FH Gene Analysis in Hereditary Leiomyomatosis and Renal Cell Cancer and Fumarate Hydratase Deficiency

Disorder Also Known As: HLRCC; FHD; Reed syndrome; Fumarase deficiency syndrome

Clinical Features:
Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) is an autosomal dominant condition that increases the risk to develop cutaneous leiomyomas (smooth muscle tumors of the skin), uterine leiomyomas (uterine fibroids), and renal cell cancer. The lifetime risk for renal cell cancer (RCC) has been estimated to be 10% to 19% for both male and female *FH* pathogenic variant carriers.[1,2] Type II papillary renal cell carcinoma is the most common type of renal cancer associated with HLRCC; however, other tumor types have been reported. The average age at diagnosis of RCC is in the early to mid 40s, but cases of onset in childhood have also been reported.[1,3] An estimated 76% of individuals with a pathogenic variant in *FH* present with single or multiple cutaneous leiomyomas located on the trunk, extremities and occasionally on the face or neck at an average age of 25 years.[4] Almost all females with HLRCC develop uterine leiomyomas, which tend to occur in multiples and at younger ages than in the general population.[5]

Fumarate hydratase deficiency (FHD) is a rare autosomal recessive condition caused by two pathogenic variants (one affecting each allele) of the *FH* gene. This condition is characterized by excessive urinary excretion of fumurate, neonatal hypotonia, growth and developmental delay, seizures, structural brain malformations, severe neurologic impairment, dysmorphic facial features, and neonatal polycythemia with death typically occurring within the first decade.[6–8]

Inheritance Pattern:
HLRCC is inherited in an autosomal dominant manner and **FHD** is inherited in an autosomal recessive manner. *De novo* (new) cases have been reported.

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *FH* 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 *FH* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of HLRCC as outlined above. Sequence analysis is expected to identify pathogenic variants in 71%-93% of individuals with HLRCC. [1,4,9,12,15] In addition, deletion/duplication analysis is expected to identify pathogenic variant in 1/7-1/20 affected individuals.[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.

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