Haploid selection, sex-ratio bias, and transitions between sex-determining systems

Michael Francis Scott[1☯*], Matthew Miles Osmond[2☯], Sarah Perin Otto[2]

1 UCL Genetics Institute, Department of Genetics, Evolution and Environment, University College London, Gower Street, London WC1E 6BT
2 Department of Zoology, University of British Columbia, #4200 - 6270 University Boulevard, Vancouver, BC, Canada V6T 1Z4

☯These authors contributed equally to this work.
* m.f.scott@ucl.ac.uk

Abstract

Sex determination is remarkably dynamic; many taxa display shifts in the location of sex-determining loci or the evolution of entirely new sex-determining systems. Predominant theories for why we observe such transitions generally conclude that novel sex-determining systems are favoured by selection if they equalise the sex ratio or increase linkage with a ~~sexually-antagonistic locus .~~ locus that experiences different selection in males vs. females. We use population genetic models to extend these theories in two ways: (1) We ~~explicitly consider selection on~~ consider the dynamics of loci very tightly linked to the ancestral sex-determining loci, e.g., within the non-recombining region of the ancestral sex chromosomes. Variation at such loci can favour the spread of new sex-determining systems in which the heterogametic sex changes (XY to ZW or ZW to XY) and the new sex-determining region is less closely linked (or even unlinked) to the locus under selection~~, which is not predicted by previous theory.~~ . (2) We ~~also~~ consider selection upon haploid genotypes either during gametic competition (e.g., pollen ~~/sperm~~ competition) or meiosis (i.e., non-Mendelian segregation), which can cause the zygotic sex ratio to become biased. ~~We find that associations with haploid selected loci~~ Haploid selection can drive transitions between sex-determining systems ~~, without requiring sexually-antagonistic selection in diploids.Unexpectedly, with~~ without requiring selection to act differently in diploid males vs. females. With haploid selection, we find that transitions between male and female heterogamety can ~~also~~ evolve where linkage with the sex-determining locus is ~~weakened. Furthermore, sex ratio biases may~~ either strengthened or weakened. Furthermore, we find that the selective forces to equalize the sex ratio are equally important to selective forces that generate skewed sex ratios when accounting for the spread of new sex chromosomes. This allows sex-ratio biases to increase or decrease with the spread of new sex chromosomes ~~. Thus, we find~~ and implies that transitions between sex-determining systems cannot be simply predicted by selection to equalise the sex ratio. Overall, our models reveal that transitions between sex-determining systems, particularly transitions where the heterogametic sex changes, can be driven by loci in previously unpredicted genomic locations that experience selection during diploid and/or haploid phases. ~~These results predict conditions under which sex-determining systems are likely to be labile and draw novel connections with sex ratio evolution.~~

Author summary

Systems of sex determination are strikingly diverse and labile in many clades. This poses the question: what drives transitions between sex-determining systems? Here, we use models to derive conditions under which new sex-determining systems spread. Prevailing views suggest that new sex-determining systems are favoured when they equalize the sex ratio and/or when they are more closely linked to genes that experience differential selection in males and females. Our models ~~extend these theories to~~ include selection upon haploid genotypes (meiotic drive or gametic competition), which ~~causes sex ratio biases~~ biases the sex-ratio and occurs differently in ~~males and females~~male and female gametes. Surprisingly, we find ~~that neither force (sex ratio selection nor associations with genes that have sex-specific effects) dominates~~ the two forces (selection to equalize the sex ratio and the benefits of hitchhiking with driven alleles that distort the sex ratio) will often be equally strong, and thus neither is sufficient to explain the spread of new sex-determining systems ~~alone. Even more unexpectedly, we find that , to spread, in every case.~~ We also find that new sex-determining alleles ~~do not necessarily have to arise in closer linkage with genes that are differentially selected in males and females. Therefore, our models predict~~ can spread despite being less closely linked to selected loci, driven by initially tight linkage or haploid selection. Our models therefore predict that loci in previously unexpected genomic locations and/or experiencing various types of selection (including haploid selection) can now be implicated as drivers of transitions between sex-determining systems.

Introduction

Animals and angiosperms exhibit extremely diverse sex-determining systems (reviewed in ~~[1–4]~~ [?, 1–4]). Among species with genetic sex determination (GSD)~~of diploid sexes~~, some taxa have heterogametic males (XY) and homogametic females (XX), including mammals and most dioecious plants [5]; whereas other taxa have homogametic males (ZZ) and heterogametic females (ZW), including Lepidoptera and birds. Within several taxa, the chromosome that harbours the master sex-determining locus changes. For example, transitions of the master sex-determining locus between chromosomes or the evolution of new master sex-determining loci where the heterogametic sex does not change (hereafter 'cis-GSD transitions') have occurred in Salmonids [6, 7], Diptera [8], and *Oryzias* [9]. In addition, many clades exhibit transitions between male and female heterogamety (XY↔ZW, hereafter 'trans-GSD transitions'), including snakes [10], lizards [11], eight of 26 teleost fish families [12], true fruit flies (Tephritids, [8]), amphibians [13], the angiosperm genus *Silene* [14], the angiosperm family *Salicaceae* [15, 16] and Coleoptera and Hemiptera (plate 2 [3]). Indeed, in some cases, both male and female heterogametic sex-determining systems can be found in the same species, as reported in houseflies [17], midges [18], frogs [19], cichlid fish [20], tilapia [21], sea bass [22], and lab-strains of Zebrafish [23, 24]. In addition, multiple transitions have occurred between genetic and environmental sex-determining systems (GSD↔ESD), e.g., in reptiles and fishes ~~[11, 12, 25–28].~~

~~Predominant theories accounting for the spread of new~~ [?, 11, 12, 25–28]. In sum, accumulating evidence indicates that transitions between sex-determining ~~systems by selection involve fitness differences between sexes (e.g., sexually antagonistic selection) or sex ratio selection [3, 29, 30]. van Doorn and Kirkpatrick [31, 32] and Muralidhar and Veller [33] have shown that new sex-determining alleles can be favoured if they arise at loci in close linkage with a locus that experiences sexual antagonism. Tighter linkage allows a stronger favourable association to build up between a male-beneficial allele, and a neo-Y allele, for example. Such associations can favour cis-GSD transitions [31], trans-GSD transitions [32], and new partially-masculinizing or partially-feminizing alleles [33]. However, any sexually-antagonistic loci that are more closely linked to the ancestral sex-determining locus will develop similar, favourable associations and are expected to hinder the spread of a new~~

sex-determining systemsystems are common [4].

The sex ratio is directly determined by the sex-determining system, and it has therefore It has been suggested that sex ratio sex-ratio selection is a particularly dominant force in the evolution of sex determination because the sex ratio is directly determined by the sex-determining system (e.g., Bull, 1983, p 66-67 [1]; Buekeboom and Perrin, 2014, Chapter 7 [3]). Classic 'Fisherian' sex ratio sex-ratio selection favours a 1:1 zygotic sex ratio when assuming that males and females are equally costly to produce [34, 35]. This follows from the fact that, for an autosomal locus, half of the genetic material is inherited from a male and half from a female [36]. Thus, if the population sex ratio is biasedtowards one sex, the average per-individual contribution of , an individual of the rarer sex will, on average, contribute more genetic material to the next generationfrom the opposite sex is greater. Therefore, a mutant that increases . Selection therefore typically favours mutants that increase investment in the rarer sexwill spread via the higher per-individual contributions made by that sex. In the case of sex-chromosome evolution , Kozielska et al. (2014) [41] consider systems in which the ancestral sex chromosomes experience meiotic drive (e.g., where driving X or Y chromosomes are inherited disproportionately often), which causes sex ratios to become biased [43]. They find that masculinizing or feminizing mutations that arise at a new, unlinked locus (i.e.,.

The evolution of sex determination is also thought to be strongly influenced by differences in selection between the sexes [3, 29, 30]. For example, loci experiencing sexual antagonism have been shown to favour the spread of new genetic sex-determining alleles that are closely linked [31–33]. Linkage allows a stronger favourable association to build up between a male-beneficial allele and a neo-Y or neo-W chromosomes) can then spread, which restore an even sex ratio. allele, for example. Such associations can favour cis-GSD transitions [31], trans-GSD transitions [32], and new partially-masculinizing or partially-feminizing alleles in a population with ESD [33]. By similar logic, however, existing sexually-antagonistic alleles associated with the current sex-determining locus are expected to hinder the spread of a new sex-determining system [31, 32].

Here we use mathematical models to find the conditions under which new One novel feature of the models developed here is that we explicitly consider the maintenance of genetic variation around the ancestral sex-determining systems spread when individuals experience selection at both diploid and haploid stages, which allows fitness differences between the sexes and sex ratio biases to occur simultaneously. Even in animal and plant species that have much larger and more conspicuous diploid phases than haploid phases, many loci experience significant haploid selection through gamete competition and /or meiotic drive [37, 38]. We use the term 'meiotic drive' to refer to the biased (non-Mendelian) segregation of genotypes during gamete production (from one parent) and the term 'gametic competition' to refer to selection upon haploid genotypes within a gamete/gametophyte pool (potentially from multiple parents); the term 'haploid selection' encompasses both processeslocus (e.g., within the non-recombining region of a sex chromosome). Counterintuitively, when linkage is tight between the sex-determining locus and a selected locus, an allele good for females can be at higher frequency on the ancestral-Y than on the ancestral-X under a variety of forms of selection. This, in turn, can favour a new ZW sex-determining locus that has weaker linkage with loci under selection (a similar argument applies to ZW→XY transitions), which was not apparent/discovered/considered in previous theory [32]. That is, we show that selected loci in very tight linkage with the ancestral GSD locus can favour trans-GSD transitions during which linkage associations are actually weakened.

Segregation distortion provides putative evidence of haploid selection and can sometimes be attributed to meiotic drive and/or gametic competition [44–49].Where it has been characterized, meiotic drive generally occurs either during the production of male or female gametes only [39, 40]. Gametic competition is also typically sex specific, occurring primarily among male gametes, because there are typically many more pollen/sperm than required for fertilization. Gametic competition may be particularly common in plants, in which 60-70% of

all genes are expressed in the male gametophyte, and these genes exhibit stronger signatures of Most significantly, we include haploid selection (gametic competition or meiotic drive) in models describing cis-GSD, trans-GSD, and GSD to ESD transitions. This poses an apparent evolutionary problem. On one hand, haploid selection than randomly-chosen genes [50–52]. In addition, artificial selection pressures applied to male gametophytes are known to cause a response to selection (e.g., [53–56]). A smaller proportion of genes are thought to be expressed and selected during competition in animal sperm, although precise estimates are uncertain [38,57,58]. Nevertheless, recent studies have demonstrated that sperm competition in animals can alter haploid allele frequencies and increase offspring fitness [59,60].

There are various ways by which genes experiencing haploid selection could influence transitions between sex-determining systems. If we assume that haploid selection at any particular locus predominantly occurs in one sex (e.g., meiotic drive during spermatogenesis), then such loci experience a form of is typically sex-specific selection. In this respect, we might expect that haploid selection would affect transitions between in that it usually occurs among gametes produced by one sex only [37–40]. Therefore, one might expect new sex-determining systems in a similar manner to sex-specific diploid selection (as explored in [31,32]). That is, new masculinizing mutations (neo-Y alleles) could be favoured via associations with alleles that are beneficial in the male haploid stagesystems to benefit from close linkage with haploid selected loci, as found for sex-differences in diploid selection [31–33]. On the other hand, sex ratios can also become biased by linkage between the associations between sex-determining locus and a locus that harbours genetic variation in haploid fitnessloci and haploid selected loci generate biased zygotic sex ratios, which should generally hinder the spread of new sex-determining systems.

Two previous studies have considered the spread of GSD with sex-specific meiotic drive [41,42] under a limited number of possible genetic architectures and diploid selective regimes. Ubeda et al. (2015) [42] considered ancestral-ESD (with no sex-ratio bias) and numerically showed that new GSD alleles can spread if they arise in linkage with meiotic drive loci. For example, there are several known cases of sex ratio bias caused by sex-linked meiotic drive alleles (Burt and Trivers, 2006, Chapter 6 [61])or selection among X- a masculinizing allele spreads in association with an allele that is favoured during male meiosis, causing sex ratios to become male-biased. This suggests that the benefits of associating with driving alleles overwhelms selection to balance the sex ratio and Y-bearing pollen [62–67]. It is not immediately clear how the spread of newsex-determining systems would be influenced by the combination of sexratio biases and associations with haploid selected alleles that haploid selection should cause increased sex-linkage. However, Kozielska et al. (2010) [41] considered an ancestral GSD system that is perfectly linked to a meiotic driver (creating a sex ratio bias). They found that new, completely unlinked, GSD systems can spread if they generate the rarer sex, creating a balanced sex ratio. This suggests that Fisherian sex-ratio selection overwhelms the benefits of being associated with driving alleles and that haploid selection should cause decreased sex-linkage.

We find that the spread of novel sex-determining systems is influenced by both Fisherian sex ratio selection and by selectionon linked alleles. Surprisingly, Fisherian sex ratio selection does not dominate; it is possible for selection on linked alleles to drive turnover between sex-determining systemsdespite causing increasingly biased sex ratios. In addition to considering haploid selection , another novel development in our model is that we consider loci that are in very tight linkage with the ancestral Here, we analytically find the conditions under which new GSD or ESD systems spread in ancestral GSD systems with generic linkage between the loci involved and generic sex-specific haploid and diploid selection. Doing so, we reconcile the results of Kozielska et al. (2010) [41] and Ubeda et al. (2015) [42] by showing when new GSD systems that increase *or* decrease linkage with loci under haploid selection spread. This result is qualitatively distinct from those for diploid selection alone [31,32] and suggests that haploid selection is more likely to promote transitions between sex-determination

systems. This also implies that transitions involving haploid selection cannot be simply explained by invoking sex-ratio selection. In particular, we show that under a wide range of conditions, transitions to sex-determining ~~locus. We find that loci tightly linked with the~~ systems that increase or decrease the sex-ratio bias are favoured *equally strongly*. Finally, we show that ESD may not evolve, even if the sex ratio is initially biased by haploid selection, which is not predicted by previous theories for transitions to ESD [1, 35, 36]. Together, our results suggest that both selection to equalize the sex ratio and the benefits of associating with haploid selected alleles can drive transitions between sex-determining ~~locus can drive transitions in which the heterogametic sex changes, even when the new sex-determining locus is less closely linked to loci under selection (either including haploid selection or not)~~systems, leading to tighter or weaker sex-linkage.

