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Clinical Study

A deletion mutation of the *VHL* gene associated with a patient with sporadic von Hippel-Lindau disease

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ABSTRACT

Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited familial cancer syndrome resulting from mutations in the VHL tumor suppressor gene, which leads to the development of a variety of benign and malignant tumors, especially central nervous system hemangioblastomas, retinal angiomas, clear-cell renal cell carcinomas and pheochromocytomas, with age-dependent penetrance. To date, nearly 400 germline mutations have been found to be involved in VHL disease according to the public Human Gene Mutation Database (HGMD). Although most index cases have a positive family history of VHL, some do not and may represent *de novo* cases. Patients diagnosed without family histories of VHL have been reported in as many as 23% of affected individuals with VHL. In this paper, we report the presence of a heterozygous deletion mutation of c.227_229delTCT in the *VHL* gene, causing the deletion of phenylalanine at codon 76 (p.Phe76del) of the VHL protein in a patient with sporadic VHL with a benign prognosis. The mutation involved may be *de novo* or the seemingly unaffected parent may be mosaic for the disease.

1. Introduction

Von Hippel-Lindau (VHL) disease (Online Mendelian Inheritance in Man [OMIM] database reference 193300) is an autosomal dominant hereditary familial cancer syndrome caused by germline mutations in the VHL tumor suppressor gene (*VHL*) and is characterized by a predisposition for a variety of benign and malignant neoplasms. The estimated incidence of VHL syndrome is 1 in 36,000 live births in the Caucasian population, and VHL has over 90% penetrance by 65 years of age.[1] VHL disease demonstrates obvious phenotypic variability and age-dependent penetrance, the most common manifestations of which are retinal and central nervous system (CNS) hemangioblastomas, renal cell carcinomas, pheochromocytomas, pancreatic neuroendocrine tumors, renal and pancreatic cysts and endolymphatic sac tumors. Epididymal and broad ligament cystadenomas are also common manifestations of VHL.[2]

Four different types of VHL disease have been described on the basis of the risk of pheochromocytoma and renal cell carcinoma. VHL type 1 is characterized by a low frequency of pheochromocytomas, but patients can develop all other tumor types generally associated with the disease; whereas VHL type 2 is characterized by a strong predisposition for pheochromocytoma, but has a low risk (type 2A) or high risk (type 2B) for renal cell carcinomas. Type 2C is characterized by pheochromocytomas only, with no other neoplastic findings of VHL.[3]

Clinical criteria for a diagnosis of VHL disease include the following: (i) a family history of, and a personal history of, a single VHL tumor (for example [e.g.] hemangioblastoma in the CNS or retina, renal cell carcinoma, pheochromocytoma or pancreatic endocrine tumor, or endolymphatic sac tumor) or (ii) no family history of VHL disease but with two typical tumors (e.g. two hemangioblastomas or a hemangioblastoma and a visceral tumor).[4,5]

The *VHL* gene responsible for VHL disease was mapped to chromosome 3p25-26 and was subsequently identified in 1993 by Latif et al.[6] The *VHL* gene product (pVHL) acts as a tumor suppressor protein, which regulates hypoxia-induced proteins. Elongin B is part of an E3 ubiquitin ligase multimeric complex called VEC that activates ubiquitylation by the E2 ubiquitin-conjugating enzyme Ubc5. VEC is composed of von Hippel-Lindau tumor suppressor protein (pVHL), elongin C, cullin 2, neural-precursor-cell-expressed developmentally down-regulated 8 (NEDD8), and ring-box protein 1 (Rbx1).[7] The major cause of VHL disease is inactivation of the VHL tumor suppressor protein caused by germline mutations, and subsequent loss of function in VHL and VEC results in dysfunction in regulating the proteolytic degradation of hypoxia-inducible factors (HIF).[8–10] The HIF transcription factors have an important

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role in coordinating cellular responses to hypoxia and the regulating transcription of a wide range of target genes involved in angiogenesis, proliferation and metabolism (e.g. vascular endothelial growth factor [VEGF] and transforming growth factor [TGF]).[11] Failure of the degradation of HIF is an important step in the development of angiogenic tumors. The identification of the *VHL* gene has led to studies aimed at developing molecular genetic diagnosis for VHL disease and to correlate the mutations with neoplastic manifestations.

In this paper, we report a sporadic case of VHL disease without positive family history and describe a variant of the *VHL* gene identified by direct sequencing. The mutation in this patient may have been *de novo*, or the seemingly unaffected parent of this patient may have been mosaic for the disease.

2. Materials and methods

2.1. Patient

The 32-year-old male patient was admitted to Xiangya Hospital in 2006 and presented with progressive back and neck pain, and

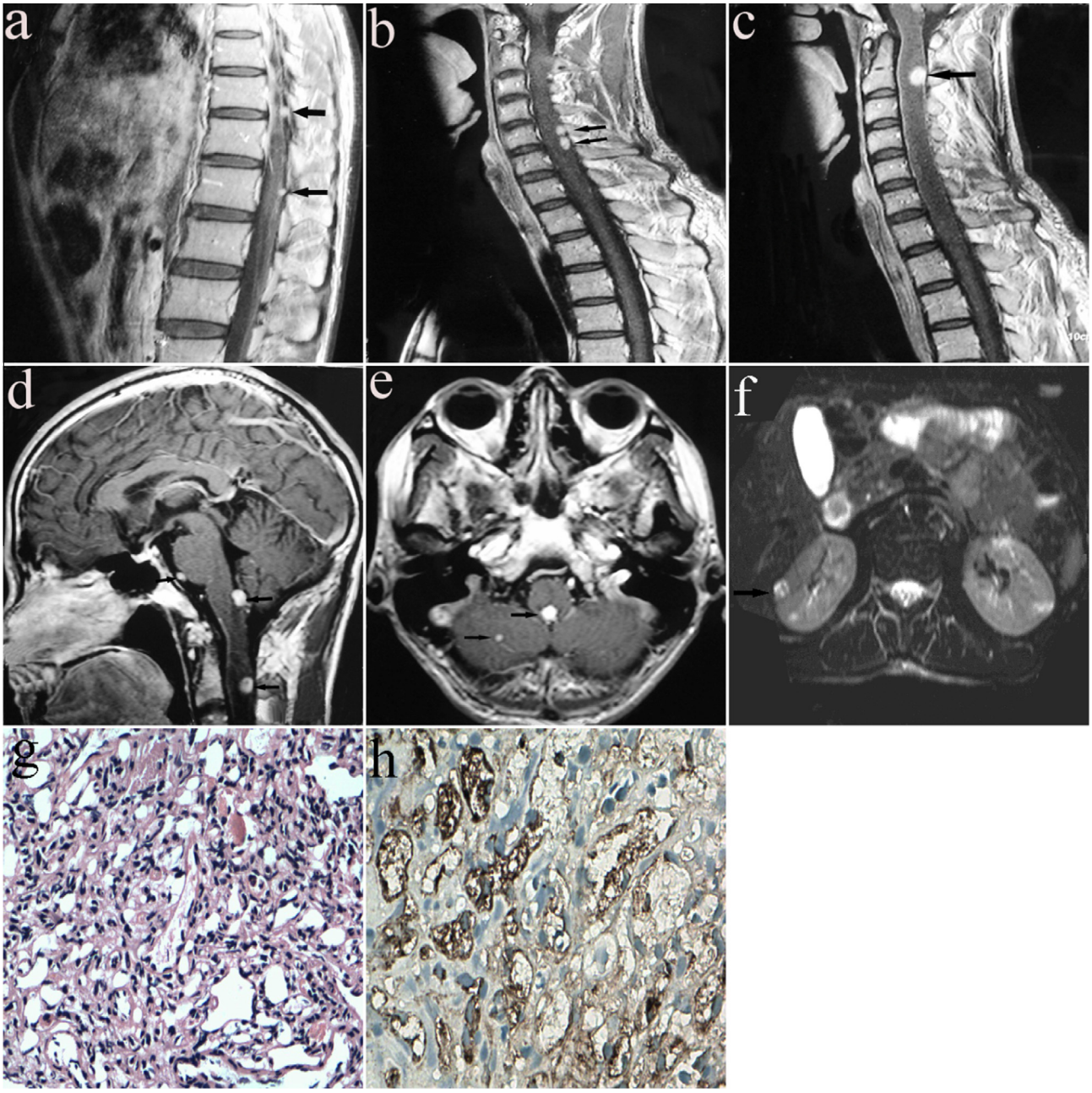

Fig. 1. Main clinical manifestations of von Hippel-Lindau (VHL) disease. (a) Sagittal T1-weighted MRI of the thoracic spinal cord showing two brightly enhancing nodular lesions with clear boundaries at T10 and T12 (arrows). (b) Sagittal T1-weighted MRI of the cervical spinal cord showing two brightly enhancing nodular lesions with clear boundaries at C5 and C6 (arrows). (c) Sagittal T1-weighted MRI of the cervical spinal cord showing a brightly enhancing nodular lesion with a clear boundary at C2 (arrow). (d) Sagittal T1-weighted MRI of the cranial–cervical region showing three brightly enhancing round lesions with clear boundaries at the posterior of the medulla oblongata, superior spinal cord and basilar part of the pons (arrows). (e) Axial T1-weighted MRI of the brain showing two brightly enhancing nodular lesions with clear boundaries at the posterior of the medulla oblongata and the right cerebellar hemisphere (arrows). (f) Sagittal T1-weighted MRI of the kidney showing the small (1.2 cm × 0.6 cm) enhancing nodular lesion (arrow). (g) Histopathological examination of the lesions at T10 and T12 in the spinal cord of the patient with VHL (hematoxylin and eosin stain, ×400). (h) Immunohistochemistry of the biopsied tissue from the lesions at T10 and T12 in the spinal cord of the patient with VHL (factor 8 related antigen stain, ×400).