CFTR-Related Disorders: CF and CBAVD
Full Gene Sequencing

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 4000 to 1 in 2000 live births.[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 azoöspermia 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 (nonclassic CF).[1,2] Early diagnosis of CF is important, since it can help prevent malnutritionand 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.[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 the presence of pancreatic sufficiency and, consequently, a more favorable prognosis. In males, such "mild" mutations in *CFTR* may lead to infertility without any or with only minor pulmonary manifestations. This phenotype is also known as congenital bilateral absence of the vas deferens (CBAVD). CBAVD is suspected in males with azoöspermia and low volume of ejaculated semen, in whom palpation or ultrasound imaging reveals absence of the vas deferens or, rarely, presence of only a rudimentary, nonfunctional vas deferens.[1] CBAVD as a cause of azoöspermia accounts for about 1% of male infertility.[6] 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]

Table 1 — Facts About CFTR-related Diseases[1-3]

		Classic CF	Nonclassic CF	CBAVD
MIM* Numbers		219700		277180
Estimated Prevalence		1:2000 – 1:4000 in Caucasians 1:9200 in Hispanic Americans 1:15,000 in African Americans 1:31,000 in Asian Americans		
Average Age at Diagnosis		**Infancy or Childhood**	**Young Adulthood**	**Adulthood**
Typical Symptoms	**Pulmonary**	Chronic cough with sputum production Chronic obstructive pulmonary disease Chronic endobronchitis Chronic sinusitis	Recurrent sinusitis and bronchitis	
	Gastrointestinal	Meconium ileus in newborns Pancreatic insufficiency (malabsorption, steatorrhea, failure to thrive in infants) Diabetes Hepatobiliary disease (elevated liver enzymes, biliary cirrhosis)	Acute or recurrent pancreatitis	
	Urogenital	Azoöspermia in males due to altered, atrophic, or fibrotic vas deferens		
Therapy	**Pulmonary**	Antibiotics Bronchodilators Anti-inflammatory agents Mucolytic agents Chest physiotherapy	Antibiotics Bronchodilators Anti-inflammatory agents	
	Gastrointestinal	Pancreatic enzyme replacement Nutritional supplements Oral ursodiol		

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

Table 2 — Molecular Genetics of CFTR-related Diseases[1-3]

Gene (Protein)	Transmission	Mutation Type	Penetrance	Comment
CFTR (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.

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, a definitive diagnosis requires detection of at least one pathogenic *CFTR* mutation.[1,2] Because CBAVD is not associated with increased chloride levels in sweat, quantitative pilocarpine iontophoresis is not a reliable diagnostic tool for CBAVD.[1]

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 between 55% and 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 the presence of other mutations in *CFTR*. In males with CBAVD or individuals with mild forms of CF (nonclassic 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] See tables for additional information.

References

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2. Moskowitz SM, Chmiel JF, Sternen DL, et al. Clinical practice and genetic counseling for cystic fibrosis and CFTR-related disorders. *Genet Med.* 2008 Dec; 10(12):851-868.
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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 Sep-Oct; 6(5):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: Practical and educational challenges. *J Mol Diagn.* 2007 Feb; 9(1):1-6.
6. Jequier AM, Ansell ID, Bullimore NJ. Congenital absence of the vasa deferentia presenting with infertility. *J Androl.* 1985 Jan-Feb; 6(1):15-19.

Table 3 — Colloquial and Systematic Names of Common *CFTR* Mutations[1-3]

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

Relevant Assays*

Test Name	Test Number
Congenital Bilateral Absence of the Vas Deferens (CBAVD): *CFTR* Full Gene Sequencing	252766
Congenital Bilateral Absence of the Vas Deferens (CBAVD): *CFTR* Full Gene Sequencing	252770
Cystic Fibrosis (CF) Profile, DNA Analysis and 5T Allele Genotyping	480555
Cystic Fibrosis (CF), 5T Allele Genotyping	480970
Cystic Fibrosis (CF): *CFTR* (Full Gene Sequencing)	252763
Cystic Fibrosis (CF): *CFTR* (Known Mutation)	252760

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.

*For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.LabCorp.com.

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