Letter to the Editor

Is Multiple Paternity Necessary for the Evolution of Genomic Imprinting?

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Genomic imprinting, the inactivation of one allele dependent upon the sex of the parent from which it was derived, has understandably generated considerable interest from theoretical evolutionary biologists. Selection should favor diploid (biallelic) expression to protect against spontaneous deleterious recessive mutations, so the fact that some genes are haploid (monoallelically) expressed clearly requires explanation (Hurst 1997). The correspondence between growth effect and imprint direction does not always hold.

The most frequently discussed hypothesis for the evolution of imprinting (but by no means the only one, see for review Hurst 1997) is the so-called conflict model (Moore and Haig 1991). The premise of this hypothesis is that under multiple paternity a rare paternally derived allele has a lower probability of being in other progeny of the same mother than does a comparably rare maternally derived allele in the same fetus (assuming the rare alleles were inherited). As a consequence, should the paternally derived allele be able to direct resources toward the embryo containing it, then it is more likely to spread than a maternally derived allele doing the same. This is because the maternally derived allele's fitness is in part the fitness of other progeny, whereas the paternally derived allele's fitness will not be reduced by the mother's reduced production of other progeny. The maternal and paternal alleles are hence under different selection pressures and this difference is hypothesized to explain why some genes are inactive when maternally inherited (putative growth enhancers) and others are inactive when paternally derived (putative growth suppressors). Under monogamy, the paternally derived allele suffers and gains every bit as much by the effects on other progeny as does a maternally derived allele and so imprinting is not expected.

Two early models, one game theoretical (Haig 1992) and one applying evolutionarily stable strategy (ESS) theory to a quantitative genetical model (Mochizuki et al. 1996), have supported the verbal model and confirm the predictions that multiple paternity is necessary for imprinting to evolve and that paternally expressed genes will be growth promoters and maternally expressed ones growth suppressors (or more generally enhancers of the individual's fitness and suppressors of the individual's fitness, respectively). In a recent article, however, Spencer et al. (1998) closely analyze diallelic population genetic models for the evolution of genomic imprinting and come to different conclusions. They find that multiple paternity is not a necessary requirement and that the correspondence between growth effect and imprint direction does not always hold.

The discrepancies between the models have been asserted by both sides of the debate to be a consequence of the class of models employed. Additionally, Spencer et al. argue that their diallelic models have the advantage of explicitly analyzing the transition from the unimprinted to the imprinted state rather than simply looking for a stable state. They therefore consider the conclusions of the other models to be restrictive (see also Spencer et al. 1999). In reply, however, Haig (1999) argues that diallelic models are limited to considering only the fate of the alleles in question and hence are not appropriate for considering what happens to such a population in the longer term when subjected to different alleles. He concludes that it is therefore Spencer et al.'s models that are misleading.

Here I address the issue of whether diallelic models can be appropriate to address this problem and whether by necessity diallelic and game theoretical models will disagree. I show that the differences between Haig's and Spencer et al.'s conclusions are not owing to a difference in the class of models used. Instead, the discrepancies stem from Spencer et al.'s restricted application of diallelic models. When one uses diallelic models to address the issue of the persistence of imprinting, as well as its initial evolution, the results conform with those of the earlier models. I start, however, by exploring more fully Spencer et al.'s models so as to highlight their limitations.

Imprinting without Sib Competition

Spencer et al. model a circumstance in which there are always two offspring per brood. Broods, then, are
of three types. Either both progeny have no imprint, in
which case both have fitness unity, or both have im-
printing, in which case both have fitness $1 + u$ or one
has imprinting and the other not. The former then has
fitness $1 - s$, the latter fitness $1 + t$.

The first model that Spencer et al. consider ($SM1 = SP1$) is one in which there is monogamy and competi-
tion between sibs. Spencer et al. show that under this
circumstance, if $u > s$, then an imprint can invade
and will go to fixation if $2u > t$.

Now consider a case in which there is no sib competi-
tion. Perhaps sibs are no more often in contact than
any two randomly selected individuals, as, for example,
in a species in which eggs are cast into water and then
fertilized. I assume that a sib's fitness is simply a function
of its size. Imagine that being larger is better and that
the imprint abolishes activity of one of two copies of
a growth suppressor, thus making imprinting progeny
larger. Then $u > 0$. By equal measure $t = 0$ because a
sib with no imprinting is of normal but suboptimal size.
Likewise, $s = -u$ because progeny fitness is a function
of size and independent of the size of sibs. According
to Spencer et al.'s calculations, an imprint will not only
always invade ($u > -u$); it will always go to fixation
($2u > 0$).

We can then extend Spencer et al.'s conclusions to predict that, not only is multiple paternity not necessary for the evolution of genomic imprinting, but sib competition is not necessary either. Spencer et al.'s models are then consistent with the prediction that all organisms that have ever been under selection for a change in size could have imprinting. Indeed, any selection pressure that can be "responded to" by alteration in gene dosage can be responded to by the evolution of genomic imprinting.

**BIALLELIC EXPRESSION vs. IMPRINTING**

The above diallelic models indicate that imprinting
can evolve under a very broad range of circumstances, but the game theoretical models predict imprinting
can evolve in only a small subset. Does this indicate a pro-
found limitation of the applicability of diallelic models,
as Haig (1999) argues, a restriction on the domain of
game theoretical models, as Spencer et al. argue, or
could the difference be owing to the specific models
that Spencer et al. analyze? Here I show that it is the latter of these possibilities.

In Spencer et al.'s models the imprinted locus ex-
dresses gene product at some rate, let us say $X$. The
population into which the imprinted gene invades has
a net expression at this locus that is not necessarily $X$.
Importantly, Spencer et al.'s models are uncontrolled
in so much as they do not address the issue of whether
it was a difference in dosage or the manner in which
the gene is expressed that is important to the allele's
spread. Therefore, imprinting in these models could be
just one means to achieve a change in size, regardless
of whether there is any conflict; if, for example, selection
favors larger progeny, then an allele making progeny
larger should invade and go to fixation. This could be
an imprinted allele and the mating system is irrelevant.
Furthermore, it does not matter how the organism does
this: an imprint could repress either a paternal or mater-
nal allele for a growth repressor or activate the maternal
or paternal allele at a previously silent locus coding for
growth promoter.

To investigate whether the spread of the imprint in
Spencer et al.'s models was due to selection for an alter-
ation in size or due to a conflict, I now consider a
different allele entering the same initial population.
The new allele is a modifier of biallelic expression and
is assumed to be dominant ($M$). The effect of this allele
is to alter the dose of the target gene's product, the one
that was considered to be imprinted in Spencer et al.'s
models. The modifier allows expression from both al-
leses at the locus, but at each the rate of expression is
$X/2$ so the net expression is $X$. The only difference,
then, between organisms with this new allele and those
with imprinted expression is the pattern of expression,
not the net dosage experienced by the organism. If the
imprinted allele spreads simply because selection favors
a change in mean size, regardless of any conflict, then
the biallelic modifier should also spread.

Given that a biallelically expressed locus is less vul-
nerable to somatic mutations, if all else is equal, we expect
the biallelically expressed state to win in competition
against individuals with an imprint at the same locus.
This being so, the conditions under which both the
biallelic modifier and the imprinted allele can invade
are also conditions in which we should not expect im-
printing to persist. For convenience, I restrict consider-
ation to Spencer et al.'s models of sib competition.

**Biallelic expression with no sib competition:** In the
above circumstance of no sib competition, $Mm$ and $MM$
types then have fitness $1 + u$ and $mm$ types have fitness
1. It follows simply that invasion and fixation occur if
$u > 0$, the same as the condition for the evolution and
fixation of the imprint in the same circumstances.

**Biallelic expression with monogamy:** With sib com-
petition under monogamy, we can ask about the same
dominant modifier. If $x_1$ is the frequency of $MM$ types,
$x_2$ the frequency $Mm$ types, and $x_3$ the frequency of $mm$
types, then, by Spencer et al.'s assumptions (i.e., the
fitness of $MM$ or $Mm$ in a brood with $mm$ is $1 - s$ and
that of $mm$ is $1 + t$),

$$
Wx_1' = (1 + u)(x_1^2 + x_1x_2) + x_2^2(4 - s + 3u)/16
$$

$$
Wx_2' = (1 + u)(x_1x_2 + 2x_2x_3) + x_3^2(4 - s + 3u)/8
+ x_2x_3(2 - s + u)/2
$$

$$
Wx_3' = x_3^2(4 + 3t)/16 + x_2x_3(2 + t)/2 + x_3^2
$$

where $W$ is the sum of the right-hand sides of these
equations. One can solve for the invasion of M when initially infinitely rare. This reveals the condition that $2 - s + u > 2$ must hold, i.e., $u > s$. This note, is the same as the condition for the invasion of the imprinted allele under the same assumptions. Hence, under monogamy with sib competition, it would be misleading to suppose that imprinting can evolve to the exclusion of alternative means to achieve the same effect on organismic size.

**Biallelic expression with multiple paternity:** We can ask the same question of a species with multiple paternity. Given that under multiple paternity maternally and paternally expressed imprinted genes have different invasion conditions, but a biallelic modifier will have only one set of invasion conditions, we may now expect at least one difference between the invasion conditions for the modifier and for the imprint. Again using Spencer et al.’s assumptions concerning relative viabilities and assuming a female mates with two different males, these chosen at random from the available pool of males, then we can derive the recursions

$$Wx_i = (1 + u)x_i^2(2 - s + u)/8 + x_i^3(4 - s + 3u)/16 + x^3_x(2 - s + u)/8$$

$$Wx_j = (1 + u)x_j^2(2x_2 + 2x_3) + x_j^3(12 - s + 11u)/8 + x_j^3(4 - s + 3u)/8 + x_j^3(2 - s + u)/8$$

$$Wx_k = x_k(x_2^2 + 4x_3(x_2 + x_3)(1 + t)/4 + x_2^3(4 + 3t)/16 + x_2^3(5 + 3t)/4 + x_2^3(8 + 3t)/4 + x_3^3$$

where $\bar{W}$ is the sum of the right-hand sides. Solving for the invasion of the biallelic modifier allele when rare, we obtain the condition that $(4 - 3s + u)/4 \geq 1$ must hold, i.e., that $3s < u$. That this is different from that previously found under monogamy is to be expected. When the allele is rare the sibs will both have it only if the mother bears it. If a father bears it, then, at invasion, only one of the progeny at most can have it, as the other father is defined as being different and hence a bearer of the wild-type allele. As a consequence the s parameter weighs more heavily than the u parameter.

Comparable calculations for maternal and paternal imprinting effectively split these two components. For a maternally effected imprint under multiple paternity, the invasion condition is $u > s$, whereas for a paternally effected imprint $s < 0$ must hold. Which alleles have the broader invasion conditions depends on the position in parameter space. Graphical representation (Figure 1) can be used to demonstrate that in no position can biallelic expression invade where an imprint cannot, whereas an imprint can invade where the modifier of biallelic expression cannot. It follows that only under multiple paternity are the conditions for the evolution of an imprint different from those of a modifier of biallelic expression.

**Conclusions**

While Spencer et al.’s models show that when adjustment in size (or alteration of gene dosage) is selected for, imprinting may well be a means to achieve this, they do not demonstrate that imprinting is the only or best means. Their models do not therefore address the issue of whether imprinting will persist in competition with alternative means to achieve the same net dosage. When one asks this question, we find that diallelic and

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**Figure 1.—The invasion conditions for a maternal imprint ($u > s$), a modifier of biallelic expression ($u/3 > s$), and for a paternal imprint ($s < 0$) under multiple mating with sib competition. For invasion of each, the parameters must sit below the lines. In space $\alpha$ the maternal imprint can invade but not others. In space $\beta$, a maternal imprint and the modifier of biallelic expression can invade. In space $\chi$, all three can invade. In space $\delta$, the biallelic modifier and the paternal imprint can invade, and in space $\epsilon$ only the paternal imprint can invade. In space $\phi$, invasion of all three is impossible.
game theoretical models come to the same conclusions about the persistence of imprinting, i.e., that it requires multiple paternity.

It follows that Spencer et al.’s models come to different conclusions from those of Haig (1992) and Mochizuki et al. (1996), not because they use diallelic models per se, but because of the restricted (and uncontrolled) set of diallelic models that they happen to employ. It is then unnecessary to suppose, as Haig (1999) does, that diallelic models are inappropriate to address these issues. Indeed, one might defend diallelic models because they can be used both to analyze short-term and long-term dynamics. In contrast, game theoretical models address the latter issue only and leave unanswered the issue of whether the E.S.S. is an attainable state and what sort of intermediate phenotypes might be found.

The models that I have presented are one way to address the issue of persistence. One could alternatively have used diallelic models to ask about the invasion conditions of a modifier that converts an imprinted locus into one with biallelic expression but of the same net dosage. If one again takes the situation with no conflict, the imprint at fixation (i.e., all individuals have monoallelic expression) and the population suffering from spontaneous somatic mutations, then it can be shown that invasion conditions for a neutral modifier conserving dosage, but allowing biallelic expression, are broad. Indeed, the condition for invasion is that somatic mutations occur and on the average they are recessive and deleterious (cf. Spencer and Williams 1997). This is as expected and the same conclusion as can be reached from the analyses presented above.

Predictions: An important realization from the above models is that in those instances in which either imprinting or the biallelic modifier can evolve, the spread of imprinting is not due to any conflict but due to selection for dosage alteration alone. Defining the conditions under which this might occur is not then defining predictions of the conflict hypothesis. That imprinting can evolve with an absence of sib competition or under monogamy or obligate selfing (as Spencer et al.’s models show) is not a prediction of the conflict model but a prediction of the “selection for dosage alteration” model. If we did find imprinting in a monogamous species or an obligately self-fertilizing one, this should then be considered as evidence against the conflict hypothesis (see, e.g., Hurst and McVean 1998).

Unfortunately, such evidence cannot be considered as falsifying. Diallelic models (see, e.g., Spencer and Williams 1997) show that the difference in fitness between individuals with imprinting and ones with biallelic expression at the same locus, where the net gene product dosage is the same, is of the order of the mutation rate at the locus (or loci) concerned. This is likely to be weak selection. Hence, once imprinting has evolved, its replacement by biallelic expression might be expected to be a slow process. An obligately self-fertilizing and/or monogamous species derived from an outbred one with multiple paternity that had imprinting is not then expected to lose imprinting instantaneously. Showing that a species has been monogamous/selfing for “long enough” is likely to be extremely difficult. The fact that diallelic models also clarify insights into the dynamics. In contrast, game theoretical models can be used both to analyze short-term and long-term dynamics. In contrast, game theoretical models address the latter issue only and leave unanswered the issue of whether the E.S.S. is an attainable state and what sort of intermediate phenotypes might be found.

Although I have not fully analyzed the issue here, following Haig (1992), it is also safest to suppose that the conflict model predicts that all autosomal paternally expressed genes should be individual fitness promoters and maternally expressed ones individual fitness suppressors. Whether the predicted pattern is actually found, and what tests we should do to establish whether the pattern holds, remain unclear (Hurst and McVean 1997, 1998).

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LITERATURE CITED


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