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NEWS AND COMMENTARY

Paternal care and imprinting

Of wolves and men: the role of paternal child care in the evolution of genomic imprinting

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At last, the author of this commentary (male, one daughter) would like to exclaim, somebody has recognized the importance of the paternal investments in rearing children! In the article 'Evolution of genomic imprinting with biparental care: implications for Prader–Willi and Angelman syndrome', evolutionary biologist Francisco Úbeda[1] has extended the kinship theory of genomic imprinting[2] beyond maternal-only investment and has come to unexpected conclusions.

Imprinting refers to an epigenetic process by which the male and the female germline silences different genes so that in the offspring only the maternal or the paternal allele is active.[3,4] The kinship theory argues that in placental mammals there is a 'battle' between the offspring's paternal and maternal genome over the allocation of maternal resources in the pre- and neonatal period. According to this theory, genes expressed from the paternal allele favour the acquisition of maternal resources and hence the growth of the foetus, whereas genes expressed from the maternal allele restrict foetal growth to preserve the mother's resources for future pregnancies. Good examples for these peculiar expression patterns are the murine *Igf2* and *Igf2r* genes: the paternally expressed *Igf2* gene codes for a growth-promoting factor, whereas the maternally expressed *Igf2r* gene codes for a protein involved in eliminating *Igf2*.

The kinship theory is currently the most widely accepted theory on the evolution of imprinting, because it can explain many aspects of the biology of imprinted genes (and it is sexy). It builds on an important difference between males and females: whereas a male can transmit his genes through different females, a female can transmit her genes only through multiple pregnancies.

The original formulation of the theory is based on two assumptions: mammals are not strictly monogamous, and the father's contribution of resources is negligible. Although there is some debate on whether humans are monogamous (the answer depends mainly on personal attitudes), observations among our fellow citizens, as well as in other species, tell us that the first assumption is probably true. But what about the second assumption? Women will generally not hesitate to agree with this statement. Úbeda concedes that biparental care is rare among mammals (less than 10% of genera), but argues that it is common in certain orders (~40% in carnivora, rodentia and primates) and 'more notably, observed in humans'. In his paper, Úbeda has generalized the kinship theory by allowing the expression of a gene in an offspring to affect both maternal and paternal investment. I will spare myself and the readers an account of the mathematics behind the new model, but will discuss the assumptions and conclusions of the model.

Although it is true that in certain species, for example, wolves, the father provides food for his lactating partner and, after weaning, for his cubs, in other species, for example, bears, the father disappears after copulation (and it is not unheard of that this also happens occasionally in our species). So, if biparental care affected the evolution of genomic imprinting, we should find species-specific differences in the set of imprinted genes. Although a few differences have been noted (apparently the human *Igf2r* gene is not imprinted), there is not much evidence for species-specific differences.

As pointed out correctly by Úbeda (and noticed by young fathers), there is little room for paternal care before weaning. During pregnancy, the foetus directly extracts resources from the mother. After birth, the suckling reflex, the babyish appearance and the babyish behaviour of the newborn stimulate the mother to provide milk and other care. All of these interactions could be affected by the offspring's paternal genes. Paternal care, however, could only be enhanced by genes expressed after weaning, and, in order to be selected for imprinting during evolution, these genes should specifically elicit a paternal response. It is difficult to imagine how a gene could do this. It certainly would have to affect the child's behaviour in a way that makes the father provide more resources than the mother. I am not aware of any observation of this kind. It should be noted that an equal share of maternal and paternal investments in rearing the young, as is frequently found in birds, does not support the evolution of imprinting.

An unexpected result of Úbeda's calculations is the prediction that there may be paternally expressed genes that do not enhance, but inhibit resource acquisition, and maternally expressed genes that do not inhibit, but enhance resource acquisition. Úbeda uses these insights to solve one of the challenges to the kinship theory in its original formulation, namely explaining the clinical findings in Prader–Willi syndrome (PWS) and Angelman syndrome (AS). The two syndromes result from a deficiency of paternally expressed (PWS) and maternally expressed (AS) genes on the long arm of human chromosome 15. As expected from the loss of paternally expressed genes, children with PWS have a low birth weight, feeding problems and a failure to thrive during early infancy. At the age of 2–4 years, however, the children develop

hyperphagia and morbid obesity if the caloric intake is not controlled. Úbeda suggests that the paternal copy of the PWS/AS domain contains a gene that enhances resource acquisition before weaning and is silent after weaning, and at least one other gene that restricts resource acquisition after weaning. If this were true, loss of the paternal copy of the PWS/AS domain would lead to a deficient demand for resources before weaning and an excess demand after weaning. This would indeed explain the biphasic nature of the PWS phenotype. However, the model also predicts that loss of the maternal PWS/AS domain leads to an excess demand for resources before weaning. This, however, is not really the case in AS, and it is not easy to relate Úbeda's theoretical genes to the real genes in the PWS/AS domain.

It should be noted that the clinical phenotype of PWS can be reconciled with the kinship theory without taking paternal care into consideration. Haig and Wharton[5], for example, have suggested that a paternally expressed gene on chromosome 15 may increase the maternal costs after birth (ie milk) by inhibiting a child's appetite for solid food. Another possibility is that the loss of the paternally active genes programs the metabolism of a newborn to develop hyperphagia and obesity after weaning. Foetal programming was first proposed by Barker *et al*[6] to explain the epidemiologically observed association between low body weight at birth and obesity-related diseases in adult life. As pointed out by Holland *et al*,[7] PWS may be a genetic model of starvation, which starts before birth and manifests as obesity in a food-rich environment.

The paper by Úbeda shows that 25 years after the discovery of genomic imprinting,[3,4] the evolution and role of imprinting is still a matter of debate. In fact, it is difficult to understand why the deliberate silencing of an allele, which makes an organism immediately vulnerable to a mutation of the other allele, has been selected during evolution. Novel and unconventional ideas are welcome■

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