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AN UNUSUAL SEX-DETERMINATION SYSTEM IN SOUTH AMERICAN FIELD MICE (GENUS *AKODON*): THE ROLE OF MUTATION, SELECTION, AND MEIOTIC DRIVE IN MAINTAINING XY FEMALES

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Abstract.—The mechanism of sex determination in mammals appears highly conserved: the presence of a Y chromosome triggers the male developmental pathway, whereas the absence of a Y chromosome results in a default female phenotype. However, if the Y chromosome fails to initiate the male pathway (referred to as Y*), XY* females can result, as is the case in several species of South American field mice (genus *Akodon*). The breeding genetics in this system inherently select against the Y* chromosome such that the frequency of XY* females should decrease rapidly to very low frequencies. However, in natural populations of *Akodon*, XY* females persist at substantial frequencies; for example, 10% of females are XY* in *A. azarae* and 30% in *A. boliviensis*. We develop a mathematical model that considers the potential roles of three evolutionary forces in maintaining XY* females: Y-to-Y* chromosome transitions (mutation), chromosome segregation distortion (meiotic drive), and differential fecundity (selection). We then test the predictions of our model using data from breeding colonies of *A. azarae*. We conclude that any single force is inadequate to maintain XY* females. However, a combination of segregation bias of the male and female Y chromosomes during spermatogenesis/oogenesis and increased fecundity in XY* females could account for the observed frequencies of XY* females.

Key words.—*Akodon*, meiotic drive, selection, sex chromosomes, sex determination, XY females, Y chromosome.

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The question of how new alleles, genotypes, and chromosomal variants are established in populations has long interested biologists (Hiraizumi et al. 1960; Lande 1979; Hedrick 1981). Often, new genotypes are slightly deleterious (e.g., chromosomal intermediates) and are quickly eliminated from a population via purifying selection or drift (Kimura and Ohta 1969). However, novel alleles can be maintained or fixed in a variety of ways, including: (1) selection, if the new allele also offers advantages under some conditions (e.g., balancing selection); (2) mutation, if the mutation rate is sufficiently high; (3) meiotic drive, if the new allele (or its chromosome) is preferentially transmitted to the next generation; (4) linkage, if the new allele is linked to a advantageous allele; or (5) drift, if the population is small, genetically subdivided, or if inbreeding is significant. Rarely does one know which evolutionary forces have influenced existing genotypes and to what extent these forces act in conjunction with one another.

Sex chromosome polymorphisms represent unique genotypes that are ideal for studying such dynamics. For example, in two species of lemmings, a mutation on an X chromosome inactivates the Y chromosome, and XY females result. Detailed studies of this sex chromosome polymorphism illustrated the importance of meiotic drive both theoretically and empirically in maintaining a novel genotype. In wood lemmings (*Myopus schisticolor*), Bengtsson (1977) suggested that the maintenance of a sex chromosome polymorphism could be explained by strong meiotic drive of an X chromosome variant in females. Female meiotic drive was also demonstrated empirically (Fredga et al. 1977). In the varying lemming (*Dicrostonyx torquatus*), meiotic drive appears to be absent in females, but present in males (Gilvea 1987). Bulmer (1988) showed mathematically that slight drive for the Y in males could maintain the polymorphism. Thus, in these two systems, a sex chromosome polymorphism appears to be maintained solely by meiotic drive.

Here, we examine a fundamentally different sex chromosome polymorphism in which XY females result from an inactivation mutation on the Y chromosome, hereafter referred to as Y*. This polymorphism has been observed in several species of South American field mice (genus *Akodon*) in which some of the females have XY* sex chromosomes and others have the normal XX genotype. In *Akodon* XY* females result from the complete failure of the Y* chromosome to activate the male developmental pathway as evidenced by karyotype, (Bianchi and Contreras 1967), molecular techniques (Vitullo et al. 1986; Bianchi et al. 1993; Hoekstra and Edwards 2000) and patterns of inheritance in breeding studies (Lizarralde et al. 1982; Espinosa and Vitullo 1996). Thus, any individual carrying this Y* chromosome is phenotypically female; the penetrance is complete.

