Prader-Willi syndrome

PWS is the most common of the genetic disorders that cause life-threatening obesity in children. The syndrome affects many aspects of the person's life, including eating, behavior and mood, physical growth, and intellectual development. The NICHD is one of many federal agencies and NIH Institutes working to understand PWS. The NICHD supports and conducts research on the factors that cause the syndrome and how best to diagnose and treat it.

Common name
Prader-Willi syndrome

Medical or scientific names
Prader-Willi
Prader-Labhart-Willi syndrome
PWS
Willi-Prader syndrome
Prader-Willi-Fanconi syndrome
Pw

What is PWS?
The term PWS refers to a genetic disorder that affects many parts of the body. Genetic testing can successfully diagnose 99% of infants with PWS.1

The syndrome usually results from deletions or partial deletions on chromosome 15 that affect the regulation of gene expression, or how genes turn on and off. Andrea Prader and Heinrich Willi first described the syndrome in the 1950s.2

One of the main symptoms of PWS is the inability to control eating. In fact, PWS is the leading genetic cause of life-threatening obesity. Other symptoms include low muscle tone and poor feeding as an infant, delays in intellectual development, and difficulty controlling emotions.

There is no cure for PWS, but people with the disorder can benefit from a variety of treatments to improve their symptoms. These treatments depend on the individual's needs, but they often include strict dietary supervision, physical therapy, behavioral therapy, and treatment with growth hormone, among others. As adults, people with PWS usually do best in special group homes for people with this disorder. Some can work in sheltered environments.


What are the symptoms of Prader-Willi syndrome (PWS)?
Scientists think that the symptoms of PWS may be caused by a problem in a portion of the brain called the hypothalamus (pronounced hahy-puh-THAL-uh-mus). The hypothalamus lies in the base of the brain. When it works normally, it controls hunger or thirst, body temperature, pain, and when it is time to awaken and to sleep.1 Problems with the hypothalamus can affect various body functions and pathways, leading to a variety of symptoms.

Individuals with PWS may have mild to severe symptoms, which often include:

Feeding and metabolic symptoms: An important early symptom of PWS is an infant's inability to suck, which affects the ability to feed. Nearly all infants with PWS need help with feeding. Infants may require feeding support for several months. Without assistance, they will not grow. Nursing systems with one-way valves and manual sucking assistive devices, similar to those used with cleft palate (such as bottles with special nipples for babies who do not
have the sucking reflex), often are needed. Occasionally, feeding tubes are required, but generally for no more than the first 6 months after birth. The infants may need fewer calories because of the reduced metabolism associated with PWS and may not demand feeding on their own. Frequent weight checks will help in adjusting the infant's diet to maintain a suitable weight gain.

As the infants grow into toddlers and children, compulsive overeating replaces the need for feeding support. Because the metabolic rate of individuals with PWS is lower than normal, their caloric intake must be restricted to maintain a healthy weight, often to 60% of the caloric requirement of comparably sized children without the syndrome.

Feeding and metabolic symptoms persist into adulthood. Unless individuals with PWS live in environments that limit access to food (such as locked cabinets and a locked refrigerator), they will eat uncontrollably, even food that is rotten or sitting in the garbage. Uncontrollable eating can cause choking, a ruptured esophagus, and blockages in the digestive system. It can also lead to extreme weight gain and morbid obesity. Because of their inability to stop eating, people with PWS are at increased risk for diabetes, trouble breathing during sleep, and other health risks.1 For these reasons, people with PWS need to be monitored by a health care professional their entire lives.

**Physical symptoms:** Many physical symptoms of PWS arise from poor regulation of various hormones, including growth hormone, thyroid hormone, and possibly adrenalin. Individuals with PWS grow slowly and experience delays in reaching physical activity milestones (e.g., standing, walking).2

Children with PWS tend to be substantially shorter than other children of similar age. They may have small hands and feet and a curvature of the back, called scoliosis (pronounced skoh-lee-OH-sis). In addition, they frequently have difficulty making their eyes work together to focus, a condition called strabismus (pronounced struh-BIZ-muhs).2,3

Infants with PWS are often born with underdeveloped sex organs, including a small penis and scrotum or a small clitoris and vaginal lips. Most individuals with PWS are infertile.1,2,4

**Intellectual symptoms:** Individuals with PWS have varying levels of intellectual disabilities. Learning disabilities are common, as are delays in starting to talk and in the development of language.2,3

**Behavioral and Psychiatric Symptoms:** Imbalances in hormone levels may contribute to behavioral and psychiatric problems. Behavioral problems may include temper tantrums, extreme stubbornness, obsessive-compulsive symptoms, picking the skin, and general trouble in controlling emotions. The individual will often repeat questions or statements. Sleep disturbances may include excessive daytime sleepiness and disruptions of sleep. Many individuals with PWS have a high pain threshold.1

**Stages of PWS symptoms**
The appearance of PWS symptoms occurs in two recognized stages:

**Stage 1 (Infancy to age 2 years)**
- "Floppiness" and poor muscle tone
- Weak cries and a weak sucking reflex
- Inability to breastfeed, which may require feeding support, such as tube feeding
- Developmental delays
- Small genital organs

**Stage 2 (Ages 2 to 8)**
- Unable to feel satisfied with normal intake of food
- Inability to control eating, which can lead to overeating if not monitored
- Food-seeking behaviors
- Low metabolism
- Weight gain and obesity
- Daytime sleepiness and sleep problems
- Intellectual disabilities
- Small hands and feet
- Short stature
- Curvature of the spine (scoliosis)
- High pain threshold
What causes Prader-Willi syndrome?

Prader-Willi syndrome is caused by genetic changes on an "unstable" region of chromosome 15 that affects the regulation of gene expression, or how genes turn on and off. This part of the chromosome is called unstable because it is prone to being shuffled around by the cell's genetic machinery before the chromosome is passed on from parent to child.

The genetic changes that cause Prader-Willi syndrome occur in a portion of the chromosome, referred to as the Prader-Willi critical region (PWCR), around the time of conception or during early fetal development. This region was identified in 1990 using genetic DNA probes. Although Prader-Willi syndrome is genetic, it usually is not inherited and generally develops due to deletions or partial deletions on chromosome 15.

Specific changes to the chromosome can include the following:

Deletions. A section of a chromosome may be lost or deleted, along with the functions that this section supported. About 65% to 75% of Prader-Willi syndrome cases result from the loss of function of several genes in one region of the father's chromosome 15, due to deletion. The corresponding mother's genes on chromosome 15 are always inactive and thus cannot make up for the deletion on the father's chromosome 15. The missing paternal genes normally play a fundamental role in regulating hunger and fullness.

Maternal uniparental disomy (pronounced yoo-nuh-puh-REN-tl DAHY-soh-mee). A cell usually contains one set of chromosomes from the father and another set from the mother. In ordinary cases, a child has two chromosome 15s, one from each parent. In 20% to 30% of Prader-Willi syndrome cases, the child has two chromosome 15s from the mother and none from the father. Because genes located in the PWCR are normally inactive in the chromosome that comes from the mother, the child's lack of active genes in this region leads to Prader-Willi syndrome.

An imprinting center defect. Genes in the PWCR on the chromosome that came from the mother are normally inactivated, due to a process known as "imprinting" that affects whether the cell is able to "read" a gene or not. In less than 5% of Prader-Willi syndrome cases, the chromosome 15 inherited from the father is imprinted in the same way as the mother's. This can be caused by a small deletion in a region of the father's chromosome that controls the imprinting process, called the imprinting center. In these cases, both of the child's copies of chromosome 15 have inactive PWCRs, leading to Prader-Willi syndrome.

How do health care providers diagnose Prader-Willi syndrome?

In many cases of Prader-Willi syndrome, diagnosis is prompted by physical symptoms in the newborn. If a newborn is unable to suck or feed for a few days and has a "floppy" body and weak muscle tone, a health care provider may conduct genetic testing for Prader-Willi syndrome. Formal diagnostic criteria for recognizing Prader-Willi syndrome depend on the age of the individual-specifically, whether the third birthday has been reached. Before
age 3, the most important symptom is extremely poor muscle tone, called hypotonia (pronounced HAHY-poh-toh-ee-uh), which makes infants feel floppy. In affected children 3 years of age and older, other symptoms become apparent, such as obesity, intellectual delays, learning disabilities, or behavior problems, especially connected with food and eating.3

- Children younger than 3 years must have at least four major criteria and at least one minor criterion for a Prader-Willi syndrome diagnosis.
- Those older than 3 years must have at least five major criteria and at least three minor criteria for a diagnosis of Prader-Willi syndrome.

**Major clinical criteria of Prader-Willi syndrome**
- Extremely weak muscles in the body's torso
- Difficulty sucking, which improves after the first few months
- Feeding difficulties and/or failure to grow, requiring feeding assistance, such as feeding tubes or special nipples to aid in sucking
- Beginning of rapid weight gain, between ages 1 and 6, resulting in severe obesity
- Excessive, uncontrollable overeating
- Specific facial features, including narrow forehead and downturned mouth
- Reduced development of the genital organs, including small genitalia (vaginal lips and clitoris in females and small scrotum and penis in males); incomplete and delayed puberty; infertility
- Developmental delays, mild-to-moderate intellectual disability, multiple learning disabilities

**Minor clinical criteria of Prader-Willi syndrome**
- Decreased movement and noticeable fatigue during infancy
- Behavioral problems—specifically, temper tantrums, obsessive-compulsive behavior, stubbornness, rigidity, stealing, and lying (especially related to food)
- Sleep problems, including daytime sleepiness and sleep disruption
- Short stature, compared with other members of the family, noticeable by age 15
- Light color of skin, eyes, and hair
- Small hands and feet in comparison to standards for height and age
- Narrow hands
- Nearsightedness and/or difficulty focusing both eyes at the same time
- Thick saliva
- Poor pronunciation
- Picking of the skin

**Additional findings**
- High pain threshold
- Inability to vomit
- Curvature of the spine (scoliosis)
- Earlier-than-usual activity in the adrenal glands, which can lead to early puberty
- Especially brittle bones (called osteoporosis, pronounced os-tee-oh-puh-ROH-sis)

Genetic testing must confirm the Prader-Willi syndrome diagnosis. More than 99% of individuals with Prader-Willi syndrome have an abnormality within a specific area of chromosome 15. Early diagnosis is best because it enables affected individuals to begin early intervention/special needs programs and treatment specifically for Prader-Willi symptoms.

Genetic testing can confirm the chance that a sibling might be born with Prader-Willi syndrome. Prenatal diagnosis also is available for at-risk pregnancies—that is, pregnancies among women with a family history of Prader-Willi syndrome abnormalities.

**Genetic counseling and testing of at-risk relatives**
Genetic counseling and testing provide individuals and families with information about the nature, inheritance, and implications of genetic disorders so that they can make informed medical and personal decisions about having children. Genetic counseling helps people understand their risks. The risk of occurrence in siblings of patients with
Prader-Willi syndrome depends on what caused the disorder to occur.2

To locate a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.


Is there a cure for Prader-Willi syndrome?
Prader-Willi syndrome has no cure. However, early diagnosis and treatment may help prevent or reduce the number of challenges that individuals with Prader-Willi syndrome may experience, and which may be more of a problem if diagnosis or treatment is delayed.

What are the treatments for Prader-Willi syndrome?
Parents can enroll infants with PWS in early intervention programs. However, even if a PWS diagnosis is delayed, treatments are valuable at any age.

The types of treatment depend on the individual’s symptoms. The health care provider may recommend the following:

Use of special nipples or tubes for feeding difficulties. Difficulty in sucking is one of the most common symptoms of newborns with Prader-Willi syndrome. Special nipples or tubes are used for several months to feed newborns and infants who are unable to suck properly, to make sure that the infant is fed adequately and grows. To ensure that the child is growing properly, the health care provider will monitor height, weight, and body mass index (BMI) monthly during infancy.

Strict supervision of daily food intake. Once overeating starts between ages 2 and 4 years, supervision will help to minimize food hoarding and stealing and prevent rapid weight gain and severe obesity. Parents should lock refrigerators and all cabinets containing food. No medications have proven beneficial in reducing food-seeking behavior.

A well-balanced, low-calorie diet and regular exercise are essential and must be maintained for the rest of the individual’s life. People with PWS rarely need more than 1,000 to 1,200 calories per day. Height, weight, and BMI should be monitored every 6 months during the first 10 years of life after infancy and once a year after age 10 for the rest of the person’s life to make sure he or she is maintaining a healthy weight. Ongoing consultation with a dietitian to guarantee adequate vitamin and mineral intake, including calcium and vitamin D, might be needed.

Growth Hormone (GH) therapy. GH therapy has been demonstrated to increase height, lean body mass, and mobility; decrease fat mass; and improve movement and flexibility in individuals with PWS from infancy through adulthood.1,2,3 When given early in life, it also may prevent or reduce behavioral difficulties. Additionally, GH therapy can help improve speech, improve abstract reasoning, and often allow information to be processed more quickly. It also has been shown to improve sleep quality and resting energy expenditure.2,3,4 GH therapy usually is started during infancy or at diagnosis with PWS. This therapy often continues during adulthood at 20% to 25% of the recommended dose for children.

Treatment of eye problems by a pediatric ophthalmologist. Many infants have trouble getting their eyes to focus together. These infants should be referred to a pediatric ophthalmologist who has expertise in working with infants with disabilities.

Treatment of curvature of the spine by an orthopedist. An orthopedist should evaluate and treat, if necessary, curvature of the spine (scoliosis). Treatment will be the same as that for people with scoliosis who do not have PWS.

Sleep studies and treatment. Sleep disorders are common with PWS. Treating a sleep disorder can help improve the quality of sleep. The same treatments that health care providers use with the general population can apply to
individuals with PWS.

**Physical therapy.** Muscle weakness is a serious problem among individuals with PWS. For children younger than age 3, physical therapy may increase muscular strength and help such children achieve developmental milestones. For older children, daily exercise will help build lean body mass.

**Behavioral therapy.** People with PWS have difficulty controlling their emotions. Using behavioral therapy can help. Stubbornness, anger, and obsessive-compulsive behavior, including obsession with food, should be handled with behavioral management programs using firm limit-setting strategies. Structure and routines also are advised.1,5

**Medications.** Medications, especially serotonin reuptake inhibitors (SRIs), may reduce obsessive-compulsive symptoms. SRIs also may help manage psychosis.

**Early interventions/Special needs programs.** Individuals with PWS have varying degrees of intellectual difficulty and learning disabilities. Early intervention programs, including speech therapy for delays in acquiring language and for difficulties with pronunciation, should begin as early as possible and continue throughout childhood.6

Special education is almost always necessary for school-age children. Groups that offer training in social skills may also prove beneficial. An individual aide is often useful in helping PWS children focus on schoolwork.

**Sex hormone treatments and/or corrective surgery.** These treatments are used to treat small genitals (penis, scrotum, clitoris).

**Replacement of sex hormones.** Replacement of sex hormones during puberty may result in development of adequate secondary sex characteristics (e.g., breasts, pubic hair, a deeper voice).

**Placement in group homes during adulthood.** Group homes offer necessary structure and supervision for adults with PWS, helping them avoid compulsive eating, severe obesity, and other health problems.2


**Additional resources**

**Foundation for Prader-Willi Research**
5455 Wilshire Blvd, Suite 2020.
Los Angeles, CA 90036
888-322-5487
https://www.fpwr.org/

**Prader-Willi Syndrome Association (USA)**
8588 Potter Park Drive, Suite 500
Sarasota, Florida 34238
800-926-4797