Cis/Trans Heritability of Expression Traits

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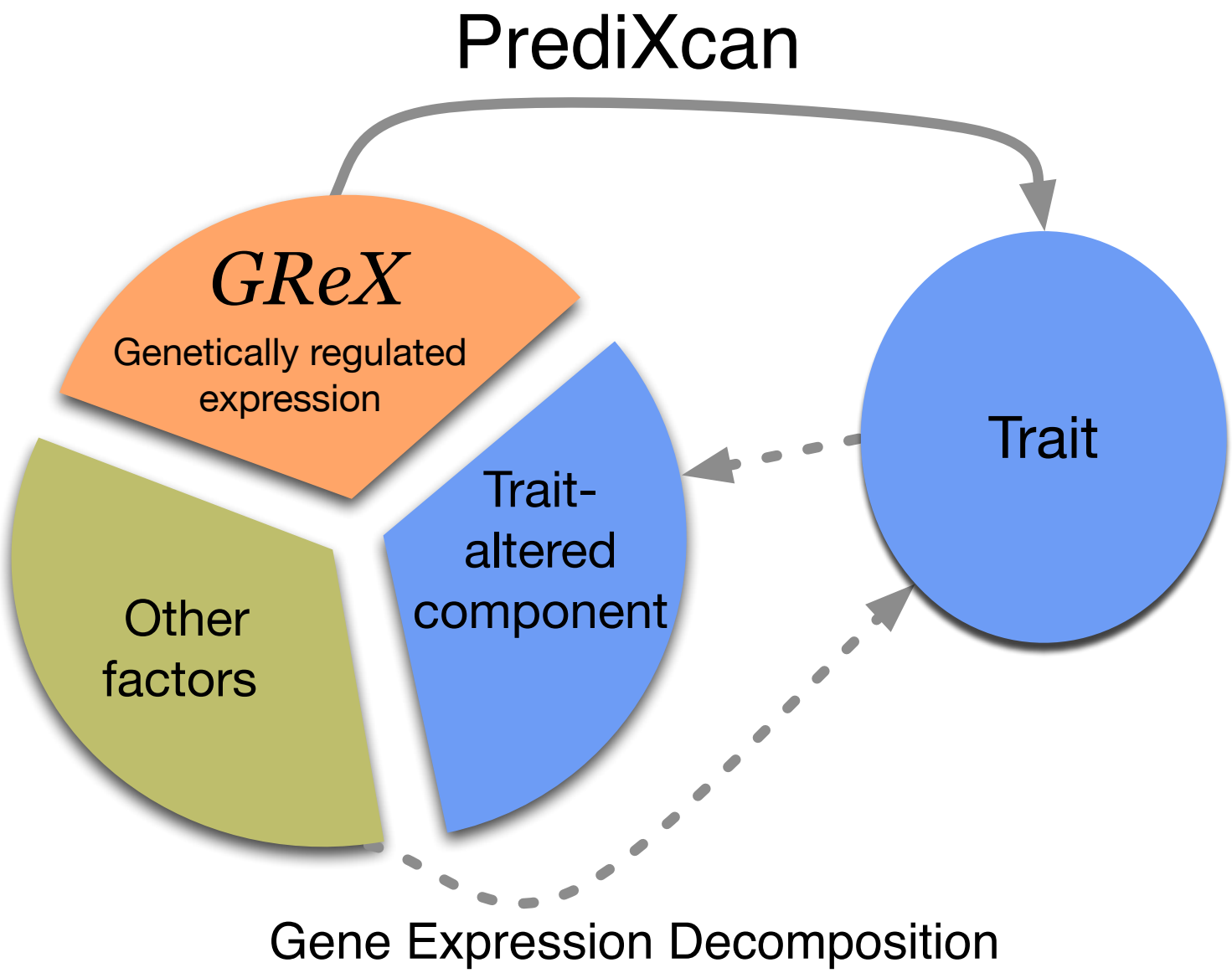
GTEx Jamboree
December 3, 2014

THE UNIVERSITY OF CHICAGO

Mechanisms Tested by PrediXcan



Genetic Architecture to Improve Prediction

- Cis and Trans heritability

- Sparsity/Polygenicity

- This information guide us to improve prediction, i.e. estimates of GReX

Cis/Trans Heritability Estimation

- Gene expression trait model

$$Y_i = \sum_{\text{local}} c_k X_{ik} + \sum_{\text{global}} c_k X_{ik} + \epsilon_i$$

- REML to estimation of local and global contributions jointly
- Covariance of local component: GRM using SNPs nearby
- Covariance of global component: GRM using all SNPs
- We use GCTA as REML calculator

Depression Genes & Networks - Whole Blood

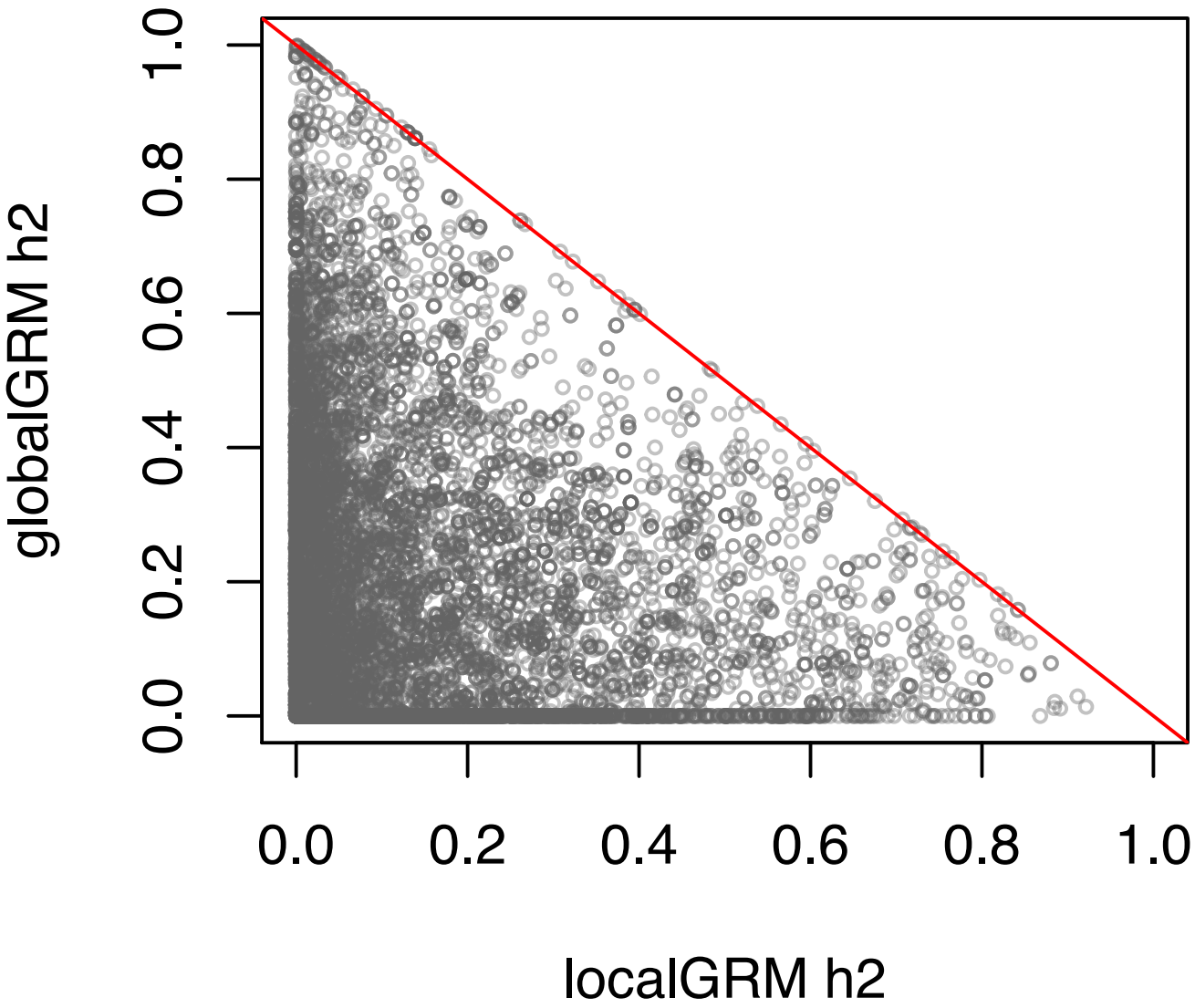
Downloaded from genome.cshlp.org on May 19, 2014 - Published by Cold Spring Harbor Laboratory Press

