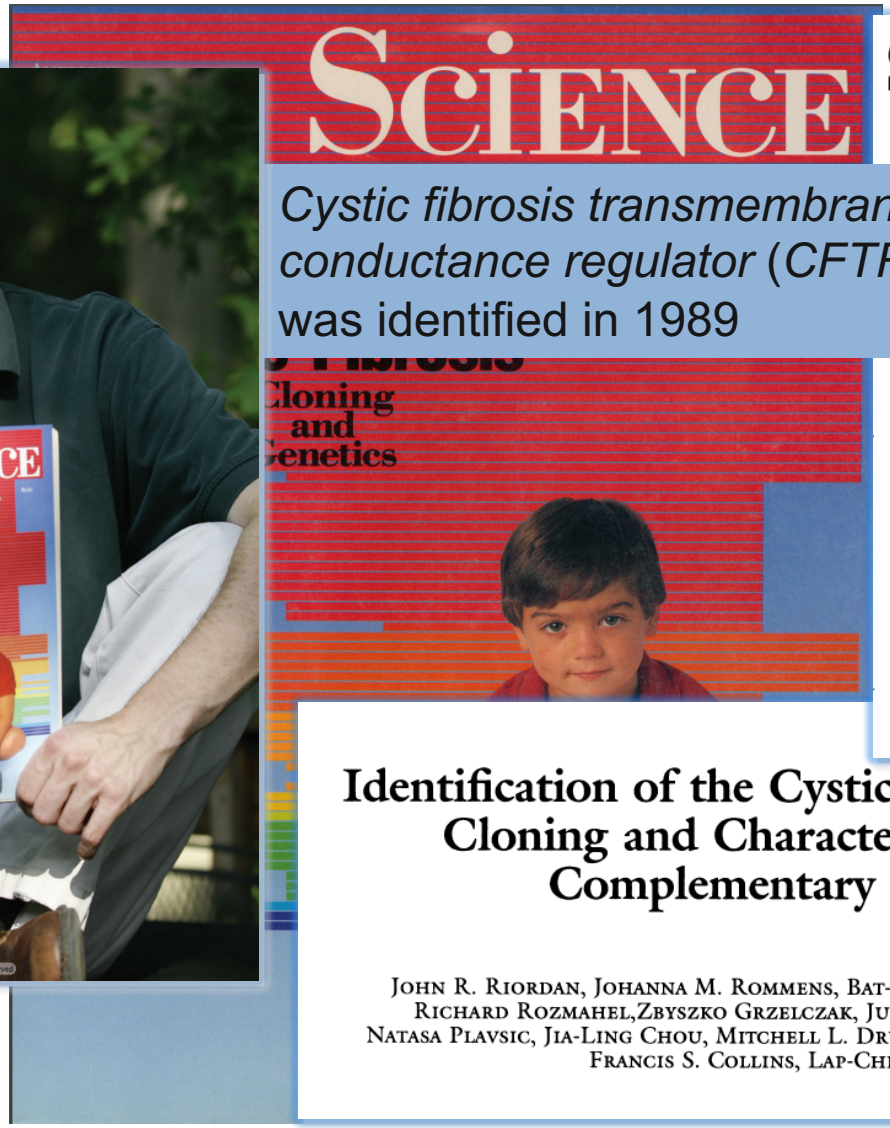
Genetics and the Science of CFTR

Objectives

- Discuss CFTR protein dysfunction: The underlying cellular defect in CF
- Review mutation types and associated nomenclature
- Understand CFTR genotype and clinical phenotype

Identification of a Gene

Cystic fibrosis transmembrane conductance regulator (*CFTR*) gene was identified in 1989



SCIENCE

8 SEPTEMBER 1989
VOLUME 245
NUMBER 4922

Story

that does not begin at the beginning or end at the
The beginning is the basic research that made it
in a haystack of DNA bases. The end is a cure for
of the cystic fibrosis gene, a milestone of major

apers published in this issue on the cystic fibrosis
eat scientific achievement that brings credit to the
uity made it possible (see the news story by Jean Marx, *Science*, 1 September, p. 923). Until now cystic fibrosis could not be studied in animals, and clues to the actual defect are circumstantial. The discovery of the gene makes possible its manipulation and insertion into experimental systems, thus bringing the day of therapy and cure much closer. This advance immediately increases the accuracy of diagnosis, both in the born and the unborn. It also has provided strategies that will be useful in searching for other disease-causing genes.

The beginning of the story explains why scientists believe in the importance of basic research. The tools that made this finding possible arose from a background of basic research into such apparently esoteric and academic subjects as the understanding of the genetic code, the recognition that enzymes from soil bacteria are able to cut DNA at specific locations, a solid familiarity with the structure of chromosomes, classical genetics, and the use of statistical probability. Much of the early basic research did not seem relevant to the cystic fibrosis problem, and was pursued in the quest for extended knowledge, not practical application. At times, legislators get impatient with scientists who emphasize such research, implying that while scientists may prefer it, society does not need it. Scientists have learned, however, that basic research often turns out to be practical, but the time scale for its application differs from that of applied research. There is a time when the search for basic knowledge is essential because there are no tools available for a direct application. Once the tools have been obtained, often by investigations that were primarily directed toward another goal, the clever and prepared investigator will apply them to the problem at hand. Thus the apparently arcane interests of ivory-tower scientists are essential and inexorable steps along the path to the triumphs of today.

Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA

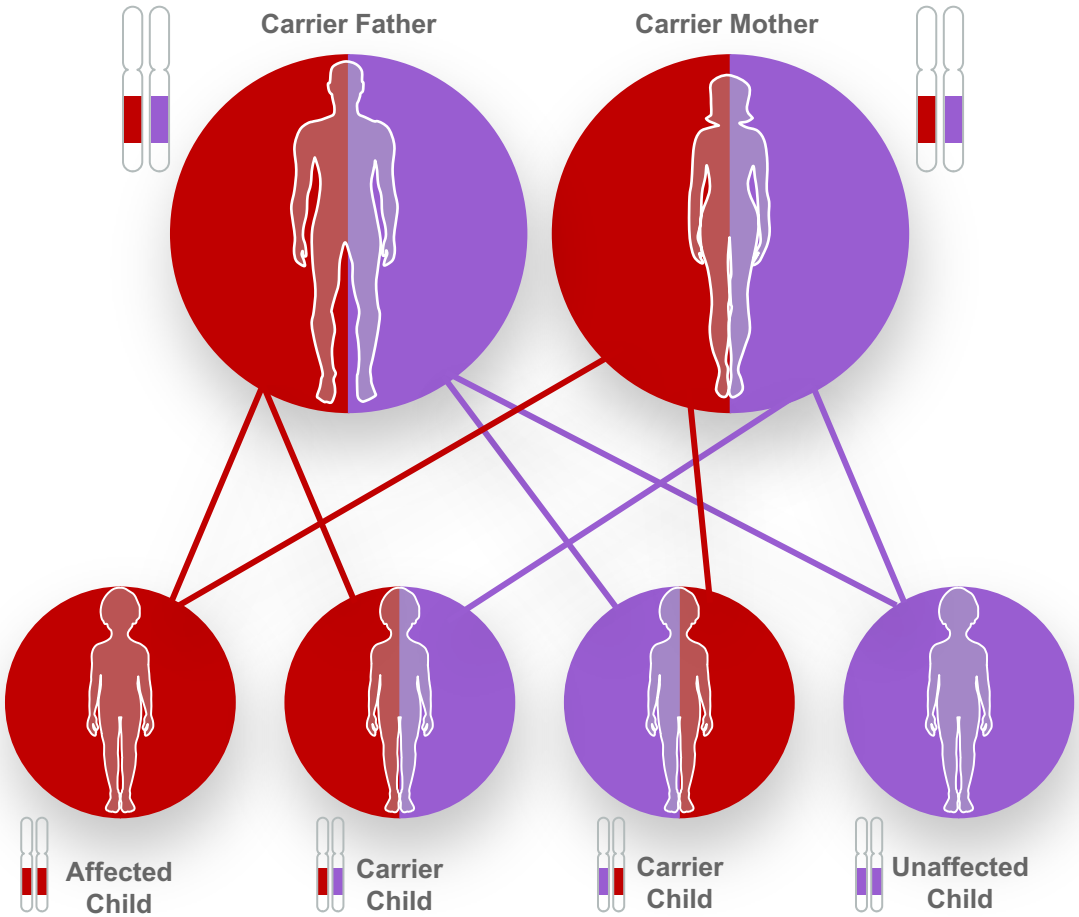
JOHN R. RIORDAN, JOHANNA M. ROMMENS, BAT-SHEVA KEREM, NOA ALON, RICHARD ROZMAHEL, ZBYSZKO GRZELCZAK, JULIAN ZIELENSKI, SI LOK, NATASA PLAVSIC, JIA-LING CHOU, MITCHELL L. DRUMM, MICHAEL C. IANNUZZI, FRANCIS S. COLLINS, LAP-CHEE TSUI

Riordan JR et al. *Science* 1989 Sep 8;245(4922):1066-73; Koshland DE Jr. *Science* 1989;245(4922):1029; Helen Pearson. *Nature* 2009; 460:164-169

VERTEX

Cystic Fibrosis (CF) Inheritance Pattern: Autosomal Recessive

- Each copy of the *CFTR* gene must carry a disease-causing mutation for the disease to develop[1]

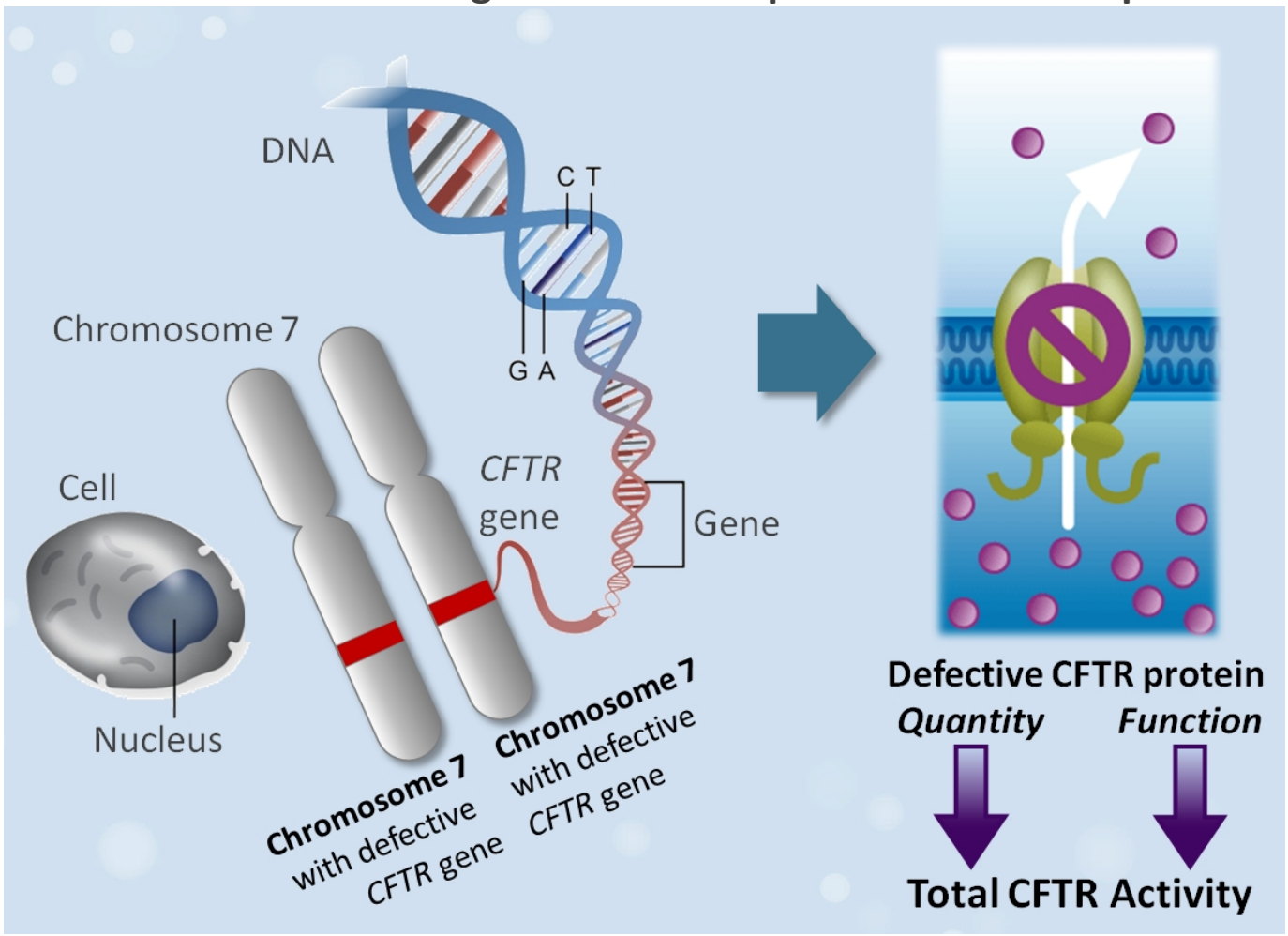


National Institutes of Health. Genetics Home Reference Handbook. Web site http://ghr.nlm.nih.gov/handbook/inheritance.pdf. Accessed April 2020

Etiology of CF

The underlying cellular defect in CF is CFTR protein dysfunction

The *CFTR* gene encodes a protein – the CFTR protein channel

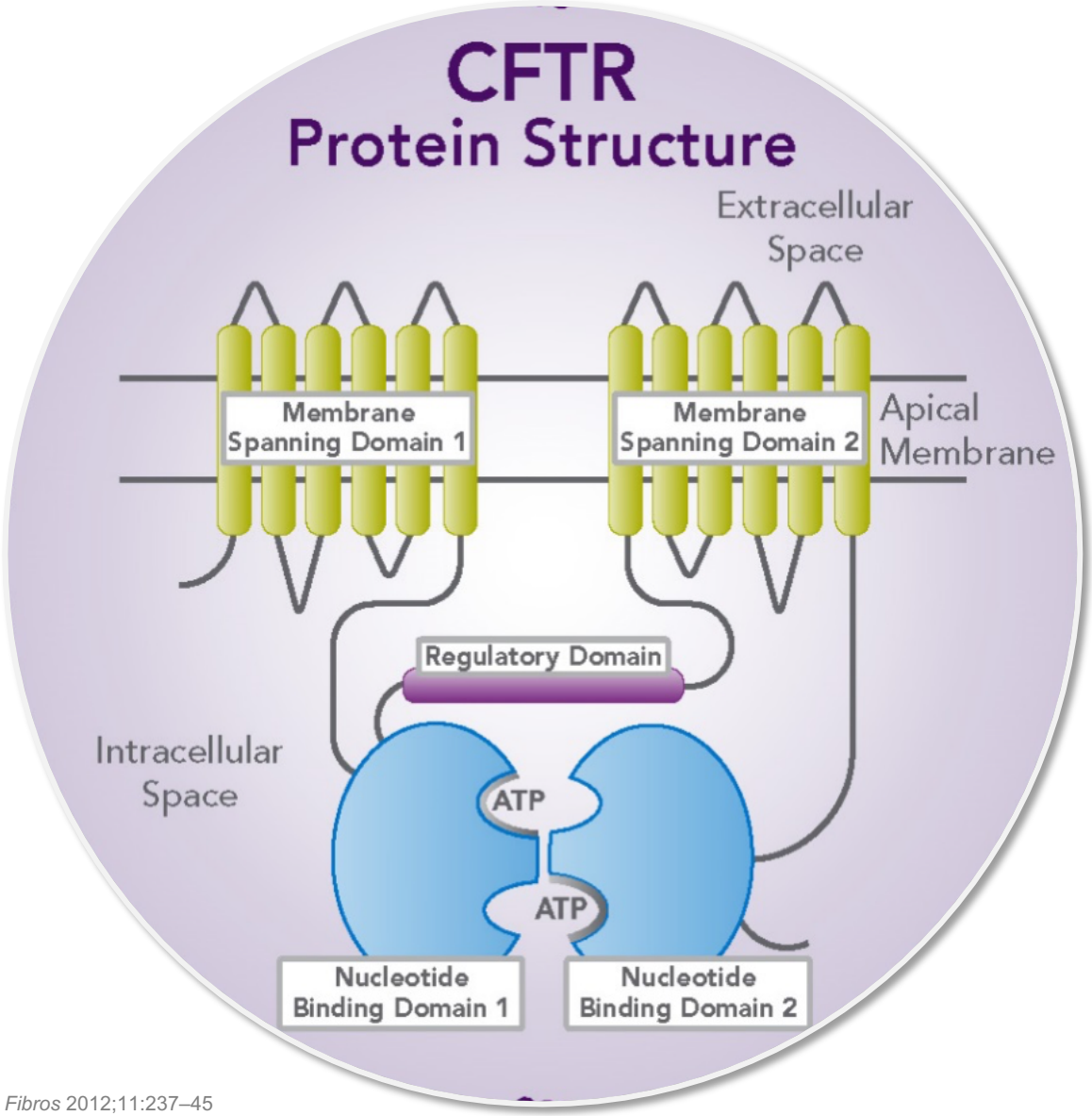


The loss of CFTR protein activity is a result of mutations in the *CFTR* gene that lead to decreased quantity and/or function of CFTR protein at the epithelial apical cell surface

Ultimately, this causes defective ion transport in the lung, pancreas, GI tract, sinuses, skin and reproductive system, leading to the symptoms of CF

Rowe SM et al. *N Engl J Med* 2005;352:1992–2001; MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10

CFTR Protein Structure



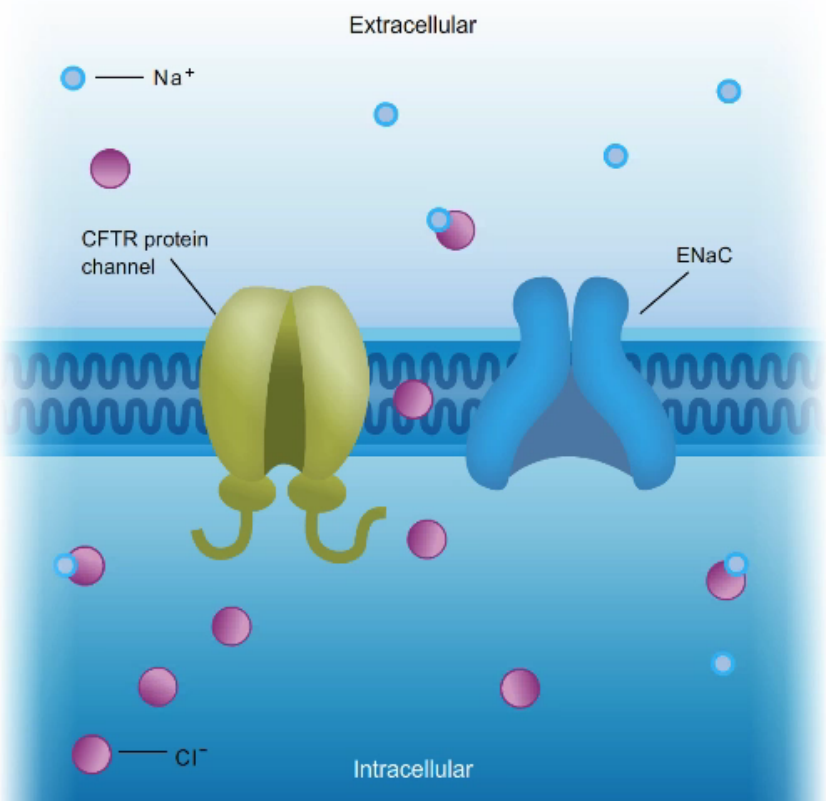
Adapted from Yu H et al. *J Cyst Fibros* 2012;11:237–45

Etiology of CF

Physiological function of the CFTR protein

Click on image to play animation

CFTR channels regulate fluid and electrolyte balance in epithelial tissues (e.g. lung)[1]
This is performed in tandem with the epithelial sodium channel (ENaC)[2]



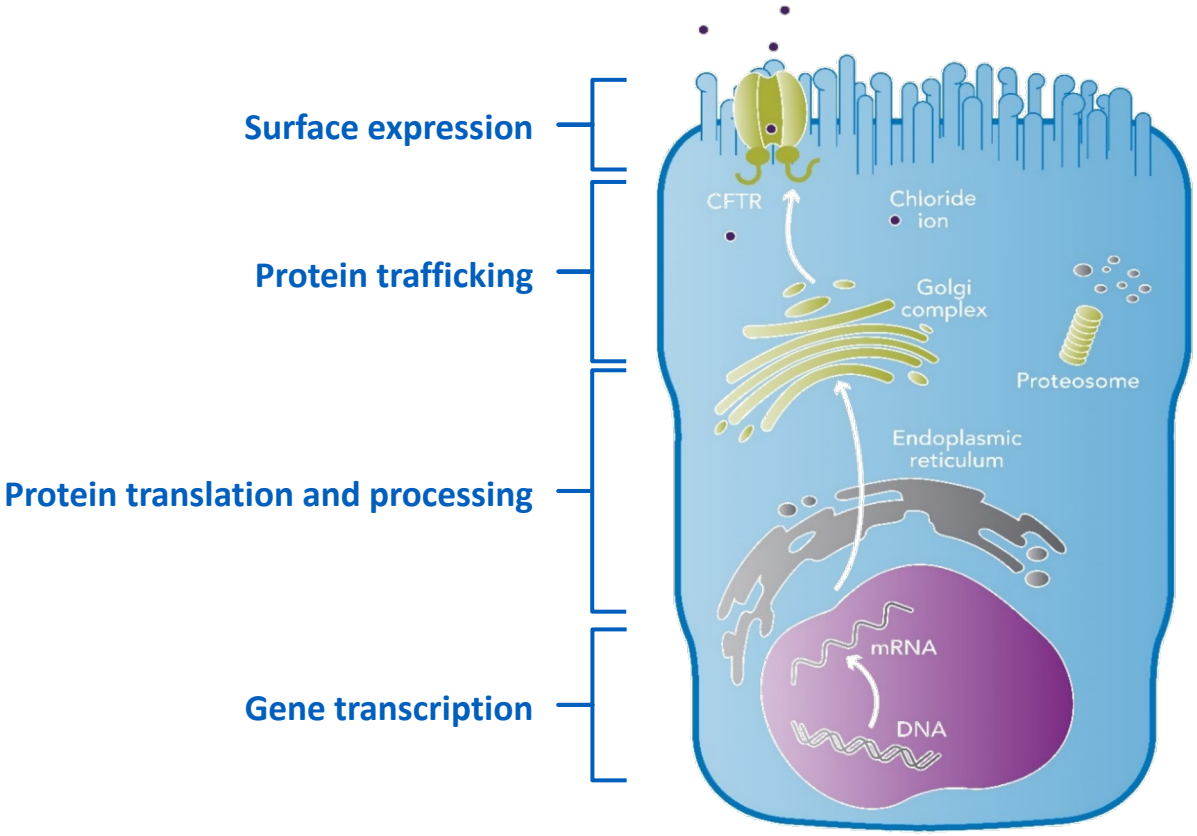
CFTR gene mutations can result in CFTR protein channel abnormalities – the underlying defect of CF disease[3]

1) MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10; 2) Goralsk JL et al. *Curr Opin Pharmacol* 2010;10:294–9; 3) Rowe SM et al. *N Engl J Med* 2005;352:1992–2001

Etiology of CF

Lifecycle of a wild-type CFTR protein channel

CFTR protein is normally synthesized, then processed and trafficked to the apical cell surface to function as a channel to transport chloride and other ions[1–3]



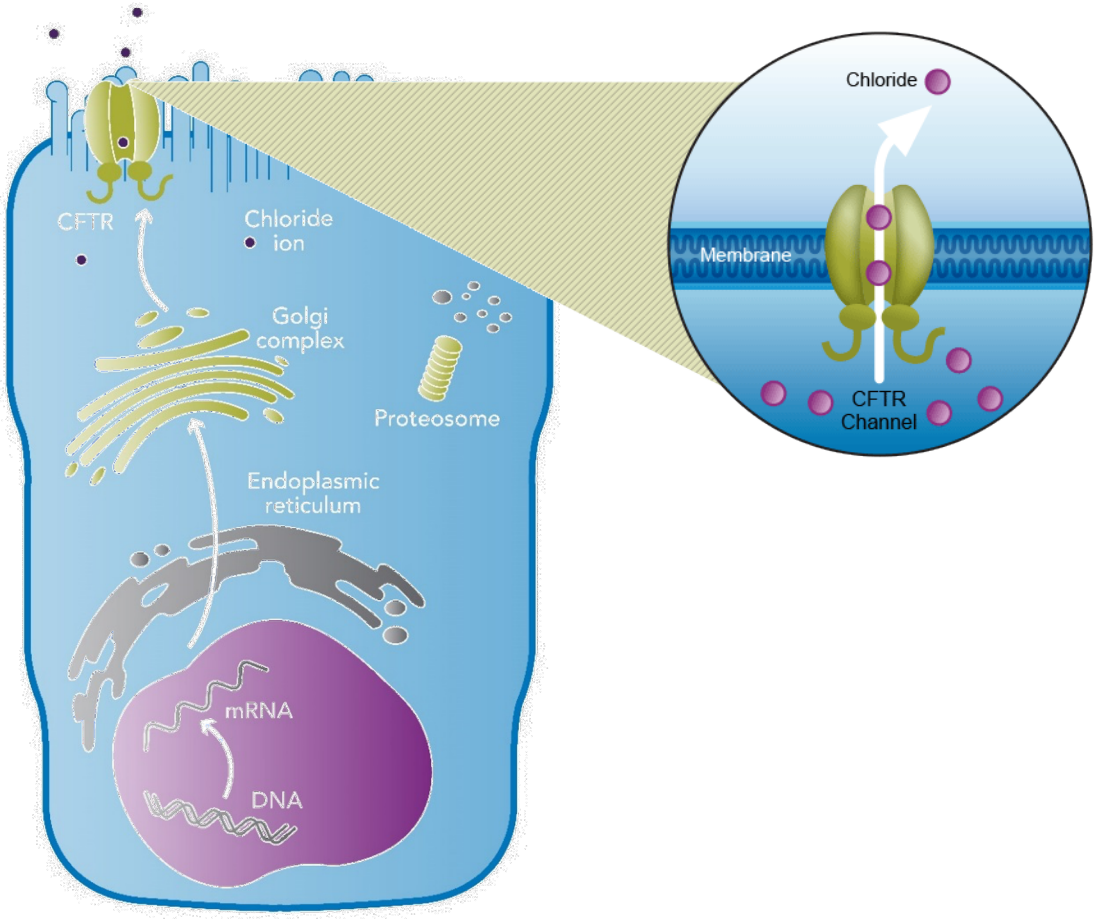
1) Rowe SM et al. *N Engl J Med* 2005;352:1992–2001; 2) MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10; 3) Lommatzsch ST & Aris R. *Semin Respir Crit Care Med* 2009;30:531–8

Etiology of CF

Lifecycle of a wild-type CFTR protein channel

CFTR Function

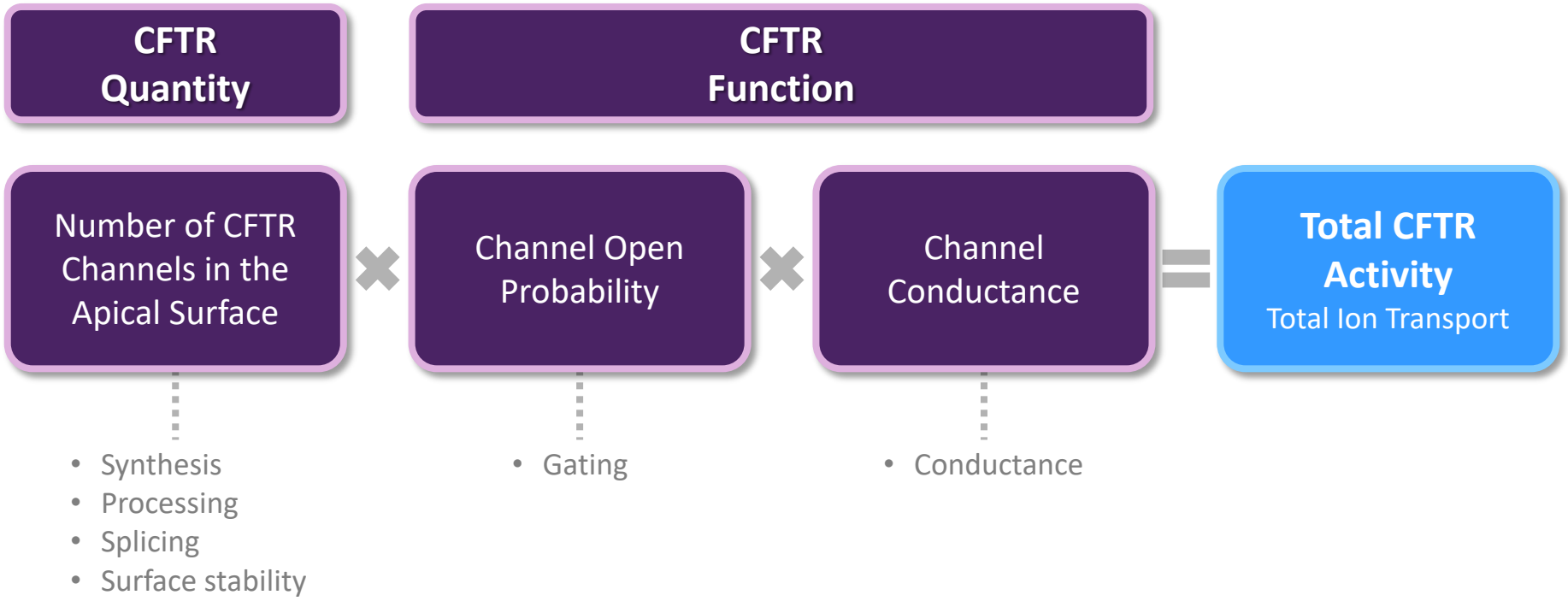
- The CFTR channel functions on the apical cell surface as a channel allowing the movement of chloride and other ions



Derichs N. *Eur Respir Rev* 2013;22:58–65; Lommatzsch ST & Aris R. *Semin Respir Crit Care Med* 2009;30:531–8; Lukacs GL & Durie PR. *N Eng J Med* 2003;349:1401–4

Etiology of CF

What determines 'Total CFTR Activity'?



