

1 **Meiotic drive reduces egg-to-adult viability in stalk-eyed flies**

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22 **Running Head: Meiotic drive viability**

23 **Abstract**

24 SR meiotic drive is a selfish genetic element located on the X chromosome in a number of
25 species that causes dysfunction of Y-bearing sperm. SR is transmitted to up to 100% of
26 offspring, causing extreme sex ratio bias. SR in several species is found in a stable
27 polymorphism at a moderate frequency, suggesting there must be strong frequency-
28 dependent selection resisting its spread. We investigate the effect of SR on female and male
29 egg-to-adult viability in the Malaysian stalk-eyed fly, *Teleopsis dalmanni*. SR meiotic drive in
30 this species is old, and appears to be broadly stable at a moderate (~20%) frequency. We
31 use large-scale controlled crosses to estimate the strength of selection acting against SR in
32 female and male carriers. We find that SR reduces the egg-to-adult viability of both sexes. In
33 females, homozygous females experience greater reduction in viability ($s_f = 0.242$) and the
34 deleterious effects of SR are additive ($h = 0.511$). The male deficit in viability ($s_m = 0.214$) is
35 not different from that in homozygous females. The evidence does not support the
36 expectation that deleterious side-effects of SR are recessive or sex-limited. We discuss how
37 these reductions in egg-to-adult survival, as well as other forms of selection acting on SR,
38 act to maintain SR polymorphism in this species.

39 **Introduction**

40 Meiotic drivers are selfish genetic elements that subvert the standard mechanisms of
41 gametogenesis to promote their own transmission (Lindholm et al. 2016). During meiosis, a
42 driver disables or prevents the maturation of gametes that contain the non-driving element
43 (Burt and Trivers 2006; Lindholm et al. 2016). In extreme cases, drive can reach 100%
44 transmission to the next generation. In male heterogametic species, drivers are most
45 frequently found on the X-chromosome (Hurst and Pomiankowski 1991), commonly known
46 as '*Sex-Ratio*' or SR (Hurst & Werren 2001). These drivers target developing sperm carrying
47 the Y chromosome, causing their dysfunction, which results in strongly female biased
48 broods.

49

50 SR is predicted to spread rapidly due to its transmission advantage. When homozygous
51 female fitness is not greatly reduced, SR could potentially spread to fixation and cause
52 population collapse and extinction through massive sex ratio imbalance (Hamilton 1967,
53 Hatcher et al. 1999). Empirical evidence for this is limited to laboratory environments where
54 drive causes extinction in small populations (Lyttle 1977, Price et al. 2010, Galizi et al. 2014)
55 and a single putative example under natural conditions (Pinzone & Dyer 2013). More
56 typically, studies in wild populations find that drive exists as a low-frequency polymorphism
57 (Pinzone & Dyer 2013; Manser et al. 2011; Price et al. 2014; Verspoor et al. 2018), with
58 persistence that can span over a million years (Silver 1993; Kovacevic & Schaeffer 2000;
59 Paczolt et al. 2017). In order for SR to persist as a polymorphism, there must be frequency-
60 dependent selection, allowing spread when rare but retarding further increases in
61 frequency as drive becomes more common. The selective counter forces that fulfil this

62 requirement may act in males or females but in general they are not well understood. We
63 discuss potential causes of selection first in males and then females in the following
64 sections.

65

66 Selection on male viability may be associated with the drive chromosome. It is likely to
67 operate in a frequency-independent manner and so not have a stabilizing effect on the
68 frequency of drive (Edwards 1961; Carvalho and Vaz 1999). But it has been suggested that
69 there will be negative frequency-dependent selection on male fertility (Jaenike 1996). This
70 has intuitive appeal because the spread of SR causes the population sex ratio to become
71 increasingly female biased. In such a population, the average male mating rate will increase.

72 If SR male fertility increases at a lower rate than non-drive (ST) male fertility when males
73 mate multiply (for instance because SR males are sperm limited), then a polymorphism
74 could be stabilised (Jaenike 1996). Decreased male fertility under multiple mating is a
75 general feature observed in many drive systems (Beckenbach, 1978; Jaenike, 1996; Atlan et
76 al. 2004). However, for this effect alone to prevent SR fixation, SR male fertility must fall to
77 less than half that of ST males as the mating rate increases (Jaenike 1996), a condition not
78 met in a number of species that nonetheless are found with stable SR polymorphism
79 (Carvalho and Vaz 1999). A related suggestion is that SR males may be out-competed at
80 higher mating rates, motivated by some evidence that SR males are poor sperm competitors
81 (Wu 1983a; Wilkinson and Fry 2001; Price and Wedell 2008). However, the strength of
82 sperm competition weakens as SR spreads, as this reduces the number of competitor males
83 in the population, which seems unlikely to exert a stabilizing effect on SR frequency. SR
84 males may do poorly in other forms of male-male competition if SR is generally associated
85 with poor performance. Such effects are likely to decrease as drive spreads and males

86 become rare, again making it unlikely that this form of selection will stabilize drive. Models
87 that combine the effects of decreased male fertility and reduced sperm competitive ability
88 on SR frequency dynamics find they can lead to a stable polymorphism (Taylor and Jaenike
89 2002). But this equilibrium can be destabilised by perturbations in either the population sex
90 ratio or the frequency of SR. In particular, given a meta-population of small demes, slight
91 fluctuations in SR frequency are likely to cause drive to spread to fixation, resulting in
92 population extinction (Taylor and Jaenike 2003).

93

94 Suppressors are another selective force operating in males that limits the spread of drive
95 alleles. Most obviously, selection favours the evolution of suppression on chromosomes
96 targeted by drivers for dysfunction. In an SR system with complete drive, if resistance is
97 linked to the Y-chromosome, it restores transmission to Mendelian levels, while non-
98 resistant Y-chromosomes are not transmitted at all (Thomson and Feldman 1975). Y-linked
99 suppressors are therefore expected to spread quickly even if they have deleterious side
100 effects (Wu 1983b). Unlinked suppressors will also be favoured because drive in males
101 causes gamete loss and is often associated with dysfunction amongst the surviving, drive-
102 carrying sperm. Reduced sperm number is likely to reduce organismal fertility. Additionally,
103 as SR spreads it causes the population sex ratio to become female-biased, providing a
104 further advantage to suppressors as they increase the production of male offspring, which
105 have higher reproductive value than female offspring (Fisher 1930; Carvalho et al. 1998).
106 The spread of suppressors reduces the advantage of drive and could lead to its loss. But
107 both types of suppressors are under negative frequency-dependent selection, because a
108 lower frequency of drive reduces selection in their favour. Under some circumstances this
109 could lead to a stable polymorphism at the drive locus. Y-linked and autosomal suppressors

110 of SR drive have been detected in a number of species including *D. simulans*, *D. affinis*, *D.*
111 *subobscura*, *D. quinara*, *D. mediopunctata* and *Aedes aegypti* (Jaenike 2001). The evolution
112 of suppressors can be remarkably rapid. For example, in the Paris SR system of *D. simulans*,
113 the increase of SR from less than 10% to more than 60% in a mere five years has been
114 matched by a similar increase in suppressor frequency over the same time period (Bastide
115 et al. 2013). While suppressors are common, they are not universal and have not been
116 detected against SR drive in *D. pseudoobscura*, *D. recens* and *D. neotestacea* (Jaenike 2001).
117 In these systems, other factors are therefore necessary to explain extant SR polymorphism.

118

119 Alternatively, SR may be prevented from reaching fixation if female carriers have reduced
120 fitness (Curtsinger and Feldman 1980). As male X-linked drive causes defects in
121 spermatogenesis, there is no obvious mechanistic carry-over to female oogenesis. Likewise,
122 examples of meiotic drive in female gametogenesis, which affect the biased segregation of
123 chromosomes into the egg or polar bodies, show no carry-over to segregation bias in male
124 gamete production (Burt and Trivers 2006). For selection to act against female carriers, the
125 drive locus must either have direct pleiotropic fitness effects or be in linkage with alleles
126 that impact fitness. Linkage is a plausible explanatory factor given that drive systems are
127 often located in genomic regions with low recombination rates, such as in inversions
128 (Beckenbach 1996; Silver 1993; Dyer et al. 2007; Reinhardt et al. 2014). If the inversion is at
129 low frequency, it will rarely be homozygous and the recombination rate among SR
130 chromosomes will be low. Inversions also severely limit the exchange of genes with the
131 homologous region on the standard chromosome (as this requires a double cross-over
132 within the inverted region; Navarro et al. 1997; 1998). The consequence is that low
133 frequency inversions will be subject to weak selection and suffer the accumulation of a

134 greater mutation load (Dyer et al. 2007; Kirkpatrick 2010). Recessive viability and sterility
135 effects are expected as they will not be evident in females until the frequency of drive is
136 sufficient for the production of homozygotes. In contrast, hemizygosity in males means
137 recessive and dominant effects are always expressed. This means that female-limited fitness
138 effects are more likely to produce relevant frequency dependence that restricts fixation of
139 drive. Severe reductions in female viability and fertility in SR homozygotes, along with SR
140 heterozygotes, have been reported in several *Drosophila* species (Wallace 1948; Curtsinger
141 and Feldman 1980; Dyer et al. 2007). But it is surprising how rarely viability effects of drive
142 in either sex have been studied, compared to fertility effects in males (Price and Weddell
143 2008). These deleterious consequences are likely to build up and lead to a reduction in SR
144 frequency through time (Dyer et al. 2007).

145
146 Large-scale chromosomal inversions are not a universal feature of SR, however. Inversions
147 are not present in the Paris SR system in *D. simulans* (Jaenike 2001). Despite this, SR must
148 be weakly deleterious in this species as it is rapidly declining in frequency in populations
149 that have recently become completely suppressed (Bastide et al. 2011). The deleterious
150 effects of the Paris SR chromosome must arise due to deleterious effects caused by the
151 drive genes themselves or a tightly linked region. The genetically distinct Winters SR system
152 in the same species also lacks association with an inversion (Kingan et al. 2010). It persists
153 despite having been completely suppressed for thousands of years, suggesting it does not
154 cause any pleiotropic fitness deficit (Kingan et al. 2010). These are the only well
155 characterised examples of meiotic drive not being associated with inversions, so this feature
156 may be a rarity.

157

158 Another aspect operating in females concerns behavioural resistance to the spread of SR.

159 Laboratory experiments suggest that increased levels of polyandry can be selected as a

160 defence mechanism against SR (Price et al. 2008). This benefit arises when drive male sperm

161 are weak competitors against wildtype male sperm (Price and Wedell 2008). Recent

162 modelling work shows that polyandry helps prevent invasion of SR, but cannot prevent

163 fixation of drive alone (Holman et al. 2015). As drive spreads, additional matings have a

164 lower probability of involving wildtype males, so the disadvantage to drive sperm declines.

165 There needs to be positive frequency-dependent costs to achieve a stable polymorphism

166 (Holman et al. 2015), for instance, when homozygous females have lower viability than

167 heterozygotes. If a stable polymorphism can evolve, the frequency of drive should decline

168 with the rate of female remating. There is evidence in favour of this idea in *D. neotestacea*

169 which exhibits a stable cline in SR frequency that correlates negatively with the frequency of

170 polyandry (Pinzone and Dyer, 2013), and a similar pattern has been reported in *D.*

171 *pseudoobscura* (Price et al. 2014). Alternatively, females may simply avoid mating with SR

172 males (Lande and Wilkinson 1999; Pomiankowski and Hurst 1999). In stalk-eyed flies,

173 females prefer to mate with males with large eyespan (Wilkinson et al. 1998; Cotton et al.

174 2010), a trait that is reduced in SR males (Wilkinson et al. 1998; Johns et al. 2005; Cotton et

175 al. 2014). Sexual selection may therefore be acting in this species to limit the spread of SR.

176 However, this form of selection against drive is likely to be restricted to a sub-set of species

177 with drive, as it requires the linkage of SR with a conspicuous trait subject to mate choice

178 (Pomiankowski and Hurst 1999). Another potential example is the autosomal *t*-locus system

179 in mice which is proposed to be detectable in mate choice through olfaction (Coopersmith

180 and Lenington 1990) but this preference has not been confirmed (Sutter and Lindholm

181 2016). A counter example is in *D. pseudoobscura*, where females do not avoid mating with
182 SR males, though there would be considerable benefit to doing so (Price et al. 2012).

183

184 In this study, we determine the effect of SR meiotic drive on viability in the Malaysian stalk-
185 eyed fly, *Teleopsis dalmanni*. Our objective was to assess whether there is a SR-linked
186 deleterious mutation load leading to higher developmental mortality before adult eclosion.

187 Populations of this species carry SR at a moderate level of ~20% but with considerable
188 variation among populations (Presgraves et al. 1997; Wilkinson et al. 2003; Paczolt et al.
189 2017). SR resides within a large paracentric inversion (or inversions) that covers most of the
190 X chromosome (Johns et al. 2005). There is no recombination between SR and ST haplotypes
191 (Paczolt et al. 2017) and the lower frequency of SR in the wild means SR and ST homozygous
192 recombination events are relatively rare (at 20%, the recombination rate of SR is a quarter
193 that of ST). SR is absent from a cryptic species of *T. dalmanni* estimated to have diverged ~1
194 Mya. X-linked meiotic drive is also present in the more distantly related species *T. whitei*,
195 which diverged on order 2-3.5 Mya (Swallow et al. 2005; Paczolt et al. 2017). But to what
196 extent the mechanism or genetic basis is conserved remains to be established.

197

198 The ancient origin of the X^{SR} chromosome and limited recombination across the X^{SR}
199 chromosome are predicted to have led to the accumulation of deleterious alleles. The main
200 evidence for this is the reduced eyespan of SR males (Wilkinson et al. 1998; Cotton et al.
201 2014). Male eyespan is an exaggerated, highly condition-dependent trait used in female
202 mate choice (Wilkinson et al. 1998; Cotton et al. 2004), as well as signalling between males
203 (Panhuis and Wilkinson 1999; Cotton et al. 2009), which reflects male genetic and
204 phenotypic quality (David et al. 2000; Cotton et al. 2004; Howie et al. 2019). However, in a

205 series of experiments Wilkinson et al. (2006) found little direct evidence that the SR reduces
206 fitness components. Although larval viability was not directly assessed, progeny production
207 showed no difference between SR and ST homozygous females (Wilkinson et al. 2006).
208 Another study compared offspring genotypes of heterozygous females mated to ST males,
209 and reported little deviation from 1:1 among SR:ST male offspring (Johns et al. 2005). Adult
210 survival did not vary with genotype in either males or females (Wilkinson et al. 2006). There
211 was no evidence for a deleterious effect of X^{SR} on female fecundity, rather heterozygotes
212 were more productive, suggesting overdominance (Wilkinson et al. 2006). However, sample
213 size in these experiments was small, and fecundity/fertility results were based on progeny
214 counts which are confounded by genotype effects on larval survival. The only significant
215 detriment reported was in SR male fertility which was reduced when males were allowed to
216 mate with large numbers of females (eight) for 24 hours (Wilkinson et al. 2006). However, a
217 further experiment that measured male fertility through counts of fertile eggs (avoiding any
218 confounding impact of larval survival), failed to show any difference between SR and ST
219 male fertility (Meade et al. 2019).

220
221 To better understand these previous results, we were motivated to explicitly test for
222 differences in larval survival. Our experimental design was similar to that used in early
223 investigations of *Drosophila pseudoobscura* (Wallace 1948; Curtsinger and Feldman 1980).
224 Controlled crosses were carried out to produce eggs with all possible SR and ST male and
225 female genotypes. These were reared together to ensure exposure to similar environmental
226 variation. The sample size was large to maximize our power to detect genotypic survival
227 differences. Offspring were genotyped at adult eclosion, yielding observed genotype ratios
228 in order to estimate the selection coefficients operating against drive in both sexes. Our

229 principal aims were to test whether the SR-drive chromosome causes viability loss during
230 egg-to-adult development, and whether fitness effects are recessive or sex-limited.

231

232 **Methods**

233 Fly stocks and maintenance

234 A standard stock population was obtained from Ulu Gombak in Malaysia (3°19'N 101°45'E)
235 in 2005 (by Sam Cotton and Andrew Pomiankowski). Stock flies are reared in high-density
236 cage culture (cage size approx. 30 x 20 x 20cm) at 25°C on a 12:12 hour light:dark cycle, and
237 fed puréed corn *ad libitum*. Fifteen minute artificial dawn and dusk phases are created by
238 illumination from a single 60-W at the start and end of each light phase. Meiotic drive is
239 absent from the standard stock population.

240

241 A meiotic drive stock was created using flies collected from the same location in 2012
242 (Cotton et al 2014). Meiotic drive is maintained in this stock by following a standard
243 protocol (Presgraves et al. 1997; Meade et al. 2018). Females heterozygous for the drive
244 chromosome are mated to males from the standard stock. It is expected that half their male
245 offspring will inherit the drive chromosome. All male offspring are crossed to three females
246 from the standard stock and the sex ratio of their progeny scored. Males that sire all-female
247 broods of at least 15 individuals are considered to be carriers of meiotic drive. In the meiotic
248 drive stock, drive strength is 100% percent, and no males are produced by X^{SR}/Y males
249 carrying the drive chromosome (Meade et al. 2018). Progeny from drive males are female
250 heterozygotes for the drive chromosome. They are subsequently mated to standard males,
251 and the process is repeated.

252

253 Experimental crosses

254 To generate the five possible genotypes of both females (X^{ST}/X^{ST} , X^{SR}/X^{ST} , X^{SR}/X^{SR}) and males

255 (X^{ST}/Y , X^{SR}/Y), two crosses were performed (Figure 1). In Cross A, drive males (X^{SR}/Y) are

256 mated to heterozygous females (X^{SR}/X). This cross produces X^{SR}/X^{SR} and X^{SR}/X^{ST} female

257 zygotes in equal proportions. In Cross B, standard males (X^{ST}/Y) are mated to heterozygous

258 females (X^{SR}/X^{ST}). This cross produces X^{ST}/Y and X^{SR}/Y male, and X^{ST}/X^{ST} and X^{SR}/X female

259 zygotes in equal proportions. Experimental males were collected from the drive stock that

260 were approximately 50:50 X^{ST}/Y and X^{SR}/Y males. They were crossed to standard stock

261 females (X^{ST}/X^{ST}) and one larva per male was genotyped to define the paternal genotype.

262 Experimental females heterozygous for drive (X^{SR}/X^{ST}) were collected from crosses between

263 drive males and females from the standard stock.

264

265 Individual males were placed with three virgin females in 500ml pots. Females that died

266 during the experiment were replaced, but males were not. 25 Cross A and 50 Cross B pots

267 were set-up. The base of each pot was lined with moistened cotton wool covered with blue

268 tissue paper to aid egg visualisation. The cotton bases were removed for egg collection and

269 replaced three times per week. Fertilised eggs were identified under light microscopy as

270 those that showed signs of development (e.g. segmental striations, development of

271 mouthparts; Baker et al. 2001) and transferred to a 90mm petri dish containing a large

272 cotton pad moistened with 15ml of water and 2.5ml of food. Three different food

273 conditions were used that varied in their corn content: 25% corn, 50% corn, and 75% corn.

274 In each mixture the remainder was made up with a sucrose solution (25% sucrose/water

275 w/w). To ensure the sucrose solution had a similar viscosity to puréed corn, an indigestible

276 bulking agent was added (methylcellulose, 3% w/w; Rogers et al. 2008). 4 eggs from Cross A
277 and 8 eggs from Cross B were transferred to each petri dish. This gives the five possible
278 genotypes (X^{ST}/X^{ST} , X^{SR}/X^{ST} , X^{SR}/X^{SR} , X^{ST}/Y , X^{SR}/Y) in an expected 1:2:1:1:1 ratio (Table 1).
279 Prior to the end of development, six Petri dishes were placed inside a large cage and all
280 eclosing adult flies were collected. The cage was used as a level of analysis of the relative
281 egg-to-adult viability of different genotypes in the analysis that follows.

282

283 Genotyping

284

285 DNA was extracted by isopropanol precipitation in 96-well plates. Half a fly thorax was
286 added to a well containing 4 μ l Proteinase K (10 mg.ml⁻¹) and 100 μ l DIGSOL (25mM NaCl,
287 1mM EDTA, 10mM Tris-Cl pH 8.2), mechanically lysed, and incubated overnight at 55°C. The
288 following day, 35 μ l of 4M ammonium acetate was added and plates were left on ice for 5
289 minutes before being centrifuged at 4500RPM at 4°C for 40 minutes. 80 μ l of supernatant
290 was then aspirated into a new 96-well plate containing 80 μ l of isopropanol. The precipitate
291 was discarded. Samples were then centrifuged again at 4500RPM and 4°C for 40 minutes to
292 precipitate the DNA. The supernatant was then discarded, 100 μ l 70% ethanol was added,
293 and samples were spun again at 4500RPM and 4°C for 20 minutes. The supernatant was
294 once again discarded and plates were left to air-dry for 45 minutes at room temperature.
295 Finally, 30 μ l of Low TE (1mM Tris-HCL pH8, 0.1mM EDTA) was added to elute the DNA. DNA
296 was PCR-amplified in 96-well plates, with each well containing 1 μ l of dried DNA, 1 μ l of
297 primer mix (consisting of the forward and reverse primers of *comp162710* at a
298 concentration of 0.2 μ M) and 1 μ l of QIAGEN Multiplex PCR Mastermix (Qiagen). The length
299 of amplified fragments was determined by gel electrophoresis. A 3% agarose gel was made

300 using 3g of molecular grade agarose, 100ml of 0.5x TBE buffer (45mM Tris (pH 7.6), 45mM
301 boric acid, 1mM EDTA), and 4 μ l ethidium bromide. PCR products were diluted with 3 μ l
302 ultrapure water and 2 μ l of gel loading dye was added. 4 μ l of this mixture was loaded into
303 each well and assessed for size against a ladder made from the PCR-amplified DNA of
304 multiple heterozygous drive females. *comp162710* is an indel marker with small alleles
305 (201bp) indicating the presence of the drive chromosome and large alleles (286bp)
306 indicating the presence of the standard chromosome.

307

308 Statistical analysis

309

310 We used two approaches to estimate the egg-to-adult viability costs of the X^{SR} chromosome.
311 The first estimates the relative egg-to-adult viability cost of each genotype. The second
312 estimates the strength of selection against drive in males and females, as well as the
313 dominance coefficient.

314

315 Egg-to-adult viability of each genotype

316 In the first analysis, the number of eclosed adult flies of each genotype were compared to
317 the number expected at the level of the cage. Each cage contained six petri dishes with 12
318 eggs, producing a maximum of 72 flies. Genotyping effort varied across cages and sexes. The
319 expected number of each genotype was determined with respect to the genotyping effort
320 of the relevant sex for a particular cage. For example, if 75% of males in a given cage were
321 genotyped, then the expected number of X^{SR} individuals is $(0.75 \times 72) / 6 = 8$. We split the
322 data by sex, then analysed the relationship between egg-to-adult viability and genotype
323 using linear mixed-effect modelling with lme4 (Bates et al. 2015) in R (R Core Team, 2018).

324 Genotype and food condition were modelled as fixed effects and cage ID and collection date
325 as random effects. Significance of model terms was determined using the lmerTest R
326 package (Kuznetsova et al. 2017). Food condition did not affect egg-to-adult viability, and so
327 is not included in subsequent analyses. Mean viability measures were estimated using
328 model terms.

329

330 *Estimating the strength of selection against drive*

331 In the second analysis, we estimated the strength of selection against drive using Bayesian
332 inference, separately for males and females. Cage survival frequencies for each genotype
333 were pooled. The probability of drawing the male genotype distribution was calculated for
334 values of the selection coefficient taken from a uniform prior distribution for $s_m = 0 - 1$, in
335 0.001 increments. We then used a binomial model to determine the likelihood of drawing
336 the observed number of X^{ST}/Y and X^{SR}/Y males for each value of s_m . As we used a uniform
337 prior, the posterior probability simplifies to the likelihood. The 95% and 99% credible
338 intervals were determined from the probability density. The probability of observing the
339 distribution of the three female genotypes was estimated under a multinomial where the
340 values of s_f and h (Table 1) were taken from a uniform prior distribution for every
341 combination of values of s_f and h ranging from 0 - 1, in 0.001 intervals. The 95% and 99%
342 credible intervals were determined in the same way as in males, and displayed as a two-
343 dimensional contour. Note that the probability of drawing X^{SR}/X^{ST} females was multiplied by
344 two because the experimental design was expected to generate twice as many heterozygote
345 eggs compared to all of the other genotypes. To determine if s_m and s_f were of different
346 strength, 1000 random samples each of s_m and s_f (taking h equal to its mode) were drawn
347 from the posterior distributions with probability of drawing a value equal to its likelihood. A

348 distribution of differences was obtained by subtracting the randomly drawn s_f values from
349 the randomly drawn s_m values. A z-score was calculated to determine if this distribution is
350 different from zero.

351

352 We also estimated the difference in the strength of selection between female genotypes. To
353 compare egg-to-adult viability between wildtype (X^{ST}/X^{ST}) and heterozygous (X^{SR}/X^{ST})
354 females, the likelihood of observing the counts of these two genotypes was determined
355 under a binomial as above, but shrinking h and s_f to a single term with a uniform prior. The
356 process was repeated to compare drive heterozygotes (X^{SR}/X^{ST}) and homozygotes (X^{SR}/X^{SR}).

357

358 **Results**

359 Effect of food condition

360 Food condition had no overall effect on the egg-to-adult viability of males ($F_{2,72} = 0.1085$, $P =$
361 0.8973) or females ($F_{2,54} = 0.1552$, $P = 0.9355$), nor did it alter the genotype response
362 (genotype-by-condition interaction, males $F_{2,79} = 0.8026$, $P = 0.4518$; females $F_{4,116} = 0.2044$,
363 $P = 0.9355$). So, offspring counts were pooled across food conditions within sexes in the
364 following analyses.

365

366 Egg-to-adult viability of each genotype

367 We collected a total of 1065 males and 2500 females, of which 798 and 1272 were
368 genotyped respectively. Male genotype had a significant effect on egg-to-adult viability,
369 with X^{SR}/Y males showing significantly reduced viability ($F_{1,81} = 11.7296$, $P < 0.001$). X^{ST}/Y
370 males had a mean viability of 0.5412, and X^{SR}/Y males had a mean viability of 0.4036 (Figure
371 2). Genotype also had a significant effect on egg-to-adult viability in females ($F_{2,120} = 4.7593$,

372 $P = 0.0103$). Mean viability was 0.6338 in X^{ST}/X^{ST} females, 0.5537 in X^{SR}/X^{ST} females, and
373 0.4695 in X^{SR}/X^{SR} individuals. A Tukey's post-hoc comparison test revealed that the viability
374 of X^{ST}/X^{ST} females is greater than X^{SR}/X^{SR} females ($P = 0.0109$), while X^{SR}/X^{ST} females have
375 intermediate viability, but not different from either homozygote ($X^{SR}/X^{ST} - X^{SR}/X^{SR}$
376 comparison: $P = 0.2949$; $X^{SR}/X^{ST} - X^{ST}/X^{ST}$ comparison: $P = 0.3293$; Figure 3).

377

378 *Estimating the strength of selection against drive*

379 The posterior probability of each value of the male selection parameter s_m is given in Figure
380 4. The mode of $s_m = 0.214$ with a 95% credible interval 0.097 – 0.316 and a 99% credible
381 interval 0.056 – 0.346. The probability of the modal value compared to the null hypothesis
382 of no viability selection against drive males has a Bayes Factor $BF_{10} = 321.79$.

383

384 The posterior probability of each combination of the female selection parameters s_f and h
385 values is shown in Figure 5. The modal values are $s_f = 0.242$ and $h = 0.511$, with the bivariate
386 95% and 99% credible interval displayed as a two-dimensional contour (Figure 4). The
387 probability of the modal s_f value compared to the null hypothesis of no viability selection
388 against drive in females has a Bayes Factor $BF_{10} = 572.89$. The strength of selection against
389 drive in males and females (s_f and s_m ; setting h to its modal value), did not differ between
390 the sexes ($|z| = 0.3785$, $\alpha = 0.01$ $P = 0.7047$).

391

392 In the pairwise comparison of individual female genotypes there was a difference between
393 the egg-to-adult viability of X^{ST}/X^{ST} and X^{SR}/X^{ST} females, with a selection coefficient mode =
394 0.126 with a 95% credible interval = 0.007 – 0.232 and a 99% credible interval = -0.017 –
395 0.261. A similar difference was observed in the comparison of X^{SR}/X^{ST} and X^{SR}/X^{SR} , with a

396 selection coefficient mode = 0.138 with a 95% credible interval of 0.008 – 0.252 and a 99%
397 credible interval of -0.038 – 0.287.

398

399 **Discussion**

400 Due to their two-fold transmission advantage in males, X chromosomes that exhibit *sex-*
401 *ratio* meiotic drive (X^{SR}) potentially can spread to fixation and cause population extinction
402 (Hamilton, 1967; Hatcher et al. 1999). Despite this, several meiotic drive systems exist in
403 broadly stable polymorphisms (Wilkinson et al. 2003; Pinzone and Dyer, 2013; Price et al.
404 2014). This suggests that there are costs of carrying the X^{SR} chromosome. In the stalk-eyed
405 fly system, the X^{SR} chromosome contains a large inversion (Johns et al. 2005), which is
406 expected to accumulate deleterious mutations as they are less efficiently removed by
407 recombination than those of the X^{ST} chromosome. This mutation load is expected to lead to
408 a decrease in fitness of the X^{SR} chromosome. Here, controlled crosses were used to estimate
409 one component of fitness, egg-to-adult viability, of meiotic drive genotypes. There was a
410 reduction in viability linked to X^{SR} in both males and females. In X^{SR} hemizygous males this
411 was $s_m = 21\%$ (Figure 4) and in X^{SR} homozygous females $s_f = 24\%$ (Figure 5). The negative
412 effect of X^{SR} in females is largely additive ($h \sim 0.5$), with heterozygotes being intermediate
413 in viability compared to homozygotes. The estimates of selection (s_m and s_f) do not differ
414 between the sexes. This probably reflects a lack of sexual dimorphism in fitness at the larval
415 stage. In *D. melanogaster*, egg-to-adult viability measured for particular genotypes is
416 strongly positively correlated across the sexes, whereas adult reproductive success is
417 typically negatively correlated (Chippendale et al. 2001; Arnqvist and Tuda 2010).

418

419 In the experiment, individual males of known genotype, either SR or ST, were crossed with
420 heterozygous females. Eggs were collected and combined in groups of 6 petri dishes each
421 containing 12 eggs. The eggs were visually inspected for signs of development, so as to be
422 able to exclude the possibility that differential fertility of the two paternal genotypes (i.e. SR
423 or ST) affected the subsequent output of adult flies. The combination of eggs from the two
424 crosses were expected to generate all five genotypes in an even ratio, except for
425 heterozygous females which were expected at double the number of the other genotypes.
426 The objective was to standardise competition between genotypes. It is hard to estimate
427 whether this objective was attained, as only surviving adults were genotyped. The observed
428 adult genotype frequencies were compared to infer genotype-specific survival in the egg-to-
429 adult stage. The number of flies genotyped was sufficiently large ($N_m = 798$, $N_f = 1272$) to
430 give reasonable assurance of the accuracy of the estimates. Even with this sizeable sample,
431 the bounds on the estimates of s_m , s_f and h remain large (Figure 4-5) but we can be
432 confident that drive is associated with loss of viability in both sexes. Our results contrast
433 with a prior study of adult lifespan which found no differences in males or females
434 (Wilkinson et al. 2006). The contrasting results may be due to a real difference between
435 larval and adult genotypic effects. But there may have been insufficient power to detect
436 adult genotypic effects as the scale of the adult experiment was one quarter of that used
437 here.

438

439 This is the first study showing a reduction in SR viability in stalk-eyed flies. Similar methods
440 have been applied previously in *D. pseudoobscura* (Wallace, 1948; Curtsinger and Feldman,
441 1980; Beckenbach, 1983). Wallace (1948) observed strong selection against X^{SR} in both
442 sexes. In high density populations, Beckenbach (1983) found a reduction in X^{SR}/Y viability

443 but no viability effect on homozygous X^{SR} female viability. In contrast, Curtsinger and
444 Feldman (1980) report stronger selection against homozygous X^{SR} females. Comparisons of
445 these three studies provides strong evidence to suggest that viability selection is density-
446 dependent, as reduction in X^{SR} viability was greatest under high density (Wallace 1948), and
447 a lack of differential viability was observed in another experiment carried out at low density
448 (Beckenbach 1983). In the present study, stalk-eyed fly larvae were cultured under low
449 density and provided with an excess of food. Future work will need to determine whether
450 varying levels of food stress enhance or restrict the deleterious effect of the X^{SR}
451 chromosome.

452
453 Strong viability selection against the X^{SR} chromosome, as found here under laboratory
454 conditions, will play a key role in determining the equilibrium level of the SR polymorphism
455 in the wild. There are several other factors that could be involved in determining SR
456 frequency, such as suppressors, polyandry and various forms of sexual behaviour which we
457 discuss further here. First, in *D. simulans*, SR commonly co-occurs with suppressors which
458 restrict the transmission advantage (Merçot et al. 1995; Kingan et al 2010). Although early
459 work on the stalk-eyed fly drive system suggested that there were suppressors (Wilkinson et
460 al. 1998), this has not been sustained by further work, either on the autosomes or Y
461 chromosomes (Paczolt et al. 2017). Second, polyandry may evolve to limit the spread of SR
462 (Price et al. 2008). Polyandry is the norm in *T. dalmani* (Baker et al. 2001; Wilkinson et al.
463 2003), and there is evidence that SR male sperm does less well under sperm competition
464 (Wilkinson et al. 2006) and may suffer from interactions with non-sperm ejaculate
465 components produced by standard males (though this has only been shown in the related
466 species *T. whitei*, Wilkinson and Fry 2001). But it has not been shown whether elevated

467 polyandry occurs in populations of *T. dalmani* with higher frequencies of SR or in stalk-
468 eyed fly species that harbour drive (compared to those that lack drive).

469

470 Third, it has long been suggested that mate choice may play a role in determining the
471 frequency of drive (Coopersmith and Lenington, 1990). This may be important in stalk-eyed
472 flies as they are canonical examples of sexual selection driven by mate choice (Burkhardt
473 and de la Motte 1983; 1985). In *T. dalmani*, drive males are expected to attract fewer
474 females as they have reduced eyespan, and hence mate less often (Wilkinson et al. 1998;
475 Cotton et al. 2014). However, there is as yet no evidence in stalk-eyed flies that the strength
476 of female mate preference has been enhanced in populations subject to drive. Nor has
477 there been investigation of whether females that carry SR show alterations in their mating
478 behaviour. A related consideration is male mate preference (Bonduriansky 2001) which has
479 been shown to be an important behavioural adaptation in *T. dalmani* favouring male
480 matings with fecund females (Cotton et al. 2015). A recent study reported that SR had no
481 direct effect on male mate choice (Finnegan et al. 2019). However, the strength of male
482 mate preference positively covaries with male eyespan. As drive males have smaller
483 eyespan (Cotton et al. 2014), we expect they will be less discriminating in their mate choice
484 (Finnegan et al. 2019).

485

486 Finally, measurements of sperm number per mating report that SR males deliver as many
487 sperm as ST males, and a single mating with a SR male results in the same female fertility as
488 a mating with a ST male (Meade et al. 2018). Whether this pattern carries over to situations
489 where a male can mate with multiple females is less clear. One experiment showed no
490 difference between SR and ST males (Meade et al. 2019), whereas another experiment

491 found lower fertility in SR males (Wilkinson et al. 2003) when multiple females were allowed
492 to mate freely with a single male for a day. The cause of this difference is unclear, but drive
493 males have been shown to have lower mating rates compared to standard males (Meade et
494 al. 2019), and this could conceivably have contributed to lower fertility in females mated to
495 SR males. As mentioned previously, P2 experiments indicate that SR males are poor sperm
496 competitors with ST males which must arise from reasons other than numerical sperm
497 transfer from the male (Wilkinson et al. 2006).

498

499 The number of different factors makes it difficult to predict the equilibrium frequency of
500 drive in the wild and whether these factors are sufficient to explain the observed frequency
501 of ~20% (Wilkinson et al. 2003; Paczolt et al. 2017). Many could act as stabilizing forces
502 which restrict the spread of drive in a frequency-dependent manner. Future work should
503 aim to examine these factors, in combination with the intensity of egg-to-adult viability
504 selection measured here, in a modelling framework in order to predict the evolutionary
505 outcomes. This can then be related to better estimation of parameters across local
506 populations of *T. dalmani* in which SR frequency is known to be highly variable (Cotton et
507 al. 2015) along with experimental evaluation of interactions between the various male and
508 female enhance or constrain the various selective forces.

509

510

511

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517 advice on experimental design and Prof Mark Thomas for help with the statistical analysis.

518

519 **Data accessibility statement**

520 Data will be made available at the Dryad Digital Repository

521

522

523 **Author contributions**

524 The research project was conceived by SRF, NJW, KF and AP. The experiment was carried
525 out by SRF and NJW, with genotyping by SRF, DK and MFC. The data was analysed by SRF,
526 NJW and AP, and the paper written by SRF and AP.

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696

697

698 **Figure legends**

699

700 Figure 1. Experimental protocol. Individual males of known genotype were crossed with
701 three heterozygous females in 500ml pots. Cross A produces no males and X^{SR}/X^{SR} and
702 X^{SR}/X^{ST} females, in equal proportions. Cross B produces X^{SR}/Y and X^{ST}/Y males and X^{ST}/X^{ST}
703 and X^{SR}/X^{ST} females, in equal proportions. 4 eggs from Cross A and 8 eggs from Cross B were
704 added to each egglay – a petri dish containing a moistened cotton pad and food. At
705 pupation, 6 egglays were placed into a population cage and their lids were removed so as to
706 allow the adult flies to eclose.

707

708 Figure 2. Male X^{SR}/Y and X^{ST}/Y mean \pm standard error proportion egg-to-adult viability.
709 Values are determined from the fraction of a given genotype observed in replicate cages.

710

711 Figure 3. Female X^{SR}/X^{SR} , X^{SR}/X^{ST} and X^{ST}/X^{ST} mean \pm standard error proportion egg-to-adult
712 viability. Values are determined from the fraction of a given genotype observed in replicate
713 cages.

714

715 Figure 4. The posterior probability density of the strength of selection against drive in males
716 (s_m). The mode is shown as a dotted red line. The dashed black lines indicate the 95%
717 credible interval. The dotted bluelines indicate the 99% credible interval.

718

719 Figure 5. The posterior probability density of the strength of selection against drive in
720 females (s_f) and the dominance coefficient (h). Colour indicates probability density, with

721 darker colours indicating higher likelihood. The black dashed contour shows the 95%
722 credible interval and the blue dotted line shows the 99% credible interval.
723

724

725

	Females			Males	
	X^{SR}/X^{SR}	X^{SR}/X^{ST}	X^{ST}/X^{ST}	X^{SR}/Y	X^{ST}/Y
Cross A $X^{SR}/X^{ST} \times X^{SR}/Y$	$1 - s_f$	$1 - hs_f$			
Cross B $X^{SR}/X^{ST} \times X/Y$		$1 - hs_f$	1	$1 - s_m$	1

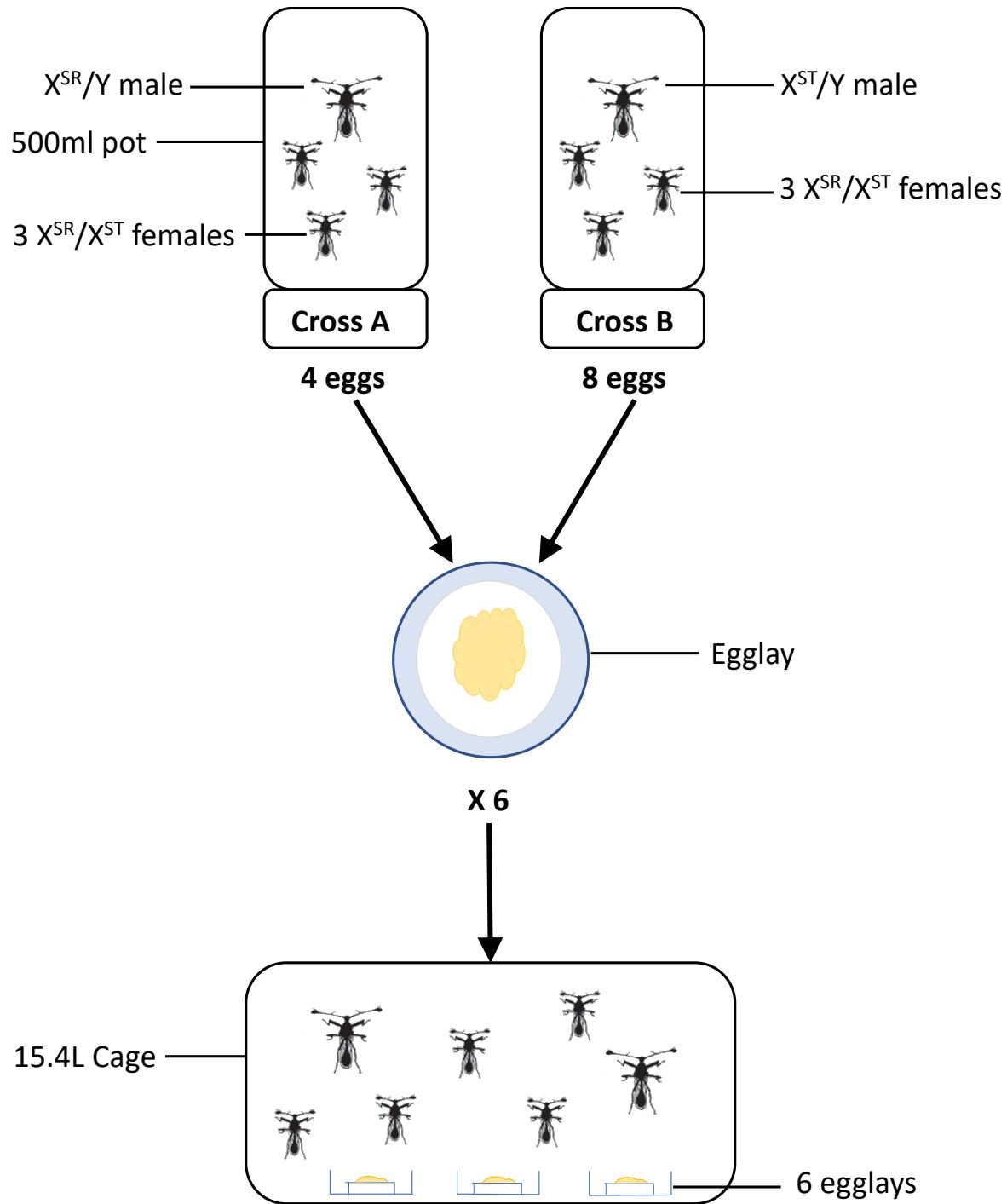
726

727 Table 1: Relative egg-to-adult viability. The five genotypes are drawn from crosses between
728 heterozygous females and drive males (Cross A) or standard males (Cross B). The selection
729 parameters, s_f and s_m , measure drive egg-to-adult viability relative to wildtype females
730 and males respectively. The dominance coefficient of drive is denoted h .

731

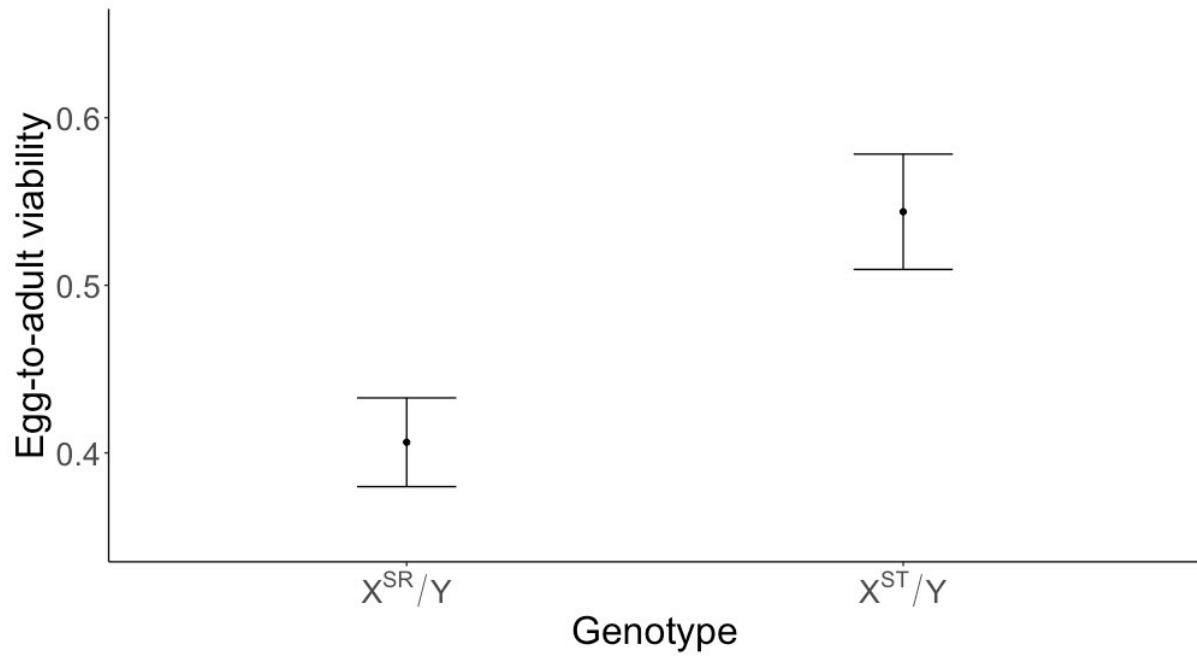
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733 Figure 1



734

735 Figure 2

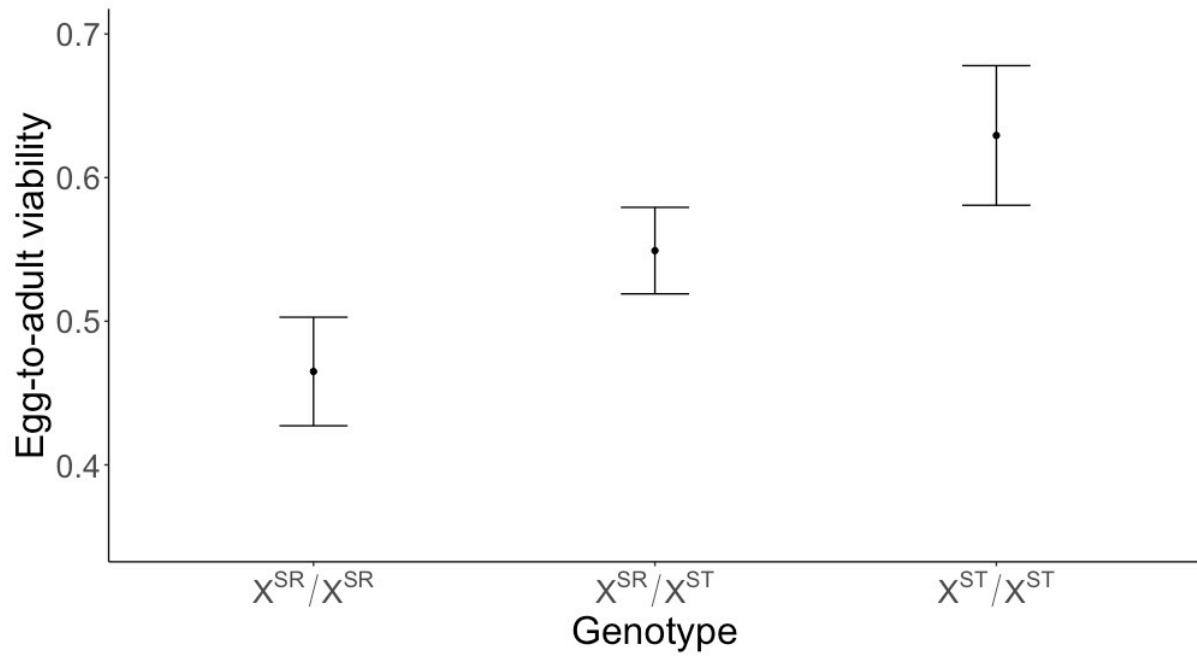


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739 Figure 3

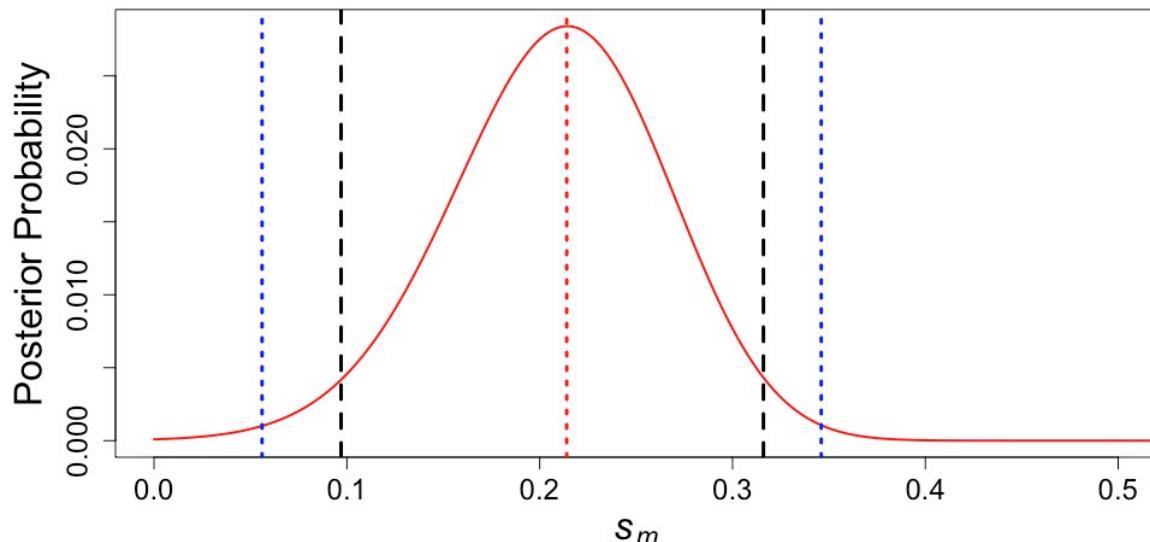


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743 Figure 4



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745

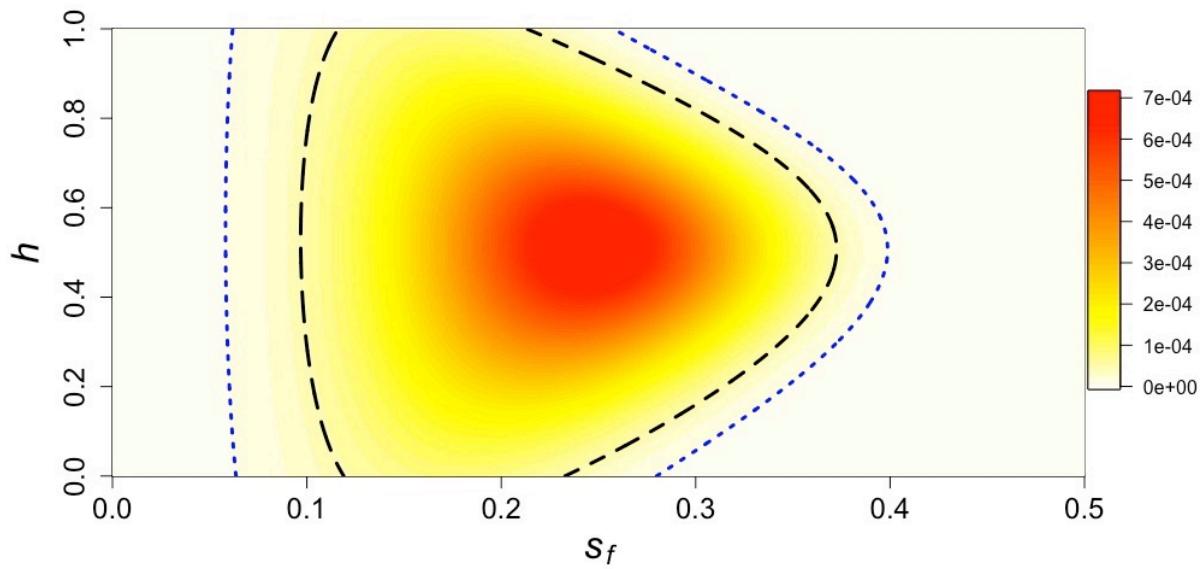
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748

749 Figure 5

750



751

752

753