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\(^1-3,6\)
  – Elevated sweat chloride (>60 mmol/L)
  – Pancreatic insufficiency
  – CBAVD\(^a\)
  – Lung function decline over time
  – *Pseudomonas aeruginosa* colonization

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\(\text{Spectrum of Phenotypes Associated With Total CFTR Activity}^{1,2}\)

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

\(^a\)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).

No patients with the CFTRdele2,3 mutation were included in this US registry study. CFTRdele2,3 is a Class I mutation, resulting in severely reduced CFTR activity.

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**

- 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).
- No patients with the CFTRdele2,3 mutation were included in this US registry study. CFTRdele2,3 is a Class I mutation, resulting in severely reduced CFTR activity.
- More recent US data (2000-2010) suggest median survival across genotypes continues to improve.
Only the Belgian country registry reports any prevalence of the \textit{CFTRdele2,3} mutation among patients with CF\textsuperscript{1}

Prevalence of the \textit{CFTRdele2,3} Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

- In the CFTR2 global database, \textasciitilde0.5\% of patients with CF have at least 1 copy of the \textit{CFTRdele2,3} mutation\textsuperscript{2}

- \textit{CFTRdele2,3} is prevalent among patients with CF of Slavic descent\textsuperscript{3,4}

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech Republic\textsuperscript{5}</td>
<td>6%</td>
</tr>
<tr>
<td>Russia\textsuperscript{5}</td>
<td>5%</td>
</tr>
<tr>
<td>Belarus\textsuperscript{5}</td>
<td>3%</td>
</tr>
<tr>
<td>Lithuania\textsuperscript{5}</td>
<td>2%</td>
</tr>
<tr>
<td>Poland\textsuperscript{5}</td>
<td>2%</td>
</tr>
<tr>
<td>Canada\textsuperscript{6}</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

The $\text{CFTRdele2,3}$ mutation results in defective biosynthesis of the CFTR protein$^{1-4}$

- $\text{CFTRdele2,3}$ is a frameshift mutation, which produces a premature stop codon$^{1-3}$
- The cell cannot synthesize a full-length CFTR protein, a Class I mutation$^{2,3}$
- As a result, few to no CFTR proteins are present at the apical cell surface$^{2-4}$

The CFTRdele2,3 allele results in little to no total CFTR activity\textsuperscript{1-5}

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\textsuperscript{5}.

1. Defective Synthesis (Class I)

2. A virtual absence of CFTRdele2,3-CFTR protein quantity...

3. ...regardless of function since few to no CFTR proteins reach the surface...

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

Both *CFTR* alleles play a role in determining phenotype or disease severity\(^1\text{-}^7\)

- A *CFTR*\(_{dele2,3}\) allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1,^2,^4\text{-}^7\).

- *CFTR*\(_{dele2,3}\) typically results in the indicated phenotypes

\[\begin{array}{c|c|c|c}
\text{Total CFTR Activity} & \text{Allele 1} & \text{Allele 2} \\
\hline
\text{Normal} & \text{Normal} & \text{Normal} \\
\text{Residual} & \text{Residual} & \text{Residual} \\
\text{Little to None} & \text{Little to None} & \text{Little to None} \\
\end{array}\]

**CFTRdele2,3** in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype\(^1-4\)

### CF Phenotype

In patients registered in the CFTR2 database with a **CFTRdele2,3** mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\)

- Elevated sweat chloride (average): 99 mmol/L
- Lung function decline over time
- Pseudomonas colonization: 43% of patients
- Pancreatic insufficiency: 99% of patients

### References

Summary

- Loss of CFTR activity is the underlying cause of CF
- Levels of CFTR activity affect survival in CF
- Only the Belgian country registry reports any prevalence of the \( CFTR^{dele2,3} \) mutation among patients with CF
- The \( CFTR^{dele2,3} \) mutation results in defective biosynthesis of the CFTR protein
- The \( CFTR^{dele2,3} \) allele results in little to no total CFTR activity
- Both \( CFTR \) alleles play a role in determining phenotype or disease severity
- \( CFTR^{dele2,3} \) in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype