A Quick Guide to the

R1162X Mutation

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Loss of CFTR activity is the underlying cause of cystic fibrosis (CF)\(^1\)

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

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

- 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 % of Normal</th>
<th>No CF Disease</th>
<th>CFTR-related Disorders</th>
<th>Cystic Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
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</tbody>
</table>

**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 R1162X 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](image)

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.

References:
Country registries listing the R1162X mutation report ≤1% prevalence among patients with CF

- In the CFTR2 global database, ~0.7% of patients with CF have at least 1 copy of the R1162X mutation

Prevalence of the R1162X Mutation in Patients With Cystic Fibrosis (% Patients With at Least 1 Allele)

Country % of Alleles

Europe:
- Netherlands 1: 1%
- Belgium 4: 1%
- France 5: 0.5%
- UK 8: 0.3%
- Germany 2: 0.3%

US 1: 0.7%
Brazil 1: 0.8%
Aus 8: 0.3%

Additional sources report frequency of the R1162X mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uruguay 10</td>
<td>4%</td>
</tr>
<tr>
<td>Slovenia 11</td>
<td>3%</td>
</tr>
<tr>
<td>Austria 11</td>
<td>2%</td>
</tr>
<tr>
<td>Spain 12</td>
<td>1%</td>
</tr>
<tr>
<td>Colombia 10</td>
<td>0.9%</td>
</tr>
<tr>
<td>Argentina 10</td>
<td>0.5%</td>
</tr>
<tr>
<td>Canada 10</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

The *R1162X* mutation results in defective biosynthesis of the CFTR protein\(^1-3\)

- *R1162X* is a nonsense mutation, which produces a premature stop codon\(^1-3\)
- The cell cannot synthesize a full-length CFTR protein, a Class I mutation\(^2,3\)
- As a result, few to no CFTR proteins are present at the apical cell surface\(^2,3\)

The **R1162X** 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. A virtual absence of R1162X-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

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N/A, not applicable.

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

- An *R1162X* 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{1-5}
- *R1162X* typically results in the indicated phenotypes

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**References:**
*R1162X* in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype\(^1-4\)

**CFTR Genotype**

- **Allele #1: R1162X**
  - Little to No CFTR Protein Activity

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

**Modifier Genes**

**Little to No Total CFTR Activity**

**Environmental Factors**

**CF Phenotype**

In patients registered in the CFTR2 database with an *R1162X* mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\)

- Elevated sweat chloride (average): 103 mmol/L
- Lung function decline over time\(^2,5\)
- Pseudomonas colonization: 47% of patients
- Pancreatic insufficiency: 97% 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 R1162X mutation report ≤1% prevalence among patients with CF
- The R1162X mutation results in defective biosynthesis of the CFTR protein
- The R1162X allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- R1162X in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype