

Spotlight

Sex chromosome evolution in action in fourspine sticklebacks

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The suppression of recombination between young X and Y chromosomes is a crucial step in their evolution, but why it occurs is not known. The detailed characterization of the polymorphic sex chromosomes of the fourspine stickleback by Liu et al. promises to shed new light on this longstanding question.

A central question still unanswered

Sex chromosomes have been the focus of research since Wilson and Stevens first uncovered their role in sex determination over 100 years ago [1]. Two types of sex chromosomes are found in animals: XY (male heterogamety) and ZW (female heterogamety: females are ZW, males are ZZ). For simplicity, I focus here on the case of XY chromosomes, but similar principles apply to ZW systems. Despite having originated independently, the X and Y pairs of many animals and plants share striking features. For instance, Y chromosomes often lack functional genes and accumulate repetitive sequences and other types of 'junk DNA'. These convergent features are now known to be the result of a stereotypical trajectory of sex chromosome evolution [2] (Figure 1A).

The first step in the evolution of sex chromosomes is the acquisition of a sex-determining gene by an autosome. For instance, if a male-determining gene either moves to, or arises on, an autosome, this chromosome becomes a proto-Y chromosome. Second, recombination around the sex-determining gene is lost between the nascent Y and X chromosomes. Several mechanisms can lead to suppression of

recombination. The best understood, which I focus on here, is the appearance and fixation of inversions on either the proto-X or Y chromosome. Such inversions prevent correct pairing of homologous DNA at meiosis in heterozygous individuals and strongly reduce the occurrence of crossing-over events, effectively suppressing recombination over much of their length. Other mechanisms that can lead to recombination suppression between X and Y chromosomes include changes to their chromatin landscape, or the extension of previously existing nonrecombining regions (e.g., centromeres). Recombination allows natural selection to function effectively. In its absence, the nonrecombining Y-linked region undergoes genetic degeneration: it accumulates deleterious mutations, transposable elements, and structural rearrangements, often resulting in extensive gene loss [3].

While the appearance of proto-sex chromosomes and the degeneration of Y chromosomes are relatively well understood, why recombination is suppressed between X and Y chromosomes remains largely speculative. Several models have been proposed for how this may occur (reviewed in [4–6], Figure 1B). One intuitively appealing hypothesis, which came to dominate the field for many years, is that alleles that benefit one sex but harm the other ('sexually antagonistic' alleles) may drive the fixation of recombination suppressors. For instance, if an inversion on a Y chromosome captures both the male-determining gene and an allele that benefits males but harms females, it will be under net positive selection, because its perfect association with male sex ensures that the harmful effects of the allele are never expressed in females. Such mutations arising on a Y chromosome can theoretically also select for inversions on the X, which also suppress X–Y recombination when present in males.

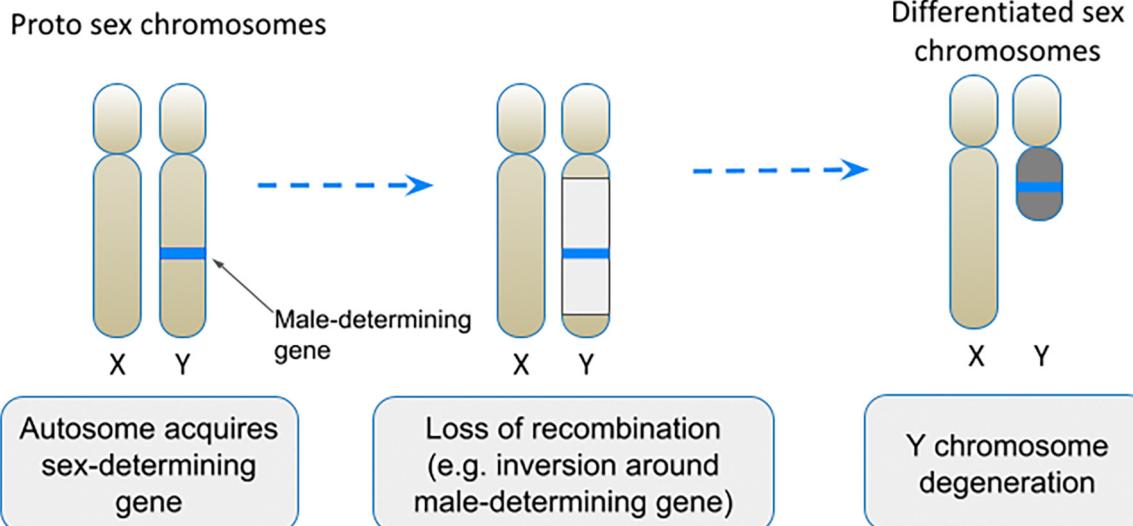
However, no clear evidence has been found so far of an enrichment of sexually

antagonistic genetic variants on young sex chromosomes, and recombination suppression has arisen in fungal groups thought to lack sexual antagonism, prompting the reexamination and development of other hypotheses [4–6]. First, linkage of the sex-determining region to alleles that are primarily beneficial to males can be favored by selection even when there is no harmful effect to the females, that is, when selection is sex specific but not sexually antagonistic. Selection may also favor inversions that link the sex-determining gene and alleles beneficial in a heterozygote state (overdominant alleles), even if they do not act in a sex-specific manner, because males are always heterozygous for Y-linked inversions. These hypotheses assume that inversions are selected because of (conditionally) beneficial alleles they carry. By contrast, all chromosomes in a population carry some harmful mutations, but some will, by chance, carry more than others. An inversion may be 'lucky' and capture a copy of a genomic region that happens to carry few deleterious mutations, giving it a selective advantage [4,5]. If such a lucky inversion arises on a Y chromosome, it may further benefit from being 'sheltered': the effects of any recessive deleterious mutations it carries will not be expressed (or less so), because the inversion is always heterozygous in males (although the conditions under which sheltering drives inversions to fixation are still under debate [7]). Finally, all these models must be considered against the possibility that inversions were simply fixed by genetic drift, that is, by chance due to random fluctuations in allele frequencies at every generation. Despite the recent full characterization of many XY and ZW pairs at the genomic and gene expression level, disentangling these hypotheses has proven difficult.

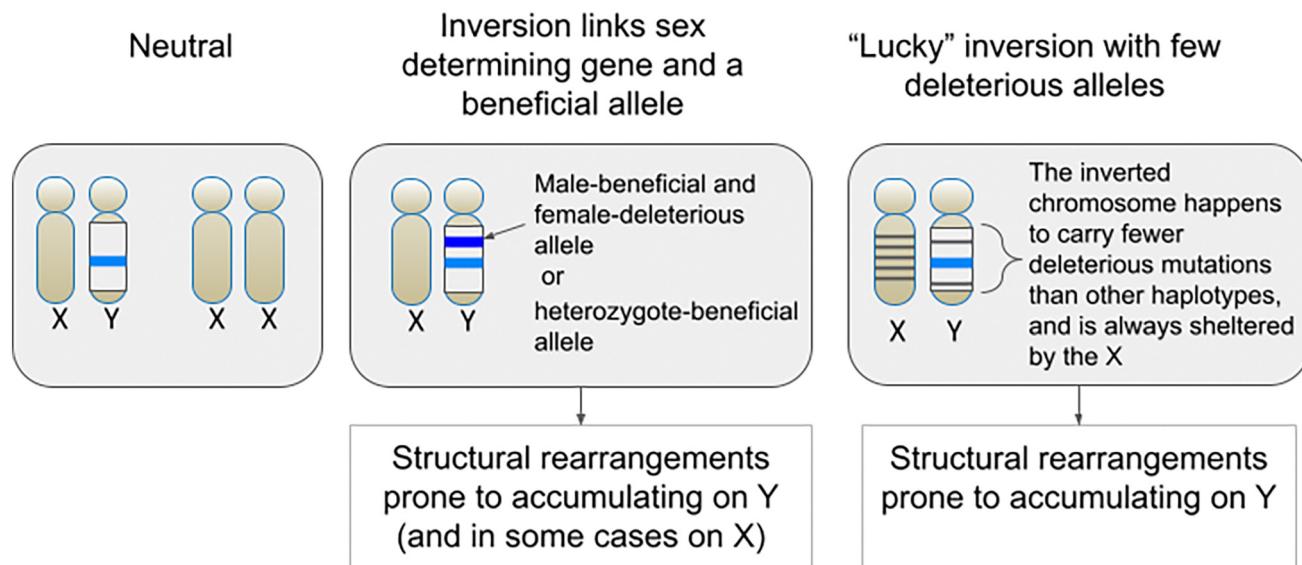
The polymorphic sex chromosomes of fourspine sticklebacks

The study of sex chromosome evolution has greatly benefited from the recent

(A) Key steps in the evolution of differentiated sex chromosomes



(B) Models for the accumulation of inversions on Y (and X) chromosomes



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Figure 1. Recombination suppression is central to sex chromosome evolution, but its cause remains under debate. (A) Main steps in the evolution of differentiated sex chromosomes. (B) Hypotheses for why X and Y chromosomes acquire inversions around the sex-determining region.

availability of genome assemblies for many non-model animals and plants, and consequent characterization of the sequence and expression of sex chromosomes with varying levels of differentiation. Sex chromosomes that have not yet become

fixed in a species (i.e., polymorphic sex chromosomes), such as those of some frogs, fish, and flies [8], provide a unique opportunity to investigate the earliest stages of sex chromosome evolution. Sticklebacks, a group of bony fish, have

long been models of interest because even closely related species can differ in which chromosome is used as the XY or ZW pair [9]. Previous cytogenetic work suggested that a ZW pair was present in fourspine sticklebacks (*Apeltes quadratus*), and that

morphological differentiation between the Z and W was present in some but not other populations in New England and Eastern Canada, suggesting the coexistence of polymorphic sex chromosomes. A recent analysis of extensive genomic data generated from males and females of multiple populations of this species [10] yielded two surprising findings: first, all the sampled populations shared the same XY pair of sex chromosomes, which includes a small inverted region on the Y chromosome. The newly described XY pair corresponds to chromosome 23, an autosome in other species of sticklebacks, adding to the known diversity of sex chromosomes in this group. Consistent with a recent origin of the XY pair, no evidence of genetic degeneration could be detected on the Y chromosome. Second, at least two of the three sampled populations harbor additional polymorphic inversions around the sex-determining region. In the Canadian population, the Y chromosome of most males (85%) carries a large inversion encompassing around a third of the chromosome. In the Connecticut population, most individuals have instead an X chromosome harboring a large inversion. While it is not yet clear why these inversions arose and were maintained, or why they are only present at some locations, their existence at high frequency in some populations suggests they are a good model for understanding the spread of recombination suppressors on young sex chromosomes.

Testing hypotheses of sex chromosome evolution with polymorphic inversions

The key difference between the various models of suppression of recombination is the effect that these suppressors (such as X- or Y-linked inversions) have on the fitness of the individuals carrying them.

Phenotypic effects can directly be tested in populations in which such inversions are polymorphic, and where the fitness of males (and females, in the case of X-linked inversions) with and without inversions can be compared. Although assessing fitness is far from trivial, some components of it, such as survival and reproductive output, can be quantified as long as individuals can be kept in sufficient numbers in an experimental setup. Population genetics approaches can also yield insights into the age of inversions and how fast they have spread through a population. A new inversion under positive selection will quickly reach high frequencies in a population without accumulating many additional mutations. By contrast, a neutral inversion can reach similarly high frequencies but typically much more slowly, allowing for further mutations to accumulate (i.e., Y chromosomes sampled from different males will, in this case, be different at many sites). A combination of experimental fitness assessments and population genomics could, in principle, discriminate between a neutral or selective cause for the spread of X- or Y-linked inversions in fourspine stickleback populations, and potentially even between different selective scenarios. Another important step will be to quantify how much of a reduction in recombination these inversions cause, and where the genomic boundaries of the recombination suppression are relative to the inversions, because even this basic aspect of recombination suppression is yet to be fully understood in the context of sex chromosome evolution. With their high-quality genome, amenability to experimental work, and polymorphic sex chromosomes, fourspine sticklebacks present an outstanding opportunity to directly test hypotheses of

sex chromosome evolution that have been the subject of extensive discussion in the field for decades.

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Declaration of interests

None declared by author.

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