A Quick Guide to the 1717-1G→A 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\(^3\)
- 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 % of Normal</th>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CF Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFTR-related Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Total CFTR Activity

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

Total CFTR Activity

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\(^{a}\)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 1717-1G→A 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.

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References:
Country registries listing the $1717-1G\rightarrow A$ mutation report 0.1% to 3% prevalence among patients with CF. 

Prevalence of the $1717-1G\rightarrow A$ Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

**References:**

In the CFTR2 global database, ~1% of patients with CF have at least 1 copy of the $1717-1G\rightarrow A$ mutation. 

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland</td>
<td>2%</td>
</tr>
<tr>
<td>Italy</td>
<td>2%</td>
</tr>
<tr>
<td>Hungary</td>
<td>2%</td>
</tr>
<tr>
<td>Poland</td>
<td>2%</td>
</tr>
<tr>
<td>Canada</td>
<td>0.4%</td>
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</tbody>
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Additional sources report frequency of the $1717-1G\rightarrow A$ mutation on CF alleles.
The 1717-1G→A mutation results in defective biosynthesis of the CFTR protein

- 1717-1G→A is a splice mutation, which produces a premature stop codon
- The cell cannot synthesize a full-length CFTR protein, a Class I mutation
- As a result, few to no CFTR proteins are present at the apical cell surface

The $1717-1G\rightarrow A$ 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.$^5$

<table>
<thead>
<tr>
<th>CFTR Quantity</th>
<th>CFTR Function</th>
<th>Total CFTR Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1717-1G\rightarrow A$ allele results in few to no CFTR channels at apical surface</td>
<td>Channel-open Probability: N/A</td>
<td>Little to No $1717-1G\rightarrow A$–CFTR Activity</td>
</tr>
<tr>
<td>Channel-open Probability: N/A</td>
<td>Conductance: N/A</td>
<td></td>
</tr>
</tbody>
</table>

A virtual absence of $1717-1G\rightarrow A$–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\(^1-6\)

- A 1717-1G→A allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1-6\)
- 1717-1G→A typically results in the indicated phenotypes

<table>
<thead>
<tr>
<th>Allele 1</th>
<th>Total CFTR Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allele 2</th>
<th>Total CFTR Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Residual</td>
</tr>
</tbody>
</table>


1717-1G→A in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype.1-5

**CF Phenotype**

In patients registered in the CFTR2 database with a 1717-1G→A mutation on 1 allele and a pancreatic insufficient mutation on the second allele:

- Elevated sweat chloride (average): 103 mmol/L
- Lung function decline over time
- Pseudomonas colonization: 54% of patients
- Pancreatic insufficiency: 97% 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 1717-1G→A mutation report 0.1% to 3% prevalence among patients with CF
- The 1717-1G→A mutation results in defective biosynthesis of the CFTR protein
- The 1717-1G→A allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- 1717-1G→A in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype