MEIOTIC SEGREGATION AND MALE RECOMBINATION IN INTERSPECIFIC HYBRIDS OF DROSOPHILA

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ABSTRACT

Male hybrids between three pairs of Drosophila species show no substantial distortion of Mendelian segregation and no appreciable male recombination. These results do not support the theories that meiotic drive alleles of large effect are often fixed within species and that transposable genetic elements cause speciation.

THE study of genetic changes that cause or accompany speciation is often difficult because it requires the deduction of historical processes from present-day patterns. Fortunately, some species can hybridize and produce fertile offspring in the laboratory, so genes that have diverged from a common ancestor can be reassembled in a single genome. Here, this technique is used to address two evolutionary questions:

1. How often have meiotically driven alleles been fixed in a species? Biologists have described alleles in several species that drastically modify segregation ratios when heterozygous against an alternative allele. These meiotic drive alleles—the most famous of which are *t* alleles in mice and the *segregation distorter* (*SD*) alleles in *Drosophila melanogaster* (HARTL and HIRAIZUMI 1976; SILVER 1985)—are often found in more than 90% of gametes produced by heterozygotes. The distortion of segregation usually occurs only in males (ZIMMERING, SANDLER and NICOLETTI 1970).

Virtually all of these meiotically driven alleles severely reduce fitness. The *t* alleles, for instance, are homozygous lethal or sterile, and *SD* homozygotes are sterile. This must be true for polymorphic drive alleles: if they are not highly deleterious, they will become fixed in the population and will then be undetectable. Indeed, if the frequency of preferential segregation is sufficiently high, such alleles can be fixed even when strongly disadvantageous (HIRAIZUMI, SANDLER and CROW 1960).

It is an evolutionary problem, then, to determine how often such alleles are fixed within species. Are the meiotic drive alleles segregating in nature only the most deleterious fraction of a class of genes regularly sweeping through populations?

LEWONTIN (1985) proposes that DNA sequencing could answer this question.

Meiotic drive alleles that have recently become fixed will carry along a segment of chromosome linked to the original mutation, leading to homozygosity by descent of this stretch of DNA in the entire species. Strong selection on a single locus will also have this effect, however, so that it is impossible to distinguish the two phenomena by sequencing alone.

Another way to answer this question is to allow fixed alleles to segregate against their putative ancestors. HIRAIZUMI, SANDLER and CROW (1960) suggested that meiotic drive might be seen in hybrids between geographically distant populations. Migration among these populations might, however, rapidly disseminate driven alleles throughout an entire species. This is likely to be a problem with the well-studied cosmopolitan species, such as mice and Drosophila. At any rate, I am unaware of any reports of extreme segregation ratios in population hybrids.

The problem of gene flow can be obviated by examining hybrids between reproductively isolated groups. Any meiotically driven allele that has been fixed in one species, but not in a relative, will show aberrant segregation in heterozygous interspecific hybrids. Although not designed to test this possibility, at least two studies have found meiotic drive in plant hybrids (CAMERON and MOAV 1957; MAGUIRE 1963). The only direct study in animals is reported by WOLFF and COUGHLIN (1961), who observed no segregation distortion in female hybrids of *Drosophila pseudoobscura* and *D. persimilis.* One can find similar results in other studies of female hybrids (*e.g.,* DOBZHANSKY 1936; SANCHEZ 1982).

Unfortunately, the frequent limitation of meiotic drive to males suggests that segregation ratios in hybrid females may be an improper test of evolutionary fixation. Studies of males, however, come up against the ubiquitous sterility or inviability of this sex in species hybrids (HALDANE 1922). Yet, there are a few pairs of species that, although reproductively isolated in nature, produce fertile male hybrids in the laboratory. Here, segregation ratios are determined in male hybrids between three such pairs in an attempt to find large deviations from Mendelian ratios like those caused by the known meiotic drive alleles.

2. Do transposable elements cause speciation? Hybrid dysgenesis in *D. melanogaster* is a condition occurring in hybrids between strains having transposable elements and strains genetically sensitive to transposition. The movement of small segments of repeated DNA in the hybrids is associated with a complex syndrome of male recombination, temperature-sensitive gonadal atrophy, chromosome breakage, sterility and elevated mutation rates (SVED 1979; ENGELS and PRESTON 1979; BREGLIANO and KIDWELL 1983). The two most well-known families of these elements—*P* and *I*—are associated with different symptoms (BREGLIANO and KIDWELL 1983). Various investigators have proposed that the fixation of transposable elements in different populations could lead to speciation by causing extreme dysgenesis in hybrids (ENGELS and PRESTON 1979; BREGLIANO and KIDWELL 1983; ROSE and DOOLITTLE 1983). The empirical evidence for this speculation is the similarity in appearance between the rudimentary gonads of some species hybrids and the rudimentary gonads produced

by *P-M* hybrid dysgenesis in *D. melanogaster* (ROSE and DOOLITTLE 1983; BREGLIANO and KIDWELL 1983).

One way to investigate the possibility of transposable-element speciation is to look for other similarities between the known symptoms of hybrid dysgenesis and the effects of interspecific hybridization. Other hybrids in the *D. melanogaster* group are already known to lack the types of gonadal atrophy or sterility caused by either *P-M* or *I-R* hybrid dysgenesis in *D. melanogaster* (COYNE 1985a). Here, the interspecific analysis is extended to another symptom of hybrid dysgenesis: male recombination. Although crossing over is either absent or very infrequent in Drosophila males, recombination values ranging from 0.5 to 4.5% are reported in male offspring of hybrid-dysgenic crosses (HIRAIZUMI 1971; KIDWELL, KIDWELL and SVED 1977; WOODRUFF and THOMPSON 1977; HENDERSON, WOODRUFF and THOMPSON 1978; EGGLESTON 1984; GREEN 1986).

Three pairs of full or incipient species were used in this analysis:

***D. pseudoobscura* vs. *D. pseudoobscura bogotana*:** *D. pseudoobscura* is widespread in the western United States, Canada and Mexico. In 1960, a disjunct population was discovered near Bogota, Colombia, separated from the rest of the species by 2400 km (DOBZHANSKY *et al.* 1963). PRAKASH (1972) found that hybrids between Bogota females and mainland males produce fertile female and sterile male offspring, and the reciprocal cross gives fertile progeny of both sexes. Later electrophoretic studies revealed large genetic divergence between Bogota and the rest of the species (COYNE and FELTON 1977; SINGH 1979), indicating a substantial age of the isolate and supporting AYALA and DOBZHANSKY's (1974) designation of the Bogota population as a subspecies.

***D. simulans* vs. *D. sechellia*:** Like its relative *D. melanogaster*, *D. simulans* is a cosmopolitan human commensal. *D. sechellia* is endemic to one island and two islets in the Seychelles, where no other species of the group is found (TSACAS and BÄCHLI 1981; LACHAISE *et al.* 1986). *D. simulans* and *D. sechellia* have identical polytene chromosome banding patterns (LEMEUNIER and ASHBURNER 1984) and can be crossed reciprocally to give fertile females and sterile males. The hybrid females can be backcrossed to either parent, yielding a small proportion of backcross males that are fertile (LACHAISE *et al.* 1986). The fertile males can be tested for segregation ratios and recombination fractions.

***D. virilis* vs. *D. lummei*:** *D. virilis*, now cosmopolitan, may have originated in China, whereas *D. lummei* occurs in northeastern Asia and Russia (THROCKMORTON 1982). The species are sympatric in Russia and perhaps Japan, but apparently do not hybridize there. They do cross readily in the laboratory. At least some F_1 males and females are fertile (although the degree of sterility has not been measured), but there is substantial sterility and inviability in the backcrosses (MITROFANOV and SIDOROVA 1981; THROCKMORTON 1982). The lack of natural hybridization coupled with the marked morphological, electrophoretic and karyotypic differences leave no doubt that these are distinct species.

MATERIALS AND METHODS

Meiotic drive. Segregation ratios were determined by backcrossing hybrid males heterozygous for a recessive mutant to parental females homozygous for that mutant.

The Mendelian expectation of offspring is a 50:50 proportion of mutant and nonmutant phenotypes. This will be distorted by any fixed meiotic drive alleles linked to the observed locus, but also by viability effects of the mutant or by linked genes causing hybrid breakdown. Intraspecific backcrosses with the same mutants served as controls for the viability effects. It was not possible to control for hybrid breakdown (interspecific viability effects), which may be responsible for the small deviations from Mendelian segregation ratios shown below. The object of these crosses was to detect only large deviations from 50:50 proportions, because extremely small deviations can be seen only in very large samples.

Segregation ratios were measured for both second and third chromosomes in *D. pseudoobscura* mainland/Bogota hybrids. *D. pseudoobscura* females homozygous for either *bright-II* (second chromosome, map position unknown [BRYANT 1980]) or *orange* (*3*-0; ANDERSON and NORMAN 1977) were crossed to Bogota males provided by JEFFREY POWELL. F_1 females were backcrossed to mutant males by *D. pseudoobscura* at a density of approximately 30 pairs per bottle.

In the *D. simulans/D. sechellia* cross, segregation of second and third chromosomes was measured in backcross males (F_1 males are sterile). *D. simulans* females homozygous for either *plum* (*2*-103) or *scarlet* (*3*-44) (map positions supplied by J. S. F. BARKER) were crossed to *D. sechellia* males from a strain supplied by HUGH ROBERTSON. Heterozygous hybrid females were backcrossed to mutant *D. simulans* males. Male offspring of this cross having a wild-type phenotype (and therefore heterozygous for the mutant) were again backcrossed *en masse* to the *D. simulans* marker stock at a density of approximately 30 females and 60 males per bottle. This analysis, unlike that of the other two pairs, produces males that are recombinant for the marked chromosome. Thus, there is a reduced probability of detecting the meiotic drive alleles, because some of them may recombine away from the marker allele during meiosis in F_1 females. However, because the mean length of the unrecombined chromosome in this backcross is 100 cM on either side of the marker (CROW and KIMURA 1970, p. 94), the recombination does not greatly diminish the detectability of alleles with large effects on segregation.

Segregation was measured on the second, third and fifth chromosomes of *D. virilis/D. lummei* hybrid males, using the mutants *varnished* (*2*-232), *gap-2* (*3*-119) and *peach* (*5*-203) (map positions from ALEXANDER 1976). Female offspring of a cross between marked *D. virilis* females and *D. lummei* males were backcrossed to the mutant strain at a density of approximately 40 pairs per bottle.

Male recombination: Recombination frequencies in hybrid males were determined as the frequency of crossing over between pairs of markers on chromosomes with no known structural differences between the species. Intraspecific controls were not made, because the detected frequency of recombination was so low. Densities in all crosses were the same as those given above.

Recombination in *D. pseudoobscura* mainland/Bogota hybrids was measured in hybrid males heterozygous in coupling phase for the second chromosome markers *upturned* (*2*-0) and *glass* (*2*-83). These males were crossed to a homozygous *D. pseudoobscura upturned, glass* stock.

Recombination in *D. simulans/D. sechellia* hybrids was scored in the offspring of males from the second backcross generation (see above). Female *D. simulans* homozygous for *forked-2; net, plum; scarlet, ebony* (*f*^{2}: *1*-60; *nt*: *2*-0; *pm*: *2*-103; *st*; *3*-44; *e*: *3*-71) were crossed to *D. sechellia* males. Heterozygous female hybrids were backcrossed to the multiply marked stock, and three classes of male progeny were collected to make a second backcross. Males having the *forked-2; net, plum* phenotype are homozygous for the *D. simulans* second-chromosome markers, but are heterozygous in coupling phase for both third-chromosome markers. When backcrossed again to *f*^{2}; *nt pm*; *st e* females, these males should produce only two mutant phenotypes in the absence of recombination: *f*^{2}; *nt pm*; *st e* and *f*^{2}; *nt pm*. Any recombination would yield *f*^{2}; *nt pm*; *st* or *f*^{2}; *nt*

TABLE 1

Segregation ratios in control (intraspecific) and experimental (interspecific) crosses

Species pair	Chromosome	Control		Experimental		Difference in segregation ratio ± 1.96 SE
		N	Mutants/total	*N*	Mutants/total	
D. pseudoobscura mainland/Bogota	2	473	0.467	872	0.489	0.021 ± 0.056
	3	564	0.447	1037	0.482	0.035 ± 0.051
D. simulans/D. sechellia	2	2300	0.490	2132	0.486	0.004 ± 0.029
	3	2163	0.457	1519	0.532	0.074 ± 0.032
D. virilis/D. lummei	2	1144	0.485	1325	0.423	0.062 ± 0.039
	3	737	0.453	1246	0.473	0.020 ± 0.046
	5	631	0.509	1040	0.475	0.034 ± 0.094

Frequencies given are the ratios of mutant types to total offspring in backcrosses of interspecific hybrid males to homozygous parental females. See the text for further explanation.

pm; *e* offspring. Similar results are expected in crosses with the other two classes of backcross male: f^2; *st e* and f^2 (the latter cross gives four nonrecombinant classes).

Recombination in *D. virilis/D. lummei* hybrid males was measured between the third-chromosome markers *shaven* and *gap-2* (*sv*: 3-25; *gp-2*: 3-119). Heterozygous F_1 males were backcrossed to the parental *sv*, *gp-2* strain of *D. virilis*.

All crosses were made at 24°.

RESULTS

There is no evidence for either highly abnormal segregation ratios or elevated rates of male recombination in these species hybrids.

Table 1 gives the ratio of mutant phenotypes/total offspring in the crosses designed to detect meiotic drive. As expected from the viability effects of mutants, this ratio is generally below 0.5, but ratios in both control and experimental crosses lie between 0.42 and 0.53. The last column in Table 1 shows the differences between control and experimental crosses in segregation ratios and the 95% confidence interval of these differences (±1.96 SE). In only two crosses (chromosome 3 in *sechellia/simulans* and chromosome 2 in *virilis/lummei* are there significant differences between control and experimental ratios. Even here, however, the differences are small: the confidence intervals show that the true difference has a low probability of being greater than 0.106 in either cross. Any meiotic drive genes operating in these hybrids cannot distort segregation ratios by more than 11% (or 21% in the case of alleles loosely linked to the markers in the *D. simulans/D. sechellia* cross).

Table 2 gives the recombination fraction among progeny of hybrid males; all of these lie below 6.7×10^{-4} and are not statistically heterogeneous. ($G_2 = 2.40$, $P > 0.25$). In the two crosses giving more than one recombinant, each crossover occurred in a different bottle; thus, there is no clustering of meiotic events as often occurs in hybrid dysgenesis. The 95% confidence intervals show that the greatest probable values of male recombination in the three crosses are only 0.00045, 0.00061 and 0.0013. The largest of these upper bounds is still only one-fourth of the lowest values of recombination reported in hybrid

TABLE 2

Male recombination in species crosses

Species	Linked loci (map distance)	Nonrecombinants	Recombinants	Recombination ± 1.96 SE
D. pseudoobscura mainland/Bogota	*upt-gl* (83.3)	6460	1	0.00015 ± 0.00030
D. simulans/D. sechellia	nt-pm (103)			
	st-e (27)	10,450	3	0.00029 ± 0.00032
D. virilis/D. lummei	*sv-gp*^{2} (115.5)	5950	4	0.00067 ± 0.00066

dysgenic crosses (HIRAZUMI *et al.* 1973), and the observed values are in the range observed in nondysgenic crosses (HIRAIZUMI 1971; KIDWELL, KIDWELL and SVED 1977).

DISCUSSION

We are able in these species to rule out the fixation of any meiotic drive genes distorting segregation ratios by more than 11%. There are several possible explanations for the absence of such fixation:

1. Meiotic drive mutations of large effect are rare, and fixations do not occur very often. Although this explanation might at first seem wrong because of the existence of several polymorphic drive alleles, they might, in fact, be very old polymorphisms that give no information about mutation rates [molecular evidence (SILVER 1985) shows that the spread of *t* alleles in mouse populations is probably a recent event].

Another explanation for the rarity of meiotic drive fixations comes from the genetic basis of known systems. In the *SD* and probably in the *t* systems, meiotic drive alleles act on polymorphic responder alleles at separate loci (HARTL 1974; SILVER 1985), and drive will not occur unless there is strong linkage disequilibrium between distorter and responder (CHARLESWORTH and HARTL 1978). Meiotic drive may thus require a combination of rare events involving several loci that are tightly linked.

2. Meiotic drive alleles of large effect always severely reduce fitness, so that they must always remain as polymorphisms. This hypothesis explains both the presence of polymorphisms and our observed lack of fixations. It is worth noting that two of the best-known examples of meiotic drive, *SD* alleles in *D. melanogaster* and the SR chromosome of *D. pseudoobscura*, involve destruction of sperm containing the nondriving chromosome (HARTL, HIRAIZUMI and CROW 1967; POLICANSKY and ELLISON 1970). This type of drive may reduce fertility. [B. CHARLESWORTH (personal communication) notes that the possibility of lowered fertility may explain why existing drive systems are almost always limited to males. If males have a more concave relationship between gamete number and offspring number than do females, drive alleles that reduce the number of gametes will be more advantageous in males.]

Nevertheless, meiotic drive alleles may not always be injurious. One can easily imagine meiotic mechanisms that do not reduce the number of gametes

in heterozygotes, such as elimination of the nondriving chromosome before sperm are formed, or, in females, segregation of the nondriven chromosome into polar bodies.

3. The same meiotically driven alleles are fixed in the separate species as recurrent, homologous mutations. The interspecific hybrids remain homozygous for the alleles and do not show abnormal segregation.

4. Different meiotically driven alleles are fixed in each species, but their effects cancel out in the hybrids, so that a 50:50 segregation ratio is seen. This assumes equal evolution of meiotic drive "strength" in two independent lineages.

It appears that the most plausible explanation is the second: meiotic drive alleles of large effect always have negative pleiotropic effects on fitness (perhaps by reducing fertility), so that intraspecific polymorphisms reflect the fitness effects of drastic meiotic drive alleles. It is important to realize, however, that only three evolutionary divergences have been sampled here and that more work is desirable. In addition, this study has no power to detect drive alleles that distort segregation by only a few percent, an effect that nonetheless could cause rapid evolutionary fixation. Tremendous sample sizes and the use of several independent mutations on the same chromosome will be necessary to detect alleles with such small effects.

There is also no evidence for high frequencies of male recombination, as might be caused by the movement of transposable elements in species hybrids. The evidence for transposable-element-induced speciation is still based primarily on the similarity between atrophied gonads in species hybrids and the rudimentary gonads caused by the *P-M* system of hybrid dysgenesis (BREGLIANO and KIDWELL 1983). These parallels broke down, however, when other species in the *D. melanogaster* groups were studied (COYNE 1985a). In addition, the strongest genetic effects on hybrid male sterility in this and other Drosophila groups map consistently to the *X* chromosome, which is difficult to understand if mobile genetic elements are the leading cause of reproductive isolation (DOBZHANSKY 1936; COYNE 1984; COYNE and KREITMAN 1986; COYNE and CHARLESWORTH 1986).

The other well-known system of hybrid dysgenesis—*I-R*—does not cause male recombination, but leads instead to sterility of hybrid females, nondisjunction and elevated mutation rates (BREGLIANO and KIDWELL 1983). This system is also an unlikely candidate for speciation because preferential female sterility is almost never observed in species crosses (HALDANE 1922; COYNE 1985b). It is possible, of course, that uncharacterized families of transposable elements could cause reproductive isolation without any of the symptoms of *P-M* or *I-R* dysgenesis; but it is the similarity between the genetic effects of *P-M* dysgenesis and the effects of hybridization that has led to the claim that the phenomena are related.

A convincing case for transposable-element speciation requires demonstrating (1) a difference in the distribution of element families among species, (2) that these differences cause reproductive isolation (temperature-sensitive gonadal dysgenesis or elevated mutation and recombination rates do not them-

selves result in isolation) and (3) the existence of reciprocal sterility effects of the elements in cases where sterility occurs in reciprocal crosses between species. Only point 1 has been demonstrated up to now (MARTIN, WIERNASZ and SHEDL 1983; BROOKFIELD, MONTGOMERY and LANGLEY 1984). One must also be aware of the possibilities that transposable elements might be inactivated after fixation or that any observed fixations among species may have occurred after, not during, speciation.

There is some evidence of an increased frequency of dysgenic-like events in species hybrids, including relatively high frequencies of new inversions (NAVEIRA and FONTDEVILA 1985), increased mutation rates in species hybrids (STURTEVANT 1939), and the presence of rare or unique alleles in moderate frequencies in hybrid zones (SAGE and SELANDER 1979; BARTON, HALLIDAY and HEWITT 1983). None of these phenomena leads to reproductive isolation. In addition, the new alleles in hybrid zones are probably caused by intragenic recombination. It is unlikely that transposable elements, the mutagenic effects of which probably result from inactivating genes by inserting DNA, could produce a structurally altered protein with a new electrophoretic mobility. Until one can show that transposable elements acting under natural conditions cause reproductive isolation, the involvement of this phenomenon in speciation will remain doubtful.

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