**The relationship between male-female allele frequency divergence at adulthood and GxSex**

We developed a model relating sex differences in additive effects on a trait at a biallelic locus (and ) and divergence in allele frequencies . Our model resembles that of Cheng and Kirkpatrick (CITEX CK16) who developed a similar model relating allele frequency differences and sex bias in gene expression. In short, we model sexually-antagonistic, post-conception viability selection on a focal complex trait. We assume allele frequencies in adult males, , and adult females, , are at equilibrium. Under these conditions, we derive the relationship

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where (CITEX Wright) is the fixation index with respect to the male and female subpopulations, i.e. the proportion of heterozygosity in the population that is due to allelic divergence between the sexes; and is the contribution to phenotypic variance due to GxSex,

|  |  |  |
| --- | --- | --- |
|  |  | ( 2 ) |

where is the mean allele frequency at adulthood. is a parameter that can be thought of as the potential for sexually antagonistic selection acting on genetic variation for the trait in question.

Allele frequencies at the autosomal locus are assumed to be equal in males and female zygotes. If we assume equally-sized male and female subpopulations, at adulthood takes the form

|  |  |  |
| --- | --- | --- |
|  |  | ( 3 ) |

Sexually-antagonistic selection acting on viability will cause divergence in allele frequencies between adult males and females. We write the relative viabilities of the homozygote for the reference allele, the heterozygote and the homozygote for the effect allele as for each sex . The selection coefficient and dominance coefficient can be frequency-dependent, in which case these coefficients take their values at equilibrium. We can write the additive selection coefficient of the effect allele as

|  |  |  |
| --- | --- | --- |
|  |  | ( 4 ) |

Assuming that zygotes are at Hardy-Weinberg equilibrium, the allele frequency in each sex at adulthood are

|  |  |  |
| --- | --- | --- |
|  |  | ( 5 ) |

where we neglected terms of order Plugging *eq. 5* into *eq. 3*, the divergence between males and females post-selection is

|  |  |  |
| --- | --- | --- |
|  |  | ( 6 ) |

We model the strength of viability selection acting on males and females as linear with the additive effect on a focal trait in each sex,

|  |  |  |
| --- | --- | --- |
|  |  | ( 6 ) |

and make the simplifying assumption that allele frequencies are at equilibrium under sexually-antagonistic viability selection at the locus, such that selection favoring an allele in one sex is balanced by selection against that allele in the other sex,

|  |  |  |
| --- | --- | --- |
|  |  | ( 7 ) |

*Eqs. 6,7* together imply

|  |  |  |
| --- | --- | --- |
|  |  | ( 8 ) |

Finally, using *eq. 6,*

|  |  |  |
| --- | --- | --- |
|  |  | ( 9 ) |

which together with *eq. 8* gives

|  |  |  |
| --- | --- | --- |
|  |  | ( 9 ) |

We denote the heritability due to GxSex at the locus as and the parameter relating this contribution to the differentiation in allele frequencies as

|  |  |  |
| --- | --- | --- |
|  |  |  |

and plug *eq. 9* into *eq. 6*, we get

|  |  |  |
| --- | --- | --- |
|  |  | ( 10 ) |

**Estimating of the potential for sexually-antagonistic selection acting on variation in a trait ()**

Matt:

1. Please add in: Description of how we estimate allele frequencies and in which populations, data filtering, QC etc. Also here we are getting the effect sizes from.
2. One thing we hadn’t discussed is the fact that the variants that you are analyzing may often be in LD with each other. Let’s discuss how to handle this—I think I have a simple-ish idea.
3. We will need to check my derivation is correct (or to put it more accurately, find the mistakes). We can do this with a simple simulation with two linear regressions where we compare eq. 25 and the variance of the squared difference of effect estimates estimated via bootstrap. I think it would be quick and worthwhile.

For each trait and population, we estimated using weighted least squares linear regression of to , with weight inversely proportional to our site-specific estimate of noise in the estimate of .

|  |  |  |
| --- | --- | --- |
|  |  | ( 12 ) |

To simplify the estimation of we treat the allele frequency as perfectly estimated, and as independent of the allele frequency in the GWAS sample—as different data are used in the GWAS (UK Biobank) and in the allele frequency estimation (gnomAD). Under these assumptions,

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| --- | --- | --- |
|  |  | ( 13 ) |

and thus the task at hand is estimating . Using the law of total variance,

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| --- | --- | --- |
|  |  | ( 14 ) |

We begin with the argument of the first term,

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | ( 15 ) | |
| where we denoted | |  |
| for each sex Plugging eq. 15 into the first term of eq. 14, | |  |
|  | |  |
|  |  | ( 16 ) | |

Where the first and second step follow from the fact that is a constant. We can take note of the fact that is Normally distributed around , and in particular that it has no skewness. Therefore,

|  |  |  |
| --- | --- | --- |
|  |  | ( 17 ) |

where is the skewness of . We can also note that

|  |  |  |
| --- | --- | --- |
|  |  | ( 18 ) |

where we defined

and therefore is a Standard Normal and therefore is Chi-squared with one degree of freedom. Eq. 18 now gives

|  |  |  |
| --- | --- | --- |
|  |  | ( 19 ) |

Plugging eq. 17 and eq. 19 into eq. 16, we find

|  |  |  |
| --- | --- | --- |
|  |  | ( 20 ) |

We now turn to the second term of eq. 14. First,

|  |  |  |
| --- | --- | --- |
|  |  | ( 21 ) |

Eq. 17 and 19 again give us

|  |  |  |
| --- | --- | --- |
|  |  | ( 22 ) |

which then gives

|  |  |  |
| --- | --- | --- |
|  |  | ( 23 ) |

Plugging eq. 20 and eq. 23 into eq. 14, we get

|  |  |  |
| --- | --- | --- |
|  |  | ( 24 ) |

Finally, we estimate with the GWAS-derived point estimate of the effect and with its standard error, . Plugging back into eq. 13, we get

|  |  |  |
| --- | --- | --- |
|  |  | ( 25 ) |