Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Cancer Prone Disease Section

Mini Review

Von Hippel-Lindau

Anne-Marie Capodano

Laboratoire de Cytogénétique Oncologique, Hôpital de la Timone, 264 rue Saint Pierre, 13005 Marseille, France

Published in Atlas Database: April 1998

Online updated version: http://AtlasGeneticsOncology.org/Kprones/VHLKpr10010.html
DOI: 10.4267/2042/37469

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 $2.5/10^5$.

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 nore 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; mutiple 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

Germinal: 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

Resche F, Moisan JP, Mantoura J, de Kersaint-Gilly A, Andre MJ, Perrin-Resche I, Menegalli-Boggelli D, Lajat Y, Richard S. Haemangioblastoma, haemangioblastomatosis, and von Hippel-Lindau disease. Adv Tech Stand Neurosurg 1993;20:197-304.

Crossey PA, Richards FM, Foster K, Green JS, Prowse A, Latif F, Lerman MI, Zbar B, Affara NA, Ferguson-Smith MA, et al. Identification of intragenic mutations in the von Hippel-Lindau disease tumour suppressor gene and correlation with disease phenotype. Hum Mol Genet 1994 Aug;3(8):1303-8.

Brauch H, Kishida T, Glavac D, Chen F, Pausch F, Höfler H, Latif F, Lerman M, Zbar B, Neumann HP. Von Hippel-Lindau (VHL) disease with pheochromocytoma in the Black Forest region of Germany : Evidence for a founder effect. Hum Genet. 1995 May;95(5):551-6.

Chen F, Kishida T, Yao M, Hustad T, Glavac D, Dean M, Gnarra JR, Orcutt ML, Duh FM, Glenn G, et al. Germline mutations in the von Hippel-Lindau disease tumor suppressor gene: correlations with phenotype. Hum Mutat 1995;5(1):66-75.

Linehan W.M.. Lerman M.I.. Zbar B. Identification of the von Hippel-Lindau (VHL) gene. Its role in renal cancer. JAMA 1995;273:564-70.

Richard S, Olschwang S, Chauveau D, Resche F. La maladie de von Hippel Lindau. Médecine-Sciences 1995;11:43-51.

No authors listed. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996. J Clin Oncol 1996 May;14(5):1730-6;discussion 1737-40.

Zbar B, Kishida T, Chen F, Schmidt L, Maher ER, Richards FM, Crossey PA, Webster AR, Affara NA, Ferguson-Smith MA, Brauch H, Glavac D, Neumann HP, Tisherman S, Mulvihill JJ, Gross DJ, Shuin T, Whaley J, Seizinger B, Kley N, Olschwang S, Boisson C, Richard S, Lips CH, Lerman M, et al. Germline mutations in the Von Hippel-Lindau disease (VHL) gene in families from North America, Europe, and Japan. Hum Mutat 1996;8(4):348-57.

Decker HJ, Weidt EJ, Bieger J. The von Hippel-Lindau tumor suppressor gene. A rare and intriguing disease opening new insight into basic mechanisms of carcinogenesis. Cancer Genet Cytogenet. 1997 Jan;93(1):74-83. Review.

Richard S, Campello C, Taillandier, Resche LF. La maladie de Von Hippel Lindau: progrès génétiques et applications cliniques. La lettre de neurologie 1997;2:55-60.

Prowse AH, Webster AR, Richards FM, Richard S, Olschwang S, Resche F, Affara NA, Maher ER. Somatic inactivation of the VHL gene in Von Hippel-Lindau disease tumors. Am J Hum Genet 1997;60:765.

This article should be referenced as such:

Capodano AM. Von Hippel-Lindau. Atlas Genet Cytogenet Oncol Haematol.1998;2(4):155-156.