Multiple endocrine neoplasia type 1 (MEN1)

Genetics

-Gene: MEN1 (Menin; 11q13)

-AD

Clinical findings/Dysmorphic features

-Varying combinations of >20 endocrine and non-endocrine tumors (overproduction of hormones by tumor or by growth of tumor)

-Parathyroid tumors: main MEN1-associated endocrinopathy; onset in 90% of individuals is 20-25 yrs with hypercalcemia --> hypercalcemia causes lethargy, depression, confusion, anorexia, constipation, nausea, vomiting, dehydration, hypercalciuria, kidney stones, increased bone resorption/fracture risk, hypertension, shortened QT interval

-Pituitary tumors (most common prolactinoma): oligomenorrhea/amenorrhea/galactorrhea in females and sexual dysfunction in males

-Well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract

-Carcinoid tumors: non-hormone-secreting, manifest as a large mass after age 50 years

-Adrenocortical tumors: associated with primary hypercortisolism or hyperaldosteronism

-Non-endocrine tumors: facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, leiomyomas and café au lait spots

Etiology

-Prevalence 1:10,000 to 1:100,000

Pathogenesis

-Menin mainly in nucleus; expressed in all tissues --> tissue-specific roles in DNA replication/repair and in transcriptional machinery

-Prevents tumorigenesis through repression of cell proliferation: 1) directly interacting with TFs (e.g., JunD, NF-kB, PPARgamma, VDR); 2) interacting with histone-modifying enzymes (MLL; HDACs; EZH2); 3) acts as TF itself

-Pathogenic variants prevent translocation to the nucleus

Genetic testing/diagnosis

-Diagnosis: identification of one or both of the following:

1) 2-3 endocrine tumors (i.e. parathryoid, pituitary, tumors of the GEP tract)

2) A heterozygous pathogenic variant in MEN1 on molecular testing

-MEN1 sequencing (familial 80-90%; sporadic: 65%)/Indel (1-4%)

Others

-MEN1 is tumor suppressor that follows Knudson's two-hit model

-PPP: Pituitary, Parathyroid, Pancreatic Islet