

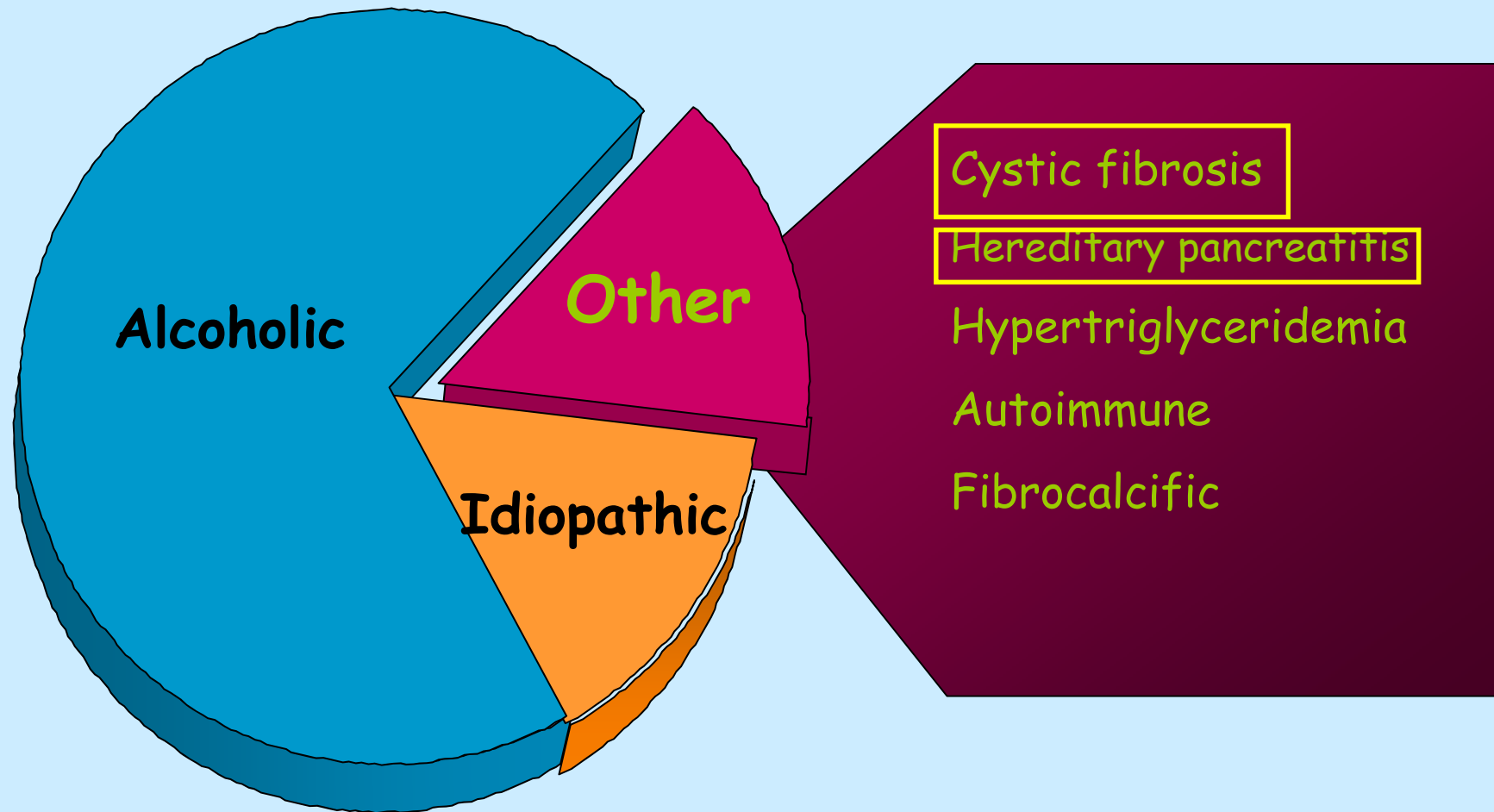


Recurrent Acute Pancreatitis in Israeli Children

Michael Wilschanski
Pediatric Gastroenterology,
Hadassah Medical Organization
Jerusalem, Israel

ISPGHAN EILAT FEBRUARY 2013

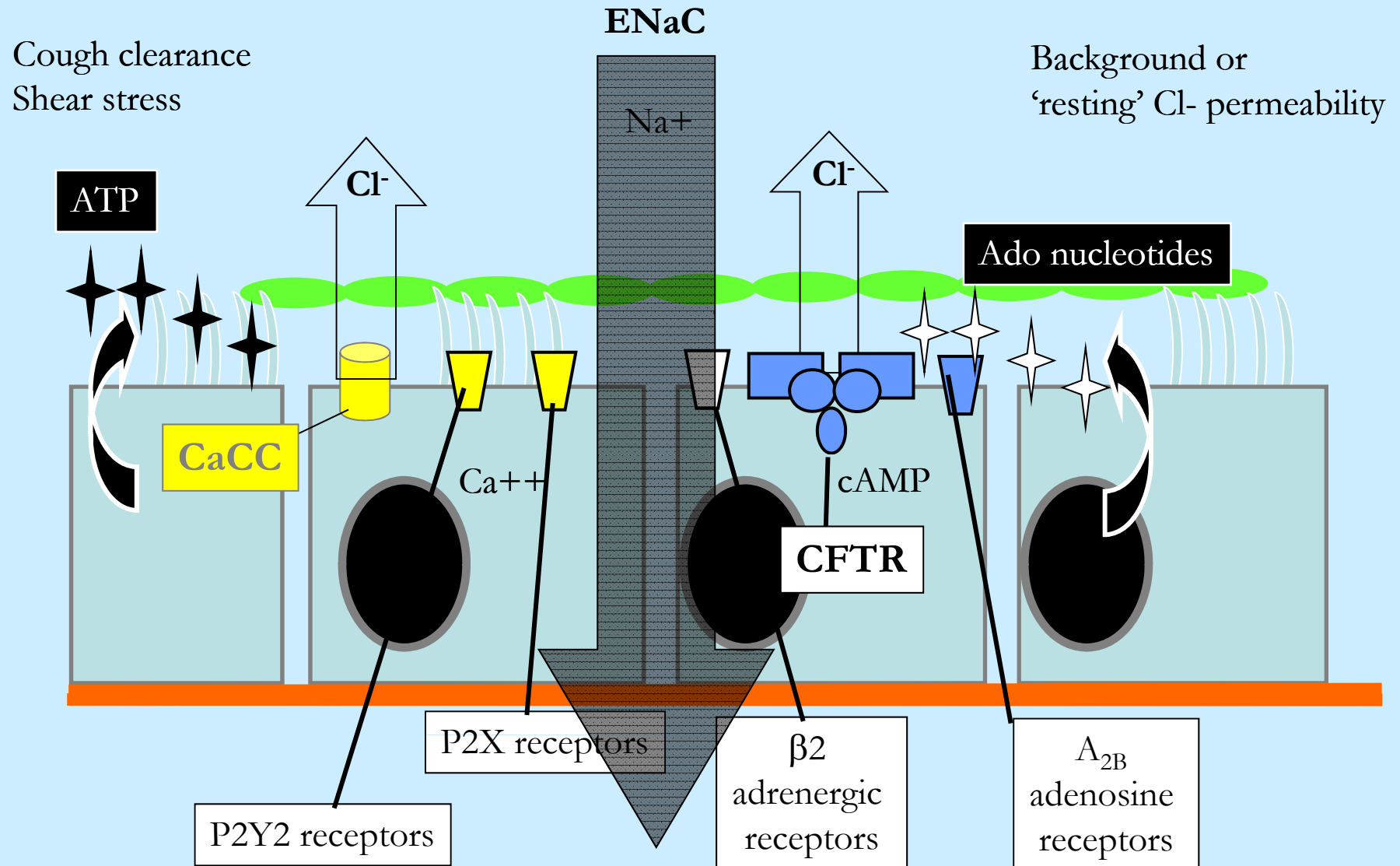
Etiologies of recurrent/chronic pancreatitis



Single Organ Presentation of CF

- nasal polyposis
- chronic sinusitis
- CBAVD (Congenital Bilateral Absence of Vas Deferens)
- allergic bronchopulmonary aspergillosis
- unexplained chronic lung disease with no other signs of CF
- primary sclerosing cholangitis
- Acute , recurrent pancreatitis

Nasal Potential Difference



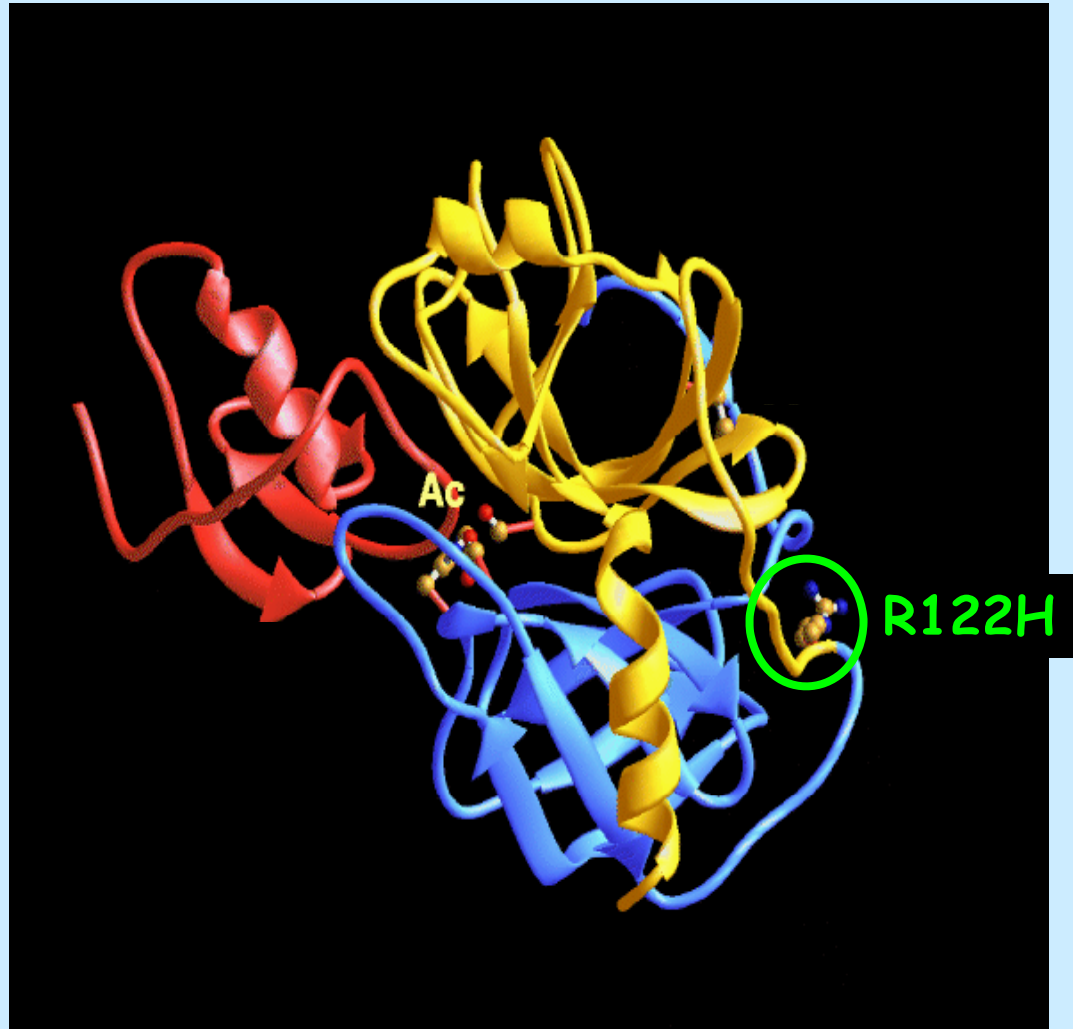
NPD Technique



Hereditary Pancreatitis

- Hereditary pancreatitis (HP) is an unusual form of acute and chronic pancreatitis that runs in families following an autosomal dominant pattern.
 - Acute Pancreatitis in 80% with the gene
 - Chronic Pancreatitis in 50% with acute pancreatitis.
- The first disease gene discovered is **TRYPSINOGEN (PRSS1)**
- The mutations appear to be “gain of function” by increasing **activation** or decreasing **inactivation**.

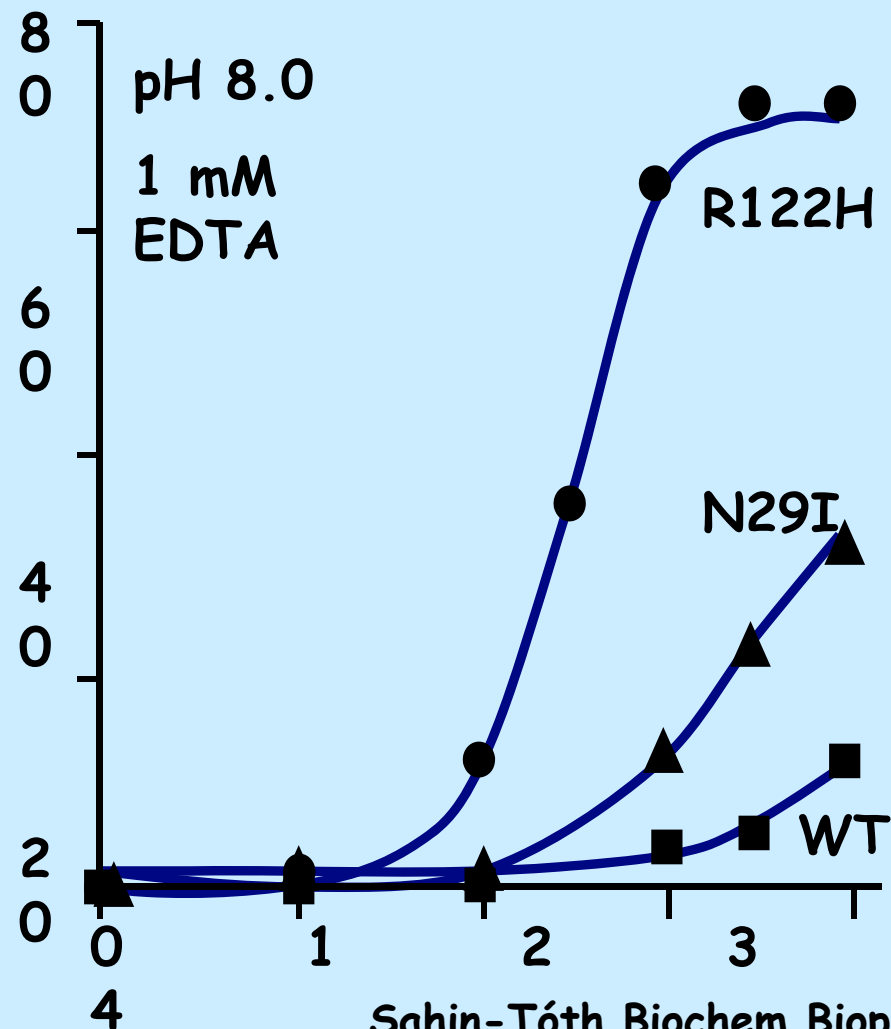
Cationic Trypsinogen (PRSS1) - R122H



modified from Whitcomb *et al.*, Nature Genetics 1996

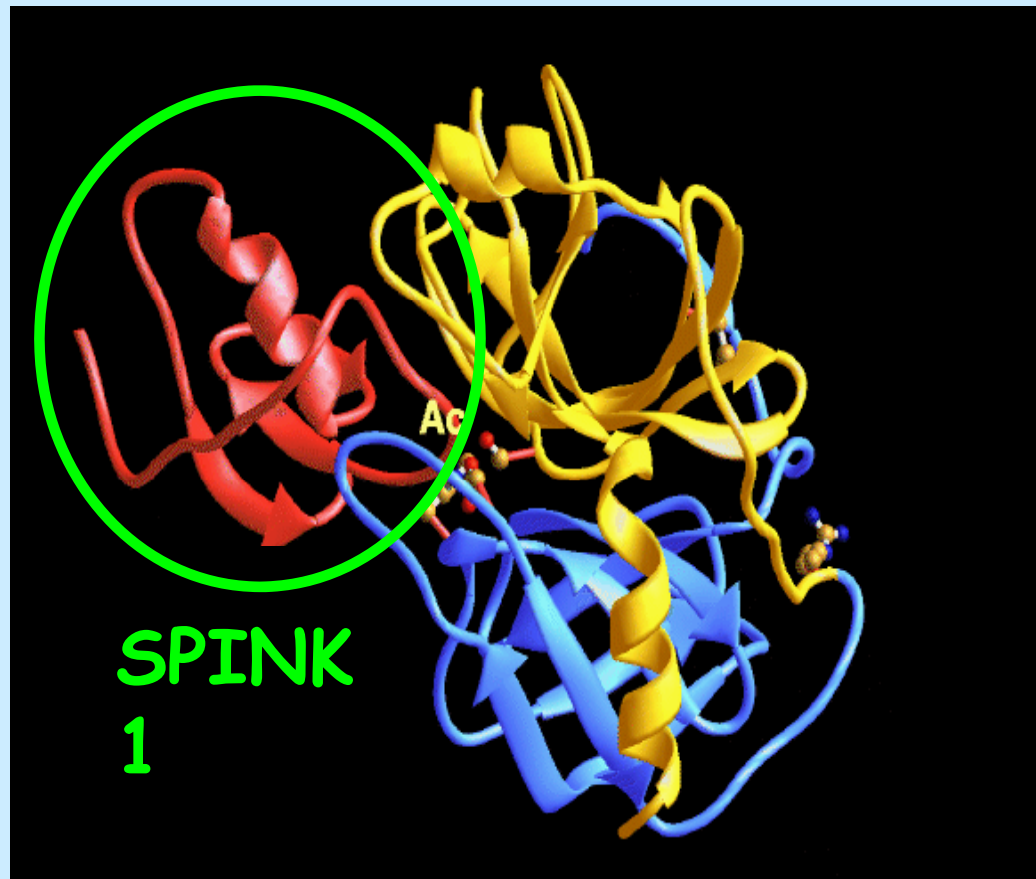
PRSS1 Variants (R122H / N29I)

