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Review

Imprinted gene expression in the brain

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Abstract

In normal mammals, autosomal genes are present in duplicate (i.e. two alleles), one inherited from the father, and one from the mother. For the majority of genes both alleles are transcribed (or expressed) equally. However, for a small subset of genes, known as imprinted genes, only one allele is expressed in a parent-of-origin dependent manner (note that the 'imprint' here refers to the epigenetic mechanism through which one allele is silenced, and is completely unrelated to classical 'filial imprinting' manifest at the behavioural level). Thus, for some imprinted genes expression is only (or predominantly) seen from the paternally inherited allele, whilst for the remainder, expression is only observed from the maternally inherited allele. Early work on this class of genes highlighted their importance in gross developmental and growth phenotypes. Recent studies in mouse models and humans have emphasised their contribution to brain function and behaviour. In this article, we review the literature concerning the expression of imprinted genes in the brain. In particular, we attempt to define emerging organisation themes, especially in terms of the direction of imprinting (i.e. maternal or paternal expression). We also emphasise the likely role of imprinted genes in neurodevelopment. We end by pointing out that, so far as discerning the precise functions of imprinted genes in the brain is concerned, there are currently more questions than answers; ranging from the extent to which imprinted genes might contribute to common mental disorders, to wider issues related to how easily the new data on brain may be accommodated within the dominant theory regarding the origins and maintenance of imprinting, which pits the maternal and paternal genomes against each other in an evolutionary battle of the sexes.

Keywords: Androgenetic; Angelman syndrome; Chimera; Cognition; Conflict theory; Genomic imprinting; Parthenogenetic; Prader–Willi syndrome

Contents

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1. Imprinted genes—what are they?

In 1984, it was discovered by Barton et al. (1984) in Cambridge, UK and McGrath and Solter (1984) in the USA that parthenogenetic (PG) and androgenetic (AG) embryos (having two maternal or paternal genome copies, respectively) showed early embryonic lethality and never developed to term, contravening Mendel's assertion that the expression of inheritance units (genes) was indifferent to their parental origin. These data suggested the existence of a new class of genes that were only expressed from one parental allele, and that were necessary for the successful completion of embryogenesis. The early experimental work also revealed major differences between the phenotypes of the AG and PG embryos insofar as AG embryos showed reduced fetal growth and excessive extraembryonic growth and PG embryos showed more advanced fetal development with relatively poor extraembryonic growth. This discrepancy in phenotype between PG and AG embryos further suggested that genes expressed from the paternal allele were functionally distinct from those that were expressed from the maternal allele. We now appreciate that these initial phenotypic findings, together with data from uniparental disomies (UPDs) of particular regions of the genome (Cattanach and Kirk, 1985), illustrated the existence and functioning of 'imprinted' genes where expression is effectively monoallelic and dependent on the parent-of-origin (Fig. 1).

In 1991, the first imprinted genes (paternally expressed *Igf2*, and maternally expressed *Igf2r* and *H19*) were definitively identified in the mouse (Bartolomei et al., 1991; Barlow et al., 1991; DeChiara et al., 1991) and since then the number of identified imprinted genes has been accumulating, facilitated in recent times by the advent of molecular and computational screens and large scale microarray studies (Peters and Beechey, 2004). As more imprinted genes are identified and studied, much effort has gone into determining the molecular and cellular mechanisms underlying imprinting. A full description of the molecular basis of imprinting is beyond the scope of this review (see (Reik and Walter, 2001 for further information) but it seems that genomic imprinting involves the biochemical marking of DNA (notably the methylation of CpG-rich domains in association with particular chromatin conformations). This 'epigenetic' mark allows the molecular machinery of each cell in the progeny to recognise and appropriately express only one allele at a particular locus.

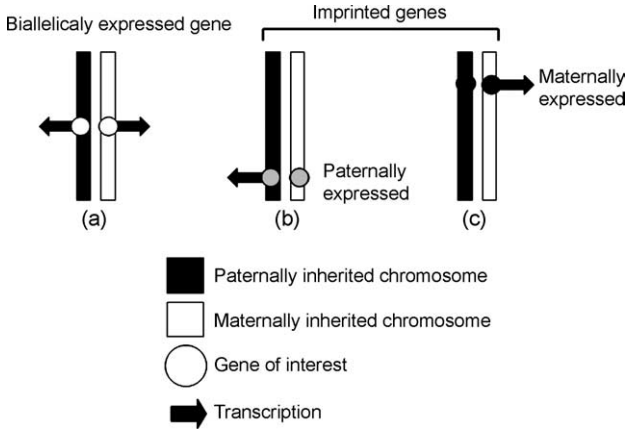

Figure 1. In contrast to the majority of genes that are transcribed biallelically from both the paternally and maternally inherited allele (a), imprinted genes are only expressed from one parental allele. Approximately 50% of known imprinted genes are only expressed from the paternally inherited allele (b), and are designated 'paternally expressed'; the remainder are only expressed from the maternally inherited allele and are designated 'maternally expressed' (c).

The imprint mark is set during gametogenesis when the germline cells in the testes or ovaries are formed and the imprinted traits passed on to the progeny via the sperm and egg at sexual reproduction (Fig. 2). It is important to note that, whilst the parental origin of the allele is crucial, the effects of autosomal genomic imprinting are indifferent to the actual sex of the offspring (see later for the special case of the X chromosome). A major functional consequence of the parent specific expression of imprinted genes are 'parent-of-origin effects' (POE) in the inheritance of traits (and disorders) dependent upon imprinted gene functioning. Traits influenced by maternally expressed genes are inherited down the matriline, whereas traits dependent upon paternally expressed genes are inherited down the patriline. This mode of transmission means that imprinted traits show non-Mendelian inheritance patterns, with the added nuance that, in some situations, traits can skip generations (Fig. 3).

Currently, there are upwards of 70 imprinted genes known to exist in the mouse, and a similar number in man (www.mgu.har.mrc.ac.uk/imprinting, http://cancer/otago.ac.nz/IGC) and recent estimates put the likely total of mammalian imprinted genes in the region of 100–200 (Falls et al., 1999). Although this number represents only a small

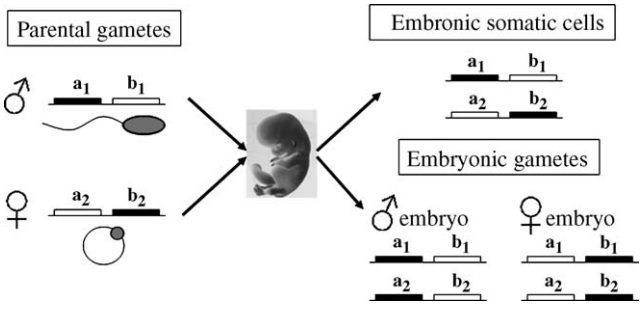

Figure 2. Schematic shows the inheritance of two imprinted genes (a and b). An imprint mark resulting in expression is indicated by a closed black bar whilst a mark leading to transcriptional silencing is indicated by an open bar. Thus, (a) is paternally expressed and (b) is maternally expressed. In the somatic cells of the embryo, the imprint mark obtained from the parents is maintained, leading to monoallelic expression of each gene. However, in the embryonic gametes, the parental imprint marks are erased and reset according to the sex of the developing embryo.

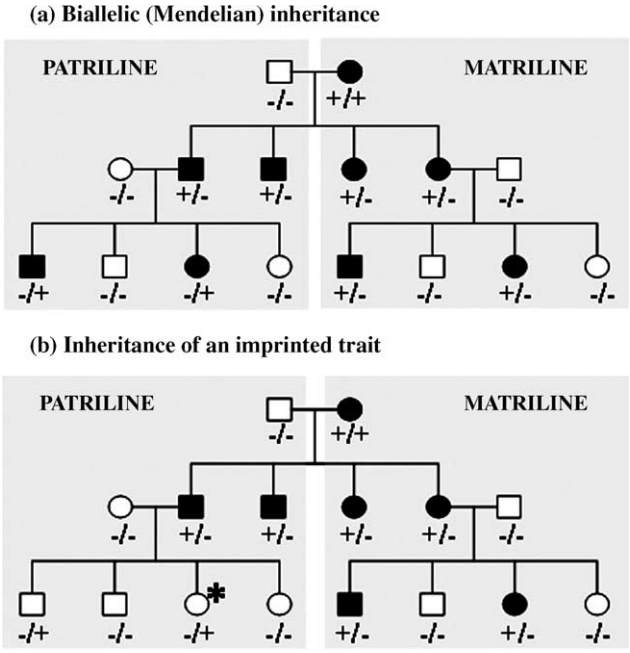

Figure 3. A schematic family tree showing the different modes of inheritance of two alleles '+' (giving rise to the dominant 'black' phenotype) and '−' of a gene, according to whether the gene is biallelically expressed (a) or is imprinted (b). Males are denoted by a square, and females by a circle. In both inheritance patterns, a homozygous grandmother (+/+) and a homozygous grandfather (−/−) produce heterozygous progeny (+/−), and all of these progeny display the 'black' trait. The important distinction between the two inheritance modes can be seen during production of the third generation; in the biallelic model, both the heterozygous father (+/−) and heterozygous mother (+/−) can parent offspring displaying the 'black' trait, whereas in the imprinted gene model, only the heterozygous mother (+/−) parents offspring displaying this trait. In the latter model, transmission of the 'black' phenotype solely through the matriline, is typical of a maternally expressed gene; passage of the trait down the patriline would indicate a paternally expressed gene. The starred heterozygous female (−/+), although herself not expressing the 'black' trait, would transmit it to half of her offspring, (hence, the trait would skip a generation) whereas her heterozygous brother (−/+) would not transmit the trait to his offspring.

fraction (less than 1%) of the total mammalian gene complement, the AG/PG and UPD studies mentioned previously, along with an increasing number of specific gene knockout studies have established that imprinted genes are very important physiologically, especially in eutherians (i.e. placental animals) although there is also some evidence for imprinting in marsupials (O'Neill et al., 2000) and flowering plants (Vinkenoog et al., 2003). Unsurprisingly, given the seminal nature of the AG and PG studies, the role of imprinted genes in placental physiology and general development/growth in utero has attracted the majority of interest to date (Reik et al., 2001). However, more recently, evidence of POE in the inheritance of neurological/psychological traits in humans, together with data from mouse models, has indicated that brain and behaviour may be another key area of imprinted gene functioning (Davies et al., 2001; Isles and Wilkinson, 2000).

2. Characteristics of imprinted gene expression in the brain

2.1. Molecular aspects

A high proportion of the imprinted genes that have been identified thus far are highly expressed in the central nervous system (CNS). Although the CNS comprises brain and spinal cord, imprinted gene expression studies have thus far generally been limited to the former structure. However, given the utility of the spinal cord as a model system, particularly in developmental neurobiology, future work should determine whether or not the conclusions made from the brain data are applicable to the CNS as a whole. From current evidence, there does not appear to be any commonalities with respect to molecular properties and imprinted genes encode a wide variety of products (both proteins and non-coding RNAs) from ubiquitination-related proteins to neurotransmitter receptor subunits (Table 1). Also, in general, most genes that display imprinted expression in the brain also show imprinted expression in other tissues. However, to illustrate the potential complexities of imprinted gene expression one murine imprinted gene, *Ube3a*, shows imprinted expression in certain brain regions (mitral cells of the olfactory bulb, hippocampus and Purkinje neurons), but biallelic expression elsewhere in the brain and in other tissues (Albrecht et al., 1997), whilst its human homologue shows imprinted expression only in the brain (Vu and Hoffman, 1997). Conversely, there are two genes involved in growth factor regulation (*Igf2* and *Grb10*) and a gene encoding a zinc-finger protein (*Zim1*) that are

Table 1
Neurally expressed imprinted genes underpin a variety of cellular functions

Physiological function	Examples	Expressed allele
Intracellular signalling	*Gnas(xl)*	Paternal
	RasGrf1	Paternal
RNA processing	*Snrpn*	Paternal
Genome modification	*Nap1l5*	Paternal
Membrane-associated receptor/transporter/structural protein	*Dlk1*	Paternal
	Sgce	Paternal
	5-Htr2a	Maternal
Non-coding RNA (regulatory?)	*H19*	Maternal
	Peg13	Paternal
	snoRNAs	Paternal
	microRNAs	Maternal
Protein trafficking/processing	*Copg2*	Maternal
	Ube3a	Maternal
	Usp29	Paternal
Transcription factor/zinc-finger protein	*Mash2*	Maternal
	Mkrn3/ Zfp127	Paternal
	Peg3	Paternal
Growth/cell cycle	*Cdkn1c*	Maternal
	Necdin	Paternal
	Zac1	Paternal

imprinted in many tissues, but that appear to be biallelically expressed in the mouse brain (DeChiara et al., 1991; Arnaud et al., 2003; Kim et al., 1999). Yet another imprinted gene, *Nnat*, has expression that is predominantly brain-specific (Joseph et al., 1995). In addition to spatially restricted imprinted expression, at least one gene (*Murr1*) shows temporally restricted imprinting in brain tissue (Wang et al., 2004), further emphasising the dynamic nature of imprinted gene expression in the brain. The precise functional significance of the restricted patterns of imprinted gene expression in brain tissue remains obscure at present but they are consistent, a priori, with highly discrete effects on neurobiological/behavioural substrates.

In the majority of cases, imprinted genes exist in clusters (Smith et al., 2004). However, there are a number of isolated imprinted genes or 'singletons'. One particularly intriguing recent finding is that in some cases these imprinted singletons have been found to reside in the introns of 'host' genes in the mouse to form so-called 'microimprinted domains'. Of more immediate interest is the fact that for three of the known microimprinted domains the host and associated imprinted gene are both highly expressed in brain (particularly in the hippocampus) (Wang et al., 2004; Davies et al., 2004) raising the possibility of local molecular interactions throughout the brain, but especially in this specific structure; these interactions may occur at the transcriptional level, either through transcription of the inserted gene influencing transcription of its host gene (and vice versa) or through transcripts of the inserted and host genes interacting directly—alternatively, it is possible that the protein products of the inserted and host genes may interact (see later). In addition to the special case of microimprinted domains, the hippocampus appears to be an important system for imprinted gene action generally, insofar as many imprinted genes are highly expressed in this structure and it is the one forebrain region where *Ube3a* is imprinted. Of the four microimprinted domains identified so far, the 'inserted imprinted genes' (*Nnat*, *Nap1l5*, *Peg13* and *U2af1-rs1*) are invariably paternally expressed (possibly a consequence of retrotransposon/retroviral insertion; Walter and Paulsen, 2003). It remains to be seen whether this pattern has any functional relevance to brain functioning and also, whether maternally expressed inserted genes exist, and if they do, whether the expression patterns of the host and imprinted gene provide any potential for co-regulatory activity. One further point of interest is that two genes that are imprinted in the brain show 'leaky' (but much reduced) expression from the 'silenced' allele (*Sgce*, Piras et al., 2000; and *RasGrf1*, Plass et al., 1996). Whether this is an artefact, or a true property of a subset of brain-expressed imprinted genes is unclear. It may be that imprinting in the brain is localized or cell-specific (see below) and that this 'leaky' expression represents the net effects of regions of monoallelic and biallelic expression. However, it is feasible that in brain tissue, silencing of one allele may not always be complete.

2.2. Cell-specific imprinting in the brain

In many cases, the specific type of brain cell in which imprinted genes are expressed has not been determined. The use of murine primary cell cultures has shown that expression of *Ras-Grf1* and, interestingly, monoallelic expression of *Ube3a* and the oppositely imprinted antisense, *Ube3a-as*, is limited to neuronal cells. In the case of *Ras-Grf1* expression is absent from glia (Zippel et al., 1997), and for *Ube3a* and *Ube3a-as*, expression is biallelic in progenitor and glial cells, but monoallelic in neurons (Yamasaki et al., 2003). Further support for cell-specific imprinting/expression in the brain has come from analysis of other known imprinted genes. In situ hybridisation data has shown that transcripts of the maternally expressed *Nesp55* gene are restricted to neurons (Bauer et al., 1999), whilst analysis of the paternally expressed *Ndn*, *Nap1l5* and *Peg13* genes also showed preferential neuronal expression (Davies et al., 2004; Taniura et al., 1998). However, immunoreactivity towards the imprinted *5-HT2a* receptor (Kato et al., 1998) in brain was observed in a considerable number of glial cells as well as in neurons (Hamada et al., 1998), although a systematic study of monoallelic expression (as has been done for *Ube3a* and *Ube3a-as*) has yet to be performed. These studies appear to highlight the possibility that, as well as being specific with regards to different brain systems in general, imprinting might, in some cases, also be cell-specific and developmentally regulated.

2.3. Patterning of imprinted gene expression relative to parental genome

One area where it has been suggested there may be evidence of a general organisational theme to imprinted gene expression in brain is in terms of the direction of imprinting. Although the initial AG/PG mouse experiments suggested distinct roles for paternally and maternally expressed genes during embryogenesis, the fact that both AG and PG subjects died early in development (at the 8 and 25 somite stage, respectively) meant they represented a poor model to investigate the relative contribution of the two parental genomes to brain development and/or function. Manipulations involving the addition of early AG or PG embryos (4–8 cell stage) to normal (i.e. containing both paternal and maternal genomes, N) early embryos produced chimeric mice (N⇔AG and N⇔PG). Low contribution (<40% AG/PG) chimeras circumvented the problem of mid-gestation lethality and these mice survived into adulthood (Allen et al., 1995).

The consequences of the AG or PG admixture were extremely interesting (Keverne et al., 1996a). First, with regard to gross brain development, PG chimeras displayed relatively large brains (especially forebrains) when compared to wildtype controls (despite their smaller body size), whilst AG chimeras possessed relatively small brains compared to wildtype controls but had larger bodies.

Additionally, as the PG/AG cells had been engineered to ubiquitously express the reporter gene *lacZ*, the fine detail of precisely where they were located in the brain could easily be determined. It was observed that, far from being dispersed randomly throughout the brain, the AG and PG cells demonstrated a clear and reciprocal pattern of distribution (see Keverne, 1997 for schematic). AG cells, despite initially colonising the telencephalon quite well, ultimately localised preferentially to the hypothalamus, septum and the pre-optic area of the bed nucleus of stria terminalis, but were excluded from the cortex early in embryogenesis. Conversely, PG cells contributed substantially to the cortex (highest contribution to the frontal cortex, lowest to the occipital cortex), striatum and hippocampus but not to the hypothalamic structures.

The mouse chimera data raises numerous questions, not least about how the AG/PG cells come to reside in different brain areas. Thus, whilst it is likely that the spatial restriction of the AG/PG brain cells resulted from early neuronal patterning events (Fundele et al., 1997) the actual physiological mechanism underlying the particular discrete patterning remains obscure. It could be that AG cells are somehow actively directed towards the hypothalamic structures, alternatively they may survive better in these areas than PG cells, or maybe it is the absence of maternally expressed genes that ensures that AG cells thrive in these areas by default (and vice versa). Furthermore (as discussed later) it is by no means certain how many imprinted genes contribute to the differential distribution of PG and AG cells, it could be the net effect of all maternally (PG cells) or paternally (AG cells) expressed genes or the result of one or two genes of large effect. Notwithstanding these issues of mechanism, the chimeric mice work was of major importance, in that it both implicated imprinted genes in processes of neurodevelopment, and further suggested that the paternal and maternal genomes may impact differentially upon functionally distinct brain systems.

At their most extreme, the findings in the PG/AG chimeras would imply that all maternally expressed imprinted genes would be expressed in the 'cognitive' cerebral cortex/hippocampal regions, and paternally expressed imprinted genes would be expressed in the 'emotional/autonomic' hypothalamic/septal/pre-optic areas. However, even with the rather limited survey of detailed individual imprinted gene expression patterns in brain available at present (which reveal a trend towards high expression of imprinted genes in the olfactory system, the cerebral cortex, the hippocampus and the hypothalamic structures) it is clear that this prediction is not confirmed in all cases. Thus, whilst there are many examples where paternally expressed genes show highest levels of expression in the hypothalamic and pre-optic regions (*Peg13* and *Nap1l5*, Davies et al., 2004; *Peg1/Mest*, Lefebvre et al., 1998; *Peg3*, Li et al., 1999; and *Magel2*, Lee et al., 2003), and the maternally expressed genes *Ube3a* and *5-ht2a* are expressed at high levels in the hippocampus and neocortex, respectively, there are numerous exceptions to this rule; including the paternally expressed *Usp29* and *RasGrf1* genes that are highly expressed in the cerebral cortex and hippocampus (Brambilla et al., 1997; Kim et al., 2000), and the maternally expressed *Nesp55* gene whose expression, although evident in regions implicated in adrenergic, noradrenergic and serotonergic control of cortical regions, is excluded in neocortical, hippocampal and cerebellar areas (Bauer et al., 1999).

3. Imprinted genes and neurodevelopment

As noted above, the early evidence from chimera studies appeared to show strong reciprocal imprinted effects on brain size (maternally expressed genes enhancing, paternally expressed genes reducing), indicating that at least some imprinted genes are likely to be involved in neurodevelopment. Furthermore, given the established role of imprinted genes in growth and development, neurodevelopment may represent an important general mechanism by which imprinted genes expressed in the brain exert an influence on brain function. Evidence regarding genomic imprinting effects on neurodevelopment has come from examining individuals with the explicit imprinted gene conditions Prader–Willi syndrome (PWS) and Angelman syndrome (AS) and mouse models of these syndromes. PWS can be caused by three different genetic mutations; deletion of the paternally inherited 15q11–13 region, maternal UPD (mUPD) for this region, or a mutation of the imprinting centre (IC) that is crucial for the gene silencing mechanism to work correctly (Cassidy et al., 2000). The main characteristics of PWS result from the lack of one or more of the paternally expressed gene products in this chromosomal region.

PWS subjects typically present with mild mental retardation and multiple endocrine abnormalities related to hypothalamic insufficiency including failure to suckle with rapid weight gain during later development (Cassidy, 1997). Currently, no definitive underlying genes have been identified for the disorder, although there are a large number of paternally expressed candidate genes within this region (including *SNRPN* and *NDN*). Interestingly, *ndn* knockout mice also show hypothalamic deficits, including a reduction in oxytocin-producing and leutinizing hormone releasing-hormone (LHRH)-producing neurons (Muscatelli et al., 2000). Additionally, MRI studies of individuals with PWS have shown anomalies in pituitary structure (Miller et al., 1996), ventriculomegaly, cortical atrophy, a small brainstem (Hashimoto et al., 1998) and abnormalities in cortical development (Yoshii et al., 2002).

AS is caused by reciprocal mutations to that of PWS (viz. deletions of the maternally inherited 15q11–13 region, paternal uniparental disomy (pUPD) of this region or IC mutations) and is due to a deficiency for one or more maternally expressed gene products (the prime candidate

being *UBE3A*) (Cassidy et al., 2000). AS subjects show mild cortical atrophy (Dorries et al., 1988) and signs of cerebellar dysmyelination and Purkinje cell loss have also been reported (Jay et al., 1991). The disruption of imprinted *UBE3A* expression in the Purkinje neurons may explain the loss of these cells in AS subjects, although mice models null for *Ube3a* do not show any overt neuroanatomical changes (Jiang et al., 1998). CT and MRI studies have also revealed Sylvian fissure anomalies in AS (Leonard et al., 1993) and ventricular enlargement with squared frontal horns (Stoll et al., 1993). A PET study revealed hypoperfusion in the left frontal and left temporo-parietal regions (Gucuyener et al., 1993).

Additional evidence of neurodevelopmental changes possibly related to imprinted gene dysfunction comes from individuals with Williams syndrome, who display mental retardation and microcephaly. Although Williams syndrome can be caused by a maternal deletion for a region of chromosome 7q11.23 (Perez Jurado et al., 1996), it is not clear whether or not this syndrome is truly caused by disruption of imprinted genes. In Williams syndrome subjects, cerebral size is diminished (Jernigan et al., 1993) whilst cerebellar volume is apparently normal, or enlarged (Jernigan and Bellugi, 1990; Jones et al., 2002). In addition, smaller, more closely packed cells in the visual cortex (Galaburda et al., 2002), and a disproportionate increase in the volume of superior temporal gyrus (Reiss et al., 2000) have been noted.

Although mice represent the most tractable genetic model, there are relatively few examples of work in this species linking neurodevelopmental phenotypes to manipulations of individual imprinted genes. One notable instance is the effect of knocking out *Peg3*, a gene that is known to influence maternal behaviour (Li et al., 1999). *Peg3* has recently been identified as playing a pivotal role in the p53-mediated cell death pathway (Yamaguchi et al., 2002) and females that are null for a paternally inherited *Peg3* have reduced numbers of oxytocin-producing neurons in the hypothalamus (Li et al., 1999). Expression analysis of the paternally expressed *Nnat* gene indicates that it too may play a role in neurodevelopment (Wijnholds et al., 1995), a proposal supported by the fact that animals with a maternal duplication (but no paternal copy) of the region containing *Nnat* exhibit abnormal cerebellar folding (Kikyo et al., 1997).

The likely contribution of imprinted genes to brain development raises many issues, including the functionally important question of when any effects might be exerted. The chimera data seem to indicate that imprinted genes can mediate neurodevelopment early in embryogenesis. However, when interpreting imprinted gene effects within the context of neurodevelopment, it is important to be aware that developmental phenotypes resulting from the disruption of imprinted gene-rich clusters may simply be due to aberrant expression of neural non-imprinted genes or, alternatively, related to imprinted gene action at non-brain sites, such as in the placenta, whereby changes in brain development could be secondary to more global effects on nutrient supply to the embryo (Reik et al., 2003). Direct (arising solely from brain-expressed imprinted genes) and indirect imprinted gene effects could be dissociated, in theory, by the use of inducible genetic methods, in which the gene(s) of interest could be manipulated at desired developmental time-points (Monteggia et al., 2004). Nonetheless, it is still possible that, in many cases, the effects of imprinted genes on general development and neurodevelopment may turn out to be closely intertwined.

A number of imprinted genes are expressed in the brain into adulthood, when there is, presumably, more limited scope for influencing neurodevelopment. One might posit a number of reasons for this; notably, that such genes may play a role in influencing ongoing brain function independently of any changes in basic brain structure/connectivity and/or these genes may continue to sculpt the brain in subtle ways throughout post-natal life. The latter option might involve effects on neuronal stem cells or structural changes in existing neurons, such as those thought to underlie activity-dependent changes in synaptic plasticity (Jiang et al., 1998). In many cases, it has to be said, the precise neurobiological function of brain-expressed imprinted genes is simply not known, emphasising the need for more work in this area. Functional assays (electrophysiological, molecular, neurochemical and behavioural) in imprinted gene knockouts and other animal models will undoubtedly be of great utility in determining the mechanisms by which imprinted genes can influence brain function (Jiang et al., 1998; Giese et al., 2001).

4. More questions than answers

Since their discovery some 20 years ago it has become clear that, whilst small in number, imprinted genes are extremely important physiologically, especially in terms of fetal growth. Moreover, they may be added to the category of genes (which also includes the monoallelically expressed olfactory receptors (Chess et al., 1994) and the glucocorticoid receptor (Weaver et al., 2004)) whose expression and brain function are tightly regulated by their epigenetic status. It is also clear that, in terms of defining the specificity, extent and overall relevance of imprinted gene action to brain and behaviour phenotypes we are only at the beginning of the endeavour. As will have become evident in this review there are large gaps in our knowledge, extending from basic information about where imprinted genes are expressed in brain and the various mechanisms by which they could influence function, to wider questions related to the evolutionary pressures that dictate why the brain appears to be a key substrate for imprinted effects.

Nonetheless, despite the relative immaturity of the field, there is already ample evidence for actual (and likely) imprinted effects on multiple brain and behavioural

phenotypes that span investigations in both mice and man (Isles and Wilkinson, 2000). The human work has highlighted the potential clinical relevance of imprinted gene action in brain, not only in terms of the explicit imprinted conditions such as PWS and AS discussed earlier, but also with respect to a range of common mental disorders, notably, autism, schizophrenia, attention deficit hyperactivity disorder (ADHD), Tourette's syndrome and bipolar disorder (Davies et al., 2001). In these disorders, an underlying imprinted genetic basis has been proposed on the basis that the disorder is inherited preferentially from one parent and/or related linkage/association findings are parent-of-origin dependent. Although it is important to be cautious regarding POE on the transmission of psychopathological traits (since other mechanisms such as maternal inheritance of mitochondrial DNA mutations or preferential trinucleotide expansion in one parental germline may also give rise to POE) the human data provide food for thought in two particular ways; first, it emphasises imprinted effects on cognitive processes (Isles and Wilkinson, 2000) and second, it suggests that imprinted genes may provide a plausible mechanism for genetic effects on those psychopathologies where there is evidence for neurodevelopmental antecedents (Levitt et al., 2004).

Another big question which remains unresolved is whether imprinted genes can contribute to sex differences in behaviour. Imprinted gene effects from autosomal loci are indifferent to the sex of the progeny but sexual dimorphisms could occur, in theory, in the special case of X-linked imprinting. The profile of this particular issue has been raised by recent data in 45,XO Turner's syndrome girls suggesting imprinting effects on aspects of cognition (Bishop et al., 2000; Skuse et al., 1997). The direction of effects offered the possibility that, in some circumstances, males may differ behaviourally from females due a lack of X-linked paternal product, an eventuality arising from the fact that males invariably inherit their single X chromosome from their mothers (Skuse, 2000). However, at the present time no suitable X-linked imprinted gene candidates have been discovered. Furthermore, any imprinted contribution to behavioural sexual dimorphisms would have to be dissociated from the major effects of the sex hormones (Arnold, 2004).

Perhaps the biggest questions posed by the presence of imprinted gene expression in the brain are the 'why' questions, those raised by evolutionary considerations. The central issue here is, are the patterns of imprinted gene expression and associated functional sequelae the manifestation of differing interests of the maternal and paternal genome? To make some progress in this very difficult area it is informative to return to the early chimera work. To recall, these experiments revealed patterns of distribution that suggested distinct roles of maternally and paternally expressed genes in the brain, with PG cells contributing mainly to neocortical and AG mainly to hypothalamic regions. If the localisation patterns for the AG and PG cells result from the net effect of numerous imprinted genes, the prediction would be that, in general, paternally expressed and maternally expressed genes are expressed (and presumably have discrete neurodevelopmental/neurobiological functions) in distinct brain systems. However, as discussed earlier, there are examples of maternally and paternally expressed imprinted genes that run counter to this general organisational theme. So what is the cause of the quite distinct pattern of distribution of PG and AG cells in the brain? One possible reason could be that cell survival/localisation is not in fact mediated by the net effect of all paternally expressed genes (in AG cells) and maternally expressed genes (in PG cells), but that there are only one or two imprinted genes having a major effect on AG/PG cell localisation. Such a 'few genes/large effect' mechanism has been put forward as the explanation for the failure of PG and AG embryos to survive into adulthood (Kono et al., 2004), and so it is not impossible that something similar applies to the distribution of PG/AG cells in the brains of chimeras.

An alternative, although not entirely separate, scenario is that the chimeras may simply represent the upshot of when the influence of one parental genome dominates the other. This links quite nicely with the evolutionary arguments attached to genomic imprinting and may suggest brain functions upon which selection has acted. Whilst there are a number of competing theories to explain how and why imprinting may have arisen and been maintained, the most robust is the conflict theory (Wilkins and Haig, 2003). Briefly, the original theory states that where asymmetry of relatedness occurs a 'conflict of interest' arises between maternally and paternally inherited alleles. The classic case where this occurs is in polygamous animals, where a father cannot guarantee paternity of all a females' offspring within a brood and/or in subsequent broods. A second scenario in which asymmetries of relatedness arise is in societies that have sex-biased dispersal, where the main group is comprised of individuals related, in the most common situation, via the maternal line. In both these situations, the maternally and paternally inherited genomes will have differing interests related to what can loosely be termed 'resources'; in the first case this would involve nutrient transfer in utero and pre-weaning from the mother to the offspring and in the latter may impact upon levels of sociality/altruism between individuals within a group.

These conflicts of interest between the parental genomes are predicted to lead to antagonistically acting paternally and maternally expressed genes. This antagonism may occur at the protein level where a paternally expressed product has a counteractive function with regards to a maternally expressed product (as in the case of *Igf2* and *Igf2r*, Haig and Graham, 1991), or, as is more common, at the transcriptional level where for instance, the expression of a maternally expressed coding gene is in turn regulated by the expression of a paternally expressed non-coding gene (Sleutels et al., 2003). We might speculate that, in N⇔AG

chimeras, the paternally derived genome in AG cells is free from antagonistically acting maternally expressed genes, and so the distribution of these cells in the brain point to the areas that paternally expressed genes 'try' to influence—namely, hypothalamic function. The same, albeit reciprocal, argument applies for N⇔PG chimeras, where the maternally derived genome in PG cells is free from antagonistically acting paternally expressed genes.

The argument would be then that there are varying levels of conflict with regards to genomic imprinting in the brain. Firstly there is conflict at the molecular level, with maternally and paternally expressed genes counteracting the expression of one another, or acting in an antagonistic manner on the same or similar biochemical pathways. Second, there is conflict generated at the brain systems level, with paternally expressed genes preferentially influencing those brain areas associated with primary motivated behaviour, and maternal expressed genes preferentially influencing those areas associated with cognition and executive functioning. This latter notion has been suggested to provide a potential genetic mechanism contributing to the expansion of the forebrain in primates (Keverne et al., 1996b), which is thought to have occurred because of the demands of increasing social complexity. The specific arguments here rely on the prediction from the conflict hypothesis that maternal genes would favour social behaviours in matrilineal groups (such as those generally found in mammals) and the suggestion from the chimera work that maternally expressed genes preferentially influence those areas of the brain that are involved in the complex cognitive processes that underlie social behaviours.

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