

Prader-Willi Syndrome: An Overview

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Prevalence of PWS

1/10,000 - 1/25,000

One of the 10 most common disorders
seen in a genetics clinic

Topics for this Presentation

- Description of manifestations of PWS and an approach to their management
- Current knowledge about the cause of PWS

With gratitude to patients whose photos are used as illustrations and to their families

Concerning Management Recommendations

- Material presented based on
 - Medical literature
 - Discussions among experts
 - My personal opinion, based on 28 years of experience and input from many families
 - Very few controlled studies on management are published
 - Other equally competent physicians will manage problems differently—I will mention some of these other approaches
 - Sometimes an one individual responds differently from the average
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Variability

- **Syndrome** = a collection of features that are found together more often than by chance alone.
 - Not every affected individual has every finding
 - The severity of each finding is quite variable
 - For the most part, the severity of one finding does not determine the severity of other findings
 - Other family characteristics and life experience influence appearance, abilities and behavior
 - People can have problems or features unrelated to PWS
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Prader-Willi Syndrome: The Major Features

- **Infantile hypotonia** and lethargy; poor suck and poor growth
 - **Characteristic appearance**
 - **Obesity**
 - **Short stature**
 - **Sex hormone deficiency** (small genitals; incomplete puberty)
 - **Developmental disability**
 - **Behavioral disturbance**
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Hypotonia of PWS

- Hypotonia is poor resistance to gravity
 - Present in all
 - Due to a problem in the brain (central hypotonia)
 - Muscles are normally formed and function normally when stimulated
 - Starts prenatally; most severe in newborn period
 - Gradual improvement, but never normal
-

Impact of Central Hypotonia

Before birth:

- Decreased movement of the fetus
 - Abnormal delivery position and timing
 - Frequent need for assisted delivery, most often Cesarean section
-

Impact of Hypotonia: Infancy

- Lethargy; poor arousal
- Weak cry
- **Poor suck** causing poor feeding
- Failure to thrive (due to poor suck & increased work of feeding)
- Delayed motor skills
- May contribute to strabismus (crossed-eyes)



Impact of Hypotonia: Childhood & Adulthood

- Decreased muscle size
- Abnormal body composition (high fat:lean)
- Poor coordination
- Decreased activity
- Spinal curvature (scoliosis)



Management of Hypotonia

- Compensate for poor suck
 - Gavage feeding
 - Special nipples
 - Frequent feeding
- Physical and occupational therapy
 - Available through county-supported agencies until age 3 years
 - Available through school systems after age 3 years
- Plenty of parental stimulation
- Lots of exercise once the child is mobile
- No tested medication for hypotonia
 - A word about CoQ10...

CoQ10 and Hypotonia in PWS

- Co-Enzyme Q10 (CoQ10) is a natural product in the body that collects toxic breakdown products of oxygen
- It is low in people with reduced energy expenditure, muscle dysfunction, and disorders of energy metabolism
- Many parents and a few doctors of infants (in the US) are treating their child with CoQ10
 - Some suggest it causes increased activity, development and tone
 - Others say no effect
- No published well-designed study of its use
- No known serious adverse effects, if used in recommended doses

Characteristic Facial Appearance

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



Not everyone has this typical appearance, and familial appearance is a strong influence

Additional Physical Features

- Short, narrow hands with tapering fingers
- Short, broad feet
- Sloping shoulders
- Straight leg borders
- Decreased pigmentation for the family (~1/3)
 - Fair coloring is associated with decreased vision and strabismus



Obesity in PWS

- **The major cause of illness and death in PWS**
- Fat is mostly “central” (abdomen, buttocks and thighs) with sparing of hands and feet



Factors Contributing to Obesity

- **Drive to eat excessively (hyperphagia)**
 - Lack of sense of satiety apparently due to abnormality in the hypothalamus of the brain
 - Biological mechanism not yet determined
- **Decreased calorie requirement**
 - Decreased muscles (hypotonia)
 - Short stature
 - Decreased activity
- **High vomiting threshold and decreased pain threshold**

Hyperphagia: Characteristics and Consequences

- Onset after 1 year of age
 - On average, 2-4 years of age
 - Usually starts after severe hypotonia resolves
 - Often starts abruptly
- Excessive eating
 - Nearly constant food seeking, variable intensity
 - Foraging, eating of unappealing food, hoarding, lying about food, stealing food and money to buy food
- Hyperphagia present regardless of weight or whether food intake is externally controlled
- It cannot be voluntarily controlled
- Severity quite variable

Medical Consequences of Hyperphagia and Obesity in PWS

- Cardiopulmonary compromise (Pickwickian): affects heart and breathing
- Increased risk for type II diabetes
- Obstructive sleep apnea
- GI problems
 - Choking (esp. hot dogs!)
 - Constipation/Diarrhea
 - Gallbladder problems (~10% of adults)
 - Gastric dilatation/ necrosis/rupture

Circumstances of Gastric Necrosis

- Usually, a relatively small stomach
 - Often after a history of significant obesity followed by gradual significant weight loss on a low calorie diet (often in a group home)
- +/- Known episode of bingeing, often at special event
- Hours later, acute onset of symptoms:
 - **Complaints of stomach pain**
 - **± Evident abdominal distention**
 - **Vomiting**
- Sudden severe illness or even death from sepsis or blood loss related to gastric necrosis and rupture

PWS Characteristics Predisposing to Gastric Necrosis

- Hyperphagia, regardless of weight or diet
- Significant weight loss, often in adulthood when in residential placement
- High pain threshold, masking symptoms
- High vomiting threshold
- Gastroparesis (weakness of the stomach) may be a frequent finding
 - Weak stomach leads to delayed emptying
- Most likely cause:
 - Thinning, loss of stomach muscle tone and decreased muscles in a shrunken stomach following weight loss

Cautions Relating to Gastric Necrosis

- Be suspicious of apparent “viral gastroenteritis” symptoms without known virus exposure
- Any vomiting or declared abdominal pain deserves thorough and immediate evaluation
- Closely monitor people with PWS (especially thin ones) after a binge for symptoms of gastric dilatation and abdominal pain
 - Holiday parties are a particular hazard
- Symptoms may occur and resolve—not everyone dies of these problems

Pathogenesis of Hyperphagia

- Problem sensing satiety (Holland; Zipf & Bernston)
 - Will eat continuously for an hour
 - Eat huge quantities without feeling “full” or uncomfortable
 - Interested in eating again in ½ hour
- No known hormonal or other physiological correlate
 - No evidence for abnormal levels of leptin (involved in sensation of satiety) or its receptor in PWS
 - Fasting levels of ghrelin (appetite-inducing factor) extremely high in PWS (not in other causes of obesity); but it decreases appropriately with eating or somatostatin

Management of Obesity in PWS

- No current pharmacologic treatment for the hyperphagia
- Surgical treatment
 - Recent review of reported results (mostly from surgeons) shows a high rate of complications, sometimes lethal, and low rate of long term weight loss success (Scheimann, 2006)
 - No clinical trials

Management of Obesity

- Low calorie diet
 - About 10 kcal/cm height, or ~1000 kcal/day
 - Assure adequate vitamins and calcium
 - Consultation with a dietitian is helpful
- Consistent frequent exercise/physical activity
 - Minimum ½ hour/day
 - More exercise makes more calorie intake (or more weight loss) possible

Management of Obesity

- Remove temptation
 - Lock kitchen; supervision at school and work
 - No high calorie foods in the home
 - Regular meals (and snacks)
 - Compensate for extra food at the next meal
 - Plan carefully for holidays, parties, meals away from home
- Regular weighing (weekly)
- Reward compliance and success
- Regular follow-up (e.g., with a physician or dietitian)



Growth in PWS--Without Intervention

- Generally normal at birth
- Failure to thrive in infancy
- Normal or slow rate of growth in 1st decade; usually <average for height (related to parental height)
- Lack of pubertal growth spurt
- Short stature for family
 - Males mean: 155 cm
 - Females mean: 148 cm

Growth Hormone (GH) in PWS

- Deficiency of GH well demonstrated in PWS
 - GH responses testing shows decreased response
 - IGF-1 levels relatively low (mean: -1.5 SD)
 - Abnormal body composition (high fat mass, low lean body mass)
- Contributor to:
 - Short stature
 - Altered body composition (high fat mass)
 - Reduced muscle mass
 - Osteopenia
 - Decreased energy, physical activity, agility
 - Obesity

Growth Hormone Replacement in PWS

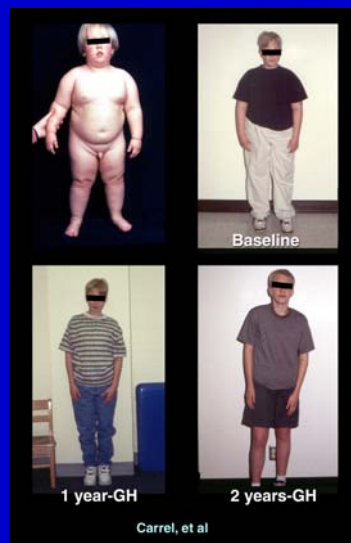
Results of controlled trials involving >100 patients

- Brisk, dramatic increase in speed of growth
- Improved body composition
 - Increased lean body mass (bone density and muscle size)
 - Decreased fat mass (lipolytic effect)
 - Increased energy expenditure
 - Improved motor skills, strength, agility and endurance
 - Increased respiratory muscle forces

Growth Hormone Replacement

Physical Effects

- Increased ultimate stature
- Increased muscle size
- Improvement in hand and foot size
- More normal body shape
- More normal facial appearance in some if started early



GH: Normalization of Facial Appearance





Growth Hormone Replacement: Possible Problems

- Daily injection (rarely an issue)
- Concern about worsening or causing scoliosis—but studies have shown no increase in frequency
- Swelling; rare pseudotumor cerebri
- Dose-dependent increase in insulin levels
 - Occasional onset of type II diabetes mellitus
- Increased strength in those with severe behavioral problems
- Possible cause of deaths in young children with PWS taking GH...

Presumed Mechanism Causing Death

- Death by airway obstruction
 - Known growth stimulating effect of GH on lymphoid tissue
 - Pre-existing compromised respiratory system
 - Pre-existing sleep disturbance
- 17 reports of death worldwide of children taking GH (P.Lee, Growth, Genetics & Hormones 22, June 2006)
 - Most were very obese (12) and/or had severe pre-existing respiratory problems (9)
 - GH improves respiratory status (Miller et al 2006) and obesity in the long term

Conclusions About Growth Hormone

- Growth hormone deficiency is a significant component of the PWS phenotype, affecting growth, appearance & body habitus, health
- Replacement therapy can improve or normalize all of these
- Although GH should be used cautiously in those with obesity and respiratory problems, both are improved by GH in the long term
- Recommendation: Evaluate for respiratory and sleep abnormalities before starting GH and during therapy
 - Consider weight loss prior to therapy for the very obese
 - Do a sleep study prior to initiation of GH therapy, and treat treatable sleep problems
 - Do a follow-up sleep study in 6 weeks to identify worsening apnea

Growth Hormone Deficiency in Adults with PWS

- Growth hormone deficiency documented in adults with PWS
 - Studies of growth hormone replacement in adults (20-25% of childhood dose) are now taking place and are promising
 - Improved body composition (decreased body fat, increased muscle)
 - Increased energy expenditure, activity, strength, agility
 - Improved respiratory function
 - Mental speed and flexibility (Hoybye et al 2005)
 - Concerns
 - Same as in children
 - Who will pay
-

Hypogonadism in PWS

- Decreased function of ovaries and testes
 - Major manifestations:
 - Small/underdeveloped genitals
 - Deficient/altered pubertal development
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Underdeveloped Genitals

- **Males:**
 - Small penis
 - Undescended testes (80%)
 - Underdeveloped scrotum (small, poor rugation & pigmentation)
 - **Females:**
 - Small labia minora & clitoris
 - Persists throughout life if not treated
-

Abnormal Pubertal Development

- Early body hair, acne, adult odor (premature adrenarche) in ~15%
 - Delayed and incomplete puberty in most
-

Pubertal Insufficiency

Females:

- Late onset of menstruation (as late as 30's)
 - No (55%) or few menstrual periods
 - Infertility
 - A few females worldwide reported to have had babies
 - **Need for birth control and sex education**
-

Pubertal insufficiency

Males:

- Lack of masculine body shape
 - Thin beard, body, pubic & axillary hair
 - Sex drive and functioning largely unknown
 - No known fertility
-

Management of Hypogonadism

- Can get normal appearing secondary sex characteristics with sex hormone replacement (estrogen or testosterone)
 - In females, menstruation can be maintained with hormone treatment
 - Few studies, no treatment trials
 - In males, an increase in behavior problems may be an issue if testosterone treatment occurs
 - Use of patch or gel may avert this issue
-

Other Issues in PWS

- Other nervous system abnormalities
 - Osteoporosis
 - Sleep abnormalities
 - Orthopedic problems
-

Other Nervous System Abnormalities

- High vomiting threshold
 - High pain threshold
 - Decreased saliva flow
 - Picking at skin, nails other places
 - Altered temperature sensation/regulation
 - Increased risk for seizures (10%-20%)
-

Management of Other Nervous System Problems

- High vomiting threshold
 - Use vomiting-inducing medications with caution
 - High pain threshold
 - Investigate any complaints of pain
 - Decreased saliva flow
 - Use saliva stimulants (e.g., Biotene)
 - Good oral hygiene
 - Regular dental visits (consider quarterly)
-

Management of Other Nervous System Problems

- Skin picking
 - Keep areas moist
 - Keep lesions covered, if possible
 - Provide distraction, especially for hands
 - Rectal picking
 - No long periods in bathroom alone
 - Altered temperature sensation/regulation
 - Charts for recommended clothing
 - Treat hyperthermia and hypothermia as in general population
-

Bone Density/Osteoporosis in PWS

- Not well studied
 - Contributing factors:
 - Sex hormone deficiency
 - Growth hormone deficiency
 - Hypotonia
 - Inactivity
 - Possibly decreased calcium intake
 - Increased long bone fractures, not spinal
-

Treatment or Prevention of Osteoporosis

- Do a bone density study (DEXA) in early adulthood
 - Assure adequate calcium and vitamin D
 - Weight-bearing exercise
 - Growth hormone helps
 - Sex hormone replacement?--not studied
 - Bisphosphonates not studied
-

Sleep and PWS

- Increase in **sleep apnea**
 - Central and/or obstructive or mixed
 - **Decreased arousal** to low O₂ & high CO₂ in sleep
 - Spells of **hypoventilation** (decreased frequency and depth of breathing) with/without low O₂
 - **Excessive daytime sleepiness**
 - **Abnormal sleep architecture**
 - Sleep-onset REM; arousals
-

Sleep and PWS

Risk for sleep problems increased by:

- Young age (infancy); severe hypotonia
 - Morbid obesity
 - Prior respiratory problems
-

Recommendations Concerning Sleep Studies in People with PWS

All individuals with Prader-Willi syndrome should have a sleep study, particularly if they have one or more of the following:

- Very severe hypotonia
 - Snoring
 - Spells of not breathing during sleep
 - Frequent respiratory problems
 - Large tonsils and adenoids
 - Planned growth hormone treatment
-

Treatment of Sleep Problems

- Same as for general population
 - Standard treatments may include
 - Tonsillectomy/adenoidectomy
 - Weight loss
 - Sleeping with head elevated
 - CPAP (continuous positive airway pressure)
 - Oxygen at night
 - Ultimately, growth hormone treatment may improve sleep
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Orthopedic problems

- Scoliosis/kyphosis
 - Congenital hip dislocation and other problems
 - Knee and ankle problems
 - Foot problems, especially flat feet and calluses
-

Treatment of Orthopedic Problems

- Check for these problems, even in the absence of complaints
 - Management is the same as in general population
 - Weight loss (or prevention of obesity) often helpful
-

What Causes People with PWS to Die?

- Very few reports until recent concern about deaths in young children started on growth hormone
 - Difficult to study in a scientific manner
 - Few families opt to have post-mortem examinations for a cause of death
-

Predisposing Characteristics in PWS

- **Hypotonia**, causing decreased respiratory effectiveness
 - Decreased respiratory muscle strength, force of breathing (FVC decreased by 40%) and lung pressures
- **Obesity** causing high fat mass on and around the heart and lungs
- **Sleep disturbance**
 - Hypoventilation & desaturation episodes; obstructive apnea when obese
- **Other brain problems**
 - Primary disturbance of central respiratory control
 - Abnormal temperature regulation
 - High pain threshold

PWSA(USA) Survey of Causes of Death

- Began in 1999, in response to concerns about deaths related to growth hormone treatment and in conjunction with a bereavement counseling program
- Information maintained in a database kept by a PWSA volunteer
- In 2004, a committee was established to investigate causes of death
 - IRB approved
 - Questionnaire to families
 - Medical records obtained

Major Causes of Death in PWS

1. Respiratory compromise (32% - 65%)
2. Cardiac arrest (23%)
3. Sudden unexplained death (no autopsy)
4. Choking on food (8%)
5. Sudden infant death (SIDS)
6. Ruptured/necrotic stomach (adults; 4% - 8%)
7. Accident

Developmental Disability

- Age at achievement of motor skills varies
 - Largely related to severity of hypotonia
 - Average: sit unsupported at 12 months, walk at 24 months
- Age at development of language varies
 - On average: words at 2 years; sentences at 3-4 years
 - Language is ultimately a skill in many
 - Severe expressive language impairment occurs in some
- Poor speech articulation-- persists
 - Hypotonic oral muscles
 - Poor palate closure (velopharyngeal insufficiency)
 - Thick saliva may have an effect

Intellectual Disability in PWS

Highly variable abilities

- Average IQ in 60's
 - Most have mild mental disability
 - 40% have IQ above 75 (cut-off for "normal" intelligence)
 - About 40% have more severe impairment
 - Abilities can be influenced by many factors
 - Other genes/familial abilities
 - Difficulties at delivery or malnutrition as an infant
 - Illnesses, sleep apnea, etc.

Intellectual Disability in PWS

- School problems in all, often more severe than expected for IQ
- Most can have supported employment and be productive
- Most adults can read (and like to), write, do simple arithmetic
- Most are very communicative
- Many enjoy jigsaw puzzles and word-find puzzles

Management of Learning Disabilities

- Involvement with educational stimulation and therapies (physical, occupational, speech) from an early age
- Parents must be an advocate for the child with the schools
 - Be sure your child has appropriate educational evaluation
- Plan for work during adulthood
- Supported employment in adulthood is very important

Behavioral Disorder in PWS

- Behavior problems usually start after onset of excessive eating
 - Temper tantrums, stubborn behavior
 - Difficulty with disturbed routine, repeating questions
 - Compulsive-like behaviors (repeated organizing, writing, collecting, need to finish one thing before moving to the next)
- Adolescence is a difficult time (as in the general population)
- Behavior problems may impact school placement, family relations, residential placement, and employment
- Behavior difficulties tend to improve late in adulthood
- Increased incidence of psychosis, onset in adolescence and young adulthood

Management of Behavior Problems

- Consistency in limit setting is extremely important in management
 - Start early; never waver
 - Good communication among care givers is critical
 - Have a low threshold for getting help from a behavior therapist
- Counseling can be of considerable benefit
- Medications may be helpful if problems are severe

Psychiatric Problems in PWS

- Increase in psychiatric disorders
 - Psychosis in some
 - Incidence still unclear: probably $\geq 10\%$
 - Onset in young adulthood
 - Appears to be more frequent in those without the deletion
 - Treatable by standard medications

Recommendations for Optimizing Outcome for PWS

- Closely monitor infants for poor growth
- Assure lots of stimulation in infancy
- Avoid (or treat) obesity
 - Exercise, exercise, exercise
 - Reduced food intake; limit temptation
 - Assure adequate intake of protein, vitamins and calcium
- Evaluate and treat sleep disturbance
- Consider growth hormone to improve body composition in children and adults
- Consider sex hormone therapy

Optimizing Outcome for PWS

- Have high but reasonable expectations
 - Be familiar with normal development and your child's developmental age
- Counseling and medication for behavioral and psychiatric problems
- Recognize the importance of stable, close relationships, the need to lead a useful life and have a sense of security
- Keep having meetings like this one, with communication among families and with researchers

Why Does PWS Happen?

Role of the Hypothalamus

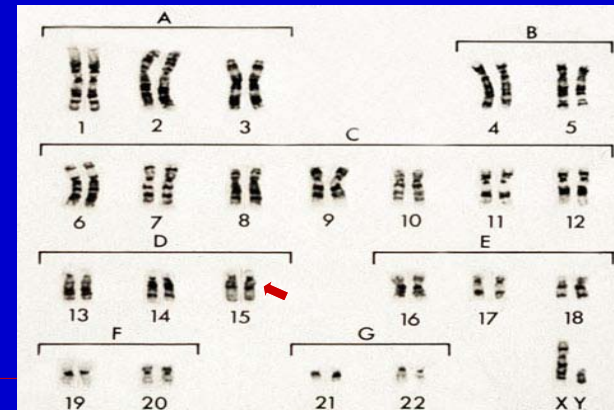
Many of the abnormalities in PWS relate to the hypothalamus in the brain

- Decreased number and size of cells in one part of the hypothalamus (Swaab)
- But the abnormality is not known

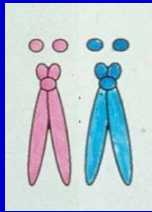
Genetics of PWS

- In 1981: First report that the genes important for preventing PWS are located on the long arm of chromosome 15 (Ledbetter et al.)

Normal Chromosome Karyotype



Genetic Expression at 15q11-13 Differs Depending on Parent of Origin

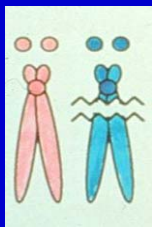


- Normally situation
- Only the genes inherited from the father are “active”
- The same genes inherited from the mother are “switched off” by a chemical reaction called methylation and do not contribute genetic information (called Genetic Imprinting)
- Anything that results in absence of those paternally-inherited genes causes PWS

Genetic Basis for PWS

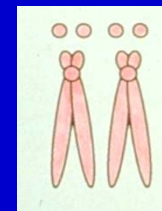
Three ways it can occur...

1. Deletion of Chromosome 15q11-13



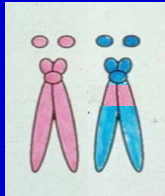
- Missing segment of the chromosome
- Deletion causes ~60-70% of PWS
- In PWS, the deletion has always occurred in the chromosome 15 inherited from the father
- Parents do not have this chromosome change, just the one sperm that resulted in the affected child
- Happens by accident due to the complexity of the process of getting chromosomes from parent to child

2. Uniparental Disomy 15 (UPD)



- Causes ~25-30% of PWS
- Two chromosome 15s from the mother, none from the father
- An accident of cell division in the egg
- Both 15q11-13s are structurally normal but inactive
- Result: deficiency of active (father's) expression of genes important for preventing PWS

3. Imprinting Defect



- ~5% of affected individuals
- Abnormality in process of activation of the father's genes important to PWS
- Most of unknown cause; it's random
- Some due to a tiny change in the genetic center that controls the chemical reaction that silences the genes (through methylation); the Imprinting Center
 - PWS can happen again in such families
- Sometimes due to rearranged chromosomes

So, There are 3 Causes of PWS

1. Deletion (70%)
 2. Uniparental disomy (25%)
 3. Imprinting defect (5%)
- Nothing that either parent did or did not do either before or during the pregnancy caused PWS
 - Only a few parents have an increased chance for PWS to happen a second time in the family—they can be identified by testing parents of a child with an imprinting center defect

PWS Diagnostic Testing

Methylation analysis

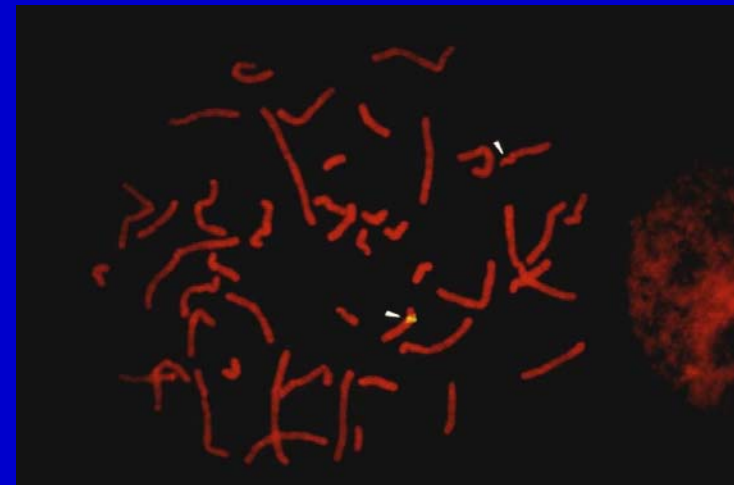
- Detects all causes of PWS (99%)
- Relatively inexpensive DNA-based test
- Does not identify genetic basis

FISH (fluorescence in situ hybridization) for 15q deletion

- If negative, do **uniparental disomy testing** by tracing genetic DNA variants in parents and child

If both are negative

- Refer to a specialized lab to look for an imprinting center defect



The Actual Genes That Cause the Features of PWS:

Still unknown...

- 15-20 genes in the 15q11-13 region, only some of which are identified
 - For none is the correlation between gene function and clinical effect well established
 - One or more must relate to function of the hypothalamus
 - Mouse models of PWS are likely to be very helpful in understanding which genes are responsible and the biology of how PWS occurs
-

Genotype-Phenotype Correlations

Compared to patients with deletions, those with UPD on average have:

- Less typical facial appearance
 - Higher average IQ (8 points)--especially verbal
 - Poorer visual-spatial skills
 - Less skill with jigsaw puzzles
 - Less maladaptive behavior
 - Fewer obsessive-compulsive symptoms
 - More autism spectrum features
 - Higher rate of psychosis
-

Genotype-Phenotype Correlations

- **There are 4 genes between the two common breakpoints at one end of the deletion**
 - Mild differences in cognitive and psychological function, behavior, and possibly speech reported between individuals with the larger type I deletion than those with the type II deletion
 - Must be interpreted in the context of much greater variability among people with the same breakpoints
-

Please Remember!

- PWS is quite variable
 - Not everyone has every feature
 - The severity of one feature often does not correlate with the severity of other features
 - Other family characteristics and life experience influence appearance, abilities and behavior
 - People can have problems or features unrelated to PWS
-

The PWS Phenotype is Highly Variable

- Individual manifestations vary independent of one another
 - Familial differences
 - Racial differences
 - Genetic basis differences
 - Other causes? Random?
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Prader-Willi Syndrome: We've Come a Long Way!

- Improved clinical characterization
 - Delineation of manifestations
 - Appreciation of natural history
 - Recognition of variability
 - Better understanding of causes of manifestations
 - Better genetic testing and better diagnosis
 - Improved management
 - Poor feeding Growth hormone
 - Medications for behavior difficulties
-

More Progress is Yet to Come!

- Improved understanding of the process that causes PWS will lead to better treatments
 - Improved understanding of and treatments for
 - Low muscle tone
 - Appetite/obesity
 - Behavior
 - Learning problems
 - Sex hormone deficiencies
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-