A Quick Guide to the

621+1G→T Mutation
Loss of CFTR activity is the underlying cause of cystic fibrosis (CF)\(^1\)

People with 2 CFTR mutations resulting in loss of CFTR activity generally have a CF phenotype, which may include\(^1\)–\(^6\):
- Elevated sweat chloride (>60 mmol/L)
- Pancreatic insufficiency
- CBAVD\(^a\)
- Lung function decline over time
- *Pseudomonas aeruginosa* colonization

**Spectrum of Phenotypes Associated With Total CFTR Activity\(^1,2\)**

<table>
<thead>
<tr>
<th>Total CFTR Activity % of Normal</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>No CF Disease</td>
</tr>
<tr>
<td>100%</td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>CFTR-related Disorders</td>
<td></td>
</tr>
</tbody>
</table>

Some *CFTR* mutations result in residual or partial CFTR activity\(^3,5\)

Some *CFTR* mutations result in little to no CFTR activity\(^3,5\)

\(^a\)CBAVD, congenital bilateral absence of the vas deferens.

Levels of CFTR activity affect survival in CF

Life expectancy in Western countries (general population born in 2000) is ~79 years.

Between 1993 and 2002, median survival for US patients with genotypes associated with little to no CFTR activity was 36.3 years (95% CI, 35.5 to 37.6 years), while median survival for those having genotypes associated with residual CFTR activity was 50 years (95% CI, 47.1 to 55.9 years).

In this study, patients with the 621+1G→T mutation (Class I) were part of the severely reduced CFTR activity group.

More recent US data (2000-2010) suggest median survival across genotypes continues to improve.

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**Survival Curves by CFTR Activity During a 10-Year Follow-Up (1993-2002) of Patients From the US CFF Registry**


This survival curve represents population-based outcomes. Individual outcomes in cystic fibrosis are variable.

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*Data are from a retrospective study of patients enrolled in the Cystic Fibrosis Foundation patient registry measuring risk of death over a 10-year observation period from 1993 to 2002. Patients were grouped as having a high-risk or low-risk genotype based on the functional effects of their class of CFTR mutation on phenotype and mortality. Patients having a Class I, II, or III mutation on both alleles were considered high-risk, while patients having at least 1 Class IV or V mutation were categorized as low-risk. A total of 15,851 patients had a CFTR genotype of a known functional class; 14,525 (93%) had a high-risk CFTR genotype and 1126 (7%) had a low-risk CFTR genotype. Adapted with permission from McKone EF et al. Chest. 2006;130(5):1441-1447.*

**References:**
In the CFTR2 global database, ~2% of patients with CF have at least 1 copy of the $621+1G\rightarrow T$ mutation.8

The $621+1G\rightarrow T$ mutation has an atypically high frequency on CF alleles in the isolated Saguenay–Lac-Saint-Jean region of northeast Quebec (25%).9

Prevalence of the $621+1G\rightarrow T$ Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

Additional sources report frequency of the $621+1G\rightarrow T$ mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece</td>
<td>10%</td>
</tr>
<tr>
<td>Turkey</td>
<td>3%</td>
</tr>
<tr>
<td>Macedonia</td>
<td>1%</td>
</tr>
<tr>
<td>Romania</td>
<td>1%</td>
</tr>
<tr>
<td>Mexico</td>
<td>1%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1%</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

The 621+1G→T mutation results in defective biosynthesis of the CFTR protein

Illustrative Example of Class I Defect

- 621+1G→T is a splice mutation, which produces a premature stop codon
- The cell cannot synthesize a full-length CFTR protein, a Class I mutation
- As a result, few to no CFTR proteins are present at the apical cell surface

The $621+1G\rightarrow T$ allele results in little to no total CFTR activity$^{1-4}$

Total CFTR activity can be defined as total ion transport mediated by CFTR protein channels at the cell surface, depending on CFTR protein \textit{quantity} and \textit{function}$^4$.

1. A virtual absence of $621+1G\rightarrow T$-CFTR protein \textit{quantity}...

2. ...regardless of \textit{function} since few to no CFTR proteins reach the surface...

3. ...results in little to no total CFTR activity

$621+1G\rightarrow T$ allele results in few to no CFTR channels at apical surface

Defective Synthesis (Class I)

CFTR Function

\begin{itemize}
\item Channel-open Probability
\item Conductance
\end{itemize}

= Total CFTR Activity

\begin{itemize}
\item Channel-open Probability: N/A
\item Conductance: N/A
\end{itemize}

Little to No $621+1G\rightarrow T$-CFTR Activity

CFTR Quantity

\begin{itemize}
\item $621+1G\rightarrow T$ allele results in few to no CFTR channels at apical surface
\end{itemize}

\begin{itemize}
\item Defective Synthesis (Class I)
\end{itemize}

N/A, not applicable.

Both CFTR alleles play a role in determining phenotype or disease severity\(^1-6\)

- A \(621+1G\rightarrow T\) allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1-6\).

- \(621+1G\rightarrow T\) typically results in the indicated phenotypes

### References


Adapted from Zielenski J. Respiration. 2000;67(2):117-133.
621+1G→T in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype \(^1-5\)

**CF Phenotype**

In patients registered in the CFTR2 database with a 621+1G→T mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\):

- Elevated sweat chloride (average): 104 mmol/L
- Lung function decline over time\(^5\)
- Pseudomonas colonization: 69% of patients
- Pancreatic insufficiency: 99% of patients

**References:**


**CFTR Genotype**

- **Allele #1:** 621+1G→T
- **Allele #2:** Little to No CFTR Protein Activity
- **Modifier Genes:** Little to No CFTR Activity
- **Environmental Factors:**
Summary

- Loss of CFTR activity is the underlying cause of CF
- Levels of CFTR activity affect survival in CF
- Country registries listing the $621+1G\rightarrow T$ mutation report 0.2% to 6% prevalence among patients with CF
- The $621+1G\rightarrow T$ mutation results in defective biosynthesis of the CFTR protein
- The $621+1G\rightarrow T$ allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- $621+1G\rightarrow T$ in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype