

Selective maintenance of recombination between the sex chromosomes

S. P. OTTO

Department of Zoology & Biodiversity Research Centre, University of British Columbia, Vancouver, BC, Canada

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Abstract

A hallmark of many sex chromosomes is the dramatically reduced rate of recombination between them in the heterogametic sex (e.g. between the X and Y). Sexually antagonistic selection is thought to be the main selective driver of this reduced recombination, with tighter linkage strengthening the association between alleles favourable to females and the X, as well as alleles favourable to males and the Y. Nevertheless, many sex chromosomes retain substantial levels of recombination over millions of years, and some old sex chromosomes remain homomorphic with few signs of recombination suppression and the chromosomal degradation expected to follow. This paper explores the selective factors that can maintain recombination between the sex chromosomes. Specifically, by analysing the dynamics of genes that modify the rate of recombination, I present results demonstrating that certain forms of selection – all involving overdominance in males – can positively maintain recombination in the pseudo-autosomal region. To understand these cases, one has to revise our standard view of sexual antagonistic selection as involving two partners (males and females) to three partners (the X in females, the X in males and the Y).

Introduction

Recombination can facilitate adaptation and the elimination of deleterious alleles by reducing selective interference among loci ('Hill–Robertson' effects), by breaking apart disadvantageous genetic associations accumulated in a different selective environment (e.g. with host–parasite dynamics) and by increasing genetic variance in cases where selection reduces variation (e.g. negative epistasis) (see reviews by Barton & Charlesworth, 1998; Otto, 2009). Yet a portion of many genomes eschews recombination: the nonrecombining portions of Y chromosomes. Fisher (1931) first explained linkage of genes on the Y as an evolved response to selective differences experienced by chromosomes that spend different amounts of time in males and females:

...favourable selection in the Y-chromosome with counter-selection in the X must constantly favour

those genotypes in which linkage with the sex-determining portion of the Y-chromosome is closest. Such selection may thus have built up the system of close sex-linkage which is now found.

Fisher (1931) p. 363

This verbal explanation has been confirmed in a series of models (Nei, 1969; Charlesworth & Charlesworth, 1980; Lenormand, 2003). In particular, Lenormand (2003) showed that reduced recombination between selected loci and the sex-determining region would generally be favoured as long as selection differed between the sexes, employing a quasi-linkage equilibrium (QLE) analysis that assumes recombination is frequent relative to the strength of selection and that genetic associations have equilibrated. Notably, this result does not require sexually antagonistic selection (Fisher's 'counter-selection'), with reduced recombination between the sex chromosomes evolving even if selection differs only in strength, and not in sign, between the sexes.

Despite the evolutionary tendency to reduce recombination between the sexes, most species retain some recombination between the sex chromosomes within 'pseudo-autosomal region' (PAR), and in others (espe-

Correspondence: Sarah P. Otto, Department of Zoology & Biodiversity Research Centre, University of British Columbia, Vancouver, BC, Canada V6T 1Z4. Tel.: +1 604 822 2778; fax: +1 604 822 2416; e-mail: otto@zoology.ubc.ca

cially plants), the nonrecombining region (NRR) of the sex chromosomes remains so limited in scope that the sex chromosomes are difficult to distinguish from autosomes, either cytologically or genetically (Ming & Moore, 2007; Otto *et al.*, 2011). While chromosomes with recently evolved sex-determining genes are likely to have smaller NRR, the relationship between the age of the sex chromosome and the relative sizes of the PAR and NRR appears to be weak (Otto *et al.*, 2011).

What explains the variation in speed and extent of recombination suppression on sex chromosomes? In many species, recombination plays a critical role in chromosomal pairing and segregation during meiosis, which is thought, for example, to maintain PARs between the X and Y in eutherian mammals (Rouyer *et al.*, 1986; Soriano *et al.*, 1987; Shi *et al.*, 2001). By contrast, some species have additional mechanisms to facilitate segregation without recombination, including *Drosophila* (McKee, 1998), yeast (Dawson *et al.*, 1986), and *Arabidopsis* (Pradillo *et al.*, 2007), which could enable the evolution of sex chromosomes without PARs. The extent of sexual dimorphism between males and females is also likely to be a major determinant of the speed of sex chromosome evolution. When the sexes are similar, there may be few genes subject to sex-specific selection, slowing the expansion of the NRR. For example, in dioecious plant species, morphological differences between male and female sporophytes are often restricted to floral development, although some growth rate, ecological and life history differences between the sexes have been documented (Lloyd and Webb 1977).

It is also possible, however, that the tightening of genetic linkage is actively opposed by selection for increased recombination. Selection for recombination may result from the population genetic mechanisms thought to maintain recombination more generally (e.g. Hill–Robertson effects or the related Muller's Ratchet; Grossen *et al.*, 2012). Here, I explore another possibility: that certain forms of selection may favour increased recombination between the sex-determining region (SDR) and a nearby selected locus.

Using a modifier model, I show that whereas most forms of selection favour reduced recombination between selected loci and the SDR in the heterogametic sex (assumed here to be males), overdominance in males with some form of selection in females generates conditions where increased recombination can be favoured. These analytical results are obtained assuming that the selected locus is initially tightly linked to the SDR, with graphical analyses exploring the longer-term evolution of recombination between the sex chromosomes. This mechanism may, in some species, oppose the cessation of recombination between the sex chromosomes. That said, the conditions on selection are restrictive. Nevertheless, understanding how it is possible for recombination to be favoured between the

SDR and a selected locus improves our understanding of the evolutionary forces acting on sex chromosomes.

Model

I track the frequency of alleles at a selected locus, **A** (with alleles *A/a*), and at a second 'modifier' locus, **M** (with alleles *M/m*), which alters the recombination rate between the **A** locus and the sex-determining region. Throughout, I assume male heterogamety, but female heterogamety may be modelled by exchanging Y with W, X with Z and male fitnesses with female fitnesses. Because of sex differences in selection and genetic associations between the **M** and **A** loci and the X and Y chromosomes, we must track the frequency of *MA*, *Ma*, *mA* and *ma* gamete combinations separately in X-bearing female gametes (denoted X^f), in X-bearing male gametes (denoted X^m) and in Y-bearing male gametes (denoted Y). These gamete types are censused separately, such that the frequencies sum to one within each type, for example $X_{MA}^m + X_{Ma}^m + X_{mA}^m + X_{ma}^m = 1$. Except where noted, we assume random mating between male and female gametes, such that the frequency of a daughter of type *MA/ma*, for example, is given by $X_{MA}^f X_{ma}^m + X_{ma}^f X_{MA}^m$, whereas the frequency of a son bearing *MA* on the X and *ma* on the Y is $X_{MA}^f Y_{ma}^m$. Natural selection follows and depends on the sex of the offspring according to:

Genotype:	AA	Aa	aa
Female fitness:	F_{AA}	F_{Aa}	F_{aa}
Male fitness:	M_{AA}	M_{Aa}	M_{aa}

Without loss of generality, fitness is measured relative to the heterozygote in each sex, with $F_{Aa} = M_{Aa} = 1$. Finally, gametes are produced with recombination, neglecting mutation. The **A** locus lies in the PAR and recombines with the SDR in XY males at rate r_i , which depends on the modifier genotype ($i = MM, Mm$ or mm) and is the main quantity of interest. In addition, the frequency of recombination between **M** and **A** loci is R_f in females and R_m in males, with double recombination events occurring at rate χ (relevant only in *Mm* males). Recombination between the **A** locus and the SDR, as well as double recombination events, is irrelevant in females, who are homozygous at the SDR). Given appropriate choices of r_i , R_m and χ , any order of the loci can be modelled, including inversions and unlinked modifiers. See Appendix 1 for recursion equations.

Equilibria with M fixed

The analysis proceeds by assuming that the **A** locus has evolved into tight linkage with the SDR, such that r_{MM} and χ are both small (of the order of a small term, ξ). All proofs were performed in *Mathematica* 8.0 (Wolfram Research, Inc, 2010).

Assuming that allele M is fixed within the population and letting p_{Xf} , p_{Xm} and p_Y represent the frequency of the A allele among female gametes, male X-bearing gametes and male Y-bearing gametes, there are five potential equilibria of the system that maintain both A and a alleles, to constant order in ξ . These equilibria were identified by Clark (1987) and are given by:

$$\begin{aligned} (A) \quad p_{Xf} &= \frac{1 + M_{aa} - 2F_{aa}M_{aa}}{2(1 + M_{aa} - F_{AA} - F_{aa}M_{aa})}, p_{Xm} \\ &= \frac{1 + M_{aa} - 2F_{aa}M_{aa}}{(1 + M_{aa})^2 - 2(F_{aa} + F_{AA})M_{aa}}, p_Y = 0 \\ (A') \quad p_{Xf} &= \frac{1 + M_{AA} - 2F_{aa}}{2(1 + M_{AA} - F_{aa} - F_{AA}M_{AA})}, p_{Xm} \\ &= \frac{M_{AA} + M_{AA}^2 - 2F_{aa}M_{AA}}{(1 + M_{AA})^2 - 2(F_{aa} + F_{AA})M_{AA}}, p_Y = 1 \\ (B) \quad p_{Xf} &= 0, p_{Xm} = 0, p_Y = 1 \\ (B') \quad p_{Xf} &= 1, p_{Xm} = 1, p_Y = 0 \\ (C) \quad p_{Xf} &= \frac{1 - M_{aa}}{2 - M_{aa} - M_{AA}}, p_{Xm} \\ &= \frac{(1 - M_{aa})(2F_{aa}(1 - M_{AA}) + M_{AA} - M_{aa})}{(M_{AA} - M_{aa})^2 + 2(F_{aa} + F_{AA})(1 - M_{AA})(1 - M_{aa})}, \\ p_Y &= \frac{2F_{AA}(1 - M_{aa}) - 2F_{aa}M_{aa}(1 - M_{AA}) - (1 + M_{aa})(M_{AA} - M_{aa})}{(M_{AA} - M_{aa})^2 + 2(F_{aa} + F_{AA})(1 - M_{AA})(1 - M_{aa})} \end{aligned}$$

Note that equilibria (A) and (A') are equivalent if we interchange alleles A and a , as are the equilibria (B) and (B'). (The ' notation indicates that the A allele is fixed on the Y chromosome, $p_Y = 1$, rather than the a allele, $p_Y = 0$.) Only one of these five equilibria involves a polymorphism on the Y chromosome, equilibrium (C), but this equilibrium is never locally stable when $r_{MM} \approx 0$ (Clark, 1987; Data S1). Thus, the Y chromosome evolves to near fixation on either the A or a allele, with the X remaining polymorphic (equilibria A and A') or fixed for the alternate allele (equilibria B and B'). These four equilibria are examples of 'high-complementarity equilibria' (HCE), which are characterized by strong linkage disequilibrium involving opposite haplotypes. HCE are found in many models when recombination rates are sufficiently low between selected loci (Bodmer & Felsenstein, 1967; Franklin & Lewontin, 1970; Feldman *et al.*, 1974). As the rate of recombination increases, these equilibria move away from the edges, bringing p_{Xf} , p_{Xm} and p_Y closer together. Clark (1988) explored these 'unusual' polymorphisms further and described how the equilibrium frequencies vary as a function of the recombination rate, assuming selection is either symmetric or dominant on the X.

Before continuing, it is worth pointing out the not-so-obvious: for loci tightly linked to the SDR, the allele frequencies at equilibrium always differ between the X and Y chromosomes whenever a polymorphism is maintained. This is true *even when selection is identical*

in males and females. This fact is easiest to understand if we consider selection at the **A** locus borne on the Y chromosome in males. There are two forms of selection that can maintain polymorphism: overdominance and sexually antagonistic selection. If there is overdominance in males, then Y chromosomes carrying the allele that is rarer on the X are selectively favoured, as these tend to produce heterozygous – hence fitter – sons. Alternatively, if there is sexually antagonistic selection, then selection uniformly favours the fixation of Y chromosomes carrying the allele fittest in males. Regardless, one allele is always driven to fixation on the Y chromosome when $r_{MM} \approx 0$ (assuming no frequency-dependent selection in males). Selection on the Y is thus akin to selection on haploids, in that polymorphism is not maintained by constant selection (Immler *et al.*, 2011). Thus, if a polymorphism is maintained at loci tightly linked to the SDR, it must be the case that the X and Y differ in allele frequency.

Two of the potentially stable equilibria, (A) and (A'), involve polymorphic X chromosomes. As shown by Clark (1987), equilibrium (A) is valid and stable when:

$$(A) \quad \frac{1}{2} \left(\frac{M_{aa}}{M_{Aa}} + 1 \right) > \frac{F_{AA}}{F_{Aa}} \quad \text{and} \quad \frac{1}{2} \left(\frac{M_{AA}}{M_{aa}} + 1 \right) > \frac{F_{aa}}{F_{AA}}$$

and

$$0 > \frac{(M_{Aa} - M_{aa})}{M_{aa}} \left[\frac{1}{2} \left(\frac{M_{aa}}{M_{Aa}} + 1 \right) - \frac{F_{AA}}{F_{Aa}} \right] + \frac{M_{AA} - M_{aa}}{M_{AA}}$$

Equivalent conditions for equilibrium (A') can be obtained by interchanging alleles A and a . Here, the heterozygous fitness terms have been retained to clarify the restrictions on selection (see also proofs in Data S1). These conditions become important in the next section when we examine how recombination evolves between the sex chromosomes. I first make some general comments about the forms of selection that are consistent with polymorphic equilibria on the X, focusing on equilibrium (A) for clarity.

Notice that the term in square brackets is always positive given the other conditions listed. Because $p_Y \approx 0$, most males are either Aa or aa . If these males are equally fit, then the conditions simplify to requiring overdominance in females and a lower fitness for the rare AA males than for the common males ($M_{AA} < M_{Aa}, M_{aa}$). When aa males are less fit than Aa males, the conditions on the fitness of aa females broaden, whereas the conditions on the fitness of AA females contract, and *vice versa* when aa males are more fit than Aa males. Equilibrium (A) cannot, however, be maintained if selection uniformly favours A in males ($M_{AA} > M_{Aa} > M_{aa}$) or if selection is absent or underdominant in females, but several possibilities remain, including sexually antagonistic selection favouring allele a in males and A in females, as well as overdominance in both sexes.

As shown in the Data S1, at equilibrium (A), allele *A* is positively selected on the X in males if $M_{Aa} > M_{aa}$ and negatively selected if $M_{aa} > M_{Aa}$, whereas the opposite must occur on the X in females for the polymorphism on the X to be maintained. Consequently, the frequency of *A* alleles is highest among X-bearing sperm, then ovules, then Y-bearing sperm when $M_{Aa} > M_{aa}$, but highest among ovules, then X-bearing sperm, then Y-bearing sperm when $M_{aa} > M_{Aa}$. An important corollary is that we cannot simply understand the dynamics as the result of selection on the X and the Y, we must consider a three-way dynamic between selection on the X in females, X in males and Y in males.

The outcome can be very counterintuitive; for example, selection can favour the same allele in females and on the Y in males, and yet that allele can be selected against when carried on the X in males, allowing a polymorphism to be maintained on the X. To emphasize this point, consider the case of strong overdominant selection, with all homozygous individuals – both males and females – being five times less fit than heterozygotes ($M_{aa} = F_{aa} = M_{AA} = F_{AA} = 0.2$; $M_{Aa} = F_{Aa} = 1$). For this case, there are two stable equilibria when r_{MM} is near zero: equilibrium (A) at $p_{Xf} = 0.583$, $p_{Xm} = 0.875$, $p_Y = 0$, and the converse equilibrium (A') at $p_{Xf} = 0.417$, $p_{Xm} = 0.125$, $p_Y = 1$. At equilibrium (A), the XA haplotype is strongly favoured in males because this haplotype is coupled with the Ya haplotype, generating fit heterozygous males. But the XA haplotype is disfavoured in females, who are often AA females of low fitness, driving p_{Xf} down. It is worth emphasizing how bizarre this equilibrium is: selection is exactly the same in males and in females, but the asymmetry of the inheritance of X and Y chromosomes yields selection acting differently on alleles in males and females, with specialization of the Y on one allele and selection actually favouring that same allele in females, but the opposite allele on the X in males.

The specialization of the X and Y on different alleles is taken to the extreme at equilibria (B) and (B'), where the two sex chromosomes are fixed for alternate alleles. Equilibrium (B) is stable when:

$$(B) \frac{1}{2} \left(\frac{M_{aa}}{M_{Aa}} + 1 \right) < \frac{F_{AA}}{F_{Aa}} \text{ and } M_{AA} < M_{Aa},$$

with equivalent conditions for equilibrium (B') when alleles *A* and *a* are interchanged (Clark, 1987; Data S1). For different alleles to be nearly fixed on the X and Y, females homozygous for the allele common on the X must be sufficiently fit, relative to the fitness of males that are homozygous for the alternate allele. In addition, males, who are nearly always heterozygous at equilibria (B) and (B'), must be more fit as heterozygotes than as homozygotes for the allele common on the X, otherwise selection will not maintain the opposite allele near fixation on the Y chromosome.

The conditions for validity and stability of equilibria (A) and (B) are mutually exclusive, and the same is true for (A') and (B'). Consequently, if allele *a* is fixed on the Y chromosome, allele *A* can be maintained within the population via a polymorphism on the X or fixation of allele *A* on the X, but not both.

The above equilibria and their properties are exact when $r_i = 0$. With a small amount of recombination between the selected locus **A** and the SDR, these equilibria move inwards from 0 and 1 (Clark, 1988), but their stability properties remain the same for low levels of recombination, according to the 'small parameter theory' of Karlin & McGregor (1972a,b).

Modifier of recombination

Let us now ask whether any form of selection at locus **A** would cause the spread of a new modifier allele, *m*, that increases recombination rates ($r_{Mm} > r_{MM}$), thereby maintaining recombination on the sex chromosomes.

The effect of the modifier on recombination is assumed weak, such that ($r_{Mm} - r_{MM}$) and ($r_{mm} - r_{MM}$) are small (of the order of ξ). Consequently, all rates involving a recombination event between the **A** locus and the SDR are of order ξ , including the rate of double recombination, χ . A local stability analysis was then conducted, introducing a small frequency of the new modifier allele, *m*, into each of the above equilibria. The leading eigenvalue, λ , of the stability matrix was determined to leading order in ξ . Specifically, I set $\lambda = \lambda_0 + \lambda_1 \xi + \dots$ and solved for the successive terms in this expansion. As expected, when the modifier had no effect on recombination when rare ($r_{Mm} = r_{MM}$), the leading eigenvalue was one ($\lambda_0 = 1$). Consequently, the sign of λ_1 determined whether a modifier increasing recombination would spread (if $\lambda_1 > 0$). Proofs were carried out in the Data S1 *Mathematica* package. The main results are summarized below.

When selection in males is underdominant or directional, only decreased recombination is favoured at the equilibria (A), (A'), (B) and (B') whenever they are valid and stable. Furthermore, if the modifier itself is very tightly linked (including events such as inversions near the SDR that further suppress recombination), only reduced recombination is favoured, regardless of the form of selection.

Interestingly, however, some forms of selection do favour the evolution of increased recombination between the X and Y (as detailed in Appendix 2). In particular, for increased recombination to evolve:

- Selection must be overdominant in males.
- The modifier must be sufficiently loosely linked (R_f and R_m sufficiently large).
- Selection must act in females and must favour the same allele as is found on the Y.

This last condition, although counterintuitive, is key to understanding why modifiers increasing recombination would ever be favoured.

When the **A** locus is tightly linked to the SDR and one allele is nearly fixed on the Y (haplotype Y_a , say), overdominant selection in males favours X chromosomes bearing the opposite allele; that is, males are fitter, on average, if they carry XA than Xa because the former are almost all heterozygotes. If there is a polymorphism on the X [equilibrium (A)], then at equilibrium selection must act against XA in females to balance selection for XA experienced in males; otherwise, allele A would be fixed on the X (equilibrium B). Thus, counterintuitively, with overdominant selection in males, selection in females must favour the *same* allele that is fixed on the Y in order for a balanced polymorphism to result. This creates a situation in which recombination in males moves the a allele from the Y- to X-bearing sperm, thereby increasing the fitness of daughters. As long as the fitness benefit to daughters is high enough relative to the costs of recombination producing less-fit Y-bearing sons, then a modifier increasing recombination can spread. If instead of a polymorphism, the X is nearly fixed on the opposite allele [haplotype XA at equilibrium (B)], then there are two possible scenarios: either selection favours XA in both sexes or selection again favours XA in males but Xa in females (with the balance favouring the fixation of XA). The conditions allowing increased recombination to evolve are only consistent with the latter case (see Appendix 2).

Figure 1 shows the parameter space within which increased recombination is favoured, assuming a loosely linked modifier and overdominance in females, setting $F_{AA} = 0.75$, $F_{Aa} = 1$ and $F_{aa} = 0.75$. Figure 2 shows how these regions shift under different forms of selection in females, whereas Fig. 3 illustrates the case where selection is equal in males and females. When selection is equal in males and females, selection must act strongly against both aa and AA genotypes for increased recombination to be favoured (Fig. 3). If the sexes differ in fitness, however, selection need not be strong (see weak selection conditions in the Appendix 2). For example, with overdominance that is similar in form but different in strength between the two sexes, equilibria at which recombination is favoured arise even when selection is weak, as long as selection in males is, at most, 40% the strength of selection in females.

The above analysis indicates when increased recombination would be favoured, assuming linkage is very tight ($r_{MM} = 0$). To supplement this analysis, I used a graphical approach to explore the longer-term evolution of recombination, assuming unlinked modifiers of small effect would repeatedly arise and allow increased or decreased recombination to evolve between locus **A** and the SDR (Fig. 4). For nine different parameter sets (as indicated by the white letters in Figs 1–3), all polymorphic equilibria were numerically calculated, as a

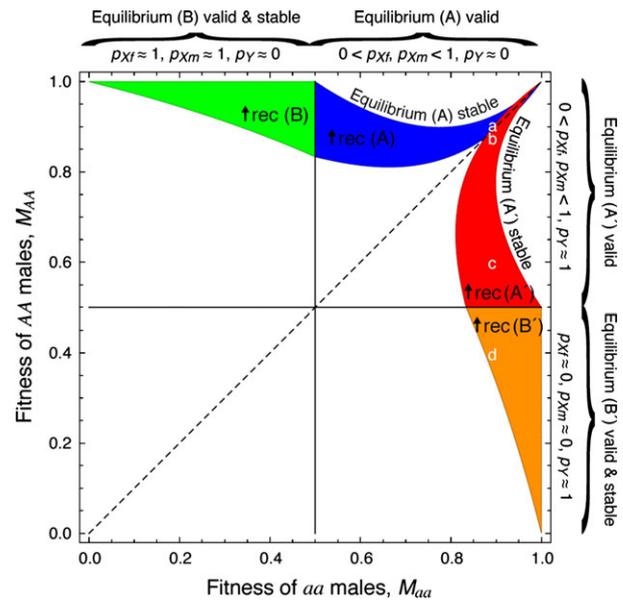


Fig. 1 Selection can favour increased recombination between the sex chromosomes. The coloured regions indicate the parameter space within which increased recombination is favoured between the SDR and a tightly linked selected locus ($r_i \approx 0$) at equilibrium (A) in blue, (B) in green, (A') in red and (B') in orange. The vertical line separates the regions of validity between equilibrium (B) on the left and equilibrium (A) on the right. The horizontal line separates the regions of validity between equilibrium (B') on the bottom and equilibrium (A') on the top. In addition, for equilibria (A) and (A') to be stable requires that selection be strong enough (below or to the left of the curves indicated). The dashed line shows $M_{AA} = M_{aa}$ for reference. White lowercase letters refer to special cases explored in Fig. 4. Selection in females is set to $F_{AA} = 0.75$, $F_{Aa} = 1$ and $F_{aa} = 0.75$, male fitness is measured relative to the heterozygote ($M_{Aa} = 1$), and the modifier is unlinked ($R_m = R_f = 0.5$).

function of the recombination rate between the selected locus and the SDR, r_{MM} (solid curves: stable equilibria; dashed curves: unstable). Whether (thick) or not (thin) increased recombination was favoured at these equilibria was then determined, with horizontal arrows illustrating the main direction of recombination evolution. In some cases, equilibria that exist for tight linkage become complex for looser linkage (when dashed and solid curves meet), in which case the system could transition to fixation or to the remaining polymorphic equilibrium, depending on their basins of attraction. Simulations were conducted to determine the dynamics in cases (b–f) when the evolution of increased recombination causes equilibria to become complex; for these cases, the result was always a transition to the other polymorphism (upwards arrows), rather than fixation (Data S1). The ultimate result of the long-term evolution of recombination rates (asterisks) depends on the selection coefficients. For cases (a), (b), (g), (h) and (i), all of which exhibit similar

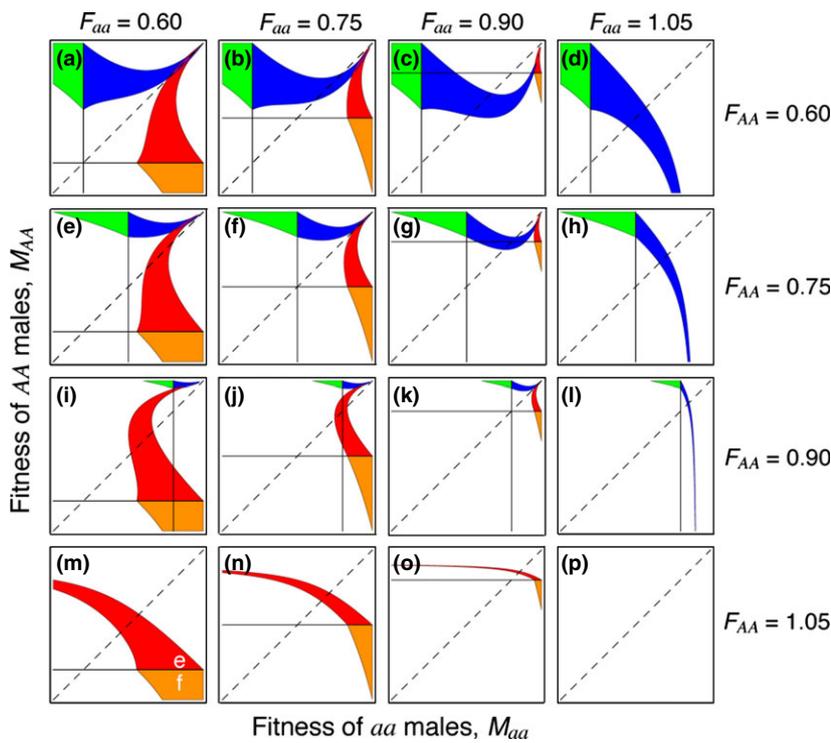


Fig. 2 Effect of changing selection in females. The grid shows multiple examples of Fig. 1, varying the strength of selection in females. In each subplot, the x- and y-axes show M_{aa} and M_{AA} , respectively, always ranging from 0 to 1. Panels d, h, l illustrate directional selection favouring a in females. Panels m, n, o illustrate directional selection favouring A in females. Panel p illustrates underdominance in females, which never allows increased recombination to evolve. The remaining panels illustrate overdominance in females (panel f is identical to Fig. 1). White letters in panel m refer to special cases explored in Fig. 4.

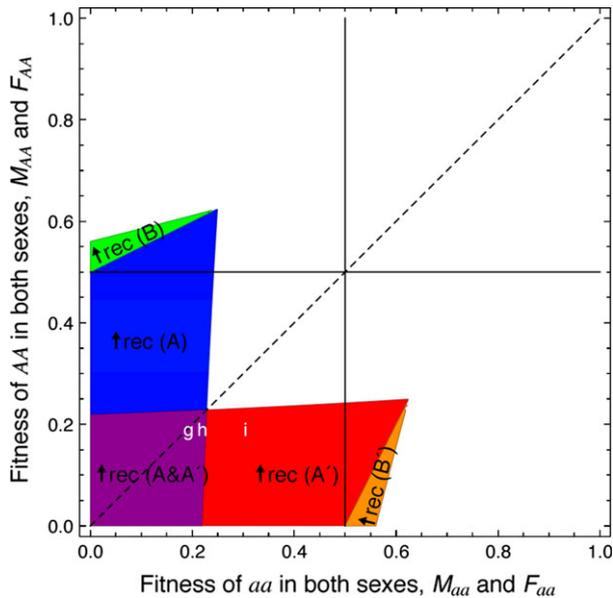


Fig. 3 When selection is equal in the two sexes, increased recombination between the sex chromosomes evolves only when selection is overdominant and strong. Coloured regions indicate when recombination is favoured, as in Fig. 1, with purple indicating regions in which recombination is favoured at both of the two polymorphic equilibria that are stable (equilibria A and A'). White letters refer to special cases explored in Fig. 4. Selection is measured relative to the heterozygote ($M_{Aa} = F_{Aa} = 1$), linkage between the SDR and the selected locus is tight ($r_i \approx 0$), and the modifier is unlinked ($R_m = R_f = 0.5$).

selection on alleles A and a , evolutionary stable states exist at which recombination can be maintained indefinitely in the face of genetic modifications to the recombination rate caused by unlinked modifiers.

Discussion

The evolutionary fate of sex chromosomes depends on the dynamics of recombination between the X and Y (or Z and W). The now-classic view is that sex differences in selection will drive the suppression of recombination between the sex chromosomes (Fisher, 1931; Nei, 1969; Bull, 1983; Rice, 1987; Lenormand, 2003), because linkage strengthens the genetic association between alleles beneficial to females and the X and between alleles beneficial to males and the Y. Indeed, in a general QLE analysis assuming loose linkage between the selected locus and the SDR, Lenormand (2003) found that decreased recombination is always favoured between the X and Y (assuming selection in the diploid phase), requiring only that selection acts differently on alleles in males and females. This requirement is naturally met when selection is sexually antagonistic, but it is also satisfied when the form of selection is similar in both sexes, as long as the strength of selection acting on each allele differs. Once recombination is suppressed, the lack of recombination on the Y, coupled with masking by X-linked copies, allows the degeneration of the Y, through the accumulation of deleterious mutations, indels and chromosomal rearrangements via drift-related

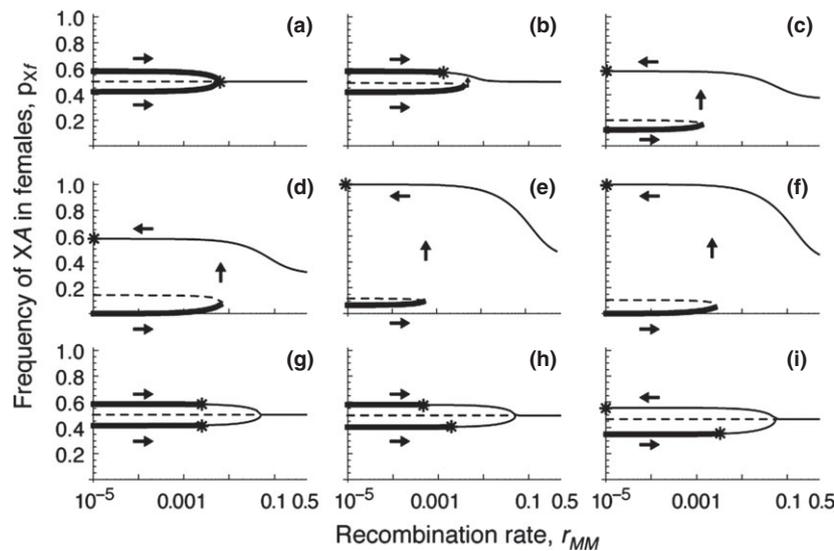


Fig. 4 Evolution of recombination between the sex chromosomes. The y-axis gives the frequency of the *A* allele in females, p_{Xf} , for each of the polymorphic equilibria, as a function of the recombination rate between the SDR and the selected locus (r_{MM}). Dashed curves indicate equilibria that are unstable. Thin solid curves indicate equilibria at which recombination is selected to decrease, whereas thick solid curves show cases where recombination is selected to increase (as determined numerically from the local stability matrix). Arrows indicate the direction of selection for recombination. Stars indicate convergence-stable evolutionary strategies. Each panel corresponds to one of the white letters in Figs 1–3. Selection coefficients: (a) $M_{AA} = 0.9$, $M_{aa} = 0.9$, $F_{AA} = 0.75$, $F_{aa} = 0.75$, (b) $M_{AA} = 0.895$ (otherwise like a), (c) $M_{AA} = 0.6$ (otherwise like a), (d) $M_{AA} = 0.4$ (otherwise like a), (e) $M_{AA} = 0.25$, $M_{aa} = 0.9$, $F_{AA} = 1.05$, $F_{aa} = 0.6$, (f) $M_{AA} = 0.15$ (otherwise like e), (g) $M_{AA} = F_{AA} = 0.2$, $M_{aa} = F_{aa} = 0.2$, (h) $M_{aa} = F_{aa} = 0.22$ (otherwise like g), (i) $M_{aa} = F_{aa} = 0.3$ (otherwise like g). Selection is measured relative to the heterozygote ($M_{Aa} = F_{Aa} = 1$), and the modifier is unlinked ($R_m = R_f = 0.5$).

processes, such as Muller's Ratchet and Hill–Robertson effects (Rice, 1994; Bachtrog, 2006).

Nevertheless, recombination is maintained between sex chromosomes in many species (reviewed by Otto *et al.*, 2011). Furthermore, some taxa seem not to have read the textbook on sex chromosome evolution, having retained recombining and homomorphic sex chromosomes for extensive periods of time (e.g. over 100MY in pythons and boas, Vicoso *et al.*, 2013a; and in ratites, Vicoso *et al.*, 2013b). While much work remains to be done to explore sex chromosome structure in plants, homomorphic sex chromosomes are also common in angiosperms (Ming *et al.*, 2011), although this may reflect the relatively young age of many dioecious lineages.

Likely the most important determinant of whether and how fast heteromorphic sex chromosomes evolve is the extent of sexually antagonistic selection. The fact that few dioecious plants exhibit cytologically differentiated sex chromosomes may, for example, reflect fewer sex differences in selection, although this remains to be demonstrated. Another important factor may be the ease by which sexually antagonistic selection can be resolved by the evolution of sex-limited expression, rather than recombination suppression. For example, Vicoso *et al.* (2013b) report that there is a disproportionate degree of male-biased gene expression on the Z chromosomes of emus, suggesting that male-beneficial alleles became associated with males through the evolution of biased

gene expression rather than tighter sex linkage. The authors note that these expression biases could potentially account for the stability of homomorphic, recombining sex chromosomes in lineages such as ratites.

