

# Genetics of Von Hippel-Lindau Disease

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**ABBREVIATIONS:** VHL = Von Hippel Lindau; pVHL = VHL protein; HIF = hypoxia-inducible factor

**V**on Hippel-Lindau (VHL) disease is a rare, autosomal dominant syndrome that is associated with the development of tumors in a variety of organ systems, most commonly hemangioblastoma of the central nervous system and retina.<sup>1</sup> The ocular manifestations of the disease were first independently described by 2 ophthalmologists, Treacher Collins in 1894<sup>2</sup> and Eugene von Hippel in 1904.<sup>3</sup> Both recognized families with angiomatous retinal growths and described them in the medical literature. In 1927, Arvid Lindau,<sup>4</sup> a Swedish pathologist, recognized that these retinal lesions were associated with an increased risk of developing hemangioblastomas of the central nervous system. Since then, VHL disease has been associated with many other lesions, including clear cell renal carcinoma, pheochromocytoma, endolymphatic sac tumors, epididymal and broad ligament cystadenomas, and islet-cell tumors.<sup>5</sup> The prevalence of VHL disease is estimated to be between 1 in 31,000 and 1 in 53,000.<sup>6,7</sup>

## DIAGNOSIS

The diagnosis of VHL is often made by using clinical criteria. Patients with a family history of VHL are diagnosed with the disease in the presence of 1 additional tumor—a CNS hemangioblastoma, pheochromocytoma, or clear cell renal carcinoma. Those without a family history must have 2 CNS hemangioblastomas or 1 CNS hemangioblastoma with either a pheochromocytoma or clear cell renal carcinoma.<sup>8,9</sup> With the current understanding of the genetic basis for VHL disease and the availability of molecular genetic testing, the diagnosis of VHL disease may be made in individuals who do not satisfy the clinical diagnostic criteria.

Despite the increased availability and detection rate of genetic testing, negative results are not always definitive. Up to 20% of

tumors in individuals with VHL disease result from de novo mutations, and these individuals do not have a family history of the disease.<sup>10</sup> Furthermore, many de novo mutations result in mosaicism, in which patients may have clinical signs of the disease but test negative genetically for it because not all tissues carry the mutation.<sup>11</sup>

## MOLECULAR GENETICS

VHL disease is an autosomal dominantly inherited disorder with marked variability in penetrance and phenotype. The *VHL* gene is located on the short arm of chromosome 3 (3p25–26) with its coding sequence represented in 3 exons.<sup>12,13</sup> The gene encodes 2 protein isoforms, a full-length 30-kDa protein (pVHL30) and a smaller 19-kDa protein (pVHL19), generated by alternative translation initiation.<sup>14</sup> The *VHL* gene is evolutionarily conserved and is expressed in all organ systems, not exclusively those affected by VHL disease.<sup>15</sup>

Patients with VHL disease have an inactivating germline mutation in 1 copy of the *VHL* gene and 1 normally functioning wild type allele. Tumor development depends on mutation of the remaining wild type allele in a susceptible target organ. A wide variety of germline mutations have been identified, but the largest group consists of deletions that alter exon sequences.<sup>16</sup> The remaining mutations are due to nonsense mutations or missense substitutions. A complex classification system has been described to correlate genotype and phenotype, but it is less useful for clinical management because an individual may move from one subtype to another.<sup>17</sup>

## FUNCTION OF THE TUMOR SUPPRESSOR PROTEIN

The *VHL* gene product is a tumor-suppressor protein that influences many cellular pathways but is best characterized by its function in the oxygen-sensing pathway. The VHL protein (pVHL) has a critical role in regulating a transcription factor called hypoxia-inducible factor (HIF). In the presence of functioning pVHL and normoxic conditions, pVHL binds to a subunit of HIF and acts as a ubiquitin ligase, leading to the destruction of HIF via

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proteasomal degradation. In the presence of functioning pVHL and hypoxic conditions, pVHL is unable to form a ubiquitin ligase and HIF is not degraded. This outcome allows HIF to induce transcription of genes involved in diverse processes including angiogenesis, proliferation, metabolism, and apoptosis (eg, *VEGF*, *PDGFB*, *TGF $\alpha$* ). In the presence of nonfunctioning pVHL, HIF will not be degraded regardless of oxygen conditions. This feature allows the inappropriate overproduction of hypoxia-inducible messenger RNAs and unregulated cell growth—the hallmark of pVHL-defective cells.<sup>13,18-20</sup>

## ROLE OF IMAGING

Imaging plays a crucial role in the diagnosis and surveillance of VHL disease, particularly with identification of CNS hemangioblastomas. These are the most common tumors in VHL disease, affecting 60%–80% of all patients and are the presenting feature in approximately 40% of cases.<sup>11,21,22</sup> VHL disease accounts for approximately one-third of patients with CNS hemangioblastomas. The most common site is the cerebellum (44%–72%), followed by the spinal cord (13%–50%), brain stem (10%–25%), and supratentorial structures (1%).<sup>18,23</sup>

Imaging is also crucial in the identification and surveillance of lesions outside the CNS, including the pancreas, kidneys, adrenal glands, and reproductive organs. Identification of renal carcinoma is of particular importance because it is the major malignant neoplasm of VHL disease and one of the leading causes of mortality.<sup>19</sup> Although retinal hemangioblastomas are the second most common tumor in VHL disease, they are typically only detectable by examination of the dilated eye.<sup>18</sup>

Screening is critical in all patients with VHL disease regardless of symptoms because lesions are treatable. Indeed, the morbidity and mortality of VHL disease has been significantly reduced during the past 20 years due to advanced screening and surgical techniques.<sup>6</sup> Particular screening guidelines vary among different centers but typically include renal, brain, and spinal cord imaging at regular intervals.<sup>24,25</sup>

## REFERENCES

- Maher ER, Neumann HP, Richard S. **von Hippel-Lindau disease: a clinical and scientific review.** *Eur J Hum Genet* 2011;19:617–23 CrossRef Medline
- Collins ET. **Intra-ocular growths (two cases, brother and sister, with peculiar vascular new growth, probably primarily retinal, affecting both eyes).** *Trans Ophthal Soc U K* 1894;14:141–49
- Von Hippel E. **Über eine sehr seltene Erkrankung der Netzhaut.** *Albrecht von Graefe's Archiv für Ophthalmologie* 1904;59:83–106 CrossRef
- Lindau A. **Zur frage der angiomatosis retinae und ihrer hirncomplication.** *Acta Ophthalmol Scand* 1927;4:193–226
- Maher ER, Kaelin WG Jr. **von Hippel-Lindau disease.** *Medicine (Baltimore)* 1997;76:381–91 CrossRef Medline
- Taouli B, Ghouadni M, Corrêas JM, et al. **Spectrum of abdominal imaging findings in von Hippel-Lindau disease.** *AJR Am J Roentgenol* 2003;181:1049–54 CrossRef Medline
- Hes FJ, Feldberg MA. **Von Hippel-Lindau disease: strategies in early detection (renal-, adrenal-, pancreatic masses).** *Eur Radiol* 1999;9:598–610 CrossRef Medline
- Melmon KL, Rosen SW. **Lindau's disease: review of the literature and study of a large kindred.** *Am J Med* 1964;36:595–617 CrossRef Medline
- Lamiell JM, Salazar FG, Hsia YE. **von Hippel-Lindau disease affecting 43 members of a single kindred.** *Medicine (Baltimore)* 1989;68:1–29 CrossRef Medline
- Richards FM, Payne SJ, Zbar B, et al. **Molecular analysis of de-novo germline mutations in the von Hippel-Lindau disease gene.** *Hum Mol Gen* 1995;4:2139–43 CrossRef Medline
- Sgambati MT, Stolle C, Choyke PL, et al. **Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents.** *Am J Hum Genet* 2000;66:84–91 CrossRef Medline
- Seizinger BR, Rouleau GA, Ozelius LJ, et al. **Von Hippel-Lindau disease maps to the region of chromosome 3 associated with renal cell carcinoma.** *Nature* 1988;332:268–69 CrossRef Medline
- Latif F, Tory K, Gnarr J, et al. **Identification of the von Hippel-Lindau disease tumor suppressor gene.** *Science* 1993;260:1317–20 CrossRef Medline
- Renbaum P, Duh FM, Latif F, et al. **Isolation and characterization of the full-length 3' untranslated region of the human von Hippel-Lindau tumor suppressor gene.** *Hum Genet* 1996;98:666–71 CrossRef Medline
- Richards FM, Schofield PN, Fleming S, et al. **Expression of the von Hippel-Lindau disease tumour suppressor gene during human embryogenesis.** *Hum Mol Genet* 1996;5:639–44 CrossRef Medline
- Franke G, Bausch B, Hoffmann MM, et al. **Alu-Alu recombination underlies the vast majority of large VHL germline deletions: molecular characterization and genotype-phenotype correlations in VHL patients.** *Hum Mutat* 2009;30:776–86 CrossRef Medline
- Gossage L, Eisen T, Maher ER. **VHL, the story of a tumour suppressor gene.** *Nat Rev Cancer* 2015;15:55–64 CrossRef Medline
- Shanhogue KP, Hock M, Fatterpaker G, et al. **von Hippel-Lindau disease: review of genetics and imaging.** *Radiol Clin North Am* 2016;54:409–22 CrossRef Medline
- Maher ER, Yates JR, Harries R, et al. **Clinical features and natural history of von Hippel-Lindau disease.** *Q J Med* 1990;77:1151–63 CrossRef Medline
- Nordstrom-O'Brien M, van der Luijt RB, van Rooijen E, et al. **Genetic analysis of von Hippel-Lindau disease.** *Hum Mutat* 2010;31:521–37 CrossRef Medline
- Courcoutsakis NA, Prassopoulos PK, Patronas NJ. **Aggressive leptomeningeal hemangioblastomatosis of the central nervous system in a patient with von Hippel-Lindau disease.** *AJNR Am J Neuroradiol* 2009;30:758–60 CrossRef Medline
- Wanebo JE, Lonser RR, Glenn GM, et al. **The natural history of central nervous system hemangioblastomas in patients with von Hippel-Lindau disease.** *J Neurosurg* 2003;98:82–94 CrossRef Medline
- Slater A, Moore NR, Huson SM. **The natural history of cerebellar hemangioblastomas in von Hippel-Lindau disease.** *AJNR Am J Neuroradiol* 2003;24:1570–74 Medline
- Leung RS, Biswas SV, Duncan M, et al. **Imaging features of von Hippel-Lindau Disease.** *Radiographics* 2008;28:65–79 CrossRef Medline
- Tomura N, Ito Y, Matsuoka H, et al. **PET findings of intramedullary tumors of the spinal cord using [18F] FDG and [11C] methionine.** *AJNR Am J Neuroradiol* 2013;34:1278–83 CrossRef Medline