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Von Hippel-Lindau Syndrome

Synonyms: VHL Disease, VHL Syndrome, Von Hippel-Lindau Disease

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Summary

Clinical characteristics

Von Hippel-Lindau syndrome (VHL) is characterized by hemangioblastomas of the brain, spinal cord, and retina; renal cysts and clear cell renal cell carcinoma; pheochromocytoma and paraganglioma; pancreatic cysts and neuroendocrine tumors; endolymphatic sac tumors; and epididymal and broad ligament cystadenomas. Retinal hemangioblastomas may be the initial manifestation of VHL and can cause vision loss. Cerebellar hemangioblastomas may be associated with headache, vomiting, gait disturbances, or ataxia. Spinal hemangioblastomas and related syrinx usually present with pain. Sensory and motor loss may develop with cord compression. Renal cell carcinoma occurs in about 70% of individuals with VHL and is the leading cause of mortality. Pheochromocytomas can be asymptomatic but may cause sustained or episodic hypertension. Pancreatic lesions often remain asymptomatic and rarely cause endocrine or exocrine insufficiency. Endolymphatic sac tumors can cause hearing loss of varying severity, which can be a presenting symptom. Cystadenomas of the epididymis are relatively common. They rarely cause problems, unless bilateral, in which case they may result in infertility.

Diagnosis/testing

The diagnosis of VHL is established in a proband who fulfills existing diagnostic clinical criteria. Identification of a heterozygous germline *VHL* pathogenic variant on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.

Management

Targeted therapies: Pazopanib is an FDA-approved treatment for advanced renal cell carcinoma. Belzutifan is approved in many countries for the treatment of adults with VHL who do not require immediate surgery for

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associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors.

Supportive care: Surgical resection for most CNS hemangioblastomas; early treatment for retinal hemangioblastomas; cryoablation or radiofrequency ablation for renal cell carcinoma; kidney transplantation following bilateral nephrectomy; removal of pheochromocytomas (partial adrenalectomy when possible); consider removal of pancreatic neuroendocrine tumors; consider surgical removal of endolymphatic sac tumors (particularly small tumors in order to preserve hearing and vestibular function); cystadenomas of the epididymis or broad ligament need treatment when symptomatic or threatening fertility; psychosocial support and care coordination as needed.

Surveillance: For individuals with VHL and at-risk relatives of unknown genetic status: annual clinical evaluation for neurologic symptoms, vision problems, and hearing disturbances beginning in the first decade of life; brain and total spine MRI every two years starting at age 11 years; ophthalmology evaluation beginning at age one year; abdominal MRI every two years starting at age 15 years; annual blood pressure starting in the first decade of life; annual plasma or 24-hour urine for fractionated metanephrines starting at age five years; audiology assessment every two to three years starting at age 11 years; MRI of the internal auditory canal in asymptomatic individuals between age 15 and 20 years; assessment of psychosocial needs at each visit.

Agents/circumstances to avoid: Tobacco products should be avoided, as they are considered a risk factor for kidney cancer; chemicals and industrial toxins known to affect VHL-involved organs should be avoided; contact sports should be avoided if adrenal or pancreatic lesions are present.

Evaluation of relatives at risk: If the pathogenic variant 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 surveillance of family members who have not inherited the pathogenic variant.

Pregnancy management: Intensified surveillance for cerebellar hemangioblastoma and pheochromocytoma prior to conception and during pregnancy; MRI without contrast of the cerebellum at four months' gestation.

Genetic counseling

VHL is inherited in an autosomal dominant manner. Approximately 80% of individuals with VHL have an affected parent and about 20% have VHL as the result of a pathogenic variant that occurred as a *de novo* event in the affected individual or as a postzygotic *de novo* event in a mosaic, apparently unaffected parent. The offspring of an individual with VHL are at a 50% risk of inheriting the *VHL* pathogenic variant. Once the *VHL* pathogenic variant has been identified in an affected family member, testing of at-risk asymptomatic family members, prenatal testing, and preimplantation genetic testing for VHL are possible.

Diagnosis

Clinical diagnostic criteria for von Hippel-Lindau syndrome (VHL) have been proposed and vary slightly between Dutch or Danish guidelines [Binderup et al 2022, Wolters et al 2022].

Suggestive Findings

VHL **should be suspected** in individuals with or without a family history of VHL who have:

- Retinal angioma, especially in a young individual
- Multiple spinal or cerebellar hemangioblastoma, or a single hemangioblastoma diagnosed at age ≤50 years
- Adrenal or extra-adrenal pheochromocytoma
- Renal cell carcinoma diagnosed at age ≤40 years
- Multiple renal and pancreatic cysts

- Multiple neuroendocrine tumors of the pancreas
- Endolymphatic sac tumors
- Less commonly, multiple papillary cystadenomas of the epididymis or broad ligament

Establishing the Diagnosis

The clinical diagnosis of VHL **can be established** in proband according to Danish or Dutch guidelines (see Table 1), or the molecular diagnosis can be established by identification of a heterozygous pathogenic (or likely pathogenic) variant in *VHL* on molecular genetic testing (see Table 2).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *VHL* variant of uncertain significance does not establish or rule out the diagnosis.

Table 1. Von Hippel-Lindau Syndrome Clinical Diagnostic Criteria

VHL Published Diagnostic Criteria	Clinical Diagnostic Criteria		VHL-Related Manifestations	
	Positive family history	No known family history	Included in all 3 published criteria	Specific to published criteria
Dutch criteria [1]	1 VHL-related tumor **AND** 1st- or 2nd-degree relative w/diagnosis of VHL	≥2 VHL-related manifestations	• Retinal HB • CNS HB • RCC • Pheo • PNET • ELST	• Paraganglioma • Multiple kidney cysts • Multiple pancreatic cysts
Danish criteria [2]	≥1 VHL-related manifestation **AND** 1st-degree relative w/ diagnosis of VHL	≥2 HB **OR** 1 HB & 1 VHL-related manifestation		None

Adapted from Wolters et al [2022]
CNS = central nervous system; ELST = endolymphatic sac tumor; HB = hemangioblastoma; Pheo = pheochromocytoma; PNET = pancreatic neuroendocrine tumor; RCC = renal cell carcinoma; VHL = von Hippel-Lindau syndrome
1. Hes et al [2001]
2. Binderup et al [2022]

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of the *VHL* coding region, intron 1, and flanking sequences is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *VHL* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to

change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in von Hippel-Lindau Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
VHL	Sequence analysis [3, 4]	~85% [5, 6]
	Gene-targeted deletion/duplication analysis [7]	~10% [5, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Sequence analysis of intron 1 should be performed in probands without an identified *VHL* pathogenic variant in the coding region; intron 1 pathogenic variants can lead to inclusion of a cryptic exon (designated exon E1') [Lenglet et al 2018].
5. Nordstrom-O'Brien et al [2010] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Approximately 5% of individuals with a clinical diagnosis of von Hippel-Lindau syndrome do not have a pathogenic variant identified.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

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

Hemangioblastomas. Central nervous system (CNS) hemangioblastoma is the prototypic lesion of VHL [Catapano et al 2005, Gläsker 2005]. Multiple CNS tumors, occurring either synchronously or metachronously, are common. Roughly 80% develop in the brain and 20% in the spinal cord. Peripheral nerve hemangiomas may be a rare manifestation [Giannini et al 1998]. Some hemangioblastomas do not cause symptoms and are discovered only on imaging.

Growth patterns of CNS hemangioblastomas can be saltatory (72%), linear (6%), or exponential (22%). Increased growth was associated with male sex, symptomatic tumors, hemangioblastoma-associated cysts [Takami et al 2022], and germline *VHL* intragenic deletions [Lonser et al 2014, Huntoon et al 2015]. CNS hemangioblastomas remain the main cause of death, although VHL-related survival has improved over time [Binderup et al 2017b].

- **Brain hemangioblastomas.** Within the brain, the vast majority are infratentorial, mainly in the cerebellar hemispheres. The pituitary stalk is the most common site for the development of supratentorial hemangioblastomas in individuals with VHL [Lonser et al 2009]. Clinical symptoms depend on 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.
- **Spinal hemangioblastomas** are generally intradural, most commonly occur in the cervical or thoracic regions, and occasionally may involve the entire spinal cord. Most symptom-producing spinal hemangioblastomas are associated with cysts/syringomyelia/syrinx [Wanebo et al 2003]. Spinal hemangioblastomas usually present with pain; sensory and motor loss may develop with cord compression.
- **Retinal hemangioblastoma,** sometimes called retinal angiomas, are histologically identical to CNS hemangioblastomas. They may be the initial manifestations of VHL and may occur in childhood. About 70% of affected individuals are identified as having retinal hemangioblastomas [Webster et al 1999, Kreusel 2005], with mean age of detection 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%).

  Retinal hemangioblastomas may be asymptomatic and may 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. Tests of retinal function may be abnormal even in the presence of quiescent retinal hemangioblastomas [Kreusel et al 2006]. While the number of retinal hemangioblastomas does not appear to increase with age, the probability of vision loss does [Kreusel et al 2006].

Renal lesions

- **Multiple and bilateral renal cysts** are common in individuals with VHL [Lonser et al 2003].
- **Renal cell carcinoma,** specifically of the clear cell subtype, developing either within a cyst or in the surrounding parenchyma, occurs in about 70% of affected individuals by age 60 years, and is a leading cause of mortality in VHL [Maher et al 1990, Maher et al 1991]. Pathogenic variants in *VHL* are the most common cause of renal cell carcinoma. Overall survival for renal cell carcinoma in individuals with VHL is associated with tumor size and age of the individual [Kwon et al 2014]. Missense variants seem to lead to faster growth [Peng et al 2019].

Pheochromocytoma may cause sustained or episodic hypertension or may not cause signs/symptoms. Due to surveillance in individuals with VHL, VHL-related pheochromocytoma are more likely to be identified at a younger age and detected incidentally by abdominal imaging in asymptomatic normotensive individuals [Li et al 2020]. Pheochromocytomas can be unilateral or bilateral and are often small and multifocal [Li et al 2020]. They are usually benign, but malignant behavior has been reported [Chen et al 2001, Jimenez et al 2009].

Paragangliomas. Similar in etiology, paragangliomas can develop along the sympathetic axis in the abdomen or thorax [Schimke et al 1998, Boedeker et al 2014]; these tumors are often nonfunctional (i.e., do not secrete catecholamines or other hormones).

Pancreatic lesions

- **Pancreatic cysts.** Most pancreatic lesions are simple cysts and have no malignant potential. While they can be numerous in individuals with VHL, they rarely cause endocrine or exocrine insufficiency. Occasionally, cysts in the head of the pancreas cause biliary obstruction.
- **Neuroendocrine tumors.** 5%-17% of individuals with VHL develop neuroendocrine tumors of the pancreas [Lonser et al 2003, Maher et al 2011]. They are not usually hormonally active and are slow growing, but malignant behavior has been observed, particularly in tumors >2.7 cm [Krauss et al 2018]. Tumors have been described from an early age, starting from the second decade [Krauss et al 2018, O'Toole et al 2018].

Endolymphatic sac tumors are seen in approximately 10%-16% of individuals with VHL, and in some instances unilateral or bilateral hearing loss is the initial clinical manifestation of VHL [Kim et al 2005, Binderup et al 2013]. The onset of hearing loss is typically sudden; severity varies, but it is often severe to profound [Choo et al 2004, Kim et al 2005]. Vertigo or tinnitus can be the initial manifestation of an endolymphatic sac tumor. More significant hearing loss and larger tumor size at presentation was reported in individuals with endolymphatic sac tumors not related to VHL than in individuals with VHL-related endolymphatic sac tumors [Nevoux et al 2014]. Large endolymphatic sac tumors can involve other cranial nerves. Endolymphatic sac tumors are rarely malignant [Muzumdar et al 2006].

Epididymal and broad ligament cystadenomas. Epididymal or papillary cystadenomas are relatively common in males with VHL. 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. Both tissues are mesonephric in origin and are likely a developmental remnant of somatic *VHL* loss.

Prognosis. One study showed that in adulthood, men have more VHL manifestations compared to women, and the risk for manifestations was not constant but varied throughout the affected individual's lifetime [Binderup et al 2016]. Age was the only predictor for the number of involved organs.

Improved surveillance guidelines have increased the life expectancy of individuals with VHL by more than 16 years since 1990 [Wilding et al 2012]. Two studies evaluated the implementation of national surveillance guidelines in Denmark and the Netherlands. One study of 84 individuals with VHL showed that more than 90% reported that they were familiar with their national VHL surveillance guidelines. However, 64% of those individuals had received information that was only partially consistent with the Dutch guidelines [Lammens et al 2011a]. In a Danish study, compliance and frequency of recommended surveillance was low for individuals with VHL and individuals at risk [Bertelsen & Kosteljanetz 2011]. These studies suggest that implementation of surveillance guidelines through a doctor- and patient-oriented information campaign could have an immediate positive impact for individuals with VHL.

Genotype-Phenotype Correlations

Four general VHL phenotypes (type 1, type 2A, type 2B, type 2C) have been suggested based on the likelihood of pheochromocytoma or renal cell carcinoma. Many lines of research support the conclusion that the molecular etiology of pheochromocytomas appears to be distinct from other VHL lesions. Therefore, the most relevant genotype-phenotype correlations rely mostly on scoring the presence/absence of pheochromocytomas associated with a given allele. The following discussion summarizes the genotype-phenotype studies published to date, with the cautionary note that further investigation is needed. Note: Patterns are not clear-cut, and genotype-phenotype correlations have no current diagnostic or therapeutic value; they are used for academic purposes only.

VHL type 1. Retinal angioma, CNS hemangioblastoma, renal cell carcinoma, pancreatic cysts, and neuroendocrine tumors. VHL type 1 is characterized by a low risk for pheochromocytoma. Pathogenic

truncating or missense variants that are predicted to grossly disrupt the folding of the VHL protein [Stebbins et al 1999] are associated with VHL type 1.

Several groups report a reduced risk for renal cell carcinoma in individuals with a deletion of *VHL* [Cybulski et al 2002, Maranchie et al 2004, McNeill et al 2009]. In particular, individuals with a complete or partial deletion that extends 5' of *VHL* to include *BRK1* (previously C3orf10) have a significantly reduced risk of renal cell carcinoma [Maranchie et al 2004, McNeill et al 2009]. This genotype may constitute a distinct phenotype, **VHL type 1B**, characterized by a reduced risk for both renal cell carcinoma and pheochromocytoma.

VHL type 2. Pheochromocytoma, retinal hemangioblastomas, and CNS hemangioblastoma. VHL type 2 is characterized by a high risk for pheochromocytoma. Individuals with VHL type 2 commonly have a pathogenic missense variant. Some pathogenic missense variants appear to correlate with a specific VHL type 2 phenotype [Weirich et al 2002, Sansó et al 2004, Abbott et al 2006, Knauth et al 2006] (see also Molecular Genetics). Pathogenic missense variants stratified by multiple in silico computational models found that variants with a high predicted risk of pathogenicity were predictive of pancreatic lesion progression [Tirosh et al 2018a]. In contrast, genotype did not appear to influence the growth of renal cell carcinomas in individuals with VHL [Farhadi et al 2018].

VHL type 2 is further subdivided:

- **Type 2A.** Pheochromocytoma, retinal hemangioblastomas, and CNS hemangioblastoma; low risk for renal cell carcinoma
- **Type 2B.** Pheochromocytoma, retinal hemangioblastomas, CNS hemangioblastoma, pancreatic cysts, and neuroendocrine tumors; high risk for renal carcinoma
- **Type 2C.** Risk for pheochromocytomas only. Note: Some individuals within families with an apparent type 2C phenotype have developed hemangioblastomas [Neumann & Eng 2009].

A higher age-related incidence of retinal hemangioblastomas, CNS hemangioblastomas, clear cell renal cell carcinoma, and pancreatic neuroendocrine tumors was described in individuals with a truncating variant compared to individuals with a missense variant or in-frame deletion of a single amino acid [Reich et al 2021].

Penetrance

VHL pathogenic variants are highly penetrant. Almost all individuals who have a *VHL* pathogenic variant are symptomatic by age 65 years [Maher et al 1991].

Nomenclature

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

Genetically Related (Allelic) Disorders

Familial erythrocytosis 2 (OMIM 263400) is caused by biallelic pathogenic variants in *VHL* (resulting in retention of a cryptic exon in intron 1) and characterized by increased circulating red blood cell mass, increased serum levels of erythropoietin, and normal oxygen affinity. Although thrombosis and/or hemorrhage has

occurred in many individuals with familial erythrocytosis 2, no individuals with this disorder or their heterozygous relatives thus far described have developed von Hippel-Lindau syndrome (VHL)-related tumors.

Note: Congenital erythrocytosis is endemic in subpopulations worldwide; pathogenic variants in *VHL* are a common cause of congenital erythrocytosis [Bento 2018].

Sporadic tumors (including clear cell renal cell carcinoma and hemangioblastoma) occurring as single tumors in the absence of any other findings of VHL may contain a somatic pathogenic variant in *VHL* that is **not** present in the germline [Iliopoulos 2001, Kim & Kaelin 2004]. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

Isolated hemangioblastoma, retinal angioma, or clear cell renal cell carcinoma. The clinical sensitivity of molecular genetic testing of *VHL* makes it possible to effectively rule out von Hippel-Lindau syndrome (VHL) with a high degree of certainty in individuals with (1) isolated hemangioblastoma, retinal angioma, or clear cell renal cell carcinoma and (2) no detectable germline *VHL* pathogenic variant. Somatic mosaicism for a *VHL* pathogenic variant could still be considered in such individuals (an estimated 5% of individuals with VHL have a somatic mosaicism [Chen et al 2022]). A younger individual, especially one with multiple lesions, is more likely to have a germline *VHL* pathogenic variant than an older individual with a single lesion [Binderup et al 2017a].

The differential diagnosis for an individual suspected of having VHL depends on the further clinical presentation (see Table 3a and Table 3b).

Pheochromocytoma. Up to 40% of individuals with pheochromocytoma have a heterozygous pathogenic variant in one of several genes: *SDHB*, *SDHD*, *VHL*, *RET*, and *NF1* (most prevalent) or *SDHA*, *SDHAF2*, *MAX*, *FH*, and *TMEM127* (less prevalent). Germline *VHL* pathogenic variants are rare in simplex cases of unilateral pheochromocytoma (i.e., an affected individual with no family history of VHL), unless the individual is younger than age 20 years.

Table 3a. Genetic Disorders Associated with an Increased Risk of Pheochromocytomas

Gene	Disorder	MOI	Clinical Characteristics
MAX *SDHA* *SDHAF2* *SDHB* *SDHC* *SDHD* *TMEM127*	Hereditary paraganglioma-pheochromocytoma syndrome	AD [1]	Characterized by PGL & Pheo
NF1	Neurofibromatosis 1	AD	Café au lait macules, intertriginous freckling, cutaneous neurofibromas, & learning disability. Pheo are more common in persons w/NF1 but are still rare & occur in <1% of adults w/ NF1.

Table 3a. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
RET	Multiple endocrine neoplasia type 2 (MEN2)	AD	• MEN2A: ↑ risk for MTC, Pheo, & parathyroid adenoma or hyperplasia. Pheo usually present after MTC or concomitantly; however, they are 1st manifestation in 13%-27%. • MEN2B: mucosal neuromas of lips & tongue, ganglioneuromatosis of GI tract, marfanoid habitus, & ↑ risk for MTC & Pheo. Pheo occur in 50% of persons w/MEN2B.

AD = autosomal dominant; GI = gastrointestinal; MOI = mode of inheritance; MTC = medullary thyroid cancer; Pheo = pheochromocytomas; PGL = paragangliomas
1. Pathogenic variants in *SDHD* demonstrate parent-of-origin effects and generally cause disease only when the pathogenic variant is inherited from the father. Pathogenic variants in *SDHAF2* and possibly *MAX* exhibit parent-of-origin effects similar to those of pathogenic variants in *SDHD*.

Renal cell carcinoma. Individuals with familial renal cell carcinoma should be evaluated for *FH* tumor predisposition syndrome and Birt-Hogg-Dubé syndrome.

Table 3b. Genetic Disorders Associated with Renal Cell Carcinoma

Gene	Disorder	MOI	Clinical Characteristics
FH	*FH* tumor predisposition syndrome	AD	Characterized by cutaneous leiomyomata, uterine leiomyomata (fibroids), &/or renal tumors. Pheo & PGL have been described in small number of families. Median age of detection is ~40 yrs.
FLCN	Birt-Hogg-Dubé syndrome	AD	Cutaneous manifestations (fibrofolliculomas, acrochordons, angiofibromas, oral papules, cutaneous collagenomas, & epidermal cysts), pulmonary cysts/history of pneumothorax, & various types of renal tumors. Median age of renal tumor diagnosis is 48 yrs.

AD = autosomal dominant; MOI = mode of inheritance; Pheo = pheochromocytomas; PGL = paragangliomas

Endolymphatic sac tumors in VHL are often misdiagnosed as Ménière disease.

Management

The first von Hippel-Lindau syndrome (VHL) care pathway was recently published by a multidisciplinary team from the Netherlands [Wolters et al 2022].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with VHL, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Von Hippel-Lindau Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	• Neurologic history & physical exam • Brain & total spine MRI	To assess for evidence of CNS or peripheral nerve hemangioblastomas
Eyes	Ophthalmologic eval	To assess for retinal hemangioblastomas
Renal/pancreatic cysts & tumors	Abdominal ultrasound in those age ≥16 yrs	Evaluate suspicious lesions in kidney, adrenal gland, or pancreas by more sophisticated techniques (e.g., CT, MRI).

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Endocrine	• Blood pressure measurement • Measurement of 24-hr urine fractionated metanephrines & catecholamine metabolites or plasma free fractionated metanephrines	In those age ≥5 yrs to evaluate for pheochromocytoma
ENT	Audiologic eval	To assess for hearing loss assoc w/endolymphatic sac tumors
	MRI of internal auditory canals	At age 15-20 yrs to assess for ELST or earlier in those w/ hearing loss, tinnitus, or vertigo
Psychological	Assess psychosocial needs.	Refer to social worker or psychologist as needed
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of VHL to facilitate medical & personal decision making

CNS = central nervous system; ELST = endolymphatic sac tumors; MOI = mode of inheritance; VHL = von Hippel-Lindau syndrome
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Pazopanib is an FDA-approved treatment for advanced renal cell carcinoma. A single-arm Phase II trial included 31 individuals with a molecular or clinical diagnosis of VHL treated with 800 mg oral pazopanib for 24 weeks [Giles & Gläsker 2018, Jonasch et al 2018]. Four of the individuals were negative for a germline *VHL* pathogenic variant. Thirteen of 31 (42%) individuals achieved a response based on RECIST criteria after treatment with pazopanib. More than half (52%) of individuals with renal cell carcinoma responded to therapy, including two individuals with complete response. Similarly, 52% of pancreatic lesions showed partial or complete response and two of 49 hemangioblastomas showed partial response. One individual died due to hemorrhage of a central nervous system (CNS) hemangioma. Response to treatment was limited to individuals with a germline pathogenic variant. The study concluded that systemic treatment with pazopanib can be considered in individuals with a germline *VHL* pathogenic variant and without a CNS hemangioblastoma requiring clinical action.

Belzutifan. Promising results were demonstrated in the LITESPARK-004 trial of hypoxia-inducible factor 2 alpha (HIF2α) inhibitor belzutifan in individuals with VHL and clear cell renal cell carcinoma. Belzutifan is a targeted oral therapy specifically altering the biology of cells lacking the VHL protein [Choueiri et al 2021]. Belzutifan has only limited side effects. The approval was based on a Phase II clinical trial following 61 individuals with VHL that reported clinical benefit for individuals with all tumor types, including a drastic reduction in the number of required surgeries [Jonasch et al 2021]. A recent update of nearly 2.5 years of follow up of the 61 individuals reported that belzutifan continued to show anti-tumor activity in VHL-related neoplasms, including tumors in the kidney, pancreas, brain, spine, and eyes, with no new safety concerns [Jonasch et al 2022]. Belzutifan induced partial responses with a renal cell carcinoma objective response rate (ORR) of 49% and a disease control rate of 98.4% after 21.8 months of treatment. All individuals with pancreatic lesions (e.g., cysts, pancreatic neuroendocrine tumors) had an ORR of 77%, and those with CNS

hemangioblastoma had a 30% response rate. In total, 33% had grade 3 or higher adverse events reported, and seven individuals (11.5%) discontinued the treatment. Belzutifan was FDA approved in August 2021, and is used in individuals not requiring immediate surgery. It is unknown if belzutifan can prevent tumors in individuals with VHL. The most prominent side effects include anemia and fatigue.

Supportive Care

No guidelines exist for the management of VHL lesions.

CNS hemangioblastomas

- Most CNS hemangioblastomas can be surgically removed completely and safely [Gläsker et al 2013]. Intraoperative videoangiography, ultrasound, and fluorescein optimize identification of CNS hemangioblastomas and their vasculature, leading to a safer resection with reduced side effects [Mazzapicchi et al 2022]. Intraoperative fluorescence angiography was helpful in reducing intraoperative bleeding and preventing spinal swelling [Mehta et al 2017].
- Some advocate early surgical removal of both symptomatic and asymptomatic CNS hemangioblastomas, while others follow asymptomatic lesions with yearly imaging studies. A study of 15 symptomatic individuals with cauda equina hemangioblastomas revealed a worse outcome in only one individual six months after surgery. The other individuals were stable or improved [Mehta et al 2017].

Spinal hemangioblastomas

- Preoperative arterial embolization may be indicated, especially for extensive spinal tumors. A minimally invasive approach for the resection of selected spinal hemangioblastomas is considered safe and allows complete tumor resection [Krüger et al 2019].
- Pathologic findings during intraoperative neurophysiologic monitoring (IONM) appear to predict worse long-term outcomes after microsurgical removal of spinal cord hemangioblastomas [Siller et al 2017]. The use of IONM seems to be associated with better neurologic outcomes [Feletti et al 2022]. Spinal cord surgery should be performed in an expert center by experienced neurosurgeons.
- Surgical intervention for cysts/syrinx in the spinal cord is recommended.
- Stereotactic therapy is increasingly popular, but there is still a need for prospective studies [Pan et al 2018]. Gamma knife surgery may be useful with small solid tumors or those in inoperable sites [Asthagiri et al 2010, Simone et al 2011]. While this technique may reduce the size of the solid tumor, it does not appear to prevent cyst formation. The unpredictable growth pattern makes it difficult to determine when to start stereotactic therapy in order to avoid unnecessary intervention. Recent studies show promising local control rates at one, three, and five years were 96%, 92%, and 92%, respectively. Clinically, 13/16 (81.2%) tumors had symptomatic improvement [Pan et al 2017].
- Factors associated with tumor control are solid, smaller tumors, VHL-associated lesions, and higher margin dose. Thirteen of 186 individuals (7%) experienced complications, 11 individuals needed steroid therapy, and one person died of refractory peritumoral edema. Two individuals required additional surgery [Kano et al 2015].
- Another study showed recurrence-free survival in six of eight individuals at a mean follow up of 48 months. Two individuals required additional surgery for persisting cerebellar symptoms. One individual showed an increase in cyst volume along with a decrease of the size of the mural nodule [Goyal et al 2016].
- A case study showed complete loss of stromal cells after a standard dose of stereotactic radiosurgery for hemangioblastoma, indicating the effectiveness of the treatment [Nambu et al 2018].

Retinal hemangioblastomas

- Ultra-widefield fluorescein angiography can be useful in the evaluation and management of retinal hemangioblastomas. This technique appears to detect more hemangioblastomas than ophthalmoscopy and conventional angiography [Chen et al 2018].
- Most ophthalmologists favor prospective treatment of retinal hemangioblastomas (but not optic nerve hemangioblastomas) 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 on 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.
- Vitreoretinal surgery is indicated when retinal hemangioblastomas are accompanied by complications such as epiretinal membrane development, vitreous hemorrhage, tractional and/or exudative retinal detachment, preretinal fibrosis, or proliferative vitreoretinopathy [Gaudric et al 2011].
- Brachytherapy could be a treatment option for larger peripheral hemangioblastomas with manageable risk and a high eye preservation rate [Dalbah et al 2021].
- External beam radiotherapy has been shown to be useful when standard therapy has not prevented progression [Raja et al 2004]. In individual reports early surgical resection and intravitreal treatment with bevacizumab and propranolol were considered safe and effective [Agarwal et al 2016, van Overdam et al 2017, Karimi et al 2020].
- There is no evidence to support the use of sunitinib for retinal hemangioblastomas.

Renal cell carcinoma

- **Local therapies.** Image-guided techniques such as cryoablation and radiofrequency ablation are now preferred over surgical resection for small renal cell carcinomas [Chan et al 2022]; outcomes are excellent and the procedures are considered safe [Allasia et al 2017, Carrion et al 2020, Wessendorf et al 2021, Chan et al 2022]. Radiofrequency ablation therapy is often applied to smaller tumors, particularly <3 cm [Best et al 2012, Carrion et al 2020]. The major complication rate resulting in a need for a radiologic, surgical, or endoscopic intervention following laparoscopic and percutaneous radiofrequency ablation therapy was 7.3% and 4.3%, respectively [Young et al 2012], but other studies showed no or only minor complications [Allasia et al 2017, Wessendorf et al 2021].
- In individuals treated with nephrectomy, the adrenal gland should be left in situ. If contralateral pheochromocytoma occurs requiring adrenalectomy, the remaining adrenal gland will prevent or delay adrenal insufficiency.
- Kidney 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 and to exclude those with VHL.

Pheochromocytomas

- Pheochromocytomas should be surgically removed. Laparoscopic approaches have been shown to be effective and safe [Dickson et al 2011, Agarwal et al 2012]. It has been proposed that active surveillance for pheochromocytomas smaller than 2 cm can be safe [Sanford et al 2021].
- Preoperative treatment with alpha-adrenergic blockade and optional additional beta-adrenergic blockade for seven to ten days is appropriate even in individuals with no known hypertension and is recommended in treatment guidelines. However, perioperative alpha-adrenergic blockade has recently been under debate. In a multicenter study, mortality rate in pretreated individuals was slightly higher than in non-pretreated individuals [Groeben et al 2020].
- Adrenal-sparing surgery should be considered and is regarded as a successful treatment strategy. Studies show low recurrence, no metastatic disease, and rare steroid dependency after cortical-sparing techniques [Sanford et al 2021, Shirali et al 2023]. Moreover, survival is not affected by adrenal-sparing surgery

[Neumann et al 2019]. Adrenal-sparing surgery is the therapy of choice in children. In ten individuals with VHL, 18 successful operations were performed. After follow up (median 7.2 years), two individuals developed a new tumor in the ipsilateral adrenal gland [Volkin et al 2012].

Pancreatic cysts and neuroendocrine tumors

- Pancreatic cysts are common, rarely influence endocrine function, and have no malignant behavior. Therefore, surgical removal is not generally required [Sharma et al 2017].
- Pancreatic neuroendocrine tumors (PNETs) need to be differentiated from cysts and serous cystadenomas. PNETs are generally slow growing and are not hormonally active, although they can cause metastatic disease. Surgical resection should be strongly considered when there is a high risk of metastases, as suggested by one of the following prognostic criteria: (1) size ≥2.5 cm or (2) tumor doubling rate <500 days [Krauss et al 2018]. Individuals with a *VHL* missense variant are reported to have a higher rate of metastases with PNET size between 1.2-3.0 cm in comparison to individuals with other types of *VHL* pathogenic variants [Tirosh et al 2018b].

Endolymphatic sac tumors (ELST). 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 [Friedman et al 2013]. Friedman et al [2013] described two individuals (2/18) with postoperative decreased facial nerve function and three (3/18) individuals with recurrent ELSTs (with a mean follow up of 67 months). In 31 individuals with VHL with 33 resected ELSTs, 29 individuals were symptomatic. After surgery, hearing was stabilized or improved in 97% of individuals, and tumor resection was complete in 91%. Complications occurred in three tumors: cerebrospinal fluid leakage in two (6%) and transient lower cranial nerve palsy in one (3%) [Kim et al 2013].

Epididymal or broad ligament papillary cyst adenomas generally do not require surgical resection unless they are symptomatic or are threatening fertility.

Surveillance

In the United States, the VHL Alliance has worked extensively with health care professionals to assemble guidelines that are generally accepted worldwide (see VHL Resources – Active Surveillance Guidelines). Additional guidelines originate from Denmark and the Netherlands [Wolters et al 2022]. Individuals with VHL and first-degree relatives who have not undergone DNA-based testing need regular clinical surveillance by a physician or medical team familiar with VHL (see Table 5).

Table 5. Von Hippel-Lindau Syndrome: Recommended Surveillance

Complication	Evaluation	Frequency	Comment
General	Clinical eval for neurologic symptoms, vision problems, &/or hearing disturbances	Annually starting in 1st decade of life	
CNS lesions	Brain & total spine MRI	Every 2 yrs starting at age 11 yrs	Attention should be given to inner / petrous temporal bone (for ELST) & posterior fossa.
Retinal angiomas	Ophthalmology eval w/indirect ophthalmoscope	Annually starting at age 1 yr, but no later than age 5 yrs	
Visceral lesions	MRI of abdomen (kidney, pancreas, & adrenal glands)	Every 2 yrs starting at age 15 yrs	
Pheochromocytoma	Blood pressure measurement	Annually starting in 1st decade of life	
	Plasma or 24-hr urine for fractionated metanephrines	Annually starting at age 5 yrs	

Table 5. continued from previous page.

Complication	Evaluation	Frequency	Comment
ELST [1]	Audiology assessment	Every 2-3 yrs starting at age 11 yrs	Audiology can be used to detect early hearing loss.
		Annually if hearing loss, tinnitus, or vertigo is present	
	MRI of internal auditory canals [2]	In asymptomatic persons age 15-20 yrs	
	MRI w/contrast & high signal intensity w/T_1 (to detect hydrops) using thin slices of internal auditory canal	At time of onset of symptoms in those w/hearing loss, tinnitus, or vertigo	ELST presents as a mass on the posterior wall of the petrous part of the temporal bone & may be missed on standard MRI; FLAIR MRI is useful to find ELST-associated hydrops. [3]
Psychological	Assess psychosocial needs. [4]	At each visit	

CNS = central nervous system; ELST = endolymphatic sac tumors; IAC = internal auditory canals
1. The best way to detect ELST is unknown.
2. Mehta et al [2021]
3. Butman et al [2013]
4. While current medical surveillance guidelines do not address structured psychological support for individuals with VHL, their partners, and their family members, research suggests a distinct need for psychosocial support [Lammens et al 2010, Lammens et al 2011b, Bond et al 2023].

Agents/Circumstances to Avoid

Avoid the following:

- Tobacco products, as they are considered a risk factor for kidney cancer
- Chemicals and industrial toxins known to affect VHL-involved organs
- Contact sports if adrenal or pancreatic lesions are present

Evaluation of Relatives at Risk

Early recognition of manifestations of VHL may allow for timely intervention and improved outcome; thus, clinical surveillance of asymptomatic at-risk individuals (including children) for early manifestations of VHL is appropriate. The American Society of Clinical Oncology identifies VHL as a Group 1 disorder – a hereditary disease for which genetic testing is considered part of the standard management for at-risk family members [Robson et al 2015].

- If the *VHL* pathogenic variant in the family is known, molecular genetic testing can be used for early identification of at-risk family members to improve diagnostic certainty and reduce the need for screening procedures in those at-risk family members who have not inherited the pathogenic variant [Priesemann et al 2006].
- If the *VHL* pathogenic variant in the family is not known and/or at-risk individuals decline genetic testing, continued screening for VHL lesions is warranted (see Surveillance).

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 is not available for testing is not straightforward. Such test results need to be interpreted with caution. A positive test result signals the presence of a *VHL* pathogenic variant 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* pathogenic variant in an at-risk family member under such circumstances suggests one of the following possibilities:

- The at-risk family member has not inherited a *VHL* pathogenic variant.
- The familial *VHL* pathogenic variant may not be detectable by the assays used.
- The clinical diagnosis of VHL in the proband is questionable.

In this situation, the presumably at-risk family member has a small but finite residual risk of having inherited a pathogenic allele (i.e., VHL or other hereditary disorder). In counseling such individuals, careful consideration should be given to the strength of the clinical diagnosis of VHL 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) pathogenic variant, and the potential need for some form of continued clinical surveillance.

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

Pregnancy Management

There is no consensus regarding medical surveillance for pregnant women with VHL. Research by the French VHL Study Group showed a significantly higher complication rate of hemangioblastomas in individuals with VHL who had had at least one pregnancy [Abadie et al 2010]. Another study concluded that pregnancy has a significant influence on cerebellar hemangioblastoma growth and causes an overall high complication rate (17%) [Frantzen et al 2012]. Intensified surveillance can be considered in a specialized medical center prior to conception and during pregnancy to allow early identification of pheochromocytomas and cerebellar hemangioblastomas. A recent study showed a decrease in new VHL manifestations during pregnancy [Binderup et al 2015]. In another study pregnancy did not correlate with the development of new hemangioblastomas or hemangioblastoma or cyst growth [Ye et al 2012], suggesting that more frequent surveillance is not needed during pregnancy. The VHL Active Surveillance Guidelines recommends MRI of the cerebellum without contrast at four months' gestation.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Certain *VHL* pathogenic variants fail to downregulate hypoxia-inducible factor alpha (HIFα), leading to overexpression of downstream effectors such as vascular endothelial growth factor (VEGF), which contribute to pathogenesis. Many experimental therapies target these misregulated signaling pathways. An intravitreal VEGF receptor inhibitor, ranibizumab, has been used with some success in individuals with retinal hemangioblastomas who have either failed local therapy or whose lesions are not amenable to local therapy [Wong et al 2008]. Intravitreal injections of bevacizumab, another VEGF inhibitor, have also proven effective in treating retinal hemangioblastomas in individuals with VHL [Hrisomalos et al 2010]. Stabilization of some (but not all) CNS hemangioblastomas has also been demonstrated [Madhusudan et al 2004].

Sunitinib, a tyrosine kinase inhibitor (TKI) that inhibits the action of VEGF receptors, has had some utility in the rare unresectable malignant pheochromocytomas, but simple surgical excision is clearly preferable for these usually benign tumors [Jimenez et al 2009]. Sunitinib has also been shown to effectively treat clear cell renal cell carcinomas – but not hemangioblastomas – in individuals with VHL [Jonasch et al 2011].

Pazopanib showed favorable effects on the clinical condition of individuals with recurrent and rapidly progressive VHL-associated hemangioblastomas [Migliorini et al 2015]. A pilot study to assess the safety and efficacy of another TKI, dovitinib, for the treatment of asymptomatic hemangioblastomas in individuals with VHL resulted in termination of the study after adverse events in all six individuals. Maculopapular rash, diarrhea, and fatigue were most common [Pilié et al 2018]. In a series of 22 individuals with VHL with a total of 311 lesions, good identification of VEGF-producing lesions suggests that ^{89}Zr-bevacizumab PET could offer a tool to select individuals for anti-VEGF therapy [Oosting et al 2016].

Somatostatin analogs could be of use in the treatment of hemangioblastomas. Nine hemangioblastomas demonstrated expression for at least three somatostatin receptor subtypes (1, 2a, 3, 4, or 5). One individual with a symptomatic irresectable suprasellar hemangioblastoma was treated with octreotide long-acting release, which resulted in clinical stability and radiographic response after nine months of treatment [Sizdahkhani et al 2017].

Propranolol could be an efficient treatment to control hemangioblastoma growth in individuals with VHL because of its antiangiogenic effects demonstrated in infantile hemangioma and the hypothetical impact on HIF levels.

Checkpoint inhibitors such as antibodies targeting programmed cell death ligand 1 (PD-L1) have shown promise in managing tumor load; however, these treatments have unknown toxicity in individuals with VHL, who will likely have dozens to thousands of small subclinical lesions present throughout their body.

Sardi et al [2009] reported three-year stabilization of previously progressive multifocal spinal hemangioblastomas with thalidomide.

Premature termination codon 124 (PTC124), also known as ataluren, may benefit a subset of affected individuals in whom nonsense variants give rise to premature stop codons in the messenger RNA [Auld et al 2010]. There are three stop codons: UAA, UAG, and UGA. PTC124 promotes read-through of all three stop codons with different efficiencies. The highest read-through efficiency takes place at UGA, followed by UAG and then UAA. PTC124 has been successfully proven to promote read-through of nonsense variants in Duchenne muscular dystrophy (DMD), cystic fibrosis (CF), and Usher syndrome type 1C. Phase I and II clinical trials have shown no serious side effects with PTC124 treatment, even after long-term use [Wilschanski et al 2011]. Preclinical investigation of PTC124 effects on VHL is ongoing.

An in vivo study of HIF2α inhibitor in *vhl*$^{-/-}$ zebra fish showed promising results in suppressing erythrocytosis and abnormal vascular proliferation in the brain and trunk. Furthermore, it promoted erythroid differentiation and decreased the number of early erythroid progenitors circulating in the peripheral blood. Therefore, there is a rationale for performing preclinical and clinical studies in optimized HIF2α inhibitors [Metelo et al 2015].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Approximately 80% of individuals diagnosed with VHL have an affected parent.
- Some individuals diagnosed with VHL have the disorder as the result of a *VHL* pathogenic variant that occurred as a *de novo* event in the affected individual or as a postzygotic *de novo* event in a mosaic,

apparently unaffected parent. The proportion of individuals with VHL due to a *de novo* pathogenic variant is about 20%.

- If the proband appears to be the only affected family member:
  - And a molecular diagnosis has been established in the proband, genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
  - And a molecular diagnosis has not been established in the proband, ophthalmologic screening and abdominal ultrasound evaluation, at a minimum, should be offered to both parents.

  Note: Screening for VHL lesions is warranted for parents without clinical manifestations but who are identified as having a *VHL* pathogenic variant and for parents who have not undergone DNA-based testing (see Surveillance).
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism* [Murgia et al 2000, Sgambati et al 2000, Santarpia et al 2007, Wu et al 2013, Coppin et al 2014, Chen et al 2022]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

    * A parent with somatic and germline mosaicism for a *VHL* pathogenic variant may be mildly/minimally affected.
- The family history of some individuals diagnosed with VHL 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 syndrome in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *VHL* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. The degree of clinical severity is not predictable in sibs who inherit a *VHL* pathogenic variant, as the manifestations and severity of VHL can be highly variable among family members with the same pathogenic variant.
- If the proband has a known *VHL* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Parental mosaicism has been described. In families in which the proband represents a simplex case, the incidence of parental mosaicism is thought to be about 5% [Chen et al 2022].
- If the genetic status of the parents is unknown but the parents are clinically unaffected and are at least age 35 years, the risk to the sibs of a proband appears to be low; however, the sibs are still at increased risk for VHL because of the possibility of failure to recognize the disorder or late onset of the syndrome in an affected parent and the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with VHL is at a 50% risk of inheriting the *VHL* pathogenic variant; the degree of clinical severity is not predictable.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has the *VHL* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Testing of 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 germline *VHL* pathogenic variant has been identified in an affected family member (see Evaluation of Relatives at Risk).

Because early detection of at-risk individuals affects medical management, testing of asymptomatic individuals during childhood is beneficial [Binderup et al 2022] (see VHL Resources – VHL Patient and Caregiver Handbook). As ophthalmologic screening for those at risk for VHL 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 pathogenic variant. 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 authors recommend the VHL Kids Handbook by the VHL Alliance (see VHL Resources – VHL Kids Handbook).

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. Referral to a genetic counselor and/or a center in which testing is routinely offered is recommended.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- Preconception considerations include possible male infertility due to cysts of the epididymis.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *VHL* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for VHL are possible.

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Von Hippel-Lindau Disease
- **NCBI Genes and Disease**
  Von Hippel-Lindau syndrome
- **VHL Alliance**
  Phone: 617-277-5667
  Email: info@vhl.org
  www.vhl.org
- **International Kidney Cancer Coalition (IKCC)**
  www.ikcc.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Von Hippel-Lindau Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
VHL	3p25.3	Von Hippel-Lindau disease tumor suppressor	Paraganglioma and Pheochromocytoma Database - VHL VHLdb	VHL	VHL

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Von Hippel-Lindau Syndrome (View All in OMIM)

193300	VON HIPPEL-LINDAU SYNDROME; VHLS
608537	VON HIPPEL-LINDAU TUMOR SUPPRESSOR; VHL

Molecular Pathogenesis

The role of von Hippel-Lindau disease tumor suppressor (pVHL) in the regulation of hypoxia-inducible genes through the targeted ubiquitinylation and degradation of hypoxia-inducible factor 1 alpha (HIF1α) has been described in great detail and won the 2019 Nobel Prize, leading to a model of how disruption of *VHL* results in renal cell carcinoma, hemangioblastoma, and the production of other highly vascularized tumors [Takamori et al 2023].

Von Hippel-Lindau syndrome (VHL) results from a germline loss-of-function variant coupled with a somatic loss-of-function variant involving the second allele. Pathogenic variants can prevent or reduce *VHL* expression

or lead to the expression of an abnormal protein. Some genotype-phenotype correlations are observed [Reich et al 2021]. Pathogenic missense variants that 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 result in loss of HIF regulation and are more likely to result in VHL type 1. Pathogenic missense variants that do not disrupt HIF regulation are more likely to be associated with VHL type 2. Furthermore, *VHL* pathogenic variants affect vessel branching and maturation via the Notch signaling pathway [Arreola et al 2018].

Pathogenic missense variants that lead to pheochromocytoma with a low (or no) risk for renal cell carcinoma (VHL types 2A and 2C) may encode pVHL that retains the ability to ubiquinate (and thereby downregulate) HIF1α in the presence of molecular oxygen to a greater degree than pathogenic variants that result in VHL with pheochromocytoma and renal cell carcinoma (VHL type 2B). Furthermore, mutated pVHL may predispose to pheochromocytoma by altering the balance among a group of proteins in a molecular pathway that controls apoptosis of sympatho-adrenal precursor cells during development.

Mechanism of disease causation. Loss of function

VHL-specific laboratory technical considerations. Sequence analysis of intron 1 should be performed in probands without an identified *VHL* pathogenic variant in the coding region, as some intron 1 pathogenic variants can lead to inclusion of a cryptic exon (designated exon E1') [Lenglet et al 2018].

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