Genomic imprinting and communicative behaviour: Prader-Willi and Angelman syndrome

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The kinship theory of genomic imprinting predicts that imprinted genes affect mother-child and child-child interactions. According to this theory paternally expressed genes will promote behaviours that increase costs of maternal investments and enable children to compete with siblings. Maternally expressed genes will promote behaviours that reduce the mother's costs of child-rearing and enable children to engage in collaborative actions. Prader-Willi syndrome and Angelman syndrome are caused by the absence of expression of imprinted genes in 15q11-q13. Children with Prader-Willi syndrome lack the expression of paternally expressed genes; children with Angelman syndrome lack maternally expressed genes. The current paper discusses the role of imprinted genes in the development of communicative behaviours during the transition from breastfeeding to (consuming) solid food. Its focus is the possible role of imprinted genes in the development of empathy out of (reactive) crying, and in the development of behaviours necessary for joint action. Observed behavioural differences between children with Angelman and Prader-Willi syndrome, and data from mouse models on the effects of imprinted genes on brain development, are used to explore possible effects of imprinted genes. (*Netherlands Journal of Psychology, 65*, 78-88).

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Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are syndromes with a known genetic cause. The prevalence of both syndromes is about 1/30,000; on a worldwide scale it is estimated that there are about 700,000 to 800,000 individuals with PWS or AS. In most of the cases these syndromes arise as the result of deletion of chromosome 15q11-q13 or as the result of disomy

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of chromosome 15[1]. PWS is the result of maternal disomy or deletion of paternal chromosome 15q11-q13; AS is the outcome of paternal disomy or deletion of maternal chromosome 15q11-q13. Since 15q11-q13 harbours paternally and maternally expressed genes (these genes are imprinted), PWS is caused by the lack of paternally expressed genes (from now on PEGs), while AS is caused by the lack of maternally expressed genes (MEGs).

PEGs and MEGs have antagonistic effects on child development. These effects are visible in the behavioural characteristics of PWS and AS (for reviews on PWS see Bittel & Butler, 2005; Goldstone, 2004; for AS see Clayton & Laan, 2003; Williams et al., 2006). For example children with PWS have a weak, abnormal cry during the early stages of development. They have a poor sucking ability and have to be fed directly through a tube to the stomach during these early stages. By contrast: children with AS have an abnormal high-pitched cry. Their suckling behaviour is disturbed in the sense that they suck longer than normal children. Children with Prader-Willi syndrome are somnolent during the early stages of development and rarely awake for feeds, while reduced sleep and frequent waking is a characteristic in children with Angelman syndrome. During the later stages, differences arise in social behaviour. The development of communicative behaviour is severely disturbed in Angelman syndrome. Children with AS hardly learn to talk. They have poor motor imitation skills and most fail to imitate non-verbal and verbal behaviour. Children with PWS have fewer problems with communication, although the development of social cognition is impaired. They develop obsessive and ritualistic behaviours and temper outbursts that reminds one of autism. A striking feature of PWS is hyperphagia ('excessive overeating'), which starts in early childhood and results in obesity if left unchecked.

The effects of imprinted genes on child development during the prenatal stages are successfully explained by kinship theory[2]. As predicted by kinship theory, imprinted genes expressed in the child have key roles in resource transfer from mother to child during prenatal development. The behavioural characteristics of children with PWS and AS show that imprinted genes also affect postnatal investments, but there is less known about the effects of imprinted genes on behavioural development. In this paper I will explore possible effects of PEGs and MEGs on the development of communicative behaviour. Since kinship theory predicts that imprinted genes modulate the demand, provision and use of resources, I will focus on effects during the suckling period, weaning, and the stages after weaning. The effects of imprinted genes on brain development, found in mouse models, will be used to elaborate hypotheses. The aim of the paper is to develop predictions that can be tested in future behavioural research on PWS and AS.

Kinship theory

Genomic imprinting is the phenomenon that the expression of an allele in the current generation depends on whether the allele was present in a sperm or egg during the previous generation. It was discovered about 20 years ago and has since then been a major research topic. At first it was studied within the fields of molecular and evolutionary biology; nowadays it is studied within the fields of neuroscience and psychology as well, because imprinted genes are involved in brain development (for a review, see Wilkinson, Davies & Isles, 2007).

1 Each cell contains two sets of chromosomes: one set inherited from the mother, the other from the father. Numerical abnormalities such as trisomies result in disease. But uniparental disomies, i.e. two sets of chromosomes from a single parent, may also result in disease if the chromosome harbours imprinted genes. For uniparental disomies lead to imbalance in gene expression. Suppose that, in an offspring, the paternal copy of a gene is normally switched on and the maternal copy is switched off. In the case of a paternal disomy, an offspring would then receive two active copies of the gene while an offspring with maternal disomy would have two inactive copies. Both uniparental disomies can result in disease. Chromosome 15 is an example: a small region of the long arm, namely the 15q11-q13 region, harbours a number of imprinted genes.

2 Kinship theory has been developed to explain the evolution of behaviour (performed by an actor) that provides a benefit to another individual (the recipient). Such behaviours pose a problem for evolutionary theory, because these behaviours reduce the fitness of the performer of that behaviour. Hamilton argued that behaviours that benefit another can benefit the performer since the two individuals may be related. If they are related, an individual gains inclusive fitness if the performed behaviour has impact on the reproductive success of the related individual. This is called kin selection. Hamilton's theory demonstrates that cooperative or altruistic behaviour evolve when $rb-c>0$, where c is the fitness cost of the actor, b is the fitness benefit to the recipient, and r is their genetic relatedness. Hence altruistic or cooperative behaviour evolve if the benefits to the recipient, weighed by the genetic relatedness of the recipient to the actor, outweigh the costs to the actor. The theory predicts greater levels of cooperation when r or b are higher and c is lower. For many relatives r differs for genes of maternal and paternal origin. For that reason a distinction is made between the probability that an individual carries a maternally derived gene (r_m) and a paternally derived gene (r_p). If $r_m>r_p$ (or $r_m<r_p$), then it is said that there is genetic conflict between paternally and maternally derived genes since an act may enhance the inclusive fitness of maternally derived genes but reduce the inclusive fitness of paternally derived genes (and vice versa).

Genomic imprinting is explained by kinship theory (reviewed in Haig, 2002)[3]. According to this theory, imprinted genes evolve when mechanisms or behaviours, influenced by genes, enhance the inclusive fitness of paternally derived genes but reduce the inclusive fitness of maternally derived genes (and vice versa). There are several causes for this asymmetry in inclusive fitness. One is that the mother may have children of different fathers. If so, then the probability that children of a particular mother carry a copy of the paternally derived allele is less than 50%, while the probability that they carry a copy of a maternally derived allele is 50%. Because of this asymmetry kinship theory predicts the evolution of PEGs that promote maternal investments at the expense of siblings and the mother. For example Plagge et al. (2004) have shown that the PEG *Gnasxl* promotes the suckling response in mice via centres in the brainstem that activate muscles in the tongue and jaw. GNASxl probably has a similar function in the human species: two children who, due to a deletion, lacked the effects of GNASxl hardly sucked (Genevieve et al., 2005). PEGs that influence suckling behaviour join forces with PEGs that modulate the use of energy gained through suckling. For example the paternally expressed snoRNA SNORD116 in humans (also called HBII-85) and *Snord116* in mice (also called MBII-85) affect growth. Mice lacking this snoRNA are of normal size at birth but fail to grow in the first three weeks when they are dependent on maternal milk. Ding et al. (2008) have shown that decreased milk intake is not the cause of this growth failure. They suggest that a disturbance in the growth hormone pathway is probably the cause of the reduced growth (another PEG with a similar effect is discussed by Itier et al., 1998).

Kinship theory also predicts the evolution of maternally expressed genes that counteract these effects of PEGs and contribute to mechanisms and behaviours that enhance inclusive fitness. A well-known example in mice demonstrating the counteracting effects of MEGs is *Igf2r*. This imprinted gene evolved in response to the evolution of the PEG *Igf2*, a growth promoter. *Igf2r* reduces growth since its product influences the effect of *Igf2*: the receptor, produced by *Igf2r*, is a decoy receptor that binds Igf2 and transports it to the lysosomes for degradation (Haig & Graham, 1991). An example of a MEG enhancing inclusive fitness is the allele coding for Gαs. This imprinted gene is involved in the production of heat by brown adipocytes. In species such as mice that huddle during the preweaning stage, heat production by one individual reduces the heating costs of other individuals. Therefore an individual's heat production is beneficial for the other individuals in a litter. The heat produced may be seen as a collective good that increases the inclusive fitness of the mother and the siblings (Haig 2008). As predicted by kinship theory, the paternally derived copy coding for Gαs is not expressed and, hence, does not contribute to the common good. It acts as a 'free rider'. This shows that the production of heat by brown adipocytes has been subject to antagonistic co-evolution of PEGs and MEGs. It also shows that PEGs and MEGs favour different allocation of energy: while PEGs favour the allocation of energy to growth processes (enhancing the fitness of the individual), MEGs favour the allocation to the production of heat (enhancing the inclusive fitness) during the same period.

The timing of weaning

Kinship theory predicts that a longer duration of breastfeeding is, in the case of the human species, beneficial for paternally derived genes, since milk is probably nutritionally and immunologically superior to solid food (see Kennedy 2005, for qualifications of this statement), and because the suckling causes lactational suppression of ovulation (and, hence, delays the arrival of a potential competitor). At face value, these objectives of paternally derived genes can be achieved quite simply, since prolongation of suckling behaviour into infancy is sufficient to realise these goals. By causing the release of oxytocin, suckling stimulates the production of milk and suppresses ovulation through gonadotropin-releasing hormone and prolactin. Because lactational anoestrus is a function of the frequency of nursing rather than the amount of milk produced, kinship theory predicts that PEGs will 'install' a pattern of regular suckling in babies by waking them up periodically (Blurton Jones & Da Costa, 1987; Haig & Wharton, 2003). There is evidence in favour of this prediction: in mice, *Gnasxl* is also expressed in structures in the brain that are involved in arousal (Plagge et al., 2004). Another PEG that may be involved is *Magel2* (Kozlov et al., 2007), for its product modulates in mice circadian rhythmicity. Interestingly, children with Prader-Willi syndrome who lack the effects of PEGs (including MAGEL2) are somnolent and rarely awake for feeds, while reduced sleep and frequent waking is a feature in children with Angelman syndrome (lacking MEGs).

3 *Imprinted genes are genes that possess, as it were, information about their parental origin. They carry a parental imprint determining whether they will be expressed in offspring. This is achieved by a so-called epigenetic mechanism of gene regulation: certain chemical groups (imprints) are attached to (or removed from) sites on DNA during the formation of the egg and sperm cells. Since these processes depend on the sex of the parent, they result in a parent-specific expression of genes in offspring. If the gene is derived from the father it may be expressed while at the same time the maternal copy is silent (or the other way around). The imprints are removed in the gonads of the children, and afterwards new imprints are established, depending on the sex of the child. There are 100-200 imprinted genes.*

Another relevant observation is that breast milk contains sedative substances such as benzodiazepines (Dencker, Johansson, & Milson, 1992): it is possible that these substances oppose effects of PEGs (see further Haig, 1993).

The (instinctive) suckling movements are generated through the brain stem and are, at first, probably not 'controlled' by the hypothalamus and the cortex. This is inferred from the fact that, in mice, the sense of taste (indicated by decreased acceptability of quinine over water) and hunger as well as satiety mechanisms are largely absent before weaning (Henning, 1981). The transition toward adult mechanisms occurs in mice during weaning (after about three weeks). Weaning in mice is a short period and marks the beginning of a life independent of nursing. Permanent molars develop and eyes and ears open just before pups begin the exploration of their environment. Hence in mice, the transition from suckling behaviour to foraging for solid food is the transition from instinctive suckling to volitional eating and foraging behaviour.

In humans, infants younger than 3 weeks of age do not respond to salty or bitter adulterations of their formulas (although eight-day-old infants are sensitive to the smell of their mother's breast pad, see Blass & Teicher, 1980). Just as in mice, the internal mechanisms involved in hunger and satiety are absent during these early stages of human development. In infants younger than 12 weeks of age suckling terminates with sleep and is reinstated with awakening. In children older than 12 weeks suckling is not terminated by sleep: children start to play with the nipple or bottle after a feed. The child's attention and motor patterns are no longer dominated by a pattern that culminates in suckling. Children start to interact with their parents and the suckling behaviour gradually develops into volitional behaviour. If infants learn to express their needs and wants verbally during the second year, this volitional behaviour is extended with linguistic behaviour. The child develops primitive forms of intentional behaviour, for it can then ask for the breast if it is hungry. It is unknown if and how PEGs affect the behaviour of children during these successive developmental stages until weaning.

In the human species, there is substantial variation in the timing of weaning: the range is 1-4 years in natural fertility populations (see table 1 in Kennedy, 2005). This variation is, in part, understandable in terms of (1) the variable environmental conditions, (2) the physical condition of the mother, and (3) the prospects of the mother. In contrast to mice, weaning does not mark the transition to solid food, since breastfeeding in humans is extended with supplementary food during the course of the first year. Are MEGs, expressed in infants, needed to defend the 'interests' of maternally derived genes? Other things being equal, kinship theory predicts that maternally derived genes benefit from earlier weaning, since it increases the chance that the mother can get pregnant. Assuming that MEGs have evolved which do contribute to an earlier transition, what are possible mechanisms (besides counteracting PEGs)?

Eating and drinking are behaviours that in adults are 'controlled' by neural circuits located in the brain stem, hypothalamus, cerebellum and the motor areas in the cortex. The cerebellum is involved in the coordination of instinctive movements with swallowing and respiratory movements. UBE3A (a maternally expressed gene) is expressed in the cerebellum. Heck, Zhao, Roy, LeDoux, and Reiter (2008) have studied the licking behaviour in 2- to 5-month-old mice lacking *Ube3a*. They have shown that these mice have problems with swallowing and other movement problems related to a dysfunctioning cerebellum. These oral-motor dysfunctions (and ataxia) also occur in children with AS (who lack the effects of UBE3A). Has UBE3A been selected in the human species since it contributed, via its effects in the cerebellum, to an earlier transition to solid food? Given the variation in the timing of weaning and the fact that UBE3A is also expressed in the hippocampus, it is unlikely that the primary effect of UBE3A is a contribution to an earlier transition from instinctive suckling to volitional drinking and eating behaviour. Yet UBE3A may have been selected because of its general contribution to behaviours that made children less dependent on maternal investments. An argument in favour of this hypothesis is that UBE3A also modulates synaptic plasticity in the hippocampus and may, therefore, be involved in the development of behaviours such as exploration and vigilance needed for an independent living. There are other imprinted genes known that are involved in the development of exploration (see Plagge et al., 2005). If UBE3A has a role in the development of explorative behaviour, then the problems with swallowing seen in children with AS are a side effect of a generally dysfunctioning cerebellum. Dysphagia, i.e. difficulty in swallowing, is a common symptom in patients with cerebellar disease. The fact that not all but about 74% of children with AS develop problems with swallowing (Heck et al., 2008) favours this possibility, but a final conclusion requires more data on the onset of effects of UBE3A in the different brain structures and processes. If UBE3A has been selected because of its contribution to an earlier transition to an independent living, then one can be expect that PEGs promote a delay in the maturation of certain motor and sensory mechanisms.

Sibling rivalry and cooperation

The effects of PEGs and MEGs in the brain have been studied in mice that produce several siblings at a litter. The occurrence of sibling rivalry in mice is no surprise, both during the prenatal

and postnatal stage until weaning. Sibling rivalry is absent during the prenatal stage in humans, since women usually conceive one child. Yet the period of breastfeeding and the transition from breastfeeding to solid food may be at the centre of sibling rivalry in the human species. This hypothesis is based on the observation that competition between human siblings has been intensified during our recent evolutionary history. Humans have a much shorter interbirth interval than our closest relatives but have a longer juvenile dependence (Kennedy, 2005). Humans wean in natural fertility populations at about 2.5 years, while chimpanzees wean at 5 and orang-utans at 7.7 years.[4] According to Kennedy (2005) this transition to shorter interbirth intervals was made possible because humans started to use protein-rich meat (but also plant food and tubers) as a supplement to and alternative for maternal milk. However, if food was in short supply, children of different ages had to compete for parental investments. Data supporting this hypothesis are, for example, studies in Malawi and India showing that child mortality increases as the interbirth interval decreases (Manda 1999; Shahidullah, 1994). Since infant mortality has been high during the largest part of human evolution (as it still is nowadays in apes: 50 to 75% die in infancy; in human foragers it is estimated that 30 to 40% of the children die, cf. Sellen, 2007), sibling rivalry has been a substantial evolutionary force. Therefore the opportunity arose for paternally and maternally derived genes to affect parent-child and child-child interactions during postnatal stages. Assuming that competition between siblings is beneficial for paternally derived genes but disadvantageous for maternally derived genes, and that offspring have been dependent on breastfeeding, supplementary food and care, kinship theory predicts that maternally derived genes promote a fair sharing of food among siblings, while paternally derived genes promote behaviours that will help an individual to compete with siblings. Imprinted genes may affect behaviours at different levels. For example, PEGs may promote the development of a larger, muscular body so that children are better competitors, while MEGs may favour a less muscular body which uses resources for increased deposition of fat, for children then have reserves and need less feeds during periods of food shortage (Haig & Wharton, 2003). PEGs may also promote behaviours that enhance maternal care at the expense of siblings (Brown & Consedine, 2004, and Hrdy, 1999; see also Smit, 2006). I will discuss two areas where PEGs and MEGs may influence the development of communicative behaviour: the development of crying and reactive crying as precursor of empathic behaviour, and the development of behaviours necessary for collaborative action.

Crying and reactive crying

There are conspicuous differences between the cry of newborn children with PWS and AS. Children with PWS have a weak cry while children with AS have a high-pitched cry. It is thought that PEGs increase the chance that children receive maternal attention through enhanced crying. Yet psychologists have noted that newborn babies also cry when they hear another infant cry. Simner (1971) found it in 2- and 3-day-old babies and noted that it was not the loudness of the cry that evoked the response. These findings have been replicated by Sagi and Hoffman (1976) in 1-day-olds. They showed that it is not a simple imitative vocal response lacking an affective component. The reactive cry is indistinguishable from the spontaneous cry of an infant who is in actual discomfort. Martin and Clark (1982) showed that infants do not react as much to the sound of their own cry. This finding has been replicated by Dondi, Simion and Caltran (1999). Based on these findings one can hypothesise that this innate response to the cry of another of the same species is an adaptive response since it increases the chance that the child receives maternal care.

Interestingly, this reactive crying is described as a precursor of the empathic response displayed by older infants as response to distress of others (Hoffman, 2000). At first, reactive crying appears to decline: 6-month-old children appear to respond to distress of another only after the other displayed several instances of distress. The cry displayed by a 6-month-old is different from a newborn's cry: the infant looks sad and puckers his lip before starting to cry, just as infants do when they are in actual distress. This fact was already noted by Darwin (1877, p. 289) who described the empathic response of his 6-month-old son to his nurse pretending to cry by 'his melancholy face, with the corners of his mouth well depressed'. Hence 6-month-old infants no longer respond 'mechanically' to another's cry. One-year-old children still respond to the distress of another by displaying distress behaviour themselves. Yet the response of a 1-year-old differs from the response of a 6-month-old. Children respond by looking sad, pucker their lips, and then start crying, but their cry is now accompanied by whimpering and silently watching or staring. Moreover, as soon as children are able to crawl and later become truly self-moving creatures, they actively seek comfort in their mother's lap. Since this latter response is also displayed when they are in distress themselves,

4 A simple calculation shows why human populations started to expand as the result of earlier weaning. Suppose that chimpanzee and human females can conceive children after they are 20 till they are 40. Assuming lactational anoestrus, and that chimpanzees wean at 5 and humans wean at 2.5 years, chimpanzee females can conceive 4 children while human females can conceive 8 children. If 50% die in infancy, only the human population grows.

seeking comfort in response to the distress of another is described as an egocentric empathic distress response (Hoffman, 2000).

At about 14 months children begin making helpful advances towards the distressed other through patting and touching, which soon gives way to more differentiated positive interventions such as kissing, hugging, giving physical assistance, getting someone else to help, giving advice and reassurance. These responses develop into primitive, veridical empathic distress responses during the second year. For example Hoffman (2000) describes a 2-year old who first brought his teddy bear to comfort a crying friend. When it did not work, he ran to the next room and returned with the friend's teddy bear and was more successful in comforting his friend. Since the response of the boy is an example of a primitive intentional action, it is important to keep two differences with instinctive responses in mind. First, one can choose to perform an intentional empathic response. Hence 2- and 3-year-olds will not always respond empathically since it is not an instinctive reaction. Secondly, the example shows that the response of the boy presupposes the development of several other skills, such as pointing and joint attention and may therefore be (in part) the result of teaching.

If imprinted genes influence the development of the empathic response out of crying and reactive crying, then one expects that PEGs contribute to crying and reactive crying as a means to increase maternal care. One can also hypothesise that egocentric crying as a response to the distress of another child (a sib or non-sib) is modulated by PEGs. These predictions can be tested by studying the responses of children with AS and PWS to the cry of another during the first year. Kinship theory predicts that MEGs will contribute to the development of the intentional, emphatic response since this response enhances the fitness of maternally derived genes: sharing, comforting, etc. increase the chance that all children will survive. This hypothesis raises the problem what the contribution of MEGs may be.

Joint attention and collaborative action

What are, from a psychological perspective, the main differences between competitive and collaborative interactions? In competitive interactions, individuals do not necessarily need to understand the motives of the opponent. Both individuals want to obtain a certain resource irrespective of what the motives and intentions of the opponent are. In collaborative actions, however, understanding the motives and intentions of others are essential: the participants need to coordinate their actions according to a shared plan. Hence a prerequisite for collaborative actions is skills such as understanding the wants and needs of others, the use of gestures like pointing, and skills like joint attention. Communication about joint action is of course much easier if the participants are language-using creatures that are able to express their needs and wants and understand the reasons for collaborative actions. The skills necessary for collaborative action start to develop at 9-14 months of age (Tomasello, Carpenter, Gall, Behne, & Moll, 2005). How can MEGs contribute to the development of collaborative actions among siblings and the mother? There are two hypotheses explaining possible effects of MEGs.

The first hypothesis is advanced by Badcock and Crespi (2006): they hypothesise that MEGs contribute to the development of the neocortex. Badcock and Crespi assume that the contribution of the father to the raising of a child is minimal compared with that of the mother, since she is the major provider of care both during prenatal and postnatal stages. Hence the father can only rely on his genes: they are the primary means for him to affect the behaviour of his child. Badcock and Crespi expect paternally derived genes to promote 'selfish' behaviour at the expense of the mother and sibs. According to them, this explains why PEGs contribute to the limbic system (this system includes in their view the hypothalamus) since this system modulates the basic drives, appetites, and emotions. Since the mother is the major provider of care and therefore can exploit her role during nurturing, Badcock and Crespi expect that maternally derived genes 'should further the mother's interests by building a cortical brain capable of integrating mental activity in the greater interests of her whole family' (Badcock & Crespi 2006, p. 1011). Hence MEGs contribute to the development of the neocortex, since this brain structure enables children to develop activities in the mother's interest (see also Fitch, 2006; Locke, 2006; Locke & Bogin, 2006). They explain: if MEGs contribute to the development of the cortex, then the mother 'will be able to use the speech centres of the cortex to teach her child its mother tongue and the inhibitory and prioritising functions of the frontal lobes to control behaviour in accordance with her commands and instructions' (Badcock & Crespi 2006; p. 1011). It is, however, unclear if and how MEGs make children sensitive to maternal commands. It may be hard to drill children, yet what is the specific contribution of MEGs to this learning process? Moreover, MEGs are supposed to promote learning processes which affect all kinds of behaviours, yet the effect of the maternally expressed UBE3A is rather specific: the gene is involved in context-dependent learning and long-term potentiation (Van Woerden et al., 2007). But the contribution of MEGs to speech development deserves serious attention, for children lacking UBE3A hardly babble and do not develop speech.

The second hypothesis emphasises the possible role of the cerebellum and hippocampus (since UBE3A is expressed in these brain structures) in

Table 1	Possible effects of PEGs and MEGs, described in catchwords, during the transition from breast-feeding to solid food.
PEGs	*MEGs*
Prolonged breastfeeding	Earlier transition to solid food
Crying, reactive crying	Babbling, sharing, joint intention
Attachment (happy disposition)	Detachment (exploration, vigilance)

the development of pro-social behaviours (see also Haig, 2008). Children with AS have poor imitation skills. They fail to imitate verbal behaviours and use nonverbal communication for making requests. If they want something, they manipulate others. For instance they take an adult by the hand and guide them to what is wanted and push a hand away if they do not want help (see Joleff & Ryan, 1993; and Didden, Korzilius, Duker, & Curfs, 2004). Children with AS hardly use nonverbal behaviour like gestures and pointing for joint action and joint attention. Hence they lack behaviours which are a prerequisite for the development of triadic interactions with caregivers. They do not, therefore, share goals with caregivers and do not participate in collaborative action. Since it is believed that language arose as an extension of babbling[5] and non-verbal behaviours displayed during triadic interactions, the absence of speech may be a feature of the general delay or absence of the development of pro-social behaviours observed in children with AS. According to the second hypothesis, the development of speech is disturbed as the result of a lack of a MEG contributing to the development of a brain that enables children to learn pro-social and later verbal behaviour. It is interesting to note that the development of babbling, joint attention, and the development of tiny incisors ('milk' teeth), all begin around the age that children receive supplementary food (Hrdy 2005). Yet future studies are needed to reveal possible effects of imprinted genes during this developmental stage.

Table 1 summarises some possible effects of PEGs and MEGs that correlate with observed (and hypothetical) behavioural differences between children with PWS and AS. It must be stated that it is unknown whether the observed behavioural differences between children with PWS and AS reflect antagonistic effects of imprinted genes, since the causal connections between genes and behaviours are poorly understood. Nevertheless the behavioural differences between AS and PWS are striking and it is a challenge to use these differences for testing predictions of kinship theory.

5 *Some scientists have hypothesised that babbling evolved in the context of cooperative breeding (see for example Hrdy, 2005; Burkart, Fehr, Efferson, Van Schaik, 2007). Hence it is possible that UBE3A influences the development of babbling since babbling optimised the functioning of sharing in the cooperative breeding system and contributes, therefore, to the inclusive fitness of maternally expressed genes.*

Disentangling direct effects and side effects

Testing the kinship theory through studying diseases caused by disturbed expression of imprinted genes requires a precise understanding of the direct and side effects of PEGs and MEGs on disease development (see also Ubeda & Wilkins, 2008, and the Appendix for a discussion of concepts). A direct effect is the functional effect of an imprinted gene on a characteristic during a specific developmental stage. A side effect is an effect of the gene not related to its function but which occurs during later developmental stages. For if the expression of an imprinted gene is disturbed, this disturbance will also affect the development of mechanisms and processes during later stages that depend on the preceding stages. Disentangling direct and side effects is far from easy if imprinted genes have pleiotropic effects: it is possible that a gene has two or more functional effects during successive developmental stages.

Since intentional behaviour grows out of instinctive behaviour in humans (Malcolm, 1982), the problem arises whether we can disentangle the direct and side effects of imprinted genes on the development of instinctive and intentional behaviour (in Table 2 the imprinted genes in the 15q11-q13 cluster are listed). I will discuss two examples.

Table 2	Imprinted genes in the 15q11-q13 cluster.
PEGs	*MEGs*
MKRN3	UBE3A
MAGEL2	ATP10C
NDN	
C15orf2	
SNURF-SNRPN	
SNORD116 (HBII-85)	
SNORD115 (HBII-52)	

SNRPN is host to multiple so-called small nucleolar snoRNAs. These snoRNAs reside in the introns of SNRPN and are released by splicing. The genes are reviewed in Nicholls and Knepper (2001).

Ding et al. (2008) have shown that the growth rate of mice, lacking the effects of *Snord116* on growth, was normalised as soon as they were weaned and started eating on their own. However, these mice developed hyperphagia after about the age of three months, although they did not develop obesity. Mice lacking the snoRNA had longer meal duration, probably due to lack of sensing satiety. The levels of ghrelin, a hormone produced mostly in the stomach that presumably has orexigenic effects, are elevated in these mice. It is, however, not known if and how ghrelin contributes to the development of hyperphagia. Interestingly, the lack of SNORD116 in patients with Prader-Willi syndrome (Sahoo et al., 2008) is probably the cause of hyperphagia too (the onset of hyperphagia is in PWS after about two years). Just as in mice, the ghrelin levels are elevated before children with PWS develop hyperphagia (Feigerlova et al., 2008). However, unlike the mice, children with PWS develop severe obesity, implying species-specific differences. Ding et al. (2008) suggest that the limited growth during the neonatal stage signals starvation to the brain and may trigger the development of a thrifty phenotype (including hyperphagia). Hence they (see also Holland et al., 2003) interpret the hyperphagia in PWS as a side effect of an earlier disturbed developmental pathway caused by the lack of SNORD116. Others, however, have discussed the thrifty phenotype as a possible direct effect of imprinted genes and have suggested that PEGs and MEGs may promote different components of thrifty and spendthrift phenotypes. Haig and Wharton (2003) have advanced the hypothesis that PEGs may cause moderate appetite (for solid food) if this would lead to a prolongation of breastfeeding. This hypothesis is, however, questionable for two reasons. First, as shown by the study by Ding et al. (2008), Haig and Wharton incorrectly assumed that the hyperphagia is related to a direct effect of PEGs in just the human species. Secondly, Haig and Wharton assumed that PEGs promote moderate appetite for solid food during weaning (with the possible effect that breastfeeding would be prolonged). Hence hyperphagia would occur in children lacking the expression of a PEG causing moderate appetite. It is, however, unlikely that the lack of satiety is the result of the deletion of a PEG that promotes moderate appetite. Although it is still possible that there are other paternally expressed genes involved that may affect components of eating and foraging behaviours (see also Ubeda, 2008), there is now evidence that the major clinical symptoms of PWS, such as the hyperphagia, are caused by the lack of expression of SNORD116 (Sahoo et al., 2008; see also Doe et al., 2009, for the role of SNORD115 in brain and behavioural development).

Children with AS, who lack the effects of UBE3A, develop ataxia and limited speech during later stages. Is the lack of speech a side effect of early oral-motor dysfunctions caused by a dysfunctioning cerebellum? Or is the development of speech a direct effect of MEGs on the development of pro-social behaviour (as discussed above)? Evidence in favour of the first possibility is that children with AS have a better understanding of language than the corresponding development of speech suggests. If there is a correlation between the severity of oral-motor dysfunctions and the development of speech, this would strengthen this hypothesis. The second possibility may be inferred from the fact that the absence of speech appears out of proportion to the level of mental retardation. An assessment of these possibilities requires data about the early development of expressive behaviours in children with AS. What are the causes of the disturbed pathway that should have culminated in

speech? Does the absence of speech and pro-social behaviour have a common aetiology?

Conclusion

Research into the role of imprinted genes in brain and behavioural development has shown that imprinted genes affect the development of suckling, eating, and foraging behaviour. Imprinted genes also affect the development of communicative behaviour, although it far less clear what the effects and relevant brain mechanisms or developmental pathways are. Hence it is a challenge to study possible effects of imprinted genes on behavioural development in animal models and through studying the early development of children lacking the expression of either PEGs or MEGs. Based on what is known about the development of children with PWS and AS, I have suggested two areas where imprinted genes may affect the development of communicative behaviour: the development of crying and reactive crying as precursors of empathy, and the development of the precursors of collaborative action such as imitation skills and babbling. A test of the ideas requires a detailed investigation of early behavioural development in children with PWS, AS and controls. Hence future longitudinal behavioural studies are needed to reveal possible effects of imprinted genes during the development of pro-social and social behaviour. Such a study is also interesting since it will provide insight into the evolution of behaviours that made the human species unique within the animal kingdom according to some scientists: the development of reasoned behaviour (Tomasello et al., 2005). One final problem must be mentioned. Studies on the evolution of the 15q11-q13 imprinted cluster have shown that this cluster originated about 105-180 million years ago (Rapkins et al., 2006). Since then the region expanded through insertions (three genes have been added 90-105 million years ago) and it underwent some rearrangements afterwards. Although homologous copies of the imprinted genes listed in Table 2 are found in mice, there is evidence that there are differences between the region in mice and humans. The 15q11-q13 cluster appears to be an unstable region still subject to selection. Hence, it is possible that imprinted genes in the 15q11-q13 cluster contribute to the development of communicative behaviours that are seen as unique for the human species. But we have to await the results of future studies to see whether this hypothesis holds.

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Appendix: Genes and the good of a being

Evolutionary theory predicts that effects of genes are selected that enhance the propagation of their copies. These effects are sometimes said to be beneficial for a particular gene. It has been argued that mechanisms and behaviours, if influenced by genes, can be viewed as adaptations for the good of the genes (Haig, 1997). Hence genes are said to have purposes or ends of their own. These ideas may mislead psychologists and medical researchers. For only living organisms can have a good since they may *act for* a purpose; i.e. they may pursue ends (see Hacker 2007, chapter 7). Although genes cannot act for a purpose, they may have functions in organisms, just as organs have functions. They *exist for* the sake of a good, i.e. are beneficial for the organism. Hence, something may benefit the gene if it prevents malfunction or suboptimal function of the gene. However, this is not the intended use of beneficial by evolutionary biologists, since they emphasise the strategic effects of genes: something is 'beneficial' if it enhances the survival and reproduction of a gene. Consequently, if evolutionary biologists say that genes have purposes of their own, then they anthropomorphise genes (as they readily admit: Haig, 1997). Why then do they talk about its survival as part of the purpose of a gene? Evolutionary biologists anthropomorphise genes since they use game theoretical models to investigate their expression patterns. These models enable them to study why certain hypothetical expression patterns are evolutionarily stable relative to conceivable alternatives. Genes are, therefore, treated as strategists, just as the behaviours of animals are treated as strategic actions by game theoreticians. The models demonstrate that certain expression patterns are 'beneficial' for survival and reproduction. For instance: they explain why genes are imprinted, i.e. they may be expressed when maternally derived but silent when paternally derived; why these imprinted genes are expressed in some tissues and in some environments; why they respond to signals from some other genes and may join forces with other genes; and so forth.