

Reciprocally Imprinted Genes and the Response to Selection on One Sex

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ABSTRACT

We explore the theoretical consequences of limiting selection to males for the evolution of imprinted genes. We find that the efficiency of male-limited selection depends on the pattern of imprinting at an imprinted locus. When selection is strong, the maternally expressed pattern of imprinting allows faster genetic change than the reciprocal, paternally expressed pattern. When selection is relatively weak, the pattern of imprinting that permits a greater rate of genetic response to selection depends on the frequency of the favored allele: the paternally expressed pattern permits faster genetic change than does the maternally expressed pattern at low frequencies of a favored allele; at higher frequencies of a favored allele, however, the maternally expressed pattern is again more conducive to a genetic response. To our knowledge, this is the first theoretical description of a difference between the two reciprocal patterns of imprinting. The selective efficiency bias we identify between the two patterns of imprinting has implications for natural and livestock populations, which we discuss.

A given mammalian genome contains dozens to hundreds of imprinted genes, with new empirical studies adjusting this estimate as they are published (MORISON *et al.* 2005; <http://igc.otago.ac.nz/home.html> maintains a current database). An imprinted gene is one that is expressed at different levels when paternally derived *vs.* when maternally derived (REIK and WALTER 2001). This unique feature, first described >20 years ago, makes their pattern of heredity non-Mendelian (McGRATH and SOLTER 1984; SURANI *et al.* 1984). Imprinted genes have been described convincingly in mammals and seed plants (reviewed recently by BURT and TRIVERS 2006, Chap. 4). We limit our consideration to mammals, although many of the same principles could in theory apply to seed plants. The difference in expression at an imprinted diploid locus takes the form of silence of one allele and exclusive expression from the other allele, which is achieved by a mechanism that involves reversible, germ-line-specific methylation of nuclear DNA (PFEIFER 2000; REIK and WALTER 2001). Imprinted expression is often tissue specific. For example, the maternally derived allele may be the only allele expressed in placenta with both alleles expressed in all other tissues.

Imprinted genes have received attention in the livestock production literature because of their effects on growth (RUVINSKY 1999). The study of imprinted genetic variation in agricultural populations has moved forward on two fronts: linear model studies, which aim to

measure the extent of imprinted variation compared to other sources of variation, and quantitative trait locus (QTL) studies, which aim to identify the specific imprinted genes or regions of the genome responsible for that variation.

First, the animal model, from which best linear unbiased predicted (BLUP) breeding values can be assessed, has been modified in two ways to permit the detection of imprinted genetic effects. SCHAEFFER *et al.* (1989) were the first to add a gametic effect (equivalent to “parent-specific” or “imprinted” effect) to the animal model (for a review of linear models and BLUP, see LYNCH and WALSH 1998 and MRODE 2005). However, a widely used approach for estimating the genetic variances with restricted maximum likelihood (REML) cannot handle this mixture of animal and gametic levels (ESSL and VOITH 2002a). TIER and SOLKNER (1993) describe a model that cleverly assigns gametic effects as animal-level effects to sidestep this problem. This latter model has been used in a handful of studies that have found evidence for imprinted genetic effects on meat and production traits (DE VRIES *et al.* 1994; ENGELLANDT and TIER 2002; ESSL and VOITH 2002b; STELLA *et al.* 2003).

Second, the standard F₂ design was modified by KNOTT *et al.* (1998) to allow for the detection of parent-specific QTL. More studies employing a QTL approach exist than those using linear models for imprinted effects. Further, these studies have not been limited solely to livestock species. Imprinted loci have now been detected in sheep, pig, and mouse for traits such as growth and other agriculturally relevant features (COCKETT *et al.* 1996; DE KONING *et al.* 2000; MANTEY *et al.* 2005). Most notably, in two separate studies, an imprinted QTL for

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meat quality traits was found in a cross between pig breeds (JEON *et al.* 1999; NEZER *et al.* 1999). The QTL was mapped to a region that contained *Igf2*—easily the best studied of all imprinted genes in mammals—and the single-nucleotide difference responsible for the effect was later demonstrated to lie within an intron of this gene (VAN LAERE *et al.* 2003), suggesting a regulatory role. The variant in this region accounted for as much as 20–30% of the variation in certain measures of meat quality. Further designs for detecting imprinted QTL in agricultural data sets have also been suggested and employed (DE KONING *et al.* 2002; CUI *et al.* 2006, 2007).

There is budding interest in the possibility that imprinted genes play a major role in agriculturally relevant traits (RUVINSKY 1999). However, there exists scant theoretical work to suggest where to begin looking for imprinted genetic variation and what shape it may take. This is why we are interested here in the population genetic features of imprinted genes under agricultural-like schemes of selection. One salient feature of many agricultural populations is the difference in selective strengths placed on males and females when particular “stud” males are used. PEARCE and SPENCER (1992) demonstrated that under most selective schemes, the population genetics of imprinted genes reduce to formal equivalence with Mendelian population genetics. The exception was when selection differed between males and females (extended in ANDERSON and SPENCER 1999). In both of Spencer and colleagues’ articles, their interests were not in comparing the two patterns of imprinting but mostly concerned with the comparison of imprinted loci with Mendelian loci. Here we pay special attention to the differences between imprinted loci that are paternally expressed and loci with the opposite pattern of imprinting (maternally expressed). Specifically, we wish to know how imprinted genes with the two patterns of imprinting evolve in response to selective breeding in agricultural settings. Knowing the theoretical underpinnings of the selective response in imprinted genes is essential, as imprinted genes have proven to be important in production traits and will likely be given more attention in the future as the techniques to detect their effects improve. Finally, since artificial selection and natural selection are at their core the same process, the work here also merits consideration by those interested in natural populations.

MODEL

We present a simple one-locus, two-allele model of evolution at an imprinted, autosomal locus, akin to Equation 1 of ANDERSON and SPENCER (1999). This model is analyzed for both maternally expressed and paternally expressed imprinted loci to compare allele-frequency changes under both patterns of imprinting.

Consider an autosomal locus with two alleles, *A* and *a*, and four genotypes (*AA*, *Aa*, *aA*, and *aa*—maternally

derived allele written first). The *A* allele is favored by selection, which acts on males only, and occurs in frequency p_e in eggs and p_s in sperm. Zygotes are formed by random union of eggs and sperm. Before selection, the genotype frequencies are the same in the two sexes. We refer to the frequencies of egg- and sperm-derived alleles in females and males as p_{ef} , p_{sf} , p_{em} , and p_{sm} , accordingly.

Selection on males at a maternally expressed locus: At a maternally expressed locus, the phenotype is determined by the egg-derived allele. Therefore, *AA* and *Aa* genotypes are phenotypically equivalent, as are *aA* and *aa* genotypes. *AA* and *Aa* males are given a fitness of 1 and the *aA* and *aa* males are given a fitness of w ($0 \leq w < 1$). Since selection does not “see” the paternally derived allele at such a locus and because there is no correlation between maternally derived and paternally derived genes, the selection process, which is acting exclusively on males, modifies only p_{em} from pre- to postselection males. The three other allele frequencies are unchanged by a round of selection. The prime (') notation denotes a postselection allele frequency. These are the frequencies of the *A* allele in the current generation after selection has acted:

$$p'_{ef} = p_e \quad (1a)$$

$$p'_{sf} = p_s \quad (1b)$$

$$p'_{em} = \frac{p_e}{p_e + (1 - p_e)w} \quad (1c)$$

$$p'_{sm} = p_s \quad (1d)$$

The corresponding changes at each of these four positions from zygotes to postselection adults within this generation are given by $\delta p = p' - p$ (we use δ for within-generation changes and Δ for between-generation changes):

$$\delta p_{ef} = 0 \quad (2a)$$

$$\delta p_{sf} = 0 \quad (2b)$$

$$\delta p_{em} = \frac{p_e}{p_e + (1 - p_e)w} - p_e = \frac{p_e(1 - p_e)(1 - w)}{p_e + w(1 - p_e)} \quad (2c)$$

$$\delta p_{sm} = 0 \quad (2d)$$

After selection, females produce eggs and males produce sperm in the frequencies p''_e and p''_s . These frequencies are calculated by averaging (1a) and (1b) to give the next generation’s egg-derived frequency and by averaging (1c) and (1d) to give the next generation’s sperm-derived frequency. Their difference is due to selection on egg-derived alleles in males and gives rise to

the difference in the frequency of the two heterozygotes in the next generation:

$$p_c'' = \frac{p_{ef}' + p_{sf}'}{2} = \frac{p_c + p_s}{2} \tag{3a}$$

$$p_s'' = \frac{p_{em}' + p_{sm}'}{2} = \frac{p_{em}' + p_s}{2} \tag{3b}$$

$$p_s'' - p_c'' = \frac{p_{em}' - p_c}{2} = (1 - p_c'')p_s'' - p_c''(1 - p_s''). \tag{3c}$$

The changes in gametic frequencies from one generation to the next are simply

$$\Delta p_c = p_c'' - p_c = \frac{p_s - p_c}{2} \tag{4a}$$

$$\Delta p_s = p_s'' - p_s = \frac{p_{em}' - p_s}{2}. \tag{4b}$$

Selection on males at a paternally expressed locus:

With the reciprocal pattern of imprinting at the *A* locus, *AA* and *aA* males are phenotypically equivalent (fitness = 1) and *aa* and *Aa* males are phenotypically equivalent (fitness = *w*, 0 ≤ *w* < 1). Selection, in this case, acts solely on sperm-derived alleles in males:

$$p_{sm}' = \frac{p_s}{p_s + (1 - p_s)w} \tag{5a}$$

$$\delta p_{sm} = \frac{p_s}{p_s + (1 - p_s)w} - p_s = \frac{p_s(1 - p_s)(1 - w)}{p_s + w(1 - p_s)}. \tag{5b}$$

The allele frequencies among the gametes that produce the next generation of zygotes are calculated as before and the difference between them is due to selection on the sperm-derived alleles of males. This difference is again the cause of—and is numerically equal to—the difference in the frequencies of the reciprocal heterozygotes of the next generation:

$$p_c'' = \frac{p_c + p_s}{2} \tag{6a}$$

$$p_s'' = \frac{p_c + p_{sm}'}{2} \tag{6b}$$

$$p_s'' - p_c'' = \frac{p_{sm}' - p_s}{2} = (1 - p_c'')p_s'' - p_c''(1 - p_s''). \tag{6c}$$

For this pattern of imprinting, the change in gametic frequencies across generations is given by

$$\Delta p_c = \frac{p_s - p_c}{2} \tag{7a}$$

$$\Delta p_s = \frac{p_{sm}' + p_c - 2p_s}{2}. \tag{7b}$$

Figure 1 gives a simulation of all of the above recursion equations, averaging across sperm-derived and egg-derived frequencies to get a single value of *p*.

Comparing the efficacy of the two forms of selection: At a maternally expressed locus, the change in frequency due to selection on egg-derived alleles in males is given by

$$\delta p_{em} = \frac{p_c(1 - p_c)(1 - w)}{p_c + w(1 - p_c)}$$

(see Equation 2c above).

At a paternally expressed locus, the change in frequency due to selection on sperm-derived alleles in males is given by

$$\delta p_{sm} = \frac{p_s(1 - p_s)(1 - w)}{p_s + w(1 - p_s)}$$

(see Equation 5b above).

Suppose that the genome contains an allele at a paternally expressed locus that increases the value of a quantitative trait and an allele at a maternally expressed locus with the same effect on the quantitative trait. Further suppose that allele frequencies, before selection, are the same at the two loci. Would one generation of artificial selection on the quantitative trait be more effective in changing the allele frequency at the paternally expressed locus or at the maternally expressed locus?:

$$\delta p_{em} > \delta p_{sm} \quad \text{if} \quad \frac{p_c(1 - p_c)}{p_c + w(1 - p_c)} > \frac{p_s(1 - p_s)}{p_s + w(1 - p_s)}. \tag{8}$$

Some rearrangement gives

$$\delta p_{em} > \delta p_{sm} \quad \text{if} \quad (p_s - p_c)[p_c p_s - w(1 - p_c)(1 - p_s)] > 0. \tag{9}$$

