

Sex-specific genetic effects on fitness and human disease

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@ted_morrow

@SexualConflict

ERC Annual Workshop 2020

Sex and Gender Dimension in Frontier Research

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2Sexes_1Genome project



- 2012 – 2016 University of Sussex, UK
- *Tanya Pennell, Ilona Flis, Fiona Ingleby, Will Gilks*
- Collaborators: *Max Reuter lab UCL (UK)*

• **Objective 1:** To identify genes with **sexually antagonistic** effects in the fruit fly *Drosophila melanogaster*

2

Current project



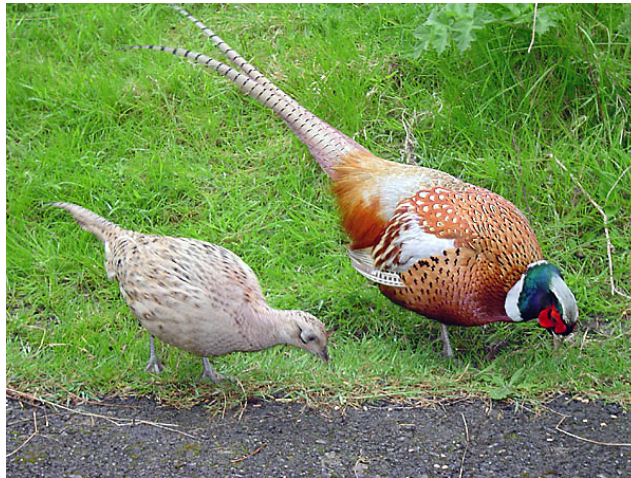
- Karlstad University
- *Jon Harper (Sussex)*
- *Tim Janicke at CNRS Montpellier (France)/Dresden (Germany)*

• **Objective 1:** To identify **sexually antagonistic genes in human disease**

Sexual dimorphism



Size

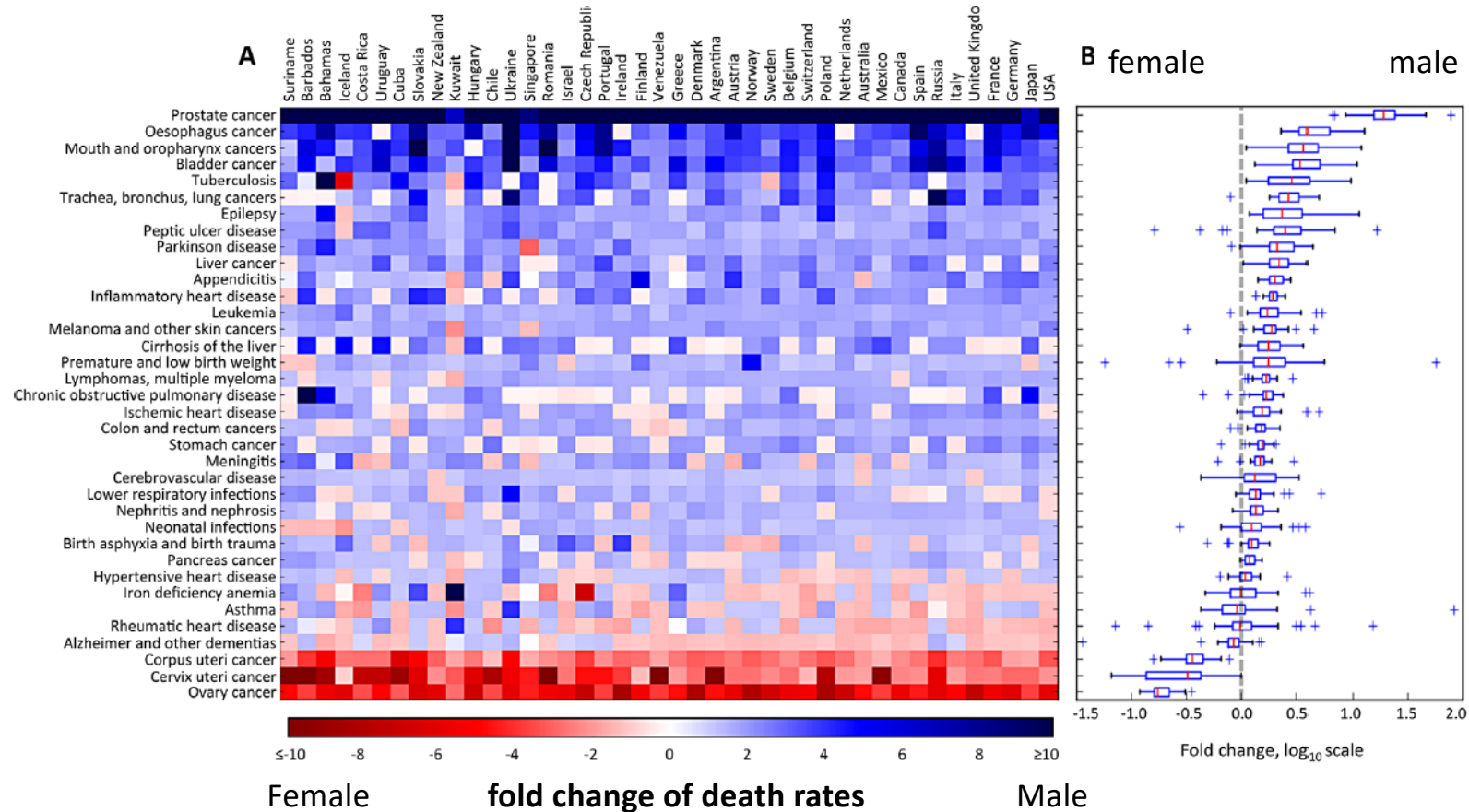


Colour



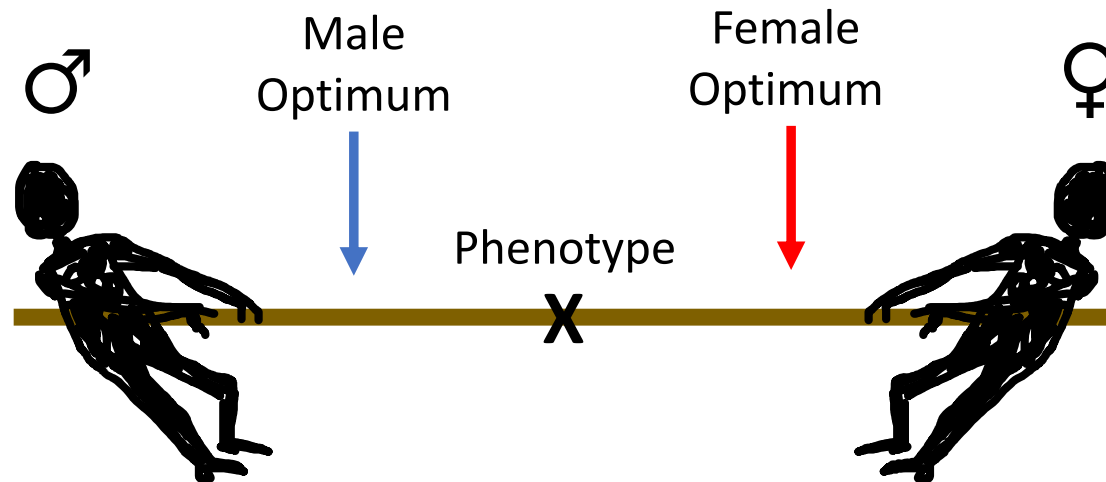
Shape

Sexual dimorphism in human disease



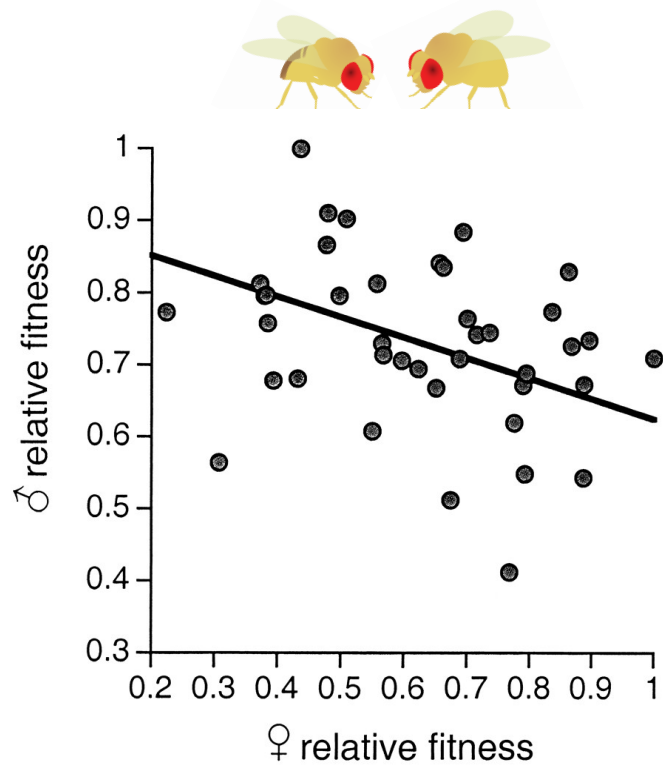
Rigby and Kulathinal (2015) *Journal of Cellular Physiology*

Sexual antagonism is an evolutionary tug-o-war



- Sexually antagonistic genes: opposing selection pressures in the two sexes
→ Beneficial in one sex, deleterious in the other
- Balancing selection maintains genetic variation
- Sexually antagonistic genes may contribute to disease risk/severity
- Resolution via the evolution of sexual dimorphism

Sexually antagonistic genes: evidence in nature



Chippindale, Gibson & Rice 2001 *PNAS*



Photo: Warren Wong

1 Which genes are sexually antagonistic?

- **Hemiclonal analysis:** quantitative genetic method in *Drosophila melanogaster*
- Measure phenotype...for multiple haplotypes...expressed as males or females

2Sexes_1Genome project:

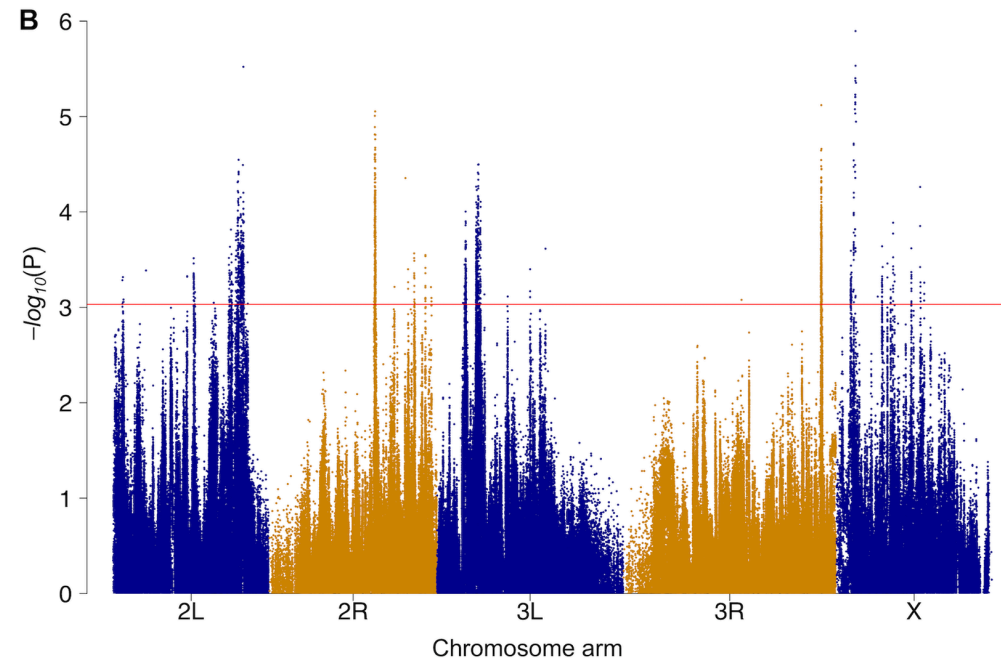
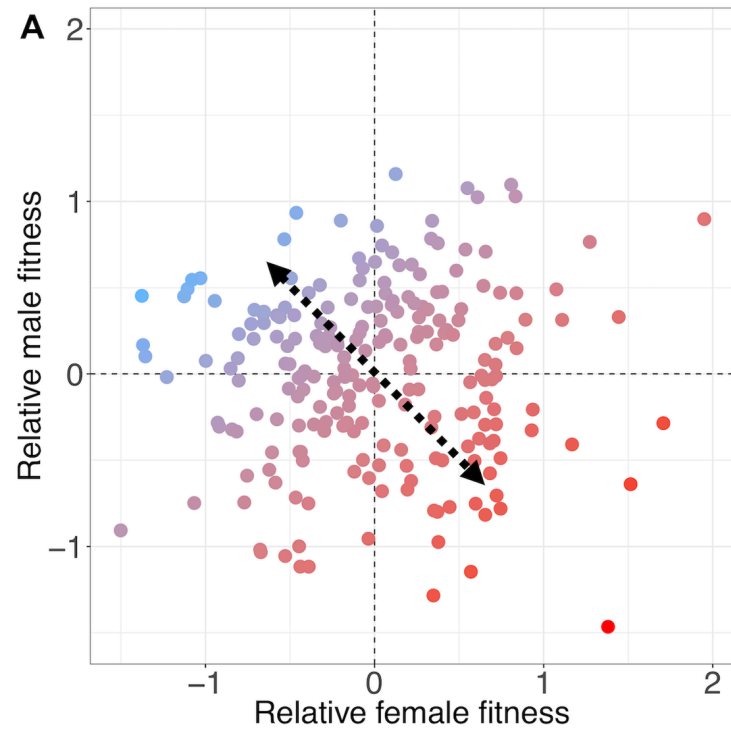
- Phenotype = Reproductive fitness
 - Whole-genome sequencing of 220 haplotypes (Gilks et al. 2016)
- Genome-wide association study for sexually antagonistic genes
(Ruzicka et al 2015)



PLOS BIOLOGY

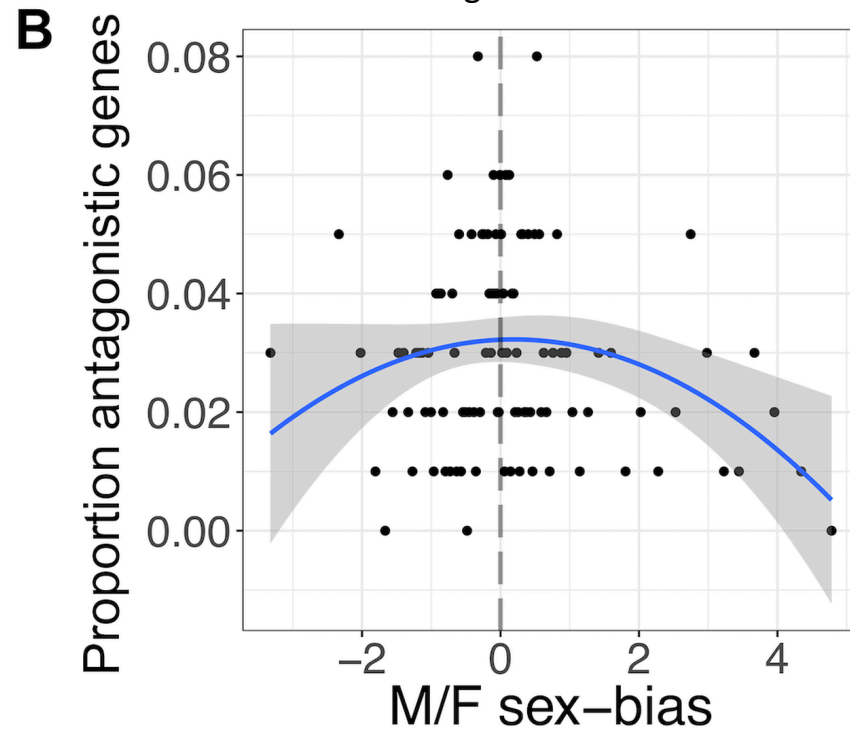
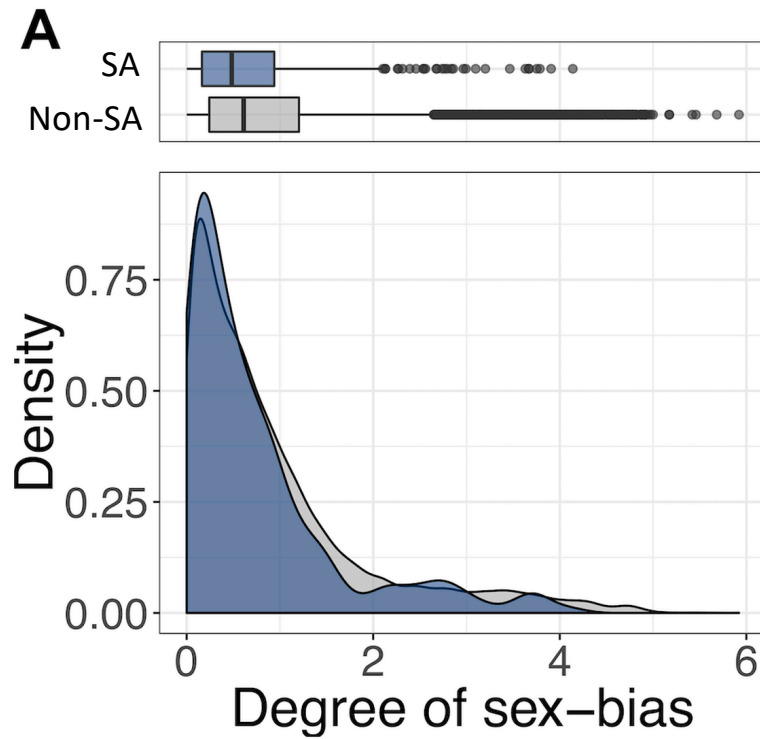
Ruzicka et al 2015, *PLOS Biology* 17(4): e3000244

2,372 candidate antagonistic SNPs
in 226 independent clusters
(FDR Q-values < 0.3)



Missense/coding sexually antagonistic SNPs over-represented

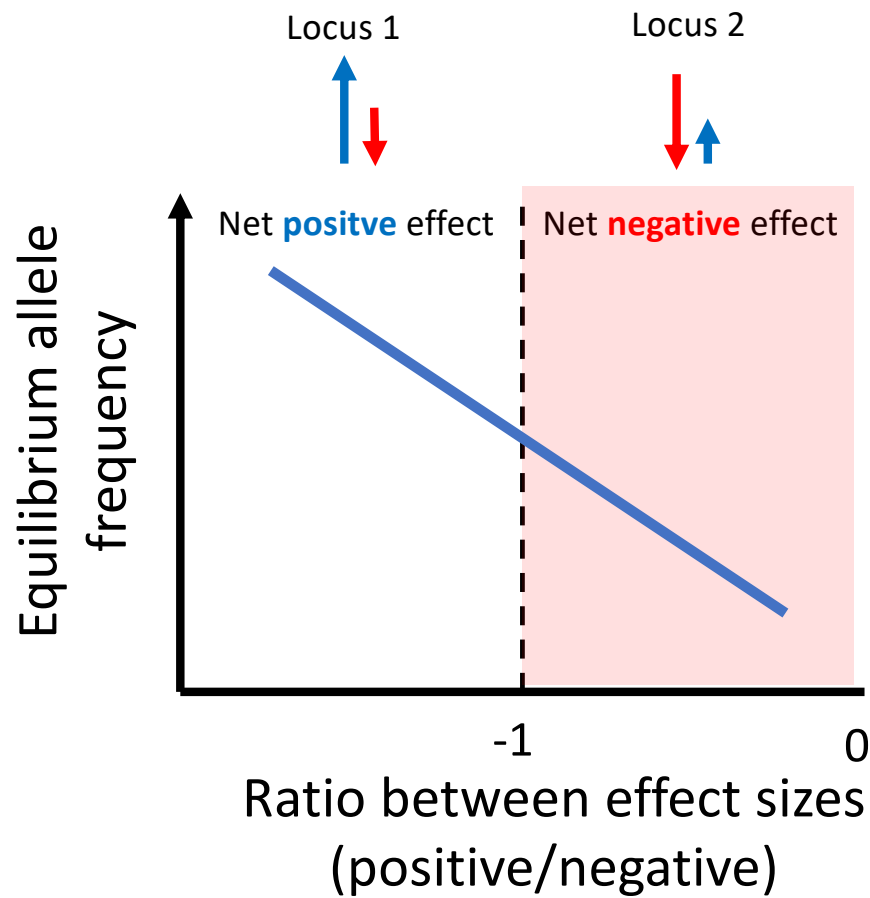
Ruzicka et al 2015, *PLOS Biology* 17(4): e3000244



Sexually antagonistic SNPs show lower degree of sex-bias

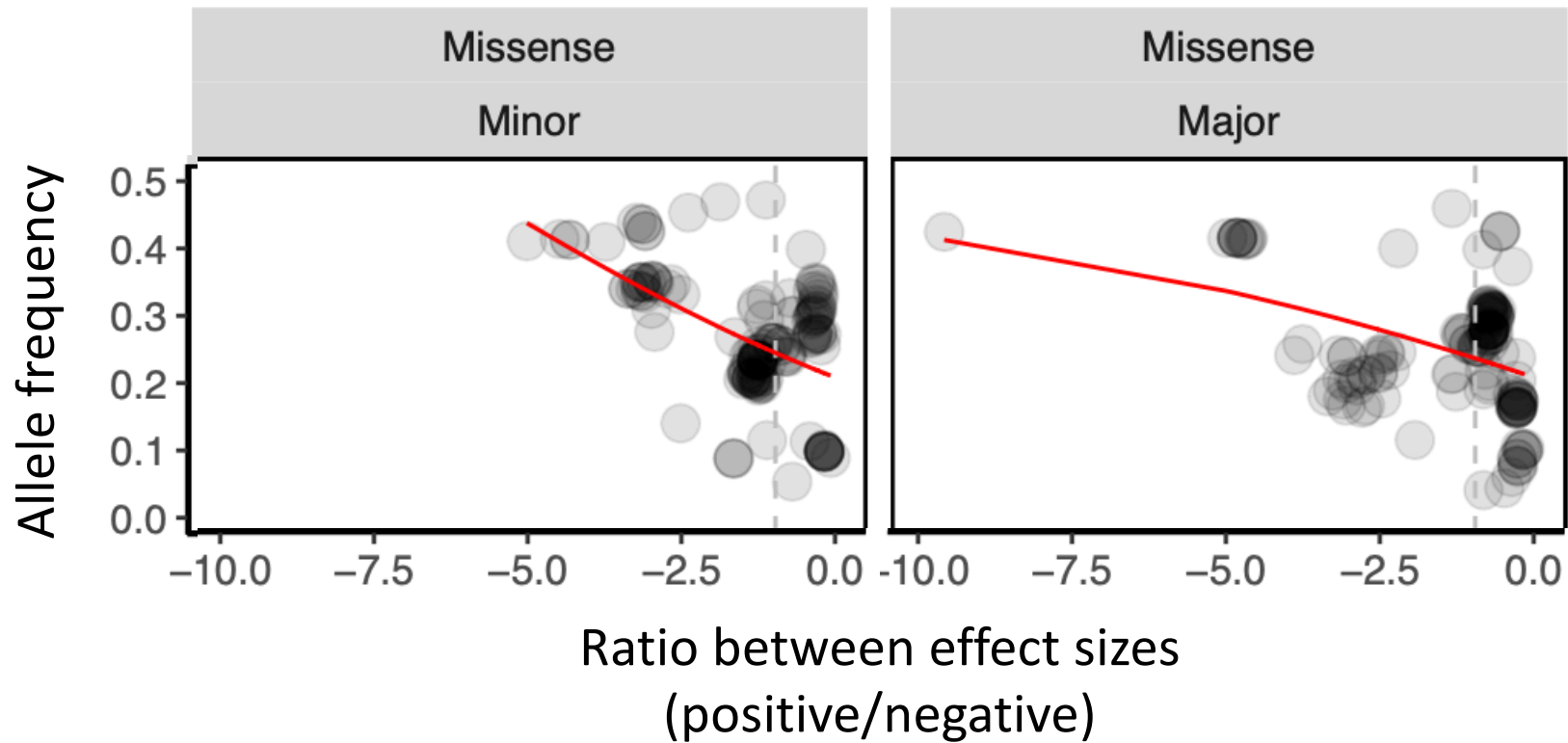
Prediction:

Sexually antagonistic alleles with **net positive** effects occur at higher frequency than alleles with **net negative** effects



Morrow & Connallon 2013

Result: Sexually antagonistic alleles with **net positive** effects occur at higher frequency than alleles with **net negative** effects



GLMs df=1,139 P < 0.0001

2

Do sexually antagonistic genes occur in humans?

- Theoretically in all species with separate sexes
- Quantitative genetic evidence
- Many sex-specific genes
- No reports of “sexually antagonistic” genes



Hypotheses:

1. **Missclassified: Biomedical scientists don't use same terminology as evolutionary biologists**
2. Discounted: Too weird to be true

Do sexually antagonistic genes occur in humans?

A systematic review in 2 stages

Stage 1: Search terms used by evolutionary biologists

Sexual antagonism

Sexually antagonistic

Intralocus sexual conflict

Stage 2: Alternative terms that may capture the same thing

sex

gender

dependent

male AND female

different

men AND women

boys AND girls

opposite

AND

“locus” OR “loci”, “gene” OR “snp” OR “polymorphism” OR “variant”

Before screening: 27 papers

Included:

0 papers – 0 loci

821 papers

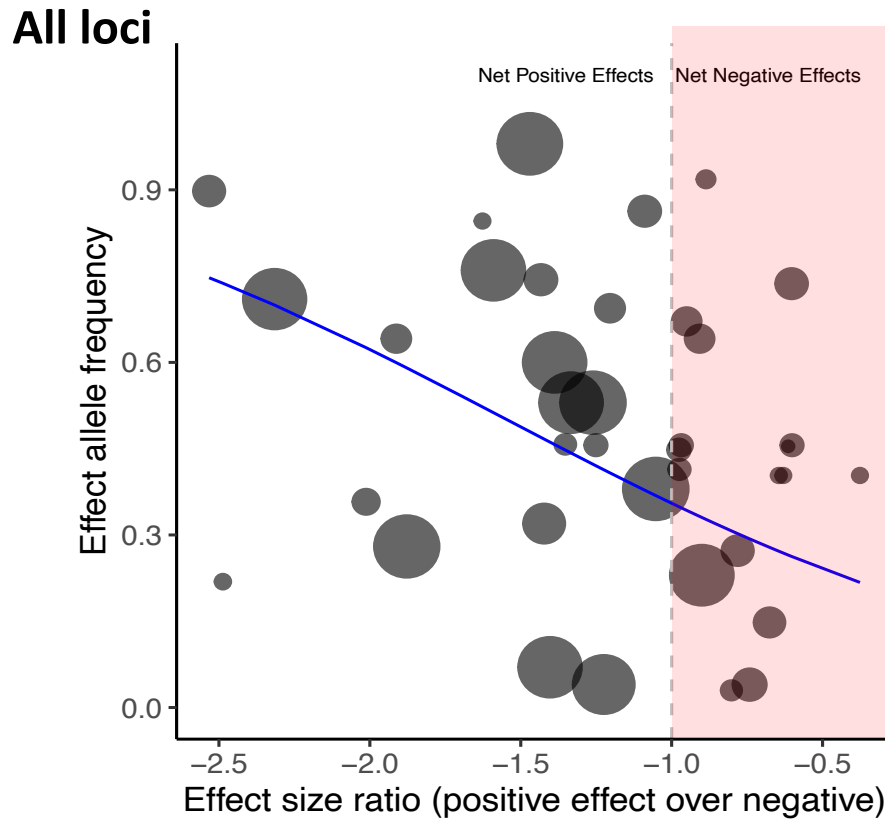
39 papers – 51 loci

Sexually antagonistic genes in humans

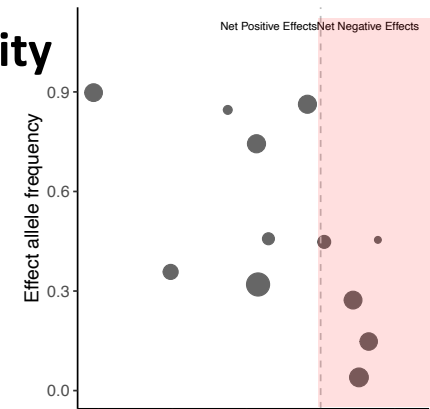
- 21 complex traits (30 loci)
e.g. waist-hip-ratio (BMI adjusted), behaviours, blood pressure traits
- 19 disease risk/severity traits (21 loci)
e.g. cancers, neurological disorders, susceptibility to viral infection
- None referred to as “sexually antagonistic” (Hypothesis 1)
- One example discounted as a false positive (Hypothesis 2)
- None validated/independently replicated

Prediction: Alleles with **net positive** effects occur at higher frequency than alleles with **net negative** effects

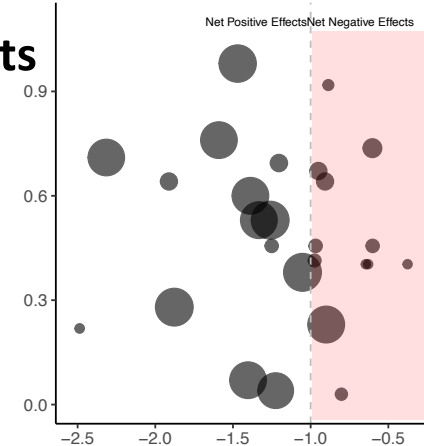
Result: Alleles with **net positive** effects occur at higher frequency than alleles with **net negative** effects



Disease risk/severity



Complex traits



GLM weighted by inverse variance, estimate \pm SE = -1.10 ± 0.50 , dfs = 1,36, deviance = 38.7×10^6 , $P = 0.024$

Some conclusions

- Many specific sexually antagonistic genes in flies...
...and they contribute to **human disease**
- But independent validation needed:
 - *Flies* – Work using CRISPR ongoing
 - *Humans* – Encourage validation by biomedical scientists
- Terminology causes serious (20 year!) block to communication between scientific disciplines
- Don't discount non-intuitive results in biology

“Nothing in biology makes sense except in the light of evolution”

Dobzhansky