Test Definition: LRCCZ

FH Full Gene Analysis

Overview

Useful For

Evaluation for patients with a personal or family history suggestive of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome or fumarate hydratase deficiency (FHD)

Establishing a diagnosis of HLRCC or FHD allowing for targeted surveillance based on associated risks

Identifying genetic variants associated with increased risk for HLRCC syndrome allowing for predictive testing of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in one gene associated with hereditary leiomyomatosis and renal cell cancer syndrome: *FH*. See Method Description for additional details.

Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for autosomal dominant hereditary leiomyomatosis and renal cell cancer syndrome and autosomal recessive fumarate hydratase deficiency (FHD).

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

For a comprehensive hereditary cancer panel that includes the *FH* gene, consider ordering 1 of the following tests:

-ENDCP / Hereditary Endocrine Cancer Panel, Varies

-HPGLP / Hereditary Paraganglioma/Pheochromocytoma Panel, Varies

-RENCP / Hereditary Renal Cancer Panel, Varies

Testing for *FH* gene as part of a customized panel is available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for this gene. For more information see FMTT / Familial Mutation, Targeted Testing, Varies.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube. **Do not** aliquot.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing (Spanish) (T826)

2. Molecular Genetics: Inherited Cancer Syndromes Patient Information Sheet (T519) in Special Instructions

3. If not ordering electronically, complete, print, and send a Oncology Test Request (T729) with the specimen.

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Minimum Volume

See Specimen Required

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

Clinical & Interpretive

Clinical Information

Germline variants in the *FH* gene are associated with autosomal dominant hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, and autosomal recessive fumarate hydratase deficiency (FHD).(1,2)

HLRCC is characterized by cutaneous and uterine leiomyomas, and increased risk for aggressive renal cell carcinoma. Other reported manifestations include pheochromocytoma and paraganglioma.(2)

FHD, also called fumaric aciduria, is a recessive inborn error of metabolism causing severe neonatal and infantile encephalopathy. Infants often present with poor feeding, hypotonia, and lethargy. It can be accompanied by dysmorphic facies, microcephaly, and brain malformations including bilateral polymicrogyria and absence of the corpus callosum.(1)

There are some reports of children born with FHD whose parents were suspected to have HLRCC, suggesting that individuals with HLRCC may be carriers for FHD.(1-3) The extent of overlap between *FH* variants causing HLRCC and FHD is not well established for certain alterations.(1-3)

Recommendations regarding cancer surveillance of children and adults with HLRCC were created at the International Second Symposium on Hereditary Leiomyomatosis and Renal Cell Cancer in 2013.(2,4)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of further testing options, or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis

as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Insertions/deletions (indels) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller indels.

Deletion/Duplication Analysis:

This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants is performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with

interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgement.

Clinical Reference

1. Kamihara J, Schultz KA, Rana HQ: *FH* tumor predisposition syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews. [Internet]. University of Washington, Seattle; 2006. Updated August 13, 2020. Accessed July 7, 2021. Available at: www.ncbi.nlm.nih.gov/books/NBK1252/

2. Coman D, Kranc KR, Christodoulou J: Fumarate hydratase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews. [Internet]. University of Washington, Seattle; 2006. Updated April 23, 2020. Accessed July 7, 2021. Available at: www.ncbi.nlm.nih.gov/books/NBK1506/

3. Zhang L, Walsh MF, Jairam S, et al: Fumarate hydratase FH c.1431_1433dupAAA (p.Lys477dup) variant is not associated with cancer including renal cell carcinoma. Hum Mutat. 2020 Jan;41(1):103-109

4. Menko FH, Maher ER, Schmidt LS, et al: Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer. 2014 Dec;13(4):637-644

5. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the *FH* gene analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for insertions/deletions (indels) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the gene analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis

as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.

The reference transcript for *FH* gene is NM_000143.3. Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing.

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.(Unpublished Mayo method)

PDF Report
Supplemental

Specimen Retention Time
Whole Blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Rochester

Fees & Codes

Test Classification
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 US Food and Drug Administration.

CPT Code Information
81405

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
LRCCZ	FH Full Gene Analysis	In Process

Result ID	Reporting Name	LOINC®
614743	Test Description	62364-5
614744	Specimen	31208-2
614745	Source	31208-2

614746	Result Summary	50397-9
614747	Result	82939-0
614748	Interpretation	69047-9
614749	Resources	99622-3
614750	Additional Information	48767-8
614751	Method	85069-3
614752	Genes Analyzed	48018-6
614753	Disclaimer	62364-5
614754	Released By	18771-6