Imprinting Disorders: Prader Willi and Angelman Syndromes

Maddie Berra

Genetics 2020

Monoallelic gene expression

The normal phenomenon of parent specific gene expression

Both alleles are inherited and in the DNA sequence, but only one is coded for expression

Silencing of non-expressed gene is based on DNA methylation (epigenetics)

The imprinted gene is the one which is not expressed

Mechanism of imprinting disorders

Deletion or mutation of expressed gene

Uniparental disomy

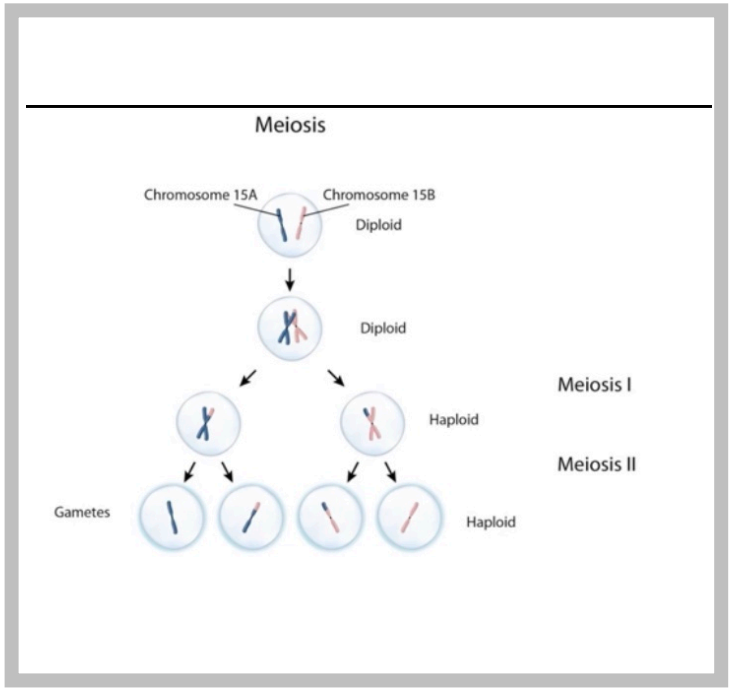
- Two copies of chromosome from 1 parent, none from other parent caused by nondisjunction

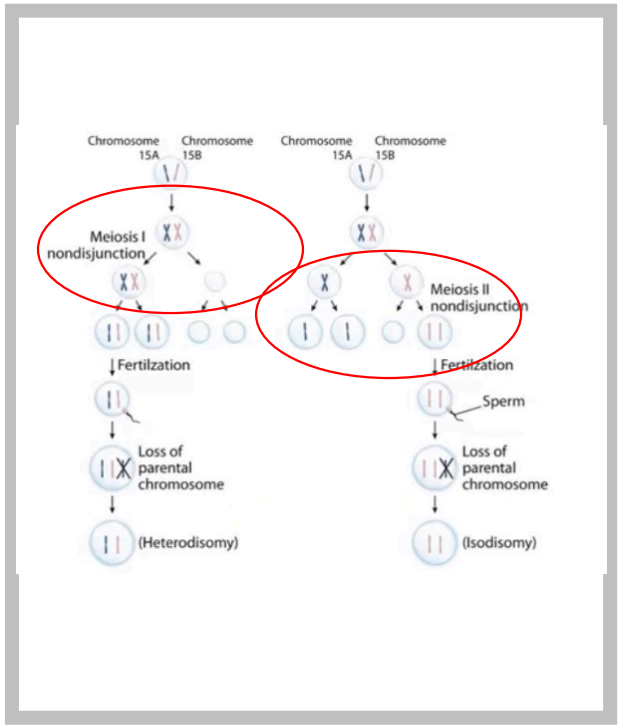
- Nondisjunction in Meiosis I = heterodisomy

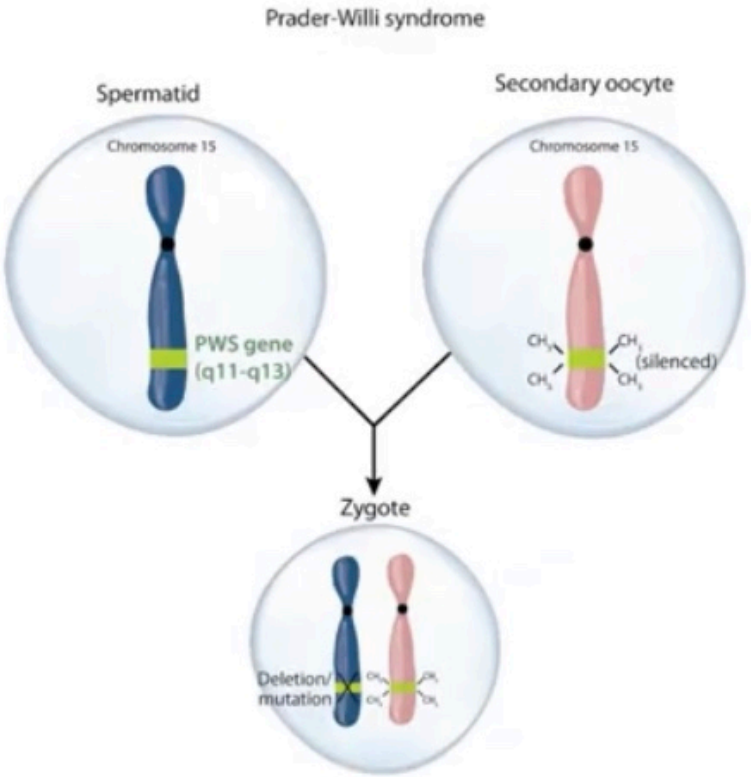
- Nondisjunction in Meiosis II = isodisomy

Imprinting

Uniparental Disomy







Prader-Willi Syndrome: Pathophysiology

There is usually monoallelic expression of the paternal PWS gene located on Chromosome 15q11-13

A lack of expression leads to Prader-Willi Syndrome

- Paternally inherited deletions (~70%)
- Maternal UPD (20-30%) (two copies from mom = two copies of silenced gene)
- More rarely: imprinting center deletions, unbalanced chromosome rearrangement

Prader-Willi Syndrome: Features

Prenatally

- 1/15,000 Live Births
- Decreased fetal movement, SGA, Polyhydraminos

Infancy

- Profound hypotonia, often causing feeding difficulties leading to FTT
- May are G-tube dependent in infancy

Childhood

- Delayed motor milestones
- Mild-moderate cognitive impairment
- Behavior problems: temper tantrums, self injurious behavior (skin picking), ASD (in 25%)
- Onset of hyperphagia (age 3-4) with insatiable and difficult to control food seeking behaviors
  - Possibly related to increased levels of ghrelin
- 25% develop epilepsy disorders

Adolescence

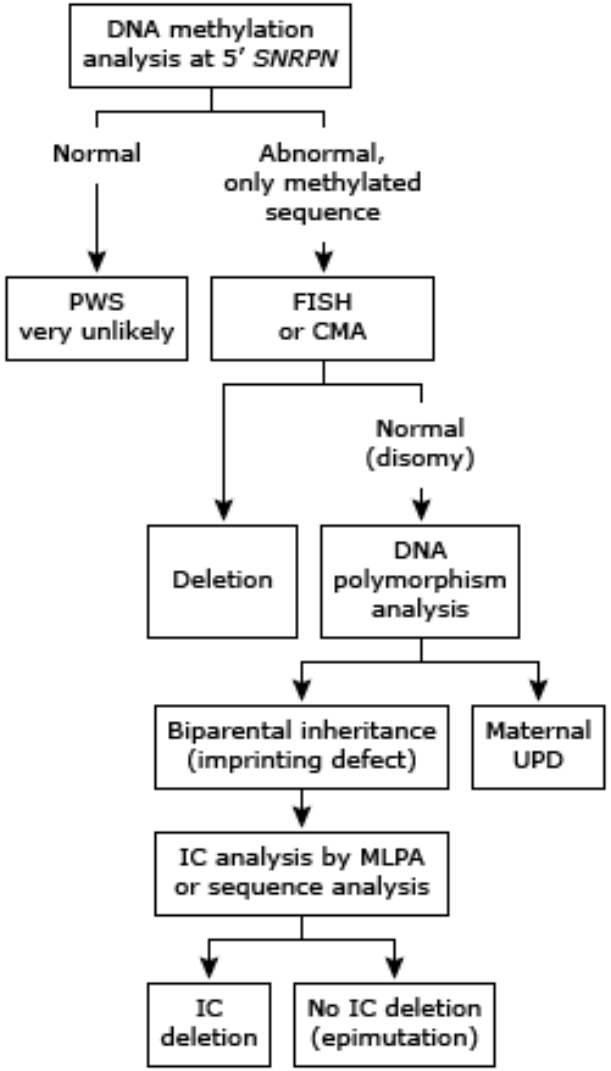
- Early adrenarche but delayed true puberty
- Short stature
- Obesity related health disorders (OSA, hypoventilation, T2DM, atherosclerosis)
- Scoliosis

Long term

- Survival past 50 is rare
- Death usually secondary to obesity related health problems

Prader-Willi Syndrome: Diagnosis

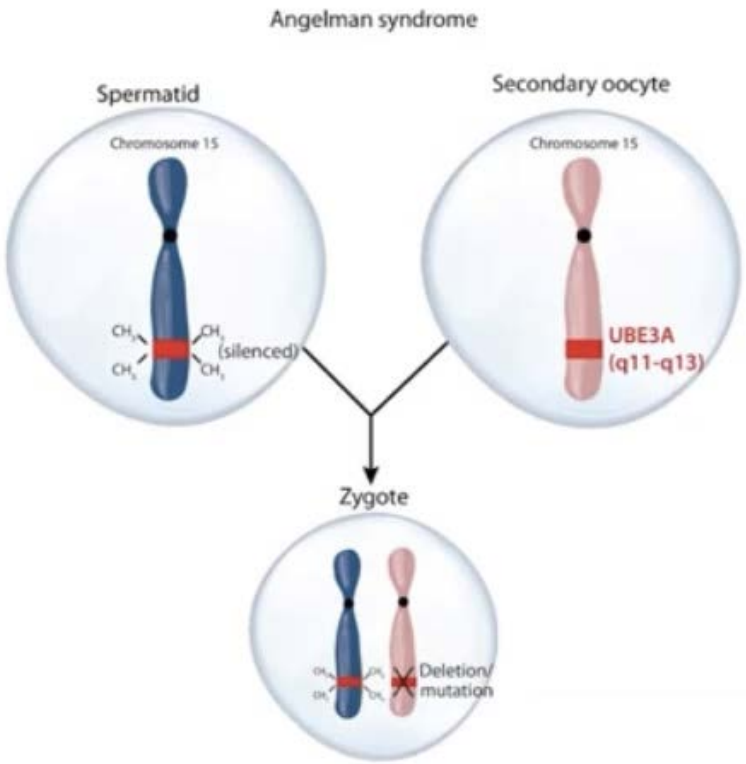
- Definitive = genetic testing
- Who to test?
  - Birth to two years
    - Hypotonia with poor suck and poor weight gain, and cryptorchidism in males
  - Two to six years
    - Hypotonia with history of poor suck
    - Global developmental delay
    - Short stature and/or growth failure associated with accelerated weight gain
  - 6 to 12 years
    - History of hypotonia with poor suck
    - Global developmental delay
    - Excessive eating (hyperphagia: obsession with food)
  - 13 years through adulthood
    - Cognitive impairment
    - Excessive eating
    - Hypogonadotropic or hypergonadotropic hypogonadism
- Diagnosis follows an algorithm to determine origin of imprinting disorder



IC = Imprinting Center

Prader-Willi Syndrome: Treatment & Interventions

- In infancy
  - Feeding therapy, g-tube if unable to safely feed or meet required nutrient intake
- Mainstay of treatment is preventing obesity and thus associated health problems
  - Requires strict adherence to low calorie diet
  - Often requires restricting physical access to food (locks on refrigerator, pantry, trash can)
  - Phentermine and weight loss surgery not shown to be helpful
- Treatment of Growth Hormone deficiency
  - May help with obesity control as well as linear growth
  - Increased risk of side effects of worsening scoliosis and type 2 diabetes



Angelman Syndrome: Pathophysiology

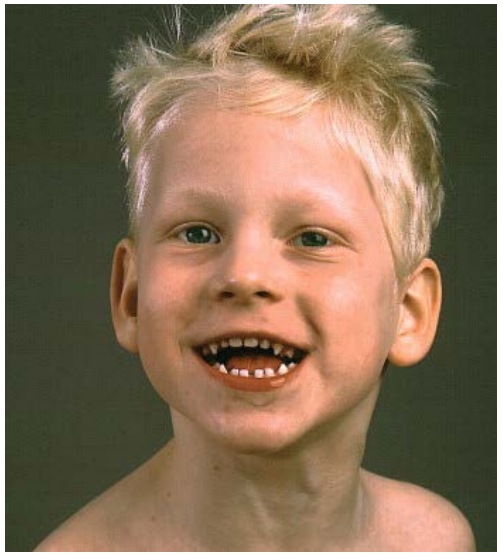
There is usually monoallelic expression of the Maternal UBE3A gene located on Chromosome 15q11-13

A lack of expression leads to Angelman Syndrome

- Maternally inherited deletions (68%)
- Paternal UPD (8%) (two copies from dad = two copies of silenced gene)
    - Nondisjunction is more common in females
- Imprinting center deletions (3%)
- UBE3A mutations (11%)

Angelman Syndrome: Features

- 1/10,000-1/20,000 live births
- Characteristic physical features (microcephaly, prognathism)
- Abnormal behaviors
  - Paroxysmal laughter (unique and specific feature)
  - Happy demeanor and emotional lability
  - Hand flapping
  - Abnormal mouthing behaviors and tongue thrusting
  - Sleep disturbance
- Developmental delays
  - Severe intellectual disability
  - Poor language development
  - Markedly delayed motor milestones with ataxia
- Seizure disorders (80% by age 2)

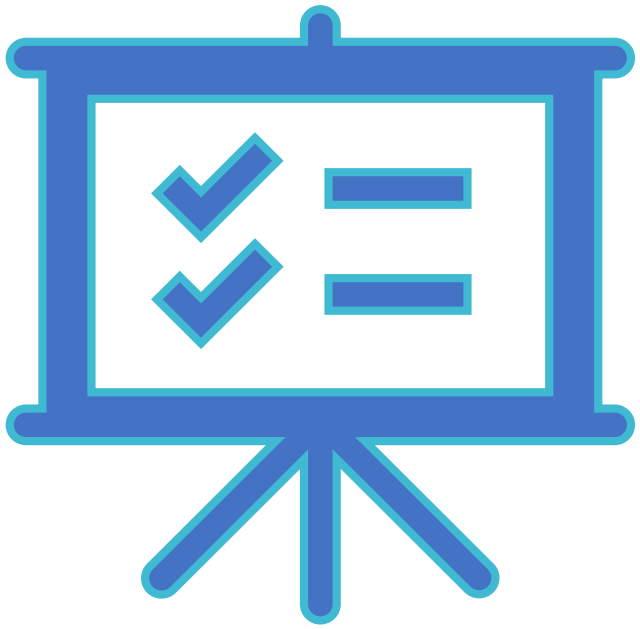


Angelman Syndrome: Diagnosis & Treatment

- Diagnosis
  - Step 1: methylation studies
  - Step 2: if methylation studies positive → CMA (array comparative genomic hybridization [aCGH])
    - This can identify the deletion type
  - If aCGH is negative → evaluate for UPD (usually by SNP)
  - If no evidence of UPD → imprinting center studies
  - If initial methylation studies negative but high clinical suspicion remains → UBE3A gene studies
- Treatment is primarily supportive
  - OT, PT, Speech
  - EEG after age 1 and treatment of seizure disorder

Screening & Genetic Counselling

- Increased frequency of imprinting disorders in advance reproductive technology (likely secondary to epigenetic disruption)
- Prader-Willi
  - <1% recurrence risk if etiology is paternal deletion or maternal UOD
  - ~50% recurrence risk in sibling if there is a deletion of the imprinting control center (<0.5% of cases)
  - 25% recurrence risk in sibling if there is a parental chromosomal rearrangement (<1% of cases)
  - There are some emerging options for non-invasive prenatal screening which may be helpful for higher risk situations
- Angelman
  - Similarly, if etiology of syndrome found to be secondary to imprinting center mutation or parental chromosome translocation, there will be increased risk to future pregnancies



References

Meeks NL, Saenz M, Tsai A, Elias ER. Genetics & Dysmorphology. In: Hay, Jr. WW, Levin MJ, Deterding RR, Abzug MJ. eds. *Current Diagnosis & Treatment: Pediatrics, 24e* New York, NY: McGraw-Hill; . http://accessmedicine.mhmedical.com/content.aspx?bookid=2390&sectionid=189084922. Accessed April 01, 2020.

Alkuraya FS. Epigenetics and Clinical Medicine. In: Murray MF, Babyatsky MW, Giovanni MA, Alkuraya FS, Stewart DR. eds. *Clinical Genomics: Practical Applications in Adult Patient Care, 1e* New York, NY: McGraw-Hill; 2014. http://accessmedicine.mhmedical.com/content.aspx?bookid=1094&sectionid=61908452. Accessed April 01, 2020.

Atypical Modes of Inheritance. In: Schaefer G, Thompson, Jr. JN. eds. *Medical Genetics: An Integrated Approach* New York, NY: McGraw-Hill; . http://accessmedicine.mhmedical.com/content.aspx?bookid=2247&sectionid=173745036. Accessed April 01, 2020.

https://www.youtube.com/watch?v=NL6UAUbUKYo

Up To date: Clinical features, diagnosis, and treatment of Prader-Willi Syndrome

Up To Date: Microdeletion syndromes (chromosomes 12 to 22)

Hiura H, Okae H, Chiba H, et al. Imprinting methylation errors in ART. *Reprod Med Biol*. 2014;13(4):193–202. doi:10.1007/s12522-014-0183-3