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DIVERGENCE OF MEIOTIC DRIVE-SUPPRESSION SYSTEMS AS AN EXPLANATION FOR SEX-BIASED HYBRID STERILITY AND INVIABILITY

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Abstract.—Two empirical generalizations about speciation remain unexplained: the tendency of the heterogametic sex to be sterile or inviable in F_1 hybrids (Haldane's rule), and the tendency of the X chromosome to harbor the genetic elements that cause this sex bias in hybrid fitness. I suggest that divergence of meiotic drive systems on the sex chromosomes can explain these observations. The theory follows from two simple facts. First, sex chromosomes are particularly susceptible to the forces of meiotic drive. Second, divergence of meiotic drive systems can cause hybrid sterility and inviability. The main objection to the theory is that meiotic drive is apparently rare, whereas the observed pattern of hybrid fitness is widespread. I answer this objection by showing that divergence of meiotic drive systems can explain the two generalizations even if large departures from Mendelian segregation are rarely observed.

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In this paper I suggest that the observed sex bias of sterility and inviability in hybrids can be explained by the divergence of meiotic drive systems. The observations are that, among the two sexes of F_1 hybrid offspring, the heterogametic sex is much more likely to be absent, inviable, or infertile (Haldane, 1922). This empirical law, known as Haldane's rule, is remarkably consistent among different groups of insects and vertebrates for both male and female heterogamety (Coyne and Orr, 1989).

The location of genes affecting sex-biased loss of fertility or viability has been determined in a few cases. The main effects are usually spread across several locations on the X chromosome, as summarized in the reviews presented by Charlesworth et al. (1987) and Coyne and Orr (1989).

At present, no plausible theory can cover the known facts about sex bias and location of genetic effects (Coyne and Orr, 1989). I propose that divergence of meiotic drive systems can explain the observations.

The main argument follows from two facts. First, sex chromosomes are particularly susceptible to rapid evolution of meiotic drive systems. Second, divergence of meiotic drive systems can cause hybrid sterility and inviability. These facts suggest two mechanisms, discussed later, by which meiotic drive can cause sex-biased depression of hybrid fitness and a concentration of genetic effects on the sex chromosomes.

After developing the theory, I mention relevant circumstantial evidence, and I suggest experimental approaches for further study. Finally, I answer the objection that meiotic drive is rarely observed but Haldane's rule is widespread, and I show why sex chromosome drive is rarely observed among hybrids even though drive systems may diverge rapidly.

Note.—The idea that sex chromosome drive may explain Haldane's rule has been put forward independently by Hurst and Pomiankowski (1991).

SEX CHROMOSOME DRIVE

This paper addresses two observations: a bias in hybrid sterility and inviability toward the heterogametic sex, and a concentration of genes causing this bias on the homogametic sex chromosome. The words "homogametic" and "heterogametic" are derived from the following conventions. The sexes can be labeled as homogametic, XX, and heterogametic, XY, based on the homogametic (X) and heterogametic (Y) sex chromosomes. The heterogametic sex may be male, as in mammals and fruit flies, or female, as in birds and butterflies (White, 1973; Bull, 1983). The heterogametic sex chromosome Y is sometimes absent, in which case the heterogametic sex is XO. In this paper, Y will be used for the heterogametic sex chromosome whether it is present or absent, unless otherwise stated.

Drive between X and Y has two unique properties that are central to the main arguments of this paper.

1) *The X is a cooperative unit against the Y; the Y is a cooperative unit against the X.* Suppose that drive depends on an interaction between two loci (Zimmering et al., 1970). A pair of alleles at different X loci that increases the gametic success of the X at the expense of the Y will spread rapidly. Similarly, an allele on the X that causes a segregation advantage for the X by interacting with an allele on the Y also spreads rapidly. Alleles on the Y that give a segregation advantage against the X spread in an analogous way. (For more on the theory of sex chromosome drive, see Gershenson, 1928; Sturtevant and Dobzhansky, 1936; Edwards, 1961; Hamilton, 1967; Thomson and Feldman, 1975).

These simple conditions for the spread of meiotic drive alleles depend on the fact that the X (usually) does not recombine with the Y (Thomson and Feldman, 1975; Dawkins, 1982; Trivers, 1988). The case of autosomal drive illustrates more clearly the importance of recombination.

Suppose that, on an autosome, there is a distorter allele. This allele can bias segregation by producing a product that destroys a chromosome carrying a responder allele. The responder and distorter are at distinct loci. When the distorter and responder are on competing homologs, the distorter gains a large segregation advantage. When the distorter and responder loci recombine, then the distorter allele will cause its own chromosome to self-destruct by attacking the susceptible responder allele. Thus, a distorter can spread only when closely linked to a cooperating immune allele at the responder locus (Prout et al., 1973; Hartl, 1975; Liberman, 1976; Thomson and Feldman, 1976; Charlesworth and Hartl, 1978; Lessard, 1985).

In summary, the entire X and Y are constantly involved in a battle over segregation. By contrast, only tightly linked regions of autosomes are in conflict with their homologs.

2) *Sex-ratio biases caused by X-Y drive reduce the fitness of autosomes and favor rapid evolution of suppressors.* Drive between X and Y causes a distortion of the sex ratio. Suppressors anywhere on the autosomes are increasingly favored as the sex-ratio bias increases (Hamilton, 1967; Lyttle, 1977, 1979) because of the frequency dependent aspect of sex-ratio selection (Fisher, 1958). Sex-ratio bias is a potent selective force. In addition, drive systems often carry deleterious alleles, adding a second force that favors the evolution of unlinked suppressors (Prout et al., 1973).

Mechanisms of Sterility, Inviability, and Sex-Biased Expression

In the previous section I suggested that X-Y drive systems may evolve rapidly. In this section I describe two mechanisms by which divergence of X-Y drive systems can lead to sex-biased depression of hybrid fitness, with a concentration of genetic effects on the sex chromosomes.

1) *There is an X-Y interaction over fertility or viability that involves diverged genes in meiotic drive systems.* Drive of X against Y may depend on X distorters and Y suppressors. For example, Figure 1a shows an ancestral X-Y pair with several X distorters (D_i) that are fully suppressed by Y suppressors (S_i), so that no drive occurs in the ancestral population. In the derived population, the loci carrying D_3 and S_3 have coevolved through a series of variants and alternating bouts of drive and suppression. The new alleles are labeled D_3* and S_3* (Fig. 1b).

In hybrids of the ancestral and diverged populations, interaction between D_3 and S_3* may yield fertile individuals, X-Y drive, sterility through meiotic aberrations, or inviability through mitotic aberrations. Any of these four outcomes may occur in the reciprocal hybrid, D_3*/S_3. There is no reason to expect equivalent phenotypes of the reciprocal hybrids.

No direct evidence supports divergence of X-Y drive as a cause of hybrid sterility or inviability. Stalker (1961) has observed divergence of X distorters and Y suppressors between two populations of *Drosophila paramelancia.* Hartl (1973) has reported crosses of an autosomal drive system in *D. melanogaster* that suggest sterility resulted from an interaction between diverged drive loci. Finally, Coyne (1985) has shown that

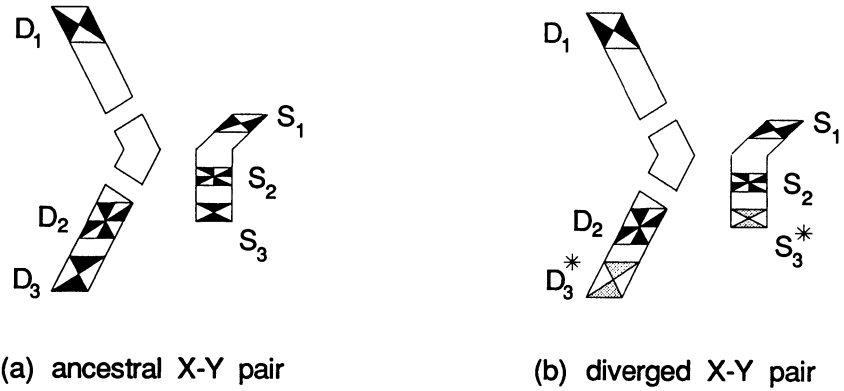

FIG. 1. Ancestral and derived X-Y chromosome sets with distorter (D) and suppressor (S) loci labeled. (a) The three suppressors on the Y are immune to the effects of the distorters on the X, therefore no drive occurs in this population. (b) In the diverged population, a new distorter replacing D_3 caused drive against Y's with S_3, setting off a bout of coevolution between variants at these two loci. Presently, the D locus carries D_3* and the S locus carries the suppressor S_3*, which successfully prevents drive. Upon hybridization, hybrid incompatibilities or drive may occur between D_3/S_3* or between D_3*/S_3.

interactions between heterospecific X and Y cause hybrid sterility in the *D. melanogaster* subgroup.

