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# Prader–Willi syndrome

**Prader–Willi syndrome (PWS) is a highly variable genetic disorder affecting multiple body systems whose most consistent major manifestations include hypotonia with poor suck and poor weight gain in infancy; mild mental retardation, hypogonadism, growth hormone insufficiency causing short stature for the family, early childhood-onset hyperphagia and obesity, characteristic appearance, and behavioral and sometimes psychiatric disturbance. Many more minor characteristics can be helpful in diagnosis and important in management. PWS is an example of a genetic condition involving genomic imprinting. It can occur by three main mechanisms, which lead to absence of expression of paternally inherited genes in the 15q11.2–q13 region: paternal microdeletion, maternal uniparental disomy, and imprinting defect.**

**In brief**

- PWS is a common and complex disorder affecting multiple systems
- Early diagnosis is important to effective long-term management
- Hypotonia, beginning prenatally, causes poor feeding and development in the perinatal period and infancy
- If untreated obesity typically begins after 1–2 years of age and is later exacerbated by hyperphagia with lack of satiety
- The major cause of morbidity and mortality is morbid obesity
- Obesity can be controlled externally by diet restrictions and behavior modification
- Parental education about appropriate parenting techniques (structure and consistency) for the behavioral and eating issues of PWS correlates with prognosis
- Growth hormone treatment improves growth, physical phenotype and body composition
- Clinical diagnostic criteria have been developed, but must be confirmed with genetic testing because of clinically overlapping disorders, particularly as an infant
- Over 99% can be diagnosed with a simple molecular test, DNA methylation analysis
- Three major genetic causes exist: 5–7 Mb deletion of the paternally inherited chromosomal 15q11.2–q13 region, maternal uniparental disomy 15, and a defect in the imprinting process in the 15q11.2–q13 region on the paternally inherited chromosome. Occasionally, deletion results from chromosomal translocation
- A number of imprinted genes have been mapped to the PWS region of 15q11.2–q13, but their role in most aspects of the phenotype is not well understood.

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## Introduction

Prader–Willi syndrome (PWS; OMIM 176270) is a relatively common (prevalence 1/15 000–1/30 000) generally sporadic disorder with a recognizable pattern of dysmorphic features and major neurologic, cognitive, endocrine and behavioral/psychiatric disturbances. PWS was the first recognized human disorder related to genomic imprinting and the first shown to be caused by uniparental disomy. It results from failure of expression of paternally inherited genes in the PWS region of chromosome 15. Major characteristics include infantile lethargy and hypotonia causing poor feeding and failure to thrive, developmental and intellectual disability, hypogonadism (small external genitalia and pubertal insufficiency), hyperphagia leading to morbid obesity if uncontrolled, short stature, characteristic facial appearance and body habitus, and a typical behavioral phenotype that includes temper tantrums and compulsive traits. Management is

symptomatic and supportive, emphasizing control of food intake, hormone replacement therapies, special education and sheltered employment, and behavior management.

## Clinical overview

### Hypotonia and abnormal neurologic function

Hypotonia is prenatal in onset, and is usually manifested as decreased fetal movement, abnormal fetal position at delivery, and increased need for assisted delivery or cesarean section. In infancy (Figure 1), there is decreased movement and lethargy with decreased spontaneous arousal, weak cry, and poor reflexes, including a poor suck that leads to early feeding difficulties and poor weight gain. Deep tendon reflexes are often spared. Assisted feeding through a feeding tube and/or special nipples with increased feeding times are invariably necessary. The hypotonia is central in origin. Mild-to-moderate hypotonia persists throughout life. Hypotonia is so characteristic that all newborns with unexplained persistent hypotonia should be tested for PWS.[1,2]

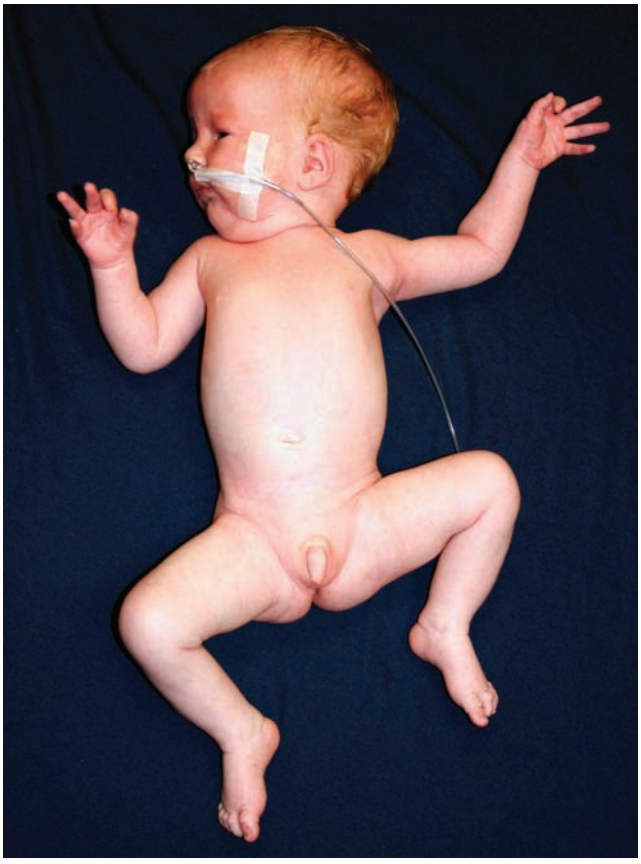

**Figure 1** Hypotonia of infancy in a one-month-old male with PWS. Note frogleg position and need for a feeding tube. Also note dolichocephaly and hypoplastic, empty scrotum.

### Hypogonadism

In both sexes, hypogonadism manifests as genital hypoplasia throughout life, incomplete pubertal development, and infertility in the vast majority.[3] In males, the penis may be small, but most characteristic is a hypoplastic scrotum that is small, poorly rugated, and poorly pigmented (Figure 1). Unilateral or bilateral cryptorchidism is present in 80–90%. In females, the labia (majora and minora) and clitoris are generally hypoplastic. Precocious adrenarche occurs in both sexes in up to about 20%. Delayed and incomplete pubertal development is characteristic. Menarche may occur as late as the 30 s, and usually there is amenorrhea or oligomenorrhea. In males, there is poor voice change and scanty beard and body hair. In both sexes, little or nothing is known about sexual activity, which is believed to be deficient, and most affected individuals are presumed to be infertile. Although very rare, several instances of reproduction have been reported, all in females. The hypogonadism is of hypothalamic origin, and generally there is hypogonadotropism with decreased testosterone or estrogen and decreased FSH and LH in both sexes.

### Developmental and cognitive delays

Gross motor and language milestones are delayed. Early milestones are reached on average at double the normal age (eg, sitting at 12 months, walking at 24 months, and words at 2 years). Cognitive disability is evident by school age. Most people with PWS are mildly mentally retarded (mean IQ: 60–70 s), with approximately 40% having borderline mental retardation or low-normal intelligence and approximately 20% having moderate retardation.[4–6] Regardless of measured IQ, most people with PWS have multiple severe learning disabilities and poor academic performance for their mental abilities. Articulation is poor.[7] Most adults require sheltered residential and employment settings because of a combination of cognitive, behavioral and food-seeking characteristics.

### Hyperphagia and obesity

Obesity typically begins between 1–4 years. In later childhood a seemingly insatiable appetite (hyperphagia) begins. The hyperphagia is hypothalamic in origin, resulting in lack of sense of satiety.[8–11] Food seeking is common (hording, foraging for food, eating of unappealing food items, and stealing of food or money to buy food). If intake is not controlled externally, central obesity results from these behaviors combined with a low metabolic rate and decreased activity level (that result in a decreased total caloric requirement) (Figure 2). Complications of obesity are the major causes of morbidity and mortality: cardiorespiratory insufficiency, obstructive sleep apnea, thrombophlebitis, and chronic leg edema. Up to 25% of obese adults have type II diabetes mellitus (NIDDM),[12] with mean age of onset of 20 years.

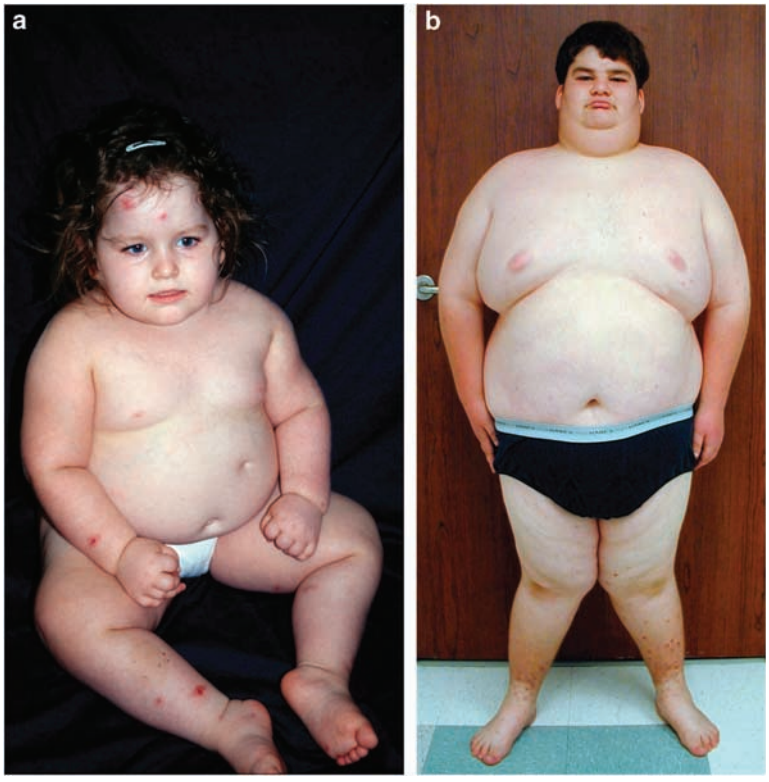


**Figure 2** Central obesity of PWS in (**a**) a 2 $\frac{1}{2}$ year old girl and (**b**) a 21-year-old male. Note also typical facial appearance, active skin picking lesions and gastrostomy feeding tube scar in the girl, pseudogynecomastia and genus valgus in the male.

### Short stature

Short stature is almost always present by the second decade in the absence of growth hormone replacement, and a deficient pubertal growth spurt results in an average adult height of 155 cm for males and 148 cm for females.[13] Data from multiple studies involving over 400 children and adults with PWS document reduced growth hormone secretion (see also Management section).

### Behavioral and psychiatric disturbances

A characteristic behavioral pattern begins in early childhood in 70–90% of affected individuals. It is typified by temper tantrums, stubbornness, controlling and manipulative behavior, compulsive-like behaviors (repeated organizing, writing, collecting, need to finish one thing before moving to the next), and difficulty with change in routine.[4,14–17] Many of the behavioral characteristics are suggestive of autism spectrum disorder, which has been diagnosed in up to 25% of the individuals.[18] Attention deficit/hyperactivity symptoms and insistence on sameness are common and of early onset.[19] The severity of behavioral problems increases with age and body mass index,[20] and then diminishes in older adults.[21] Psychosis is evident by young adulthood in at least 5–10% of the individuals.[17,22,23]

### Other characteristics

A number of less consistent features are nonetheless common and/or characteristic, and may be important for diagnosis or management (Figures 2–3; Table 1)

### Sleep abnormalities

Individuals with PWS have sleep-disordered breathing, including central and obstructive sleep apnea, abnormal arousal, abnormal circadian rhythm in REM sleep, reduced REM latency, and abnormal response to hypercapnia[26,27] as well as excessive daytime sleepiness. Obesity can worsen the sleep disorder.

### Mortality

Several reports of deaths in PWS[28,29] and surveys within large cohorts[30,31] found that obesity-related cardiovascular and respiratory disorders were the most frequent causes of death in both children and adults. Based on a population study, the death rate has been estimated at 3% per year.[12] Another large study suggested a 6-fold relative risk of death in PWS *versus* other developmentally disabled individuals.[30] Specific concerns have been raised about eating-related fatalities, including choking on gorged food[32] and gastric necrosis and rupture following binging, particularly in slim but previously obese individuals.[33] Recently, it was found that central adrenal insufficiency (CAI) was present

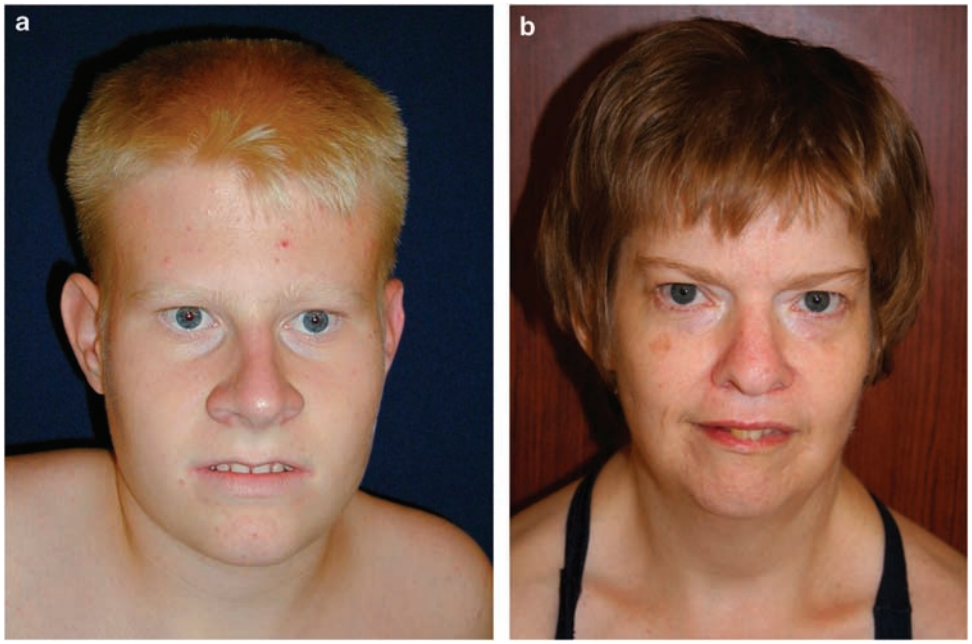


**Figure 3** Classical facial phenotype of PWS in adolescence and adulthood. (**a**) A 15-year-old male. (**b**) A 41-year-old female. Note narrow bifrontal diameter, almond-shaped and slightly upslanting eyes, narrow nasal bridge, and thin upper lip.

**Table 1** Other characteristic findings of PWS

| *Finding* | *Description* | *Frequency* |
|---|---|---|
| Dysmorphic features | Narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, and thin upper lip with downturned mouth (Figure 2 and 3) evolve over time | Very common with deletion, less common with UPD |
| Hypopigmentation | Fair hair, eyes and skin for the family | Very common with deletion, less common with UPD |
| Small hands and feet | Short total hand, narrow palm with hypoplastic hypothenar bulge, short feet with short toes. Present by 10 years of age, unless growth hormone treated. | Very common |
| Strabismus | | Common |
| Visual acuity deficit | Myopia or hyperopia | Common |
| Scoliosis | Can occur at any age, beginning in infancy. May require surgery | Common |
| Hip dysplasia[24] | May be undetected because of hypotonia | ~10% |
| Osteopenia/osteoporosis | May cause increased fracture rate | Common in adults |
| Seizures | Usually easily controlled | <10% |
| Decreased saliva volume[25] | Leads to dry mouth, thick and viscous saliva, dental caries, and possibly contributes to articulation problems | Very common |
| High pain threshold | May lead to decreased recognition of severe injury or illness | Very common |
| High vomiting threshold | Some never vomit. Vomiting often reflects very serious illness | Very common |
| Skin picking | May lead to infection, chronic open wounds, and scarring | Common |
| Easy bruising | No known cause | Common |
| Altered temperature perception and regulation | Altered perception of ambient temperature; occasionally infantile hypothermia, fevers of unknown origin | Common |

in 60% of tested individuals with PWS and the authors suggest that CAI during times of stress could explain many of the sudden and unexplained deaths in PWS.[34]

## Diagnostic approaches

### Clinical diagnosis

Although consensus clinical diagnostic criteria have been published[35] and validated, they were published before comprehensive laboratory testing for PWS was available. Diagnosis should not rest on clinical grounds alone. Revised criteria, designed to trigger diagnostic testing, were published based on the frequency of criteria in molecularly proven individuals[2] (Table 2).

### Diagnostic testing

Although the DNA sequence of imprinted maternally and paternally inherited alleles is the same, multiple epigenetic factors (such as DNA methylation) ultimately will

**Table 2** Findings that should prompt diagnostic testing for PWS (modified from Gunay-Aygun *et al* 2001[2])

| *Age range* | *Sufficient indications for PWS diagnostic testing* |
|---|---|
| Birth to 2 years | Hypotonia with poor suck in the neonatal period |
| 2–6 years | Hypotonia with history of poor suck and global developmental delay |
| 6–12 years | History of hypotonia with poor suck (hypotonia often persists) and global developmental delay and excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled |
| 12 years through adulthood | Cognitive impairment, usually mild mental retardation, and excessive eating with central obesity if uncontrolled, and hypothalamic hypogonadism and/or typical behavior problems (including temper tantrums and compulsive features) |

Within each age period, the presence of all listed findings should prompt diagnostic laboratory testing.

determine if the allele is expressed or repressed. The differential DNA methylation of certain maternal and paternal alleles in the 15q11.2–q13 region provides a tool for assessing paternal-only, maternal-only and normal (biparental) inheritance.

DNA methylation analysis is the only technique that will diagnose PWS correctly in all three molecular classes[36] as well as differentiate PWS from the clinically distinct Angelman syndrome in deletion cases.[37] It is frequently the first genetic test used for PWS. The most robust and most widely used DNA methylation test targets the 5′ end of the *SNURF-SNRPN* (typically referred to as *SNRPN*) locus.[36,38] The promoter region of *SNRPN* is unmethylated on the paternally expressed allele and methylated on the maternally repressed allele. Normal individuals have both a methylated and an unmethylated allele, whereas individuals with PWS have only the maternally methylated allele.

DNA methylation cannot distinguish the molecular class (Figure 4). Deletion of the paternally contributed 15q11.2–q13[39,40] occurs in about 70% and is diagnosed typically using the *SNRPN* fluorescence *in situ* hybridization (FISH) probe.[41] Chromosome analysis should be included in testing for a deletion, as occasionally the deletion is a result of a chromosomal translocation. Maternal uniparental disomy (UPD) 15[42] (ie, two chromosomes 15 from the mother and none from the father) occurs in about 20–30% of individuals. This class is diagnosed using DNA polymorphism analysis on the proband's and parents' DNA. The third molecular class is the imprinting defects. These disrupt the imprinting process on the paternally inherited chromosome 15. They account for about 2–5% of individuals. Most imprinting defects are epigenetic (epimutations) and demonstrate a maternal-only DNA methylation pattern despite the presence of both the parental alleles (biparental). DNA sequence changes are not found in these epimutations and they are thought to be random stochastic errors occurring in spermatogenesis of the fathers.[43] By contrast, about 15% of individuals with an imprinting defect are found to have a very small deletion in the PWS imprinting center region located at the 5′ end of the *SNRPN* gene. Tests for the specific mechanism causing PWS are useful for genetic counselling purposes (see Genetic counselling section).

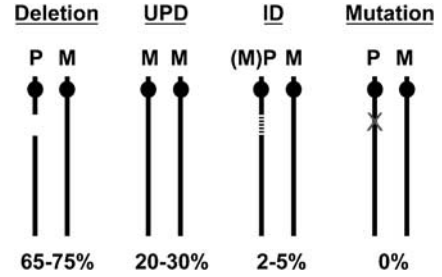


**Figure 4** Molecular classes of PWS and their frequencies. Deletion 15q11.2–q13, maternal uniparental disomy (UPD), imprinting defect (ID) and single gene mutation. The parent of origin of each chromosome is indicated with M (maternal) or P (paternal). Note that there is biparental contribution of the two chromosomes 15 in the case of ID, but the paternal (P) contribution in 15q11.2–q13 has maternal (M) epigenetic markings (eg, DNA methylation) and behaves accordingly.

### Differential diagnosis

Several disorders that can strongly resemble PWS should be considered during the diagnostic process. Infantile hypotonia has a very long list of causes, central and peripheral, syndromic and isolated. Angelman syndrome (AS) must be considered if the diagnosis was made in an infant by FISH, because AS also presents with hypotonia and feeding difficulties. AS is also frequently caused by a 15q11.2–q13 deletion (70%), but on the maternal 15. Therefore all infants less than 2 years of age with a deletion should have DNA methylation testing to distinguish AS and PWS. A subset of individuals with Fragile X syndrome can become hyperphagic and obese. A number of other conditions associate obesity and developmental disability, including UPD 14, Cohen syndrome, Bardet–Biedl syndrome, Alstrom syndrome, duplications of 3p25.3–p26.2 and of Xq27.2-ter and deletions 1p36, 6q16.2, and 10q26.

## Molecular and genetic basis of the disease

### A genomic, imprinted, contiguous gene disorder

PWS is an example of a 'genomic disorder', as it results from altered genomic structure (an epigenetic phenomenon) and not a specific DNA sequence change. The various genomic changes causing PWS all lead to loss of expression of the paternally expressed genes on

chromosome 15q11.2–q13 through loss or failure of expression because the maternal contribution has been programmed by epigenetic factors (eg, DNA methylation) to be silenced.[41]

### The structure of the PWS region

Most cases of PWS result from a deletion of 5–7 Mb in 15q11.2–q13. This region is highly complex and contains a number of imprinted and non-imprinted genes (Figure 5). The vast majority of individuals with deletions have one of two common proximal breakpoints (BP1 and BP2) and a common distal breakpoint (BP3).[44–47] This is on account of the presence of low copy repeat sequences flanking the deleted region,[45] which may result in aberrant recombination of the segment during meiosis.

### The genes related to PWS

The 15q11.2–q13 region can be roughly divided into four distinct regions (Figure 5): (1) a proximal non-imprinted region between BP1 and BP2 containing four biparentally expressed genes; (2) a 'PWS paternal-only expressed region' containing five protein coding genes (*MKRN3, MAGEL2, NECDIN*, and the bicistronic *SNURF-SNRPN*), a cluster of five repetitious snoRNA genes (*HBII-436, HBII-13, HBII-438, HBII-85* and *HBII-52*) and several antisense transcripts (including the antisense transcript to *UBE3A*); (3) an 'AS region' containing the preferentially maternally expressed genes *UBE3A* and *ATP10A* and (4) a distal non-imprinted region containing a cluster of three GABA receptor genes, the gene for oculocutaneous albinism type 2 (*OCA2*) and the *HERC2* gene. The exact function of each of these genes in the PWS phenotype is still being elucidated. The various created gene knock out mouse models will be useful in uncovering these contributions. Although no single gene alteration has been found that explains all the features of PWS, several unique translocation and deletion patients have narrowed a 'key' region to explain much of the PWS phenotype to the *HBII-85* snoRNA gene (reviewed in Sahoo *et al*).[48]

### Genotype–phenotype correlations

Individuals with UPD are less likely to have the hypopigmentation,[49] typical facial appearance,[50,51] or skill with jigsaw puzzles;[52] they also have a somewhat higher verbal IQ and milder behavioral problems.[53,54] However, psychosis[55] and autism spectrum disorders[56,57] occur with significantly greater frequency among those with uniparental disomy. A recent report suggests that individuals with type 1 deletions (BP1 to BP3) had more compulsions and poorer adaptive behavior, intellectual ability, and academic achievement than those with type 2 deletions (BP2 to BP3).[46] However, two other studies found much more subtle differences.[58,59]

## Management

Management of PWS is focused on anticipatory guidance and addressing the consequences of the syndrome, and is very age-dependent. Detailed discussions can be found elsewhere.[60,61] Early diagnosis, preferably in the nursery, offers the opportunity to greatly improve health and quality of life in people with PWS and their families.

## Initial evaluation

Please see Table 3 for recommended evaluations at the time of initial diagnosis. Genetic counselling should also take place at the time of diagnosis, as should referral to support organizations.

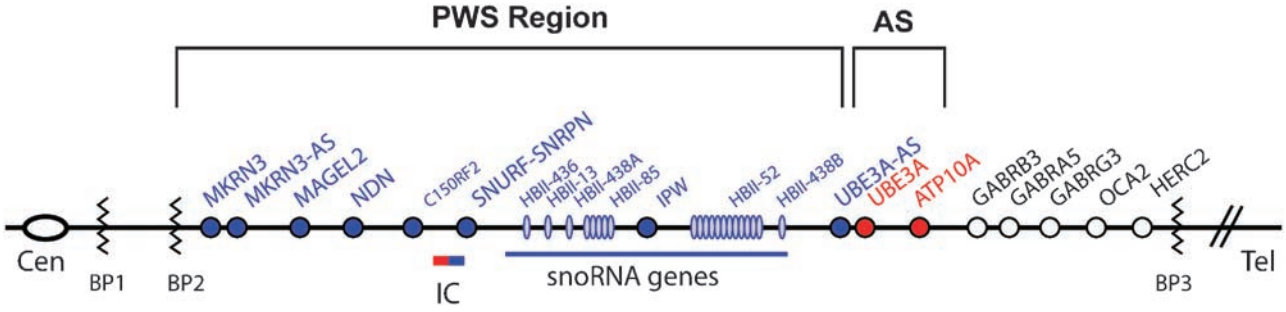


**Figure 5** Summary of the genetic and expression map of chromosomal region 15q11.2–q13. The position of genes and genetic markers (circles) are shown. In the PWS region (shown in blue), there are six paternal-only (PWS region) expressed unique copy genes (*MKRN3, MAGEL2, NECDIN, C15ORF2* and *SNURF- SNRPN* and a family of five paternal-only expressed snoRNA genes). Only *UBE3A* and *ATP10A* (shown in red), related to Angelman syndrome (AS), have maternal-only expression in mouse and humans, and this imprinted expression is limited to certain tissue-specific regions (ie, brain). The bipartite imprinting center (IC) lies proximal to *SNURF-SNRPN* and within the 3 Mb PWS/AS imprinted region. The cluster of GABA receptor genes (*GABRB3*, *GABRA5* and *GABRG3*), *OCA2* (type II albinism) and *HERC2* are not imprinted and have biparental expression (shown in black). The jagged vertical lines denote the common 5–7 Mb AS and PWS deletion breakpoints, which lie within the segmental duplications associated with BP1, BP2 and BP3.[45] There are two common proximal breakpoints and one distal common breakpoint.[44] In between BP1 and BP2 lie four additional, non-imprinted genes *GCP5 (TUBGCP5), CYFIP1, NIPA2* and *NIPA1*.[46] Type 1 deletions extend from BP1 to BP3 and type 2 deletions extend from BP2 to BP3. Note that there are more copies of the *HBII-85* and *HBII-52* genes than are shown.

## Treatment and care

### Hypotonia

In infancy, the major focus should be on assuring adequate nutrition and growth. Compensation for the poor suck almost always requires gavage feeding or use of special nipples (eg, enlarged nipple holes or those designed for cleft palate). As infants rarely wake to feed, a regular feeding schedule should be established. Caloric intake should be assessed, and height, weight and head circumference plotted on growth charts monthly for the first 6 months and quarterly for 12–24 months. Feeding problems are transient, so a gastrostomy tube is rarely necessary. Fats should not be restricted as they are essential for brain development.

Early infant stimulation programs are strongly recommended to assure adequate interactions and optimize strength and milestone achievement. Encouragement of physical activity is important for strength and agility at all ages.

Scoliosis can occur at any time throughout childhood and is treated in a standard manner.

### Obesity predisposition

Nutritional counselling for good long-term weight management should begin in early infancy to prevent the inappropriate weight gain that would otherwise typically begin between 12–36 months of age. Caloric requirement is low on account of decreased calorie utilization, often as low as 60% of that for unaffected children of the same body weight[62] so that care should be taken to not overfeed the infant with PWS. It is important to monitor growth and record measurements on a standard growth curve regularly (monthly in early infancy, every 2–3 months from 2 to 6 years, and at least two times yearly thereafter throughout

**Table 3** Age-dependent recommended evaluations at initial diagnosis. Genetic counseling and referral to support groups should occur at diagnosis regardless of age

| *Category* | *Evaluation* | *0–3 months* | *3–24 months* | *2–12 years* | *Adolescents and adults* |
|---|---|---|---|---|---|
| **Feeding, weight and growth** | Assess feeding ability and need for gavage or other assisted feeding | * | * | | |
| | Measure and plot weight and body mass index | * | * | * | * |
| | Conduct nutritional evaluation | * | * | * | * |
| | Measure and plot length/height and head circumference | * | * | * | * |
| | Thoroughly assess diet, exercise and supervision status for obesity prevention; and review plans for obesity avoidance/treatment | | | * | * |
| | Refer to endocrinology for discussion/initiation of growth hormone therapy[a] | * | * | * | * |
| | Assess thyroid function | * | * | * | * |
| | Evaluate for type II diabetes mellitus, if obesity is present | | | * | * |
| **Development and function** | Physical therapy evaluation | * | * | * | * |
| | Assess developmental abilities and refer for early intervention[a] | * | * | | |
| | Conduct psycho-educational testing and assess adequacy of programming[a] | | | * | * |
| **Behavior and Psychiatric** | Assess parenting/ caregiver skills needed for PWS | | * | * | * |
| | Enquire about behavior problems and how they are managed. Reinforce importance of limit setting. Refer for treatment, if indicated | | * | * | * |
| | Obtain history of personality change or signs of psychosis or depression. Refer for treatment, if indicated | | | | * |
| **Hypogonadism** | Evaluate testicular descent. Refer to urology or surgery for orchidopexy, if undescended[a] | * | * | * | * |
| | Consider the need for sex hormone replacement | | | | * |
| **Skeletal** | Assess for hip dysplasia[a] | * | * | | |
| | Evaluate clinically for scoliosis; obtain spine films if it is suspected | | * | * | * |
| | Obtain bone densitometry[a] | | | | * |
| **Sleep** | Obtain sleep history. Refer for poly-somnography, if suspect for apnea[a] | | * | * | * |
| **Ophthalmologic** | Ophthalmologic evaluation for strabismus and visual acuity[a] | | * | * | * |
| **Dental** | Evaluate for dry mouth/stringy saliva and refer for dental care | | * | * | * |
| **Skin** | Carefully evaluate skin for evidence of severe skin picking, edema, skin breakdown | | | * | * |
| **Future planning** | Issues of wills, trusts guardianship should be addressed | | | * | * |

[a]If not done previously.

childhood) so that excess weight gain can be identified and dealt with early. At least twice yearly weights in adulthood, with comparison to prior weights, are also important to monitor for weight gain. Vitamin and mineral intake (especially calcium and vitamin D) should be monitored, and supplements given as needed.

Once hyperphagia begins, the feeling of hunger is typically never completely relieved, even after a large meal. No known pharmacologic agent is effective. This lack of satiety should be considered at school, work and home, and all caretakers and supervisors need to understand these factors. Consistent limit setting and close supervision at all ages, including locking of cabinets and refrigerator at home and avoidance of work environments with available food, decreases anxiety and conflict. It is imperative to begin good meal management and education at an early age. This includes sticking to a strict schedule for meals and snacks, and limiting portion sizes. Exercise is also a very important factor in weight maintenance, and early establishment of a routine of regular daily physical activity (at least 30 min) is strongly recommended. More and more individuals with PWS are now growing up having avoided the obesity that used to be so typical of this syndrome (Figure 6).

### Growth deficiency

The benefits of growth hormone therapy in infants, children and adults with PWS have been well-demonstrated in multiple well-designed and well-controlled studies.[63–67] Growth hormone replacement therapy improves linear growth velocity and ultimate height, body composition (increased lean body mass, decreased fat mass), muscle function, and level of activity. There is evidence of improvement in the respiratory drive and function. Growth hormone helps maintain muscle bulk and body composition in adults. When treatment occurs from infancy, facial appearance and body habitus normalize in conjunction with good dietary management (Figure 6). Rare side effects of human growth hormone therapy include pedal edema, hastening of scoliosis, slipped capital femoral epiphysis and risk of pseudotumor cerebri. Premature adrenarche has been reported to occur more commonly.[65] Because of concerns about unexpected death on account of respiratory obstruction early in growth hormone treatment, sleep polysomnography and assessment for enlarged tonsils and adenoids are recommended before initiating growth hormone treatment and 6–8 weeks after starting.[68] However, there is controversy among experts about a direct role of growth hormone in these unexpected deaths.[31,63,68] In addition, thyroid function should be assessed before growth hormone therapy, as 15% of patients have hypothyroidism. Serum IGF-1 levels, growth velocity and head circumference should be monitored during treatment and kept in the normal range.[68]

### Hypogonadism

Cryptorchidism in males is common and often requires surgical intervention. A trial of chorionic gonadotropin will enlarge the scrotum so it can better contain the testes post-surgically, and might circumvent the need for surgery. Pubertal deficiency can be treated with replacement of sex hormones, which produces adequate secondary sexual characteristics. Concerns about testosterone replacement possibly causing behavior problems in males have been largely alleviated by daily administration through the patch or gel *versus* previously used monthly intramuscular depot injections. In females there are concerns about hygiene issues with monthly menstruation and the increased risk of strokes with estrogen replacement. Few well-designed studies of sex hormone replacement are published. The high frequency of osteopenia/osteoporosis in PWS argues in favor of sex hormone replacement. Although sex drive appears decreased in PWS, sex education should not be neglected because of the risk of sexually transmitted diseases and the rare pregnancy in females.

### Developmental disability

Children with PWS should have early intervention (including physical, occupational, and speech therapies) and individualized appropriate education. This ideally includes social skills training. Optimally, a one-to-one aide in the classroom will help the child focus on learning and diminish behavioral disturbances. Adults require sheltered employment and housing.

### Behavior and psychiatric problems

Behavioral problems should be detected early and treated appropriately with parental education/training (including consistent limit setting) and, if needed, consideration of counselling and/or psychotropic medication. Serotonin agonists have been the most successful in reducing temper outbursts and improving compulsivity.[69–71] Families should be made aware of the signs of psychosis and urged to have psychiatric assessment early if a thought disorder is apparent. It is particularly important to be aware that psychosis develops in a substantial number of adults with UPD or imprinting defects.[22,23] Psychosis is treated in a standard manner.

## Genetic counselling

Recurrence risk is dependent on the genetic mechanism causing PWS in the individual. Deletion 15q11.2–q13 is sporadic (recurrence $<1\%$) except in the rare cases where a chromosomal rearrangement (translocation or inversion) is present in the father. Fathers of children with deletion should be offered chromosomal and FISH analysis of the 15q11.2–q13 region as the recurrence risk is significantly increased in these cases. Maternal UPD 15 is typically *de novo* (recurrence $<1\%$) except if a Robertsonian

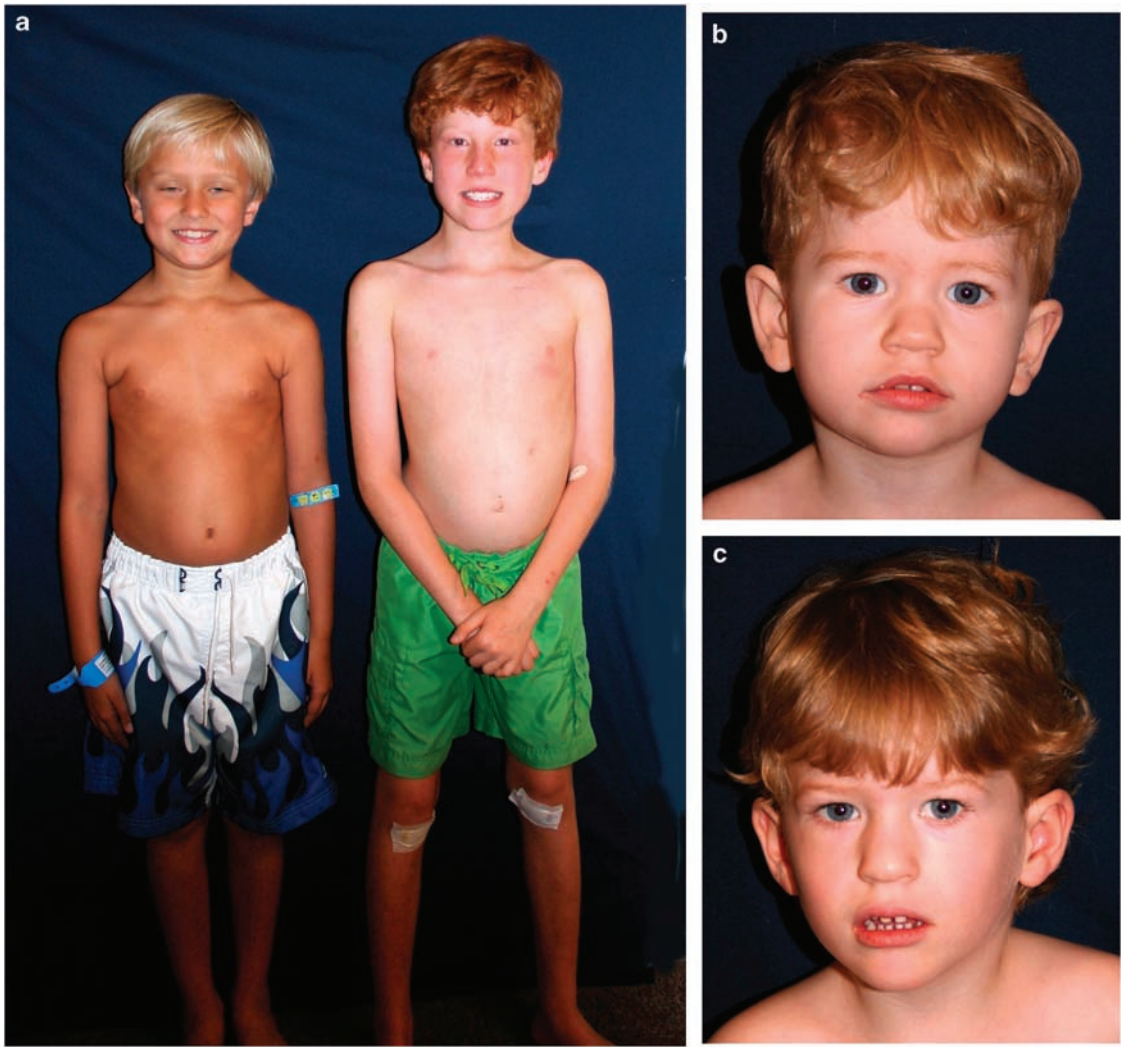


**Figure 6** Normalization of the body and facial phenotype of PWS following treatment with growth hormone from infancy. (**a**) A 7-year-old unaffected sibling on the left and his 8-year-old brother with PWS on the right. Note lighter pigmentation in affected brother who has a typical deletion, and scar from the gastrostomy tube used in infancy. The unaffected brother has 24% body fat and the brother with PWS has 20% body fat. (**b**) A 2-year-old boy. (**c**) A 4-year-old unrelated boy.

translocation is present in either parent, so a chromosomal analysis is indicated. If this is normal, then the father of the child should be offered a chromosomal analysis to ensure that he does not have a Robertsonian translocation. A proportion of those with an imprinting defect have a microdeletion in the Imprinting Center; this can be familial and has a 50% recurrence risk when it is. However, the greater proportion of those with an imprinting defect have an epigenetic mutation and the recurrence risk is $<1\%$ for this group.

PWS cannot be identified clinically before birth. FISH, DNA polymorphism studies for UPD, and DNA methylation analysis have all been validated for prenatal diagnosis in amniocytes or chorionic villi, and all three are available clinically. Only DNA methylation analysis will identify the imprinting defects.[72]

## Conclusion

Growth hormone replacement in PWS has resulted in dramatic benefits to the phenotype, health and self-image of those treated. But much is yet to be learned about this complex disorder. Clinically, the most urgent need is arguably to identify the cause of hyperphagia in hopes of finding pharmacologic agents that can diminish its impact. Would the effect of such a drug be to improve behavior and cognitive ability as well as health? If obesity could be more easily avoided, the major cause of morbidity and mortality would be eliminated and significantly improved health and quality of life could be expected.

It has been 27 years since the genetic region responsible for PWS was first identified; yet we still do not know the precise gene(s) responsible for the phenotype. Recent data suggests a key role for the *HBII-85* snoRNA gene,[48,73] and

the near future should uncover its gene targets and hopefully lead to treatments. Identification of the responsible gene(s) may also be extremely instructive concerning causes of obesity, hypogonadism, other hypothalamic deficiencies, psychosis, and autism in the general population. PWS has already taught us much about imprinting, and may have much more to teach us.

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