In most mammalian species, XY females experience deleterious fitness consequences. XY females have to overcome decreases in both fertility and in fecundity, the latter due to the loss of YY zygotes. (Ohno 1967; Bull 1983; Marin and Baker 1998). In some *Akodon* species, however, XY* females are viable and fully fertile (although the mechanism remains unknown). Although XY* female *Akodon* do not suffer fertility consequences, as humans (Watchel and Simpson 1994) or other mice (Eicher et al. 1982) do, the way the Y* chromosome is inherited results in a decrease in frequency of XY* females each generation (see model). This creates an evolutionary puzzle: theoretically, XY* females should not

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persist in a population, yet they are found at relatively high frequencies in natural populations of several species of *Akodon* (10% in *A. azarae* and 30% in *A. boliviensis*). Additionally, XY* females have evolved independently in at least six species of *Akodon* (Hoekstra and Edwards 2000). This evidence suggests that the evolution of this sex chromosome polymorphism is recent and, perhaps more importantly, that the mechanism maintaining XY* females may have evolved repeatedly as well.

In this paper, we explore the single and joint effects of mutation, segregation distortion (which we will refer to as meiotic drive), and selection in maintaining the sex chromosome polymorphism in natural populations of *Akodon* mice. Using a mathematical model, we generate hypotheses about how these forces may act independently and in combination to maintain XY* females in a population. We then test these hypotheses with reproductive data from a laboratory colony of *A. azarae*. By combining theoretical approaches and empirical data, we can better address the question of how XY* female *Akodon* are maintained in real populations.

Study System

South American field mice (genus *Akodon*) are found in almost all habitats across South America, absent only from the wet forests of Brazil (Smith and Patton 1991). Currently, 35 species are recognized (Wilson and Reeder 1993). A molecular survey of 16 *Akodon* species found XY* females to be present in eight and maintained at equilibrium frequencies ranging from 10% to 30% of all females (Hoekstra and Edwards 2000).

The breeding genetics of XY* females are unique and have important evolutionary consequences. Expected offspring genotype/phenotype frequencies are readily drawn from Punnett squares for XX/XY and XY*/XY pairings. Offspring born to an XX mother consist of XX daughters and XY sons in equal proportions, resulting in an offspring sex ratio of 1:1 at birth. In contrast, an XY* mother produces offspring that are XX female, XY* female, and XY male in equal proportions, resulting in a 2:1 female-biased offspring sex ratio at birth; YY* zygotes are inviable and do not implant. XY* females appear to compensate completely for lost zygotes by ovulating more eggs than they implant to maintain similar litter sizes (Espinosa and Vitullo 1996). Note that Y chromosomes are inherited paternally and Y* chromosomes are inherited maternally (Y and Y* are never found in a single individual and thus do not have any opportunity to recombine). These breeding genetics have three major consequences for the evolution of the XY* genotype: (1) barring new mutations, XY* female offspring only result from XY* mothers (Lizarralde et al. 1982); (2) XY* females will never go to fixation within a population because XY* mothers produce both XY* and XX daughters; and (3) the proportion of XY* females should decrease by at least one-third every generation (see model).

MODEL

Basic Model Structure and Preliminary Analysis

To evaluate how mutation, meiotic drive, and natural selection could interact to maintain XY* females in natural populations of *Akodon*, we derive recursion models to determine the conditions under which positive frequencies of the XY* genotype could be maintained. Let f_t be the proportion of females with the XY* genotype at time t. To predict the equilibrium frequency of XY* females, we model f_{t+1} as a discrete time function of f_t, and solve for the equilibrium frequency, $\hat{f}$, when $f_{t+1} = f_t$. We assume infinite population size and random mating in all permutations of the model. We also assume that matings are not male limited such that the female genotype frequencies are independent of the number of males in the population (Suarez and Kravetz 1998).

The basic recursions underlying our model are derived by considering the expected genotype frequencies for offspring born to XX and XY* females. Assuming no mutation, no meiotic drive, no natural selection, and complete compensation for YY* zygotes, the relative frequencies of the two female genotypes in the next generation are predicted by multiplying expected offspring genotype frequencies by maternal genotype frequencies. The frequency of XY* females among all females in the next generation thus becomes:

$$f_{t+1} = \frac{\frac{1}{3} f_t}{\frac{2}{3} f_t + \frac{1}{2}(1 - f_t)} = \frac{2 f_t}{3 + f_t}. \quad (1)$$

For any f_t greater than zero, $f_{t+1} \leq \frac{2}{3} f_t$ such that the frequency of XY* females in a population will decline, even the in the absence of organism-level selection against XY* females. This rapid decline is a consequence of the breeding genetics of this system, whereby the Y* chromosome is transmitted to only one-third of an XY* female's offspring. Thus, XY* females cannot be maintained in a population without invoking a mechanism by which the effect of the breeding genetics is counteracted.

Mutation

To model the effect of mutation on the equilibrium frequency of XY* females, we derive an equation analogous to equation (1) by considering how mutation of Y chromosomes to Y* chromosomes would change expected offspring genotype frequencies. We define μ to be the rate at which Y mutates to Y*. Expected genotype frequencies for offspring born to XX and XY* females become $\frac{1}{2}$XX:$\frac{1}{2}(1 - \mu)$XY:$\frac{1}{2}\mu$XY* and $\frac{1}{3}$XX:$\frac{1}{3}(1 - \mu)$XY:$\frac{1}{3}(1 + \mu)$XY*, respectively.

The predicted frequency of XY* females in the next generation is, after simplification:

$$f_{t+1} = \frac{3\mu + (2 - \mu) f_t}{3(1 + \mu) + (1 - \mu) f_t}. \quad (2)$$

Note that equation (2) simplifies further to equation (1) if μ is set equal to zero. Solving for $\hat{f}$ yields one positive root predicting the equilibrium frequency of XY* females as a function of μ:

$$\hat{f} = \frac{1 + 4\mu - \sqrt{1 + 20\mu + 4\mu^2}}{2(-1 + \mu)}. \quad (3)$$

Equation (3) suggests that mutation could maintain a positive frequency of XY* females. However, to maintain XY*

females at frequencies observed in natural populations of *Akodon*, mutation rates would have to be extraordinarily high (e.g., $\mu = 0.042$ to maintain 10% XY* females as in *A. azarae*; Fig. 1A, Table 1). In light of these results and an assessment of data from a laboratory colony of *Akodon* described below, we conclude that mutation is not likely to strongly influence the maintenance of XY* females. Mutation is, therefore, omitted from subsequent model permutations.

Meiotic Drive and Natural Selection

Meiotic drive could affect the frequency of XY* females by distorting offspring genotype frequencies, whereas natural selection could change maternal genotype frequencies. To allow for meiotic drive in both XY males and XY* females, we define γ to be the proportion of sperm carrying the Y chromosome and δ to be the proportion of XY* female ova carrying the Y* chromosome. Expected genotype frequencies for offspring born to XX and XY* females become $(1 - \gamma)$ XX:γXY and $(1 - \gamma)(1 - \delta)/C$ XX:$(1 - \gamma)\delta/C$ XY*:$\gamma(1 - \delta)/C$ XY, respectively, where $C = 1 - \delta\gamma$ compensates for inviable YY* zygotes.

To allow for natural selection via differential fitness between the two female genotypes, we define ω to be the fitness of XY* females relative to that of XX females. The relative fitness of XX females is normalized to one. The frequency of XY* females in the next generation is predicted, after simplification, to be:

$$f_{t+1} = \frac{\delta\omega f_t}{[1 - \delta\gamma - f_t(1 - \delta\gamma - \omega)]}. \quad (4)$$

One solution is the trivial case $\hat{f} = 0$, when there are no XY* females in the population. The second solution predicts $\hat{f}$ as a function of the meiotic drive and relative fitness parameters:

$$\hat{f} = \frac{1 - \delta\gamma - \delta\omega}{1 - \delta\gamma - \omega}. \quad (5)$$

To isolate the individual effect of natural selection, we substitute $\gamma = 0.5$ and $\delta = 0.5$ (cases representing no meiotic drive) into equation (5) to predict $\hat{f}$ as a function of ω:

$$\hat{f} = \frac{3 - 2\omega}{3 - 4\omega}. \quad (6)$$

For values of ω greater than 1.5, $\hat{f}$ is positive, suggesting that natural selection could maintain XY* females in a population if their fitness were sufficiently greater than that of XX females (Fig. 1B, Table 1).

Substituting $\delta = 0.5$ (no meiotic drive for the Y* chromosome) and $\omega = 1$ (no selection for XY* females) into equation (5) predicts $\hat{f}$ as a function of γ, the strength of meiotic drive in males:

$$\hat{f} = \frac{\gamma - 1}{\gamma}. \quad (7)$$

The only nonnegative solution is $\hat{f} = 0$, indicating that meiotic drive in males is not sufficient to maintain XY* females (Table 1).