While sex differences in selection, particularly sexually antagonistic selection, provide the fuel for recombination suppression (Lenormand, 2003), complete suppression may be opposed by a number of factors. As mentioned in the introduction, recombination aids in the pairing of chromosomes during meiosis, reducing the rate of aneuploidy. As a consequence, selection may maintain some amount of recombination in PARs. Indeed, recombination rates per base pair are often higher in PARs than on autosomes, presumably to ensure that a cross-over does occur (Otto *et al.*, 2011). Recombination may also be selectively maintained to avoid degeneration and the accumulation of deleterious alleles in finite populations (Grossen *et al.*, 2012). In Grossen *et al.*'s study, recombination occurring via sex-reversed individuals (XY females) was modelled and shown to evolve towards zero in the presence of sexually antagonistic selection alone (as this paper predicts) but towards a positive value when deleterious mutations were present as well. Given that the fitness effects of deleterious mutations were multiplicative and equal in the two sexes, deterministic models would predict no change in recombination (Barton, 1995; Lenormand, 2003), leading Grossen *et al.* (2012) to conclude that stochastic effects were responsi-

ble for the maintenance of recombination in their simulations (i.e. Muller's Ratchet and related Hill–Robertson effects). Given that sex reversal allows recombination across the entire chromosome, more work is needed to determine whether avoiding Muller's Ratchet and Hill–Robertson effects would similarly maintain recombination in the face of modifiers such as inversions that gradually and locally suppress recombination between the sex chromosomes.

In this work, I have shown that selection may also actively maintain recombination when it benefits fathers to pass alleles linked to their Y to daughters, which requires that the same allele is favoured on the Y and on the X in daughters, but not on the X in males. This seemingly odd requirement turns out to be reasonably common as long as there is overdominance in males ($M_{aa} < M_{Aa} > M_{AA}$) and tight linkage between the selected locus and the SDR. Indeed, for equilibria polymorphic for both *A* and *a* alleles on the X when $r_{MM} \approx 0$ (equilibria A and A'), overdominance in males ensures that the same allele is always favoured on the Y and in females. This requirement can even be met when X and Y chromosomes are nearly fixed on different alleles (equilibria B and B'), as long as selection on the X in females and favours the opposite allele compared to selection on the X in males, with the latter selective force being stronger. Thus, while we commonly view selection as acting differently in males and females, these equilibria instruct us that we must separately consider the selection pressures acting on the X in females, the X in males and the Y in males. Only by considering all three selective pressures is it possible to understand why recombination between the sex chromosomes can be maintained.

In addition to requiring overdominance in males and selection for the same allele on the X in females and on the Y in males, recombination is only favoured if the advantage of recombining the Y allele onto the X is greater for daughters than the disadvantage of doing the opposite for sons. Furthermore, because the advantage is transient (a recombination event that benefits daughters would harm those daughters' sons), increased recombination between the **A** locus and the SDR is most likely to evolve when the genes modifying the recombination rates are loosely linked (high R_M and R_F) and rapidly disassociate from the sex chromosomes that they have affected.

Despite the peculiar behaviour of equilibria tightly linked to the SDR and the possibility that increased recombination is positively selected, it must be emphasized that across the vast majority of parameter space – and always if selection in males does not display overdominance – recombination is selected downwards from very low levels to complete linkage between the selected locus and the SDR. In particular, complete linkage is always favoured at equilibria involving sexually antagonistic selection. Even when there is over-

dominance in males, the population must settle at one of the equilibria at which recombination is favoured, causing the system to lie in one of the coloured 'moustache' regions in Figs 1–3. Thus, it is highly unlikely that recombination between the sex chromosomes is maintained in all species because of the mechanism described here, but it may be in some species, particularly if overdominance is prevalent.

Another point worth emphasizing is that the nature of recombination modification also matters. If genes that modify the recombination rate are themselves tightly linked to the SDR (low R_m and R_f), modifier alleles will spread only if they reduce recombination; in particular, inversions close to the SDR would always be favoured. The fact that loosely linked modifiers are more conducive to the maintenance of recombination between the sex chromosomes echoes work on modifiers of recombination in the presence of sex ratio distortion (Feldman & Otto, 1989), where the SDR experiences segregation distortion at a rate that depends on a sex ratio distorter gene lying within the PAR (the latter being equivalent to the **A** locus). There too, increased recombination between the sex chromosomes is most likely when the modifier of recombination is loosely linked, because of the short-term benefits of equalizing the sex ratio. For modifiers that are tightly linked to the SDR, however, decreased recombination is favourable; tightly linked modifiers gain an advantage from remaining associated with favourable gene combinations, that is, particular driver alleles and the sex chromosomes they drive (akin to the advantage of remaining associated with particular alleles at a selected locus **A** and the sex in which those alleles are favoured).

Finally, it is worth recalling that constant fitnesses have been assumed throughout the analyses described in this paper. Future work exploring other forms of selection, particularly spatially varying, temporally varying or frequency-dependent fitnesses, would shed light on the nature of selection that is required to prevent the complete suppression of recombination between the sex chromosomes.

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Appendix 1: Recursions

The recursions track the fate of each gamete type through a generation consisting of a census, gamete union, selection and reproduction. Numbering the allele combinations within a gamete as 1: *MA*, 2: *Ma*, 3: *mA*, 4: *ma*, random union of gametes generates diploid females bearing combinations *i* and *j* at frequency $x_{ij} = X_i^f X_j^m$ and diploid males at frequency $y_{ij} = X_i^f Y_j^m$. Note that in females (but not males), individuals with genotype *ij* are equivalent to those with genotype *ji*; thus, to simplify the notation, we set the frequency of genotype *ij* in females (for $i \neq j$) to the average of these frequencies, $x_{ij} = (X_i^f X_j^m + X_j^f X_i^m)/2$.

Selection depends only on the **A** locus genotype, *k*, that individual *ij* bears, changing the diploid frequencies to $x_{ij}^s = F_k x_{ij}/\bar{F}$ in females and $y_{ij}^s = M_k y_{ij}/\bar{M}$ in males, with mean female fitness $\bar{F} = \sum_{i=1}^4 \sum_{j=1}^4 F_k x_{ij}$ and mean male fitness $\bar{M} = \sum_{i=1}^4 \sum_{j=1}^4 M_k y_{ij}$. These diploid individuals then undergo meiosis to produce the next generation of gamete frequencies. The frequencies of gamete combinations among eggs depend only on the recombination rate between **M** and **A**:

$$X_{MA}^f = \left(\sum_{j=1}^4 x_{1j}^s \right) - R_f (x_{14}^s - x_{23}^s) \quad (\text{A1a})$$

$$X_{Ma}^{f'} = \left(\sum_{j=1}^4 x_{2j}^s \right) + R_f(x_{14}^s - x_{23}^s) \tag{A1b}$$

$$X_{mA}^{f'} = \left(\sum_{j=1}^4 x_{3j}^s \right) + R_f(x_{14}^s - x_{23}^s) \tag{A1c}$$

$$X_{ma}^{f'} = \left(\sum_{j=1}^4 x_{4j}^s \right) - R_f(x_{14}^s - x_{23}^s) \tag{A1d}$$

