Achondroplasia

Genetics

-Gene: FGFR3 (Fibroblast growth factor receptor 3; 4p16.3)

-AD (80% de novo)

Clinical findings/Dysmorphic features

-Rhizomelic (proximal limb) shortening of the limbs; macrocephaly; frontal bossing; midface retrusion; trident hand

-In infancy: hypotonia is typical, developmental motor milestones often delayed

-Intelligence and life span are usually near normal

-Complications: craniocervical junction compression, obstructive sleep apnea, middle ear dysfunction, kyphosis, spinal stenosis

Etiology

-Most common form of inherited disproportionate short stature; 1:26,000-1:28,000 live births

Pathogenesis

-FGFR-3: membrane-spanning tyrosine kinase receptor: extracellular ligand-binding domain (three immunoglobulin (Ig) subdomains), transmembrane domain, a split intracellular tyrosine kinase domain

-WT-FGFR-3: neg. regulator of bone growth (inhibition of chondrocyte proliferation and diff.)

-p.Gly380Arg in transmembrane domain --> constitutive activation and excess inhibitory signaling in growth plate chondrocytes

Genetic testing/diagnosis

-Individuals with typical findings do not need molecular confirmation of the diagnosis

-c.1138G>A (p.Gly380Arg) in 98% and c.1138G>C (p.Gly380Arg) in 1%

Others

-Family of bone dysplasias (hypochondroplasia, achondroplasia, SADDAN dysplasia, thanatophoric dysplasia type I and II) due to FGFR3 variants --> graded FGFR-3 activation

-De novo mutations occur exclusively on paternally-derived allele