Understanding the genetic architecture of gene expression

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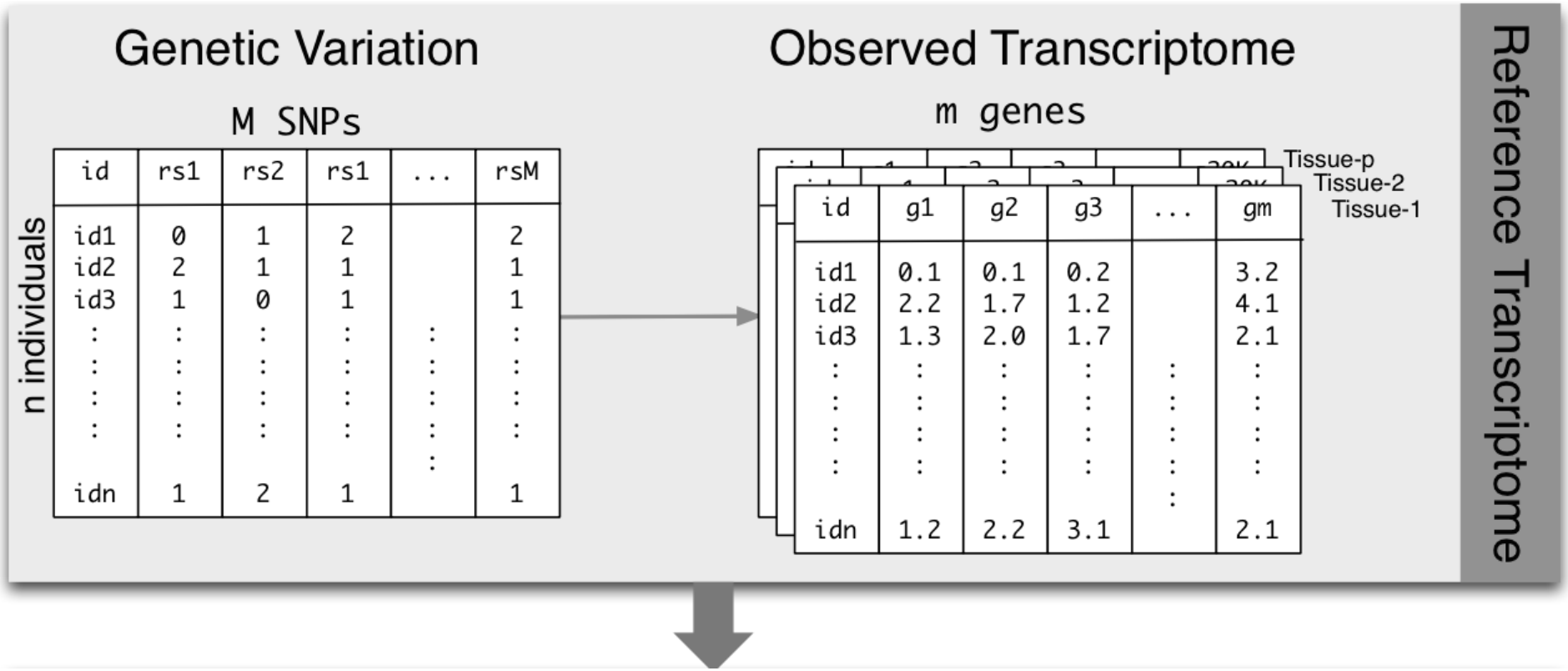
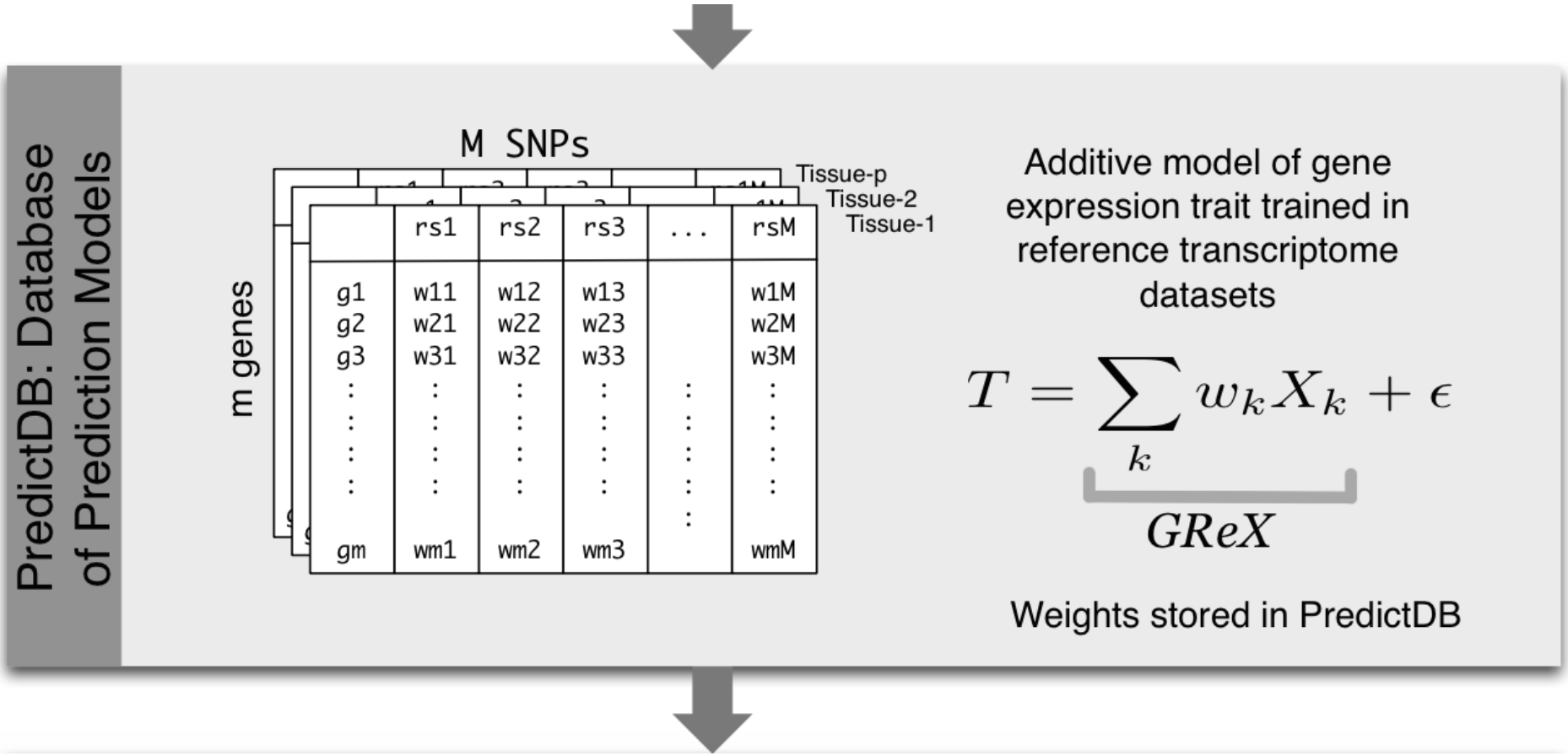
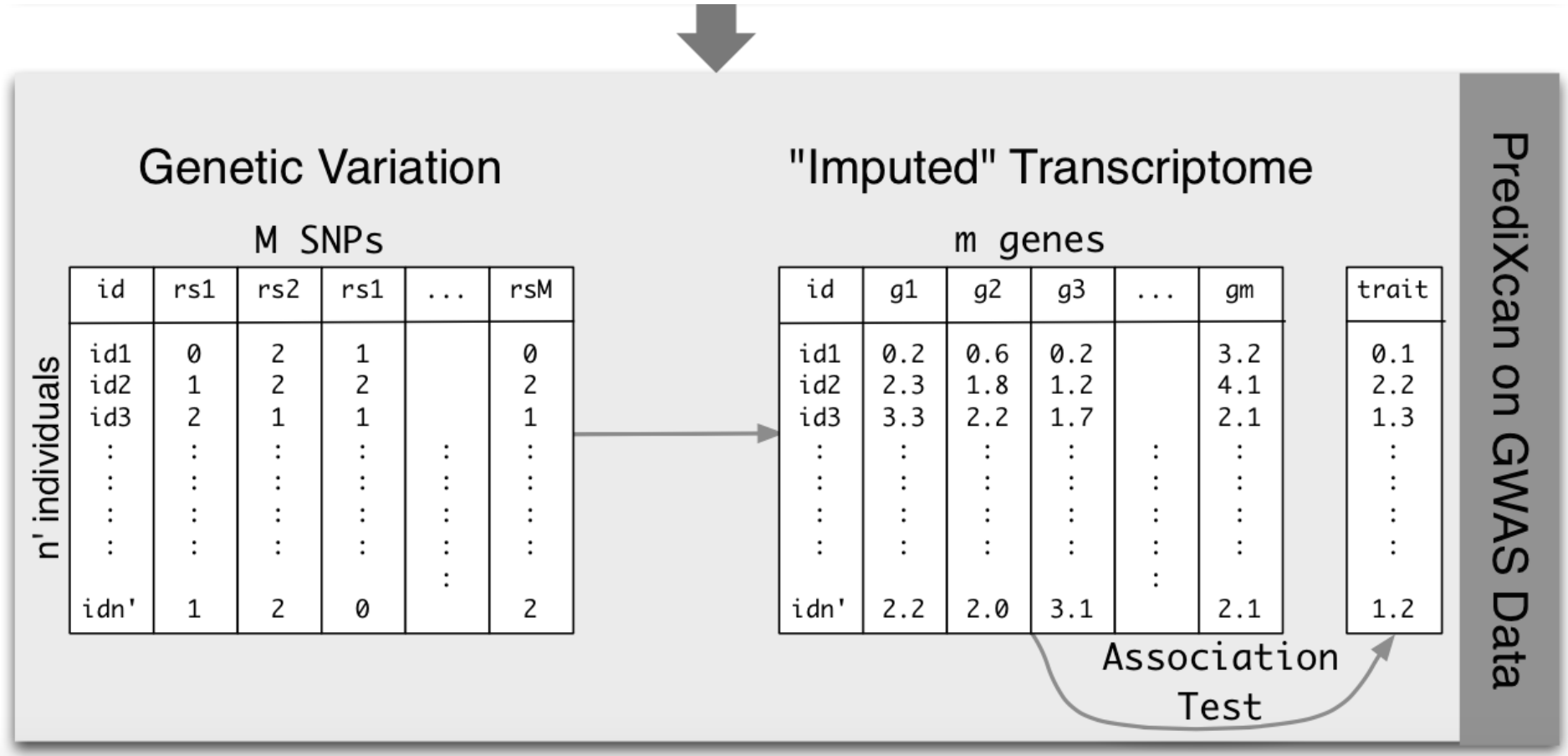
PrediXcan Step 1: Build and Test Predictors



PrediXcan Step 2: Build database of Best Predictors



PrediXcan Step 3: Impute gene expression and test for association with phenotype



Explore the Genetic Architecture of Transcriptome Regulation

Optimizing predictors for PrediXcan also tells us about the underlying genetic architecture of gene expression.

We can ask what proportion of genes have:

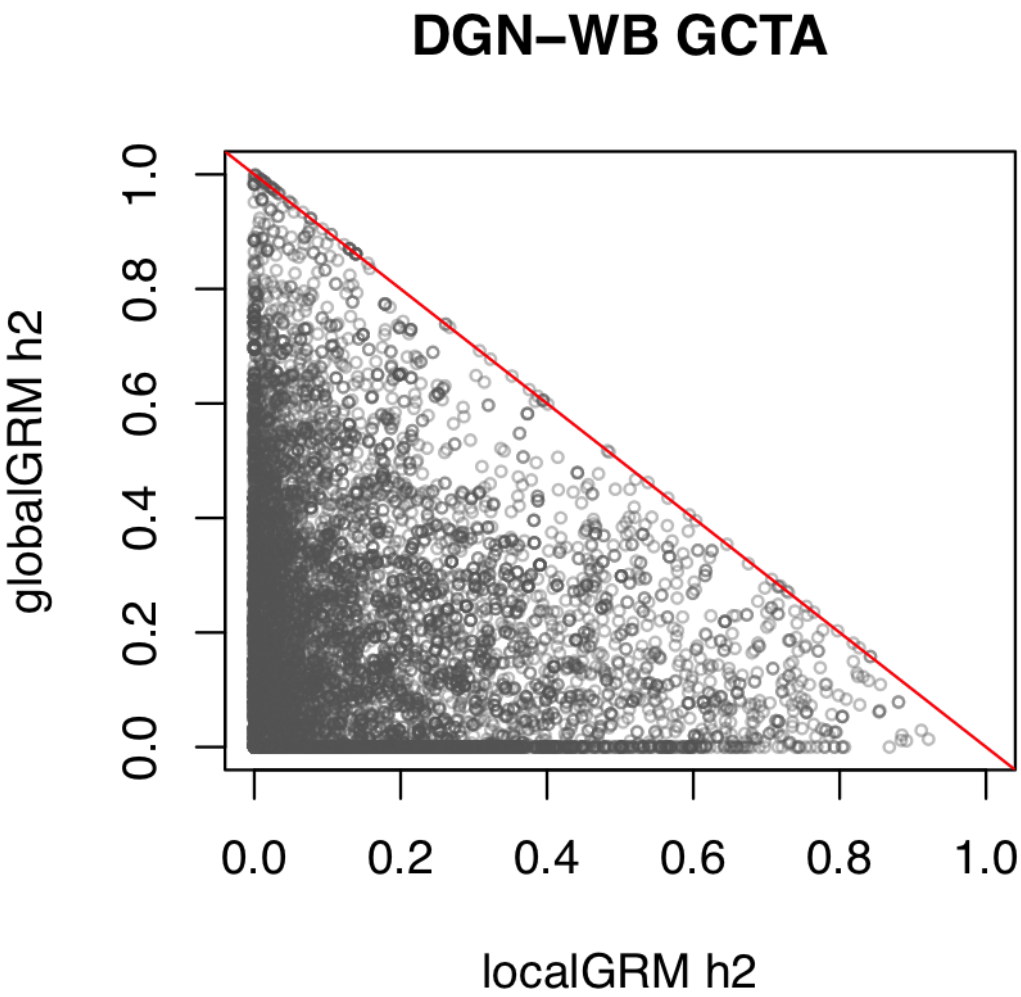
- *cis* vs. *trans* effects
- sparse vs. polygenic effects
- cross-tissue vs. tissue-specific effects

Primary cohort: DGN

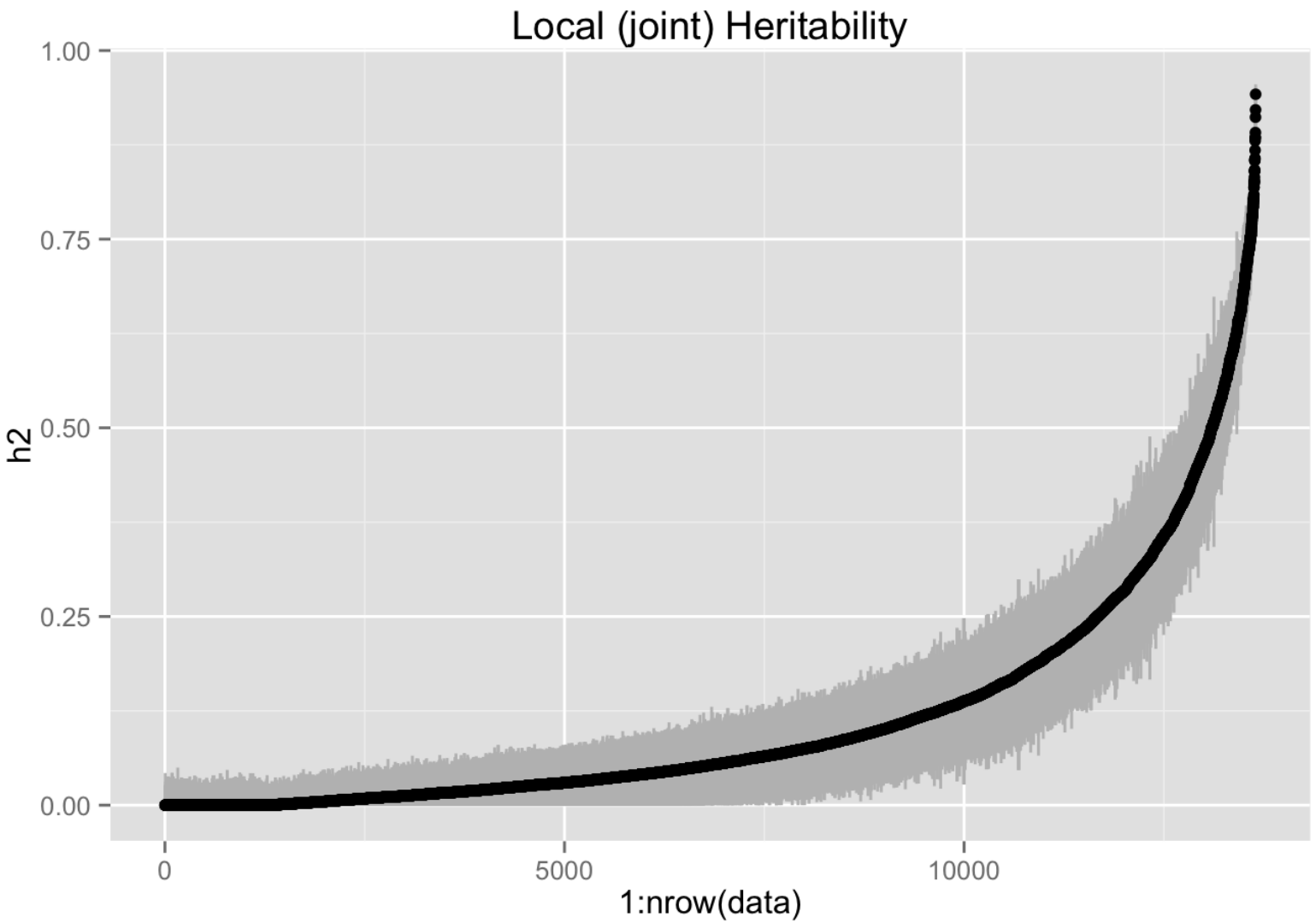
- Battle et al. "Characterizing the genetic basis of transcriptome diversity through RNA-sequencing of 922 individuals." Genome Research 2014, 24(1):14-24
- Whole blood from Depression Genes and Networks study
- n = 922
- RNA-seq: "normalized gene-level expression data used for trans-eQTL analysis. The data was normalized using HCP (Hidden Covariates with Prior) where the parameters were optimized for detecting 'trans' trends"
- 600K genotypes: I have imputed to 1000 Genomes, but some earlier analyses were genotyped data only.

cis vs. *trans* effects

Estimate the heritability of gene expression in a joint analysis: localGRM (SNPs w/in 1Mb) + globalGRM (all SNPs)

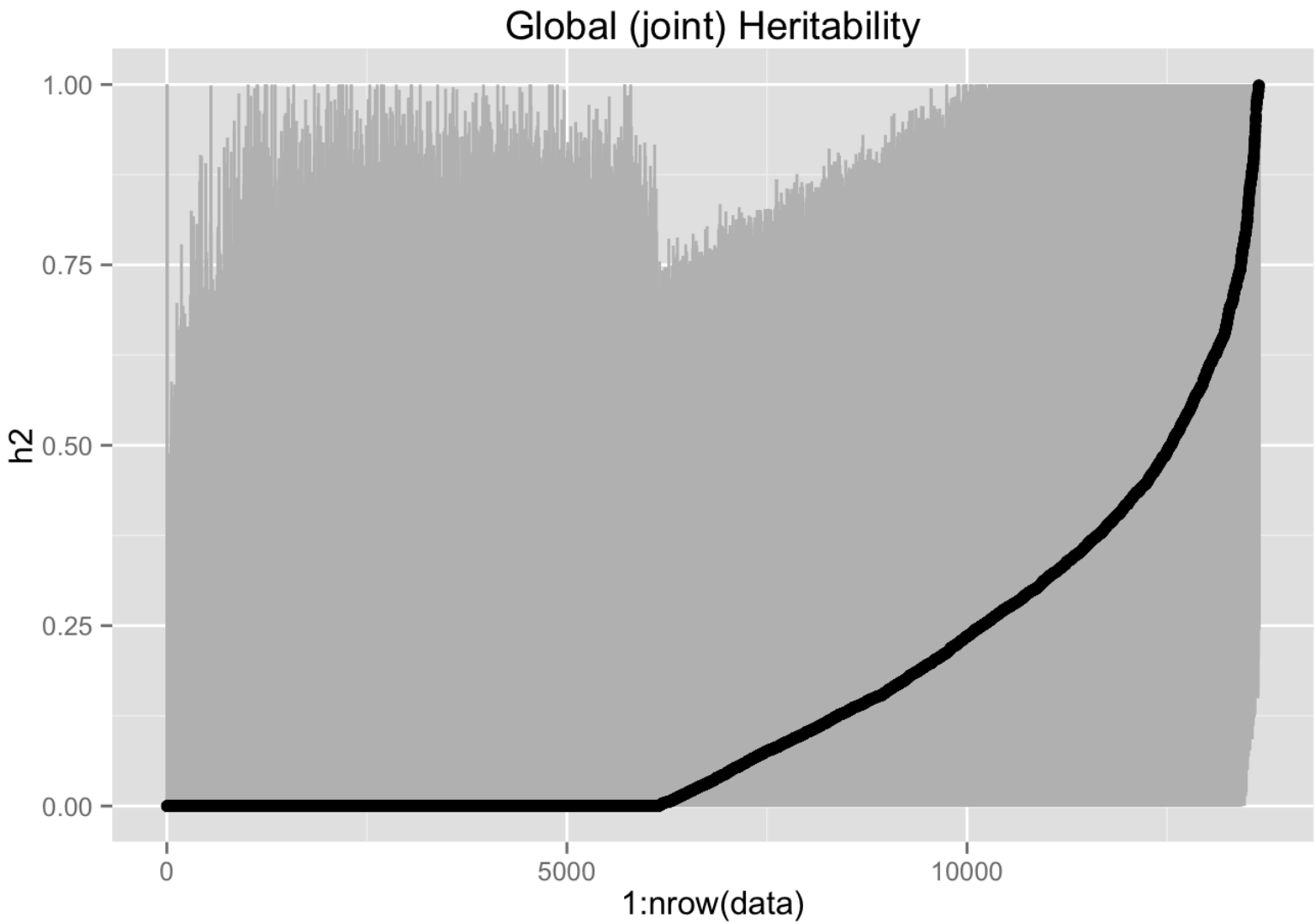


Local (joint) sorted h^2 estimates with 95% CI from GCTA



https://github.com/hwheeler01/cross-tissue/blob/master/analysis/sources/heritab_analysis.html

Global (joint) sorted h^2 estimates with 95% CI from GCTA



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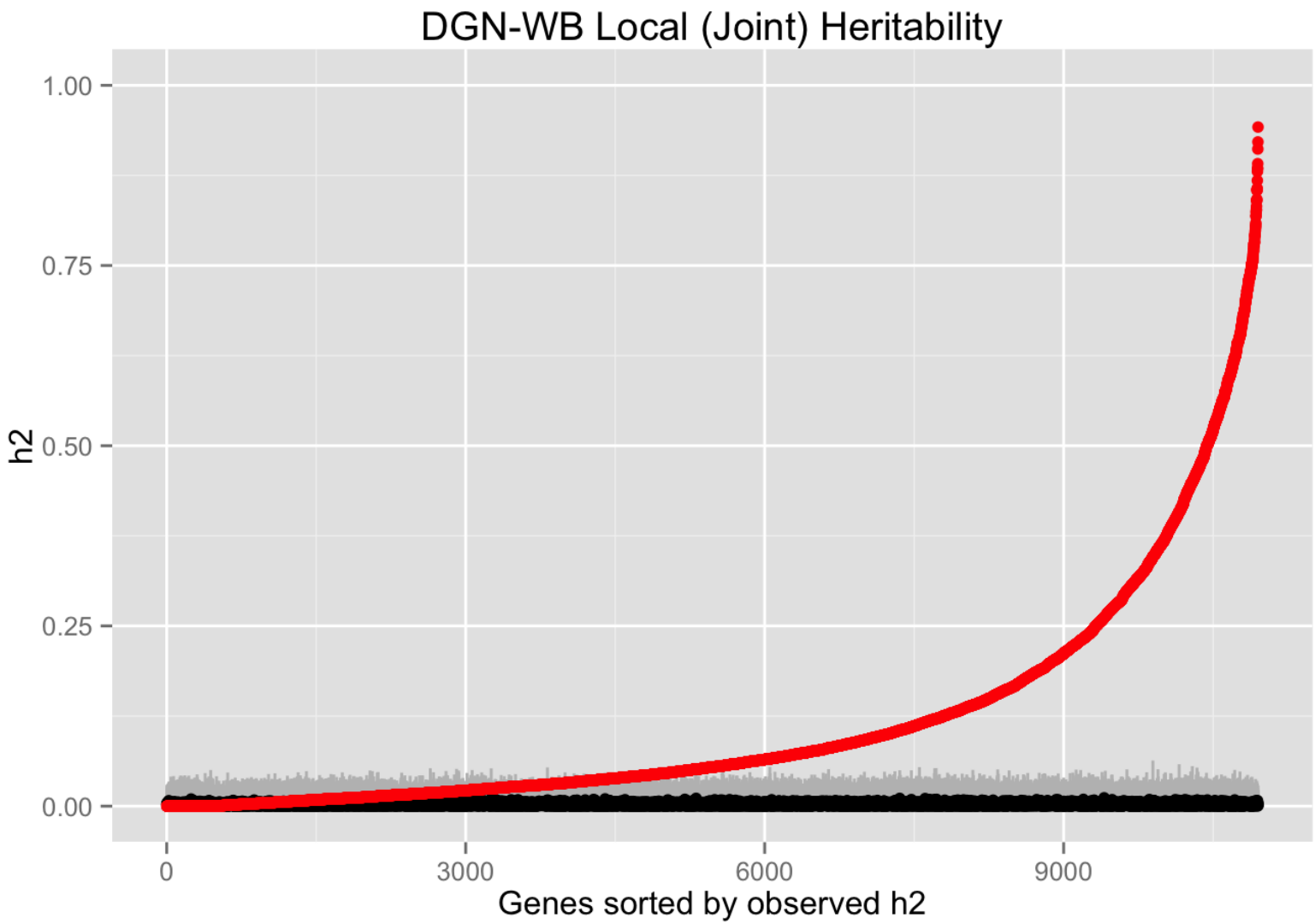
100 permutations to determine expected distribution of h^2 estimates



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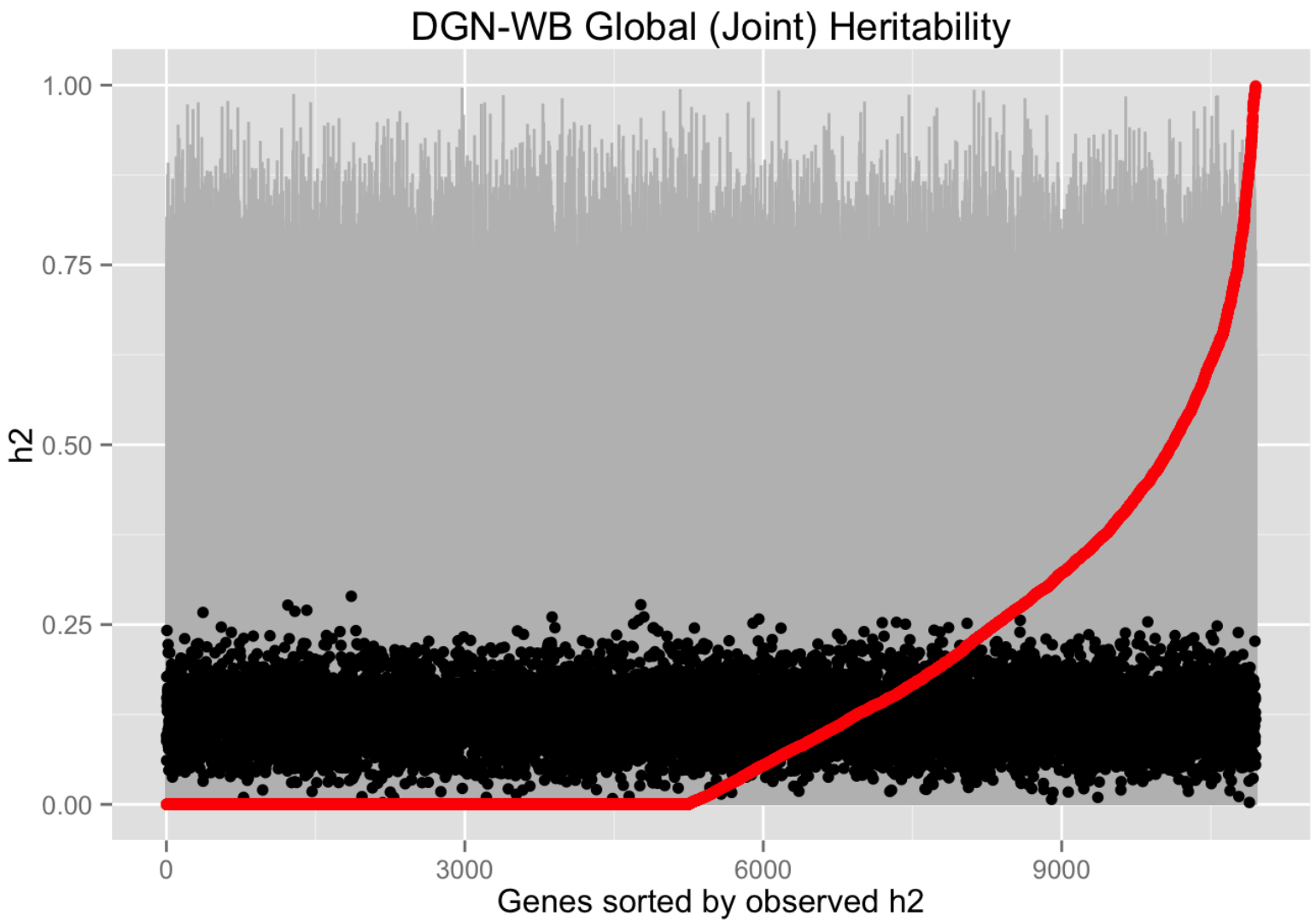
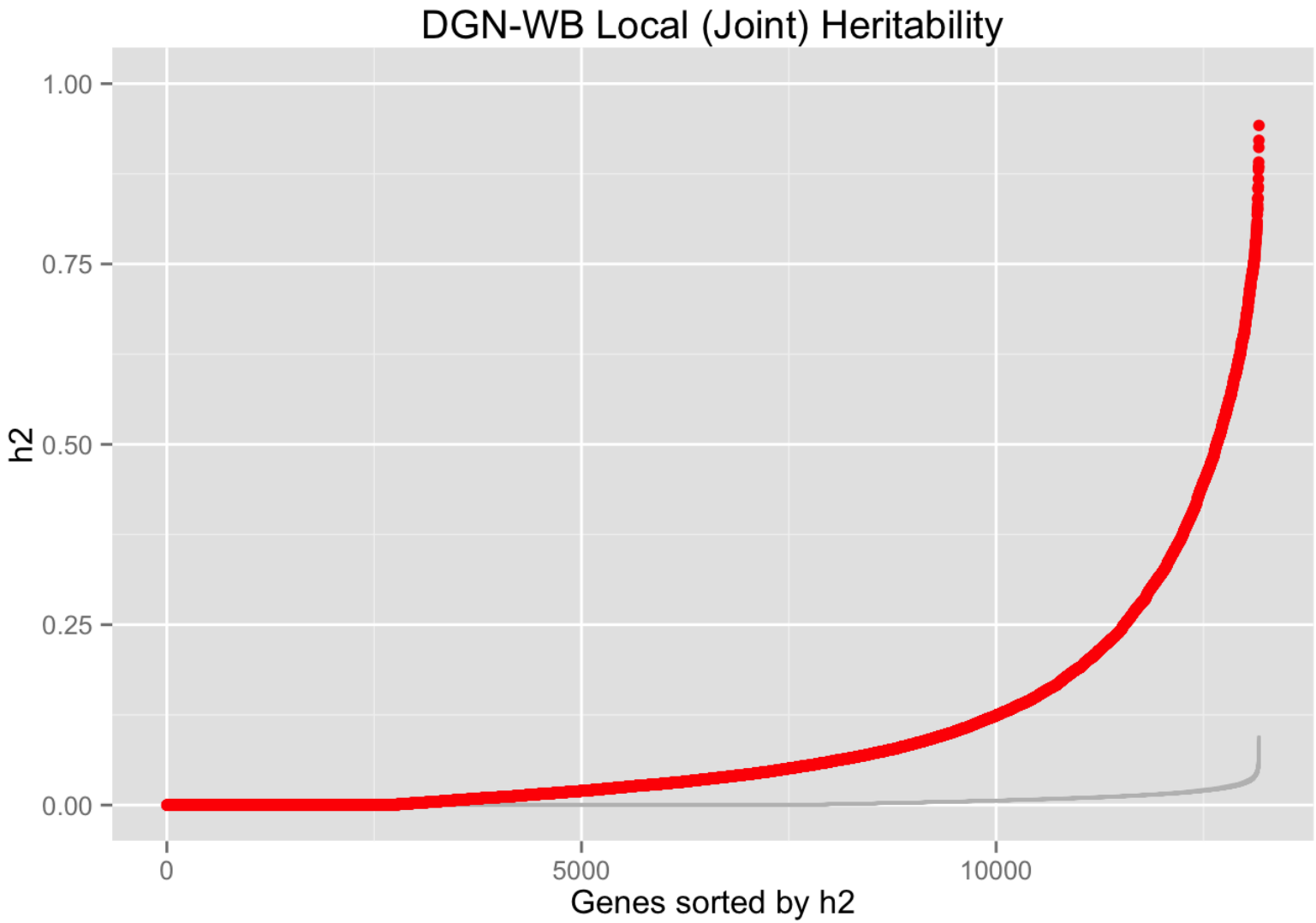


Sort the h^2 from each permutation



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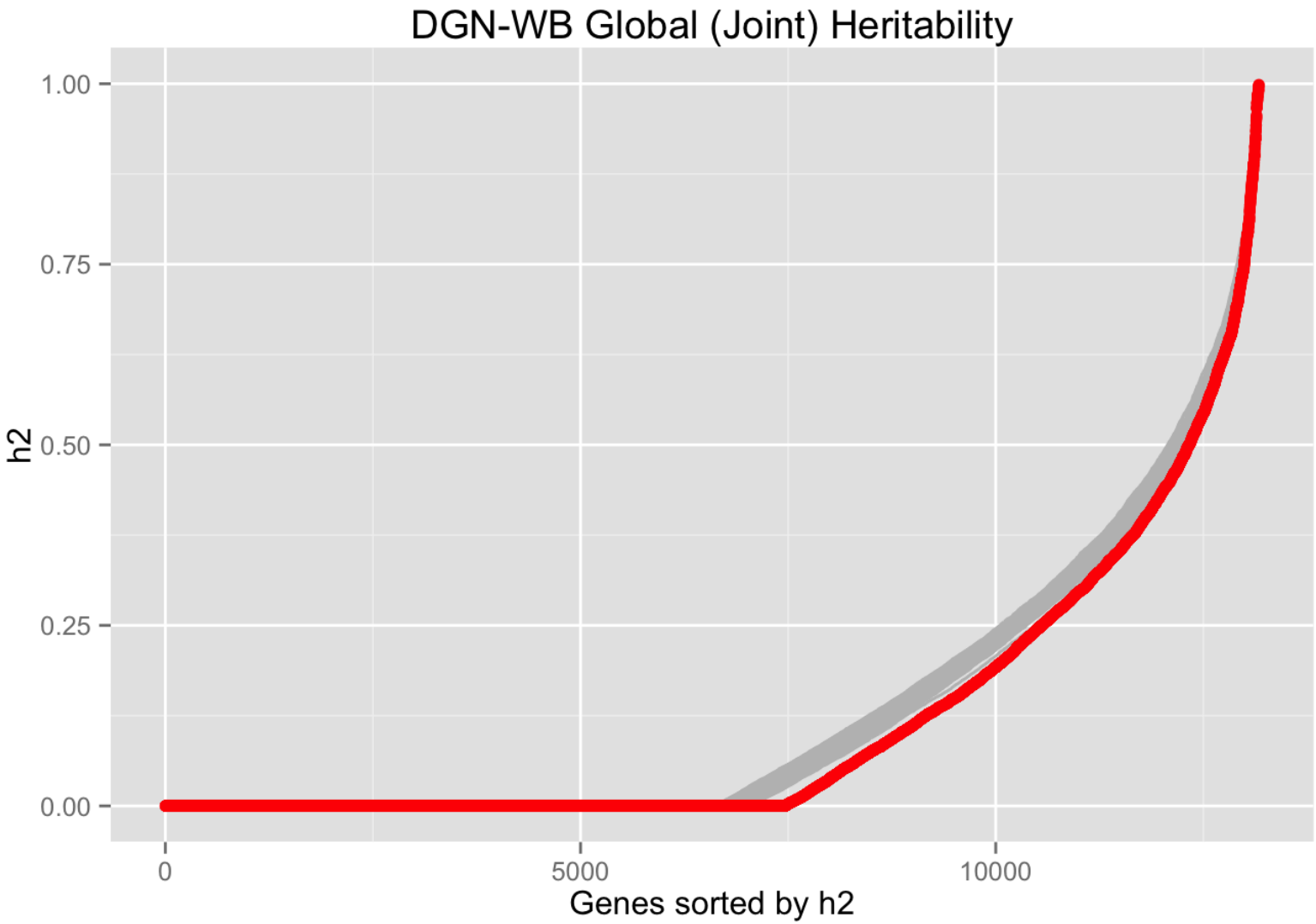

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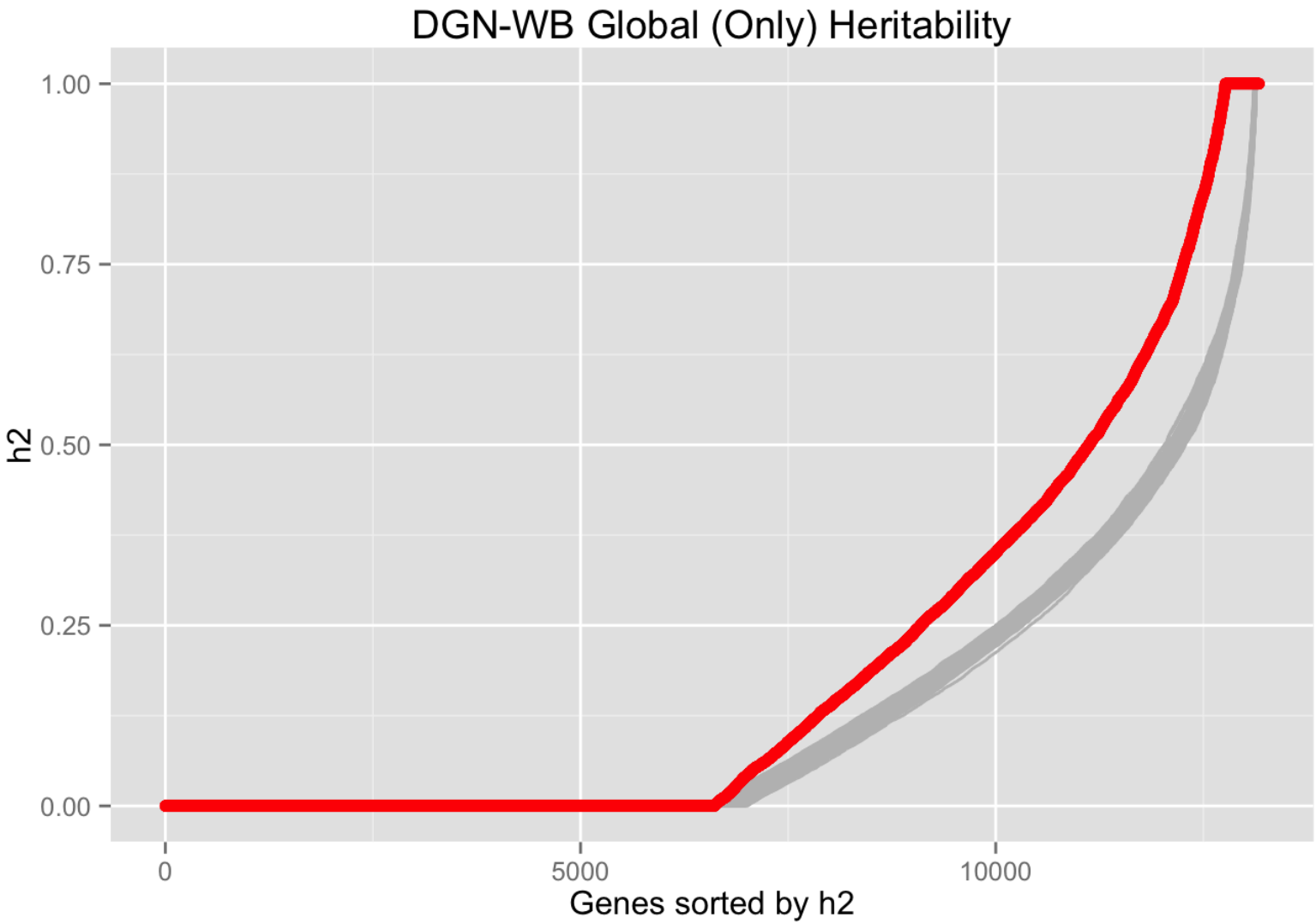


cis vs. *trans* effects

Try a larger sample to better caputure *trans* effects

Framingham Heart Study

- n = 5257
- exon expression array and genotype array

sparse vs. polygenic effects

`glmnet` solves the following problem

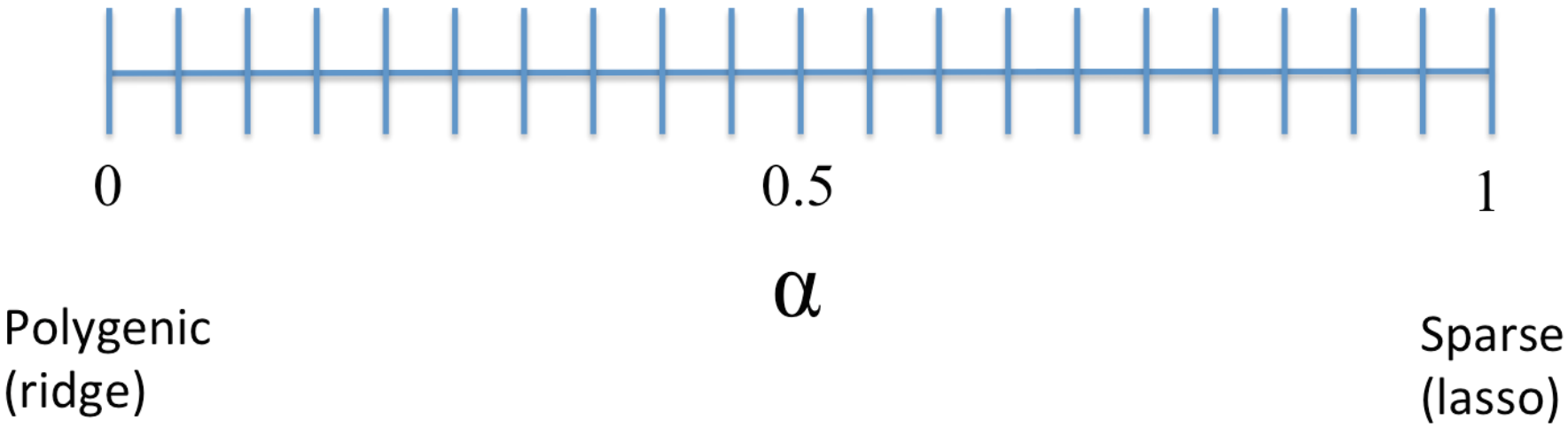
$$\min_{\beta_0,\beta} \frac{1}{N} \sum_{i=1}^{N} w_i l(y_i, \beta_0 + \beta^T x_i) + \lambda \left[(1-\alpha)||\beta||_2^2/2 + \alpha||\beta||_1 \right],$$

over a grid of values of λ covering the entire range.

The elastic-net penalty is controlled by α, and bridges the gap between lasso ($\alpha = 1$, the default) and ridge ($\alpha = 0$). The tuning parameter λ controls the overall strength of the penalty.

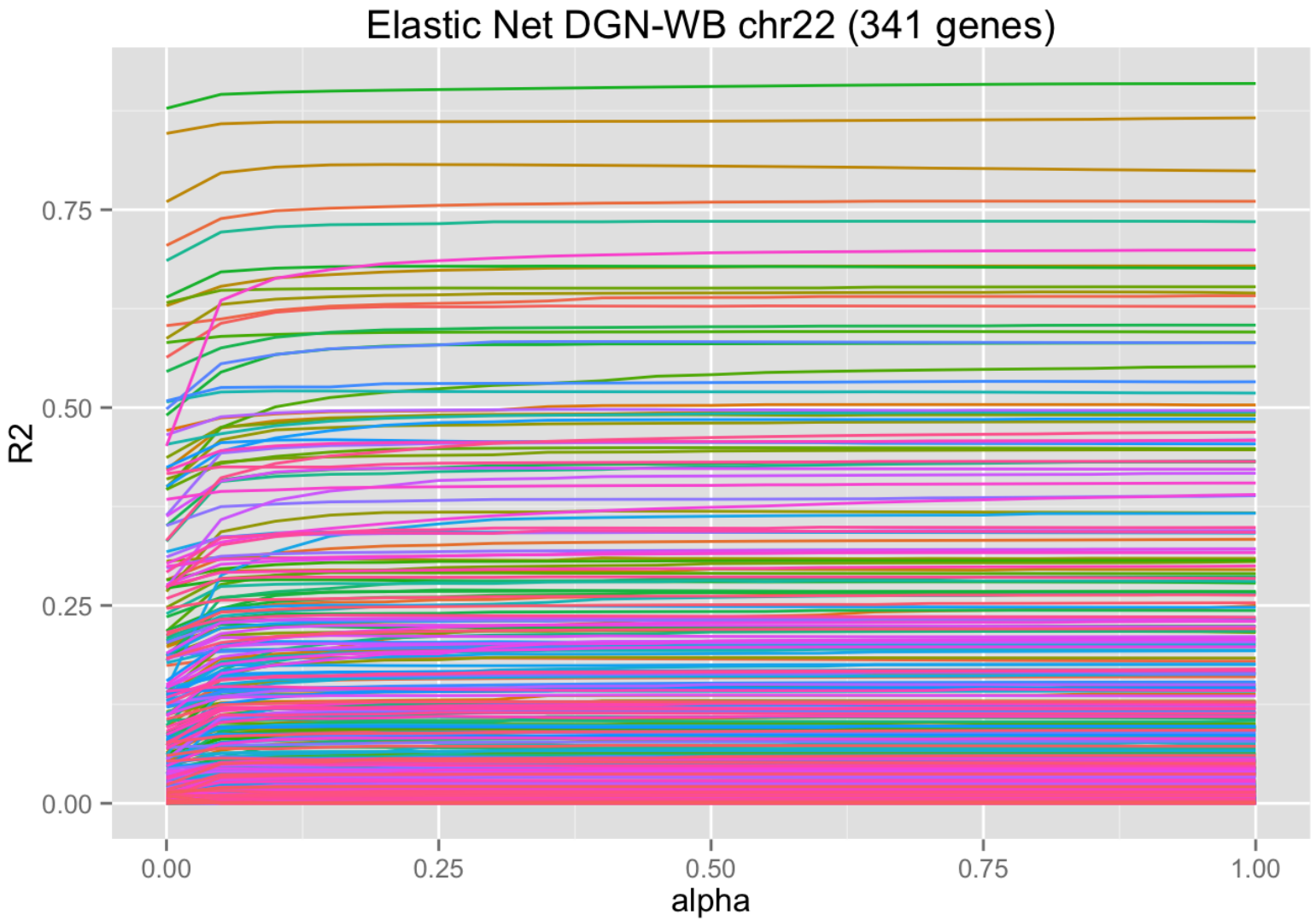
`http://web.stanford.edu/~hastie/glmnet/glmnet_alpha.html`

sparse vs. polygenic effects

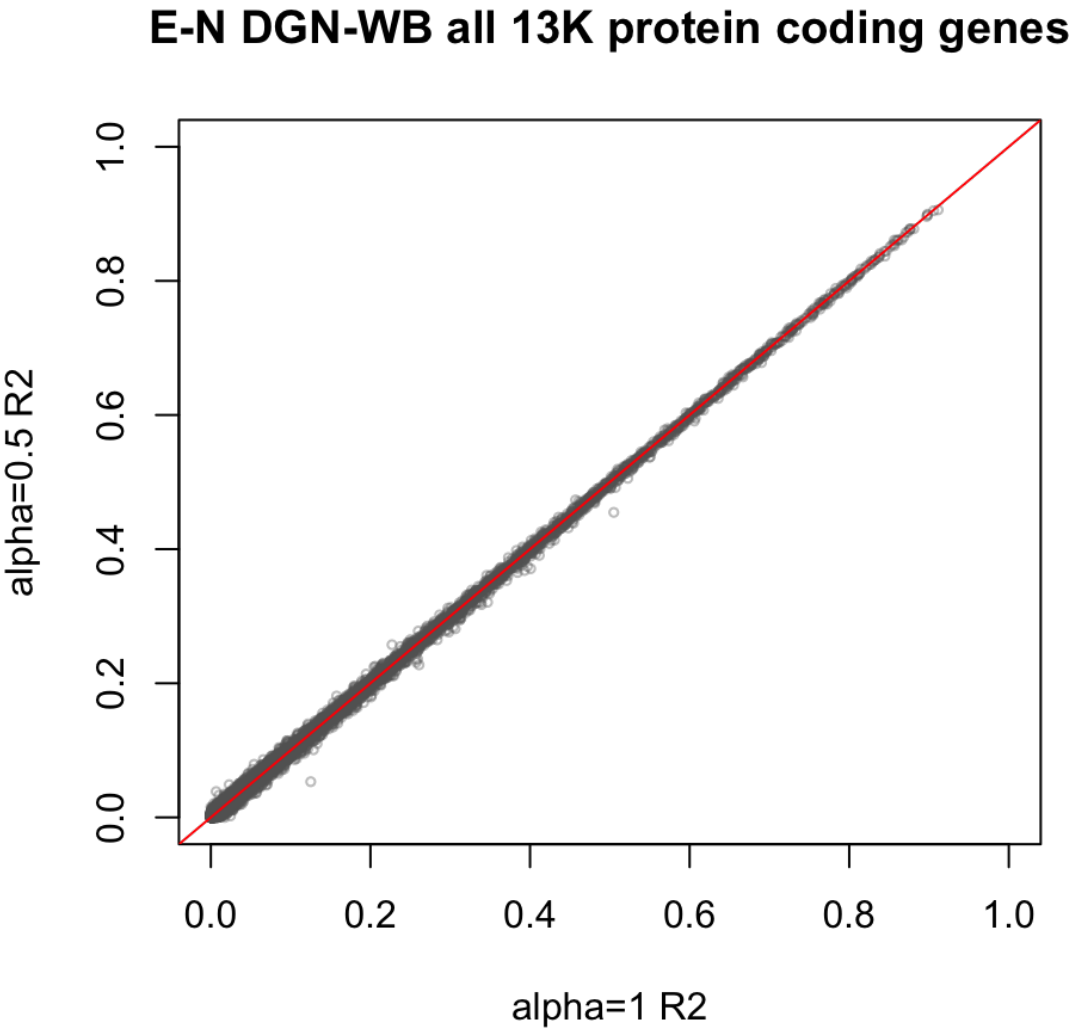


For each gene, determine α with best 10-fold CV predictive performance using *cis* SNPs.

Predictive performance consistent across most alphas



Predictive performance consistent between α=0.5 and α=1



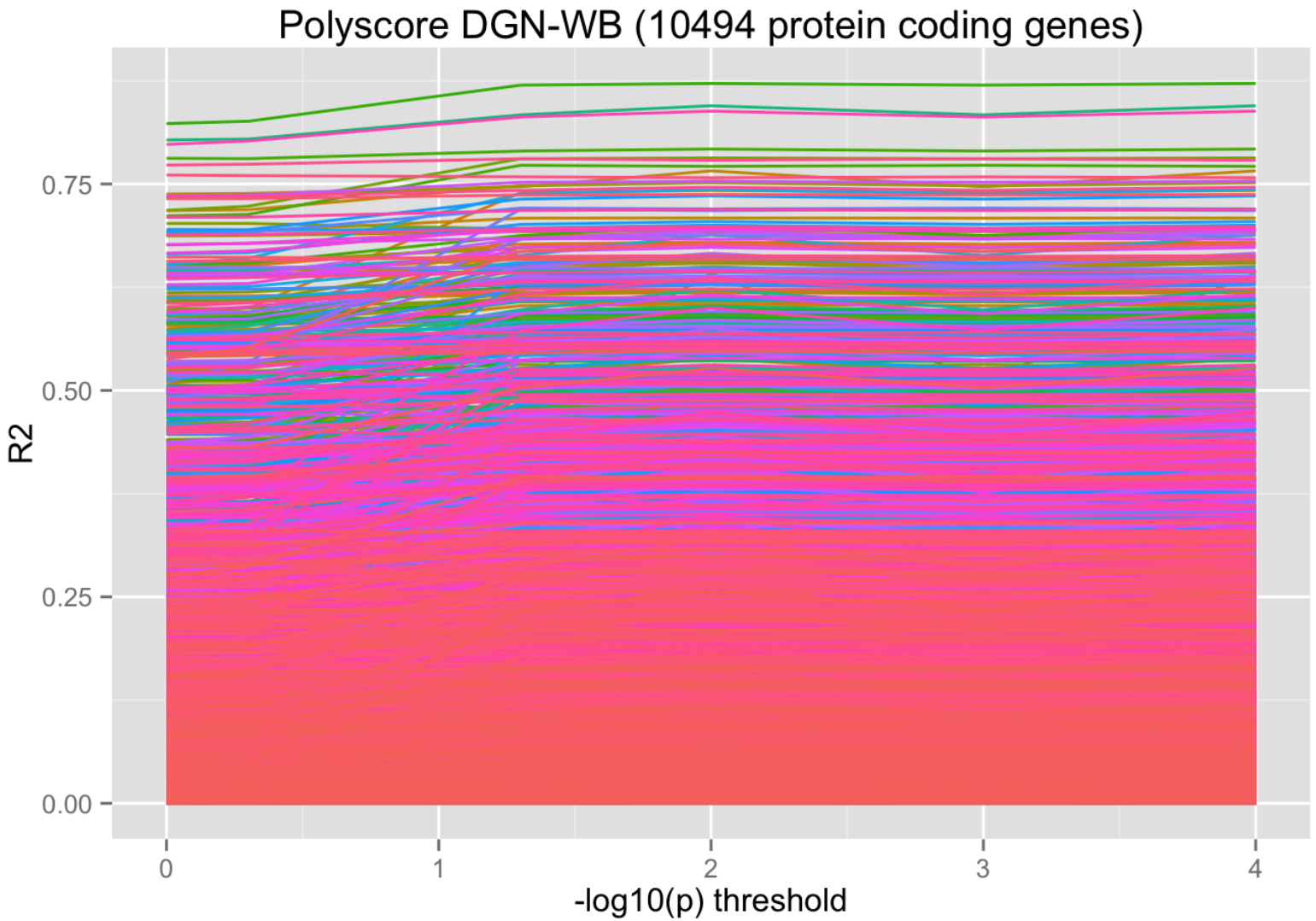
Also tested Polyscore predictive performance using 10-fold CV

$expression = \sum \hat{w} * gt$

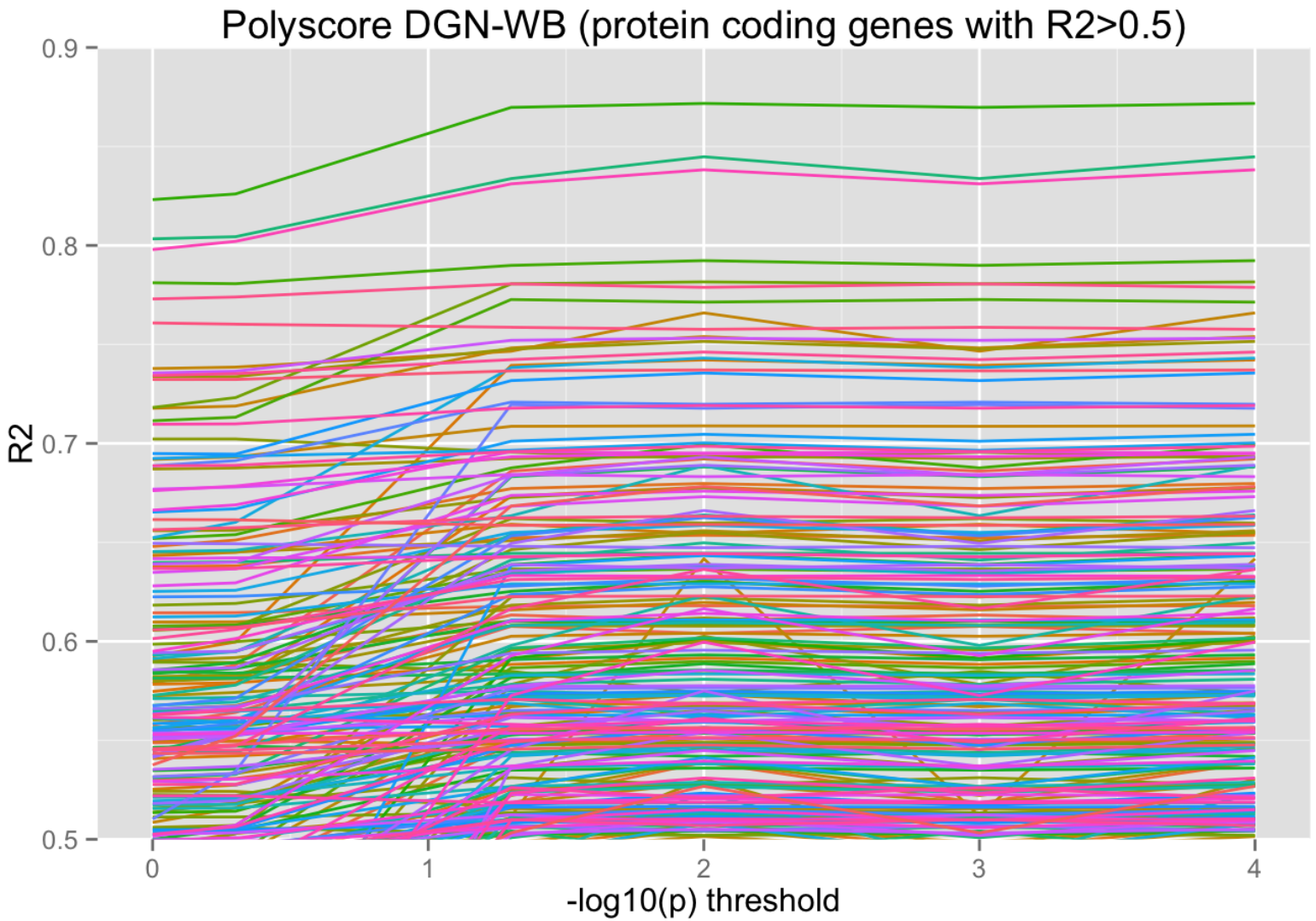
Single variant linear regression coefficients (w) at several P-value thresholds included in the additive model:

- $P < 0.0001$
- $P < 0.001$
- $P < 0.01$
- $P < 0.05$
- $P < 0.5$
- $P < 1$

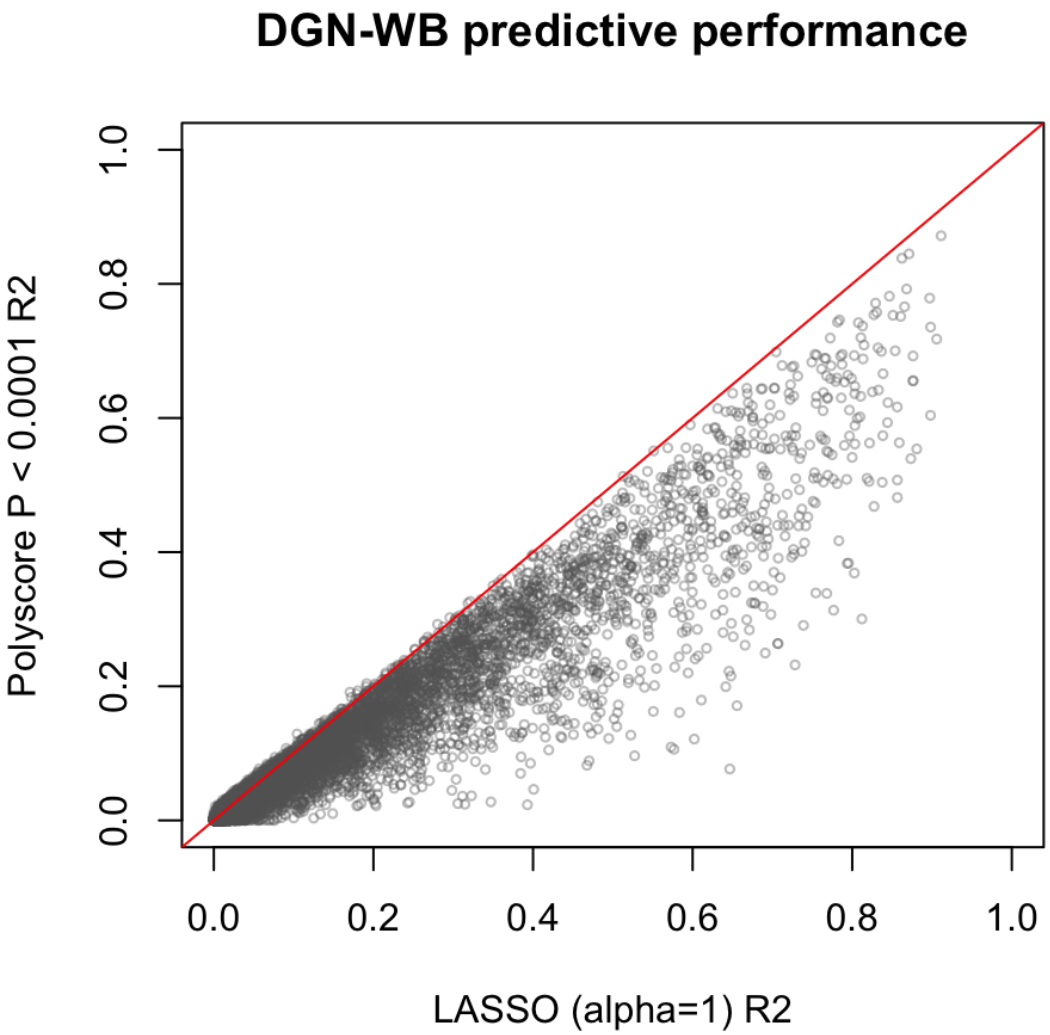
Polyscore (*cis* SNPs only) predictive performance



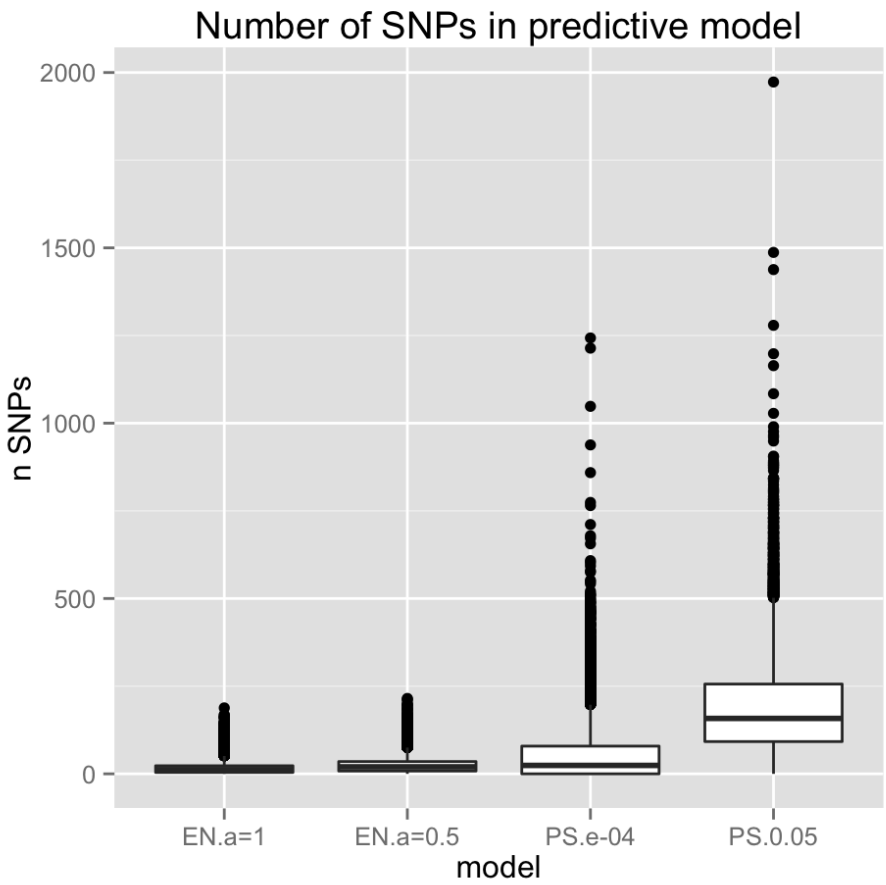
Polyscore (*cis* SNPs only) predictive performance

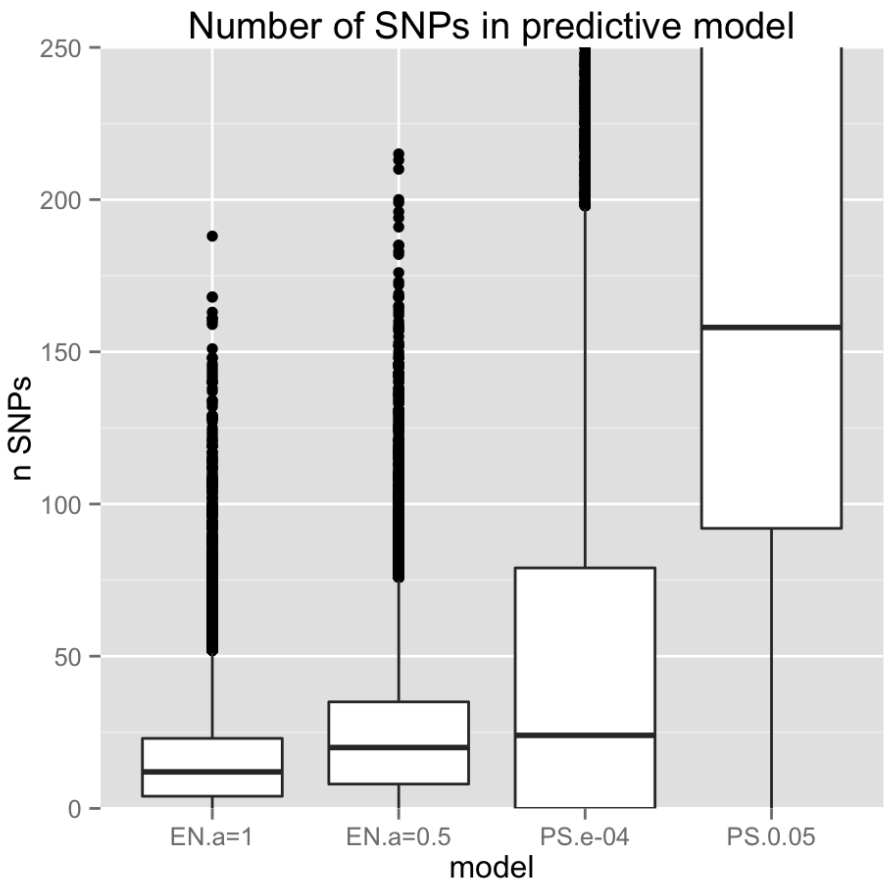


LASSO predicts gene expression better than Polyscore

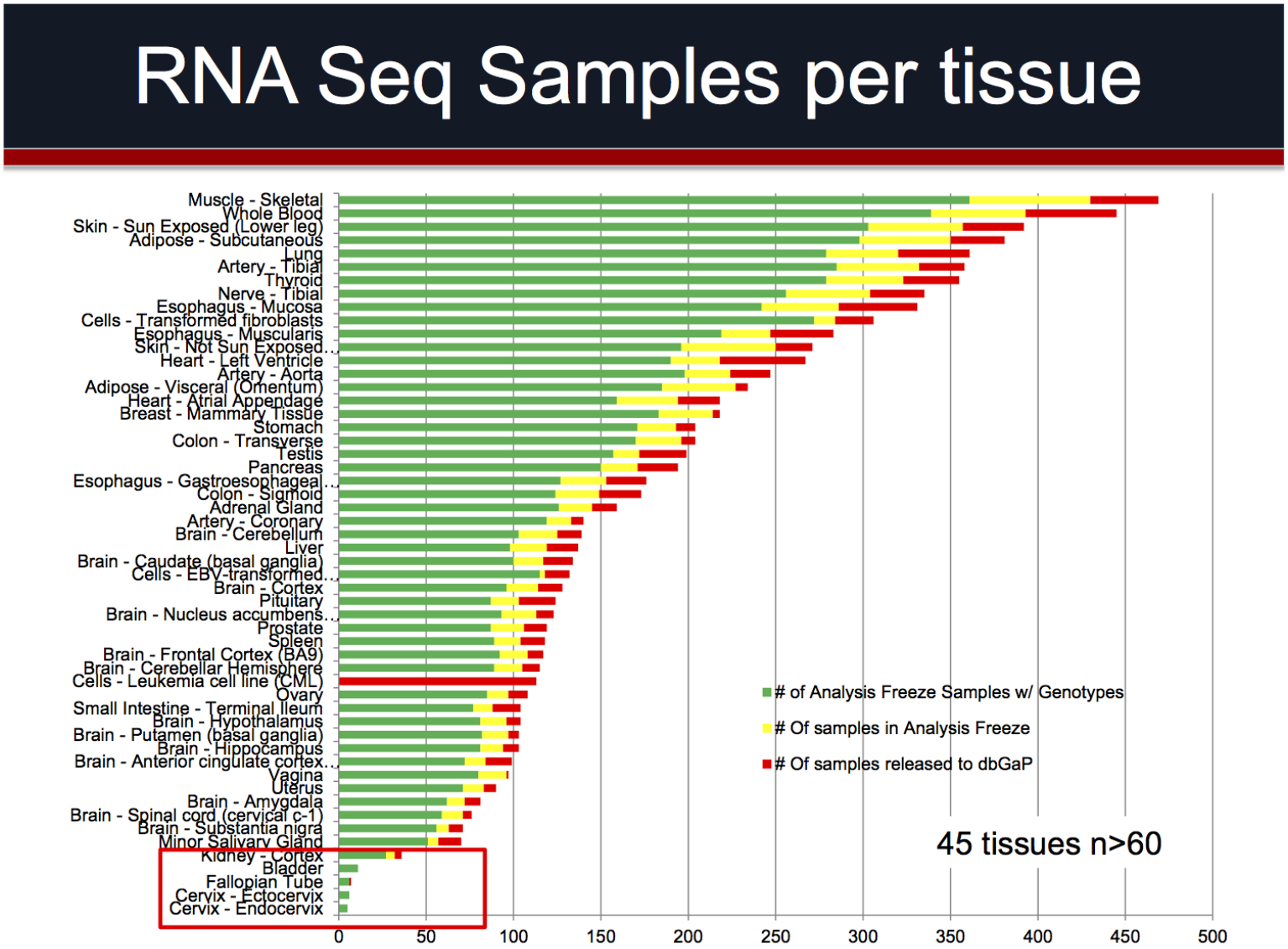


For robustness, consider EN (alpha=0.5) for PrediXcan





cross-tissue vs. tissue-specific effects with GTEx



Modeling cross-tissue expression

Linear mixed effect model

```
library(lme4)

fit <- lmer(expression ~ (1|SUBJID) + TISSUE
+ GENDER + PEERs)

#cross-tissue expression
fitranef <- ranef(fit)

#tissue-specific expression
fitresid <- resid(fit)
```

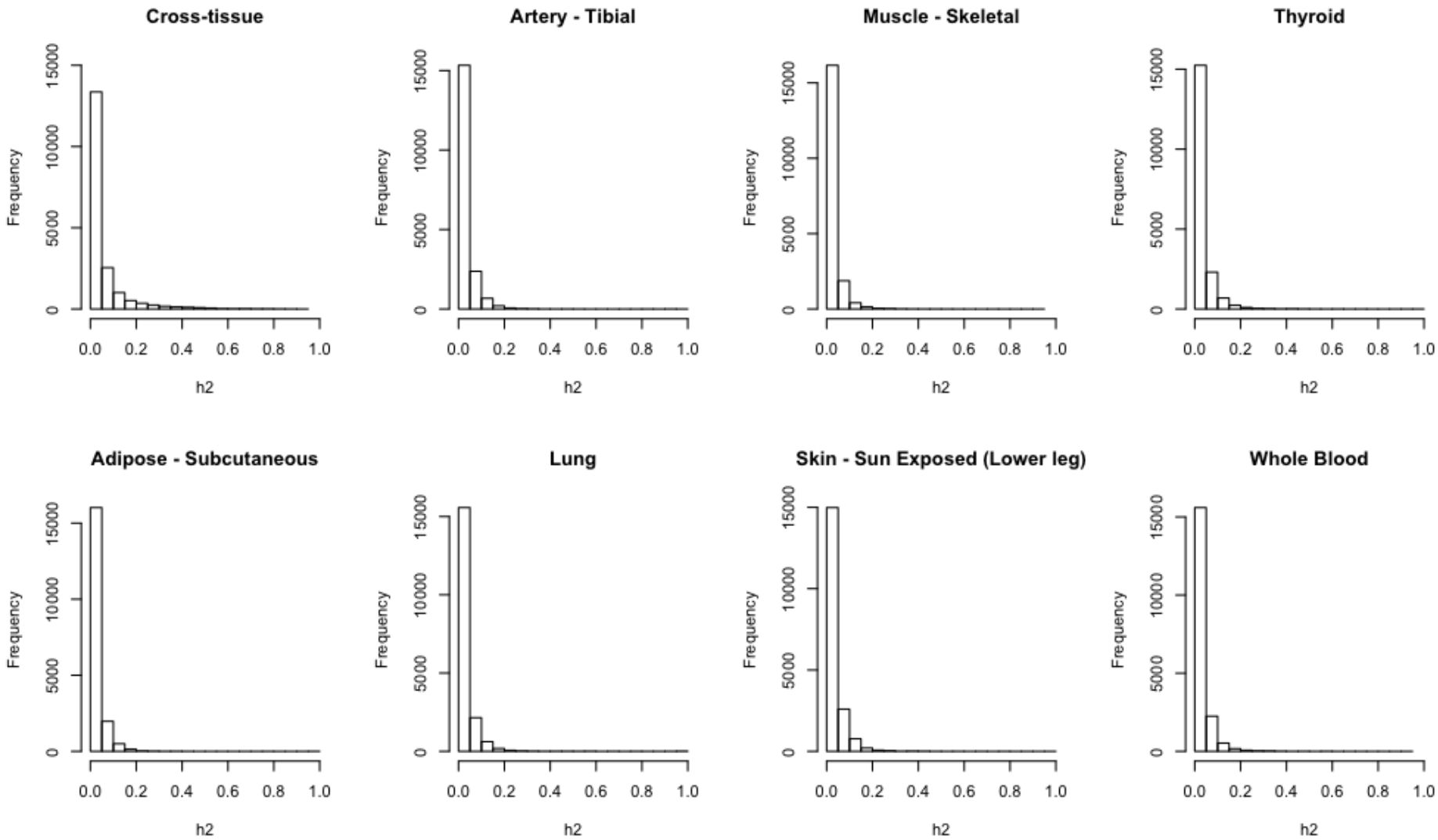
Estimating heritability with GCTA

Tested two genetic relationship matrix (GRM) models for each expressed gene

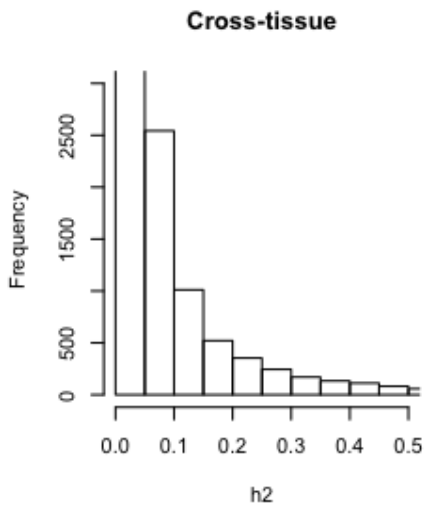
- localGRM (SNPs within 1 Mb of gene)
- localGRM + globalGRM (all SNPs)

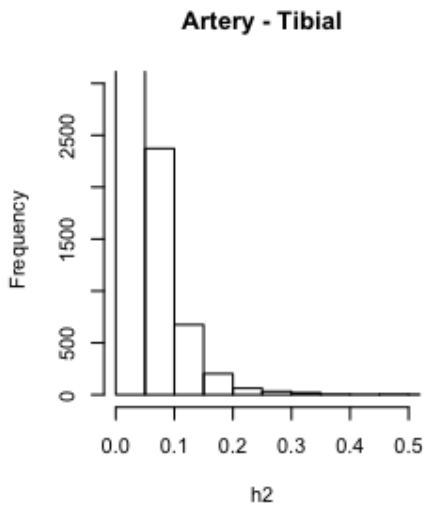
First pass: estimated h^2 of cross-tissue expression and tissue-specific expression in the 7 tissues with the most samples

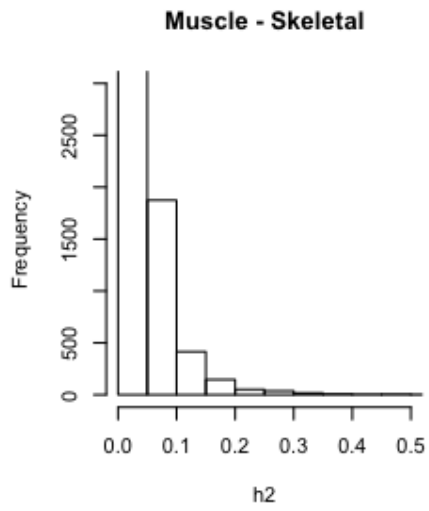
GCTA heritability: Y ~ localGRM h2

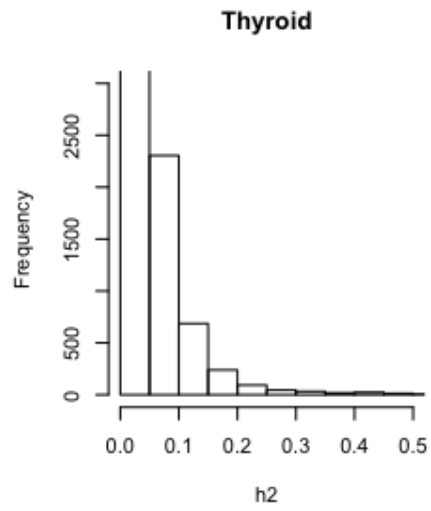


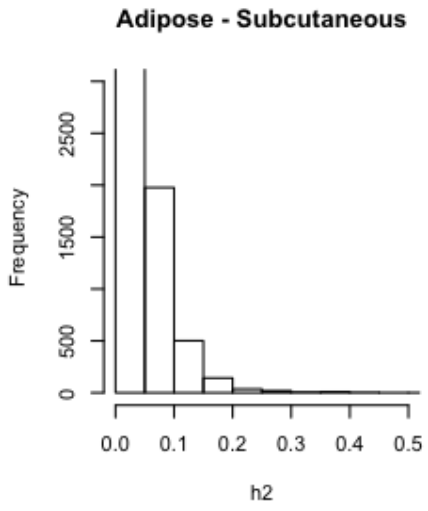
GCTA heritability: Y ~ localGRM h2 **ZOOM**

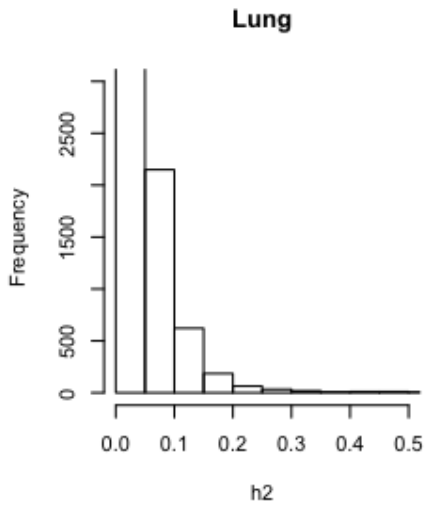


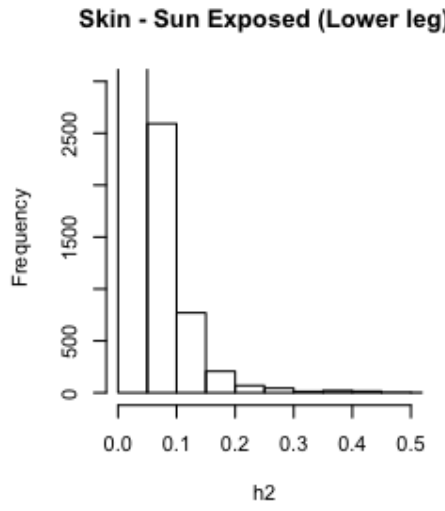


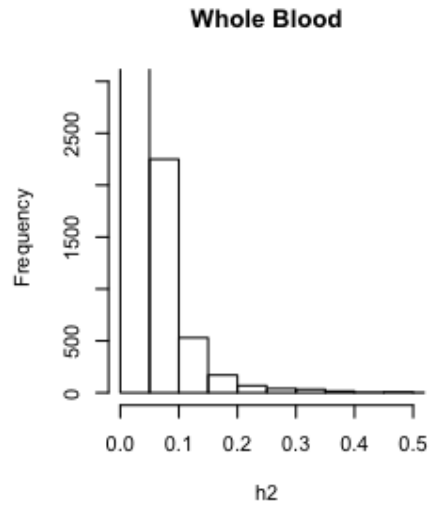




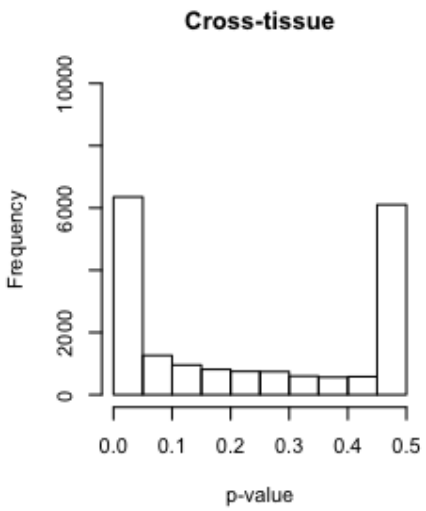


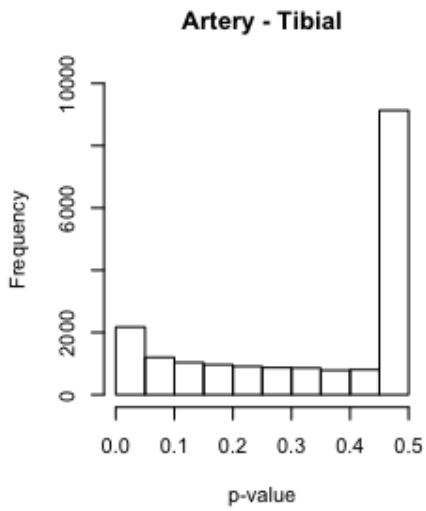


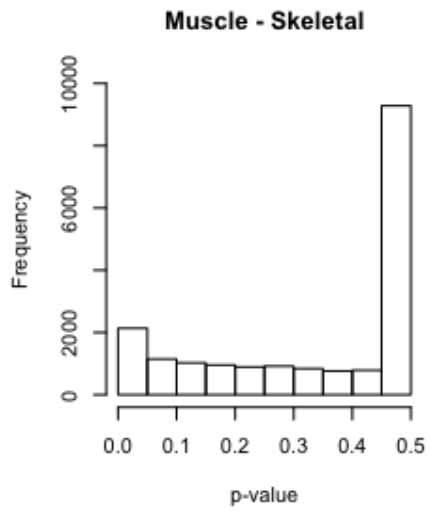


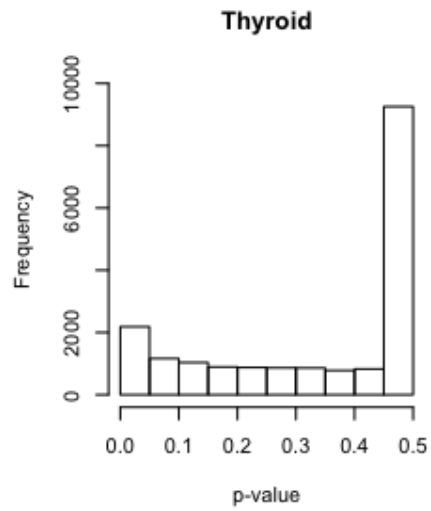


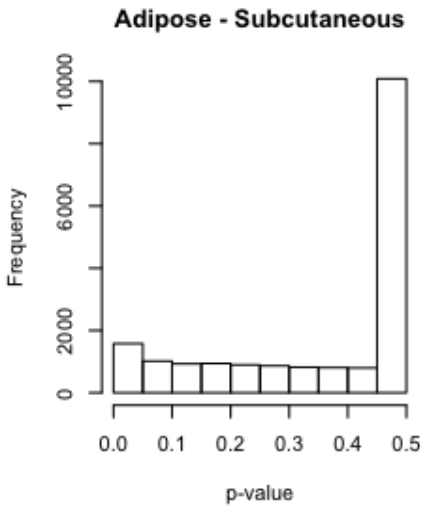
GCTA heritability: Y ~ localGRM p-values

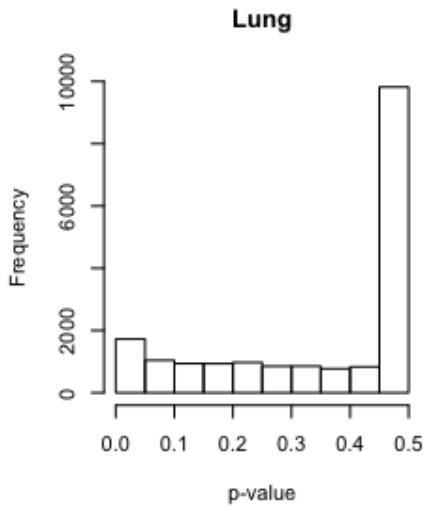


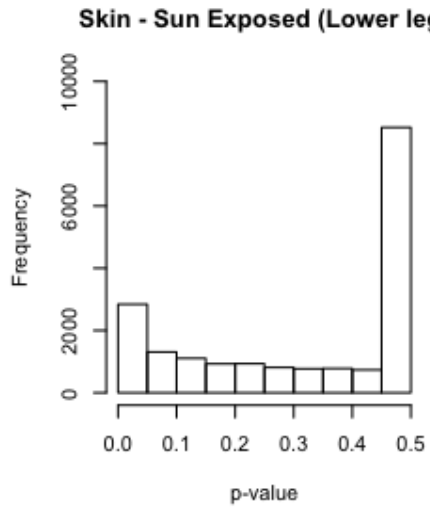


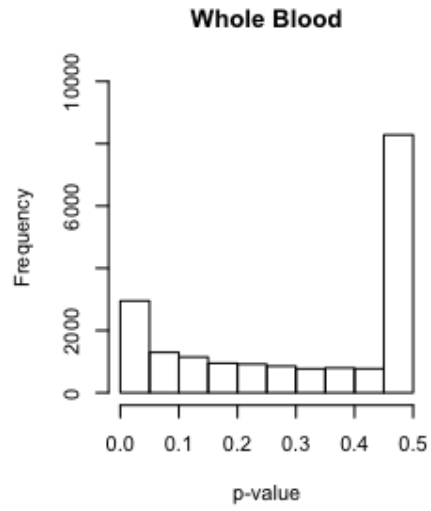




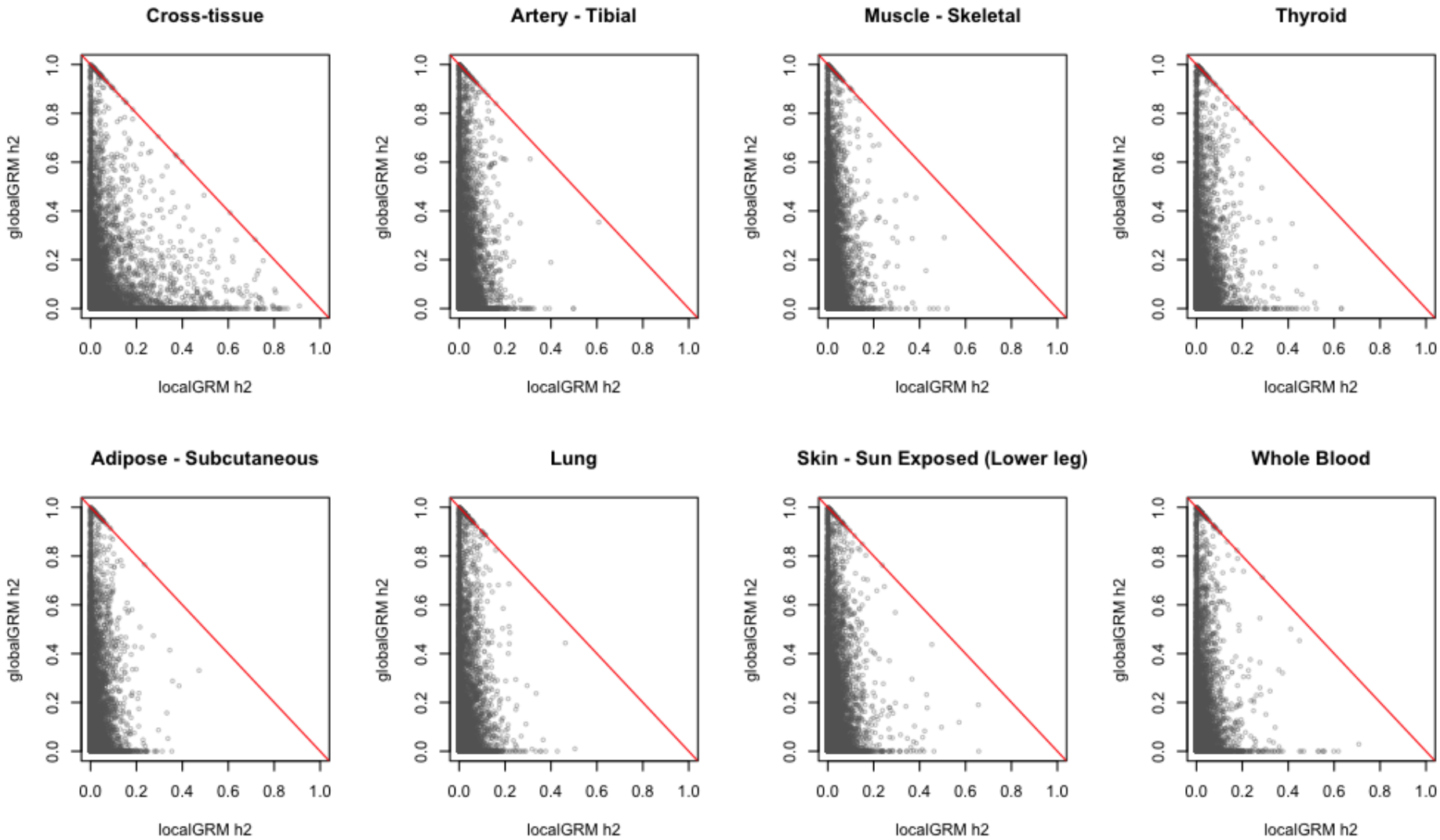








GCTA heritability: Y ~ localGRM + globalGRM h2



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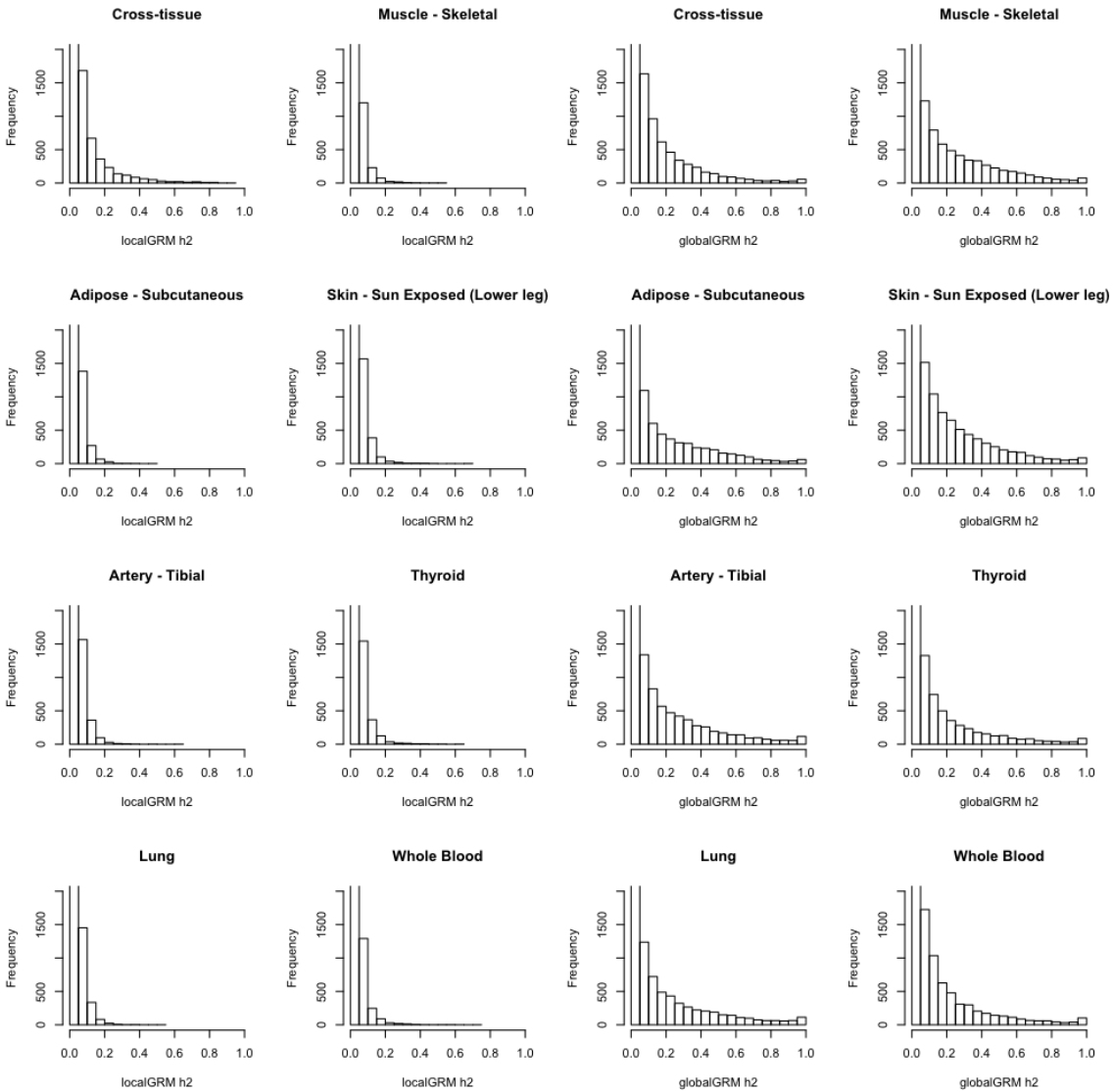

GCTA heritability: Y ~ localGRM + globalGRM SE