



JOHNS HOPKINS
M E D I C I N E
CYSTIC FIBROSIS CENTER

CF-Causing Mutations

21 October 2014

Patrick Sosnay MD

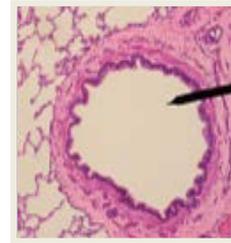
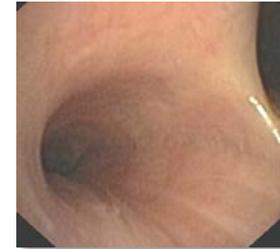
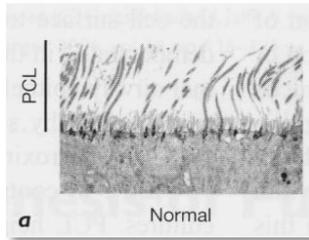
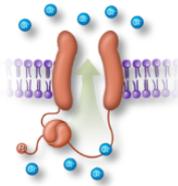
Johns Hopkins University

Potential Conflicts of Interest

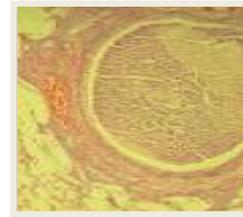
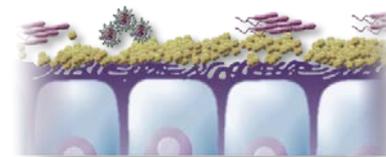
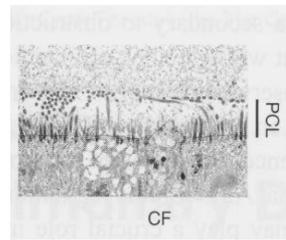
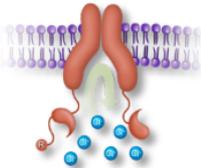
- Research done in collaboration with Vertex pharmaceuticals – no financial compensation
- Continuing Medical Education speaker – compensation through DKBMed and Johns Hopkins University office of CME
- Research funding through the US Cystic Fibrosis Foundation
- Care for CF patients

Cystic Fibrosis (CF) Pathophysiology

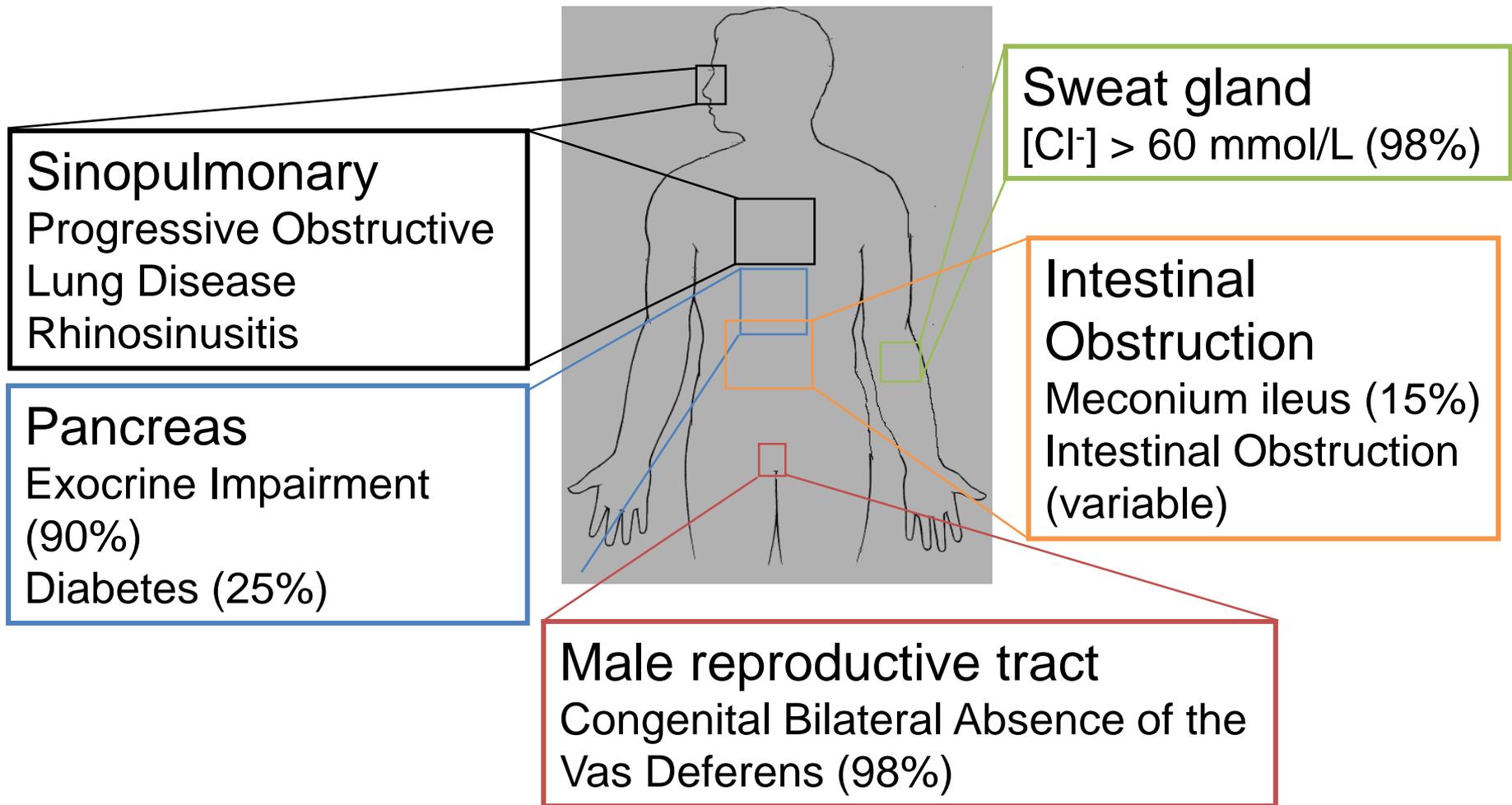
Normal



CF

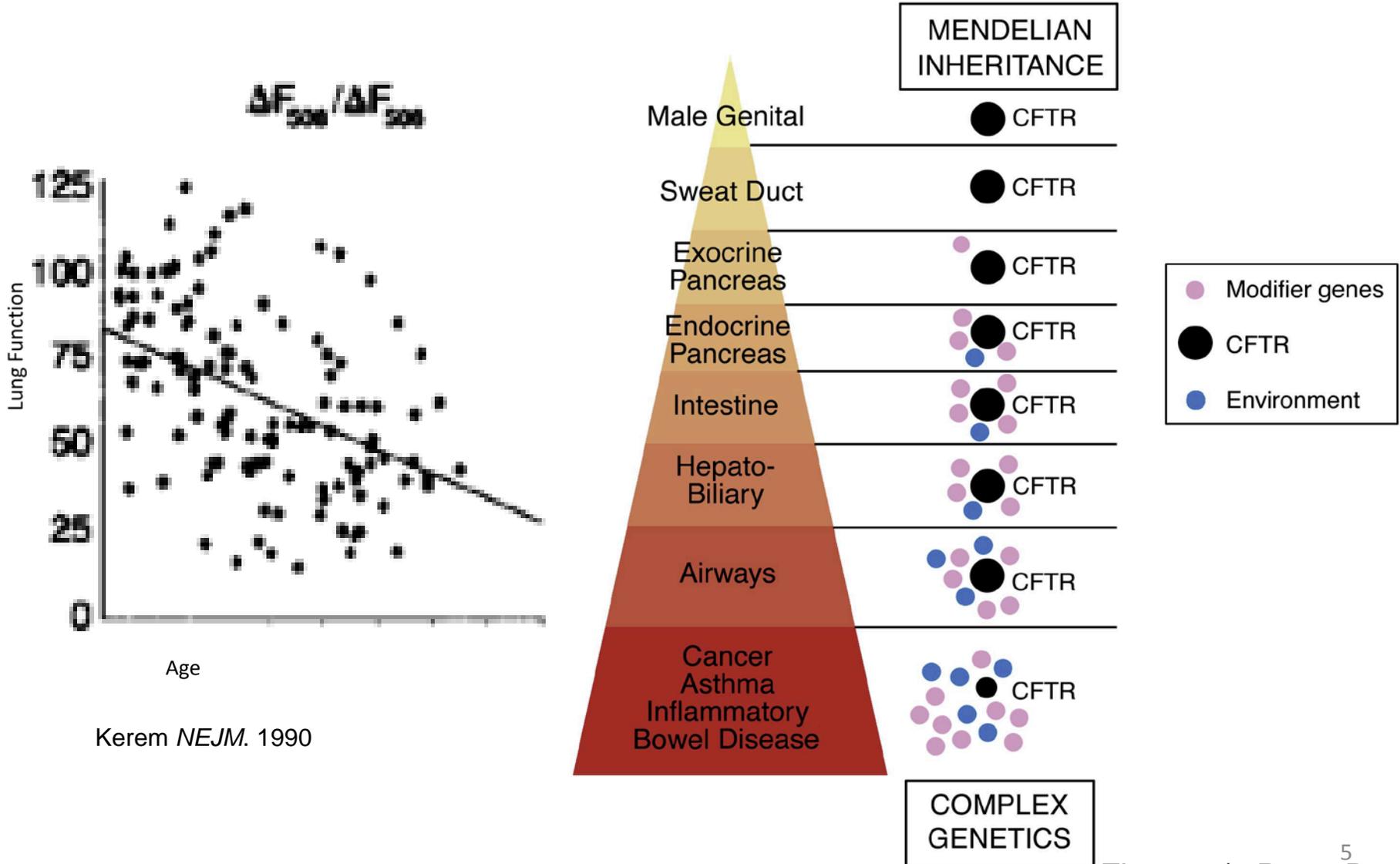


Cystic Fibrosis (CF) is an autosomal recessive disorder with a highly variable phenotype



Aberrant fluid and ion transport across epithelial tissues 4

CFTR mutation has different effect on organ system manifestations of CF



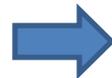
Allelic Heterogeneity in CF

- There are nearly 2000 different CFTR variants that have been described.
 - CF Mutation Database (<http://www.genet.sickkids.on.ca/app>)
- A small number are well known to cause CF, the majority have an unknown disease liability.
- There is growing (but incomplete) knowledge of how different mutations contribute to differences in phenotype.

Clinical and Functional Translation of CFTR: CFTR2

Clinical Data from 39,696 CF patients N. America, Europe:

- CFTR genotype
- Sweat Chloride concentration
- Lung Function
- Pancreatic Status



1036 mutations

Completed for 159 mutations
Allele frequency > 0.01%

Functional Analysis:

- Prioritized by mutation type
- Cell line based testing
- Splice analysis

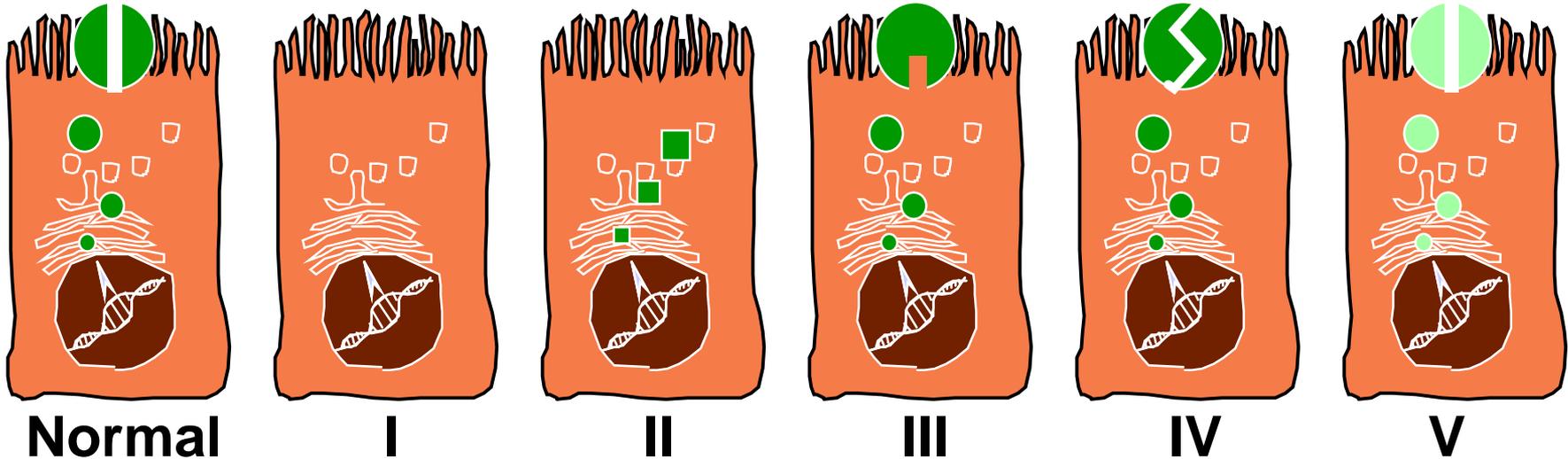
Clinical Analysis:

- Mutations with null allele in trans
- Confirm clinical features and diagnosis

Population Analysis:

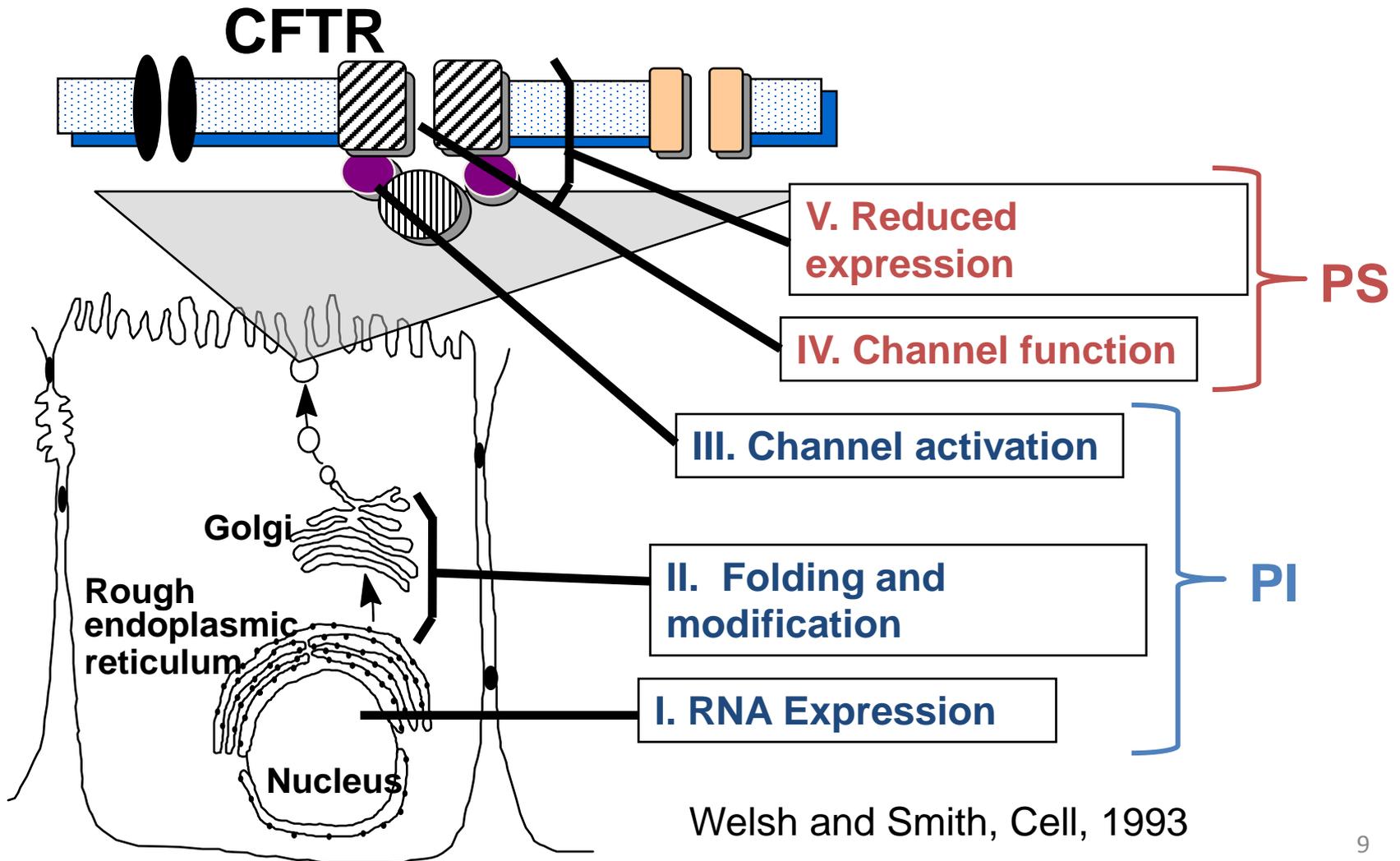
- Allele frequency in the general public
- Allele frequency in obligate heterozygotes

Classes of CFTR Mutations



Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
	G542X 3659delC 621+1G->A	F508del	G551D	R117H D1152H	3849+10kbC->T 5T A455E
	12%	87%	4%	4%	4%

Pancreatic status can be predicted from mutation class



G551D

DNA

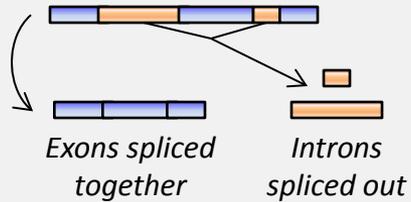
Substitution of **G** -> **A** at **position 551** results in an Asp codon

AGT	GGA	GGT	CAA	CGA
Ser	Gly	Gly	Gln	Arg
549		551		553

This is a **missense** mutation

RNA

Normal RNA splicing



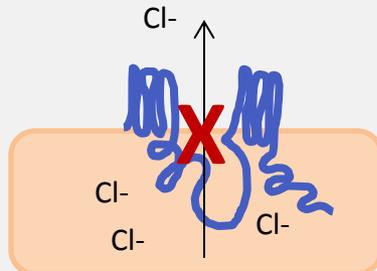
Protein

CFTR protein **produced**



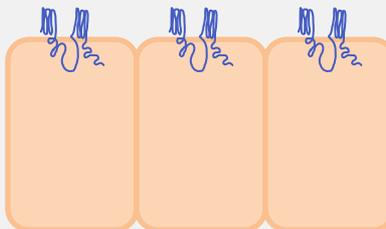
Protein function

CFTR protein **can not be turned on and opened**



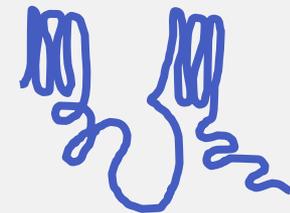
Protein trafficking

CFTR protein **correctly localized** to cell membrane

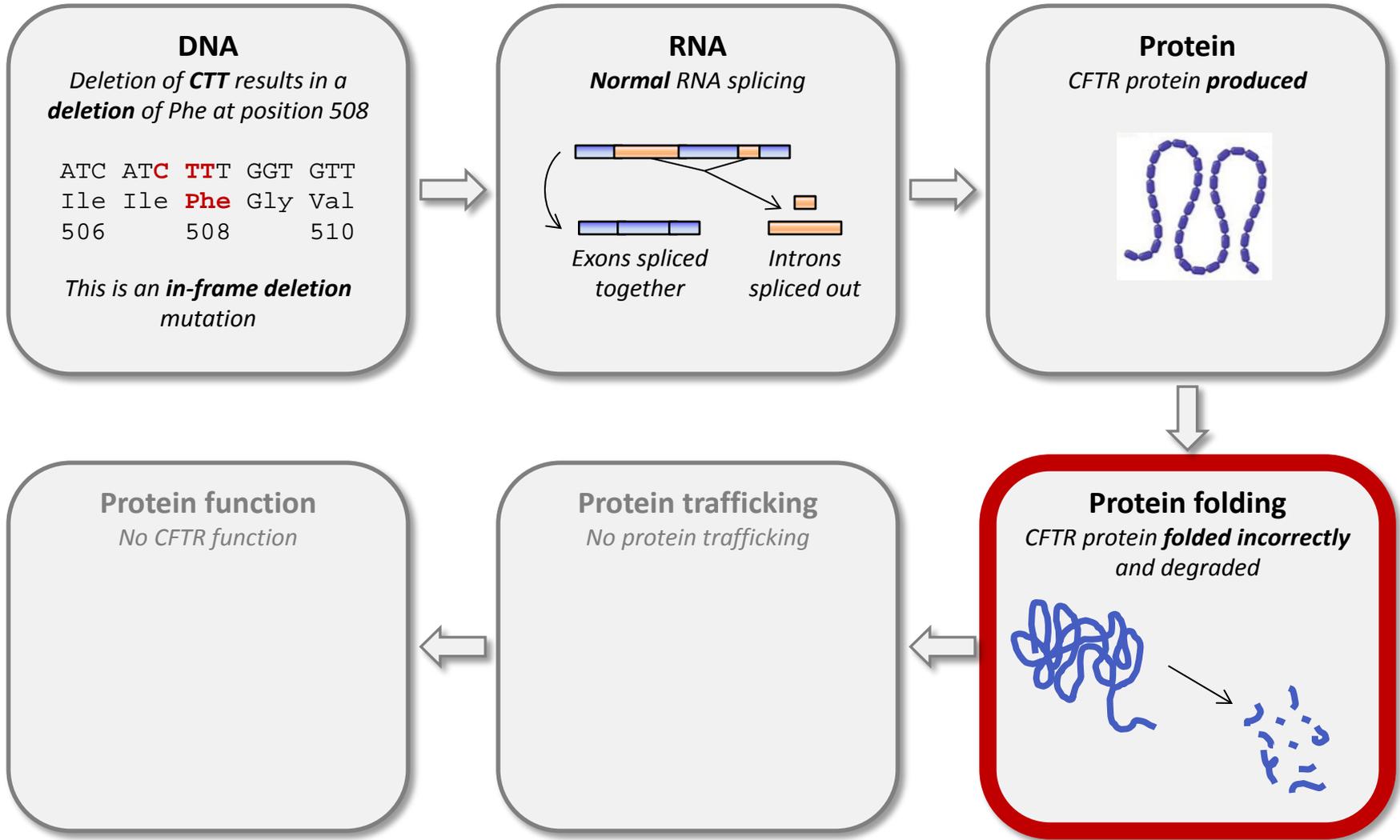


Protein folding

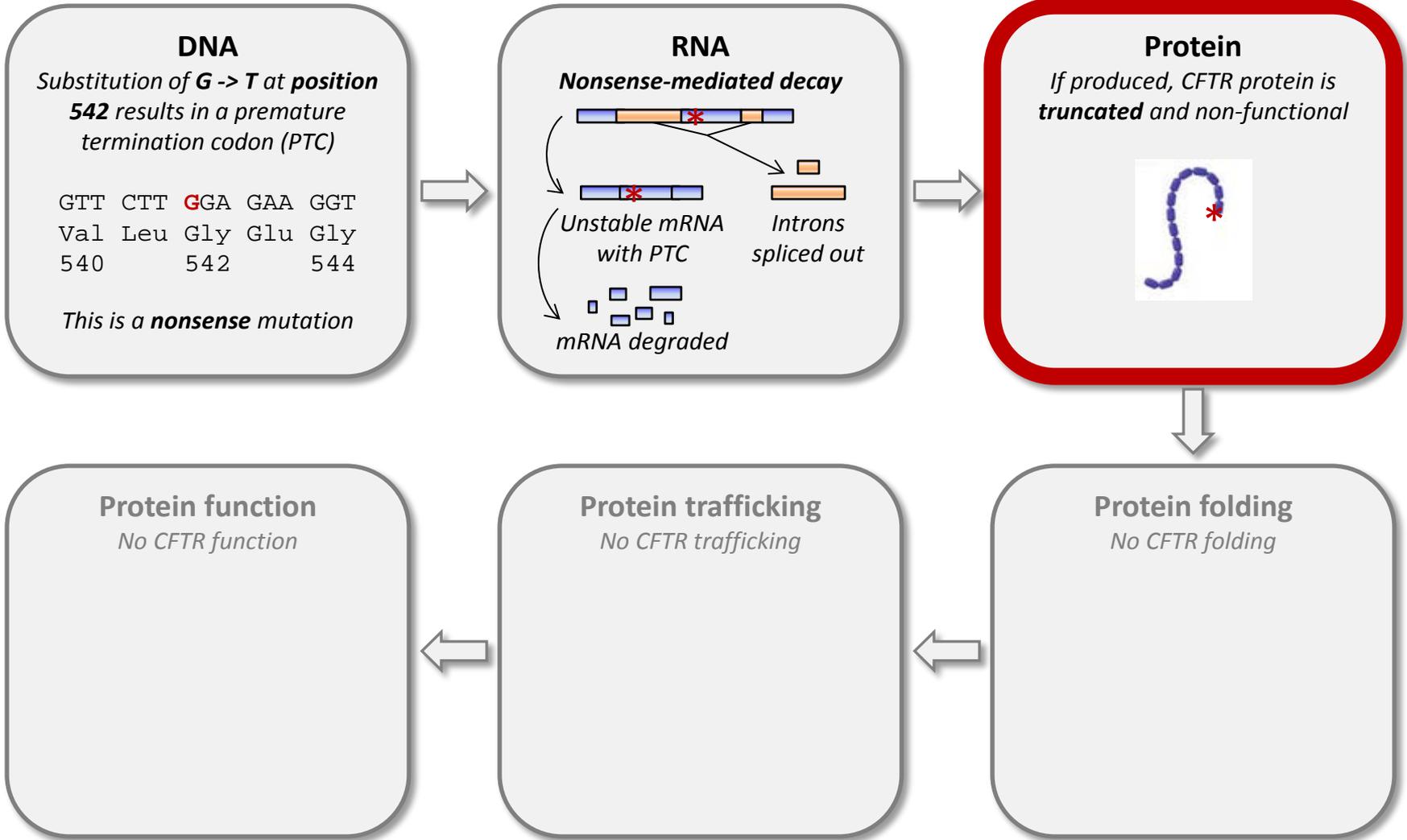
CFTR protein **folded correctly**



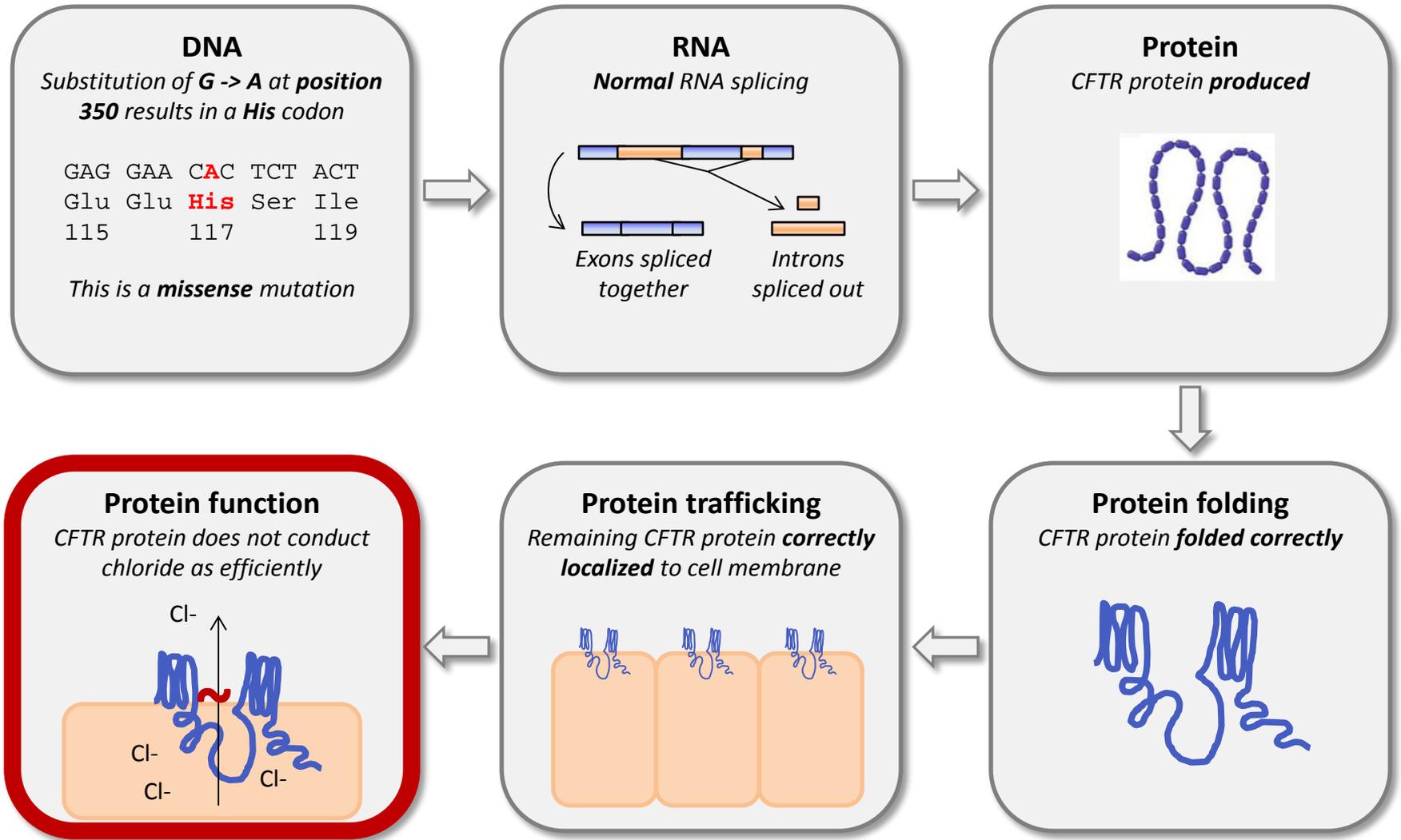
F508del



G542X



R117H – appears to affect channel function



In in vitro studies R117H-CFTR conducted chloride at 25-40% of WT-CFTR levels.
VanGoor *JCF*. 2012., Sheppard *Nature*, 1993., Choi *Nature*, 2001.

R117H



Clinical and Functional Translation of CFTR



Quick Links

- Home
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Scientific/medical view



The CFTR2 project is partially supported by Grant Number 5R37DK044003 from the National Institute of Digestive, Diabetes and Kidney Diseases of the National Institutes of Health, by funding from the US Cystic Fibrosis Foundation, and by an unrestricted educational grant from Sequenom to the US Cystic Fibrosis Foundation.

This is the scientific / medical view. [Click to switch to the general user view.](#)

FOR PATIENTS AND FAMILY MEMBERS: This detailed medical and genetics information is complicated and potentially confusing. We encourage you to discuss this information with your doctor, a genetic counselor, or a CF specialist. The information shown is for educational purposes only and it's not intended for diagnostic use. You should not make any medical or reproductive decisions or change your health behaviour based on this information without talking to your doctor. To find a genetic counselor near you, click [here](#). To find a CF care center near you, click [here](#).

Summary: R117H is seen in 793 patients in our worldwide CF database. The clinical and functional analysis of this mutation shows that this mutation has variable expression or penetrance.
The R117H mutation is a special case. It is subject to intragenic modification (see [Glossary](#)) by the poly-T tract, located in another region of the CFTR gene. For more information about how the poly-T tract influences R117H, click [here](#).



The information displayed below shows how we came to this decision.

Clinical Characteristics

Additional Information Patients with this mutation who are followed at a CF center and entered into the CFTR2 database have the following clinical characteristics (this will not include any patients that have this mutation and are not followed at CF centers).

Please select a patient group from the list below

- Average of 590 patients carrying mutation R117H and mutation F508del
- Average of 715 patients carrying mutation R117H and an ACMG mutation
- Average of 703 patients carrying mutation R117H and a pancreatic insufficient mutation
- **Average of 793 patients carrying mutation R117H**

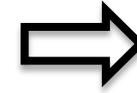
CLINICAL FEATURE (RANGE IN INDIVIDUALS WITHOUT CF)	AVERAGE OF ALL PATIENTS WITH MUTATION R117H	AVERAGE OF ALL PATIENTS
Sweat Chloride ? (non-CF is less than 40mEq/L in children and older, less than 30mEq/L in infants)	60	97
Lung Function expressed as % predicted (non-CF 80%-120% predicted)	<p>Box plot showing Lung function (expressed as % predicted) for R117H mutation and All patients. The y-axis ranges from 0 to 150. The x-axis shows R117H mutation and All patients. The legend indicates age groups: < 10 (red), 10 - 20 (blue), > 20 (green), and not enough data (triangle). Sample sizes are shown above each box: 51, 98, 285 for R117H; 3472, 9503, 10432 for All patients.</p>	
Pancreatic Insufficiency ? (less than 1% of non-CF expected to be PI)	26 %	87 %
Pseudomonas ? (less than 1% of non-CF expected to have Pseudomonas)	24 %	53%
Average Age	23	19

R117H has incomplete penetrance

- R117H occurs commonly (6th most common *CFTR* mutation in CF patients)
- However, R117H was seen more frequently in asymptomatic individuals undergoing carrier screening. Several individuals with F508del and R117H were found that had no detectable phenotype.

F508del (or another CF-causing mutation)

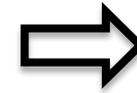
R117H



CF

F508del (or another CF-causing mutation)

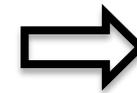
R117H



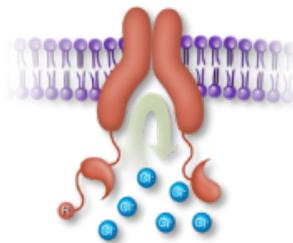
normal

F508del (or another CF-causing mutation)

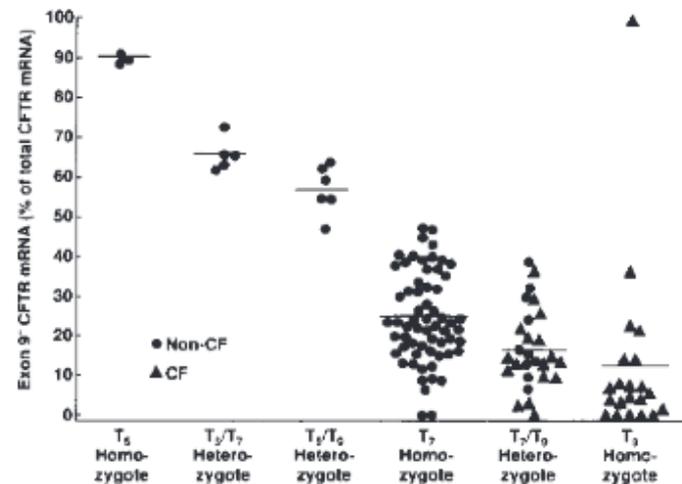
R117H



Obstructive azoospermia



CFTR Cl⁻ conductance is reduced

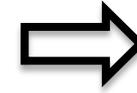


Intron 9 variants affect quantity of *CFTR* transcript that contains exon 10

Chu Nature Genet. 1993

F508del (or another CF-causing mutation)

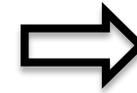
R117H with 5T



CF

F508del (or another CF-causing mutation)

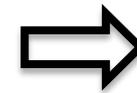
R117H with 9T



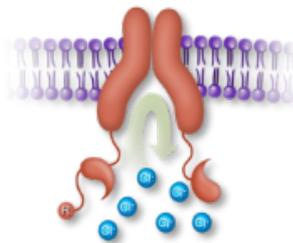
normal

F508del (or another CF-causing mutation)

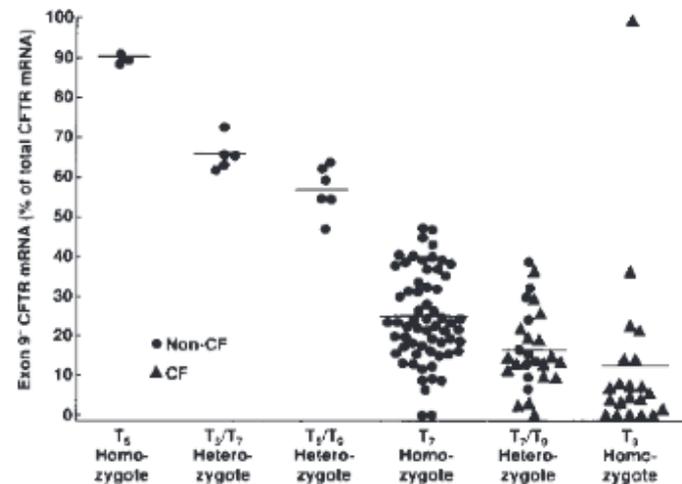
R117H with 7T



Obstructive azoospermia



CFTR Cl⁻ conductance is reduced



Intron 9 variants affect quantity of CFTR transcript that contains exon 10

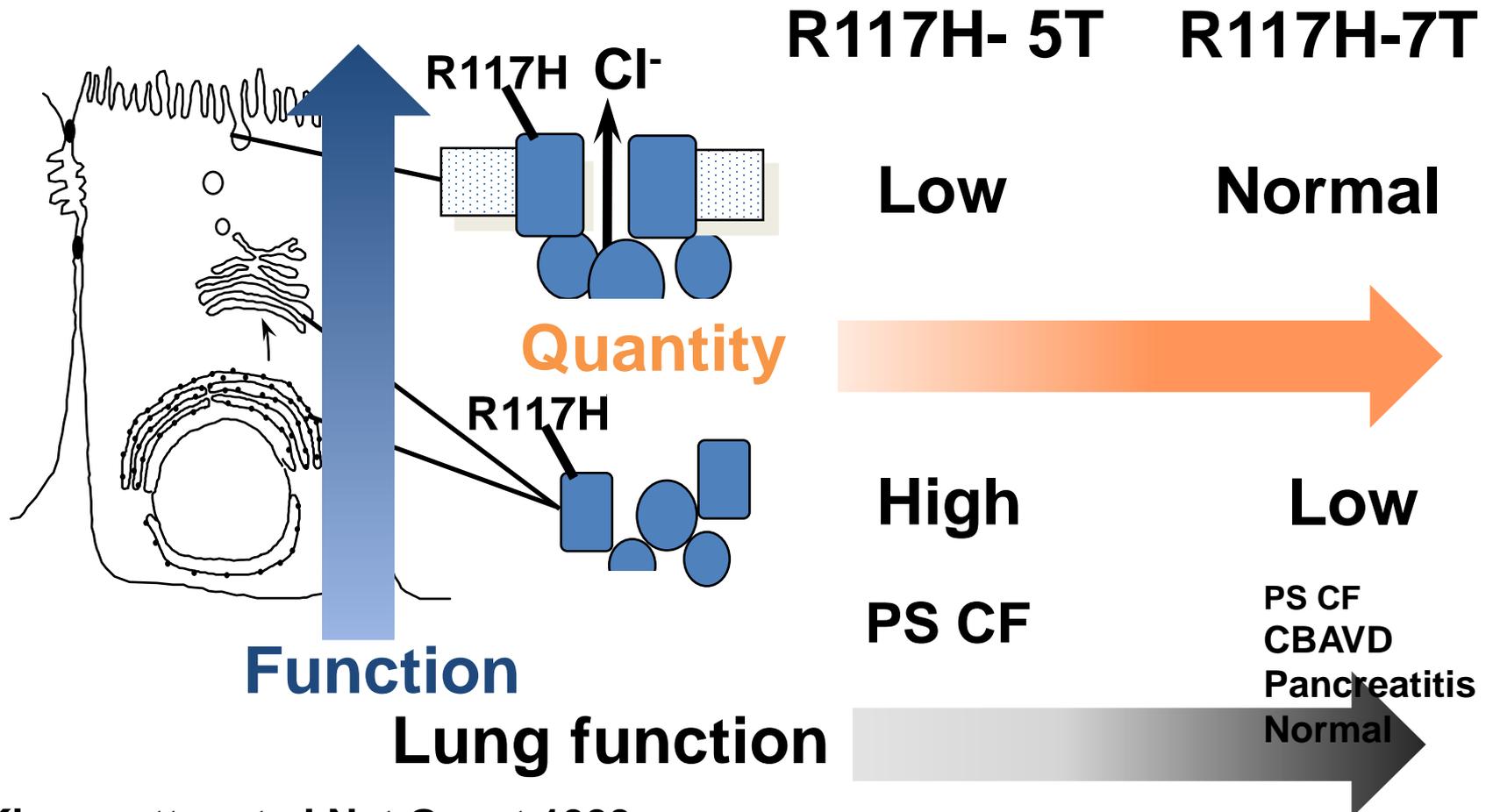
Chu Nature Genet. 1993

The incomplete penetrance of patients with R117H is explained by Intron 9 polyT

- The affect of the R117H mutation is subject to intragenic modification based on the quantity of correctly spliced *CFTR*
- Variations in Intron 9 have been shown to affect the splicing of Exon 10

- R117H with a 5T causes CF
- R117H with a 7T causes CF in small minority, single organ system disease, or no effect
- R117H with 9T does not cause CF

Quantity of partially functional CFTR correlates with lung function



Summary

- R117H is a frequently seen CF-causing CFTR mutation
- R117H is most deleterious when seen with the 5T variation in the same *CFTR* gene
 - Both the effect of the amino acid substitution and the alternative splicing contribute to the dysfunctional protein
- R117H is associated with retained pancreatic function; even though milder still associated with life shortening disease