The Sex-Ratio Trait in Drosophila simulans: Genetic Analysis of Distortion and Suppression

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ABSTRACT

The sex-ratio trait described in several Drosophila species is a type of naturally occurring X-linked meiotic drive that causes males bearing a sex-ratio X chromosome to produce progenies with a large excess of females. We have previously reported the occurrence of sex-ratio X chromosomes in Drosophila simulans. In this species, because of the co-occurrence of drive suppressors, the natural populations and the derived laboratory strains show an equal sex-ratio even when sex-ratio X chromosomes are present at a high frequency. The presence of sex-ratio X chromosomes is established via crosses with a standard strain that is devoid of drive suppressors. In this article, we show first that the sex-ratio trait in D. simulans results from the action of several X-linked loci. Second we describe drive suppressors on each major autosome as well as on the Y chromosome. The Y-linked factors suppress the drive partially whereas the autosomal suppression can be complete.

THE sex-ratio trait is a type of meiotic drive due to X-linked factors that appears widespread among Drosophila species. Males that bear a sex-ratio X chromosome (sex-ratio males) transmit mainly X-bearing sperm and therefore produce only or mostly female progeny. Driver sex-ratio X chromosomes were first described within the subgenus Sophophora, in seven species belonging to the D. obscura species group (MORGAN et al. 1925; GERSHENSON 1928; STURTEVANT and DOBZHANSKY 1936; JUNGEN 1968). They have also been found in species belonging to four different groups of the subgenus Drosophila: D. paramelanica (STALKER 1961), D. mediopunctata (de CARVALHO et al. 1989), D. testacea (JAMES and JAENIKE 1990), D. quinaria and D. reensa (JAENIKE 1996). Since they should be transmitted by males at higher rates than a normal X, sex-ratio X are expected to invade the populations and cause their extinction, once fixed, if the bias toward females is complete (GERSHENSON 1928; HAMILTON 1967). However sex-ratio X chromosomes are usually maintained at low or moderate frequency in natural populations (STURTEVANT and DOBZHANSKY 1936; DOBZHANSKY and EPLING 1944; DOBZHANSKY 1958; JUNGEN 1968; de CARVALHO et al. 1989; HAUSCHTECK-JUNGEN 1990; JAENIKE 1996). Two mechanisms are put forward that may prevent their spread through populations: countervailing selection on individuals bearing sex-ratio X (reviewed in JAENIKE 1996) and selection on autosomal and Y-linked suppressors of drive (THOMSON and FELDMAN 1975; WU 1983a; CLARK 1987). Drive suppressors have been found in D. affinis (VOELKER 1972), D. paramelanica (STALKER 1961), D. mediopunctata (de CARVALHO and KLACZKO 1993, 1994) and possibly occur in D. subobscura (HAUSCHTECK-JUNGEN 1990). Nevertheless, in all these species, sex-ratio males are observed within populations. Thus, the drive suppression is incomplete at the population level.

The situation appears rather different in D. simulans, a species that belongs to the D. melanogaster group. A first report of female-biased sex-ratio, in a stock derived from a natural population of California, has been accounted for by a recessive autosomal drive factor (FAULHABER 1967). A second report (de MAGALHAES et al. 1985) also refers to a recessive autosomal factor, in Brazilian populations, that might correspond to the same system as FAULHABER's. Autosomal sex-ratio factors have never been reported in other Drosophila species and theoretically, an autosomal driver acting on sex-chromosomes cannot be selected for (HAMILTON 1966). Thus, a possible interpretation of FAULHABER's data is that a "hidden" sex-ratio X chromosome, whose action was suppressed by an autosomal factor, was present in the Californian population and that the few males expressing the drive were those that bore an inefficient allele at the suppressor locus (HURST and POMIANOWSKI 1991). In fact, the presence of hidden sex-ratio X chromosomes in D. simulans has been recently reported in our laboratory (MERCOT et al. 1995). Such chromosomes have been characterized in stocks originating from many locations over the world (ATLAN et al. 1997). By contrast with other species, sex-ratio X chromosomes may reach high frequencies (up to 60%) in natural populations of D. simulans (ATLAN et al. 1997). However, they rarely if ever express their drive ability within the natural populations or the derived laboratory stocks.
because of the systematic co-occurrence of drive suppressors (Atlan et al. 1997). The presence of sex-ratio X chromosomes is revealed via crosses with a standard strain (ST) that is devoid of drive suppressors. F1 hybrid males that bear a sex-ratio X and a standard Y are typical sex-ratio males: they exhibit spermiogenic failure (Montchamp-Moreau and Joly 1997) and usually produce between 70% and 100% females in their progeny. The bias toward females is not associated with postzygotic mortality nor does it depend on the type of female the males are mated with (Mercot et al. 1995).

The aim of the present work is to characterize the genetic components of the sex-ratio system in D. simulans, using a laboratory stock (SR) in which sex-ratio X became spontaneously virtually fixed. First we show that several X-linked factors are responsible for the sex-ratio trait, second that recessive autosomal drive suppressors on the second and the third chromosomes, as well as Y-linked ones, together are responsible for a complete suppression of the sex-ratio trait in the SR strain.

 MATERIAL AND METHODS

Strains: ST is a reference standard strain, free of sex-ratio distorters and drive suppressors (Mercot et al. 1995). The distribution of frequency of females among progeny of 53 ST males individually crossed with ST females is shown on Figure 1A. SR is our reference strain for the sex-ratio system (Atlan et al. 1997). It shows an equal sex-ratio (Figure 1B) and the distribution of female percentage among individual progeny of 55 SR males does not differ significantly from that of the ST males (x² = 9.733, 5 d.f., P = 0.14). However, it carries driver X chromosomes, resulting in a large excess of females in most of the individual progenies of the F1 hybrid males bearing an X chromosome from the SR strain (XSR) and a standard Y chromosome (YST) (Figure 1C). The SR5 strain carries a standard genetic background together with driver X chromosomes (XSR) whose driving factors come from a unique X chromosome of the SR strain. As a result, SR5 males express the sex-ratio trait. We assume that SR5 got rid of autosomal drive suppressors present in the SR strain because no drive resistance has evolved in this strain for 2 years. This strain was obtained as follows. (1) A parental cross between one ST female and one SR male was followed by alternate backcrosses with ST females (even generations) or ST males (odd generations). At each even generation (F0 to F2), only males producing more than 80% females were retained, and their female progenies (odd generations) were used in the subsequent cross. (2) One pair of F2 male and female, which had produced only sex-ratio F1 males, was used as founder of the SR5 strain. The net e strain bears the recessive mutants net (net) and ebony (e) on the second and third chromosomes, respectively. np lz v/C(1)RM, y w females were mass-crossed with 40 ST males, bearing XSR chromosomes together with YST, and the males were individually crossed with ST females. F1 females were mass-crossed with 40 males of the np/lz/v YST strain, and the sex-ratio was measured as above.

RESULTS

Segregation of the sex-ratio trait on the XSR chromosomes: Twenty SR5 females were mass-crossed with 30 np/lz/v males, then 40 F1 females (XSR/YST =) were individually crossed with ST males to obtain recombinant X chromosomes in F2 flies. Distortion ability of recombinant X chromosomes against YST was measured by individually crossing F2 males of each genotype with ST females. Because of variable expressivity of np, the genotype of F1 males with a np/yR phenotype was checked on F2 females through F1 sib-mating. As a control, sex-ratios in the progeny of males bearing "parental" combinations of sex chromosomes (XSR/YST and XST/YST) were also measured: (1) 30 SR5 females were mass-crossed with 40 ST males, and sex-ratios in the progeny of XSR/YST F1 males were measured by individually crossing them with ST females, (2) 30 np/lz/v/C(1)RM, y w females were mass-crossed with 40 ST males, 30 YST/C(1)RM, y w F1 males were mass-crossed with 40 males of the np/lz/v YST strain and sex-ratios in the individual progenies of np/lz/v YST F2 males were measured as above.

Test for Y-linked drive suppressors in the SR strain: Forty SR males were mass-crossed with 40 net e females. Then, 40 F1 males were mass-crossed with 40 net e females. F2 males, bearing YSR chromosomes together with YST, second and third chromosomes from the net e stock, were mass-crossed with SR5 females. Sensitivity of YSR chromosomes to XSR distortion was measured using individual crosses of 32 F1 males (XSR/YST, YST/P'R, YST/P'; YST/P') with ST females. The same protocol, starting with 40 ST males, was used to test YST sensitivity against XST distortion. In this case, 49 F3 males (XSR/YST, YST/P'R, YST/P'; YST/P') were tested. Only crosses producing at least 100 males were taken into account.

Test for autosomal drive suppressors in the SR strain: Eight SR females were individually crossed with net e males. Three to eight F1 males from each progeny were then individually crossed with SR females. F2 males, together with Y chromosomes from the net e stock, could have four different autosomal combinations: heterozygous for P'R and P', homozygous for either P'R, P', or both (see Figure 4). The genotype of these males as well as their distorting ability were checked by crossing them with net e females.

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Sex-Ratio in *D. simulans*

![Gene expression in D. simulans](https://example.com/gene_expression.png)

To allow for a statistical comparison of the distributions, each individual progeny consists of 50 individuals randomly sampled (sampling without replacement among the whole individual progeny scored).

To eliminate any potential interaction with autosomal suppressors when looking for linkage relationships of the drive factor(s), we used the SR5 strain that was suppressor-free and whose driving factors came from a unique X chromosome of the SR strain (see MATERIALS AND METHODS). The distortion ability of parental Xp and Ym chromosomes (from the np lz and SR5 strains, respectively) against Y67t is shown in Figure 2, A and B. The 94 Xp chromosomes we tested did not induce distortion and led to equal mean sex-proportions among progenies (from 31% to 69% females). By contrast, the XSRr chromosomes were found to induce a variable but always significant excess of females (from 67% to 100%) among the individual progenies of the 126 tested males. These males produced a mean of 91.6% females, which was similar to the value obtained with hybrid XSRr/Y67t males (91.4%, Figure 1C). This strongly suggests that the XSRr chromosomes retained most if not all the drive factors present on the XSRr chromosomes.

The distortion ability of six classes of X chromosomes obtained among the male progeny of F1 hybrid females XSRr/Xp hv is shown in Figure 2, B–H. Double recombinant chromosomes np + v and + lz + were rarely obtained and seemed to behave like np + and + lz v, respectively (data not shown). It can be inferred from Figure 2, C–F that the sex-ratio factor(s) is tightly linked to the np lz region. (1) All but 11 of the 238 np lz v F2 males (Figure 2C) and all of the 51 np lz + F2 males (Figure 2E) produced progenies whose sex-ratios lay within the range observed with the parental Xp hv (30–

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**Figure 1.**—Expression of the sex-ratio trait. Distribution of female percentage among individual progenies of males from ST strain (A), SR strain (B), F1 hybrids obtained by crosses between SR females and ST males (C), F2 males, sons of F1 hybrids females, obtained by crosses between SR females and ST males (D). Mean female percentages are indicated in the corresponding histogram.
70% females). Figure 2, A and B, showed that the two parental distributions partially overlapped over the range 65–70%. Thus the distortion ability of the five np lz v F₂ chromosomes lying within this range was checked on the np lz v F₂ male progenies, following F₃ sib-mating. None of them were found to possess a heritable driving effect [since the sex-ratio factors(s) are tightly linked with the np lz region, the probability for one of them to be present in a np lz v F₂ male but not in its np lz v F₁ male progeny is very low]. Only 11 np lz v F₂ males (4.6%), which produced >70% females, were classified as sex-ratio. (2) Similarly, the sex-ratio trait (criterion >70% females) appears expressed by all of the + + v F₂ males and all but five of the + + + ones. A strong distortion ability was recovered among F₄ male progeny from four out of these five. Thus, at most 0.4% of the + + + F₂ males appeared to lack an heritable drive ability. In addition, there were significantly more moderate or weak distorsers (<85% females) among + + + F₂ chromosomes than among XSR₅ ones (Fisher exact test $P = 3.10^{-4}$), which suggests a partial lost of drive ability by a few of the former.

