Hermansky-Pudlak Syndrome

Genetics

-AP3B1 (HPS2), AP3D1, BLOC1S3, BLOC1S6, DTNBP1, HPS1, HPS3, HPS4, HPS5, HPS6

-AR

-Proteins associate into four HPS protein complexes --> involved in intracellular vesicle formation and trafficking

Clinical findings/Dysmorphic features

-Oculocutaneous albinism, bleeding diathesis, granulomatous colitis (colon inflammation)

-Eye: reduced iris pigment with iris transillumination, reduced retinal pigment, foveal hypoplasia with significant reduction in visual acuity, nystagmus (wandering eye movements), increased crossing of the optic nerve fibers

-Pulmonary fibrosis (early 30s; can progress to death within a decade) --> HPS1, HPS2, HPS4

-Neutropenia and/or immune defects primarily in ind. with variants in AP3B1 and AP3D1

Etiology

-1-9 per 1,000,000

-Prevalence of HPS1-related HPS in northwestern Puerto Rico is 1:1800

Pathogenesis

-Mechanism of pulmonary fibrosis, colitis, cardiomyopathy, renal failure unknown

-Likely associated with aberrant biogenesis of lysosome-related organelles in specialized cells

Genetic testing/diagnosis

-Diagnosis: oculocutaneous albinism + absence of platelet delta granules (dense bodies)

-Multigene panel; biallelic pathogenic variants in AP3B1 (10%), AP3D1, BLOC1S3, BLOC1S6, DTNBP1, HPS1 (37%), HPS3 (12%), HPS4 (12%), HPS5 (10%), or HPS6 (17%) confirms the diagnosis if clinical features are inconclusive

-HPS1: c.1470\_1486dup16 or HPS3 3.9kb deletion in ind. from northwestern Puerto Rican

-HPS3 splice site variant c.1163+1G>A can be performed first in individuals AJ

Others

-Annual ophthalmologic examination; annual examination of the skin for solar keratoses (premalignant lesions), basal cell carcinoma, squamous cell carcinoma

-Annual pulmonary function testing in those older than age 20 years