Genetics of Childhood Disorders: XV. Prader-Willi Syndrome: Genes, Brain, and Behavior

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Prader-Willi syndrome (PWS) is a developmental disorder characterized by mental retardation or learning disability, infantile hypotonia and poor suck reflex, growth retardation, delayed sexual development, and the childhood onset of pronounced hyperphagia. Food-related difficulties are the most striking and widely recognized sequelae of this syndrome. Without appropriate dietary and behavioral intervention, almost everyone with PWS will become dangerously obese. However, in addition to these well-known problems with food, those with PWS also suffer from a range of psychiatric and behavioral difficulties, including high rates of depression, obsessions, and compulsions.

PWS is a relatively rare disorder, with an incidence of approximately 1 in 10,000 to 15,000 live births. Nonetheless, it has figured prominently in the recent history of genetics. This is due in large part to its surprising relationship with Angelman syndrome (AS) and the resulting identification of genomic imprinting in humans. Moreover, as research into the various aspects of this disorder has progressed, it has become increasingly evident that PWS may provide neuroscientists a valuable window into the complex interplay of genes, brain, and behavior.

At first glance, the genetics of PWS appear to be rather straightforward. For most affected individuals, a sporadic (as

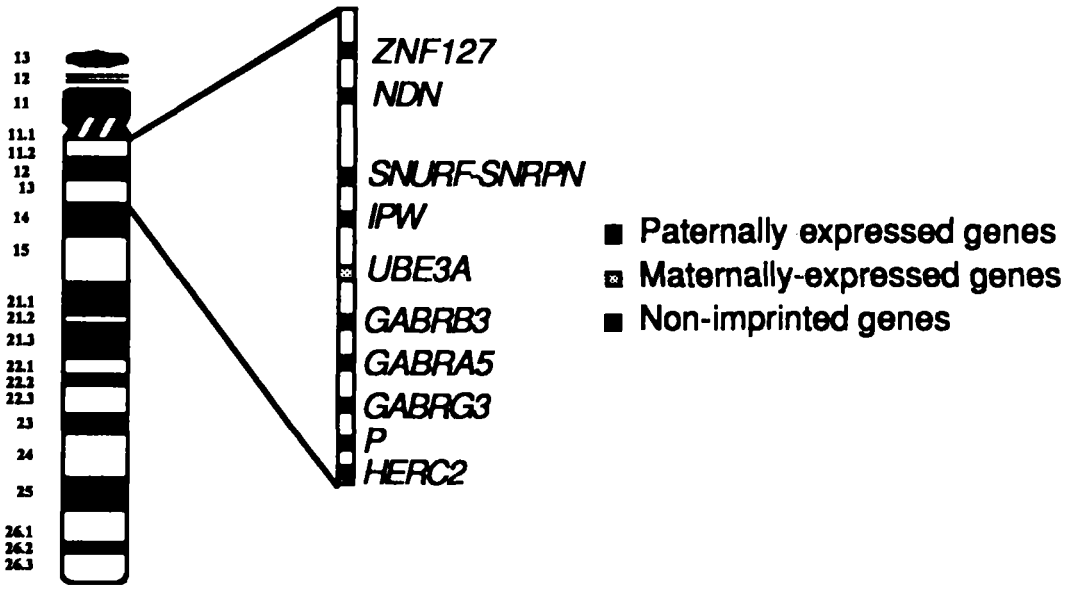

Fig. 1 An ideogram of chromosome 15 (left) and a representation of the approximately 4 million base pair region most commonly deleted in patients with Prader-Willi syndrome (PWS) or Angelman syndrome (AS) (right). The diagram is not to scale. Multiple genes contained within the commonly deleted region are shown by the small boxes contained within the vertical bar. These genes include a zinc finger protein (*ZNF127*), necdin (*NDN*), small nuclear ribonucleoprotein associated polypeptide upstream reading frame (*SNURF*), small nuclear ribonucleoprotein associated polypeptide N (*SNRPN*), imprinted in the Prader-Willi region (*IPW*), E6-AP ubiquitin ligase (*UBE3A*), 3 γ-aminobutyric acid receptor subunits (*GABRB3, A5,* and *G3*), the human orthologue of the mouse pink eyed dilution locus (*P*) locus, and *HERC2* (for *HE*ct domain and *RC*c1 domain protein 2). As noted on the far right of the figure, the first 5 of these genes are paternally expressed, *UBE3A* is maternally expressed, and the other genes are expressed from both chromosomes. Given the similarities between the phenotypes that result from abnormalities in imprinting and those that result from deletions, it is unlikely that the nonimprinted genes in the region play a substantial role in PWS or AS. As noted in the text, a specific gene responsible for PWS has not yet been identified. Moreover, the list of transcripts in this region remains a work in progress, and it remains probable that several genes together contribute to the clinical phenotype. In contrast, mutations in a single gene, *UBE3A*, have been found to cause some cases of Angelman syndrome.

opposed to familial) loss of chromosomal material in the region 15q11-q13 leads to the predictable clinical phenotype. However, a closer look suggests that there is considerable subtlety and complexity to the genetic mechanisms involved. At first, geneticists were baffled by the observation that AS is caused by a deletion involving the same chromosomal region in which PWS is involved. The relationship between the two syndromes was particularly unexpected because of the absence of any significant clinical overlap between the two, with AS leading to severe mental retardation, seizures, and the absence of language.

