

Cystic Fibrosis (*CFTR*) 32 Mutations

TO CONFIRM A DIAGNOSIS OR DETERMINE CARRIER STATUS

Disease Overview

- Classically affected individuals have chronic lung infections and pancreatic insufficiency; newborns may experience meconium ileus and failure to thrive.
- Life expectancy for individuals with classic CF is approximately 35 years.
- Nonclassic cases of CF may present with a single organ system symptom, such as pancreatitis, bilateral absence of the vas deferens, bronchiectasis, sinusitis, or nasal polyps. Mutations associated with nonclassic disease are often not identified by the CF 32 Mutation Panel and may require *CFTR* gene sequencing for detection.
- American College of Obstetrics and Gynecology recommends offering carrier screening to all expectant couples or those planning a pregnancy.

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

- Autosomal recessive.
- Penetrance is high for severe mutations and variable for mild mutations.
- The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene was cloned in 1989.
- More than 1,600 mutations are now documented; most are very rare.
- If the mild mutation (R117H) is identified, testing for the 5T variant should be performed. If both R117H and 5T are detected, testing should be done to determine if the variant and mutation are on separate chromosomes.

Indications for Ordering

- Expectant couples or those planning a pregnancy.
- Individuals with symptoms of cystic fibrosis.
- Individuals with a positive family history of cystic fibrosis.

Interpretation

- For optimal test interpretation, provide information regarding patient symptoms of CF, family history of CF, and ethnicity.
- Healthy individuals with no detectable mutations have a reduced CF carrier risk. A table, with risk reduction based on ethnicity, is provided to predict the specific carrier risk reduction.
- If an individual with a family history of CF has no detectable panel mutations, Bayesian analysis is necessary to determine the carrier risk reduction (unless the familial mutations are known to be included on the panel).
- Healthy individuals with a single mutation identified are predicted to be carriers of CF.
- Symptomatic individuals with two mutations identified are predicted to be affected with CF.
- Symptomatic individuals with only one or no identified mutations are provided a chart based on ethnicity showing the percentage of affected individuals without two identified mutations. For those with a positive or borderline sweat chloride, *CFTR* sequencing with reflex to deletion/duplication testing should be considered.

Methodology

- PCR, oligonucleotide ligation assay (OLA), fluorescent hybridization probes, and capillary electrophoresis.
- Mutations tested: F508del, I507del, G542X, G551D, W1282X, N1303K, R553X, 621+1GT, R117H, 1717-1GA, A455E, R560T, R1162X, G85E, R334W, R347P, 711+1GT, 1898+1GA, 2184delA, 1078delT, 3849+10kbCT, 2789+5GA, 3659delC, 2183delAA>G, 3120+1GA, R347H, V520F, S549N, S549R, 3905insT, 3876delA, and 394delTT.
- For samples positive for R117H, the IVS-8/poly T variant is analyzed.
- Clinical sensitivity for carrier detection by ethnicity: Ashkenazi Jewish: 94 percent; Caucasian: 89 percent; Hispanic: 73 percent; African-American: 65 percent; Asian- American: 55 percent.
- Analytical sensitivity and specificity are 99 percent.

Limitations

- This assay will not detect or determine the chromosomal origin of *CFTR* mutations other than R117H and 5T variant.
- Mutations within the primer/probe regions could affect the analytical sensitivity of this assay.

Related Tests

- Familial Mutation, Targeted Sequencing (2001961): detects the specific familial *CFTR* mutation(s) previously identified; order when the specific familial mutations are not on the CF 32 mutation panel.
- Cystic Fibrosis (*CFTR*) Sequencing (0051110): detects mutations in all *CFTR* exons and intron/exon borders; large *CFTR* duplications and deletions are not detected.
- Cystic Fibrosis (*CFTR*) 32 Mutations with Reflex to Sequencing (2001968): detects 32 common *CFTR* mutations; sequencing of all *CFTR* exons and intron/exon borders is performed if two panel mutations are not identified.
- Cystic Fibrosis (*CFTR*) Deletion/Duplication (0051642): detects large *CFTR* duplications and deletions.
- Cystic Fibrosis (*CFTR*) Sequencing with Reflex to Deletion/Duplication (0051640): detects mutations in all *CFTR* exons and intron/exon borders; large duplication/ deletion analysis is performed if two pathogenic mutations are not detected by sequencing.
- Cystic Fibrosis (*CFTR*) 32 Mutations with Reflex to Sequencing and Reflex to Deletion/Duplication (2001967): detects 32 common CF mutations; sequencing of all *CFTR* exons and intron/exon borders is performed if two panel mutations are not identified; large duplication/deletion analysis is performed if two pathogenic mutations are not detected by sequencing.
- Cystic Fibrosis (*CFTR*) 32 Mutations, Atypical (2001969): detects 32 common *CFTR* mutations and the 5T variant.
- Cystic Fibrosis, 3199del6 Only (0050098): detects the 3199del6 mutation; only for individuals positive for the I148T polymorphism.
- Cystic Fibrosis Cis-Trans (*CFTR*) R117H & 5T Mutations (0056006): determines if the R117H mutation is on the same chromosome as the 5T variant; only for individuals positive for the R117H mutation and 5T variant.
- Cystic Fibrosis (*CFTR*) 32 Mutations, Fetal (2001970): detects 32 common *CFTR* mutations in amniocytes.

References

1. Grody W, et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Gen in 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. *Gen in Med* 2004; 6(5):387–91.

Test Information

2001933

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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.