Hutchinson-Gilford Progeria Syndrome

Genetics

-Gene: LMNA (Lamin-A/C; 1q21.2)

Clinical findings/Dysmorphic features

-Onset in childhood: accelerated aging; profound FTT during the first year

-Characteristic facial features: disproportionately large head for the face, narrow nasal ridge, narrow nasal tip, thin vermilion of upper and lower lips, small mouth, retro- and micrognathia

-Common features: loss of subcutaneous fat, delayed eruption and loss of primary teeth, abnormal skin with small outpouchings over the abdomen and upper thighs, alopecia, nail dystrophy, coxa valga (deformity of the hip), progressive joint contractures

-Later: low-frequency conductive HL, dental crowding, partial lack of secondary tooth eruption

-Motor and mental development is normal

-Death occurs as a result of severe atherosclerosis, cardiac disease (myocardial infarction or heart failure) or cerebrovascular disease (stroke) between 6 and 20 years

Etiology

-1 in 20,000,000

Pathogenesis

-c.1824C>T, p.Gly608= leads to activation of cryptic splice site in exon 11 --> production of a prelamin A that lacks 50 amino acids near the C terminus --> still retains the CAAX box and is therefore farnesylated, but is missing the site for endoproteolytic cleavage of the final 16 amino acids along with the farnesyl moiety --> resulting protein, named progerin

-Lack of farnesyl cleavage --> long-term progerin association with inner nuclear membrane

Genetic testing/diagnosis

-Classic genotype: heterozygous for c.1824C>T, p.Gly608= (~90% of individuals with HGPS)

-Non-classic genotype: characteristic clinical features and het for another LMNA pathogenic variant in exon 11 or intron 11 (~10% of individuals with HGPS)