

Cystic Fibrosis (*CFTR*) 32 Mutations, Atypical

TO DIAGNOSE NONCLASSIC CYSTIC FIBROSIS

Disease Overview

- Individuals with classic CF 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.
- 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.

Epidemiology

- 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 is affected with classic disease.
- The incidence of nonclassic CF is unknown.

Genetics

- Autosomal recessive.
- Over 1,600 mutations have been documented in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene; most are very rare and not well characterized.
- Penetrance is high for severe mutations and variable for mild mutations.
- A panel of common *CFTR* mutations is useful for detecting classic CF. However, nonclassic CF cases are commonly caused by rare *CFTR* mutations detectable by gene sequencing. Testing for the 5T variant in the *CFTR* intron 8 should be performed for atypical CF patients.
- The 5T variant leads to improper splicing, removing exon 9 from 90 percent of the final *CFTR* mRNA transcript. Thus, only 10 percent of the *CFTR* protein produced by an allele with the 5T variant may be functional.
- Of men with CBAVD, approximately 25 percent have two *CFTR* mutations; 25 percent have one *CFTR* mutation and one 5T variant; 20 percent have one *CFTR* mutation; and 10 percent have a single 5T variant. Thus, approximately 80 percent have at least one *CFTR* mutation.
- Of individuals with idiopathic pancreatitis, up to 40 percent are predicted to have at least one *CFTR* mutation.
- Approximately 30 percent of adults with purulent pansinusitis or nasal polyposis starting early in life or associated with chronic infection have one *CFTR* mutation and 7 percent have two.

Indications for Ordering

Individuals with a single symptom of CF, including CBAVD, pancreatitis, bronchiectasis, chronic sinusitis, or nasal polyps.

Interpretation

- For optimal test interpretation, provide information regarding patient symptoms, family history of CF, and ethnicity.
- Symptomatic individuals with two severe mutations are predicted to be affected with CF.
- Symptomatic individuals with one severe and one mild mutation (or a 5T variant) are predicted to be affected with nonclassic CF.
- Symptomatic individuals with only one or no identified mutations should consider *CFTR* gene sequencing.

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, 394delTT, and 5T variant.
- Analytical specificity and sensitivity are 99 percent.
- Clinical sensitivity for nonclassic CF is unknown.

Limitations

- Mutations other than the 32 tested and 5T variant will not be identified.
- Rare diagnostic errors can occur due to primer- or probe-site mutations.

Related Tests

- Cystic Fibrosis (*CFTR*) 32 Mutations (2001933): detects 32 common *CFTR* mutations.
- 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, 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. Casals T, et al. Different *CFTR* mutational spectrum in alcoholic and idiopathic chronic pancreatitis. *Pancreas* 2004;4:374–9.
2. Claustres M, et al. Spectrum of *CFTR* mutations in cystic fibrosis in congenital absence of the vas deferens in France. *Hum Mutat* 2000;16:143–56.
3. Coste A, et al. Atypical sinusitis in adults must lead to looking for cystic fibrosis and primary ciliary dyskinesia. *Laryngoscope* 2004;114:839–43.
4. 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

2001969

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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.