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Offspring genetic effects on maternal care

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ABSTRACT

Parental care is found widely across animal taxa and is manifest in a range of behaviours from basic provisioning in cockroaches to highly complex behaviours seen in mammals. The evolution of parental care is viewed as the outcome of an evolutionary cost/benefit trade-off between investing in current and future offspring, leading to the selection of traits in offspring that influence parental behaviour. Thus, level and quality of parental care are affected by both parental and offspring genetic differences that directly and indirectly influence parental care behaviour. While significant research effort has gone into understanding how parental genomes affect parental, and mostly maternal, behaviour, few studies have investigated how offspring genomes affect parental care. In this review, we bring together recent findings across different fields focussing on the mechanism and genetics of offspring effects on maternal care in mammals.

1. Introduction

Almost all traits are underpinned by complex interactions between an organism's genes and the environment in which they live. Breeding partners, family members and other conspecifics constitute a significant part of the environment in social animals including many mammals, birds, and insects (Frank, 2007; Wolf, 2003). Hence, a given behavioural trait in a focal individual will not only be influenced by their own genes (a direct genetic effect) but also by interactions with members of their social group. Because the behaviour of non-focal individuals is again dependent on their own genes, behavioural traits of a focal individual will also be indirectly influenced by genetic factors in their social partners (indirect genetic effects; Fig. 1A). In this review, we first outline concepts of parent-offspring interactions before reviewing the evidence for offspring genetic effects on maternal care. We will concentrate on mammals, particularly rodents and humans, as these species provide the greatest depth of data. The current understanding of the mechanisms by which indirect genetic effects influence maternal investment will be outlined, drawing on a wide range of literature including agricultural and biomedical research.

2. Parental care

Parental care can be defined as any phenotype displayed by a parent that evolved, and is currently maintained, due to its ability to enhance the fitness of offspring (Smiseth et al., 2012). Parental care has evolved independently multiple times across different taxa, including mammals, birds and insects (Klug and Bonsall, 2014). In many species, allocation of resources (energy, time) for parental care behaviour, known as parental investment, is essential for offspring survival, thus ensuring that parental genes are passed on to future generations. In most mammalian species the burden of parental investment falls disproportionately to the mother – estimates suggest that approximately 5–10% of mammalian species exhibit paternal care, for example the common marmoset, *Callithrix jacchus* (Stockley and Hobson, 2016; Woodroffe and Vincent, 1994), although this increases dramatically to 59% in socially monogamous species (Lukas and Clutton-Brock, 2013). A key cost to parents is resource provisioning before and often after birth. For example, in all mammals and some insects, milk let-down provides offspring with the full complement of nutrients, water and immune factors such as antibodies, at a considerable cost to mothers in terms of immediate energy and time expenditure, opportunity costs and increased predation risk (Cox and Hager, 2016; König et al., 1988; Williford et al., 2004). Mammalian mothers have evolved a range of maternal behaviours aimed to ensure offspring survival and subsequent reproductive success (Lynch and Possidente, 1978). In rodents, for example, mothers will anticipate parturition by preparing a nest to provide warmth (Carlier et al., 1982; Lynch and Possidente, 1978) and protect offspring from extreme

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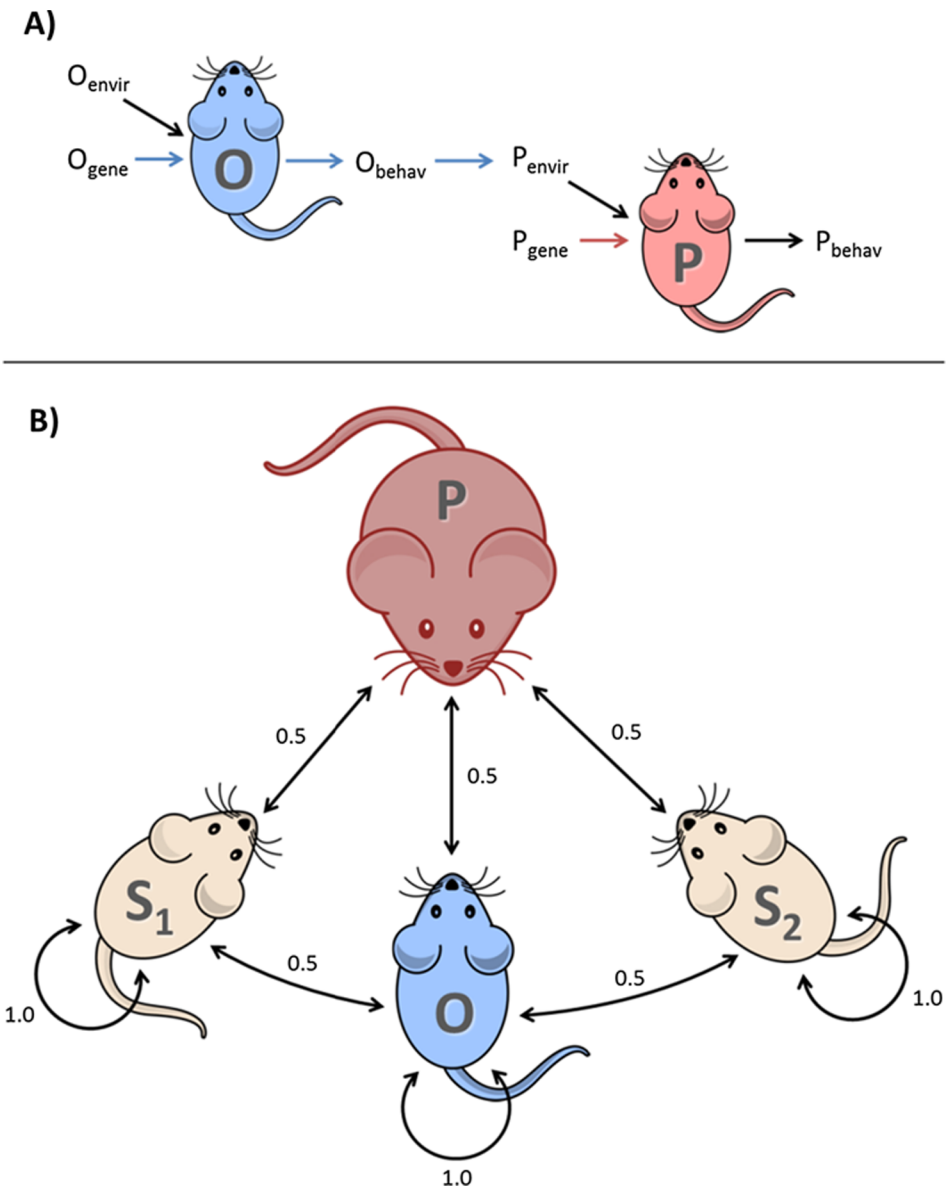

Fig. 1. Social behaviours such as parental investment in offspring depend on a range of complex, interacting genetic and environmental factors. (A) A focal individual such as a parent (P) will display behavioural traits (P_{behav}) which are influenced by both their environment (P_{envir}) and genotype (P_{gene}). Parent-offspring behavioural interactions form a large and significant part of the early postnatal environment in many species and as such the behaviour of offspring (O_{behav}) impacts P_{behav}. O_{behav} is, in turn, influenced by offspring genes and environment (O_{gene} and O_{envir} respectively). Hence, indirect genetic effects (blue arrows) and direct genetic effects (red arrow) are important influencers of behaviour. (B) Parent-offspring conflict theory predicts that parental resource investment and offspring solicitation behaviours are influenced by the fitness benefit to a focal individual (O), cost to a social partner such as a sibling (S_1 and S_2) or parent (P), and by their coefficient of relatedness (black arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

temperature fluctuations and predation (Lisk et al., 1969). Licking and grooming of offspring serves several functions including keeping pups clean as well as priming the developing nervous and endocrine systems for an appropriate stress response in later life (Champagne et al., 2008). Furthermore, the impact of impaired maternal licking/grooming behaviour in early postnatal life has been shown to induce structural and molecular changes in the offspring brain including epigenetic deficits in glucocorticoid gene promoter regions (Weaver et al., 2004), reduced dendritic spine complexity in the hippocampus (Champagne et al., 2008), and impaired dopaminergic development and reward processing (Pena et al., 2014). Differences in the amount of maternal licking/grooming behaviour have been associated with changes in methylation of cytosine-guanine (CpG) dinucleotides within specific gene promoters in the offspring brain. Specifically, female offspring born to low licking/grooming mothers have an increased proportion of CpG methylation in the promoter region of the estrogen receptor-α (*Esrα*) gene in the medial preoptic area of the hypothalamus, a key brain region in determining the maternal behavioural response to hormonal and pup-related stimuli, which was related to low transcription factor (Stat5) binding (Champagne et al., 2006).

3. Hormonal and neural control of maternal care

In most mammals, maternal care is initiated by hormonal changes experienced during pregnancy mediated centrally by the pituitary gland and peripherally by endocrine organs including the ovaries, adrenal gland and placenta (Bridges, 2015). In humans and non-human primates, however, the endocrine system appears to play a modulatory role since nulliparous adult females exhibit spontaneous maternal behaviours when presented with young (Bridges, 2015). For example, whilst endocrine signals such as prolactin and oxytocin (OT) stimulate the steroid-receptor rich medial preoptic area of the hypothalamus in the maternal brain to initiate and maintain maternal care behaviours, non-endocrine signals such as olfactory cues from pups concurrently stimulate upstream brain regions such as the olfactory bulb (Bridges, 2015; Numan, 1974). Moreover, lesions to the medial preoptic area lead to the abolition of maternal care behaviours in rats, whereas direct stimulation to the same area by estrogen, prolactin, dopamine, or OT induces such behaviours (Numan and Callahan, 1980). Estrogen, particularly in its most bioactive form as estradiol-17β, plays an important role in the initiation of maternal care through ESRα-mediated signalling

(Ribeiro et al., 2012), as evidenced by the onset maternal care behaviours in nulliparous rats following subcutaneous administration of estradiol benzoate (Siegel and Rosenblatt, 1975). Production of the steroid hormone progesterone is elevated throughout gestation which is thought to prime and sensitise the maternal brain to pup-related stimuli, as well as serving functions relating to lactogenesis (Bridges, 1984). OT is a key hormone which underpins and initiates maternal behaviours in mammals. Anticipation of parturition follows a sharp decrease in the concentration of the estrogen and progesterone produced during pregnancy, which induces production and insertion of OT receptors in the medial preoptic area to sensitise the maternal brain to the OT (Rilling and Young, 2014). In rats, nulliparous virgin females that would not normally engage in maternal behaviours with pups display nursing and nest-building behaviours following intracerebroventricular infusion of OT, as well as reduced latencies towards foster pups, consistent with the behaviour of parous females (Fahrbach et al., 1984). Furthermore, rats that show high levels of maternal care have been shown to have differential expression of the OT receptor in specific brain regions compared to those that show low levels of care. For example, Francis et al. (2000) show that mothers who engage in high levels of arched-back nursing have a significantly higher protein expression of the OT receptor in the central nucleus of the amygdala (Francis et al., 2000), a region known to control the fear and anxiety response and thought to underlie inhibition of pup aversion following parturition (Rilling and Young, 2014).

Maternal care has been shown to induce stable epigenetic alterations in genes relating to maternal care in offspring, which in turn affects their parental behaviour towards their own offspring. Champagne et al. (2006) show that low levels of licking/grooming behaviour induce increased promoter CpG methylation of *Esrα* in the medial preoptic area of female offspring, with concurrent decreased transcription factor binding in the promoter region and reduced *Esrα* expression (Champagne et al., 2006). Furthermore, expression of *Esrα* in the medial preoptic area directly correlated with levels of maternal care in later life. Chronic upregulation of the *Esrα* gene in neonatal rats can reverse the effects of low licking/grooming in offspring, leading to increased numbers of ESRα immunoreactive cells in the medial preoptic area and increased immunoreactivity of dopaminergic projections to the ventral tegmental area as a key region of the reward system. Furthermore, cross-fostering pups of low licking/grooming mothers to high licking/grooming mothers soon after birth reverses these epigenetic deficits. By contrast, crossing offspring from high licking/grooming to low licking/grooming mothers is sufficient to induce epigenetic deficits, suggesting that levels of maternal care induce molecular changes in the gene promoters of offspring which prime them for similar behaviours in later life (Champagne et al., 2006).

We have thus evidence that the presence of offspring is instrumental in triggering maternal behaviours and for the hormonal pathways involved. Research on offspring genetic effects then sought to identify which specific offspring traits are affecting maternal behaviour, and what their genetic basis is. Clearly, the complex behavioural interactions between parent and offspring are closely influenced by one another. In rodents, for example, mothers adapt their behaviour by providing a larger share of resources to pups that display conspicuous solicitation behaviours, such as emitting 40 kHz ultrasonic vocalizations (USVs; Shair, 2007). Indeed, offspring are predicted to concurrently adapt their begging behaviour in response to the amount of parental investment that is given to maximise their fitness through increased resource allocation (Kilner and Johnstone, 1997). These and earlier observations of parent-offspring interactions were instrumental in the development of theories of the evolution of parental care and specifically parental and offspring traits expressed during parent-offspring interactions as outlined in the following section.

4. Parent-offspring conflict

Our conceptual understanding of parental care in biology goes back to the earliest days of evolutionary biology. Darwin mused in 1871 that 'parental affections' are the root of all sociality and must have been gained through natural selection (Darwin, 1871). Over the years a large body of theoretical and empirical research established why and under what conditions we predict parental care to evolve and why some species exhibit care while others do not. A key contribution to our understanding of the evolution of parental care was made by Robert Trivers in 1974 who developed, based on Hamilton's earlier work on social evolution (Hamilton, 1964), the theory of parent-offspring conflict (Trivers, 1974). He observed that maternal behaviours are energetically expensive and ultimately reduce future fecundity; hence mothers will be selected to balance investment in current offspring with reduced future reproductive success. For offspring, by contrast, the cost of this reduction in future reproductive success of their parents has to be weighed by their relatedness to their future siblings. Offspring value a given amount of parental investment in themselves more highly than investment in their future siblings because offspring are more closely related to themselves than they are to any future siblings (Fig. 1B). Therefore, offspring favour a greater level of parental investment than parents, and the evolutionary conflict depends on the degree of difference between the two optima.

This concept can be extended to all family members: parents may disagree over how much each should invest in their offspring, and siblings may claim a larger than fair share during sibling competition (Parker et al., 2002). Again, we see that parental and offspring behaviours are very much interdependent, which are therefore predicted to co-evolve. In this scenario, genes expressed in parents will be selected for their effects on parental behaviour while genes expressed in offspring will be selected for their effects on influencing parental behaviour.

At the genetic level the predicted conflict between paternal and maternal genomes is thought to have led to the evolution of genomic imprinting (monoallelic gene expression). Genomic imprinting effects are good examples of offspring genetic effects on maternal care because of the impact on the quality of maternal care and level of resource provisioning (e.g. Li et al., 1999). Imprinted genes show monoallelic expression, with the expressed allele being dependent upon which parent it was inherited from, unlike most other genes, which are expressed biallelically (Fig. 2A). Therefore, some imprinted genes are expressed only from the maternally inherited allele or only from the paternally inherited allele, and as such these parent-of-origin effects mean offspring with the same genotype may have different phenotypes (Fig. 2B). In reality, expression may not be entirely binary but we may see a bias to expression of one allele over the other (Pinter et al., 2015; Wolf et al., 2008) or that full monoallelic expression is shown in only a subset of tissues. The evolution of monoallelic gene expression has been a puzzle because of the high cost of showing a deleterious allele to selection when no other functional copy is able to compensate for deleterious effects. In general, paternally expressed genes in offspring favour greater maternal investment than maternally expressed genes because of asymmetries of cost and benefits of parental investment in polygynous species (Ashbrook and Hager, 2013; Haig, 2010; John, 2017; Moore, 2012; Moore and Haig, 1991). In particular in polygynous species, a female's offspring may have different fathers and are thus more closely related through the maternal than the paternal line. Therefore, any fitness cost to mothers, such as increased provisioning and care, affect maternally derived genes more strongly than paternally derived genes, leading to the silencing of the maternal copy (i.e. paternal expression) of genes that increase resource transfer.

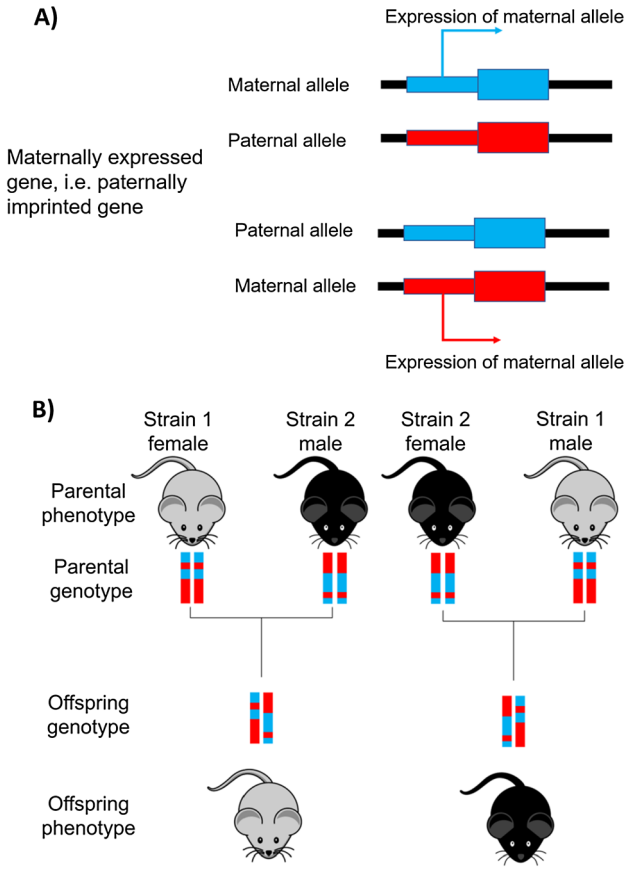

Fig. 2. Genomic imprinting can result in divergent phenotypes from the same genotype. (A) A paternally imprinted gene, i.e. maternally expressed. Here, two genetically identical heterozygotes are shown, but in the first the 'blue' allele is inherited from the mother (and therefore expressed) and in the second the 'red' allele is inherited from the mother (and therefore expressed). (B) Production of reciprocal heterozygotes to demonstrate parent-of-origin effects, such as genomic imprinting. Reciprocal heterozygotes are bred from two fully inbred parental strains (Strain 1 and Strain 2) to produce offspring with identical genotypes. If there is a difference in the phenotype of the reciprocal F1 offspring (in this hypothetical example coat colour showing a maternal expression pattern) it demonstrates a parent-of-origin effect, such as genomic imprinting. Modified from Ashbrook and Hager (2013).

5. Coadaptation between offspring and maternal traits

The genetics of the co-evolution of parental and offspring traits has been investigated using quantitative genetics models and in several empirical studies (Agrawal et al., 2001; Kölliker et al., 2005; Wolf and Brodie, 1998; Wolf and Hager, 2006). These studies focussed on the co-evolution of parental provisioning and offspring solicitation behaviours and predict a genetic correlation between the two (i.e. coadaptation), which has also been confirmed at the phenotypic level (e.g. Agrawal et al., 2001; Hager and Johnstone, 2003, 2005). Specifically, levels of provisioning and offspring solicitation have been shown to be both positively and negatively correlated, depending on the study system. While in mice and burying beetles a positive correlation was observed (Curley et al., 2004; Lock et al., 2004) a negative correlation was found in macaques (Maestripieri, 2004). A model proposed by Kölliker et al. (2005) showed that when selection acts on offspring solicitation the relationship between phenotypes should be positive, as solicitation is selected for but can only be supported by generously provisioning parents. However, when provisioning is the main target of selection the correlation is predicted to be negative to produce less costly solicitation while maintaining relatively high levels of provisioning.

The conceptual frameworks of parent-offspring or family conflicts and coadaptation between parental and offspring traits predict a genetic basis to variation in these traits. Following on from studies conducted at the purely phenotypic level, several studies have begun to unravel the genetic architecture of both parental care and offspring behaviours.

6. Indirect genetic effects

The genetic architecture of parent-offspring interactions has been investigated using standard genetic approaches such as linkage mapping, knock-out studies or variance partitioning approaches. Critical for our understanding of offspring effects on parental behaviour is that they are indirect effects. As with any other trait, variation seen between members of a population is principally due to genetic differences between individuals, the environments they experienced and the interaction between the two. Therefore, an individual's own genotype directly influences its phenotype. This is known as a direct genetic effect, which has been studied to elucidate the genetic basis for almost any type of phenotype in many different model systems (e.g. Hager et al., 2012; Weimar et al., 1982; Williams et al., 2016), but also specifically parental care behaviour (e.g. Bendesky et al., 2017; Peripato and Cheverud, 2002).

Indirect genetic effects occur when genes expressed in one individual alter the phenotype of an interacting individual (Fig. 1A). The concept of indirect genetic effects has long been known and described in plants, as well as domestic, wild and model organisms (Frank, 2007; Mutic and Wolf, 2007; Sakai and Suzuki, 1955). The best known indirect effects are maternal genetic effects, where the maternal genotype impacts on her offspring's phenotype (Dickerson, 1947; Falconer, 1965). Maternal genetic effects are distinguished from maternal environmental effects, which refer to shared environments (e.g. diet) between offspring and mothers that lead to a similarity between the two not caused by shared genetic material. Maternal genetic effects on offspring phenotypes have been investigated in the fields of agriculture (Cundiff, 1972; Dickerson, 1947; Ellen et al., 2014; Hanrahan, 1976; Willham, 1963, 1972; Wilson and Reale, 2006), evolutionary biology (Bailey et al., 2018; Bijma and Wade, 2008; Kirkpatrick and Lande, 1989; McGlothlin et al., 2010; Moore et al., 1997, 2002; Mousseau and Fox, 1998; Wolf and Cheverud, 2012; Wolf and Wade, 2009) and in humans (Koellinger and Harden, 2018; Kong et al., 2018). Indeed, for most mammals, conspecifics are part of the social environment so we expect such indirect genetic effects to be a common phenomenon in social animals.

The important point about indirect genetic effects is that they represent a genetic component of the environment, which can therefore respond to selection and evolve. Several studies have demonstrated, using a quantitative genetic approach, that the evolution of traits (including parental care) can be significantly altered in the presence of indirect genetic effects compared to a scenario without (Bijma and Wade, 2008; McGlothlin et al., 2010; Moore et al., 1997). Therefore, a recent research effort has been to identify genetic variants that indirectly modify behaviours, and particularly parental behaviours. To date, only a handful of studies have been able to demonstrate such indirect genetic effects (Ashbrook et al., 2015, 2017; Bailey and Hoskins, 2014; Baud et al., 2017, 2018; Biscarini et al., 2010; Mutic and Wolf, 2007).

6.1. Indirect genetic effects on maternal care

Parental care provides a very clear example of indirect genetic effects: parental care behaviour is influenced by parental genes (e.g. Peripato and Cheverud, 2002), and this behaviour alters offspring phenotypes (Ashbrook et al., 2015), which may affect offspring fitness. While indirect genetic effects in the form of maternal genetic effects have been well researched (e.g. Hager et al., 2008; Wolf and Cheverud, 2012), much less attention has been paid to indirect genetic effects

working in the reverse direction: phenotypes expressed in offspring which alter parental phenotypes. Clearly, offspring are not passive objects, receiving a parentally predetermined level of care and investment. Rather they are active participants, with a distinctive repertoire of behaviours regulated by their own genotype. One important example is offspring solicitation and begging behaviours, which are very common across the animal kingdom (Wright and Leonard, 2002), manifest in begging calls in birds, following mothers or other solicitation behaviours. Many studies have demonstrated that these behaviours have an impact on parental care levels and as such show that the assumptions of theoretical conflict and coadaptation models are parameterized realistically and model the dynamics of real biological systems (Kilner and Johnstone, 1997; Kölliker et al., 2005).

Indirect genetic effects on parental care have been studied in some detail by our group using experimental mouse populations and cross-fostering of litters combined with quantitative trait locus (QTL) analyses. In a series of experiments, Ashbrook and colleagues used genetically uniform (i.e. inbred) mice of the C57BL/6J (B6) strain and mice of the genetically diverse BXD genetic reference population (Peirce et al., 2004; Taylor, 1978; Taylor et al., 1999; Williams et al., 2001; Williams and Williams, 2017). Recombinant inbred mouse strains consist of a number of lines, each with a unique genotype that has been generated from a cross of two inbred strains (for BXD this is C57Bl/6J and DBA2/J). Therefore, within each BXD line, all animals are genetically identical and represent one constant genotype. However, the entire BXD population, consisting of over 150 extant lines now, represents a genetically diverse and defined population (Williams and Williams, 2017). It is thus possible to experimentally generate mouse families in which the maternal or the offspring genotype varies, while the other part remains constant across a given experiment, for example through cross-fostering genetically variable offspring to genetically uniform B6 mothers. This enabled us to map variation in maternal phenotype (such as maternal provisioning behaviour) as a function of offspring genotype and thus to show that offspring genotype affects maternal behaviour through indirect genetic effects (Ashbrook et al., 2015, 2017). Because differences in maternal behaviour cannot be due to genetic differences among mothers (but may be due to non-genetic differences between mothers, which can be statistically controlled for), one can identify regions in the offspring genome at which genetic variation impacts on maternal behaviours. Ashbrook et al. (2015) identified a locus on offspring chromosome 7 that affected maternal nest-building activity at an early postnatal day (PD6). B6 mothers that fostered BXD pups carrying the D2 allele at this locus had an increased trait value for nest-building activity, suggesting that offspring genotype indirectly influences a specific maternal behaviour. In addition, B6 mothers who fostered BXD pups carrying the D2 allele of a locus on distal chromosome 5 displayed increased levels of maternal behaviour at a later postnatal day (PD14). Indeed, maternal provisioning and offspring solicitation were positively correlated showing that indirect offspring effects do impact on maternal behaviours (Ashbrook et al., 2015).

Following on from this study, the authors used a split litter design in a new experimental population to identify candidate genes that play a role in indirect genetic effects on sibling and maternal behaviours (Ashbrook et al., 2017). Maternal and offspring behaviours were recorded in families comprising of C57BL/6J mothers and mixed litters, consisting of half her own pups and the remaining half of BXD mice. Several loci were found to indirectly affect maternal suckling behaviour, and these genomic regions were found to contain several candidate genes which have previously been linked to brain development and behaviour. For example, genetic differences on chromosome 10 between 97.112 and 103.025 Mb were shown to indirectly affect sibling sucking and maternal suckling behaviours. Candidate genes within this region included *Dusp6* (encoding a protein phosphatase important for early development) and *Cep290* (encoding a centrosomal protein), mutations in which lead to reduced postnatal weight gain and sensory impairments (Ashbrook et al., 2017). Using a variance partitioning type analysis, it was found that ~60% of the variation in maternal suckling of the pups was due to differences in offspring genotype. Table 1 details the candidate genes identified by Ashbrook et al. (2017) with relevance to mammalian (neuro)development and offspring solicitation behaviours.

In rats, the effect of offspring solicitation has been investigated by Brunelli et al. using two lines of rats that were selected for either high or low levels of pup USVs on postnatal day 10 (Brunelli et al., 2015). A cross-fostering experiment demonstrated that the postnatal maternal environment did not have an effect on offspring USV solicitation behaviour, suggesting that variation in these behaviours is largely genetically-determined. Interestingly, mothers with low-USV pups spent significantly longer engaged in arched-back nursing and licking/grooming compared to mothers of high-USV pups during the first 6 days of lactation (Brunelli et al., 2015). A similar correlation was seen by Ashbrook et al. (2015) in mice using a whole litter cross-fostering experiment: BXD strains in which offspring had high levels of solicitation behaviour (compared to other genotypes) showed correspondingly low levels of maternal provisioning, whereas BXD strains in which offspring showed lower levels of solicitation have biological mothers with high maternal provisioning (Fig. 3). These two findings suggest that coadaptation between mothers and offspring may occur during the production of inbred lines, manifest in those genotypes that successfully overcome the dip in reproductive performance associated with inbreeding.

6.2. Mechanisms of indirect genetic effects on maternal care

6.2.1. Prenatal effects

Offspring effects on maternal investment and postnatal behaviour begin *in utero*. The placenta is vital for the development of offspring in eutherian mammals (John and Surani, 2000) by regulating transfer of nutrients from mother to offspring (Constância et al., 2002), which in turn increases maternal food intake (Newbern and Freemark, 2011) and also primes the maternal brain for parenting behaviour (Bridges et al., 1990, 1997). Hormones are produced from the offspring-derived placenta and as such make it a key site for potential indirect genetic effects and maternal-offspring conflict (Haig, 1993, 1996; John, 2017). An interesting example of this is the ability of the imprinted gene *Phlda2* to influence maternal behaviour due to *Phlda2* expression in the offspring-derived placenta (Tunster et al., 2016). Tunster et al. (2016) found that *Phlda2* is important for expansion of the spongiotrophoblast lineage but not other placental cell types. Spongiotrophoblast cells express a number of placental lactogens (*Prls*) and pregnancy specific glycoproteins (*Psgs*), both of which induce changes in the mother required for pregnancy (John, 2013; Simmons et al., 2008; Tunster et al., 2016). Several of these *Prls* and *Psgs* were elevated in expression in *Phlda2* knockouts but were reduced with biallelic *Phlda2* expression (rather than the normal, imprinted, monoallelic expression; Tunster et al., 2016). Therefore, we have a clear indirect genetic effect: altered *Phlda2* gene expression in the offspring (offspring genotype), affects the spongiotrophoblast population (offspring phenotype), which in turn alters the expression of hormones acting on the maternal system (maternal phenotype). This study used embryo transfer to remove the confounding correlation between offspring and maternal genotype. More recently, in a follow-up study, offspring *Phlda2* was shown to directly regulate gene expression in the hippocampus and hypothalamus of the mother (Creeth et al., 2018). The authors could also demonstrate behavioural consequences, the step missing in their previous work, and that it was not a simple case of increased or decreased maternal care, but rather specific aspects of maternal care that were altered. The final step, in our opinion, would be to confirm these behavioural changes in response to natural variation in *Phlda2* expression (e.g. using the BXD population).

Another imprinted gene, *paternally-expressed gene 3* (*Peg3),* may represent both epistasis amongst-genomes and an indirect genetic effect

Table 1
Candidate genes for direct genetic effects and indirect genetic effects on maternal care and sibling phenotype in mice. Candidate genes were identified by a QTL mapping analysis with a focus on those coding for proteins with functions relating to mammalian development. Data from Ashbrook et al. (2017).

Chromosomal position (Mb)	Direct genetic effect	Indirect genetic effect	Candidate gene	Gene/protein function
Chromosome 2, 73.310–77.355	Offspring solicitation on postnatal day 14	Maternal suckling	*Chn1*	Involved in axonal and dendritic outgrowth and guidance. *Chn1* knockout causes impaired spinal interneuron development, manifesting in an abnormal hopping gait in mice (Borgius et al., 2014). Knockouts also show impaired electrophysiological control of the central pattern generator (a neuronal network essential for muscular contraction) and so animals show impaired hind limb locomotion (Wegmeyer et al., 2007). In humans, heterozygous missense mutations in the *CHN1* gene have been shown to cause Duane's retraction syndrome, a congenital eye movement disorder (Miyake et al., 2008; Whitman and Engle, 2017)
			Atf2	Neuronal transcription factor, with CNS expression highest in cortical neurons (Zhang et al., 2014). Chronic stress increases activation of ATF2, which is reversed by protracted antidepressant treatment (Laifenfeld et al., 2003). Atf2 has also been shown to regulate the expression of the pro-inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α in mice (Reimold et al., 2001)
			Nfe2l2 (Nrf2)	A transcription factor which regulates cellular responses to oxidative stress and inflammation. *Nrf2* has a critical role in adipogenesis, as evidenced by a reduction in white adipose tissue in global or adipocyte-specific *Nrf2*-knockout mice (Xue et al., 2013). Reduced NRF2 activity in humans has been associated with several neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis, highlighting the anti-inflammatory role of NRF2 in the central nervous system (Sandberg et al., 2014)
Chromosome 4, 10.826–13.031	Offspring sucking	Maternal suckling, sibling activity, suckling behaviour on postnatal day 6	*Dpy19l4*	A multi-transmembrane protein highly expressed in mouse embryonic cortical glutamatergic neurons. Knockdown of similar family members impairs both neuronal migration (Watanabe et al., 2011) and neurite outgrowth in the developing mouse cortex (Watanabe et al., 2016)
			Rbm35a (Esrp1)	Regulates alternative splicing in epithelial cells important for a range of epithelial-specific processes during mammalian development. For example, ablation of *Rbm35a* causes cleft palate which may affect offspring suckling ability and impairs epidermal skin barrier formation (Bebee et al., 2015)
Chromosome 10, 97.112–103.025	Offspring sucking	Sibling sucking, maternal suckling	*Dusp6*	A protein phosphatase involved in regulation of several metabolic pathways as well as mammalian development. *Dusp6* mutations in mice lead to skeletal dwarfism, congenital hypogonadism, and hearing loss (Li et al., 2007)
			Cep290	A centrosomal protein important for sensory stimuli processing including vision and olfaction (Chang et al., 2006). Mutations in *Cep290* lead to a range of abnormalities associated with ciliopathies including vision loss and retinal pathologies, hydrocephalus, cystic kidneys and associated renal pathology (Rachel et al., 2015)
Chromosome 15, 3.229–7.273	Offspring sucking	Maternal suckling and activity, sibling sucking on postnatal day 14	*Ghr*	A member of the type I cytokine receptor family (growth hormone receptor) important for growth hormone signalling. Mutations lead to growth hormone insensitivity syndrome, impaired response to the feeding-related hormone ghrelin, increased risk for obesity and hypolipidemia in mice (Egecioglu et al., 2006)
			Sepp1	Selenoprotein expressed in the liver and contains the majority of plasma selenium. Deletions lead to neurological dysfunction, weight loss, deficits in motor coordination and reduced fertility in mice (Hill et al., 2003). In addition, *Sepp1-/-* mice display reduced rearing and grooming behaviours (Raman et al., 2012)

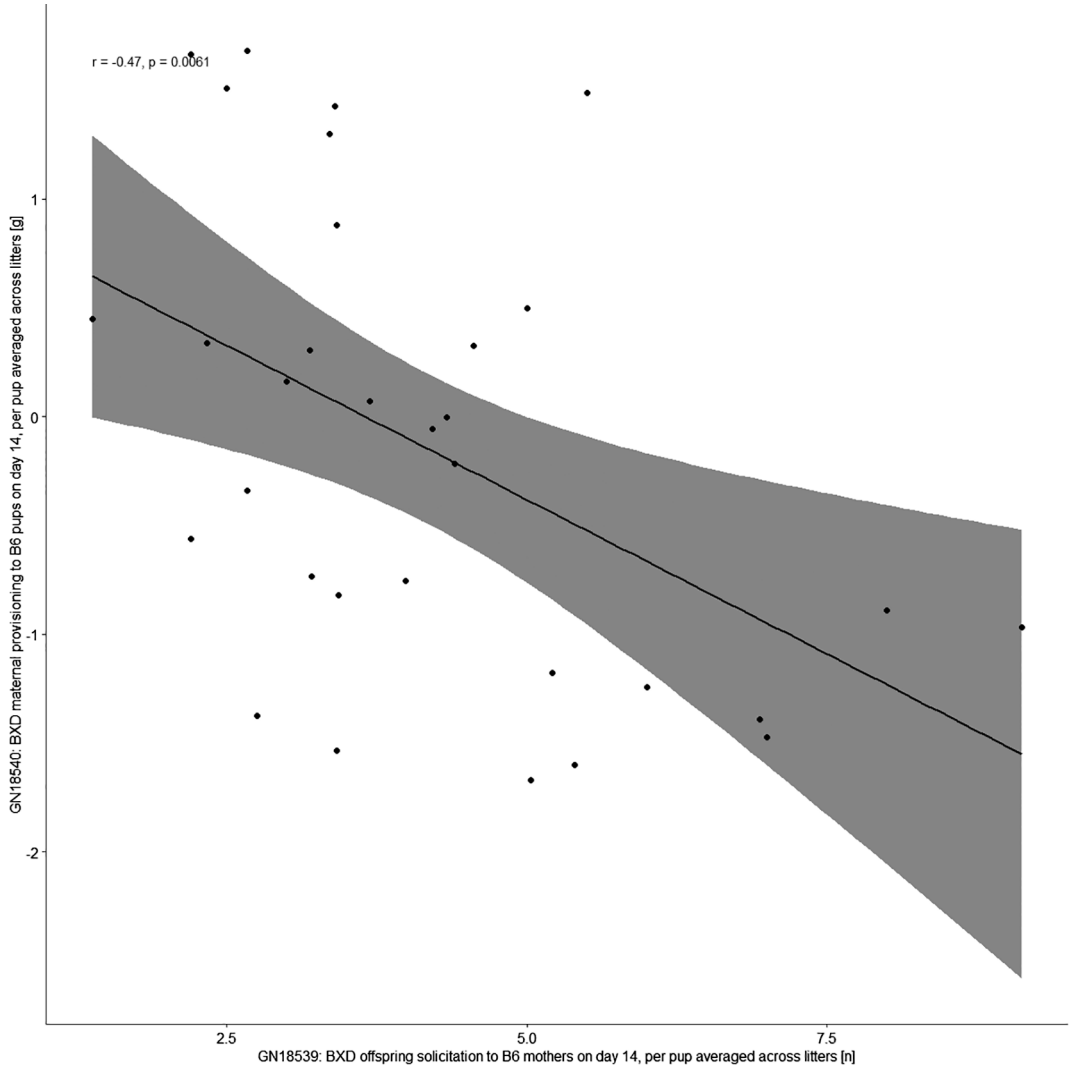

Fig. 3. Mapping of an indirect genetic effect modifying maternal behaviour. (A) Experimental design of a split litter cross-fostering design using the BXD recombinant inbred population. Half a litter of genetically variable BXD pups and half a litter of genetically uniform B6 pups were fostered to genetically uniform B6 mothers to determine the effect of BXD offspring genotype on the phenotype of B6 mothers and of B6 foster siblings (offspring indirect genetic effects and sibling indirect genetic effects, respectively). (B) Quantitative trait loci (QTL) map produced using GeneNetwork.org. The phenotype mapped was the amount of maternal care genetically uniform B6 foster-pups received from genetically uniform B6 foster-mothers as a function of the genotype of genetically varied BXD foster-pups. Traits were winsorized (Shete et al., 2004) and mapped using the 2017 updated genotype markers for the BXD population. The blue line represents the genome scan, showing the likelihood ratio statistic (LRS) associated with each marker across the 19 autosomal and the X chromosome. The top, pink, line marks genome-wide significance, the lower, grey, line the suggestive significance threshold. The green or red lines show the additive coefficient, with green showing that the DBA/2J alleles increase trait values and red that the C57BL/6J alleles increase trait values. The green axis on the right shows by how much the respective alleles increase trait values. Data from Ashbrook et al. (2017) remapped using updated tools on GeneNetwork (http://www.genenetwork.org; GeneNetwork ID 18787).

(Curley et al., 2004; Li et al., 1999). Curley and colleagues studied a *Peg3* mutant which resulted in no expression of *Peg3* in those mice carrying the mutation. An indirect genetic effect of offspring genotype on maternal phenotype was seen in wildtype mothers carrying *Peg3* mutant offspring; the mothers gained less weight during the last week of pregnancy compared to mothers carrying wildtype offspring. An indirect genetic effect of sibling genotype was also shown, as *Peg3* mutant offspring in a mixed litter with wildtype siblings had a lower weight on postnatal day 28 than *Peg3* mutants raised in a *Peg3* mutant only litter. By contrast, wildtype offspring raised with *Peg3* mutant siblings showed greater weight on day 28 than wildtype offspring from all wildtype litters.

It is not just through the placenta that offspring are able to influence their mothers *in utero*. An elegant study by Cleaton et al. (2016) showed that DLK1 protein levels rise during late pregnancy, but that knockout of *Dlk1* in the mother did not change its expression during late pregnancy, demonstrating that circulating DLK1 comes from the embryonic genome. They then used conditional knockouts to show that DLK1 came directly from the embryo, and is not produced in the placenta. This reduced level of circulating DLK1 in the mother altered maternal lipid metabolism during pregnancy (Cleaton et al., 2016), which in turn is likely to affect offspring provisioning and fitness. Unfortunately, behaviour was not measured, but it would be interesting to investigate if this metabolic alteration leads to behavioural changes in mothers, for example changes in feeding behaviour.

In a classic experiment, Cowley et al. (1989) used a more complex cross-fostering method whereby embryos from C3HeB/FeJ and SWR/J strains and their F1 cross were transferred between the strains, and then the offspring were cross-fostered to a BALB/cJ by C57BL/6J F1 foster-mother. This allowed the examination of the effects of both maternal uterine environment and offspring strain on early life growth, independent of the postnatal maternal environment. Again, their results

demonstrated that different combinations of *in utero* and offspring genotypes altered a range of offspring quantitative phenotypes, such as body weight and tail length. It would be interesting to repeat this experiment but concentrating on offspring genetic effects rather than the maternal effect on offspring. In this case, the indirect genetic effect arising from different offspring embryo genotypes on surrogate mother traits, during and after pregnancy, and on postnatal foster-mother traits, could be measured without the confound of different offspring *in utero* environments.

6.2.2. Postnatal effects

The hormonal fluctuations after parturition contribute to the induction of maternal care behaviours in order to ensure offspring survival. It has been demonstrated that pregnancy can induce marked changes in the maternal brain including increased concentration of dendritic spines in the CA1 region of the hippocampus (Kinsley et al., 2006), white matter plasticity and enhanced remyelination (Gregg et al., 2007). Whilst the hormonal mechanisms outlined above prime mothers to alter postpartum behaviour in order to care for offspring, several studies have investigated the impact of exposure to offspring as an additional factor influencing maternal care. For example, Fleming and Rosenblatt (1974) demonstrated that exposure of virgin rats to pups induces a sudden onset of maternal behaviour, producing a pattern and intensity of maternal care similar to that of lactating mothers (Fleming and Rosenblatt, 1974). It was later demonstrated that pregnancy alone, without any exposure to live pups through a Caesarean-section on gestational day 22, is not sufficient to induce the full set of maternal behaviours seen in primiparous females (Bridges, 1975). By delineating prenatal (i.e. hormonal changes driven throughout pregnancy) and postnatal (i.e. exposure to offspring behaviour) influences on maternal care, cross-fostering studies have further demonstrated that the maternal brain, particularly in specific cognitive domains, is affected by offspring behaviour. For example, Kinsley et al. (1999) demonstrate that multiparous Sprague-Dawley rats have significantly improved spatial learning between 84 and 90 days after first giving birth compared to age-matched nulliparous females, as assessed on a radial arm maze task (Kinsley et al., 1999).

A study by Lambert et al. (2005) showed that the presence of pups in nulliparous rats has a differential effect on maternal behaviour. In a dry land version of the Morris water maze (Kesner and Dakis, 1995) dams were tested for spatial memory performance (underpinned by hippocampal function) and foraging strategies. Dams were either nulliparous (experiencing no pregnancy effects or pup exposure), primiparous (having a single exposure to pregnancy and pups), nulliparous with foster pups (exposed to six age-matched and age-progressed pups daily), or multiparous with pups removed (experiencing pregnancy but no pup exposure) in order to establish whether pup exposure affected task performance. Whilst the presence of pups following parturition decreased the latency to identify the baited well in primiparous mothers, it had no such effect in nulliparous mothers on all but one trial day (Kinsley et al., 1999; Lambert et al., 2005). However, on the fifth trial of the task the presence of pups significantly reduced the latency to identify the baited well indicating an improvement in spatial memory. This suggests that exposure to pup behaviour, even in nulliparous mothers who have not been exposed to the hormonal changes associated with pregnancy and parturition, can improve cognitive performance in a time- and task-specific manner (Lambert et al., 2005). To further understand whether the presence of pups affected the spatial search strategy of mothers, a subsequent trial in the test apparatus, where food cues were not present, was conducted. Similarly to the baited task, primiparous mothers spent significantly longer at the previously baited well compared to both primiparous mothers who had their pups removed, as well as both groups of nulliparous mothers who were either exposed to, or had never experienced pup behaviour (Lambert et al., 2005). Several other offspring behaviours also manipulate maternal phenotypes. For example, offspring suckling maintains maternal production of milk and suppresses maternal reproductive behaviour (Garcia-Winder et al., 1984; Woodside et al., 2000). Therefore, genes expressed in offspring which alter suckling, e.g. by increasing the length of sucking bouts or their intensity, will also increase the amount of milk the mother produces, or suppress her reproduction for longer. This has been particularly well studied in domestic cattle (e.g. Garcia-Winder et al., 1984).

While the above studies do not directly show indirect genetic effects, they illustrate possible mechanism by which offspring influence the behaviour of parents and alloparents (e.g. simply the presence of pups induces maternal care in virgin rats; Rosenblatt, 1967). However, a simple way to test this would be to examine if different genotypes of foster-pups (e.g. different inbred strains) have different effects on maternal behaviour in virgin females of a given genotype. This would inform us if the presence of pups *per se* alters alloparental behaviour, or if specific pup behaviours are needed to induce the behaviour.

Another example of a postnatally expressed gene which influences maternal care is the imprinted gene *Grb10* (Cowley et al., 2014). Pups with no *Grb10* expression were shown to have increased postnatal growth, and a cross-fostering experiment demonstrated that this was due to increased demand for nutrients and a subsequent increase in foster-mother provisioning (Cowley et al., 2014). Further, wildtype foster-siblings of *Grb10* knockout pups showed increased weight gain due to increased maternal provisioning, which is the same pattern found in a study in a different mouse genotype (Ashbrook et al., 2017). *Grb10* knockout mothers also provided less maternal provisioning, and this negative correlation between maternal provisioning and offspring demand again was also seen by Ashbrook et al. (2015). Both of these studies are evidence for co-adaptation between parental and offspring genomes. However, *Grb10* is not found in any of the QTL studies described by Ashbrook et al. (2015, 2017) suggesting that their QTL are due to different genes with similar phenotypic outcomes, and not due to *Grb10* itself.

6.2.3. Ultrasonic vocalizations

As all parents have experienced, a well-known mechanism by which offspring may attempt to manipulate parental behaviour is through the use of vocalizations (Lingle et al., 2012). In rodents, USVs are a key communication mechanism, and are present from the first postnatal day (Arriaga, 2014; Doty, 1974; Ehret and Haack, 1982; Maggio and Whitney, 1986; Oller et al., 2013). High frequency USVs allow mouse pups to signal to their parents, and can be induced by loss of body temperature (Okon, 1970a), intense tactile stimulation (Okon, 1970b), or hunger and maternal separation (Ehret, 2005; Noirot, 1966). As these USVs have been clearly shown to trigger parental attention and provisioning (Branchi et al., 2001; Cohen-Salmon et al., 1985; D'Amato and Populin, 1987; Ehret and Haack, 1982; Hernandez-Miranda et al., 2017; Noirot, 1964; Smith, 1976), and to differ depending on offspring genotype (Bell et al., 1972; Cohen-Salmon et al., 1985; Hahn et al., 1987, 1997; Roubertoux et al., 1996) they provide an excellent example of an indirect genetic effect of the offspring genome (genetic variants expressed in offspring effect different offspring vocalization) on parental behaviour (e.g. altered provisioning). Although genes influencing aspects of infant USVs have been found (Nakagawa et al., 2012; Scattoni et al., 2008; Scearce-Levie et al., 2008; Shu et al., 2005; Winslow et al., 2000), and QTL for indirect genetic effects of offspring genome on maternal phenotype have been mapped (e.g. Ashbrook et al., 2015), these have not yet been systematically recorded in the same study or from the same set of inbred strains. Given the important function of maternal provisioning in offspring survival throughout the mammalian order, and the evolutionarily conserved function of infant vocalizations in manipulating this provisioning, it is highly probable that genetic and physiological mechanisms are conserved throughout mammals (Lingle and Riede, 2014; Moore et al., 1997).

Offspring USVs are not just important for soliciting specific parental behaviours, but also for kin recognition. Specific call patterns have been

shown to play a role in the recognition of pups by mothers (Brunelli et al., 2015; Mogi et al., 2016). As mice are known to exhibit communal nesting behaviour (e.g. Heiderstadt et al., 2014; König, 1994; Roulin and Hager, 2003; Weidt et al., 2014) there is a clear fitness advantage in being able to direct maternal care to own offspring, as demonstrated in mixed litter studies of house mice (Hager and Johnstone, 2005). Remarkably, in Mexican free-tailed bats crèches, which contain up to 4000 pups per square meter, mothers are able to reliably recognise the calls of their own pups (McCracken and Gustin, 2010).

7. Conclusion

It has long been established that the maternal genotype can influence the phenotype of their offspring, however, the reciprocal effect of offspring genotype on maternal phenotype has been much less well studied. In this review we have shown that there is clear evidence for such offspring indirect genetic effects, but we are currently limited in our understanding of natural variants underlying these indirect genetic effects. Our two major sources of knowledge have been from linkage studies, in which we can detect genetic variants that cause indirect genetic effects but cannot identify the specific genes, and from knockout studies, which target specific genes. However, these do not necessarily represent natural variation within a population. A number of genes showing indirect genetic effects are imprinted. Genomic imprinting is most commonly observed in the placenta and the brain (Peters, 2014). The middle “junctional” region and inner layer of the placenta are derived from the offspring genome, and the brain controls postnatal offspring behaviour, which are important sites for indirect genetic effects.

Declaration of interest

The authors declared that there is no conflict of interest.

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