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Imprinted genes and the manipulation of parenting in mammals

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Abstract

Genomic imprinting refers to the parent-of-origin expression of genes, which originates from epigenetic events in the mammalian germline. The evolution of imprinting may reflect a conflict over resource allocation early in life, with silencing of paternal genes in offspring soliciting increased maternal provision and silencing of maternal genes limiting demands on the mother. Parental caregiving has been identified as an area of potential conflict, with several imprinted genes serendipitously found to directly influence the quality of maternal care. Recent systems biology approaches, based on single-cell RNA sequencing data, support a more deliberate relationship, which is reinforced by the finding that imprinted genes expressed in the offspring influence the quality of maternal caregiving. These bidirectional, reiterative relationships between parents and their offspring are critical both for short-term survival and for life-long wellbeing, with clear implications for human health.

[H1] Introduction

Genomic imprinting describes an epigenetic process present in most mammals¹ (and in some plants²), whereby certain genes become monoallelically expressed based on their parent of origin. The process of imprinting is developmentally determined, initiating during gametogenesis, and classically involves the epigenetic marking by differential DNA methylation of discrete regions of the genome in a parent-of-origin specific manner, although imprinting conferred solely by repressive histone modifications in gametes has also been described in rodents³. Upon fertilization, these inherited epigenetic marks are recognized and built on by further epigenetic processes, resulting in domains of maternally and paternally expressed genes, some of which span many megabases of the genome. For some imprinted genes, monoallelic expression is tissue restricted — for example, in the placenta; for other imprinted genes, monoallelic expression is only apparent early in life. Nonetheless, the initial gametic DNA methylation marks are maintained throughout the life of the organism except in the germline, where they are erased to establish the correct imprint for the next generation. The extent of imprinting within mammalian lineages seems to coincide with the degree of viviparity, the maturity of the young at birth and subsequent need for periods of parental care. To date, no imprinted gene has been identified in the egg-laying monotremes and only some genes are imprinted in marsupials, whereas over 200 protein-coding imprinted genes and imprinted non-coding RNAs have been reported in Eutherian mammals such as mice and humans^{4,5}, who undergo more extensive *in utero* development.

The existence of genomic imprinting raises a conundrum, because monoallelic gene expression seems to negate the benefits of diploidy⁶. Many theories proposed to explain imprinting focus on the fact that, due to *in utero* development, the major investment in offspring comes from the mother⁷. Essentially, a parent–offspring conflict emerges, because individual offspring are expected to maximize the investment they receive from parents, whereas parents will aim to equalize their investment across their reproductive lifespan⁸. Kinship ideas predict that this conflict will extend to the parental genomes in the offspring wherever there is an asymmetry of relatedness. This occurs starkly *in utero*, where the maternal genome of the offspring is guaranteed to share relatedness with other siblings, whereas there is no guaranteed paternal relatedness with siblings. This means that the maternal and paternal genomes within an individual have differential interests in relation to the level of maternal investment they receive and provide, and that imprinting evolved as a consequence of this intragenomic conflict. Imprinting is expected to act on genes that influence the quantity of resources allocated by the parents, with the paternal genome driving larger offspring and the maternal genome counter-balancing resource provision to offspring⁹. In support of these ideas, studies in mice where imprinted genes are knocked out or overexpressed have identified phenotypes involving fetal growth, placental development, behaviour and metabolism with, in many cases, antagonistic functions¹⁰. However, the idea that parental care is one of these resources over which there might be conflict has received less consideration.

Here, we review the influence of genomic imprinting on parenting behaviour. Firstly, the review will focus on the parent, starting with the early studies in mice that knocked out individual imprinted genes and identified deficits in maternal behaviour^{11,12}. We then cover recent evidence from unbiased systems biology approaches with predictive value^{13,14} that strengthen the arguments that the neuronal circuitry controlling parental care in the brain is a key area of action for imprinted genes. We next summarize experiments demonstrating that imprinted genes can act in the offspring, either via signalling from the fetal placenta^{15,16} or by affecting postnatal behaviour¹⁶⁻²⁰, to manipulate the quality of parental care. Finally, we highlight studies suggesting that changes in parental care and behaviour may be linked to abnormal imprinted gene expression in humans.

[H1] Parenting

Parenting is a sophisticated social behaviour directed towards the survival and optimal development of offspring. However, although high-quality parenting enhances the fitness and reproduction chances of offspring, it comes at the expense of the caregiving individual and reduces their likelihood of producing additional offspring²¹. Hence, although parenting is present across a broad spectrum of the animal kingdom, it is highly diverse with respect to the degree of care provided. Many animal species escape committing resources to their offspring and leave their eggs/offspring unattended after laying²². Others are known to attend to their eggs and minimally to the offspring once hatched. Mammals tend to their offspring intensely pre- and postnatally, and arguably display the highest degree of care (**Figure 1**). This variability in care is directly associated with the ability of the offspring

to care for itself upon birth/hatching, with high dependence associated with more adaptable offspring at maturity²³⁻²⁵.

There is also a paternal–maternal care bias, with a more balanced division of labour in non-mammals, whereas mammalian mothers principally, and often exclusively, invest in their offspring with such intensity that care can be maintained long after the young have reached adulthood in the form of herds and social groups²⁶. Although mammalian fathers naturally have the same motivation for the survival of their offspring as mothers, the quantity and consistency of their care varies from species to species, depending on the specific environment, including social group structure, opportunities and dependency of the offspring²⁷. This difference in parental investment may be due to the initial exclusive investment by mothers, who dedicate a large amount of resources to the offspring before they are born and continue to invest postnatally, for example, in the form of milk and nurture. Mothers are primed in advance of the birth by pregnancy hormones produced by the ovaries, pituitary and placenta²⁸. Additionally, internal fertilization means that only mothers can be certain of their maternity. Whatever the explanation, biparental care is reported in only 5–10% of mammalian species, which means that most mammalian fathers escape high parental investment²⁶. As outlined above, this disparity is one of the factors that could lead to a differential interest between the parental genomes, and so be a key battleground for imprinted gene action.

[H2] Neural circuitry of parenting

Parenting is made up of many different sub-behaviours, such as nursing and grooming, pup retrieval and nest building, and hence requires many distinct neural mechanisms. However, and of great interest to evolutionary biologists, the core circuitry for parenting (that is, the neural circuit necessary to prompt parental response upon exposure to offspring) is deeply conserved amongst Eutherian mammals and between the sexes, and centres on the medial preoptic area (MPOA) of the hypothalamus²⁹. Unsurprisingly, the MPOA is highly sensitive to the hormones associated with pregnancy and lactation^{30,31}, receiving input from the pituitary, and also expresses the receptors for progesterone, estrogen and prolactin^{32,33} (**Figure 2**). Recent studies in mice determined that a specific neuronal population within the MPOA that expresses *Gal* (which encodes the neuropeptide Galanin) is both necessary and sufficient for parental care. MPOA *Gal*-expressing neurons that also express *Th* (which encodes tyrosine hydroxylase), *Calcr* (which encodes calcitonin receptor) and/or *Brs3* (which encodes bombesin receptor subtype 3) are the most active during parenting in mothers, fathers and virgin female mice³⁴. Moreover, ablation of these neurons removes parenting behaviour³⁵, whereas optogenetic stimulation produces parenting behaviour, even in innately avoidant animals³⁶.

The *Gal*-expressing neurons of the MPOA do not act in isolation. From within the broader hypothalamus, they receive additional input from oxytocin and vasopressin neurons of the paraventricular nucleus (PVN) that mediate parental bonding³⁷⁻³⁹, and agouti-related protein (*Agrp*) neurons from the arcuate nucleus (ARC) that regulate feeding and inhibit parental behaviour⁴⁰. The MPOA also receives input from the major sensory regions of the brain and serotonergic input from

the dorsal raphe nucleus (DRN)⁴¹ and peptidergic input from the Edinger-Westphal nucleus⁴². The primary output of the MPOA is to the dopamine system and, in turn, the reward and motor circuitry required to perform the behaviour⁴³. There is also direct inhibitory activity on an innate avoidance circuit regulated by the medial amygdala⁴⁴. This circuitry has been confirmed and further delineated in relation to the specific *Gal*-expressing neurons of the MPOA using retroactive viral tracing methodology³⁶, and it is clear that these neurons act as a 'parenting hub', receiving input signals from a range of systems and coordinating the output to produce the repertoire of behaviours necessary for correct parental care⁴³. If parenting is a key site of action for imprinting, this predicts that imprinted genes will function within this 'parenting hub', and its associated input and output systems, to influence many different aspects of parenting behaviour.

[H2] Individual imprinted genes linked to parental care

In the late 1990s, two distinct imprinted genes were characterized in terms of their contribution to maternal care in the mouse (**Table 1**). Together these studies demonstrated that paternal loss of *Mest* (*Mesoderm-specific transcript*; also known as *Peg1*)¹¹ and *Peg3* (*Paternally expressed 3*)¹² in female mice resulted in catastrophic failure of maternal care. In both studies, the initial observation was that primiparous mothers had high levels of pup mortality, with approximately 10% survival rate. Further testing found that both *Mest* and *Peg3* mutant mothers displayed poor pup retrieval and nest building behaviour. Interestingly, *Mest* mutant females also failed to perform placentophagia¹¹, the natural process of cleaning the pups following birth by consuming the placenta and extraembryonic tissues. Although no neural mechanism has been established to explain the behavioural phenotype of *Mest* knockout mice, loss of *Peg3* expression was shown to reduce the number of oxytocin neurons in the PVN and supraoptic nucleus (SON)¹² by a third, possibly via the action of *Peg3* as a regulator of *Oxtr* (the gene encoding the oxytocin receptor) transcription⁴⁵.

Since these landmark studies, knockout models of three other brain-expressed imprinted genes have been investigated in terms of their maternal behaviour. Loss of *Dio3* (*Type 3 deiodinase*) expression resulted in poor pup retrieval behaviour by mothers and a general increase in aggression, possibly linked to low circulating levels of both oxytocin and arginine vasopressin⁴⁶. Extensive investigation of the role of *Calcr* in parenting identified its importance within the known circuitry. *Calcr* is expressed from the maternal allele in the mouse brain⁴⁷, and reduction of *Calcr* expression (or inactivation of *Calcr*⁺ neurons) induced deficits in maternal care and nurturing behaviour, whilst activation of *Calcr*⁺ neurons inhibited infanticide in virgin males⁴⁸. Interestingly, *Grb10* (which encodes Growth factor receptor-bound protein 10) is expressed from the paternal allele in the mouse brain, and a paternal knockout demonstrated a number of behavioural changes⁴⁹⁻⁵¹, but females showed no difference in pup retrieval or nest building⁵². A caveat to this study⁵² is that the comparison was made with maternal knockout mice rather than wild-type littermates; these do have metabolic and physiological phenotypes owing to the loss of *Grb10* expression in non-central nervous system (CNS) tissues, where it is expressed solely from the maternal allele. As a consequence of these

different findings, the idea that maternal care is altered by imprinted gene action in the mother has become established³³ and informs theories relating the evolution of genomic imprinting^{53,54}.

Although findings are reproducible, it is worth noting that there have been failed attempts to replicate the maternal care deficits seen in *Mest* and *Peg3* mutant females using different mutant models. Recent *Mest* deletion⁵⁵ and *Peg3* deletion⁵⁶ models recapitulated the growth retardation phenotypes but had no gross deficits in pup retrieval behaviour and, in the case of *Peg3*, normal circulating levels of oxytocin. Various ideas have been put forward to explain these discrepancies. The original studies were performed on 129/Sv (129) and the newer studies on C57Bl/6J (B6). Strain background can be a key contributing factor to differences in behaviour⁵⁷. Nevertheless, at least for the contribution of *Peg3* this seems unlikely, as the findings in the original model were essentially replicated on both the 129 and B6 background at a second institution⁵⁸ (**Table 1**). Targeting approaches differed between the models since in both original studies a LacZ cassette was inserted as part of the knockout construct, and the presence of this reporter itself has been shown to alter the function of sensory neurons⁵⁹. In addition to the presence of LacZ, the targeting strategies in the newer models led to subtle differences in molecular outcomes. In contrast to the original models, targeting of *Mest* in the newer models leaves the expression of *miR-335*, a microRNA cluster harboured within the *Mest* intronic regions, intact⁴⁵. It could be that loss of *miR-335* expression is the key factor underpinning the original observation of maternal care deficits, particularly as this microRNA has been shown to play a role in neuronal development⁶⁰. A similar idea holds true for the differences in maternal care between *Peg3* models, although here the opposite is a possibility. An antisense-*Peg3* (*Apeg3*) is transcribed from exon 9, and both *Peg3* and *Apeg3* are disrupted in the newer model, whereas the targeting of exons 5 and 6 in the original studies leaves *Apeg3* intact. Albeit slightly more convoluted, it is possible that continued expression of *Apeg3* in the absence of *Peg3* (which the antisense transcript is thought to regulate⁶¹) leads to changes in the oxytocin system and maternal care deficits.

[H2] The extent of imprinted gene expression in the parenting hub of the hypothalamus

To circumvent variability between knockout studies, and to address the question of whether genomic imprinting plays a role in regulating parental care more broadly, the latest studies have taken a systems-based approach and asked the question: where is imprinted gene expression enriched? The principle is that significant over-representation of imprinted genes as a group in the transcriptome of a system, organ or cell type implies convergence on a particular physiological function, something that is predicted when considering how imprinting is thought to have evolved⁶². The findings consistently identify the brain as having one of the highest proportions of imprinted gene expression, and the hypothalamus in particular^{13,63}. More recently, we have used this systems-based approach and focused specifically on the MPOA and *Gal+* 'parenting hub' circuitry detailed above⁴³ (**Figure 2**). Based on three independent single-cell RNA sequencing (scRNA-seq) datasets, 21 imprinted genes (1/6 of the genes analysed) were significantly over-represented in the *Gal+* neurons

of the parenting hub. Although imprinted status was not assessed directly in this study, those analysed were limited to genes previously shown to be monoallelically expressed in brain, and the highly expressed genes included those previously implicated in maternal care. To test the validity of the approach, we selected a gene not previously linked to maternal care, *Magel2* (*MAGE Family Member L2*). In addition to assessing maternal behaviour in *Magel2* mutant mothers, the analysis was extended to males (fathers) and virgin females, as the same neuronal circuitry is now known to control parental behaviour across the sexes and in experienced and inexperienced individuals¹⁴. Primiparous mothers, fathers and virgin females with paternal *Magel2* deletion all showed deficits in parenting performance and motivation, albeit not as catastrophically impaired as seen in the original *Mest* and *Peg3* mutant studies. Although there was a gradation in the deficits across groups (mothers least affected, then fathers and virgin females), a reduction in parental behaviour across all groups suggests a central neuronal deficit in the MPOA, rather than disruption to the priming effect of pregnancy hormones, and cellular analysis of the MPOA of *Magel2* mothers indicated a loss of Gal-expressing neurons that may underlie the behavioural deficits¹⁴.

[H2] Imprinted gene expression in the broader circuitry controlling parenting

These data strongly underline the importance of genomic imprinting to the MPOA parenting hub and parental care behaviour. Nonetheless, as outlined above, this hub receives input from, and sends signals to, several other brain regions (**Figure 2**). Abnormal imprinted gene expression in these regions could also functionally manifest as parental care deficits, a good example being *Peg3* and the loss of oxytocin neurons in the PVN. Consequently, the screen of expression enrichment in the *Gal+* neurons of the MPOA may not capture the full breadth of the contribution of imprinted genes to the neural control of parenting behaviour. Indeed, imprinted gene expression is also significantly over-represented in the transcriptomes of other key parenting brain regions, such as the PVN, the Tuberoinfundibular Dopamine (TIDA) in the ARC of the hypothalamus, and the serotonergic DRN¹³.

Outside of the brain, the pituitary gland, which provides the key hormonal signalling input to the maternal hypothalamus and mammary gland during pregnancy and lactation, is also central to the control of parental care⁶⁴⁻⁶⁶ and is a site of enrichment of imprinted gene expression^{13,67}. Imprinted gene expression is particularly strong during the development of the gland and in the stem cell compartment⁶⁷, but in the adult imprinted genes were found to cluster in the lactotrophs and gonadotrophs⁶⁷, with converging evidence for lactotroph enrichment from other studies¹³. The lactotrophs are the key prolactin-releasing cells of the pituitary, and production is controlled by a pituitary–hypothalamic feedback loop involving dopaminergic circuits, most notably the TIDA neurons, which arise from the hypothalamic ARC. Prolactin enters the brain via a transport system now known to be independent of prolactin receptors⁶⁸, stimulating the production of tyrosine hydroxylase and, in turn, dopamine. Dopamine is secreted from the TIDA neurons and acts on D2 dopamine receptors on the lactotrophs to suppress prolactin secretion. As outlined above, these TIDA neurons are also a site of imprinted gene over-representation, identified as one of several

hypothalamic neural subpopulations with a significant number of imprinted genes expressed¹³, and so this pituitary–hypothalamic loop that is critical to parental care and lactation also seems to be a key focus for genomic imprinting.

[H2] Is there intragenomic conflict?

Strikingly, all the examples presented above, where imprinted genes have been manipulated in mice, lead to decreased parental behaviour (for example, slower retrieval, poor nest building or infanticide). Importantly, most of those genes tested are normally paternally expressed only. However, loss of the one maternally expressed genes (*Calcr*) has similar effects, and there are currently no examples of maternally expressed genes whose loss-of-expression in the mother boosts her caregiving behaviour, as might be predicted given the antagonistic influences of oppositely imprinted genes⁶². This may be because it is much easier to disrupt a process than to improve it. A substantial number of non-imprinted genes have also been found to influence mothering, for which mutations nearly always impair the level of care¹⁵. It may be that loss of function of any one gene has a negative impact on a complex behavioural process such as parental care. Alternatively, it may be because laboratory experiments measure parental behaviour in the wrong social context. In the wild, female mice giving birth at the same time form a communal nest and contribute together to pup care, thermoregulation and nursing⁶⁹⁻⁷¹. Indeed, the combination of communal nesting in females, male-biased dispersal, and increased reproductive variance in males, means the natural social context of the mouse meets all the requirements for the predicted evolution of genomic imprinting in the adult brain⁷². Future experiments looking at the trade-off between own-parenting and communal care in mutant mouse dams carrying imprinted gene manipulations may reveal the different direction of effects of maternally and paternally expressed genes. Similarly, extending these studies to eutherian mammals with different social group-types may shed further light on the evolution of imprinted genes expressed in the parent.

[H1] Prenatal programming of maternal caregiving

Just as there is conflict between parents over resource allocation to their shared offspring, there is also potential for parent–offspring conflict. Whereas offspring benefit from higher parental investment, this investment can come at the cost of the parents' future reproductive potential⁸. Offspring are well known to influence their mother's metabolism through the production of placental hormones during pregnancy to ensure nutrients are adequately supplied for fetal growth⁷³. This function predicts that placental hormones or their receptors might be subject to genomic imprinting⁷⁴. Although imprinting of a placental lactogen in the new world mouse, *Peromyscus*, has been reported⁷⁵, there is no evidence that placental hormone-encoding genes or their receptors are directly imprinted in humans or laboratory mice. Rather, imprinted genes seem to function above the level of individual hormones as master regulators of placental endocrine lineage development, and thus indirectly influence the production of hormones⁷⁶. Consequently, if placental hormones act on the mother's brain to induce

changes in behaviour, this predicts that offspring can manipulate their mother's behaviour before they are even born.

Evidence that placental hormones might influence the behaviour of mothers primarily comes from studies in rodents focused on understanding the function of prolactin-like hormones⁷⁷. Prolactin is synthesized local to the brain by the pituitary, and many prolactin-like peptides are also synthesized by the rodent placenta including placental lactogens that bind and signal via the maternal prolactin receptor⁷⁸. In a rodent pregnancy, prolactin secretion is initially stimulated by mating⁷⁹ followed by twice daily surges until mid-gestation^{80,81}. From mid-gestation, pituitary prolactin is replaced first by placental lactogen I and then by placental lactogen II synthesized by the endocrine cells of the placenta. Hence, the maternal brain is exposed sequentially to high levels of prolactin locally and placental lactogen systemically for the duration of pregnancy. Prolactin-like hormones have multiple functions primarily ensuring a flow of nutrients across the placenta to the offspring during pregnancy and then postpartum, in the form of milk⁷³. There is compelling evidence that placental hormones also contribute to the programming of maternal behaviours, as recently reviewed⁷⁷. Briefly, infusion of prolactin or placental lactogen directly into the brain of non-pregnant rodents stimulates parenting behaviour, whereas ablation of the maternal prolactin receptor — either global heterozygous loss-of-expression or homozygous loss-of-expression restricted to the MPOA — results in deficits in maternal behaviour⁷⁷. Signalling via the maternal prolactin receptor, by either prolactin or placental lactogen, is therefore critically important in the programming of maternal behaviour, at least in rodents.

Placental hormones including prolactin-like hormones are initially synthesized by extraembryonic membranes that lie in contact with maternal uterine tissue^{82,83}. In some marsupials and all Eutherian mammals, a specialized organ, termed the chorioallantoic placenta, forms later in gestation with more direct and invasive contact with maternal tissue. This substantial organ supports the rapid growth of the fetus and the birth of relatively mature offspring. In rodents, the mature placenta is organized into a maternally derived decidua (formed by modification of the uterine endometrium at the implantation site) and two fetally derived compartments: the junctional zone and the labyrinthine zone⁸⁴. Placental hormones are synthesized primarily by cells within the junctional zone called spongiotrophoblast and five trophoblast giant cell lineages (parietal, spiral artery, channel, sinusoidal and canal) which are located throughout the placenta, and in direct contact with maternal blood (haemochorial). In contrast, the human placenta consists of multiple placental villi. Placental hormones including placental lactogen are synthesized by a continuous layer of multinucleated syncytiotrophoblast covering these villi bathed in maternal blood. This means that, in both rodents and humans, placental hormones are directly secreted into the maternal circulation.

Several imprinted genes have been experimentally demonstrated to regulate the number of endocrine cells in the mouse placenta, and influence hormone production⁷⁶. An example is the maternally expressed *Phlda2* (which encodes Pleckstrin homology-like domain family A member 2) gene. *Phlda2* is a fetal growth-restricting gene that constrains birth weight by restricting the number

of endocrine cells that develop in the placenta^{85,86}. Two-fold expression (modelling loss of imprinting) resulted in fewer endocrine cells and decreased expression of placental hormones. Wild-type mothers carrying these mutant offspring are exposed to low placental hormones during pregnancy and were found to be excessively focused on rebuilding nests at the expense of time spent on their pups and self-care¹⁵. These neglected offspring developed into anxious adults, with male offspring additionally exhibiting deficits in cognitive function, atypical social behaviour and mild depressive-like behaviour, all attributable to the adverse environment⁸⁷. By contrast, mothers exposed in pregnancy to higher levels of placental hormones (knockout of maternal *Phlda2* allele in offspring) increased their pup-directed nursing and grooming behaviours, and self-grooming at the expense of rebuilding nests¹⁵. Changes to the maternal hypothalamus and hippocampus present 4 days before delivery indicated prenatal programming of the behaviours validated by the maintenance of enhanced maternal behaviour when mutant pups were replaced by fully wild-type pups shortly after birth. The findings from this study support the idea that imprinted genes play a role in parent-offspring conflict⁷⁴. Specifically, silencing of the paternal allele of *Phlda2* by genomic imprinting is predicted to have boosted the production of placental hormones, extorting more resources from the mother in the form of enhanced caregiving. *Phlda2* is maternally expressed in Eutherians but not marsupials⁸⁸ consistent with their more intense maternal behaviour.

An example of a paternally imprinted gene that may function antagonistically to *Phlda2* is *Peg3*. Knockout of *Peg3* resulted in a smaller placenta with a decreased number of endocrine cells⁸⁹. Wild-type mothers carrying and caring for *Peg3* mutant pups exhibited enhanced novelty reactivity during pregnancy and were slower to sniff and retrieve their mutant pups¹⁶. Despite their wild-type status, these mouse mothers also exhibited anxiety-like behaviour which was not reported in the *Phlda2* model. Moreover, there was no change in grooming or nursing behaviour. The differences in maternal phenotype may be explained by differences in experimental approach, differences in placental endocrine lineages regulated by these genes or *Peg3*'s function in other processes known to be important for maternal behaviour, as discussed later. There are a number of other imprinted genes expressed in the placenta that regulate the size of the placental endocrine compartment, including maternally expressed *Cdkn1c*⁹⁰ and *Ascl2*^{91,92} (**Table 2**). These might be predicted to similarly influence the behaviours of mothers but have not yet been tested in this context. Imprinted genes can also function directly as fetally derived hormones, as has been shown for paternally expressed *Dlk1*⁹³, and have the capacity to regulate the production of hormones intrinsically within the placental endocrine cells as reported for the paternally expressed *Igf2* gene⁹⁴. In both these examples the primary target appears to be the maternal metabolism although this does not exclude a role in maternal behaviour.

The explicit demonstration that imprinted genes expressed in the offspring influence maternal behaviour in a reciprocal manner lends significant weight to the hypothesis that maternal caregiving is a resource that has been manipulated by genomic imprinting. Importantly, these findings may have relevance to human health. Lower levels of placental *PEG3* have been associated with prenatal

depression⁹⁵ (**Box 1**). Although human data on additional imprinted genes in the context of maternal mood disorders is lacking, there is a clear potential for other imprinted genes expressed in the placenta to influence maternal mood and the quality of parenting (**Box 2, Box 3**).

[H1] Postnatal programming of maternal caregiving

Once born, offspring have further opportunities to influence their mother's behaviour, including through sucking and ultrasonic vocalization.

[H2] Sucking

Pups suck to obtain milk. Sucking stimulates the milk ejection reflex, at least in part, by activating maternal oxytocin neurons, with disruption to oxytocin signalling impacting aspects of maternal behaviour⁹⁶. Imprinted genes expressed in the offspring that influence sucking therefore have potential to secure more nutrition in the form of milk and more caregiving from mothers. The most compelling evidence that imprinting functions to regulate sucking comes from studies on paternally expressed *Mage12*¹⁷. Defective sucking was determined by the absence of milk in the stomach of *Mage12* mutants, and through a specific test involving anaesthetised mothers where individual pups are allowed to latch and feed independently. Loss of expression of *MAGEL2* in humans is linked to the rare imprinting disorder Prader–Willi syndrome, where babies cannot suck properly (**Box 3**). *Peg3* knockout has also been associated with poor sucking, with mutant pups but not wild-type pups in mixed litters lacking milk in their stomach^{18,19}. *Gnasxl* is a third paternally expressed gene associated with sucking defects with mutant pups having little or no externally recognizable milk in their stomachs^{97,98}. The *Gnasxl* transcript encodes three proteins: XLas, XLN1 and ALEX. Mice carrying an inactivating point mutation specific to XLas sucked normally, suggesting sucking could be controlled by neural XLN1 and/or ALEX⁹⁹. Pups with elevated expression of the normally paternally expressed gene *Dlk1* (which encodes Delta-like homologue 1) failed to thrive and had lower milk content in their stomach potentially explained by poor sucking¹⁰⁰. However, this phenotype is the opposite to that predicted since this is a model of loss-of-imprinting rather than loss-of-expression. Studies on the maternally expressed *Grb10* allele provide evidence of a more purposeful relationship. Wild-type pups with *Grb10* loss-of-expression littermates gained more weight than wild-type pups in fully wild-type litters when raised by wild-type foster mothers⁵². This study indicates that the mutant pups drive increased availability of maternal milk, with all members of the litter benefitting. In this example, paternal silencing increased the provision of milk. Knockout of two other maternally expressed genes result in sucking deficits. However, *Cdkn1c* mutant pups have cleft palate^{101,102} and *Igf2r* mutant pups have difficulty in breathing, are cyanotic and unable to move effectively¹⁰³, both suggestive of a physical defect rather than a direct effect on sucking.

[H2] Ultrasonic vocalization

Pups can also solicit care by calling. Mouse pups begin vocalizing in the form of ultrasonic whistles and clicks shortly after birth, inducing maternal behaviours such as nest building, pup retrieval and nursing¹⁰⁴. Isolation of pups from their mothers elicits increases in ultrasonic vocalization to draw the mother's attention, which can be easily quantified. Two imprinted genes have been shown to influence isolation-induced ultrasonic vocalization: *Magel2*²⁰ and *Peg3*¹⁶. *Peg3* knockout pups called on average 40% less than wild-type pups during maternal separation¹⁶. Their wild-type mothers were slower to retrieve them, consistent with the idea that ultrasonic vocalization solicits retrieval behaviour. However, it is not possible to exclusively attribute slower retrieval to reduced ultrasonic vocalization due to the presence of placental endocrine insufficiency in this model⁸⁹. In the case of *Magel2*, knockout pups vocalized 50% less than their wild-type littermates. Moreover, when given a choice, mothers preferentially retrieved wild-type over *Magel2* mutant pups, suggesting a dynamic relationship. Studies on mouse models interrogating the function of genes associated with Prader–Willi syndrome and Angelman syndrome (**Box 3**) suggest the presence of at least one more paternally expressed gene influencing ultrasonic vocalization. Paternal inheritance of a chromosomal duplication spanning *Mkx3* to *Herc2* resulted in increased ultrasonic vocalization, with continuation of calling beyond the time at which wild-type pups normally cease¹⁰⁵. Interpreting this model is complicated by the number of gene changes with two-fold overexpression of *Necdin*, excess expression of *Snrpn*, 1.5-fold overexpression of three non-imprinted GABAA receptor subunit genes and *Herc2*, and no change in *Ube3a* and *Apt10a*. Nonetheless, taken together, these data can be interpreted to mean that the maternal silencing reduces ultrasonic vocalization. Pups maternally inheriting a large chromosomal deletion from *Ube3a* to *Gabrb3* also showed evidence of increased ultrasonic vocalization¹⁰⁶. This mutation results in loss-of-expression of *Ube3a* and *Apt10a* (which are not thought to be disrupted in the paternal duplication model) and reduced expression of *Gabrb3*. However, rat pups maternally inheriting a *Ube3a*-specific deletion emit significantly less ultrasonic vocalizations¹⁰⁷, the opposite phenotype to that observed on maternal deletion of *Ube3a* in mice¹⁰⁶.

[H1] Conclusion and future perspectives

Considerable evidence from existing studies suggests that genomic imprinting functions to manipulate the provision of care from the mother and the complementary behaviours from the infant to elicit such care. As we discuss, the pattern of effects generally fits with the most prominent theory of genomic imprinting evolution, namely intragenomic conflict between the parental genomes, that is, maternal caregiving is another resource that has been manipulated. For instance, the paternal silencing of genes in the fetal placenta functions to programme the maternal brain during pregnancy to increase provisioning after birth. Similarly, imprinting has acted on genes in the pup that affect the ability to suck and solicit maternal care, with a broad pattern of paternal silencing of genes leading to increased demand, and maternal silencing of genes restricting demand. Imprinted genes expressed in the adult that influence the provision of parental care are less straightforward to explain in the context of intragenomic conflict, but we may not be using the best models as most involve

loss-of-function rather than a change in gene dosage. Moreover, we may be measuring behaviour in the wrong ecological context. It is also important to stress that other ideas have been invoked to explain the evolution of imprinting¹⁰⁸, and some explicitly in response to the role of imprinted genes in the provision of maternal care^{18,53}. What is needed is a fuller picture of what imprinted genes are doing in the systems that contribute to the provision and solicitation of parental care.

Our ability to detect monoallelic gene expression in single cells¹⁰⁹ and to undertake allele-specific long-range differential DNA methylation sequencing¹¹⁰ will ultimately identify the full repertoire of imprinted genes across development and into adulthood. As additional candidate genes for parenting are identified, they will need to be systematically tested across a range of behaviours. For genes expressed in the adult, it will be important to include virgin females, parous females and males to fully assess the role of imprinting in parenting. For genes expressed in the offspring, it will be necessary to demonstrate an effect on the genetically wild-type mother, and to distinguish between prenatal and postnatal influences. Critical to the interpretation of these findings will be the inclusion of genetic models which manipulate gene dosage rather than simply knock out function. Currently most studies report deficits in behaviour. The most persuasive evidence for a purposeful phenomenon will come from studies reporting enhanced parenting with a change in gene dosage — increased dosage of a normally paternally expressed gene and decreased dosage of a normally maternally expressed gene.

Defining the function of imprinted genes in parenting has relevance beyond our understanding of mammalian evolution. There are a number of rare imprinting disorders which overtly have an impact on human health, and more subtle alterations in the expression of imprinted genes may contribute more widely to disease¹. Parenting is generally not examined when children are born with an imprinting disorder or low birth weight as the clinical focus is on the child. However, our understanding that changes in the expression of an imprinted gene in the offspring can influence the behaviour of the parent — both during pregnancy and postpartum — has important implications. Exposure to maternal depression, anxiety and poor quality parental care are all known to contribute to adverse health outcome for children. Consequently, children with imprinting disorders or born low birth weight as a consequence of a defect in imprinting may be doubly disadvantaged, carrying both the direct burden of their condition and a suboptimal child:parent dynamic. It would be pertinent to examine these relationships to establish the extent to which findings in mouse models carry through to human populations.

While changes in the expression of imprinted genes may manifest as disease in human populations, their epigenetic flexibility could be beneficial under certain criteria, providing a mechanism for phenotypic variability within short time frames. Some imprinted genes epigenetically respond to dietary adversity during *in utero* with persistent changes in allelic expression^{111,112}. This environmental responsiveness could be advantageous. For example, if maternal nutritional shortages acted on imprinted genes that regulate placenta endocrine lineage development, this could constrain placental hormone production limiting resources demanded by the fetus. Moreover,

as suggested by the study on *Phlda2*¹⁵, behaviourally dams would focus their attention more on survival (nest building) with the ability to switch back in subsequent pregnancies to more pup-focused behaviours. It remains to be seen to what extent imprinted genes in the placenta respond in this way. In conclusion, the involvement of imprinted genes in parenting behaviour is entirely consistent with the idea of conflict over resource allocation during evolution, with both positive and negative implications for modern-day mammals.

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Competing interests

The authors declare no competing interests.

Author contributions

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Table 1. Imprinted genes expressed in the parent shown or predicted to influence parenting behaviour

Gene	Normally expressed allele	Parenting phenotype	References
<i>Peg3</i> (KO); (1 st targeting studied on 129)	Paternal	129: increased latency to retrieve pups; increased latency to nest build; failure to consume membranes and placenta; decrease in oxytocin-expressing neurons	¹¹
<i>Peg3</i> (KO) (1 st targeting studied on 129 and B6)	Paternal	129: increased latency to sniff/approach the pups; no difference in pup retrieval; increased the latency to nest build; less licking/grooming and nursing of pups B6: no effect on latency to approach/sniff pups; increased latency to retrieve pups; longer latencies to	⁵⁸

		nest build; less licking/grooming and nursing of pups. B6 with fostered wild-type pups: less frequent licking/ grooming of pups; less overall contact with pups	
<i>Peg3</i> (KO) (2 nd targeting; B6)	Paternal	No effect on maternal behaviour or nest building; no difference in number of oxytocin-expressing neurons in the MPOA	56
<i>Peg1</i> (KO); (1 st targeting;129)	Paternal	increased latency to retrieve pups; increased latency to crouch over pups; increased time to retrieve all; increased latency to nest build;	12
<i>Peg1</i> (KO); (2 nd targeting; B6)	Paternal	No effect on maternal behaviour or nest building	55
<i>Dio3</i> (KO); (129:B6 hybrid)	Paternal	Increased latency and failure to retrieve pups; less time interacting with the pups or crouching; increased aggressive behaviour towards pups; abnormalities in oxytocin/vasopressin.	46
<i>Calcr</i> (ablation or activation of <i>Calcr</i> +ve neurons in MPOA; KO in MPOA)	Maternal (brain)	Ablation: pups scattered; increased latency to retrieve; poor nest quality. Activation: reduced infanticide by virgin males. Knockdown: minor increased latency to group pups; increased latency to retrieve and group pups in EPM.	113
<i>Magel2</i> (KO)	Paternal	Increased latency to retrieve pups (male, virgin female), increased latency to nest build and poorer nest quality (dam, male), less time spent interacting with pups (dam, male, virgin female).	14
<i>Asb4</i> ^a , <i>B3gnt2</i> , <i>Bag3</i> , <i>Blcap</i> ^b , <i>Ccdc40</i> , <i>Cdh15</i> , <i>Cdkn1c</i> ^a , <i>Ddc</i> , <i>H13</i> ^b , <i>Herc3</i> , <i>Klhdc10</i> , <i>Meg3</i> ^b , <i>Nap115</i> ^a , <i>Ndn</i> , <i>Nnat</i> ^b ,	Paternal and maternal	Predicted based on systems biology approaches	13,14,67

<i>Peg10, Rtl1, Th, Usp29, Zim1</i>			
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Table includes genes predicted to have a role on parenting based on unbiased systems biology approaches. 129, 129/Sv; B6, C57BL/6J; EPM, elevated plus maze; KO, knockout of the normally active allele; MPOA, medial preoptic area. ^aBoth brain and pituitary screens. ^bPituitary-specific.

Table 2. Imprinted genes expressed in offspring shown or predicted to influence parenting

Gene	Normally expressed allele	Placental endocrine phenotype	Pup phenotype	Wild-type dam mothering mutant phenotype	Refs
<i>Phlda2</i> (LOI)	Maternal	Lighter with loss of endocrine lineages	Growth restricted <i>in utero</i> ; no deficit in USVs or sucking.	No difference in sniffing or retrieval of pups by wild-type mothers, decreased pup-nurturing and self-nurturing; enhanced nest building.	15,85,86
<i>Phlda2</i> (KO)	“	Heavier with expansion of endocrine lineages	Growth restricted <i>in utero</i> ; no deficit in USVs or sucking noted	Decreased latency to sniff and retrieve pups by wild-type mothers, increased pup-nurturing and self-nurturing behaviours; poorer nest building	15,86
<i>Peg3</i> (KO); (1 st targeting)	Paternal	Lighter with loss of endocrine lineages (more severe in male)	Growth restricted <i>in utero</i> ; Reduction in number of USVs at P2; reduction in sucking	Delayed sniffing and retrieval of mutant pups by wild-type mothers at P2; wild-type mothers more anxious on P4	12,16,18,19
<i>Peg3</i> (KO) (2 nd targeting; B6)		Lighter	Growth restricted <i>in utero</i> ; No reduced sucking		56

<i>Magel2</i> (KO)	Paternal	Normal weight	Normal birth weight; Reduction in number of USVs at P8 (males more than females); decreased sucking.	Delayed retrieval of mutant versus control pups by wild-type dam at P8	17,20,114
<i>Gnasxl</i> (KO) XLN1 and ALEX)	Paternal	No endocrine phenotype reported	Normal birth weight; Poor sucking (inferred).	Not reported	97-99
<i>Dlk1</i> (LOI)	Paternal	Normal weight	Heavier at birth; Poor sucking (inferred).	Not reported	100
<i>Grb10</i> (KO)	Maternal	Heavier	Heavier at birth; Enhanced sucking	Not reported	52,115
<i>Cdkn1c</i> (KO)	Maternal	Heavier placenta with defects in endocrine lineages	Overgrowth <i>in utero</i> , normal birth weight; lack of suckling (physical defect – cleft palate)	Not reported	90,101,102,116
<i>Igf2r</i> (KO)	Maternal	Heavier; no defects in placental endocrine lineages reported	Born heavier; lack of sucking (physical defect?)	Not reported	103
<i>Igf2</i> (<i>TpbpaCre</i> KO)	Paternal	Loss of endocrine lineages (female only)	Growth restricted	Not reported	117
<i>Necdin</i> and <i>Snrpn</i> (LOI); no change in <i>Ube3a</i>	Paternal	No endocrine phenotype reported	Increased USVs at P7 and P14	Not reported	105
<i>Ube3a</i> and <i>Apt10a</i> (KO)	Maternal	No endocrine phenotype reported	No developmental defect; increased	Not reported	106

			USVs at P10 and 12		
<i>Ube3a</i> (KO; rat)	Maternal	No endocrine phenotype reported	Decreased USVs P8-12	Not reported	¹⁰⁷

Table including genes predicted to influence maternal behaviour. KO, knockout of the normally active allele; LOI, loss of imprinting/overexpression; P, postnatal day; USVs, ultrasonic vocalizations.

Figure 1. Overall maternal investment and the emergence of genomic imprinting in vertebrates. Genomic imprinting is a uniquely therian phenomena amongst vertebrates. Reptiles, amphibians, birds and the mammalian egg-laying monotremes have not shown monoallelic expression in the loci examined²², and as a consequence are assumed to have biallelic expression only. Marsupials and Eutheria diverged 160 million years ago (MYA) and both lineages have monoallelically expressed genes suggesting this epigenetic phenomenon evolved following the divergence of the therian ancestor from the monotremes (220 MYA). Marsupials have significantly fewer imprinted genes than Eutherians, with 23 imprinted genes validated thus far and modern estimates predicting around 60¹¹⁸. Eutherians on the other hand have been shown to have >200 genes showing monoallelic expression^{4,5} again suggesting that something in the evolution of therians selected for monoallelic expression and something in the evolution of eutherians increased this selection pressure over marsupials. Although there are some exceptions (such the maternal care shown by crocodilians), the majority of reptile species show abandonment behaviour of offspring, in which eggs are left following laying. Viviparity evolved in the therians and monotremes, marsupials and eutherians show a spectrum of increasing levels of maternal investment. Monotreme young develop *in utero* surrounded by a porous egg shell that absorbs maternal nutrients. Once young hatch, mothers provide offspring care including lactation and the protection of their young. Marsupials carry offspring for extremely short periods in the womb before producing relatively under-developed foetuses which self-navigate to the pouch (or mammary glands in pouchless ones). Within the pouch, the offspring are fed and kept thermoregulated by the mother who also stimulates urination and defecation for the whole of pouch life by licking the anal region of the young. Maternal care is most obvious at the time of weaning when the young continue to drink milk while beginning to eat vegetation. The mother has to first accept the re-entry of the pouch young and then constrict the pouch muscle to help keep retain it. In Eutherian mammals there is prolonged internal development of the young with invasive placentation and a level of maternal investment which is not matched by the other mammals. Despite longer gestation, Eutherian offspring are born at an earlier developmental stage compared to the marsupial young once they have left the pouch. Eutherian mothers (and sometimes fathers and alloparents) have to care for postnatal offspring in a less developed state than marsupials, demanding an increased parental concern and motivation. Hence,

within mammals, there is a convergence of the expansion of genomic imprinting, the level of maternal investment prenatally and the level of parental care-giving necessary to raise offspring to maturity.

Figure 2. Parenting neural circuitry and suspected imprinted gene action. A simplified parenting circuit as identified through lesion and pharmacological studies¹¹⁹ primarily in female rats and further validated by more recent work focusing on the MPOA(*Ga*) hub^{34,36}. By default, virginal mice and rats display avoidance or aggressive behaviour towards pups, which is mediated by chemical signals through the vomeronasal organ (VNO) feeding directly to the MEA. When rodents are primed to be parental (either through pregnancy hormones in the case of females or via cohabitation with pregnant females which leads to VNO inhibition in the case of males) the MPOA(*Ga*) circuitry takes prominence over the behavioural output and parental care behaviour is displayed. This circuitry is principally activated by the main olfactory epithelium (MOE) that feeds to the MPOA hub, which then proceeds to coordinate the major parental care responses of the mouse. Highlighted here is the classic output of this circuitry, into the dopaminergic regions of the brain, to promote parental motivation for riskier behaviours such as pup retrieval. Paternally expressed genes (in blue) and maternally expressed genes (in red) shown to be associated with parenting behaviour thus far; their suspected point of action in the circuit is principally through the MPOA hub or the PVN inputs into the hub but also via regulating hormonal levels within the animal.

Figure 3. Imprinted genes experimentally demonstrated to affect parenting. Imprinted genes have been shown to impact parenting via the parent and via the offspring providing two co-ordinated routes of manipulation of parental capacity. Parental care has been shown to be affected when disrupting imprinted genes influence in the dam, and in one case in the father too, in five imprinted genes, all of which have a negative impact on parenting when disrupted. Offspring-mediated influences on parental care have several routes and, for the most part, follow conflict theory style patterns in which the paternal genome has silenced care-suppressing genes to elicit increased maternal care provision and the maternal genome has silenced care-promoting genes to conserve maternal resources. Several of these genes (*Peg3*, *Magel2*) have mirrored effects in offspring-mediated care and parent-mediated care, suggesting some convergence of function.

Box 1. Clinical consequences: Low birth weight, maternal depression and language delays

Mental health research in pregnancy has been identified as an under-researched area of major clinical need¹²⁰ due to the number of affected women and the consequence for their children. Anxiety and depression are highly common during pregnancy, with around one in five women experiencing symptoms¹²¹. Exposed infants are more likely to be born preterm birth and low birth weight^{122,123}. Independent from low birth weight, poor maternal mental health has been linked to language delays at 1 year of age specifically in boys¹²⁴ with deficits in cognition, motor development, language, poor temperament, and both internalizing and externalizing problems emerging as children get older^{125,126}.

This may be a linear relationship, with susceptible women developing depression and anxiety in pregnancy and the exposure of the child to mood symptoms driving their detrimental outcomes. However, experimental studies on imprinted genes suggest an alternative scenario could occur in some instances, where both the mood symptoms and the child outcomes result from the same underlying pathological process, which is placental endocrine insufficiency. Evidence that this might be the case comes from studies on the imprinted *PEG3* gene and placental lactogen. Lower placental gene expression of *PEG3* and *CSH1/2* (which encodes placental lactogen) have been reported in pregnancies where mothers are diagnosed with depression or have responded to questionnaires identifying depressive symptoms⁹⁵. Lower levels of serum placental lactogen have been associated with higher symptoms of postnatal depression irrespective of prior mental health status in a separate study¹²⁷. Women with obesity in pregnancy have lower levels of placental lactogen^{127,128}, and obesity is also a major risk factor for depression¹²⁹. In this respect, it is interesting to note that imprinted genes expressed in the developing fetus are epigenetically responsive to environmental exposures. There are at least two validated examples of loss-of-imprinting occurring in response to dietary adversity in pregnancy (low-protein and high-fat diet) mediated by changes in epigenetic marks^{111,112}. Recent epigenome-wide placental DNA methylation studies link pre-pregnancy body mass index to differential DNA methylation in the placenta¹³⁰, albeit not at imprinted loci. Together, these findings suggest that obesity may contribute to maternal mood disorders and poor outcomes for children by disrupting imprinting in the placenta.

Box 2. Beckwith–Wiedemann and Silver–Russell syndrome

Beckwith–Wiedemann and Silver–Russell syndrome are rare imprinting disorders with essentially opposite growth phenotypes that are associated with genetic and epigenetic alterations at human chromosome 11p15¹³¹. While mutations in patients are complex and not all seem to involve the same set of genes, there are at least three maternally expressed imprinted genes in the region that function to regulate placental hormone production in mice (*CDKN1C*, *PHLDA2* and *ASCL2*)⁷⁶. If this function is conserved in the human placenta, some mothers carrying affected children may be exposed to abnormally high (Beckwith–Wiedemann syndrome) or abnormally low (Silver–Russell syndrome) levels of placental hormones. Findings from the *Phlda2* mouse model¹⁵ suggest that mothers of babies with Beckwith–Wiedemann syndrome, for whom loss-of-expression of *PHLDA2* is predicted (loss of methylation of the *KCNQ1OT1* promoter), might be protected against mood disorders. Conversely, mothers of offspring with Silver–Russell syndrome, with gain-in-expression of *PHLDA2*, would be predicted to be at higher risk, with potential difficulties in parenting. While very few cases of Silver–Russell syndrome involve *PHLDA2*, higher levels of this gene have been reported in the placenta for babies exhibiting growth restriction *in utero*¹³². This will be difficult to quantify as children diagnosed with imprinting disorders are likely to receive substantial medical attention and parents significant counselling, so the child:parent dynamic is far from normal. Low birth weight babies may

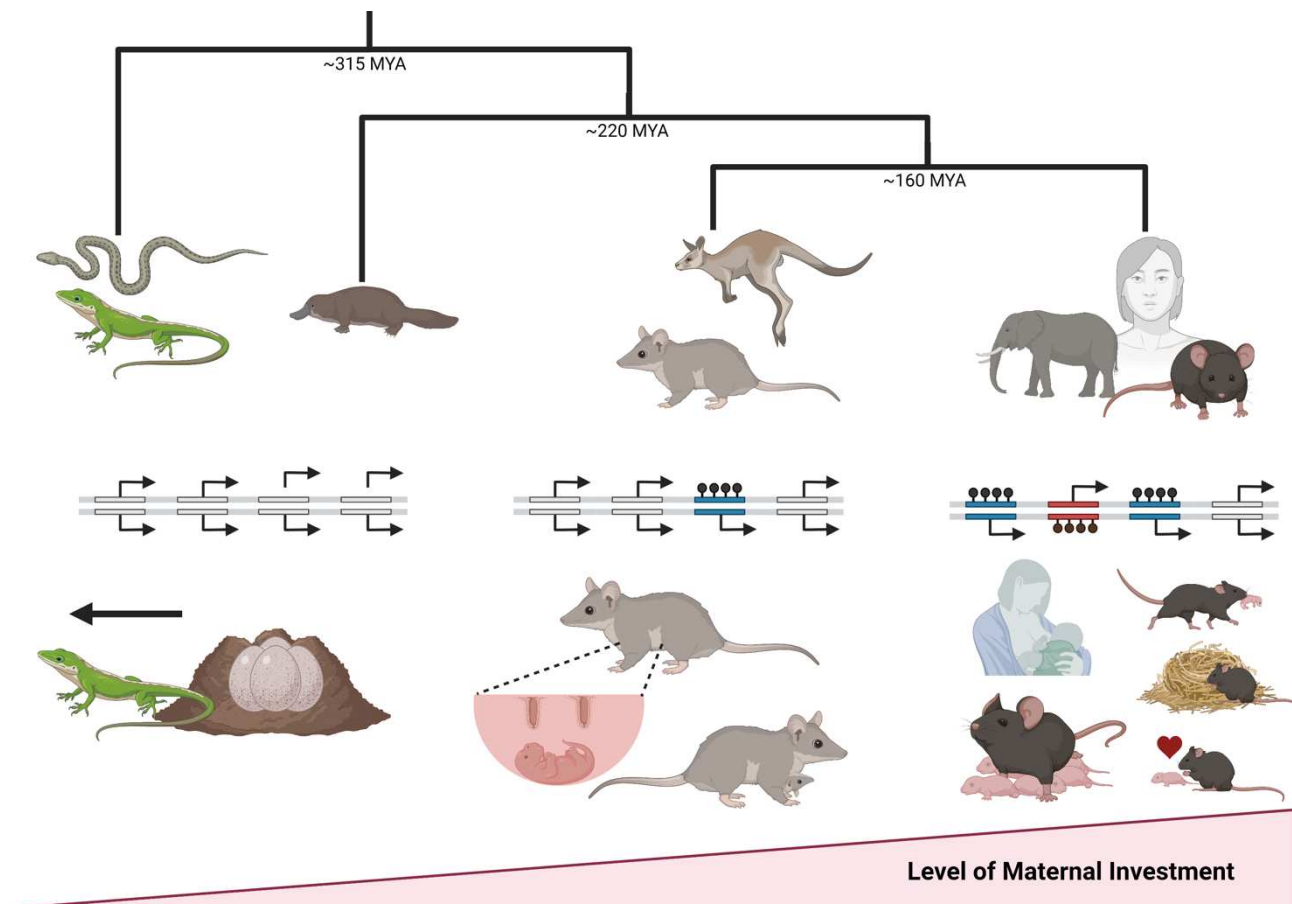
be similarly affected by these external factors. Nonetheless, findings from mouse models highlight the possibility that aberrant imprinting disrupts the reciprocal relationship between mother and child.

