

Regulability (Heritability of the Regulome)

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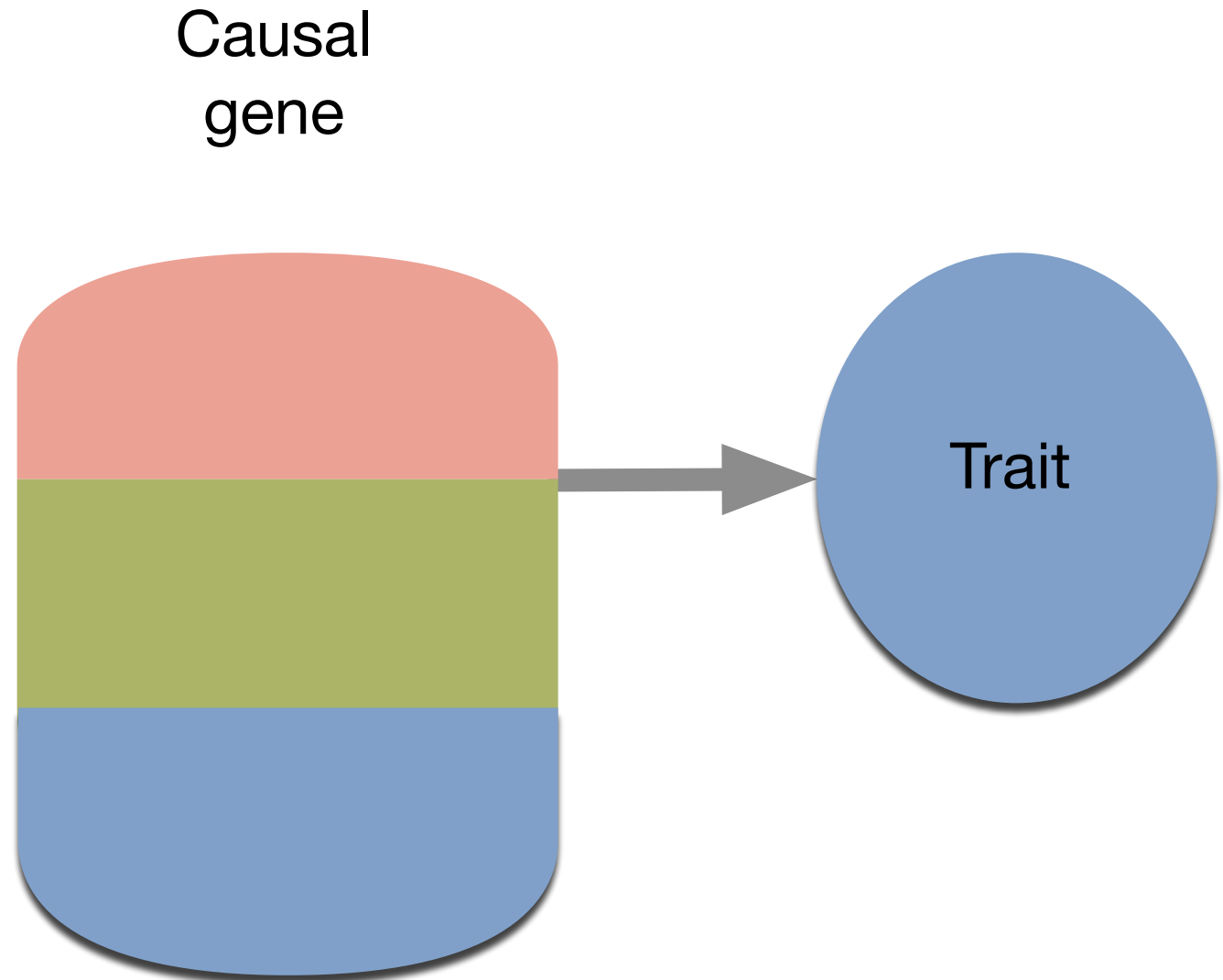
GTEx Jamboree

October 17, 2014

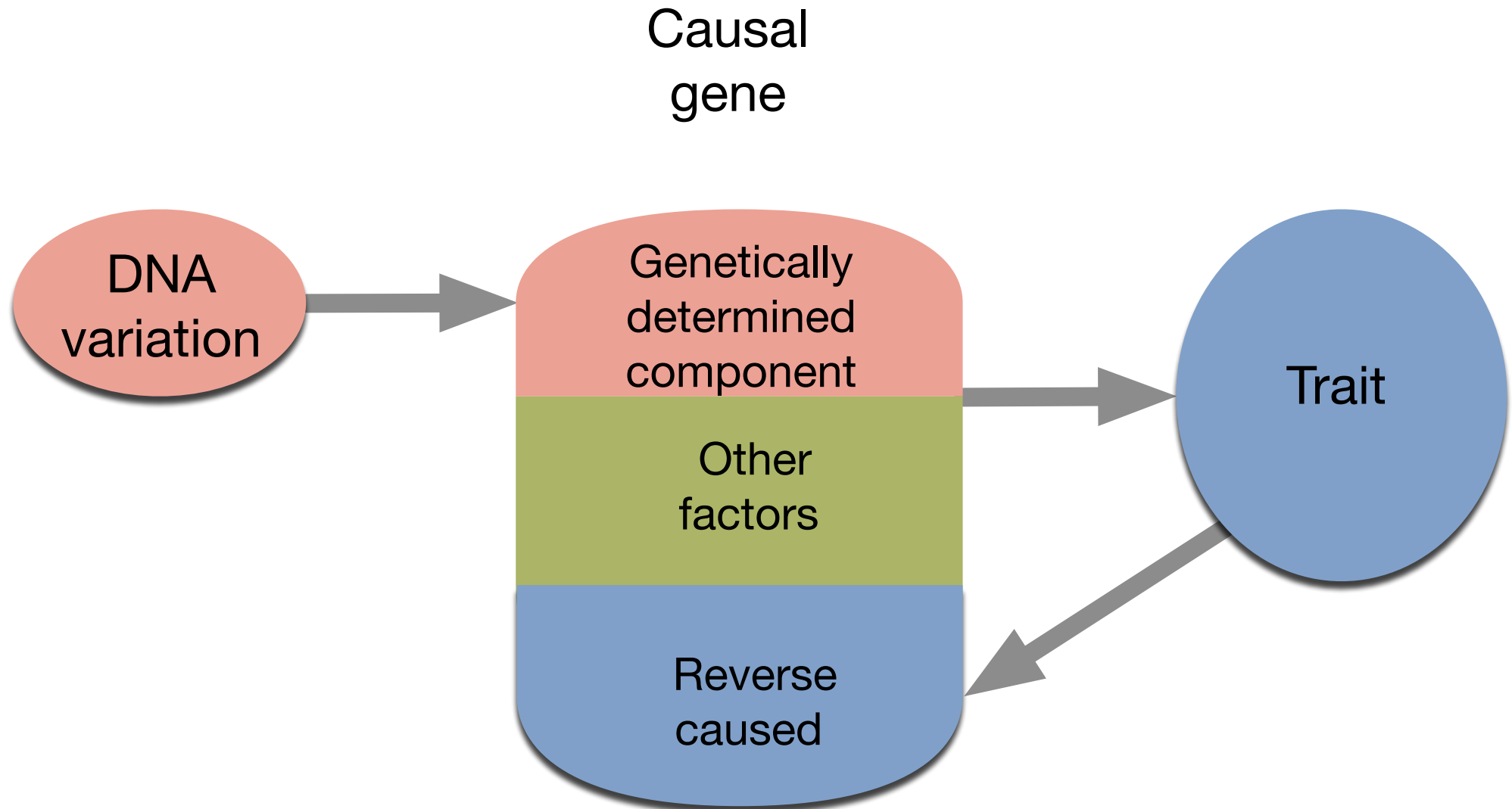


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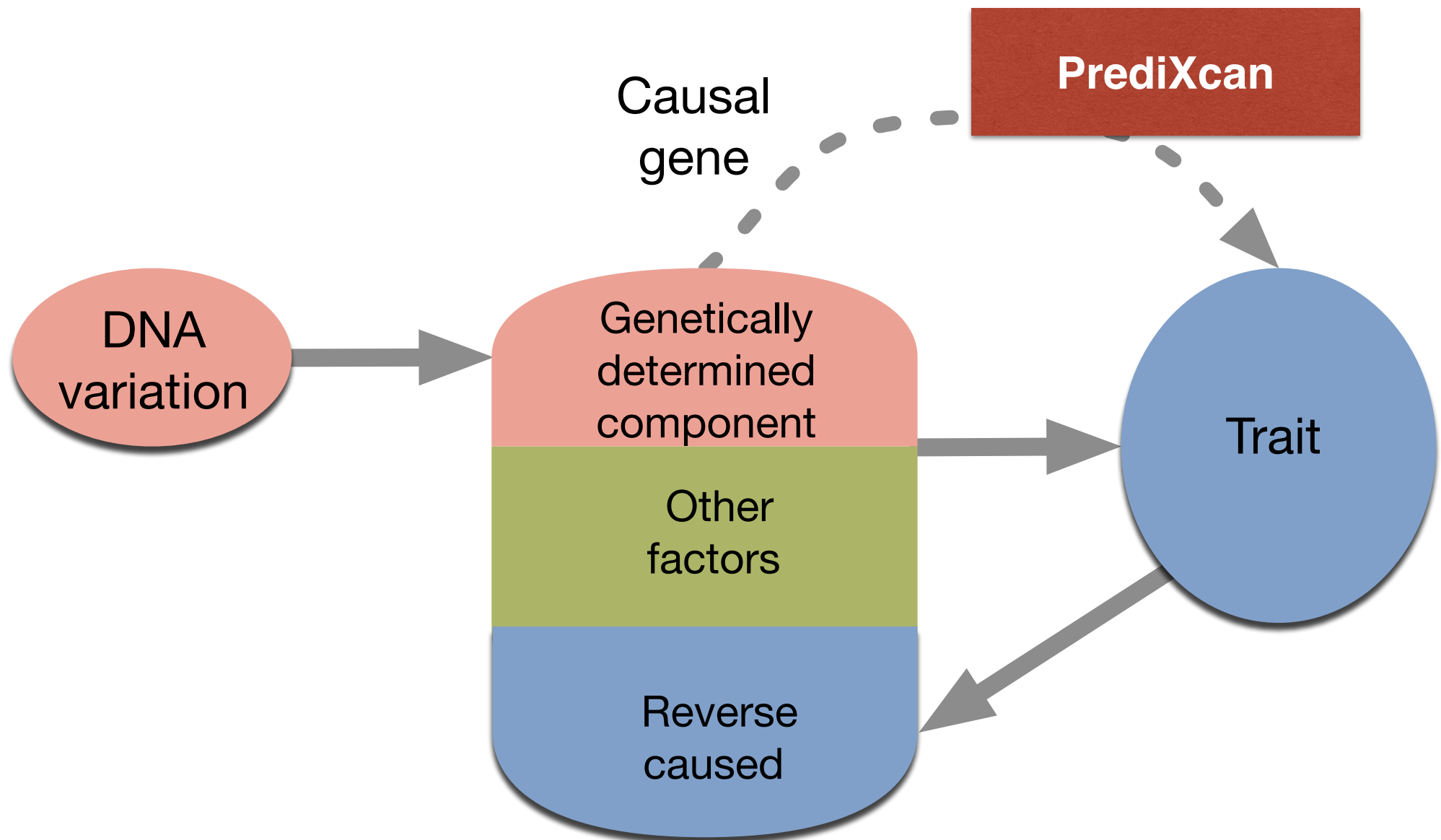
Gene Expression Effect on a Trait



Components of Gene Expression Level



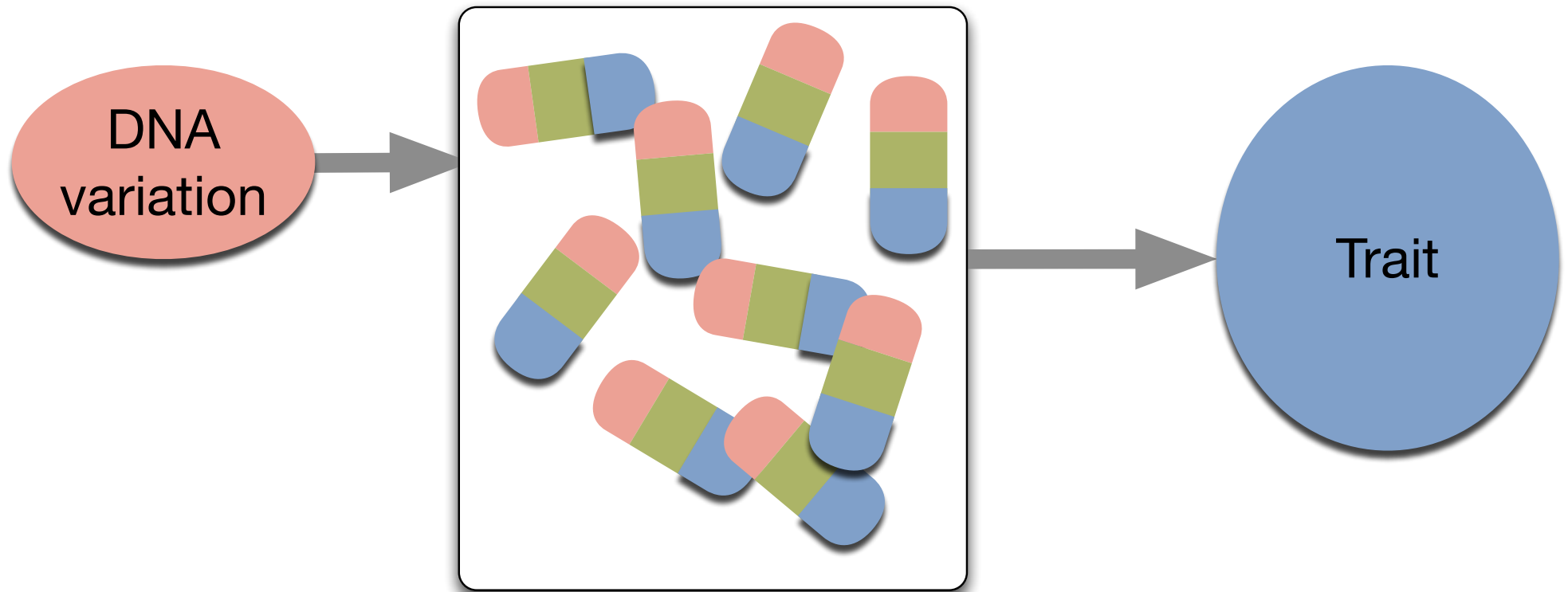
PrediXcan: Gene-Based Association Test



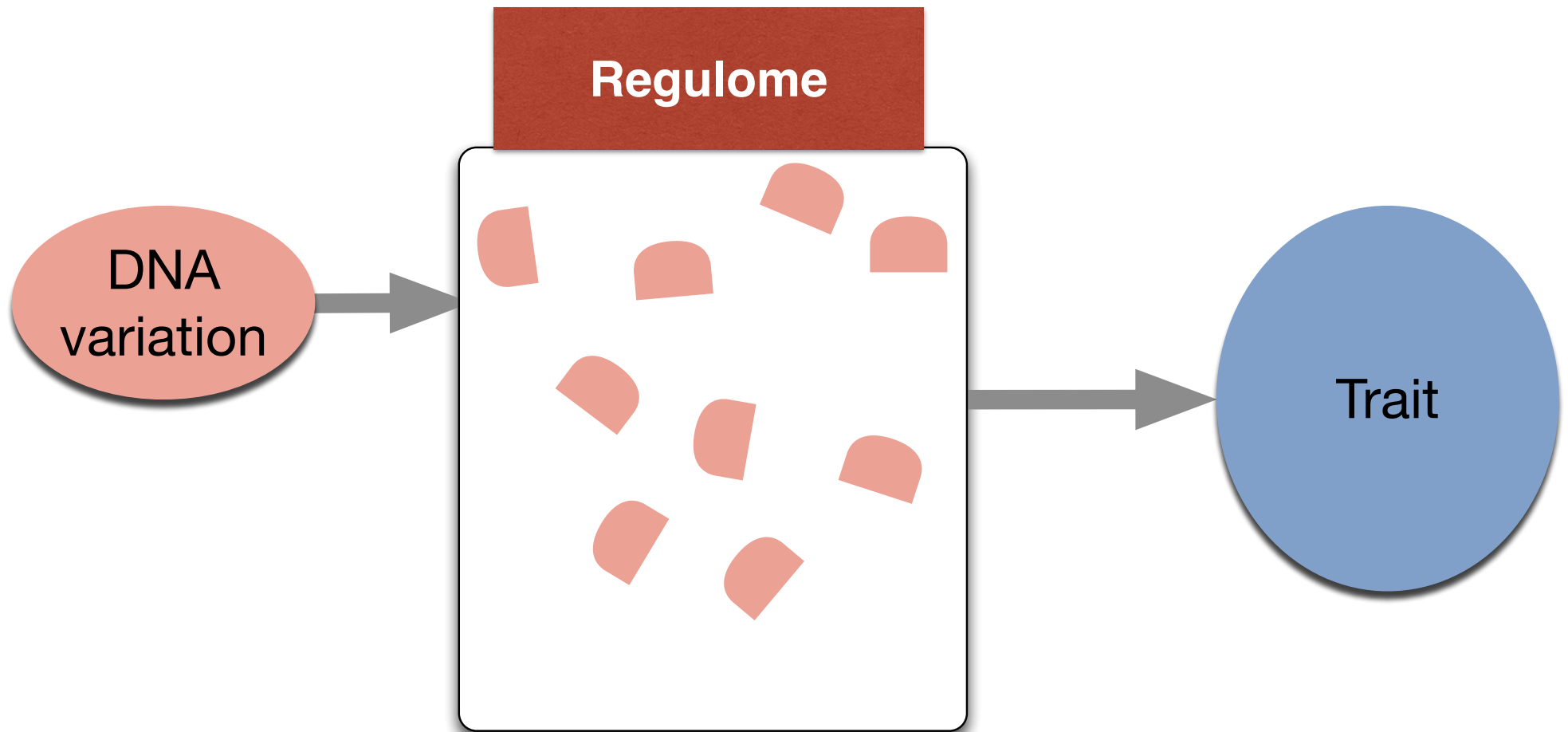
PrediXcan: Mechanism-driven Gene-Based Test

- Directly tests the molecular mechanism through which genetic variants affect phenotype
- Genes more attractive than genetic variants
 - A lot is known 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
- Applicable to all GWAS/sequencing studies
- Multiple tissues can be tested

Transcriptome Regulation



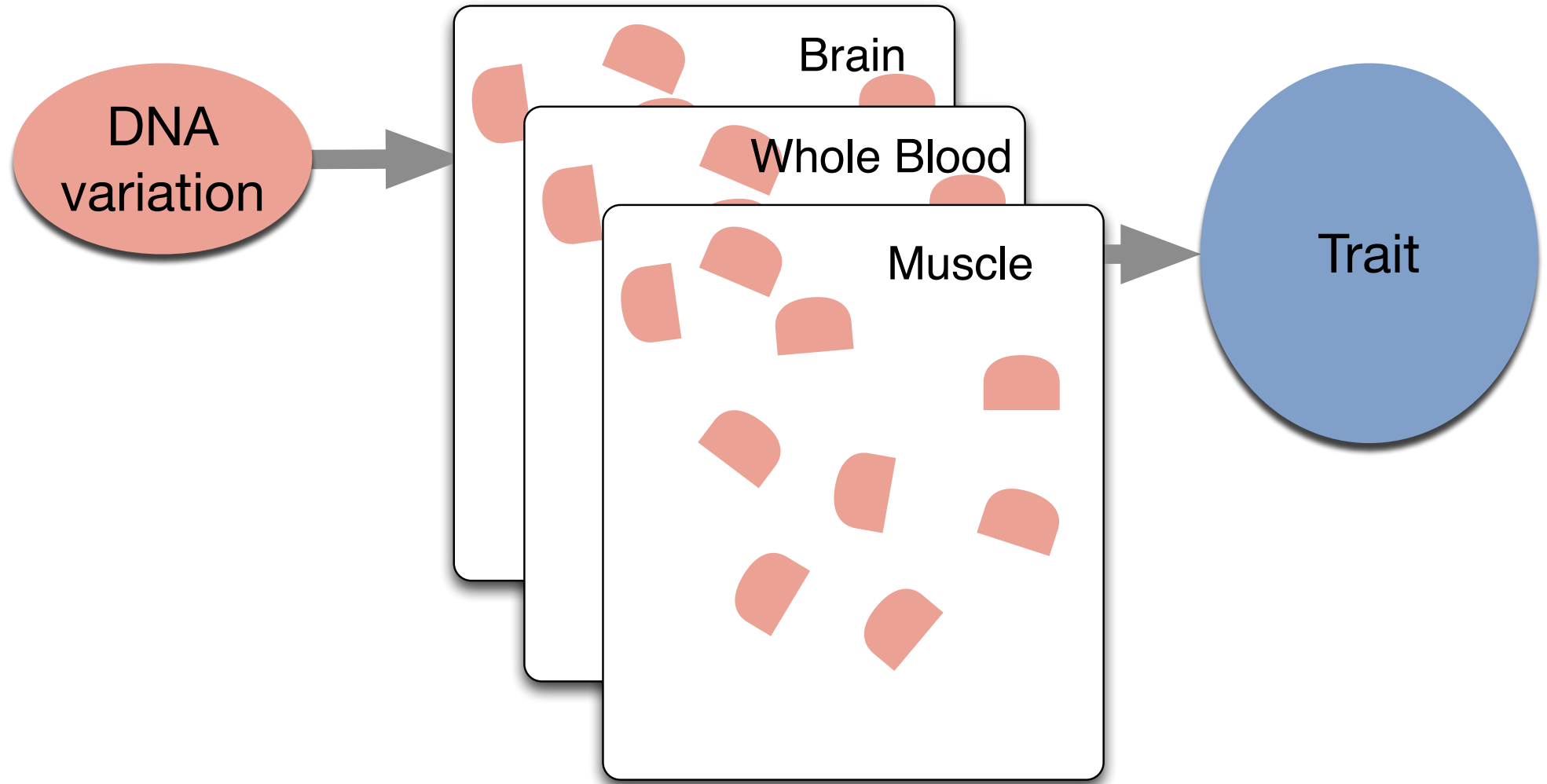
Regulability - Heritability of the Regulome



Regulability Definition

Total trait variability explained by the regulome

Regulability by Tissue



Chip Heritability & Regulability

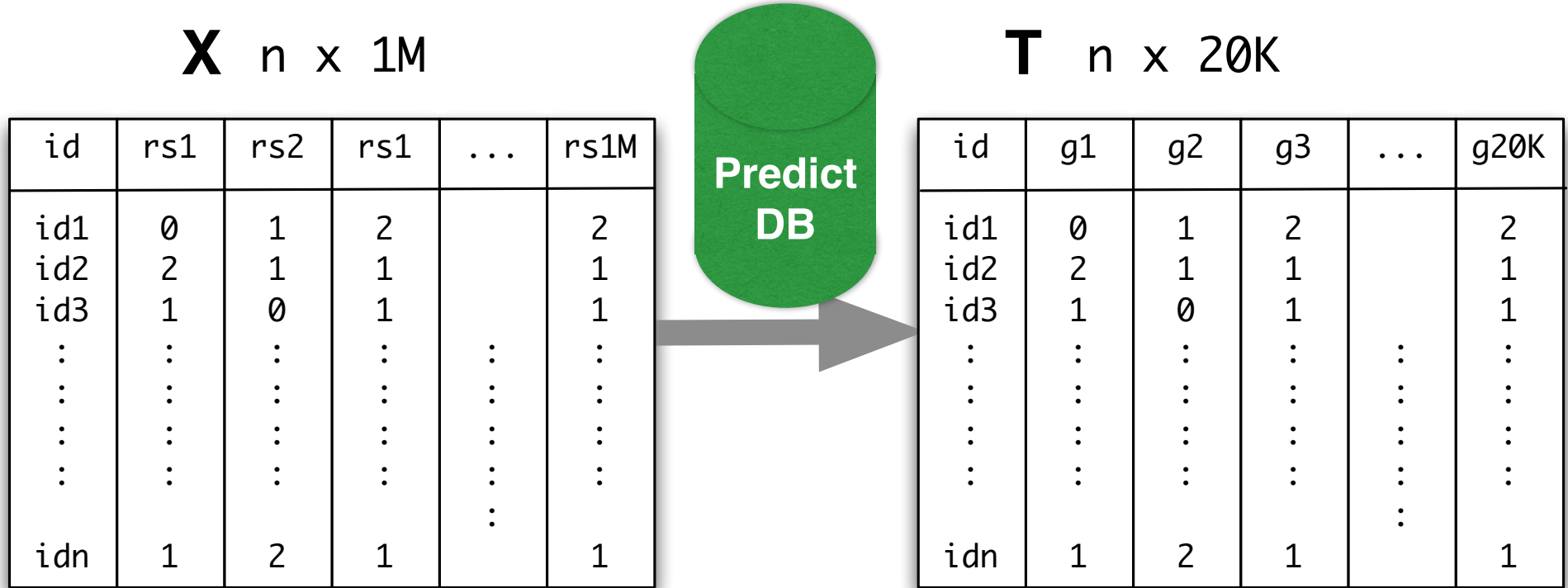
- Chip heritability: proportion of trait variability explained by genotyped variants

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

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

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

Regulability Calculation



- Compute Predicted Transcriptome: **T**
- Compute covariance matrix of **T**
- Compute REML estimate of variance of summation term in

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

Orthogonal Tissue Decomposition

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

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

- Develop cross tissue, tissue-specific, and sub-tissue-specific expression traits
 - Perform eQTL analysis
 - Build prediction models
 - Compute regulability of traits

Acknowledgements

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Contributors

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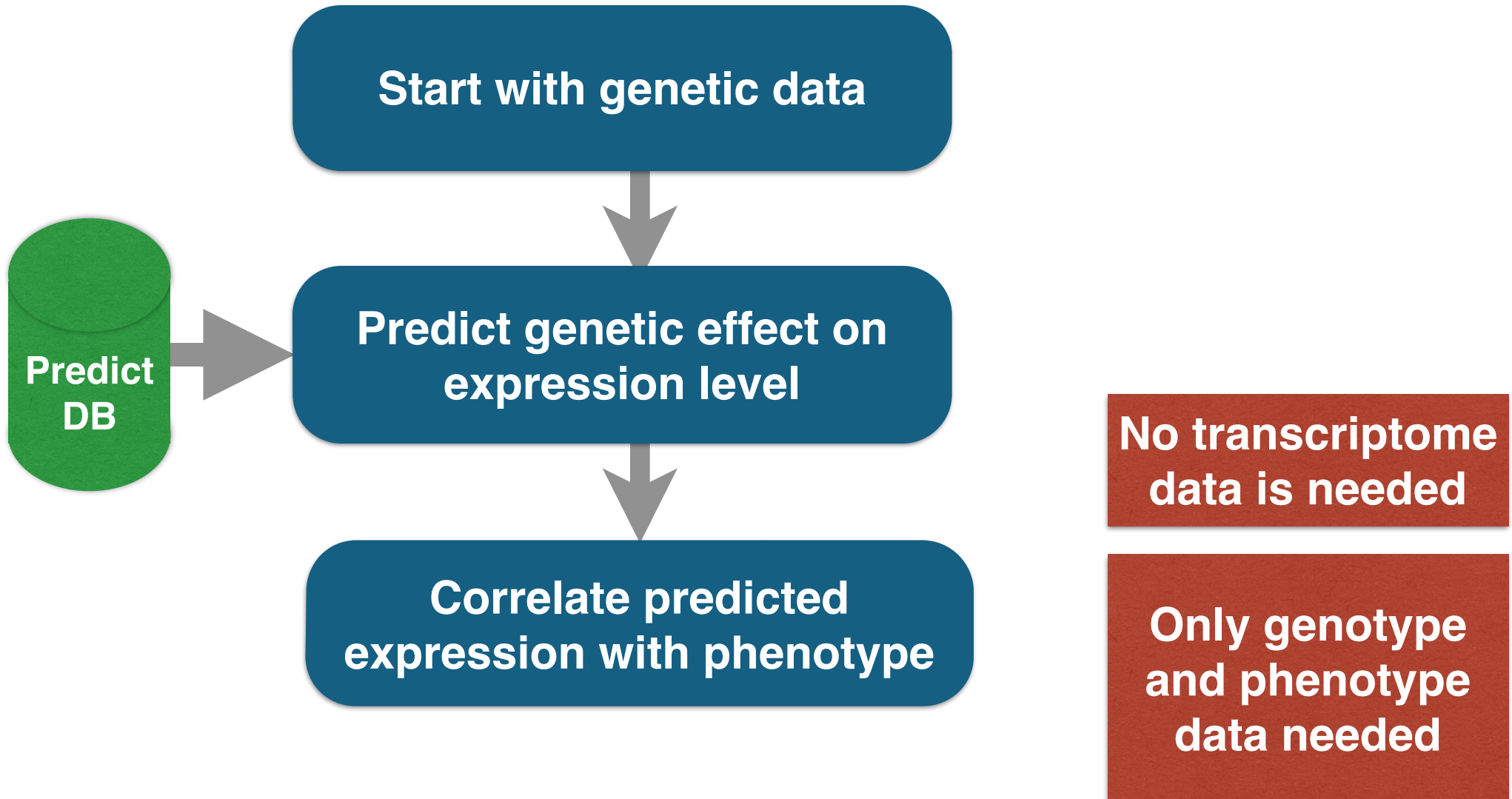
Data sources

- WTCCC
- GAIN Bipolar Disease

Funding

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PrediXcan Flow



Additive Model for Genetic Effect Prediction

Predicted Expression Trait

$$t_i = \sum_{k=1}^M w_k G_{ki}$$

t_i is predicted effect on gene expression level for individual i

G_{ki} number of reference alleles for SNP k and individual i

w_k weight for SNP k

Simple Polygenic Model



**PredictDB hosts
prediction
models**

- ▶ w_k = single variant regression coefficient (Matrix eQTL output)
- ▶ w_k set to zero if p value > 0.05 for cis SNPs (1Mb TSS)
- ▶ w_k set to zero if p value $> 10^{-6}$ for trans SNPs

Expression Data for Prediction Model Building

Predicted Expression Trait

- GTEx - Genotype of Tissue Expression
 - Large scale Common Fund project
 - 900 organ donors
 - 45 tissues
 - RNAseq, whole exome seq, whole genome seq

gEUVADIS

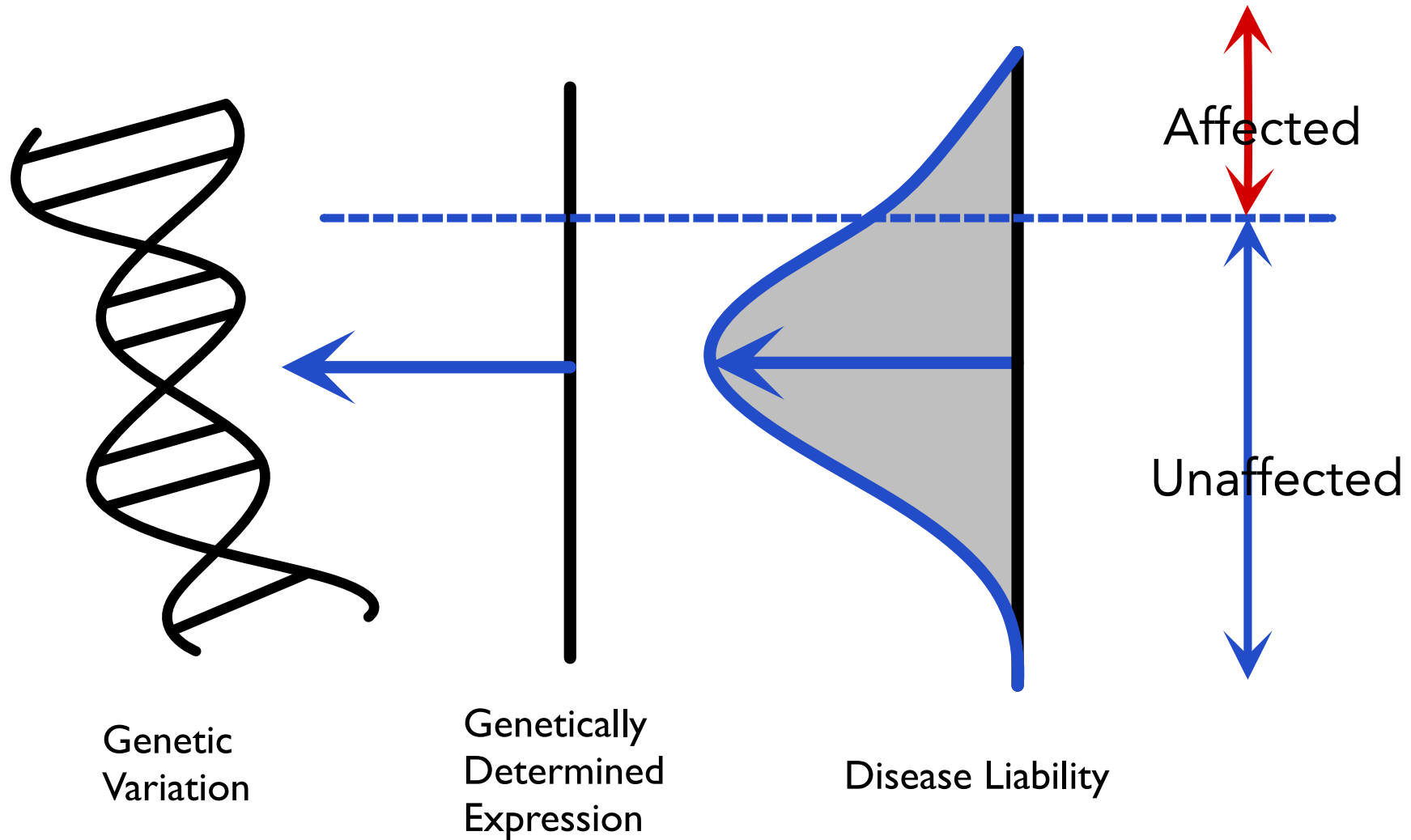
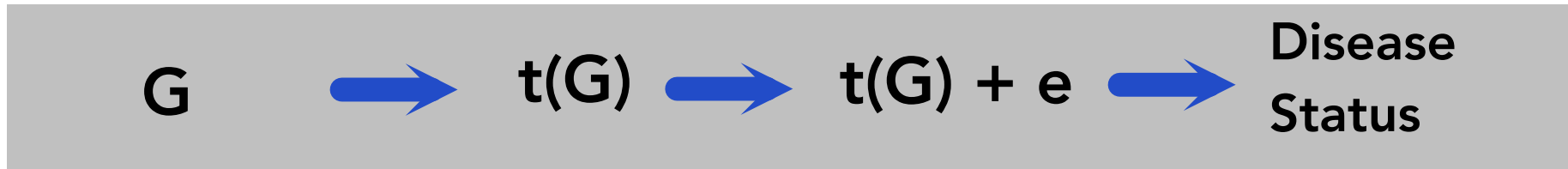
- RNAseq 462 individuals from the 1000 Genomes Project

Other array data

Extension to Other Molecular Phenotypes

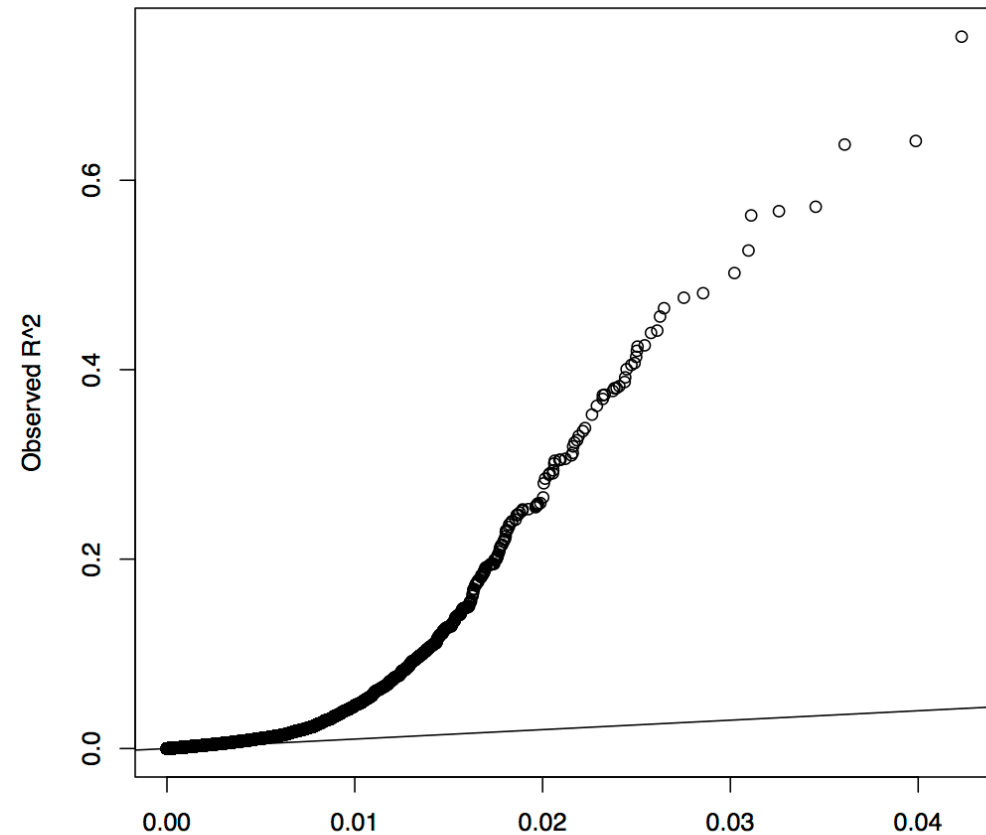
- microRNA levels
- lncRNA levels
- Methylation status

Genetic Control of Disease Through Gene Regulation



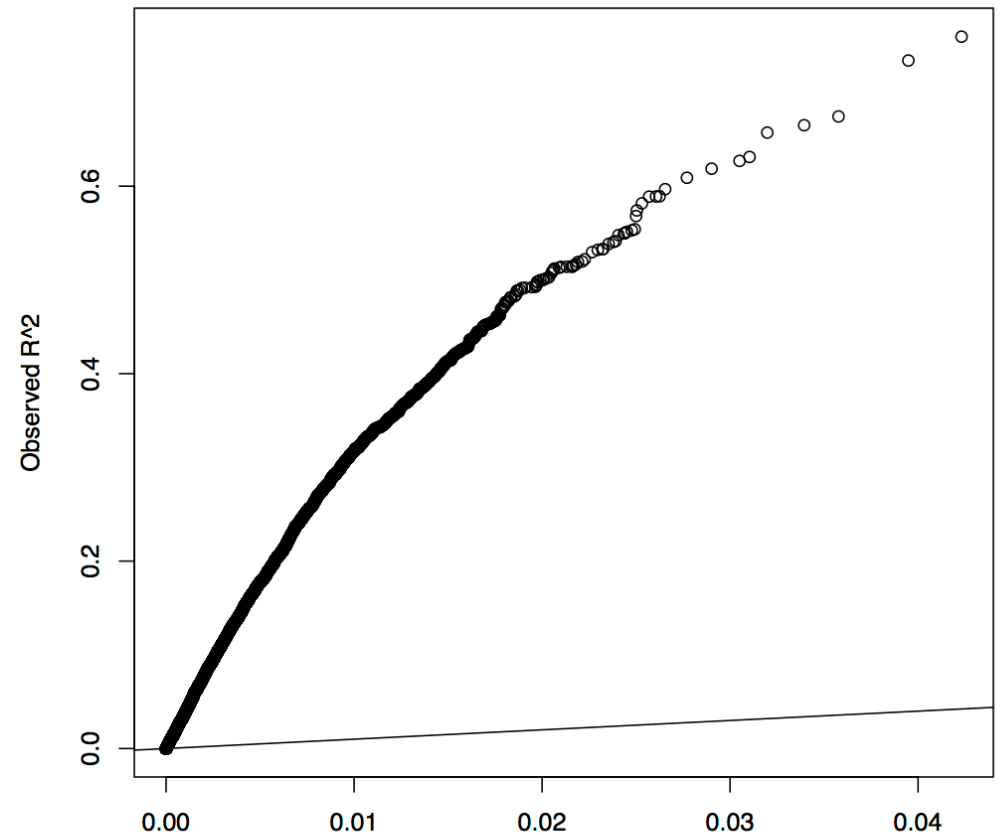
Good Prediction Performance

Prediction R^2



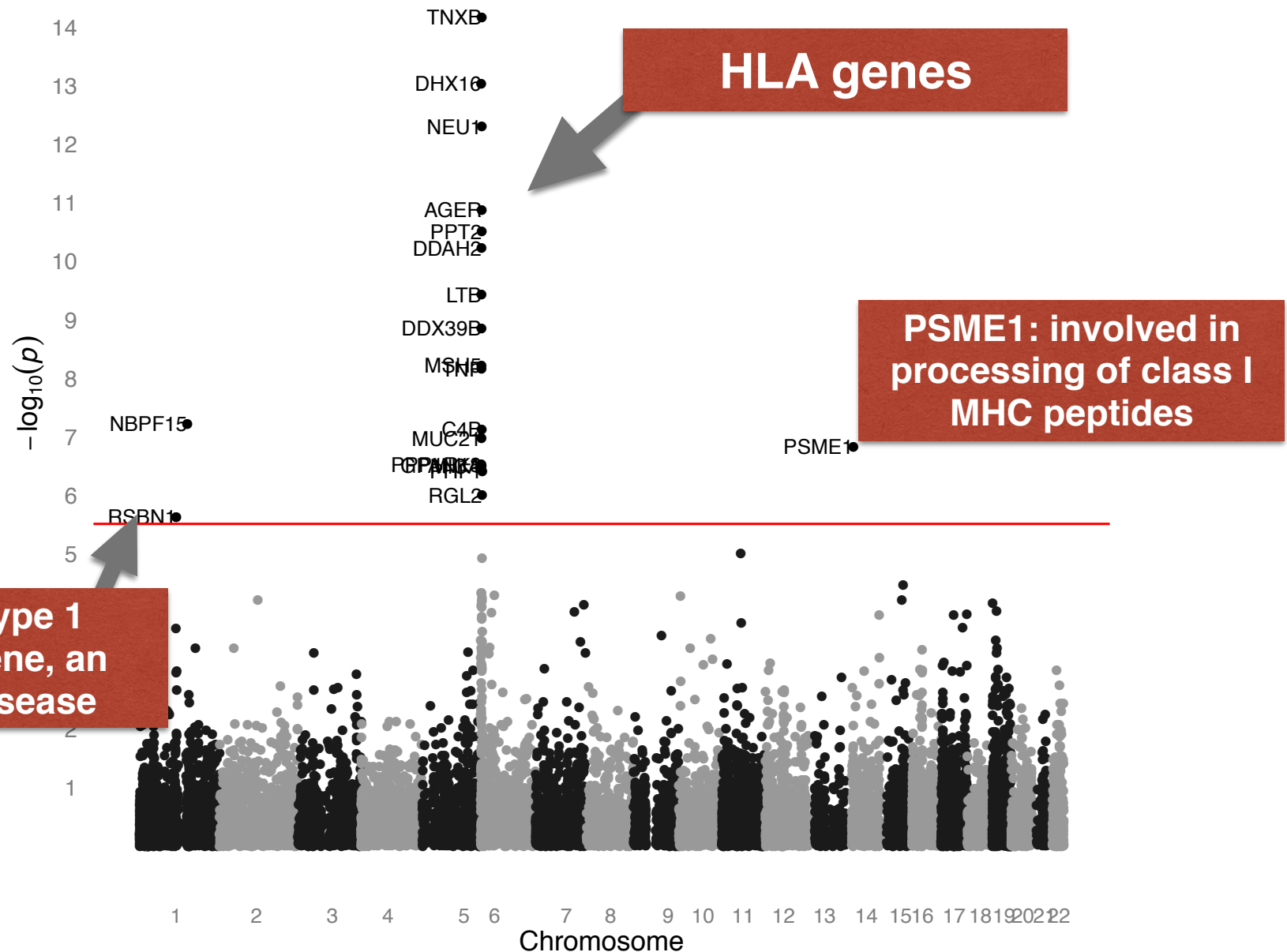
Training with GTEx
Testing in 1K Genomes

Replication R^2



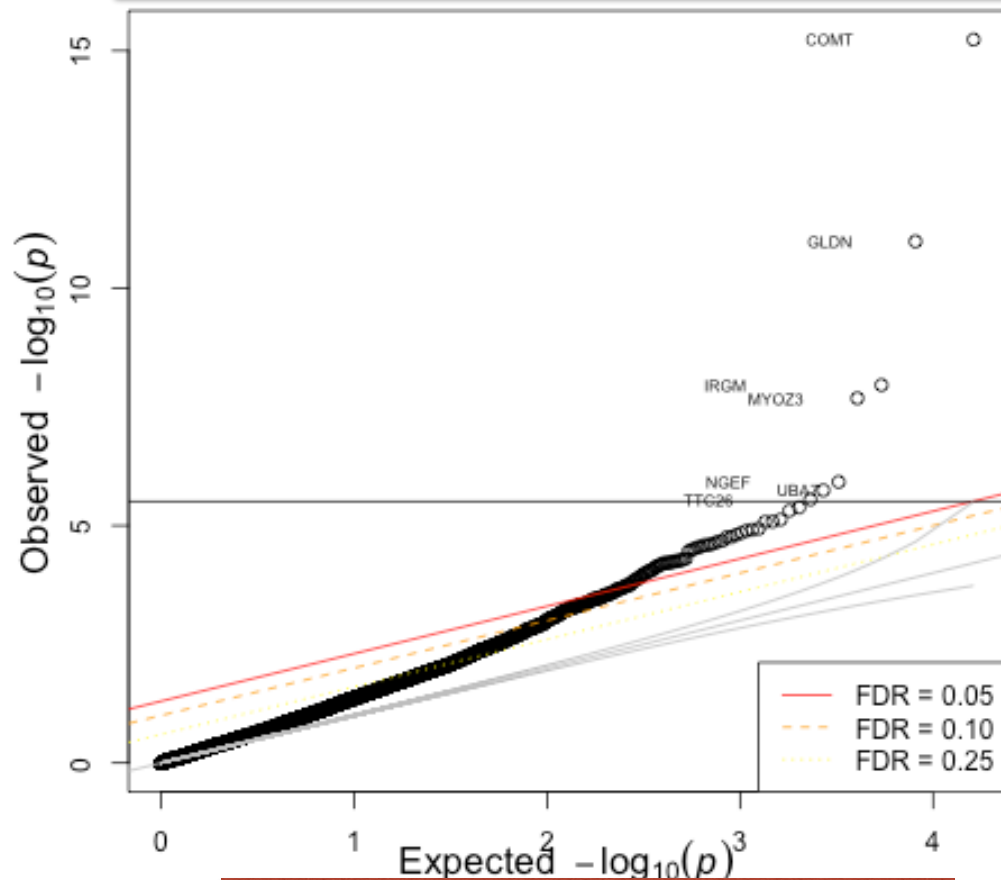
Replicate RNAseq
Pickrell et al 2010 vs.
1K Genomes 2013

Genes Associated with Rheumatoid Arthritis



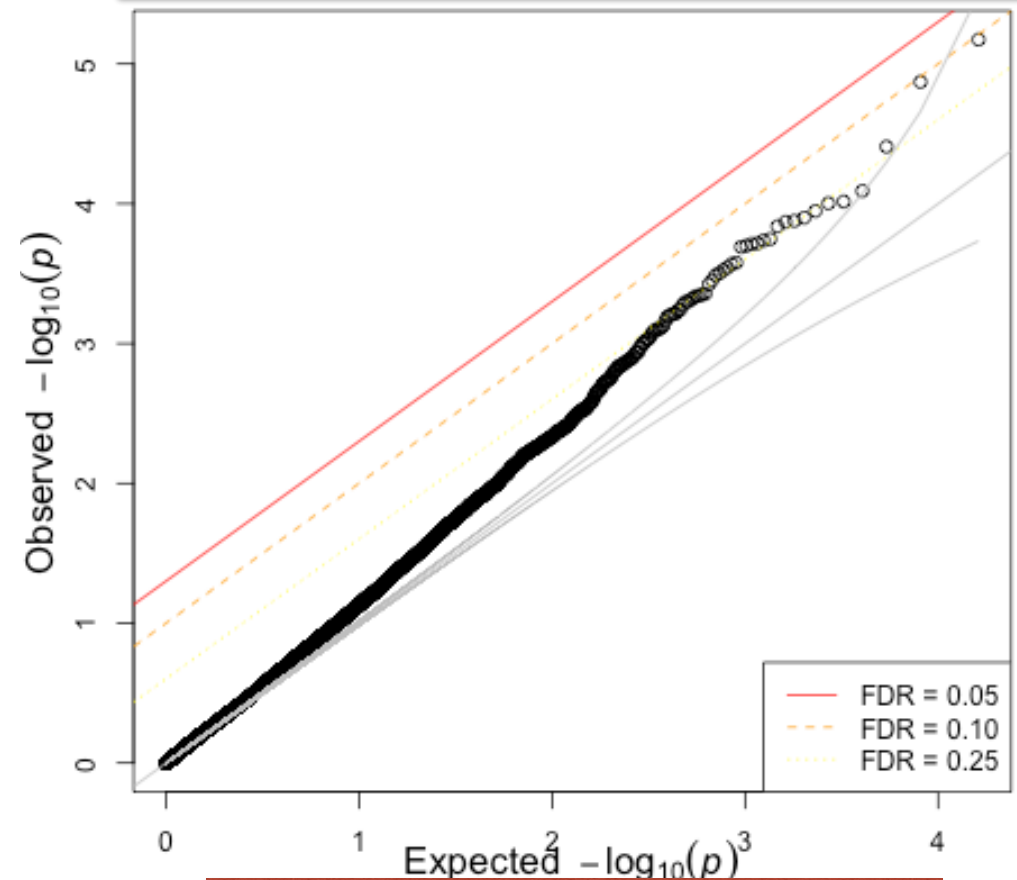
PrediXcan Results for Crohn's Disease and Hypertension

Crohn's Disease



**IRGM is a known
Crohn's gene**

Hypertension



**Whole blood may not be
relevant tissue**

Significant Concordance Between Independent Bipolar Studies