The effect of a recombination between np and lz is shown in Figure 2, G and H. The distribution on Figure
2G is bimodal and the proportion of sex-ratio among + \( k \) v \( F_2 \) males (criterion >70% females) was significantly higher than that observed among the \( np \) k v males (\( \chi^2 = 11.77, 1 \text{ d.f., } P < 0.001 \)), as expected from a mono- 

genic trait with a drive factor located between the \( np \) and \( k \) loci. However, it must be pointed out that the right tail of the 35–75% group included sex-ratio males: the three + \( k \) v \( F_2 \) males that had led to between 65% and 75% females were found to possess an heritable 

drive effect (tests on \( k \) \( F_2 \) males). Interestingly, the distribution of the percentage of females among individual 

progenies of \( np \) + + males was not bimodal (Figure 2G): more than one third of these progenies showed a 

moderate bias toward females (60–85%). Such values were rarely observed with both parental X chromosomes. 

The distortion ability of the 26 recombinant \( np \) + + chromosomes that resulted in between 55% and 70% females was checked on the corresponding \( np \) \( F_2 \) male progenies. Most of them (22) were found to possess an heritable drive ability. This supports the hypothesis that 

at least two loci, in the \( np-k \) region, are responsible for the sex-ratio trait. Because moderate distorters (60–85% 

females) seldom occur among + \( k \) v \( F_2 \) males when compared to \( np \) + + ones, more than two loci may be 

involved and/or these may have quantitatively different effects on the trait.

This model is doubtless overly simple, because the recovery of 4.6% of distorters (some of them strong ones) among \( np \) k v \( F_2 \) males and the excess of weak distorters among the + + + \( F_2 \) ones (Figure 2, C and D) can hardly be explained by double recombination 
events within a 16 cM region. Although major roles are played by loci in the \( np-k \) region, additional gene(s) 

outside this region may be involved in the expression of the sex-ratio trait.

Test for \( Y \)linked suppressors of drive: In this experiment, \( X^{SR} \) chromosomes were found to induce a mean of 66.4% females in the progeny of \( X^{SR} \)-bearing males (Figure 3A). Meanwhile, control \( X^{SR}/Y^{ST} \) males produced a mean of 81.2% females (Figure 3B). These means were significantly different (Mann-Whitney rank sum test \( u_{obs} = 6.9, P < 10^{-11} \)). Thus, the \( Y^{SR} \) chromosomes are less affected by \( X^{SR} \) drive than the \( Y^{ST} \) ones: assuming, after LYITTEL (1979), that the frequency of nonfunctional "Y-spermatids" is \( z = (2k - 1)/k \) (where \( k \) is the observed frequency of females in the progeny), then 77% of \( Y^{ST} \)-spermatids but only 50% of \( Y^{SR} \)-spermatids were assumed to degenerate during the spermiogenesis.

Both distributions of sex-ratios of \( X^{SR}/Y^{ST} \) and \( X^{SR}/ 

\( Y^{SR} \) males did not fit binomial distributions (\( \chi^2 = 42.1, 3 \text{ d.f., } P < 10^{-8} \) and \( \chi^2 = 66.3, 5 \text{ d.f., } P < 10^{-12} \), respectively). In fact they presented an extra-binomial variance. SHARP and HILLIKER (1990) have shown that segregation ratios within Segregation Distorter lines of \( D. 

melanogaster \) can conform to beta-binomial distributions, this means that the segregation ratio shows stochastic varia-

tions, following a beta distribution, between males of the same genotype, and that the sampling adds a binomial variability. Using the same methods with our data, we found that a beta-binomial distribution can be fitted to each of the observed distributions of sex-ratios (best fit for \( X^{SR}/Y^{ST} \): \( \mu = 0.812, \sigma^2 = 0.007, \chi^2 = 5.58, 5 \text{ d.f., } P = 0.13 \) and for \( X^{SR}/Y^{SR} \): \( \mu = 0.664, \sigma^2 = 0.005, \chi^2 = 5.42, 4 \text{ d.f., } P = 0.25 \)). Therefore, both the ST and SR strains were assumed to be monomorphic for the \( Y \) chromosomes regarding their drive sensitivity.

Test for autosomal drive suppressors in the SR strain: Figure 4 presents the distributions of the percentages of females among \( X^{SR}/Y^{ST} \) males bearing different combinations of autosomes from the SR strain. Heterozygous \( IFR^{SR}/IIFR^{SR} \) or \( IFR^{SR}/IIFR^{ST} \) males produced a mean of 81.3% females, males homozygous only for the \( IFR^{SR} \) or the \( IIFR^{SR} \) chromosomes produce, respectively, 66.4% and 60.7% females and males double homozygous \( IFR^{SR}/ 

IFR^{SR} \) or \( IFR^{SR}/IIFR^{ST} \) show an equal sex-ratio (52.6% females). Therefore both the \( IFR^{SR} \) and the \( IIFR^{SR} \) chromosomes carry autosomal drive suppressors. When compared by a Mann-Whitney test (rank sum test) the \( IFR^{SR} \) chromosomes present more powerful suppressors of drive than the \( IFR^{SR} \) chromosomes (\( u_{obs} = 2.249, P = 0.025 \)); either of the two autosomes can restore a normal sex-ratio in the homoygous state in some cases. The combination of \( IFR^{SR} \) and \( IIFR^{SR} \) suppressors (Figure 4D) restores an even sex-ratio in all but two cases. In fact, for each of the four chromosomal combinations tested, there is a great variability for drive ability among males, which suggests a polymorphism of \( IFR^{SR} \) and \( IIFR^{SR} \) for their suppression ability. Alternatively, this variability may be due to a polymorphism of \( X^{SR} \) sensitivity to the autosomal suppression.
DISCUSSION

An X-linked complex of sex-ratio genes probably occurs in *D. simulans*: Our results clearly show that several X-linked genes are involved in the sex-ratio trait expressed by the *X^{05}* chromosomes. A major role is played by loci in the *np*-*l* region that is ~16 cm long. Nevertheless, additional gene(s) outside of this region may be involved. Data on *X^{05}* chromosomes may reflect the general structure of sex-ratio X chromosomes of the SR strain, since similar results were obtained using *X^{05}* chromosomes instead of *X^{05}* ones (data not shown).

Because several loci appear to be implicated in distortion, we cannot exclude that some of them were polymorphic among *X^{05}* and also among *X^{05}* (*X^{05}* driving factors come from a unique X chromosome of the SR strain, but extensive recombination was allowed with *X^{ST}* chromosomes). Such a polymorphism could result in a minor drive effect and explain the variations in drive ability of these chromosomes between the experiments (Figure 1C vs. 4A for *X^{05}* and Figure 2B vs. 3A for *X^{05}*). However it must be pointed out that in experiments using the SR5 strain, a strong drive ability can be recurrently recovered among the second generation male progeny of weakly distorting males (comments of Figure 2 and data not shown). In addition, some *X^{ST}* chromosomes isolated in lines with attached-X females and a standard genetic background exhibit variable drive ability (data not shown). Thus, variation in drive ability of *X^{ST}* and *X^{05}* chromosomes may be due as well to variable expressivity of the driving factors.

Enhancers of drive are expected to evolve on sex-ratio X chromosomes since any increase in distortion will be favored unless associated with fertility loss (THOMSON and FELDMAN 1975). Therefore, if several loci acting on drive are polymorphic in a population, no matter where they are located on the X chromosome, the allelic combination inducing the greatest distortion will be selected for, unless fitness is affected. The effect of linkage strength between X-linked driving loci on their fate within populations has not yet been analyzed. However, intuitively, when a new allelic combination occurs that results in a stronger driver X chromosome, the more linked the responsible loci are the more easily this combination will be selected for, since it will be split up less frequently by crossing-over events. This may lead to complexes of sex-ratio genes as we suppose to be the case in *D. simulans*. In Drosophila species where inversions prevent crossing-over along the major part of the X chromosome, more than one region of this chromosome is generally involved in the sex-ratio trait (STALKER 1961; WU and BECKENBACH 1983). The lack of inversion polymorphism in *D. simulans* probably explains that a single and small region on the X chromosome contains most of the factors responsible for the drive.

A multifactorial system restores an equal sex-ratio in the SR strain: We showed that *X^{05}* drive is weaker against *Y^{05}* chromosomes than against *Y^{ST}* chromosomes. However, it is not possible by now to determine whether this difference results from differential sensitivity of the target sequences or from the presence of suppressors on *Y^{05}* chromosomes. We arbitrarily decided to use the terminology of Y-linked suppressors of drive as in other Drosophila species (STALKER 1961; DE CARVALHO and KLACZKO 1994). Drive resistant Y chromosomes are not unexpected since they are subject to strong selection in natural populations carrying sex-ratio X chromosomes (THOMSON and FELDMAN 1975). CLARK (1987) has shown, through theoretical models, that conditions for a stable Y polymorphism are very unlikely. Stable polymorphism would only occur in the presence of X polymorphism for meiotic drive ability associated with differences in males and females fitnesses. Even in these conditions, the possible values of
the parameters allowing a stable polymorphism are very restrictive. Polymorphism of $X$ and $Y$ have been described in $D.\ paramelanica$ (Stalker 1961), but it is not clear whether or not this is an intrapopulation polymorphism, given that the different types of $Y$ and $X$ seem to only partially overlap in their geographical distributions. De Carvalho and Klaczko (1994) described an intrapopulation polymorphism for $Y$-linked sex-ratio suppressors but did not know whether the polymorphism was stable or not. Moreover, in both $D.\ paramelanica$ and $D.\ mediopunctata$, $Y$-linked suppressors can restore an equal sex-ratio and the described polymorphism was $Y^{suppressor}$ and $Y^{non-suppressor}$. In $D.\ simulans$ the $Y^{6k}$ chromosomes were found to partially suppress $X^{6k}$ drive. Sex-ratio distortion among individual progenies of $X^{6k}/Y^{6k}$ males fits a beta-binomial distribution, which suggests there could be no polymorphism of $Y^{6k}$ regarding their suppressor effect against $X^{6k}$ but that sex-ratio expression varies stochastically between males as shown for Segregation Distorter in $D.\ melanogaster$ (Sharp and Hilliker 1990). However, we cannot exclude that the Figure 3B shows a bimodal distribution (two peaks around 62 and 72%, respectively), resulting from two kinds of $Y^{6k}$ that would present a very slight difference in their suppressor effect. More $Y^{6k}$ chromosomes have to be tested to look for such a polymorphism. Alternatively, many uncontrolled factors resulting from the ST or SR5 background may explain the extra-binomial variability of sex-ratio shown by both $X^{6k}/Y^{6k}$ and $X^{6k}/Y^{6k}$ males.

On the other hand, we showed that autosomal drive suppressors, possibly polymorphic, occur on the two major autosomes in the SR strain. Such suppressors are expected to evolve in response to the sex-ratio bias in populations (Fisher's principle in Fisher 1930). Conditions for their polymorphism do not seem stringent (Wu 1983a). Autosomal suppressors have been reported in $D.\ mediopunctata$ and $D.\ paramelanica$, but they appear to have a restricted effect in these species when compared to $Y$-linked suppressors. In $D.\ mediopunctata$, partially dominant autosomal modifiers, described on all major autosomes, together can lead to complete autosomal suppression of drive as shown in a line devoid of $Y$-linked suppressors that had been selected for non-distorting males (De Carvalho and Klaczko 1993). However in the wild most of the males bearing the chromosomal arrangement associated with the sex-ratio trait seem to express it (De Carvalho et al. 1989). Similarly, the autosomal suppression in $D.\ paramelanica$ consists of a so-called “minor suppression system” that seems efficient in the wild, at least in some males, but only partially suppresses drive (Stalker 1961). Unlike the previously described autosomal suppressors, those in $D.\ simulans$ seem recessive and appear responsible for a “major effect”: the sex-ratio trait is well expressed (90% females) when SR autosomes are in a heterozygous state and a complete SR autosomal sets usually restores an equal sex-ratio. Probably because in other Drosophila species studies only led to the recovery of dominant autosomal suppressors of drive (De Carvalho and Klaczko 1993), theoretical studies on the invasion of recessive autosomal suppressors were never performed. Such suppressors would have to be homozygous to be selected, which may occur in small or structured populations. In our case it is not clear whether autosomal suppressors are completely recessive or not. In fact the proportions of sexes vary among progenies of SR/ST hybrid males (Figure 1G vs. 4A). F1 hybrid males studied on Figure 4A are sons of $F_1$, sex-ratio males, and the more the sex-ratio in the progeny of a $F_1$ male was skewed toward females, the more his $F_2$ sons where sterile (Mercot et al. 1995 and unpublished results).

Therefore it is possible that we selected combinations of autosomes with dominant suppressors.

In the SR strain, we found more suppressors than necessary: on the one hand autosomal suppressors are sufficient to restore an equal sex-ratio in the progeny of $X^{6k}$ males, on the other hand, $Y$ chromosomes themselves partially resist the drive. By now, it is not possible to determine how such a complex regulation system of sex-ratio drive evolved in $D.\ simulans$. Assuming that more potential modifier sites occur on autosomes, autosomal suppressors of drive are more likely to appear than $Y$-linked ones. Alternatively, drive insensitivity of $Y$ chromosomes can result from modifications of the target. Since the $Y$ chromosome is mainly heterochromatic, an analogy can be made with the SD system, where the sensitivity of the heterochromatic target locus ($Rsp$) correlates with repeat copy number (Wu et al. 1988). If so, $Y$ chromosome insensitivity should be more likely to evolve than autosomal suppression. When drive is rare, selection on resistant $Y$ chromosomes is stronger than on autosomal suppressors (Hurst and Pomiankowski 1991), which could give the former an advantage. Then it is probable that drive-resistant $Y^{6k}$ chromosomes were fixed before autosomal suppression was able to completely repress the drive.

The common pattern among Drosophila species is that sex-ratio $X$ chromosomes are at low frequencies in natural populations whereas drive is not or only partially suppressed, as discussed above. This implies that the spread of these chromosomes has been halted by countervailing selection on individuals that carry them. A reduced fertility of sex-ratio males is commonly observed when there is a high rate of mating (Wallace 1948; Beckenbach 1981; Wu 1983b;c; Jaenike 1996). In addition, in species where the trait is associated with chromosomal inversions, females homozygous for the sex-ratio arrangement suffer reduction in fitness (Curtis and Feldman 1980; Jaenike 1996). By contrast in $D.\ simulans$, sex-ratio $X$ chromosomes can reach high frequencies in natural populations (and up to 100% in laboratory stocks derived from wild caught flies) and a complete or nearly complete suppression of drive oc-
curs within these populations and strains (MERCOT et al. 1995; ATLAN et al. 1997). This strongly suggests that the fitness of sex-ratio X bearing flies is little or not at all affected in D. simulans. Given the lack of inversions in D. simulans, this supports the hypothesis that in other species, the low fitness of flies carrying sex-ratio factors tied up within chromosomal inversions is due to linked lethal alleles and not to the driver loci themselves.

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