

Cystic Fibrosis – an Overview

Disease Summary

Cystic Fibrosis (CF) is one of the most common familial recessive diseases. Prevalence varies with ethnicity and is especially high in Caucasians, affecting about 1 in 2000 to 1 in 4000 live births (for review, see 1-3). In Hispanic Americans, African Americans, and Asian Americans, the disorder is less prevalent (1 in 9200, 1 in 15,000, and 1 in 31,000, respectively) (1-3). CF is a multisystem disease, affecting the respiratory, digestive, and male reproductive systems (1-3). Pulmonary disease is the major cause of morbidity and mortality, with chronic lower airway infection and inflammation leading to bronchiectasis and, eventually, to extensive airway damage and fibrosis of lung parenchyma (1,2). Disease severity can range from infertility (in males) without any pulmonary manifestations to recurrent sinusitis and bronchitis with onset in young adulthood to severe lung, pancreatic, and liver disease with onset in infancy. The great majority of CF patients suffer from pancreatic insufficiency, and more than 95% of males with CF are infertile, due to azoospermia secondary to agenesis of Wolffian duct structures (1,2). Some affected individuals demonstrate pancreatic sufficiency, which is correlated with a milder clinical course and increased survival (non-classic CF) (1,2). Early diagnosis of CF is important, since it can help to prevent malnutrition and failure to thrive in infants and children through pancreatic enzyme replacement and chronic bacterial airway infection through antibiotic prophylaxis.

CF has been linked to mutations in the gene *CFTR*, which codes for the cystic fibrosis transmembrane conductance regulator (for review, see 3). Defects in the *CFTR*-encoded membrane ion channel can lead to impaired ionic balance in the cell, giving rise to such manifestations as thick lung secretions and impaired exocrine function of the pancreas. Certain mutations in *CFTR* are associated with presence of pancreatic sufficiency and thus a more favorable prognosis. In males, such “mild” mutations in *CFTR* may lead to infertility without any or with only minor pulmonary manifestations, a phenotype also known as congenital bilateral

absence of the vas deferens (CBAVD). Patients with CBAVD harbor a “mild” *CFTR* mutation (or allele) on at least one chromosome copy (1,2). The second chromosome copy may carry another such “mild” mutation or it may harbor a “severe” mutation associated with classic CF. Risk of CF in blood relatives of patients with CBAVD therefore varies based on the nature of the patient’s *CFTR* mutations (1,2).

CF is usually diagnosed by detecting increased chloride levels in sweat through quantitative pilocarpine iontophoresis. Detection of a characteristic transepithelial nasal potential difference (NPD) is also diagnostic. Newborn screening is usually based on the immunoreactive trypsinogen (IRT) assay, which detects increased trypsinogen levels associated with CF. Diagnosis by sweat testing, NPD, or IRT is often followed by genetic testing, which can confirm the diagnosis and identify the *CFTR* mutations present in an affected individual. Genetic testing for the presence of these familial mutations can then identify disease carriers in the patient’s blood relatives, allowing reproductive counseling (1,2). In cases of CBAVD, which is not associated with increased chloride levels in sweat, genetic testing can provide a definitive diagnosis (1,2).

Initial genetic testing is typically based on routine carrier screening for 23 of the most common mutations as recommended by the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) (4). These mutations account for from 55% to 97% of *CFTR*-related disease, depending on ethnicity (1,4). If none or only one heterozygous occurrence of these 23 mutations is detected in an affected individual, full gene sequencing can be used to screen for presence of other mutations in *CFTR*. In males with CBAVD or individuals with mild forms of CF (non-classic CF), analysis of the 5/7/9T tract is recommended (1,2). The 5T allele is known to modify the disease expression attributable to the R117H mutation (c.350G>A) when both are located on the same chromosome (*in cis*) (2). In addition, the 5T allele by itself can cause

CBAVD in conjunction with a canonical mutation on the other chromosome (1,2). The combination of a canonical mutation and the 5T allele can also lead to nonclassic CF, depending on

the number of TG repeats in the TG tract adjacent to the 5T allele (1,2).

For additional information, see Tables 1-3 below and references 1-3.

Table 1: Disease Facts about *CFTR*-Related Diseases (1-3)

Disease Fact	Classic CF	Non-classic CF	CBAVD
MIM* number		219700	277180
Estimated Prevalence	<ul style="list-style-type: none"> 1:2000-1:4000 in Caucasians 1:9,200 in Hispanic Americans 1:15,000 in African Americans 1:31,000 in Asian Americans 		
Average Age at Diagnosis	<ul style="list-style-type: none"> • Infancy or childhood 	<ul style="list-style-type: none"> • Young adulthood 	<ul style="list-style-type: none"> • Adulthood
Typical Symptoms	<p>Pulmonary</p> <ul style="list-style-type: none"> • Chronic cough with sputum production • Chronic obstructive pulmonary disease • Chronic endobronchitis • Chronic sinusitis <p>Gastrointestinal</p> <ul style="list-style-type: none"> • Meconium ileus in newborns • Pancreatic insufficiency (malabsorption, steatorrhea, failure to thrive in infants) • Diabetes • Hepatobiliary disease (elevated liver enzymes, biliary cirrhosis) <p>Urogenital</p> <ul style="list-style-type: none"> • Azoospermia in males due to altered, atrophic, or fibrotic vas deferens 	<ul style="list-style-type: none"> • Recurrent sinusitis and bronchitis <ul style="list-style-type: none"> • Acute or recurrent pancreatitis 	
Therapy	<p>Pulmonary</p> <ul style="list-style-type: none"> • Antibiotics • Bronchodilators • Anti-inflammatory agents • Mucolytic agents • Chest physiotherapy <p>Gastrointestinal</p> <ul style="list-style-type: none"> • Pancreatic enzyme replacement • Nutritional supplements • Oral ursodiol 	<ul style="list-style-type: none"> • Antibiotics • Bronchodilators • Anti-inflammatory agents 	

*MIM: Mendelian Inheritance in Man, see <http://www.ncbi.nlm.nih.gov/omim>

NOTE: Specimens must be accompanied by a completed consent form. In the case of family tests (ie, known mutations) a copy of the result of the first patient tested in the family (the index case) must be submitted if the test was not performed at Correlagen. Other family members are subsequently tested for the specific mutation found in the first patient tested.

Table 2: Molecular Genetics of *CFTR*-Related Diseases (1-3)

<i>Gene</i> (Protein)	Transmission	Mutation type	Penetrance	Comments
<i>CFTR</i> (cystic fibrosis transmembrane conductance regulator)	Autosomal recessive	Loss of function	Symptom dependent; high for male infertility and pulmonary disease	Certain mutations or alleles are associated with milder disease

Table 3: Colloquial and Systematic Names of Common *CFTR* mutations (5)

Common Name	Systematic Name
G85E	c.254G>A
R117H	c.350G>A
621+1G>T	c.489+1G>T
711+1G>T	c.579+1G>T
R334W	c.1000C>T
R347P	c.1040G>C
TG12	c.1210-13_1210-12dupGT
TG13	c.1210-15_1210-12dupGTGT
5T	c.1210-7_1210-6delTT
A455E	c.1364C>A
ΔI507	c.1519_1521delATC
ΔF508	c.1521_1523delCTT
1717-1G>A	c.1585-1G>A
G542X	c.1624G>T
G551D	c.1652G>A
R553X	c.1657C>T
R560T	c.1679G>C
1898+1G>A	c.1766+1G>A
2184delA	c.2052delA
2789+5G>A	c.2657+5G>A
3120+1G>T	c.2988+1G>T
3659delC	c.3437delC
R1162X	c.3484C>T
W1282X	c.3846G>A
3849+10kbC>T	c.3718-2477C>T
N1303K	c.3909C>G

References

1. Moskowitz SM, Chmiel JF, Stern DL, Cheng E, Cutting GR. (Updated March 26, 2001.) CFTR-related disorders. In: *GeneReviews at GeneTests: Medical Genetics Information Resource* (database online). Copyright, University of Washington, Seattle. 1997-2010. Available at <http://www.genetests.org>. Accessed February 21, 2010.
2. Moskowitz SM, Chmiel JF, Stern DL, et al. Clinical practice and genetic counseling for cystic fibrosis and CFTR-related disorders. *Genet Med*. 2008;10:851-868.
3. Lommatzsch ST, Aris R. Genetics of cystic fibrosis. *Semin Respir Crit Care Med*. 2009;30:531-538.
4. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med*. 2004; 6:387-391.
5. Ogino S, Gulley ML, den Dunnen JT, Wilson RB and the Association for Molecular Pathology Training and Education Committee. Standard mutation nomenclature in molecular diagnostics. *J Mol Diagn*.2007;9:1-6.