Multiple Endocrine Neoplasia Type 2 (MEN2)

Genetics

-Gene: RET (proto-oncogene tyrosine-protein kinase receptor RET; 10q11.2)

-AD

Clinical findings/Dysmorphic features

-3 subtypes:

1) MEN 2A: medullary thyroid carcinoma (MTC), pheochromocytoma (adrenal glands tumor), parathyroid adenoma/hyperplasia

2) MEN 2B: MTC, pheochromocytoma, mucosal neuromas of lips and tongue, distinctive facies with enlarged lips, ganglioneuromatosis of the gastrointestinal tract, "marfanoid" habitus

3) FMTC (familial medullary thyroid carcinoma): MTC only

-MTC typically occurs in early childhood in MEN 2B, early adulthood in MEN 2A, and middle age in FMTC

Etiology

-Prevalence of MEN 2 has been estimated at 1:35,000

Pathogenesis

-RET: receptor tyrosine kinase (extracellular, transmembrane, intracellular domains)

-Pathogenic variants in cysteine-rich extracellular domain (609, 611, 618, 620, 634) cause ligand-independent RET dimerization --> constitutive activation (gain of function)

Genetic testing/diagnosis

-Clinical criteria:

-MEN 2A: ≥2 specific endocrine tumors (MTC, pheochromocytoma, parathyroid adenoma/hyperplasia) in a single individual or in close relatives

-FMTC: in families with ≥4 cases of MTC without pheochromocytoma or parathyroid adenoma/hyperplasia

-Select exon testing (majority of pathogenic variants in exons 10, 11, 13-16) --> single-gene testing (sequencing of RET if no pathogenic variant is found by exon testing) --> multigene panel that includes RET and other genes of interest

-No In/Dels since gain-of-function

Others

-Prophylactic thyroidectomy (by age 1 for MEN2B, by age 5 for most of MEN2A), screen for pheochromocytoma annually and prior to any surgery, annual calcitonin stimulation test, annual parathyroid hormone screening

-Pathogenic variant in codon 918 causes 95% of the MEN 2B phenotype