Genetic architecture of transcriptome regulation and orthogonal tissue decompositon

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Abstract

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Introduction

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Results

Local genetic variation explains a large proportion of gene expression variance

We estimated the heritability of gene expression in whole blood from the Depression Genes and Networks (DGN) cohort (n=922) [1] using a mixed-effects model (see Materials and Methods) and calculated variances using restricted maximum likelihood as implemented in GCTA [2]. We fit a joint model with a local and a global genetic relationship matrix (GRM). The local GRM was derived from SNPs within 1 Mb of each gene and the global GRM was derived from SNPs that are located on non-gene chromosomes and are eQTLs in the Framingham Heart Study (FHS) cohort (n=5257, FDR < 0.05) [3]. The mean local h^2 was 0.130 and 54.6% of genes had a positive 95% confidence interval (CI), while the mean global h^2 was 0.076 and just 4.2% of genes had a positive CI (Fig 1). The maximum local h^2 was 0.93 with a standard error (SE) of 0.009 while the maximum global h^2 was 0.91 with a SE of 0.16. Similar results were observed for the 1194 genes with *trans*-eQTLs (FHS FDR < 0.05) when the global GRM was limited to known *trans*-eQTLs (Fig 2). That is,

the mean local h^2 was 0.133 and 61.3% of genes had a positive 95% confidence interval (CI), while the mean *trans* h^2 was just 0.021 and 4.2% of genes tested had a positive CI.

The effect of local genetic variation on gene expression is sparse rather than polygenic

Cross-tissue and tissue-specific gene expression by orthogonal tissue decomposition

Citations

The relationship was first described by Reference 4. However, there are also opinions that the relationship is spurious [5]. We used R for our calculations [6], and we used package `knitcitations` [7] to make the bibliography.

Discussion

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Methods

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Equations

The deterministic part of the model is defined by this **in-line equation** as $\mu_i = \beta_0 + \beta_1 x$, and the stochastic part by the **centered equation**:

$$\frac{1}{\sqrt{2\pi}\sigma} e^{-(x-\mu_i)^2/(2\sigma^2)}$$

Tables

```
## Warning: package 'knitr' was built under R version 3.1.3
```

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	0.02	0.10	0.26	0.8
x	2.01	0.09	21.46	0.0

Table 1: This is a GLM summary table.

Figures

Supplemental Figures

References

1. Battle A, Mostafavi S, Zhu X, Potash JB, Weissman MM, McCormick C, et al. Characterizing the genetic basis of transcriptome diversity through RNA-sequencing of 922 individuals. Genome Research. Cold Spring Harbor Laboratory Press; 2013;24: 14–24. doi:10.1101/gr.155192.113

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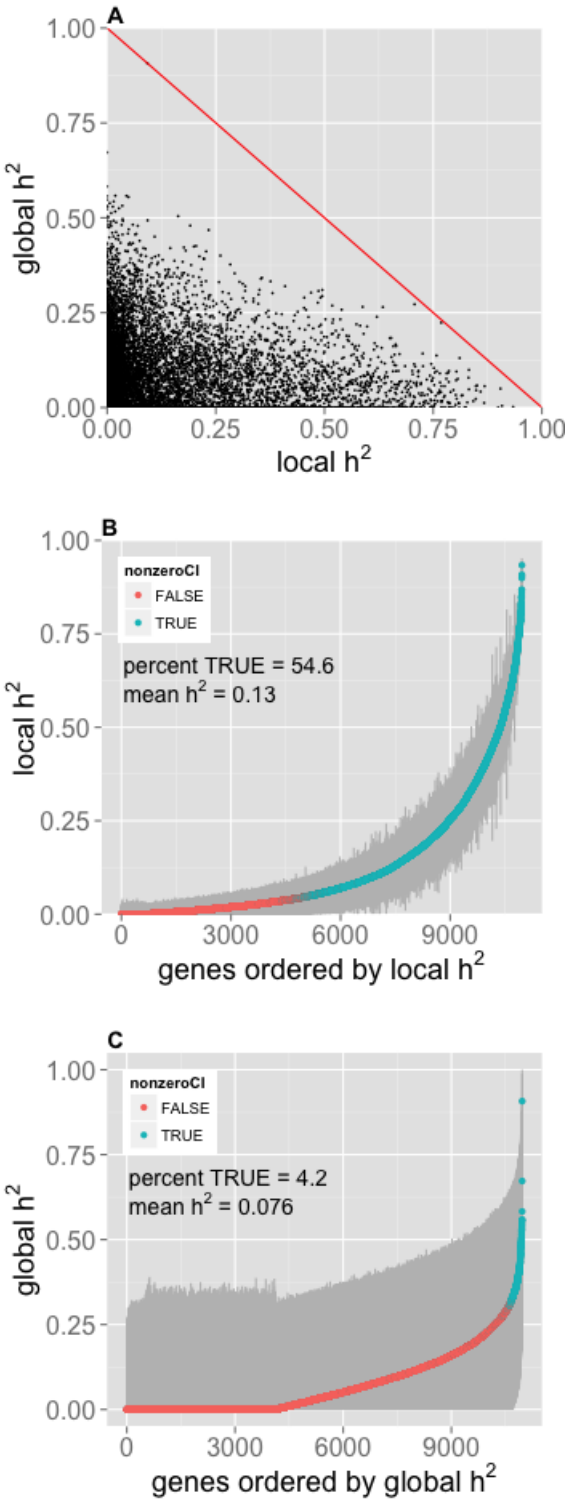

Figure 1: DGN whole blood expression joint heritability (h^2). Local (SNPs within 1 Mb of each gene) and global (SNPs that are eQTLs in the Framingham Heart Study on other chromosomes [FDR < 0.05]) h^2 for gene expression were jointly estimated. (**A**) Global h^2 compared to local h^2 per gene. (**B**) Local and (**C**) global gene expression h^2 estimates ordered by increasing h^2. The 95% confidence interval (CI) of each h^2 estimate is in gray and genes with a lower bound greater than zero are in blue.

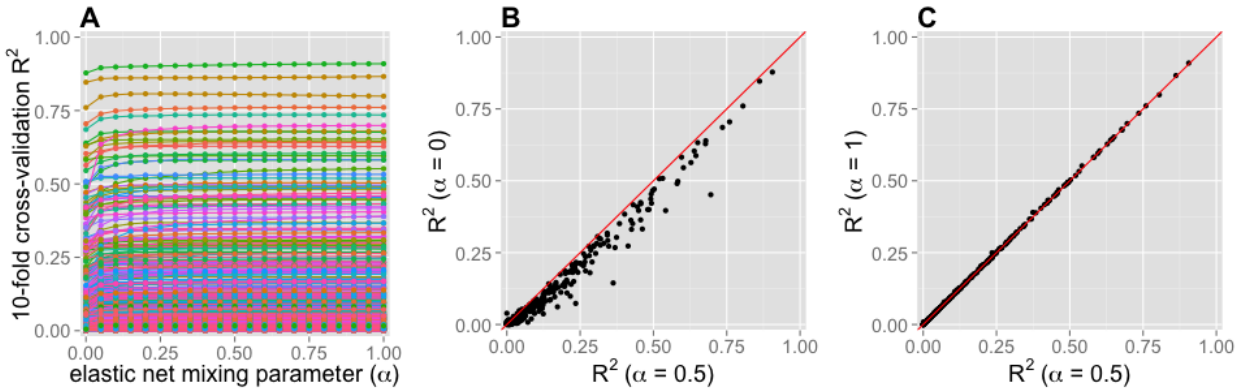

Figure 2: Cross-validated predictive performance across the elastic net. (**A**) 10-fold cross-validated R^2 of predicted vs. observed expression in DGN whole blood compared to a range of elastic net mixing parameters (α) for 341 genes on chromosome 22. (**B**) Predictive R^2 for $\alpha = 0$ (ridge regression) compared to $\alpha = 0.5$. (**C**) Predictive R^2 for $\alpha = 1$ (lasso) compared to $\alpha = 0.5$.

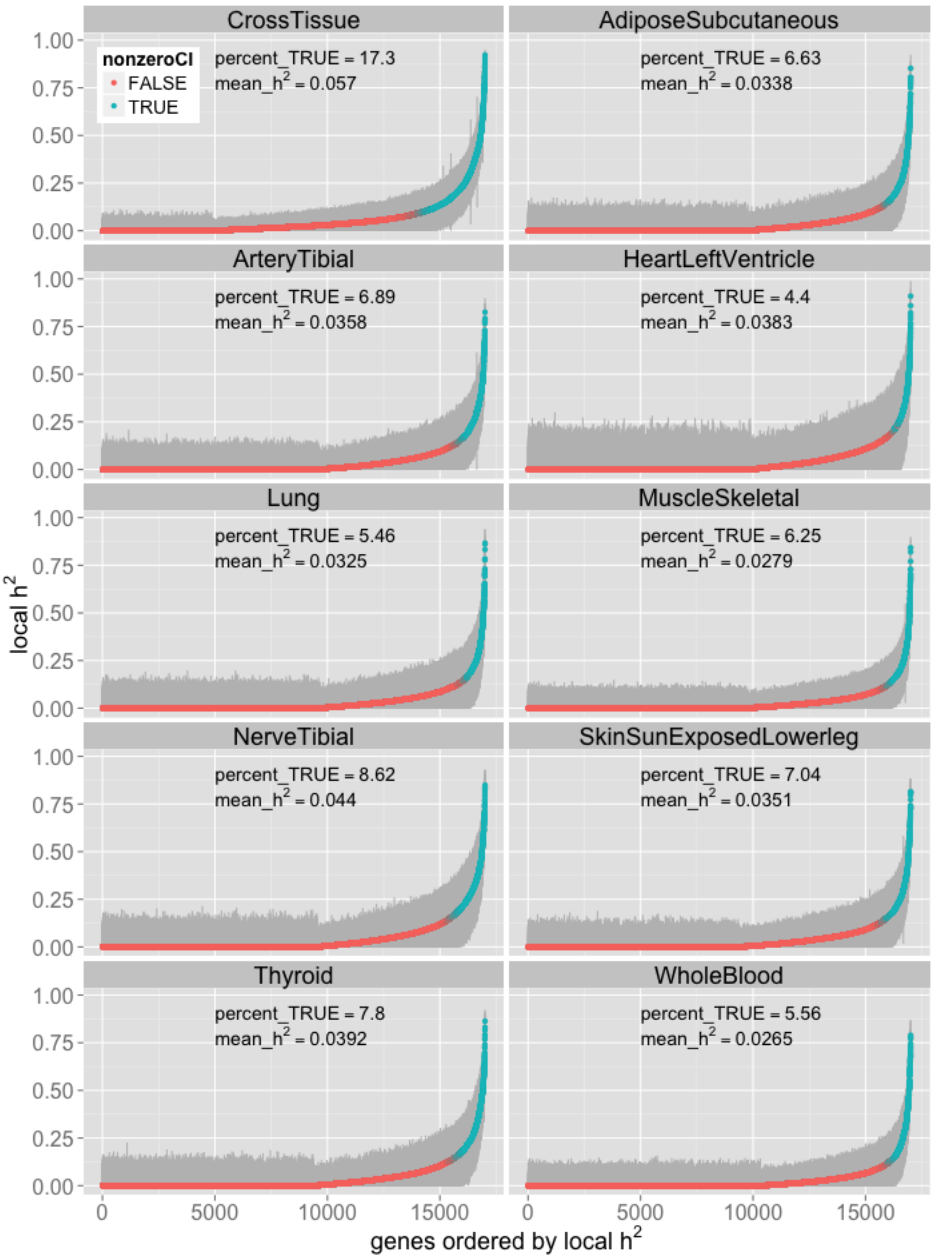

Figure 3: Cross-tissue heritability (h^2) compared to tissue-wide h^2. Cross-tissue local h^2 is estimated using the cross-tissue component (random effects) of the mixed effects model for gene expression and SNPs within 1 Mb of each gene. Tissue-wide local h^2 is estimated using the measured gene expression for each respective tissue and SNPs within 1 Mb of each gene.

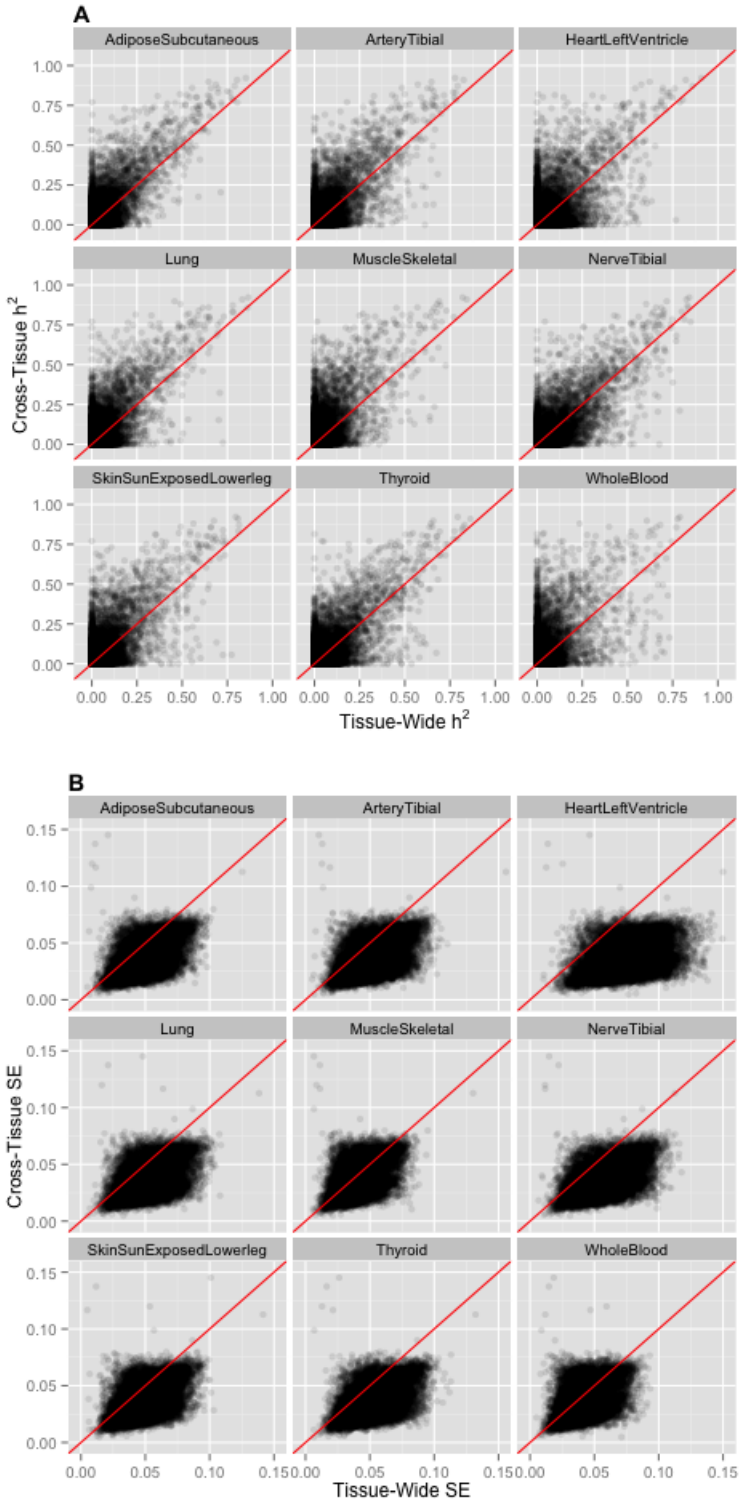

Figure 4: Cross-tissue and tissue-wide comparison of heritability (h^2, **A**) and standard error (SE, **B**). Cross-tissue local h^2 is estimated using the cross-tissue component (random effects) of the mixed effects model for gene expression and SNPs within 1 Mb of each gene. Tissue-wide local h^2 is estimated using the measured gene expression for each respective tissue and SNPs within 1 Mb of each gene.

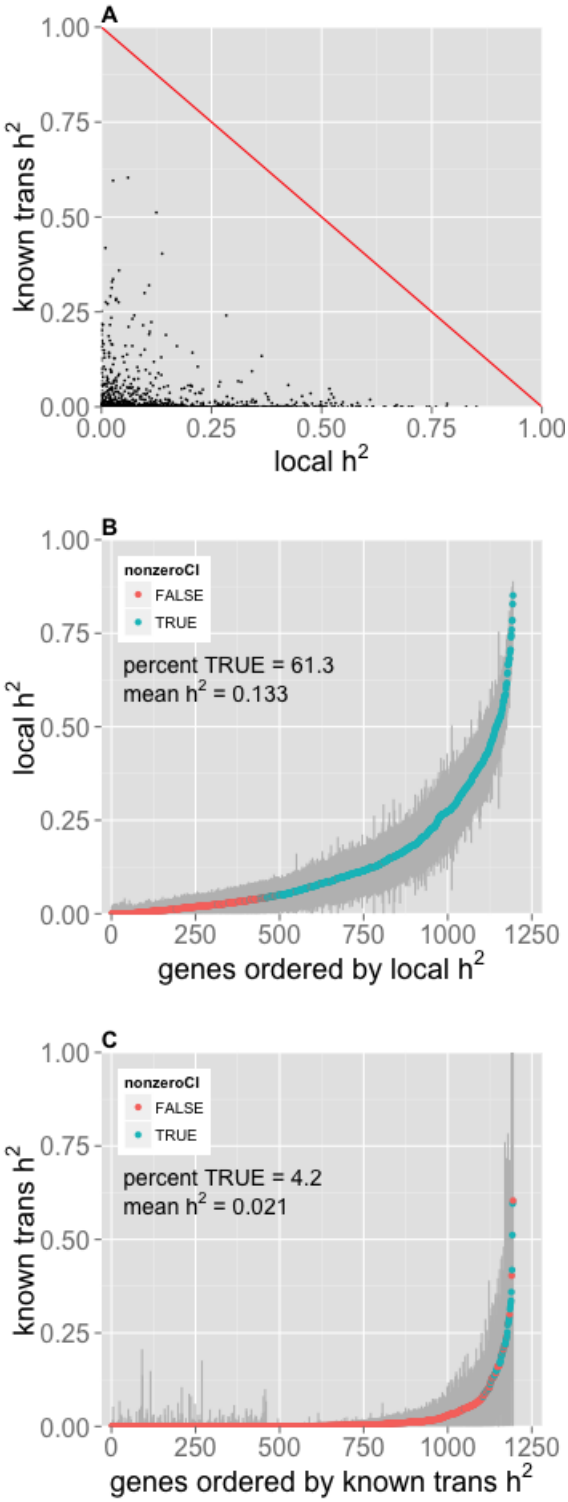

Figure 5: DGN whole blood expression joint heritability (h^2) with known trans-eQTLs. Local (SNPs within 1 Mb of each gene) and known trans (SNPs that are trans-eQTLs in the Framingham Heart Study for each gene [FDR < 0.05]) h^2 for gene expression were jointly estimated. (**A**) Known trans h^2 compared to local h^2 per gene. (**B**) Local and (**C**) known trans gene expression h^2 estimates ordered by increasing h^2. The 95% confidence interval (CI) of each h^2 estimate is in gray and genes with a lower bound greater than zero are in blue.

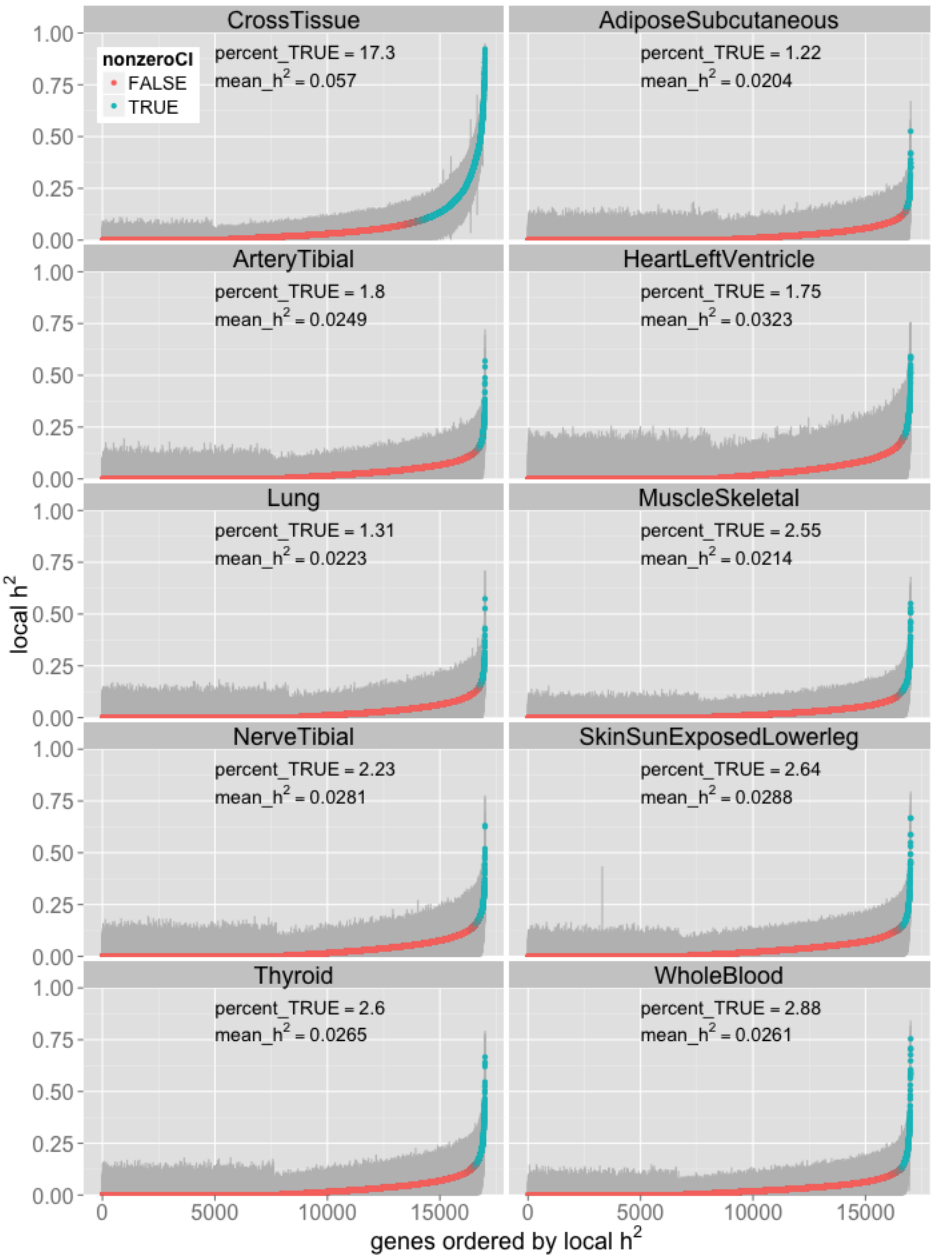

Figure 6: Cross-tissue heritability (h^2) compared to tissue-specific h^2. Cross-tissue local h^2 is estimated using the cross-tissue component (random effects) of the mixed effects model for gene expression and SNPs within 1 Mb of each gene. Tissue-specifc local h^2 is estimated using the tissue-specific component (residuals) of the mixed effects model for gene expression for each respective tissue and SNPs within 1 Mb of each gene.

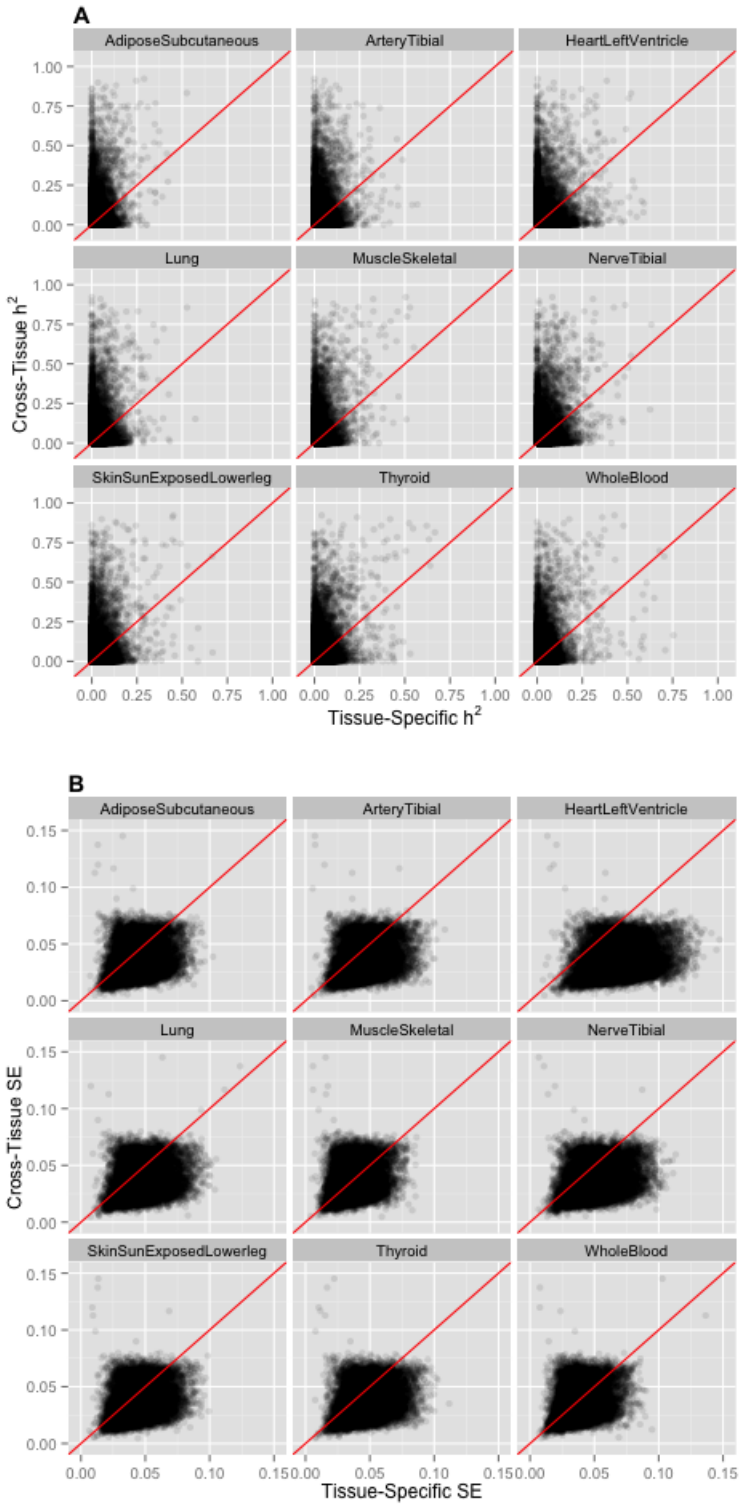

Figure 7: Cross-tissue and tissue-specific comparison of heritability (h^2, **A**) and standard error (SE, **B**) estimation. Cross-tissue local h^2 is estimated using the cross-tissue component (random effects) of the mixed effects model for gene expression and SNPs within 1 Mb of each gene. Tissue-specifc local h^2 is estimated using the tissue-specific component (residuals) of the mixed effects model for gene expression for each respective tissue and SNPs within 1 Mb of each gene.