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Maternal-Zygotic Gene Conflict Over Sex Determination: Effects of Inbreeding

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ABSTRACT

There is growing evidence that sex determination in a wide range of organisms is determined by interactions between maternal-effect genes and zygotically expressing genes. Maternal-effect genes typically produce products (*e.g.*, mRNA or proteins) that are placed into the egg during oogenesis and therefore depend upon maternal genotype. Here it is shown that maternal-effect and zygotic genes are subject to conflicting selective pressures over sex determination in species with partial inbreeding or subdivided populations. The optimal sex ratios for maternal-effect genes and zygotically expressing genes are derived for two models: partial inbreeding (sibmating) and subdivided populations with local mating in temporary demes (local mate competition). In both cases, maternal-effect genes are selected to bias sex determination more toward females than are zygotically expressed genes. By investigating the invasion criteria for zygotic genes in a population producing the maternal optimum (and vice versa), it is shown that genetic conflict occurs between these genes. Even relatively low levels of inbreeding or subdivision can result in maternal-zygotic gene conflict over sex determination. The generality of maternal-zygotic gene conflict to sex determination evolution is discussed; such conflict should be considered in genetic studies of sex-determining mechanisms.

DETERMINATION of sex is one of the earliest and most basic "decisions" made by a developing embryo. It is therefore not unreasonable to expect genetic and biochemical mechanisms of sex determination to be among the most conserved of developmental processes. In contrast, sex-determination mechanisms are extraordinarily diverse (White 1973; Bull 1983). Even when the apparent sex-determining system is the same (*e.g.*, male heterogamety), the underlying genetic mechanisms can be quite different. For example, *Drosophila melanogaster* has male heterogamety due to an X:A balance system (reviewed in Cline 1993), whereas the housefly has male heterogamety due primarily to a dominant male-determining locus (Duebendorfer *et al.* 1992).

Why are sex-determination mechanisms so evolutionarily labile? One potential explanation is the inherent "genetic conflict" that occurs in sex-determining systems (Cosmides and Tooby 1981; Werren *et al.* 1988; Hurst *et al.* 1996; Werren and Beukeboom 1998). Genetic conflict occurs when different genetic elements are selected to "push" a phenotype in different directions. In the case of sex determination, conflicting selective pressures occur on genetic elements on the basis of differences in their inheritance pattern. The most obvious example concerns cytoplasmically inherited elements (*e.g.*, mitochondria and inherited microorganisms) and autosomal genes. Cytoplasmic elements have a uniparental inheritance through females. As a result, cytoplasmically inherited factors are selected to skew sex determination toward females (the transmitting sex), even if this produces highly female-biased sex ratios (Eberhard 1980; Cosmides and Tooby 1981). Similarly, genes located on chromosomes with non-Mendelian inheritance patterns are selected to bias sex ratio toward the sex most strongly associated with their transmission (Hamilton 1967). In contrast, autosomal nuclear genes are generally selected to produce a balance in the sex ratio, often favoring a 50:50 sex ratio (Fisher 1930).

Werren and Beukeboom (1998) proposed that conflicting selective pressures might occur between maternal and zygotic genes involved in sex determination. In particular, they proposed that inbreeding could result in differential selection of maternal-effect and zygotic sex-determining genes, thus leading to genetic conflict. Hamilton (1967) first pointed out that an inbreeding population structure, particularly one involving competition among male siblings for mates (termed local mate competition), will select for females that bias sex ratio toward females. Extensive theoretical and empirical studies generally support Hamilton's local mate competition theory (Charnov 1982; Antolin 1993). However, studies typically consider only selection acting upon mothers to alter their sex ratio, particularly through mechanisms such as haplodiploidy, which give the mother "control" over sex ratio among progeny by controlling fertilization of eggs. There has been very little consider-

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ation of how inbreeding and local mate competition will affect selection acting upon sex-determination genes expressed in the zygote. In addition, theoretical and empirical studies of the sex ratio have generally not considered the role of maternal-effect genes in sex-determination evolution. Maternal-effect genes are expressed in the female but act in the zygote to influence its phenotype. Maternal effects are due primarily to the production of proteins or messenger RNA that are placed into the developing egg. For example, a number of early developmental processes, such as embryonic polarity and segmentation, are determined by interactions between maternal products and zygotically expressed genes (Gerhart and Kirschner 1997). There is also growing evidence that sex determination is influenced both by zygotically expressed genes and by maternal-effect genes. Maternal-effect sex-determining genes have been described in *D. melanogaster* (Steinemann-Zwicky *et al.* 1990; Cline 1993), *Musca domestica* (Schmidt *et al.* 1997), *Caenorhabditis elegans* (Ahringer *et al.* 1992), and *Chrysomia rufescens* (Ullerich 1984). As more systems are dissected genetically, maternal-effect sex-determining genes are likely to be a common feature.

The possibility of maternal-zygotic gene conflict over sex determination has not been extensively explored. Because maternal genes are expressed in the mother (prior to meiosis), they may be subject to different selective pressures for sex determination than are zygotically expressed sex-determination genes. Werren and Beukeboom (1998) suggested that partial inbreeding and local mate competition would cause divergent selection on maternal-effect and zygotic sex-determining genes. The basic cause for this conflict is that inbreeding results in different associations of maternal and zygotic sex-determining genes in males and females within families, with consequent different fitness effects acting upon the two categories of genes. Figure 1 shows a specific example illustrating the principle, mating between a heterozygous male and female ($Aa \times Aa$), where A is either a dominant-maternal or dominant-zygotic sex-determining locus. For maternal-effect genes, the sex ratio among the progeny is determined by maternal genotype, and therefore zygotic genotypes are distributed evenly among males and females in the family. The fitness consequences of a particular maternal genotype therefore affect all progeny within a sex similarly. In contrast, for zygotic sex-determining genes, sex is determined by the zygotic genotype. As a result, the different genotypes are not distributed evenly among the male and female progeny of a family. The fitness consequences of a particular genotype affect that genotype directly. Inbreeding alters the distribution of A allele genotypes in males and females.

