

Before, Between & Beyond Pregnancy
**The National Preconception Curriculum and Resources Guide
for Clinicians**

**Guidance for Preconception Cystic Fibrosis
Carrier Screening**

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Zielenski J. Genotype and phenotype in cystic fibrosis. Respiration 2000;67:117-133.

The cystic fibrosis transmembrane conductance regulator gene (CFTR), located on chromosome 7q31.2, consists of a TATA-less promoter and 27 exons spanning about 215 kb of genomic sequence. It encodes a transmembrane protein that acts as a cAMP-regulated chloride transport channel in epithelial cells. CFTR has also been associated with regulation of other ion channels, membrane trafficking, pH regulation and apoptosis.

The first recognized mutation in the CFTR gene was delta F508 (Δ F508), a 3-bp deletion in exon 10 that leads to a loss of phenylalanine at the amino acid position 508 of the protein product. According to the Cystic Fibrosis Genetic Analysis Consortium (CFGAC), the Δ F508 mutation accounts for approximately 66% of mutations in the CFTR gene. The mutation is most prevalent in Denmark (90%) and least prevalent in Tunisia (17.9%).

All types of mutations have been identified and are distributed throughout the gene. Mutations can be divided into difference classes based on their known or predicted molecular mechanisms and the related impact on the CFTR protein. The classes include:

- Class I: Defective protein synthesis
- Class II: Abnormal processing and trafficking (e.g. Δ F508)
- Class III: Defective protein regulation
- Class IV: Decreased conductance, some residual function (e.g. R117H)
- Class V: Reduced synthesis/trafficking, some residual function
- Class VI: Decreased stability, functional but unstable product

Genotype-phenotype correlations are complicated by the variability in the disease, which is relatively low for sweat gland involvement and male infertility, higher for pancreatic function and very high for respiratory involvement.

Overall, there is a good association between specific CFTR alleles and exocrine pancreatic function. A severe allele (Classes I, II, III, and IV) confers pancreatic insufficiency when paired with another severe allele. The combination of a severe allele and a mild allele (Classes V and VI) most often results in sustained pancreatic function. Expression of other less common gastrointestinal complications (meconium ileus, liver disease, diabetes) is not genotype dependent. Other factors, including secondary genetic and environmental conditions, as well as time, are thought to play a larger role.

With few exceptions, the severity of lung disease cannot be predicted reliably by genotype. Earlier pulmonary function in affected infants may set the course for a slower or faster progression of pulmonary disease. Later pulmonary function may be largely influenced by environmental conditions such as inhaled pollutants and infectious pathogens.

It is important to test patients with obstructive azoospermia and their spouses for CFTR mutations. The genotype in patients with CBAVD often consists of at least one mild Class IV or V missense or splice variant, such as the 5T allele. The 5T allele is present in approximately 40-50% of patients with CBAVD, at a rate up to 6 times higher than the general population. When paired with the R117H mutation and the inheritance of a second CFTR mutation, the 5T allele can be associated with symptoms of classic CF.