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Long-term fragility of Y chromosomes is dominated by short-term resolution of sexual antagonism

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ABSTRACT The evolution of heteromorphic sex chromosomes has fascinated biologists, inspiring theoretical models, experimental studies, and studies of genome structure. This work has produced a clear model, in which heteromorphic sex chromosomes result from repeated fixations of inversions (or other recombination suppression mechanisms) that tether sexually antagonistic alleles to sex-determining regions, followed by the degeneration of these regions induced by the lack of sex chromosome recombination in the heterogametic sex. However, current models do not predict if inversions are expected to preferentially accumulate on one sex-chromosome or another, and do not address if inversions can accumulate even when they cause difficulties in pairing between heteromorphic chromosomes in the heterogametic sex increasing aneuploidy or meiotic arrest. To address these questions, we developed a population genetic model in which the sex chromosome aneuploidy rate is elevated when males carry an inversion on either the X or Y chromosome. We show that inversions fix more easily when male-beneficial alleles are dominant, and that inversions on the Y chromosome fix with lower selection coefficients than comparable X chromosome inversions. We further show that sex-chromosome inversions can often invade and fix despite causing a substantial increase in the risk of aneuploidy. As sexual antagonism can lead to the fixation of inversions that increase sex chromosomes aneuploidy (which underlies genetic diseases including Klinefelter and Turner syndrome in humans) selection could subsequently favor diverse mechanisms to reduce aneuploidy—including alternative meiotic mechanisms, translocations to and fusions with the sex chromosomes, and sex chromosome turnover.

KEYWORDS pseudoautosomal region; sexual antagonism; Y chromosome loss; sex chromosome; inversion; aneuploidy

The origin and evolution of sex chromosomes has fascinated evolutionary biologists since their discovery more than a century ago (Stevens 1905; Wilson 1905). Existing evolutionary theory clearly explains the initial stages of sex chromosome evolution – in which (1) recombination is suppressed between one or a small number of loci underlying development of the sexes, (2) genes on non-recombining sex chromosomes decay by Mueller's ratchet, and (3) alleles with sex-specific fitness effects are recruited onto regions of the sex chromosome with suppressed recombination (Nei 1969; Charlesworth and Charlesworth 1978; Bachtrog 2008; but see Vicoso *et al.* 2013) However, theory has not addressed two critical questions concerning the later stages of sex chromosome evolution. First, current theory does not predict whether inversions tying together sexually antagonistic loci and sex chromosomes should preferentially occur on the X or Y chromosome. Second, theory has ignored the necessity of a recombining region in species with chiasmatic meiosis—as recombination suppression spreads across sex chromosomes, the region available for meiotic pairing of sex chromosomes in the heterogametic sex becomes small, likely creating problems during male meiosis (Dumont 2017a). The theory we develop below addresses these questions. Our results suggest that sex chromosome inversions can more easily invade Y(W) than X(Z) chromosomes and that the fixation of these inversions can occur even if they cause an increase in aneuploidy rate. We argue that the continued accumulation of inversions and the aneuploidy that indirectly results from these inversions shape the evolution of sex chromosomes and transitions to alternative meiotic segregation mechanisms.

The first step in the evolution of sex chromosomes is the origin of a Sex-Determining Region (SDR) defining the former autosomes as sex chromosomes (Westergaard 1958). Reduced

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recombination near the SDR in nascent sex chromosomes facilitates their divergence, which often begins once the SDR is established (Charlesworth 1991). Once recombination is suppressed around the SDR, this portion of the Y chromosome becomes effectively asexual and the irreversible accumulation of deleterious mutations leads to the decay of non-essential genes on the Y (Bachtrog 2008, 2013). In contrast, the X chromosome can avoid this fate since it recombines when present in females. The decay of the Y chromosome often leads to a visible difference in the size or staining properties of the sex chromosomes, a characteristic that was central to the recognition of their role in sex determination (Stevens 1906). We focus on male heterogametic species throughout this manuscript, however this same process, and the theory developed below applies to female heterogametic taxa as well as male heterogametic taxa.

Following the initial establishment of sex chromosomes, Sexually Antagonistic (SA) loci – loci where alternative alleles benefit one sex at the expense of the other, play a central role in sex chromosome divergence (Rice 1987). Specifically, selection to decrease recombination between the SDR and adjacent sexually antagonistic loci can drive the fixation of chromosomal inversions that further spread the reduction of recombination across the sex chromosome beyond the initial SDR (Nei 1969; reviewed in Kirkpatrick 2010). Such inversions are favored because males with an inversion on either the X or Y that captures an allele that is favored in females or males respectively will produce both sons and daughters of higher fitness than those produced by males, who lacking an inversion, allow sexually antagonistic alleles to recombine onto the opposite sex chromosomes. In many groups (e.g. mammals and insects) recombination reduction has continued through a series of cascading inversions until the X and Y share only a small region of colinearity known as the Pseudo-Autosomal Region (PAR), which undergoes pairing and recombination in the heterogametic sex (Ohno 1967; Blackmon *et al.* 2017).

This model of sex chromosome evolution highlights a fundamental, but underappreciated, tension in sex chromosome evolution. As PARs shrink, additional inversions that link sexually antagonistic loci to the non-recombining region still increase the fitness of a male's viable offspring, but such inversions can directly impact his fitness by increasing the probability of aneuploidy. This increased aneuploidy risk follows from the critical role of recombination in proper segregation of chromosomes in species with chiasmatic meiosis (Mather 1938; Jacobs *et al.* 1997; Dumont 2017b). Chiasmata, the physical connections between homologous chromosomes formed during recombination, generate the tension between homologs needed to ensure proper segregation during meiosis I. The absence of chiasmata can lead to aneuploid gametes, as homologs leave Meiosis I together and end up in the same daughter cell (Hassold and Hunt 2001). Indeed, empirical evidence suggests that the majority (2/3) of paternal origin XXY offspring result from a failure of recombination in the PAR region during spermatogenesis (Thomas *et al.* 2000). While we focus on the fitness cost of a reduced PAR induced by elevated aneuploidy risk, we note that this cost may manifest in other ways. For example, a missing or reduced PAR can result in early meiotic arrest due to the failed segregation of the sex chromosomes, rather than the production of aneuploid gametes (Mohandas *et al.* 1992; Burgoyne and Evans 2000; Dumont 2017a). In fact, complete azoospermia was observed in a human with a deletion of the PAR region (Mohandas *et al.* 1992).

Current theory does not explicitly address this tension between sexual antagonism favoring sex-chromosome inversions, and the resultant aneuploidy or meiotic arrest that disfavors them. Rather, prevailing wisdom holds that recombination reduction between sex chromosomes stops when the PAR becomes small because it is essential for proper segregation in species with chiasmatic meiosis (White 1977). This view would suggest that, given enough time, PAR sizes in all species would be roughly equal—reflecting a boundary of the minimum size required for proper segregation. However, the seven-fold differences in PAR size among eutherians (Raudsepp *et al.* 2012; Raudsepp and Chowdhary 2015) suggests that this is not the case.

We argue that rather than a strict minimum PAR size requirement, proper meiotic segregation of sex-chromosomes is likely a probabilistic function of PAR size. This view is supported by the negative relationship between autosome size and aneuploidy rates, which explains twenty to forty percent of the variation in aneuploidy risk among human chromosomes (Templado *et al.* 2011; McCoy *et al.* 2015). The "fragile Y hypothesis" extends this idea to sex chromosomes, as it posits a negative relationship between PAR size and sex chromosome aneuploidy during spermatogenesis across species (Blackmon and Demuth 2014, 2015b). Within this framework, PAR size can be seen as a dynamic balance between selection to resolve sexual antagonism and selection to avoid aneuploidy or even complete failure of spermatogenesis.

Starting from the canonical model described above, we develop an evolutionary model of sex chromosome evolution that incorporates the cost of aneuploidy associated with the evolution of inversions on heteromorphic sex chromosomes. Additionally, we extend models of sex chromosome evolution to include both X and Y inversions that could unite an SDR and a sexually antagonistic locus, in addition to the traditional case of an inversion uniting the Y chromosome and a male-beneficial allele (Clark 1988).

From this model, we identify the strength of sexual antagonism required for the invasion of alternative types of inversions across a range of aneuploidy rates, dominance coefficients, and recombination rates. Our results show that Y inversions can invade and fix over a broader portion of parameter space and with lower selection coefficients than can X chromosome inversions. This result predicts the previously unexplained observation that inversions appear more common on the Y than X chromosome (Lahn and Page 1999; Kuroiwa *et al.* 2001; Wang *et al.* 2012). Finally, our results show that even low levels of sexual antagonism could drive large increases in aneuploidy rates of sex chromosomes.

We argue that elevated rates of sex-chromosome aneuploidy are a pleiotropic result of selection favoring sex chromosome inversions in species with chiasmatic meiosis and highly heteromorphic sex chromosomes. Additionally, we argue that sexual antagonism not only drives the divergence of our sex chromosomes but is also the ultimate cause of and determinant of the incidence rates of paternal origin Turner syndrome and Klinefelter syndrome – two human diseases caused by sex-chromosome aneuploidy – an interpretation that is consistent with the observations that 90% of autosomal aneuploidy is maternal in origin while 75% of sex chromosome aneuploidy is paternal in origin (Hassold and Jacobs 1984; Uematsu *et al.* 2002). We therefore interpret numerous features of meiosis and sex chromosome evolution, including alternative meiotic mechanisms (achiasmatic or asynaptic meiosis), translocations to the PAR or fusions

with the sex chromosomes, and sex chromosome turnover, as mechanisms that may have evolved to reduce the aneuploidy or meiotic arrest generated by inversions that resolve intralocus sexual conflict.

Model Formulation

We develop a model with three biallelic loci in a diploid species with discrete and nonoverlapping generations. The SDR locus defines sex chromosomes as either X or Y. Individuals that are homozygous at this locus (XX) are female and individuals that are heterozygous (XY) are males. At the Sexually Antagonistic (SA) locus, allele a is beneficial to males, and allele A is beneficial to females. For simplicity, we use a symmetric fitness function where the increase in fitness that a male receives from an a allele is matched by an equal reduction in fitness for females carrying an a allele. Although a case of sex-limited fitness effects is possible (e.g. because of sex limited expression or sex limited inheritance), we do not model this because these cases are more likely the result of resolved sexual antagonism rather than a driving force in sex chromosome evolution (Vicoso *et al.* 2013; Beukeboom and Perrin 2014). Indeed when female mice carry the normally male limited and testis specific RMBY gene cluster their fitness is reduced in proportion with the number of copies they carry (Vernet *et al.* 2014). This is consistent with a gene that was ancestrally antagonistic that has now been isolated through sex chromosome divergence. The dominance coefficient, h, defines the impact of the a allele in heterozygotes – when h equals zero a is recessive, when h equals one a is dominant, and h of a half corresponds to full additivity.

The third "locus" is the presence or absence of an inversion that unites the SA locus and the SDR. Recombination between the SA locus and the SDR locus occurs at rate r in individuals homozygous for the ancestral orientation and is fully suppressed in inversion heterozygotes. Because the shuffling of alleles at the SA locus onto different X chromosomes does not influence the dynamics of our model, we ignore recombination in females. In our primary analyses, we assume that inversions do not affect genotype fitness in females but reduce male fitness by a multiplicative factor, u, representing the hypothesized increased rate of aneuploidy or meiotic arrest during spermatogenesis in males carrying an inversion reducing the size of the PAR. We do so because our model represents highly diverged sex chromosomes where the PAR is a small fraction of the size of the X chromosome overall. Thus, in female meiosis the size of the inversion pales in comparison to the overall size of the region that could still pair and recombine normally. To evaluate the robustness of our results to this assumption, we explored an alternative model where both sexes suffer from aneuploidy, which we present in the supplemental material (File S1). To evaluate if inversions are more likely to spread on X or Y chromosomes, we explore the dynamics of X and Y chromosome inversions capturing the A or the a allele respectively at the SA locus.

We denote genotypes with a capital X or Y to indicate the allele at the SDR locus and then a subscript of A or a to indicate the allele at the SA locus. Inversions are indicated by a subscript i. For example, X_AY_{ai} would indicate a male with the female-beneficial allele on the X chromosome and a Y chromosome with an inversion linking the male-beneficial allele to the male determining allele. We assume that both types of heterozygotes have equal fitness (e.g. $X_AY_a = X_aY_A$). We show the fitness of all genotypes in Table 1. Based on this model we developed a system of recursion equations that track the change in frequency of 4 possible chromosome types in eggs (X_{fA}, X_{fa}, X_{fAi}, X_{fai}) and 8 possible chromosome types in sperm (X_{mA}, X_{ma}, Y_A, Y_a, X_{mAi}, X_{mai}, Y_{Ai}, Y_{ai}) subscripts f and m indicate X chromosomes in egg or sperm respectively. We assume mating is random with respect to the SA locus such that the frequency of a genotype in the next generation is the sum of the product of the frequencies of the chromosome pairings that will yield that genotype and their relative fitness (full recursion equations are in File S1). Our approach extends the model of Otto (2014) by including a male-specific fitness cost for carrying an inversion under the special case in which inversions fully suppress recombination and symmetric sexual antagonism.

Table 1 Genotype finesses: s is the selection coefficient and h is the degree of dominance and u is the aneuploidy rate in male carriers of an inversion.

Female genotypes	Fitness	Male genotypes	Fitness
X_AX_A	1	X_AY_A	1
X_AX_a	$1/(1+hs)$	$X_AY_a = X_aY_A$	$1+hs$
X_aX_a	$1/(1+s)$	X_aY_a	$1+s$
		$X_{Ai}Y_A = X_AY_{Ai}$	$1(1-u)$
		$X_{Ai}Y_a = X_AY_{ai}$	$(1+hs)(1-u)$
		$X_{ai}Y_A = X_aY_{Ai}$	$(1+hs)(1-u)$
		$X_aY_{ai} = X_{ai}Y_a$	$(1+s)(1-u)$

We evaluated our model by beginning sexually antagonistic alleles at their equilibrium frequency, as a function of recombination rates, dominance, and selection coefficients (see File S1 and Figure S1 for details) (Rice 1987; Clark 1988) and then introduced an inversion at a frequency of 0.01%. This low frequency effectively allows us to observe the behavior of a new mutation when it first enters the population. Next, we iterated the recursion equations until the change in chromosome frequencies between generations was less than 10^{-6}. We repeated this process for both X and Y chromosome inversions across a broad range of selection coefficients and aneuploidy rates that fully encompass those observed in empirical studies (Gibson *et al.* 2002; Cox and Calsbeek 2009; Connallon *et al.* 2010; Templado *et al.* 2011; Uroz *et al.* 2011; McCoy *et al.* 2015). Briefly, we tested 100 selection coefficients (s) equally spaced from zero to one and 100 aneuploidy rates (u) from zero to 0.2. We used the 10,000 points tested to define the minimum selection coefficient that would allow an inversion to fix or be maintained as a stable polymorphism across this range of aneuploidy rates. We repeated this process with 100 dominance factors (h) ranging from zero to one. In each of these cases, we used recombination rates (r) of 0.1 and 0.3.

The biological motivation for our model suggests that larger inversions may be associated with higher aneuploidy rates because these large inversions will greatly decrease the opportunity for proper pairing. While we do not explicitly incorporate this expectation into our model, we explore this possibility by holding the dominance factor at 1 (male-beneficial allele a dominant) and explored recombination rates (r) ranging from zero to 0.5 and aneuploidy rates (u) from zero to 0.3. This pairing of parameters allowed us to determine if increased recombination rates allowed for higher aneuploidy rates to evolve. In

all analyses described below, the fate of X chromosome inversions introduced in either male or female backgrounds were qualitatively the same and are not discussed separately. Finally, although we describe an XY sex chromosome systems our results would apply equally to a ZW system by exchanging: Z for X and W for Y, and male and female fitness functions. The R script containing the full recursions and scripts for iteration are available in the supplemental material (File S1).

Data availability

Supplemental file S1 contains full recursion equations representing our model. This file also includes a full discussion of the alternative model where both males and females suffer from aneuploidy if heterozygous for an inversion. Finally file S1 contains the R code we used to implement our model and process the results of our iterations.

Results

Our results indicate that the fate of sex chromosome inversions that increase aneuploidy are strongly affected by the genetic architecture and the recombination rate between the SDR and the SA locus. Below we report the fate of X and Y chromosome inversions across a range of dominance values, recombination rates, and aneuploidy rates. We first illustrate the way that selection and genetic architecture interact to determine the fate of inversions. Next we identify the minimum selection coefficient that will allow an inversion to invade across a range of dominance values given a specified aneuploidy rate. Finally, we explore the relationship between aneuploidy rate and recombination rate between the SDR and the SA locus.

Impact of selection

To understand the impact of selection, we held recombination and aneuploidy rates constant and varied the dominance and selection coefficient to identify the final frequency of inversions. For fixed recombination and aneuploidy rates, the strength of sexual antagonism interacts with dominance to determine whether an inversion can or cannot invade. However, the strength of sexual antagonism has little impact on the equilibrium frequency of an inversion – which is largely controlled by the dominance coefficient. For instance, in Figure 1 we see that when the selection coefficient is above 0.05 – 0.12 both X and Y inversions are able to invade. Within this narrow range of selection coefficients, the dominance factor determines the point where an inversion can invade. In contrast, Figure 1B shows that increasing the selection coefficient has little effect on the eventual fate of an inversion. For instance, when the dominance factor (h) is less than approximately 0.3 an X inversion will invade if the selection coefficient is larger than 0.06. However, increasing the selection coefficient higher than this has little effect on the final frequency of the X inversion.

Impact of dominance

To understand the impact of dominance, we held recombination rate constant and varied the dominance factor and aneuploidy rate to identify the minimum selection coefficient required for an inversion to invade or fix. Our analysis indicates that X chromosome inversions are more sensitive to the dominance factor than are Y chromosome inversions. When the male-beneficial allele is recessive ($h < 0.3$), an X chromosome inversion that captures the female-beneficial allele cannot fix and instead is maintained as a stable polymorphism (Figure 2C and 2F). In contrast, when the male-beneficial allele is dominant an X chromosome inversion capturing the female-beneficial allele can fix but requires a higher selection coefficient than does a Y chromosome inversion carrying the male-beneficial allele. These results are robust to variance in the recombination rate between the SDR and the SA locus (Figure 2A–C vs. 2D–F).

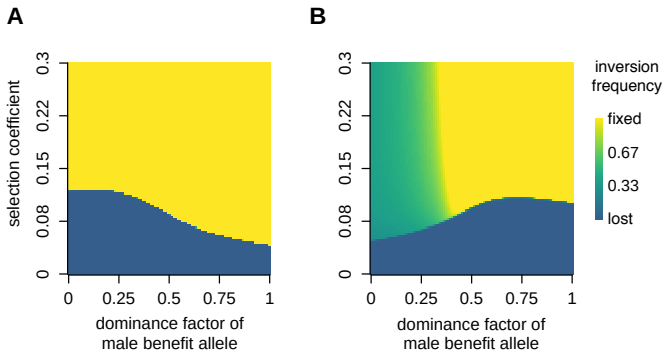

Figure 1 Sex chromosome inversions across a range of dominance factors and selection coefficients with a recombination distance of 0.3 and an aneuploidy rate of 0.02. The color in the plot indicates the stable frequency of the inversion. A) Y chromosome inversion capturing a male benefit allele B) X chromosome inversion capturing a female benefit allele.

The unique distribution of sex chromosomes among males and females along with the specifics of our model explain the differences between X and Y chromosome inversions. First, X chromosomes are found in both sexes and the dominance factor determines the degree to which reductions in recombination can lead to a resolution of sexual antagonism. Second, Y chromosomes occur only in males and can be selected strictly for male function thus as long as the selection benefit outweighs the cost of the increased aneuploidy risk, these inversions fix. When the male-beneficial allele is recessive sexual antagonism cannot be eliminated by cessation of recombination, males and females select for different allele frequencies on the X chromosome and an X inversion can be maintained as a stable polymorphism. In contrast, when the male-beneficial allele is dominant an inversion of either the X or Y chromosome will allow the X to fix the female-beneficial allele and the Y chromosome to fix the male-beneficial allele and sexual antagonism will be completely resolved.

Impact of recombination rate

Our model suggests that when the recombination rate between the SDR and the SA locus is larger there is a greater benefit to an inversion. This result reflects the fact that inversions suppress more recombination events (and are therefore more beneficial), the greater the background recombination rate between the two loci. This is illustrated in Figure 3 where we see that a given selection coefficient allows inversions with larger aneuploidy cost to fix as the recombination rate increases. This is more pronounced in Y chromosome inversions than it is in X chromosome inversions. In the case of X chromosome inversions, recombination rates of greater than 0.3 provide little additional benefit to inversions (Figure 3B). However, this result depends on the relationship between aneuploidy risk and recombination rate. A model where PAR size was explicitly tracked and aneuploidy risk was a function of PAR size would allow for a prediction of the size of inversions that are most likely to be favored by

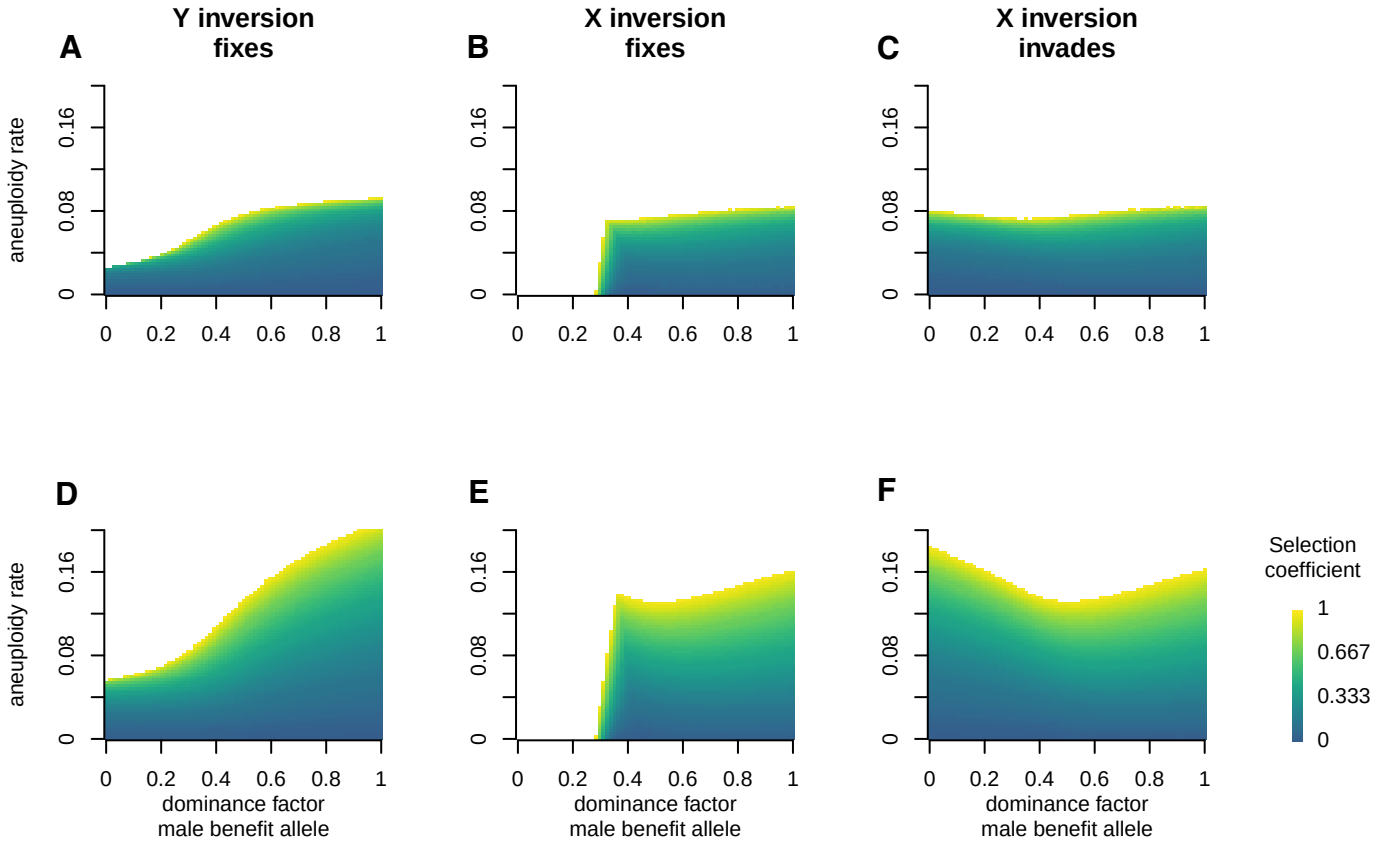

Figure 2 The fate of X and Y chromosome inversions across a range of dominance factors and aneuploidy rates. In panels A–C the recombination distance between the sex determining region and the sex antagonistic locus is 0.1. In panels D–F the recombination distance between the sex determining region and the sex antagonistic locus is 0.3. In each plot the color in the field indicates the selection coefficient required for an inversion to invade or fix. A) minimum selection coefficient for Y inversion to fix B) minimum selection coefficient for X inversion to fix C) minimum selection coefficient for X inversion to invade D) minimum selection coefficient for Y inversion to fix E) minimum selection coefficient for X inversion to fix F) minimum selection coefficient for X inversion to invade.

selection.

Discussion

Despite the extensive theory concerning sex chromosome evolution, previous models have not considered the elevated aneuploidy risk in the heterogametic sex associated with sex chromosome inversions. Therefore, it was not clear whether selection could favor such inversions in the face of this cost to species with chiasmatic meiosis where the pairing region is small. Our model fills this gap by incorporating this cost of inversions in the elevated risk of aneuploidy in the heterogametic sex. Our model indicates that, despite this cost, inversions tying together sexually antagonistic loci and sex determination regions can be favored by natural selection.

Additionally, our work suggests that inversions involving the Y chromosome are more likely to evolve than those involving the X chromosome. This result, and the impact of dominance on it, reflects the fact that male-beneficial alleles on the non-recombining portion of the Y chromosomes will never occur in females, while female-beneficial alleles on X chromosomes will be exposed in both sexes. Because of this, any Y inversion that captures the allele better for males will fix if its benefit outweighs its associated aneuploidy cost (Figure 1a).

The results for the X chromosome are best understood if we consider the ability of recombination cessation to resolve sexual antagonism. In the case of a recessive male-beneficial allele, X chromosome inversions are unable to resolve sexual antagonism. In contrast, when the male-beneficial allele is dominant, X or Y chromosome inversions are able to resolve sexual antagonism. Our model has clear implications for sex chromosome evolution and the evolution of meiosis, potentially explaining the evolution of achiasmatic meiosis in the heterogametic sex, the recruitment of autosomal regions onto the sex chromosome, and the preponderance of inversions on Y chromosomes relative to the X.

The fragile Y hypothesis argues that, in species with chiasmatic meiosis, sex chromosome aneuploidy rates increase with decreasing PAR size, and that evolutionary pressure to reduce this aneuploidy can favor translocations and fusions with autosomes and even drastic changes in mechanisms of meiosis (Blackmon and Demuth 2014, 2015b). Our model shows that even in the face of the cost of aneuploidy, inversions that tie sexually antagonistic alleles to sex chromosomes can be favored by natural selection. For instance, if the male-beneficial allele is dominant

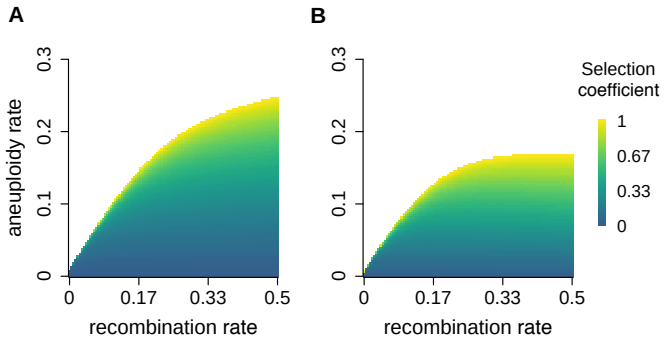

Figure 3 The effect of recombination on the fate of inversions that link a sexually antagonistic locus with the sex determining region while also increasing aneuploidy rate. Results are shown for the case where the male benefit allele is dominant and the female benefit allele is recessive. A) Y chromosome inversion linking the sex determining region and the male benefit allele. B) X chromosome inversion linking the sex determining region and the female benefit allele.

a selection coefficients as small as 0.2 is sufficient to fix Y chromosome inversions that increase aneuploidy by approximately 4–6% (Figure 2A and 2D). Thus the Y chromosome's long-term fragility can be driven by its short-term evolutionary interests.

The Haldane-Huxley rule refers to the observation that when one sex fails to recombine during meiosis (i.e. achiasmatic meiosis), it is usually the heterogametic sex (Haldane 1922; Huxley 1928; Bell 1982; Korol 1990). Numerous theoretical explanations of the Haldane-Huxley rule assume that the key feature of achiasmatic meiosis is a reduction in recombination in the heterogametic sex (Haldane 1922; Trivers 1988; Burt *et al.* 1991; Lenormand 2003). By contrast, rather than arguing that the genome-wide suppression of recombination in the heterogametic sex is directly advantageous, Huxley (1928), interpreted the Haldane-Huxley rule as a pleiotropic effect of a mechanism to suppress recombination between heteromorphic sex chromosomes. Like Huxley, we interpret the absence of recombination in the autosomes of the heterogametic sex as a pleiotropic consequence of selection. However, we argue that achiasmatic meiosis often evolves as a mechanism to ensure proper segregation not as a mechanism to reduce recombination.

Traditional theory predicts that achiasmy will evolve to reduce recombination between sex chromosomes in groups where substantial PARs could harbor large amounts of standing sexual antagonism (Otto *et al.* 2011). However, our explanation for the Haldane-Huxley rule predicts the opposite—that male achiasmy evolves to allow proper segregation in species with small PARs. Our theory is, therefore, consistent with the recurrent and recent origins of achiasmatic meiosis in the rodent genus *Microtus*, which have highly heteromorphic sex chromosomes that are already largely non-recombining (Borodin *et al.* 2012).

Asynaptic meiosis is a functional intermediate between achiasmatic and chiasmatic meiosis, which has evolved on multiple occasions and is phylogenetically widespread (Solari and Bianchi 1975; Smith and Virkki 1978; Blackmon and Demuth 2015a). In species with asynaptic meiosis, the homogametic sex and autosomes in the heterogametic sex undergo conventional chiasmatic meiosis. However, the sex chromosomes do not synapse or recombine in the heterogametic sex. Instead, a structure which seems to vary slightly among lineages forms between the sex chromosomes and holds them together at a distance until meiosis proceeds to the point that the chromosomes are ready to segregate to opposing poles (Wolf 1994; Page *et al.* 2003). The restriction of asynaptic meiosis to the heterogametic sex further supports the interpretation that the selective forces responsible for the Haldane-Huxley rule may well be limited to the sex chromosomes of the heterogametic sex and that impact on autosomes may well be a simple pleiotropic effect.

The stability of X chromosomes in eutherians was predicted based on the assumption that the X chromosome would be shielded from many types of mutations (double stranded breaks, inversions, tandem duplications etc.) since one copy is largely condensed and silenced in females (Ohno 1967). As we discuss below, our model shows that it is much easier for inversions involving the Y chromosome to invade and fix than those involving the X chromosome. Therefore, our model predicts that inversions on the Y will be the primary drivers of sex-chromosome divergence, without invoking Ohno's explanation. Empirical evidence of sex chromosome strata (regions where X and Y homologs have experienced approximately equal divergence) is consistent with this pattern. In humans, these strata consistently increase in divergence as we move from the PAR to the SDR of the X chromosome (Lahn and Page 1999; Pandey *et al.* 2013), while this order is shuffled on the Y chromosome. This suggests a set of many nested inversions and other rearrangements on the Y chromosome and relative stability of the X chromosome. Limited data from rats is also consistent with a model of a largely collinear X with inversion concentrated on the Y (Kuroiwa *et al.* 2001). All of these species silence one X chromosome and can potentially be explained by Ohno's model. However, recent data from papaya (which do not silence an X chromosome) also support the relative stability of the X relative to the Y chromosome (Wang *et al.* 2012), This suggests Y chromosomes may inherently be more likely to undergo the structural changes that lead to sex chromosome divergence. Although outside the scope of this paper, variation in mutation rates among chromosomes may have an impact on the expected contribution of X and Y inversions to the divergence of sex chromosomes. For instance, although fusions of autosomes with Y chromosomes are more strongly selected than X chromosome autosome fusions under some models of mutation this benefit does not translate to more fixed Y chromosome autosome fusions (Charlesworth and Charlesworth 1980; Pennell *et al.* 2015).

While our model suggests that inversions can more readily invade the Y than X chromosome, this prediction is not absolute – it depends on the dominance of sexually antagonistic alleles. We argue that both the general ease at which Y inversions accumulate and the exceptions to this general pattern are consequences of the fact that alleles on the non-recombining portion of Y chromosomes do not occur in females, while alleles on the X are found in both sexes, despite residing more frequently in females. For instance, when the male-beneficial allele has a dominance value less than approximately 0.3, X chromosome inversions will not fix (Figure 2B, 2E). Additionally, it is only under a narrow range of dominance factors (a allele, h $\approx$ 0.3–0.5) where X chromosome inversions can fix with a selection coefficient slightly lower than required for the fixation of a Y chromosome inversion (Figure 2D vs 2E). We explored an alternative version of our model where both sexes suffered equally from aneuploidy when they were heterozygous for an inversion. Under this model the dynamics of Y chromosome inversions remain the same but

the conditions for X chromosome inversions to fix become even more restrictive (Figure S2).

The size of inversions that fix on sex chromosomes has been largely ignored by previous theoretical work. Our work demonstrates that the fate of an inversion will ultimately be determined by the balance between the fitness benefit of resolving sexual antagonism and the fitness cost of elevated aneuploidy risk. The relative strength of these opposing forces are determined by the change in recombination rate produced by the inversion and the physical size of the PAR remaining after the inversion. For instance, a large inversion will benefit because it will substantially reduce the recombination load generated when e.g. a male-beneficial allele recombines onto an X-chromosome. However such a large inversion will also likely pay an increased cost, because it could have a large impact on the aneuploidy risk.

Additionally, because crossover in the PAR is obligate in chiasmatic species the effective recombination rate per base pair can be elevated orders of magnitude above the genome wide recombination rate when the PAR is small (Otto *et al.* 2011). This means that a physically small inversion in a species with a small PAR region may benefit from a high recombination rate between the SA locus and the SDR even though they are physically close together. Reciprocally, a physically large inversion in a species with a large PAR region may not benefit from a high recombination rate between the SA locus and the SDR even though they are physically much farther apart. Therefore, before we can make strong predictions about the expected distribution of inversion sizes we must know the relationship between aneuploidy risk and PAR size, a relationship that may itself vary across lineages.

The continued existence of Y chromosomes despite the population genetic forces driving their decay is a major mystery of sex-chromosome evolution (Steinemann and Steinemann 2005). Comparative genomic analyses suggest that translocations of autosomal material onto sex chromosomes may rejuvenate the PAR region of sex chromosomes (Disteche *et al.* 1992; Watson *et al.* 1993; Toder *et al.* 1995; reviewed in Blackmon and Demuth 2015c). However, the material that is transferred to the sex chromosomes eventually faces the same fate as the original sex chromosomes – recombination reduction and decay in the sex-limited chromosome. This pattern of translocation or fusion followed by decay was described by Graves as the addition-attrition hypothesis 1995. Although no selective force was initially proposed, theoretical models illustrate that sexual antagonism can drive fusions of sex chromosomes and autosomes to fixation (Charlesworth and Charlesworth 1980; Van Doorn and Kirkpatrick 2007; Matsumoto and Kitano 2016). Our model suggests an alternative explanation—that both the recruitment of genes onto the recombining portion of the sex chromosome and sex chromosome autosome fusion evolve to increase PAR size and decrease the risk of sex chromosome aneuploidy. Characterizing the relative contribution of these two forces will be difficult, but both molecular and broad comparative investigations may help. Future work determining the proportion of translocations on to the PAR and fusions with the PAR that contain molecular signatures of early sexually antagonistic selection may reveal the relative contribution of these two driving forces. Likewise, comparative studies that could test whether clades with small PARs experience more translocation or fusions than sister clades with large PARs would help to define the relative importance of these forces. Based on our results though, it seems clear that aneuploidy will increase in importance in chiasmatic species as the PAR region shrinks.

There are several important caveats to consider when interpreting our results. We considered the deterministic fate of a new mutation, ignoring both the source of mutational input and the effect of random genetic drift. Because species with equal sex ratios have three times more X chromosomes than Y chromosomes, considering the process of mutational input may change our predictions, as there are more opportunities for inversions to occur on X chromosomes than on Y chromosomes. However the commonly observed male bias in the rate of germline mutations could counterbalance this effect (Campbell and Eichler 2013). Determining what level of sex-biased mutation rates and variations in effective population sizes are necessary to make X chromosome inversions more likely than Y chromosome inversion is a promising area of future research. We do not comment on the effect of random genetic drift on our predictions as this will only be relevant for a narrow band of parameter space.

In sum, our work has two major implications. First, our work shows that the resolution of intralocus sexual conflict could incidentally increase the rates of sex-chromosome aneuploidy and that this can drive major features of meiosis and genome evolution. Second, our work predicts that inversions will preferentially occur on the Y chromosome as compared to the X. This latter prediction is broadly consistent with recurrent patterns of sex chromosome evolution, which has received little theoretical attention.

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