Characterizing the genetic basis of transcriptome diversity through RNA-sequencing of 922 individuals

Alexis Battle, Sara Mostafavi, Xiaowei Zhu, et al.

Genome Res. published online October 3, 2013
Access the most recent version at doi:10.1101/gr.155192.113

Cis and Trans Heritability Whole Blood DGN (n~922)



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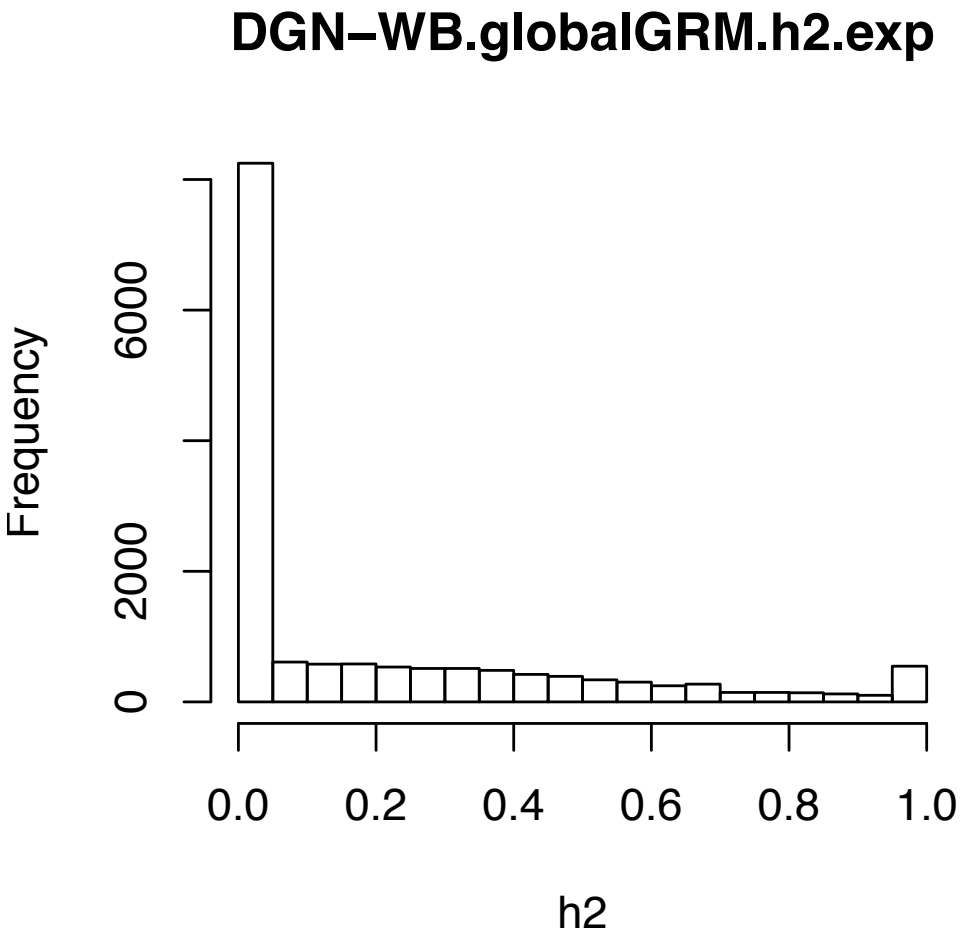
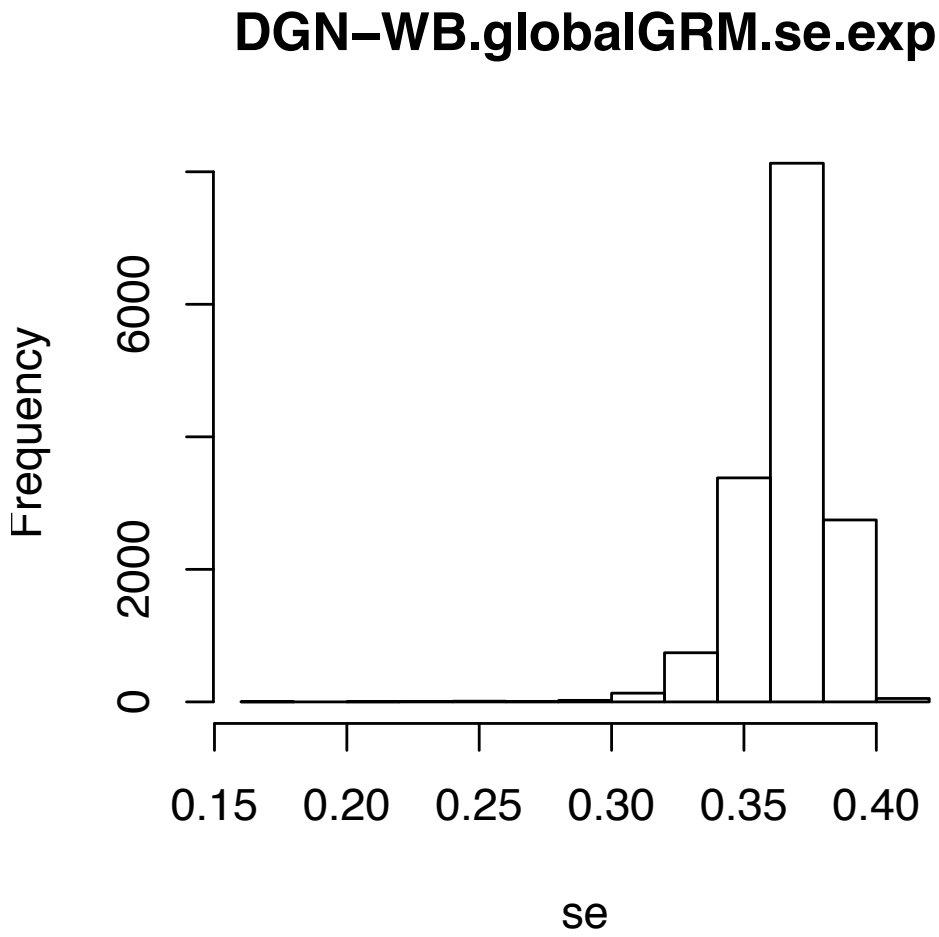
Global Heritability





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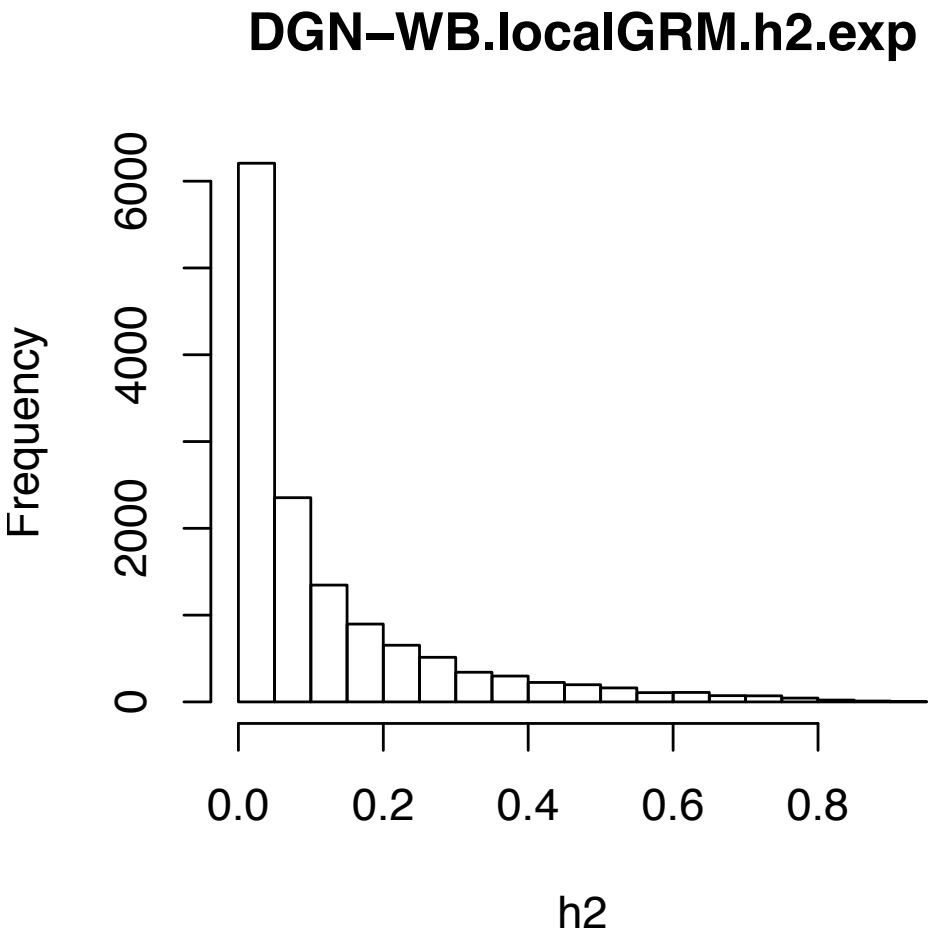
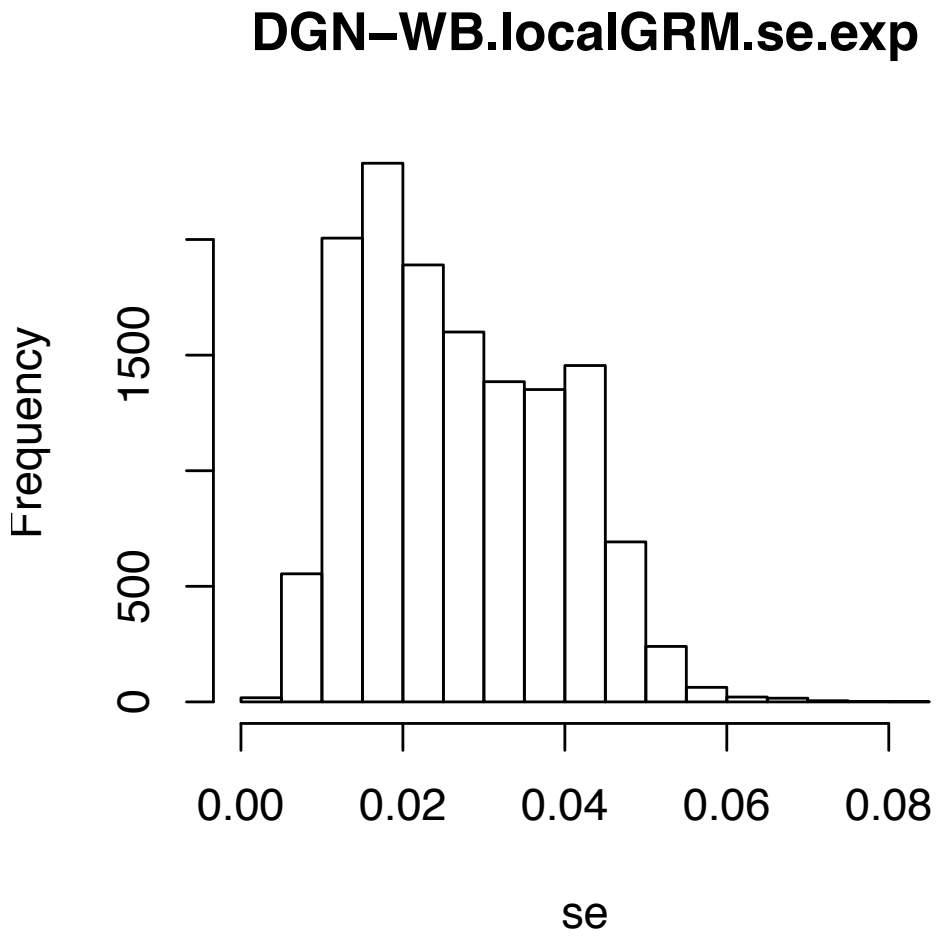
Local Heritability





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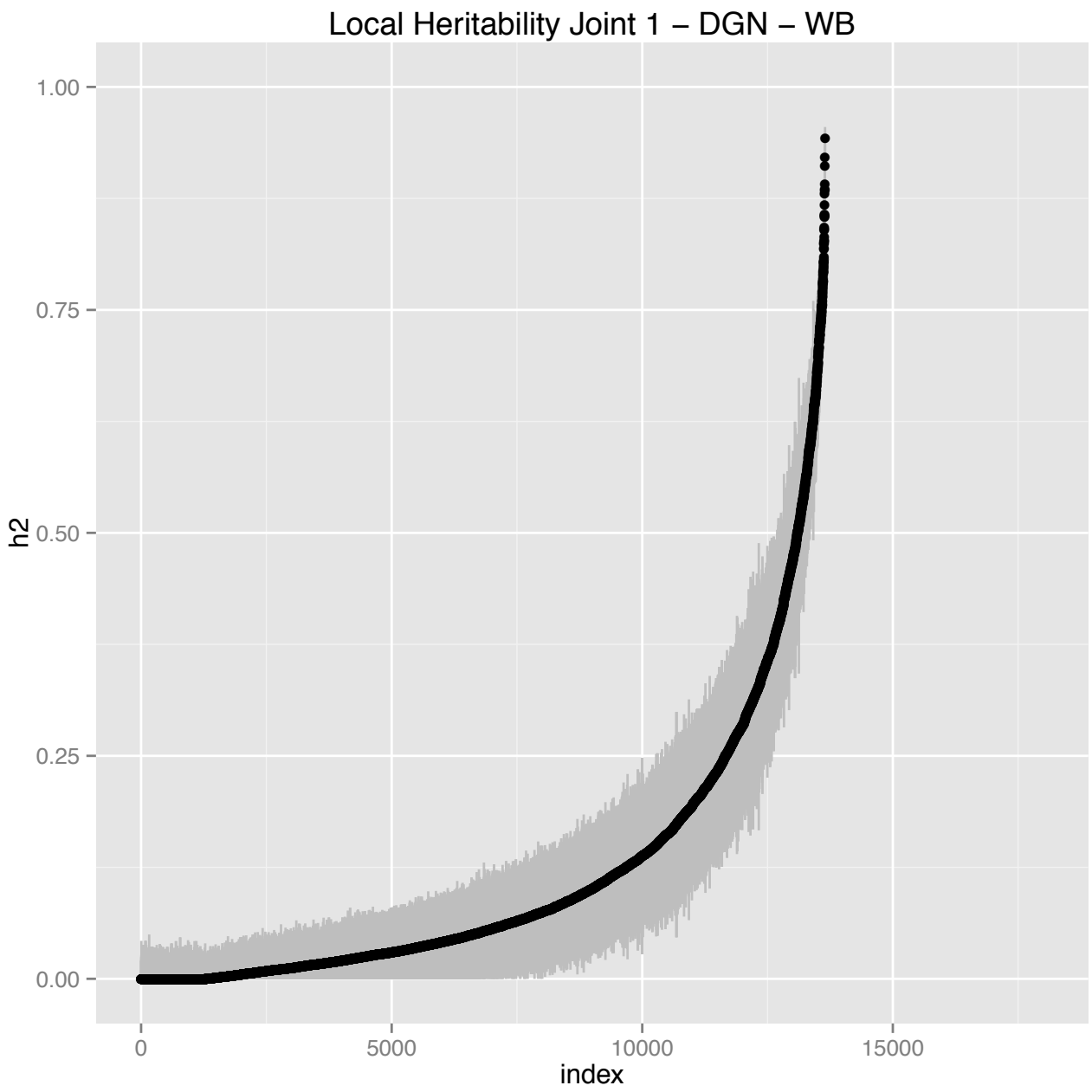
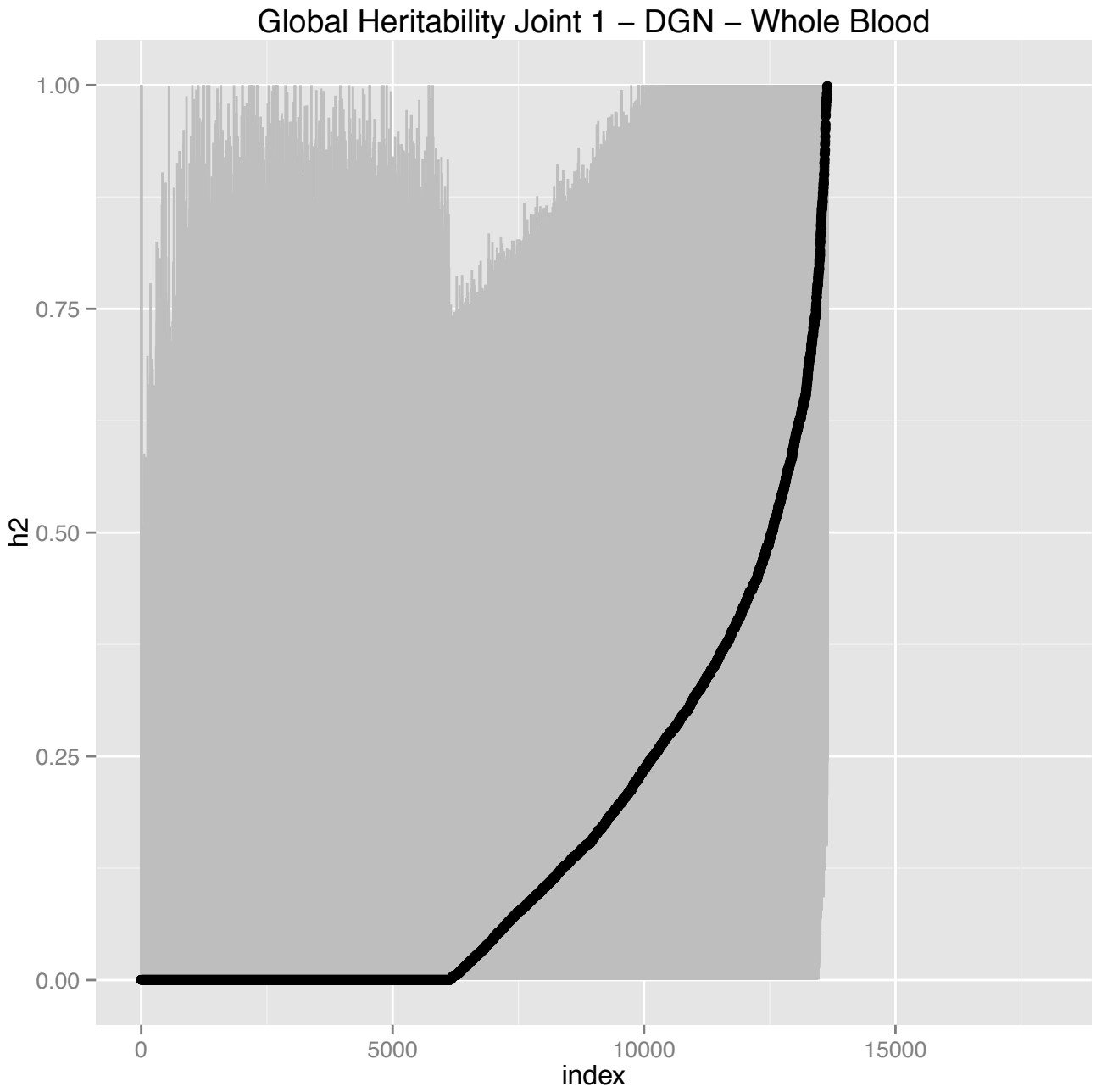
Local Heritability



Global Heritability



Validation Data

OPEN ACCESS Freely available online

PLoS GENETICS

Single-Tissue and Cross-Tissue Heritability of Gene Expression Via Identity-by-Descent in Related or Unrelated Individuals

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1 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America, **2** Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, United States of America, **3** Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge, Massachusetts, United States of America, **4** deCODE Genetics, Reykjavik, Iceland, **5** University of Iceland, Reykjavik, Iceland, **6** Department of Genetics, Harvard Medical School, Boston, Massachusetts, United States of America

Abstract

Family studies of individual tissues have shown that gene expression traits are genetically heritable. Here, we investigate *cis* and *trans* components of heritability both within and across tissues by applying variance-components methods to 722 Icelanders from family cohorts, using identity-by-descent (IBD) estimates from long-range phased genome-wide SNP data and gene expression measurements for ~19,000 genes in blood and adipose tissue. We estimate the proportion of gene expression heritability attributable to *cis* regulation as 37% in blood and 24% in adipose tissue. Our results indicate that the correlation in gene expression measurements across these tissues is primarily due to heritability at *cis* loci, whereas there is little sharing of *trans* regulation across tissues. One implication of this finding is that heritability in tissues composed of heterogeneous cell types is expected to be more dominated by *cis* regulation than in tissues composed of more homogeneous cell types, consistent with our blood versus adipose results as well as results of previous studies in lymphoblastoid cell lines. Finally, we obtained similar estimates of the *cis* components of heritability using IBD between unrelated individuals, indicating that transgenerational epigenetic inheritance does not contribute substantially to the

Validation of Cis Heritability Estimates

lm(formula = h2bloodcis ~ local1.h2, data = h2_all2)

Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)	
local1.h2	0.38159	0.00948	40.3	<2e-16	***

Residual standard error: 0.136 on 8874 degrees of freedom

(130 observations deleted due to missingness)

Multiple R-squared: 0.154, Adjusted R-squared: 0.154

F-statistic: 1.62e+03 on 1 and 8874 DF, p-value: <2e-16

Validation of Trans Heritability Estimates

lm(formula = h2bloodtra ~ global1.h2, data = h2_all2)

Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)	
global1.h2	0.02265	0.00832	2.72	0.0065	**

Residual standard error: 0.16 on 8874 degrees of freedom

(130 observations deleted due to missingness)

Multiple R-squared: 0.000835, Adjusted R-squared: 0.000723

F-statistic: 7.42 on 1 and 8874 DF, p-value: 0.00646

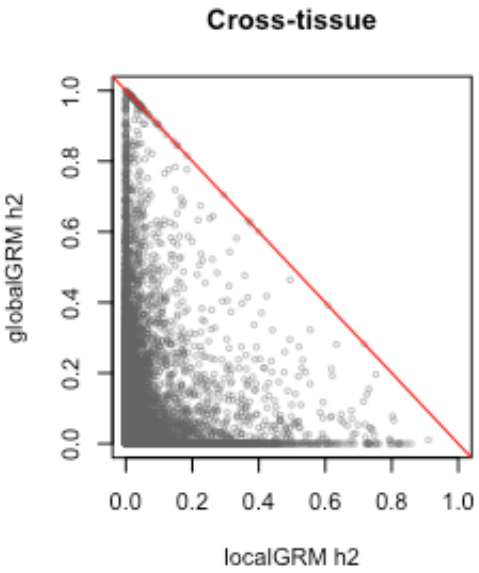
Orthogonal Tissue Decomposition

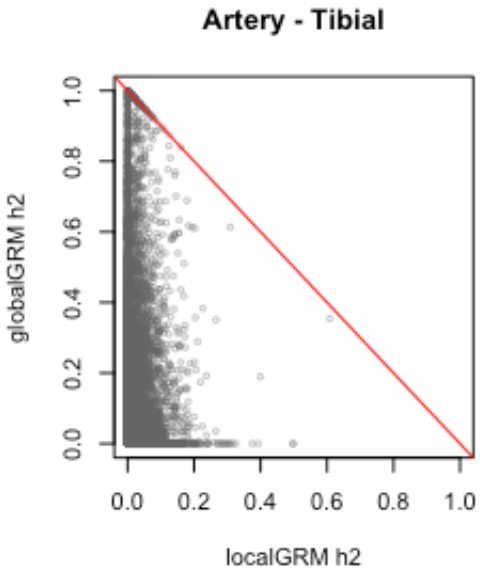
$$Y_i = T_{i,\text{cross}} + T_{i,\text{tissue}} + T_{i,\text{subtissue}}$$

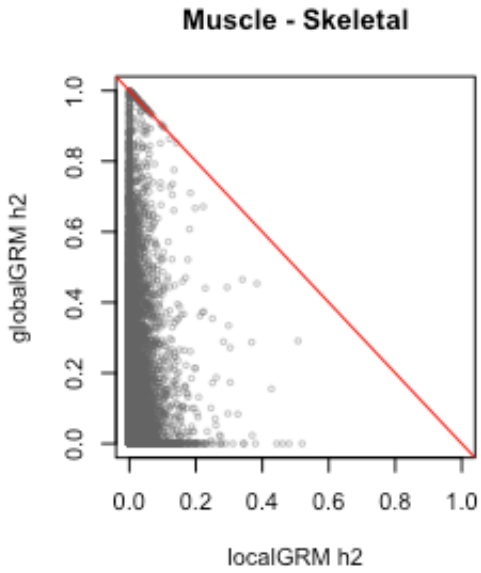
$$Y \sim (1|\text{id}) + (1|\text{id} * \text{tissue}) + (1|\text{id} * \text{tissue} * \text{subtissue})$$

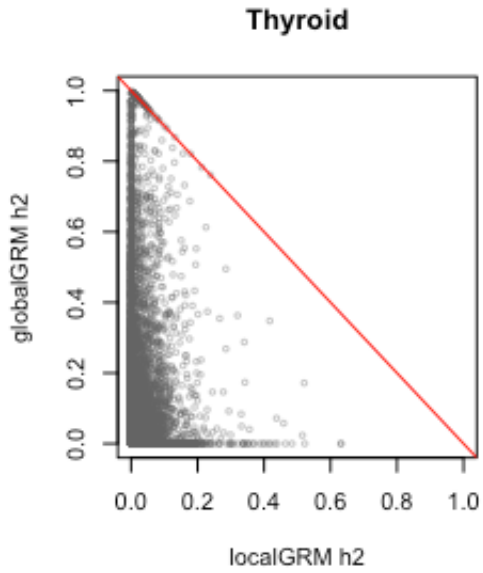
- Derived phenotypes
  - Cross tissue expression
  - tissue-specific expression
  - sub-tissue-specific expression traits
- Orthogonal by construction

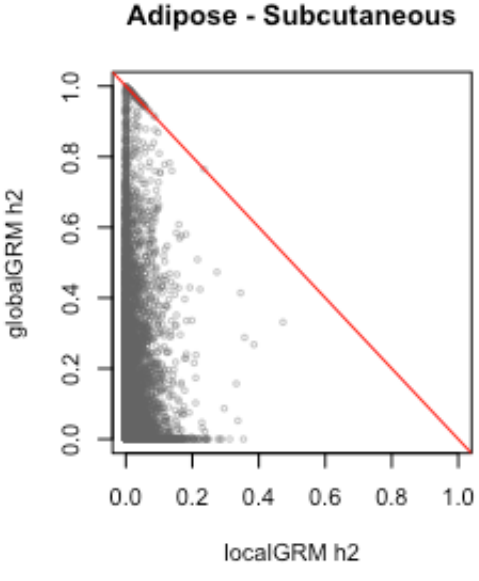
Trans vs. Cis Heritability by Tissue

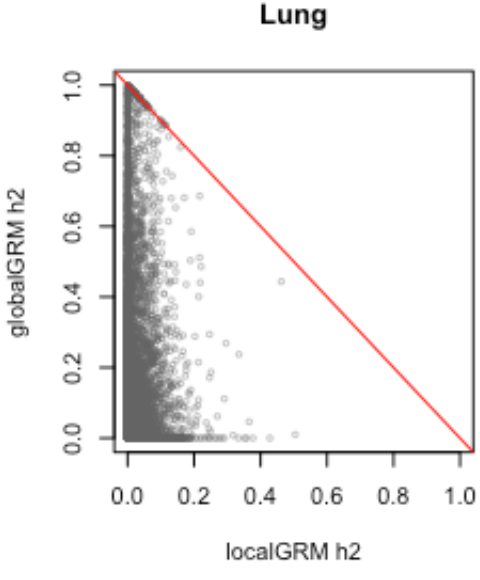


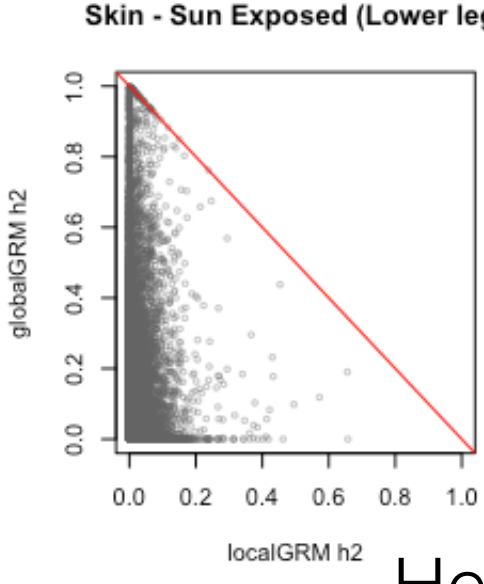


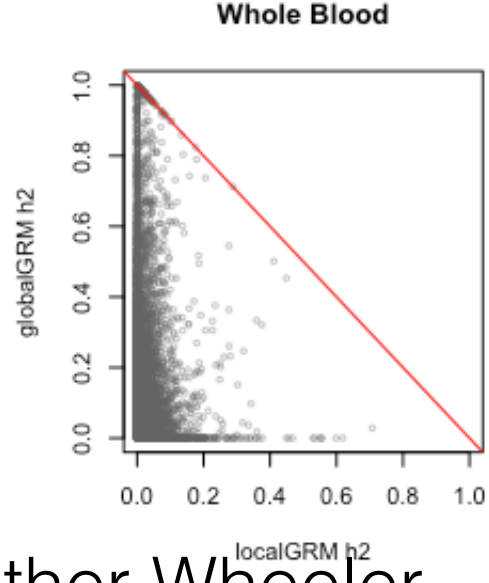












