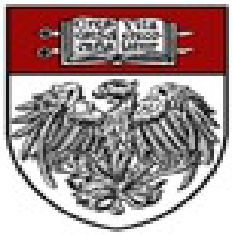
GTEx X NHGRI Catalog



Nancy J. Cox, Ph.D.

The University of Chicago

http://genemed.uchospitals.edu

Overview

- Introduction to GTEx
- Results of studies crossing the NHGRI catalog and GTEx
- Additional hypotheses that might be tested using data and results from the NHGRI catalog and GTEx
- Pitfalls particular to tests of enrichment using the NHGRI catalog

WE ACCELERATE DISCOVERY

HOME PROGRAMS RESEARCH FUNDING NEWS & EVENTS MULTIMEDIA HIGHLIGHTS ABOUT CONTACTS

Genotype-Tissue Expression (GTEx)

Publications Search GO

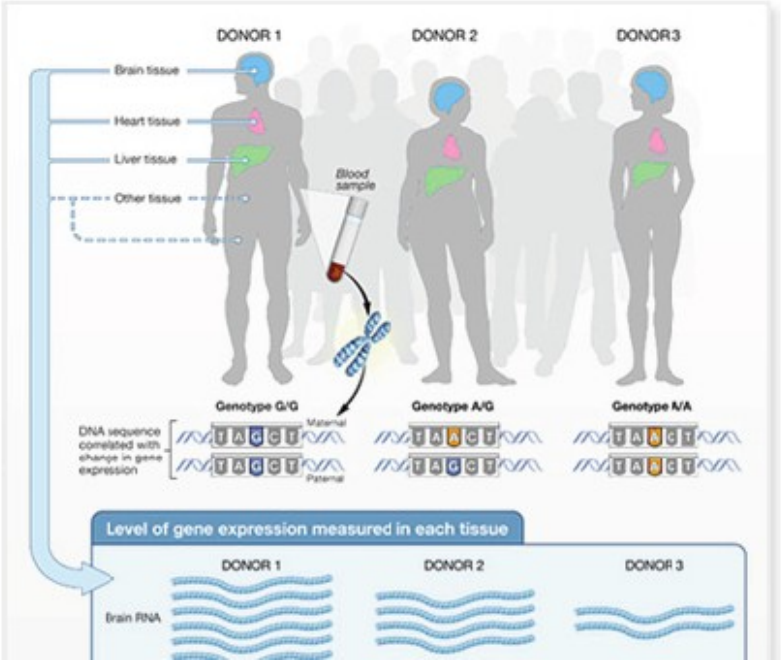
OVERVIEW WORKING GROUP MEMBERS FUNDING PROGRAM RESOURCES PUBLICATIONS/NEWS MEETING/ACTIVITIES

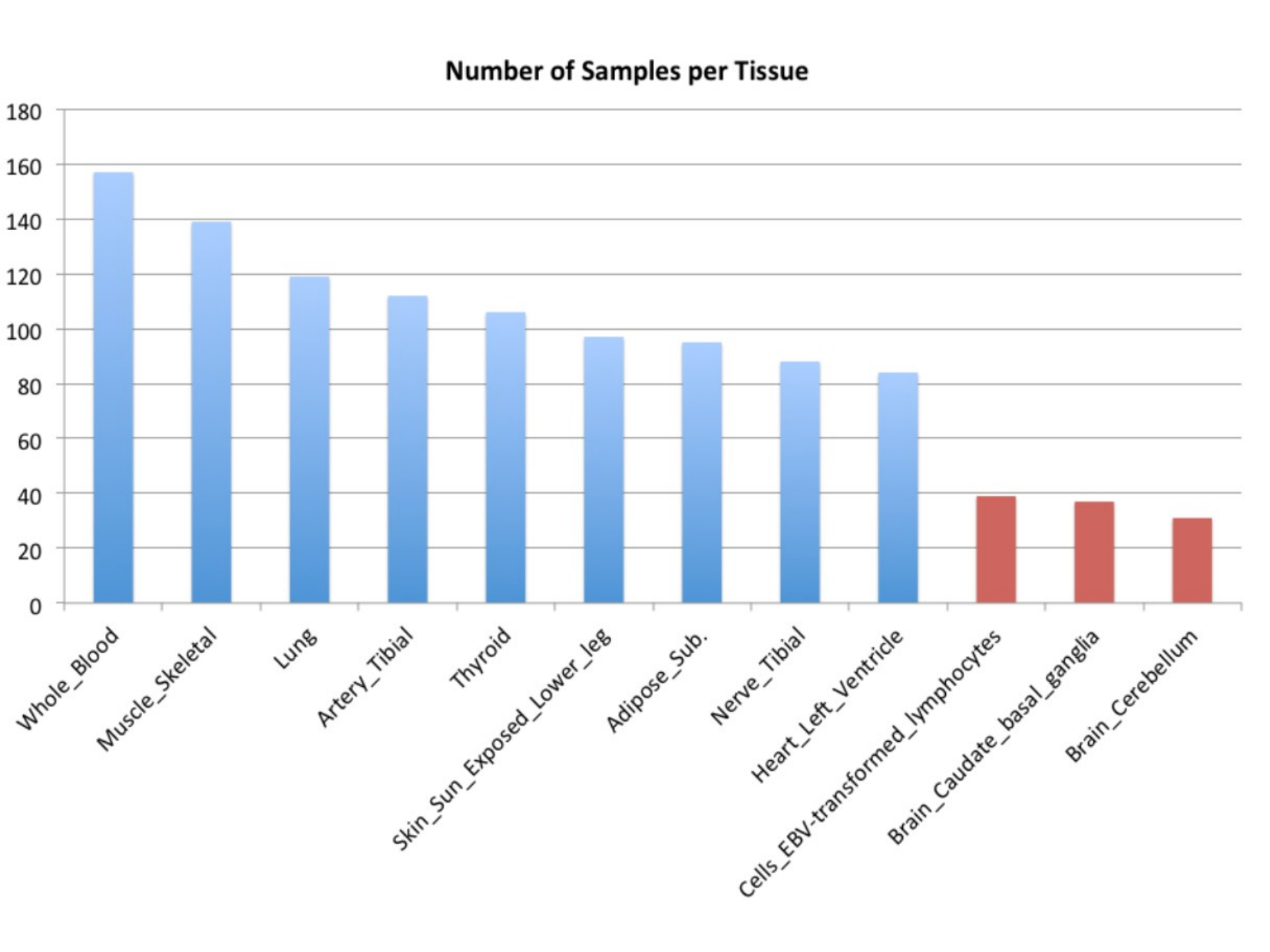
Program Snapshot

The Common Fund's **Genotype-Tissue Expression (GTEx)** program aims to study human gene expression and regulation in multiple tissues, providing valuable insights into the mechanisms of gene regulation and, in the future, its disease-related perturbations. Genetic variation between individuals will be examined for correlation with differences in gene expression level to identify regions of the genome that influence whether and how much a gene is expressed. The GTEx project includes the following initiatives:

- Novel Statistical Methods for Human Gene Expression Quantitative Trait Loci (eQTL) Analysis
- Laboratory, Data Analysis, and Coordinating Center (LDACC)
- caHUB Acquisition of Normal Tissues in Support of the GTEx Project

Read more...



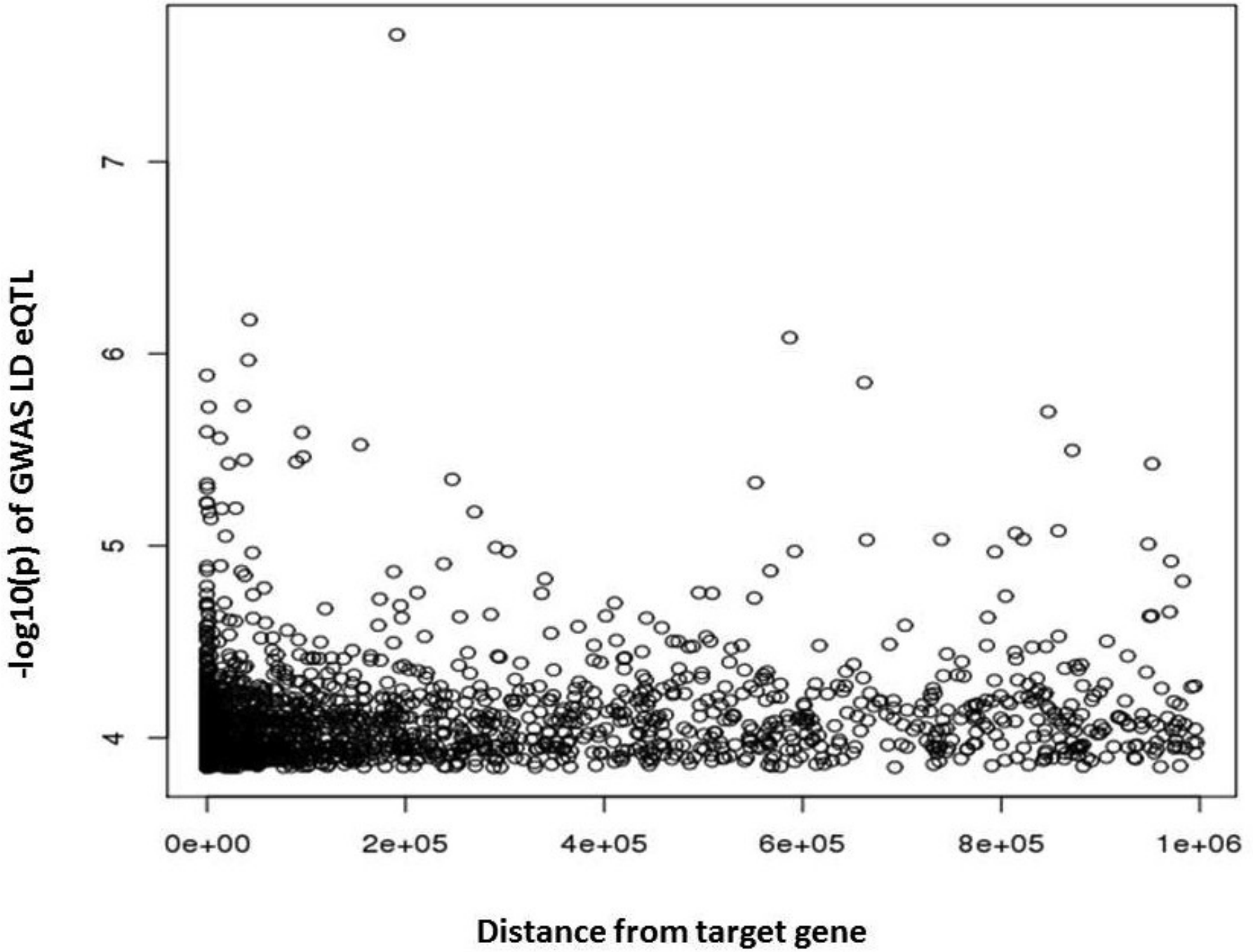

Number of Samples per Tissue
180
160
140
120
100
80
60
40
20
0
Whole_Blood
Muscle_Skeletal
Lung
Artery_Tibial
Thyroid
Skin_Sun_Exposed_Lower_leg
Adipose_Sub.
Nerve_Tibial
Heart_Left_Ventricle
Cells_EBV-transformed_lymphocytes
Brain_Caudate_basal_ganglia
Brain_Cerebellum

Classes of Functional Variants Enriched in SNPs Associated with Complex Human Traits

- eQTLs – SNPs associated with mRNA transcript levels
- mQTLs – SNPs associated with methylation status at sites variably methylated
- pQTLs – SNPs associated with protein levels (independent of mRNA)
- miRNA QTLs – SNPs associated with levels of miRNAs
- ENCODE annotations
- …

Results of Studies: GTEx X NHGRI Catalog

Where are the gene targets of trait-associated variants that might be regulatory?


-log10(p) of GWAS LD eQTL
4
5
6
7
0e+00
2e+05
4e+05
6e+05
8e+05
1e+06
Distance from target gene

Where are the gene targets of trait-associated variants that might be regulatory?

- 20% are in the gene physically closest to the “best” eQTL (across tissues)
- Higher proportion are for cis-, but more distant, genes

Potential Studies:
GTEx X NHGRI Catalog

What Aspects of Genetic Architecture Should Be Investigated?

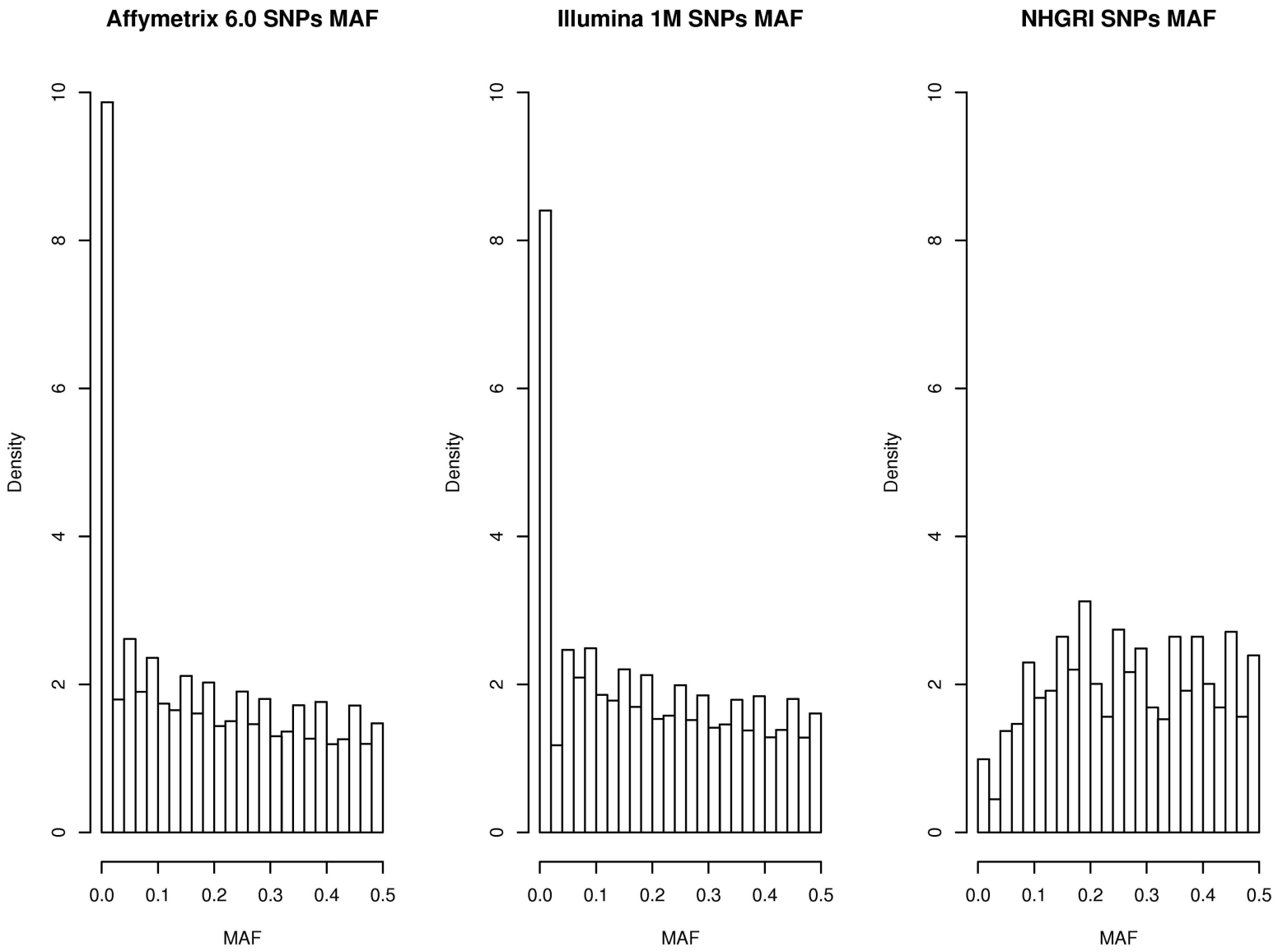
Genetic Architecture

Recessive

Dominant

Additive

Risk Allele Frequency Spectrum



More Architecture

Cross-tissue eQTLs

Single (or limited) Tissue eQTLs

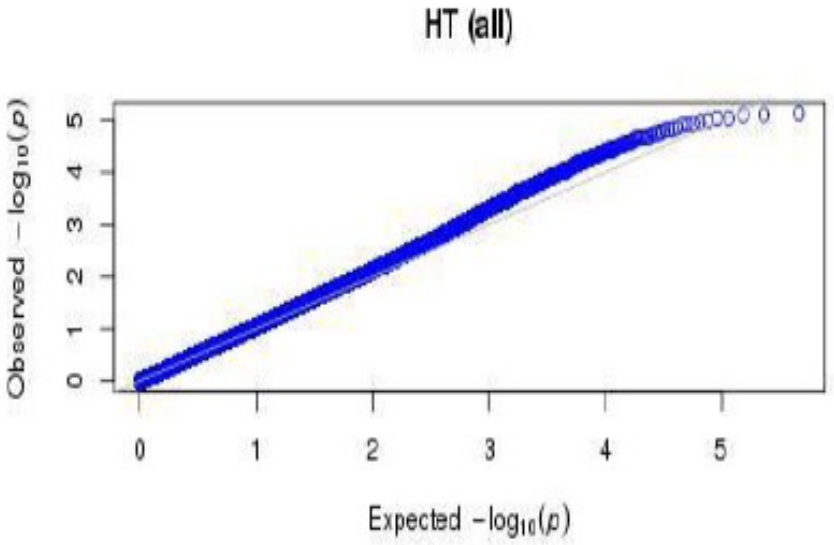
Cross-Tissue eQTLs

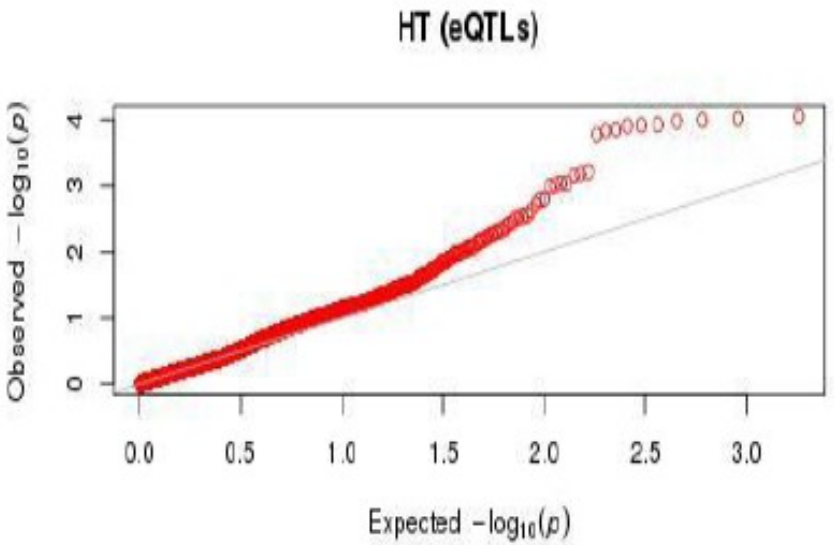
- SNPs associated with the same transcript across multiple tissues
- SNPs associated with the same transcript in all tissues in which the transcript is sufficiently expressed
- SNPs associated with the same transcript in at least a subset of the tissues in which the transcript is sufficiently expressed

Single- (or Limited-) Tissue eQTLs

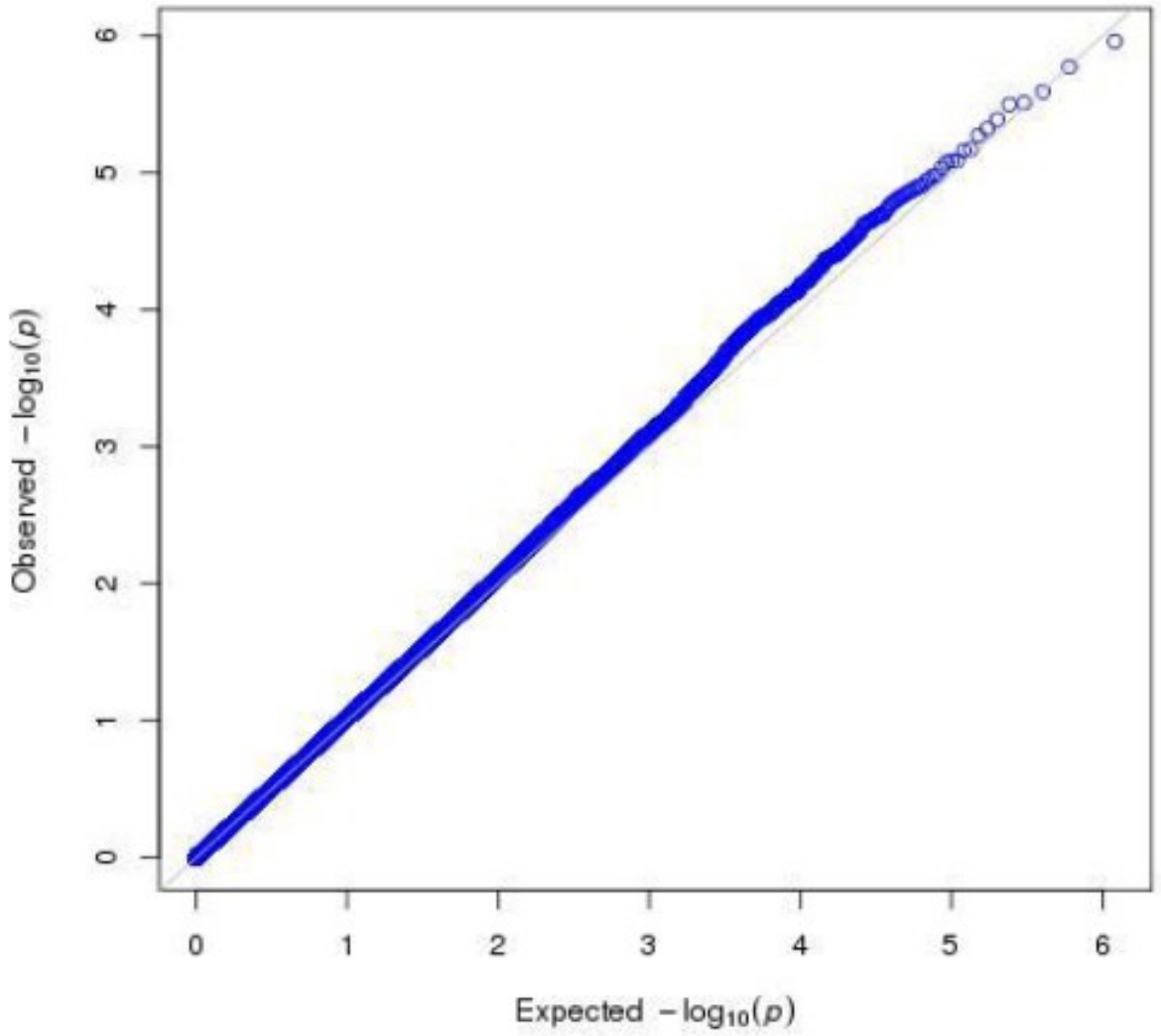
- SNPs associated with a transcript expressed in a single tissue
- SNPs associated with a transcript in only one (or a limited subset) of the tissues in which the transcript is adequately expressed
- It is clear there are examples of each of these types of eQTLs

Hypertension and Adipose eQTLs

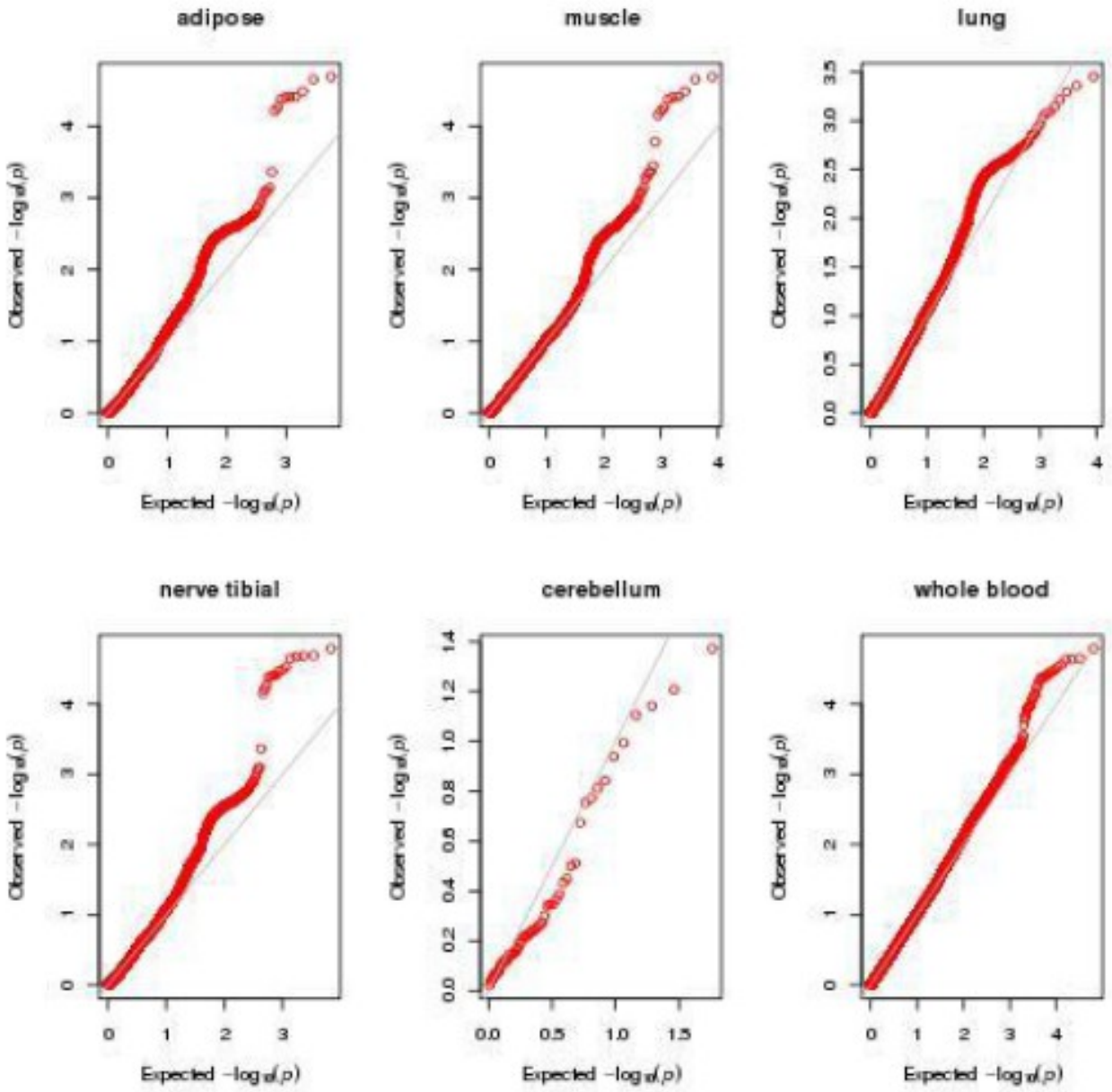




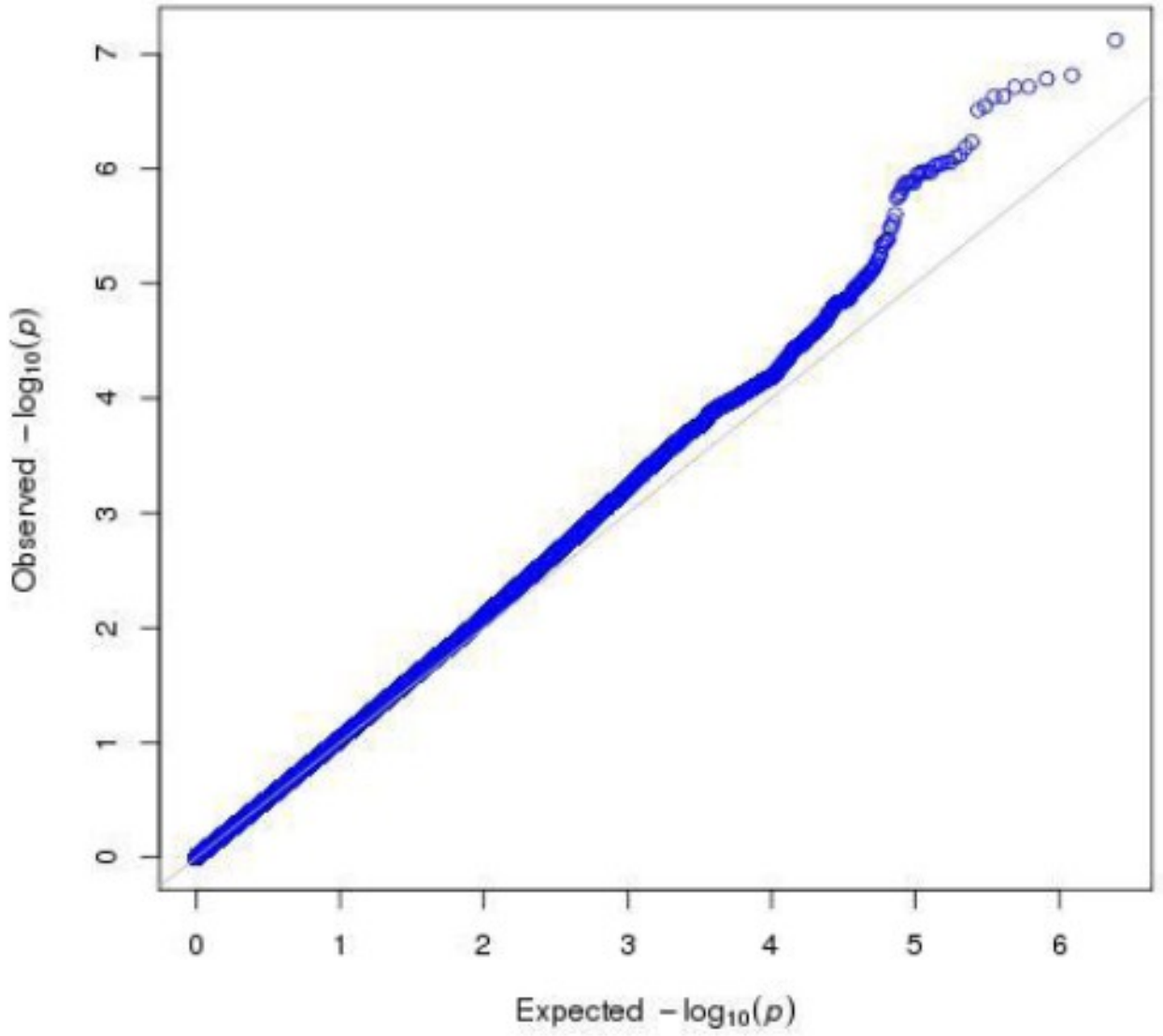
PGC: ADHD (all SNPs)



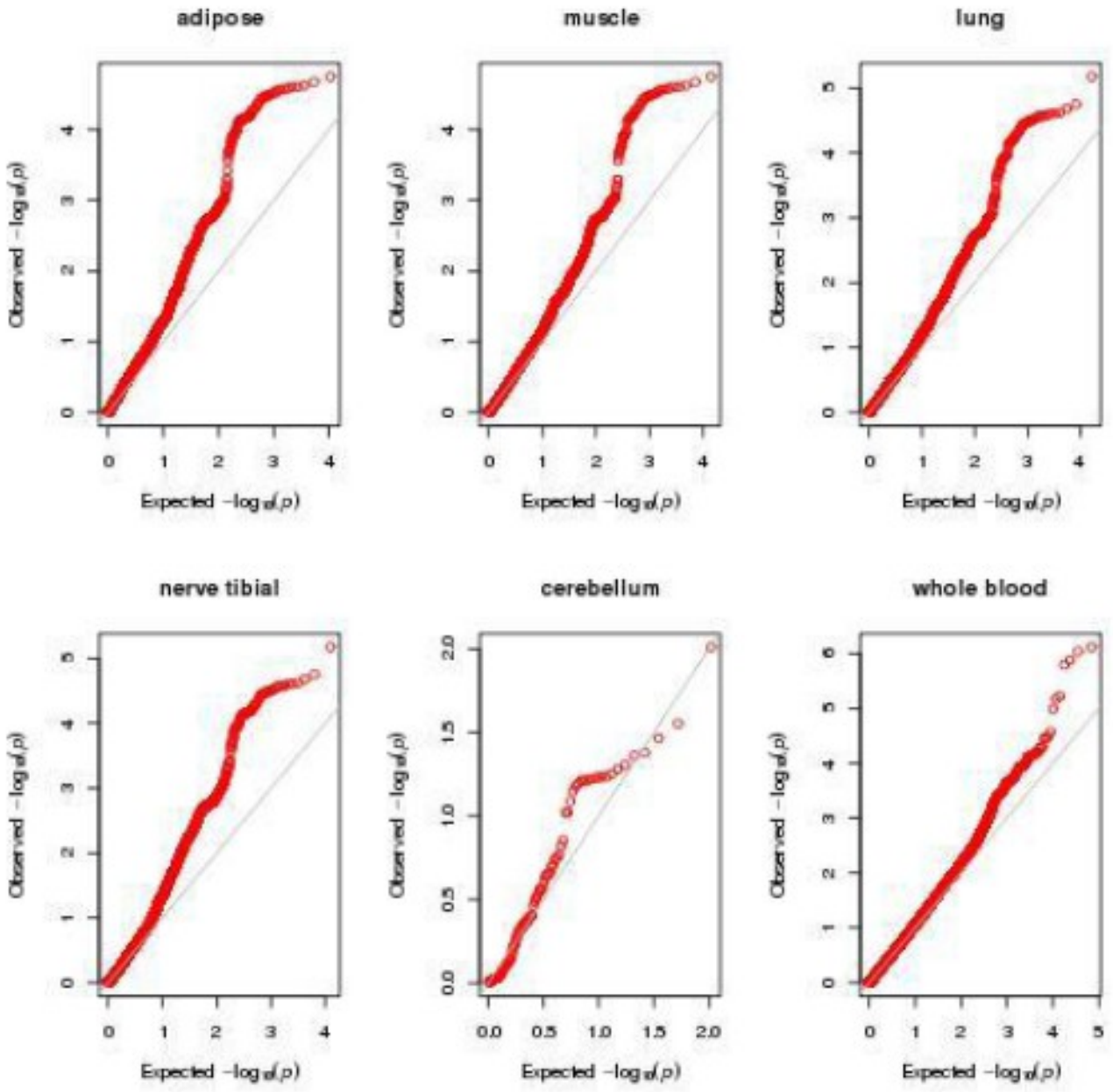
PGC: ADHD


adipose
muscle
lung
nerve tibial
cerebellum
whole blood
Observed −log10(p)
Expected −log10(p)

MAGIC: HOMA-IR (all SNPs)



MAGIC: HOMA-IR

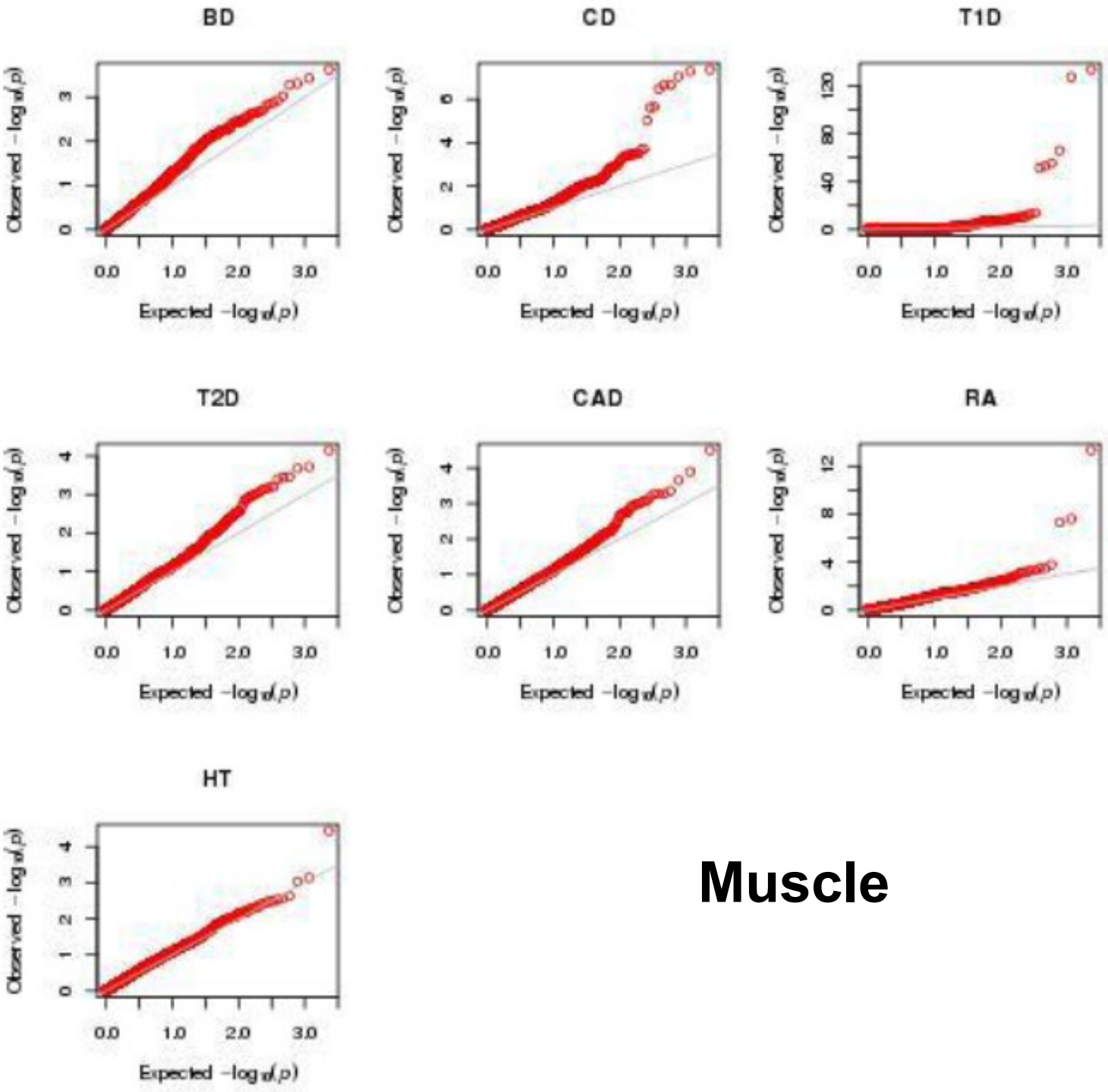


Architecture Related to Specificity of Regulation

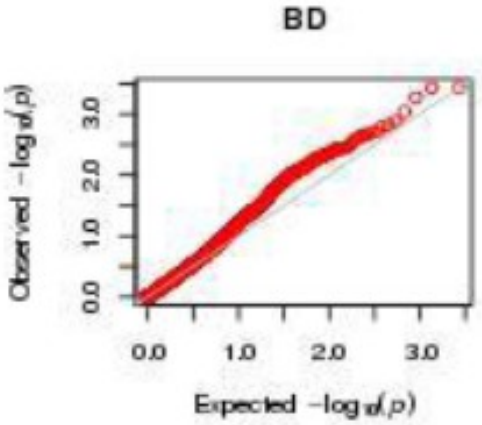
- **Will multi-system disorders tend to have trait-associated SNPs that are cross-tissue eQTLs?**
- **Will disorders that seem to be more clearly about a single tissue have trait-associated SNPs that are single-tissue eQTLs?**

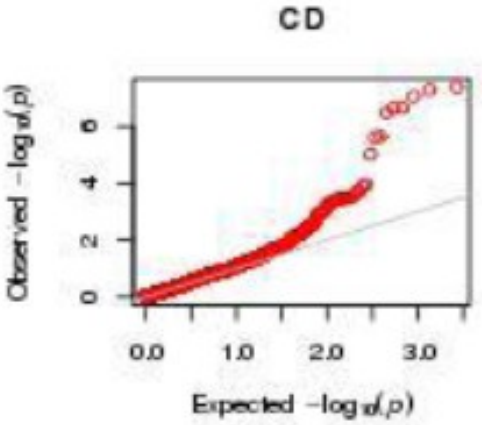
Potential Studies:
GTEx X NHGRI Catalog

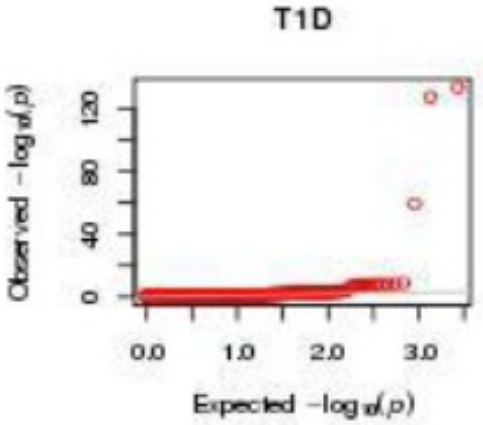
Refining Information on Biology:
Tissues with Excess Signal

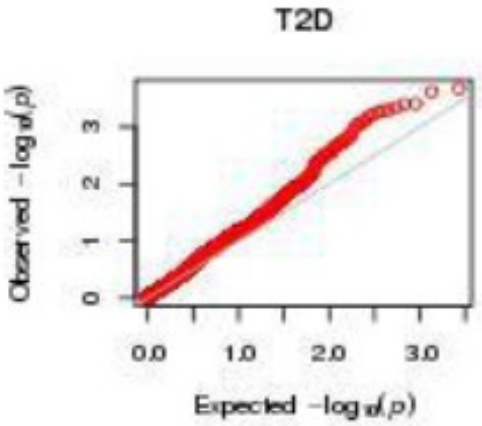

BD
CD
T1D
T2D
CAD
RA
HT
Observed −log10(p)
Expected −log10(p)
0.0
1.0
2.0
3.0

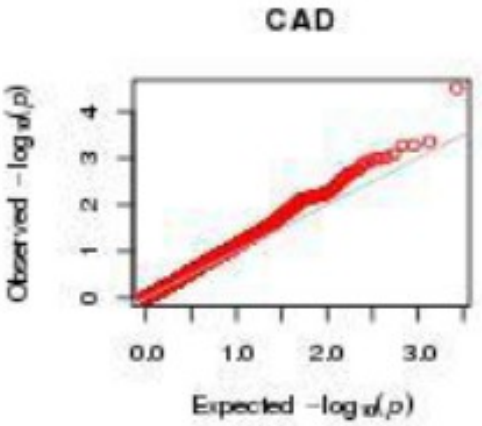
Muscle

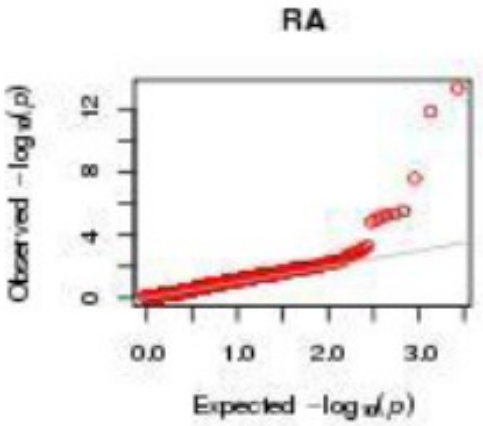

BD
Observed −log10(p)
Expected −log10(p)

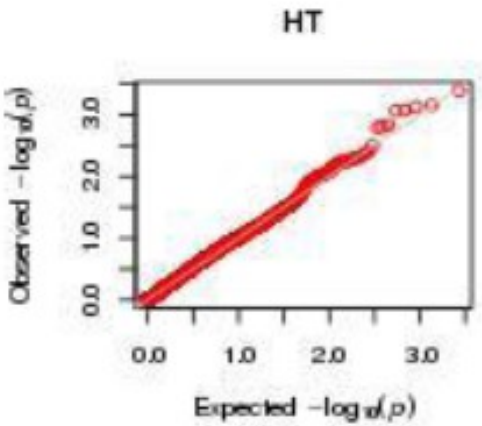

CD
Observed −log10(p)
Expected −log10(p)


T1D
Observed −log10(p)
Expected −log10(p)

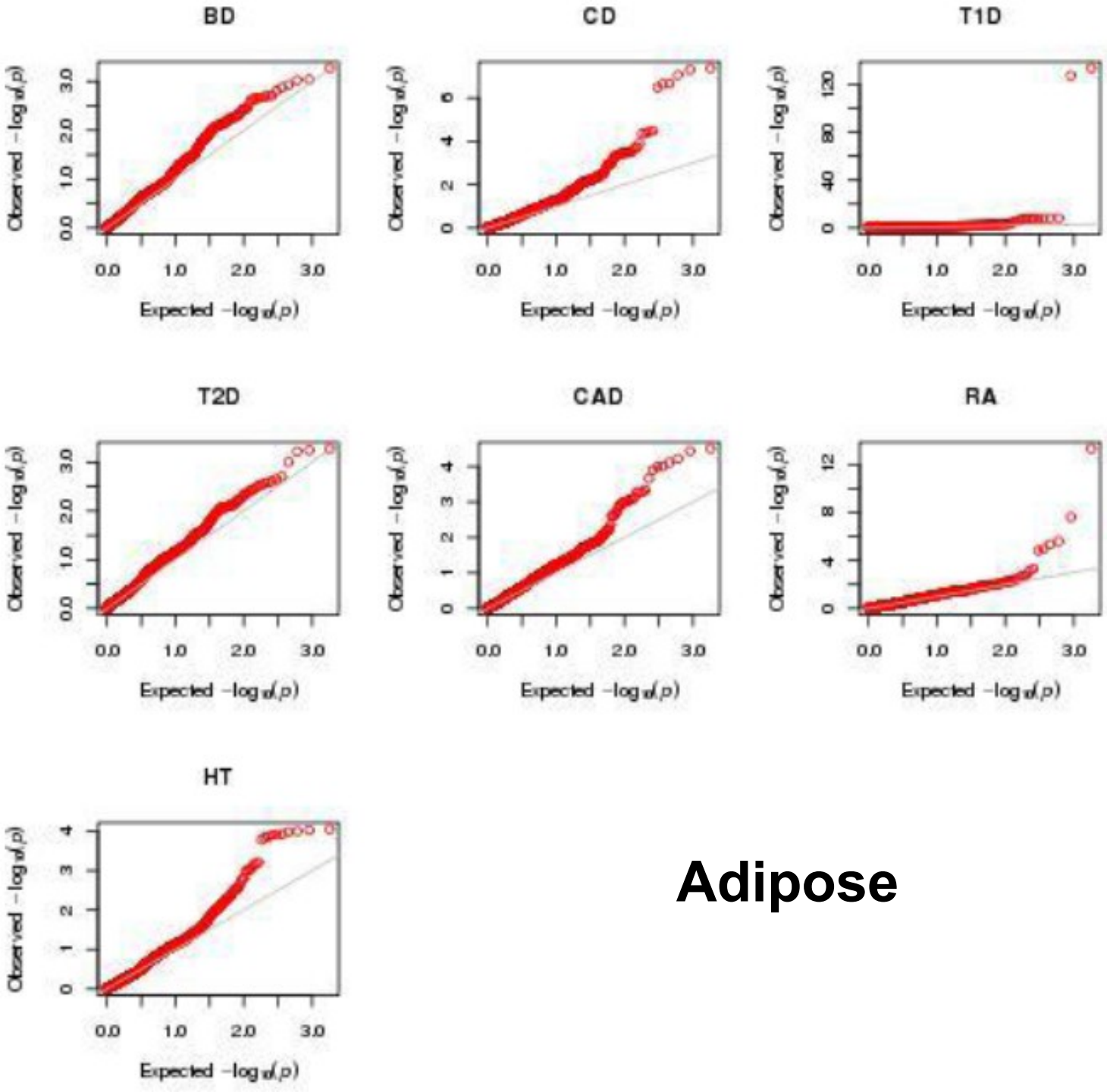

T2D
Observed −log10(p)
Expected −log10(p)


CAD
Observed −log10(p)
Expected −log10(p)


RA
Observed −log10(p)
Expected −log10(p)

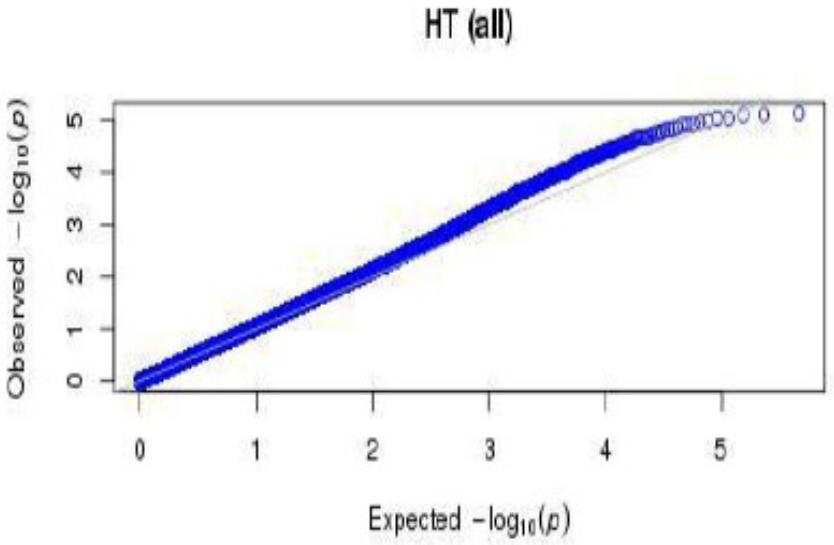

HT
Observed −log10(p)
Expected −log10(p)

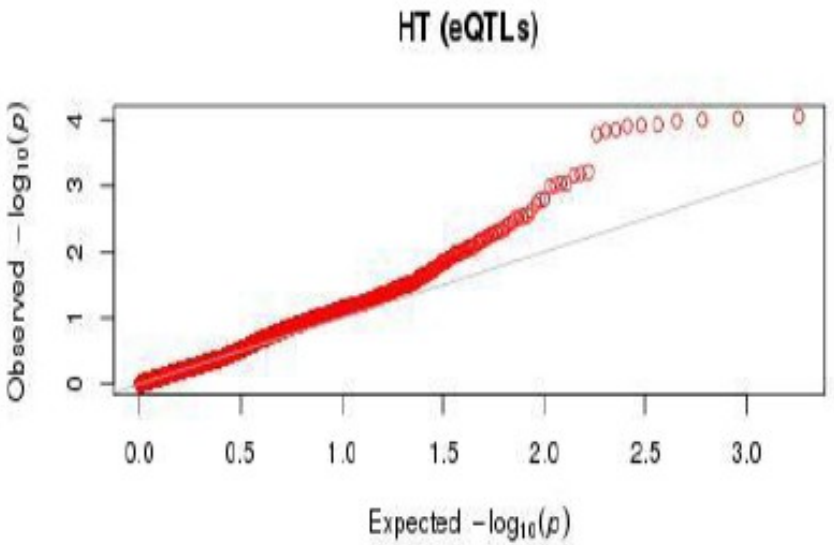
Lung

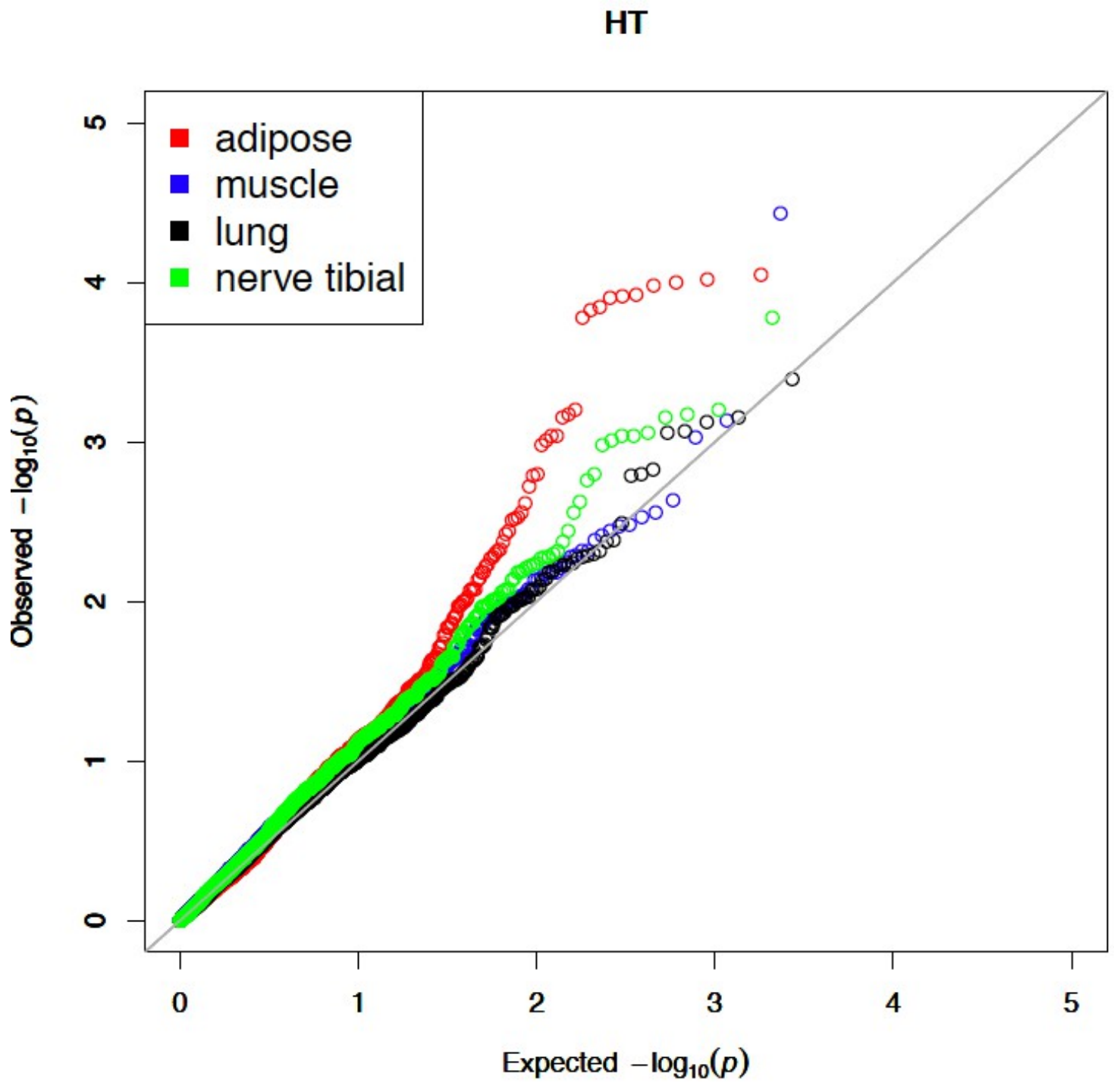


Adipose

Hypertension and Adipose eQTLs






HT
adipose
muscle
lung
nerve tibial
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$
0
1
2
3
4
5

Biology by Tissue?

- Does tissue specificity relate to developmental ontologies and shared signalling pathways?
- Adipose eQTLs implicated in hypertension GWAS yield additional evidence for both known and new biology

We Have Been Picking the Cherries


The Pie Factory
FLORIDA KEYS FINEST KEY LIME PIE
COFFEE HOUSE

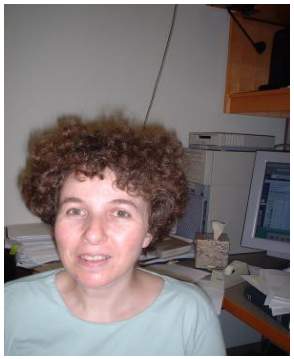
Pitfalls in Enrichment Studies within Catalog

- How do we adequately characterize a null distribution?
- Conditioning on MAF, distance to nearest gene, gene density, appropriately accounting for LD not necessarily adequate
- Aspects of “functionality” may be shared across classes of variants

Pitfalls in Enrichment Studies within Catalog

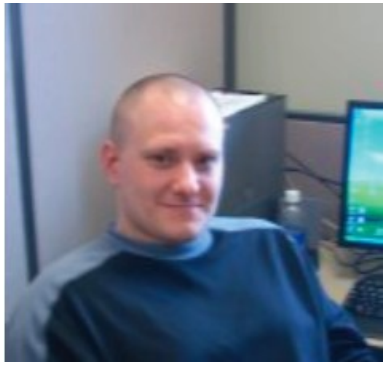
- Straightforward methods for dealing with pitfalls for enrichment studies in individual GWAS (e.g. permutation) may not translate to catalog
- Biases may be more pronounced because of higher proportion of real findings

Cox Lab



Anna Pluzhnikov

Steven Zhang



Pat Evans

Jason Torres

Anna Tikhomirov

Lea Davis (Bridget)

Anuar Konkashbaev

Keston Aquino-Michaels

Carolyn Jumper

Vasily Trubetskoy

Eric Gamazon

Colleagues & Collaborators

Dan Nicolae

M. Eileen Dolan

Haky Im

All of our GTEx Collaborators!

EMMANOUIL DERMITZAKIS, RODERIC GUIGO, DAPHNE KOLLER, MARK MCCARTHY
JUN LIU
JONATHAN PRITCHARD, MATTHEW STEPHENS
IVAN RUSYN, ANDREW NOBEL, FRED WRIGHT
KRISTIN ARDLIE, GADDIE GETZ, MANOLIS KELLIS, …