Greig Cephalopolysyndactly Syndrome

Genetics

-GLI3 (Zinc finger protein GLI3; 7p13)

-AD

Clinical findings/Dysmorphic features

-Preaxial polydactyly or mixed pre-and postaxial polydactyly; cutaneous syndactyly; true widely spaced eyes; macrocephaly/hydrocephalus; prominent forhead; developmental delay; ID; seizures (<10%)

-Features highly variable, ranging from very mild to severe

-ID more common in those with large (>300 kb) deletions including GLI3

Etiology

-GCPS is rare and pan-ethnic; prevalence is unknown; ~ 100 cases are known

Pathogenesis

-GLI proteins regulate genes distal to sonic hedgehog in the SHH pathway

-Pathogenesis of GCPS is haploinsufficiency

Genetic testing/diagnosis

-GLI3 is only gene; GLI3 alterations (i.e., cytogenetic abnormalities involving GLI3 or pathogenic variants of GLI3) in more than 75% of typically affected individuals

-Seq: 70%, In/Del: 5-10%, LoH (detects GLI3 deletions): 50-75%

Others

-Allelic with Pallister-Hall syndrome (bifid epiglottis) --> GCPS is caused by pathogenic variants of all types, whereas PHS is caused by truncating variants and one splice variant that generates a frameshift