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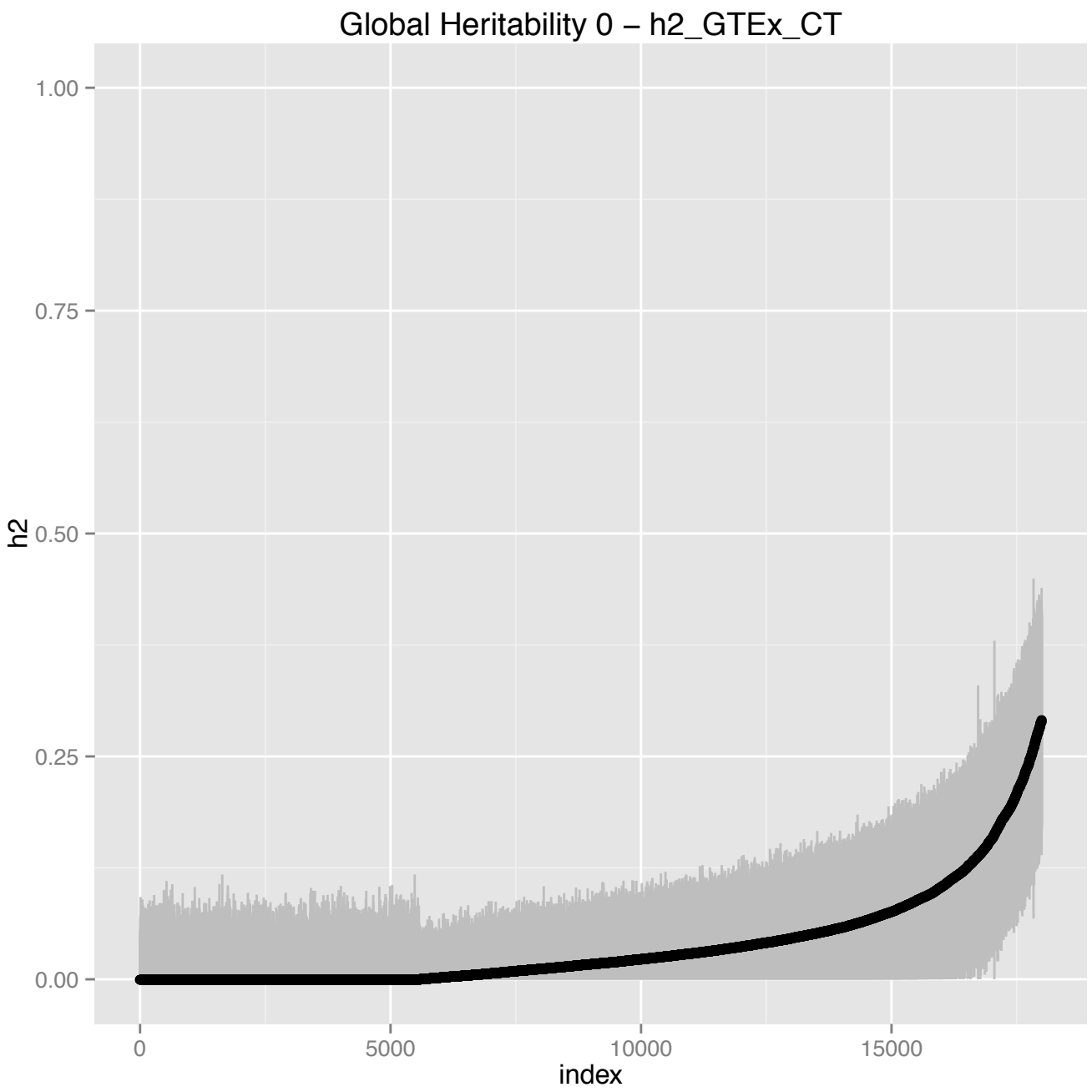
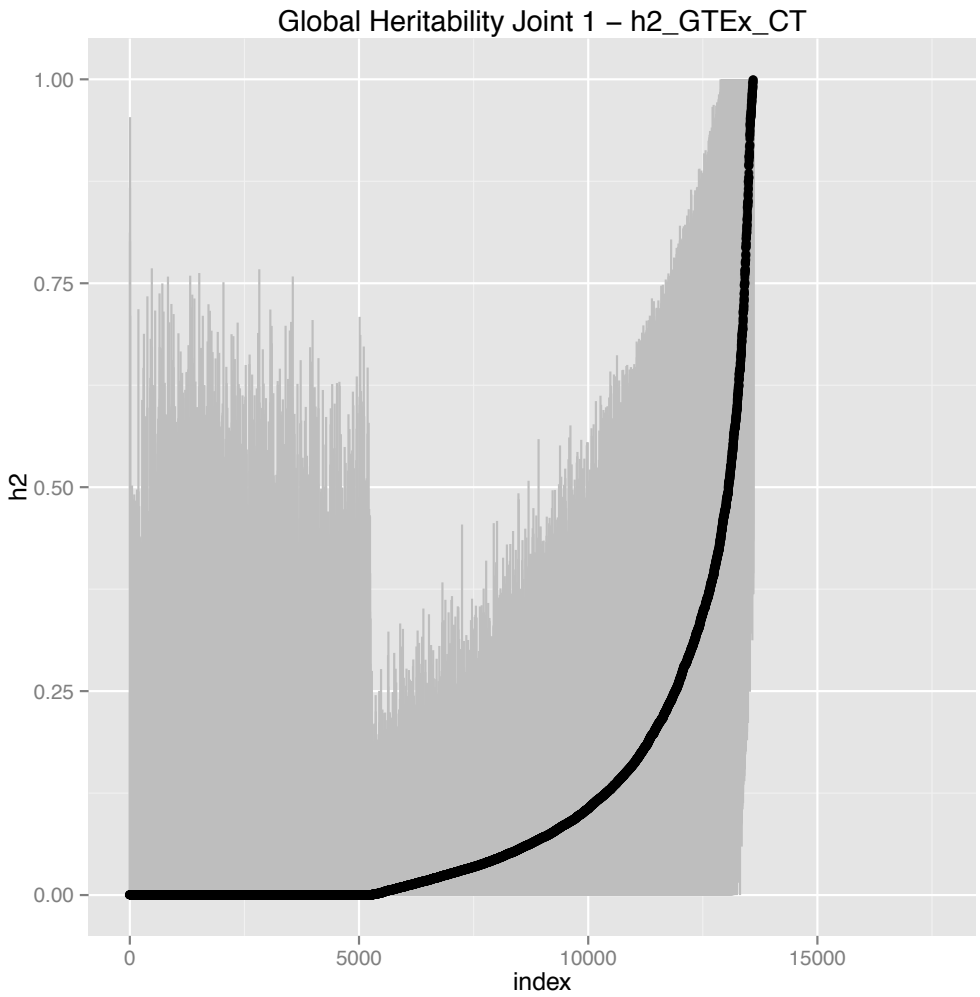
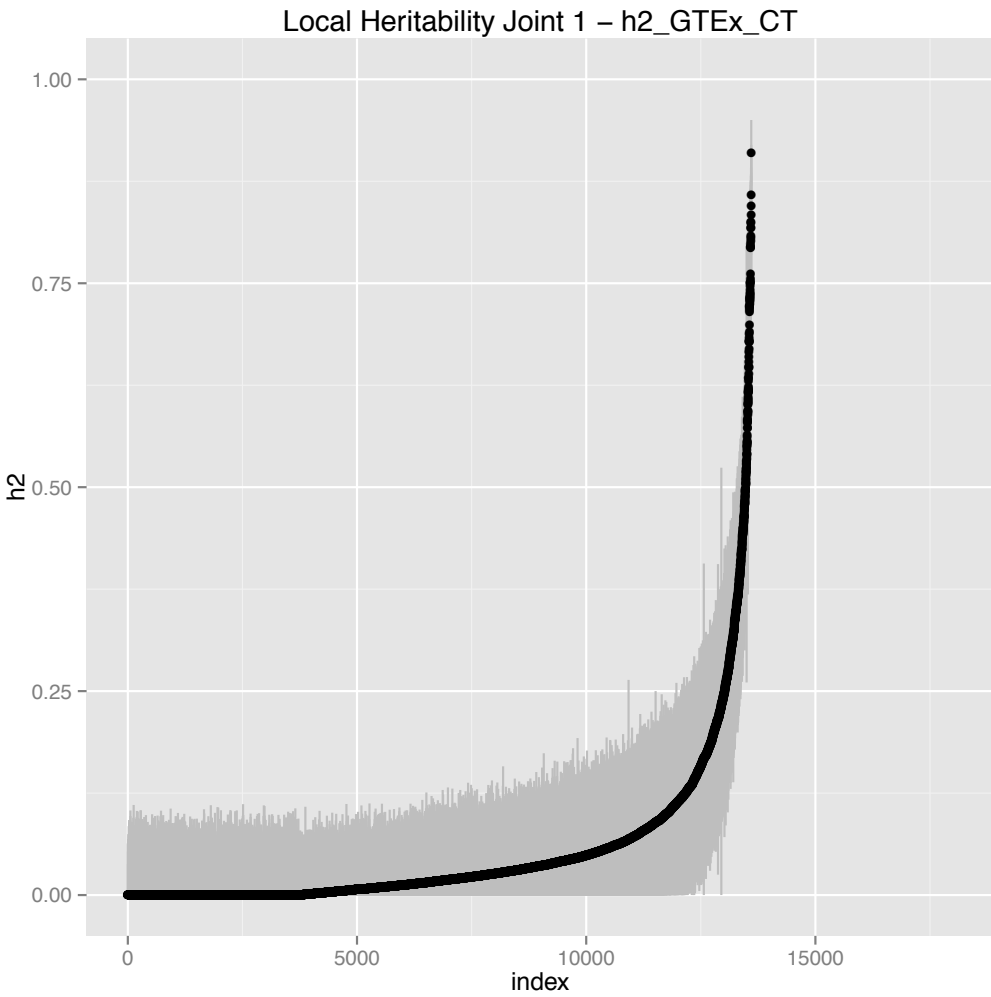
Heritability Cross Tissue Expression (Global GRM)



Cis/Trans Heritability of Cross Tissue Expression





Cross Tissue vs. Tissue Specific

```
> anova(lm(h2bloodcis ~ GTEx_WB_local1.h2 + GTEx_CT_local1.h2,
data=h2_all2))
```

Whole Blood

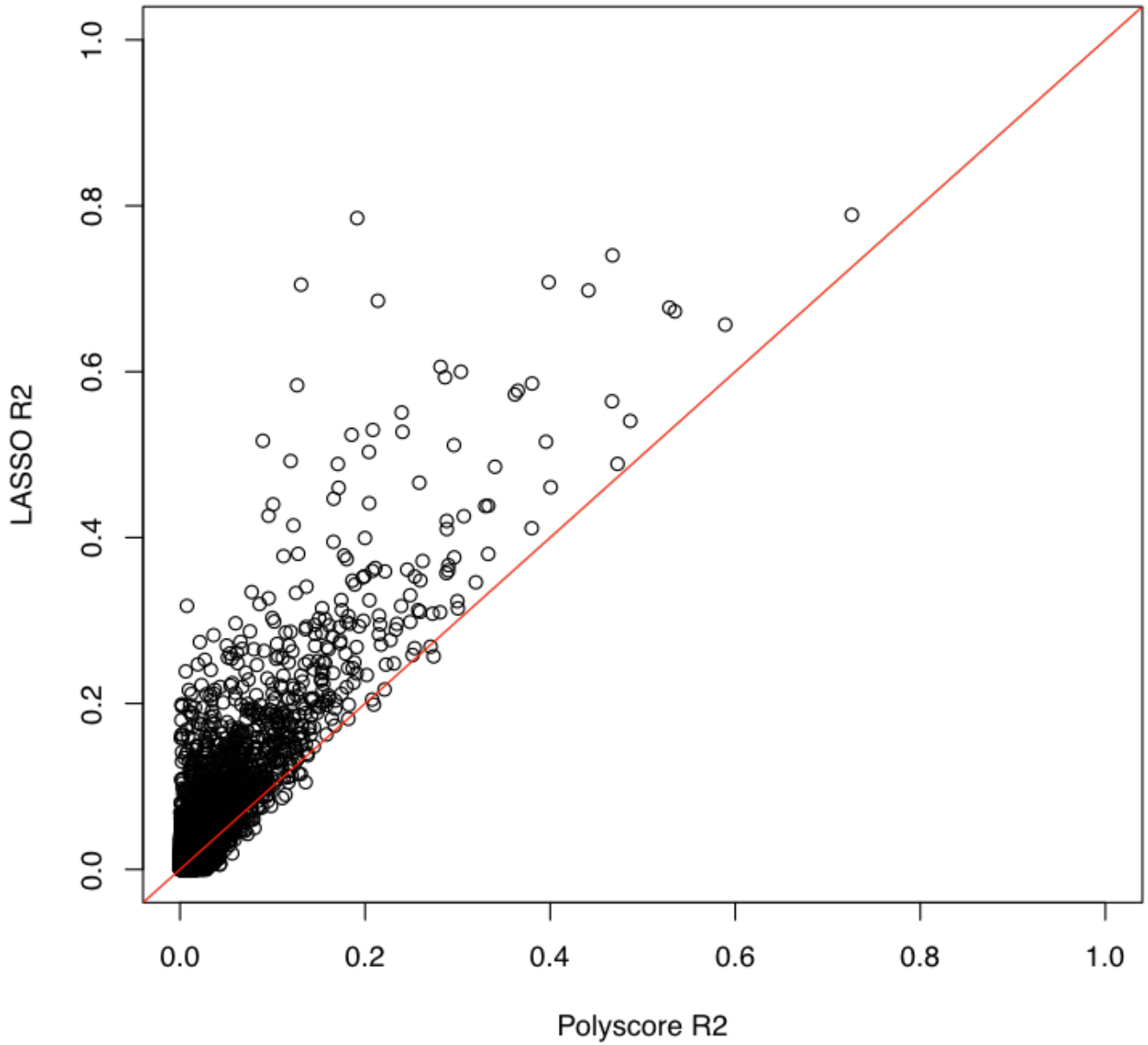
	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
GTEx_WB_local1.h2	**1**	**4.3**	**4.32**	**201.0**	**< 2e-16**	*******
GTEx_CT_local1.h2	**1**	**1.2**	**1.20**	**55.8**	**9.7e-14**	*******
Residuals	**4575**	**98.3**	**0.02**			

```
> anova(lm(h2adipcis ~ GTEx_adipose_local1.h2 + GTEx_CT_local1.h2,
data=h2_all2))
```

Adipose

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
GTEx_adipose_local1.h2	**1**	**1.1**	**1.137**	**44.0**	**3.7e-11**	*******
GTEx_CT_local1.h2	**1**	**2.6**	**2.577**	**99.7**	**< 2e-16**	*******
Residuals	**3951**	**102.2**	**0.026**			

Simple Polygenic Score vs. LASSO



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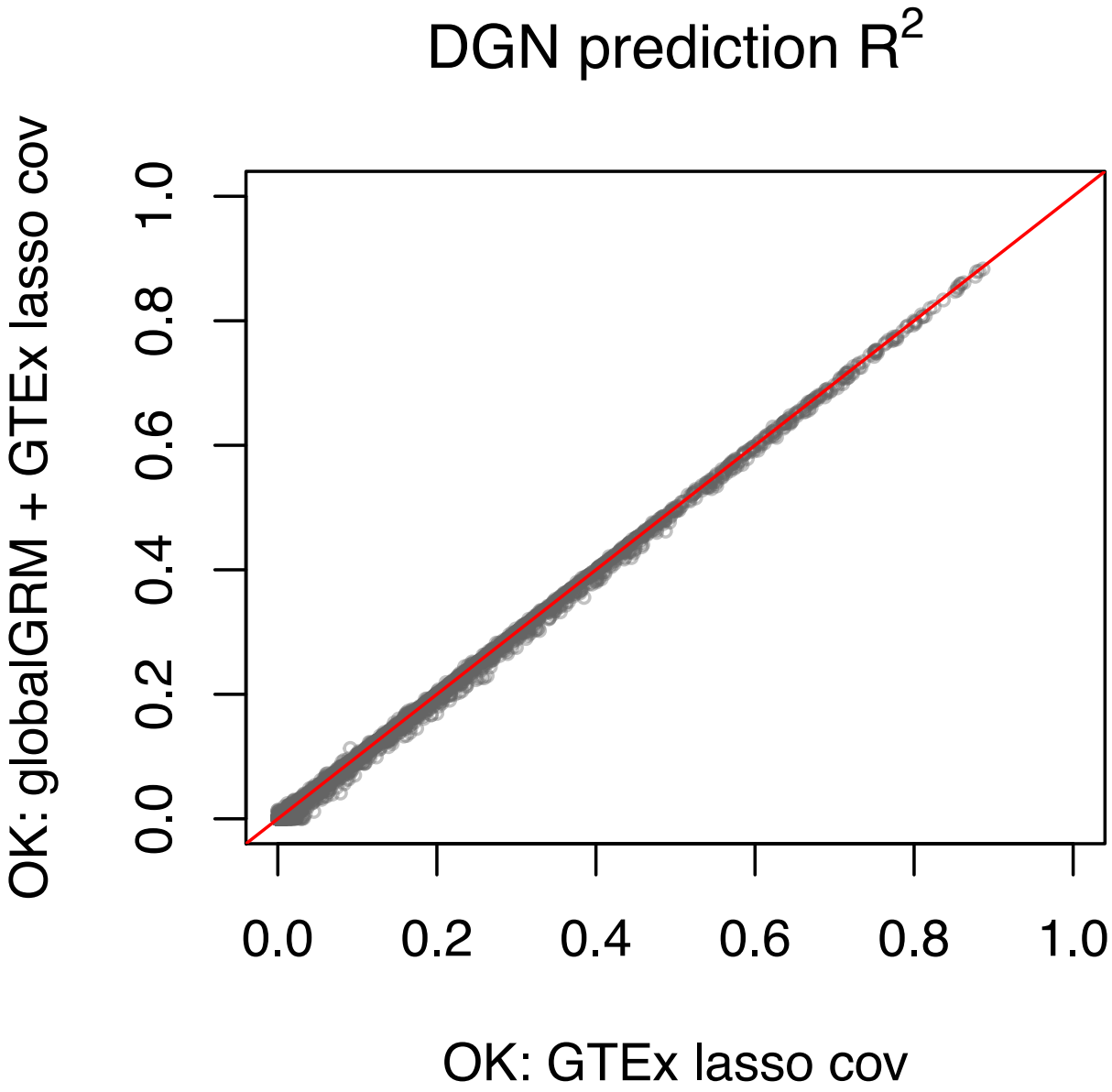
BLUP Does Not Improve Over LASSO



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Summary

- Computed local and global heritability of expression traits
- Local heritability can be well estimated with current sample sizes
- Global heritability is not well estimated
- Concordance with previous estimates of local and global heritability
- Orthogonal tissue decomposition
  - We investigate tissue specificity by decomposing at the trait level
- Expression traits seem substantially determined by sparse components

Acknowledgements

Thank you!

Contributors

- **Heather E. Wheeler did most of the computations**
- Nancy J. Cox
- Dan Nicolae
- GTEx Consortium

Data sources

- GEUVADIS
- DGN - Levis

Funding

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- Pharmacogenomics of Anticancer Agents PAAR UO1GM61393
- Pharmacogenomics Research Network (PGRN) Statistical Analysis Resource (P-STAR) U19 HL065962
- Conte Center grant P50MH094267

Orthogonal Tissue Decomposition

```
library(lme4)

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

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

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