

**Complemento aula prática Genoma Humano II**

# **Patologia Molecular**

RCG0117 - Genética Humana

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# “Mutaç o, Polimorfismo e Variaç o”

O que significam esses termos?

Mutaç o ?  $\longrightarrow$  mudanç a no DNA que causa doenç a  
mudanç a no DNA que causa ou n o doenç a



Polimorfismo ?  $\longrightarrow$  mudanç a no DNA que n o causa doenç a  
Frequ ncia da mutaç o em uma populaç o  
>1% < 99%



**Patog nica ou n o**

**(afetam a funç o prot ica)**

**VUS (Variants of Uncertain Significance)**

Sequ ncia variante  
Alteraç o  
Alelo variante

**Variaç o**

Transição

Transversão

Inserção/Deleção (InDel)



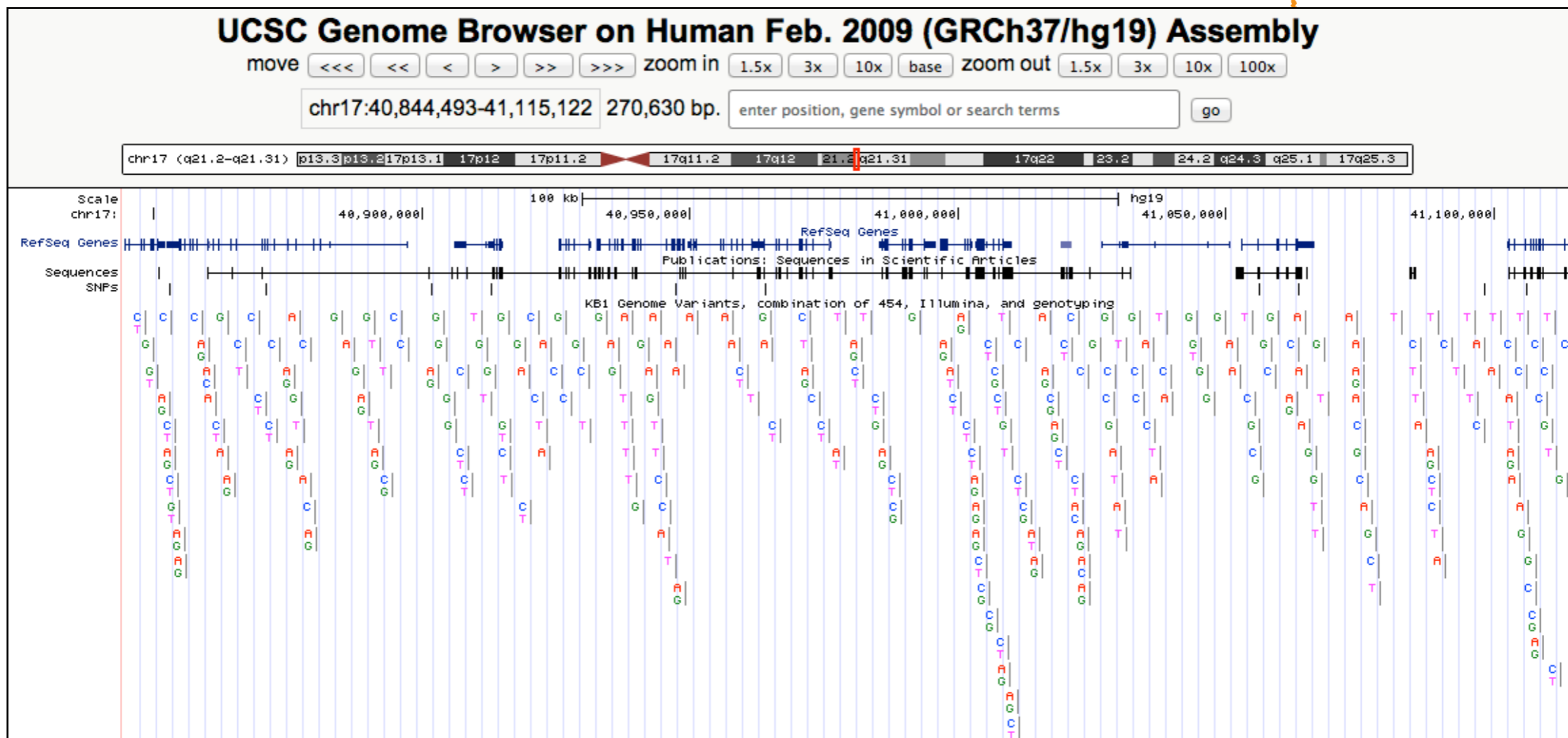
Germinativas

Somáticas



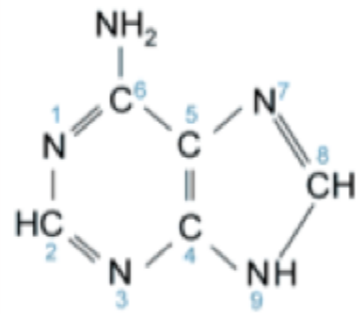
Intergênicas

Gênicas

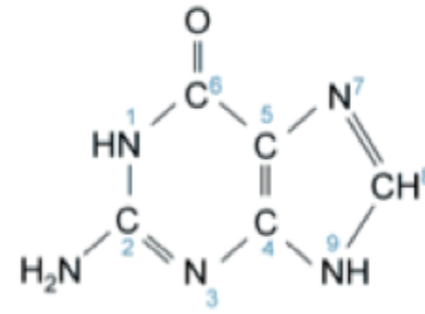


Varição Genética: Origem e detecção

## Purinas

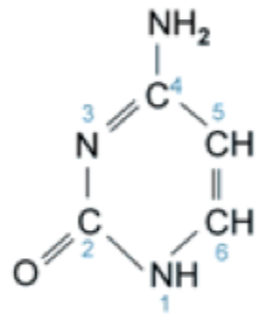


Adenine (A)

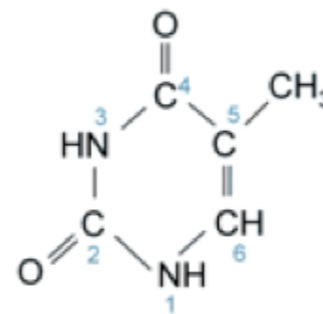


Guanine (G)

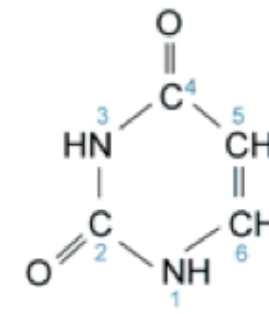
## Pirimidinas



Cytosine (C)



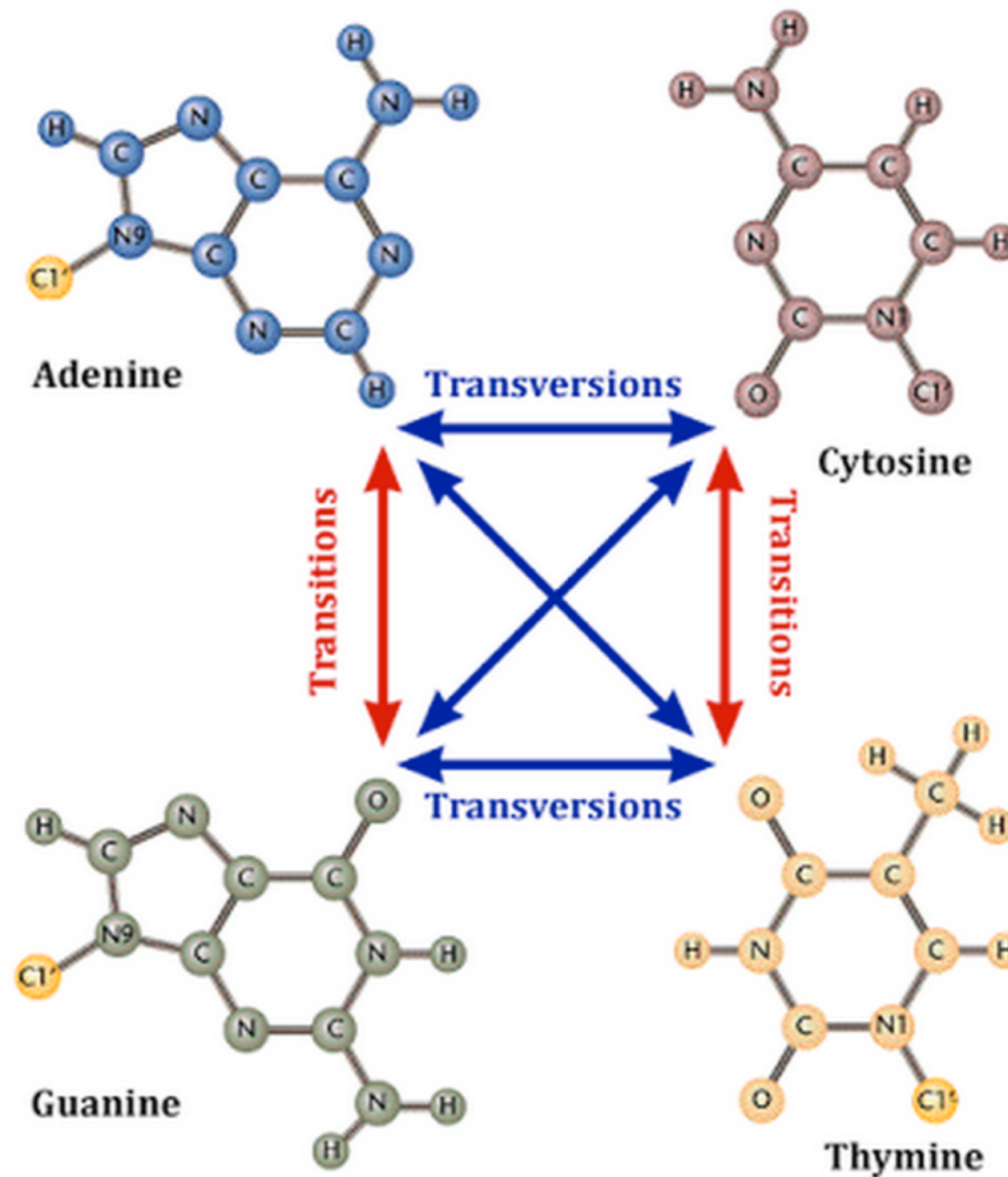
Thymine (T)

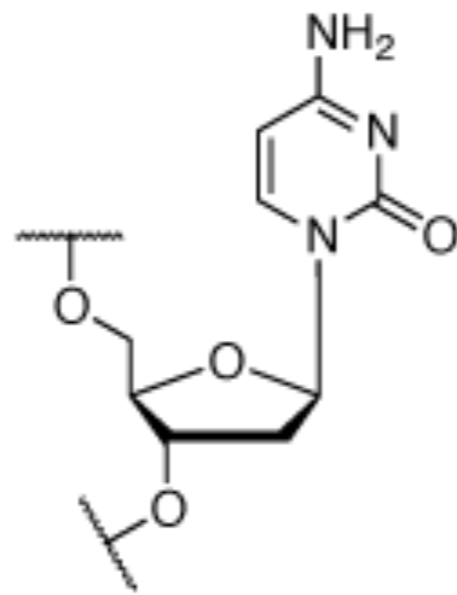


Uracil (U)

# Transição

# Transversão





cytosine

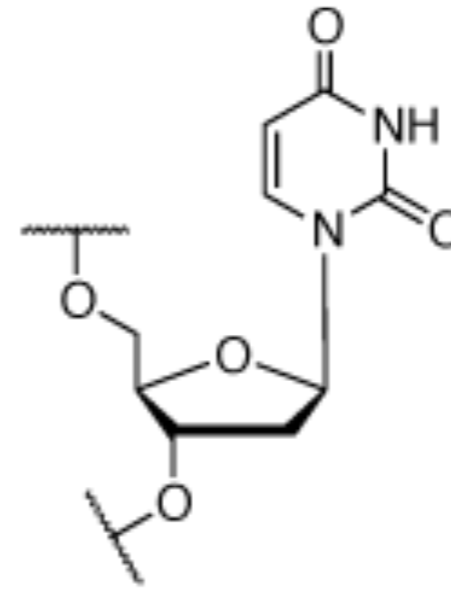
deamination



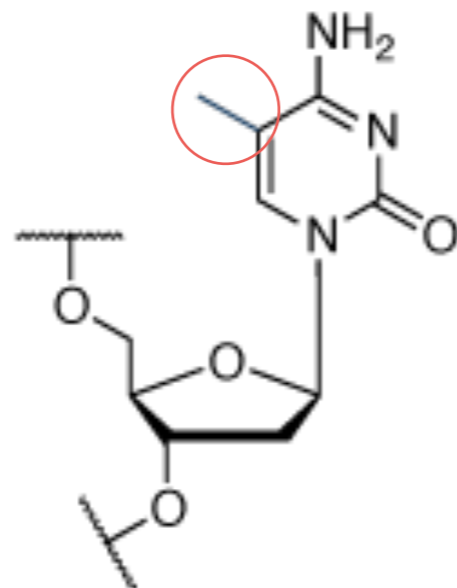
DNA repair



UDG



uracil

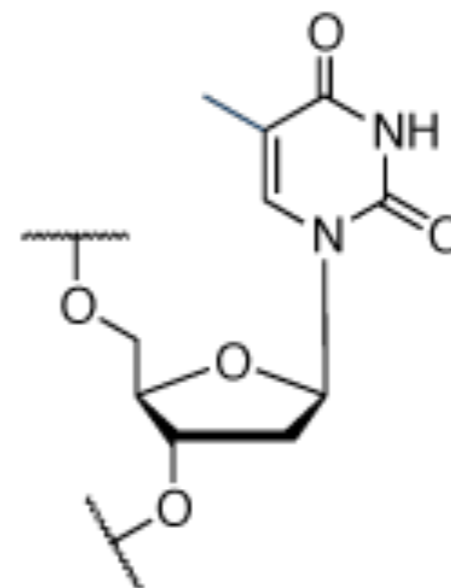


5-methylcytosine

deamination



not repaired



thymine

Transição

Transversão

Inserção/Deleção (InDel)



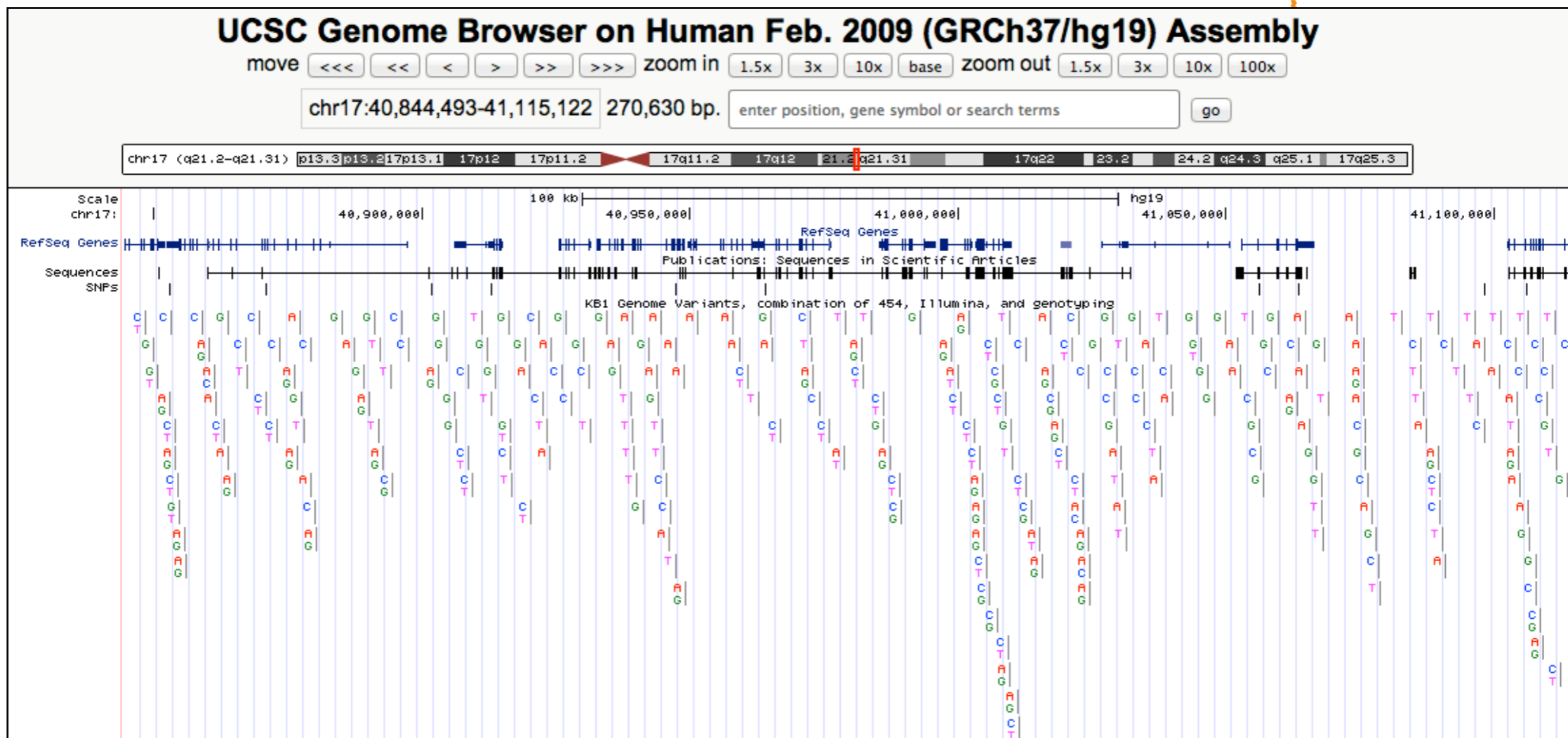
Germinativas

Somáticas

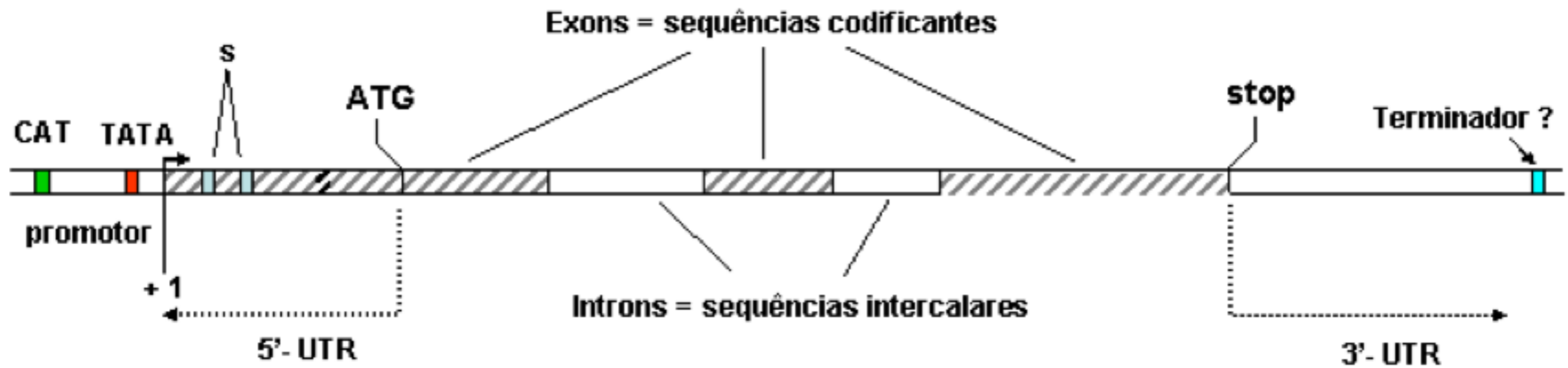


Intergênicas

Gênicas



# Mutações Gênicas (introns e regiões codificadoras)





# Código genético

	T			C			A			G		
T	TTT	Phe	F	TCT	Ser	S	TAT	Tyr	Y	TGT	Cys	C
	TTC			TCC			TAC			TGC		
	TTA	Leu	L	TCA			TAA	STOP		TGA	STOP	
	TTG			TCG			TAG			TGG	Trp	W
C	CTT	Leu	L	CCT	Pro	P	CAT	His	H	CGT	Arg	R
	CTC			CCC			CAC			CGC		
	CTA			CCA			CAA	Gln	Q	CGA		
	CTG			CCG			CAG			CGG		
A	ATT	Ile	I	ACT	Thr	T	AAT	Asn	N	AGT	Ser	S
	ATC			ACC			AAC			AGC		
	ATA			ACA			AAA	Lys	K	AGA	Arg	R
	ATG	Met	M	ACG			AAG			AGG		
G	GTT	Val	V	GCT	Ala	A	GAT	Asp	D	GGT	Gly	G
	GTC			GCC			GAC			GGC		
	GTA			GCA			GAA	Glu	E	GGA		
	GTG			GCG			GAG			GGG		

AAA	22.2	] Lys	CCA	14.6	] Pro	AGA	9.9	] Arg	CUC	19.9	] Leu
AAG	34.9		CCC	20.0		AGG	11.1		CUU	10.7	
AAC	22.6	] Asn	CCG	6.6		CGA	5.4		CUA	6.2	
AAU	16.6		CCU	15.5		CGG	10.4		CUG	42.5	
CAA	11.1	] Gln	GCA	14.0	CGC	11.3	UUA	5.3			
CAG	33.6		GCC	29.1	CGU	4.7	UUG	11.0			
CAC	14.2	] His	GCG	7.2	GG A	17.1	] Phe	UUC	22.6		
CAU	9.3		GCU	19.6	GG C	25.4		UUU	15.8		
GAA	26.8	] Glu	UCA	9.3	GG G	17.3	] Val	GU A	5.9		
GAG	41.4		UCC	17.7	GG U	11.2		GUC	16.3		
GAC	29.0	] Asp	UCG	4.2	UGC	14.5		UGG	30.9		
GAU	21.7		UCU	13.2	UGU	9.9		GUU	10.4		
UAC	18.8	] Tyr	AGC	18.7	UGG	13.8	Trp				
UAU	12.5		AGU	9.4	AUA	5.8	] Ile				
ACA	14.4	] Thr			AUC	24.3		] Met			
ACC	23.0				AUU	14.9					
ACG	6.7				AUG	22.3					
ACU	12.7										

Key:

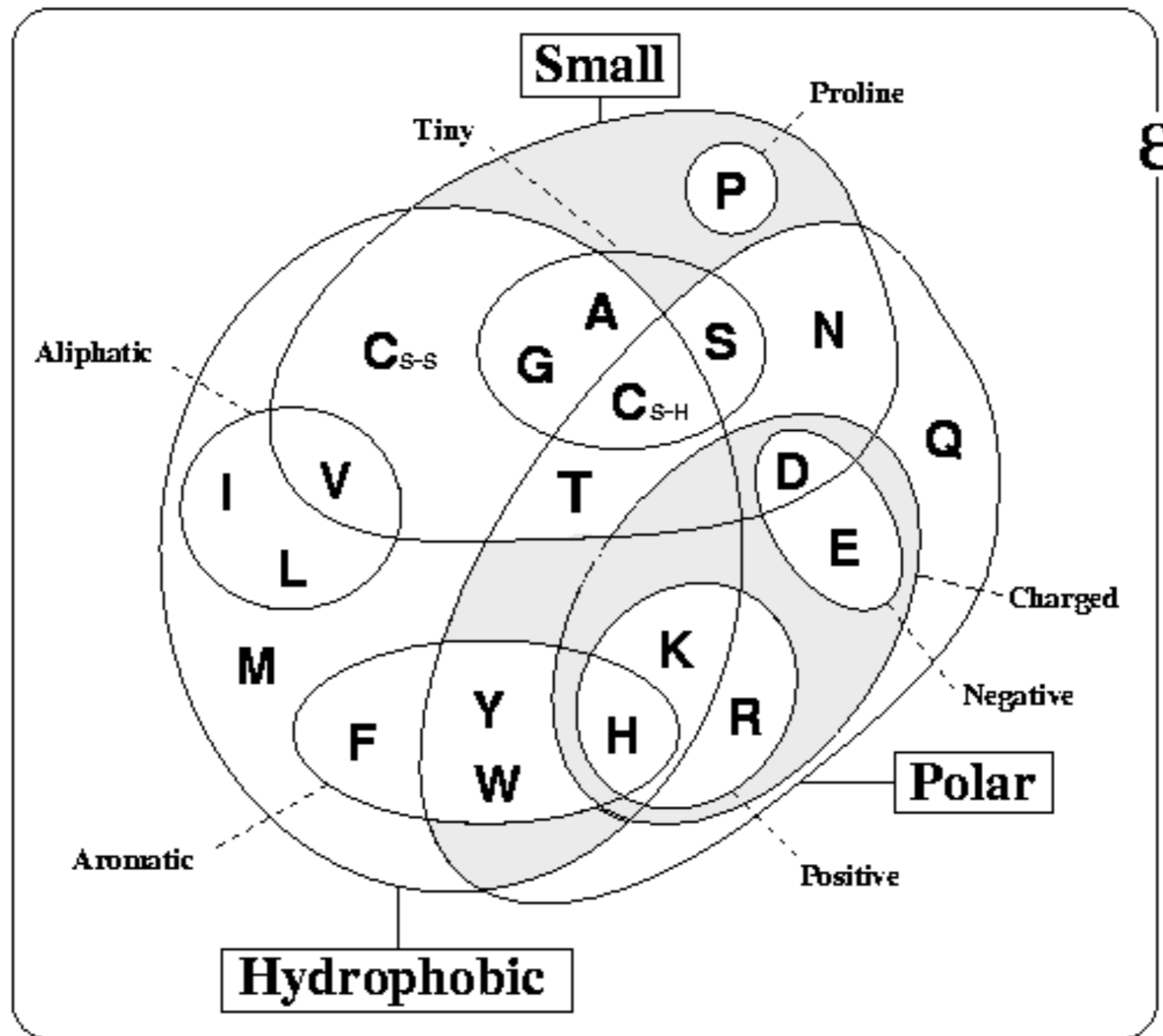
- N Nondegenerate site
- N Twofold degenerate site
- N Fourfold degenerate site

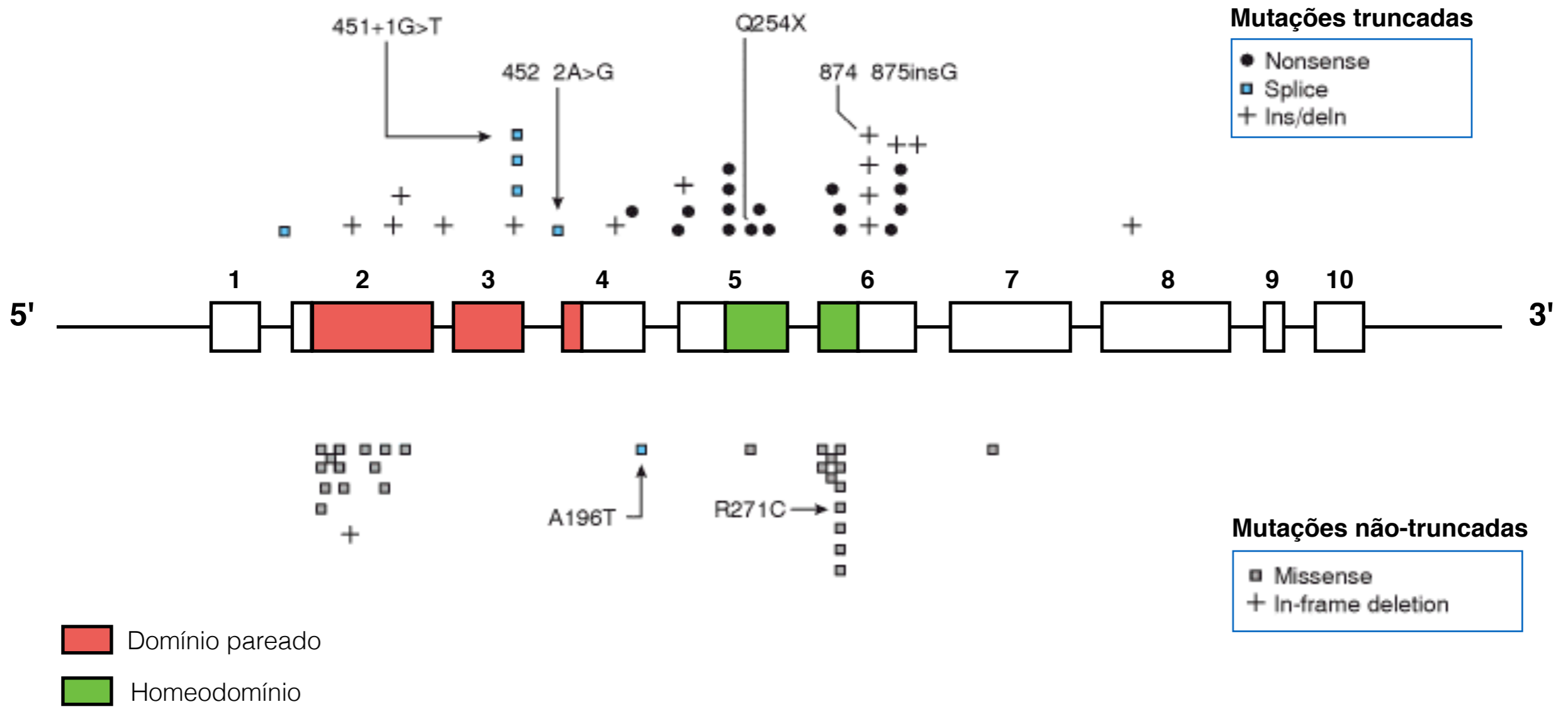
# Mutações Gênicas (Regiões codificadoras)

- 1)      Ile   Cys   Ile   Lys   Ala   Leu   Val   Leu   Leu   Thr  
 ATG TGT ATA AAG GCA CTG GTC CTG TTA ACA      (sinônima)
- ↓
- ATG TGT ATA AAG GCA CTG **GT**A CTG TTA ACA
- 2)      Ile   Cys   Ile   Lys   Ala   Leu   Val   Leu   Leu   Thr  
 ATG TGT ATA AAG GCA CTG GTC CTG TTA ACA      (não sinônima ou *missense*)
- ↓
- ATG TGT ATA AAG GCA CTG **TTC** CTG TTA ACA  
    Phe
- 3)      Ile   Cys   Ile   Lys   Ala   Leu   Val   Leu   Leu   Thr  
 ATG TGT ATA AAG GCA CTG GTC CTG TTA ACA      (sem sentido ou *nonsense*)
- ↓
- ATG TGT ATA **TAG** GCACTGGTACTGTTAACA  
    Ter
- 4)      Ile   Cys   Ile   Lys   Ala   Leu   Val   Leu   Leu   Thr  
 ATG TGT ATA AAG**G** GCA CTG GTC CTG TTA ACA      (mudança de fase ou *frameshift*)
- ↑
- His   Leu   Ser   Cys   Ter  
 ATG TGT ATA AAG CAC TGG TCC TGT TAA CA

# Mutações Não-sinônimas

## *Conservativa e não-conservativa*





**QUADRO 13.2 Nomenclatura para descrever variantes de DNA e de aminoácidos**

Cada polimorfismo de nucleotídeo único (SNP, na sigla em inglês) presente no banco de dados público dbSNP (<http://www.ncbi.nlm.nih.gov/projects/SNP>) pode ser referido por seu identificador único, como o rs212570, em que rs se refere a “SNP referencia” (na sigla em inglês) e 212570 é um número serial único. Polimorfismos de repetições curtas em *tandem* (STRPs, na sigla em inglês) possuem identificadores tais como D6S282, em que D se refere a segmento de DNA, 6 é o número do cromossomo no qual o marcador está localizado, S significa mutação de cópia única (do inglês *single copy sequence*) e 282 é um número serial único.

Qualquer mudança na sequência pode ser descrita utilizando-se as convenções definidas no endereço eletrônico da *Human Genome Variation Society*, <http://www.hgvs.org/mutnomen/>. Os casos mais comuns são descritos a seguir.

Todas as variantes apresentam o prefixo g. (genoma), c. (cDNA), r. (RNA) ou p. (proteína).

**Substituições de nucleotídeos**

Para mudanças em um gene, o A do códon iniciador ATG é numerado como +1; a base imediatamente anterior a ele é -1. Não existe zero. O número do nucleotídeo alterado é seguido da mudança.

- **g.1162G>A** – no DNA genômico, substituição de uma guanina na posição 1162 por uma adenina.

Para mudanças nos íntrons, quando apenas a sequência do cDNA é conhecida por completo, especifica-se o número do íntron com IVS (do inglês *intervening sequence*) ou o número do éxon mais próximo.

- **g.621+1G>T** ou **IVS4+1G>T** – substituição de G por T na primeira base do íntron 4 (o nucleotídeo 621 é a última base do éxon 4).

**Substituições de aminoácidos**

Utiliza tanto códigos de uma letra (X indica um códon de parada) como códigos de três letras. Proteínas são numeradas com o iniciador metionina como códon 1.

- **p.R117H** ou **Arg117His** – substitui a arginina 117 por uma histidina.
- **p.G542X** ou **Gly542Stop** – substitui o códon da glicina 542 por um códon de parada.

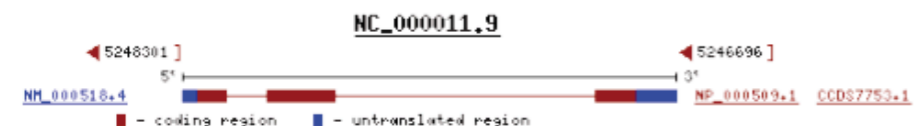
**Deleções e inserções**

Utilize *del* para deleções e *ins* para inserções, precedido pela posição do nucleotídeo ou do intervalo (para mudanças no DNA) ou o símbolo do aminoácido (código de uma letra; para trocas de aminoácidos).

- **p.F508del** – em uma proteína (p), deleção da fenilalanina (F) 508.
- **c.6232\_6236del** ou **c.6232\_6236delATAAG** – deleção de cinco nucleotídeos começando pelo nucleotídeo 6232 do cDNA. A identidade dos nucleotídeos deletados pode ser especificada.
- **g.409\_410insC** – insere C entre os nucleotídeos 409 e 410 do DNA genômico.

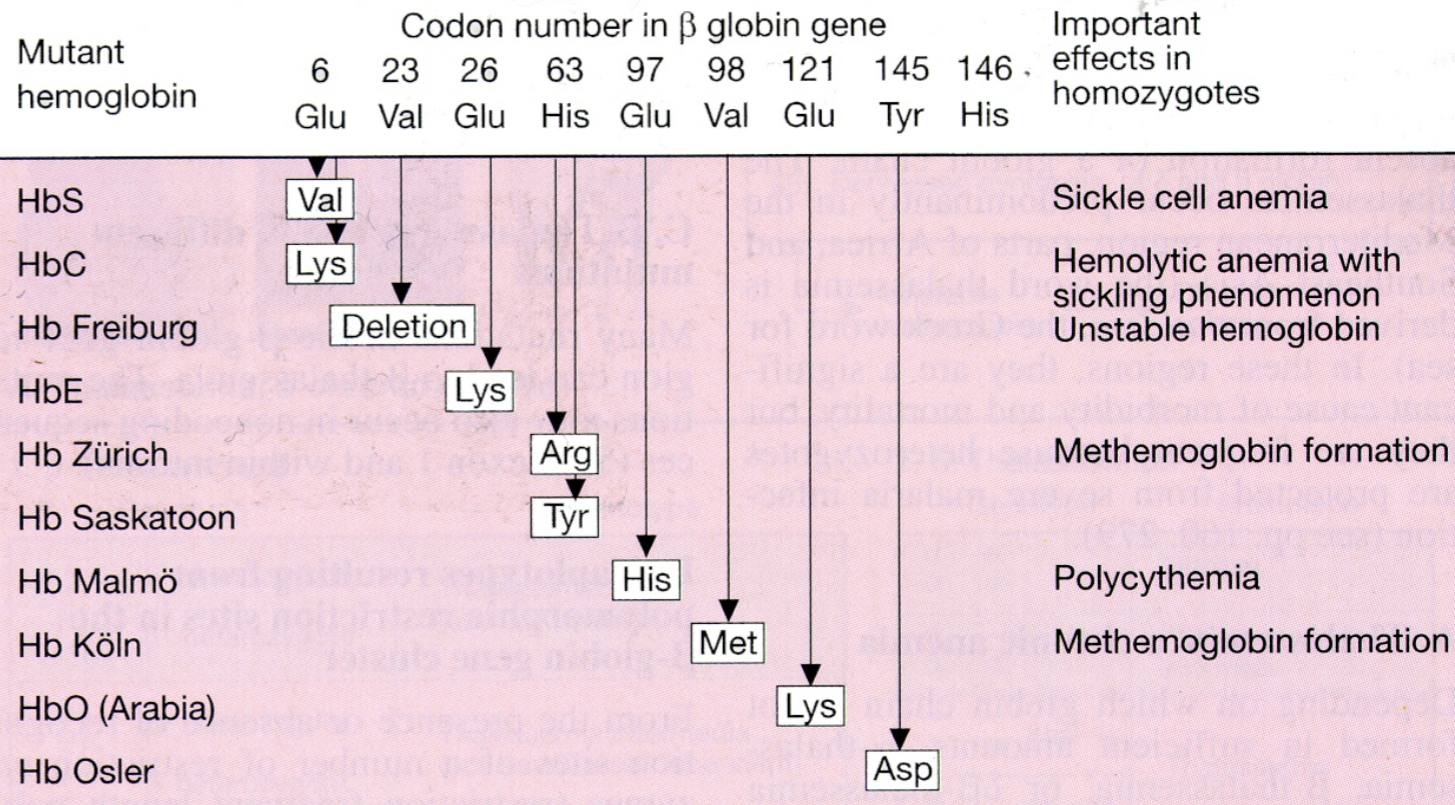
O programa, Mutalyzer, foi desenvolvido para garantir o nome correto para qualquer variante de sequência que o usuário inserir; ver em <http://www.lovd.nl/mutalyzer/>.

## HBB: hemoglobin, beta



```

1   ggaacttgaatcaaggaaatgattttaaaacgcagattctttagtgactagaggaaaaa 60
61   aataatctgagccaagtagaagacctttccctccctaccctacttttctaagtcacaga 120
121  ggctttttggtccccccagacactcttgagattagtcaggcagaaacagttagatgtcc 180
181  ccagttaacctcctattttgacaccactgattacccattgatagtcacactttgggtgt 240
241  aagtgactttttattttattttgactgcttaagaggtctctagttttttatct 300
301  cttgtttcccaaacctaaataagtaactaatgcacagagcacattgatttgtattatc 360
361  ttttttagacataatttattagcatgcatgagcaattaagaaaaacaacaacaatga 420
421  atgcatatataatgtatgtatgtgtgtatatacacacatatataatatttttc 480
481  ttttctaccagaagggttttaatacacaataaggagaagatagcttagaacaggagtaga 540
541  gttttcatccattctgtcctgtaagtattttgcatattctggagacgcaggaagagatcc 600
601  atctacatatccccaaagctgaattatggttagacaaaaactctccacttttagtcacaa 660
661  cttctattttggtgtaataagaaaattgggaaaacgatcttcaatatgcttaccagctgt 720
721  gattccaaatattacgtaaacacttgcaaaggaggatgttttttagtagcaattgttac 780
781  tgatggtatggggccaagagatatcttagagggagggtgagggtttgaagtcacact 840
841  cctaagccagtgccagaagagccaaggacaggtacggctgtcatcacttagacctcacc 900
901  tgtggagccacaccctagggttggccaatctactcccaggagcagggagggcaggagcca 960
961  gggctgggcataaaaagtcagggcagagccatctattgcttacatttgccttgacacaac 1020
1    M V H L T P E E K S
1021 tgtgttcactagcaacctcaaacagacaccATGGTCATCTGACTCCTGAGGAGAAGTCT 1080
11   A V T A L W G K V N V D E V G G E A L G
1081 GCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGGGCCCTGGGC 1140
31   R
1141 AGgttggtatcaagggtacaagacaggtttaaaggagaccaatagaaactgggcatgtgga 1200
1201 gacagagaagactcttgggtttctgataggcactgactctctctgcctattgggtctatt 1260
32   L L V V Y P W T Q R F F E S F G
1261 tcccacccttagGCTGCTGGTGGTCTACCCCTGGACCCAGAGGTTCTTTGAGTCCTTTGG 1320
48   D L S T P D A V M G N P K V K A H G K K
1321 GGATCTGTCCACTCCTGATGCTGTTATGGGCAACCCTAAGGTGAAGGCTCATGGCAAGAA 1380
68   V L G A F S D G L A H L D N L K G T F A
1381 AGTGCTCGGTGCCTTTAGTATGGCCTGGCTCACCTGGACAACCTCAAGGGCACCTTTGC 1440
88   T L S E L H C D K L H V D P E N F R
1441 CACTGAGTGAGCTGCACCTGTGACAAGCTGCACGTGGATCCTGAGAACTTCAGGgtgag 1500
1501 tctatgggacgcttgatgttttcttccctctcttttctatggttaagttcatgtcatag 1560
1561 gaaggggataagtaacaggggtacagtttagaattgggaaacagacgaatgattgcatcag 1620
1621 gtggaagtctcaggatcgttttagtttcttttattttgctgttcataacaattgttttctt 1680
1681 ttgtttaattcttcttcttttttttcttctccgcaatttttactattatacttaagt 1740
1741 ccttaacattggtgataacaaaaggaatatctctgagatataaagtaacttaaaaaa 1800
1801 aaactttacacagctctgcctagtacattactattttggaatatatgtgtgtcttatttgc 1860
1861 attcataatctcctactttattttcttttatttttaattgatacataatcattatacat 1920
1921 atttatgggttaagtgtaatgttttaatatgtgtacacataattgacaaaatcagggtaa 1980
1981 ttttgcatttgaatttttaaaaatgctttcttttataatactttttgtttatctt 2040
2041 atttctaatactttccctaatcttttctttcagggcaataatgatacaatgtatcatgc 2100
2101 ctctttgcaccattctaaagaataacagtgataatttctgggttaaggcaatagcaatat 2160
2161 ctctgcatataaattttctgcatataaattgttaactgatgtaagaggtttcatattgct 2220
2221 aatagcagctacaatccagctaccattctgtttttattttatggttgggataaggctgga 2280
2281 ttattctgagtcctcaagctaggcccttttgtaaatcatgttcataacctttattctctcc 2340
106  L L G N V L V C V L A H H F G K E F T
2341 cacagCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAATTCA 2400
125  P P V Q A A Y Q K V V A G V A N A L A H
2401 CCCACCAGTGCAGGCTGCCTATCAGAAAGTGGTGGCTGGTGGCTAATGCCCTGGCCC 2460
145  K Y H *
2461 ACAAGTATCACTAAgctcgtcttcttctgtgtcctaatctattaaagggttcctttgttcc 2520
2521 ctaagtccaactactaaactgggggatattatgaagggccttgagcatctggattctgcc 2580
2581 taataaaaaacatttttttattgcaatgatgtatttaaattttctgaatattttac 2640
2641 taaaaaggggaatgtgggaggtcagtgcatttaaaacataaaagaaatgaagagctagtcca 2700
  
```



### A. Examples of point mutations in the $\beta$ -globin gene (10 of 310)

	T		C		A		G					
T	TTT	Phe	F	TCT	Ser	S	TAT	Tyr	Y	TGT	Cys	C
	TTC			TCC			TAC			TGC		
	TTA	Leu	L	TCA			TAA	STOP		TGA	STOP	
	TTG			TCG			TAG			TGG	Trp	W
C	CTT	Leu	L	CCT	Pro	P	CAT	His	H	CGT	Arg	R
	CTC			CCC			CAC			CGC		
	CTA			CCA			CAA	Gln	Q	CGA		
	CTG			CCG			CAG			CGG		
A	ATT	Ile	I	ACT	Thr	T	AAT	Asn	N	AGT	Ser	S
	ATC			ACC			AAC			AGC		
	ATA			ACA			AAA	Lys	K	AGA	Arg	R
	ATG	Met	M	ACG			AAG			AGG		
G	GTT	Val	V	GCT	Ala	A	GAT	Asp	D	GGT	Gly	G
	GTC			GCC			GAC			GGC		
	GTA			GCA			GAA	Glu	E	GGA		
	GTG			GCG			GAG			GGG		

# VHL (von Hippel-Lindau tumor suppressor)

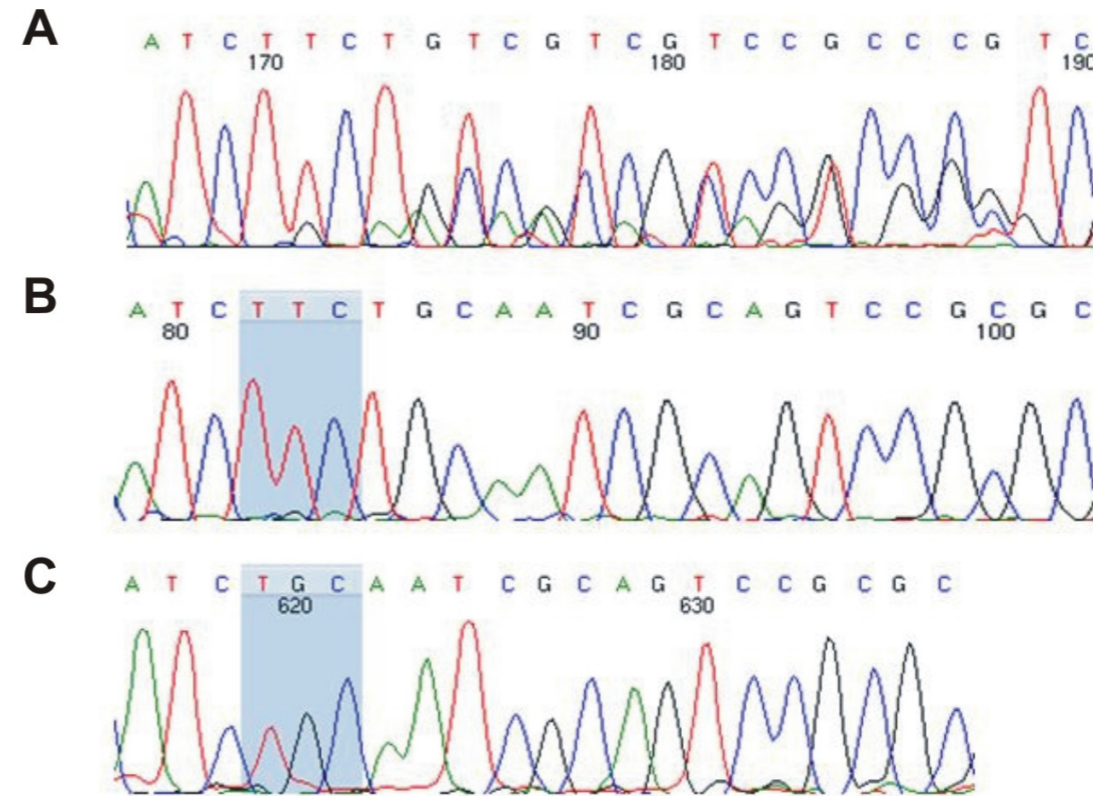
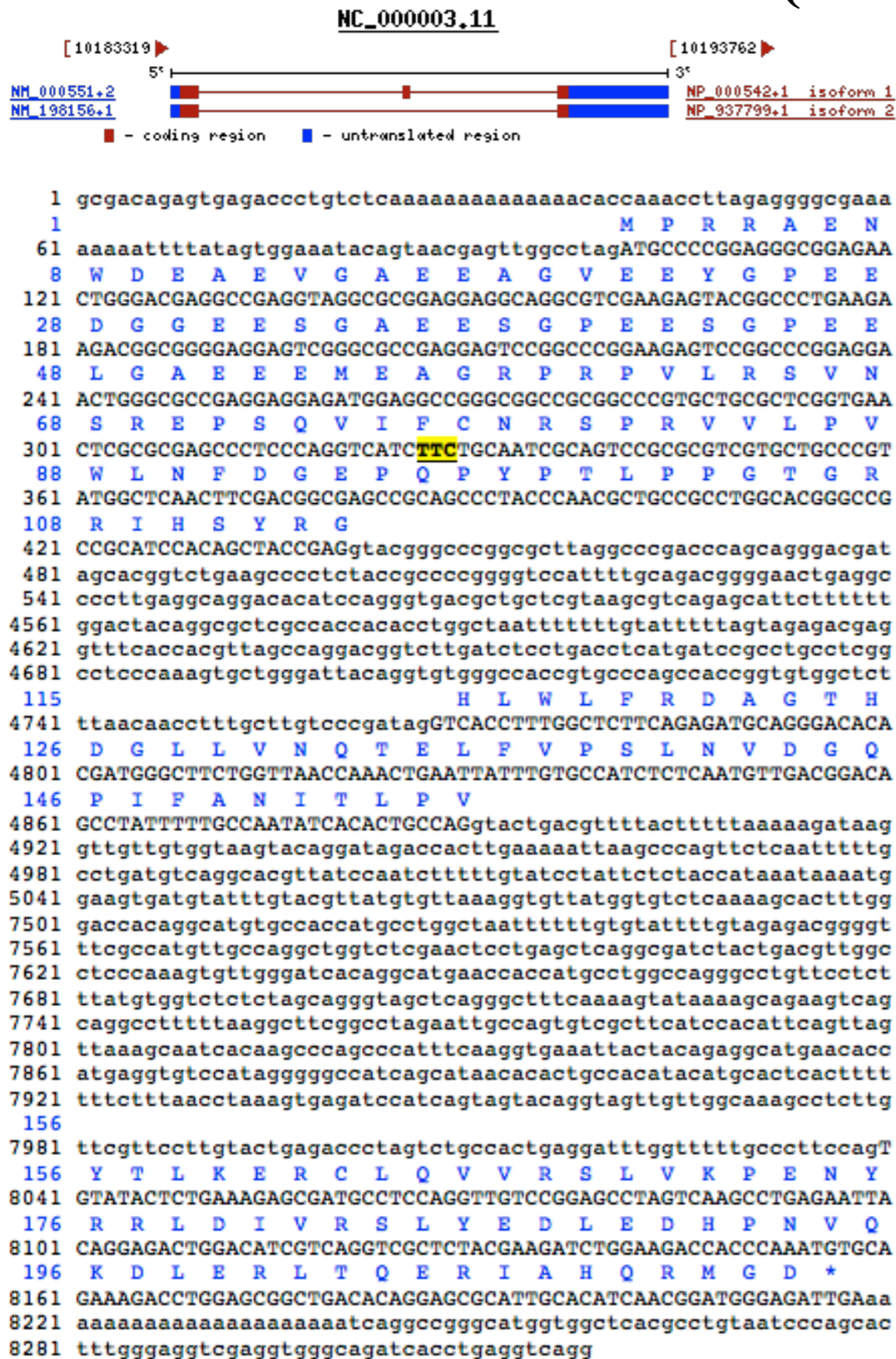
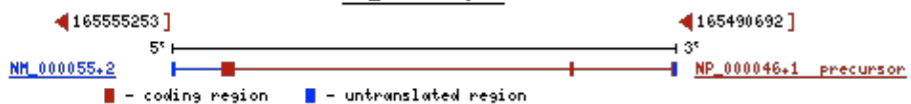


Figura 24. Deleção do códon 76 do éxon 1 (c.226\_228delTTC). A) Seqüência gerada do produto do PCR do éxon 1 típico de mutação do tipo *frameshift*. B) Seqüência do clone normal. C) Seqüência do clone mutado.



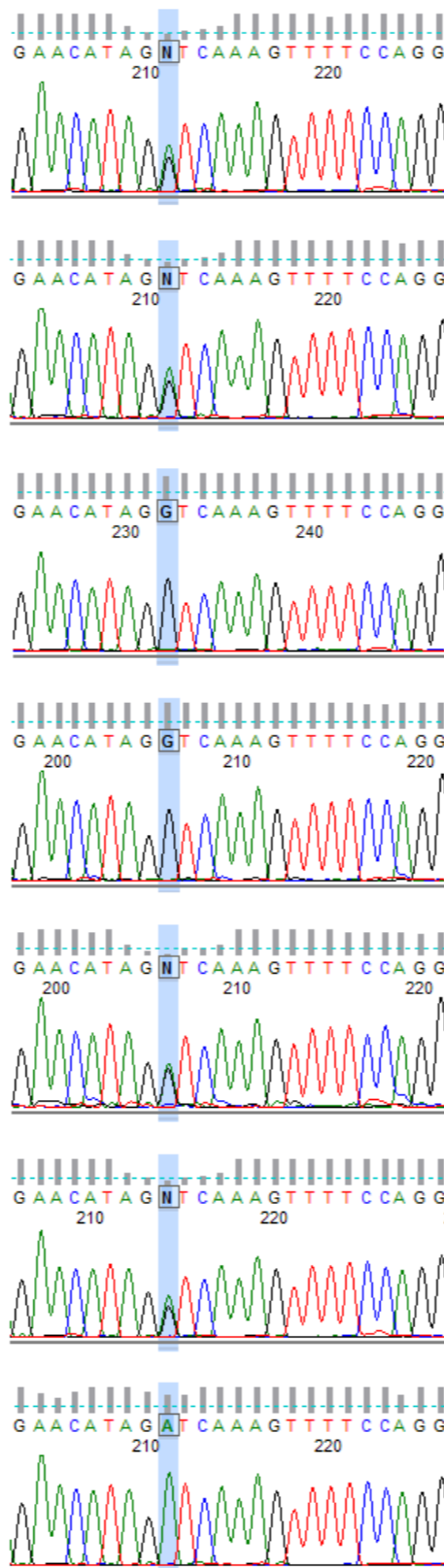
NC\_000003.11



# BCHE (butyrylcholinesterase)

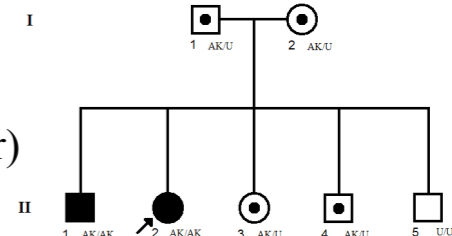
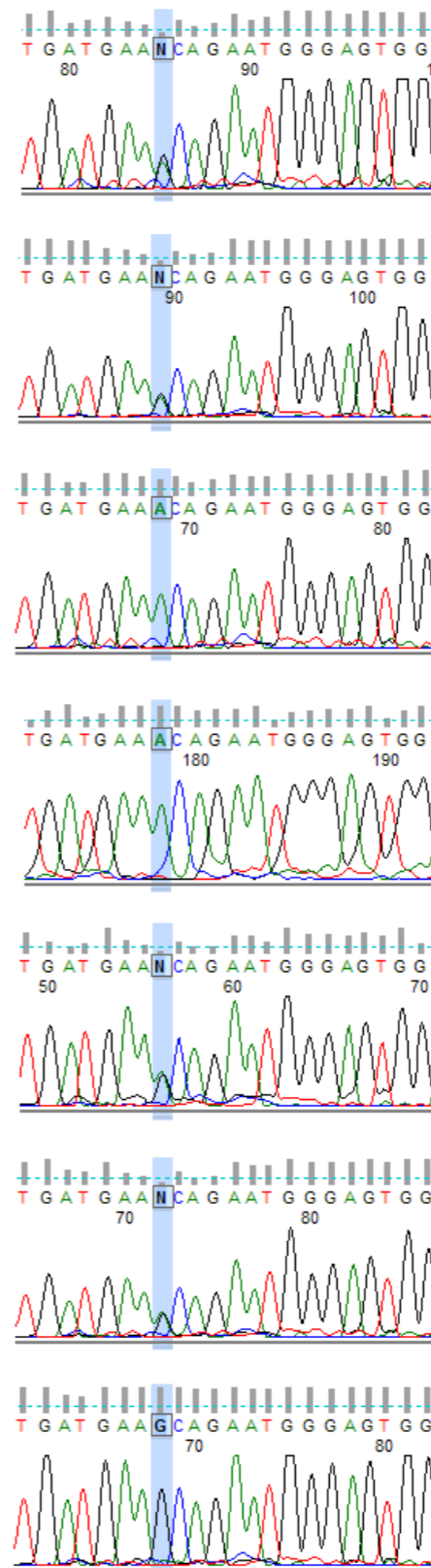
GAT → GGT (Asp70Gly)

Exon 2



GCA → ACA (Ala539Thr)

Exon 4



```

1 catgaatcctgtaataactctctgtaaatgaatcactattgcattatataaccattagcctctg
1 M H S K V T I
61 aacagattttcaagttgctgctgccaactctcgagctttatgcataagcaagtcacaat
8 I C I R F L F W F L L L C M L I G K S H
121 CATATGCATCAGATTCTCTTTGGTTCTTTTGGCTCTGCATGCTTATTGGGAAGTCACA
28 T E D D I I T T A T K N G K V R G M N L T
181 TACTGAAGATGACATCATAATTGCAACAAAGAATGAAAAAGTCAGAGGGATGAACCTGAC
48 V F G G T V T A F L G I P Y A Q P P L G
241 AGTTTTGGTGGCAGGTAAACAGCCTTTCTTGGAAATTCCTGACACAGCCACTCTGG
68 R L R F K K P Q S L T K W S D I W N A T
301 TAGACTTCGATTCAAAAAGCCACAGCTCTGACCAAGTGGTCTGATATTTGGAATGCCAC
88 K Y A N S C C Q N I D Q S F P G F H G S
361 AAAAATGCAAAATCTTGGCTGTGCAACAATAGATCAAAGTTTTCCAGGCTCCATGGATC
108 E M W N P N T D L S E D C L Y L N V W I
421 AGAGATGTGGAACCCAAACACTGACCTCAGTGAAGACTGTTTATATCTAAATGTATGGAT
128 P A P T P K P K N A T V L I W I Y G G G F Q
481 TCCAGCACCTAAACCAAAAATGCCACTGTATTGATATGGATTATGGTGGTGGTTTCA
148 T G T S S L H V Y D G K F L A R V E R V
541 AACTGGAACATCATCTTACATGTTTATGATGGCAAGTTTCTGGCTCGGGTGAAGAGT
168 I V V S M N Y R V G A L G P L A L P G N
601 TATTGTAGTGTCAATGAACATATAGGGTGGGTGCCCTAGGATTCTTAGCTTGGCAGGAAA
188 P E A P G N M G L P D Q Q L A L Q W V Q
661 TCCTGAGGCTCCAGGAACATGGGTTTATTGATCAACAGTTGGCTCTCAGTGGGTCA
208 K N I A A F G G N P K S V T L F G E S A
721 AAAAAATATAGCAGCCTTGGTGGAAATCCTAAAAGTGAACCTCTTTGGAGAAAATGTC
228 G A A S V S L H L L S P G S H S L P T R
781 AGGAGCAGCTTCAGTTAGCCTTGCATTTGCTTCTCCTGGAAGCATTTCATTTACCAG
248 A I L Q S G S F N A P W A V T S L Y E A
841 AGCCATTCGAAAAGTGGATCCTTTAATGCTCCTGGGCGGTAAACCTCTCTTATGAAGC
268 R N R T L N L A K L T G C S R E N E T E
901 TAGGAACAGAACCTTGAACCTAGCTAAATGACTGGTGGCTCTAGAGAGAATGAGACTGA
288 I I K C L R N K D P Q E I L L N E A F V
961 AATAATCAAGTGTCTTAGAAAATAAGATCCCAAGAAATCTTCTGAATGAAGCATTGT
308 V P Y G T P L S V N F G P T V D G D F L
1021 TGTCCTTATGGACTCCTTTGTGCTAGTAACTTTGGTCCGACCGTGGATGGTATTTCT
328 T D M P D I L L E L G Q F K K T Q I L V
1081 CACTGACATGCCAGACATTACTTGAACCTGGACAATTTAAAAAACCAGATTTTGGT
348 G V N K D E G T A P L V Y G A P G P S K
1141 GGGTGTAAATAAAGGAGGACAGCTTTTGTAGTCTATGGTCTCCTGGCTTCAGCAA
368 D N N S I I T R K E F Q E L K I F P P
1201 AGATAACAATAGTATCATAACTAGAAAAGAAATTCAGGAAGGTTAAAAATATTTTTCC
388 G V S E F G K E S I L F H Y T D W V D D
1261 AGGAGTGAAGTGGTTGAAAGGAATCCATCCTTTTTCATTACAGAGCTGGGTAGATGA
408 Q R P E N Y R E A L G D V G D Y N F I
1321 TCAGAGACCTGAAAACACCGTGAGGCTTGGTGTATGTTGGGGATTATAATTTTCAT
428 C P A L E F T K K F S E W G N N A F F Y
1381 ATGCCCTGCCCTGGAGTTCCACAAGAAGTTCTCAGAATGGGAAATAATGCCTTTTCTA
448 Y F E H R S S K L P W P E W M G V M H G
1441 CTATTTGAACACCGATCCTCCAACCTCCGTGGCCAGAAATGATGGAGTATGCATGG
468 Y E I E F V F G L P L E R R D N Y T K A
1501 CTATGAAATGAAATTTGTCTTTGGTTTACCTCTGAAAGAAGAGATAATYACACAAAAGC
488 E E I L S R S I V K R W A N P A K Y G
1561 CGAGGAAATTTGAGTAGATCCATAGTGAACCGTGGGCAAAATTTGCAAAATATGGgta
1621 agtgcgtatgtttgtcattgtctctgcttgggtttgatocgttttgcttagctttgctt
1681 ggtctctgggtgagacttttagtataaagacacagaaaatgttttaattattgttctattt
44701 atatccacatttttctgtcttaattctttaaagctcttgaacagtgtagaaaaca
44761 atattcttttaatacaaatgattcaattttactataatgtctctattttatttattt
507 N P N E T Q N N S F S W F K S T E
44821 agGAATCCAAATGAGACTCAGAACAATAGCACAAAGCTGGCCTGTCTTCAAAGCACTGAA
526 Q K Y L T L N T E S T R I M T K L R A Q
44881 CAAAAATATCAACCTTGAATACAGAGTCAACAAGAATAATGACAGACTACGTGCTCAA
546 Q C R F W T S F P P K V L E M T G
44941 CAATGTCGATTCTGGACATCATTTTTCCAAAAGTCTTGGAAATGACAGgtgtgtctgtt
45001 ttagtgtttggttatttaataagatgatgggttatgtaaaaaagggatgaagtatactct
57481 gagctaatacaaaataaagaataaataaagaaaataatgctgtaactgtgtagttaga
57541 gaaaatggcttttgattcgaattatttttcagtttaataaagacagataaaaaatgtgat
563 N I D E A E W E W K A
57601 taatacaacttattccatattttacagGAAATATGATGAAACAGAAATGGGAGTGGAAAAG
574 G F H R W N N Y M M D W K N Q P N D Y T
57661 CAGGATTCATCGCTGGAACAATTACATGATGGACTGGAAAAATCAATTTAACGATTACA
594 S K E S C V G L *
57721 CTAGCAAGAAAAGTTGTGTGGGTCTTAAcattggtctctttgtttttatataaag
57781 gcaagaagaatcttaaatgagaggctcagccactttaaacaccttataatagaaca
57841 gaatgctgctac
    
```



# Tipos de Cromossopatias

## Numéricas

### Aneuploidias

Conjunto de cromossomos incompletos  
 $2n+1$ ,  $2n-1$ , etc.

### Euploidias

Conjunto de cromossomos completos  
 $3n$ ,  $4n$ , etc.

### Monossomias

### Trissomias

### Poliploidias

### Síndrome de Turner

Síndrome de Down  
Síndrome de Edwards  
Síndrome de Patau  
Síndrome de Klinefelter

## Estruturais

### Deleção

### Inversão

### Translocação recíproca

### Translocação robertsoniana

### Instabilidade cromossômica

### Síndrome de Cri Du Chat (Síndrome do Miado do Gato)

### Leucemia Mieloide Crônica

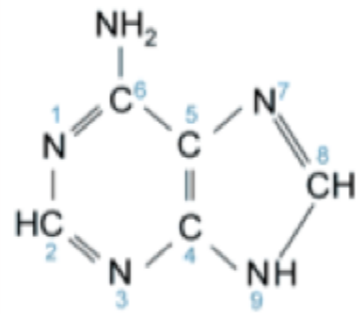
### Leucemia Promielocítica

### Síndrome do X-frágil

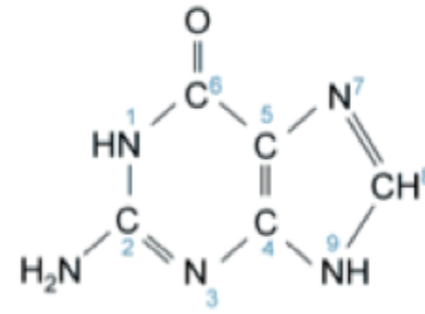
### Ataxia-telengenciana

### Síndrome do X-frágil

## Purinas

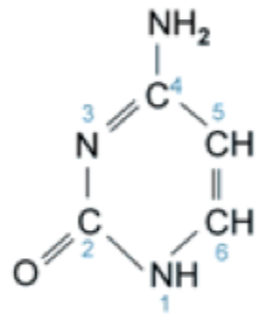


Adenine (A)

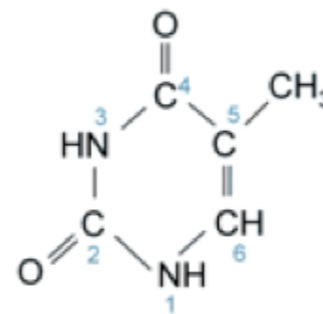


Guanine (G)

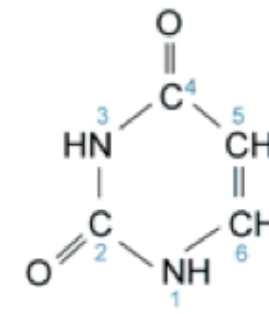
## Pirimidinas



Cytosine (C)



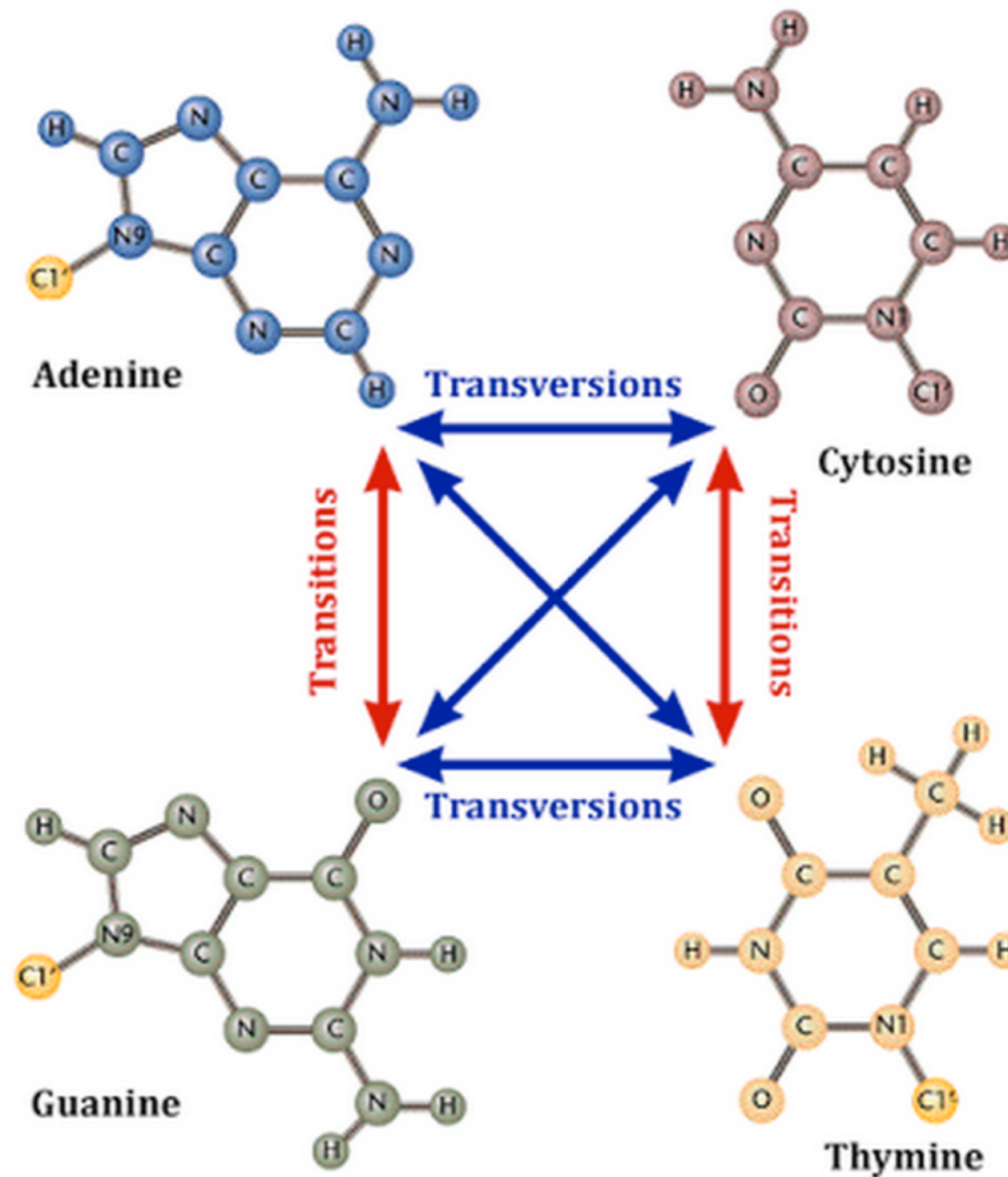
Thymine (T)

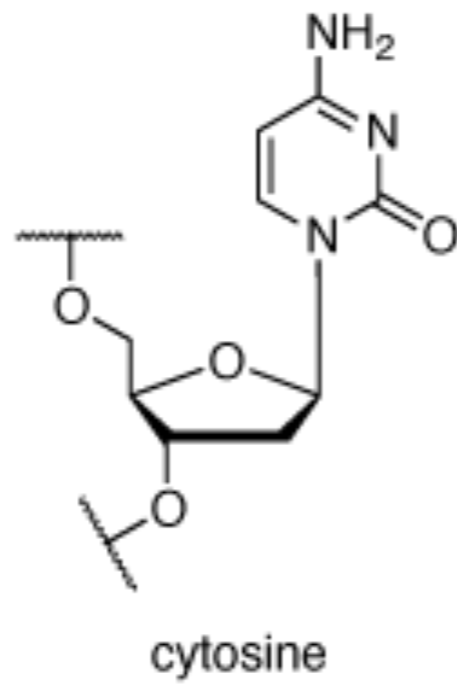


Uracil (U)

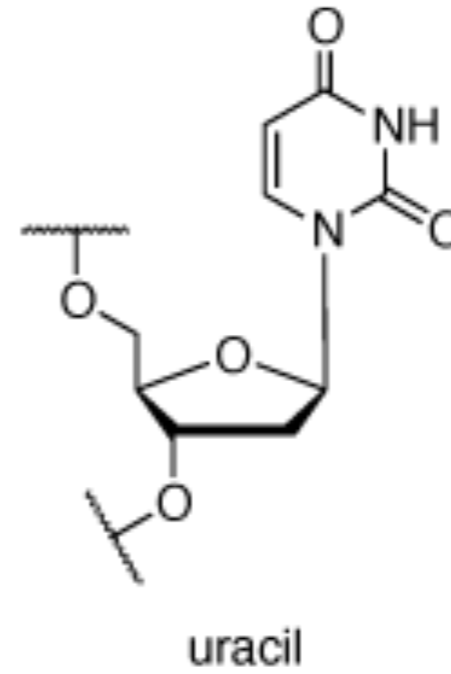
# Transição

# Transversão

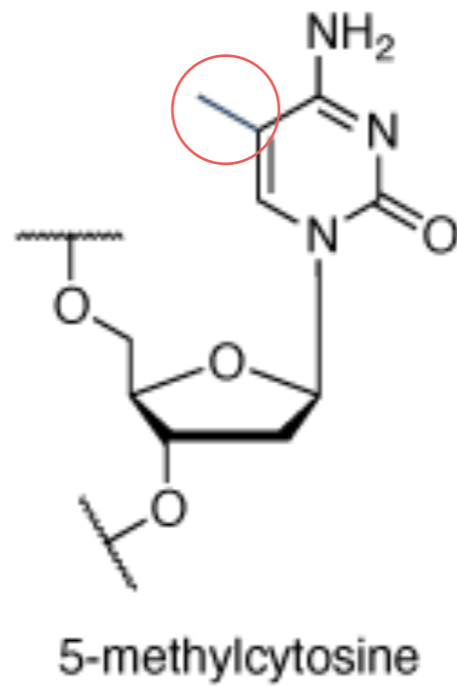




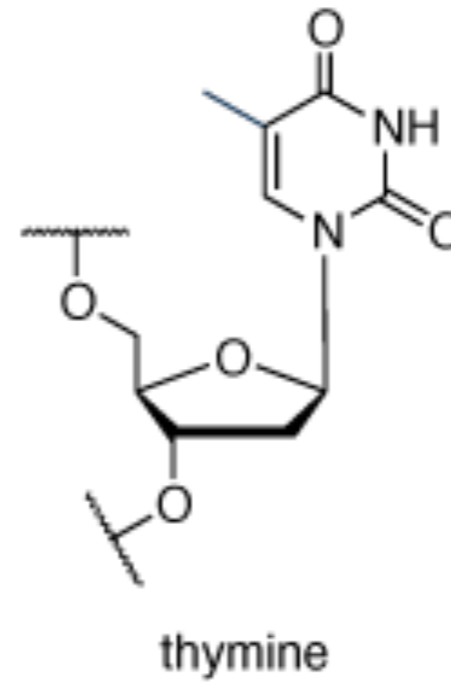
deamination  
→



DNA repair  
←  
UDG

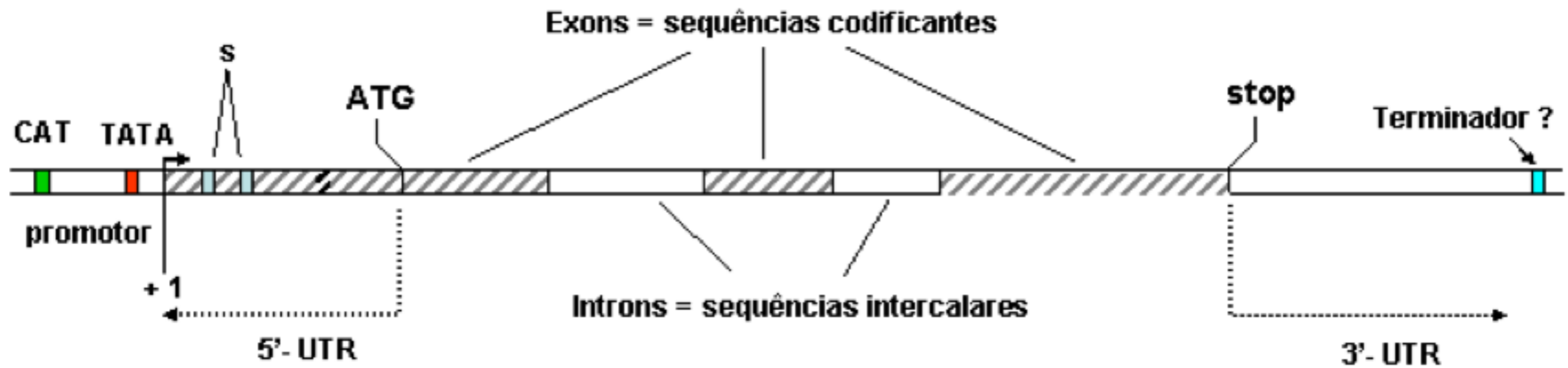


deamination  
→



not repaired  
←  
✗

# Mutações Gênicas (introns e regiões codificadoras)



# Código genético

	T			C			A			G		
T	TTT	Phe	F	TCT	Ser	S	TAT	Tyr	Y	TGT	Cys	C
	TTC			TCC			TAC			TGC		
	TTA	Leu	L	TCA			TAA	STOP		TGA	STOP	
	TTG			TCG			TAG			TGG	Trp	W
C	CTT	Leu	L	CCT	Pro	P	CAT	His	H	CGT	Arg	R
	CTC			CCC			CAC			CGC		
	CTA			CCA			CAA	Gln	Q	CGA		
	CTG			CCG			CAG			CGG		
A	ATT	Ile	I	ACT	Thr	T	AAT	Asn	N	AGT	Ser	S
	ATC			ACC			AAC			AGC		
	ATA			ACA			AAA	Lys	K	AGA	Arg	R
	ATG	Met	M	ACG			AAG			AGG		
G	GTT	Val	V	GCT	Ala	A	GAT	Asp	D	GGT	Gly	G
	GTC			GCC			GAC			GGC		
	GTA			GCA			GAA	Glu	E	GGA		
	GTG			GCG			GAG			GGG		



AAA	22.2	Lys	CCA	14.6	Pro	AGA	9.9	Arg	CUC	19.9	Leu
AAG	34.9		CCC	20.0		AGG	11.1		CUU	10.7	
AAC	22.6	Asn	CCG	6.6		CGA	5.4		CUA	6.2	
AAU	16.6		CCU	15.5		CGG	10.4		CUG	42.5	
CAA	11.1	Gln	GCA	14.0	CGC	11.3	UUA	5.3			
CAG	33.6		GCC	29.1	CGU	4.7	UUG	11.0			
CAC	14.2	His	GCG	7.2	GG A	17.1	Phe	UUC	22.6		
CAU	9.3		GCU	19.6	GG C	25.4		UUU	15.8		
GAA	26.8	Glu	UCA	9.3	GG G	17.3	Val	GU A	5.9		
GAG	41.4		UCC	17.7	GG U	11.2		GU C	16.3		
GAC	29.0	Asp	UCG	4.2	UGC	14.5		GU G	30.9		
GAU	21.7		UCU	13.2	UGU	9.9		GU U	10.4		
UAC	18.8	Tyr	AGC	18.7	UGG	13.8	Met	AUA	5.8		
UAU	12.5		AGU	9.4	AUA	5.8		AUC	24.3		
ACA	14.4	Thr			AUU	14.9		AUG	22.3		
ACC	23.0										
ACG	6.7										
ACU	12.7										

Key:

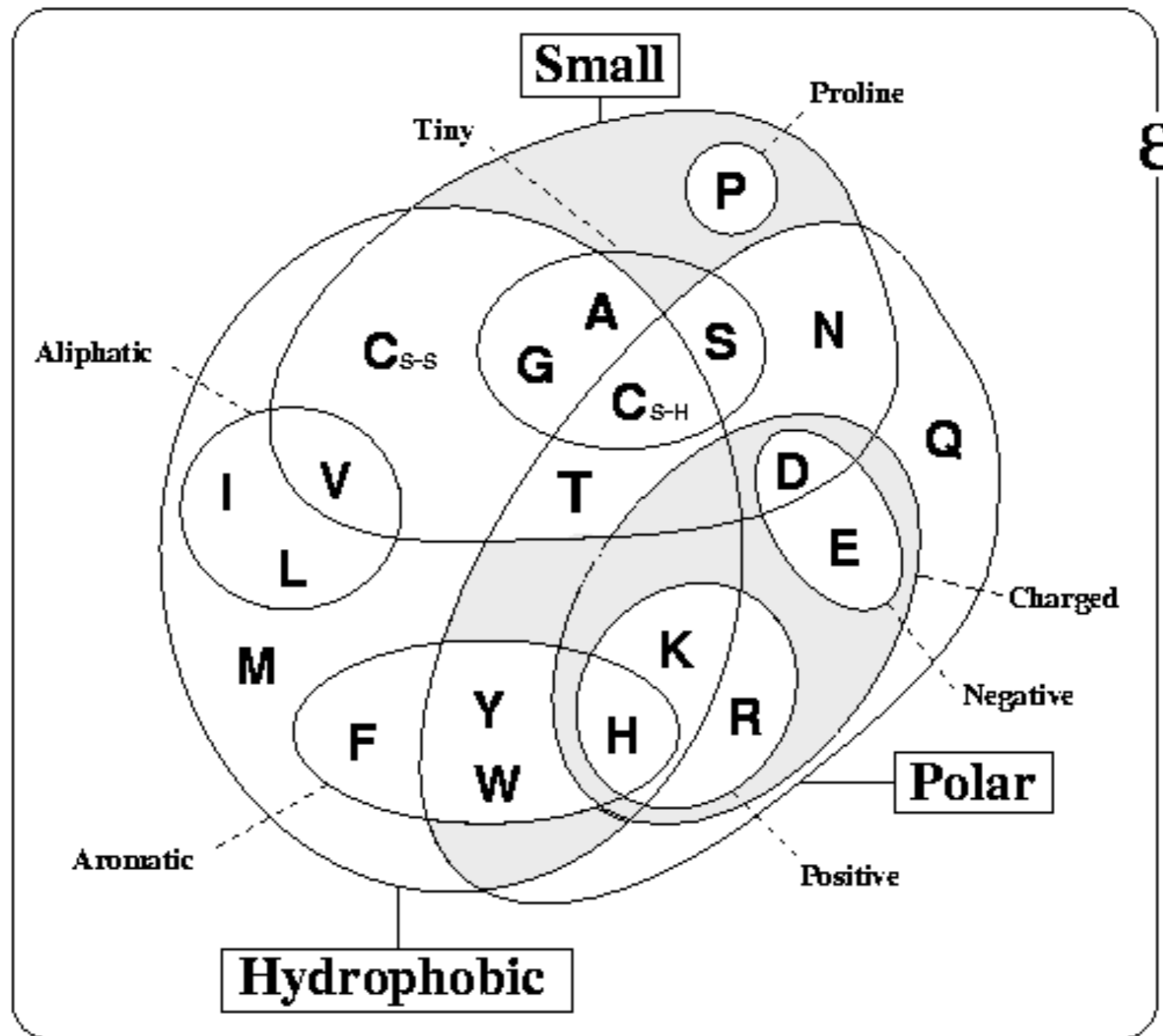
- N Nondegenerate site
- N Twofold degenerate site
- N Fourfold degenerate site

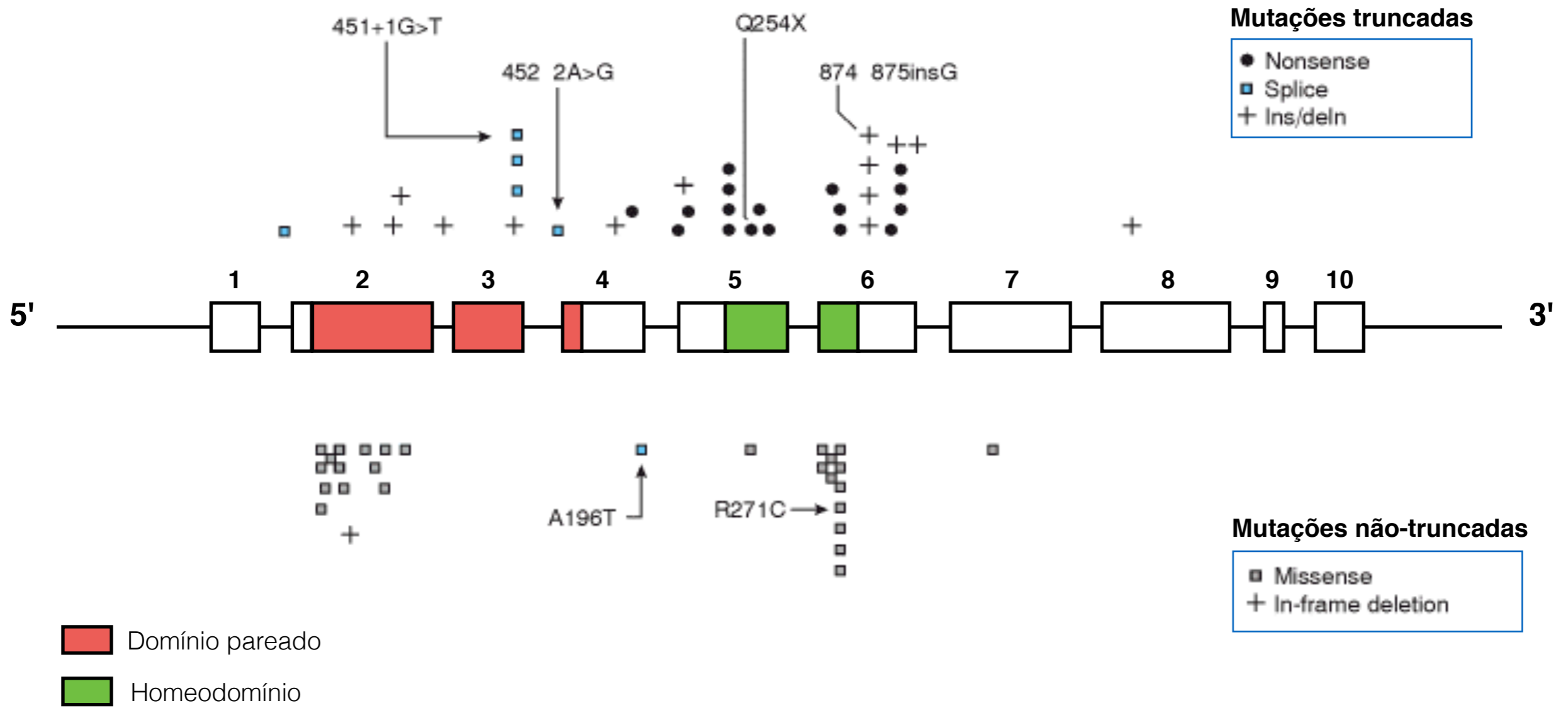
# Mutações Gênicas (Regiões codificadoras)

- 1) Ile Cys Ile Lys Ala Leu Val Leu Leu Thr  
 ATG TGT ATA AAG GCA CTG GTC CTG TTA ACA (sinônima)
- ↓
- ATG TGT ATA AAG GCA CTG GT**A** CTG TTA ACA
- 2) Ile Cys Ile Lys Ala Leu Val Leu Leu Thr  
 ATG TGT ATA AAG GCA CTG GTC CTG TTA ACA (não sinônima ou *missense*)
- ↓
- ATG TGT ATA AAG GCA CTG **TTC** CTG TTA ACA  
 Phe
- 3) Ile Cys Ile Lys Ala Leu Val Leu Leu Thr  
 ATG TGT ATA AAG GCA CTG GTC CTG TTA ACA (sem sentido ou *nonsense*)
- ↓
- ATG TGT ATA **TAG** GCACTGGTACTGTAAACA  
 Ter
- 4) Ile Cys Ile Lys Ala Leu Val Leu Leu Thr  
 ATG TGT ATA AAG**G** GCA CTG GTC CTG TTA ACA (mudança de fase ou *frameshift*)
- ↑
- His Leu Ser Cys **Ter**  
 ATG TGT ATA AAG CAC TGG TCC TGT TAA CA

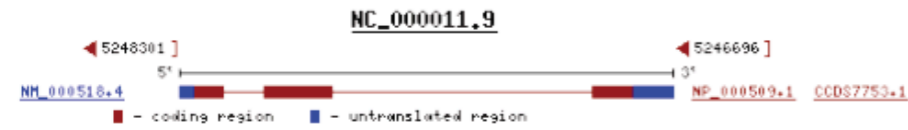
# Mutações Não-sinônimas

## *Conservativa e não-conservativa*

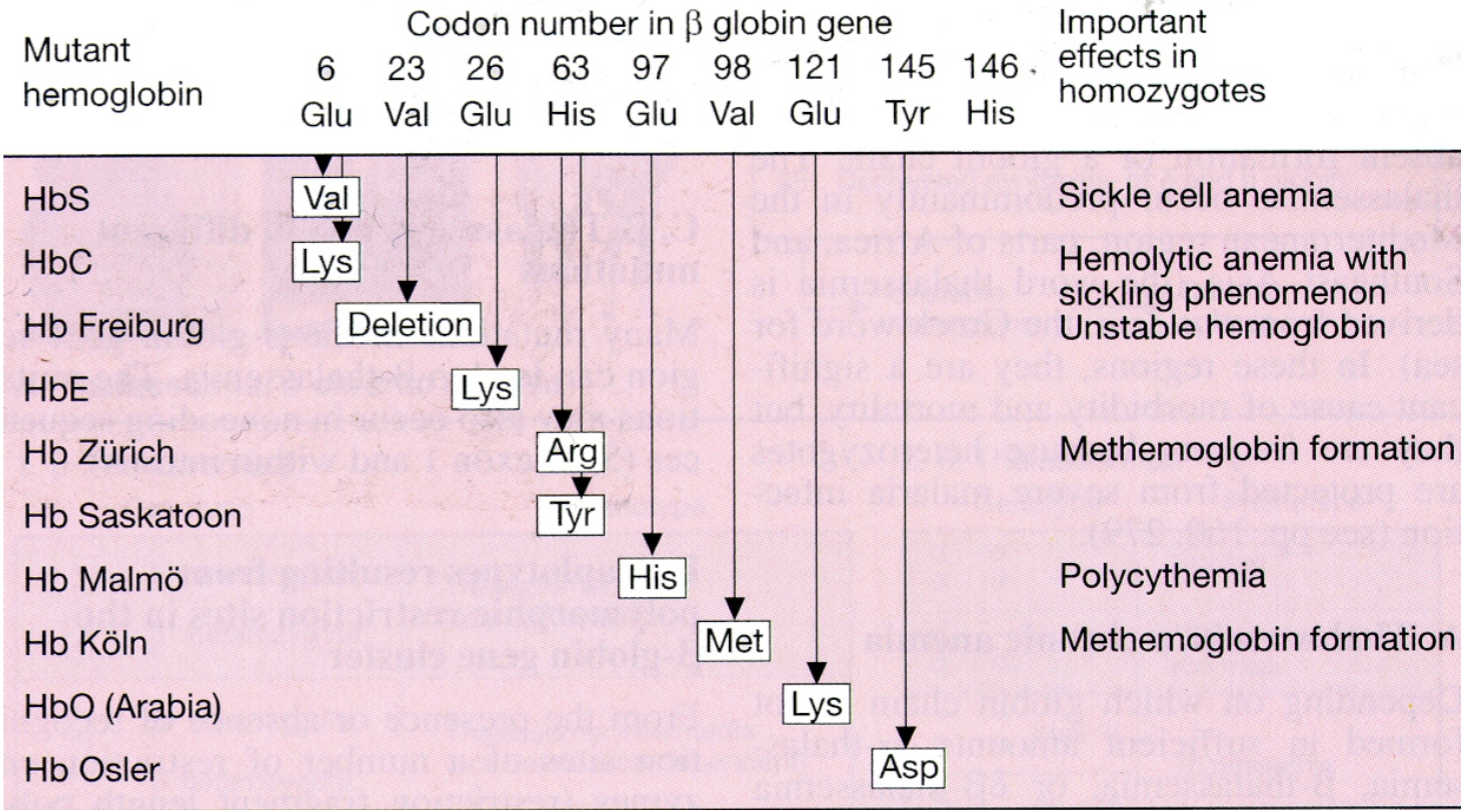




# HBB: hemoglobin, beta



1 ggaacttgaatcaaggaaatgattttaaacgcagatattccttagtgactagaggaaaaa 60  
61 aataatctgagccaagtagaagacctttccctcctaccctactttcttaagtcacaga 120  
121 ggcttttgttccccagacactcttgagattagtcaggcagaacagtttagatgtcc 180  
181 ccagttaacctcctatttgacaccactgattacccattgatagtcacactttgggtgt 240  
241 aagtgactttttatttatttatttatttatttatttatttatttatttatttatttattt 300  
301 cttgtttcccaaacctaataagtaactaatgcacagagcacattgatttatttatttattt 360  
361 tatttttagacataatttatttagcatgcatgagcaaattaagaaaaacaacaacaaatga 420  
421 atgcatatatatgtatatgtatgtgtgtatataacacatatatatatattttttc 480  
481 ttttctaccagaagggttttaatacaataaggagaagatagcttagaaccgaggtaga 540  
541 gttttcatccattctgtcctgtaagtattttgcatatttctggagacgcaggaagagatcc 600  
601 atctacatatcccaagctgaattatggtagacaaaactctccacttttagtgcatcaa 660  
661 cttctatttgtgtaataagaaaaattgggaaaacgatctcaatagcttaccgaagtgt 720  
721 gattccaaatattacgtaaacacttgcaaaaggaggatgttttttagtagcaatttgtac 780  
781 tgatggtatggggccaagagatatatttagaggaggagggtgagggtttgaagtccaact 840  
841 cctaagccagtgccagaagagcaaggacaggtacggctgcatcacttagacctcacc 900  
901 tgtggagccacaccctagggttggcaatctactcccaggagcagggagggcaggagcca 960  
961 gggctgggcatataaaagtcagggcagagccatctattgcttaccatttgccttgacacaac 1020  
1 M V H L T P E E K S  
1021 tgtgttcactagcaacctcaaacagacacc**ATGGTGCATCTGACTCCTGAGGAGAAGTCT** 1080  
11 A V T A L W G K V N V D E V G G E A L G  
1081 GCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGGGCCCTGGGC 1140  
31 R  
1141 AGgttggatcaagggtacaagacaggtttaaggagaccaatagaaactgggcatgtgga 1200  
1201 gacagagaagactcttgggtttctgataggcactgactctctgacctattgggtctattt 1260  
32 L L V V Y P W T Q R F F E S F G  
1261 tcccacccttagGCTGCTGGTGGTCTACCCTTGGACCCAGAGGTTCTTTGAGTCCTTTGG 1320  
48 D L S T P D A V M G N P K V K A H G K K  
1321 GGATCTGTCCACTCCTGTGATGCTGTTATTGGGCAACCTAAGGTGAAGGCTCATGGCAAGAA 1380  
68 V L G A F S D G L A H L D N L K G T F A  
1381 AGTGCTCGGTGCCTTTAGTGATGGCCTGGCTCACCTGGACAACCTCAAGGGCACCTTTGC 1440  
88 T L S E L H C D K L H V D P E N F R  
1441 CACTGAGTGAGCTGCACCTGTGACAAGCTGCACGTGGATCCTGAGAACTTCAGGgtgag 1500  
1501 tctatgggacgcttctgatttttctttccctccttttctatggttaagttcatgcatag 1560  
1561 gaaggggataagtaacaggggtacagtttagaatgggaaacagacgaatgattgcatcagt 1620  
1621 gtggaagtctcaggatcggttttagttttcttttatttctgctttcataacaattgttttcct 1680  
1681 ttgtttaattcttctttcttttttttctttctcgcgaatttttactattataacttaagt 1740  
1741 ccttaacattgtgtatacaaaaaggaaatattctctgagatacattaagtaacttaaaaaa 1800  
1801 aaactttacacagctctgacctagtacattactatttggaaatattatgtgtgcttatttgc 1860  
1861 attcataatctccctactttattttcttttttttatttttatttgaatacaatcattatacat 1920  
1921 atttatgggttaaagtgtaattgttttaatatgtgtacacataattgaccaaactcagggtaa 1980  
1981 ttttgcatgttaatttttaaaaatgctttcttttttaataacttttttggtttatctt 2040  
2041 atttctaatactttccctaactctttttcttttcagggcaataatgatacaatgtatcatgc 2100  
2101 ctctttgcaccatttctaagaataacagtgataatttctgggttaaggcaatagcaatat 2160  
2161 ctctgcatataaatatttctgcatataaatgttaactgatgtaagaggtttcatattgct 2220  
2221 aatagcagctacaactcagctaccattctgcttttattttatggttgggataaggctgga 2280  
2281 ttattctgagtcctcaagctagggccttttggtaatactgattcacaaccttattctctcc 2340  
106 L L G N V L V C V L A H H F G K E F T  
2341 cacagCTCCTGGGCAACGTGCTGGTCTGTGTCTGGCCCATCACTTTGGCAAAGAATTCA 2400  
125 P P V Q A A Y Q K V V A G V A N A L A H  
2401 CCCACCAGTGCAGGCTGCCATCAGAAAGTGGTGGCTGGTGGCTAATGCCCTGGCCC 2460  
145 K Y H \*  
2461 ACAAGTATCACTAAgctcgtttcttctgtgtcctcaatttctattaaagggttcctttgttcc 2520  
2521 ctaagtccaactactaaactgggggatattatgaaggccttgagcatctggattctgcc 2580  
2581 taataaaaaacatttattttcattgcaatgatgtatttaattatttctgaatattttac 2640  
2641 taaaaggggaatgtgggaggtcagtgcatttaaaacataaagaatgaagagctagtcca 2700



A. Examples of point mutations in the  $\beta$ -globin gene (10 of 310)

	T	C	A	G
T	TTT Phe F TTC TTA Leu L TTG	TCT Ser S TCC TCA TCG	TAT Tyr Y TAC TAA STOP TAG	TGT Cys C TGC TGA STOP TGG Trp W
C	CTT Leu L CTC CTA CTG	CCT Pro P CCC CCA CCG	CAT His H CAC CAA Gln Q CAG	CGT Arg R CGC CGA CGG
A	ATT Ile I ATC ATA ATG Met M	ACT Thr T ACC ACA ACG	AAT Asn N AAC AAA Lys K AAG	AGT Ser S AGC AGA Arg R AGG
G	GTT Val V GTC GTA GTG	GCT Ala A GCC GCA GCG	GAT Asp D GAC GAA Glu E GAG	GGT Gly G GGC GGA GGG

