The Sound of a Silent SNP in CFTR

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What are sSNPs?

- SNPs, "snips" are DNA sequence variations that occur when a single nucleotide in the genome sequence is altered

- **sSNPs are present in the protein coding regions**
- The single nucleotide change does not alter the amino acid sequence of the protein

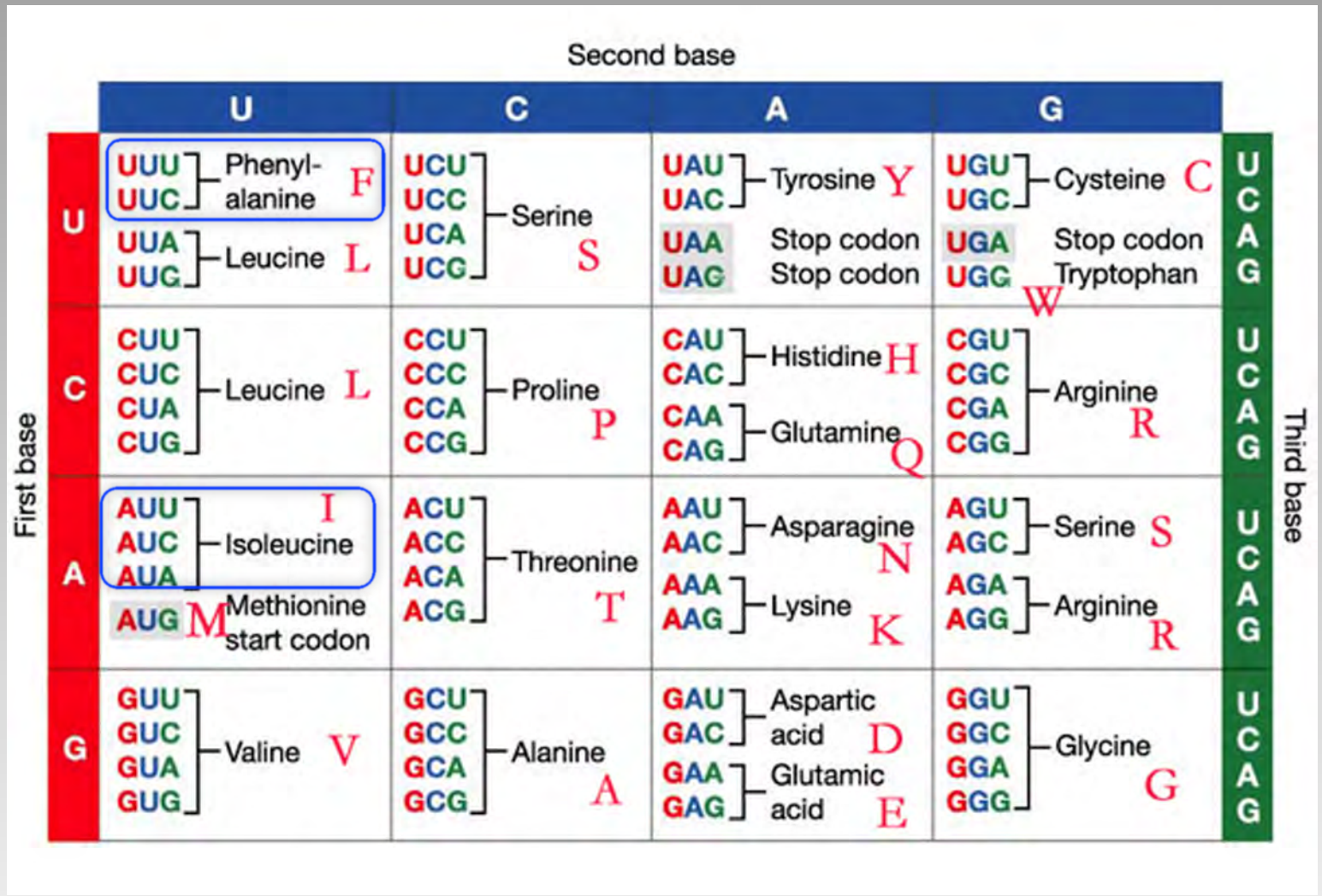
~ACC~ATT~AAA~GAA~AAT~AT**C**~TT**T**~GGT~GTT~TCC~

T **C**

Ile Phe

- sSNPs exist based on the redundancy of the genetic code

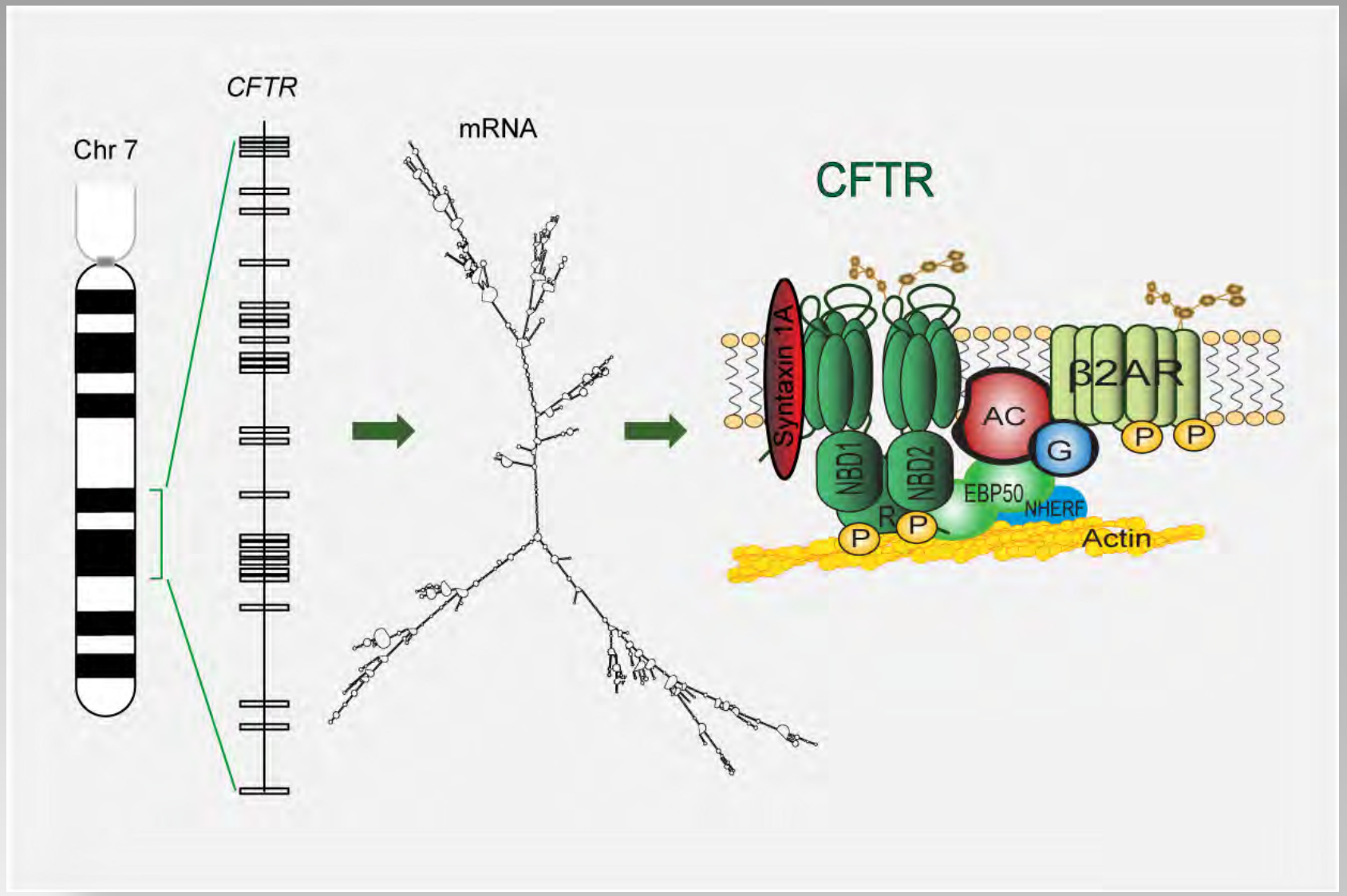
The redundancy of the genetic code



The significance of SNPs

- Disease development, severity
- Development of complex genetic traits
- Response to pathogens
- Response to drugs

CFTR


CFTR
Chr 7
CFTR
mRNA
CFTR
Syntaxin 1A
NBD1
NBD2
AC
G
β2AR
P
P
EBP50
NHERF
R
P
P
Actin

ΔF508 Mutation

WT DNA	ATC	ATC	TTT	GGT	GTT
AA	Ile	Ile	Phe	Gly	Val
	506	507	508	509	510

ΔF508 DNA	ATC	ATC	Δ	GGT	GTT
AA	Ile	Ile	Δ	Gly	Val
	506	507	Δ	509	510

(Phe codons: TTT, TTC)