Model

We consider transitions between ancestral and novel sex-determining systems using a three-locus model, each locus having two alleles (Fig 1). A full description of our model, including recursion equations, is given in S1 Appendix. Locus **X** is the ancestral sex-determining region, with alleles X and Y (or Z and W). Locus **A** is a locus under selection, with alleles A and a. Locus **M** is a novel sex-determining region, at which the null allele (M) is initially fixed in the population such that sex of zygotes is determined by the genotype at the ancestral sex-determining region, **X**; XX genotypes become females and XY become males (or ZW become females and ZZ become males). To evaluate the evolution of new sex-determining systems, we consider the ~~invasion, fixation, maintenance, and/or loss~~ spread of a novel sex-determining allele (m) at the **M** locus. ~~We~~

Here, we assume that the **M** locus is ~~epistatically dominant~~ 'epistatically dominant' over the **X** locus such that zygotes with at least one m allele develop as females with probability k and as males with probability $1 - k$, regardless of the **X** locus genotype. With $k = 0$, the m allele is a masculinizer (a neo-Y allele) and with $k = 1$ the m allele is a feminizer (a neo-W allele). With intermediate k, we can interpret m as an environmental sex-determination (ESD) allele, such that zygotes develop as females in a proportion (k) of the environments they experience. The assumption that derived sex-determining loci are epistatically dominant is motivated by empirical systems in which multiple sex determining alleles segregate (i.e., X, Y, Z, and W alleles present), such as, cichlid fish [20], platyfish (*Xiphophorus maculatus* [76]), houseflies (*Musca domestica* [**?**]), western clawed frogs (*Xenopus tropicalis* [**?**]) and *Rana rugosa* [19]. Nevertheless, our supplementary analysis file (S1 File) allows other dominance relationships between loci to be specified (see also [31] supplementary material for a numerical analysis).

~~In each generation, we census the genotype frequencies in male and female~~ We consider two forms of selection upon haploid genotypes, 'gametic competition' and 'meiotic drive'. During gametic competition, we assume that a representative sample of all gametes/gametophytes (hereafter gametes) ~~before gametic competition. A full description of our model, including recursion equations, is given in . First, competition occurs among male gametes (sperm/pollen competition) and among female gametes (egg/ovule competition) separately. Selection~~ compete with others of the same sex for fertilization, which implies a polygamous mating system. Relative fitnesses in sex $\circ \in \{♀, ♂\}$ during gametic competition ~~depends on the **A** locus genotype; relative fitnesses~~ are given by $w_A^{\circlearrowleft}$ ~~and~~ $w_a^{\circlearrowleft}$ ($\circlearrowleft \in \{♀, ♂\}$; w_A° and w_a° (see table 1). ~~We assume that all gametes compete for fertilization during gametic competition , which implies a polygamous mating system.Gametic competition in monogamous mating systems is, however, equivalent to meiotic drivein our model (described below), as either only alters~~ On the other hand, meiotic drive in our model only affects the segregation of gametes produced by heterozgotes. Specifically, gametes produced by *Aa* heterozgotes of sex $\circ$ bear allele A with probability α°. We note that competition between

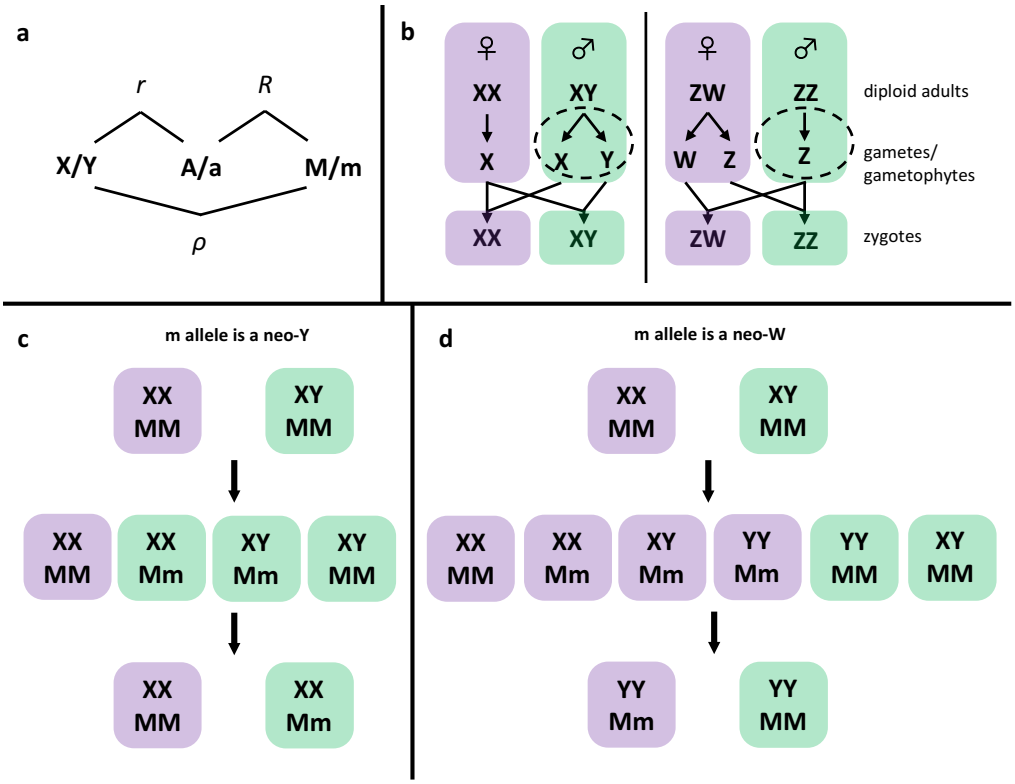

Fig 1. Outline of model features. Panel A: Recombination rate parameters between the ancestral-sex-determining locus (**X**, here assumed to have alleles X and Y), a locus under selection (**A**, with alleles A and a), and a new sex-determining locus (**M**, with alleles M and m). If $r < 1/2$, then associations between ancestral sex-determining alleles and selected alleles can be maintained ~~past recombination~~ in males. Panel B: Haploid selection is often sex-specific, occurring during haploid production or competition in either males or females. For example, haploid selection in males only is represented by the dashed circle. If X or Y alleles remain associated with alleles that experience haploid selection in males ($r < 1/2$), then zygotic sex ratios can become biased because either X- or Y-bearing male gametes/gametophytes will be more abundant after haploid selection. However, the zygotic sex ratio is not biased by male haploid selection in ZW sex-determining systems. Similarly, zygotic ~~sex ratio~~ sex-ratio biases can ~~occur~~ arise if haploid selected alleles are associated with new sex-determining alleles ($R < 1/2$). Panel C: During cis-GSD transitions (XY to XY or ZW to ZW), a neo-Y allele spreads to pseudo-fixation (its maximum frequency among male gametes) and the ancestral Y allele is lost. Panel D: During trans-GSD transitions (XY to ZW or ZW to XY), a neo-W allele spreads to pseudo-fixation (its maximum frequency among female gametes) and the ancestral X allele is lost. Neo-W alleles allow Y-associated alleles into females, which may impede or aid their spread.

sperm produced by a single male (e.g. in a monogamous mating system) would be appropriately modelled as male meiotic drive, as only the frequency of gametes produced by heterozygotes ~~.~~ would be affected. However, we do not consider scenarios in which there is competition among gametes produced by a small number of males/females (e.g., [**?**]).

In each generation, we census the genotype frequencies in male and female gametes before gametic competition. After gametic competition, conjugation between male and female gametes occurs at random. The resulting zygotes develop as males or females, depending on their genotypes at the **X** and **M** loci. Diploid males and females then experience viability and/or

individual-based fertility selection, with relative fitnesses $w^{\sigma^\delta}_{AA}$, $w^{\sigma^\delta}_{Aa}$, and $w^{\sigma^\delta}_{aa}$ w°_{AA}, w°_{Aa}, and w°_{aa}. We do not consider fertility selection based on the mating pair or sexual selection. The next generation of gametes is produced by meiosis, during which recombination and sex-specific meiotic drive can occur. Recombination (i.e., an odd number of cross-overs) occurs between loci **X** and **A** with probability r, between loci **A** and **M** with probability R, and between loci **X** and **M** with probability ρ. Any linear order of the loci can be modelled with appropriate choices of r, R, and ρ (see Fig 1A and S1 Table). Individuals that are heterozygous at the **A** locus may experience meiotic drive; a gamete produced by *Aa* heterozgotes of sex σ^δ bears allele *A* with probability α^{σ^δ}. Thus, the **A** locus can experience sex-specific gametic competition, diploid selection, and/or meiotic drive. Our model is entirely deterministic and hence ignores chance fluctuations in allele frequencies due to genetic drift.

Table 1. Relative fitness of different genotypes in sex $\sigma^\delta \in \{\varphi, \sigma\}$ $\circ \in \{\varphi, \sigma\}$

Genotype	Relative fitness during gametic competition
A	$w^{\sigma^\delta}_{A} = 1 + t^{\sigma^\delta}$ $w^{\circ}_{A} = 1 + t^{\circ}$
a	$w^{\sigma^\delta}_{a} = 1$ $w^{\circ}_{a} = 1$
Genotype	Relative fitness during diploid selection
AA	$w^{\sigma^\delta}_{AA} = 1 + s^{\sigma^\delta}$ $w^{\circ}_{AA} = 1 + s^{\circ}$
Aa	$w^{\sigma^\delta}_{Aa} = 1 + h^{\sigma^\delta} s^{\sigma^\delta}$ $w^{\circ}_{Aa} = 1 + h^{\circ} s^{\circ}$
aa	$w^{\sigma^\delta}_{aa} = 1$ $w^{\circ}_{aa} = 1$
Genotype	Transmission during meiosis in *Aa* heterozygotes
A	$\alpha^{\sigma^\delta} = 1/2 + \alpha^{\sigma^\delta}_{\Delta}/2$ $\alpha^{\circ} = 1/2 + \alpha^{\circ}_{\Delta}/2$
a	$1 - \alpha^{\sigma^\delta} = 1/2 - \alpha^{\sigma^\delta}_{\Delta}/2$ $1 - \alpha^{\circ} = 1/2 - \alpha^{\circ}_{\Delta}/2$

Results

The model outlined above describes both ancestral XY and ZW sex-determining systems. Without loss of generality, we refer to the ancestrally heterogametic sex as male and the ancestrally homogametic sex as female. That is, we primarily describe an ancestral XY sex-determining system but our model is equally applicable to an ancestral ZW sex-determining system (relabelling the ancestrally heterogametic sex as female and the ancestrally homogametic sex as male and switching the labels of males and females throughout). We use a superscript to specify the ancestral sex-determining system described, e.g., $^{(XY)}$ for ancestral XY sex-determination.

In the ancestral population, it is convenient to follow the frequency of the *A* allele among female gametes (eggs), p^{φ}_{X}, and among X-bearing, p^{σ}_{X}, and among Y-bearing, p^{σ}_{Y}, male gametes (sperm/pollen). We also track the fraction of male gametes that are Y-bearing, q, which may deviate from 1/2 due to meiotic drive in males. We consider only equilibrium frequencies of alleles, $\hat{p}^{\circ}_{i}$, and Y-bearing male gametes, $\hat{q}$, when determining the invasion of new sex-determining factors.

Results

Generic invasion by a neo-Y or neo-W

We begin by describing the conditions under which new sex determining alleles can spread within a population, without explicitly specifying ancestral allele frequencies. These general conditions then allow us to consider several special cases of interest in subsequent sections, where equilibrium ancestral allele frequencies are explicitly calculated.

The evolution of a new sex-determining system ~~requires that~~ depends on the growth rate of a rare mutant allele, m, at the novel sex-determining locus, $\mathbf{M}$~~, increases in frequency when rare. This~~. This growth rate is determined by the leading eigenvalue ($\lambda_m^{(XY)}$) of the system of eight equations describing the frequency of eggs and sperm carrying the m allele in the next generation (equations S1.1). This system simplifies substantially for ~~a~~ an epistatically dominant neo-Y ($k = 0$) or neo-W ($k = 1$), see S3 Appendix. The leading eigenvalue for a rare neo-Y or neo-W allele, $m \in \{Y', W'\}$, is the largest value of ~~X~~ x that solves $x^2 + bx + c = 0$~~. The coefficients are~~, where $b = -(\Lambda_{mA}^{(XY)} + \Lambda_{ma}^{(XY)}) + (\chi_{mA}^{(XY)} + \chi_{ma}^{(XY)})$ and $c = (\Lambda_{mA}^{(XY)} - \chi_{mA}^{(XY)})(\Lambda_{ma}^{(XY)} - \chi_{ma}^{(XY)}) - \chi_{mA}^{(XY)}\chi_{ma}^{(XY)}$~~, where~~. The variable $\Lambda_{mi}^{(XY)} > 0$ is the multiplicative growth rate ~~(which we will call the "haplotypic growth rate") of the neo-sex determination~~ of the neo-sex-determining allele m on background $i \in \{A, a\}$ without accounting for loss due to recombination ($R = 0$)~~, and~~. We will call $\Lambda_{mi}^{(XY)}$ the "haplotypic growth rate". The variable $\chi_{mi}^{(XY)} > 0$ is the rate at which mutant haplotypes on background $i \in \{A, a\}$ recombine onto the other $\mathbf{A}$ locus background in heterozygotes (proportional to R)~~, see Table 2. In the ancestral population, it is convenient to follow the frequency of the A allele among female gametes (eggs), $p_X^{\mathbb{Q}}$, and among X-bearing, $p_X^{\mathbb{O}}$, and among Y-bearing, $p_Y^{\mathbb{O}}$, male gametes (sperm/pollen). We also track the fraction of male gametes that are Y-bearing, q, which may deviate from 1/2 due to meiotic drive in males. We will consider only equilibrium frequencies of alleles, $\hat{p}_i^{\mathbb{O}}$, and Y-bearing male gametes, $\hat{q}$, when calculating the eigenvalues~~. We call $\chi_{mi}^{(XY)}$ the "dissociative force", as it breaks down linkage disequilibrium. Both variables are listed in Table 2 for neo-Y and neo-W mutants.

The new sex-determining allele increases in frequency when rare when the largest eigenvalue is greater than one ($\lambda_m^{(XY)} > 1$). If both haplotypic growth rates are greater than one ($\Lambda_{mA}^{(XY)}, \Lambda_{ma}^{(XY)} > 1$) ~~,~~then the new sex-determining allele invades regardless of the rate of recombination between the new sex-determining locus and the selected locus (R)~~, ~~; see S3 Appendix for details). Conversely, if both haplotypic growth rates are less than one ($\Lambda_{mA}^{(XY)}, \Lambda_{ma}^{(XY)} < 1$) ~~,~~then invasion can never occur. Finally, if only one haplotypic growth rate is greater than one, the new sex-determining allele can always invade when arising at a locus that is tightly linked to the selected locus ($R \approx 0$). Furthermore, it can be shown that the leading eigenvalue declines with R, and invasion requires that R is sufficiently small such that:

$$\chi_{ma}^{(XY)} / \left(\Lambda_{ma}^{(XY)} - 1\right) + \chi_{mA}^{(XY)} / \left(\Lambda_{mA}^{(XY)} - 1\right) < 1. \quad (1)$$

This condition may or may not be satisfied for the full range of locations of the new sex-determining locus, including $R = 1/2$, depending on the nature of selection. Interpreting this condition, if we assume that only the mA haplotype would increase in frequency when $R = 0$ ($\Lambda_{ma}^{(XY)} < 1 < \Lambda_{mA}^{(XY)}$) then the first term on the left-hand side of (1) is negative and invasion requires that ~~rate of growth of~~ growth rate of mA haplotypes ($\Lambda_{mA}^{(i)} - 1 > 0$) and the rate at which ~~*mA* haplotypes~~ they are produced by recombination ~~in *ma* haplotypes~~ ($\chi_{ma}^{(i)}$) are sufficiently large relative to the rate of decline of ma haplotypes ($1 - \Lambda_{ma}^{(i)} > 0$) and the rate ~~of loss of *mA* haplotypes due to~~ at which m and A are dissociated by recombination ($\chi_{mA}^{(i)}$).

We ~~can draw a number of key~~ draw three main points about the generic invasion of neo-Y and neo-W mutations from Table 2. First, ~~Fisherian sex ratio~~ invasion by a neo-Y (neo-W) does not directly depend on the fitness of female (male) diploids. This is because a dominant neo-Y (neo-W) is always found in males (females), and therefore the frequency of the neo-Y (neo-W), m, only changes in males (females), Fig 1C,D. Second, Fisherian sex-ratio selection will favour

Table 2. Parameters determining invasion of mutant neo-Y and neo-W alleles into an ancestrally XY system

m is a neo-Y ($k = 0$)
$\Lambda^{(XY)}_{Y'A} = (2\zeta)^{-1}\left[\hat{p}^{\varphi}_{X} w^{\varphi}_{A} w^{\sigma}_{A} w^{\sigma}_{AA} + (1-\hat{p}^{\varphi}_{X}) w^{\varphi}_{a} w^{\sigma}_{A} w^{\sigma}_{Aa}(1+\alpha^{\sigma}_{\Delta})\right] / \left(\bar{w}^{\varphi}_{H}\bar{w}^{\sigma}_{H}\bar{w}^{\sigma}_{D}\right)$
$\Lambda^{(XY)}_{Y'a} = (2\zeta)^{-1}\left[(1-\hat{p}^{\varphi}_{X}) w^{\varphi}_{a} w^{\sigma}_{a} w^{\sigma}_{aa} + \hat{p}^{\varphi}_{X} w^{\varphi}_{A} w^{\sigma}_{a} w^{\sigma}_{Aa}(1-\alpha^{\sigma}_{\Delta})\right] / \left(\bar{w}^{\varphi}_{H}\bar{w}^{\sigma}_{H}\bar{w}^{\sigma}_{D}\right)$
$\chi^{(XY)}_{Y'A} = R(2\zeta)^{-1}\left[(1-\hat{p}^{\varphi}_{X}) w^{\varphi}_{a} w^{\sigma}_{A} w^{\sigma}_{Aa}(1+\alpha^{\sigma}_{\Delta})\right] / \left(\bar{w}^{\varphi}_{H}\bar{w}^{\sigma}_{H}\bar{w}^{\sigma}_{D}\right)$
$\chi^{(XY)}_{Y'a} = R(2\zeta)^{-1}\left[\hat{p}^{\varphi}_{X} w^{\varphi}_{A} w^{\sigma}_{a} w^{\sigma}_{Aa}(1-\alpha^{\sigma}_{\Delta})\right] / \left(\bar{w}^{\varphi}_{H}\bar{w}^{\sigma}_{H}\bar{w}^{\sigma}_{D}\right)$
m is a neo-W ($k = 1$)
$\Lambda^{(XY)}_{W'A} = [2(1-\zeta)]^{-1}\left[\bar{p}^{\sigma} w^{\sigma}_{A} w^{\varphi}_{A} w^{\varphi}_{AA} + (1-\bar{p}^{\sigma}) w^{\sigma}_{a} w^{\varphi}_{A} w^{\varphi}_{Aa}(1+\alpha^{\varphi}_{\Delta})\right] / \left(\bar{w}^{\varphi}_{H}\bar{w}^{\sigma}_{H}\bar{w}^{\varphi}_{D}\right)$
$\Lambda^{(XY)}_{W'a} = [2(1-\zeta)]^{-1}\left[(1-\bar{p}^{\sigma}) w^{\sigma}_{a} w^{\varphi}_{a} w^{\varphi}_{aa} + \bar{p}^{\sigma} w^{\sigma}_{A} w^{\varphi}_{a} w^{\varphi}_{Aa}(1-\alpha^{\varphi}_{\Delta})\right] / \left(\bar{w}^{\varphi}_{H}\bar{w}^{\sigma}_{H}\bar{w}^{\varphi}_{D}\right)$
$\chi^{(XY)}_{W'A} = R[2(1-\zeta)]^{-1}\left[(1-\bar{p}^{\sigma}) w^{\sigma}_{a} w^{\varphi}_{A} w^{\varphi}_{Aa}(1+\alpha^{\varphi}_{\Delta})\right] / \left(\bar{w}^{\varphi}_{H}\bar{w}^{\sigma}_{H}\bar{w}^{\varphi}_{D}\right)$
$\chi^{(XY)}_{W'a} = R[2(1-\zeta)]^{-1}\left[\bar{p}^{\sigma} w^{\sigma}_{A} w^{\varphi}_{a} w^{\varphi}_{Aa}(1-\alpha^{\varphi}_{\Delta})\right] / \left(\bar{w}^{\varphi}_{H}\bar{w}^{\sigma}_{H}\bar{w}^{\varphi}_{D}\right)$

$\hat{p}^{\varphi}_{X}$ is the frequency of A among female gametes. $\bar{p}^{\sigma} = (1-\hat{q})\hat{p}^{\sigma}_{X} + \hat{q}\hat{p}^{\sigma}_{Y}$ is the average frequency of the A allele among X- and Y-bearing male gametes. ζ is the zygotic sex ratio (fraction male). ~~$\bar{w}^{\sigma}_{D}$~~ $\bar{w}^{\circ}_{D}$ is the mean fitness of diploids of sex ~~σ. $\bar{w}^{\sigma}_{H}$~~ $\circ \in \{\varphi, \sigma\}$. $\bar{w}^{\circ}_{H}$ is the mean fitness of haploids from sex ~~σ~~ $\circ$, see S2 Table. R is the rate of recombination between the neo-sex-determiner and the selected locus. Selection terms (w°_{i}, α°_{Δ}) are described in Table 1.

the spread of a ~~neo-Y~~ neo-W and inhibit the spread of a ~~neo-W~~ neo-Y if the ancestral zygotic sex ratio is biased towards ~~females, $\zeta < 1/2$~~ males (i.e., the first factor of the $\Lambda^{(XY)}_{mi}$ is greater than one for a ~~neo-Y~~ neo-W and less than one for a ~~neo-W)~~neo-Y when $\zeta > 1/2$), as might occur when the ancestral sex-determining locus is linked to a locus experiencing meiotic drive in males, for example. However, the spread of a neo-Y (neo-W) also depends on the male (female) fitness of associated alleles (see terms involving equilibrium allele frequencies, $\hat{p}$'s). ~~Second, invasion by a neo-Y (neo-W) does not directly depend on the fitness of female (male) diploids. This is because a dominant neo-Y (neo-W) is always found in males (females), and therefore the frequency of the neo-Y (neo-W), m, only changes in males (females), Fig 1C,D. Finally, invasions by a neo-Y and a neo-W~~, including haploid selection that additionally biases the sex ratio. This implies that both Fisherian selection to equalize the sex-ratio and selection favoring sex-linked drivers that distort the sex ratio play roles in the invasion dynamics of a new sex-determining allele, allowing the sex ratio to become more or less biased during a transition (as previously shown in two special cases; [41,42]). And thirdly, Table 2 also shows that cis- and trans-GSD transitions are qualitatively different. This is because, in an ancestrally XY system, a gamete with the neo-Y always pairs with a female gamete containing an X ~~,~~ (Fig 1C). By contrast, a gamete with a neo-W can pair with an X- or Y-bearing male gamete ~~,~~ (Fig 1D). Consequently, neo-W-bearing females obtain a different frequency of A alleles from mating (when $\hat{p}^{\sigma}_{X} \neq \hat{p}^{\sigma}_{Y}$) compared to ancestral (MM) females, which can inhibit or favour its spread.

In order to explicitly determine the conditions under which a ~~rare~~ new sex-determining allele spreads, we ~~must~~ next calculate the equilibrium frequency of the A allele (i.e., $\hat{p}^{\varphi}_{X}$, $\hat{p}^{\sigma}_{X}$, and $\hat{p}^{\sigma}_{Y}$) and Y-bearing male gametes ($\hat{q}$) in the ancestral population. ~~Since~~ Because only the **A** locus experiences selection directly, any deterministic evolution requires that there ~~is~~ be a polymorphism at the **A** locus. Polymorphisms can be maintained by mutation-selection balance or transiently present during the spread of beneficial alleles. ~~However,~~ Here, however, we focus

on polymorphisms maintained by selection, which can maintain alleles at intermediate ~~allele~~ frequencies for longer periods. ~~Here, we focus on polymorphisms maintained by selection, where the *A* allele reaches a stable intermediate equilibrium frequency under the ancestral sex-determining system before the new sex-determining allele (*m*) arises.~~ Such polymorphisms can be maintained by heterozygote advantage, sexually-antagonistic selection, ploidally-antagonistic selection, or a combination [68]. We ~~can analytically calculate the allele frequency of the *A* allele~~ analytically calculate equilibrium frequencies using two alternative simplifying assumptions: (1) the **A** locus is ~~within (or~~ tightly linked to ~~)~~ the non-recombining region around the ancestral sex-determining locus ($r \approx 0$) or (2) selection is weak relative to recombination (~~$s^{\sigma}, t^{\sigma}, \alpha_{\Delta}^{\sigma}$ of order $\epsilon << 1$).~~

~~Tight linkage with the ancestral sex-determining locus ($r \approx 0$)~~

~~The ancestral equilibrium allele frequencies~~ $s^{\circ}, t^{\circ}, \alpha_{\Delta}^{\circ} << r$). The ancestral equilibria and their stability conditions are given in S2 Appendix.

Tight linkage with the ancestral sex-determining locus ($r \approx 0$)

When there is complete linkage between the ancestral sex-determining locus and the **A** locus ($r = 0$), either the *A* allele or the *a* allele must be fixed in gametes containing a Y allele. Because the labelling of alleles is arbitrary, we will assume that the *a* locus is fixed in gametes with a Y ($p_Y^{\sigma} = 0$), without loss of generality. If there are two alleles maintained at the **A** locus, the *A* allele can be fixed ($\hat{p}_X^{\varphi} = \hat{p}_X^{\sigma} = 1$) or segregating at an intermediate frequency ($0<\hat{p}_X^{\varphi}, \hat{p}_X^{\sigma}<1$) in gametes with an X.

We find that a neo-Y allele can never invade an ancestral XY system that already has tight linkage with the locus under selection ($\lambda_{Y'}^{(XY)} \leq 1$ when $r = 0$~~,~~; for details see S1 File). ~~When $R = 0$, a neo-Y haplotype with the same allele as the ancestral Y is neutral ($A_{Y'a}^{(XY)} = 1$) and does not change in frequency. The other neo-Y haplotype will not spread ($A_{Y'A}^{(XY)} < 1$) given that the initial equilibrium is stable. Therefore, a neo-Y mutation cannot spread in an ancestral XY system ($\lambda_{Y'}^{(XY)} \leq 1$, regardless of *R*) where selected loci are within or very near the non-recombining region around the sex-determining locus.~~ In essence, through tight linkage with the **A** locus, the ancestral Y becomes strongly specialized on the allele that has the highest fitness across male haploid and diploid phases. ~~Given that the ancestral Y is at this equilibrium, it is~~ It is thus not possible for a neo-Y to create males that have higher fitness than the ancestral Y, and cis-GSD transitions are never favoured.

Neo-W alleles, on the other hand, can invade an ancestral XY system ~~under some conditions~~ (the full invasion conditions are given in S3 Appendix; equations S3.1 and S3.2). ~~Counterintuitively, selection on loci within the non-recombining region around the sex-determining locus can favour the invasion of a less closely linked~~ Thus,

Conclusion 1: **Selection on loci in or near the non-recombining region around the sex-determining locus ($r \approx 0$) prevents cis-GSD transitions (XY ↔ XY, ZW ↔ ZW) but can spur trans-GSD transitions (XY ↔ ZW).**
[Not clear from van Doorn & Kirkpatrick 2007, 2010]

Trans-GSD transitions can occur because, under some conditions, the neo-W ~~, whatever~~ can become more strongly specialized for females. This does not depend on the form of selection maintaining a polymorphism (sexually-antagonistic selection, overdominance, ploidally-antagonistic selection, or some combination, Fig 2, S2 Fig, S8 Fig, and S3 Fig). ~~The conditions~~

The conditions allowing trans-GSD transitions become more restrictive ~~, however,~~ with increasing recombination (R) between the new sex-determining locus and the selected locus. The invasion of completely unlinked neo-W alleles ($R = 1/2$) can occur with overdominance in males or with haploid selection (e.g., when male drive is opposed by diploid selection, as in [41]) but is not possible with only sexually-antagonistic selection ~~if~~ where selection is directional in each diploid sex (see S1 File). To ~~develop an intuition for how less closely linked neo-W alleles invade ($R > r$), we here focus~~ clarify the conditions under which trans-GSD transitions occur, we focus here on cases where there is no haploid selection (Fig 2A) and discuss the additional effect of haploid selection in S3 Appendix ~~.~~ (see also Conclusion 2B).

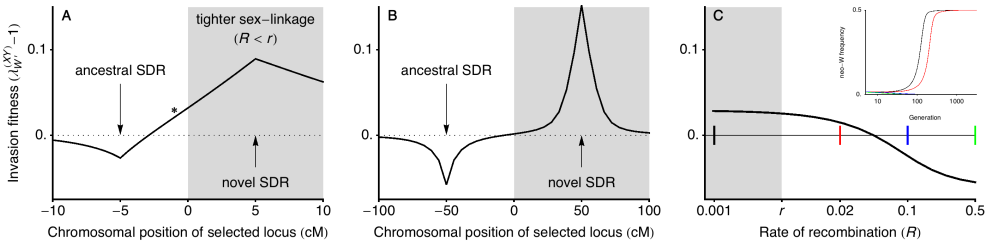

Fig 2. Transitions between XY and ZW systems can occur even when the new sex-determining locus is less tightly linked to a locus under sexually-antagonistic selection (~~even without~~ no haploid selection). In panel A, linkage is ~~loose enough~~ initially tight relative to selection ~~that the analytical results assuming weak selection hold,~~ and a neo-W ~~allele~~ can ~~only~~ invade even when it ~~arises at a locus more~~ is less tightly linked with the selected locus (~~$R < r$~~$r < R$; ~~shaded~~ unshaded region around *). In panel B, linkage is ~~tight~~ loose enough relative to selection that the analytical results assuming weak selection ~~do not~~ hold, and a neo-W allele can only invade ~~even~~ when it ~~is less~~ arises at a locus more tightly linked with the selected locus (~~$r < R$~~$R < r$; ~~unshaded~~ shaded region~~around *~~). In panel C we vary the recombination rate between the neo-W and the selected locus (R) for a fixed recombination rate between the ancestral sex-determining locus and the selected locus ($r = 0.005$). Coloured markers show recombination rates for which the temporal dynamics of invasion are plotted in the inset, demonstrating that neo-W alleles can reach pseudo-fixation if they are more (black) or less (red) closely linked to a locus experiencing sexually-antagonistic selection. A very loosely linked neo-W does not spread in this case (blue and green lines overlap and go to 0 in inset). Fitness parameters are: $w^{\female}_{AA} = 1.05$, $w^{\male}_{aa} = 1.2$, $w^{\female}_{aa} = w^{\male}_{AA} = 0.85$, ~~$w^{\female}_{Aa} = 1, t^{\male} = \alpha^{\female}_{\Delta} = 0$~~ $w^{\circ}_{Aa} = 1$.

~~If we categorise the a allele as being ancestrally 'male-beneficial' via the fact that it is fixed on Y backgrounds, then~~ The reason that neo-W-A haplotypes can spread ($\Lambda^{(XY)}_{W'A} > 1$~~indicates that the neo-W spreads when found with the ancestrally 'female-beneficial' allele~~) is because they can sometimes produce higher fitness females that are unleashed from counterselection in males. Broadly, this is possible because ancestral X alleles are ~~sometimes in males and~~ found in both males and females and are therefore unable to perfectly ~~specialise~~ specialize on the 'female-beneficial' allele. For example, when ~~the~~ A is female beneficial and a ~~allele is favoured on ancestral X backgrounds in males~~is male beneficial, a polymorphism ~~of A and a alleles~~ can be maintained on the X ~~background despite selection for~~ when the A allele ~~in females ($s^{\female} > 0$, $0 < h^{\female} < 1$), see outlined region in Fig 3A. When the a allele is strongly favoured on the X background~~ is strongly counterselected in males (~~$w^{\male}_{aa}$ sufficiently large relative to $w^{\male}_{Aa}$~~), ~~neo-W-A haplotypes can spread ($\Lambda^{(XY)}_{W'A} > 1$, see grey~~ $w^{\male}_{Aa}$ sufficiently small relative to $w^{\male}_{aa}$). Neo-Ws, however, spend no time in males and can build stronger associations with the female-beneficial allele (see gray region in Fig 3A)~~because they produce higher fitness females (AA or Aa genotypes) and are unleashed from counterselection in males~~.

~~When only one neo-W haplotype has growth rate greater than one (see Fig 3), a neo-W~~

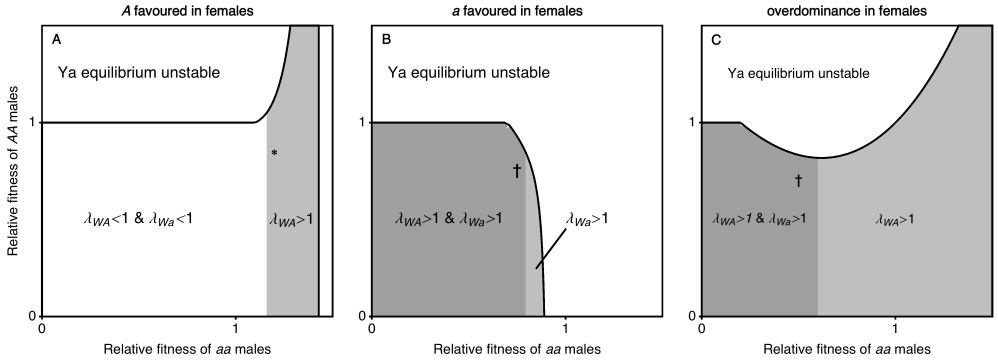

Fig 3. When the ancestral XY locus is tightly linked to a locus under selection ($r = 0$), one or both neo-W haplotypes can spread (no haploid selection). We vary the fitness of male homozygotes relative to heterozygotes (~~$w^{\male}_{Aa} = 1$~~$w^{\circ}_{Aa} = 1$) and only consider stable equilibria at which both **A** locus alleles are maintained and the *a* allele is initially fixed on the Y ~~backgrounds,~~ (region outlined). Here, selection in females can favour the *A* allele (panel A, $w^{\female}_{aa} = 0.85$, $w^{\female}_{AA} = 1.05$), favour the *a* allele (panel B, $w^{\female}_{aa} = 1.05$, $w^{\female}_{AA} = 0.85$), or be overdominant (panel C, $w^{\female}_{aa} = w^{\female}_{AA} = 0.6$). If either haplotypic growth rate ($\Lambda^{(XY)}_{W'A}$ or $\Lambda^{(XY)}_{W'a}$) is greater than one, then a rare neo-W allele can spread for, at least, some values of $R > r$. The parameter values marked with an asterisk correspond to the fitnesses used in Fig 2C. Where both haplotypic growth rates are greater than one, a neo-W will spread when rare, regardless of linkage with the selected locus (for any R). S1 Fig shows the dynamics arising with the parameters marked with a dagger. ~~Here, there is no haploid selection $t^{\male} = \alpha^{\male}_{\Delta} = 0$.~~

~~allele can invade as long as Eq is satisfied, which may require that the recombination rate, R, is small enough. Nevertheless, because we assume here that r is small, these results indicate that a more loosely linked sex-determining region ($r < R$) can spread. For example, tightly sex-linked loci that experience sexually-antagonistic selection can drive trans-GSD transitions in which the new sex-determining locus is less closely linked to the locus under selection (Fig 2).~~

Given that the *a* allele is fixed on the Y and can be considered ancestrally 'male-beneficial' ~~because it is fixed on Y backgrounds~~, it is surprising that neo-W-*a* haplotypes can sometimes be favoured by selection in females ($\Lambda^{(XY)}_{W'a} > 1$). Again, this occurs because ancestral X alleles ~~also~~ experience selection in ~~males, where they are ancestrally always paired with a Y~~ both males and females, and conditions can arise where increases in the *a* ~~gamete. If~~ allele would be favored in females too. For example, if there is overdominance in males, X-*A* Y-*a* males have high fitness and the *A* allele is favoured by selection on the X background in males. Therefore, the *A* allele can be polymorphic or even fixed on the X background despite selection favouring the *a* allele in females (e.g., see outlined region in Fig 3B and [69, 70]). In such cases, neo-W-*a* haplotypes can spread because they create more *Aa* and *aa* females when pairing with an X-bearing gamete from males and because they bring Y-*a* haplotypes into females, where it has higher fitness (Fig 1D).

When only one neo-W haplotype has growth rate greater than one (see Fig 3), a neo-W allele can invade as long as Eq (1) is satisfied, which may require that the recombination rate, R, is small enough. Nevertheless, because we assume here that r is small, these results indicate that a more loosely linked sex-determining region ($r < R$) can spread. For example, tightly sex-linked loci that experience sexually-antagonistic selection can drive trans-GSD transitions in which the new sex-determining locus is less closely linked to the locus under selection (Fig 2).

In some cases, both W-*A* and W-*a* haplotypes can spread. For example, when *AA*

individuals have low fitness in females yet the A is polymorphic or fixed on the X background due to overdominance in males (Fig 3B and 3C), both neo-W-A and neo-W-a haplotypes produce fewer unfit AA females. This is true for the neo-W-A haplotype because it can pair with a Y-a haplotype and still be female. Wherever both haplotypic growth rates are greater than one, invasion by a neo-W is expected regardless of its linkage with the selected locus (i.e., for any R, see S1 Fig and S2 Fig for examples). As a consequence, evolution can favor a new sex determination system on a different chromosome, despite the fact that this unlinks the sex-determining locus from the selected locus.

Assuming selection is weak relative to recombination, van Doorn and Kirkpatrick [32] showed that invasion by a neo-W allele occurs under the same conditions as ~~'pseudo-fixation' (at pseudo-fixation the neo-W reaches its maximum frequency among eggs, which is usually 1/2, but can deviate from 1/2 when there is haploid selection before censusing).~~ its fixation in females. An equivalent analysis is not possible where recombination rates are low. However, numerical simulations demonstrate that~~new sex-determining~~, with tight sex linkage, neo-Y or neo-W alleles do not necessarily reach ~~pseudo-fixation,~~ fixation in males or females, respectively, which can lead to the stable maintenance of a mixed sex-determining system, in which X, Y, ~~Z, and W~~ and neo-W alleles all segregate (e.g., S9 FigB,C).

From the arguments above and in S3 Appendix we conclude that

Conclusion 2A: **With tight linkage between a selected locus and the ancestral sex-determining locus ($r \approx 0$), trans-GSD transitions (XY ↔ ZW) can be driven by selection to better specialize on the ancestrally-non-heterogametic sex. These transitions weaken sex-linkage ($r < R$), potentially shifting sex determination to a different chromosome ($R = 1/2$). Such transitions can lead to polymorphic sex-determination systems.** [consistent with special case of Kozielska et al 2010]

S3 Appendix shows that Conclusion 2A holds with or without haploid selection and further demonstrates that

Conclusion 2B: **With tight linkage between a haploid selected locus and the ancestral sex-determining locus ($r \approx 0$), trans-GSD transitions (XY ↔ ZW) can be driven by selection to better specialize on the ancestrally-non-heterogametic sex and/or sex-ratio selection. Such transitions reduce sex ratio bias.**
[consistent with special case of Kozielska et al 2010]

Loose linkage with the ancestral sex-determining region

Here we assume that selection is weak (~~$s^{\male}, t^{\male}, \alpha_{\Delta}^{\male}$ of order $\epsilon << 1$~~$s^{\circ}, t^{\circ}, \alpha_{\Delta}^{\circ}$ of order ϵ, where ϵ is some number much less than one) and thus implicitly assume that all recombination rates (r, R and ρ) are large relative to selection. To leading order in selection, ~~the leading eigenvalues are:~~

$$\lambda_{Y'}^{(XY)} = 1 + \frac{1}{4} V_A S_A^2 \frac{(r-R)}{rR} + O\left(\epsilon^3\right) \tag{2}$$

and

$$\lambda_{W'}^{(XY)} = \lambda_{Y'}^{(XY)} + \left[\left(2\alpha_{\Delta}^{\male} - 2\alpha_{\Delta}^{\female} + t^{\male} - t^{\female}\right)\left(\hat{p}_Y^{\male} - \hat{p}_X^{\male}\right)/2\right] + O\left(\epsilon^3\right) \tag{3}$$

where $V_A = \bar{p}(1-\bar{p})$ is the variance in the equilibrium frequency of A and ~~$S_A = (D^{\male} + \alpha_{\Delta}^{\male} + t^{\male}) - (D^{\female} + \alpha_{\Delta}^{\female} + t^{\female})$~~ $S_A = (\bar{s}^{\male} + \alpha_{\Delta}^{\male} + t^{\male}) - (\bar{s}^{\female} + \alpha_{\Delta}^{\female} + t^{\female})$ describes sex differences in selection for the A versus a allele across diploid selection, meiosis, and gametic competition. The diploid selection term,

~~$D^{\mathcal{\delta}} = \left[\bar{p}s^{\mathcal{\delta}} + (1-\bar{p})h^{\mathcal{\delta}}s^{\mathcal{\delta}}\right] - \left[\bar{p}h^{\mathcal{\delta}}s^{\mathcal{\delta}} + (1-\bar{p})\right]\bar{s}^{\circ} = \left[\bar{p}s^{\circ} + (1-\bar{p})h^{\circ}s^{\circ}\right] - \left[\bar{p}h^{\circ}s^{\circ} + (1-\bar{p})\right]$~~, is the difference in fitness between A and a alleles in diploids of sex ~~$\mathcal{\delta} \in \{\mathcal{\varphi}, \mathcal{\delta}\}$~~ $\circ \in \{\mathcal{\varphi}, \mathcal{\delta}\}$, where $\bar{p}$ is the leading-order probability of mating with an ~~A-bearing~~ A-bearing gamete from the opposite sex (equation S2.3) ~~. The~~ and the difference in A-allele-frequency among Y-bearing sperm versus X-bearing sperm is~~given by~~

~~$\hat{p}_Y^{\mathcal{\delta}} - \hat{p}_X^{\mathcal{\delta}} = V_A\left(D^{\mathcal{\delta}} - D^{\mathcal{\varphi}} + \alpha_\Delta^{\mathcal{\delta}} - \alpha_\Delta^{\mathcal{\varphi}} + t^{\mathcal{\delta}} - t^{\mathcal{\varphi}}\right)(1-2r)/(2r)$~~, at equilibrium,

$\hat{p}_Y^{\mathcal{\delta}} - \hat{p}_X^{\mathcal{\delta}} = V_A S_A (1-2r)/(2r)$.

Eq (2) demonstrates that, under weak selection, a neo-Y allele will invade an XY system ($\lambda_{Y'}^{(XY)} > 1$) if and only if it is more closely linked to the selected locus than the ancestral sex-determining locus (i.e., if $R < r$; note that $V_A S_A^2$ is strictly positive as long as **A** is polymorphic). This echoes our results above where a neo-Y could never invade if $r \approx 0$. It is also consistent with the results of [31], who considered diploid selection only and also found that cis-GSD transitions can only occur when the new sex-determining locus is more closely linked to a locus under sexually-antagonistic selection.

~~With weak selection and no~~ When selection is weak relative to recombination, the absence of haploid selection (~~$t^{\mathcal{\delta}} = \alpha_\Delta^{\mathcal{\delta}} = 0$~~), $t^{\circ} = \alpha_\Delta^{\circ} = 0$), implies that the spread of a neo-W is equivalent to the spread of a neo-Y ($\lambda_{W'}^{(XY)} = \lambda_{Y'}^{(XY)}$), such that trans-GSD transitions can also occur only if the new sex-determining locus is more closely linked to a locus under selection ($R < r$), as found by [32]. When there is haploid selection, invasion also typically occurs when the neo-W is more closely linked to the selected locus than the ancestral sex-determining region (Fig 4). For example, if the **A** locus is unlinked to the ancestral sex-determining locus ($r = 1/2$, which implies that $\hat{p}_Y^{\mathcal{\delta}} - \hat{p}_X^{\mathcal{\delta}} = 0$), a more closely linked neo-W ($R < 1/2$) can always invade. ~~In this case, there is no ancestral association between **A** alleles and sex chromosomes in males, $\left(\hat{p}_Y^{\mathcal{\delta}} - \hat{p}_X^{\mathcal{\delta}}\right) = 0$, see Eq . The second term in Eq therefore disappears and invasion depends only on the sign of $(r - R)$.~~

~~Ploidally-antagonistic selection allows a less tightly linked neo-W allele to invade.In panel A, male drive ($\alpha_\Delta^{\mathcal{\delta}} = -1/20, t^{\mathcal{\delta}} = \alpha_\Delta^{\mathcal{\varphi}} = 0$) opposes selection in diploids (no sex-differences: $s^{\mathcal{\delta}} = 1/10, h^{\mathcal{\delta}} = 7/10$), in which case the new sex-determining allele can invade regardless of its linkage with the selected locus (R). In panel B, gametic competition in males ($t^{\mathcal{\delta}} = -1/10, t^{\mathcal{\varphi}} = \alpha_\Delta^{\mathcal{\delta}} = 0$) opposes selection in diploids (sex-differences: $s^{\mathcal{\delta}} = 3/20, s^{\mathcal{\varphi}} = 1/20, h^{\mathcal{\delta}} = 7/10$), in which case the new sex-determining allele can once again invade regardless of R.~~

However, with haploid selection and some ancestral sex-linkage ($r < 1/2$~~, the additional term in~~ ; allowing allele frequency differences on the X and Y), the term in square brackets in Eq (3) can be positive. This ~~can allow neo-W invasion ($\lambda_{W'}^{(XY)} > 1$), even when the new sex-determining locus is less closely linked to the selected locus ($R > r$).~~ implies the following two conclusions:

Conclusion 3A: **New sex-determining alleles (causing cis- *or* trans-GSD transitions) can spread if they arise more closely linked with a locus that experiences selection than the ancestral-sex-determining locus is ($R < r$).**
[consistent with van Doorn & Kirkpatrick 2007, 2010]

Conclusion 3B: **New sex-determining alleles (causing trans-GSD transitions, XY ↔ ZW) can spread even if they arise less closely linked with a locus that experiences selection than the ancestral-sex-determining locus is ($r < R$), requiring haploid selection and some initial sex-linkage ($r < 1/2$).** [consistent with examples in Ubeda et al 2015]

To clarify the parameter space under which invasion occurs ~~despite looser sex-linkage~~ with weak selection ($\lambda_{W'}^{(XY)} > 1$~~despite $R > r$~~), we focus on ~~the special case where $R = 1/2$ and~~

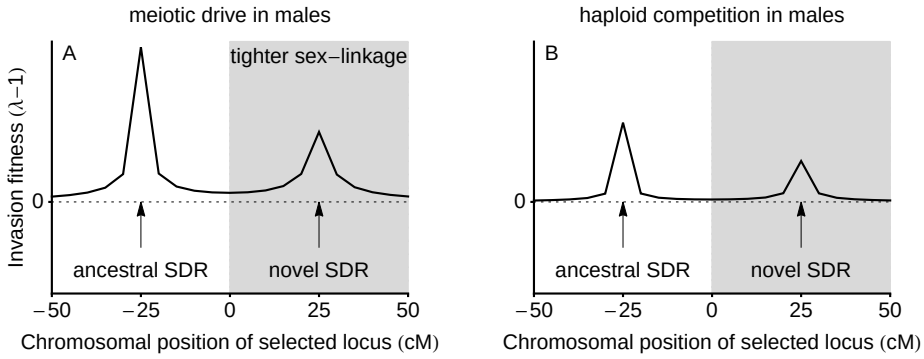

Fig 4. Ploidally-antagonistic selection allows a less tightly linked neo-W allele to invade. In panel A, male drive ($\alpha_{\Delta}^{\male} = -1/20$, $t^{\circ} = \alpha_{\Delta}^{\female} = 0$) opposes selection in diploids (no sex-differences: $s^{\circ} = 1/10$, $h^{\circ} = 7/10$). In panel B, gametic competition in males ($t^{\male} = -1/10$, $t^{\female} = \alpha_{\Delta}^{\circ} = 0$) opposes selection in diploids (sex-differences: $s^{\male} = 3/20$, $s^{\female} = 1/20$, $h^{\circ} = 7/10$). In either case the new sex-determining allele can invade regardless of R.

~~$r < 1/2$ (e.g., the selected locus is on the ancestral sex chromosome and the novel sex-determining locus arises on an autosome). In Table 3 we give the conditions where invasion occurs when we further assume that~~ cases where dominance coefficients are equal in the two sexes, $h^{\female} = h^{\male}$, and haploid selection only occurs in one sex (e.g., during male meiosis only)~~and dominance coefficients are equal in the two sexes, $h^{\female} = h^{\male}$. When there is no gametic competition and meiotic drive is in one sex only, an unlinked neo-W can invade as long as the same allele is favoured during diploid selection in males and females ($s^{\female}s^{\male} > 0$, see Fig 4A and Fig 5B)~~. ~~When there is no meiotic drive and gametic competition occurs in one sex only, an unlinked~~ Table 3 then gives the conditions required for unlinked ($R = 1/2$) neo-W ~~can invade as long as the same allele is favoured in male and female diploid selection and there are sex differences in selection of one type (~~invasion when there is some ancestral sex-linkage ($r < 1/2$; e.g., ~~$s^{\female}(s^{\male} - s^{\female}) > 0$, see Fig 4B).~~ the selected locus is on the ancestral sex chromosome and the novel sex-determining locus arises on an autosome). These special cases indicate that neo-W invasion occurs for a ~~relatively~~ large fraction of the parameter space, even ~~if~~ though the neo-W uncouples the sex-determining locus from a locus under selection. Fig 4 then demonstrates that under these conditions neo-W alleles can spread when they are more loosely *or* more closely linked to the locus that experiences haploid selection (c.f., Fig 2A for diploid sexually-antagonistic selection alone).

Table 3. Invasion conditions for a neo-W allele at an unlinked locus ($R = 1/2$) into an ancestral XY system with linkage ($r < 1/2$) and ~~one~~ a single form of haploid selection

Scenario	Assumptions	neo-W spreads ($\lambda_{W'}^{(XY)} > 1$) if
male drive only	$h^{\male} = h^{\female}$, $t^{\female} = t^{\male} = \alpha_{\Delta}^{\female} = 0$	$s^{\female}s^{\male} > 0$
female drive only	$h^{\male} = h^{\female}$, $t^{\female} = t^{\male} = \alpha_{\Delta}^{\male} = 0$	$s^{\female}s^{\male} > 0$
~~sperm~~ male gametic competition only	$h^{\male} = h^{\female}$, $t^{\female} = \alpha_{\Delta}^{\female} = \alpha_{\Delta}^{\male} = 0$	$s^{\female}(s^{\male} - s^{\female}) > 0$
~~egg~~ female gametic competition only	$h^{\male} = h^{\female}$, $t^{\male} = \alpha_{\Delta}^{\female} = \alpha_{\Delta}^{\male} = 0$	$s^{\male}(s^{\female} - s^{\male}) > 0$

~~Fisherian sex ratio selection alone is not a good predictor of turnover between~~

~~sex-determining systems.In this figure, selection is ploidally antagonistic with haploid selection favouring the *a* allele during male meiosis. In panel A, male meiotic drive in an ancestral XY system causes a male bias (see Fig 1B), allowing a neo-W to invade and replace the ancestral sex-determining system (inset shows neo-W frequency among female gametes, reaching pseudo-fixation), which balances the zygotic sex ratio. In panel B, male drive in an ancestral ZW system has no effect on the zygotic sex ratio yet a neo-Y can invade and replace the ancestral sex-determining system (inset shows neo-Y frequency among male gametes, reaching pseudo-fixation). Parameters: $s^{♀} = s^{♂} = 0.2$, $h^{♀} = h^{♂} = 0.7$, $t^{♀} = t^{♂} = \alpha_{\Delta}^{♀} = 0$, $\alpha_{\Delta}^{♂} = -0.1$, $r = 0.02$.~~

~~Previous research suggests that when the ancestral sex-determining locus is linked to a locus that experiences haploid selection (e.g., meiotic drive), alleles at a new, unlinked sex-determining locus invade to restore equalsex ratios [41]. Consider, for example, the case where the **A** locus is linked to the ancestral sex-determining locus ($r < 1/2$) and experiences~~ We can also compare transitions in genetic sex-determination where sex-ratio bias increases, decreases, or remains equal. For example, if there is meiotic drive in males only ($\alpha_{\Delta}^{♂} \neq 0$, $\alpha_{\Delta}^{♀} = 0$), without gametic competition ($t^{♀} = t^{♂} = 0$) ~~. In this case,~~ the zygotic sex ratio ~~can be~~ is initially biased only ~~if~~ when the ancestral sex-determining system is XY (Fig 1A and Fig 5A) and not ZW (Fig 5B). If Fisherian ~~sex ratio~~ sex-ratio selection were dominant, we would thus expect a difference in the potential for XY to ZW and ZW to XY transitions. However, invasion by a neo-W allele into an XY system and invasion by a neo-Y allele into a ZW system occur under the same conditions ($\lambda_{Y'}^{(XY)} = \lambda_{W'}^{(ZW)}$ and $\lambda_{W'}^{(XY)} = \lambda_{Y'}^{(ZW)}$, at least to order ϵ^2)~~.~~, implying that,

Conclusion 4A: **When selection is weak relative to recombination, the presence of haploid selection equally favors the spread of new sex determination systems that reduce sex-ratio bias (benefiting from Fisherian sex ratio selection) or generate a sex-ratio bias (benefiting from associations with selected alleles).** [new result]

For example, in Fig 5A neo-W alleles invade an ancestral-XY system where females are initially rare, equalizing the sex ratio (as occurs in [41]). However, Fig 5B shows that a neo-Y can invade the resulting ZW system under the same conditions. When $R < 1/2$, the invading neo-Y becomes associated with the male meiotic drive allele and the zygotic sex ratio actually evolves to become male-biased (as occurs in [42], beginning from ESD). In this case, the neo-Y spreads because it is often found in males and can, if it carries the driven allele a, benefit from haploid selection in males (Fig 5B).

While equalizing the sex ratio and benefiting from ~~drive~~ associations with selected alleles are two primary reasons why haploid selection spurs sex chromosome transitions, more complex situations also arise. For example with $R = 1/2$ in Fig 5B (green curve), the neo-Y allele spreads despite the fact that it cannot benefit from drive because free recombination moves it randomly between driven and non-driven backgrounds. Nevertheless, the unlinked neo-Y can spread because ~~diploids~~ males bearing it more often carry the non-driven allele A ~~, which is found at high frequency on the W background and has~~ and have higher average diploid fitness ~~.~~compared to ZZ males, which bear a high frequency of the driven allele (since $r < R$).

Environmental sex determination

We next consider the case where the new sex-determining ~~mutation~~allele, m, causes sex to be determined probabilistically or by heterogeneous environmental conditions (environmental sex determination, ESD)~~, with~~ . In particular, we assume individuals carrying allele m ~~developing~~ develop as females with probability ~~k~~$k \in (0, 1)$. ~~Here, we do not~~ In our deterministic model this means the fraction female in the subpopulation containing m is exactly k, even when m is rare (i.e., ESD does not introduce any additional variance in sex determination). We also

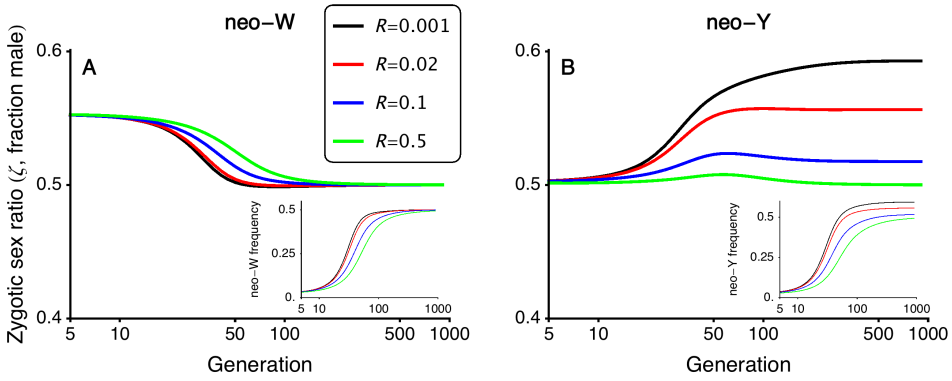

Fig 5. Fisherian sex-ratio selection alone is not a good predictor of turnover between sex-determining systems. In this figure, selection is ploidally antagonistic with haploid selection favouring the *a* allele during male meiosis. In panel A, male meiotic drive in an ancestral XY system causes a male bias (see Fig 1B), allowing a neo-W to invade and replace the ancestral sex-determining system (inset shows neo-W frequency rising to fixation among female gametes), which balances the zygotic sex ratio. In panel B, male drive in an ancestral ZW system has no effect on the zygotic sex ratio yet a neo-Y can invade and replace the ancestral sex-determining system (inset shows neo-Y frequency rising to fixation among male gametes). Parameters: $s^{\varphi} = s^{\sigma} = 0.2$, $h^{\varphi} = h^{\sigma} = 0.7$, $t^{\varphi} = t^{\sigma} = \alpha_{\Delta}^{\varphi} = 0$, $\alpha_{\Delta}^{\sigma} = -0.1$, $r = 0.02$.

assume that the environmental conditions that determine sex ~~also~~ do not differentially affect the fitness of males versus females. Such correlations can favour environmental sex-determining systems by allowing each sex to be produced in the environment in which it has highest fitness; in the absence of these correlations ~~,~~previous theory would predict that ESD is favoured when it produces more equal sex ratios than the ancestral system (see reviews by [1, 35, 36]).

The characteristic polynomial determining the leading eigenvalue (equations S1.1) does not factor for ESD ($0 < k < 1$) as it does for a neo-Y ($k = 0$) or neo-W ($k = 1$) allele. We therefore focus on weak selection here, where the leading eigenvalue is

$$\lambda_{ESD'}^{(XY)} = 1 + \frac{(1-2k)^2}{4} V_A {S_A}^2 \frac{r-R}{rR} + \frac{k(\hat{p}_Y^{\sigma} - \hat{p}_X^{\sigma})}{2} \left[k\left(2\alpha_{\Delta}^{\sigma} - 2\alpha_{\Delta}^{\varphi} + t^{\sigma} - t^{\varphi}\right) - 2(1-k)S_A \right] + O\left(\epsilon^3\right). \quad (4)$$

This reduces to $\lambda_{Y'}^{(XY)}$ when $k = 0$ and $\lambda_{W'}^{(XY)}$ when $k = 1$.

Of particular interest are ESD mutations that cause half of their carriers to develop as females and half as males ($k = 1/2$), creating equal sex ratios. The spread of such ~~ESD~~ mutations is determined by

$$\lambda_{ESD'}^{(XY)} = 1 + \frac{1}{2} \frac{(\lambda_{Y'|R=1/2}^{(XY)} - 1) + (\lambda_{W'|R=1/2}^{(XY)} - 1)}{2} + O\left(\epsilon^3\right), \quad (5)$$

where $\lambda_{Y'|R=1/2}^{(XY)}$ and $\lambda_{W'|R=1/2}^{(XY)}$ represent $\lambda_{Y'}^{(XY)}$ and $\lambda_{W'}^{(XY)}$ when evaluated at $R = 1/2$ (Equations 2 and 3). That is, recombination between the selected locus and the novel sex-determining locus, R, does not enter into the $k = 1/2$ results. This is because sex is essentially randomized each generation, preventing associations from building up between

alleles at locus **A** and sex. Eq (5) shows that the ESD mutation gets half of the fitness of a feminizing mutation (neo-W) and half of the fitness of a masculinizing mutation (neo-Y), but only has an effect one half of the time (the other half of the time it produces the same sex as the ancestral system would have). As discussed above, $\lambda^{(XY)}_{Y'|R=1/2}$ is necessarily less than one (cis-GSD transition), but $\lambda^{(XY)}_{W'|R=1/2}$ (trans-GSD transition) can be greater than one if there is haploid selection (see Conclusion 3B). That is, ~~when there is~~ with haploid selection, ~~ESD~~ an allele causing environmental-sex-determination can invade an ancestrally-XY system because it generates females that are either rare or have high fitness, in the same manner as a neo-W ~~.~~ (likewise, ESD invades a ZW system for the same reasons a neo-Y can).

Significantly, Eq (5) is the same whether ESD is invading an ancestrally XY or ZW system (because $\lambda^{(XY)}_{Y'} = \lambda^{(ZW)}_{W'}$ and $\lambda^{(XY)}_{W'} = \lambda^{(ZW)}_{Y'}$). Thus, ~~Fisherian sex ratio selection alone does not easily~~ focusing solely on Fisherian selection to equalize the sex-ratio does not fully explain GSD to ESD transitions. For example, when the ancestral sex-determining system is XY ~~, but not ZW,~~ the sex ratio is biased by male haploid selection. When the ancestral sex-determining system is ZW the sex ratio is not biased. Nevertheless, ESD is equally likely to invade ~~when it equalizes the zygotic sex ratio~~ both XY (through $\lambda^{(XY)}_{W'}$) ~~as when it doesn't~~ and ZW (through $\lambda^{(ZW)}_{Y'}$) ~~.~~ systems, equalizing the zygotic sex ratio in the former case but not in the latter. In addition, we note that ESD may not invade, even if the sex ratio is initially biased (e.g., with drive in males only, $r < 1/2$, $h^{♀} = h^{♂}$, and $s^{♀}s^{♂} < 0$, then $\lambda^{(XY)}_{W'} < 1$, see Table 3). We conclude that, as with neo-W and neo-Y ~~loci, associations with selected loci mean that the evolution of ESD is not straightforwardly predicted by selection to balance the zygotic sex ratio when haploid selection is present.~~ mutations:

~~Discussion~~

Conclusion 4B: **Transitions from genetic to environmental sex-determination are not straightforwardly predicted by selection to balance the zygotic sex ratio when haploid selection is present.** [new result]

~~Two predominant theories explaining the remarkably high frequency of transitions between sex-determining systems are sexually-antagonistic selection and sex ratio selection (reviewed in [29,30]). The former predicts that new sex-determining alleles can invade when they arise in closer linkage with a sexually-antagonistic locus ($r < R$, [31–33]). The latter predicts that new sex-determining systems are generally favoured if they result in more equal sex ratios than the ancestral system. In contrast to these prevailing views, we show that selection (including sexually-antagonistic selection, overdominance, and~~

Discussion

New sex-determination systems are typically expected to spread when they equalise the sex ratio and/~~or ploidally-antagonistic selection) on loci tightly linked to the ancestral sex-determining locus~~ or when they increase linkage with loci that experience sex-differences in selection [29,30]. In accordance with the latter mechanism, we find that sex-differences in selection at the haploid stage can favour trans-GSD transitions ~~(XY ↔ ZW) to new sex-determining systems that are less closely linked to the selected loci (e.g., see Fig 2). Similarly, even when linkage is weak relative to selection, we show that~~ that tighten sex-linkage (Conclusion 3A). However, we also find that trans-GSD transitions can ~~occur where the new~~ be favoured in cases where linkage with the sex-determining locus is ~~less closely linked to the locus under selection if~~ actually weakened (Conclusions 2A, 2B & 3B, Fig 2 & 3), especially when there is haploid selection (~~e.g.~~ Conclusion 3B, Figs 4 ~~and~~ & 5).

~~We find~~ Furthermore, we show that the spread of new ~~sex-determining systems cannot be simply predicted from their effect on~~ sex-determination systems is not dominated by selection to balance the sex ratio ~~.~~ (Conclusions 4A & 4B, Fig 5).

On one hand, ~~sex ratio~~ sex-ratio biases caused by haploid selection can facilitate trans-GSD transitions or transitions from genetic to environmental sex determination [41]. For instance, alleles favoured by haploid selection in males often become associated with the Y allele, which leads to ~~a~~ an ancestral male-biased zygotic sex ratio. This male bias increases the potential for a neo-W or ESD allele to invade (Table 2), which can equalize the sex ratio (e.g., see Fig 5B, for related examples see [41]). On the other hand, ~~sex ratio~~ sex-ratio selection can be overwhelmed by additional selective effects, preventing a neo-W or ESD allele from invading, even if it would balance the sex ratio (e.g., when selection also acts in opposite directions in male and female diploids, Table 3). Indeed, transitions between sex-determining systems can generate stronger ~~sex ratio~~ sex-ratio biases (e.g., Fig 5A and step 1 in [42]). Significantly, with weak selection, we find that there is no difference in conditions allowing XY to ZW and ZW to XY transitions ~~,~~ ~~indicating that sex chromosome transitions are not predominantly predicted by their effect on the sex ratio (i.e., the sex ratio~~ (Conclusion 4A) even when haploid selection always acts in the same sex (e.g., males). That is, the sex-ratio bias created by male haploid selection facilitates the spread of a neo-W allele into an XY system to the same degree that male haploid selection drives the spread of a neo-Y into a ZW system with a 1:1 sex ratio~~). Thus, haploid selection can favour trans-GSD transitions both via sex ratio selection~~ .

Because both Fisherian selection to equalize the sex ratio and the benefits of hitchhiking with driven alleles can facilitate transitions among sex chromosome systems, we predict that haploid selection should increase the lability of sex determination systems. Even in animal and plant species that have much larger and more conspicuous diploid phases than haploid phases, many loci have been shown to experience haploid selection through gamete competition and/or meiotic drive [37–40, 44–49]. In some cases, meiotic drive (Burt and Trivers, 2006, Chapter 6 [61]) or gametic competition [62–67] among X- and ~~via selection on alleles associated with the new sex-determining allele, and these selective pressures are often predicted to be of equal magnitude.~~ Y-bearing gametes is known to cause sex-ratio biases. In animals, recent studies have demonstrated that sperm competition, even within a single ejaculate, can alter haploid allele frequencies and increase offspring fitness [59, 60]. Although precise estimates are uncertain, a relatively small proportion of all genes are thought to be expressed and selected during competition in animal sperm [38, 57, 58]. However, expression is not required for haploid selection if the fitness of a gamete depends on its ability to condense DNA [**?**]. In plants haploid selection may be particularly important. For example, 60-70% of all genes are expressed in the male gametophyte, and these genes exhibit stronger signatures of selection than randomly-chosen genes [50–52]. Furthermore, artificial selection pressures applied to male gametophytes are known to cause a response to selection (e.g., [53–56]).

~~We have shown that the spread of new sex-determining systems can be driven by loci experiencing haploid selection . In agreement with this hypothesis~~Linking haploid expression with the evolution of sex-determination, a recent transcriptome analysis in ~~Rumex~~ *Rumex* shows that pollen-biased expression (relative to expression in flower buds or leaves) is enhanced among XY-linked genes compared to autosomal genes or compared to hemizygous genes that are only linked to the X ~~(Sandler et al. , 2018, personal communication).~~ [**?**]. In addition, Y-linked genes are over-expressed relative to X-linked genes in pollen (but not in flower buds or leaves). This suggests that the spread of neo-Y chromosomes in this clade could have been favoured through linkage with haploid selected genes rather than those under sexual antagonism. ~~In general, we predict that haploid selection increases lability of sex-determining systems, particularly because haploid selection can cause transitions that increase or decrease sex-linkage (e.g., the final state of the red line in Fig 5B is the starting state in Fig 5A).~~

Frequent turnovers driven by haploid selection may help to explain the relative rarity of heteromorphic sex chromosomes in plants~~, which are thought to experience more selection~~

~~during their multicellular haploid stage.~~

. If haploid selection is strong but selective differences between male and female diploids are weak, we ~~find~~ specifically predict that trans-GSD transitions are favoured more strongly than cis-GSD transitions, with transitions to ESD intermediate (e.g., with $|D^{\sigma} - D^{\varphi}| << |\alpha_{\Delta}^{\sigma} - \alpha_{\Delta}^{\varphi} + \iota^{\sigma} - \iota^{\varphi}| |\bar{s}^{\sigma} - \bar{s}^{\varphi}| << |\alpha_{\Delta}^{\sigma} - \alpha_{\Delta}^{\varphi} + \iota^{\sigma} - \iota^{\varphi}|$ we have $\lambda_{W'}^{(XY)} > \lambda_{Y'}^{(XY)}$; ~~Eqs 3and S2.4~~Eq 3). Among the relatively few dioecious clades in which multiple species have well characterized sex chromosomes [5], trans-GSD transitions have been inferred in *Silene* subsection *Otites* [14] and in *Salicaceae* [15, 16]. Assuming that transitions from dioecy to hermaphroditism (equal parental investment in male and female gametes) are favoured in a similar manner to the ESD examined here (equal probability of zygotes developing as males or females), our results suggest that competition ~~during the haploid stage could also~~ among haploid pollen could drive transitions between dioecy and hermaphroditism, which are frequent in plants [71, 72].

~~In support of their role in sex chromosome turnover, genes expected to be under sexually-antagonistic selection~~To further examine this link, future theory could simultaneously include inbreeding, haploid selection, and sex chromosomes when investigating transitions between dioecy and hermaphroditism. Future empirical studies could look for evidence of haploid selection acting on former sex chromosomes in hermaphroditic species (e.g., ~~those causing bright male colouration)have been found~~ a study such as [?] on ancestral, rather than derived, sex chromosomes).

New sex-determining alleles have previously been shown to spread when they arise in linkage with loci that experience sex differences in selection because beneficial associations build up between alleles that determine sex and alleles that are favoured in that sex [31–33, 42]. In support of this hypothesis, researchers have identified genes on recently derived sex chromosomes that might be under sexually-antagonistic selection [20, 73, 74]. ~~Our results show, however, thattight ancestral linkage of polymorphic loci , maintained by sexually-antagonistic selection or otherwise, can also~~ However, we show that, if selected loci are tightly linked to the ancestral sex-determining locus, they can drive trans-GSD transitions which reduce sex-linkage (Conclusions 2A, 2B, & 3B), thus widening the range of genomic locations that could be driving observed trans-GSD transitions. In addition, we find that polymorphic sex determining systems (X, Y, ~~W, and Z alleles all present~~and neo-W alleles all segregating) can be maintained when a selected locus is tightly linked to the ancestral sex-determining system (e.g., S9 FigB and S9 FigC), which is not possible with loose linkage [32]. These conclusions apply in cases with or without haploid selection.

Our tight linkage result, in particular the prediction that invasion can lead to polymorphic sex determination, is consistent with empirical data from species in which new feminizing mutations are found segregating with ancestral XY loci. For example, ~~our results suggest a potential mechanism maintaining multiple sex determining alleles~~ in the platyfish (*Xiphophorus maculatus*), ~~in which~~ X,Y, and W alleles segregate at one locus (or two closely-linked loci) near to potentially sexually-antagonistic genes for pigmentation and sexual maturity [75–78]. ~~Several rodent species also maintain~~ Furthermore, several rodent species maintain dominant? feminizing alleles along with the ancestral X and Y sex-determination alleles (reviewed in [79]). ~~For example, in~~ In nine *Akadon* rodent species, it appears that male-determining-*sry* expression is suppressed by an autosomal feminizing allele (a neo-W allele), creating XY females [80, 81]~~, which~~ . XY females have increased fitness relative to XX females [82]. ~~In *Mus microtoides*,~~ However, it is not yet clear whether loci linked to the feminizing factor or the ancestral Y cause this effect. Most convincingly, in *Mus minutoides*, females can have XX, XX^* or X^*Y genotypes [83]. Previous theory would predict that the dominant X^* chromosome (~~or the autosome it is fused to~~potentially an autosome that has fused with the sex chromosome) harbours female beneficial alleles, driving its spread. However, XX and XX^* females have similar fitness, whereas X^*Y female fitness is enhanced [84–86]. Although Y-linkage of female-beneficial alleles is counterintuitive, our model suggests that it can be stably maintained

and then favour when linkage is initially tight between the sex determining region and the selected locus, subsequently favoring new feminizing mutations, which is would be a parsimonious explanation for the spread of feminizing alleles in these rodent speciesthis case.

