A Quick Guide to the
3849+10kbC→T
Mutation
Loss of CFTR activity is the underlying cause of cystic fibrosis (CF)\(^1\)

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

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

- People with 2 CFTR mutations resulting in loss of CFTR activity generally have a CF phenotype, which may include\(^1-3,6\):
  - Elevated sweat chloride (>60 mmol/L)
  - Pancreatic insufficiency
  - CBAVD\(^3\)
  - Lung function decline over time
  - *Pseudomonas aeruginosa* colonization

\(\text{CBAVD, congenital bilateral absence of the vas deferens.}\)

**References:**
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 a 3849+10kbC→T mutation (Class V) were part of the residual CFTR activity group.

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

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References:
Country registries listing the $3849+10kbC\rightarrow T$ mutation report 0.2% to 2% prevalence among patients with CF$^{1-9}$

- In the CFTR2 global database, ~1% of patients with CF have at least 1 copy of the $3849+10kbC\rightarrow T$ mutation$^{10}$
- The $3849+10kbC\rightarrow T$ mutation occurs with a 6% frequency on CF alleles of Ashkenazi Jews$^{11}$

### Additional sources report frequency of the $3849+10kbC\rightarrow T$ mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel$^{12}$</td>
<td>5%</td>
</tr>
<tr>
<td>Slovak Republic$^{13}$</td>
<td>3%</td>
</tr>
<tr>
<td>Poland$^{11}$</td>
<td>3%</td>
</tr>
<tr>
<td>Mexico$^{11}$</td>
<td>2%</td>
</tr>
<tr>
<td>Canada$^{12}$</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

References:
8. Australian Cystic Fibrosis Data Registry. Australian Cystic Fibrosis Data Registry 2013–16th Annual Report. © 2015; Cystic Fibrosis Australia; Baulkham Hills NSW, Australia.
3849+10kbC→T is a splicing mutation that results in some functional CFTR at the apical cell surface

Illustrative Example of Class V Defect

- **3849+10kbC→T** is associated with alternative splicing and reduced synthesis of CFTR proteins, typical of a Class V mutation
- This results in some functional CFTR proteins at the apical cell surface

The 3849+10kbC→T allele results in residual total CFTR activity

Total CFTR activity can be defined as total ion transport mediated by CFTR protein channels at the cell surface, depending on CFTR protein quantity and function.\(^3\)

1. \(3849+10kbC\rightarrow T\) reduces CFTR protein quantity...

2. ...but does not appear to reduce CFTR function...

3. ...and results in residual total CFTR activity

\[\text{Total CFTR Activity} = \text{CFTR Quantity} \times \text{CFTR Function} \times \text{Total CFTR Activity} = \text{Residual} \, 3849+10kbC\rightarrow T - \text{CFTR Activity}\]

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

- A \(3849+10\text{kb}C\rightarrow T\) allele results in residual CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1-6\).
- \(3849+10\text{kb}C\rightarrow T\) typically results in the indicated phenotypes.

**3849+10kbC→T** in combination with another allele that produces little to no CFTR activity can result in CF symptoms that may emerge later in life\(^1-5\)

**References:**


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**CF Phenotype**

In patients registered in the CFTR2 database with a **3849+10kbC→T** mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\):

- Sweat chloride levels (average): 66 mmol/L
- Later onset of CF lung disease compared to homozygous *F508del* patients\(^2\)
- Pseudomonas colonization: 57% of patients
- Pancreatic insufficiency: 33% of patients

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**CFTR Genotype**

- **Modifier Genes**
- **Residual Total CFTR Activity**
- **Environmental Factors**
- **Residual CFTR Protein Activity**
- **Little to No CFTR Protein Activity**

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**Allele #1: 3849+10kbC→T**

- Little to No CFTR Protein Activity

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**Allele #2**

- Residual CFTR Protein Activity

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**Residual Total CFTR Activity**
Summary

• Loss of CFTR activity is the underlying cause of CF
• Levels of CFTR activity affect survival in CF
• Country registries listing the 3849+10kbC→T mutation report 0.2% to 2% prevalence among patients with CF
• 3849+10kbC→T is a splicing mutation that results in some functional CFTR at the apical cell surface
• The 3849+10kbC→T allele results in residual total CFTR activity
• Both CFTR alleles play a role in determining phenotype or disease severity
• 3849+10kbC→T in combination with another allele that produces little to no CFTR activity can result in CF symptoms that may emerge later in life