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Evolution of Sex Determination and Sex Chromosomes: A Novel Alternative Paradigm

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Sex chromosomes can differ between species as a result of evolutionary turnover, a process that can be driven by evolution of the sex determination pathway. Canonical models of sex chromosome turnover hypothesize that a new master sex determining gene causes an autosome to become a sex chromosome or an XY chromosome pair to switch to a ZW pair (or vice versa). Here, a novel paradigm for the evolution of sex determination and sex chromosomes is presented, in which there is an evolutionary transition in the master sex determiner, but the X chromosome remains unchanged. There are three documented examples of the novel paradigm, and it is hypothesized that a similar process could happen in a ZW sex chromosome system. Three other taxa are also identified where the novel paradigm may have occurred, and how it could be distinguished from canonical trajectories in these and additional taxa is also described.

1. Introduction

Many eukaryotes have separate male and female individuals, a situation that requires developmental regulation of sex determination and sexual dimorphism.[1,2] Master regulators of sex determination initiate gene regulatory pathways that establish sexually dimorphic phenotypes through differential gene expression and splicing of genes between males and females.[3,4] The master regulatory signal can be an environmental cue or a genetic difference between males and females.[5,6]

When the sex determination signal is a genetic difference between males and females, the master sex determining gene can be (but is not always) found on a sex chromosome.[2] In contrast, downstream genes in the sex determination pathway are not expected to be on a sex chromosome. For example, *Sry* is the master male-determining gene on the mammalian Y chromosome,[7] but *Dmrt1*—a downstream gene involved in testis differentiation—is autosomal.[8] In *Drosophila*, a handful of X-linked genes serve as readouts of X chromosome dosage, which is the master regulatory signal for sex determination.[4] The downstream targets of these X-linked genes include the autosomal genes *transformer* (*tra*), *doublesex*, and *fruitless*.[9] Both mammals and *Drosophila* have XY sex chromosome systems—females are "homogametic" with two X chromosomes (XX genotype), and males are "heterogametic" with one X and one Y (XY genotype). Other animals, such as birds and Lepidoptera (i.e., butterflies and moths), have ZW sex chromosome systems,[10] in which males are the homogametic sex (ZZ), and females are heterogametic (ZW).

Sex chromosomes have originated independently in multiple plant and animal taxa as a result of new sex determining genes arising in different evolutionary lineages.[2,6] For example, the XY sex chromosomes found in mammals, reptiles, fish, *Drosophila*, and beetles are not homologous. However, the same genes are sometimes found on independently derived sex chromosomes, presumably as a result of convergent evolution.[11–13] Characterizing the causes and effects of sex chromosome turnover has been an important and long-term goal in evolutionary genetics.[5,14–16] Most previous research described three types of sex chromosome turnovers. In the first two, a new sex chromosome can be created from an autosome, a situation in which the old sex chromosome reverts to an autosome. In the third, an existing XY sex chromosome pair can be converted into a ZW chromosome pair, or vice versa. Here, I propose a novel alternative paradigm based on recent studies of insect and fish sex chromosomes.[17–19] In this alternative trajectory, a new male-determining locus arises on an existing X or Y chromosome. This changes the sex determination pathway and possibly creates a new Y chromosome, but the ancestral X chromosome remains unchanged. Similarly, a new female-determining locus could create a new W chromosome, while the ancestral Z chromosome is not affected.

2. Sex Chromosome Turnover Can be Caused by Evolution of the Sex Determination Pathway

Evolutionary transitions in the regulation of sex determination are an important cause of sex chromosome turnovers. These evolutionary transitions can happen when a new master regulatory gene usurps control of a sex determination pathway from the ancestral master regulator.[3,20,21] The new sex determining gene can create a new sex chromosome, resulting in evolutionary turnover of the sex chromosomes. Three canonical types of sex chromosome turnovers have previously been described (**Figure** 1A–C). These sex chromosome turnovers only apply

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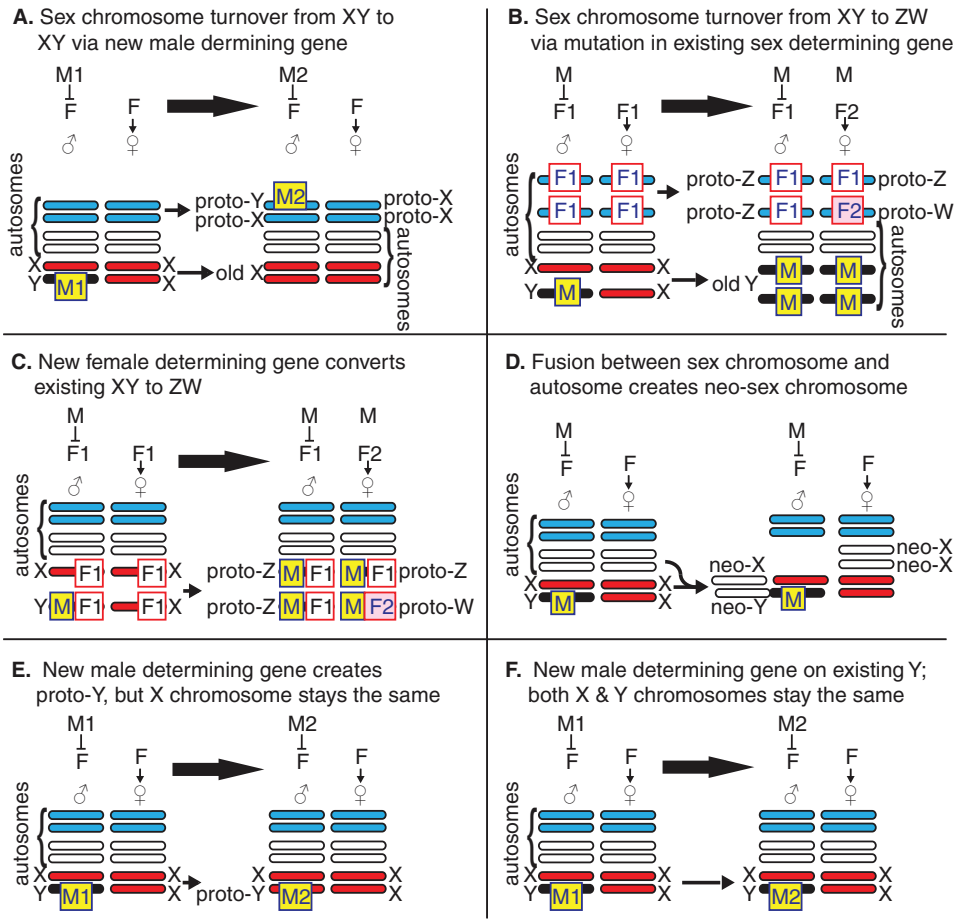

Figure 1. Canonical trajectories and novel paradigms in sex chromosome evolution. In the ancestral state, a male-determining gene (M1 or M) on the Y chromosome is a negative regulator of F or F1. A) In an example of sex chromosome turnover, a mutation creates a new male-determining gene (M2) on an ancestral autosome, which replaces M1 as the master regulator of sex determination. The chromosome containing M2 is converted into a proto-Y, and the homolog of that chromosome becomes a proto-X. The ancestral X chromosome reverts to an autosome, and the ancestral Y is lost. B) In an example of XY to ZW turnover involving different chromosomes, a mutation creates a new allele of F (F2), which is not sensitive to the negative regulation of M. This converts the chromosome upon which F2 is found into a proto-W, and the homolog of that chromosome becomes a proto-Z. The ancestral Y chromosome reverts to an autosome, and the ancestral X is lost. C) In an example of XY to ZW turnover involving the same chromosome, F1 is found on the same chromosome as M. A mutation creates a new allele, F2, which is not sensitive to the negative regulation of M. This converts the X or Y chromosome upon which F2 is found into a proto-W chromosome. X or Y chromosomes without F2 become proto-Z chromosomes. D) A neo-Y chromosome arm is created when an autosome fuses to the Y chromosome. The homologous copy of that autosome becomes a neo-X chromosome. The neo-X chromosome could fuse to an autosome or sex chromosome. An X-autosome fusion could similarly create a neo-X chromosome without a Y-autosome fusion. E) In the novel paradigm, if the M2 gene arises on the ancestral X chromosome, it will convert the X into a proto-Y. Copies of the ancestral X chromosome that do not have M2 remain X-linked, and the ancestral Y is lost. F) If M2 arises on the ancestral Y chromosome, it will change the molecular regulation of the sex determination pathway, but both the X and Y chromosome will remain the same. In cases where the ancestral X or Y chromosome is lost, any X- or Y-specific genes would transpose to other chromosomes.

when the ancestral state is genetic sex determination with sex chromosomes—additional trajectories are possible if the ancestral state is sex determination by environmental cues or some form of hermaphroditism.[2,6]

In the first canonical trajectory, a new XY chromosome pair arises in a species with a different existing pair of X and Y chromosomes (Figure 1A). This can happen if a new male-determining locus arises on an autosome and takes control of the sex determination pathway. This process has happened at least twice in the past 10 million years (My) in *Oryzias* fishes.[22–26] Similarly, a male-determining gene could transpose from a Y chromosome to an autosome.[27–30] The new male-determining locus converts the autosome into a "proto-Y" chromosome, and its homolog becomes a "proto-X". Shortly after the origin of the new male-determiner, there will be a period of polygenic sex determination (**Figure 2A**), wherein the ancestral and derived sex determiners (and sex chromosomes) segregate as polymorphisms within a species.[31] If the new sex determining locus and proto-sex chromosome establish themselves in the population, the ancestral X (or possibly Y) chromosome can revert to an autosome.[32] A similar phenomenon could also happen in a taxon with a ZW sex chromosome system (i.e., an autosome becomes a new ZW pair).

Second, a new ZW chromosome pair can arise in a species with XY sex chromosomes if a female-determining gene or allele arises on an autosome[33] (Figure 1B). For example, when a new

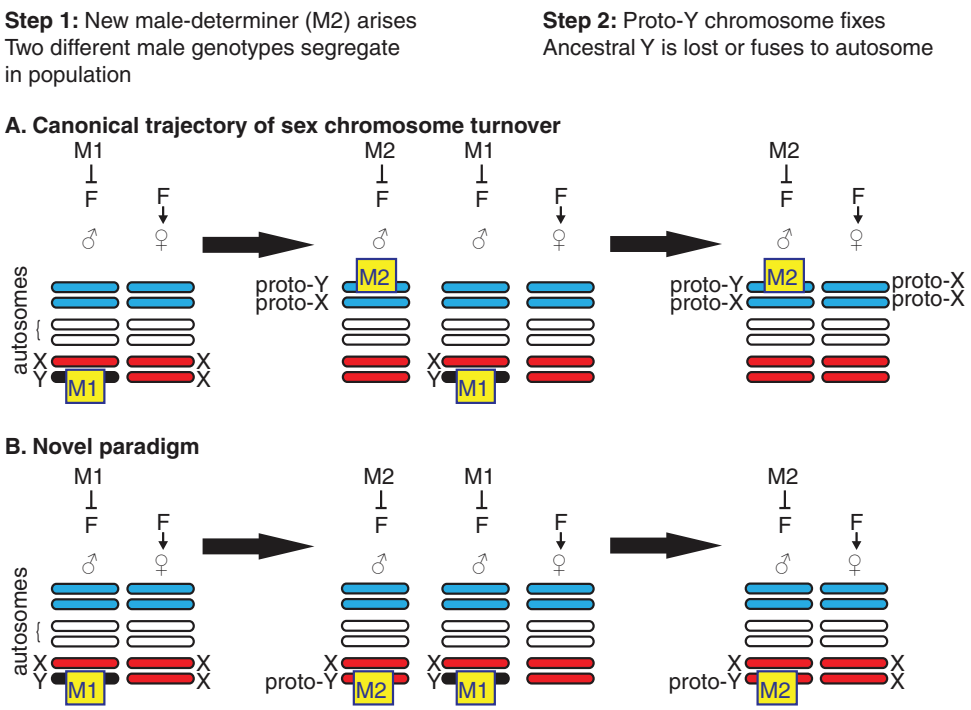

Figure 2. Steps in the evolutionary turnover of sex chromosomes. In the ancestral state, a male-determining gene (M1) on the Y chromosome is a negative regulator of F. A) In a canonical trajectory of sex chromosome turnover, a mutation creates a new male-determining gene (M2) on an autosome. The chromosome containing M2 is converted into a proto-Y, and the homolog of that chromosome becomes a proto-X. There is a period of polygenic sex determination, during which both the ancestral (M1) and derived (M2) genotypes segregate in a population. Eventually, if the M2 genotype fixes, there has been a sex chromosome turnover, and the ancestral X chromosome reverts to an autosome. B) In the novel paradigm, M2 arises on a copy of the ancestral X chromosome, converting the X into a proto-Y. As with the canonical trajectory, there is a period of polygenic sex determination, during which both the M1 and M2 genotypes segregate. Eventually, if the M2 genotype fixes, the proto-Y chromosome fixes, and, in the new trajectory, the ancestral X chromosome remains.

female-determining gene took over control of the sex determination pathway in a cichlid fish, the autosome upon which it was located became a proto-W chromosome, its homolog was converted into a proto-Z, and the ancestral X or Y chromosome reverted to an autosome.[34] Similarly, a new ZW system was created in house fly. In most flies, a Y-linked male-determiner regulates the splicing of the autosomal *tra* gene, which then regulates the splicing of downstream genes in the sex determination pathway.[35,36] However, a dominant allele of *tra* (*Md-tra*^{D}) exists in some house fly populations; *Md-tra*^{D} is a female-determiner that is resistant to regulation by the male-determining gene.[29,37] The autosome carrying *Md-tra*^{D} has thus been converted into a proto-W chromosome, but this is still segregating as a polymorphism in natural populations.[38] Likewise, a new XY sex chromosome could be created from an autosome in a species with an existing ZW system.

Third, an evolutionary transition in the sex determination pathway can convert an existing XY chromosome pair into a ZW pair, or vice versa (Figure 1C). In this trajectory, the same chromosome remains sex-linked, but the heterogametic sex changes. For example, an XY chromosome pair was converted into a ZW chromosome pair in the frog *Rana rugosa*.[39] Similarly, in the platyfish, *Xiphophorus maculatus*, a single chromosome segregates as both an XY and ZW pair.[40,41] In addition, a single chromosome can be a Y, W, or Z in the frog *Xenopus tropicalis*.[42]

Sex chromosomes can also experience substantial evolutionary change when they fuse with an autosome, creating a "neo-sex chromosome"[43] (Figure 1D). X-autosome and Y-autosome fusions (as well as translocations) have happened in numerous taxa, including insects, vertebrates, and plants.[44–50] These neo-sex chromosomes differ from the proto-sex chromosomes described above in an important way: neo-sex chromosomes are the result of fusions between autosomes and sex chromosomes, whereas proto-sex chromosomes are created when a new sex determining locus arises on a chromosome. The novel paradigm for the evolution of sex determination and sex chromosomes that I describe below is best contrasted with canonical proto-sex chromosomes.

During polygenic sex determination or shortly after the establishment of a new sex chromosome, the X and Y (or Z and W) chromosomes will be undifferentiated, or homomorphic. In the most extreme example of homomorphic sex chromosomes, the X and Y chromosomes of the tiger pufferfish, *Takifugu rubripes*, differ only in a single missense allele in the *anti-Müllerian hormone receptor type II* gene.[51] Over time, the X and Y (or Z and W) can become differentiated from each other as they evolve into a heteromorphic sex chromosome pair.[43] When the sex chromosome pair is differentiated, the X or Z chromosome typically resembles an autosome in gene content and density, although the X or Z can have its own regulatory machinery or be enriched for genes with sex-specific regulation.[52–55] In contrast, Y (or W) chromosomes are often referred to as "degenerated" because they

harbor a small number of genes with male (female) specific functions and an enrichment of repetitive DNA sequences.[56–59] Y and W chromosome degeneration results from a smaller effective population size (one quarter that of autosomes) and low X-Y (or Z-W) recombination, which reduces the efficacy of purifying selection.[57,60]

3. Genomic Approaches Identify Sex Chromosome Turnovers and Determine the Fate of Old Sex Chromosomes

Historically, sex determining genes and sex chromosomes were only identified in a limited number of model organisms.[4,7,22,61,62] Advances in molecular biology and genomics have improved our ability to characterize sex chromosomes, sex determining genes, and sex chromosome turnovers across animal taxa.[29,36,63–67] This work has largely confirmed that sex chromosome turnovers occur via the canonical trajectories described above (Figure 1A–C). For example, a sex chromosome turnover was identified in the lineage leading to *Drosophila*—an autosome was converted into a sex chromosome, and the ancestral X chromosome reverted to an autosome.[32] Similarly, a test for sex-specific DNA sequence markers discovered that canonical sex chromosome turnovers are common in geckos.[68] These canonical sex chromosome turnovers were inferred by determining which chromosome is sex-linked in each species and testing if it is an XY or ZW sex chromosome. Notably, the master sex-determining genes involved in these sex chromosome turnovers are largely unknown.

Genomic data have also helped resolve what happens to the ancestral sex chromosomes following turnover or formation of a neo-sex chromosome. Y chromosomes—such as those in mammals and *Drosophila*—often contain genes that are essential for male fertility and are not found elsewhere in the genome.[59,69] In *Drosophila*, when a neo-X chromosome forms, the ancestral Y chromosome genes can translocate to an autosome.[70,71] Alternatively, the ancestral Y can fuse to the homolog of the neo-X chromosome, creating a neo-Y chromosome.[72] However, it is often the case that the ancestral X and Y (or Z and W) are undifferentiated, in which case there are not any essential X-specific or Y-specific genes that would be lost during a sex chromosome turnover (other than the old master sex determiner). In this case, whether the ancestral X or Y is retained or lost might depend on the mechanism of sex determination. For example, the X would be lost and the Y retained if the ancestral male determiner were required for male development in the new sex determination pathway (Figure 1B). On the other hand, some Y chromosomes are dispensable because they contain no genes essential for male fertility, as is the case in *Drosophila affinis*.[73] When the Y chromosome is dispensable, it could be lost via genetic drift or nondisjunction, with the X retained.

4. A Novel Alternative Paradigm for Sex Chromosome Turnover

Recent analyses of sex chromosomes across insects and fish have revealed a novel alternative paradigm in the evolution of sex determination and sex chromosomes.[17–19] In the novel paradigm, there is an evolutionary transition in the master regulator of sex determination, but the ancestral X chromosome remains unchanged. This can happen if a new male-determining gene arises on an existing X chromosome, converting a copy of the X into a proto-Y, and leaving other copies of the X chromosome unchanged (Figure 1E). As in the canonical trajectories, the new paradigm includes a period in which both the ancestral Y and proto-Y chromosomes segregate as polymorphisms, before the proto-Y chromosome reaches fixation (Figure 2B). The new paradigm is similar to one of the canonical trajectories of sex chromosome turnover, in which an XY chromosome pair is converted into a ZW pair, or vice versa (Figure 1C). In the new paradigm, as in the canonical trajectory, the same chromosome remains sex-linked. The difference, however, is that in the new paradigm the X chromosome remains an X chromosome (i.e., it is not converted into a Z or W). In the novel paradigm, it is also possible for a new male-determiner to arise on the ancestral Y chromosome (Figure 1F). In this case, both the X and Y chromosomes would remain unchanged, although this has not yet been documented. An example of the novel paradigm in a ZW system has also not yet been observed, but it is theoretically possible.

The first documented example of the novel paradigm was in house fly (**Figure 3A**). The ancestral fly karyotype contains a gene-poor X chromosome, known as Muller element F.[32] In many fly species, this X chromosome is paired with a Y chromosome that carries a male-determining gene.[35,36] Element F is an X chromosome in many house fly populations, but other chromosomes can also be sex-linked.[38] This is because the house fly has a new male-determining gene (*Mdmd*) that transposed onto multiple different chromosomes,[29] and each chromosome carrying *Mdmd* is a proto-Y.[17] Notably, *Mdmd* can be found on element F,[17,29] which means the ancestral X chromosome (element F) has been converted into a proto-Y. Meanwhile, copies of element F without *Mdmd* remained X-linked. Therefore, there was an evolutionary transition in the sex determining pathway when *Mdmd* took over master regulatory control, which caused a copy of the ancestral X chromosome to be converted into a proto-Y, but copies of the ancestral X chromosome without *Mdmd* remained unchanged (Figure 1E).

The second example of the novel paradigm emerged from the discovery that fly X chromosome (element F) genes are disproportionately found on the X chromosome in the German cockroach.[18] Therefore, some flies and some cockroaches may share an evolutionary conserved X chromosome despite 400 My divergence (Figure 3A). German cockroach females are XX and males are XO, with one copy of the X chromosome and no Y.[47] Sex in the German cockroach is thus determined by the number of copies of the X chromosome, although the mechanism by which X chromosome dosage determines sex is not yet resolved.[74] In contrast, in flies where element F is X-linked, males have a Y chromosome with a male-determining gene.[35,36] Therefore, flies and cockroaches share a homologous X chromosome (element F), but they use different mechanisms of sex determination. An evolutionary transition in the sex determination pathway must have happened in the lineage leading to cockroaches, flies, or both. However, element F appears to have been the X chromosome of the most recent common ancestor (MRCA) of cockroaches and flies, remaining X-linked in both lineages

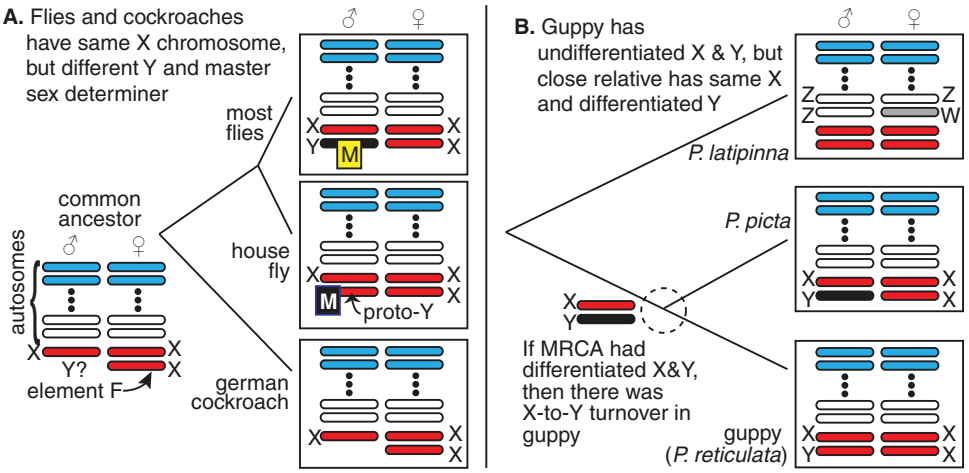

Figure 3. Examples of the novel paradigm. A) The German cockroach and most flies share a common X chromosome (element F), but have different mechanisms for sex determination—a Y-linked male-determiner in flies, and X chromosome dosage in cockroach.[18] It is not clear if the MRCA of flies and cockroaches had XY or XO males. Therefore, there was an evolutionary transition in the sex determination pathway, changing the Y chromosome, but the X chromosome remained the same. In addition, a new male-determiner in house fly converted the ancestral X chromosome into a proto-Y.[17,29] B) The guppy, *P. reticulata*, has undifferentiated X and Y chromosomes, while the close relative *P. picta* has the same X chromosome and a differentiated Y.[76] If the MRCA of *Poecilia* had a differentiated X and Y, then the guppy Y chromosome likely arose from an X chromosome that acquired a male-determining locus.[19]

(Figure 3A). This suggests that there was an evolutionary transition in the sex determination pathway, but the X chromosome was not affected, consistent with the novel paradigm.

The third example of the novel paradigm comes from poeciliid fish (Figure 3B). The guppy, *Poecilia reticulata*, has an XY pair that is homomorphic and minimally differentiated in DNA sequence.[75] Other species in the genus, including *Poecilia picta*, have the same X chromosome, suggesting it has been conserved for at least 20 My.[76] However, the *P. picta* XY pair is highly differentiated.[76] Therefore, the MRCA of *Poecilia* may have had a differentiated XY pair that includes the X chromosome found in *P. reticulata* and *P. picta*.[19] If that is the case, then *P. reticulata* has a new Y chromosome that is highly similar to the ancestral X chromosome of the genus. It is thus possible that a new male-determining gene on the ancestral X chromosome took control of the *P. reticulata* sex determination pathway, or the ancestral male-determiner may have transposed onto a copy of the X chromosome.[19] This would have created a proto-Y chromosome from a copy of the ancestral X chromosome, while copies of the ancestral X without the male-determiner remained unchanged (Figure 1E).

5. Three Candidate Examples of the Novel Paradigm in Fish and Frogs

There are at least three additional candidates for the novel paradigm, two in fish and one in frogs (**Table 1**). In these examples, the same chromosome is sex-linked in multiple species, but in most cases very little is known about the mechanism of sex determination. First, in the Pseudocrenilabrinae subfamily of cichlid fish, linkage group (LG) 3 is a ZW pair in species from three different tribes that last shared a common ancestor 45 My ago.[77] Other species within those tribes have different sex-linked chromosomes. In at least one of the species in which LG3 is a sex chromosome, there is some sequence differentiation between the Z and W chromosomes,[78] although the sex chromosomes are homomorphic across the subfamily.[77] In all species in which LG3 is a sex chromosome, the master sex determining gene is unknown. It is possible that LG3 was a Z chromosome in the MRCA of Pseudocrenilabrinae cichlids, and it remained a Z chromosome in at least three different evolutionary lineages. In at least one of those lineages, a new master female-determining locus could have recently arisen on the Z chromosome, converting the Z into a new W chromosome (**Figure 4A,B**). The recent origin of the female-determiner would explain why the Z and W chromosomes are homomorphic. Testing this hypothesis will require characterizing the master sex determining loci in cichlids in which LG3 is sex-linked. If there was an evolutionary transition in the sex-determining locus, but conservation of the Z chromosome since the MRCA, this would be evidence for the novel paradigm.

Table 1. Three taxa that are candidates for the novel paradigm.

Taxon	Evidence for new trajectory
Pseudocrenilabrinae cichlids	LG3 is a homomorphic ZW pair in three different tribes.[77]
Ranidae (true frogs)	*X. tropicalis* chromosomes 1, 3, and 5 are X-linked in independent evolutionary lineages with homomorphic XY chromosomes.[79]
Oryzias ricefish	LG10 is a homomorphic XY pair in two independent evolutionary lineages.[82]

The second candidate for the novel paradigm is in Ranidae, or true frogs (Table 1). Most ranid frogs have homomorphic XY sex chromosomes. In multiple independent evolutionary lineages within Ranidae, one of three chromosomes (corresponding to *X. tropicalis* chromosomes 1, 3, and 5) is X-linked.[79] The MRCA of

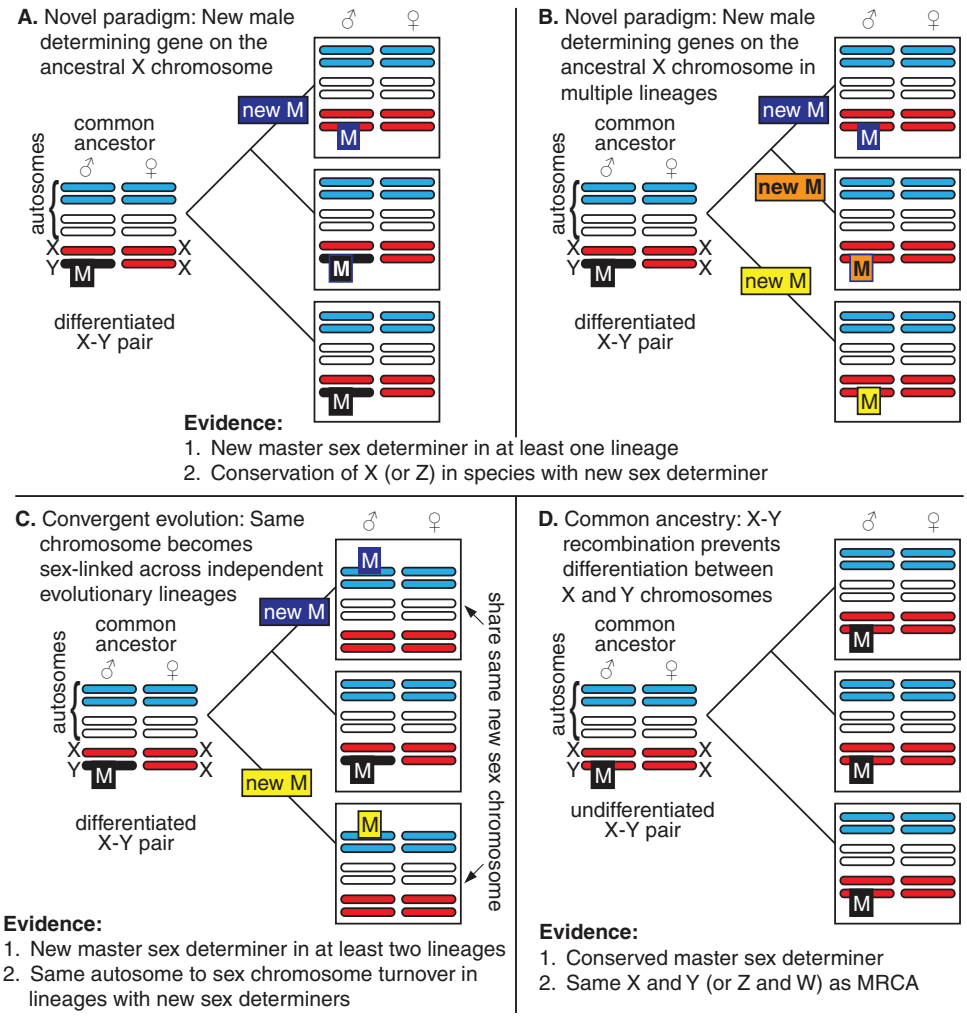

Figure 4. Inferring the novel paradigm using inter-species comparisons. Three species are descended from an ancestor with an XY sex chromosome system in which a male-determiner (M) is on the Y chromosome. The common ancestor can either have differentiated X and Y chromosomes A–C), or the X and Y can be undifferentiated D). A) In the novel paradigm, a new male-determiner arises on the ancestral X chromosome. B) If the novel paradigm happens in multiple evolutionary lineages, a new male-determiner independently arises on the ancestral X chromosome multiple times. All species with new male-determiners will have the same pair of undifferentiated sex chromosomes. Alternative scenarios can create outcomes similar to the novel paradigm. C) If a new male-determiner independently arises on the same autosome in two separate evolutionary lineages, two species will share the same undifferentiated sex chromosomes. D) If the common ancestor had an undifferentiated XY pair, then recombination between the X and Y will allow the XY pair to remain undifferentiated in all extant species. Distinguishing between these scenarios requires knowing the evolutionary relationships of the species, the identities of the sex chromosomes, and the master sex determining loci.

Ranidae, which existed 50–60 My ago, likely had XY sex chromosomes, probably corresponding to *X. tropicalis* chromosomes 1 or 5.[79] In addition, chromosome 3 was possibly the sex chromosome of the MRCA of the *Pelophylax* genus within Ranidae. The master sex-determining gene has not yet been identified in any of these species. Chromosome 1 or 5 may have been independently conserved as an X chromosome along multiple evolutionary lineages within Ranidae (or chromosome 3 in *Pelophylax*). Because the X and Y chromosomes are homomorphic across Ranidae, they may all be very young sex chromosome pairs. It is therefore possible that a new male-determining locus recently arose on the existing X chromosome in at least one evolutionary lineage, converting it into a new Y chromosome, but the ancestral X chromosome remained unchanged (Figure 4B). The new origin of the proto-Y would explain the homomorphic sex chromosomes. Testing this hypothesis will require characterizing the sex determining genes across Ranidae.

The third candidate for the novel paradigm is in the *Oryzias* ricefish (Table 1). The same chromosome (LG10) with the same male-determining gene (*Sox3*) is an XY pair in three different *Oryzias* species: two species within the *celebensis* group and *Oryzias dancena* within the *javanicus* group.[80–82] One explanation for this is that LG10 was an autosome in the MRCA of the *celebensis* and *javanicus* groups, and there was convergent recruitment of *Sox3* as a master male-determining gene in the evolutionary lineages leading to both groups (Figure 4C). This would have converted LG10 from an autosome into a sex chromosome in both lineages independently, consistent with a canonical

trajectory (Figure 1A,B). Alternatively, if this is an example of the novel paradigm, LG10 would have been the X chromosome of the MRCA of the two groups, and *Sox3* was independently recruited as a new male-determiner on that X chromosome in the lineages leading to the *celebensis* and *javanicus* groups (Figure 4B). Testing this hypothesis will require characterizing the sex determining loci in more *Oryzias* species and determining which chromosome was sex-linked in the MRCA of the genus.

6. Testing if the Novel Paradigm Occurred in Fish, Frogs, and Other Taxa

Evidence for the novel paradigm of sex chromosome turnover includes an X or Z chromosome that is homologous across species, but the master regulator of sex determination is not the same in all species (Figure 4A,B). Collecting such evidence requires identifying the sex chromosomes, characterizing the sex determining genes, and testing for homologies in sex-linked elements and sex determiners across species. If cichlids, frogs, and ricefish include examples of the novel paradigm (Table 1), a new male- (or female-) determiner would have arisen recently on the ancestral X (or Z) chromosome. The recent origin of the sex determiner would explain why the X and Y (or Z and W) chromosomes are undifferentiated in these taxa. This could have happened in one evolutionary lineage (Figure 4A) or along multiple lineages (Figure 4B).

There are at least two alternative explanations for the same sex-linked chromosome across species in cichlids, frogs, and ricefish. The first is convergent evolution of sex chromosomes from autosomes following a canonical trajectory (Figure 4C). This could happen if a new master sex determining locus recently arose on the same ancestral autosome in multiple evolutionary lineages. This convergent evolution would have occurred recently because the sex chromosomes of cichlids, frogs, and ricefish are homomorphic, and, as such, it is conventional wisdom to infer that they are young.[83] One explanation for convergent evolution is that these chromosomes are primed to be recruited as sex chromosomes because they contain genes that are well suited to regulate the top of the sex determination pathway.[11–13,21] That may be the case with *Sox3* on LG10 in ricefish.[81,82]

The other alternative explanation for the same sex-linked chromosome across species in cichlids, frogs, and ricefish is that different species share their X (or Z) chromosomes, Y (or W) chromosomes, and master sex determining loci by common ancestry (Figure 4D). This common ancestry hypothesis is similar to the novel paradigm because the ancestral X or Z chromosome is conserved in all species, but it differs from the novel paradigm in two important ways. First, in the common ancestry hypothesis, the ancestral master sex determining locus is conserved in all extant species, and in the novel paradigm there is a new master sex determining locus in at least one evolutionary lineage (Figure 4). Second, in the common ancestry hypothesis, the Y or W chromosome in each species is the same as in the MRCA, whereas in the novel paradigm there can be a new Y or W chromosome in at least one evolutionary lineage as a result of the new master sex determining locus (Figure 4). The common ancestry hypothesis does not itself explain why the conserved X and Y (or Z and W) chromosomes have remained homomorphic in all species. One explanation for homomorphic sex chromosomes shared by common ancestry is continuous recombination between X and Y (or Z and W) chromosomes in the heterogametic sex.[83–85]

Distinguishing between the three explanations for the same sex-linked chromosome across species (the novel paradigm, convergent turnover by a canonical trajectory, or common ancestry) requires characterizing the sex chromosomes and master sex determining genes of multiple species, and using those data to infer the genotype of the MRCA (Figure 4). The novel paradigm would be supported if there is a new master male- (female-) determining gene in at least one evolutionary lineage, and the ancestral X (or Z) chromosome remained unchanged in those lineages. Convergent evolution by a canonical trajectory would be supported if there was the same autosome-to-sex-chromosome turnover via new master sex determining genes in at least two evolutionary lineages. Common ancestry with continuous recombination would be supported if the ancestral master sex determiner and both sex chromosomes (i.e., X and Y) are conserved across all species with the same sex-linked chromosome. Current genomic approaches are well-suited to identify sex chromosomes,[67] but characterizing the master sex determining genes is far more challenging.

The aforementioned comparisons are suited to test for the novel paradigm in taxa where there are shared homomorphic sex chromosomes across different lineages (Figure 4), as is the case in cichlids, frogs, and ricefish (Table 1). However, the novel paradigm does not require that the sex chromosomes be undifferentiated—in one of the best characterized examples, most flies have highly divergent X and Y chromosomes,[32] and cockroach males have an XO genotype[18] (Figure 3). The point in highlighting taxa with shared homomorphic sex chromosomes is that they are promising candidates for the novel paradigm.

7. Causes of the Novel Paradigm

There are at least five possible causes of the novel paradigm for the evolution of sex determination and sex chromosomes (**Figure 5**). Each cause has been previously invoked to explain canonical trajectories of sex chromosome turnover (Figure 1A–C), and they also help in understanding why the novel paradigm might be favored in some cases. The first three causes result from selection on alleles that are linked to the master sex determining locus, and the last two come about from direct effects of the sex determiner itself.

The first two causes are possible if there are deleterious effects associated with one of the ancestral sex chromosomes. First, the "hot potato" model (Figure 5A) hypothesizes that the accumulation of deleterious mutations on a non-recombining Y (or W) chromosome could favor a sex chromosome turnover.[86] These deleterious mutations accumulate because a lack of recombination between the X and Y chromosomes prevents the purging of deleterious mutations from the Y.[57,60] In the hot potato model, a new male-determiner on an existing X chromosome (converting the X into a Y) could allow for the loss of an existing Y chromosome that is laden with deleterious alleles (or similarly for a W chromosome). This would result in evolutionary turnover of the Y chromosome (creating a new Y from the X) without affecting the X chromosome.

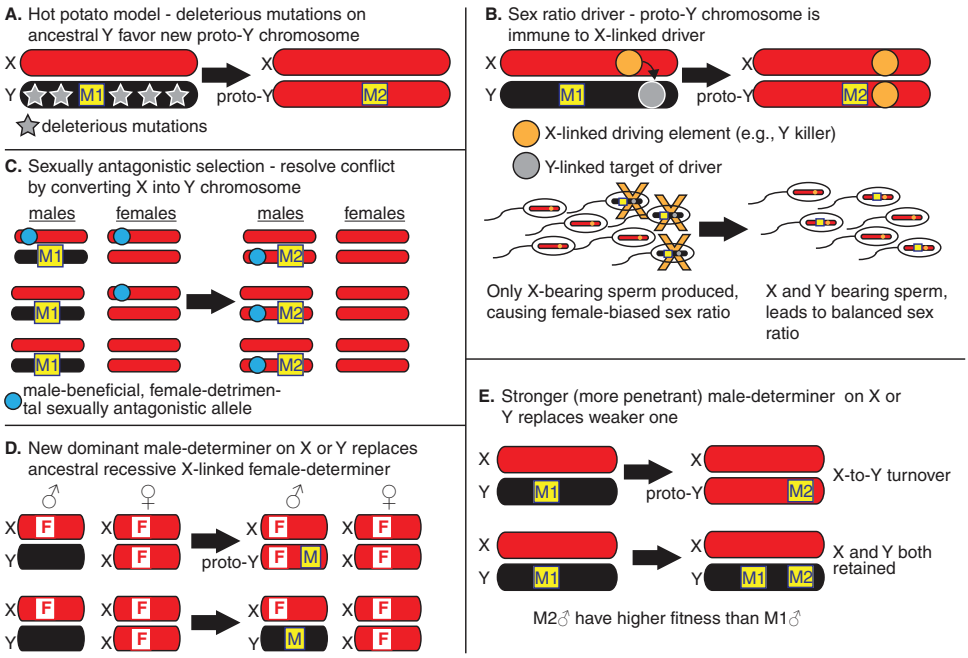

Figure 5. Causes of the novel paradigm. A) In the hot potato model, a new proto-Y chromosome with a new male-determiner will be favored because the ancestral Y chromosome carries deleterious mutations.[86] B) If a sex ratio driver on the X chromosome leads to the elimination of Y-bearing sperm, a proto-Y chromosome (created from the ancestral X) will be favored that is immune to the X-linked driver.[87–94] C) A sexually antagonistic (male-beneficial and female-detrimental) allele on the ancestral X chromosome can fix in a population if a copy of the X with the allele obtains a new male-determiner, converting it into a proto-Y and resolving the conflict by limiting inheritance of the allele to males only.[97] D) A dominant male-determiner (M) is more likely to replace a recessive female-determiner (F) than vice versa.[98] E) A stronger, more penetrant male-determiner can replace a weak male-determiner [33,99] if the stronger male-determiner leads to higher male fitness (e.g., more reproductive output). D,E) A dominant or more penetrant male-determiner could arise on either the ancestral X chromosome (creating a proto-Y) or the ancestral Y (allowing both X and Y to be retained).

Second, if an existing sex chromosome pair experiences non-Mendelian inheritance (e.g., via a sex ratio drive system that biases the inheritance of the X or Y[87]), there will be selection in favor of a mutation that produces the rarer sex.[88–91] For example, X chromosome drivers in flies can act by eliminating Y-bearing sperm,[92] causing female-biased sex ratios.[93,94] One way to overcome the effect of the X chromosome driving against the Y is for a male-determining locus to arise on the X chromosome, creating a proto-Y that is immune from the X chromosome driver (Figure 5B). This would result in equal transmission of the ancestral X and the proto-Y (thereby balancing the sex ratio), and it would cause evolutionary turnover of the Y chromosome without affecting the X chromosome.

Third, sexually antagonistic selection could favor a sex chromosome turnover that converts an existing X into a Y, or Z into W (Figure 5C). For example, a male-beneficial and female-detrimental allele on an X chromosome may be unlikely to invade a population (unless it is recessive) because the female-biased transmission of the X favors female-beneficial alleles.[95,96] However, if a male-determining locus arises on a copy of the X chromosome that carries the sexually antagonistic allele, it would limit the inheritance of the allele only to males, thereby resolving the inter-sexual conflict. If the male-determiner and sexually antagonistic allele are genetically linked, this could drive evolutionary turnover of the X into a proto-Y chromosome.[97] The result would be an evolutionary transition in the master regulator of sex determination and turnover of the Y chromosome, but X chromosomes without the male-determiner would remain unchanged.

The last two causes result from direct effects of the master sex determining gene. In the fourth mechanism, a new dominant male-determiner on an existing X or Y chromosome is likely to invade if it is replacing a recessive female-determining X chromosome, or vice versa in a ZW system[98] (Figure 5D). In the fifth mechanism, the "strength" or penetrance of a new master sex determiner may favor its invasion if it is more likely to produce fertile adults (or results in higher fitness) of a particular sex[33,99] (Figure 5E). Both of these could explain how a new male- (female-) determiner can arise on an existing Y (or W) chromosome. In both, there would be a transition in the master regulator of sex determination, possibly evolutionary turnover of the Y or W chromosome, and the X or Z chromosome would remain unchanged.

8. The Novel Paradigm is Likely Rare but May Affect Estimates of the Rate of Sex Chromosome Turnover

The extent to which the novel paradigm occurs relative to the canonical trajectories is not yet resolved. Despite the uncertainty about its frequency, it is unlikely that the novel paradigm is the norm in the evolution of sex determination. Most of the

previously documented sex chromosome turnovers, and all neo-sex chromosomes, fit in one of the canonical trajectories (Figure 1A–D). In addition, transitions from environmental sex determination to genetic sex determination, which is common in reptiles,[100] cannot occur via the novel paradigm because there is not an existing sex chromosome to retain. The same is true for transitions from hermaphrodity to separate sexes, which has occurred in many plant lineages.[101–103] Therefore, the novel paradigm is likely rare, but additional tests are required to assess the frequency with which it occurs relative to the canonical trajectories of sex chromosome turnover.

Despite being rare, the novel paradigm should be considered when estimating the rate of sex chromosome turnover using phylogenetic approaches. Most phylogenetic methods that quantify sex chromosome turnovers test if the same chromosome is sex-linked across species.[79,104] When the same chromosome is sex-linked in different species, it is commonly inferred to be the result of either convergent evolution or common ancestry of both the X and Y, or Z and W (Figure 4C,D). The sex chromosome of the MRCA can also be ambiguous using phylogenetic approaches, even with deep taxonomic sampling.[79] In addition, these tests of sex chromosome turnover are used to infer evolution transitions of the master regulators of sex determination, but they do not directly identify the master sex determining genes across species. Without identifying the sex chromosomes of the MRCA and master sex determining genes, methods that map sex chromosome turnover onto a phylogeny may mischaracterize the novel paradigm as a conserved or convergently evolved XY (or ZW) pair (Figure 4). If the novel paradigm is mischaracterized as conserved sex chromosomes, this will lead to an underestimate of evolutionary transitions in sex determination.

9. Conclusions and Outlook

I have described a novel paradigm for the evolution of sex determination and sex chromosomes in which there is an evolutionary transition in the sex determination pathway, which can cause turnover of the Y chromosome, but the ancestral X chromosome remains unchanged (Figure 1). After the new sex determining locus arises, there will be a period during which the ancestral and derived sex chromosomes both segregate as polymorphisms before the new sex determiner reaches fixation in the population, as with canonical trajectories of sex chromosome turnover (Figure 2). To date, there are three documented examples of the novel paradigm, two within insects and one in fish (Figure 3). However, I identified three other taxa where this new trajectory may have occurred, including one that may involve a Z chromosome (Table 1). Future work is needed to characterize the master sex determining loci in these taxa (and other candidate taxa) to test if they are bona fide examples of the novel paradigm (Figure 4). This work will likely be possible in the near future with continuing advances in sequencing and molecular biology technologies, although characterizing master sex determining genes is still an immense challenge. Additional developments in theoretical and empirical population genetics are also needed to evaluate the possible causes of the novel paradigm (Figure 5). Studies of the evolutionary dynamics of sex chromosomes have a rich history of contributing toward our understanding of fundamental population genetics processes, including the adaptation and inter-sexual conflict.[95–97,105] Insights gained from evaluating the novel paradigm for sex chromosome turnover could similarly contribute toward our general understanding of genome evolution.

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Conflict of Interest

The author declares no conflict of interest.

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[1] T. M. Williams, S. B. Carroll, *Nat. Rev. Genet.* **2009**, *10*, 797.
[2] D. Bachtrog, J. E. Mank, C. L. Peichel, M. Kirkpatrick, S. P. Otto, T.-L. Ashman, M. W. Hahn, J. Kitano, I. Mayrose, R. Ming, N. Perrin, L. Ross, N. Valenzuela, J. C. Vamosi, *PLoS Biol.* **2014**, *12*, e1001899.
[3] P. Graham, J. K. M. Penn, P. Schedl, *BioEssays* **2003**, *25*, 1.
[4] H. K. Salz, J. W. Erickson, *Fly* **2010**, *4*, 60.
[5] J. J. Bull, *Evolution of Sex Determining Mechanisms*, Benjamin/Cummings, Menlo Park, CA **1983**.
[6] L. W. Beukeboom, N. Perrin, *The Evolution of Sex Determination*, Oxford University Press, Oxford **2014**.
[7] P. N. Goodfellow, R. Lovell-Badge, *Annu. Rev. Genet.* **1993**, *27*, 71.
[8] C. S. Raymond, M. W. Murphy, M. G. O'Sullivan, V. J. Bardwell, D. Zarkower, *Genes Dev.* **2000**, *14*, 2587.
[9] H. K. Salz, *Curr. Opin. Genet. Dev.* **2011**, *21*, 395.
[10] H. Ellegren, *Nat. Rev. Genet.* **2011**, *12*, 157.
[11] D. O'Meally, T. Ezaz, A. Georges, S. D. Sarre, J. A. M. Graves, *Chromosome Res.* **2012**, *20*, 7.
[12] B. L. S. Furman, B. J. Evans, *G3: Genes, Genomes, Genet.* **2016**, *6*, 3625.
[13] T. Ezaz, K. Srikulnath, J. A. M. Graves, *J. Hered.* **2017**, *108*, 94.
[14] N. M. Stevens, *Studies in Spermatogenesis With Especial Reference to the "Accessory Chromosome"*, Carnegie Institution of Washington, Washington, DC **1905**.
[15] M. J. D. White, *J. Genet.* **1940**, *40*, 303.
[16] G. S. van Doorn, *Cold Spring Harbor Perspect. Biol.* **2014**, *6*, a017681.
[17] R. P. Meisel, C. A. Gonzales, H. Luu, *Genome Res.* **2017**, *27*, 1417.
[18] R. P. Meisel, P. J. Delclos, J. R. Wexler, *BMC Biol.* **2019**, *17*, 100.
[19] R. Bergero, J. Gardner, D. Charlesworth, *Evolution of a Y Chromosome from an X Chromosome*, CellPress, Cambridge, USA **2019** ssrn.3417937.
[20] A. S. Wilkins, *BioEssays* **1995**, *17*, 71.
[21] A. Herpin, M. Schartl, *EMBO Rep.* **2015**, *16*, 1260.

[22] M. Matsuda, Y. Nagahama, A. Shinomiya, T. Sato, C. Matsuda, T. Kobayashi, C. E Morrey, N. Shibata, S. Asakawa, N. Shimizu, H. Hori, S. Hamaguchi, M. Sakaizumi, *Nature* **2002**, *417*, 559.
[23] I. Nanda, M. Kondo, U. Hornung, S. Asakawa, C. Winkler, A. Shimizu, Z. Shan, T. Haaf, N. Shimizu, A. Shima, M. Schmid, M. Schartl, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11778.
[24] M. Kondo, I. Nanda, U. Hornung, M. Schmid, M. Shartl, *Curr. Biol.* **2004**, *14*, 1664.
[25] K. Tanaka, Y. Takehana, K. Naruse, S. Hamaguchi, M. Sakaizumi, *Genetics* **2007**, *177*, 2075.
[26] T. Myosho, H. Otake, H. Masuyama, M. Matsuda, Y. Kuroki, A. Fujiyama, K. Naruse, S. Hamaguchi, M. Sakaizumi, *Genetics* **2012**, *191*, 163.
[27] J. J. Faber-Hammond, R. B. Phillips, K. H. Brown, *Genome Biol. Evol.* **2015**, *7*, 1972.
[28] K. P. Lubieniecki, S. Lin, E. I. Cabana, J. Li, Y. Y. Y. Lai, W. S. Davidson, *G3: Genes, Genomes, Genet.* **2015**, *5*, 2513.
[29] A. Sharma, S. D. Heinze, Y. Wu, T. Kohlbrenner, I. Morilla, C. Brunner, E. A. Wimmer, L. van de Zande, M. D. Robinson, L. W. Beukeboom, D. Bopp, *Science* **2017**, *356*, 642.
[30] J. A. Tennessen, N. Wei, S. C. K. Straub, R. Govindarajulu, A. Liston, T.-L. Ashman, *PLoS Biol.* **2018**, *16*, e2006062.
[31] E. C. Moore, R. B. Roberts, *Curr. Biol.* **2013**, *23*, R510.
[32] B. Vicoso, D. Bachtrog, *Nature* **2013**, *499*, 332.
[33] J. J. Bull, E. L. Charnov, *Heredity* **1977**, *39*, 1.
[34] R. B. Roberts, J. R. Ser, T. D. Kocher, *Science* **2009**, *326*, 998.
[35] M. J. Scott, M. L. Pimsler, A. M. Tarone, *Sex. Dev.* **2014**, *8*, 29.
[36] A. Meccariello, M. Salvemini, P. Primo, B. Hall, P. Koskinioti, M. Dalíková, A. Gravina, M. A. Gucciardino, F. Forlenza, M.-E. Gregoriou, D. Ippolito, S. M. Monti, V. Petrella, M. M. Perrotta, S. Schmeing, A. Ruggiero, F. Scolari, E. Giordano, K. T. Tsoumani, F. Marec, N. Windbichler, K. P. Arunkumar, K. Bourtzis, K. D. Mathiopoulos, J. Ragoussis, L. Vitagliano, Z. Tu, P. A. Papathanos, M. D. Robinson, G. Saccone, *Science* **2019**, *365*, 1457.
[37] M. Hediger, C. Henggeler, N. Meier, R. Perez, G. Saccone, D. Bopp, *Genetics* **2010**, *184*, 155.
[38] R. L. Hamm, R. P. Meisel, J. G. Scott, *G3: Genes, Genomes, Genet.* **2015**, *5*, 371.
[39] I. Miura, *Sex. Dev.* **2007**, *1*, 323.
[40] K. D. Kallman, in *Genetics and Mutagenesis of Fish* (Ed: J. H. Schröder), Springer, Berlin, Heidelberg **1973**, pp. 19–28.
[41] C. Schultheis, A. Böhne, M. Schartl, J. N. Volff, D. Galiana-Arnoux, *Sex. Dev.* **2009**, *3*, 68.
[42] Á. S. Roco, A. W. Olmstead, S. J. Degitz, T. Amano, L. B. Zimmerman, M. Bullejos, *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E4752.
[43] A. E. Wright, R. Dean, F. Zimmer, J. E. Mank, *Nat. Commun.* **2016**, *7*, 12087.
[44] M. Steinemann, S. Steinemann, *Genetica* **1998**, *102*, 409.
[45] P. D. Waters, B. Duffy, C. J. Frost, M. L. Delbridge, J. A. Graves, *Cytogenet. Genome Res.* **2001**, *92*, 74.
[46] E. C. Howell, S. J. Armstrong, D. A. Filatov, *Genetics* **2009**, *182*, 1109.
[47] V. B. Kaiser, D. Bachtrog, *Annu. Rev. Genet.* **2010**, *44*, 91.
[48] I. Pala, S. Naurin, M. Stervander, D. Hasselquist, S. Bensch, B. Hansson, *Heredity* **2012**, *108*, 264.
[49] M. W. Pennell, M. Kirkpatrick, S. P. Otto, J. C. Vamosi, C. L. Peichel, N. Valenzuela, J. Kitano, *PLoS Genet.* **2015**, *11*, e1005237.
[50] A. J. Mongue, P. Nguyen, A. Voleníková, J. R. Walters, *G3: Genes, Genomes, Genet.* **2017**, *7*, 3281.
[51] T. Kamiya, W. Kai, S. Tasumi, A. Oka, T. Matsunaga, N. Mizuno, M. Fujita, H. Suetake, S. Suzuki, S. Hosoya, S. Tohari, S. Brenner, T. Miyadai, B. Venkatesh, Y. Suzuki, K. Kikuchi, *PLoS Genet.* **2012**, *8*, e1002798.
[52] B. Vicoso, B. Charlesworth, *Nat. Rev. Genet.* **2006**, *7*, 645.
[53] R. P. Meisel, J. H. Malone, A. G. Clark, *Genome Res.* **2012**, *22*, 1255.
[54] J. E. Mank, *Trends Genet.* **2013**, *29*, 677.
[55] L. Gu, J. R. Walters, *Genome Biol. Evol.* **2017**, *9*, 2461.
[56] B. Charlesworth, D. Charlesworth, *Philos. Trans. R. Soc. B* **2000**, *355*, 1563.
[57] D. Bachtrog, *Nat. Rev. Genet.* **2013**, *14*, 113.
[58] D. W. Bellott, J. F. Hughes, H. Skaletsky, L. G. Brown, T. Pyntikova, T.-J. Cho, N. Koutseva, S. Zaghlul, T. Graves, S. Rock, C. Kremitzki, R. S. Fulton, S. Dugan, Y. Ding, D. Morton, Z. Khan, L. Lewis, C. Buhay, Q. Wang, J. Watt, M. Holder, S. Lee, L. Nazareth, J. Alföldi, S. Rozen, D. M. Muzny, W. C. Warren, R. A. Gibbs, R. K. Wilson, D. C. Page, *Nature* **2014**, *508*, 494.
[59] J. F. Hughes, D. C. Page, *Annu. Rev. Genet.* **2015**, *49*, 507.
[60] W. R. Rice, *BioScience* **1996**, *46*, 331.
[61] M. Beye, M. Hasselmann, M. K. Fondrk, R. E. Page, S. W. Omholt, *Cell* **2003**, *114*, 419.
[62] D. Zarkower, in *WormBook* (Ed: The *C. elegans* Research Community), WormBook **2006**.
[63] A. Yano, R. Guyomard, B. Nicol, E. Jouanno, E. Quillet, C. Klopp, C. Cabau, O. Bouchez, A. Fostier, Y. Guiguen, *Curr. Biol.* **2012**, *22*, 1423.
[64] A. B. Hall, S. Basu, X. Jiang, Y. Qi, V. A. Timoshevskiy, J. K. Biedler, M. V. Sharakhova, R. Elahi, M. A. Anderson, X. G. Chen, I. V. Sharakhov, Z. N. Adelman, Z. Tu, *Science* **2015**, *348*, 1268.
[65] F. Criscione, Y. Qi, Z. Tu, *eLife* **2016**, *5*, e19281.
[66] E. Krzywinska, N. J. Dennison, G. J. Lycett, J. Krzywinski, *Science* **2016**, *353*, 67.
[67] D. H. Palmer, T. F. Rogers, R. Dean, A. E. Wright, *Mol. Ecol.* **2019**, *28*, 4709.
[68] T. Gamble, J. Coryell, T. Ezaz, J. Lynch, D. P. Scantlebury, D. Zarkower, *Mol. Biol. Evol.* **2015**, *32*, 1296.
[69] A. B. Carvalho, L. B. Koerich, A. G. Clark, *Trends Genet.* **2009**, *25*, 270.
[70] A. B. Carvalho, A. G. Clark, *Science* **2005**, *307*, 108.
[71] A. M. Larracuente, M. A. F. Noor, A. G. Clark, *Mol. Biol. Evol.* **2010**, *27*, 1612.
[72] S. V. Flores, A. L. Evans, B. F. McAllister, *BMC Evol. Biol.* **2008**, *8*, 33.
[73] R. A. Voelker, K.-I. Kojima, *Evolution* **1971**, *25*, 119.
[74] J. Wexler, E. K. Delaney, X. Belles, C. Schal, A. Wada-Katsumata, M. J. Amicucci, A. Kopp, *eLife* **2019**, *8*, e47490.
[75] A. E. Wright, I. Darolti, N. I. Bloch, V. Oostra, B. Sandkam, S. D. Buechel, N. Kolm, F. Breden, B. Vicoso, J. E. Mank, *Nat. Commun.* **2017**, *8*, 14251.
[76] I. Darolti, A. E. Wright, B. A. Sandkam, J. Morris, N. I. Bloch, M. Farré, R. C. Fuller, G. R. Bourne, D. M. Larkin, F. Breden, J. E. Mank, *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 19031.
[77] W. J. Gammerdinger, T. D. Kocher, *Genes* **2018**, *9*, 480.
[78] M. A. Conte, W. J. Gammerdinger, K. L. Bartie, D. J. Penman, T. D. Kocher, *BMC Genomics* **2017**, *18*, 341.
[79] D. L. Jeffries, G. Lavanchy, R. Sermier, M. J. Sredl, I. Miura, A. Borzée, L. N. Barrow, D. Canestrelli, P.-A. Crochet, C. Dufresnes, J. Fu, W.-J. Ma, C. M. Garcia, K. Ghali, A. G. Nicieza, R. P. O'Donnell, N. Rodrigues, A. Romano, Í. Martínez-Solano, I. Stepanyan, S. Zumbach, A. Brelsford, N. Perrin, *Nat. Commun.* **2018**, *9*, 4088.
[80] Y. Takehana, D. Demiyah, K. Naruse, S. Hamaguchi, M. Sakaizumi, *Genetics* **2007**, *175*, 1335.
[81] Y. Takehana, M. Matsuda, T. Myosho, M. L. Suster, K. Kawakami, T. Shin-I, Y. Kohara, Y. Kuroki, A. Toyoda, A. Fujiyama, S. Hamaguchi, M. Sakaizumi, K. Naruse, *Nat. Commun.* **2014**, *5*, 4157.
[82] T. Myosho, Y. Takehana, S. Hamaguchi, M. Sakaizumi, *G3: Genes, Genomes, Genet.* **2015**, *5*, 2685.
[83] M. Stöck, A. Horn, C. Grossen, D. Lindtke, R. Sermier, C. Betto-Colliard, C. Dufresnes, E. Bonjour, Z. Dumas, E. Luquet, T. Maddalena, H. C. Sousa, I. Martinez-Solano, N. Perrin, *PLoS Biol.* **2011**, *9*, e1001062.
[84] N. Perrin, *Evolution* **2009**, *63*, 3043.
[85] A. Brelsford, C. Dufresnes, N. Perrin, *Evolution* **2016**, *70*, 840.

[86] O. Blaser, S. Neuenschwander, N. Perrin, *Am. Nat.* **2014**, *183*, 140.
[87] Q. Helleu, P. R. Gérard, C. Montchamp-Moreau, *Cold Spring Harbor Perspect. Biol.* **2015**, *7*, a017616.
[88] W. D. Hamilton, *Science* **1967**, *156*, 477.
[89] M. G. Bulmer, J. J. Bull, *Evolution* **1982**, *36*, 13.
[90] J. H. Werren, L. W. Beukeboom, *Annu. Rev. Ecol. Syst.* **1998**, *29*, 233.
[91] M. Kozielska, F. J. Weissing, L. W. Beukeboom, I. Pen, *Heredity* **2010**, *104*, 100.
[92] D. Policansky, J. Ellison, *Science* **1970**, *169*, 888.
[93] A. H. Sturtevant, T. Dobzhansky, *Genetics* **1936**, *21*, 473.
[94] J. Jaenike, *Am. Nat.* **1996**, *148*, 237.
[95] W. R. Rice, *Evolution* **1984**, *38*, 735.
[96] J. D. Fry, *Evolution* **2010**, *64*, 1510.
[97] G. S. van Doorn, M. Kirkpatrick, *Nature* **2007**, *449*, 909.
[98] C. Veller, P. Muralidhar, G. W. A. Constable, M. A. Nowak, *Genetics* **2017**, *207*, 711.
[99] M. Beye, C. Seelmann, T. Gempe, M. Hasselmann, X. Vekemans, M. K. Fondrk, R. E. Page Jr, *Curr. Biol.* **2013**, *23*, 2559.
[100] S. D. Sarre, A. Georges, A. Quinn, *BioEssays* **2004**, *26*, 639.
[101] Q. Yu, R. Navajas-Pérez, E. Tong, J. Robertson, P. H. Moore, A. H. Paterson, R. Ming, *Trop. Plant Biol.* **2008**, *1*, 49.
[102] E. Kejnovsky, B. Vyskot, *Cytogenet. Genome Res.* **2010**, *129*, 250.
[103] S. S. Renner, *Am. J. Bot.* **2014**, *101*, 1588.
[104] H. Blackmon, L. Ross, D. Bachtrog, *J. Hered.* **2017**, *108*, 78.
[105] B. Charlesworth, J. A. Coyne, N. H. Barton, *Am. Nat.* **1987**, *130*, 113.