Mucolipidosis II (I-cell disease)

Genetics

-GNPTAB (UDP-N-acetylglucosamine-1-phosphate transferase; 12q23.3)

-AR

Clinical findings/Dysmorphic features

-Slowly progressive; clinical onset at birth; fatal most often in early childhood

-FTT, contractures in large joints; thickened skin; coarse facial features; hypertrophic gingiva

-Orthopedic (present at birth): thoracic deformity, kyphosis, clubfeet, deformed long bones, and/or dislocation of hip(s); skeletal radiographs reveal dysostosis multiplex

-Cardiac: thickening and insufficiency of the mitral valve

-Progressive mucosal thickening --> narrow airways and gradual stiffening of the thoracic cage --> respiratory insufficiency (most common cause of death)

-Breaking of the lumbar vertebrae, a J-shaped sella tursica, and ribs that widen anteriorly

Etiology

-Overall carrier rate: 1:158 and 1:316; high prevalence (1:6184 live births; carrier rate of 1:39) in Quebec, Canada (founder variant GNPTAB, c.3503\_3504delTC)

Pathogenesis

-Deficiency of GlcNAc-phosphotransferase --> no addition of the common mannose-6-phosphate (M6P) moiety to lysosomal acid hydrolases --> no binding to M6P receptors in trans-Golgi network --> no receptor-mediated transport of enzymes to lysosomal compartment --> hydrolases leave cells; appear in excessive amounts in culture media/patient’s body fluid

Genetic testing/diagnosis

-Activity of nearly all lysosomal hydrolases 5- to 20-x higher in plasma and other body fluids than in normal controls; M6P cannot be added to the glycan part of glycoproteins

-Nearly complete inactivity (<<1%) of UDP-N-acetylglucosamine confirms the diagnosis

Others

-Dark and dense granules in cytoplasm of patient fibroblasts --> “inclusion cells” (I-cells)

-elevated levels of Arylsulfatase A and beta-glucuronidase