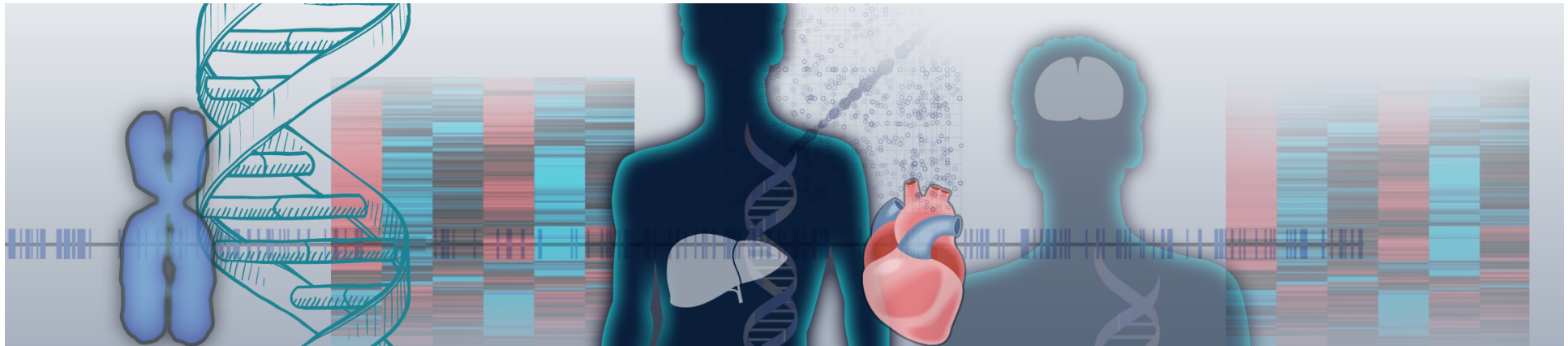




The Genotype-Tissue Expression (GTEx) pilot analysis: multi-tissue gene regulation in humans.

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



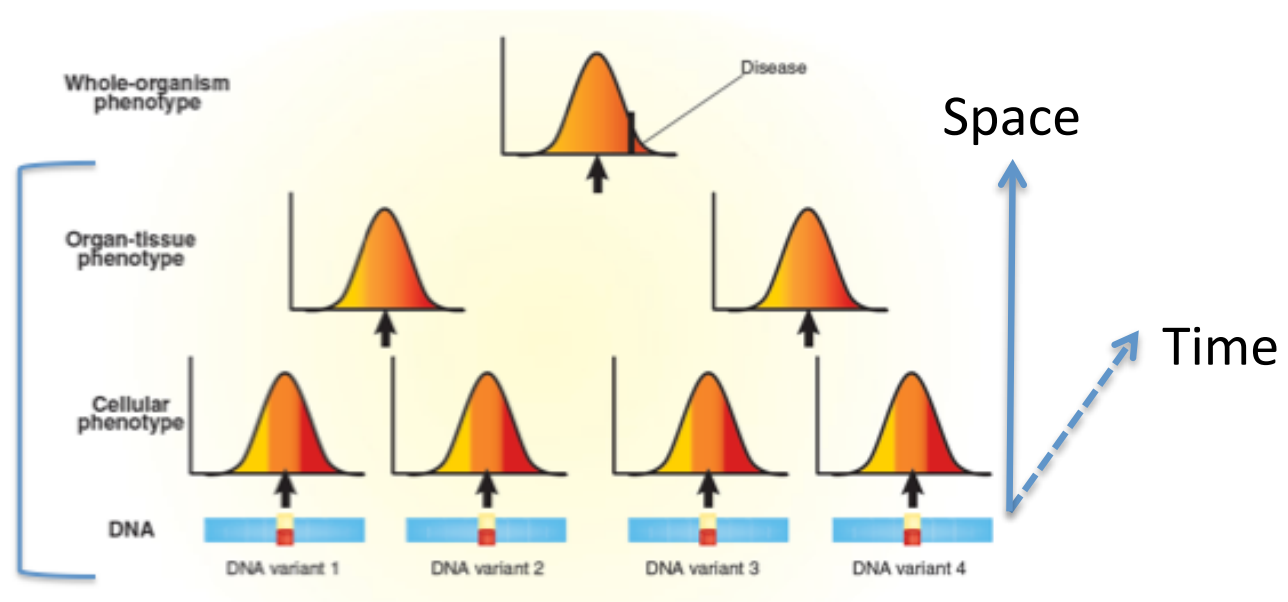
UNIVERSITÉ
DE GENÈVE



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

ENVIRONMENT

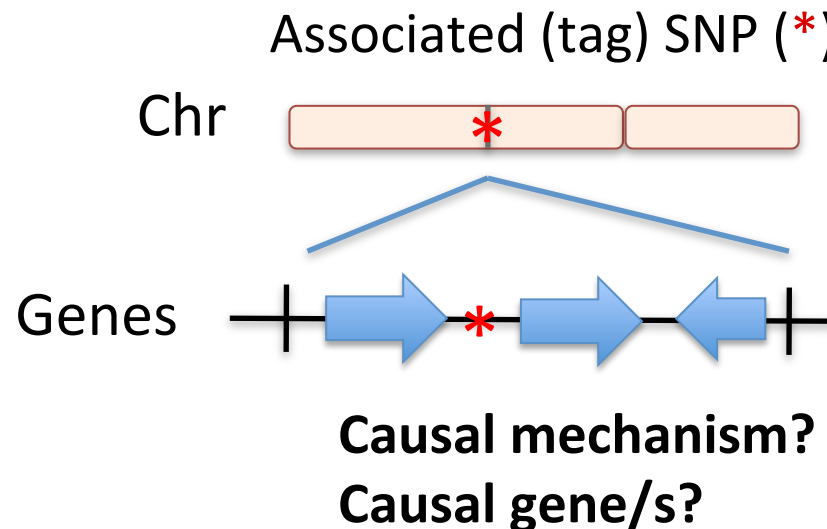
- Behavior
- Infections
- External factors
- etc



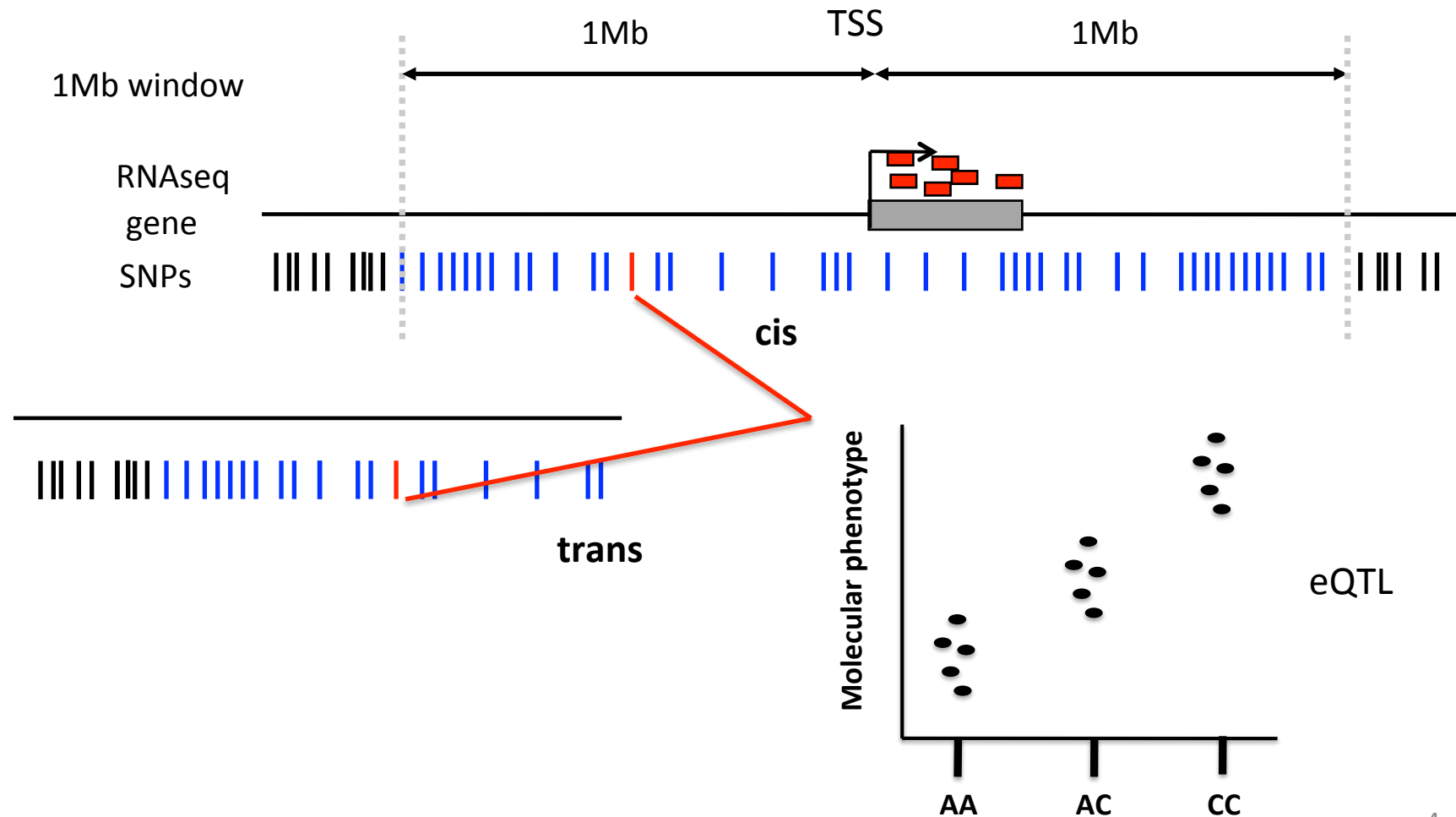
Background Rationale

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

OPEN ACCESS Freely available online

PLoS GENETICS

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

LCL
eQTLs

Dan L. Nicolae^{1,2,3}, Eric Gamazon¹, Wei Zhang¹, Shiwei Duan^{1*}, M. Eileen Dolan^{1,2}, Nancy J. Cox^{1,2*}

¹ Department of Medicine, University of Chicago, Chicago, Illinois, United States of America, ² Department of Human Genetics, University of Chicago, Chicago, Illinois, United States of America, ³ Department of Human Genetics, University of Chicago, Chicago, Illinois, United States of America

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PLoS GENETICS

LCL
eQTLs

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

Alexandra C. Nica^{1,2}, Stephen B. Montgomery^{1,2}, Antigone S. Dimas^{1,2}, Barbara E. Stranger^{1,3}, Claude Beazley¹, Inês Barroso¹, Emmanouil T. Dermitzakis^{1,2*}

¹ Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, United Kingdom, ² Department of Genetic Medicine and Development, University of Geneva Medical School, Geneva, Switzerland, ³ Harvard Medical School/Brigham and Women's Hospital, Boston, Massachusetts, United States of America

Coanalysis of GWAS with eQTLs reveals disease-tissue associations

Hyunseok Peter Kang, M.D.¹, Alex A. Morgan, Ph.D.¹, Rong Chen, Ph.D.¹,
Eric E. Schadt, Ph.D.², Atul J. Butte, M.D., Ph.D.¹

¹ Division of Systems Medicine, Department of Pediatrics,
Stanford University School of Medicine, Stanford, CA

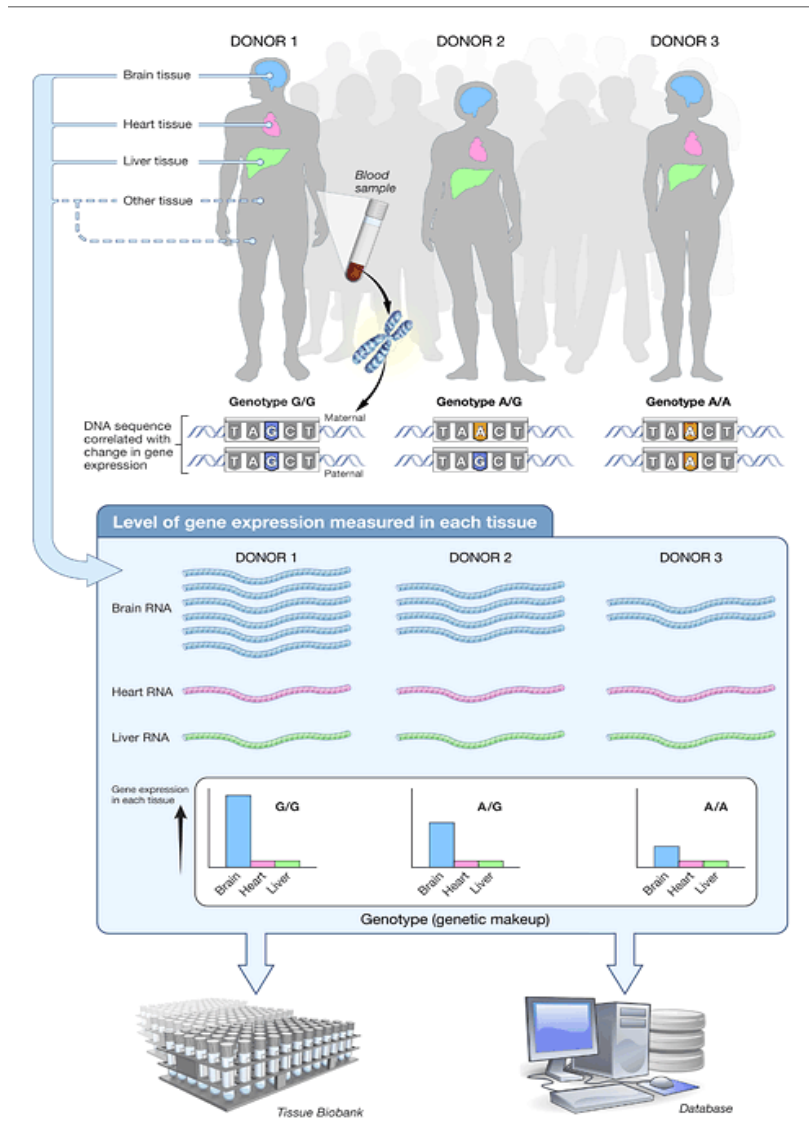
² Department of Genetics and Genome Sciences, Mount Sinai School of Medicine,
New York, NY

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

GTEx = Genotype-Tissue Expression



GTEx 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):

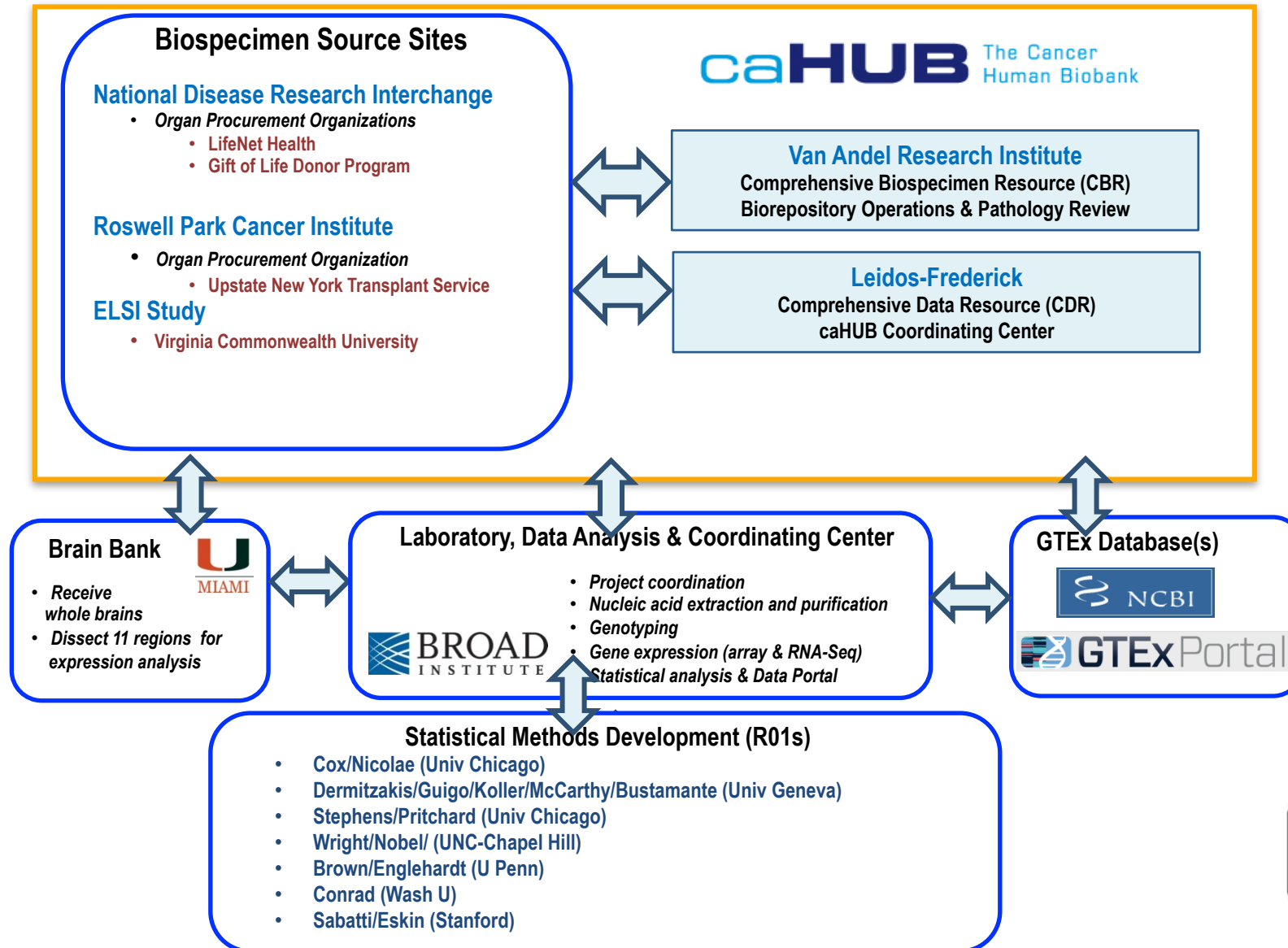
- 900 Postmortem Donors
- Whole exome sequencing
- Whole genome sequencing
- RNA-Seq of ~30 tissues/donor (>20,000 tissues)



PILOT PHASE (in 2010):

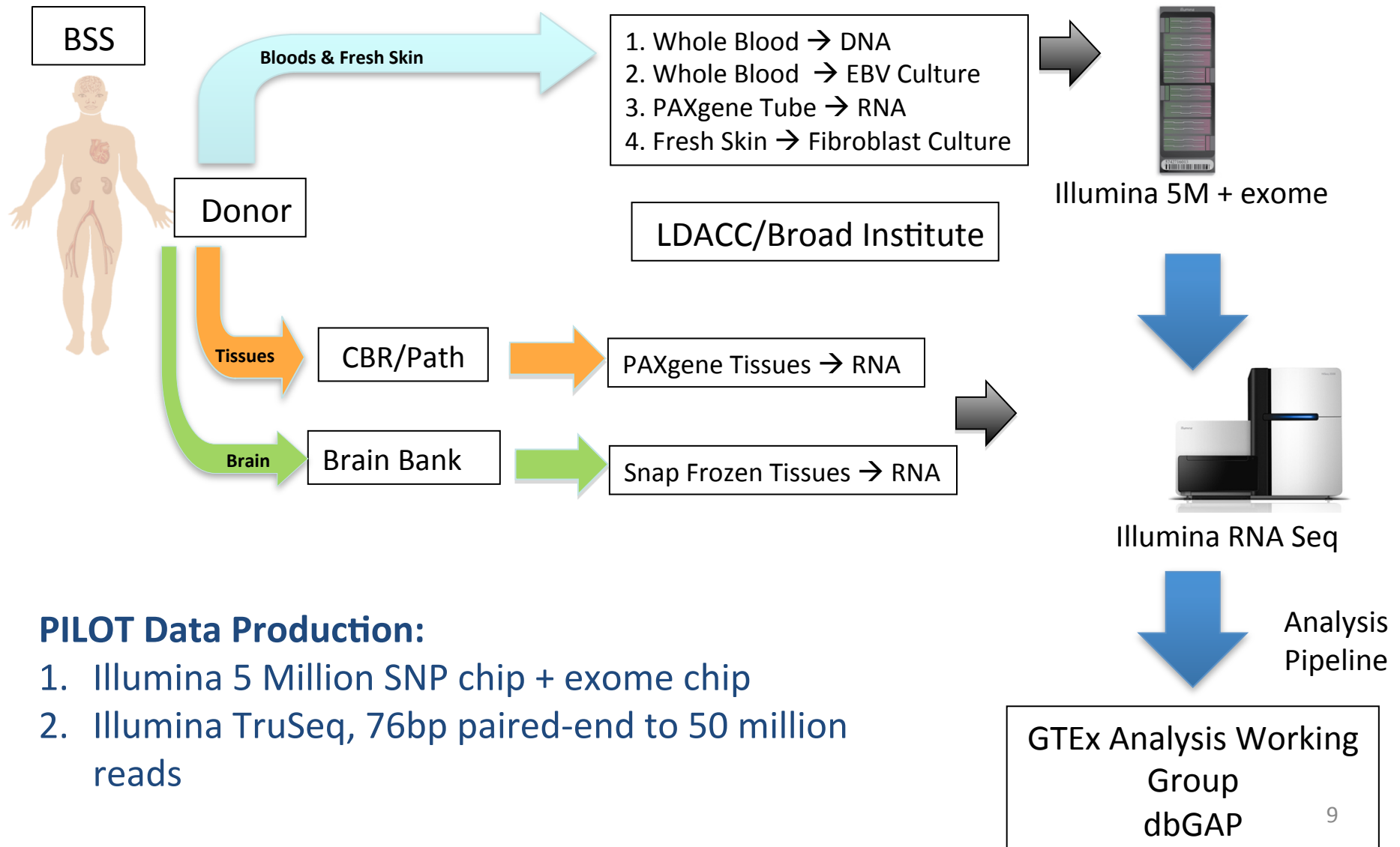
- 175 Postmortem Donors
- 1641 RNA-Seq of ~28 tissues/donor

Pilot GTEx Consortium

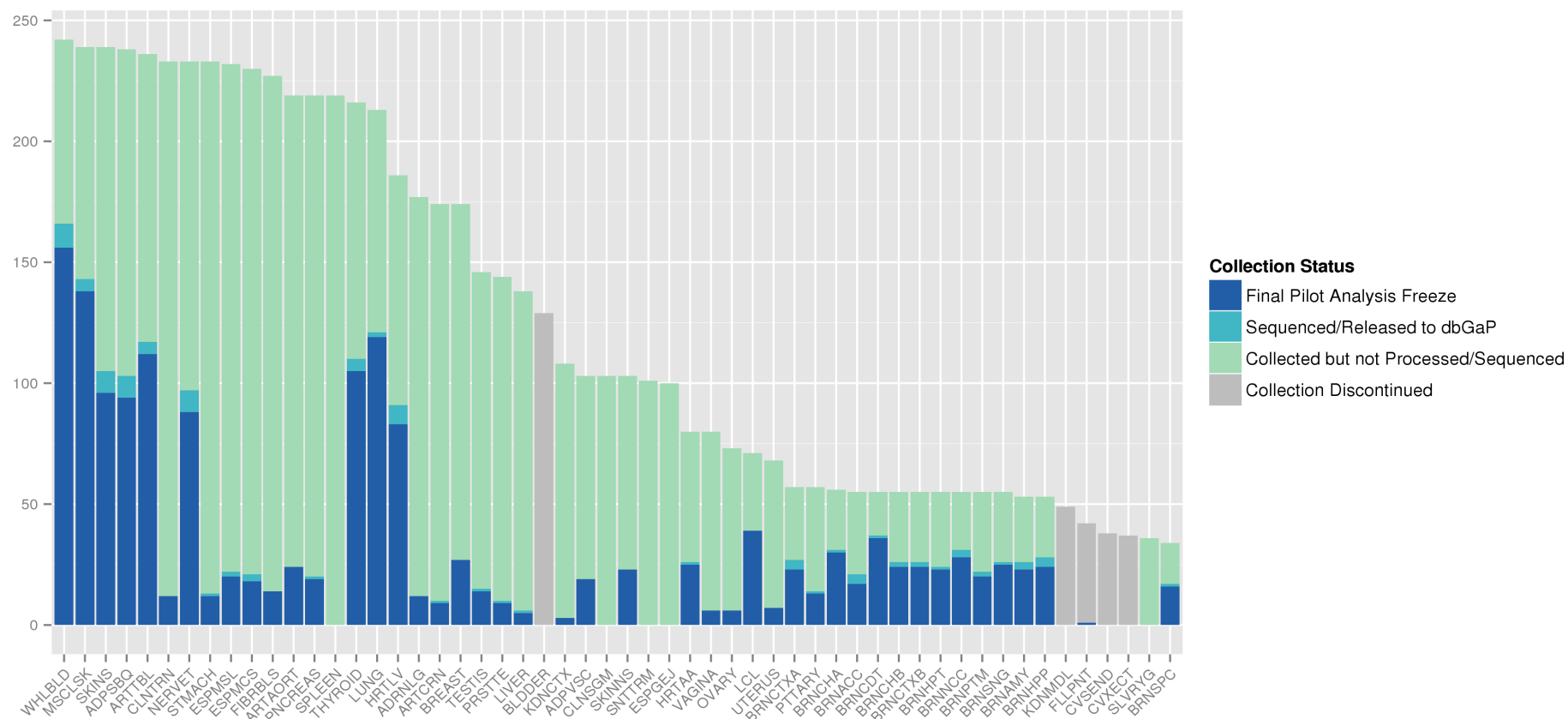


Laboratory Data Analysis and Coordinating Center

GTEx Workflow



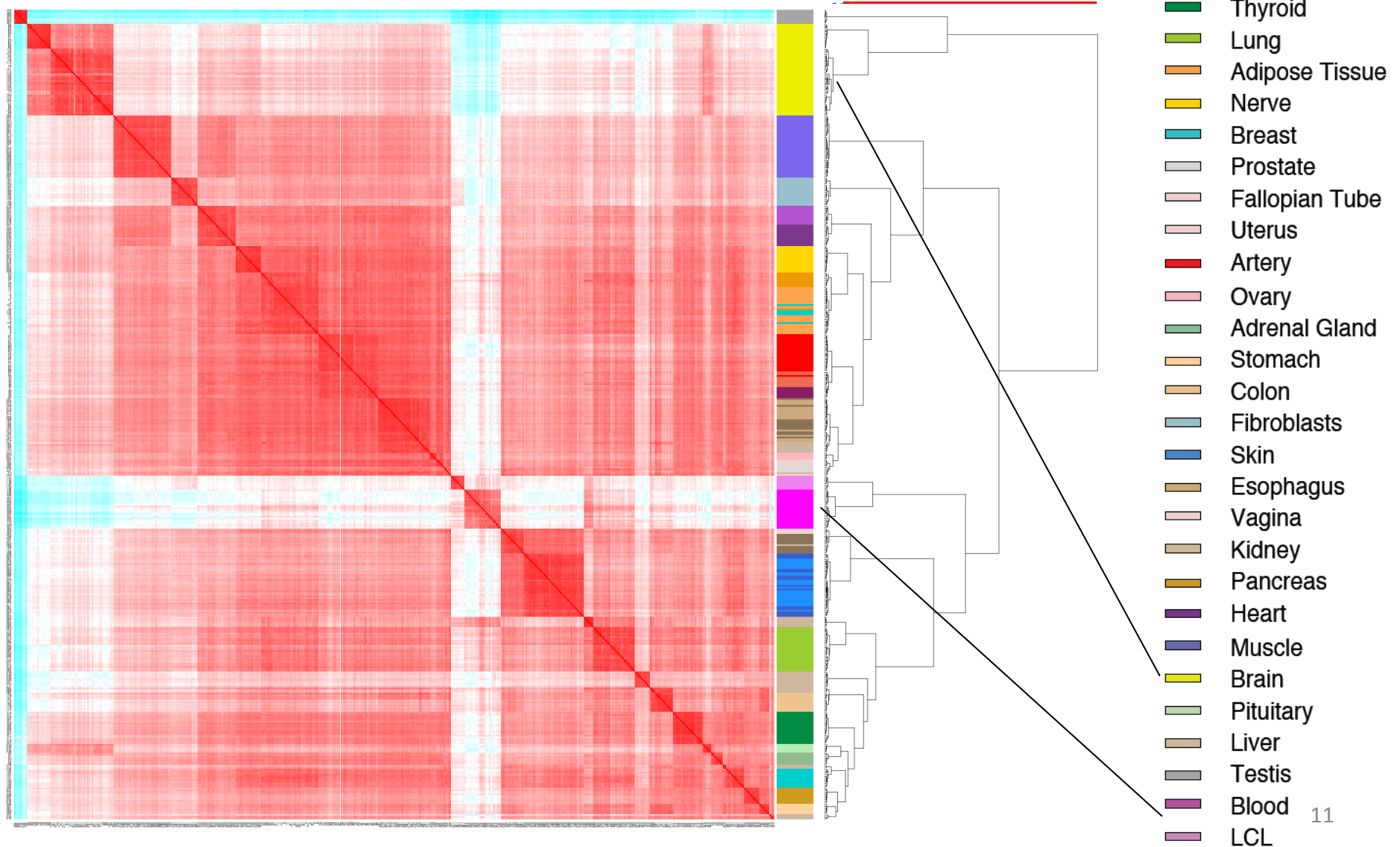
Pilot Phase Data



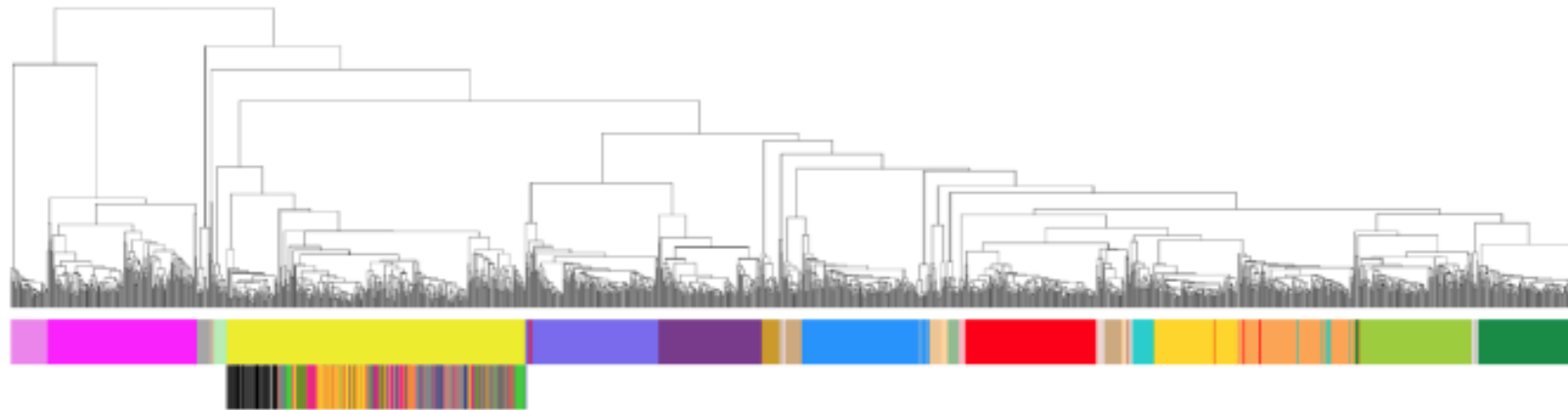
Pilot phase collected an average of ~ 28 tissue samples per donor from 54 distinct sites

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

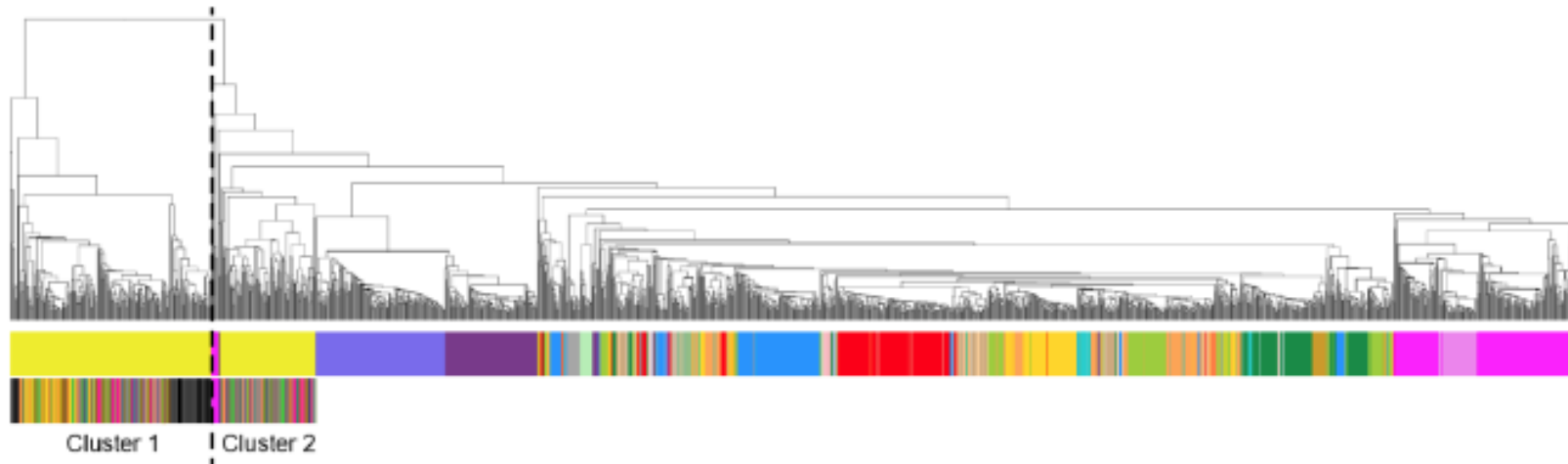
Clustering of Expression Data



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)

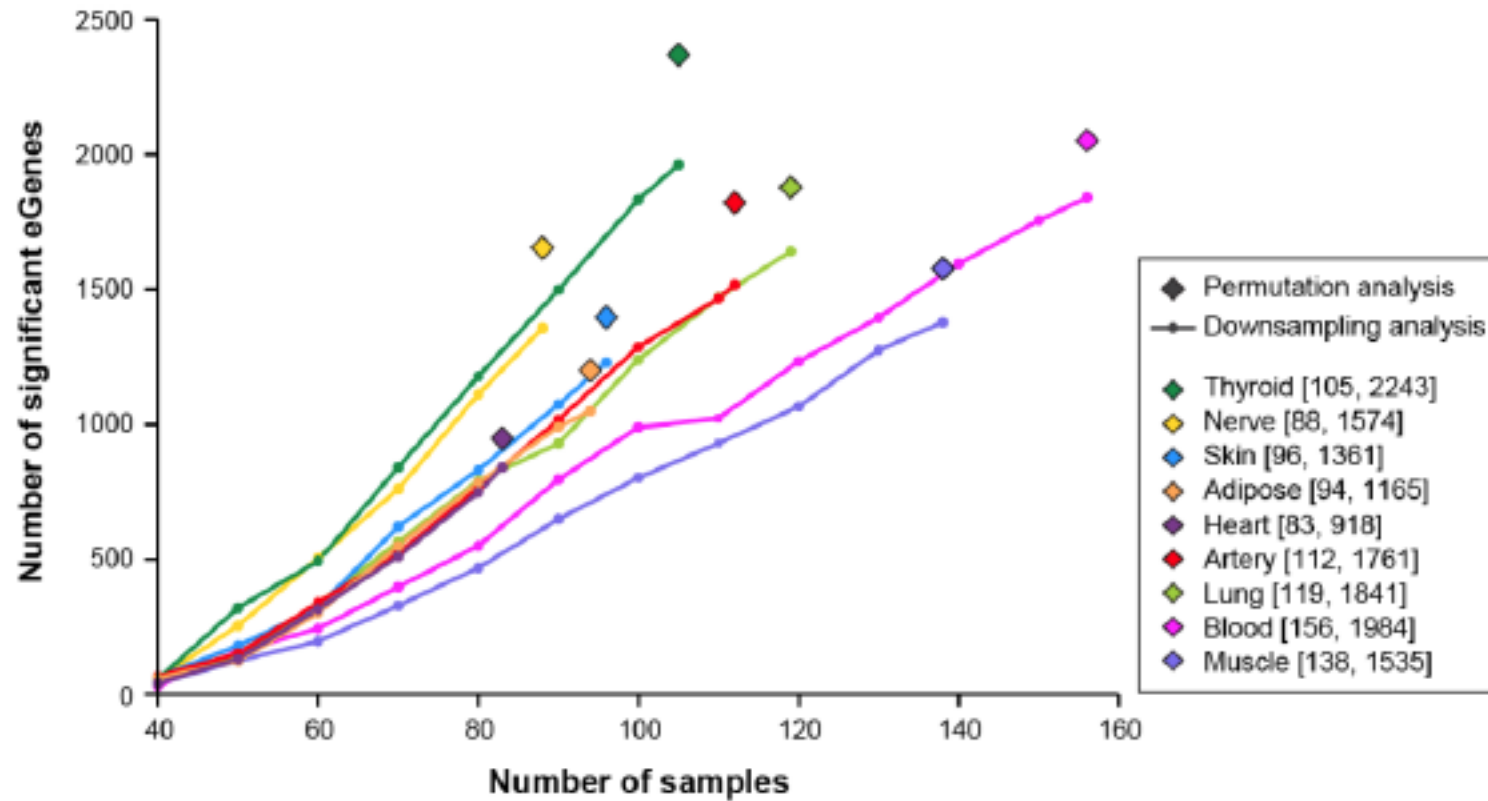
■ Adipose tissue	■ Colon	■ Lung	■ Prostate
■ Adrenal gland	■ Esophagus	■ Muscle	■ Reproductive organs
■ Artery	■ Fibroblasts	■ Nerve	■ Skin
■ Blood	■ Heart	■ Ovary	■ Stomach
■ Brain	■ Kidney / Liver	■ Pancreas	■ Testis
■ Breast	■ LCL	■ Pituitary	■ Thyroid

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

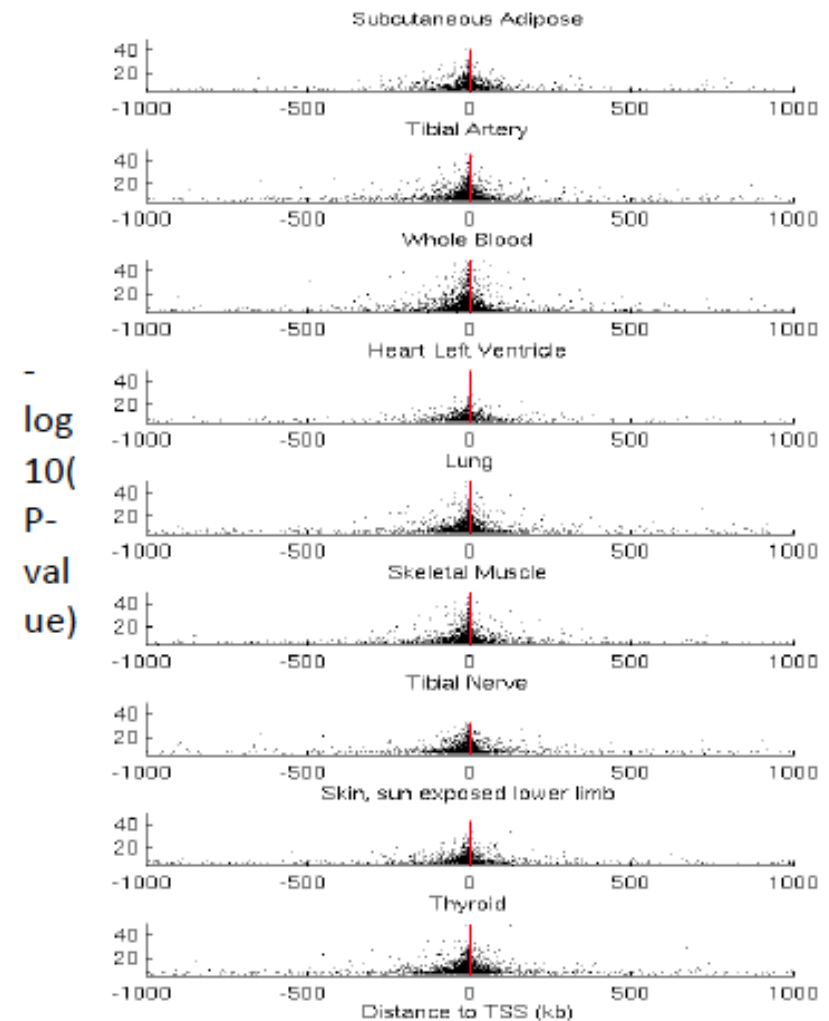
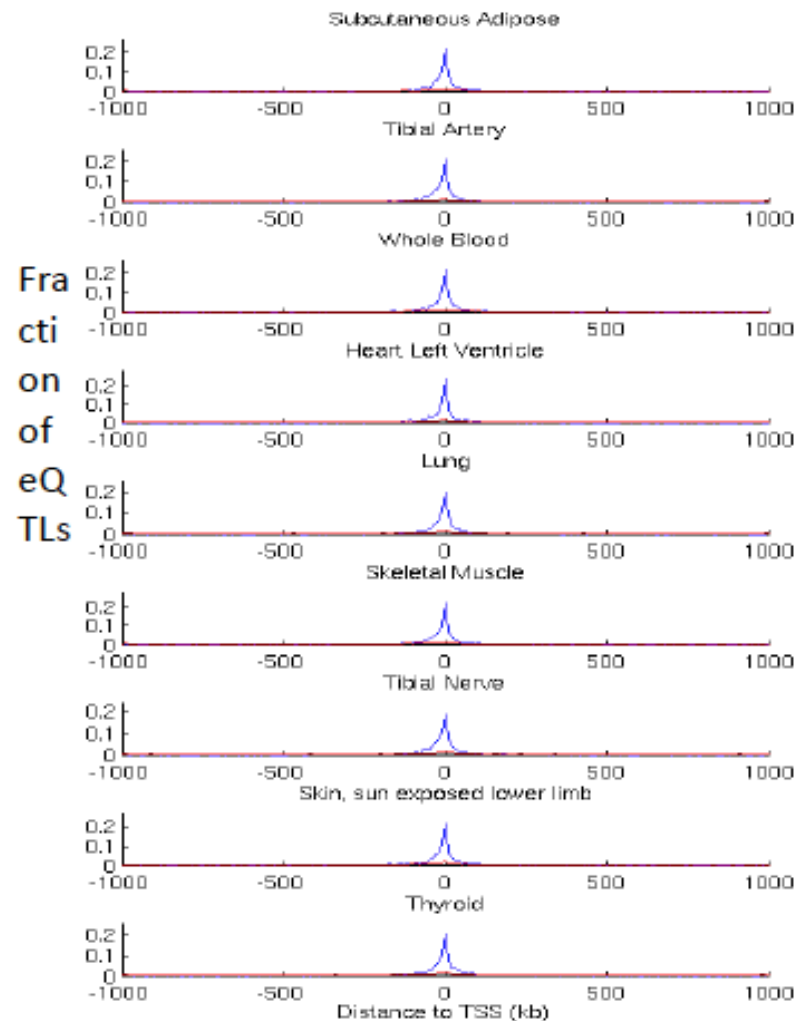
(now we use FastQTL developed by Olivier Delaneu)

eQTL discovery



A.

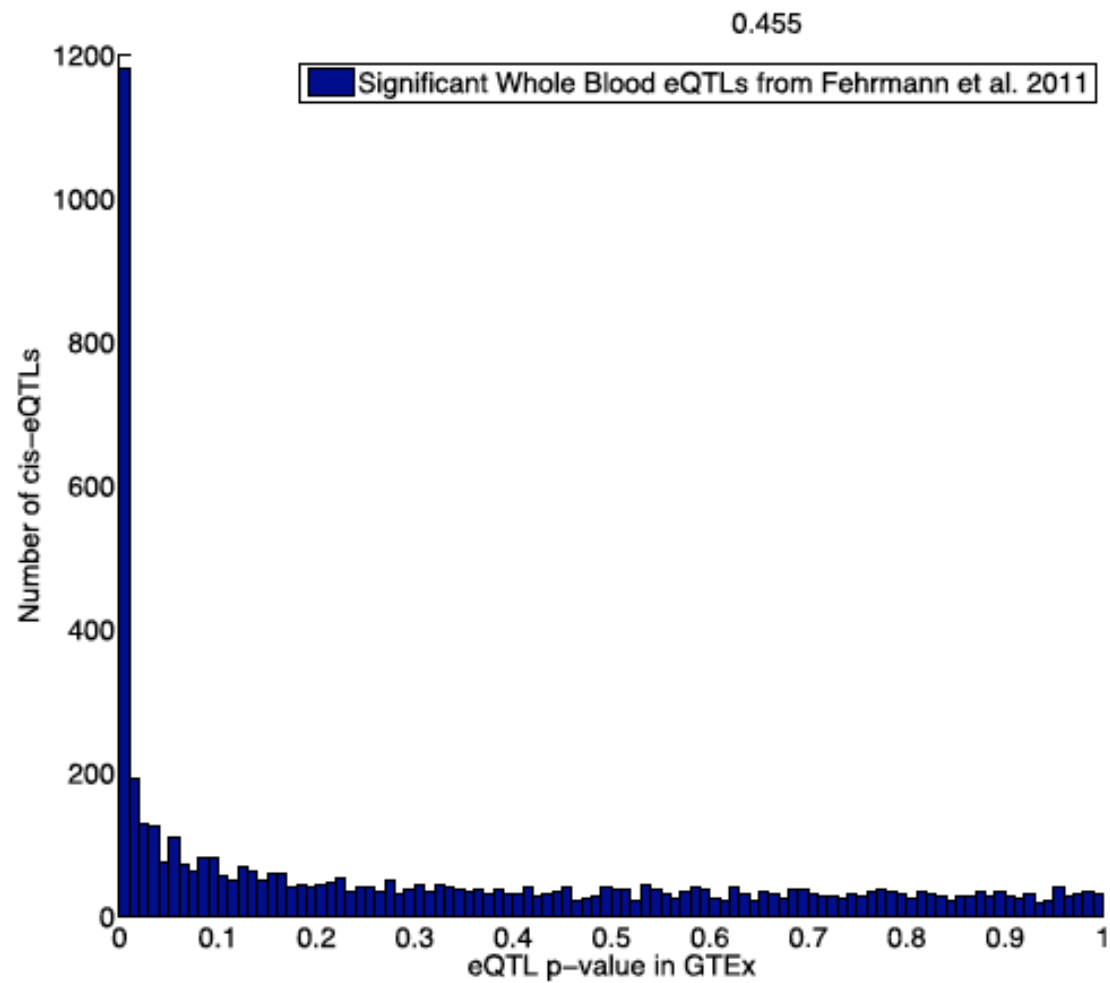
eQTL properties



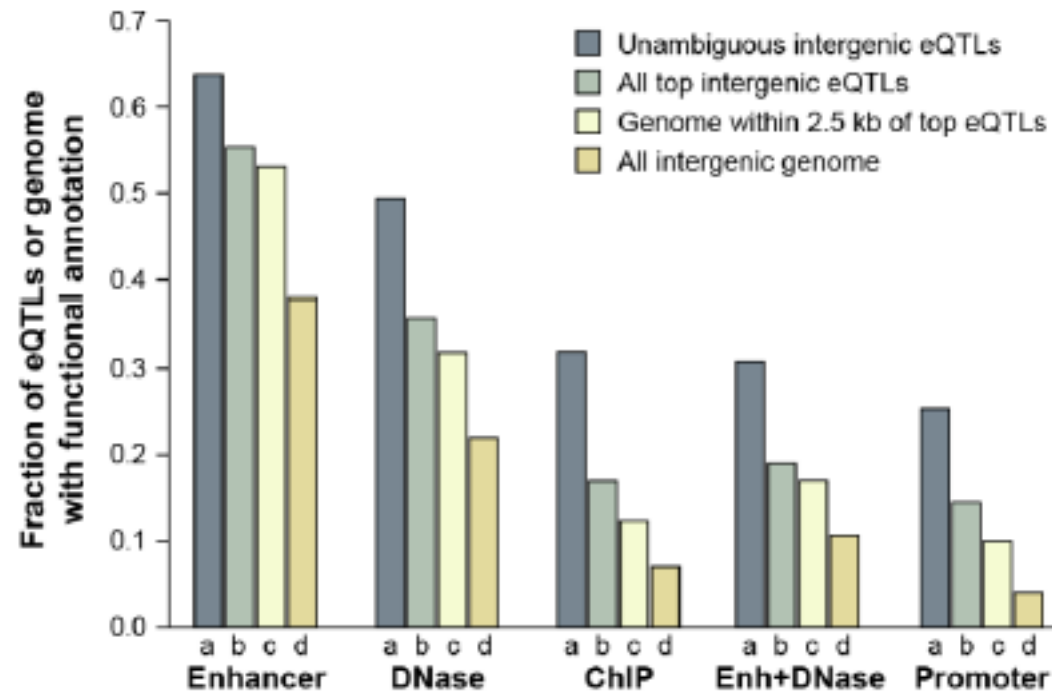
- Significant best eQTLs per gene, FDR < 5%
- Non-significant best eQTLs per gene, FDR > 5%
- All SNP-gene pairs

eQTL replication

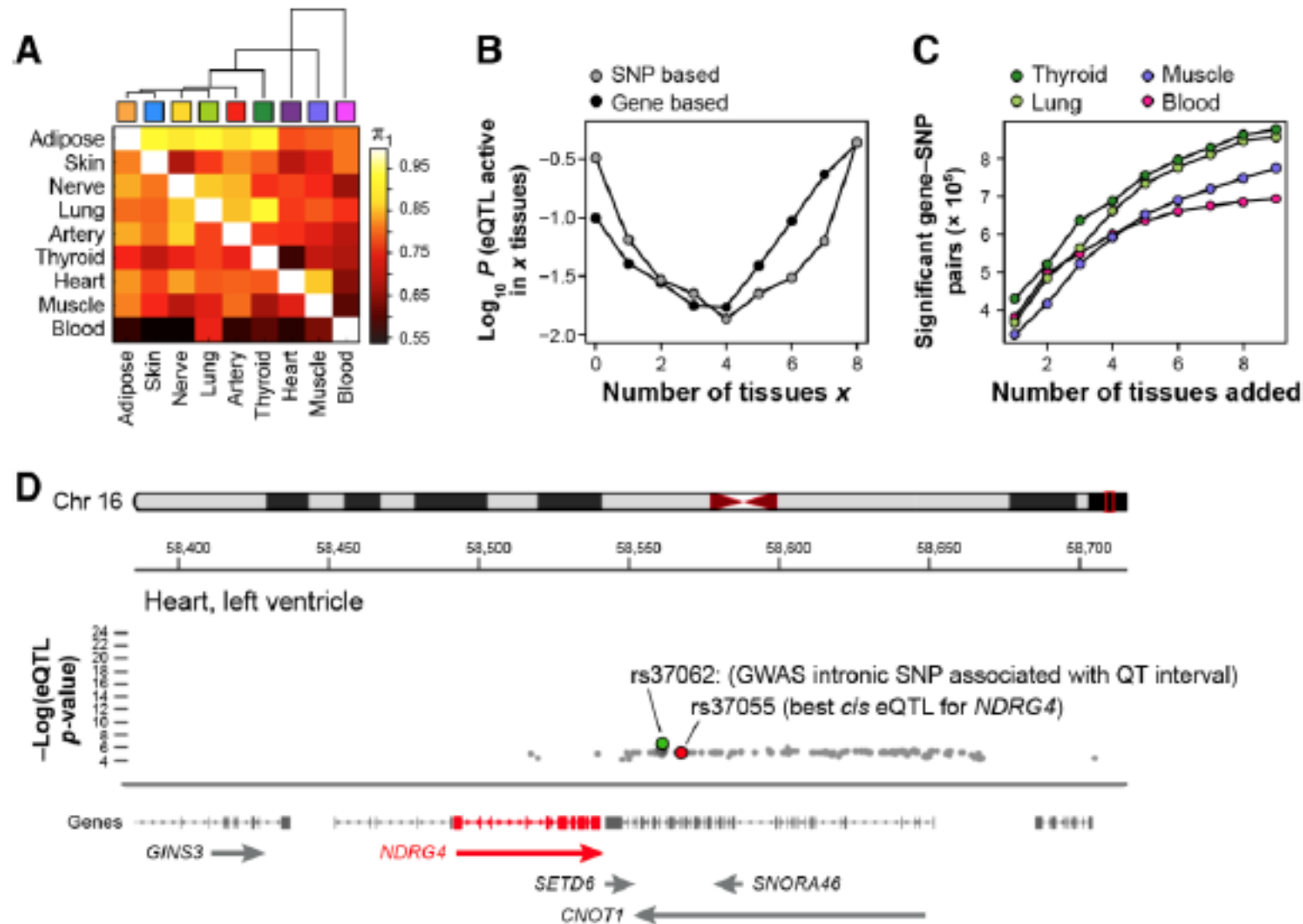
A.



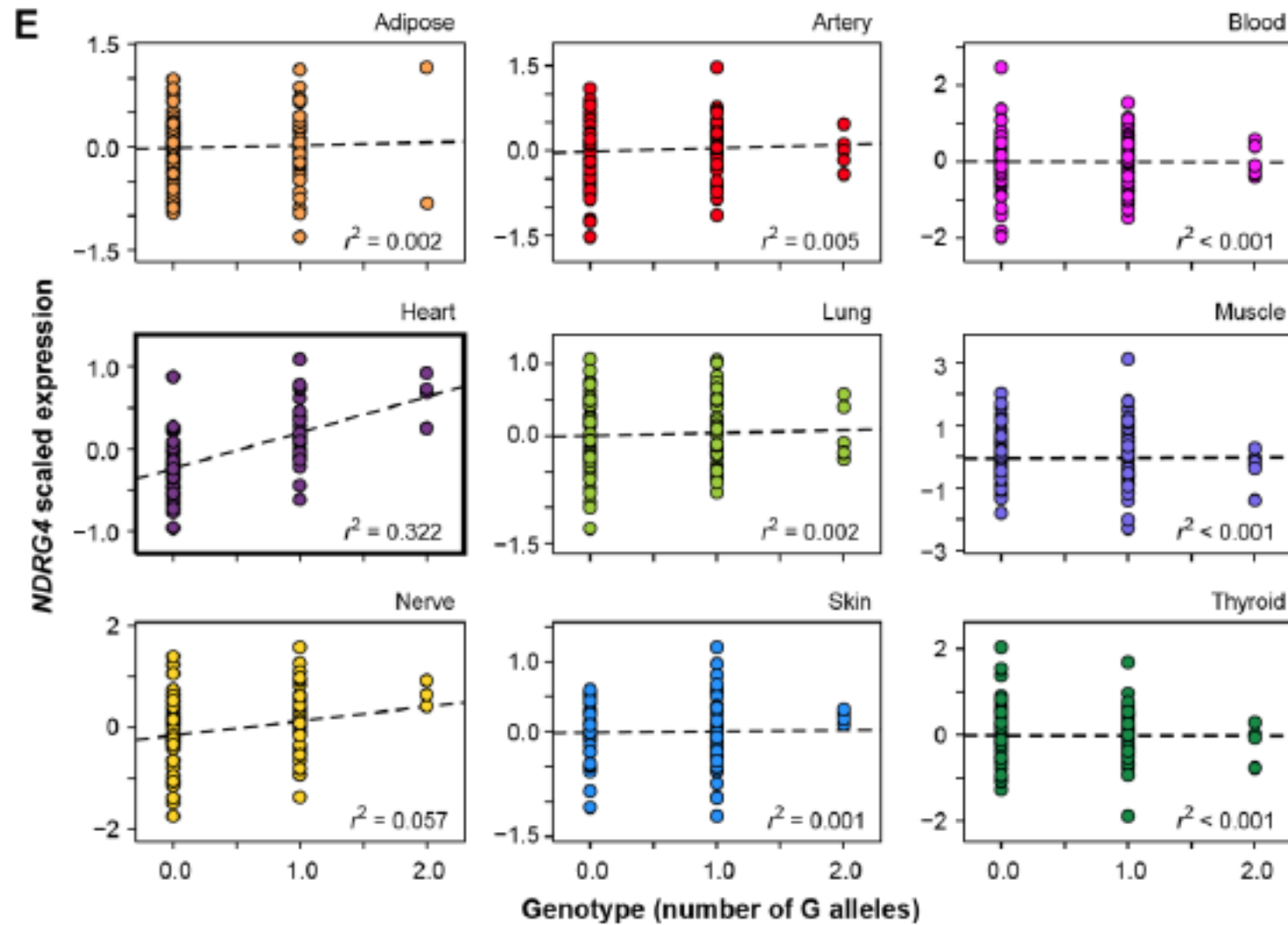
eQTL functional enrichment



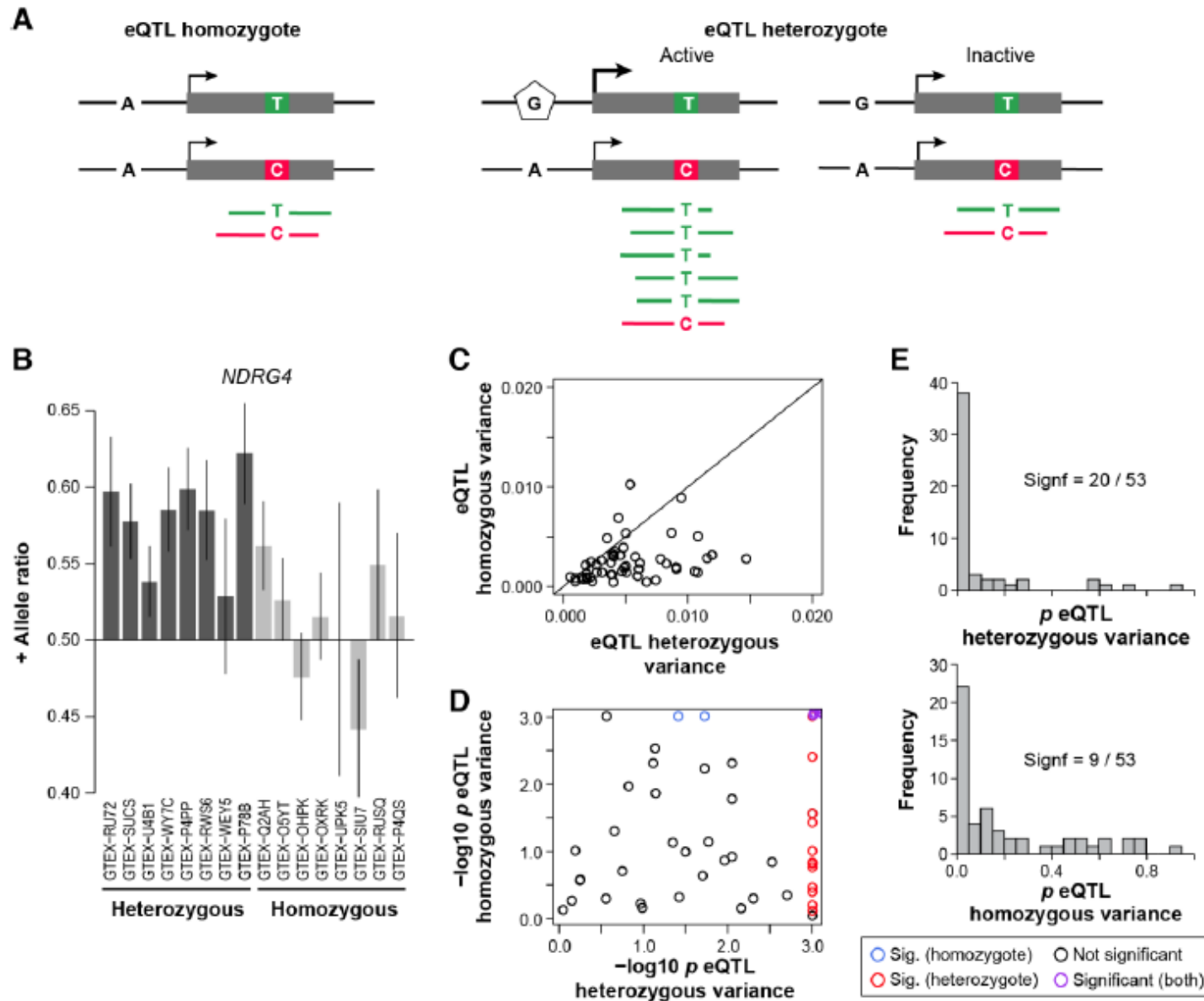
Multi-tissue eQTL discovery



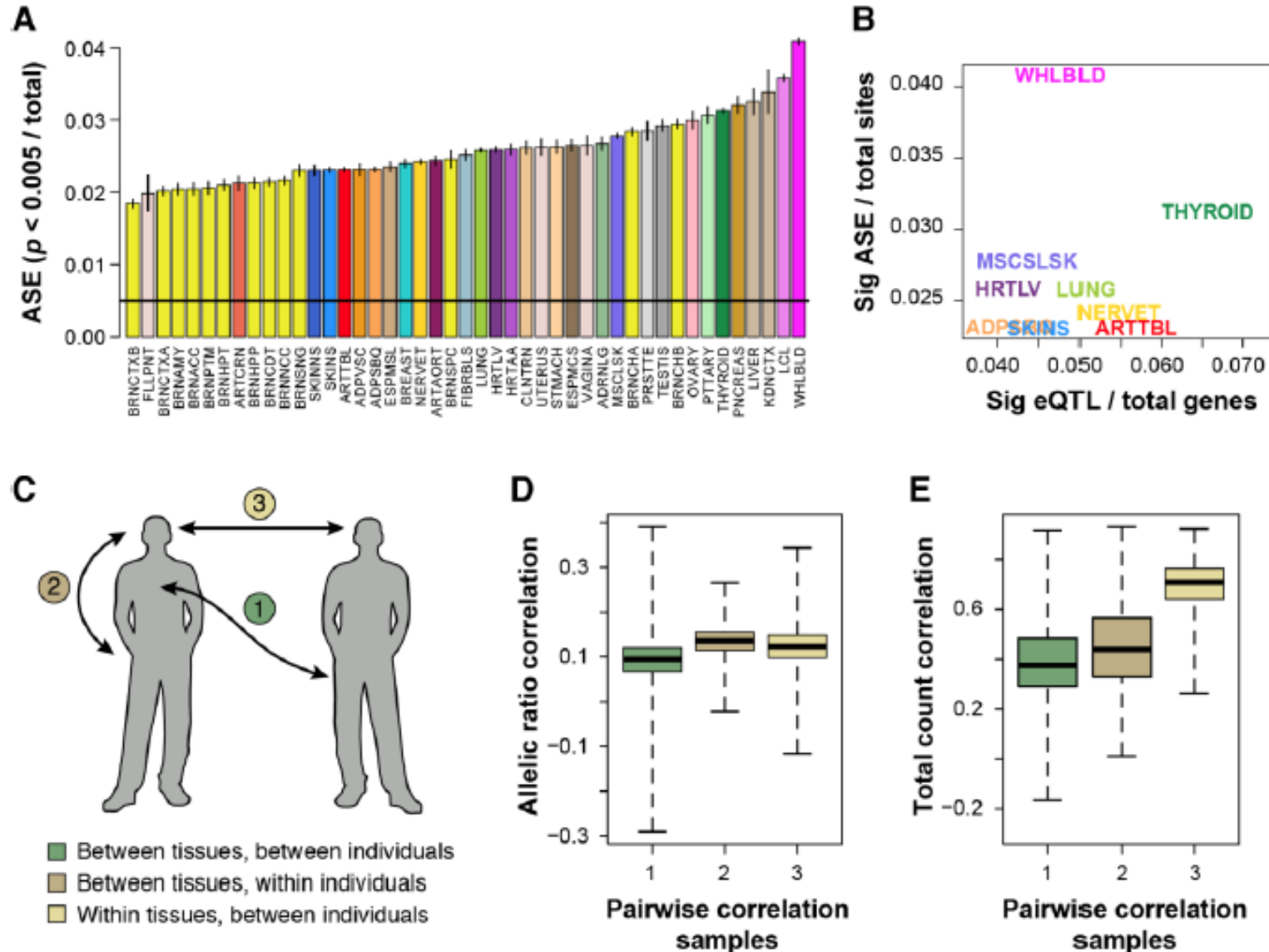
Multi-tissue eQTL discovery



Allele Specific Expression and eQTLs

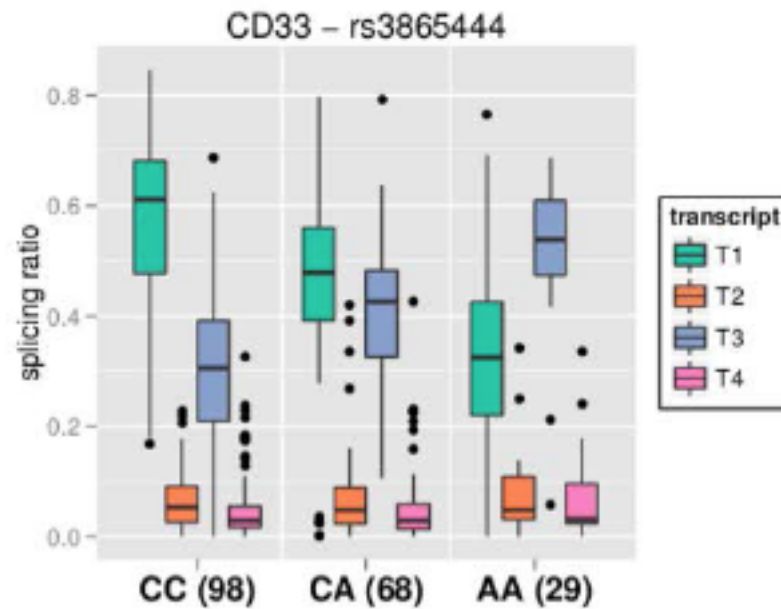


Allele Specific Expression

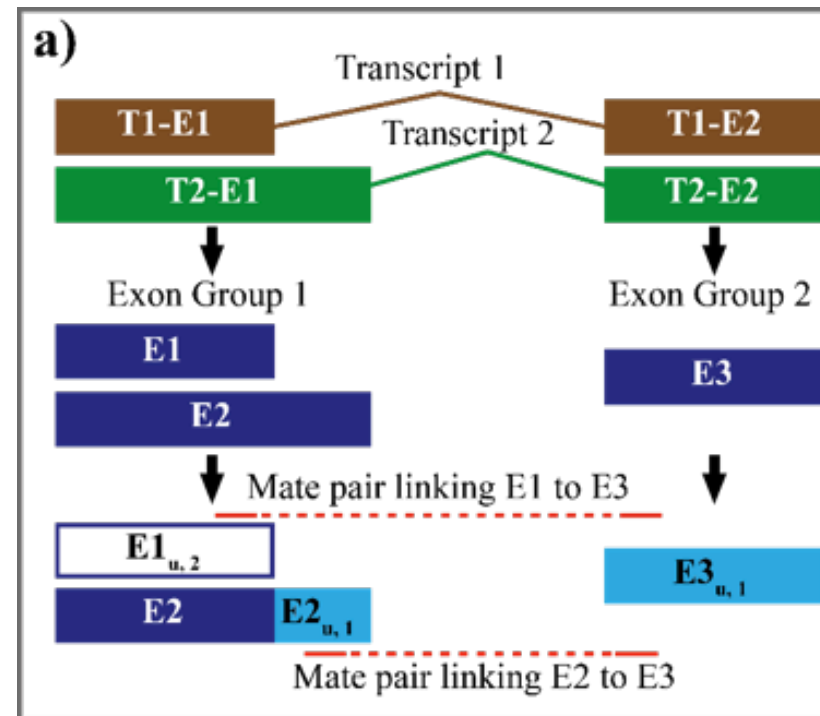


Alternative splicing QTLs

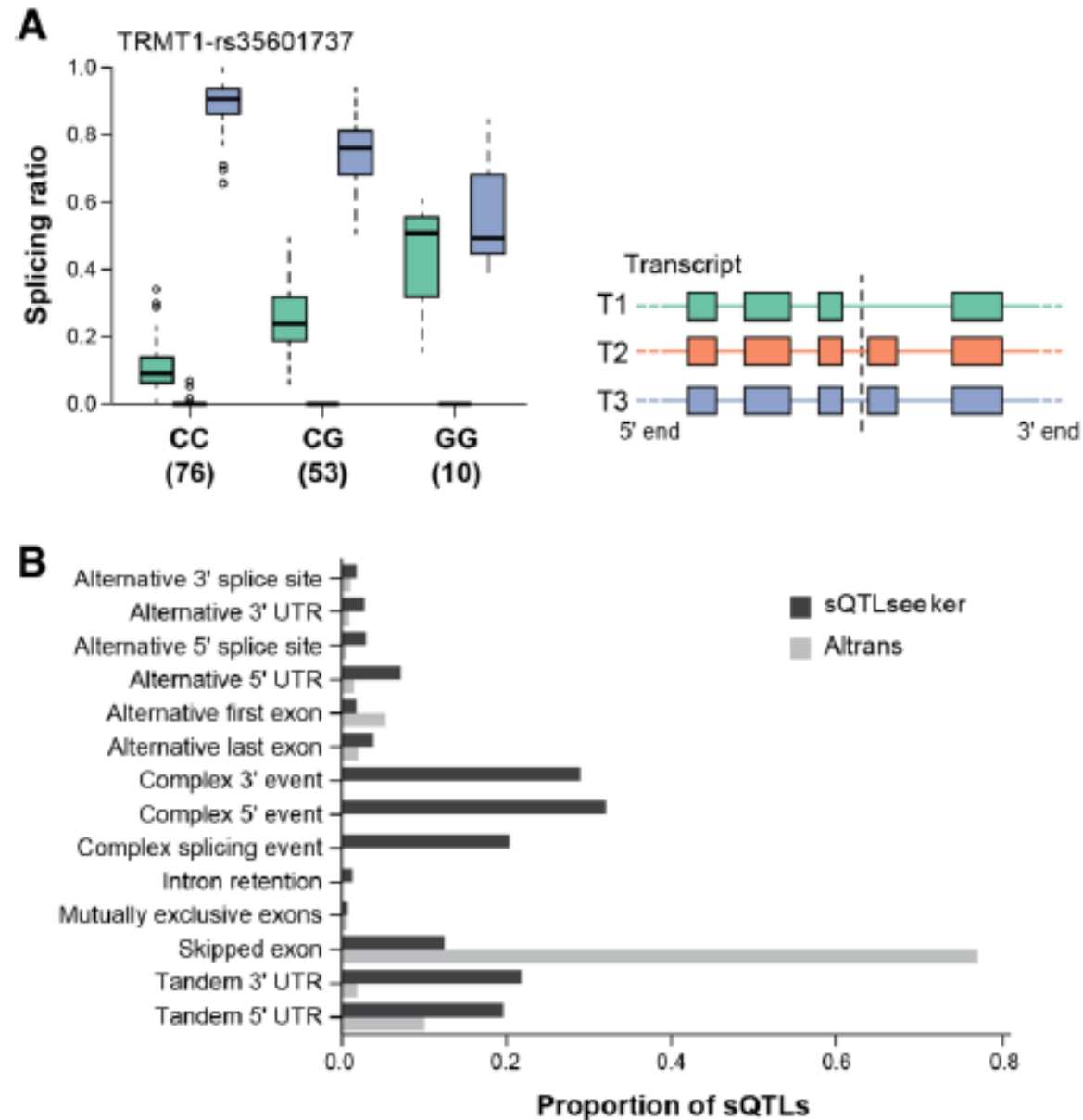
sQTL seeker



Altrans

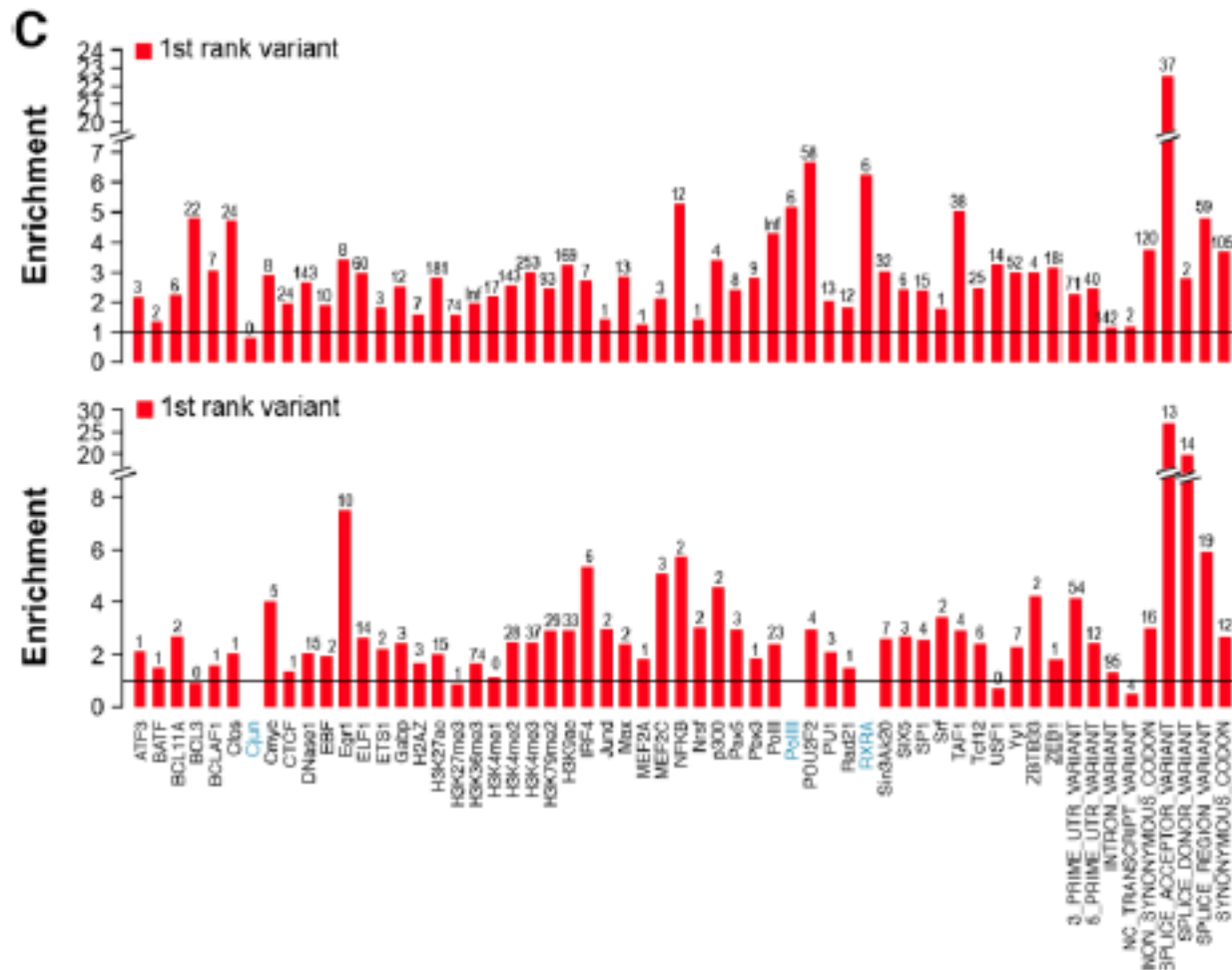


Alternative splicing QTLs

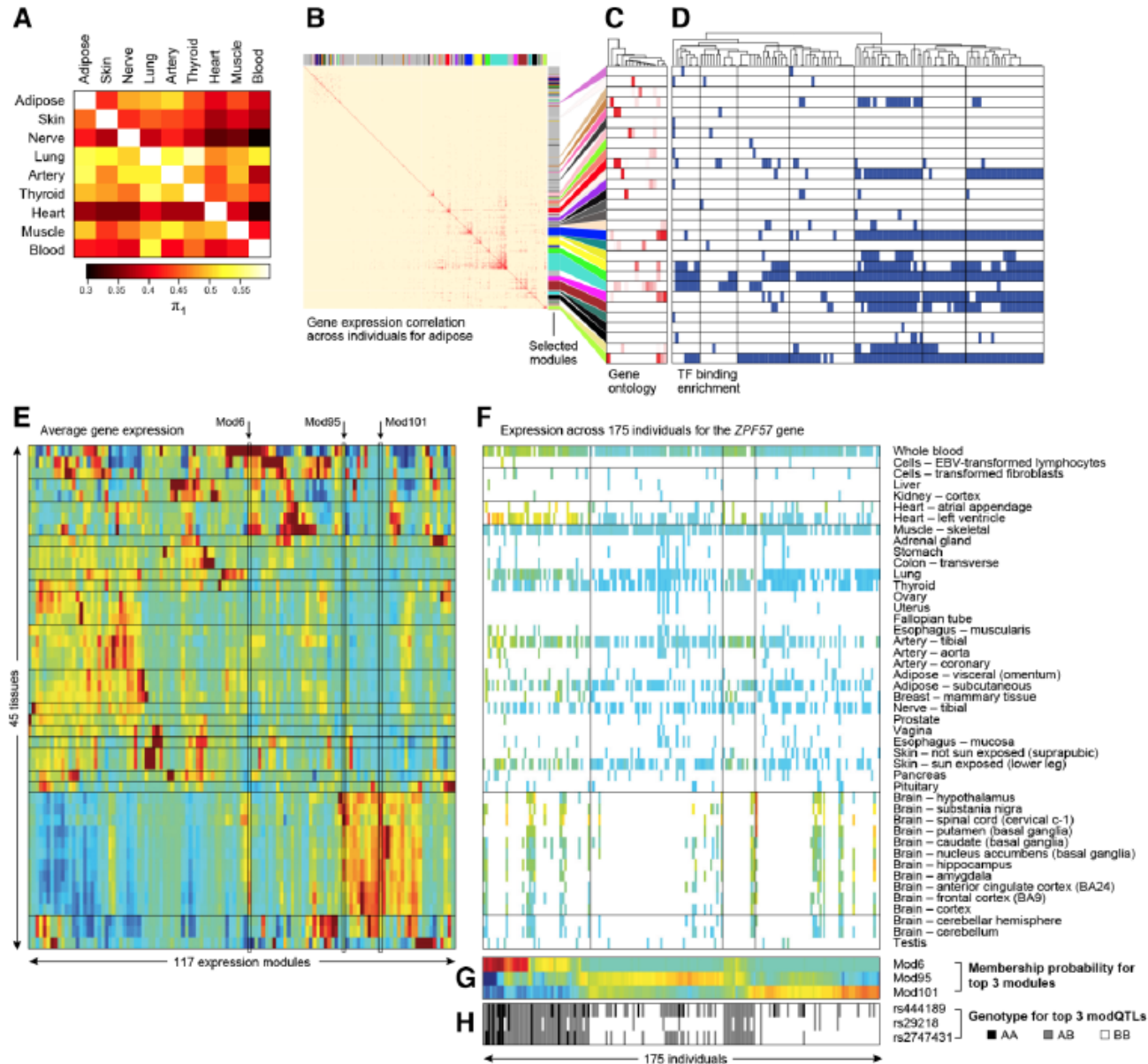


Alternative splicing QTLs

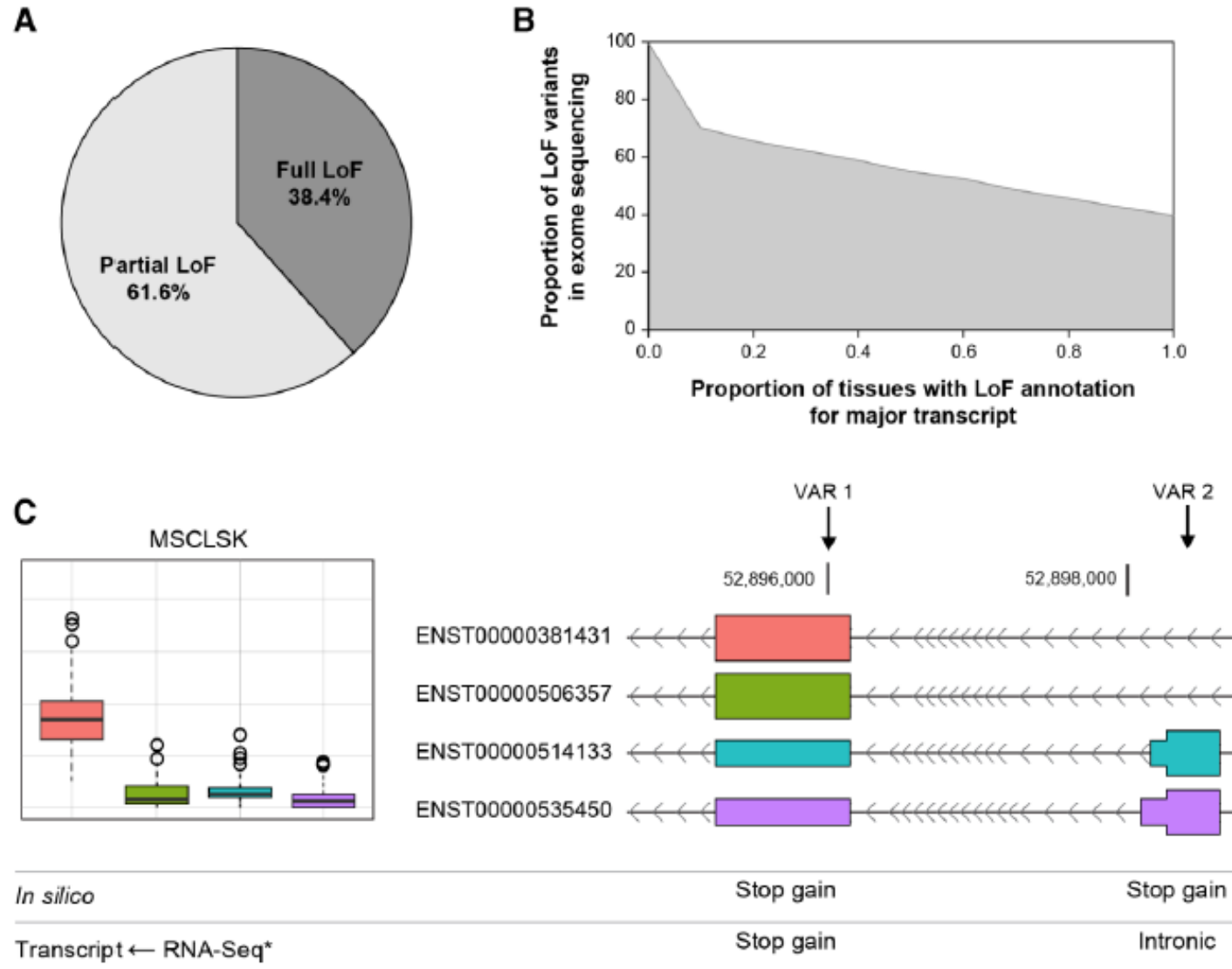
Functional element enrichment



Network module QTLs

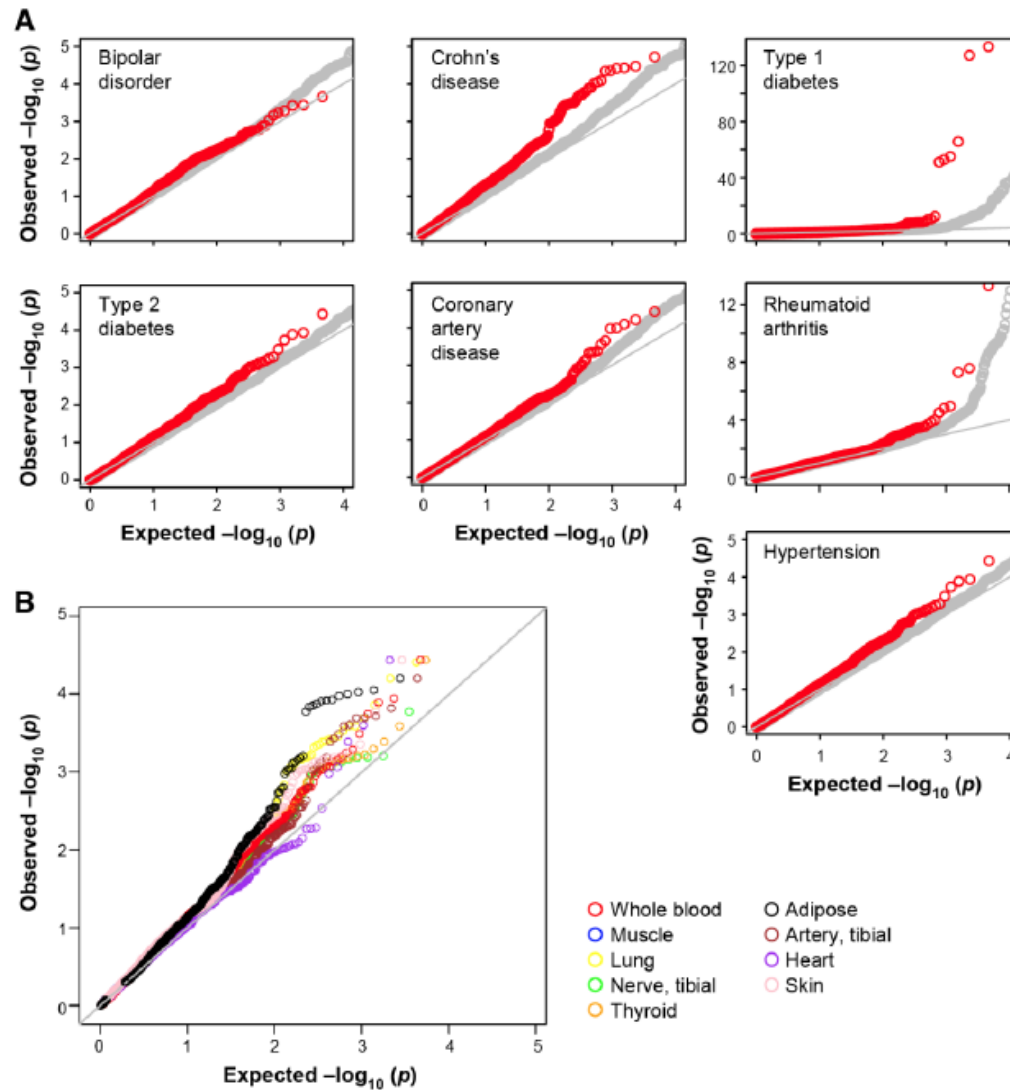


Truncating Variants in the transcriptome

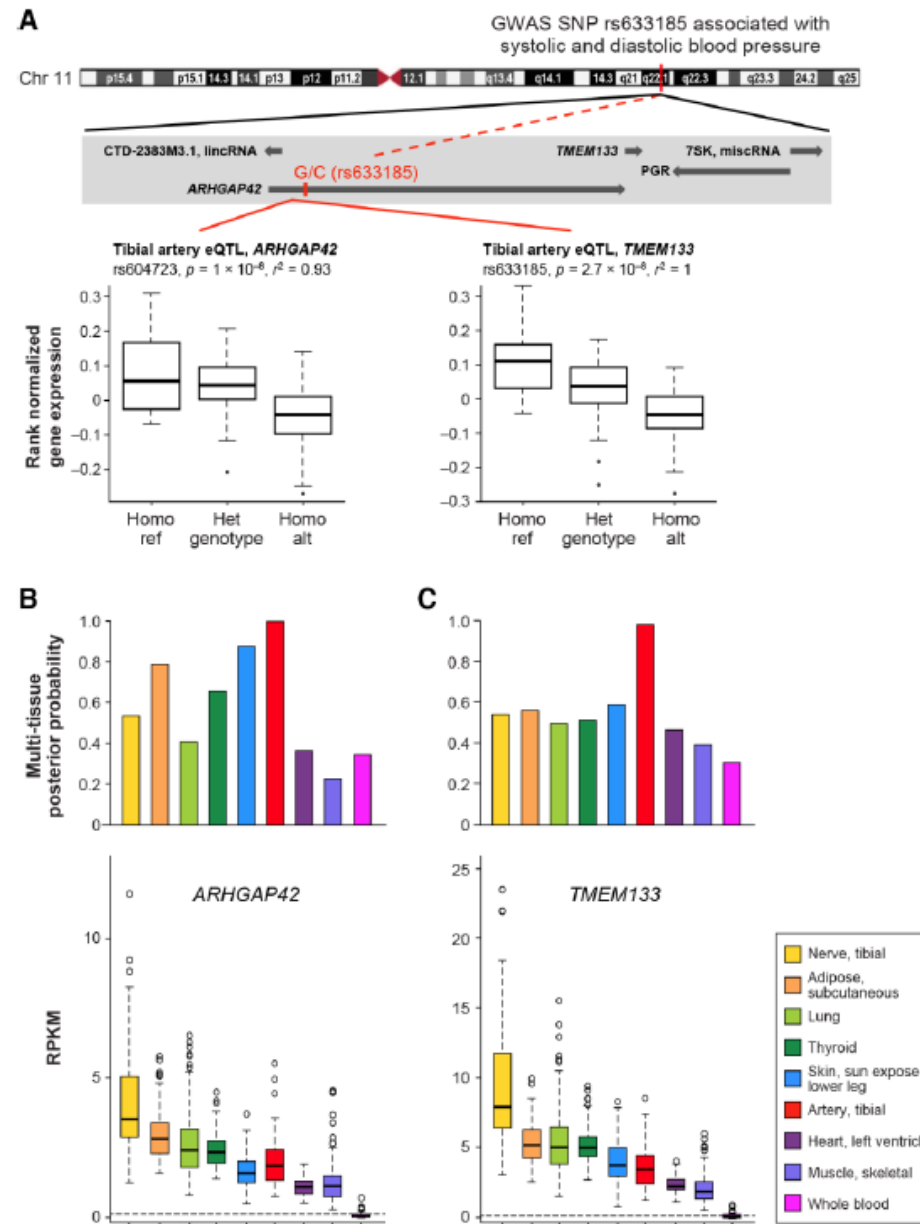


* DNA variant annotation informed by tissue RNA-Seq quantification.

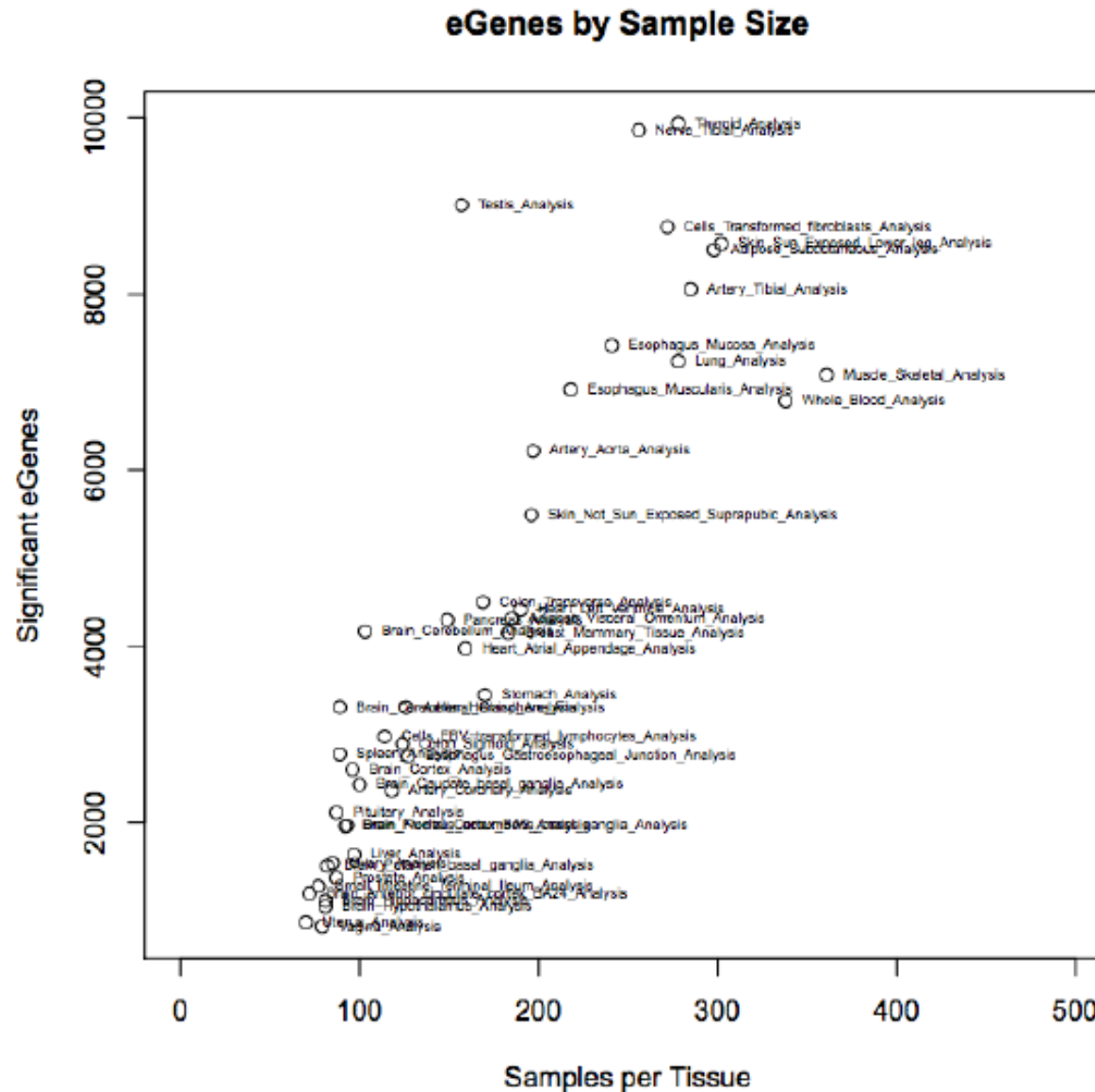
Link eQTLs to GWAS



Link eQTLs to GWAS

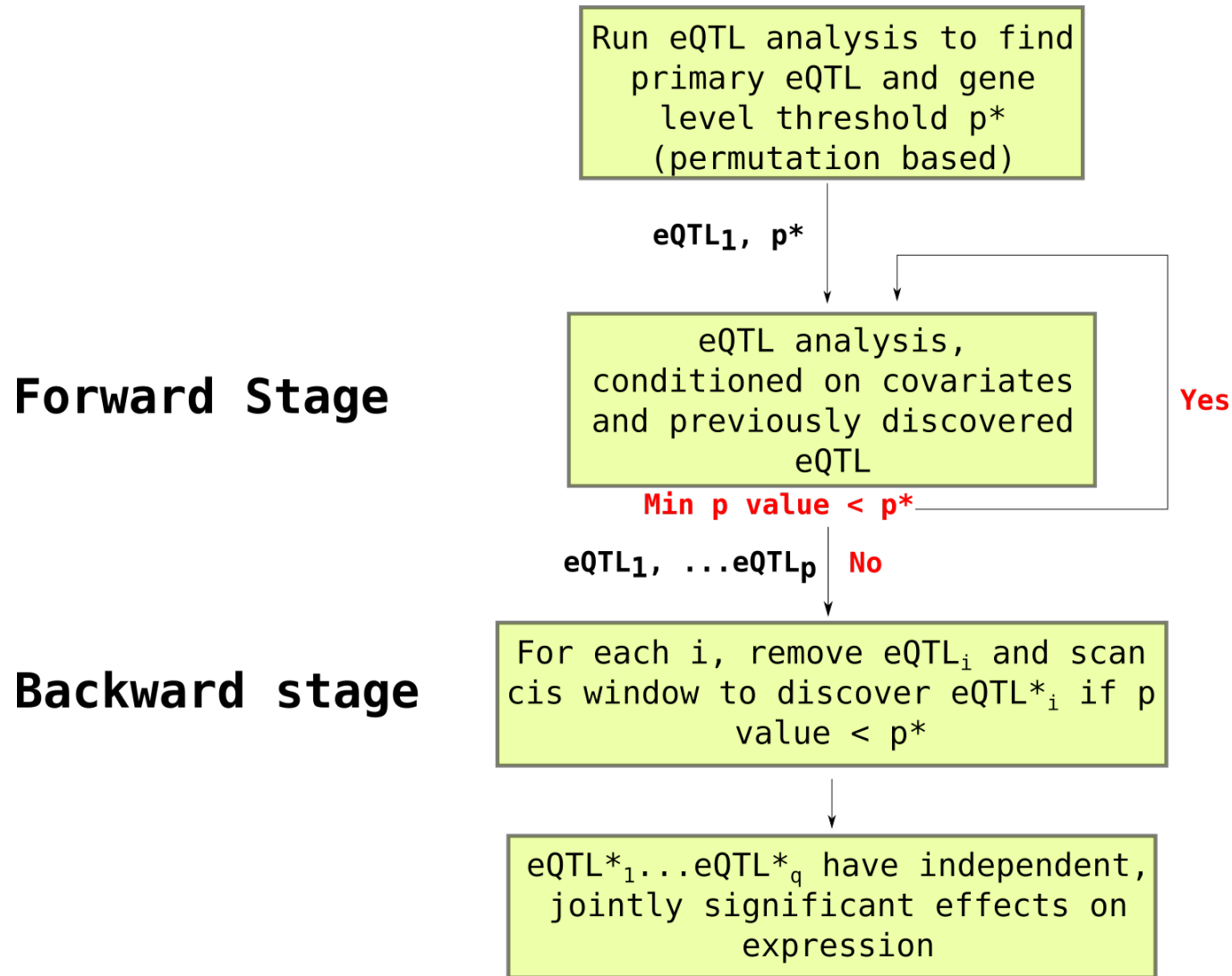


GTEx eQTLs in 44 tissues



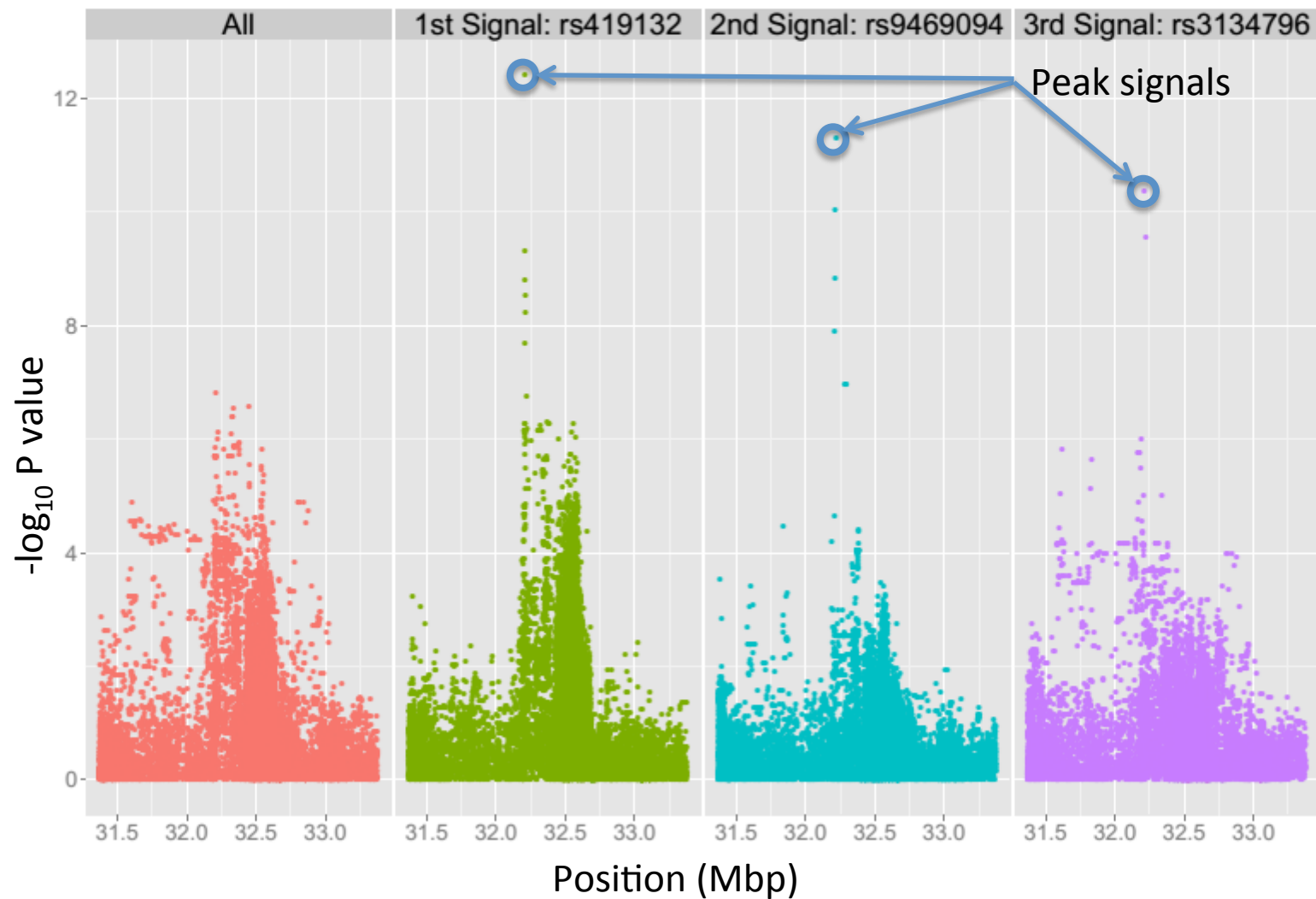
David Deluca

Multiple eQTLs per gene

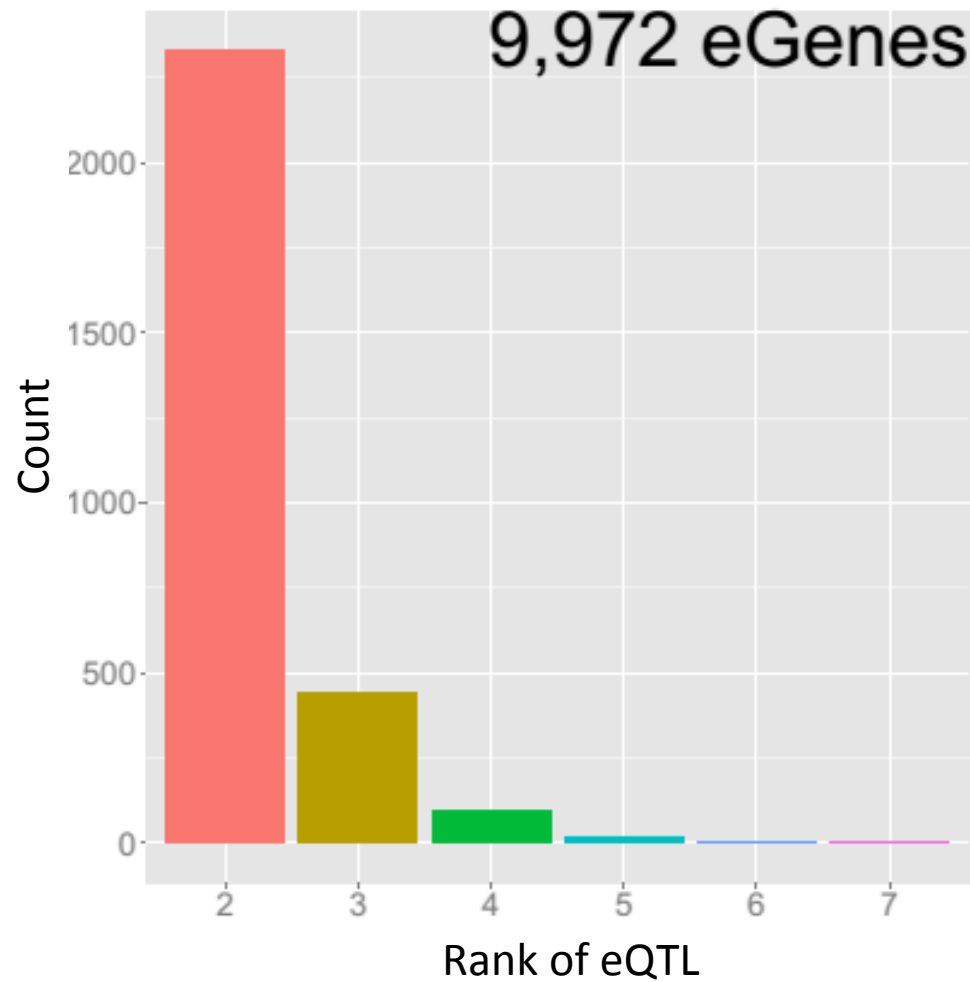


Example

We discovered 3 independent eQTLs for *BTNL2*, in the MHC region

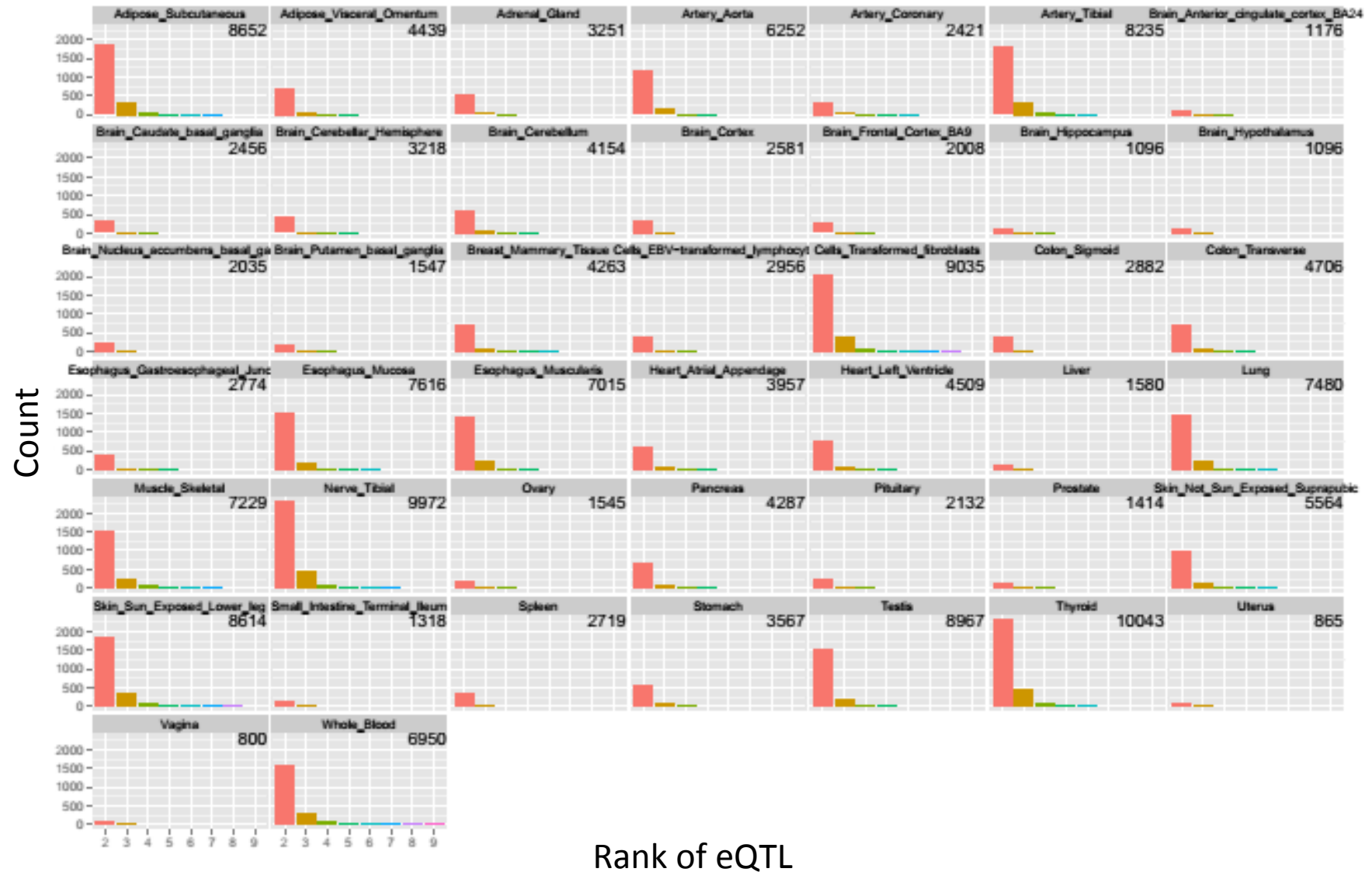


Number of additional eQTLs discovered in Nerve Tibial tissue

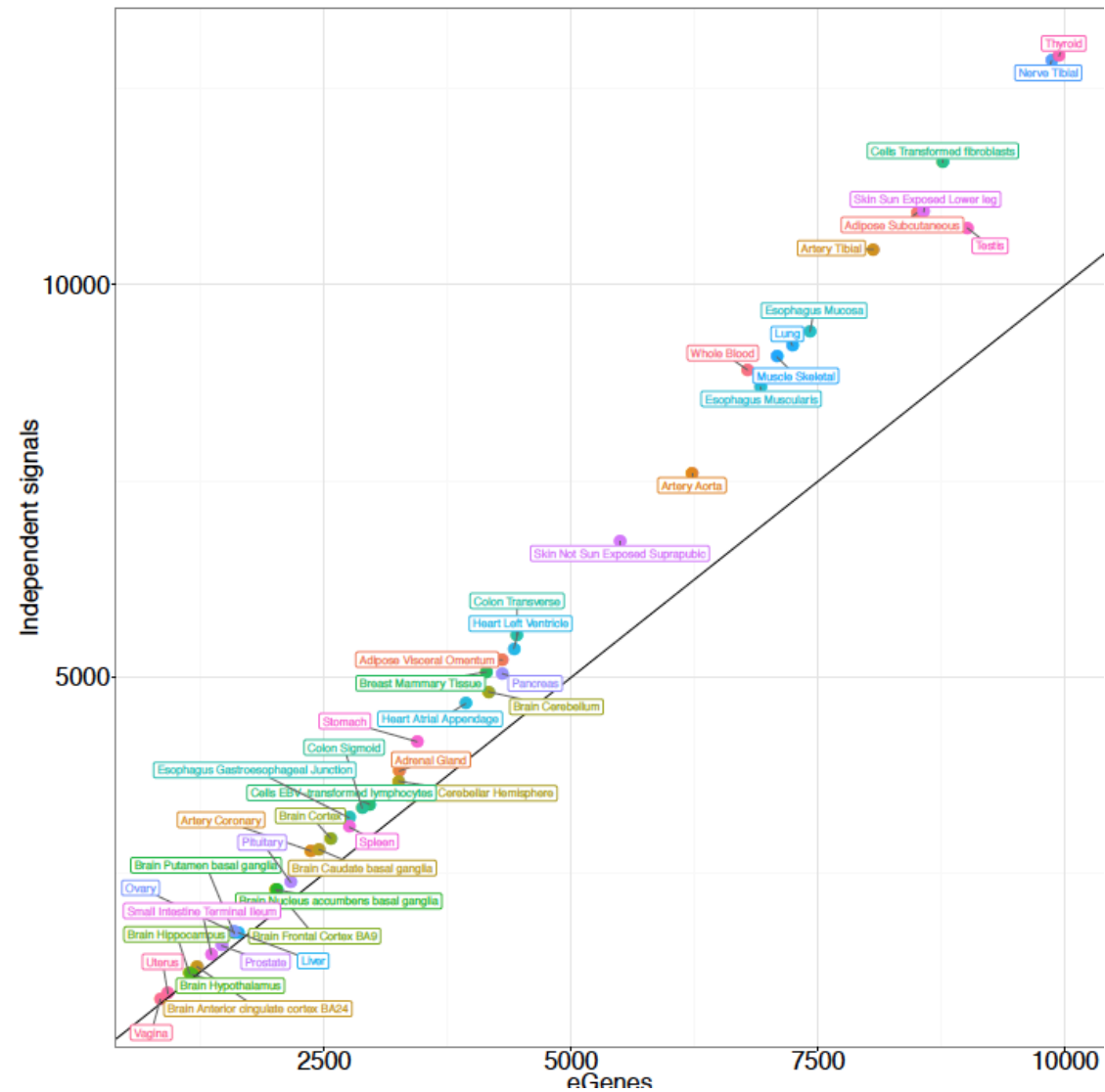


2284 Secondary signals
in total

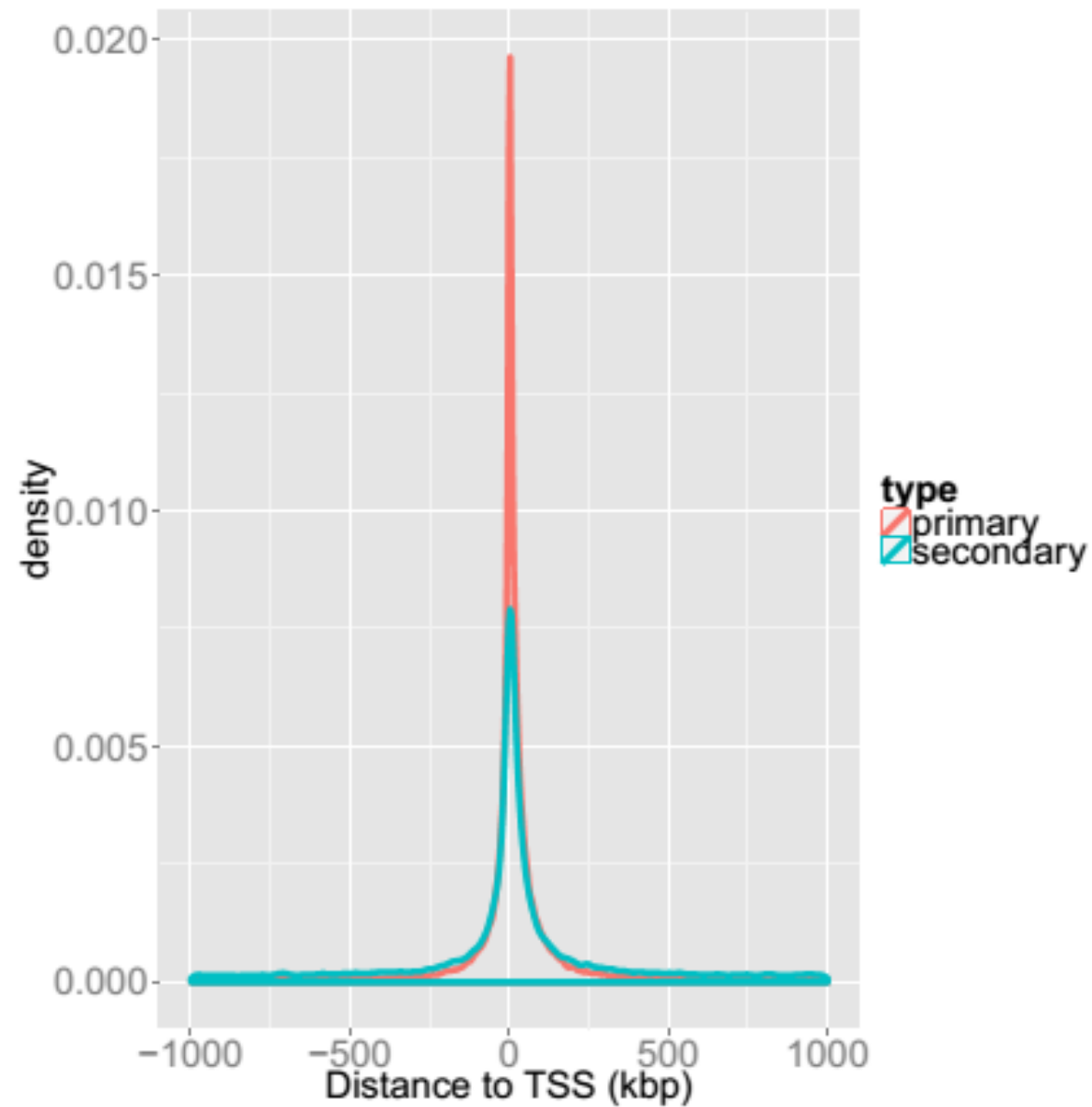
Number of additional eQTLs discovered in all tissues



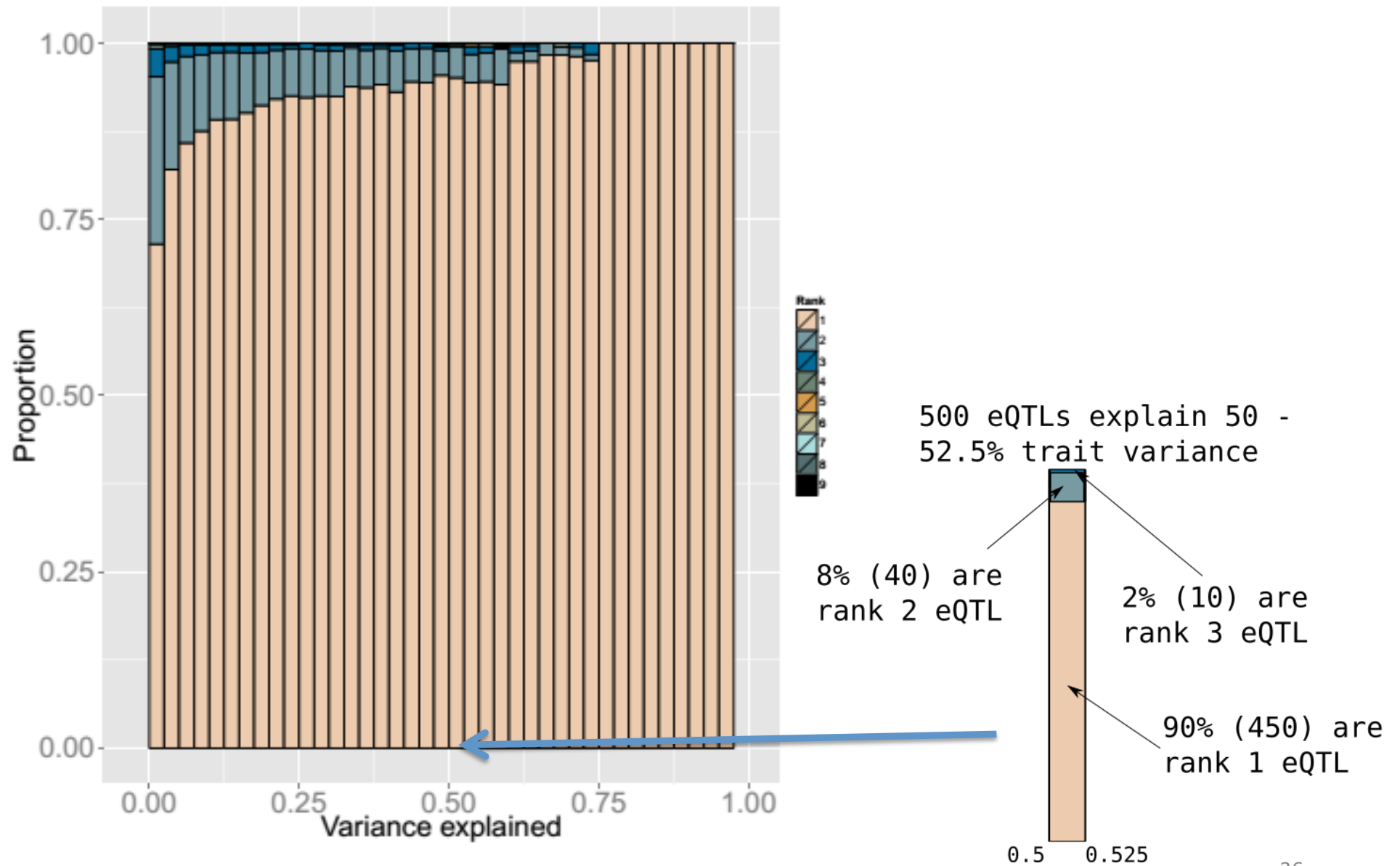
Additional signals discovered is a simple function of power



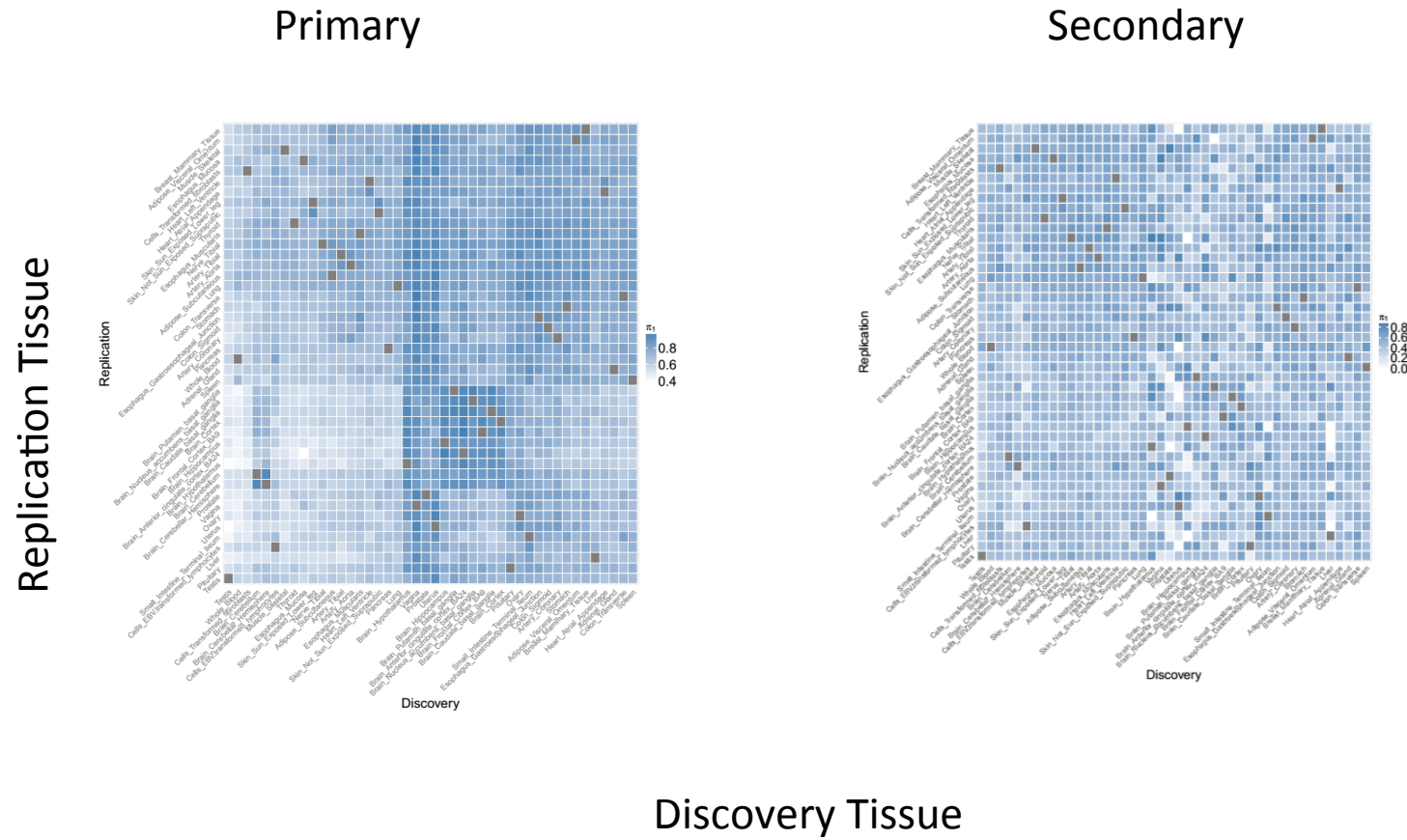
Secondary eQTL are less enriched around TSS



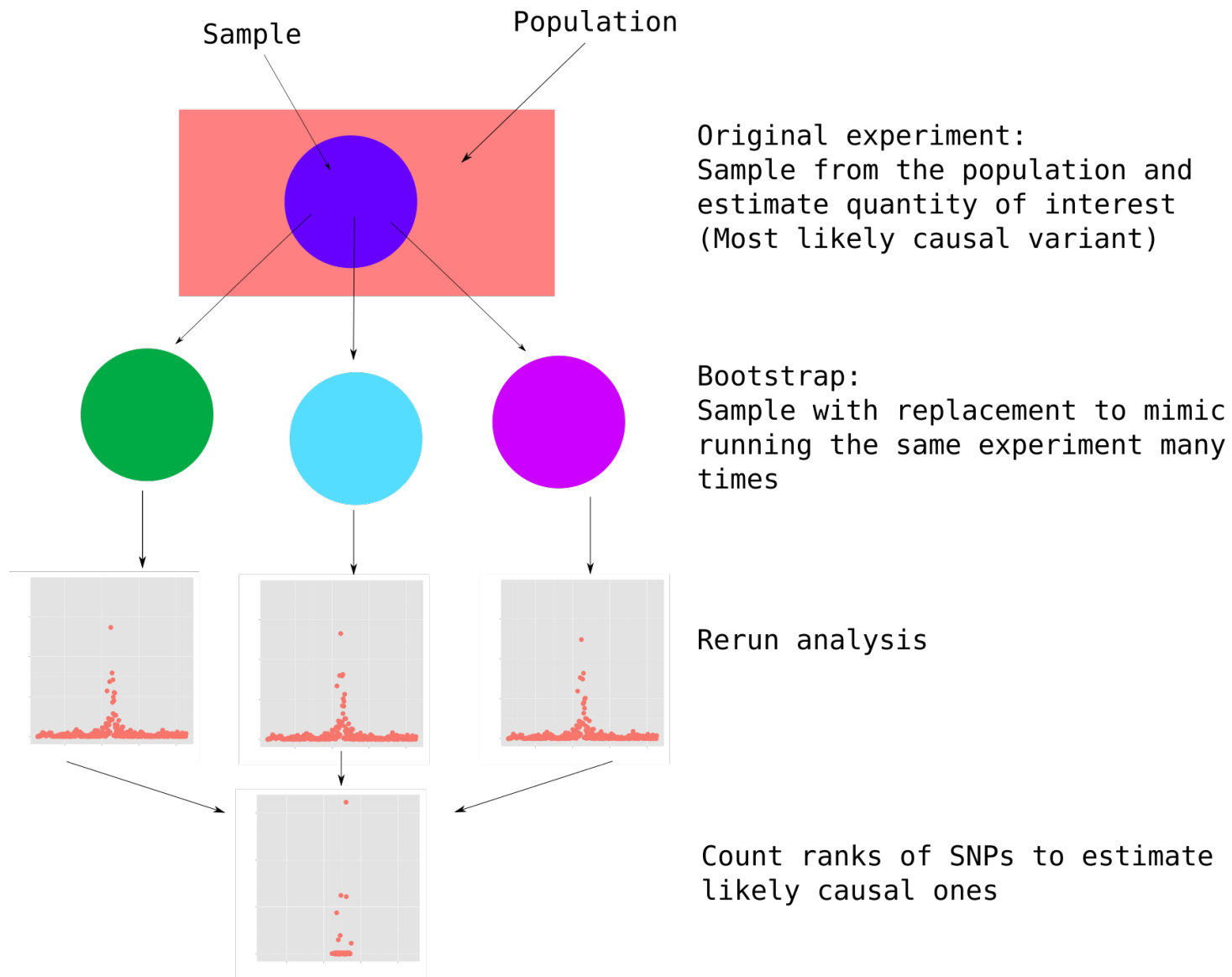
Variance explained by rank of eQTL



Replication in other tissues



Mapping causal variants using resampling



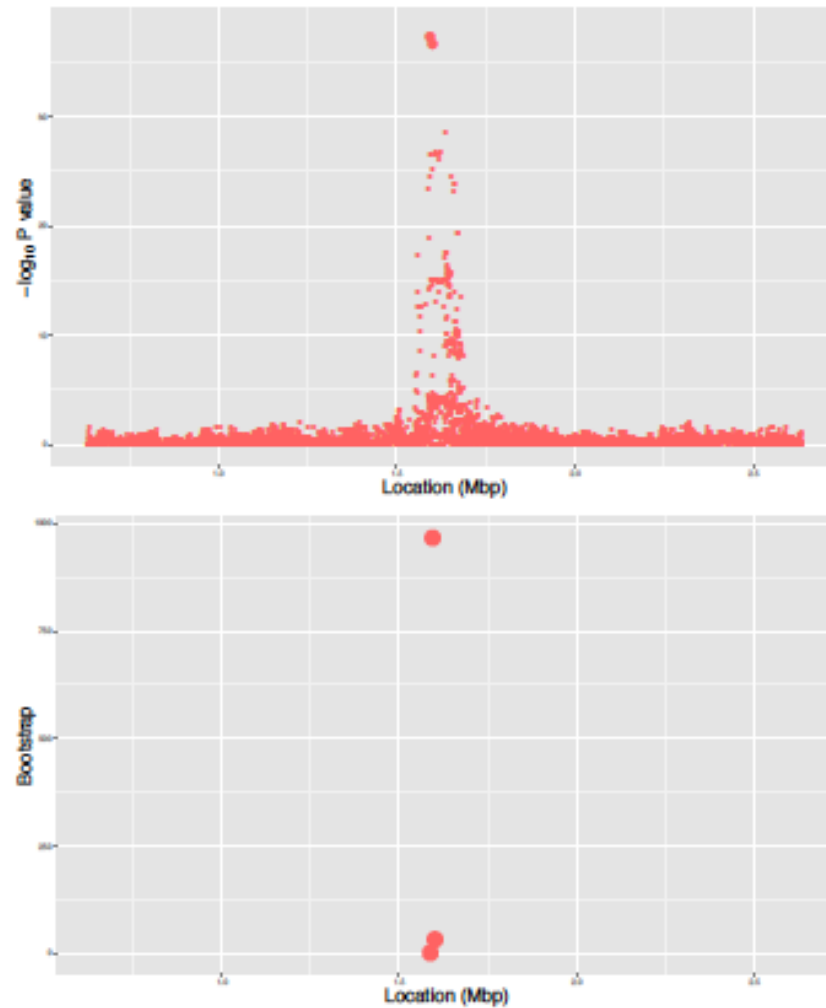
Applied to GTEx Data

- Bootstrap likelihoods are estimated as:

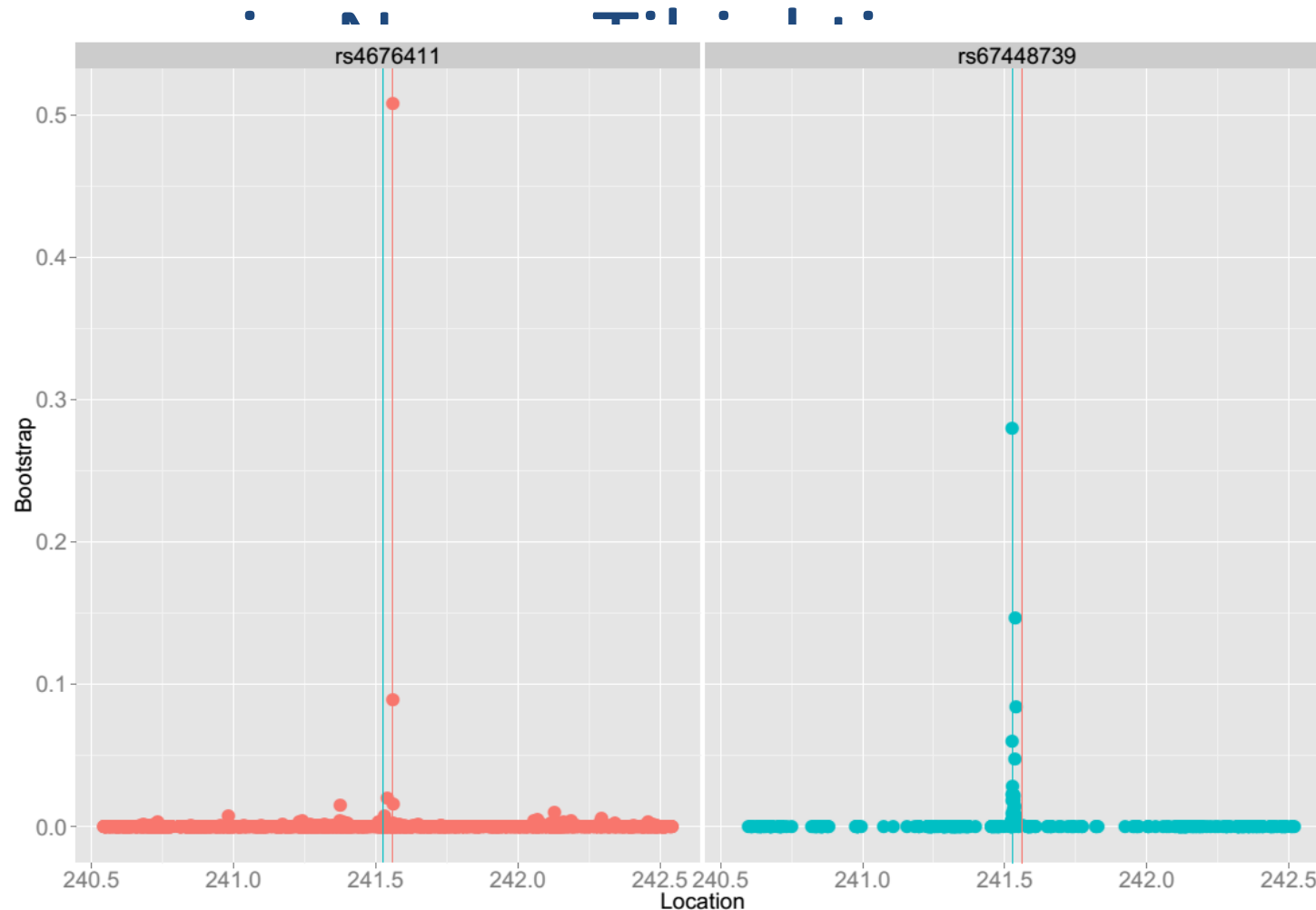
$$P(\text{SNP } x \text{ is causal}) = \sum_{\text{ranks and bootstraps}} P(\text{SNP } x \text{ in rank } i)P(\text{rank } i \text{ is causal})$$

- Applied to 6 GTEx tissues: Brain caudate, Brain cortex, Lung, Muscle skeletal, Nerve Tibial and Testis.
- We use “single signal” phenotypes produced by conditional analysis.
- Also applied “pairwise bootstrap” to Nerve tibial and Muscle skeletal and to Brain caudate and Brain cortex together.

Resolving causal eQTL variants



Example applied to *GPR35* expression

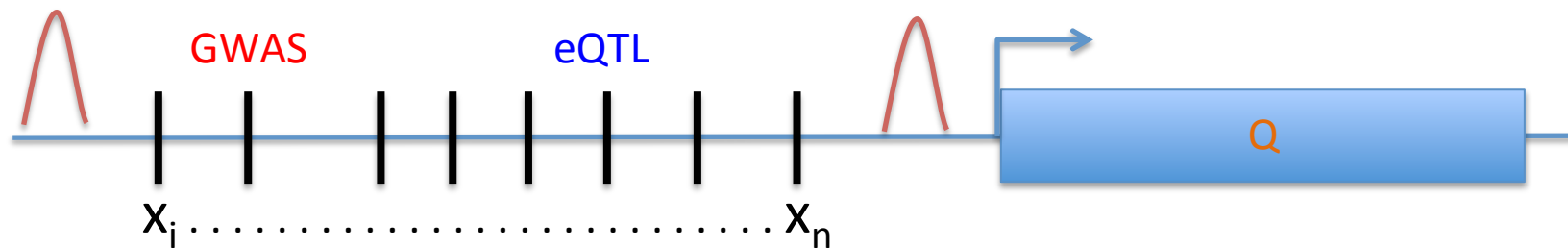


Applying bootstrap to conditional phenotypes we can map causal variants separately

Regulatory Trait Concordance (RTC) Score

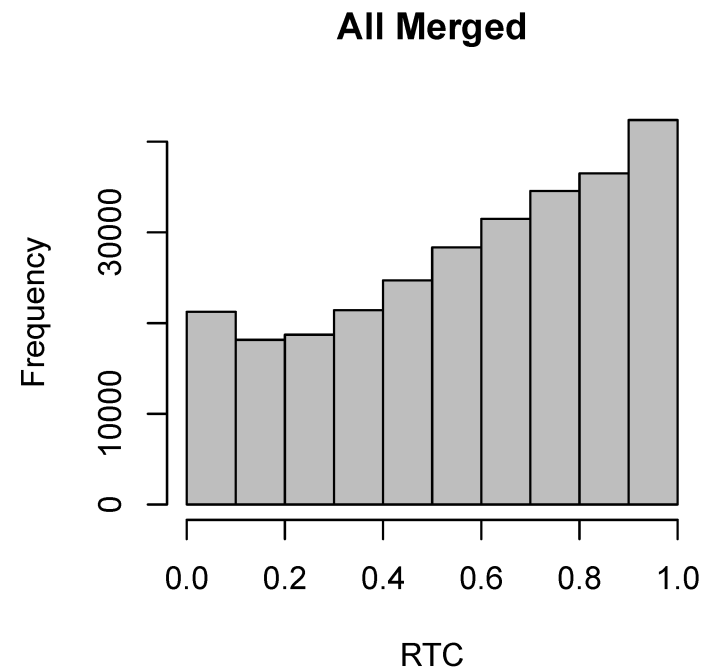
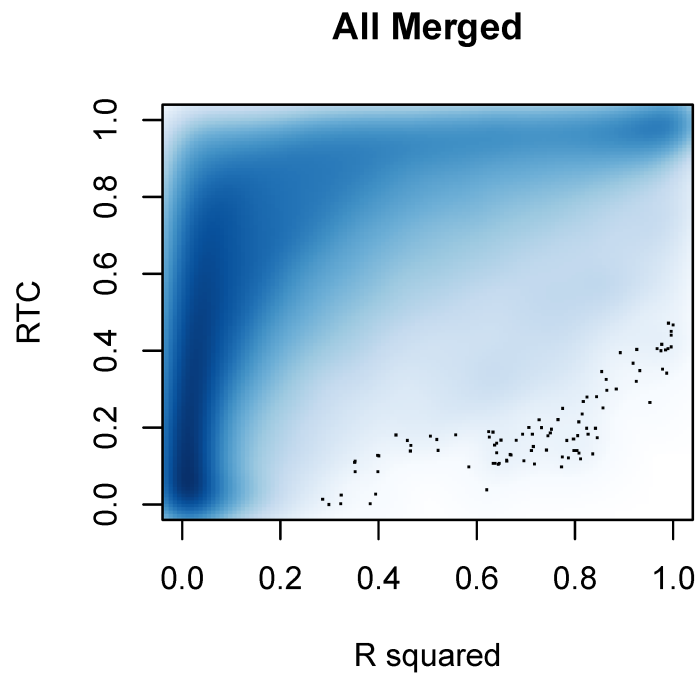
- For a GWAS variant falling into the same recombination coldspot interval with an eQTL, with N number of variants in a given coldspot:
 1. Correct the phenotype for each of the variants in the region separately by linear regression, resulting in N number of pseudo-phenotypes (residuals).
 2. Redo the eQTL variant association with all of these pseudo-phenotypes.
 3. Sort (descending) the resulting p-values and find the rank of the eQTL to GWAS_{SNP}-pseudo-phenotype among all eQTL to pseudo-phenotype associations.
 4. $RTC = \text{Rank}_{\text{GWAS}_{\text{SNP}}} / N$
- RTC scores ≥ 0.9 signify the eQTL and GWAS_{SNP} are the same casual variant (determined empirically).

Regulatory Trait Concordance (RTC) Score



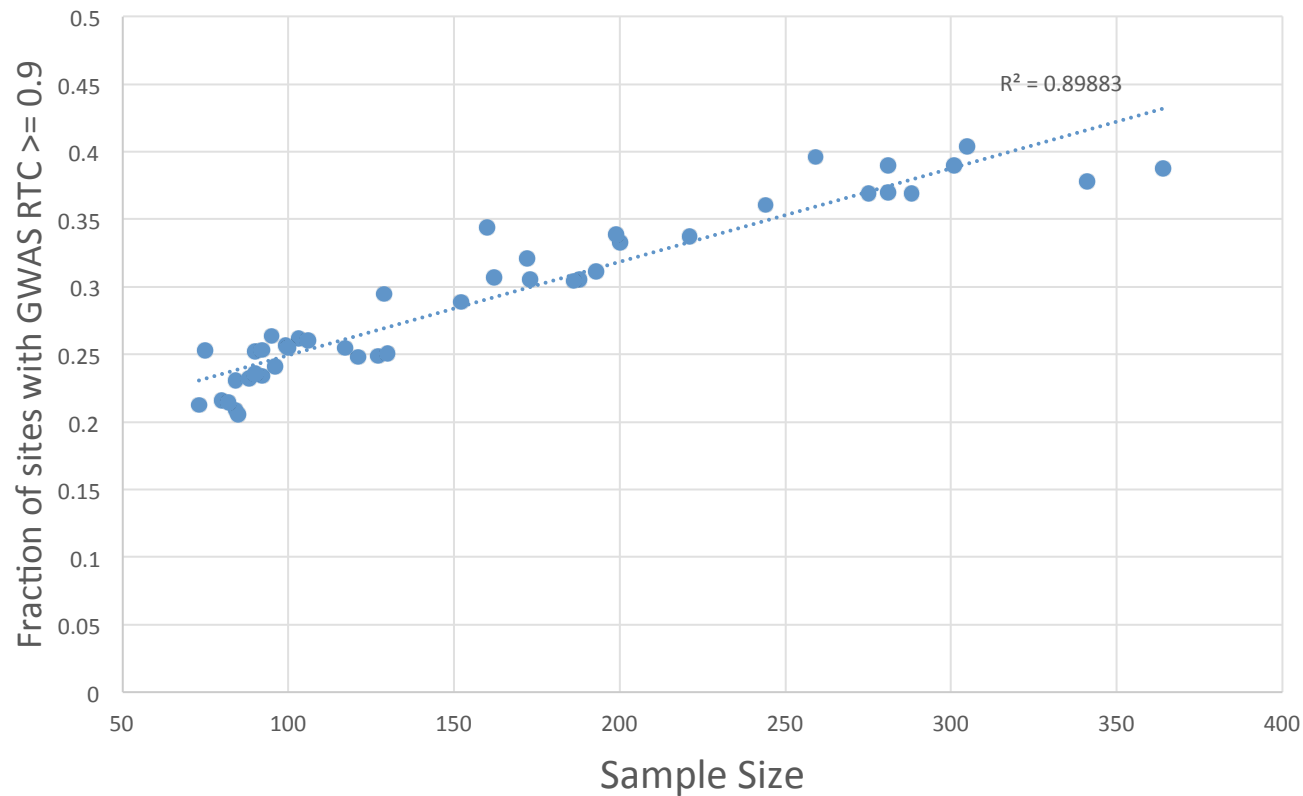
1. For $x_i \dots x_n$:
 - Correct Q for x_i (linear regression) $\rightarrow$ pseudo-phenotype $x_i Q$ (residuals)
2. For $x_i \dots x_n$:
 - Calculate p-value for $eQTL$ - $x_i Q$ association
3. Sort (ascending) p-values $eQTL$ - $x_{i \dots n} Q$ and find the rank of $eQTL$ - $x_{GWAS} Q$
4. $RTC = \text{Rank}_{GWAS} / n$

RTC score in the new 44 GTEx tissues



GWAS variants with RTC ≥ 0.9 by tissue

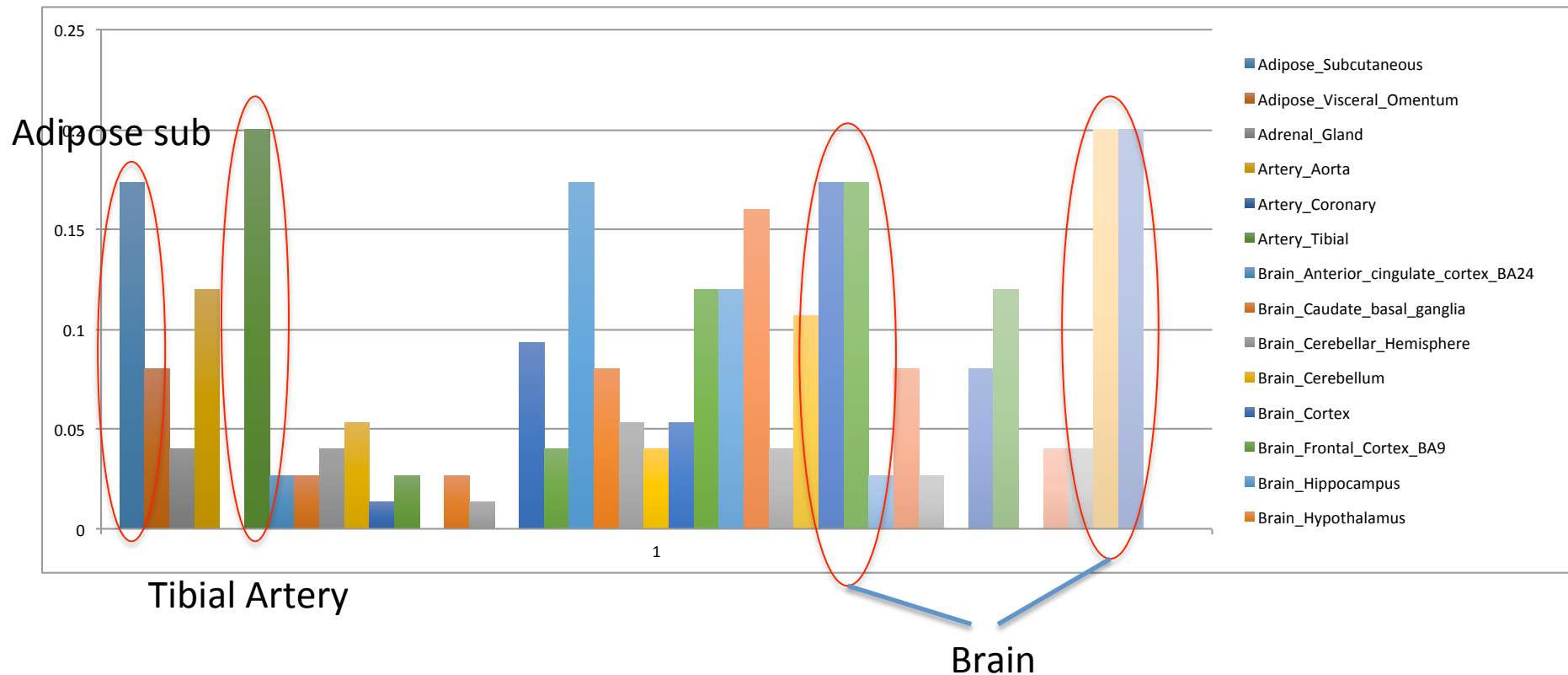
Relationship of sample size to ratio of GWAS RTC ≥ 0.9 to the total number of overlap between eQTL and GWAS



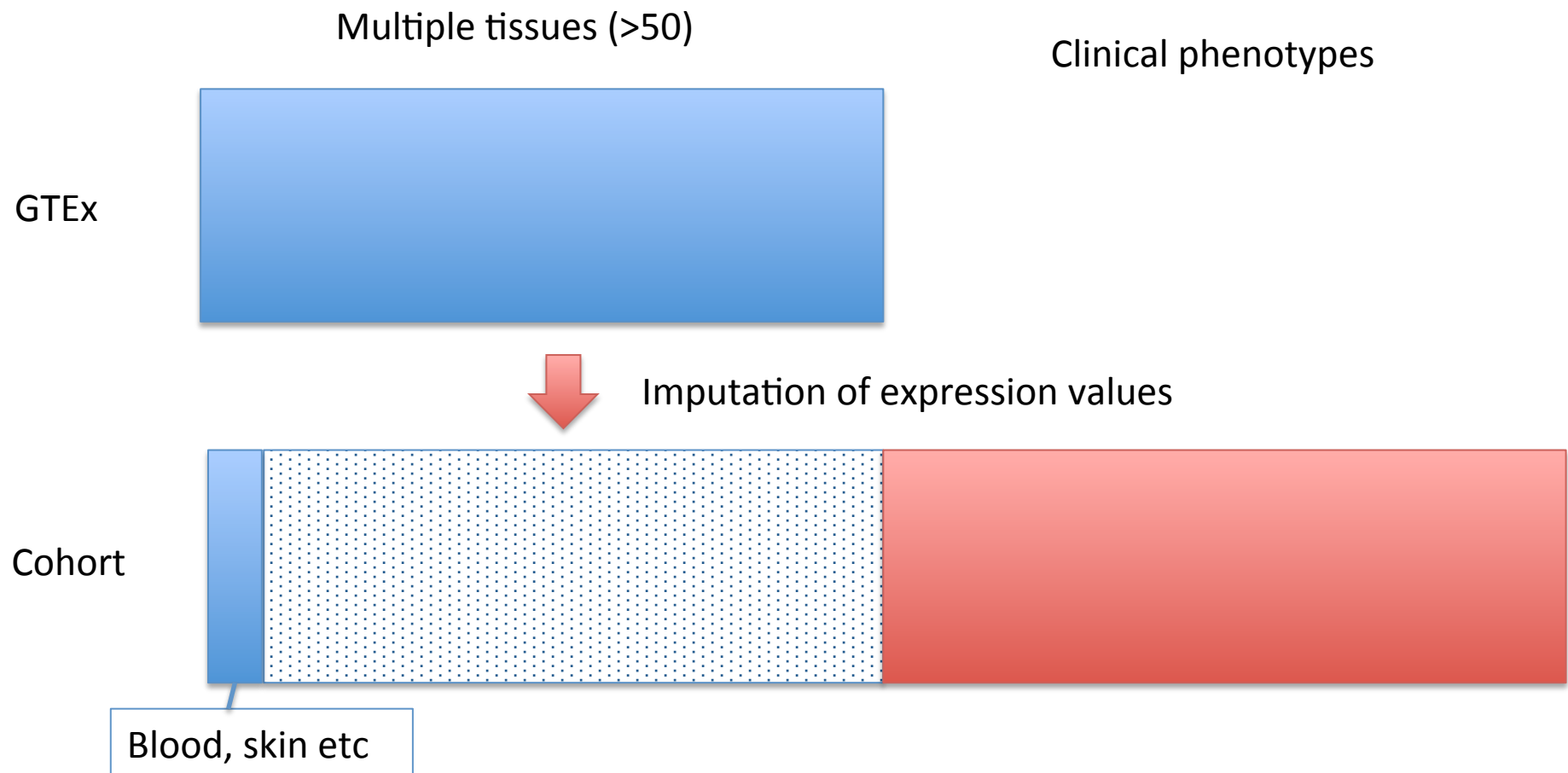
Tissue activity of GWAS in multiple tissues

Adipose_Subcutaneous	40	33	20	31	24	47	22	28	24	27	28	29	30	20	22	27	37	22	43	26	30	29	45	40	28	34	25	41	41	48	24	29	29	23	36	44	15	28	31	37	41	23	16	42		
Adipose_Visceral_Omentum	29	23	24	31	24	36	10	17	22	26	15	21	13	14	15	22	29	16	41	14	34	20	35	28	24	32	21	29	34	41	13	24	23	15	32	37	15	26	24	34	40	20	21	39		
Adrenal_Gland	27	21	20	32	25	40	10	20	26	25	15	26	19	11	16	33	32	15	41	13	32	22	37	28	25	31	21	30	37	42	23	25	17	34	37	7	30	27	36	38	22	21	36			
Artery_Aorta	27	19	20	29	21	40	11	18	24	24	14	20	25	15	12	15	32	31	15	42	12	31	21	35	27	24	30	20	28	35	39	10	22	24	16	33	38	5	27	26	35	38	12	17	31	
Artery_Coronary	62	35	38	49	16	56	20	29	28	42	27	31	30	17	16	19	35	30	49	28	35	28	46	42	36	47	28	43	59	55	39	46	20	38	43	49	13	33	41	51	57	13	16	42		
Brain_Anterior_cingulate_cortex_BA24	51	46	36	48	38	57	41	36	31	35	43	53	36	27	39	25	38	45	44	42	55	49	39	54	37	41	39	56	52	63	37	41	36	38	50	53	47	55	41	47	54	45	32	58		
Brain_Caudate_basal_ganglia	49	26	21	33	31	48	33	38	27	37	15	33	15	26	23	20	31	27	27	33	33	20	48	41	48	27	25	48	42	45	21	23	31	19	39	50	26	25	17	42	45	50	20	41		
Brain_Cerebellar_Hemisphere	54	34	44	59	38	57	20	27	26	30	23	28	38	25	14	17	42	28	53	37	46	29	44	49	31	51	24	43	51	41	33	22	38	59	48	28	33	39	44	58	23	29	33			
Brain_Cerebellum	45	43	44	48	52	39	44	33	44	43	47	57	51	44	35	38	49	36	39	39	38	47	49	45	49	43	38	55	58	54	23	48	41	33	36	43	32	37	45	39	62	36	25	55		
Brain_Frontal_Cortex_BA9	53	44	24	31	21	54	18	32	39	36	29	38	27	21	35	38	36	41	45	36	40	38	45	44	32	30	24	48	35	56	23	38	25	29	43	57	28	21	38	36	51	30	33	53		
Brain_Hippocampus	46	41	27	40	31	45	12	21	28	24	12	27	33	13	25	41	31	45	13	24	23	38	32	29	23	24	39	35	47	28	28	19	33	34	33	8	26	15	43	43	25	43	54			
Brain_Hypothalamus	43	32	20	22	7	42	22	21	10	15	21	6	0	0	7	9	24	24	31	43	24	17	21	25	50	36	43	30	32	40	8	35	14	0	22	28	40	21	29	37	39	0	0	41		
Brain_Nucleus_accumbens_basal_ganglia	49	34	38	51	35	55	29	38	32	30	33	45	38	40	35	47	39	33	52	32	50	48	31	35	45	30	15	56	46	40	50	39	36	31	40	48	30	35	32	41	40	38	38	53		
Brain_Putamen_basal_ganglia	34	22	22	33	15	36	0	14	17	28	6	12	9	0	7	12	22	11	26	6	23	10	39	22	14	13	15	41	38	31	0	22	6	0	26	28	12	0	24	33	39	0	0	26		
Breast_Mammary_Tissue	21	21	25	25	12	26	22	14	29	27	25	27	33	17	21	33	37	12	57	22	27	33	32	41	29	28	7	30	38	31	7	12	29	15	31	32	11	20	22	18	35	25	33	37		
Cells_EBV-transformed_lymphocytes	55	67	49	45	37	63	29	48	41	47	41	51	27	33	54	38	54	38	54	37	48	35	49	63	56	55	22	58	57	35	50	44	52	46	65	28	48	51	51	50	67	54	67			
Colon_Sigmoid	50	35	29	30	36	43	30	38	40	22	47	50	100	29	19	12	42	35	42	38	33	33	44	25	32	30	41	35	41	20	41	25	40	28	41	30	43	37	20	32	29	0	44			
Esophagus_Gastroesophageal_Junction	47	44	57	42	43	55	42	38	23	39	30	26	50	43	26	60	47	48	51	38	50	42	54	44	39	43	53	57	68	61	14	39	32	53	59	62	33	41	48	36	43	57	48			
Esophagus_Mucosa	36	28	35	49	14	42	15	41	30	36	27	25	33	29	20	12	26	29	45	25	36	30	46	54	36	44	29	34	44	63	44	41	7	45	46	50	23	13	46	55	59	14	33	36		
Esophagus_Muscularis	39	21	25	42	11	52	14	31	27	25	21	13	50	27	20	21	33	12	35	24	30	15	38	52	25	38	23	29	43	32	17	35	12	30	24	41	8	15	36	41	47	17	17	23		
Heart_Atrial_Appendage	47	55	25	31	35	62	30	19	12	32	11	17	33	9	17	20	44	50	55	31	42	25	39	50	35	46	10	34	46	51	40	29	23	27	34	32	25	57	41	31	57	14	33	43		
Heart_Left_Ventricle	65	61	48	60	33	63	33	56	20	42	38	20	22	22	46	36	52	43	57	59	44	74	35	76	59	56	33	81	42	61	55	46	29	54	44	66	27	53	39	61	58	40	20	63		
Liver	53	41	27	44	38	41	29	41	28	30	37	23	18	36	32	48	50	35	39	45	37	64	35	42	40	43	21	46	53	54	22	40	12	10	34	53	18	35	39	37	49	20	29	41		
Lung	41	12	0	38	0	35	0	17	8	33	25	38	36	0	0	0	20	15	12	47	21	15	11	24	29	13	25	14	43	19	21	0	7	0	0	17	32	0	0	17	21	29	0	0	39	
Muscle_Skeletal	27	7	20	17	10	40	0	0	29	12	86	0	0	0	0	0	0	0	8	0	1	6	11	18	20	28	30	42	0	17	46	16	0	12	0	25	18	23	0	0	0	117	20	0	33	23
Nerve_Tibial	26	17	33	26	21	43	0	33	20	25	20	12	0	17	10	0	25	25	33	21	28	7	26	26	29	22	0	20	25	11	20	25	8	25	24	35	25	18	25	25	42	25	0	17		
Ovary	56	33	67	44	57	43	33	36	27	18	43	50	30	44	29	36	71	50	62	33	39	45	59	47	42	47	46	42	50	45	22	54	77	58	67	58	60	33	62	52	57	0	0	57		
Pancreas	38	21	13	11	29	39	0	22	23	38	15	22	29	29	25	29	20	9	12	17	19	8	41	25	8	27	21	35	31	25	27	8	0	29	38	0	0	21	35	44	0	0	7			
Pituitary	18	46	33	25	0	33	25	0	14	33	11	25	17	33	33	14	17	33	12	38	22	31	40	33	12	21	29	0	39	11	21	27	13	0	17	23	18	25	17	18	37	50	0	11	31	
Prostate	25	25	25	22	31	41	22	22	18	33	20	11	33	12	17	25	40	41	29	24	45	30	35	38	24	33	24	38	29	17	41	43	11	29	30	20	29	25	47	40	11	43				
Skin_Not_Sun_Exposed_Lower_leg	25	11	29	29	40	64	33	50	20	25	0	20	40	50	33	33	20	0	33	29	30	33	18	27	20	22	40	31	18	42	0	0	0	33	22	25	0	10	20	17	13	0	0	38		
Skin_Sun_Exposed_Lower_leg	25	36	50	33	17	27	0	67	30	30	0	67	0	39	0	0	20	25	90	46	12	31	15	58	27	15	18	11	50	23	25	0	18	20	67	14	31	0	0	27	42	50	0	18		
Small_Intestine_Terminal_Ileum	13	14	20	27	14	19	0	29	17	20	33	0	25	9	17	0	0	0	1	11	17	35	0	33	0	40	14	36	25	0	23	47	25	17	12	25	0	36	35	20	39	42	56	0	31	
Stomach	26	17	33	26	21	43	0	33	20	25	20	12	0	17	10	0	25	25	33	21	28	7	26	26	29	22	0	20	25	11	20	25	8	25	24	35	25	18	25	25	42	25	0	17		
Testis	56	33	67	44	57	43	33	36	27	18	43	50	30	44	29	36	71	50	62	33	39	45	59	47	42	47	46	42	50	45	22	54	77	58	67	58	60	33	62	52	57	0	0	57		
Thyroid	38	21	13	11	29	39	0	22	23	38	15	22	29	29	25	29	20	9	12	17	19	8	41	25	8	27	21	35	31	25	27	8	0	29	38	0	0	21	35	44	0	0	7			
Uterus	18	46	33	25	0	33	25	0	14	33	11	25	17	33	33	14	17	33	12	38	22	31	40	33	12	21	29	0	39	11	21	27	13	0	17	23	18	25	17	18	37	50	0	11	31	
Vagina	25	25	25	22	31	41	22	22	18	33	20	11	33	12	17	25	40	41	29	24	45	30	35	38	24	33	24	38	29	17	41	43	11	29	30	20	29	25	47	40	11	43				
Whole_Blood	25	11	29	29	40	64	33	50	20	25	0	20	40	50	33	33	20	0	33	29																										

Type II Diabetes tissue activity



Use of GTEx as reference



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

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