Enhanced Autoactivation



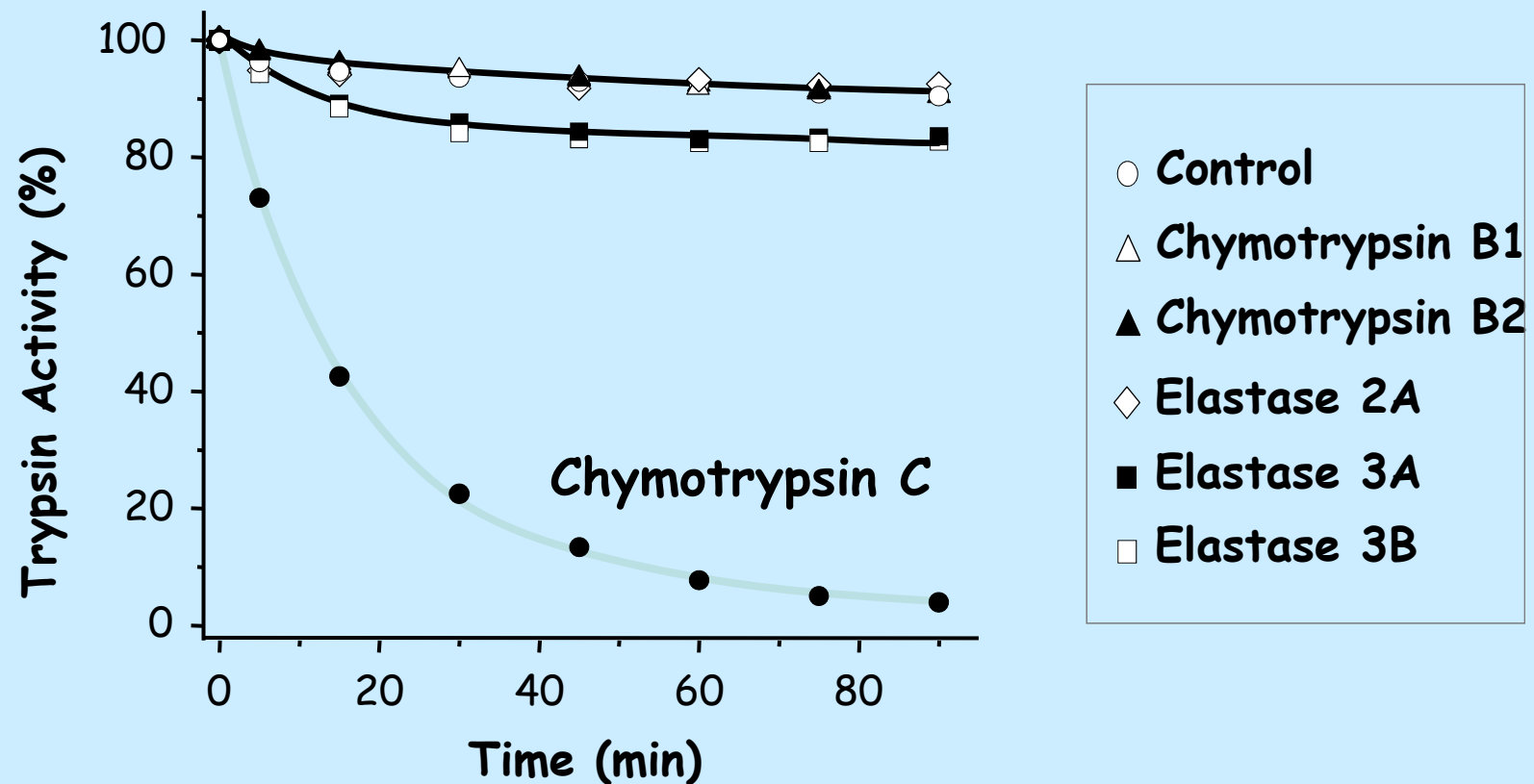
SPINK1

Serine Protease Inhibitor, Kazal Type 1



Chymotrypsin C (*CTRC*)

Degradation of Cationic Trypsin



Szmola & Sahin-Tóth, PNAS 2007

Aim

To present the work-up of children
with recurrent pancreatitis
referred for genetic analysis and
electrophysiological testing

METHODS

- ❖ Children with recurrent pancreatitis (at least twice) whose diagnostic work-up (usually extensive including imaging) was negative
- ❖ referred for nasal potential difference measurements
- ❖ genetic testing PRSS1 , SPINK1, CTSC and CFTR (Paris)

Demographics and clinical data of patients with recurrent acute pancreatitis

No. of patients	30 (17 females, 13 males)
Age (years)	10±5 (range: 1.5-18 yrs)
No. of episodes	range 2-16
Ethnic origin	84% Jewish 16% Arab
Sweat test	23 out of 30 patients
NPD test	22 out of 30 patients

Sweat chloride results

14/30 patients with results ≤ 40 mmol/L

9/30 patients with results > 40 mmol/L

Nasal Potential Difference (NPD) Results

NPD test was performed on 22 out of 30 patients:

20 patients with normal NPD

2 patients with abnormal NPD

2 patients with abnormal NPD Results

Age (years)	CFTR and/or Pancreatitis Mutations	Additional symptoms	Sweat Cl^- (mmol/L)
7	-/-		25
14	-/-		68

Mutations in the PRSS1 Gene

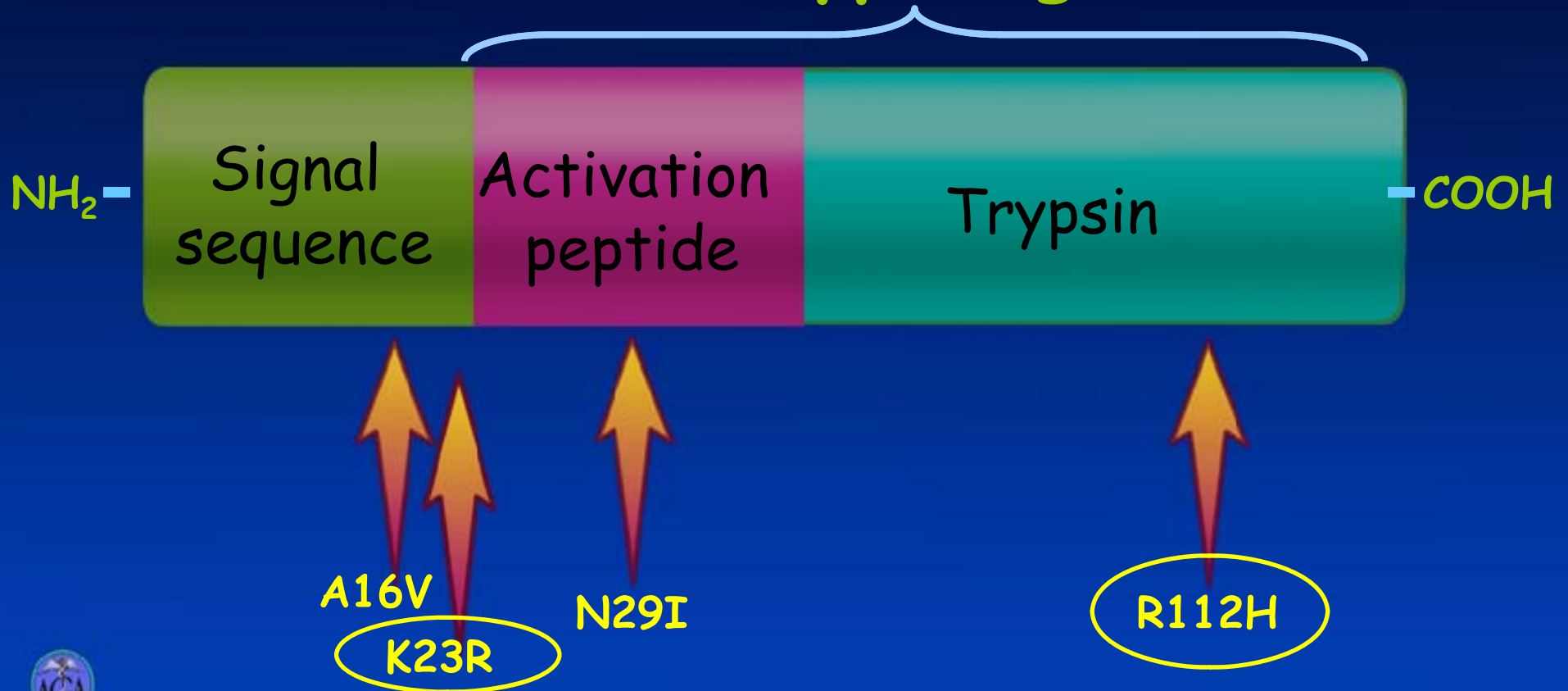
Patient no.	Age (yrs)	mutations	Ethnic origin
1	6	R112H/-	Ashkenazi Jewish
2	13	R112H/-	Jewish Georgian
3*	12.5	K23R/-	Jewish Georgian
4 (sib)	4	K23R/-	Jewish Georgian/Moroccan
5 (sib)	2	K23R/-	Jewish Georgian/Moroccan
6	17	K23R/-	Jewish Egypt-Syria / Ashkenazi
7	7	D21A/-	Ashkenazi Jewish/ Georgian

* Brother with the same genetic profile [K23R/-]

Hereditary Pancreatitis

Cationic trypsinogen mutations

Trypsinogen



DC Whitcomb, Med. Clinics of North America 2000; 84:531

Mutations in the SPINK1 Gene

Patient no.	Age (yrs)	mutations	Ethnic origin
8	17	R67H/ R67H	Arab - Bedouin

Mutations in the CTSC Gene

Patient no.	Age (yrs)	mutations	Ethnic origin
9	4	K172E/ -	Arab - Bedouin

Mutations in the CFTR Gene

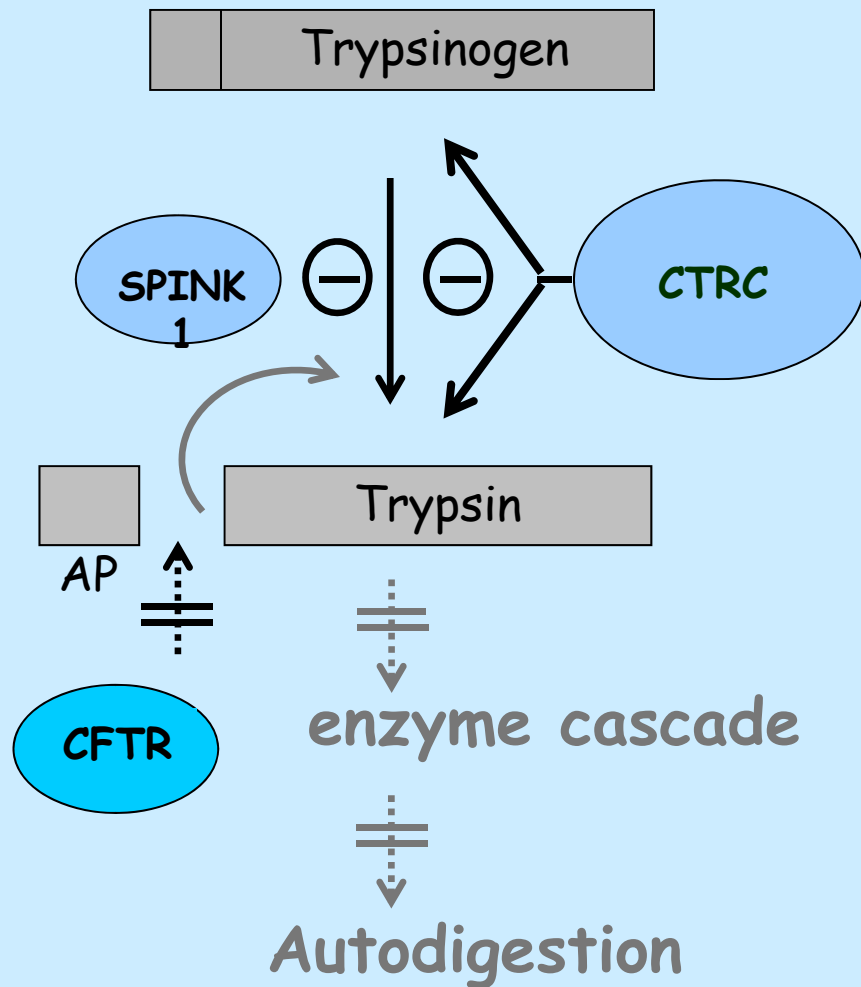
Patient no.	Age (yrs)	Mutations	Ethnic origin
10	4	W1282X/- (CFTR)	Ashkenazi Jewish

Mutations in the SPINK1+CTRC+CFTR Genes

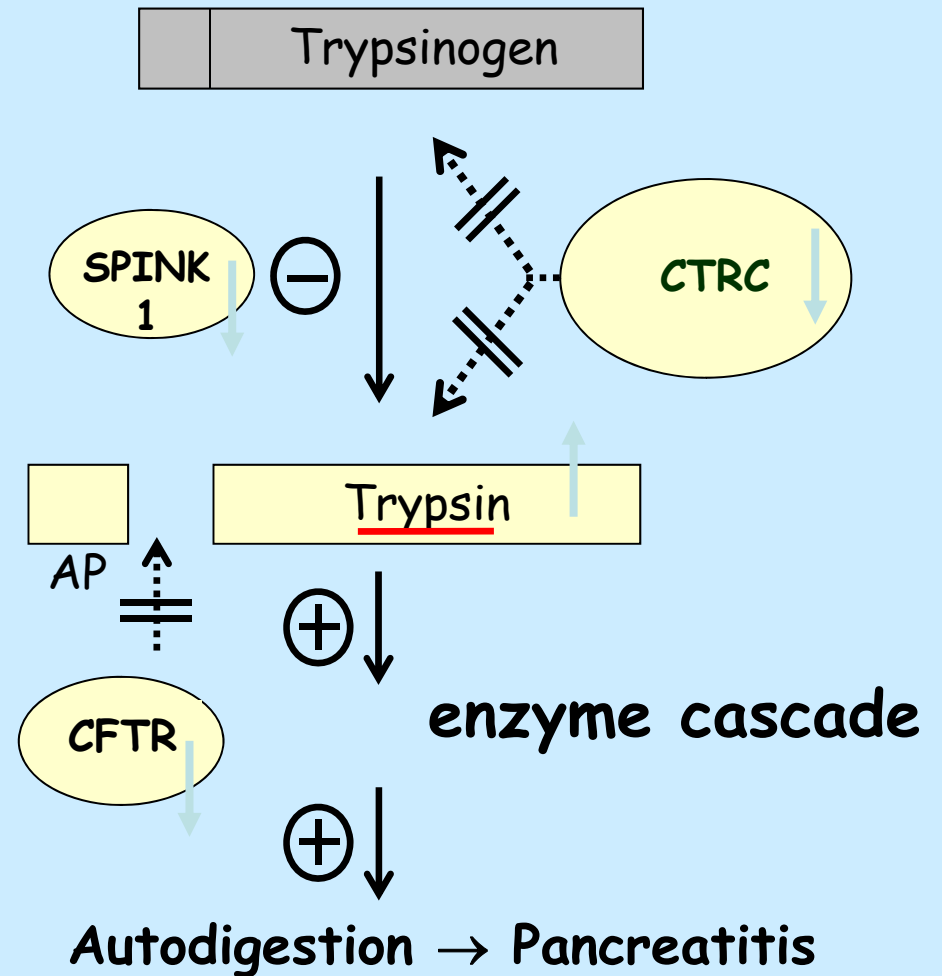
Patient no.	Age (yrs)	Mutations	Ethnic origin
11	1.5	I42M(SPINK1)/V235I(CTRC) ΔF508/5T (CFTR)	Ashkenazi /Iraqi Jewish