Zielenski J. *Respiration* 2000;67:117–33; MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10; Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63; Welsh MJ & Smith AE. *Cell* 1993;73:1251–4; 5) Castellani C. *J Cyst Fibros* 2008;7:179–96

CFTR Gene Mutations Give Rise to CFTR Protein Channel Defects That Reduce Cl^- and Other Ion Transport

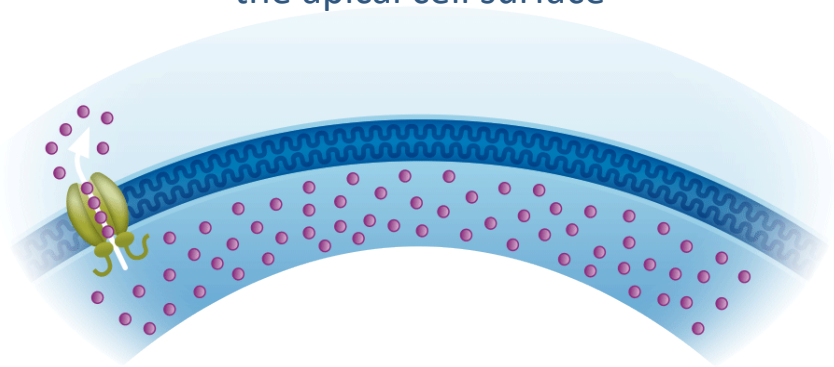
CFTR Quantity

Number of CFTR Channels in the Apical Surface

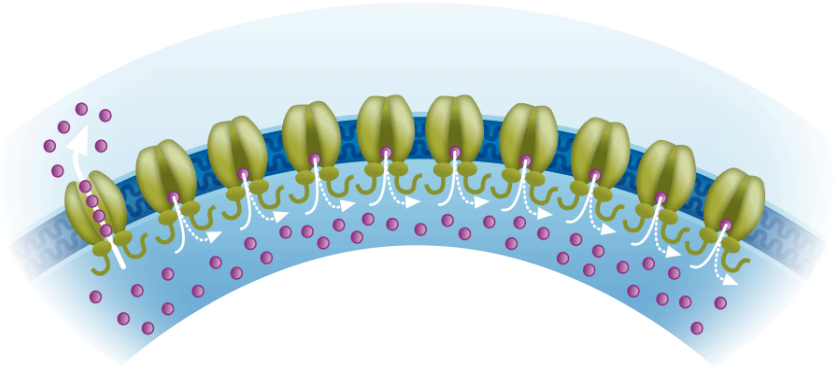
CFTR Function

Channel Open Probability × Channel Conductance

Mutations that reduce the **QUANTITY** of functional CFTR proteins that reach the apical cell surface



Mutations that reduce the **FUNCTION** of CFTR proteins at the apical cell surface



MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10

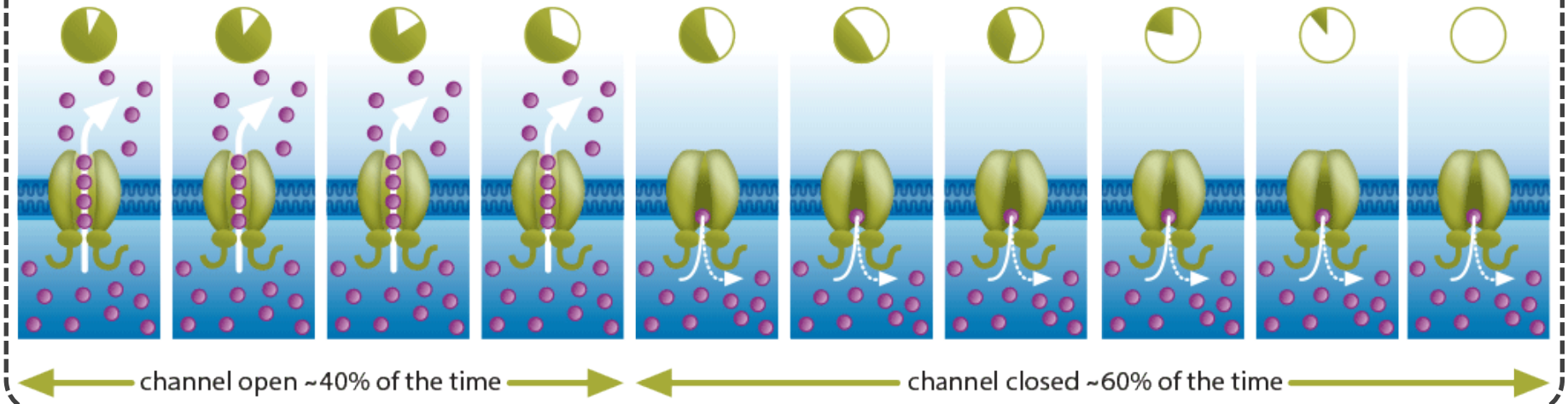
VERTEX

CFTR Protein Channel Physiology

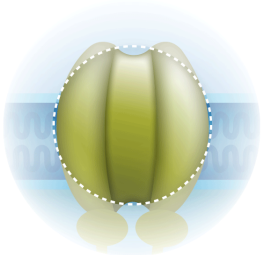
Channel open probability and channel conductance

Normal CFTR channels have a channel open probability of ~40%[1]

*Status of a **single channel** over time*



Channel conductance



Rate at which chloride ions move through open channels[2]

1) Yu H et al. *J Cyst Fibros* 2012;11:237–45; 2) Wang W & Linsdell P. *Biochimica et Biophysica Acta* 2012;1818:851–60

Nomenclature for Mutations

Traditional[1]

- Evolved before mutation nomenclature recommendations
- Imprecise in location of the mutation—amino acid vs. nucleotide
- Descriptive rather than standardized

cDNA[1]

- Standardized nomenclature based on coding DNA reference utilized
- Precise location and change at the nucleotide level
- c./nucleotide number/wildtype nucleotide/> (indicating a change)/mutant nucleotide

CFTR Example

R117H **refers to an arginine (R) to histidine (H) change at amino acid 117**

CFTR Example

R117H **translates to c.350G>A indicating a change from guanine to adenine at nucleotide 350 of the coding DNA**

Additional Terms and Symbols[1-2]

Deletion	del
Insertion	ins
Substitution	>
Duplication	dup
Stop codon	X

1) Ogino S, et al. *J Mol Diagn*. 2007;9(1):1-6; 2) Daen Dunnen JT and Antonarakis E. *Hum Genet.* 2001;109:121-124

From DNA to RNA to Polypeptide

Bases[1]

A= Adenine
T= Thymine (DNA only)
C= Cytosine
G= Guanine
U= Uracil (RNA only)

Codon Wheel

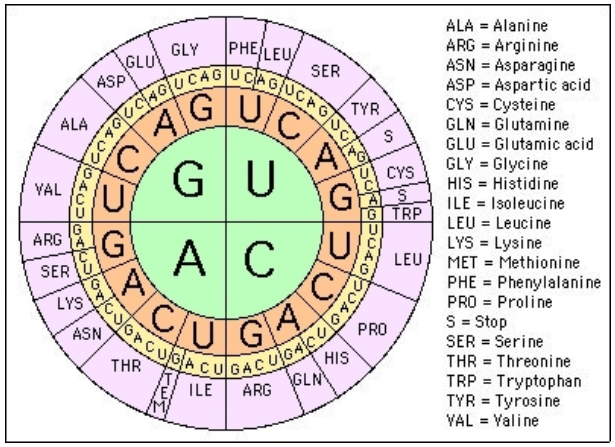


Image from http://www2.sluh.org/bioweb/bi100/tutorials/thegeneticcode.htm

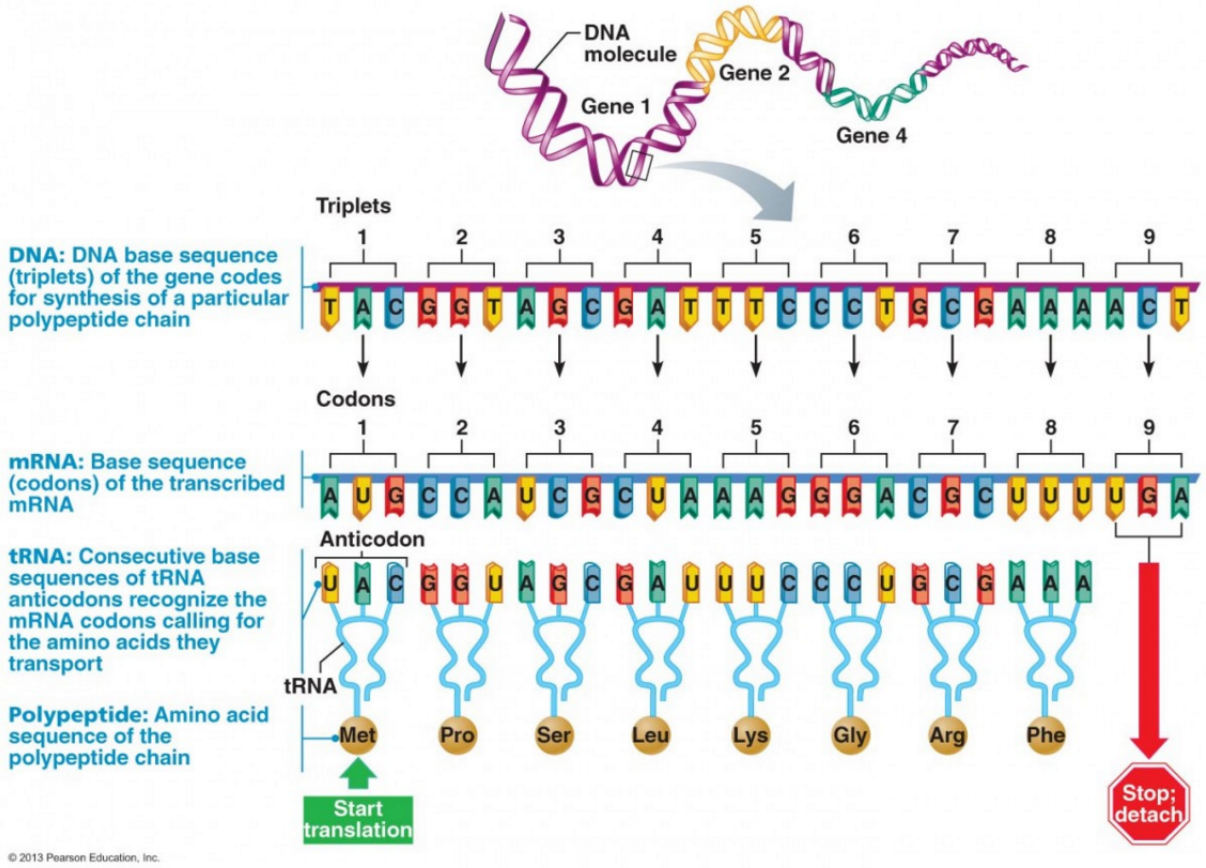
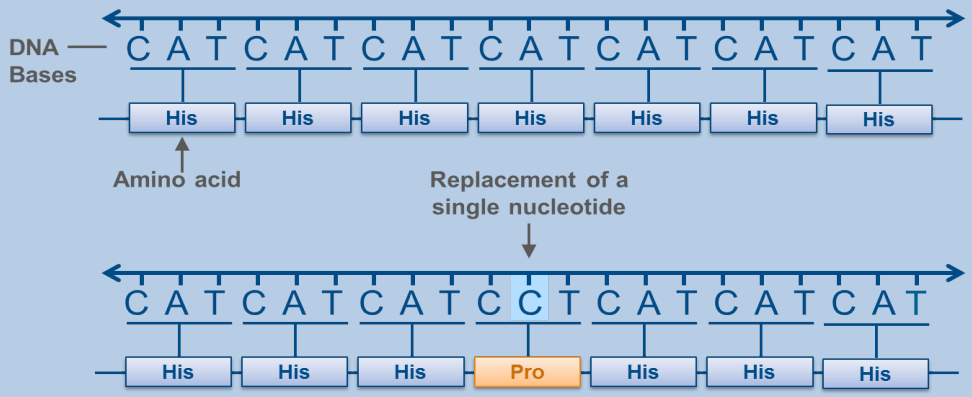
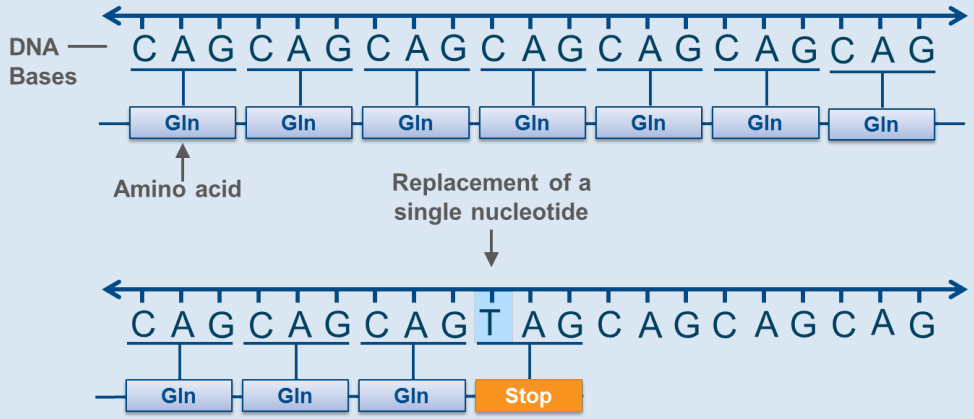


Image from Pearson Education, Inc 2013

Talking Glossary of Genetic Terms Web site. http://www.genome.gov/glossary/index.cfm?id=2. Accessed April 2020

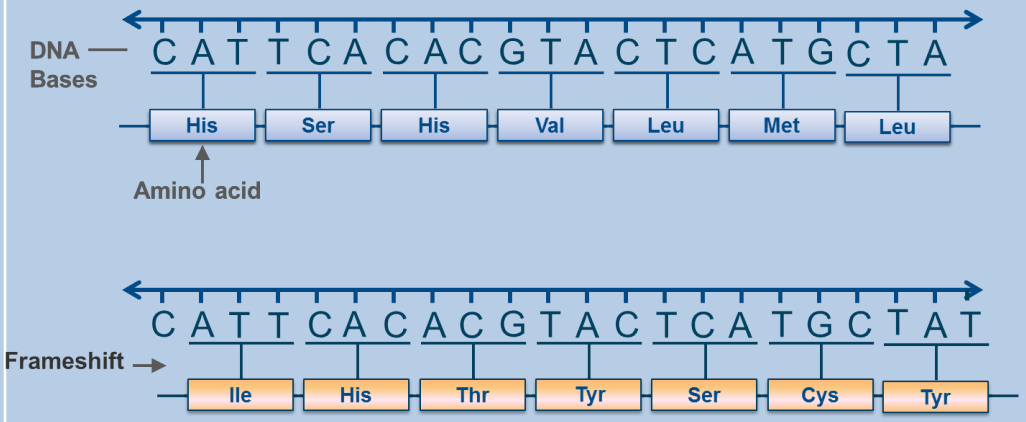
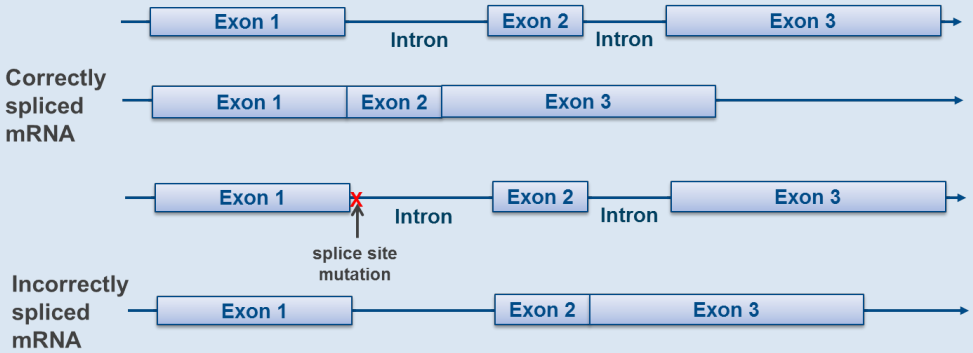
Types of Mutations

Type of mutation	Definition	Illustration	*CFTR* Examples
Missense[1-2]	A change in DNA that results in the substitution of one amino acid for another		*G551D (c.1652G>A)* *R117H (c.350G>A)*
Nonsense[1-2]	A change in DNA that results in a premature stop codon, leading to a truncated protein that may function improperly or not at all		*G542X (c.1524G>T)*

Images adapted from Genetics Home Reference http://ghr.nlm.nih.gov/handbook/mutationsanddisorders/possiblemutations

1) Clinical and Functional of CFTR Web site https://cftr2.org/welcome. Accessed April 2020 2) Genetics Home Reference Web site. http://ghr.nlm.nih.gov/handbook/mutationsanddisorders/possiblemutations. Accessed April 2020.

Types of Mutations

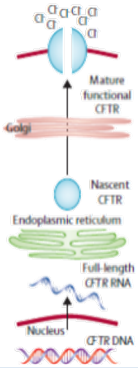
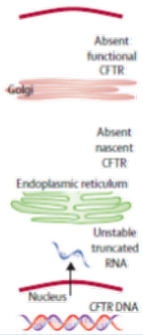
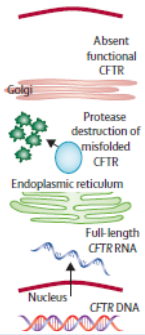
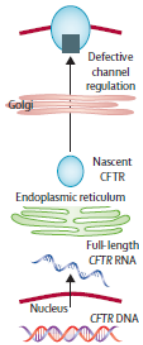
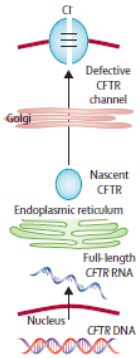
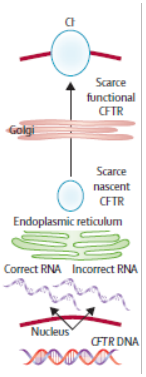
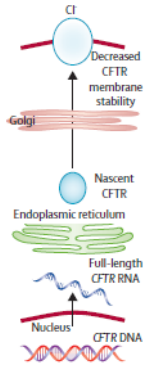
Type of mutation	Definition	Illustration	*CFTR* Examples
Frameshift[1-3]	An insertion or deletion of nucleotide(s) that changes the reading frame		*1460delAT* *(c.1330_1331delAT)*
Splicing[2-3]	A mutation that alters or abolishes the specific sequence denoting the site at which the splicing of an intron takes place		*1811+1.6kbA->G* *(c.1679+1.6kbA>G)*

Images adapted from Genetics Home Reference http://ghr.nlm.nih.gov/handbook/mutationsanddisorders/possiblemutations

1) Genetics Home Reference Web site. http://ghr.nlm.nih.gov/handbook/mutationsanddisorders/possiblemutations. Accessed April 2020. 2) Clinical and Functional of CFTR Web site https://cftr2.org/welcome. Accessed April 2020. 3) Cystic Fibrosis Mutations Database Web site. http://www.genet.sickkids.on.ca Accessed April 2020

Classification of *CFTR* Mutation Defects

Overview

Normal	I	II	III	IV	V	VI
						
CFTR defect	Synthesis defect	Processing defect	Gating defect	Conductance defect	Splicing defect	Surface stability defect
Type of mutations	Nonsense, frameshift, canonical splice	Missense, amino acid deletion	Missense, amino acid change	Missense, amino acid change	Missense, splicing	Missense, amino acid change
Functional consequence	No functional protein	Misfolded protein fails to reach cell membrane or present in very small amounts	Decreased or lack of protein channel opening	Impaired movement of ions through the protein channel	Reduced protein synthesis resulting in fewer proteins reaching the apical cell membrane	Decreased protein stability resulting in fewer proteins reaching the apical cell membrane
Example mutations	*G542X*, *W1282X*, *621+1G→T*	*F508del*, *N1303K*, *I507del*	*G551D*, *S549N*, *S1251N*, *F508del*, *R117H*	*R117H*, *R347P*, *R334W*	*2789+5G→A*, *3849+10kbC→T*	*4326delTC*, *Q1412X*, *4279insA*

A single *CFTR* mutation can result in multiple defects in the CFTR protein
Any particular defect has a continuum of severity leading to a range in Total CFTR Activity

Adapted from: Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63
Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63; Rowe SM et al. *N Engl J Med* 2005;352:1992–2001

Molecular Effects of *CFTR* Gene Mutations

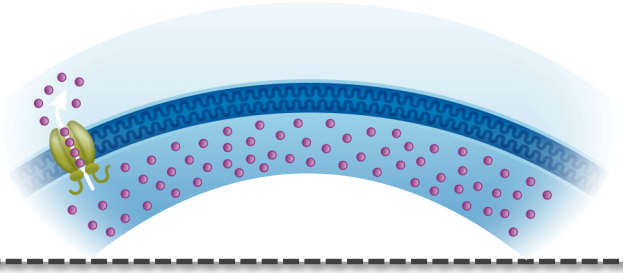
A single *CFTR* mutation can result in multiple defects in the CFTR protein

Any particular defect has a continuum of severity leading to a range in Total CFTR Activity

CFTR Quantity

Little to No CFTR Quantity

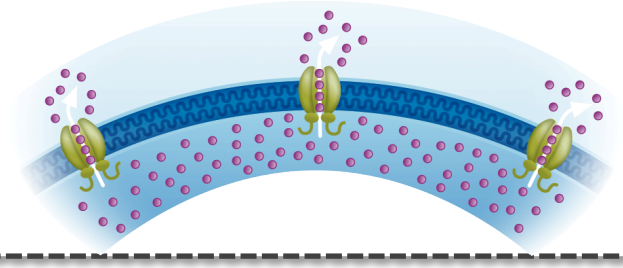
at cell surface resulting in Little to No Total CFTR Activity



Due to defective synthesis or impaired processing

Some CFTR Quantity

at cell surface resulting in Residual CFTR Activity

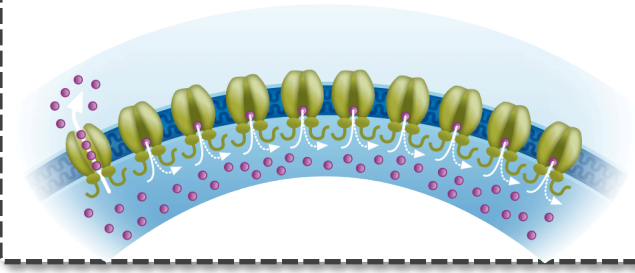


Due to reduced synthesis

CFTR Function

Little to No CFTR Function

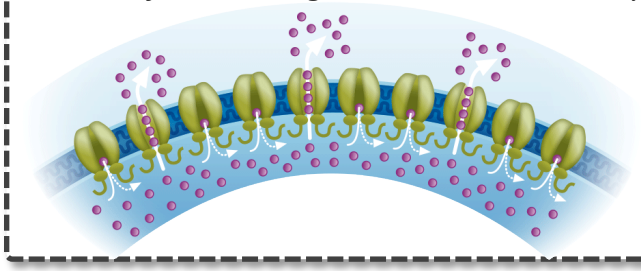
at cell surface resulting in Little to No Total CFTR Activity



Due to severely decreased channel opening or channel conductance

Some CFTR Function

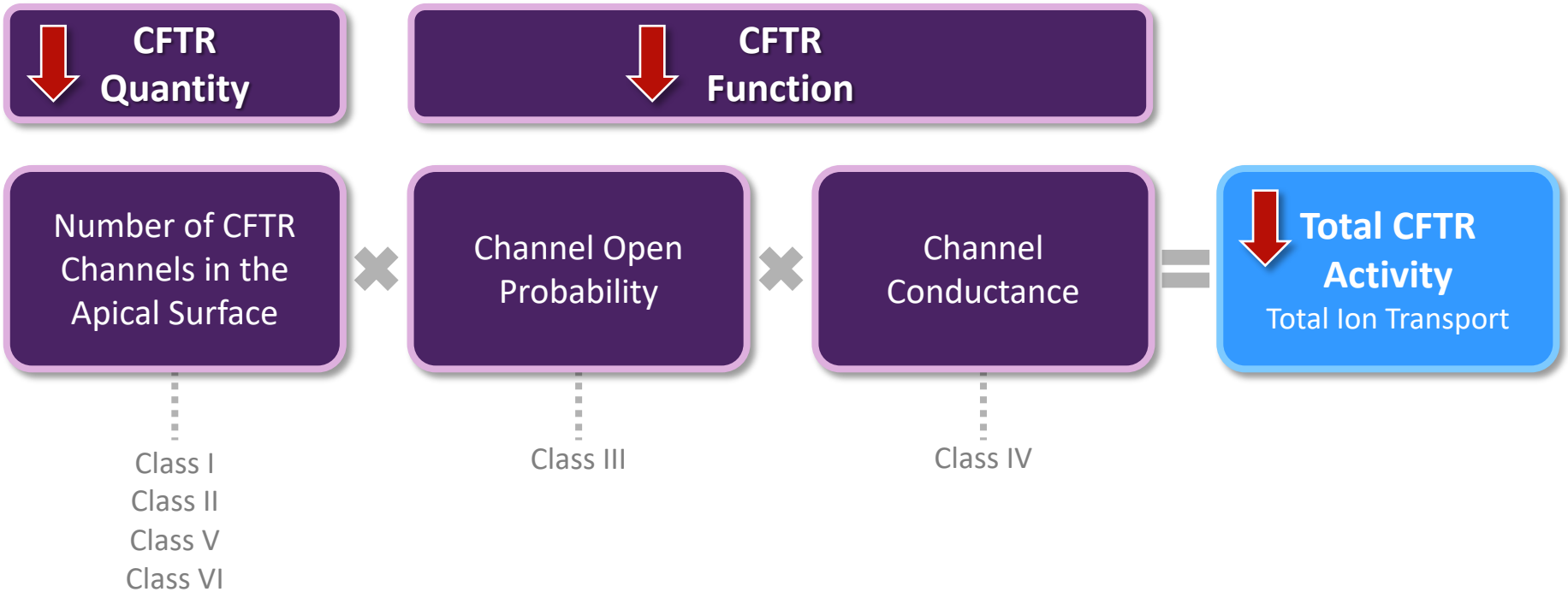
at cell surface resulting in Residual CFTR Activity



Due to moderately decreased channel opening or channel conductance

Zielenski J. *Respiration* 2000;67:117–33; Castellani C et al. *J Cyst Fibros* 2008;7:179–96

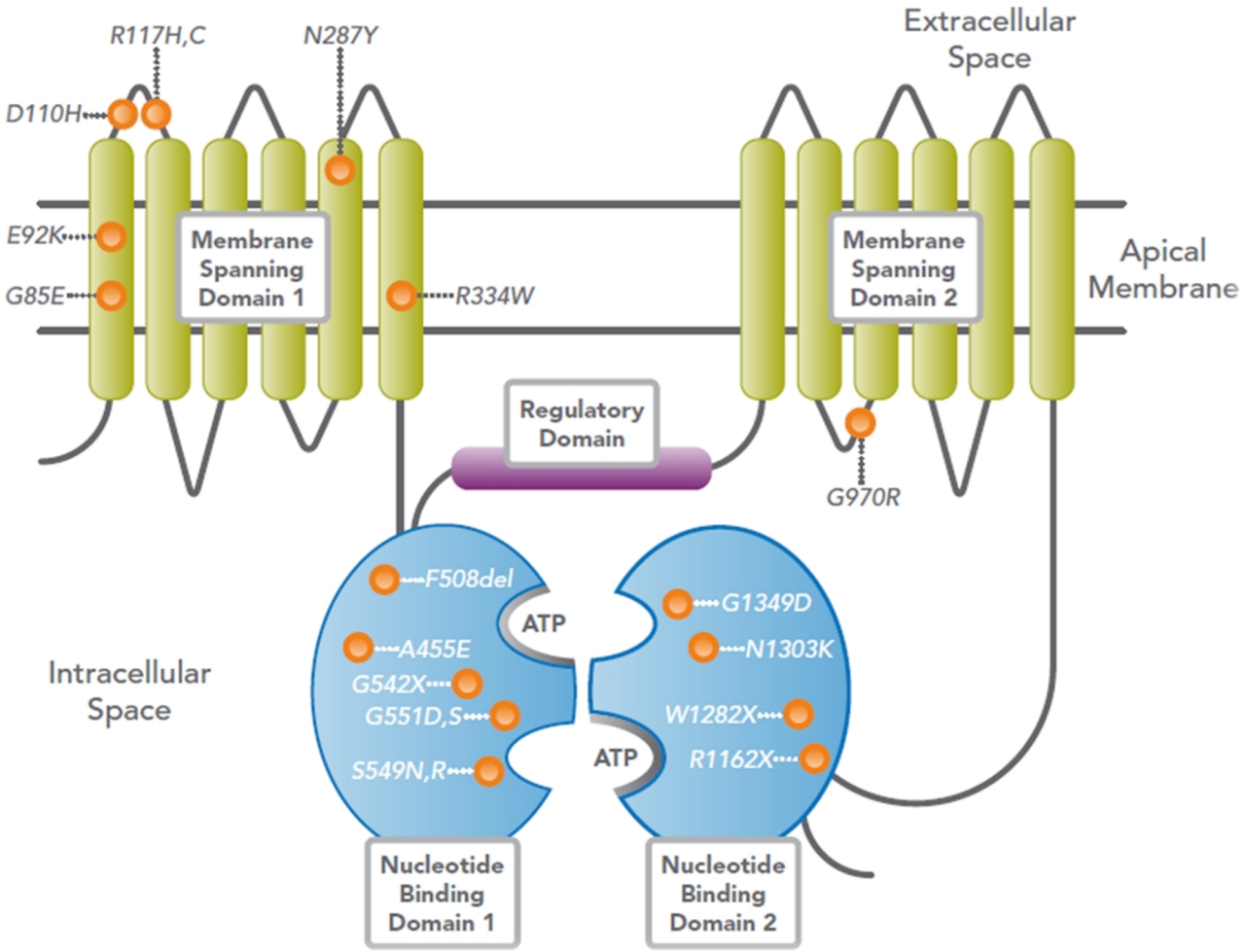
Mutations Affecting CFTR Quantity or CFTR Function Affect Total CFTR Activity



Single mutations may result in multiple defects
Mutations have been classed into the primary defect in the class system

Zielenski J. *Respiration* 2000;67:117–33; MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10; Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63; Welsh MJ & Smith AE. *Cell* 1993;73:1251–4; Castellani C. *J Cyst Fibros* 2008;7:179–96; Derichs N. *Eur Respir Rev* 2013;22:58–65

Location of Various Amino Acid Alterations in the CFTR Protein caused by *CFTR* Gene Mutations



Adapted from Yu H et al. *J Cyst Fibros* 2012;11:237–45

CFTR Genotype and Clinical Phenotype

CFTR Mutation Defects

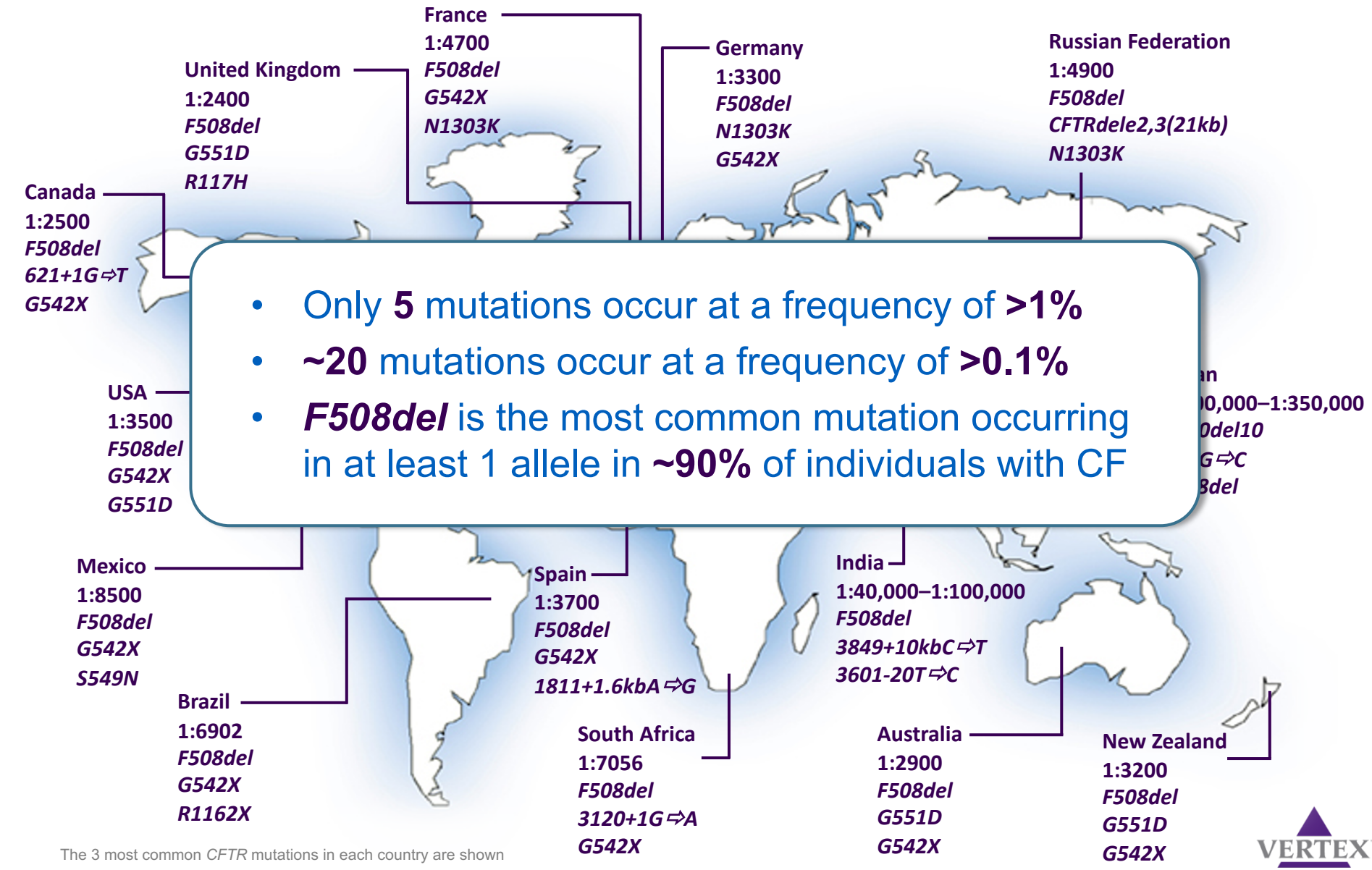
~2,000 *CFTR* mutations have been identified

cftr2.org is a publicly available website with a searchable database on ~88,000 individuals with CF[1,2]

- Data on ~276 of the most common *CFTR* mutations
- Searchable for reported lung function, sweat chloride levels, and other data
- 127 *CFTR* mutations have been identified as causing CF

1) Sosnay PR et al. *Nat Genet* 2013;45:1160–7; 2) Clinical and Functional of CFTR Web site https://cftr2.org/welcome. Accessed April 2020

Global *CFTR* Mutational Diversity



- Only **5** mutations occur at a frequency of **>1%**
- **~20** mutations occur at a frequency of **>0.1%**
- ***F508del*** is the most common mutation occurring in at least 1 allele in **~90%** of individuals with CF

The 3 most common *CFTR* mutations in each country are shown

Genotype and Phenotype

Overview

CFTR genotype can be associated with clinical phenotype[1,2]

- Provides some predictive information about clinical outcomes at the population level
- Pancreatic status strongly correlated with genotype; poorer correlation for lung function and other organs[1–3]

Many other factors also contribute to clinical status

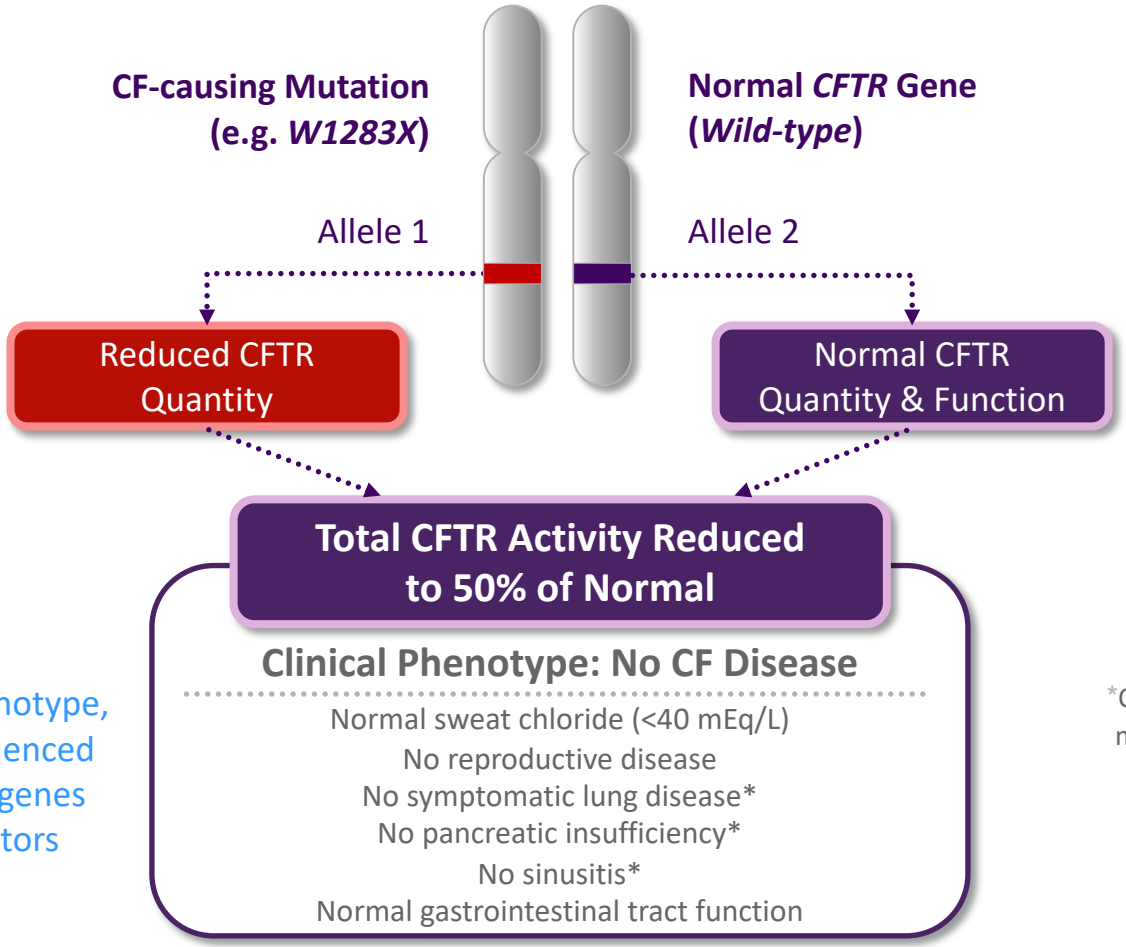
- Non-genetic factors (e.g. environmental) are known to contribute to disease course[1,4]
- Genes other than *CFTR* also affect lung function and disease course[5]
  - Modifier genes

1. Zielenski J. *Respiration* 2000;67:117–33; 2. Castellani C et al. *J Cyst Fibros* 2008;7:179–96; 3. Wilschanski M et al. *Gut* 2007;56:1153–63;
4. Cutting GR. *Ann N Y Acad Sci* 2010;1214:57–69; 5. Collaco JM et al. *Curr Opin Pulm Med* 2008;14:559–66

Genotype and Phenotype

CFTR carriers (e.g. *W1282X/Wild-type CFTR*) have a normal phenotype

Total CFTR Activity as low as 50% of normal can be associated with no CF disease phenotype



In addition to *CFTR* genotype, phenotype is also influenced by non-*CFTR* modifier genes and environmental factors

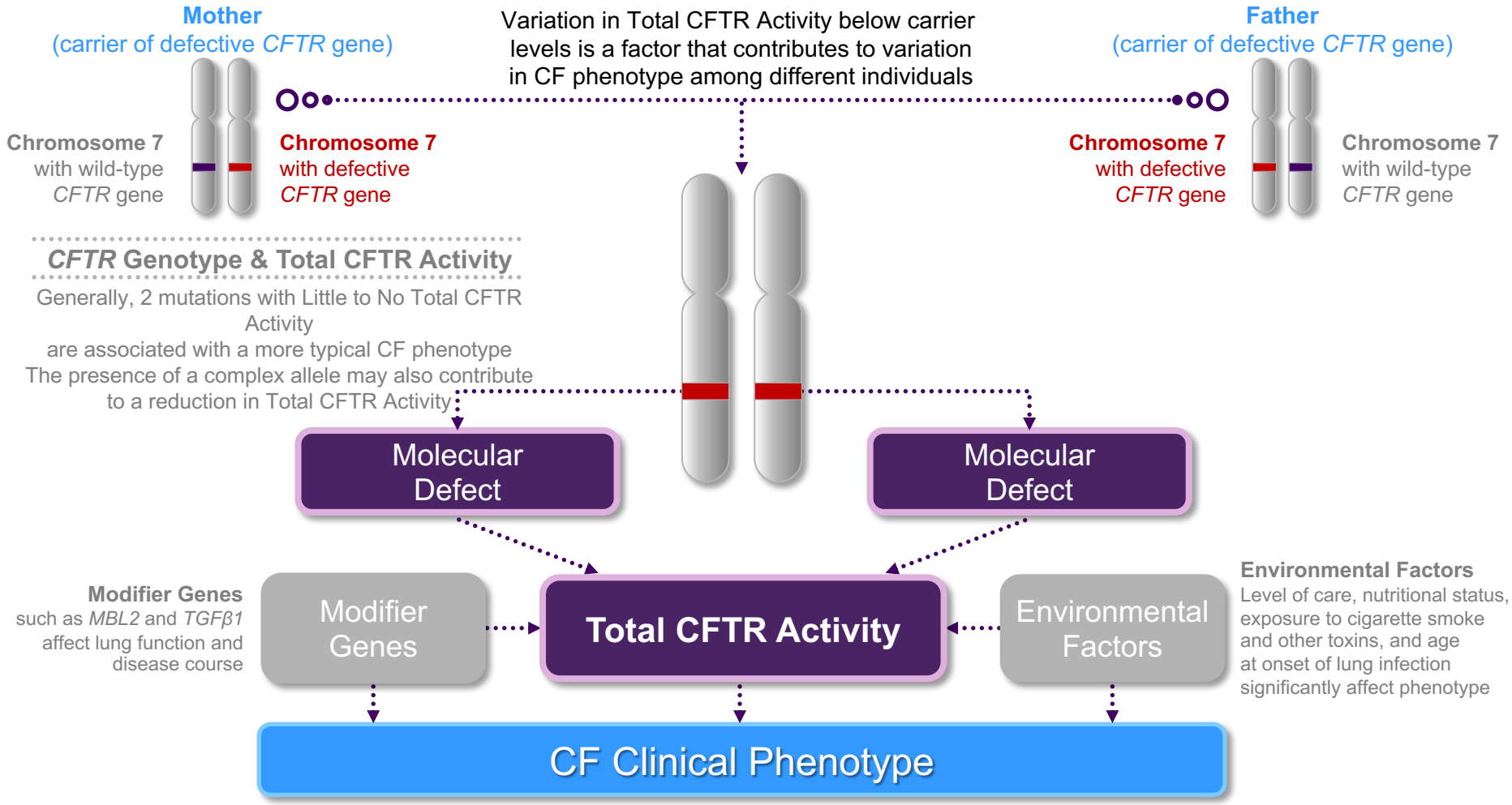
*Carriers of *CFTR* mutations may have an increased risk for pancreatitis, sinusitis or bronchiectasis

Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63; Griesenbach U et al. *Thorax* 1999;54(Suppl 2):S19–23; Zielenski J. *Respiration* 2000;67:117–33; Davis PB. *Am J Respir Crit Care Med* 2006; 173:475–82; Wilschanski M & Durie PR. *Gut* 2007;56:1153–63; Castellani C et al. *J Cyst Fibros* 2008;7:179–96

Genotype and Phenotype

CF-causing mutations on both alleles result in a CF phenotype

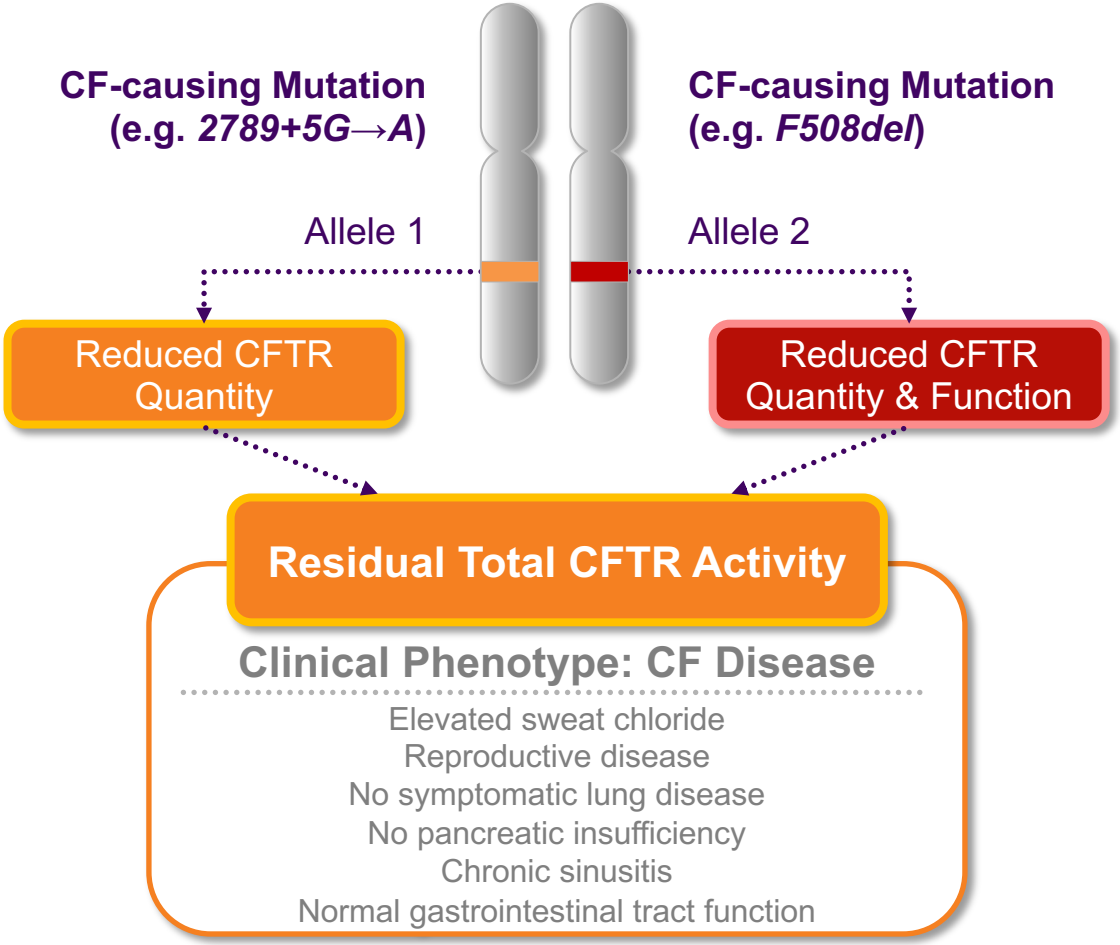
CFTR genotype of both alleles is a determinant of Total CFTR Activity



Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63; Griesenbach U et al. *Thorax* 1999;54(Suppl 2):S19–23; Zielenski J. *Respiration* 2000;67:117–33; Cutting GR. *Annu Rev Genomics Hum Genet* 2005;6:237–60; Davis PB. *Am J Respir Crit Care Med* 2006; 173:475–82; Wilschanski M & Durie PR. *Gut* 2007;56:1153–63; Castellani C et al. *J Cyst Fibros* 2008;7:179–96

Individual with CF

Example genotype: *2798+5G→A/F508del*

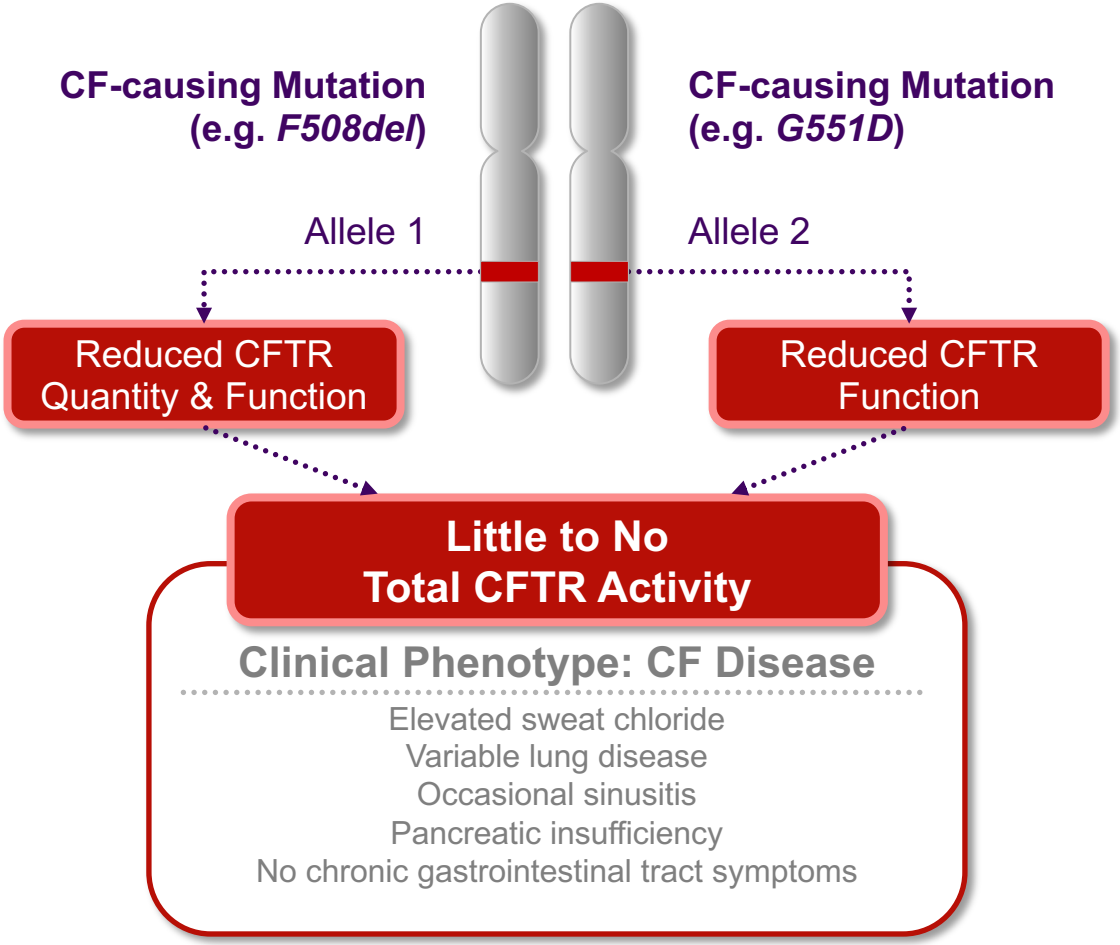


In addition to *CFTR* genotype, phenotype is also influenced by non-*CFTR* modifier genes and environmental factors

Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63;Griesenbach U et al. *Thorax* 1999;54(Suppl 2):S19–23; Zielenski J. *Respiration* 2000;67:117–33; Davis PB. *Am J Respir Crit Care Med* 2006;173:475–82; Wilschanski M & Durie PR. *Gut* 2007;56:1153–63; Castellani C et al. *J Cyst Fibros* 2008;7:179–96

Individual with CF

Example genotype: *F508del/G551D*

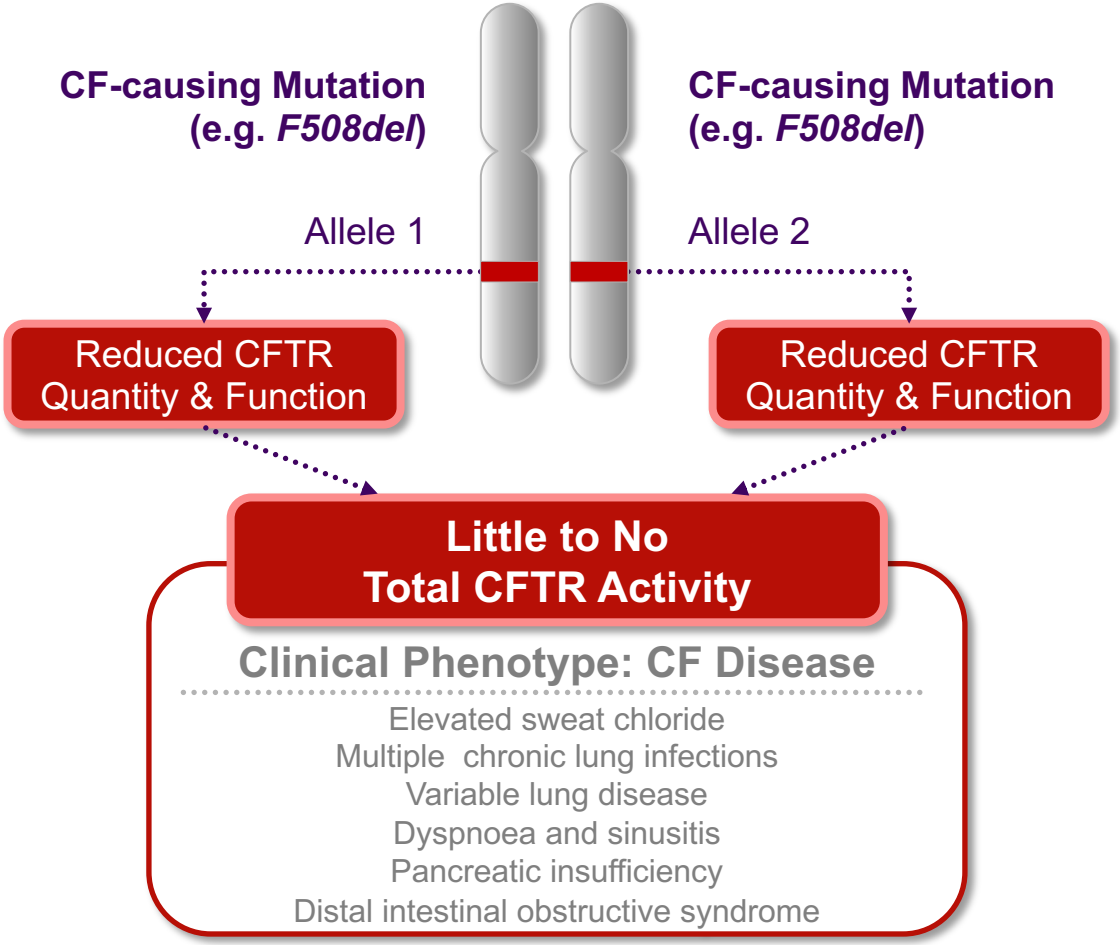


In addition to *CFTR* genotype, phenotype is also influenced by non-*CFTR* modifier genes and environmental factors

Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63; Griesenbach U et al. *Thorax* 1999;54(Suppl 2):S19–23; Wilschanski M & Durie PR. *Gut* 2007;56:1153–63; Castellani C et al. *J Cyst Fibros* 2008;7:179–96

Individual with CF

Example genotype: *F508del/F508del*

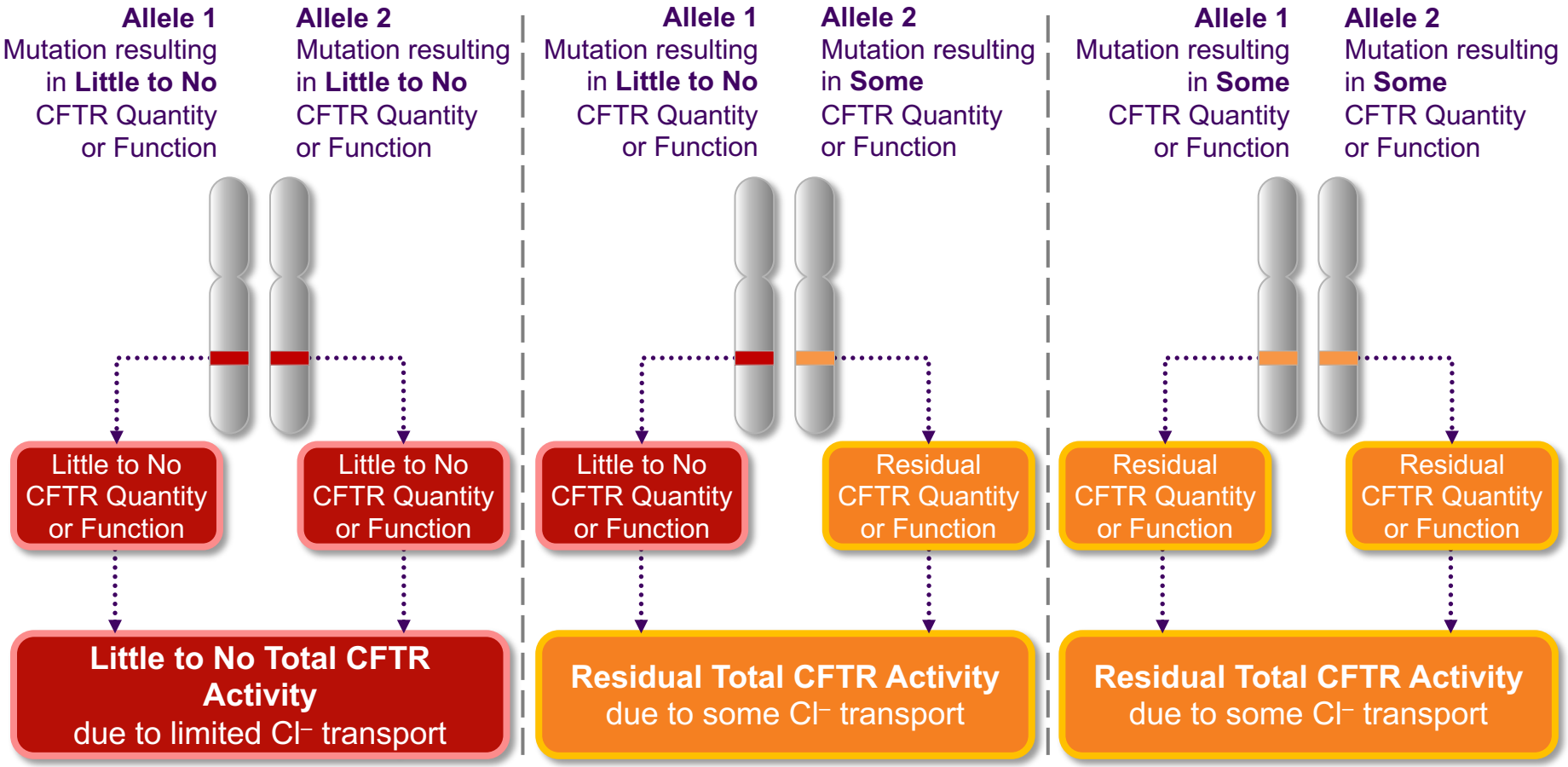


In addition to *CFTR* genotype, phenotype is also influenced by non-*CFTR* modifier genes and environmental factors

Boyle MP & De Boeck K. *Lancet Respir Med* 2013;1:158–63; Griesenbach U et al. *Thorax* 1999;54(Suppl 2):S19–23; Wilschanski M & Durie PR. *Gut* 2007;56:1153–63; Castellani C et al. *J Cyst Fibros* 2008;7:179–96

Genotype and Phenotype

CFTR genotype of both alleles



There is a range of phenotypes for each *CFTR* mutation. Although correlations exist, it is very difficult to predict exactly what will happen to any particular individual with CF

Zielenski J. *Respiration* 2000;67:117–33; Collaco JM et al. *Curr Opin Pulm Med* 2008;14:559–66

VERTEX

Genotype and Phenotype

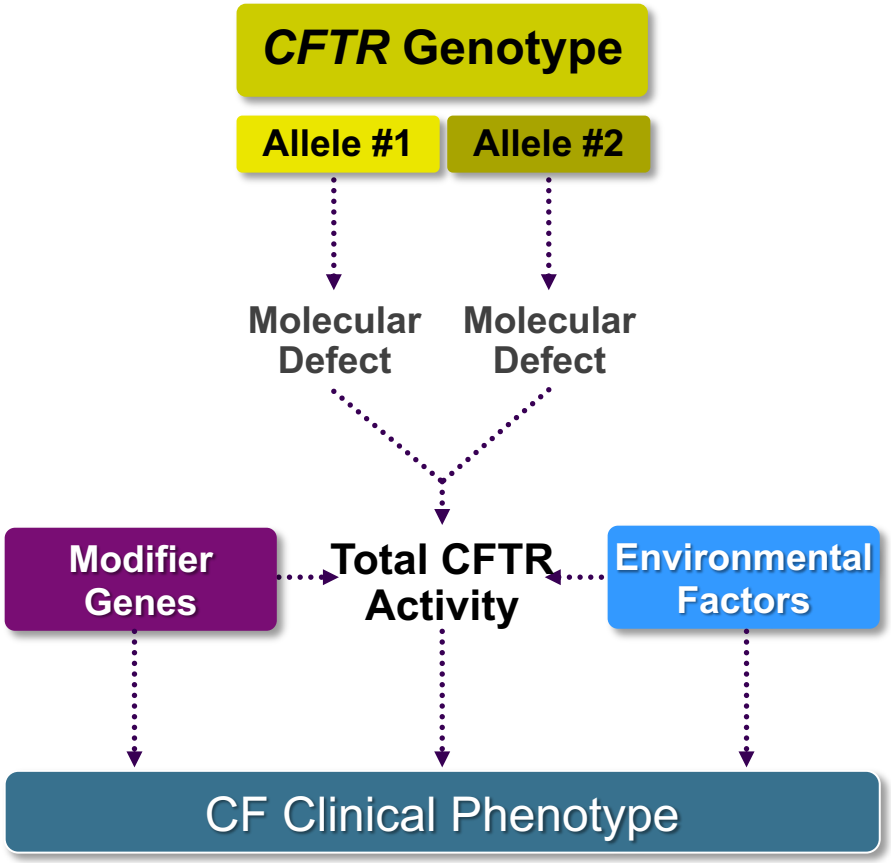
Many other factors also contribute to clinical status

Modifier Genes

Modifier genes, such as *MBL2* and *TGFβ1*, affect lung function and disease course

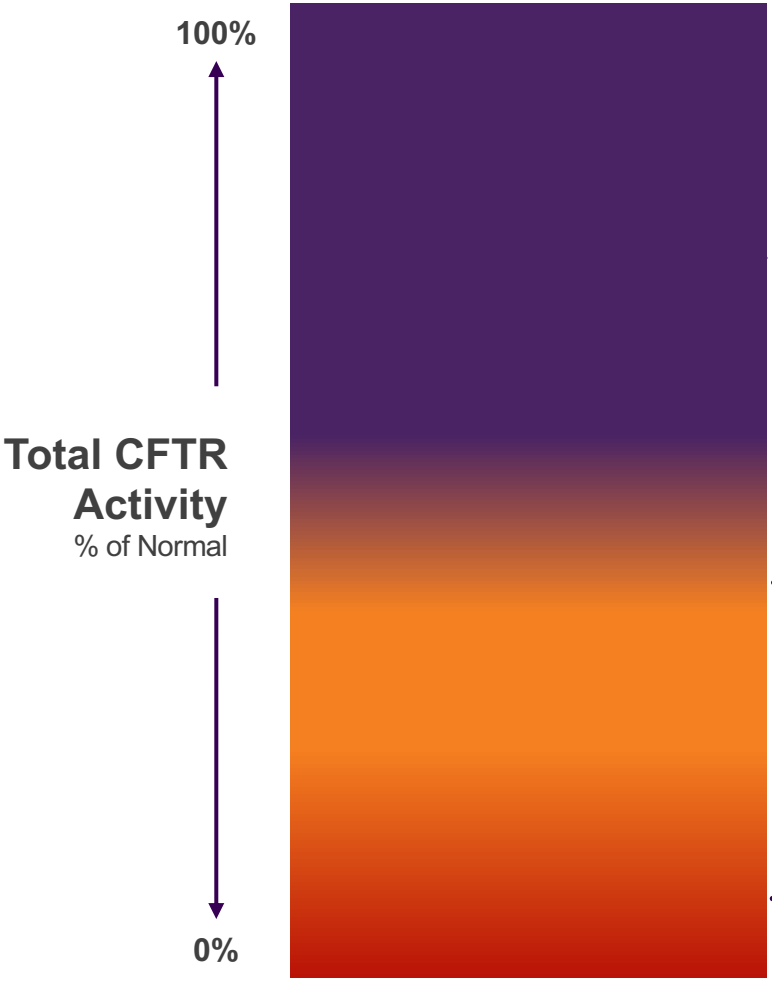
Environmental Factors

Level of care, nutritional status, exposure to cigarette smoke and other toxins, and age at onset of lung infection significantly affect phenotype



Castellani C et al. *J Cyst Fibros* 2008;7:179–96; Cutting GR. *Annu Rev Genomics Hum Genet* 2005;6:237–60; Wilschanski M & Durie PR. *Gut* 2007;56:1153–63

Genotype-determined Total CFTR Activity Contributes to the CF Clinical Phenotype



Clinical Phenotype

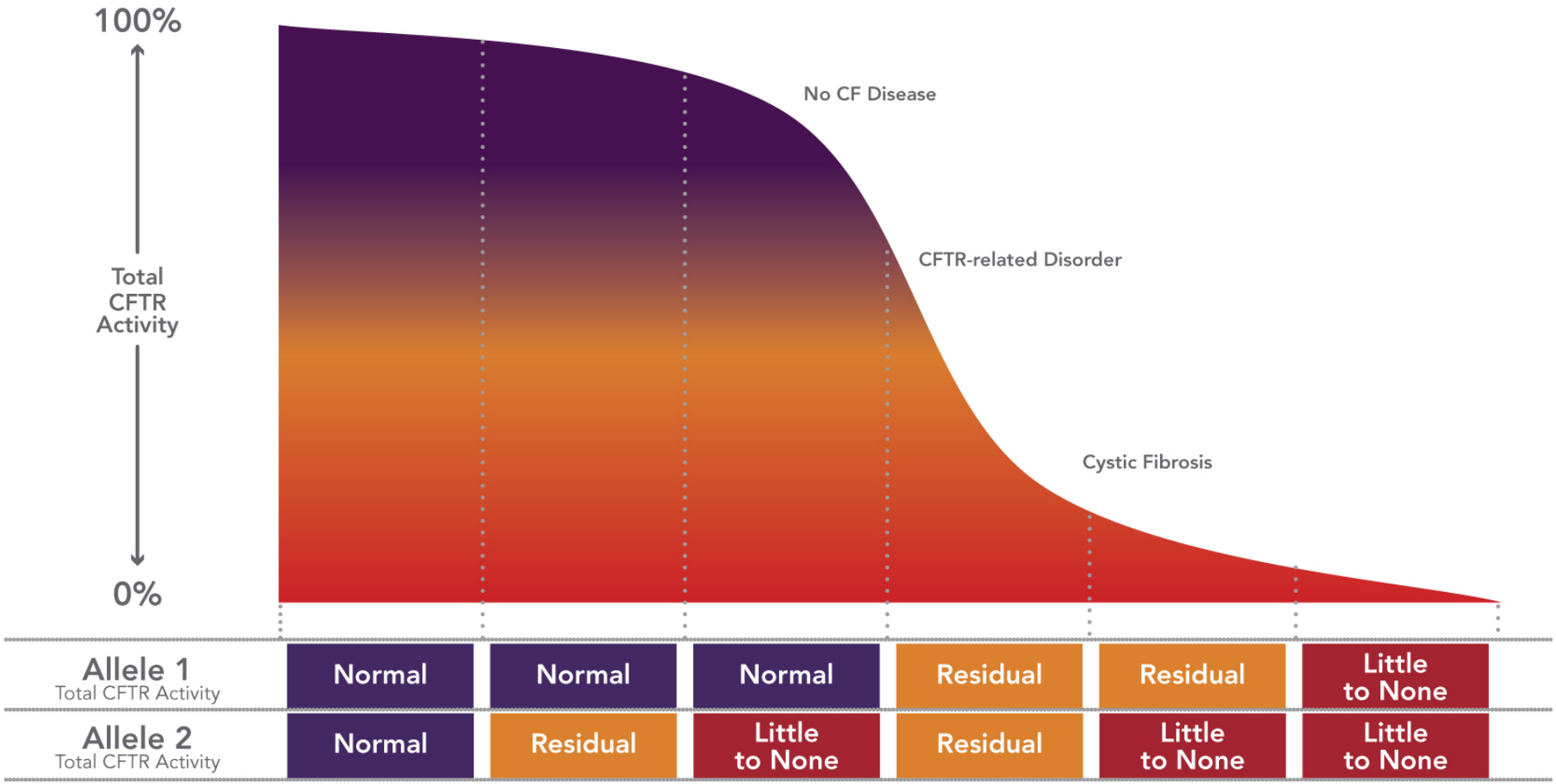
Healthy individuals and *CFTR* carriers

Clinical entities associated with CFTR dysfunction that do not fulfill diagnostic criteria for CF (e.g. congenital bilateral absence of vas deferens [CBAVD], acute recurrent or chronic pancreatitis and bronchiectasis)

Typical phenotype: sinopulmonary disease, sweat chloride >60 mmol/L, pancreatic insufficiency, appearing early in life. In some individuals, progression of disease is delayed or not all features are present

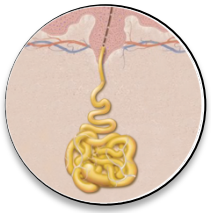
Griesenbach U et al. *Thorax* 1999;54(Suppl 2):S19–23; Bombieri C et al. *J Cyst Fibros* 2011;10:S86–102; Moskowitz SM. *GeneReviews* 2001; Davis PB et al. *J Respir Crit Care Med* 1996;154:1229–56; Davis PB. *Am J Respir Crit Care Med* 2006;173:475–82

CFTR Genotype of Both Alleles is a Determinant of Total CFTR Activity That Affects CF Phenotype



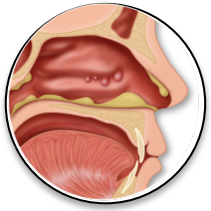
Adapted from Zielenski J. *Respiration* 2000;67:117–33

Sensitivity to Depressed Total CFTR Activity Affects Severity of Disease Between Organ Systems



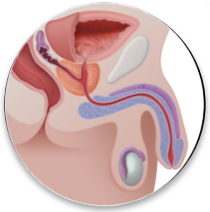
Sweat Glands

Range in sweat chloride levels from <40 mmol/L to ≥90 mmol/L



Sinuses

From opacification of sinuses to refractory sinusitis

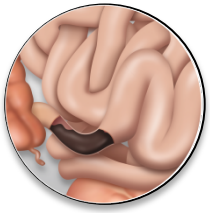


Reproductive System

In males, from oligospermia to congenital bilateral absence of vas deferens (CBAVD) and infertility

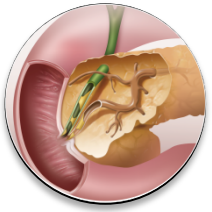
Lungs

From air trapping and atelectasis to bronchiectasis, mucus plugging, bacterial and fungal infections, bronchial cysts, pneumothorax, and end-stage lung disease



Gastrointestinal System

Meconium ileus, distal intestinal obstruction syndrome (DIOS), liver disease and cirrhosis



Pancreas

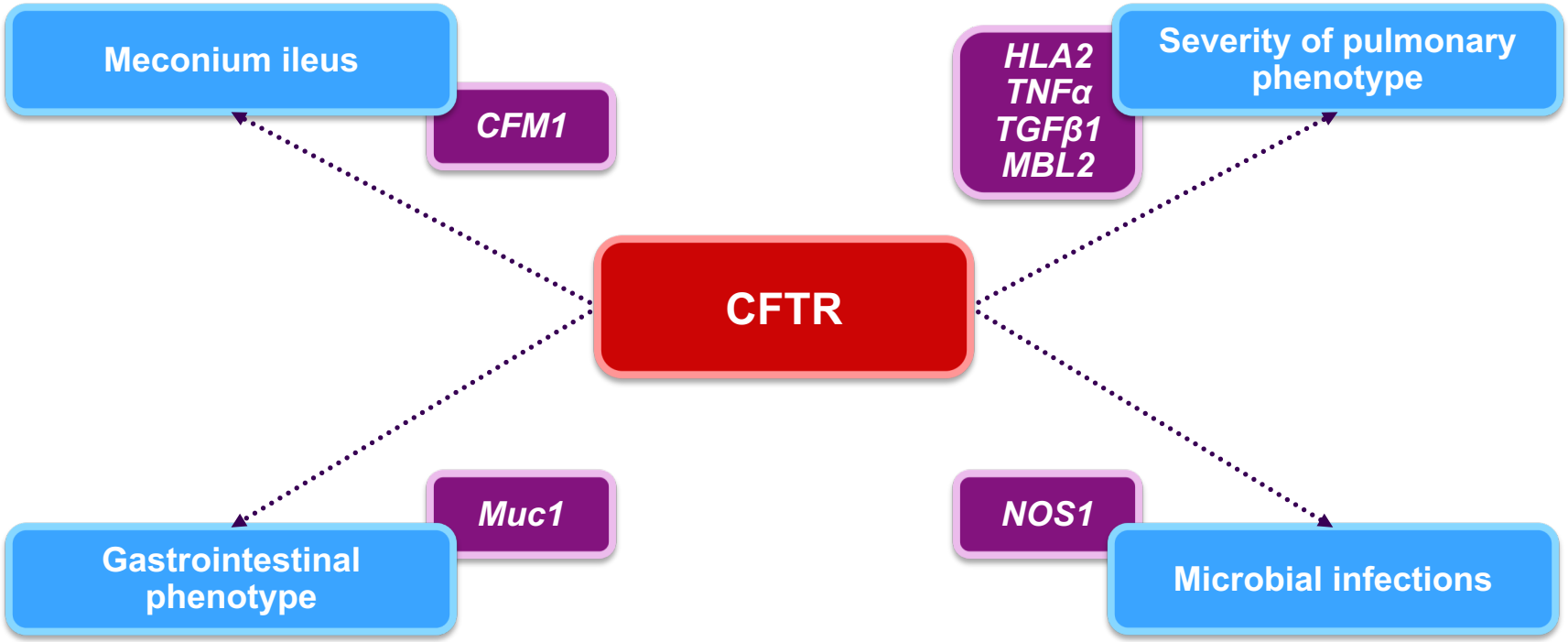
From pancreatic sufficiency with pancreatitis to pancreatic insufficiency, CF-related diabetes

Davis PB. *Am J Respir Crit Care Med* 2006;173:475–82; Tiddens HA & de Jong PA. *Proc Am Thorac Soc* 2007;4:343–6; Walkowiak J et al. *Eur J Gastroenterol Hepatol* 2008;20:157–60; Colombo C et al. *Pediatr Gastroenterol Nutr* 2006;43(Suppl 1):S49–55

Genotype and Phenotype

Role of modifier genes

Genetic variation in non-*CFTR* genes, or modifier genes, may influence the severity of disease expression[1–6]



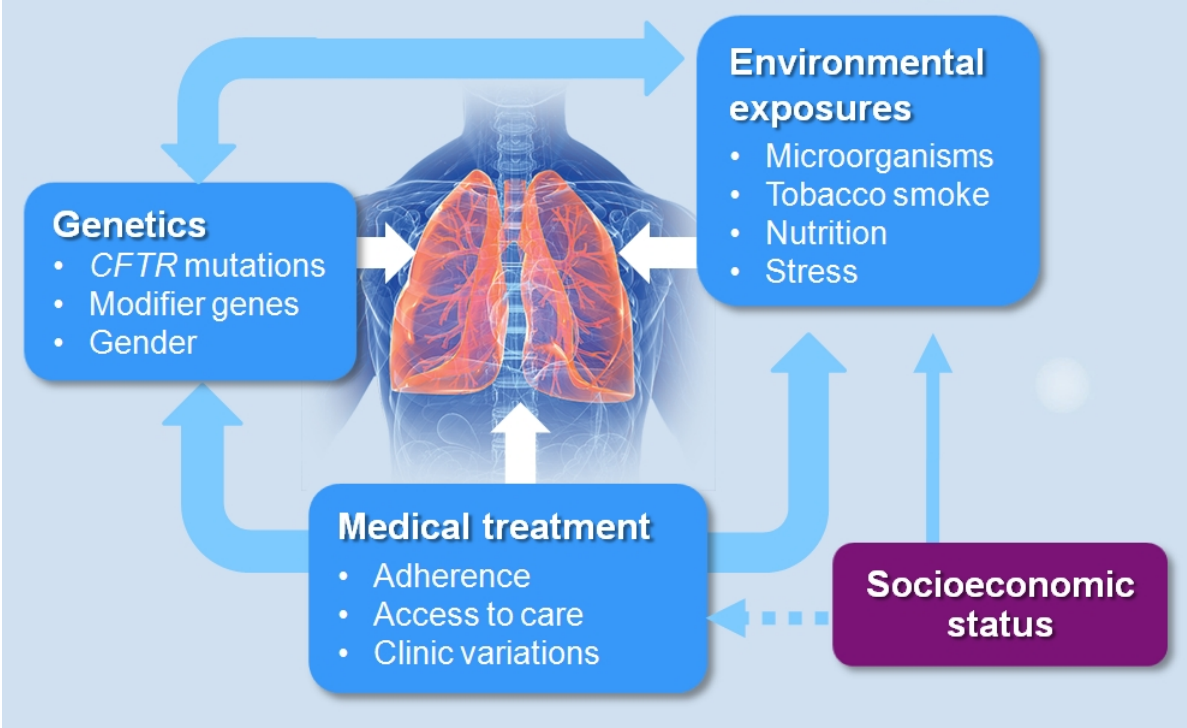
Adapted from Badano JL & Katsanis N, 2002

1) Cutting GR. *Ann N Y Acad Sci* 2010;1214:57–69; 2) Drumm ML et al. *Annu Rev Pathol* 2012;7:267–82; 3) Bartlett JR. *JAMA* 2009;302:1076–83; 4) Collaco JM et al. *Curr Opin Pulm Med* 2008;14:559–66; 5) Drumm ML et al. *N Engl J Med* 2005;353:1443–53; 6) Badano JL & Katsanis N. *Nat Rev Genet* 2002;3:779–89

Genotype and Phenotype

Role of the environment

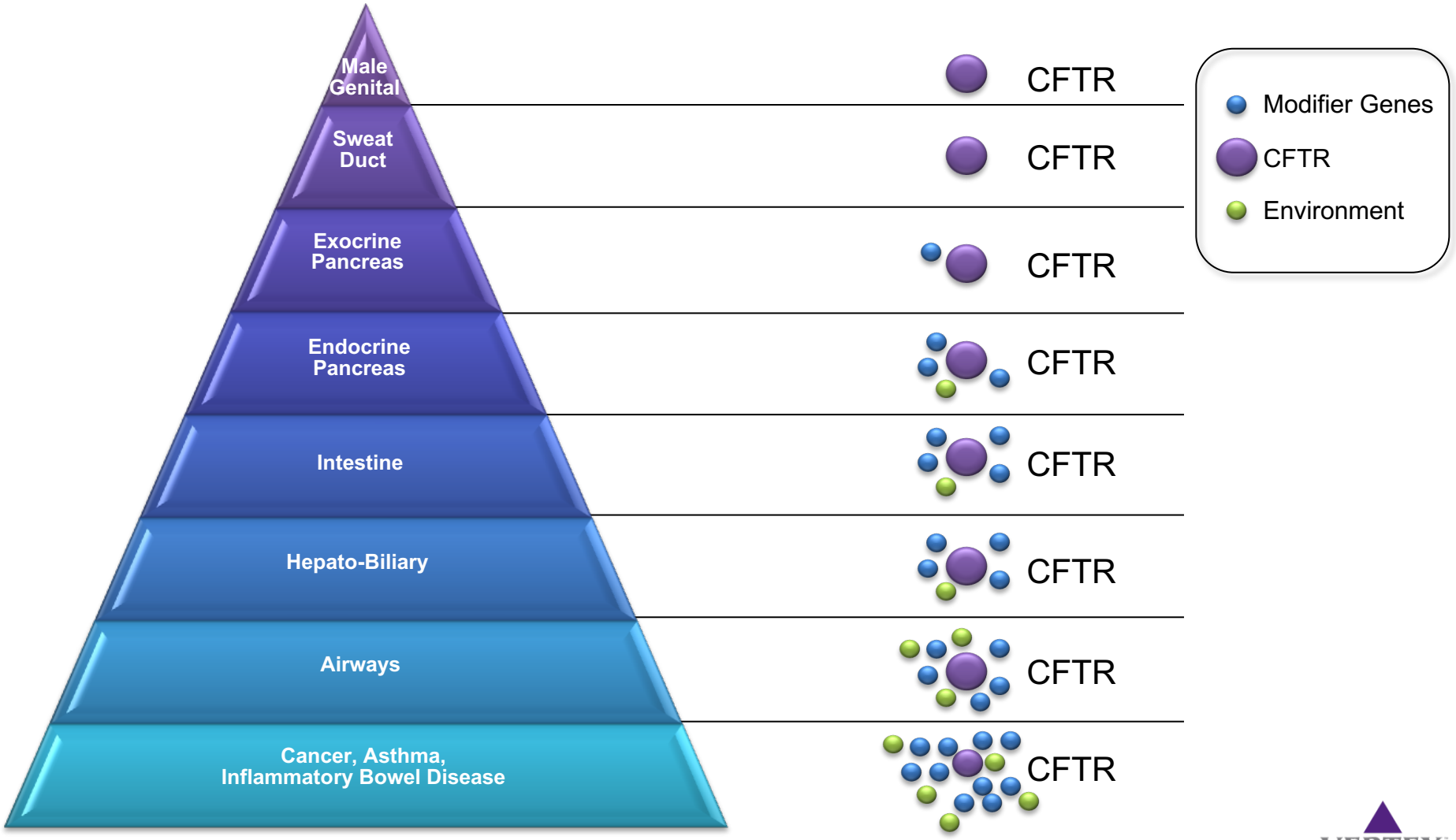
- Environmental factors are a source of variation in CF severity and clinical course
- Environmental factors, including treatment and adherence, have complex interactions with genetic determinants of phenotype



Adapted from Wolfenden LL & Schechter MS. *Ped Resp Rev* 2009;10:32–6

Genotype and Phenotype

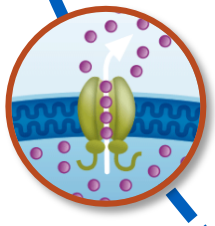
Contribution to CF disease phenotype



Adapted from Borowitz D et al. *J Pediatr Gastroenterol Nutr* 2005;41:273–85

Summary

CFTR gene mutations can result in CFTR protein channel abnormalities – the underlying defect of CF disease[1]



CFTR gene mutations can reduce Cl^- and other ion transport (total CFTR activity) through CFTR channels by affecting:[1–3]

Quantity of CFTR channels at the cell surface, and/or

Function of CFTR as an ion channel

Reduced quantity and/or function of CFTR channels leads to pathophysiologic changes in the epithelial cells of many organ systems[1,2,4]

1) MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10; 2) Rowe SM et al. *N Engl J Med* 2005;352:1992–2001; 3) Lommatzsch ST & Aris R. *Semin Respir Crit Care Med* 2009;30:531–8; 4) Davis PB. *Am J Respir Crit Care Med* 2006;173:475–82

Questions

Do all *CFTR* mutations result in the same cellular defect?

A. Yes

B. No

Questions

Do all *CFTR* mutations result in the same cellular defect?

A. Yes

B. No

Questions

What other factor(s) in addition to mutations in *CFTR* contribute to clinical phenotype?

A. Modifier genes

B. Environmental factors

C. Geographic location

D. A+B

Questions

What other factor(s) in addition to mutations in *CFTR* contribute to clinical phenotype?

A. Modifier genes

B. Environmental factors

C. Geographic location

D. A+B

Questions

What is the most common *CFTR* mutation worldwide?

A. *1811+1.6kb A->G*

B. *F508del*

C. *G551D*

D. *N1303K*

Questions

What is the most common *CFTR* mutation worldwide?

A. *1811+1.6kb A->G*

B. *F508del*

C. *G551D*

D. *N1303K*

Questions

The *F508del* mutation results in

A. Reduced quantity of CFTR protein at the cell surface

B. Reduced function of CFTR protein

C. Increased quantity of CFTR protein at the cell surface

D. Both A&B

Questions

The *F508del* mutation results in

A. Reduced quantity of CFTR protein at the cell surface

B. Reduced function of CFTR protein

C. Increased quantity of CFTR protein at the cell surface

D. Both A&B