A Quick Guide to the 2183AA→G 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:\(^1\)\(^-\)\(^3\)\(^,\)\(^6\)

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

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### 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

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 2183AA→G mutation were included in this US registry study. 2183AA→G 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.
Country registries listing the $2183AA\rightarrow G$ mutation report ≤1% prevalence among patients with CF$^{1-5}$

In the CFTR2 global database, ~0.6% of patients with CF have at least 1 copy of the $2183AA\rightarrow G$ mutation$^6$

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey$^7$</td>
<td>3%</td>
</tr>
<tr>
<td>Italy$^8$</td>
<td>2%</td>
</tr>
<tr>
<td>Greece$^7$</td>
<td>2%</td>
</tr>
<tr>
<td>Russia$^7$</td>
<td>1%</td>
</tr>
<tr>
<td>Mexico$^7$</td>
<td>1%</td>
</tr>
<tr>
<td>Spain$^9$</td>
<td>0.7%</td>
</tr>
<tr>
<td>Germany$^7$</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Additional sources report frequency of the $2183AA\rightarrow G$ mutation on CF alleles

The $2183AA\rightarrow G$ mutation results in defective biosynthesis of the CFTR protein$^{1-4}$

- $2183AA\rightarrow G$ is a frameshift mutation, which produces a premature stop codon$^{1,2}$
- The cell cannot synthesize a full-length CFTR protein, a Class I mutation$^{1,3}$
- As a result, few to no CFTR proteins are present at the apical cell surface$^{3,4}$
The **2183AA→G** 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 \textit{quantity} and \textit{function}.\(^4\)

<table>
<thead>
<tr>
<th>CFTR Function</th>
<th>Total CFTR Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channel-open Probability</td>
<td>\x</td>
</tr>
<tr>
<td>Conductance</td>
<td>=</td>
</tr>
</tbody>
</table>

\[ \text{Total CFTR Activity} = \text{CFTR Quantity} \times \text{CFTR Function} \]

\(\text{CFTR Quantity} \times \text{CFTR Function} = \text{Total CFTR Activity}\)

1. **Defective Synthesis (Class I)**

2. A virtual absence of 2183AA→G-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

\(\text{N/A, not applicable.}\)

Both *CFTR* alleles play a role in determining phenotype or disease severity\textsuperscript{1-7}

- A $2183\text{AA} \rightarrow \text{G}$ 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{1-7}
- $2183\text{AA} \rightarrow \text{G}$ typically results in the indicated phenotypes

**References:**
2183AA→G in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype¹⁻⁶.

**CFTR Genotype**

- **Allele #1:** 2183AA→G
- **Allele #2:** 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 a 2183AA→G mutation on 1 allele and a pancreatic insufficient mutation on the second allele¹:

- Elevated sweat chloride (average): 102 mmol/L
- Lung function decline over time
- Pseudomonas colonization: 46% of patients
- Pancreatic insufficiency: 96% of patients

**References:**
Summary

- Loss of CFTR activity is the underlying cause of CF.
- Levels of CFTR activity affect survival in CF.
- Country registries listing the $2183AA\rightarrow G$ mutation report ≤1% prevalence among patients with CF.
- The $2183AA\rightarrow G$ mutation results in defective biosynthesis of the CFTR protein.
- The $2183AA\rightarrow G$ allele results in little to no total CFTR activity.
- Both CFTR alleles play a role in determining phenotype or disease severity.
- $2183AA\rightarrow G$ in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype.