Note

Sex-Chromosome Turnovers: The Hot-Potato Model

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abstract: Sex-determining systems often undergo high rates of turnover but for reasons that remain largely obscure. Two recent evolutionary models assign key roles, respectively, to sex-antagonistic (SA) mutations occurring on autosomes and to deleterious mutations accumulating on sex chromosomes. These two models capture essential but distinct key features of sex-chromosome evolution; accordingly, they make different predictions and present distinct limitations. Here we show that a combination of features from the two models has the potential to generate endless cycles of sex-chromosome transitions: SA alleles accruing on a chromosome after it has been co-opted for sex induce an arrest of recombination; the ensuing accumulation of deleterious mutations will soon make a new transition ineluctable. The dynamics generated by these interactions share several important features with empirical data, namely, (i) that patterns of heterogamety tend to be conserved during transitions and (ii) that autosomes are not recruited randomly, with some chromosome pairs more likely than others to be co-opted for sex.

Keywords: heterogamety, mutational load, sex determination, sexually antagonistic genes.

Introduction

Ongoing genomic studies are revealing that sex-determination (SD) systems are extremely dynamic, much more than thought just 1 decade ago. Particularly high rates of sex-chromosome turnover are being documented in fishes (e.g., Phillips et al. 2001; Woram et al. 2003; Mank et al. 2006; Volff et al. 2007; Mank and Avise 2009) and amphibians (e.g., Miura 2007; Stöck et al. 2011*a*; Evans et al. 2012). The evolutionary causes of such turnovers, however, remain obscure. Van Doorn and Kirkpatrick (2007, 2010) recently proposed a role for sexually antagonistic (SA) genes: a male-benefiting mutation appearing on an autosome automatically induces a selective pressure favoring any masculinizing mutation in its vicinity. These authors showed analytically that a transition from an established sex chromosome pair A to a proto–sex chromosome B is expected to occur when $S_B L_B V_B > S_A L_A V_A$, where S_I corresponds to the strength of sexual selection on chromosome I (a complex function of the frequency of SA alleles and their effects on male and female fitness), L_I measures the linkage between the SD locus and the SA locus, and V_I is the genetic variance at the SA locus (with $I = [A, B]$). This mechanism (hereafter, "SA-driven") is well illustrated by a situation described in Cichlidae, where a new *ZW* system recently invaded an initial *XY* system via a mutation on the proto–W chromosome that conferred a blotched pattern of coloration. This mutation is beneficial to females because it confers a cryptic phenotype but costly to males because it disrupts mating coloration (Roberts et al. 2009; Ser et al. 2010). Alternatively, Blaser et al. (2013) proposed a role for the mutational load (ML) that accumulates on sex chromosomes. Epistatic interactions between SA and SD genes are expected to select for an arrest of recombination (Bull 1983; Rice 1996) so that male-beneficial mutations are transmitted only to sons and not daughters (and vice versa). However, deleterious loss-of-function mutations will soon accumulate in genes that happen to be trapped in the nonrecombining region (e.g., Charlesworth and Charlesworth 2000). In the absence of dosage compensation, this deleterious load is expected to lower survival in the heterogametic sex. Transitions should occur as soon as this survival cost exceeds the benefits brought by the SA alleles fixed on the decaying sex chromosome (Blaser et al. 2013).

These two models capture essential but distinct key features of sex-chromosome evolution (the roles of autosomal SA genes and deleterious mutations, respectively). Accordingly, they make different predictions and show distinct limitations. Regarding the timing of events, the SA-driven mechanism posits an initial SA mutation, followed by an SD takeover. In contrast, the alternative mechanism (hereafter, "ML-driven") posits an initial SD takeover, possibly followed by the spread of SA genes on the new sex chromosome. The SA-driven mechanism also allows for heterogametic transitions (as exemplified by Cichlidae; see

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above), which are prevented under the ML-driven mechanism: transitions from *XY* to *ZW* are expected to fix the Y homologue as an autosomal pair (van Doorn and Kirkpatrick 2010), which is of course detrimental if transitions are precisely triggered by the mutational load accumulating on these Y chromosomes. Importantly, the SA-driven mechanism allows for only a finite and limited number of transitions. As the above inequality makes explicit, a transition will occur only if SA effects and/or SA-SD linkage on the emerging sex chromosome exceed/s those on the established one, which should become less and less likely as transitions proceed. Moreover, both SA effects and SA-SD linkage are expected to reinforce once a chromosome is co-opted for sex (SA-SD linkage is strengthened by recombination arrest, which in turn selects for alleles with stronger SA effects). This escalation should soon come to an end, unless drastic changes occur in the selective regime (e.g., a sudden loss of SA effects on the current sex chromosome due to shifts in the patterns of female choice). In contrast, the ML-driven mechanism might allow for a potentially infinite recycling of sex chromosomes. After a first turnover, new SA alleles should accrue on the proto–sex chromosome, inducing an arrest of recombination and the ensuing accumulation of deleterious mutations. Thus, a new transition will soon become ineluctable, with a new pair of chromosomes seizing the leading role.

In our study, we combine features of these two mechanisms to model the dynamics of sex-chromosome turnover. As in the SA-driven model, we consider two pairs of chromosomes, both of which carry genes with the potential to fix SD and SA alleles, respectively. As in the ML-driven model, due to the absence of recombination in the heterogametic sex, either pair will accumulate deleterious mutations as soon as it is co-opted for sex. As our individual-based simulations show, this combination of features has the potential to generate endless cycles of transitions in sex chromosomes.

Methods

General Model

Our model consists of two pairs of chromosomes (1 and 2), each harboring (i) one gene involved in the sex-determining pathway (SD_1 and SD_2, respectively), (ii) one gene involved in sex differentiation (SA_1 and SA_2, respectively), potentially harboring sex-antagonistic alleles, and (iii) a series of 10 other functional genes.

The SD_1 and SD_2 genes carry recessive feminizing alleles (*X* and *x*, respectively) that mutate with probability 10^{-5} toward a dominant masculinizing form (*Y* and *y*, respectively). Accordingly, *XXxx* females can mutate toward either *XYxx* or *XXxy* males. The chromosomes harboring the *X* and *Y* (*x* and *y*, respectively) alleles are referred to as X and Y (x and y) chromosomes, respectively. The SA_1 and SA_2 genes similarly carry recessive female-benefiting alleles (*a* and *b*) that mutate with probability 10^{-5} toward a dominant male-benefiting form (*A* or *B*). These might represent, for example, coloration genes, with *aabb* individuals being dull, while *A-bb* or *aaB-* are brightly colored. Males lacking both *A* and *B* alleles have a fitness reduced by δ_m (due, e.g., to a reduced mating success), while females carrying either *A* or *B* have a fitness reduced by δ_f (due, e.g., to visual predation). We also performed simulations where SA_1 and SA_2 genes encode distinct and independent SA traits, bearing different costs or benefits to males and females (appendix, "Independent Sexually Antagonistic Traits"; appendix available online).

The other functional genes mutate at rate $\mu = 10^{-4}$ to deleterious forms, which decreases by *s* the fitness of homozygotes and by *hs* the fitness of heterozygotes (relative to the wild-type homozygote). Fitness effects on survival (*p*) are multiplicative, so that

$$p = (1 - s)^{n_s}(1 - hs)^{n_{hs}}, \quad (1)$$

where n_s and n_{hs} are the numbers of homozygous and heterozygous loci, respectively, for deleterious mutations. The chromosomal segment considered here recombines in females (with a distance of 10 cM between loci) but not in males. Thus, the Y (respectively, y) copies of functional genes will accumulate deleterious mutations as soon as their linkage group is co-opted for sex. Note that turnover rates would be lowered if there is a delay before recombination is actually reduced. We also performed simulations allowing for some male recombination.

Starting from an *XX/XY* system fixed on chromosome 1, transitions toward proto–sex chromosomes may occur along several paths (fig. 1). First, sex determination can be taken over by a masculinizing mutation occurring on either the autosome ($x \rightarrow y$) or the established sex chromosome ($X \rightarrow Y$). These will be referred to as heterologous and homologous transitions, respectively (sensu van Doorn and Kirkpatrick 2007, 2010). Second, both kinds of transitions may occur along two possible paths, corresponding to the SA-driven and ML-driven mechanisms, respectively. The male-benefiting mutation (SA locus) may appear and spread first (fig. 1, path 2 or 4) and then favor the spread of the masculinizing allele at the SD locus (fig. 1, path 2' or 4'). Alternatively, the masculinizing mutation may appear and spread first (driven by the mutational load accumulating on the decaying Y chromosome; fig. 1, path 1 or 3) and then trigger the spread of associated male-benefiting alleles at the SA locus (fig. 1, path 1' or 3').

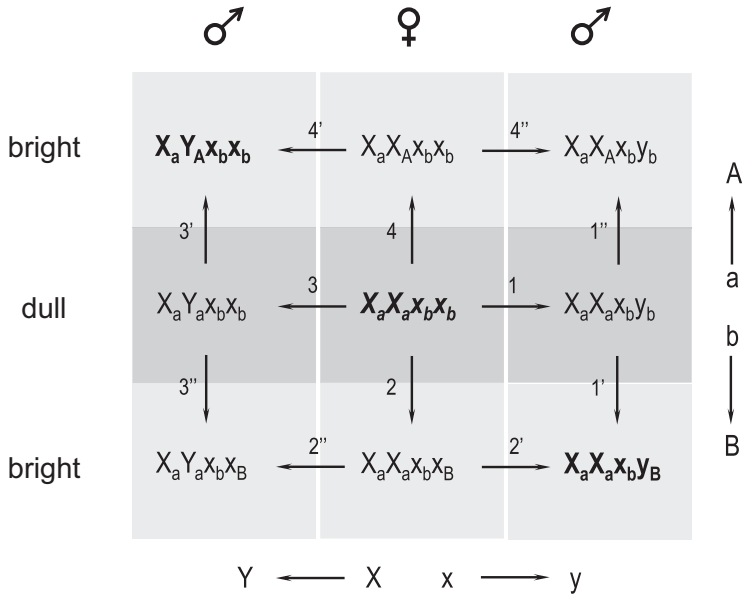

Figure 1: Starting from an $X_aX_ax_bx_b$ genotype (dull female; *center*), masculinization may occur either by an $X \rightarrow Y$ mutation (path 3) or an $x \rightarrow y$ mutation (path 1). Similarly, a mutation conferring a bright coloration may be either X linked (path 4) or x linked (path 2). The two mutations must combine to produce bright males, with sex and coloration determined by either the XY (*upper left corner*) or the xy (*lower right corner*) pair of chromosomes.

Simulations

Individual-based simulations were performed with quantiNemo (Neuenschwander et al. 2008; appendix, "Implementation Details"). Effective population size was fixed at $N = 1{,}000$, the selection coefficient of deleterious mutations at $s = 0.015$, and the dominance coefficient at $h = 0.1$. These values were chosen because the resulting *Nhs* value (1.5) was shown to maximize the deleterious load of mutations on nonrecombining sex chromosomes and, thereby, the rate of turnovers (Blaser et al. 2013). In a first set of simulations, we varied the values for δ_f and δ_m (0, 0.01, 0.025, and 0.05) in a fully factorial way (i.e., 16 different settings, 200 replicates each). Under each setting, the SA alleles on both chromosomes were assigned the same δ_f and δ_m values so that turnover dynamics were not led by the higher male benefits from the autosomal SA gene (or stronger linkage disequilibrium with the SD gene) as under the SA-driven mechanism but by the intrinsic decay of the male-determining chromosome (ML-driven). In a second set of simulations, different costs and benefits were assigned to SA_1 and SA_2 alleles and varied independently (appendix, "Independent Sexually Antagonistic Traits"). In a third set of simulations, some recombination was allowed in males (0.001 and 0.01 cM between loci), while still keeping this value to 10 cM in females.

All simulation sets started with an *XY* sex-determining system fixed on chromosome 1, a bright allele *A* fixed on the Y chromosome, and a dull allele *a* on the X chromosome. The chromosome 2 (autosome) was fixed for the recessive *x* and *b* alleles at its SD loci and SA loci. All functional genes were fixed for the wild-type alleles. All simulations were run over a time horizon of 100,000 generations, during which the number of turnovers and the proportion of heterologous transitions (number of heterologous transitions/total) were assessed (appendix, "Implementation Details").

Results and Discussion

Turnovers occurred at high rates in some of our simulations. Rates were highest for $\delta_m = \delta_f = 0$ (fig. 2, upper left panel), with about 3–16 transitions per 100,000 generations. In the absence of SA selection, transitions are indeed expected as soon as a few deleterious mutations accrue to the nonrecombining Y chromosome, according to the ML-driven mechanism. Increasing δ_m decreased the turnover rate regardless of the δ_f value (fig. 2, *rows*), because the cost paid by dull males increased the level of mutational load required to induce turnovers, thereby limiting transitions through paths 1 and 3 in figure 1 (Blaser et al. 2013). However, the strength of the effect varied with δ_f, being strong at $\delta_f > 0$ (fig. 2, *rows 2–4*) but moderate at $\delta_f = 0$ (fig. 2, *row 1*). In the latter case, bright alleles could still neutrally accumulate in females (fig. 1, path 2

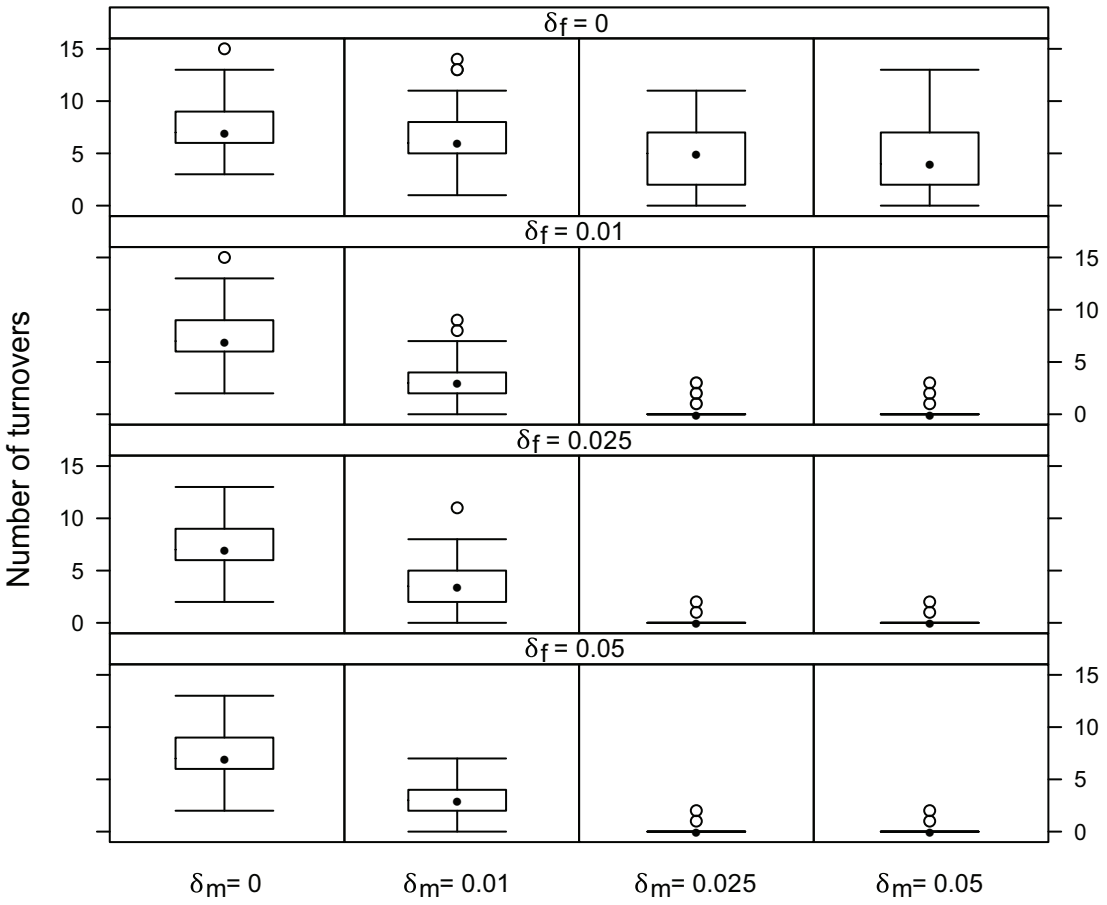

Figure 2: Number of transitions that occurred within $T = 10^5$ generations (averaged over 200 replicates) for different values of sexually antagonistic costs to males (δ_m) and females (δ_f). Transition rates were maximal in the absence of costs (*upper left panel*), decreased more heavily with increasing costs to males (*columns*) than to females (*rows*), and in the presence of female costs, stopped when δ_m exceeded 0.015 (*columns 3, 4*), corresponding to the maximal mutational load that could accumulate under our settings.

or 4), followed by masculinizing mutations (2' and 2'', and 4' and 4'', respectively). In the absence of costs to females, the male-beneficial allele could also spread on autosomes (i.e., 2'' and 4'', respectively) and thus get fixed in both sexes. Reciprocally, the effect of assuming a cost to bright females ($\delta_f > 0$) also depended on δ_m value. There was no effect of δ_f in the absence of costs to dull males ($\delta_m = 0$; fig. 2, *column 1*) because masculinizing mutations could neutrally accumulate in dull individuals (fig. 1, paths 1 and 3), followed by SA mutations (1' and 3', respectively). However, these paths were greatly limited as soon as $\delta_m > 0$, and transitions stopped for δ_m values in excess of 0.015 (*columns 3, 4*). This value corresponds to $1 - (1 - hs)^{10}$, that is, the maximal load of deleterious mutations that could accumulate under our settings. Our conclusions were not qualitatively affected when assuming independent and asymmetric effects of the sexually antagonistic genes SA_1 and SA_2 (appendix, "Independent Sexually Antagonistic Traits"); turnovers still occurred at high rates, decreasing as the average SA values increased (figs. A1, A2; figs. A1–A4 available online). Within simulations, the rates of turnovers were constant over the 100,000 generations, showing no acceleration or deceleration with time (fig. A3). Turnovers never occurred in the absence of deleterious mutations ($\mu = 0.00$; results not shown).

As our simulations show, therefore, the combination of deleterious mutations and autosomal SA genes has the potential to induce an indefinite cycling of sex chromosomes. The key mechanism operating here starts with the progressive lowering of fitness in established Y chromosomes (due to the accumulation of deleterious mutations) that will eventually favor any masculinizing mutation appearing on an autosome (or on an X chromosome). Being first dull, the neomales will soon turn bright via SA mutations on the proto–sex chromosome. As this autosome is co-opted for sex, however, it will stop recombining in

the heterogametic sex (thereby maximizing SA-SD linkage), which will reinitiate the process leading to its progressive decay and eventual replacement. Like a hot potato, sex determination "burns the hands" of the chromosome in charge until passed to the next player. It is worth underscoring that the key role of autosomal SA genes under our settings is not that of favoring new SD mutations in their vicinity (as in the SA-driven model) but that of inducing recombination arrest once this autosome has been co-opted for sex, thereby provoking the subsequent accumulation of deleterious mutations that will lead to the next turnover.

The rate of male recombination is crucial in this context. As our simulations also show, even very low rates (cM = 0.001 and 0.01; fig. A4) are enough to purge the deleterious load and strongly reduce the turnover rate (although not entirely suppress it, depending on δ_m and δ_f values). Indeed, occasional X-Y recombination was proposed as an alternative to turnovers to account for the overwhelming prevalence of homomorphic sex chromosomes among ectothermic vertebrates (the "fountain of youth"; Perrin 2009), and it likely accounts for the absence of sex-chromosome decay in tree frogs (Stöck et al. 2011*b*; Guerrero et al. 2012) and green toads (Stöck et al. 2013). X-Y recombination should be favored by the deleterious load accumulating on Y but opposed by SA genes due to the unwanted production of dull males and bright females. Under these counteracting forces, the equilibrium rate of X-Y recombination is in the order of 10^{-5} lower than X-X recombination (Grossen et al. 2012), which is, however, still enough to keep sex chromosomes homomorphic.

The size of the nonrecombining segment also matters. We included only 10 genes in our simulations; larger and more realistic values are expected to induce a much quicker decay and thereby a higher rate of turnover. Although our mutation rate per locus was relatively high (10^{-4}), the resulting net flux of deleterious mutations per Y chromosome ($U_Y = 10^{-3}$) was far below actual rates, estimated, for example, to exceed 10^{-1} in *Drosophila* (Charlesworth 1996). The effects of varying the size of this segment, as well as effective population sizes, are presented and discussed in length in Blaser et al. (2013).

Heterologous transitions occurred slightly more often than homologous ones in our simulations. Their frequency did not differ from 4/7 = 0.57, which under our settings measures the ratio of autosomes over the total number of chromosomes available for a masculinizing mutation (namely, four autosomes and three X chromosomes per mating pair). Real genomes normally contain more autosomes, which will increase the expected proportion of heterologous transitions. Homologous transitions, however, are bound to be much more difficult to identify empirically because they do not affect sex-linkage groups. Incidentally, this ascertainment problem also calls into question the evidence for X-Y recombination in *Hyla* gathered from the patterns of X-Y similarity at sex-linked markers (Stöck et al. 2011*b*; Guerrero et al. 2012). Theoretically, it is possible that the clustering of alleles by species (rather than by gametologues) actually stems from recurrent homologous transitions (namely, recurrent masculinizing mutations of the female-determining *X* allele). Fully excluding this possibility would require a phylogenetic analysis of the sex-determining gene itself: the fountain of youth predicts shallow phylogenies for all genes except for those involved in sex determination or differentiation, while the homologous-transition hypothesis predicts shallow phylogenies for all genes (including SD and SA).

Our settings did not allow for heterogametic transitions. These might be implemented by including the possibility of dominant female-beneficial mutations at SA loci and dominant feminizing mutations at SD loci. As mentioned in the introduction, such transitions should be possible only when the Y is still fit (which may occur for long evolutionary periods in case of rare X-Y recombination) and the autosomal SA mutation is strongly female beneficial. Interestingly, our combination of SA and ML processes could facilitate heterogametic transitions in a unique way. A current XY system with degenerated Y cannot transition to a ZW system. Sufficiently strong SA effects and SA-SD linkage should also prevent transition to another male-heterogametic system under an SA-driven mechanism alone. However, transition might first occur to a mutation-free xy system via the ML mechanism and subsequently to a ZW system via the SA mechanism. Thus, by resetting the SA clock, the mutation load might contribute to heterogametic transitions in a manner that would be impossible under either mechanism alone.

Interestingly, empirical data from vertebrates suggest that transitions tend to keep the patterns of heterogamety. Despite high turnover rates, all *Rana* species and populations reviewed by Miura (2007) are male heterogametic (XY), with the exception of *Rana rugosa* (characterized by both XY and ZW populations). In *Xenopus laevis*, the emergence of a new sex-determining *DM-W* gene has kept the ancestral female-heterogametic state (Yoshimoto et al. 2008; Olmstead et al. 2010). Similarly, all Salmonidae investigated so far are male heterogametic, but sex is determined by different linkage groups depending on species (Phillips et al. 2001; Woram et al. 2003). Among exceptions has to be counted the SA-driven heterogametic transition documented in Cichlidae (Roberts et al. 2009). Overall, empirical data gathered from vertebrates support expectations from the ML-driven model that transitions should generally not affect the patterns of heterogamety.

Another striking empirical trend is that autosomes are

not randomly recruited: some pairs seem more likely than others to be co-opted as sex chromosomes (Graves and Peichel 2010; O'Meally et al. 2012). In ranid frogs, 5 pairs out of 13 have been recurrently recruited (Miura 2007); one of them (harboring the candidate sex-determining gene *Dmrt1*) was also independently co-opted in deeply divergent groups of anurans from the hylids and the bufonids (Brelsford et al. 2013). The mechanisms explored in this study might also account for this trend. A chromosome pair that has already been involved in sex determination is more likely to seize back this role in the future (once purged from its deleterious mutation load) because it harbors genes with the potential to mutate toward SD or SA alleles. This is even more likely given that this chromosome pair is a priori expected to display some heterochiasmy (assuming recombination to be controlled by gender rather than X-Y divergence): male recombination on a given chromosome is strongly counterselected during the period spent as a sex chromosome and neutral during the periods spent as an autosome (female recombination being sufficient to prevent autosomal decay). Thus, reduced male recombination on an autosome might constitute the long-lasting signature of its sex chromosome past.

This latter expectation might be tested through further extensions of the present model by letting male recombination evolve independently on the different chromosome pairs during their times as sex chromosomes or autosomes. The predicted outcome is that any chromosome pair should quickly evolve reduced male recombination the first time it is co-opted for sex and that the sex-determining role will then cycle among a restricted set of chromosomes with lowered male recombination. Other developments involving the occurrence of dominant feminizing mutation at SD genes and female-beneficial mutations at SA genes might also provide insights on the conditions favoring changes in heterogamety and the expected frequencies of such transitions.

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