Published in final edited form as:

J Neurosurg. 2014 August ; 121(2): 384–386. doi:10.3171/2014.2.JNS131190.

De novo *VHL* germline mutation detected in a patient with mild clinical phenotype of von Hippel-Lindau disease:

Case report

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Abstract

Von Hippel-Lindau (VHL) disease is an autosomal dominant multiorgan tumor syndrome caused by a germline mutation in the *VHL* gene. Characteristic tumors include CNS hemangioblastomas (HBs), endolymphatic sac tumors, renal cell carcinomas, pheochromocytomas, and pancreatic neuroendocrine tumors. Sporadic VHL disease with a de novo germline mutation is rare. The authors describe a case of multiple CNS HBs in a patient with a heterozygous de novo germline mutation at c.239G>T [p.S80I] of *VHL*. This is the first known case of a sporadic de novo germline mutation of *VHL* at c.239G>T. Clinicians should continue to consider VHL disease in patients presenting with sporadic CNS HBs, including those without a family history, to confirm or exclude additional VHL-associated visceral lesions.

Keywords

hemangioblastoma; von Hippel-Lindau disease; de novo mutation; oncology

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. This work was supported by the intramural program of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health.

Author contributions to the study and manuscript preparation include the following. Conception and design: M Zhang, Ding, C Zhang, Frerich, Yang, Mao, Zhuang. Acquisition of data: Ding, C Zhang, Germanwala, Yang, Mao. Analysis and interpretation of data: C Zhang, Frerich, Zhuang. Drafting the article: C Zhang, Frerich. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Study supervision: M Zhang, Zhuang.

Cases of sporadic von Hippel-Lindau (VHL) disease with a de novo germline mutation are rare.^{6,11} The patient with a mild clinical phenotype in this setting would be considered to have a sporadic disease. Characteristic neoplasms in VHL disease include CNS hemangioblastomas (HBs), endolymphatic sac tumors, renal cell carcinomas (RCCs), pheochromocytomas, and pancreatic cystadenomas. Central nervous system HBs are the most common tumor in VHL disease, and approximately 30% of all CNS HBs occur in the setting of this disease.^{4,5,11} We present the genomic findings in a 23-year-old woman with multiple CNS HBs and no family history of VHL disease.

Case Report

History and Examination

A 23-year-old woman presented with a 3-month history of severe neck pain, acroanesthesia, and blurred vision, as well as a 1-month history of frequent headaches associated with vomiting. Brain and cervical MRI with contrast revealed 4 enhancing lesions in the cerebellum and cervical spinal cord (Fig. 1A–C). No detectable tumors were found in other organs on CT or MRI of the viscera.

Operation and Postoperative Course

Symptomatic cerebellar and C-2 tumors were resected. Pathological diagnosis confirmed both lesions as HB. Hematoxylin and eosin staining of tumor revealed characteristic HB phenotype, including a mixture of diffuse small spindle cells and clear cytoplasmic lipid-laden stromal cells within an extensive capillary network (Fig. 1D). The patient's clinical signs and symptoms had resolved by the 7-month follow-up.

Gene Analysis

To determine VHL disease status, we collected tumor, oral mucosa, and peripheral blood from the patient, both of her parents, and her brother and son. Exons of *VHL* were amplified from genomic DNA by polymerase chain reaction. The primer sets for exon amplification were as follows: exon 1, forward 5'-GCGAAGACTACGGAGGTC-3' and reverse 5'-ATGTGTCCTGCCTCAAGG-3'; exon 2, forward 5'-CCTAGACCTCATGATCCGC-3' and reverse 5'-TTGGATAACGTGCCTGACATC-3'; and exon 3, forward 5'-GGTAGTTGTTGGCAAAGCCTC-3' and reverse 5'-GAACTAAGGAAGGAACCAGTCC-3'. Sanger DNA sequencing was performed. Each exon was identified and confirmed by both forward and reverse directional analyses. A heterozygous germline mutation in exon 1 of *VHL* (c.239G>T [p.S80I]) was detected in genomic DNA from the HB, oral mucosa, and peripheral blood samples collected from the patient (Fig. 2A–D). No mutation was detected in the peripheral blood of any of the family members (Fig. 2E).

Discussion

Von Hippel-Lindau disease is a progressive multisystem familial tumor syndrome characterized by phenotypically similar vascular tumors in the CNS and viscera. It has an estimated incidence of 1 in 36,000 persons.⁶ The disease is caused by a germline mutation in

the *VHL* tumor suppressor gene located on the short arm of chromosome 3 (3p25–26). Tumor development occurs after loss of the wild-type allele within a susceptible cell type in at-risk organ systems during embryogenesis, resulting in a consistent tumor phenotype.^{3,7,10}

Shared tumor characteristics in VHL disease can be attributed to a decrease in functional VHL protein (pVHL) in affected tumor cells. The pVHL is necessary for the degradation of hypoxia-inducible factors (HIF-1 α and HIF-2 α), which in response to tissue hypoxia play significant roles in cellular metabolism, growth, and proliferation, as well as induction of angiogenesis and erythropoiesis through the production of vascular endothelial growth factor, platelet-derived growth factor, erythropoietin, and endothelin.¹

Von Hippel-Lindau disease can be clinically diagnosed in a patient with a positive family history and either a CNS HB, RCC, or pheochromocytoma (Table 1). In patients with no family history, two or more HBs or one HB and one visceral tumor (RCC, pheochromocytoma, or pancreatic tumor) are required for diagnosis.⁶ Our patient presented with multiple CNS HBs, without a family history of VHL disease, and with no additional detectable visceral tumors. We detected a germline mutation of *VHL* (c.239G>T) in the patient.

The c.239G>T mutation found in this study is predicted to cause a serine-to-isoleucine substitution at amino acid position 80 within pVHL [p.S80I]. Serine at amino acid position 80 is highly conserved among different species, and several studies have reported mutations at this position associated with Type 2 VHL disease ([p.S80G], [p.S80N], and [p.S80R]).^{8,13} However, all previously described patients with this mutation have had a positive family history of VHL disease. Furthermore, this patient was found to be heterozygous for the mutation, indicating the disease should have been inherited in an autosomal dominant manner. No relatives of the patient carried this mutation or demonstrated any clinical signs of VHL disease. It is possible that a de novo mutation occurred in either a germ cell of the parents or at the embryo stage.^{2,9,12} Moving forward, such patients should consider genetic testing to provide potentially important information, to investigate other possible mutations, and to provide additional understanding of this disease.

Conclusions

Sporadic VHL disease or de novo *VHL* germline mutation is rare. We report the first known incidence of a heterozygous germline c.239G>T [p.S80I] mutation of *VHL* occurring in a patient with no family history of VHL disease. In addition, the patient had only a mild clinical phenotype of VHL disease. Clinicians should consider the possibility of sporadic VHL in a patient presenting with HB, even without evidence of other VHL-associated lesions or a positive family history of VHL disease, to establish appropriate follow-up care.

Abbreviations used in this paper

HB	hemangioblastoma
pVHL	VHL protein

RCC	renal cell carcinoma
VHL	von Hippel-Lindau

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Fig. 1.

Contrast-enhanced T1-weighted MR images (A–C) of the brain revealing enhancing lesions in the cerebellum and ventral spinal cord at C-2. Photomicrograph (D) demonstrating characteristic HB phenotype with lipid-laden stromal cells (*arrows*) distributed within a dense capillary network. H & E, original magnification $\times 20$.

Fig. 2.

A resultant chromatogram profile after direct DNA sequencing of exon 1 of *VHL*. The wild-type sequence was detected in the patient's father, mother, brother, and son (A). A heterozygous c.239G>T mutation was identified in both HBs and in peripheral blood and oral mucosa tissue samples (B–D). Pedigree of the kindred displaying the sporadic development of VHL disease (E).

TABLE 1
Diagnostic criteria for clinical diagnosis of VHL disease*

Patient	Criterion
w/ a family history of VHL	patient must have 1 CNS HB, pheochromocytoma, or RCC
w/o a family history of VHL	patient must have 2 CNS HBs or 1 CNS HB & 1 visceral tumor (pheochromocytoma, RCC, or pancreatic tumor)

* Based on data from Lonser et al., 2003.