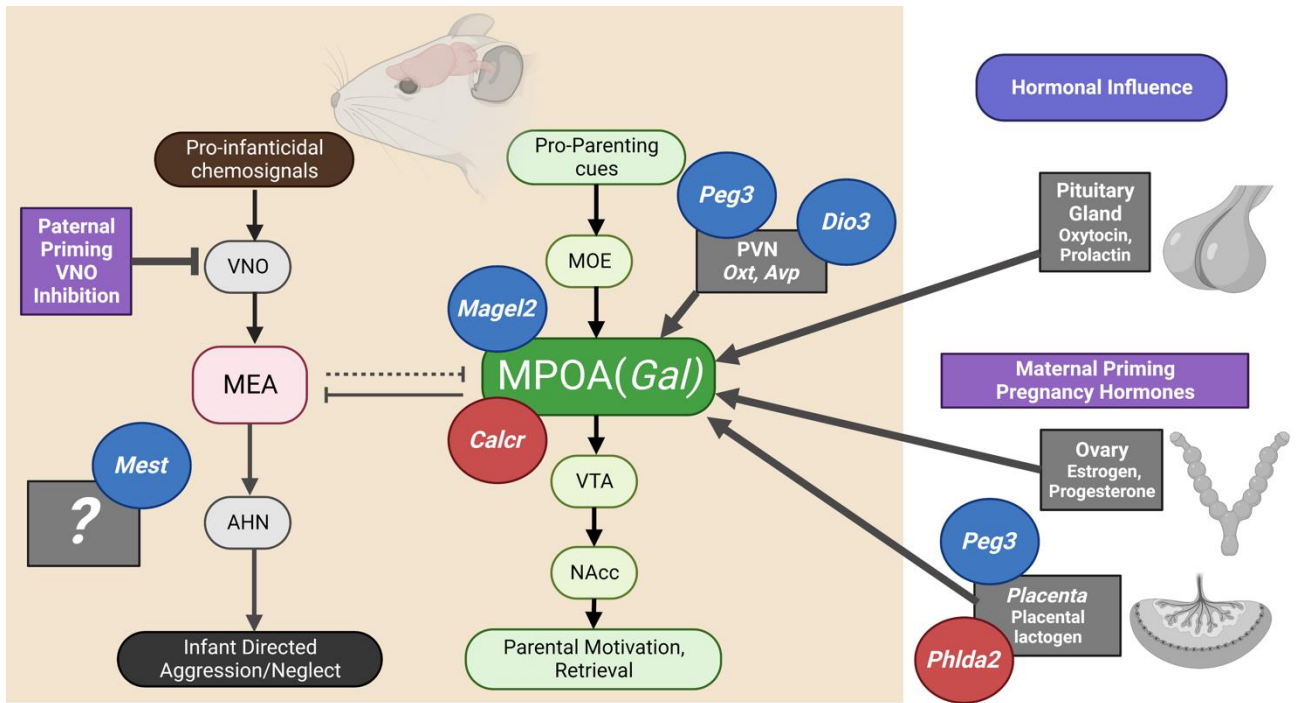
Box 3. Prader–Willi syndrome and Angelman syndrome

At the time of writing, there are no connections between imprinted genes known to mediate parental caregiving through action in the parent and clinical conditions where abnormal parental care is a feature. Whilst there are clinical conditions linked to some of these imprinted genes — most notably, *MAGEL2* and *UBE3A* to the imprinted gene neurodevelopmental disorders Prader–Willi and Angelman syndromes, respectively — parental care behaviour is irrelevant as the disorders lead to reproductive issues and/or are so severe that the patients are unlikely to have and raise their own children. More generally, genome-wide studies of parental caregiving are difficult for reasons related to the ability to robustly measure the phenotype itself and for ethical reasons, and to date none have been conducted. Conversely, there are studies of the solicitation of care from parents (or care givers) by individuals with Prader–Willi syndrome and Angelman syndrome. As these two disorders are caused by loss of paternal gene expression (Prader–Willi syndrome) and maternal gene expression (Angelman syndrome), any contrasting phenotypes are often discussed in the context of evolution of genomic imprinting and conflict theory¹³³. The most obvious illustration is the poor sucking seen in newborn individuals with Prader–Willi syndrome, which fits with classic predictions relating to the differential interests of parental genomes in terms of postnatal resource extraction, and how PEGs are expected to maximize this conflict. It has also been suggested that the distinct sleep behaviours seen in Prader–Willi syndrome (sleeping a lot) and Angelman syndrome (frequent night-waking) are related to the differential interests of the maternal and paternal genomes in extending the mothers nutritional resource provision and lactational amenorrhea¹³⁴. However, behavioural changes seen in both syndromes are not only centred on nutritional provision but also parental care and attention more generally. This was first shown in children with Angelman syndrome, whose happy disposition was shown to not be inappropriate and generalized, as previously thought, but was in fact directed to care givers^{135,136}, fitting with the idea that losing the ‘brake’ imposed by the maternally expressed genes leads to greater attention-seeking^{137,138}. More recent support for this idea comes from studies showing opposite responses by individuals with Angelman syndrome and Prader–Willi syndrome to infant song by parents, which is thought to be an ‘honest’ signal of care-giver attention¹³⁹. Specifically, children with Angelman syndrome showed relatively reduced relaxation in response to song (suggesting an increased demand for attention)¹⁴⁰, whereas those with Prader–Willi syndrome showed enhanced relaxation in response to music¹⁴¹.

ToC blurb

Genomic imprinting — the monoallelic expression of genes based on their parent of origin — may have evolved due to an intragenomic conflict between maternal and paternal genomes within an individual, with differential interests regarding the level of parental caregiving. Here, the authors review the influence of genomic imprinting on parenting behaviour in mammals, with a focus on studies in mice.





Parent-Mediated

Mest
Peg3
Dio3
Magel2
Calcr

Offspring-Mediated

Placental Hormones

Peg3
Phlda2
Cdkn1c
Ascl2

Ultrasonic Vocalisations

Peg3
Magel2
Ube3a

Sucking

Peg3
Magel2
Gnasxl
Dlk1
Grb10

