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Inbreeding, Maternal Care and Genomic Imprinting

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Inactivation of expression of the paternal allele at two maternally silent imprinted loci has recently been reported to diminish the quality of care that female mice lavish on their offspring. This suggests that there can be disagreement between the maternally and paternally derived genomes of mothers over how much care for offspring is appropriate, with the paternally derived genome favoring greater care. The reason for such disagreement is not obvious because the maternally and paternally derived alleles at a locus have equal probabilities of being transmitted to each of the mother's ova and, therefore, would appear to have equal interests in a mother's offspring. However, if a female mates with a related male, her two alleles may have different probabilities of being present in the sperm that fertilize her ova. Natural selection can favor silencing of the maternally derived allele at a locus that enhances the quality of maternal care if the average patrilineal relatedness between a female and her mates decreases more rapidly than the average matrilineal relatedness. Just such an asymmetrical decrease in relatedness over time would be expected in a structured population in which patrilineal inbreeding is more common than matrilineal inbreeding.

1. Introduction

The kinship (or conflict) theory of genomic imprinting (Trivers & Burt, 1999; Haig, 2000) attributes imprinted expression of a locus to a conflict of interests between alleles of maternal and paternal origin. Such conflicts arise when a gene's expression in one individual has fitness consequences for other individuals to whom the first has different coefficients of matrilineal and patrilineal relatedness. In this case, the level of expression that maximizes the individual's matrilineal inclusive fitness may differ from the level that maximizes its patrilineal inclusive fitness, and the unimprinted state, where alleles of maternal and paternal origin have equal expression, ceases to be evolutionarily stable. Each increase in expression from alleles of one parental origin can be matched by a decrease in expression from alleles of the other parental origin, but only until the time that the latter are silent. The evolutionary stable outcome is therefore one in which the allele that prefers the higher level of expression (summed over both alleles at the locus) produces this favored amount, and the allele that prefers the lesser amount is silent.

The theory has recently been challenged by the report of two paternally expressed loci, *Peg1* (Kaneko-Ishino *et al.*, 1995; Lefebvre *et al.*, 1998) and *Peg3* (Li *et al.*, 1999), that influence

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the quality of care that a mouse mother directs towards her offspring. Loss-of-function of the paternal allele at either locus results in intrauterine growth retardation and defects of maternal behaviors—such as placentophagy, pup retrieval, and nest building—when females become mothers. The latter defects appear to be specific to maternal behavior, because other tasks, such as food localization, were unaffected. The identification of *Peg1* as a "maternal-care locus" has recently been questioned because the maternal uniparental disomy for this locus does not exhibit defective maternal care (Beechey, 2000), a result that has yet to be reconciled with the paternal loss-of-function data.

The effects on prenatal growth of *Peg1* and *Peg3* knockouts are clearly compatible with the kinship theory, which predicts that imprinted genes whose products are involved in acquiring extra resources from mothers will be expressed only when paternally derived (Haig & Graham 1991). The source of the prenatal intragenomic conflict is obvious: a female's offspring sometimes have different fathers but always share the same mother. Therefore, offspring are more likely to share their maternally derived alleles than their paternally derived alleles. As a result, costs to the mother's residual reproductive value are of greater consequence for each offspring's matrilineal inclusive fitness than for its patrilineal inclusive fitness.

A similar genetic asymmetry is not so readily apparent for loci that affect the quality of maternal care displayed by adult females. Each allele in a mother is equally likely to be transmitted via an ovum to each of her offspring. Yet imprinting at *Peg1* and *Peg3* suggests that a mother's paternally derived alleles have been selected to favor higher investment in her current litter than the amount favored by her maternally derived alleles. Thus, the effects on maternal care of *Peg1* and *Peg3* knockouts have sparked some controversy regarding the generality of the kinship theory (Hurst, 1998; Hurst & McVean, 1998; Haig, 1999a; Hurst, *et al.*, 2000; Smits *et al.*, 2000; Li *et al.*, 2000).

Part of the confusion regarding the relationship between maternal care and the kinship theory arises from the use of ambiguous terminology. It is common in the literature on genomic imprinting to find statements that confuse the interests of genes in parents with the interests of genes in offspring. In particular, the denotation of *maternal* is frequently ambiguous, possibly referring to the interests of a gene in a mother (with no specification of the gene's parental origin) or the interests of a maternally derived gene in the mother's offspring. In the past we have used the terms *madumnal* and *padumnal* to refer to the maternally derived and paternally derived alleles present in an individual (Haig, 1996; Wilkins & Haig, 2001). These terms are used in contrast with *maternal* and *paternal*, which refer to alleles present in the individual's mother and father. In the case of an imprinted maternal-care locus, we are concerned with a potential conflict between a mother's madumnal and padumnal alleles, not with a conflict between her offspring's madumnal and padumnal alleles. In this paper we present a simple model designed to suggest conditions under which natural selection could favor imprinting at a locus affecting maternal care.

2. The Model

An inbred offspring may inherit an allele from its father that is identical by descent to one of the alleles in its mother. Thus, inbreeding may result in a mother's madumnal and padumnal alleles having different probabilities of being present in the mother's offspring (Haig, 1999b). Consider a locus at which increased expression results in more resources being devoted to a mother's current litter at a cost to offspring in future litters (i.e. at a cost to the mother's residual reproductive value). Let r_1 represent an allele's probability of being present in each of a female's current offspring and r_2 its average probability of being present in the female's future offspring. From the allele's perspective, the optimal allocation of maternal resources between current and future reproduction is governed by the ratio of the current relatedness to the mean future relatedness:

$$V = \frac{r_1}{r_2}. \tag{1}$$

The larger the value of V, the higher the level of expression (summed over both alleles at a locus) that optimizes this trade-off.

If females sometimes mate with male relatives, V can differ for a female's madumnal and padumnal alleles. Natural selection would favor a higher summed level of expression when an allele is paternally derived than when the allele is maternally derived if $V_p > V_m$, or the reverse if $V_m > V_p$. The imprinted effects of *Peg1* and *Peg3* on maternal behavior could therefore potentially be explained if $V_p > V_m$ in mice.

Let r_{m1} and r_{p1} be the average relatedness of current offspring for a female's madumnal and padumnal alleles, respectively, and r_{m2} and r_{p2} be the corresponding values for future average relatedness. In an infinite, outbred population, $r_{m1} = r_{p1} = r_{m2} = r_{p2} = 1/2$. In this special case, $V_m = V_p = 1$, and the summed level of expression that maximizes matrilineal inclusive fitness will also maximize patrilineal inclusive fitness. However, this symmetry can be broken in a finite population if the probability of producing inbred offspring changes over the course of a female's reproductive life, and if the rate of change in this probability differs for madumnal and padumnal alleles.

The degree of inbreeding for each of a female's successive litters is likely to decrease, rather than increase, over time. In a geographically structured population, females are surrounded at birth by males to whom they have an average degree of relatedness greater than for a male chosen at random from the global population. Dispersal away from the local population by females, or into the local population by unrelated males, will decrease expected rates of inbreeding for older females. Mortality of male relatives could also contribute to such a decrease. For example, rates of father–daughter incest will be greatest for daughters' early litters, and will diminish for subsequent litters as fathers die (or as fathers or daughters disperse).

The tendency for the degree of inbreeding to decrease as a female ages is likely to be true for both matrilineal and patrilineal inbreeding (complicated by factors such as the birth of new relatives who become potential mates). However, matrilineal and patrilineal relatedness to an individual's own offspring may change at different rates because r_{m1} and r_{m2} are affected by mating with matrilineal kin, whereas r_{p1} and r_{p2} are affected by mating with patrilineal kin. A female's patrilineal kin include her father, offspring, paternal uncles, full brothers, and paternal half-brothers. Her matrilineal kin include her offspring, maternal uncles, full brothers, and maternal half-brothers. There is no male counterpart of her father in a female's matriline, so the possibility of father-daughter incest increases the female's r_p values in a manner that does not occur for r_m.

In summary, r_{m1}, r_{p1}, r_{m2}, r_{p2} will all be greater than 1/2 due to inbreeding; r_{p1} will be greater than r_{m1} if patrilineal inbreeding predominates over matrilineal inbreeding; and $r_{m1} > r_{m2}$,$r_{p1} > r_{p2}$ because of the effects of dispersal and mortality. These relations however are insufficient to favor the evolution of imprinting because this requires that the *relative* relatedness to current and future offspring differ for madumnal and padumnal alleles (i.e. $V_p \neq V_m$). We believe that this will often be the case. Consider a population for which the variance of male reproductive success is greater than the variance of female reproductive success. In such populations, a female will tend to have more paternal half-brothers than maternal half-brothers. Therefore, random matings between half-sibs will, on average, increase patrilineal relatedness more than matrilineal relatedness. This effect will be exacerbated if females avoid mating with members of their own litter (as occurs in mice, Penn & Potts, 1998), because littermates are either full sibs or maternal half-sibs, but never paternal half-sibs. Suppose that the age-related decline in r_m and r_p can be modeled as an exponential decay toward $(1 + F)/2$, where F is a female's own degree of inbreeding (Fig. 1). If the decay constant is the same for matrilineal and patrilineal relatedness and $r_{p1} > r_{m1}$, then

$$V_p > V_m > 1. \tag{2}$$

Inequality (2) implies that both of a mother's alleles are more closely related to her early offspring than to her later offspring, but this difference is more pronounced for her padumnal

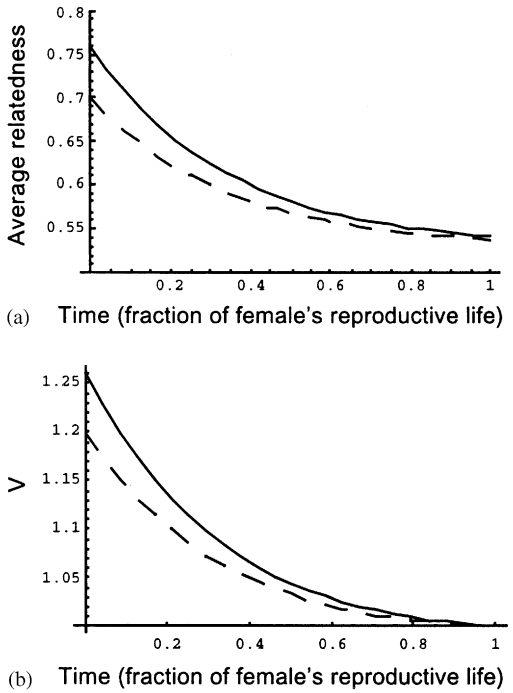

FIG. 1. (a). The relatedness between a female's alleles and those of her offspring is illustrated here. A higher variance of male reproductive success means that the likelihood of a copy of her paternally derived allele being present in her offspring, r_p (solid line), is greater than that for her maternally derived allele, r_m (dashed line). Both values decrease as the female's mating pool comes to include fewer related males as a result of dispersal, asymptotically approaching $(1+F)/2$, where F is the female's own inbreeding coefficient. (b) This figure shows the ratio of present to future relatedness (V) for the curves in part (a). The female's paternally derived allele (solid line) favors higher investment in present offspring at a cost to future offspring ($V_p > 1$). Her maternally derived allele (dashed line) favors a more equitable distribution of resources among litters ($V_m < V_p$). Under conditions such as these, theory predicts that an imprinted maternal care locus will be expressed only from the paternally derived copy.

alleles than for her madumnal alleles. Therefore, padumnal alleles will favor a relatively greater allocation of resources to current offspring at the expense of future reproduction, and higher expression at loci enhancing maternal care. Conversely, her madumnal alleles will favor relatively more resources being directed toward future offspring, and a lower level of expression at loci promoting maternal investment in current offspring. Put in other words, her madumnal and padumnal alleles will have different 'time preferences' with respect to investment now vs. later.

3. Population Structure and Phylogenetic Inertia

In its most naïve interpretation, the kinship theory predicts genomic imprinting whenever the level of a gene's expression has asymmetric effects on the fitness of matrilineal and patrilineal kin, and predicts that a locus will be unimprinted only when these effects are symmetric. In fact, perfect symmetry of effects on matrilineal and patrilineal kin is an ideal that will rarely be achieved in nature for any locus, although approximate symmetry may be common (in which case the selective forces favoring imprinting will be weak). Thus, whether we expect to find imprinting at a particular locus will be determined not only by the relative size of these asymmetries and the corresponding strength of the selective forces favoring imprinted expression relative to those favoring biallelic expression, but also on the consistency of these selective forces over time and the strength of phylogenetic inertia.

This paper has identified one potential asymmetry of kinship — arising from inbreeding — that could favor imprinting of loci affecting the quality of maternal care. The contributing factors, geographic structure and a higher variance of male than female reproductive success, are likely to be present in most mammalian populations. However, other asymmetries could make similar predictions about imprinting of genes responsible for maternal care: for example, padumnal alleles of a mother might favor higher investment in offspring if increased maternal care were associated with costs for the mother's matrilineal kin (Haig, 1999a). These alternative models are not mutually exclusive, and deciding between the relative importance of different kinship asymmetries for particular taxa would require either careful measurements of costs and benefits in the present (and an assumption that similar forces operated in the past) or comparisons between taxa in which the different factors vary in relative strength.

4. Pleiotropy and Imprinting

Even though the asymmetries of relatedness that could favor imprinting at maternal-care loci are likely to be present in many mammals, the

asymmetries and the associated selective forces may be weak. In this context, it is worth noting that both *Peg1* and *Peg3* also have effects on prenatal growth that are associated with strong selection for imprinting. It may be that imprinting at the *Peg1* and *Peg3* loci evolved originally in response to their effects on prenatal growth, with pleiotropic effects on maternal care evolving only after the loci were already imprinted. Haig (2000) has pointed out that once a locus is madumnally silent, any new functions acquired by the locus will be selected to maximize patrilineal inclusive fitness without regard for matrilineal inclusive fitness. Thus, madumnally silent loci will tend to accumulate pleiotropic effects that benefit patrilineal interests. It would therefore be interesting to learn not only the phylogenetic distribution of imprinting of *Peg1* and *Peg3*, but also whether unimprinted homologues in other taxa also combine effects on prenatal growth and maternal care, and which one of these functions is ancestral.

5. Learning and Maternal Care

The quality of maternal care may change over the course of a female's reproductive life. Commonly, older mothers achieve higher survival of offspring than do younger mothers, but this observation can have multiple competing explanations. The trend is consistent with a simple learning mechanism (more experienced mothers are more effective at caring for offspring), but could also be explained by an adaptive shift in reproductive strategy (older mothers have lower expectation of future reproductive success and therefore favor greater investment in current offspring: Clutton-Brock, 1991; Cameron *et al*., 2000).

Maternal care by *Peg3*-deficient females improves for subsequent litters, such that the difference in the quality of care exhibited by mutant and wild-type mice decreases with parity (Li, *et al*., 1999). These observations are consistent with learning compensating for innate deficits, but would also be consistent with the influence of imprinted genes declining with age. The model presented in this paper predicts that the asymmetry in matrilineal and patrilineal relatedness to offspring will diminish over time, and this decrease might be expected to correlate with a shift in the control of maternal behavior from imprinted to unimprinted loci. Whereas the benefits of learning are likely to be associated with increasing parity, rather than with age *per se*, the reduction in the probability of inbreeding is likely to be more strictly age-related. This might allow for a partial test of these alternative explanations.

6. Conclusion

We have presented a model of the selective forces that could favor the evolution of genomic imprinting at a locus that affects the quality of maternal care. The model assumes a finite, geographically structured population with some dispersal and a higher variance of male than female reproductive success and predicts madumnal silencing at a locus at which increased expression enhances the quality of maternal care. We believe that these conditions are common in mammalian populations and have probably been present at many points during mammalian evolution (see below). This model thus provides the source of a consistent selective asymmetry of the type that will favor the evolution of genomic imprinting.

The model identifies a selective asymmetry that favors greater investment in current offspring by padumnal alleles, but the selective forces associated with this asymmetry might be sufficiently weak in real populations to make the evolution of imprinting unlikely. What one would need to know is the relative frequency of matrilineal and patrilineal inbreeding in a population, and how this changes with a female's age. Among other requirements, one would need to identify all of the grandparents, maternal and paternal, of a large sample of offspring from a natural population. Such information does not appear to be available for wild mice (and may not be available for any nonhuman species).

While the ideal information to test the model proposed here is not currently available, what data there is confirms that geographic structuring is often present in mammalian populations and suggests potential avenues for future research. A recent meta-analysis of studies of

genetic structuring in social mammals (Storz, 1999) found varying degrees of genetic differentiation among taxa, with F_{ST} values ranging from 0.006 to 0.227. The four populations from the order Rodentia that were considered had F_{ST} values ranging from 0.045 to 0.227. Depending on the strength of phylogenetic inertia at loci like *Peg1* and *Peg3*, this variation could provide a means for testing the model, possibly by looking for the presence or absence of imprinting at more or less structured populations, respectively. Alternatively, maternal care differences might manifest in reciprocal crosses between more or less structured species, in a manner analogous to the birthweight differences observed between species with greater and lesser degrees of multiple paternity (Vrana *et al.*, 1998).

The discovery of genomic imprinting at loci affecting maternal care is an exciting development that poses a challenge to theory and demands further observation. We hope that the model proposed here will serve to motivate and orient the empirical work—both the detailed observation of breeding patterns in nature and the further characterization of maternal-care loci in multiple taxa—required for us to fully understand this phenomenon.

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