COMMENT

Commentary: Von Hippel–Lindau disease: A clinical and scientific review

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Von Hippel-Lindau (VHL) disease results from germline mutation in the VHL tumour suppressor gene on chromosome 3 short arm and remains one of the most frequently occurring familial cancer syndromes. In VHL, tumorigenesis typically follows the two-hit mechanism where the wild-type VHL allele is either lost or inactivated via multiple mechanisms, which may include somatic methylation of the VHL promoter region, point mutations, small insertions/deletions, or loss-of-heterozygosity [1]. VHL disease is associated with a high morbidity and mortality and it presents with different phenotypes from family to family, affecting multiple organ systems during the lifetime.

Mutation in the VHL gene affects numerous cellular processes including transcriptional regulation, extracellular matrix formation, and the cellular adaptive response to hypoxia. VHL disease manifests as widespread development of tumours, which include retinal and central nervous system haemangioblastomas (in the cerebellum, brain stem or spinal cord), clear cell renal cell carcinoma (cRCC), phaeochromoctyma/paraganglioma (PPGL), non-secretory pancreatic neuroendocrine tumours and endolymphatic sac tumours [2]. Occurrence of visceral (renal, pancreatic and epididymal) cysts is frequent, but they rarely compromises the organ function and may be indicative of VHL disease diagnosis when detected in combination with a VHL-related tumour [3].

VHL disease is unique for the clinical community because the discovery of any of the associated syndrome components should raise suspicion of this disease. As multiple organ systems may be involved in VHL disease, diagnosis and the follow-up of this syndrome is a challenge in the clinical practice, requiring a multidisciplinary approach. In this commentary, we reflect upon the advancements in understanding of this disease and highlight important molecular and clinical aspects and the potential of these advancements on the natural history of the disease and improve patient outcomes, as reviewed by Maher and colleagues [3].

The genetic aspect of VHL disease includes *VHL* variants which are heterogeneous and include single or multi-exon deletions in around 30–40% of cases. Truncating mutations account for around 30% of cases and missense variants account for another 30% [4]. The *VHL* gene encodes two proteins which include a full length 213 amino acid protein and a shorter protein which is translated from a second initiation site at codon 54. Loss of function variants that impact both proteins are pathogenic. No phenotype has been associated with variants that only alters the longer form [5] and genotype-phenotype correlations are a well- recognised feature of VHL disease

Current clinical diagnostic criteria for VHL disease includes a typical VHL type tumour in an individual with a family history of VHL disease or in sporadic cases two haemangioblastomas or a haemangioblastoma and a visceral tumour. These criteria may result in under- or late diagnoses of the disease, especially in patients without a family history. The authors highlight the importance of routine molecular genetic testing in these cases to facilitate early and accurate diagnosis. Currently, a molecular diagnosis can be made in around 95% or more of individuals with a clinical diagnosis of VHL disease.

While there is no evidence for locus heterogeneity in VHL disease and next generation sequencing techniques have confirmed that a subset of patients without a molecular diagnosis are mosaic for a pathogenic variant in peripheral blood. Interestingly, low levels of mosaicism have been reported in individuals with a classical VHL disease phenotype [6] and promoter region variants have also been reported to be pathogenic [7]. Variants in exon 2 of three *VHL* exons, which is associated with dysregulated splicing, also result in VHL disease, familial phaeochromocytoma and erythrocytosis [8]. These novel findings emphasize the importance of re-evaluation of mutation negative individuals for further testing of somatic tissues, which may help diagnose the small number of cases without an evidence of mosaicism in blood.

Treatment of VHL disease remains a challenge and the development of non-toxic systemic therapies for VHL and identification and validation of biomarkers for early disease diagnosis remain important aims to be achieved. As VHL tumour suppressor gene plays an important role in the development of sporadic cRCC, research and development on pharmacological agents targeting cRCC could benefit individuals with VHL disease.

Genetic testing of individuals combined with establishment of surveillance programs can enable identification of at-risk relatives. The tools for molecular diagnosis are available but it remains a question of health care policy, if all individuals have equal access to genetic testing. There are several pharmacological and biologic agents entering clinical trials and it is hoped that an earlier and accurate clinical and molecular diagnosis, and lifelong surveillance programmes will help in reducing the morbidity and mortality associated with VHL disease.

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ADDITIONAL INFORMATION

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