A Quick Guide to the G542X 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

\(^a\)CBAVD, congenital bilateral absence of the vas deferens.


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>5-36%</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>100%</td>
</tr>
</tbody>
</table>

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

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

\(^a\)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 G542X 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.

Survival Curves by CFTR Activity During a 10-Year Follow-Up (1993-2002) of Patients From the US CFF Registry

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 15,851 patients had a CFTR genotype of a known functional class; 14,525 (93%) had a high-risk CFTR genotype and 1126 (7%) had a low-risk CFTR genotype.

References:
**G542X** is the second most common **CFTR** mutation in the world

In the CFTR2 global database, ~4% of patients with CF have at least 1 copy of the **G542X** mutation.

The **G542X** mutation was found at a higher frequency in certain regions of Spain, including the Canary Islands (25%), Murcia (21%), Navarra (17%), and Valencia (11%).

Prevalence of the **G542X** Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

- **Brazil**: 4%
- **Can**: 4%
- **US**: 5%
- **Aus**: 3%
- **Europe**:
  - Belgium: 5%
  - UK: 4%
  - France: 3%
  - Germany: 2%
  - Netherlands: 2%
  - Ireland: 2%
- **New Zealand**: 3%

Additional sources report frequency of the **G542X** mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tunisia</td>
<td>9%</td>
</tr>
<tr>
<td>Spain</td>
<td>8%</td>
</tr>
<tr>
<td>Greece</td>
<td>4%</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>4%</td>
</tr>
<tr>
<td>Austria</td>
<td>3%</td>
</tr>
<tr>
<td>Italy</td>
<td>3%</td>
</tr>
</tbody>
</table>

The G542X mutation results in defective biosynthesis of the CFTR protein\textsuperscript{1-3}

- G542X is a nonsense mutation, which produces a premature stop codon\textsuperscript{1-3}
- The cell cannot synthesize a full-length CFTR protein, a Class I mutation\textsuperscript{1-2}
- As a result, few to no CFTR proteins are present at the apical cell surface\textsuperscript{1-2}

The *G542X* allele results in little to no total CFTR activity\textsuperscript{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.\textsuperscript{4}

\begin{align*}
\text{CFTR Quantity} \times \text{CFTR Function} \times \text{Conductance} &= \text{Total CFTR Activity} \\
\text{G542X allele results in few to no CFTR channels at apical surface} \times \text{Channel-open Probability: N/A} \times \text{Conductance: N/A} &= \text{Little to No G542X-CFTR Activity}
\end{align*}

1. Defective Synthesis (Class I)
2. A virtual absence of G542X-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

N/A, not applicable.

Both CFTR alleles play a role in determining phenotype or disease severity\textsuperscript{1-6}

- A G542X 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{1-6}
- G542X typically results in the indicated phenotypes

Adapted from Zielenski J. Respiration. 2000;67(2):117-133.

**G542X** in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype.1-5

**CFTR Genotype**

- **Allele #1:** G542X
- **Allele #2:**

**CF Phenotype**

In patients registered in the CFTR2 database with a G542X 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: 56% of patients
- Pancreatic insufficiency: 98% of patients

**References:**
Summary

- Loss of CFTR activity is the underlying cause of CF
- Levels of CFTR activity affect survival in CF
- G542X is the second most common CFTR mutation in the world
- The G542X mutation results in defective biosynthesis of the CFTR protein
- The G542X allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- G542X in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype