Von Hippel-Lindau Syndrome

Genetics

-Gene: VHL (Von Hippel-Lindau disease tumor suppressor; 3p25)

-AD

Clinical findings/Dysmorphic features

-Hemangioblastomas (CNS tumors, originate from vascular system) of brain, spinal cord, retina:

-->cerebellar: associated with headache, vomiting, gait disturbances, ataxia

-->spinal: usually present with pain (cord compression may cause sensory/motor loss)

-->retinal: may be the initial manifestation and may cause vision loss

-Renal cysts and clear cell renal cell carcinoma (in 70%, leading cause of death)

-Pheochromocytoma (adrenal glands tumors), pancreatic cysts, neuroendocrine tumors; endolymphatic sac tumors (can cause HL); epididymal and broad ligament cysts

Etiology

-Incidence approx. 1 in 36,000 births; de novo mutation rate: 4.4x10-6 gametes per generation

Pathogenesis

-pVHL is tumor suppressor --> variety of functions including transcriptional regulation, post-transcriptional gene expression, apoptosis, extracellular matrix formation, ubiquitinylation

-Regulation of hypoxia-inducible genes through targeted ubiquitinylation and degradation of HIF1α --> disruption of VHL results in renal cell carcinoma, hemangioblastoma, and other highly vascularized tumors

Genetic testing/diagnosis

-Sequence analysis of the VHL coding region, intron 1, and flanking sequences

-VHL sequencing: 89%; Del/Dup: 11%; 35% of patients with VHL have missense mutations!

Others

-Arginine codon 167 is considered a mutational hot spot