Understanding the genetic architecture of gene expression

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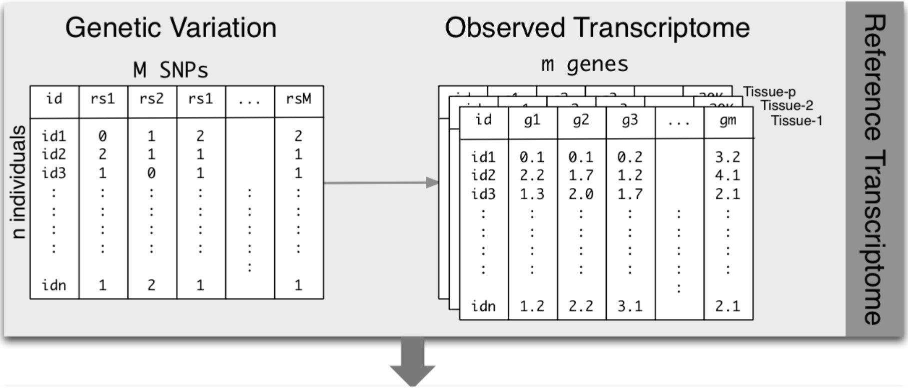
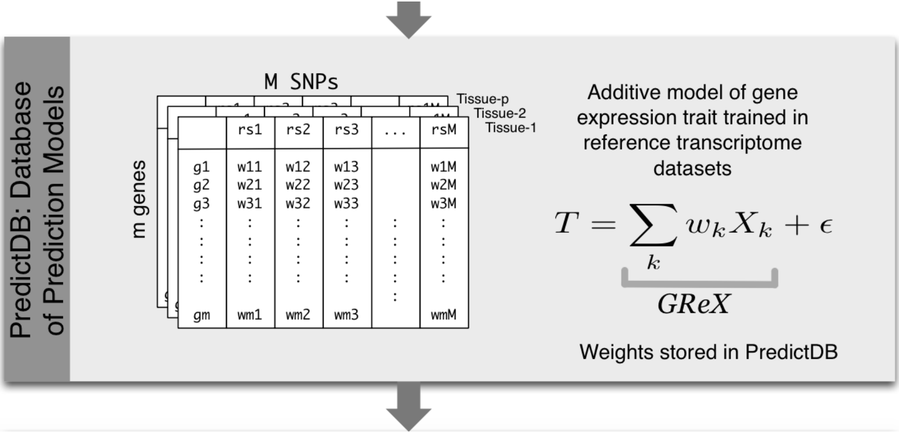
PrediXcan Step 1: Build and Test Predictors



id	rs1	rs2	rs1	...	rsM
id1	0	1	2		2
id2	2	1	1		1
id3	1	0	1		1
:	:	:	:	:	:
idn	1	2	1		1

id	g1	g2	g3	...	gm
id1	0.1	0.1	0.2		3.2
id2	2.2	1.7	1.2		4.1
id3	1.3	2.0	1.7		2.1
:	:	:	:	:	:
idn	1.2	2.2	3.1		2.1

PrediXcan Step 2: Build database of Best Predictors



PredictDB: Database of Prediction Models

M SNPs

m genes

Tissue-p
Tissue-2
Tissue-1

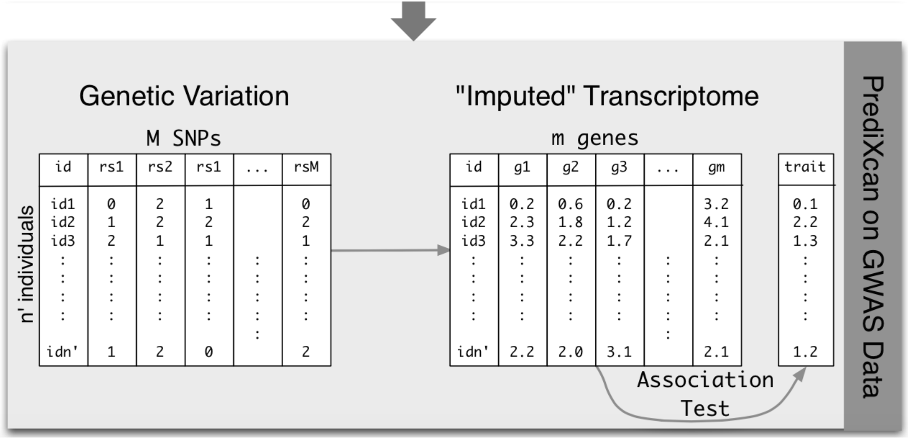
	rs1	rs2	rs3	. . .	rsM
g1	w11	w12	w13		w1M
g2	w21	w22	w23		w2M
g3	w31	w32	w33		w3M
⋮	⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮	⋮
				⋮	
gm	wm1	wm2	wm3		wmM

Additive model of gene expression trait trained in reference transcriptome datasets

$$T = \underbrace{\sum_k w_k X_k}_{GReX} + \epsilon$$

Weights stored in PredictDB

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



id	rs1	rs2	rs1	...	rsM
id1	0	2	1		0
id2	1	2	2		2
id3	2	1	1		1
⋮	⋮	⋮	⋮	⋮	⋮
idn'	1	2	0		2

id	g1	g2	g3	...	gm
id1	0.2	0.6	0.2		3.2
id2	2.3	1.8	1.2		4.1
id3	3.3	2.2	1.7		2.1
⋮	⋮	⋮	⋮	⋮	⋮
idn'	2.2	2.0	3.1		2.1

trait
0.1
2.2
1.3
⋮
1.2

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:

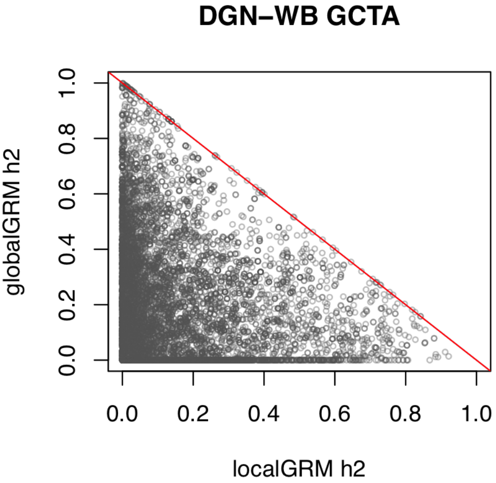
- *cis* vs. *trans* effects
- sparse vs. polygenic effects
- cross-tissue vs. tissue-specific effects

Primary cohort: DGN

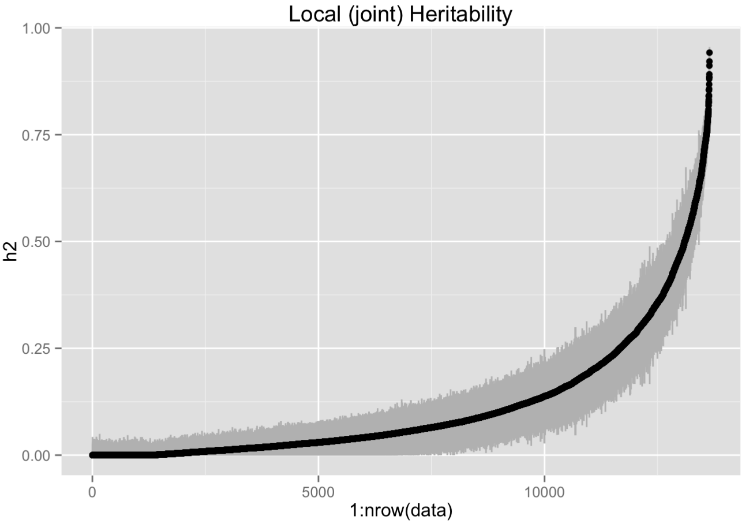
- Battle et al. "Characterizing the genetic basis of transcriptome diversity through RNA-sequencing of 922 individuals." Genome Research 2014, 24(1):14-24
- Whole blood from Depression Genes and Networks study
- n = 922
- RNA-seq: "normalized gene-level expression data used for trans-eQTL analysis. The 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)

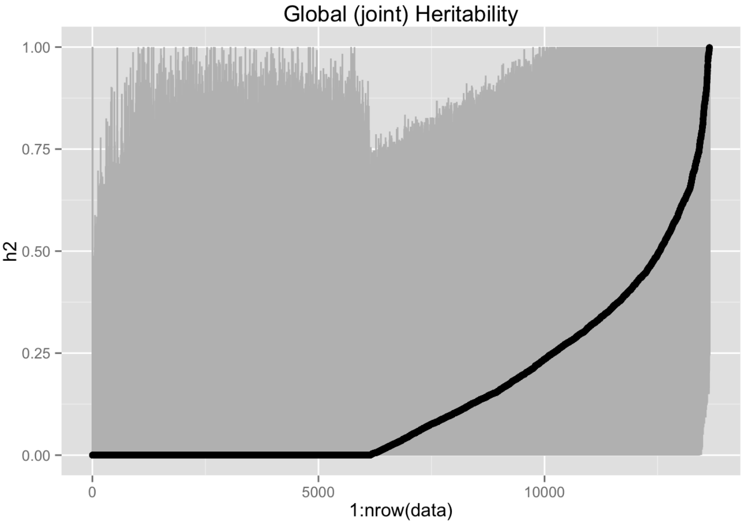


Local (joint) sorted h^2 estimates with 95% CI from GCTA



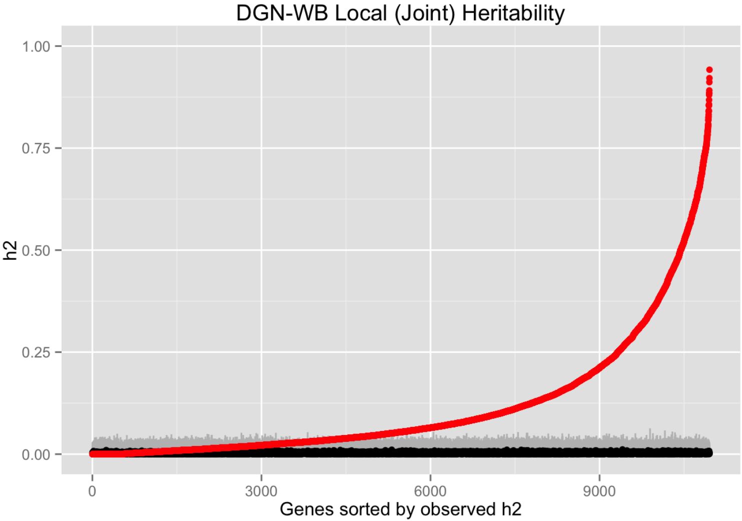
https://github.com/hwheeler01/cross-tissue/blob/master/analysis/sources/heritab_analysis.html

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

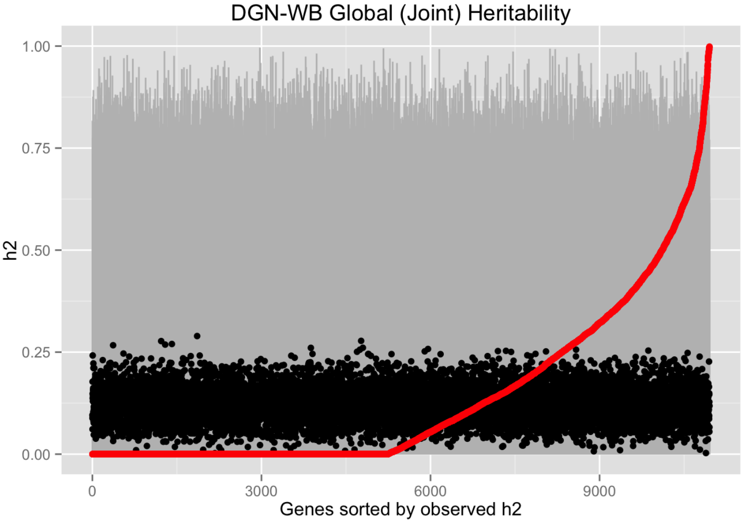


`https://github.com/hwheeler01/cross-tissue/blob/master/analysis/sources/heritab_analysis.html`

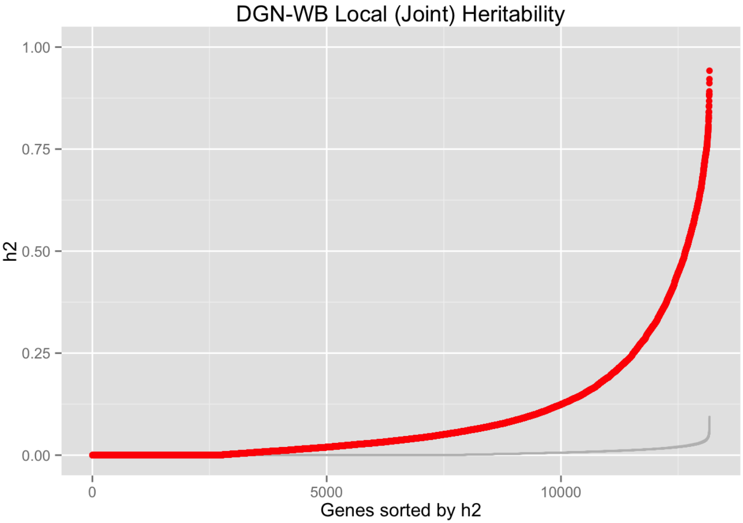
100 permutations to determine expected distribution of h^2 estimates



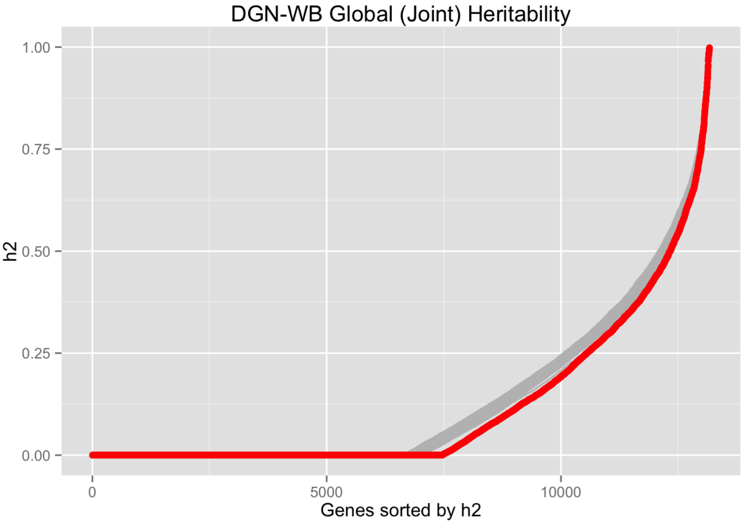
100 permutations to determine expected distribution of h^2 estimates



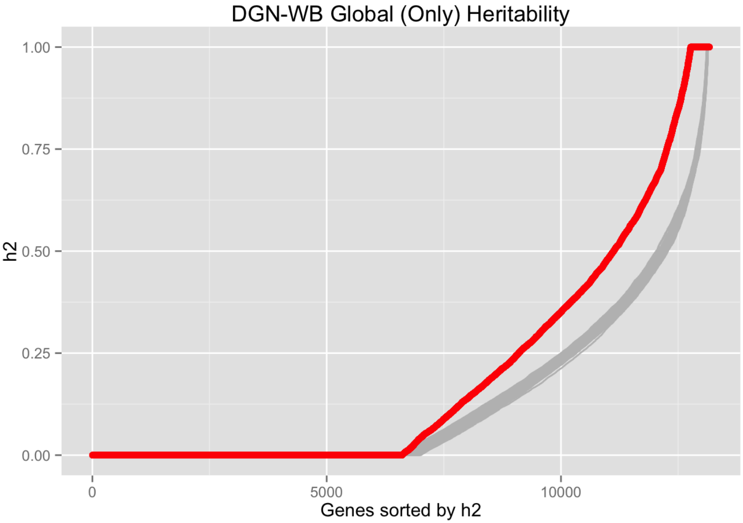
Sort the h^2 from each permutation



Sort the h^2 from each permutation



Sort the h^2 from each permutation



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

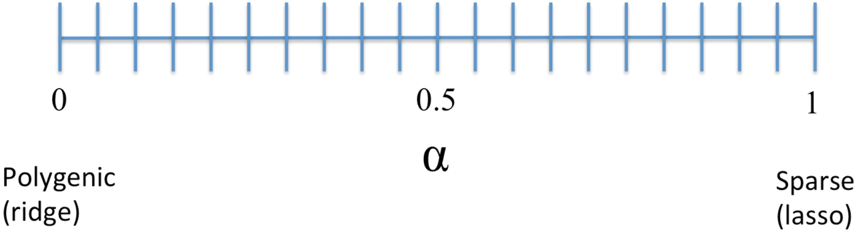
$$\min_{\beta_0,\beta} \frac{1}{N} \sum_{i=1}^{N} w_i l(y_i, \beta_0 + \beta^T x_i) + \lambda \left[(1-\alpha)||\beta||_2^2/2 + \alpha||\beta||_1\right],$$

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.

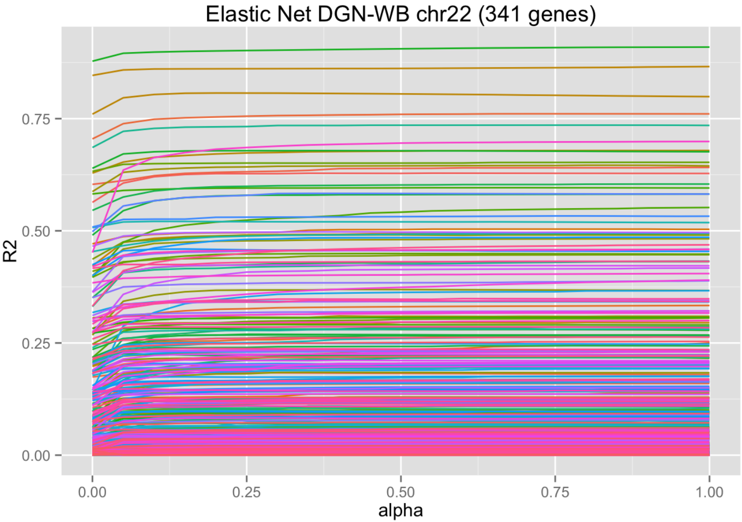
`http://web.stanford.edu/~hastie/glmnet/glmnet_alpha.html`

sparse vs. polygenic effects

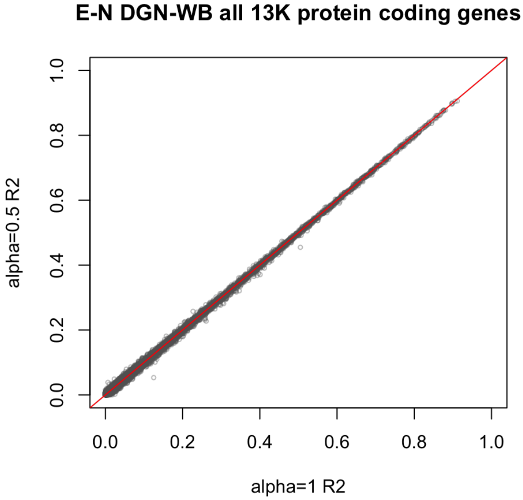


For each gene, determine α with best 10-fold CV predictive performance using *cis* SNPs.

Predictive performance consistent across most alphas



Predictive performance consistent between α=0.5 and α=1



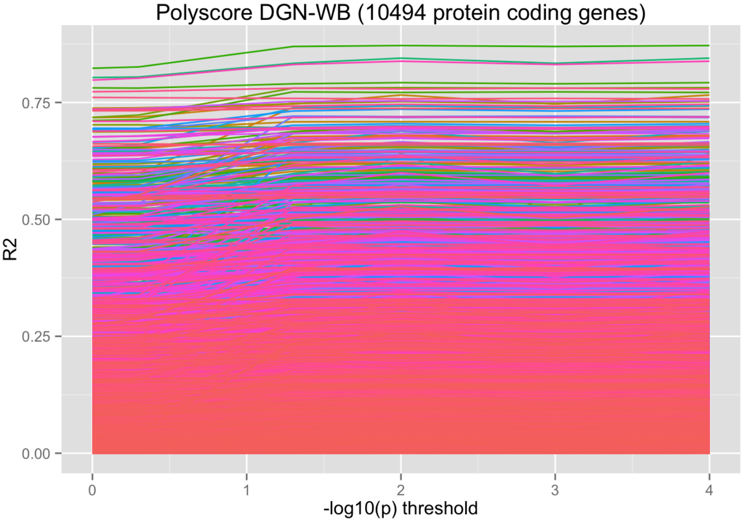
Also tested Polyscore predictive performance using 10-fold CV

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

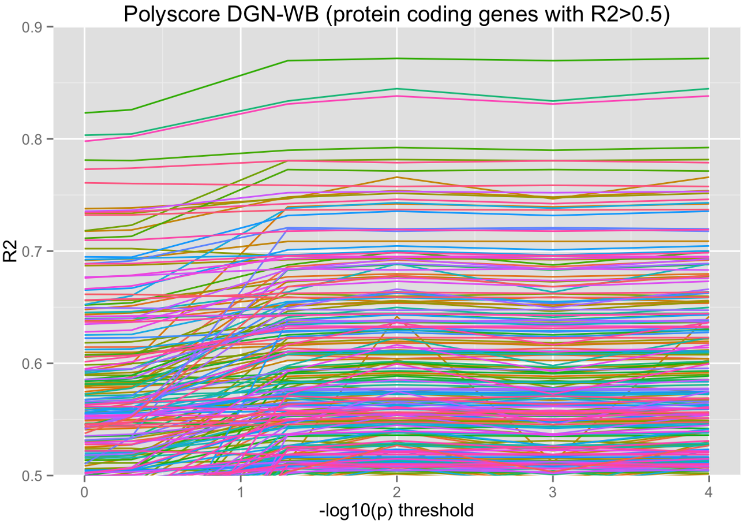
Single variant linear regression coefficients (w) at several P-value thresholds included in the additive model:

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

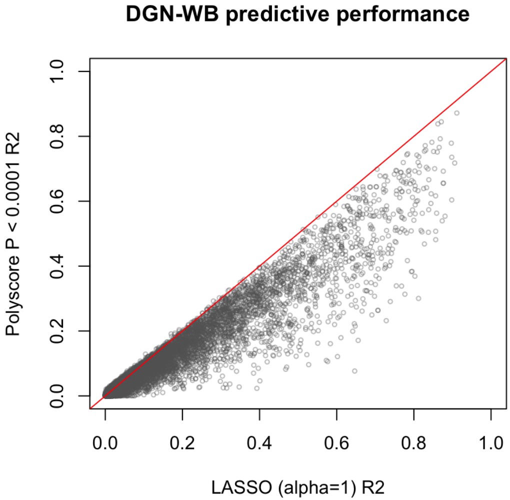
Polyscore (*cis* SNPs only) predictive performance



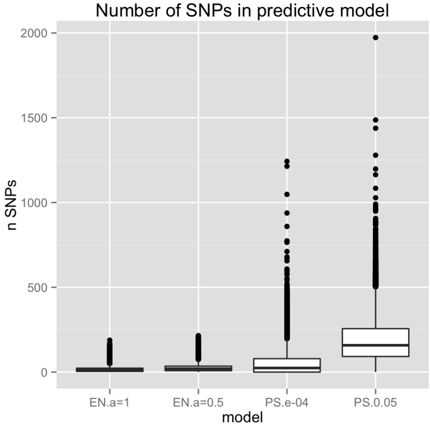
Polyscore (*cis* SNPs only) predictive performance

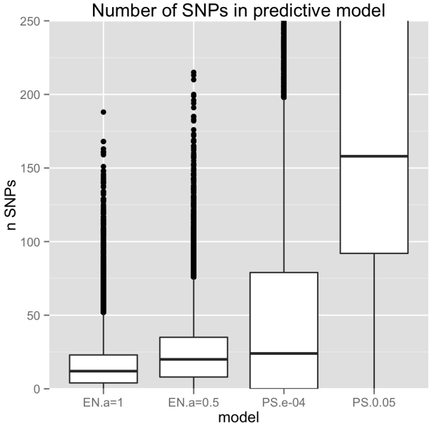


LASSO predicts gene expression better than Polyscore

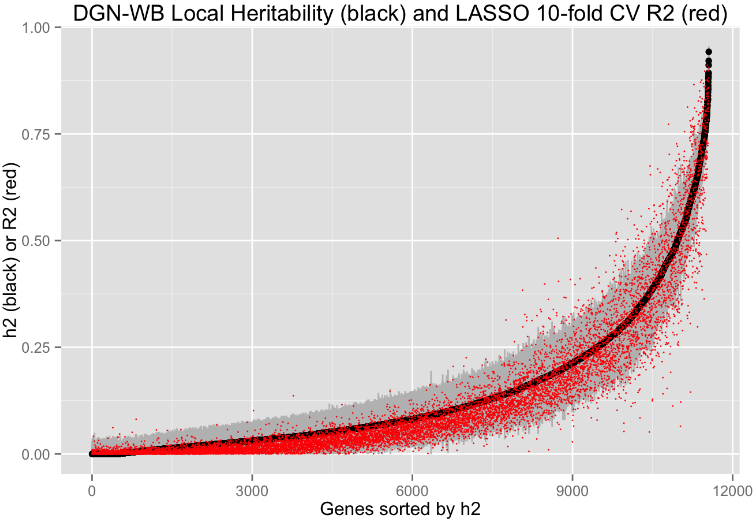


For robustness, consider EN (alpha=0.5) for PrediXcan

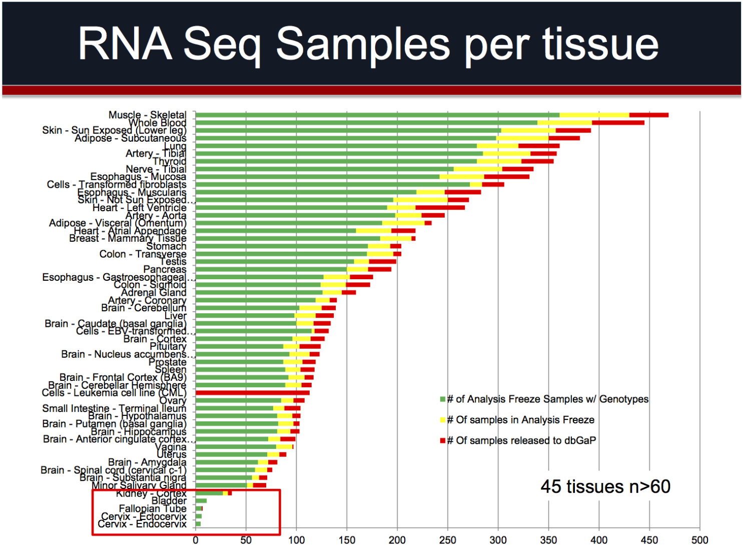




LASSO predictive performance reaches (or exceeds?) local h^2 of most genes



cross-tissue vs. tissue-specific effects with GTEx



RNA Seq Samples per tissue

45 tissues n>60

Modeling cross-tissue expression

Linear mixed effect model using `GTEx_Data_2014-06-13` release

- 8555 tissues across 544 subjects
- limited to ∼17K protein coding genes

```
library(lme4)

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

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

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

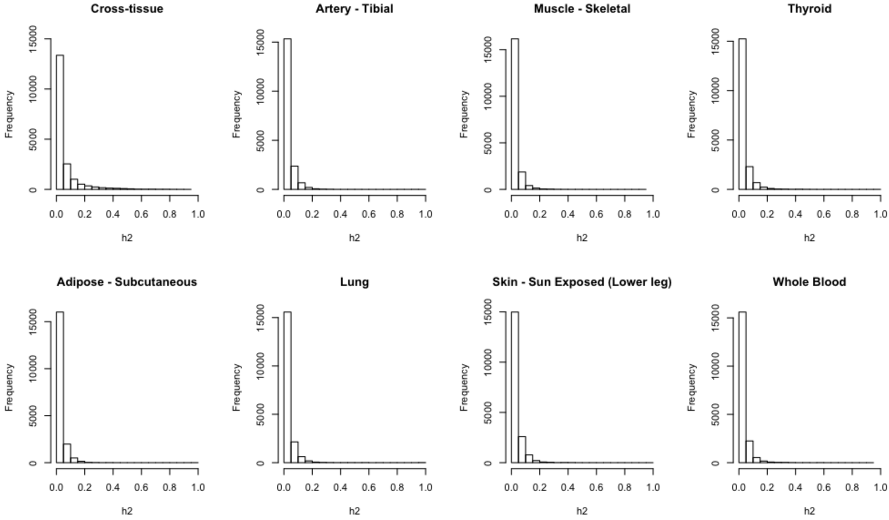
Estimating heritability with GCTA

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

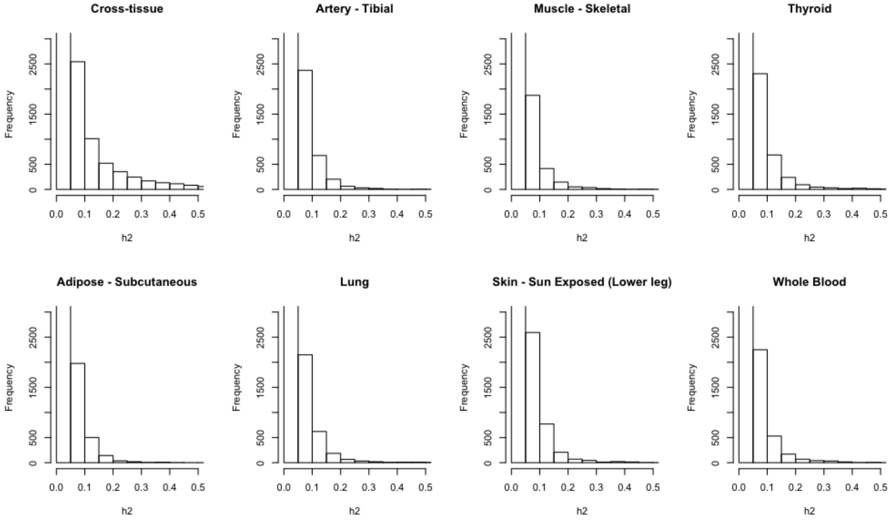
- localGRM (SNPs within 1 Mb of gene)
- localGRM + globalGRM (all SNPs)

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

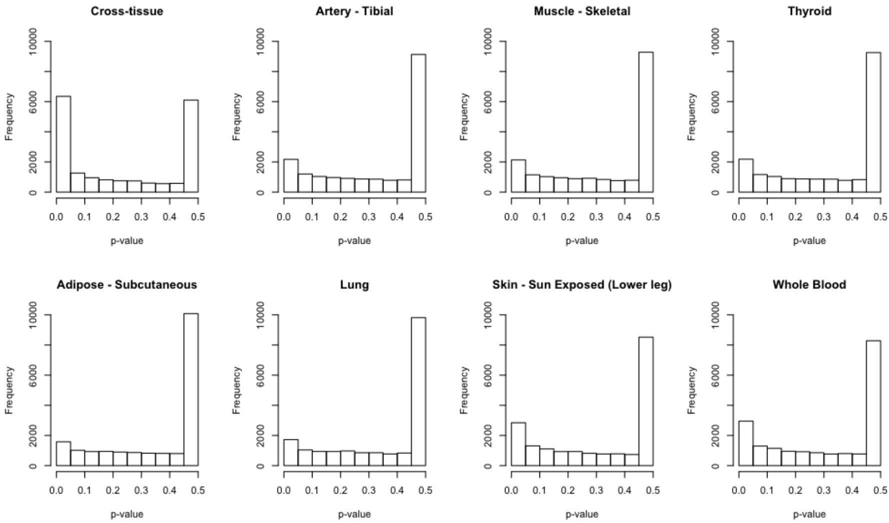
GCTA heritability: Y ∼ localGRM h2



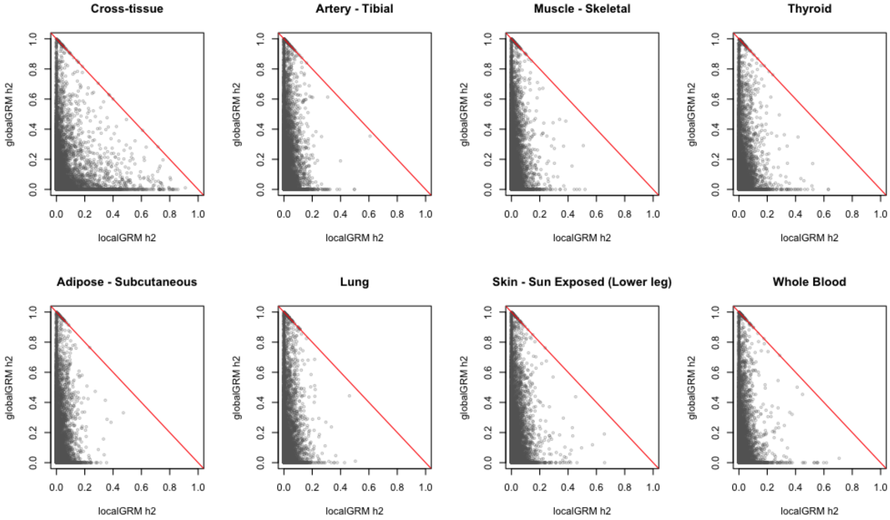
GCTA heritability: Y ~ localGRM h2 **ZOOM**



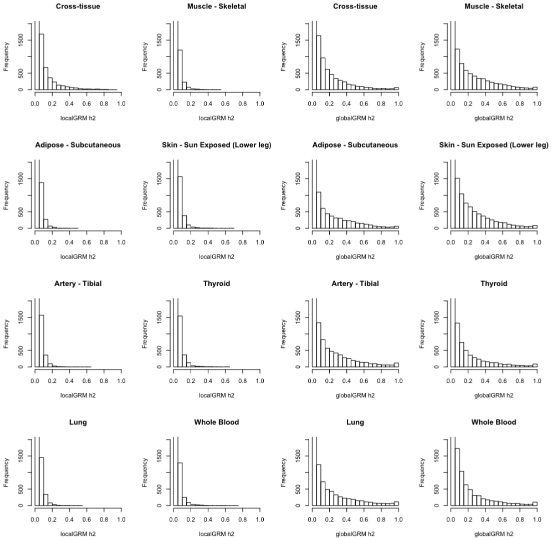
GCTA heritability: Y ~ localGRM p-values



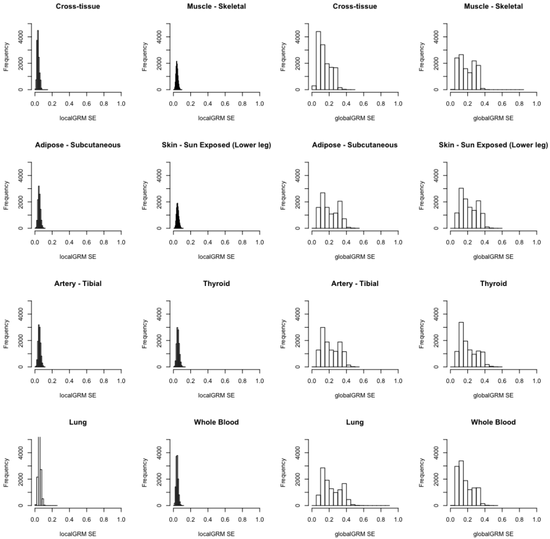
GCTA heritability: Y ~ localGRM + globalGRM h2



GCTA heritability: Y ~ localGRM + globalGRM h2



GCTA heritability: Y ~ localGRM + globalGRM SE


Cross-tissue
Muscle - Skeletal
Cross-tissue
Muscle - Skeletal
Adipose - Subcutaneous
Skin - Sun Exposed (Lower leg)
Adipose - Subcutaneous
Skin - Sun Exposed (Lower leg)
Artery - Tibial
Thyroid
Artery - Tibial
Thyroid
Lung
Whole Blood
Lung
Whole Blood
Frequency
localGRM SE
globalGRM SE