



Prader-Willi Syndrome

Synonym: Prader-Labhart-Willi Syndrome

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Summary

Clinical characteristics

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

Diagnosis/testing

PWS is a contiguous gene syndrome due to abnormal DNA methylation within the Prader-Willi critical region (PWCR) at 15q11.2-q13. The diagnosis and molecular cause can be identified in a proband by simultaneous DNA methylation analysis and oligo-SNP combination array (OSA). DNA methylation analysis identifies maternal-only imprinting within the PWCR. OSA can identify the molecular cause in those with a 15q11.2-q13 deletion, imprinting center deletion, and uniparental isodisomy and segmental isodisomy. In individuals with maternal-only imprinting identified on DNA methylation analysis and a normal OSA, DNA polymorphism analysis can be used to distinguish uniparental heterodisomy from an imprinting defect by epimutation.

Management

Treatment of manifestations: In infancy, special nipples or nasogastric tube feeding to assure adequate nutrition. In childhood, strict supervision of daily food intake based on height, weight, and body mass index (BMI) to

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provide energy requirements while limiting excessive weight gain (maintain BMI z score <2); encourage physical activity. Developmental services and educational support; hormonal and surgical treatments can be considered for cryptorchidism; growth hormone therapy to normalize height, increase lean body mass and mobility, and decrease fat mass; endocrine management of sex hormone replacement at puberty; treatment for those with precocious puberty, type 2 diabetes, and hypothyroidism; urgent evaluation for those with acute gastrointestinal manifestations; topiramate or N-acetylcysteine as needed for skin picking; standard treatment for neurobehavioral and ophthalmologic manifestations, sleep issues, scoliosis, hip dysplasia, and seizures; modafinil may be helpful for daytime sleepiness; calcium and vitamin D supplementation to avoid osteoporosis; sex steroid therapy, growth hormone, or bisphosphonates for low bone density; products for dry mouth and frequent dental hygiene; social work support and care coordination. In adulthood, a residential facility for individuals with PWS that helps regulate behavior and weight management may prevent morbid obesity, and growth hormone may help to maintain muscle mass.

Surveillance: Monitor development, growth, skin, sleep issues, and family needs at each visit. Assess testicular position annually in males; assess glycosylated hemoglobin and/or glucose tolerance test in adolescents and those with obesity or rapid weight gain; and assess free T4 and TSH every six to 12 months. Assess for central adrenal insufficiency as needed; monitor height, weight, and BMI monthly in infancy, every six months until age ten years, and then annually. Assess for behavioral issues annually after age two years, and for psychosis annually in adolescent and adults. Assess for vision issues and sleep issues annually; sleep study prior to starting growth hormone therapy and four to eight weeks after starting growth hormone therapy. Clinical examination for scoliosis at each visit when child can sit independently; spine x-rays annually in those with clinical findings of scoliosis or obesity; DXA scan every two years beginning in adolescence. Assess for new seizures or monitor those with seizures at each visit. Dental evaluations every six months or more frequently in those with dental issues.

Genetic counseling

Individuals with PWS typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration. The vast majority of families have a recurrence risk of less than 1%. However, certain etiologies involve a recurrence risk as high as 50%, and a scenario with a risk of almost 100%, though very unlikely, is theoretically possible. Reliable PWS recurrence risk assessment therefore requires identification of the genetic mechanism of PWS in the proband (i.e., a 15q deletion, UPD 15, or an imprinting defect) and parental testing to discern the presence of a predisposing genetic alternation (e.g., a parental chromosome rearrangement or paternal heterozygosity for an imprinting center deletion). Once the causative genetic mechanism has been identified in the proband, prenatal testing for PWS is possible.

Diagnosis

Suggestive Findings

Prader-Willi syndrome (PWS) **should be suspected** in individuals with the following specific clinical findings and/or laboratory findings.

Clinical Findings

Clinical findings differ by age group. The presence of **all** the findings for a given age group in an individual of that age is sufficient to justify molecular analysis for PWS (see Establishing the Diagnosis).

Neonatal period. Hypotonia with poor suck

Age one month to two years

- Hypotonia with poor appetite and suck in the neonatal period
- Developmental delay

Age two to six years

- Hypotonia with history of poor suck
- Developmental delay

Age six to 12 years

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

Age 13 years to adulthood

- Cognitive impairment, usually mild intellectual disability
- Excessive eating and hyperphagia with central obesity if uncontrolled externally
- Hypothalamic hypogonadism and/or typical behavioral findings

Laboratory Findings

Deletion of the 15q11.2-q13 genomic region is suggestive of PWS but not diagnostic.

Establishing the Diagnosis

The diagnosis of PWS is **established** in a proband by identification of abnormal DNA methylation within the Prader-Willi critical region (PWCR) at 15q11.2-q13 in which the region demonstrates maternal-only imprinting due to one of the following:

- Deletion of the paternally inherited 15q11.2-q13 region
- Uniparental disomy of the maternal chromosome 15q11.2-q13 region (UPD 15)
- An imprinting defect of the paternal chromosome 15q11.2-q13 region either due to an imprinting center deletion or epimutation

Molecular genetic testing approaches include first-tier, second-tier, and other testing options.

Recommended first-tier testing. Testing should begin with both DNA methylation analysis and oligo-small nucleotide polymorphism (SNP) combination array (OSA) to establish the diagnosis and identify the molecular cause in most individuals (see Figure 1 and Table 1).

- **DNA methylation analysis**, typically by methylation-specific PCR (MSP), can establish the diagnosis of PWS by identification of maternal-only imprinting at 15q11.2-q13 but cannot identify the cause of the abnormal DNA methylation (i.e., test results cannot distinguish between a 15q deletion, UPD 15, or imprinting defect).
- **OSA** uses a combination of both oligonucleotide and SNP probes to detect deletions/duplications, distinguish type 1 and 2 deletions as well as atypical deletions (see Figure 2), and determine if there are any other significant chromosomal abnormalities (in the rare instances of unbalanced translocations). Most current OSAs will also detect small imprinting center deletions, as well as other genetic conditions that have clinical features that overlap with PWS (e.g., deletions of the *SNORD116* gene cluster; see Differential Diagnosis). In addition, an OSA will identify individuals with UPD 15 due to isodisomy and segmental isodisomy.

Recommend second-tier testing. In individuals with abnormal DNA methylation at 15q11.2-q13 demonstrating maternal-only imprinting and no 15q deletion or UPD 15 (no absence of heterozygosity by

isodisomy or segmental isodisomy) identified on OSA, **DNA polymorphism testing** of the proband and parents is recommended to identify UPD 15 due to heterodisomy or abnormal DNA methylation due to an epigenetic imprinting defect.

Other testing options

- **Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA)** can establish the diagnosis of PWS by identification of maternal-only imprinting at 15q11.2-q13 and can (1) identify and approximate the size of the deletion of the paternally inherited 15q11.2-q13 region; (2) identify type 1 and 2 deletions (see Figure 2); (3) interrogate six differentially methylated regions versus only one region interrogated by MSP; (4) often identify and quantify mosaicism; and (5) identify imprinting center and *SNORD116* deletions (see Figure 1 and Differential Diagnosis). MS-MLPA cannot distinguish UPD 15 from an imprinting defect by epimutation.
- **DNA sequence analysis.** In individuals with abnormal DNA methylation at 15q11.2-q13 demonstrating maternal-only imprinting, DNA sequence analysis can identify imprinting defects due to imprinting center deletions. Note: This test is not often used, since MS-MLPA and most OSAs have concentrated probes to detect imprinting center deletions.
- **FISH analysis** is limited by the specific probes used (e.g., *SNRPN*) and can identify a deletion of 15q11.2-q13. FISH **does not** (1) query the whole PWCR; (2) determine the size of the deletion; (3) provide information about the rest of the chromosomes; or (4) identify UPD 15 or imprinting defects. FISH analysis is not a recommended first-tier test but may be used to clarify recurrence risk (see Tables 9 and 10).

Note: The underlying genetic etiology of PWS is important to discern for genetic counseling (see Tables 9 and 10).

Table 1. Molecular Genetic Testing Used in Prader-Willi Syndrome

Mechanism ¹	Proportion of PWS Attributed to Mechanism	DNA Methylation Analysis ²	OSA ³	DNA Polymorphism Testing ⁴	MS-MLPA ⁵
15q deletion	~60%-70%	DNA methylation abnormal; cannot distinguish cause	+		+
UPD 15 complete isodisomy	4%-5%		+		DNA methylation abnormal; cannot distinguish cause
UPD 15 segmental isodisomy	17%-23%		+		
UPD 15 heterodisomy ⁶	~8%-11%			+	
Imprinting center deletion	<0.5%		+		+
Imprinting defect by epimutation	~2%-4%				+

+ = mechanism can be identified by test method; MS-MLPA = methylation-specific multiplex ligation-dependent probe amplification; OSA = oligo-small nucleotide polymorphism (SNP) combination array; PWS = Prader-Willi syndrome; UPD = uniparental disomy

1. See Molecular Genetics for more details.

2. Typically by methylation-specific PCR (MSP).

3. OSA can detect genome-wide large deletions/duplications that cannot be detected by sequence analysis and provide detailed information regarding the size of the deletion, including most imprinting center deletions (see Figure 1). In addition, use of small nucleotide polymorphisms (SNP) will allow detection of UPD 15 by complete isodisomy and segmental isodisomy but not heterodisomy.

4. Not a first-tier test; performed after DNA methylation analysis establishes the diagnosis of PWS to distinguish between methylation abnormalities due to UPD 15 heterodisomy and imprinting defect by epimutation.

5. Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) can identify 15q deletions and most imprinting center deletions (see Figure 1); it can identify abnormal DNA methylation but cannot distinguish UPD from an imprinting defect by epimutation.

6. Includes UPD 15 without any regions of isodisomy (i.e., resulting in absence of heterozygosity)

Clinical Characteristics

Clinical Description

Prader-Willi syndrome (PWS) is a complex, multisystem disorder characterized by neonatal hypotonia with poor suck and poor weight gain without nutritional support, developmental delay, mild cognitive impairment, hypogonadism leading to genital hypoplasia and pubertal insufficiency, short stature if untreated with growth hormone (GH), childhood-onset obesity if excessive eating is not limited, behavioral findings, and typically a characteristic facial appearance. Less consistent but common features include decreased fetal movements, small hands and/or feet, hypopigmentation compared to the affected individual's family members, skin picking, strabismus and visual acuity abnormalities, sleep disturbance (including daytime sleepiness and sometimes sleep apnea), thick, viscous saliva, and articulation differences. There is some variability in clinical findings depending on the molecular cause of PWS.

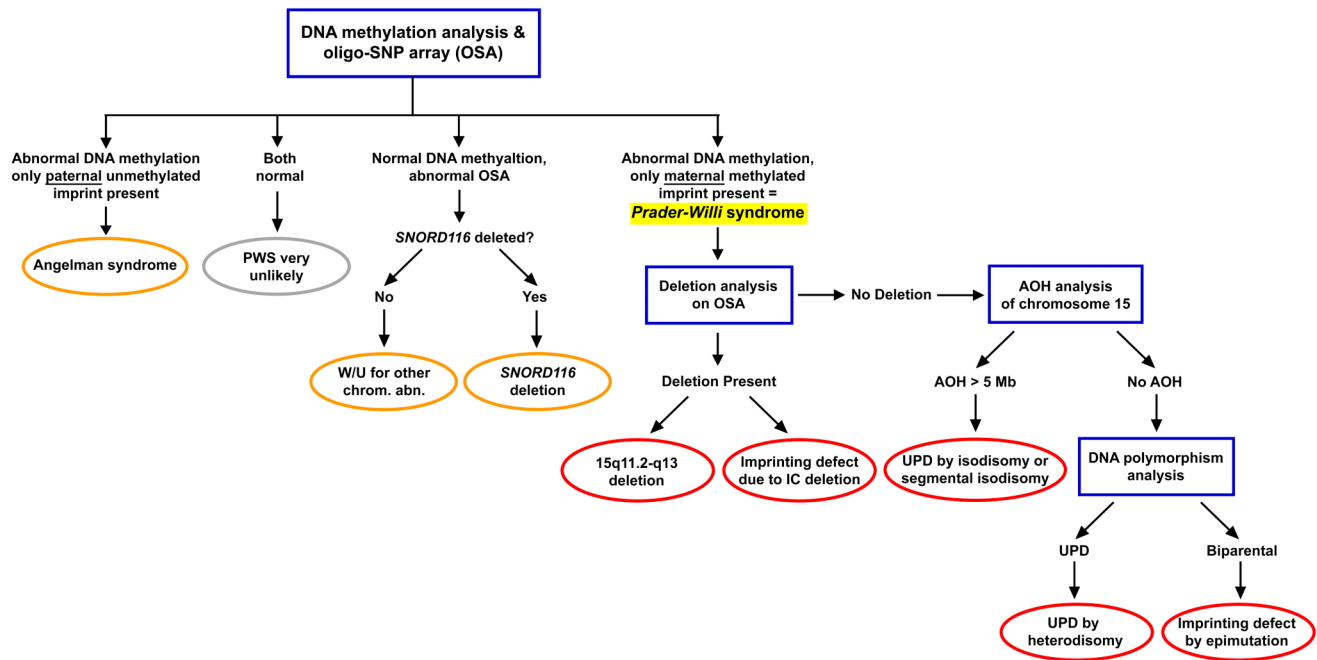


Figure 1. Comprehensive testing strategy to diagnose Prader-Willi syndrome and to establish the genetic mechanism

AOH = absence of heterozygosity; chrom abn = chromosomal abnormality; IC = imprinting center; OSA = oligo-SNP array; PWS = Prader-Willi syndrome; UPD = uniparental disomy; W/U = workup

Expression in PWS/AS region: 15q11-13

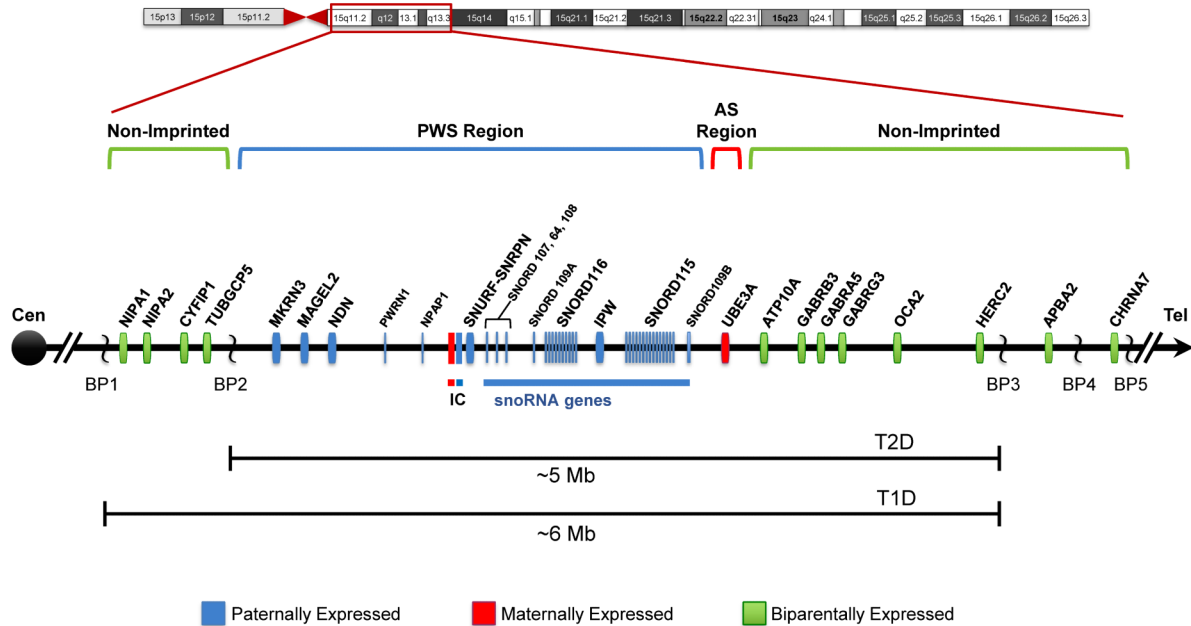


Figure 2. Summary of the genetic and expression map of chromosome region 15q11.2-q13.3

The Prader-Willi syndrome (PWS) critical region (shown in blue) has several paternally (PWS region) expressed genes (*MKRN3*, *MAGEL2*, *NDN*, *PWRN1*, *NPAP1*, and *SNURF-SNRPN*), a family of paternally expressed small nucleolar RNA (snoRNA) genes, and *IPW*, a long noncoding RNA. Three of these genes (*SNURF-SNRPN*, *MAGEL2*, and *NDN*) have differentially methylated CpG islands in their promoter region that are methylated on the repressed maternal alleles. Only *UBE3A* (shown in red), associated with [Angelman syndrome](#) (AS), has preferential maternal-only expression, and this imprinted expression is limited to certain tissue-specific regions (specifically the brain). The imprinting center (IC) has a bipartite structure with an AS (maternal, shown in red) and a PWS (paternal, shown in blue) component. The PWS shortest region of deletion overlap (PWS-SRO) has been localized to a 4.3-kb region that includes the promoter, CpG island, exon 1, and a small part of intron 1 of bicistronic *SNURF-SNRPN*. The AS-SRO lies approximately 35 kb proximal to exon 1 of *SNURF-SNRPN*. The bipartite IC lies within the 2.5-Mb PWS/AS imprinted region. The cluster of GABA receptor genes (*GABRB3*, *GABRA5*, and *GABRG3*), *ATP10A*, *OCA2* (pathogenic variants of which cause oculocutaneous albinism type 2), and *HERC2* are not imprinted and have biparental expression (shown in green). The jagged vertical lines denote the three common 5- to 6-Mb PWS and AS deletion breakpoints: BP1, BP2, and BP3. On rare occasions there will be a distal breakpoint at BP4 or BP5. Between BP1 and BP2 lie four additional, nonimprinted genes: *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*. Type 1 and type 2 deletions account for more than 90% of the deletions identified in individuals with PWS. Type 1 deletions (T1D) extend from BP1 to BP3, and type 2 deletions (T2D) extend from BP2 to BP3. Note that there are more copies of *SNORD116* (approximately 24 copies) and *SNORD115* (approximately 47 copies) than are shown, and the map has not been precisely drawn to scale. The map order was determined by the latest human genome assembly (UCSC Genome Browser, GRCh38/hg38).

Table 2. Prader-Willi Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Infantile hypotonia	95%-100%	Assoc w/poor suck; results in poor weight gain w/o feeding support
Dysphagia	90%-100%	Typically present at birth & persists to adulthood
Motor delay	90%-100%	
Language delay	90%-100%	Incl abnormal speech articulation, speech apraxia
Intellectual disability	90%-100%	Most w/mild disability; ranges from severe learning disabilities to significant cognitive disability

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Endocrine manifestations	90%-100%	Hypogonadism, abnormal pubertal development, growth deficiency, diabetes mellitus, hypothyroidism
Hyperphagia & obesity	90%-100%	
Characteristic behavior profile	70%-90%	Anxiety, tantrums, rigidity, OCD, manipulative behavior, autistic features, ADHD; psychosis becomes evident in young adults, esp those w/UPD 15
Increased pain threshold	60%-80%	May mask urgent medical issues
Dysmorphic facial features	50%-70%	May attenuate w/GH therapy; more common in persons w/15q deletion
Hypopigmentation	50%-70%	Primarily in those w/15q deletion
Skin picking	50%-60%	Decreases in older adults
Strabismus	40%-60%	
Sleep abnormalities	30%-40%	Central apnea (in infants), obstructive sleep apnea, daytime sleepiness, narcolepsy
Scoliosis	40%-80%	
Seizures	10%-20%	Typically generalized & treatable

ADHD = attention-deficit/hyperactivity disorder; GH = growth hormone; OCD = obsessive-compulsive disorder; UPD = uniparental disomy

Perinatal findings. A retrospective study of prenatal ultrasounds of 47 individuals with PWS younger than age ten years found that affected individuals had decreased fetal movements (88%), were small for gestational age (65%), had asymmetrical intrauterine growth with increased head-to-abdomen circumference ratio (43%), and had polyhydramnios (34%) when compared to controls [Gross et al 2015]. Prenatal hypotonia usually results in decreased fetal movements, abnormal fetal position at delivery, and increased incidence of assisted delivery or cesarean section. Fetal size is generally within the normal range, but the birth weight and body mass index (BMI) are on average 15% lower than in typically developing sibs [Miller et al 2011].

Hypotonia. Infantile hypotonia is a nearly universal finding, causing decreased movement and lethargy with decreased spontaneous arousal, weak cry, and poor reflexes, including poor suck. 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.

Poor suck, dysphagia, lethargy, and poor appetite result in poor weight gain in early infancy without assisted feeding. Feeding difficulties are reported in 99% of infants; nasogastric tube feeding (a gastrostomy tube is rarely needed) or the use of special nipples is generally required for a variable period of time, usually weeks to months. By the time the child is drinking from a cup or eating solids, a period of approximately normal eating behavior occurs.

The hypotonia improves over time. However, children and adults remain mildly hypotonic, with decreased muscle bulk and tone.

Developmental delay. Early motor milestones are achieved at approximately double the normal age (e.g., sitting at 12 months, walking at 24 months). Language milestones are also typically delayed and speech is impaired [Dimitropoulos et al 2013]. Speech articulation is abnormal in many individuals with PWS. Speech apraxia has been reported in 7%-10% and is more common in those with 15q deletion. Although a small proportion of affected individuals have extremely impaired language development, verbal ability is a relative strength for most.

Intellectual disabilities are generally evident by the time the child reaches preschool age. Testing indicates that most individuals with PWS have mild intellectual disability (mean IQ: 60-70), with approximately 40% having borderline disability or low-normal intelligence and approximately 20% having moderate disability. Regardless of measured IQ, most children with PWS have multiple severe learning disabilities and poor academic performance for their intellectual abilities [Whittington & Holland 2017]. Based on the authors' experiences, a small percentage of individuals with PWS are able to attend and graduate from college. Increased skill with jigsaw puzzles is reported, particularly in individuals with a 15q deletion.

Endocrine manifestations

- **Hypogonadism** is present in both sexes and manifests as genital hypoplasia, incomplete pubertal development, and infertility in the vast majority. Genital hypoplasia is evident at birth and throughout life.
 - **Males.** The penis may be small, and most characteristic is a hypoplastic scrotum with poorly rugated scrotal skin and decreased pigmentation. Unilateral or bilateral cryptorchidism is present in 80%-90% of males.
 - **Females.** Genital hypoplasia is often overlooked; however, the labia majora, labia minora, and clitoris are often small from birth.

Hypogonadism is usually associated with low serum concentration of gonadotropins and causes incomplete, delayed, and sometimes disordered pubertal development. Infertility is almost universal, although a few instances of reproduction in females have been reported [Cassidy et al 2012]. Although hypogonadism in PWS has long been believed to be entirely hypothalamic in origin, studies have suggested a combination of hypothalamic and primary gonadal deficiencies [Eldar-Geva et al 2009, Hirsch et al 2009, Eldar-Geva et al 2010, Gross-Tsur et al 2012], a conclusion largely based on the absence of hypogonadotropism and abnormally low inhibin B levels in some affected individuals of both sexes.

Male infants with PWS and cryptorchidism can be treated with human chorionic gonadotropin (hCG), which results in anatomically lower testes as well as improvement in the size of the penis and scrotal sac, prior to urologic surgery. Undergoing orchiopexy at a younger age, as well as higher levels of inhibin B and testosterone after hCG treatment, have been associated with a greater number of germ cell-containing tubules on testicular histology [Bakker et al 2015].

Premature pubarche has been reported in 15%-20% of males and 30% of females. Premature adrenarche was reported in 15%-20% of individuals with PWS. Premature pubarche and adrenarche have been associated with elevated dehydroepiandrosterone sulfate levels. Advanced bone age is also reported. Central precocious puberty, typically idiopathic, has been reported in 5% of individuals.

- **Growth deficiency.** Data from at least 15 studies involving more than 300 affected children document reduced GH secretion in individuals with PWS [Burman et al 2001]. Short stature is reported in 60%-70% of untreated individuals; if not apparent in childhood, short stature is almost always present during the second decade in the absence of GH treatment. The lack of a pubertal growth spurt results in an average untreated height of 155 cm for males and 148 cm for females. GH deficiency is also seen in adults with PWS [Grugni et al 2006, Höybye 2007]. Treatment with GH is beneficial in individuals with PWS regardless of GH sufficiency status [Alves & Franco 2020, Höybye et al 2021]. Growth charts for affected infants and children not treated with GH have been published [Butler et al 2011, Butler et al 2015], and growth charts for GH-treated children with PWS have been developed [Butler et al 2016].

The hands and feet grow slowly and are generally below the fifth centile by age ten years (70%-90% of individuals) in the absence of GH treatment, with an average adult female foot size of 20.3 cm and average adult male foot size of 22.3 cm.

- **Hypothalamic pituitary dysfunction.** Impaired hypothalamic development and function results in multiple hormonal deficiencies, including GH deficiency, hypogonadism, hypothyroidism, corticotropin deficiency, and abnormal oxytocin neurons [Tauber & Hoybye 2021].
- **Type II diabetes.** Up to 25% of adults with PWS (particularly those with significant obesity) have type II diabetes [Tauber & Hoybye 2021], with a mean age of onset of 20 years. Earlier diagnosis, education of parents, GH therapy, and the availability of group homes specific for adults with PWS have led to a reduction in the development of morbid obesity and type II diabetes.
- **Central hypothyroidism,** with a normal thyroid-stimulating hormone and low free thyroxine, has been documented in up to 25% of individuals with PWS. The mean age of diagnosis is two years [Miller et al 2008, Diene et al 2010].
- **Central adrenal insufficiency (CAI).** A Dutch study initially suggested that CAI was common in individuals with PWS [de Lind van Wijngaarden et al 2008], but subsequent studies, including one large international study, found that CAI is rare (1.2%) in adults with PWS [Rosenberg et al 2020]. The international study concluded that there is no need for hydrocortisone supplementation in individuals with PWS in the absence of clinical manifestations and confirmation of adrenal insufficiency.

Appetite, obesity, and gastrointestinal manifestations. In contrast to the long-held view that there are only two distinct nutritional phases in PWS (i.e., poor weight gain followed by hyperphagia leading to obesity), a multicenter study found that the transition between nutritional phases is much more complex, with seven different nutritional phases through which individuals with PWS typically progress [Miller et al 2011] (see Table 3).

Table 3. Nutritional Phases in Prader-Willi Syndrome

Phase	Median Ages	Clinical Characteristics
0	Prenatal to birth	↓ fetal movements & lower birth weight than sibs
1a	Birth to 9 mos	Hypotonia w/difficulty feeding & ↓ appetite
1b	9 to 25 mos	Improved feeding & appetite; growing appropriately
2a	2.1 to 4.5 yrs	Weight ↑ w/o appetite ↑ or excess calories
2b	4.5 to 8 yrs	↑ appetite & calories but can feel full
3	8 yrs to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite no longer insatiable for some

Adapted from Miller et al [2011]

- **Hyperphagia** in PWS is believed to be caused by a hypothalamic abnormality resulting in lack of satiety. Food-seeking behaviors such as hoarding or foraging for food, eating of inedible objects, and stealing of food or money to buy food are common. At this time there are no consistently identified hormonal abnormalities to explain the hyperphagia, and the metabolic correlates of hyperphagia in PWS remain uncertain.
- **Obesity** results from these hyperphagic behaviors and from decreased total caloric requirement. The latter is due to decreased resting energy expenditure resulting from decreased activity and decreased lean body mass (primarily muscle) compared with unaffected individuals. Obesity in individuals with PWS is primarily central (abdomen, buttocks, and thighs) in both sexes. Interestingly, there is less visceral fat in obese individuals than would be expected for the degree of obesity. Obesity and its complications are the major causes of morbidity and mortality (see **Life span** at the end of this section).

Early diagnosis allows the clinician to begin anticipatory guidance concerning the natural history of PWS, and in particular the nutritional phases (see Table 3), informing the family about the risks of obesity and the need to monitor weight gain and restrict calories beginning around age 18 to 36 months. Obesity may be prevented if the diet, exercise, and supervision program described in Treatment of Manifestations is instituted.

If started at a young age, GH treatment, along with good dietary control, may prevent obesity and the high proportion of fat mass. It may also modify the typical PWS facial appearance, improve motor milestones, and improve some cognitive abilities [Butler et al 2019b, Ayet-Roger et al 2022].

- **Acute gastrointestinal manifestations.** In most affected individuals, gastric emptying is delayed (60%-80% of individuals), and vomiting is rare; decreased vomiting is reported in 80%-90%, increasing the risk of gastric necrosis with significant hyperphagia. Abdominal distention, bloating, pain, lethargy, loss of appetite, and vomiting may be signs of life-threatening gastric inflammation or necrosis. Individuals with these symptoms should be urgently evaluated by a medical professional and may require hospitalization. Radiographic imaging and possibly emergency surgery may be required. Use of antidiarrheal medications can lead to severe colonic distention, necrosis, and rupture.

Behavior. A characteristic behavior profile with anxiety, temper tantrums (outbursts), rigidity/resistance to change, obsessive-compulsive behaviors, and social cognition deficits becomes evident in early childhood in individuals with PWS [Ishii et al 2017, Schwartz et al 2021]. These behaviors increase with age and BMI in childhood and adolescence, although it was noted by Dykens [2013] that externalizing behavioral issues (e.g., aggression, impulsivity) tend to decline in older adults (age >40 years).

- Many of the behavioral characteristics are suggestive of autism. A recent meta-analysis including 786 individuals with PWS reported that 26.7% met criteria for autism spectrum disorder, including 18.5% of those with 15q deletion and 35.3% of those with UPD 15 [Bennett et al 2015].
- Attention-deficit/hyperactivity disorder is common and of early onset.
- Psychosis is evident by young adulthood in some affected individuals and is significantly more frequent in those with UPD 15. A meta-analysis of 95 individuals with PWS from five studies suggested an overall incidence of psychosis of about 25% in those with 15q deletion and 64% in those with UPD 15 [Yang et al 2013].

Behavioral and psychiatric issues interfere most with the quality of life in adolescence and adulthood, including affecting ability to live independently.

Pain insensitivity. Diminished typical pain perception is common and may mask the presence of infection, injury, or fractures. Individuals with PWS may not report pain until the condition is severe, and they may have difficulty localizing pain.

Dysmorphic features. Characteristic facial features (narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, thin vermilion of the upper lip with down-turned corners of the mouth) may or may not be apparent at birth and may slowly evolve over time [Cassidy & Driscoll 2009, Cassidy et al 2012]. Treatment with GH may attenuate the dysmorphic features over time.

