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Heterochromatin and genetic conflict

Colin D. Meiklejohn
University of Nebraska - Lincoln, cmeiklejohn2@unl.edu

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Meiosis is a dangerous business. The two alleles in diploid organisms share an evolutionary interest in the survival and reproduction of their host individual; however, as soon as they segregate into haploid gametes, these alleles find themselves competing for transmission to the next generation (1). In males, the development of all four meiotic products into functional gametes fosters the evolution of alleles that disrupt the development or viability of gametes carrying the alternate allele. Systems that distort Mendelian segregation (hence, segregation distorters) typically comprise at least two loci: a *trans*-acting drive locus (such as a gene that encodes a poison) that targets alleles that are sensitive to the poison at a second, linked locus (2). A major impediment to the evolution of segregation distorters is the requirement that the poisonous allele be tightly linked to resistant alleles at the target locus; otherwise, distorters will commit suicide when paired with a sensitive allele (3). As a result, segregation distorters on autosomes are invariably associated with inversions that suppress recombination between the distorter and target loci. In contrast, heteromorphic sex chromosomes, where the Y chromosome is highly degenerated, can facilitate the evolution of segregation distorters because the X and Y frequently share little homologous sequence and do not recombine along most or all of their length. Thus, sex-chromosome segregation distorters that distort the sex ratio of the progeny of males that carry them (hence, sex-ratio distorters) are predicted to evolve frequently (4). The presence of sex-ratio distorters in populations selects for resistant Y chromosomes and autosomal suppressors that restore male fertility and a balanced sex ratio, and may lead to either balanced polymorphisms or open-ended arms races between loci that function in the male germ line (5). A recent study in PNAS has identified a gene required for sex-ratio distortion in *Drosophila simulans* (6), providing novel insight into the genetic and molecular mechanisms used by these selfish elements and their effects on genome evolution and species formation.

The recurrent evolution of sex-ratio distorters and suppressors may contribute to otherwise puzzling observations regarding the genetics and evolution of spermatogenesis in animals with XY sex chromosomes. First, at least 10% of protein-coding genes in the *Drosophila melanogaster* genome are expressed solely in the male germ line, and ~two-thirds of all *D. melanogaster* genes whose expression is restricted to a single tissue are expressed specifically in testes. In contrast, less than 1% of the *D. melanogaster* genome is specified for function during oogenesis (7). Thus, in *Drosophila*, an extraordinarily large fraction of the genome is dedicated to spermatogenesis. Second, in both Diptera and mammals, testis-specific genes show exceptionally high rates of regulatory and protein sequence evolution (8, 9), comprise the majority of new lineage- or species-specific genes (10), and these new genes are frequently X-linked (11, 12). Thus, the large component of the genome dedicated to spermatogenesis is also a major source of rapid

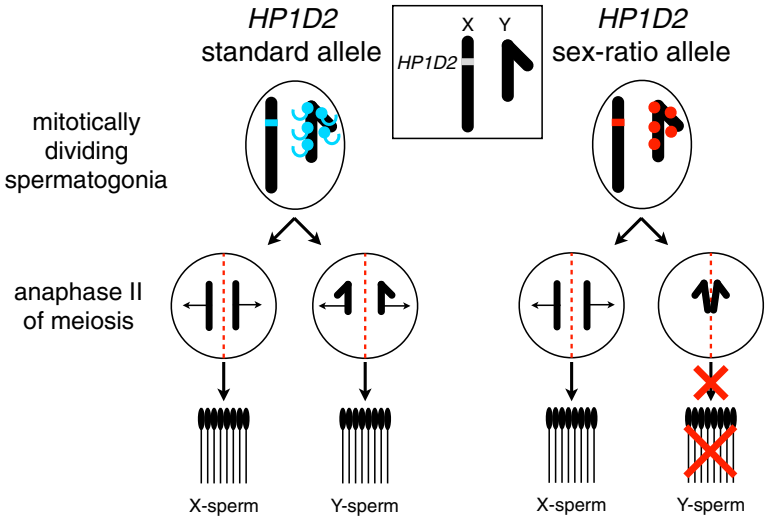

Fig. 1. A model for *HP1D2*'s role in segregation distortion. The X-linked *HP1D2* gene is expressed before meiosis in spermatogonia, where the protein localizes to the Y chromosome. The sex-ratio allele of *HP1D2* produces a truncated protein that lacks the chromo-shadow domain present in the standard allele. In males carrying X chromosomes with the sex-ratio allele of *HP1D2*, sister Y chromatids fail to properly disjoin during the second meiotic division, leading to inviable Y-bearing sperm and a female-biased sex ratio among the male's progeny.

[a]School of Biological Sciences, University of Nebraska–Lincoln, Lincoln, NE 68588

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See companion article on page 4110.

[1]Email: cmeiklejohn2@unl.edu.

evolution and genetic novelty, especially on the X chromosome. Third, in multiple lineages, epigenetic mechanisms have evolved that recognize and silence the X during male meiosis (13). These mechanisms may have evolved to combat sex-ratio distorters and the fertility and skewed sex-ratio costs they incur on their host genome (14). Finally, in animals with XY sex chromosomes, the earliest hybrid incompatibilities to accumulate between species cause male sterility (15), because of an enrichment of sterility factors on the X chromosome (16, 17). Thus, the genetic architecture, molecular evolution, epigenetic regulation, and accumulation of interspecific incompatibilities among genes that function in spermatogenesis may all be shaped by recurrent evolution of sex-ratio distorters and suppressors (5, 14, 18).

D. simulans is the premiere genetic model system for studies of sex-ratio distortion, as a result of the presence of at least three independent sex-ratio systems (19) and a lack of inversions that restrict genetic analysis in other species. Studies of the Paris sex-ratio system (Paris SR) have revealed the spatial, temporal, and selective dynamics acting on the Paris X-chromosome distorter and its Y-linked and autosomal suppressors (20, 21). The Paris SR comprises two X-linked loci approximately 100 kb apart that are both required for distortion (22). One locus is a 37-kb tandem duplication of six genes whose mechanistic role in segregation distortion may be related to the dosage of one or more duplicated genes (23). Now Helleu et al. (6) have taken a significant step forward in our understanding of the Paris SR by identifying the second distorter locus. Using forward genetic mapping, Helleu et al. (6) localized the second distorter locus to a 4.5-kb interval that includes *HP1D2*, a member of the *HP1* heterochromatin protein gene family. Like other *HP1* relatives, *HP1D2* is predicted to encode a protein with chromo and chromo-shadow domains that mediate interactions with chromatin and other proteins, respectively (24). Sequencing the parental chromosomes used for the genetic mapping revealed that, relative to the standard allele of *HP1D2* ($HP1D2^{ST}$), the sex-ratio allele ($HP1D2^{SR}$) harbors two deletions: one is upstream of *HP1D2* and the other removes 371 bp of coding sequence, including the chromo-shadow domain. Functional genetic experiments confirmed that *HP1D2* is indeed the second Paris SR locus and suggest that both reduced expression and loss of the chromo-shadow domain each independently contribute to sex-ratio distortion by $HP1D2^{SR}$ (6). The *HP1* gene family is rapidly evolving in *Drosophila*, with frequent gene losses and gains of lineage-specific paralogs expressed solely in the male germ line (24). *HP1D2* exemplifies this pattern; this gene is less than 25 million y old and has been lost at least twice since its origin, including in *D. melanogaster*.

The developmental etiology of the Paris SR first manifests as a failure of Y chromatids to separate at meiosis II (25), suggesting roles for chromatin structure and chromosome segregation in distortion. Cytological observations indicate that both the sex-ratio and standard alleles of *HP1D2* are expressed in spermatogonia before meiosis, and that both HP1D2 protein variants colocalize with the Y chromosome in these cells (6). Thus, $HP1D2^{ST}$ is likely involved in proper Y-chromosome segregation, and the mechanism of $HP1D2^{SR}$ distortion does not involve gross mislocalization of the protein (Fig. 1). At this point, it is unclear whether $HP1D2^{SR}$ behaves as a loss-of-function allele.

The identification and characterization of *HP1D2* enables future experiments to determine the molecular mechanism of distortion, and suggests more detailed hypotheses regarding how sex-ratio distorters could contribute to the evolutionary dynamism of spermatogenesis. First, the fact that HP1D2 protein localizes to the Y chromosome suggests that the interaction between this distorter and its target locus could be direct. A key question is how *HP1D2* recognizes the Y. In populations of *D. simulans* with high frequencies of Paris SR X chromosomes, Y chromosomes show resistance to distortion (26). Can Y-chromosome resistance evolve through loss of Y-linked sequences targeted by *HP1D2*? Second, *HP1D2* highlights a central role for chromatin and chromatin-binding proteins in segregation distortion.

The genetic dissection of the Paris SR extends our understanding of the mechanisms and evolution of selfish genes, and thus yields insight into important aspects of both basic and translational biology.

Failure of Y-chromatids to properly segregate at meiosis II is also seen in the *Drosophila pseudoobscura* SR system (27); in the *D. simulans* Winters sex-ratio system chromatin fails to condense in the head of developing Y-bearing spermatids (19). In this context, it is notable that the *D. melanogaster* Y chromosome has acquired a new gene predicted to organize heterochromatin (28). Perhaps cycles of segregation distortion and resistance favor both X- and Y-chromosome acquisition of such genes, but the reduced efficacy of selection on the Y leads to rapid gene losses from this chromosome.

More generally, to what extent can genetic conflict over segregation of the sex chromosomes explain the evolutionary history of the *HP1* gene family, and the rapid evolution and abundance of the testis-specific complement of the genome? Answering this question will in part require discovering which details of the *HP1D2* story are general vs. idiosyncratic. For example, what fraction of newly evolved X-linked testis-specific genes code for RNAs or proteins that localize to the Y chromosome? It will be instructive to discover whether HP1D2 protein localizes to the Y in species other than *D. simulans*. If Y-chromatid segregation and Y-bearing sperm development often relies on X-linked genes that can become segregation distorters via deletion or loss-of-function alleles, then the mutation rate to distorters may be quite high.

Selfish genetic elements are pervasive in genomes, and their machinations have shaped genome architecture, regulatory networks, and have driven the evolution of elaborate host immune responses (1). Selfish genes have also attracted attention as a potential mechanism for controlling pest and insect vector populations (29). The genetic dissection of the Paris SR (6) extends our understanding of the mechanisms and evolution of selfish genes, and thus yields insight into important aspects of both basic and translational biology.

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