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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 it 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. Accurate consensus clinical diagnostic criteria have been developed, but the mainstay of diagnosis is DNA-based **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 (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. Management differs in infancy, childhood, and adulthood. In infancy, special nipples or gavage feeding may be needed to assure adequate nutrition, and physical therapy may improve muscle strength. Infants should be

screened for strabismus, and hormonal and surgical treatments can be considered for cryptorchidism. During childhood, height, weight, and body mass index (BMI) should be monitored and daily food intake calculated and strictly supervised to provide energy requirements while limiting weight gain (keeping BMI <30). Growth hormone replacement therapy normalizes height and increases lean body mass. Educational planning should be instigated and speech therapy provided if needed. Firm limit setting should be instituted to treat behavioral problems; serotonin re-uptake inhibitors are helpful for most individuals. Replacement of sex hormones produces adequate secondary sexual characteristics. 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.

Genetic counseling. PWS is caused by absence of the paternally derived PWS/AS 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](#), 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 any of the known genetic mechanisms.

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](#)]. Major criteria are weighted at one point each; minor criteria are one-half point each. For children under three years of age, five points are required for diagnosis, four of which must be major criteria. For individuals three years of age and older, eight points are required for diagnosis, at least five of which must be major criteria. Supportive findings only increase or decrease the level of suspicion of the diagnosis.

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 or other special feeding techniques
- Onset of rapid weight gain between 12 months and six years of age, causing central obesity
- Hyperphagia
- Characteristic facial features: narrow bifrontal diameter, almond-shaped palpebral fissures, down-turned mouth
- Hypogonadism:
 - 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 15 years of age
- Hypopigmentation
- Small hands and feet 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 satisfied diagnostic criteria 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 are sufficient to justify [methylation analysis](#) for PWS:

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](#) at the 650-band level 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.

About 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

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work. Listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. Clinicians must communicate directly with the laboratories to verify information. —ED.

Gene. More than 99% of individuals with PWS have a diagnostic abnormality in the parent-specific [methylation](#) imprint within the Prader-Willi [critical region](#) (PWCR).

Molecular genetic testing: Clinical uses

- [Diagnostic testing](#)
- [Recurrence risk](#) assessment.
- [Prenatal diagnosis](#)

Molecular genetic testing: Clinical methods

- **Diagnosis**
 - **Methylation abnormality.** Abnormal parent-specific [methylation imprinting](#) within *PWCR* can be detected using [methylation analysis](#) (Southern analysis with a methylation-sensitive [probe](#) (SNRPN or PW71B) or [PCR](#) with parent-specific (methylation-sensitive) [PCR](#) primers). Most laboratories utilize [PCR](#) analysis [[Zeschnigk et al 1997](#)].

Note: If the [methylation](#) pattern is characteristic of maternal inheritance only, the diagnosis of PWS is confirmed. [DNA methylation analysis](#) indicates maternal inheritance in PWS caused by [deletions](#), [uniparental disomy \(UPD\)](#), 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].
- **Uniparental disomy (UPD).** UPD can be detected with [uniparental disomy studies](#) that rely upon 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 quantitative [Southern blot analysis](#) and [sequence analysis](#) 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].

Table 1 summarizes [molecular genetic testing](#) for this disorder.

Table 1. Testing Used in Prader-Willi Syndrome

Test Methods	Mutations Detected	Percent of Individuals	Test Availability
Methylation analysis	Methylation abnormality	99%	Clinical Testing
FISH/Quantitative PCR	Deletion of PWCR ¹	70%	
Uniparental disomy studies	UPD of PWCR	25%	
Sequence analysis ²	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 about 15% of [imprinting](#) center mutations [Buiting et al 2003]. The majority of [imprinting](#) defects are epimutations (i.e., alterations in the imprint, not the DNA).

Testing Strategy for a Proband

Testing to determine if an individual has Prader-Willi syndrome 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 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.
- If PWS is one of several possible diagnoses, [cytogenetic](#) analysis with [FISH](#) for 15q11.2-q13 [deletion](#) can be done initially.
 - If neither a [deletion](#) of [chromosome](#) 15 nor any other [cytogenetic](#) anomaly is identified, [methylation](#) testing or [UPD](#) testing should be performed.

Genetically Related (Allelic) Disorders

[Angelman syndrome](#) 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

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

PWS is characterized by severe hypotonia and feeding difficulties in early infancy. By early childhood (generally, ages one to six years), most children develop an insatiable appetite and become obese unless strict external control is imposed. Gross motor milestones and language are delayed. Virtually all individuals with PWS have some degree of intellectual impairment, which ranges from borderline to moderate mental retardation. Behavior problems, particularly temper tantrums, are common.

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

In both sexes, hypogonadism 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, but most characteristic is a hypoplastic scrotum that is small, poorly rugated, and poorly pigmented. Unilateral or bilateral cryptorchidism is present in 80-90% of individuals. Although genital hypoplasia is often overlooked in females, the labia minora and clitoris are generally small from birth. The hypogonadism, which is of hypothalamic origin, causes incomplete, delayed, and sometimes disordered pubertal development. Precocious adrenarche occurs in about 20%. Infertility is the rule, although two instances of reproduction in females have been reported [[Akefeldt et al 1999](#) , [Schulze et al 2001](#)]. The manifestations of hypogonadism in PWS have recently been reviewed [[Crino et al 2003](#)].

Delayed motor development is present in 90-100% of individuals with PWS, with average early milestones achieved at about double the normal age (e.g., sitting at 12 months, walking at 24 months). Usually, language milestones are also delayed. Cognitive abnormalities are evident as the child reaches school age. Testing indicates that most people 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 academic performance that is poor for their mental abilities [[Whittington et al 2004a](#)].

Between the ages of one and six years, hyperphagia and obesity begin. 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. Obesity results from these behaviors and a low metabolic rate that results in a decreased total caloric requirement. 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 et al 2004]. Interestingly, after a meal, ghrelin levels do not decrease in adults with PWS [Haqq et al 2003], but do decrease in children [Bizzarri et al 2004]. Thus, the relationship between hyperphagia and ghrelin remains unclear.

A characteristic behavior profile becomes evident in early childhood in 70-90% of affected individuals, with temper tantrums, stubbornness, controlling and manipulative behavior, obsessive-compulsive characteristics, and difficulty with change in routine. This behavior disorder has been reported to increase with age and body mass index (BMI) [Steinhausen et al 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]. Behavioral problems interfere most with the quality of life in adolescence and adulthood, though they diminish considerably in older adults [Dykens 2004].

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 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 Prader-Willi syndrome.

Characteristic facial features may or may not be apparent at birth and slowly evolve over time [Aughton & Cassidy 1990]. 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 25% of adults (particularly those with significant obesity) have non-insulin-dependent diabetes mellitus (NIDDM) [Butler et al 2002]; mean age of onset is 20 years. Some studies have indicated that up to 50% of affected individuals may have recurrent respiratory infections, and there are increased rates of bone fractures, leg ulceration, and sleep disorders.

Complications of obesity are the major cause of morbidity and mortality in PWS, including cardiorespiratory insufficiency, diabetes mellitus, obstructive sleep apnea, thrombophlebitis, and skin problems on the legs, such as chronic edema. 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], though this is not a common finding. Acute gastric distention and necrosis have been seen in a number of individuals with PWS, one of whom died [Wharton et al 1997].

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 [Schrander-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. In addition, 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 in obese individuals with pre-existing respiratory problems. The relationship of growth hormone administration to unexpected death is unclear.

Genotype-Phenotype Correlations

Some clinical differences exist between individuals with PWS who have [deletion 15q](#) and those who have maternal uniparental disomy; notably, individuals with [uniparental disomy](#) are less likely to have the typical facial appearance, hypopigmentation [[Cassidy et al 1995](#) , [Gillesen-Kaesbach et al 1995](#)], 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](#)]. However, psychosis [[Holland et al 2003](#)] and autism spectrum disorders [[Veltman et al 2004](#) , [Whittington et al 2004b](#)] are more common among those with [uniparental disomy](#).

A recent report suggests that individuals with [deletions](#) with breakpoint 1 (breaking more proximally), have more behavioral problems than those with [deletions](#) with breakpoint 2 (see [Molecular Genetics](#)). Behavior problems include poorer adaptive behavior skills and specific obsessive-compulsive behaviors [[Butler, Bittel, Kibiryeva et al 2004](#)]. They also had poorer reading and math skills [[Butler, Bittel, Kibiryeva et al 2004](#)]; however, another study failed to show these differences between the two groups [[Curran et al 2005](#)].

Nomenclature

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

Prevalence

The estimated prevalence of PWS is 1/10,000 to 1/25,000 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.
- Rare [cytogenetic](#) anomalies (e.g., dup Xq27.2-ter, del 6q16.2, del 1p36, del 10q26)
- [Angelman syndrome](#) (AS), characterized by: 1) severe developmental delay or mental retardation; 2) severe speech impairment; 3) gait ataxia and/or tremulousness of the limbs; and 4) 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 maternal *UBE3A* and may be diagnosed in 80% of [affected](#) individuals using [methylation analysis](#) of [chromosome](#) 15. In infancy, only hypotonia may be evident. [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. The diagnosis of fragile X syndrome rests upon the detection of an alteration in the *FMR1* [gene](#) consisting of expansion of a triplet repeat and [gene methylation](#). In infancy, only hypotonia may be evident. [Affected](#) individuals lack the characteristic sucking problems, hypogonadism, and facial appearance of PWS.

In childhood, [Rett syndrome](#) can present with hypotonia, obesity and gynecomastia as well as mental retardation. Beginning at 6-18 months of age, [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 *MCP2* detects 80% of Rett syndrome.

Developmental delay/mental retardation, obesity, and hypogonadism can be seen in a number of disorders:

- [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, dysmorphic obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary

malformations, and renal dysfunction. It has a different facial [phenotype](#) from PWS. [Diagnostic testing](#) is available for the common [mutation](#) in *BBS1*, one of five [genes](#) known to cause BBS.

- [Cohen syndrome](#), characterized by downslanting eyes, 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*.
- Borjeson-Forssman-Lehmann syndrome, seen in males, can be distinguished by microcephaly, severe retardation, nystagmus, and coarse facies with ptosis and deep-set eyes.

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

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Newborns and young infants should be assessed for sucking problems and failure to thrive.
- Regardless of age, height and weight should be measured and plotted on either age-appropriate growth charts or charts developed for PWS. Calculation of BMI may be helpful.
- Developmental assessment should be made in infants, educational assessment in children. This should include a speech evaluation.
- Males should be assessed for the presence of cryptorchidism regardless of age.
- Children with prolonged failure to thrive should be assessed for hypothyroidism.
- Regardless of age, individuals should be assessed for the presence of scoliosis clinically, and, if indicated, radiographically.
- Infants and young children should be evaluated for strabismus.
- Assess for the presence of behavioral problems and obsessive compulsive features after age two years, and for psychosis in adolescents and adults.
- A careful assessment of respiratory status and a sleep study are appropriate regardless of age. They are specifically recommended by some experts prior to initiation of growth hormone therapy, particularly in the obese child.
- Evaluation for the presence of diabetes mellitus by standard methods (such as obtaining glycosylated hemoglobin) is appropriate for anyone with significant obesity or rapid significant weight gain.
- Bone [densitometry](#) to evaluate for possible osteoporosis is appropriate in adulthood.

Treatment of Manifestations

- A team approach to management is strongly 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 under three years, particularly physical therapy, may improve muscle strength and encourage achievement of developmental

milestones.

- 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 the kitchen, refrigerator, and/or cupboards is often needed. The energy requirement of people with PWS, which rarely exceeds 1000 to 1200 Kcal/day, should be considered in planning daily food intake.
- Growth hormone treatment normalizes height, increases lean body mass, decreases fat mass, and increases mobility, which are beneficial to weight management. 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](#) , [Eiholzer & Whitman 2004](#) , [Mogul et al 2000](#) , [Carrel et al 2002](#) , [Carrel et al 2004](#) , [Hoybe 2004](#) , [Whitman et al 2004](#)]. Dose recommendations are generally similar to those for individuals with [isolated](#) growth hormone deficiency, i.e., about 1 mg/m² in childhood. It can be started in infancy or at diagnosis.
- Initiate appropriate educational programming in children.
- Begin speech therapy for language delay and articulation abnormalities in infancy and childhood.
- Special educational, 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 re-uptake inhibitors have helped the largest proportion of [affected](#) individuals, particularly those with obsessive-compulsive symptoms [[Brice 2000](#) , [Dykens and Shah 2003](#)].
- Psychosis, if present, should be treated as in the general population.
- 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 in females. Concern about 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.
- Disturbed sleep in children and adults should prompt a sleep study, as treatment may be available [[Hertz et al 1995](#)].
- For adults with PWS, one successful 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 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 above 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 of benefit, since low-calorie diets are often low in dairy [products](#) and osteoporosis has been documented in most older children and adults with PWS.

Surveillance

- Monitor height, weight and body mass index (BMI; weight in kg/height in m²) regularly.
- Monitor for development of scoliosis. This is particularly important in those on growth hormone therapy.

Therapies Under Investigation

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

- 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](#)]

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(10) for one year in children younger than two years of age did not show improvement in body composition [[Eiholzer et al 2004](#)].

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](#). —ED.

Mode of Inheritance

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](#).
- Evaluation of the parents depends upon 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 depends on the genetic mechanism causing lack of expression of the paternally contributed PWS/AS region and is summarized in [Table 2](#) .

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% ¹
Uniparental disomy (UPD)	<1% ²
Imprinting defect with mutation	≤50% ³
Imprint defect without mutation	<1% ³
Apparently <i>de novo</i> balanced chromosome translocation breaking within the PWS/AS critical region ^{4, 5}	<1% ⁵

1. Although the majority of these are *de novo* [deletions](#), a small number of individuals have a [chromosome 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](#)

- Most individuals with PWS do not reproduce.
- The risk to the child of an [affected](#) individual depends upon 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 have a 50%

risk of having Angelman syndrome 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 of the offspring 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) Angelman syndrome 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 a theoretical risk of $\leq 50\%$ of having PWS (never reported).
- If the **proband** has a chromosomal **translocation**, there is a theoretical increased risk of an offspring with PWS or Angelman syndrome depending on the sex of the **proband** (never reported).

Other family members. If a **chromosome 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 about 10-12 weeks' gestation or amniocentesis usually performed at about 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 **uniparental disomy** 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 of 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 (UPD) studies should be performed after confirmation of a [deletion](#) to determine if the [deletion](#) is maternally derived (fetus has [Angelman syndrome](#)) 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) 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](#) and [parent-of-origin studies](#) should be done.

Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —ED.

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](#).

OMIM Entries for Prader-Willi Syndrome

[176270](#) PRADER-WILLI SYNDROME; PWS
[182279](#) SMALL NUCLEAR RIBONUCLEOPROTEIN POLYPEPTIDE N; SNRPN
[602117](#) NECDIN; NDN

Genomic Databases for Prader-Willi Syndrome

Critical Region	Entrez Gene	GeneCards	GDB	GenAtlas
PWCR	176270	PWCR	120325	PWCR1

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

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.

Critical region: PWS/AS (Prader-Willi syndrome/Angelman syndrome)
[critical region](#)

Normal allelic variants: A number of [genes](#) have been mapped within the PWS/AS region:

- ***SNRPN*** (small nuclear ribonucleoprotein N), the best described [gene](#) that is likely to cause some of the features of PWS. Based on studies in the mouse [[Ozcelik et al 1992](#)] and human, [gene](#) expression is from the paternally inherited [chromosome](#) only [[Glenn et al 1993](#)] 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 small nucleolar [RNAs](#) (snoRNAs)
- ***IPW***, which is thought to be an [RNA](#) transcript only, as it does not encode a [protein](#)
- Anonymous transcripts, ***PAR1***, ***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 Angelman syndrome
- ***HERC2*** and multiple [duplications](#) occur at the common [deletion](#) breakpoints.
- ***NECDIN*** (*NDN*), which encodes a [DNA](#) binding [protein](#)
- ***MAGEL2***, an intronless [gene](#) in proximity to the *NDN* [locus](#). Transcribed only by the paternal [allele](#) and expressed predominantly in the brain
- ***MKRN3***, (***Markorin 3***, ***ZNF127***), a [zinc finger protein](#) expressed only from the paternal [chromosome](#)
- 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 about 500 kb; four **genes** have been identified in the region between BP1 and BP2: *CYFIP1*, *GCP5*, *NIPA1*, and *NIPA2* [Chai et al 2003]. These **genes** are not **imprinted**. *NIPA1* is widely expressed in the central nervous system.
- Small **deletions** of the promotor 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 **uniparental disomy**. This pattern is considered an **imprinting** defect.
- Other individuals have biparental inheritance, but maternal-only **methylation** patterns in this region without detectable promotor 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 the *SNRPN* and *MKRN3* **genes**. *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*) 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 [Buiting et al 1994 , 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 **uniparental disomy** [Saitoh et al 1997]. Other individuals demonstrate **sporadic imprinting** defects [Buiting et al 1998 , Buiting et al 2003].

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. -ED.

- **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
pwsa.co.uk/main.php

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

5700 Midnight Pass Road Suite 6
Sarasota FL 34242
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 & Prader-Willi Syndromes Consortium Registry](#)

 **Resources Printable Copy**

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[PubMed](#)

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