To isolate the effect of meiotic drive in XY* females, we substitute $\gamma = 0.5$ (no meiotic drive for Y chromosomes) and $\omega = 1$ (no selection for XY* females) into equation (5), yielding:

$$\hat{f} = \frac{3\delta - 2}{\delta}. \quad (8)$$

This equation has a positive solution only if $\delta > \frac{2}{3}$, suggesting that sufficiently strong meiotic drive favoring the Y* chromosome could maintain XY* females (Fig. 1C, Table 1).

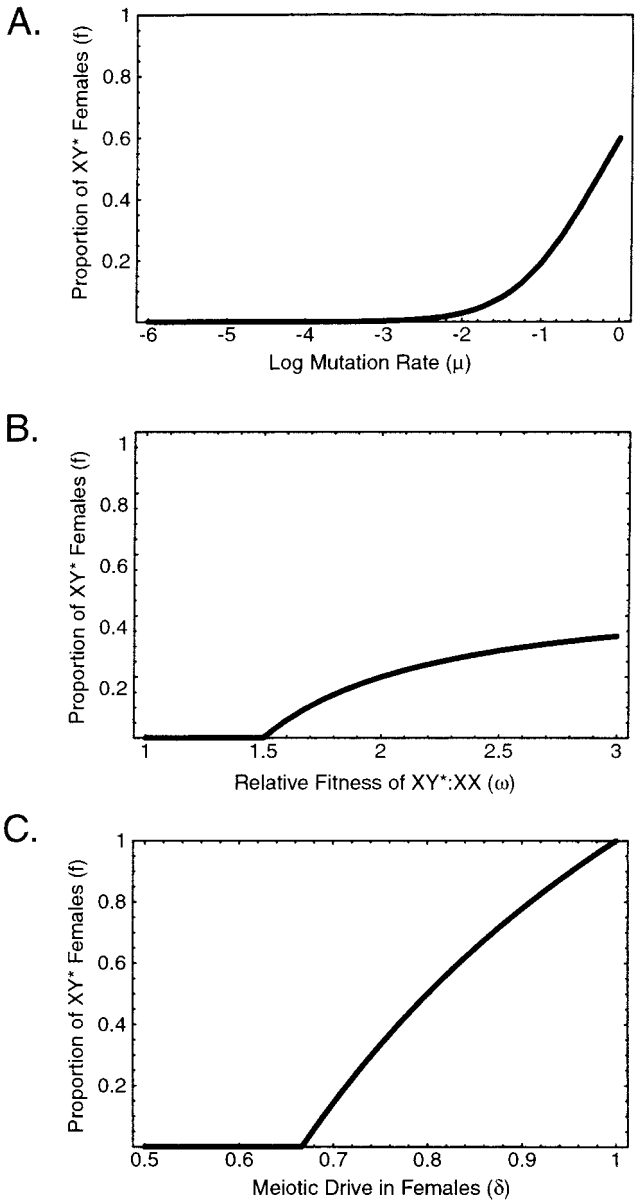

FIG. 1. The independent effects of mutation, meiotic drive, and selection on the predicted equilibrium frequency of XY* females. (A) The effect of increasing Y to Y* mutation rate (μ) on a log scale. If $\mu = 1$, the maximum frequency of XY* females is 60%. (B) The effect of increasing relative fitness advantage of XY* over XX females (ω). Fitness differences alone cannot increase the frequency of XY* females over 50%. (C) The effect of increasing female meiotic drive (δ). If $\delta = 1$, all females will be XY*.

TABLE 1. Predicted strengths of evolutionary forces necessary to maintain XY* females. Table shows the minimum strength of mutation (μ), meiotic drive in XY males (γ) and XY* females (δ), and selection (ω) to independently maintain XY* females at three equilibrium levels: 0.1%, 10%, and 30%. The first frequency was chosen as a minimal value. The latter frequencies approximate those observed in natural populations of *Akodon azarae* and *A. boliviensis*, respectively.

	Equilibrium frequency of XY* females		
Parameter	0.1%	10%	30%
μ	0.0003	0.0421	0.2063
γ	n/a	n/a	n/a
δ	0.6669	0.6897	0.7407
ω	1.5015	1.6875	2.6250

The combined effects of meiotic drive and natural selection predicted by equation (5) are illustrated in the contour plot in Figure 2. The solid contours identify combinations of δ and ω that would maintain XY* females at indicated frequencies when $\gamma = 0.5$; the dotted contours identify the combinations of δ and ω that would maintain XY* females at indicated frequencies when $\gamma = 0.55$. Note that the solid contour for $\hat{f} = 0.1\%$ intersects the ω and δ axes at the threshold values predicted analytically in equations (6) and (8), respectively.

All contours in Figure 2 are concave-upward, indicating that natural selection and meiotic drive interact positively to maintain XY* females at a higher equilibrium frequency than would be predicted if the effects were simply additive. Furthermore, once threshold levels of meiotic drive or natural selection parameters are exceeded, relatively small increases in the parameter values yield substantial increases in the predicted equilibrium frequency of XY* females.

Comparison of the solid and dotted contours in Figure 2 suggest that meiotic drive for the Y chromosome in males interacts positively with meiotic drive in XY* females and natural selection to facilitate maintenance of XY* females. Increasing γ from 0.5 to 0.55, reduces the levels of meiotic drive in XY* females and relative fitness necessary to maintain XY* females at a particular frequency. This result contrasts with analysis of equation (7) above that predicts meiotic drive in males to be ineffective in maintaining XY* females. Additional analyses (not presented here) suggest that mutation would also have a complementary interaction with drive and selection, but its effect would be negligible unless mutation rates were on the order of 0.01 or more.

ESTIMATION OF PARAMETERS

To test whether the quantitative predictions of our model are biologically plausible for *Akodon* species, we estimated parameter values for mutation, meiotic drive, and relative fitness with data collected from a laboratory colony of *A. azarae* (Table 2). We then compared the equilibrium frequency of XY* females predicted by these parameter values with the frequency observed in natural populations. The data available to us comprised information on reproductive timing, litter sizes, and offspring sex ratios for a colony of *A. azarae* maintained for approximately 20 years at Universidad de Buenos Aires (Espinosa 1991, 1995; Espinosa and Vitullo 1996, unpubl. data). Additional data on offspring sex ratios

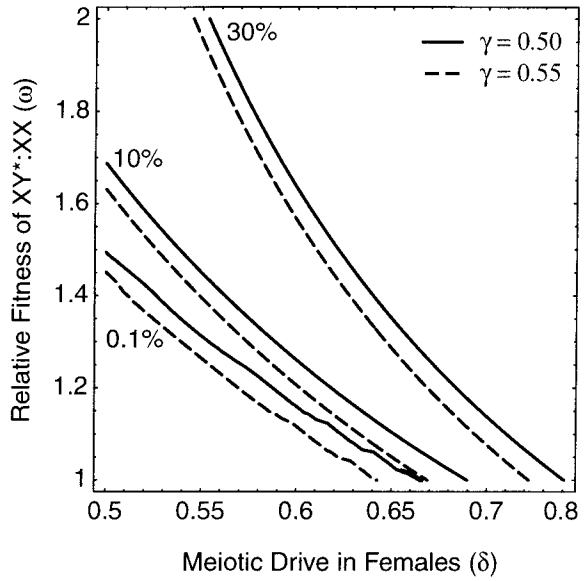

FIG. 2. The interaction of meiotic drive and selection in maintaining different frequencies of XY* females. Solid contours indicate the combinations of parameter values for meiotic drive for Y* chromosome (δ) and natural selection for XY* females (ω) necessary to maintain XY* females at equilibrium frequencies of 0.1% (threshold frequency), 10% (as observed in *Akodon azarae*) and 30% (as observed in *A. boliviensis*). For solid contours, the parameter for meiotic drive in males (γ) is set equal to 0.5. Dotted lines complement each solid line, reflecting parameter combinations when meiotic drive in males ($\gamma = 0.55$) is included in the model.

were also taken from Lizarralde et al. (1982). These data are reprinted, with permission, in the Appendix.

The mutation rate, μ, was estimated from the numbers of XY* females and XY males born to XX females. Available data indicated that of 278 progeny born to XX females, 153 were XY males but none were XY* females (Lizarralde et al. 1982; Espinosa and Vitullo 1996, unpubl. data). Assuming that the genotype frequencies were drawn from a binomial distribution with expectation μ, the mutation rate could be as high as 0.019 ($P = 0.05$ that data derived by chance; Table 2; Zar 1984). We stress, however, that there have been no observations of XX females producing XY* female offspring during the past 20 years that a colony has been maintained (M. B. Espinosa, pers. comm.). Thus, we expect the true mutation rate is much lower.

Rates of meiotic drive in males (γ) and XY* females (δ) were estimated jointly using sex-ratio data for offspring born

TABLE 2. Parameter estimates using data from a laboratory colony of *Akodon azarae*. Mutation rate (μ) is the highest value the data cannot exclude. Meiotic drive in males (γ) and XY* females (δ) were estimated by maximum likelihood (Hilborn and Mangel 1997). Relative fitness (ω) was estimated from life-history tables; 95% confidence intervals calculated by likelihood ratios are shown where appropriate.

Parameter	Best estimate	CI
μ	$\ll$0.019	n/a
γ	0.550	(0.493, 0.606)
δ	0.632	(0.507, 0.727)
ω	1.35	n/a

to XX and XY* females reported in two independent studies (Espinosa 1991; Espinoza and Vitullo 1996, unpubl. data; Lizarralde et al. 1982; see Appendix). Assuming that data were drawn from binomial distributions, we calculated maximum-likelihood estimates for γ and δ by minimizing the sum of negative log-likelihoods of the data using the likelihood function (Hilborn and Mangel 1997):

$$-\ln[L] = \sum_i [-N^i_{males}\ln(p^i_{males}) - N^i_{females}\ln(1 - p^i_{males})], \quad (9)$$

where i = maternal genotype (XX or XY*), N^i_{males} = observed number of males born to females of genotype i, $N^i_{females}$ = observed number of females born to females of genotype i, and p^i_{males} = expected proportion of male offspring born to females of genotype i, given values of γ and δ. For XX females, $p_{males} = \gamma$. For XY* females, $p_{males} = (1 - \delta)\gamma/(1 - \delta\gamma)$. We estimated 95% confidence intervals for the parameter estimates using likelihood ratios (Hilborn and Mangel 1997).

The maximum-likelihood parameter values for γ and δ were 0.55 and 0.632, respectively; 95% confidence intervals were (0.493, 0.606) and (0.507, 0.727), respectively (Table 2). A null hypothesis of no meiotic drive in males could not be excluded because the confidence interval spans 0.5, but the data do indicate meiotic drive for the Y* chromosome.

We estimated the relative fitness of XY* females as the ratio of intrinsic rates of increase for each female genotype. Rates of increase for XY* and XX females were calculated using a discretized approximation of the Euler equation (Birch 1948) into which age-specific fecundity and survivorship schedules were substituted:

$$1 = \sum_x e^{-rx} l_x m_x. \quad (10)$$

Fecundity schedules were constructed with data on ages at first and last parturitions, interlitter intervals, and litter sizes (Espinosa et al. 1996). Relative to XX females, XY* females in the laboratory generally started reproducing earlier, continued to reproduce longer, had shorter intervals between litters, and had similarly sized litters (see Appendix). We estimated fecundity at age x, m_x, as:

$$m_x = (p^{first}_x - p^{last}_x) \cdot i \cdot n_x, \quad (11)$$

where p^{first}_x = cumulative probability that a female of age x would have had her first litter, p^{last}_x = cumulative probability that a female of age x would have had her last litter, $(p^{first}_x - p^{last}_x)$ = probability that a female of age x would be of reproductive age i = inverse of mean interlitter interval, and n_x = mean litter size at age x. Available data were aggregated over various time intervals. We resolved data to a consistent 1-week scale by assuming that data were uniformly distributed within coarser intervals.

Quantitative data on age-specific survivorship were not available. However, a plot of survivorship to age x of males and females in the laboratory colony (Espinosa et al. 1996) suggested Type II survivorship in which survivorship from one 1-week interval to the next was constant at about 0.98. In the absence of any genotype-specific data, we assumed identical survivorship schedules for XY* and XX females.

The intrinsic rate of increase for each genotype was estimated by substituting fecundity and survivorship schedules into equation (10) and solving for r. For XX females, r = 0.063. For XY* females, r = 0.084. Normalizing on the fitness of XX females, we estimated the relative fitness of XY* females to be 1.35 (Table 2). Because our primary purpose was to identify the best estimate of relative fitness given the data, we did not attempt to estimate confidence intervals around this estimate.

Predictions of the Model Given Parameter Estimates

To evaluate how well our model might explain the maintenance of XY* females in natural populations of *A. azarae*, we compared the observed frequency of XY* females to that predicted by our model given the estimated parameter values. Five of 43 female *A. azarae* specimens collected from the field in 1998 (by H. E. Hoekstra) had the XY* genotype (Hoekstra and Edwards 2000), yielding an estimated frequency of 11.6%.

When substituted into equations (6) and (8), respectively, neither ω = 1.35 nor δ = 0.632 is individually sufficient to maintain XY* females at the observed frequency. However, when these values are substituted into equation (5) along with γ = 0.55, $\hat{f}$ is predicted to be 28.8%. Thus, the combination of estimated parameter values is sufficient to maintain XY* females at, or even above, the observed frequency.

Discussion

Analysis of our model suggested that mutation, meiotic drive in XY* females, and natural selection are each potential mechanisms by which XY* females could be maintained in a population. However, estimated rates of mutation, meiotic drive, and relative fitness of XY* females from a laboratory colony of *A. azarae* suggested that each force in isolation was unable to maintain XY* females at the observed frequency. However, our model predicted that an excess of XY* females could be maintained by meiotic drive and natural selection acting in combination at the estimated rates. Although our results do not prove that these are the mechanisms responsible for maintaining the novel XY* genotype, they demonstrate that the combined action of meiotic drive and natural selection are a sufficient and biologically plausible explanation for the maintenance of 10% XY* females in *A. azarae*. Furthermore, similar combinations of meiotic drive and natural selection could also explain maintenance of XY* females at different frequencies in other *Akodon* species. For instance, XY* females occur at a frequency of approximately 30% in *A. boliviensis*. This higher frequency of XY* females could be maintained if XY* females of this species had a greater relative fitness or if meiotic drive were stronger.

Estimation of XY Female Frequency*

Many studies exploring the establishment of novel alleles exclusively use mathematics to make predictions and define parameters (e.g., Hedrick 1981; Walsh 1982; Bulmer 1988). Often, however, it is unknown if these parameters are biologically realistic. Here, we combined a mathematical model with data from a laboratory colony of *A. azarae* to determine

if the predictions of the model could be met by the organism. This approach allowed us not only to test the feasibility of our model but also to identify discrepancies between predicted and observed measures. Using the empirical measures of selection and meiotic drive from the laboratory population, the model predicts more XY* females (29%) than are observed in natural populations of *Akodon* (~10%). This suggests that (1) we overestimated the strength of selection and/or meiotic drive; (2) other factors may be deflating the frequency of XY* females; or (3) field estimates of XY* females are low.

We estimated selection (via relative reproductive fitness) using data from a laboratory colony of *A. azarae*. Differences in fitness between the two female genotypes may be reduced in the field if, for example, resources are limited and XY* females do not reach their full breeding potential. Additionally, differences in mortality between XX and XY* females can also influence our measure of relative fitness. Our estimates of meiotic drive in males and XY* females were based on sex ratios of litters. One advantage of this method is that it can detect segregation distortion acting at any time from spermatogenesis and oogenesis through implantation. This is especially advantageous when the exact mechanism of distortion is unknown. However, this method also requires large sample sizes. Although the samples we used for our estimates were sizable, the confidence intervals around our estimates remained fairly broad. We used our best estimates, but recognize that they may be over- or underestimated, and thus explain, in part, the discrepancy between observations and model predictions.

Interestingly, other well known meiotic drive systems including segregation distorter (*SD*), sex ratio (*SR*), and *t*-haplotypes that are maintained as polymorphisms in natural populations are also found at low frequencies compared to theoretical predictions that account for measures of drive in laboratory colonies (Ardlie and Silver 1998). Whereas drive modifiers (i.e., suppressors) were shown to be unimportant in the *t*-haplotype system, (Ardlie and Silver 1996), they could be acting in the *Akodon* XY* female system. Still other forces that have been suggested to decrease *t*-haplotype frequencies include drift in deme-structured populations (Lewontin 1962), systematic inbreeding, and mate choice.

It is also possible that XY* female frequencies are influenced by genetic drift in addition to the deterministic factors considered by our model. If populations were small or structured, drift could randomly increase the frequency of a slightly deleterious allele via population sampling (Kimura and Ohta 1969). Because XY* females cannot be fixed in a population (because XY* mothers produce XX daughters), random drift may be less important for maintaining the XY* genotype than for alleles that can beome fixed locally and then spread via migration. However, drift could help to increase the frequency of XY* females enough for them disperse among demes. Importantly, the effects of drift may be tested using genetic data to quantify population structure, degree of inbreeding, and assortative mating. If populations were highly structured, further sampling of field populations can determine whether the presence of XY* females is population specific or if the frequency of XY* females varies among populations.

