Usher syndrome

Genetics

-Multiple genes, majority of cases due to MYO7A (Type 1) and USH2A (Type 2)

-AR

Clinical findings/Dysmorphic features

-Type I: congenital profound HL, balance problems, retinitis pigmentosa (RP) onset pre-puberty

-Type II: congenital mild-severe HL, normal balance, RP onset in teens-20’s

-Type III: progressive later onset HL, progressive balance problems, variable onset RP

Etiology

-Prevalence may be as high as 1 in 6,000

Pathogenesis

-Proteins part of “Usher interactome" --> localizing and organizing the assembly of larger protein complexes at the plasma membrane --> signal transduction, cell adhesion, subcellular transport --> one missing --> sensorineural degeneration occurs in the inner ear and the retina

-MYO7A is myosin --> migration of retinal pigment epithelial (RPE) melanosomes and phagosomes/differentiation, morphogenesis and organization of cochlear hair cell bundles

-RP is caused by degeneration of rod and cone functions of the retina

-For at least some genes: inner hair cell function and structure are affected in the ear

Genetic testing/diagnosis

-Diagnosis of Usher syndrome type I: electrophysiologic and subjective tests of hearing and retinal function --> identification of biallelic pathogenic variants in one of six genes (MYO7A (40-50%), USH1C, CDH23, PCDH15, USH1G, and CIB2) establishes diagnosis

-Type II: USH2A sequencing (65%)

Others

-Digenic or oligogenic inheritance described

-MYO7A mutation can lead to AD deafness, AR deafness, or Usher syndrome