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REVIEW

Coadaptation and conflict, misconception and muddle, in the evolution of genomic imprinting

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Common misconceptions of the 'parental conflict' theory of genomic imprinting are addressed. Contrary to widespread belief, the theory defines conditions for cooperation as well as conflict in mother–offspring relations. Moreover, conflict between genes of maternal and paternal origin is not the same as conflict between mothers and fathers. In theory, imprinting can evolve either because genes of maternal and paternal origin have divergent interests or because offspring benefit from a phenotypic match, or mismatch, to one or other parent. The latter class of models usually require maintenance of polymorphism at imprinted loci for the maintenance of imprinted expression. The conflict hypothesis does not require maintenance of polymorphism and is therefore a more plausible explanation of evolutionarily conserved imprinting.
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INTRODUCTION

The theory of parent-offspring conflict defines conditions under which natural selection favors different outcomes for genes expressed in parents and offspring. As a corollary, the theory defines complementary conditions under which parents and offspring have shared interests (Trivers, 1974; Haig, 2010). The kinship (or parental conflict) theory of genomic imprinting similarly defines conditions under which genes of maternal origin (matrigenes) and genes of paternal origin (patrigenes) have conflicting interests and, in the process, defines complementary conditions under which matrigenes and patrigenes have shared interests (Haig, 2000, 2004; Queller, 2003; Wilkins and Haig, 2003a). Cooperation and conflict are two sides of one coin.

Nobody denies some degree of coordination between maternal supply and offspring demand nor that mothers have a genetic interest in the survival of their offspring and offspring an interest in the well-being of their mother during the period of maternal care. But many still question a role of evolutionary conflict between mothers and offspring. In recent years, mother–offspring coadaptation has gained popularity as an explanation of the evolution of genomic imprinting that does not invoke evolutionary conflict and is considered by some to fit the empirical data better than the parental conflict hypothesis (Bourc'his and Proudhon, 2008). This coadaptation hypothesis is sometimes presented as an amalgam of the verbal arguments of Keverne and colleagues (Curley *et al.*, 2004; Swaney *et al.*, 2007; Keverne and Curley, 2008; Keverne, 2009) and an explicit model of Wolf and Hager (2006). What the former have to do with the latter is obscure, apart from use of the common term 'coadaptation,' and this paper will consider them separately.

The paper has five major sections. The first briefly presents the kinship theory and dispels the pervasive misunderstanding that conflict between genes of maternal and paternal origin is simply an extension of conflict between the parents. My clarification is presented in the context of a discussion of transgenerational *cis* versus *trans* effects. The second addresses the coadaptation hypothesis of Keverne and colleagues, both as a positive proposal to explain the evolution of genomic imprinting and as a negative critique of the kinship theory. The hypothesis is muddled and the criticisms misdirected. The third discusses hypotheses in which imprinting facilitates phenotypic resemblance between parent and offspring. Wolf and Hager's (2006) model is discussed in this section. The fourth views mother–offspring relations as a problem of how genes in parents divide resources among themselves. An analogy is developed between the fair allocation of resources among offspring and the fair segregation of alleles to successful gametes. The fifth discusses models of transgenerational epistasis between genes expressed in mothers and genes expressed in offspring. Although these models do not directly consider genomic imprinting, they are relevant to a more complete understanding of the complex evolution of mother–offspring relations.

THE KINSHIP THEORY

Parent-offspring conflict and genomic imprinting

Trivers (1972) defined parental investment as 'any investment by the parent in an individual offspring that increases the offspring's chances of surviving (and hence reproductive success) at the cost of the parent's ability to invest in other offspring.' In other words, parental investment provided a benefit (B) to the offspring at a cost (C) to other offspring. His definition implied an evolutionary conflict between parents and offspring (Trivers, 1974). From a parent's perspective, investment is favored as long as $B>C$ but, from an offspring's perspective, investment is favored as long as $B>rC$, where r measures the relatedness of the offspring receiving the benefit to other offspring bearing the cost. Thus, parents and offspring have conflicting interests when $C>B>rC$ but congruent interests

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when $B<C$ (both agree the cost is too great) or $B>rC$ (both agree the benefit justifies the cost).

The kinship theory of genomic imprinting was initially developed in the context of mother–offspring relations (Haig and Westoby, 1989) but generalizes to all interactions among kin (Haig, 1997a). As Haig and Graham (1991) noted, natural selection can favor imprinted expression 'whenever an individual's interactions are asymmetric with respect to maternal- and paternal-side relatives.' Different probabilities that individuals share genes of maternal or paternal origin break the symmetry of selective forces acting on matrigenes and patrigenes and thus favor the evolution of genomic imprinting.

With respect to genes that influence nutrient transfers from mothers, the value of r differs for matrigenes and patrigenes of offspring. Specifically, $r_m>r_p$ because mothers sometimes have offspring by multiple fathers. Therefore, incremental investment is favored by patrigenes but opposed by matrigenes whenever $r_mC>B>r_pC$. Matrigenes and patrigenes 'agree' about maternal investment outside this zone of conflict (Haig, 1992, 2010).

The theory has also been proposed to explain imprinted expression of genes that regulate communal warmth (Haig, 2008), communal care of offspring (Úbeda and Gardner, 2011), and hygienic behavior (Haig and Úbeda, 2011). An important property of the theory is that imprinted expression is evolutionarily stable in the absence of genetic polymorphism (Úbeda and Haig, 2003; Van Cleve *et al.*, 2010; Brandvain *et al.*, 2011).

Phenotypic conflict between matrigenes and patrigenes is the outward manifestation of *allelic competition*. This distinction, between conflict and competition (Cosmides and Tooby, 1981), can be illustrated with an analogy. A chess game involves *conflict* between black and white pieces, but a chess tournament involves *competition* between contestants who play both black and white and who adopt different strategies in the two roles. Similarly, *conflict* between matrigenes and patrigenes is the outward manifestation of *competition* among alleles that are sometimes matrigenes and sometimes patrigenes. Imprinted expression can be viewed as a conditional strategy of an allele that adopts matrigenic and patrigenic roles in different rounds of an evolutionary tournament (Haig, 1997a; Úbeda and Haig, 2003). Natural selection favors imprinted expression when conditional (imprinted) strategies outperform unconditional (unimprinted) strategies.

Transgenerational *cis* versus *trans* effects

A pervasive misunderstanding of the kinship hypothesis conflates conflict between matrigenes and patrigenes of offspring with conflict between mothers and fathers. This subsection explains why the two kinds of conflict are conceptually and quantitatively distinct.

Haig and Westoby (1989) proposed that parent-specific gene expression (PSGE) has evolved because genes of maternal and paternal origin have conflicting interests with respect to how much mothers should invest in offspring. Our paper attracted little immediate attention and subsequent publications abandoned use of PSGE in favor of imprinting, but it is worth explaining my initial misgivings about use of 'imprinting'. Our aim was to explain why some genes are expressed differently when inherited from a mother or father. We viewed differential expression as an adaptation of the differentially-expressed gene rather than of the genes that encoded the machinery causally responsible for differential expression. In other words, PSGE was presented as an adaptation of the 'imprinted' gene not of the genes doing the 'imprinting'. For this reason, I have been careful to describe the conflict that underlies PSGE as existing between maternally-derived and paternally-derived genes of offspring rather than between mothers' and fathers' genes. This may seem semantic quibbling but reflects an evolutionarily significant distinction (Haig, 1992; Burt and Trivers, 1998; Úbeda and Haig, 2003).

Consider an epigenetic modification of a sequence that occurs in a parental germline but affects expression of the sequence in offspring. The modification can be considered to be determined by *cis* effects, intrinsic to the sequence, and *trans* effects, determined by the products of other genes. Natural selection acts differently on allelic variation in parents responsible for *cis* and *trans* effects experienced by offspring. Suppose a parent is heterozygous for alleles at an imprinted locus that differ in their imprinting status because of *cis* effects. Such effects will segregate among the parent's offspring depending on which allele each offspring inherits. Therefore, alleles associated with transgenerational *cis* effects evolve to favor offspring with their copies over offspring without. The *cis* effect could either establish an epigenetic mark (Figure 1a) or protect from an epigenetic mark (Figure 1b).

Suppose instead that the parent is heterozygous for alleles at an imprinting locus that affects in *trans* the expression in offspring of an imprinted locus. If a *trans*-acting allele causes the same modification of both alleles at the imprinted locus in the parent, then all of the parent's offspring will inherit the same imprint (Figure 1c). If a *trans*-acting allele causes allele-specific modifications at the imprinted locus, then the *trans* effects will segregate among offspring independently of alleles at the *trans*-acting locus provided that modifying and modified loci are unlinked (Figure 1d). Therefore, loci responsible for transgenerational *trans* effects evolve to maximize the aggregate fitness of all the parent's offspring.

Haig and Westoby (1989) assumed that the evolutionary interests of *cis* factors would tend to prevail over the interests of *trans* factors in the control of PSGE. Our reasoning was that *trans* factors would affect the expression of many genes, not just those with PSGE, but *cis* factors would be specific to a single gene. Over evolutionary time, the

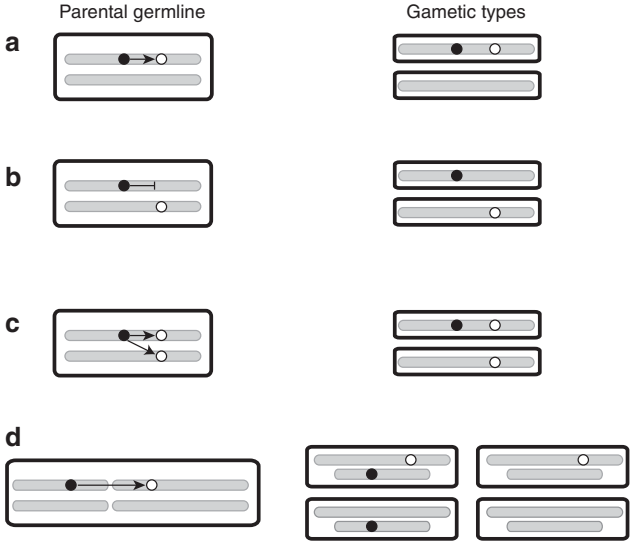

Figure 1 An allele (black dot, *B*) at an 'imprinting' locus expressed in a parental germline epigenetically modifies sequences at an 'imprinted' locus. The imprint (white dot) subsequently determines expression in offspring. (**a**) *B* acts in *cis* to establish an imprint. *B* and the imprint are co-inherited. (**b**) *B* acts in *cis* to block an imprint. *B* and the absence of imprint are co-inherited. (**c**) *B* acts in *trans* to establish an imprint. All gametes receive the same imprint. (**d**) *B* acts in *trans* to establish an allele-specific imprint at an unlinked locus. *B* and the imprint segregate independently to offspring.

sequence of each imprinted gene would evolve to be recognized (or ignored) by the imprinting machinery. Specificity would reside in *cis* rather than *trans*. Consistent with this expectation, the local DNA sequence is the primary determinant of where methylation occurs in the mammalian genome (Lienert *et al.*, 2011).

The distinction between *cis* and *trans* effects on PSGE has been expressed in various ways. Haig (1992, 1999) distinguished the interests of genes in mothers (maternal interests) from the interests of maternally-derived genes in offspring (madumnal interests), with a similar distinction between the interests of genes in fathers (paternal interests) and paternally-derived genes in offspring (padumnal interests). Queller (2003) proposed matrigenic and patrigenic as euphonious synonyms of madumnal and padumnal. Spencer and Williams (1997) contrasted gametic (*cis*) and genotypic (*trans*) modifiers. Burt and Trivers (1998) described conflict between imprinting genes and imprinted genes (also see Wilkins, 2005; Wolf and Wade, 2009). Van Cleve and Feldman (2007) distinguish *cis*-acting and *trans*-acting modifiers. The key theoretical distinction is whether an allele's effects discriminate among sibs on the basis of whether an offspring inherits the allele, not whether the allele is expressed in the parent or offspring generation.

Epigenetic modifications in *cis* and *trans* are subject to divergent selection when a modification occurs in parents but has its effect in offspring. Epigenetic modifications with effects in the same generation are not subject to divergent selection. A modification with effects on parental survival affects the fitness of all parental genes equally whether modifications occur in *cis* or *trans*. Similarly, a modification that occurs in offspring with effects on offspring survival affects the fitness of all offspring genes equally whether modifications occur in *cis* or *trans*.

COADAPTATION VERSUS CONFLICT

What is the hypothesis?

The coadaptation 'hypothesis' was first presented in a discussion of the effects of mutations that inactivate the padumnal copy of *Peg3* in mice (Curley *et al.*, 2004). *Peg3* influences food intake and milk letdown when expressed in mothers, and placental uptake of nutrients and suckling when expressed in offspring. Curley *et al.* (2004) wrote: 'The significance of these coadaptive traits being synchronized in mother and offspring by the same paternally expressed imprinted gene ensures that offspring that have extracted 'good' maternal nurturing will themselves be both well provisioned and genetically predisposed towards 'good' mothering.' No reasons were given why the sentence could not be written with *maternally-expressed imprinted* or *unimprinted* substituted for *paternally-expressed imprinted*.

In a subsequent paper, Keverne and Curley (2008) proposed that monoallelic expression has evolved because it increases the rate at which favorable mutations are fixed by natural selection. Adaptation is faster, it was claimed, when a gene is paternally expressed because a successful male can sire more offspring than any individual female. This hypothesis does not explain the direction of imprinting, because monoallelic maternal expression in males would provide the same benefit, nor does it explain why some genes, but not others, should be imprinted, because the purported advantage of monoallelic expression applies equally well (or poorly) to any adaptive process, not just maternal-offspring coadaptation.

The hypothesis of Keverne and colleagues boils down to a statement that mother and offspring have shared interests (nobody disputes this) but then fails to explain why this favors the evolution of parent-specific expression. However, they also present reasons to reject the parental-conflict hypothesis based on perceived inconsistencies between its predictions and the empirical evidence. Their critique has two prongs. First, most imprinting marks are established in maternal germlines and are therefore under maternal control. Second, imprinted genes affect the provision of resources by mothers as well as the demand for resources by offspring. The maternal bias in 'control' of imprinting will be addressed in the next subsection and imprinting of genes for maternal care in the subsequent subsection.

Maternal biases in imprinting

Reik and Walter (2001) observed that twelve out of fourteen imprinted genes possessed imprinting control regions (ICRs) that were methylated in the maternal rather than the paternal germline. These included loci that were both padumnally and madumnally silent. This bias is compatible with the kinship theory once one adopts the *cis* perspective of imprinted genes rather than the *trans* perspective of imprinting genes. From the *cis* perspective, an allele's optimal strategy is to act differently in madumnal and padumnal roles but it does not matter whether this strategy is achieved by methylation in maternal or paternal germlines. Natural selection can act at cross purposes on *cis*- and *trans*-acting factors. Therefore, imprinted alleles will evolve to achieve differential expression by whatever mechanisms, in whichever germline, are resistant to modification by selection on *trans*-acting factors.

DNA of the sperm pronucleus is subject to programmed demethylation by maternal factors deposited in the oocyte. Reik and Walter (2001) proposed that demethylation evolved as a maternal adaptation to remove paternal imprints. Therefore, they argued, differential methylation has been evolutionarily difficult to maintain in paternal germlines and most imprinted genes achieve imprinted expression via methylation in the maternal germline. In other words, maternal *trans*-acting factors have been selected to demethylate the sperm pronucleus. As a countermeasure, imprinted loci have evolved to establish differential methylation in the pronucleus that it is not subject to demethylation.

A complementary hypothesis was presented by Wilkins and Haig (2002). We showed that paternal *trans*-acting factors are selected to remove imprints established in paternal germlines when mating is sufficiently monogamous but maternal *trans*-acting factors are never selected to remove imprints established in maternal germlines. Therefore, maternal imprints are more evolutionarily stable than paternal imprints and the former will tend to replace the latter.

Mutational biases could also contribute to a tendency for control of imprinted expression to be transferred from paternal to maternal germlines. Methylated cytosines are subject to deamination, with substitution of a thymine for the original cytosine. Cytosines become methylated prenatally in prospermatogonia but postnatally in growing oocytes. Therefore, methylated cytosines have more opportunities to mutate to thymine in paternal germlines than maternal germlines. As a result, selection favors ICRs that are methylated in maternal germlines (Bourc'his and Bestor, 2006; Bourc'his and Proudhon, 2008).

Thus, multiple hypotheses have been proposed to explain why most ICRs are methylated in the maternal germline. These hypotheses are not mutually exclusive. Future work will show whether these, or other, hypotheses explain the preponderance of maternal imprints. The key point for the current review is that the observed bias in favor of maternally-methylated ICRs does not invalidate the kinship theory. Despite this theoretical understanding, the observed bias is commonly perceived as inconsistent with the kinship theory by those who equate

conflict between genes of maternal and paternal origin with conflict between mothers and fathers.

Keverne and Curley (2008) argued that the predominance of maternally-methylated ICRs was inconsistent with parental conflict: '… if genes which extract resources from mother achieve paternal expression by the active process of maternal allele silencing, the question arises as to how natural selection might have initially operated at the maternal locus to effect the foetal-placental phenotype which is disadvantageous to mothers.' *Igf2*, a gene that encodes a promoter of fetal growth and that is expressed only from its paternal allele, was used as an example. Under the presupposition of parental conflict, 'it is difficult to comprehend … why the maternal genome actively relinquishes expression of a maternal allele and actively facilitates the expression of a paternal allele in the case of *Igf2*.' These arguments are 'difficult to comprehend.' Why is silencing of the maternal allele of a fetal growth enhancer disadvantageous to mothers and why does this mean relinquishment of maternal control? How does the maternal genome facilitate expression of paternal alleles? Moreover, the example of *Igf2* was ill-chosen because this is one of the few imprinted genes with an ICR that is methylated in paternal rather than maternal germlines (Schulz *et al.*, 2010).

Imprinted genes affecting maternal care

Perhaps the strongest challenge to the parental-conflict hypothesis has been observations that inactivation of two imprinted genes in mice, *Peg1* and *Peg3*, cause defective maternal care (Lefebvre *et al.*, 1998; Curley *et al.*, 2004). The evidence for *Peg1* is equivocal because mice with uniparental maternal disomy for the region containing *Peg1* are competent mothers (Beechey, 2000).

Matrigenes and patrigenes of mothers are transmitted at equal frequency to offspring. Therefore, natural selection should act symmetrically on genes for maternal care whether these genes are derived from the mother's mother or mother's father (Hurst *et al.*, 2000). Two hypotheses have proposed ways this symmetry may be broken to favor madumnal silencing of genes promoting maternal care:—

The first invokes a conflict between a mother's matrigenes and patrigenes because of indirect costs of her behavior for maternal-side relatives. Maternal matrigenes and patrigenes are (usually) equally related to offspring but may be unequally related to other individuals. If care of offspring has costs for these other individuals, say because of increased competition for resources, then natural selection may favor imprinting of a gene for maternal care (Haig, 1999; Úbeda and Gardner, 2011).

The second invokes a benefit of mothers' current reproduction to paternal-side relatives at a cost to mothers' future reproduction. Matrigenes and patrigenes of mothers are equally related to outbred offspring but may be unequally related to inbred offspring. If young females sometimes mate with paternal-side relatives, then maternal patrigenes may favor increased expenditure in early inbred litters at the expense of later outbred litters (Wilkins and Haig, 2003b). Both of these hypotheses are based on testable assumptions about mating systems and social structures of wild mice.

Effects of imprinted genes on maternal care have been interpreted as favoring a coadaptational explanation of the evolution of genomic imprinting (Curley *et al.*, 2004). This is odd because coadaptation does not explain imprinting of genes *in mothers*. Matrigenes and patrigenes of mothers are equally likely to be matrigenes of offspring. Therefore, an advantage of resembling one's mother does not break the symmetry of forces acting on maternal genes for infant care. Moreover, imprinting of genes in mothers undermines the putative advantage of imprinting in offspring when an offspring inherits and expresses a mother's silent allele. The coadapted gene of Wolf and Hager's (2006) model, discussed in the next section, is *unimprinted in mothers* but *imprinted in offspring*.

PHENOTYPIC MATCHING

Engel (1997) noted that imprinting increases resemblance of offspring to one parent but decreases resemblance to the other. He suggested greater resemblance might, in some circumstances, enhance fitness. The direction of predictions is straightforward: if resemblance between mothers and offspring enhances fitness, then selection favors silencing of paternal alleles in offspring; if resemblance between fathers and offspring enhances fitness, then selection favors silencing of maternal alleles. These predictions are reversed if selection favors less resemblance between parent and offspring (Wolf and Hager, 2009).

