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.

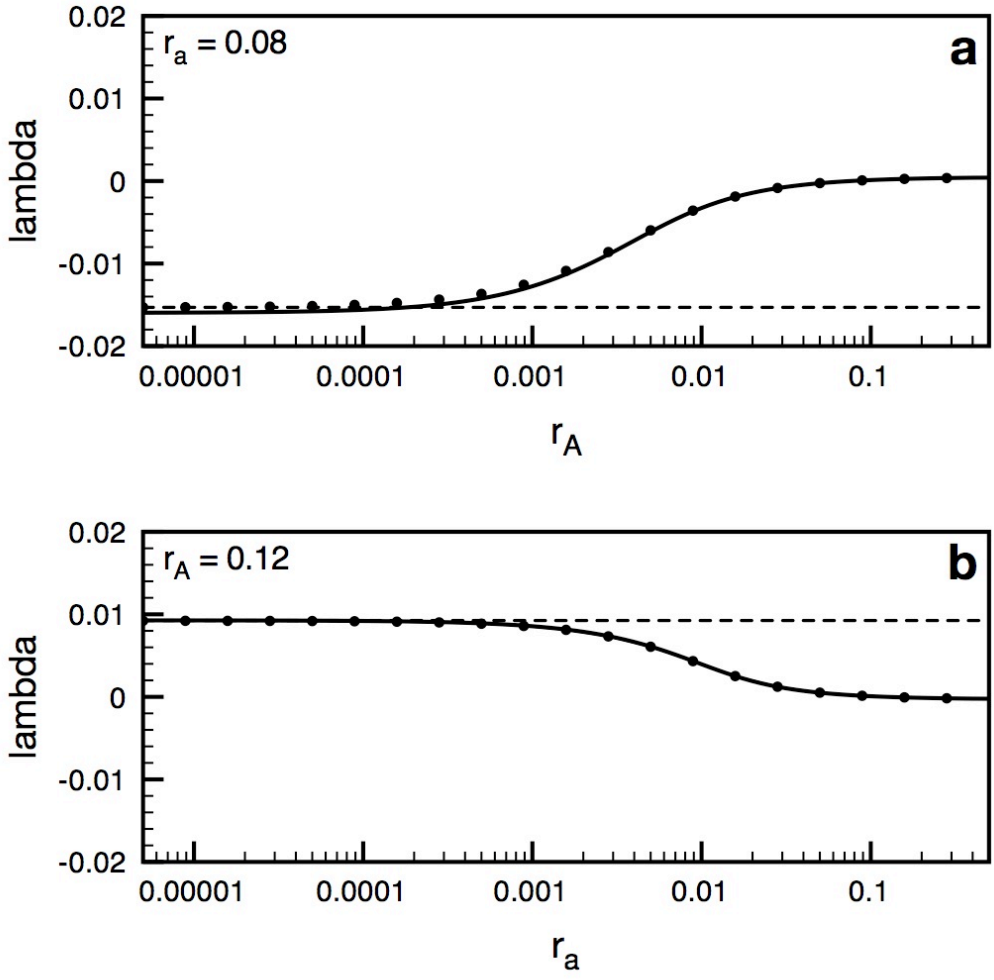

Figure 1 | Exponential growth rates at low values of the recombination coefficients. Solid lines indicate values for the exponential rate of increase of the neo-Y calculated from Equation (1) in the main text. The filled circles show the results of exact numerical simulations. For low values of the recombination 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.

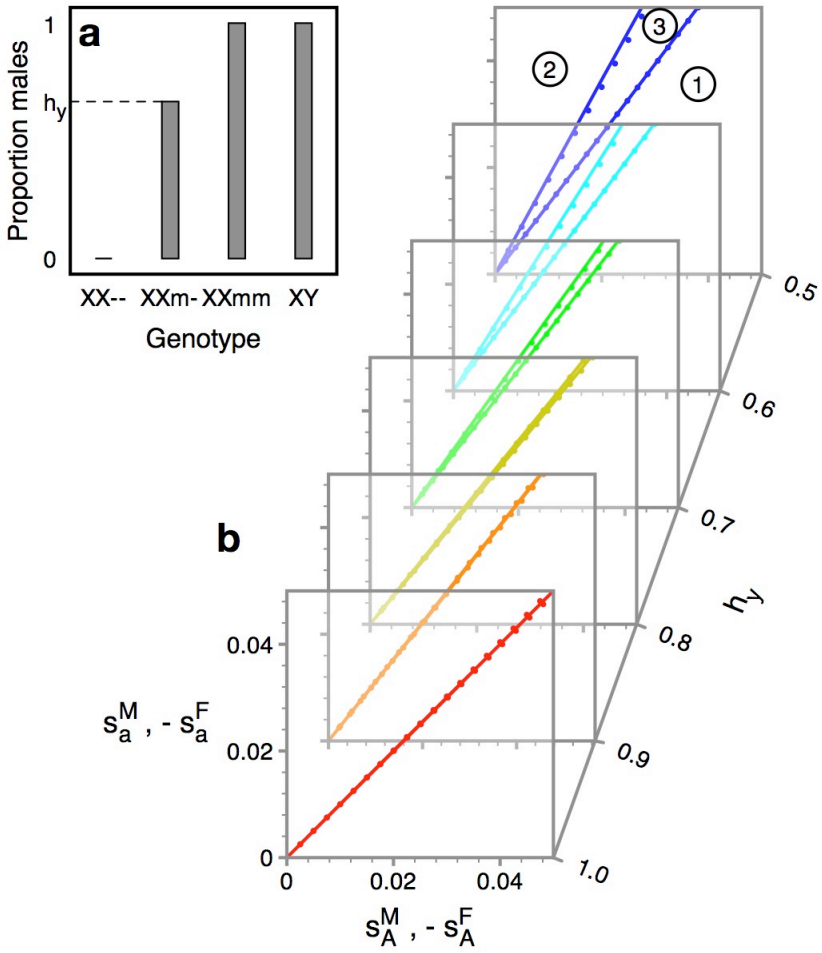

Figure 2 | Partial dominance. (**a**) Other than in the main text, we here assume that the novel sex determining factor is a partially dominant masculinizing mutation. Only a fraction h_y of the zygotes that carry a single copy of the novel sex determining allele (indicated as *m* in the genotype labels 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.

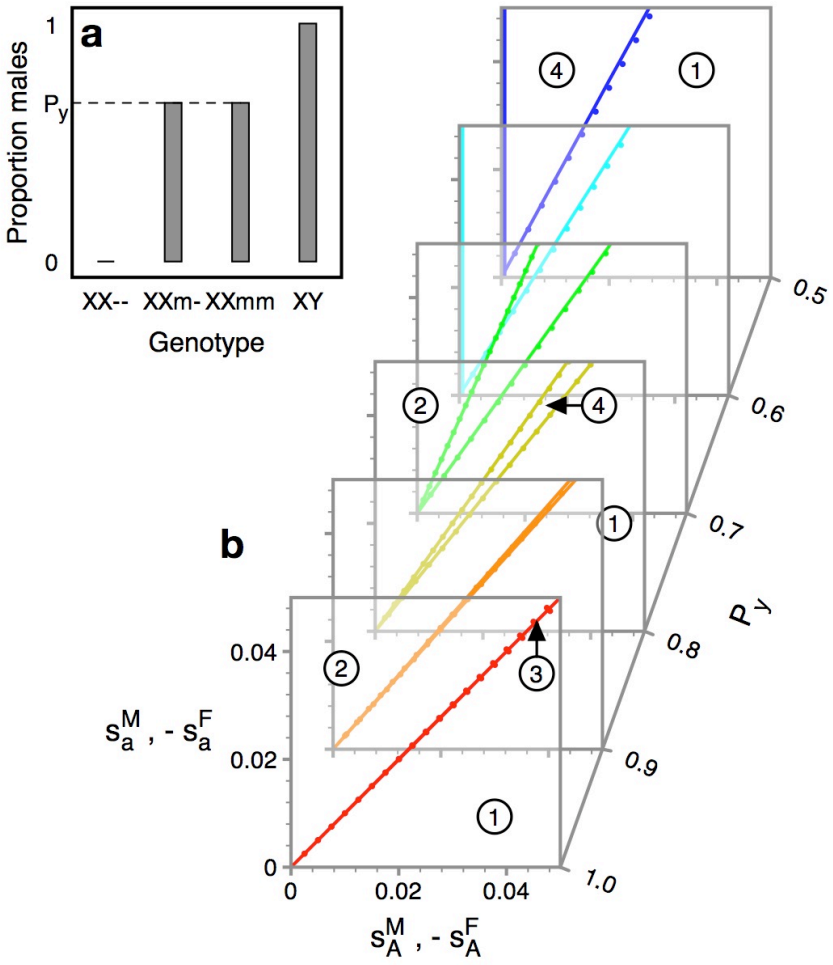

Figure 3 | Incomplete penetrance. (**a**) Other than in the main text, we here assume that the novel sex determining factor is a dominant masculinizing mutation with incomplete penetrance. Only a fraction P_y of the zygotes that carry one or more copies of the novel sex determining allele (indicated 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.

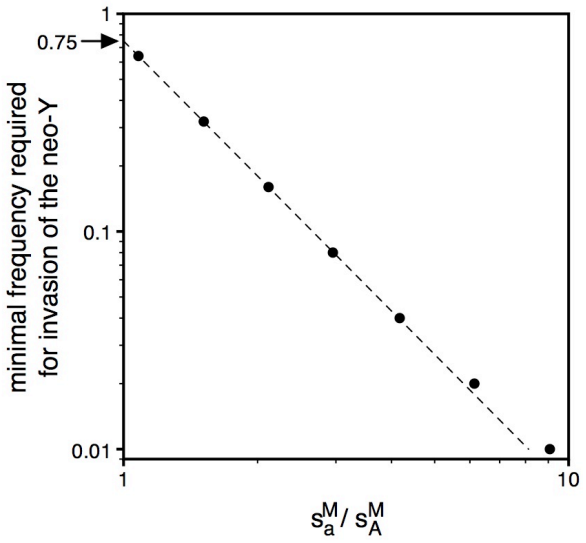

Figure 4 | Invasion threshold frequencies for a recessive masculinizing allele. Depending on the intensity of sex-antagonistic selection at the autosomal locus relative to that at the sex linked locus (horizontal axis; as in Figure 2, we took $s_A^F = -s_A^M$ and $s_a^F = -s_a^M$), genetic drift must 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.