(Ile codons: ATC, ATT, ATA)

ΔF508 mutation

Effect on protein:

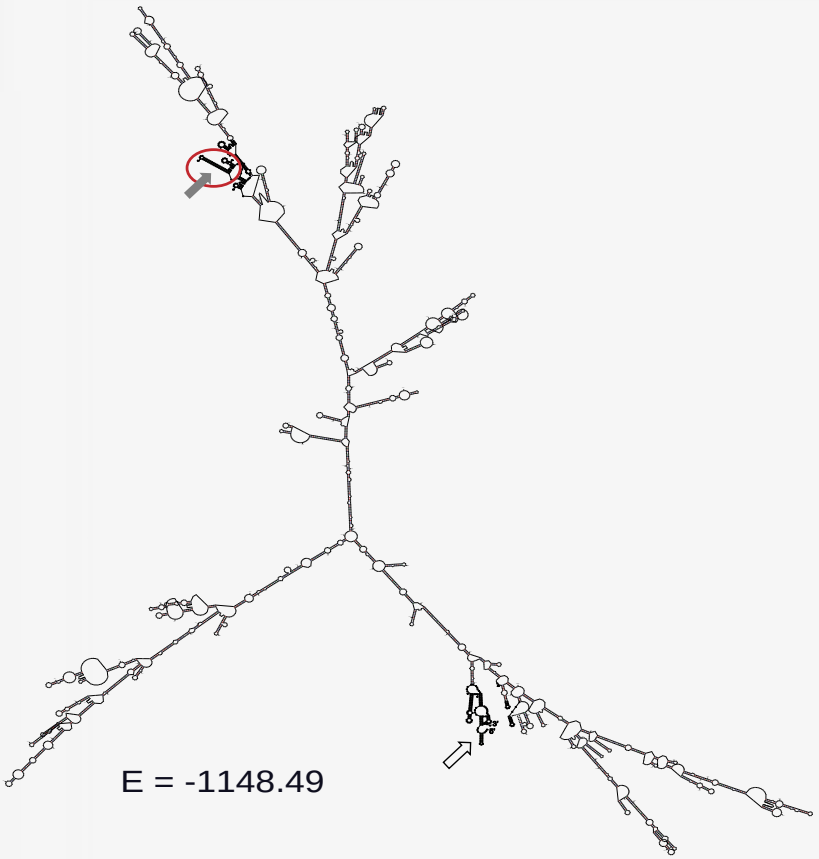
ΔF508 CFTR is misfolded and degraded by ERAD

What are the effects on mRNA?

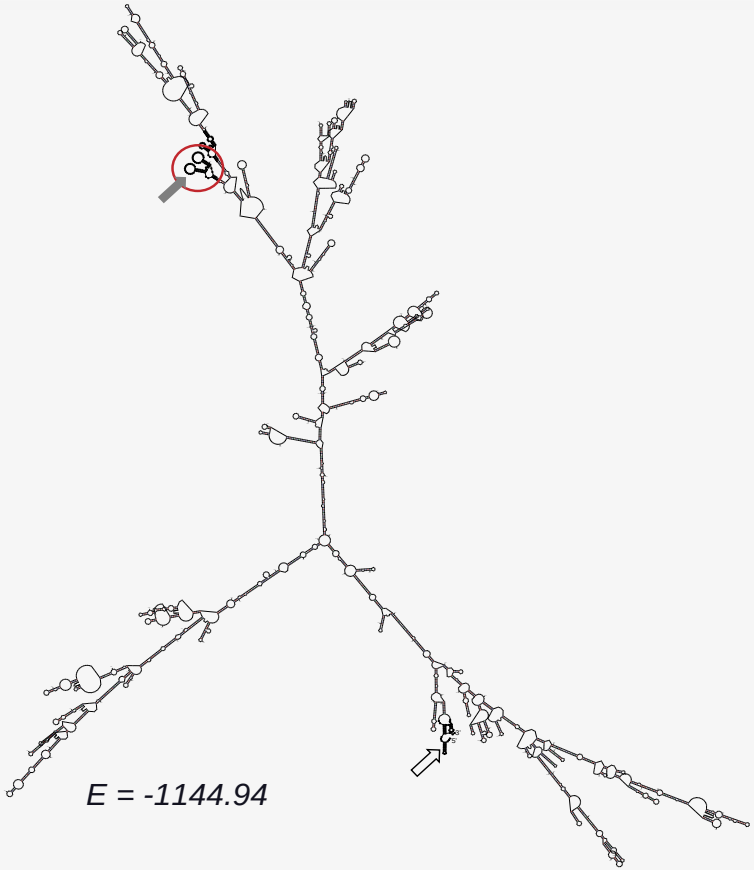
What are the effects function?

CFTR mRNA models

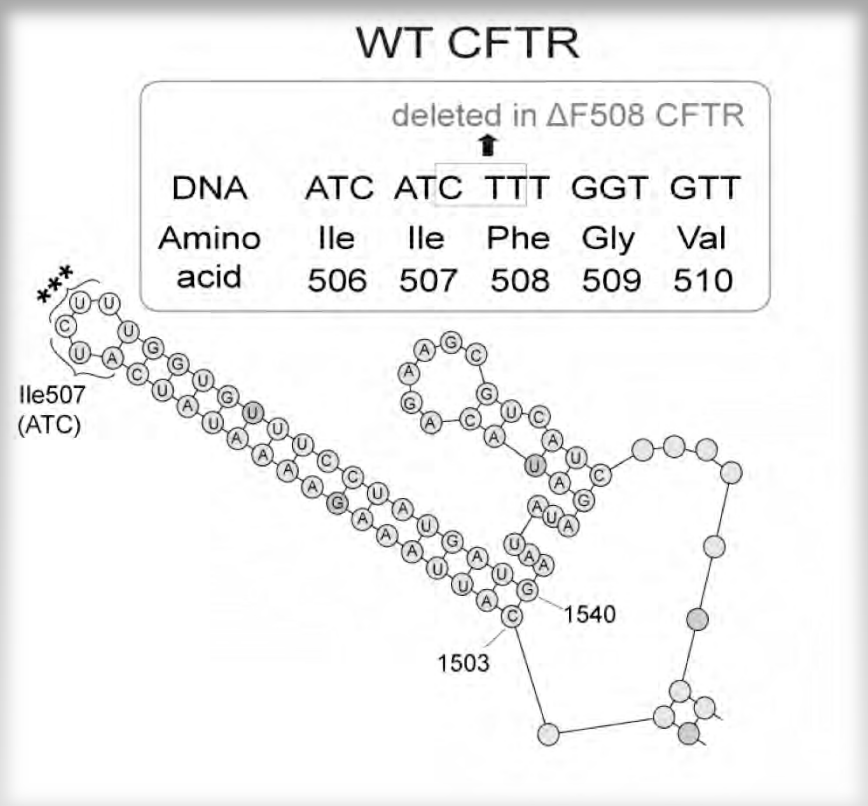
Wild type

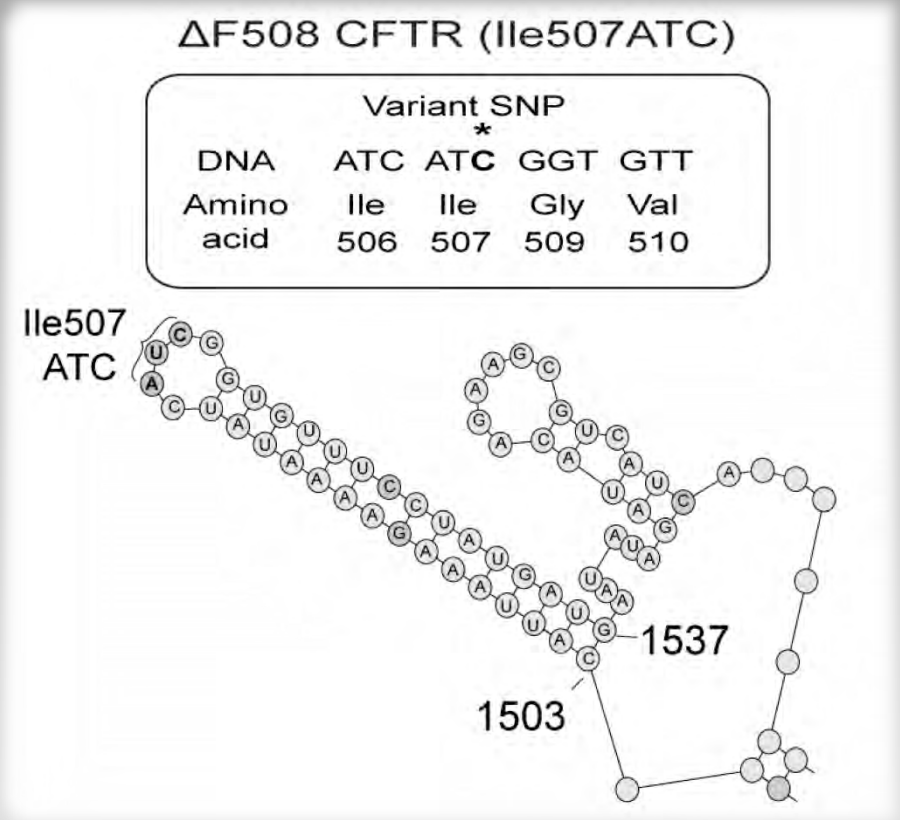


ΔF508



The ΔF508 Mutation Region





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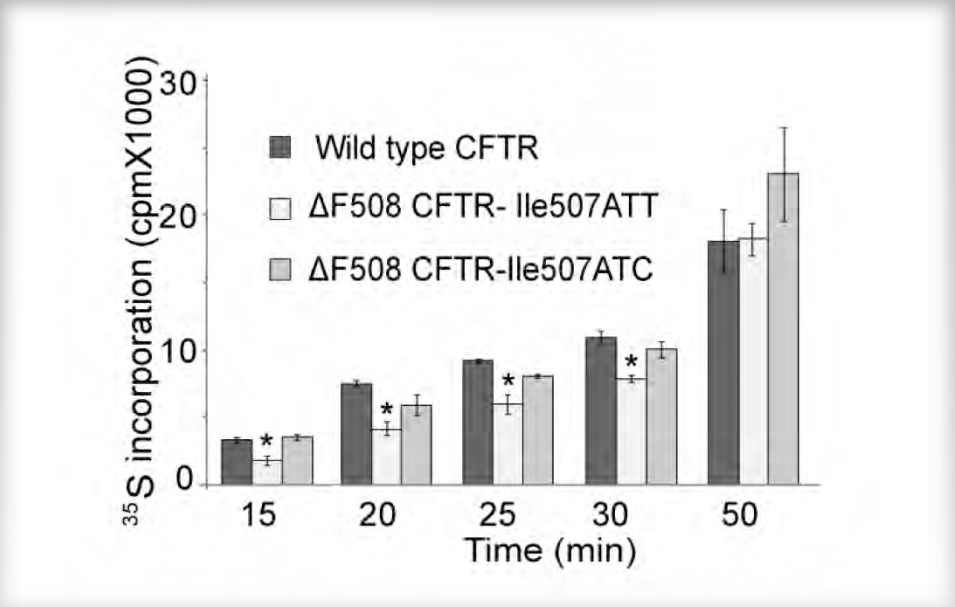
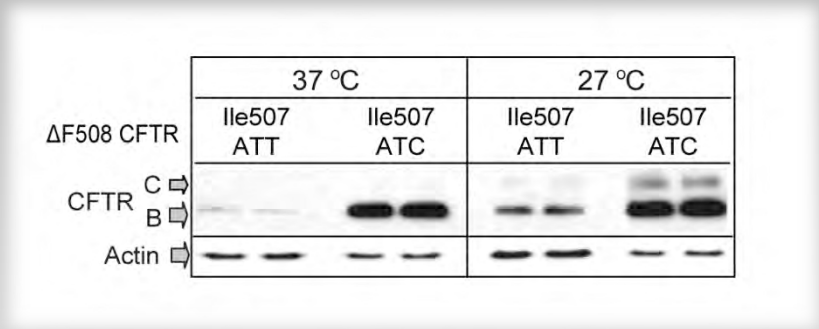
(JBC, 2010)

The consequences of the I507ATT

Translation



Protein levels and stability



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Functional consequences of I507ATT

CFTR channel stability

- Functionally and thermally stable I507-ATC ΔF508 CFTR

CFTR channel gating

- Wild type CFTR-like gating properties of I507-ATC ΔF508 CFTR

Conclusions

- The I507 ATT ΔF508 CFTR mRNA is "misfolded"
- The translation of the I507-ATT ΔF508 CFTR mRNA is compromised
- The function of the revertant, I507-ATC ΔF508 CFTR is improved
- The channel defect in ΔF508 CFTR was believed to be loss of F508, but our results indicate the channel defect is due to the I507 sSNP

- Functional consequences of sSNPs need to be explored
- Identification of sSNPs is an important task of genomics