

Cancer Prone Disease Section

Review

Von Hippel-Lindau

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Identity

Note

Von Hippel-Lindau (VHL) disease is a hereditary devastating cancer syndrome, predisposing to the development of various benign and malignant tumours (Central Nervous System [CNS] and retinal hemangioblastomas, endolymphatic sac tumours, renal cell carcinoma (RCC) and/or renal cysts, pheochromocytomas, pancreatic cysts and neuroendocrine tumours, endolymphatic sac tumours, epididymal and broad ligament cystadenomas). VHL disease is the first cause of hereditary kidney cancer.

Inheritance

An autosomal dominant disorder with high penetrance (increasing with age: 97% by age 60 years) but variable expressivity (with phenotype/genotype correlations); frequency is estimated at about $2.5/10^5$; neomutations represent about 20% of cases.

Clinics

Phenotype and clinics

Onset of the disease usually occurs between 18 and 30 yrs, often with retinal or cerebellar hemangioblastomas, but can also manifests in children, especially by retinal hemangioblastomas and pheochromocytoma.

Central nervous system (CNS) hemangioblastomas occur in 60-80% of patients (infratentorial localisation in 60 % of cases, intraspinal in 30-40%; supratentorial in 1%). Multiple tumours are frequent (hemangioblastomatosis).

Retinal hemangioblastomas, often multiple and bilateral, occur in about 50% of patients. Most retinal

hemangioblastomas occur peripherally but optic disc (papillary or juxtapapillary) locations are encountered in almost 15% of cases.

Renal cell carcinomas occur in up to 75% of cases. They are mostly multifocal and bilateral. Tumors have a classical solid or a more specific mixed cystic/solid appearance and are always of clear cell subtype. Multiple benign cysts are also observed.

Pheochromocytomas, often bilateral, are mostly found in a subset of families, where it can be the only sign of VHL. Extraadrenal paragangliomas are sometimes encountered.

Pancreas manifestations occur in up to 77% of patients: isolated or multiple cysts and serous cystadenomas are the most frequent lesions, neuroendocrine tumours occur in about 10-15 % of cases.

Endolymphatic sac tumours, only recently recognised as a manifestation of VHL disease, occur in up to 11% of cases.

Epididymal cysts, often bilateral, occur in about 54% of men.

Cystadenomas of the broad ligament ("adnexal papillary tumour of probable mesonephric origin") are extremely rare but highly specific.

There are two main clinical types of VHL according to the absence (type 1) or presence of pheochromocytoma (type 2). The type 2 is subdivided in three subtypes, 2A (with low risk of renal cancer and pancreatic tumors); 2B (the full multi-tissues subtype), and 2C (pheochromocytomas only, recently individualised by molecular genetics).

Neoplastic risk

Central nervous system (CNS) hemangioblastomas may cause life-threatening complications in spite of

their benign nature and classic slow-growing course and remain a major cause of morbidity and mortality in VHL disease.

Retinal hemangioblastomas may cause retinal detachment, haemorrhage, glaucoma and cataract, leading to blindness, in absence of early detection and treatment.

Renal cell carcinomas is becoming the main cause of death in the disease, because of secondary dissemination mainly due to delay in diagnosis.

Pheochromocytomas are malignant in about 5-10% of cases.

Neuroendocrine pancreatic tumours tend to be slow growing but have the potential of a truly malignant course with locoregional dissemination.

Endolymphatic sac tumours is a low grade papillary adenocarcinoma resulting in progressive hearing loss. It can grow to the pontocerebelline angle and/or the middle ear, then destroying the temporal bone.

Epididymal cysts and cystadenomas of the broad ligament are benign tumors.

Treatment

Regular clinical follow-up of patients and gene-carriers is imperative in order to detect manifestations early and to avoid complications;

Treatment of symptomatic CNS hemangioblastoma remains mainly neurosurgical, often in emergency, but stereotactic radiosurgery is emerging as an alternative therapeutic procedure in patients with multifocal solid hemangioblastomas.

Retinal hemangioblastoma are treated by cryotherapy or laser depending on the location, size and number of tumours.

Endolymphatic sac tumours require surgical treatment with the help of ENT specialists as soon as possible in order to prevent definitive hearing loss. Preoperative embolisation is sometimes performed to avoid bleeding.

Renal cell carcinomas have to be treated when their size is about 3 cm in diameter. Nephron sparing surgery is the choice method and may delay bilateral nephrectomy and dialysis. When binephrectomy is inevitable, renal transplantation can be discussed after a 2 year period without metastasis.

Pheochromocytomas have to be surgically removed, preferentially with the use of laparoscopy. When possible, partial adrenalectomy appears to be a safe method of preserving adrenocortical function and quality of life.

Pancreatic neuroendocrine tumours require surgical removal at a 2-3 cm size in order to avoid metastatic dissemination.

Pancreatic cysts and serous cystadenomas do not require resection but sometimes a percutaneous drainage or endoscopic implantation of a biliary stent is indicated in cases of compression.

Surgery is indicated for broad ligament cystadenomas and for symptomatic epididymal cystadenomas.

Medical perspectives: several clinical studies are ongoing with specific drugs that block VEGF in the hope of causing stabilisation or recession of CNS and retinal hemangioblastomas. Such clinical trials are in processing in France, England and Poland.

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 is about 50 yrs and renal cell carcinomas and CNS hemangioblastomas are the major causes of death. As treatment of VHL manifestations in first stages will improve significantly the clinical outcome and the quality of life of patients, early and unambiguous diagnosis is mandatory. Thus, DNA testing is emerging as a major progress in this consideration, paving the way to an effective presymptomatic diagnosis.

Genes involved and proteins

VHL

Location: 3p25-26

DNA/RNA

Description: 3 exons.

Protein

Description: 213 amino acids.

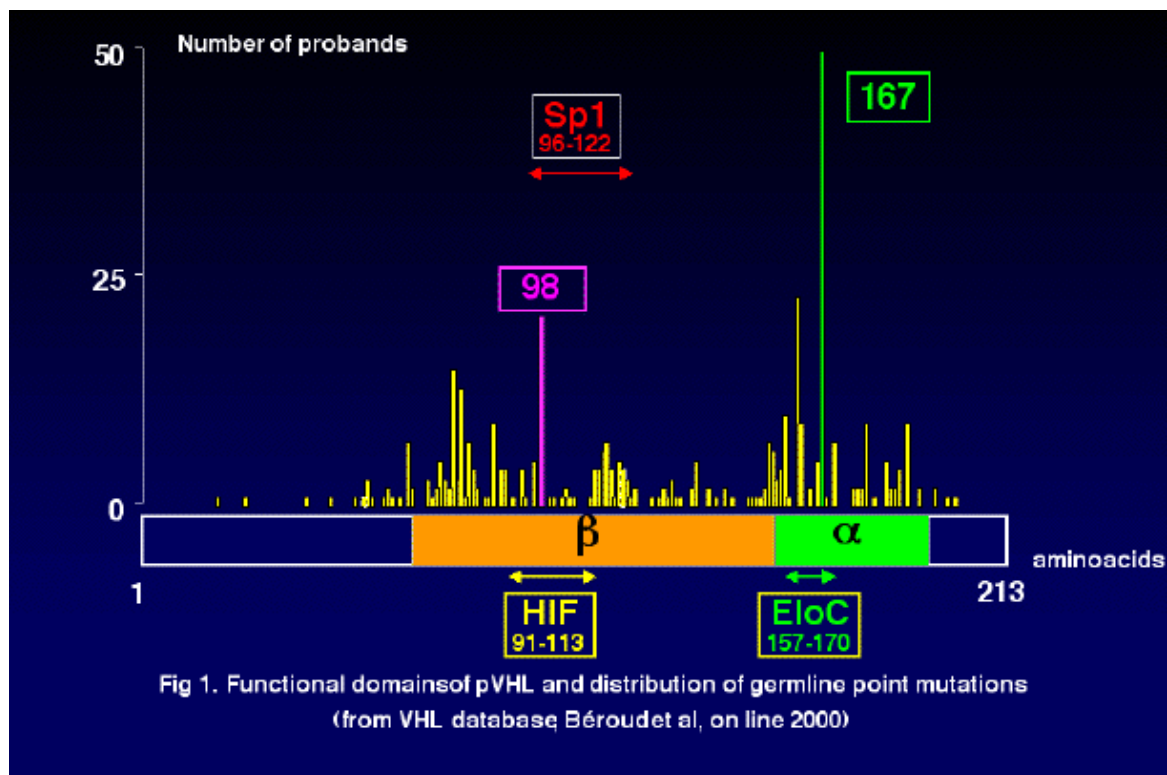
Expression: Wide.

Function: Tumour-suppressor gene. pVHL interacts with elongins B and C and cullin 2 through a complex exhibiting ubiquitine ligase activity. Its main function is to negatively regulate VEGF mRNAs (and angiogenesis as a result) by targeting hypoxia inducible transcription factors HIF for degradation by the proteasome. pVHL has also major functions in extra cellular matrix formation and cell cycle control.

Mutations

Germinal: Causes VHL disease.

More than 400 mutations have been identified, comprising for more than 150 independent intragenic mutational events; virtually 100% of mutations are detectable. The majority of mutations are represented by point mutations including missense, nonsense mutations, splicing, microinsertions or microdeletions. In about 25 % of cases, a large deletion of the VHL gene is observed.



Functional domains of pVHL and distribution of germline point mutations.

Mutations resulting in a truncated protein are mostly associated with type 1 VHL. In type 2, mutations are generally missense mutations affecting preferentially the critical contact region between pVHL and elongin C (residues 157-171) with a hot-spot at codon 167. In type 2A there is a founder effect for a specific missense mutation at codon 98. In type 2C, mutations occur in regions potentially involved in critical function exclusive to the adrenals (as codon 188). Last, patients with identical VHL germline mutations may display different phenotypes, indicating that the issue of genotype-phenotype correlations is complex in VHL. Evidence was recently provided that unknown modifier genes and environmental influences could play an additional role in the clinical expression of the disease. Somatic: Somatic VHL gene inactivation is frequent in sporadic hemangioblastomas and moreover in sporadic renal cell carcinoma, representing a significant event in the development of these tumors. Different mutational mechanisms lead to the inactivation of the VHL gene including loss of heterozygosity, small intragenic mutations or hypermethylation of the promoter.

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