Hypotheses

The fragile Y hypothesis: Y-chromosome aneuploidy as a selective pressure in sex chromosome and meiotic mechanism evolution

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Loss of the Y-chromosome is a common feature of species with chromosomal sex determination. However, our understanding of why some lineages frequently lose Y-chromosomes while others do not is limited. The fragile Y hypothesis proposes that in species with chiasmatic meiosis the rate of Y-chromosome aneuploidy and the size of the recombining region have a negative correlation. The fragile Y hypothesis provides a number of novel insights not possible under traditional models. Specifically, increased rates of Y aneuploidy may impose positive selection for (i) gene movement off the Y; (ii) translocations and fusions which expand the recombining region; and (iii) alternative meiotic segregation mechanisms (achiasmatic or asynaptic). These insights as well as existing evidence for the frequency of Y-chromosome aneuploidy raise doubt about the prospects for long-term retention of the human Y-chromosome despite recent evidence for stable gene content in older non-recombining regions.

Keywords:
achiasmatic meiosis; aneuploidy; fragile Y; sex chromosome evolution; Turner syndrome; Y-chromosome loss

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Introduction

Although the forces that promote Y-chromosome origins and degeneration are reasonably well understood, those that result in Y-chromosome loss are not [1]. Population genetic theory and empirical data both demonstrate that sex specific (i.e. non-recombining) regions of Y-chromosomes rapidly lose genes soon after ceasing recombination but eventually stabilize, retaining a subset of genes that are important for male fertility, transcriptional regulation, and/or sex determination (Box 1) [2–8]. The phylogenetically widespread occurrence of XO taxa also indicates that decay must ultimately lead to complete Y-chromosome loss in many cases; however, traditional models do little to predict when Y-chromosomes will ultimately become dispensable. Conventional wisdom suggests that at some point Y-chromosomes become sufficiently depauperate of essential genes that loss has minimal fitness effect and may consequently be lost by random genetic drift [9]. But this view does little to address the question, why do some lineages retain highly degenerated Y-chromosomes for long periods while others more frequently lose and regain Y-chromosomes [1]?

As a case study, consider the human Y-chromosome. Over the past 300 million years, the ancestral mammalian autosome that gave rise to the human Y lost all but 19 of its distinct protein-coding genes [10]. Early predictions based on a linear rate of decay suggested that the human Y might be gone within 15 million years [11], but comparative genomics revealed that gene losses on our Y-chromosome have been punctuated rather than gradual. The human Y ceased recombining with the X chromosome in five segments. Within each newly non-recombining segment,

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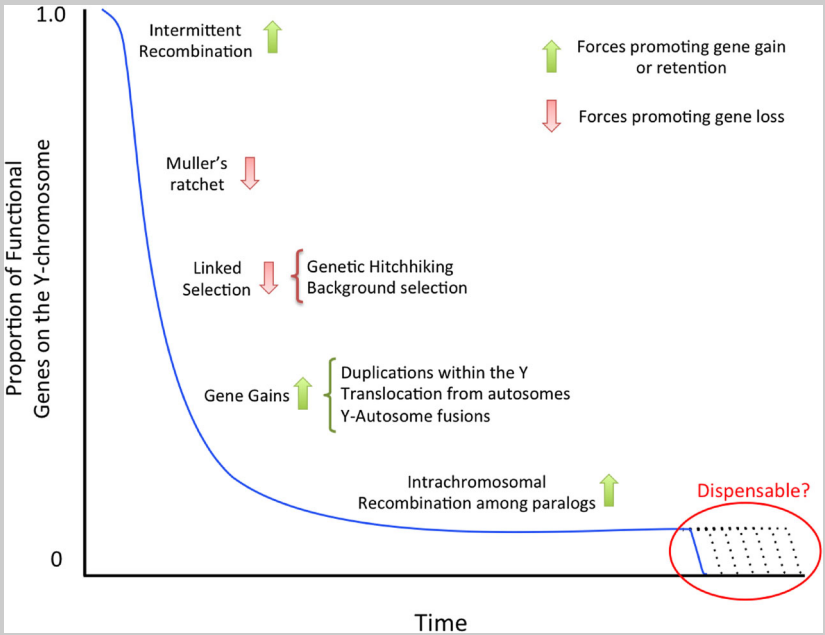
Abbreviation:
PAR, pseudoautosomal region.

Box 1

Population genetics of Y-chromosome evolution

A neo-Y originates by the acquisition of a male determining factor. So long as the nascent sex-chromosomes retain intermittent recombination over their length, genes are mostly retained. Selection for linkage between the male determining factor and male beneficial mutations will reduce local recombination. As recombination ceases and regions of the Y consequently become sex specific, gene content rapidly decays as the least mutated Y haplotypes are lost by drift (Muller's ratchet) and nonsense mutations are dragged to fixation via linked selection (Genetic Hitchhiking and Background selection). As the number of genes diminishes, these forces become weaker, and theory predicts that gene content will stabilize, or at least decline more slowly. Gene duplications within the Y that promote intrachromosomal recombination, translocation of autosomal regions to the Y, and Y-autosome fusions may all contribute to the stability or rejuvenation of the Y as well. This process does not predict or provide a mechanism for when (or if) the Y will become dispensable.



most genes were lost very rapidly. The few genes that survived initial decay have subsequently been stably retained and gene number has even increased occasionally via gene duplication and translocation from autosomes [7, 12]. The stability of gene content in older non-recombining segments coupled with functional importance of several Y-linked genes (e.g. sex determination gene SRY, genes important for male fertility, and genes that are particularly sensitive to dosage imbalance) argues that our Y is unlikely to be lost soon [12–14].

If Y chromosome degeneration typically results in a stable collection of important genes, as it appears to in human, then what factors foster complete loss in some taxa?

The fragile Y hypothesis

Based on a large comparative analysis of Coleoptera, we recently found that the propensity for Y loss is best predicted by variation in meiotic mechanisms (Box 2) [1]. Lineages that evolve a way to faithfully segregate chromosomes without forming chiasmata are much less likely to lose the Y. Surprising to us, the effect of meiotic mechanism overwhelms predictions based on traditional theory, which suggests that the most degenerated Y-chromosomes are most likely to be lost. In beetles the largest suborder (Polyphaga) has evolved asynaptic meiosis and very rarely loses Y-chromosomes even though they are typically highly degenerated. In contrast, the other major beetle suborder (Adephaga) generally requires chiasmata during meiosis and loses Y-chromosomes much more frequently despite their Ys being less degenerated on average. In light of this discovery, we proposed the fragile Y hypothesis, arguing that as population genetic forces constantly pressure diverging sex chromosomes to reduce the pseudoautosomal region (PAR) – that is the region required for chiasmata – there is an increasing cost in terms of production of aneuploid gametes that lack the Y (Fig. 1). Put differently, increased aneuploidy (i.e. mutation rate to XO) associated with reduced pairing makes Y chromosome retention fragile.

Several lines of evidence support the fragile Y hypothesis. Following, we first review recent work on the relationship between PAR size and Y aneuploidy rates in domestic mammals and then show that in beetles, smaller PARs are only associated with Y loss over evolutionary times scales in taxa that require chiasmatic meiosis. We then put the fragile Y in the broader context of three potential Y-chromosome fates, emphasizing the previously unrecognized potential connection between the evolution of sex chromosomes and meiotic mechanisms. We also highlight where data for certain fragile Y predictions are lacking and propose research avenues that would further elucidate particular dynamics of Y-chromosome loss. Finally, we argue why long-term retention of the human Y seems unlikely despite the relative stability of gene content in old non-recombining regions.

PAR size and frequency of Y-chromosome loss

During the first division of chiasmatic meiosis, homologous chromosomes

Box 2

Meiotic mechanisms

Chiasmatic meiosis: is the canonical form of meiosis where during the first meiotic division each pair of sister chromatids pair with their homologs and recombination occurs forming chiasmata between the homologs. This process insures that chromosomes are held together until they segregate to opposing poles.

Achiasmatic meiosis: exhibited almost exclusively in the heterogametic sex, this form of meiosis is characterized by all chromosomes tightly pairing with their homologs but no recombination occurs. The mechanism that holds the homologs together until segregation to the poles appears to vary among organisms [49, 50].

Asynaptic sex chromosome segregation: autosomes segregate in the canonical fashion but the X and Y chromosomes remain visibly separated from one another throughout meiosis until they segregate to the poles. Often the sex chromosomes appear physically separated from the autosomes with unique structures responsible for pairing and segregation (e.g. the dense plate in marsupials [51]).

physically pair, forming the chiasmata where recombination occurs. This physical pairing of chromosomes is necessary to ensure proper segregation (reviewed in [15]). Population genetic theory indicates that selection to maintain linkage between a male determining factor and sexually antagonistic alleles that benefit males will regionally suppress recombination and start the inexorable process of Y degeneration (Box 1). As the portion of the Y that recombines with the X-chromosome (i.e. the PAR) erodes, the region capable of forming chiasmata is reduced and consequently the frequency of aneuploidy is expected to increase (Fig. 1).

Observing the rate of sex chromosome aneuploidy is difficult, particularly since the resulting offspring are often inviable. Consequently, the evidence available to support or refute the strength of correlation between PAR size and aneuploidy rate is scant. It is clear that at the extremes there is an association between size of recombining region and aneuploidy rate. Fully recombining autosomes, though not all equal, provide a de facto baseline expectation for rates of aneuploidy. At the opposite extreme, where the PAR is deleted, the X and Y fail to pair and spermatogenesis is arrested in most cells [16]. The pattern between these end points is less clear. Recent work examining the frequency of XO offspring and PAR size in mammals supports the idea of an increasingly fragile Y as PAR size gets smaller. XO offspring are one of the most common chromosomal abnormalities in horses, humans, and mice, all species with a PAR size less than 3 Mb [17]. Furthermore, all evolutionary losses of the Y in mammals have occurred in the order Rodentia which harbors the smallest identified PARs (e.g. *Mus musculus* PAR = 0.7 Mb) [18]. On the other hand, XO offspring are rare in cow, dog, cat, pig, and alpaca all of which have PAR sizes greater than 6 Mb [17]. While these observations from mammals are consistent with the fragile Y hypothesis in supporting the role for PAR size in determining the probability of Y loss, most of the data conflate the rate of nondisjunction with the viability of Y aneuploid embryos since observations are based on live births. For instance, the observation of rare XO offspring in large PAR species could be a result of lower viability since more genes are newly exposed to the hemizygous state than when aneuploidy occurs in small PAR species. Additional studies documenting the frequency of Y aneuploid gamete production in relation to PAR size would be particularly valuable as a way to disentangle such potential ascertainment biases.

A related prediction of the fragile Y hypothesis is that when species require chiasmata, smaller PARs should result in more frequent Y losses. To test this prediction, we analyzed the association between chromosome number and Y loss using data from the Coleoptera Karyotype Database [19] and phylogenetic analysis from our previous study [1]. Here, we use chromosome number as a proxy for PAR size since, as chromosomal fusions reduce chromosome number, those that occur between a sex chromosome and an autosome will enlarge the PAR. Similarly fissions will increase chromosome number and those that occur in the PAR will reduce the PAR size. While there are several potential caveats to using chromosome number as a proxy for PAR size, Fig. 2 illustrates a crude validation, showing that for all 36 available metazoans with genes mapped to chromosomes, on average those with fewer chromosomes have larger proportions of their genomes sex-linked (i.e. available as PAR; data for Fig. 2 available as Supplementary Table S1). Furthermore, violations of our assumption should only obscure the signal of a PAR size affect on Y loss, making it less likely that the data will support the predicted association.

Using a posterior distribution of 100 phylogenic trees from our previous work [1], we performed an ancestral state reconstruction of autosome number and sex chromosome state in the Coleoptera suborders Adephaga (255 taxa) and Polyphaga (790 taxa) (trees are available from dryad: http://dx.doi.org/10.5061/dryad.g8010). We modeled chromosome evolution across the trees using a Brownian motion model [20] for autosomes (continuous trait) and an MK model for sex chromosomes (discrete states) and allowed the rate of transitions between XO and XY to be different [21]. To identify nodes that subtend a loss of the Y chromosome, we used stochastic mapping [22]. Five ancestral state reconstructions were performed for each of the 100 sampled trees. All analyses were completed using the R package Phytools version 0.4–31 [23]. Figure 3 depicts the distribution of chromosome number at the nodes associated with a Y chromosome loss as well as a null distribution created

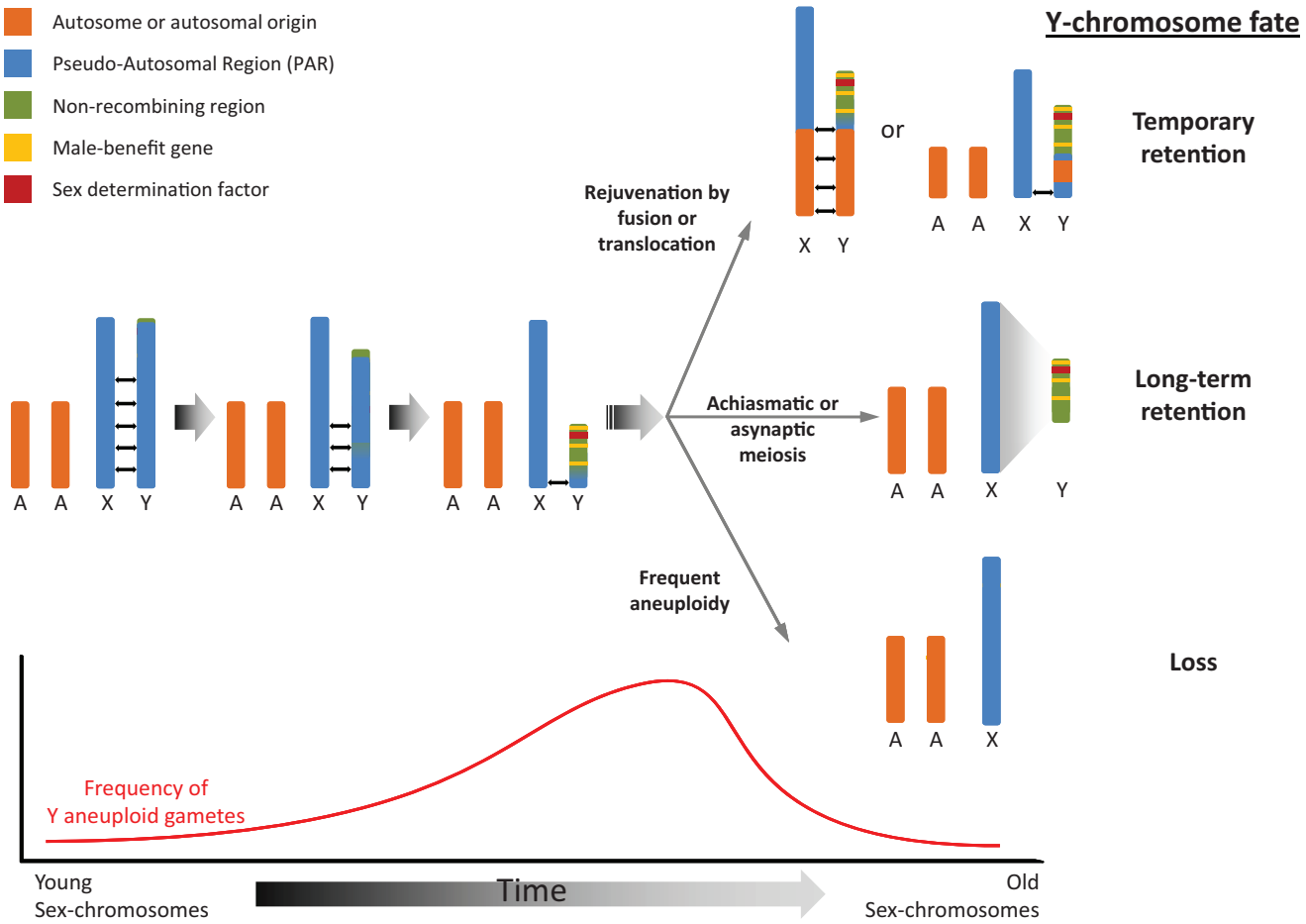


Figure 1. Three fates of Y-chromosomes: population genetic forces are expected to lead to an increasingly small PAR region. The graph across the bottom represents the hypothesized increasing frequency of Y aneuploidy that accompanies Y-chromosome decay. The cost of increased aneuploidy may be alleviated by one of three Y chromosome fates: (top) temporary retention through rejuvenation of the PAR region, (middle) long-term retention through the evolution of alternative meiotic mechanisms, (bottom) loss of the Y-chromosome and a transition to an XO sex chromosome system.

by drawing an equivalent number of random nodes from the tree.

Consistent with our prediction, we find that smaller PARs are associated with more frequent Y loss in chiasmatic but not asynaptic taxa. More specifically, having a higher number of autosomes (smaller PAR) is associated with more Y-chromosome losses in Adephaga, the suborder with chiasmatic meiosis. The distribution of autosome number on nodes that subtend a branch where Y loss occurs does not even overlap with the distribution of autosome number from randomly selected nodes in Adephaga (Fig. 3A). However, in Polyphaga, where asynaptic meiosis evolved, we find no evidence for an association between the number of autosomes and probability of Y-chromosome loss. The distribution of autosome numbers at nodes that subtend Y losses in Polyphaga is almost indistinguishable from randomly selected nodes (Fig. 3B). These results suggest that when meiotic segregation depends on chiasmata, the size of the PAR plays an important role in probability of Y-chromosome loss.

Three fates of Y-chromosomes

Late in the degeneration of Y-chromosomes, the fragile Y hypothesis predicts increasing tension between pressure from high rates of sex chromosome aneuploidy and pressure from forces that favor Y retention. This tension can be relieved in three general ways: rejuvenation, altered meiotic mechanism, and Y loss. We believe an increasingly fragile Y better explains these outcomes than traditional explanations.

Rejuvenation

Addition of DNA to the Y chromosome by fusion or translocation may prolong Y retention by rejuvenating either its PAR or its gene content. First, the Y may be rejuvenated by fusion between all or part of an autosome to both sex chromosomes. Such fusions will increase PAR size, effectively rewinding the clock on Y differentiation temporarily (Fig. 1). This mode of rejuvenation is observed in placental mammals where most of the PAR gene content is autosomal in marsupials, suggesting that rejuvenation by translocation

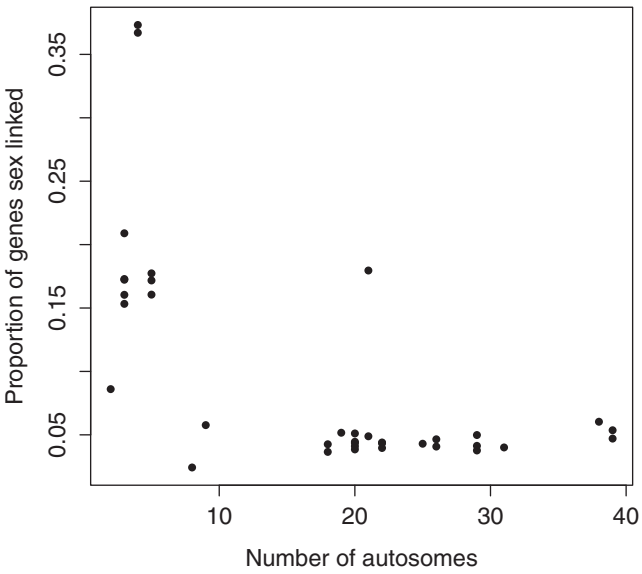


Figure 2. Chromosome number and sex linkage: scatterplot of number of autosomes and the proportion of genes that are sex-linked. Data are drawn from 36 genomes with assignment to chromosomes available from genbank and flybase.

occurred between 80 and 130 million years ago [24]. Fusions between sex chromosomes and autosomes are traditionally thought to fix by meiotic drive or selection for linkage between sex determining loci and previously autosomal genes that have differential sex-specific fitness effects (i.e. sexually antagonistic loci) [25–27]. However, fusions that renew the size of the PAR would presumably reduce the frequency of Y aneuploidy and may consequently fix by positive selection even in the absence of sexual antagonism or meiotic drive. The PAR may also be rejuvenated by duplicative translocations from the X. Such X to Y duplications are responsible for at least one (and possibly two) additional PARs in the human lineage [28, 29].

Not all translocations will result in PAR rejuvenation. In well studied Y-chromosome systems such as human and Drosophila, translocations of autosomal genes onto the male-specific (non-recombining) portion of the Y are known to contribute important male benefit genes [30]. These translocations do not provide a region of homology between the X and Y and thus are not expected to influence the rate at which Y aneuploid gametes are produced. However, translocations to the Y are likely to fix only when the fitness benefit to males is greater than the cost associated with Y aneuploidy. In such situations, we expect longer Y retention despite potentially high rates of Y aneuploid gamete production.

Long-term retention due to altered meiotic mechanisms

A novel insight of the fragile Y hypothesis is that sex chromosome evolution may promote the evolution of alternative segregation mechanisms. Thus we view the evolution of mechanisms such as achiasmatic or asynaptic meiosis (Box 2), which both allow faithful segregation in the absence of chiasmata, as a second potential fate for the Y because it helps foster long-term retention. Evidence for the connection between Y loss and pressure to evolve achiasmatic meiosis is found in comparison of Y loss rates between related groups that differ in meiotic mechanism.

Within the Coleoptera suborder, Adephaga two clades have independently evolved achiasmatic meiosis. The two groups Trechitae and Cicindelinae + Colyrinae both exhibit relatively few Y-chromosome losses. To determine whether these groups have experienced fewer Y-chromosome losses than expected, we compared the observed number of XO species in each group to the number expected from 1,000 simulations based on the overall rate of Y-chromosome loss estimated across all Adephaga. Among the 45 taxa within Trechitae, simulations suggest we should expect 16 XO species; however, only three are observed and only 8% of simulations resulted in three or fewer XO taxa. We find a similar pattern in Cicindelinae + Colyrinae. Among the 21 taxa, only one is XO but simulations suggest we should expect six and only 5% of simulations results in one or zero XO taxa. These patterns suggest that alternative segregation mechanisms reduce the rate of Y loss relative to chiasmatic segregation found in the rest of the suborder.

At a very broad level, we can also make a similar comparison between the marsupial and placental mammals. Marsupials, which have asynaptic sex chromosome segregation, have no recorded Y-chromosome losses while placentals, which normally require chiasmata, have two or three losses [31].

Closer inspection of the rare cases of Y loss and evolution of achiasmatic meiosis in placental mammals reveal additional patterns consistent with fragile Y predictions. Since rodents have the smallest PARs among mammals, we expect them to experience fragile Y pressure most acutely, and indeed all cases of Y loss and achiasmatic meiosis in placental mammals occur in rodents. There have been at least two independent Y-chromosome losses; one in the family Cricetidae and one in the family Muridae [32, 33]. These two groups also exhibit multiple origins of achiasmatic meiosis [34–36]. In the family Cricetidae, the genus *Ellobius* has at least one (possibly two) instances of Y-chromosome loss [33]. The related genus *Microtus* exhibits at least three origins of achiasmatic sex chromosomes, and as the fragile Y hypothesis predicts, there are no reported Y-chromosome losses in the achiasmatic species [34]. The other family of interest, Muridae, contains the genus *Tokudaia* in which two of three species have lost the Y-chromosome [32] and the third has a rejuvenated PAR formed by the fusion of the ancestral sex chromosome with an autosome [37]. Muridae also

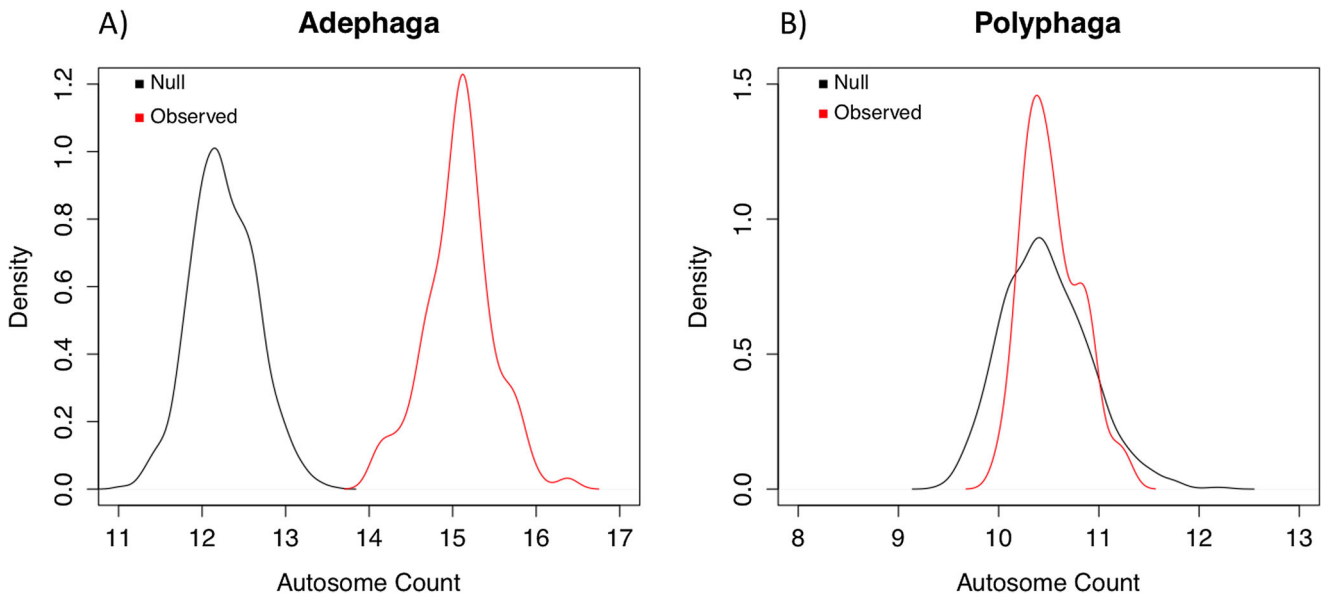


Figure 3. Chromosome number and Y chromosome loss: estimated number of autosomes present at nodes that subtend a loss of the Y chromosome in Adephaga (**A**) and Polyphaga (**B**). The black lines indicate the expectation if Y chromosome losses are random with respect to chromosome number. The red lines indicate the distribution of autosome number at nodes subtending a Y loss.

contains the subfamily Gerbillinae, which has evolved achiasmatic sex chromosomes and has no cases of Y loss [35, 38]. The evolution of XO species and achiasmatic meiosis, each of which are absent or rare in other placental mammal families, suggests that both states may be responses to an underlying difficulty in properly segregating the Y chromosome.

The fragile Y explains the evolution of alternative meiotic mechanisms better than previous models, but it too has exceptions. Achiasmatic meiosis results in a complete cessation of recombination between the X and Y chromosome. Therefore, it could be selected for in the presence of sexually antagonistic loci, similar to traditional arguments for selection that reduces the size of the PAR. However, if sexually antagonistic selection were the primary driver, then we would expect achiasmatic meiosis to evolve early in the evolution of sex chromosomes when there are many potentially sexually antagonistic genes. As such, we would expect achiasmatic meiosis to be broadly fixed across clades that share sex chromosome origins; instead we find achiasmatic meiosis independently arising within genera or subfamilies whose sex chromosomes arose much earlier and are sister to taxa retaining chiasmatic meiosis. In the mammal examples above the transitions to achiasmatic meiosis are associated with the families that have the smallest PAR, where there is consequently little opportunity for sexual antagonism to be a strong selective pressure. This pattern suggests that achiasmatic meiosis may instead evolve as a way to reduce the fitness cost associated with a poorly segregating Y-chromosome. Despite our prediction for the cause of achiasmatic meiosis, there are a few notable exceptions. For instance, both scorpion flies and some mantids appear to have already lost the Y before evolving achiasmatic meiosis [26]. These cases do not fit with sexual antagonism or the fragile Y. To our knowledge, the only remaining explanation would be selection to reduce recombination. Studying the frequency of recombination in the homogametic sex would shed some light on the likelihood of this explanation but is currently unavailable.

Y-loss

The final potential outcome of Y evolution is loss. In fact, this is a common outcome with 25% (1,925 of 7,561) of animals with sex chromosomes exhibiting an XO karyotype [31]. At least two factors clearly obstruct complete Y loss by eliminating males or reducing their fitness: (i) haploinsufficiency of PAR genes; and or (ii) loss of essential male genes (e.g. sex determination or fertility) [12]. Furthermore, the Y may play broad roles in transcriptional and translational regulation [13, 39]. Just as in traditional genic models of Y degeneration, completely losing the Y-chromosome requires moving the essential genes off of the Y or otherwise making them non-essential. In particular, the sex determination mechanism, which is typically modeled as a dominant male determining factor, must change for Y loss to occur. If the male determining factor is only translocated, it will form a neo-sex chromosome system, redefining the Y. Instead, Y loss must be accompanied, or preceded, by a change to a sex determining mechanism like that of *Drosophila* where the X:autosome ratio determines sex.

The Y chromosome losses in mammals noted above were originally assumed to involve translocations of the Y to an autosome defining a neo-sex chromosome system. However, screening males and females for genes from the ancestral Y-chromosome have painted a more complex picture. In *Ellobius*, neither SRY nor other Y markers have been found in either sex [33]. The loss of these genes indicates that both the sex determining

gene SRY and important male fertility genes have become non-essential. In contrast, in *Tokudaia* SRY is absent but other Y genes are present in both males and females [32]; suggesting that the sex determination pathway has changed but that some genes from the ancestral Y remain essential and have been translocated to either an autosome or the X chromosome.

Under the fragile Y, as mutations to XO increase, selection should increasingly favor any mechanism that mitigates the fitness consequence of Y loss or reduces the mutation rate to XO. This allows a number of novel insights. First, increased aneuploidy may impose a selective pressure to move genes off the Y whereas traditional models rely only on mutational decay in the absence of recombination. Second, high aneuploidy rates may impose selection for fusions and translocation that rejuvenate the PAR whereas traditional models focus on sexual antagonism or meiotic drive. Third, high aneuploidy rates may impose selection for achiasmatic meiosis. In some lineages, Y-chromosomes will take the route of rejuvenation or achiasmatic meiosis before the fitness cost of Y aneuploidy is sufficiently reduced to allow Y loss. However, for other lineages the increasing input of aneuploidy will prevail and the Y will be lost.

Future research

There are a number of directions that could lead to understanding the dynamics of Y-chromosome loss better. Most sequenced genomes do not include Y-chromosome assemblies and even fewer include annotation of the PAR. For instance, recent work in Diptera indicates that Y-chromosomes that appear cytogenetically similar may have no homology [40]. So the appearance of Y-chromosome stability from cytogenetic evidence may be hiding frequent gains and losses of Y-chromosomes or sex chromosome turnover. Sequencing technology and assembly software has advanced to a state that separate sequencing of males and females should be the default for new genome sequencing projects allowing robust assembly of these important parts of the genome.

Our hypothesis predicts that Y-chromosome losses and origins of achiasmatic meiosis should be concentrated in taxa with small PAR size. Documentation of PAR sizes in clades that have origins of achiasmatic meiosis or Y-chromosome losses would allow us to test this prediction. For instance, in the Coleoptera suborder Adephaga, are Y-chromosome losses associated with small PAR sizes? Likewise, within mammals in the genus *Microtus* (*sensu lato*) are origins of achiasmatic meiosis associated with smaller PAR size? Additionally, identifying Y aneuploidy rates through sperm genotyping in mammals that vary in PAR size would be particularly useful in determining the effect of PAR size on mutational input of Y aneuploid gametes.

Population genetics modeling of Y-chromosome evolution could be leveraged to help us better understand the ultimate fate of Y-chromosomes. Most work thus far has focused only on the forces that lead to Y chromosome decay [4, 41]. However, these models could be extended to include the evolution of PAR size, fusions, translocations, aneuploidy, and achiasmatic meiosis. More realistic models of this nature may allow us to predict when we expect to see rejuvenation, loss, or alternative segregation mechanisms.

In addition to the beetle and mammal systems noted above, Diptera is a potentially powerful group that could help to build a better understanding of Y-chromosome loss. Diptera have both achiasmatic and chiasmatic meiosis and also have numerous Y-chromosome losses. Recent evidence suggests that the linkage groups involved in sex determination may experience frequent turnover [8] and may allow comparisons across relatively small evolutionary time scales where the genes and meiotic mechanisms differ.

The state of the human Y-chromosome

So will the human lineage lose the Y? Recent comparative genomics evidence for gene content stability since at least our split with rhesus macaque [7] and population genomic evidence for abundant purifying selection [14] lead recent studies to conclude that the human Y is likely to be stable for the foreseeable future. However, the fragile Y predicts that since humans require chiasmata between small PARs, we should expect a relatively high burden of sex chromosome aneuploidy. Indeed, sex chromosome aneuploidies are the most common chromosome abnormality among human births [42]. Further, a particularly high frequency of errors in fathers indicates that humans already have difficulty segregating the Y. Turner syndrome (TS) is a disease caused primarily by meiotic XY pairing mistakes in fathers, which leaves potential offspring with only a single X-chromosome from their mother [43]. TS occurs in ~3% of all conceptions, a high frequency for a mutation that acts effectively as a dominant lethal (TS causes 99% prenatal mortality) [44–46]. Of the 1% of surviving children, most are mosaic for all or part of a second sex chromosome [46]. Additionally, a recent study of over 6,000 men found that Y loss is by far the most common somatic mutation in peripheral blood [47, 48]. Although the mechanism of such mitotic loss is different than in meiosis, it nonetheless points to difficulty with proper Y segregation that may impose selection to mitigate the consequences of cells lacking Y-chromosomes. The burden of high mutation rate coupled with severity of the associated phenotype suggests that as an evolutionary lineage we are in fact experimenting with Y loss already and that there is strong selection for Y loss, an alternative segregation mechanism (achiasmatic), or expansion of the PAR. Thus, recent assurances about long-term Y persistence in our lineage may be unwarranted.

Conclusions and outlook

In conclusion, the fragile Y hypothesis ties together well-established empirical and theoretical explanations for Y-chromosome origins and decay, with novel predictions about the forces that determine the Y's ultimate retention or loss. Although the hypothesis originated from phylogenetic analysis of Y loss rates among beetle clades [1], the broad implication is that the evolution of sex chromosomes and mechanisms of meiosis are intimately linked. Going forward, key aspects of the hypothesis

should be straightforward to test. Perhaps most importantly, the "fragile Y" derives its name from the proposition that as PAR size inevitably shrinks, the rate of Y aneuploidy will increase (i.e. the Y becomes more fragile). While the available observations are consistent with that premise, the data are neither abundant nor precise.

Measuring PAR size in more species and getting unbiased estimates of aneuploidy rate (e.g. not based on aneuploidy among live births) are important first steps to further validating the hypothesis. The latter should be feasible without a major technical challenge by interrogating the frequency of Y loss among individual sperm. However, measuring PAR size is challenging. Even for species with sequenced genomes, the Y-chromosome and PAR are typically among the least well-characterized parts of the genome. Advances in sequencing technology that provide longer, more accurate reads, are improving the outlook for understanding Y specific sequence content, and rough estimates of PAR size can sometimes be gained by cytological analysis; however, determining PARs at the sequence level seems likely to remain a challenge for most species for the foreseeable future.

The authors have declared no conflicts of interest.

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