Sex differences at the molecular level: Lessons from the human transcriptome and a role in complex traits

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GTEx
Sex-Analysis
Working group

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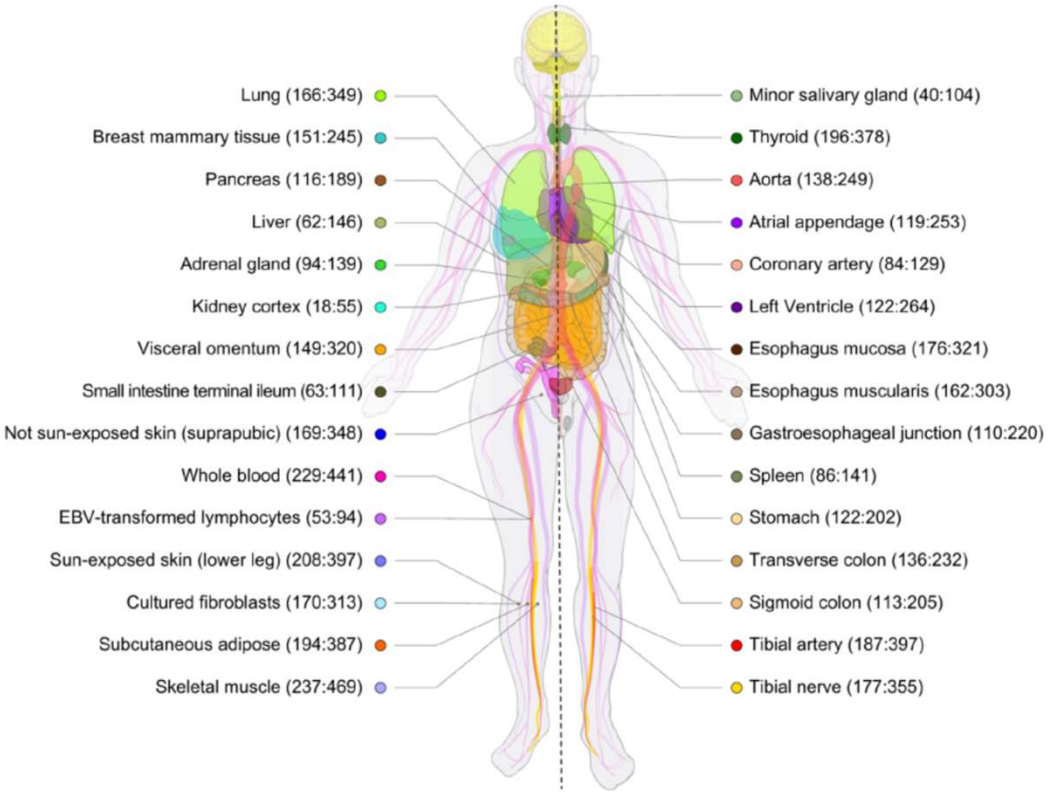
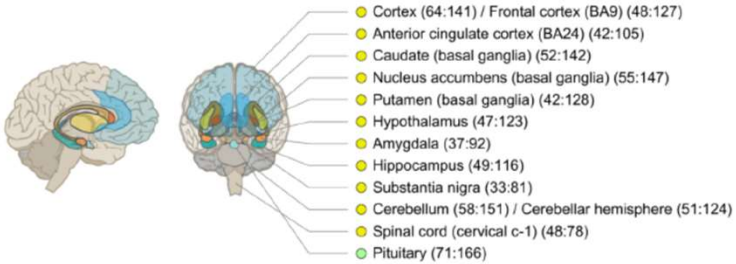
NIH Genotype-Tissue Expression (GTEx) Project

N=17,382 RNASeq + genotypes from N=838 donors





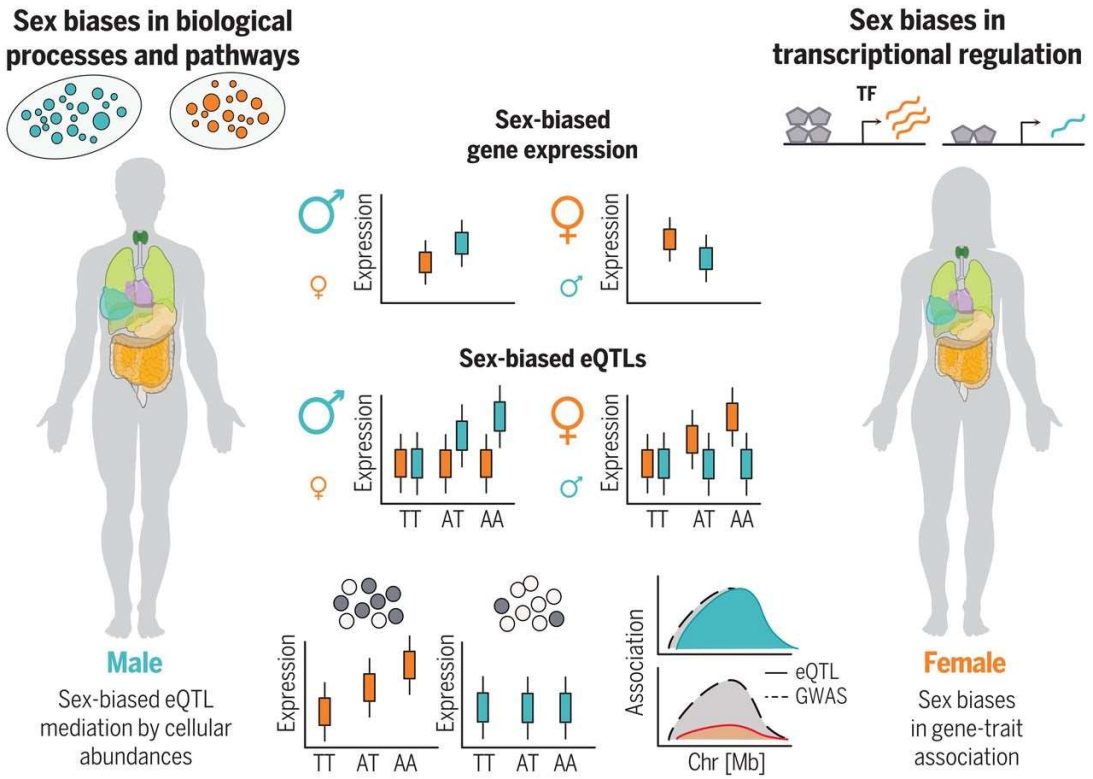
genotyping, DNA sequencing

Publicly-available database of eQTLs

Enhancing GTEx (eGTEx) adds additional genomics data

GTEx

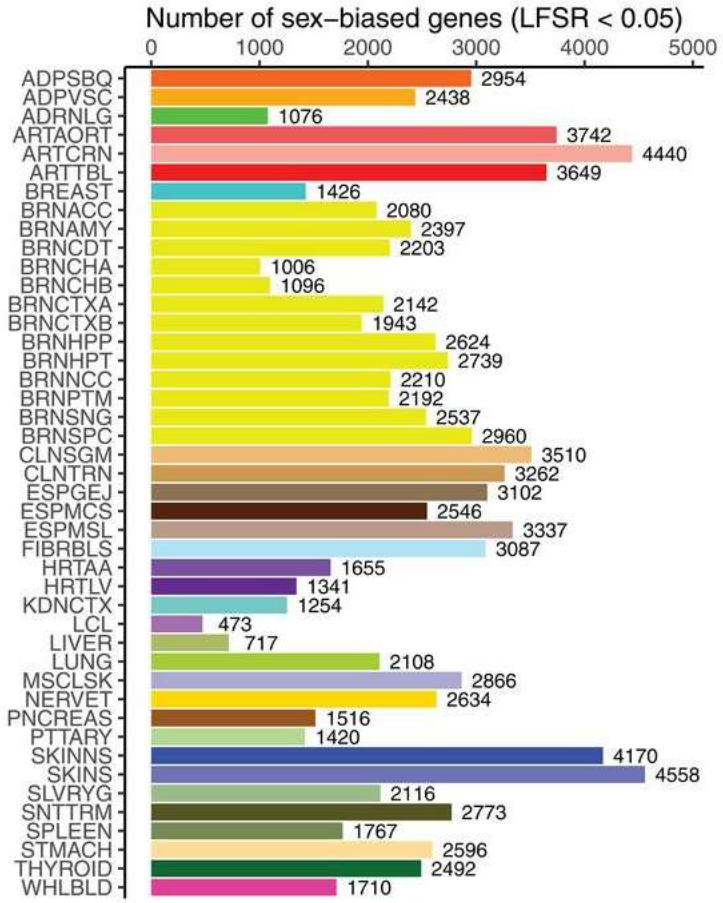
Sex effects in the GTEx transcriptome



- *N* = 44 tissue sources present in both sexes with ≥70 samples.
- two cell lines, 40 tissues, and two replicates for brain cerebellum and cortex tissues.
- 838 subjects
- Male/Female: 2:1

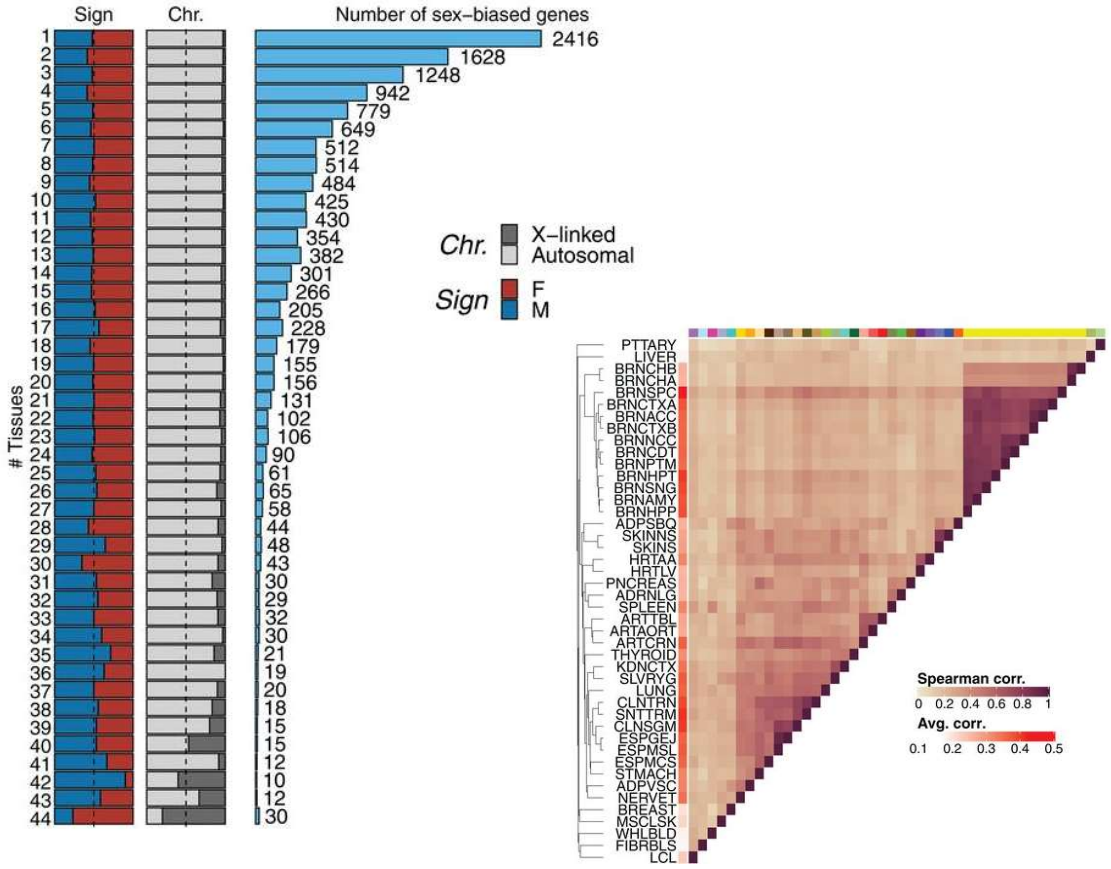
M. Oliva et al. Science 2020;369:eaba3066

Male/Female differential gene expression



- 473 to 4,558 per tissue (1.3% to 12.9% of tested genes)
- 13,294 (37%) differentially expressed genes (sex-biased genes)
- 4% were X-linked and 96% autosomal

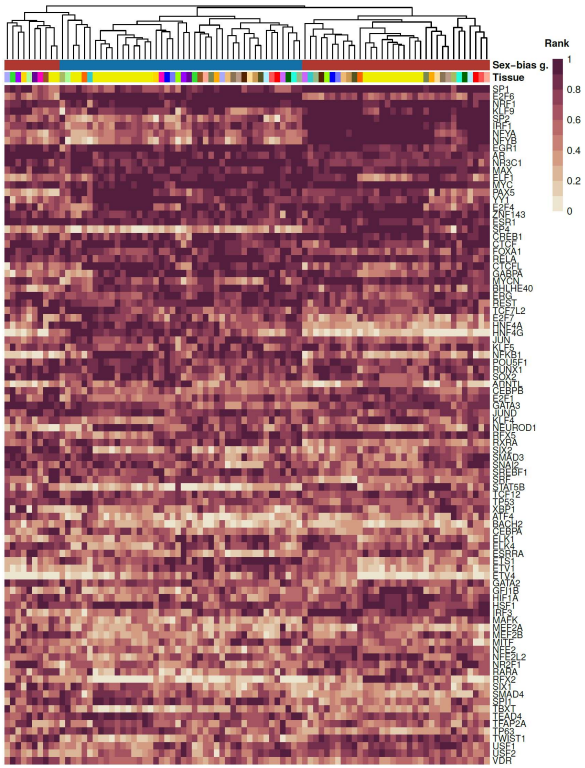
Sex-biased gene expression is largely tissue specific



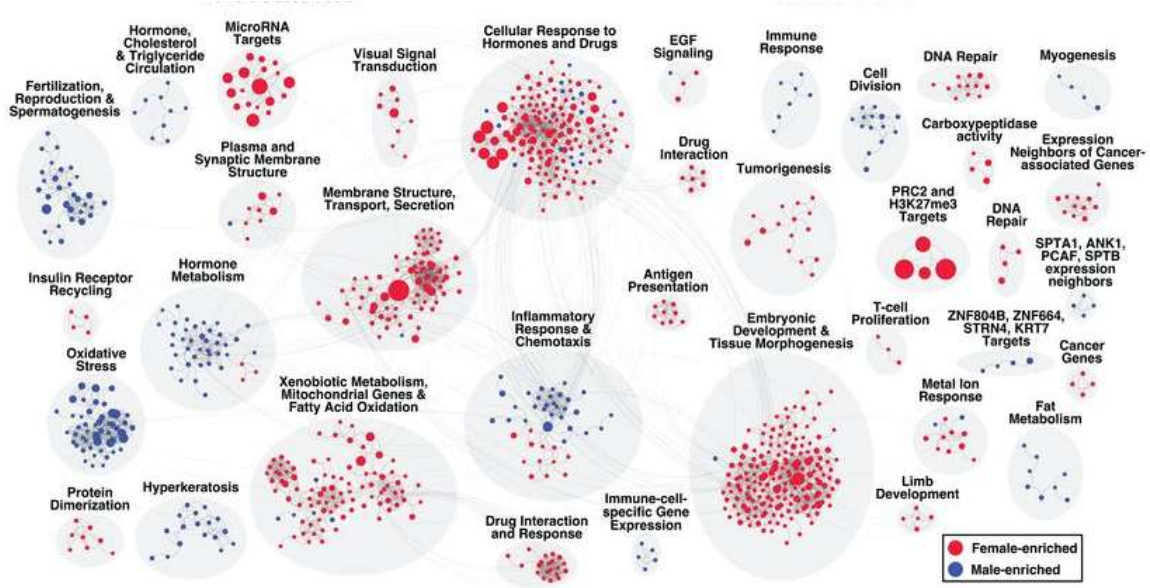
13,294 sex-biased genes

- 18.2% of sex-biased genes DE in only 1 tissue
- 30 genes consistent across all 44 tissue sources.
- 76% of genes with sex bias in ≥2 tissues exhibit consistent direction across tissues, especially X-linked genes
- whole blood and cell lines **not** representative; sex-biased genes in blood only 12.9% of all sex-biased genes

Which types of genes exhibit sex-biased expression?



Specific Transcription Factors

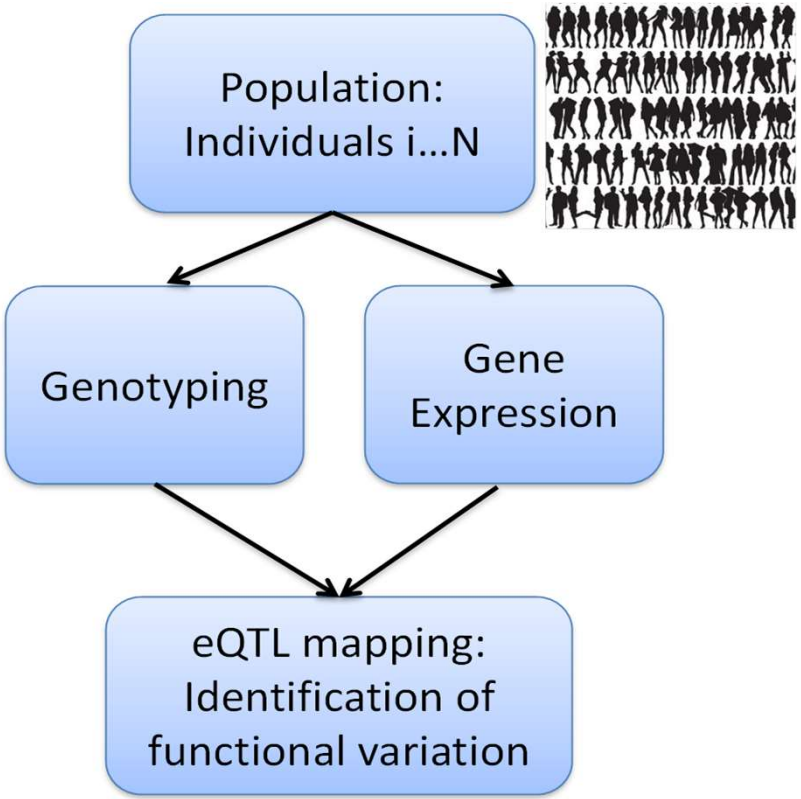


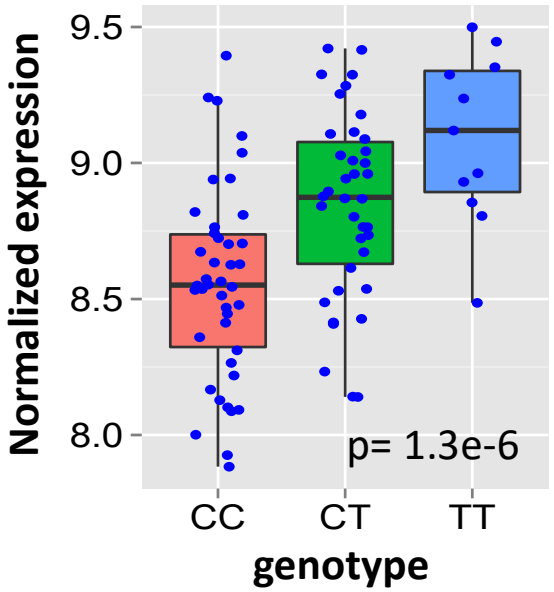
Enrichment: drug and hormone response, epigenetic marks, embryonic development and tissue morphogenesis, fertilization, sexual reproduction and spermatogenesis, fat metabolism, cancer, immune response, and others…

Observations: sex-differential expression and splicing

- Sex-differential expression and splicing is widespread across human tissues
  - 37% of genes are DE
- Tissues differ qualitatively and quantitatively with respect to sex differences at the transcriptome level
- Affected genes are enriched for many biological functions and targets of specific transcription factors and microRNAs
- Affected genes include OMIM and GWAS-implicated disease genes
- Identify novel XCI-escape genes and quantify across tissue XCI

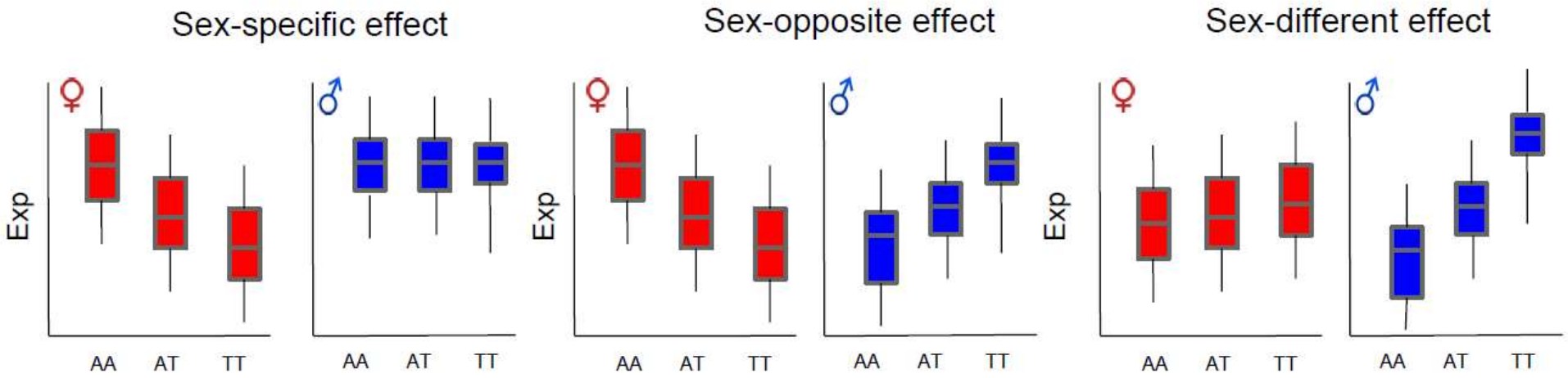
Expression quantitative trait locus (eQTL) mapping: to identify genomic regions affecting expression levels





Sex-biased eQTLs

- eQTLs that behave in a sex-dependent manner.
- Motivation: sex-dependent genetic effects may contribute to sex-biases seen in various human traits

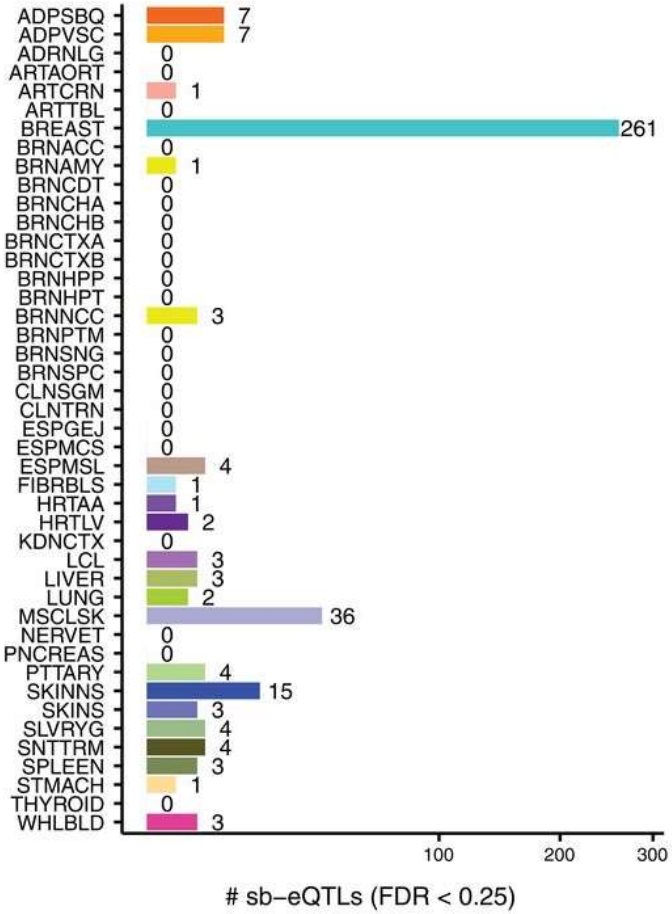


Model: $Y_i \sim \beta_0 + \beta_1 Sex + \beta_2 Genotype + \beta_{(1\text{-}n)} BasalCovs + \beta_{(1\text{-}m)} PEERS + \beta_3 Genotype \times sex + \varepsilon$

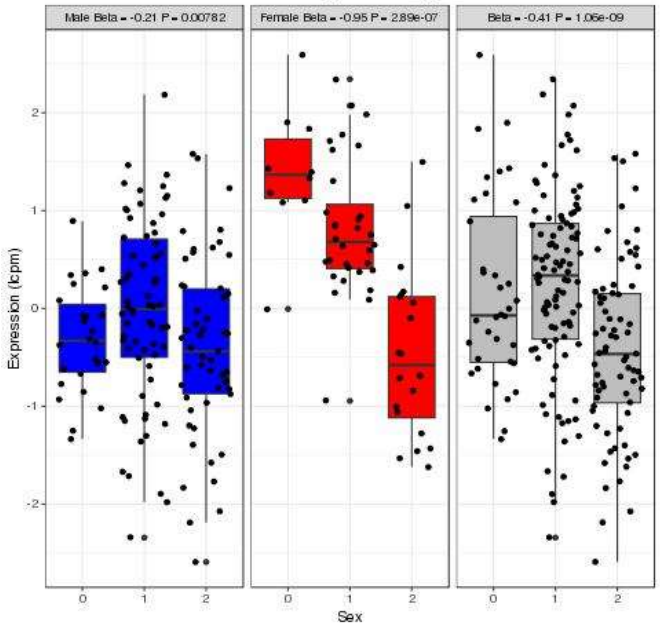
sex-biased-eQTLs, 44 tissues

366 total genes with sb-eQTLs

per tissue:
0-261 sb-eQTLs

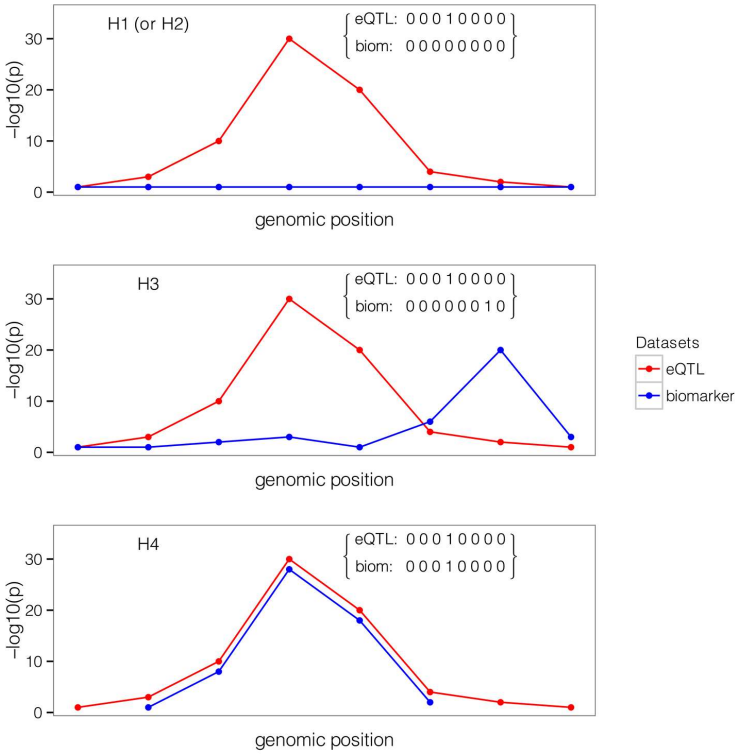


Liver: HDKC1



♂ ♀ Combined

Colocalization GWAS + eQTLs

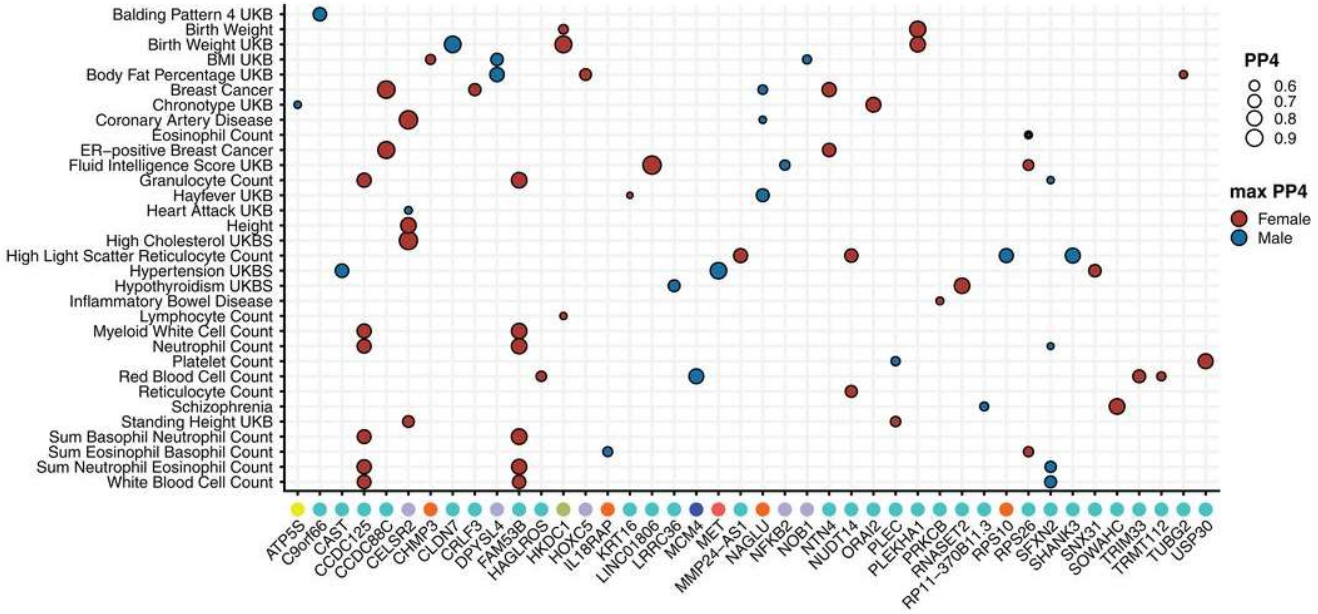


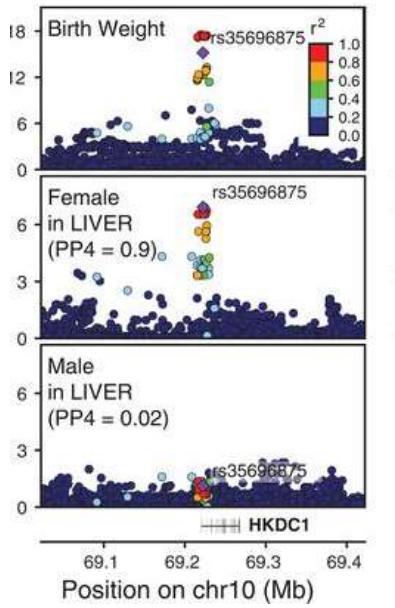
Giambartolomei *et al.* 2014 *PLoS Genetics*

Statistical approach to test likelihood that a GWAS association and eQTL have same causal variant

Creates hypothesis:
SNP → gene expression → trait

Colocalization: 87 GWAS + sex-stratified and sex-combined eQTLs





74 colocalized gene-traits, **58 sex-specific**

35 colocalizations detected with combined M/F eQTLs, but due to effect in only a single sex

Considering SABV leads to new discoveries + highlights that previous discoveries were due to only one sex

Observations: sex-biased eQTLs

- Sex-biased eQTLs are present across human tissues
- Relative to cis-eQTLs, overall signal is much lower. Single tissue analysis suggests tissue-specificity much higher.
- Demonstrate that some previously identified cis-eQTLs are driven by signal in a single sex
- Sex-biased genetic regulation provide links between disease genetics, genes, and mechanisms.

Summary GTEx

- Widespread differences in gene expression and splicing across adult human tissues
- Tissue specificity (qualitative and quantitative)
- Differential gene expression not only due to sex chromosomes and hormones.
- Sex-biased genetic regulation of gene expression (cis-eQTLs, ASE)
- These sex differences at the genetic and transcriptomic level involve disease implicated genes and genetic variants.

Many more things to do…

- Need studies specifically designed to evaluate sex differences (healthy, diseased, cell line models)
- Different developmental points, Longitudinal cohorts with hormone measurements, other –omics
- Analyze data with sex-aware framework, share sex-disaggregated results

GTEx Sex-Analysis Working group

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