By the mid-1980s, it had become clear that the key to the genetic distinction between PWS and AS was the parental origin of the chromosome containing the deletion. In PWS, the deletion is always found on the paternally donated chromosome. Conversely, in AS, the deletion is always located on the maternally donated chromosome. This discovery led to the recognition that gene expression in humans may be dictated by the chromosome on which the particular copy of that gene resides. This phenomenon, known as genomic imprinting, has been discussed in greater detail in 2 recent columns.

Over the past decade, researchers discovered that PWS may result not only from a chromosomal deletion, but also from maternal uniparental disomy (UPD). In this situation, 2 copies of the maternal chromosome are inherited with no paternal contribution. In the normal circumstance, the paternally donated chromosome expresses multiple genes in the PWS region, while the maternal chromosome is largely silent. In the case of UPD, without the presence of a chromosome donated from the father, normal imprinting on the 2 maternally donated chromosomes leads to the absence of gene expression in this interval. As a result, despite the presence of 2 intact chromosomes, there is a *functional* abnormality that is largely equivalent to the *structural* abnormality found in the more common 15q11-q13 deletions. In addition, in about 5% of affected individuals, abnormalities in the mechanism of imprinting may lead to the absence of gene expression from the paternally donated chromosome, resulting in the PWS phenotype. This occurs when the imprinting control center is itself mutated.

The specific genes in the 15q11-q13 region that result in the various manifestations of PWS have not yet been identified. The small nuclear ribonucleoprotein associated polypeptide N (SNRPN) has been the object of considerable study. This gene is involved in protein splicing, it is expressed throughout the brain, and its promoter resides within the smallest chromosomal region of overlap among all deletions leading to PWS. However, findings from animal knockouts and rare cases of chromosomal rearrangements in humans have suggested that the PWS phenotype may not be the direct result of a loss of *SNRPN* expression. A number of other candidate genes have been identified as well, including the neuronal protein, necdin (NDN). This gene, when knocked out, leads to failure-to-thrive in certain strains of mice, a phenotype that is clearly analogous to the poor suck reflex and failure-to-thrive seen in infants with PWS. It is interesting that knockout mice that survive these initial difficulties go on to develop normally. Figure 1 illustrates the genes contained within the PWS/AS region.

There has long been speculation that the genetic abnormalities found in PWS lead to hypothalamic dysfunction, which in turn is responsible for the clinical phenotype. There are multiple lines of evidence in support of this hypothesis. For instance, the frequent occurrence of premature and postdates delivery of PWS infants suggests that there may be abnormalities in the fetal hypothalamus because of its known role in the regulation of labor. Moreover, the combination of abnormal food intake regulation, delayed sexual development, sleep irregularities, difficulties with thermoregulation, and growth hormone problems often found in individuals with PWS all point to this brain region playing a key role in the clinical manifestations of the syndrome.

Several controlled studies have provided additional clues about the neuropathology of PWS. One small but important postmortem study showed relatively few oxytocin-secreting neurons in certain regions of the hypothalamus. A subsequent study of 5 subjects with PWS showed that the level of oxytocin in their CSF was actually increased compared with controls. While the direction of the difference was surprising in light of the postmortem data, taken together the results suggest some abnormality in the regulation of this important hypothalamic peptide. Finally, a structural magnetic resonance imaging (MRI) study of individuals with PWS hinted at functional abnormalities in this same brain region based on the absence in several patients of what is known as the "posterior pituitary bright spot," which is thought to be a marker for hypothalamic function.

Despite the multiple signs pointing in the direction of the hypothalamus, several studies have identified other brain regions and neuropeptides as possibly being involved in PWS. A study that included both MRI and magnetic resonance spectroscopy showed diffuse minor abnormalities in subjects versus controls, including slightly enlarged ventricles, cortical atrophy, and a small brainstem. In addition, there has been a report of abnormalities in plasma γ-aminobutyric acid (GABA) in PWS subjects. This neurotransmitter has been the subject of some interest, because loci for GABA receptor subunits are located in the vicinity of 15q11-q13, just telomeric to the PWS/AS critical region.

For those who are not familiar with the syndrome, it may be difficult to grasp just how profound and far-reaching chronic hyperphagia is for those with PWS and their loved ones. Hoarding food is common, as is stealing or sneaking to circumvent dietary restrictions. Without significant intervention, which often includes locking cabinets and refrigerators, almost everyone with PWS will become obese. Given the combination of poor muscle tone, small stature, and a driven appetite, the extent of this obesity may readily become life-threatening. During

childhood and into adolescence, restrictions on food may lead to constant conflicts, and parents and other caregivers are often in the difficult position of having to enforce diets that would leave a person of normal appetite feeling constantly hungry.

If this difficulty with food were not a sufficient hurdle, persons with PWS also suffer from a range of behavioral and psychiatric difficulties apart from food, including obsessions, compulsions, mood lability, and depression, which may often be quite severe. While children and adolescents with PWS have, on average, mild levels of cognitive delay, their behavioral and psychiatric difficulties typically result in highly restrictive levels of care and are often the source of enormous distress for patients and their families.

These types of difficulties have been the subject of a growing body of research over the past decade. Conventional clinical wisdom as well as descriptive studies have long held that some personality characteristics and psychiatric difficulties observed in those with PWS are in fact a distinctive feature of the syndrome, a so-called "behavioral phenotype." As the number of well-controlled investigations into the adaptive and psychological functioning of those with PWS has grown, this clinical folklore has been largely substantiated by experimental data.

The notion that those with PWS have a distinctive behavioral phenotype is nonetheless still somewhat controversial. There is an understandable reluctance on the part of clinicians and researchers to paint a group of individuals with an overly broad brush. However, in the case of PWS, several carefully done studies have identified both a set of behaviors and personality attributes that do, on average, distinguish those with the syndrome from other developmentally delayed individuals with and without clearly identified genetic syndromes. The concept of a behavioral phenotype may be difficult to accept if it is taken as a description of every person with a syndrome. A more useful definition is that a behavioral phenotype is simply a heightened probability that people with a given syndrome will exhibit behavioral or developmental characteristics relative to others without the syndrome. For example, hyperphagia is not unique to persons with PWS, and not everyone with the syndrome exhibits it. However, the odds are that a 1-year-old with PWS will develop this difficulty in the succeeding 3 years.

Several recent studies demonstrate that such a heightened probability clearly applies to obsessions and compulsions apart from the issues around food. A study in the mid-1990s showed that more than 60% of PWS subjects had obsessive-compulsive symptoms with moderate to severe levels of symptom-related distress and adaptive impairment. More than half of subjects met clinical criteria for obsessive-compulsive disorder (OCD). Their symptoms were of similar type and severity to those found in persons with OCD without mental retardation. Two subsequent studies supported these data and demonstrated that increased obsessive-compulsive symptomatology could not be easily accounted for by rater bias, obesity, or even hyperphagia.

Recent studies have compared those with PWS to other groups with genetic syndromes as well as those with mental retardation of mixed etiology. Overall, those with PWS appear to have more behavioral disturbances than controls, including tantrums, irritability, and agitation. Those with PWS also seem likely to have skin-picking, repetitive speech, and "underactivity." There have been numerous observations that those with PWS suffer from both depression and anxiety, although controlled studies regarding depressive and anxious symptoms (apart from OCD) have yet to be conducted.

The PWS behavioral phenotype is not limited to psychiatric and behavioral difficulties. Many individuals with PWS also show a distinctive, although not necessarily unique, profile of cognitive strengths and weaknesses. Those with the disorder span a large range of intelligence, from average ability to severe retardation. The mean IQ is 70, which is high relative to that found in other genetic mental retardation syndromes. Adaptively, however, even those with normal IQ rarely function at a level commensurate with this measure of intelligence, usually because of interference from the food-related and other behavioral problems. Academically, reading/decoding and comprehension may exceed arithmetic skills, although academic performance may not be sufficiently uneven to meet learning disability criteria. Some people with PWS have relative strengths in spatial-perceptual organization and visual processing. By contrast, weaknesses have commonly been noted in sequential processing and short-term memory tasks, including visual, motoric, and auditory short-term memory.

In summary, research into PWS over the past decade has begun to establish some links between genetic abnormalities, brain function, and behavioral and cognitive attributes. Genes in the region of 15q11–13 may be abnormally expressed as the result of either a structural or functional abnormality in this chromosomal region. Although the specific genetic culprits have not yet been identified, the genetic lesion(s) appear to lead to hypothalamic dysfunction. Finally, the accumulated evidence suggests that whatever the underlying neuropathology, those with PWS often display some evidence of a behavioral phenotype that clearly includes obsessive-compulsive symptoms, skin-picking, hyperphagia, low activity levels, behavioral outbursts, and a distinctive cognitive profile compared to controls with mental retardation.

This emerging picture of gene–brain–behavior relationships suggests a range of important research questions. For instance, is the hypothalamus the key brain region affected by the gene or genes underlying the behavioral aspects of PWS? What roles do the hypothalamus and hypothalamic peptides play in the rituals, obsessions and compulsions, and mood lability often seen in those with PWS? Does this brain region contribute to similar manifestations in those without PWS? Are all persons with PWS, regardless of the underlying genetic mechanism, equally

likely to display aspects of the behavioral as well as physical and developmental phenotype?

As these questions are answered, it is likely that avenues for improved treatment will reveal themselves. More broadly, this view of how genes, brain, body, and mind interact will provide some unexpected clues about the roots of psychopathology in other psychiatric conditions.

WEB SITES OF INTEREST

http://www.ncbi.nlm.nih.gov/omim/
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ADDITIONAL READINGS

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Accepted December 17, 1999.

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