Von Hippel–Lindau disease genetics

Genetic screening for Von Hippel-Lindau disease can be done at a few centers. Information for patients and families can be found at www.vhl.org.

The Von Hippel–Lindau gene is a tumor suppressor gene on chromosome 3p25-26 that codes for Von Hippel–Lindau protein, which is part of protein complex VCB-CUL2. Biallelic inactivation (2-hit model) is required for tumor development.

Most patients inherit the autosomal dominant VHL gene (allele) with the germline mutation from the affected parent and a normal somatic (wild-type) VHL gene from the unaffected parent, with ≈ 95% penetrance by age 60 yrs [1) 2)].

However, about 20% of cases result from a spontaneous mutation that occurs in the egg or sperm, or very early in development [3)].

The disease is caused by mutations of the von Hippel–Lindau tumor suppressor (VHL) gene on the short arm of chromosome 3 (3p25-26). There are over 1500 germline mutations and somatic mutations found in VHL disease.

Von Hippel–Lindau disease is inherited in an autosomal dominant pattern. Every cell in the body has 2 copies of every gene. In VHL disease, one copy of the VHL gene has a mutation and produces a faulty VHL protein (pVHL). However, the second copy still produces a functional protein. Tumours form from only those cells where the second copy of the gene has been mutated. This is known as the two-hit hypothesis. A lack of this protein allows tumors characteristic of von Hippel–Lindau syndrome to develop

Approximately 20% of cases of VHL disease are found in individuals without a family history, known as de novo mutations. An inherited mutation of the VHL gene is responsible for the remaining 80 percent of cases.

30-40% of mutations in the VHL gene consist of 50-250kb deletion mutations that remove either part of the gene or the whole gene and flanking regions of DNA. The remaining 60-70% of VHL disease is caused by the truncation of pVHL by nonsense mutations, indel mutations or splice site mutations.

Sinonasal renal cell-like adenocarcinoma is an emerging tumor associated with VHL syndrome and it is hoped that future studies shed light on the underlying biology of this unique tumor [4)].

1)
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