Parental antagonism, relatedness asymmetries, and genomic imprinting

DAVID HAIG

Department of Organismic and Evolutionary Biology, Harvard University, 26 Oxford Street, Cambridge, MA 02138, USA
(dhaig@oeb.harvard.edu)

SUMMARY

The theory of inclusive fitness can be modified to consider separate coefficients of relatedness for an individual's maternal and paternal alleles. A gene is said to have *parentally antagonistic* effects if it has an inclusive fitness benefit when maternally derived, but an inclusive fitness cost when paternally derived (or vice versa). Parental antagonism favours the evolution of alleles that are expressed only when maternally derived or only when paternally derived (genomic imprinting).

1. INTRODUCTION

My mother's kin are not my father's kin. I am equally related to full-siblings through my mother and father but, in the absence of inbreeding (and excluding my relationship to myself and my direct descendants), all other relations are asymmetric, through either the maternal or paternal line. These asymmetries can be a source of conflict within my genome because any action that affects the chances of survival or reproduction of individuals to whom I am asymmetrically related has different fitness consequences for the genes I inherit from my mother and the genes I inherit from my father.

The classical theory of inclusive fitness implicitly assumed that a gene's expression was unaffected by its parental origin, but this assumption is now known to be violated in cases of *genomic imprinting* (Efstratiadis 1994). In the classical theory, classes of relatives with different maternal and paternal coefficients of relatedness were assigned an average coefficient (Hamilton 1964). This paper shows that the theory can easily be modified to consider maternal and paternal relatedness separately. The revised theory then specifies conditions under which natural selection acts differently on a gene's expression depending on whether the gene is maternally derived or paternally derived. Genomic imprinting is favoured when a gene's expression in one individual has fitness consequences for other individuals to whom the first is asymmetrically related on the maternal and paternal side. Maternalpaternal conflicts have previously been identified in the context of behaviours that affect half-siblings (Haig & Westoby 1989; Moore & Haig 1991), but the theory presented in this paper generalizes to all interactions among relatives.

2. EVOLUTIONARILY STABLE STRATEGIES

The coefficient of relatedness of individual i to individual 0 (r_i) can be defined as the expected number of copies (in individual i) of a specified gene in individual 0, where the statistical expectations are calculated for identity by recent common descent. In conventional calculations of inclusive fitness, the specified gene is randomly chosen from the two alleles at a locus in individual 0. If a_i is the reproductive value of individual i, then an estimate of the total reproductive value accruing to the gene and its identical-by-descent copies is given by the weighted sum

$$W = \sum_{i=0} r_i a_i. \tag{1}$$

Suppose that a_i is a function of X (the amount of gene product produced by individual 0), and that individual 0 is heterozygous for the established allele in the population (expression level x^*) and a rare allele (expression level x), then the *inclusive fitness effect* (δW) of the rare allele is simply the sum of its effects on the reproductive values of each individual i (δa_i) weighted by r_i (see Taylor (1990) for discussion of the appropriate reproductive values to be used in models of inclusive fitness).

$$\begin{aligned} \delta W &= \sum_{i=0} r_i \delta a_i \\ \delta a_i &= f_i(X) - f_i(2x^*) \\ X &= x^* + x,\ x^* \geqslant 0,\ x \geqslant 0. \end{aligned} \tag{2}$$

The rare allele will be favoured by selection if $\delta W > 0$, but will be disfavoured if $\delta W < 0$. An allele's level of expression can be considered to be its strategy in an evolutionary game (Maynard Smith 1982). If the functions $f_i(X)$ are differentiable, and W has a local maximum ($\partial W/\partial x = 0, \partial^2 W/\partial x^2 < 0$) when $x = x^*$, then a population in which x^* is the established level of expression will be evolutionarily stable to invasion by alleles that cause small increases or decreases of expression. If so, x^* is the best (local) response to

itself, and constitutes an evolutionarily stable strategy (ESS). Thus, x^* is an ESS if

$$\frac{\partial W}{\partial x} = \sum_{i=0} r_i \frac{\partial a_i}{\partial X} = 0, \text{ when } X = 2x^*. \quad (3)$$

Because the functions $f_i(X)$ are defined only for non-negative values of x and x^*, a 'null' ESS (no expression; $x^* = 0$) exists if $\partial W/\partial x < 0$ when X is close to zero.

The models presented in this and subsequent sections use calculus to define an ESS and show its stability to invasion by mutations causing small changes in gene expression. Such models do not address evolutionary dynamics. The initial approach to an ESS need not proceed by small incremental changes, but fine-tuning of gene expression in the neighbourhood of an ESS seems plausible.

3. PARENT-SPECIFIC RELATEDNESS

In any particular generation, the direction of natural selection will be determined by the effects of a gene's expression on the fitness of matrilineal relatives if the gene is maternally derived, but by its effects on patrilineal relatives if the gene is paternally derived. (For ease of discussion, I will use 'matriline' and 'patriline' to distinguish relatives who have a chance of carrying individual 0's maternally derived allele from relatives who have a chance of carrying individual 0's paternally derived allele. By this definition, individual 0 and individual 0's direct descendants are members of both the matriline and the patriline.)

A rare autosomal allele in individual 0 is either maternally derived or paternally derived, but the two possibilities will occur with equal frequency over the course of several generations. Half of the time, the gene's expression will be subject to selection for its effects on matrilineal kin, and half of the time, for its effects on patrilineal kin. Different subscripts will be used to identify these different sets of relatives. Thus, if the allele is maternally derived, its expected numbers of copies in individual i will be represented by m_i, whereas if the allele is paternally derived, its expected number of copies in individual j will be represented by p_j. The reproductive values of matrilineal and patrilineal kin will be represented by a_i and b_j, respectively. Equations (1)–(3) can then be rewritten as

$$W = \frac{1}{2}\left(\sum_{i=0} m_i a_i + \sum_{j=0} p_j b_j\right) \quad (4)$$

$$\partial W = \frac{1}{2}(\delta W_m + \delta W_p) = \frac{1}{2}\left(\sum_{i=0} m_i \delta a_i + \sum_{j=0} p_j \delta b_j\right) \quad (5)$$

$$\frac{\partial W}{\partial x} = \frac{1}{2}\left(\sum_{i=0} m_i \frac{\partial a_i}{\partial X} + \sum_{j=0} p_j \frac{\partial b_j}{\partial X}\right) = 0. \quad (6)$$

The average inclusive fitness effect of a rare allele (δW) is therefore the average of its effects when maternally derived (δW_m) and paternally derived (δW_p). A non-null ESS may be either 'symmetric' or 'parentally antagonistic'. At a symmetric ESS, both terms of summation from equation (6) are zero. That is,

$$\sum_{i=0} m_i \frac{\partial a_i}{\partial X} = \sum_{j=0} p_j \frac{\partial b_j}{\partial X} = 0, \text{ when } X = 2x^*. \quad (7)$$

A sufficient condition for a symmetric ESS is that expression of the gene does not affect the fitness of individuals with different matrilineal and patrilineal coefficients of relatedness to individual 0. The simplest case occurs when the gene's expression has fitness consequences for individual 0 alone. At a parentally antagonistic ESS, the terms have opposite sign but equal magnitude, i.e.

$$\sum_{i=0} m_i \frac{\partial a_i}{\partial X} = -\sum_{j=0} p_j \frac{\partial b_j}{\partial X} \neq 0, \text{ when } X = 2x^*. \quad (8)$$

At such an ESS, a marginal cost when the gene is maternally derived (the first term is negative) is balanced by a marginal benefit when the gene is paternally derived (the second term is positive), or vice versa. This requires that the gene's expression has fitness consequences for individuals that are asymmetrically related to individual 0 via the patriline and via the matriline.

