THE ROLE OF CFTR MUTATIONS IN CAUSING CYSTIC FIBROSIS (CF)
Overview

CF is a complex, genetic disease

- CF occurs when a child inherits two copies of a CFTR gene mutation resulting in a CF genotype\(^1,2\)
- CFTR protein activity is determined by CFTR protein quantity and function\(^1,3\)
- In CF, there is a reduction in total CFTR protein activity leading to an imbalance of fluid and ions in organs throughout the body\(^1,3,4\)
- Different CFTR mutations produce different effects on CFTR protein quantity and function\(^1,3,4\)
- When patients and caregivers are educated about their genotype, they are empowered to be active partners in their own care\(^5\)


CFTR, cystic fibrosis transmembrane conductance regulator.
CFTR proteins in normal cells
CFTR proteins: An important regulator of fluid and ion balance in organs throughout the body

- CFTR proteins are found on epithelial cell surfaces in organs throughout the body\(^1\)\(^-\)\(^4\)

- Normally, CFTR protein channels transport ions, such as chloride and bicarbonate, through the epithelial cell surface in these organs\(^1\)\(^-\)\(^4\)

- Maintaining water and salt balance at the epithelial cell surface requires an adequate quantity and function of CFTR proteins\(^5\)

• **Total CFTR activity** can be defined as total ion transport mediated by CFTR protein channels at the cell surface. It is dependent on CFTR protein **quantity** and **function**\(^4\)\(^,\)\(^6\)


\[ \text{Total CFTR activity} \ = \ \text{CFTR quantity} \times \text{CFTR function} \times \text{Conductance} \]
**CFTR protein function is determined by channel-open probability and channel conductance**

**Channel-open probability**: the fraction of time that a single CFTR protein channel is open and transporting ions.¹

**Channel conductance**: rate at which ions move through open CFTR protein channels.²

Status of a single channel over time³*

$\text{Normal CFTR channel-open probability}^{3}$

$\text{Normal CFTR channel conductance}^{1}$

*Based on in vitro experimentation.

CFTR proteins reach the cell membrane through a multi-step process

CFTR mutations may affect different steps of this process to reduce CFTR quantity and/or function and reduce total CFTR protein activity\textsuperscript{1,2}

The importance of understanding *CFTR* mutations and their nomenclature
CFTR mutations are inherited genetically

If a person inherits 2 copies of a disease-causing CFTR mutation (one from each parent), CFTR protein dysfunction can occur:

- CFTR protein dysfunction impairs cellular chloride transport
- CF disease can be the result

**CFTR mutations can be referred to by different names**

<table>
<thead>
<tr>
<th>Name</th>
<th>Definition</th>
<th>Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legacy name (F508del)</td>
<td>Commonly used colloquial nomenclature</td>
<td>Used primarily in genetic clinics and diagnostic laboratories</td>
</tr>
<tr>
<td>cDNA name (c.1521_1523delCTT)</td>
<td>DNA sequence</td>
<td>Used to identify mutations as listed in global sequence databases such as GenBank®</td>
</tr>
<tr>
<td>Protein name (p.Phe508del)</td>
<td>Amino acid sequence (three-letter code)</td>
<td>Used to identify pathogenic mechanism of mutation based on altered protein synthesis</td>
</tr>
</tbody>
</table>

*Different naming conventions are used by researchers in publications, genetic clinics, and diagnostic laboratories*

Certain *CFTR* mutations may affect CFTR quantity and/or function, reducing total CFTR activity

Spectrum of phenotypes associated with total CFTR activity

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

CBAVD, congenital bilateral absence of vas deferens.

The effects of *CFTR* mutations on total CFTR activity
Different *CFTR* mutations produce different effects on CFTR protein quantity and function

*CFTR* mutations are grouped into classes according to their effects on CFTR protein synthesis, trafficking, or function\(^1-3\)

- Defective synthesis (Class I)
- Defective processing and trafficking (Class II)
- Decreased splicing (Class V)
- Decreased protein stability (Class VI)
- Defective gating (Class III)
- Defective conductance (Class IV)

\[
\text{CFTR quantity } \times \frac{\text{Channel-open probability}}{\text{Conductance}} \times \text{CFTR function} = \text{Total CFTR activity}
\]

*The top 25 mutations are comprised of those in classes I-V*\(^4\)

Examples of CFTR mutations that result in defective biosynthesis of the CFTR protein

Defective synthesis yields no functional CFTR protein\(^1-3\)

Channel-open probability: Little to none

Conductance: Little to none

Little to none\(^1-3\)

An absence of CFTR protein…

…regardless of function since few to no CFTR proteins reach the surface...

…results in little to no total CFTR activity

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**Examples (Class I)**

<table>
<thead>
<tr>
<th>Legacy Name(^4,5)</th>
<th>cDNA Name(^4,5)</th>
<th>Protein Name(^4,5)</th>
<th>Type(^4)</th>
<th>US Prevalence (%)(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G542X</td>
<td>c.1624G&gt;T</td>
<td>p.Gly542X</td>
<td>Nonsense</td>
<td>4.7</td>
</tr>
<tr>
<td>1717-1G--&gt;A</td>
<td>c.1585-1G&gt;A</td>
<td>No Protein Name</td>
<td>Splice defect</td>
<td>1.6</td>
</tr>
<tr>
<td>3659delC</td>
<td>c.3528delC</td>
<td>p.Lys1177SerfsX15</td>
<td>Frameshift</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Examples of CFTR mutations that result in defective processing and trafficking of the CFTR protein

<table>
<thead>
<tr>
<th>Legacy Name</th>
<th>cDNA Name</th>
<th>Protein Name</th>
<th>Type</th>
<th>US Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F508del</td>
<td>c.1521_1523delCTT</td>
<td>p.Phe508del</td>
<td>Amino acid deletion</td>
<td>86.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>N1303K</td>
<td>c.3909C&gt;G</td>
<td>p.Asn1303Lys</td>
<td>Missense</td>
<td>2.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Homozygous and heterozygous.

Example of CFTR mutations that reduce channel-open probability in the CFTR protein

- **CFTR quantity**: Normal
- **CFTR function**: Defective channel gating at cell membrane, Conductance: Normal
- **Total CFTR activity**: Little to none

Although CFTR protein quantity may be normal, function is severely reduced due to decreased channel-open probability, resulting in little to no total CFTR activity.

### Examples (Class III)

<table>
<thead>
<tr>
<th>Legacy Name</th>
<th>cDNA Name</th>
<th>Protein Name</th>
<th>Type</th>
<th>US Prevalence (%)</th>
</tr>
</thead>
</table>

**References:**
Example of CFTR mutations that result in a CFTR protein with defective conductance

<table>
<thead>
<tr>
<th>Legacy Name</th>
<th>cDNA Name</th>
<th>Protein Name</th>
<th>Type</th>
<th>US Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R117H</td>
<td>c.350G&gt;A</td>
<td>p.Arg117His</td>
<td>Missense</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Although CFTR protein quantity may be normal… 
…function is reduced due to decreased conductance... 
…and results in some total CFTR activity

Examples of CFTR mutations that result in some functional CFTR at the cell surface

<table>
<thead>
<tr>
<th>Legacy Name</th>
<th>cDNA Name</th>
<th>Protein Name</th>
<th>Type (^{4,5})</th>
<th>US prevalence (%) (^{5})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3849+10kbC-&gt;T</td>
<td>c.3717+12191C&gt;T</td>
<td>p.Phe508del</td>
<td>Splice defect</td>
<td>1.5</td>
</tr>
<tr>
<td>A455E</td>
<td>c.1364C&gt;A</td>
<td>p.Ala455Glu</td>
<td>Missense</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The importance of patients and caregivers knowing their CF genotype
Patients benefit from knowing their CF genotype

• Patients/Caregivers who are educated about their CF genotypes may be empowered to be active partners in their own care

• Patients/Caregivers who know about their genotype may¹:
  – Better understand their CF symptoms and how CF may progress
  – Seek access to treatment plans that are most appropriate for them
  – Actively participate in making care decisions with their doctor or healthcare team
  – Be informed about research studies that may be an option for them

Engaging patients and caregivers in conversations about CF

Communicating with patients and/or caregivers about how their CF genotype can impact care and treatment decisions is important; but helping them understand the reasons can be challenging. Below are some points that can be useful when talking with patients/caregivers about their CF genotype:

Consider discussing how:

- Every person with cystic fibrosis inherited two mutated CF-causing genes which together form a person's CF genotype

- Different mutations impair CFTR function in different ways leading to variations in the symptoms, disease severity, and disease progression each person with CF experiences

- Despite the variation in presentation, all genotypes experience disease progression, making personalized disease management important throughout a patient’s lifetime

- A care plan can also be personalized based on environment, physiology, patient and caregiver preferences, and lifestyle

The most important thing for the patient/caregiver to remember is that when the genotype is known, the care team can customize CF care and treatment plans to help optimize each patient’s situation

Summary
Summary

CFTR protein is an important cellular regulator in organs throughout the body\textsuperscript{1,2}

CFTR mutations result in a loss of total CFTR protein activity, which is the underlying cause of CF\textsuperscript{1,2}

Different types of CFTR mutations vary in their effects on CFTR protein quantity and/or function\textsuperscript{2,3}

Both CFTR mutations play a role in determining phenotype or disease severity\textsuperscript{4}

Discussing genotype with patients helps them understand their CF disease presentation and treatment options\textsuperscript{5}