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Evolution of Imprinting: imprinted gene function in human disease

Article definition

A subset of genes in mammals, known as imprinted genes, show a conditional expression strategy in which transcription depends on an allele's parental origin. Several explanations have been advanced to explain this phenomenon and these, with varying levels of success, predict the functions of imprinted genes. After outlining these explanations, we summarize what is known about human genetic disorders involving abnormal expression of imprinted genes and ask what this can tell us about the evolution of imprinting.

81 words (<100)

Key Words

Imprinting; kinship; sexual conflict; human behaviour; growth disorders

Contents List

1. Introduction

Imprinted genes are expressed in a manner that depends upon their parental origin. Taking the first discovered imprinted genes in mice as an example, *Igf2* is transcribed solely from the paternal allele in each individual with silencing of the maternally derived allele (DeChiara *et al.*, 1991). *Igf2r*, on the other hand, shows the opposite pattern with maternal transcription and paternal silencing (Barlow *et al.*, 1991). These patterns are referred to as parental-specific gene expression or PSGE (after Haig and Westoby, 1989) and they distinguish imprinting from random monoallelic expression (Gimelbrant *et al.*, 2007).

Imprinted genes are important in human disease in several ways. Misregulation of imprinting is implicated in certain cancers (reviewed in Jelinic and Shaw, 2007) and imprinted gene involvement has been suggested in psychiatric conditions such as autism (Badcock and Crespi, 2006) and in normal cognition (Goos and Silverman, 2006). But here we review efforts to understand human genetic

disorders in which imprinted genes are affected in the context of models for the evolution of PSGE. We thus emphasize the proximate and putative ultimate functions of imprinted genes in humans.

2. Definition and discovery of imprinting

Imprinting depends on some way to distinguish homologous chromosomes or chromosome regions based on parental origin. This can be achieved, while alleles are separated in the parental germ lines, by the acquisition of an imprint or mark. Imprinted gene expression underlies the observation that maternal and paternal genomes are both required for normal development in mammals. This was demonstrated by a series of elegant experiments in which pronuclei were transferred between fertilized mouse eggs (McGrath and Solter, 1984; Surani *et al.*, 1984). In general gynogenetic embryos (developing from two female pronuclei) suffered deficits in placental development, and androgenetic embryos (from two male pronculei) deficits in the embryo proper, with neither category developing to term (Solter, 1988). These creations can be regarded as the murine equivalents of ovarian teratomas and complete hydatidiform moles. More subtle effects have been noted later in development with tissue-specific restriction of parthenogenetic and androgenetic cells observed in the mouse brain in chimaera studies (Allen *et al.*, 1995; Keverne *et al.*, 1996).

Later experiments involving uniparental duplications (UPDs) of whole chromosomes or chromosome regions in mice helped map out those regions showing parent-of-origin effects (Cattanach and Kirk, 1985). We now know that these regions contain imprinted genes and that effects on imprinted gene expression were responsible for many of the anomalous phenotypes (Beechey *et al.*, 2007). Intriguingly it seems that oppositely imprinted genes can act in antagonistic ways. Lethality caused by losing maternal *Igf2r* is, for example, rescued by paternal inheritance of an *Igf2* null mutation (Filson *et al.*, 1993; Wang *et al.*, 1994).

3. Mechanisms of imprinting

Imprinted genes tend to exist in clusters and co-ordinate regulation of clusters by one or more imprinting control elements (ICRs) is a common theme (Edwards and Ferguson-Smith, 2007). ICRs show methylation of cytosine residues on only one parental allele, this differential methylation being acquired during male and female gametogenesis and maintained during development. **See also: 1206.**

Maintenance of DNA methylation is required for correct imprinting of many genes (Edwards and Ferguson-Smith, 2007), but at least one other genetic factor, besides the known DNA methyltransferase enzymes, is implicated in imprinting control in humans (Hayward *et al.*, 2003). Further, DNA methylation does not seem to be required to maintain imprinting of genes in the placenta (reviewed in Wagschal and Feil, 2006) and the imprinting of many genes is accompanied by parental allele differences in chromatin structure (e.g. Umlauf *et al.*, 2004).

Imprinting is a complex process and the manner in which monallelic expression is executed varies between chromosomes or clusters.

4. Origins of imprinting

The phylogenetic distribution of imprinted gene expression is probably limited to therian mammals and angiosperms (although PSGE have been noted on a mini-X chromosome in *Drosophila*: Lloyd *et al.*, 1999). Thus autosomal PSGE seems to have evolved independently in two clades in each case affecting genes that are unimprinted in sister taxa. However non-transcriptional, parent-of-origin-dependent phenomena have a broader distribution than PSGE and a common substrate may underlie these and PSGE.

Sleutels and Barlow (2002) argue for an accidental origin of the mechanisms underlying PSGE based on the importance of DNA methylation in genome defence. Methylation is used in prokaryotes to repress the function of alien DNA entering the cell and, in eukaryotes, to repress transposon activity. This repressive function is particularly important during meiosis and takes place separately in male and female gametes. Different silencing mechanisms might therefore evolve in male and female gametes targeting different subsets of sequences for methylation. Matching this, homozygous disruption of *Dnmt3L*, a regulator of its paralogous DNA methyltransferases, results in demethylation and reactivation of retrotransposons in spermatogenesis (Bourc'his and Bestor, 2004; Webster *et al.*, 2005), but not in oogenesis (Bourc'his *et al.*, 2001). Given this sexual dimorphism, a mutation could emerge in a gene, perhaps by transposon insertion, that makes it a target for one system but not for the other (see also Barlow, 1993). A suggestive observation is that essential roles for two paternally expressed genes, *Peg10* and *Rtl1/Peg11*, which both contain retrotransposon-derived sequence, have recently been demonstrated (Ono *et al.*, 2006; Sekita et al., 2008).

An extension of the host-defence hypothesis has been suggested in which imprinting of recently duplicated retrogenes in mammals might serve to mitigate the resultant dosage imbalance (Wood and Oakey, 2006). The evolutionary relationship between gene dosage and imprinting is the subject of the functional hypotheses discussed in the next section.

5. Functions of imprinting

Many hypotheses, which assume imprinting machinery is present, have been advanced for the evolution of PSGE at some genes. The proposed benefits of PSGE in each case must be set against the costs of monoallelic expression, costs that might accrue, in the germline or soma, from hemizygous expression of deleterious recessive alleles or from loss of heterozygosity at overdominant loci (though monoallelic expression may aid efficient removal of germline deleterious recessives). These costs aside, the relative success of each hypothesis depends

on its linking the known physiological functions of imprinted genes to fitness benefits at some level.

5.1. Physiological functions of imprinted genes

Many of the known imprinted genes are involved in the control of pre- and postnatal growth and metabolism and in a range of neuro-behavioural phenotypes (Tycko and Morison, 2002). Known functions are asymmetrically distributed between imprinted genes: the evidence to date suggests that, if they affect growth, paternally expressed genes tend to promote it and maternally expressed genes, to suppress it (Smith *et al.*, 2006). There also seems to be a preponderance of maternally expressed genes that are imprinted in the placenta only (Wagschal and Feil, 2006).

In the next sections we adumbrate candidate explanations for the evolution of PSGE that make increasingly general predictions about the pattern of imprinting.

5.2. Functional hypotheses

The variance-minimization hypothesis posits that monoallelic expression is selected for because it reduces variation in gene expression (for models see Weisstein and Spencer, 2003). Imprinted expression would be a consequence of using existing parent-specific imprints to achieve this. Effectively extending and providing a rationale for this, Wolf and Hager (2006) have developed models of parent-offspring co-adaptation in which PSGE is favoured as a way to increase the covariance in gene expression between parent and offspring. The crux of these models is that gene expression is coordinated between mother and offspring by silencing the paternal allele and this helps mother and offspring to achieve an optimal shared outcome. This idea explains the preponderance of maternally expressed imprinted genes in the mouse placenta (Wolf and Hager, 2006), but the benefit of paternally expressed genes that promote growth at embryonic stages is less clear. Nor is it clear why placenta-specific imprinting would be relaxed in humans (Monk et al., 2006) while infant behavioural effects persist (section 6).

In another idea, short-term benefits associated with sexual versus asexual reproduction might have selected for imprinting as a mechanism to inhibit parthenogenesis (Solter, 1988). But preventing asexual reproduction is not the same as evolving sexual reproduction and, while the latter may be entrenched, it is expected that the benefits to individuals of asexual reproduction outweigh group selection for sexual reproduction. The inefficacy of group selection also afflicts the “rheostat” model proposed by Beaudet and Jiang (2002), which invokes the benefits to a population of functional haploidy. According to this model the protection of a pool of alleles from selection each generation can facilitate future adaptation by sustaining high genetic variance, but this seems more a consequence than a cause of PSGE.

Varmuza and Mann (1994) have bypassed group selection concerns by proposing that the capacity of PSGE to inhibit parthenogenetic development of activated oocytes was a reason for its selection. This is because it protects females from ovarian teratomas. While the “ovarian time bomb” hypothesis can explain maternal repression of growth promoting genes it has been criticized for failing to account for the opposite trend in which paternal genes promote growth (Haig, 1994). However stabilising selection acting against the effects of maternal growth suppression could explain this (Iwasa, 1998). A more cogent criticism is that selection under this scenario would likely only result in imprinted expression at one or a few loci before the marginal benefits of imprinting in terms of reducing cancer risk were outweighed by the costs of hemizygosity. **See also 6139.**

5.3. Sexual conflict theories

Males and females of the same species often experience different selection pressures, so, for a given gene, the allele passed on by a reproductively successful male is of greater benefit to his sons than his daughters; conversely a maternal allele benefits daughters more. Day and Bonduriansky (2004) show that, when one sex is under directional selection, silencing of alleles from the other-sex parent should be favoured in offspring. Sexually antagonistic selection is predicted to lead to sex-specific imprinting in which males silence maternally derived alleles and females silence paternal alleles. However, a mechanism that links imprinting (which distinguishes maternal and paternal homologues) to sexual differentiation may be lacking. Under this assumption, alleles from the parental sex subject to lesser selection pressures will be silenced (Day and Bonduriansky, 2004).

