A Quick Guide to the G85E 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 include¹⁻³,⁶:
- Elevated sweat chloride (>60 mmol/L)
- Pancreatic insufficiency
- CBAVD³
- Lung function decline over time
- *Pseudomonas aeruginosa* colonization

### Spectrum of Phenotypes Associated With Total CFTR Activity¹,²

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

Some CFTR mutations result in residual or partial CFTR activity³⁻⁵

Some CFTR mutations result in little to no CFTR activity³⁻⁵

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³CBAVD, 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)
  - In this study, patients with the G85E mutation (Class II) were part of the severely reduced CFTR activity group
- More recent US data (2000-2010) suggest median survival across genotypes continues to improve

References:

Adapted with permission 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.

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:
Country registries listing the G85E mutation report <1% prevalence among patients with CF\textsuperscript{1-7}

Prevalence of the G85E Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

- In the CFTR2 global database, ~0.7% of patients with CF have at least 1 copy of the G85E mutation\textsuperscript{8}

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uruguay\textsuperscript{9}</td>
<td>4%</td>
</tr>
<tr>
<td>Tunisia\textsuperscript{10}</td>
<td>3%</td>
</tr>
<tr>
<td>Ecuador\textsuperscript{9}</td>
<td>2%</td>
</tr>
<tr>
<td>Portugal\textsuperscript{9}</td>
<td>2%</td>
</tr>
<tr>
<td>Greece\textsuperscript{10}</td>
<td>1%</td>
</tr>
<tr>
<td>Turkey\textsuperscript{10}</td>
<td>1%</td>
</tr>
<tr>
<td>Spain\textsuperscript{11}</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Additional sources report frequency of the G85E mutation on CF alleles

References:
The **G85E** mutation results in defective processing and trafficking of the CFTR protein\(^1-3\)

- **G85E** is a missense mutation resulting in a severe defect in CFTR processing and trafficking, typical of a Class II mutation\(^1-3\).
- Due to degradation of immature CFTR proteins in the endoplasmic reticulum, they fail to reach the apical cell surface\(^3\).

**Illustrative Example of Class II Defect**

- **CFTR Synthesis**: mRNA → Transcription → DNA
- **CFTR Processing**: mRNA → Translation → Immature CFTR
- **CFTR Trafficking**: Immature CFTR → Endoplasmic reticulum → Posttranslational modification → Golgi complex → Proteosome → Endoplasmic reticulum
- **CFTR Turnover**

The *G85E* 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}

1. Significantly reduced G85E-CFTR protein quantity...

2. ...regardless of function since few to no CFTR proteins reach the surface...

3. ...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 *G85E* allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele. Patients with a *G85E* mutation may have variability in pancreatic sufficiency\(^1\),\(^3\)-\(^6\).
- *G85E* typically results in the indicated phenotypes.

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**References:**

**G85E** in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype\(^1-6\)

**CFTR Genotype**

- **Allele #1:** G85E
  - Little to No CFTR Protein Activity
  - Little to No Total CFTR Activity

- **Modifier Genes**

- **Environmental Factors**

**CF Phenotype**

In patients registered in the CFTR2 database with a G85E mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\):

- Elevated sweat chloride (average): 100 mmol/L
- Lung function decline over time
- Pseudomonas colonization: 55% of patients
- Pancreatic insufficiency: 86% 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 G85E mutation report <1% prevalence among patients with CF
• The G85E mutation results in defective processing and trafficking of the CFTR protein
• The G85E allele results in little to no total CFTR activity
• Both CFTR alleles play a role in determining phenotype or disease severity
• G85E in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype