Prader-Willi Syndrome

Genetics

-15q11.2-q13; 4 distinct regions; 3 common deletion breakpoints within segmental duplication

-Penetrance is complete

Clinical findings/Dysmorphic features

-Severe hypotonia and feeding difficulties in early infancy --> excessive eating and gradual development of morbid obesity in later infancy/early childhood

-Delayed motor milestones/language development; some degree of cognitive impairment

-Temper tantrums, stubbornness, manipulative behavior, obsessive-compulsive features

-Hypogonadism in both males and females (manifests as genital hypoplasia, incomplete pubertal development, infertility)

-Short stature (if not treated with growth hormone); characteristic facial features; strabismus; scoliosis; thick/sticky saliva

Etiology

-1:10,000 to 1:30,000

Pathogenesis

-Genomic and epigenetic changes causing PWS all lead to a loss of expression of the normally paternally expressed genes on chromosome 15q11.2-q13

-PWS paternal-only expressed region:

--> 5 protein-coding genes (MKRN3, MAGEL2, NECDIN, bicistronic SNURF-SNRPN)

--> NPAP1 (intron-less gene; biallelically expressed in testis, only from paternal allele in brain)

--> Cluster of C/D box snoRNAs and antisense transcripts (incl. antisense transcript to UBE3A)

-AS maternally-only expressed region: with maternally expressed genes UBE3A and ATP10A

Genetic testing/diagnosis

-DNA methylation analysis --> abnormal parent-specific imprinting within the PW critical region

-70% have paternal deletions in 15q11q13; 25% have maternal uniparental disomy; <5% have methylation defects; <1% have translocations involving the 15q11q13 region

-DNA methylation analysis (e.g. MS-MLPA) at 5' SNRPN locus will identify imprinting defects

Others

-Risk to the sibs of affected child depends on genetic mechanism:

--> Less than 1% if affected child has deletion or uniparental disomy

--> Up to 50% if the affected child has an imprinting defect

--> Up to 25% if a parental chromosome translocation is present

-Prenatal testing is possible for pregnancies at increased risk if underlying mechanism is known

-SNRPN is methylated on maternal allele