A Quick Guide to the

3659delC 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</th>
<th>% of Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- **No CF Disease**
- **CFTR-related Disorders**
- **Cystic Fibrosis**

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

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

- 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\(^a\)
  - 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 3659delC 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.

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 (91%) had a high-risk CFTR genotype and 1126 (7%) had a low-risk CFTR genotype.

Country registries listing the 3659delC mutation report ≤1% prevalence among patients with CF

Prevalence of the 3659delC Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

Europe:
UK²: 0.9%
Belgium³: 0.7%
France⁴: 0.4%

US¹: 0.7%
Aus⁵: 0.3%

Additional sources report frequency of the 3659delC mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden⁷</td>
<td>5%</td>
</tr>
<tr>
<td>Estonia⁷</td>
<td>2%</td>
</tr>
<tr>
<td>Denmark⁷</td>
<td>0.6%</td>
</tr>
<tr>
<td>Germany⁷</td>
<td>0.6%</td>
</tr>
<tr>
<td>Netherlands⁸</td>
<td>0.3%</td>
</tr>
<tr>
<td>Norway⁸</td>
<td>0.2%</td>
</tr>
<tr>
<td>Canada⁸</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

The *3659delC* mutation results in defective biosynthesis of the CFTR protein\(^1\text{-}\text{3}\)

- *3659delC* is a frameshift mutation, which produces a premature stop codon\(^1\text{,}^2\)
- The cell cannot synthesize full-length CFTR proteins, a Class I mutation\(^1\text{,}^3\)
- As a result, few to no CFTR proteins are present at the apical cell surface\(^3\)

**Illustrative Example of Class I Defect**

The 3659delC 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. A virtual absence of 3659delC-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

N/A, not applicable.

Both *CFTR* alleles play a role in determining phenotype or disease severity\textsuperscript{1-6}

- A \textit{3659delC} allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\textsuperscript{1-6}

- \textit{3659delC} typically results in the indicated phenotypes


Adapted from Zielenski J. Respiration. 2000;67(2):117-133.
3659delC in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype.1-6

CF Phenotype

In patients registered in the CFTR2 database with a 3659delC mutation on 1 allele and a pancreatic insufficient mutation on the second allele:

- Elevated sweat chloride (average): 105 mmol/L
- Lung function decline over time4
- Pseudomonas colonization: 66% 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 3659delC mutation report ≤1% prevalence among patients with CF
- The 3659delC mutation results in defective biosynthesis of the CFTR protein
- The 3659delC allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- 3659delC in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype