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

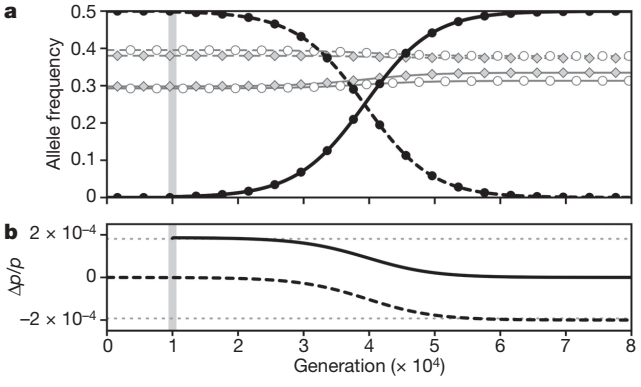

Figure 1 | Sex determination hijacked by an autosomal sex-determining factor. **a**, Black lines show the evolution of allele frequencies at sex-determination loci in males during a sex-chromosome switch (solid line, neo-Y; dashed line, ancestral Y). The frequencies of sex-antagonistic alleles change 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: $s_A^F = 0.024$, $s_A^M = -0.026$, $s_a^F = -0.029$, $s_a^M = 0.025$, $h_A^F = h_a^M = 0.6$, $h_A^M = h_a^F = 0.4$, $r_A = 0.12$, $r_a = 0.08$.

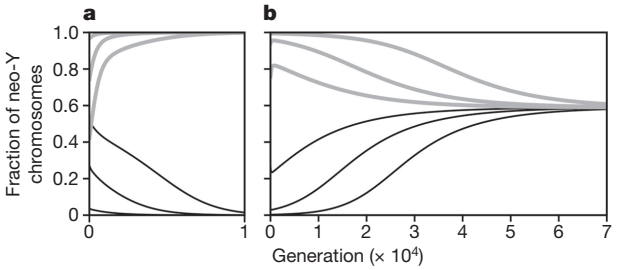

Figure 2 | Bistability and protected polymorphism of sex-determining factors. The two panels show examples of cases in which invasion of the neo-Y and its potential to spread to fixation do not coincide. **a**, Bistability: the neo-Y cannot invade a population in which sex is determined by the ancestral 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

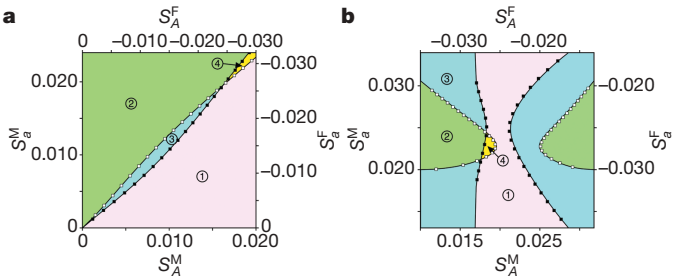

Figure 3 | Dependence of evolutionary outcomes on the selection coefficients. Systematically varying the values of the selection coefficients, we delineated four regions in parameter space that correspond to qualitatively different evolutionary outcomes of the model. In region 1 the ancestral Y is stable 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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