Cystic Fibrosis (CFTR) Sequencing and Deletion/Duplication

Cystic fibrosis (CF) is an autosomal recessive disorder caused by pathogenic variants in the *CFTR* gene. Age of onset, manifestations, and symptom severity vary greatly. Symptoms of classic CF include chronic sinopulmonary disease, pancreatic insufficiency, hepatic disease, prolapsed rectum, meconium ileus, obstructive azoospermia, and salt loss syndromes. Classic CF results in reduced life expectancy. *CFTR*-related disorders are less severe and may be characterized by isolated pancreatitis, bilateral absence of the vas deferens, chronic bronchiectasis, and/or nasal polyposis. These disorders typically present in adulthood and often do not decrease life expectancy.

Featured ARUP Testing

Cystic Fibrosis (CFTR) Sequencing and Deletion/Duplication 3004745

Method: Massively Parallel Sequencing/Sequencing

- Use for individuals with symptoms of CF or a *CFTR*-related disorder
- Not intended for routine obstetric carrier screening; for information on CF carrier screening from ARUP, refer to the Cystic Fibrosis (CFTR) Expanded Variant Panel Test Fact Sheet

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information

Disease Overview

Incidence

- Classic CF[1]
  - Ashkenazi Jewish: 1/2,300
  - Caucasian/White: 1/2,500
  - Hispanic American: 1/13,500
  - African American/Black: 1/15,100
  - Asian American: 1/35,100
- Other *CFTR*-related disorders: unknown

Genetics

Gene

CFTR (NM_000492)

Inheritance

Autosomal recessive

Penetrance

- Two severe variants on opposite chromosomes
  - Complete penetrance
  - Causative for classic CF
- Combinations of severe and mild, varying clinical consequences (VCC) and mild, or two mild variants on opposite chromosomes
  - Incomplete penetrance
  - May or may not cause symptoms of a *CFTR*-related disorder

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage or known low quality, and in certain situations, to confirm variant calls.

- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Sensitivity/Specificity

Clinical Sensitivity

CFTR sequencing and deletion/duplication: 99%[2,3,4]

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Interpretation
Positive	Two severe pathogenic variants identified	Predicted to be affected with classic CF disease Refer patient to a CF clinic and offer carrier screening to reproductive partner and family members
	One mild pathogenic variant and another (mild, VCC, or severe) pathogenic variant on the opposite chromosome	Increased risk for a *CFTR*-related disorder; if a severe variant is present, offer carrier screening to family members and reproductive partner
	One severe pathogenic variant identified	At least a CF carrier Offer carrier screening to family members and reproductive partner
	One mild pathogenic variant identified	At least a carrier of a *CFTR*-related disorder
Negative	No pathogenic variants identified	Risk for being affected with, or a carrier of, CF or a *CFTR*-related disorder is reduced
Uncertain	Variant(s) of uncertain identified	Unknown if variant(s) are disease causing or benign

Limitations

- A negative result does not exclude a diagnosis of CF.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the *CFTR* gene
  - Regulatory region and deep intronic variants other than 5T (IVS8), c.1680-886A>G (c.1679+1.6kbA>G), and c.3718-2477C>T
  - Breakpoints of large deletions/duplications

- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions

References

1. Abeliovich D, Lavon IP, Lerer I, et al. Screening for five mutations detects 97% of cystic fibrosis (CF) chromosomes and predicts a carrier frequency of 1:29 in the Jewish Ashkenazi population. *Am J Hum Genet*. 1992;51(5):951-956.

2. Cystic Fibrosis Mutation Database. Cystic Fibrosis Centre at the Hospital for Sick Children in Toronto. 2011. [Updated: Apr 2011; Accessed: Feb 2022]

3. Ong T, Marshall SG, Karczeski BA, et al. Cystic fibrosis and congenital absence of the vas deferens. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews. University of Washington, Seattle; 1993-2022. [Updated: Feb 2017; Accessed: Feb 2022]

4. Strom CM, Huang D, Chen C, et al. Extensive sequencing of the cystic fibrosis transmembrane regulator gene: assay validation and unexpected benefits of developing a comprehensive test. Genet Med. 2003;5(1):9-14.

Related Information

Cystic Fibrosis
Cystic Fibrosis (CFTR) Expanded Variant Panel

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