Juvenile Polyposis Syndrome

Genetics

-Genes: BMPR1A (28%; Bone morphogenetic protein receptor type-1A; 10q23.2); SMAD4 (27%; Mothers against decapentaplegic homolog 4; 18q21.2); 45% unknown cause

-AD; 1/3 inherited

Clinical findings/Dysmorphic features

-Predisposition to hamartomatous polyps in GI tract (stomach, small intestine, colon, rectum)

-Most ind. with some polyps by age 20y; some with only 4-5 over lifetime, some with >100

-If polyps untreated --> bleeding and anemia

-Most juvenile polyps are benign; however, malignant transformation can occur

-Risk for GI cancers: 9% to 50%.

Etiology

-Incidence between 1:16,000 and 1:100,000

Pathogenesis

-SMAD4 (tumor suppressor; intracellular mediator of TGF-β signaling); BMPR1A (unclear if tumor suppressor; type I cell surface receptor for BMP pathway --> ligands, such as TGF-β or BMP, bind to receptor and activate signaling pathways --> protein complexes that migrate to nucleus --> bind DNA sequences to regulate transcription

Genetic testing/diagnosis

-Diagnosis is established in proband with any of the following:

--> more than five juvenile polyps of colorectum;

--> multiple juvenile polyps throughout GI tract;

--> any number of juvenile polyps and a family history of juvenile polyposis

-Identification of a heterozygous pathogenic variant in SMAD4 or BMPR1A confirms diagnosis if clinical features are inconclusive

-BMPR1A: Seq 69-85%; InDel 15%; SMAD4: Seq 83%; InDel 17%

Others

-Close proximity of BMPR1A to PTEN (both on 10q22-q23), but not members of same pathways

-Contiguous gene deletion of PTEN and BMPR1A associated with severe form of early-onset JPS

-"Juvenile" refers to type of polyp rather than to the age of onset

-Combined syndrome of JPS and HHT is present in most individuals with SMAD4 variant