

## Introduction

### Cystic Fibrosis and CFTR protein

- In the United States, approximately 30,000 individuals have Cystic Fibrosis (CF). CF is usually caused by point mutations in the gene which produces the 1480-amino-acid cystic fibrosis transmembrane conductance regulator (CFTR).
- It is known that CFTR is the transporter required for chloride (and accompanying water) secretion both in the intestines and in the upper airways of the lungs. Mutations in CFTR lead to various expressions of CF, which is still a lethal genetic disease.
- CFTR is a cyclic-AMP mediated chloride channel which regulates and participates in the transport of electrolytes across epithelial-cell membranes. The classic form of cystic fibrosis is caused by loss-of-function mutations in the CFTR gene.

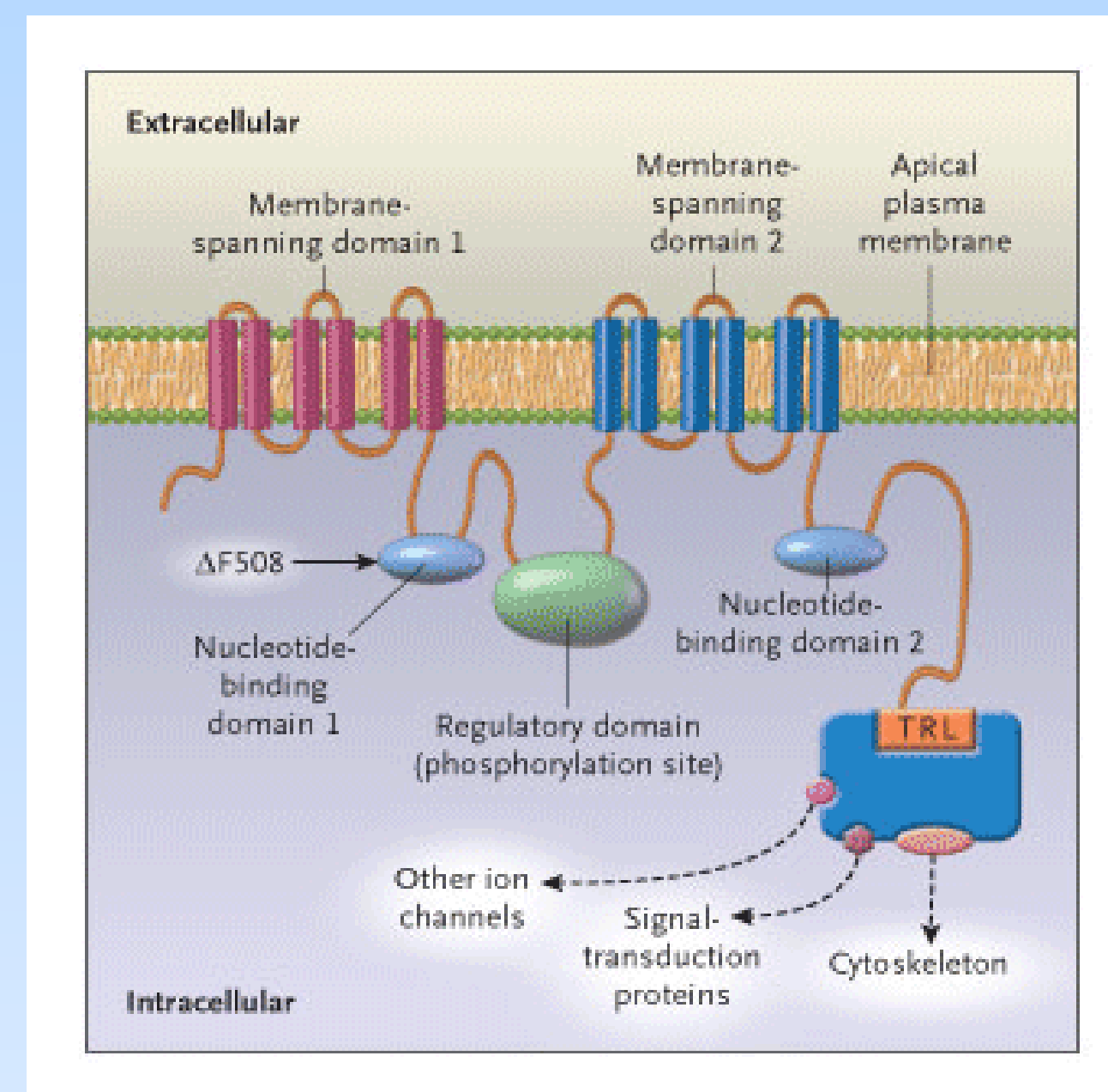


Figure 1: Hypothesized Structure of CFTR<sup>1</sup>

## Case Summary

### History of Present Illness:

A 24-year-old white male was admitted for dehydration, diarrhea, and cachexia. Given the severity and chronicity of the patient's diarrhea, his primary physician thought he would benefit from IV fluids as well as consideration for TPN. He had worsening diarrhea for three years that continued with fasting, but improved slightly with Lomotil (diphenoxylate and atropine).

He recalled having abdominal bloating as a teenager, and undergoing colonoscopy, which was negative. For the last 3 years, he developed more severe diarrhea and weight loss with brown, nonbloody, non-steatorrheac stools up to 10x daily. He had lost 30 pounds over 3 years, but denies fevers, chills, arthralgias, myalgias, or rashes.

Extensive workup for infection, including stool studies and HIV has been negative. Patient denies a history of travel or sick contacts.

**Past Medical History:** He has had a chronic cough for many years and sinusitis requiring sinus surgery.

### Physical Examination:

Weight 58.2 kg, height 182.5 cm, BMI 17.5 kg/m<sup>2</sup>, Blood Pressure: 108/70, Temperature: 36° C, Heart Rate: 98, Respiratory Rate: 20.

Examination was notable for temporal wasting and clubbing.



Fig 2. Digital clubbing  
Not this patient

### Lab Tests and Imaging:

Na 141, K 4.2, Cl 104, HCO<sub>3</sub> 30, Cr 0.7, WBC 9.45, Hgb 11, platelet count 392.

Coccidioides serologies were negative.  
HIV antibody negative.

Stool workup for infectious causes were negative.

A chest CT scan was done because of clubbing and a history of cough; this showed diffuse severe bronchiectasis. Sputum culture grew out pseudomonas. A sweat chloride test was significantly elevated, consistent with a diagnosis of cystic fibrosis.

## Imaging

Figure 3: Frontal chest x-ray in cystic fibrosis shows diffuse interstitial disease with bronchiectasis and nodular densities of mucoid impaction

Not this patient<sup>6</sup>



Figure 4: Bronchiectasis appearance on chest computed tomography<sup>2</sup>

Not this patient



Figure 5: Pathology specimen showing bronchiectasis with abnormally and permanently dilated airways with variable amounts of mucus and inflammation. In cystic fibrosis, the changes are diffuse, often with green-yellow mucoid impaction.  
Not this patient<sup>3</sup>

## Discussion

- The classic form of cystic fibrosis is caused by loss-of-function mutations in the CFTR gene.
- Seventy mutations can be used to identify more than 90 percent of all CF genes. However, in all, more than 500 CFTR mutations associated with CF are known. The non-classic form of cystic fibrosis, which our patient has, makes up roughly 10% of CF cases and represents CFTR mutations that cause reduction but not complete loss of CFTR activity.
- This patient, due to his late presentation, had a significant but likely milder mutation.
- The various mutations (>1,300) that have been shown to cause CF have been categorized into four classes
- Class I mutations cause defective protein production with a total loss of functional CFTRs.
- Class II mutations cause defective protein processing leading to CFTR that is not in its correct location in the cell or that is different from CFTRs in normal individuals (less glycoproteins and gangliosides on the cell surface in CF cells). The most common mutation found in 70% of CF patients (the F508 deletion) is one of the Class II mutations. Class III and IV mutations are less severe.
- An interesting correlation can be made with our patients secretory diarrhea and *V. cholerae*, an infectious cause of profound secretory diarrhea.

TABLE 2. RELATION BETWEEN THE AMOUNT OF FUNCTIONAL CFTR PRODUCED AND THE PHENOTYPE.<sup>4</sup>

PERCENTAGE OF NORMAL CFTR FUNCTION	MANIFESTATIONS OF CYSTIC FIBROSIS
<1	Pancreatic exocrine deficiency (plus manifestations listed below)
<4.5†	Progressive pulmonary infection (plus manifestations listed below)
<5†	Clinically demonstrable sweat abnormality (plus manifestations listed below)
<10	Congenital absence of the vas deferens
10-49	No known abnormality
50-100‡	No known abnormality (this range represents the level in asymptomatic heterozygotes and normal persons)

<sup>†</sup>The percentages of normal CFTR function are approximate, and correlations are not absolute. However, the information in the table helps guide an appropriate workup for specific symptoms and clinical findings. Data were obtained from Davis et al.<sup>4</sup>

<sup>‡</sup>These levels are very close, and there are patients with normal sweat electrolyte levels but characteristic pulmonary disease, and other patients with abnormal sweat electrolyte levels but no pulmonary disease.

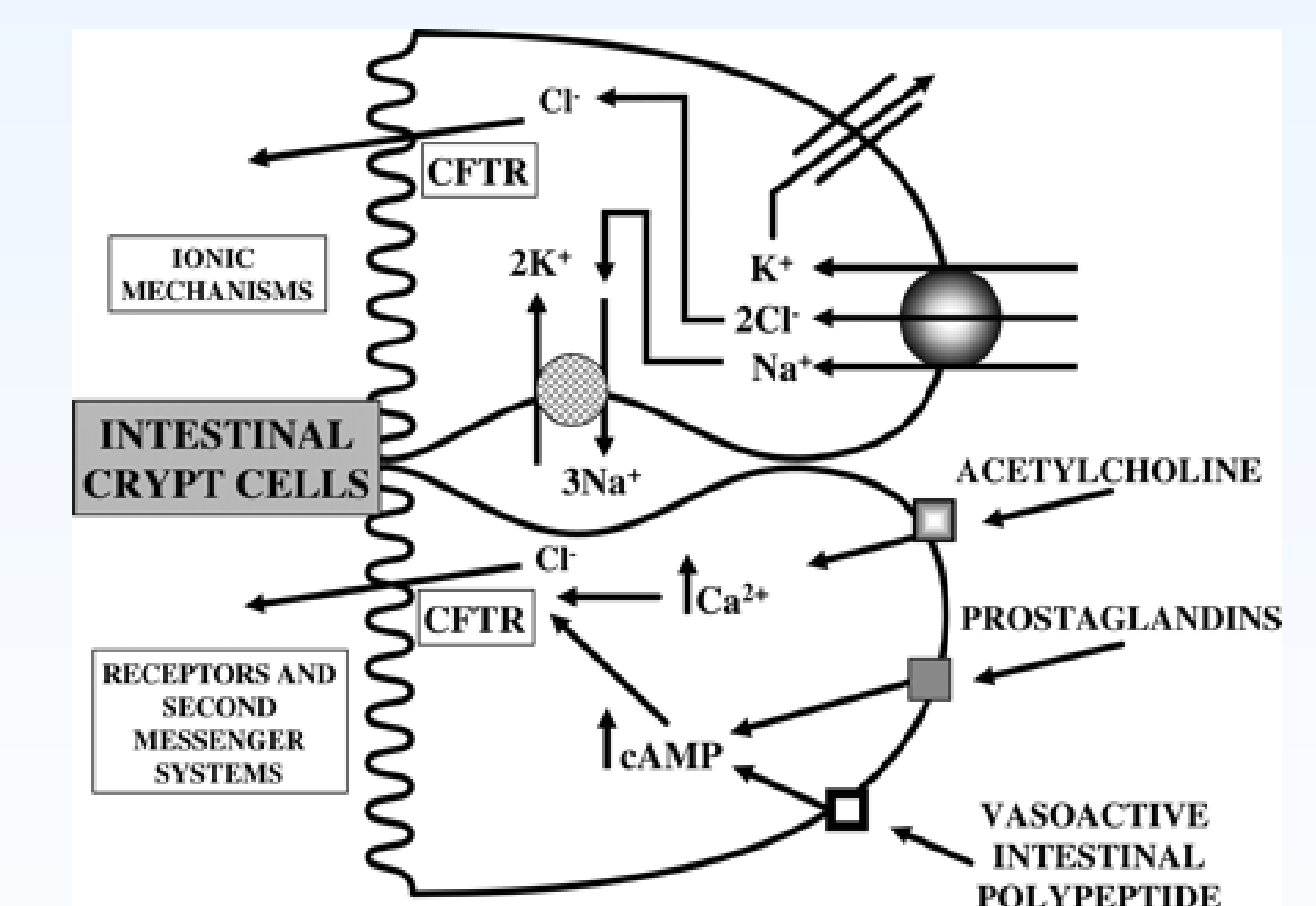
<sup>§</sup>The percentage of functional CFTR in heterozygotes is not completely known and may be below 50 percent.

Table 1:  
Relation between the Amount of Functional CFTR Produced and the Phenotype<sup>4</sup>.

### Cholera and CFTR protein

Cholera toxin activates the adenylate cyclase enzyme in cells of the intestinal mucosa, leading to increased levels of intracellular cAMP. Intestinal crypt cells, the primary secretory cells found in the small intestinal mucosa, respond to the second messengers Ca<sup>2+</sup> and cAMP and cause chloride secretion through CFTRs located on the apical (luminal) side of the cells

Figure 6: Mechanism of Secretion of Chloride with Cholera Infection<sup>5</sup>



## References

- Rowe S et al. *N Engl J Med* 2005;352:1992-2001
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