

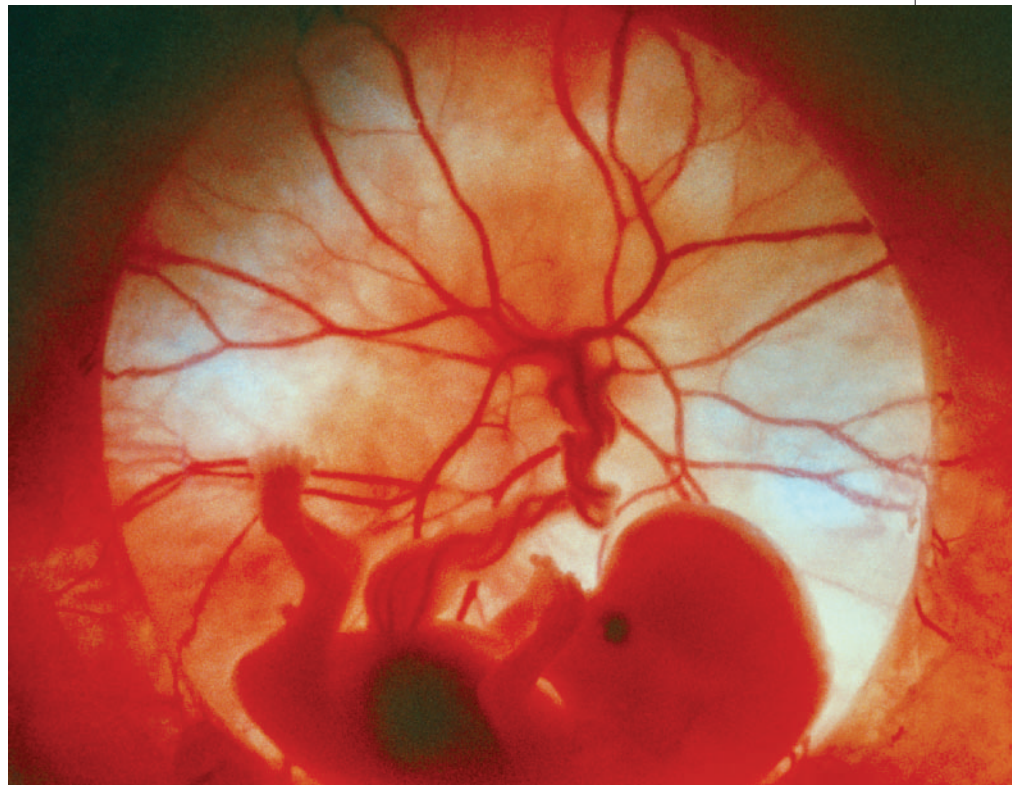
# Resourceful imprinting

**A child's genes are not all equal: in some cases, the copy from either the mother or the father is turned off. This affects the child's ability to acquire resources in the womb, after birth, and perhaps throughout life.**

**Miguel Constância, Gavin Kelsey and Wolf Reik**

Children spend about a third of their lives acquiring resources from their parents. Parental investment often continues after children finish full-time education and establish their own families. Resources at this stage vary from money to advice; earlier in life they include the teaching of complex social behaviours, social, intellectual and language skills, and knowledge about our world. Although these are not acquired with the mother's milk, the rapid development of the necessary motor and sensory skills does depend on feeding and milk metabolism during the earliest part of post-natal life. How well the newborn baby fares depends in turn on how well it was nourished in the womb, allowing it to grow and develop the organs it needs for life after birth.

This matters because the more resources parents invest in their offspring, the better the offspring's chances of surviving and being attractive as a sexual partner, and therefore of reproducing. Contrast this enormously drawn-out process, particularly in primates, with species of fish, for example, that leave their masses of young to fend for themselves, with the result that most end up as food for the local community instead of reproducing. So, in higher mammals in particular, genes in offspring that make them acquire and store resources, and genes in parents that make them donate resources to their offspring, are crucial for a long and reproductively successful life.



But the tangible contributions that mothers and fathers make to their children are very different — indeed, some might ask what fathers do beyond donating sperm. During a child's development in the womb, and post-natal feeding up to weaning, the father is clearly not a major direct player. Because of this fundamental asymmetry, resource-acquisition genes in offspring have different, and conflicting, strategies depending on which parent they come from. (It is important to distinguish genes in the parents, that is, maternal or paternal genes, from maternally or paternally inherited genes in the offspring.)

These genetic asymmetries are the subject of kinship theory, also known as genetic conflict theory<sup>1</sup>. This proposes that paternally inherited resource-acquisition genes are 'interested' in extracting as many resources from the mother as possible — in the form of nutrients through the placenta during gestation, or milk after birth, for example — as this normally costs the father little. The possibility that the same mother will bear offspring by different males strengthens this drive.

Maternally inherited genes, by contrast, are not interested in exhausting maternal resources prematurely, but rather in ensuring that these resources are dished out evenhandedly to all offspring.

## Imprinting in theory

How can maternally and paternally inherited genes be made to behave differently? The only real option is to switch one gene copy off. This is achieved by an epigenetic mechanism of gene regulation — one in which the gene's sequence is unchanged, but its labelling with certain chemical groups is altered. The mechanism in question is termed genomic imprinting<sup>2,3</sup>, and it ensures that the relevant parental genes are marked in the germ cells (egg and sperm) to be active or inactive in the offspring (Box 1, overleaf). The conflict between parental gene sets works at different levels. For instance, a gene that confers a growth advantage when inherited from the father might have been subject during evolution to silencing of the maternal copy. Conflict

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## Box 1 Control of imprinting

The distinguishing feature of imprinted genes is that the two parental gene copies, or alleles, are expressed differently. In many cases, one allele is silent in most tissues throughout development. This means that the alleles retain a memory of their parental origin. In molecular terms, imprinted genes acquire different marks in the sperm and egg, and these marks must be heritable through subsequent cell divisions<sup>2,3</sup>. Part of the marking is DNA methylation — the covalent addition of methyl groups to cytosine residues in CpG dinucleotides, which occurs in imprinting control regions (ICRs) of DNA.

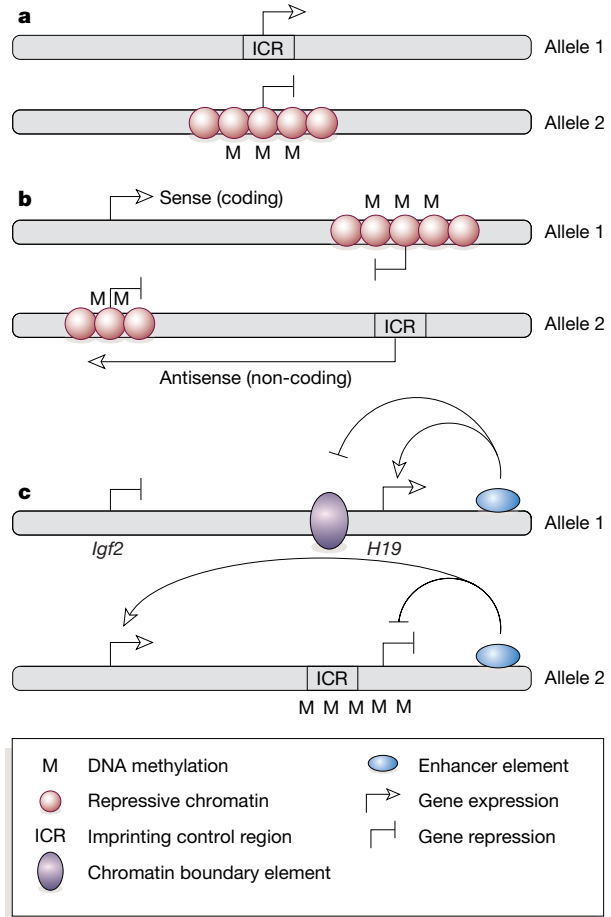
DNA methylation on imprinted genes is established by the *de novo* methyltransferase enzyme Dnmt3a, together with the Dnmt3l protein<sup>29</sup>. After fertilization, the maintenance methyltransferase Dnmt1 ensures the faithful copying of methylation marks through subsequent cell divisions. DNA methylation marks are usually erased only when the alleles encounter the germline again, in the primordial germ cells, before they are re-established according to the sex of the individual.

DNA methylation and associated differences in chromatin — the way

in which DNA is packaged — are read after fertilization to ensure that the correct allele is expressed. This occurs in different ways depending on the gene<sup>2,3</sup> (see figure). In the simplest case (a), DNA methylation and repressive chromatin may directly overlie one allele's promoter region (from which gene expression begins), silencing that allele (allele 2 in this case).

In an indirect mechanism (b), the ICR contains the promoter of a non-protein-coding gene, which can be expressed to produce an 'antisense' RNA; this RNA then somehow (perhaps through methylation) silences the protein-coding imprinted gene on the same chromosome. On the other chromosome, methylation of the ICR ensures that the antisense RNA is not expressed.

In a third mechanism (c), the ability of shared activating sequences (enhancers) to activate one or other imprinted gene is determined by a chromatin boundary element present on the unmethylated allele between the two genes, as exemplified by *Igf2* and *H19*. Finally, reading mechanisms may vary in different tissues, resulting in tissue-specific imprinting of some genes. ■



may also operate at the protein level: thus, the insulin-like growth factor type 2 receptor (*Igf2r*), which is expressed only from the maternal gene copy, encodes a receptor protein that degrades excess *Igf2* — a paternally expressed growth enhancer.

Although only some 80 of the 30,000 genes in the human genome are currently known to be imprinted<sup>4,5</sup>, they undoubtedly have key roles in resource acquisition. Crucially, paternally and maternally expressed imprinted genes also affect resource transfer in the expected direction — genes expressed from the paternally inherited copy generally increase resource transfer to the child, whereas maternally expressed genes reduce it<sup>6</sup>.

If imprinted genes are indeed intimately linked with acquiring resources from parents, we would not expect any in the fish that leave their offspring to their own devices after conception. Indeed, early indications provide little evidence of genomic imprinting in fish, amphibians, reptiles and birds<sup>7</sup>. But imprinting does also exist in seed plants, the endosperm tissue of which is the equivalent of a placenta to feed the embryo. And, although imprinted genes concerned with fetal resources seem particularly prominent in

placental mammals (which are divided into marsupials, and others, including humans, that are collectively known as eutherians), genes involved in suckling could also be imprinted in egg-laying mammals (monotremes). Imprinted genes affecting behaviour might also operate in many other situations in which there is parental asymmetry in investment, especially in higher primates.

If imprinted genes are crucial in mammalian development, one would also expect mutations in these genes to cause diseases, and that these diseases might be recognizable by their exclusive maternal or paternal transmission in families. There is indeed a growing number of known imprinting disorders<sup>5</sup>, many of which affect fetal growth (resulting in babies that are too small or too large), hormone systems after birth, or adult behaviour (Fig. 1). As imprinting is an epigenetic mechanism of gene regulation, epimutations — mistakes in maintaining epigenetic marks — also cause imprinting disorders.

### Imprinting in the womb

Kinship theory predicts that selective forces will favour parent-specific gene expression most strongly during mother-offspring

interactions in the womb and soon after birth<sup>1</sup>. But how does imprinting affect life *in utero*?

The human fetus is tucked neatly away in the womb for nine months, feeding off the mother's nutrient supplies. This is possible because of the evolution of an organ for exchanging nutrients, gases and waste products between mother and fetus — the placenta. The human placenta is remarkable, providing 11 square metres of exchange surface at the time of birth, and is almost as efficient as the lungs in gas exchange. What are the advantages of having acquired such an organ? For a start, the placenta allows for a prolonged gestation period, which in turn allows larger, more-developed young at birth, with more advanced central nervous systems. Like eutherian mammals, marsupials also benefit from a period of life in the womb supported by a placenta, although the period is briefer, the placenta is much more rudimentary, and the baby is less developed at birth.

A fetus, although entirely dependent on its mother's nutrients, is not just a passive recipient, but influences its own development and growth. Indeed, it subverts many

Disorder	Effect	Imprinted genes suspected or known to be affected	Expressed gene copy
<b>Intra-uterine growth</b>			
Beckwith–Wiedemann syndrome	Fetal and postnatal overgrowth; excessively large organs; predisposition to tumours	<i>IGF2</i> (encoding a growth factor) <i>CDKN1C</i> (encoding a cell-division regulator)	Paternal Maternal
Silver–Russell syndrome	Severe intra-uterine growth restriction	Maternal uniparental disomy and duplications of chromosome 7	
Pre-eclampsia	Pregnancy-associated hypertension, often accompanied by intra-uterine growth restriction	Linkage studies suggest involvement of maternally expressed imprinted genes in some families	
<b>Behaviour and brain</b>			
Prader–Willi syndrome	Moderate mental retardation; severe obesity; short stature; poor muscle tone	Numerous imprinted genes on chromosome 15	Paternal
Angelman syndrome	Severe motor and mental retardation; paroxysms of laughter; autistic-like behaviour	<i>UBE3A</i> (encoding a protein-degradation regulator)	Maternal
Turner syndrome (monosomy X)	Affects females only; associated with a characteristic neurocognitive profile, short stature and ovarian failure	Enhanced social cognitive skills in patients inheriting the paternal, rather than maternal, X chromosome may indicate imprinting	
Schizophrenia	Perceived distortions of reality; disturbance of thought and language; withdrawal from social contact	Some forms of schizophrenia show lower age of onset after paternal inheritance	
Maternal behaviour defects (in mice)	Lack of maternal postnatal care of offspring	<i>Peg3</i> (encodes a DNA-binding protein) <i>Peg1</i> (encodes an enzyme of the $\alpha/\beta$ -hydrolase family)	Paternal Paternal
<b>Hormones and metabolism</b>			
Albright hereditary osteodystrophy	Short stature; round face; obesity; mental retardation; subcutaneous calcification	<i>GNAS</i> (encodes a G-protein subunit)	Maternal (tissue specific)
Pseudohypoparathyroidism 1A	As above, accompanied by resistance to parathyroid hormone and other hormones	Occurs only on maternal transmission of inactivating <i>GNAS</i> mutations	Maternal (tissue specific)
Transient neonatal diabetes mellitus	Pancreatic insufficiency and low secretion of insulin during fetal life; intra-uterine growth restriction	<i>PLAGL1</i> (encodes a DNA-binding protein)	Paternal

**Figure 1 Imprinting and disease.** Several disorders (not all of which are shown) are caused by the absence or misexpression of imprinted genes. The mechanisms responsible may be genetic, such as gene deletions, or the inheritance of both chromosome sets — or parts of them — from just one parent instead of two (uniparental disomy). The mechanisms might also be epigenetic, involving for instance alterations in imprint marks or how they are 'read' (see Box 1). Most imprinting-associated defects arise from the loss of function of imprinted genes. A few result from increased

'dosage' of an imprinted-gene product, because of uniparental disomy or re-activation of the normally silent allele (loss of imprinting). Many other diseases may involve imprinted genes — they might, for instance, contribute to cancer — but this is unproven. The well-defined imprinting disorders are quite rare, affecting fewer than one person in 10,000. See ref. 30 for a detailed description of these diseases and their genetic causes; see also refs 4, 5, 8, 22, 31. Human genes are in upper-case, mouse genes in lower-case.

of the mother's physiological activities to its own end, to ensure adequate mobilization of nutrients and oxygen. So it is unsurprising that the asymmetry of interests of paternally and maternally inherited genes — the desire to make a large, fit baby versus the desire to withhold resources for future offspring — is most tangible during life in the womb<sup>1,8</sup>. One area for competition is in the placenta, over the control of the supply of nutrients.

The placenta comprises two components: a fetal portion that develops from trophoblast derivatives (the first lineage specified in the early embryo) and a maternal portion derived from the inner layer of the uterine wall. This juxtaposes fetal and maternal blood vessels for efficient nutrient transfer. The role of imprinting specifically in the placenta has been difficult to test by the traditional means of knocking out genes in experimental organisms and studying the effects, mainly because most imprinted genes are also expressed in the fetus, where

they may have additional roles (see below). Nonetheless, knock-outs of several imprinted genes in mice do affect the growth, thickness and organization of the placental tissues interposed between mother and fetus<sup>6</sup> (Fig. 2, overleaf).

The direction of the effects supports the notion of competition — eliminating genes that are expressed from the paternal copy decreases the surface area for the exchange of nutrients; knocking out genes expressed from the maternal copy increases it. For example, removal of *Igf2* (the product of a paternally expressed gene) from the cells of the exchange barrier is enough to cause thickening of the barrier and decreased nutrient exchange<sup>9</sup>. A future challenge is to understand the impact of imprinting in other areas that may influence nutrient supply, such as fetal and maternal blood flow and the transport of nutrients themselves. So far, there are hints that imprinted genes might be involved in the development of the placental

blood vessels, and there are several imprinted genes that code for nutrient transporters (Fig. 2).

Another arena for the different interests of parental genomes to play out is the fetus, at the level of the demand for resources. Growth and cell proliferation impose demands on maternal provision. Thus, paternally inherited, demand-enhancing genes make babies grow, and increased fetal demand can be signalled back to the placenta, which can respond with increased supply<sup>10</sup>. Understanding such signalling systems between the fetus, the placenta and the mother will be important, particularly as there are situations in humans in which growth of the baby is compromised (Fig. 1; see below).

The connection between mother and fetus via the placenta, and then through suckling, is unique to mammalian reproduction. As imprinted genes have so far been identified only in placental mammalian species among vertebrates, it is possible that imprint-

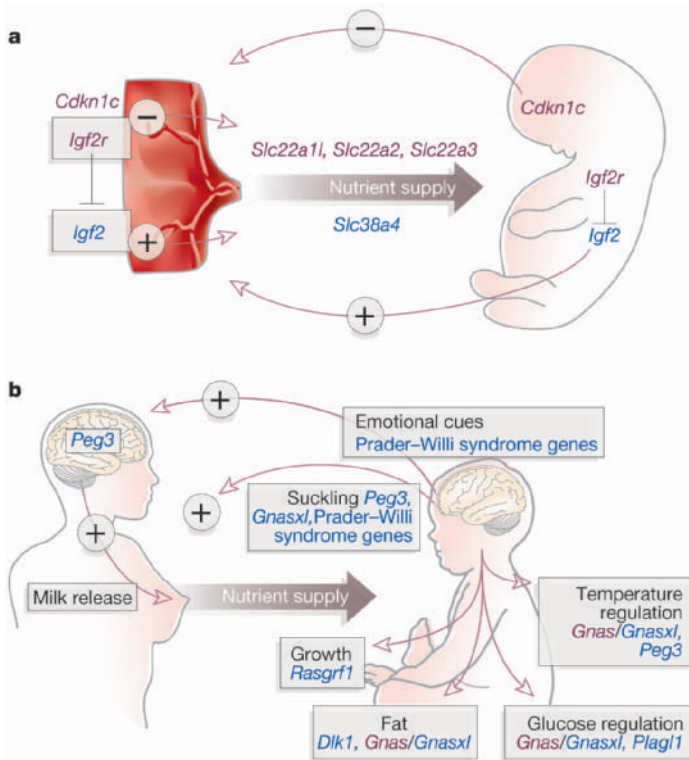


Figure 2 Effects of imprinted genes on resource acquisition by offspring<sup>6</sup>. Imprinted genes that are expressed from the maternally derived copy are in purple; those expressed from the paternally derived copy are in blue. a, Growth of the fetus — promoted by, for example, *Igf2*, a paternally expressed imprinted gene — may signal increased demand to the placenta. *Igf2* also increases the placenta’s nutrient-transport capacity<sup>9,10</sup>. Several nutrient-transporter-encoding genes (*Slc* genes) are also imprinted. Maternally expressed genes (such as *Igf2r* and *Cdkn1c*) may reduce nutrient supply or demand<sup>6</sup>. b, Imprinted genes might also control resource provision after birth, acting in the mother’s brain to regulate milk release, or in the infant to regulate nipple attachment, suckling and feeding behaviours, including emotional interactions with the mother. Within the infant, imprinted genes may also affect the allocation of acquired resources into growth, fat reserves and homeostatic mechanisms, such as glucose and temperature regulation. Most genes shown were discovered through experiments in mice, but might be common to humans.

ing coevolved with placentation, or itself drove the evolution of the placenta. A fundamental connection between imprinting and placentation is supported by the finding that erasing all genomic imprints results in catastrophic development of extra-embryonic tissues and the placenta in mice<sup>11,12</sup>. And in humans, a failure to set imprints in the female germline gives rise to a hydatidiform mole — a tumour-like mass resulting from uncontrolled growth of placental material<sup>13</sup>. So far, however, only a single imprinted gene, coding for the gene-transcription factor *ASCL2*, has been shown to be essential for forming a placenta, in mice<sup>14</sup>.

Can we make predictions about the strength of imprinting in different mammals? We might expect imprinting in species with a simple placenta, such as marsupials, to be weak, and not as widespread as in species with a more complex, longer-lived and functionally more important placenta. It remains to be seen whether this is true.

**Imprinting after birth**

Does imprinting matter after birth to the extent that it does *in utero*? There is every reason to believe that it does. For instance, one of the first human genetic diseases found to be caused by mutations in imprinted genes was Prader–Willi syndrome (PWS; Fig. 1). This is a complex childhood disorder that affects the nervous and hormonal systems and ultimately leads to excessive weight gain. It arises from the loss of activity of several imprinted genes, found on chromosome 15, that are usually expressed from the paternally inherited copy. Another reason for sus-

pecting that imprinting is still important after birth is that the epigenetic marks imprinted on genes in the male and female germ cells (Box 1) persist into adulthood, and many imprinted genes continue to be expressed from a single parental copy. Epimutations sustained during development may thus deregulate imprinted genes throughout life, as there seems to be no way to correct such changes — at least until the gene passes through the germline once again.

Birth is a traumatic process for mother and baby alike, requiring a host of physiological adaptations to meet the challenges of the postnatal environment and the need of the infant to take more responsibility for its own well-being. After birth, we must find our own sources of nutrition, first from the mother’s breast, later from supplemental or foraged foods (Fig. 2). We must learn to recognize when we are hungry and when sated. For the first time we need to regulate numerous metabolic processes, such as ensuring that blood sugar levels remain adequate to nourish the brain. Our bodies must make decisions about how much energy to devote to the demanding processes of growth and development, and how much to other essential functions, such as keeping ourselves warm. On top of this, we are subject to far greater influences from the environment and from competition with siblings (and possibly half-siblings).

This complexity makes it more difficult to predict what imprinting is doing after birth. But we might expect imprinted genes

to be most influential in situations in which investment in young comes at a direct cost to mothers and their ability to invest in current or future offspring, and where there may be competition within or between the offspring of unrelated fathers.

The obvious place to look first is suckling, while the infant is still nutritionally dependent on, and demands a great deal from, mum. Returning to our example above, PWS children are born profoundly listless, show little interest in feeding and suckle poorly for the first months of their lives; their voracious appetites and consequent obesity develop from weaning onwards. Moreover, the expression pattern of one imprinted gene with an apparently key role in neonatal adaptations — coding for the paternally expressed *XLas* protein — coincides quite remarkably with the centres in the brain that innervate the apparatus involved in suckling<sup>15</sup>.

It is unlikely that maternally expressed imprinted genes exist to prevent suckling, but the antagonism among imprinted genes may continue after birth. A striking example comes from mice in which the maternally expressed *Gnas* gene is knocked out. One of the processes *Gnas* is involved in is metabolism. It codes for a subunit of a G protein — a common type of molecular switch — that transduces signals from hormone receptors to an enzyme known as adenylate cyclase, which in turn promotes the production of the molecule cyclic AMP (cAMP). One effect is to stimulate heat production in fat tissue. If

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mice receive a mutant copy of this gene from mothers, they develop a depressed metabolic rate, increase their storage of lipid in fat tissues, and become relatively obese. Surprisingly, mice inheriting the mutation in the paternal copy have an elevated metabolic rate, reduce stored lipid and remain lean<sup>16</sup>.

These effects seem paradoxical, until we learn that the mutation also hits a paternally expressed gene in this complicated imprinted genetic region; this gene encodes a variant G-protein subunit that may attenuate cAMP signalling<sup>15</sup>. Why should imprinting have evolved to control metabolic rate? Maintaining body temperature in young mammals is costly, and it may be that selfish paternal genes have sought to invest less in heat production (and so more in growth) by free-riding on the heat production of littermates<sup>17</sup>.

Intriguingly, imprinted genes in the mothers themselves can intervene in this conflict. The *Peg3* gene, the paternally derived copy of which is expressed, dictates not only how well pups thrive, controlling their suckling and weight gain, but also how good mothers are at provisioning their offspring<sup>18</sup>. Female mice lacking *Peg3* put on fewer reserves during pregnancy and show poor maternal care and impaired milk release. Combining the *Peg3* deficit in both pups and mums is particularly devastating, raising the intriguing prospect of co-adaptation of this gene in its effects in mother and infant.

The extent to which imprinting controls postnatal physiology and metabolism in mammals remains to be fully explored, and it may be premature to expect a unifying explanation of its effects after birth. That its influence may be quite wide-ranging is suggested by the imprinting of such a central player as a G-protein subunit, and the resistance to numerous hormones caused by loss of the maternal copy of *GNAS* in humans (Fig. 1). Potent effects on the development of fat tissue and on pancreatic function are also associated, respectively, with the imprinted genes *Dlk1* (ref. 19) and *PLAGL1* (ref. 20), mutations in the latter being responsible for an inherited form of diabetes in humans. The imprinting of the gene encoding D3 — the enzyme that inactivates thyroid hormone — also points to a role for imprinting in controlling the activity of a potent developmental

and metabolic hormone, certainly *in utero*, but possibly also after birth<sup>21</sup>. Given the range of physiological effects, particularly those underlying common human diseases, this is an important area for future investigation.

### Perspectives

Imprinting is a genetic mechanism that regulates the demand, provision and use of resources in mammals. Its influence extends from the fetus (particularly in eutherian mammals), through the suckling period (in all mammals, perhaps including monotremes), to after weaning. At this stage, complex behaviours and social cognitive processes may be affected, particularly in higher primates<sup>22</sup>. For example, in both

humans and mice there seem to be imprinted genes on the X chromosome that regulate social or cognitive behaviours<sup>23</sup> (W. Davies *et al.*, personal communication). And children with Angelman's syndrome, which arises from the opposite

imprinting defects to those described in Prader–Willi syndrome, laugh and smile often and have a generally happy disposition — an indication, perhaps, that paternal genes may be exploiting emotional cues to increase the attention and resources the child receives from the mother<sup>24</sup>. Moreover, the paternally expressed *Peg3* gene affects the behaviour of the mother as well as fetal growth<sup>18</sup>. Once we recognize this common theme of resource regulation, we may be able to make sense of imprinting-associated disorders that otherwise seem to defy explanation.

The fact that many imprinted genes are expressed in the placenta, the fetus and the brain — both neonatal and adult — suggests that imprinting might accompany our life from fetus to baby to adult, and from child to parent. That maternal (and perhaps paternal) genes, and maternally and paternally inherited genes in offspring, deploy different strategies in this game is both fascinating and scary — fascinating because it provides unique insights into mammalian biology and reproduction, and scary because the conflicting strategies can cause disease.

This is particularly important because imprinting can be altered by both classical mutations and epimutations, which may be more common. Epimutations contribute to human disease<sup>25</sup>; how they arise is not well

understood, but one trigger is apparently the culture and manipulation of early embryos, as increased rates of imprinting disorders have been observed after assisted reproduction techniques, such as *in vitro* fertilization and intracytoplasmic sperm injection, in humans<sup>26</sup>.

Changes in imprinting might also explain why restricted growth of the fetus in the womb (intrauterine growth restriction) can be associated with an increased risk of cardiovascular disease, diabetes and mental defects later in life (the 'fetal programming' hypothesis of adult diseases<sup>27</sup>). It is not yet known how, but environmental influences during life in the womb might affect epigenetic marks, including perhaps those in imprinted genes, shifting resource regulation over the course of a lifetime<sup>28</sup>. ■

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