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FURTHER EVIDENCE AGAINST MEIOTIC-DRIVE MODELS OF HYBRID STERILITY

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One of the most striking generalizations in evolutionary biology is "Haldane's rule," the observation that if only one sex is sterile or inviable in the offspring of a cross between two species, it is nearly always the heterogametic sex (Haldane, 1922). This rule applies regardless of which sex is heterogametic: in birds and butterflies, for example, it is the heterogametic females that are sterile or inviable (Haldane, 1922; Coyne, 1992). The dependence of Haldane's rule on heterogamety and not on gender implies that the sex chromosomes play an important role in postzygotic reproductive isolation. This, in turn, is supported by genetic studies in several groups, which have repeatedly shown that the sex chromosomes have very large effects on hybrid sterility and inviability (Coyne and Orr, 1989). Coyne and Orr (1989) and Coyne (1992) review the many explanations of this rule. No explanation, however, is satisfactory, as they all require unproved assumptions or are contradicted by data (Coyne, 1992).

One recently proposed evolutionary explanation posits that both Haldane's rule and large sex-chromosome effects results from genes that cause meiotic drive (Frank, 1991*a*; Hurst and Pomiankowski, 1991). According to this view, mutations causing preferential segregation of a chromosome may arise frequently, but are more likely to increase in frequency when on sex chromosomes than on autosomes. This is because the restricted recombination between heterogametic sex chromosomes may allow linkage disequilibrium to build up between loci causing meiotic-drive and "insensitivity" loci that prevent the driven chromosome from self-destructing. (Such systems may involve the X chromosome driving the Y, or vice versa.) When such drive produces distorted sex ratios within a species, natural selection will favor its suppression through the accumulation of modifier alleles that restore the sex ratio to normal.

If different sex-linked drive-and-suppression systems evolve independently in two related species, and the suppressor alleles are not completely dominant, then meiotic drive will reappear in the hybrids. This could lead to the mutual annihilation of the sex chromosomes in heterogametic hybrids, causing sterility of only the heterogametic sex. This is the meiotic-drive explanation for Haldane's rule. Moreover, genetic analysis would show that the sterility is due largely to the sex chromosomes, explaining large X (and Y) effects. It should be noted that this theory explains only hybrid sterility and not inviability, because inviability is not caused by meiotic drive. Other assumptions, such as pleiotropic effects of drive on mitosis (Frank, 1991*a*) or the mobilization of drive-inducing transposons (Hurst and Pomiankowski, 1991), must be invoked to produce a general explanation of postzygotic reproductive isolation.

These meiotic-drive theories have been criticized by Coyne et al. (1991), Charlesworth et al. (1992), and Johnson and Wu (1992) on both theoretical and empirical grounds [see Frank (1991*b*) for counterarguments]. For example, Coyne et al. (1991) note that, in many cases, meiotic-drive alleles may actually accumulate faster on autosomes than on sex chromosomes. Here we provide a direct experimental test of these hypotheses.

A natural prediction of meiotic-drive theories of hybrid sterility is the appearance of sex-chromosome drive in species hybrids (Hurst and Pomiankowski, 1991; Coyne et al., 1991; Johnson and Wu, 1992). One can, for example, produce interspecific hybrids between species obeying Haldane's rule. If the sterility of heterogametic hybrids is produced by meiotic-drive alleles suppressed within one species but reexpressed in hybrids (i.e., the suppressor alleles are not completely dominant), then meiotic drive may reappear in semisterile hybrids, who should then produce progeny with distorted sex ratios.

Johnson and Wu (1992) report such a test in hybrids between *D. simulans* and *D. sechellia*, a pair of species that obey Haldane's rule and show strong X-effects on sterility (Coyne and Kreitman, 1986). In this experiment, semisterile backcross hybrids produced progeny with a normal sex ratio, militating against a meiotic-drive theory. We investigated this possibility in three other pair of *Drosophila* species that are not closely related to *D. simulans* and *D. sechellia*. All three species obey Haldane's rule, and genetic analysis has shown that hybrid male sterility is due largely to the X chromosome (Orr, 1989; Orr and Coyne, 1989). All three hybridizations produced semisterile backcross males whose progeny were examined for sex-ratio distortion.

D. virilis/D. texana.—*D. virilis* females from a Pasadena, California, strain were crossed to males of a *D. texana* strain from Morrilton, Arkansas (the latter strain was used in the genetic analysis of Orr and Coyne, 1989). The semisterile F_1 males were backcrossed to *D. virilis* females, and the male and female offspring

TABLE 1. Sex ratios of interspecific backcrosses between closely related species and subspecies of *Drosophila*. *N* is the total number of offspring scored in determining the sex ratio. 95% confidence intervals are given for the progeny sex ratios. See text for further description of the crosses.

Hybridization	Backcross generation	*N*	Proportion male	95% CI
D. virilis/D. texana	1	275	0.509	0.450–0.568
	2	203	0.492	0.438–0.546
	3	163	0.528	0.451–0.605
	4	407	0.472	0.424–0.520
D. virilis/D. novamexicana	1	2,146	0.477*	0.456–0.498
	2	1,999	0.491	0.469–0.513
	3	2,492	0.501	0.481–0.521
D. pseudoobscura USA/Bogota	1	1,464	0.517	0.492–0.542

* $0.025 < P < 0.05$ (two-tailed test).

counted in the first backcross generation. In this backcross, both X and Y chromosomes have significant effects on hybrid sterility (Orr and Coyne, 1989). Male offspring were again backcrossed to *D. virilis,* and this procedure repeated to produce a second, third, and fourth backcross generation. These crosses result in a genome that contains autosomal material from both species (the proportion of *D. virilis* genome increases each generation), but that always has a Y chromosome from *D. texana* and an intact X chromosome from *D. virilis.* These crosses were raised at 18° on banana–agar–yeast medium. The sample of offspring was rather small because of the extreme sterility of the backcross males.

D. virilis/D. novamexicana.—This pair of species also obeys Haldane's rule and shows strong X-effects, although no Y-effect was found in a small sample of backcross progeny (Orr and Coyne, 1989). The cross described above was repeated, but using instead of *D. texana* a *D. novamexicana* strain from San Antonio, Texas (Orr and Coyne, 1989). Three generations of backcrosses to *D. virilis* females were made, with the rearing conditions identical to those in the *D. texana/D. virilis* cross.

D. pseudoobscura USA/D. pseudoobscura bogotana.—These two subspecies produce sterile males in one direction of the cross [*USA* males × *bogotana* females (Prakash, 1972)]. Genetic analysis shows that the X chromosome plays a large role in this sterility while the Y has no discernible effect (Orr, 1989). Hybrid sterility results from an incompatibility between the Bogota X and the *USA* autosomes (Orr, 1989 and unpubl. data). Wild-type *USA* females were crossed to *bogotana* males and the resulting fertile F_1 males backcrossed to *bogotana* females. The male offspring of this backcross carry complete *bogotana* X and Y chromosomes, but have a mixture of autosomes from *USA* and *bogotana.* Previous work has shown that many of these males are partially sterile: approximately half of them have no motile sperm, and roughly one-third of the remaining males produce very few mature sperm (Orr, unpubl. data). To test for the possibility of meiotic drive, these first-generation backcross males were crossed en masse to *bogotana* females, and the sex ratio of the resulting progeny scored. These crosses were made at 22° on Davis medium.

None of the three sets of crosses show consistent or pronounced deviations from a 50:50 sex ratio (Table 1). The observed sex ratios (proportion of males) all fell within the range 0.47 to 0.53, with only one cross, the offspring of the first-generation backcross between *D. virilis* and *D. novamexicana,* having a sex ratio deviating significantly from 50:50 (0.477). In that case, the 95% confidence interval was 0.456 to 0.498, so that the true sex ratio is unlikely to differ from equality by more than 4%. [This deviation could, of course, be due to small viability differences between the sexes, and it was not observed when we repeated the cross (N = 2,666, sex ratio = 0.492, 95% CI = 0.0019, $\chi^2(1\ df)$ = 0.726).] The largest deviation that could have gone undetected in all our samples is 10.5%, in generation 3 of the *D. virilis/D. texana* cross. The absence of strong sex-ratio distortion, despite pronounced semisterility of hybrid males, is further evidence against a meiotic-drive hypothesis for hybrid sterility, extending the conclusions of Johnson and Wu (1992).

It is important to note that two distinct meiotic-drive theories have been offered to explain Haldane's rule (Frank, 1991; Hurst and Pomiankowski, 1992). In the first, X-linked drive alleles may be suppressed within species via Y-linked suppressors; in the second, by autosomal suppressors. In either case, species hybrids may partially or completely lack these suppressors, allowing the reappearance of meiotic drive. The present data allow us to test both theories.

The *D. virilis/D. texana* and *D. virilis/D. novamexicana* crosses test the Y-suppressor version of the theory, as these hybrid males carry an X chromosome from one species and a Y from another. If X-linked drive alleles are normally suppressed by conspecific Y-linked genes, these suppressors are missing in the hybrid males, who should therefore show meiotic drive. Nevertheless, despite their partial sterility, hybrids in these crosses show no sex-chromosome drive.

Similarly, the *D. pseudoobscura bogotana/USA* cross tests the autosomal-suppressor version of the theory: because the *bogotana* X chromosome causes male sterility when in the presence of *USA* autosomes, one could argue that an X-linked drive sequence from *bogotana* is normally suppressed by (incompletely dominant) autosomal alleles from *bogotana.* Meiotic drive would thus reappear among hybrid males, causing ste-

rility. However, our results show that males carrying a *bogotana* X and (on average) one-fourth of their autosomes from *USA* produce offspring with a normal sex ratio. Despite the partial sterility of these males, we again see no sex-chromosome drive.

Our results, combined with those of Johnson and Wu (1992), provide a sample of four *Drosophila* hybridizations obeying Haldane's rule and showing large effects of the X chromosome on hybrid sterility. Each of these cases is evolutionarily independent of the others, and none of them show any evidence for sex-chromosome meiotic drive.

Although it is obviously difficult to reconcile these findings with the notion that meiotic drive causes Haldane's rule and the large X-effect, one must consider two possible objections to our experiments. First, even if meiotic drive were usually the cause of hybrid sterility, one might occasionally find exceptional cases of Haldane's rule that do not involve meiotic drive. While possible, this explanation obviously becomes less and less plausible as the number of tested hybridizations increases. It is difficult to believe that meiotic drive is a general explanation for Haldane's rule when such drive has not been found in the first four hybridizations examined.

Second, Frank (1991) has claimed that the meiotic-drive theory does not necessarily predict that partially sterile hybrids will show segregation distortion. He notes that invasion of meiotic-drive alleles, while initially causing segregation distortion, may later disrupt gametogenesis in hybrids without causing drive. However, there is no known biological basis for this speculation. Moreover, this explanation requires us to believe that, for unspecified reasons, meiotic-drive alleles behave in opposite ways on hybrid and pure-species genetic backgrounds, causing sterility or inviability (but not drive) on the former and drive (but not sterility or inviability) on the latter.

In sum, we find no evidence of meiotic drive in three independent hybridizations obeying Haldane's rule. Although we remain ignorant of the actual cause of this rule, our data, combined with those of Johnson and Wu (1992), suggest that it is not meiotic drive.

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