A Quick Guide to the R347P 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

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 an R347P mutation (Class IV) were part of the residual CFTR activity group
- More recent US data (2000-2010) suggest median survival across genotypes continues to improve

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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.

Country registries listing the $R347P$ mutation report ≤1% prevalence among patients with CF$^{1-6}$

- In the CFTR2 global database, ~0.6% of patients with CF have at least 1 copy of the $R347P$ mutation$^7$
- The $R347P$ mutation has been found on alleles of German, Slovak, and Czech patients with CF$^8$

Prevalence of the $R347P$ Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

![Map showing prevalence of R347P mutation around the world](image)

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulgaria$^9$</td>
<td>2%</td>
</tr>
<tr>
<td>Slovakia$^9$</td>
<td>1%</td>
</tr>
<tr>
<td>Slovenia$^9$</td>
<td>1%</td>
</tr>
<tr>
<td>Czech Republic$^9$</td>
<td>0.8%</td>
</tr>
<tr>
<td>Switzerland$^9$</td>
<td>0.6%</td>
</tr>
<tr>
<td>Canada$^{10}$</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Additional sources report frequency of the $R347P$ mutation on CF alleles

**References:**
The *R347P* mutation results in a CFTR protein with defective conductance\(^1\)-\(^3\)

\(\text{CFTR Synthesis} \rightarrow \text{Transcription} \rightarrow \text{mRNA} \rightarrow \text{Translation} \rightarrow \text{Immature CFTR} \rightarrow \text{Post-translational modification} \rightarrow \text{CFTR Trafficking} \rightarrow \text{Apical cell surface} \rightarrow \text{CFTR Function} \rightarrow \text{Defective conductance}\)

- *R347P* is a missense mutation that results in CFTR protein with decreased conductance, a Class IV mutation\(^1\)-\(^3\).

- Although an adequate number of CFTR protein channels are present at the apical cell surface, their function is decreased\(^1\)-\(^3\).

The **R347P** mutation results in residual 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**.$^{2}$

$\text{Total CFTR Activity} = \text{CFTR Quantity} \times \text{CFTR Function}$

$\text{CFTR Function} = \text{Channel-open Probability} \times \text{Conductance}$

1. Normal quantity of CFTR channels at the apical cell surface
2. Normal Channel-open Probability
3. $R347P$ allele results in reduced conductance

Defective Conductance (Class IV)

$R347P$ does not diminish CFTR protein **quantity**...

...but it reduces their **function** through reduced conductance...

...and results in residual total CFTR activity

Both CFTR alleles play a role in determining phenotype or disease severity\textsuperscript{1-5}

- An \textit{R347P} allele results in residual CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\textsuperscript{1-5}
- \textit{R347P} typically results in the indicated phenotypes
**R347P** in combination with another allele that produces little to no CFTR activity can result in CF symptoms that may emerge later in life\(^1-3\)

**CFTR Genotype**

- **Allele #1: R347P**
  - Residual CFTR Protein Activity
  - Residual Total CFTR Activity

- **Modifier Genes**

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

- **Environmental Factors**

**CF Phenotype**

In patients registered in the CFTR2 database with an **R347P** mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\)

- Elevated sweat chloride (average): 100 mmol/L
- Later onset of CF lung disease compared to homozygous **F508del** patients\(^3\)
- Pseudomonas colonization: 56% of patients
- Pancreatic insufficiency: 67% 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 $R347P$ mutation report ≤1% prevalence among patients with CF
- The $R347P$ mutation results in a CFTR protein with defective conductance
- The $R347P$ mutation results in residual total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- $R347P$ in combination with another allele that produces little to no CFTR activity can result in CF symptoms that may emerge later in life