A Quick Guide to the G551D Mutation
Loss of CFTR activity is the underlying cause of cystic fibrosis (CF)\textsuperscript{1}

People with 2 CFTR mutations resulting in loss of CFTR activity generally have a CF phenotype, which may include:\textsuperscript{1-3,6}
- Elevated sweat chloride (>60 mmol/L)
- Pancreatic insufficiency
- CBAVD\textsuperscript{3}
- Lung function decline over time
- \textit{Pseudomonas aeruginosa} colonization

Some CFTR mutations result in residual or partial CFTR activity\textsuperscript{3-5}

Some CFTR mutations result in little to no CFTR activity\textsuperscript{3-5}

\textsuperscript{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 G551D mutation (Class III) 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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**Adapted from McKone EF et al. Chest. 2006;130(5):1441-1447.**

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

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**G551D** is the third most common CFTR mutation in the world¹

Prevalence of the G551D Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

- **Can²**: 3%
- **US³**: 4%
- **Brazil**: 0.3%

Europe:
- Ireland⁵: 15%
- UK⁶: 6%
- Germany⁷: 2%
- France⁸: 1%
- Belgium⁹: 0.3%

· In the CFTR2 global database, ~3% of patients with CF have at least 1 copy of the G551D mutation¹

Additional sources report frequency of the G551D mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech Republic¹²</td>
<td>4%</td>
</tr>
<tr>
<td>Hungary¹²</td>
<td>1%</td>
</tr>
<tr>
<td>Croatia¹²</td>
<td>1%</td>
</tr>
<tr>
<td>Austria¹²</td>
<td>1%</td>
</tr>
<tr>
<td>Norway¹²</td>
<td>1%</td>
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The G551D mutation greatly reduces channel-open probability in the CFTR protein\textsuperscript{1,2}

- G551D is a missense mutation that results in CFTR proteins with a severe reduction in channel-open probability (or gating), a Class III mutation\textsuperscript{1,3}
The **G551D** 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 **quantity** and **function**.\(^4\)

1. Although CFTR protein **quantity** is normal…
2. …**function** is severely reduced due to decreased channel-open probability…
3. …and results in little to no total CFTR activity

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

- A *G551D* allele results in little to no *CFTR* activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1\text{-}^6\).

- *G551D* typically results in the indicated phenotypes

![Diagram showing total CFTR activity and its relation to disease phenotypes.


**G551D** in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype.\(^1\)\(^-\)\(^4\)

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**CFTR Genotype**

- **Allele #1: G551D**
  - Little to No CFTR Protein Activity

- **Allele #2**
  - Little to No CFTR Protein Activity

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**CF Phenotype**

In patients registered in the CFTR2 database with a **G551D** mutation on 1 allele and a pancreatic insufficient mutation on the second allele:\(^1\):

- Elevated sweat chloride (average): 104 mmol/L
- Lung function decline over time
- Pseudomonas colonization: 61% of patients
- Pancreatic insufficiency: 96% 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
• G551D is the third most common CFTR mutation in the world
• The G551D mutation greatly reduces channel-open probability in the CFTR protein
• The G551D allele results in little to no total CFTR activity
• Both CFTR alleles play a role in determining phenotype or disease severity
• G551D in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype