

## Hypothesis

# The paradox of Prader-Willi syndrome: a genetic model of starvation

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**The neurodevelopmental disorder, Prader-Willi syndrome, is generally regarded as a genetic model of obesity. Although the values of some hypothalamic neuropeptides are as expected in obesity, and should result in satiety, we propose that abnormal hypothalamic pathways mean that these are ineffective. We postulate that the body incorrectly interprets the absence of satiety as starvation, and therefore, paradoxically, this syndrome should be redefined as one of starvation that manifests as obesity in a food-rich environment. Also, this syndrome is generally believed to be a contiguous gene disorder, which results from the absence of expression of the paternally derived alleles of maternally imprinted genes on chromosome 15 (15q11–13). We argue, however, that the whole phenotype can be explained by one mechanism and, by implication, the failure of expression of the paternal allele of a single maternally imprinted gene that controls energy balance. We suggest clinical and laboratory approaches to test our hypotheses.**

## Phenotype

Prader-Willi syndrome is thought to result from the absence of expression of the paternally derived alleles of maternally imprinted genes in a critical region of about 121 kb of the SNRPN locus at 15q11–13.<sup>1</sup> The syndrome is mainly characterised by two distinct phenotypes. In the first, fetal movement is restricted, and evidence of fetal growth retardation and severe hypotonia is noted at birth. The infant fails to thrive and tube feeding is necessary. The second phenotype is seen from about age 2 years, by which time most children are weaned. Individuals show a striking propensity to eat excessively throughout life, and obesity can only effectively be prevented by controlled access to food. Developmental delay, impaired acquisition of educational and functional skills, and below-average intellectual ability are also seen.<sup>2</sup> Short stature, small hands and feet, a narrow biparietal diameter of the head, and impaired sexual development make up the physical phenotype. Ritualistic behaviours, severe temper outbursts, and skin picking are frequently noted, together with an abnormal sleep pattern, poor temperature regulation, and a high pain threshold.<sup>2</sup> For some, especially those whose syndrome is caused by chromosome 15 disomy, a third phenotype might emerge in early adult life characterised by the development of severe affective psychotic illness.<sup>3</sup>

## Pathophysiology

The mechanisms underpinning the physical phenotype include growth hormone deficiency and central hypogonadism. Thyroid and adrenal function are normal.<sup>4</sup> Growth hormone replacement in childhood is recommended and not only improves adult height, but also size of hands and feet, facial dysmorphism, and muscle bulk.<sup>5</sup> Growth hormone and gonadotropin deficiencies might also, together with other abnormalities, partly account for the disproportionate fat versus lean

body mass in people with Prader-Willi syndrome that is atypical compared with other forms of obesity.<sup>6</sup>

The severe obesity regarded as characteristic of the syndrome is largely due to excessive eating if allowed access to food, compounded by a low metabolic rate and high fat versus lean body mass. An abnormal satiety response could be why food intake does not lead to loss of hunger, resulting in continued eating.<sup>7</sup> Neonatal hypotonia, failure to thrive, hypogonadism, and overeating are the features that are invariably present in Prader-Willi syndrome. The absence of any one of these signs is associated with a negative genetic diagnosis.

The intelligence quotient (IQ) of a population-based sample of people with Prader-Willi syndrome is normally distributed with a mean full scale IQ of 60. This shift in IQ is probably due to a single major effect; parental IQ and psychosocial factors account for the distribution, as they do in the general population. In the same study, ritualistic behaviours were present in 80% of the participants. These behaviours had similar characteristics to the rituals and routines arising as part of healthy childhood development. These cognitive and behavioural characteristics can be best explained by arrested brain development.<sup>2</sup>

Thus for a single mechanism, and thereby a single gene model to be accepted, the endophenotypic characteristics that would need one explanation are: growth and gonadotropin hormonal deficiencies (physical phenotype), arrested brain development (mental retardation and behaviour pattern), and the abnormal satiety response (obesity), together with the childhood characteristics of neonatal hypotonia and failure to thrive.

## Hypothesis

We propose that this syndrome should be redefined as one of starvation that manifests as obesity in a food-rich environment, and that the whole phenotype can be explained by a single mechanism. We put forward two main arguments in support of our hypothesis of starvation. Neither contains all the research evidence, and some evidence is contradictory, but together they provide strong support for this idea. The first is related to the body's ability to balance energy intake and energy expenditure over time to support growth and metabolic, physical, and cerebral activity, and reproduction. This

*Lancet* 2003; **362**: 989–91

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balance is achieved by complementary and counterbalancing feedback mechanisms through the release of gut hormones that stimulate or inhibit eating by their action on hypothalamic nuclei.<sup>8</sup> The second is the role of imprinted genes in the placenta.

Of the anorexigenic agents investigated in Prader-Willi syndrome, blood cholecystokinin concentrations increase after food intake<sup>7</sup> and leptin concentrations are as would be expected in relation to the fat mass.<sup>6</sup> High leptin levels are associated, as would be predicted, with reduced levels of the orexigenic neuropeptide Y and agouti-related protein in the hypothalamus, as is seen in other obese groups.<sup>9</sup> Oxytocin-containing neurones in the hypothalamus are also reduced, which might contribute to the abnormal satiety response. Importantly, these values of cholecystokinin, leptin, and hypothalamic neuropeptide Y and agouti-related protein would usually be associated with a state of satiation, but clearly are not in Prader-Willi syndrome. Thus, we propose that the fundamental pathophysiological abnormality in this syndrome is that these particular peripheral factors do not lead to the metabolic and psychological changes (eg, loss of hunger) controlled by the hypothalamus that usually follow food intake. In this syndrome, because of a postulated interruption of the normal hypothalamic pathways (caused by the genetic abnormality), the body incorrectly perceives itself to be in a state of starvation. As a result, the metabolic rate is low and gonadotropin release is impaired, as in starvation states such as anorexia nervosa.

Further support for the starvation model comes from evidence that concentrations of the orexigenic hormone ghrelin are substantially raised in people with Prader-Willi syndrome, compared with groups of obese and non-obese people who do not have this syndrome,<sup>10</sup> and people with anorexia nervosa.<sup>11</sup> Ghrelin concentrations in Prader-Willi syndrome do not vary with food intake nor correlate with hunger ratings. A finding that links eating and growth hormone secretion is that ghrelin is a ligand of the growth hormone secretagogue receptor (GHS-R),<sup>12</sup> and stimulates growth hormone-releasing hormone and therefore growth hormone release.<sup>13</sup> However, in this disorder, contrary to expectation, high ghrelin concentrations are not associated with high or even normal values of growth hormone, despite the presence of normal growth hormone-releasing hormone neurones. This observation might be explained by findings in rats that continuous stimulation by ghrelin results in desensitisation of the growth hormone secretory response.<sup>14</sup> We postulate that the desensitisation of GHS-R, caused by chronically increased values of ghrelin, is one possible explanation for the growth hormone deficiency. The eating behaviour, and the growth hormone and gonadotropin deficits (and thereby the physical phenotype) can therefore be accounted for by a single pathophysiological mechanism.

### Fetal starvation

Other features of the phenotype that also need to be clarified are neonatal hypotonia, failure to thrive, and arrested brain development. We believe that the starvation model could also apply to the early phenotype. We propose that absence of expression of the imprinted gene for Prader-Willi syndrome in the placenta could disrupt nutrition to the fetus, resulting in fetal starvation and abnormal brain development. Another factor might be the detrimental effects of low concentrations of growth hormone and insulin-like growth hormone (IGF) on brain development<sup>15</sup> and on muscle mass in the fetus. During fetal and infant life until weaning, growth is controlled by

the mother, through regulation across the placenta and, after birth, by milk supply. After weaning, control of energy balance is centrally regulated by the infant.

Prader-Willi syndrome is caused by one or more imprinted genes and there is considerable evidence that such genes are important in the control of fetal growth.<sup>16</sup> For example, results of investigations in mice have shown that manipulation of expression of the maternally imprinted IGF2 gene results in dwarfing, and the product of this gene is thought to be a growth factor for both placental and embryonic compartments.<sup>17</sup> We do not yet know which imprinted genes on chromosome 15 are expressed in the human placenta, and we have not come across results of investigations of hormone concentrations (such as growth hormone, ghrelin, or leptin) in babies with the syndrome. However, all three hormones have been studied in cord blood from healthy babies at delivery.<sup>18</sup> The role of ghrelin in the placenta is not known, but leptin and leptin receptor integrity is believed to be important for placental function.<sup>19</sup> Indirect support for the deficit being placental rather than fetal in origin comes from the evidence of pronounced catch-up growth that takes place with augmented feeding immediately after birth.<sup>5</sup>

Deletion, disomy, and knockout mouse models of this syndrome have been developed but because the animals do not thrive they do not live long enough for a full Prader-Willi syndrome phenotype to develop. Investigations of mouse hypothalamus in the deletion model have also found down-regulation of neuropeptide Y and agouti-related protein, and up-regulation of pro-opiomelanocortin in the early mouse phenotype.<sup>20</sup> These findings are contrary to what would be expected from a starvation model. However, the paradox is that in this preweaned state, the mouse pup is primed to behave as if not needing energy when in fact its body is undernourished (starved). We propose that after weaning, when new hypothalamic mechanisms come into play, a switch takes place, and later mechanisms that restrict food intake do not operate in individuals with Prader-Willi syndrome. Only when animal models are developed that survive to adult life can such a hypothesis be tested.

### Testing the hypothesis

Although people with this disorder are not starved, their behaviour and much of the associated physiology is as if they are in a state of starvation. This hypothesis led us to the idea that the mechanisms giving rise to the phenotype could result from a single abnormality in energy balance, and by implication, the absence of expression of a single gene. Other phenotypic characteristics, such as the high pain threshold and skin picking, might also originate from associated dysfunction of the endorphin and serotonergic systems, respectively. Abnormalities of vasopressin and oxytocin could also be important. The later development of psychopathology does not seem to be directly associated with Prader-Willi syndrome but rather with chromosome 15 disomy. In this case, either underexpression of a maternally imprinted gene or overexpression of a paternally imprinted gene on chromosome 15 would probably be the genetic mechanism.

These different models can be tested, first, by investigation of expression of maternally imprinted genes for Prader-Willi syndrome in the placenta of healthy and affected individuals. They could also be tested by study of leptin and ghrelin and their receptors in placenta and in hypothalamic pathways, in both human tissue and animal models. Additionally, a single gene model would predict

that there should be individuals who meet all the criteria for Prader-Willi syndrome inherited via the paternal line and who might be negative on the standard genetic test. The absence of this last finding so far, is one of the strongest arguments against Prader-Willi syndrome being a single gene disorder. However, investigation of individuals meeting clinical criteria for Prader-Willi syndrome, who are negative on routine methylation diagnostic testing, for mutations in possible Prader-Willi genes, and a detailed family history would be indicated. Finally, animal models of this syndrome that include knockouts of putative genes for the disorder offer a powerful means to explore genotype and phenotype associations. Although failure to thrive is a notable feature for some models, few have lived long enough to establish whether overeating and other behaviours become apparent. This hypothetical model points to these new directions in Prader-Willi syndrome research.

#### Contributors

A Holland had the original idea for this Hypothesis and wrote the first draft. All authors were involved in discussion and in the development of the ideas in this report. J Whittington worked on subsequent drafts and A Holland prepared the final draft.

#### Conflict of interest statement

None declared.

#### Acknowledgments

AH holds the PPP Foundation Chair in Learning Disabilities, and JW is supported by a grant from the Wellcome Trust and the UK Prader-Willi Syndrome Association (PWSA), and EH by a bequest to the UK PWSA. We acknowledge the support of these organisations and also the help we received from people with Prader-Willi syndrome, and their families and carers, during the course of our own research. None of these funding bodies have had any influence on the content of this report.

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