A Quick Guide to the

2789+5G→A

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\(^1,3,5\)
  - Elevated sweat chloride (>60 mmol/L)
  - Pancreatic insufficiency
  - CBAVD\(^a\)
  - Lung function decline over time
  - *Pseudomonas aeruginosa* colonization

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**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>
<td></td>
<td></td>
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</tbody>
</table>

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

<table>
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Some CFTR mutations result in little to no CFTR activity\(^3,5\)

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\(^a\)CBAVD, congenital bilateral absence of the vas deferens.

**References:**

Levels of CFTR activity affect survival in CF\textsuperscript{1}

![Survival Curves by CFTR Activity During a 10-Year Follow-Up (1993-2002) of Patients From the US CFF Registry\textsuperscript{a}](image)

- Life expectancy in Western countries (general population born in 2000) is \sim 79 years\textsuperscript{2}
- 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)\textsuperscript{1}
  - In this study, patients with a 2789+5G→A mutation (Class V) were part of the residual CFTR activity group
- More recent US data (2000-2010) suggest median survival across genotypes continues to improve\textsuperscript{3}

\textsuperscript{a}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.\textsuperscript{1}

\textsuperscript{1}Adapted with permission from McKone EF et al. Chest. 2006;130(5):1441-1447.

\textsuperscript{2}This survival curve represents population-based outcomes.\textsuperscript{3} Individual outcomes in cystic fibrosis are variable.

Country registries listing the $2789+5G\rightarrow A$ mutation report 0.3% to 2% prevalence among patients with CF$^{1-5}$

Prevalence of the $2789+5G\rightarrow A$ Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Republic of Moldova$^7$</td>
<td>5%</td>
</tr>
<tr>
<td>Slovenia$^8$</td>
<td>4%</td>
</tr>
<tr>
<td>Turkey$^8$</td>
<td>4%</td>
</tr>
<tr>
<td>Lebanon$^8$</td>
<td>3%</td>
</tr>
<tr>
<td>Austria (Tyrol)$^8$</td>
<td>2%</td>
</tr>
<tr>
<td>Greece$^8$</td>
<td>2%</td>
</tr>
<tr>
<td>Canada$^9$</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

2789+5G→A is a splicing mutation that results in some functional CFTR at the apical cell surface\textsuperscript{1-3}

- 2789+5G→A is associated with alternative splicing and reduced synthesis of CFTR proteins, typical of a Class V mutation\textsuperscript{1-3}

- This results in some functional CFTR proteins at the apical cell surface\textsuperscript{1-3}

Illustrative Example of Class V Defect

The 2789+5G→A allele results in residual total CFTR activity\textsuperscript{1-3}

Total CFTR activity can be defined as total ion transport mediated by CFTR protein channels at the cell surface, depending on CFTR protein \textit{quantity} and \textit{function}.\textsuperscript{3}

\begin{align*}
\text{Total CFTR Activity} &= \text{CFTR Quantity} \times \text{CFTR Function} \\
&= \text{Channel-open Probability} \times \text{Conductance}
\end{align*}

1. 2789+5G→A reduces CFTR protein \textit{quantity}...

2. ...but does not appear to reduce CFTR \textit{function}...

3. ...and results in residual total CFTR activity

Both CFTR alleles play a role in determining phenotype or disease severity\(^1\text{-}^7\)

- A 2789+5G→A allele results in residual CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^4\text{-}^5\).
- 2789+5G→A typically results in the indicated phenotypes.

Adapted from Zielenski J. Respiration. 2000;67(2):117-133.

2789+5G→A in combination with another allele that produces little to no CFTR activity can result in CF symptoms that may emerge later in life

References:

CF Phenotype
In patients registered in the CFTR2 database with a 2789+5G→A mutation on 1 allele and a pancreatic insufficient mutation on the second allele:

- Elevated sweat chloride (average): 97 mmol/L
- Later onset of CF lung disease compared to homozygous F508del patients
- Pseudomonas colonization: 39% of patients
- Pancreatic insufficiency: 42% 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 2789+5G→A mutation report 0.3% to 2% prevalence among patients with CF
- 2789+5G→A is a splicing mutation that results in some functional CFTR at the apical cell surface
- The 2789+5G→A allele results in residual total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- 2789+5G→A in combination with another allele that produces little to no CFTR activity can result in CF symptoms that may emerge later in life