Joubert syndrome

Genetics

-34 genes are known; TMEM67 (6-20%), AHI1 (7-10%), CPLANE1 (8-14%), CC2D2A (8-11%), CEP290 (7-10%), NPHP1 (1-2%), TMEM216 (2-3%)

-33 AR, 1 XLR (OFD1); digenic inheritance has been reported; M:F, 2:1

Clinical findings/Dysmorphic features

-1) Cerebellar/brain stem malformation: molar tooth sign (MRI: cerebellar vermis hypoplasia)

-2) Hypotonia in infancy --> ataxia later in life

-3) DD/ID

-Additional findings: oculomotor apraxia (difficulty in smooth visual pursuits and jerkiness in gaze tracking; abnormal eye movements); retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, endocrine abnl

Etiology

-Approx. 1:100,000

Pathogenesis

-All proteins localize to primary cilium and/or basal body and centrosome --> play role in formation, morphology, and/or function of these organelles

Genetic testing/diagnosis

-Molecular diagnosis can be established in 62%-94% of individuals with a clinical diagnosis

-Combination of gene-targeted (multigene panel) + genomic testing (genomic sequencing)

-Targeted testing in some ethnicities first: AJ --> p.Arg73Leu in TMEM216; Dutch --> p.Arg2904Ter in CPLANE1; French Canadian --> several variants in CPLANE1, CC2D2A, NPHP1, and TMEM231; Japanese --> c.6012-12T>A in CEP290

Others

-Apnea monitoring, G tube if dysphagia, surgery for eye disease, dialysis for nephronophthisis

-Ciliopathies: conditions caused by defects in proteins important in ciliary function --> share many features including renal disease, retinal dystrophy, polydactyly