Hereditary Nonpolyposis Colon Cancer (Lynch syndrome)

Genetics

-Genes: MLH1 (DNA mismatch repair protein MLH1), MSH2 (DNA mismatch repair protein MSH2), MSH6 (DNA mismatch repair protein MSH6), PMS2 (PMS1 protein homolog 2), EPCAM

-AD

Clinical findings/Dysmorphic features

-Increased risk for CRC (50-80%), endometrium cancer (25-60%), stomach (6-13%), ovary (4-12%), small bowel, hepatobiliary tract, urinary tract, brain, skin

Etiology

-Prevalence ~ 1:440; accounts for ~ 1%-3% of CRCs and 0.8%-1.4% of endometrial cancers

Pathogenesis

-Genes involved in mismatch repair (MMR) pathway --> functions to identify and remove single-nucleotide mismatches or insertions and deletion loops

-Germline deletions within EPCAM (not an MMR gene) --> disrupt MMR pathway by inactivating adjacent MSH2 (even though MSH2 itself is not mutated)

Genetic testing/diagnosis

-Amsterdam II Criteria: ≥3 family members (at least one 1st degree) with HNPCC related cancers; 2 successive affected generations; ≥1 or more of the HNPCC-related cancers diagnosed before age 50; exclusion of FAP

-Bethesda 2004: CRC diagnosed under age 50yrs; 2 HNPCC related tumors at once; CRC with high MSI in someone <age 60yrs; CRC in ≥ 1st degree relatives with HNPCC related tumor with 1 cancer diagnosed before age 50yrs; CRC diagnosed in ≥ 1st or 2nd degree relatives (any age)

-MSI of tumor; immuno-histochemistry of tumor for MLH1, MSH2, MSH6 and PMS2

-Sequencing/InDel of MLH1 (50% of cases; 90%/10%); MSH2 (40% of cases; 80%/20%); MSH6 (7-10% of cases; 95%/5%); PMS2 (<5% of cases); EPCAM (1-3%; 0%/100%)

Others

-Colonoscopy with removal of precancerous polyps every 1-2y beginning at 20-25y or 2-5 years before earliest age of diagnosis in family