# VHL (von Hippel-Lindau tumor suppressor)

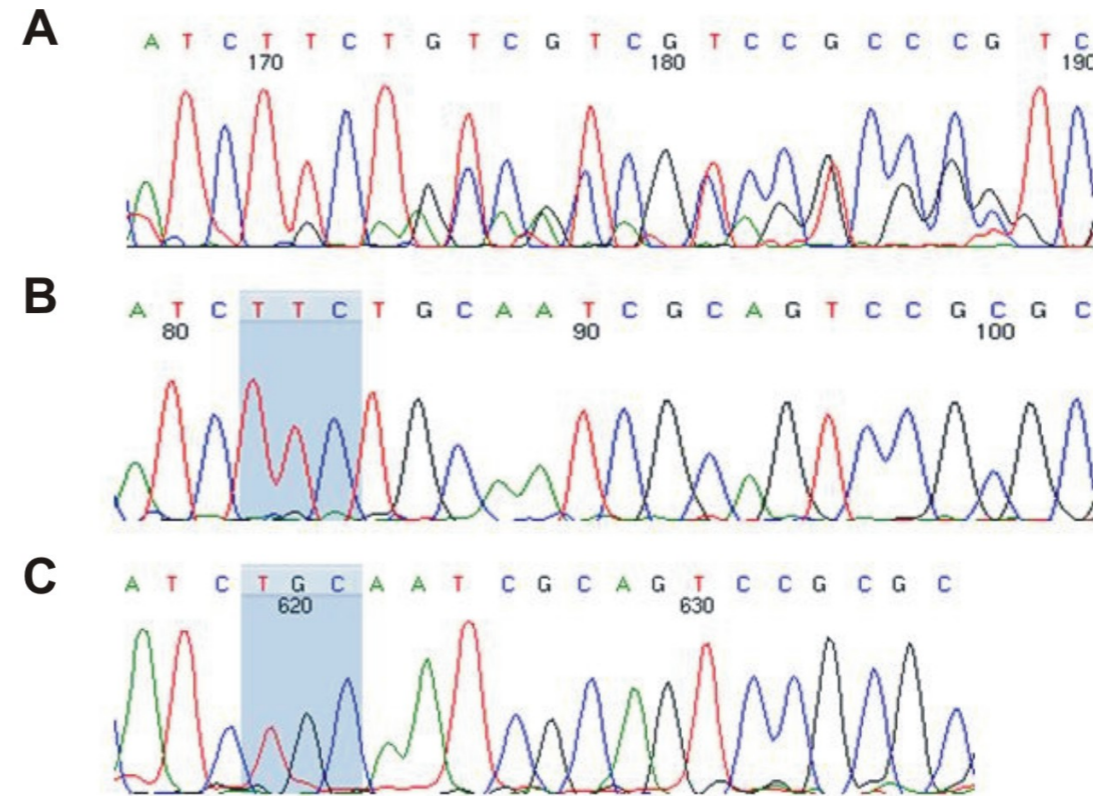
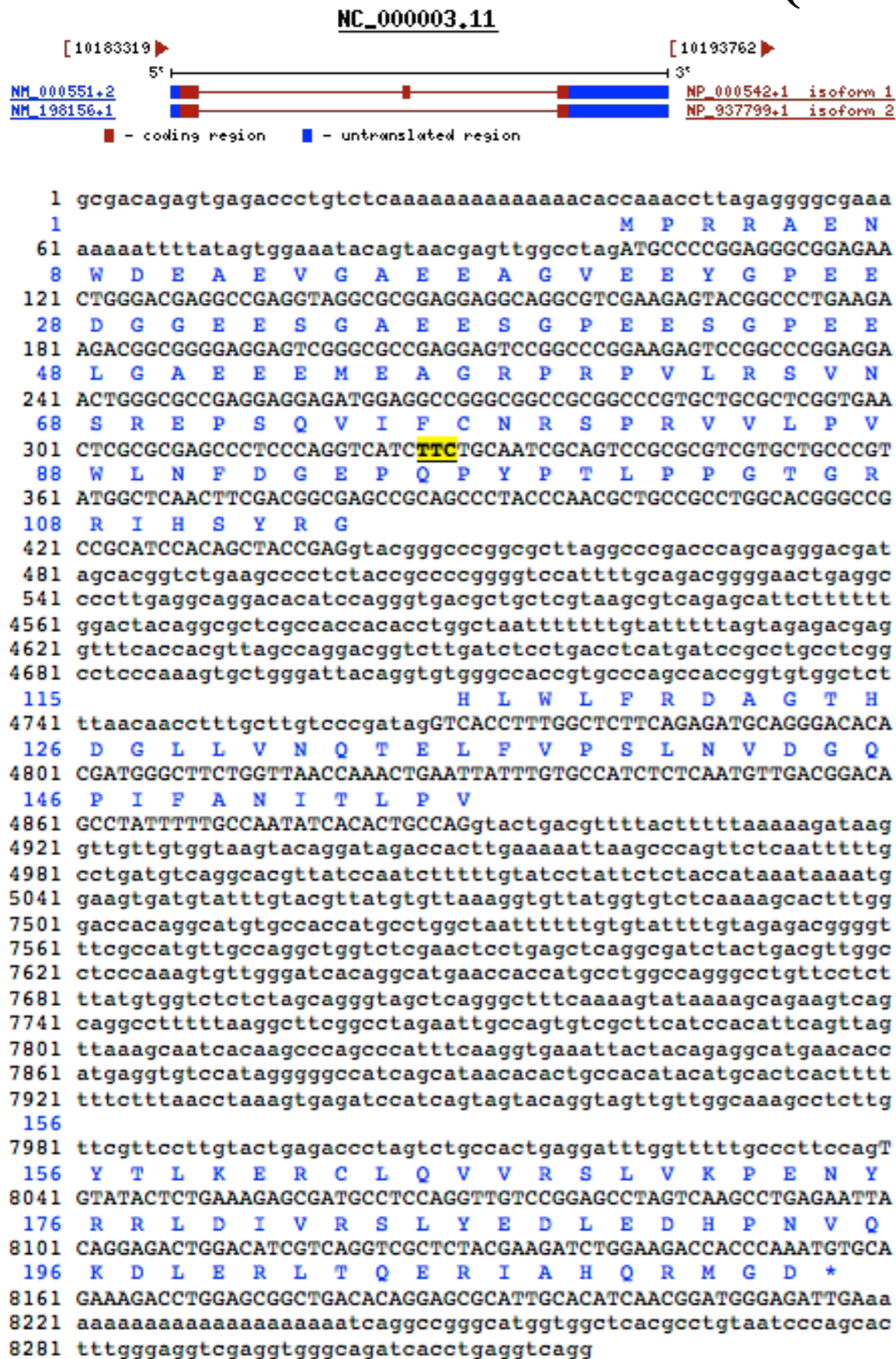
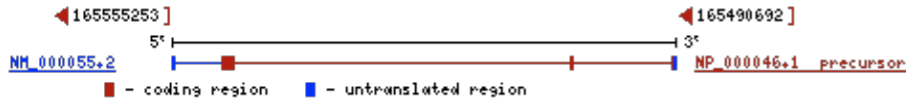


Figura 24. Deleção do códon 76 do éxon 1 (c.226\_228delTTC). A) Seqüência gerada do produto do PCR do éxon 1 típico de mutação do tipo *frameshift*. B) Seqüência do clone normal. C) Seqüência do clone mutado.

NC\_000003.11



BCHE (butyrylcholinesterase)

GAT→GGT (Asp70Gly)

GCA→ACA (Ala539Thr)

1 catgaatcctgtaataactctctgtaaatgaatcactattgcattatataaccattagcctctg  
 1 M H S K V T I  
 61 aacagattttcaagttgctgctgccaactctcgcgagctttATGCATAGCAAAGTCACAAAT  
 8 I C I R F L F W F L L L C M L I G K S H  
 121 CATATGCATCAGATTCTCTTTTGGTTCTTTTGGCTCTGCATGCTTATTGGGAAGTCACA  
 28 T E D D I I I A T T K N G K V R G M N L T  
 181 TACTGAAGATGACATCATAATTGCAACAAAGAATGAAAAAGTCAGAGGGATGAACCTGAC  
 48 V F G G T V T A F L G I P Y A Q P P L G  
 241 AGTTTTGGTGGCAGGTAACAGCCTTTCTTGGAAATTCCTGCACAGCCACCTCTTGG  
 68 R L R F K K P Q S L T K W S D I W N A T  
 301 TAGACTTCGATTCAAAAAGCCACAGTCTCTGACCAAGTGGTCTGATATTTGGAATGCCAC  
 88 K Y A N S C C Q N I D Q S F P G F H G S  
 361 AAAAATGCAAAATCTTGTCTGCAACAATAGATCAAAGTTTCCAGGCTTCCATGGATC  
 108 E M W N P N T D L S E D C L Y L N V W I  
 421 AGAGATGTGGAACCCAAACACTGACCTCAGTGAAGACTGTTTATATCTAAATGTATGGAT  
 128 P A P T P K P K N A T V L I W I Y G G G F Q  
 481 TCCAGCACCTAAACCAAAAATGCCACTGTATTGATATGGATTATGGTGGTGGTTTCA  
 148 T G T S S L H V Y D G K F L A R V E R V  
 541 AACTGGAACATCATCTTTACATGTTTATGATGGCAAGTTTCTGGCTCGGGTTGAAAGAGT  
 168 I V V S M N Y R V G A L G P F L A L P G N  
 601 TATTGTAGTCTCAATGAACATATAGGGTGGGTGCCCTAGGATCTTAGCTTTGCCAGGAAA  
 188 P E A P G N M G L P D Q Q L A L Q W V Q  
 661 TCCTGAGGCTCCAGGAACATGGGTTTATTGATCAACAGTTGGCTCTCAGTGGGTCA  
 208 K N I A A F G G N P K S V T L F G E S A  
 721 AAAAAATATAGCAGCCTTTGGTGGAAATCCTAAAAGTGAACCTCTTTGGAGAAAATGTC  
 228 G A A S V S L H L L S P G S H S L P T R  
 781 AGGAGCAGCTTTCAGTTAGCCTTTCCTTCTCCTGGAAGCATTTCATGTTCCACAG  
 248 A I L Q S G S F N A P W A V T S L Y E A  
 841 AGCCATCTGCAAAGTGGATCCTTTAATGCTCCTTGGGCGSTAACTCTCTTTATGAAGC  
 268 R N R T L N L A K L T G C S R E N E T E  
 901 TAGGAACAGAAGCTTGAACCTTAGCTAAATGACTGGTGGCTCTAGAGAGAATGAGACTGA  
 288 I I K C L R N K D P Q E I L L N E A F V  
 961 AATAATCAAGTCTTAGAAAATAAGATCCCAAGAAATCTTCTGAATGAAGCATTGT  
 308 V P Y G T P L S V N F G P T V D G D F L  
 1021 TGTCCTTATGGGACTCCTTTGTCTAGTAACTTTGGTCCGACGCTGGATGGTATTTCT  
 328 T D M P D I L L E L G Q F K K T Q I L V  
 1081 CACTGACATGCCAGACATTAAGTGAACCTGGACAATTTAAAAAACCAGATTTTGGT  
 348 G V N K D E G T A P L V Y G A P G P S K  
 1141 GGGTGTAAATAAAGGAGGACAGCTTTTGTAGTCTATGGTCTCCTGGCTTCAGCAA  
 368 D N N S I I T R K E F Q E L K I F P P  
 1201 AGATAACAATAGTATCATAACTAGAAAAGAAATTCAGGAAGGTTAAAAAATATTTTTCC  
 388 G V S E F G K E S I L F H Y T D W V D D  
 1261 AGGAGTGAGTGGTTTGGAAAGGAATCCATCCTTTTTCATTACAGAGCTGGGTAGATGA  
 408 Q R P E N Y R E A L G D V G D Y N F I  
 1321 TCAGAGACCTGAAAACACCGTGGGCTTGGGTGATGTTGTTGGGGATTATAATTTTCAT  
 428 C P A L E F T T K K F S E W G N N A F F Y  
 1381 ATGCCCTGCCCTGGAGTTCCACAAGAAGTTCTCAGAATGGGAAATAATGCCTTTTCTA  
 448 Y F E H R S S K L P W P E W M G V M H G  
 1441 CTATTTGAAACCCGATCCTCCAACCTCCGTGGCCAGAAATGGATGGGAGTATGCATGG  
 468 Y E I E F V F G L P L E R R D N Y T K A  
 1501 CTATGAAATGAAATTTGTCTTTGGTTTACCTCTGGAAGAAGAGATAATYACACAAAAGC  
 488 E E I L S R S I V K R W A N P A K Y G  
 1561 CGAGGAAATTTGAGTAGATCCATAGTGAACCGTGGGCAAAATTTTGCAAAATATGGgta  
 1621 agtgcgattttttgctcattgtctctgctggtttgatccgttttgccttagctttgctt  
 1681 ggtctctgggtgagacttttagtataaagacacagaaaatgttttaattattgttctatt  
 44701 atatccacattttttctgtcttaaatctttaaagctcttgtaacagtgtagaaaaca  
 44761 atattcttttaatacaaatgattcaattttactataatgtctctattttattatt  
 507 N P N E T Q N N S F S W F K S T E  
 44821 agGAATCCAAATGAGACTCAGAACAATAGCACAAAGCTGGCCTGTCTCAAAGCACTGAA  
 526 Q K Y L T L N T E S T R I M T K L R A Q  
 44881 CAAAAATATCAACCTTGAATACAGAGTCAACAAGAATAATGACCAACTACGTGCTCAA  
 546 Q C R F W T S F P P K V L E M T G  
 44941 CAATGTCGATTCTGGACATCATTTTTCCAAAAGTCTTGGAAATGACAGgtgtgtctgt  
 45001 ttagtgtttggttatttaatatagatgatgggttatgtaaaaaaggatgaagtatactct  
 57481 gagctaatacaaaaataaagaataaataaagaaaataatgctgtagctgtgtagttaga  
 57541 gaaaatggcttttgattcgaattatttttcagtttaagaaacagataaaaaatgtag  
 563 N I D E A E W E W K A  
 57601 taatacaacttattccatattttacagGAAATATGATGAAACAGAAATGGGAGTGGAAA  
 574 G F H R W N N Y M M D W K N Q P N D Y T  
 57661 CAGGATTCATCGCTGGAACAATTACATGATGGACTGGAAAAATCAATTTAACGATTACA  
 594 S K E S C V G L \*  
 57721 CTAGCAAGAAAGAAAGTTGTGTGGGTCTCTAAcattggtctcttttttatataaag  
 57781 gcaagaagaatcttaaatgagaggtcagccactttaaacaccttataatagaaca  
 57841 gaatgctgctac

Exon 2

Exon 4

I-1

I-2

II-1

II-2

II-3

II-4

II-5

