

## Prader-Willi Syndrome

[PWS, Prader-Labhart-Willi Syndrome]

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### Summary

**Disease characteristics.** Prader-Willi (PWS) syndrome 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; characteristic facial features, strabismus, and scoliosis are often present, and non-insulin-dependent diabetes mellitus often occurs in obese individuals.

**Diagnosis/testing.** Consensus clinical diagnostic criteria are accurate, but the mainstay of diagnosis is DNA-based methylation testing to detect abnormal parent-specific imprinting within the Prader-Willi critical region (PWC) 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. Methylation-specific testing is important to confirm the diagnosis of PWS in all individuals, but especially 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 gavage feeding to assure adequate nutrition; physical therapy to improve muscle strength; consideration of hormonal and surgical treatments for cryptorchidism. In childhood, strict supervision of daily food intake based on height, weight, and body mass index (BMI) to provide energy requirements while limiting weight gain (keeping BMI <30); 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; speech therapy as needed. Firm limit-setting to treat behavior problems; serotonin reuptake inhibitors are helpful for most individuals. Replacement of sex hormones at puberty produces adequate secondary sexual characteristics. In adulthood, a group home for individuals with PWS that regulates behavior and weight management may prevent morbid obesity; growth hormone may help to maintain muscle bulk. *Prevention of secondary complications:* weight control to prevent development of diabetes mellitus; calcium supplementation to prevent osteoporosis. *Surveillance:* screening of infants for strabismus; routine monitoring of height,

weight, and BMI to assure appropriateness of exercise program and diet. *Other:* No medications are known to aid in controlling hyperphagia.

**Genetic counseling.** PWS is caused by absence of the paternally derived PWS/AS (Angelman syndrome) region of chromosome 15 by one of several genetic mechanisms. The risk to the sibs of an affected child of having PWS depends upon the genetic mechanism that resulted in the absence of the paternally contributed PWS/AS region. The risk to sibs is less than 1% if the affected child has a deletion or uniparental disomy (UPD), up to 50% if the affected child has a mutation of the imprinting control center, and up to 25% if a parental chromosomal translocation is present. Prenatal testing is possible for pregnancies at increased risk if the underlying genetic mechanism is known.

## Diagnosis

### Clinical 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]. However, confirmation of diagnosis requires molecular genetic testing.

Major criteria are weighted at one point each; minor criteria are one-half point each. Supportive findings only increase or decrease the level of suspicion of the diagnosis.

- For children under age three years, five points are required for diagnosis, four of which must be major criteria.
- For individuals age three years and older, eight points are required for diagnosis, at least five of which must be major criteria.

#### Major criteria

- Neonatal and infantile central hypotonia with poor suck and improvement with age
- Feeding problems and/or failure to thrive in infancy, with need for gavage feeding or other special feeding techniques
- Onset of rapid weight gain between ages 12 months and six years, causing central obesity
- Hyperphagia
- Characteristic facial features: narrow bifrontal diameter, almond-shaped palpebral fissures, down-turned mouth
- Hypogonadism manifest as:
  - Genital hypoplasia: small labia minora and clitoris in females; hypoplastic scrotum and cryptorchidism in males
  - Incomplete and delayed puberty
  - Infertility
- Developmental delay / mild to moderate mental retardation / multiple learning disabilities

#### Minor criteria

- Decreased fetal movement and infantile lethargy, improving with age
- Typical behavior problems, including temper tantrums, obsessive-compulsive behavior, stubbornness, rigidity, stealing, and lying

- Sleep disturbance/sleep apnea
- Short stature for the family by age 15 years
- Hypopigmentation
- Hands and feet small for height age
- Narrow hands with straight ulnar border
- Esotropia, myopia
- Thick, viscous saliva
- Speech articulation defects
- Skin picking

#### **Supportive findings**

- High pain threshold
- Decreased vomiting
- Scoliosis and/or kyphosis
- Early adrenarche
- Osteoporosis
- Unusual skill with jigsaw puzzles
- Normal neuromuscular studies (e.g., muscle biopsy, EMG, NCV)

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 the following findings is sufficient to justify methylation analysis for PWS (see Molecular Genetic Testing):

**Birth to two years.** Hypotonia with poor suck in the neonatal period

#### **Two to six years**

- Hypotonia with history of poor suck
- Global developmental delay

#### **Six to 12 years**

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

#### **13 years to adulthood**

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

## Testing

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

Note: The typical deletion is one of two sizes: extending from the distal breakpoint (BP3) to one of two proximal breakpoints (BP1 and BP2). Clinical FISH testing detects both of these deletions and cannot distinguish between them.

Approximately 1% of affected individuals have a detectable chromosomal rearrangement resulting in a deletion of bands 15q11.2-q13.

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

### Molecular Genetic Testing

**Molecular Genetic Testing —Gene.** More than 99% of individuals with PWS have a diagnostic abnormality in the parent-specific methylation imprint within the Prader-Willi critical region (PWC).

#### Clinical testing

- **Diagnosis**
  - **Methylation abnormality.** Abnormal parent-specific methylation imprinting within *PWC* can be detected using methylation analysis. Most laboratories utilize PCR analysis with parent-specific (methylation-sensitive) PCR primers [Zeschnigk et al 1997]. A methylation-specific melting analysis (MS-MA) method for a rapid screening of PWS/Angelman syndrome (AS) evaluates methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) for diagnosis of PWS/AS associated with deletions, uniparental disomy 15 (UPD15), or rare duplications [Procter et al 2006].  
  
Note: If the methylation pattern is characteristic of maternal inheritance only, diagnosis of PWS is confirmed. DNA methylation analysis indicates maternal inheritance in PWS caused by deletions, UPD, and imprinting defects, the molecular mechanisms that account for more than 99% of PWS cases.
- **Mutation identification**
  - **Deletion.** Deletions can be detected using either FISH analysis with the probe *SNRPN* or quantitative PCR [Roberts & Thomas 2003].
  - **UPD.** UPD can be detected with UPD studies that rely on analysis of microsatellite markers.
- **Imprinting defect.** An imprinting defect is presumed to be present in individuals with an abnormality in the parent-specific methylation imprint without evidence of a deletion or UPD [Ohta et al 1999].
  - Imprinting defects caused by microdeletions are detected using sequence analysis or MLPA of the PWS-SRO (smallest region of overlap).

- Most imprinting defects are epimutations (i.e., alterations in the imprint, not the DNA) and cannot be detected by sequence analysis [Buiting et al 1998, Buiting et al 2003, Horsthemke & Buiting 2006].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Testing Used in Prader-Willi Syndrome

| Test Method                      | Mutations Detected            | Mutation Detection Frequency by Test Method | Test Availability       |
|----------------------------------|-------------------------------|---|-------------------------|
| Methylation analysis             | Methylation abnormality       | 99%   | Clinical <b>Testing</b> |
| FISH/Quantitative PCR            | Deletion of PWCR <sup>1</sup> | 70%-75%                                     |                         |
| Uniparental disomy (UPD) studies | UPD of PWCR                   | 25%-29%                                     |                         |
| Sequence analysis <sup>2</sup>   | Imprinting center defect      | <1%   |                         |

PWCR = Prader-Willi critical region

1. Deletion varies in size, but always includes the PWCR.

2. Sequence analysis detects small deletions that account for approximately 15% of imprinting center mutations [Buiting et al 2003]. Most imprinting defects are epimutations (i.e., alterations in the imprint, not the DNA).

**Interpretation of test results.** For issues to consider in interpretation of sequence analysis results, click [here](#).

## Testing Strategy

**Testing to determine whether an individual has PWS** can proceed in one of two ways:

- If the individual appears to fulfill the clinical diagnostic criteria for PWS, methylation testing may be used initially.
- If PWS is one of several possible diagnoses:
  - Cytogenetic analysis with FISH for 15q11.2-q13 deletion can be performed initially.
  - If neither a deletion of chromosome 15 nor any other cytogenetic anomaly is identified, methylation testing should be performed. If positive, the type of mutation detected (see Table 1) should be determined.

**For recurrence risk assessment.** If the methylation pattern is characteristic of maternal inheritance only, the underlying molecular class of the mutation (deletion, UPD, or imprinting mutation) can be determined for genetic counseling purposes.

It is most efficient to begin with FISH for the 15q11.2-q13 deletion. Simultaneous cytogenetic studies allow detection of a translocation or other anomaly involving proximal 15q.

If no deletion or other chromosomal abnormality is detected, UPD studies (requiring blood from both parents) are conducted.

If UPD is not detected, referral to a specialized laboratory for sequence analysis of the imprinting center for a microdeletion can be accomplished. Individuals with an imprinting center defect are the only ones at significant risk of recurrence.

**Prenatal diagnosis** for at-risk pregnancies requires prior identification of the disease-causing abnormality (deletion, UPD, or imprinting mutation) in the family.

## Genetically Related (Allelic) Disorders

Angelman syndrome (AS) is caused by loss of the maternally contributed PWS/AS region. It is clinically distinct from PWS.

Duplication of the PWS/AS region causes mental retardation, seizures, and autism.

## Clinical Description

### Natural History

Fetal size is generally normal. Prenatal hypotonia usually results in decreased fetal movement, abnormal fetal position at delivery, and increased incidence of assisted delivery or cesarean section.

Infantile hypotonia is a nearly universal finding, causing decreased movement and lethargy with decreased spontaneous arousal, weak cry, and poor reflexes, including a 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 and lethargy result in failure to thrive in early infancy, and gavage 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.

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). Language milestones are also typically delayed. Cognitive disabilities are generally evident by the time the child reaches school age. Testing indicates that most persons with PWS fall in the mildly mentally retarded range (mean IQ: 60s to 70s), with approximately 40% having borderline retardation or low-normal intelligence and approximately 20% having moderate retardation. Regardless of measured IQ, most children with PWS have multiple severe learning disabilities and poor academic performance for their mental abilities [Whittington et al 2004a]. Although a small proportion of affected individuals have extremely impaired language development, verbal ability is a strength for most.

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.

- In males, the penis may be small; 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.
- In females, the genital hypoplasia is often overlooked; however, the labia minora and clitoris are generally small from birth.

The hypogonadism, which is largely of hypothalamic origin and usually associated with low serum concentration of gonadotropins, 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].

In one study of 84 individuals with PWS (half males, half females) ages two to 35 years, the following were identified:

- **In males.** Cryptorchidism: 100%; small testes: 76%; scrotal hypoplasia: 69%
- **In females.** Labia minora and/or clitoral hypoplasia: 76%; primary amenorrhea: 56%; spontaneous menarche (mostly spotting): 44% of those over age 15 years
- **In both sexes.** Premature pubarche: 14%; precocious puberty: 3.6% (one male, two females) [Crino et al 2003]

Hyperphagia and obesity usually begin between ages one and six years. Hyperphagia 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. Gastric emptying is delayed. Obesity results from these behaviors and decreased total caloric requirement, resulting from decreased resting energy expenditure resulting from decreased activity and decreased lean body mass (primarily muscle) [Butler et al 2007].

Up to 25% of adults with PWS (particularly those with significant obesity) have non-insulin-dependent diabetes mellitus (NIDDM) [Butler et al 2002] with a mean age of onset of 20 years.

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].

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 affected individuals.

- Many of the behavioral characteristics are suggestive of autism; a recent study shows 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 & Hanson 2005].
- The characteristic 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 5%-10% of affected individuals [Boer et al 2002, Clarke et al 2002, Vogels et al 2004]; significantly higher proportions have been reported by others [Holland, personal communication].

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

Short stature, if not apparent in childhood, is almost always present during the second decade in the absence of growth hormone 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.

Data from at least 15 studies involving more than 300 affected children (reviewed in Burman et al 2001) document reduced growth hormone secretion in PWS. Growth hormone deficiency is also seen in adults with PWS [Grugni et al 2006, Hoybye 2007]



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

Hypopigmentation of hair, eyes, and skin resulting from a tyrosinase-positive albinoidism occurs in about one-third of affected individuals.

Strabismus is seen in 60%-70%.

Hip dysplasia occurs in approximately 10% [West & Ballock 2004].

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

Up to 50% of affected individuals may have recurrent respiratory infections.

Rates of the following are increased:

- Bone fractures caused by osteopenia
- 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 has been estimated at 3% per year [Butler et al 2002]. Two series of individuals from several centers who died of PWS have been reported [Schrandt-Stumpfel 2004, Stevenson et al 2004]. 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 gastroenterologic infections resulting in unexpected death; of these, three who died as a result were noted to have small adrenal glands [Stevenson et al 2004]; this finding is uncommon.

Acute gastric distention and necrosis have been reported in a number of individuals with PWS [Stevenson et al 2007, J Pediatr Gastroenterol Nutr], 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 2007, Am J Med Genet A].

Concern about the possible contribution of growth hormone administration to unexpected death has been raised by reported deaths of individuals within a few months of starting growth hormone therapy [reviewed in van Vliet et al 2004]. The few reported deaths were mostly in obese individuals with preexisting respiratory problems. In the database of one pharmaceutical company, five of 675 children treated with growth hormone died suddenly of respiratory



problems [Craig et al 2006]. In another study, the rate of death in affected individuals on and off growth hormone did not differ [Nagai et al 2005]. The relationship of growth hormone administration to unexpected death remains unclear.

**Neuroimaging.** In a recent study, 20/20 individuals with PWS 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 2006]. 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% [Lughetti et al 2007]. The implications of these findings are unknown.

**Pathophysiology.** Very elevated levels of ghrelin (a growth hormone secretagogue that is generally high in fasting states and decreases with eating) have been identified in individuals with PWS [Butler, Bittel, Talebizadeh 2004] but do not seem to be present prior to the onset of hyperphagia [Erdie-Lalena et al 2006]. After a meal, ghrelin levels in adults decrease, as is normal, but still remain high [Goldstone et al 2005], although another report indicated that they do not decrease in adults with PWS [Haqq et al 2003]. Ghrelin levels do decrease in children with PWS [Bizzarri et al 2004]. Thus, the relationship between hyperphagia and ghrelin remains unclear. It has been proposed that the hyperghrelinemia may be the result of hypoinsulinemia [Goldstone et al 2005]. Obestatin, which works in opposition to ghrelin, was high in young children and infants compared with age- and sex-matched controls in one small study [Butler & Bittel 2007]; the authors raise the possibility that it causes the lack of appetite observed in infants. The metabolic correlates of hyperphagia are as yet uncertain.

### Genotype-Phenotype Correlations

Some clinical differences exist between individuals with PWS who have deletion 15q and those who have maternal uniparental disomy (UPD).