In males, however, we must also account for recombination between the loci and the SDR, generating more complicated recursion equations for the frequencies of gamete combinations among X-bearing sperm:

$$\begin{aligned} X_{MA}^{m'} &= \left(\sum_{j=1}^4 y_{1j}^s \right) - r_{MM}(y_{12}^s - y_{21}^s) \\ &\quad - (R_m + r_{Mm} - 2\chi)(y_{13}^s - y_{31}^s) - (R_m + r_{Mm} - \chi)y_{14}^s \\ &\quad + (r_{Mm} - \chi)y_{41}^s + \chi y_{23}^s + (R_m - \chi)y_{32}^s \end{aligned} \tag{A2a}$$

$$\begin{aligned} X_{Ma}^{m'} &= \left(\sum_{j=1}^4 y_{2j}^s \right) - r_{MM}(y_{21}^s - y_{12}^s) \\ &\quad - (R_m + r_{Mm} - 2\chi)(y_{24}^s - y_{42}^s) - (R_m + r_{Mm} - \chi)y_{23}^s \\ &\quad + (r_{Mm} - \chi)y_{32}^s + \chi y_{14}^s + (R_m - \chi)y_{41}^s \end{aligned} \tag{A2b}$$

$$\begin{aligned} X_{mA}^{m'} &= \left(\sum_{j=1}^4 y_{3j}^s \right) - r_{mm}(y_{34}^s - y_{43}^s) \\ &\quad - (R_m + r_{Mm} - 2\chi)(y_{31}^s - y_{13}^s) - (R_m + r_{Mm} - \chi)y_{32}^s \\ &\quad + (r_{Mm} - \chi)y_{23}^s + \chi y_{41}^s + (R_m - \chi)y_{14}^s \end{aligned} \tag{A2c}$$

$$\begin{aligned} X_{ma}^{m'} &= \left(\sum_{j=1}^4 y_{4j}^s \right) - r_{mm}(y_{43}^s - y_{34}^s) \\ &\quad - (R_m + r_{Mm} - 2\chi)(y_{42}^s - y_{24}^s) - (R_m + r_{Mm} - \chi)y_{41}^s \\ &\quad + (r_{Mm} - \chi)y_{14}^s + \chi y_{32}^s + (R_m - \chi)y_{23}^s \end{aligned} \tag{A2d}$$

and among Y-bearing sperm:

$$\begin{aligned} Y_{MA}^{m'} &= \left(\sum_{j=1}^4 y_{j1}^s \right) - r_{MM}(y_{21}^s - y_{12}^s) \\ &\quad - (R_m + r_{Mm} - 2\chi)(y_{31}^s - y_{13}^s) - (R_m + r_{Mm} - \chi)y_{41}^s \\ &\quad + (r_{Mm} - \chi)y_{14}^s + \chi y_{32}^s + (R_m - \chi)y_{23}^s \end{aligned} \tag{A3a}$$

$$\begin{aligned} Y_{Ma}^{m'} &= \left(\sum_{j=1}^4 y_{j2}^s \right) - r_{MM}(y_{12}^s - y_{21}^s) \\ &\quad - (R_m + r_{Mm} - 2\chi)(y_{42}^s - y_{24}^s) - (R_m + r_{Mm} - \chi)y_{32}^s \\ &\quad + (r_{Mm} - \chi)y_{23}^s + \chi y_{41}^s + (R_m - \chi)y_{14}^s \end{aligned} \tag{A3b}$$

$$\begin{aligned} Y_{mA}^{m'} &= \left(\sum_{j=1}^4 y_{j3}^s \right) - r_{mm}(y_{43}^s - y_{34}^s) \\ &\quad - (R_m + r_{Mm} - 2\chi)(y_{13}^s - y_{31}^s) - (R_m + r_{Mm} - \chi)y_{23}^s \\ &\quad + (r_{Mm} - \chi)y_{32}^s + \chi y_{14}^s + (R_m - \chi)y_{41}^s \end{aligned} \tag{A3c}$$

$$\begin{aligned} Y_{ma}^{m'} &= \left(\sum_{j=1}^4 y_{j4}^s \right) - r_{mm}(y_{34}^s - y_{43}^s) \\ &\quad - (R_m + r_{Mm} - 2\chi)(y_{24}^s - y_{42}^s) - (R_m + r_{Mm} - \chi)y_{14}^s \\ &\quad + (r_{Mm} - \chi)y_{41}^s + \chi y_{23}^s + (R_m - \chi)y_{32}^s \end{aligned} \tag{A3d}$$

The equilibria and stability properties of these recursions are analysed in the Data S1.

Appendix 2: Conditions for the invasion of modifiers increasing recombination

The conditions required for a modifier that increases recombination to have a leading eigenvalue greater than one were calculated (details in Data S1) and are provided here for equilibria (A) and (B). Swapping alleles *A* and *a* yields the analogous conditions for equilibria (A') and (B'). Throughout, fitnesses are measured relative to the heterozygote in each sex and linkage is assumed tight between the SDR and the selected locus ($r_i \approx 0$).

Equilibrium (A) with $0 < p_{Xf}, p_{Xm} < 1, p_Y \approx 0$:

The conditions for validity and stability of equilibrium (A) can be rewritten as $\alpha_1, \alpha_2, \alpha_3 > 0$, where $\alpha_1 = (M_{aa} + 1)/2 - F_{AA}$, $\alpha_2 = (1/M_{aa} + 1)/2 - F_{aa}$, and $\alpha_3 = 1 - M_{AA} - (1 - M_{aa})\alpha_1/(M_{aa}\alpha_2)$. In addition to these conditions, increased recombination is favoured if and only if $M_{aa} < 1$ and $M_{AA} < 1$ (hence requiring overdominance in males) and:

$$- \text{coef}_m R_m - \text{coef}_f R_f + \text{coef}_{mf} R_m R_f > 0, \tag{B1}$$

where coef_m is strictly positive:

$$\text{coef}_m = 8M_{aa}^2 \alpha_2 \alpha_3 (F_{aa} \alpha_1 + M_{aa} \alpha_2) (\alpha_1 + F_{AA} M_{aa} \alpha_2),$$

coef_f may be positive or negative:

$$\begin{aligned} \text{coef}_f &= 4M_{aa} (1 + M_{aa}) \alpha_2 \alpha_3 (2M_{aa} (\alpha_1 + M_{aa} \alpha_2)^2 \\ &\quad + \alpha_1 \alpha_2 (2M_{aa} (1 - M_{aa}) \alpha_2 - (1 - M_{aa})^3 - 2(\alpha_1 + \alpha_2) M_{aa}^2)) \end{aligned}$$

coef_{mf} is strictly positive:

$$\begin{aligned} \text{coef}_{mf} &= 4M_{aa}^2 \alpha_2 \alpha_4 (1 - M_{aa}) \\ &\quad \left((1 + M_{aa}) (\alpha_1 + \alpha_2) \left(\frac{\alpha_1}{M_{aa} \alpha_2} + (1 - \alpha_3) \right) + \alpha_1 \alpha_3 \right) + 4M_{aa}^2 \alpha_2 \alpha_3 \\ &\quad \left((2F_{aa} + (1 - M_{aa})) \alpha_1^2 + M_{aa} \alpha_1 \alpha_2 (3 + M_{aa} + 2F_{AA} (1 - M_{aa})) \right. \\ &\quad \left. + 2M_{aa}^2 F_{AA} \alpha_2^2 \right) \end{aligned}$$

and where $\alpha_4 = F_{AA} + F_{aa} - 2F_{AA}F_{aa}$. Because overdominance in males is required, AA homozygotes must be less fit than heterozygotes in females ($F_{AA} < 1$) for α_1 to be positive, but aa homozygotes may be more or less fit. Nevertheless, α_4 must be positive; this is trivially true if both $F_{aa} < 1$ and $F_{AA} < 1$, but remains true even if $F_{aa} > 1$; even at the largest value of F_{aa} consistent with the equilibrium being valid ($F_{aa} \rightarrow (1/M_{aa} + 1)/2$ given $\alpha_2 > 0$), α_4 remains positive and approaches α_1/M_{aa} .

Thus, for a modifier increasing recombination to spread, we must have:

$$R_f > \frac{\text{coef}_m R_m}{-\text{coef}_f + \text{coef}_{mf} R_m} \geq 0 \quad (\text{B2})$$

Consequently, looser linkage of the modifier, especially in females, facilitates the evolution of increased recombination between the sex chromosomes. Looser linkage ensures that, even when daughters benefit from inheriting the a allele from the Y of their fathers (by recombination), the modifier does not stay linked with the Xa combination so created, which would be selected against in grandsons.

When selection is weak, we can simplify the above conditions by defining fitness for males and females of genotype i as $M_i = 1 - t_i$ and $F_i = 1 - s_i$, respectively.

$$F_{AA} < 1 - \left\{ \frac{2(1 - M_{AA})((1 - M_{aa}) + M_{aa}R_f) + ((1 - M_{aa})M_{AA} + (1 - M_{AA})M_{aa})R_m(1 - R_f)}{4(1 - M_{AA}) + 2M_{AA}R_m} \right\} \quad (\text{B5})$$

Then, to leading order in the selection coefficients, the conditions for validity and stability of the equilibrium, $\alpha_1, \alpha_2, \alpha_3 > 0$, become:

$$\alpha_1 = s_{AA} - \frac{t_{aa}}{2}, \alpha_2 = s_{aa} + \frac{t_{aa}}{2}, \text{ and } \alpha_3 = t_{AA} - t_{aa} \frac{\alpha_1}{\alpha_2}$$

With weak selection, recombination is favoured when:

$$R_m R_f (t_{AA} + t_{aa}) > \alpha_3 (R_m + 2R_f). \quad (\text{B3})$$

Considered together with the fact that recombination rates cannot be greater than 1/2, these conditions can only be satisfied with overdominance in males ($0 < t_{aa}, t_{AA}$), selection against the AA genotype in females ($0 < s_{AA}$) and a sufficiently loosely linked modifier. Putting all of these conditions together for an unlinked modifier ($R_m = R_f = 1/2$), recombination is favoured near equilibrium (A) only with overdominance in males and $\frac{5t_{AA} - t_{aa}}{6t_{aa}} < \frac{2t_{AA}}{2t_{aa}}$. If the form of selection is similar in the two sexes but the strength of selection differs by a factor f (i.e. if $t_i = f s_i$), the condition for recombination to be favoured reduces to requiring

$f < 2/5$, implying substantially weaker selection in males than in females. Only then are the benefits of recombining the Y-linked allele (a) onto the X greater for daughters than the cost to sons of recombining the opposite allele (A) onto the Y.

Equilibrium (B) with $p_{Xf} \approx 1, p_{Xm} \approx 1, p_Y \approx 0$:

Measuring fitness relative to the heterozygotes, we can simplify the conditions for stability of equilibrium (B) to $\beta > 0$ and $M_{AA} < 1$, where $\beta = -\alpha_1 = F_{AA} - (M_{aa} + 1)/2$. Because of the opposite restriction on α_1 , equilibrium (B) can never be stable when equilibrium (A) exists and is stable. When equilibrium (B) is stable, increased recombination is favoured in the vicinity of this equilibrium if and only if:

$$\begin{aligned} & -4(1 - M_{AA})\beta - (2\beta M_{AA} + (1 - M_{AA})M_{aa})R_m \\ & - 2(1 - M_{AA})M_{aa} \left(1 - \frac{R_m}{2}\right) R_f \\ & + (1 - M_{aa})M_{AA}R_m R_f > 0 \end{aligned} \quad (\text{B4})$$

Only the last term can be positive, which itself requires that $M_{aa} < 1$. Thus, increased recombination can evolve only if there is overdominance in males and the modifier is sufficiently loosely linked. Equation (B4) can be rearranged to show further that selection in females must satisfy:

Because the term in braces is positive, F_{AA} must be less than one. That is, the most common type of female (AA) must be less fit than rare heterozygous females (Aa). This in turn implies that, within females, allele a must be positively selected for recombination to be favoured, despite the fact that the A allele is nearly fixed on the X chromosome at equilibrium (B). When these conditions are met, selection favours Xa in females but XA in males, such that recombination in fathers facilitates the production of more-fit Xa -bearing daughters.

Assuming weak selection (with $M_i = 1 - t_i$ and $F_i = 1 - s_i$), the conditions for stability of the equilibrium become $\beta = -s_{AA} + \frac{t_{aa}}{2} > 0$ and $t_{AA} > 0$, while recombination is favoured if:

$$R_m R_f (t_{AA} + t_{aa}) > t_{AA} (R_m + 2R_f) + 2\beta R_m. \quad (\text{B6})$$

Considered together, these conditions can only be satisfied with overdominance in males ($0 < t_{aa}, t_{AA}$) and a sufficiently loosely linked modifier. Putting all of these

conditions together for an unlinked modifier ($R_m = R_f = 1/2$), recombination is favoured near equilibrium (B) only with overdominance in males and $\frac{5t_{AA} + t_{aa}}{4} < s_{AA} < \frac{t_{aa}}{2}$. If the form of selection is similar in the two sexes but the strength of selection differs by a factor f (again, $t_i = f s_i$), this condition reduces to $\frac{f s_{aa}}{4 - 5f} < s_{AA} < \frac{f s_{aa}}{2}$. For there to be an interval of selection coefficients allowing recombination to be favoured, we again require that selection be substantially weaker in males than in females ($f < 2/5$), in which case s_{AA} must lie within this interval.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Data S1 *Mathematica* 8.0 (Wolfram Research, Inc. 2010) package detailing the recursion equations, analyses, and simulations conducted.

Data deposited at Dryad: doi:10.5061/dryad.5ds40

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