Familial Adenomatous Polyposis

Genetics

-Gene: APC (Adenomatous polyposis coli protein; 5q21-22)

-AD (15-30% de novo; 75-80% inherited)

Clinical findings/Dysmorphic features

1) FAP:

-Colon cancer predisposition syndrome; hundreds - thousands of adenomatous colonic polyps

-Onset ~16 years; by age 35 years --> 95% of individuals have polyps

-Colon cancer risk 100% without colectomy; diagnosis in untreated individuals at ~ 39 years

-Extracolonic manifestations: polyps of gastric fundus and duodenum; osteomas; dental anomalies; congenital hypertrophy of the retinal pigment epithelium (CHRPE); soft tissue tumors; desmoid tumors

2) Attenuated FAP:

-Multiple colonic polyps (less than 100, average of 30), more proximally located

-Diagnosis of colon cancer at a later age than in FAP

-Extracolonic manifestations: gastric and duodenal polyps or cancers

3) Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS):

-Gastric fundic gland polyposis, increased risk of gastric cancer, limited colonic involvement

Etiology

-Prevalence of FAP: 1:7,000 to 1:30,000 live births

Pathogenesis

-Pathogenic APC variants produce usually truncated protein --> no longer binds to GSK-3b --> does not target beta-catenin for destruction --> high levels of free cytosolic beta-catenin --> migrates to nucleus --> binds to Tcf-4 or Lef-1 --> expression oncogenes (c-Myc and cyclin D1)

Genetic testing/diagnosis

-APC-associated polyposis condition should be suspected in individuals with any of the following clinical features: 1) Multiple colorectal adenomatous polyps (at least 10-20); 2) Family history of multiple colorectal adenomatous polyps (>10 in a single individual, or fewer if >1 relative has multiple polyps, especially if diagnosed at a young age) and/or extracolonic features; 3) Hepatoblastoma (very rare cancerous tumor, starts in liver); 4) Multifocal/bilateral CHRPE; 5) Desmoid tumor (noncancerous growths in the connective tissue); 6) Cribriform-morular variant of papillary thyroid cancer

Others

-Colorectal screening beginning at age 10-12 years for FAP and in late teens for attenuated FAP

-Mutations in attenuated FAP located in three distinct regions of the APC gene, including the 5′ end spanning exons 3 to 5, exon 9 and the 3′ distal end

-If thousands of polyps and no SNV --> highest yield is to send for del/dup

-Screening for hepatoblastoma in children identified to have APC variant recommended (10% of children with hepatoblastoma carry a mutation in APC)