We note that we Our models assume that sex-determining alleles do not experience direct selection except via their associations with sex and selected alleles. However, in some cases, there may be significant degeneration around the sex-limited allele (Y or W) in the ancestral sex-determining region because recessive deleterious mutations and/or deletions accumulate in this the surrounding non-recombining regions [87–90]. During trans-GSD transitions, but not cis-GSD transitions, any recessive deleterious alleles linked to the Y or W are revealed to selection in YY or WW individuals [4]. This phenomenon was studied by van Doorn and Kirkpatrick (2010) [32], who found that degeneration can prevent fixation of a neo-W or a neo-Y allele, leading to a mixed sex-determining system where the ancestral and new sex-determining loci are both segregating. However, they noted that very rare recombination events around the ancestral sex-determining locus can allow these the completion of trans-GSD transitionsto complete. Degeneration around the Y or W could explain why trans-GSD transitions are not observed to be much more common than cis-GSD transitions (citation?) despite the fact that our models demonstrate that they are favoured under a wider range of conditions, especially with haploid selection. For example, there are a dozen sex chromosome configurations among Dipteran species but only one transition between male and female heterogamety [8], but Y degeneration or absence is also very common among *Diptera* [8].

In this study, we have only considered new sex-determining alleles of large effect. However, we expect similar selective forces to act on masculinizing/feminizing alleles of weaker effect. For example, small effect masculinizing/feminizing alleles within a threshold model of sex determination can be favoured when linked to loci that experience sexually-antagonistic selection [33]. These results echo those for large-effect neo-Y/neo-W alleles [31, 32]. Finally, while we have considered cis-GSD, trans-GSD, and GSD to ESD transitions, we have not explicitly considered ESD to GSD transitions. Recent models of ESD to GSD transitions [33, 42] show that It should be noted, however, that neo-Y/neo-W alleles can be favoured when they arise near to haploid and/or diploid selected loci, which also occurs in our modelthe dynamics of sex-determining alleles with very weak effect will be influenced by genetic drift, which itself has been shown to bias transitions towards epistatically-dominant sex-determining systems when there is no selection [91].

Conclusion

We have shown that tight sex-linkage and haploid selection can drive previously unexpected transitions between sex-determining systems. In particular, both can select for new sex-determining loci that are more loosely linked to loci under selection (Conclusions 2A, 2B & 3B). In addition, haploid selection can cause transitions in GSD analogous to those caused by purely sexually-antagonistic selection, eliminating the need for differences in selection between male and female diploids (Conclusion 2B & 3B). We conclude that haploid selection should be considered as a pivotal factor driving transitions between sex-determining systems. Perhaps counterintuitivelyFurther, transitions involving haploid selection can be driven by sex ratio sex-ratio selection or cause sex ratio sex-ratio biases to evolve; we do not find Fisherian sex ratio selection to be an overwhelming forceto leading order, selection to balance the sex ratio and the benefits of hitch-hiking with haploid selected alleles are of equal magnitude (Conclusions 4A & 4B). Overall, our results suggest several new scenarios under which new sex-determining systems are favoured, which could help to explain why the evolution of sex-determining systems is so dynamic.

Supporting information

S1 File. Supplementary *Mathematica* file. This file can be used to re-derive our results and generate figures.

S1 Table Substitutions for different loci orders assuming no interference.

S2 Table Mean fitnesses and zygotic sex ratio in the resident population (M fixed, XY sex determination).

S1 Appendix. Recursion equations and complete model description.

S2 Appendix. Equilibria and stability conditions when M allele is fixed.

S3 Appendix. Invasion conditions for the m allele.

S1 Fig. With overdominance, loci near to the ancestral sex-determining locus ($r \approx 0$) can favour neo-W alleles that are less tightly linked ($R > r$). In panels A and B, the a allele is favoured in females ($w^{\varphi}_{aa} = 1.05$, ~~$w^{\sigma}_{Aa} = 1$~~ $w^{\circ}_{Aa} = 1$, $w^{\varphi}_{AA} = 0.85$) and selection in males is overdominant ($w^{\sigma}_{aa} = w^{\sigma}_{AA} = 0.75$). In panels C and D, selection in males and females is overdominant ($w^{\varphi}_{aa} = w^{\varphi}_{AA} = 0.6$, $w^{\sigma}_{aa} = 0.5$, $w^{\sigma}_{AA} = 0.7$, ~~$w^{\varphi}_{Aa} = 1$~~ $w^{\circ}_{Aa} = 1$). There is no haploid selection ~~$t^{\sigma} = \alpha^{\varphi}_{\Delta} = 0$~~ $t^{\circ} = \alpha^{\circ}_{\Delta} = 0$. These parameters are marked by daggers in Fig 3B and C, which show that neo-W invasion is expected for any R ($\Lambda^{(XY)}_{W'A}, \Lambda^{(XY)}_{W'a} > 1$) if the a allele is nearly fixed on the Y (black lines in this figure; not stable for $r >> 0$). Equilibria where the A allele is more common among Y-bearing male gametes can also be stable and allow neo-W invasion for these parameters (blue lines).

S2 Fig. Following invasion by a neo-W allele, there can be a complete transition to a new sex-determining system, maintenance of both ancestral-XY and neo-ZW sex determining systems, or loss of the new sex-determining allele. Here, we plot the frequency of the neo-W allele among female gametes. Panels A, C and D show cases where a steady state is reached with the neo-W at a frequency below 0.5, in which case ancestral-X and Y alleles also both segregate. In all cases, we assume that the a allele is initially more common than the A allele on the Y background (Y-a is fixed when $r = 0$). When $r > 0$ (panels B and D), Y-A haplotypes created by recombination can become more common than Y-a haplotypes as the neo-W spreads. In B, this leads to loss of the neo-W and the system goes to an equilibrium with X-a and Y-A haplotypes fixed (equilibrium A'), such that all females have the high fitness genotype aa and all males are Aa. For the parameters in B, neo-W alleles have negative invasion fitness when the Y-A haplotype is ancestrally more common than Y-a (compare blue to black curves in S1 FigA and S1 FigB near the ancestral sex-determining locus). In contrast, the neo-W is not lost in panel D as it is favoured regardless of whether Y-A or Y-a haplotypes predominate (again, compare blue to black curves in S1 FigC and S1 FigD).

S3 Fig. When there is sexually-antagonistic selection and haploid selection, a neo-W allele may invade for any R. Panel A shows that the invasion fitness of a neo-W is positive, even when $r < R$ (unshaded region). In panel B, we vary the recombination rate between the neo-W and the selected locus (R) for a fixed recombination rate between the ancestral sex-determining locus and the selected locus ($r = 0.005$). Coloured markers show recombination rates for which the temporal dynamics of neo-W invasion are plotted in panel C

(black $R = 0.001$, red $R = 0.02$, blue $R = 0.1$, green $R = 0.5$). The diploid selection parameters used in this plot are the same as in Fig 2. There is also meiotic drive in males favouring a ($\alpha_\Delta^\male = -0.08$), this full set of parameters is marked by an asterisk in S4 FigA. When $R = 0.5$ (green curve), the neo-W does not reach fixation and X, Y, Z, and W alleles are all maintained in the population, see S9 FigC.

S4 Fig. Parameters for which neo-W-*A* and neo-W-*a* haplotypes spread when there is male meiotic drive at a locus that is tightly linked to the ancestral XY locus ($r = 0$). This figure is equivalent to Fig 3 but with meiotic drive in males. In panels A-C, meiotic drive in males favours the a allele ($\alpha_\Delta^\male = -0.16$), creating male-biased sex ratios and generally increasing $\Lambda_{W'A}^{(XY)}$ and $\Lambda_{W'a}^{(XY)}$. By contrast, $\Lambda_{W'A}^{(XY)}$ and $\Lambda_{W'a}^{(XY)}$ tend to be reduced when meiotic drive in males favours the A allele ($\alpha_\Delta^\male = 0.16$), panels D-F.

S5 Fig. Parameters for which neo-W-*A* and neo-W-*a* haplotypes spread when there is male gametic competition at a locus that is tightly linked to the ancestral XY locus ($r = 0$). This figure is equivalent to Fig 3 but with gametic competition in males. The a allele is favoured during male gametic competition in Panels A-C ($w_a^\male = 1.16$, $w_A^\male = 1$), which creates male biased sex ratios and increases $\Lambda_{W'A}^{(XY)}$ and $\Lambda_{W'a}^{(XY)}$. By contrast, $\Lambda_{W'A}^{(XY)}$ and $\Lambda_{W'a}^{(XY)}$ tend to be reduced when the A allele is favoured during male gametic competition, panels D-F. Compared to the meiotic drive parameters in S4 Fig, the effect of these male gametic competition parameters on the sex ratio is smaller. For example, in S4 FigA-C, the ancestral sex ratio is $\alpha^\male = 0.58$ at equilibrium (B) and in panels A-C of this plot, the ancestral sex ratio is $w_a^\male/(w_A^\male + w_a^\male) = 0.537$ at equilibrium (B).

S6 Fig. Parameters for which neo-W-*A* and neo-W-*a* haplotypes spread when there is female meiotic drive at a locus that is tightly linked to the ancestral XY locus ($r = 0$). This figure is equivalent to Fig 3 but with meiotic drive in females. The a allele is favoured by meiotic drive in females in Panels A-C ($\alpha_\Delta^\female = -0.16$), which increases $\Lambda_{W'a}^{(XY)}$ and decreases $\Lambda_{W'A}^{(XY)}$. Female meiotic drive in favour of the A allele (panels D-F, $\alpha_\Delta^\female = -0.16$) has the opposite effect.

S7 Fig. Parameters for which neo-W-*A* and neo-W-*a* haplotypes spread when there is female gametic competition at a locus that is tightly linked to the ancestral XY locus ($r = 0$). This figure is equivalent to Fig 3 but with gametic competition in females. The a allele is favoured during female gametic competition in females in Panels A-C ($w_a^\female = 1.16$, $w_A^\female = 1$), which increases $\Lambda_{W'a}^{(XY)}$ and decreases $\Lambda_{W'A}^{(XY)}$. The A allele is favoured during gametic competition in panels D-F ($w_a^\female = 1$, $w_A^\female = 1.16$), giving the opposite effect on $\Lambda_{W'a}^{(XY)}$ and $\Lambda_{W'A}^{(XY)}$.

S8 Fig. Ploidally-antagonistic selection can drive the spread of neo-W alleles. A-D show when each of the neo-W haplotypes invades an internally stable equilibrium with a fixed on the Y (found by setting $r = 0$). The y-axis shows directional selection in diploids of both sexes, $s^\female = s^\male$, and the x-axes show sex-specific drive, $\alpha_\Delta^\female - \alpha_\Delta^\male$, or haploid competition, $t^\female - t^\male$. The top left and bottom right quadrants therefore imply ploidally-antagonistic selection (and these are the only places where neo-W haplotypes can invade). Dominance is equal in both sexes, $h^\female = h^\male = 3/4$. E-F show the temporal dynamics of neo-W frequency in females with parameters given by the asterisks in the corresponding A-D plot, with $r = 1/200$, for four different R. Black $R = 1/1000$, Red $R = 2/100$, Blue $R = 1/10$, Green $R = 1/2$.

S9 Fig. Pseudo-fixation of neo-W or maintenance of multiple sex-determining alleles. The curves show the frequencies of the neo-W (red), ancestral Y (blue), and A allele (black)

among female gametes (solid curves) and among male gametes (dashed curves). In panel A, there is a complete transition from XY sex determination (XX-ZZ females and XY-ZZ males) to ZW sex determination (YY-ZW females and YY-ZZ males). In panels B and C a polymorphism is maintained at both the ancestral XY locus and the new ZW locus, such that there are males with genotypes XY-ZZ and YY-ZZ and females with genotypes XX-ZZ, XX-ZW, XY-ZW, and YY-ZW. In panel A, selection is ploidally-antagonistic with drive in males (parameters as in the green curve in Fig 5B). In panel B, there is overdominance in both sexes and no haploid selection (parameters as in the green curve in S2 FigC). In panel C, there is sexually-antagonistic selection in diploids with drive in males (parameters as in the green curve in S4 FigC). In all cases, the initial equilibrium frequency has *a* near fixation on the Y.

Acknowledgments

We thank Georgy Sandler and Stephen Wright for sharing their results with us, and we thank Bret Payseur and three anonymous reviewers for helpful comments on this manuscript.

References

1. Bull JJ. Evolution of sex determining mechanisms. Menlo Park, CA: The Benjamin Cummings Publishing Company; 1983.
2. Charlesworth D, Mank JE. The birds and the bees and the flowers and the trees: lessons from genetic mapping of sex determination in plants and animals. Genetics. 2010;186(1):9–31.
3. Beukeboom LW, Perrin N. The evolution of sex determination. Oxford, UK: Oxford University Press; 2014.
4. Bachtrog D, Mank JE, Peichel CL, Kirkpatrick M, Otto SP, Ashman TL, et al. Sex determination: why so many ways of doing it? PLoS Biol. 2014;12(7):e1001899.
5. Ming R, Bendahmane A, Renner SS. Sex chromosomes in land plants. Annu Rev Plant Biol. 2011;62(1):485–514.
6. Li J, Phillips RB, Harwood AS, Koop BF, Davidson WS. Identification of the sex chromosomes of brown trout (*Salmo trutta*) and their comparison with the corresponding chromosomes in Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*). Cytogenetic and Genome Research. 2011;133(1):25–33.
7. Yano A, Nicol B, Jouanno E, Quillet E, Fostier A, Guyomard R, et al. The sexually dimorphic on the Y-chromosome gene (sdY) is a conserved male-specific Y-chromosome sequence in many salmonids. Evolutionary Applications. 2012;6(3):486–496.
8. Vicoso B, Bachtrog D. Numerous transitions of sex chromosomes in Diptera. PLoS Biol. 2015;13(4):e1002078.
9. Myosho T, Otake H, Masuyama H, Matsuda M, Kuroki Y, Fujiyama A, et al. Tracing the emergence of a novel sex-determining gene in medaka, *Oryzias luzonensis*. Genetics. 2012;191(1):163–170.
10. Gamble T, Castoe TA, Nielse SV, Banks JL, Card DC, Schield DR, et al. The discovery of XY sex chromosomes in a *Boa* and *Python*. Current Biology. 2017;27:2148–2152.
11. Ezaz T, Sarre SD, O'Meally D. Sex chromosome evolution in lizards: independent origins and rapid transitions. Cytogenetic and Genome Research. 2009;127:249–260.

12. Mank JE, Promislow DEL, Avise JC. Evolution of alternative sex-determining mechanisms in teleost fishes. Biological Journal of the Linnean Society. 2006;87(1):83–93.

13. Hillis DM, Green DM. Evolutionary changes of heterogametic sex in the phylogenetic history of amphibians. Journal of Evolutionary Biology. 1990;3(1):49–64.

14. Slancarova V, Zdanska J, Janousek B, Talianova M, Zschach C, Zluvova J, et al. Evolution of sex determination systems with heterogametic males and females in *Silene*. Evolution. 2013;67(12):3669–3677.

15. Pucholt P, Rönnberg-Wästljung AC, Berlin S. Single locus sex determination and female heterogamety in the baskey willow (*Salix viminalis* L.). Heredity. 2015;114:575–583.

16. Pucholt P, Wright A, Conze LL, Mank JE, Berlin S. Recent sex chromosome divergence despite ancient dioecy in the willow *Salix viminalis*. Molecular Biology and Evolution. 2017;34:1991–2001.

17. McDonald IC, Evenson P, Nickel CA, Johnson OA. House fly genetics: isolation of a female determining factor on chromosome 4. Annals of the Entomological Society of America. 1978;71:692–694.

18. Thompson PE. Male and female heterogamety in population of *Chironomus tentans* (Diptera: Chironomidae). The Canadian Entomologist. 1971;103:369–372.

19. Ogata M, Hasegawa Y, Ohtani H, Mineyama M, Miura I. The ZZ/ZW sex-determining mechanism originated twice and independently during evolution of the frog, *Rana rugosa*. Heredity. 2007;100(1):92–99.

20. Ser JR, Roberts RB, Kocher TD. Multiple interacting loci control sex determination in lake Malawi cichlid fish. Evolution. 2010;64(2):486–501.

21. Lee BY, Hulata G, Kocher TD. Two unlinked loci controlling the sex of blue tilapia (*Oreochromis aureus*). Heredity. 2004;92:543–549.

22. Vandeputte M, Dupont-Nivet M, Chavanne H, Chatain B. A polygenic hypothesis for sex determination in the European sea bass *Dicentrarchus labrax*. Genetics. 2007;176:1049–1057.

23. Liew WC, Bartfai R, Lim Z, Sreeninvasan R, Siegfried KR, Orban L. Polygenic sex determination system in Zebrafish. Plos One. 2012;4:e34397.

24. Wilson CA, High SK, McCluskey BM, Amores A, Yan Y, Titus TA, et al. Wild sex in Zebrafish: loss of the natural sex determinant in domesticated strains. Genetics. 2014;198(3):1291–1308.

25. Conover DO, Heins SW. Adaptive variation in environmental and genetic sex determination in a fish. Nature. 1987;326(6112):496–498.

26. Pokorná M, Kratochvíl L. Phylogeny of sex-determining mechanisms in squamate reptiles: are sex chromosomes an evolutionary trap? Zoological Journal of the Linnean Society. 2009;156:168–183.

27. Pen I, Uller T, Feldmeyer B, Harts A, While GM, Wapstra E. Climate-driven population divergence in sex-determining systems. Nature. 2010;468(7322):436–438.

28. Holleley CE, O'Meally D, Sarre SD, Marshall Graves JA, Ezaz T, Matsubara K, et al. Sex reversal triggers the rapid transition from genetic to temperature-dependent sex. Nature. 2015;523(7558):79–82.

29. Blaser O, Grossen C, Neuenschwander S, Perrin N. Sex-chromosome turnovers induced by deleterious mutation load. Evolution. 2012;67:635–645. doi:10.5061/dryad.pk14p.

30. van Doorn GS. Patterns and mechanisms of evolutionary tranistions between genetic sex-determining systems. Cold Spring Harbour Perspectives in Biology. 2014;6:a017681.

31. van Doorn GS, Kirkpatrick M. Turnover of sex chromosomes induced by sexual conflict. Nature. 2007;449(7164):909–912.

32. van Doorn GS, Kirkpatrick M. Transitions between male and female heterogamety caused by sex-antagonistic selection. Genetics. 2010;186(2):629–645.

33. Muralidhar P, Veller C. Sexual antagonism and the instability of environmental sex determination. Nature Ecology and Evolution. 2018;doi.org/10.1038/s41559-017-0427-9.

34. Fisher R. The genetical theory of natural selection. London: Clarendon Press; 1930.

35. Charnov EL. The theory of sex allocation. Princeton, NJ: Princeton University Press; 1982.

36. West S. Sex allocation. Princeton, NJ: Princeton University Press; 2009.

37. Mulcahy DL, Sari-Gorla M, Mulcahy GB. Pollen selection - past, present and future. Sexual Plant Reproduction. 1996;9(6):353–356.

38. Joseph S, Kirkpatrick M. Haploid selection in animals. Trends in Ecology & Evolution. 2004;19(11):592–597.

39. Úbeda F, Haig D. On the evolutionary stability of Mendelian segregation. Genetics. 2005;170(3):1345–1357.

40. Lindholm AK, Dyer KA, Firman RC, Fishman L, Forstmeier W, Holman L, et al. The ecology and evolutionary dynamics of meiotic drive. Trends in Ecology & Evolution. 2016;31(4):315–326.

41. Kozielska M, Weissing FJ, Beukeboom LW, Pen I. Segregation distortion and the evolution of sex-determining mechanisms. Heredity. 2010;104:100–112.

42. Úbeda F, Patten MM, Wild G. On the origin of sex chromosomes from meiotic drive. Proceedings of the Royal Society B: Biological Sciences. 2015;282(1798):20141932.

43. Hamilton WD. Extraordinary sex ratios. Science. 1967;156(3774):477–488.

44. Lalanne E, Michaelidis C, Moore JM, Gagliano W, Johnson A, Patel R, et al. Analysis of transposon insertion mutants highlights the diversity of mechanisms underlying male progamic development in *Arabidopsis*. Genetics. 2004;167:1975–1986.

45. Fishman L, Willis JH. A novel meiotic drive locus almost completely distorts segregation in *Mimulus* (monkeyflower) hybrids. Genetics. 2005;169:347–353.

46. Leppälä J, Bechsgaard JS, Schierup MH, Savolainen O. Transmission ratio distortion in *Arabidopsis lyrata*: effects of population divergence and the S-locus. Heredity. 2008;100:71–78.

47. Leppälä J, Bokma F, Savolainen O. Investigating incipient speciation in *Arabidopsis lyrata* from patterns of transmission ratio distortion. Genetics. 2013;194:697–708.

48. Didion JP, Morgan AP, Clayschulte AMF, Mcmullon RC, Yadgary L, Petkov PM, et al. A multi-megabase copy number gain causes maternal transmission ratio distortion on mouse chromosome 2. PLoS Genetics. 2015;11:e1004850.

49. Didion JP, Morgan AP, Yadgary L, Bell TA, McMullan RC, Ortiz de Solorzano L, et al. R2d2 drives selfish genetic sweeps in the house mouse. Molecular Biology and Evolution. 2016;33:1381–1395.

50. Borg M, Brownfield L, Twell D. Male gametophyte development: a molecular perspective. Journal of Experimental Botany. 2009;60(5):1465–1478.

51. Arunkumar R, Josephs EB, Williamson RJ, Wright SI. Pollen-specific, but not sperm-specific, genes show stronger purifying selection and higher rates of positive selection than sporophytic genes in *Capsella grandiflora*. Molecular Biology and Evolution. 2013;30(11):2475–2486.

52. Gossmann TI, Schmid MW, Grossniklaus U, Schmid KJ. Selection-driven evolution of sex-biased genes is consistent with sexual selection in *Arabidopsis thaliana*. Molecular biology and evolution. 2014;31(3):574–583.

53. Hormaza JI, Herrero M. Male gametophytic selection as a plant breeding tool. Scientia horticulturae. 1996;65(4):321–333.

54. Ravikumar RL, Patil BS, Salimath PM. Drought tolerance in sorghum by pollen selection using osmotic stress. Euphytica. 2003;133:371–376.

55. Hedhly A, Hormaza JI, Herrero M. Effect of temperature on pollen tube kinetics and dynamics in sweet cherry, *Prunus avium* (Rosaceae). American journal of botany. 2004;91(4):558–564.

56. Clarke HJ, Khan TN, Siddique KHM. Pollen selection for chilling tolerance at hybridisation leads to improved chickpea cultivars. Euphytica. 2004;139(1):65–74.

57. Zheng Y, Deng X, Martin-DeLeon PA. Lack of sharing of Spam1 (Ph-20) among mouse spermatids and transmission ratio distortion. Biology of Reproduction. 2001;64(6):1730–1738.

58. Vibranovski MD, Chalopin DS, Lopes HF, Long M, Karr TL. Direct evidence for postmeiotic transcription during *Drosophila melanogaster* spermatogenesis. Genetics. 2010;186(1):431–433.

59. Immler S, Hotzy C, Alavioon G, Petersson E, Arnqvist G. Sperm variation within a single ejaculate affects offspring development in Atlantic salmon. Biology letters. 2014;10(2):20131040.

60. Alavioon G, Hotzy C, Nakhro K, Rudolf S, Scofield DG, Zajitschek S, et al. Haploid selection within a single ejaculate increases offspring fitness. PNAS. 2017;114:8053–8058.

61. Burt A, Trivers R. Genes in conflict: the biology of selfish genetic elements. Cambridge, MA: Belknap Press; 2006.

62. Lloyd DG. Female-predominant sex ratios in angiosperms. Heredity. 1974;32(1):35–44.

63. Conn JS, Blum U. Sex ratio of *Rumex hastatulus*: the effect of environmental factors and certation. Evolution. 1981;35(6):1108–1116.

64. Stehlik I, Barrett S. Mechanisms governing sex-ratio variation in dioecious *Rumex nivalis*. Evolution. 2005;59(4):814–825.

65. Stehlik I, Barrett SCH. Pollination intensity influences sex ratios in dioecious Rumex nivalis, a wind-pollinated plant. Evolution. 2006;60(6):1207–1214.

66. Field DL, Pickup M, Barrett SCH. The influence of pollination intensity on fertilization success, progeny sex ratio, and fitness in a wind-pollinated, dioecious plant. International Journal of Plant Sciences. 2012;173(2):184–191.

67. Field DL, Pickup M, Barrett SCH. Comparative analyses of sex-ratio variation in dioecious flowering plants. Evolution. 2013;67(3):661–672.

68. Immler S, Arnqvist G, Otto SP. Ploidally antagonistic selection maintains stable genetic polymorphism. Evolution. 2012;66(1):55–65.

69. Lloyd DG, Webb C. Secondary sex characters in plants. Botanical Review. 1977;43:177–216.

70. Otto SP. Selective maintenance of recombination between the sex chromosomes. Journal of Evolutionary Biology. 2014;27:1431–1442.

71. Käfer J, Marais GAB, Pannell J. On the rarity of dioecy in flowering plants. Molecular Ecology. 2017;26:1225–1241.

72. Goldberg EE, Otto SP, Vamosi JC, Mayrose I, Sabath N, Ming R. Macroevolutionary synthesis of flowering plant sexual systems. Evolution. 2017;71:898–912.

73. Lindholm A, Breden F. Sex chromosomes and sexual selection in poeciliid fishes. The American Naturalist. 2002;160 Suppl 6:S214–24.

74. Tripathi N, Hoffmann M, Willing EM, Lanz C, Weigel D, Dreyer C. Genetic linkage map of the guppy, *Poecilia reticulata*, and quantitative trait loci analysis of male size and colour variation. Proceedings of the Royal Society B: Biological Sciences. 2009;276(1665):2195–2208.

75. Kallman K. Genetics and Geography of Sex Determination in the Poeciliid Fish, *Xiphphorus maculatus*. Zoologica. 1965;50(13):151–190.

76. Kallman K. Evidence for the existence of transformer genes for sex in the telost *Xiphphorus maculatus*. Genetics. 1968;60:811–828.

77. Volff JN, Schartl M. Variability of genetic sex determination in poeciliid fishes. Genetica. 2001;111(1):101–110.

78. Schulteis C, Zhou Q, Froschauer A, Nanda I, Selz Y, Schmidt C, et al. Molecular analysis of the sex-determining region of the platyfish *Xiphophorus maculatus*. Zebrafish. 2006;3(3):299–309.

79. Fredga K. Bizarre mammalian sex-determining mechanisms. In: Short RV, Balaban E, editors. The differences between the sexes. Cambridge, USA: Cambridge University Press; 1994. p. 419–432.

80. Bianchi NO. *Akodon* sex reversed females: the never ending story. Cytogenetic and Genome Research. 2002;96:60–65.

81. Sánchez A, Marchal JA, Romero-Fernández I, Pinna-Senn E, Ortiz MI, Bella JL, et al. No differences in the *Sry* gene between males and XY females in *Akodon* (Rodentia, Cricetidae). Sexual Development. 2010;4:155–161.

82. Hoekstra HE, Hoekstra JM. An unusual sex-determination system in South American field mice (genus *Akodon*): the role of mutation, selection, and meiotic drive in maintaining XY females. Evolution. 2001;55(1):190–197.

83. Veyrunes F, Chevret P, Catalan J, Castiglia R, Watson J, Dobigny G, et al. A novel sex determination system in a close relative of the house mouse. Proceedings of the Royal Society B: Biological Sciences. 2010;277(1684):1049–1056.

84. Saunders PA, Perez J, Rahmoun M, Ronce O, Crochet PA, Veyrunes F. XY females do better than the XX in the African pygmy mouse, *Mus minutoides*. Evolution. 2014;68(7):2119–2127.

85. Saunders PA, Franco T, Sottas C, Maurice T, Guila G, Veyrunes F. XY females do better than the XX in the African pygmy mouse, *Mus minutoides*. Scientific Reports. 2016;6:22881e.

86. Veyrunes F, Perez J. X inactivation in a mammal species with three sex chromosomes. Chromosoma. 2017;doi.org/10.1007/s00412-017-0657-2:1–7. doi:10.1007/s00412-017-0657-2.

87. Rice WR. Evolution of the Y sex chromosome in animals. BioScience. 1996;46(5):331–343.

88. Charlesworth B, Charlesworth D. The degeneration of Y chromosomes. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2000;355(1403):1563–1572.

89. Bachtrog D. A dynamic view of sex chromosome evolution. Current opinion in genetics & development. 2006;16(6):578–585.

90. Marais GAB, Nicolas M, Bergero R, Chambrier P, Kejnovsky E, Monéger F, et al. Evidence for degeneration of the Y chromosome in the dioecious plant *Silene latifolia*. Current Biology. 2008;18(7):545–549.

91. Veller C, Muralidhar P, Constable GWA, Nowak MA. Drift-Induced Selection Between Male and Female Heterogamety. Genetics. 2017;207(2):711–727. doi:10.1534/genetics.117.300151.