Sexually antagonistic selection is expected to lead to imprinted expression of X-linked genes without this assumption (Iwasa and Pomiankowski, 1999). Males inherit one maternal X chromosome only and random X inactivation in females leads to an expression level that is the average of the maternal and paternal alleles. Silencing of the paternal allele therefore leads to reduced expression in females cf. males, while silencing of the maternal allele achieves the opposite. Imprinted gene expression of this type allows sexually dimorphic gene expression before sexual maturation and provides a resolution to antagonistic selection pressures (Iwasa and Pomiankowski, 1999). **See also: 6128, 6139.**

Autosomal and X-linked sexual conflict models predict that PSGE will be seen at loci subject to sexually antagonistic selection. So in species where males are larger than females (such as humans: Wells, 2007) they predict paternal-specific expression of growth promoting genes and maternal-specific expression of growth suppressing genes or the reverse pattern for X-linked genes. Sexual conflict models do not explain the preponderance of maternally expressed genes in the placenta (section 5.1), but this may be a consequence of anisogamy and dominant maternal control of imprinting (most imprints being maternally applied: Schaefer *et al.*, 2007). Since male and female behaviour may be subject to

different selection pressures, sexual conflict models also offer an explanation for imprinted gene effects on behaviour.

Two paternally expressed genes in mice, *Peg1* and *Peg3*, constitute a problem for sexual conflict models because they positively influence pup growth ***and*** maternal behaviour (Lefebvre *et al.*, 1998; Li *et al.*, 1999; Curley *et al.*, 2004). Under sexual conflict (or under mother-infant co-adaptation) maternal expression of genes for maternal care is predicted.

5.4. Intra-genomic conflict

Perhaps the most popular hypothesis ascribing an evolutionary function to PSGE explains the pattern of imprinting in terms of intra-genomic conflict between maternal and paternal alleles. This idea is known as the conflict hypothesis (Haig and Westoby, 1989; Moore and Haig, 1991; although note Haig and Westoby, 2006 on prior formulation) or as the kinship theory according to the level of generality employed in its description. **See also 5978.**

The conflict hypothesis is an amalgam of parent-offspring conflict theory (Trivers, 1974) and inclusive fitness theory (Hamilton, 1964). In outline, maternal investment in offspring is supposed to impose a cost on the mother's future reproductive value (RV). This can lead to mother-offspring conflict as, under Hamilton's law, offspring discount this cost by their relatedness to future siblings (Trivers, 1974). Under polyandry, paternally derived alleles in sibs are on average less related to one another than maternal alleles. So paternally derived alleles are selected to be even more resource-demanding than maternal alleles (Haig and Westoby, 1989). For a locus that promotes foetal growth (at a cost to the mother's RV) this would lead to an "arms-race" in which increases in paternal allele expression are countered by decreases in maternal allele expression. Absent countervailing effects, the endpoint is maternal silencing and paternal expression, or the reverse at a growth-repressing locus.

This explanation predicts that paternally expressed genes will be growth promoting and maternally expressed genes, growth suppressing as seems generally to be the case (section 5.1). The existence of behavioural effects is also explicable in a kinship theoretic framework if these can be shown to mediate transfers between asymmetrically related kin (as for example would offspring solicitation/begging behaviours, which are subject to intra-brood competition between half-sibs: Haig and Wilkins, 2000). As with sexual conflict models, models based on kinship do not explain the preponderance of maternally expressed genes in the placenta (section 5.1).

Kinship theory also contributes novel insights. Because the level of control that offspring have over resource transfer limits parent-offspring conflict, the restriction of autosomal PSGE to therians and angiosperms, groups in which offspring' acquisitive tissues are linked to the mother, is suggestive. From another perspective, paternally expressed alleles might have played a key role in the evolution of placentation in the first place (Crespi and Semeniuk, 2004).

Under kinship assumptions, maternally and paternally derived genes in mothers should both be selected to provide equally to offspring since they are equally represented in all offspring. So the involvement of *Peg1* and *Peg3* in maternal care (section 5.3) can be taken as a problem for the conflict theory. Wilkins and Haig (2003a) suggest a solution in which the relative risk of patrilineal inbreeding decreases over the lifespan of a mother. Paternal genes in the mother are then selected to favour higher investment in offspring in order to shift the benefits to early, more closely patrilineally related, litters.

6. Evolution and human disease

We now turn to human disease to illuminate the functions and evolution of imprinted genes.

6.1. Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome (BWS; OMIM 130650) is an overgrowth disorder characterized by pre- and postnatal growth enhancement and variably accompanied by localized developmental defects including increased risk of paediatric tumours. BWS occurs in sporadic and familial forms and with a complex genetic aetiology: cytogenetic abnormalities involving chromosome 11p15.5, epigenetic anomalies, and germline mutations within one BWS gene have all been described (Engel *et al.*, 2000). The BWS locus in 11p15.5 comprises an extensive imprinting cluster that can be divided between two independently regulated domains, IC1 and IC2.

The IC1 domain contains the paternally expressed *IGF2* gene and the adjacent, maternally transcribed, but non-coding *H19*, which is a *cis*-acting regulator of *IGF2* imprinting and expression. Five percent of BWS patients have epigenetic defects in the *H19* differentially methylated region (DMR) coupled to loss of imprinting (LoI) of *IGF2* (Cooper *et al.*, 2005). Patients with IC1 defects or uniparental paternal disomy (pUPD) of 11p have significantly higher birth weights and greater risk of neoplasia than those with an IC2 aetiology (Cooper *et al.*, 2005).

The IC2 (or *KCNQ1*) domain contains several genes all regulated by a single control region, the KvDMR. Inactivating mutations have been found in one of these, maternally expressed *CDKN1C* (cyclin-dependent kinase inhibitor; also known as *p57Kip2*), in > 40% of familial BWS cases, and in some sporadic ones (Engel *et al.*, 2000) implicating this as a BWS-causative gene. A majority of BWS cases have an epigenetic defect in this domain and loss of methylation (LoM) of the KvDMR is predicted to result in reduced expression of *CDKN1C* and the other maternally expressed genes.

Functional evidence in mice places *Cdkn1c* in a pathway downstream of *Igf2* (Grandjean *et al.*, 2000), and a combination of an inactivating mutation for *Cdkn1c* and *Igf2* LoI produces a phenotype that resembles BWS better than either disruption alone (Caspary *et al.*, 1999). Paternal uniparental disomy for

11p15.5 is similarly predicted to result in reciprocal changes in expression of the two BWS genes, and the assumed severity of this combination may account for why UPD cases are invariably mosaic.

The other gene in the IC2 domain for which there is evidence for a role in growth control is *PHLDA2*. Disruption of the orthologous gene in mice results in placental overgrowth with expansion of spongiotrophoblast (Frank *et al.*, 2002), and two studies in humans have shown an association between elevated *PHLDA2* expression in term placentae and low birth weight (McMinn *et al.*, 2006; Apostolidou *et al.*, 2007).

BWS is the prototypical imprinting disorder and, with its combination of paternally expressed genes enhancing pre- and early postnatal growth and maternally expressed genes restricting growth, it provides a good match to the predictions of the conflict hypothesis. However, these observations might also be anticipated under sexually antagonistic selection of body size. Adjudicating between kinship and sexual conflict models is difficult without knowledge of the fitness effects of marginal changes in gene expression, although we note that one common feature of BWS, macroglossia, is compatible with kinship theory (because mild increases in tongue size might be expected to facilitate suckling) but not with sexual conflict (male tongues being no larger than females': Abu Allhaija and Al-Khateeb, 2005).

The orthologous imprinted domain in mice, on distal chromosome 7 (Beechey *et al.*, 2007), contains a larger number of imprinted genes, but these additional genes exhibit PSGE only in extra-embryonic tissues and placenta (Monk *et al.*, 2006). This suggests that imprinting exerts greater control over placental growth and function in mice than in humans. From a kinship theoretic perspective this might be explained by multiparity in mice (which promotes intra-brood competition for parental investment) as against uniparity in humans.

6.2. Intra-uterine growth restriction and Silver-Russell syndrome

Silver-Russell syndrome (SRS; OMIM 180860) is characterized by intrauterine growth restriction (IUGR) resulting in low birth weight and various abnormalities. SRS displays considerable genetic heterogeneity, but is associated with uniparental maternal disomy (mUPD) for chromosome 7 in 10% of cases (Abu-Amero *et al.*, 2007). This implicates absence of a growth-promoting paternal allele or over-expression of a growth-inhibitory maternal allele.

Two candidate SRS regions have been identified on chromosome 7. The first of these is 7p11.2-p13 and the orthologous region in the mouse, which contains the maternally expressed imprinted gene *Grb10*, also has growth effects in UPDs (Beechey *et al.*, 2007) with. *Grb10* knockout mice displaying placental and foetal growth enhancement and adult metabolic effects (Charalambous *et al.*, 2003). However, expression of human *GRB10* is biallelic in most tissues and there has been no evidence of disrupted *GRB10* imprinting in non-UPD SRS patients (Arnaud *et al.*, 2003). The second candidate region implicated from chromosomal

anomalies is 7q32, which contains the paternally expressed coding gene *PEG1/MEST* and maternally expressed *CPA4*. The orthologous region in mice also has pre- and postnatal growth effects (Beechey *et al.*, 2007) and *Peg1* knockout mice exhibit IUGR (Lefebvre *et al.*, 1998), but there has been no further evidence that *PEG1/MEST* is an SRS gene.

Maternal duplications encompassing the BWS region on 11p15 have been described as causing syndromic IUGR akin to SRS (Fisher *et al.*, 2002). Recent work has identified hypomethylation of the *H19* DMR in as many as 30% of SRS patients (Gicquel *et al.*, 2005; Bliek *et al.*, 2006), with resultant biallelic expression of *H19* and down-regulation of *IGF2*. In another case, deletion of the 11p15.5 IC2 domain was found (Schonherr *et al.*, 2007). From this perspective, SRS is the reciprocal disorder to BWS and the growth effects are similarly consistent with selection under kinship models and with sexual conflict.

Up to a half of SRS patients have been reported as having motor and neurological problems, including hypotonia, motor and neuropsychological delay, and feeding difficulties (Abu-Amero *et al.*, 2007). This suggests similarities to Prader-Willi syndrome (section 6.3) in imprinted gene function in the brain. In this regard, it is interesting to note that *GRB10* expression is imprinted in the brain, both in human and mouse, but with *maternal allele silencing* (Arnaud *et al.*, 2003). These symptoms are found in mUPD7 cases, but it has not been reported whether they occur with a similar frequency in SRS patients with 11p15.5 defects. These observations are suggestive and seem to fit with kinship theory at least in so far as it predicts tissue-specific silencing of alleles according to their functions in those tissues (Wilkins, 2006).

6.3. Prader-Willi Syndrome

Prader-Willi Syndrome (PWS; OMIM 176270) is an obesity syndrome caused by loss of paternal gene expression in chromosome 15q11-13 and characterized by two distinct clinical stages. In the first stage, neonates and infants show developmental delay, feeding difficulties (with a poor suck) and hypotonia among other signs (Bittel and Butler, 2005). In early childhood, the second stage is indicated, among other signs, by hyperphagia, which leads to obesity and associated complications (Bittel and Butler, 2005).

In about 70% of cases, PWS is caused by deletions in paternal chromosome 15q11-13 and, in about 25% of cases, by maternal disomy for chromosome 15, the latter associated with reduced phenotypic severity (Bittel and Butler, 2005). The genes responsible for the PWS phenotype are not known and several genes in the extensive imprinted domain could contribute to this complex disease. Most significant in terms of regulation is the maternally silenced bicistronic *SNURF-SNURPN* transcript. The PWS ICR is located in the first exon and promoter of this transcript and some PWS cases result from ICR micro-deletions that affect the expression of all PWS genes (Dittrich *et al.*, 1996). Other paternally expressed genes such as the neurally expressed *NECDIN* (*NDN*) and *MAGEL2* genes might play a role in the behavioural features of PWS. A role is also

indicated for multi-copy, small nucleolar RNA (snoRNAs) encoded by the *SNURF-SNRPN* transcript (the HBII-52 snoRNA is implicated in alternative splicing of the serotonin receptor 5-HT(2C)R: Kishore and Stamm, 2006), and for two out of three downstream genes encoding receptors for the inhibitory neurotransmitter gamma aminobutyric acid (GABA), for which there is tentative evidence for paternal expression (Meguro *et al.*, 1997).

The phenotype in first stage PWS matches predictions of the conflict hypothesis: loss of paternal gene function compromises feeding in PWS neonates and infants. The onset of hyperphagia and obesity in second stage PWS is a challenge to kinship theory, but Haig and Wharton (2003) noted that paternal gene copies might be selected to reduce dependence on supplemental foods in childhood. This would have the effect that infants would obtain more calories from their mother's milk than from their own foraging efforts. In support they note increased foraging behaviour in PWS children accompanied by non-fastidious yet non-impulsive eating. As well as assuming a trade-off between maternal milk provisioning, with a cost to the mother's RV, and childhood foraging, without this, this also requires that suckling has greater benefits for children than foraging for food. Haig and Wharton (2003) hypothesized that these benefits include increased nutritive value and provision of antibodies in milk and, possibly, the delayed arrived of siblings resulting from the contraceptive effect on the mother of continued milk letdown. Also consistent with kinship theory, the authors noted that hypersomnolence, observed at all stages in PWS, might reduce the need for and costs of maternal vigilance (Haig and Wharton, 2003).

6.4. Angelman Syndrome

Angelman syndrome (AS; OMIM 105830) can be regarded genetically as the reciprocal imprinting disorder to PWS. AS is characterized by severe mental retardation, abnormal brain and motor functioning, global developmental delay and a range of behavioural abnormalities including paroxysmal laughter. Abnormal weight gain is observed in some cases (Lossie *et al.*, 2001). AS causes range from *de novo* mutations affecting maternal 15q11-13 (in about 70% of cases) to pUPD for this region or imprinting mutations (Lalande and Calciano, 2007). Mutations within a single gene, *UBE3A*, encoding an E3 ubiquitin ligase, have been found in ~10% of cases (Lalande and Calciano, 2007).