Previous studies have derived the optimal [or evolutionarily stable strategy (ESS)] sex ratio under maternal control for diploids with partial sibmating (Maynard Smith 1978; Taylor and Bulmer 1980; Uyenoyama and Bengtsson 1982) or local mate competition (Hamilton 1967; Karlin and Lessard 1986). Here, we compare the optimal sex ratio for maternal-effect and zygotic-effect sex determiners under inbreeding and local mating and determine the conditions for alleles of one type to invade a population producing an alternative sex ratio. Our results show that partial inbreeding and local mate competition result in genetic conflict between maternal-effect and zygotic sex-determining genes.

PARTIAL SIBMATING MODEL

Basic model: Details of methods are presented in the appendix. Here we describe the basic modeling approach for the partial sibmating model. Assume an infinite population of diploid dioecious organisms that have a probability p of mating with their siblings. The remaining individuals mate randomly in the population at large (probability $1 - p$). The probability of developing as a male is determined by alleles at a single autosomal locus; *aa* individuals produce $\hat{r}$ proportion sons. We introduce a mutant A gene, which is dominant to a and codes for an arbitrarily different sex determining ratio, r. The ESS (r^*) is found by solving for the value of $\hat{r}$ against which A genes cannot increase when rare. Invasion criteria are determined by calculating the dominant eigenvalue for the transmission matrix when r and $\hat{r}$ are set at different values. By contrasting the optimal sex ratios and invasion conditions for maternal-effect and zygotic sex-determining genes, we can determine the extent of genetic conflict between these two categories of genes.

Comparison of ESS sex ratios: When sex determination is under zygotic control, the probability of an individual being male depends upon its genotype rather than that of its mother. Solving (see appendix) for the equilibrium zygotic sex determiner $r^*_{p,z}$ in relation to sibmating probability p, we obtain

$$r^*_{p,z} = \frac{1 - p}{2 - p}. \tag{1}$$

Similarly, solving for the ESS $r^*_{p,m}$ under maternal control yields

$$r^*_{p,m} = \frac{1 - p}{2}. \tag{2}$$

The latter derivation is identical to the ESS under maternal control derived by Taylor and Bulmer (1980), using similar methods (see also Maynard Smith 1978; Karlin and Lessard 1986). As can be seen, the ESS sex ratio under partial inbreeding is different for zygotic *vs.* maternal genes (see Figure 2). In both cases, increasing levels of sibmating select for a female-biased sex ratio in sex-determining genes. However, as predicted by Werren and Beukeboom (1998), under partial inbreeding, sex-determining genes in the zygote are selected to produce a *less* extreme bias than that favored for maternal-effect genes. The optimum sex ratio for a

