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# Cystic Fibrosis, R117H, and the Poly-T/ TG Tracts



In October of 2001, the American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics (ACMG) joined the National Institutes of Heath (NIH) in recommending cystic fibrosis (CF) carrier testing for all Caucasian couples who seek prenatal or pre-conception care. In addition, testing for CF should be made available to other ethnic groups. In pursuing this testing, most individuals will find that they do not carry a CF gene mutation, while some will discover that they are a carrier for this disorder. For a few individuals, the test results may be more difficult to interpret. A brief review of CF may help to better understand those test results.

Cystic fibrosis is a genetic disease which causes changes in secretions of the body. Thick mucus accumulates in the lungs and leads to chronic and severe respiratory problems. Pancreatic ducts are blocked, and this can interfere with digestion. Classic CF typically leads to numerous hospitalizations throughout life. A person's intelligence is not affected. According to the Cystic Fibrosis Foundation, individuals with classic CF have a median life span of 37 years. Death is most often due to respiratory failure.

***In addition to classic CF, there are variant types of CF which have less severe symptoms including milder respiratory problems, sinusitis, or infertility.*** In some males, infertility, caused by congenital bilateral absence of the vas deferens (CBAVD) may be the only clinical finding. CBAVD is a condition that causes a male to be infertile, because the vas deferens, a small tube which allows the sperm to travel from the testis to the penis, is not present. Reproduction for men with CBAVD may still be possible through the use of assisted reproductive technology. There are no other medical problems associated with CBAVD.

Classic CF is inherited as an autosomal recessive genetic disorder caused by mutations in a particular gene (referred to here as the CF gene). Everyone has two copies of this gene; one copy of the gene is inherited from each parent. A person with one normal copy of the gene and one non-working copy of the gene due to a gene mutation is a carrier of CF. In the vast majority of cases, carriers do not have disease symptoms. A person will have **classic** CF if they inherit a non-working copy of the gene from **both** parents.

In 2004, the American College of Medical Genetics recommended that a person undergoing screening for CF should be tested for 23 different gene mutations. One of these gene mutations, called R117H, is present in 0.3% of the Caucasian population, and can result in a wide variety of clinical outcomes depending on what combination of other genetic variations are present. These other genetic differences, called the Poly-T tract and the TG tract, also occur in the CF gene and can sometimes impact its function. The Poly-T tract can occur in 3 forms: 5T, 7T, and 9T. Similarly, the TG tract typically occurs in 3 forms, called TG11, TG12, and TG13. Various combinations of the R117H mutation and these other genetic differences can result in a person's CF gene working improperly, leading to a range of CF clinical presentations, from CBAVD to classic CF. *Please see the chart on the reverse side.*

In a prenatal context, precise predictions as to the clinical outcome of a fetus are not possible, and therefore, counseling couples in this situation is difficult. As a general rule, medical geneticists do not recommend testing for conditions that would not become apparent until adulthood, and

therefore, testing that can reveal information about infertility is controversial. Given this, testing for the 5T allele as well as TG12 and TG13 alleles have not always been recommended. Recently, with greater appreciation for the wide spectrum of clinical implications that can arise with CF gene variation, medical professionals and families are being forced to reconsider the value of prenatal testing. Hopefully, future research will clarify this situation further.

**How Poly-T/ TG Tract Affects CF DNA Test Results**

| One Partner | Other Partner | Offspring Range of Clinic Presentations |
|---|---|---|
| Negative for CF mutations | Negative for CF Mutations | <1/1000 risk for CF or CBAVD |
| Positive for Classic CF mutation | Positive for Classic CF mutation | 1 in 4 risk for Classic CF |
| Positive for Classic CF mutation | Positive for R117H and 5T | Variant to Classical CF<br>Males at increased risk for CBAVD |
| Positive for Classic CF mutation | Positive for R117H and 7T | Females - Asymptomatic<br>Males - Variant CF to CBAVD |
| Positive for Classic CF mutation | Positive for 5T/TG13 or TG12 | Asymptomatic to Variant CF<br>Males at increased risk for CBAVD |
| Positive for Classic CF mutation | Positive for 5T/TG11 | Females - Asymptomatic<br>Males at increased risk for CBAVD |

This table is adapted from Moskowitz SM, Chmiel JF, Sternen DL, Cheng E, Cutting GR (Updated [19 February 2008]). *CFTR-Related Disorders* In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2008. Available at **http://www.genetests.org**. Accessed [31 October 2008], and is based on risk after testing for the ACMG recommended panel of mutations.

**References and Resources:**

Moskowitz SM, Chmiel JF, Sternen DL, Cheng E, Cutting GR (Updated [19 February 2008]). *CFTR-Related Disorders* In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2008. Available at **http://www.genetests.org**. Accessed [31 October 2008].

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http://www.cff.org/AboutCF/