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

Case report

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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. (http://thejns.org/doi/abs/10.3171/2014.2.JNS131190)

Key Words • hemangioblastoma • von Hippel-Lindau disease • de novo mutation • oncology

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’-CCTAGA

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De novo VHL gene germline mutation

CCTCATGATCCGC-3\-' and reverse 5\-TTGGATAACG
TGCCTGACATC-3\-'; and exon 3, forward 5\-'GGTAGTT
GTTGGCAAAGCCTC-3\-' and reverse 5\-'GAAACTAAG
GAAGGAACCAGTCC-3\-' . Sanger DNA sequencing was
performed. Each exon was identified and confirmed by
both forward and reverse directional analyses. A hetero-
zygous 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 multi-
system familial tumor syndrome characterized by pheno-
typically similar vascular tumors in the CNS and viscera.
It has an estimated incidence of 1 in 36,000 persons.\" The
disease is caused by a germline mutation in the VHL tu-
mor suppressor gene located on the short arm of chromo-
some 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.\"\"\"\"\"\"

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\-a
and HIF-2\-a), which in response to tissue hypoxia play
significant roles in cellular metabolism, growth, and pro-
liferation, as well as induction of angiogenesis and eryth-
rogenesis through the production of vascular endothelial
growth factor, platelet-derived growth factor, erythropoi-
etin, and endothelin.\"\"\"\"\"\"

Von Hippel-Lindau disease can be clinically diag-
nosed in a patient with a positive family history and ei-
ther 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.\"\"\"\"\"\"
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 pre-
dicted 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]). 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. 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.

Disclosure

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References


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