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 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] and autism spectrum disorders [Veltman et al 2004, Whittington et al 2004b, Veltman et al 2005, Descheemaeker et al 2006]. Recent studies suggest that as many as 62% of those with UPD develop atypical psychosis compared with 16% of those with deletion 15q [Soni et al 2007].

Individuals with 15q 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].

In one study individuals with deletions with breakpoint 1 (breaking more proximally) were reported to have more behavior problems than those with deletions with breakpoint 2 (see Molecular Genetics). The behavior problems included poorer adaptive behavior skills and specific obsessive-compulsive behaviors [Butler, Bittel, Kibiryeve et al 2004] and physical depression [Hartley et al 2005]. They also had poorer reading and math skills [Butler, Bittel, Kibiryeve et al 2004]; however, other studies failed to show these differences between the two groups [Milner et al 2005, Hartley et al 2005, Milner et al 2005]. The study by Hartley et al (2005) showed greater physical depression in those with breakpoint 1 than in those with breakpoint 2.

## 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.

## Differential Diagnosis

*For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.*

**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, 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, methylation analysis should distinguish this disorder from PWS.

**Hypotonia** in infancy is also seen in the following conditions:

- Neonatal sepsis
- CNS depression
- Congenital myotonic dystrophy type 1, characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; mental retardation is common. It is caused by expansion of a CTG trinucleotide repeat in the *DMPK* gene.
- 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 mental retardation, 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 absence of the maternal copy of *UBE3A* and may be diagnosed in 80% of individuals with AS using 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 PWS.
- Fragile X syndrome, characterized by moderate mental retardation in affected males and mild mental retardation 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 (see Autism Overview). The diagnosis of fragile X syndrome rests on the detection of an alteration in *FMR1* consisting of expansion of a triplet repeat and gene methylation. In infancy, hypotonia may be the only manifestation of fragile X syndrome. Affected individuals lack the characteristic sucking problems, hypogonadism, and facial appearance of PWS.

In childhood, Rett syndrome (see *MECP2*-Related Disorders) can present with hypotonia, obesity, and gynecomastia as well as mental retardation. Beginning at age six to 18 months, affected girls enter a short period of lack of progress followed by rapid regression in language and motor skills. The hallmark of the disease is the loss of purposeful hand use and its replacement with repetitive stereotyped hand movements. Affected individuals lack the characteristic sucking problems, hypogonadism, and facial appearance of PWS. Genetic testing of *MECP2* can establish the diagnosis of Rett syndrome in the majority of affected girls.

**Developmental delay/mental retardation and obesity** with or without hypogonadism can be seen in the following disorders:

- Angelman syndrome (AS)
- Fragile X syndrome
- Uniparental disomy for chromosome 14, which also includes feeding problems and short stature [Cox et al 2004]
- Albright hereditary osteodystrophy, which also includes short stature, but lacks hypotonia and has different characteristic facial appearance (round face). Specific testing is available by measurement of Gs receptor-coupling protein.
- Bardet-Beidl syndrome (BBS), characterized by cone-rod dystrophy, dystrophic obesity, postaxial polydactyly, cognitive impairment, male hypogonadotrophic hypogonadism, complex female genitourinary malformations, and renal dysfunction. It has a different facial phenotype from PWS. Diagnostic testing is available for a few of the 12 known causative genes. Inheritance is autosomal recessive.
- Cohen syndrome, characterized by down-slanting palpebral fissures, short philtrum, large central incisors, tapered fingers, and more severe retardation. Microcephaly, progressive pigmentary retinopathy, severe myopia, and intermittent neutropenia are also present. Cohen syndrome is caused by mutations in *COH1*. Inheritance is autosomal recessive.
- Borjeson-Forssman-Lehmann syndrome, seen in males, is 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 retardation, the presence of nystagmus, and a characteristic facial appearance with prominent superciliary ridges, ptosis, and deep-set eyes. Mutations in *PHF6* are causative. Inheritance is X-linked. Heterozygous females who show manifestations of the disorder have skewed X-chromosome inactivation.
- Alström syndrome is 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 hypogonadotrophic 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. Mutations in *ALMS1* are found in 25%-40% of affected individuals.

**Cytogenetic abnormalities** are seen the following:

- A study of 87 individuals with a "PWS-like phenotype" of syndromic obesity revealed one individual with an interstitial deletion of 6q16.2, which includes the *SIM1* gene [Varela et al 2006]. This deletion had been reported five times previously in syndromic obesity.
- Another study of 41 individuals with hypotonia, developmental delay, obesity, and/or hyperphagia and behavior problems with negative PWS testing revealed one with a 1p36 deletion syndrome [D'Angelo et al 2006].
- Reports of other cytogenetic anomalies in individuals with a PWS-like phenotype have included duplication 3p25.3.p26.2, dup Xq27.2-ter, del 6q16.2, del 1p36, and del 10q26.

Features similar to those of PWS in the presence of joint contractures suggest Urban-Roger, Camera, or Vasquez syndrome, all of which are rare.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Prader-Willi syndrome (PWS), the following evaluations are recommended:

- Assess newborns and young infants for sucking problems and failure to thrive.
- Regardless of age, measure height and weight; plot on either age-appropriate growth charts or charts developed for PWS [Butler et al 2006]. Calculation of BMI (weight in kg/height in m<sup>2</sup>) may be helpful.
- Assess development in infants; assess educational development in children including speech evaluation.
- Refer for ophthalmologic evaluation if strabismus is present; refer for assessment of visual acuity by age one year or at diagnosis if it is later.
- Regardless of age, assess males for the presence of cryptorchidism.
- Assess children with prolonged failure to thrive for hypothyroidism.
- Regardless of age, assess for the presence of scoliosis clinically, and, if indicated, radiographically.

Note: Very obese individuals cannot be adequately assessed clinically.

- Assess for the presence of behavior 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.
- Regardless of age, evaluate respiratory status and perform a sleep study. These studies are specifically recommended prior to initiation of growth hormone therapy, along with assessment of the size of tonsils and adenoids, particularly in the obese individual.

### Treatment of Manifestations

A team approach to management is recommended [Eiholzer & Whitman 2004, Cassidy 2005].

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.

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].

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.

Management of strabismus is as for any infant.

When hyperphagia begins or weight centiles are increasing (often age two to four years), a program of a well-balanced, low-calorie diet, regular exercise, and close supervision to minimize food stealing should be instituted to prevent obesity 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 of the kitchen, refrigerator, and/or cupboards is often required. The energy requirement of people with PWS, which rarely exceeds 1000 to 1200 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 are indicated, especially for calcium and vitamin D.

Growth hormone treatment normalizes height, increases lean body mass, decreases fat mass, and increases mobility, which are beneficial to weight management. Dose recommendations in children are generally similar to those for individuals with isolated growth hormone deficiency, i.e., about 1 mg/m<sup>2</sup>. Treatment 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.

Controlled trials of growth hormone therapies have demonstrated significant benefit from infancy through adulthood [Lindgren et al 1997, Carrel et al 1999, Ritzen et al 1999, Eiholzer et al 2000, Mogul et al 2000, Carrel et al 2002, Carrel et al 2004, Eiholzer & Whitman 2004, Hoybye 2004, Whitman et al 2004, Hoybye et al 2005, Hoybye 2007, Myers et al 2007]:

- 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 [Hoybye 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].
- Although there was initial concern that growth hormone treatment contributed to scoliosis in PWS, recent studies show no difference in frequency or severity in those treated compared to those who were not treated [Nagai et al 2006, Angulo et al 2007].

Appropriate educational programming should be initiated 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 individuals, 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].

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, or use of slow-release testosterone injection every three months, may avert exacerbation of behavior problems by providing a more even blood level. The risk of osteoporosis should be considered in deciding about hormone replacement.

Management of scoliosis, hip dysplasia, and complications of obesity is as in the general population.

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

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, as in the general population.

For adults with PWS, one successful living situation for behavior and weight management is a group home specially designated for individuals with PWS. Affected individuals generally require a sheltered employment environment.

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

Recent reports of fertility in two women with PWS raise the issue of the need for birth control [Akefeldt et al 1999, Schulze et al 2001].

### **Prevention of Primary Manifestations**

Obesity may be prevented if the diet, exercise, and supervision program described in Treatment of Manifestations is instituted.

If started at a young age, growth hormone therapy may prevent obesity and high proportion of fat mass. It may also prevent development of the typical facial appearance.

### **Prevention of Secondary Complications**

Diabetes mellitus rarely occurs in the absence of obesity.

Calcium supplementation may be beneficial, as low-calorie diets are often low in dairy products and osteoporosis has been documented in most older children and adults with PWS.

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

To assure appropriateness of exercise program and diet, including adequacy of vitamin and mineral intake, monitor height, weight, and BMI (weight in kg/height in m<sup>2</sup>) as follows:

- Monthly 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) in anyone with significant obesity or rapid significant weight gain.

Obtain history of any sleep disturbance; if present, perform 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 three to five years in adulthood.

Obtain history for behavioral and psychiatric disturbance at least annually.

## Testing of Relatives at Risk

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

## Therapies Under Investigation

Treatment of individuals with PWS with octreotide, a somatostatin agonist, decreases ghrelin concentrations [Haqq et al 2003] but did not change eating behavior in one study [Tan et al 2004]. Further studies are needed.

One study demonstrated decreased skin picking with topiramate treatment [Shapira et al 2004]

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

## Other

No medications are known to aid in controlling hyperphagia.

Trials of osteoporosis treatments other than calcium supplements have not been reported.

The only study of the use of coenzyme Q<sub>10</sub> for one year in children younger than age two years did not show improvement in body composition [Eiholzer et al 2004].

**Genetics clinics** are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.



**Support groups** have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

## 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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.*

### Mode of Inheritance

Prader-Willi syndrome (PWS) is caused by lack of expression of the paternally derived PWS/AS (Angelman syndrome) 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.
- Evaluation of the parents depends on the etiology of the lack of expression of the PWS critical region in the proband.

**Sibs of a proband.** The risk to sibs of a proband with PWS (see Table 2) depends on the genetic mechanism causing lack of expression of the paternally contributed PWS/AS region.

Table 2. Risks to Sibs of a Proband with PWS by Genetic Mechanism

| Genetic Mechanism   | Risk to Sibs of a Proband with PWS |
|---|------------------------------------|
| Deletion PWS/AS region  | <1% <sup>1</sup>                   |
| Uniparental disomy (UPD)  | <1% <sup>2</sup>                   |
| Imprinting defect with mutation   | ≤50% <sup>3</sup>                  |
| Imprint defect without mutation   | <1% <sup>3</sup>                   |
| Apparently <i>de novo</i> balanced chromosomal translocation breaking within the PWS/AS critical region <sup>4, 5</sup> | <1% <sup>5</sup>                   |

1. Although most of these are *de novo* deletions, a small number of individuals have a chromosomal translocation with a concomitant deletion. The presence of a balanced chromosomal translocation in a parent in these cases can predispose to abnormal segregation. In this instance, the recurrence risk could be as high as 25%.

2. In rare cases, UPD has resulted from malsegregation of a Robertsonian translocation and subsequent trisomy rescue. Empiric data suggest that the risk of recurrence in these cases would also be less than 1%, although the theoretical risk would be higher.

3. Recurrence of PWS in sibs who have an identified or suspected mutation in the imprinting control center has been observed [Buiting et al 1994, Nicholls 1994]. A theoretical recurrence risk of up to 50% pertains when a healthy parent carries a mutation or microdeletion causing an imprinting defect. Recent evidence points to some of these imprinting defects being *de novo* mutations, in which case recurrence risk would be low. Abnormal methylation in the presence of normal FISH for deletion and normal uniparental disomy studies can result from *de novo* defects in imprinting that are not associated with a detectable imprinting center mutation; such cases have a <1% recurrence risk [Buiting et al 2003].

4. Breaks within the PWS critical region that separate the imprinting center from the genes that it imprints lead to lack of proper imprinting, causing PWS.

5. All of these cases have been *de novo*. If a familial case is detected, the theoretical risk of inheritance of the balanced translocation could be as high as 25%.

#### Offspring of a proband

- With rare exception, individuals with PWS do not reproduce.
- The risk to the child of an affected individual depends on the etiology of the absence of the paternally derived PWS critical region and the sex of the affected individual.
- If the proband has PWS as the result of a deletion, the offspring are at a 50% risk of having AS if the proband is female (reported once) and PWS if the proband is male (never reported).
- If the proband has UPD, there is a theoretical risk to offspring of inheriting two chromosomes 15 from the proband, which could lead to: (1) fetal demise if trisomy rescue does not occur; (2) PWS if the proband is female; and (3) AS if the proband is male. None of these possibilities has been reported. There is a single report of a female with PWS caused by UPD having a normal child [Schulze et al 2001].
- If the proband has PWS as the result of an imprinting mutation, the offspring have as high as a 50% theoretical chance of having PWS (never reported).
- If the proband has a chromosomal translocation, there is a theoretical increased risk to offspring of having PWS or AS, depending on the sex of the proband (never reported).

**Other family members.** If a chromosomal translocation or imprinting mutation 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 the determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

**DNA banking.** 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA. See DNA Banking for a list of laboratories offering this service.

### Prenatal Testing

**High risk.** Prenatal detection of all the molecular genetic alterations in the PWS/AS region that give rise to PWS is possible through analysis of DNA extracted from cells obtained by chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation or amniocentesis usually performed at approximately 15-18 weeks' gestation. See Note: (1) Methylation analysis. Prenatal testing should only be undertaken after molecular confirmation of PWS has been established in the individual and the couple has been counseled regarding the risk to the unborn child.

- Parents who have had one child with PWS caused either by deletion or UPD are not routinely offered prenatal testing in subsequent pregnancies, but could be offered such testing for reassurance.
- Parents who have had one child with PWS caused by a defect in the imprinting control element should be offered prenatal testing because of the high recurrence risk; methylation analysis can also be used in these cases. See Note: (1) Methylation analysis.
- Prenatal testing for an inherited translocation involving chromosome 15 and resulting in a deletion is relevant because of the theoretical 25% risk for PWS in the offspring.

Note: (1) Although methylation analysis has been validated in both CVS and amniocentesis samples [Kubota et al 1996], it should be noted that most laboratories offer methylation studies on cells obtained from amniocentesis only. Laboratories offering prenatal testing typically perform FISH deletion studies or uniparental disomy studies on cells from either CVS or amniocentesis. (2) Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

**Low risk.** For low-risk pregnancies in which no family history of PWS exists, PWS may be a possibility:

- If a 15q deletion is suspected on cytogenetic studies from CVS or amniocentesis. FISH 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 trisomy 15 or mosaic trisomy 15 is detected on CVS and if subsequent 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 methylation analysis on amniocytes should be considered [EUCROMIC 1999, Shaffer et al 2001]. See Note: (1) Methylation analysis.
- 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 studies (to rule out UPD) are indicated.

**Preimplantation genetic diagnosis (PGD)** may be available for families in which a mutation in the imprinting control element has been identified. For laboratories offering PGD, see

### Testing

PGD can also be used in cases of familial translocation to rule out UPD.

## Molecular Genetics

*Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.*

Table A. Molecular Genetics of Prader-Willi Syndrome

| Critical Region | Chromosomal Locus | Protein Name |
|-----------------|-------------------|--------------|
| PWCR            | 15q11-q13         | Unknown      |

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Prader-Willi Syndrome

|        |  |
|--------|--|
| 176270 | PRADER-WILLI SYNDROME; PWS                           |
| 182279 | SMALL NUCLEAR RIBONUCLEOPROTEIN POLYPEPTIDE N; SNRPN |
| 600161 | PRADER-WILLI/ANGELMAN REGION 1                       |
| 601491 | IMPRINTED IN PRADER-WILLI SYNDROME; IPW              |
| 602117 | NECDIN; NDN  |
| 603856 | MAKORIN 3; MKRN3                                     |
| 603857 | ZINC FINGER PROTEIN 127, ANTISENSE; ZNF127AS         |
| 605283 | MAGE-LIKE 2; MAGEL2                                  |
| 605436 | PRADER-WILLI CRITICAL REGION GENE 1; PWCR1           |
| 605837 | HECT DOMAIN AND RCC1-LIKE DOMAIN 2; HERC2            |
| 609837 | RNA, HBII-52 SMALL NUCLEOLAR                         |
| 610922 | CHROMOSOME 15 OPEN READING FRAME 2; C15ORF2          |
| 611215 | PRADER-WILLI REGION NONCODING RNA 1; PWRN1           |

Table C. Genomic Databases for Prader-Willi Syndrome

| Critical Region | Entrez Gene           |
|-----------------|-----------------------|
| PWCR            | 6638 (MIM No. 176270) |

For a description of the genomic databases listed, click [here](#).

**Note:** HGMD requires registration.

### Molecular Genetic Pathogenesis

Several of the genes in the PWS/AS deletion region (*SNURF-SNRPN*, *MKRN*, *MAGEL2*, *NDN*) are subject to genomic imprinting, thus accounting for the fact that the PWS phenotype only results when the paternally contributed PWS/AS region is absent. However, the precise cause of PWS is still unknown. Five paternally expressed genes that encode polypeptides have been identified: *SNURF-SNRPN*, *MKRN3*, *MAGEL2*, and *NDN*. *SNRPN* is a small ribonuclear protein involved in alternative mRNA splicing. No abnormal gene product associated with PWS has been identified.

The small nucleolar RNA (snoRNA) HBII-52 has been localized to the Prader-Willi critical region and is thought to be important in processing an mRNA expressed from a gene located on a different chromosome. However, Runte et al (2005) studied individuals with complete deletion of all copies of HBII-52 who had no obvious clinical phenotype. The role of HBII 52 in the phenotype of PWS is as yet unknown.

**Critical region:** PWS/AS critical region

**Normal allelic variants:** The following genes have been mapped within the PWS/AS region:

- ***SNRPN***(small nuclear ribonucleoprotein N), the best-described gene that is likely to cause some features of PWS. Based on studies in the mouse and human, gene expression is from the paternally inherited chromosome only and is primarily in brain and heart.
- ***SNURF***, a ring finger bifunctional protein that possesses DNA binding activity

- ***SNURF-SNRPN***, a complex gene that also encodes five classes of snoRNAs
- ***IPW***, thought to be an RNA transcript only as it does not encode a protein
- Anonymous transcripts, ***PARI***, ***PAR4***, ***PAR5***, and ***PAR7***
- The ***P***gene, which 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
- ***E6AP***(***UBE3A***), the gene for Angelman syndrome
- ***ATP10C***, a maternally expressed gene within the most common interval of deletion responsible for AS
- ***HERC2***, in which multiple duplications occur at the common deletion breakpoints
- ***NECDIN***(***NDN***), which encodes a DNA-binding protein (necdin). An *NDN* knockout mouse model has indicated that necdin mediates intracellular processes essential for neurite outgrowth, and loss of necdin impinges on axonal outgrowth [Lee et al 2005]. A mouse necdin knockout model with defects similar to those seen in individuals with PWS has been reported, indicating 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; transcribed only by the paternal allele and expressed predominantly in the brain. Studies of *Magel2*-null mice have demonstrated several findings that are associated with key aspects of PWS, including neonatal growth retardation, excessive weight gain after weaning, and increased adiposity with altered metabolism in adulthood [Lee et al 2005, Bischof et al 2007]. It has been implicated in circadian rhythm in mice [Kozlov et al 2007].
- ***MKRN3***, (***Markorin 3***, ***ZNF127***), a zinc finger protein expressed only from the paternal chromosome
- ***C15orf2***, an intronless gene that is biallelically expressed in adult testis, but is 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; shown to have monoallelic expression in the fetal brain
- Several newly identified imprinted genes and transcripts of unknown function

**Pathologic allelic variants:** The typical large paternally derived deletion of the PWS/AS region deletion is of two sizes and involves a distal breakpoint (BP3) and two proximal breakpoints (BP1 and BP2). The distance between the two proximal breakpoints is approximately 500 kb. Four genes (*CYFIP1*, *GCP5*, *NIPAI*, *NIPAI2*) have been identified in the region between BP1 and BP2 and (in at least one study) found to be related to behavior differences [Chai et al 2003, Bittel et al 2006]. These genes are not imprinted. *NIPAI* is widely expressed in the central nervous system.

Small deletions of the promoter region and the proximal upstream region of the *SNRPN* gene (including the putative imprinting control element) have been identified in individuals with PWS who have maternal-specific 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 imprinting mutation.

Other individuals have biparental inheritance, but maternal-only methylation patterns in this region without detectable promoter region abnormalities. This pattern is considered an imprinting defect. Because the DNA is unchanged, it is considered an epimutation.

**Normal gene product:** The only identified protein products are those for *SNRPN* and *MKRN3*. *SNRPN* is a small nuclear ribonucleoprotein involved in alternative mRNA splicing.

**Abnormal gene product:** Unknown

- **Imprinting:** Several of the genes in the PWS/AS region (*SNURF-SNRPN*, *MKRN3*, *NDN*, *MAGEL2*, *C15orf2*, *PWRN1*) are subject to genomic imprinting, thus accounting for the fact that the PWS phenotype results only when the paternally contributed PWS/AS region is absent. Methylation, which is involved in the process of genomic imprinting, has been demonstrated for several of the genes identified within the PWS/AS region [Glenn et al 1997, MacDonald & Wevrick 1997]. Upstream of the *SNRPN* gene, 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 methylation patterns but have neither the usual large paternally derived deletion of the PWS/AS region nor maternal UPD [Saitoh et al 1997]. Other individuals demonstrate sporadic imprinting defects [Buiting et al 1998, Buiting et al 2003]. Recently, two Rb-binding protein-related genes, *Rbbp1/Arid4a* and *Rbbp111/Arid4b*, have been implicated in the regulation of imprinting of the imprinting center (IC) [Wu et al 2006].

## Resources

*GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests for this*

*disorder and select **Resources** for the most up-to-date Resources information.—ED.*

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

c/o BIRD Europe Foundation Onlus  
via Bartolomeo Bizio 1  
36023 Costozza  
Italy  
[www.ipwso.org](http://www.ipwso.org)

### **National Library of Medicine Genetics Home Reference**

Prader-Willi syndrome

### **NCBI Genes and Disease**

Prader-Willi syndrome

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

125a London Road  
Derby DE1 2QQ  
United Kingdom  
**Phone:** 01332 365676  
**Fax:** 01332 360410  
**Email:** [website@pwsa-uk.demon.co.uk](mailto:website@pwsa-uk.demon.co.uk)  
[pwsa.co.uk/main.php](http://pwsa.co.uk/main.php)

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

8588 Potter Park Drive Suite 500

Sarasota FL 34238

**Phone:** 800-926-4797; 941-312-0400**Fax:** 941-312-0142**Email:** national@pwsusa.org

www.pwsausa.org

**Angelman, Rett & Prader-Willi Syndromes Consortium Registry**

Department of Molecular and Human Genetics

Baylor College of Medicine

One Baylor Plaza Rm. T619

Houston TX 77030

**Phone:** 713-798-4795**Fax:** 713-798-7773**Email:** sweaver@bcm.tmc.edu

Angelman, Rett &amp; Prader-Willi Syndromes Consortium Registry

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. [PubMed](#)

**Published Statements and Policies Regarding Genetic Testing**

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American College of Medical Genetics (2001) Statement on diagnostic testing for uniparental disomy (pdf)

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## Suggested Readings

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## Chapter Notes

### Revision History

- 24 March 2008 (me) Comprehensive update posted to live Web site
- 12 July 2006 (sc) Revision: clarification of availability/reliability of methylation analysis done on CVS
- 16 June 2005 (me) Comprehensive update posted to live Web site
- 8 April 2004 (cd) Revision: quantitative PCR clinically available
- 1 May 2003 (me) Comprehensive update posted to live Web site
- 13 November 2000 (me) Comprehensive update posted to live Web site
- 6 October 1998 (pb) Review posted to live Web site
- Spring 1997 (sc) Original submission