

Cystic Fibrosis (*CFTR*) 32 Mutations with Reflex to Sequencing and Deletion/Duplication

TO CONFIRM A CLINICAL DIAGNOSIS OF CYSTIC FIBROSIS (CF) USING A COST-EFFICIENT, TIERED TESTING STRATEGY

Disease Overview

- Characteristics of classic CF include chronic sino-pulmonary disease, gastrointestinal malabsorption/ pancreatic insufficiency, and obstructive azoospermia in males; newborns may present with meconium ileus and failure to thrive.
- Life expectancy for individuals with classic CF is approximately 35 years.
- Sweat chloride testing has a clinical sensitivity of 90 percent in classic CF and is considered the gold standard for diagnosis.
- Individuals with nonclassic CF may have clinical findings limited to a single organ system, such as idiopathic pancreatitis, bilateral absence of the vas deferens, nasal polyposis, or bronchiectasis.
- Nonclassic CF often presents in adulthood and may not decrease life expectancy.
- Sweat chloride values in individuals with nonclassic CF are often borderline but may also be elevated or in the normal range.

Epidemiology

- Classic CF occurs in one in 3,000 Caucasians and Ashkenazi Jewish individuals, one in 8,000 Hispanics, one in 15,000 African-Americans, and one in 32,000 Asians.
- The incidence of nonclassic CF is unknown.

Genetics

- Inheritance is autosomal recessive.
- The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene was cloned in 1989.
- There are more than 1,600 documented *CFTR* mutations; most are very rare and not well characterized.
- *CFTR* mutations that result in a dysfunctional or deficient protein are classified as severe, while those that produce a partially functional protein are considered moderate or mild.
- Penetrance is high for severe mutations and variable for mild mutations.
- Classic CF is caused by two severe pathogenic *CFTR* mutations on opposite chromosomes. Nonclassic CF may be caused by one severe and one mild *CFTR* mutation or two moderate/mild mutations on opposite chromosomes.

- Over 97 percent of *CFTR* mutations are base-pair substitutions, small insertions or deletions, or splice-site mutations detectable by gene sequencing.
- As a group, large gene deletions represent approximately 1–2 percent of all *CFTR* mutations.

Additional Ordering Notes

For optimal test interpretation, please submit a Patient History for Cystic Fibrosis Testing form (http://www.aruplab.com/guides/ug/tests/iconpdf_18.pdf) detailing patient symptoms, family history of CF, and ethnicity.

Contraindications for Ordering

- Carrier screening of healthy individuals.
- Prenatal diagnosis.
- Testing for individuals with previously identified familial *CFTR* mutation(s). If the family member has mutation(s) found on the CF 32 mutation panel, then order the panel. If the family member has a non-panel *CFTR* mutation, it is more cost-effective to order Familial Mutation, Targeted Sequencing (ARUP test #2001961) and provide a copy of the lab report detailing the familial mutation.

Interpretation

- If the CF 32 mutation panel identifies fewer than two pathogenic mutations, *CFTR* gene sequencing will be performed. After *CFTR* gene sequencing, if fewer than two pathogenic mutations are identified, the *CFTR* deletion/duplication assay will be performed.
- Symptomatic individuals with two pathogenic *CFTR* mutations on opposite chromosomes are predicted to be affected with CF.
- Symptomatic individuals with one or no identifiable mutations are unlikely to be affected with CF. However, rare deep intronic and promoter mutations are not detected by this test.
- *CFTR* gene sequencing may identify mutations of unknown clinical significance.
- Rarely, two *CFTR* mutations may occur on the same chromosome and by themselves would not result in CF. In these cases, parental testing for the identified mutations may help confirm their chromosomal origin and, thus, their significance.

Methodology

For 32 Mutation Panel:

- Polymerase chain reaction (PCR), oligonucleotide ligation assay (OLA), fluorescent hybridization probes, and capillary electrophoresis to detect the following *CFTR* mutations: G85E, R117H, R334W, R347P, R347H, 394delTT, A455E, I507del, F508del, V520F, G542X, S549N, S549R, G551D, R553X, R560T, 621+1G>T, 711+1G>T, 1078delT, R1162X, W1282X, N1303K, 1717-1G>A, 1898+1G>A, 2184delA, 2789+5G>A, 3120+1G>A, 3659delC, 3849+10kbC>T, 3876delA, 3905insT, and 2183delAA>G.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity varies by ethnicity.

For Sequencing:

- PCR followed by bidirectional sequencing of the entire *CFTR* coding region, intron/exon boundaries.
- Analytical sensitivity and specificity of sequencing are 99 percent.
- Clinical sensitivity is 97 percent.

For Deletion/Duplication Analysis:

- Multiplex ligation-dependent probe amplification (MLPA) to detect large *CFTR* coding-region deletions/duplications.
- Analytical sensitivity and specificity of MLPA are 90 percent.
- Clinical sensitivity and specificity of MLPA are 1–2 percent and 99 percent, respectively.

Limitations

- Rare diagnostic errors can occur due to primer- or probe-site mutations.
- The breakpoints of large *CFTR* deletions/duplications will not be determined.
- Regulatory region and deep intronic mutations will not be detected.

Related Tests

- Cystic Fibrosis (*CFTR*) 32 Mutations (2001933): Clinical sensitivity of 94 percent in Ashkenazi Jews, 89 percent in Caucasians, 73 percent in Hispanics, 65 percent in African-Americans and 55 percent in Asians.
- Cystic Fibrosis (*CFTR*) Sequencing (0051110): Clinical sensitivity of 97–98 percent for *CFTR* mutations.
- Cystic Fibrosis (*CFTR*) Deletion/Duplication (0051642): Clinical sensitivity of 1–2 percent for *CFTR* mutations.

References

1. Grody W, et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genet Med* 2001;3(2):149–54.
2. Watson M, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med* 2004;6(5):387–91.

Test Information

2001967 Cystic Fibrosis (*CFTR*) 32 Mutations with Reflex to Sequencing and Reflex to Deletion/Duplication

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.