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Research Article

The Genetic and Clinical Aspects of Von Hippel-Lindau Syndrome

Hira Burhan*, Abdul Basit Ansari, Mudassir Shah, Noman Lateef, Murtaza Kazmi

Abstract:
Von Hippel-Lindau syndrome is a genetic disorder, which predisposes the individual to the formation of highly vascularized tumors that demonstrate age dependent penetrance. The disease is caused by mutations in Von Hippel-Lindau tumor suppressor gene present in short arm of chromosome 3. The disease is characterized by development of CNS hemangioblastomas, phaeochromocytoma, renal cyst, clear cell renal cell carcinoma. The Diagnosis of VHL can be made in a patient with confirmed family history using molecular genetic testing of the VHL gene and presence of tumor. Average life expectancy in patients with VHL has been about 50 years. The protein products encoded by VHL gene recognize and destroy α-subunit of Hypoxia inducible factor. Cells lacking functional VHL protein accumulates HIF-α which up regulate hypoxia responsive genes. These genes products include proteins that control glucose uptake and metabolism, extracellular pH, growth factors, which regulate vascular development, angiogenesis, and lymphangiogenesis by binding to its receptor. Hence, VHL is a tumor suppressor gene based on both genetic and functional criteria, and VHL inactivation appears to be a very early step in renal carcinogenesis. VHL disease is classified into type 1 and type 2 depending on the phenotype but it is only helpful for research studies.

The treatment of patient with VHL depends upon the specific complications of the disease present. Screening is recommended from childhood once diagnosis has been established. CNS hemangioblastomas are the most common manifestation, detailed neurologic history, CNS examination and baseline brainstem and spine MRIs should be done for any symptomatic conditions. Opthalmoscopic screening from early childhood and yearly follow-ups to prevent visual impairment. Audio logic tests and MRI auditory canal should be done when symptomatic for endolymphatic sac tumors. Blood pressure evaluations and yearly urinary catecholamines level for pheochromocytoma. Abdominal ultrasound screening should be started at 8 years of age; any abnormality should be evaluated by CT or MRI.

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Dow University of Health Sciences, Karachi, Pakistan

***Corresponding author:** Hira Burhan, Dow University of Health Sciences, Baba-e-Urdu Road, Karachi 74200, Pakistan, Tel: +92 332 3587197;
E-mail: hira.burhan91@gmail.com

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Introduction

Von Hippel-Lindau syndrome is a genetic disorder, which predisposes the individual to the formation of highly vascularized tumors that demonstrate age dependent penetrance. The disease is caused by mutations in von Hippel-Lindau tumor suppressor gene present in short arm of chromosome 3[1,2]. The disease is characterized by development of CNS hemangioblastomas, phaeochromocytoma, renal cyst, clear cell renal cell carcinoma [ccRCC], pancreatic cysts, neuroendocrine tumors, and cystadenomas of the epididymis, broad ligament, and endolymphatic sac tumors [ELST][3-5]. A specific form of VHL missense mutation can cause an autosomal recessive form of polycythemia called Chuvash polycythemia without any other evidence of VHL disease[6,7]. VHL patients are highly susceptible to tumor development because they already carry one mutated VHL allele in their every cell. The inactivation of the second allele in a single cell leads to formation of neoplastic growth[8,9].

The Diagnosis of VHL can be made in a patient with confirmed family history if there is a single VHL tumor (e.g. retinal or CNS hemangioblastoma, clear cell RCC, phaeochromocytoma, pancreatic endocrine tumor or endolymphatic sac tumor). All of the tumors typically found in VHL disease can occur as a sporadic (non-familial) event and so a clinical diagnosis of VHL disease in a patient without a positive family history requires the presence of two tumors (e.g., two haemangioblastomas or a

hemangioblastoma and a visceral tumor). Approximately 20% of VHL disease patients result from a de-novo mutation and do not have a family history[10]. In these cases, de novo mutations may demonstrate mosaicism and therefore be difficult to detect. For this reason, Clinical diagnosis may be the sole indication for initiation of a screening protocol.

Average life expectancy in patients with VHL has been about 50 years[8]. Retinal and CNS hemangioblastoma are the most common manifestation, occurring in 60 – 80% of affected individuals, and ccRCC is the most common cause of early mortality[8-11]. Pancreatic lesions may be cysts or neuroendocrine tumors, which together occur in 17 – 56% of patients.

Genetics and Molecular Aspect

The human VHL gene is a 10-kb region located on the short arm of chromosome 3 (3p25.3)[12]. It was isolated in 1993 using a positional cloning strategy[1]. The VHL gene consists of three exons[1,13] and encodes two different protein isoforms: a 30-kDa full-length 213 amino acid protein (pVHL30) and a smaller 19-kDa protein (pVHL19) that lacks the first 53 amino acids. The two isoforms exist because this gene has two alternative codons for translation initiation[14,15]. Both isoforms are capable of suppressing renal cell carcinoma growth *in vivo*. The two protein products encoded by VHL gene are 30-kDa full-length protein (p30, 213 amino acids) and a 19-kDa protein (p19, 160 amino acids)[14,15]. Both the p30 and p19 isoforms were shown to suppress tumor formation in mice, and both can regulate hypoxia inducible factor α (HIF-α). VHL protein is found in multiple cellular compartments. It shuttles back and forth between the nucleus and cytoplasm and can be found in association with the endoplasmic reticulum and mitochondria[16,17].

Function of VHL gene

The function of pVHL related to VHL disease is to recognize and destroy α-subunit of HIF-1 and HIF-2[18]. VHL protein is a part of E3 ubiquitin ligase enzymes that degrade α subunits of Hypoxia inducible factor (HIF)[19]. It forms complexes with elongin B, elongin C, Cul2, and Rbx1 and target specific proteins for destruction[20,21]. These complexes attach polyubiquitin tails to specific proteins, which serve as signals for such proteins to be degraded by the proteasome. Several pVHL-targeted proteins have been identified, including HIF-1 and HIF-2.HIF is a family of transcription factors that regulate cellular response to hypoxia[22]. HIF is continuously synthesized and rapidly destroyed by VHL protein in the presence of oxygen because of activation of certain enzymes, which increase its affinity to VHL protein[23]. Normally, HIF is a highly unstable and is readily degraded except under low-oxygen conditions[24,25].

Cells lacking functional VHL protein due to germline or somatic mutations in VHL gene accumulate HIF-α which combines with HIF-β and up regulate hypoxia responsive genes[23]. These genes products include proteins that control glucose uptake and metabolism (such as the Glut1 glucose transporter), extracellular pH (such as carbonic anhydrase), growth factors (like Vascular Endothelial Growth Factors (VEGF), Platelet-derive Growth Factor-β (PDGF- β) and Transforming Growth Factor α (TGF-α)[2]. VEGF, a type PDGF, regulate vascular development, angiogenesis, and lymphangiogenesis by binding to its receptor[26-28]. Conversely, inhibition of HIF in VHL-/- renal cell carcinoma is sufficient to suppress their ability to form tumors *in vivo*[29,30]. Similarly, Restoring VHL function in VHL-/- renal cell carcinoma cells is sufficient to suppress their ability to form tumors in animals[31,32]. Hence, VHL is a tumor suppressor gene based on both genetic and functional criteria, and VHL inactivation appears to be a very early step in renal carcinogenesis.

Classification of VHL syndrome

Patients with VHL disease are VHL (+/-) heterozygotes. They acquired one normal and one mutated allele of VHL gene from their parents. The development of pathological features, such as premalignant renal cysts and CNS lesions, depends upon the remaining functioning VHL allele in a susceptible cell[33,34]. It is presumed that additional mutations involving genes other than VHL are required for the conversion of such premalignant cysts to malignant tumors. VHL gene mutations have been reported in > 900 VHL disease families[35,36]. VHL disease is classified into type 1 and type 2 depending on the phenotype. Type 2 is further classified as Type 2A, Type 2B, and Type 2C. Type 1 VHL disease is characterized by families' with the development of retinal and CNS haemangioblastomas and ccRCC but a low risk of phaeochromocytoma[35,37-39]. These patients most often have deletional mutations. A subgroup of patients with deletion of all or part of VHL and the HSPC300 gene also develop retinal and CNS haemangioblastomas but are often protected from the development of ccRCC[40,42]. Families' with phaeochromocytoma are designated as Type 2 VHL disease and usually have a germline missense mutation. Type 2A is at risk of hemangioblastomas and pheochromocytomas, but not clear-cell renal cell carcinomas. Type 2B is at risk of all three tumors, with a higher risk of clear-cell renal carcinoma. Families with Type 2C is at risk for only pheochromocytoma[[35,39,43]. A third type of disease presentation can be Chuvash polycythemia, which is due to homozygous germline mutation in the VHL gene[6,37]. It is an autosomal recessive disorder, characterized by elevated hemoglobin, elevated serum erythropoietin (Epo), and elevated serum concentration of vascular endothelial growth factor, low blood pressure, varicose veins, and early death secondary to cerebral vascular events or peripheral thrombosis[44].

This classification is only helpful for research studies correlating the effects of a specific mutation with pVHL function and phenotype but is less useful for clinical management as a family may move from one subtype to another. An example of this will be if an individual may present with a retinal angioma or CNS haemangioblastomas and a RCC (Type 1 phenotype) but with the diagnosis of a phaeochromocytoma in a relative, it then becomes Type 2B kindred.

Clinical Features

Epidemiology: The incidence of Von Hippel-Lindau syndrome is 1 in 36,000 live births. The penetrance of the disease increases with age and is over 90% by the age of 65[45]. Age of diagnosis varies from infancy to 60-70 years. The average age of clinical diagnosis in patients is 26 years[46]. Approximately 20% of VHL disease patients result from a de-novo mutation and do not have a family history[47]. Historically, life expectancy in patients with VHL has been about 50 years[8]. It seems reasonable that this would increase using standardized comprehensive screening protocols.

Diagnosis: The diagnosis of VHL is confirmed by using molecular genetic testing of the VHL gene[48]. Patients with family history of VHL present with 100% VHL mutation detection rate[49]. However, patients with sporadic forms (no family history) of VHL may present with disease mosaicism where not all tissues may carry the disease mutation[50]. These patients would yield negative test results for VHL mutation if their peripheral leucocytes do not carry the VHL mutation[51].

Additional clinical investigations are undertaken to confirm the diagnosis and determine the extent of clinical manifestations. CNS tumors (hemangioblastomas) can be detected by fundoscopy (retinal angiomas), CT and MRI (cerebellar, brain stem subtentorial and spinal hemangioblastomas). ELST's may be seen on thin slice MRI on contrast as mass on the posterior wall of the petrous bone. Visceral lesions are better appreciated with techniques such as CT, MRI (kidney, pancreatic and adrenal gland lesions), ultrasound (cysts of epididymis and broad ligament), and blood and urine catecholamine metabolites (pheochromocytoma).

Management: The best course of treatment of patient with VHL is dictated by the specific complications of the disease present. However, since it is a complex multisystem disorder it requires multidisciplinary management and serial screening[8,52]. Screening is recommended from childhood once diagnosis has been established since lesions may present in childhood. Yet there is no established screening protocol for VHL, most of them have been developed by experts in their respective fields hence they remain controversial[48].

Once diagnosis has been established, the individual must undergo a series of tests to evaluate the extent of the disease. Opthalmoscopic screening should be started from early childhood and yearly follow-ups should be done as it offers a greater chance to prevent visual impairment[52]. Detailed neurologic history, CNS examination and baseline brainstem and spine MRIs should be done to check for CNS and peripheral nerve hemangioblastomas[53]. Audiologic tests and MRI auditory canal should be done when symptoms such as tinnitus, vertigo, hearing loss present, as they may be in association with endolymphatic sac tumors[48]. Blood pressure evaluations and yearly urinary catecholamines level should be conducted for pheochromocytoma. Abdominal ultrasound screening should be started at 8 years of age[3,8,52], and any suspicious finding or lesions in the kidneys, pancreas, or adrenals should be evaluated by sophisticated techniques such as CT and MRI[53].

CNS hemangioblastomas are the most common manifestation of the disease occurring in 60 - 80% of the cases[8,52]. They are usually benign tumors with unpredictable growth rates[54,55], often these may remain stable for number of years before enlarging, and hence observation is recommended for asymptomatic tumors[48]. However, enlargement or bleeding within the CNS may cause neurologic damage and even death[36,56]. CNS tumors produce symptoms depending on their location such as Headache, gait difficulties, dysmetria, hydrocephalus, nausea and vomiting in association with cerebellar hemangioblastomas[57].

Hypesthesia, hyperreflexia, dysesthesia, weakness, proprioceptive deficit, and bowel and bladder complaints are most commonly associated with spinal cord hemangioblastomas[58,59].

Swallowing difficulties, headache, sensory changes, hiccupping and impaired gait is seen in brainstem hemangioblastomas[60,61].

For symptomatic tumor, surgical resection is recommended which is often curative. Preoperative arterial embolization is performed for extensive spinal cord tumors[53]. Gamma knife surgery is helpful for small tumors or those in inoperable areas[62,63]. Although it may reduce tumor size, overall operative mortality is roughly 10% with higher figures for brain stem tumors[1].

Retinal angiomas are histopathologically similar to CNS hemangioblastomas[64]. They are also one of the most common and earliest manifestations of the disease[65,66]. The tumor is often slow growing and stable however it can enlarge and cause visual deficits through either exudative or traction effects over the retina[67]. Management of these lesions concerns mainly with identification of asymptomatic lesions, these lesions can then be treated using laser photocoagulation and cryotherapy. They can be monitored using modalities such as applied color Doppler sonography[68].

Individuals with VHL are at increased risk for development of clear cell carcinoma of kidney, which is the most common histological type of renal cancer, and the most common cause of early mortality. Multiple renal cysts, which rarely compromise renal function, may be present but the lining epithelium may become dysplastic and give rise to RCC. Most RCC are detected during regular screening at a presymptomatic stage and immediate intervention is not necessary. Such tumors have slow growth rates and are monitored regularly[69]. Once it reaches 3cm diameter, partial nephrectomy (or alternatively radiofrequency ablation) should be performed[70,71]. During this surgery, additional accessible smaller lesions are also removed to delay need for reoperation. Follow up of these patients reveals high rate of local recurrence of primary tumors but low rate of metastasis[72]. Concurrently 25% of patients with advanced RCC (> 3 cm) develop metastatic disease[73]. Renal function may be compromised by repeated renal surgery prompting the need for renal replacement therapy. Renal transplant has been successfully performed and immunosuppression has not adversely affected the course of VHL[74]. Nephrectomy should leave the adrenal gland in situ, as is done in individuals with RCC who do not have a confirmed diagnosis of VHL. If contralateral pheochromocytoma occurs, the remaining adrenal gland will prevent or delay steroid replacement therapy[75]. Therapeutic approach currently being tested for RCC includes agents that target HIF responsive gene products, drugs such as bevacizumab[74], PTK787[75], SU11248[76], and BAY 43–9006[77].

The risk of pheochromocytoma varies according to the clinical subtype of VHL and the underlying mutation. It occurs in 7 - 18% of VHL patients[30,31,32]. It usually develops in young patients, with declining risk after 30 years[65]. They may be either adrenal or extra adrenal. They are usually benign with a very low rate of malignancy < 5%[70]. Often classical symptoms of pheochromocytoma (tachycardia, diaphoresis, postural hypotension, tachypnea, cold and clammy skin, severe headache, angina, palpitations, nausea, vomiting, or epigastric pain) are absent, which makes it difficult to diagnose[78]. A CT scan and an additional biochemical and radiological test are needed for diagnosis. Plasma epinephrine or norepinephrine may be detected in the blood; however, vanillylmandelic acid must be detected in the urine[79].

Untreated pheochromocytomas can result in hypertension and subsequent acute heart disease, brain edema, and stroke. Studies have shown surgical resection to be the best way to treat pheochromocytomas in patients with VHL syndrome, with no recurrences[80,81]. Studies have also shown that preoperative management should include administration of alpha-adrenergic blockers, calcium channel blockers, or a combination of alpha- and beta-adrenergic blocker. Administration of an alpha-adrenergic blocker for 2 to 3 weeks preoperatively normalizes blood pressure and decreases the risk of operative complications. For surgery either laparoscopic or conventional approach may be taken, however in the last decade laparoscopic adrenalectomy has become the gold standard.

Pancreatic lesions of VHL are mostly cysts (70%) which rarely cause any symptoms or develop into malignant tumors[59]. Less than 5% of Pancreatic Endocrine Tumors (PETs) may cause symptoms because of either expansion or local invasion, which is the indication for surgical intervention. Because most PETs reported in patients with VHL remain asymptomatic, show indolent growth, no liver metastases and are < 3 cm, it is recommended that only PETs ≥ 3 cm should be routinely resected. A recent study of 108 patients with VHL and PETs reported all patients with metastatic disease had at least two of three important factors associated with malignancy: a primary tumor > 3 cm, mutation in exon 3 of the *VHL* gene or a primary tumor doubling time > 500 days. This study recommended that VHL patients without two of these three PET prognostic factors could be followed. One study recommended that VHL patients with PETs < 1cm be followed at 12-month intervals with serial CT scans and patients with PETs 1 – 3 cm should be monitored and resection is recommended if growth to > 2 cm. Metastatic disease is more common for tumors larger than 3 cm and reportedly ranges from 11% to 17%.

Endolymphatic sac tumors may present 10 - 15% of the patients with VHL; they are bilateral in 30% of the cases[82-84]. ELSTs commonly present with vestibulocochlear symptoms, including sensorineural hearing loss (95% of patients), tinnitus (90%), episodic vertigo or disequilibrium (66%), and aural fullness (30%). Facial nerve involvement (facial paresis) may be seen in larger tumors that invade the petrous bone (8%). The hearing loss associated with this may be in stepwise or a more insidious manner[58,85]. Surgical resection of radiographically visible tumors is recommended in patients with hearing as early intervention has shown to preserve both hearing and vestibular function[58]. In patients without hearing, surgery is recommended when compression symptoms are present. In surgical resection of larger tumors where intra-operative blood loss is a concern, pre-operative embolization helps to reduce tumor vascularity[86]. Most common surgical approach to small and medium sized tumors is retro labyrinthine posterior petrosectomy, which offers excellent exposure to the sac while allowing for the preservation of hearing[58]. Since surgical resection is often curative for ELSTs, radiation therapy is not commonly used; however, it does play an important role in the management of unresectable tumors (those involving the jugular bulb, intrapetrous, internal carotid artery, or facial nerve) or in patients who are not candidates for surgical resection.

Conclusion

Von Hippel-Lindau syndrome is a genetic disorder due to mutation in tumor suppressor gene present in chromosome 3. The treatment of which depend on specific complication. Routine screening is the best way to prevent and manage compilations. Genetic counseling should be advised to the affected families.

References

1. Latif, F., Tory, K., Gnarra, J., et al. Identification of the von Hippel- Lindau disease Tumor Suppressor Gene. (1993) Science 260(5112): 1317–1320.
PubMed | CrossRef | Others
2. Kaelin, W.G. Jr. The von Hippel-Lindau tumor suppressor gene and kidney cancer. (2004) Clin Cancer Res 10(18 Pt 2): 6290S-6295S.
PubMed | CrossRef | Others
3. Clark, P.E., Cookson, M.S. The von Hippel-Lindau gene: turning discovery into therapy. (2008) Cancer 113: 1768–1778.
PubMed | CrossRef | Others
4. Richard, S., Gardie, B., Couvé, S., et al. Von Hippel-Lindau: how a rare disease illuminates cancer biology. (2013) Semin Cancer Biol 23(1): 26-37.
PubMed | CrossRef | Others
5. Woodward, E.R., Buchberger, A., Clifford, S.C., et al. Comparative sequence analysis of the VHL tumor suppressor gene. (2000) Genomics 65: 253–265.
PubMed | CrossRef | Others
6. Ang, S.O., Chen, H., Hirota, K, et al. Disruption of oxygen homeostasis underlies congenital Chuvash polycythemia. (2002) Nat Genet 32(4): 614-621.
PubMed | CrossRef | Others
7. Gordeuk, V.R., Sergueeva, A.I., Miasnikova, G.Y., et al. Congenital disorder of oxygen sensing: association of the homozygous Chuvash polycythemia VHL mutation with thrombosis and vascular abnormalities but not tumors. (2004) Blood 103(10): 3924-3932.
PubMed | CrossRef | Others
8. Maher, E.R., Yates, J.R., Harries, R., et al. Clinical features and natural history of von Hippel-Lindau disease. (1990) Q J Med 77(283): 1151-1163.
PubMed | CrossRef | Others
9. Mandriota, S.J., Turner, K.J., Davies, D.R., et al. HIF activation identifies early lesions in VHL kidneys: evidence for site-specific tumor suppressor function in the nephron. (2002) Cancer Cell 1(5): 459-468.
PubMed | CrossRef | Others
10. Richards, F.M., Payne, S.J., Zbar, B., et al. Molecular Analysis of De-Novo Germline Mutations in the von Hippel-Lindau Disease Gene. (1995) Hum Mol Gen 4(11): 2139–2143.
PubMed | CrossRef | Others
11. Melmon, K.L., Rosen, S.W. Lindau's disease. Review of the literature and study of large kindred. (1964) Am J Med 36(4): 595-617.
PubMed | CrossRef | Others
12. Richards, F.M., Maher, E.R., Latif, F., et al. Detailed genetic mapping of the von Hippel-Lindau disease tumour suppressor

gene. (1993) J Med Genet 30(2): 104-107.
PubMed | CrossRef | Others
13. Kuzmin, I., Duh, F.M., Latif, F., et al. Identification of the promoter of the human von Hippel-Lindau disease tumor suppressor gene. (1995) Oncogene 10(11): 2185-2194. 14
PubMed | CrossRef | Others
14. Schoenfeld, A., Davidowitz, E., Burk, R.D. A second major native von Hippel-Lindau gene product, initiated from an internal translation start site, functions as a tumor suppressor. (1998) Proc Natl Acad Sci U S A 95(15): 8817-8822. 16
PubMed | CrossRef | Others
15. Iliopoulos, O., Ohh, M., Kaelin, W.G. Jr. pVHL19 is a biologically active product of the von Hippel-Lindau gene arising from internal translation initiation. (1998) Proc Natl Acad Sci USA 95(20): 11661–11666. 17
PubMed | CrossRef | Others
16. Iliopoulos, O., Kibel, A., Gray, S., et al. Tumor suppression by the human von Hippel-Lindau gene product. (1995) Nat Med 1(8): 822–826.
PubMed | CrossRef | Others
17. Duan, D.R., Humphrey, J.S., Chen, D.Y., et al. Characterization of the VHL tumor suppressor gene product: localization, complex formation, and the effect of natural inactivating mutations. (1995) Proc Natl Acad Sci USA 92(14): 6495–6499.
PubMed | CrossRef | Others
18. Maxwell, P.H., Wiesener, M.S., Chang, G.W., et al: The tumor suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. (1999) Nature 399(6733): 271–275.
PubMed | CrossRef | Others
19. Kondo, K., Kaelin, W.G. Jr. The von Hippel-Lindau tumor suppressor gene. (2001) Exp Cell Res 264(1): 117-125.
PubMed | CrossRef | Others
20. Kim, W., Kaelin, W.G. Jr. The von Hippel-Lindau tumor suppressor protein: new insights into oxygen sensing and cancer. (2003) Curr Opin Genet Dev 13(1): 55–60.
PubMed | CrossRef | Others
21. George, D.J., Kaelin, W.G. Jr. The von Hippel-Lindau protein, vascular endothelial growth factor, and kidney cancer. (2003) N Engl J Med 349(5): 419–421.
PubMed | CrossRef | Others
22. Formenti, F., Constantin-Teodosiu, D., Emmanuel, Y., et al. Regulation of human metabolism by hypoxia-inducible factor. (2010) Proc Natl Acad Sci U S A 107(28): 12722-12727.
PubMed | CrossRef | Others
23. Smith, T.G., Robbins, P.A., Ratcliffe, P.J. The human side of hypoxia-inducible factor. (2008) Br J Haematol 141(3): 325-334.
PubMed | CrossRef | Others
24. Berra, E., Benizri, E., Ginouves, A., et al. HIF prolyl-hydroxylase 2 is the key oxygen sensor setting low steady state levels of HIF-1alpha in normoxia. (2003) EMBO J 22(16): 4082–4090.
PubMed | CrossRef | Others
25. Bruick, R.K., McKnight, S.L. A Conserved family of prolyl-4-hydroxylases that modify HIF. (2001) Science 294(5545): 1337–1340.
PubMed | CrossRef | Others
26. Holmes, K., Roberts, O.L., Thomas, A.M., et al. Vascular endothelial growth factor receptor-2: structure, function, intracellular signalling and therapeutic inhibition. (2007) Cell Signal 19(10): 2003-2012.
PubMed | CrossRef | Others
27. Olofsson, B., Pajusola, K., Kaipainen, A., et al. Vascular endothelial growth factor B, a novel growth factor for endothelial cells. (1996) Proc Natl Acad Sci U S A 93(6): 2576-2581.
PubMed | CrossRef | Others
28. Joukov, V., Pajusola, K., Kaipainen, A., et al. A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. (1996) EMBO J 15(2): 290-298.
PubMed | CrossRef | Others
29. Kondo, K., Kim, W.Y., Lechpammer, M., et al. Inhibition of HIF2alpha is sufficient to suppress pVHL-defective tumor growth. (2003) PLoS Biol 1(3): E83.
PubMed | CrossRef | Others
30. Zimmer, M., Doucette, D., Siddiqui, N., et al. Inhibition of hypoxia-inducible factor is sufficient for growth suppression of VHL-/- tumors. (2004) Mol Cancer Res 2(2): 89–95.
PubMed | CrossRef | Others
31. Gnarra, J.R., Zhou, S., Merrill, M.J., et al. Post-transcriptional regulation of vascular endothelial growth factor mRNA by the product of the VHL tumor suppressor gene. (1996) Proc Natl Acad Sci U S A 93(20): 10589-10594.
PubMed | CrossRef | Others
32. Iliopoulos, O., Kibel, A., Gray, S., et al. Tumor suppression by the human von Hippel-Lindau gene product. (1995) Nat Med 1(8): 822–826.
PubMed | CrossRef | Others
33. Lubensky, I.A., Gnarra, J.R., Bertheau, P., et al. Allelic deletions of the VHL gene detected in multiple microscopic clear cell renal lesions in von Hippel-Lindau disease patients. (1996) Am J Pathol 149(6): 2089–2094.
PubMed | CrossRef | Others
34. Mandriota, S.J., Turner, K.J., Davies, D.R., et al. HIF activation identifies early lesions in VHL kidneys: evidence for site-specific tumor suppressor function in the nephron. (2002) Cancer Cell 1(5): 459–468.
PubMed | CrossRef | Others
35. Crossey, P., Richards, F.M., Foster, K., et al. Identification of intragenic mutations in the von Hippel-Lindau disease tumor-suppressor gene and correlation with disease phenotype. (1994) Hum Mol Gen 3(8): 1303–1308.
PubMed | CrossRef | Others
36. Nordstrom-O'Brien, M., van der Luijt, R.B., van Rooijen, E., et al: Genetic analysis of von Hippel-Lindau disease. (2010) Hum Mutat 31(5): 521–537.
PubMed | CrossRef | Others
37. Calzada, M.J. Von Hippel-Lindau syndrome: molecular mechanisms of the disease. (2010) Clin Transl Oncol 12(3): 160-165.
PubMed | CrossRef | Others
38. Garcia, A., Matias-Guiu, X., Cabezas, R., et al. Molecular diagnosis of von Hippel-Lindau disease in a kindred with a predominance of familial phaeochromocytoma. (1997) Clin Endocrinol (Oxf) 46(3): 359–363.
PubMed | CrossRef | Others
39. Mulvihill, J.J., Ferrell, R.E., Carty, S.E., et al. Familial pheochromocytoma due to mutant von Hippel-Lindau disease gene.

(1997) Arch Intern Med 157(12): 1390–1391.
PubMed | CrossRef | Others
40. Franke, G., Bausch, B., Hoffmann, M.M., et al. Alu-Alu recombination underlies the vast majority of large VHL germline deletions: Molecular characterization and genotype-phenotype correlations in VHL patients. (2009) Hum Mutat 30(5): 776–786.
PubMed | CrossRef | Others
41. Maranchie, J.K., Afonso, A., Albert, P.S., et al: Solid renal tumor severity in von Hippel Lindau disease is related to germline deletion length and location. (2004) Hum Mutat 23(1): 40–46.
PubMed | CrossRef | Others
42. Cascón, A., Escobar, B., Montero-Conde, C., et al. Loss of the actin regulator HSPC300 results in clear cell renal cell carcinoma protection in Von Hippel-Lindau patients. (2007) Hum Mutat 28(6): 613–621.
PubMed | CrossRef | Others
43. Maher, E.R., Webster, A.R., Richards, F.M., et al: Phenotypic expression in von Hippel-Lindau disease: Correlations with germline VHL gene mutations. (1996) J Med Genet 33(4): 328–332.
PubMed | CrossRef | Others
44. Gordeuk, V.R., Prchal, J.T. Vascular complications in Chuvash polycythemia. (2006) Semin Thromb Hemost 32(3): 289-294.
PubMed | CrossRef | Others
45. Kim, J.J., Rini, B.I., Hansel, D.E. Von Hippel Lindau syndrome. (2010) Adv Exp Med Biol 685: 228-249.
PubMed | CrossRef | Others
46. Nordstrom-O'Brien, M., van der Luijt, R.B., van Rooijen, E., et al. Genetic analysis of von Hippel-Lindau disease. (2010) Hum Mutat 31(5): 521–537.
PubMed | CrossRef | Others
47. Richards, F.M., Payne, S.J., Zbar, B., et al. Molecular Analysis of De-Novo Germline Mutations in the von Hippel-Lindau Disease Gene. (1995) Hum Mol Gen 4(11): 2139–2143.
PubMed | CrossRef | Others
48. Teplick, A., Kowalski, M., Biegel, J.A., et al. Educational paper: screening in cancer predisposition syndromes: guidelines for the general pediatrician. (2011) Eur J Pediatr 170(3): 285-294.
PubMed | CrossRef | Others
49. Stolle, C., Glenn, G., Zbar, B., et al. Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. (1998) Hum Mutat 12(6): 417-423.
PubMed | CrossRef | Others
50. Sgambati Stolle, C., Choyke, P.L., Walther, M.M., et al. Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents. (2000) Am J Hum Genet 66(1): 84-91.
PubMed | CrossRef | Others
51. Butman, J.A., Linehan, W.M., Lonser, R.R. Neurologic manifestations of von Hippel-Lindau disease. (2008) JAMA 300(11): 1334-1342.
PubMed | CrossRef | Others
52. Choyke, P.L., Glenn, G.M., Walther, M.M., et al. von Hippel-Lindau disease: genetic, clinical, and imaging features. (1995) Radiology 194(3): 629-642.
PubMed | CrossRef | Others
53. Frantzen, C., Links, T.P., Giles, R.H. Von Hippel-Lindau Disease. (2000) In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
PubMed | CrossRef | Others
54. Richard, S., David, P., Marsot-Dupuch, K., et al. Central nervous system hemangioblastomas, endolymphatic sac tumors, and von Hippel-Lindau disease. (2000) Neurosurg Rev 23(1): 1-22; discussion 23-4.
PubMed | CrossRef | Others
55. Wanebo, J.E., Lonser, R.R., Glenn, G.M., et al. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. (2003) J Neurosurg 98(1): 82-94.
PubMed | CrossRef | Others
56. Pavesi, G., Feletti, A., Berlucchi, S., et al. Neurosurgical treatment of von Hippel-Lindau-associated hemangioblastomas: benefits, risks and outcome. (2008) J Neurosurg Sci 52(2): 29-36.
PubMed | CrossRef | Others
57. Jagannathan, J., Lonser, R.R., Smith, R., et al. Surgical management of cerebellar hemangioblastomas in patients with von Hippel-Lindau disease. (2008) J Neurosurg 108(2): 210-222.
PubMed | CrossRef | Others
58. Lonser, R.R., Oldfield, E.H. Microsurgical resection of spinal cord hemangioblastomas. (2005) Neurosurgery 57(4 Suppl): 372-376; discussion 372-376.
PubMed | CrossRef | Others
59. Mehta, G.U., Asthagiri, A.R., Bakhtian, K.D., et al. Functional outcome after resection of spinal cord hemangioblastomas associated with von Hippel-Lindau disease. (2010) J Neurosurg Spine 12(3): 233-242.
PubMed | CrossRef | Others
60. Weil, R.J., Lonser, R.R., DeVroom, H.L., et al. Surgical management of brainstem hemangioblastomas in patients with von Hippel-Lindau disease. (2003) J Neurosurg 98(1): 95-105.
PubMed | CrossRef | Others
61. Wind, J.J., Bakhtian, K.D., Sweet, J.A., et al. Long-term outcome after resection of brainstem hemangioblastomas in von Hippel-Lindau disease. (2011) J Neurosurg 114(5): 1312-1318.
PubMed | CrossRef | Others
62. Asthagiri, A.R., Mehta, G.U., Zach, L., et al. Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel-Lindau disease. (2010) Neuro Oncol 12(1): 80-86.
PubMed | CrossRef | Others
63. Simone, C.B., Lonser, R.R., Ondos, J., et al. Infratentorial craniospinal irradiation for von Hippel-Lindau: a retrospective study supporting a new treatment for patients with CNS hemangioblastomas. (2011) Neuro Oncol 13(9): 1030–1036.
PubMed | CrossRef | Others
64. Chan, C.C., Collins, A.B., Chew, E.Y. Molecular pathology of eyes with von Hippel-Lindau (VHL) Disease: a review. (2007) Retina 27(1): 1-7.
PubMed | CrossRef | Others
65. Welch, R.B. Von Hippel-Lindau disease: the recognition and treatment of early angiomatosis retinae and the use of cryosurgery as an adjunct to therapy. (1970) Trans Am Ophthalmol Soc 68: 367-424.
PubMed | CrossRef | Others

66. Dollfus, H., Massin, P., Taupin, P., et al: Retinal hemangioblastoma in von Hippel-Lindau disease: a clinical and molecular study. (2002) Invest Ophthalmol Vis Sci 43(9): 3067–3074.
PubMed | CrossRef | Others
67. Kreusel, K.M., Bechrakis, N.E., Krause, L., et al. Retinal angiomatosis in von Hippel-Lindau disease: a longitudinal ophthalmologic study. (2006) Ophthalmology 113(8): 1418–1424.
PubMed | CrossRef | Others
68. Kim, W.Y., Kaelin, W.G. Role of VHL gene mutation in human cancer. (2004) J Clin Oncol 22(24): 4991-5004.
PubMed | CrossRef | Others
69. Choyke, P.L., Glenn, G.M., Walther, M.M., et al. The natural history of renal lesions in Von Hippel-Lindau disease: a serial CT study in 28 patients. (1992) AJR Am J Roentgenol 159(6): 1229–1234.
PubMed | CrossRef | Others
70. Walther, M.M., Choyke, P.L., Glenn, G., et al. Renal cancer in families with hereditary renal cancer: Prospective analysis of a tumor size threshold for renal parenchymal sparing surgery. (1999) J Urol 161(5): 1475–1479.
PubMed | CrossRef | Others
71. Roupret, M., Hopirtean, V., Mejean, A., et al. Nephron sparing surgery for renal cell carcinoma and von Hippel-Lindau's disease: A single center experience. (2003) J Urol 2003 170(5): 1752-1755.
PubMed | CrossRef | Others
72. Steinbach, F., Novick, A.C., Zincke, H., et al: Treatment of Renal-Cell Carcinoma in von Hippel-Lindau Disease - a Multicenter Study. (1995) J Urol 153(6): 1812-1816.
PubMed | CrossRef | Others
73. Goldfarb, D.A., Neumann, H.P., Penn, I., et al. Results of renal transplantation in patients with renal cell carcinoma in Von Hippel-Lindau disease. (1997) Transplantation 64(12): 1726-1729.
PubMed | CrossRef | Others
74. Yang, J., Haworth, L., Sherry, R., et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. (2003) N Engl J Med 349(5): 427–434.
PubMed | CrossRef | Others
75. Drevs, J., Hofmann, I., Hugenschmidt, H., et al. Effects of PTK787/ZK 222584, a specific inhibitor of vascular endothelial growth factor receptor tyrosine kinases, on primary tumor, metastasis, vessel density, and blood flow in a murine renal cell carcinoma model. (2000) Cancer Res 60(17): 4819-4824.
PubMed | CrossRef | Others
76. Mendel, D.B., Laird, A.D., Xin, X., et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. (2003) Clin Cancer Res 9(1): 327-337.
PubMed | CrossRef | Others
77. Lee, J.T., McCubrey, J.A. BAY-43–9006 Bayer/Onyx. (2003) Curr Opin Investig Drugs 4(6): 757-763.
PubMed | CrossRef | Others
78. Vaganovs, P., Bokums, K., Miklaševics, E., et al. Von hippel-lindau syndrome: diagnosis and management of hemangioblastoma and pheochromocytoma. (2013) Case Rep Urol 2013: 624096.
PubMed | CrossRef | Others
79. Lenders, J.W., Eisenhofer, G., Mannelli, M., et al. Phaeochromocytoma. (2005) Lancet 366(9486): 665-675.
PubMed | CrossRef | Others
80. Eisenhofer, G., Walther, M.M., Huynh, T.T., et al. Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. (2001) J Clin Endocrinol Metab 86(5): 1999-2008.
PubMed | CrossRef | Others
81. Baghai, M., Thompson, G.B., Young, W.F. Jr, et al. Pheochromocytomas and paragangliomas in von Hippel-Lindau disease: a role for laparoscopic and cortical-sparing surgery. (2002) Arch Surg 137(6): 682-688; discussion 688-9. [PubMed: 12049539]
PubMed | CrossRef | Others
82. Manski, T.J., Heffner, D.K., Glenn, G.M., et al. Endolymphatic sac tumors. A source of morbid hearing loss in von Hippel-Lindau disease. (1997) JAMA 277(18): 1461-1466.
PubMed | CrossRef | Others
83. Choo, D., Shotland, L., Mastroianni, M., et al. Endolymphatic sac tumors in von Hippel– Lindau disease. (2004) J Neurosurg 100(3): 480-487.
PubMed | CrossRef | Others
84. Megerian, C.A., Haynes, D.S., Poe, D.S., et al. Hearing preservation surgery for small endolymphatic sac tumors in patients with von Hippel–Lindau syndrome. (2002) Otol Neurotol 23(3): 378-387.
PubMed | CrossRef | Others
85. Lonser, R.R., Kim, H.J., Butman, J.A., et al. Tumors of the endolymphatic sac in von Hippel–Lindau disease. (2004) N Engl J Med 350(24): 2481-2486.
PubMed | CrossRef | Others
86. Richards, P.S., Clifton, A.G. Endolymphatic sac tumours. (2003) J Laryngol Otol 117(8): 666-669.
PubMed | CrossRef | Others