Y CHROMOSOME ORIGINS

Y recombination arrest and degeneration in the absence of sexual dimorphism

Thomas Lenormand[1]* and Denis Roze[2,3]

Current theory proposes that degenerated sex chromosomes—such as the mammalian Y—evolve through three steps: (i) recombination arrest, linking male-beneficial alleles to the Y chromosome; (ii) Y degeneration, resulting from the inefficacy of selection in the absence of recombination; and (iii) dosage compensation, correcting the resulting low expression of X-linked genes in males. We investigate a model of sex chromosome evolution that incorporates the coevolution of cis and trans regulators of gene expression. We show that the early emergence of dosage compensation favors the maintenance of Y-linked inversions by creating sex-antagonistic regulatory effects. This is followed by degeneration of these nonrecombining inversions caused by regulatory divergence between the X and Y chromosomes. In contrast to current theory, the whole process occurs without any selective pressure related to sexual dimorphism.

Many species have chromosomal sex-determination systems (*1*). In XX/XY systems, as in mammals, males are heterogametic (XY). In ZZ/ZW systems, as in birds, females are heterogametic (ZW). We mention only XY systems below, but all arguments are equally applicable to ZW systems. Y chromosomes are often nonrecombining and have degenerated through the loss of most of the genes present on ancestral autosomes. In several chiasmate species, such as mammals or birds, suppression of recombination involves successive events, each affecting Y subregions of different sizes, called strata (*2*). These strata are detected on the basis of different degrees of sequence divergence from the homologous X regions (*2*).

After the establishment of a sex-determining locus on an autosome, current theory (*3*–*5*) proposes that Y chromosomes evolve through three steps: First, sex chromosomes evolve recombination suppression because selection favors linkage between sex-determining and sexually antagonistic genes (*6*–*9*). These sexually antagonistic genes occur when trait optima differ between the sexes, driving the evolution of sexual dimorphism. In the second step, the absence of recombination reduces the efficacy of natural selection by causing "selective interference." Such interference leads to an accumulation of deleterious mutations on the Y chromosome and genetic degeneration (*10*). Finally, dosage compensation evolves to restore optimal gene expression in males, whose Y-linked genes have lowered expression due to degeneration, and possibly in females if dosage compensation mechanisms alter expression in that sex (*7*, *11*, *12*). The compensation process involves various mechanisms in different species, and compensation is not always complete for all X-linked genes (*13*–*15*).

This theory has been explored over the past ~50 years, both empirically and theoretically (*3*–*6*, *16*). Empirical support for the first step is equivocal—despite decades of investigation, decisive evidence for a causal role of sexually antagonistic loci on recombination arrest is lacking (*16*–*19*). The second step is difficult to reconcile with the observation of small degenerated strata (*16*), within which selective interference should be minimal. Lastly, the causal ordering of events has also been challenged by observations of the early evolution of partial dosage compensation in young sex chromosomes (*20*–*24*).

Theoretically, each step suffers from limitations (*25*). However, an important global limitation is that each step has generally been considered independently from the others, resulting in a piecemeal set of models lacking integration. In particular, changes in gene regulation have not been consistently studied throughout sex chromosome evolution. Yet, such changes can influence the evolution of sex-limited expression, contribute to compensatory adaptive silencing, and are pivotal for the evolution of dosage compensation.

We propose that the joint evolution of regulatory changes and accumulation of deleterious mutations can transform an autosome into a degenerated sex chromosome with dosage compensation. We use individual-based stochastic simulations assuming a population of N_{pop} diploid individuals, with XY males and XX females (*25*) (Fig. 1). We consider the evolution of a pair of autosomes carrying hundreds of genes subject to partially recessive deleterious mutations, with one homolog that has recently acquired a sex-determining locus. Gene expression is controlled by cis-regulatory sequences (affecting expression only on the same chromosome as themselves) interacting with trans regulators that can affect the gene copies on both homologs (*26*). All of these elements can mutate. To allow for dosage compensation on a gene-by-gene basis while keeping the model symmetric for males and females, we assume that each gene is controlled by one male- and one female-expressed trans regulator (*25*) (Fig. 1). As in (*27*), we assume that each gene's overall expression level is under stabilizing selection around an optimal level and that the relative expression of the two copies of each gene determines the dominance level of a deleterious mutation occurring in the coding gene. For instance, a deleterious mutation occurring in

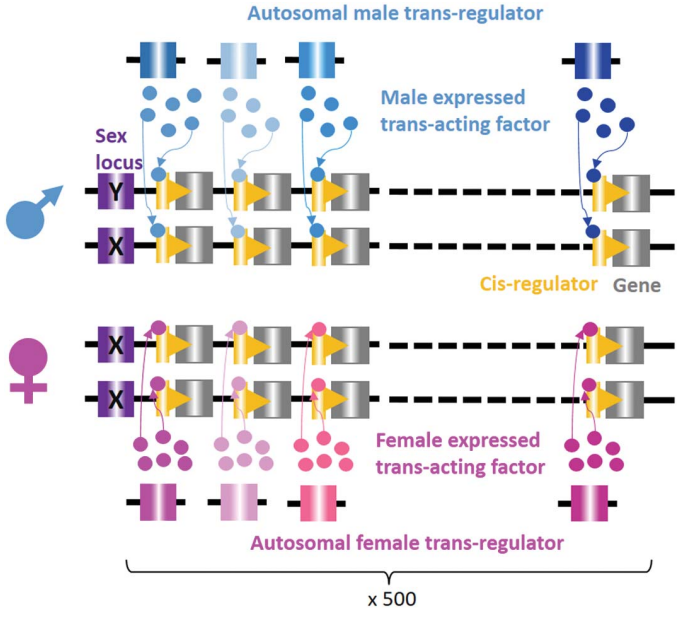

Fig. 1. An overview of the simulated genome evolving sex chromosomes. A chromosome pair carries the sex locus at one end with two alleles (purple, X; light purple, Y) determining two sexes (XX, female; XY, male). This chromosome carries 500 coding genes, each with a cis-regulatory region. Each cis regulator interacts with a trans acting factor. This trans acting factor is not on the sex chromosomes but is expressed from a pair of autosomal trans regulators, which differ in males and females. See main text for other assumptions of the model.

[1]CEFE, Univ. Montpellier, CNRS, EPHE, IRD, Montpellier, France. [2]CNRS, IRL 3614, Roscoff, France. [3]Sorbonne Université, Station Biologique de Roscoff, Roscoff, France.
*Corresponding author. Email: thomas.lenormand@cefe.cnrs.fr

a less expressed gene copy is assumed to be less harmful than one in a more highly expressed copy (*25*).

We then assume that mutations occur that suppress recombination on a segment of the Y. For simplicity, we refer to these mutations as inversions, although they could correspond to other mechanisms causing recombination arrest (*25*). Inversions of any size can occur, but we follow only those on the Y that include the sex-determining locus, which will necessarily be confined to males and cause recombination arrest. We assume that inversions can add up, such that new inversions can occur on chromosomes carrying a previous inversion and thus extend the nonrecombining part of the Y. Finally, we assume that reversions restoring recombination can occur, and for simplicity, that such reversions cancel only the most recent inversion (*25*).

To understand the dynamics of sex chromosome evolution in our model, first consider the case where the cis and trans regulators do not mutate. In this case, all inversions on the Y are eventually reversed and lost. This occurs in two steps: First, an inversion appears on a given Y and "freezes" a segment of the chromosome. If by chance this Y carries relatively few or milder deleterious mutations, this "lucky" inversion has a selective advantage. Consequently, it tends to fix among Y chromosomes, causing recombination suppression in this portion of the sex chromosomes. Larger inversions are overrepresented among these lucky inversions, as they contain more genes and exhibit a larger fitness variance (*25*) (fig. S1A). Once fixed, these Y chromosomes start accumulating deleterious mutations as a result of selective interference. Fitness declines faster for larger inversions because of stronger selective interference (fig. S1B). When the marginal fitness of the inversion becomes lower than the fitness of the corresponding chromosomal segment on the X, reversions are selectively favored and spread, which restores recombination. Thus, Y-specific inversions are short lived and maintained only transiently in the population in the absence of regulatory mutations (fig. S1C). These periods of recombination suppression do not last long enough to lead to Y chromosome degeneration.

A radically different four-step process emerges when the regulatory sequences can mutate and evolve (Fig. 2). The first step starts, as before, with the fixation of a lucky inversion on the Y. However, once the inversion stops recombination, the X and Y cis regulators start evolving independently; this is step two. This creates a positive feedback loop that causes rapid degeneration of Y-linked alleles (*27*); by chance, some genes on the Y become slightly less expressed than their X-linked allelic counterparts and accumulate more deleterious mutations (because lower expression makes mutations more recessive), selecting for a further reduction of expression of these Y linked genes. This process can work on individual genes irrespective of the size of the nonrecombining region created by the inversion (*27*), and the subsequent degeneration does not involve selective interference. However, like in the absence of regulator evolution, recombination arrest also triggers the accumulation of deleterious mutations by selective interference, especially if the inversion includes many genes.

The key step is the third, in which inversions are stabilized in the long term, even when they become entirely degenerated (Fig. 3 and fig. S5). Cis-regulator divergence and degeneration in step 2 cause a departure from optimal expression levels in males. Assuming that gene expression is under stabilizing selection, this causes divergence in sex-specific trans regulators, which evolve to maintain optimal expression in both sexes. For instance, if a Y cis regulator mutates, causing lower expression, this will favor a stronger allele of the male trans regulator, to maintain optimal expression levels. The divergence of X- and Y-linked cis regulators and the divergence of sex-limited trans regulators automatically generate sexually antagonistic fitness effects: X

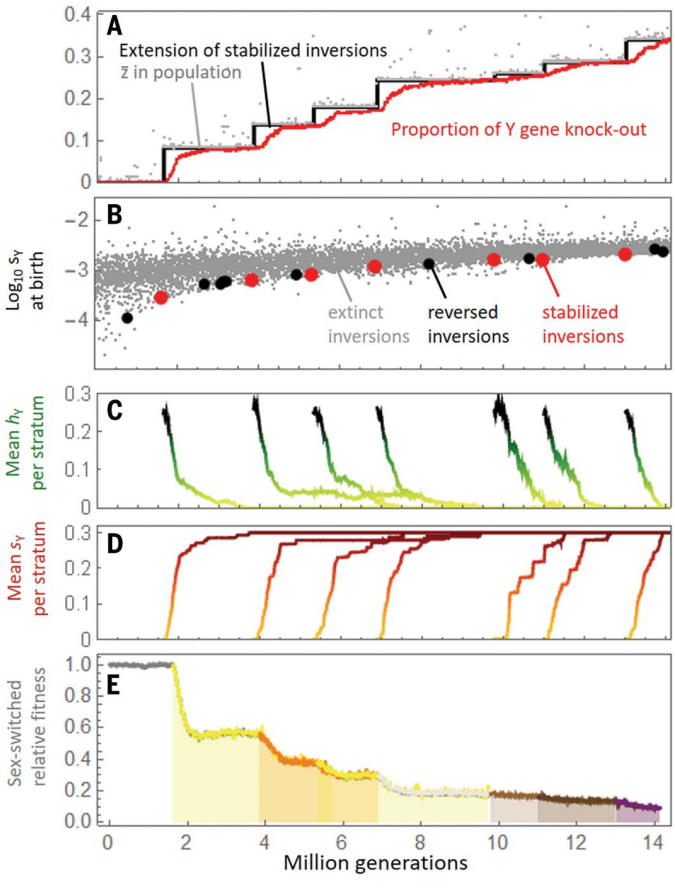

Fig. 2. Example of a typical Y degeneration process. The Y progressively degenerates by the accumulation of inversions, which accumulate deleterious mutations, evolve dosage compensation with sex-antagonistic fitness effects, and become immune to reversions. (**A**) The black stairplot shows the extension of each successive stratum of the Y (expressed as the fraction of the physical length of the Y), corresponding to stabilized inversions. Gray dots, average fraction of the physical length of the nonrecombining Y in the population. Red, proportion of Y genes that are silenced and knocked out (i.e., they accumulated deleterious mutation effects up to the maximal value s_{max}; here, s_{max} = 0.3). At this time scale, silencing and degeneration appear simultaneous, but silencing is slightly ahead. (**B**) Log_{10} plot of the average effect of deleterious mutations carried by inversions when they first arise in the population (averaged over the different genes within the inversion). Gray dots, random subsample of inversions that are lost before fixing in the population; black dots, inversions that reach fixation but are lost after the occurrence of a reversion; red dots, inversions that reach fixation and become stabilized strata on the Y. (**C**) Mean dominance of deleterious mutations on each stabilized inversion (noted h_Y). Initial dominance of deleterious mutations is assumed to be 0.25 (*25*). Fig. S7 shows the detailed dynamics of h_Y at a smaller time scale. (**D**) Accumulation of deleterious mutations on each stabilized inversion (the maximum effect s_{max}, is set to 0.3 for all genes). (**E**) Fitness that the Y carrying the stabilized inversions would have on average, if expressed in a female (relative to the actual average fitness of males). The different colors highlight the occurrence of the successive strata. The average fitness of males that would carry two X chromosomes at that time is indicated in gray, but yields very similar values and is therefore almost indistinguishable. This simulation considers a population of $N_{pop} = 10^4$ individuals, an intensity of stabilizing selection on dosage I = 0.1, and a mean effect of deleterious mutations s_{mean} = 0.05. See (*25*) for other parameter values.

cis-regulators that recombine onto the Y would result in overexpression in males (as a result of mismatches with male trans regulators); similarly, Y cis regulators recombined onto the X would cause underexpression in females. Hence, if a reversion occurs, the reestablished recombination between X and Y would likely reduce offspring fitness by creating a mismatch between cis and trans regulators. This sexually antagonistic effect caused by nascent dosage compensation protects diverging inversions from reversion. This is the ultimate cause of Y recombination suppression in our model (*25*). However, suppose dosage compensation does not evolve quickly enough. In such a case, recombination can be restored: After a reversion, a new recombinant Y can be produced that carries a nondegenerated part of the X without causing strong cis and trans-regulator mismatch in males. This new Y can then replace the previous nonrecombining degenerated Y, which restores recombination on the part of the Y derived from the reversion.

Of course, only a minority of inversions evolve this nascent dosage compensation within a fast enough time frame relative to the speed of degeneration to remain immune to reversion (meaning that they remain, at all times, unlikely to be selectively outcompeted by recombinant chromosomes arising after a reversion). However, a positive-feedback loop is also operating here. Namely, when an inversion starts evolving dosage compensation it becomes relatively immune to reversion and is maintained longer in the population, giving it more time to evolve further dosage compensation. The inversion eventually becomes completely degenerated with complete dosage compensation (for dosage-sensitive genes). This leads to very strong sexually antagonistic regulatory effects, which effectively make the inversion irreversibly immune to reversions.

In our model, recombination suppression evolves along with regulatory evolution, but paradoxically, it is opposed by selective interference. The evolution of nascent dosage compensation involves the fixation of compensatory mutations and is partly adaptive. However, if selective interference is too strong, inversions accumulate deleterious mutations too fast and are quickly replaced by reversions. Accordingly, stabilized inversions tend to be strongly biased toward small sizes, though less so when the population size is larger (fig. S2C). In large populations, recombination suppression and degeneration evolve more quickly, because more inversions occur and selective interference (the effect of which is stronger in smaller populations) is relatively less efficient at removing large inversions (fig. S2). Finally, as expected, this overall process is faster when the intensity of stabilizing selection on gene expression levels is strong. This is because selection on dosage fosters the evolution of dosage compensation and concurrently protects partially degenerated inversions from reversions (fig. S3).

