Cystic fibrosis and the polyT/TG tracts

What is cystic fibrosis?

Cystic fibrosis (CF) is an inherited genetic condition, which can cause abnormal mucus production that leads to lung disease and nutritional deficiencies. Genetic changes, also called variants, in the *CFTR* gene interfere with the gene's ability to function. This can lead to both CF and other *CFTR*-related disorders.[1,2]

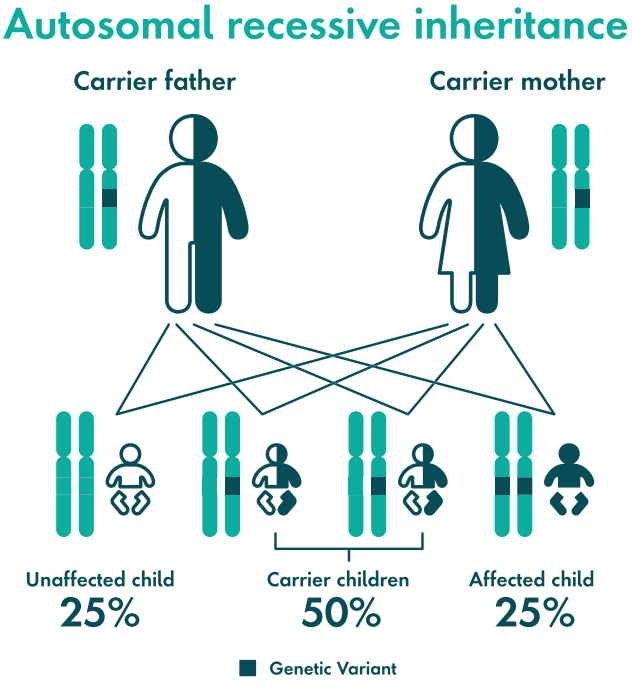
- **CF** is a condition that typically begins in childhood. CF is characterized by multiple health issues including abnormal mucus, which blocks the airways and causes serious lung disease; interference with the production of digestive enzymes, which leads to poor nutrition and growth; and abnormal pancreatic function, which may lead to pancreatic insufficiency or recurrent pancreatitis. The severity of the disease varies from person to person but usually includes all of these symptoms. In addition, affected males typically also experience infertility related to the congenital absence of the vas deferens (CAVD). Patients with CF have variants in **both** copies of their *CFTR* gene that together greatly impair gene function.
- ***CFTR*-related disorders** include lung disease that can vary in severity, chronic sinus infections, recurrent pancreatitis, and/or congenital absence of the vas deferens (CAVD), which causes male infertility. Recurrent pancreatitis may develop in childhood or adolescence and may lead to chronic disease. Patients with *CFTR*-related disorders usually have changes in both copies of their *CFTR* gene that together interfere with gene function to a lesser extent than the variants that cause CF. Depending on the specific clinical and laboratory findings and newborn screening results, these disorders can also be referred to as *CFTR*-related metabolic syndrome (CRMS) or CF screen positive, inconclusive diagnosis (CFSPID).[3]

How is CF inherited?

CF and *CFTR*-related disorders follow an autosomal recessive inheritance pattern. In order for an individual to be affected with an autosomal recessive disorder, they must have two disease-causing genetic variants, one in each copy of the *CFTR* gene.

What does it mean to be a CF carrier?

Individuals with a variant in only one copy of their *CFTR* gene are called "carriers." Although carriers of CFTR variants are not affected with CF,they may have an increased risk for pancreatitis, lung damage (bronchiectasis), and possibly chronic sinus infections. Additional genetic and environmental factors are believed to play a role in determining the risk of developing these complex conditions. Carriers of *CFTR* variants may also be at risk of having children affected with CF or a *CFTR*-related disorder.



Carrier screening for CF

Carrier screening for common genetic conditions, such as CF, allows at-risk reproductive couples to be identified and informed of their reproductive risks and options. When both members of a reproductive couple are found to be carriers of a variant in the *CFTR* gene, they have a **1 in 4 (25%)** risk with each embryo/pregnancy to have a child with two *CFTR* variants who is at risk of developing symptoms.

The specific genetic variants that each parent has helps to determine the possible set of symptoms and severity of disease that their offspring may develop. Traditionally, carrier screening for CF looked at a set of variants known to be associated only with severe disease. As testing technology has improved, it is now possible to identify more variants, including some that have a wider range of possible clinical features.

The polyT tract and TG tract

The *CFTR* gene is impacted by specific variants in regions known as the polyT tract and TG tract.

PolyT tract

The polyT tract is a region of the *CFTR* gene in which the genetic letter T is repeated multiple times. The majority of individuals will have one of three lengths on each copy of the gene: 5T, 7T, and/or 9T. The 5T version is known to disrupt *CFTR* gene function and is associated with the full spectrum of disease, from severe CF to milder *CFTR*-related disorders.[4-8] The 7T and 9T are considered normal, as these versions do not affect *CFTR* function and do not lead to clinical symptoms.

TG tract

The TG tract is a region of the *CFTR* gene next to the polyT tract in which the genetic letters TG are repeated multiple times. The length of the TG tract modifies the potential disease severity and penetrance (i.e., the likelihood of having symptoms) of the 5T variant.[6-11] The length of the TG tract in most people ranges from 10 to 13 TGs. When a 5T is next to a 13TG (TG13-5T) or 12TG (TG12-5T), *CFTR* gene function is most severely disrupted and may be associated with CF. When the 5T is next to the 11TG (TG11-5T), the effect on *CFTR* gene function is much less severe, so it is typically associated with milder *CFTR*-related disorders, not severe CF. The 5T next to a 10TG (TG10-5T) does not affect *CFTR* function and does not lead to clinical symptoms.

Penetrance of the TG-T variants

The possibility of having disease can vary dramatically depending on which of the TG-T variants have been inherited. Several studies show that most (>80%) males who inherit a TG13-5T or TG12-5T from one parent and a CF-causing variant (e.g. Phe508del) from the other parent have symptoms of *CFTR*-related disorders, while a much smaller proportion (~5-10%) of males and females with these variants have been found to have CF.[7,10,11] By contrast, individuals with the TG11-5T variant from one parent and one CF-causing variant from the other parent may have a *CFTR*-related disorder (~30-55% in males and ~5% in females), but have not been observed to have CF.

Unfortunately, our understanding of the likelihood of having disease is limited when a person has two copies of TG13-5T, TG12-5T, or TG11-5T (i.e., homozygotes); there simply have not been enough reported cases. However, we do know that CF and *CFTR*-related disorders are caused when genetic variants limit *CFTR* protein activity, and we know how much of this protein activity is likely to be limited by each of the 5T variants.[4-8] Based on this, we expect a person with two TG13-5T variants to be comparable to someone with one TG13-5T variant and one CF-causing variant, but a person with two TG12-5T variants is expected to be more similar to someone with one TG11-5T variant and one CF-causing variant (i.e., may cause *CFTR*-related disorders, but not likely to be associated with CF).[7,10,11,20] Most individuals with two TG11-5T variants are asymptomatic, although there may be an increased risk for mild *CFTR*-related symptoms, including CAVD and recurrent pancreatitis.[21]

R117H and its impact on the polyT and TG tracts

R117H is another specific variant within the *CFTR* gene. Historically, the R117H variant was thought to be associated with an increased risk of CF and *CFTR*-related disorders.[12,13] However, as testing technology improved, both the TG and polyT tracts have been evaluated more frequently, which has led to an improved understanding of the R117H, 5T, and TG variants.

Recent data suggests that the 5T variant with 11, 12, or 13 TG lengths is the primary cause of CF and *CFTR*-related disorders in people who do not have R117H variant.[7,8,10,11] When the R117H is found on the same chromosome (meaning it is *"in cis"*) with a 5T/TG variant, together these variants may disrupt the *CFTR* gene function more than having that 5T/TG variant alone,[14-17] which may also result in increased severity of CF and *CFTR*-related symptoms.[18,19]

The impact of having the R117H variant on the same chromosome (in *cis*) with a 7T or 9T is currently unclear[16,18,19] and, as a result, Invitae has classified this as a variant of uncertain significance (VUS). Importantly, this is a change from how the R117H has been historically described in the literature but is consistent with Invitae's understanding of the most recently published data.

Symptoms associated with different *CFTR* variants

Individuals who inherit disease-causing variants on both copies of the *CFTR* gene can have a wide range of symptoms, which are determined in part by the specific variants they have inherited (see table below).

Range of clinical presentations seen in individuals who inherit both variants[1-19]

If one partner is positive for:	And the other partner is positive for:	Then possible clinical presentations include:
CF-causing variant (e.g., Phe508del)	CF-causing variant (e.g., Trp1098*)	Cystic fibrosis
CF-causing variant (e.g., Phe508del)	TG13-5T	Cystic fibrosis or *CFTR*-related disorder
CF-causing variant (e.g., Phe508del)	TG12-5T	Cystic fibrosis or *CFTR*-related disorder
CF-causing variant (e.g., Phe508del)	TG11-5T	*CFTR*-related disorder or asymptomatic
TG13-5T or TG12-5T	TG13-5T or TG12-5T	Cystic fibrosis, *CFTR*-related disorder, or asymptomatic
TG13-5T or TG12-5T	TG11-5T	*CFTR*-related disorder or asymptomatic
TG11-5T	TG11-5T	*CFTR*-related disorder or asymptomatic

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