A Quick Guide to the

R117H

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

### Spectrum of Phenotypes Associated With Total CFTR Activity\(^{1,2}\)

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

- 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.

**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

- 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, R117H was considered only as a Class IV CFTR mutation and patients were part of the residual CFTR activity group

- More recent US data (2000-2010) suggest median survival across genotypes continues to improve

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

These data represent population-based outcomes. Individual outcomes in cystic fibrosis are variable.

**R117H** is the most common residual function *CFTR* mutation and the fifth most common *CFTR* mutation in the world\(^1,2\)

In the CFTR2 global database, ~2% of patients with CF have at least 1 copy of the *R117H* mutation\(^2\)

Prevalence of the *R117H* 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>Norway(^1)</td>
<td>3%</td>
</tr>
<tr>
<td>Greece(^1)</td>
<td>1%</td>
</tr>
<tr>
<td>Austria(^1)</td>
<td>0.7%</td>
</tr>
<tr>
<td>Canada(^1)</td>
<td>0.6%</td>
</tr>
<tr>
<td>Denmark(^1)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Switzerland(^1)</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Additional sources report frequency of the *R117H* mutation on CF alleles:


4
The **R117H** mutation results in reduced channel-opening and conductance of the CFTR protein\(^1\)-\(^4\)

- **R117H** is a missense mutation. R117H-protein channels reach the apical cell surface, but their function is decreased\(^1\)-\(^4\).
  - **R117H** produces a CFTR protein with reduced channel-open probability (or gating), characteristic of a Class III mutation.
  - **R117H** also results in decreased chloride conductance, typical of a Class IV mutation.

**References:**
CF disease in patients with the \textit{R117H} mutation is influenced by the CFTR poly-T tract variant\textsuperscript{1-8}

\begin{itemize}
  \item \textbf{R117H-5T:} Causes the greatest reduction of functional CFTR at the apical cell surface. Typically, 5T in \textit{cis} with \textit{R117H} (i.e., on the same allele) is associated with a CF phenotype\textsuperscript{2-5,9,10}.
  \item \textbf{R117H-7T:} Less likely than \textit{R117H-5T} to result in CF, however, individuals can develop CF. Patients who have 7T in \textit{cis} with \textit{R117H} may still need to be monitored for the development of CF\textsuperscript{5-10}.
  \item \textbf{R117H-9T:} Highly unlikely to result in CF\textsuperscript{4,5}.
\end{itemize}

\textbf{Intron 8 Poly-T Variant Length Affects Splice Efficiency During R117H-CFTR Protein Synthesis\textsuperscript{1-3}}

\begin{center}
\begin{tabular}{c|c|c|c|c}
Number of thymidine residues & TGmTTTTTTTTAAACAG & TGmTTTTTTTTAAACAG & TGmTTTTTTTTAAACAG & 9T & 7T & 5T \\
\end{tabular}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node (exon9) at (0,0) {Exon 9};
  \node (exon8) at (-1.5,-1.5) {Exon 8};
  \node (exon7) at (-3,-3) {Exon 7};
  \node (intron8) at (-1.5,-3) {Intron 8};
  \node (intron9) at (1.5,-3) {Intron 9};
  \node (exon10) at (1.5,-1.5) {Exon 10};
  \node (cftr) at (0,0) {CFTR gene};
  \draw [->] (exon9) -- (exon8);
  \draw [->] (exon8) -- (exon7);
  \draw [->] (exon7) -- (intron8);
  \draw [->] (intron8) -- (exon9);
  \draw [->] (exon9) -- (exon10);
  \draw [->] (exon8) -- (exon10);
  \draw [->] (exon7) -- (exon10);
\end{tikzpicture}
\end{center}

\begin{itemize}
  \item \textbf{Normal CFTR protein:} Full-length CFTR mRNA results in normal CFTR protein.
  \item \textbf{Longer poly-T length:} More channels, more chloride transport.
  \item \textbf{Shorter poly-T length:} Fewer channels, less chloride transport.
  \item \textbf{mRNA without exon 9:} No CFTR protein.
\end{itemize}

\textbf{Adapted with permission from Claustres M. Reprod Biomed Online. 2005;10(1):14-41.}

The \textit{R117H} allele results in residual total CFTR activity\textsuperscript{1-6}

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\textsuperscript{5}.

The \textit{R117H}-7T allele diminishes CFTR protein quantity less than the \textit{R117H}-5T allele.

The \textit{R117H}-5T allele diminishes CFTR protein quantity more than the \textit{R117H}-7T allele.

- The \textit{R117H}-7T allele results in reduced channel-open probability
- The \textit{R117H}-5T allele results in reduced conductance

- Resulting in reduced but residual total CFTR activity

Both CFTR alleles play a role in determining phenotype or disease severity\textsuperscript{1-7}

- An \textit{R117H} allele results in residual CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele. The \textit{R117H} allele results in variable phenotypes\textsuperscript{1-7}

- \textit{R117H} typically results in the indicated phenotypes

### Table: CFTR-related Disorder

<table>
<thead>
<tr>
<th>Allele 1</th>
<th>Allele 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CFTR Activity</td>
<td>Total CFTR Activity</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>Little to None</td>
</tr>
<tr>
<td>Little to None</td>
<td>Little to None</td>
</tr>
<tr>
<td>Little to None</td>
<td>Little to None</td>
</tr>
</tbody>
</table>

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

**R117H** in combination with another allele that produces little to no CFTR activity can result in CF symptoms that may emerge later in life\(^1-6\)

---

**CF Phenotype**

In patients registered in the CFTR2 database with an **R117H** mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\)

- **Sweat chloride (average):** 60 mmol/L
- **A range of pulmonary phenotypes,** including classic CF, delayed onset of pulmonary symptoms, or no pulmonary symptoms\(^6\)
- **Pseudomonas colonization:** 28% of patients
- **Pancreatic insufficiency:** 23% of patients

---

Summary

- Loss of CFTR activity is the underlying cause of CF
- Levels of CFTR activity affect survival in CF
- R117H is the most common residual function CFTR mutation and the fifth most common CFTR mutation in the world
- The R117H mutation results in reduced channel-opening and conductance of the CFTR protein
- CF disease in patients with the R117H mutation is influenced by the CFTR poly-T tract variant
- The R117H allele results in residual total CFTR activity
- Both CFTR alleles play a role in determining phenotype or disease severity
- R117H in combination with another allele that produces little to no CFTR activity can result in CF symptoms that may emerge later in life