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

Disorder Also Known As: VHL; Hippel-Lindau disease; von Hippel-Lindau disease; cerebelloretinal angiomatosis, familial; angiomatosis retinae; VHL syndrome; familial erythrocytosis; ECYT2; CP

Clinical Features:
Von Hippel-Lindau syndrome (VHL) is a hereditary cancer predisposition syndrome caused by germline variants in the VHL tumor suppressor gene. VHL is characterized by an increased risk for central nervous system hemangioblastomas (60–80%), retinal capillary hemangiomas (also referred to as retinal angiomas) (50–60%), renal cysts and carcinomas (30–60%), pancreatic cysts (30–65%), pheochromocytomas (11–19%), epididymal cystadenomas (26%), and endolymphatic sac tumors (2–10%). Retinal capillary hemangiomas may be the initial presenting symptom as early as the first year of life. Individuals with VHL have up to a 69% risk for renal cell carcinoma, specifically the clear cell subtype, by age 60. Paragangliomas and pheochromocytomas are also associated with VHL. Pheochromocytomas, in one or both adrenal glands, occur in about 11-19% of cases and are usually benign, although malignant pheochromocytomas have been reported. VHL is highly penetrant and virtually all individuals who harbor a variant in the VHL gene will develop symptoms by 70 years of age. However, the clinical manifestations and disease severity are highly variable, even among family members with the same variant.

Chuvash-type polycythemia (CP) is an autosomal recessive condition caused by two pathogenic variants in the VHL gene. It 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. Cancer predisposition is not associated with the CP phenotype.

Inheritance Pattern:
VHL is inherited in an autosomal dominant manner. Approximately 22% of VHL cases are de novo (new).

CP is inherited in an autosomal recessive manner. Individuals with this condition harbor two pathogenic variants in VHL (either in homozygous or compound heterozygous state).
Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of \( VHL \) are PCR amplified and capillary sequencing is performed. Bi directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of \( VHL \) depends in part on the patient’s clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of VHL syndrome as outlined above. Sequence analysis is expected to identify pathogenic variants in 54%-67% of individuals with VHL, while deletion/duplication analysis is expected to identify 19%-33% of affected probands.\(^9\),\(^10\)

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

References: