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Prader-Willi Syndrome and the Evolution of Human Childhood

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ABSTRACT The kinship theory of genomic imprinting predicts that imprinted genes have effects on asymmetric kin (relatives with different degrees of matrilineal and patrilineal relatedness). The most important interaction with such a relative is a child's interaction with its mother. Therefore, the study of imprinted genes and their phenotypic effects promises to provide insights into the evolution of mother–child relations. Prader-Willi syndrome (PWS) is caused by the absence of expression of genes at 15q11–q13 that are normally expressed only when paternally derived. The kinship theory predicts that children with PWS will fail to express behaviors that have increased mothers' costs of child-rearing. Our analysis focuses on aspects of the PWS phenotype that affect appetite and feeding. Immediately after birth, children with PWS have little appetite and are usually unable to suckle, but at some stage (usually within the first 2 years) they develop a voracious appetite and an obsession with food. We conjecture that this change in appetite reflects evolutionary forces associated with weaning. Immediately after birth, when a child is completely dependent on the breast, poor appetite reduced maternal costs. However, once a child was able to consume supplemental foods, maternal costs would have been reduced by children with increased, nonfastidious appetites. Am. J. Hum. Biol. 15:320–329, 2003.

Trivers (1972) defined parental investment to be any investment by a parent in an individual offspring that increases the offspring's chances of survival at a cost to the parent's ability to invest in other offspring. He subsequently argued that offspring would be selected to obtain — or attempt to obtain — greater investment from parents than parents would be selected to provide, resulting in an evolutionary conflict between progeny and progenitors (Trivers, 1974). Put in other words, natural selection acting on genes expressed in parents attaches different relative weight to benefits to offspring and costs to the residual reproductive value of parents than does natural selection acting on genes expressed in offspring. Haig and Westoby (1989) recognized that the appropriate weighting of costs and benefits also differs for maternally and paternally derived alleles of offspring. This difference would result in an evolutionary conflict within offspring between alleles inherited from mothers and alleles inherited from fathers, provided that a gene's effects are not constrained to be independent of the gene's parental origin.

For most loci in the human genome, a gene's effects appear to be independent of its parental origin. But, for a small subset of loci, a gene's effects when inherited via an egg differ from its effects when inherited via a sperm. This phenomenon is known as genomic imprinting and the affected genes are said to be imprinted (Reik and Walter, 2001). The kinship (or parental conflict) theory of genomic imprinting posits that imprinting evolves at a locus when the level of gene expression that maximizes matrilineal inclusive fitness (W_m) is different from the level that maximizes patrilineal inclusive fitness (W_p). W_m and W_p are calculated in the same manner as traditional inclusive fitness, except that effects on relatives are weighted by coefficients of parent-specific relatedness rather than coefficients of average relatedness (Haig, 2000). At evolutionary equilibrium, the allele (maternal or paternal) that "favors" the lesser amount of gene product is predicted to be silent and the allele that "favors" the greater amount is predicted to produce this amount (Fig. 1).

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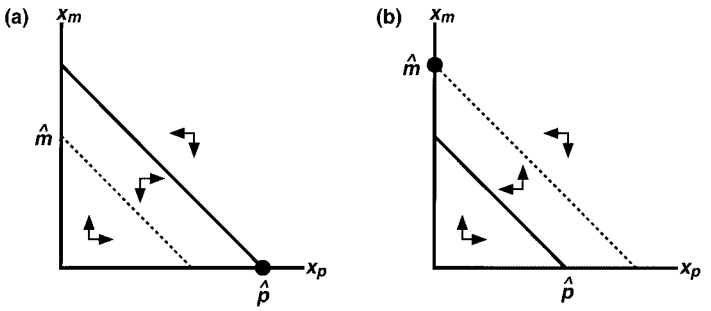

Fig. 1. The total production of gene product is the sum of x_m and x_p, the amounts produced by the maternal and paternal alleles at a locus. Matrilineal inclusive fitness (W_m) is maximized by an amount $\hat{m}$ (corresponding to points on the dashed diagonals). Patrilineal inclusive fitness (W_p) is maximized by an amount $\hat{p}$ (corresponding to points on the solid diagonals). The arrows represent the direction of selection on x_m and x_p. In the region between the solid and dashed diagonals, selection acts in opposite directions on x_m and x_p. Evolutionary equilibria are represented by filled circles: (**a**) If $\hat{p} > \hat{m}$, the maternal allele is predicted to be silent and the paternal allele is predicted to produce $\hat{p}$; (**b**) If $\hat{m} > \hat{p}$, the paternal allele is predicted to be silent and the maternal allele is predicted to produce $\hat{m}$ (Haig, 2000).

A necessary condition for W_m and W_p to differ is that a gene's expression has fitness consequences for asymmetric kin (i.e., individuals for whom matrilineal and patrilineal coefficients of relatedness differ). In the absence of inbreeding, an individual's asymmetric kin include the individual's mother, father, half-sibs, aunts, uncles, and cousins. The individual's symmetric kin include the individual herself, her offspring, her full-sibs, and their descendants. The kinship theory applies to all interactions among asymmetric kin, but the selective forces are likely to be strongest in the context of an offspring's relations with its parents because it is here that asymmetries of relatedness are most pronounced. From an offspring's perspective, a mother has a coefficient of matrilineal relatedness of one, but a coefficient of patrilineal relatedness of zero (and conversely for fathers). Thus, the theory predicts silencing of maternal genes in offspring that benefit an offspring's individual fitness but impose costs on its mother's residual reproductive value (RRV) and silencing of paternal genes in the offspring that benefit the mother's RRV at cost to the offspring's individual fitness.

Prader-Willi syndrome (PWS) is a genetic disorder caused by the absence of paternal copies of maternally silent imprinted genes. It has a complex phenotype with effects on suckling behavior, appetite, growth, reproduction, arousal, and social relations. In this article we will first describe the genetic causes and phenotypic consequences of PWS and then attempt to use the kinship theory to understand the PWS phenotype, and to use the phenotype to make inferences about parent–offspring relations during human evolution.

PRADER-WILLI SYNDROME

Genetic causes

Prader-Willi syndrome is associated with the absence of a paternal copy of 15q11–q13, either secondary to a deletion or because of uniparental maternal disomy of chromosome 15 (i.e., both copies inherited from an affected individual's mother). Therefore, PWS is caused by the absence of expression of one or more genes that are normally silent when maternally derived but expressed when paternally derived. By contrast, Angelman syndrome (AS) is associated with the absence of a maternal copy of 15q11–q13, either because of a deletion or because of uniparental paternal disomy. Therefore, AS is caused by the absence of expression of one or more genes that are normally silent when paternally derived but expressed when maternally derived. Several imprinted loci are found in the PWS/AS chromosome region. These include loci that are silent when maternally derived and loci that are silent when paternally derived (for a recent review, see Nicholls and Knepper, 2001).

Prenatal growth

Gillessen-Kaesbach et al. (1995) reported highly significant reductions in birth weight

and birth length for a group of 167 infants with PWS. Standard growth curves for individuals with PWS from Europe (Wollmann et al., 1998) and Japan (Nagai et al., 2000) have recently been published. The latter studies reported that mean birth weight, but not birth length, is significantly reduced in PWS (the nature of the statistical comparisons, however, are unclear). Both Gillessen-Kaesbach et al. (1995) and Wollmann et al. (1998) report that head circumference is not reduced in newborns with PWS.

A reduction in birth weight, with relative sparing of length and head circumference, has been suggested to be typical of nutrient restriction in the later stages of pregnancy (Villar and Belizan, 1982). In a retrospective analysis of the birth records of 48 individuals with PWS, only one of eight (12%) born before 38 weeks was classified as small for gestational age, whereas 14 of 40 (35%) delivered at 38 weeks or later were so classified (Wharton and Bresnan, 1989). These data do not attain statistical significance but suggest that growth in PWS may be relatively normal until the final stages of pregnancy. A larger study of the relation between birth measures and gestational age is clearly needed. Human fetuses deposit large amounts of fat during the final weeks of pregnancy (see discussion in Haig, 1999). Therefore, it seems reasonable to conjecture that neonates with PWS are relatively lean, but we know of no systematic studies of body composition in PWS before the onset of childhood obesity.

A late onset of intrauterine growth retardation could be explained by the placental capacity for nutrient transfer reaching its limits earlier in PWS than in normal pregnancies. If so, growth restriction might reflect early events in placental development that do not compromise growth until late pregnancy. Alternatively, placental development might be normal but the placenta operates below its capacity in late pregnancy because fetuses with PWS fail to escalate their physiological demands on the mother. Unfortunately, we know of no studies of placental morphology in PWS.

The interpretation of birth measures that do not take account of gestational age is complicated in PWS by a high variance in gestation length. Both preterm and postterm deliveries are increased among PWS births, relative to the general population (Hall and Smith, 1972; Wharton and Bresnan, 1989).

Postnatal growth and puberty

Median height of children with PWS has fallen close to the third percentile by 3 years and follows this percentile until puberty, when children with PWS fall further behind growth standards because of the absence of pronounced pubertal growth (Wollmann et al., 1998; Nagai et al., 2000; Hauffa et al., 2000). Despite their reduced height, children with PWS are significantly heavier than their peers from about 3 years, due to the onset of obesity (Wollmann et al., 1998; Nagai et al., 2000). For their height, PWS children have low fat-free masses, high fat masses, and low bone mineral densities (Brambilla et al., 1998; Davies, 1999; van Mil et al., 2001). Thus, PWS could be characterized as growth retardation with superimposed obesity. Its distinctive feature, relative to other forms of obesity, is the low fat-free mass and delayed growth.

The reduced linear growth of children with PWS, and their unusual body composition, appears to be partly due to growth hormone (GH) deficiency (Eiholzer et al., 2000). Not only are levels of GH reduced in children with PWS (Costeff et al., 1990; Angulo et al., 1991), but these children also show blunted GH release in response to GH-releasing hormones and peptides (Cappa et al., 1998; Grugni et al., 2001). Finally, treatment with exogenous GH reduces fat mass, increases lean tissue mass, and increases linear growth (Davies et al., 1998; Carrel et al., 1999; Eiholzer and l'Allemand, 2000).

Most individuals with PWS suffer from hypogonadotropic hypogonadism (for a recent review, see Burman et al., 2001). Puberty (more strictly gonadarche) is often delayed, and may not occur in some individuals. However, many experience premature adrenarche. Pubertal development is notable for its high variability, including cases of precocious menarche (Kauli et al., 1978; Walterspiel et al., 1981). This variation in the onset of puberty is reminiscent of the unusually variable gestation length also observed in PWS (see above).

Activity levels and energy expenditure

Newborn infants with PWS are dramatically somnolent and rarely awake for feeds (Wharton et al., 1992). Neonatal sleepiness is probably a continuation of behavior in

utero. Hiroi et al. (2000) observed prolonged inactive periods and shortened active periods in a fetus subsequently diagnosed with PWS. Hypersomnolence remains a general feature of PWS at all ages (Vela-Bueno et al., 1984; Clarke et al., 1989; Vgontzas et al., 1996; Manni et al., 2001). By contrast, reduced sleep with frequent waking is a feature of Angelman syndrome (Magenis et al., 1990; Clayton-Smith, 1993). For example, an 8-month-old daughter with AS of a mother with PWS slept only 6–8 hours per day (Schulze et al., 2001).

An early observation of clinicians who attempted to control obesity in PWS by dietary restriction was that children would gain weight on diets that would result in a loss of weight in obese controls (Pipes and Holm, 1973; Holm and Pipes, 1976). Basal and resting metabolic rates appear to be normal at the tissue level, with reduced energy expenditure a consequence of low activity and the unusual body composition of high adiposity with low fat-free mass (Schoeller et al., 1988; Schrander-Stumpel et al., 2000; Goldstone et al., 2002).

Appetite

The appetite of children with PWS undergoes remarkable developmental change. PWS children are born with profound central hypotonia and poor suck (Morgan and Rolles, 1984; Butler, 1990; Holm et al., 1993), with most requiring several weeks of tube feeding (e.g., Ehara et al., 1995). Changes in appetite can be noted during early childhood. Some children may develop a voracious appetite rather quickly, while others follow a pattern with "nonselective" eating at first, followed by consistently finishing their meals, which in turn precedes excessive eating, food stealing, and foraging that develop later in childhood. The timing of these changes is poorly defined but typically precedes obesity. Holm and Pipes (1976) report onset of rapid weight gain from 15 months to 4 years, 6 months; Butler (1990) reports the onset of obesity between 1 and 6 years, with an average age of 2 years (some cases as early as 6 months: Butler et al., 1991); Holland et al. (1995) report a mean age of onset of excessive eating of 3.4 years (range 1–9 years); whereas Ehara et al. (1995) report that weight gain in Japanese individuals with PWS increases dramatically after 10–18 months.

After their change in appetite, children with PWS are described as being obsessed or preoccupied with food and eating and are sometimes described as "foraging" for food (Page et al., 1993; Holm et al., 1993). When given free access to food, they do not eat more rapidly than other children, but eat for longer periods (Zipf and Berntson, 1987; Lindgren et al., 2000). While such observations have led to the suggestion that PWS is characterized by decreased satiety (Lindgren et al., 2000), increased hunger certainly also plays a role.

Individuals with PWS are more likely than controls to choose a larger amount of a less-preferred food than a smaller amount of a preferred food (Glover et al., 1996) and are more likely to choose a larger amount of a food delivered after a delay than a smaller amount delivered immediately (Joseph et al., 2002). The latter indicates that they are not simply impulsive eaters. Unlike their peers, children with PWS are not fastidious eaters and will eat unappealing foods, including frozen food and other people's discarded leftovers (Holm and Pipes, 1976; Dykens, 2000).

PRADER-WILLI SYNDROME IN EVOLUTIONARY PERSPECTIVE

PWS is caused by the absence (or absence of expression) of paternally derived alleles at one or more imprinted loci from 15q11–q13. Therefore, the kinship theory predicts that small decreases in expression at these loci would have reduced a child's individual fitness but have increased its mother's resdiual reproductive value. This prediction is based on the plausible assumption that humans have not been strictly monogamous, otherwise costs to mothers would be associated with equal costs to fathers — because her offspring are his offspring — and there would be no selective force maintaining differential gene expression (see Burt and Trivers, 1998; Lessells and Parker, 1999, for qualifications to the last statement).

Three caveats deserve mention before discussing the PWS phenotype in an evolutionary context. First, PWS is associated with the absence of expression of paternally derived alleles, but the kinship theory does not make direct predictions about the fitness consequences of zero expression at imprinted loci; rather, it predicts the consequences of small increases and decreases of expression (Fig. 1). That is, absence of

expression is a major perturbation and its effects must be interpreted with caution. Nevertheless, these effects can provide important clues about the selective forces that have acted on smaller changes of expression. Second, the complex PWS phenotype may have components that have evolved outside the context of selection on the maternal costs of child-rearing. Third, genes in the PWS region need not affect all the costs of child-rearing. Our discussion will focus on feeding costs and how these are related to changes in a child's appetite.

Alternative foods

During human evolution, four sources of nutrients have supported the growth of dependent children: first, transfer across the placenta; second, breast milk; third, foraged food obtained by the child; and, fourth, supplemental food obtained by the foraging efforts of other group members (including the child's mother). A major reliance on supplemental food is a distinctive feature of the human life cycle and has allowed human mothers to wean their offspring earlier than do other great apes (Kaplan, 1997; Hawkes et al., 1998). As a result, human childhood includes a prolonged juvenile period in which offspring are weaned but still nutritionally dependent on adults.

The relative importance of these different sources of nutrients varied over the course of a child's development. Placental transfer ceased abruptly at birth and was replaced by lactation. Anthropological data suggest that most children were weaned before their third birthday (Marlowe, 2001; Sellen and Smay, 2001), with supplemental foods introduced early, usually within the first six months (e.g., Waterlow et al., 1980; Winikoff et al., 1988; Dupras et al., 2001). The age at which children began to make a substantial contribution to their own nutrition is less clear. Among modern hunter-foragers, !Kung children made little economic contribution to their own subsistence (Draper, 1976), whereas Hadza children younger than 10 years regularly brought home more than 50% of their daily caloric requirements (Blurton Jones et al., 1997).

We assume that mothers have typically borne more of the costs of bearing and rearing a child than have fathers. In the case of prenatal and suckling costs, this is a direct consequence of ancient features of mammalian reproduction, but mothers have probably also provided a greater share of supplemental foods. Even in hunter-gatherer societies in which men made a greater contribution to a group's total food production than did women, most of a woman's foraging efforts were directed to feeding her own family, whereas the products of a male's effort were more widely shared (Hill and Kaplan, 1988; Hawkes, 1993). Moreover, when a male provided food to children of his current wife, these need not have been his own offspring, either because they were offspring of a previous marriage or because his wife had other sexual partners.

Before the introduction of supplemental food, the more milk that a child consumes, the greater the cost to its mother. But once infants are able to take alternative foods, the situation becomes more complex. Maternal costs would be reduced by replacing milk with food that infants forage for themselves, or with supplemental foods provided by other group members, but the costs and benefits for a mother of replacing milk with supplemental foods obtained by her own efforts are less clear, because this depends on the relative cost of the two modes of delivery. No absolute statement is possible but, other things being equal, it would be energetically more efficient for a mother to provide food directly to a child than for the mother to add an extra step in the food chain by consuming the food herself and converting it into milk to be fed to the child.

Appetite and Prader-Willi syndrome

For the maternal and paternal genomes of an offspring to "disagree" over the level of costs imposed on a mother, maternal costs must be associated with offspring benefits. The maternal costs of lactation clearly satisfy this condition. Thus, the kinship theory predicts paternal expression (and maternal silence) of genes that enhance a child's appetite at an age when the child is solely dependent on breast milk. PWS provides evidence in support of this prediction because, in the absence of paternally expressed genes, newborns have a profoundly depressed suckling reflex.

Can the kinship theory also explain the change of appetite observed in PWS? The timing of the change suggests some association with the weaning process, but an

adaptive interpretation is not immediately obvious. However, we will offer some tentative suggestions, on the principle that it is better to have a weak hypothesis, to be refined or rejected, than no hypothesis at all.

Paternal expression (and maternal silence) of genes that inhibit a child's appetite for supplemental food would be predicted given two conditions: first, the reduced intake of supplemental food must have increased maternal costs; second, reduced intake of supplemental food must have benefited offspring. We have argued above that reduced intake of supplemental food would have increased maternal costs if the shortfall were made up by increased suckling, but we are yet to give reasons why offspring would benefit from substituting milk for supplemental foods. Among direct benefits, milk might be a nutritionally or immunologically superior food. Among indirect benefits, offspring might benefit from the contraceptive effects of suckling that delay the arrival of a younger sib (Blurton Jones and da Costa, 1987).

The correspondence between the age at which appetite increases in children with PWS and the age at which our ancestors probably introduced supplemental food suggests that offspring fitness was enhanced by reduced appetite for such foods, but the nature of the benefit to children from refusing proffered food is unclear. Was refusal compensated by increased provision of milk? Perhaps, but the infant who turns down a carrot does not immediately demand the breast. He is more likely to demand a popsicle. The evolutionary trade-off facing children and their mothers may have been between alternative supplemental foods; between difficult-to-obtain foods of high value and those that were more easily collected. Prepubertal children grow at well below the rate permitted by their food supply, suggesting that there may have been advantages of staying small (Haig, 1999). More may not always have been better.

In the conventional interpretation of parent–offspring conflict, offspring are envisaged as demanding more food from parents than parents are willing to supply. But this interpretation does not ring true to parents who have experienced the frustration of coaxing and cajoling an infant to eat. Most parents would find it strange to be told that an infant would eat whenever, and whatever, food was placed in front of it, but this is just the behavior reported for children with PWS. In this section, we have tentatively suggested that offspring fitness was enhanced by reduced appetite. Our interpretations are largely based on anecdotal observations of food-related behaviors in modern industrial societies. It would be useful to have more systematic data on food behaviors in diverse cultures. The subjective impression of anthropologists that we have consulted who have personal experience of modern foraging societies is that food-refusal by infants is an oddity of our own culture (K. Hawkes, F. Marlowe, pers. commun.).

Children with PWS differ from the general population in what their bodies do with food. Specifically, there is a shift of resources from general activity and growth of lean body mass toward increased deposition of fat. Is there a hint here of the expression of a "thrifty" maternal epigenotype that is unmasked by the absence of a "spendthrift" paternal epigenotype? Why should the maternal genome favor a physiology that is better suited to an unpredictable food supply than to a guaranteed daily supply? If the costs of feeding offspring were particularly intense during times of food shortage, mothers may have benefited from having to allocate less of limited food to satisfying the needs of a smaller, plumper child who had relatively low maintenance costs and substantial caloric reserves.

Maternal fitness is also likely to have benefited from shifts in the means of meeting infant requirements to a greater reliance on food collected by a child's own efforts. Anecdotal reports of "foraging" by children with PWS suggest paternally expressed genes may also suppress food-seeking in favor of other activities, but the foraging behaviors of children with PWS are poorly characterized.

Nonfeeding costs

The maternal costs of rearing a child have not been limited to the feeding cost of providing nutrients to support the child's growth and metabolism, but have also included the carrying cost of transporting the child (Blurton Jones and Sibly, 1978), and the attention cost of supervising the child's exploratory activities. That is, children have been able to learn about the world in relative safety by using the sensory and motor systems of their mothers (or other

care-providers) to avoid danger, but this supervision has come at the expense of less time and attention available to mothers for other fitness-enhancing activities.

Our discussion has focused on questions of appetite and feeding costs, but other aspects of the PWS phenotype, and other kinds of costs to mothers, may also repay evolutionary analysis. Most parents will have experienced a sense of relief when an infant finally falls asleep. The hypersomnolence of PWS suggests that paternally expressed genes at 15q11–q13 enhance an infant's wakefulness and that this has increased costs to mothers (an unsurprising observation) for infant benefit (an interesting observation). For other aspects, the story is less clear, and therefore potentially more interesting. What, if anything, does the highly variable onset of puberty have to tell us about the selective forces favoring the prolongation of human childhood?

CONCLUSIONS

If the kinship theory is accepted as the explanation for the origin and maintenance of genomic imprinting, then the fact that a locus is imprinted provides considerable inferential power about the selective forces acting on the locus. That is, at least some of the locus's phenotypic effects must have had fitness consequences for asymmetric kin. Therefore, the study of imprinted genes in humans can potentially provide insight into kin interactions in our evolutionary past.

We have illustrated this approach with the example of Prader-Willi syndrome. Marginal decreases in expression of the paternally active loci, whose absence of expression is responsible for PWS, would be predicted to reduce offspring fitness but increase the mother's expected return from other, concurrent or future, offspring. The PWS phenotype suggests that the internal "conflict," between the maternal and paternal genomes of a child, has partly been played out by subtle shifts in behavioral thresholds that increase the child's probability of engaging in some activities but not others (e.g., choices among play, sleep, and feeding) and shifts in the timing of important developmental transitions (birth, weaning, puberty). Some of our conclusions are unsurprising. Placental and mammary transfers benefit an offspring at an opportunity cost to its mother. Other conclusions are less obvious. Young children's relative disinterest in eating is proposed to have enhanced their individual fitness at a cost to their mothers' residual reproductive values.

Thus, a detailed study of PWS has the potential to illuminate important issues in human evolution, but are there reciprocal benefits? Does an evolutionary analysis have anything to contribute to understanding the etiology of PWS? Imprinted expression of genes in the PWS/AS chromosome region has been conserved between mice and humans. The kinship theory can be used to generate predictions about what aspects of the PWS phenotype are likely to reflect evolutionarily conserved mechanisms and what aspects are likely to be distinctively human. The best available models of PWS are mice with paternal deletions of all, or most, of the PWS/AS gene cluster (Gabriel et al., 1999; Tsai et al., 1999). These mice display neonatal hypotonia, reduced (but not absent) suckling, and reduced postnatal growth; all aspects of the PWS phenotype. The conservation of effects on suckling and on suckling-fueled growth is consistent with the conservation of maternal costs associated with lactation. However, the mice do not develop hyperphagia or obesity. We suggest that these differences reflect the distinctively human reliance on supplemental foods and our long period of postweaning dependence.

The prevention of excessive food intake is one of the major problems for parents and clinicians caring for children with PWS. What can evolutionary biology contribute to amelioration of this problem? The short answer is, little, directly. Medical interventions must be tested against results and major progress is likely to come from advances in understanding the molecular, neurological, and endocrine causes of PWS. Evolutionary biology can, however, provide a new perspective and suggest questions that might otherwise not be asked.

Our analysis suggests that the absence of expression of paternal copies of genes at 15q11–q13 may not be responsible for an unbridled appetite per se, but only for a voracious appetite for particular categories of foods; that is, for foods that reduced costs to mothers in the evolutionary past. Is this true? If so, could it help to explain the feeding and appetite disorder seen in children with PWS? Further, could such an understanding be exploited to reduce the

overeating associated with PWS? Does bottle-feeding evoke a lack of appetite appropriate to breast feeding or an active appetite appropriate to supplemental foods? If children with PWS are primed to expend more energy to obtain food, could this behavioral tendency be utilized to increase their physical activity, with associated health benefits? We do not have answers to any of these questions, but they suggest that a detailed study of the "natural history" of PWS may provide useful insights.

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