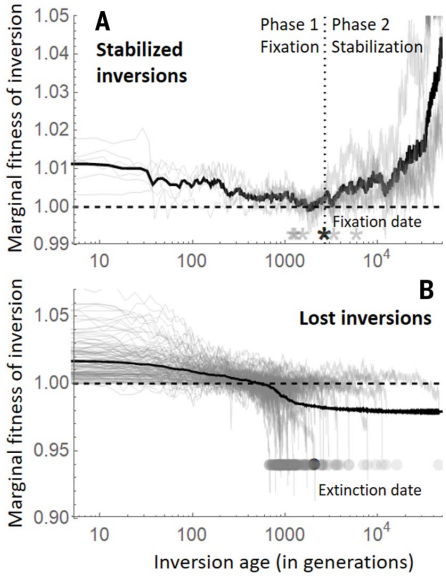

Fig. 3. Fitness trajectories of stabilized and lost inversions. The *x* axis shows inversion age, i.e., the number of generations since the appearance of the inversion (in log scale). The *y* axis indicates marginal fitness of the inversion relative to the same chromosomal segment on the X if it was in a male, noted W_{margX} (*25*). After fixation, this measures the sexually antagonistic effect of nascent dosage compensation. The marginal fitness of the inversion relative to the same chromosomal segment among Y chromosomes not carrying the inversion, noted W_{margY} (*25*), yields indistinguishable results before the inversion fixes (W_{margY} cannot be computed after the inversion fixes, as all Y chromosomes carry the inversion). Gray, individual trajectories; black, average values. (**A**) Inversions that are stabilized as first Y strata, collected over 10 evolutionary replicates after 1 million generations. Their fixation date is indicated by an asterisk at the bottom. (**B**) Top 15 longest-lived inversions before stabilization of the first stratum, collected over 10 evolutionary replicates and simulated over 1 million generations. Their extinction date is indicated by a gray disk at the bottom (and the average extinction date by the black disk). The time-averaged fitness at time *t* (in black) is computed over all inversions, counting their last achieved fitness if they are extinct at *t*. The dashed line indicates value 1.

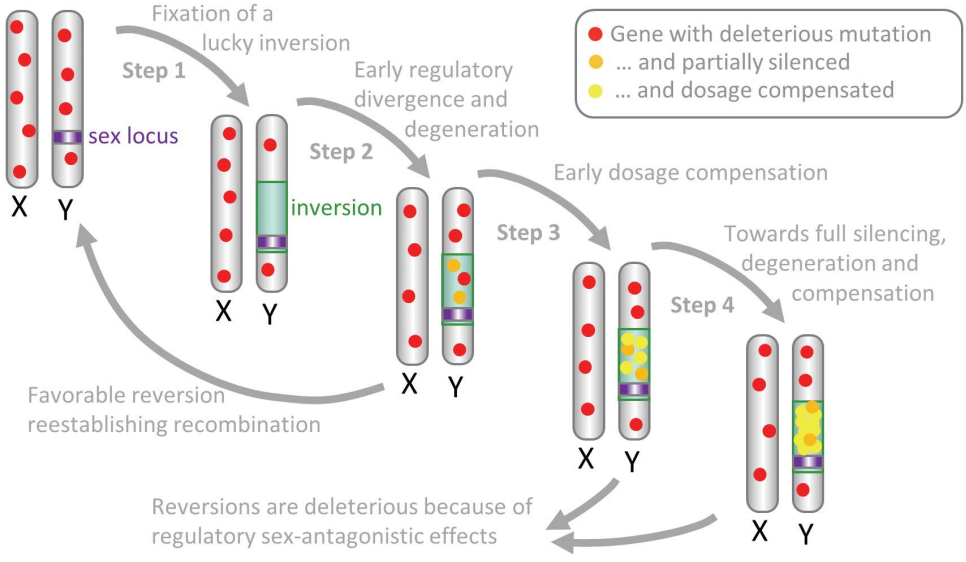

Fig. 4. Steps involved in the evolution of a Y nonrecombining stratum. The process involves four steps, as explained in the text, and is briefly described by captions on the figure. Only the first stratum is illustrated, but steps one to four are repeated for strata extending the nonrecombining portion of the until the whole chromosome is degenerated, silenced, and dosage-compensated.

Thus, our model suggests that the Y chromosome is entangled in a regulatory trap leading to recombination arrest and degeneration, even in the absence of selective pressures related to sexual dimorphism. Indeed, unlike previous theories (*6*–*9*), our model only includes genes with the same optimal expression level in males and females and deleterious mutations that have the same effect in both sexes. This process is inherently stochastic, as it involves the rare stabilization of a handful of inversions and is highly variable (fig. S4). However, it works faster in larger populations, as selective interference opposes recombination arrest and the stabilization of large strata.

Our model also reverses the causality proposed by previous theories by showing that dosage compensation can cause recombination suppression, rather than being a consequence of degeneration after such suppression. Sexually antagonistic effects are involved in the evolution of suppressed recombination. However, they result from the fact that one sex is heterogametic, not from males and females having divergent sex-specific optima for reproductive traits or expression levels. All genes for which dosage affects fitness can contribute to the process, not just a subset of sexually antagonistic loci. The potential sexually antagonistic effect of dosage compensation has long been appreciated (*7*, *12*, *28*–*30*). However, its potential role in recombination arrest has not been previously recognized, as it is usually thought to occur late in the degeneration process. Once recombination has stopped, sexually antagonistic alleles can arise and be maintained (*9*, *31*), but they are not required for recombination arrest, as shown here.

We showed that the emergence of nonrecombining and degenerated sex chromosomes in diploid organisms requires very few ingredients: genetic sex determination, deleterious mutations, inversions, sex-specific trans regulators, and stabilizing selection on gene expression levels. This theory includes all steps (Fig. 4 and fig. S8) in a single set of assumptions and is compatible with current data on sex chromosome evolution in chiasmate species (*25*). It predicts the occurrence of strata, including small ones (*16*) and the occurrence of early regulatory changes in young sex chromosomes (*20*–*24*). It also accounts for the lack of decisive evidence for a causal role of sexually antagonistic loci on recombination arrest (*16*–*19*). Overall, this theory explains the rapid expansion, degeneration, and dosage compensation of the nonrecombining region of sex chromosomes without requiring preexisting selection pressures favoring sexual dimorphism.

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SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.abj1813
Materials and Methods
Supplementary Text
Figs. S1 to S8
References (*33*–*46*)
MDAR Reproducibility Checklist

View/request a protocol for this paper from *Bio-protocol*.

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Thomas Lenormand and Denis Roze

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Evolutionary models of the Y chromosome

A major question in evolutionary genetics is how and why sex chromosomes form from otherwise undifferentiated chromosomes. The sexual antagonism theory posits that antagonistic alleles that benefit males but harm females lie on the same chromosome as an initial male-determining locus, resulting in selection against recombination. Lenormand and Roze have developed a four-step model proposing an alternative evolutionary path (see the Perspective by Muralidhar and Veller). Chance fixation of an inversion leads to recombination arrest on a portion of the Y chromosome. This triggers divergence of X and Y cis-regulators, selecting for dosage compensation and sexually antagonistic regulatory effects. This sexual antagonism protects inversions from reestablishment of recombination. Thus, expansion of the non-recombining region of sex chromosomes, instrumental in the progressive degeneration of the Y chromosome, does not rely on the recruitment of sexually antagonistic genes. —LMZ