Prader-Willi syndrome is a neurogenetic disorder characterized by hypotonia and feeding difficulties in infancy, followed by hyperphagia, hypogonadism, mental retardation, and short stature. It was the first recognized microdeletion syndrome identified with high-resolution chromosome analysis, the first recognized human genomic imprinting disorder, and the first recognized disorder resulting from uniparental disomy. The incidence of Prader-Willi syndrome is approximately 1/10,000 to 1/15,000 individuals.

**GENETICS/BASIC DEFECTS**

1. **Inheritance**
   a. Usually sporadic events (de novo deletions of 15q11-q13)
   b. Rare familial transmission (balanced translocations involving 15q11-q13) (<1%)
2. A contiguous gene syndrome involving multiple paternally expressed genes
3. Caused by the lack of expression of normally active paternally inherited genes at chromosome 15q11-q13 because of a phenomenon called genomic imprinting
   a. The relevant region on chromosome 15q11-q13: normally expressed on the paternally derived chromosome and imprinted on maternally derived chromosome
   b. The imprinted maternal allele is unable to produce functional protein since the normally expressed paternal copy is often deleted in Prader-Willi syndrome
4. **Molecular subclassification of Prader-Willi syndrome:** all involving loss of paternal gene expression from chromosome 15q11-q13
   a. Paternal deletion 15q11-q13 (70% of cases): microdeletion of the actively transcribed segment on the paternally derived chromosome 15q11-q13
   b. Maternal uniparental disomy (UPD15) (25–30% of cases)
      i. Inheritance of two copies of the maternal chromosome without paternal contribution
      ii. In normal individuals, the paternally donated chromosome expresses multiple genes in the Prader-Willi syndrome region while the maternal chromosome is largely silent
      iii. In case of maternal uniparental disomy, without the presence of a chromosome donated from the father, normal imprinting on the 2 maternally donated chromosomes leads to the absence of gene expression in this region
   c. Mutation in the imprinting control center
      i. Deletion of the imprinting center (1–2% of the cases) of the SNRPN (small nuclear ribonucleoprotein polypeptide N) gene causing inability to establish the normal methylation status
      ii. Without imprinting center deletion (1–2% of cases)

**CLINICAL FEATURES**

1. **Neonatal presentation**
   a. Central hypotonia in infancy
   b. Poor feeding/sucking
   c. Poor weight gain (failure to thrive)
   d. Genital hypoplasia/hypogonadism
   e. Diminished deep tendon reflexes
   f. Abnormal squeaky weak cry
   g. History of fetal inactivity (*in utero* hypotonia)
2. Developmental delay
3. Mild dysmorphic features
   a. Almond-shaped eyes
   b. Dolichocephaly
   c. Narrow bifrontal diameter
   d. Narrow nasal bridge
   e. Small mandible
   f. Small mouth
   g. High-arched palate
   h. Down-turned lips
   i. Thick viscous saliva
4. Hyperphagia after the 1st-2nd postnatal years
5. Severe obesity without significant intervention
6. Retinal hypopigmentation
7. Small hands and feet (acromicria)
8. Mild to moderate mental retardation
9. Hypothalamic insufficiency suggested by several autonomic dysfunctions that affect appetite regulation, growth, pubertal development, control of breathing, and alertness
10. Behavioral and psychiatric difficulties
    a. Excessive food-seeking behaviors
    b. Obsessions
    c. Compulsions
    d. Mood lability
    e. Depression
11. Other manifestations
    a. Infantile lethargy
    b. Sleep disturbance and/or sleep apnea
    c. Short stature
    d. Hypopigmentation
    e. Skin sores from constant picking
    f. Esotropia/myopia
    g. Speech articulation defects
    h. High pain threshold
    i. Ineffective thermoregulation
    j. Early adrenarche
    k. Osteoporosis
    l. Kyphoscoliosis
12. Prognosis
    a. Obesity: the major cause of morbidity and mortality
    b. Cardiopulmonary compromise (*Pickwickian syndrome*) resulting from excessive obesity
13. Diagnostic criteria (adapted from Holm et al., 1993): 5 points for children under 3 years (3 from major criteria); 8 points for children above 3 years (4 from major criteria)
   a. Major Criteria (1 points each)
      i. Infantile central hypotonia
      ii. Infantile feeding problems/failure to thrive
      iii. Rapid weight gain between 1 and 6 years
      iv. Characteristic facial features
      v. Hypogonadism (genital hypoplasia, pubertal deficiency)
      vi. Developmental delay/mental retardation
   b. Minor Criteria (1/2 point each)
      i. Decreased fetal movement and infantile lethargy
      ii. Typical behavioral problems
      iii. Sleep disturbance/sleep apnea
      iv. Short stature for the family by age 15 years
      v. Hypopigmentation
      vi. Small hands and feet for height age
      vii. Narrow hands with straight ulnar border
      viii. Esotropia/myopia
      ix. Thick viscous saliva
      x. Speech articulation defects
      xi. Skin picking
   c. Supportive Criteria (no points)
      i. High pain threshold
      ii. Decreased vomiting
      iii. Temperature control problems
      iv. Scoliosis/kyphosis
      v. Early adrenarche
      vi. Osteoporosis
      vii. Unusual skill with jigsaw puzzles
      viii. Normal neuromuscular studies

DIAGNOSTIC INVESTIGATIONS

1. Cytogenetic studies
   a. Microscopic or submicroscopic del(15)(q11-q13) confirmed by fluorescence in situ hybridization (FISH probe for SNRPN) (60–80%)
   b. Paternally derived chromosome 15 that is deleted
   c. De novo events in most cases with cytogenetically normal father’s chromosomes
   d. Balanced chromosomal rearrangement with break in 15q11-q13 (<1%)

2. Molecular analyses
   a. Uniparental disomy identified by using microsatellite repeat sequences of chromosome 15 in the patient and both parents
      i. Maternal uniparental disomy for chromosome 15 in most of non-deletion cases (20–40%)
      ii. Inheriting both copies of chromosome 15 from the mother
      iii. Absence of the paternally inherited copy of chromosome 15q11-q13
   b. Rare familial Prader-Willi syndrome; associated with very small mutations in 15q11-q13 region leading to the loss of expression of multiple genes from the paternal chromosome
   c. DNA methylation analyses (by Southern blotting and PCR) of the SNRPN or PW71 (D15S63) loci to detect absence of paternal methylation patterns on the basis of deletion, uniparental disomy, or defective methylation: detects over 99% of cases and is highly specific

GENETIC COUNSELING

1. Recurrence risks
   a. De novo deletion or maternal uniparental disomy in an affected child: a low recurrence risk ≤1% due to possible paternal balanced insertion or gonadal mosaicism)
   b. Imprinting center mutation in an affected child: recurrence risk up to 50%
   c. Presence of a parental balanced chromosomal rearrangement: up to 25% recurrence risk

2. Prenatal diagnosis
   a. High risk pregnancies
      i. Parents who have had a previous child with Prader-Willi syndrome, caused by deletion or uniparental disomy, for assurance purpose
      ii. Parents who have had a previous child with Prader-Willi syndrome, caused by a defect in the imprinting control center, because of the high recurrence risk
      iii. Inherited translocation involving chromosome 15 and resulting in a deletion, because of the theoretical 25% risk of Prader-Willi syndrome in the offspring
   b. Low risk pregnancies in which no family history of Prader-Willi syndrome exists
   c. Cytogenetic study to detect del(15q11-q13) from amniocytes or CVS cells, complemented by FISH probe
   d. Molecular studies of uniparental disomy 15 using microsatellite dinucleotide polymorphism analysis of amniocytes and parental DNA
   e. DNA methylation analysis of amniocytes

3. Management
   a. Manage feeding problems with special nipples or gavage feeding if needed to assure adequate nutrition, to avoid failure to thrive, and to improve hypotonia
   b. Early intervention programs with speech, physical, and occupational therapies after careful educational, behavioral, and psychological assessments
   c. Dietary control
      i. Monitoring of weight and nutritional counseling
      ii. Low-calorie and well-balanced diet combined with a regular exercise program
      iii. Limit access to food
      iv. Close supervision to minimize food stealing
   d. Management of endocrine problems
      i. Growth hormone replacement in patients with deficient growth hormone
      ii. Testosterone treatment in males to improve changes in voice and body hair, beard growth, genital size, body mass and strength, and self-image
      iii. Treatment with estrogen, cycling hormones or birth control pills in females has resulted in increasing breast size and menstrual periods
e. Management of scoliosis as in the general population
f. Behavioral management
i. Firm limit setting and enforcement
ii. Consult with a behavioral psychologist or other behavior specialist for behavioral management programs
g. Psychiatric management
i. Psychosis
ii. Manic-depressive illness
iii. Obsessive-compulsive disorder
h. Treatment of complications resulting from excessive obesity
i. Cardiopulmonary compromise
ii. Type II diabetes mellitus
iii. Thrombophlebitis
iv. Management of skin picking, chronic skin changes, and peripheral edema

REFERENCES


Fig. 1. A 10-month old girl with Prader-Willi syndrome showing severe hypotonia, strabismus, and small hands and feet. Parent-of-origin specific DNA methylation studies at 15q11-q13 for Prader-Willi syndrome revealed the presence of maternal 4.2 kb hybridization band only but not paternal 0.9 kb band consistent with Prader-Willi syndrome. Uniparental disomy DNA analysis revealed that the patient has only maternal alleles based on the Mendelian inheritance of 2 informative markers (D15S205 and D15S1002) and 2 partial informative markers (D15S130 and D15S1007), indicative of uniparental disomy for chromosome 15.

Fig. 2. An infant with Prader-Willi syndrome [del(15)(q11-q13)] showing hypotonia and failure to thrive.

Fig. 3. A girl with Prader-Willi syndrome [del(15)(q11-q13)] showing obesity, short stature, almond-shaped eyes, and small hands and feet.

Fig. 4. A boy with Prader-Willi syndrome [del(15)(q11-q13)] showing almond-shaped eyes, bitemporal narrowing, obesity, hypogenitalism, and small hands and feet.
Fig. 5. A girl with Prader-Willi syndrome [del(15)(q11-q13)] showing extreme obesity, characteristic facial appearance, small hands and feet, and multiple skin sores from constant picking.

Fig. 6. Sore on the hand in a patient with Prader-Willi syndrome [del(15)(q11-q13)] (shown by partial karyotypes and ideogram) and trimethylaminuria.

Fig. 7. A woman with Prader-Willi syndrome [del(15)(q11-q13)] and neurofibromatosis 1 showing obesity and axillary freckles.