A Quick Guide to the

I507del

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:

- Elevated sweat chloride (>60 mmol/L)
- Pancreatic insufficiency
- CBAVD\(^a\)
- Lung function decline over time
- *Pseudomonas aeruginosa* colonization

\(^a\)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 I507del mutation (Class II) 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**

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 15,651 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.

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

Country registries listing the \textit{I507del} mutation report ≤1% prevalence among patients with CF\textsuperscript{1-6}

Prevalence of the \textit{I507del} Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

- **Australia**: 0.3%
- **US**: 0.8%

**Europe**:
- **Germany**: 0.1%
- **UK**: 0.9%
- **Belgium**: 0.9%
- **France**: 0.7%

- Additional sources report frequency of the \textit{I507del} mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
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<tbody>
<tr>
<td>Mexico\textsuperscript{8}</td>
<td>3%</td>
</tr>
<tr>
<td>Uruguay\textsuperscript{9}</td>
<td>1%</td>
</tr>
<tr>
<td>Spain\textsuperscript{10}</td>
<td>1%</td>
</tr>
<tr>
<td>Ireland\textsuperscript{9}</td>
<td>0.8%</td>
</tr>
<tr>
<td>Greece\textsuperscript{8}</td>
<td>0.7%</td>
</tr>
<tr>
<td>Italy\textsuperscript{8}</td>
<td>0.7%</td>
</tr>
<tr>
<td>Canada\textsuperscript{9}</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

The I507del mutation results in defective processing and trafficking of the CFTR protein.\(^1\)\(^-\)\(^3\)

- I507del has a severe defect in CFTR processing and trafficking with degradation of immature CFTR proteins in the endoplasmic reticulum, typical of a Class II mutation.\(^1\)\(^-\)\(^3\)
- Few to no CFTR channels are present at the apical cell surface.\(^1\)\(^-\)\(^3\)

References:
The *I507del* 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 quantity and function.\(^4\)

1. Significantly reduced *I507del*-CFTR protein quantity...
2. ...regardless of function since few to no CFTR proteins reach the surface...
3. ...results in little to no total CFTR activity

Both *CFTR* alleles play a role in determining phenotype or disease severity\(^1-5\)

- An *I507del* allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1-5\).
- *I507del* typically results in the indicated phenotypes.

<table>
<thead>
<tr>
<th>Allele 1</th>
<th>Total CFTR Activity</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Normal</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>Little to None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allele 2</th>
<th>Total CFTR Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>Little to None</td>
</tr>
<tr>
<td>Little to None</td>
<td>Residual</td>
</tr>
<tr>
<td>Little to None</td>
<td>Little to None</td>
</tr>
</tbody>
</table>


**I507del** in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype

**CFTR Genotype**
- Allele #1: **I507del**
- Allele #2
  - Little to No CFTR Protein Activity
  - Little to No CFTR Protein Activity

**Modifier Genes**
- Little to No Total CFTR Activity

**Environmental Factors**
- CF Phenotype
  - In patients registered in the CFTR2 database with an I507del mutation on 1 allele and a pancreatic insufficient mutation on the second allele
  - Elevated sweat chloride (average): 102 mmol/L
  - Lung function decline over time
  - Pseudomonas colonization: 62% of patients
  - Pancreatic insufficiency: 98% of patients

Summary

- Loss of CFTR activity is the underlying cause of CF
- Levels of CFTR activity affect survival in CF
- Country registries listing the *I507del* mutation report ≤1% prevalence among patients with CF
- The *I507del* mutation results in defective processing and trafficking of the CFTR protein
- The *I507del* allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- *I507del* in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype