MUTHY-Associated polyposis

Genetics

-Gene: MUTYH (Adenine DNA glycosylase; 1p34.1)

-AR

Clinical findings/Dysmorphic features

-Increased lifetime risk of CRC (almost 100% in absence of timely surveillance)

-10-100s colonic adenomatous at 50 years (CRC can develop in absence of polyposis)

-Duodenal adenomas in 17%-25% of individuals with MAP (lifetime risk: 4%)

-Serrated adenomas, hyperplastic/sessile serrated polyps, and mixed (hyperplastic and adenomatous) polyps can occur

-Modestly inc. risk for late-onset malignancies of ovary, bladder, skin, breast, endometrial

-Some ind. develop sebaceous gland tumors (recently, thyroid abnormalities were reported)

Etiology

-1-2% are carriers --> prevalence of 1:40,000 to 1:20,000 for biallelic germline variants

Pathogenesis

-Adenine DNA glycosylase plays role in DNA damage repair (base excision repair, caused by ionizing radiation, chemical oxidants, ROS) --> lack of MUTYH leads to accumulation of G:C>T:A transversions in daughter DNA strands post-replication

Genetic testing/diagnosis

-MUTYH: Seq 99%. In/del ?

-Two mutations account for 75% (c.536A>G (p.Tyr179Cys) and c.1187G>A (p.Gly396Asp))

Others

-Hallmark of MUTYH carcinomas: KRAS c.34G>T in codon 12 in 64% of MAP CRCs cancers

-MUTYH tumors are mainly MSI-stable

-Colonoscopy every 1-2 years starting age 20-25