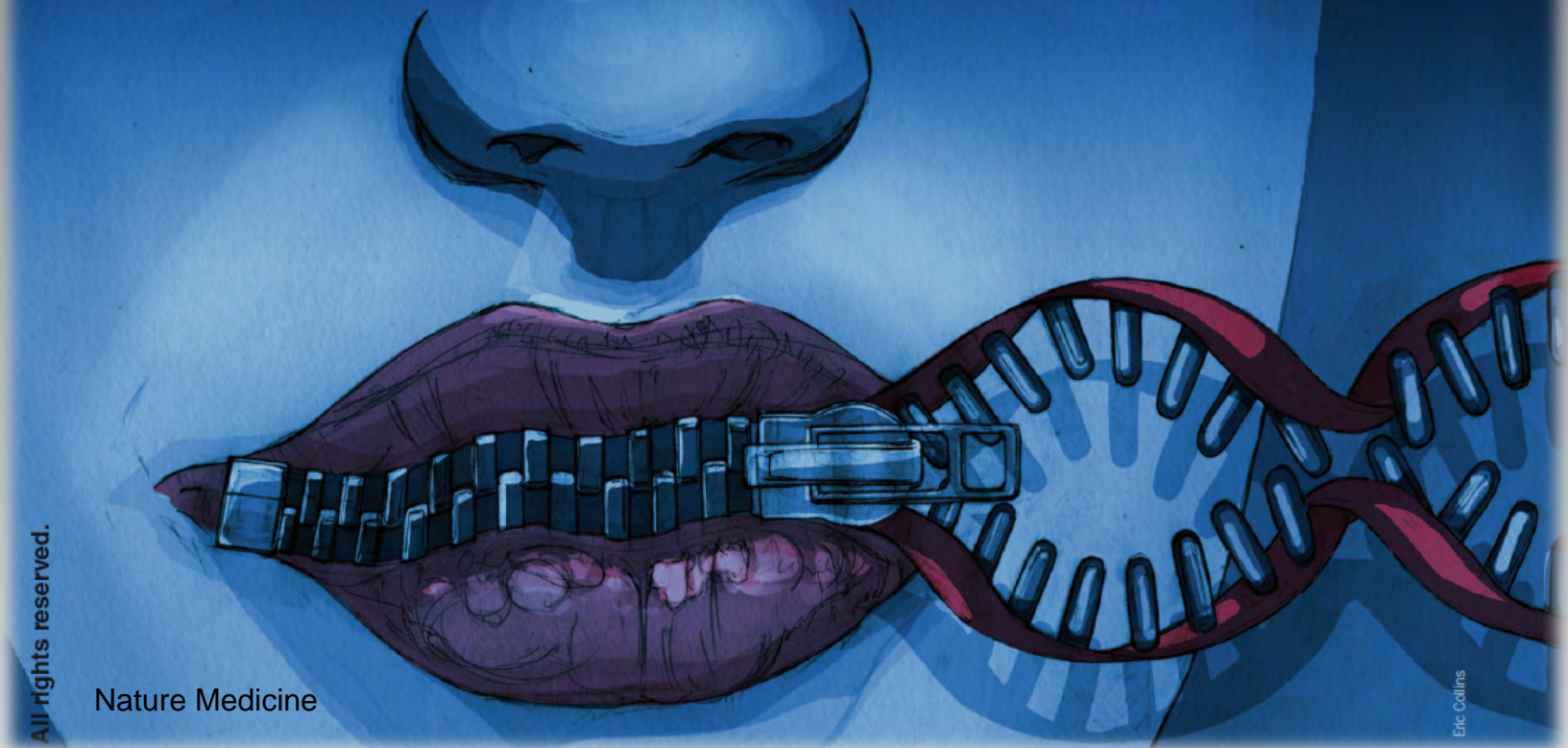


# Breaking the silence



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Nature Medicine

Eric Collins

## 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

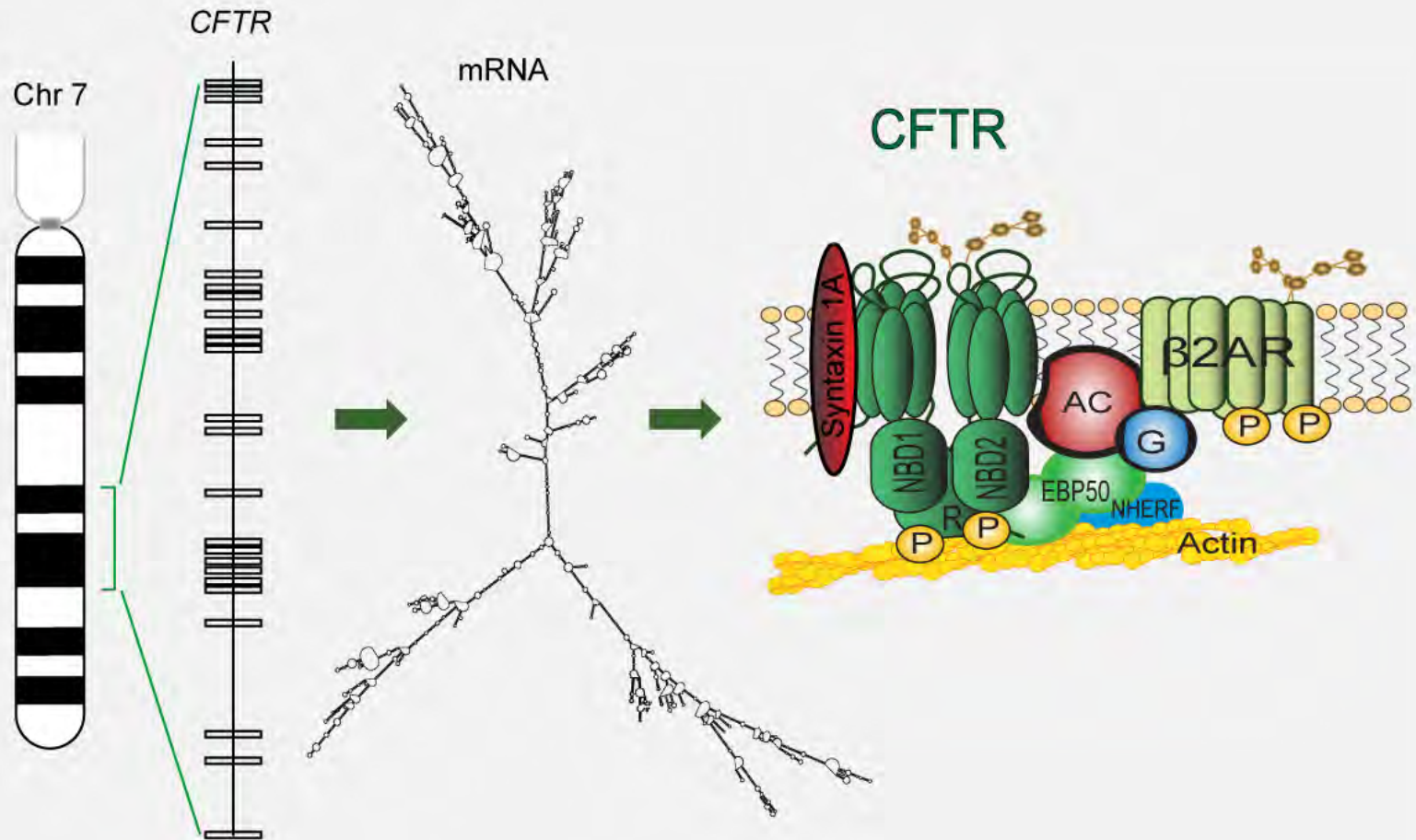
		Second base					
		U	C	A	G		
First base	U	UUU } Phenylalanine <b>F</b> UUC } UUA } Leucine <b>L</b> UUG }	UCU } UCC } Serine <b>S</b> UCA } UCG }	UAU } Tyrosine <b>Y</b> UAC } UAA } Stop codon UAG } Stop codon	UGU } Cysteine <b>C</b> UGC } UGA } Stop codon UGG } Tryptophan <b>W</b>	Third base	U
	C	CUU } CUC } Leucine <b>L</b> CUA } CUG }	CCU } CCC } Proline <b>P</b> CCA } CCG }	CAU } Histidine <b>H</b> CAC } CAA } Glutamine <b>Q</b> CAG }	CGU } CGC } Arginine <b>R</b> CGA } CGG }		C
	A	AUU } Isoleucine <b>I</b> AUC } AUA } AUG } Methionine <b>M</b> start codon	ACU } ACC } Threonine <b>T</b> ACA } ACG }	AAU } Asparagine <b>N</b> AAC } AAA } Lysine <b>K</b> AAG }	AGU } Serine <b>S</b> AGC } AGA } Arginine <b>R</b> AGG }		A
	G	GUU } GUC } Valine <b>V</b> GUA } GUG }	GCU } GCC } Alanine <b>A</b> GCA } GCG }	GAU } Aspartic acid <b>D</b> GAC } GAA } Glutamic acid <b>E</b> GAG }	GGU } GGC } Glycine <b>G</b> GGA } GGG }		G

# The significance of SNPs

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

# CFTR



# ΔF508 Mutation

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



<b>ΔF508 DNA</b>	<b>ATC</b>	<b>ATC</b>	<b>Δ</b>	<b>GGT</b>	<b>GTT</b>
AA	Ile	Ile	Δ	Gly	Val
	506	507	Δ	509	510

*(Phe codons: TTT, TTC)*

*(Ile codons: ATC, ATT, ATA)*

# $\Delta F508$ mutation

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## Effect on protein:

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$\Delta F508$  CFTR is misfolded and degraded by ERAD

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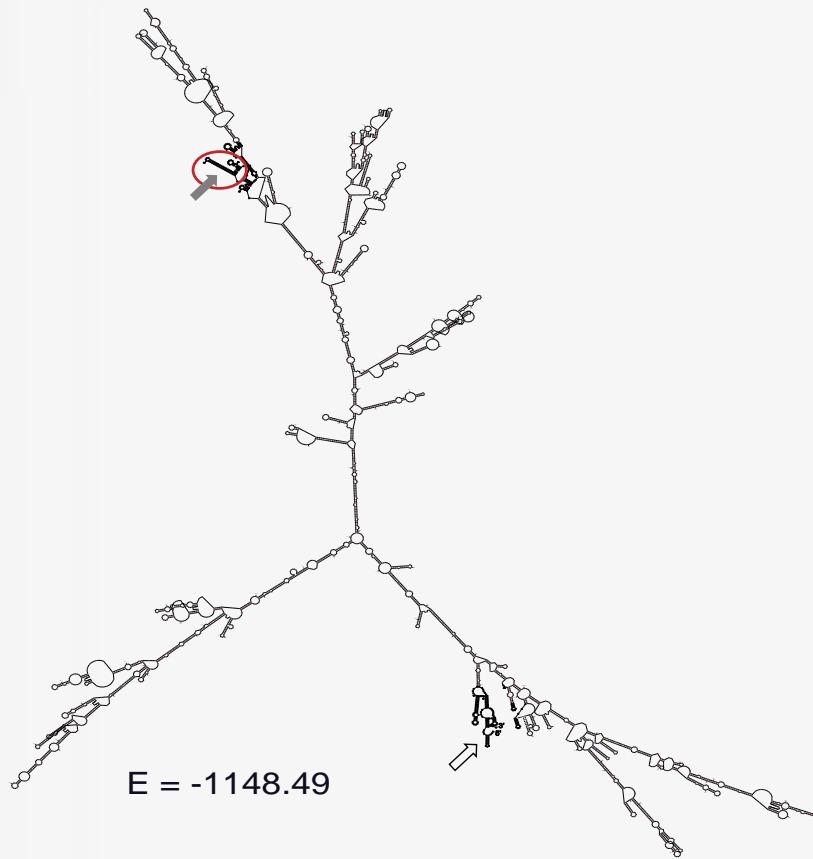
**What are the effects on mRNA?**

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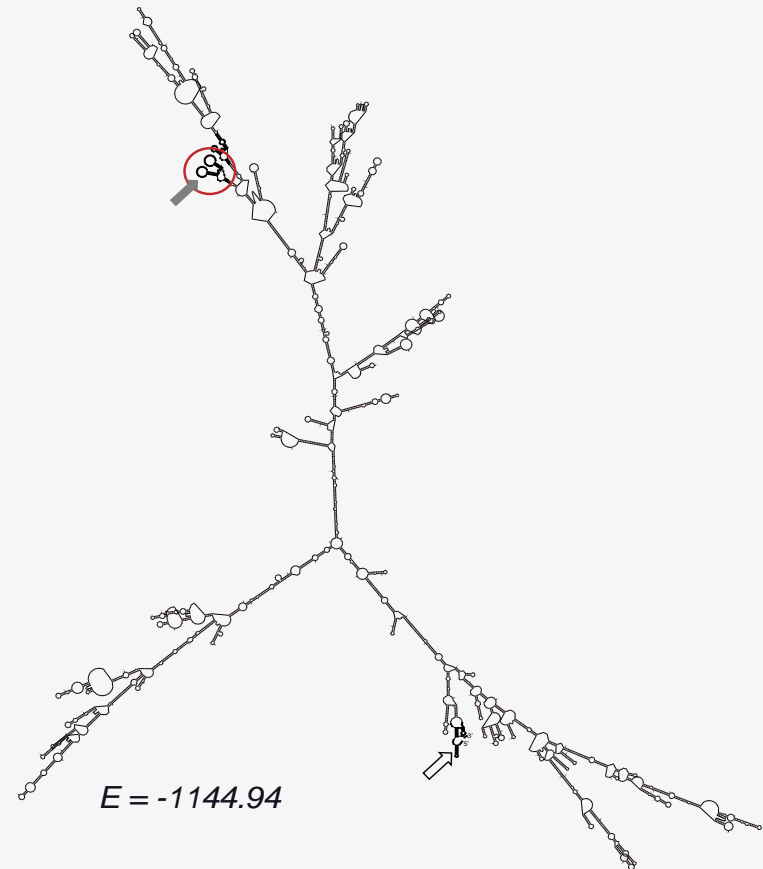
**What are the effects function?**

# CFTR mRNA models

Wild type



$\Delta F508$





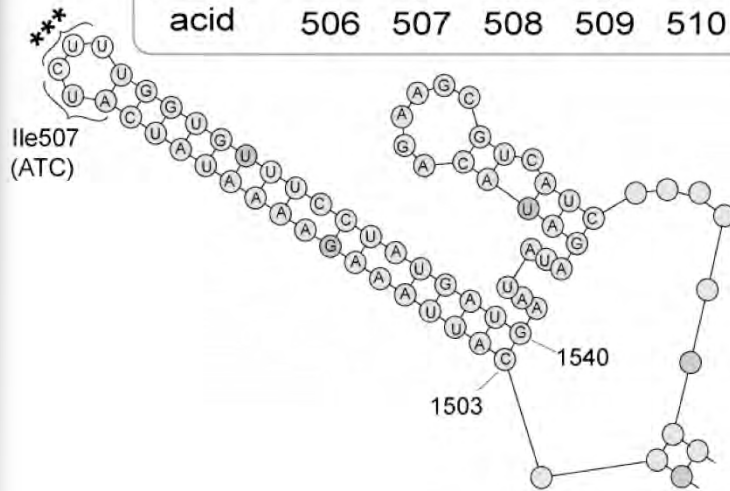
# The $\Delta F508$ Mutation Region

## WT CFTR

deleted in  $\Delta F508$  CFTR



DNA	ATC	ATC	TTT	GGT	GTT
Amino acid	Ile	Ile	Phe	Gly	Val
	506	507	508	509	510

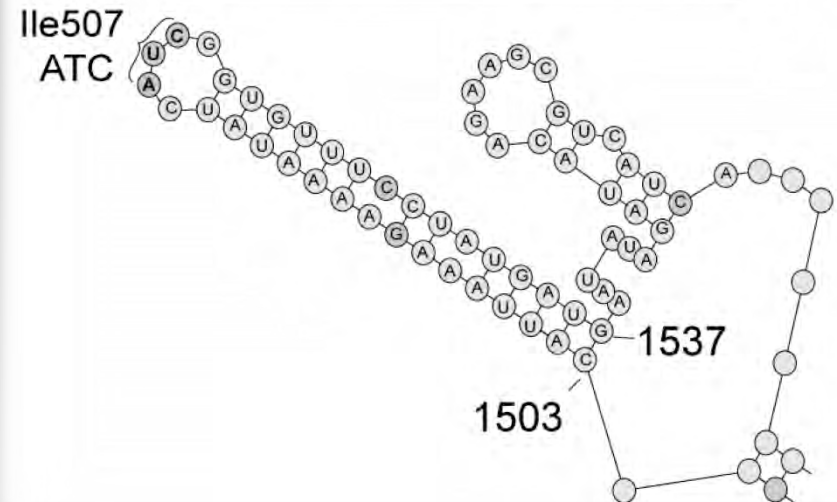


## $\Delta F508$ CFTR (Ile507ATC)

Variant SNP

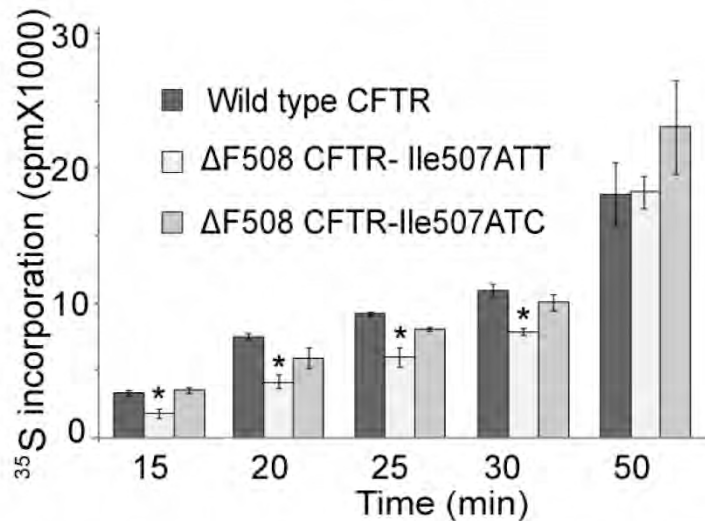
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DNA	ATC	ATC	GGT	GTT
Amino acid	Ile	Ile	Gly	Val
	506	507	509	510

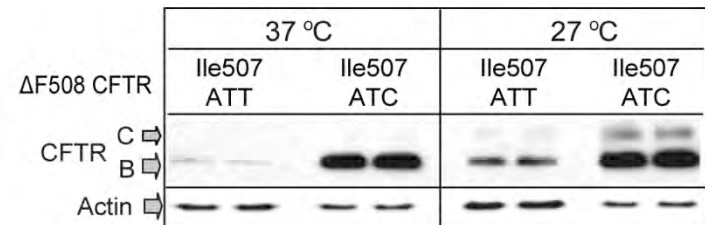


# The consequences of the I507ATT

## Translation



## Protein levels and stability



# Functional consequences of I507ATT

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## CFTR channel stability

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- Functionally and thermally stable I507-ATC  $\Delta$ F508 CFTR

## CFTR channel gating

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- Wild type CFTR-like gating properties of I507-ATC  $\Delta$ F508 CFTR

# Conclusions

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- The I507 ATT  $\Delta$ F508 CFTR mRNA is “misfolded”
- The translation of the I507-ATT  $\Delta$ F508 CFTR mRNA is compromised
- The function of the revertant, I507-ATC  $\Delta$ F508 CFTR is improved
- The channel defect in  $\Delta$ F508 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