Nevoid basal cell carcinoma syndrome (Gorlin syndrome)

Genetics

-PTCH1 (Protein patched homolog 1; 9q22.32); SUFU (Suppressor of fused homolog; 10q24.32)

-AD; 70-80% inherited

Clinical findings/Dysmorphic features

-Formation of multiple jaw keratocysts (2nd decade) and/or basal cell carcinomas (3rd decade)

-60% with macrocephaly, frontal bossing, coarse facial features, facial milia (keratin-filled cysts)

-Most with skeletal anomalies (e.g., bifid ribs, wedge-shaped vertebrae)

-Ectopic calcification (falx cerebri) in > 90% of affected individuals by 20 years

-Cardiac (2%) and ovarian (20%) fibromas; ~5% of affected children develop medulloblastoma (primitive neuroectodermal tumor; risk higher in ind. with SUFU variant (33%) vs. PTCH1 (<2%)).

Etiology

-Prevalence approx. 1:57,000

Pathogenesis

-PTCH1 is membrane protein with 12 transmembrane regions, 2 extracellular loops, and putative sterol-sensing domain --> functions as SHH receptor --> represses signaling activity of the co-receptor smoothened --> in complex with SHH, protein patched homolog 1 is not a repressor --> signaling happens

-Pathogenic variants result in a truncated protein and missense variants --> LoF

-SUFU protein --> negative regulator in SHH pathway --> heterozygous LoF variants cause NBCCS

Genetic testing/diagnosis

-PTCH1: Seq 50-85%; InDel 6-21%; SUFU: Seq 5%; InDel 1%; Unknown: 15-27%

Others

-Life expectancy in NBCCS is not significantly different from average