2) *There is an X-autosome interaction over X-Y or X-O drive leading to reduced hybrid fitness.* Drive of the X may be suppressed by autosomal modifiers (references below). For example, Figure 2a shows an ancestral set of one X chromosome and two nonhomologous autosomes. Each distorter (D_i) is suppressed by two suppressor loci (S_i). For example, D_1 is suppressed by S_1 and S_4. In the derived population, the loci carrying D_1, S_1, and S_4 have coevolved through a series of distorter and suppressor variants, labelled D_1*, S_1*, and S_4* (Fig. 2b).

The S and D loci affect the delicate meiotic process. Hybrid incompatibility at these loci may cause sterility or drive. Incompatibilities may also disrupt mitosis to the extent that mitosis and meiosis share common mechanisms.

CIRCUMSTANTIAL EVIDENCE AND FURTHER TESTS

Hybrid Sterility Caused by Divergence of Drive Loci

The autosomal *Segregation Distorter* complex (*SD*) of *Drosophila melanogaster* can cause meiotic drive in males, but has no effect on females. Hartl (1973) studied

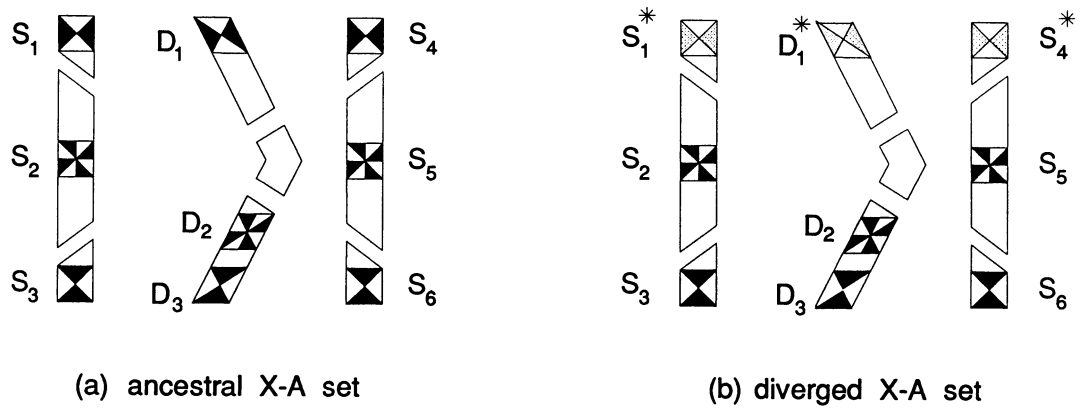

FIG. 2. Ancestral and derived X-autosome sets with distorter (D) and suppressor (S) loci labeled. The two autosomes are distinct chromosomes, not homologs. (a) The ancestral state. (b) The derived condition, following a sequence similar to that described in Figure 1b.

crosses between 11 *SD* chromosomes extracted from different populations, where a genotype is SD_i/SD_j for $i, j = 1, \ldots, 11$. Homozygotes SD_i/SD_i are nearly always lethal in both sexes, probably because of homozygosity for lethal recessives. Of the remaining 55 combinations, all females were fertile; among males, 36 were sterile or nearly sterile, 15 were partially fertile, and 4 were lethal. Because the only relevant difference between the sexes is the sex-limited expression of drive, the results implicate the divergence of the drive system as the cause of sterility and inviability in males.

