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Intralocus Sexual Conflict Can Drive the Evolution of Genomic Imprinting

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ABSTRACT

Genomic imprinting is a phenomenon whereby the expression of an allele differs depending upon its parent of origin. There is an increasing number of examples of this form of epigenetic inheritance across a wide range of taxa, and imprinting errors have also been implicated in several human diseases. Various hypotheses have been put forward to explain the evolution of genomic imprinting, but there is not yet a widely accepted general hypothesis for the variety of imprinting patterns observed. Here a new evolutionary hypothesis, based on intralocus sexual conflict, is proposed. This hypothesis provides a potential explanation for much of the currently available empirical data, and it also makes new predictions about patterns of genomic imprinting that are expected to evolve but that have not, as of yet, been looked for in nature. This theory also provides a potential mechanism for the resolution of intralocus sexual conflict in sexually selected traits and a novel pathway for the evolution of sexual dimorphism.

THE insulin-like growth factor loci coding for *Igf2* and *Igf2r* in mice are two of the best-known examples of genomic imprinting (Barlow 1995; Ferguson-Smith and Surani 2001). High levels of *Igf2* are associated with increased offspring growth, and this growth factor is typically expressed only by paternally inherited alleles (Wilkins and Haig 2003). *Igf2r* is thought to be involved in growth factor regulation through its ability to bind with, and cause the degradation of, *Igf2* product (Wilkins and Haig 2003). Interestingly, *Igf2r* experiences genomic imprinting as well, but it is typically expressed only by maternally inherited alleles (Wilkins and Haig 2003). More generally, genomic imprinting is believed to play a role in the finding that both maternally and paternally inherited genetic complements are required for normal offspring development in some organisms [*i.e.*, uniparental diploid genotypes typically display various abnormalities (McGrath and Solter 1984)]. This suggests that male-female coevolution has played an important role in the evolution of genomic imprinting.

One of the primary hypotheses for the evolution of genomic imprinting via male-female coevolution is the parental conflict hypothesis (Moore and Haig 1991). This hypothesis supposes that there is a suite of potential alleles at the imprinted locus, and each allele differs in its susceptibility to being imprinted. Thus, the locus (or loci) coding for the imprinting machinery is taken as given, and one then considers the evolution of varying levels of susceptibility to this machinery at other, imprinted, loci. Each allele at a potentially imprinted locus is characterized by a couplet, (x_m, x_f), specifying that allele's level of expression when inherited from a male (m) or from a female (f), and then the evolutionarily stable expression pattern, (x_m^*, x_f^*), is sought, given that an organism's phenotype, z, is additively determined by its genotype [*e.g.*, $z = (x_m + x_f)/2$].

The parental conflict hypothesis assumes that the species in question has a polyandrous mating system and that maternal provisioning of offspring continues after fertilization (Trivers and Burt 1999). The first assumption implies that the genetic relatedness among offspring from the perspective of a maternally inherited allele is higher than that from the perspective of a paternally inherited allele (Haig 1996), because all offspring get their maternal genetic complement from the same mother, but may get their paternal genetic complement from different fathers. The second assumption allows for the opportunity that paternal alleles in developing offspring affect the level of extraction of maternal resources. Both conditions are met in some mammals and plants (Moore 2001). In these organisms, selection is thought to favor paternally inherited alleles that express high levels of resource extraction in the offspring [*e.g.*, through the production of *Igf2*, which causes a high growth rate (Wilkins and Haig 2003)]. Conversely, selection also favors maternally inherited alleles that express low levels of resource extraction, thereby countering the effects of paternally inherited alleles (*e.g.*, through the production of *Igf2r*, which reduces growth rate by degrading *Igf2* (Wilkins and Haig 2003).

The hypothesis proposed here also involves male-female coevolution, but does not require asymmetric relatedness for maternally and paternally inherited al-

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leles or any particular mode of offspring provisioning. Rather, it is based on an assumption of intralocus sexual conflict, which occurs when selection at a locus favors different alleles in males *vs.* females (Anderson and Spencer 1999; Rice and Chippindale 2001). Since intralocus sexual conflict is thought to play a role in the evolution of many traits (particularly those under sexual selection) in a wide variety of animal and plant taxa (Andersson 1994; Chippindale *et al.* 2001; Gibson *et al.* 2002), our hypothesis has the potential for very broad applicability. Importantly, our hypothesis differs fundamentally from previous hypotheses such as the parental conflict hypothesis by focusing on the evolution of the locus causing the imprinting rather than on the locus that is imprinted (see also Spencer 1997; Burt and Trivers 1998).

Our theory is based on a very simple idea. Given that the individuals that are successful in transmitting their alleles to the next generation (*i.e.*, sires and dams) are those that have passed the tests of sex-specific selection, it follows that sires are more likely to transmit high male-fitness alleles to their offspring, whereas dams are more likely to transmit high female-fitness alleles to their offspring. As a result, natural selection should favor modifier loci that silence maternally inherited alleles in males and that silence paternally inherited alleles in females. Thus, intralocus sexual conflict selects for genomic imprinting because this form of epigenetic inheritance mitigates the severity of intralocus sexual conflict.

THEORETICAL DEVELOPMENT

Genomic imprinting is typically expressed as the silencing of a maternally or paternally inherited allele. With this in mind we make the following definitions: the *trait-coding locus* is a locus coding for the trait of interest (*e.g.*, body size, antler size, male courtship behavior, etc.). The *modifier locus* is a locus that affects the level of transcription of the trait-coding locus, either downregulating it or allowing it to be expressed. We assume that the trait-coding locus is modified during gametogenesis. This modification is assumed to result from some type of epigenetic biochemical marking that is inherited by the offspring. Therefore, the actual biochemical action of the modifier locus (*i.e.*, the epigenetic marking that it induces on the trait-coding locus) occurs in the parental generation during gametogenesis, but the resultant phenotypic effect (*i.e.*, the altered level of transcription of the trait-coding locus) occurs in the offspring. Under these assumptions, situations in which the level of expression of the trait-coding locus depends on the parent of origin are a result of sexually dimorphic action of the modifier locus during gametogenesis. For example, a pattern in which the trait-coding locus is silenced when maternally inherited but expressed when paternally inherited would result from the allele at the modifier locus applying the epigenetic silencer marking during gametogenesis in females but not in males.

The above assumptions are all well within the realm of what is currently known about gene action (*e.g.*, we know that sexually dimorphic gene action is possible). For maximum generality, however, we also allow the epigenetic marking of the trait-coding locus to have a sexually dimorphic effect in the offspring. Therefore, not only can the action of the modifier locus display sexual dimorphism, either by marking or not marking the trait-coding locus depending on whether the gametogenesis is taking place in a male or a female, but also the effect of such a marking in the offspring can be different depending upon whether the offspring is a male or a female (we call this "sexually dimorphic imprinting"). For example, a marking might cause the silencing of a trait-coding allele inherited from father to daughter, but allow the expression of a trait-coding allele inherited from father to son. To our knowledge, this level of flexibility in genomic imprinting has not yet been observed in nature, but we incorporate it in the theory to make it as general as possible. We stress, however, that it is not an essential component of the theory. Our basic conclusion—that intralocus conflict can drive the evolution of genomic imprinting—holds, even in the absence of this assumption (see results).

Consider a trait-coding locus, x, that codes for some quantitative phenotypic trait, z, and a modifier locus, ξ. For simplicity, we assume that these two loci are freely recombining. Our qualitative conclusions are not altered if we were to allow arbitrary recombination rates (T. Day and R. Mahaffey, unpublished results). The functions $W_m(z)$ and $W_f(z)$ are used to represent the fitness of a male and female, respectively, with trait value z. Intralocus sexual conflict is represented by these two fitness functions having a maximum at different trait values (Figure 1). We assume that all females obtain mates and that there is competition among males for access to females. Thus, a male's mating success depends on his fitness relative to that of his competitors. The population is assumed to have reached an evolutionary equilibrium at the trait-coding locus, x, with genetic variation being maintained. We are then interested in factors causing evolution at the modifier locus, ξ.

To model evolution at the modifier locus we first need to specify the mapping between genotype and phenotype. Consider an example where a male inherits the two particular alleles $\tilde{x}$, $\tilde{\xi}$ from one parent and the two particular alleles $\hat{x}$, $\hat{\xi}$ from the other parent, where the symbols $\tilde{x}$, $\hat{x}$ and $\tilde{\xi}$, $\hat{\xi}$ refer to the quantitative allelic values that are inherited at loci x and ξ, respectively. The expression of the trait-coding locus, x, might differ between males and females, reflecting some degree of sexual dimorphism (indeed, we are interested in situations where this is the case, as a result of sex-specific

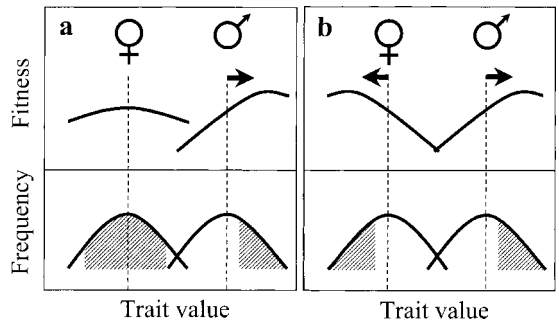

FIGURE 1.—Phenotypic frequency distributions (bottom) and corresponding fitness functions (top) for two hypothetical sexually dimorphic traits. (a) Moderate conflict: a trait under directional selection in males, but weak stabilizing selection in females. (b) Severe conflict: a trait under opposing directional selection in both sexes (*i.e.*, sexually antagonistic selection). Vertical, dashed lines indicate female and male phenotypic trait means, and arrows indicate the direction of selection. Hatched areas below the phenotypic distributions indicate the phenotypes of individuals that contribute 90% of total reproductive success.

selection), and therefore these two alleles will express the allelic values $\bar{x}^{\mathrm{m}}$ and $\hat{x}^{\mathrm{m}}$, respectively, if they are transcribed and in a male. We use the *superscripts* m and f to refer to the *sex* of the individual in which an allele currently resides. We also use the *subscripts* m and f to refer to the *sex* of the parent from which an allele was inherited. The extent to which each allele is transcribed, however, will depend on the modifier allele with which it was inherited because this modifier allele might have applied an epigenetic mark during gametogenesis in the parent. In our analysis, we suppose that the extent of the epigenetic marking, and therefore the degree to which the trait-coding locus will be downregulated in the offspring, is a quantitative character. Thus, the notations $\tilde{\xi}_j$ and $\hat{\xi}_j$ are used to denote this quantitative level of downregulation caused by the two modifier alleles in question, given that they are inherited from sex j. Since we also want to allow for the possibility that the modifier alleles have different effects in male and female offspring (*i.e.*, the effect of the epigenetic marking is sex specific), we signify offspring sex using superscripts just as we do for alleles at the trait-coding locus. Thus, assuming that alleles $\bar{x}$, $\tilde{\xi}$ were inherited from the father and alleles $\hat{x}$, $\hat{\xi}$ were inherited from the mother, the degrees of downregulation effected by the two modifier alleles within the male in question are $\tilde{\xi}^{\mathrm{m}}_{\mathrm{m}}$ and $\hat{\xi}^{\mathrm{m}}_{\mathrm{f}}$. Again we note that, although the biochemical action of the modifier alleles takes place during gametogenesis in the parent, we use $\tilde{\xi}^{\mathrm{m}}_{\mathrm{m}}$ to denote the resulting level of downregulation of the trait-coding locus that occurs in the soma of the offspring, given that allele $\tilde{\xi}$ was inherited by a male, from a male.

With the above notation, the genotype-phenotype map for the male is specified as $z[(\bar{x}^{\mathrm{m}}, \tilde{\xi}^{\mathrm{m}}_{\mathrm{m}}); (\hat{x}^{\mathrm{m}}, \hat{\xi}^{\mathrm{m}}_{\mathrm{f}})] = \bar{x}^{\mathrm{m}} h(\tilde{\xi}^{\mathrm{m}}_{\mathrm{m}}, \hat{\xi}^{\mathrm{m}}_{\mathrm{f}}) + \hat{x}^{\mathrm{m}}(1 - h(\tilde{\xi}^{\mathrm{m}}_{\mathrm{m}}, \hat{\xi}^{\mathrm{m}}_{\mathrm{f}}))$, where $h(\tilde{\xi}^{\mathrm{m}}_{\mathrm{m}}, \hat{\xi}^{\mathrm{m}}_{\mathrm{f}})$ is defined to be the level of dominance of the paternally inherited, trait-coding allele that results from the downregulation levels, $\tilde{\xi}^{\mathrm{m}}_{\mathrm{m}}$ and $\hat{\xi}^{\mathrm{m}}_{\mathrm{f}}$, of the two homologous modifier alleles. The function h is assumed to be bounded by 0 and 1 (*i.e.*, no over- or underdominance) and to be strictly decreasing in its first argument (which, by convention, is the level of downregulation caused by the paternally inherited modifier allele) and strictly increasing in its second argument (which, by convention, is the level of downregulation caused by the maternally inherited modifier allele). This reflects the operational assumption that heightened downregulation (*e.g.*, through increased methylation) will decrease the expression of the trait-coding allele. All else being equal, this should make such alleles less dominant. Analogously, the phenotype of a female that inherits these two sets of alleles in the same way is $z[(\bar{x}^{\mathrm{f}}, \tilde{\xi}^{\mathrm{f}}_{\mathrm{m}}); (\hat{x}^{\mathrm{f}}, \hat{\xi}^{\mathrm{f}}_{\mathrm{f}})] = \bar{x}^{\mathrm{f}} h(\tilde{\xi}^{\mathrm{f}}_{\mathrm{m}}, \hat{\xi}^{\mathrm{f}}_{\mathrm{f}}) + \hat{x}^{\mathrm{f}}(1 - h(\tilde{\xi}^{\mathrm{f}}_{\mathrm{m}}, \hat{\xi}^{\mathrm{f}}_{\mathrm{f}}))$.

The direction of selection on the expression level of the four possible levels of downregulation is given by the sign of the four expressions

$$\xi^{\mathrm{m}}_{\mathrm{m}}\colon -\frac{dW_{\mathrm{m}}}{dz}E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}], \quad \xi^{\mathrm{m}}_{\mathrm{f}}\colon \frac{dW_{\mathrm{m}}}{dz}E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}],$$

$$\xi^{\mathrm{f}}_{\mathrm{m}}\colon -\frac{dW_{\mathrm{f}}}{dz}E[X^{\mathrm{f}}_{\mathrm{pat}} - X^{\mathrm{f}}_{\mathrm{mat}}], \quad \xi^{\mathrm{f}}_{\mathrm{f}}\colon \frac{dW_{\mathrm{f}}}{dz}E[X^{\mathrm{f}}_{\mathrm{pat}} - X^{\mathrm{f}}_{\mathrm{mat}}] \quad (1)$$

(APPENDIX), where $E[\cdot]$ denotes expectation over all individuals in the population, and X^{i}_{pat} and X^{i}_{mat} are the values of the paternally and maternally inherited trait-coding alleles, respectively, in a randomly chosen individual of sex i. These expressions yield several interesting conclusions. First, if the optimal level of sexual dimorphism can evolve, so that selection on the trait is stabilizing in both sexes, then $dW_{\mathrm{m}}/dz = 0$ and $dW_{\mathrm{f}}/dz = 0$, so that there is no selective advantage to a modifier allele that silences the trait-coding locus.

Instead, suppose that there is continued antagonistic selection between males and females over allelic expression, such that the optimal level of sexual dimorphism does not evolve. There is growing evidence for the maintenance of this sort of genetic variation in populations, resulting from a lack of appropriate genetic variance in one or both sexes and/or from mutation selection balance in the two sexes (CHIPPINDALE *et al.* 2001; RAND *et al.* 2001). Without loss of generality, we assume that selection favors larger traits in males and smaller traits in females, so that $dW_{\mathrm{m}}/dz > 0$ and $dW_{\mathrm{f}}/dz < 0$. In this case, a modifier allele that downregulates the trait-coding locus can have a selective advantage. For example, selection on the level $\xi^{\mathrm{m}}_{\mathrm{m}}$ is in a direction given by the sign of $-E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}]$ whereas selection on the level $\xi^{\mathrm{m}}_{\mathrm{f}}$ is in a direction given by the sign of $E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}]$. Therefore, if $E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}] > 0$, then selection will favor an increase in $\xi^{\mathrm{m}}_{\mathrm{f}}$ and a decrease in $\xi^{\mathrm{m}}_{\mathrm{m}}$, meaning a reduced level of downregulation caused by paternally

inherited modifier alleles in males and an increased level of downregulation caused by maternally inherited modifier alleles in males. Both effects will increase the level of dominance, h, of the paternally inherited trait-coding locus. More generally, we expect the level of dominance, h, of the paternally inherited trait-coding locus in males, to evolve in a direction given by the sign of $E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}]$. This is simply the expected difference between the expression levels of paternally inherited and maternally inherited trait-coding alleles in males.

What is the value of $E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}]$? Given that selection favors males with larger traits, the paternally inherited allele (as it is expressed in males) will have an expected value that is higher than that of the population prior to the male-specific selection. This occurs because such alleles have survived selection in males and have been successful at getting transmitted into the next generation. On the other hand, the maternally inherited allele (as it is expressed in males) will tend to have an expected value that will be either (i) equivalent to the population average prior to selection, if there is no correlated response in the male-specific expression level from selection on female-specific expression, or (ii) lower than the population average prior to selection if male-specific expression is positively genetically correlated with female-specific expression. In either case, $E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}] > 0$, and selection therefore favors alleles at the modifier locus that increase the dominance of the paternally inherited trait-coding allele, h. For females, a similar argument demonstrates that selection favors alleles at the modifier locus that cause the dominance, h, of the paternally inherited trait-coding locus in females to change in a direction given by the sign of $-E[X^{\mathrm{f}}_{\mathrm{pat}} - X^{\mathrm{f}}_{\mathrm{mat}}]$.

Although we have focused so far on sexually antagonistic selection, the same process can operate in traits that are under directional selection in one sex only (such as sex-limited traits, or traits that are sexually selected in males, but exhibit no intersexual genetic correlation), provided that both sexes carry alleles for the trait. For example, suppose a trait such as a particular mating behavior is expressed in males only. The fitness of all female genotypes at the locus encoding this male-limited trait will then be equivalent, and selection will favor the behavior in males only. In such a case, the silencing of maternally inherited trait-coding alleles in offspring of both sexes can evolve because sons will benefit from expressing the paternally inherited trait-coding allele (as it more closely matches the male optimum), whereas the fitness of daughters is independent of the alleles carried at this locus. In other words, male offspring will benefit by expressing only paternally inherited trait-coding alleles because some alleles inherited from the mother would have been eliminated by sexual selection, had they been expressed in a male.

In general, under sex-specific selection (*e.g.*, as a result of sexual selection on a trait in males), a trait-coding allele that a male offspring inherits from its father has an allelic value that matches the male optimum more closely than does a trait-coding allele inherited from its mother (on average). Therefore, natural selection favors alleles at the modifier locus that silence the maternal trait-coding allele but not the paternal allele *in males*. If the trait-coding locus is under directional selection in males only, then a modifier allele that silences maternally inherited alleles in offspring of both sexes can spread to fixation. However, if the trait-coding locus is under sexually antagonistic selection (*e.g.*, as a result of sexual selection on a trait in males and indirect selection on the homologous trait in females), then offspring of both sexes will inherit trait-coding alleles from the same-sex parent that match their sex-specific optimum more closely than do the trait-coding alleles inherited from the opposite-sex parent. Thus, in this case, selection favors alleles at the modifier locus that silence the maternally inherited trait-coding allele *in males*, as well as the paternally inherited trait-coding allele *in females*.

Note that, for a trait-coding locus under directional selection in one sex only, the above results predict the silencing of alleles from the same parent in offspring of both sexes—the typical pattern observed at imprinted loci. In contrast, for a trait-coding locus under opposing directional selection in both sexes, the above results predict the evolution of a "sexually dimorphic" form of genomic imprinting, where the modifier locus should act so that only maternally inherited trait-coding alleles are expressed in females, whereas only paternally inherited trait-coding alleles are expressed in males. To our knowledge, sexually dimorphic imprinting has not been looked for in nature.

It is conceivable, however, that this sort of sexual dimorphism in the degree to which the trait-coding locus is silenced is not possible. The modifier locus acts during the process of gamete formation in the parent (Butler 2002), and there might be little scope for a mechanism to evolve that would result in such biochemical modifications having different effects once they are transmitted to male *vs.* female offspring. In such a case, a modifier allele that causes silencing can still be favored as a result of sexually antagonistic selection. Specifically, an allele at the modifier locus that downregulated the maternally inherited trait-coding allele in both sons and daughters can spread provided that the benefit of doing so in sons (by making their trait value closer to the male optimum) more than outweighs the costs of doing so in daughters (by making their trait value farther from the female optimum). This requires

$$\frac{dW_{\mathrm{m}}}{dz}E[X^{\mathrm{m}}_{\mathrm{pat}} - X^{\mathrm{m}}_{\mathrm{mat}}] > -\frac{dW_{\mathrm{f}}}{dz}E[X^{\mathrm{f}}_{\mathrm{pat}} - X^{\mathrm{f}}_{\mathrm{mat}}] \qquad (2)$$

(appendix).

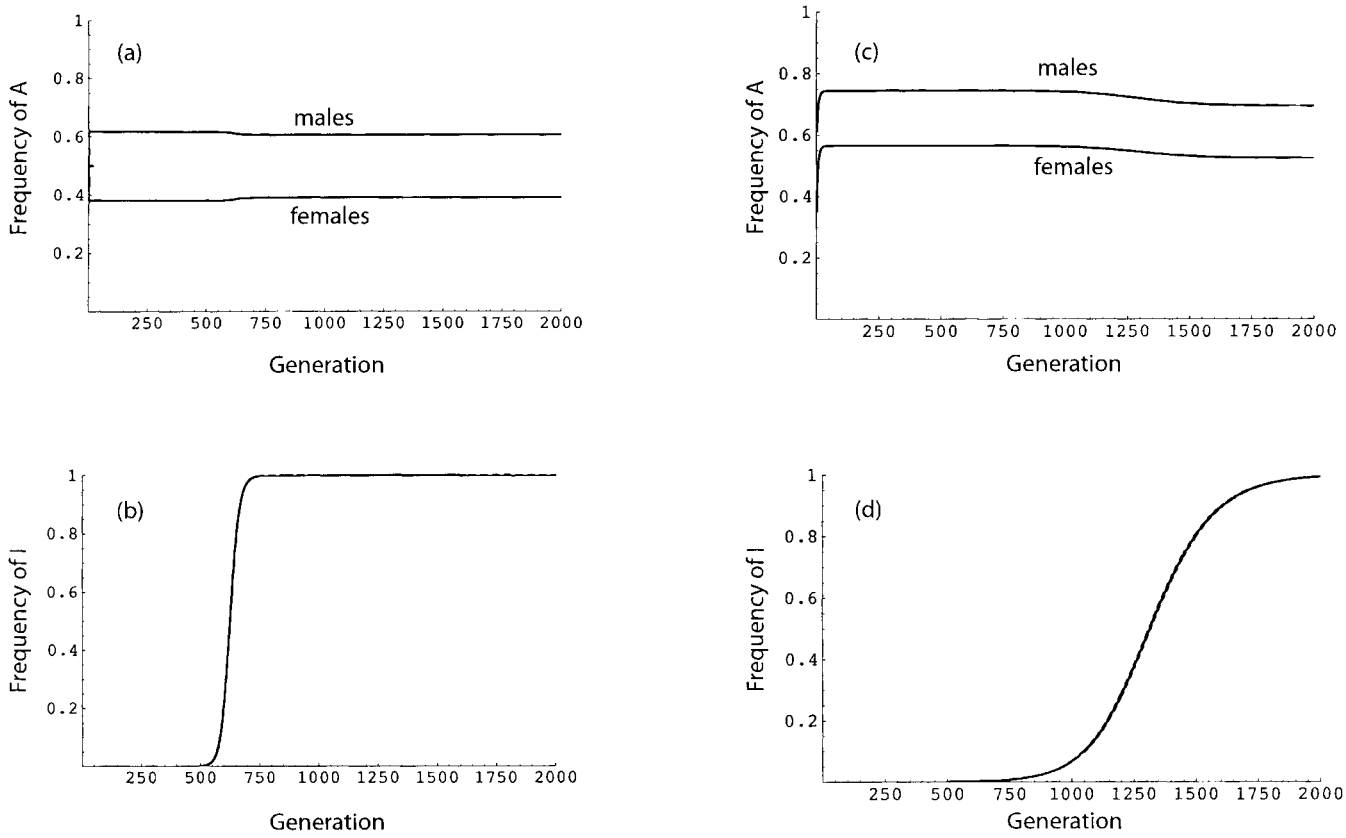

FIGURE 2.—Allele frequencies *vs.* time. The silencing allele at the modifier locus was introduced at generation 500, at a frequency of 0.001, and this allele was assumed to result in sexually dimorphic imprinting (see MATERIALS AND METHODS for details). Mutation between the two trait-coding alleles occurs in each generation with a probability of 0.01 in each direction. (a and b) The strength of selection is equal (and in opposite directions) in males and females ($W^{m}_{AA} = 3$, $W^{m}_{Aa} = 2$, $W^{m}_{aa} = 1$; $W^{f}_{AA} = 1$, $W^{f}_{Aa} = 2$, $W^{f}_{aa} = 3$). The frequency of the allele favored in males (*i.e.*, *A*) is shown in a. The frequency of the modifier (imprinter) allele (*i.e.*, *I*) is shown in b. (c and d) The strength of selection differs in males and females ($W^{m}_{AA} = 3$, $W^{m}_{Aa} = 2$, $W^{m}_{aa} = 1$; $W^{f}_{AA} = 1$, $W^{f}_{Aa} = 1.8$, $W^{f}_{aa} = 2$). The frequency of the allele favored in males (*i.e.*, *A*) is shown in c. The frequency of the modifier (imprinter) allele (*i.e.*, *I*) is shown in d.

If the reverse inequality in (2) holds, then downregulation of the paternally inherited trait-coding alleles in both sons and daughters can evolve.

SIMULATIONS AND NUMERICAL EXAMPLES

The above analytical results provide insight into when and why an allele at the modifier locus that silences the trait-coding locus will spread. To determine the long-term evolutionary dynamics, we carried out simulations using standard two-locus population-genetic recursion equations modified for sex-specific selection (OWEN 1953; MANDEL 1971; KIDWELL *et al.* 1977; HARTL and CLARK 1989; available upon request from T. Day).

When genetic variation is maintained at the trait-coding locus as a result of sexually antagonistic selection, sexually dimorphic imprinting easily evolves to fixation (Figure 2, a and b). This is true regardless of the strength of selection in the two sexes (Figure 2, c and d). At equilibrium, paternally inherited trait-coding alleles are silenced in females and maternally inherited trait-coding alleles are silenced in males. However, if genetic variation for sexually dimorphic imprinting does not exist, then inequality (2) gives the conditions under which an allele at the modifier locus causing the maternally inherited trait-coding allele to be silenced in both sexes can invade. Provided the benefits of doing so to sons exceed the costs of doing so to daughters, the modifier allele can still spread to fixation. For example, if selection on the trait is stronger in males than in females (*e.g.*, because of sexual selection) then a modifier allele causing the silencing of maternally inherited trait-coding alleles in both sexes easily reaches fixation (Figure 3, a and b). Likewise, for traits under directional selection in males only, a modifier allele that silences the maternally inherited allele in offspring of both sexes readily increases to fixation.

There are also some conditions under which a polymorphism occurs at the modifier locus. As an example, consider an allele at the modifier locus that silences the

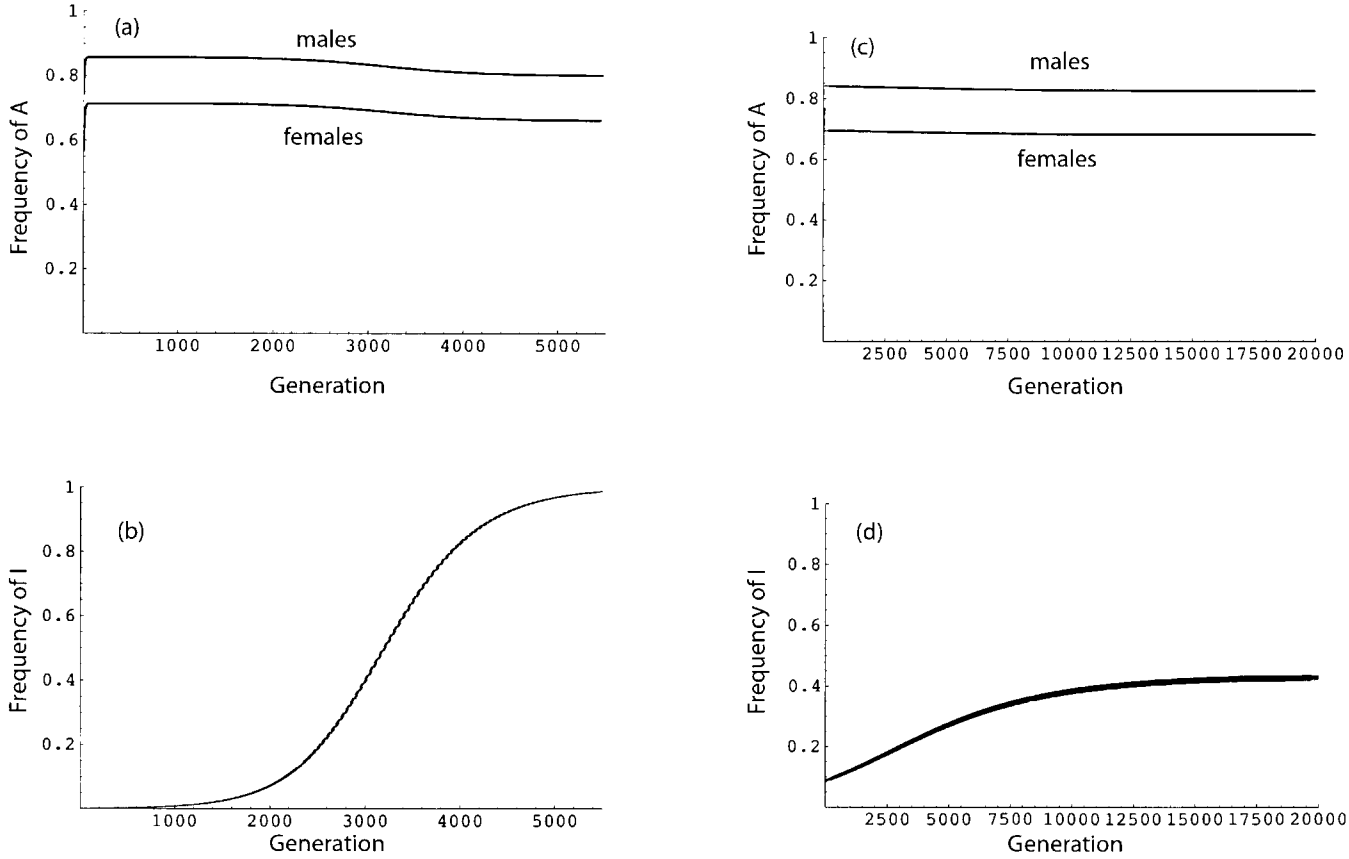

FIGURE 3.—Allele frequencies *vs.* time. Imprinter alleles at the modifier locus were introduced at a frequency of 0.001 in a and b and a frequency of 0.1 in c and d. The imprinter allele was assumed to silence the maternally inherited trait-coding allele in all offspring (see MATERIALS AND METHODS for details). Mutation between the two trait-coding alleles occurred in each generation with a probability of 0.01 in each direction. (a and b) The strength of selection in males and females was $W^{m}_{AA} = 5$, $W^{m}_{Aa} = 3$, $W^{m}_{aa} = 1$; $W^{f}_{AA} = 1$, $W^{f}_{Aa} = 1.5$, $W^{f}_{aa} = 2$. The frequency of the allele favored in males (*i.e.*, *A*) is shown in a. The frequency of the modifier (imprinter) allele (*i.e.*, *I*) is shown in b. (c and d) A case where a polymorphism results at the imprinter locus. The strength of selection in males and females was $W^{m}_{AA} = 5$, $W^{m}_{Aa} = 3.1$, $W^{m}_{aa} = 1$; $W^{f}_{AA} = 1$, $W^{f}_{Aa} = 1.5$, $W^{f}_{aa} = 2$. The frequency of the allele favored in males (*i.e.*, *A*) is shown in c. The frequency of the modifier (imprinter) allele (*i.e.*, *I*) is shown in d.

maternally inherited trait-coding allele in both sons and daughters. To understand how a polymorphism can arise in this context, first consider the initial invasion of this allele. For invasion to occur, selection must be stronger on the trait in males than in females, and thus before this modifier allele spreads, the allele at the trait-coding locus that is favored in males (allele *A*, say) will reach a frequency >50%. The modifier allele then spreads because it masks heterozygous individuals in a manner that results in a net selective advantage. For instance, when silencing occurs in an *Aa* male (where the ordering refers to paternal and maternal contributions), it will have the advantageous AA phenotype, whereas when silencing occurs in an *aA* male, it will have the selectively disadvantageous aa phenotype. Because the former heterozygotes will be more plentiful than the latter (because the frequency of the *A* allele is higher in fathers than in mothers) this results in a net selective advantage to imprinting in males. A similar argument illustrates that such silencing results in a net selective disadvantage in females, but the advantage in males outweighs the disadvantage in females because selection is stronger in males.

As the silencing allele at the modifier locus increases in frequency, it begins to ameliorate the difference in the strength of selection between males and females, thereby slowing its own spread. This occurs because the silencing shields the disadvantageous *a* allele from selection in male heterozygotes on average, reducing the strength of selection against the *a* allele at the trait-coding locus in males. Conversely, the silencing exposes the disadvantageous *A* allele to selection in female heterozygotes on average, increasing the strength of selection against the *A* allele at the trait-coding locus in females. At some point, the strength of selection in the two sexes will equalize, and if this occurs before the silencing allele at the modifier locus reaches fixation, a stable polymorphism will result (Figure 3, c and d).

DISCUSSION

Intralocus conflict provides a potential explanation for the evolution of genomic imprinting in a broad range of traits subject to sex-specific selection, provided that ample genetic variation is maintained at trait-coding loci (Figure 1). This theory thus predicts the evolution of genomic imprinting in traits and taxa where this phenomenon was not previously expected, such as sexually selected traits. Sexually selected traits tend to experience sex-specific selection (Andersson 1994), express autosomal or X-linked genetic variation (Reinhold 1998; Rhen 2000; Lindholm and Breden 2002), and exhibit abundant additive genetic variance (Houle 1992; Pomiankowski and Møller 1995). Together, these factors generate strong selection for genomic imprinting. Although sexually selected traits also tend to exhibit high levels of nongenetic variation (Houle 1992), this will not alter the qualitative predictions of the theory as long as some level of additive genetic covariance between the trait and fitness is maintained (Rausher 1992).

Although our model is based on a single trait-coding locus under sex-specific selection, the theory should also apply to traits that are coded by multiple loci. The only requirement is that the modifier locus be able to simultaneously silence all trait-coding loci during gamete formation. In principle this should be possible regardless of where the trait-coding loci are found within the genome, provided that they can be "recognized" by the modifier locus during gametogenesis. It also seems likely, however, that physical linkage between the modifier locus and the trait-coding loci would facilitate the evolution of imprinting under intralocus conflict. This is because it would provide a convenient proximate mechanism through which the trait-coding loci can be effectively identified by the modifier.

Iwasa and Pomiankowski (1999, 2001) constructed a theory for the evolution of genomic imprinting on sex chromosomes (particularly the X chromosome) by considering the effects of sex-specific selection as we have done here (see also Spencer *et al.* 2004). However, they examined this question by assuming (as in Haig's 1996 theory) that the imprinting machinery is given and supposing that there is variation in alleles at loci on the X chromosome in terms of their susceptibility to imprinting. They found that if higher transcription is favored in males (females), then selection favors alleles that are silent when maternally (paternally) inherited so as to allow each sex to evolve further toward its optimal level of transcription. Our theory, which essentially focuses on the evolution of the imprinting machinery itself (by examining the fate of modifier loci that silence alleles at trait-coding loci) also provides an explanation for the evolution of genomic imprinting at loci on X chromosomes. Because males always inherit their X chromosome from their mother, we would expect that sexually antagonistic trait-coding loci located on the (maternally inherited) X chromosome would always be silenced in male offspring, and likewise these loci on the paternally inherited X would be silenced in female offspring. On the other hand, if such sexual dimorphism in genomic imprinting is not possible, then we would expect that such trait-coding loci on the paternally inherited X are silenced in both male and female offspring (because paternally derived X's are never found in male offspring). Interestingly, however, under some conditions, maternal silencing might also be favored, albeit more weakly (T. Day and R. Bonduriansky, unpublished data), and this presents an interesting area for future research.

The theory presented here will require direct empirical testing, but our predictions are broadly consistent with several observed patterns. First, the theory predicts the evolution of genomic imprinting in sexually selected traits, and this may be manifested in unequal trait heritabilities through the mother and father (Spencer 2002). Such patterns of inheritance have been observed in some sexually selected traits (Butlin and Hewitt 1986; Reinhold 1998; Beukeboom and van den Assem 2001, 2002), including a case that suggests sexually dimorphic imprinting (R. Bonduriansky and L. Rowe, unpublished results). Second, many sexually selected traits exhibit patterns of inheritance that, to date, have been interpreted as being the result of sex linkage (Reinhold 1998; Iyengar *et al.* 2002; Lindholm and Breden 2002). These patterns of inheritance are equally consistent with the theory of genomic imprinting presented here, and therefore the genetic architecture of such traits will need to be reexamined in light of this theory. Third, although the functions of many known imprinted genes remain elusive, many well-studied imprinted genes in humans and mice appear to be involved in the regulation of growth (*e.g.*, *Igf2* and *Igf2r*) or in the control of brain development and behavior (Goos and Silverman 2001; Tycko and Morison 2002; Gorlova *et al.* 2003). Since many aspects of growth and behavior exhibit sexually dimorphic expression in mammals, these imprinted genes are likely subject to sex-specific selection in the two sexes, which might have driven the evolution of imprinting. Indeed, if we assume that sexually dimorphic imprinting is *not* possible, then our theory predicts the well-known pattern of paternal expression of *Igf2* in mammals. Males are larger than females in many species of mammals, suggesting that there is antagonistic selection between the sexes in a direction that would favor this form of imprinting. Interestingly, the theory also predicts maternal expression of *Igf2r* in such mammals, as is observed (T. Day and R. Bonduriansky, unpublished results). Finally, some imprinted genes (including *Igf2* and *Igf2r*) appear to exhibit polymorphisms (*e.g.*, Xu *et al.* 1993; Giannoukakis *et al.* 1996; Bunzel

et al. 1998; Croteau *et al.* 2001), which is a pattern predicted by our model. More research is required to identify imprinted genes and elucidate their functions, and this work will be facilitated by new tools of genomic analysis (Yang *et al.* 2003); however, it appears that much of the currently available evidence is consistent with the intralocus conflict theory.

The evolution of genomic imprinting can mitigate the severity of intralocus sexual conflict by allowing males and/or females to approach their sexually dimorphic phenotypic optima more closely. This occurs because, as the silencing allele at the modifier locus spreads, it enables a greater proportion of individuals to express high-fitness phenotypes. For example, for a trait under antagonistic selection (Figure 1), the evolution of a sexually dimorphic form of imprinting will increase the proportion of males expressing the high male-fitness phenotype (*e.g.*, large trait size) and the proportion of females expressing the high female-fitness phenotype (*e.g.*, small trait size). Genomic imprinting may thus contribute to the evolution of sexual dimorphism. The genetic architecture of sexually dimorphic traits remains poorly understood, with sex linkage (Rice 1984; Reinhold 1998), condition dependence (Rowe and Houle 1996), sex-limited gene expression (Rhen 2000; Rice and Chippindale 2002), genomic imprinting (this study), and others mechanisms (Wilcockson *et al.* 1995) all potentially involved.

A number of extensions to the theory presented here also warrant further exploration. First, most of our analyses and simulations were carried out under the assumption that the fitness of the heterozygote phenotype is the average of the two homozygous phenotypes in both males and females (*i.e.*, additivity). The potential outcome when phenotypes are nonadditive is much more complex and beyond the scope of the present analysis. The evolutionary dynamics of single-locus models with sex-specific selection and nonadditive phenotypes can themselves generate multiple equilibria in the absence of any considerations of imprinting (Owen 1953; Mandel 1971; Kidwell *et al.* 1977). Therefore, a complete analysis of this situation is left for future research.

Finally, the theory presented here is not mutually exclusive with previous explanations for the evolution of genomic imprinting. For example, Haig's (1996) theory for the evolution of genomic imprinting as a result of relatedness asymmetries between maternally and paternally inherited alleles might well work in conjunction with the selective forces elucidated here. The same is true for Iwasa and Pomiankowski's (1999, 2001) theory of X-linked genomic imprinting. Indeed, examining the interplay between the evolution of the level of transcription that is selectively favored at a trait-coding locus and the evolution of modifier loci that affect transcription at such trait-coding loci is another area requiring further development (Burt and Trivers 1998).

SUMMARY

We present a novel theory showing that intralocus sexual conflict can drive the evolution of genomic imprinting at loci under sex-specific selection. In traits under directional selection in one sex only (*e.g.*, sex-limited traits or sexually selected traits exhibiting no intersexual genetic correlation), selection favors silencing of trait-coding alleles that are inherited from the parent not experiencing directional selection. For example, in traits that are expressed only by males, the maternal contribution should always be silenced, resulting in a lower heritability through maternal grandfathers than through paternal grandfathers. In traits under sexually antagonistic selection, selection favors a sexually dimorphic form of imprinting, where individuals of both sexes express only those trait-coding alleles that are inherited from the same-sex parent. However, if sexually dimorphic imprinting cannot evolve because of a lack of appropriate genetic variation, then selection can still favor the silencing of trait-coding alleles from the less-strongly selected parent in both sons and daughters. Thus, traits that are under strong sexual selection in males should display stronger heritability either through the father (relative to the mother) or through the same-sex parent (relative to the opposite-sex parent) in offspring of both sexes.

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APPENDIX

Analysis: We consider an autosomal modifier locus of a diploid organism and allow the expression of an allele at this locus to depend on the sex of its parent of origin as well as the sex of the individual in which it will reside. Thus, a single allele, ξ, has four (potentially different) states of expression: $\xi^{\mathrm{m}}_{\mathrm{m}}$, paternally derived and in a male; $\xi^{\mathrm{m}}_{\mathrm{f}}$, maternally derived and in a male; $\xi^{\mathrm{f}}_{\mathrm{m}}$, paternally derived and in a female; and $\xi^{\mathrm{f}}_{\mathrm{f}}$, maternally derived and in a female.

Suppose that the population first contains only a single allele, $\hat{\xi}$, at the modifier locus but that variation is maintained at the trait-coding locus. Also, suppose the population dynamics have reached a stable equilibrium. Now ask if a rare mutant allele, ξ, that differs from the "resident" allele (in the coding region and thus in the four expression states ξ^i_j) can increase in frequency. The mutant allele will occur in four different states at any given time, t, and therefore we define: (i) $n^{\mathrm{m}}_{\mathrm{m}}(t)$, the number paternally derived and in a male; (ii) $n^{\mathrm{m}}_{\mathrm{f}}(t)$, the number maternally derived and in a male; (iii) $n^{\mathrm{f}}_{\mathrm{m}}(t)$, the number paternally derived and in a female; and (iv) $n^{\mathrm{f}}_{\mathrm{f}}(t)$, the number maternally derived and in a female. The recursion equations for the number of mutant alleles (when rare) are given by $n(t+1) = E[\mathbf{A}] \cdot \mathbf{n}(t)$, where $E[\ ]$ denotes the expectation over all individuals in the population, and

$$\mathbf{n}(t) = [n^{\mathrm{m}}_{\mathrm{m}}(t) \quad n^{\mathrm{m}}_{\mathrm{f}}(t) \quad n^{\mathrm{f}}_{\mathrm{m}}(t) \quad n^{\mathrm{f}}_{\mathrm{f}}(t)]^{\mathrm{T}},$$

$$\mathbf{A} = \frac{1}{2}\begin{bmatrix} F^{\mathrm{m}}_{\mathrm{m}}/2 & F^{\mathrm{m}}_{\mathrm{f}}/2 & 0 & 0 \\ 0 & 0 & F^{\mathrm{f}}_{\mathrm{m}}/2 & F^{\mathrm{f}}_{\mathrm{f}}/2 \\ F^{\mathrm{m}}_{\mathrm{m}}/2 & F^{\mathrm{m}}_{\mathrm{f}}/2 & 0 & 0 \\ 0 & 0 & F^{\mathrm{f}}_{\mathrm{m}}/2 & F^{\mathrm{f}}_{\mathrm{f}}/2 \end{bmatrix},$$

and

$$F_{\mathrm{m}}^{\mathrm{m}} = \frac{W_{\mathrm{m}}\left(X_{\mathrm{pat}}^{\mathrm{m}} h(\xi_{\mathrm{m}}^{\mathrm{m}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{m}}) + X_{\mathrm{mat}}^{\mathrm{m}}(1 - h(\xi_{\mathrm{m}}^{\mathrm{m}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{m}}))\right)}{W_{\mathrm{m}}\left(X_{\mathrm{pat}}^{\mathrm{m}} h(\hat{\xi}_{\mathrm{m}}^{\mathrm{m}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{m}}) + X_{\mathrm{mat}}^{\mathrm{m}}(1 - h(\hat{\xi}_{\mathrm{m}}^{\mathrm{m}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{m}}))\right)} \times W_{\mathrm{f}}\left(X_{\mathrm{pat}}^{\mathrm{f}} h(\hat{\xi}_{\mathrm{m}}^{\mathrm{f}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{f}}) + X_{\mathrm{mat}}^{\mathrm{f}}(1 - h(\hat{\xi}_{\mathrm{m}}^{\mathrm{f}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{f}}))\right),$$

$$F_{\mathrm{f}}^{\mathrm{m}} = \frac{W_{\mathrm{m}}\left(X_{\mathrm{pat}}^{\mathrm{m}} h(\hat{\xi}_{\mathrm{m}}^{\mathrm{m}}, \xi_{\mathrm{f}}^{\mathrm{m}}) + X_{\mathrm{mat}}^{\mathrm{m}}(1 - h(\hat{\xi}_{\mathrm{m}}^{\mathrm{m}}, \xi_{\mathrm{f}}^{\mathrm{m}}))\right)}{W_{\mathrm{m}}\left(X_{\mathrm{pat}}^{\mathrm{m}} h(\hat{\xi}_{\mathrm{m}}^{\mathrm{m}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{m}}) + X_{\mathrm{mat}}^{\mathrm{m}}(1 - h(\hat{\xi}_{\mathrm{m}}^{\mathrm{m}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{m}}))\right)} \times W_{\mathrm{f}}\left(X_{\mathrm{pat}}^{\mathrm{f}} h(\hat{\xi}_{\mathrm{m}}^{\mathrm{f}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{f}}) + X_{\mathrm{mat}}^{\mathrm{f}}(1 - h(\hat{\xi}_{\mathrm{m}}^{\mathrm{f}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{f}}))\right),$$

$$F_{\mathrm{m}}^{\mathrm{f}} = W_{\mathrm{f}}\left(X_{\mathrm{pat}}^{\mathrm{f}} h(\xi_{\mathrm{m}}^{\mathrm{f}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{f}}) + X_{\mathrm{mat}}^{\mathrm{f}}(1 - h(\xi_{\mathrm{m}}^{\mathrm{f}}, \hat{\xi}_{\mathrm{f}}^{\mathrm{f}}))\right),$$

$$F_{\mathrm{f}}^{\mathrm{f}} = W_{\mathrm{f}}\left(X_{\mathrm{pat}}^{\mathrm{f}} h(\hat{\xi}_{\mathrm{m}}^{\mathrm{f}}, \xi_{\mathrm{f}}^{\mathrm{f}}) + X_{\mathrm{mat}}^{\mathrm{f}}(1 - h(\hat{\xi}_{\mathrm{m}}^{\mathrm{f}}, \xi_{\mathrm{f}}^{\mathrm{f}}))\right).$$

The ½ in the matrix for **A** results from the fact that, in a diploid organism, one-half of the offspring produced by a female will carry the mutant allele (when it is rare). All entries of this matrix are also divided by 2, reflecting the fact that we are assuming the sex ratio of the offspring is 50:50. Also, note that mutant male fitness is measured relative to the population-wide male fitness, reflecting the fact that there is male-male competition for access to females. Finally, X_{pat}^{i} and X_{mat}^{i} are random variables representing the value of the paternally and maternally inherited trait-coding allele in a randomly chosen individual of sex i.

The dominant eigenvalue of **A** represents the growth rate of the rare mutant allele, and we can determine the direction of selection on various mutant alleles (under an assumption of small mutational steps) by differentiating this eigenvalue with respect to the mutant gene, ξ, for each of the four different states, and then evaluating at the resident gene $\hat{\xi}$. It can be shown that $E[\partial\lambda/\partial\xi_j^i] \propto [1, 1, 1, 1]E[\partial\mathbf{A}/\partial\xi_j^i][1, 1, 1, 1]^{\mathrm{T}}$, where everything is evaluated at $\xi = \hat{\xi}$. This expression represents the selection gradient, and carrying out this calculation leads to expressions (1). Expression (2) is obtained by assuming that ξ is expressed in the same way in males and females, and therefore by calculating $E[\partial\lambda/\partial\xi_j^{\mathrm{m}} + \partial\lambda/\partial\xi_j^{\mathrm{f}}]$.

Simulations: We use standard two-locus, two-allele population genetic recursion equations for the frequency of the four possible gametes (Hartl and Clark 1989), but they are generalized to track these frequencies separately for male and female gametes (Owen 1953; Mandel 1971; Kidwell *et al.* 1977; equations available upon request). The model is completely specified once the recombination rate between the loci is specified, along with the fitnesses of the 32 possible genotypes (16 genotypes for each sex). The alleles are denoted *A* and *a* for the trait-coding locus and *I* and *O* for the modifier locus (with *I* being the imprinter and *O* being the wild type). In all examples, there are six different possible phenotypes, and thus six different possible fitnesses that any of the genotypes might produce: males, W_{AA}^{m}, W_{Aa}^{m}, or W_{aa}^{m}, and females, W_{AA}^{f}, W_{Aa}^{f}, or W_{aa}^{f}. Thus, each of the 32 genotypes will produce a phenotype that has one of the above six fitnesses, and the mapping from genotype to fitness depends on the scenario being modeled.

We explore two different scenarios.

1. Sexual dimorphism in imprinting is allowed. In this scenario, if the trait-coding allele is inherited with the imprinter, *I*, then that allele is expressed only if it is found in the sex that matches its parent of origin. For example, if a male inherits *A* and *I* from its mother, then the *A* allele is silenced. On the other hand, if it inherits *A* and *I* from its father, the *A* allele is expressed. All trait-coding alleles that are inherited without an imprinter allele at the modifier locus are expressed, and the phenotype is assumed to be additively determined by all expressed alleles. The fitness of each of the 32 genotypes is therefore given as follows (where, in the notation below, the paternally inherited gamete is written first, and the superscript on the genotype refers to the sex of that genotype):

   Males:
   $\{AIAI^{\mathrm{m}}, AIAO^{\mathrm{m}}, AIaI^{\mathrm{m}}, AOAI^{\mathrm{m}}, AOAO^{\mathrm{m}}, AOaI^{\mathrm{m}}\} \in W_{AA}^{\mathrm{m}}$
   $\{AIaO^{\mathrm{m}}, AOaO^{\mathrm{m}}, aIAO^{\mathrm{m}}, aOAO^{\mathrm{m}}\} \in W_{Aa}^{\mathrm{m}}$
   $\{aIAI^{\mathrm{m}}, aIaI^{\mathrm{m}}, aIaO^{\mathrm{m}}, aOAI^{\mathrm{m}}, aOaI^{\mathrm{m}}, aOaO^{\mathrm{m}}\} \in W_{aa}^{\mathrm{m}}.$

   Females:
   $\{AIAI^{\mathrm{f}}, AIAO^{\mathrm{f}}, AOAI^{\mathrm{f}}, AOAO^{\mathrm{f}}, aIAI^{\mathrm{f}}, aIAO^{\mathrm{f}}\} \in W_{AA}^{\mathrm{f}}$
   $\{AOaI^{\mathrm{f}}, AOaO^{\mathrm{f}}, aOAI^{\mathrm{f}}, aOAO^{\mathrm{f}}\} \in W_{Aa}^{\mathrm{f}}$
   $\{AIaI^{\mathrm{f}}, AIaO^{\mathrm{f}}, aIaI^{\mathrm{f}}, aIaO^{\mathrm{f}}, aOaI^{\mathrm{f}}, aOaO^{\mathrm{f}}\} \in W_{aa}^{\mathrm{f}}.$

2. Sexual dimorphism in imprinting is not allowed. Instead, the imprinter allele silences the maternally inherited trait-coding allele in both male and female offspring. For example, all offspring who inherit *A* and *I* from their mother will have this *A* allele silenced. On the other hand, all offspring who inherit *A* and *I* from their father will have this *A* allele expressed. Again, all trait-coding alleles that are inherited without an imprinter allele at the modifier locus are expressed, and the phenotype is assumed to be additively determined by all expressed alleles. As a result, the male fitness specifications are the same as those in scenario 1 but the female fitness specifications now change as detailed below:

   Males:
   $\{AIAI^{\mathrm{m}}, AIAO^{\mathrm{m}}, AIaI^{\mathrm{m}}, AOAI^{\mathrm{m}}, AOAO^{\mathrm{m}}, AOaI^{\mathrm{m}}\} \in W_{AA}^{\mathrm{m}}$
   $\{AIaO^{\mathrm{m}}, AOaO^{\mathrm{m}}, aIAO^{\mathrm{m}}, aOAO^{\mathrm{m}}\} \in W_{Aa}^{\mathrm{m}}$
   $\{aIAI^{\mathrm{m}}, aIaI^{\mathrm{m}}, aIaO^{\mathrm{m}}, aOAI^{\mathrm{m}}, aOaI^{\mathrm{m}}, aOaO^{\mathrm{m}}\} \in W_{aa}^{\mathrm{m}}.$

   Females:
   $\{AIAI^{\mathrm{f}}, AIAO^{\mathrm{f}}, AIaI^{\mathrm{f}}, AOAI^{\mathrm{f}}, AOAO^{\mathrm{f}}, AOaI^{\mathrm{f}}\} \in W_{AA}^{\mathrm{f}}$
   $\{AIaO^{\mathrm{f}}, AOaO^{\mathrm{f}}, aIAO^{\mathrm{f}}, aOAO^{\mathrm{f}}\} \in W_{Aa}^{\mathrm{f}}$
   $\{aIAI^{\mathrm{f}}, aIaI^{\mathrm{f}}, aIaO^{\mathrm{f}}, aOAI^{\mathrm{f}}, aOaI^{\mathrm{f}}, aOaO^{\mathrm{f}}\} \in W_{aa}^{\mathrm{f}}.$