Xeroderma Pigmentosum

Genetics

-Genes: DDB2 (3%), ERCC1, ERCC2 (20-30%), ERCC3 (1%), ERCC4 (~5%), ERCC5 (3-9%), POLH (10-25%), XPA (10-50%), XPC (3-43%)

-AR

Clinical findings/Dysmorphic features

-Sun sensitivity (severe sunburn with blistering, persistent erythema on minimal sun exposure); marked freckle-like pigmentation of the face before age 2 yrs

-Sunlight-induced ocular involvement (photophobia, keratitis, atrophy of the skin of the lids)

-More than 1000x increased risk of sunlight-induced cutaneous neoplasms (basal cell carcinoma, squamous cell carcinoma, melanoma)

-25% have neurologic manifestations (acquired microcephaly, diminished or absent deep tendon stretch reflexes, progressive SNHL, progressive cognitive impairment)

-Most common causes of death: skin cancer, neurologic degeneration, internal cancer

-Median death: XP w neurodegeneration (29 years); XP w/o neurodegeneration (37 years)

Etiology

-Prevalence is 1:1,000,000 in US and Europe

Pathogenesis

-DNA repair system: senses, excises, repairs UV-induced dipyrimidine photoproducts --> if defective: replication errors and subsequent tumorigenesis

Genetic testing/diagnosis

-Founder variant testing can be considered (XPA: India, Japan, Tunisia; XPC: North Africa; ERCC2: Iraqi Jewish; POLH: Tunisia, North Africa, Japan, Basque)

-Multigene panel