The mechanism of *SD* drive depends on an interaction between distorter and responder loci on the second chromosome (Zimmering et al., 1970). From the perspective of the present theory about hybrid sterility, it is easy to imagine that, in either *SD* or in other instances of meiotic drive complexes, isolated populations may harbor a spectrum of alleles at the responder locus that are more sensitive to distorter alleles of other populations than to distorter alleles from their own population. Hybridization of diverged populations would therefore be more likely to cause sterility rather than segregation distortion. Divergence may have occurred even when no segregation distortion is observed within each population, because responders are insensitive to their local distorters.

Hartl's study suggests that divergence of meiotic drive systems may be fairly rapid and that hybrids of diverged populations are more likely to exhibit sterility or inviability rather than drive. The details of *SD* divergence are only indirectly related to the present thesis, since *SD* is autosomal. But any results that suggest meiotic drive systems are prone to complex interactions, and widespread polymorphism are favorable to the theory. Along these lines, Hiraizumi's (1990) recent study of *SD* is particularly intriguing. His results suggest that previous models of *SD* have oversimplified the amount of polymorphism and the complex interactions that occur among distorter and responder loci. This is reminiscent of the increasing polymorphism and complexity that is inevitably discovered with further study of any system of cytoplasmic male sterility (Frank, 1989). Cytoplasmic male sterility occurs independently in many families of plants and is currently the best understood case of genomic conflict.

Rapid Evolution of Suppressors of Sex Chromosome Drive

Lyttle (1979) obtained a Y chromosome in *D. melanogaster* that had the *SD* complex from chromosome two attached by translocation. This Y exhibited meiotic drive and was susceptible to suppressors scattered across the genome in the same manner as the normal *SD* complex. Lyttle introduced this *Y* into a cage population that lacked suppressors and documented the accumulation of numerous suppressors each of small effect. This demonstrates the rapid evolution of interactions between autosomes and sex chromosomes over X-Y drive. The rapid evolution of suppressors also shows that evolutionary change in drive systems does not necessarily lead to observable drive within a species.

In wild populations, suppressors of drive have been found scattered throughout the genome (*D. melanogaster,* Hartl, 1970; Hiraizumi and Thomas, 1984; *Mus domesticus,* Gummere et al., 1986), although Policansky and Dempsey (1978) failed to find suppressors of X chromosome drive in *D. pseudoobscura.* Spatial variation in drive-suppressor systems has been documented in *Drosophila* by Stalker (1961) and Hartl (1970), and summarized by Hartl and Hiraizumi (1976). Silver (1985) also discussed spatial variation in the meiotic drive *t* complex of mice.

Wu and Beckenbach (1983) studied the evolution of X chromosome drive and of male hybrid sterility in *Drosophila pseudoobscura* and *D. persimilis.* Their results suggest that significant divergence of drive loci and suppressors has occurred between recently derived X's. Their data do not, however, provide a clear relationship between divergence of drive loci and the observed male sterility in hybrids. Orr (1987, 1989) studied the same hybridizations as Wu and Beckenbach and found that the loci with the largest effect on male sterility map to the arm of the X opposite from the known drive loci. Orr also found loci with sterility effects near the main drive complex. According to the present theory, the distant X

locus found by Orr may have diverged because it was a distorter that eventually became suppressed by unlinked loci.

Test of the Theory

Lyttle's (1979) design could be extended to perform many interesting experiments. For example, several cages could be allowed to evolve independently, each with similar meiotic drive complexes attached either to an X or Y chromosome. After several generations, flies from the different cages could be "hybridized." If the meiotic drive-suppression systems have diverged, then hybrid crosses may exhibit lower male fertility than within-cage crosses.

Discussion

The theory presented here provides a plausible explanation for Haldane's rule and the underlying genetic causes. Two objections are likely to be raised:

1) *Haldane's rule is widespread, but meiotic drive is rare.* Lyttle's (1979) experiments show that suppressors may accumulate rapidly upon introduction of novel distorters. Thus rapid divergence may occur, even though observable drive is rare.

2) *Crosses between species do not show the high levels of sex chromosome drive expected if divergence of drive systems is common.* The basis of my theory is that hybridizations between diverged populations lead to sterility or inviability rather than drive (e.g., Hartl, 1973). Since X-Y drive is a sex-limited trait with genes on the sex chromosomes, Haldane's rule and the observed location of genetic effects follow immediately from diverged X-Y drive systems.

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