PTEN Hamartoma Tumor Syndrome

Genetics

-Genes: PTEN (Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase; 10q23)

-AD

Clinical findings/Dysmorphic features

-Cowden syndrome (CS): multiple hamartoma syndrome; high risk for benign and malignant tumors (breast (LTR:85%), thyroid (LTR:35%), endometrium (LTR:28%)); macrocephaly; trichilemmomas (benign cutaneous neoplasm); papillomatous papules; present by late 20s

-Bannayan-Riley-Ruvalcaba syndrome (BRRS): congenital disorder characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, pigmented macules of the glans penis (Koppe)

-PTEN-related Proteus syndrome (PS): complex, highly variable; congenital malformations and hamartomatous overgrowth of multiple tissues, connective tissue nevi, epidermal nevi, hyperostosis (excessive bone growth)

Etiology

-1 in 200,000

Pathogenesis

-PTEN is major phosphatase for phosphoinositide-3,4,5-triphosphate --> downregulates PI3K/AKT pathway

-Majority (76%) of germline pathogenic variants: truncated or dysfunctional PTEN; many missense variants are functionally null (haploinsufficiency)

-PTEN is absent --> phosphorylation of AKT1 is uninhibited --> inability to activate cell cycle arrest and/or to undergo apoptosis; mitogen-activated protein kinase (MAPK) pathway is dysregulated, leading to abnormal cell survival

Genetic testing/diagnosis

-Identification of a heterozygous germline pathogenic variant in PTEN

-Sequence analysis of PTEN first --> gene-targeted deletion/duplication --> PTEN promoter seq