

Cystic Fibrosis (*CFTR*) 3199del6 Mutation

TO DETERMINE IF THE CYSTIC FIBROSIS (CF) 3199DEL6 MUTATION IS PRESENT IN INDIVIDUALS WITH THE I148T VARIANT

Disease Overview

- Individuals affected with classic CF often have chronic lung infections and pancreatic insufficiency; newborns may experience meconium ileus and failure to thrive.
- Life expectancy is approximately 35 years.
- In 2001, the American College of Medical Genetics (ACMG) recommended a 25 mutation panel, which included the I148T mutation, to screen expectant couples for CF carrier status.
- In 2004, ACMG recommended removal of I148T from the CF mutation panel as it was no longer believed to represent a severe mutation. Several healthy adults undergoing carrier screening for CF were reported to be either homozygous for the I148T variant or compound heterozygous for I148T and the classic F508del mutation on the opposite chromosome.
- Additionally, CF patients who had a copy of the I148T mutation were found to have the c.3067_3072del6 (commonly known as 3199del6) mutation on the same allele. The latter mutation was determined to be deleterious.

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 CF.
- Allele frequency of the I148T variant in individuals affected with CF is 0.08 percent.
- Frequency of the I148T variant is 50–100 times higher in the general United States population than in individuals affected with CF.

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.
- The I148T variant was originally thought to be deleterious. It is now believed to represent a very mild deleterious mutation or a benign polymorphism when not found on the same chromosome as the 3199del6 mutation.
- Approximately 2 percent of chromosomes with the I148T variant also harbor the 3199del6 mutation.

Indications for Ordering

For individuals found to have the I148T variant as part of a CF mutation panel.

Interpretation

- For optimal test interpretation, please provide information regarding patient symptoms, family history of CF, and ethnicity.
- If the 3199del6 mutation is not present, the I148T variant is believed to represent a benign polymorphism or a very mild mutation. The patient's reproductive partner should not be offered CF mutation screening based on the presence of an isolated I148T variant.
- If the 3199del6 mutation is identified, the patient is a carrier of a classic CF mutation and his/her reproductive partner should be offered CF mutation screening.

Methodology

- Polymerase chain reaction followed by fluorescent monitoring to detect the c.3067_3072del6 (p.Ile1023_Val1024del) *CFTR* mutation.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is 99 percent.

Limitations

- *CFTR* mutations, other than 3199del6, are not evaluated by this assay.
- 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 (*CFTR*) 32 Mutations, Atypical (2001969): detects 32 common *CFTR* mutations and the 5T variant.
- 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. Buyse IM, et al. Use of MALDITOF mass spectrometry in a 51-mutation test for cystic fibrosis: evidence that 3199del6 is a disease causing mutation. *Genet Med* 2004;6:426–30.
2. Grody W, et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Gen in Med* 2001;3(2):149–54.
3. Rolfs EM, et al. The I148T *CFTR* allele occurs on multiple haplotypes: A complex allele is associated with cystic fibrosis. *Genet Med* 2002;4:319–23.
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

0050098

Cystic Fibrosis 3199del6 Only

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.