A Quick Guide to the

3120+1G→A Mutation
Loss of CFTR activity is the underlying cause of cystic fibrosis (CF)

People with 2 CFTR mutations resulting in loss of CFTR activity generally have a CF phenotype, which may include:

- Elevated sweat chloride (>60 mmol/L)
- Pancreatic insufficiency
- CBAVD
- Lung function decline over time
- Pseudomonas aeruginosa colonization

Spectrum of Phenotypes Associated With Total CFTR Activity

<table>
<thead>
<tr>
<th>Total CFTR Activity</th>
<th>No CF Disease</th>
<th>CFTR-related Disorders</th>
<th>Cystic Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Normal</td>
<td>100%</td>
<td>50%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- CBAVD, congenital bilateral absence of the vas deferens.

References:
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](image)

- 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).
  - No patients with the 3120+1G→A mutation were included in this US registry study. 3120+1G→A is a Class I mutation, resulting in severely reduced CFTR activity.
- More recent US data (2000-2010) suggest median survival across genotypes continues to improve.

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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.

**References:**

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Country registries listing the $3120+1G\rightarrow A$ mutation report ≤1% prevalence among patients with CF$^{1-4}$

In the CFTR2 global database, ~0.5% of patients with CF have at least 1 copy of the $3120+1G\rightarrow A$ mutation$^5$

There is a high frequency of the $3120+1G\rightarrow A$ mutation among patients of African-American descent in the United States (12%)$^6$

Prevalence of the $3120+1G\rightarrow A$ Mutation in Patients With Cystic Fibrosis (% Patients With at Least 1 Allele)

Additional sources report frequency of the $3120+1G\rightarrow A$ mutation on CF alleles

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>17%</td>
</tr>
<tr>
<td>Reunion Island</td>
<td>13%</td>
</tr>
<tr>
<td>Jordan</td>
<td>10%</td>
</tr>
<tr>
<td>Bahrain</td>
<td>4%</td>
</tr>
<tr>
<td>Greece</td>
<td>0.6%</td>
</tr>
<tr>
<td>Colombia</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

The 3120+1G→A mutation results in defective biosynthesis of the CFTR protein\textsuperscript{1-3}

- 3120+1G→A is a splice mutation, which produces a premature stop codon\textsuperscript{1,2}
- The cell cannot synthesize full-length CFTR proteins, a Class I mutation\textsuperscript{1,3}
- As a result, few to no CFTR proteins are present at the apical cell surface\textsuperscript{3}

The \(3120+1G\rightarrow A\) 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 \(3120+1G\rightarrow A\)-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 3120+1G→A allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1-^6\).

3120+1G→A typically results in the indicated phenotypes.


Adapted from Zielenski J. Respiration. 2000;67(2):117-133.
3120+1G→A in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype \(^1-3\)

**CFTR Genotype**

- **Allele #1:** 3120+1G→A
- **Allele #2:** Little to No CFTR Protein Activity

**Modifier Genes** → **Little to No Total CFTR Activity** → **Environmental Factors** → **CF Phenotype**

**CF Phenotype**

In patients registered in the CFTR2 database with a 3120+1G→A 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 \(^4\)
- Pseudomonas colonization: 55% 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 $3120+1G\rightarrow A$ mutation report ≤1% prevalence among patients with CF
- The $3120+1G\rightarrow A$ mutation results in defective biosynthesis of the CFTR protein
- The $3120+1G\rightarrow A$ allele results in little to no total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- $3120+1G\rightarrow A$ in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype