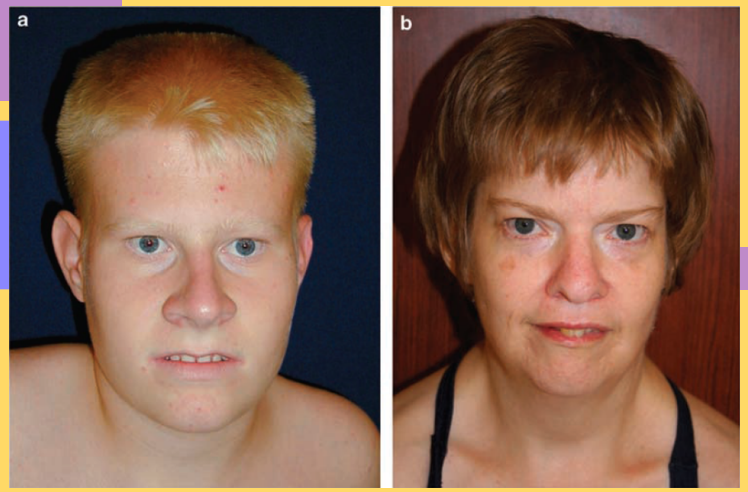
Prader-Willi Syndrome



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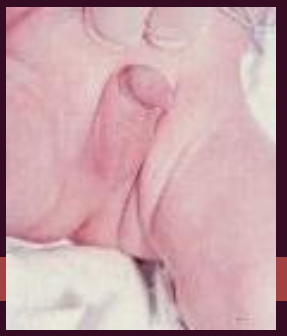
Genetics Pd 3

Physiology



- Incidence: 1 in 10,000 to 1 in 15,000

- Early onset: birth/infancy stage

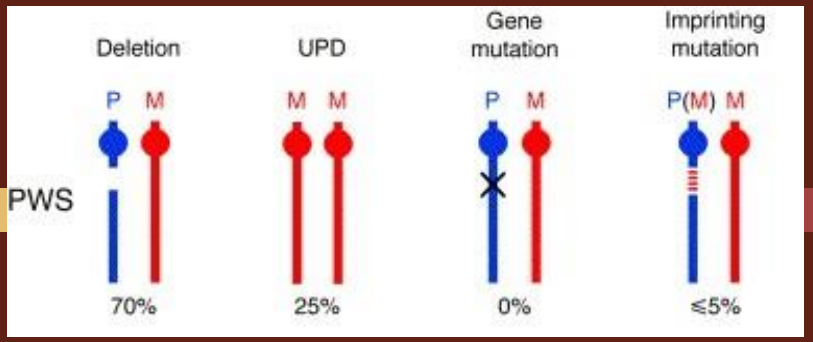
- Multiple systems are affected

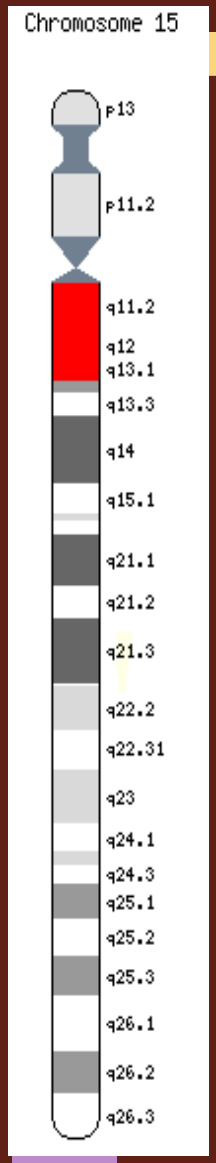
From birth: hypotonia (weak muscle tone), trouble feeding due to difficulty in sucking, almond shaped eyes, narrow bifrontal skull, short stature, small hands and feet

After year one: hyperphagia (uncontrolled eating habits/extreme cravings to consume food), slow mental and motor development, underdevelopment/ late development of reproductive organs and hypogonadism which can lead to sterility and osteoporosis, and Scoliosis

- Genetic defect causes malfunction of the hypothalamus (controls feelings of hunger and release of hormones and other substances for growth and development)

Molecular Cause





- It is observed that the absence of a paternally imprinted 15q11-q13 is linked to PWS, but exact cause of this disease is unknown

-Doesn'tfollow the classical mendelian inheritance patterns

-This is due to genomic imprinting so certain genes in this region are suppressed on the maternal chromosome so they have to be expressed from the paternal one

- Deletion of the region q11-q13, known as the long arm, on the paternally inherited chromosome 15 (Multiple genes involved)

-Three genetic forms of Prader-Willi Syndrome

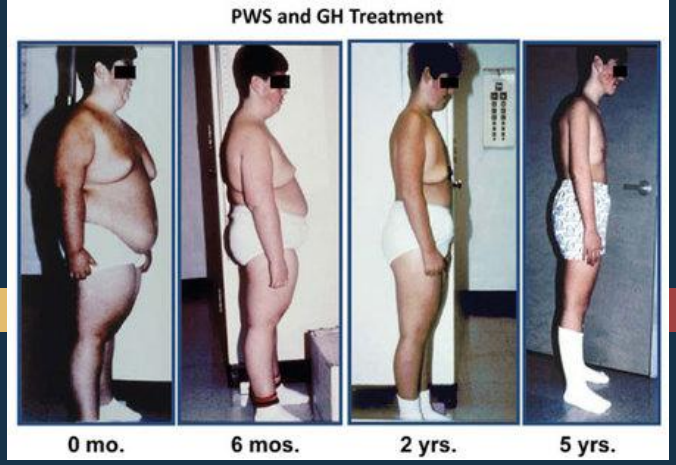
Paternal deletion - absence of genes in q11-13 region of paternally derived chromosome 15 (70%)

Maternal uniparental disomy- offspring has two chromosome 15 inherited from the mother and none from the father (25%)

Imprinting defect- balanced chromosomal rearrangement leading to breaking or deletion of bands in the region (<5%)

- No abnormal gene product identified with PWS, but there is a lack of the normal gene product SNRPN - Small Nuclear Ribonucleoprotein Polypeptide N (used in pre-mRNA processing and tissue-specific alternative splicing)

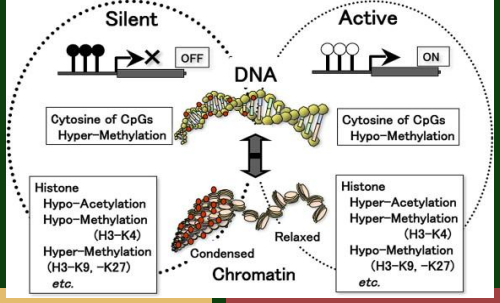
Treatments/Risks and Limits



- Human Growth Hormone treatment
  -Advantages: double previous growth rate, greater bone mineral density, hands and feet grow to more proportionate sizes, increase muscle development, decrease amount of body fat, improvement of motor skills, increase in muscle strength - better respiratory system, greater ability for more physical activity/higher performance levels.
  -Limitations/weaknesses: increased risk of spinal curvature abnormalities, risk of developing sleep apnea (abnormal breathing while sleeping), artificial/unnatural hormone fixation/addition at a young age , still need to maintain a regulated diet
- Tubes/ Special nipples - during early stages to make sure infant that has trouble sucking can be adequately fed and grow properly
-Medications (SRIs) - serotonin reuptake inhibitors can reduce obsessive compulsive symptoms and helps to manage psychosis
- Physical therapy increases muscular strength
- Behavior therapy and special education improves behavioral/psychiatric problems
- Sex hormones treatment/ corrective surgery treats small genitals and replacement of sex hormones during puberty helps fully develop secondary sex characteristics

Proposed Cure/Limits

Restoring serotonin function and snoRNA activity



- Absence of a gene sequence that regulates the serotonin 5-HT2C receptor (5-HT2CR) affects brain serotonin (5-HT) pathways (regulate hunger, satiety, and mood). Drugs that help to regulate such processes don't work if the 5-HT2CR is blocked or not present. Part of the 5-HT2CR molecule interacts with the protein PTEN. Peptides that act as selective inhibitors of the 5-HT2CR:PTEN interaction may enhance 5-HT2CR signaling. By changing the presence of PTEN in cultured cells with 5-HT receptors, intracellular responses can be observed and give more insight in enhancing the 5-HT2CR function.

-An important processing system for HTR2c pre-mRNA involves SNORD115 (snoRNA), also referred to as HBII-52. It plays a large role in allowing interaction of the U1 processing pathway with HTR2c pre-mRNA to create a fully functional serotonin receptor. The absence of SNORD115 forces HTR2c pre-mRNA to go through secondary processing pathway (ADAR) with a less effective receptor. Drugs that will make HTR2c pre-mRNA change its shape to bring back interaction with the U1 processing system will allow for normal function without SNORD115. The HTR2c pre-mRNA is ideal since it forms a defined, stable structure in cells, allowing for binding of other molecules.

Epigenetic DNA modification / DNA methylation

-Suppression of expression of genes as it become specific tissue may also be effective. This can be controlled by use of repressor proteins that bind to silencer regions of the DNA. (No change in DNA sequence) By looking at a histone, we focus on the suppressed gene where DNA is inaccessible because the gene is inactive. By adding an epigenetic factor, such as a methyl group, to histone tails, the genes can become unsuppressed and active, making DNA accessible. Modification of gene expressed or suppressing maternal gene expression in the region that is missing from the father could work.

-McCP2 (encodes methyl cpb-binding protein 2) binds to methylated CpG sites to repress these genes from transcription. It regulates loci that are subject to parental imprinting, specifically 15q11-13 Recent studies show that MeCP2 can also be a transcriptional activator when combined with the transcription factor CREB1.

-Recent studies of drugs activating only the paternal version of a gene - relating to Angelman's Syndrome

References

Title (Images)
http://en.wikipedia.org/wiki/File:Prader_Willi_Facial_Features.png

File:Prader Willi Facial Features.png

Physiology
Images
http://pediatricneuro.com/alfonso/pg111.htm
Figure 111.2- B and A
http://medgen.genetics.utah.edu/photographs/pages/praderwilli.htm
Prader-Willi Syndrome
http://library.thinkquest.org/06aug/00440/mwpraderintro.html
Prader-Willi syndrome symptoms

Content
"Prader-Willi Syndrome." *Mayo Clinic*. Mayo Foundation for Medical Education and Research, 12 Apr. 2011. Web. 21 Mar. 2013.

Molecular Cause

Images

http://www.sciencedirect.com/science/article/pii/S0168952598014322

Fig. 2

Content:

FPWR. "About Prader-Willi Syndrome." *Fpwr*. Foundation for Prader-Willi Research, n.d. Web. 18 May 2013.

"Genetics of PWS." *Genetics of PWS*. Prader-Willi Syndrome Association, 9 Feb. 2012. Web. 21 Mar. 2013.

National Center for Biotechnology Information (US). Genes and Disease [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 1998-. Prader-Willi Syndrome. Available From: Http://www.ncbi.nlm.nih.gov/books/NBK22195/

Thompson, Margaret Wilson., Huntington F. Willard, Robert L. Nussbaum, and Roderick R. MacInnes. *Genetics in Medicine: Thompson & Thompson*. Philadelphia: Saunders, 2004. Print.

Treatments:

Images

http://www.healio.com/endocrinology/pediatric-endocrinology/news/print/endocrine-today/%7Bd761cb1e-43e2-4fd0-9e97-600fc22180b7%7D/increased-awareness-earlier-detection-bring-relief-to-challenges-of-prader-willi-syndrome

Moris Angulo, MD.

Content:
Keder, Linda S. "Chapter 3: Effects of Growth Hormone Treatment in Children with Prader-Willi Syndrome." *Growth Hormone and Prader-Willi Syndrome: A Reference for Families and Care Providers*. Sarasota, FL: Prader-Willi Syndrome Association, 2001. N. pag. *Prader-Willi Syndrome Growth Hormone Deficiency and Treatment*. Prader-Willi Syndrome Association. Web. 10 Mar. 2013.

NICHD. *What Are the Treatments for Prader-Willi Syndrome?* NIH, 30 Nov. 2012. Web. 21 Mar. 2013.

Proposal

Images:
http://www.sciencedirect.com/science/article/pii/S0143400407002482
Gene silencing by DNA methylation

Content:

Mann, Mellissa R. W., and Marisa S. Bartolomei. "Human Molecular Genetics." *Towards a Molecular Understanding of Prader-Willi and Angelman Syndromes*. Oxford Journals, 2 June 1999. Web. 21 Mar. 2013.

Strong, Theresa. "Replacing Missing 'snoRNA' Activity and Restoring Serotonin Function with Drugs." *fpwr*. Foundation for Prader-Willi Research, 18 Apr. 2013. Web. 18 May 2013.

http://arstechnica.com/science/2011/12/undoing-the-genetic-imprinting-that-causes-a-neurodegenerative-disorder/
http://m.hmg.oxfordjournals.org/content/6/11/1873.full
http://m.hmg.oxfordjournals.org/content/14/6/785.full
http://en.m.wikipedia.org/wiki/MECP2