Fanconi anemia

Genetics

-FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, BRCA2, BRIP1

-AR, AD (RAD51), XLR (FANCB)

Clinical findings/Dysmorphic features

-Physical abnormalities (75%): short stature, abnormal skin pigmentation (40%), skeletal malformations of upper and lower limbs (35%), microcephaly, ophthalmic and GI anomalies

-Progressive bone marrow failure: pancytopenia (typically in the 1st decade, 6-8 years)

-Incidence of acute myeloid leukemia is 13% by age 50 years (500-fold increase)

-Solid tumors (head, neck, skin, gastrointestinal tract, and genitourinary tract) more common

Etiology

-Most common genetic cause of aplastic anemia and one of the most common genetic causes of hematologic malignancy

-Carrier frequency of 1:180 in North Americans

Pathogenesis

-Proteins encoded by the FA-related genes work together in pathway called "the FA pathway”

-Regulates cellular resistance to DNA cross-linking agents

Genetic testing/diagnosis

-Increased chr breakage and radial forms of lymphocytes with diepoxybutane and mitomycin C

-Biallelic pathogenic variants in one of 18 genes, known to cause AR FA

-Heterozygous pathogenic variant in RAD51, known to cause AD FA

-Hemizygous pathogenic variant in FANCB, known to cause XLR FA

Others

-More common in females (1.2:1)

-Biallelic path variants in BRCA2 associated with early-onset acute leukemia and solid tumors