A Quick Guide to the R553X 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{a}
- Lung function decline over time
- \textit{Pseudomonas aeruginosa} colonization

\textsuperscript{a}CBAVD, congenital bilateral absence of the vas deferens.

References:
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 R553X 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.

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References:

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**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 15,651 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.

Adapted with permission from McKone EF et al. Chest. 2006;130(5):1441-1447.
Prevalence of the \( R553X \) Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

**References:**

**Additional sources report frequency of the \( R553X \) mutation on CF alleles**

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
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<tbody>
<tr>
<td>Lithuania</td>
<td>4%</td>
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<tr>
<td>Russia</td>
<td>4%</td>
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<tr>
<td>Ukraine</td>
<td>4%</td>
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<tr>
<td>Slovakia</td>
<td>4%</td>
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<tr>
<td>Switzerland</td>
<td>3%</td>
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<tr>
<td>Canada</td>
<td>0.4%</td>
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</table>

In the CFTR2 global database, ~1% of patients with CF have at least 1 copy of the \( R553X \) mutation.
The *R553X* mutation results in defective biosynthesis of the CFTR protein\(^1\text{-}^5\)

- *R553X* is a nonsense mutation, which produces a premature stop codon\(^1\text{-}^4\)
- The cell cannot synthesize a full-length CFTR protein, a Class I mutation\(^1\text{-}^4\)
- As a result, few to no CFTR proteins are present at the apical cell surface\(^1,^2,^5\)

**Illustrative Example of Class I Defect**

**CFTR Turnover**

**CFTR Function**

**CFTR Trafficking**

**CFTR Processing**

**CFTR Synthesis**

The *R553X* allele results in little to no total CFTR activity\(^1\text{-}^6\)

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.\(^6\)

<table>
<thead>
<tr>
<th>CFTR Function</th>
<th>Total CFTR Activity</th>
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<tbody>
<tr>
<td>Channel-open Probability</td>
<td>Little to No <em>R553X</em>-CFTR Activity</td>
</tr>
<tr>
<td>Conductance</td>
<td></td>
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</tbody>
</table>

\(^1\) A virtual absence of *R553X*-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

1. Defective Synthesis (Class I)

2. \(\text{Channel-open Probability: N/A} \times \text{Conductance: N/A} = \text{Little to No } R553X\text{-CFTR Activity}\)

N/A, not applicable.

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

- An **R553X** allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1\)\(^{-6}\).
- **R553X** typically results in the indicated phenotypes.
R553X in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype. The CF phenotype includes:

- Elevated sweat chloride (average): 103 mmol/L
- Lung function decline over time
- Pseudomonas colonization: 59% of patients
- Pancreatic insufficiency: 97% 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 \textit{R553X} mutation report 0.2\% to 2\% prevalence among patients with CF
- The \textit{R553X} mutation results in defective biosynthesis of the CFTR protein
- The \textit{R553X} allele results in little to no total CFTR activity
- Both \textit{CFTR} alleles play a role in determining phenotype or disease severity
- \textit{R553X} in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype