MAYO CLINIC LABORATORIES

1-800-533-1710

TFH

FH Mutation Analysis, Next-Generation Sequencing, Tumor

Patient ID	Patient Name		Birth Date	Sex	Age
SA00175019	TESTINGRNV, ABNORMAL		1987-08-11	F	37
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00175019	SA00175019	CLIENT,CLIENT			
Account Information		**Collected**			
C7028846 DLMP Rochester		28 Mar 2025 00:00			

FH Mutation Analysis, Tumor

Result

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Provided diagnosis: kidney renal cell carcinoma involving lymph node

The following CLINICALLY RELEVANT VARIANT was detected:
Gene: FH
DNA Change: c.954_956dup (Exon 7)
Amino Acid Change: p.D319dup (Asp319dup)
Variant Allele Frequency: 50.4%

The following VARIANT OF UNCERTAIN SIGNIFICANCE was detected:
Gene: FH
DNA Change: c.278T>G (Exon 3)
Amino Acid Change: p.I93S (Ile93Ser)
Variant Allele Frequency: 44.6%

No other reportable sequence variants were detected within the analyzed regions of the tested genes listed in the method description.

Interpretation

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1) FH c.954_956dup (p.D319dup) (Exon 7)

FH, a tumor suppressor gene, encodes the protein fumarate hydratase, an enzyme that converts fumarate to malate in the TCA cycle in its mitochondrial form, and also metabolizes amino acids in its cytosolic form [PMID:24346898, PMID:24568598, PMID:24684806].

FH-associated tumors include renal cell carcinoma, uterine and cutaneous leiomyomas, pheochromocytomas, and paragangliomas [PMID: 31326218, PMID: 33664427, PMID: 31831373]. FH alterations in these tumors can be sporadic or associated with hereditary leiomyomatosis and renal cell cancer (HLRCC) [PMID: 31326218]. This test does not distinguish between germline and somatic (not inherited) genetic variants. The presence of this alteration in this specimen should be interpreted in correlation with histopathological (including immunohistochemistry for fumarate hydratase and 2SC) and clinico-radiological findings.

There are currently no known clinically approved therapies that specifically target FH mutations.

Germline (inherited) mutations in FH are associated with a hereditary cancer syndrome. This test does not distinguish between germline and somatic (not inherited) genetic variants. If a hereditary cancer syndrome is suspected for this patient, clinical correlation with their personal and family history as well as a referral for genetic counseling is recommended.

VARIANT OF UNCERTAIN SIGNIFICANCE

One variant of uncertain significance was detected. The variant was not observed at significant frequency in population germline/cancer somatic variant databases nor predicted to be functionally significant based on variant type/in silico algorithm results. Additionally, there was no convincing published evidence of cancer association. Therefore, the clinical significance of the detected variant is unknown.

Additional Information

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CLINICAL TRIALS

Possible clinical trials of benefit for this patient can be found at the following sites:
1) ClinicalTrials.gov: www.clinicaltrials.gov/ct2/search/advanced
2) Mayo Clinic: www.mayo.edu/research/clinical-trials/ 3) National Cancer Institute: www.cancer.gov/clinicaltrials/search

REFERENCE TRANSCRIPTS

Sequence variant nomenclature is based on the following RefSeq accession numbers (build GRCh37 (hg19)):FH NM_000143.

Specimen

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Tissue, Tumor

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	Nikola Baumann Ph.D.	24D0404292

Patient ID	Patient Name		Birth Date	Sex	Age
SA00175019	TESTINGRNV, ABNORMAL		1987-08-11	F	37
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C7028846 DLMP Rochester		28 Mar 2025 00:00			

Tissue ID

MCR

12345

Method

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Microscopic examination is performed by a pathologist to identify areas of tumor for enrichment by macrodissection. DNA is extracted from FFPE or cytology slides, and next generation sequencing is performed to evaluate the presence of a mutation in all coding regions and exon/intron boundaries of the FH gene

Variant nomenclature is based on build GRCh37 (hg19). For details about gene transcripts (RefSeq accession numbers), specific targeted regions of each gene, and additional information on this test, see www.mayocliniclabs.com (Test ID TFH).

Disclaimer

[1] MCR

This test cannot differentiate between somatic and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.

DNA variants of uncertain significance may be identified.

A negative result does not rule out the presence of a variant that may be present but below the limits of detection of this assay. The analytical sensitivity of this assay for sequence reportable alterations is 5% mutant allele frequency with a minimum coverage of 500X in a sample with at least 20% tumor content.

Point mutations and small insertion/deletion mutations will be detected in the FH gene only. This test may detect single exon deletions but does not detect multi-exon deletions, duplications, larger-scale genomic copy number variants, copy neutral loss of heterozygosity (LOH), or epigenetic modifications such as promoter methylation. DELINS of 1,000 bp or less are detectable with at least 50 or more supporting reads.

Variant allele frequency (VAF) is the percentage of sequencing reads supporting a specific variant divided by the total sequencing reads at that position. In somatic testing, VAF should be interpreted in the context of several factors including, but not limited to: tumor purity/heterogeneity/copy number status (ploidy, gains/losses, loss of heterozygosity) and sequencing artifact/misalignment [PMID: 27144058, PMID: 29769535].

Rare polymorphisms may be present that could lead to false-negative or false-positive results.

The presence or absence of a variant may not be predictive of response to therapy in all patients.

Test results should be interpreted in the context of clinical, tumor sampling, histopathological, and other laboratory data. If results obtained do not match other clinical or laboratory findings, contact the laboratory for discussion. Misinterpretation of results may occur if the information provided is inaccurate and/or incomplete.

Reliable results are dependent on adequate specimen collection and processing. This test has been validated on cytology slides and formalin-fixed, paraffin-embedded tissues; other types of fixatives are discouraged. Improper treatment of tissues, such as decalcification, may cause PCR failure.

Released By

MCR

Gang Zheng, M.D., Ph.D.

Received: 29 Mar 2025 17:00 **Reported:** 04 Apr 2025 18:00

Laboratory Notes

[1] This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

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