Prader-Willi Syndrome: The Whole Picture

An Overview for Families of Children Birth to 5 Years

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Where My Knowledge Comes From

- Pediatrician and Medical Geneticist
- Clinical and Research Focus on PWS for over 30 years
  - Multidisciplinary clinics, hundreds of patients
  - Clinical research and collaboration
  - Educational talks, medical articles
  - Involved support organizations (PWSA USA and IPWSO)

Changes in PWS over Time

- Improved knowledge about the disorder
- Dramatically improved diagnostic testing
- Much earlier diagnosis, so earlier initiation of treatment
- Improved function with use of growth hormone replacement
- Improved health and life expectancy
- Improved living situations and care guidelines
- Improved public, medical and government awareness

- ***These changes resulted from partnerships among clinicians, scientists, PWS organizations, and patients***

Topics Covered in this Overview

- **Characteristics**, with emphasis on young child
  - Will incorporate information from the IPWSO scientific session, where appropriate
  - Management mostly discussed by other speakers
- **Genetic changes**, diagnostic testing and chances of recurrence

Prevalence

- Approximately 1/10,000 - 1/25,000
- Occurs equally in males and females, all races and geographic origins

- The most common genetic syndrome associated with obesity

PWS is Highly Variable

- An affected individual may not have every finding
- Severity of each finding is quite variable
- Severity of one finding does not predict the severity of another finding
- Other family characteristics and life experience influence appearance, abilities and behavior
- Affected people can have features or problems that are not related to the syndrome

PWS: Major Features

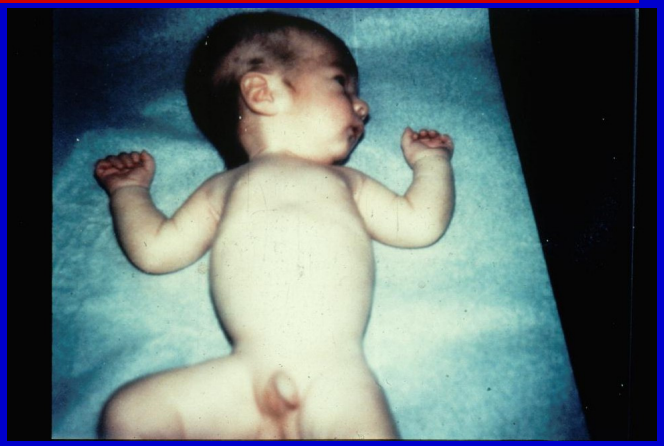
- **Hypotonia** (low muscle tone)
- **Characteristic physical appearance**
- **Hypogonadism** (poor sexual development)
- **Abnormal control of appetite/satiety predisposing to obesity**
- **Short stature for the family**
- **Developmental delay, learning and intellectual disability**
- **Behavioral disturbance**

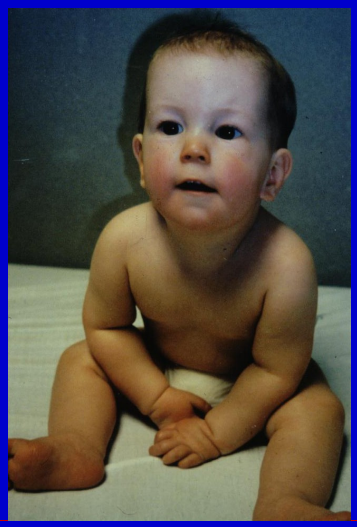
Hypotonia of PWS

- Low muscle tone: resistance to gravity at rest
- Most consistent feature of PWS
- Problem with signals from the brain to the muscles (central hypotonia), not an abnormality of the muscle itself
- Starts prenatally
  - Decreased fetal movement; abnormal delivery position (often breach) and timing (premature or post-mature)
  - Frequent need for assisted delivery, most often Cesarean section
- Most severe in newborn period
- Tone gradually improves, but not completely

Impact of Hypotonia: Infancy

- Poor suck causing poor feeding
  - Need for tube feeding or other special feeding methods for weeks to months
  - Rarely able to breast feed
- Poor weight gain and poor growth
- Delay in obtaining motor abilities
- Increase in hip problems from birth
- Increase in strabismus/squint (crossed eyes)



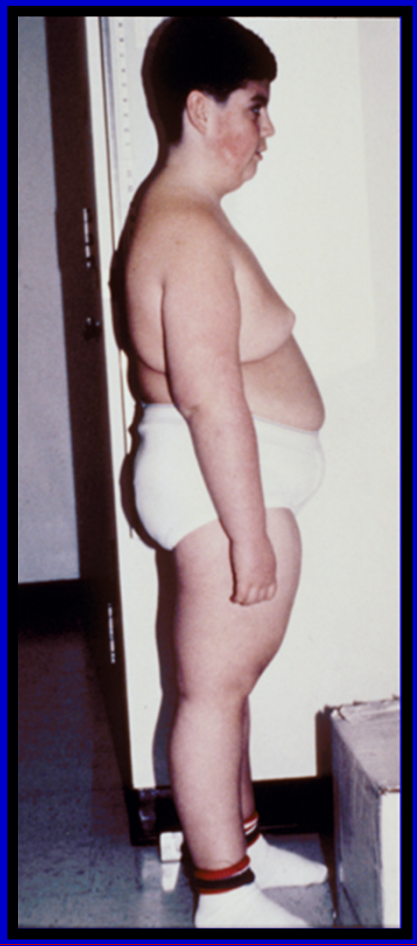


Other Features in Infancy:

- Lethargy; poor arousal, sleepiness
- Weak cry

Impact of Hypotonia: After Infancy

- Decreased muscle size and firmness
- Altered body composition
  - High fat:muscle & bone ratio
- Impaired coordination
- Decreased physical activity
- Sloping shoulders, poor posture
- Scoliosis/kyphosis (spinal curvature)
  - Can appear any time during childhood



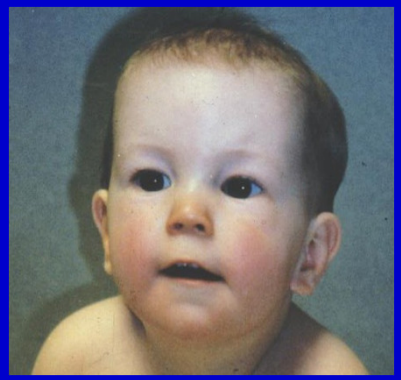
Treatment of Consequences of Hypotonia

No tested medication for hypotonia

- **Poor suck**: compensate with special feeding techniques (Dr. Tauber to discuss)
- **Poor weight gain** : close monitoring to assure it's normal
  - Added calories if needed
- **Hip problems**: check carefully in infancy (Dr. Van Bosse to discuss)
- **Delayed motor skills**: physical and occupational therapy & infant stimulation; plenty of interaction and activity (Janice Agarwal to discuss)
- **Scoliosis**: monitor (Dr. Van Bosse to discuss)
- **Decreased muscle size**: lots of exercise/physical activity once the individual is walking to compensate with strength

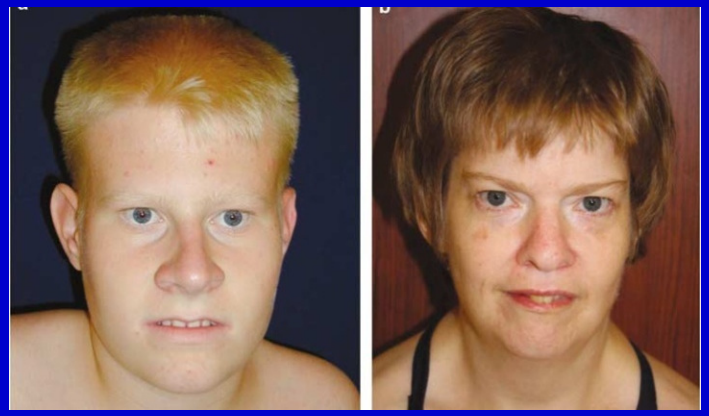
Characteristic Facial Appearance

- Narrow forehead
- “Almond-shaped” eyes, sometimes slanting upward
- Narrow nose bridge
- Down-turned mouth with thin upper lip



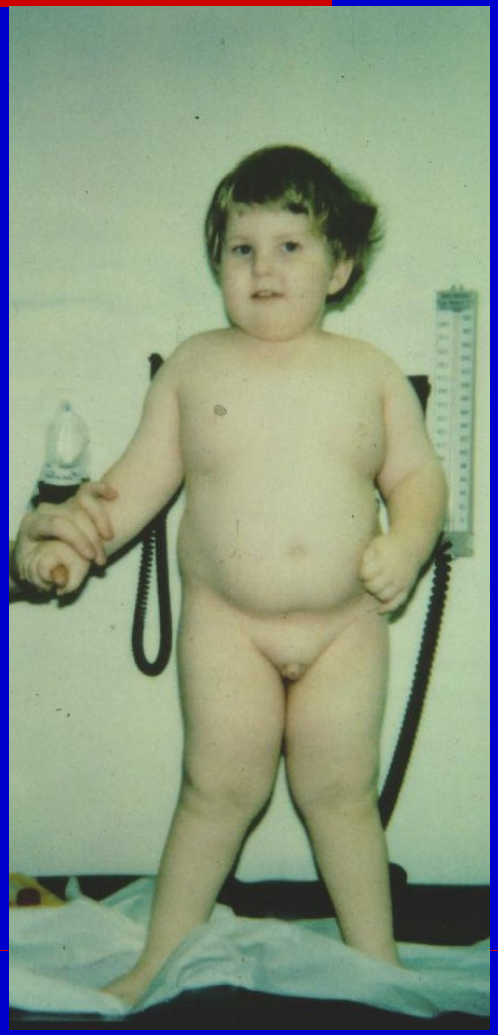
Probably related to altered pull by facial muscles on bones of the face due to hypotonia

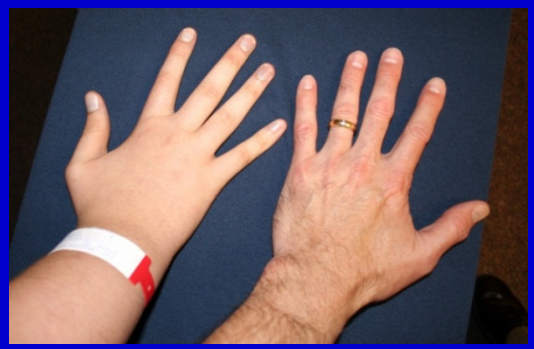
Highly variable



Additional Physical Features

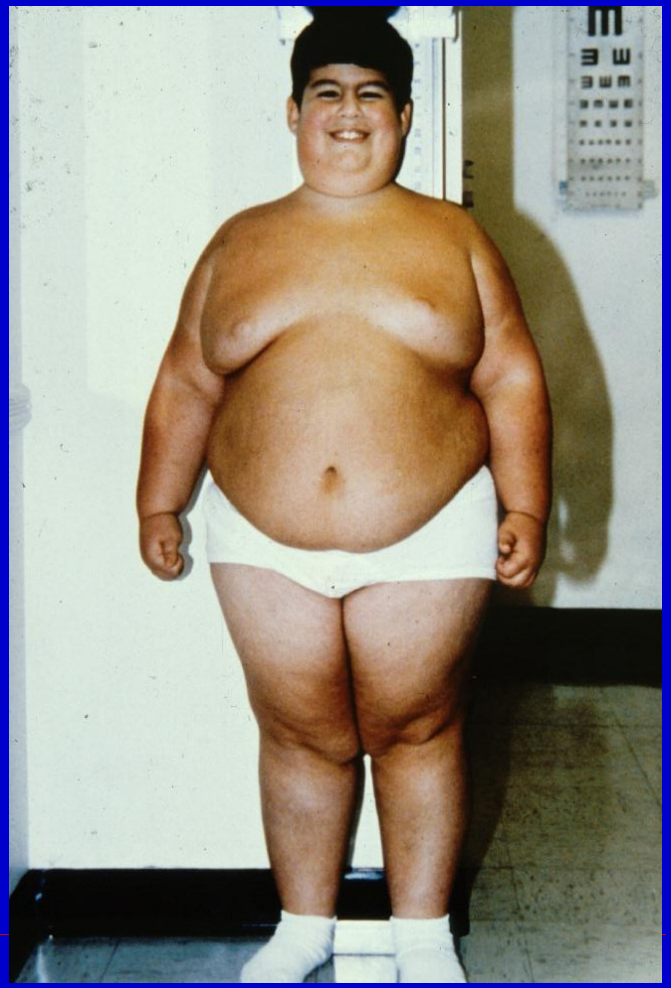
- Short, narrow hands
- Short, broad feet
- Knock knees
- Fair coloring for the family (~1/3)
- Increased bruising





Predisposition to Obesity in PWS

- Obesity and its consequences are the major causes of illness and death in PWS



Factors Predisposing to Obesity

(Discussed by Dr.Goldstone)

- **Hyperphagia** (excessive appetite and eating)
  - Abnormal perception of satiety by the brain
- **Decreased calorie needs**
  - Decreased muscle size
  - Short stature
  - Decreased physical activity
- **Decreased vomiting and decreased pain perception**
  - Lack of discomfort leads to eating too much too quickly

Hyperphagia: Characteristics and Consequences

- Onset after 1 year of age, sometimes after several years of age
- Highly variable intensity
- Excessive eating
  - Nearly constant seeking of food
  - Eating of unappealing food, hiding food, lying about getting food, stealing food and stealing money to buy food
- Hyperphagia present regardless of weight or whether food intake is controlled
  - ***Biological problem, not a psychological problem or a habit or behavior***
  - Behavior management alone does not control eating

Medical Consequences of Obesity

- Cardiopulmonary problems (heart strain, breathing problems)
- Increased risk for type II diabetes (obesity-related; mostly adults)
- Obstructive sleep apnea
- Skin and hygiene problems
- Digestive tract problems
  - Gallbladder disease (~10% of adults)
  - **Choking** on large pieces of solid food, especially when eaten quickly
  - **Gastroparesis** (weak stomach muscles causing slow emptying)
  - **Stomach bloating/ death of stomach cells/stomach rupture**
    - Since pain & vomiting are decreased in PWS, take them VERY seriously if they occur

Treatment of Obesity in PWS

- No proven effective medication to treat the excess appetite
  - Trials underway, some quite promising (discussed by Dr. Goldstone)
- Surgical treatment
  - High rate of serious complications
  - Low rate of long term weight loss success
- Management of obesity
  - **Very low calorie diet** (discussed by Constanze Lammer)
  - **Keep food secure** (environmental controls and constant supervision)
  - **Lots of physical activity** (discussed by Anne Livesey)
  - Growth hormone can help—by changing the ratio of fat to muscle and increasing activity (discussed by Dr. Kanumakala)

Growth in PWS: Untreated

- Length at birth usually normal
- Poor growth in infancy, presumed related to poor nutrition from poor suck plus growth hormone insufficiency
- Normal or slow rate of growth in first 10 years
- Lack of normal adolescent growth spurt
- Mild short stature for family

Growth Hormone in PWS

(Growth hormone deficiency and its treatment to be discussed in more detail by Dr. Kanumakala)

- Growth hormone insufficiency in most
- Positive effects on growth, body composition and shape, breathing, and physical abilities and activity
- Concern about worsening obstructive apnea early in treatment
  - **Sleep assessment and evaluation of tonsil size recommended in USA prior to GH treatment**

Hypogonadism: Small Genitals

- **Males:**
  - Undescended testicles (80%-100%)
  - Small penis
  - Small testicles
  - Underdeveloped scrotum sac (small, flat)
- **Females:**
  - Small labia minora & clitoris

Delayed and Incomplete Puberty

Males:

- Lack of masculine body shape and decreased body hair
- Unknown sex drive and functioning ; No documented fertility

Females:

- Significantly delayed onset of menstruation if it occurs
- No menstruation in over 50%; few & scanty menstrual periods in the remainder
- Four known cases of fertility worldwide

Both Sexes:

- Early underarm and pubic hair in 15%-20% ; rare true early puberty
- Much interest in dating, romantic activity and marriage

Hypogonadism in PWS

- Low sex hormones in most
- Secondary sex characteristics respond to treatment with sex hormones in both sexes
  - Doctors do not all agree on whether, when or how to treat
  - Some recent research studies, no published treatment trials
  - Not known to improve fertility

Other Hormone Problems

- **Hypothyroidism** (low thyroid hormone)
  - Thyroid gland controls the speed of the body's metabolism, so hypothyroidism causes slow metabolism
  - 10% to 25% of PWS
- **Central adrenal insufficiency** (poor adrenalin response to stress)
  - Conflicting studies as to whether or not it is increased in PWS (differ by method of testing)
  - No consensus on whether, when or how to test
    - Consider at times of surgery, severe illness or trauma

Sleep and PWS

- Daytime sleepiness and other abnormal sleep characteristics
- Increase in sleep apnea (central and/or obstructive)—pauses in breathing
  - Central apnea common in infants, decreases with age
  - Obstructive apnea most common in the obese (occurs in up to 50%)
  - Risk for obstructive apnea increased by chronic or acute respiratory problems or infections
- Recommendations:
  - Sleep assessment in everyone, especially if snoring during sleep
  - Treat as in general population

Other Nervous System Abnormalities

- **Decreased saliva flow**
  - May predispose to dental problems
  - Products are available to increase saliva flow
- **Skin picking**
  - Present in 1/3 – ½ of people with PWS
  - Some recent studies of possible medications
- **Altered temperature sensation/regulation**
  - Reports of low body temperature or fever of unknown cause
  - Altered ability to sense temperature, so need help with appropriate dress
- **Increased risk for seizures** (25%)
  - Usually mild and responsive to medication and outgrown

Developmental Delay/ Intellectual Disability

- Delayed motor and language skills
  - Average in PWS is twice the average age for general population
  - Poor speech pronunciation
- Typical IQ in 60's (range 40-90)
  - Most have mild intellectual disability; 40% have IQ above 70
- School problems in all
- Many adults can read, write, do simple arithmetic
- Treatment similar to others with disability
  - Early stimulation and therapies (physical, occupational, speech)
  - Special education, individualized to person's assessment

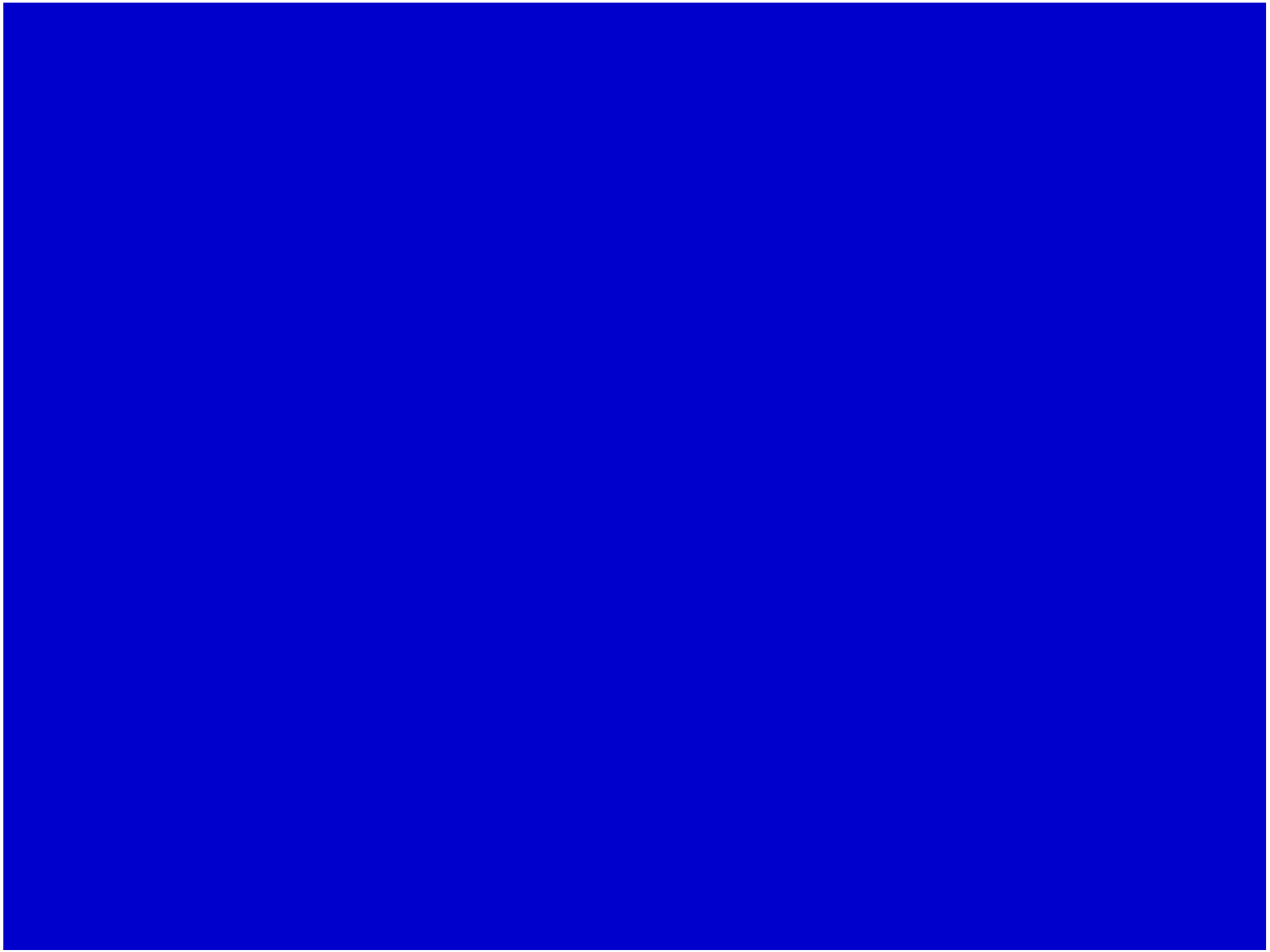
Behavior Disorder and Psychiatric Disturbance

- Behavior problems usually start after onset of increased appetite
  - Temper tantrums, stubborn & controlling behavior
  - Difficulty with disturbed routine, repetition
  - Impaired social skills
- Behavior problems may affect school placement, family relations, residential placement, and employment

- Significant increase in true psychiatric disorders/psychosis, onset in late adolescence and adulthood

Treatment of Behavior Problems

- **Importance of consistent limits**
  - Start early; never waver
  - Same rules for home, school, work, other caregivers
  - Communication is vital
- Anticipate difficulties with disturbed routine
- High expectations, but keep developmental age in mind
- Medications if necessary for severe problems to improve behavior or treat psychosis



What is the Cause of PWS

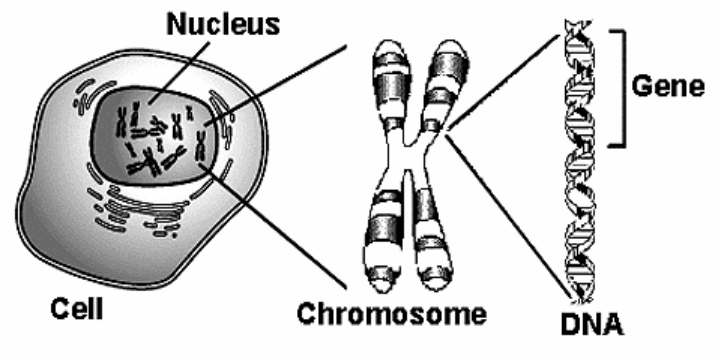
- **Many abnormalities in PWS relate to the hypothalamus**
  - Part of the brain that controls many functions
    - Appetite/satiety, secretion of growth hormone & sex hormones, temperature control, etc.
  - Special studies have revealed a decrease in the number of satiety nerve cells (oxytocin secreting) in the hypothalamus in PWS
  - Difficult to study the brain in a living person, but research progresses

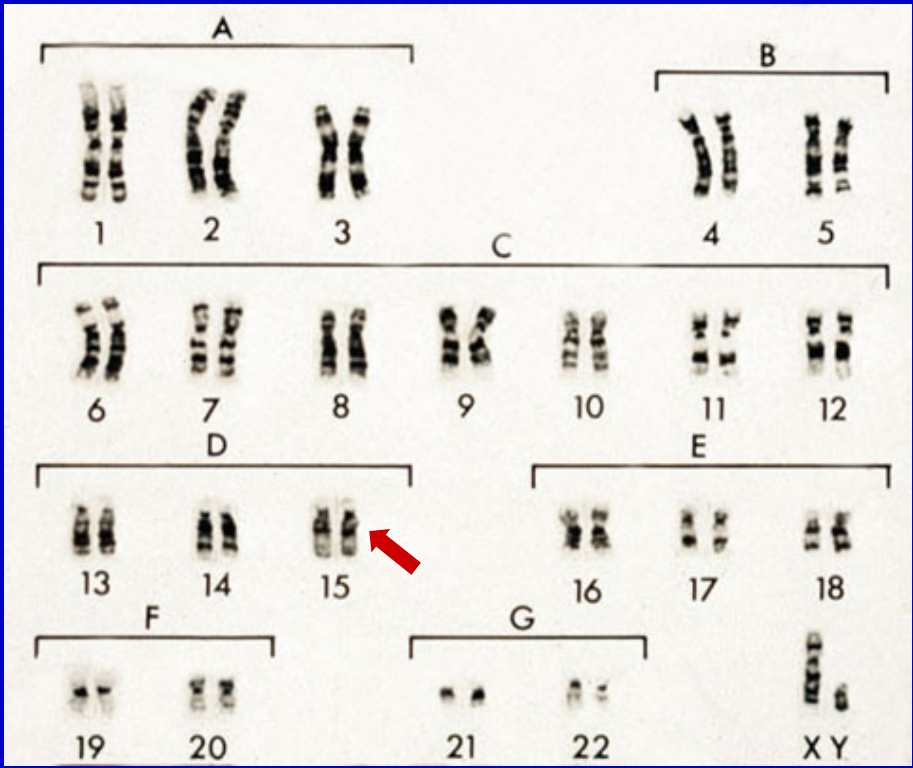
- **Much has been learned about the genetic basis of PWS**
  - Still learning how the genetic changes cause the findings of PWS

Some Basic Genetic Concepts

- DNA is our inherited information—instructions for how to make and operate a person
- A **gene** is a segment of DNA containing instructions to make a protein or a regulator of how much of a protein is made
  - Genes are connected to one-another in long strands of DNA
- Normally, all our genes come in **pairs**, one from each parent
- Genes are packaged and coiled up in **chromosomes**, which are in the nucleus of every cell in our body
- During conception, each the parent normally passes on one member of each chromosome pair in the egg or sperm, so the pairs are reconstituted in the offspring

Genes, Chromosomes and Karyotype





Genetic (Genomic) Imprinting:
A Complicated but Important Concept for PWS:

- Most genes expressed (provide instructions for making a protein or controlling substance) from both members of the chromosome pair, but not all
  - For a few (<5%), the gene or a segment of genes from one sex of parent gets silenced (not expressed)
  - These are called "imprinted" genes
  - Normal process to control the dosage of gene product
- The gene or genes relevant to PWS are imprinted:
  - Normally only expressed from the copy inherited from the father

PWS is Due to Lack of Expression of Important Genes

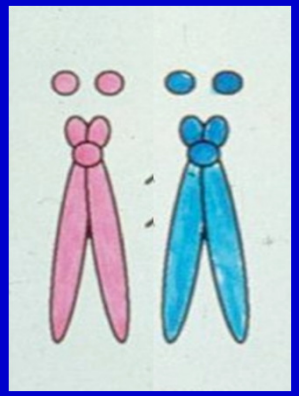
PWS occurs when there is no expression of those genes within band q11-13 from the member of the chromosome 15 pair inherited from the father

- The genes on the chromosome from the mother are already (normally) inactive (not expressed)
- This silencing process occurs by a chemical reaction with the DNA called methylation

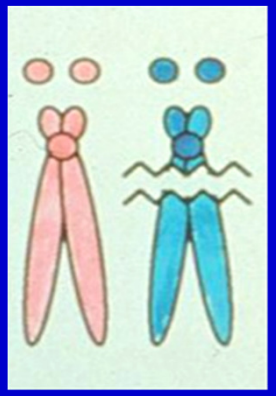
3 Major Genetic Causes of PWS

- **Deletion** of paternal 15q11-q13 (“deletion”, “del 15q”)
  - About 70% of people with PWS
- **Maternal uniparental disomy** for chromosome 15 (“UPD”)
  - Two maternal chromosomes 15, no paternal 15
  - About 25% of PWS
- **Defect in imprinting process** (“imprinting defect”)
  - The chromosome 15 inherited from the father is inactive like the chromosome 15 inherited from a mother

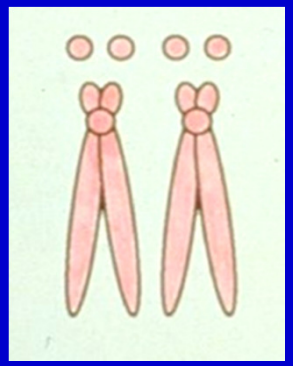
Chromosome 15 Pair in PWS



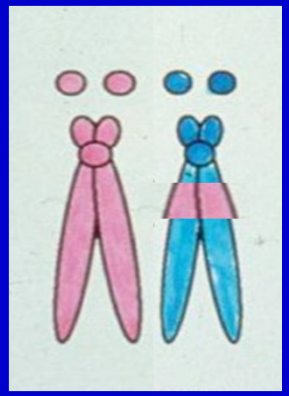
Typical



Deletion
70%



UPD
25%



Imprinting Defect
5%

Genetic Testing is Available for all Types

Methylation analysis

- **Detects all causes of PWS (>99%)**
- Does not identify genetic type

FISH for 15q deletion or Microarray

Uniparental disomy testing

- Traces genetic DNA variants in parents and child

If both FISH and disomy studies are negative

- Assume imprinting center defect
- Refer to a specialized lab to look for an imprinting center mutation for genetic counseling purposes

Differences Based on Genetic Cause

- No feature exclusive to one genetic type; ***Unable to predict presence or severity of features in an individual due to variability***
- Statistical differences in frequency or severity of some features between UPD and deletion
  - More common in UPD:
    - Post-term delivery
    - Slightly higher verbal IQ
    - Somewhat milder behavior problems
    - Greater frequency of psychosis and autism spectrum disorders
  - More common in Deletion:
    - Fair coloring
    - Characteristic facial appearance
    - Skill with jigsaw puzzles

Genetic Does Not Mean Inherited

Even though PWS is caused by a genetic change:

- Nothing that either parent did or did not do either before or during the pregnancy caused PWS
- Nothing could have been done to prevent it
- With only occasional exception, it is not inherited; Only a very few identifiable families have an increased chance of recurrence

The Future is Bright for PWS

- International community of families, care providers and researchers
- Improved health care and education through collaborative research efforts and education
- Improved public understanding of the issues faced by individuals with PWS and their families and caregivers
- Improved understanding of the cause and biological development of PWS, leading to improved treatments