A Quick Guide to the

1898+1G→A

Mutation

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

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

<table>
<thead>
<tr>
<th>Total CFTR Activity</th>
<th>% of Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CF Disease</td>
<td>0%</td>
</tr>
<tr>
<td>CFTR-related Disorders</td>
<td>3-5%</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>100%</td>
</tr>
</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

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\(^a\)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)
  - No patients with the 1898+1G→A mutation were included in this US registry study. 1898+1G→A 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

Data are 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 1,126 (7%) had a low-risk CFTR genotype.

Country registries listing the 1898+1G→A mutation report ≤1% prevalence among patients with CF1-4

Prevalence of the 1898+1G→A Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

- In the CFTR2 global database, ~0.5% of patients with CF have at least 1 copy of the 1898+1G→A mutation5

Additional sources report frequency of the 1898+1G→A mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romania5</td>
<td>1%</td>
</tr>
<tr>
<td>Slovakia6</td>
<td>1%</td>
</tr>
<tr>
<td>Canada7</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

The 1898+1G→A mutation results in defective biosynthesis of the CFTR protein\textsuperscript{1-5}

- 1898+1G→A is a splice mutation\textsuperscript{1,2}
- While there is no stop codon introduced, the cell cannot synthesize a full-length CFTR protein, a Class I mutation\textsuperscript{1-5}
- As a result, few to no CFTR proteins are present at the apical cell surface\textsuperscript{1,4,5}

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\end{itemize}

The 1898+1G→A 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}

A virtual absence of 1898+1G→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\(^1\)–\(^5\)

- An **1898+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\(^1\)–\(^5\).
- **1898+1G→A** typically results in the indicated phenotypes.

**References:**
1898+1G→A in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype\textsuperscript{1-7}

**CFTR Genotype**

- Allele #1: 1898+1G→A
- 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 an 1898+1G→A mutation on 1 allele and a pancreatic insufficient mutation on the second allele\textsuperscript{1}

- Elevated sweat chloride (average): 103 mmol/L
- Lung function decline over time
- Pseudomonas colonization: 69% 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
- Country registries listing the $1898+1G\rightarrow A$ mutation report $\leq 1\%$ prevalence among patients with CF
- The $1898+1G\rightarrow A$ mutation results in defective biosynthesis of the CFTR protein
- The $1898+1G\rightarrow A$ allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- $1898+1G\rightarrow A$ in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype