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

**Clinical Features:**

**Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)** is a tumor predisposition syndrome that increases the risk for a triad of features: cutaneous leiomyomas (smooth muscle tumors of the skin), uterine leiomyomas (more commonly referred to as uterine fibroids), and renal cell cancer.[1,2,3] An estimated 76% of patients present with single or multiple cutaneous leiomyomas distributed over the trunk and extremities, and more rarely on the face and neck. The skin findings manifest at a mean age of 25 years. Uterine leiomyomas are present in almost all women with HLRCC and occur at a younger age than in the general population. Uterine fibroids are generally large and numerous. Renal tumors occur in ~10-18% of patients with HLRCC, with a median age at detection of 44 years.[1,3,4,5] Most tumors are classified as 'type 2' papillary renal cancer, although tubulo-papillary, tubular, and solid tumor types have been described. The renal tumors are typically unilateral, solitary, and more aggressive than those associated with other hereditary cancer syndromes.

The differential diagnosis for HLRCC includes Von Hippel-Lindau (VHL) syndrome and Birt-Hogg-Dubé (BHD) syndrome, both of which are associated with an increased risk for renal cancer. BHD syndrome may present with cutaneous fibrofolliculomas, a skin feature reminiscent of cutaneous leiomyomas in HLRCC. Variants in the SDHB gene associated with Hereditary Paraganglioma-Pheochromocytoma Syndrome have also been reported in patients with apparently isolated familial renal cell carcinoma. [1] **Genetic testing for all four syndromes is available at GeneDx.**

**Fumarate hydratase deficiency (FHD)** is a rare disorder characterized by excessive urinary excretion of fumarate, severe neurologic impairment, seizures, hypotonia, growth and developmental delay, structural brain malformations, dysmorphic facial features, and neonatal polycythemia with death typically occurring within the first decade.[6,7,8] There have been approximately 30 patients with FHD described in the literature.

**Genetics:**

HLRCC and FHD are caused by pathogenic variants in the FH gene located on chromosome 1q42.1. The FH gene encodes fumarate hydratase (or fumarase), which catalyzes the conversion of fumarate to malate in the TCA cycle.

In HLRCC, affected individuals have a single FH variant consistent with autosomal dominant inheritance. FH likely acts as a tumor suppressor in HLRCC since loss of the wild type allele in cutaneous, uterine, and renal tumor tissue has been demonstrated, and FH enzyme activity is

low/absent in these tumors. In HLRCC, the majority of variants in FH are missense and frameshift variants, most of which occur at residues near to the enzyme's active site leading to deficient enzyme activity. Nonsense and splice site variants have been observed less frequently. Variants commonly occur in exon 5, although variants are distributed throughout the gene. One partial deletion encompassing exon 1 and two large deletions (~2.5 Mb and 1.9 Mb, respectively) encompassing the FH gene and several flanking genes within chromosomal band 1q43 have been described.[9,10] These individuals were not phenotypically distinct from those with point variants.

Individuals with autosomal recessive FHD are homozygous or compound heterozygous for germline variants in the FH gene. In FHD, the majority of variants in FH are missense, although a single splice site variant and small deletion have also been described. Parents of children with FHD (heterozygous carriers) have been reported to develop cutaneous leiomyomas (similar to individuals affected with HLRCC).

**Test Methods:**
For HLRCC, bi -directional sequence analysis of the FH gene is offered in two tiers. Tier 1 includes analysis of exon 5, where >34% of variants have been identified. If this test is negative, Tier 2 analysis includes sequencing of the remaining exons of the FH gene (exons 1-4 and 6-10). If no variant is identified by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) can be ordered to evaluate for a deletion/duplication of one or more exons of the FH gene. For FHD, full sequence analysis of the FH gene (exons 1-10) is performed. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

**Test Sensitivity:**
In three separately published studies comprising a total of 169 individuals with a clinical diagnosis of HLRCC, FH variants were identified in 76%-100% of patients.[1,2] Genomic deletions of the FH gene were reported 2 of 46 HLRCC probands, and a partial FH gene deletion was identified in 1 of 7 patients with a clinical diagnosis of HLRCC and no variant by sequencing. [9,10] In a single study of 7 unrelated patients with FHD, single-strand conformation polymorphism analysis followed by sequencing identified 12 of 14 expected variants.[5] The sequencing approach used by GeneDx will identify >99% of existing small, intragenic variants.

| Gene | Protein | Inheritance | Disease Associations |
|---|---|---|---|
| *FH* | Fumarate hydratase | AD, AR | HLRCC, FHD |

Abbreviations:
AD – Autosomal Dominant
AR – Autosomal Recessive
HLRCC – Hereditary leiomyomatosis and renal cell cancer
FHD – Fumarate hydratase deficiency

## References:


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