Understanding the genetic basis of sexual dimorphism: **sex-bias eQTLs**

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Motivation

What is sexual conflict?

- Females and males often have **conflicting** ecological or reproductive **interests**.
- Because most traits under conflict have **shared genetic basis between the sexes**, sex-specific optima cannot be simultaneously expressed and **sexual conflict** arises.
- The fitness cost of the unresolved sexual conflict pulls the evolution of mechanisms that allow for **sex-specific expression** of the shared genome, leading to evolution of **sexual dimorphism**.
- Such mechanisms involve (i) sex linkage and (ii) sex-biased gene expression.
- Nevertheless, **sexual conflict is widespread.**

Main questions

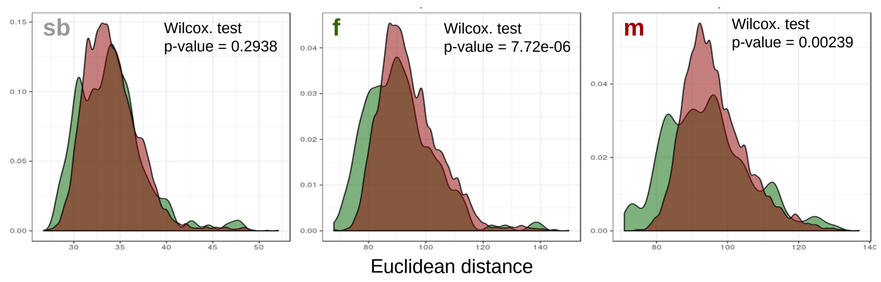
- If it has potential for resolution, why does sexual conflict persist for long evolutionary scales?
- What mechanisms resolve sexual conflict and why are they inefficient?
- We explore these questions by looking at **genetic variation underlying sex-biased expression**

Why studying resolution of sexual conflict via eQTLs for **sex bias** in expression?

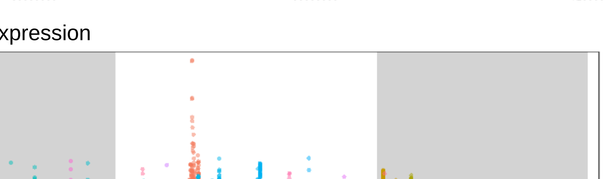
- Since most genes are autosomal, **sex-biased expression** of shared genes is expected to be the **main sexual conflict resolution mechanism**.
- Previous work has determined eQTLs for male and female expression separately. Nevertheless, **genetic variation underlying sex bias vs sex-specific expression seems to be**:

(1) Lower

Euclidean distance of gene expression vectors **within** and **between** lines



(2) Different



Dimas et al. (2012), Genome Res

Results

The data:

Drosophila
Genetic
Reference
Pannel

185 inbred lines (2 replicates)
1,913,487 SNPs

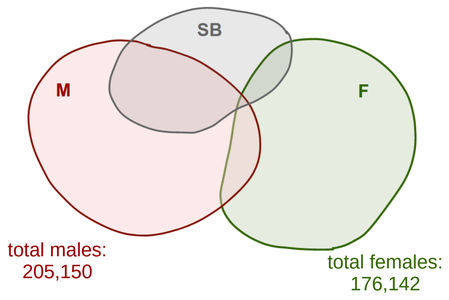
GWAS

18,140 gene expression (phenotypes)
- Females
- Males
- Sex bias $= log_2 \frac{expF}{expM}$

Counts

	# eQTLs Loci associated with the expression of a gene	# eQTL genes Genes whose expression values are associated with (at least) a locus
	~2M SNPs	~20.000 genes
Females	6.4%	58.3%
Males	6.7%	57.1%
Sex bias	2.5%	46.2%

Considering single eQTL → gene interactions



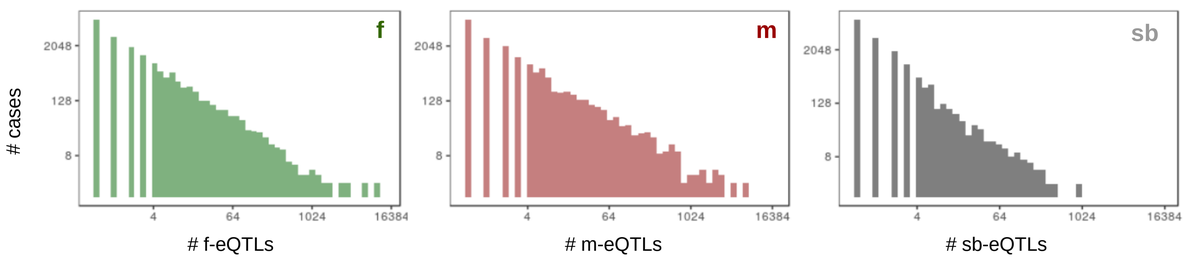
How do sex bias-eQTLs operate?

59,658 sb-eQTL – gene interactions

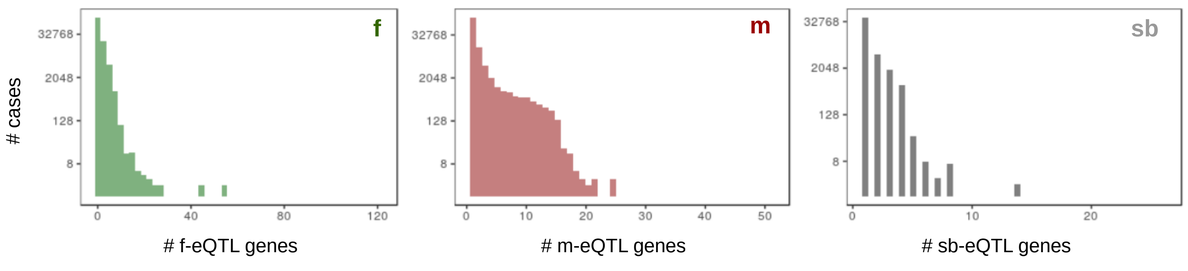
- sex-specific **35,404**
  - f-specific **9,048**
  - m-specific **26,356**
- affect both sexes **424**
  - different direction **7**
  - different magnitude **417**
    - f > m **93**
    - m > f **324**
- no effect on f or m **23,830**

Comparing distributions

 # eQTLs affecting exvpression of each gene

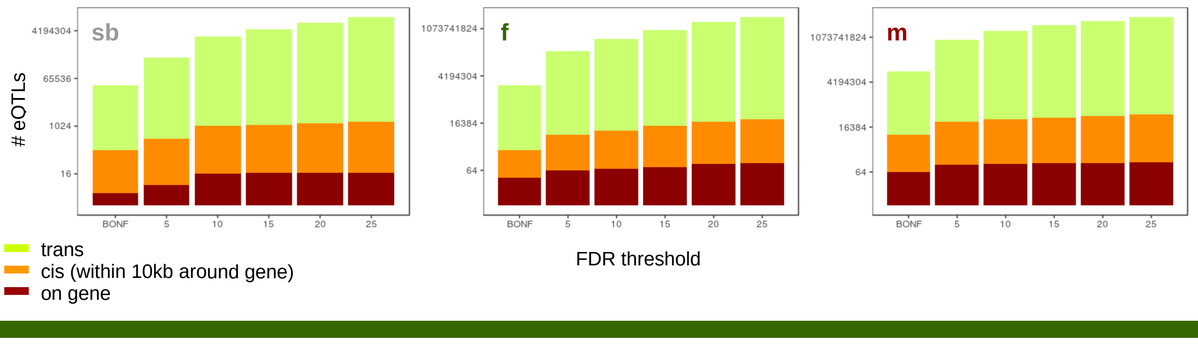


 # genes affected by each eQTL



cis- or trans-eQTLs?

 # cis-/trans-eQTLs for different FDR thresholds



Overall picture

Association results for all (18,140) genes

Ongoing work

New gene expression dataset

Why a new gene expression dataset?

DGRP lines

- Have covariates
  - Wolbachia infection (53% of the lines)
  - 16 segregating inversions
  - Population structure (cryptic relatedness)
- Are **highly inbred** (patterns of gene expression and genetic variation not representative of natural populations)

How to generate a new gene expression dataset?

DGRP F1 lines

- Heterozygous
- Genetically identical within line → sex bias per genotype
- Without Wolbachia infection (*)

F line	1	3	5	7	9	11	13	...	189
M line	2	4	6	8	10	12	14	...	190

(*) Wolbachia infected lines as paternal (maternal transmission)

95 crosses
- 2 replicates
- Females and males
- 2 tissues
  - Heads
  - Gonads

760 samples

- eQTL analyses
  - exp F
  - exp M
  - sex bias
  - heads
  - gonads

Mathematical modelling

Characterizing the genetic landscape of phenotypic variation with separate sexes

Relevant quantity for extent of association detected by GWAS:

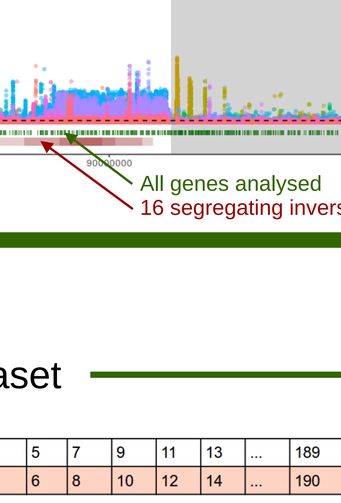
Additive genetic variance contributed by each site

geometric argument → **α: effect size on trait**

diffusion approximation → **p: allele frequency**

$$E[2\alpha_{fi}^2 p_i(1-p_i)|s_f, s_m] = E[\alpha_{fi}^2|s_f, s_m]\ E[2p_i(1-p_i)|s_f, s_m]$$

s_f, s_m: sex-specific selection coefficients



Adapted from Connallon & Clark (2014)

Predictions:

Will disproportionately contribute to genetic variation maintained:

- **Sexually-antagonistic mutations**: balancing selection
- **Sex-specific deleterious mutations**: purged in only half of the population
- **(Deleterious) mutations with asymmetric effects across sexes**: asymmetric contribution to genetic variance

How to consider sex in GWAS?