4. SEPARATING STRATEGIES

So far the candidates for an ESS have all been *pooling strategies* in which a gene has a single level of expression, independent of its parental origin. What happens if this constraint is relaxed so that alleles can adopt *separating strategies*, with one level of expression when maternally derived and a different level when paternally derived? A separating strategy can be represented by a vector whose elements are an allele's level of maternal and paternal expression. Suppose that the established allele has a strategy $\{x_m^*, x_p^*\}$ and that individual 0 is heterozygous for this allele and a rare allele with strategy $\{x_m, x_p\}$. Then, the following identities can be substituted in equations (4) and (5):

$$\begin{aligned} X' &= x_m + x_p^* \\ X'' &= x_m^* + x_p \\ a_i &= f_i(X') \\ b_j &= f_j(X'') \\ \delta a_i &= f_i(X') - f_i(x_m^* + x_p^*) \\ \delta b_j &= f_j(X'') - f_j(x_m^* + x_p^*) \\ x_m, x_p, x_m^*, x_p^* &\geqslant 0. \end{aligned} \quad (9)$$

δW_p is zero for a rare allele $\{x_m, x_p^*\}$ with the same level of paternal expression as the established allele. Therefore, the sign of δW_m determines whether such an allele will be favoured or disfavoured by selection. Conversely, δW_m is zero for a rare allele $\{x_m^*, x_p\}$ with the same level of maternal expression as the established allele, and the direction of selection is determined by the sign of δW_p.

A symmetric ESS is simultaneously a local maximum for matrilineal and patrilineal inclusive

fitness. If separating strategies are possible, condition (7) becomes

$$\left.\begin{aligned}\frac{\partial W}{\partial x_m} &= \sum_{i=0} m_i \frac{\partial a_i}{\partial X'} = 0 \\ \frac{\partial W}{\partial x_p} &= \sum_{j=0} p_j \frac{\partial b_j}{\partial X''} = 0\end{aligned}\right\}, \text{ when } X' = X'' = 2x^*. \qquad (10)$$

Therefore, if $\{x^*, x^*\}$ is a symmetric ESS in the absence of separating strategies, it remains an ESS in their presence. However, if $\{x^*, x^*\}$ is a symmetric ESS, any strategy $\{x^*_m, x^*_p\}$ for which $x^*_m + x^*_p = 2x^*$ will also satisfy equations (10). Strategies of this kind with $x^*_m \neq x^*_p$ can also be classified as symmetric ESSs, but are probably only of mathematical interest.

A parentally antagonistic pooling strategy corresponds to neither a local maximum of matrilineal inclusive fitness nor of patrilineal inclusive fitness. Therefore, if $\{x^*, x^*\}$ is a parentally antagonistic ESS in the absence of separating strategies, it cannot be an ESS in their presence. Furthermore, given the assumptions of the model, no strategy in which x_m and x_p are both positive can be evolutionarily stable for all possible separating strategies, unless the strategy is a symmetric ESS. At a parentally antagonistic ESS, either the maternal allele $\{0, x^*_p\}$ or the paternal allele will be silent $\{x^*_m, 0\}$ (Haig 1996; Mochizuki *et al*. 1996).

Suppose that a pooling strategy benefits patrilines at the expense of matrilines. If so, the strategy can be displaced by a separating strategy with reduced expression when maternally derived or with increased expression when paternally derived, or with both. Because patrilineal inclusive fitness is maximized by a higher level of expression than matrilineal inclusive fitness, each increase in paternal expression can be matched by a decrease in maternal expression, until maternal expression is zero (at which point no further reduction is possible). However, once maternal alleles are silent, paternal alleles can 'choose' the level of gene expression that maximizes benefits to patrilines. Haig (1996) has called this the 'loudest voice prevails' principle.

At a maternally silent ESS $\{0, x^*_p\}$,

$$\left.\begin{aligned}\frac{\partial W}{\partial x_m} &= \sum_{i=0} m_i \frac{\partial a_i}{\partial X'} < 0 \\ \frac{\partial W}{\partial x_p} &= \sum_{j=0} p_j \frac{\partial b_j}{\partial X''} = 0\end{aligned}\right\}, \text{ when } X' = X'' = x^*_p \qquad (11)$$

whereas, at a paternally silent ESS $\{x^*_m, 0\}$,

$$\left.\begin{aligned}\frac{\partial W}{\partial x_m} &= \sum_{i=0} m_i \frac{\partial a_i}{\partial X'} = 0 \\ \frac{\partial W}{\partial x_p} &= \sum_{j=0} p_j \frac{\partial b_j}{\partial X''} < 0\end{aligned}\right\}, \text{ when } X' = X'' = x^*_m \qquad (12)$$

Conditions (11) and (12) specify the effects of small changes in the level of gene product near an ESS. At a maternally silent ESS $\{0, x^*_p\}$, small increments of gene product will decrease *both* matrilineal and patrilineal inclusive fitness. By contrast, small decrements of gene product will increase matrilineal inclusive fitness, but decrease patrilineal inclusive fitness. Large decrements, however, may reduce matrilineal inclusive fitness because the fitness of matrilines will often be maximized by a non-zero level of gene product. These properties are important for understanding the effects of loss-of-imprinting mutations that reactivate a silent maternal allele, or of loss-of-function mutations that silence the active paternal allele.

A loss-of-imprinting mutation will result in a level of expression $2x^*_p$ (or $2x^*_m$), whereas a loss-of-function mutation will result in zero expression. *Both* kinds of mutation are likely to decrease *both* matrilineal and patrilineal inclusive fitness. Therefore, the observation that 'knocking-out' maternally active *Mash2* results in a failure of placental development (Guillemot *et al*. 1995) or that paternal duplications of proximal 7 result in growth-retarded mice (Cattanach *et al*. 1992) does not directly contradict the genetic conflict hypothesis, as is sometimes claimed. However, such observations do provide clues about the effects of small changes in gene expression. For example, the placentas of *Mash2* null mice have a virtual absence of spongiotrophoblast cells, but a thicker layer of trophoblast giant cells (Guillemot *et al*. 1995). The genetic conflict hypothesis suggests that a partial re-allocation of cells from spongiotrophoblast cells to the giant-cell lineage would benefit patrilines.

The model presented in this section assumes that the levels of gene-product, X' and X'', are sums of fixed, allele-specific contributions. A parentally antagonistic ESS with bi-allelic expression is possible if this assumption is violated. For example, the model would not apply if transcription was subject to negative feedback and alleles shut down at different thresholds of gene product. In this case, the allele with the higher threshold would determine the level of expression in heterozygotes, alleles with higher thresholds would behave as dominants to alleles with lower thresholds, and $\{t^*_m, t^*_p\}$ would be an ESS if t^*_m and t^*_p were the thresholds that maximized matrilineal and patrilineal inclusive fitness. If $t^*_m > t^*_p$, then the usual level of expression at the ESS would be t^*_m. Selection to maintain t^*_p would be weak, because the paternal threshold would have strategic significance only when an individual was heterozygous for the established allele $\{t^*_m, t^*_p\}$ and a rare maternally derived allele $\{t_m, t_p\}$, with $t_m < t^*_p$.

5. IGF2 AND *IGF2R*

Some properties of maternally silent and paternally silent strategies—and of their interaction—can be illustrated using two functionally related loci from mice: *Igf2* (insulin-like growth factor 2) is expressed when paternally derived, but is silent when maternally derived, whereas *Igf2r* (insulin-like growth factor 2 receptor) has the opposite pattern of expression. Paternally expressed *Igf2* promotes embryonic growth, whereas maternally expressed *Igf2r* inhibits growth by degrading the product of *Igf2* (DeChiara *et al*. 1991; Lau *et al*. 1996; Ludwig *et al*. 1996). Haig & Graham (1991) proposed that this complementary pattern of imprinting has evolved because costs imposed by an

embryo on its mother during gestation have fitness consequences for half-siblings to which the embryo is related maternally but not paternally ($m = 0.5$; $p = 0$). This argument explains the imprinting of *Igf2* and *Igf2r* in terms of indirect sibling rivalry mediated via the mother. The same hypothesis can be rephrased in terms of motheroffspring conflict. The maternal and paternal relatedness of an offspring to its mother shows extreme asymmetry ($m = 1$; $p = 0$) because the offspring's maternal allele is definitely present in the mother whereas the paternal allele is definitely absent. This internal conflict is mitigated when mother and father share the parentage of multiple offspring, because the residual reproductive value of the father is then correlated with that of the mother.

A useful distinction can be made between *competition* among strategies and *conflict* between roles (for a similar distinction see Cosmides & Tooby (1981)). The separating strategies of *Igf2* and *Igf2r* each have two roles: that of a maternal allele and that of a paternal allele. Phenotypic conflict between these roles is expressed as the degradation of paternal IGF2 by maternal IGF2R (the lack of italics signifying gene products rather than genes). However, at the strategic level, paternal expression of *Igf2* and maternal expression of *Igf2r* are mutually reinforcing (just as the 'hawks' of the former Soviet Union and the United States justified each other's military budgets in competition with their own nation's 'doves'). Another analogy reinforces this distinction between strategy and role. The poor usually favour policies that shift taxes onto the rich, and vice versa. However, when an individual's wealth changes, his attitude to taxation often changes to match. Thus, there can be a *conflict* between the roles of rich and poor, even though all individuals employ the same separating strategy 'tax the rich when poor, tax the poor when rich' that *outcompetes* pooling strategies that do not change with an individual's circumstances ('always tax the rich' or 'always tax the poor').

A property of evolutionarily stable separating strategies is that the fitness return from playing a particular role depends on another allele playing the opposite role. A paternal allele of *Igf2* relies on zero production by the maternal allele. Loss-of-imprinting of the maternal allele would double the production of IGF2, and result in reduced patrilineal (as well as matrilineal) inclusive fitness. Similarly, an *Igf2* allele in the paternal role relies on an *Igf2r* allele in the maternal role to degrade some of its excess product. Some biologists would interpret this mutual dependence of roles as evidence for straightforward cooperation, but the underlying conflict is revealed by the possibility of more efficient (but evolutionarily unstable) cooperative outcomes. For example, if maternal and paternal alleles shared equally in the production of IGF2, loss-of-function mutations would not result in functional hemizygosity. Alternatively, the same functional level of IGF2 could be achieved with reduced expression of both *Igf2* and *Igf2r*.

The model of the previous section has several limitations, of which I will discuss two. First, the strategy set was restricted to variation in expression level but new alleles can vary in many ways besides their level of expression. The model may still have value because some of these allelic differences could be modelled as if they caused differences in expression. For example, an allele that reduced the affinity of IGF2 for IGF2R might have similar phenotypic consequences to an allele that increased production of IGF2. Second, ESS conditions were derived for alleles at a single locus, and the model's conclusions might not apply when alleles at two or more loci interact. Should we expect *Igf2* and *Igf2r* to come to a joint ESS, a *modus vivendi* at which alleles at neither locus can benefit from a unilateral change to the *status quo*? Or should we expect a continuing arms race in which selection at each locus prevents alleles at the other from reaching an evolutionary equilibrium? The *a priori* expectation is unclear (at least to me). McVean & Hurst (1997) could find no evidence for ongoing antagonistic coevolution in the sequences of *Igf2* and *Igf2r*, and interpreted their result as evidence against the genetic conflict hypothesis, but the absence of an arms race could also be interpreted as evidence of a joint ESS (i.e. for a 'resolution' of the conflict in the sense of Godfray (1995)).

6. WHY ARE THERE SO FEW IMPRINTED GENES?

Separating strategies will be favoured when the expression of an unimprinted allele has parentally antagonistic effects, because imprinting allows a reduction of costs to patrilines while retaining the benefits to matrilines, or vice versa. However, only a small minority of genes appear to be imprinted. Why should this be?

Few genes may have the kind of parentally antagonistic effects that favour the evolution of imprinting. A pelagic fish, conceived by external fertilization, may never interact with relatives, and the same may be true of many other organisms that lack post-zygotic parental care and complex social behaviour. Even within social species, the principal effect of most genes may be to increase or decrease the fitness of the individual in which the gene is expressed, with minimal consequences for relatives. Furthermore, loss-of-function mutations are recessive at many, if not most, loci. At such loci, inactivation of one allele has little discernible effect on the phenotype, and selection in favour of imprinted alleles would be weak or non-existent, even if other conditions for the evolution of imprinting were satisfied. Therefore, imprinted alleles may be restricted to the subset of loci with parentally antagonistic effects that are highly sensitive to the level of gene product. If the advantages of a separating strategy are weak, they may be outweighed by subsidiary costs of imprinting, such as occur when a paternal allele has a loss-of-function mutation and the imprinted maternal allele is silent (Mochizuki *et al*. 1996).

Despite these caveats, the selective conditions that favour the evolution of imprinting probably exist in many social organisms. Genomic imprinting may be more widespread than is currently recognized because it is difficult to detect in taxa (or for behaviours) that lack a well-developed molecular genetics. The two most obvious sources of relatedness asymmetries are

multiple paternity of a female's offspring and sex-biased dispersal. For example, in a species in which males disperse but females remain in their natal group, group members will often be more closely related to each other maternally than paternally (the precise prediction depends on the rate at which males, who enter the group from outside, are replaced by new males and on the number of offspring a male sires during his tenure). Major effects of imprinting on embryonic development may be largely restricted to viviparous species because actions that take place in an egg before hatching will usually have little direct effect on the mother and other relatives (there may, however, be consequences for post-hatching behaviour that does affect relatives).

The paucity of imprinted genes could also be explained if alleles with parent-specific expression rarely, if ever, arise at most loci. Non-existent alleles cannot be subject to selection. Three strands of evidence suggest that imprinting may be difficult to evolve. First, some unimprinted genes have phenotypic effects similar to the effects of imprinted genes: for example, *Igf1* (like *Igf2*) enhances embryonic growth in the mouse, but (unlike *Igf2*) is not imprinted (Liu *et al*. 1993). Second, imprinted loci appear to be clustered, with the bulk of the genome devoid of significant imprinting effects (Saitoh *et al*. 1996; Lee *et al*. 1997). Such a pattern would be predicted if the evolution of imprinting is rare, but once one locus in a region has evolved imprinted expression, neighbouring loci can exploit the epigenetic difference between maternal and paternal chromosomes to become imprinted themselves. Mochizuki *et al*. (1996) make the related suggestion that clustering could be explained if imprinting is physiologically costly, but costs can be shared among neighbouring loci. Third, mechanisms may exist that eliminate the epigenetic differences between chromosomes on which imprinting depends. The genome-wide demethylation—followed by remethylation—that occurs during early mouse development erases most methylation differences between maternal and paternal chromosomes (Kafri *et al*. 1993). The conditions under which natural selection would favour genome-wide suppressors of imprinting—for that purpose, rather than as a side-effect of some other function—is a theoretical question deserving further study.

7. SEXUAL AND PARENTAL ANTAGONISM

Genes with *parentally antagonistic* effects are associated with an inclusive fitness benefit when derived from one parent but an inclusive fitness cost when derived from the other. This terminology was chosen to emphasize the analogy to genes with *sexually antagonistic* effects that are beneficial in one sex but costly in the other (Rice 1987). Autosomal genes spend half of their ancestry in male bodies and half in female bodies. Therefore, an allele with sexually antagonistic effects will be selectively favoured if the cost to one sex is less than the benefit to the other. By the same token, autosomal genes are maternally derived half of the time, paternally derived half of the time, and an allele with parentally antagonistic effects will be selectively favoured if the benefit to matrilines is greater than the cost to patrilines (or the benefit to patrilines is greater than the cost to matrilines). Just as sexual antagonism favours strategies in which a gene is expressed in one sex but not the other (sex limitation), so does parental antagonism favour strategies in which a gene is expressed when derived from one sex but not the other (imprinting). From this perspective, parental antagonism is sexual antagonism shifted by one generation. Sexually antagonistic and parentally antagonistic effects are orthogonal in the sense that an *autosomal* allele has the same probability of being present in a male or female body, irrespective of its parental origin. Complex strategies can be imagined in which a gene's expression depends on the sex of both its present and previous bearer.

Alan Grafen, Jon Seger, Robert Trivers, and an anonymous reviewer have made useful contributions to the final version of this paper.

REFERENCES

Cattanach, B. M., Barr, J. A., Evans, E. P., Burtenshaw, M., Beechey, C. V., Leff, S. E., Brannan, C. I., Copeland, N. G., Jenkins, N. A. & Jones, J. 1992 A candidate mouse model for Prader-Willi syndrome which shows an absence of Snrpn expression. *Nat. Genet.* **2**, 270–274.

Cosmides, L. M. & Tooby, J. 1981 Cytoplasmic inheritance and intragenomic conflict. *J. Theor. Biol.* **89**, 83–129.