Spatial and temporal variability in the *t*-haplotype system has been implicated in deflating the frequency of the *t*-allele below mathematical expectations (Ardlie and Silver 1998). However, in *A. azarae*, the frequency of XY* females appears to have remained roughly constant over time. For example, among a small sample of 25 *A. azarae* females from Buenos Aires taken before 1970, eight were likely XY* females (Bianchi et al. 1971), but anecdotal karyotyping studies from the 1980s with larger sample sizes estimated closer to a 10% frequency in *A. azarae* (A. Vitullo, pers. comm.). XY* females also appear in all populations sampled thus far in species with XY* females (H. E. Hoekstra, unpubl. data). More detailed sampling of populations is necessary to better assess temporal and spatial variation in the frequency of XY* females.

Implications for the Establishment of Sex Chromosome Polymorphisms

Our results suggest several conclusions regarding the evolution of XY* females in *Akodon* and, more generally, the evolution of sex chromosome polymorphisms. First, the maintenance of XY* females in *Akodon* appears to be one of only a few examples of selection and meiotic drive operating in parallel to maintain a genotype. In most cases, these forces act antagonistically to maintain a balanced polymorphism. For example, a dynamic balance of drive (increasing the frequency of an allele) and selection (decreasing the frequency of that allele) was observed at the myotonic dystrophy locus (Chakraborty et al. 1996) and may be responsible for the maintenance of sex-ratio (*SR*) loci in *Drosophila* (Curtsinger 1991).

Second, our model predicts that evolutionary forces (in this case, selection and meiotic drive) interact nonadditively, such that forces acting in combination need not be as strong as one might expect. Although detection may be more difficult, combined action of evolutionary forces may be more common in nature than we presently realize (Hedrick 1981; but see Hiraizumi et al. 1960; Lande 1979). Thus, even though strong meiotic drive may be rare, in part due to the evolution of modifiers, our model predicts that even small effects of meiotic drive can be important when acting in combination with other forces.

This *Akodon* system presents a unique opportunity to examine these conclusions in greater depth. XY* females have evolved independently in several species, providing natural replicates. Because XY* females appear to be maintained at different frequencies in different *Akodon* species, we can estimate selection and meiotic drive in other *Akodon* species to test how XY* females may be maintained at different frequencies. Does selection, meiotic drive, or both increase to maintain XY* females at higher frequencies? Or, do forces other than selection and meiotic drive play a role in maintaining higher frequencies of XY* females in other *Akodon* species? Answers to these questions will provide greater insight into how sex chromosome polymorphisms are maintained.

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Appendix

The raw data included here are a compilation of data from Lizarralde et al. (1982), Espinosa (1991), Espinosa et al. (1996), and unpublished data from M. B. Espinosa. These data were used to construct fecundity schedules used to estimate fitness of XX and XY* females.

Sex Ratio of Offspring

Number of male and female offspring produced by XX and XY* mothers of *Akodon azarae* in two independent studies.

	Females	Males
XX mother[1]	92	104
XY* mother[1]	267	113
XX mother[2]	33	49
XY* mother[2]	59	34

[1] From Espinosa (1991, 1996, unpubl. data).
[2] From Lizarralde et al. (1982).

Age of First Parturition

Age of XX or XY* *A. azarae* mother when she produces her first litter.

	XX	XY*
Before 3 months	0	4 (13%)
3–5 months	17 (71%)	22 (69%)
6–8 months	6 (25%)	3 (9%)
9–11 months	1 (4%)	3 (9%)
Total	24	32

Age of Last Parturition

Age of XX or XY* *A. azarae* mother when she produces her last litter.

	XX	XY*
3–5 months	1 (4%)	1 (2%)
6–8 months	11 (46%)	5 (16%)
9–12 months	9 (37%)	12 (38%)
13–21 months	3 (13%)	11 (34%)
>22 months	0	3 (9%)
Total	24	32

Intervals between Litters

Numbers of days between litters born to XX and XY* *A. azarae* mothers.

	XX	XY*
<20 days	2 (3%)	2 (1%)
21–35 days	29 (46%)	84 (57%)
36–60 days	23 (37%)	49 (33%)
>60 days	9 (14%)	12 (9%)
Total	63	147