Leveraging GTEx Data to Dissect Existing GWAS

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GWAS subgroup call
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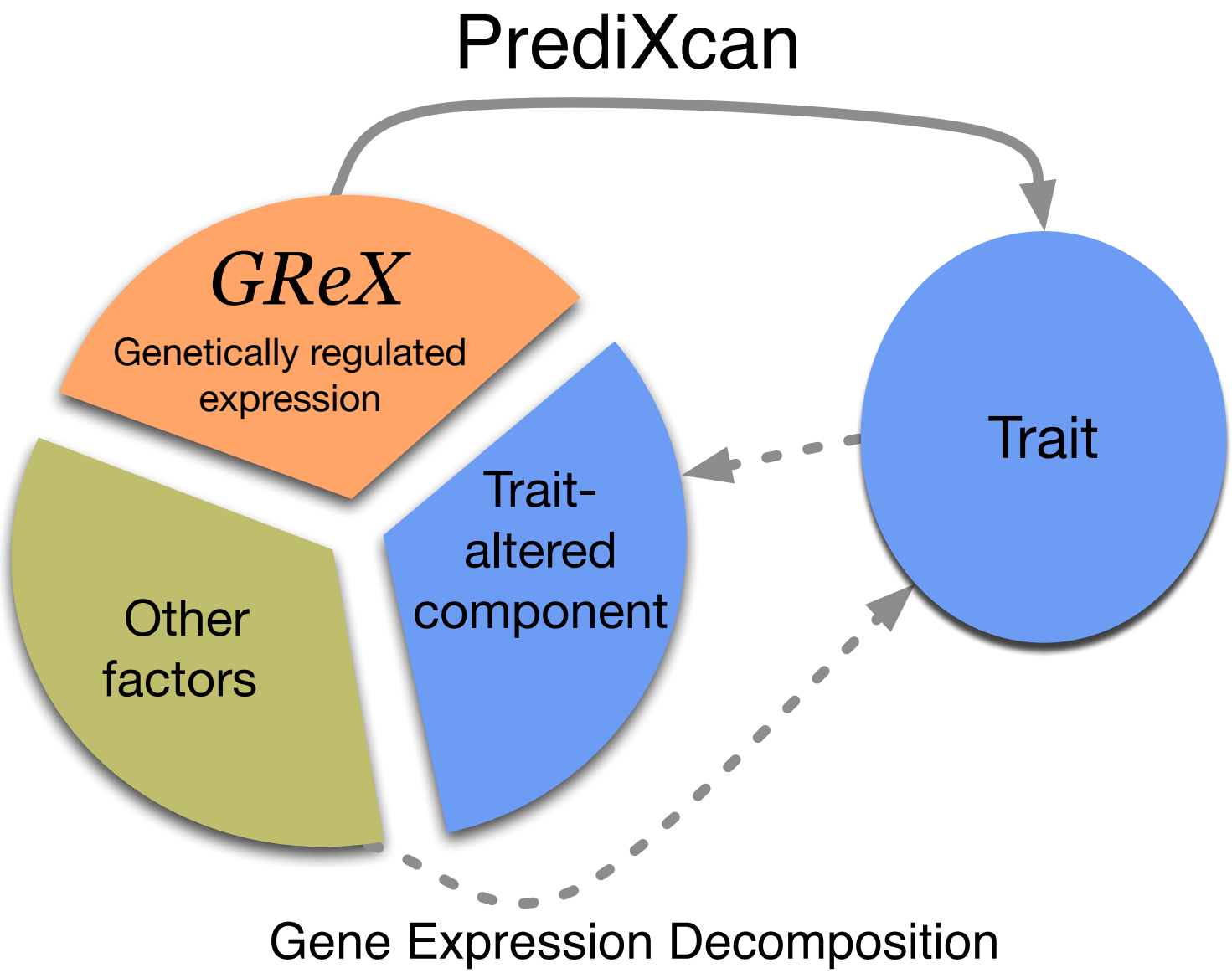
Leveraging GTEx and Existing GWAS

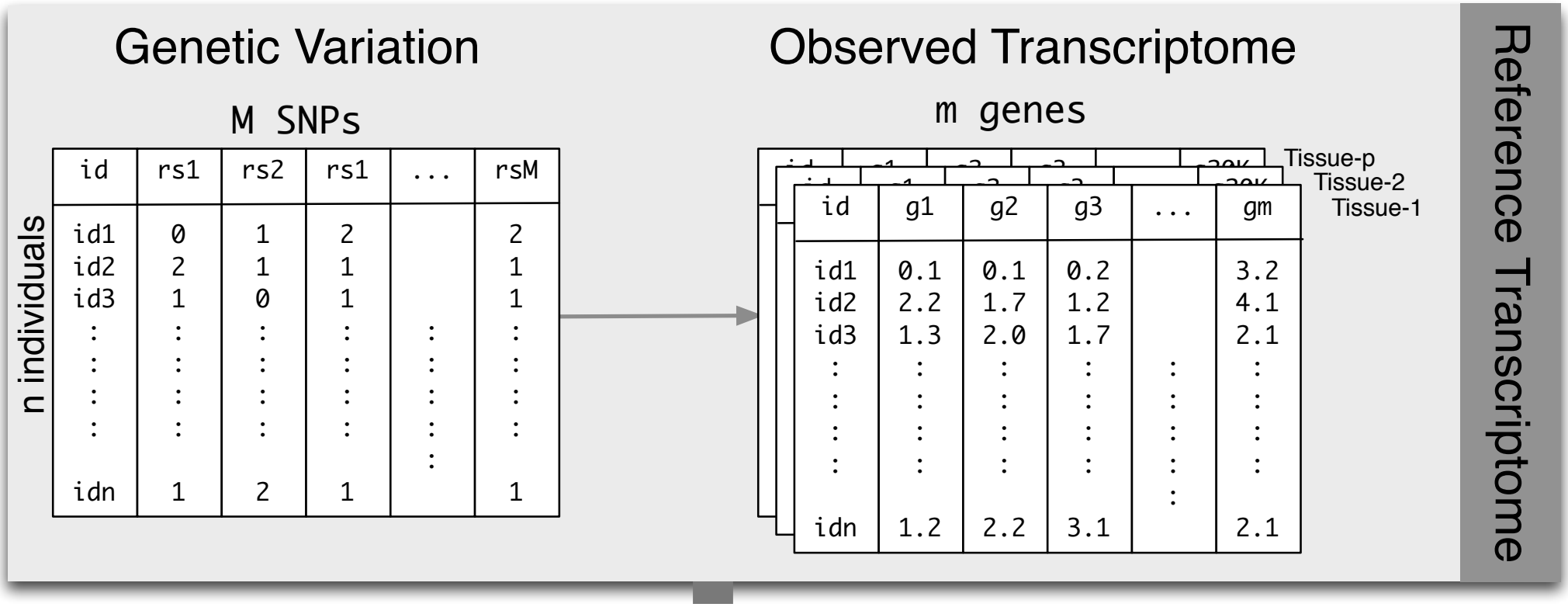
- PrediXcan
  - Gene-based test that tests tissue-specific mediating effects of gene expression traits on phenotypes
  - Imputation quality improvement with option 1 data
  - Application to drug-induced peripheral neuropathy data

- Regulability
  - Heritability of the regulome
  - Application to WTCCC

Mechanisms Tested by PrediXcan

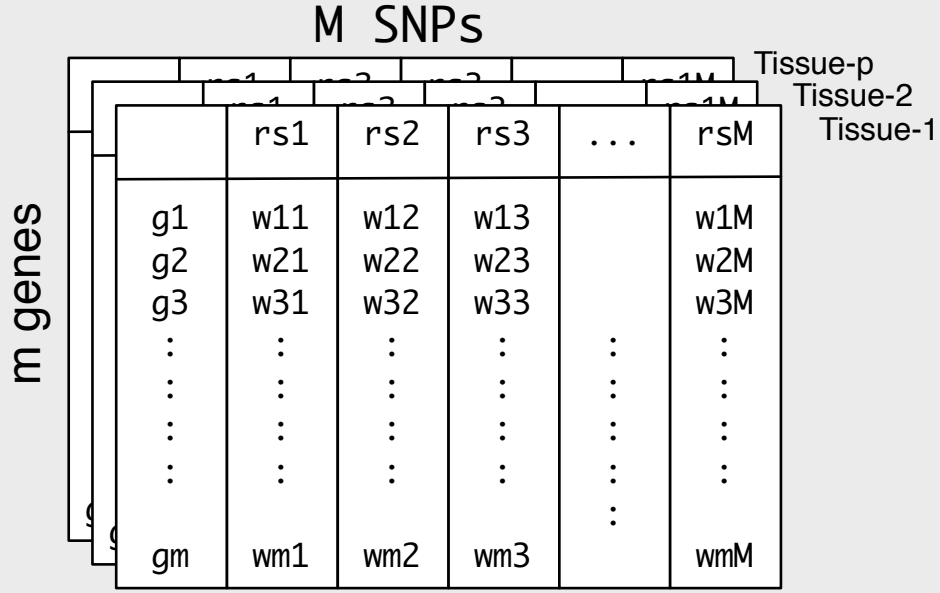


PrediXcan uses Reference Transcriptome



PredictDB: Public Database of Weights for GReX

PredictDB: Database of Prediction Models

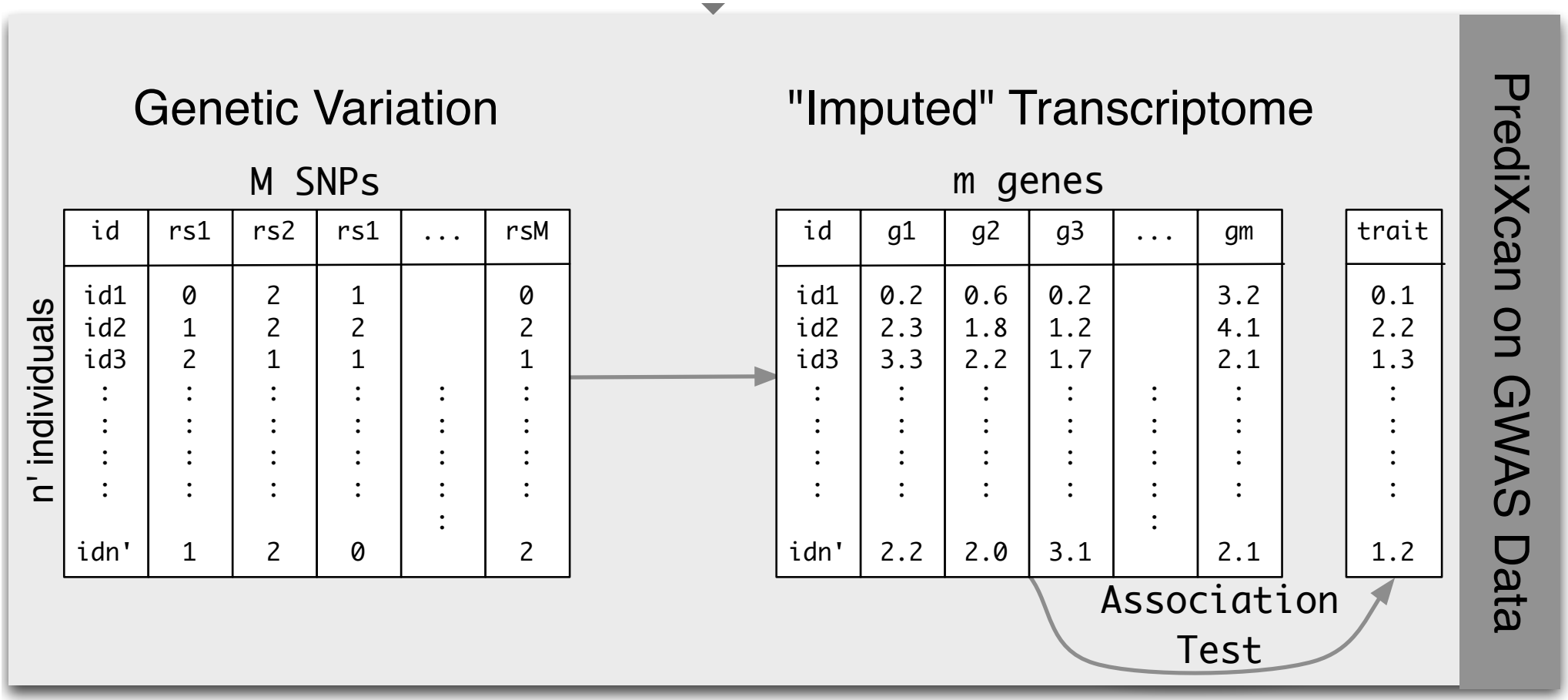


Additive model of gene expression trait trained in reference transcriptome datasets

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

Weights stored in PredictDB

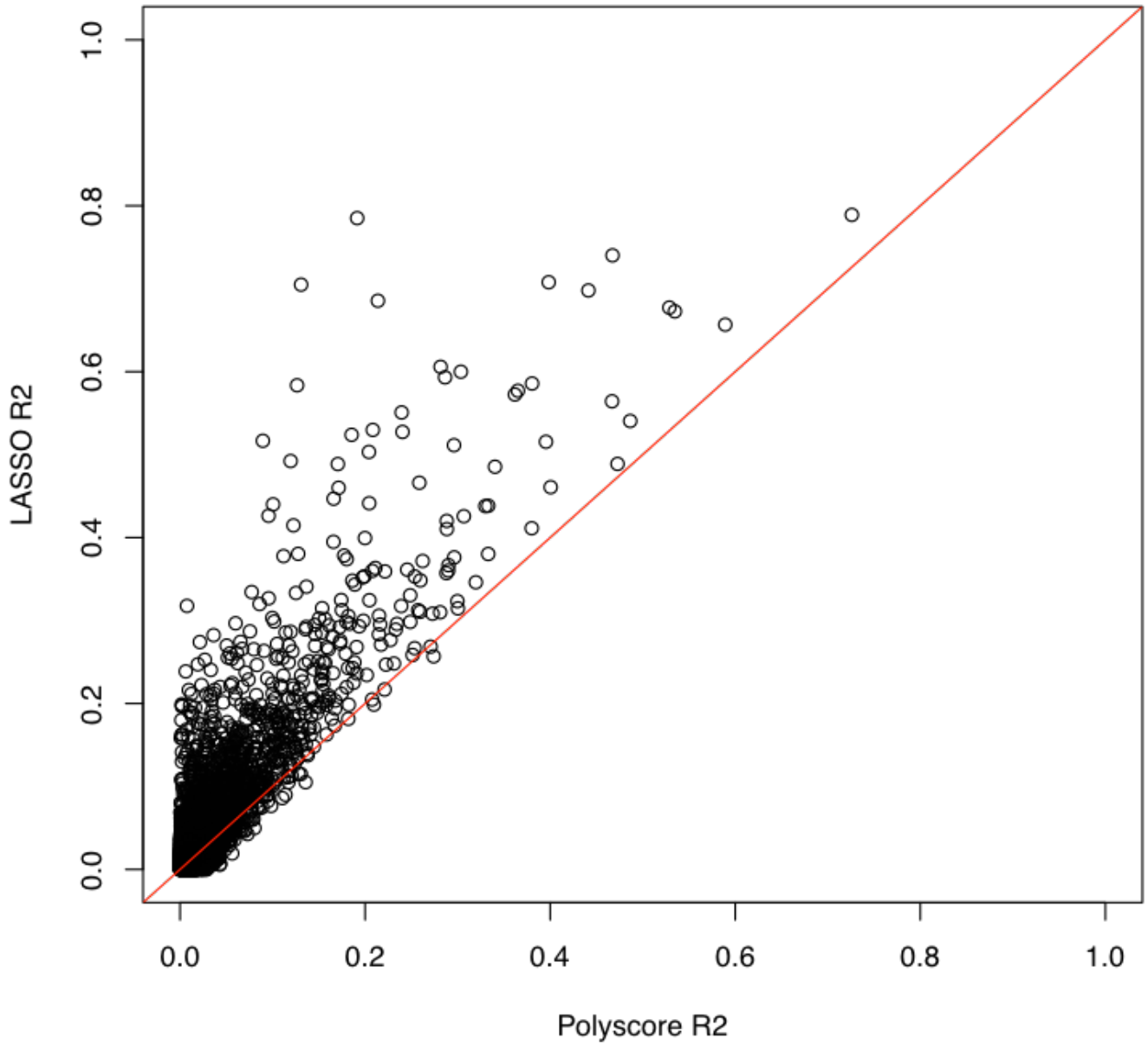
PrediXcan Imputes Transcriptome & Tests Assoc.