Hypopigmentation of hair, eyes, and skin is frequently found in individuals with 15q deletion due to the deletion of OCA2 located at 15q.

Dermatologic manifestations. Skin and mucosal picking, often leaving chronic open sores, is one of the more difficult issues. Picking at the nose, rectum, or vagina is common and often unknown to caregivers. Picking can result in pigmentary changes, scarring, and infections.

Peripheral edema is not uncommon in obese individuals with PWS and may lead to chronic changes of the legs.

Ophthalmologic manifestations. Strabismus in those with PWS is often diagnosed by age five years. Myopia and hyperopia are common [Bohonowych et al 2021].

Sleep abnormalities are well documented and include reduced rapid eye movement (REM) latency, altered sleep architecture, oxygen desaturation, and both central and obstructive apnea [Festen et al 2006, Priano et al 2006]. Primary hypothalamic dysfunction is thought to be the cause of the alterations in sleep microstructure and abnormalities in ventilation during sleep. Some individuals with PWS have excessive daytime sleepiness, which resembles narcolepsy, with rapid onset of REM sleep and decrease in non-REM sleep instability [Bruni et al 2010]. Narcolepsy, reported in 10%-35%, is often undiagnosed in individuals with PWS due to the prevalence of excessive daytime somnolence. Multiple sleep latency tests must be done to diagnose narcolepsy. Cataplexy has been known to occur in individuals with PWS, but the prevalence is not known.

Skeletal findings. Scoliosis, present in 40%-80% of affected individuals, varies in age of onset and severity, and may be present from infancy. It is presumed to be related to hypotonia, since there are no underlying structural anomalies. Kyphosis occurs commonly in adolescents and adults with PWS. Hip dysplasia occurs in approximately 20%-30% [Trizno et al 2018]. The incidence of osteopenia and osteoporosis is increased in individuals with PWS. Frequency of bone fractures, particularly of long bones, seems increased, although no well-designed study has been published.

Seizures, typically generalized seizures, may occur in early childhood. They tend to be infrequent and often resolve after a few years of anti-seizure medication [Takeshita et al 2013].

Dental issues. Saliva flow is decreased in people with PWS and can lead to increased dental caries and speech articulation difficulties. Dried material on the lips is common. Dental crowding and enamel hypoplasia are also more common.

Life span. The mortality rate in individuals with PWS is higher than in controls with intellectual disability. With improved management, the death rate has declined to 1.25% per annum [Whittington et al 2015]. Several large studies have indicated that respiratory failure and other febrile illnesses are the most frequent causes of death in children, and cardiac disease and failure, pulmonary thromboembolism, obesity-related complications, and gastric causes are most frequent in adults [Butler et al 2017, Pacoricona Alfaro et al 2019]. Of note, a family questionnaire-based survey of more than 2,000 individuals known to the Prader-Willi Syndrome Association (USA), of whom 114 were deceased, showed that those who were living had a significantly higher rate of GH treatment (threefold higher) than those who were deceased, even after adjusting for the greater age of those who were deceased [Proffitt et al 2019].

Acute gastric distention with gastric rupture and necrosis has been reported as a cause of death in several individuals with PWS, particularly following an eating binge among those who are thin but were previously obese. It may be unrecognized because of a high pain threshold.

Choking, especially on hot dogs, has been reported as cause of death in approximately 8% of deaths in individuals with PWS. Disordered pharyngeal and esophageal swallowing and lack of attempt to clear residue or coughing is common in PWS [Gross et al 2017], and combined with rapid eating may increase the risk of aspiration-related mortality.

Concern about the possible contribution of GH administration to unexpected death has been raised by reported deaths of individuals within a few months of starting GH therapy. The few reported deaths were mostly in obese individuals who had preexisting respiratory or cardiac disorders with evidence of upper airway obstruction and uncorrected tonsillar and adenoidal hypertrophy. In other studies, the rate of death in affected individuals on and off GH therapy did not differ; thus, the relationship of GH administration to unexpected death remains unclear. See Management for recommended evaluations prior to starting GH therapy.

Neuroimaging. Reported abnormalities on brain imaging include white matter lesions, ventriculomegaly, decreased volume of brain tissue in the parietal and occipital lobes, Sylvian fissure polymicrogyria, incomplete insular closure, gray matter volume changes, and reduced pituitary height. Their relationship to clinical manifestations remains unclear.

Genotype-Phenotype Correlations

No phenotypic feature is known to correlate exclusively with any one of the three main molecular mechanisms that result in PWS. However, some statistical differences in the frequency or severity of certain features between the two largest molecular classes (15q deletion and UPD 15) have been observed.

- Post-term delivery [Butler et al 2009] and advanced maternal age is more common with UPD 15 [Miller et al 2011].
- Individuals with UPD 15 are less likely to have the typical facial appearance, hypopigmentation [Mahmoud et al 2021], or skill with jigsaw puzzles [Dykens 2002]. They also have a somewhat higher verbal IQ [Rosenberg et al 2022] than those with 15q deletion.
- Individuals with UPD 15 are more likely to have psychosis [Yang et al 2013] and autism spectrum disorder [Bennett et al 2015]. Studies suggest that as many as 64% of those with UPD 15 develop atypical psychosis compared with 25% of those with 15q deletion [Yang et al 2013].

Penetrance

Penetrance is complete.

Nomenclature

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

PWS is sometimes called Willi-Prader syndrome or Prader-Labhart-Willi syndrome.

Prevalence

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

A recent study screening 16,579 newborns for PWS in Australia found a birth incidence of 1:8,290 [Godler et al 2022].

Genetically Related Disorders

Angelman syndrome (AS) is caused by loss of the maternally contributed PWS/AS critical region. It is clinically distinct from Prader-Willi syndrome (PWS) after age two years (see Differential Diagnosis).

Schaaf-Yang syndrome is caused by pathogenic truncating variants on the paternally inherited *MAGEL2* gene in the PWS critical region of 15q11.2.

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

Differential Diagnosis

Many disorders can mimic *parts* of the Prader-Willi syndrome (PWS) phenotype.

SNORD116 deletion. Loss of expression of the *SNORD116* gene cluster plays a major role in the PWS phenotype (see Molecular Pathogenesis). Rare individuals with a *SNORD116* deletion have been described in the literature

with many, but not all, of the major features of PWS [Tan et al 2020]. These individuals have a milder phenotype typically without the PWS facial gestalt, and many also have characteristics not typical for PWS (e.g., macrocephaly, tall stature without growth hormone [GH] therapy, hirsutism, normal pubertal development, normal intelligence). Of note, most current oligo-SNP combination arrays will detect deletions of the *SNORD116* gene cluster.

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

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

Hypotonia in infancy is also seen in neonatal sepsis, central nervous system depression, and other genetic disorders (see Table 4). In some instances, these disorders can be distinguished from PWS by the presence of poor respiratory effort, a feature rarely seen in PWS.

Table 4. Genetic Disorders with Hypotonia in Infancy in the Differential Diagnosis of Prader-Willi Syndrome

Disorder	Gene(s)	MOI	Clinical Features / Comment
Angelman syndrome (AS)	<i>UBE3A</i> ¹	Recurrence risk is mechanism dependent. ²	Severe DD or ID, severe speech impairment, gait ataxia &/or tremulousness of the limbs, & unique behavior w/happy demeanor, frequent laughing, smiling, & excitability. Microcephaly & seizures are common. Hypotonia may be the only manifestation of AS in infancy. Affected persons lack characteristic sucking issues, hypogonadism, & facial appearance of those w/PWS.
Congenital myasthenic syndromes (CMS)	>30 genes incl: <i>CHAT</i> <i>CHRNE</i> <i>COL13A1</i> <i>COLQ</i> <i>DOK7</i> <i>RAPSN</i>	AR AD ³	Typically presents w/fatigable weakness involving ocular, bulbar, & limb muscles w/onset typically age <2 yrs. In the classic presentation, a CMS is limited to weakness of skeletal muscles.
Congenital myotonic dystrophy type 1	<i>DMPK</i>	AD	Hypotonia & severe generalized weakness at birth, often w/respiratory insufficiency & early death; ID is common.
Fragile X syndrome (See <i>FMRI</i> Disorders.)	<i>FMRI</i>	XL	Moderate ID in affected males & mild ID in affected females. Males may have a characteristic appearance, connective tissue findings, & large testes (post pubertal). Behavioral abnormalities are common. Hypotonia may be the only manifestation in infancy. Affected persons lack characteristic sucking issues, hypogonadism, & facial appearance of those w/PWS.
<i>GARS1</i> infantile-onset SMA (See <i>GARS1</i> -Assoc Axonal Neuropathy.)	<i>GARS1</i>	AD	Initial manifestations are typically respiratory distress, poor feeding, & muscle weakness (distal > proximal).

Table 4. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features / Comment
Infantile-onset Pompe disease	GAA	AR	Onset is typically at median age of 4 mos w/hypotonia, generalized muscle weakness, feeding difficulties, poor weight gain, respiratory distress, & hypertrophic cardiomyopathy. (Note: In PWS, hypotonia is noted at birth, not several months later.)
Schaaf-Yang syndrome	MAGEL2	AD w/imprinting ⁴	Hypotonia & feeding difficulties in infancy are similar to PWS, but joint contractures incl arthrogyrosis are features not typical of PWS. ASD is frequent as well as ID, which can be profound. Some persons develop obesity & hyperphagia in late childhood/adolescence that ↑ w/age.
Spinal muscular atrophy	SMN1	AR	Poor respiratory effort may be present, a feature rarely seen in PWS.
WAC-related ID	WAC	AD	Variable degrees of DD &/or ID. Behavioral abnormalities are observed in the majority of older children & adults. Most affected infants have significant but nonspecific features at birth (e.g., neonatal hypotonia, feeding issues).
X-linked infantile SMA	UBA1	XL	Congenital hypotonia, areflexia, & evidence of degeneration & loss of anterior horn cells (i.e., lower motor neurons) in spinal cord & brain stem. Often congenital contractures &/or fractures are present.
Zellweger spectrum disorder (ZSD)	ZSD-PEX genes	AR ⁵	Affected newborns are hypotonic w/poor feeding. They have distinctive facies, congenital malformations, & liver disease that can be severe. (Note: The brain MRI findings are very striking & distinctive in ZSD, while the brain MRIs of persons w/PWS are typically relatively normal.)

AD = autosomal dominant; AR = autosomal recessive; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; PWS = Prader-Willi syndrome; SMA = spinal muscular atrophy; XL = X-linked

1. Angelman syndrome (AS) is associated with deficient expression or function of the maternally inherited *UBE3A* allele, which can be caused by a variety of different mechanisms.
2. Individuals with AS typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration associated with a very low recurrence. Less commonly, an individual with AS has the disorder as the result of a genetic alteration associated with an imprinting pattern of autosomal dominant inheritance or variable recurrence risk.
3. Congenital myasthenic syndromes (CMS) are typically inherited in an autosomal recessive manner. Less commonly, CMS are inherited in an autosomal dominant manner.
4. Schaaf-Yang syndrome is inherited in an autosomal dominant imprinted manner (a heterozygous pathogenic variant on the paternally derived *MAGEL2* allele results in disease).
5. Zellweger spectrum disorder (ZSD) is typically inherited in an autosomal recessive manner (one *PEX6* variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state).

Developmental delay / intellectual disability and obesity with or without hypogonadism can be seen in the disorders summarized in Table 5.

Table 5. Genetic Disorders with Developmental Delay / Intellectual Disability and Obesity with or without Hypogonadism in the Differential Diagnosis of Prader-Willi Syndrome

Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features / Comment
Albright hereditary osteodystrophy (See Disorders of GNAS Inactivation.)	<i>GNAS</i>	AD w/imprinting ¹	Also characterized by short stature but lacks hypotonia & is assoc w/characteristic facial appearance (round face) unlike the facial appearance in PWS.
Alström syndrome	<i>ALMS1</i>	AR	The 1st clinical manifestation is usually nystagmus caused by cone-rod dystrophy &/or infantile-onset cardiomyopathy. Later-onset findings incl obesity that manifests during the 1st yrs of life, progressive SNHL, insulin resistance / type II DM, adolescent- or adult-onset restrictive cardiomyopathy, hepatic steatosis, & progressive kidney dysfunction.
Angelman syndrome (AS)	<i>UBE3A</i> ²	Recurrence risk is mechanism dependent. ³	Persons w/AS caused by paternal UPD 15 frequently have ↑ BMI for age. In a large study >70% were overweight & >40% were obese. ⁴
Bardet-Beidl syndrome (BBS)	~26 genes incl: <i>ARL6</i> <i>BBS1</i> <i>BBS2</i> <i>BBS4</i> <i>BBS10</i> <i>BBS12</i> <i>CEP290</i> <i>MKKS</i> ⁵	AR	Cone-rod dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, & kidney dysfunction. Persons w/BBS have a different facial phenotype from those w/PWS.
Borjeson-Forssman-Lehmann syndrome (BFLS) (OMIM 301900)	<i>PHF6</i>	XL	In males, severe cognitive deficit, epilepsy, hypogonadism, hypometabolism, marked obesity, infantile hypotonia, & growth deficiency. BFLS can be distinguished from PWS by the severity of ID, the presence of nystagmus, & characteristic facial appearance w/prominent superciliary ridges, ptosis, & deep-set eyes.
Cohen syndrome	<i>VPS13B</i>	AR	Poor weight gain in infancy & childhood; truncal obesity in the teenage years; early-onset hypotonia & DD; microcephaly developing during the 1st yr; moderate-to-profound DD/ID; progressive retinochoroidal dystrophy & high myopia; neutropenia in many persons w/recurrent infections & aphthous ulcers in some; cheerful disposition; joint hypermobility. Characteristic facial features are different from those in PWS.
Fragile X syndrome (See FMRI Disorders.)	<i>FMRI</i>	XL	A subset of affected persons have a "PWS-like" phenotype incl hyperphagia & obesity. ⁶
PWS-like syndromic obesity ⁷	<i>SIM1</i>	Recurrence risk is mechanism dependent.	Obesity, DD, plus hypotonia &/or short extremities

Table 5. continued from previous page.

Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features / Comment
Temple syndrome (OMIM 616222)	Maternal UPD 14, paternal chromosome 14 deletion, or loss of methylation at 14q32	Recurrence risk is mechanism dependent.	Prenatal growth restriction, hypotonia, infant feeding issues w/DD/ID, childhood obesity, & short stature are common to both Temple syndrome & PWS. Characteristic facial features & precocious puberty distinguish PWS. ⁸

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; PWS = Prader-Willi syndrome; UPD = uniparental disomy; SNHL = sensorineural hearing loss; DM = diabetes mellitus; XL = X-linked

1. Disorders of *GNAS* inactivation are inherited in an autosomal dominant manner, with the specific phenotype determined by the parental origin of the defective allele.
2. Angelman syndrome (AS) is associated with deficient expression or function of the maternally inherited *UBE3A* allele.
3. Individuals with AS typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration associated with a very low recurrence. Less commonly, an individual with AS has the disorder as the result of a genetic alteration associated with an imprinting pattern of autosomal dominant inheritance or variable recurrence risk.
4. Lossie et al [2001]
5. Listed genes represent the most commonly associated genes.
6. de Vries et al [1993]
7. A "PWS-like phenotype" of syndromic obesity has been identified in individuals with 6q16.2 deletions involving *SIMI* [Bonaglia et al 2008, El Khattabi et al 2015] and in individuals with intragenic *SIMI* pathogenic variants [Bonnefond et al 2013].
8. Hosoki et al [2009]

Cytogenetic abnormalities with a phenotype similar to PWS include the following:

- A PWS-like phenotype was reported in an individual with a 6q16.3q23.3 duplication (the duplication did not encompass *SIMI*) [Desch et al 2015].
- Several reports have associated a PWS-like phenotype with 1p36 deletion; findings include hypotonia, developmental delay, obesity, hyperphagia, and behavioral issues [Tsuyusaki et al 2010, Stagi et al 2014].
- Multiple reports describe a PWS-like phenotype with deletions at 16p11.2 including *SHB2B1*, which is involved in leptin and insulin signaling [Maillard et al 2015].
- Reports of other cytogenetic anomalies in individuals with a PWS-like phenotype have included dupXq27.2-ter and del10q26 [Lukusa & Fryns 2000, Ben-Abdallah-Bouhjar et al 2012, Rocha & Paiva 2014].

Management

Management of the manifestations of Prader-Willi syndrome (PWS) is age dependent and should include both addressing the consequences of PWS and anticipatory guidance. A team approach is recommended. Several approaches to management have been published [McCandless 2011, Cassidy et al 2012, Duis et al 2019]. In addition, a detailed description of management issues in infancy, early childhood, adolescents, and adults written by the Clinical and Scientific Advisory Board for the International Prader-Willi Syndrome Organization can be found at the [IPWSO Guides for Doctors: Consensus Documents](#).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PWS, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Prader-Willi Syndrome

System/Concern	Evaluation	Comment
Hypotonia	<ul style="list-style-type: none"> Assessment of newborns & young infants for sucking issues & poor growth Nutrition consultation 	<ul style="list-style-type: none"> PT eval If prolonged, eval for hypothyroidism
Developmental delay	Developmental assessment	<ul style="list-style-type: none"> To incl motor, adaptive, cognitive, & speech-language eval Eval for early intervention / special education
Hypogonadism	<ul style="list-style-type: none"> Assessment of males for presence of cryptorchidism regardless of age Assessment of pubertal stage 	<ul style="list-style-type: none"> Urologic consultation for consideration of orchiopexy If pubertal stage is not age appropriate, refer to endocrinologist for eval & potential hormone therapy.
Endocrine	<ul style="list-style-type: none"> Referral to endocrinologist for treatment w/GH therapy to be considered at diagnosis Glycosylated hemoglobin concentration &/or glucose tolerance test to assess for diabetes if obese at diagnosis Free T4 & TSH levels to assess for hypothyroidism Assessment for manifestations of central adrenal insufficiency 	
Hyperphagia/Obesity	<ul style="list-style-type: none"> Plot height, weight, head circumference, & BMI on either age-appropriate growth charts or charts developed for PWS. Nutritional consultation 	
Behavior	<ul style="list-style-type: none"> Assess for behavioral findings & obsessive-compulsive features after age 2 yrs. Assess family support, parenting skills, & psychosocial/emotional needs to assist in designing family interventions. 	
Dermatologic	Clinical assessment for open sores &/or infection secondary to skin picking	
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, strabismus
Sleep	<ul style="list-style-type: none"> Evaluate respiratory status during sleep w/sleep study prior to initiation of GH therapy. Evaluate excessive daytime sleepiness / narcolepsy / cataplexy w/overnight sleep study followed by multiple sleep latency testing & video EEG. 	
Scoliosis	Assess clinically & radiographically, if indicated.	Very obese persons cannot be adequately assessed clinically for scoliosis & x-rays are necessary to establish the diagnosis.
Hip dysplasia	<ul style="list-style-type: none"> Assess infants for hip dysplasia. Hip ultrasound at age 6 wks 	
Seizures	Consider EEG if seizures are a concern.	
Dental	Dental exam for ↑ risk of caries, dental crowding, & enamel hypoplasia	

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals ¹	To inform affected persons & their families re nature, MOI, & implications of PWS to facilitate medical & personal decision making
Family support & resources	Assess need for: <ul style="list-style-type: none"> Community or online resources such as Parent to Parent; Social work involvement for parental support; Home nursing referral. 	

BMI = body mass index; GH = growth hormone; MOI= mode of inheritance; PT = physical therapy; PWS = Prader-Willi syndrome; T4 = thyroxine; TSH = thyroid-stimulating hormone

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management by multidisciplinary specialists typically starting with neonatologists and followed by medical geneticists and genetic counselors, primary care physicians, endocrinologists, orthopedists, nutritionists, psychologists, psychiatrists, physical, occupational, and speech therapists, and educators is recommended.

Table 7. Treatment of Manifestations in Individuals with Prader-Willi Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Poor infantile feeding	Special feeding techniques, incl special nipples or gavage feeding by nasogastric tube, are typically necessary for the 1st weeks to months of life to assure adequate nutrition & avoid poor growth.	Persons diagnosed w/PWS typically do not require a gastrostomy tube since feeding will improve w/time.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Hypogonadism	<ul style="list-style-type: none"> Consider hCG treatment in infancy for cryptorchidism. Orchiopexy as needed for cryptorchidism 	
	Individualized treatment by endocrinologist for hormone replacement therapy at puberty & beyond	The possibility of osteoporosis & fertility/ pregnancy are important to consider in the treatment plan.

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Endocrine manifestations	GH treatment: <ul style="list-style-type: none"> • Normalizes height, ↑ lean body mass, ↓ fat mass, & ↑ mobility, which are beneficial to weight mgmt. • Treatment in 1st yr of life assists in developmental milestones. • In young children, dose is similar to that for persons w/isolated GH deficiency (i.e., ~1 mg/m²/day) but GH dose must be individualized as child grows. • The adult dose of GH is 20%-25% of the dose recommended in children. 	<ul style="list-style-type: none"> • Therapy can be started in infancy or at time of diagnosis. • Obtain sleep study before initiation of GH therapy & 4-8 wks after starting GH therapy to ensure that GH treatment has not caused or worsened sleep-disordered breathing.¹ • To avoid overtreatment, monitor growth velocity, head circumference, & serum IGF-1.
	Treatment for precocious puberty, type 2 diabetes, hypothyroidism, &/or central adrenal insufficiency as directed by endocrinology	
Hyperphagia/Obesity	Dietary mgmt: <ul style="list-style-type: none"> • Consultation w/dietician w/close follow up when weight centiles begin ↑ (typically age 18-36 mos) • Well-balanced, low-calorie diet,² regular exercise, & close supervision to minimize food stealing & prevent obesity (maintain BMI z score of <2) • Adequate intake of vitamins & minerals as assessed by dietician; prescription for vitamin/mineral supplementation when indicated, esp for calcium & vitamin D GH therapy (See Endocrine manifestations in this table.)	<ul style="list-style-type: none"> • The same program is appropriate if obesity is present at any time. • Locking the kitchen, refrigerator, &/or cupboards is often needed once the child can open the refrigerator & cupboards. • Gastric bypass is not recommended in PWS, as it does not appear to correct the lack of satiety & will not prevent overeating. In addition, complication rates are high.³
Acute gastrointestinal manifestations	Vomiting &/or loss of appetite may signal a life-threatening illness (gastric inflammation or necrosis) requiring immediate hospitalization &/or surgery.	Use of antidiarrheal medications can lead to severe colonic distention, necrosis, & rupture.
Neurobehavioral manifestations	<ul style="list-style-type: none"> • ABA therapy in childhood helps ameliorate some of the common behavioral issues. • Standard pharmacologic therapy for behavioral issues is helpful in many persons. • Affected persons generally require a sheltered employment environment. 	
Dermatologic manifestations	Consider topiramate (25-50 mg/day) or N-acetylcysteine (450-1,200 mg/day) to ↓ or eliminate skin picking if not managed w/distraction or covering lesions. ⁴	A history of frequent nose bleeds or rectal bleeding should prompt eval for skin sores secondary to picking.
Ophthalmologic manifestations	Treatment of strabismus &/or refractive errors per ophthalmologist	
Sleep issues	<ul style="list-style-type: none"> • Individualized treatment depending on cause, which may incl tonsillectomy & adenoidectomy &/or CPAP or BiPAP, as in general population. • Modafinil can be used to treat excessive daytime sleepiness that is unrelated to degree of sleep apnea. 	

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Skeletal issues	Mgmt of scoliosis & hip dysplasia as in general population	<ul style="list-style-type: none"> • Spinal casting & bracing are typically undertaken early in life, depending on degree of spine curvature. • Nonsurgical treatment for hip dysplasia is usually adequate.
	<ul style="list-style-type: none"> • Calcium & vitamin D supplementation • Low bone density: implementation of sex steroid therapy, GH therapy, or bisphosphonate therapy as clinically indicated 	
Seizures	Standardized treatment w/ASM by experienced neurologist	<ul style="list-style-type: none"> • Many ASMs may be effective; none has been demonstrated effective specifically for PWS. • Education of parents/caregivers ⁵
Decreased saliva production	Manage w/products developed for treatment of dry mouth such as special toothpastes, gels, mouthwash, & gum ⁶	Dental evals & dental hygiene should be considered every 3-4 mos beginning when teeth are present
Family/Community	<ul style="list-style-type: none"> • Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. • Issues of guardianship, wills, trusts, & advocacy should be investigated no later than adolescence. 	<ul style="list-style-type: none"> • Ongoing assessment of need for home nursing • Consider involvement in adaptive sports or Special Olympics. • Support organizations for PWS are very helpful & exist in many countries.

ABA = applied behavioral analysis; ASM = anti-seizure medication; BiPAP = bilevel positive airway pressure; BMI = body mass index; CPAP = continuous positive airway pressure; GH = growth hormone; hGC = human chorionic gonadotropin; IGF-1 = insulin-like growth factor 1; PWS = Prader-Willi syndrome

1. Miller et al [2006b]

2. Caloric needs of infants and children with PWS are typically 60%-80% of the recommended daily allowance. The energy requirement of adults with PWS rarely exceeds 1,200-1,400 kcal/day.

3. Scheimann et al [2012], Gantz et al [2022]

4. Bonnot et al [2016]

5. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see [Epilepsy Foundation Toolbox](#).

6. Ritwik & Vu [2021]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
 - An IEP provides specially designed instruction and related services to children who qualify.
 - IEP services will be reviewed annually to determine whether any changes are needed.
 - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
 - Vision consultants should be a part of the child's IEP team to support access to academic material.
 - Physical and occupational therapy and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
 - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox[®], anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., [augmentative and alternative communication](#) [AAC]) for individuals who have expressive language difficulties. An AAC evaluation

can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat obsessive-compulsive symptoms or psychosis, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Health supervision guidelines from the American Academy of Pediatrics (AAP) have been published [McCandless 2011] ([full text](#)). A multidisciplinary approach to care was recently published based on a survey of a group of experts on PWS and literature review [Duis et al 2019].

Table 8. Recommended Surveillance for Individuals with Prader-Willi Syndrome

System/Concern	Evaluation	Frequency
Developmental delay / Intellectual disability	Monitor developmental progress & educational needs.	At each visit
Cryptorchidism	Monitor testicular position, as cryptorchidism may recur after orchidopexy.	Annually
Endocrine	Glycosylated hemoglobin concentration &/or glucose tolerance test to assess for diabetes	Annually if obese or beginning in adolescence or w/rapid significant weight gain or other symptoms (e.g., polyuria/polydipsia)
	Free T4 & TSH levels to assess for hypothyroidism	Every 6-12 mos beginning in infancy
	Assess for central adrenal insufficiency	As needed based on symptoms & during illness & surgery
Growth/Appetite/Obesity	Monitor height, weight, & BMI ¹	<ul style="list-style-type: none"> • Every month in infancy • Every 6 mos in 1st decade of life • At least annually thereafter • More frequently if caregivers identify rapid weight gain
Behavioral/Psychiatric	Assess for presence of behavioral findings & obsessive-compulsive features w/family or caregivers.	Annually after age 2 yrs
	<ul style="list-style-type: none"> • Assess for psychosis. • Evidence of radical behavior change, hallucinations, delusions, or disorientation should prompt psychiatry eval. 	Annually in adolescents & adults
Dermatologic	Skin exam for sores &/or signs/symptoms of cutaneous infection	At each visit

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
Vision	Ophthalmologic exam to assess for strabismus &/or refractive errors	Annually
Sleep	Assess for snoring, frequent nocturnal awakening, & new behavioral issues w/family or caregivers.	Annually
	Evaluate respiratory status during sleep w/sleep study.	Prior to initiation of GH therapy & 4-8 wks after starting GH therapy, & if clinical symptoms arise thereafter (e.g., snoring, frequent nocturnal awakening, behavioral issues)
	Overnight sleep study followed by multiple sleep latency testing & video EEG	In those w/excessive daytime sleepiness / narcolepsy / cataplexy
Scoliosis	Clinical exam for scoliosis	At each visit beginning when child can sit independently
	Spine x-rays for scoliosis in those w/: <ul style="list-style-type: none"> • Clinical findings suggestive of scoliosis • Obesity 	Annually
Osteoporosis	Bone densitometry by DXA scan	Every 2 yrs beginning in adolescence
Seizures	Assess for new seizures or monitor those w/seizures as clinically indicated.	At each visit
Dental	Dental eval	At least every 6 mos after teeth erupt or every 3-4 mos if dental issues are present
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

BMI = body mass index; DXA = dual-energy x-ray absorptiometry; GH = growth hormone; T4 = thyroxine; TSH = thyroid-stimulating hormone

1. Weight in kg, height in m²

Agents/Circumstances to Avoid

Unsupervised access to food should be avoided, as hyperphagia may result in rapid ingestion and fatal choking, silent aspiration, and exposure to spoiled food.

Emetics are typically ineffective for induction of vomiting after ingestion of uncooked/spoiled food items, with potential toxicity from repeated administration. Instead, a nasogastric tube should be used for gastric decompression.

Antidiarrheal medications can cause severe colonic distention, necrosis, and rupture in individuals with PWS and should be avoided. Abdominal distention, bloating, pain, lethargy, loss of appetite, and/or vomiting may be signs of life-threatening gastric inflammation or necrosis. Individuals with these symptoms should be urgently evaluated by a medical professional and may require hospitalization. Radiographic imaging and possibly emergency surgery may be required.

Sedatives and other medications. People with PWS may have unusual reactions to standard dosages of medications. Use extreme caution in giving medications, especially those that may cause sedation; prolonged and exaggerated responses have been reported. The presence of obesity may also affect appropriate dosing.

Evaluation of Relatives at Risk

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

Pregnancy Management

Pregnancy is rare in women with PWS. Pregnancies in those with PWS require more frequent monitoring, given the high pain threshold observed in individuals with PWS, particularly in those who are obese.

Therapies Under Investigation

To date, the most promising data for treatment of hyperphagia has been reported in trials of **diazoxide choline controlled release (DCCR)**. DCCR is a K-ATP channel agonist, which may exert beneficial effects in individuals with PWS by downregulating insulin secretion from pancreatic beta cells, downregulating neuropeptide Y secretion, and activating K-ATP channels in adipose tissue. DCCR improved hyperphagia questionnaire scores by more than nine points after one year of treatment. Data from an ongoing trial also shows improvements in body composition (improved lean body mass and lean-to-fat mass ratio by DXA scan) as well as improvements in many of the characteristic behavioral issues in PWS (e.g., repetitive questioning, anxiety, compulsive behaviors, skin picking) [Miller et al 2023]. This treatment is currently under review by the FDA.

Some reduction of hyperphagia was also demonstrated with **carbetocin** (a synthetic oxytocin analog). Carbetocin is an oxytocin receptor-specific compound designed to decrease activation of arginine vasopressin. The Phase II trial of this medication demonstrated promising results over a two-week trial, with reductions in hyperphagia questionnaire scores [Dykens et al 2018]. The recently completed Phase III trial of low-dose carbetocin (3.2 mg) showed improved hyperphagia questionnaire scores of 3.1 points, as well as improvements in obsessive-compulsive behaviors and anxiety [Roof et al 2023]. The FDA rejected the new drug application in November 2021 and indicated that further trials are necessary.

Several additional Phase II clinical trials are ongoing for treatment of hyperphagia in individuals with PWS, including investigations of oxytocin, canabadiolvarin, a melanin-concentrating hormone receptor 1 antagonist, a compound that activates bitter taste receptors in the gut, and cannabidiol.

There is an ongoing Phase II clinical trial of pitolisant for treatment of excessive daytime somnolence, as well as narcolepsy/cataplexy.

Transcutaneous vagal nerve stimulation showed significant positive effects on decreasing the frequency and intensity of temper outbursts in a small study in adults with PWS. Larger, placebo-controlled studies are being planned to determine the reproducibility and duration of effects [Manning et al 2019].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions. In addition, see a detailed review by Mahmoud et al [2023] of the clinical trials involving PWS.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Individuals with Prader-Willi syndrome (PWS) typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration. The vast majority of families have a recurrence risk of less than 1%. However, certain etiologies involve a recurrence risk as high as 50%, and a scenario with a risk of almost 100% (i.e., a mother with a 15/15 Robertsonian translocation), though very unlikely, is theoretically possible. Reliable PWS recurrence risk assessment therefore requires identification of the genetic mechanism of PWS in the proband (i.e., a 15q deletion, uniparental disomy [UPD] 15, or an imprinting defect) and the underlying genetic etiology, as well as parental testing to discern the presence of a predisposing genetic alteration (i.e., a parental chromosome rearrangement or paternal heterozygosity for an imprinting center deletion).

Risk to Family Members

Parents of a proband. The parents of the proband are unaffected.

Sibs of a proband

- The risk to sibs of a proband with PWS depends on the underlying genetic mechanism and genetic etiology of PWS in the proband and the genetic status of the parents (see Tables 9 and 10).
- Once a diagnosis of PWS is established in the proband through identification of abnormal DNA methylation at 15q11.2-q13 and an underlying genetic mechanism (15q deletion, maternal UPD 15, or an imprinting defect) has been identified on oligo-SNP combination array (OSA), the genetic etiology should be determined for recurrence risk assessment. Recommended testing to discern genetic etiology in the proband and the genetic status of the parents is summarized in Tables 9 and 10 (see also Figure 1).

Table 9. Risks to Sibs of a Proband with Prader-Willi Syndrome by Genetic Mechanism

Genetic Mechanism	Possible Genetic Etiologies	Proportion of PWS	Recommended Testing to Distinguish Genetic Etiology & Discern Presence of Predisposing Parental Genetic Alteration	Risk to Sibs
15q deletion	<i>De novo</i> deletion	60%-70%	<ul style="list-style-type: none"> • Proband: karyotype & FISH ¹ • Father: karyotype & FISH (to identify cryptic translocation or paracentric inversion of 15q11.2) 	<1% ²
	Deletion resulting from unbalanced chromosome rearrangement	<1%		Up to 25%
UPD 15	<i>De novo</i> UPD 15	~30%-40%	Proband: karyotype	<1%
	UPD 15 w/predisposing chromosomal abnormality (e.g., paternal 15/15 Robertsonian translocation, marker chromosome)	<1%	<ul style="list-style-type: none"> • If proband has normal karyotype, then karyotype in father ³ • If proband has marker chromosome, then karyotype in both parents • If proband has 15/15 Robertsonian translocation, then karyotype in mother 	<1% to 100% ⁴
Imprinting center (IC) deletion	<i>De novo</i>	<0.5%	<ul style="list-style-type: none"> • Proband: no additional testing • Father: DNA methylation & OSA or MS-MLPA. 	<1% ²
	IC deletion inherited from father	<0.5% ⁵		50%

Table 9. continued from previous page.

Genetic Mechanism	Possible Genetic Etiologies	Proportion of PWS	Recommended Testing to Distinguish Genetic Etiology & Discern Presence of Predisposing Parental Genetic Alternation	Risk to Sibs
Imprinting defect by epimutation	<i>De novo</i>	2%-4%	No additional testing	<1%

MS-MLPA = methylation-specific multiplex ligation-dependent probe amplification; OSA = oligo-small nucleotide polymorphism (SNP) combination array; PWS = Prader-Willi syndrome; UPD = uniparental disomy

1. Oligo-SNP combination array (OSA) does not detect translocations & inversions involving proximal 15q.
2. Germline mosaicism in the father is rare but has been observed in cases of 15q11.2 deletions [Kokkonen & Leisti 2000, Fernández-Novoa et al 2001] and IC deletions [Buiting et al 2003; Wey et al 2005; D Driscoll, personal observation].
3. If the father has a 15/15 Robertsonian translocation, aberrant segregation at meiosis I could result in a nullisomic sperm; this, combined with monosomy rescue to disomy, would result in an embryo with maternal isodisomic UPD 15.
4. Empiric data suggest that the risk for recurrence in most of these cases would also be less than 1%, although the theoretic risk would be much higher.
5. Half of imprinting center (IC) deletions are inherited from the father; the other half are *de novo*.

Table 10. Risks to Sibs of a Proband with Prader-Willi Syndrome by Genetic Mechanism and Genetic Etiology

Genetic Mechanism	Recommended Testing to Distinguish Genetic Etiology & Discern Presence of Predisposing Parental Genetic Alternation	Genetic Etiology	Proportion of PWS	Risk to Sibs
15q deletion	<ul style="list-style-type: none"> • Proband: karyotype & FISH ¹ • Father: karyotype & FISH (to identify cryptic translocation or paracentric inversion of 15q11.2) 	<i>De novo</i> deletion	60%-70%	<1% ²
		Deletion resulting from unbalanced chromosome rearrangement	<1%	Up to 25%
UPD 15	Proband: karyotype <ul style="list-style-type: none"> • If proband has normal karyotype, then karyotype in father ³ • If proband has marker chromosome, then karyotype in both parents • If proband has 15/15 Robertsonian translocation, then karyotype in mother 	<i>De novo</i> UPD 15	~30%-40%	<1%
		UPD 15 w/predisposing chromosomal abnormality (e.g., paternal 15/15 Robertsonian translocation, marker chromosome)	<1%	<1% to 100% ⁴
Imprinting center (IC) deletion	<ul style="list-style-type: none"> • Proband: no additional testing • Father: DNA methylation & OSA (or MS-MLPA) 	<i>De novo</i>	<0.5%	<1% ²
		IC deletion inherited from father	<0.5% ⁵	50%

Table 10. continued from previous page.

Genetic Mechanism	Recommended Testing to Distinguish Genetic Etiology & Discern Presence of Predisposing Parental Genetic Alternation	Genetic Etiology	Proportion of PWS	Risk to Sibs
Imprinting defect by epimutation	No additional testing	<i>De novo</i>	~2%-4%	<1%

MS-MLPA = methylation-specific multiplex ligation-dependent probe amplification; OSA = oligo-small nucleotide polymorphism (SNP) combination array; PWS = Prader-Willi syndrome; UPD = uniparental disomy

1. Oligo-SNP combination array (OSA) does not detect translocations & inversions involving proximal 15q.
2. Germline mosaicism in the father is rare but has been observed in cases of 15q11.2 deletions [Kokkonen & Leisti 2000, Fernández-Novoa et al 2001] and imprinting center (IC) deletions [Buiting et al 2003; Wey et al 2005; D Driscoll, personal observation].
3. If the father has a 15/15 Robertsonian translocation, aberrant segregation at meiosis I could result in a nullisomic sperm; this, combined with monosomy rescue to disomy, would result in an embryo with maternal isodisomic UPD 15.
4. Empiric data suggest that the risk for recurrence in most of these cases would also be less than 1%, although the theoretic risk would be much higher.
5. Half of IC deletions are inherited from the father; the other half are *de novo*.

Offspring of a proband

- With rare exceptions in females, individuals with PWS do not reproduce. No male with genetically confirmed PWS has ever been reported to have reproduced.
- The risk to offspring should be determined in the context of formal genetic counseling.

Other family members

- If a chromosome rearrangement (e.g., translocation or inversion) is identified in the proband and a parent, the sibs of the carrier parent should be offered genetic counseling and the option of genetic testing.
- If a proband's father is heterozygous for an imprinting center deletion, the father's sibs are also at risk of having the imprinting center deletion.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to the parents of affected individuals.

Prenatal Testing

Families who have a child with PWS. Once the causative genetic mechanism has been identified in the proband, prenatal testing for PWS is possible [Butler 2017]. The approach to prenatal testing depends on the molecular mechanism identified in the proband; prenatal detection of all three molecular classes of PWS are possible. Note that DNA methylation analysis at the 5' *SNRPN* locus is the most reliable method to identify imprinting defects in prenatal tissue [Glenn et al 2000, Beygo et al 2019].

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

- If a 15q11.2 deletion is suspected on cytogenetic studies from testing of cells obtained by chorionic villus sampling (CVS) or amniocentesis, OSA 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 [Angelman syndrome](#)) or paternally derived (fetus has PWS).

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

Noninvasive prenatal tests (NIPT) using fetal cell-free DNA is available for testing for deletions of 15q11.2 but has a high false positive rate (unlike testing for the major trisomy conditions [13, 18, and 21], which has high sensitivity and specificity). Also, NIPT will not distinguish an AS deletion from a PWS deletion and will not detect UPD and imprinting defects.

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

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

- **International Prader-Willi Syndrome Organisation (IPWSO)**
Salisbury House
Station Road
United Kingdom
Email: info@ipwso.org
www.ipwso.org
- **International Prader-Willi Syndrome Organisation: Members Around the World**
Our members are constituted PWS Associations representing families around the world.
[PWS Associations](#)
- **Medical Home Portal**
[Prader-Willi Syndrome](#)
- **Prader-Willi Syndrome Association USA**
Phone: 941-312-0400
www.pwsausa.org
- **Foundation for Prader-Willi Research**
Phone: 888-322-5487
Email: info@fpwr.org
www.fpwr.org

- **Prader-Willi Syndrome Association UK**

United Kingdom

Phone: +44 (0)1332 365676

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pwsa.co.uk

Molecular Genetics

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

Table A. Prader-Willi Syndrome: Genes and Databases

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

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

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

137142	GAMMA-AMINOBUTYRIC ACID RECEPTOR, ALPHA-5; GABRA5
137192	GAMMA-AMINOBUTYRIC ACID RECEPTOR, BETA-3; GABRB3
176270	PRADER-WILLI SYNDROME; PWS
182279	SMALL NUCLEAR RIBONUCLEOPROTEIN POLYPEPTIDE N; SNRPN
600161	PRADER-WILLI/ANGELMAN REGION RNA 1; PWAR1
600233	GAMMA-AMINOBUTYRIC ACID RECEPTOR, GAMMA-3; GABRG3
601491	IMPRINTED IN PRADER-WILLI SYNDROME; IPW
601623	UBIQUITIN-PROTEIN LIGASE E3A; UBE3A
602117	NECDIN; NDN
603856	MAKORIN 3; MKRN3
603857	MKRN3 ANTISENSE RNA; MKRN3AS
605283	MAGE-LIKE 2; MAGEL2
605436	SMALL NUCLEOLAR RNA, C/D BOX, 116-1; SNORD116-1
605837	HECT DOMAIN AND RCC1-LIKE DOMAIN 2; HERC2
605855	ATPase, PHOSPHOLIPID-TRANSPORTING, 10A; ATP10A
609837	SMALL NUCLEOLAR RNA, C/D BOX, 115-1; SNORD115-1
610922	NUCLEAR PORE ASSOCIATED PROTEIN 1; NPAP1
611215	PRADER-WILLI REGION NONCODING RNA 1; PWRN1
611409	OCA2 MELANOSOMAL TRANSMEMBRANE PROTEIN; OCA2

Molecular Pathogenesis

The Prader-Willi syndrome (PWS) critical region (PWCR) is localized to a 5- to 6-Mb genomic region on the proximal long arm of chromosome 15 (15q11.2-q13) (see Figure 2). It lies within a smaller 2.5-Mb differentially

imprinted region. PWS is a contiguous gene disorder; studies thus far indicate that the complete phenotype is due to the loss of expression of several genes [Cassidy et al 2012]. However, it has been shown that the loss of expression of the *SNORD116* gene cluster plays a major role in the phenotype [Tan et al 2020]. PWS is also an imprinted condition, since the expression of relevant genes in the 15q11.2-q13 region is dependent on parental origin [Cassidy et al 2012].

The genomic and epigenetic changes causing PWS all lead to a loss of expression of the normally paternally expressed genes on chromosome 15q11.2-q13. Absence of the paternally inherited copy of these genes, or failure to express them, causes total absence of expression for those genes in the affected individual because the maternal contribution for these genes has been programmed by epigenetic factors to be silenced [Cassidy & Driscoll 2009, Cassidy et al 2012].

Deletion mechanism. An interstitial 15q11.2-q13 microdeletion on the paternal allele accounts for 60%-70% of individuals with PWS. The vast majority of deletions have one of two common proximal breakpoints (BP1 or BP2) and a common distal breakpoint (BP3) resulting in a 5- to 6-Mb deletion (see Figure 2). Multiple tandem repeats flank the common breakpoints (BP1, BP2, and BP3). These low copy 250- to 400-kb repeat sequences are subject to nonhomologous pairing during meiosis, leading to deletions (causing PWS or [Angelman syndrome](#) [AS] depending on parental origin), duplications (both maternal and paternal), triplications, and inverted duplication of chromosome 15. About 8% of individuals with PWS have unique or atypical-sized deletions caused by a variety of etiologies, including unbalanced translocations [Kim et al 2012, Butler et al 2019a]. Atypical deletions may result in clinical features that are milder or more severe than typical individuals with PWS.

Imprinting center deletion. Small deletions of the promoter region and the proximal upstream region of *SNRPN* (including the putative imprinting control element) have been identified in individuals with PWS who have maternal-specific DNA methylation patterns but do not have a 15q11.2-q13 deletion or maternal uniparental disomy (UPD).

Other individuals have biparental inheritance but maternal-only DNA methylation patterns in this region without detectable abnormalities in the imprinting center. These individuals are considered to have an imprinting defect by an epimutation.

Genes of interest in this region. The following genes have been mapped within the PWS/AS critical region (see Figure 2):

- *ATP10A* was originally thought to have preferential maternal expression, but subsequent publications in mice [DuBose et al 2010] and humans [Hogart et al 2008] have cast doubt on this gene being imprinted. Rather, it may have random monoallelic expression [Hogart et al 2008].
- *GABRB3*, *GABRA5*, and *GABRG3* are all GABA receptor subunit genes involved in neurotransmission within the brain.
- *HERC2* shuttles between the nucleus and cytoplasm and functions as an E3 ubiquitin ligase for the ubiquitination and degradation of target proteins, as an activator of other E3 ubiquitin ligases, and as an adaptor for assembly of DNA damage response proteins. The *OCA2-HERC2* locus is responsible for the greatest proportion of eye color variation in humans [Suarez et al 2021]. This probably explains why individuals with PWS who have a deletion that encompasses this region are generally hypopigmented compared to their family members.
- *IPW* is a long noncoding RNA located between *SNORD116-1* and *SNORD115-1*. It has been shown to be a regulator of the *DLK1-DIO3* imprinted region on chromosome 14, and it may be involved in regulating other non-chromosome 15 imprinted regions in the genome [Stelzer et al 2014]. Its role in PWS is unclear, but interestingly this locus is included in all seven individuals with a *SNORD116* deletion who have many of the major features of PWS [Tan et al 2020].

- *MAGEL2* is transcribed only by the paternal allele and expressed predominantly in the brain. Individuals with loss-of-function variants in the paternal allele of *MAGEL2* have [Schaaf-Yang syndrome](#), a disorder with features that overlap with PWS.
- *MKRN3* encodes a zinc finger protein expressed only from the paternal chromosome. Paternally inherited loss-of-function variants in *MKRN3* are a cause of familial central precocious puberty in humans [Abreu et al 2013, Macedo et al 2014].
- *NDN* is only paternally expressed and encodes a DNA-binding protein that acts as an antiapoptotic or survival factor in the early development of the nervous system [Andrieu et al 2006]. It may play a role in gonadotropin-releasing hormone neurons [Chung et al 2020].
- *NPAP1* is an intronless gene that is biallelically expressed in adult testes but monoallelically expressed in the fetal brain.
- *OCA2* encodes a melanosomal protein, and pathogenic variants in this gene cause oculocutaneous albinism type 2; its deletion is associated with the hypopigmentation frequently seen in individuals with PWS.
- *PWRN1*, expressed in testes, demonstrates lower expression in the prostate, heart, kidneys, liver, lungs, skeletal muscles, trachea, spinal cord, and fetal brain; it is shown to have monoallelic expression in the fetal brain.
- *SNORD115* (**snoRNA HBII-52**) is a cluster of C/D small nucleolar RNAs (snoRNAs) and consists of approximately 47 copies. It is almost exclusively expressed in neurons and only from the paternal contribution. It has been proposed that *SNORD115* promotes the generation of the serotonin 2c receptor. However, there are some rare individuals with PWS whose deletion does not include this locus. Thus, it is not a major contributor to the PWS phenotype, but its absence may contribute to some of the behavioral features of PWS [Chung et al 2020].
- *SNORD116* (**snoRNA HBII-85**). Evidence suggests that the snoRNA *SNORD116* cluster, which consists of approximately 24 gene copies, is causative of many of the major features of PWS. There have been a few rare individuals with a *SNORD116* deletion described in the literature who have many of the major features of PWS [Tan et al 2020]. The snoRNAs are probably involved in the modification of mRNA by alternative splicing, and each snoRNA gene may have multiple targets; however, no definitive targets have yet been found for *SNORD116*.
- *SNURF-SNRPN* (typically abbreviated as just *SNRPN*) is a complex bicistronic gene encoding two different proteins. Exons 4-10 were described first and encode the protein SmN, which is a spliceosomal protein involved in mRNA splicing. *SNURF* is encoded by exons 1-3 and produces a polypeptide of unknown function. It also serves as the host for the seven snoRNA genes located telomerically, which are regulated by the expression of *SNURF-SNRPN* [Chung et al 2020].
- *UBE3A* is an E3 ubiquitin ligase involved in protein degradation in the brain and is associated with AS.

Imprinted genes in the region. A number of the genes in the PWCR (*MKRN3*, *MAGEL2*, *NDN*, *NPAP1*, *PWRN1*, *SNORD116*, *IPW*, *SNORD115*, *SNURF-SNRPN*) are subject to genomic imprinting, thus accounting for the fact that the PWS phenotype results only when the paternally contributed PWCR is absent. DNA methylation, which is involved in the process of genomic imprinting, has been demonstrated for several of the genes identified within the PWCR [Cassidy et al 2012, Beygo et al 2019, Chung et al 2020]. Upstream of *SNRPN*, very small deletions of the putative imprinting control element for the PWCR have been identified in a few individuals with PWS who have maternal-specific DNA methylation patterns but have neither the usual large paternally derived deletion of the PWS/AS critical region nor maternal UPD [Cassidy et al 2012, Beygo et al 2019]. Other individuals demonstrate sporadic imprinting defects that are epimutations [Beygo et al 2019].

Chapter Notes

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Dr Driscoll is board certified in Pediatrics, Clinical Genetics, and Clinical Cytogenetics. He has been conducting clinical and laboratory research on Prader-Willi syndrome (PWS) since the late 1980s. He has been a major contributor to the understanding of the genetics of PWS and genomic imprinting in the PWS critical region, as well as to the elucidation of the natural history of PWS. His group first developed the technique (DNA methylation analysis) that is used around the world to diagnose PWS and also elucidated the nutritional phases of PWS that has gained wide acceptance by PWS experts.

Dr Driscoll is widely published on PWS and a major spokesperson on PWS in the US and internationally. He has had an active PWS clinic for the last 32 years and was the principal investigator for the PWS component of the NIH-funded 12-year national Rare Disease Center grant on the natural history of PWS. He served on the Prader-Willi Syndrome Association | USA (PWSA | USA) Board of Directors for 21 years and as Chair of the Clinical Advisory Board for PWSA | USA for 23 years. He is currently the Chair of the Clinical and Scientific Advisory Board for the International Prader-Willi Syndrome Organization (IPWSO).

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