Model of Inherited Pancreatitis

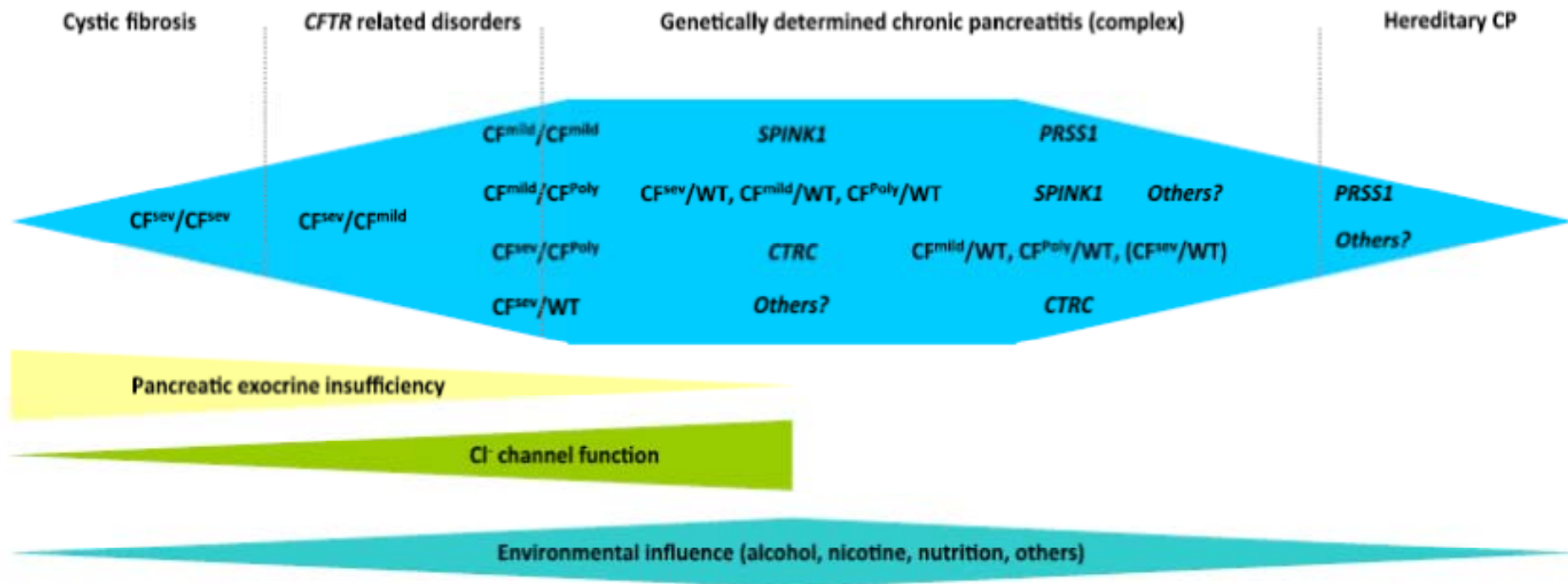
Normal Pancreas



Inherited Pancreatitis



CHRONIC PANCREATITIS IS A COMPLEX GENETIC DISORDER



Rosendahl J CFTR, SPINK1, CTRC and PRSS1 variants in chronic pancreatitis: is the role of mutated CFTR overestimated GUT 2012 epub

Conclusion

- ❖ This is the first study on recurrent pancreatitis in Israeli children examining both the presence of susceptibility gene mutations for pancreatitis and CFTR dysfunction
- ❖ We have started establishing a national clinical registry for idiopathic recurrent pancreatitis
- ❖ A prospective study with a larger number of patients may further clarify the impact of genetic mutations and CFTR dysfunction on the clinical presentation and outcome of recurrent pancreatitis

FUTURE.....

INSPPIRE

International Study Group Of Pediatric Pancreatitis:
In Search For A Cure

NIH FUNDING!!!!!!

**Definitions of Pediatric Pancreatitis And Survey Of Current Clinical
Practices: Report From Insppire**

Morinville VD, Husain SZ, Bai H, Barth B, Alhosh R, Durie PR, Freedman SD,
Himes R, Lowe ME, Pohl J, Werlin S, Wilschanski M, Uc A; on behalf of the
INSPPIRE Group. JPGN 2012;55: 261-5

Acknowledgements

Yasmin Yaakov and Michael Cohen

(Electrophysiology Lab, Pediatric
Gastroenterology Unit, Hadassah Medical
Center) 02-5844922

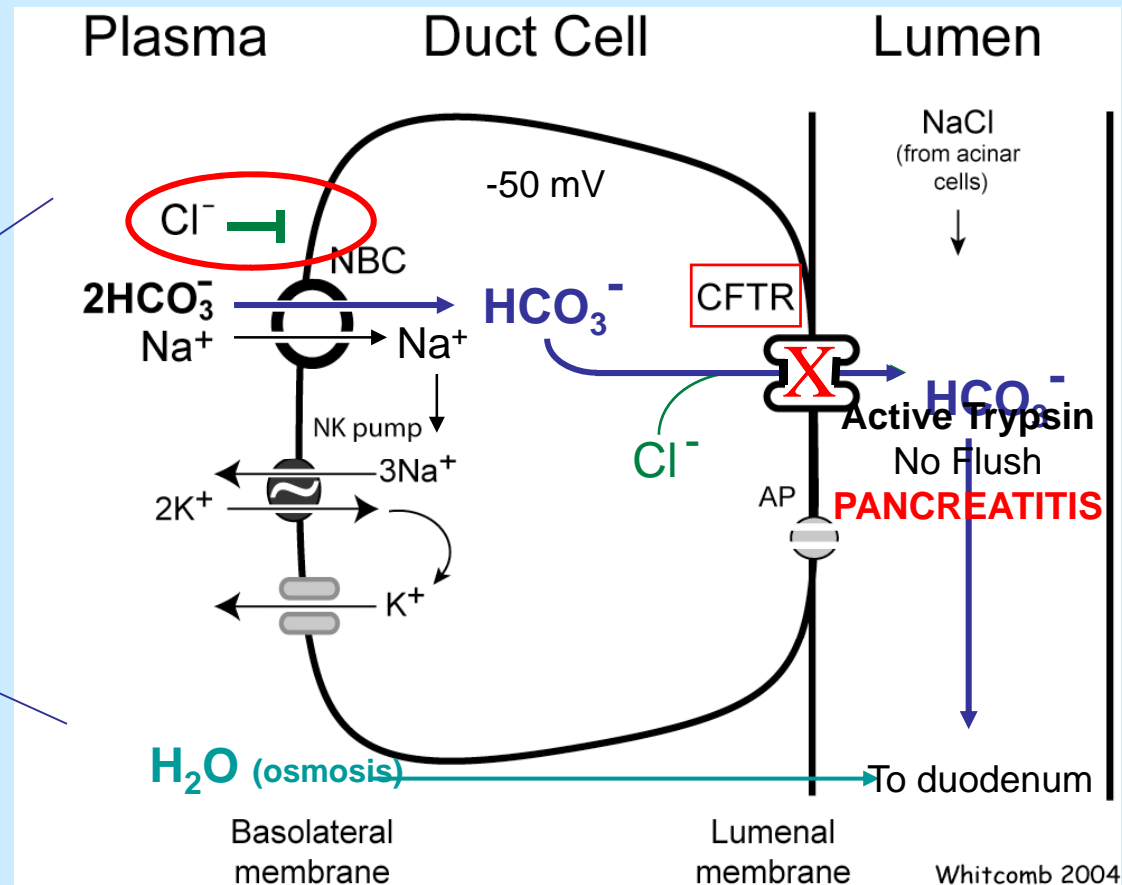
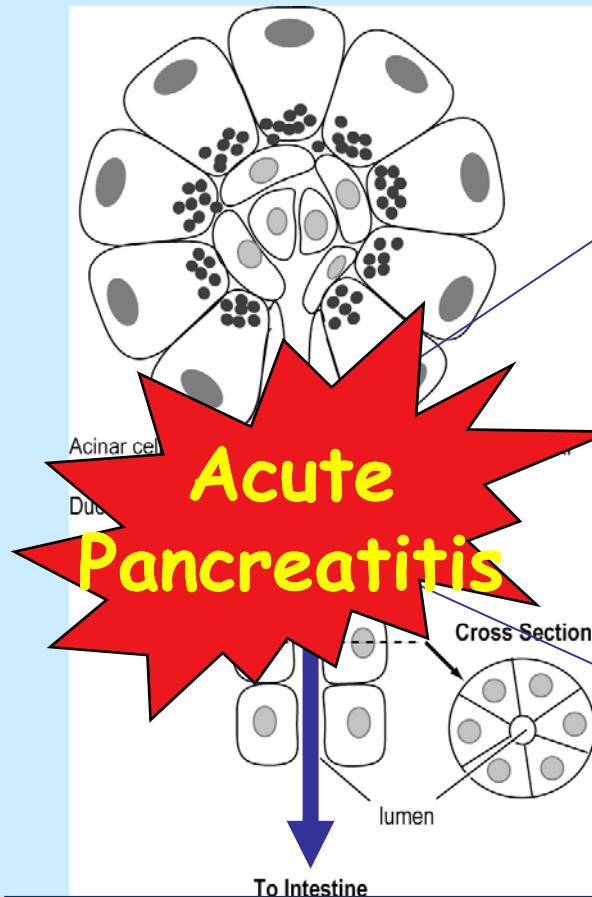
Shteyer E, Klar A, Broide E, Shaoul R,
Bentur L, Branski D, Konikoff F, Goldin E,
Segal I, Yaron A, Yerushalmi B, Pinsk V,
Shamaly H, Shamir R, Turner D, Santo E

Ferec C, Ruszniewski P (France)

CFTR and Bicarbonate Secretion

Next

Whitcomb DC & Ermentrout DB. *Pancreas* 2004; 29(2):E30-E40



CFTR Mutations limit bicarbonate secretion, increasing susceptibility to pancreatitis.

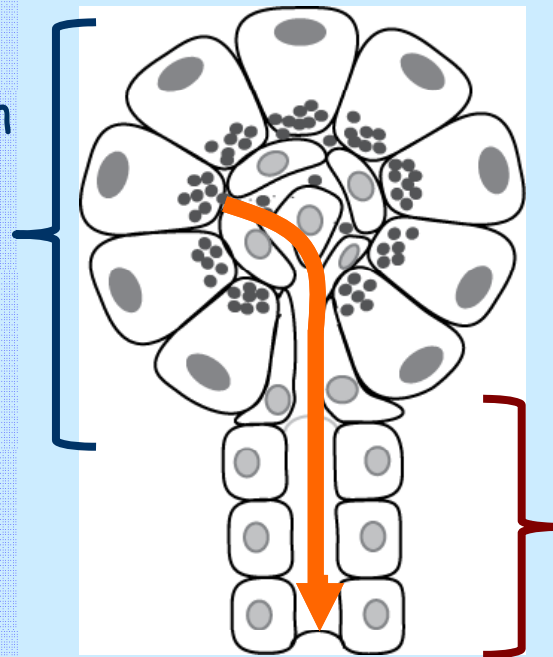
Opening of CFTR starts ion secretion
Chloride washes out and cannot enter on the basolateral side. **Chloride** is replaced by bicarbonate

Risk for Trypsinogen Activation (AP)

Acinus

- Calcium Regulation
 - Hypercalcemia
 - Hyperstimulation
 - Alcohol
- Trypsin related
 - **PRSS1**
 - **CTRC**
 - Acidosis
- Inflammation related
 - **SPINK1**

Premature
Trypsinogen
Activation



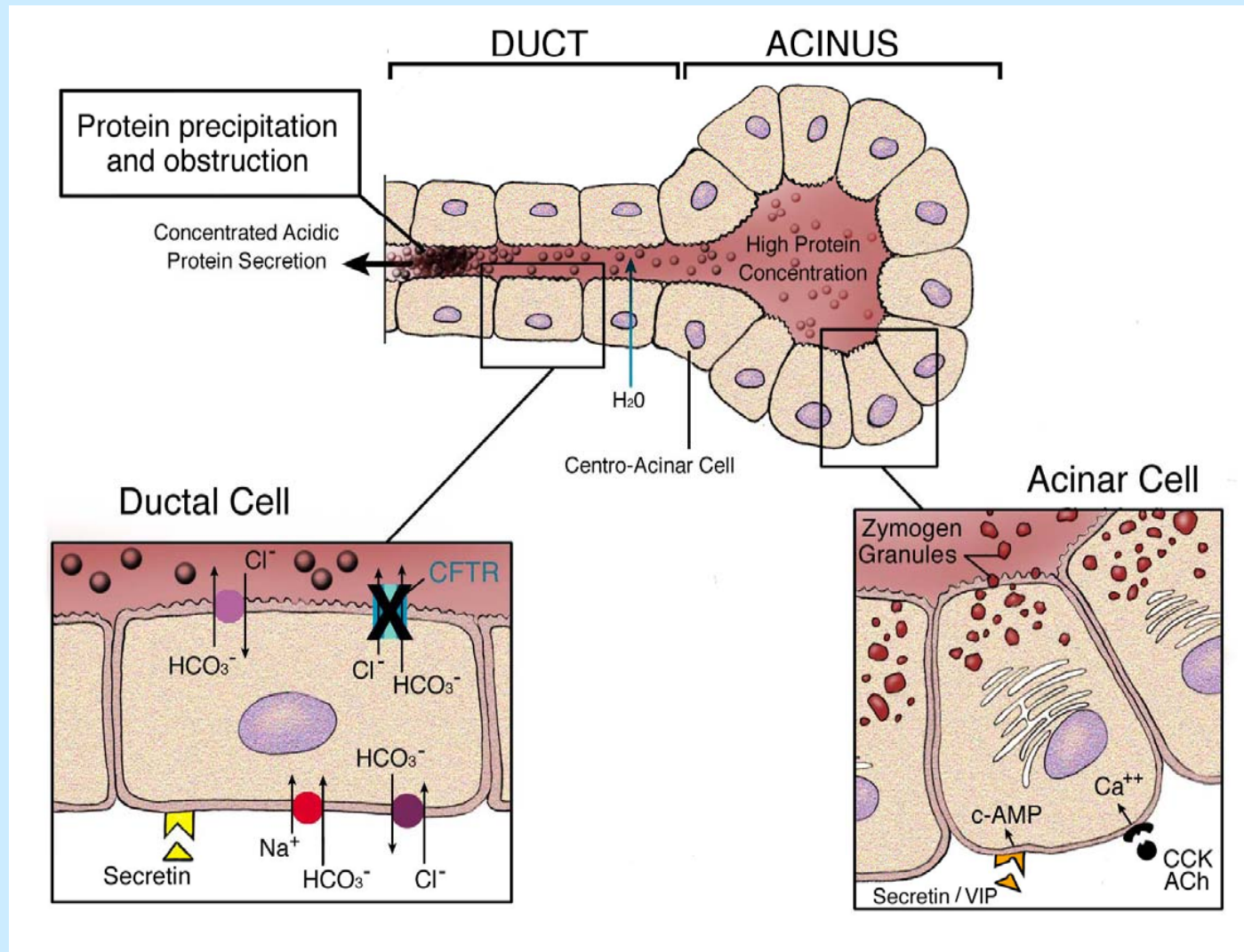
Secretion
(to the duodenum)

Acute
Trypsinogen activation
Pancreatitis

Duct

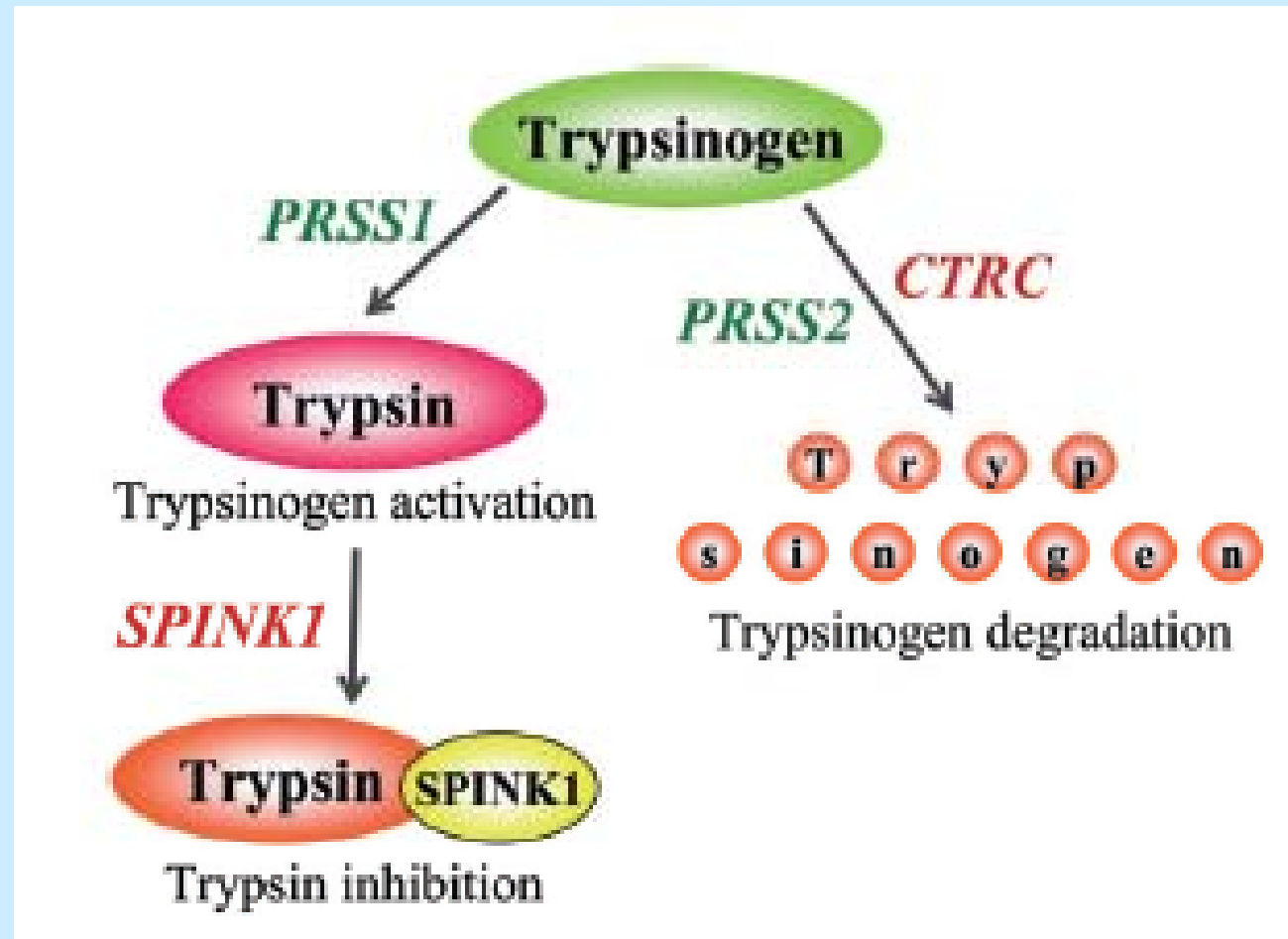
- Duct Cell Secretion
 - **CFTR**
 - ? Stimulation (PPI)
- Duct Obstruction
 - Gallstone
 - Duct stones
 - Tumor
 - Mucus
 - Other.....
- Inflammation related
 - **SPINK1**

PATHOGENESIS OF PANCREATIC DISEASE IN CF



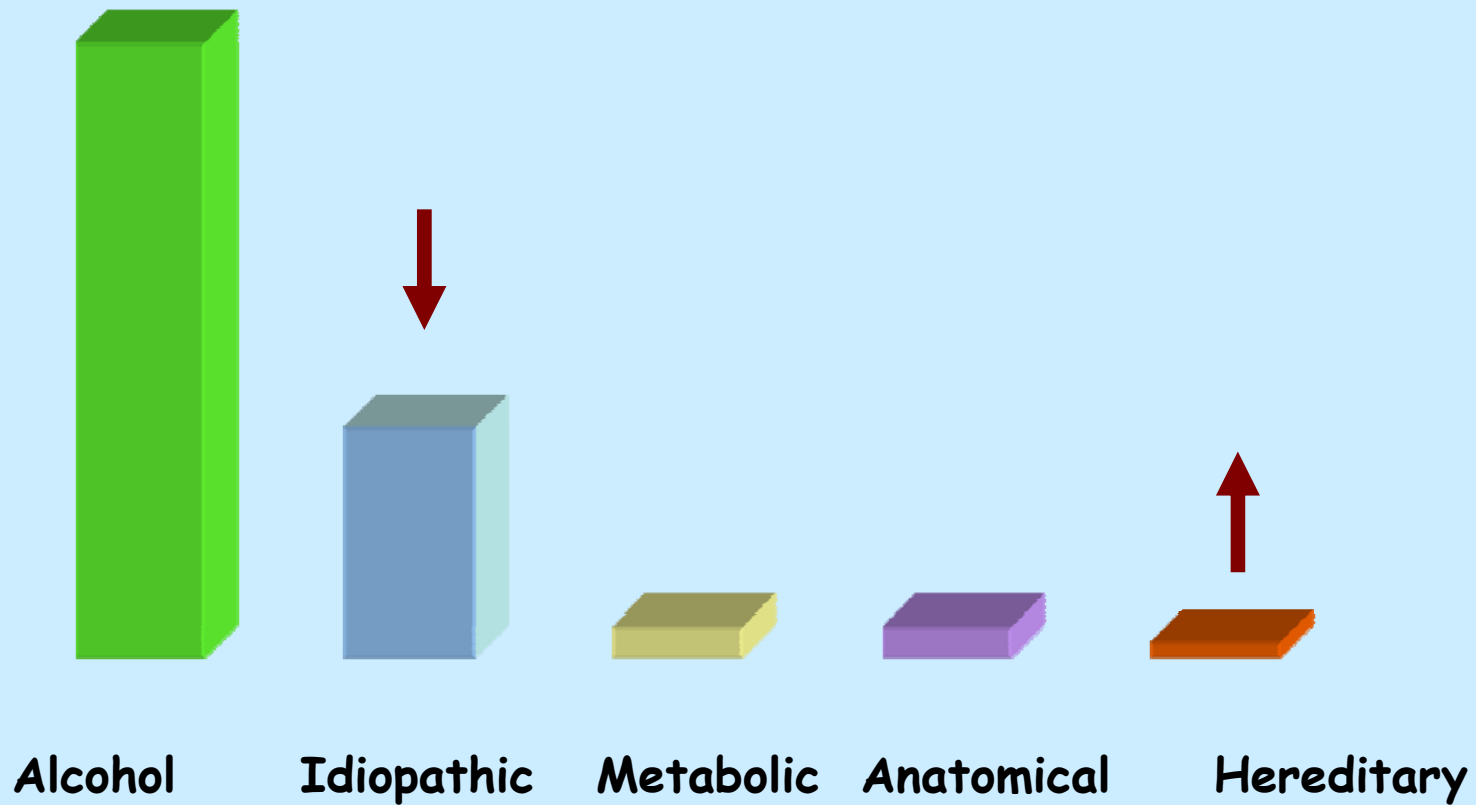
Slide courtesy of P Durie

Hereditary Pancreatitis Mutations

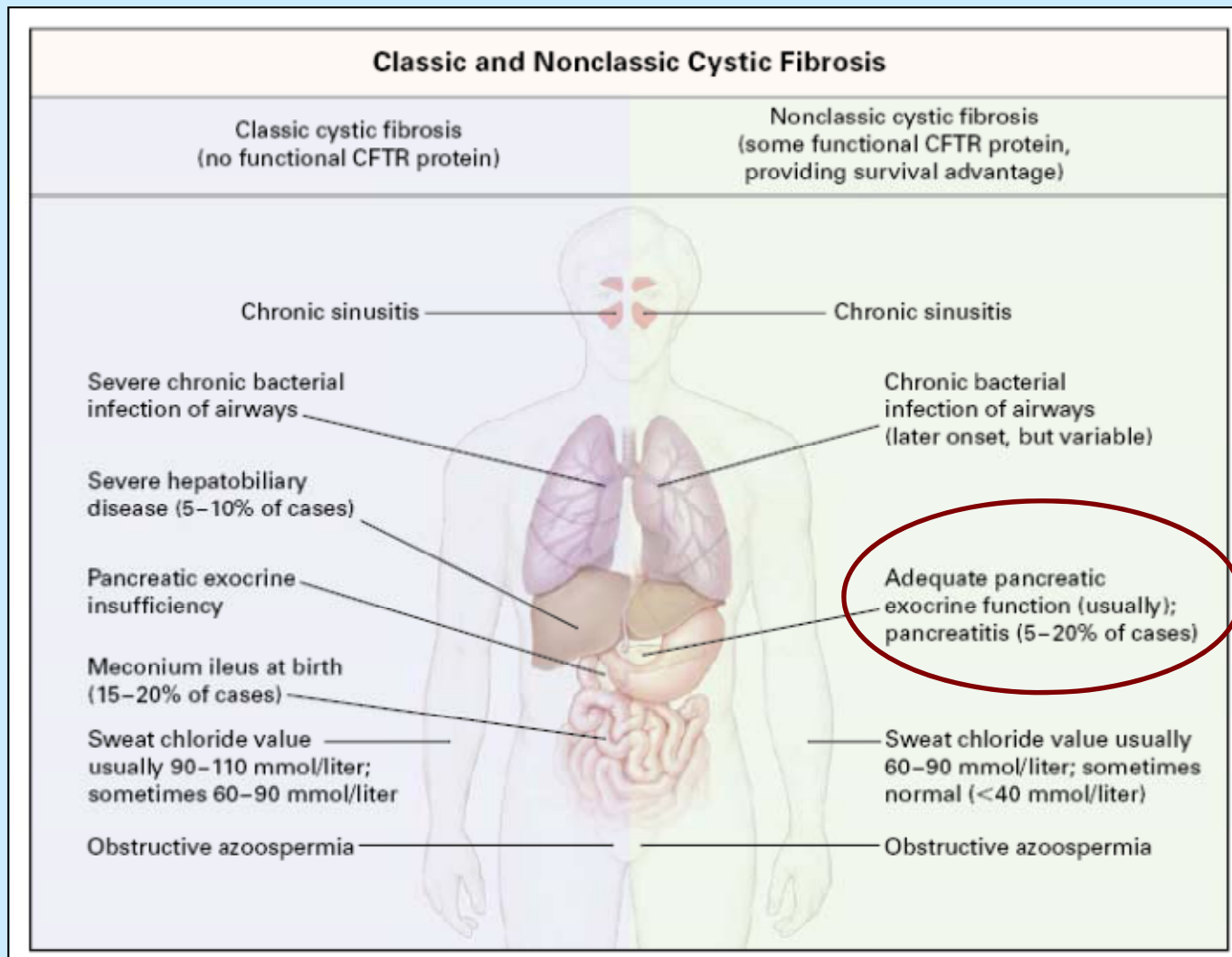


Chronic Pancreatitis

Aetiology



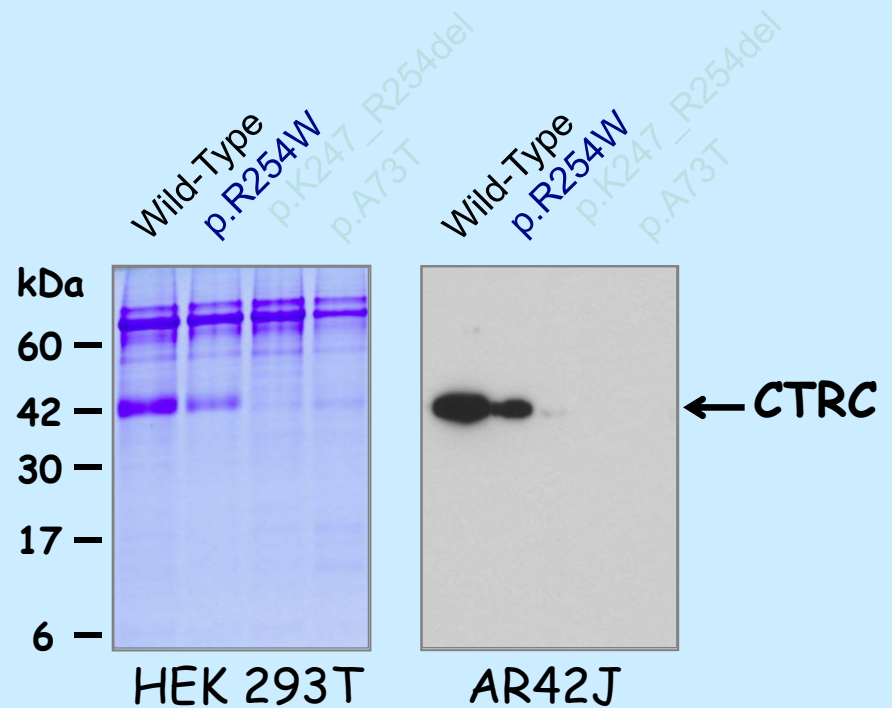
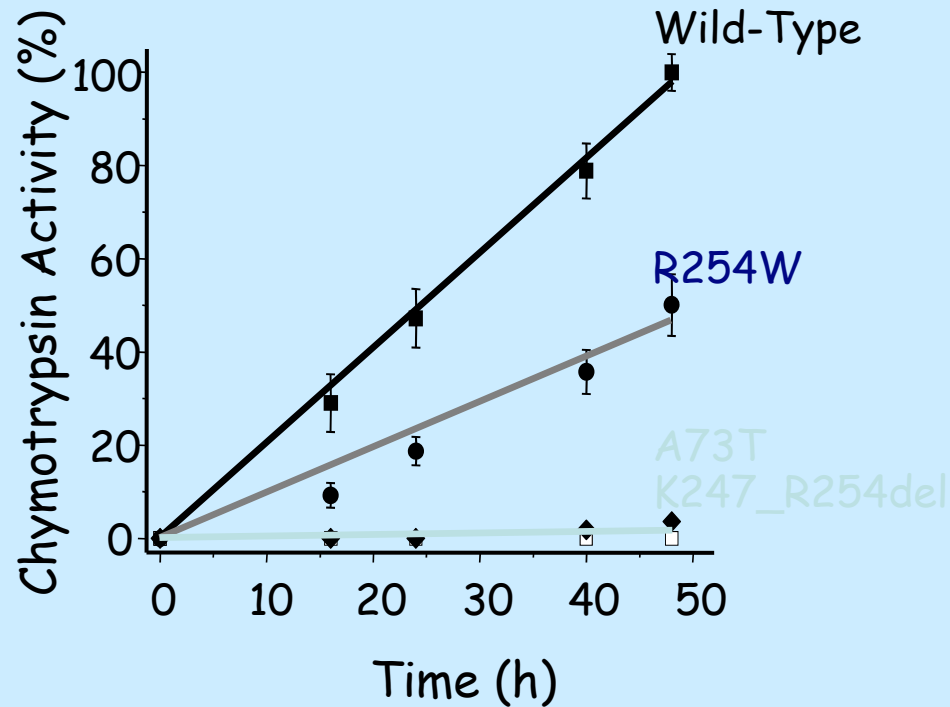
CLASSIC AND NONCLASSIC CF



Knowles and Durie, NEJM 2002

Chymotrypsin C (*CTRC*)

Effect of Variants on Activity & Secretion



Rosendahl *et al.*, Nature Genetics 2008

Non classic CF patients (partial presentation of CF)

- Age of diagnosis over 5 years
- Chronic sino-pulmonary disease.
- Pancreatic sufficiency.
- Sweat chloride levels can be normal, borderline or mildly elevated.

Hereditary Pancreatitis Family (*PRSS1*)

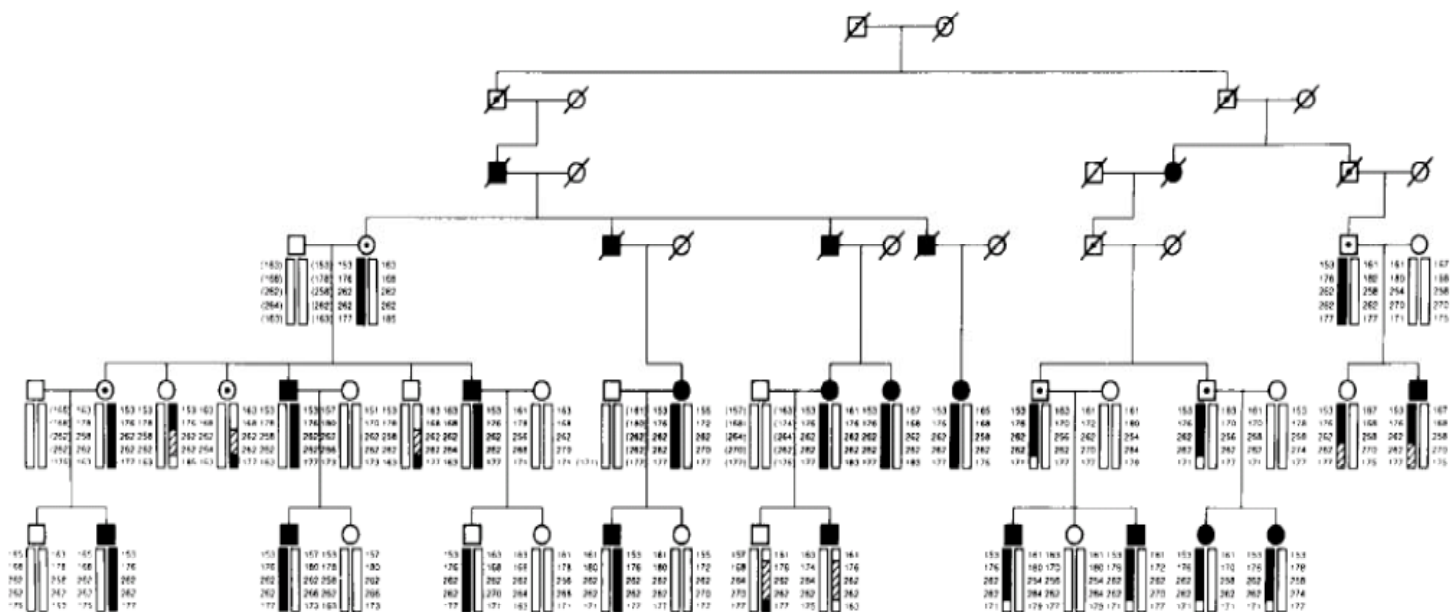


Figure 1. A limited pedigree of the S family showing the haplotypes determined by microsatellite linkage analyses of a region on chromosome 7q. Affected family members are represented by *solid boxes*, obligate carriers are represented with a *dot within the box*, and unaffected individuals are represented by *open boxes*. The affected chromosome is represented by a *shaded bar*, and the unaffected chromosome is depicted by an *open bar*. Recombinant chromosomes are depicted with partially shaded and partially unshaded bars; the breakpoint between shaded and unshaded areas corresponds to the point of recombination as determined by haplotype analysis. *Hatching* refer to regions where it is not possible to determine if recombination has occurred due to uninformative markers.