ARTICLE

Neurobehavioral Phenotype in Prader–Willi Syndrome

JOYCE WHITTINGTON* AND ANTHONY HOLLAND

The focus of this article is on the lifetime development of people with Prader–Willi syndrome (PWS) and specifically on the neurobehavioral phenotype. We consider studies of this aspect of the phenotype (the ''behavioral phenotype'' of the syndrome) that have confirmed that there are specific behaviors and psychiatric disorders, the propensities to which are increased in those with PWS, and cannot be accounted for by other variables such as IQ or adaptive behavior. Beginning with a description of what is observed in people with PWS, we review the evolving PWS phenotype and consider how some aspects of the phenotype might be best explained, and how this complex phenotype may relate to the equally complex genotype. We then consider in more detail some of the neurobehavioral aspects of the phenotype listed above that raise the greatest management problems for parents and carers.

KEY WORDS: Prader–Willi syndrome; behavioral phenotypes; genomic imprinting; abnormal satiety; psychotic illness

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INTRODUCTION

Prader–Willi syndrome (PWS) was first described in the scientific literature over 50 years ago [Prader et al., 1956]. Whilst a genetic origin for the syndrome was suspected at the time, it was over 30 years before the different genetic subtypes of PWS were described and potential candidate genes at the 15q11-13 locus were identified. Although there has been a reliable diagnostic test for some time [Ramsden et al., 2010] the genetic complexity at the PWS locus and identified epigenetic effects in the etiology of PWS has meant that initial optimism that the genetics of the syndrome would soon be fully elucidated has, however, not as yet been fulfilled. From a different perspective, that of endocrinology, the characterization of the relative growth hormone and sex hormone deficiencies in PWS [Burman et al., 2001] and now the routine use of growth hormone supplementation have led to significant benefits in terms of improved stature and muscle mass, and in other phenotypic characteristics. Perhaps the most significant advance has, however, been in the depth of understanding we now have about the nature of the PWS phenotype and some possible mechanisms that link genotype to phenotype. When this knowledge is combined with early diagnosis it is now possible to advise parents about the eating disorder and other characteristic of PWS so that severe obesity can be avoided and family and educational support can be fully informed. Compared to 20 years ago in many countries there is now a generation of children who have been diagnosed with PWS within days or, at most, weeks after birth. These children have access to food in a managed environment and therefore gross obesity has been avoided and, with growth hormone supplementation, many have normal growth trajectories and final heights compatible with parental height. With the establishment of national PWS Associations and the availability of information via the Internet, parents are now much more knowledgeable. Best practice guidance is also available for health practitioners [Goldstone et al., 2008]. The challenge has increasingly shifted from childhood to support in adult life when the propensity to overeat becomes a problem with increasing independence and new problems may arise with the onset of co-morbid physical and psychiatric illnesses such as diabetes mellitus and affective disorders [Butler et al., 2002].

In reviewing the progress that has been made the focus of this article is on

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the lifetime development of people with PWS and specifically on the neurobehavioral phenotype. This aspect of the phenotype (now often referred to as the "behavioral phenotype" of the syndrome) has been very well described in many studies from different countries. Essentially these studies have confirmed that there are specific behaviors and psychiatric disorders, the propensities to which are increased in those with PWS and cannot be accounted for by other variables such as IQ or adaptive behavior. Behaviors include excessive eating, specific repetitive and ritualistic behaviors, self-injurious behaviors (e.g., skin picking), temper outbursts, lying and stealing, reduced levels of activity, and mood and sleep disturbances [Dykens and Kasari, 1997; Einfeld et al., 1999; Dimitropoulos et al., 2001; Wigren and Hansen, 2003; Holland et al., 2003b]. In this article we review the evolving PWS phenotype and consider how some aspects of the phenotype might be best explained, and how this complex phenotype may relate to the equally complex genotype. We then consider in more detail some of the neurobehavioral aspects of the phenotype listed above that raise the greatest management problems for parents and carers. We begin by describing what is observed in people with PWS.

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THE OBSERVED PHENOTYPES

PWS is a relatively rare, genetically determined neurodevelopmental disorder with a birth incidence of 1:22,000–1:25,000 [Whittington et al., 2001; Smith et al., 2003; Vogels et al., 2003]. There is also a relatively high mortality rate across all ages, compared to both the general population and to other groups of people with intellectual disabilities (ID) [Whittington et al., 2001; Einfeld et al., 2006]. Consequently, there is a very small older population of people with PWS. It has long been acknowledged that there are two distinct phenotypic stages characterizing people with PWS, from the neonate through to adulthood [Holm et al., 1993]. More recently it has been proposed that there may be other intermediate and also later stages [Butler et al., 2010; Driscoll, 2010] but this has not yet been generally accepted or fully researched. The first stage is present at birth and lasts for a variable period, usually 1–3 years. It is characterized by hypotonia, feeding difficulties (in our population sample 100% were both hypotonic and had feeding difficulties), failure to thrive, hypogonadism (100% of males in our cohort had undescended testes), lethargy, and no interest in feeding. Birth length is within the normal range but birth weight is low [Dudley and Muscatelli, 2007; Whittington et al., 2008]. Gradually the hypotonia diminishes, although physical milestones are usually delayed and activity levels usually remain low. The baby starts to feed more normally, although very few can be breast-fed. Many babies with PWS at this early age still require specially adapted teats and feeds may take much longer than normal. Interest in food appears to become more normal before increasing and eventually becoming greater than normal. This interest may manifest itself in different ways, such as being a major component of the child's play activities, in their topic of conversation, as a constant request for food, or as active foraging [Butler et al., 2010]. Height gradually falls behind what is expected and weight can gradually overtake that of peers in the absence of any intervention [Butler et al., 2010]. As described later, it is the onset of the apparent insatiable appetite relatively early in life and the resultant risk of severe and life-threatening obesity, if access to food is not managed, that has a very significant impact on the lives of people with PWS and that of their families. It is this eating behavior that accounts for the high rates of obesity-related morbidity (such as diabetes mellitus), [see Butler et al., 2002] and contributes to the increased mortality across the lifespan.

Other physical features, which may be observed early in life, include the characteristic facial appearance, such as narrow forehead, almond-shaped eyes and triangular mouth [Holm et al., 1993]; eye problems, especially squint; and scoliosis, that are sometimes present from birth or may emerge later,

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especially in adolescence [de Lind van Wijngaarden et al., 2008; Odent et al., 2008]. Regulatory abnormalities may also be observed including excessive daytime sleepiness [Maas et al., 2010], temperature instability and/or insensitivity, and a high pain threshold [Whittington and Holland, 2004a]. Other neurobehavioral aspects that emerge early and persist throughout life, often reaching a peak in late adolescence and early adulthood, include obsessiveness (especially insistence on routine, the need to ask or tell, and hoarding), temper outbursts that are often related to disappointed expectations (such as a meal that is late or an outing that is cancelled); brief mood swings changing rapidly even over the course of a day; and skin picking that can be severe enough to require hospitalization [Holm et al., 1993; Holland et al., 2003b].

By school age intellectual and social difficulties become more apparent. Most people with PWS have mild to moderate ID. Although some people with PWS have an IQ in what is considered the normal range, they still appear less able than IQ-matched peers in the general population [Sulzbacher et al., 1981; Whittington and Holland, 2004b]. Abstract concepts, in general, and concepts of time, in particular, present difficulties for people with PWS. Social cognition may also be impaired. Most people with PWS have difficulties relating to their peer groups and often prefer to be with older or younger groups. People with PWS may withdraw into solitary activities, for example, doing word searches and jigsaw puzzles, rather than activities with their peers. In adolescence there is lack of a growth spurt, resulting in small stature. Females usually do not menstruate or menstruation is sporadic and infrequent [Holm et al., 1993]. In adulthood, occasionally earlier in life, severe psychiatric illness may develop and affective disorder (depression) and affective psychosis (particularly in those with PWS due to mUPD) are relatively common [Boer et al., 2002; Vogels et al., 2004; Soni et al., 2007].

In the above descriptions of phenotypic features of PWS, we need to distinguish those that appear to be universally present (“core” characteristics), from those that appear to have a lower, but still high, prevalence rate. For example, core features include hypotonia, feeding difficulties and hypogonadism in the neonatal period, and later they also include excessive interest in food and cognitive difficulties. These appear to be universal (an absence of one of these predicts negative genetics). In contrast, skin picking, mood swings, and scoliosis are not universal [Whittington et al., 2002]. The variability in the salience of the various phenotypic features across individuals also needs to be stressed. How can we account for these observations? We consider the genetics of the syndrome first and then how mechanisms that link genotype to phenotype might account for some of the observations described above and the implications for support and intervention.

THE GENETICS OF PWS

PWS is caused by the absence of expression of genes, located in the region q11-q13 of chromosome 15 (the PWS critical region or PWSCR), in which the alleles of maternal origin are imprinted and not expressed and only the alleles of paternal origin are expressed [Nicholls, 1993]. Most often this loss of expression from the normally active allele (of paternal origin) is due to an interstitial deletion of all or part of the PWSCR in the chromosome 15 of paternal origin (delPWS). A deletion in a similar area of chromosome 15 but of maternal origin results in a very different syndrome—Angelman syndrome [Knoll et al., 1989]. Most other cases of PWS are due to the inheritance of two chromosome 15s from the mother and none from the father (known as maternal uniparental disomy or mUPD). The proportion of mUPD cases has been found to be variable, ranging from 25% to 50%, depending on the proportion of older mothers in the population under consideration [Whittington et al., 2006]. A much smaller proportion of people with PWS (2–5%) have the presence of an imprinting error. In these cases the paternal grandmother’s imprint fails to reset. As a result the paternally inherited alleles of the maternally imprinted genes at 15q11-q13 inherited by the grandchild via his/her father have the maternal pattern of imprinting and are therefore not expressed.

Importantly, whilst the genetic subtypes of PWS have in common the absence of expression of specific maternally imprinted genes in the PWSCR, there are also genotypic differences between the two main genetic subtypes. The mUPD and imprinting error genotypes of PWS lack expression of all maternally imprinted genes on chromosome 15 and also express both copies of any paternally imprinted genes. They also have two alleles of all non-imprinted genes on chromosomes 15 in the PWSCR. Those with delPWS lack maternally imprinted/paternally expressed alleles of paternal origin in the PWSCR (and therefore have PWS) but, in contrast to those with PWS due to mUPD, they have a normal single copy of paternally imprinted/maternally expressed genes of maternal origin and only a single copy of non-imprinted genes within the PWSCR (giving rise to increased probability that a recessive gene is expressed). These variations in genotype result in phenotypic differences, which are currently popular and informative research topics.

The mUPD and imprinting error genotypes are consistent with respect to the copy number of the various types of gene, but for those with delPWS, the deletions can vary in size. Most people with delPWS have one breakpoint (known as breakpoint 3) in common

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and the other breakpoint in one of two locations (known as breakpoints 1 and 2, the former giving the larger deleted region) [Buiting et al., 1998]. These deletion genotypes are known as Type 1 and Type 2, respectively. Phenotypic differences between these genetic subtypes are beginning to be researched and may yield information about the function of genes in the region between breakpoint 1 and breakpoint 2. Unfortunately, the rarity of the syndrome, individual differences in the strength of phenotypic characteristics, and the rarity and inconsistency of other deletion breakpoints means that we cannot infer the influence of individual genes on phenotype characteristics from deletions that include or exclude alleles of such genes. Moreover, since almost all people with PWS lack expression of all the maternally imprinted genes between breakpoints 2 and 3, with the exception of those described below, we do not know which of these genes are necessary in explaining the common phenotype. The study of people who are found to have most of the PWS phenotype but who have unusual genetics is one strategy that is being used to narrow down the key gene or genes whose absence of expression results in the core and/or extended PWS phenotype. There have now been three reports that abnormalities in the SNORD116 C/D box snoRNA cluster HBII-85 are sufficient for the core features of PWS to be present. These observations suggest that the absence of expression of this gene may be crucial [Sahoo et al., 2008; de Smith et al., 2009; Duker et al., 2010].

MECHANISMS LINKING GENOTYPE TO PHENOTYPE

The above findings on the genetics of PWS have led to various theoretical proposals with respect to the links between genotype and phenotype. Proposals have ranged from the absence of expression of a single gene for each PWS phenotypic characteristic, through the absence of expression of a gene for a group of characteristics—supported by findings from knock-out mouse models [Muscatelli et al., 2000] and by a factor analysis of PWS behaviors—to the absence of expression of a single gene for all common "core" characteristics [Holland et al., 2003a]. The proposals also have variants according to whether there is a direct causal link from the absence of expression of a single gene on phenotypic features or there is an indirect link in which the absence of expression of a gene sets a threshold or results in arrested development at a certain age. In the case of such an indirect link, one would predict that the relevant aspect of the phenotype would not be universal and that other environmental or biological factors would influence whether it became manifest or not and whether, in the case of a particular behavior, it was maintained over time.

It is clear, however, that some PWS characteristics are linked. For example, a lack of growth hormone underlies the slow growth in childhood and the small stature in adulthood, as well as the facial appearance and the abnormal low muscle mass/high fat mass body composition. All of these are ameliorated by administration of growth hormone. The poor muscle tone is implicated in the reported eye problems, scoliosis, and inactivity or reluctance to exercise. The high pain threshold and temperature insensitivity are highly correlated and the hypothalamus is involved in the regulatory systems that control eating behavior, hormone release, and temperature and sleep regulation. A more paradoxical and speculative link is between the drive to eat, the low levels of sex hormones and the high levels of the circulating orexigenic peptide, ghrelin, observed in PWS adults. These are all symptoms of starvation. This latter observation, that these symptoms in PWS are similar to those in starvation states such as anorexia nervosa, has led to the suggestion that a single gene regulating energy balance could explain the core phenotype [Holland et al., 2003a] (see further discussion below).

While mechanisms, such as growth hormone deficiency, may account for clusters of symptoms, genetic subtypes have been observed to result in phenotypic differences. Such observations provide important clues to potential mechanisms. Some of the links between genotype and phenotype can be readily explained, some are partially explained, while others are more difficult to account for. For example, the standard deletion subtype contains more people rated as "fair for family" because they have a single copy of the non-imprinted pigmentation OCA2 gene and so a recessive "fair" allele is more likely to be expressed. The observation that psychiatric illness is more likely to take the form of depression in those with the deletion subtype and, in contrast, affective psychosis in 76–100% of those with the mUPD and imprinting error subtypes, has led to the hypothesis that the psychosis can be explained by double expression of a paternally imprinted gene on chromosome 15 [Webb et al., 2008]. However, the observation of cognitive differences—the deletion subtype having higher performance IQ and the mUPD subtype higher verbal IQ—is more difficult to explain. In addition, with respect to this trait there seems to be different influences of background genetics on the intellectual ability of the person with PWS [Whittington et al., 2009].

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INDIVIDUAL DIFFERENCES IN PHENOTYPIC CHARACTERISTICS

PWS is a genetic syndrome. We should therefore expect associated phenotypic characteristics to be, at least partly if not largely, under genetic influence. This suggests that the strength of a characteristic in an individual would depend on family genetic background. Thus the first explanation for individual differences in the strength or severity of phenotypic characteristics is family background. But family background alone cannot account for the high rates of extreme (abnormal) ratings of characteristics in PWS. How does the genetics of PWS interact with the genetics of family background? The old literature on PWS tended to report characteristics of the PWS phenotype as all-or-nothing; that is, as present or absent. One way to explain phenotypic differences was by postulating that the imprinting of the imprinted gene giving rise to the characteristic was incomplete and "leaky" and that the resulting low level of gene expression was sufficient to suppress the development of that PWS characteristic.

An adaptation allowing for variable levels of the characteristic would be to postulate varying levels of "leakiness" in different individuals. However, an all-or-nothing view cannot be supported. Characteristics vary in PWS as they do in the general population. For example, parents report eating behavior ranging from "no problems, never takes food without asking, never steals food or money to buy food, just eats everything that is provided" to "have to lock food and money away, never given the opportunity to steal from others, never allowed into a food shop." However, all parents agree that independent living would result in loss of control. Again, although temper outbursts seem to be almost universal, severity varies from crying or shouting to violence toward property or people. Another way to look at these observations is to imagine a frequency distribution of the strength of each characteristic for the whole PWS population. This is most easily illustrated by the IQ distribution in PWS, which is roughly a normal curve similar to that for the general population. Then imagine this distribution compared to that for the general population. The PWS distribution will be shifted towards one end of that for the general population—in the case of IQ about 40 points towards the lower end [Whittington et al., 2004]. For some characteristics, such as skin picking, there will be a threshold of what is considered normal and very few people in the general population will be above this threshold, whereas the PWS distribution will place over 50% above this threshold. This is the "threshold shift" model [Holland et al., 2003b].

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For characteristics such as obsessive behavior and temper tantrums, there is a problem in using the above model. In normal development, there is a period in childhood in which such behavior is the norm. However, in normal development the child grows out of obsessive behaviors such as bedtime routines and repetitive questioning. In PWS this is not the case; obsessive behaviors similar to those of normally developing children and temper outbursts persist into adulthood and throughout the lifespan. In this respect, people with PWS appear to show arrested development [Holland et al., 2003b].

NEUROBEHAVIORAL ASPECTS OF PWS: IMPLICATIONS FOR INTERVENTIONS

Families of people with PWS are subject to more stress than those of people with ID of mixed etiologies [Hodapp et al., 1997] and 70% of mothers have high levels of stress needing psychological counseling [Sarimski, 1995]. Parents are divided on which particular phenotypic characteristic is most stressful for them, but most cite either the eating behavior or the obsessiveness, depending on which of these is predominant in their offspring's behavior. Closely related to these two characteristics is the problem of temper outbursts, which most often occur when expectations are not met, such as expectations about food and routine, and also of concern is the extreme hoarding behavior. Worries about their offspring's health and well-being also cause stress, and in the cases of severe skin picking and psychiatric illness, may also be exacerbated by social stigma. We consider each of these phenotypic characteristics in turn and specifically what we know about them and what our knowledge tells us about management.

The Eating Behavior in PWS

This phenotypic characteristic deserves special mention for several reasons. It is the distinguishing feature of PWS, giving rise to the most difficulties for the family and leading to social isolation for both the person with PWS and for the family. It is also one of the aspects of the syndrome most researched. Research in this area has proceeded at different levels that are best characterized as the following: (a) at a peripheral level, such as the hormonal response to food entering the mouth and into the gastro-intestinal system and being absorbed; (b) at the level of the control pathways of the hypothalamus; and (c) at the level of higher brain function, including the way cortical and sub-cortical systems respond and how that correlates with reported feelings (such as hunger and fullness) and with eating behavior. With respect to

the last of these, behavioral and brain imaging studies suggest that the eating behavior does not arise from abnormal hunger but from abnormal satiety mechanisms [Holland et al., 1993; Hinton et al., 2006]. As with other regulatory systems, such as pain, sleep, and temperature, that also malfunction in PWS, the ability to reach a state of satiation is not lacking completely, rather it requires a greater caloric intake to reach the threshold that then results in a state of satiation. Thus there is a mismatch between the calorie intake required to bring about and maintain satiation and the calorie requirement of the person—the former being much greater than the latter. Research has also shown that eating a meal stimulates regions of the brain that appear to be "reward centers" [Miller et al., 2007]. These regions are also stimulated by drugs in those with drug dependence and it has been proposed that excessive eating in PWS is an addiction [von Deneen et al., 2009]. Support for this theory comes also from anecdotal reports of people with PWS substituting smoking for their previous interest in food [see McAllister et al., 2010 for review].

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Goldstone [2006] has reviewed the relationship between hypothalamic function, peripheral hormones, and behavior in PWS. Hypothalamic dysfunction is responsible for the relative growth and sex hormone deficiencies observed in PWS and there has been the assumption that the fundamental abnormality explaining the eating disorder would be a direct consequence of a genetically determined disruption of one of the hypothalamic feeding pathways, similar to that observed in the case of melanocortin-4 receptor deficits [Farooqi et al., 2000]. However, investigation of such feeding pathways in PWS and also genetic studies, have failed to identify an equivalent abnormality or to identify an imprinted gene located in the PWSCR whose action directly relates to such a pathway. However, reduced levels of oxytocin containing cells in the paraventricular nucleus of the hypothalamus, has been proposed as a possible mechanism to account for the abnormal satiety response observed [Swaab et al., 1995].

At a peripheral level there was considerable interest following the observation that people with PWS have high circulating levels of the orexigenic hormone ghrelin [Cummings et al., 2002]. This hormone peaks just prior to meals and is the only circulating hormone that stimulates food intake. However, subsequent research using a somatostatin infusion or octreotide administration to reduce ghrelin levels failed to show any reduction in eating behavior or weight [Haqq et al., 2003; Tan et al., 2004; De Waele et al., 2008]. It seems unlikely that high ghrelin levels in PWS are a direct cause of the over-eating behavior, rather it is an epiphenomenon.

As yet research on the over-eating behavior in PWS has not resulted in any treatment that enables those with the syndrome to control their own eating behavior. What it has done, however, is to make it very clear that there is an underlying biological abnormality that makes control of food intake very problematic for those with the syndrome. For parents there is a clear responsibility, once the diagnosis has been made, to manage and regulate food intake. The dilemma is how to manage access to food and money to buy food in adult life when people with PWS can be increasingly independent [Hooren et al., 2002]. As described earlier, we are increasingly aware that, whilst the propensity to over-eating is ever present, it varies between individuals with PWS and it may vary in the same person over time. What we do not know is whether anything can be done in childhood that may affect this propensity in adult life. For example, will this new generation of children with PWS find it more or less easy to control food intake than the previous generations, given the fact that food intake has been more strictly controlled for this younger generation? At present the main strategies remain that of monitoring the food environment and controlling it to various degrees, as well as designing diets that are high in bulk and low in calories, and various other strategies that optimize any degree of control that the persons with PWS may themselves be able to assert.

Repetitive and Ritualistic Behaviors and Temper Outbursts

These specific aspects of the neurobehavioral phenotype of PWS are considered together as these behaviors have been found to cluster, possibly consequent upon developmental arrest [Holland et al., 2003b]. In a hypothesis article Woodcock et al. [2009] proposed a multi-layered model to account for these specific behaviors in PWS. Their model takes account of interactions between a genetic predisposition to such behaviors and the environment at biological, cognitive, physiological, and behavioral levels. This type of model moves our thinking away from what had previously been suggested was best conceptualized as an "Obsessive Compulsive Disorder (OCD)" [Dykens et al., 1996]. For example, evidence indicated that the most frequent symptoms were different from those of OCD and, in fact, resemble those of typically developing children relatively early in life [Feurer et al., 1998; Clarke et al., 2002] as had been described earlier [Evans et al.,

1997] and loaded on a single scale of the factor analysis of behaviors found in OCD [Baer, 1993]. People with PWS have restricted interests, similar to those observed in people with autistic spectrum disorders. Because of the involvement of multiple copies of genes on the maternal chromosome 15 in cases of autism, it has been suggested that the mUPD form of PWS is a risk factor for autistic symptoms in PWS. This has been weakly supported [Veltman et al., 2004], but autistic symptoms have been found to load on only one general factor of the autism profile [Greaves et al., 2006], similar to the repetitive and ritualistic behaviors characteristic of autism.

Parents have long reported that temper outbursts are most often connected with disappointed expectations and in PWS this usually is connected with food or routine. Recently, an investigation of the antecedents of repetitive questions in PWS and fragile X syndrome (these syndromes have this behavior in common) showed that when routine was changed or other expectations were not met, temper outbursts and repetitive questions became more frequent. It was hypothesized that in both syndromes unpredictability is aversive, resulting in characteristic behaviors (temper outbursts in PWS, anxiety in fragile X), and leading to repetitive questions which may serve to try and increase predictability [Woodcock et al., 2009]. People with PWS have also been shown to have significant difficulties with set shifting so they become rooted to a particular activity or idea and cannot change from it [Woodcock et al., 2009]. Thus, people with PWS seek to maintain predictability where possible, yet life requires the ability to change from one topic to another and to be able to tolerate the unexpected.

People with PWS have also been shown to have significant difficulties with set shifting so they become rooted to a particular activity or idea and cannot change from it. Thus, people with PWS seek to maintain predictability where possible, yet life requires the ability to change from one topic to another and to be able to tolerate the unexpected.

These new interactive models that have been reported to account for such behaviors in people with PWS point to the need for more sophisticated intervention regimes. Unless depression coexists with the repetitive and ritualistic behaviors, SSRI antidepressant medications may be of little value. Interventions are going to have to be modeled more on applied behavioral analytical principles and the identification of the biological and environmental factors that predispose to, precipitate and maintain such behaviors. Whilst some identified factors may not be amenable to change, others clearly will. The focus is away from the concept of treatment and more towards the idea of effective management.

Skin Picking

Skin picking is sometimes regarded as one of the obsessive–compulsive symptoms shown by people with PWS. However, it has been found that it is not closely associated with such symptoms [Holland et al., 2003b; Wigren and Hansen, 2005]. Neither does it appear to be closely associated with the eating behavior [State et al., 1999; Holland et al., 2003b]. The findings that skin picking can be reduced by treatment with topiramate [Shapira et al., 2004], which does not affect eating behavior or repetitive or ritualistic behaviors, and that in a factor analysis of PWS behaviors it loaded on the same factor as mood swings [Holland et al., 2003b] support these conclusions. How skin picking in PWS is best conceptualized remains uncertain. At one extreme it has been argued that the abnormal grooming behavior seen in Necdin knockout mice [Muscatelli et al., 2000] may be the equivalent of skin picking in humans with PWS and therefore a manifestation of the absence of expression of that particular gene in the PWSCR. Alternatively it may be conceptualized as a consequence of serotonergic disturbance [Holland et al., 2003b]. There have been no formal trials of SSRI medications in the treatment of skin picking in people with PWS but case reports suggest some beneficial results [see Dykens and Shah, 2003 for review]. As with maladaptive behaviors in general the approach has to be one of detailed observation and the identification of predisposing, precipitating, and maintaining factors of the particular behavior and of internal and external setting events that increase or decrease the risk of such behaviors (e.g., whether skin picking occurs at times of low mood or lack of activity). The formulation that follows such observation then determines interventions. These interventions may include designing activities incompatible with skin picking (i.e., activities that involve extensive use of the hands), treatment of any co-morbid mood disorder with SSRIs, or strategies to reinforce alternative behaviors.

Psychiatric Illness

The first report of genetic subtype differences in the prevalence of psychosis in PWS appeared in 2002 [Boer et al., 2002]. The 100% prevalence rate in non-deletion PWS over the age of 28 (mainly those with PWS due to mUPD) reported in this study suggested that increased expression of a single paternally imprinted/maternally expressed imprinted gene on chromosome 15 could be responsible. The high prevalence rate in non-deletion PWS has been confirmed, and the course and outcome of the illness has been described [Vogels et al., 2004; Soni et al., 2007], as has the phenomenology [Soni et al., 2008]. Moreover, genetic studies of psychosis in those rarer case occurrences in delPWS provide supportive evidence for the genetic hypothesis. The region in which such a causative gene must lie has been delineated [Webb et al., 2008]. The study of the phenomenology of

mental illness in PWS suggests that depressive illness is more prevalent in deletion subtypes and an atypical affective psychosis in the non-deletion subtypes. This latter description does not fit comfortably into standard classifications and probably explains the variety of diagnoses found in the literature.

The treatment of affective disorder and or psychotic illness first requires that it is recognized for what it is. The diagnosis may be over looked because a thorough diagnostic assessment is not undertaken when there is an increase in problem behaviors or the development of new problem behaviors. The diagnosis depends upon a comprehensive history and mental state examination seeking evidence for whether or not there is a recent mood instability and/or abnormal mental beliefs and experiences such as hallucinations and/or delusions. The onset of psychosis is usually rapid and very distressing for the person with PWS and for those supporting them. The management includes trying to maintain a predictable and low demand environment, keeping the person safe if there are concerns about their behavior and/or suicidal thoughts, and the use of appropriate medication usually starting at lower than normal doses because of the potential for sensitivity to such medication. The medications suggested are those known to help in the case of affective and/or psychotic illness including the atypical antipsychotics and SSRI antidepressant medications. Research into the effectiveness of such medications in PWS is limited. There is some indication that atypical antipsychotic medications (avoiding those most notorious for increasing weight) and SSRIs that target anxiety as well as depressed mood used either singly or in combination, depending on symptomatology, have the best outcomes [Soni et al., 2007]. An on-going follow-up study of those adults with PWS who have had a serious psychotic illness has found good outcomes with the vast majority remaining on a low dose of the above medications.

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FUTURE DIRECTIONS

The first question raised in this article concerned the number of phenotypic stages in PWS. The consensus diagnostic criteria of 1993 recognized the two stages described above and these are universally recognized. But other stages have been proposed: in particular, a "normal eating" stage between these two established stages and a "milder" phenotypic stage in older adults. A study of the transition between the established phases appears to support the first of these proposals, but a larger longitudinal study not relying on retrospective data is needed. People with PWS, like those in the general population, do seem to show an increase in behavioral problems in adolescence and young adulthood with a gradual decrease with maturity. But should these be described as separate phases? Is there an even later stage (corresponding to Shakespeare's "seventh age") of senility? Large-scale collaborative work is needed to obtain sufficiently large samples to answer some of these questions.

To distinguish between the different models for relationships between genotype and phenotype, one promising approach seems to be the use of knock-out mouse models. A limitation of this research may be imperfect gene correlations between human and mouse chromosomes. However, this research has already yielded results by eliminating several candidate genes as being fundamental in PWS and has shown how most of the knock-out genes could account for small subsets of the PWS phenotypic features [Muscatelli et al., 2000; Mercer and Wevrick, 2009]. Another approach would be to search for people with PWS with unusually small deletions; this has the added difficulty of needing to specify the "core features" of PWS since a fundamental gene would not necessarily be responsible for all features.

Exploitation of genetic subtype differences to explain phenotypic differences has already begun. Thus the "fair for family" phenotypic characteristic of the consensus diagnostic criteria has been traced to a non-imprinted pigmentation gene. There is evidence that the affective psychosis found in PWS will be traced to over-expression (due to more than a single expressed copy) of a paternally imprinted/maternally expressed gene in the PWS critical region.

There has clearly been very significant progress in our understanding of PWS. However, there are major gaps. Most striking of these is the clarification of the complex genetics of the syndrome. Whilst the accepted genetic model is to consider PWS as a contiguous gene syndrome in which the absence of expression of several maternally imprinted/paternally expressed genes at 15q11-q13 is required to explain the full phenotype, this is perhaps now more in doubt. Disruption of the SNORD116 C/D box snoRNA cluster HBII-85 may be sufficient at least for the core features of PWS. If this was the case two questions then arise. The first is to explain how this genetic abnormality can then account for the early hypotonia and failure to thrive, the changing eating behavior resulting in an impaired satiety response to food intake, the low growth and sex hormone levels, and the ID—the core features of the syndrome. The second is to explain the mechanisms that result in some of the non-core features of PWS. The identification of such mechanisms to explain core and non-core features have the real potential to lead to the development of interventions that might modify the neurobehavioral phenotype much as growth hormone supplementation has done for the physical phenotype.

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