PAFAH1B1-Associated Lissencephaly

Genetics

-Miller-Dieker syndrome (MDS): small cytogenetically visible deletions/FISH-detectable microdeletions of 17p13.3 (include PAFAH1B1 (former LIS1) and YWHAE + intervening genes)

-80% with MDS have de novo deletion involving 17p13.3; 20% have inherited a deletion from a parent who carries a balanced chromosome rearrangement

-Isolated lissencephaly sequence (ILS): smaller submicroscopic deletions, intragenic in/del or sequence variants of PAFAH1B1 (all PAFAH1B1 intragenic pathogenic variants are de novo)

Clinical findings/Dysmorphic features

-PAFAH1B1-associated lissencephaly includes MDS and ILS

-Lissencephaly: cortical malformations caused by deficient neuronal migration during embryogenesis (agyria or pachygyria)

-MDS is characterized by lissencephaly, typical facial features, severe neurologic abnormalities

-ILS is characterized by lissencephaly; DD; ID; seizures

Etiology

-Prevalence 12 to 40 in 1,000,000 births

Pathogenesis

-Central role in organization of cytoskeleton --> interaction with proteins including tubulin, centrosomes and microtubule dynamics --> role in neuronal proliferation and migration

-Pathogenic variants in PAFAH1B1 --> reduction in amount of correctly folded protein

Genetic testing/diagnosis

-High-res chromosome (> 450-band level) identify cytogenetically visible deletions/structural rearrangements of 17p13.3 in ~ 70% of individuals with MDS but not in individuals with ILS