

Cystic Fibrosis Cis-Trans (*CFTR*) R117H & 5T Mutations

TO DETERMINE IF THE CYSTIC FIBROSIS (CF) R117H MUTATION AND 5T VARIANT ARE ON THE SAME CHROMOSOME

Disease Overview

- Individuals affected with classic CF often have chronic lung infections and pancreatic insufficiency; newborns may have meconium ileus and failure to thrive.
- Life expectancy for individuals with classic CF is approximately 35 years.
- Mild 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. Mild CF often presents in adulthood and may not decrease life expectancy.
- The American College of Obstetrics and Gynecology recommends offering a 23 mutation panel, including the mutation R117H, to screen expectant couples for CF carrier status. R117H functions as a mild mutation when not found on the same chromosome as the 5T variant.
- The 5T variant in intron 8 of the *CFTR* gene leads to improper splicing, removing exon 9 from 90 percent of the final mRNA transcript. Thus, only 10 percent of the CFTR protein produced by an allele with the 5T variant may be functional.
- If R117H is detected, 5T testing is recommended. If both are found, then additional testing (haplotyping) should be performed to determine if they are located on the same chromosome or not.
- When R117H and 5T are found on the same chromosome, the effect is believed to be similar to a classic CF mutation. If they are on opposite chromosomes, both the 5T variant and R117H mutation function as mild mutations.
- Determining if the mutation is severe or mild impacts the risk of having offspring with classic CF; it may also help establish whether a diagnosis of CF is likely in symptomatic individuals.

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.
- Allele frequency of the R117H mutation is 0.5 percent in individuals in the United States who are affected with CF.
- Allele frequency of the 5T variant is 5 percent in the general United States population.

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.

Indications for Ordering

Haplotyping should be performed as a reflex test in all individuals found to be heterozygous for both the *CFTR* R117H mutation and 5T variant.

Interpretation

- For optimal test interpretation, provide information regarding patient symptoms, family history of CF, and ethnicity.
- If the R117H mutation and 5T variant are located on the same chromosome, the individual is a carrier of a severe *CFTR* mutation. His/her reproductive partner should be offered CF-mutation screening as they are at increased risk for having offspring with CF.
- If the R117H mutation and 5T variant are on separate chromosomes, the individual is a carrier of two mild *CFTR* mutations.

Methodology

- Long-range and allele-specific PCR followed by oligonucleotide ligation assay, electrophoresis, and fluorescent hybridization probes.
- Mutations tested: R117H and 5T variant.

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

- 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*) 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 (*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. Kieseewetter, et al. A mutation in *CFTR* produces different phenotypes depending on chromosomal background. *Nat Genet* 1993;5:274–8.
3. Strom CM, et al. Cystic fibrosis screening using the college panel: platform comparison and lessons learned from the first 20,000 samples. *Genet Med* 2002;4:289–96.
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

0056006

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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.