Cancer Prone Disease Section
Mini Review

Von Hippel-Lindau
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Identity

Inheritance: 'autosomal dominant' disorder with high penetrance (increasing with age: 97% by age 60 yrs) but variable expressivity (with phenotype/genotype correlations); frequency is about 2.5/105.

Clinics

The Von Hippel-Lindau (VHL) disease is a multi system disease predisposing to a variety of benign and malignant tumours, often with multifocal and/or bilateral localization.

Phenotype and clinics

Onset of the disease between 18 and 30 yrs, often with retinal or cerebellar hemangioblastomas.
There are two clinical types of VHL: type I, without pheochromocytoma, and type II with pheochromocytoma; in the subtype 2A, there are no renal or pancreatic lesions; the subtype 2B is the full multi-tissues subtype.

Neoplastic risk

Central nervous system hemangioblastomas are the most frequent lesion (infratentorial localization in 60 % of cases, and intraspinal in 30-40 %); hemangioblastomas are benign vascular proliferations. Retinal hemangioblastomas are quasi pathognomonic; most often multifocal and bilateral; peripheral localization preferentially.
Renal cell carcinomas of the clear cell type, multifocal and bilateral; multiple cysts and intermediate tumours are also found.
Pheochromocytomas (bilateral); found in a subset of families, where it is often the only sign.
Pancreas tumours: multiple cysts, mainly; islet cell tumours, rare.

Endolymphatic sac tumours (adenocarcinomas) of the petrus bone.

Treatment

Screening and regular follow up are essential; treatments: surgery for central nervous system hemangioblastomas and for renal carcinomas; laser treatment of retinal hemangioblastoma; treatment of pheochromocytomas are according their symptomatic consequences.

Prognosis

According to the severity of the disease in a given patient, and to the quality of a regular follow up; mean age at death: 50 yrs; a presymptomatic diagnosis may improve survival data; renal manifestations have become the first cause of death.

Genes involved and Proteins

VHL

Location: 3p25-26
DNA / RNA
Description: 3 exons; recessive mode of inheritance, although the disease appears as pseudo dominant, as is found with the RB1 gene: this is the result of the combination of a rare probability (2nd mutation) in a large cell population (e X 1/e = 1).

Protein
Description: 284 amino acids.
Function: Tumour suppressor; down-regulate transcriptional elongation by binding to components of the elongin complex.

Mutations
Germinial: More than 250 mutations have been reported, comprising for more than 100 independant intragenetic mutational events; 70 % of the mutations
are detectable; when a patient is diagnosed, all at-risk relatives must be tested for the mutation; this reduces significantly the mortality and morbidity; phenotype/genotype correlations: large deletions, frameshifts and nonsense mutations are often found in cases without pheochromocytoma, while missence mutations are associated with a high susceptibility to pheochromocytoma, which indicates that VHL functions may be tissue-specific.

Somatic: Mutation and allele loss events in VHL, and somatic mutations, frequent in sporadic renal cell carcinomas and hemangioblastomas, are in accordance with the two-hit model for neoplasia, as is found in retinoblastoma; however, somatic mutations of VHL are rare in sporadic pheochromocytomas; gene methylation, an epigenetic event, can also occur in tumours.

References


This article should be referenced as such: