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Genomic imprinting and the social brain

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Genomic imprinting refers to the parent-of-origin-specific epigenetic marking of a number of genes. This epigenetic mark leads to a bias in expression between maternally and paternally inherited imprinted genes, that in some cases results in monoallelic expression from one parental allele. Genomic imprinting is often thought to have evolved as a consequence of the intragenomic conflict between the parental alleles that occurs whenever there is an asymmetry of relatedness. The two main examples of asymmetry of relatedness are when there is partiality of parental investment in offspring (as is the case for placental mammals, where there is also the possibility of extended postnatal care by one parent), and in social groups where there is a sex-biased dispersal. From this evolutionary starting point, it is predicted that, at the behavioural level, imprinted genes will influence what can broadly be termed bonding and social behaviour. We examine the animal and human literature for examples of imprinted genes mediating these behaviours, and divide them into two general classes. Firstly, mother–offspring interactions (suckling, attachment and maternal behaviours) that are predicted to occur when partiality in parental investment in early postnatal offspring occurs; and secondly, adult social interactions, when there is an asymmetry of relatedness in social groups. Finally, we return to the evolutionary theory and examine whether there is a pattern of behavioural functions mediated by imprinted genes emerging from the limited data, and also whether any tangible predictions can be made with regards to the direction of action of genes of maternal or paternal origin.

Keywords: imprinted genes; evolution; behaviour; cognition; X-chromosome

1. INTRODUCTION

As our knowledge of genes and genomes has grown, it has become increasingly clear that in some cases the epigenetic status of genes is as important as the information encoded by DNA sequence itself. One class of genes that falls under the 'epigenetics' umbrella is imprinted genes. Here, the epigenetic marking, which consists of DNA methylation and chromatin modification, occurs in a parent-of-origin-specific manner (Delaval & Feil 2004). This epigenetic mark is established in the developing embryo by early post-implantation and distinguishes the maternal and paternal genomes, leading to a bias in expression between maternally and paternally inherited imprinted genes that in some cases results in expression solely from one parental allele. This is in contrast to normal (non-imprinted) autosomal gene expression which is generally biallelic, or indifferent to the parental origin of the allele being expressed.

Although the number of known imprinted genes is relatively small (at present approximately 80 coding genes and 37 non-coding RNAs), their very existence contravenes Mendel's third law of inheritance (that maternal and paternal genomes are functionally equivalent). Furthermore, despite their relatively small number, the first studies suggesting the existence of imprinted genes, in which androgenetic (diploid for paternally derived chromosomes only) and parthenogenetic (diploid for maternally derived chromosomes only) mouse embryos failed to survive beyond mid-gestation (Barton *et al.* 1984; McGrath & Solter 1984; Surani *et al.* 1984), demonstrated that they have important developmental functions. Since these discoveries, the genomic imprinting field has expanded rapidly, with many efforts focused on understanding the underpinning epigenetic control mechanisms and the physiological role of imprinted genes.

(a) *Kinship and evolution of imprinted genes*

Imprinted genes often show monoallelic expression, meaning an individual is effectively haploid at this locus, thus negating any benefits of diploidy and sexual reproduction (Orr 1995). This has led to an extensive debate as to why genomic imprinting has evolved (Hurst 1997). Although many theories have been put forward, the most resilient, in terms of predictions and explaining the existing data, is the kinship (or conflict) theory (Haig & Westoby 1989; Moore & Haig 1991). This theory is an extension of the parent–offspring conflict theory developed by Trivers (1974) which suggested that, with regard to resource provisioning, the interests of the offspring do not necessarily equate to the interests of the parents (or mother) who have to take into account their lifetime reproductive output. The conflict theory in relation to imprinted genes takes this thinking to the genomic level, and suggests that,

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owing to relatedness asymmetries, maternally and paternally derived genomes may be selected to favour differential outcomes in the offspring. There are a number of presumptions that underlie this thinking; critically, a male would not anticipate fathering all a given female's offspring; either within her lifetime and/or within a given brood. This would lead to an asymmetry of relatedness between the maternal and the paternal genomes in the offspring: maternal genomes in a given female's offspring would be shared with the mother and among all her other offspring; however, paternal genomes are not shared with the mother, and are possibly shared with some, but not all her other offspring (figure 1*a*). It is this asymmetry of relatedness that gives rise to the differential interests of the maternal and paternal genomes of an individual.

The possibility of intragenomic conflict is particularly obvious during the development of mammalian offspring *in utero*, where the system is possibly easiest to manipulate (Moore & Haig 1991). In this situation, paternally derived genes in the offspring would be expected to maximize nutrient resource acquisition from the mother via the placenta, given that the paternal genome is not shared with the mother and may not be shared with any of her subsequent offspring. However, this strategy may compromise the mother's overall lifetime fitness. The maternal genome is shared with the mother, and will be shared with all the offspring she has throughout her reproductive lifetime. Consequently, it is in the maternal genome's interest to redress the balance so that the mother can provide equal resources for all of her offspring, thus maximizing the overall lifetime fitness of the maternally derived genes. This prediction received strong support as the first few imprinted genes to be identified consisted of growth factors and their antagonistic counterparts acting mainly *in utero*, with paternally derived genes increasing, and maternally derived genes limiting, foetal growth (Dechiara *et al.* 1990; Barlow *et al.* 1991; Leighton *et al.* 1995).

The conflict between parental genomes with regards to *in utero* resource allocation has often been used as an evolutionary framework in which to place observed functions of many imprinted genes (Haig & Graham 1991; Itier *et al.* 1998; Lefebvre *et al.* 1998; Li *et al.* 1999). However, the original synthesis of the conflict hypothesis merely suggested that *in utero* may be one of the potential battlegrounds. Certainly, it is easy to see that the critical period between birth and weaning may provide an additional area where intragenomic conflict, with regard to resources allocation between the mother and the offspring, can arise. However, a number of researchers have also shown in theoretical models that imprinting is unlikely to be confined to resource allocation between parents and offspring, and may evolve whenever there are asymmetries of relatedness (Haig 1997; Trivers & Burt 1999; Haig 2000); the two classic scenarios when this occurs are multiple paternity of a female's offspring (either within-brood or over a reproductive lifetime), and when there is sex-biased dispersal from a social group. The latter scenario, although common in mammals (Greenwood 1980; Pusey 1987), has rarely been invoked when discussing the evolution of imprinted genes, and yet it provides an excellent starting point for discussion of those imprinted genes/parent-of-origin effects that influence postnatal functions extending into the adult. The main group of postnatal functions for which there is a growing body of evidence of imprinted gene/parent-of-origin effects from both mouse work and studies of human mental disease is brain and behavioural functioning (Isles & Wilkinson 2000; Davies *et al.* 2001). A large number of imprinted genes are expressed in the brain (Davies *et al.* 2005*b*), and yet very few have questioned why imprinting should persist in the adult brain or why imprinted genes have evolved to affect brain functioning at all.

In this article, we argue that, from the evolutionary standpoint, it is predicted that imprinted genes will influence what can broadly be termed social behaviours. We expand on the reasons for this, and examine the animal and human literature for examples of imprinted genes mediating social behaviour, and divide these into two general classes. Firstly, mother–offspring interactions that are predicted to occur when partiality in parental investment of offspring occurs; and secondly, adult social interactions, where there is an asymmetry of relatedness in social groups.

2. THE PRE-WEANING PERIOD AND MOTHER–OFFSPRING BONDING

There is ample evidence from a number of mouse studies regarding imprinted genes and resource allocation *in utero* that appears to support the predictions made by the kinship theory (Reik *et al.* 2003). However, as discussed previously, there is also predicted to be selective pressure for the involvement of imprinted genes in the pre-weaning period, when the offspring are still dependent on their mother for resources (Constancia *et al.* 2004; Isles & Holland 2005). Support for this general idea is increasing, and there are a number of examples of imprinted genes affecting growth in the pre-weaning period (Itier *et al.* 1998; Curley *et al.* 2004; Plagge *et al.* 2004).

(a) *Suckling*

Within the context of nutrient supply during the pre-weaning period, evidence from animal models (Curley *et al.* 2004; Plagge *et al.* 2004), and clinical conditions (Holm *et al.* 1993; Haig & Wharton 2003), suggests that imprinted genes may impact on suckling behaviour, with paternally expressed genes enhancing resource acquisition as they do *in utero*. A case in point is the paternally expressed gene *Gnasxl*, which encodes an isoform of the stimulatory G-protein subunit Gsα (XLαs). *Gnasxl* is expressed (among other places) in the facial, hypoglossal and trigeminal motor nuclei (Plagge *et al.* 2004), the key areas of the brain that provide innervation of the orofacial muscles controlling the jaw and the tongue (Lund *et al.* 1998; Sawczuk & Mosier 2001). Mice carrying a targeted deletion of this gene show a postnatal phenotype that includes deficits in suckling behaviour; they have substantially reduced milk content in their stomachs and postnatal weight gain is much less when compared with wild-type littermates (Plagge *et al.* 2004). Although not demonstrated directly, these suckling deficits in the targeted

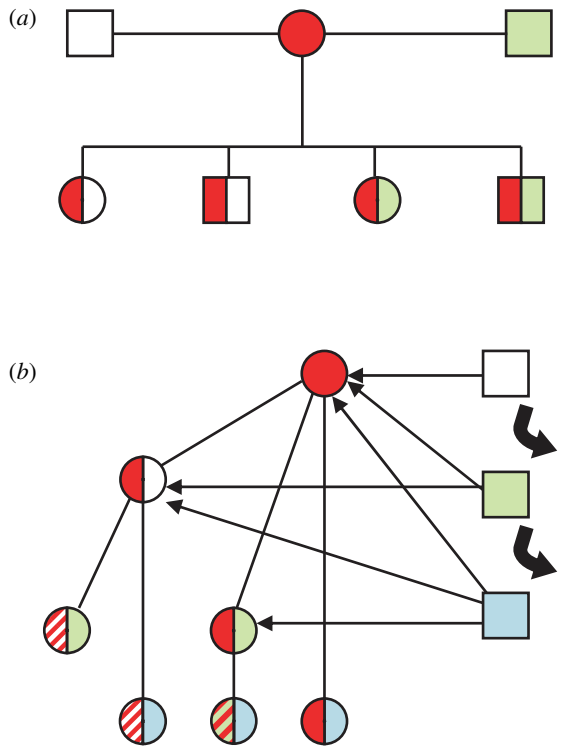

Figure 1. A diagram showing how asymmetries of relatedness can occur through multiple paternity of a female's offspring, and in a simple matrilineal society with sex-biased dispersal. (*a*) With multiple paternity either within a brood or, as is more likely, across a female's reproductive lifetime, offspring from the same mother differ in their relatedness owing to the presence of different paternal genomes. (*b*) Schematic of a simple matrilineal society as described in the text. Males, coming in from outside the group, hold short breeding tenure (matings with females are indicated by thin arrows). Male offspring (not shown) leave the group when sexually mature. What can be seen is that all females share, to differing degrees, maternally derived genes (in red)—this would of course also be true for male offspring. However, paternally derived genes are only present in the strata of the social group and are not shared as widely.

mutant mice are presumably owing to impaired activity in the orofacial motor neurons and the muscles they innervate.

(b) *Emotional cues and positive affect signals*

However, in many animals, mother–offspring interactions are not just about the supply and demand of food. Intragenomic conflict over resource allocation may also include aspects of care (licking and grooming) and emotional cues. A good example of where imprinted genes impact on this kind of function is provided by the neurogenetic disorder Angelman syndrome (AS). AS, which is characterized by abnormalities in neurological, motor and intellectual functioning, is caused by genetic anomalies involving a cluster of imprinted genes on chromosome 15. These causal anomalies include paternal chromosome 15 uniparental disomy, maternal deletion of the critical region (15q11–13) and mutations in the maternally expressed/paternally imprinted gene *UBE3A* (Clayton-Smith & Laan 2003). A key characteristic of individuals with AS is their unusually sociable disposition and frequent laughter and smiling, with reduced displays of negative affect signals such as crying and tantrums (Summers *et al.* 1995; Brown & Consedine 2004). These positive affect behaviours, although originally considered to occur inappropriately (Clayton-Smith & Laan 2003), are increasingly thought to occur specifically in a social context (Yamada & Volpe 1990; Oliver *et al.* 2002). This suggests that one or both of the two known maternally expressed genes in the critical region (*UBE3A* and *ATP10C*) normally act as brake-limiting positive affect signals, and that this function is lost in AS when these gene products are absent.

This idea is further supported by evidence from the clinical condition caused by the reciprocal mutation at 15q11–13, Prader–Willi syndrome (PWS). The main PWS characteristics are caused by an absence of paternally expressed gene product from this critical region (Goldstone 2004). However, two genetic subtypes, maternal chromosome 15 uniparental disomy and PWS-imprinting centre mutations, also have an overdosage of the maternally expressed *UBE3A* and *ATP10C* gene products owing to the presence of two maternal copies and a relaxation of the silencing of the paternal copy, respectively. In addition to the classic PWS symptoms, these individuals show increased negative affect signals (stubbornness and temper tantrums) and a much increased propensity to develop an affective psychosis (Boer *et al.* 2002; Vogels *et al.* 2003). In these cases of PWS, the overdosage of maternal gene products presumably leads to a greater than normal application on the brake that acts to limit positive affect signals.

Taken together, these clinical data have led to the proposal that one or both of these maternally expressed genes influence attachment between offspring and mother, in that they limit the display of positive affect signalling (Isles & Holland 2005). This idea is predicted by the kinship theory (Brown & Consedine 2004), the suggestion being that these positive affect signals manipulate the sensory systems of receivers with respect to the allocation of social 'resources'. In the same manner as manipulating nutrient resources, it is in the 'interest' of the paternal genome to maximize the amount of social resources received from the mother; whereas it is in the 'interest' of the maternal genome to equalize the amount of these resources across all maternally related kin.

(c) *Maternal behaviour*

So far, the focus has been on situations where imprinted genes impact on the ability of the offspring to extract 'resources' from the mother in the pre-weaning period. However, two classic studies examining mice with targeted mutations demonstrate that imprinted genes also influence maternal behaviours (Lefebvre *et al.* 1998; Li *et al.* 1999). *Peg1* and *Peg3* are both paternally expressed imprinted genes that were identified in a screen for novel imprinted genes (Kanekoishino *et al.* 1995; Kuroiwa *et al.* 1996). Both have enhancing effects on foetal growth and are highly expressed in the adult brain (Lefebvre *et al.* 1998; Li *et al.* 1999). Females who carry a targeted (null) copy of *Peg1* or *Peg3* inherited from their fathers show similar

gross deficits in maternal care that are independent of any possible effects in the pups (Lefebvre *et al.* 1998; Li *et al.* 1999; Curley *et al.* 2004). *Peg1* mutant females were deficit in normal aspects of maternal behaviour such as placentophagia, retrieval of pups, nest building and crouching (suckling). Needless to say, the consequence of these behavioural deficits is a reduced survivability of the offspring.

Similarly, *Peg3* mutant females also displayed deficits in aspects of normal maternal care (retrieval, nest building and crouching). Like the *Peg1* mutant females (Lefebvre *et al.* 1998), this maternal care deficit was not due to olfactory dysfunction, and furthermore the *Peg3* mutant females showed normal reaction to newly introduced pups (Li *et al.* 1999). Additionally, *Peg3* mutant females showed reduced milk letdown, despite having histologically normal mammary glands. This suggested a deficit in the neurobiological control of lactation, and investigations demonstrated a reduced number of oxytocin-positive neurons in the hypothalamus of *Peg3* mutant females (Li *et al.* 1999). Given the central role played by oxytocin in both maternal behaviour and milk letdown, the indication is that this is the neurobiological pathway via which Peg3 is exerting an effect (Keverne 2001), an idea that sits nicely with its involvement in the tumour necrosis factor signalling pathway affecting NFκB phosphorylation, apoptosis and cell survival (Relaix *et al.* 1998, 2000).

At first glance, the effect of imprinted genes on maternal behaviour seems to fit quite nicely with the idea of intragenomic conflict over food resources, care and emotional bonds in the pre-weaning period (Constancia *et al.* 2004). However, this aspect of *Peg1* and *Peg3* functions is inconsistent with a kinship/intragenomic conflict explanation, as relatedness asymmetries between parent and offspring do not carry over between generations (Hurst *et al.* 2000). Nevertheless, the gross physiological effects of mutant *Peg1* and *Peg3* on foetal growth (lack of paternally expressed product produces smaller offspring) are consistent with intragenomic conflict, leading to the suggestion that this is the main selective force behind the evolution of imprinting at these loci (Wilkins & Haig 2003). Additionally, *Peg3* has recently been shown to have a role regulating suckling behaviour in pups in a similar manner to *Gnasxl* (Curley *et al.* 2004). This mutant phenotype also fits with intragenomic conflict as it relates to resource acquisition during the pre-weaning period, and may be due to disruption of similar hypothalamic processes that underlie maternal behaviour (Curley *et al.* 2004). Whether or not the effect of these two imprinted genes on maternal behaviour can be reconciled within the kinship hypothesis, or whether this function of these genes is subservient to their effects on *in utero* and pre-weaning resource acquisition remains to be seen.

3. SEX-BIASED DISPERSAL, INTRAGENOMIC CONFLICT AND SOCIAL BEHAVIOUR

Asymmetries of relatedness can also be established in animal societies in which individuals of one or other of the sexes move away from the natal group (sex-biased dispersal). Take an animal social group that consists of maternally related females: sisters, maternal half-sisters, maternal cousins, maternal aunties, etc. Male offspring leave the group on becoming sexually mature, and the dominant/reproductive males come from outside of the group, holding tenure for only a few breeding cycles before being replaced by others. When a given female gives birth to an offspring, owing to the asymmetric relatedness of the group, this individual, regardless of gender, will share a large proportion of its maternally derived alleles with the other members of the group (figure 1*b*). Consequently, owing to this asymmetry of relatedness, the overall fitness benefit to these maternally derived alleles may, for example, be increased if this individual delays its own reproduction for a period in order to help the other members of the group raise their offspring. However, as a breeding male only holds tenure for a certain period, paternally derived alleles are less likely to be shared between individuals within the group. As a result, delaying reproduction to help the other female members of the group raise their offspring will be of no benefit and will in fact incur a cost to paternally derived alleles (unless the benefit can be tailored towards paternal relatives only—see later). Obviously, we can see that this scenario leads to conflict between the paternally and the maternally derived genomes within the offspring, and yet equally it does not necessarily involve growth or food allocation between mother and offspring. What is clear is that such an internal conflict would be manifest at the behavioural level, impacting on how individuals interact socially within the group.

In social/family groups, as in our example, where relatedness asymmetries occur owing to sex-biased dispersal, imprinted genes are predicted to influence those behaviours that relate to how an individual interacts with the other members of a social group to which they belong (Trivers & Burt 1999). Unlike the asymmetry of relatedness situation *in utero*, where the predicted mode of action of imprinted genes is limited to the supply and demand for nutrient resources (Moore & Haig 1991), the potential functions of imprinted genes in social behaviours are far more expansive and complex. For instance, these could include one or many functions such as kin recognition, alarm calls, risk taking, grooming, communal nursing and aggressive behaviour (Hurst 1997; Trivers & Burt 1999; Isles *et al.* 2002; Roulin & Hager 2003). There are tentative suggestions from mouse studies that some of these functions are indeed subject to the action of imprinted genes.

(a) *Kin recognition*

Kin recognition is obviously a key factor in the cohesion of social groups, and in mice, like in many mammals, this is olfactory system based (Brennan 2004). Using reciprocal crosses between inbred strains of mice, Isles *et al.* (2001) demonstrated that there is a parent-of-origin effect on olfactory-based kin-recognition mechanisms. Specifically, reciprocal F1 mice were more sensitive to, and avoided, female urinary odour from their genetic maternal strain (Isles *et al.* 2002). As the F1 mice had never been exposed to these maternal odours previously (all the animals were embryo transferred to foster mothers of a separate strain), the most parsimonious explanation for this behavioural

parent-of-origin effect was that it was genetic in basis, and is therefore probably due to imprinted genes. Further investigations into the neurobiological basis of this behaviour suggested that this was not due to self-referent phenotype matching (Mateo & Johnston 2000), as the urinary odours produced by the reciprocal F1 mice themselves were indistinguishable (Isles *et al.* 2001, 2002). Therefore, the action of this imprinted gene effect is most probably exerted via the neural systems controlling olfactory cue perception and/or information processing.

(b) *Exploratory behaviour and risk taking*

Another behavioural output that comes under the umbrella of social behaviour is risk taking, either in terms of alarm calling, looking for food or defending the group. Although caution needs to be used when discussing a behavioural construct as complex as 'risk-taking', a recent study by us suggests that imprinted genes may impact on one aspect of this behaviour, namely exploration of a novel environment (Plagge *et al.* 2005). Mice carrying a maternally derived targeted allele of the gene *Nesp* showed a reduced propensity to explore a novel environment. *Nesp* is expressed only maternally, and is found in discrete locations in the brain including the noradrenergic locus coeruleus (Plagge *et al.* 2005), a key brain area in the control of reactivity to novel stimuli (Sara *et al.* 1995; Cole *et al.* 1988). In mice at least, it appears that the paternal interest may be to limit risk-taking (by silencing the paternal copy of *Nesp*), while it is in the maternal interest to promote these behaviours.

(c) *Imprinted genes and adult cognition*

Nevertheless, despite these examples, direct evidence for imprinted gene effects on adult social behaviours is limited. However, the fact that there are many examples of genes that are still subject to genomic imprinting in the adult brain (Davies *et al.* 2005*b*) suggests that not only is there a role for these genes in the brain, but that their imprinted status is also important. Consequently, further progress may be made by examining the role of imprinted genes in adult brain functions such as discrete aspects of cognition. This has been reviewed elsewhere (Isles & Wilkinson 2000), but in summary animal studies have so far demonstrated that imprinted genes impact on behavioural flexibility (Davies *et al.* 2005*a*) and several different aspects of memory functioning, including emotional (Brambilla *et al.* 1997), context dependent (Jiang *et al.* 1998) and spatial (Muscatelli *et al.* 2000). Studies on human mental dysfunction indicate a similar array of possible roles for imprinted genes in cognitive functioning (reviewed in Davies *et al.* 2001), including behavioural flexibility (Skuse *et al.* 1997), spatial memory (Curfs *et al.* 1991) and mental rotation (Bishop *et al.* 2000), and what can be broadly described as 'social cognition' (Cook *et al.* 1997; Skuse *et al.* 1997; Boer *et al.* 2002). Such 'cold' cognitive functions may seem remote from social behaviours such as grooming and alarm calls, but there is an accumulating body of evidence elucidating the neural basis of social interactions that suggests behaviours even as complex as deception, result as a consequence of the concerted action of a number of basic psychological functions (Blakemore & Frith 2004). Consequently, knockout experiments in mice and studies on human mental dysfunction may shed light on the function of imprinted genes in distinct aspects of cognition and psychology that underpin how individuals interact socially.

A good example of this is the case of E6-AP ubiquitin ligase encoded by the gene *Ube3a*. Imprinting of this gene is maintained in discrete regions of the adult brain (Albrecht *et al.* 1997; Rougeulle *et al.* 1997; Vu & Hoffman 1997), and as we have seen previously, this gene is involved in aspects of social functioning in the young (Oliver *et al.* 2002), so may well have a similar function in the adult. This idea is supported by the fact that *UBE3A* has been implicated in autism-spectrum disorders (Cook *et al.* 1997; Samaco *et al.* 2005). A study of mice carrying a maternally derived null *Ube3a* allele demonstrated the importance of E6-AP ubiquitin ligase in the degradation of certain effector proteins such as p53 in neurons, long-term potentiation in the hippocampus, and consequently context-dependent learning (Jiang *et al.* 1998). Clearly, it may be these neural and cognitive functions of E6-AP ubiquitin ligase underlying its role in social behaviour, particularly given the importance of contextual learning in social groups (Kamil 2004). The challenge is to make similar such links for those imprinted genes that are known to have a function in cognitive processes.

(d) *The special case of the X-chromosome*

Although limited, there is evidence for the existence of a number of X-linked imprinted genes in mice and humans (Skuse *et al.* 1997; Davies *et al.* 2005*a*; Raefski & O'Neill 2005). Interestingly, so far the vast majority of this evidence is brain based: brain-expressed imprinted genes (Davies *et al.* 2005*a*; Raefski & O'Neill 2005); parent-of-origin effects on structural changes and cognition in Turner syndrome (TS; Skuse *et al.* 1997; Bishop *et al.* 2000; Kesler *et al.* 2003); and cognitive functioning in mice (Davies *et al.* 2005*a*). These X-linked imprinted genes pose interesting questions in terms of the consequences of their expression and, interwoven with this, their evolution. What effect would an X-linked imprinted gene have on the hypothetical matrilineal society described above? An important factor to consider here is that recombination of genetic material between the sex chromosomes during meiosis in males is limited to the small pseudo-autosomal region, which constitutes less than 1% of the genes on the X. As a dominant male sires all the offspring during his tenure, it means that there will be strata of females in the group who are all effectively clonal for their paternally derived X-chromosomes (see figure 1*b*). In this case, the kinship theory would predict that X-linked paternally derived genes may lead to increased social interaction—restricted, however, to paternal female relatives.

There is evidence from a number of social animals that individuals can recognize paternal sibs (Holmes 1986; Alberts 1999; Wahaj *et al.* 2004), suggesting that the mechanisms are in place for specific discrimination between maternal and paternal relatives. Furthermore,

two separate primate studies have shown that this kin recognition can lead to altered behaviour, in that within groups females do bias their social behaviour towards their female paternal sisters (Widdig *et al.* 2001; Smith *et al.* 2003). These studies, one of rhesus macaques (Widdig *et al.* 2001) and the other of baboons (Smith *et al.* 2003), both showed that females demonstrated more approach, cohesion and grooming-related behaviours to paternal kin than non-kin. In both cases (although to varying degrees), this was present against a backdrop of strong maternal-kin bias as is found among matrilineal primate groupings such as these. Clearly, imprinted genes expressed from the paternally derived X could be a genetic mechanism that contributes to this bias in social behaviour, possibly via kin-recognition mechanisms alone or by influencing the behavioural output upon encountering paternal kin (i.e. increasing social behaviour). Conversely, genes expressed from the maternally derived X, which are shared much more widely within the group, would be expected to limit such a bias in behaviour towards paternal kin specifically.

(e) *Genetic sexual dimorphism*

Nevertheless, although it is clear that there are X-linked imprinted genes, some researchers have expressed dissatisfaction with a kinship explanation for their evolution. Instead, they argue that X-linked imprinting has evolved as a genetic mechanism to generate sexual dimorphisms, as male mammals (XY) always inherit their sole X from their mother, and therefore lack any paternally derived X-linked genes (provided there are no Y-linked homologues), and only females (XX) inherit a paternally derived X (Iwasa & Pomiankowski 1999; Iwasa & Pomiankowski 2001). Although gonadal hormones are a strong factor in generating sexually dimorphic traits, there is increasing evidence that genetic factors may also have an independent role (Arnold & Burgoyne 2004). A number of recognized sex differences, particularly in the brain, are observed before the advent of sex differences in gonadal hormones (Sibug *et al.* 1996; Dewing *et al.* 2003), and indeed occur independently of gonadal steroids (Carruth *et al.* 2002). These differences in brain development/function could be explained, for instance, by the action of X-linked imprinted genes. Indeed, this theory for the existence of X-linked imprinted genes has been used to explain the TS data in terms of generating the sexual dimorphism in social cognition (Skuse 1999), and possibly the differential vulnerability of males to mental diseases such as autism (Skuse 2000).

4. CONCLUDING REMARKS

In this review, we have attempted to give an overview of the role played by imprinted genes in social behaviour. In line with the predictions from the most robust evolutionary hypothesis for genomic imprinting, the kinship theory, we have been able to classify imprinted gene effects on the social brain into mother–offspring bonding and adult interactions in social groups. The main idea behind the kinship theory is that there is an asymmetry of relatedness which leads to intragenomic conflict owing to the differential interests of the paternal and maternal genome. With regard to mother–offspring interactions, this asymmetry is generated by a father's uncertain paternity of all of the mother's offspring; while in social groups, an asymmetry of relatedness can become established when there is sex-biased dispersal from the group leading to matrilineal or patrilineal social groupings.

With regards to the former (mother–offspring interactions), the predictive actions of maternally and paternally imprinted genes are relatively straightforward, being an extension of previously established effects *in utero* (Reik *et al.* 2003). However, whereas *in utero* where the differential interest regards the distribution of nutrient resources across the placenta, in the early postnatal period the definition of resources can be extended to include aspects of maternal care and mother–infant bonding. Classically, it would be in the paternal genome's interest to increase resource acquisition from the mother by influencing suckling and consequently nutrient transfer; but acquisition of other resources such as care and emotional cues via affective signalling may also be affected (Brown & Consedine 2004). Conversely, it is in the maternal genome's interest to reduce these effects, equalizing resource distribution across all the offspring in her lifetime.

The second situation in which asymmetries of relatedness occur, and therefore imprinted genes are expected to evolve, is in social groups with sex-biased dispersal. Sex-biased dispersal of this kind is certainly not a theoretical convenience, and in fact is widespread among vertebrates (Pusey 1987). Indeed, although there are examples of female dispersal, it is mainly males that disperse in mammalian societies (Dobson 1982; Pusey 1987), particularly in primates (Wrangham 1980), mirroring the structure of the hypothetical society described above. This fact has led to the suggestion that the expansion of the forebrain regions in primates is related to increased sociality and that developmentally this brain evolution may have been mediated in part by imprinted genes (Keverne *et al.* 1996). Therefore, it is possible to make a tentative suggestion that in adults autosomal genes predominantly expressed from the maternally derived allele will generally promote social, cooperative behaviour among all group members, whereas those genes predominantly expressed from the paternally derived allele may suppress or inhibit such behaviour. However, these predictions may not hold up universally, and are very much dependent on the exact relatedness dynamics of the social group in question.

Generally, there is increasing evidence, from both animal and human studies, that imprinted genes impact on social functioning, both in terms of affecting the mother–infant bond, and by influencing adult social behaviour and cognition. Overall, these data appear to support the theoretical standpoint, particularly with regards to mother–infant bonding. However, there are notable exceptions (for instance, the affect of *Peg1* and *Peg3* on maternal behaviour), and it is important to bear in mind that as there is an inherent flexibility in conflict-based theories to explain data (Hurst 1997), caution is needed when using the theory to explain data *post hoc*. Nevertheless, regardless of

the evolutionary arguments, what is clear is that imprinted genes do have a role in brain functioning, and their effects are often felt via actions on social behaviour, both in early life and in the adult.

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