PrediXcan: Mechanism-driven Gene-Based Test

- Directly tests the molecular mechanism through which genetic variants affect phenotype
- Genes more attractive than genetic variants
  - A lot is know about their function
  - Follow up experiments can be easily devised
  - Reduced multiple testing burden
- Direction of effects
  - Positive effects: down regulation is therapeutic option
  - Negative effects: more likely to harbor deleterious rare variants
- No reverse causality issues
- Can be systematically applied to existing GWAS studies
- Tissue-specificity can be inferred

Simple Polygenic Score vs. LASSO

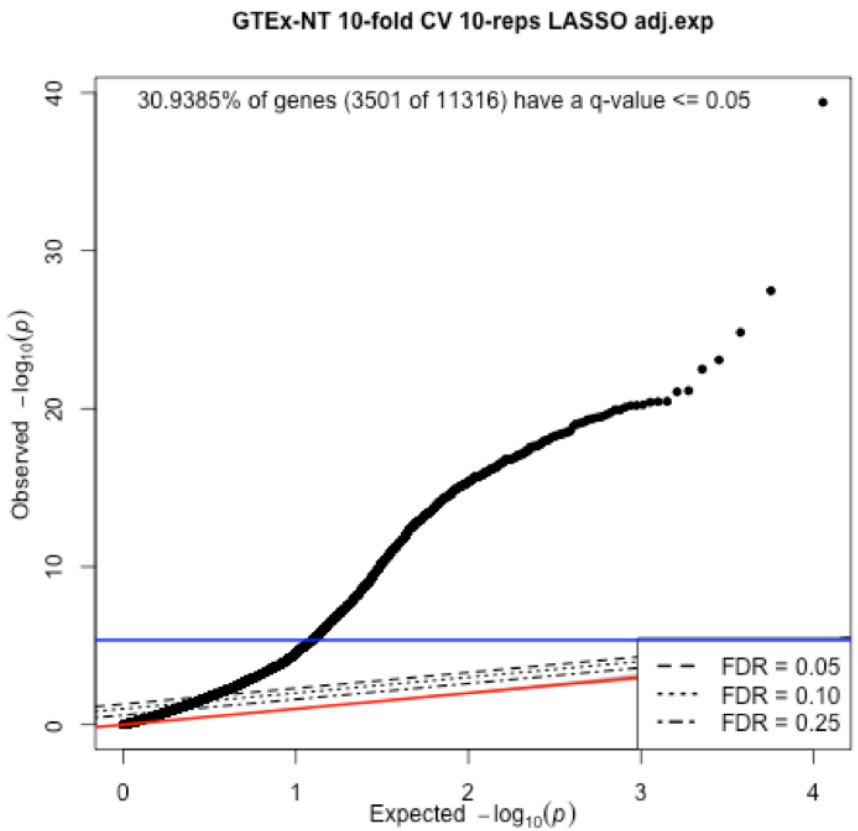


GEUVADIS

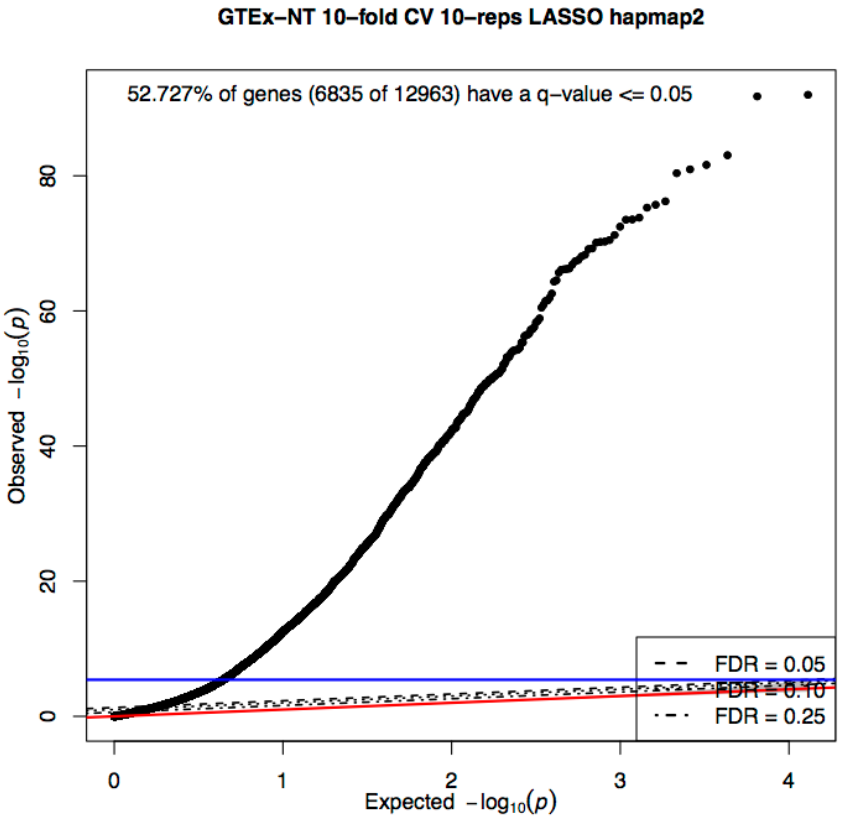
Heather Wheeler

Imputation QualityTibial Nerve

N=97
all (3.5M) SNPs
(pilot data)



N=256
HapMap2 unamb. 2.6M SNPs
(2014-06-13 data)



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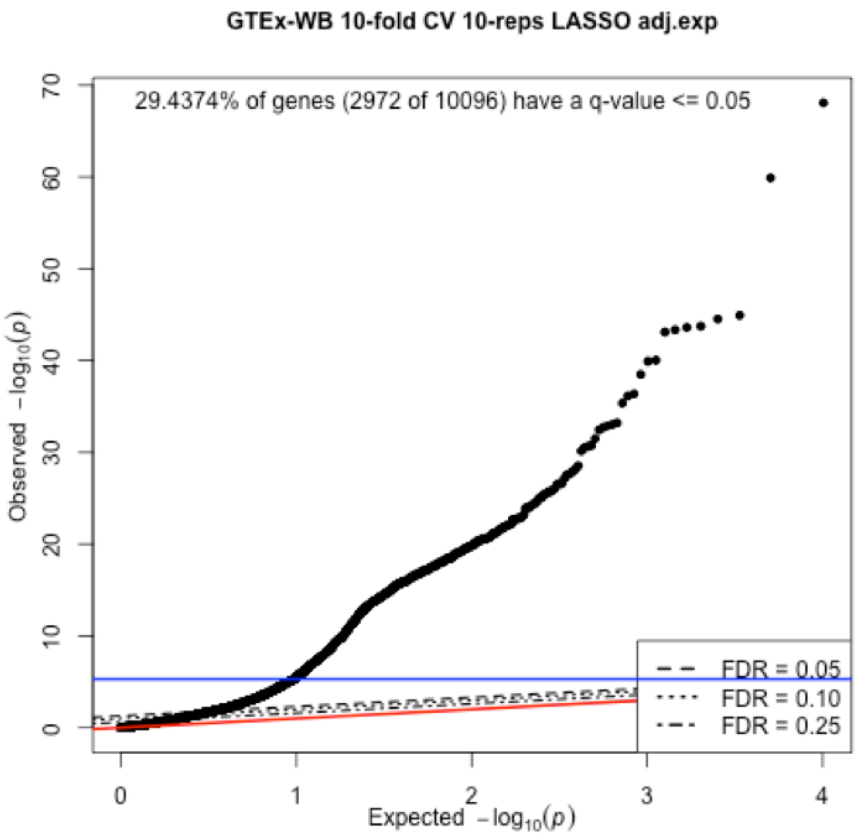
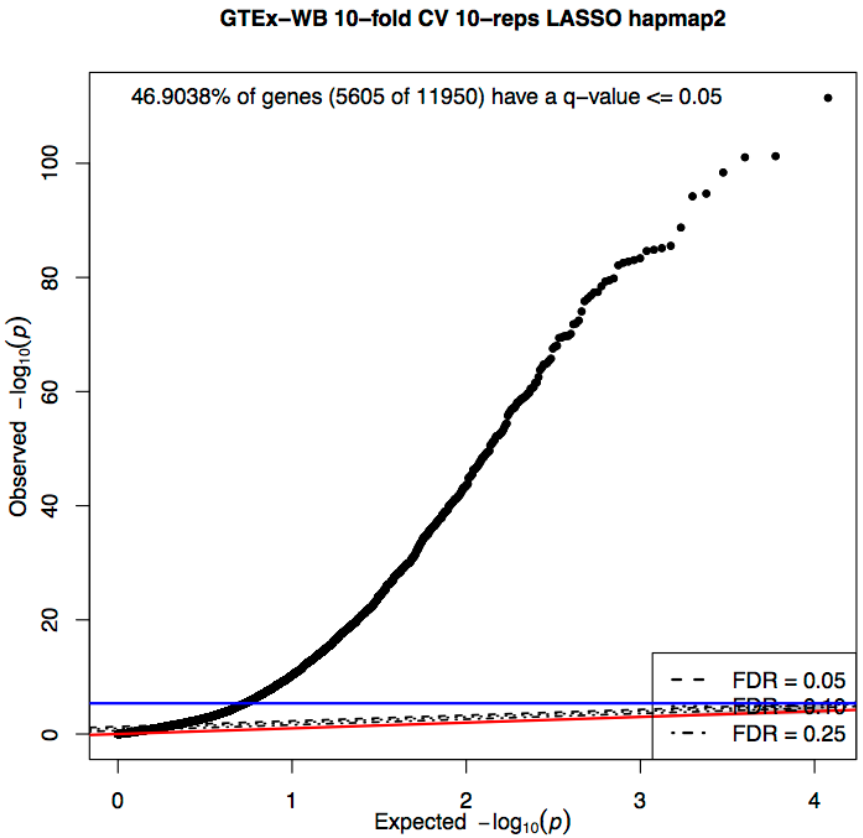
Imputation Quality Whole Blood

N=169
all (3.5M) SNPs
(pilot data)



N=339
HapMap2 unamb. 2.6M SNPs
(2014-06-13 data)



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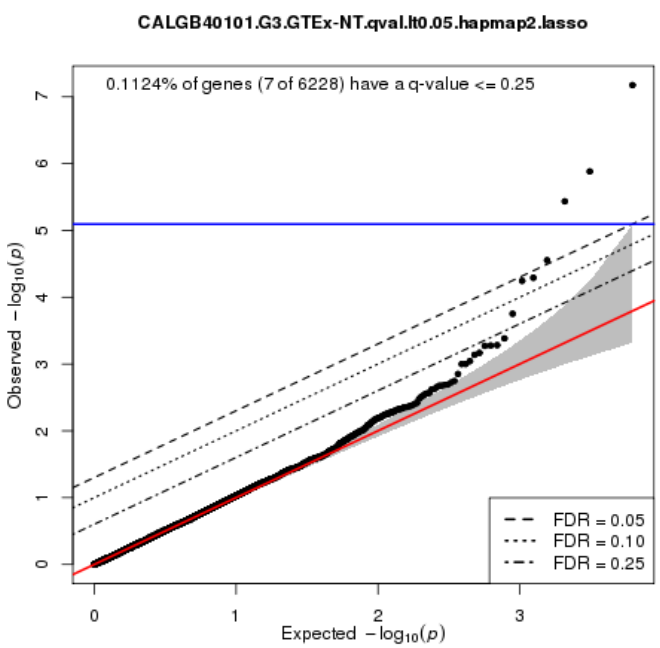
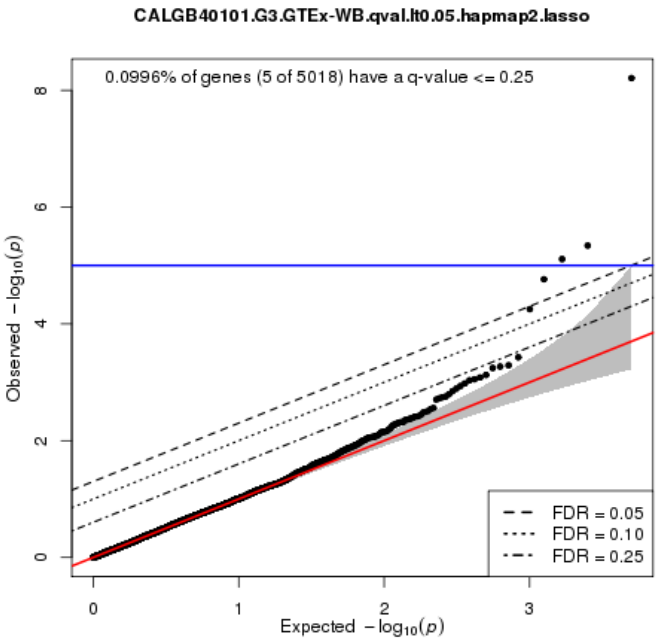
Drug Induced Peripheral Neuropathy

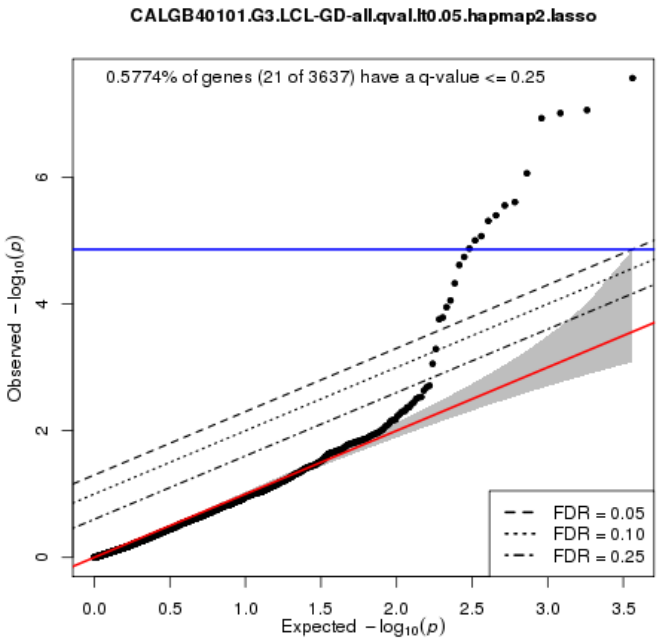
Tibial Nerve



Whole Blood



LCLs



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Chip Heritability & Regulability

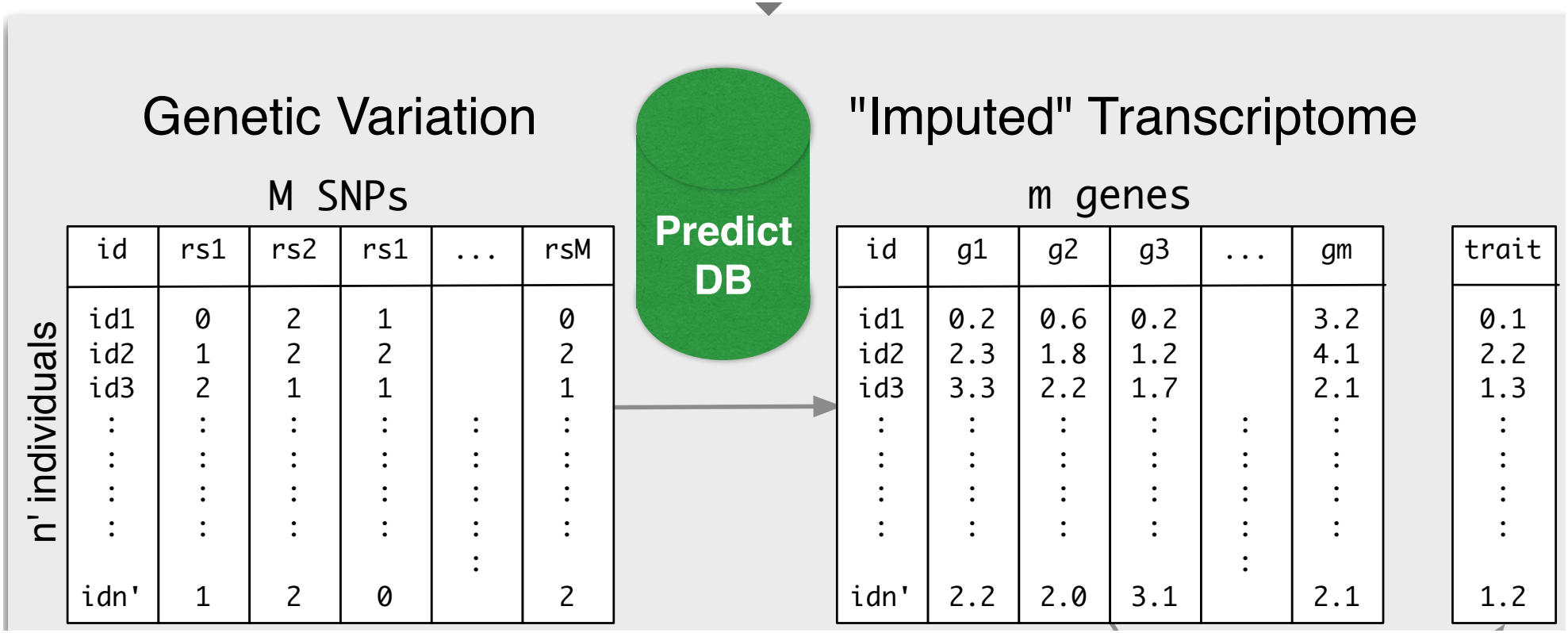
- Chip heritability: proportion of trait variability explained by genotyped variants

$$Y_i = \sum_k c_k X_{ik} + \epsilon_i$$

- Regulability: proportion of trait variability explained by the genetically predicted transcriptome —regulome

$$Y_i = \sum_g \gamma_g T_{ig} + \eta_i$$

Regulability Calculation



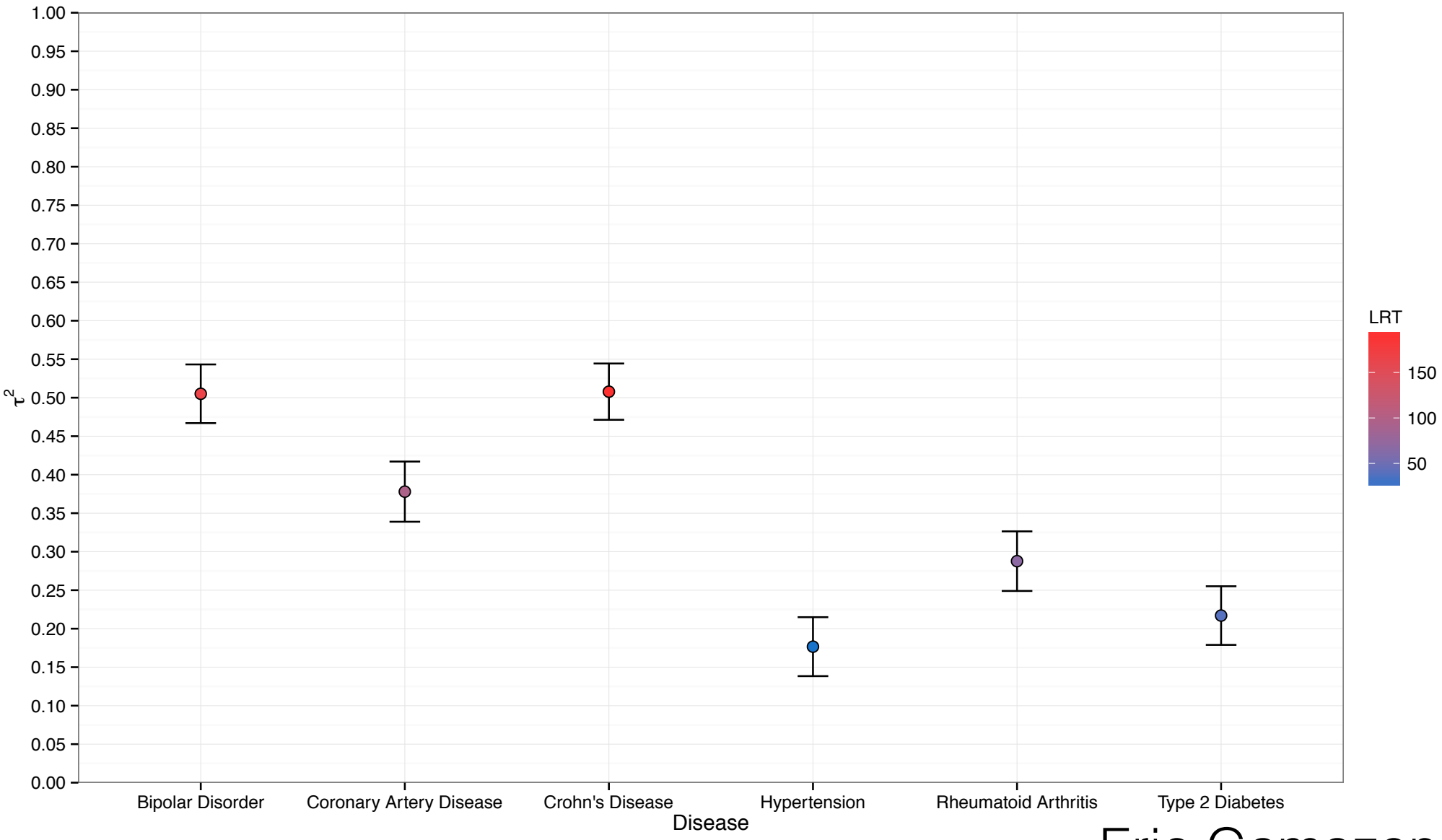
id	rs1	rs2	rs1	...	rsM
id1	0	2	1		0
id2	1	2	2		2
id3	2	1	1		1
:	:	:	:	:	:
:	:	:	:	:	:
:	:	:	:	:	:
:	:	:	:	:	:
idn'	1	2	0		2

id	g1	g2	g3	...	gm	trait
id1	0.2	0.6	0.2		3.2	0.1
id2	2.3	1.8	1.2		4.1	2.2
id3	3.3	2.2	1.7		2.1	1.3
:	:	:	:	:	:	:
:	:	:	:	:	:	:
:	:	:	:	:	:	:
:	:	:	:	:	:	:
idn'	2.2	2.0	3.1		2.1	1.2

- “Impute” transcriptome
- Compute covariance matrix of imputed transcriptome
- Compute REML estimate of variance

$$Y_i = \sum_g \gamma_g T_{ig} + \eta_i$$

WTCCC - Regulability Estimates using Whole Blood



Eric Gamazon

Acknowledgements

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- WTCCC
- GEUVADIS

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