

## Congenital Bilateral Absence of the Vas Deferens – an Overview

### Disease Summary

Congenital bilateral absence of the vas deferens (CBAVD) as a cause of azoospermia accounts for about 1% of male infertility (1). CBAVD is a recessively inherited condition that has been linked to mutations in the gene *CFTR*. *CFTR* mutations can also cause cystic fibrosis (CF), an often life-limiting multisystem disease affecting the respiratory, digestive, and male reproductive systems (reviewed in 2 and 3). Patients with CBAVD harbor a “mild” *CFTR* mutation (or allele) on at least one chromosome copy. The second chromosome copy may carry another such “mild” mutation, or it may harbor a “severe” mutation associated with classic CF (2,3). Risk of CF in blood relatives of patients with CBAVD therefore varies based on the nature of the patient’s *CFTR* mutations (2,3).

CBAVD is suspected in males with azoospermia 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 (2). A definitive diagnosis requires detection of at least one pathogenic *CFTR* mutation (2). Because CBAVD is not associated with increased chloride levels in sweat, quantitative pilocarpine iontophoresis – which is

typically used for diagnosis of CF – is not a reliable diagnostic tool for CBAVD (2).

Initial genetic testing is typically based on 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 55% to 97% of *CFTR*-related disease, depending on ethnicity (2-4). 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* (2). Analysis of the 5/7/9T tract is also recommended. The 5T allele is known to modify expression of the R117H mutation (c.350G>A) if located on the same chromosome (*in cis*). In addition, the 5T allele by itself can cause CBAVD in conjunction with a canonical mutation on the other chromosome. The combination of a canonical mutation and the 5T allele can also lead to a mild form of CF (nonclassic CF), depending on the number of TG repeats in the TG tract adjacent to the 5T allele (2,3).

For additional information, see Tables 1-3 below and references 2 and 3.

**Table 1: Disease Facts about *CFTR*-Related Diseases (2-4)**

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

\*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 (2-4)**

<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

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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.