Li-Fraumeni Syndrome

Genetics

-Gene: TP53 (Cellular tumor antigen P53; 17p13)

-AD (7-20% de novo)

Clinical findings/Dysmorphic features

-Cancer predisposition syndrome: 1) soft tissue sarcoma; 2) osteosarcoma; 3) pre-menopausal breast cancer; 4) brain tumors (including choroid plexus carcinoma); 5) adrenocortical carcinoma (ACC); 6) leukemias

-LFS-related cancers often occur in childhood or young adulthood

Etiology

-Frequency of germline TP53 mutation may be as high as 1:5,000 to 1:20,000

Pathogenesis

-P53 is an important TF --> in response to cellular stress/damage, p53 gets activated --> regulates target genes to induce the following processes: cell cycle arrest, apoptosis, senescence, DNA repair

-Absent p53 --> DNA-damaged cells survive and proliferate --> diverse number of malignancies

Genetic testing/diagnosis

-Diagnosis by presence of all of the following criteria: 1) Proband with a sarcoma (soft tissue tumor) diagnosed before age 45 years; 2) 1st-degree relative with any cancer before age 45 years 3) 1st or 2nd-degree relative with any cancer before age 45 years or a sarcoma at any age

-80% of families with features of LFS have identifiable TP53 pathogenic variant

-TP53: seq 95%, In/Del 1%

Others

-Surveillance:

1) Children and adults undergo comprehensive annual physical examination

2) Children and adults should see physician promptly for lingering symptoms and illnesses

3) Women undergo breast cancer monitoring, with annual breast MRI and twice annual clinical breast examination beginning at age 20-25 years (mammograms = radiation risk)

4) Adults consider routine screening for colorectal cancer with colonoscopy every 2-3 years beginning no later than age 25 years

5) Individuals consider organ-targeted surveillance based on pattern of cancer in their family

-Intensified surveillance with whole-body MRI for adults/children are being evaluated in investigational settings

-NCCN suggests TP53 testing for any woman with breast cancer < 35 if BRCA1/2 is negative