

CYSTIC FIBROSIS AND CFTR-RELATED DISORDERS

Cystic fibrosis (CF) is the most common autosomal recessive disorder among Caucasians of Northern European descent, but can be found in all ethnic groups with varying frequency. CF is characterized by production of thick mucous that clogs respiratory airways. The mucous provides a breeding ground for infections and subsequent damage of lung tissue, which can result in respiratory failure. The mucous may cause intestinal obstructions, block pancreatic and bile ducts and interfere with liver function. Milder forms of CF have also been described in which not all defining features are present or age of onset is delayed.

CFTR-related disorders refer to a group of diseases that are associated with CF mutations but do not meet diagnostic criteria for CF. Congenital absence of the vas deferens (CAVD) is the most well-characterized of these disorders, where 80% of affected individuals are found to have CF mutations. CAVD accounts for 1-5% of male infertility. Individuals with pancreatitis, recurrent sinusitis or bronchitis also demonstrate a greater frequency of mutations in the CF gene than the general population.

GENETICS

CF is caused by mutations in the *CFTR* gene located on chromosome 7 (7q31.2) (see common CF mutations table). DeltaF508 is the most common mutation, and is associated with about 70% of CF cases in Caucasians of Northern European descent. Other *CFTR* mutations are less common, but may be more prevalent in certain ethnic groups. To be affected with CF, an individual must have two mutations in the *CFTR* gene.

The intron 8 poly T-tract adjacent to the *CFTR* exon 9 splicing acceptor site contains 5, 7 or 9 thymidine bases, which vary among individuals. The 7T and 9T tract are considered to be benign. The 5T allele alone has not been reported to cause classical CF, but may increase the severity of other mutations depending if they are on the same (cis) or opposite (trans) *CFTR* mutation allele. The 5T variant is thought to decrease intron 8 splicing resulting in loss of exon 9. This results in reduced function of the CFTR protein.

WHO SHOULD BE TESTED?

- Individuals clinically suspected of being affected with cystic fibrosis or CF-related conditions
- Individuals with a family history of CF and their reproductive partners to determine carrier status
- Pregnancies at risk due to family history of CF
- Parents of a fetus with echogenic bowel detected by ultrasound
- Infants with meconium ileus who are too young to produce enough sweat

TEST METHODS

- A direct mutation detection assay is used to test for the common mutations and T-tract status listed in the chart below
- Complete sequencing of the coding region and flanking exon/intron boundaries of the *CFTR* gene to identify point mutations and small insertions or deletions
- Quantitative testing of the *CFTR* gene to detect larger deletions or duplications, using MLPA (Multiplex Ligation-dependent Probe Amplification)

COMMON CF MUTATIONS

G542X	G85E	R334W	Y122X
G551D	R117H	A455E	S549R
R553X	V520F	R1162X	R347H
N1303K	S549N	R347P	R560T
S1255X	A559T	Y1092X	M1101K
W1282X	3659delC	394delTT	3905insT
1078delT	deltaF508	delta I507	3876delA
2184delA	2307insA	711+1G>T	1717 -1G>A
2789 +5G>A	1898 +5G>T	3120 +1G>A	621 +1G>T
3849 +10kbC> T	1898 +1G>A	2183 AA>G	5/7/9T

POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

CFTR Gene Mutations	Explanation
None detected	This result does not support a diagnosis of cystic fibrosis, or This individual is unlikely to be a carrier of cystic fibrosis
One detected	This result is unable to confirm a diagnosis of cystic fibrosis, or This individual is a carrier of cystic fibrosis and may pass the mutation to offspring
Two detected	This result confirms a diagnosis of cystic fibrosis

For More Information

Online Mendelian Inheritance in Man <http://www.ncbi.nlm.nih.gov/omim/> Item # 219700

GeneReviews online clinical information resource <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cf>

Canadian Cystic Fibrosis Foundation <http://www.ccff.ca>

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org



1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility that the individual carries a rare CF mutation not included in this assay.

2. Detection rates vary significantly between ethnic groups. The common mutations tested for account for more than 90% of those in North American Caucasians and ~95% in the Ashkenazi Jewish population.

3. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

4. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

5. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.