An AS ICR, responsible for switching the region towards the maternal epigenotype, is located upstream of the PWS ICR, which it appears to control (Dittrich *et al.*, 1996). The mouse homologue of *UBE3A* shows PSGE principally in the hippocampus and cerebellum and a study with *Ube3a* knockout mice has implicated abnormalities in the cerebellum in ataxia (Cheron *et al.*, 2005).

Some of the behavioural features of AS, relating to the signalling of positive affect, might be explained by kinship theory. Since paternal alleles' interests are served by reducing the likelihood of maternal rejection, frequent smiling and laughter, observed in AS children, may be selected for to facilitate social bonding (Brown and Consedine, 2004). Supporting this, a recent study confirmed that AS

children smile more frequently, especially in social contexts (Oliver *et al.*, 2007). Smiling by AS children was also more frequently preceded by approaches to a target adult and more often followed by increased adult smiling, attention and eye contact (Oliver *et al.*, 2007). Brown and Consedine (2004) also suggested that decreased signalling of negative affect might help retain maternal attention. In this context they noted that relatively low anxiety levels in AS children, as reported by parents, were dissociated from high levels inferred by objective measures, the latter possibly indicating scanning for changes in adult investment. Also following Haig and Wharton's (2003) rationale, hyposomnolence in AS children was hypothesized to increase maternal vigilance costs.

6.5. Transient neonatal diabetes mellitus

Transient neonatal diabetes mellitus (TNDM; OMIM 601410) is a rare form of diabetes which presents with severe IUGR and hyperglycaemia caused by lack of insulin production at perinatal stages (Temple and Shield, 2002). Insulin is a major growth factor during third trimester growth and deposition of fat reserves. TNDM patients experience remission in the first months after birth, with subsequent growth being normal, but many individuals relapse during adolescence into permanent diabetes. Three causes of TNDM have been described: pUPD 6q24, paternally inherited duplications involving 6q24, and LoM of the DMR at the *ZAC/PLAGL1* locus, this being the candidate TNDM gene (Temple and Shield, 2002). All three causes implicate over-expression of a paternally expressed imprinted locus as causing TNDM and mice over-expressing human *ZAC/PLAG1* exhibit impaired glucose homeostasis superficially similar to TNDM (Ma *et al.*, 2004).

TNDM is a conundrum for functional theories of PSGE. It appears contrary to expectations of the conflict hypothesis as over-expression of a paternally expressed imprinted locus results in *reduced* birth weight. That a paternal gene should be involved in mother-offspring co-adaptation, which is more likely than father-offspring co-adaptation in the context of intrauterine effects, seems unlikely (unless we assume high levels of patrilineal inbreeding). Since insulin resistance may be a female adaptation leading to reduced birth weight (Wilkin and Murphy, 2006), paternal rather than maternal expression is also inconsistent with sexual conflict explanations.

The situation is complicated by the fact that *Zac1* knockout mice also exhibit reduced birth weights (Varrault *et al.*, 2006), and paternally inherited deletions of 6q24 covering *ZAC/PLAGL1* result in IUGR (Nowaczyk et al., 2008). These observations suggest deviations from an expression optimum, and it may be that IUGR in paternal 6q24 duplications and deletions has different developmental causes. The conflict hypothesis, it should be noted, depends on a monotonic relation between fitness and imprinted gene expression, at least with respect to marginal changes rather than the gross changes caused by deletion or UPD (Wilkins and Haig, 2003b). It is very difficult to make predictions about the effects of small increases in *ZAC/Zac1* expression from a conflict perspective since we

do not know whether a patrilineal fitness optimum has been reached and/or whether pleiotropic effects might select against maternal allele reactivation.

6.6. Uniparental disomies for chromosome 14

Well-characterized clinical phenotypes are associated with maternal and paternal UPDs for chromosome 14. Maternal UPD14 (mUPD14) presents with pre- and postnatal growth retardation, early onset of puberty, and a range of other problems. Paternal UPD14 (pUPD14), for which fewer cases have been reported, is characterized by growth retardation and severe developmental delay among other signs (Sutton and Shaffer, 2000). The consistently distinct presentation of mUPD14 and pUPD14 implicates an imprinted aetiology, and segmental UPD and deletion cases have mapped the region involved to 14q (Sutton and Shaffer, 2000; Kagami *et al.*, 2005). 14q32 contains the extensive *DLK1/GTL2* imprinted gene cluster, which is likely to be controlled by a region of sperm-derived DNA methylation, the IG-DMR (Geuns *et al.*, 2007). A very recent study reports a case with the mUPD14-like phenotype and LoM of the IG-DMR, strongly suggesting that the *DLK1/GTL2* imprinted domain is indeed responsible for the mUPD14 phenotype (Kagami *et al.*, 2008).

UPD14 phenotypes might have a complex molecular basis. Knockout studies in mice have demonstrated that deficiency of *Dlk1*, a paternally expressed gene encoding a member of the Notch/delta family, causes pre- and postnatal growth retardation, reduced postnatal viability, accelerated adiposity and skeletal abnormalities (Moon *et al.*, 2002), and deletion of the retrotransposon-derived *Rtl1/Peg11* gene causes perinatal lethality, via an effect on placental development (Sekita et al., 2008). The functions of the numerous imprinted snoRNAs and microRNAs encoded in the locus have not been ascertained.

Growth retardation associated with mUPD14 *and with* pUPD14 is problematic for models based on kinship theory or sexual conflict, although these both depend upon the effects of marginal changes in gene expression, which are not reflected by the gross changes caused by UPD (section 6.5). On the other hand, precocious sexual development in mUPD14 and developmental delay in pUPD14 may match expectations derived from sexual conflict or kinship theory since human females undergo puberty earlier than males (Wells, 2007) and maternal alleles might be selected to decrease offspring dependence on parental care by abbreviating childhood.

6.7. Pseudohypoparathyroidism

Loss-of-function mutations affecting *GNAS* on 20q13 lead to a condition known as Albright hereditary osteodystrophy (AHO), but, indicating an imprinting effect, they also lead to parathyroid hormone (PTH) resistance when and only when maternally inherited (Davies and Hughes, 1993). In mice *Gnas* is expressed predominantly from the maternal allele in the renal cortex (Yu et al., 1998). This potentially explains the human inheritance pattern because the renal cortex

contains the proximal tubules, which are the site of action for PTH in respect of its phosphaturic effect. Biallelic expression in other tissues suggests that AHO results from haploinsufficiency for *GNAS*.

Haig (2004) has offered a speculative explanation for imprinting of *GNAS* limited to the proximal renal tubule based on the conflict theory. Under conditions of calcium stress any marginal increase in phosphate excretion might result in decreased calcium flux across the placenta since this flux appears to be regulated by foetal demand and in such a manner as to avoid foetal hypercalcaemia. Reduced calcium flux would serve matrilineal “interests” more than patrilineal interests since it would limit maternal calcium loss, but at the expense of skeletal calcium accretion in foetal bone (Haig, 2004).

GNAS is perhaps the archetypal tissue-specifically imprinted gene, with (relative) silencing of the paternal allele not just in the renal cortex, but in several other tissues leading to a variety of hormone resistance effects associated with pseudohypoparathyroidism (PHP). Patients with PHP and AHO (jointly known as PHP 1a) differ from those with AHO alone (pseudo-PHP) for example, in the severity of their obesity (Long *et al.*, 2007), indicative of imprinting of *GNAS* in a pathway(s) regulating fat accretion. As yet, no evolutionary explanation for this diversity of neuroendocrine effects has been attempted. More knowledge of the genesis of sex differences in growth and metabolism is required to identify effects not dependent on gonadal hormones and to test sexual conflict models.

GNAS is arguably the most complex imprinted locus, comprising two additional, overlapping protein coding transcripts which share downstream exons with *GNAS* but have opposing patterns of imprinting (Hayward *et al.*, 1998). Although knockouts of these genes in mice reveal metabolic and behavioural phenotypes (Plagge *et al.*, 2004; Plagge *et al.*, 2005) which have been interpreted in support of kinship theory, there is no clear evidence yet that deficiency of either gives rise to a distinct condition, or modifies the presentation of PHP 1a/PHPP, in humans. A report of two girls with interstitial deletions of paternal chromosome 20q associated with severe pre- and postnatal growth restriction and feeding difficulties (Genevieve *et al.*, 2005) fits well with the conflict hypothesis, although the paternal transcript(s) involved have not been identified.

6.7. Turner’s syndrome

Turner’s syndrome results from a karyotype in which all or part of one X chromosome is deleted in females. Skuse et al. (1997) showed that the parental origin of the remaining X chromosome predicted differential social adjustment in individuals with Turner’s syndrome. Among individuals with complete chromosome loss, those retaining paternally (45,X^p) rather than maternally (45,X^m) derived X chromosomes had superior social cognition as revealed by scores on a questionnaire delivered to parents. 45,X^p females also showed higher verbal IQs and better performance on a behavioural inhibition task than 45,X^m females. Performance on the latter task reflected sex differences in normal participants with females (46,X^mX^p) outperforming males (46,X^mY) and has also

been recapitulated in a mouse model of Turner's syndrome. 39,X^m mice showed deficits in a reversal learning paradigm contrasted with 39,X^p and 40,XX mice (Davies *et al.*, 2005). This occurs despite the fact that 39,X^m mice show enhanced growth at foetal stages cf. 40,XX mice while 39,X^p mice are retarded (Thornhill and Burgoyne, 1993). Using an animal model allowed Davies et al. (2005) to exclude maternal effects (by comparing normal females from various genetic backgrounds) and other genetic abnormalities (such as cryptic mosaicism for the deleted X chromosome).

Extensive screens in mice (Davies *et al.*, 2005; Raefski and O'Neill, 2005) led to the discovery of the *Xlr3b* locus with imprinted expression on the X chromosome (and subject to X inactivation: Davies *et al.*, 2005). PSGE for *Xlr3b* was identified in the brain in the frontal cortex and hypothalamus, regions involved in reversal learning (Davies *et al.*, 2005). Deletions affecting the homologous region in humans have been implicated in autism (Thomas *et al.*, 1999) and schizophrenia (Milunsky *et al.*, 1999).

Effects on embryonic development are consistent with sexually antagonistic selection for body size and inconsistent with the conflict hypothesis (in the direction of effects observed). Quantitative genetic modelling also predicts that sexually antagonistic selection results in more extreme effects on gene expression than selection under the conflict hypothesis (Iwasa and Pomiankowski, 2001). Although Davies et al. (2005) interpreted leaky imprinting of *Xlr3b* in light of the conflict hypothesis (after Haig, 2000), the reversal learning phenotype itself is consistent with sexual conflict (Iwasa and Pomiankowski, 1999), especially considering the existence of cognate sex differences in humans and of *Xlr3b* expression in mice.

7. Conclusions: Arguing for theoretical pluralism

Reviewing data from human and murine UPDs, Hurst and McVean (1997) took the view that the conflict hypothesis cannot account for all, or in humans even many, of the phenotypes observed. But we believe the effects of disruption of imprinted genes in humans lend qualified support to several theories for the evolution of PSGE.

The main beneficiary of this support is kinship theory, which offers explanations for prenatal growth effects, pre- and postnatal feeding behaviours, childhood affect signalling and sleeping patterns and possibly also for changes in the timing of puberty. Developments in our theoretical understanding of PWS/AS in particular have offered new interpretations based on kinship theory since Hurst and McVean's (1997) review. Models based on sexually antagonistic selection have also entered the marketplace by offering plausible explanations for pre- and perinatal effects on growth, but the action of gonadal hormones may negate a wider role for these later in development. More specific information on hormone-independent effects is needed. Given the existence of intra-uterine effects attributable to paternal gene function, Wolf and Hager's (2006) co-adaptation

models also seem to be of limited applicability although mixed postnatal effects may be predicted under biparental care.

On the other hand, we believe that kinship theory cannot adequately explain all the phenomena here reviewed. This can be seen in the complexity of growth effects observed in TNDM and UPD14 individuals (section 6 and Hurst and McVean, 1997), but is most evident in Turner's syndrome where the predictions of kinship theory contradict those of PSGE evolution under sexually antagonistic selection, the latter providing a better match to the observed effects both in theory and in practice (section 6.7).

The incomplete explanatory utility of any one theory argues for a pluralist perspective in which different functional theories for the evolution of PSGE are invoked to explain PSGE for different genes. Such a perspective is evident within kinship theory in which placentally mediated conflict, emphasized in its original formulation (Moore and Haig, 1991), is not considered the only source of asymmetrical selection on parental alleles (Haig, 2000). Given its limited phylogenetic distribution, it also seems likely that PSGE is an exaptation in which imprinting machinery that has evolved for other reasons (section 4) is co-opted by new selection pressures.

Extending and testing the diversity of hypotheses on offer will depend on studies that take a comparative approach. We allude to life history differences between humans and mice in the context of placental imprinting (section 6.1), but the elongated human childhood, during which children are dependent on different adult relatives for food, shelter and learning opportunities, may present a particularly complex substrate for selection under kinship theoretic considerations making tests of the theory problematical. Unfortunately parsing kinship and sexual conflict models may also be complicated by correlations between the degree of sexual dimorphism and other life history traits relevant to kinship or co-adaptation such as the extent of polyandry or biparental care, respectively.

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Glossary

Parental-specific gene expression (PSGE)
a gene expression pattern in which an allele's level of expression depends on its parental origin in the previous generation

Uniparental duplication (UPD)
chromosomal aberration in which both copies of a chromosome or chromosome region are derived from one parent; whole chromosome duplications are usually referred to as disomies

Ovarian time-bomb
the hypothesis that imprinting evolved to prevent the development of ovarian teratomas (section 5.2)

Co-adaptation
reciprocal adaptation that occurs in two transacting entities because changes in one affect the other; the entities may be separate individuals (as envisaged in parent-offspring coadaptation: section 5.2) or parts of the same genome

X inactivation
the process in females whereby expression of most genes on one X chromosome is repressed; this occurs at random in non-placental tissues of eutherian mammals

Sexual conflict
in this review, the name given to a family of hypotheses for the evolution of PSGE in which sexually antagonistic selection plays a key role (section 5.3)

Intra-genomic conflict
functional antagonism between different genetic elements within the same genome based on divergent selection pressures

Conflict hypothesis
the hypothesis that maternal care and mating systems interact so that paternal alleles are selected to be relatively more resource-demanding than maternal alleles, resulting in predictable patterns of PSGE at resource-influencing loci

Kinship theory
the theory, derived from the conflict hypothesis, that explains PSGE in terms of differing selection pressures operating on maternal and paternal alleles by virtue of transactions with asymmetrically related kin (section 5.4)

Exaptation
an organismal trait that was once selected for one function but now serves another; describing a trait as an exaptation is often contrasted with the apparently naïve assumption that it owes it's existence to selection for the same purpose it currently serves