DeChiara, T. M., Robertson, E. J. & Efstratiadis, A. 1991 Parental imprinting of the mouse insulin-like growth factor II gene. *Cell* **64**, 849–859.

Godfray, H. C. J. 1995 Evolutionary theory of parent–offspring conflict. *Nature* **376**, 133–138.

Guillemot, F., Caspary, T., Tilghman, S. M., Copeland, N. G., Gilbert, D. J., Jenkins, N. A., Anderson, D. J., Joyner, A. L., Rossant, J. & Nagy, A. 1995 Genomic imprinting of *Mash2* required for trophoblast development. *Nat. Genet.* **9**, 235–241.

Efstratiadis, A. 1994 Parental imprinting of autosomal mammalian genes. *Curr. Opin. Genet. Devl.* **4**, 265–280.

Haig, D. 1996 Placental hormones, genomic imprinting, and maternal–fetal communication. *J. Evol. Biol.* **9**, 357–380.

Haig, D. & Graham, C. 1991 Genomic imprinting and the strange case of the insulin-like growth factor-II receptor. *Cell* **64**, 1045–1046.

Haig, D. & Westoby, M. 1989 Parent-specific gene expression and the triploid endosperm. *Am. Nat.* **134**, 147–155.

Hamilton, W. D. 1964 The genetical evolution of social behaviour. *J. Theor. Biol.* **7**, 1–52.

Kafri, T., Gao, X. & Razin, A. 1993 Mechanistic aspects of genome-wide demethylation in the pre-implantation mouse embryo. *Proc. Natn. Acad. Sci. USA* **90**, 10 558–10 562.

Lau, M. M. H., Stewart, C. E. H., Liu, Z., Bhatt, H., Rotwein, P. & Stewart, C. L. 1994 Loss of the imprinted IGF2/cation-independent mannose 6-phosphate receptor results in fetal overgrowth and perinatal lethality. *Genes Devl.* **8**, 2953–2963.

Lee, M. P., Hu, R.-J., Johnson, L. A. & Feinberg, A. P. 1997 Human *KVLQT1* gene shows tissue-specific imprinting and encompasses Beckwith-Wiedemann syndrome chromosomal rearrangements. *Nat. Genet.* **15**, 181–185.

Liu, J.-P., Baker, J., Perkins, A. S., Robertson, E. J. & Efstratiadis, A. 1993 Mice carrying null mutations of the genes encoding insulin-like growth factor I (*Igf-I*) and type 1 IGF receptor (*Igf1r*). *Cell* **75**, 59–72.

Ludwig, T., Eggenschwiler, J., Fisher, P., D'Ercole, A. J., Davenport, M. L. & Efstratiadis, A. 1996 Mouse mutants lacking the type 2 IGF receptor (IGF2R) are rescued from perinatal lethality in *Igf2* and *Igf1r* null backgrounds. *Devl Biol.* **177**, 517–535.

Maynard Smith, J. 1982 *Evolution and the theory of games.* Cambridge University Press.

McVean, G. T. & Hurst, L. D. 1997 Molecular evolution of imprinted genes: no evidence for antagonistic coevolution. *Proc. R. Soc. Lond.* B **264**, 739–746.

Mochizuki, A., Takeda, Y. & Iwasa, Y. 1996 The evolution of genomic imprinting. *Genetics* **144**, 1283–1295.

Moore, T. & Haig, D. 1991 Genomic imprinting in mammalian development: a parental tug-of-war. *Trends Genet.* **7**, 45–49.

Rice, W. R. 1987 The accumulation of sexually antagonistic genes as a selective agent promoting the evolution of reduced recombination between primitive sex chromosomes. *Evolution* **41**, 911–914.

Saitoh, S., Buiting, K., Rogan, P. K., Buxton, J. L., Driscoll, D. J., Arnemann, J., König, R., Malcolm, S., Hortshemke, B. & Nicholls, R. D. 1996 Minimal definition of the imprinting center and fixation of a chromosome 15q11-q13 epigenotype by imprinting mutations. *Proc. Natn. Acad. Sci. USA* **93**, 7811–7815.

Taylor, P. D. 1990 Allele frequency change in a class-structured population. *Am. Nat.* **135**, 95–106.

Received 17 July 1997; accepted 30 July 1997