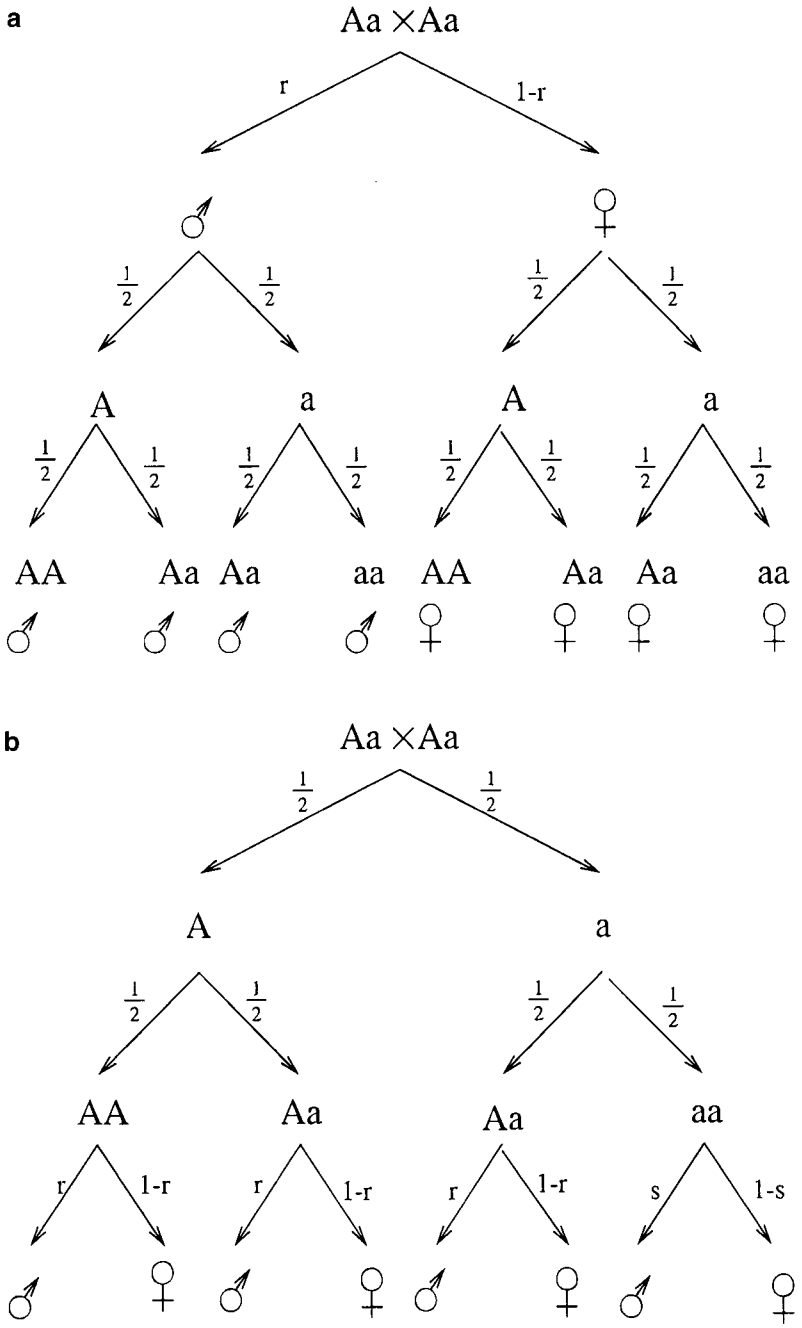

Figure 1.—Probability trees for (a) maternal and (b) zygotic sex determination. Assortment of maternal-effect and zygotic alleles is shown, where *r* and *s* are the sex ratios (the proportion of males produced under maternal control or the probability of male determination under zygotic control) coded by *A* and *a* alleles, respectively. The diagrams illustrate that the order of events differs for the two mechanisms and may lead to differing offspring sex ratios in heterozygous crosses.

zygotic sex-determining locus is always less female-biased than for a maternal-effect sex determiner for all values of p between $0 < p < 1$. For example, when $p = 0.20$ (20% sibmating) the optimal sex ratio for a maternal-effect gene is 0.400, whereas that of a zygotic sex-determining gene is 0.444. Even for low levels of sibmating (*e.g.*, 5%) the optimal sex ratios differ; 0.475 for a maternal-effect gene *vs.* 0.487 for a zygotic gene. These differences, although small, suggest maternal-zygotic conflict over sex ratio control and may be sufficient to cause a successive turnover in genes modifying sex determination.

Invasion of alternative control strategies: We can demonstrate the occurrence of genetic conflict by examining the invasion characteristics of a mutant strategy against alternative backgrounds. The rare allele will increase (or decrease) in the population at a rate equal to the dominant eigenvalue (λ) of its transmission matrix. Hence ($\lambda - 1$) measures the selective advantage (fitness differential) of the invading strategy. We consider (a) the invasion of maternal and zygotic alleles coding for their respective ESS solution into a population at the alternative ESS and (b) the spectrum of maternal (and zygotic) alleles that can invade when a population is at the alternative ESS.

Rare maternal alleles in a zygotic ESS background: When the population sex ratio is at the zygotic optimum (setting $= \hat{r} = r^*_{p,z}$), a maternal-effect mutant producing the

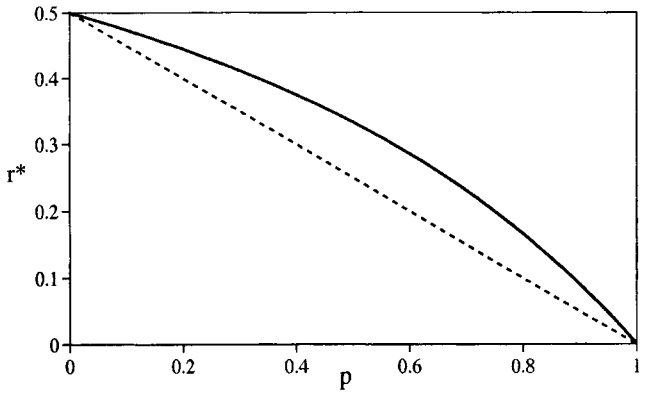

Figure 2.—ESS sex-determining strategies under partial sibmating. The evolutionary stable sex ratio r^* (proportion males) is plotted against the probability of inbreeding (p) for a maternal-effect gene (dotted line) and for a zygotic sex-determining gene (solid line).

maternal optimum $r^*_{p,m}$ will invade for all values of inbreeding $0 < p < 1$. The maximum selective advantage is 3.03% (at $p = 0.721$). However, even when inbreeding is quite uncommon, such an allele has a selective advantage when rare (*e.g.*, with $p = 0.05$, the selective advantage is 0.03%). Next we investigated the range of maternal alleles that can invade a population at the zygotic ESS. Any maternal-effect mutant producing a more female-biased sex ratio can invade a population at the zygotic ESS (excepting the special case for $r = 0$; see the appendix). For a given $\hat{r}$, the selective differential λ for the maternal-effect mutant increases with decreasing r; hence more female-biased sex ratios have a greater selective advantage and will spread faster initially. The maximum selective differential for maternal-effect mutants in a population at the zygotic ESS can be quite substantial ($\lambda = 1.108$ with $r = 0.01$, $p = 0.5$). At low levels of inbreeding (*e.g.*, $p = 0.05$), a strongly female-biasing maternal control allele ($r = 0.01$) will spread initially at rate of 2.20% per generation. These results establish that conflicting selective pressures occur between maternal and zygotic sex-determining alleles when the population is at the zygotic optimum.

Rare zygotic alleles in a maternal ESS background: When a population sex ratio is at the maternal optimum, a rare zygotic ESS allele will increase for all levels of inbreeding $0 < p < 1$. The maximum of spread is 4.49% per generation (for $p = 0.746$), although even at low levels of inbreeding the zygotic ESS will increase when rare (with $p = 0.05$, the selective advantage is 0.221%). Additionally, for all levels of inbreeding $0 < p < 1$, any zygotic sex determiner with a sex ratio (proportion male) greater than the maternal ESS will increase in frequency when rare. Genes producing the most extreme male bias ($r = 1$) have the greatest selective advantage. The fitness differential of such mutants can be very great; at high levels of inbreeding a zygotic sex determiner producing all males is predicted to spread at a rate approaching 50% per generation against the maternal ESS (for example, for $r = 1$, $\lambda = 1.500$ at $p = 0.99$). Note that we are assuming no reduced fitness of inbred offspring (*i.e.*, no inbreeding depression). Even for low levels of inbreeding ($p = 0.05$), an all-male zygotic control allele will increase at a significant rate ($\lambda = 1.017$) in a population at the maternal ESS. Recall that such a zygotic all-male allele will not produce an all-male family, because it determines zygotic sex, not family sex ratio. Such an allele is equivalent to a dominant male sex-determining locus; *AA* genotypes cannot be generated as all *Aa* individuals develop as males. The results establish that conflicting selection pressures occur between maternal and zygotic sex-determining alleles when the population is at the maternal ESS. Results also indicate that dominant zygotic sex-determining alleles can increase in such populations, at least when rare.

In summary, both maternal and zygotic genes producing a strongly female-biased sex ratio will invade populations at a 50:50 sex ratio. When the population sex ratio is more female-biased than the zygotic optimum, conflict between maternal and zygotic sex determiners occurs. One outcome of this conflict in natural populations could be sex-determination polymorphisms with zygotic genes for strong male bias and maternal genes for strong female bias. Although we have established that such alleles will invade a population initially, we have not determined how far they can spread before reaching an equilibrium frequency or what additional coevolutionary dynamics will occur. The solution to these problems is complex (even the rare gene criteria require an 8×8 matrix) and can be investigated most effectively by simulation.

DEMIC (LOCAL MATE COMPETITION) MODEL

An alternative model of mating structure is local mate competition (LMC; Hamilton 1967, 1979; Taylor and Bulmer 1980). LMC populations are composed of temporary demes of size n (the number of mated foundresses per deme); foundresses reproduce and the resulting offspring mate at random within the deme. The mated females so produced then disperse at random to found demes for the subsequent generation. The population structure differs from sibmating because females mate in a local deme, where they may mate with either sibs or males from other foundresses. The fitness of males is affected by the local sex ratio, because the local sex ratio affects both the level of mate competition and the availability of mates. We used the techniques described above to analyze transmission of maternal and zygotic sex-determining alleles, assuming (a) an infinite number of demes and (b) the *A* allele is sufficiently rare that demes founded by more than one mated female carrying the *A* allele can be ignored. Using the same

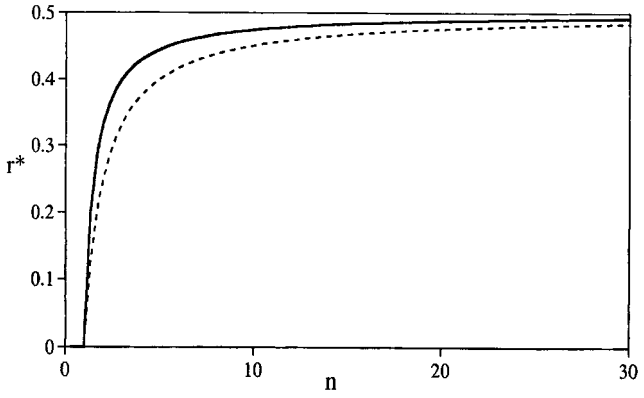

Figure 3.—ESS sex-determining strategies under local mate competition. The evolutionary stable sex ratio r^* (proportion males) is plotted against deme size (n) for a maternal-effect gene (dotted line) and for a zygotic sex-determining gene (solid line).

methodology that was applied for partial sibmating, the ESS obtained is

$$r^*_{n,z} = \frac{n-1}{2n-1} \tag{3}$$

and the ESS under maternal control is

$$r^*_{n,m} = \frac{n-1}{2n}. \tag{4}$$

The latter is the same as derived by Hamilton (1967) using different methods and by Taylor and Bulmer (1980) using similar methods to those employed here.

As with partial sibmating, although both ESSs are female-biased under mating structure, the zygotic ESS is *less* biased than the maternal optimum (Figure 3). Genetic conflict between the zygotic- and maternal-effect genes for an LMC situation was analyzed as before.

Invasion of alternative ESS: When the population performs the zygotic ESS ($\hat{r} = r^*_{n,z}$), a maternal-effect mutant producing the maternal ESS ($r = r^*_{n,m}$) has a selective advantage of up to 1.24% (for $n = 2$). With less extreme demic structure, maternal-effect alleles have a decreasing (but still positive) fitness differential; for example, a deme size of 10 results in a selective advantage of ~0.11% for the maternal ESS. When the population is set to the maternal ESS ($\hat{r} = r^*_{n,m}$), a zygotic sex determiner producing the zygotic ESS ($r = r^*_{n,z}$) increases at a rate up to 2.24% per generation (at $n = 2$). As deme size is increased, the selective advantage of such mutants reduces, but remains positive: at $n = 10$, a zygotic ESS mutant has a selective advantage of 0.21%.

Maximum selective differentials of rare alleles: Numerical iterations were used to determine the mutant strategy with the largest fitness differential for $0 \le r \le 1$ and $0 \le \hat{r} \le 1$. For both maternal- and zygotic-effect mutants, the maximum rate of increase was achieved at *intermediate* values of r. It can be shown analytically that maternal-effect genes producing all-female offspring and zygotic genes coding for all-male development cannot invade the alternative ESS for any n. A population performing the zygotic ESS $r^*_{n,z}$ can be invaded by maternal-effect mutants producing a more female-biased sex ratio; however, mutants producing extreme female biases cannot invade. For instance, for $n = 2$, maternal-effect genes producing $0.167 < r < r^*_{n,z}$ can invade, and for $n = 10$, mutants producing $0.237 < r < r^*_{n,z}$ can invade. A population at the maternal ESS $r^*_{n,m}$ can be invaded by a zygotic sex determiner with a more male-biased strategy, but again the maximal rate of increase is achieved for an intermediate r. Mutants producing all males cannot invade: for $n = 2$, initial spread of the mutant requires that $r^*_{n,m} < r < 0.447$; for $n = 10$ the condition is $r^*_{n,m} < r < 0.940$. The maximum selective differentials can be substantial for strong demic structure; for $n = 2$ a maternal control mutant producing $r = 0.24$ has an advantage $\lambda = 1.013$ over $\hat{r} = r^*_{n,z} = 0.33$ and a zygotic allele producing $r = 0.38$ has advantage $\lambda = 1.025$ over $\hat{r} = r^*_{n,m} = 0.25$.

The differences in the shapes of the ESS responses (Figures 2 and 3) and relative selective advantages and maximal r for the two strategies between local mate competition and partial sibmating demonstrate that these models are fundamentally different in their treatment of population structure and inbreeding (see, *e.g.*, Uyenoyama and Bengtsson 1982). However, results clearly show a genetic conflict between maternal-effect and zygotic sex-determining genes when the population sex ratio falls between the optima for the two types of genes.

DISCUSSION

Trivers (1974) first pointed out the potential for genetic conflict between parents and offspring over reproductive decisions. He considered conflict over resource allocation to progeny and concluded that progeny are generally selected to seek more resources from a parent than the parent is selected to provide, assuming that providing the extra resource imposes a future reproductive cost to the parent. Various theoretical treatments have verified this effect (*e.g.*, Parker and McNair 1979; Parker 1985; Godfray 1995) and have been used to consider other aspects of parent-offspring conflict (*e.g.*, Ellner 1986; Haig 1993). However, there has been very little consideration of genetic conflict between maternal and zygotic genes over sex determination. An exception is Eshel and Sansone (1994), who considered conflict between genes for maternal behavioral manipulation of the sex ratio (*e.g.*, by selective abortion of offspring) and zygotic responses to the manipulation, when maternal costs of rearing sons and daughters differ. Similarly, Trivers and Hare (1976) and others (*e.g.*, Matessi and Eshel 1992) have consid-

ered worker-queen conflict over sex ratio in social insects. These treatments concern different topics from the models of maternal and zygotic sex-determination evolution presented here.

Our results show that maternal-zygotic gene conflict occurs over sex determination in populations with partial inbreeding or a local mating population structure. An intuitive explanation for the conflict can be gained by considering levels of selection. There are two selective levels acting on sex ratio in the inbred portion of these populations, between-family selection and within-family selection. Between-family selection favors more strongly female-biased sex ratios (maximizing propagation of familial alleles; Wilson and Colwell 1981); however, within-family selection favors less-biased sex ratios, because the rarer sex within the family (males in this situation) have higher fitness (*i.e.*, transmit their alleles at higher frequency; Fisher 1930). Maternally acting genes are subject only to between-family selection, because the family sex ratio is determined by maternal genotype. Zygotic genes are subject to both between-family and within-family sex ratio selection. Less female-biased alleles have greater transmission within the family and therefore are selectively favored. The result is conflicting selective pressures for maternal and zygotic sex ratio genes.

When a population has partial inbreeding or local mating structure and produces a 50:50 or more male-based sex ratio, female biasing alleles are selectively favored by both maternal and zygotic expressing genes. Hence, there is initially no conflict. However, if the population were to approach the zygotic optimum (which is less female-biased than the maternal optimum), then selection will favor maternal-effect genes to bias the sex ratio further. As the population sex ratio approaches the maternal optimum, more male-biasing alleles can be selected. In fact, zygotic alleles producing all males can be selectively favored when the population sex ratio is overly biased toward females. Our analysis considers only the invasion criteria for alleles in populations producing different sex ratios, and therefore we have not determined how far all-male-producing zygotic genes will spread through a population initially producing the maternal optimum (or vice versa). However, results suggest that polymorphisms for sex-determining alleles may be likely in populations with partial inbreeding, since all-male alleles will not spread to fixation in the population, but will be selectively favored when rare. In contrast to zygotic alleles, which can be selected for all-male determination when the population sex ratio is sufficiently biased toward females, maternal-effect alleles are not selected to produce all-female sex ratios under any circumstance modeled here. An intuitive explanation for this is that maternal alleles "lose" the substantial fitness gains through sons under sibmating or local mate competition if an all-female brood is produced.

Levels of inbreeding do not have to be high to cause conflicting selective pressures between maternal effect and zygotic genes. For example, in populations with 5% sibling matings, the zygotic optimum sex ratio is 0.4872 whereas the maternal optimum is 0.475. These represent relatively small deviations from a 50:50 sex ratio. But, under these circumstances, a maternal gene inducing a 0.01 probability of male determination in zygotes has a fitness differential of 1.0463 relative to one remaining at 50:50. In population genetic terms, this represents a substantial fitness differential and will lead to initial rapid increase of the gene ($\sim$4.6% per generation). The internal dynamics of this system are complicated and might result in coevolutionary dynamics (*e.g.*, evolutionary "arms races") between zygotic and maternal sex-determining loci. Exploration of these will probably require simulation.

How likely is maternal-effect-zygotic gene conflict over sex determination in nature? The potential relevance of these models to sex-determination evolution depends on (a) the extent to which partial inbreeding occurs in natural populations and (b) the extent to which maternal-effect genes have influence over zygotic sex determination. Some species are known to routinely sibmate at a high level (Hamilton 1967; Godfray 1994; Godfray and Werren 1996). Examples include many parasitic wasps (Godfray 1994), bark beetles (Kirkendall 1983), parasitic nematodes, fungal gnats, and a variety of plants. Many other species mate in local populations, where some level of inbreeding (and local mate competition among males) is likely. This scenario applies to a wide range of organisms, including herbivorous insects that form localized populations feeding on plants, rodents with local population structures, including partial inbreeding (Dallas *et al.* 1995), and even humans in isolated populations. Inbreeding is especially likely during the early stages of founding events, when local population numbers are low and the population has been founded by relatively few individuals. When these situations occur commonly as part of the population structure of a species, then maternal-zygotic gene conflict will occur over sex determination. Our results show that even low levels of inbreeding cause maternal-zygotic conflict.

To what extent do maternal genes affect sex determination? There is growing evidence in a number of systems that maternal-effect genes play important roles in sex determination. In *D. melanogaster*, sex is grossly determined by an X chromosome/autosome ratio. Decades of study have revealed some of the genetic underpinnings of this system, including the inputs of several maternal expressing genes. Both zygotically expressing "numerator" elements on the X chromosome (*e.g.*, *sisterless-a* and *sisterless-b*) and maternally expressing genes *daughterless* (*da*) and *sans fille* (*snf*) affect expression of the master switch gene *Sex lethal* (*Sxl*). Activation of *Sxl* leads to female somatic sex determination. Sex determi-

nation in *M. domestica* is complex and can vary between populations (reviewed in Duebendorfer *et al.* 1992). The standard form of sex determination involves XY males, in which the (undifferentiated) Y chromosome carries a dominant male-determining factor (*M*). However, some natural populations have XX males, and a dominant *M* factor appears to have been translocated onto an autosome. Other populations harbor a dominant female-determining gene *FD*, effectively rendering such populations as female heterogametic. *FD* is epistatically dominant over *M*. Maternal effects on sex determination have been found in *M. domestica*. In the recessive maternal-effect gene *transformer* (*tra*), *tra*/*tra* mothers produce intersexes and fertile phenotypic XX males among a large fraction of their *tra*/*tra* progeny. Heterozygous *tra*/+ progeny are also transformed, although less frequently. The data indicate that *tra* is both maternally and zygotically active (Inoue and Hiroyoshi 1986). The wild-type *tra* gene likely produces a feminizing product both maternally (*i.e.*, in the developing oocyte) and zygotically, and if sufficient product is present then female development results. Duebendorfer *et al.* (1992) suggest on the basis of genetic data that *tra* and *FD* are the same gene, with *FD* being an overexpressing feminizing mutant and *tra* an underexpressing mutant. *Arrhenogenic* (*Ag*) is a dominant mutation with maternal effects. Heterozygous *Ag*/+ females produce nearly all-male (plus some intersex) progenies, and it is hypothesized the *Ag* may be a maternally overexpressing *M* locus. Evidence indicates that maternal product contributions to sex determination can be substantial in *M. domestica*. Dominant feminizing maternal-effect genes have also been described in the blowfly *C. rufifacies* (Ullerich 1984).

In the nematode *C. elegans*, hermaphrodites are XX whereas males are XO. As in Drosophila, sex is generally determined by an X:A balance, and these clearly represent two independent evolutions of X:A balance. The gene *fem-3* is required for male development in *C. elegans*. Both maternal and zygotic activities are needed for spermatogenesis in XX hermaphrodites and for somatic and germline determination in XO males (Ahringer *et al.* 1992). RNA from *fem-3* is placed into the egg during oogenesis, accounting for the maternal effect. Currently, we know of no evidence for maternal effects in sex determination of the housemouse (*Mus musculus*) or in humans (*Homo sapiens*). The sciarid fly *Sciara coprophila* has a form of sex determination that indicates maternal-effect genetic control (Metz 1957; Gerbi 1986). Females heterozygous for a particular X chromosome variant (X′X) produce all-female progeny and females homozygous for the "standard" X (XX) produce all-male progeny. Among the daughters of X′X females, half are all-female producers (X′X) and half are all-male producers (XX). The pattern is best explained by a dominant maternal-effect sex determiner on the X′ chromosome. Maternal-effect sex determination is also shown in many scale insects (Nur 1989). Thus, it can be concluded that maternal effects on sex determination are common in systems that have been studied in some detail.

To what extent is our inbreeding-induced maternal-zygotic conflict model relevant to the systems just described? Sex determination in *D. melanogaster* may have evolved to a state where maternal-zygotic conflict is restricted. Mutagenic studies show that large-effect mutations on sex determination often cause inviability or sterility. This occurs because somatic sex determination and dosage compensation are genetically coupled in *D. melanogaster*. Mutations that cause XY female development typically also lead to abnormal X chromosome gene expression that results in lethality. Somatic and germline sex determinations are partially uncoupled, and germline determination in *D. melanogaster* is cell autonomous (Steinemann-Zwicky *et al.* 1990). Thus alterations in somatic sex determination can result in infertility. Such highly evolved systems may restrain conflict. However, to understand the current structure of sex determination in Drosophila, it is necessary to consider its evolution from an ancestral state, prior to the evolution of heteromorphic sex chromosomes and dosage compensation. The ancestral system probably involved a dominant male-determining gene (similar to *M. domestica*) and undifferentiated sex chromosomes. From this situation a system of multiple female-determining loci of small cumulative effect on the X chromosome, maternal-effect genes, and (presumed) male-determining autosomal genes of small effect arose. *D. melanogaster* is currently a globally distributed species with huge population sizes, where inbreeding is unlikely except during local founding events. However, the ancestral situation could easily have involved local populations with low to moderate inbreeding levels. As described above, this scenario could lead to the accumulation of maternal and zygotic genes, each of small effect. However, this remains to be explicitly modeled. In addition, it is possible that other models of maternal-zygotic conflict will apply to this system (J. Werren, M. Hatcher and C. Godfray, unpublished results).

M. domestica has a much more labile sex-determining system. The possibility of maternal-zygotic conflict in the current system is real, especially given the discoveries of maternal effects on sex determination. As with *D. melanogaster*, partial inbreeding in local and founder populations is not unlikely in Musca, particularly at low population densities. Inbreeding is likely also in local populations of the nematode *C. elegans*, and therefore the possibility that inbreeding causes maternal-zygotic conflict should be explored. The housemouse *M. musculus domesticus* and related species (*M. m. musculus*) clearly have demic population structures where some level of inbreeding is likely (Dallas *et al.* 1995; Ardlie 1998). We therefore expect to see maternal inputs into sex

determination in these organisms and maternal-zygotic conflict.

It could be argued that mammalian sex-determining systems are too constrained to allow such conflict; however, the finding that XY females can be fertile in some mammals, and that interpopulation variation in "strength" of the mammalian testis-determining factor *Sry* in interaction with other sex-determining loci occurs in mice (Nagamine *et al.* 1994), indicates that these systems may be evolutionarily labile. There is growing evidence that several autosomal or X-linked genes are involved in early events in the mammalian sex-determination cascade (Burgoyne 1989; McElreavey *et al.* 1993; Foster and Graves 1994; Foster *et al.* 1994; Wagner *et al.* 1994). The *SRY*-related autosomal gene *SOX9* is associated with sex reversal in humans and mice and appears to have a fundamental role in sex determination (da Silva *et al.* 1996; Kent *et al.* 1996). The X-linked gene *DAX1* is implicated in dosage-sensitive sex reversal in mice and humans (Swain *et al.* 1998), but has an autosomal location in marsupials (Pask *et al.* 1997), testifying to the evolutionary plasticity of sex determination in mammals. Rapid sequence evolution of *Sry* (Tucker and Lundrigan 1993; Whitfield *et al.* 1993), XY sex reversal, and unusual sex chromosomal systems in cricetid rodents (*Myopus shisticolor*; *Akodon azare*; Fredka 1970; Lau *et al.* 1992) and moles (*Talpa europaea, T. occidentalis*) have been interpreted as evidence of genetic conflict between sex-linked meiotic drive genes (or selfish growth factors) and autosomal suppressers (Hurst 1994; McVean and Hurst 1996).

Other vertebrates show even greater variation in sex-determining mechanism. For example, most birds exhibit female heterogamety, but the system shares similarities with an X(Z):A balance system (Sittmann 1984). The dosage of Z chromosomes appears to influence testicular development, but the W chromosome may be required for ovarian differentiation (Thorne and Sheldon 1993). A great variety of systems are reported in reptiles, ranging from environmental sex determination to XY/WZ or mixed systems (Bull 1980; Janzen and Paukstis 1991; Viets *et al.* 1994).

In *M. domestica* and *C. elegans*, individual genes have been shown to have both maternal and zygotic inputs into sex determination. It may seem counterintuitive that genetic conflict could occur within a single gene for maternal and zygotic expression patterns. However, the domains controlling maternal and zygotic expression can indeed be under different selective pressures (J. Werren, M. Hatcher and C. Godfray, unpublished results). The exact nature of the conflict will depend upon the nature of interaction of the maternally and zygotically produced product in the zygote; but in general, such genes can be selected for opposed expression patterns. In addition, unlinked modifiers of the maternal and zygotic expression patterns will clearly be subject to conflict over expression of genes that have both maternal and zygotic inputs into sex determination.

Given that many of the genetic sex determination systems that have been studied in detail reveal maternal effects, it is likely that maternal inputs into the sex determination "decision" are widespread. Therefore, maternal-effect-zygotic conflict over sex determination appears to be genetically possible. It is currently not known to what extent maternal-effect-zygotic conflict over sex determination occurs in nature, or whether this conflict influences the evolution of sex-determining systems. Classical sex allocation theory has tended to abstract the problem in terms of sex ratio, the definition of which tends to imply maternal (or other external) control mechanisms. Future theoretical efforts should focus on modeling specific genetic sex determination systems for conflict between maternal-effect and zygotic inputs. Those studying the genetics and molecular biology of sex determination may wish to consider the possibility that maternal-effect and zygotic genes affecting sex determination have evolved under conflicting selective pressures.

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APPENDIX

We followed the basic approach of Taylor and Bulmer (1980) to investigate the equilibrium (ESS) sex ratio under maternal and zygotic gene control, for both partial inbreeding and for local mate competition structured populations. The dynamics of a rare dominant allele (A) are determined, producing sex ratio r in a population otherwise producing sex ratio $\hat{r}$. Because inbreeding is possible, the frequencies of each mating type in the population are considered, including matings among *AA*, *Aa*, and *aa* individuals. Thus, recursion formulas for eight mating types are determined (the ninth is defined by one minus the sum of the other eight).

Below, we present the recursion formulas for zygotic control under partial sibmating to illustrate the approach. Formulas for maternal control under partial sibmating or zygotic and maternal control under local mate competition are available upon request. It should also be pointed out that the formulas for $r = 0$ (all females) and $r = 1$ (all males) under partial sibmating require modification to deal with the possibility that no males (females) would be present within the family for mating. Under these circumstances, it was assumed that the offspring mated in the population at large (*i.e.*, p for that sibship was set to 0 when the family sex ratio was equal to r).

Partial sibmating and zygotic sex-determining locus: The transmission dynamics of a rare dominant *A* allele affecting zygotic sex determination are given below, assuming that p proportion of individuals mate with sibs and $1 - p$ mate in the population at large.

The following additional terms are defined (male × female):

ε_1 = frequency of *AA* × *AA* matings
ε_2 = frequency of *AA* × *Aa* matings
ε_3 = frequency of *AA* × *aa* matings
ε_4 = frequency of *Aa* × *AA* matings
ε_5 = frequency of *Aa* × *Aa* matings
ε_6 = frequency of *Aa* × *aa* matings
ε_7 = frequency of *aa* × *AA* matings
ε_8 = frequency of *aa* × *Aa* matings.

It is customary in ESS analyses for random mating populations to ignore homozygous *AA* individuals. The rationale is that the *A* allele is considered to be rare (*e.g.*, 10^{-6}), and therefore *AA* individuals are extremely rare (*e.g.*, $\sim 10^{-12}$), and their contribution to the dynamics is therefore negligible. However, in inbred populations this is not the case because matings occur among relatives, and *AA* individuals cannot be neglected. Similarly, ESS analyses of random mating populations usually ignore matings between two *A* individuals (*e.g.*, *Aa* × *Aa*), again because of their extreme rarity. However, inbreeding can result in appreciable frequencies of mating among such individuals and the frequency of these events could influence the dynamics of sex-determining alleles in partial inbreeding populations. For this reason, we track frequencies of all mating types (*e.g.*, *AA* male × *AA* female, *AA* male × *Aa* female, etc.) in the population. To develop the transmission formulas for the different mating types, contributions of the sibmating portion (at probability p) and outbred portion (probability $1 - p$) must be considered. For the inbred portion, all mating types are calculated, because matings among siblings with the *A* allele (*AA* × *AA*, *AA* × *Aa*, *Aa* × *AA*, and *Aa* × *Aa*) can occur at appreciable frequencies. However, in the outbred portion, such mating types are extremely rare (in the order of ε^2) and can be ignored because they have negligible contribution to allele dynamics when *A* is rare.

Using this approach, the frequency of the mating type in the next generation (ε_i') under partial sibmating is defined by the following:

$$\varepsilon_1' = \frac{p(1-r)}{F_w}\varepsilon_1 + \frac{p(1-r)}{4F_w}\varepsilon_2 + \frac{p(1-r)}{4F_w}\varepsilon_4 + \frac{pr(1-r)}{16F_wM_a}\varepsilon_5$$

$$\varepsilon_2' = \frac{p(1-r)}{4F_w}\varepsilon_2 + \frac{p(1-r)}{4F_w}\varepsilon_4 + \frac{pr(1-r)}{8F_wM_a}\varepsilon_5$$

$$\varepsilon_3' = \frac{(1-p)r}{\hat{r}}\varepsilon_1 + \frac{(1-p)r}{2\hat{r}}\varepsilon_2 + \frac{(1-p)r}{2\hat{r}}\varepsilon_4 + \left(\frac{pr}{16M_a} + \frac{(1-p)r}{4\hat{r}}\right)\varepsilon_5$$

$$\varepsilon_4' = \frac{p(1-r)}{4F_w}\varepsilon_2 + \frac{p(1-r)}{4F_w}\varepsilon_4 + \frac{pr(1-r)}{8F_wM_a}\varepsilon_5$$

$$\varepsilon_5' = \frac{p(1-r)}{4F_w}\varepsilon_2 + \frac{p(1-r)}{F_w}\varepsilon_3 + \frac{p(1-r)}{4F_w}\varepsilon_4 + \frac{pr(1-r)}{4F_wM_a}\varepsilon_5 + \frac{pr(1-r)}{4F_wM_b}\varepsilon_6 + \frac{p(1-r)}{F_w}\varepsilon_7 + \frac{pr(1-r)}{4F_wM_b}\varepsilon_8$$

$$\varepsilon_6' = \frac{(1-p)r}{2\hat{r}}\varepsilon_2 + \frac{(1-p)r}{\hat{r}}\varepsilon_3 + \frac{(1-p)r}{2\hat{r}}\varepsilon_4 + \left(\frac{pr}{8M_a} + \frac{(1-p)r}{2\hat{r}}\right)\varepsilon_5 + \left(\frac{pr}{4M_b} + \frac{(1-p)r}{2\hat{r}}\right)\varepsilon_6 + \frac{(1-p)r}{\hat{r}}\varepsilon_7 + \left(\frac{pr}{4M_b} + \frac{(1-p)r}{2\hat{r}}\right)\varepsilon_8$$

$$\varepsilon_7' = \frac{(1-p)(1-r)}{(1-\hat{r})}\varepsilon_1 + \frac{(1-p)(1-r)}{2(1-\hat{r})}\varepsilon_2 + \frac{(1-p)(1-r)}{2(1-\hat{r})}\varepsilon_4 + \left(\frac{p\hat{r}(1-r)}{16F_wM_a} + \frac{(1-p)(1-r)}{4(1-\hat{r})}\right)\varepsilon_5$$

$$\varepsilon_8' = \frac{(1-p)(1-r)}{2(1-\hat{r})}\varepsilon_2 + \frac{(1-p)(1-r)}{(1-\hat{r})}\varepsilon_3 + \frac{(1-p)(1-r)}{2(1-\hat{r})}\varepsilon_4 + \left(\frac{p\hat{r}(1-r)}{8F_wM_a} + \frac{(1-p)(1-r)}{2(1-\hat{r})}\right)\varepsilon_5 + \left(\frac{p\hat{r}(1-r)}{4F_wM_b} + \frac{(1-p)(1-r)}{2(1-\hat{r})}\right)\varepsilon_6 + \frac{(1-p)(1-r)}{(1-\hat{r})}\varepsilon_7 + \left(\frac{p\hat{r}(1-r)}{4F_wM_b} + \frac{(1-r)(1-p)}{2(1-\hat{r})}\right)\varepsilon_8$$

with

$$F_w = 1 - \hat{r}, \quad M_a = \frac{3r + \hat{r}}{4}, \quad M_b = \frac{r + \hat{r}}{2}. \quad \text{(A1)}$$

The ESS solution r^* is found by determining the value of $\hat{r}$ that allows no increase in the A gene, producing a different sex-determining strategy. The solution for r^* is found by obtaining the characteristic equation for the A transmission matrix, differentiating with respect to $\hat{r}$, setting the differential to 0, and then setting the dominant eigenvalue (λ) = 1, $r = \hat{r}$, and solving for $\hat{r}$ (see Werren 1987). These manipulations were carried out using the algebraic software package Maple, and results were checked by numerical simulation. For the zygotic sex determiner, we obtain the following expression:

$$\frac{(4 - 3p)(4 - p)(1 - p + p\hat{r} - 2\hat{r})}{32\hat{r}(1 - \hat{r})} = 0 \Rightarrow r^*_{pz} = \frac{1 - p}{2 - p}. \quad \text{(A2)}$$

Analysis of the second differential of the dominant eigenvalue with $\hat{r} = r^*$ confirms that (A2) represents a unique ESS in the range of $0 < r^* < 1$ for all p in the range $0 < p < 1$.