



The Genotype-Tissue Expression (GTEx) pilot analysis: multi-tissue gene regulation in humans.

Manolis Dermitzakis

(University of Geneva, Switzerland - GTEx analysis PI)
on behalf of the GTEx consortium



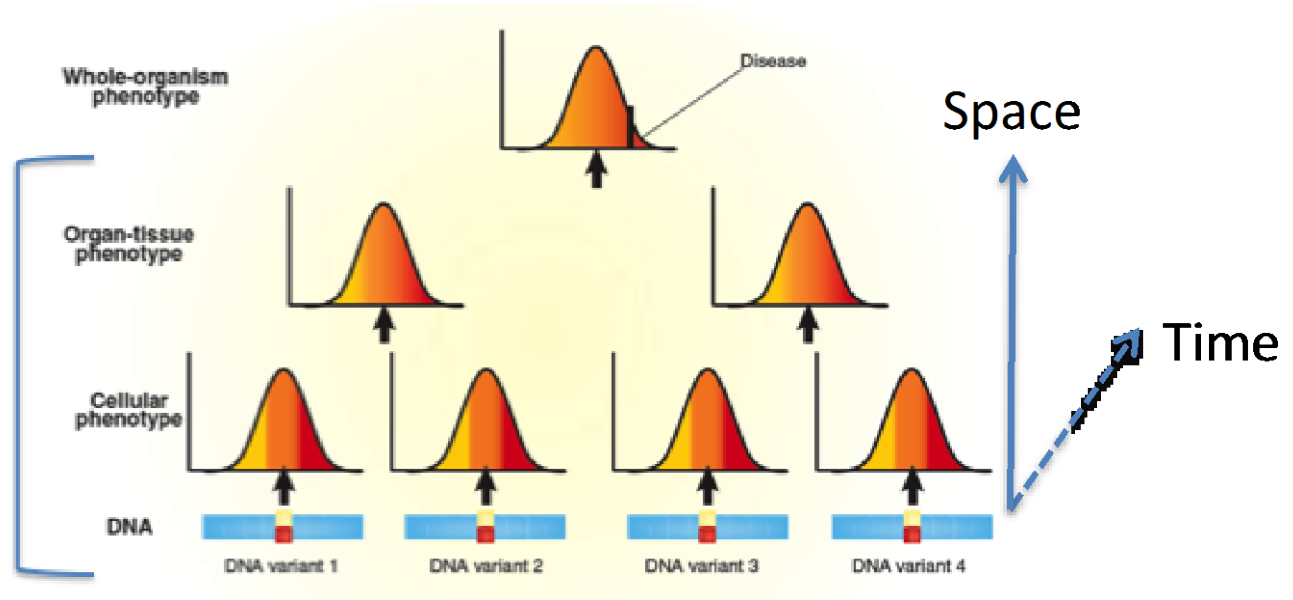
UNIVERSITÉ
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Challenge: How do we go from trait-associated variants to biological mechanism?

ENVIRONMENT

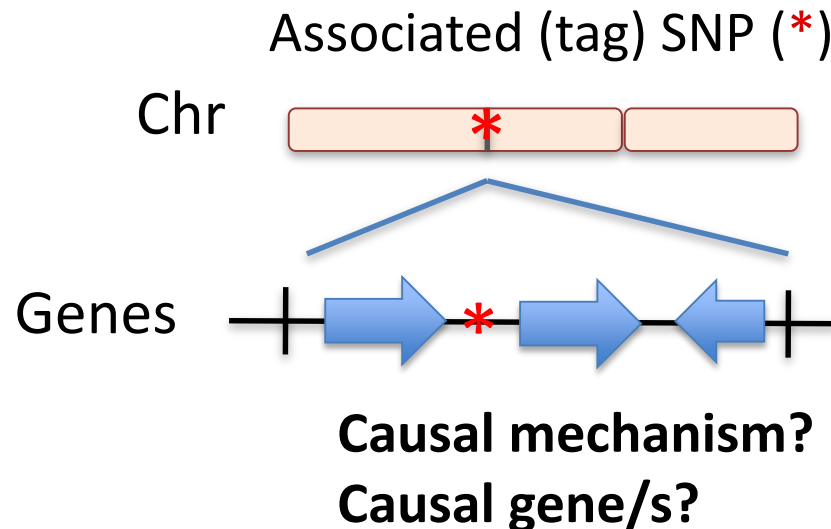
- Behavior
- Infections
- External factors
- etc



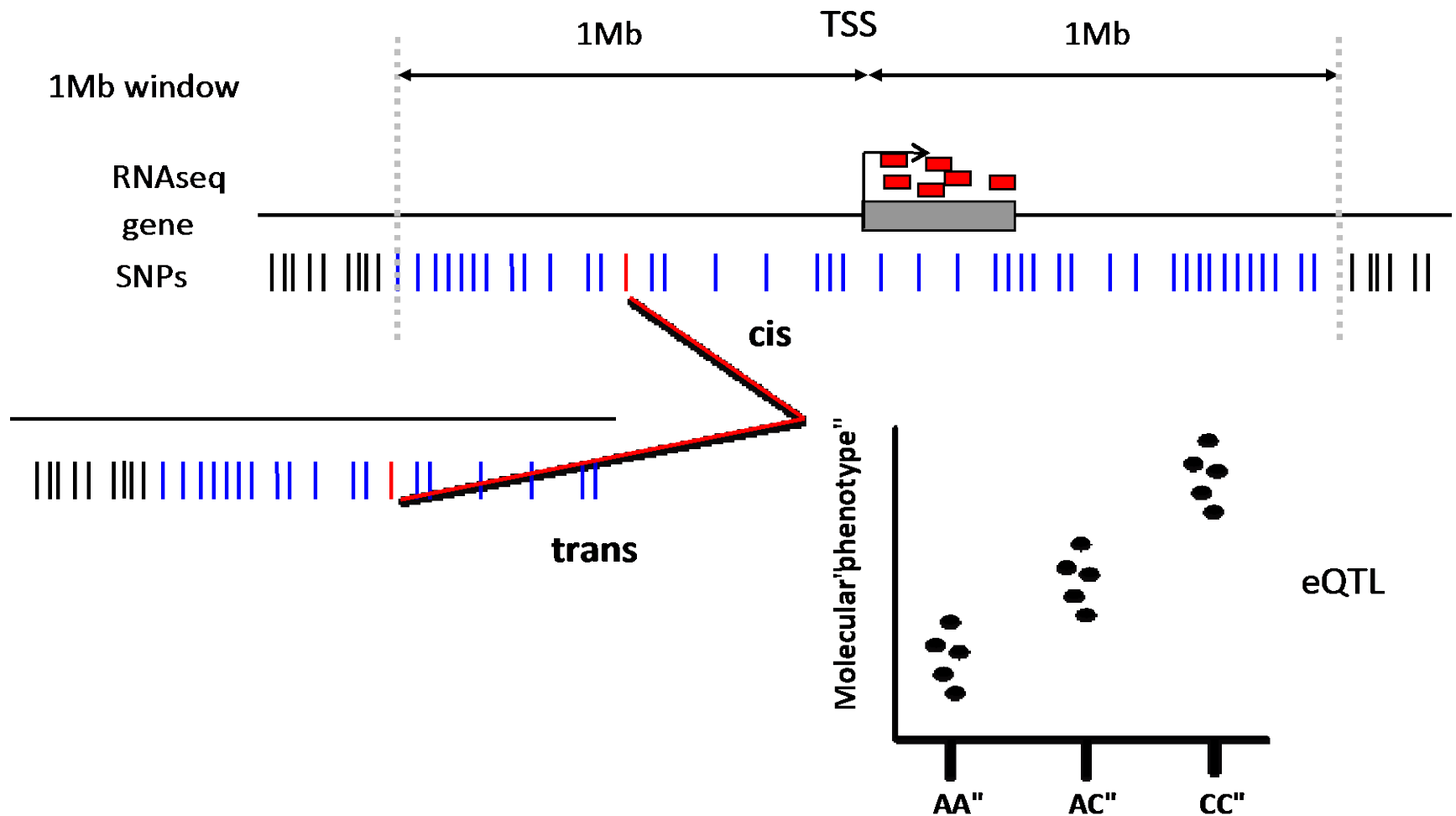
Background Rationale

Genome-wide association studies (**GWAS**) have identified **hundreds of common DNA variants** associated with multiple **complex diseases and traits**.

>2/3 GWAS SNPs lie in noncoding regions (e.g. intergenic, introns).



Expression Quantitative Trait Loci (eQTL)



Many studies show trait-associated SNPs enriched for eQTLs

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PLoS GENETICS

Trait-Associated SNPs Are More Likely to Be eQTLs: Annotation to Enhance Discovery from GWAS

LCL
eQTLs

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PLoS GENETICS

LCL
eQTLs

Candidate Causal Regulatory Effects by Integration of Expression QTLs with Complex Trait Genetic Associations

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Coanalysis of GWAS with eQTLs reveals disease-tissue associations

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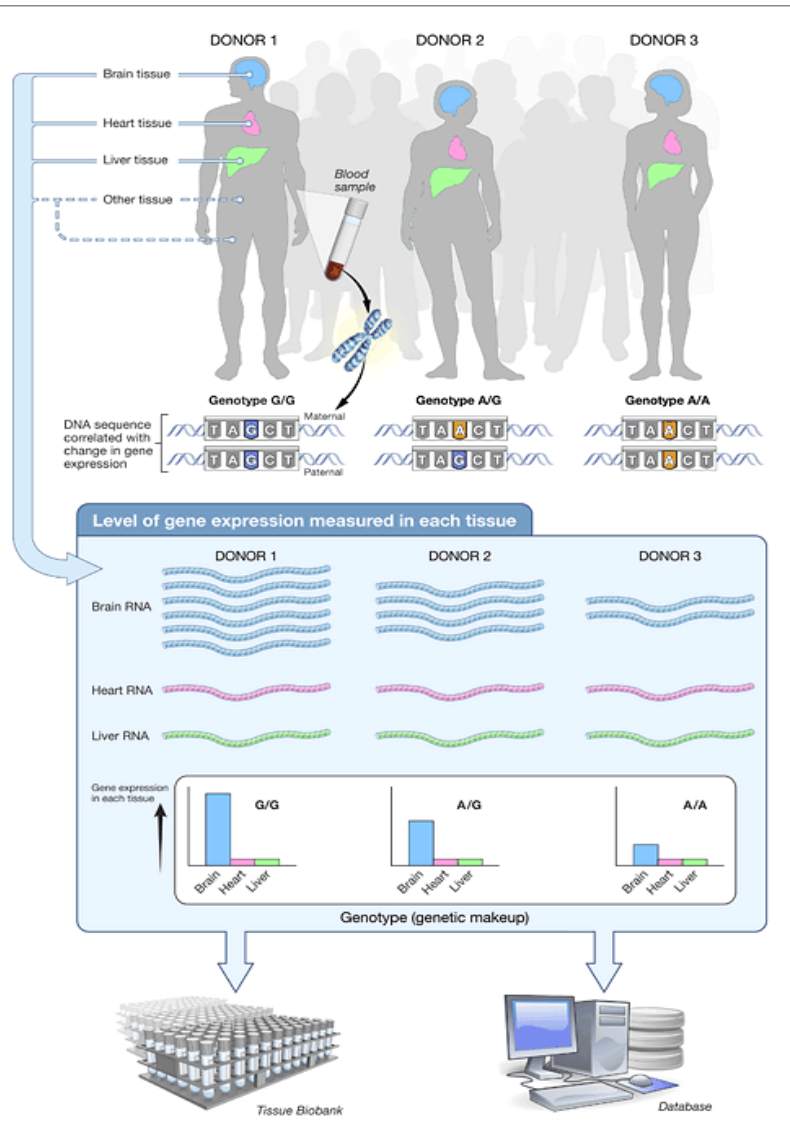
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Peripheral blood
monocyte, liver and
adipose eQTLs

Challenges in using eQTLs to interpret disease associations

- Measuring eQTLs in disease-relevant tissues or cell types
- Most human tissue types are hard to obtain
- Large sample sizes are required for statistical power

GTE_x = Genotype-Tissue Expression



GTE_x GOALS:

- Atlas (database) of gene expression, regulation, and eQTLs from a wide range of non-diseased human tissues
- Biobank of tissues, DNA, RNA

ULTIMATE STUDY SIZE (by 1/2016):

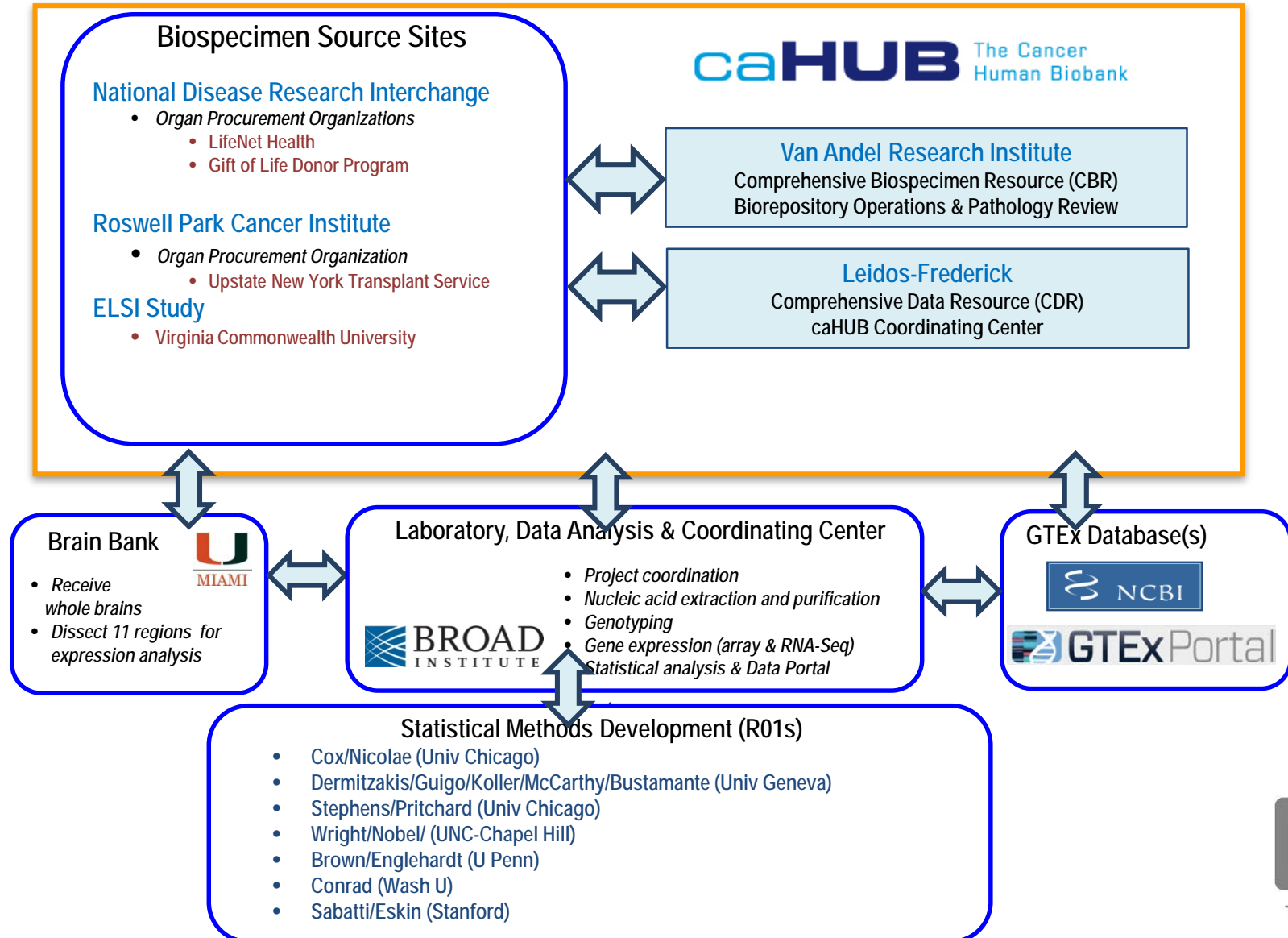
- 900 Postmortem Donors
- Whole exome sequencing
- Whole genome sequencing
- RNA-Seq of ~30 tissues/donor (>20,000 tissues)



PILOT PHASE (in 2010):

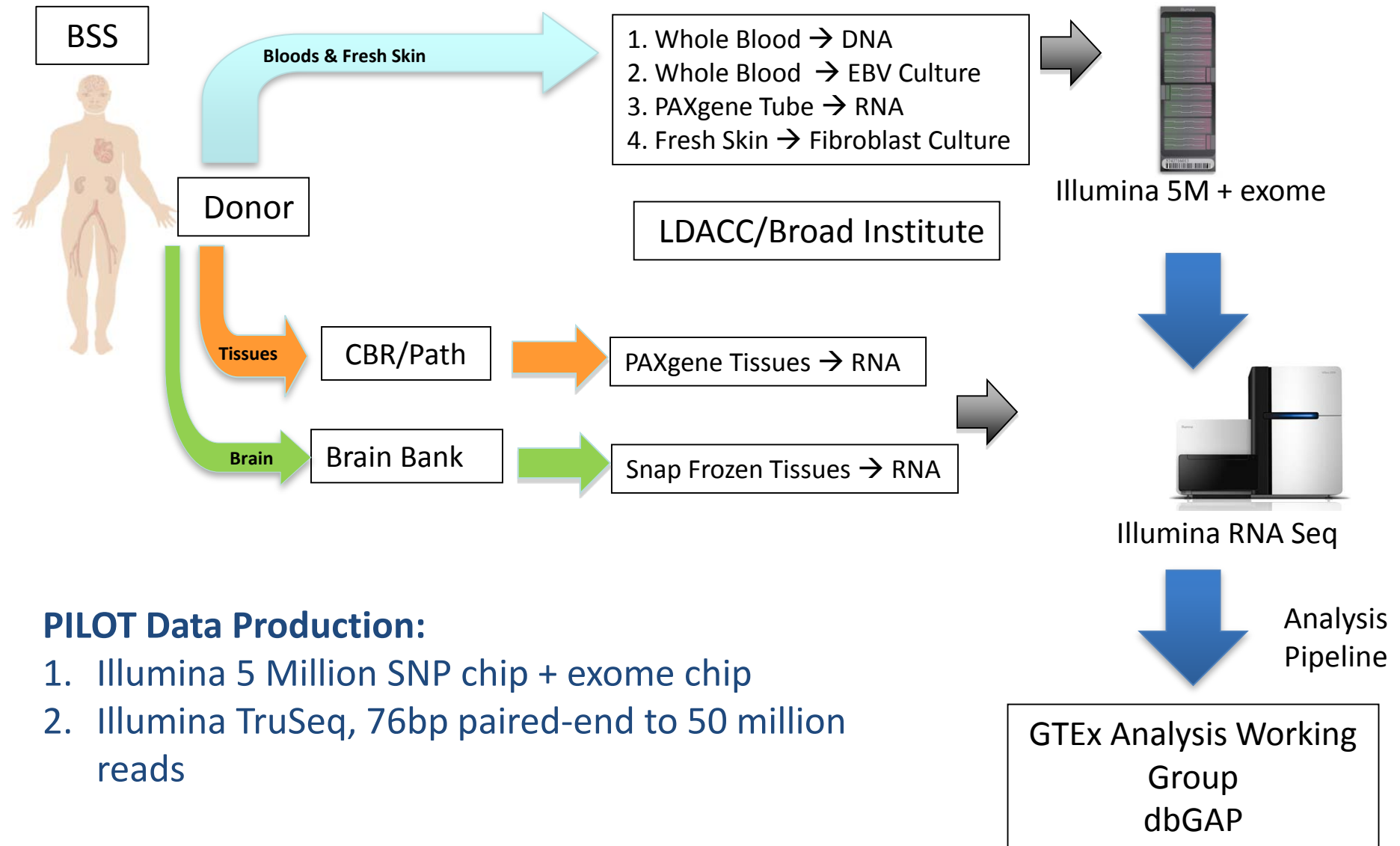
- 175 Postmortem Donors
- 1641 RNA-Seq of ~28 tissues/donor

Pilot GTEx Consortium

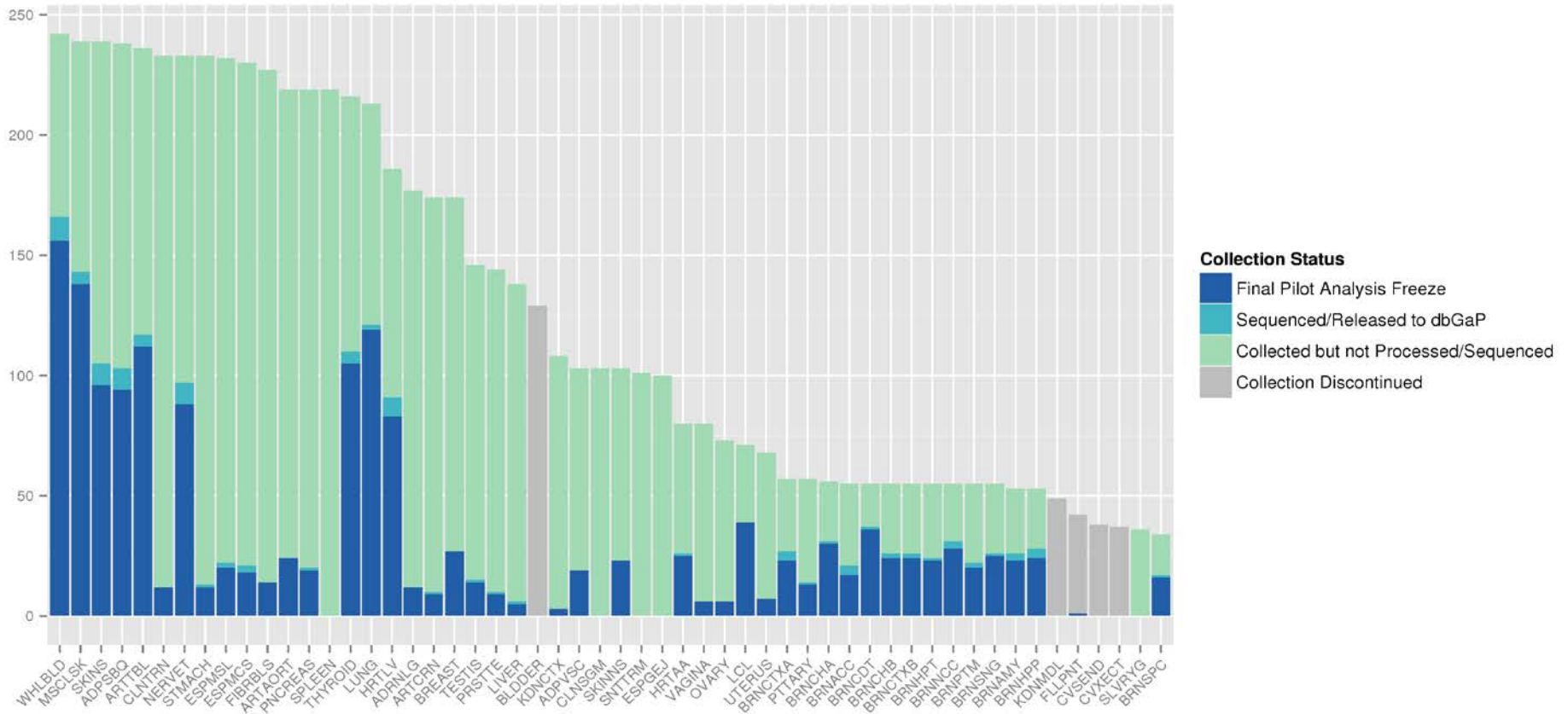


Laboratory Data Analysis and Coordinating Center

GTEx Workflow



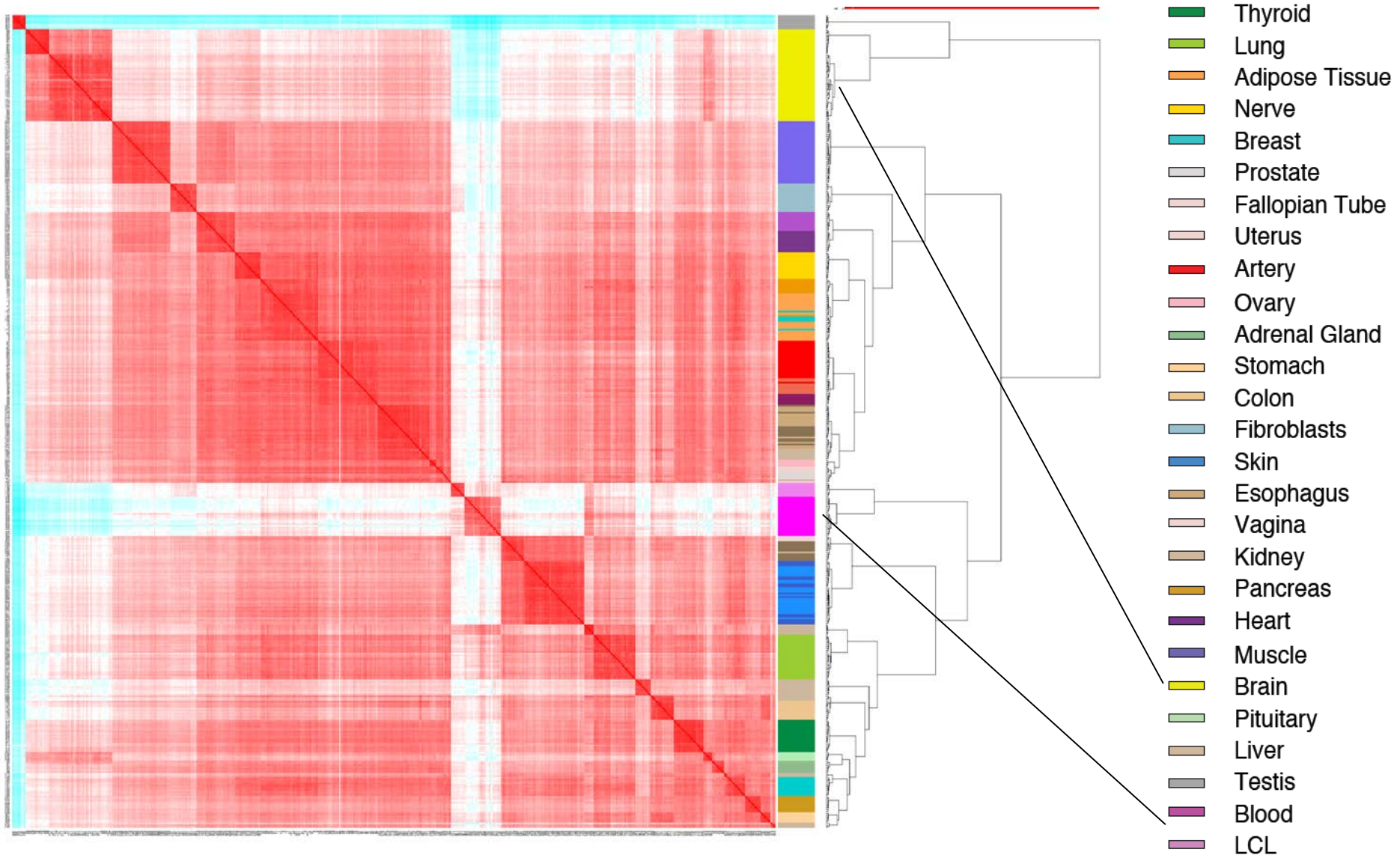
Pilot Phase Data



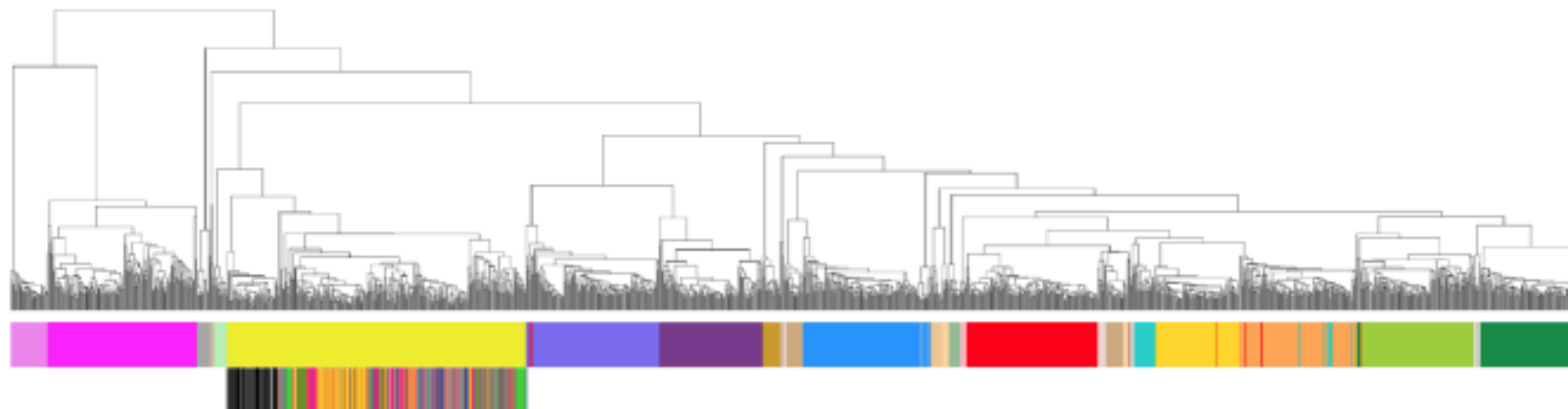
Pilot phase collected an average of ~ 28 tissue samples per donor from 54 distinct sites

Analysis Freeze = 175 Donors and 1,641 tissue RNA-seq samples

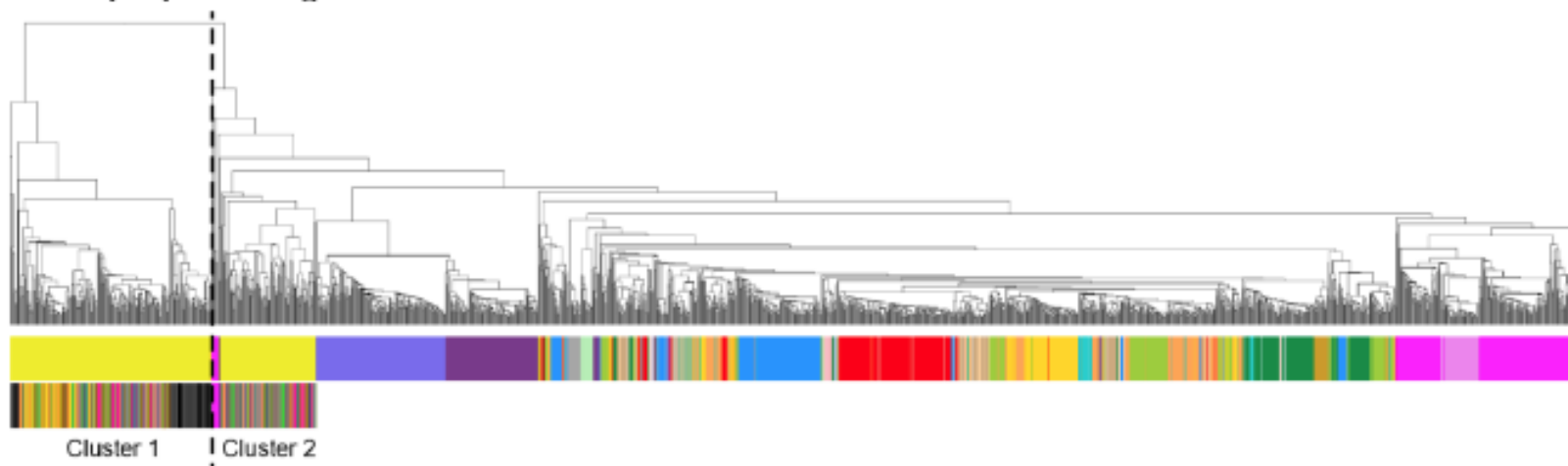
Clustering of Expression Data



A Gene expression clustering



B Exon (PSI) clustering



Brain subregions

■ Amygdala	■ Frontal cortex (BA9)
■ Anterior cingulate cortex (BA24)	■ Hippocampus
■ Caudate (basal ganglia)	■ Hypothalamus
■ Cerebellar hemisphere	■ Nucleus accumbens (basal ganglia)
■ Cerebellum	■ Putamen (basal ganglia)
■ Cortex	■ Spinal cord (cervical c.1)
	■ Substantia nigra

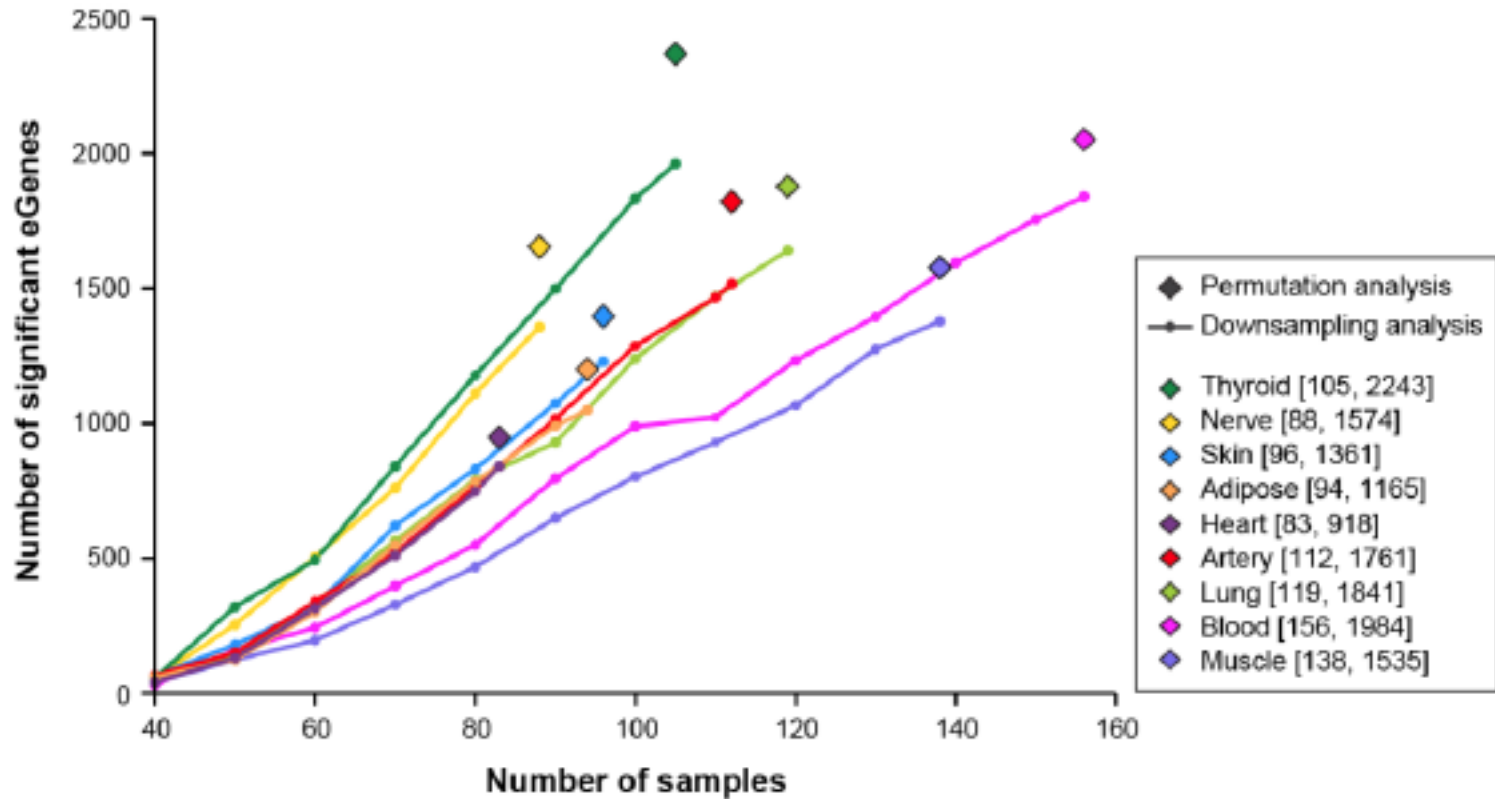
All tissues (main tissues in bold)

■ Adipose tissue	■ Colon	■ Lung	■ Prostate
■ Adrenal gland	■ Esophagus	■ Muscle	■ Reproductive organs
■ Artery	■ Fibroblasts	■ Nerve	■ Skin
■ Blood	■ Heart	■ Ovary	■ Stomach
■ Brain	■ Kidney / Liver	■ Pancreas	■ Testis
■ Breast	■ LCL	■ Pituitary	■ Thyroid

eQTL methodology

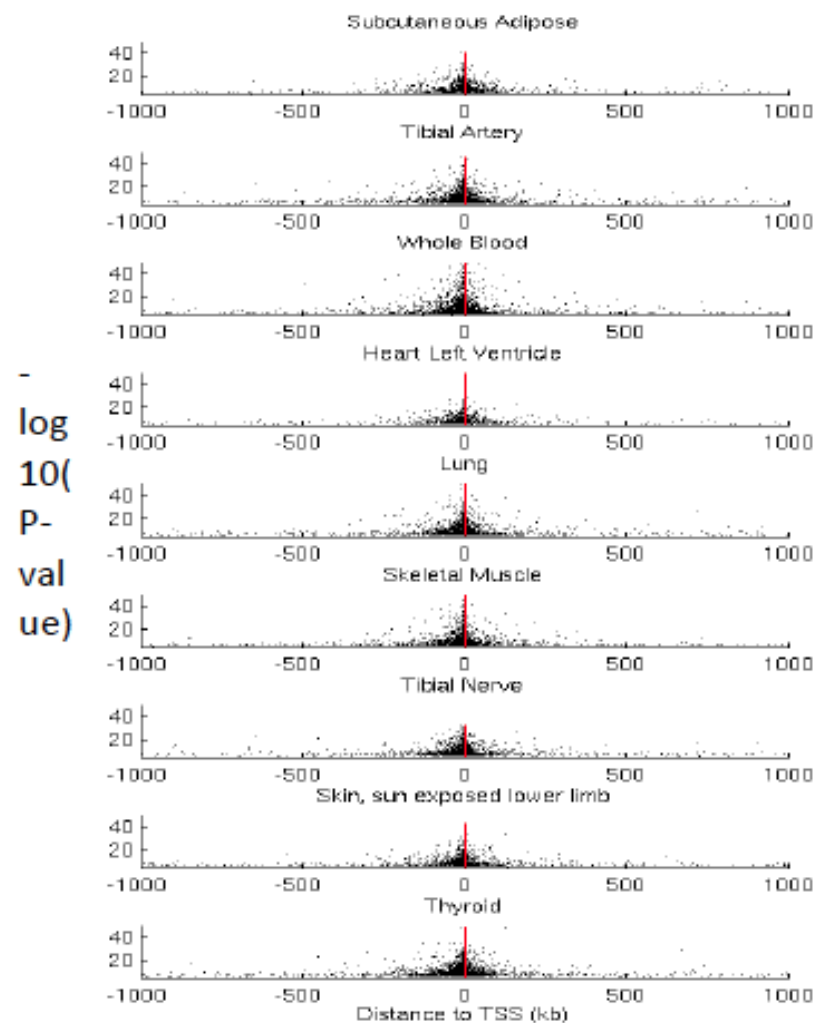
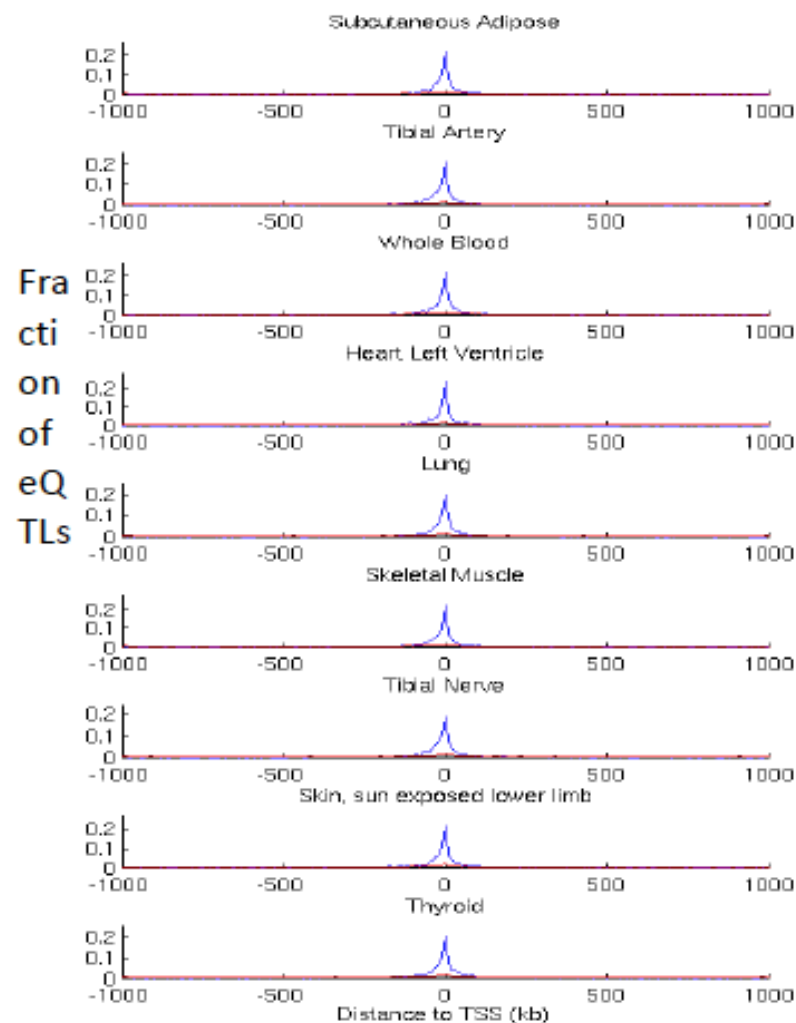
- 1 Mb (or 100Kb from TSS)
- PEER correction to remove undesirable effects (batch, other experimental etc)
- Matrix eQTL with permutations to discover eQTLs

eQTL discovery



A.

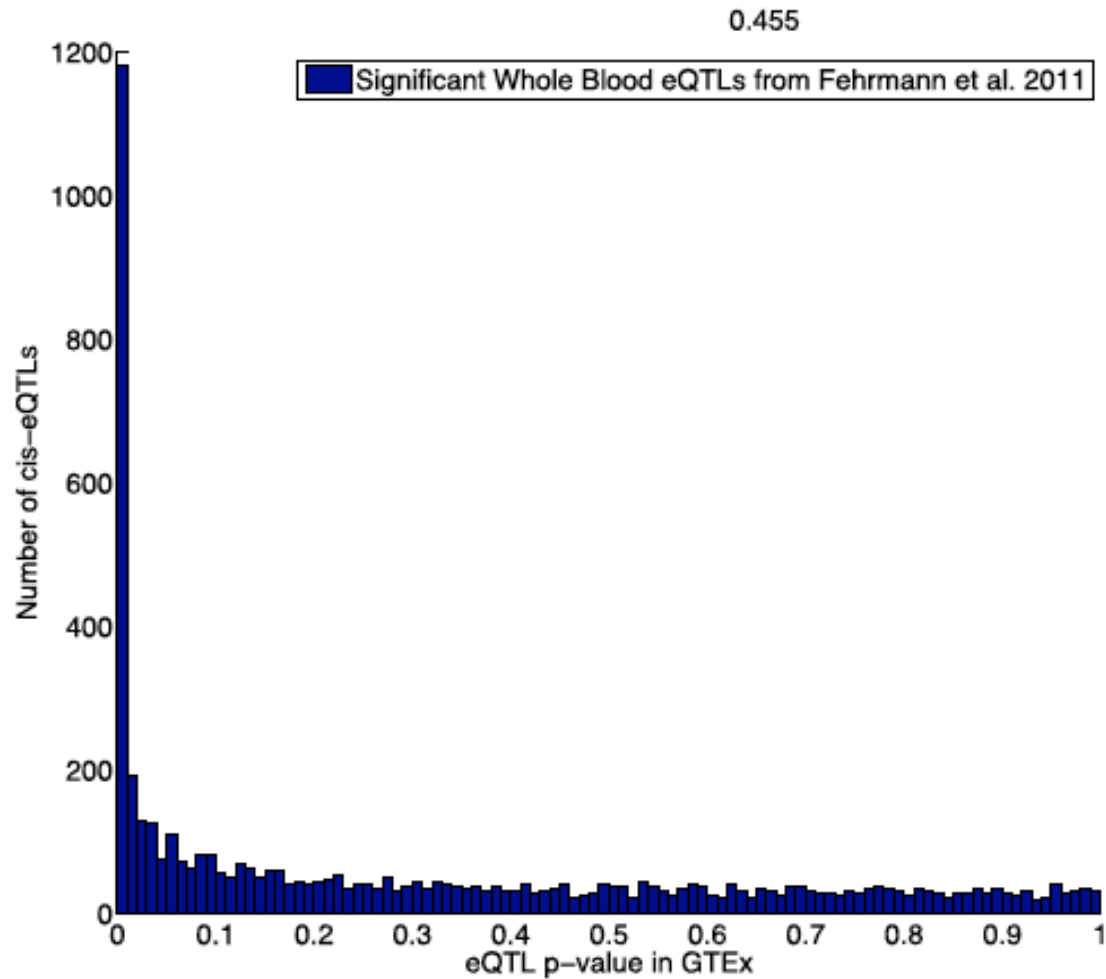
eQTL properties



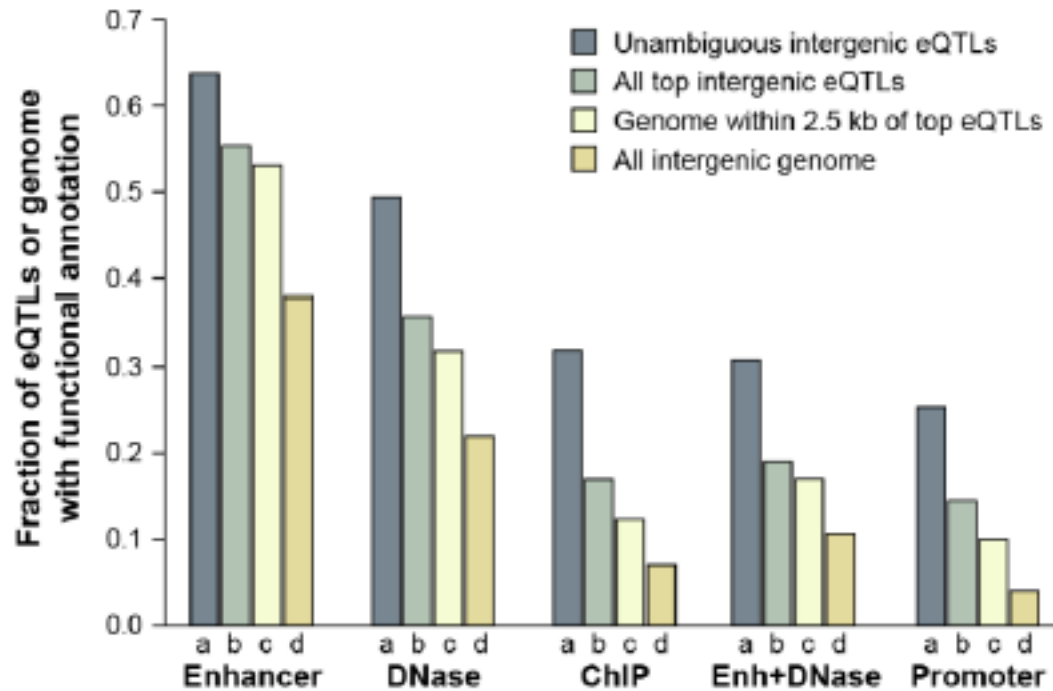
- Significant best eQTLs per gene, FDR<5%
- Non-significant best eQTLs per gene, FDR>5%
- All SNP-gene pairs

eQTL replication

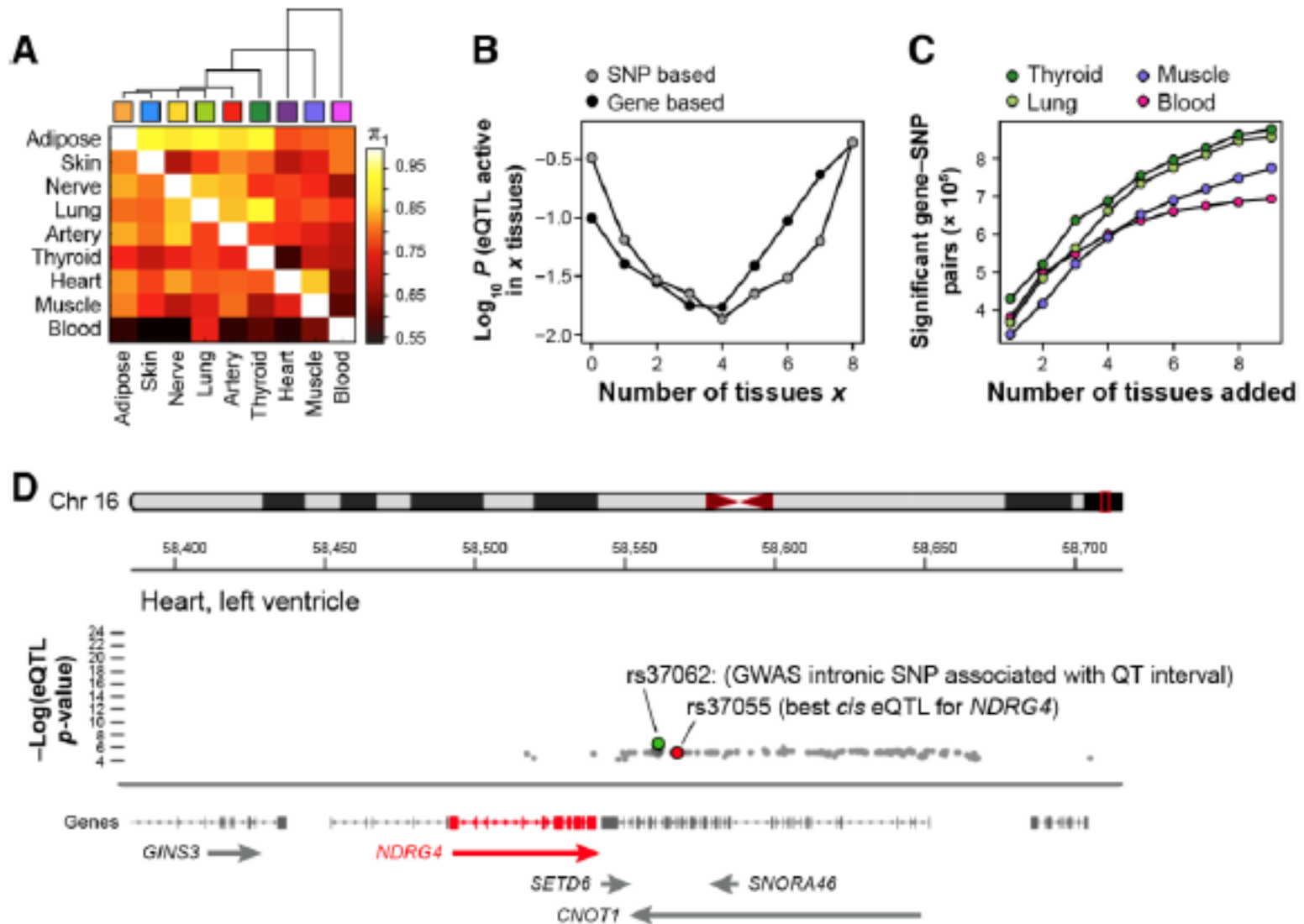
A.



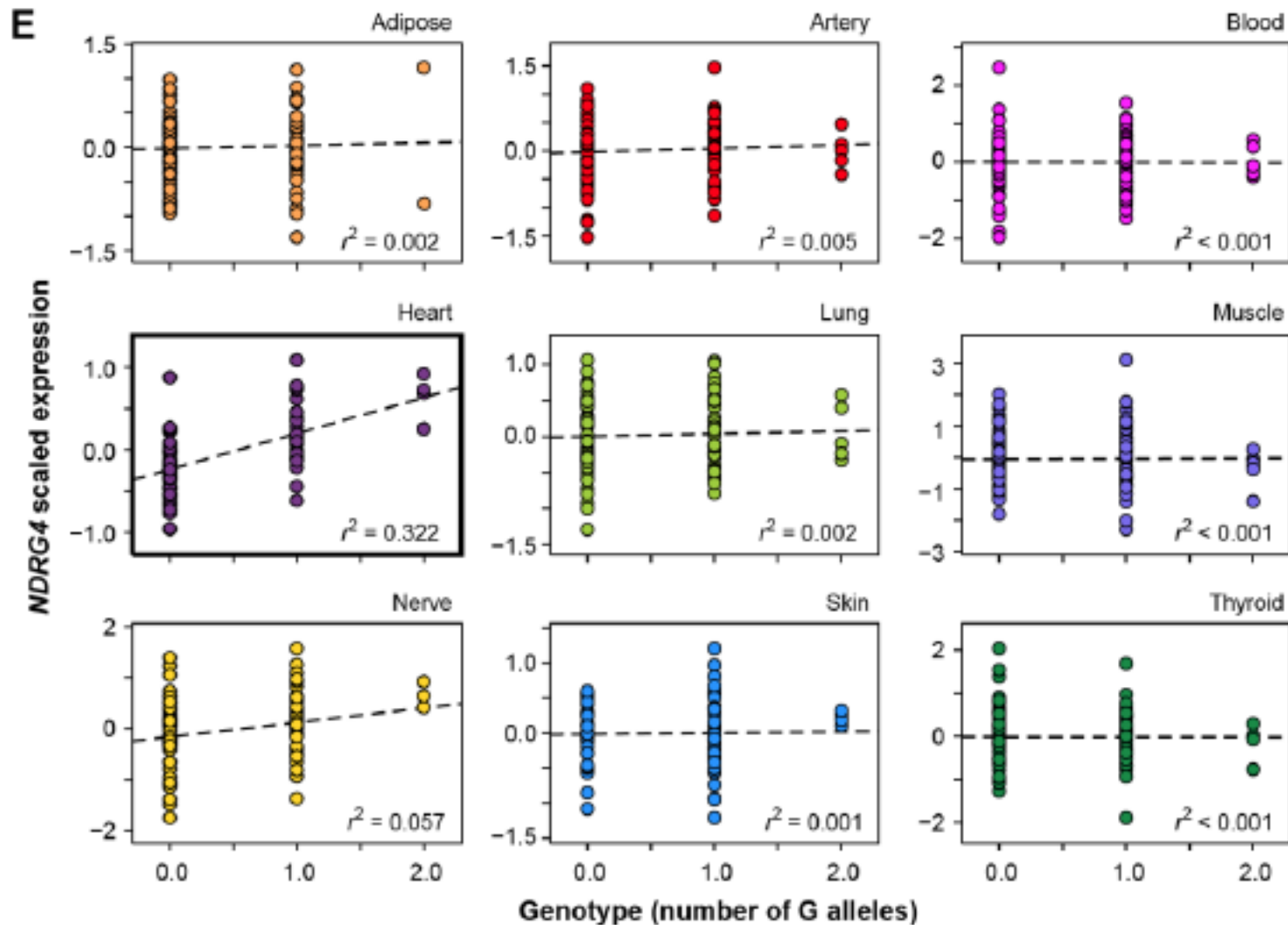
eQTL functional enrichment



Multi-tissue eQTL discovery

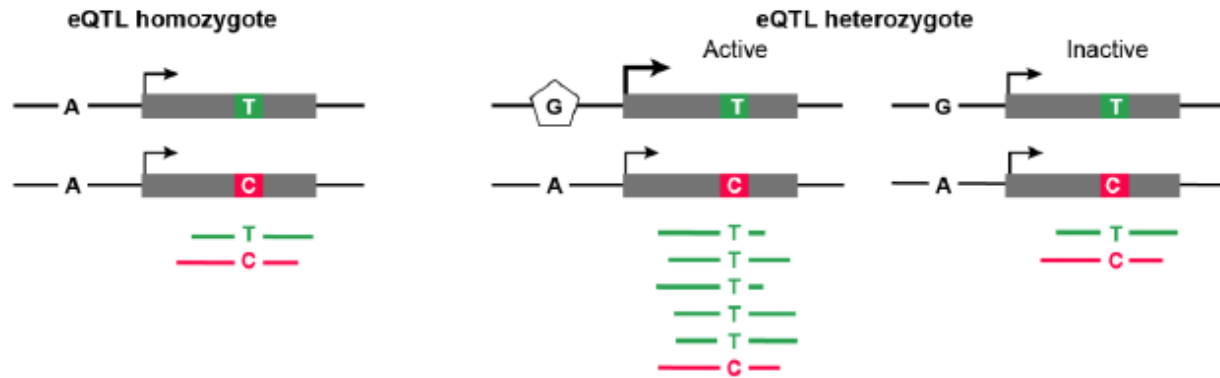


Multi-tissue eQTL discovery

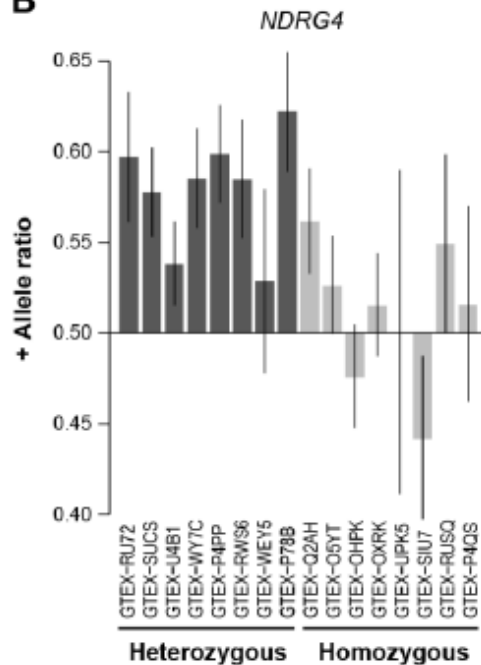


Allele Specific Expression and eQTLs

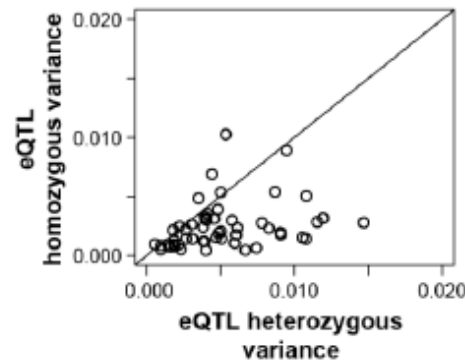
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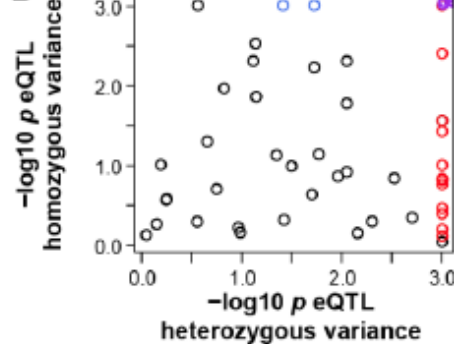
B



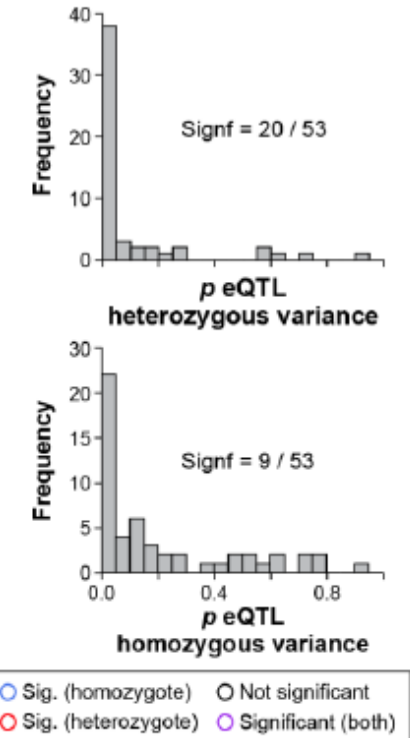
C



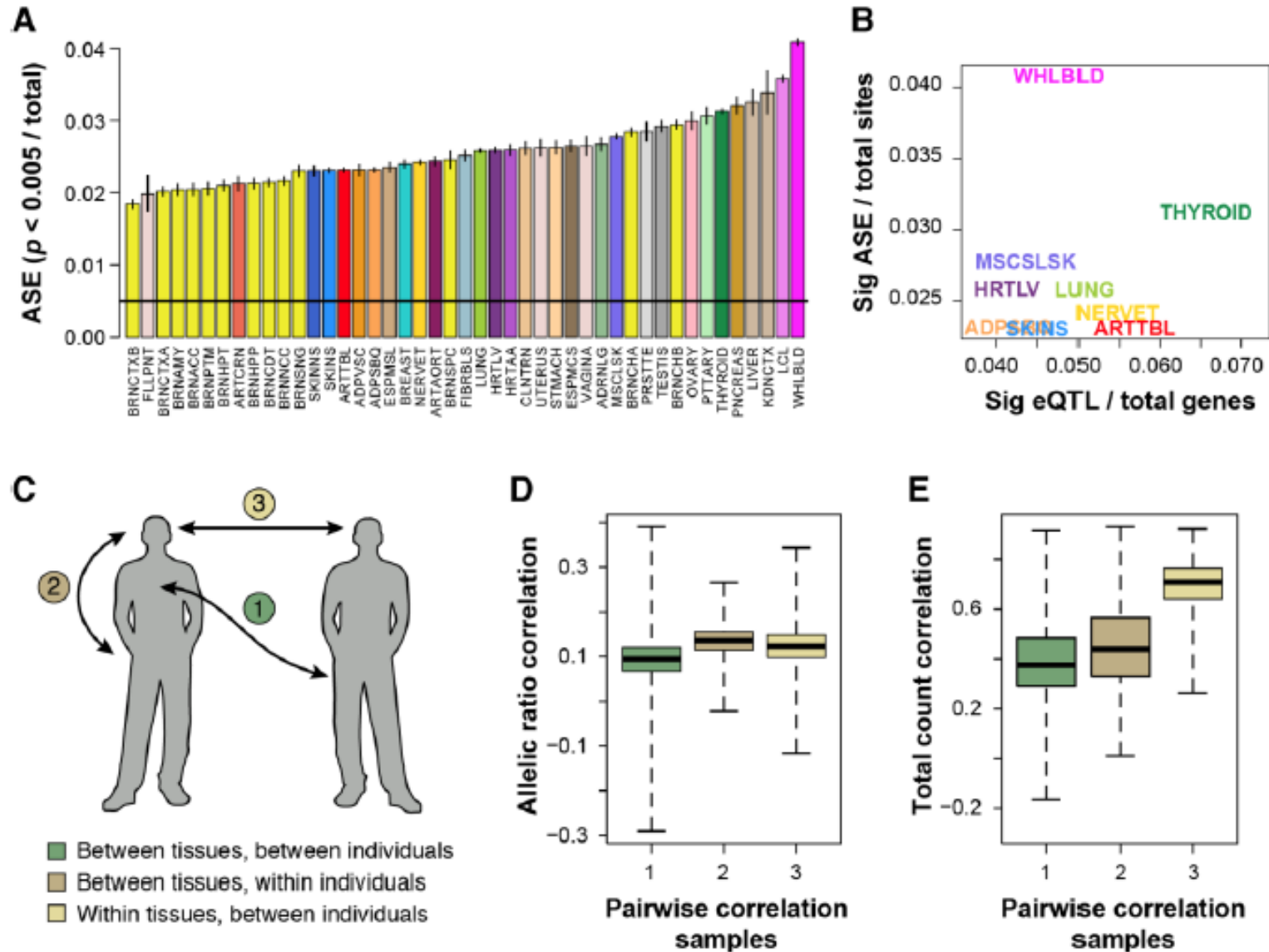
D



E

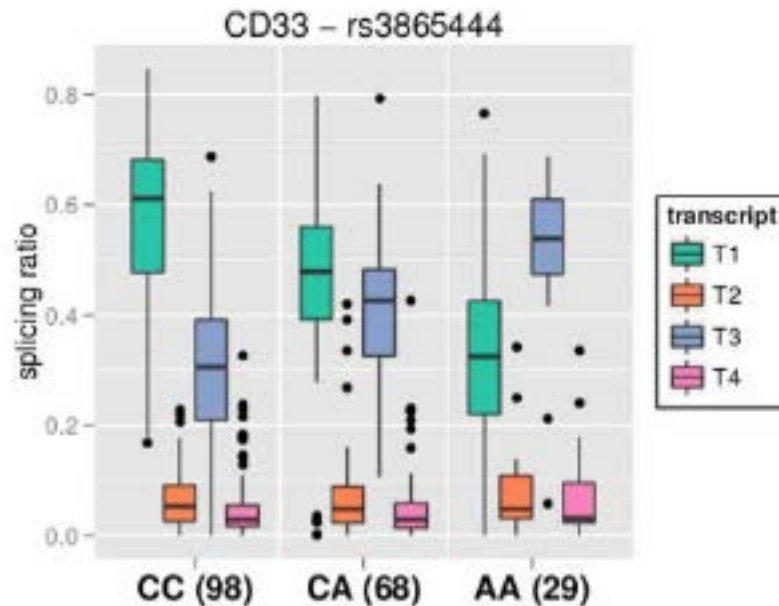


Allele Specific Expression

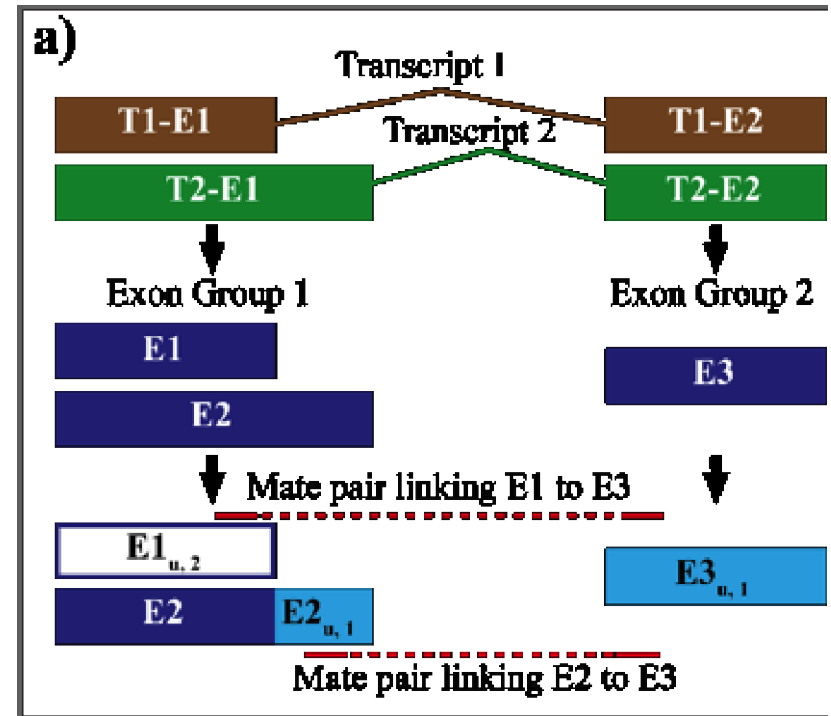


Alternative splicing QTLs

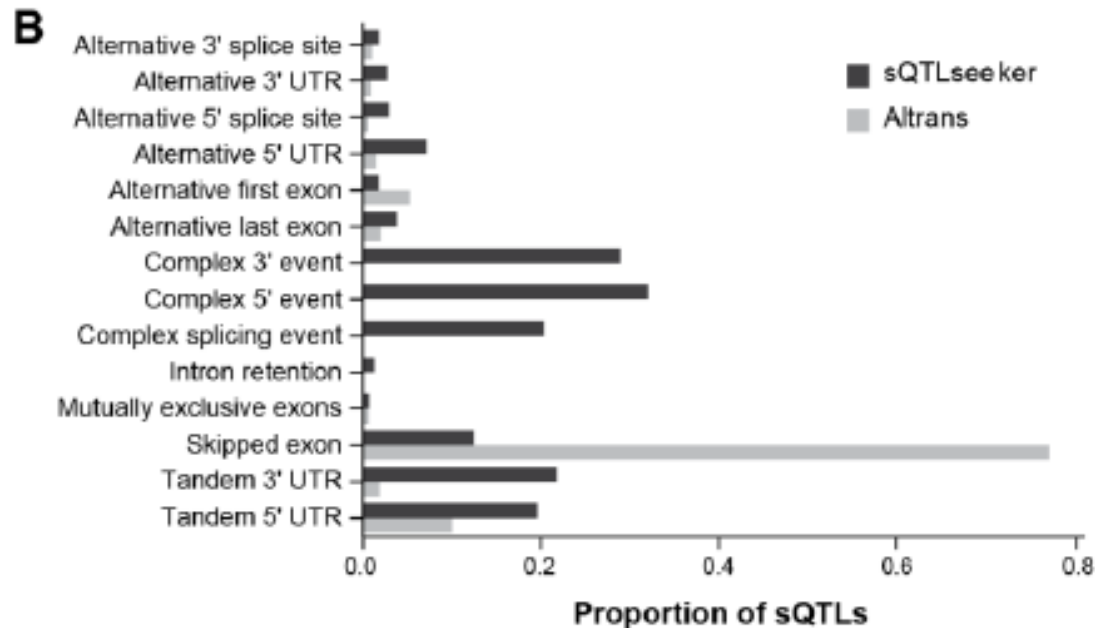
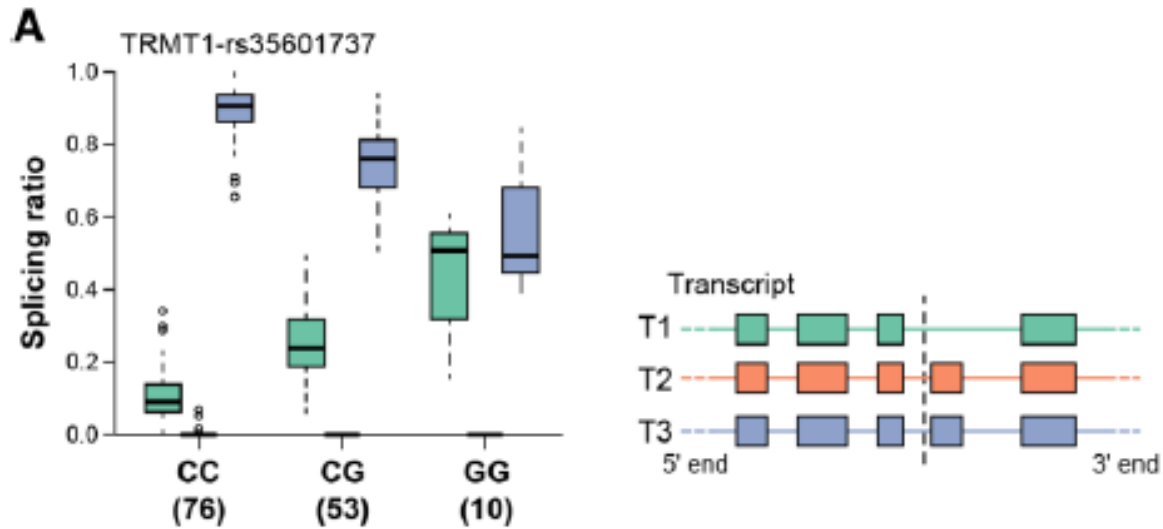
sQTL seeker



Altrans

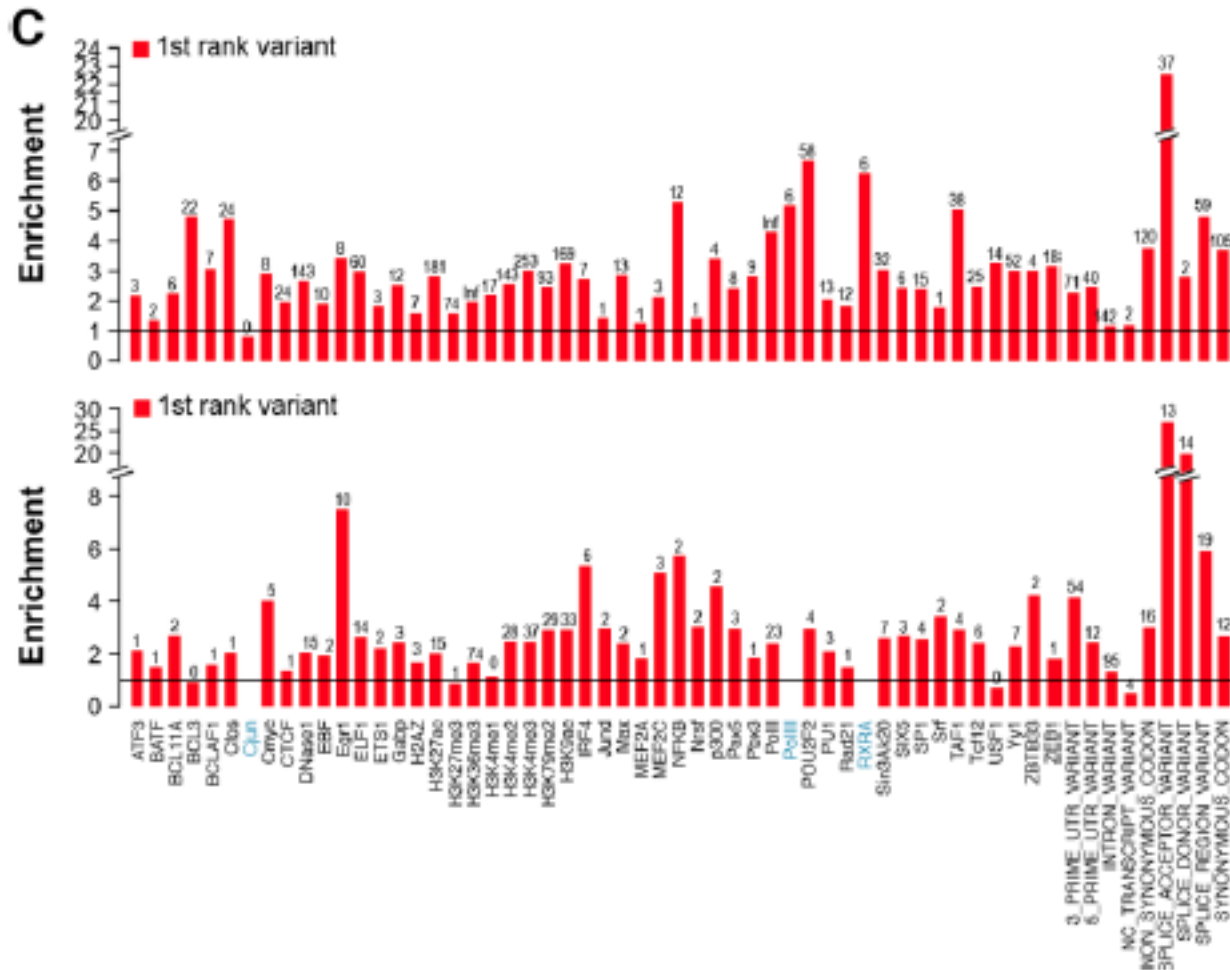


Alternative splicing QTLs

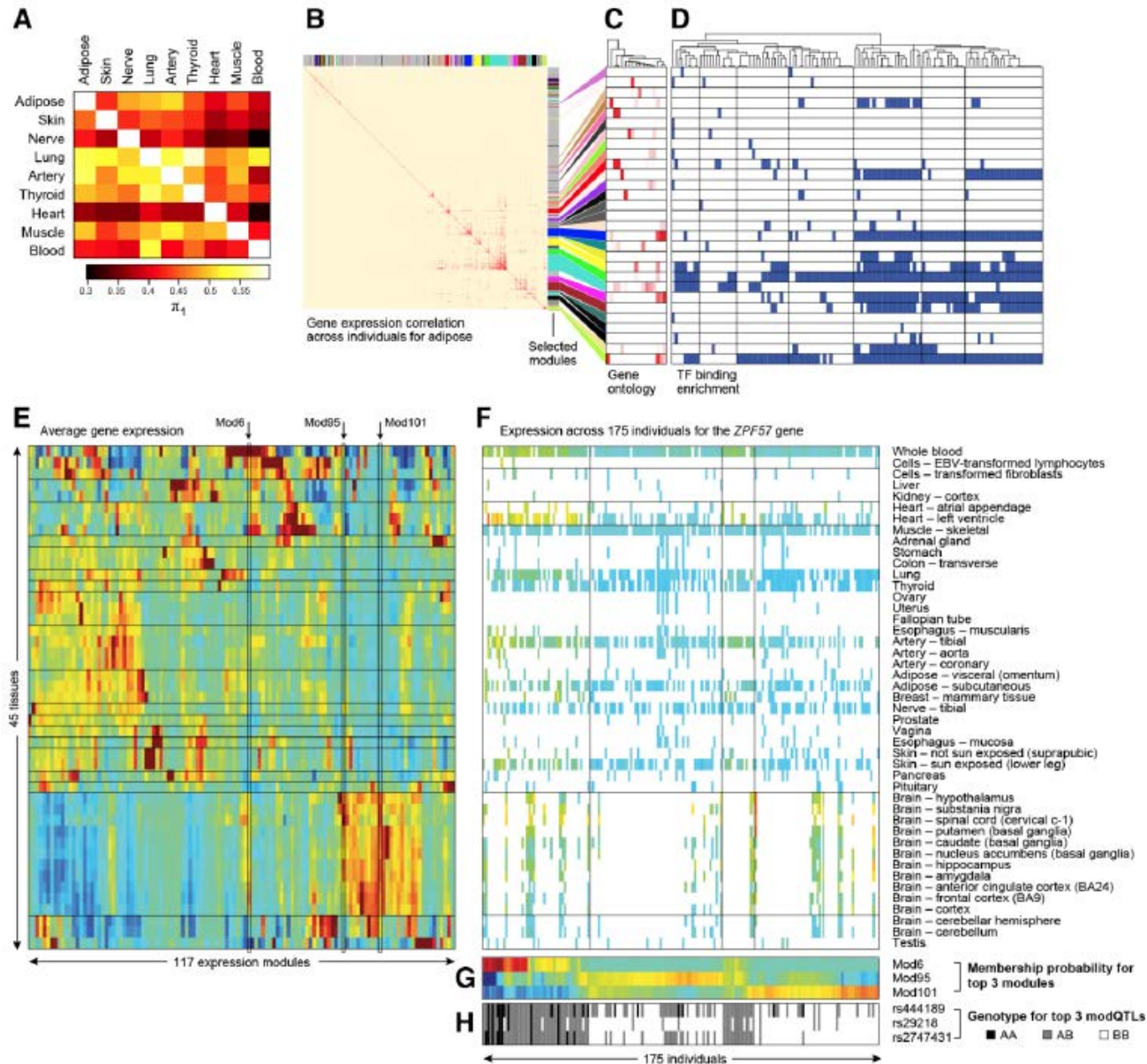


Alternative splicing QTLs

Functional element enrichment

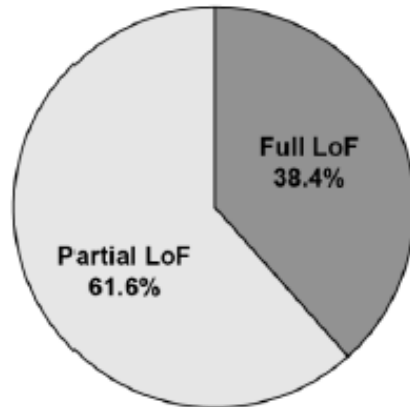


Network module QTLs

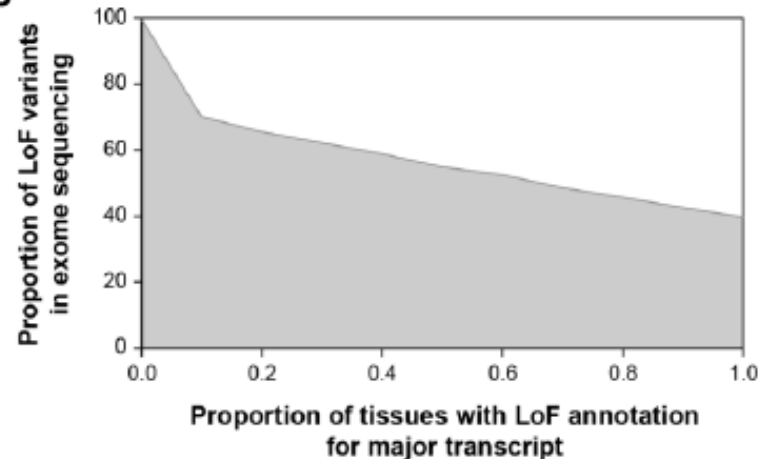


Truncating Variants in the transcriptome

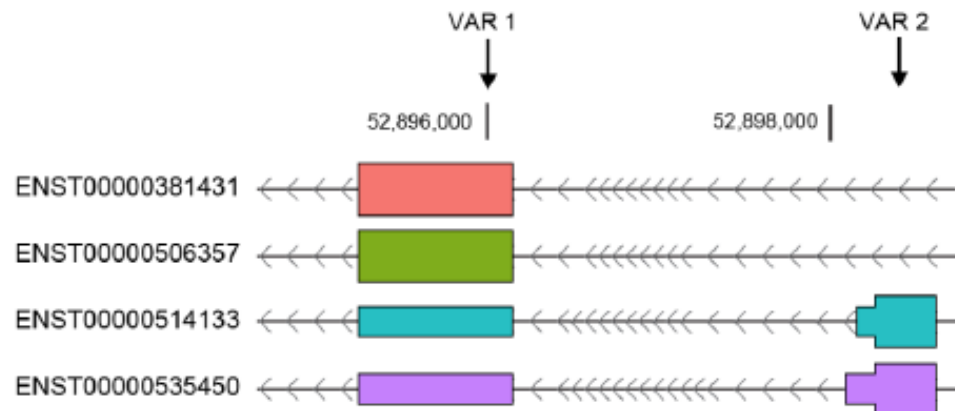
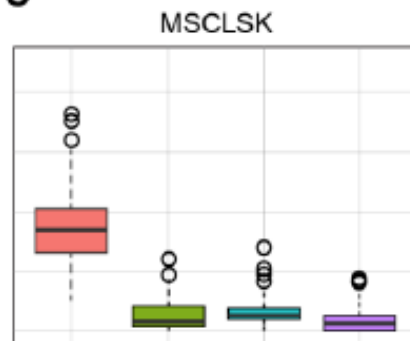
A



B



C



In silico

Stop gain

Stop gain

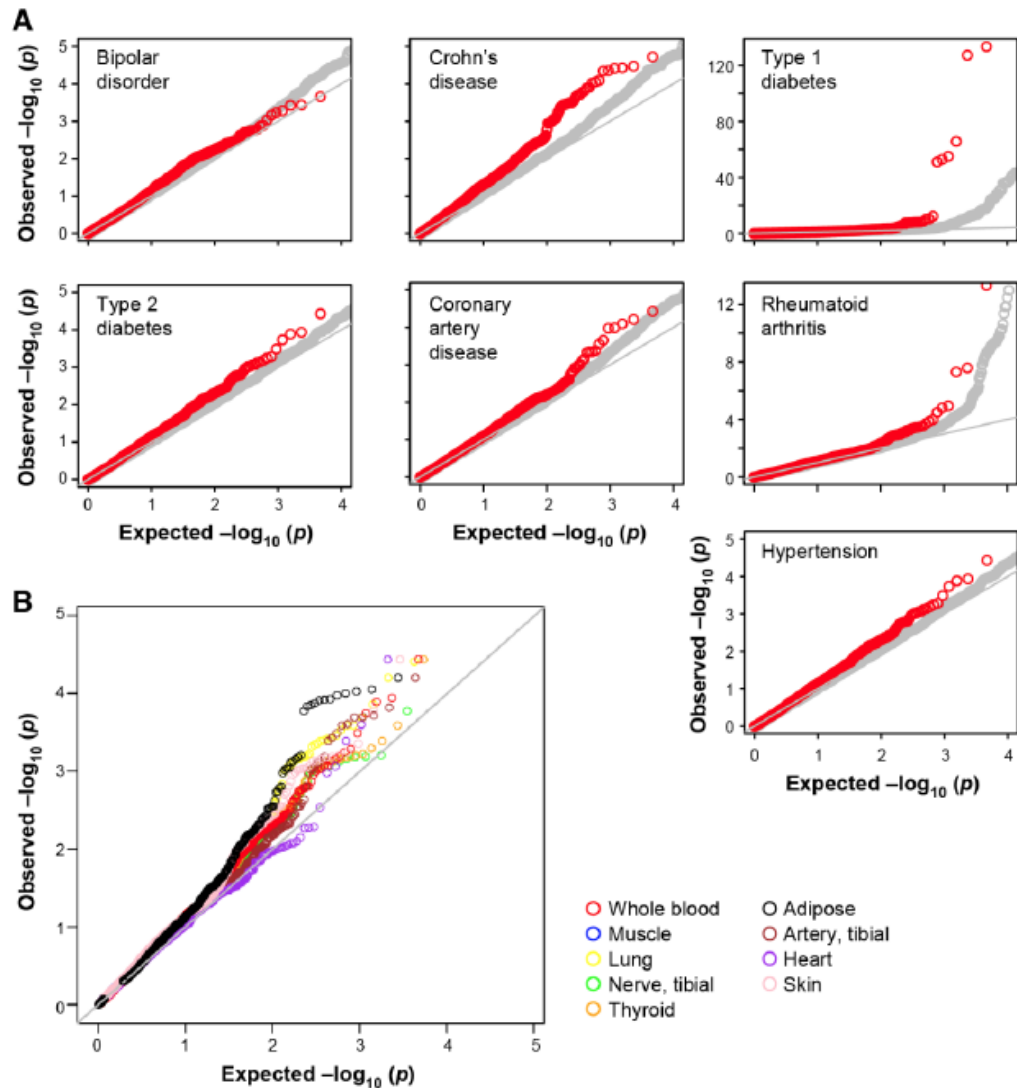
Transcript ← RNA-Seq*

Stop gain

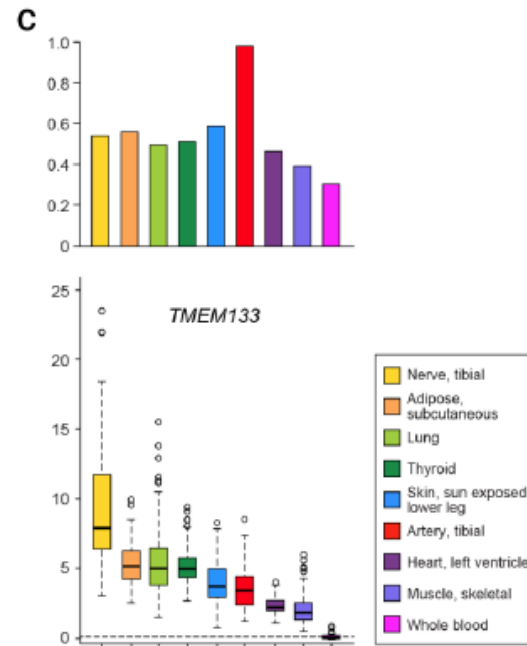
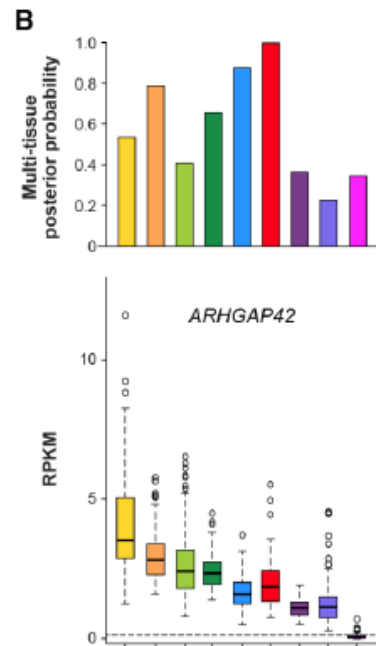
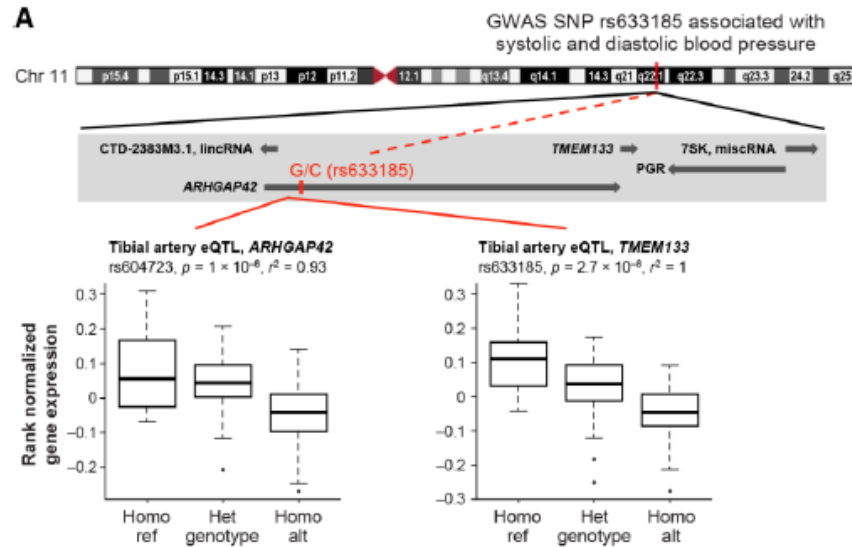
Intronic

* DNA variant annotation informed by tissue RNA-Seq quantification.

Link eQTLs to GWAS



Link eQTLs to GWAS



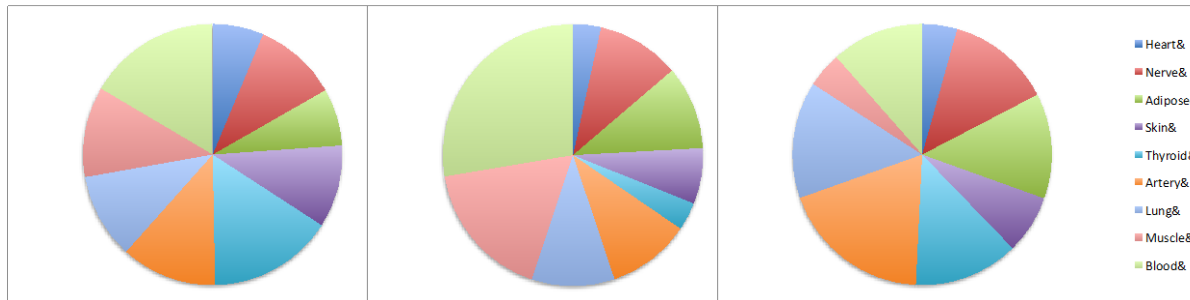
Link eQTLs to GWAS

0.31	0.47	0.31	0.31	0.79	0.31	0.94	0.16	0.47	Obesity-related traits
2.10	3.03	0.70	2.33	0.70	2.10	1.17	2.10	1.86	Height
0.00	0.90	0.30	0.90	0.60	0.90	0.30	1.20	0.90	IgG glycosylation
0.00	2.23	0.00	0.56	2.79	1.68	2.79	3.35	4.47	Blood metabolite levels
0.57	2.29	1.14	1.71	2.29	0.57	2.86	1.14	2.86	Crohn's disease
0.57	0.57	0.00	1.72	0.00	0.00	0.57	0.00	0.57	Type 2 diabetes
0.00	1.28	0.00	0.64	1.28	1.28	1.92	1.92	5.77	Rheumatoid arthritis
2.07	1.38	0.69	0.69	3.45	0.69	2.07	4.14	2.07	Multiple sclerosis
0.70	1.41	0.00	1.41	0.70	0.70	0.00	2.11	2.11	Body mass index
0.00	0.00	0.00	0.72	0.72	0.72	0.00	1.45	0.72	Breast cancer
0.00	0.00	2.38	3.17	1.59	0.00	0.79	2.38	2.38	HDL cholesterol
2.44	1.63	0.81	1.63	4.07	2.44	2.44	4.07	0.81	Schizophrenia
0.00	0.83	0.00	0.83	1.67	0.00	0.00	1.67	3.33	Coronary heart disease
0.84	1.68	0.00	0.84	0.84	0.00	0.84	0.00	2.52	Bipolar disorder
2.63	2.63	0.88	2.63	4.39	2.63	1.75	0.88	7.02	Inflammatory bowel disease
Adipose	Subcutaneous	Artery	Tibial	Heart	Left	Ventricle	Lung	Muscle	Skeletal
Nerve	Tibial	Skin	Sun	Exposed	Lower	leg	Thyroid	Whole	Blood

ALL

IBD

HEIGHT



TISSUE CAUSALITY PROFILES

Summary

- Unprecedented catalogue of eQTLs in multiple tissues
- eQTL tissue specificity estimates
- First glimpse into effect of genetic variation in diverse tissues/organs of the human body
- GWAS and other disease variant interpretation and causal effects

Acknowledgments

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The Common
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