Benefits of 'resemblance' that have been proposed to explain the evolution of parent-specific expression include: paternally-inherited antigens of the placenta are silenced to avoid mismatch between maternal and fetal antigens (Elinson, 1989); maternally-derived genes are silenced to increase a child's resemblance to its father and thereby increase the amount of paternal care the child receives (Christenfeld and Hill, 1995); imprinting matches the size of a baby's head to the size of its mother's pelvis (Pembrey, 1996); inactivation of patrigenes in daughters and matrigenes in sons increases resemblance to same-sex parents and enhances sex-specific fitness (Day and Bonduriansky, 2004); local adaptation is enhanced by matching offspring phenotype to the parent who disperses less (Spencer *et al.*, 2004; Spencer and Clark, 2006).

Wolf and Hager's (2006) model of 'maternal-offspring coadaptation' is often cited as the theoretical underpinning of the coadaptation hypothesis for the evolution of genomic imprinting. The single-locus model of their paper assigned 'phenotypic values' to maternal (m_i) and offspring genotypes (o_j)

	A_1A_1	A_1A_2	A_2A_1	A_2A_2
m_i	a_m	0	0	$-a_m$
o_j	a_o	Ia_o	$-Ia_o$	$-a_o$

where A_iA_j individuals inherit A_i from their mother and A_j from their father. The parameters a_o, a_m were assumed to be positive, with $I=0$ at an unimprinted locus and $I=1$ at a padumnally-silent locus. When $I>0$, the locus exhibits parent-of-origin effects in the offspring but not in the mother. The advantage of matching was represented by an assumption that the effect of different mother–offspring combinations on offspring fitness (Δw_{ij}) was proportional to the product of phenotypic values, $\Delta w_{ij}=m_i o_j s$ where s was a positive constant representing the strength of selection. It is immediately apparent that offspring genotype has no effect on fitness when mothers are heterozygous because multiplying by zero always gives zero. For simplicity, let $a_o a_m s=\Phi$. Then, the Δw_{ij} are:

Offspring	*Mother*			
	A_1A_1	A_1A_2	A_2A_1	A_2A_2
A_1A_1	Φ	0	0	—
A_1A_2	$I\Phi$	0	0	—
A_2A_1	—	0	0	$I\Phi$
A_2A_2	—	0	0	Φ

Imprinting increases mean fitness because the fitness of heterozygous offspring of homozygous mothers increases with the strength of paternal silencing (I) and the fitness of all other offspring are unaffected. The model assumes that offspring have higher fitness when they express the same allele as their mother then shows that, *under this assumption*, silencing of padumnal alleles increases offspring fitness.

Two further features of the model are worth mentioning. First, the model describes a gene that is unimprinted in mothers but maternally-expressed in offspring. Therefore, the model does not explain imprinting of *Peg3* which is paternally-expressed in both mothers and offspring. Second, heterozygous mothers are less fit than homozygous mothers. Therefore, selection should eliminate whichever allele is less common. Once polymorphism dissipates, presence or absence of imprinting has no effect on fitness and is not subject to selection. Wolf and Hager (2006) side-step this difficulty with an appeal to the ubiquity of genetic variation in natural populations.

A requirement for polymorphism is likely to be a general feature of matching models because all alleles match, regardless of parental origin, in a population with only one allele at a locus. Matching models are implausible candidates to explain the maintenance of imprinted expression over long evolutionary periods. Therefore, such models are unlikely to explain imprinting of *Igf2* because this has been maintained in multiple lineages since the divergence of marsupial and eutherian mammals (O'Neill *et al.*, 2000) or imprinting of *Peg3* because this has been maintained at least since the common ancestor of cattle, mice, and humans (Kim *et al.*, 2007).

Benefits of resembling one parent more than the other break the symmetry of selective forces acting on matrigenes and patrigenes of offspring because matrigenes, but not patrigenes, are necessarily present in an offspring's mother whereas patrigenes, but not matrigenes, are necessarily present in an offspring's father. For this reason, advantages of resembling or not resembling a parent can, in theory, favor the evolution of imprinted gene expression. These hypotheses have not considered trade-offs between parental and offspring fitness. If a gene's effects involve such a trade-off, then genetic conflict will be present, and should be considered, along with advantages of matching.

DIVIDING A MATERNAL PIE

Mothers invest time, energy, and materials in the production of offspring. Sibs differ genetically from each other, and from their mother, because one of the two alleles at each maternal locus is passed at random to each sib and because each sib receives a random choice of one-out-of-two alleles from its father. Thus, a sibship may contain multiple alleles that compete with each other for limited maternal time, energy, and materials. Allelic competition is expressed phenotypically as parent-offspring conflict if it is mediated via demands on mothers but as sibling rivalry if it is mediated via direct interactions among sibs.

The distinction between increasing the size of a pie and increasing the size of a slice provides a convenient metaphor. The pie, of this metaphor, is maternal investment measured in units of surviving offspring. Selection among sibships favors larger pies but selection within sibships favors larger slices. Genes expressed in offspring are subject to both levels of selection but genes expressed in mothers are subject only to the first. The metaphor is imperfect because the size of a pastry pie is determined before it is cut but total maternal investment is influenced by the number and relative size of the slices. One might say that genes expressed in mothers are selected to maximize the size of the pie via its optimal divisions into slices.

A fallacious reason for rejecting parent-offspring conflict dates back to Alexander (1974) who argued that conflict between generations is illusory because an individual who gains a benefit at a cost to a parent later experiences the same cost as a parent. The fallacy comes from viewing fitness as a property of individuals rather than genes (Blick, 1977). One of the alleles at a heterozygous locus in a mother can increase in frequency, at the expense of the other maternal allele, by causing offspring that inherit its copies to take more than their 'fair' share of the pie. By this process, some maternal genes gain higher fitness than others.

Models of parent–offspring conflict are formally analogous to models of meiotic drive (Haig, 1996). In the former, distortion occurs in the allocation of maternal investment whereas, in the latter, distortion occurs in formation of zygotes. Genes in parents make investment decisions behind a meiotic 'veil of ignorance' (Okasha, 2012) that hides information about which offspring inherit their copies, but genes in offspring have come out from behind the veil and can compete among themselves for larger slices of the maternal pie.

Post-meiotic interactions among sibs may influence the size of the pie to be divided. Actions that enlarge the pie can be considered contributions to a public good. Larger groups should contribute less to public goods than smaller groups because marginal costs are borne by each but marginal benefits are shared by all (Olson, 1961). The relevant group size is the number of alleles not the number of sibs. The maternal pie is divided by two maternal alleles but more than two paternal alleles when a mother's offspring have multiple fathers. Genomic imprinting allows an imprinted allele to contribute less, or demand more, as a member of the larger group of patrigenes (Haig and Wilkins, 2000).

Epistasis between a locus expressed in mothers and a locus expressed in offspring has the formal property that a gene in the mother discriminates among offspring based on the offspring's genotype at another locus. The evolutionary dynamics of this transgenerational epistasis depend critically on whether the interacting loci are linked or unlinked because this determines whether alleles at the maternal locus segregate to offspring independently of their discriminatory effects in offspring. 'Epistasis' is intended here in the population geneticists' sense that allelic variation at one locus interacts in its effects on fitness with allelic variation at another locus.

Transgenerational epistasis between closely-linked loci will be called *cis* epistasis and between unlinked loci will be called *trans* epistasis because of a close parallel to my earlier discussion of epigenetic modifications in *cis* and *trans*. The parallel is inexact because, in the previous discussion, the interacting loci were both expressed in germ cells before meiosis with the epigenetic modification subsequently inherited by offspring whereas, in the current discussion, a locus expressed in the mother interacts with a locus expressed postzygotically in the offspring. In the former case, one is concerned with an interaction of the diploid maternal genotype at one locus with the haploid madumnal genotype at a second locus. In the second case, one is concerned with the interaction of a maternal locus with a diploid offspring locus (i.e., one must consider the padumnal contribution at the second locus). *cis* epistasis grades into *trans* epistasis as the recombination fraction between the loci increases.

Consider the interaction between an imprinting control region (ICR) and a nearby promoter of an imprinted gene controlled by the ICR. The ICR (locus B) acquires an imprint in the mother that controls expression of the promoter (locus A) in offspring where control is exerted in *cis*. The two maternal haplotypes can be labelled AB and ab. If B and b acquire different imprints, then the maternal imprint at B affects the expression of A but not a in offspring and the

maternal imprint at *b* affects the expression of *a* but not *A*. This can be considered epistasis, in *cis*, between the *B* locus in mothers and the *A* locus in offspring.

Now consider a protein-coding *B* locus expressed in mothers that interacts with a tightly-linked *A* locus expressed in offspring. Expression of *B* in *AB*/*ab* mothers differentially affects the fitness of offspring that inherit *AB* rather than *ab* from their mother. *A* is favored if it preferentially directs resources to its own copies in offspring. Thus, transgenerational *cis* epistasis entails a 'green-beard effect' (Haig, 1996). The 'meiotic veil of ignorance' is transparent for genes with transgenerational *cis* effects.

In simple terms, successful *AB* haplotypes could confer benefits on offspring with *AB* haplotypes (altruistic green-beards, Figure 1a) or costs on offspring with *ab* haplotypes (spiteful green-beards, Figure 1b) (West and Gardner, 2010). This phenomenon, gestational drive, is discussed at greater length in the next section. For present purposes, I elide complexities that arise because offspring are diploid and possess a paternal, as well as a maternal, haplotype.

If *A* and *B* are unlinked protein-coding genes, alleles at the two loci assort independently to offspring, linkage disequilibrium is absent, and epistasis between the generations is analogous to an epigenetic modification in *trans*. Maternal genes with transgenerational *trans* effects evolve behind the 'meiotic veil of ignorance' to maximize maternal fitness (Figure 1d).

The possibility of conflict within maternal genomes between loci with transgenerational *cis* and *trans* effects is possibly mitigated by two interrelated considerations. First, each locus in a mother segregates independently of most other loci. Therefore, most epistatic interactions involve *trans* effects that are selected to enhance maternal fitness, including effects that suppress the gestational drive of genes that interact in *cis*. Second, *cis* epistasis between linked genes that is powerful enough to generate significant linkage disequilibrium may be relatively rare. Such interactions should be most likely in gene-rich regions with low recombination.

Matrigenes and patrigenes of offspring are more evenly matched than are transgenerational *cis* and *trans* actors of maternal genomes. Each *cis*-acting region must act on its own against the combined weight of the rest of the maternal genome. By contrast, each matrigene or patrigene has many allies. All matrigenes have concordant interests, independent of their location in the genome, as do all patrigenes. The observation of physical associations within the nucleus between imprinted regions on different chromosomes (Göndör *et al.*, 2011) may facilitate complex coordinated actions by madumnal and padumnal sub-organisms.

The following section reviews models of the joint evolution of genes expressed in mothers and offspring. These models do not consider imprinting but provide a deeper evolutionary understanding of maternal–offspring relations. Transgenerational epistasis favors some allelic combinations over others and thus generates linkage disequilibrium between linked loci. The favored combinations can be considered 'coadapted' if this adjective sheds the implication that coadaptation necessarily enhances maternal or offspring fitness.

TRANSGENERATIONAL EPISTASIS

Gestational drive

Consider a mother who is heterozygous (*Aa*) at a locus expressed in offspring that mediates a fitness trade-off among sibs. For simplicity, assume that the fathers of her offspring are *aa* (as would be the case in an outbred population when *A* is rare) and that *aa* offspring of two *aa* parents have unit fitness. Half of the mother's offspring will be *Aa* and half will be *aa*. If the effect of *A* is to benefit *Aa* sibs (fitness: $1+\beta$) at the expense of *aa* sibs (fitness: $1-\gamma$), then *A* will increase in frequency when rare for all $\beta>0$ (regardless of cost to sibs γ), because sibs who suffer the cost do not carry the allele imposing the cost. Therefore, *A* can increase in frequency even if it reduces maternal fitness ($\gamma>\beta$). This phenomenon has been called 'gestational' or 'zygotic' drive (Haig, 1996; Rice *et al.*, 2008).

Now consider a mother who is heterozygous (*Bb*) at a second locus that interacts with an offspring locus (*Aa*) where *B*, expressed in mothers, causes *Aa* offspring to gain benefit β at cost γ to *aa* sibs. The difference from the previous scenario is that now it is *B* in mothers rather than *A* in offspring that causes the redistribution of fitness between *Aa* and *aa* sibs. *B* can be considered a modifier of gestational drive at the *A* locus.

For simplicity, assume that the mother is doubly heterozygous (*AB*/*ab*), the fathers of her offspring are *ab*/*ab*, and that *ab*/*ab* offspring of two *ab*/*ab* parents have unit fitness. The fitness of *B* is $(1-\rho)(1+\beta)+\rho(1-\gamma)$ where ρ is the recombination fraction between *A* and *B*. If *B* and *A* are unlinked ($\rho=0.5$), *B* will be favored by natural selection if $\beta>\gamma$, because expression of *B* does not favor *Bb* over *bb* sibs. By contrast, expression of *B* benefits *Bb* sibs at the expense of *bb* sibs if *B* and *A* are tightly coupled ($\rho=0$). In this case, *B* will be favored for all $\beta>0$, regardless of the cost to sibs γ. Thus, maternal modifiers with the same effects can be subject to divergent selection depending on their chromosomal location relative to the offspring locus being modified. *B* evolves according to maternal interests when unlinked to *A* but according to madumnal interests when tightly linked to *A*.

This informal analysis disregards effects of offspring who inherit *A* from their fathers. Incorporation of such effects, in the population-genetic models reviewed in the next section, adds complexity without negating the need to consider distortions of maternal investment within broods in models of mother–offspring 'coadaptation'.

Population genetic models

Population-genetic models of epistasis between a locus expressed in mothers and a locus expressed in offspring give a range of outcomes depending on details of the model (Feldman and Eshel, 1982; Hedrick and Thomson, 1988, Eshel and Feldman, 1991; Haig, 1997b; Bergstrom and Bergstrom, 1999; Wolf, 2000). As expected for epistatic selection, linkage disequilibrium is generated between maternal and offspring loci and outcomes depend on the tightness of linkage between the loci. As expected for models of distortion within broods, natural selection need not maximize the number of surviving offspring.

Alliances between maternal alleles that punish 'selfish' offspring and tightly-linked 'altruistic' alleles that escape punishment can, in some scenarios, increase mean fitness near fixation (Feldman and Eshel, 1982; Bergstrom and Bergstrom, 1999). It should be noted that the 'altruistic' haplotypes in these models increase in frequency when rare despite decreasing maternal fitness because of the distortion within broods. In other scenarios, nepotistic alliances go to fixation without increasing mean fitness (Haig, 1996). The genetic complexities of maternal–offspring relations defy simple generalizations. The key feature in all these models is the unequal distribution of maternal invetsment in the broods of heterozygous mothers.

Feldman and Eshel (1982) will be considered in detail to emphasize the similarity of their conclusions to the heuristic analysis of the previous section. Their model considers an offspring locus (alleles *A* and *a*) and maternal locus (alleles *B* and *b*). An 'altruist' allele (*a*) at the offspring locus causes its bearers to pay a personal cost to provide a benefit to all members of mixed sibships whereas bearers of the

'selfish' allele (*A*) do not provide the benefit nor pay the cost. An 'interfering' allele at the maternal locus (*B*) takes resources from one class of sibs, defined at the *A* locus, and redistributes them to all sibs. The other maternal allele (*b*) does not interfere.

(1) At the 'selfish corner' (fixation of *A* and *b*), neither an altruistic allele *a* nor an interfering allele *B* can invade by itself but a tightly-linked *aB* haplotype can invade. Although the *aB* haplotype is labeled 'altruistic' it behaves selfishly when rare by causing a net transfer of resources from *AA* to *Aa* sibs.

(2) At the 'altruistic corner' (fixation of *a* and *b*), the selfish allele *A* can always invade, unaffected by simultaneous introduction of *B*. The result is unsurprising. If *A* and *B* occur on different haplotypes, then they do not interact when rare. On the other hand, *B* eliminates itself when *A* and *B* are coupled by taking resources from *Bb* sibs in favor of *bb* sibs.

(3) At a 'structural equilibrium' (*A* and *a* both present, *b* near fixation), *B* can invade (if tightly linked to *a*) even though it causes a fitness loss to the brood. The 'altruistic' *aB* haplotype increases in frequency by behaving selfishly when rare.

Readers who consult Feldman and Eshel (1982) should note that, in their paper, *A* is fixed at both selfish and altruistic corners but *A*'s phenotypic effects are switched between the corners. Although this procedure is mathematically elegant, for clarity of verbal exposition, my exegesis has *a* fixed at the altruistic corner so that *A* and *a* maintain the same phenotypic effects.

Quantitative genetic models

Wolf and Brodie (1998) and Kölliker *et al.* (2005) present quantitative-genetic models of maternal–offspring coadaptation. Their models assume that parent–offspring conflict is 'resolved' and that stabilizing selection acts on maternal and offspring traits. Genetic correlations between these traits are taken as evidence of coadaptation. All forms of epistasis generate linkage disequilibrium. Therefore, genetic correlations between maternal supply and offspring demand are not decisive evidence of 'coadaptation' unless the term simply refers to the generation of linkage disequilibrium by epistatic selection. If this is all that is meant, then coadaptation encompasses both phenotypic cooperation and conflict between the generations.

Maternal investment in one offspring involves an opportunity cost of time or resources that are unavailable for other maternal activities. This opportunity cost is expected to translate into reduced maternal investment in other offspring. Models that simply ignore this trade-off, or sweep it under the carpet by saying that conflict is resolved, seem to me to commit Alexander's (1974) fallacy. The results of such models should be treated with caution until their conclusions are shown to be robust to incorporation of the trade-off or reasons are given why the trade-off is absent.

SUMMARY

Maternal care involves trade-offs between the residual reproductive value of mothers and the fitness of offspring. Trivers (1974) defined when benefits to offspring are evolutionarily balanced by costs to mothers and showed that the fulcrum is placed differently for genes in mothers and in offspring. Haig (1992) showed that the fulcrum is placed differently for genes of maternal and paternal origin in offspring. Cooperative outcomes are predicted when benefits more than compensate for costs for both parties. Thus, maternal-offspring relations are predicted to be neither purely cooperative nor purely conflictual, as confirmed by everday observations.

Kinship theory explains the evolution of genomic imprinting by an appeal to asymmetric relatedness of matrigenes and patrigenes to social partners, because relatedness determines the placement of the evolutionary fulcrum that balances costs to partners against benefits to self (Brandvain, 2010; Úbeda and Gardner, 2010, 2011, 2012). Imprinted expression is resistant to invasion by unimprinted alleles once imprinted alleles have gone to fixation (Úbeda and Haig, 2003; Van Cleve *et al.*, 2010; Brandvain *et al.*, 2011).

Matching models explain the evolution of genomic imprinting by an appeal to advantages of greater or lesser resemblance between parents and offspring. An offspring's matrigenes are necessarily present in its mother and its patrigenes are necessarily present in its father. Therefore, silencing of patrigenes could be favored if offspring benefit from phenotypically matching their mother or suffer a disadvantage from matching their father. Silencing of matrigenes could be favored if these relations are reversed. Maintenance of imprinting in matching models requires maintenance of polymorphism; otherwise the benefits of imprinted expression are lost.

Both kinship and matching models can, in principle, explain the evolution of imprinted gene expression. Whether a particular model explains actual examples of imprinting must be decided by showing concordance between the model's assumptions and particular genes' effects on fitness. At present, several imprinted genes have phenotypic effects consistent with the parental-conflict hypothesis but none have been shown to exhibit the kind of interaction between maternal and offspring genotypes that would support the matching model of Wolf and Hager (2006).

Transgenerational epistasis generates linkage disequilibrium among loci and genetic correlations among traits. Genetic correlations between maternal and offspring traits are often implicitly assumed, and sometimes explicitly stated, to enhance the individual fitness of mothers and offspring who are said to be 'coadapted' but this is not a necessary consequence of correlated traits. If a coadapted haplotype distorts the allocation of maternal investment among offspring, then it can increase in frequency despite reducing a mother's fitness as measured by number of surviving offspring (Haig, 1996).

An important distinction exists between selection on genes that benefit all members of a brood (*trans* benefits) and selection on genes that preferentially benefit offspring carrying their copies (*cis* benefits). In the context of mother–offspring epistasis, this distinction corresponds to a difference between maternal loci that are unlinked (*trans*) or linked (*cis*) to the offspring loci with which they interact. Unlinked modifiers will generally promote maternal fitness but linked modifiers can favor redistribution of benefits among offspring in ways that reduce maternal fitness.

DATA ARCHIVING

There were no data to deposit.

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