One generation of male-limited selection ensures *p_s* > *p_c*. If this further restriction is accepted, then

$$\delta p_{em} > \delta p_{sm} \quad \text{if} \quad p_c p_s > w(1 - p_c)(1 - p_s). \tag{10}$$

This condition states that male-limited selection on a maternally expressed locus is more effective than male-limited selection on a paternally expressed locus when the frequency of the favored homozygote (*AA*) is greater than the frequency of the disfavored homozygote (*aa*) scaled by its relative fitness. For 0 < *w* < 1, this condition is satisfied when *a* is sufficiently rare but is not satisfied when *A* is sufficiently rare. Thus, male-limited selection is more effective at enriching rare favored alleles at paternally expressed loci but is more effective at purging rare disfavored alleles at maternally expressed loci. For the special case of *w* = 0, male-limited selection is more effective when acting on a maternally expressed locus at all gene frequencies.

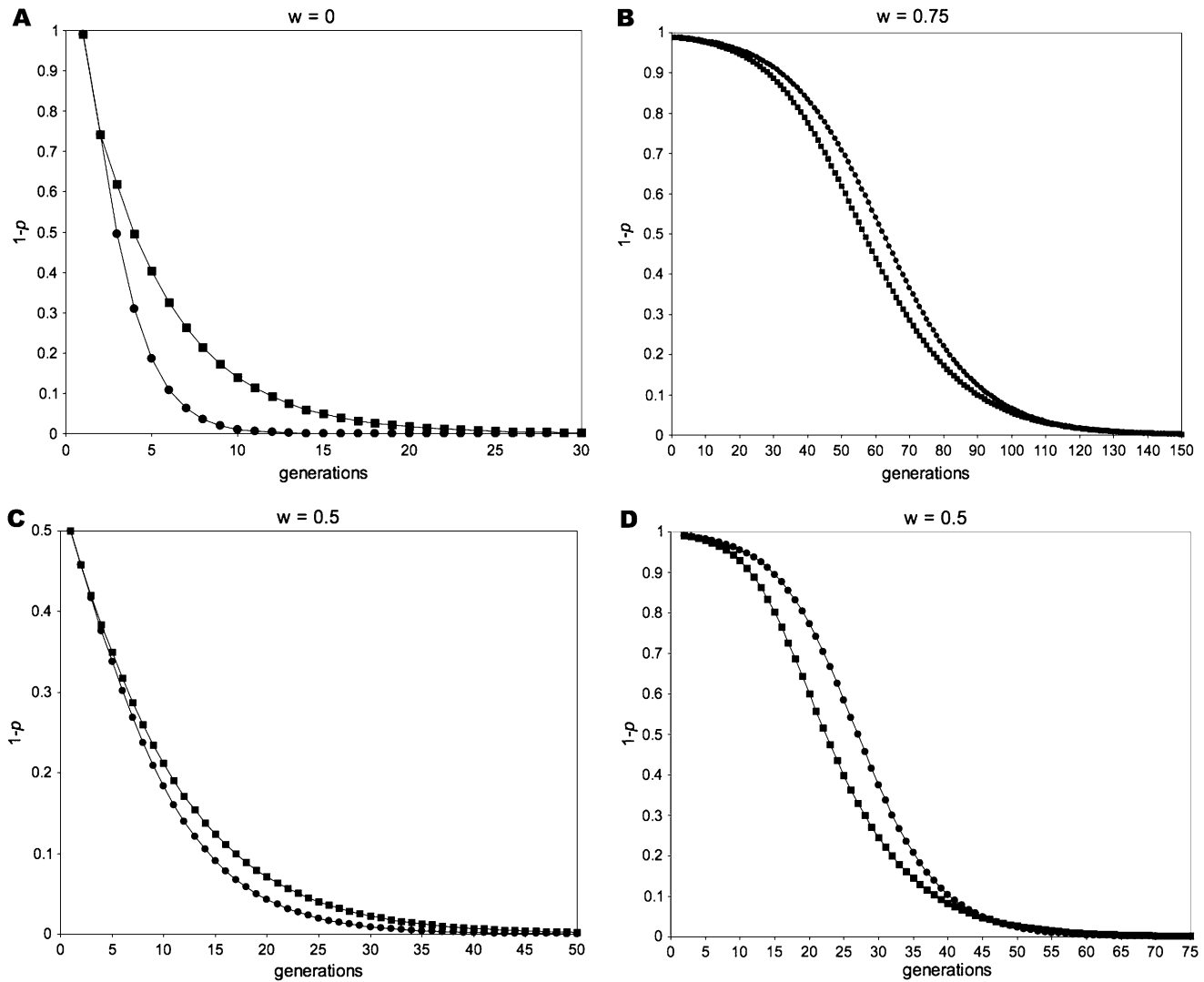


FIGURE 1.—Allele-frequency dynamics under male-limited selection. (A) $w = 0$, $p_o = 0.01$; (B) $w = 0.75$, $p_o = 0.01$; (C) $w = 0.5$, $p_o = 0.5$; (D) $w = 0.5$, $p_o = 0.01$. Each of the four graphs shows the decrease of the disfavored allele frequency, $1 - p$, with fitness equal to w relative to that of the favored allele. We use the average of sperm-derived and egg-derived frequencies to give a single point for each generation at a maternally expressed locus (circles) and a paternally expressed locus (squares). A and C show instances in which maternally expressed loci evolve faster in response to selection: this occurs when selection is strong ($w = 0$ in A) and/or when the initial value of the favored allele frequency is high ($p = 0.5$ initially in C). B and D are examples in which a paternally expressed locus shows more change in the early part of the dynamic than a maternally expressed locus; this pattern reverses as the favored allele increases, however, with the reversal occurring at lower frequencies of p for smaller values of w . When selection is sufficiently weak, the difference between imprinting patterns is virtually negligible for both allele-frequency change and fixation time. When selection is strong, however, the difference between the imprinting patterns is more readily apparent.

DISCUSSION

First, we offer an intuitive explanation for the source of the bias in selection response that we have found between the two reciprocal patterns of imprinting. Imprinted genes differ from Mendelian genes in that reciprocal heterozygotes differ with respect to phenotype and fitness. Further, each heterozygote is lumped into the same fitness class as one of the homozygotes, creating inefficiencies in the removal of disfavored alleles and the promotion of favored alleles. As an illustration of this “efficiency gap” consider a maternally expressed

locus. Among males, two genotypes (aA and aa) have lower fitness than the other two genotypes (Aa and AA). Selection is inefficient because favored A alleles are ignored in aA heterozygotes and disfavored a alleles are ignored in Aa heterozygotes. With male-limited selection, the aA heterozygote will always outnumber the Aa heterozygote (by a difference of $p_s - p_e$, from Equations 3c and 6c). When an allele is rare, it occurs only in heterozygotes. Thus, for maternally expressed loci, the average effect of the efficiency gap at low frequency of A is the loss of desired A alleles relative to an optimal system of selection. At high frequency, the a allele occurs only in

heterozygotes and the result flips. Here, the paternally expressed pattern of imprinting has the average effect of inefficiently dragging along unwanted a alleles. The magnitude of w dictates the degree to which aA heterozygotes outnumber Aa heterozygotes, given by Equations 3c and 6c.

We have demonstrated for the first time, to our knowledge, an explicit consequence of the difference between the two reciprocal patterns of imprinting. We offer some discussion of the relevance of this consequence to livestock populations as well as to natural populations.

Consequences for livestock populations: The most striking result of the models above is that when male-limited selection is strong, the response at maternally expressed loci is more efficient than the response at paternally expressed loci. Thus, if a breeder were aware that paternally expressed imprinted loci contribute to variation in the trait of interest, then consideration of alternatives to male-limited selection would be prudent. Female- rather than male-limited selection flips the result above: paternally expressed loci evolve more efficiently in response to female-limited selection than maternally expressed loci. However, selective deaths in females are undesirable as the number of breeding females is typically a limiting factor in production. Information from relatives may ameliorate some of the bias between maternally expressed and paternally expressed loci that male-limited selection introduces. What this information provides, essentially, is a window into the average effect of the silent allele. It is the difference between the average effect of the silent allele between paternally expressed and maternally expressed loci that causes the efficiency gap between the types of imprinting patterns. Paternally expressed loci are hiding an allele that certainly did not experience selection in the previous generation in a male; by contrast, maternally expressed loci have a 50% chance of having been seen by selection in the previous generation (that is, if they had been maternally derived in the sire of the focal individual). Thus, at maternally expressed loci, the allele that is hidden is more likely to be a favorable allele, relative to paternally expressed loci. Information from relatives helps recover some of the difference in what is known about the average effect of the silent allele at an imprinted locus.

Our models deal with single-generation changes. When selection is weak, it is not clear which type of imprinting pattern would lead to fixation of a rare A allele first. At low frequencies, paternally expressed imprinting is most efficient, while at higher frequencies (in fact, all above $p > 0.5$) the maternally expressed pattern is most efficient. An analytic solution to this problem would need to track four genotype frequencies with different fitnesses in males and females. Numerical simulations of our recursion equations find that the imprinting pattern that permits a faster fixation depends on the initial allele frequency (and depends on

how one defines fixation in an infinite population). When favored alleles are initially rare, higher frequencies of favored alleles are reached faster at paternally expressed loci than at maternally expressed loci until the point in the dynamic at which the inefficiency of purging the disfavored alleles becomes limiting. This point is reached sooner for stronger selection. Some numerical examples are given in Figure 1.

One scenario that permits a clear prediction, regardless of selection strength, is when two breeds are hybridized with the intent of introgressing certain genetic traits from one breed into another. Hybridization will make all alleles begin at a frequency of $p = 0.5$. Thus, male-limited selection will reap more genetic gains if the gene of interest is maternally expressed than if it is paternally expressed because $p = 0.5$ is a high enough frequency such that for any strength of selection, the maternally expressed pattern of imprinted expression is more efficient. This follows from inequality (10), which can be used to show that the crossover between more efficiency at paternally expressed to maternally expressed imprinting patterns necessarily occurs when $p \leq 0.5$.

Breeding programs that have not considered the possibility that imprinted loci contribute to traits of interest may have inefficiently tapped a store of imprinted genetic variation. A breeder who naively assigns fitness according to male breeding value (measured as the average value of his offspring) ignores any effects of maternally expressed imprinted genes. Under such a scheme, heritability will be higher on dams than on sires once paternally expressed imprinted variation is quenched. Conversely, if a breeder has naively assigned fitness according to phenotypes only, then such a breeder will be subject to the bias that we model above. Thus, this breeder is expected to have higher heritability for selected traits on sires than on dams. A combined approach, such as BLUP, which incorporates information from all relatives including the focal individual, will make up for some of the naïveté of the pure breeding value or pure phenotype breeding plans sketched above.

Consequences for natural populations: Finally, in naturally selected populations, all favorable mutations arise in low frequency. Since selection is more efficient at driving change at paternally expressed loci when favorable alleles are rare, this may bias which types of alleles can invade a population under male-limited selection. Therefore, novel variants that are adaptive in males and unselected in females may more likely be lost by drift at maternally expressed loci early in their evolutionary dynamic. In this sense, maternally expressed loci may be disadvantaged in adaptation under male-limited selection.

Models with sex-specific fitness and parent-specific gene expression, such as the one presented here, present the possibility of unexpected evolutionary dynamics. Previous authors have shown that alleles at a modifier of imprinted expression can be selectively favored when a

second trait-coding locus is subject to selection of varying direction or strength in the two sexes (IWASA and POMIANKOWSKI 2001, DAY and BONDURIANSKY 2004, SPENCER and CLARK 2006, and VAN CLEVE and FELDMAN 2007 examine the X-linked version of this). Our model differs in several regards from these: ours is a one-locus model, imprinted expression is already established, and the imprinted pattern that is most conducive to genetic evolution depends on allele frequency. While all of these models address the complex situation in which imprinted expression meets a fitness scheme with two sexes, it is not clear how to translate between our model and these previous models.

Our model can be applied to natural and agricultural settings because selection is the same process whether it is a breeder or nature that imposes fitness differences. However, the effects of the bias demonstrated here are most likely to be seen in agricultural populations because these have the requisite degree of strong, sex-limited selection.

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