A Quick Guide to the

F508del Mutation
Loss of CFTR activity is the underlying cause of cystic fibrosis (CF)\(^1\)

<table>
<thead>
<tr>
<th>Spectrum of Phenotypes Associated With Total CFTR Activity(^{1,2})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total CFTR Activity</strong> % of Normal</td>
</tr>
<tr>
<td><strong>0%</strong></td>
</tr>
<tr>
<td><strong>No CF Disease</strong></td>
</tr>
<tr>
<td><strong>Cystic Fibrosis</strong></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\(^a\)
  - Lung function decline over time
  - *Pseudomonas aeruginosa* colonization

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

**References:**
Levels of CFTR activity affect survival in CF

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

- 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 F508del 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.

Data 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.

References:
The \textit{F508del} mutation is the most common \textit{CFTR} mutation in the world\textsuperscript{1-12}

Prevalence of the \textit{F508del} Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

- In a number of countries, the prevalence of the homozygous \textit{F508del} genotype among patients with CF is \textgreater 40%:
  - 57% in Ireland\textsuperscript{5}
  - 54% in Netherlands\textsuperscript{6}
  - 52% in New Zealand\textsuperscript{10}
  - 51% in the United Kingdom and Australia\textsuperscript{4,11}
  - 50% in Canada\textsuperscript{1}
  - 47% in the United States and Germany\textsuperscript{2,8}
  - 42% in France\textsuperscript{9}

- In the CFTR2 global database, \textasciitilde 73% of patients with CF have at least 1 copy of the \textit{F508del} mutation\textsuperscript{12}:
  - \textasciitilde 38% of these patients are homozygous \textit{F508del} \textsuperscript{12}.

The *F508del* mutation results in multiple CFTR protein defects\(^1-\)\(^5\)

• *F508del* 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. Few to no CFTR channels are present at the apical cell surface\(^2-\)\(^5\).

• *F508del* has also been shown to be a Class III mutation, resulting in CFTR proteins with reduced channel-open probability (or gating)\(^1,\)\(^2\).

• *F508del* also manifests characteristics of a Class VI mutation so that the few CFTR proteins that reach the cell surface have decreased surface stability\(^3,\)\(^4\).

The *F508del* allele results in little to no total CFTR activity\(^1\text{-}^5\)

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. Significantly reduced *F508del*-CFTR protein quantity...
2. ...and severely reduced function due to decreased channel-open probability...
3. ...results in little to no total CFTR activity

### References:
Both *CFTR* alleles play a role in determining phenotype or disease severity$^{1-7}$

<table>
<thead>
<tr>
<th>Allele 1: Total CFTR Activity</th>
<th>Normal</th>
<th>Normal</th>
<th>Normal</th>
<th>Residual</th>
<th>Residual</th>
<th>Little to None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele 2: Total CFTR Activity</td>
<td>Normal</td>
<td>Residual</td>
<td>Little to None</td>
<td>Residual</td>
<td>Little to None</td>
<td>Little to None</td>
</tr>
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</table>

- An *F508del* allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele$^{1-7}$.

- *F508del* typically results in the indicated phenotypes.


**F508del** in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype\(^1\text{-}^6\)

**CFTR Genotype**

- **Allele #1:** F508del
- **Allele #2:** Little to No CFTR Protein Activity
- **Modifier Genes:** Little to No Total CFTR Activity
- **Environmental Factors:** Little to No CFTR Protein Activity

**CF Phenotype**

In patients registered in the CFTR2 database with an **F508del** mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\)

- Elevated sweat chloride (average): 102 mmol/L
- Lung function decline over time\(^2,3\)
- Pseudomonas colonization: 59% of patients
- Pancreatic insufficiency: 98% of patients

**References:**
Summary

- Loss of CFTR activity is the underlying cause of CF
- Levels of CFTR activity affect survival in CF
- The *F508del* mutation is the most common CFTR mutation in the world
- The *F508del* mutation results in multiple CFTR protein defects
- The *F508del* allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- *F508del* in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype