GENEReviews

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Von Hippel-Lindau Syndrome

[*Angiomatosis Retinae, VHL Syndrome, von Hippel-Lindau Disease*]

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Summary

Disease characteristics. Von Hippel-Lindau syndrome (VHL syndrome) is characterized by hemangioblastomas of the brain, spinal cord, and retina; renal cysts and clear cell renal cell carcinoma; pheochromocytoma; and endolymphatic sac tumors. Cerebellar hemangioblastomas may be associated with headache, vomiting, and gait disturbances or ataxia. Retinal hemangioblastomas may be the initial manifestation of VHL syndrome and can cause vision loss. Renal cell carcinoma occurs in about 40% of individuals with VHL and is the leading cause of mortality. Pheochromocytomas can be asymptomatic but may cause sustained or episodic hypertension. Endolymphatic sac tumors can cause hearing loss of varying severity, which can be a presenting symptom.

Diagnosis/testing. The diagnosis of VHL syndrome is suspected in individuals with characteristic lesions including hemangioblastomas, renal cysts and renal cell carcinoma, pheochromocytoma, and endolymphatic sac tumors. *VHL* is the only gene known to be associated with VHL syndrome. Molecular genetic testing of the *VHL* gene detects mutations in nearly 100% of affected individuals. Such testing is clinically available.

Management. *Treatment of manifestations:* intervention for most CNS lesions; remove spinal lesions completely; treat retinal (but not optic nerve) angiomas prospectively; early surgery (nephron-sparing or partial nephrectomy when possible) for renal cell carcinoma; renal transplantation following bilateral nephrectomy; remove pheochromocytomas; consider surgical removal of endolymphatic sac tumors (particularly small tumors in order to preserve hearing and vestibular function). *Prevention of secondary complications:* early detection and removal of tumors to prevent/minimize secondary deficits such as hearing loss, vision loss, and neurologic symptoms. *Surveillance:* for individuals with known VHL syndrome or known to have a VHL disease-causing mutation and at-risk relatives with unknown genetic status: annual ophthalmologic examination, beginning before age five years; annual blood pressure

monitoring and measurement of urinary catecholamine metabolites beginning at age five years in families with a high incidence of pheochromocytoma; annual abdominal ultrasound examination beginning at age 16 years with evaluation of suspicious lesions by CT scan or MRI; audiologic evaluation if hearing deficits are suspected; T1-weighted MRI of the temporal bone if hearing loss is detected. *Testing of relatives at risk:* If the disease-causing mutation in a family is known, molecular genetic testing can be used to clarify the genetic status of at-risk family members to eliminate the need for costly surveillance of family members who have not inherited the disease-causing mutation.

Genetic counseling. VHL syndrome is inherited in an autosomal dominant manner. Approximately 80% of individuals with VHL syndrome have an affected parent and about 20% have VHL syndrome as the result of a *de novo* gene mutation. Parental mosaicism has been described; the incidence is not known. The offspring of an individual with VHL syndrome are at a 50% risk of inheriting the *VHL* disease-causing mutation. Prenatal testing for pregnancies at risk is available if the disease-causing mutation has been identified in a family member.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of von Hippel-Lindau syndrome (VHL syndrome) is established in:

- **A simplex case** (i.e., an individual with no known family history of VHL syndrome) presenting with two or more characteristic lesions (e.g., two or more hemangioblastomas of the retina or brain or a single hemangioblastoma in association with a visceral manifestation such as kidney or pancreatic cysts; renal cell carcinoma; adrenal or extra-adrenal pheochromocytomas, and, less commonly, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumors of the pancreas);
- **An individual with a positive family history of VHL syndrome** in whom one or more of the following disease manifestations is present: retinal angioma, spinal or cerebellar hemangioblastoma, pheochromocytoma, multiple pancreatic cysts, epididymal or broad ligament cystadenomas, multiple renal cysts, or renal cell carcinoma before age 60 years.

The following tests are used to establish the diagnosis and determine the extent of clinical manifestations:

- **CT scan or MRI** to establish the presence of:
  - CNS tumors
  - Pheochromocytomas that exhibit high signal intensity on T2-weighted MRI, which may help differentiate them from adrenal cortical nodules
  - Endolymphatic sac tumors identified with high signal intensity with T1 imaging on MRI as a mass on the posterior wall of the petrous part of the temporal bone
- **Ultrasound examination** for evaluation of the epididymis and broad ligament, and for less expensive screening of the kidneys
- **Radioiodine-labeled MIBG** for the evaluation of suspected extra-adrenal tumors
- **18F DOPA whole-body PET,** which shows promise as a sensitive and specific method for detection of pheochromocytomas [Hoegerle et al 2002]

- **Measurement of urinary catecholamine metabolites** (VMA, metanephrine, and total catecholamine) to detect elevations that may suggest pheochromocytoma even in the absence of hypertension

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *VHL* is the only gene known to be associated with VHL syndrome.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predictive testing
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Molecular genetic testing: Clinical methods

- **Sequence analysis.** Sequence analysis of all three exons can be used to detect point mutations in the *VHL* gene (~72% of *VHL* mutations) [Stolle et al 1998].
- **Deletion analysis.** Various methods (e.g., quantitative Southern blot analysis, relative quantitative PCR) can be used to detect partial or complete gene deletions, which account for approximately 28% of all *VHL* mutations [Stolle et al 1998, Hoebeeck et al 2005].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in VHL Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*VHL* sequence variants	~72%	Clinical Testing
Deletion analysis	*VHL* partial or complete deletion	~28%	

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

- Molecular genetic testing is indicated in all individuals known to have or suspected of having VHL syndrome [Rasmussen et al 2006].
- Since the detection rate for *VHL* gene mutations is nearly 100%, molecular testing may also be used to evaluate individuals with a single VHL-associated tumor and a negative family history of the disease.
- For individuals with manifestations of VHL syndrome who do not meet strict diagnostic criteria and who do not have a detectable *VHL* germline mutation, somatic mosaicism for a *de novoVHL* disease-causing mutation should be considered

[Sgambati et al 2000]. In some instances, molecular genetic testing of the offspring of such individuals reveals a *VHL* mutation.

Genetically Related (Allelic) Disorders

VHL type 2C. Some individuals with familial pheochromocytoma or non-familial bilateral pheochromocytoma may have mutations in the *VHL* gene without the presence of the characteristic eye and CNS tumors (VHL type 2C) [Ritter et al 1996, Abbott et al 2006].

Chuvash polycythemia. Individuals with Chuvash polycythemia, an autosomal recessive disorder endemic to the mid-Volga region in central Russia, have elevated erythropoietin levels, and most are homozygous for a 598C>T (Arg200Trp) mutation in the *VHL* gene [Ang et al 2002]. Other individuals outside the mid-Volga region with congenital polycythemia, some as compound heterozygotes for other *VHL* gene mutations, have been found to harbor the 598C>T mutation [Pastore et al 2003]. The Chuvash mutation has subsequently been found in individuals of diverse ethnic backgrounds. Mutations in the *VHL* gene may be responsible for as much as 17% of congenital erythrocytosis; haplotype analysis suggests that the 598C>T mutation arose independently in at least two populations [Cario et al 2005]. *VHL* mutation analysis is indicated in all persons with congenital erythrocytosis regardless of ethnicity.

Although thrombosis and/or hemorrhage has occurred in many, none of the affected individuals or their heterozygous relatives thus far described have developed VHL-related tumors [Gordeuk et al 2004].

Somatic mutations. Acquired mutations in the *VHL* gene may give rise to sporadic VHL-type tumors (i.e., clear cell RCC, pheochromocytoma) [Iliopoulos 2001] without other associated tumors characteristic of the heritable disease.

Clinical Description

Natural History

Von Hippel-Lindau syndrome (VHL syndrome) is characterized by hemangioblastomas of the brain, spinal cord, and retina; renal cysts and renal cell carcinoma; pheochromocytoma; and endolymphatic sac tumors. Some clustering of tumors occurs, resulting in the designation of specific VHL syndrome phenotypes. The manifestations and severity are highly variable both within and between families, even among those with the same mutation.

Hemangioblastoma. CNS hemangioblastoma is the prototypic lesion of VHL syndrome [Catapano et al 2005, Glasker 2005]. Roughly 80% develop in the brain and 20% in the spinal cord. Within the brain the vast majority are infratentorial, mainly in the cerebellar hemispheres. Multiple CNS tumors, occurring either synchronously or metachronously, are common. Spinal hemangioblastomas are generally intradural, most commonly occur in the cervical or thoracic regions, and occasionally may involve the entire cord. Rarely, peripheral nerve hemangiomas may develop [Giannini et al 1998].

Clinical symptoms depend upon the site of the tumor. With infratentorial tumors, headache, vomiting, and gait disturbances or ataxia predominate. With tumors above the tentorium, symptoms depend on the location of the lesion. Hemangioblastomas are generally slow growing, but on occasion include rapidly enlarging cysts that produce hydrocephaly with papilledema. Spinal hemangioblastomas usually present with pain, but sensory and motor loss may develop with cord compression. Most symptom-producing spinal hemangioblastomas are associated with syringomyelia [Wanebo et al 2003].

Some hemangioblastomas are not symptomatic and are discovered only with MRI. CNS hemangioblastoma has even been identified on fetal ultrasound examination [Diguet et al 2002].

Retinal hemangioblastoma. These retinal lesions, sometimes called retinal angiomas, are histologically identical to CNS hemangioblastomas. They may be the initial manifestations of VHL syndrome. About 70% of affected individuals are identified as having retinal angiomas [Webster et al 1999, Kreusel 2005] with mean age of about 25 years [Dollfus et al 2002]. The tumors are most often located in the temporal periphery of the retina with feeder and draining vessels going to and from the optic disc. However, they may develop in the posterior pole (1%) and optic disc (8%). They may be asymptomatic and be detected on routine ophthalmoscopy. Others present with a visual field defect or a loss of visual activity resulting from retinal detachment, exudation, or hemorrhage.

The number of retinal angiomas does not appear to increase with age, but the probability of vision loss increases with age [Kreusel et al 2006].

Tests of retinal function may be abnormal even in the absence of retinal angiomas [Lubinski et al 2003].

Renal lesions. Multiple renal cysts are common in VHL syndrome.

Renal cell carcinoma (RCC), specifically of the clear cell type developing either within a cyst or in the surrounding parenchyma, occurs in about 40% of affected individuals and is a leading cause of mortality in VHL syndrome.

Pheochromocytoma. Pheochromocytoma may present with sustained or episodic hypertension or be totally asymptomatic, being detected incidentally by an abdominal imaging procedure. Pheochromocytomas are usually located in one or both adrenal glands, but may present anywhere along the sympathetic axis in the abdomen or thorax (paragangliomas) [Bender et al 1997] or head and neck (chemodectomas) [Schimke et al 1998]. They are normally greater than 2 cm in size.

Pheochromocytomas are usually benign, but malignant behavior has been reported [Chen et al 2001].

Pancreatic lesions. Most pancreatic lesions are simple cysts and are frequently multiple. They rarely cause endocrine or exocrine insufficiency unless extensive. Occasionally, cysts in the head of the pancreas cause biliary obstruction.

Rarely, neuroendocrine tumors of the pancreas develop. They are usually not hormonally active and are slow growing, but more malignant behavior has been observed, particularly in tumors greater than 3 cm [Marcos et al 2002].

Endolymphatic sac tumors. The endolymphatic sac and duct are ectodermal extensions of the membranous labyrinth. Tumors of the sac cause deafness of varying severity, often severe to profound and of sudden onset [Choo et al 2004, Kim et al 2005]. Less commonly, vertigo or tinnitus is the presenting complaint [Manski et al 1997]. Large tumors can involve other cranial nerves. Endolymphatic sac tumors are seen in approximately 10% of individuals with VHL syndrome, and in some instances the associated uni- or bilateral hearing loss is the initial feature of the disease [Kim et al 2005]. In rare cases, the tumors may be malignant [Muzumdar et al 2006].

Epididymal tumors. Epididymal or papillary cystadenomas are relatively common in males with VHL syndrome. They rarely cause problems, unless bilateral, in which case they may result in infertility. The equivalent, much less common, lesion in women is a papillary cystadenoma of the broad ligament.

Genotype-Phenotype Correlations

Four classic VHL disease phenotypes have been described based on the likelihood of pheochromocytoma or renal cell carcinoma [Zbar et al 1996].

VHL type 1 is characterized by a low risk for pheochromocytoma. Truncating mutations or missense mutations that are predicted to grossly disrupt the folding of the VHL protein [Stebbins et al 1999] are associated with VHL type 1.

VHL type 2 is characterized by a high risk for pheochromocytoma. Individuals with VHL type 2 almost invariably have a missense mutation. Some missense mutations seem to correlate with a specific type 2 VHL phenotype [Zbar et al 1996, Weirich et al 2002, Sanso et al 2004, Abbott et al 2006, Knauth et al 2006].

VHL type 2 is further subdivided:

- **Type 2A,** characterized by a low risk of renal cell carcinoma;
- **Type 2B,** carrying a high risk of renal carcinoma; and
- **Type 2C,** carrying a risk for pheochromocytoma only.

More recently, two groups reported a reduced risk for renal cell carcinoma in individuals with a complete deletion of the *VHL* gene [Cybulski et al 2002, Maranchie et al 2004]. This group of individuals defines a new VHL phenotype characterized by a low risk for both renal cell carcinoma and pheochromocytoma.

Penetrance

VHL mutations are highly penetrant. Almost all individuals who have a mutation in the *VHL* gene express disease-related symptoms by age 65 years.

Anticipation

Anticipation is not observed with VHL syndrome.

Nomenclature

Obsolete terms for VHL syndrome include: angiophakomatosis retinae et cerebelli, familial cerebello-retinal angiomatosis, cerebelloretinal hemangioblastomatosis, Hippel disease, Hippel-Lindau syndrome, Lindau disease, and retinocerebellar angiomatosis [Molino et al 2006].

Prevalence

The incidence of VHL syndrome is thought to be about one in 36,000 births per year with an estimated *de novo* mutation rate of 4.4×10^{-6} gametes per generation [Maher et al 1991].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The level of mutation detection obtained by molecular genetic testing of the *VHL* gene makes it possible to effectively rule out von Hippel-Lindau syndrome (VHL syndrome) with a high degree of certainty in individuals with isolated hemangioblastoma, retinal angioma, or clear cell renal cell carcinoma, who have no detectable *VHL* disease-causing germline mutation; somatic mosaicism for a *VHL* gene mutation still needs to be considered in such individuals. A younger individual, especially one with multiple lesions, is more likely to have a germline *VHL* mutation than an older individual with a single lesion [Neumann et al 2002].

Since pheochromocytoma is part of the VHL syndrome spectrum and may occur as the exclusive manifestation of VHL syndrome (type 2C), individuals with a family history of these tumors, or those in whom the disease is bilateral or multifocal, should be offered molecular genetic testing for *VHL* germline mutations [Richards et al 1998]. Germline *VHL* mutations are rare in simplex cases of unilateral pheochromocytoma (i.e., an affected individual with no family history of VHL syndrome), unless the individual is younger than age 20 years. Exceptions are those individuals with a family history that is more consistent with familial paragangliomas of the head and neck, which are caused by mutations in various subunits of the gene encoding succinic dehydrogenase *(SDH*) [Maher & Eng 2002, Bryant et al 2003], or those individuals who have features of other heritable diseases associated with pheochromocytoma such as multiple endocrine neoplasia type 2A or 2B or neurofibromatosis type 1 [Neumann et al 2002].

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is characterized by cutaneous leiomyomata. Affected females usually develop uterine leiomyomata (fibroids) at an early age. Predisposition to renal tumors occurs in a subset of families. Most renal tumors are classified as 'type 2' papillary renal cancer, displaying distinct papillary architecture and characteristic histopathology. Other types of renal tumors include a spectrum ranging from tubulo-papillary renal cell carcinomas to collecting-duct renal cell carcinomas. Inheritance is autosomal dominant. Heterozygous defects in the gene *FH*, encoding fumarate hyphatase, are causative [Lehtonen et al 2006].

Birt-Hogg-Dubé (BHD) syndrome is characterized by cutaneous findings (fibrofolliculomas, trichodiscomas, and acrochordons). Pulmonary cysts/history of pneumothorax, and various types of renal tumors are frequently found in persons with BHD syndrome and/or their families. The most common tumors are a hybrid of oncocytoma and chromophobe histologic cell types, so-called oncocytic hybrid tumor (67%), chromophobe renal cell carcinoma (23%), and renal oncocytoma (3%). Only renal oncocytoma is considered a benign tumor. Other types of renal tumors reported in lower frequency include clear cell renal cell carcinoma and papillary renal carcinoma. Mutations in *FLCN (BHD*) are causative. Inheritance is autosomal dominant.

Individuals with RCC and no other evidence of VHL syndrome are unlikely to have germline *VHL* mutations [Richards et al 1998].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with von Hippel-Lindau syndrome (VHL syndrome):

- Neurologic history and physical examination for evidence of CNS or peripheral nerve hemangioblastomatosis
- Ophthalmologic evaluation for retinal hemangioblastomas
- Audiologic evaluation for hearing loss associated with endolymphatic sac tumors

- Blood pressure determination, supplemented by measurement of urinary catecholamine metabolites after age five years in those families with a high incidence of pheochromocytoma
- Abdominal ultrasound examination after age 16 years. Suspicious lesions in the kidney, adrenal gland, or pancreas should be evaluated by more sophisticated techniques, such as CT scan or MRI.

A baseline MRI of the brain and spine in young adulthood has been suggested by some; however, this procedure is expensive and the overall value in an asymptomatic individual remains questionable.

Treatment of Manifestations

Nervous system hemangioblastoma

- Some advocate early surgical removal of both symptomatic and asymptomatic CNS lesions, while others follow asymptomatic lesions with yearly imaging studies. Most CNS lesions eventually require intervention.
- Preoperative arterial embolization may be indicated, especially for extensive spinal tumors.
- Gamma knife surgery may be useful with small tumors or those in inoperable sites. While this technique may reduce the size of the solid tumor, it does not seem to prevent cyst formation. Overall operative mortality is roughly 10%, with higher figures for brain stem tumors.
- It is recommended that spinal lesions be completely removed. Paraplegia is the major complication following removal of spinal tumors.

Retinal hemangioblastoma

- Most ophthalmologists favor prospective treatment of retinal, but not optic nerve, angiomas to avoid blindness, although spontaneous regression has occurred.
- Therapeutic modalities used to treat retinal hemangioblastomas include diathermy, xenon, laser, and cryocoagulation, with variable degrees of success depending upon the location, size, and number of lesions. Recurrent tumors have been noted, even after many years, but some may be new tumors in the same general area rather than recurrent disease.
- External beam radiotherapy has been shown to be useful when standard therapy has not prevented progression [Raja et al 2004].

Renal cell carcinoma

- Early surgery is the best option for renal cell carcinoma. Depending on the size and location of the tumor, nephron-sparing or partial nephrectomy may be possible without compromising survival [Grubb et al 2005].
- Cryoablation is being increasingly used for small lesions or in individuals at high risk for a surgical procedure [Shingleton & Sewell 2002].
- Renal transplantation has been successful in individuals in whom bilateral nephrectomy has been necessary. It is imperative to evaluate any living, related potential donor for VHL syndrome and to exclude those found to have VHL syndrome.

Pheochromocytomas

- Pheochromocytomas should be surgically removed. Laparascopic approaches have been shown to be effective.
- Preoperative treatment with alpha-adrenergic blockade for seven to ten days is appropriate even in individuals with no known hypertension.

Endolymphatic sac tumors. Consideration of surgical removal of these slow-growing tumors must include discussion of the possible complication of total deafness. Early intervention with small tumors has been shown to preserve both hearing and vestibular function [Kim et al 2005].

Epididymal or broad ligament papillary cyst adenomas. These generally do not require surgery.

Prevention of Secondary Manifestations

Early detection through surveillance and removal of tumors may prevent or minimize deficits such as hearing loss, vision loss, and neurologic symptoms.

Surveillance

Individuals with known VHL syndrome, individuals without clinical manifestations but known to have a *VHL* disease-causing mutation, and at-risk relatives who have not undergone DNA-based testing need regular clinical monitoring by a physician or medical team familiar with the spectrum of VHL syndrome.

Monitoring includes the following:

- Annual ophthalmologic screening, preferably beginning before age five years [Kreusel et al 2006]
- Annual blood pressure monitoring supplemented by measurement of urinary catecholamine metabolites beginning at age five years in those families with a high incidence of pheochromocytoma
- Annual abdominal ultrasound examination beginning at age 16 years. Suspicious lesions in the kidney, adrenal gland, or pancreas should be evaluated by more sophisticated techniques, such as CT scan or MRI.
- Audiologic evaluation of individuals with any recognized hearing deficit, followed by T1-weighted MRI of the temporal bone if abnormalities are found [Kim et al 2005]

Testing of Relatives at Risk

Use of molecular genetic testing for early identification of at-risk family members improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation [Priesemann et al 2006]. The American Society of Clinical Oncologists (ASCO) identifies VHL syndrome as a Group 1 disorder, i.e., a hereditary syndrome for which genetic testing is considered part of the standard management for at-risk family members [ASCO 2003].

Early recognition of manifestations of VHL syndrome may allow for timely intervention and improved outcome; thus, clinical surveillance of asymptomatic at-risk individuals, including children, for early manifestations of VHL syndrome is appropriate.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Certain *VHL* mutations fail to down-regulate HIFα, leading to overexpression of vascular endothelial growth factor (VEGF). A VEGF receptor inhibitor, SU5416, has been used with some success, particularly in individuals with retinal hemangioblastomas who have either failed local therapy or whose lesions are not amenable to local therapy [Aiello et al 2002, Girmens et al 2003]. Stabilization of some, but not all, CNS hemangioblastomas has also been demonstrated [Madhusudan et al 2004]. However, paradoxical secondary polycythemia has occurred in some individuals with VHL syndrome in whom this drug has been used [Richard et al 2002].

Another antiangiogenic drug, halofuginone, has been shown to inhibit growth of a VHL-related pheochromocytoma transplanted in mice [Gross et al 2003]. This drug may have some utility in the rare, unresectable malignant pheochromocytomas, but simple surgical excision is clearly preferable for the usual benign tumors.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Von Hippel-Lindau syndrome (VHL syndrome) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 80% of individuals diagnosed with VHL syndrome have an affected parent.
- *De novo* mutations of the *VHL* gene are estimated to occur in about 20% of probands.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include molecular genetic testing if the *VHL* disease-causing mutation in the proband is known. If the disease-causing *VHL* mutation in the proband is not known, ophthalmologic screening and abdominal ultrasound evaluation, at a minimum, should be offered to both parents.

Note: The family history may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. If the parent is the individual in whom the mutation first occurred, (s)he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

Sibs of a proband

- The risk of VHL syndrome to sibs depends upon the genetic status of the parents.
- If a parent of a proband is clinically affected or has a disease-causing *VHL* mutation, the sibs of the proband are at 50% risk of inheriting the altered gene.
- If neither parent has the disease-causing *VHL* mutation identified in the proband, the sibs have a small risk of VHL syndrome because of the possibility of germline mosaicism in one parent.
- Mosaicism has been described; the incidence is not known [Sgambati et al 2000].

Offspring of a proband. Each offspring of an affected individual has a 50% risk of inheriting the mutant *VHL* gene; the degree of clinical severity is not predictable.

Other family members. The risk to other family members depends upon their biological relationship to the affected family member and can be determined by pedigree analysis and/or molecular genetic testing.

Related Genetic Counseling Issues

Genetic cancer risk assessment and counseling. For comprehensive descriptions of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see:

- Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors
- Elements of Cancer Genetics Risk Assessment and Counseling (part of PDQ®, National Cancer Institute)

Testing at-risk asymptomatic family members. Molecular genetic testing of at-risk family members is appropriate in order to determine the need for continued clinical surveillance. Interpretation of molecular genetic test results is most accurate when a disease-causing germline mutation has been identified in an affected family member. Those who have the disease-causing mutation require regular surveillance, whereas family members who have not inherited the disease-causing mutation and their offspring need have no future concern.

Because early detection of at-risk individuals affects medical management, testing of asymptomatic individuals during childhood is beneficial [ASCO 2003]. As ophthalmologic screening for those at risk for VHL syndrome begins as early as possible, certainly before age five years, molecular genetic testing may be considered in young children. Molecular genetic testing may be performed earlier if the results would alter the medical management of the child.

Parents often want to know the genetic status of their children prior to initiating screening in order to avoid unnecessary procedures in a child who has not inherited the altered gene. Special consideration should be given to education of the children and their parents prior to genetic testing. A plan should be established for the manner in which results are to be given to the parents and their children.

The use of molecular genetic testing for determining the genetic status of presumably at-risk relatives when a family member with a clinical diagnosis of VHL syndrome is not available for testing is less straightforward. Such test results need to be interpreted with caution. A positive test result signals the presence of a *VHL* disease-causing mutation in the at-risk family member and indicates that the same molecular genetic testing method can be used to assess the genetic status of other at-risk family members. However, a negative test for a *VHL* gene mutation under such circumstances suggests one of the following possibilities:

- The at-risk family member has not inherited a *VHL* disease-causing mutation;
- The familial *VHL* mutation may not be detectable by the assays used; or
- The diagnosis of VHL syndrome in the affected family member is questionable.

In this situation, the presumably at-risk family member has a small, but finite, residual risk of having inherited a disease-causing allele (i.e., VHL syndrome or other hereditary disorder). In counseling such individuals, careful consideration should be given to the strength of the clinical diagnosis of VHL syndrome in the affected family member, the relationship of the at-risk individual to the affected family member, the perceived risk of an undetected *VHL* (or other) gene mutation, and the potential need for some form of continued clinical surveillance.

Other issues to consider. It is recommended that physicians ordering *VHL* molecular genetic testing and individuals considering undergoing testing understand the risks, benefits, and limitations of the testing prior to sending a sample to a laboratory. A study demonstrated that for almost one-third of individuals assessed for familial adenomatous polyposis, an autosomal dominant colon cancer syndrome, the physician misinterpreted the test results [Giardiello et al 1997]. Referral to a genetic counselor and/or a center in which testing is routinely offered is recommended.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be carefully explored.

Family planning. The optimal time for determination of genetic risk and genetic counseling regarding prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA, particularly in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at 50% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as VHL syndrome that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) has been successfully used in pregnancies at risk for VHL syndrome [Rechitsky et al 2002, Simpson et al 2005] and may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Von Hippel-Lindau Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
VHL	3p26-p25	Von Hippel-Lindau disease tumor suppressor

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Von Hippel-Lindau Syndrome

193300	VON HIPPEL-LINDAU SYNDROME; VHL
608537	VHL GENE; VHL

Table C. Genomic Databases for Von Hippel-Lindau Syndrome

Gene Symbol	Entrez Gene	HGMD
VHL	7428 (MIM No. 608537)	VHL

For a description of the genomic databases listed, click here.

Normal allelic variants: The *VHL* gene, which consists of three exons spanning about 10 kb of genomic DNA, is highly conserved among worms, flies, rodents, and humans (reviewed in Kaelin 2002). An mRNA about 4.5 kb in size is almost ubiquitously expressed and encodes proteins of 213 and 159 amino acid residues. The latter isoform is the major product in most tissues and results from initiation of translation from an internal methionine codon at position 54. Both protein isoforms appear to be functional.

Pathologic allelic variants: Over 300 germline mutations have been identified in families with von Hippel-Lindau syndrome (VHL syndrome) [Beroud et al 1998]. They consist of partial and complete gene deletions and frameshift, nonsense, missense, and splice site mutations. The mutations occur in all three exons, with only a handful of mutations found in four or more families (i.e., delPhe76, Asn78Ser, Arg161X, Arg167Gln, Arg167Trp, Leu178Pro). Codon 167 is a mutation "hot spot." A database of mutations in the *VHL* gene is maintained on the Human Gene Mutation Database Web site.

Normal gene product: Von Hippel-Lindau disease tumor suppressor protein (pVHL) has been implicated in a variety of functions including transcriptional regulation, post-transcriptional gene expression, protein folding, extracellular matrix formation, and ubiquitinylation (reviewed in Kaelin 2002). The role of pVHL in the regulation of hypoxia-inducible genes through the targeted ubiquitinylation and degradation of HIF1α has been elucidated, leading

to a model of how disruption of the *VHL* gene results in renal cell carcinoma and the production of highly vascularized tumors.

Normal pVHL binds to elongin C, which forms a complex with elongin B and cullin-2 (CUL-2). This complex resembles the SCF ubiquitin ligase or E3 complex in yeast that catalyzes the polyubiquitinylation of specific proteins and targets them for degradation by proteosomes. Under normoxic conditions, HIF1α is hydroxylated at two specific proline residues by a member of the EGLN family of prolyl hydroxylase enzymes.

The VHL protein then binds to hydroxylated HIF1α and targets it for degradation. Under hypoxic conditions, HIF1α is not hydroxylated, pVHL does not bind, and HIF1α subunits accumulate. HIF1α forms heterodimers with HIF1β and activates transcription of a variety of hypoxia-inducible genes (i.e., *VEGF*, *EPO*, *TGF* α, *PDGF* β). Likewise, when pVHL is absent or mutated, HIF1α subunits accumulate, resulting in cell proliferation and the neovascularization of tumors characteristic of VHL disease [Kaelin 2002].

Abnormal gene product: Mutations in the *VHL* gene either prevent its expression (i.e., deletions, and frameshifts, nonsense mutations, splice site mutations) or lead to the expression of an abnormal protein (i.e., missense mutations). The effect of missense mutations may be deduced from the three-dimensional structure of the protein [Stebbins et al 1999]. Missense mutations that result in VHL syndrome type 1 are predicted to destabilize packing of the alpha-helical domains, decrease the stability of the alpha-beta domain interface, interfere with binding of elongin C and HIF1α, or disrupt hydrophobic core residues, thereby leading to loss of protein function.

Missense mutations that cause VHL syndrome type 2 include those not predicted to unravel the protein structure completely. Most type 2 mutations map either to residues that contact elongin C or to solvent-exposed residues that make up a second protein-binding site. Missense mutations that lead to pheochromocytoma with a low (or no) risk of RCC (types 2A and 2C) may encode a VHL protein that retains the ability to ubiquinate (and so down-regulate) HIF1α in the presence of molecular oxygen to a greater degree than mutations that result in VHL syndrome with pheochromocytoma and RCC (type 2B). Alternatively, mutant pVHL may predispose to pheochromocytoma by up-regulating JunB, which antagonizes c-Jun, resulting in an inability to regulate apoptosis which is mediated by c-Jun [Kaelin 2005].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Von Hippel-Lindau syndrome

NCBI Genes and Disease
Von Hippel-Lindau syndrome

VHL Family Alliance
2001 Beacon St Suite 208
Boston MA 02135-7787
Phone: 800-767-4VHL; 617-277-5667
Fax: 858-712-8712

Email: info@vhl.org
www.vhl.org

Kidney Cancer Association
1234 Sherman Avenue Suite 203
Evanston IL 60202-1375
Phone: 800-850-9132; 847-332-1051
Fax: 847-332-2978
Email: office@kidneycancerassociation.org
CureKidneyCancer.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

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Suggested Readings

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Chapter Notes

Revision History

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