VHL Gene Analysis in Von Hippel-Lindau syndrome (VHL) and Chuvash-type Polycythemia (CP)

Clinical Features:

Von Hippel-Lindau syndrome (VHL) is a hereditary cancer predisposition syndrome with a reported prevalence between 1:36,000 and 1:85,000. VHL is characterized by an increased risk for central nervous system hemangioblastomas (60–80%), retinal capillary hemangiomas (50–60%), renal cysts and carcinomas (30–60%), pancreatic cysts (30–65%), pheochromocytomas (11–19%), epididymal cystadenomas (26%), and endolymphatic sac tumors (2–10%).[1] Clinically, VHL families can be subdivided on the basis of absence (Type 1) or presence (Type 2) of pheochromocytoma (PCC). Patients with VHL type 1 are at high risk for hemangioblastoma (HB) and renal cell carcinoma (RCC) and low risk for PCC. Patients with VHL type 2A have an increased risk for HB and PCC, but low risk for RCC. VHL type 2B are at high risk for HB, RCC and PCC while type 2C are at low risk for HB and RCC and high risk for PCC. VHL is highly penetrant and all individuals who harbor a variant in the VHL gene will develop symptoms by 65 years of age. However, the clinical manifestations and disease severity are highly variable, even among family members with the same variant. Predisposition to pheochromocytoma is not unique to VHL. It is shared by some other cancer predisposition syndromes, including MEN2 (RET gene), hereditary PGL/PCC syndrome (SDHD, SDHB, SDHC genes), NF1 (NF1 gene) and rarely Carney complex (PRKAR1A gene). Renal cell carcinoma is also a characteristic of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) and Birt-Hogg-Dube (BHD) hereditary cancer predisposition syndromes. Genetic testing for all these syndromes (with the exception of NF1) is available at GeneDx.

Chuvash-type polycythemia (CP) is a rare congenital disorder characterized by elevated hemoglobin, elevated serum erythropoietin (Epo), elevated serum concentration of vascular endothelial growth factor, low blood pressure, vertebral hemangiomas, varicose veins, and early death secondary to cerebral vascular events or peripheral thrombosis. Predisposition to cancer is *not* associated with the CP phenotype.

Genetics:

VHL and CP are caused by germline variants in the VHL tumor suppressor gene located on chromosome 3p25.3. The VHL gene encodes the von Hippel-Lindau protein (pVHL), which has 312 amino acid residues and is implicated in a variety of functions, such as transcriptional regulation, post-transcriptional gene expression, protein folding and degradation, and formation of the extracellular matrix. It may also regulate genes that respond to tissue hypoxia.[2]

VHL is an autosomal dominant disorder, and affected individuals have a single variant in the VHL gene. CP is an autosomal recessive disorder, and individuals have homozygous or compound heterozygous (in which two variants are present, one on each VHL allele) variants in the VHL gene. Chuvash-type polycythemia is endemic in the Chuvash Republic of the Russian Federation and due to a founder mutation (Arg200Trp).[3] Additional variants in the VHL gene have been associated with the polycythemia phenotype. Parents of individuals affected with CP are likely obligate carriers; heterozygote carriers for CP have *not* been reported to have VHL syndrome-associated tumors. [4]

Test Methods:
Using genomic DNA obtained from the submitted biological material, bidirectional sequence of the coding regions (exons 1-3) and splice sites of the VHL gene are analyzed for variants contributing to VHL or CP. For individuals in whom VHL is clinically suspected, concurrent, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of this gene. Any variant is confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR, or other appropriate method.

Test Sensitivity:
For VHL, bi-directional sequence analysis of the three coding exons of the VHL gene has been shown to identify variants in ~72% of affected individuals. The remaining ~28% of patients have a partial or complete deletion of the VHL gene. Thus, the testing strategy employed by GeneDx is expected to identify a variant in almost all individuals clinically diagnosed with VHL.[4, 5] In individuals with congenital erythrocytosis suspected of having CP, two previous studies have identified that at least one variant in the VHL gene is identified in 17% and 50% of probands respectively.[4,5] Deletions of the VHL gene have not been associated with CP. The sequencing approach used by GeneDx is expected to identify >99% of those variants in the VHL gene that can be detected by DNA sequencing. Array CGH analysis (ExonArrayDx) is expected to detect a complete VHL gene deletion, as well as any partial gene deletion that involves one or more exons.

More than 300 distinct variants have been identified in VHL, the vast majority of which are missense variants, although nonsense variants, splice site defects and small deletion or insertions also have been reported. Almost 30% of patients have a deletion of one or more exons of the VHL gene, half of those (15%) include the entire gene.[8,9] Some genotype-phenotype correlations have emerged in VHL syndrome. Patients with VHL Type 2 and a high frequency of pheochromocytoma virtually always have a missense VHL variant (dominant negative effect). In fact, missense variants of codon 167 are reportedly associated with a high risk for PCC (53% and 82% at ages 30 and 50 years).[13] In contrast, patients with type 1 VHL and a low rate of pheochromocytoma generally have a variety of other variant types, including

nonsense and frameshift variants as well as large deletions of one or more exons of VHL that result in loss-of-function.[11,12] The age-related risks for developing renal cell carcinoma and hemangioblastoma, however, do not seem to differ between VHL type 1 and 2.[13] Of note, patients with a complete VHL deletion also were reported to have the lowest prevalence of ocular disease and the most favorable visual outcome.[10] For CP, the Chuvash founder mutation (R200W) is the most commonly identified variant, but many other missense variants have been reported.[4,6,9]

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