Angelman syndrome

Genetics

-UBE3A (Ubiquitin protein ligase E3A, 15q11-q13)

-Loss of the maternally imprinted contribution in the 15q11.2-q13 (AS/PWS) region

Clinical findings/Dysmorphic features

-Severe DD or ID, severe speech impairment; gait ataxia and/or tremulousness of the limbs

-Inappropriate happy demeanor that includes frequent laughing, smiling, excitability; excessive saliva production (vs. PWS)

-Acquired microcephaly by age two years; seizures before 3y, abnormal EEG: pattern of large amplitude slow-spike wave

-Facial features: Protruding tongue, prognathia, wide mouth, widely spaced teeth, strabismus, light hair and eye color

Etiology

-Prevalence: 1:12,000 - 1:24,000

Pathogenesis

-Disruption of UBE3A affects neuronal processes of protein degradation and replacement

-Ubiquitin-proteasome pathway is essential for cellular functioning including signal transduction, cell cycle progression, DNA repair, transcriptional regulation

Genetic testing/diagnosis

-68% with deletions in 15q11q13; 11% with UBE3A mutations; 7% with paternal UPD; 3% with methylation defects; <1% with translocations involving the 15q11q13 region; 10% with normal molecular and cytogenetic analysis

-DNA methylation analysis first test --> identifies 80% of AS (Del+UPD+ID); if DNA methylation analysis is normal --> testing of UBE3A (additional 10%)

-Testing strategies:

1) Detection of methylation status at SNRPN locus by methylation specific PCR (MS-PCR) or Southern blot analysis

2) Simultaneous assessment of methylation status and genomic dosage at numerous sites across the 15q11-q13 region, by MS-MLPA

Others

-Imprinting inheritance in AS: inheritance of UBE3A pathogenic variant from dad has no effect who inherit the variant because the mutated UBE3A has been inactivated in dad’s germ cells and because the children also inherit a normally activated UBE3A from mum

-Carrier females transmit the UBE3A pathogenic variant to sons and daughters --> both will have AS since each will have also inherited an inactivated UBE3A from their father

-Recurrence risk: <1% for UPD and del; up to 50% for imprint defect; 100% for paternal UPD with Robertsonian translocation