanded catalog of tissues improves GWAS interpretation

Acknowledgements

- GTEx analysis working group, eQTL working group
- Kristin Ardlie, Manolis Dermitzakis, Gad Getz, Matthew Stephens, Fred Wright, Andrew Noble, Chiara Sabatti, Roderic Guigo, Mark McCarthy, Eleazar Eskin, Barbara Engelhardt, Alexis Battle, Manolis Kellis

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- eQTL discovery: Ayellet Segre, Francois Aguet
- ASE: Pejman Mohammedi, Tuuli Lappalainen
- Fine mapping, CREs: Andrew Brown
- GWAS integration: YoSon Park

- Penn: Katerina Gawronski, Rachel Kember, Maja Bucan, Dan Rader

www.gtexportal.org

- Summary level data available without restriction
- Utilities for eQTL browsing
- SNP, gene level queries
- Expression, splicing, PTVs
- Much, much more