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

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

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

\(^a\)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)

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

Country registries listing the \textit{W1282X} mutation report 0.5\% to 2\% prevalence among patients with CF\textsuperscript{1-8}

- In the CFTR2 global database, \textasciitilde{}2\% of patients with CF have at least 1 copy of the \textit{W1282X} mutation\textsuperscript{9}
- The frequency of the \textit{W1282X} mutation is high among Ashkenazi-Jewish and Middle Eastern populations\textsuperscript{10}

Additional sources report frequency of the \textit{W1282X} mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel\textsuperscript{11}</td>
<td>22%</td>
</tr>
<tr>
<td>Lebanon\textsuperscript{12}</td>
<td>20%</td>
</tr>
<tr>
<td>Argentina\textsuperscript{12}</td>
<td>4%</td>
</tr>
<tr>
<td>Latvia\textsuperscript{12}</td>
<td>3%</td>
</tr>
<tr>
<td>Tunisia\textsuperscript{12}</td>
<td>3%</td>
</tr>
<tr>
<td>Hungary\textsuperscript{12}</td>
<td>2%</td>
</tr>
<tr>
<td>Canada\textsuperscript{13}</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

The \textit{W1282X} mutation results in defective biosynthesis of the CFTR protein\textsuperscript{1-4}

\begin{itemize}
  \item \textit{W1282X} is a nonsense mutation, which produces a premature stop codon\textsuperscript{1-4}.
  \item The cell cannot synthesize a full-length CFTR protein, a Class I mutation\textsuperscript{1-4}.
  \item As a result, few to no CFTR proteins are present at the apical cell surface\textsuperscript{1-4}.
\end{itemize}

\textbf{Illustrative Example of Class I Defect}

The **W1282X** allele results in little to no total CFTR activity\(^1\)\(^-\)\(^5\)

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**\(^5\).

1. **Defective Synthesis** (Class I) - *W1282X* allele results in few to no CFTR channels at apical surface

2. **CFTR Function** - Channel-open Probability: N/A \(\times\) Conductance: N/A

3. **Total CFTR Activity** - Little to No \(W1282X\)-CFTR Activity

A virtual absence of \(W1282X\)-CFTR protein quantity... 
...regardless of function since few to no CFTR proteins reach the surface... 
...results in little to no total CFTR activity

N/A, not applicable.

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

- A *W1282X* allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1\text{-}^6\)
- *W1282X* typically results in the indicated phenotypes

*W1282X* in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype\(^1\)-\(^5\)

**CFTR Genotype**

- **Allele #1:** *W1282X*
- **Allele #2:** Little to No CFTR Protein Activity

**CF Phenotype**

In patients registered in the CFTR2 database with a *W1282X* mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\)

- Elevated sweat chloride (average): 103 mmol/L
- Lung function decline over time\(^2\)
- Pseudomonas colonization: 55% of patients
- Pancreatic insufficiency: 98% of patients

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**References:**

Summary

• Loss of CFTR activity is the underlying cause of CF
• Levels of CFTR activity affect survival in CF
• Country registries listing the W1282X mutation report 0.5% to 2% prevalence among patients with CF
• The W1282X mutation results in defective biosynthesis of the CFTR protein
• The W1282X allele results in little to no total CFTR activity
• Both CFTR alleles play a role in determining phenotype or disease severity
• W1282X in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype