Opinion

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Genetic conflict and sex chromosome evolution

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Chromosomal sex determination systems create the opportunity for the evolution of selfish genetic elements that increase the transmission of one sex chromosome at the expense of its homolog. Because such selfish elements on sex chromosomes can reduce fertility and distort the sex ratio of progeny, unlinked suppressors are expected to evolve, bringing different regions of the genome into conflict over the meiotic transmission of the sex chromosomes. Here we argue that recurrent genetic conflict over sex chromosome transmission is an important evolutionary force that has shaped a wide range of seemingly disparate phenomena including the epigenetic regulation of genes expressed in the germline, the distribution of genes in the genome, and the evolution of hybrid sterility between species.

Selfish genes and genetic conflict

Mendelian segregation and recombination are integral components of the vast majority of eukaryotic genetic systems. Both processes maximize the efficacy of natural selection [1], and are directly favored under many circumstances [2]. However, selfish genetic elements (see glossary) such as retroviruses and transposable elements (TEs) populate most genomes, and can spread through a population by achieving greater than Mendelian representation among the offspring of their host, even if the host incurs a significant fitness cost as a result [3]. These intragenomic parasites can drive cycles of co-evolution between loci in the same genome, as the selfish locus adapts to exploit the host, and the host adapts to ameliorate negative effects of the parasite.

One type of selfish genetic element are segregation distorters (also known as meiotic drive elements [4]), which manipulate meiosis or gametogenesis so that the chromosome where they reside is transmitted to more than 50% of the offspring of a heterozygous carrier. Segregation distorters gain their transmission advantage by multiple mechanisms, such as incapacitating gametes that carry the alternative allele or influencing the geometry of chromosome segregation during the first meiotic division [3]. Segregation distorters give rise to genetic conflicts among loci because natural selection favors alleles at unlinked loci that suppress distortion (owing to fertility costs associated with distortion) and alleles in close linkage that enhance distortion [2]. In this opinion piece, we argue that these conflicts are particularly common in species with chromosomal sex determination, and are a cause of

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Glossary

De novo genes: new genes that arise primarily from previously non-coding sequences, and thus do not share homology with any other known genes.
Epigenetic regulation: the regulation of gene activity or function by changing the physical and chemical properties of a region of DNA through modification of the DNA (without altering its nucleotide sequence) or the proteins with which it is associated (such as histones). Epigenetic states usually persist through cell divisions, and sometimes can be transmitted across generations.
Fisherian sex ratio: the ratio of males to females in a population that is determined by equal parental investment in the two sexes. In most populations, the Fisherian sex ratio is approximately 1:1, but this will not necessarily be the case if one sex requires more parental investment than the other. When the sex ratio in a population is far from the Fisherian equilibrium, parental investment in the rarer sex will have a higher fitness return in subsequent generations and push the population sex ratio back towards equilibrium.
Haldane's rule: J. B. S. Haldane observed in 1922 that ''when in the F1 offspring of two different animal races one sex is absent, rare, or sterile, that sex is the heterozygous [heterogametic] sex.'' This rule holds remarkably well across all animal taxa with XY/XX or ZW/ZZ sex determining systems.
Hybrid incompatibility: interactions between loci that function normally within species but cause a loss of fitness (typically sterility or lethality) in hybrids between species.
Intragenomic conflict: intragenomic conflict occurs when alleles that are favored at one locus cause a loss of fitness at other loci in the same individual or genome (also referred to as genetic conflict). For example, an X-linked allele that kills Y-bearing sperm will reduce the fitness not only of the Y chromosome, but of autosomes as well, if killing gametes decreases fertility. This generates conflict between the X chromosome and the autosomes over the transmission of the sex chromosomes in males, as alleles on the X chromosome favor killing Y-bearing sperm, but alleles on the autosomes favor suppressing this phenotype. In a population with an excess of females, autosomal genes gain a benefit from being in a male, creating an analagous conflict between the X chromosome and the autosomes over the proportion of sons and daughters that a father sires.
Large X-effect: the observation that the genes underlying postzygotic reproductive isolation, particularly hybrid male sterility in XY/XX animal species, are enriched on the X chromosome relative to the autosomes. Empirical evidence from Drosophila and mice strongly support the large X-effect.
Large Z-effect: analagous to the large X-effect, the hypothesis that hybrid female sterility loci should be enriched on the Z chromosome. There is currently little empirical evidence to support the large Z-effect.
Meiotic sex chromosome inactivation (MSCI): the transcriptional repression of the sex chromosomes during meiosis, at a time when the autosomes are still transcriptionally active, usually starting from the pachytene stage and lasting through diplotene.
Retrotransposition: a type of gene transposition that requires an RNA intermediate. The descendent DNA sequences are retro-transcribed from mature mRNA and so differ from their progenitor gene by lacking intronic sequences.
Segregation distorter: the two alleles in a diploid organism are normally represented equally in gametes because of Mendelian segregation of homologous chromosomes during meiosis (Mendel's First Law). Segregation distortion occurs when one allele, the distorter, is represented in more than 50% of the gametes. Segregation distorters subvert the meiotic machinery by being preferentially included in functional gametes, or by producing toxins capable of killing gametes that carry the alternate allele. Segregation distortion is often called meiotic drive.
Selfish genetic element: selfish genetic elements are DNA sequences that attain greater than Mendelian transmission rates, often at the expense of other genes in the genome. Transposable elements, retroviruses and segregation distorters are classic examples of selfish genetic elements.
Sex-ratio distorter: a segregation distorter located on the X or Y chromosome. As a result of the distortion, the X (or Y) will be over-represented in functional gametes, thus skewing the sex ratio towards females (or males) among the progeny of individuals carrying the distorter.

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multiple genomic and evolutionary patterns associated with sex chromosomes that are observed across the animal kingdom.

Sex chromosomes and segregation distortion

Segregation distorters can arise on all chromosomes, but are particularly important in species with chromosomal sex determination (for brevity, we will refer to the heterogametic sex as male and the sex chromosomes as X and Y, except where we explicitly compare XY and ZW systems). Theory proposes that segregation distorters are more likely to arise on sex chromosomes than on autosomes, and are more likely to subsequently invade a population if they are on sex chromosomes [5–7]. To gain a transmission advantage, segregation distorters must meet two conditions. First, the distorter must be able to discriminate its host chromosome from its homolog [8]. In most cases where the mechanism of segregation distortion is known, the distorter locus produces a gene product (RNA or protein) which then acts on a responder locus to impair that chromosome or a gamete bearing it. The distorter discriminates its host chromosome via a resistant or insensitive allele at the responder locus. Second, the distorter and responder loci must be in strong linkage because otherwise recombination will generate suicide chromosomes that carry the distorter and a sensitive responder [8–11]. This explains why all characterized autosomal distorters are found in regions with little or no recombination, such as inversions [7]. Most X and Y chromosomes have highly divergent sequences from each other and do not recombine along much of their length, facilitating the evolution of segregation distorters on these chromosomes [5,6,8].

Sex linked segregation distorters can spread in a population and even fix, as long as any deleterious effects are offset by their transmission advantage [12]. However, disruption of equal transmission of the X and Y chromosomes has the additional consequence of influencing the sex ratio of the progeny of carrier males (hence, sex-linked segregation distorters are also called sex-ratio distorters). Sex-ratio distorters generate an additional conflict between the sex chromosomes and the rest of the genome because of their effect on the population sex ratio.

Sex ratio evolution

In organisms with separate sexes, parents maximize their fitness by investing equally in both sexes. This insight dates back to Darwin's contemporary Carl Düsing [13], but is generally attributed to R.A. Fisher [14]. As a result of equal investment, populations attain an equilibrium sex ratio that reflects the cost to parents of producing offspring of each sex (the Fisherian sex ratio). In a population with a biased sex ratio, alleles which cause parents to produce an excess of the rarer sex are favored, ultimately restoring the population to the Fisherian equilibrium [15], whereas in a population at equilibrium, genetic variants that change the sex ratio of progeny are selectively neutral [14,16].

Selection favors the Fisherian sex ratio only at loci that have both biparental and Mendelian inheritance [16]. For example, cytoplasmic genes, which are maternally inherited, will maximize their fitness if their host produces a female-biased sex ratio (Figure 1). Similarly, sex chromosomes favor biased sex ratios because an X chromosome is always transmitted from father to daughter, and a Y chromosome from father to son. The invasion probability of a newly evolved sex-ratio distorter is therefore determined solely by its transmission advantage and any deleterious effects it has on its host, and is not influenced by the population sex ratio. However, if the distorter increases to an appreciable frequency, it will skew the population sex ratio. This in turn favors suppressors of the distorter that arise on an autosome or the other sex chromosome (Figure 2) [15,16]. Because of these intrinsic disagreements among genetic factions within an organism over the sex ratio among its progeny (Figure 1), genes that control the transmission of the sex chromosomes will commonly be involved in intragenomic conflicts [3,17] (Box 1). Ecological circumstances, such as local mate competition, can also favor non-Fisherian sex ratios [15]. These considerations suggest that population sex ratios could often be influenced by both intrinsic (genetic) and extrinsic factors, and raise the possibility that populations might be frequently perturbed away from Fisherian sex ratios.

We propose that recurrent conflict over the transmission of sex chromosomes has shaped widespread cytological and evolutionary patterns, including the epigenetic regulation of sex chromosomes, the genomic distribution of genes expressed in the germline, and the evolution of hybrid sterility between species. We refer to this hypothesis as the genetic conflict theory of sex chromosome evolution (Figure 2). Much of the evidence we present consists of detailed molecular and genetic studies of gametogenesis in pure species and interspecific hybrids, which by necessity are restricted to a few intensively studied model organisms. Although the data are taxonomically concentrated, we argue that the evolutionary principles that are ultimately explanatory should hold generally for organisms with sex chromosomes and meiosis, and we predict that similar results will emerge from other taxa.

Meiotic sex chromosome inactivation (MSCI)

MSCI is the precocious transcriptional repression and heterochromatization of the sex chromosomes during the pachytene stage of meiosis, when the rest of the genome is actively transcribed [18]. MSCI has been described from both male-heterogametic and female-heterogametic taxa. In nematodes (XO males), mice (XY males) and chickens (ZW females), the sex chromosomes form a condensed chromatin structure termed the "sex body" during pachytene that is localized to the periphery of the nucleus [19–22]. In *C. elegans* and mice, where MSCI has been extensively studied, sex body formation is associated with multiple epigenetic modifications (histone deacetylation, methylation, ubiquitylation and the incorporation of non-canonical histone variants), some of which accompany the loss of transcription and the formation of heterochromatin, and some of which persist throughout meiosis and into spermiogenesis [20,21]. In mice, the majority of X-linked protein-coding genes are down-regulated during MSCI, and most of these remain silent post-meiosis [23]. However, many X-linked microRNAs (miRNAs), about 20 multi-copy gene families, and a few single-copy genes appear to escape MSCI, or show strong reactivation in

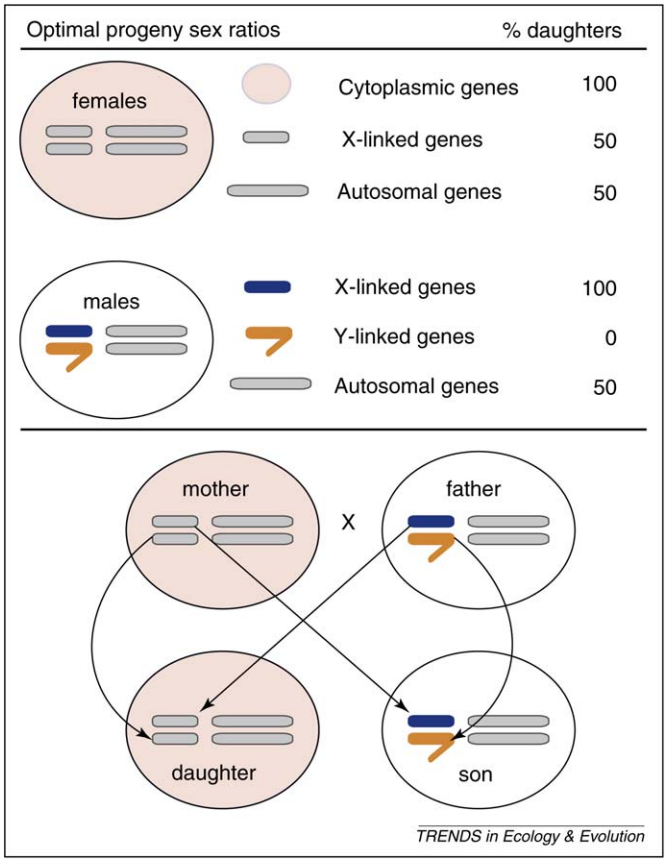

Figure 1. Optimal sex ratios. Genetic factions consist of genes with shared patterns of inheritance, and favor unique progeny sex ratios that will maximize their fitness. Factions with Mendelian segregation and biparental inheritance (autosomes in both sexes and X chromosomes in females, grey) favor Fisherian sex ratios determined by the cost of investing in the two sexes (here the Fisherian sex ratio is assumed to be 1:1). When cytoplasmic genes (pink shading) are uniparentally inherited, they favor 100% female progeny, since a son inherits his mother's cytoplasm but will not transmit it to his offspring. X chromosome fitness when transmitted through males (blue) is highest with all female progeny. Note that the X chromosome when transmitted through females has the same optimal progeny sex ratio as the autosomes, since it segregates away from another X chromosome and cannot influence the sex of its carrier in the next generation. Y chromosome (orange) fitness is maximized when 100% of progeny are male.

post-meiotic cells [24–26]. MSCI was first postulated to exist in *Drosophila* as a mechanism to explain the male-specific sterility of X-autosome translocations [27]. New evidence consistent with MSCI in *Drosophila* comes from the differential expression of transgenes carrying a promoter active during spermatogenesis when they are inserted on the X chromosome versus the autosomes [28]. However, direct cytological or epigenetic evidence for MSCI is still lacking in this model organism.

The inability of the X and Y chromosome to pair and synapse during meiosis is thought to be the signal that initiates MSCI [29]. More generally, regions of DNA that are unpaired during meiosis are often transcriptionally repressed and accumulate epigenetic modifications similar to those that characterize MSCI [30–33]. These mechanisms have been proposed to be a defense against selfish genetic elements that might be unpaired during meiosis [34]. It seems equally plausible that the evolutionary advantage of MSCI is also as a form of defense against sex-ratio distorters [8,15,35]. Transcriptional silencing of the unpaired regions of the sex chromosomes during the early stages of meiosis would suppress gene expression in the regions where sex-ratio distorters are predicted to reside and at the time when they are likely to be active. If MSCI is triggered by a lack of pairing during meiosis, this also suggests that MSCI might evolve in a piecemeal fashion as the Y chromosome degenerates and regions of the X and Y lose homology. The fact that genes escape MSCI, and that sex-ratio distorters exist, indicates that this genome defense is not perfect. This raises the possibility that genomes might respond to new or active distorters that evade MSCI by evolving to extend or enhance MSCI in the region where the distorter resides, and that there might be repeated bouts of co-evolution between selfish elements and the MSCI machinery.

Genomic biases in the location of sex-biased genes

Whole genome transcription and sequencing studies have revealed that genes with elevated expression in male reproductive tissues relative to somatic or female reproductive tissues (male-biased genes) are under-represented on the X chromosome in mammals, fruit flies, and nematodes [36–39] (with a possible exception in mosquitoes [40]); female-biased genes are under-represented on the Z chromosome in birds [41]. A similar pattern is found for duplicate genes formed by retrotransposition of an existing gene. In both flies and mammals, there is a tendency for such retrotransposed duplicates to be located on the autosomes, derived from X-linked parental genes, and expressed in testes [42–45]. In contrast, in *Drosophila* at least, new genes that arise *de novo* from ancestral non-coding sequences are frequently expressed in the testes but are preferentially located on the X chromosome [46–48].

The evolution of sex-ratio systems (distorters and their suppressors) could contribute to these patterns in three ways. First, some *de novo* genes with testis-specific expression might be segregation distorters. X-linked segregation distorters are more likely than autosomal distorters to invade a population. Therefore, if newly created genes have distorting activity, this might contribute to the observed excess of X-linked *de novo* genes. Second, some autosomal retrotransposed copies of X-linked genes might function as suppressors of sex-ratio distorters via RNAi. The RNAi pathway, which is known to have a major role in suppressing selfish genetic elements such as TEs, provides a mechanism for specifically suppressing the activity of individual loci through the recognition of sequence homology to small RNAs [49]. These two possibilities are inspired by work in *Drosophila simulans* that revealed the genesis of an X-linked segregation distorter from both coding and non-coding ancestral DNA sequences and its suppressor via retrotransposition of the distorting sequence to an autosome [50,51] (Box 2).

Third, MSCI is a likely contributor to the biased location and movement of genes expressed in male germline tissue [27,28,45,52]. The transcriptional silencing of the X during MSCI interferes with X-linked genes required for male meiosis, conferring a selective benefit to a retrotransposed autosomal copy (contributing to the bias in gene movement), or a mutation at an autosomal locus that co-opts the required meiotic function (contributing to the biased chromosomal distribution of testis-expressed genes). If MSCI

Box 1. Sex-ratio meiotic drive in *D. simulans*: one species, three systems

Three independent sex-ratio systems have been described from *D. simulans*: Paris, Winters and Durham [51] (Figure I). The Paris sex-ratio was discovered by crossing stocks from different geographic origins and consists of two X-linked distorters, each of which is necessary but not sufficient for effective drive. Suppressors on the Y and autosomes have been detected but have not yet been mapped [98]. Both the distorters and the suppressors are polymorphic across populations of *D. simulans* worldwide, and the distorters appear to have undergone a selective sweep as recently as 100 years ago [99]. The dysgenic etiology of the Paris sex-ratio includes both frequent Y chromosome loss during meiosis and postmeiotic developmental failure of the remaining Y-bearing sperm.

The Winters sex-ratio is also polymorphic within *D. simulans*. Two X-linked distorters, distorter on the X (*Dox*) and Mother of *Dox* (*MDox*), have been identified, and as in the Paris system, each of the two distorters is necessary but not sufficient for drive [50]. One suppressor on the third chromosome, not much yang (*Nmy*), has been characterized [51]. Sequence analysis of the distorters and suppressors suggests an intriguing evolutionary history and molecular mechanism underlying this conflict (see Box 2).

The Durham sex-ratio system was discovered by introgressing genomic segments from *D. mauritiana* into *D. simulans*. A sex-ratio suppressor, *too much yin* (*Tmy*), was mapped to the third chromosome [56]. The sequence of *Tmy*, like *Nmy*, has X-linked paralogs, which are strong candidates for the X-linked distorters (see Box 2). The *Tmy* allele from *D. mauritiana* is also the strongest hybrid male sterility locus on the third chromosome, indicating a direct connection between segregation distortion and reproductive isolation.

The independence of these three sex-ratio distortion systems is evidenced by the different genetic locations to which the distorters and suppressors map, as well as successful complementation tests between them [51]. The existence of three independent sex-ratio systems in a single species, as well as the dual roles of the *Tmy* gene as a sex-ratio suppressor and hybrid male sterility factor, supports the contention that sex-ratio systems could be prevalent and play a significant role in reproductive isolation.

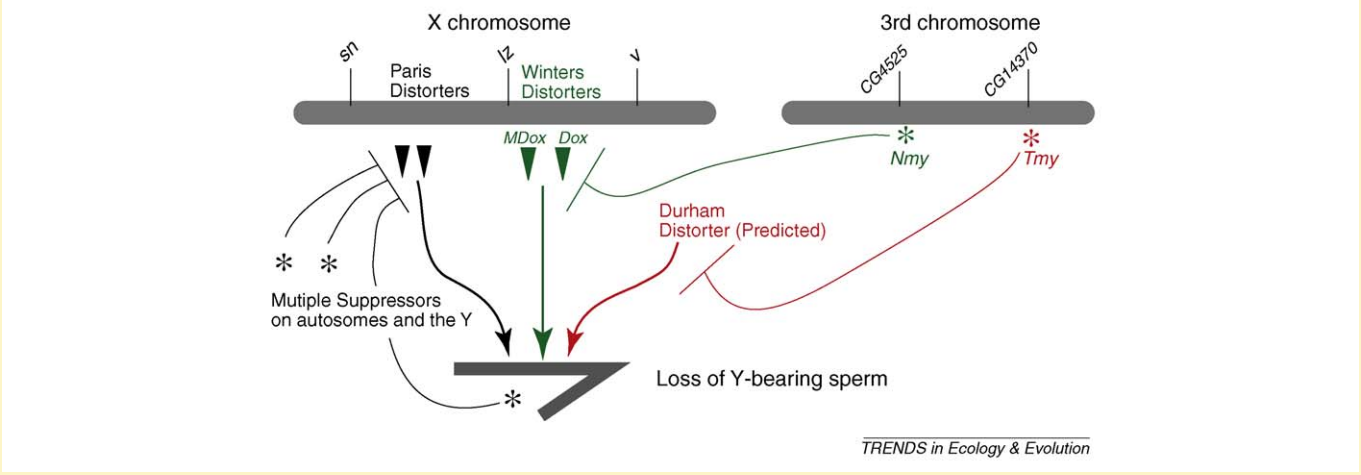

Figure I. Three sex-ratio systems in *D. simulans*. The known, predicted and unmapped loci of distorters (arrow head) and suppressors (*) are shown. Visible genetic markers *sn* (singed), *lz* (lozenge), and *v* (vermillion) were used to map the X-linked distorters. *CG4245* and *CG14370* are molecular markers used to localize the autosomal suppressors *Nmy* and *Tmy*.

evolved to suppress sex-ratio distorters, then genetic conflict might be both a proximate (in the first two cases described above) and ultimate cause of these patterns. However, conflict among genes over progeny sex ratios is likely to be only one of a number of explanations for these genomic patterns. For example, this hypothesis cannot fully explain the observed deficit of X-linked male-biased genes, since accessory gland proteins (which are primarily expressed in the somatic tissue of the accessory gland and show some of the most extreme male-biased expression of all genes [36]) are almost entirely absent from the X chromosome in *Drosophila*.

Genetic conflict and hybrid sterility

Genetic conflict over sex chromosome transmission might also contribute to two well-known patterns of reproductive isolation: the large contribution of the sex chromosomes to hybrid sterility (the large X-effect), and Haldane's rule. J.B.S. Haldane observed that in interspecific crosses, unisexual inviability or sterility predominantly affects the heterogametic sex [53]. A causal link between segregation distortion and Haldane's rule was originally proposed 18 years ago [5,6], and recent data on the genetic basis for hybrid sterility and the unique role the sex chromosomes play in its evolution has renewed interest in this hypothesis [7,54–56].

Haldane's rule

The conflict theory predicts that interspecific hybrid sterility in the heterogametic sex arises as a result of the rapid evolution of genes that influence the sex ratio through their effects on sex chromosome transmission [5,6]. This rapid evolution results from the recurrent invasion (and potentially fixation) of sex-ratio distorters and their suppressors, leading to incompatibilities that cause sterility in hybrids. Hybrid sterility is confined to the heterogametic sex because of the largely independent genetic control of meiosis and gametogenesis in the two sexes. Mechanistically, genetic conflict could give rise to hybrid sterility in three ways. First, the heterospecific autosomes or sex chromosome could fail to suppress or resist sex-ratio distorters, leading directly to segregation distortion in hybrids. If multiple distorters on both sex chromosomes are derepressed in hybrids, this could lead to concomitant sterility because of mutual destruction of each sex chromosome by the other. In two clades of *Drosophila*, hybrid sterility loci have recently been found to be associated with sex-ratio distortion. *Too much yin* (*Tmy*) is an autosomal locus that

Box 2. The Winters sex-ratio system

The Winters sex-ratio system was discovered from an inbred recombinant line between *D. simulans* and *D.* sechellia, using a *D. simulans* stock collected in Winters, California [100]. A sex-ratio suppressor, *Nmy* (not much yang), and its corresponding X-linked sex-ratio distorters, *Dox* (distorter on the X) and *MDox* (*Mother of Dox*), were identified by fine mapping and positional cloning [50,51]. The suppressing activity of *Nmy* requires a pair of inverted repeats, IR′ and IR″, inserted into the otherwise non-suppressing gene *CG14370* (Figure Ia).

Sequence comparisons among *Dox*, *MDox* and *Nmy* clearly indicate that *Nmy* originated from *Dox*, which in turn originated from *MDox*. Genotypes mutant for both *Dox* and *Nmy* express neither sex-ratio nor sterility, indicating that these genes are not essential for fertility and that their evolution was driven solely by their roles in this sex-ratio system [50]. We favor the hypothesis that *Mdox* evolved first, and then *Dox* subsequently arose as an enhancer of sex-ratio distortion or to re-establish distortion in the presence of an unknown suppressor.

The sex-ratio suppressing function of *Nmy* requires a pair of inverted repeats of 345 bp [51].The inverted repeat structure indicates that *Nmy* transcripts have a double-stranded stem that could be used to generate siRNAs that could silence *MDox* and/or *Dox* via an RNAi mechanism (Figure Ib). The RNAi pathway might be frequently involved in the suppression of segregation distorters, as RNAi is known to have a major role in regulating the activity of other selfish genetic elements such as viruses and transposable elements [49]. RNAi could mediate specific interactions between individual distorters and suppressors (such as is hypothesized for *Dox* and *Nmy*), or small RNAs might be more generally involved in the establishment or maintenance of meiotic sex chromosome inactivation (MSCI). This makes the observation that X-linked microRNAs seem to escape MSCI [24] particularly intriguing.

Cytological and ultrastructural data reveal that as a result of the activity of *Dox* and *MDox*, Y-bearing sperm do not mature normally, apparently because of a failure in sperm nuclear condensation [51]. The exact molecular mechanism for this failure is unknown, but a strong candidate is chromatin modification during spermiogenesis, such as the idiosyncratic histone replacement, or transportation of nucleoplasm across the nuclear envelope.

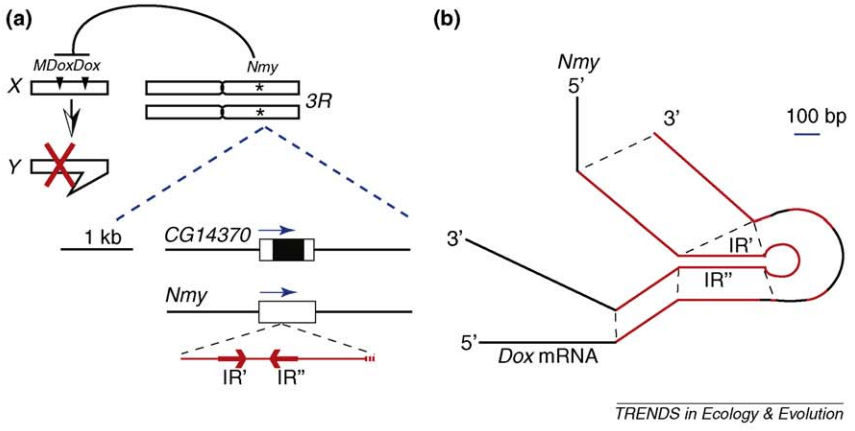

Figure I. The Winters sex-ratio system. **(a)** Components of the Winters sex-ratio system (modified from [50]). *Dox* and *MDox* are X-linked segregation distorters; *Nmy* is their autosomal suppressor. *Dox* originated from *MDox* and together they cause sex-ratio distortion by rendering Y-bearing sperm dysfunctional. The suppressor *Nmy* requires a pair of inverted repeats (IR′ and IR″) that inserted into the gene *CG14370* to function as sex-ratio suppressor. The blue arrow indicates the location and orientation of the *CG14370/Nmy* transcript, and the black box indicates the protein coding region of *CG14370,* which is disrupted by the inverted repeats in *Nmy*. **(b)** Sequence comparison between *Nmy* and *Dox* indicates that *Nmy* originated from *Dox* and subsequent rearrangement created the pair of inverted repeats (IR). The inverted repeats are likely used to generate endogenous siRNAs that target *Dox* for gene silencing. Sequences in red are homologous between *Dox* and *Nmy*.

contributes to both male sterility and sex-ratio distortion in introgression hybrids between *D. simulans* and *D. mauritiana* [56]. The excess of daughters sired by males homozygous for the *D. mauritiana* allele results from the failure of this allele to suppress one or more X-linked segregation distorters found in *D. simulans* (Box 1). *Overdrive* (*Ovd*) is an X-linked locus that causes both male sterility and sex-ratio distortion in F1 hybrids between the USA and Bogotá races of *D. pseduoobscura* [57,58].

Second, if there is co-evolution between sex-ratio distorters and MSCI, divergence between species at loci controlling MSCI could give rise to sterility-causing incompatibilities [27,59,60]. *Prdm9* is a histone trimethyltransferase that causes male sterility in hybrids between *Mus m. musculus* and *Mus m. domesticus*, and is associated with a failure of MSCI during spermatogenesis [61]. This supports the possibility that disruption of MSCI in hybrids might provide a mechanistic basis for sterility.

Third, rapid divergence between components of sex-ratio systems could select for compensatory mutations at other genes that function during meiosis or gametogenesis but which are not themselves directly associated with segregation distortion [62]. Independent cascades of compensatory substitutions in separate species could give rise to hybrid incompatibilities causing sterility. In this scenario, genetic conflict over sex chromosome segregation is a cause of rapid sequence and functional evolution of meiotic genes in the heterogametic sex, leading to a pattern of "faster heterogametic evolution" [55,63]. This contrasts with the idea that Haldane's rule results from sexual selection driving the rapid divergence of male reproductive functions, also known as the "faster male" hypothesis [64], which cannot explain the obedience of ZW taxa to Haldane's rule [63].

These three hypotheses all share an assumption that the loci involved in sterility are evolving rapidly. This assumption derives from the fact that hybrid incompatibilities require functional evolutionary substitutions [65,66], and natural selection fixes beneficial mutations much faster than drift will fix neutral or deleterious ones. This assumption appears to hold for hybrid inviability loci, which have invariably been the target of recurrent positive selection in the history of one or both parental species (*e.g.* [67]). Rapid rates of molecular substitution are often

thought to be associated with co-evolutionary arms races, so genetic conflict is a good candidate for the selective engine driving rapid evolutionary turnover [3], resulting in incompatibilities when formerly allopatric species are reunited [68].

The large X-effect

In addition to Haldane's rule, a second pattern suggests that hybrid sterility is shaped by conflict between genetic factions over progeny sex ratios: the X chromosome contributes disproportionately to sterility in hybrids relative to other chromosomes [69]. This effect results from incompatible interactions between genes located on the X chromosome inherited from one species and the rest of the genome (*i.e.* the autosomes or the Y) inherited from the other species [70,71]. Because sex-ratio distortion is a conflict between the sex chromosomes and the rest of the genome, we expect a large contribution of the sex chromosomes to hybrid sterility, if sex-ratio distortion is ultimately responsible. The data demonstrating the large X-effect can be grouped into two categories: genetic analyses and comparative patterns of hybrid sterility.

Genetic analyses show the large X-effect in interspecific crosses from multiple species of *Drosophila* [72,73], at least one species pair in *Anopheles* [74], and between *Mus Musculus* and *M. domesticus* [75]. Data on the genetic basis for hybrid female sterility in ZW taxa, although sparse, are consistent with a large Z-effect in Lepidoptera [76]. The large X-effect has also been implicated from natural hybrid zones, as X-linked (and Z-linked) loci show steeper clines across hybrid zones than autosomal loci [77,78]. There is no large X-effect for interspecific differences in other male sexual phenotypes, such as genital morphology [73,79], indicating that a greater efficacy of selection in the hemizygous sex cannot be a general explanation for the large X-effect on hybrid sterility [55].

In principle, both Haldane's rule and the large X-effect could result from the exposure of recessive incompatibilities in the heterogametic sex [64]. This possibility has been refuted for hybridizations between the species in the *D. simulans* clade, where fine-scale mapping experiments clearly demonstrate an enrichment of hybrid male sterility factors on the X relative to the autosomes [80–82]. Understanding the large X-effect and Haldane's rule (in these species at least) seems to require understanding why the X accumulates hybrid male sterility loci faster than the autosomes, and faster than either linkage group accumulates hybrid female sterility loci [60]. We believe that genetic conflict over the sex ratio provides the most likely explanation for these observations.

The conflict theory predicts an association between size and degree of heteromorphism of the sex chromosomes and the incidence of hybrid sterility that results from the mutational opportunity for sex-ratio distorters to arise. Two comparative studies in Dipteran taxa indicate that the rate of accumulation of sterility-inducing incompatibilities is indeed positively correlated with the proportion of the genome that is X-linked and does not recombine with the Y. First, species of *Drosophila* with larger X chromosomes evolve hybrid male sterility sooner than those with smaller X chromosomes [83] (in *Drosophila* the entire Y chromosome is heterochromatic and does not recombine). Second, unisexual hybrid male sterility occurs far more frequently among species of *Anopheles* mosquitoes, which have heteromorphic sex chromosomes, than among species of *Aedes* mosquitoes [84], which have a sex-determining locus located in a region of suppressed recombination and divergent chromatin banding on otherwise homomorphic sex chromosomes [85]. In spite of the limited divergence between the *Aedes* X and Y, multiple Y-linked sex-ratio distorters have been inferred in *A. aegypti* [86]. We propose that, owing to the larger non-recombining region on the X and Y, sex-ratio distorters will be found to occur more often in *Anopheles* than in *Aedes*, and that this accounts for the increased proportion of unisexual hybrid sterility in *Anopheles*.

These two comparative patterns result from a larger mutational target in species with a larger non-recombining sex-linked region (such as *Anopheles* vs. *Aedes*), and in species with similarly degenerated Y chromosomes but a greater fraction of X-linkage in the genome (such as different species of *Drosophila*). Curiously, Lepidopteran species evolve hybrid female sterility as rapidly as *Drosophila* species with large X chromosomes (up to 2/5 of the genome), despite the fact that the Lepidopteran Z chromosome is small (~1/30 of the genome) [87]. This suggests that the effect of the Z on hybrid female sterility might be large, as has been observed for other species-diagnostic traits in Lepidoptera [88].

Genetic conflict over the sex ratio in taxa without sex chromosomes

Although we have focused on animals with chromosomal sex determination, patterns of hybrid sterility in other taxa are also broadly consistent with an important role for conflict among genes with different patterns of inheritance over progeny sex ratios [5,89]. Most flowering plants do not have genetic sex determination, and in the species where the genetic basis of hybrid sterility has been studied, hybrid male and female sterility map to the same loci [90] and evolve at similar rates [91], in contrast to the unisexual sterility seen in animals with sex chromosomes. However, cytoplasmic male sterility (CMS), which is common in plant hybrids from interspecific or interpopulation crosses [92], and is often caused by rearrangements in the mitochondrial genome which are detrimental to pollen development [93], provides a notable exception. CMS is likely the result of genetic conflict between the cytoplasm and the nucleus over the sex ratio, as cytoplasmic alleles will be favored if they gain even a slight benefit through female function as a result of aborting male reproductive function [94] (Figure 1). Similarly, in animals, maternally transmitted intracellular endosymbionts are known to modulate the sex ratio in favor of their own transmission by converting genetic males into phenotypic females or simply killing male embryos [89].

The genetic basis of postzygotic isolation in haplodiploid insects such as wasps provides an important test of the conflict theory. Haploid males in these species develop from unfertilized eggs, generate sperm through mitosis,

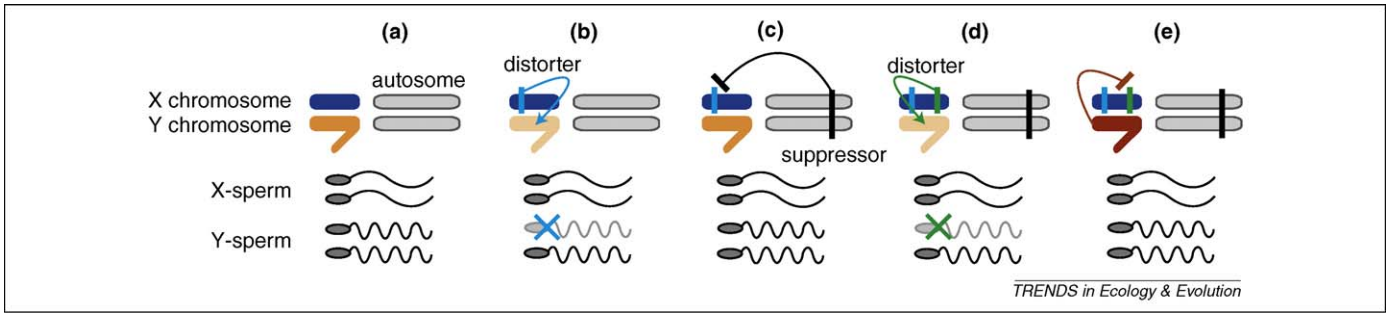

Figure 2. Model for the rapid evolution of the genetic control of sex chromosome transmission driven by recurrent cycles of co-evolution between sex-ratio distorters and suppressors. **(a)** The chromosomes of a male heterogametic species are represented, along with the two types of sperm he produces. **(b)** In the first bout of co-evolution, a sex-ratio distorter on the X chromosome invades the population owing to its ability to incapacitate Y-bearing sperm, and skews the population sex ratio once it comes to high frequency. **(c)** This produces a selective benefit to any autosomal suppressor that arises, as individuals carrying the suppressor will sire more sons, which have a mating advantage, leading to more grandchildren for individuals carrying the suppressor. Any loss of fertility because of the sex-ratio distorter will also favor autosomal suppressors. **(d)** In the second bout, another X-linked distorter arises, producing a selective benefit to any Y chromosome that is resistant the distorter **(e)**. The entire Y chromosome is depicted as harboring resistance since it is not known whether the Y carries discrete suppressing loci, or, owing to gene paucity, resistance results from general properties of the Y, such as the amount of heterochromatin.

and thus cannot evolve segregation distorters. The conflict theory predicts that unlike diploid species such as *Drosophila*, where hybrid male sterility factors accumulate at least five times more rapidly than hybrid lethality factors [81,82], haplodiploid species should not accumulate hybrid male sterility faster than other kinds of hybrid incompatibilities. Indeed, in the few interspecific crosses that have been reported from haplodiploids, there is a striking paucity of hybrid male sterility, and hybrid male sexual dysfunction seems mostly to be behavioral [95].

Future directions: who are the genes?

In this opinion piece, we have argued that the loss of recombination between sex chromosomes facilitates conflicts between selfish genetic parasites and genes controlling the sex ratio, and that these conflicts are likely to have shaped genomic and evolutionary patterns associated with the sex chromosomes. With a few recent exceptions, the evidence for our hypothesis is largely comparative. The most pressing need, therefore, is for studies that will discover the functions of the individual genes associated with these patterns: *de novo* or transposed genes, or loci involved in hybrid sterility. If a significant number of these genes can convincingly be connected to sex-ratio systems, then this will build support for the genetic conflict theory. These studies will be particularly important for resolving the lack of data elucidating a direct mechanistic link connecting genetic conflict and hybrid sterility. The fact that a biased sex ratio is rarely observed in the progeny of non-sterile F1 hybrids was cited in objection to the original proposal of a connection between segregation distortion and Haldane's rule [96] (but there are exceptions [57,97]). Ultimately, proof and understanding of a connection between distortion and sterility awaits the molecular characterization of these loci and their functions, both in their native context, and in generating a sterile hybrid phenotype.

Additionally, it is critical that future experimental work corrects the imbalance that currently exists between our understanding of the genetic control of meiosis and hybrid sterility in male and female heterogametic taxa. The recent characterization of MSCI in birds [22] indicates that this phenomenon, previously only known from XY species [18], is likely to be associated with heteromorphic sex chromosomes in general. Fine-scale genetic analyses that definitively demonstrate a large Z-effect for hybrid female sterility would confirm that Haldane's rule has similar genetic bases in XY and ZW taxa, and the identity and function of hybrid sterility loci would confirm or refute a role for sex-ratio distortion. Ultimately, understanding the full significance of selfish genetic elements for genome evolution will require identifying the mechanisms underlying their selfish behavior, the ways in which genomes have responded to their presence, and the evolutionary divergence of the factions in these conflicts.

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References

1 Hill, W.G. and Robertson, A. (1966) The effect of linkage on limits of artificial selection. *Genet. Res.* 8, 269–294
2 Crow, J.F. (1991) Why is Mendelian segregation so exact? *BioEssays* 13, 305–312
3 Burt, A. and Trivers, R. (2006) *Genes in Conflict: the Biology of Selfish Genetic Elements*, Belknap Press of Harvard University Press
4 Sandler, L. and Novitsky, E. (1957) Meiotic drive as an evolutionary force. *Am. Nat.* 91, 105–110
5 Hurst, L.D. and Pomiankowski, A. (1991) Causes of sex ratio bias may account for unisexual sterility in hybrids: a new explanation of Haldane's rule and related phenomena. *Genetics* 128, 841–858
6 Frank, S.A. (1991) Divergence of meiotic drive-suppression systems as an explanation for sex-biased hybrid sterility and inviability. *Evolution* 45, 262–267
7 Presgraves, D.C. (2008) Drive and sperm: the evolution and genetics of male meiotic drive. In *Sperm Biology: An Evolutionary Perspective* (Birkhead, T.R. *et al.*, eds), pp. 471–522, Academic Press
8 Haig, D. and Grafen, A. (1991) Genetic scrambling as a defence against meiotic drive. *J. Theor. Biol.* 153, 531–558
9 Charlesworth, B. and Hartl, D.L. (1978) Population dynamics of the segregation distorter polymorphism of *Drosophila melanogaster*. *Genetics* 89, 171–192
10 Hartl, D.L. (1974) Genetic dissection of segregation distortion. I. Suicide combinations of SD genes. *Genetics* 76, 477–486
11 Thomson, G.J. and Feldman, M.W. (1974) Population genetics of modifiers of meiotic drive. II Linkage modification in the segregation distortion system. *Theor. Popul. Biol.* 5, 155–162

12 Edwards, A.W.F. (1961) The population genetics of "sex-ratio" in *Drosophila pseudoobscura*. *Heredity* 16, 291–304
13 Edwards, A.W.F. (1998) Natural selection and the sex ratio: Fisher's sources. *Am. Nat.* 151, 564–569
14 Fisher, R.A. (1930) *The Genetical Theory of Natural Selection*, Oxford University Press
15 Hamilton, W.D. (1967) Extraordinary sex ratios. A sex-ratio theory for sex linkage and inbreeding has new implications in cytogenetics and entomology. *Science* 156, 477–488
16 Bull, J.J. and Charnov, E.L. (1988) How fundamental are Fisherian sex ratios? In *Oxford Surveys in Evolutionary Biology* (Harvey, P.H. and Partridge, L., eds), pp. 97–135, Oxford University Press
17 Jaenike, J. (2001) Sex chromosome meiotic drive. *Annu. Rev. Ecol. Syst.* 32, 25–49
18 Solari, A.J. (1993) *Sex Chromosomes and Sex Determination in Vertebrates*, CRC Press, Inc
19 Ohno, S. (1967) *Sex Chromosomes and Sex-linked Genes*, Springer-Verlag
20 Turner, J.M. (2007) Meiotic sex chromosome inactivation. *Development* 134, 1823–1831
21 Kelly, W.G. *et al.* (2002) X-chromosome silencing in the germline of *C. elegans*. *Development* 129, 479–492
22 Schoenmakers, S. *et al.* (2009) Female meiotic sex chromosome inactivation in chicken. *PLoS Genet.* 5, e1000466 doi:10.1371/journal.pgen.1000466 (www.plosgenetics.org)
23 Namekawa, S.H. *et al.* (2006) Postmeiotic sex chromatin in the male germline of mice. *Curr. Biol.* 16, 660–667
24 Song, R. *et al.* (2009) Many X-linked microRNAs escape meiotic sex chromosome inactivation. *Nat. Genet.* 41, 488–493
25 Mueller, J.L. *et al.* (2008) The mouse X chromosome is enriched for multicopy testis genes showing postmeiotic expression. *Nat. Genet.* 40, 794–799
26 Turner, J.M. *et al.* (2006) Pachytene asynapsis drives meiotic sex chromosome inactivation and leads to substantial postmeiotic repression in spermatids. *Dev. Cell* 10, 521–529
27 Lifschytz, E. and Lindsley, D.L. (1972) The role of X-chromosome inactivation during spermatogenesis. *Proc. Natl. Acad. Sci. U.S.A.* 69, 182–186
28 Hense, W. *et al.* (2007) X chromosome inactivation during *Drosophila spermatogenesis*. *PLoS Biol.* 5, e273 doi:10.1371/journal.pbio.0050273 (www.plosbiology.org)
29 Turner, J.M. *et al.* (2004) BRCA1, histone H2AX phosphorylation, and male meiotic sex chromosome inactivation. *Curr. Biol.* 14, 2135–2142
30 Bean, C.J. *et al.* (2004) Meiotic pairing and imprinted X chromatin assembly in *Caenorhabditis elegans*. *Nat. Genet.* 36, 100–105
31 Turner, J.M. *et al.* (2005) Silencing of unsynapsed meiotic chromosomes in the mouse. *Nat. Genet.* 37, 41–47
32 Baarends, W.M. *et al.* (2005) Silencing of unpaired chromatin and histone H2A ubiquitination in mammalian meiosis. *Mol. Cell Biol.* 25, 1041–1053
33 Shiu, P.K. *et al.* (2001) Meiotic silencing by unpaired DNA. *Cell* 107, 905–916
34 Kelly, W.G. and Aramayo, R. (2007) Meiotic silencing and the epigenetics of sex. *Chromosome Res.* 15, 633–651
35 Ellis, P.J. *et al.* (2005) Deletions on mouse Yq lead to upregulation of multiple X- and Y-linked transcripts in spermatids. *Hum. Mol. Genet.* 14, 2705–2715
36 Ranz, J.M. *et al.* (2003) Sex-dependent gene expression and evolution of the *Drosophila* transcriptome. *Science* 300, 1742–1745
37 Parisi, M. *et al.* (2003) Paucity of genes on the *Drosophila* X chromosome showing male-biased expression. *Science* 299, 697–700
38 Reinke, V. *et al.* (2000) A global profile of germline gene expression in C. elegans. *Mol. Cell* 6, 605–616
39 Kamath, R.S. *et al.* (2003) Systematic functional analysis of the *Caenorhabditis elegans* genome using RNAi. *Nature* 421, 231–237
40 Hahn, M.W. and Lanzaro, G.C. (2005) Female-biased gene expression in the malaria mosquito *Anopheles gambiae*. *Curr. Biol.* 15, R192–193
41 Ellegren, H. *et al.* (2007) Faced with inequality: chicken do not have a general dosage compensation of sex-linked genes. *BMC Biol.* 5, 40 doi:10.1186/1741-7007-5-40 (http://www.biomedcentral.com/1741-7007/5/40)
42 Emerson, J.J. *et al.* (2004) Extensive gene traffic on the mammalian X chromosome. *Science* 303, 537–540
43 Marques, A.C. *et al.* (2005) Emergence of young human genes after a burst of retroposition in primates. *PLoS Biol.* 3, e357 doi:10.1371/journal.pbio.0030357 (www.plosbiology.org)
44 Bai, Y. *et al.* (2007) Comparative genomics reveals a constant rate of origination and convergent acquisition of functional retrogenes in *Drosophila*. *Genome Biol.* 8, R11 doi:10.1186/gb-2007-8-1-r11 (http://genomebiology.com)
45 Betran, E. *et al.* (2002) Retroposed new genes out of the X in *Drosophila*. *Genome Res.* 12, 1854–1859
46 Begun, D.J. *et al.* (2007) Evidence for de novo evolution of testis-expressed genes in the *Drosophila yakuba/Drosophila erecta* clade. *Genetics* 176, 1131–1137
47 Levine, M.T. *et al.* (2006) Novel genes derived from noncoding DNA in *Drosophila melanogaster* are frequently X-linked and exhibit testis-biased expression. *Proc. Natl. Acad. Sci. U.S.A.* 103, 9935–9939
48 Chen, S.T. *et al.* (2007) Evolution of hydra, a recently evolved testisexpressed gene with nine alternative first exons in *Drosophila melanogaster*. *PLoS Genet.* 3, e107 doi:10.1371/journal.pgen.0030107 (www.plosgenetics.org)
49 Aravin, A.A. *et al.* (2007) The Piwi-piRNA pathway provides an adaptive defense in the transposon arms race. *Science* 318, 761–764
50 Tao, Y. *et al.* (2007) A sex-ratio meiotic drive system in *Drosophila simulans*. II: an X-linked distorter. *PLoS Biol.* 5, e293 doi:10.1371/journal.pbio.0050293 (www.plosbiology.org)
51 Tao, Y. *et al.* (2007) A sex-ratio meiotic drive system in *Drosophila simulans*. I: an autosomal suppressor. *PLoS Biol.* 5, e292 doi:10.1371/journal.pbio.0050292 (www.plosbiology.org)
52 Wu, C-I. and Xu, E.Y. (2003) Sexual antagonism and X inactivation - the SAXI hypothesis. *Trends Genet.* 19, 243–247
53 Haldane, J.B.S. (1922) Sex ratio and unisexual sterility in hybrid animals. *J. Genet.* 12, 101–109
54 Orr, H.A. *et al.* (2007) Speciation in *Drosophila*: from phenotypes to molecules. *J. Hered.* 98, 103–110
55 Tao, Y. and Hartl, D.L. (2003) Genetic dissection of hybrid incompatibilities between *Drosophila simulans* and *Drosophila mauritiana*. III. Heterogenous accumulation of hybrid incompatibilities, degree of dominance, and implications for Haldane's Rule. *Evolution* 57, 2580–2598
56 Tao, Y. *et al.* (2001) Sex-ratio segregation distortion associated with reproductive isolation in *Drosophila*. *Proc. Natl. Acad. Sci. U.S.A.* 98, 13183–13188
57 Orr, H.A. and Irving, S. (2005) Segregation distortion in hybrids between the Bogota and USA subspecies of *Drosophila pseudoobscura*. *Genetics* 169, 671–682
58 Phadnis, N. and Orr, H.A. (2009) A single gene causes both male sterility and segregation distortion in *Drosophila* hybrids. *Science* 323, 376–379
59 Jablonka, E. and Lamb, M.J. (1991) Sex chromosomes and speciation. *Proc. Biol. Sci.* 243, 203–208
60 Presgraves, D.C. (2008) Sex chromosomes and speciation in *Drosophila*. *Trends Genet.* 24, 336–343
61 Mihola, O. *et al.* (2009) A mouse speciation gene encodes a meiotic histone H3 methyltransferase. *Science* 323, 373–375
62 Frank, S.A. (1991) Haldane rule - a defense of the meiotic drive theory. *Evolution* 45, 1714–1717
63 Laurie, C.C. (1997) The weaker sex is heterogametic: 75 years of Haldane's Rule. *Genetics* 147, 937–951
64 Wu, C-I. and Davis, A.W. (1993) Evolution of post-mating reproductive isolation: the composite nature of Haldane's rule and its genetic bases. *Am. Nat.* 142, 187–212
65 Muller, H.J. (1942) Isolating mechanisms, evolution, and temperature. *Biol. Symp.* 6, 71–125
66 Dobzhansky, T. (1937) *Genetics and the Origin of Species*, Columbia University Press
67 Presgraves, D.C. *et al.* (2003) Adaptive evolution drives divergence of a hybrid inviability gene between two species of *Drosophila*. *Nature* 423, 715–719
68 Presgraves, D.C. (2007) Does genetic conflict drive rapid molecular evolution of nuclear transport genes in Drosophila? *BioEssays* 29, 386–391
69 Coyne, J.A. and Orr, H.A. (2004) *Speciation*, Sinauer Associates, Inc
70 Coyne, J.A. (1985) The genetic basis of Haldane's rule. *Nature* 314, 736–738

71 Johnson, N.A. *et al.* (1992) A test of reciprocal X–Y interactions as a cause of hybrid sterility in *Drosophila*. *Nature* 358, 751–753
72 Coyne, J.A. and Orr, H.A. (1989) Patterns of speciation in *Drosophila*. *Evolution* 43, 362–381
73 Charlesworth, B. *et al.* (1987) The relative rates of evolution of the sex chromosomes and autosomes. *Am. Nat.* 130, 113–146
74 Slotman, M. *et al.* (2004) The genetics of inviability and male sterility in hybrids between *Anopheles gambiae* and *An. arabiensis*. *Genetics* 167, 275–287
75 Good, J.M. *et al.* (2008) A complex genetic basis to X-linked hybrid male sterility between two species of house mice. *Genetics* 179, 2213–2228
76 Jiggins, C.D. *et al.* (2001) Sex-linked hybrid sterility in a butterfly. *Evolution* 55, 1631–1638
77 Macholan, M. *et al.* (2007) Genetic analysis of autosomal and X-linked markers across a mouse hybrid zone. *Evolution* 61, 746–771
78 Sætre, G-P. *et al.* (2003) Sex chromosome evolution and speciation in *Ficedula* flycatchers. *Proc. Biol. Sci.* 270, 53–59
79 Zeng, Z.B. *et al.* (2000) Genetic architecture of a morphological shape difference between two *Drosophila* species. *Genetics* 154, 299–310
80 True, J.R. *et al.* (1996) A genome-wide survey of hybrid incompatibility factors by the introgression of marked segments of *Drosophila mauritiana* chromosomes into *Drosophila simulans*. *Genetics* 142, 819–837
81 Tao, Y. *et al.* (2003) Genetic dissection of hybrid incompatabilities between *Drosophila simulans* and *D. mauritiana*. I. Differential accumulation of hybrid male sterility effects on the X and autosomes. *Genetics* 164, 1383–1397
82 Masly, J.P. and Presgraves, D.C. (2007) High-resolution genome-wide dissection of the two rules of speciation in *Drosophila*. *PLoS Biol.* 5, e243 doi:10.1371/journal.pbio.0050243 (www.plosbiology.org)
83 Turelli, M. and Begun, D.J. (1997) Haldane's rule and X-chromosome size in Drosophila. *Genetics* 147, 1799–1815
84 Presgraves, D.C. and Orr, H.A. (1998) Haldane's rule in taxa lacking a hemizygous X. *Science* 282, 952–954
85 Newton, M.E. *et al.* (1974) X and Y chromosomes of *Aedes aegypti* (L.) distinguished by Giemsa C-banding. *Chromosoma* 49, 41–49
86 Wood, R.J. and Newton, M.E. (1991) Sex-ratio distortion caused by meiotic drive in mosquitoes. *Am. Nat.* 137, 379–391
87 Presgraves, D.C. (2002) Patterns of postzygotic isolation in Lepidoptera. *Evolution* 56, 1168–1183
88 Prowell, D.P. (1998) Sex linkage and speciation in Lepidoptera. In *Endless Forms: Species and Speciation* (Howard, D.J. and Berlocher, S.H., eds), Oxford University Press
89 Werren, J.H. and Beukeboom, L.W. (1998) Sex determination, sex ratios, and genetic conflict. *Annu. Rev. Ecol. Syst.* 29, 233–261
90 Sweigart, A.L. *et al.* (2006) A simple genetic incompatibility causes hybrid male sterility in mimulus. *Genetics* 172, 2465–2479
91 Moyle, L.C. and Graham, E.B. (2005) Genetics of hybrid incompatibility between *Lycopersicon esculentum* and *L. hirsutum*. *Genetics* 169, 355–373
92 Budar, F. *et al.* (2003) The nucleo-mitochondrial conflict in cytoplasmic male sterilities revisited. *Genetica* 117, 3–16
93 Hanson, M.R. and Bentolila, S. (2004) Interactions of mitochondrial and nuclear genes that affect male gametophyte development. *Plant Cell* 16 Suppl, S154–169
94 Lewis, D.L. (1941) Male sterility in natural populations of hermaphrodite plants. The equilibrium between females and hermaphrodites to be expected with different types of inheritance. *New Phytol.* 40, 56–63
95 Koevoets, T. and Beukeboom, L.W. (2009) Genetics of postzygotic isolation and Haldane's rule in haplodiploids. *Heredity* 102, 16–23
96 Coyne, J.A. and Orr, H.A. (1993) Further evidence against meiotic-drive models of hybrid sterility. *Evolution* 47, 685–687
97 Yang, Y-Y. *et al.* (2004) Sex ratio distortion in hybrids of *Drosophila albomicans* and *D. nasuta*. *Zool. Stud.* 43, 622–628
98 Montchamp-Moreau, C. (2006) Sex-ratio meiotic drive in *Drosophila simulans*: cellular mechanism, candidate genes and evolution. *Biochem. Soc. Trans.* 34, 562–565
99 Derome, N. *et al.* (2008) Selective sweeps in a 2-locus model for sex-ratio meiotic drive in Drosophila simulans. *Mol. Biol. Evol.* 25, 409–416
100 Dermitzakis, E.T. *et al.* (2000) Non-Mendelian segregation of sex chromosomes in heterospecific *Drosophila* males. *Genetics* 154, 687–694