



Prader-Willi Syndrome

Synonyms: Prader-Labhart-Willi Syndrome, PWS

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Summary

Clinical characteristics

Prader-Willi syndrome (PWS) is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity (unless eating is externally controlled). Motor milestones and language development are delayed. All individuals have some degree of cognitive impairment. A distinctive behavioral phenotype (with temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics) is common. Hypogonadism is present in both males and females and manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. Short stature is common (if not treated with growth hormone); characteristic facial features, strabismus, and scoliosis are often present.

Diagnosis/testing

Consensus clinical diagnostic criteria are accurate, but the mainstay of diagnosis is DNA methylation testing to detect abnormal parent-specific imprinting within the Prader-Willi critical region (PWCR) on chromosome 15; this testing determines whether the region is maternally inherited only (i.e., the paternally contributed region is absent) and detects more than 99% of affected individuals. DNA methylation-specific testing is important to confirm the diagnosis of PWS in all individuals, but especially in those who have atypical findings or are too young to manifest sufficient features to make the diagnosis on clinical grounds.

Management

Treatment of manifestations: In infancy, special nipples or enteral tube feeding to assure adequate nutrition; physical therapy may improve muscle strength; hormonal and surgical treatments can be considered for

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cryptorchidism. In childhood, strict supervision of daily food intake based on height, weight, and body mass index (BMI) to provide energy requirements while limiting excessive weight gain (keeping BMI Z score <2 or better) and encouraging physical activity. Growth hormone replacement therapy to normalize height, increase lean body mass and mobility, and decrease fat mass. Evaluation and treatment of sleep disturbance per the general population. Educational planning should be instigated and speech therapy provided if needed. Firm limit-setting to manage behavioral problems; serotonin reuptake inhibitors are helpful for most teenagers and adults. Replacement of sex hormones at puberty produces adequate secondary sexual characteristics. N-acetylcysteine or topiramate may help reduce skin picking. Modafinil has been successful in treating daytime sleepiness in many children. In adulthood, a group home for individuals with PWS that regulates behavior and weight management may prevent morbid obesity, and growth hormone may help to maintain muscle bulk.

Prevention of secondary complications: Weight control to avoid development of type 2 diabetes mellitus; calcium and vitamin D supplementation to avoid osteoporosis; if osteoporosis develops, consider treatment with a bisphosphonate.

Surveillance: Infants should be screened for strabismus; routine monitoring of height, weight, and BMI to assure appropriateness of exercise program and diet; annual testing for hypothyroidism.

Other: No medications are currently known to aid in controlling hyperphagia, although several are under investigation.

Genetic counseling

PWS is caused by an absence of expression of imprinted genes in the paternally derived PWS/Angelman syndrome (AS) region (i.e., 15q11.2-q13) of chromosome 15 by one of several genetic mechanisms (paternal deletion, maternal uniparental disomy 15 and rarely an imprinting defect). The risk to the sibs of an affected child of having PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region. The risk to sibs is typically less than 1% if the affected child has a deletion or uniparental disomy, up to 50% if the affected child has an imprinting defect, and up to 25% if a parental chromosome translocation is present. Prenatal testing is possible for pregnancies at increased risk if the underlying genetic mechanism is known.

Diagnosis

Consensus diagnostic criteria for Prader-Willi syndrome (PWS) developed in 1993 [Holm et al 1993] have proven to be accurate [Gunay-Aygun et al 2001] and continue to be useful for the clinician. However, confirmation of the diagnosis requires molecular genetic testing, which was not widely available when the criteria were developed.

Suggestive Findings

Prader-Willi syndrome **should be suspected** in individuals with the specific clinical findings listed below or findings on cytogenetic/FISH/chromosomal microarray.

Clinical findings that should prompt diagnostic testing have been proposed based on analysis of diagnostic criteria met in individuals in whom the diagnosis of PWS has been molecularly confirmed [Gunay-Aygun et al 2001]. These differ by age group. The presence of **all** of the following findings at the age indicated is sufficient to justify DNA methylation analysis for PWS (see Establishing the Diagnosis):

Birth to age two years

- Hypotonia with poor suck (neonatal period)

Age two to six years

- Hypotonia with history of poor suck
- Global developmental delay

Age six to 12 years

- History of hypotonia with poor suck (hypotonia often persists)
- Global developmental delay
- Excessive eating with central obesity if uncontrolled

Age 13 years to adulthood

- Cognitive impairment, usually mild intellectual disability
- Excessive eating with central obesity if uncontrolled
- Hypothalamic hypogonadism and/or typical behavior problems

Cytogenetic/FISH/chromosomal microarray findings. Approximately 70% of individuals with PWS have a deletion on one chromosome 15 involving bands 15q11.2-q13, which can be detected using high-resolution chromosome studies and fluorescence in situ hybridization (FISH) testing or chromosomal microarray.

Note: The typical deletion is one of two sizes: extending from the distal breakpoint (BP3) to one of two proximal breakpoints (BP1 or BP2). Clinical FISH testing detects both of these deletions and typically will not distinguish between them. Additional atypical and unique deletions occur in approximately 8% of deletion cases [Kim et al 2012].

Approximately 1% of affected individuals have a detectable chromosome rearrangement (i.e., translocation or inversion) resulting in a deletion of bands 15q11.2-q13.

Fewer than 1% of individuals have a "balanced" chromosome rearrangement breaking within 15q11.2-q13 and detectable by chromosome analysis and FISH.

Establishing the Diagnosis

The diagnosis of PWS **is established** in a proband with DNA methylation analysis demonstrating abnormal parent-specific imprinting within the Prader-Willi critical region (PWCR) on chromosome 15 in which the region demonstrates maternal-only imprinting (i.e., the absence of paternal-only expressed genes).

Three main molecular mechanisms that result in PWS include paternal deletion, maternal uniparental disomy (UPD) 15 and imprinting defect (ID). DNA methylation analysis is the only technique that will diagnose PWS caused by all three genetic mechanisms as well as differentiate PWS from [Angelman syndrome \(AS\)](#) in deletion cases [Glenn et al 1996, Kubota et al 1996, Glenn et al 1997].

See Table 1 for a summary of molecular genetic testing used to define the underlying genetic mechanism in a proband.

The main molecular mechanisms are further classified by specific genetic etiology into molecular class Ia-IIIb, which is important for genetic counseling (see Table 3).

See Figure 1 for a comprehensive testing strategy to establish the genetic mechanism of an individual with DNA methylation analysis consistent with PWS.

Note: A DNA methylation analysis consistent with PWS is sufficient for clinical diagnosis but not for genetic counseling, which requires identification of the underlying genetic mechanism (Table 1). See Genetic Counseling.

Table 1. Testing Used in Prader-Willi Syndrome

Method	Genetic Mechanisms Detected ¹	Proportion of PWS Detected by Method
DNA methylation ²	Deletions, UPD & ID	>99%
MS-MLPA ³	Deletions, UPD & ID	>99%
FISH ⁴	Deletions	65%-75%
CMA ⁵	Deletions	65%-75%
CMA-SNP array ⁶	Deletions & some UPDs	80%-90%
DNA polymorphisms ⁷	UPD and ID	20%-30%
DNA sequence ⁸	ID with IC deletions	<1%

IC = imprinting center; ID = imprinting defect; UPD = uniparental disomy

1. See Molecular Genetics for more details.

2. Can establish diagnosis, but will not distinguish genetic mechanism; can be done by Southern blot or methylation-specific PCR.

3. Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA):

- Will distinguish deletion from disomy (UPD and ID);
- Will not distinguish UPD from ID;
- Can give approximate size of deletion and identify type 1 and 2 deletions (see Figure 2);
- Can also detect most IC and *SNORD116* microdeletions (see Figure 2 and Molecular Pathogenesis).

4. FISH is typically done in conjunction with a karyotype. Information is limited to AS/PWS region and the specific probes used (e.g., *SNRPN*). FISH does not query the whole AS/PWS region and will miss small deletions. It does not give information about the rest of the chromosomes, and does not distinguish between normal, UPD, and ID.

5. Chromosomal microarray (CMA) has a slightly higher detection frequency than FISH and will provide detailed information regarding size of the deletion. Also, it gives information regarding deletions and duplication in the remainder of the genome. CMA is far more precise than karyotype and FISH; it will detect *SNORD116* microdeletions (see Figure 2 and Molecular Pathogenesis).

6. Same as CMA; in addition, use of small nucleotide polymorphisms (SNP) will allow detection of UPD in cases with long stretches of homozygosity.

7. Not a first line test; performed after DNA methylation analysis diagnoses PWS, but FISH or CMA analysis indicates disomy.

8. DNA sequencing has a very specific role in IDs to distinguish IC deletions from epimutations. It is limited to a region of <4.3 kb in the PWS IC smallest region of deletion overlap (SRO) [Ohta et al 1999]. The map location is approximately 25,196,494 to 25,200,794 bp [UCSC Genome Browser, hg19].

Clinical Characteristics

Clinical Description

Perinatal. Fetal size is generally within the normal range. Prenatal hypotonia usually results in decreased fetal movement, abnormal fetal position at delivery, and increased incidence of assisted delivery or cesarean section. Birth weight and body mass index (BMI) are on average 15% less than in normal sibs [Miller et al 2011].

Hypotonia. Infantile hypotonia is a nearly universal finding, causing decreased movement and lethargy with decreased spontaneous arousal, weak cry, and poor reflexes, including poor suck. The hypotonia is central in origin, and neuromuscular studies including muscle biopsy, when done for diagnostic purposes, are generally normal or show nonspecific signs of disuse.

The poor suck, lethargy, and poor appetite result in failure to thrive in early infancy, and enteral tube feeding or the use of special nipples is generally required for a variable period of time, usually weeks to months. By the time that the child is drinking from a cup or eating solids, a period of approximately normal eating behavior occurs.

The hypotonia improves over time. Adults remain mildly hypotonic with decreased muscle bulk and tone.

Developmental delay. Delayed motor development is present in 90%-100% of children with PWS, with average early milestones achieved at about double the normal age (e.g., sitting at 12 months, walking at 24 months).

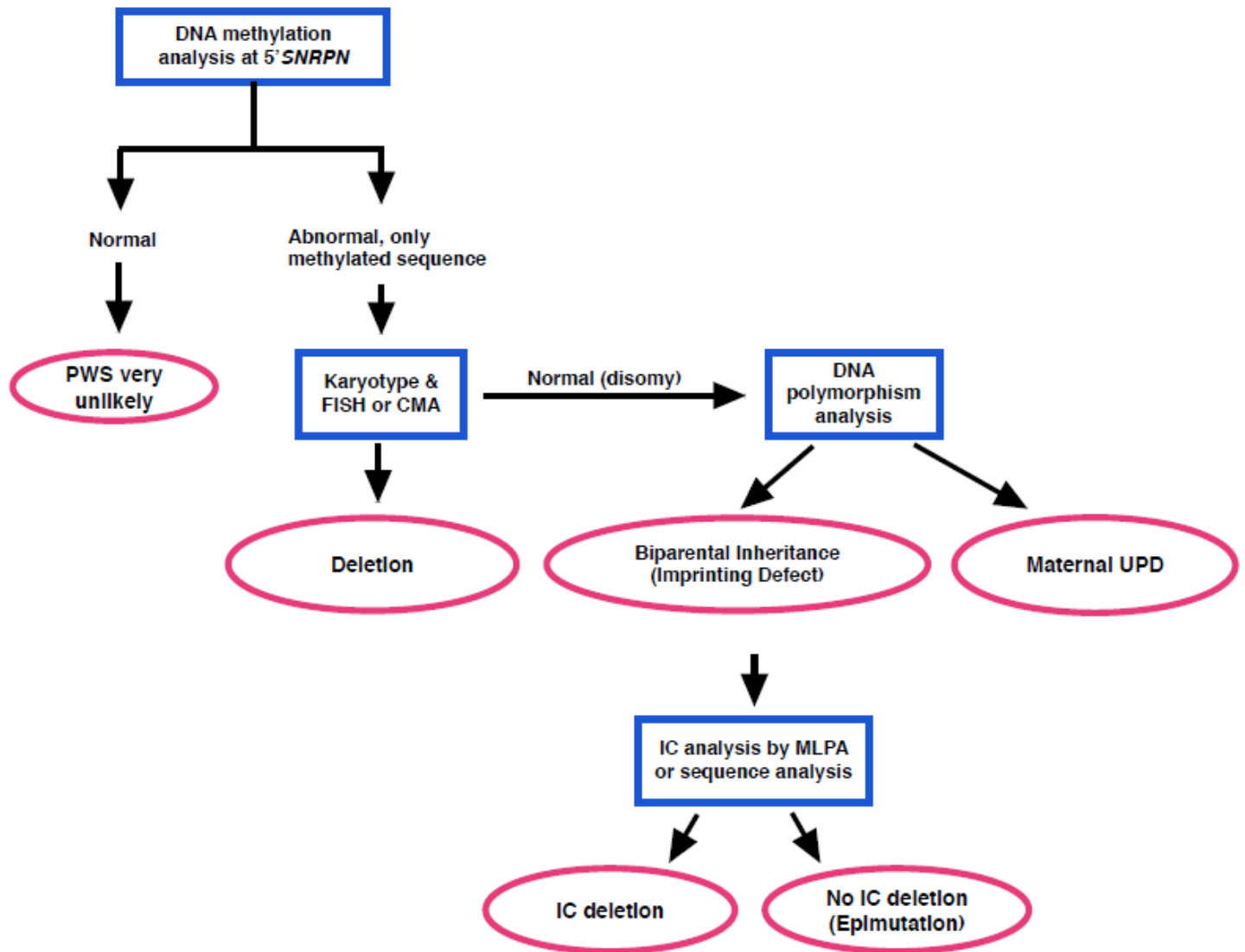


Figure 1. Comprehensive testing strategy to establish the molecular class of PWS

FISH = fluorescence in situ hybridization

CMA = chromosomal microarray

UPD = uniparental disomy

IC = imprinting center

MLPA = multiplex ligation probe amplification

Language milestones are also typically delayed. Intellectual disabilities are generally evident by the time the child reaches preschool age. Testing indicates that most persons with PWS fall in the mildly intellectually disabled range (mean IQ: 60s to 70s), with approximately 40% having borderline disability or low-normal intelligence and approximately 20% having moderate disability. Regardless of measured IQ, most children with PWS have multiple severe learning disabilities and poor academic performance for their intellectual abilities [Whittington et al 2004a]. Although a small proportion of affected individuals have extremely impaired language development, verbal ability is a relative strength for most. Based on the authors' experiences, a small percentage of individuals with PWS are able to attend and graduate from college.

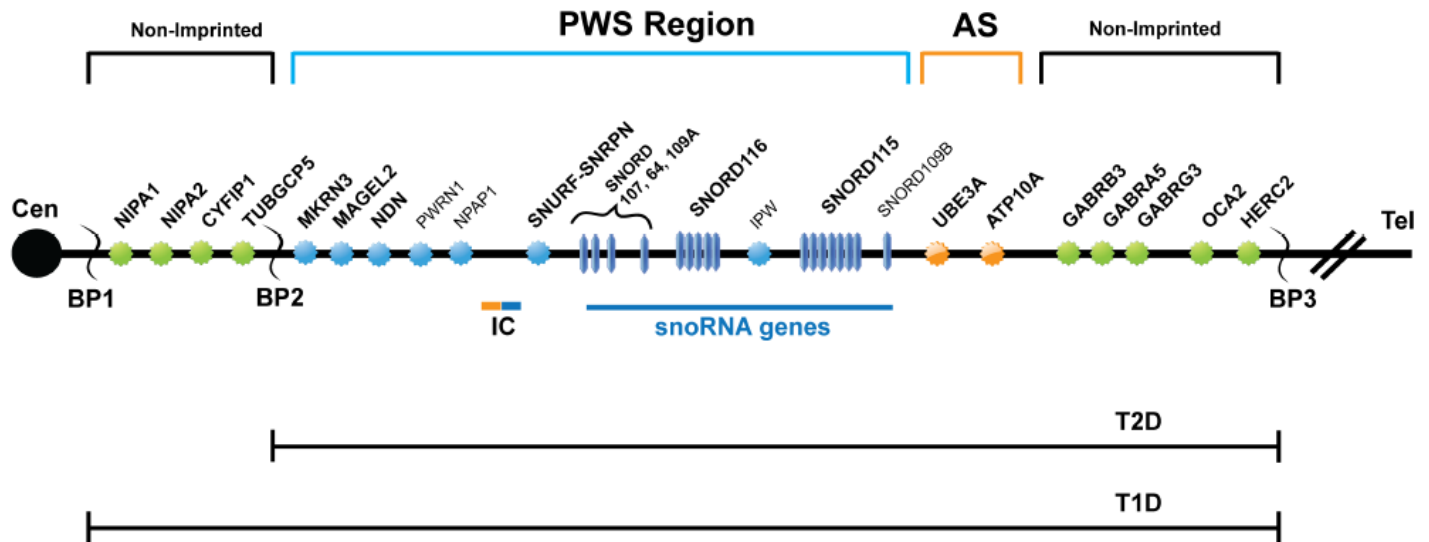


Figure 2. Summary of the genetic and expression map of chromosome region 15q11.2-q13

The Prader-Willi syndrome (PWS) region (shown in blue) has five paternal-only (PWS region) expressed unique-copy genes that encode polypeptides (MKRN3, MAGEL2, NECDIN, and SNURF-SNRPN) and a family of six paternal-only expressed snoRNA genes and IPW, a long non-coding RNA. Only UBE3A and ATP10A (shown in orange), related to Angelman syndrome (AS), have preferential maternal-only expression, and this imprinted expression is limited to certain tissue specific regions (specifically brain). The imprinting center (IC) has a bipartite structure with an AS (maternal, shown in orange) and a PWS (paternal, shown in blue) component. The PWS-SRO has been localized to a 4.3-kb region which includes the promoter, CpG island, exon 1, and a small part of intron 1 of bicistronic SNURF-SNRPN [Ohta et al 1999]. The AS-SRO lies approximately 35 kb proximal to exon 1 of SNURF-SNRPN [Horsthemke & Buiting 2006]. The bipartite IC lies within the 2.5-Mb PWS/AS imprinted region. The cluster of GABA receptor genes (GABRB3, GABRA5, and GABRG3), OCA2 (type II albinism) and HERC2 are not imprinted and have biparental expression (shown in green). The jagged vertical lines denote the three common 5-6-Mb PWS and AS deletion breakpoints: BP1, BP2, and BP3. On rare occasions there will be a distal breakpoint at BP4 or BP5. Between BP1 and BP2 lie four additional, non-imprinted genes: NIPA1, NIPA2, CYFIP1, and GCP5. Type 1 deletions (T1D) extend from BP1 to BP3 and type 2 deletions (T2D) extend from BP2 to BP3. Note that there are more copies of SNORD116 and SNORD115 than are shown and the map has not been precisely drawn to scale.

Hypogonadism. In both sexes, hypogonadism is present and manifests as genital hypoplasia, incomplete pubertal development, and infertility in the vast majority. Genital hypoplasia is evident at birth and throughout life.

- **Males.** The penis may be small, and most characteristic is a hypoplastic scrotum that is small, poorly rugated, and poorly pigmented. Unilateral or bilateral cryptorchidism is present in 80%-90% of males.
- **Females.** The genital hypoplasia is often overlooked; however, the labia majora and minora and the clitoris are generally small from birth.

The hypogonadism is usually associated with low serum concentration of gonadotropins and causes incomplete, delayed, and sometimes disordered pubertal development. Precocious adrenarche occurs in approximately 15%-20%. Infertility is the rule, although a few instances of reproduction in females have been reported [Akefeldt et al 1999; Schulze et al 2001; Vats & Cassidy, unpublished data]. Although the hypogonadism in PWS has long been believed to be entirely hypothalamic in origin, recent studies have suggested a combination of hypothalamic and primary gonadal deficiencies [Eldar-Geva et al 2009, Hirsch et al 2009, Eldar-Geva et al 2010, Gross-Tsur et al 2012], a conclusion largely based on the absence of hypogonadotropism and abnormally low inhibin B levels in some affected individuals of both sexes.

In one study of 84 individuals with PWS (half males, half females) age two to 35 years [Crinò et al 2003], the following were identified:

- **Males.** Cryptorchidism 100%, small testes 76%, scrotal hypoplasia 69%
- **Females.** Labia minora and/or clitoral hypoplasia 76%, primary amenorrhea 56%, spontaneous menarche (mostly spotting) 44% of those older than age 15 years
- **Both sexes.** Premature pubarche 14%, precocious puberty 3.6% (1 male, 2 females)

Appetite and obesity. In contrast to the long-held view that there are only two distinct nutritional phases in PWS (i.e., failure to thrive followed by hyperphagia leading to obesity) a multicenter study [Miller et al 2011] found that the transition between nutritional phases is much more complex, with seven different nutritional phases through which individuals with PWS typically progress (Table 2).

Table 2. Nutritional Phases in PWS

Phase	Median Ages	Clinical Characteristics
0	Prenatal - birth	Decreased fetal movements & lower birth weight than sibs
1a	0-9 months	Hypotonia with difficulty feeding & decreased appetite
1b	9-25 months	Improved feeding & appetite; growing appropriately
2a	2.1-4.5 years	Weight increasing without appetite increase or excess calories
2b	4.5-8 years	Increased appetite & calories, but can feel full
3	8 years - adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite no longer insatiable for some

Miller et al [2011]

The hyperphagia that occurs in PWS is believed to be caused by a hypothalamic abnormality resulting in lack of satiety. Food-seeking behavior, with hoarding or foraging for food, eating of inedibles, and stealing of food or money to buy food, are common. In most, gastric emptying is delayed, and vomiting is rare. Obesity results from these behaviors and from decreased total caloric requirement. The latter is due to decreased resting energy expenditure resulting from decreased activity and decreased lean body mass (primarily muscle) compared with unaffected individuals. The obesity in PWS is primarily central (abdomen, buttocks, and thighs) in both sexes, and interestingly, there is less visceral fat in obese individuals than would be expected for the degree of obesity. Obesity and its complications are the major causes of morbidity and mortality (see **Morbidity and mortality**).

Several independent groups have shown that ghrelin levels are significantly elevated in hyperphagic older children and adults with PWS before and after meals [Cummings et al 2002, DelParigi et al 2002, Haqq et al 2003b]. Ghrelin is a potent circulating orexigenic hormone that is produced mainly in the stomach. Circulating ghrelin levels rise after fasting and are suppressed by food intake. The appetite-inducing effect acts through the appetite regulating pathway in the hypothalamus. Ghrelin levels are lower in non-PWS obese individuals than in lean controls, and they decrease with age [Scerif et al 2011].

A small study of nine non-hyperphagic children with PWS (age 17-60 months) found similar levels of circulating ghrelin as in the eight control children matched for BMI, age, and sex [Erdie-Lalena et al 2006]. By contrast, in two much larger and younger study cohorts of children and adolescents with PWS ghrelin levels were significantly elevated in the PWS group at any age compared to controls [Feigerlová et al 2008, Kweh et al 2015]. In fact, the highest ghrelin levels in PWS were found in the youngest children. Thus, in these two large studies the hyperghrelinemia occurred at an age long before the development of obesity and increased appetite in PWS. Furthermore, several groups have now shown that pharmacologic reduction of ghrelin to normal levels in PWS, using either short- or long-acting agents, did not affect the weight, appetite, or eating behavior in hyperphagic individuals [Haqq et al 2003a, Tan et al 2004, De Waele et al 2008]. At this time there are no consistently identified hormonal abnormalities to explain the hyperphagia, and the metabolic correlates of hyperphagia in PWS remain uncertain.

Endocrinologic concerns. Up to 25% of adults with PWS (particularly those with significant obesity) have type 2 diabetes [Butler et al 2002] with a mean age of onset of 20 years. In the last 15 years, earlier diagnosis and education of parents, use of growth hormone therapy, and the frequency of group homes specific for PWS have led to reduction in the development of morbid obesity (and as a result, in type 2 diabetes) among individuals with PWS.

Central hypothyroidism, with a normal thyroid-stimulating hormone value and low free thyroxine level, has been documented in up to 25% of individuals with PWS, with a mean age of diagnosis and treatment of two years [Miller et al 2008, Diene et al 2010].

Central adrenal insufficiency (CAI) following overnight single-dose metyrapone tests was noted in 60% of children with PWS in one study, suggesting that this may be the cause of the high incidence of sudden death in this population [de Lind van Wijngaarden et al 2008]. It is known that introducing GH therapy can precipitate adrenal crisis in individuals with incipient adrenal insufficiency by accelerating the peripheral metabolism of cortisol, which may explain the correlation between the incidence of sudden death at the beginning of GH treatment and CAI in individuals with PWS [Scaroni et al 2008]. However, subsequent studies have found normal cortisol responses to low- and high-dose synacthen testing, as well as to insulin tolerance testing [Nyunt et al 2010, Farholt et al 2011]; thus, whether CAI is a true issue for individuals with PWS remains uncertain at this time and no consensus exists among endocrinologists as to whether evaluation for CAI should be performed on every individual with PWS or only those with symptoms consistent with adrenal insufficiency.

Sleep abnormalities are well documented and include reduced REM (rapid eye movement) latency, altered sleep architecture, oxygen desaturation, and both central and obstructive apnea [Festen et al 2006, Priano et al 2006]. Primary hypothalamic dysfunction is thought to be the cause of the alterations in sleep microstructure and abnormalities in ventilation during sleep, with studies showing low levels of orexin and hypocretin in the cerebrospinal fluid and decreased levels of acetyl-cholinergic neurons in the pedunculo-pontine tegmental nucleus [Dauvilliers et al 2003, Nevsimalova et al 2005, Bruni et al 2010, Hayashi et al 2011]. Some individuals with PWS have excessive daytime sleepiness, which resembles narcolepsy, with rapid onset of REM sleep and decrease in non-REM sleep instability [Bruni et al 2010].

Behavior. A characteristic behavior profile with temper tantrums, stubbornness, controlling and manipulative behavior, compulsivity, and difficulty with change in routine becomes evident in early childhood in 70%-90% of individuals with PWS.

- Many of the behavioral characteristics are suggestive of autism; one study showed that 19% of 59 individuals with PWS versus 15% of age-, sex-, and IQ-matched controls satisfy diagnostic criteria for autism [Descheemaeker et al 2006].
- In another study of 58 children, attention deficit/hyperactivity symptoms and insistence on sameness were common and of early onset [Wigren & Hansen 2005].
- This behavior disorder has been reported to increase with age and body mass index (BMI) [Steinhausen et al 2004], although it diminishes considerably in older adults [Dykens 2004].
- Psychosis is evident by young adulthood in 10%-20% of affected individuals, and is more frequent in those with UPD [Boer et al 2002, Clarke et al 2002, Vogels et al 2004, Yang et al 2013].

Behavioral and psychiatric problems interfere most with the quality of life in adolescence and adulthood.

Growth. Short stature, if not apparent in childhood, is almost always present during the second decade in the absence of growth hormone (GH) replacement, and lack of a pubertal growth spurt results in an average untreated height of 155 cm for males and 148 cm for females. The hands and feet grow slowly and are generally below the fifth centile by age ten years, with an average adult female foot size of 20.3 cm and average adult male foot size of 22.3 cm. Growth charts for affected infants and children not treated with growth hormone have been

published [Butler et al 2011, Butler et al 2015] and growth charts for growth hormone-treated children with PWS have been developed [MG Butler & DJ Driscoll, unpublished data].

Data from at least 15 studies involving more than 300 affected children [Burman et al 2001] document reduced GH secretion in PWS. GH deficiency is also seen in adults with PWS [Grugni et al 2006, Höybye 2007].

Dysmorphic features. Characteristic facial features (narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, thin vermilion of the upper lip with down-turned corners of the mouth) may or may not be apparent at birth and slowly evolve over time.

Hypopigmentation of hair, eyes, and skin is frequently found in patients with a deletion due to loss of a single copy of the gene *OCA2*.

Ophthalmic issues. Strabismus is seen in 60%-70%.

Skeletal findings. Hip dysplasia occurs in approximately 10%-20% [West & Ballock 2004, Shim et al 2010]. Bone fractures are a risk due to the increased frequency of osteopenia and osteoporosis.

Scoliosis, present in 40%-80%, varies in age of onset and severity.

Other. Rates of the following are increased:

- Possibility of recurrent respiratory infections (in $\leq 50\%$ of individuals)
- Leg edema and ulceration (especially in the obese)
- Skin picking
- Altered temperature sensation
- Decreased saliva flow
- High vomiting threshold
- Seizures (in 10%-20%)

Morbidity and mortality. Mortality rate in PWS is higher than in controls with intellectual disability, with obesity and its complications being factors [Einfeld et al 2006]. Based on a population study, the death rate was estimated at 3% per year [Butler et al 2002], although a later study of the same population showed the rate to be decreasing to 1.25% per annum with improved management [Whittington et al 2015]. Two multicenter series of individuals who died of PWS have been reported [Schrandt-Stumpel et al 2004, Stevenson et al 2004], and an extensive case and literature review of 64 cases of death in PWS was performed [Tauber et al 2008]. Respiratory and other febrile illnesses were the most frequent causes of death in children, and obesity-related cardiovascular problems and gastric causes or sleep apnea were most frequent in adults. Other causes of morbidity include diabetes mellitus, thrombophlebitis, and skin problems (e.g., chronic edema, infection from skin picking).

A few individuals have been reported to have respiratory or gastrointestinal infections resulting in unexpected death; of these, three who died as a result were noted to have small adrenal glands [Stevenson et al 2004], although this is not a common finding. The report of central adrenal insufficiency (CAI) in 60% of tested individuals [de Lind van Wijngaarden et al 2008] suggests a possible explanation for some of these unexpected and sudden deaths. Other studies have not demonstrated a high incidence [Farholt et al 2011, Grugni et al 2013] of CAI in PWS.

Acute gastric distention and necrosis have been reported in a number of individuals with PWS [Stevenson et al 2007a], particularly following an eating binge among those who are thin but were previously obese. It may be unrecognized because of high pain threshold and can be fatal.

Choking, especially on hot dogs, has been reported as cause of death in approximately 8% of deaths in individuals with PWS [Stevenson et al 2007b].

Concern about the possible contribution of growth hormone (GH) administration to unexpected death has been raised by reported deaths of individuals within a few months of starting GH therapy [Eiholzer 2005, Sacco & Di Giorgio 2005]. The few reported deaths were mostly in obese individuals who had pre-existing respiratory or cardiac disorders with evidence of upper airway obstruction and uncorrected tonsillar and adenoidal hypertrophy. In the database of one pharmaceutical company, five of 675 children treated with GH died suddenly of respiratory problems [Craig et al 2006]. In another study, the rate of death in affected individuals on and off GH did not differ [Nagai et al 2005]. A study of the natural history of PWS in one region of the UK found the overall death rate of individuals with PWS to be as high as 3% per year without GH therapy [Whittington et al 2001]. Thus, the relationship of GH administration to unexpected death remains unclear. However, it is advisable to obtain a sleep study before the initiation of GH therapy and again four to eight weeks after the beginning of GH therapy to ensure that GH treatment has not caused or worsened sleep-disordered breathing [Miller et al 2006b]. A long-term study of 48 treated children suggests that the benefits of treatment with GH greatly exceed the risks [Carrel et al 2010].

Neuroimaging. In one study, all 20 individuals with PWS who were evaluated had brain abnormalities that were not found in 21 sibs or 16 individuals with early-onset morbid obesity who did not have PWS [Miller et al 2007]. All had ventriculomegaly; 50% had decreased volume of brain tissue in the parietal-occipital lobe; 60% had Sylvian fissure polymicrogyria; and 65% had incomplete insular closure. In another study, these authors reported white matter lesions in some people with PWS [Miller et al 2006a]. A study of brain MRIs from 91 individuals with PWS from another group showed reduced pituitary height in 49% and some neuroradiologic abnormality in 67% [Iughetti et al 2008]. The implications of these findings are unknown.

Genotype-Phenotype Correlations

No phenotypic feature is known to correlate exclusively with any one of the three main molecular mechanisms that result in PWS. However, some statistical differences in the frequency or severity of certain features between the two largest molecular classes (deletion and UPD) are observed.

UPD

- Post-term delivery is more common with UPD [Butler et al 2009].
- Individuals with UPD are less likely to have the typical facial appearance, hypopigmentation, or skill with jigsaw puzzles [Dykens 2002]; they also have a somewhat higher verbal IQ and milder behavior problems [Dykens et al 1999, Roof et al 2000, Hartley et al 2005].
- Individuals with UPD are more likely to have psychosis [Holland et al 2003, Yang et al 2013] and autism spectrum disorders [Veltman et al 2004, Whittington et al 2004b, Veltman et al 2005, Descheemaeker et al 2006]. Studies suggest that as many as 62% of those with UPD develop atypical psychosis compared with 16% of those with a deletion [Soni et al 2007].

Deletion

- Individuals with a deletion showed a higher frequency of need for special feeding techniques, sleep disturbance, hypopigmentation, and speech articulation defects in a recent study of 91 children [Torrado et al 2007].
- Individuals with the slightly larger, type 1 deletions (BP1 to BP3; see Figure 2) have been reported to have more compulsions and poorer adaptive behavior, intellectual ability, and academic achievement than those with type 2 deletions (BP2 to BP3) [Butler et al 2004, Hartley et al 2005]. Two other studies found much less clinically significant differences between individuals with these two deletion types [Milner et al 2005, Varela et al 2005]. Larger studies are needed to determine whether there are significant clinical differences between the two most frequent deletion classes.

Penetrance

Penetrance is complete.

Nomenclature

The term HHHO (hypogonadism, hypotonia, hypomentia, obesity) is no longer used.

The condition is sometimes called Willi-Prader syndrome or Prader-Labhart-Willi syndrome.

Prevalence

The estimated prevalence of PWS is 1:10,000 to 1:30,000 in a number of populations.

Genetically Related Disorders

[Angelman syndrome](#) (AS) is caused by loss of the maternally contributed PWS/AS region. It is clinically distinct from PWS after age two years.

Maternally inherited duplication of the PWS/AS region causes intellectual disability, seizures, and autism [Boyar et al 2001]. See [15q Duplication Syndrome and Related Disorders](#).

Differential Diagnosis

Many disorders can mimic *parts* of the PWS phenotype.

Craniopharyngioma and the results of its treatment show the greatest overlap with PWS. Damage to the hypothalamus causes most of the same findings that characterize PWS, particularly when craniopharyngioma occurs at an early age. History and, if uncertain, DNA methylation analysis will distinguish craniopharyngioma from PWS.

Hyperphagic short stature is an acquired condition related to psychosocial stress that includes growth hormone insufficiency, hyperphagia, and mild learning disabilities [Gilmour et al 2001]. History and, if uncertain, DNA methylation analysis should distinguish this disorder from PWS.

Hypotonia in infancy is also seen in the following conditions:

- Neonatal sepsis
- Central nervous system depression
- [Congenital myotonic dystrophy type 1](#), characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; intellectual disability is common. It is caused by expansion of a CTG trinucleotide repeat in *DMPK*.
- Several myopathies and neuropathies, including some instances of [spinal muscular atrophy](#) (SMA) [Miller et al 1999, Richer et al 2001]. In these situations, poor respiratory effort may be present, a feature rarely seen in PWS. Molecular genetic testing, EMG/NCV, and/or muscle biopsy are often required to differentiate these conditions.
- [Angelman syndrome](#) (AS), characterized by severe developmental delay or intellectual disability, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and a unique behavior with an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. Microcephaly and seizures are also common. AS is caused by deficient expression or function of the maternally inherited *UBE3A* allele and may be diagnosed in 75%-80% of individuals with AS using DNA methylation analysis of chromosome 15. In infancy, hypotonia may be the only manifestation of AS. Affected individuals lack the characteristic sucking problems, hypogonadism, and facial appearance of individuals with PWS.

- **Fragile X syndrome**, characterized by moderate intellectual disability in affected males and mild intellectual disability in affected females. Males may have a characteristic appearance (large head, long face, prominent forehead and chin, protruding ears), connective tissue findings (joint laxity), and large testes (postpubertally). Behavioral abnormalities, sometimes including autism spectrum disorder, are common. The diagnosis of fragile X syndrome rests on the detection of an alteration in *FMR1* consisting of expansion of a triplet repeat and aberrant gene methylation. In infancy, hypotonia may be the only manifestation. Affected individuals lack the characteristic sucking problems, hypogonadism, and facial appearance of individuals with PWS.
- **WAC-related intellectual disability** is typically characterized by variable degrees of global developmental delay and/or intellectual disability. Behavioral abnormalities including anxiety, attention deficit/hyperactivity disorder, and/or autism spectrum disorder are observed in the majority of older children and adults. Most affected infants have significant but nonspecific features at birth such as neonatal hypotonia and feeding problems. Some affected individuals come to medical attention with respiratory or vision problems. Facial features may be mildly dysmorphic, but are nonspecific. To date, 18 individuals have been identified with WAC-related ID. The diagnosis of WAC-related ID is established in a proband by identification of a heterozygous pathogenic variant in *WAC* on molecular genetic testing.

Developmental delay/intellectual disability and obesity with or without hypogonadism can be seen in the following disorders:

- **Angelman syndrome (AS)**. Individuals with AS caused by paternal UPD 15 frequently have an elevated BMI for age. In one large study overweight was found in more than 70% and obesity in more than 40% [Lossie et al 2001].
- **Fragile X syndrome**. A subset have been found with a "Prader-Willi-like" phenotype including hyperphagia and obesity [de Vries et al 1993].
- Maternal uniparental disomy for chromosome 14, which also includes prenatal growth retardation, feeding problems, short stature, and precocious puberty [Cox et al 2004, Hosoki et al 2009]
- Albright hereditary osteodystrophy (OMIM 103580), which also includes short stature, but lacks hypotonia and has different characteristic facial appearance (round face). Specific testing is possible by measurement of Gs receptor-coupling protein.
- **Bardet-Beidl syndrome (BBS)**, characterized by cone-rod dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, and renal dysfunction. Individuals with BBS have a different facial phenotype from those with PWS. Inheritance is typically autosomal recessive, although in fewer than 10% of individuals inheritance may be more complex.
- **Cohen syndrome**, characterized by failure to thrive in infancy and childhood; truncal obesity in the teen years; early-onset hypotonia and developmental delays; microcephaly developing during the first year of life; moderate to profound psychomotor retardation; progressive retinochoroidal dystrophy and high myopia; neutropenia in many with recurrent infections and aphthous ulcers in some; a cheerful disposition; joint hypermobility; and characteristic facial features which are different from PWS. Cohen syndrome is caused by pathogenic variants in *VPS13B*. Inheritance is autosomal recessive.
- Borjeson-Forssman-Lehmann syndrome (OMIM 301900), seen in males, characterized by severe cognitive deficit, epilepsy, hypogonadism, hypometabolism, marked obesity, infantile hypotonia and failure to thrive, and short stature. It can be distinguished by the severity of intellectual disability, the presence of nystagmus, and characteristic facial appearance with prominent superciliary ridges, ptosis, and deep-set eyes. Pathogenic variants in *PHF6* are causative. Inheritance is X-linked. Heterozygous females who show manifestations of the disorder have skewed X-chromosome inactivation or a genomic deletion including *PHG6*.
- **Alstrom syndrome**, characterized by cone-rod dystrophy, early-onset obesity, progressive sensorineural hearing impairment, dilated cardiomyopathy (>60%), the insulin resistance syndrome/type 2 diabetes

mellitus associated with acanthosis nigricans, and developmental delay (~50%). Other endocrine abnormalities can include hypothyroidism and male hypogonadotropic hypogonadism. Urologic disorders of varying severity, characterized by detrusor-urethral dyssynergia, appear in females in their late teens. Severe renal disease is usually a late finding. Pathogenic variants in *ALMS1* are found in 70%-80% of individuals of northern European descent, and about 40% of affected individuals worldwide.

Cytogenetic abnormalities with a similar phenotype include the following:

- A "PWS-like phenotype" of syndromic obesity has been identified in individuals with an interstitial deletion of 6q16.2, which includes *SIM1* [Varela et al 2005]. This deletion had been reported at least five times previously in syndromic obesity [Bonaglia et al 2008] as well a duplication [Desch et al 2015]. Also, pathogenic variants in *SIM1* alone have been found in patients with severe obesity [Bonnefond et al 2013, Ramachandrapa et al 2013].
- Several reports have associated a Prader-Willi-like phenotype with 1p36 deletion; additional findings include hypotonia, developmental delay, obesity, hyperphagia, and behavioral problems [Tsuyusaki et al 2010, Stagi et al 2014].
- Multiple reports describe deletions at 16p11.2 including *SHB2B1*, which is involved in leptin and insulin signaling [Maillard et al 2015].
- Reports of other cytogenetic anomalies in individuals with a PWS-like phenotype have included dupXq27.2-ter and del10q26 [Lukusa & Fryns 2000, Ben-Abdallah-Bouhjar et al 2012, Rocha & Paiva 2014].

Management

Management of the manifestations of Prader-Willi syndrome (PWS) is age dependent and should include both addressing of the consequences of PWS and anticipatory guidance. It is recommended that a team approach be used, if possible. Several approaches to management have been published [Goldstone et al 2008, Cassidy & Driscoll 2009, Cassidy & McCandless 2010, McCandless 2011, Cassidy et al 2012].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PWS, the following evaluations are recommended:

- Consultation with a clinical geneticist and/or genetic counselor
- Endocrinology consultation
- Nutritional consultation
- Assessment of newborns and young infants for sucking problems and failure to thrive
- Regardless of age, measurement and plotting of height, weight, head circumference and body mass index (BMI) on either age-appropriate growth charts or charts developed for PWS [Butler et al 2011, Butler et al 2015]
- Assessment for hypothyroidism in children, especially those with prolonged failure to thrive, those with excess weight gain in the absence of increased food intake, and those with poor linear growth despite growth hormone treatment
- Evaluation of respiratory status with a low threshold for performing a sleep study regardless of age. These studies are specifically recommended prior to the initiation of growth hormone therapy (GHT) and four to eight weeks after starting GHT, along with assessment of the size of tonsils and adenoids, particularly in the obese individual.

- Assessment of development of infants and of educational development of children including a speech evaluation
- Assessment for the presence of behavioral problems and obsessive-compulsive features after age two years, and for psychosis in adolescents and adults. If history reveals evidence of these problems, referral for more detailed assessment is indicated.
- Assessment of males for the presence of cryptorchidism regardless of age
- Referral for ophthalmologic evaluation if strabismus is present, and for assessment of visual acuity by age one year or at diagnosis if it is later
- Regardless of age, assessment for the presence of scoliosis clinically, and, if indicated, radiographically
Note: Very obese individuals cannot be adequately assessed for scoliosis clinically; x-rays are necessary to establish the diagnosis.

Treatment of Manifestations

A team approach to management is recommended [Goldstone et al 2008, Cassidy & McCandless 2010].

Feeding, hyperphagia, and obesity. Special feeding techniques, including special nipples or gavage feeding, may be necessary for the first weeks to months of life to assure adequate nutrition and avoid failure to thrive. Individuals diagnosed with PWS typically do not need a G-tube since the feeding will improve with time.

When weight centiles begin increasing in nutritional phase 2a (typically between 18 and 36 months), a program of a well-balanced, low-calorie diet, regular exercise, and close supervision to minimize food stealing should be instituted to prevent obesity (i.e., BMI Z score of <2) and its consequences. The same program is appropriate if obesity is present at any time. Consultation with a dietician and close follow up are usually necessary, and locking the kitchen, refrigerator, and/or cupboards is often needed once the child is able to open the refrigerator and cupboards. Caloric needs of infants and children with PWS are typically 60%-80% of the recommended daily allowance (RDA). The energy requirement of adults with PWS, which rarely exceeds 1200-1400 Kcal/day, should be considered in planning daily food intake. Assessment of adequacy of vitamin and mineral intake by a dietician, and prescription of appropriate supplementation, is indicated, especially for calcium and vitamin D.

No medications are known to aid in controlling hyperphagia, but several clinical trials are underway (see Therapies Under Investigation).

Gastric bypass is not recommended in PWS, as it does not appear to correct the lack of satiety and will not prevent overeating. In addition, complication rates are high [Scheimann et al 2012].

Growth hormone treatment normalizes height, increases lean body mass, decreases fat mass, and increases mobility, which are beneficial to weight management. Dose recommendations in young children are generally similar to those for individuals with isolated growth hormone deficiency (i.e., ~1 mg/m²/day) but the dose must be individualized as the child grows. Therapy can be started in infancy or at the time of diagnosis. The adult dose of growth hormone is 20%-25% of the dose recommended in children. Monitoring of growth velocity, head circumference, and serum IGF-1 is important to avoid overtreatment.

Controlled trials of growth hormone therapies have demonstrated significant benefit from infancy through adulthood [Carrel et al 2010, Sode-Carlson et al 2010, Wolfgram et al 2013].

- An increase in language and cognitive skills in treated infants [Myers et al 2007] and an improvement in mental speed and flexibility as well as motor performance in adults [Höybye et al 2005] have been reported based on controlled trials.

- A review of the results of one to two years of growth hormone treatment among 328 children documented in the database of one pharmaceutical company indicated improved height velocity, particularly in prepubertal children, but no change in BMI [Craig et al 2006].
- Significantly greater adult height was demonstrated in 21 individuals treated long term versus 39 untreated individuals without an increase in adverse side effects [Angulo et al 2007].
- Some improvements in cognition have been suggested with growth hormone therapy in individuals with PWS [Osório 2012, Siemensma 2012], but more work and longer studies need to be done.
- Although there was initial concern about growth hormone treatment contributing to scoliosis in PWS, later studies showed no difference in frequency or severity in those treated compared to those who were not treated [Nagai et al 2006, Angulo et al 2007].

Decreased saliva production can be addressed with products developed for the treatment of dry mouth, including special toothpastes, gels, mouthwash, and gum.

Therapies, education and behavior management. Early intervention in children before age three years, particularly physical therapy, may improve muscle strength and encourage achievement of developmental milestones. In older individuals, daily muscle training increases physical activity and lean body mass [Schlumpf et al 2006].

Initiate appropriate educational programming in children:

- Begin speech therapy for language delay and articulation abnormalities in infancy and childhood.
- Special education, either in an inclusion setting or in a self-contained classroom setting, is usually necessary during school age. An individual aide is helpful in assuring attendance to task. Social skills training groups have been beneficial.

Behavioral disturbance should be addressed with behavioral management programs, including firm limit setting. While no medication is beneficial in managing behavior in all individuals with PWS, serotonin reuptake inhibitors have helped the largest proportion of affected teenagers and adults, particularly those with obsessive-compulsive symptoms [Brice 2000, Dykens & Shah 2003].

Psychosis is reported to respond well to selective serotonin reuptake inhibitors, but not to mood stabilizers [Soni et al 2007]. There are no well-designed studies of the effectiveness of treatment for psychosis in PWS [Ho & Dimitropoulos 2010].

Hypogonadism. Cryptorchidism may resolve spontaneously, even up to adolescence, but usually requires hormonal and surgical approaches; however, preservation of fertility is not an issue. Standard treatment is appropriate. Human chorionic gonadotropin treatment for infants with undescended testes should be considered as it can improve the size of the scrotal sac and improve surgical outcome [McCandless 2011; Angulo & Miller, unpublished data].

Replacement of sex hormones produces adequate secondary sexual characteristics but is somewhat controversial because of the possible role of testosterone replacement in behavior problems in males and the role of estrogen replacement in the risk of stroke as well as hygiene concerns related to menstruation in females. Daily use of the testosterone patch or gel may avert exacerbation of behavioral problems by providing a more even blood level than use of a slow-release depo-testosterone injection every month. Also, it was shown in the non-PWS adult population that depo- testosterone injections were associated with a greater risk of cardiovascular events, hospitalizations, and deaths compared with gels and patches [Layton et al 2015].

Concern about osteoporosis should be considered in deciding about hormone replacement. Recent reports of fertility in four women with PWS raise the issue of need for birth control [Akefeldt et al 1999; Schulze et al 2001; Vats & Cassidy, unpublished data].

Sleep issues. Disturbed sleep in children and adults should prompt a sleep study, as treatment may be available. Treatment depends on the cause and may include tonsillectomy and adenoidectomy and/or CPAP or BiPAP, as in the general population.

Excessive daytime sleepiness (unrelated to the degree of sleep apnea) is frequently seen in individuals with PWS. Modafinil has been shown to be a safe and effective treatment for this condition [De Cock et al 2011].

Skin picking. One study demonstrated decreased skin picking with topiramate treatment in some individuals [Shapira et al 2004]; other clinicians have reported anecdotally that approximately half of individuals with PWS who skin pick benefit from low-dose (25-50 mg daily) topiramate.

A recent study of 35 individuals with PWS (age 5-39 years) using 450-1200 mg/day of N-acetylcysteine found a high degree of success in reducing or eliminating skin picking [Miller & Angulo 2014].

Other

- Management of strabismus is as for any infant.
- Management of scoliosis, hip dysplasia, and complications of obesity is as in the general population.

Adulthood. For adults with PWS, the most successful living situation for behavior and weight management is a group home specially designated for individuals with PWS, where diet and access to food are tightly restricted and exercise is included in daily activities. Affected individuals generally require a sheltered employment environment.

Issues of guardianship, wills, trusts, and advocacy should be investigated no later than adolescence.

Prevention of Primary Manifestations

Obesity may be prevented if the diet, exercise, and supervision program described in Treatment of Manifestations is instituted. Early diagnosis allows the clinician to begin anticipatory guidance concerning the natural history of PWS, and in particular the nutritional phases, informing the family about the risk of obesity and the need to monitor weight increase and to restrict calories beginning around 18-36 months of age.

If started at a young age, growth hormone treatment, along with good dietary control, may retard obesity and the high proportion of fat mass. It may also prevent development of the typical facial appearance and improve motor milestones.

Prevention of Secondary Complications

Diabetes mellitus rarely occurs in the absence of obesity.

Calcium and vitamin D supplementation are probably beneficial, as low-calorie diets are often low in dairy products and osteoporosis has been documented in the majority of older children and adults with PWS.

If osteoporosis develops, consider treatment with a bisphosphonate.

Although no formal study exists, individuals with PWS tend to be very sensitive to medications of all kinds. Starting with lower doses is recommended.

Surveillance

Health supervision guidelines from the American Academy of Pediatrics (AAP) have been published [McCandless 2011] ([full text](#)).

To assure appropriateness of exercise program and diet, including adequacy of vitamin and mineral intake and monitor height, weight, and BMI (weight in kg/height in m²):

- Every month in infancy;
- Every six months in the first decade of life;
- At least annually thereafter.

Cryptorchidism can recur after orchidopexy; therefore, testicular position should be monitored.

Evaluate for the presence of diabetes mellitus by standard methods (e.g., obtaining glycosylated hemoglobin concentration and/or glucose tolerance test) in anyone with significant obesity or rapid significant weight gain.

Test annually for hypothyroidism, including free T4 and TSH levels.

Obtain history of any sleep disturbance; if present, obtain a sleep study.

Monitor for development of scoliosis clinically or, in the presence of obesity, radiographically at least annually.

Perform bone densitometry by DEXA to evaluate for possible osteoporosis every two years in adulthood.

Obtain history for behavioral and psychiatric disturbance at least annually.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

In the last few years there has been great interest by the pharmaceutical industry in testing treatments for the major manifestations of PWS – particularly the hyperphagia, obesity, and behavioral problems. For a detailed description of these studies, click [here](#) (pdf).

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Prader-Willi syndrome (PWS) is caused by lack of expression of the paternally derived PWS/AS region of chromosome 15q11.2-q13 by one of several genetic mechanisms.

Risk to Family Members

Parents of a Proband

- The parents of the proband are unaffected.
- Recommendations for genetic testing of the parents depend on the genetic mechanism of PWS in the proband (see Sibs of a Proband and Table 3).
- Note: Germline mosaicism in the father is rare but has been observed in cases of 15q11.2 deletions [Fernández-Novoa et al 2001] and IC deletions [Buiting et al 2003, Wey et al 2005]. Recurrent meiotic nondisjunction of maternal chromosome 15 has also been observed [Harpey et al 1998].

Sibs of a Proband

The risk to sibs of a proband with PWS depends on the genetic mechanism of PWS in the proband and the molecular class (summarized in Table 3). The vast majority of families have a recurrence risk of less than 1%. However, certain etiologies involve a recurrence risk as high as 50%, and a scenario with a risk of almost 100% (i.e., a mother with a 15/15 Robertsonian translocation), though very unlikely, is theoretically possible.

For recurrence risk assessment. If the DNA methylation pattern is characteristic of maternal inheritance only, the underlying genetic mechanism (deletion, UPD, or ID) and the specific genetic etiology (molecular class) should be determined for genetic counseling purposes (see Figure 1 and Table 3).

It is typically most efficient to begin with a karyotype and FISH analysis for the 15q11.2-q13 deletion. Simultaneous cytogenetic studies allow detection of a translocation or other anomaly involving proximal 15q. With the increasing use of chromosomal microarray (CMA) in clinical genetics, arrays (particularly SNP arrays) may replace FISH analysis for the identification of deletions in PWS. However, each technique has its advantages.

- CMA will precisely identify the deletion size, which is anticipated to become increasingly important for genotype-phenotype correlations in the future [Kim et al 2012]. In addition, in the non-deletion cases an SNP array will identify a high percentage of UPDs.
- However, CMA will not detect the rare chromosome rearrangements (translocations and inversions) involving proximal 15q; these are detectable by simultaneous karyotype and FISH analysis and are important in recurrence risk determination.
- For genetic counseling purposes, a chromosome analysis is advised in the proband to discern an interstitial *de novo* deletion from a balanced or unbalanced chromosome rearrangement involving the 15q11.2 region.
- CMA would also be indicated if an individual with PWS had a more severe phenotype than is typical in order to discern if there was a larger deletion present or an additional chromosome abnormality elsewhere in the genome.

If no deletion or other chromosome abnormality is detected, DNA polymorphism studies (requiring blood from both parents and the proband) are conducted. Increasingly, clinical geneticists are using a CMA combined with SNPs (i.e., oligo-SNP arrays) which will detect approximately 75% of UPDs by demonstrating long (>13.5 Mb) contiguous stretches of homozygosity limited to the chromosome 15s [Papenhausen et al 2011; Butler & Driscoll, unpublished data]. In these cases DNA polymorphism analysis is probably not necessary to diagnose UPD.

If UPD is not detected, referral to a specialized laboratory for microdeletion analysis of the imprinting center (IC) is indicated.

Table 3. Risks to Sibs of a Proband with PWS by Genetic Mechanism

Molecular Class ¹	Proportion of PWS by Molecular Class	Genetic Mechanism	Risk to Sibs
Ia	65%-75%	Interstitial 5- to 6-Mb 15q11.2-q13 deletion	<1%
Ib	<1%	Unbalanced chromosome rearrangement	Possibly as high as 50%
IIa	20%-30%	Maternal UPD	<1%
IIb	<1%	Maternal UPD w/predisposing parental translocation or marker chromosome	Increased; can vary from <1% to 100%
IIIa	<0.5%	ID w/deletion in the IC	As high as 50% if father also has IC deletion

Table 3. continued from previous page.

Molecular Class ¹	Proportion of PWS by Molecular Class	Genetic Mechanism	Risk to Sibs
IIIb	2%	Epimutation - ID w/out IC deletion	<1%

IC = imprinting center; ID = imprinting defect; UPD = uniparental disomy

1. Based on terminology by Jiang et al [1999]

Ia. Fathers of individuals with deletions should have chromosome and FISH analyses to determine if they have a chromosome rearrangement. For probands with one of the typical (type 1 or type 2) large *de novo* 5- to 6-Mb deletions, the risk to sibs is less than 1%. Germline mosaicism for these large deletions has been reported on rare occasion [Kokkonen & Leisti 2000].

Ib. If a chromosome rearrangement has been identified in a proband, the risks to sibs and other family members depend on whether the rearrangement is paternally inherited or *de novo* [Cassidy et al 2012].

IIa. Maternal UPD 15 is typically *de novo* with a recurrence risk to sibs of less than 1% except if a Robertsonian translocation is present in either parent. Therefore chromosome analysis is indicated in the proband. If this does not identify a chromosome abnormality, the father of the child should be offered chromosome analysis to ensure that he does not have a Robertsonian translocation. It is presumed that the mother does not have a Robertsonian translocation since the two maternal chromosomes 15 are normal in the proband. However, it is theoretically possible that the father has a Robertsonian translocation involving chromosome 15 which led to aberrant segregation at meiosis I and resulted in a sperm that was nullisomic for 15. This, combined with monosomy rescue to disomy, would result in an embryo with maternal UPD 15.

IIb. Individuals with UPD 15 should have chromosome analysis to ensure that they do not have a maternally inherited Robertsonian translocation that would theoretically increase the family's recurrence risk. In rare cases, UPD has resulted from malsegregation of a Robertsonian translocation and subsequent trisomy rescue. Empiric data suggest that the risk for recurrence in most of these cases would also be less than 1%, although the theoretic risk would be much higher.

If the mother has a 15/15 Robertsonian translocation, trisomy rescue will lead to PWS. If the father has a 15/15 Robertsonian translocation, monosomy rescue will lead to PWS. While most parents with a 15/15 Robertsonian translocation will probably have spontaneous abortions rather than a child with PWS, some may have a live-born child with PWS by the mechanisms described above.

Rarely, a small marker chromosome is also present in a proband with maternal UPD 15 [Liehr et al 2005]. In these instances it is important to examine both parents' karyotypes, as it appears that these small marker chromosomes may increase the risk for non-disjunction and UPD [Kotzot 2002].

IIIa. Individuals with PWS caused by an imprinting defect (ID) should be tested for an IC deletion by a lab experienced in detecting them. About 15% of those with an ID have it on the basis of a microdeletion in the IC. In about half of these individuals the IC deletion is familial and the familial recurrence risk is 50%. Therefore, fathers of children with an IC deletion should have DNA methylation and dosage analysis (or sequence analysis) in the PWS smallest region of deletion overlap (SRO) to determine if they carry the IC deletion.

IIIb. The majority (~85%) of those with an ID have a *de novo* epigenetic pathogenic variant and the recurrence risk to sibs is less than 1% for this group.

Offspring of a Proband

- With rare exception in females, individuals with PWS do not reproduce.

- The risk to the child of an affected individual depends on the molecular class and the sex of the affected individual.
- If the proband has PWS as the result of a deletion, the offspring have a 50% chance of having Angelman syndrome (AS) if the proband is female and PWS if the proband is male (the latter has never been reported)
- If the proband has UPD, the offspring would be expected to be unaffected. A single report described a female with PWS caused by UPD who had a normal child [Schulze et al 2001].
- If the female proband has PWS as the result of an ID by an IC deletion, the offspring are at a 50% theoretic risk of having AS if the microdeletion extends into the AS SRO (never reported).
- If the proband has a chromosome translocation, the offspring are theoretically at increased risk of having PWS or AS, depending on the sex of the proband (never reported).

Other Family Members

If a chromosome rearrangement (e.g., translocation or inversion) is identified in the proband and a parent, the sibs of the carrier parent should be offered genetic counseling and the option of genetic testing.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

Families who have a child with PWS (in whom the causative genetic mechanism has been identified) should be aware that prenatal testing for PWS is possible. Depending on the molecular mechanism, FISH, CMA, DNA methylation analysis, MS-MLPA, or DNA polymorphism studies for UPD may be appropriate. Note that only DNA methylation analysis (e.g., using MS-MLPA) at the 5' *SNRPN* locus will identify the imprinting defects [Kubota et al 1996, Glenn et al 2000, Ramsden et al 2010]. While prenatal detection of all three molecular classes of PWS is possible, availability may be limited. Laboratories offering PWS prenatal testing by DNA methylation analysis typically accept only amniocytes (vs chorionic villi) for analysis because of the known hypomethylation of tissue derived from the placenta [Driscoll & Migeon 1990, Glenn et al 2000].

- Parents who have had one child with PWS caused either by deletion or UPD, and who do not have a chromosome rearrangement, have a low recurrence risk.
- Parents who have had one child with PWS caused by an IC deletion, and in whom the father is a known carrier, have a high recurrence risk; DNA methylation analysis can be used in these cases.
- Prenatal testing for an inherited translocation involving chromosome 15 and resulting in a deletion is relevant because of the theoretic 50% risk of PWS in the offspring.

Pregnancies in which no family history of PWS exists. PWS may be a possibility in the following situations:

- If a 15q11.2 deletion is suspected on cytogenetic studies from testing of cells obtained by CVS or amniocentesis, FISH or CMA is indicated. In this instance, parent-of-origin studies should be performed

after confirmation of a deletion to determine if the deletion is maternally derived (fetus has AS) or paternally derived (fetus has PWS).

- If a trisomy 15 or mosaic trisomy 15 is detected on testing of cells obtained by CVS, and if subsequent testing of cells obtained by amniocentesis reveals 46 chromosomes, the possibility of trisomy rescue leading to AS (paternal UPD) through loss of a maternal chromosome 15 or PWS (maternal UPD) through loss of a parental chromosome 15 can be considered. In this instance, parent-of-origin (UPD) studies or DNA methylation analysis on amniocytes should be considered [EUCROMIC 1999, Shaffer et al 2001].
- If an inherited or *de novo* translocation involving chromosome 15 is present or if a supernumerary chromosome derived from chromosome 15 is detected, FISH (to rule out a deletion) and parent-of-origin or DNA methylation studies (to rule out the possibility of UPD) are indicated.

Recently noninvasive prenatal tests (NIPT) using fetal cell-free DNA have become available for testing the major trisomy conditions as well as the common microdeletion (including PWS and AS) conditions [Norton et al 2012]. If CMA is used in NIPT it will pick up 15q11.2 deletions, but it will not distinguish an AS deletion from a PWS deletion and it will not pick up the UPD and ID mechanisms.

Preimplantation genetic testing (PGT) may be an option for some families in which an IC deletion has been identified. PGT can also be used in cases of familial translocation to rule out UPD.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **International Prader-Willi Syndrome Organisation (IPWSO)**

c/o BIRD Europe Foundation Onlus

Via Bartolomeo Bizio 1

Costozza 1-36023

Italy

Phone: +39 0444 555557

Fax: +39 0444 555557

Email: info@ipwso.org

www.ipwso.org

- **My46 Trait Profile**

[Prader-Willi Syndrome](#)

- **Prader-Willi Syndrome Association (USA)**

8588 Potter Park Drive

Suite 500

Sarasota FL 34238

Phone: 800-926-4797 (toll-free); 941-312-0400

Fax: 941-312-0142

Email: national@pwsusa.org; pwsausa@pwsausa.org

www.pwsausa.org

- **Foundation for Prader-Willi Research (FPWR)**

Phone: 888-322-5487

Fax: 888-559-4105

Email: info@fpwr.org

www.fpwr.org

- **Medical Home Portal**

The Parents & Families section of the Medical Home Portal provides information and resources to help families learn how to better care for a child with chronic and complex conditions and to become more effective partners in their child's care.

Department of Pediatrics University of Utah

P.O. Box 581289

Salt Lake City UT 84158

Phone: 801-213-3920

Email: info@medicalhomeportal.org

[For Parents & Families](#)

- **Prader-Willi Syndrome Association (UK)**

125a London Road

Derby DE1 2QQ

United Kingdom

Phone: 01332 365676

Fax: 01332 360401

Email: admin@pwsa.co.uk

pwsa.co.uk

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Prader-Willi Syndrome: Genes and Databases

Critical Region	Gene	Chromosome Locus	Protein	ClinVar
PWCR	Unknown	15q11.2	Unknown	

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Prader-Willi Syndrome ([View All in OMIM](#))

137142	GAMMA-AMINOBUTYRIC ACID RECEPTOR, ALPHA-5; GABRA5
137192	GAMMA-AMINOBUTYRIC ACID RECEPTOR, BETA-3; GABRB3
176270	PRADER-WILLI SYNDROME; PWS
182279	SMALL NUCLEAR RIBONUCLEOPROTEIN POLYPEPTIDE N; SNRPN
600161	PRADER-WILLI/ANGELMAN REGION RNA 1; PWAR1

Table B. continued from previous page.

600233	GAMMA-AMINOBUTYRIC ACID RECEPTOR, GAMMA-3; GABRG3
601491	IMPRINTED IN PRADER-WILLI SYNDROME; IPW
601623	UBIQUITIN-PROTEIN LIGASE E3A; UBE3A
602117	NECDIN; NDN
603856	MAKORIN 3; MKRN3
603857	MKRN3 ANTISENSE RNA; MKRN3AS
605283	MAGE-LIKE 2; MAGEL2
605436	SMALL NUCLEOLAR RNA, C/D BOX, 116-1; SNORD116-1
605837	HECT DOMAIN AND RCC1-LIKE DOMAIN 2; HERC2
605855	ATPase, CLASS V, TYPE 10A; ATP10A
609837	SMALL NUCLEOLAR RNA, C/D BOX, 115-1; SNORD115-1
610922	NUCLEAR PORE ASSOCIATED PROTEIN 1; NPAP1
611215	PRADER-WILLI REGION NONCODING RNA 1; PWRN1
611409	OCA2 MELANOSOMAL TRANSMEMBRANE PROTEIN; OCA2

Molecular Pathogenesis

The PWS region is localized to a 5- to 6-Mb genomic region on the proximal long arm of chromosome 15 (15q11.2-q13) (Figure 2). It lies within a smaller 2.5-Mb differentially imprinted region. PWS is a contiguous gene disorder: studies thus far indicate that the complete phenotype is due to the loss of expression of several genes. It is also an example of an imprinted condition, since the expression of relevant genes in the 15q11.2-q13 region is dependent on parental origin [Glenn et al 1997, Bittel et al 2006].

The genomic and epigenetic changes causing PWS all lead to a loss of expression of the normally paternally expressed genes on chromosome 15q11.2-q13. Absence of the paternally inherited copy of these genes, or failure to express them, causes total absence of expression for those genes in the affected individual because the maternal contribution for these genes has been programmed by epigenetic factors to be silenced [Glenn et al 1997, Cassidy & Driscoll 2009]. Conversely, a loss of expression of preferentially maternally expressed *UBE3A* in this region by several different possible mechanisms leads to Angelman syndrome [Lossie et al 2001, Williams et al 2010].

The 15q11.2-q13 region can be roughly divided into four distinct regions which are delineated by three common deletion breakpoints [Christian et al 1999] lying within segmental duplications [Amos-Landgraf et al 1999] (see Figure 2 and Table 4):

- A proximal non-imprinted region between the two common proximal breakpoints (BP1 and BP2) containing four biparentally expressed genes, *NIPA1*, *NIPA2*, *CYFIP1*, and *GCP5* [Chai et al 2003]
- The "PWS paternal-only expressed region" containing five polypeptide-coding genes (*MKRN3*, *MAGEL2*, *NECDIN*, and the bicistronic *SNURF-SNRPN*); *NPAP1* (previously known as *C15orf2*) (an intronless gene that is biallelically expressed in testis, but only expressed from the paternal allele in brain); a cluster of C/D box small nucleolar RNA genes (snoRNAs) and several antisense transcripts (including the antisense transcript to *UBE3A*)
- The "Angelman syndrome (AS) region" containing the preferentially maternally expressed genes *UBE3A* and *ATP10A*

- A distal non-imprinted region containing a cluster of three GABA receptor genes, the gene for oculocutaneous albinism type 2 (*OCA2*), *HERC2*, and the common distal breakpoint (BP3)

Table 4. PWS Recurrent Deletions

Deletion	ISCA ID ¹	Region Location ²
15q11-q13, class 1 (type 1)	ISCA-37404	GRCh37/hg19 chr15: 22,876,632-28,557,186
15q11-q13, class 2 (type 2)	ISCA-37478	GRCh37/hg19 chr15: 23,758,390-28,557,186

1. Standardized clinical annotation and interpretation for genomic variants from the [Clinical Genome Resource \(ClinGen\) project](#) (formerly the International Standards for Cytogenomic Arrays (ISCA) Consortium)

2. Genomic coordinates represent the minimum deletion size associated with the PWS recurrent microdeletions as designated by ClinGen. Deletion coordinates may vary slightly based on array design used by the testing laboratory. Note that the size of the microdeletion as calculated from these genomic positions may differ from the expected microdeletion size due to the presence of segmental duplications near breakpoints.

Central to the PWS region is *SNURF-SNRPN*, a bicistronic gene encoding two proteins. A CpG island at the 5' end of *SNURF-SNRPN*, which encompasses the promoter, exon 1 and intron 1, is differentially methylated: the unmethylated paternally inherited allele is expressed and the methylated maternally inherited allele is repressed [Glenn et al 1996]. The CpG island and exon 1 are within the 4.3-kb smallest region of deletion overlap (SRO) for the paternal PWS imprinting center (IC) [Ohta et al 1999]. Six snoRNA genes located at this locus are regulated by the expression of *SNURF-SNRPN*. The *UBE3A* antisense transcript also arises from transcription of *SNURF-SNRPN* and is hypothesized to repress paternal *UBE3A* [Cavaillé et al 2000, Chamberlain & Brannan 2001, Runte et al 2001].

Deletion mechanism. Most cases of PWS result from an interstitial 15q11.2-q13 microdeletion on the paternal allele [Ledbetter et al 1981, Butler & Palmer 1983, Glenn et al 1997]. Deletions account for 65%-75% of individuals with PWS, with the vast majority of deletions having one of two common proximal breakpoints (BP1 or BP2) and a common distal breakpoint (BP3) (see Figure 2 and Table 4) [Christian et al 1995, Amos-Landgraf et al 1999]. These recurrent common interstitial deletions measure about 5-6 Mb and are mediated by multiple copies of tandem repeats flanking the common breakpoints (BP1, BP2, and BP3). These low copy 250-400-kb repeat sequences are subject to non-homologous pairing during meiosis, leading to deletions (causing PWS or AS depending on parental origin), duplications (both maternal and paternal), triplications, and inverted dup (15) [Robinson et al 1998, Amos-Landgraf et al 1999, Boyar et al 2001, Maggouta et al 2003, Depienne et al 2009]. About 8% of cases have unique or atypical-sized deletions (i.e., not type 1 or 2) caused by a variety of etiologies, including an unbalanced translocation [Kim et al 2012]. A deletion that is smaller or larger than typically seen in PWS may result in clinical features distinct from PWS.

Small deletions of the promoter region and the proximal upstream region of *SNRPN* (including the putative imprinting control element) have been identified in individuals with PWS who have maternal-specific DNA methylation patterns, but who have neither the usual large paternally derived deletion of the PWS/AS region nor maternal UPD. This pattern is considered an ID via an IC microdeletion.

Other individuals have biparental inheritance, but maternal-only DNA methylation patterns in this region without detectable abnormalities in the SRO for the IC. These individuals are considered to have an ID by an epimutation.

Genes of interest in this region. The following genes have been mapped within the PWS/AS region:

- *SNURF-SNRPN* is a complex bicistronic gene encoding two different proteins. Exons 4-10 were described first and encode the protein SmN, which is a spliceosomal protein involved in mRNA splicing [Glenn et al 1996]. *SNURF* is encoded by exons 1-3 and produces a polypeptide of unknown function [Gray et al

1999]. It also serves as the host for the six snoRNA genes located telomerically which are regulated by the expression of *SNURF-SNRPN*.

- **IPW** is a long non-coding RNA located between *SNORD116-1* and *SNORD115-1*. It had been thought to have no function, but has recently been shown to be a regulator of the *DLK1-DIO3* imprinted region on chromosome 14, and it may be involved in regulating other non-chromosome 15 imprinted regions in the genome [Stelzer et al 2014]. *IPW* was deleted in the four patients with *SNORD116* deletion described below.
- **PAR1, PAR4, PAR5, and PAR7** are anonymous transcripts.
- **OCA2** (previously known as **P**) codes for tyrosinase-positive albinism; its deletion is associated with the hypopigmentation seen in one third of individuals with PWS.
- **GABRB3, GABRA5, and GABRG3**, all GABA-receptor subunit genes
- **UBE3A** (previously known as **E6AP**) is associated with **AS**.
- **ATP10A**, a maternally expressed gene, is within the most common interval of deletion responsible for AS.
- **HERC2** and multiple duplications occur at the common deletion breakpoints.
- **NECDIN** (*NDN*) encodes a DNA binding protein. An *Ndn* knockout mouse model has indicated that *NDN* mediates intracellular processes essential for neurite outgrowth, and loss of *necdin* impinges on axonal outgrowth [Lee et al 2005]. A mouse *Ndn* knockout model has been reported with similar defects to individuals with PWS and indicates that *necdin* is an antiapoptotic or survival factor in the early development of the nervous system [Andrieu et al 2006].
- **MAGEL2**, an intronless gene in proximity to the *NDN* locus, is transcribed only by the paternal allele and expressed predominantly in the brain. Also recently four individuals with truncating variants in the paternal allele of *MAGEL2* have been described with features that overlap with PWS [Schaaf et al 2013]. All four individuals clinically had autism spectrum disorder, intellectual disability, excessive weight gain and/or hyperphagia and a lack of satiety. It was concluded that "these patients are phenotypically distinct from patients with classic PWS" and the condition was renamed from "Prader-Willi-like syndrome" to "Schaff-Yang syndrome" [Fountain & Schaaf 2015; CP Schaaf, personal communication]. Studies of *Magel2*-null mice have demonstrated several findings that are associated with key aspects of PWS, including neonatal growth retardation, poor suck, excessive weight gain after weaning, and increased adiposity with altered metabolism in adulthood [Lee et al 2005, Bischof et al 2007]. *Magel2* has been implicated in circadian rhythm in mice [Kozlov et al 2007]. Recently, *Magel2*-null mice were shown to have progressive decline in leptin sensitivity in arcuate hypothalamic neurons [Pravdivyi et al 2015].
- **MKRN3** (*Markorin 3, ZNF127*) is a zinc finger protein expressed only from the paternal chromosome. Recently it has been shown that paternally inherited loss-of-function variants in *MKRN3* are a cause of familial central precocious puberty in humans [Abreu et al 2013, Macedo et al 2014].
- **NPAP1** is an intronless gene that is biallelically expressed in adult testis but monoallelically expressed in fetal brain.
- **PWRN1**, expressed in testis, demonstrates lower expression in prostate, heart, kidney, liver, lung, skeletal muscle, trachea, spinal cord, and fetal brain; it is shown to have monoallelic expression in the fetal brain.
- **SNORD116 (snoRNA HBII-85)**. Two lines of evidence suggest that snoRNA *SNORD116* cluster, which consists of 29 gene copies, is causative of PWS features. Balanced translocations that preserve the expression of *SNURF-SNRPN* and centromeric genes that separate the *SNORD116* cluster from its promoter cause PWS. More recently a microdeletion of the *SNORD116* cluster has been reported in four individuals with many PWS features [Sahoo et al 2008, de Smith et al 2009, Buiting 2010, Duker et al 2010, Bieth et al 2015]. However, three of these individuals [Sahoo et al 2008, de Smith et al 2009, Duker et al 2010] also have features not typical of classic PWS, including tall stature in childhood, large head circumference, lack of a "PWS facial gestalt", and hand features not typical of PWS. The snoRNAs are probably involved in the modification of mRNA by alternative splicing and each snoRNA gene may have multiple targets; however, no targets have yet been found for *SNORD116*. A crucial role for the related gene cluster, *SNORD115*, was ruled out in a case of familial AS [Runte et al 2005].

- Several other imprinted genes and transcripts of unknown function have been identified.

Imprinted genes in the region. Several of the genes in the PWS region (*SNURF-SNRPN*, *MKRN3*, *NDN*, *MAGEL2*, *NPAP1*, *PWRN1*, *SNORD116*, *IPW*, and *SNORD115*) are subject to genomic imprinting, thus accounting for the fact that the PWS phenotype results only when the paternally contributed PWS region is absent. DNA methylation, which is involved in the process of genomic imprinting, has been demonstrated for several of the genes identified within the PWS region [Glenn et al 1996, Glenn et al 1997, MacDonald & Wevrick 1997]. Upstream of *SNRPN*, very small deletions of the putative imprinting control element for the region have been identified in a few individuals with PWS who have maternal-specific DNA methylation patterns but have neither the usual large paternally derived deletion of the PWS/AS region nor maternal UPD [Saitoh et al 1997, Ohta et al 1999]. Other individuals demonstrate sporadic imprinting defects that are epimutations [Buiting et al 1998, Buiting et al 2003].

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Chapter Notes

Revision History

- 14 December 2017 (aa) Revision: WAC-related intellectual disability added to Differential Diagnosis
- 4 February 2016 (ha) Comprehensive update posted live
- 23 January 2014 (cd) Revision: additional information about *MAGEL2*

- 11 October 2012 (me) Comprehensive update posted live
- 3 September 2009 (cd) Revision: added information about (i) case report of adrenocortical insufficiency in an individual with PWS and (ii) snoRNA HBII-85, which has been implicated as a cause of PWS
- 24 March 2008 (me) Comprehensive update posted live
- 12 July 2006 (sc) Revision: clarification of availability/reliability of methylation analysis done on CVS
- 16 June 2005 (me) Comprehensive update posted live
- 8 April 2004 (cd) Revision: quantitative PCR clinically available
- 1 May 2003 (me) Comprehensive update posted live
- 13 November 2000 (me) Comprehensive update posted live
- 6 October 1998 (pb) Review posted live
- Spring 1997 (sc) Original submission

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