LETTERS

Turnover of sex chromosomes induced by sexual conflict

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Sex-determination genes are among the most fluid features of the genome in many groups of animals[1,2]. In some taxa the master sex-determining gene moves frequently between chromosomes, whereas in other taxa different genes have been recruited to determine the sex of the zygotes. There is a well developed theory for the origin of stable and highly dimorphic sex chromosomes seen in groups such as the eutherian mammals[3]. In contrast, the evolutionary lability of genetic sex determination in other groups remains largely unexplained[1]. In this theoretical study, we show that an autosomal gene under sexually antagonistic selection can cause the spread of a new sex-determining gene linked to it. The mechanism can account for the origin of new sex-determining loci, the transposition of an ancestral sex-determining gene to an autosome, and the maintenance of multiple sex-determining factors in species that lack heteromorphic sex chromosomes.

Fish provide examples of the dynamic nature of genetic sex determination seen in some groups of animals[4]. At least four different chromosomes determine sex in different species of salmon[5], the master sex-determining gene can differ between congeneric species[6], and sex determination is polygenic in some fish species[7].

Several mechanisms have been suggested to explain the puzzling diversity of genetic sex-determination mechanisms. These include random genetic drift[1,8], pleiotropic selection favouring new sex-determining alleles[9,10], sex-ratio selection[11,12] and various kinds of transmission distortion[13]. Although each is plausible for certain cases, these mechanisms involve fairly special biological conditions (for example, small population size or fortuitous pleiotropy).

Here we suggest a mechanism that extends the theory on the origin of sex chromosomes[1,14] to explain the movement of male determination from an ancestral Y chromosome to an autosome that then invades to become a neo-Y chromosome. The underlying force driving the change is sexually antagonistic selection, which is thought to be widespread on both theoretical and empirical grounds[15].

The mechanism begins with an autosomal locus segregating for two alleles that have sexually antagonistic effects (that is, different relative fitnesses in males and females). Consider the consequences of a mutation nearby on the same chromosome that causes individuals to develop into males regardless of what sex chromosomes they carry. This mutation could occur in a gene involved in the sex-determination cascade, for example, or result from transposition of the male-determining factor from the Y chromosome to the autosome. A genetic association (linkage disequilibrium) will develop naturally between the new allele that makes zygotes male and the allele that makes them good at being male. If this combination of genes produces males that have higher fitness than those carrying the original Y, the neo-Y can spread, effectively hijacking sex determination from the original sex chromosomes.

This verbal argument raises a series of questions. For example, how will additional sexually antagonistic loci located on the original sex chromosomes affect the process? Will invasion of a neo-Y always cause the loss of the ancestral Y, or can both be maintained in a multifactorial sex-determination system?

To address these issues, we developed a formal population-genetic model consisting of four loci. The first two are sex-determination factors: locus *Y* is the ancestral master sex-determination gene located on the sex chromosomes, whereas the autosomal locus *y* carries a dominant masculinizing mutation. The remaining two loci each segregate for two alleles with sexually antagonistic effects. Locus *a* is on the same autosome as locus *y*, whereas locus *A* is on the ancestral sex chromosome with locus *Y*. Locus *A* is included to account for the effects of genes with sex-antagonistic effects that tend to accumulate on the sex chromosomes[16]. Our primary aim is to explain the lability of sex determination in groups without highly differentiated sex chromosomes. We therefore assume that the sex chromosomes are non-heteromorphic. Locus *A* is present on both X and Y chromosomes, and we allow for recombination between *A* and *Y*. The evolutionary dynamics of the model are described by a system of 255 equations. Although it is not possible to do a full analysis, we were able to derive an approximation that describes how the population evolves when either the new masculinizing mutation or the ancestral Y chromosome is rare. Details are given in the Supplementary Information, where we also support our results by exploring the consequences of alternative assumptions on the genetic properties of the new sex-determining allele (partial dominance, incomplete penetrance or recessiveness).

When the masculinizing mutation is rare, its frequency changes at the exponential rate:

$$\lambda = S_a L_a V_a - S_A L_A V_A \quad (1)$$

The mutation spreads if λ is positive, and is lost if it is negative. The first of the two terms on the right represents the effect of locus *a*, which is linked to the new masculinizing mutation and favours it to invade. The second term results from locus *A*, which is carried on the ancestral sex chromosome and inhibits invasion of the new mutation. This inhibition is a consequence of the linkage disequilibrium between the ancestral sex-determining factor and male-beneficial alleles at locus *A*. Males that carry the neo-Y also carry two ancestral X chromosomes. The ancestral X chromosomes are enriched for the sex-antagonistic allele that is beneficial to females. Normal males carry an ancestral Y chromosome, which, in contrast, is enriched for the male-beneficial allele. Neo-Y carriers thus suffer a fitness reduction, quantified exactly by the second term on the right-hand side of equation (1). Both this fitness reduction and the fitness gain resulting from the genetic association between the new masculinizing

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factor at locus y and the male-beneficial allele at locus a can be decomposed in three contributing factors. The coefficients S_a and S_A represent the strength of sexually antagonistic selection acting on a and A, whereas $L_a = (1-r_a)/r_a$ and $L_A = (1-r_A)/r_A$ measure how closely linked those loci are to the sex-determining genes on their respective chromosomes (r_a and r_A are the recombination rates). The last elements of equation (1) are V_a and V_A, which measure the genetic variation at loci a and A. S and V depend on the allele frequencies at the sex-antagonistic loci, and their values can evolve. Full definitions for S and V are given in the Methods.

Equation (1) verifies the verbal argument: a masculinizing mutation can spread because of sexually antagonistic selection. The mutation's evolutionary advantage is strengthened by stronger sex-antagonistic selection and greater genetic variation at locus a, as well as tighter linkage between that gene and the new masculinizing factor at locus y. Conversely, sexually antagonistic selection acting on locus A on the sex chromosome favours the ancestral Y chromosome over the new mutation. Selection favours the Y chromosome that has the highest mean fitness, which in turn is determined by the pattern of sex-antagonistic selection and the amount of recombination.

What is the ultimate fate of a masculinizing mutation if it does invade? We can determine this fate by noting that equation (1) describes the dynamics of the ancestral Y chromosome when it is rare if we interchange indices A and a, and recalculate the values of S and V for the case that nearly all males carry the neo-Y. The simplest situation is when the sex-antagonistic genes are loosely linked to the sex determination loci (L_a, $L_A \ll 1$); in this case, the values of S and V change very little as the masculinizing mutation spreads (see Methods). Consequently, equation (1) implies that conditions that favour the new masculinizing mutation to spread when it is rare also favour the ancestral Y to be lost when it is rare. In short, if the masculinizing mutation increases when rare, it will spread to fixation. This process is exemplified by Fig. 1, which shows, for a particular set of parameters, predictions for the relative growth rates based on equation (1) together with corresponding simulation results. The agreement between the analytical approximation and the exact numerical simulations is generally as accurate as in Fig. 1b when selection is weak.

In the case illustrated by Fig. 1, sex determination is hijacked by the autosome from the ancestral sex chromosomes. The ancestral Y

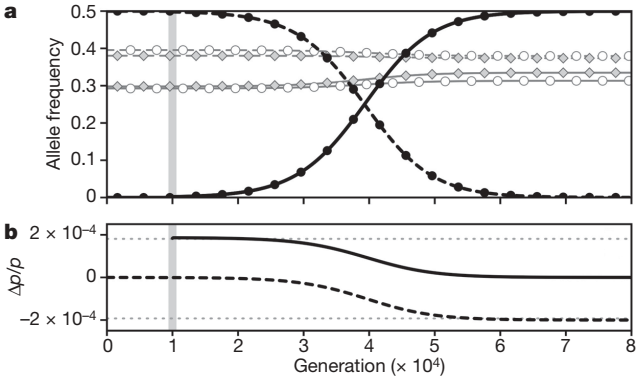

Figure 1 | Sex determination hijacked by an autosomal sex-determining factor. **a**, Black lines show the evolution of allele frequencies at sex-determination loci in males during a sex-chromosome switch (solid line, neo-Y; dashed line, ancestral Y). The frequencies of sex-antagonistic alleles change only slightly as the neo-Y spreads to fixation. Grey lines depict frequencies in females (open circles) and males (filled diamonds) at loci a (solid) and A (dashed). **b**, Equation (1) accurately predicts the asymptotic values (grey dotted lines) of the relative rates of increase of the neo-Y ($\Delta p_y/p_y$, solid black line) and the ancestral Y ($\Delta p_Y/p_Y$, dashed black line). The grey bar in panels **a** and **b** marks when the neo-Y first appeared by mutation. Parameters are: $s_A^F = 0.024$, $s_A^M = -0.026$, $s_a^F = -0.029$, $s_a^M = 0.025$, $h_A^F = h_a^M = 0.6$, $h_A^M = h_a^F = 0.4$, $r_A = 0.12$, $r_a = 0.08$.

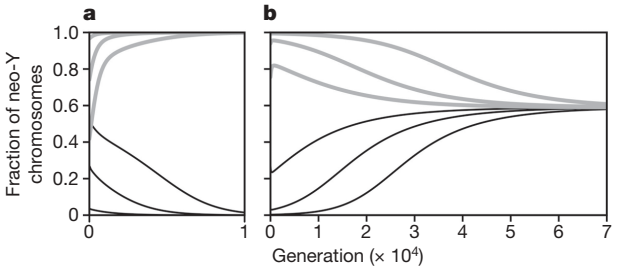

Figure 2 | Bistability and protected polymorphism of sex-determining factors. The two panels show examples of cases in which invasion of the neo-Y and its potential to spread to fixation do not coincide. **a**, Bistability: the neo-Y cannot invade a population in which sex is determined by the ancestral sex chromosomes (thin black lines depict runs with different initial frequencies of the neo-Y), but neither can the ancestral Y when the neo-Y is the established sex-determination factor (thick grey lines, for three different initial frequencies of the ancestral Y). Selection coefficients are: $s_A^F = -0.028$, $s_A^M = 0.017$, $s_a^F = -0.023$, $s_a^M = 0.027$. **b**, Protected polymorphism: the neo-Y can invade, but it cannot completely replace the ancestral Y, resulting in multifactorial sex determination (this is for $s_A^F = -0.027$, $s_A^M = 0.018$, $s_a^F = -0.028$, $s_a^M = 0.022$). Other parameters, for both panels, are: $h_A^F = 0.375$, $h_A^M = 0.625$, $h_a^F = 0.4$, $h_a^M = 0.6$, $r_A = 0.009$, $r_a = 0.012$.

disappears and the ancestral X becomes a new autosome. A neo-X and neo-Y are formed from the autosome that carries the masculinizing locus y. During this substitution YY males are not produced and so the potential deleterious effects of such genotypes do not affect the evolutionary process. Moreover, the substitution does not affect the sex ratio, which remains stable at 1:1 throughout.

More complex outcomes can occur when the sex-determining and sexually antagonistic loci are tightly linked (Figs 2 and 3). Here the dynamics of the sex-determination factors can induce considerable change in the genetic variances at the sexually antagonistic loci, such that invasion of the masculinizing mutation no longer implies loss of the ancestral Y. For some combinations of viability effects and linkage, both the ancestral Y and the new masculinizing mutation are lost when rare (Fig. 2a and region 3 in Fig. 3). The system is thus bistable: the population evolves to a single-factor sex-determination system governed by either locus Y or locus y, depending on the initial conditions. It is possible that random genetic drift could trigger

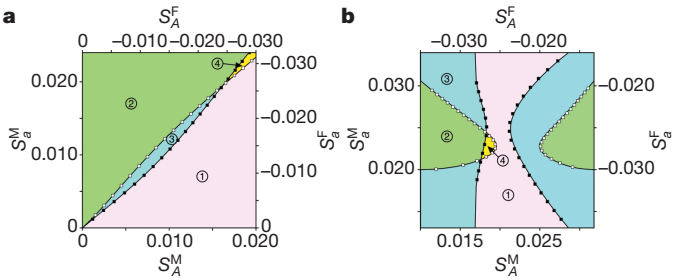

Figure 3 | Dependence of evolutionary outcomes on the selection coefficients. Systematically varying the values of the selection coefficients, we delineated four regions in parameter space that correspond to qualitatively different evolutionary outcomes of the model. In region 1 the ancestral Y is stable against invasion and further spread of the neo-Y. In region 2 the neo-Y can invade and replace the ancestral Y (as in Fig. 1). Regions 3 and 4 demarcate the selective regimes that give rise to bistability (as in Fig. 2a) or stable multifactorial sex determination (Fig. 2b), respectively. The boundaries between the regions were calculated from equation (1) (black lines) and by means of exact numerical simulations (open squares mark the invasion boundary of the neo-Y; filled squares mark its fixation boundary). In **a**, we varied the magnitude of sex-antagonistic fitness effects while keeping the ratio s_i^F/s_i^M ($i = a$ or A) constant. In **b**, the difference $s_i^M - s_i^F$ was fixed and we varied the average of the selection coefficients for males and females. Other parameters are as in Fig. 2.

transitions between these two equilibria. For other selection regimes, both the ancestral Y chromosome and the masculinizing mutation will increase when rare (Fig. 2b and region 4 in Fig. 3). The result is a protected polymorphism at both sex-determining loci, and the population evolves a two-factor sex-determination system. To our knowledge, sex-antagonistic selection is the only mechanism known that can produce a nuclear sex-determination system that can show stable multifactorial inheritance (see ref. 17) or bistability.

All else being equal, bistability and protected polymorphism occur when the intensities of sexually antagonistic selection at the sex-linked and autosomal loci are of comparable magnitude. This can be seen in Fig. 3a, in which the regions 3 and 4 extend over the diagonal. Away from the diagonal, one of the sex factors is associated with significantly stronger sex-antagonistic fitness effects, and that factor replaces the other. Figure 3b provides further insights in the population-genetic mechanisms responsible for bistability and protected polymorphism. Bistability is prominent in the corner regions of Fig. 3b, where the fitness effects of the sex-antagonistic alleles are strongly biased towards one sex or the other. In such cases, much less genetic variation can be maintained at autosomal loci than at sex-linked loci. Whichever sex factor is rare is thus linked to a sex-antagonistic locus that harbours little genetic variation, whereas the established sex factor is linked to a more variable sex-antagonistic locus. This causes an intrinsic disadvantage of rarity resulting in bistability. The opposite effect acts on sex-antagonistic alleles that are nearly neutral on average, and this explains why the region of protected polymorphism is located centrally in Fig. 3b. Sexually antagonistic alleles with equal but opposite fitness effects are maintained at a frequency close to one-half at autosomal loci, but tend to go to fixation at sex-linked loci, especially when linkage is tight. Genetic variation at the sex-linked locus, expressed as an average of X- and Y-linked variation (see Methods), will thus be smaller than the genetic variation at the autosomal sex-antagonistic locus. The result is an inherent advantage of rare sex factors allowing for the maintenance of multiple sex-determination alleles.

Three factors inhibit the hijacking process and might account for the great evolutionary stability of sex chromosomes in groups such as mammals and birds[18]. The first is the presence of genes essential for male fertility or viability that are located on the ancestral Y chromosome and that are absent from the ancestral X. Unless the neo-Y resulted from a major translocation containing the male-determining factor and the essential genes from the ancestral Y chromosome, such genes would absolutely prevent the invasion of the new masculinizing factor. A second inhibiting factor is the evolution of dosage compensation in genes that are close to the sex-determining locus, and the third brake on the process is produced by sex-antagonistic genes on the ancestral sex chromosomes (represented by the second term of equation (1)). Long-term evolution of the sex chromosomes typically results in the accumulation of sex-antagonistic polymorphisms[16], the reduction of recombination rates[1,3] and divergence of the X and Y chromosomes in the vicinity of the master sex-determining gene. As the sex chromosomes progressively differentiate, these factors make the conditions for hijacking more restrictive (by increasing S_A and L_A in equation (1)), enhancing the evolutionary stability of the established sex-determination system. In contrast, the evolution of sex-limited expression of sex-antagonistic genes on the ancestral sex chromosomes makes these chromosomes more vulnerable to the invasion of new sex-determining factors. Sex-limited expression reduces the sexual conflict, or may even fully resolve it, leading to a loss of polymorphism at the ancestral sex chromosomes. The long-term stability or lability of sex-determination may thus depend on a balance between sexual conflict, the evolution of gene regulation and structural evolution of the sex chromosomes[18].

What is the scope for the mechanism described here? The two essential ingredients are sexually antagonistic polymorphisms and new sex-determining loci on autosomes. Polymorphism at sexually antagonistic loci can be maintained by constant selection pressures, as we assumed in this study, but only for a restricted range of parameters, particularly at autosomal loci. Yet, the mechanism we portray here can also operate if some other evolutionary force maintains the sexually antagonistic polymorphism, for example, frequency-dependent selection, migration or mutation. Alternatively, even transient polymorphisms could trigger the hijack mechanism, providing that the total fitness variation at sexually antagonistic loci generated by transient polymorphisms is sufficiently large at any point in time. Recent data from expression studies reveal that a remarkable fraction—between 15% and 70%—of genes has sexually dimorphic expression in a variety of organisms[19–21]. Any segregating gene among those with sex-specific effects could participate in the hijack process. Given the ubiquity of sexually dimorphic expression, we do not expect sex-chromosome switches to be precluded by a lack of variation at sexually antagonistic loci, even if we are ignorant about the mechanisms that support the high levels of polymorphism found in nature.

The second ingredient, sex-determining mutations on autosomes, may also be quite common. Our model applies equally to transposition of an existing master sex-determining gene as to mutations at other loci that result in sex determination. Both processes are known. In humans, for example, there are many autosomal mutations that reverse sex (see http://www.ncbi.nlm.nih.gov/omim/). Translocation of a master male-determining gene to an autosome has been suggested in several groups of animals (for example, flies[22,23] and salmonid fishes[5]). Thus, in some taxa there may be a sufficient flux of mutations that satisfy equation (1) to explain the observed turnover of sex chromosomes. Another possibility is that an inversion can, by chance, capture a masculinizing allele and a sex-antagonistic gene, instantly increasing the linkage between the two (the term L_a in equation (1)) and therefore triggering a hijack.

In the discussion above, males are the heterogametic sex (that is, the sex determination system is XY). The mechanism also applies to female heterogamety (ZW sex determination, as in birds and butterflies), in which case a dominant feminizing mutation on an autosome hijacks sex determination from the ancestral sex chromosomes. The model does not address heterogamety switches, however, in which there is an evolutionary transition between XY and ZW sex determination. We expect that heterogamety switches, which are known from several groups of vertebrates[2], might also be driven by sexually antagonistic selection. The evolutionary process involved, however, is more complex because YY (or WW) individuals are produced.

A prediction from our model is that recently derived sex-determining regions will be associated with genes that are targets of sexually antagonistic selection. Observations consistent with this prediction are that sexually selected colour genes are closely linked to the sex-determining genes in poeciliid[7] and cichlid[24] fishes. This is a weak test of the hypothesis, however, because the sexually antagonistic genes may have accumulated after the new sex chromosomes were established rather than driving the process. A more stringent test would be to look for sexually antagonistic genes in very young sex chromosomes, and in the homologous autosomal regions of closely related species that have not undergone the hijacking. Promising systems for these investigations include the medaka[6] and the three-spined stickleback[25].

Sexually antagonistic selection is thought to result most often from behavioural strategies shaped by sexual selection, through either male–male competition or female choice[15]. Although it has long been known that genes contribute importantly to differences in behaviour between individuals within a species, the model presented here suggests that the arrow of causality can also point in the opposite direction. Behaviour may drive the evolution of the genome, as well as the converse.

METHODS SUMMARY

The relative viabilities of the (0,0), (0,1) and (1,1) genotypes in females are 1: $1+h_i^F s_i^F$: $1+s_i^F$ for locus i (= A or a), where s_i^F and h_i^F represent selection and

dominance coefficients, respectively. The notation for viabilities in males is analogous, but with F (female) replaced by M (male). We assume that loci *A* and *a* have independent (multiplicative) effects on fitness and that mating is random.

We distinguish between the frequency of allele 1 at locus *A* on the ancestral X chromosome, denoted p_A^X, and its frequency on the ancestral Y chromosome, denoted p_A^Y. The frequency of allele 1 at locus *a* on chromosomes carrying the masculinizing mutation at locus *y* is denoted p_a^y, and its frequency averaged over all chromosomes is $\bar{p}_a$.

The factors S_A and S_a appearing in equation (1) measure the effects that sexually antagonistic selection on loci *A* and *a* have on the masculinizing mutation at locus *y*. These terms, which are derived in the Supplementary Information, are defined as:

$$S_a = \frac{1}{2} s_a^M[\bar{p}_a + h_a^M(1-2\bar{p}_a)]\{s_a^M[\bar{p}_a + h_a^M(1-2\bar{p}_a)] - s_a^F[\bar{p}_a + h_a^F(1-2\bar{p}_a)]\}$$

$$S_A = \frac{4\{s_A^M[p_A^X + h_A^M(1-2p_A^X)]\}^2\{2s_A^F[p_A^X + h_A^F(1-2p_A^X)] + s_A^M[p_A^Y + h_A^M(1-2p_A^Y)]\}}{2s_A^F[p_A^X + h_A^F(1-2p_A^X)] + s_A^M[p_A^Y + h_A^M(1-2p_A^Y)] - 3s_A^M[p_A^X + h_A^M(1-2p_A^X)]}$$

The terms in equation (1) that represent genetic variation at those loci are: $V_a = p_a^y(1-p_a^y)$, $V_A = \frac{1}{4}[3p_A^X(1-p_A^X) + p_A^Y(1-p_A^Y)]$

For our analyses, we evaluated these expressions using the equilibrium allele frequencies at loci *A* and *a* before the masculinizing mutation appears[16]. Those frequencies depend only weakly on the frequency of the neo-Y chromosome when linkage is weak (L_A, $L_a \ll 1$) (Fig. 1a), a fact that can be used to show that if the masculinizing mutation at locus *y* is favoured when rare then the ancestral Y chromosome will be lost.

The analytical results presented in equation (1) and the Supplementary Information were checked by means of numerical simulations based on a full set of recursions for the genotype frequencies that did not involve the approximations used in the analytical treatment. Results of these simulations are shown in Figs 1–3.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Turnover of sex chromosomes induced by sexual conflict: Supplementary online material

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The text describes a model consisting of 4 loci: locus *Y* (the ancestral sex-determining locus), locus *A* (a sexually-antagonistic locus linked to *Y*), locus *y* (an autosomal locus segregating for a new dominant masculinizing mutation), and locus *a* (a sexually-antagonistic locus linked to *y*). In Sections (1) - (3) of this supplementary material we derive an analytic approximation for the evolution of the new masculinizing allele at locus *y*. The main result appears in the text as Equation (1).

The analysis is simplified by the following consideration. If selection coefficients at the sex-antagonistic loci *A* and *a* are small, then their contributions to the evolution at locus *y* are approximately additive (to leading order in the selection coefficients). This follows because locus *A* is unlinked to both *a* and *y*, and so departures from additivity (which depend on 3-way linkage disequilibria) are negligible relative to the individual effects of *A* and *a* on *y* (which depend only on two-way disequilibria). We have verified this intuitive argument with a formal analysis using the methods of Kirkpatrick et al. (2002, Genetics 161: 1727-1750).

Our strategy is therefore to decompose the 4-locus model into two models of three loci. In Section (1), we calculate the rate of evolution for the masculinizing mutation in a model that includes loci *Y*, *y*, and *A*. In Section (2), we calculate its evolutionary rate in a model that includes loci *Y*, *y*, and *a*. Finally, in Section (3), we add the result from Sections (1) and (2) to arrive at text Equation (1). Following that, in Section (4), we evaluate the validity of our results in the limit of full linkage (no recombination), and we present simulation results for a number of cases that deviate from our basic model assumptions (Section (5)).

This document has been generated using *Mathematica* (Wolfram 2003). The original file is available from the authors on request and can be used to verify the calculations.

1 - Effect of a sex-antagonistic locus on the sex chromosome

In the first submodel we keep track only of the loci *Y*, *y* and *A*. A fraction ϵ_y of the males in the population carry a novel masculinizing sex determination allele at locus *y*. Our analysis focuses on the evolution of this mutation when it is rare (that is, $\epsilon_y \ll 1$). Four additional variables are needed to describe the genetic state of the population. These variables measure the frequency of the allele 1 on locus *A* in female or male gametes with a particular combination of sex determination alleles. They are defined as follows: X_{A_F} represents the frequency of allele 1 at locus *A* on X chromosomes in female gametes. The variables X_{A_M} and Y_A denote the frequency of allele 1 at locus *A* on the X- and Y chromosomes transmitted via the gametes of normal males. The final variable, x_A, corresponds to the frequency of allele 1 at locus *A* on X chromosomes in the gametes of males that carry the novel mutant sex determination factor.

Recursion equations

To derive the recursions that describe how the population evolves, we start by calculating the frequencies of genotypes at locus *A* in female zygotes, normal male zygotes and mutant male zygotes. We assume that mating is random. Genotype frequencies are listed in the order {11, 10, 01, 00}, where the first and second numbers in a genotype represent the alleles inherited from the mother or the father, respectively. In individuals homozygous for the original sex determination factor (females and mutant males), the genotype classes 10 and 01 can be grouped together.

When the mutation is rare, the frequencies of the genotypes in males and females that do not carry the mutation can be calculated approximately by neglecting the mutation:

$$\text{femaleZygoteFreq} = \{X_{A_F} X_{A_M},\ X_{A_F}(1 - X_{A_M}) + (1 - X_{A_F}) X_{A_M},\ (1 - X_{A_F})(1 - X_{A_M})\};$$

$$\text{normalMaleZygoteFreq} = \{X_{A_F} Y_A,\ X_{A_F}(1 - Y_A),\ (1 - X_{A_F}) Y_A,\ (1 - X_{A_F})(1 - Y_A)\};$$

The frequencies of the genotypes among males that carry the mutation are:

$$\text{mutantMaleZygoteFreq} = \{\epsilon_y X_{A_F} x_A,\ \epsilon_y X_{A_F}(1 - x_A) + \epsilon_y (1 - X_{A_F}) x_A,\ \epsilon_y (1 - X_{A_F})(1 - x_A)\};$$

Next, we define the genotype fitness values for the different kinds of individuals.

$$\text{femaleFitness} = \{1 + s_{A_F},\ 1 + h_{A_F} s_{A_F},\ 1\};$$

$$\text{normalMaleFitness} = \{1 + s_{A_M},\ 1 + h_{A_M} s_{A_M},\ 1\};$$

$$\text{mutantMaleFitness} = \{1 + s_{A_M},\ 1 + h_{A_M} s_{A_M},\ 1\};$$

A genotype's frequency in adults is given by the product of its frequency in zygotes and its fitness, normalized by the mean fitness. Since the frequency of the mutant allele is low, we may neglect the impact of mutant individuals on the mean fitness. Thus we have:

$$\text{femaleFreq} = \frac{\text{femaleZygoteFreq} * \text{femaleFitness}}{\bar{W}_F}$$

$$\left\{\frac{(1 + s_{A_F}) X_{A_F} X_{A_M}}{\bar{W}_F},\ \frac{(1 + h_{A_F} s_{A_F})(X_{A_F}(1 - X_{A_M}) + (1 - X_{A_F}) X_{A_M})}{\bar{W}_F},\ \frac{(1 - X_{A_F})(1 - X_{A_M})}{\bar{W}_F}\right\}$$

$$\text{normalMaleFreq} = \frac{\text{normalMaleZygoteFreq} * \text{normalMaleFitness}}{\bar{W}_M}$$

$$\left\{\frac{(1 + s_{A_M}) X_{A_F} Y_A}{\bar{W}_M},\ \frac{(1 + h_{A_M} s_{A_M}) X_{A_F}(1 - Y_A)}{\bar{W}_M},\ \frac{(1 + h_{A_M} s_{A_M})(1 - X_{A_F}) Y_A}{\bar{W}_M},\ \frac{(1 - X_{A_F})(1 - Y_A)}{\bar{W}_M}\right\}$$

$$\text{mutantMaleFreq} = \frac{\text{mutantMaleZygoteFreq} * \text{mutantMaleFitness}}{\bar{W}_M}$$

$$\left\{\frac{(1 + s_{A_M}) x_A X_{A_F} \epsilon_y}{\bar{W}_M},\ \frac{(1 + h_{A_M} s_{A_M})(x_A (1 - X_{A_F}) \epsilon_y + (1 - x_A) X_{A_F} \epsilon_y)}{\bar{W}_M},\ \frac{(1 - x_A)(1 - X_{A_F}) \epsilon_y}{\bar{W}_M}\right\}$$

The mean fitnesses in females and males are:

$$\bar{W}_F = \sum_{i=1}^{3} (\text{femaleZygoteFreq} * \text{femaleFitness})[[i]]$$

$$(1 - X_{A_F})\,(1 - X_{A_M}) + (1 + s_{A_F})\,X_{A_F}\,X_{A_M} + (1 + h_{A_F}\,s_{A_F})\,(X_{A_F}\,(1 - X_{A_M}) + (1 - X_{A_F})\,X_{A_M})$$

$$\bar{W}_M = \sum_{i=1}^{4} (\text{normalMaleZygoteFreq} * \text{normalMaleFitness})[[i]]$$

$$(1 - X_{A_F})\,(1 - Y_A) + (1 + h_{A_M}\,s_{A_M})\,X_{A_F}\,(1 - Y_A) + (1 + h_{A_M}\,s_{A_M})\,(1 - X_{A_F})\,Y_A + (1 + s_{A_M})\,X_{A_F}\,Y_A$$

By calculating the frequencies of the different haplotypes in gametes from females, normal males and mutant males, we obtain the following recursion equations for the variables of the model.

$$\text{eqXAF} = \text{femaleFreq}[[1]] + \frac{\text{femaleFreq}[[2]]}{2} \;//\; \text{FullSimplify}$$

$$\frac{-(1 + h_{A_F}\,s_{A_F})\,X_{A_M} + X_{A_F}\,(-1 + s_{A_F}\,(-h_{A_F} + 2\,(-1 + h_{A_F})\,X_{A_M}))}{-2 + 2\,s_{A_F}\,(-X_{A_F}\,X_{A_M} + h_{A_F}\,(-X_{A_M} + X_{A_F}\,(-1 + 2\,X_{A_M})))}$$

$$\text{eqXAM} = \text{normalMaleFreq}[[1]] + (1 - r_A)\,\text{normalMaleFreq}[[2]] + r_A\,\text{normalMaleFreq}[[3]] \;//\; \text{FullSimplify}$$

$$\frac{-r_A\,(1 + h_{A_M}\,s_{A_M})\,Y_A + X_{A_F}\,((-1 + r_A)\,(1 + h_{A_M}\,s_{A_M}) + (-1 + h_{A_M})\,s_{A_M}\,Y_A)}{-1 + s_{A_M}\,(-X_{A_F}\,Y_A + h_{A_M}\,(-Y_A + X_{A_F}\,(-1 + 2\,Y_A)))}$$

$$\text{eqYA} = \text{normalMaleFreq}[[1]] + r_A\,\text{normalMaleFreq}[[2]] + (1 - r_A)\,\text{normalMaleFreq}[[3]] \;//\; \text{FullSimplify}$$

$$\frac{(-1 + s_{A_M}\,(h_{A_M}\,(-1 + X_{A_F}) - X_{A_F}))\,Y_A + r_A\,(1 + h_{A_M}\,s_{A_M})\,(-X_{A_F} + Y_A)}{-1 + s_{A_M}\,(-X_{A_F}\,Y_A + h_{A_M}\,(-Y_A + X_{A_F}\,(-1 + 2\,Y_A)))}$$

$$\text{eqxA} = \frac{\text{mutantMaleFreq}[[1]] + \frac{1}{2}\,\text{mutantMaleFreq}[[2]]}{\sum_{i=1}^{3} \text{mutantMaleFreq}[[i]]} \;//\; \text{FullSimplify}$$

$$\frac{-(1 + h_{A_M}\,s_{A_M})\,x_A + (-1 + s_{A_M}\,(-2\,x_A + h_{A_M}\,(-1 + 2\,x_A)))\,X_{A_F}}{-2 + 2\,s_{A_M}\,(-x_A\,X_{A_F} + h_{A_M}\,(-x_A + (-1 + 2\,x_A)\,X_{A_F}))}$$

The dynamics of the mutant masculinizing allele can be described by the ratio of its frequency in successive generations. This ratio is:

$$R_A = \frac{\sum_{i=1}^{3} \text{mutantMaleFreq}[[i]]}{\epsilon_Y} \;//\; \text{FullSimplify}$$

$$\frac{-1 + s_{A_M}\,(-x_A\,X_{A_F} + h_{A_M}\,(-x_A + (-1 + 2\,x_A)\,X_{A_F}))}{-1 + s_{A_M}\,(-X_{A_F}\,Y_A + h_{A_M}\,(-Y_A + X_{A_F}\,(-1 + 2\,Y_A)))}$$

Thus to determine how the mutation evolves we now need expressions for the genotype frequencies (X_{A_M}, Y_A and x_{A_M}) that appear in that expression. When the modifier is rare, the relative sizes of these frequencies converge towards an equilibrium. Below we calculate that equilibrium and use it to solve for R_A under two different assumptions about the relative strengths of recombination and selection.

Weak selection

To make the analysis tractable, we now assume that selection is weak. Specifically, we assume that selection coefficients are of the order of ϵ_s, with $\epsilon_s \ll 1$. It will be convenient to use the following substitution:

```
weakSelectionApproximation = {s_{A_M} → ϵ_s s̃_{A_M} + ϵ_s^2 ξ_{s_{A_M}} , s_{A_F} → ϵ_s s̃_{A_F} + ϵ_s^2 ξ_{s_{A_F}} };
```

Throughout this workbook, the coefficients ξ represent higher-order terms. Our goal here will be to develop expressions for the dynamics of the masculinizing mutation that are second order in the selection coefficients (that is, $\mathcal{O}[\epsilon_s^2]$).

Approximation for weak linkage ($r_A \gg \epsilon_s$)

The recursion equations suggest that the difference between any two variables of our model is $\mathcal{O}[\epsilon_s]$ when selection is weak relative to recombination ($r_A \gg \epsilon_s$). To exploit this situation, we apply the following change of variables:

```
pASubs = {X_{A_F} → p̄_A + 1/3 ϵ_s Δp_{A_{X,Y}} + ϵ_s Δp_{A_{X_F,X_M}} + ϵ_s^2 ξ_{X_{A_F}} ,
          X_{A_M} → p̄_A + 1/3 ϵ_s Δp_{A_{X,Y}} - ϵ_s Δp_{A_{X_F,X_M}} + ϵ_s^2 ξ_{X_{A_M}} ,
          Y_A → p̄_A - ϵ_s Δp_{A_{X,Y}} - ϵ_s Δp_{A_{X_F,X_M}} + ϵ_s^2 ξ_{Y_A} ,
          x_A → p̄_A + 1/3 ϵ_s Δp_{A_{X,Y}} - ϵ_s Δp_{A_{X_F,X_M}} + 2 ϵ_s Δp_{A_{x,X_M}} + ϵ_s^2 ξ_{x_A} };
```

Here, $\overline{p}_A$ denotes the average frequency of allele 1 at locus A, and $\Delta p_{A_{\{X,Y\}}}$, $\Delta p_{A_{\{X_F,X_M\}}}$ and $\Delta p_{A_{\{x,X_m\}}}$ are respectively the differences in the frequencies of allele 1 between X- and Y-chromosomes, between X-chromosomes inherited from the female (mother) and male (father), and between X-chromosomes in males with the novel and original sex determination factors. Using these variables, the approximate expression for R_A that includes terms up to second order in the selection coefficient is:

```
approxRA = Series[R_A /. weakSelectionApproximation /. pASubs, {ϵ_s, 0, 2}] // Simplify
```

$$1 - \frac{2}{3}\left(\left(3\,\Delta p_{A_{\{x,X_M\}}} + 2\,\Delta p_{A_{\{X,Y\}}}\right)\left(-\bar{p}_A + h_{A_M}\left(-1 + 2\,\bar{p}_A\right)\right)\tilde{s}_{A_M}\right)\epsilon_s^2 + O[\epsilon_s]^3$$

We see that the dynamics of the modifier depends on three types of quantities: the average allele frequency at the sex-antagonistic locus ($\overline{p}_A$), differences in allele frequencies between different kinds of chromosomes ($\Delta p_{A_{\{X,Y\}}}$ and $\Delta p_{A_{\{x,X_m\}}}$), and the selection parameters (ϵ_s, $\tilde{s}_{A_M}$, and h_{A_M}). The allele frequency differences themselves depend on the selection parameters, and we will now find expressions for them

The recursion for $\Delta p_{A_{\{X,Y\}}}$ is:

```
eqΔpAXY =
 Series[(2 eqXAF + eqXAM - eqYA) - (2 X_{A_F} + X_{A_M} - Y_A) /. weakSelectionApproximation /.
    pASubs, {ϵ_s, 0, 1}] // Simplify
```

$$\left(-\frac{4}{3}\,r_A\left(2\,\Delta p_{A_{\{X,Y\}}} + 3\,\Delta p_{A_{\{X_F,X_M\}}}\right) + 2\left(-1 + \bar{p}_A\right)\bar{p}_A\left(-\bar{p}_A + h_{A_F}\left(-1 + 2\,\bar{p}_A\right)\right)\tilde{s}_{A_F}\right)\epsilon_s + O[\epsilon_s]^2$$

That recursion depends in turn on $\Delta p_{A_{\{X_F,X_M\}}}$, whose recursion is:

```
eqΔpAXfXm = Series[(eqXAF - eqXAM) - (X_{A_F} - X_{A_M}) /. weakSelectionApproximation /. pASubs,
   {ϵ_s, 0, 1}] // Simplify
```

$$\left(-3\,\Delta p_{A_{\{x_F,x_M\}}} + r_A\left(\frac{4}{3}\,\Delta p_{A_{\{X,Y\}}} + 2\,\Delta p_{A_{\{x_F,x_M\}}}\right) + (-1+p_A)\,p_A\,(h_{A_F}\,(-1+2\,p_A)\,\tilde{s}_{A_F} + h_{A_M}\,\tilde{s}_{A_M} + p_A\,(-\tilde{s}_{A_F} + (1-2\,h_{A_M})\,\tilde{s}_{A_M}))\right)\epsilon_s + O[\epsilon_s]^2$$

When the modifier is rare (or absent), $\Delta p_{A_{\{X,Y\}}}$ and $\Delta p_{A_{\{x_F,x_M\}}}$ will reach equilibrium values:

```
ΔpASubs1 =
 Solve[{eqΔpAXY == 0, eqΔpAXfXm == 0}, {Δp_{A_{X,Y}}, Δp_{A_{x_F,x_M}}}] // Flatten // FullSimplify
```

$$\left\{\Delta p_{A_{\{X,Y\}}} \to \frac{(-1+\bar{p}_A)\,\bar{p}_A\,(-(-3+4\,r_A)\,(-\bar{p}_A + h_{A_F}\,(-1+2\,\bar{p}_A))\,\tilde{s}_{A_F} + 2\,r_A\,(-\bar{p}_A + h_{A_M}\,(-1+2\,\bar{p}_A))\,\tilde{s}_{A_M})}{4\,r_A},\right.$$
$$\left.\Delta p_{A_{\{x_F,x_M\}}} \to \frac{1}{3}\,(-1+\bar{p}_A)\,\bar{p}_A\,(2\,(-\bar{p}_A + h_{A_F}\,(-1+2\,\bar{p}_A))\,\tilde{s}_{A_F} - (-\bar{p}_A + h_{A_M}\,(-1+2\,\bar{p}_A))\,\tilde{s}_{A_M})\right\}$$

The remaining allele frequency difference that appears in the expression for R_A above is $\Delta p_{A_{\{x,X_m\}}}$. Its recursion is

```
eqΔpAxXm =
 Series[(eqXAM - eqxA) - (X_{A_M} - x_A) /. weakSelectionApproximation /. pASubs, {ϵ_s, 0, 1}] //
  Simplify
```

$$\left(\Delta p_{A_{\{x,x_M\}}} + \Delta p_{A_{\{x_F,x_M\}}} - \frac{2}{3}\,r_A\left(2\,\Delta p_{A_{\{X,Y\}}} + 3\,\Delta p_{A_{\{x_F,x_M\}}}\right)\right)\epsilon_s + O[\epsilon_s]^2$$

which has the non-trivial equilibrium

```
ΔpASubs2 = Solve[eqΔpAxXm == 0, Δp_{A_{x,x_M}}] // Flatten // FullSimplify
```

$$\left\{\Delta p_{A_{\{x,x_M\}}} \to \frac{4}{3}\,r_A\,\Delta p_{A_{\{X,Y\}}} + (-1+2\,r_A)\,\Delta p_{A_{\{x_F,x_M\}}}\right\}$$

Substituting in the earlier results for $\Delta p_{A_{\{X,Y\}}}$ and $\Delta p_{A_{\{X_F,X_M\}}}$ gives

```
ΔpASubs2 = ΔpASubs2 /. ΔpASubs1 // Simplify
```

$$\left\{\Delta p_{A_{\{x,x_M\}}} \to \frac{1}{3}\,(-1+\bar{p}_A)\,\bar{p}_A\,(h_{A_F}\,(-1+2\,\bar{p}_A)\,\tilde{s}_{A_F} - h_{A_M}\,\tilde{s}_{A_M} - \bar{p}_A\,(\tilde{s}_{A_F} + (1-2\,h_{A_M})\,\tilde{s}_{A_M}))\right\}$$

We now substitute the results for $\Delta p_{A_{\{X,Y\}}}$ and $\Delta p_{A_{\{x,X_M\}}}$ into our early expression for R_A to get

```
approxRA = approxRA /. ΔpASubs1 /. ΔpASubs2 // FullSimplify
```

$$1 + \frac{1}{3\,r_A}\,((-1+\bar{p}_A)\,\bar{p}_A\,(-\bar{p}_A + h_{A_M}\,(-1+2\,\bar{p}_A))\,\tilde{s}_{A_M} \\ ((-3+2\,r_A)\,(-\bar{p}_A + h_{A_F}\,(-1+2\,\bar{p}_A))\,\tilde{s}_{A_F} - 4\,r_A\,(-\bar{p}_A + h_{A_M}\,(-1+2\,\bar{p}_A))\,\tilde{s}_{A_M})\,\epsilon_s^2) + O[\epsilon_s]^3$$

The results to this point are expressed in terms of $\bar{p}_A$, the average allele frequency at the sexually-antagonistic locus. Polymorphism at locus A can be maintained by selection under certain combinations of parameters (Rice 1987). We will now find expressions for $\bar{p}_A$ assuming that polymorphism is maintained by selection. Intuitively, we expect that the results above also apply more generally, when other forces besides selection maintain polymorphism at A. More specifically, we expect the previous results expressed in terms of $\bar{p}_A$ to be a valid approximation when mutation and migration maintain the polymorphism so long as the mutation and migration rates are small relative to the selection coefficients.

When the mutation is rare, it has a negligible effect on the average allele frequency $\bar{p}_A$. The rate of change in that frequency is, to first order in the selection coefficients, then

```
eqavgpA =
 Series[(2 eqXAF + eqXAM + eqYA) - (2 X_{A_F} + X_{A_M} + Y_A) /. weakSelectionApproximation /.
     pASubs, {ϵ_s, 0, 1}] / 4 // Simplify
```

$$\frac{1}{2}\,(-1+\bar{p}_A)\,\bar{p}_A\,(h_{A_F}\,(-1+2\,\bar{p}_A)\,\tilde{s}_{A_F} - h_{A_M}\,\tilde{s}_{A_M} - \bar{p}_A\,(\tilde{s}_{A_F} + (1-2\,h_{A_M})\,\tilde{s}_{A_M}))\,\epsilon_s + O[\epsilon_s]^2$$

The (nontrivial) equilibrium for the average frequency of allele 1 at locus A when the mutant is rare is:

```
avgpASubs = Solve[eqavgpA == 0, p̄_A][[3]] // FullSimplify
```

$$\left\{p_A \to \frac{h_{A_F}\,\tilde{s}_{A_F} + h_{A_M}\,\tilde{s}_{A_M}}{(-1+2\,h_{A_F})\,\tilde{s}_{A_F} + (-1+2\,h_{A_M})\,\tilde{s}_{A_M}}\right\}$$

This result can be used to simplify the expression for the geometric growth rate. First, we define the fitness differentials σ_{A_M} and σ_{A_F}, which measures the intensity of selection in males and females, S_A, which measures the degree of sexual conflict, L_A, which measures how closely locus A is linked to locus Y, and V_A, the genetic variance at locus A

```
simpleSubs = { σ_{A_M} → (p̄_A + h_{A_M} (1 - 2 p̄_A)) ϵ_s s̃_{A_M},
        σ_{A_F} → (p̄_A + h_{A_F} (1 - 2 p̄_A)) ϵ_s s̃_{A_F},
        S_A → σ_{A_M} (σ_{A_M} - σ_{A_F}) / 2,
        L_A → (1 - 2 r_A) / r_A,
        V_A → p̄_A (1 - p̄_A)};
```

We now observe that the average selection differential $(\sigma_{A_M} + \sigma_{A_F})/2$ vanishes at population-genetic equilibrium

```
(σ_{A_M} + σ_{A_F}) / 2 /. simpleSubs /. avgpASubs // FullSimplify
```

```
0
```

Using this fact, the geometric rate of increase R_A can be written as

```
RASimple = 1 - V_A L_A S_A;
```

We check that this expression is consistent with our earlier result:

```
checkResult =  approxRA - RASimple  //. simpleSubs /. avgpASubs // FullSimplify
```

```
O[ϵ_s]^4
```

Approximation for tight linkage ($r_A = \mathcal{O}[\epsilon_s]$)

If the rate of recombination between the loci Y and A is of the same order of magnitude as the selection coefficients, we can no longer assume the difference between the average allele frequencies on the X- and Y-chromosome to be small. We therefore use a different change of variables.

```
pASubsStrongLinkage = {X_{A_F} → p_{A_X} + ϵ_s Δp_{A_{{x_F, x_M}}},
   X_{A_M} → p_{A_X} - 2 ϵ_s Δp_{A_{{x_F, x_M}}}, Y_A → p_{A_Y}, x_A → p_{A_X} + ϵ_s Δp_{A_{{x, X}}}, r_A → ϵ_s r̃_A + ϵ_s^2 ξ_{r_A}};
```

Here, p_{A_X} and p_{A_Y} denote the (average) frequencies of the allele 1 at locus A on X- and Y-chromosomes, when the mutation is absent or rare. Our approximation for strong linkage is highly accurate for $r_A = \mathcal{O}[\epsilon_s]$, and performs well even in cases where linkage is tighter than that (e.g., $r_A = \mathcal{O}[\epsilon_s^2]$, or $r_A = 0$; see Section 4).

Under this change of variables, the geometric growth rate R_A is approximated as

```
approxRA =
 Series[R_A /. weakSelectionApproximation /. pASubsStrongLinkage, {ϵ_s, 0, 1}] // Simplify
```

```
1 - (-p_{A_X} + h_{A_M} (-1 + 2 p_{A_X})) (p_{A_X} - p_{A_Y}) s̃_{A_M} ϵ_s + O[ϵ_s]^2
```

As before, the dynamics of the modifier depends on the allele frequencies at the sex-antagonistic locus (p_{A_X} and p_{A_Y}), the selection parameters (ϵ_s, $\tilde{s}_{A_M}$, and h_{A_M}), and differences in allele frequencies between different kinds of chromosomes. In this case, the relevant allele frequency difference is that between the X and Y chromosomes. This quantity changes according to the recursion

```
eqΔpAXY =
 Series[(2 eqXAF + eqXAM - 3 eqYA) - (2 X_{A_F} + X_{A_M} - 3 Y_A) /. weakSelectionApproximation /.
    pASubsStrongLinkage, {ϵ_s, 0, 1}] // FullSimplify
```

```
(-4 (p_{A_X} - p_{A_Y}) r̃_A + 2 (-1 + p_{A_X}) p_{A_X} (-p_{A_X} + h_{A_F} (-1 + 2 p_{A_X})) s̃_{A_F} +
     (-p_{A_X} (2 + p_{A_X} - 3 p_{A_Y}) p_{A_Y} + h_{A_M} (3 (-1 + p_{A_Y}) p_{A_Y} + p_{A_X}^2 (-1 + 2 p_{A_Y}) + p_{A_X} (1 + 4 p_{A_Y} - 6 p_{A_Y}^2)))
      s̃_{A_M}) ϵ_s + O[ϵ_s]^2
```

The rate of change of the average allele frequency $\overline{p}_A$ ($\overline{p}_A = (3\,p_{A_X} + p_{A_Y})/4$) is, to first order in the selection coefficients, given by

```
eqavgpA =
 Series[(2 eqXAF + eqXAM + eqYA) - (2 X_AF + X_AM + Y_A) /. weakSelectionApproximation /.
     pASubsStrongLinkage, {ϵs, 0, 1}] / 4 // FullSimplify
```

$$\frac{1}{4}\,(2\,(-1+p_{A_X})\,p_{A_X}\,(-p_{A_X}+h_{A_F}\,(-1+2\,p_{A_X}))\,\tilde{s}_{A_F} + (-p_{A_X}\,p_{A_Y}\,(-2+p_{A_X}+p_{A_Y})+h_{A_M}\,(-1+p_{A_X}+p_{A_Y})\,(-p_{A_Y}+p_{A_X}\,(-1+2\,p_{A_Y})))\,\tilde{s}_{A_M})\,\epsilon_s + O[\epsilon_s]^2$$

To simplify these two equations, we define the genetic variances $V_{A_X} = p_{A_X}(1-p_{A_X})$ and $V_{A_Y} = p_{A_Y}(1-p_{A_Y})$ and the selection differentials σ_{A_X} and σ_{A_Y}.

```
simpleSubs = {σ_AX → 2 / 3 (p_AX + h_AF (1 - 2 p_AX)) ϵs s̃_AF + (p_AY + h_AM (1 - 2 p_AY)) ϵs s̃_AM / 3,
        σ_AY → (p_AX + h_AM (1 - 2 p_AX)) ϵs s̃_AM,
        V_AX → (1 - p_AX) p_AX,
        V_AY → (1 - p_AY) p_AY};
```

Using these coefficients, we can rewrite eqΔpAXY.

```
eqΔpAXYSimple = -4 (p_AX - p_AY) r_A + 3 V_AX σ_AX - 3 V_AY σ_AY
```

$$-4\,(p_{A_X}-p_{A_Y})\,r_A + 3\,V_{A_X}\,\sigma_{A_X} - 3\,V_{A_Y}\,\sigma_{A_Y}$$

which we check to be consistent with the earlier expression:

```
checkResult = eqΔpAXYSimple - eqΔpAXY /. simpleSubs /. {r_A → ϵs r̃_A} // Simplify
```

$$O[\epsilon_s]^3$$

From the simplified expression eqΔpAXYSimple, it follows that, at equilibrium,

```
eqΔpAXYEquilibrium = p_AY - p_AX == 3 (V_AY σ_AY - V_AX σ_AX) / (4 r_A)
```

$$-p_{A_X} + p_{A_Y} == \frac{3\,(-V_{A_X}\,\sigma_{A_X} + V_{A_Y}\,\sigma_{A_Y})}{4\,r_A}$$

Similarly, the average allele frequency is at equilibrium when

```
eqavgpAsimple = 3 V_AX σ_AX + V_AY σ_AY == 0
```

$$3\,V_{A_X}\,\sigma_{A_X} + V_{A_Y}\,\sigma_{A_Y} == 0$$

This equation allows us to express the genetic variation at the X- and Y-chromosomes in terms of the average variance $V_A = \frac{3}{4}\,V_{A_X} + \frac{1}{4}\,V_{A_Y}$

```
variances = Solve[{eqavgpAsimple, V_A == (3 V_AX + V_AY) / 4}, {V_AX, V_AY}] // Flatten
```

$$\left\{V_{A_X} \to -\frac{4\,V_A\,\sigma_{A_Y}}{3\,(\sigma_{A_X}-\sigma_{A_Y})},\ V_{A_Y} \to \frac{4\,V_A\,\sigma_{A_X}}{\sigma_{A_X}-\sigma_{A_Y}}\right\}$$

such that the geometric rate of increase R_A can now be written as

```
RASimple = 1 - σ_AY (3 (-V_AX σ_AX + V_AY σ_AY)) / (4 r_A) /. variances // Simplify
```

$$1 - \frac{4\, V_A\, \sigma_{A_X}\, \sigma_{A_Y}^2}{r_A\, (\sigma_{A_X} - \sigma_{A_Y})}$$

As for the weak-linkage approximation, the geometric growth rate can be written as $R_A = 1 - V_A\, S_A\, L_A$. In fact, by choosing $S_A = 4\, \frac{\sigma_{A_Y}^2\, \sigma_{A_X}}{\sigma_{A_X} - \sigma_{A_Y}}$, $V_A = \frac{3}{4}\, p_{A_X}(1 - p_{A_X}) + \frac{1}{4}\, p_{A_X}(1 - p_{A_X})$ and $L_A = \frac{1-2\, r_A}{r_A}$, this expression converges to the weak linkage result when $r_A \gg \epsilon_s$, and to the strong linkage result when $r_A = \mathcal{O}[\epsilon_s]$.

2 - Effect of a sex-antagonistic locus on the autosome

In the second submodel we ignore the presence of the sexually antagonistic locus on the sex chromosome. Hence, we keep track only of the loci Y, y and a. As in the four-locus model, locus a is a sexually-antagonistic locus located on an autosome together with locus y. Again, the original sex determination factor segregates at locus Y, and a small fraction $\epsilon_y \ll 1$ of the individuals carries a novel masculinizing sex determination allele at locus y.
This time, three additional variables are needed to describe the genetic state of the population. The three variables measure the frequency of the allele 1 on locus a in female or male gametes with a particular combination of sex determination alleles. They are defined as follows: U_{a_F} represents the frequency of allele 1 at locus a in female gametes, U_{a_M} denotes that frequency in the gametes of normal males, and u_a corresponds to the frequency of allele 1 at locus a in male gametes that also carry the novel mutant sex determination factor.

Recursion equations

To derive the recursions that describe how the population evolves, we start by calculating the frequencies of genotypes at locus a in normal male and female zygotes, and in mutant male zygotes. We assume that mating is random. Genotype frequencies are listed in the order {11, 10, 01, 00}, where the first and second numbers in a genotype represent the alleles inherited from the mother or the father, respectively. In individuals homozygous for the null allele at locus y (normal males and females), the genotype classes 10 and 01 can be grouped together.

When the mutation is rare, the frequencies of the genotypes in zygotes that do not carry the mutation can be calculated approximately by neglecting the mutation:

```
normalZygoteFreq = {U_aF U_aM, U_aF (1 - U_aM) + U_aM (1 - U_aF), (1 - U_aM) (1 - U_aF)};

mutantMaleZygoteFreq = {ϵ_Y U_aF u_aM, ϵ_Y U_aF (1 - u_aM), ϵ_Y u_aM (1 - U_aF), ϵ_Y (1 - u_aM) (1 - U_aF)};
```

Next, we define the genotype fitness values for the different kinds of individuals.

```
femaleFitness = {1 + s_aF, 1 + h_aF s_aF, 1};

normalMaleFitness = {1 + s_aM, 1 + h_aM s_aM, 1};

mutantMaleFitness = {1 + s_aM, 1 + h_aM s_aM, 1 + h_aM s_aM, 1};
```

A genotype's frequency in adults is given by the product of its frequency in zygotes and its fitness, normalized by the mean fitness. Since the frequency of the mutant allele is low, we may neglect the impact of mutant individuals on the mean fitness. Thus we have:

$$\text{femaleFreq} = \frac{\text{normalZygoteFreq} * \text{femaleFitness}}{\bar{w}_F}$$

$$\left\{\frac{(1+s_{a_F})\,U_{a_F}\,U_{a_M}}{\bar{w}_F},\ \frac{(1+h_{a_F}\,s_{a_F})\,(U_{a_F}\,(1-U_{a_M})+(1-U_{a_F})\,U_{a_M})}{\bar{w}_F},\ \frac{(1-U_{a_F})\,(1-U_{a_M})}{\bar{w}_F}\right\}$$

$$\text{normalMaleFreq} = \frac{\text{normalZygoteFreq} * \text{normalMaleFitness}}{\bar{w}_M}$$

$$\left\{\frac{(1+s_{a_M})\,U_{a_F}\,U_{a_M}}{\bar{w}_M},\ \frac{(1+h_{a_M}\,s_{a_M})\,(U_{a_F}\,(1-U_{a_M})+(1-U_{a_F})\,U_{a_M})}{\bar{w}_M},\ \frac{(1-U_{a_F})\,(1-U_{a_M})}{\bar{w}_M}\right\}$$

$$\text{mutantMaleFreq} = \frac{\text{mutantMaleZygoteFreq} * \text{mutantMaleFitness}}{\bar{w}_M}$$

$$\left\{\frac{(1+s_{a_M})\,u_{a_M}\,U_{a_F}\,\epsilon_y}{\bar{w}_M},\ \frac{(1+h_{a_M}\,s_{a_M})\,(1-u_{a_M})\,U_{a_F}\,\epsilon_y}{\bar{w}_M},\right.$$
$$\left.\frac{(1+h_{a_M}\,s_{a_M})\,u_{a_M}\,(1-U_{a_F})\,\epsilon_y}{\bar{w}_M},\ \frac{(1-u_{a_M})\,(1-U_{a_F})\,\epsilon_y}{\bar{w}_M}\right\}$$

The mean fitnesses in females and males are:

$$\bar{w}_F = \sum_{i=1}^{3} (\text{normalZygoteFreq} * \text{femaleFitness})[[i]]$$

$$(1-U_{a_F})\,(1-U_{a_M})+(1+s_{a_F})\,U_{a_F}\,U_{a_M}+(1+h_{a_F}\,s_{a_F})\,(U_{a_F}\,(1-U_{a_M})+(1-U_{a_F})\,U_{a_M})$$

$$\bar{w}_M = \sum_{i=1}^{3} (\text{normalZygoteFreq} * \text{normalMaleFitness})[[i]]$$

$$(1-U_{a_F})\,(1-U_{a_M})+(1+s_{a_M})\,U_{a_F}\,U_{a_M}+(1+h_{a_M}\,s_{a_M})\,(U_{a_F}\,(1-U_{a_M})+(1-U_{a_F})\,U_{a_M})$$

By calculating the frequencies of the different haplotypes in gametes from females, normal males and mutant males, we obtain the following recursion equations for the variables of the model.

```
eqUaF = femaleFreq[[1]] + femaleFreq[[2]]/2 // FullSimplify
```

$$\frac{-(1+h_{a_F}\,s_{a_F})\,U_{a_M}+U_{a_F}\,(-1+s_{a_F}\,(-h_{a_F}+2\,(-1+h_{a_F})\,U_{a_M}))}{-2+2\,s_{a_F}\,(-U_{a_F}\,U_{a_M}+h_{a_F}\,(-U_{a_M}+U_{a_F}\,(-1+2\,U_{a_M})))}$$

```
eqUaM = normalMaleFreq[[1]] + normalMaleFreq[[2]]/2 // FullSimplify
```

$$\frac{-(1+h_{a_M}\,s_{a_M})\,U_{a_M}+U_{a_F}\,(-1+s_{a_M}\,(-h_{a_M}+2\,(-1+h_{a_M})\,U_{a_M}))}{-2+2\,s_{a_M}\,(-U_{a_F}\,U_{a_M}+h_{a_M}\,(-U_{a_M}+U_{a_F}\,(-1+2\,U_{a_M})))}$$

```
equaM = (mutantMaleFreq[[1]] + r_a mutantMaleFreq[[2]] + (1 - r_a) mutantMaleFreq[[3]]) /
    Sum[mutantMaleFreq[[i]], {i, 4}] // FullSimplify
```

$$\frac{-r_a\,(1+h_{a_M}\,s_{a_M})\,U_{a_F}+u_{a_M}\,((-1+r_a)\,(1+h_{a_M}\,s_{a_M})+(-1+h_{a_M})\,s_{a_M}\,U_{a_F})}{-1+s_{a_M}\,(-u_{a_M}\,U_{a_F}+h_{a_M}\,(-U_{a_F}+u_{a_M}\,(-1+2\,U_{a_F})))}$$

The dynamics of the mutant masculinizing allele can be described by the ratio of its frequency in successive generations. This ratio is:

$$R_a = \frac{\sum_{i=1}^{4} \text{mutantMaleFreq}[[i]]}{\epsilon_y} \text{ // FullSimplify}$$

$$\frac{-1 + s_{a_M} \left(-u_{a_M} U_{a_F} + h_{a_M} \left(-U_{a_F} + u_{a_M} \left(-1 + 2 U_{a_F}\right)\right)\right)}{-1 + s_{a_M} \left(-U_{a_F} U_{a_M} + h_{a_M} \left(-U_{a_M} + U_{a_F} \left(-1 + 2 U_{a_M}\right)\right)\right)}$$

As in section (1), we now need expressions for the genotype frequencies (U_{a_M}, U_{a_F} and u_a) to determine how the mutation evolves . When the modifier is rare, the relative sizes of these frequencies converge towards an equilibrium. Below we calculate that equilibrium and use it to solve for R_a under two different assumptions about the relative strengths of recombination and selection.

Weak selection

To make the analysis tractable, we now assume that selection is weak. Specifically, we assume that selection coefficients are of the order of ϵ_s, with $\epsilon_s \ll 1$. It will be convenient to use the following substitution:

```
weakSelectionApproximation =
  Join[weakSelectionApproximation , {s_aM → ϵs s̃_aM + ϵs^2 ξ_saM , s_aF → ϵs s̃_aF + ϵs^2 ξ_saF }];
```

Approximation for weak linkage ($r_a \gg \epsilon_s$)

The recursion equations suggest that the difference between any two variables of our model is $\mathcal{O}[\epsilon_s]$ when selection is weak relative to recombination. To exploit this situation, we apply the following change of variables:

```
paSubs = {U_aF → p̄_a + ϵs Δp_a{U_F,U_M} / 2 + ϵs^2 ξ_UaF ,
          U_aM → p̄_a - ϵs Δp_a{U_F,U_M} / 2 + ϵs^2 ξ_UaM ,
          u_aM → p̄_a - ϵs Δp_a{U_F,U_M} / 2 + ϵs Δp_a{u,U_M} + ϵs^2 ξ_p1m2 };
```

Here, $\overline{p}_a$ denotes the average frequency of allele 1 at locus a, and $\Delta p_{a\{U_F,U_M\}}$ and $\Delta p_{a\{u,U_M\}}$ measure respectively frequency differences between chromosomes inherited from the father and the mother, and between males with the original and novel sex determination factor.

Our strategy is again to find expressions for the allele frequency differences ($\Delta p_{a\{U_F,U_M\}}$ and $\Delta p_{a\{u,U_M\}}$). Many processes could be responsible for the maintenance of polymorphism at the autosomal sex-antagonistic locus, but, as before, we will assume that polymorphism at locus a is maintained by selection.

At equilibrium, the new variables satisfy the following equations

```
eqavgpa = Series[(eqUaF + eqUaM) - (U_aF + U_aM) /. weakSelectionApproximation /. paSubs,
    {ϵs, 0, 1}] == 0 // Simplify
```

$$(-1+\bar{p}_a)\,\bar{p}_a\,(h_{a_F}\,(-1+2\,\bar{p}_a)\,\tilde{s}_{a_F}-h_{a_M}\,\tilde{s}_{a_M}-\bar{p}_a\,(\tilde{s}_{a_F}+(1-2\,h_{a_M})\,\tilde{s}_{a_M}))\,\epsilon_s+O[\epsilon_s]^2==0$$

```
eqΔpaUfUm = Series[(eqUaF - eqUaM) - (U_aF - U_aM) /. weakSelectionApproximation /. paSubs,
    {ϵs, 0, 1}] == 0 // Simplify
```

$$\left(-\Delta p_{a_{\{U_F,U_M\}}}+(-1+\bar{p}_a)\,\bar{p}_a\,(h_{a_F}\,(-1+2\,\bar{p}_a)\,\tilde{s}_{a_F}+h_{a_M}\,\tilde{s}_{a_M}+\bar{p}_a\,(-\tilde{s}_{a_F}+(1-2\,h_{a_M})\,\tilde{s}_{a_M}))\right)\epsilon_s+O[\epsilon_s]^2==0$$

```
eqΔpauUm = Series[(equaM - eqUaM) - (u_aM - U_aM) /. weakSelectionApproximation /. paSubs,
    {ϵs, 0, 1}] == 0 // FullSimplify
```

$$\left(-r_a\,\Delta p_{a_{\{u,U_M\}}}+\frac{1}{2}\,(-1+2\,r_a)\,\Delta p_{a_{\{U_F,U_M\}}}\right)\epsilon_s+O[\epsilon_s]^2==0$$

which have as non-trivial solutions

```
avgpaSubs = Solve[eqavgpa, p̄a][[3]]
```

$$\left\{p_a\to\frac{h_{a_F}\,\tilde{s}_{a_F}+h_{a_M}\,\tilde{s}_{a_M}}{-\tilde{s}_{a_F}+2\,h_{a_F}\,\tilde{s}_{a_F}-\tilde{s}_{a_M}+2\,h_{a_M}\,\tilde{s}_{a_M}}\right\}$$

```
ΔpaSubs = Solve[{eqΔpaUfUm, eqΔpauUm}, {Δp_a{UF,UM}, Δp_a{u,UM}}] // FullSimplify // Flatten
```

$$\left\{\Delta p_{a_{\{u,U_M\}}}\to\frac{(-1+2\,r_a)\,(-1+\bar{p}_a)\,\bar{p}_a\,((-\bar{p}_a+h_{a_F}\,(-1+2\,\bar{p}_a))\,\tilde{s}_{a_F}-(-\bar{p}_a+h_{a_M}\,(-1+2\,\bar{p}_a))\,\tilde{s}_{a_M})}{2\,r_a},\right.$$
$$\left.\Delta p_{a_{\{U_F,U_M\}}}\to(-1+\bar{p}_a)\,\bar{p}_a\,(h_{a_F}\,(-1+2\,\bar{p}_a)\,\tilde{s}_{a_F}+h_{a_M}\,\tilde{s}_{a_M}+\bar{p}_a\,(-\tilde{s}_{a_F}+(1-2\,h_{a_M})\,\tilde{s}_{a_M}))\right\}$$

The final step is to approximate the geometric rate of increase for weak selection, and to substitute the equilibrium values for $\Delta p_{a_{\{U_F,U_M\}}}$ and $\Delta p_{a_{\{u,U_M\}}}$.

```
approxRa =
 Series[R_a /. weakSelectionApproximation /. paSubs, {ϵs, 0, 2}] /. ΔpaSubs // Simplify
```

$$1+\frac{1}{2\,r_a}((-1+2\,r_a)\,(-1+\bar{p}_a)\,\bar{p}_a\,(h_{a_M}\,(1-2\,\bar{p}_a)+\bar{p}_a)$$
$$\tilde{s}_{a_M}\,((-\bar{p}_a+h_{a_F}\,(-1+2\,\bar{p}_a))\,\tilde{s}_{a_F}-(-\bar{p}_a+h_{a_M}\,(-1+2\,\bar{p}_a))\,\tilde{s}_{a_M})\,\epsilon_s^2)+O[\epsilon_s]^3$$

To simplify this expression, we define the fitness differentials σ_{a_M} and σ_{a_F}, which measures the intensity of selection in males and females, S_a, which measures the degree of sexual conflict, L_a, which measures how closely locus a is linked to locus y, and V_a, the genetic variance at locus a

```
simpleSubs = { σ_aM → (p̄a + h_aM (1 - 2 p̄a)) ϵs s̃_aM ,
    σ_aF → (p̄a + h_aF (1 - 2 p̄a)) ϵs s̃_aF ,
    S_a → σ_aM (σ_aM - σ_aF) / 2,
    L_a → (1 - 2 r_a) / r_a ,
    V_a → p̄a (1 - p̄a)};
```

The geometric rate of increase R_a can now be written as

```
RaSimple = 1 + Va La Sa;
```

We check that this expression is consistent with our earlier result

```
checkResult =  approxRa - RaSimple  //. simpleSubs /. avgpaSubs // FullSimplify
```

```
O[ϵs]^3
```

Approximation for tight linkage ($r_a = \mathcal{O}[\epsilon_s]$)

If the rate of recombination between the loci y and a is of the same order of magnitude as the selection coefficients, we can no longer assume the difference between the average allele frequencies in normal and mutant males to be small. We therefore use a different change of variables.

```
paSubsStrongLinkage = {UaF → p̄a + ϵs Δpa{UF,UM} / 2 + ϵs^2 ξUaF ,
      UaM → p̄a - ϵs Δpa{UF,UM} / 2 + ϵs^2 ξUaM ,
      uaM → paY ,
      ra → ϵs r̃a + ϵs^2 ξra };
```

Under this change of variables, we obtain a new recursion equation for the difference $\overline{p}_a - p_{a_y}$, where p_{a_y} is the frequency of allele 1 at locus a in males that carry the sex determination mutation at locus y.

```
eqΔpauUm = Series[
   ((eqUaF + eqUaM) / 2 - equaM) - ((UaM + UaF) / 2 - uaM) /. weakSelectionApproximation /.
    paSubsStrongLinkage, {ϵs, 0, 1}] // FullSimplify
```

$$\frac{1}{2}\,(-2\,p_{a_y}^2\,(-p_a + h_{a_M}\,(-1+2\,p_a))\,s_{a_M} + 2\,p_{a_y}\,(r\!\!\!^{\sim}_a + (-p_a + h_{a_M}\,(-1+2\,p_a))\,s_{a_M}) + p_a\,(-2\,r\!\!\!^{\sim}_a + (-1+p_a)\,((-p_a + h_{a_F}\,(-1+2\,p_a))\,s_{a_F} + (-p_a + h_{a_M}\,(-1+2\,p_a))\,s_{a_M})))\,\epsilon_s + O[\epsilon_s]^2$$

Using the previous definitions of the fitness differentials σ_{a_M} and σ_{a_F}, this expression is rewritten to show that, at population genetic equilibrium

```
eqΔpauUmSimple = p̄a - p̄ay == Vay σaM / ra;
```

The geometric growth rate R_a is approximated as

```
approxRa =
 Series[Ra /. weakSelectionApproximation /. paSubsStrongLinkage, {ϵs, 0, 1}] // Simplify
```

$$1 - (p_{a_y} - p_a)\,(-p_a + h_{a_M}\,(-1+2\,p_a))\,s_{a_M}\,\epsilon_s + O[\epsilon_s]^2$$

In view of the previously obtained equilibrium condition for the allele frequency difference $\overline{p}_a - p_{a_y}$, the geometric growth rate can now be written as

```
RaSimple = 1 + Vay σaM^2 / ra;
```

As for the weak-linkage approximation, the growth rate can be written as $R_a = 1 - V_a\,S_a\,L_a$. In fact, by choosing $S_a = \frac{1}{2}\,\sigma_{a_M}\,(\sigma_{a_M} - \sigma_{a_F})$, $V_a = p_{a_y}\,(1 - p_{a_y})$ and $L_A = \frac{1-2\,r_a}{r_a}$, this expression converges to the weak linkage result when

$r_a \gg \epsilon_s$, and to the strong linkage result when $r_a = \mathcal{O}[\epsilon_s]$. As illustrated in Section (4), the approximation is accurate also when the recombination rate on the autosome is (vanishingly) small relative to the strength of selection ($r_a \ll \epsilon_s$).

3 - Combining the effects of loci *A* and *a*

As explained in the introduction, the sexually antagonistic loci *A* and *a* have additive effects on the dynamics of the masculinizing mutation at locus *y* when selection is weak. To find the relative rate of increase of the frequency of the modifier for the four-locus model described in the text, we may combine the results of section (1) and (2) by multiplying the geometric growth rates of the two submodels. In other words, the change of the allele frequency of the mutant sex determination allele is given by

```
Δp_y = (1 - S_A L_A V_A) (1 + S_a L_a V_a) p_Y - p_y ;
```

The relative rate of increase of the mutant allele, λ, is defined as $\Delta p_y / p_y$. We calculate λ up to first order in S_A and S_a (i.e., for weak selection).

```
λ = Normal[Series[(Δp_y / p_Y /. {S_A → ϵ_s S̃_A, S_a → ϵ_s S̃_a}), {ϵ_s, 0, 1}]] /.
    {S̃_a → S_a / ϵ_s, S̃_A → S_A / ϵ_s} // Simplify
```

```
L_a S_a V_a - L_A S_A V_A
```

which is Equation(1) in the text.

4 - Complete linkage

In deriving the results for tight linkage, we assumed that the recombination rates were of the same order of magnitude as the selection coefficients. We now study the performance of our approximation when linkage is tighter than that ($0 < r_A \ll \epsilon_s$ or $0 < r_a \ll \epsilon_s$) or when recombination on the sex chromosomes or the autosomes is absent altogether. The linkage terms L_A and L_a diverge to infinity under these conditions, whereas the genetic variances V_A and V_a approach zero. It is not immediately clear how these two processes combine, and to what extent our results are accurate in the limit of very low recombination rates.

To address these issues, we recalculate the geometric growth rates R_A and R_a for the two submodels under the assumption that recombination on the sex chromosome or the autosome is fully absent. We then study to what extent our previous approximation converges to these limit values as we decrease the recombination rate.

No recombination on the sex chromosomes ($r_A = 0$)

We start with the first submodel, and define the following procedure to obtain weak-selection approximations that are valid in the absence of recombination between the loci *Y* and *A*.

```
completeLinkage[x_] :=
 Series[x /. {r_A → 0} /. weakSelectionApproximation /. pASubsStrongLinkage, {ϵ_s, 0, 1}] /.
    {S̃_A_F → s_A_F / ϵ_s, S̃_A_M → s_A_M / ϵ_s} // Normal // FullSimplify
```

The following recursions for the sexually-antagonistic-allele frequencies result from applying this procedure.

```
eqpAX = completeLinkage[ (2 eqXAF + eqXAM - (2 X_AF + X_AM)) / 3 ]
```

$$\frac{1}{3}\left(-1+p_{A_X}\right)p_{A_X}\left(2\left(-p_{A_X}+h_{A_F}\left(-1+2\,p_{A_X}\right)\right)s_{A_F}+\left(-p_{A_Y}+h_{A_M}\left(-1+2\,p_{A_Y}\right)\right)s_{A_M}\right)$$

```
eqpAY = completeLinkage[eqYA - Y_A]
```

$$\left(-p_{A_X}+h_{A_M}\left(-1+2\,p_{A_X}\right)\right)\left(-1+p_{A_Y}\right)p_{A_Y}\,s_{A_M}$$

The expression for the geometric growth rate simplifies to

```
eqRA = completeLinkage[R_A ]
```

$$1-\left(-p_{A_X}+h_{A_M}\left(-1+2\,p_{A_X}\right)\right)\left(p_{A_X}-p_{A_Y}\right)s_{A_M}$$

The recursions for p_{A_X} and p_{A_Y} have seven different equilibrium solutions

```
Solve[{eqpAX == 0, eqpAY == 0}, {p_AX , p_AY }]
```

$$\left\{\{p_{A_X}\to 0,\ p_{A_Y}\to 0\},\ \{p_{A_X}\to 0,\ p_{A_Y}\to 1\},\ \{p_{A_X}\to 1,\ p_{A_Y}\to 0\},\ \{p_{A_X}\to 1,\ p_{A_Y}\to 1\},\right.$$
$$\left\{p_{A_X}\to -\frac{-2\,h_{A_F}\,s_{A_F}-h_{A_M}\,s_{A_M}}{2\left(-1+2\,h_{A_F}\right)s_{A_F}},\ p_{A_Y}\to 0\right\},\ \left\{p_{A_X}\to -\frac{-2\,h_{A_F}\,s_{A_F}-s_{A_M}+h_{A_M}\,s_{A_M}}{2\left(-1+2\,h_{A_F}\right)s_{A_F}},\ p_{A_Y}\to 1\right\},$$
$$\left.\left\{p_{A_Y}\to -\frac{2\,h_{A_F}\,s_{A_F}-2\,h_{A_M}\,s_{A_F}+h_{A_M}\,s_{A_M}-2\,h_{A_M}^2\,s_{A_M}}{\left(-1+2\,h_{A_M}\right)^2 s_{A_M}},\ p_{A_X}\to \frac{h_{A_M}}{-1+2\,h_{A_M}}\right\}\right\}$$

The first and the fourth equilibrium are stable only under parameter conditions that do not allow for the maintenance of sex-antagonistic fitness variation, and are therefore irrelevant. The fifth and the sixth equilibrium can be stable under a limited range of biologically relevant parameter conditions, but this requires a large difference between the dominance coefficients h_{A_M} and h_{A_F}. We will ignore these equilibria for the purpose of the present analysis. The seventh equilibrium must be discarded altogether, since it is unstable or features biologically impossible allele frequencies. What remains are the following two equilibria:

```
equilibrium1 = {p_AX → 0, p_AY → 1};
equilibrium2 = {p_AX → 1, p_AY → 0};
```

Standard stability analysis yields the eigenvalues of these two equilibria

```
jacobian = {{D[eqpAX, p_AX ] + 1, D[eqpAX, p_AY ]}, {D[eqpAY, p_AX ], D[eqpAY, p_AY ] + 1}};
```

```
eigenvalues1 = Eigenvalues[jacobian /. equilibrium1]
```

$$\left\{1-h_{A_M}\,s_{A_M},\ 1+\frac{1}{3}\left(2\,h_{A_F}\,s_{A_F}-\left(-1+h_{A_M}\right)s_{A_M}\right)\right\}$$

```
eigenvalues2 = Eigenvalues[jacobian /. equilibrium2]
```

$$\left\{1-\left(-1+h_{A_M}\right)s_{A_M},\ 1+\frac{1}{3}\left(2\left(-1+h_{A_F}\right)s_{A_F}-h_{A_M}\,s_{A_M}\right)\right\}$$

In what follows, we concentrate on cases where the fitness of a heterozygote is between the two homozygote fitness values.

```
parameterConstraints = 0 < h_{A_M} < 1 && 0 < h_{A_F} < 1
```

$0 < h_{A_M} < 1 \&\& 0 < h_{A_F} < 1$

The equilibrium $p_{A_Y} = 1,\ p_{A_X} = 0$ is stable if

```
Reduce[-1 < Re[eigenvalues1[[1]]] < 1 && -1 < Re[eigenvalues1[[2]]] < 1 &&
   parameterConstraints, {s_{A_M}, s_{A_F}}, Reals] // FullSimplify
```

$$0 < h_{A_F} < 1 \&\& 0 < h_{A_M} < 1 \&\& 0 < s_{A_M} < \frac{2}{h_{A_M}} \&\& -\frac{3}{h_{A_F}} < s_{A_F} - \frac{(-1 + h_{A_M})\, s_{A_M}}{2\, h_{A_F}} < 0$$

i.e., if $0 < s_{A_M} < -s_{A_F}\ \frac{2\,h_{A_F}}{1-h_{A_M}}$.

Under these conditions, the geometric rate of increase of the novel sex-determining allele is given by

```
eqRA /. equilibrium1
```

$1 - h_{A_M}\ s_{A_M}$

The other equilibrium ($p_{A_Y} = 0,\ p_{A_X} = 1$) is stable if

```
Reduce[-1 < Re[eigenvalues2[[1]]] < 1 && -1 < Re[eigenvalues2[[2]]] < 1 &&
   parameterConstraints, {s_{A_M}, s_{A_F}}, Reals] // FullSimplify
```

$$0 < h_{A_F} < 1 \&\& 0 < h_{A_M} < 1 \&\& \frac{2}{-1 + h_{A_M}} < s_{A_M} < 0 \&\& \frac{3}{-1 + h_{A_F}} < s_{A_F} + \frac{6 - h_{A_M}\ s_{A_M}}{2\ (-1 + h_{A_F})} < 0$$

i.e., if $0 < -s_{A_M} < s_{A_F}\ \frac{2\,(1-h_{A_F})}{h_{A_M}}$.

When these conditions hold, the geometric rate of increase is given by

```
eqRA /. equilibrium2
```

$1 - (-1 + h_{A_M})\ s_{A_M}$

No recombination on the autosomes ($r_a = 0$)

To study the second submodel in the limit of no recombination and weak selection, we define the following procedure

```
completeLinkage[x_] :=
 Series[x /. {r_a → 0} /. weakSelectionApproximation /. paSubsStrongLinkage, {ϵ_s, 0, 1}] /.
    {s̃_{a_F} → s_{a_F} / ϵ_s, s̃_{a_M} → s_{a_M} / ϵ_s} // Normal // FullSimplify
```

and apply it to the recursion for the sexually-antagonistic-allele frequency on the neo-Y that we derived in Section (2)

```
eqpay = completeLinkage[equaM - p_{a_y}]
```

$(-1 + p_{a_y})\ p_{a_y}\ s_{a_M}\ (-p_a + h_{a_M}\ (-1 + 2\ p_a))$

This recursion has two simple equilibrium solutions

```
Solve[eqpay == 0, p_{a_y}]
```

```
{{p_{a_y} → 0}, {p_{a_y} → 1}}
```

The first one is stable when $s_{a_M} < 0$, and then the geometric rate of increase of the neo-Y is given by

```
completeLinkage[R_a] /. solutions[[1]] // Simplify
```

```
1 + s_{a_M} p̄_a (-p̄_a + h_{a_M} (-1 + 2 p̄_a))
```

The second equilibrium is stable when $s_{a_M} > 0$. In that case, the geometric rate of increase of the neo-Y is given by

```
completeLinkage[R_a] /. solutions[[2]] // Simplify
```

```
1 + s_{a_M} (-1 + p_a) (-p_a + h_{a_M} (-1 + 2 p_a))
```

Simulation results

We evaluated Equation (1) in the main text for low values of the recombination rates, and compared the results to the limiting values calculated in this section. As shown in Figure 1, our main result agrees well with exact numerical simulations, even for very low recombination rates (r_A, $r_a \ll \epsilon_s$). Moreover, the exponential growth rates calculated from Equation (1) and the numerical simulation results converge smoothly to the values that are expected in the absence of recombination.

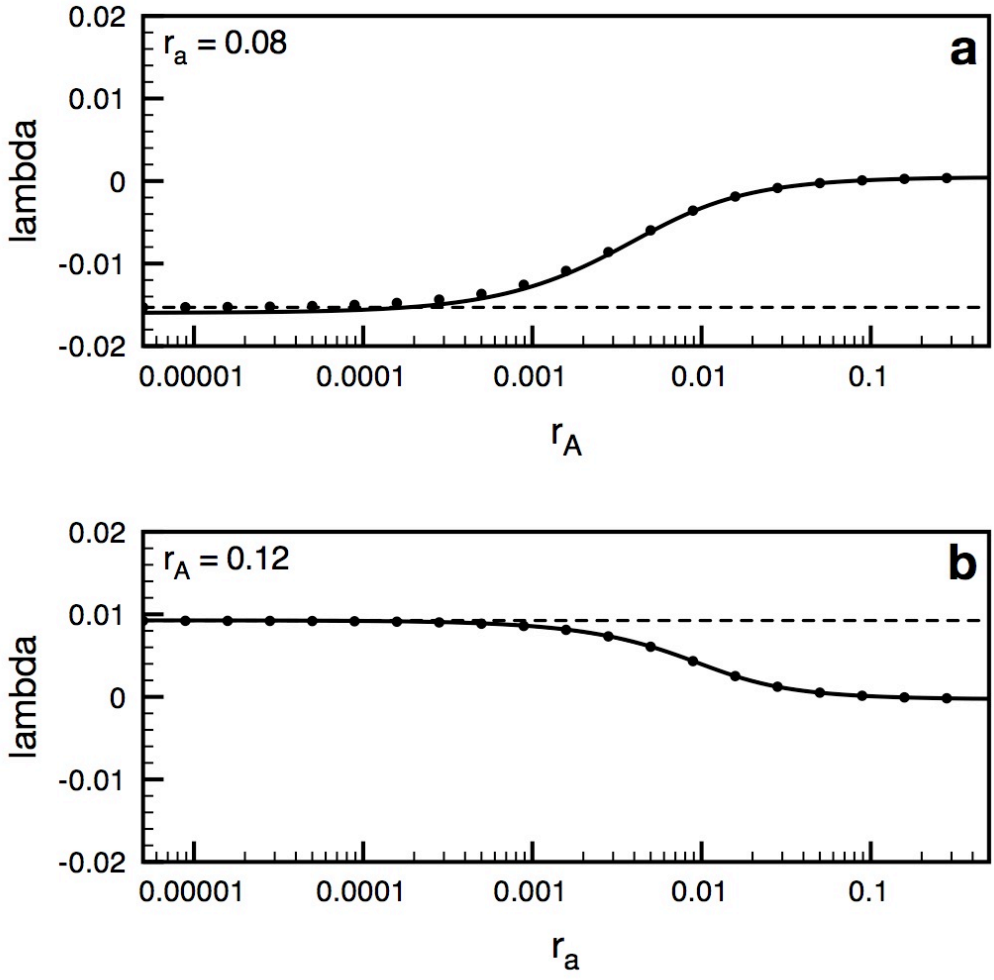

Figure 1 | Exponential growth rates at low values of the recombination coefficients. Solid lines indicate values for the exponential rate of increase of the neo-Y calculated from Equation (1) in the main text. The filled circles show the results of exact numerical simulations. For low values of the recombination rates, the exponential growth rates are expected to converge to the limit values indicated by the dashed lines (these represent the no-recombination limits calculated in Section (4) of the supplementary material). In panel **a**, we vary the recombination rate at the ancestral sex chromosome, while keeping r_a fixed at 0.08. In panel **b**, we vary the recombination rate between the autosomal loci, while r_A is held constant at 0.12. The selection and dominance coefficients are as in Figure 1 in the main text.

5 - Simulation results for a selection of alternative genetic scenarios

In this section we present simulation results for a number of genetic scenarios that deviate from our original model assumptions. In particular, we explore the effects of alternative types of genetic interactions between the sex-determination factors.

Partial dominance and incomplete penetrance

The situation analyzed in the main text is one where the novel sex-determination factor is a completely dominant and fully penetrant mutation. Here, we investigate the effects of partial dominance (Figure 2) and incomplete penetrance (Figure 3). Partial dominance and incomplete penetrance shift the invasion boundary, such that invasion of the mutant sex allele requires a lower recombination rate r_a or a higher level of sexual antagonism S_a at the autosomal sex-antagonistic locus. The magnitude of this effect increases smoothly as we deviate more and more from our original model assumptions, i.e., as we shift from complete dominance to additive interactions (Figure 2), or from high to low penetrance (Figure 3). More importantly, however, neither partial dominance nor incomplete penetrance fully preclude invasion of novel sex determination factors, supporting the robustness of our main results.

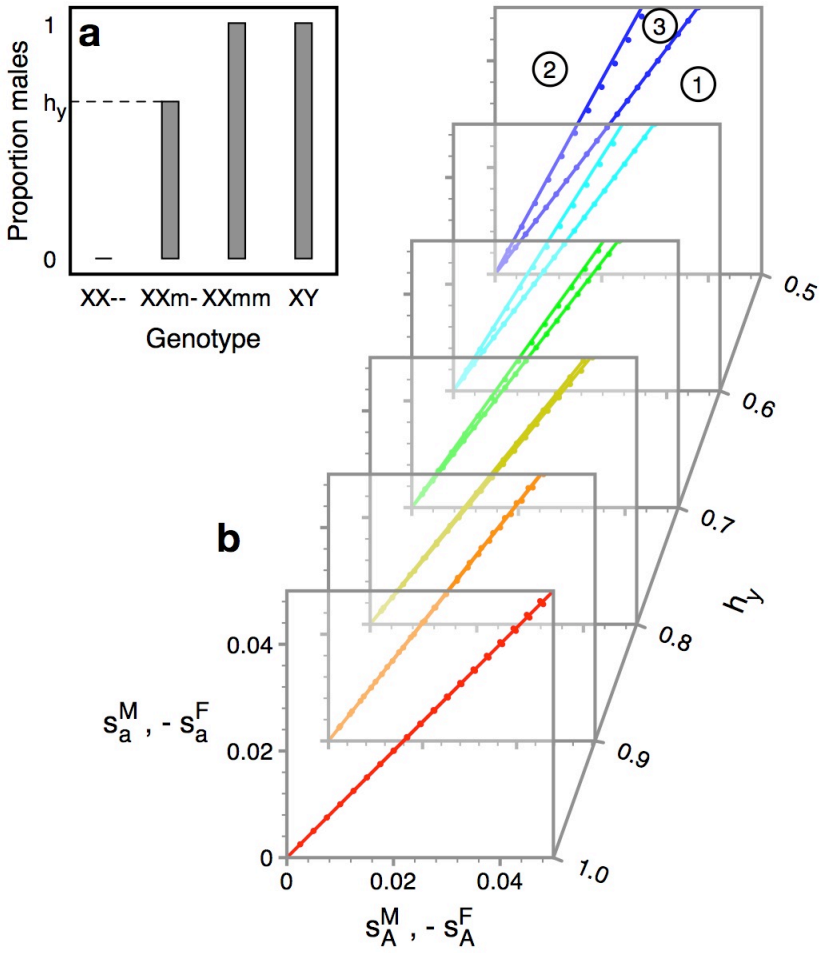

Figure 2 | Partial dominance. (**a**) Other than in the main text, we here assume that the novel sex determining factor is a partially dominant masculinizing mutation. Only a fraction h_y of the zygotes that carry a single copy of the novel sex determining allele (indicated as *m* in the genotype labels on the horizontal axis) develop as males; zygotes that carry two copies of the mutant allele (genotype *XXmm*) develop as males with certainty. (**b**) The stacked panels show invasion and fixation boundaries for the neo-Y based on numerical simulations for six values of h_y ranging from 1.0 (complete dominance) to 0.5 (additive interaction between alleles). The labeling of the different regions (shown only for the last panel) corresponds to that used in Figure 3 of the main text. As h_y decreases, higher levels of sexual antagonism at the autosomal sex-antagonistic locus are required in order for the neo-Y to invade and to replace the ancestral Y (region 2 becomes smaller as h_y decreases). Conversely, the conditions for stability of the ancestral sex-determination system (region 1) or bistability (3) become more favorable. These effects are due to the fact that partial dominance reduces the efficiency of selection on the mutant allele in heterozygotes. Initially, when its frequency is still low, the novel sex-determination factor will almost exclusively be found in heterozygotes. Invasion of the neo-Y thus relies on stronger sexual antagonism (or stronger linkage) on the neo-Y to compensate for the reduced exposure to selection. Results are for symmetrical parameter conditions: $s_A^M = -s_A^F$, $s_a^M = -s_a^F$, $h_A^M = h_a^M = 0.6$, $h_A^F = h_a^F = 0.4$, and for different degrees of linkage: $r_A = r_a = 0.05$ (dots) and $r_A = r_a = 0.25$ (lines). The invasion and fixation boundaries are virtually overlapping for the two different sets of values for the recombination rates that we considered.

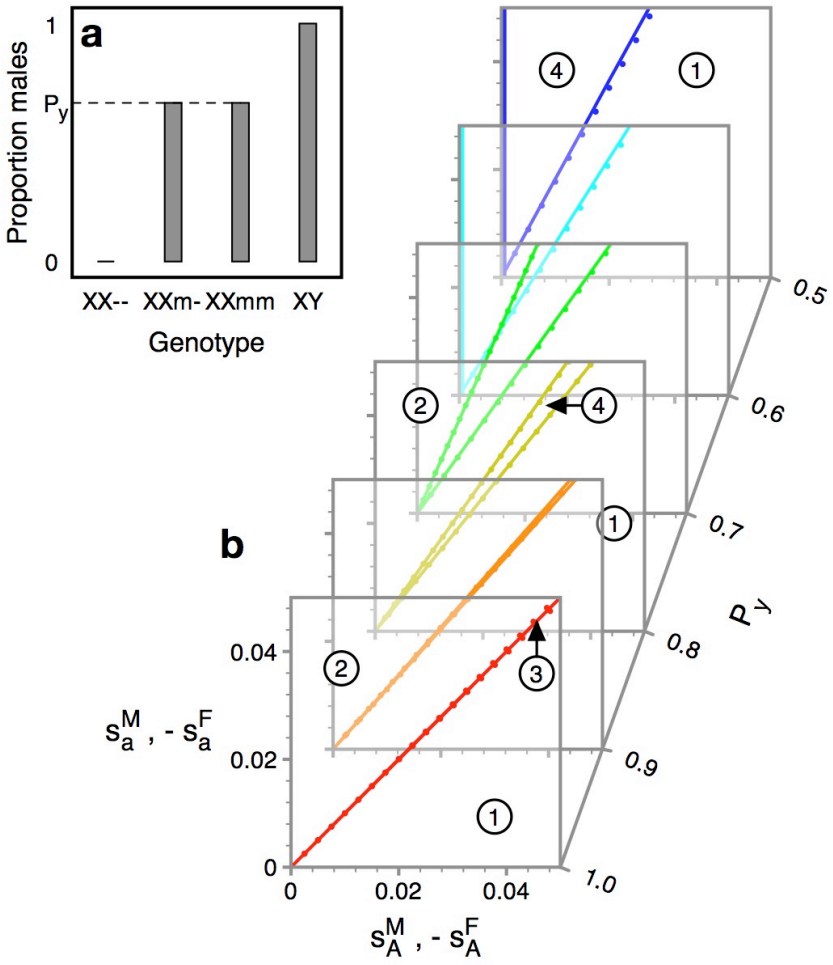

Figure 3 | Incomplete penetrance. (**a**) Other than in the main text, we here assume that the novel sex determining factor is a dominant masculinizing mutation with incomplete penetrance. Only a fraction P_y of the zygotes that carry one or more copies of the novel sex determining allele (indicated as *m* in the genotype labels on the horizontal axis) develop as males. (**b**) The stacked panels show invasion and fixation boundaries for the neo-Y based on numerical simulations for six values of P_y ranging from 1.0 (complete penetrance) to 0.5 (random sex determination). The labeling of the different regions corresponds to that used in Figure 3 of the main text. As P_y decreases, higher levels of sexual antagonism at the autosomal sex-antagonistic locus are required in order for the neo-Y to invade and to replace the ancestral Y. Below a certain degree of penetrance (roughly at $P_y = 0.64$), the neo-Y can still invade for a reasonable range of selection coefficients but it can never fully replace the ancestral Y, leading to the establishment of a protected polymorphism of sex factors (region 4). The possibility of protected polymorphism arises already at lower values of P_y. If the neo-Y is to replace the ancestral Y, it must attain a relatively high overall frequency in order to maintain a 1:1 sex ratio (as P_y approaches 0.5, the neo-Y must approach fixation in both sexes). At low frequency of the ancestral Y, the neo-Y thus finds itself relatively often in a female. As a consequence, the linkage disequilibrium between the novel masculinizing allele and the sex-antagonistic allele beneficial to males is reduced, favoring an increase in the frequency of the ancestral Y chromosome and eventually leading to the maintenance of both the ancestral and the neo-Y. Parameters are as in Figure 2. The difference between the invasion and fixation boundaries for $r_A = r_a = 0.05$ (dots) and those for $r_A = r_a = 0.25$ (lines) is again marginal.

A recessive sex-determination mutation, heterogamety switches

To conclude this section, we consider the case that the mutant sex-determination allele is a recessive masculinizing allele. A fully recessive sex-determination allele cannot increase in frequency from arbitrarily low initial frequencies. However, a recessive allele could first increase in frequency by drift. Once a sufficiently high frequency has been reached, the allele will be expressed in homozygotes such that selection can cause the frequency to increase further. By means of numerical simulation, we determined the threshold frequency of the recessive allele above which selection would lead it to increase in frequency, for given ratios of the selection coefficients s_a^M / s_A^M (Figure 4). For example, if sex antagonistic selection at the autosomal locus is twice as strong as sex-antagonistic selection at the sex-linked locus (i.e., $s_a^M = 2\, s_A^m$), genetic drift must bring the frequency of the novel sex-determination above 17% before selection can lead to a further increase.

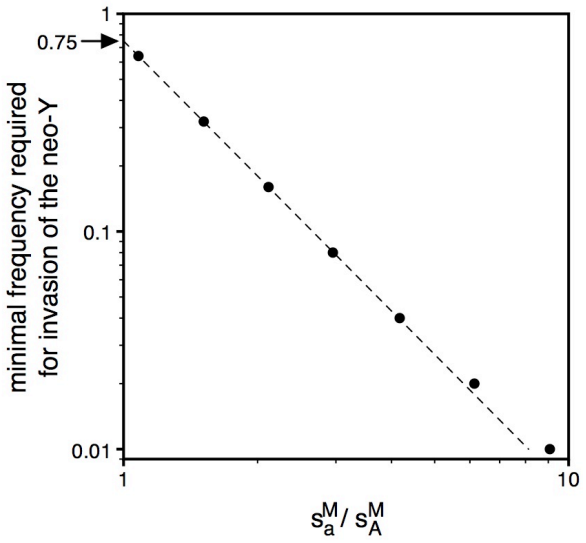

Figure 4 | Invasion threshold frequencies for a recessive masculinizing allele. Depending on the intensity of sex-antagonistic selection at the autosomal locus relative to that at the sex linked locus (horizontal axis; as in Figure 2, we took $s_A^F = -s_A^M$ and $s_a^F = -s_a^M$), genetic drift must bring the frequency of the novel, recessive sex determination allele above a threshold frequency (vertical axis), before selection can lead to a further increase of the frequency of the mutation. Dots represent simulation results, the dashed line shows a power-law fit based on the five leftmost data points (numerical inaccuracies disproportionately affect the rightmost datapoints). The fitted line intersects the y-axis at 0.75, the theoretically expected value when the autosomal and sex-linked sex-antagonistic loci have identical selection coefficients. Other parameters are as in Figure 2.

Even though the conditions for invasion of a recessive masculinizing allele are quite restrictive (Figure 4), once genetic drift has triggered the invasion of the masculinizing mutation, the mutant allele is very likely to spread to fixation. In that case, the ancestral Y will disappear. The sex-determination that results is a ZZ/ZW system governed by a recessive sex-determination locus. Invasion of a recessive masculinizing allele is not the only mechanism that could lead to heterogamety switches. Also the invasion of a novel, (partially) dominant feminizing allele could induce a switch from male to female heterogamety. Invasion of such an allele would not be dependent on genetic drift, but it would be opposed by selection against YY individuals. Since such selection cannot easily be incorporated in our present analysis, we leave the investigation of heterogamety switches involving dominant feminizing alleles for future consideration.