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(9) www.vhl.org/ and www.hippel-lindau.de/

General Information

It is strongly recommended that the decision for or against molecular genetic VHL analysis, transfer of reports and interpretation of test results is accompanied by qualified genetic counselling of the patient.

Once the patient or proband has received qualified genetic councelling, a written declaration of consent or confirmation of informed consent must be submitted with every sample.

Request Form

"Molecular genetic analyses" (informed consent on back of form) is available from bioscientia on request.

Sample Material

1 sample of 5 ml of EDTA-blood (a closed system such as Vacutainer® - or Monovettes, must be used) Send the sample at room temperature within maximal 3 days after blood sampling.

Shipment

Contact any of our local offices in your area or the address on this leaflet.

Turn-Around Time

2 - 6 weeks from receipt

Results

The final report comprises of detailed interpretation of the test result and result comparison with data entries in international data bases.

Anonymity of the test result is guaranteed. Results will only be reported to the patient's physician. Comparison with existing data bases will only be performed by anonymization of personal data.

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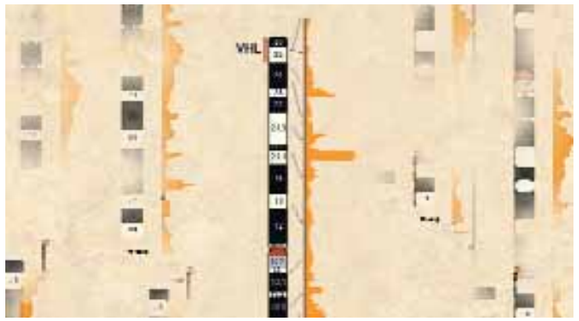

Genetic Testing for Von Hippel-Lindau Disease

VHL Analysis

Schematic representation of chromosomes 3p25-p26. The localization of the VHL gene is indicated by the red vertical bar. For the original link to this illustration see also: www.nebi.nlm.nih.gov/SCIENCE96/chr.cgi?3

Introduction

Von Hippel-Lindau (VHL) disease is an inherited tumor susceptibility syndrome predisposing gene carriers to a variety of benign and malignant tumors. VHL segregates in affected families as an autosomal dominant inherited trait. Penetrance is approximately 90% at the age of 65 years and phenotypic expression is highly variable.

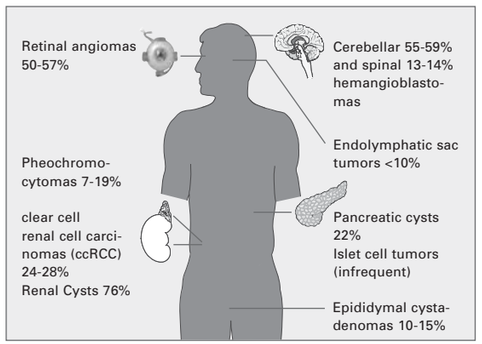

Fig.1:
Affected organs, symptoms and frequencies modified from Decker and Brauch (1)

- tumors and cysts are frequently bilateral and/or multiple in origin
- birth incidence is estimated 1/39,000 (Germany) to 1/53,000 (East Anglia, England)
- prevalence is 1/31,000 to 1/85,000
- incidence of de novo mutations is about 5%
- mean age at diagnosis is 26 years
- most severe complications are hemangioblastmas due to unrestricted growth in the confined space of skull or spinal canal, and ccRCC due to metastasis
- major cause of death are secondary complications due to hemangioblastomas

The von Hippel-Lindau tumor suppressor gene (VHL) is a gene that is required for normal development and differentiation. VHL was discovered in families with the hereditary von Hippel-Lindau (VHL) syndrome by virtue of its two hit mechanism of inactivation and identified in 1993 following a positional cloning strategy (2). If the VHL gene is mutated in the germline, the systemic VHL disease is caused. Mutations that develop in somatic renal epithelial cells result in sporadic renal clear cell carcinoma (3).

Indication for VHL Gene Analyses

Classical clinical definition (4):

- known family history of retinal or cerebellar hemangioblastoma: the presence of a single hemagioblastoma or a visceral manifestation, i.e. clear cell renal cell carcinoma in one patient will define him as a carrier.
- isolated cases, possibly indicating a de novo mutation: two or more hemangioblastomas or a single hemangioblastoma in association with a visceral manifestation, are sufficient to establish the diagnosis.

	Type 1	Type 2A	Type 2B	Type 2C
CH	+	+	+	-
AR	+	+	+	-
RCC	+	-	+	-
Pheo	-	+	+	+
Panc	+	-	+	-

Table 1:
Phenotypical subclassification of VHL
CH = cerebellar hemangioblastoma
AR = angioblastoma retinae
RCC = renal cell carcinoma (clear cell)
Pheo = pheochromocytoma
Panc = pancreatic neoplasms & cysts
modified from: Wildhardt et al. (5)

It is possible to determine VHL carrier status by mutation testing of DNA isolated from blood. This can either be performed to assist clinical diagnosis or to establish carrier status presymptomatically for at risk individuals. In VHL type 2C disease, it is important to establish carefully the diagnosis in affected patients since pheochromocytoma is also a manifestation of other inherited syndromes such as multiple endocrine neoplasia type 2 or neurofibromatosis type 1.

Molecular Diagnosis and Implications

The molecular genetic analysis consists of sequence analysis of the VHL-gene in addition to the screening for large genomic deletions of the gene by Multiplex Ligation-dependent Probe Amplification (MLPA).

The molecular genetic analysis of the VHL-gene is the only method to identify patients as mutation carriers. It should be noted that the result of such a molecular diagnostic test may have special consequences for the patient. Therefore it is recommended that this analysis is accompanied by genetic counselling (6). In such a setting the patient will be provided with detailed information about possibilities, limitations, potential benefits and risks of this procedure. Supported by counselling, the patient can decide whether genetic testing is to be performed or not (“informed consent”).

Patients with VHL disease should be tested by molecular analysis to determine their family specific VHL germline mutation. Once a mutation has been identified in an individual, family members can be tested for VHL mutation carrier status. This means gene-carriers and those who do not carry the mutation can be identified in a family. Only family members with a VHL germline mutation should be subjected to clinical diagnostic procedures. This approach will significantly reduce the psychological stress of unnecessary clinical screening examinations for the non-carrier. Also, by this approach, costs will be reduced. Affected patients should be tested according to a standard protocol (7,8).

Clinical Management

Molecular testing of VHL disease today is used to sustain clinical diagnosis. In principle the diagnosis can be established presymptomatically. Early detection allows treatment of lesions prior to the onset of symptoms. For retinal hemangioblastomas adequate laser treatment will significantly reduce the risk of blindness. Cerebellar or spinal hemangioblastomas can be removed prior to the onset of neurological impairment. Pheochromocytoma should be treated only if they are leading to symptoms. Renal lesions require specific attention. Cysts may be critical as their lining epithelium may be the origin of malignoma. Thus, any cysts in VHL patients should be regarded as potentially malignant especially when they are accompanyied by solid or fast growing tumors. With respect to the size and location nephron sparing surgery is the treatment of choice for renal clear cell carcinoma.

The involvement of a variety of different organ systems requires interdisciplinary cooperation of experts from different medical fields for the appropriate management of VHL disease.

Patient information on all aspects of VHL disease are available online from patient support groups (9).