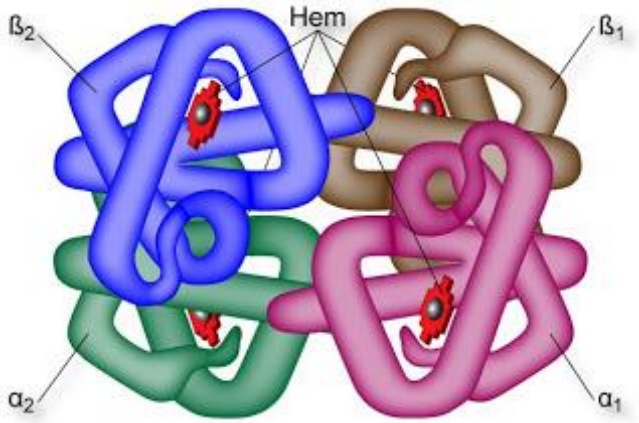
Patologia Molecular

RIB0102 - Genética Molecular

Wilson Araújo Silva Jr
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Hemoglobinopatias

É um grupo de doenças que afeta a função da hemoglobina.



População Humana

Hemoglobinopatias **5%**

7.7×10^9 **habitantes**

385 milhões de afetados

Hemoglobinopatias

Tipos

Hemoglobinas Variantes

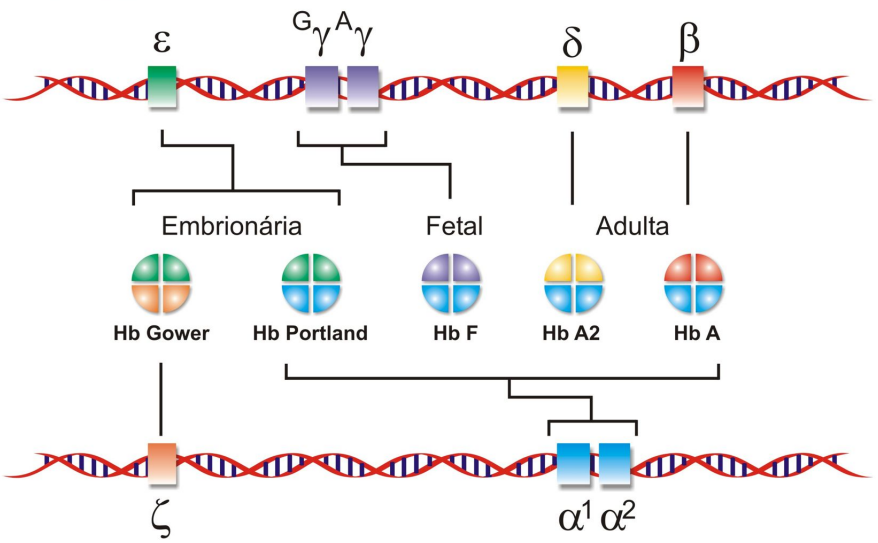
Mutações pontuais

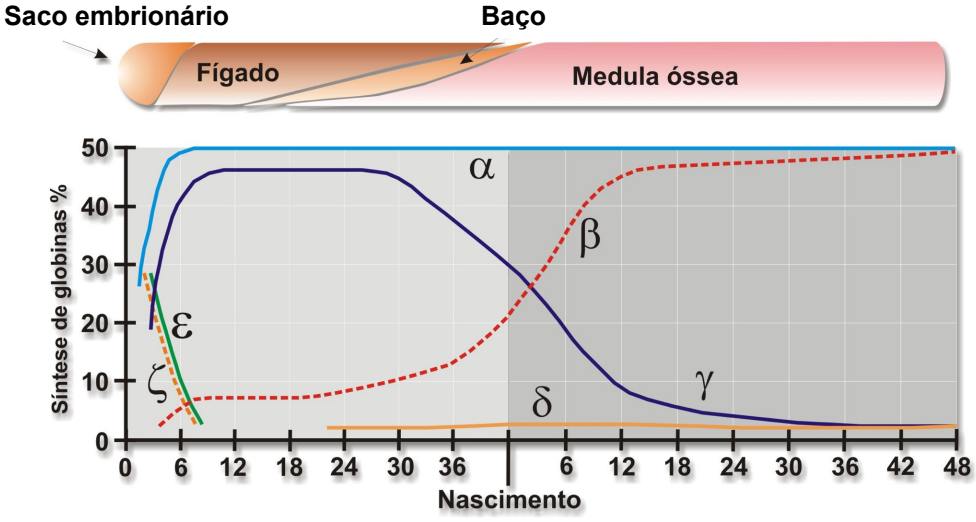
Talassemias

Redução parcial ou total dos genes das globinas

Complexo β das globinas

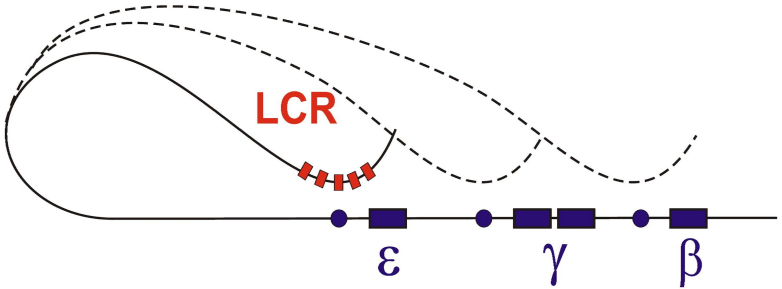
Cromossomo 11





Complexo α das globinas

Cromossomo 16

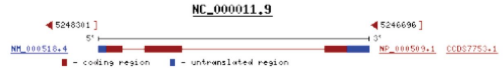


Translation (147 aa):

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AFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVAN
ALAHKYH



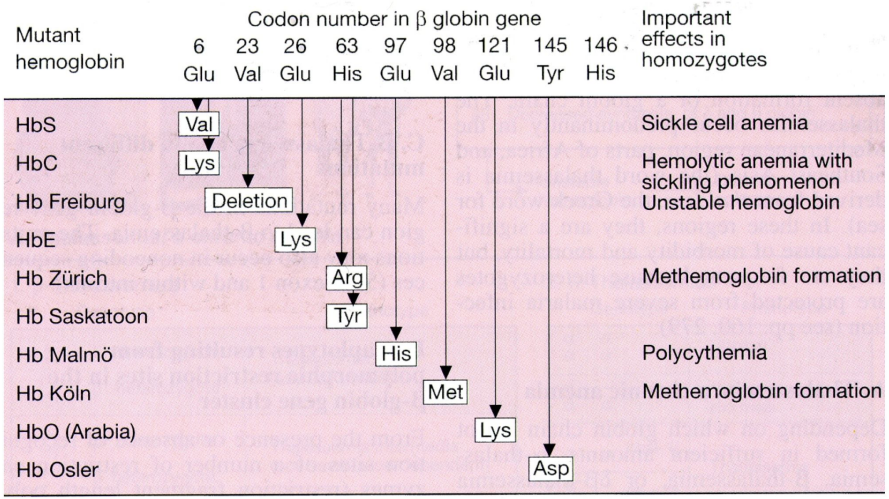
HBB: **hemoglobin, beta**



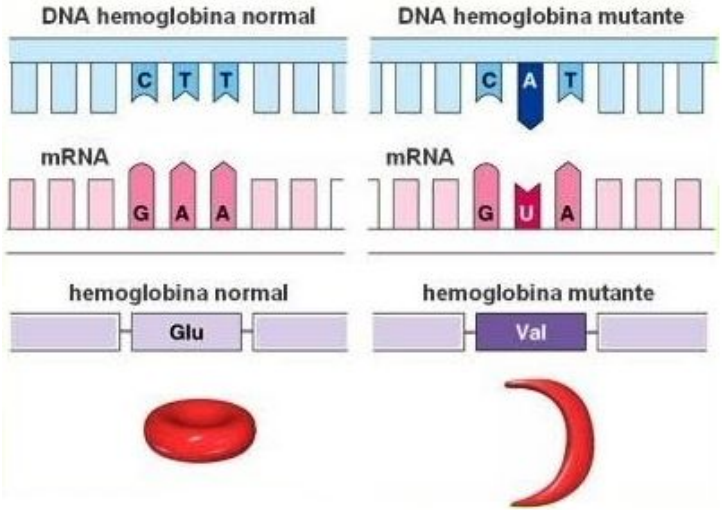

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121  ggctttttgttccccagacactcttgcagattagtccaggcagaaacagttagatgtcc 180
181  ccagttaacctcctatttgacaccactgattaccccattgatagtcacactttgggttgt 240
241  aagtgacttttattattttgtatttttgactgcattaagaggtctctagttttttatct 300
301  cttgtttcccaaaacctaataagtaactaatgcacagagcacattgatttgtatttattc 360
361  tatttttagacataatttattagcatgcatgagcaaattaagaaaaacaacaacaaatga 420
421  atgcatatatatgtatatgtatgtgtgtatatatacacacatatatatatatttttttc 480
481  ttttcttaccagaaggttttaatccaaataaggagaagatatgcttagaaccgaggtaga 540
541  gttttcatccattctgtcctgtaagtattttgcatatttctggagacgcaggaagagatcc 600
601  atctacatatcccaaagctgaattatggtagacaaaactcttccacttttagtgcatcaa 660
661  cttcttatttgtgtaataagaaaatgggaaaacgatcttcaatatgcttaccaagctgt 720
721  gattccaaaatattacgtaaatacacttgcaaaggaggatgtttttagtagcaatttgtac 780
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841  cctaagccagtgccagaagagccaaggacaggtacggctgtcatcacttagacctcaccc 900
901  tgtggagccacaccctagggttggccaatctactccccaggagcagggagggcaggagcca 960
961  gggctgggcataaaagtcagggcagagccatctattgcttacatttgcttctgacacaac 1020
1                                    M  V  H  L  T  P  E  E  K  S
1021 tgtgttcactagcaacctcaaacagacaccATGGTGCATCTGACTCCTGAGGAGAAGTCT 1080
11   A  V  T  A  L  W  G  K  V  N  V  D  E  V  G  G  E  A  L  G
1081 GCCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGAGGCCCTGGGC 1140
31   R
1141 AGgttggtatcaaggttacaagacaggtttaaggagaccaatagaaactgggcatgtgga 1200
1201 gacagagaagactcttgggtttctgataggcactgactctctctgcctattggtctatttt 1260
32                L  L  V  V  Y  P  W  T  Q  R  F  F  E  S  F  G
1261 tcccaccctagGCTGCTGGTGGTCTACCCTTGGACCCAGAGGTTCTTTGAGTCCTTTGG 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 AGTGCTCGGTGCCTTTAGTGATGGCCTGGCTCACCTGGACAACCTCAAGGGCACCTTTGC 1440
88   T  L  S  E  L  H  C  D  K  L  H  V  D  P  E  N  F  R
1441 CACACTGAGTGAGCTGCACTGTGACAAGCTGCACGTGGATCCTGAGAACTTCAGGgtgag 1500
1501 tctatgggacgcttgatgttttctttcccctcttttctatggttaagttcatgtcatag 1560
1561 gaaggggatgaagtaacagggtacagtttagaatgggaaacagacgaatgattgcatcagt 1620
1621 gtggaagtctcaggatcgttttagtttcttttatttgctgttcataacaattgttttctt 1680
1681 ttgtttaatttcttgctttcttttttttttcttctccgcaatttttactattatacttaatg 1740
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1861 attcataatctccctactttatttcttttatttttaatttgatacataatcattatacat 1920
1921 atttatgggttaaagtgtaatgttttaatatgtgtacacatattgaccaaatcagggtaa 1980
1981 ttttgcatttgtaatttttaaaaaatgcttttcttctttttaatatactttttgtttatctt 2040
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2101 ctctttgcaccattctaaagaataacagtgataatttctgggttaaggcaatagcaatat 2160
2161 ctctgcatataaatatttctgcatataaattgtaactgatgtaagaggtttcatattgct 2220
2221 aatagcagctacaatccagctaccattctgcttttatttttatggttgggataaggctgga 2280
2281 ttattctgagtccaagctaggcccttttgctaatcatgttcatacctcttatcttcctcc 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 CCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGTGGCTGGTGTGGCTAATGCCCTGGCCC 2460
145    K  Y  H  *
2461 ACAAGTATCACTAAgctcgctttcttgctgtccaatttctattaaaggttcctttgttcc 2520
2521 ctaagtccaactactaaactgggggatattatgaagggccttgagcatctggattctgcc 2580
2581 taataaaaaacatttatttttcattgcaatgatgtatttaaattatttctgaatattttac 2640
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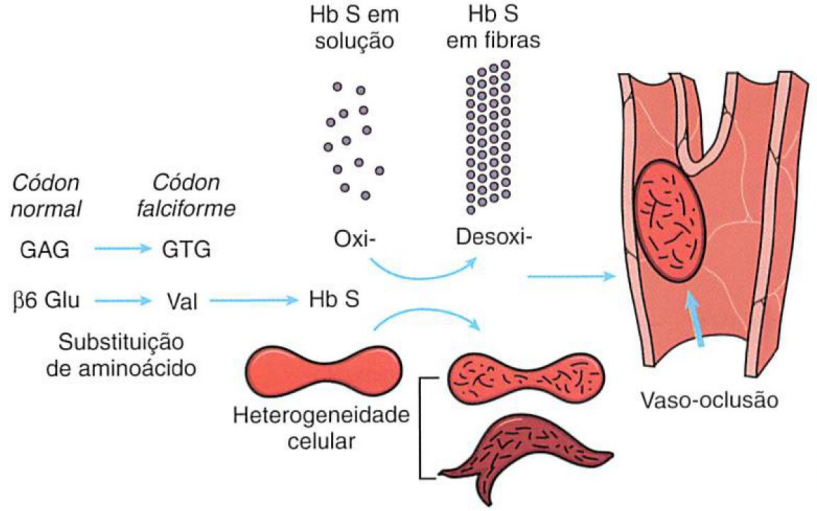
Hemoglobinas Variantes

Mutações pontuais



	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		





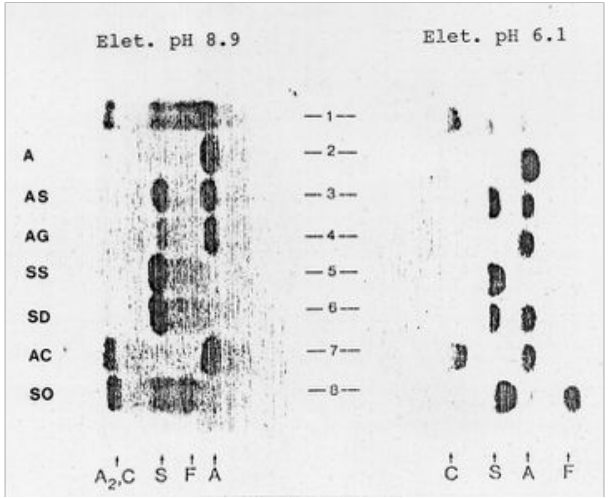


Ulcerações

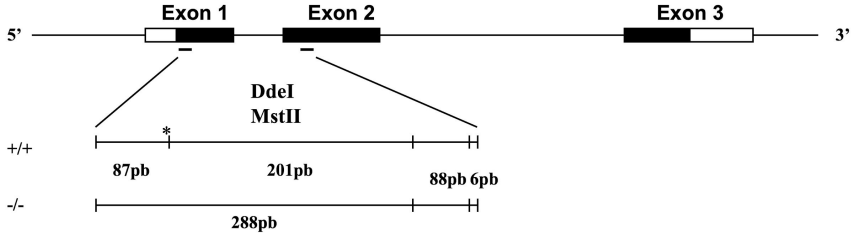


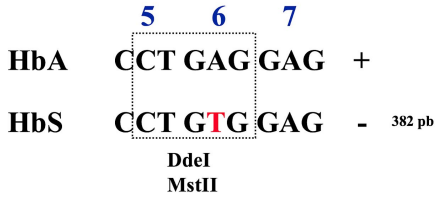
Diagnóstico Citológico

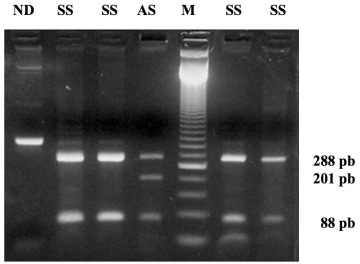
Método Clássico

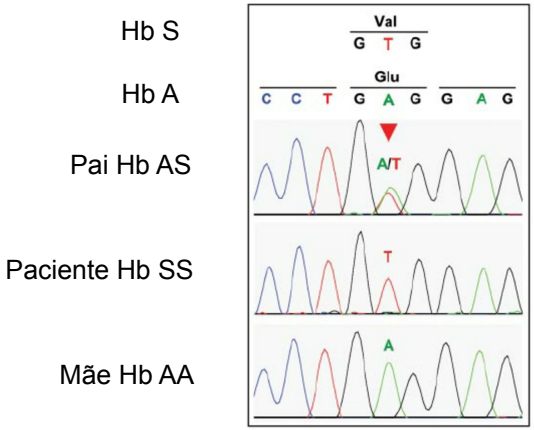


Diagnóstico Molecular







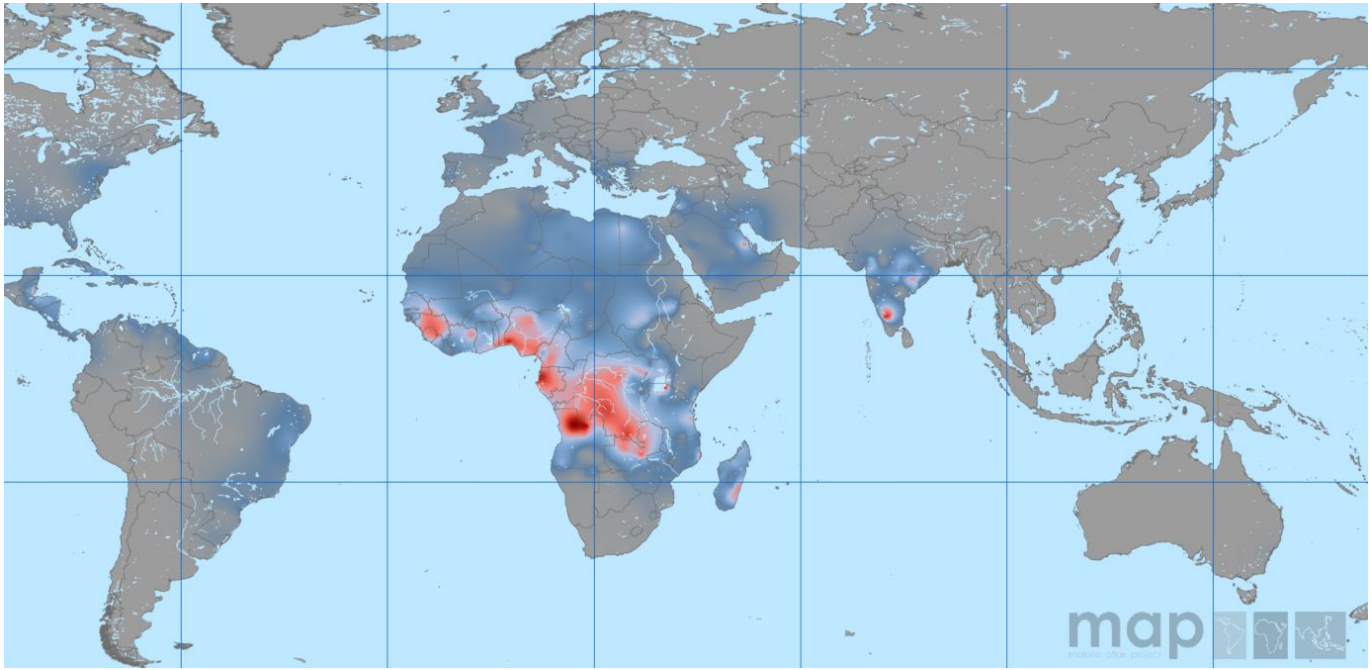


Incidência de portadores de Hb S e Hb C na população geral de diferentes regiões do Brasil

Regiões	Hb S	Hb C
Norte	4.3 %	-
Nordeste	4.2 – 7.5 %	4.1 %
Centro-Oeste	3.2 %	-
Sudeste	1.9 %	0.8 %
Sul	2.0 %	-

THE MALARIA ATLAS PROJECT

Anemia falciforme na África



Origem dos Negros do Brasil

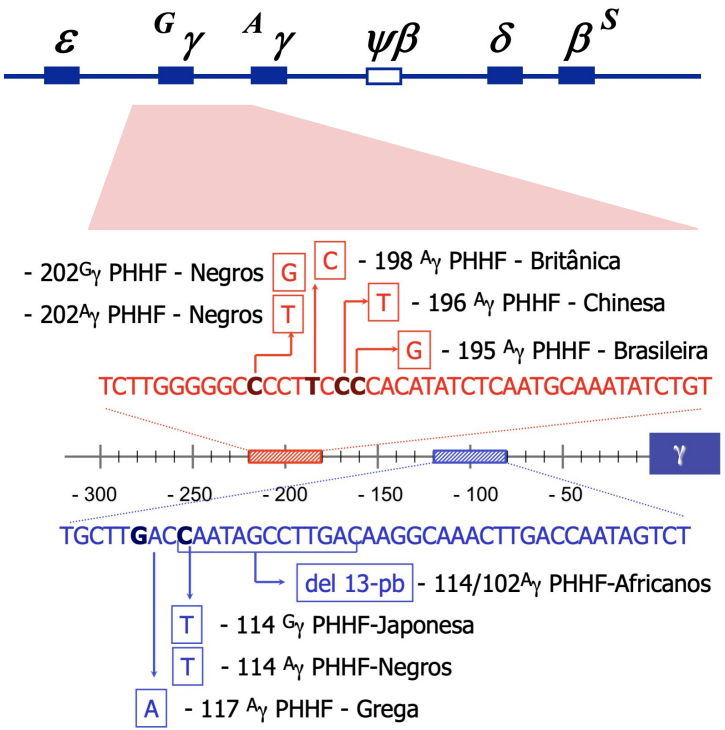


Haplótipos do Complexo β das globinas

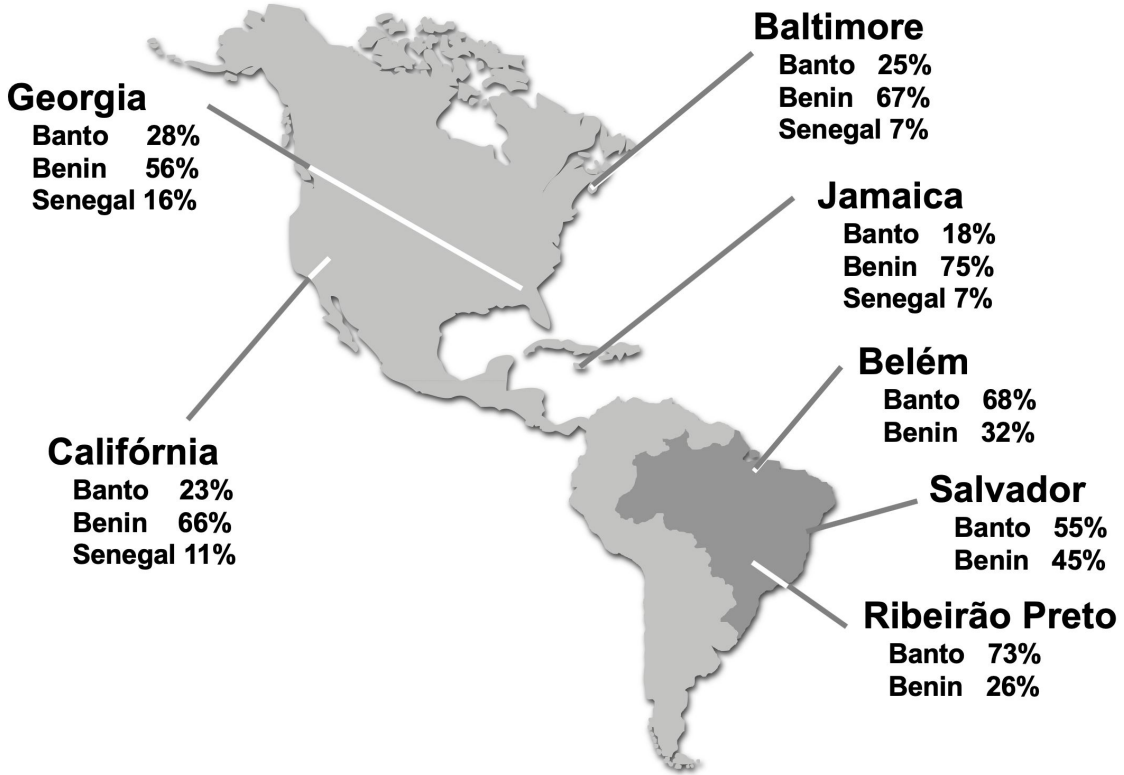


-	-	-	-	-	+	-	+	Benin
-	-	+	-	-	-	-	+	Banto
-	+	+	-	+	+	+	+	Senegal
+	+	+	-	+	+	-	-	Indiano
-	-	+	+	-	+	+	-	Camarões

Haplótipos do Complexo β das globinas

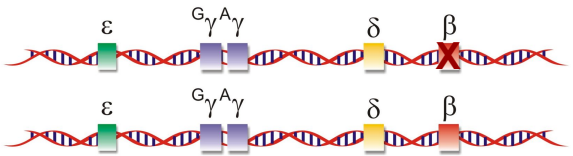


Origem africana nas Americas

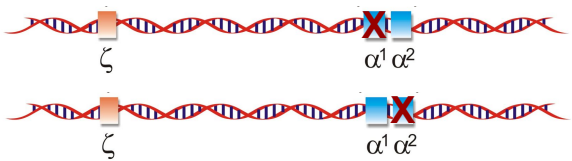


Hemoglobinas raras encontradas no Brasil

Mutações de Cadeia β		Mutações de cadeia α	
Hb D Los Angeles	β 122 Glu → Gln	Hb Hasharon	α 47 Asp → His
Hb Porto Alegre	β 9 Ser → Cys	Hb Stanleyville II	α 78 Asn → Lys
Hb Zurich	β 63 His → Arg	Hb J Rovigo	α 53 Ala → Asp
Hb K Woolwich	β 132 Lys → Gln	**outras**	
Hb Niteroi	β 42-44 del	PHHF Brasileira-195	Aγ C → G
Hb Santa Ana	β 8 Leu → Pro	PHHF tipo 2	105 kb del
Hb Camperdown	β 104 Arg → Ser	Hb Lepore Baltimore	δ50 Ser β86 Ala



Cromossomo 11



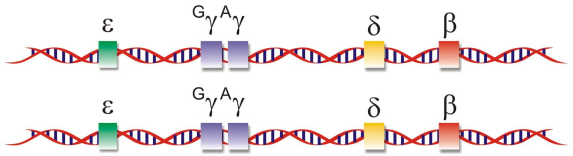
Cromossomo 16

Talassemias

Redução parcial ou total dos genes das globinas

Beta Talassemias

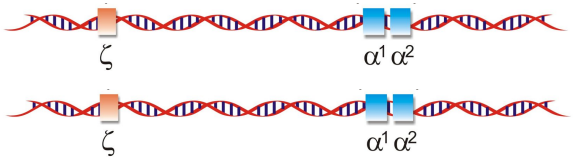
Mutações pontuais



Cromossomo 11

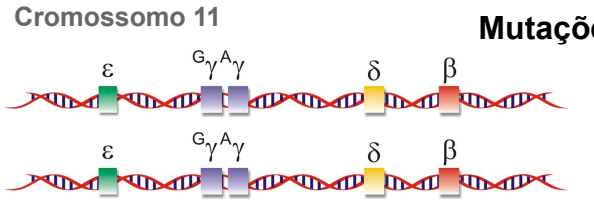
Alfa Talassemias

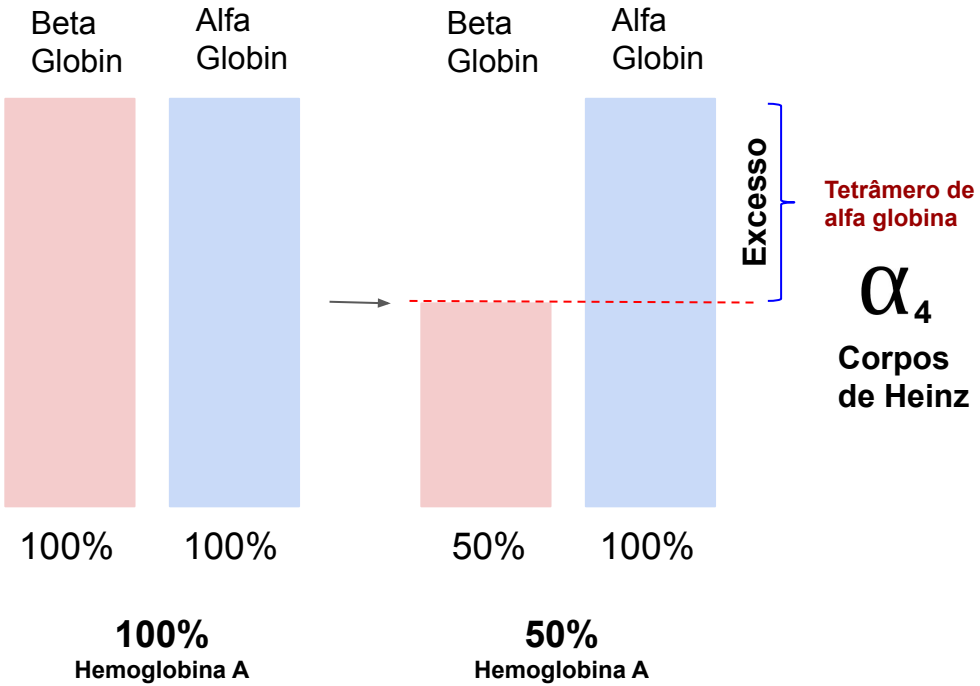
Deleções



Cromossomo 16

Beta Talassemias





Tetrâmero de alfa globina

α_4

Corpos de Heinz

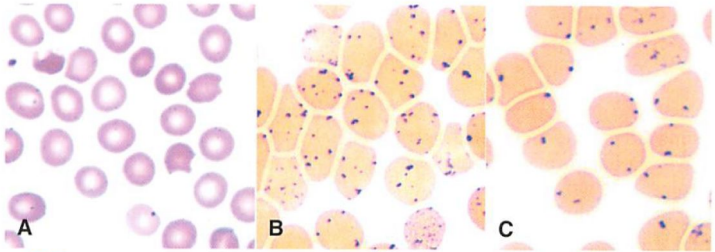


Figura 11-8 Visualização de um efeito patológico da deficiência de cadeias β na β-talassemia: a precipitação do excesso de cadeias α normais para formar o corpo de Heinz nas hemácias. A-C, O esfregaço de sangue periférico (A) mostra células "mordidas" com áreas semicirculares da membrana, correspondentes aos corpos de Heinz, removidas por macrófagos do baço, causando destruição prematura da hemácia. A preparação do corpo de Heinz (B) mostra corpos de Heinz aumentados no mesmo espécime quando comparado ao controle (C). *Veja Fontes & Agradecimentos.*

Beta Talassemias

TABELA 11-5 A Base Molecular de Algumas Causas de β-Talassemia Simples

Tipo	Exemplo	Fenótipo	População Afetada
Síntese de RNAm Defeituosa			
Defeitos no *splicing* de RNA (Fig. 11-11C)	Sítio aceptor anormal no intron 1: AG → GG	β^0	Negros
Mutantes de promotor	Mutação no TATA *box* *–31 –30 –29 –28 –31 –30 –29 –28* *A T A A → G T A A*	β^+	Japoneses
Sítio de *cap* do RNA anormal	Transversão de A → C no sítio de *cap* do RNAm	β^+	Asiáticos
Defeitos no sinal de poliadenilação	AATAAA → AACAAA	β^+	Negros
RNAms Não Funcionais			
Mutações sem sentido (*nonsense*)	Códon 39 Gln→ término CAG → UAG	β^0	Mediterrâneos (especialmente na Sardenha)
Mutações de mudança na matriz de leitura (*frameshift*)	Códon 16 (deleção de 1 pb) *Normal* trp gly lys val asn 15 16 17 18 19 UGG GGC AAG GUG AAC UUG GCA AGG UGA *Mutante* trp ala arg término	β^0	Indianos
Mutações em Região Codificante que também Alteram o *Splicing**			
Mutações sinônimas	Códon 24 gly → gly GGU --GGA	β^+	Negros

*Uma outra hemoglobina variante estrutural que causa β-talassemia é mostrada na Tabela 11-3. RNAm, RNA mensageiro.

Derivada parcialmente de Weatherall DJ, Clegg JB, Higgs DR, Wood WG: The hemoglobinopathies. In Scriver CR, Beaudet AL, Sly WS, Valle D, editors: *The metabolic and molecular bases of inherited disease*, ed 7, New York, 1995, McGraw-Hill, pp 3417-3484; and Orkin SH: Disorders of hemoglobin synthesis: the thalassemias. In Stamatoyannopoulos G, Nienhuis AW, Leder P, Majerus PW, editors: *The molecular basis of blood diseases*, Philadelphia, 1987, WB Saunders, pp 106-126.

Beta Talassemias

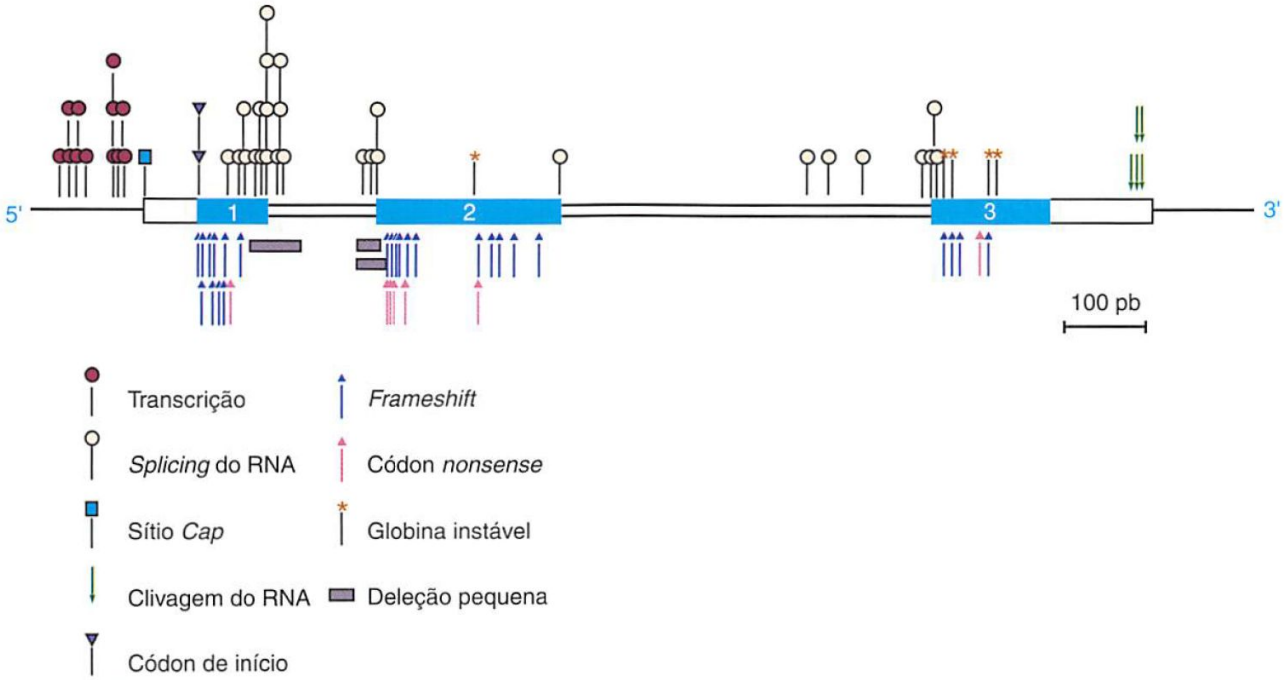
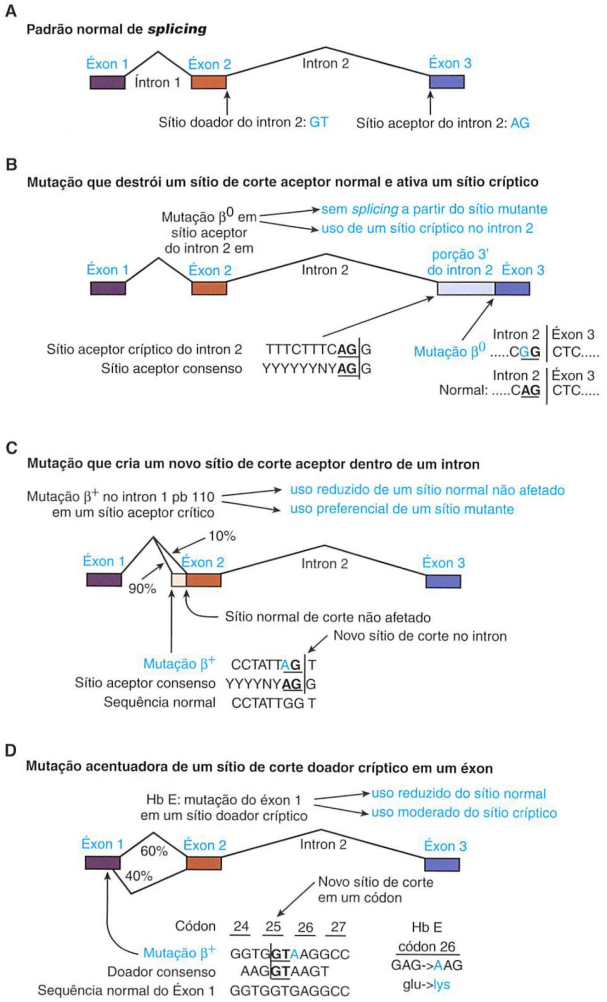


Figura 11-10 **Mutações pontuais e pequenas deleções representativas que causam β-talassemia.** Note a distribuição de mutações ao longo do gene e que as mutações afetam praticamente todos os processos necessários para a produção da β-globina normal. Mais de 100 mutações pontuais diferentes na β-globina estão associadas com a β-talassemia simples. *Veja Fontes & Agradecimentos.*

Beta Talassemias



Beta Talassemias

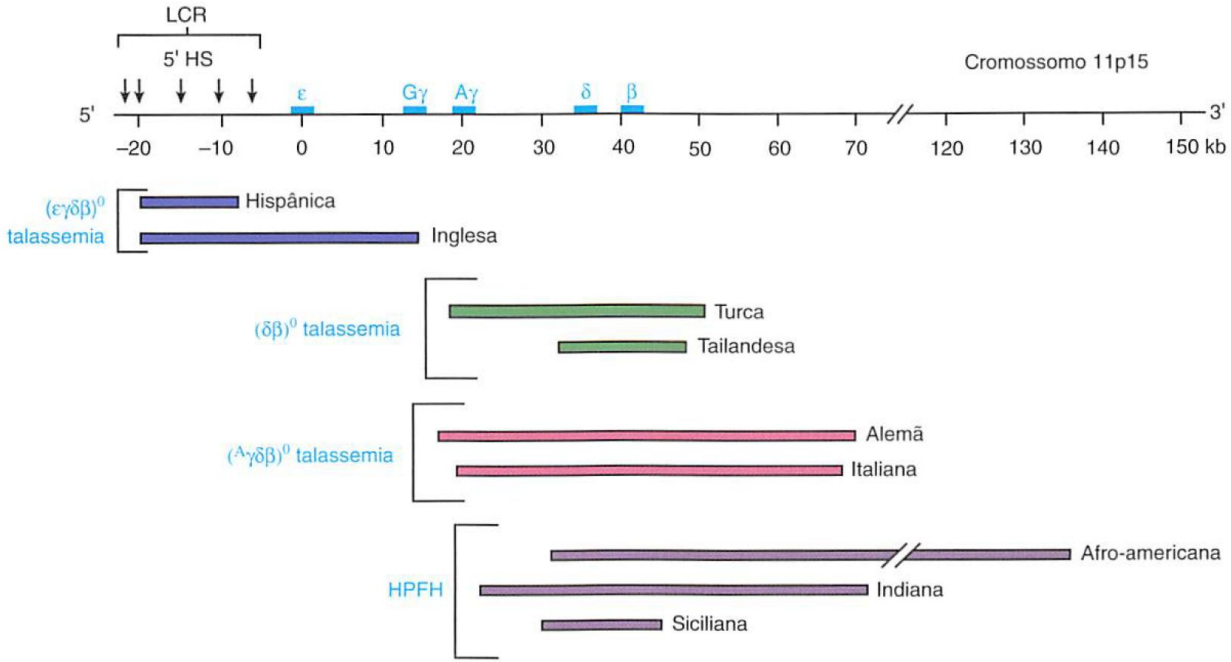


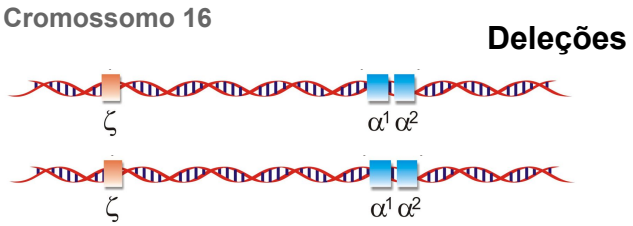
Figura 11-12 Localização e tamanho das deleções de vários mutantes de $(\varepsilon\gamma\delta\beta)^0$-talassemia, $(\delta\beta)^0$-talassemia, $(^A\gamma\delta\beta)^0$-talassemia e HPFH. Note que as deleções na região controladora de *locus* (LCR) impedem a expressão de todos os genes do *cluster* de β-globina. As deleções responsáveis pela δβ-talassemia, $^A\gamma\delta\beta$-talassemia e HPFH se sobrepõem (veja o texto). HPFH, persistência hereditária da hemoglobina fetal; HS, sítios hipersensíveis. *Veja Fontes & Agradecimentos.*

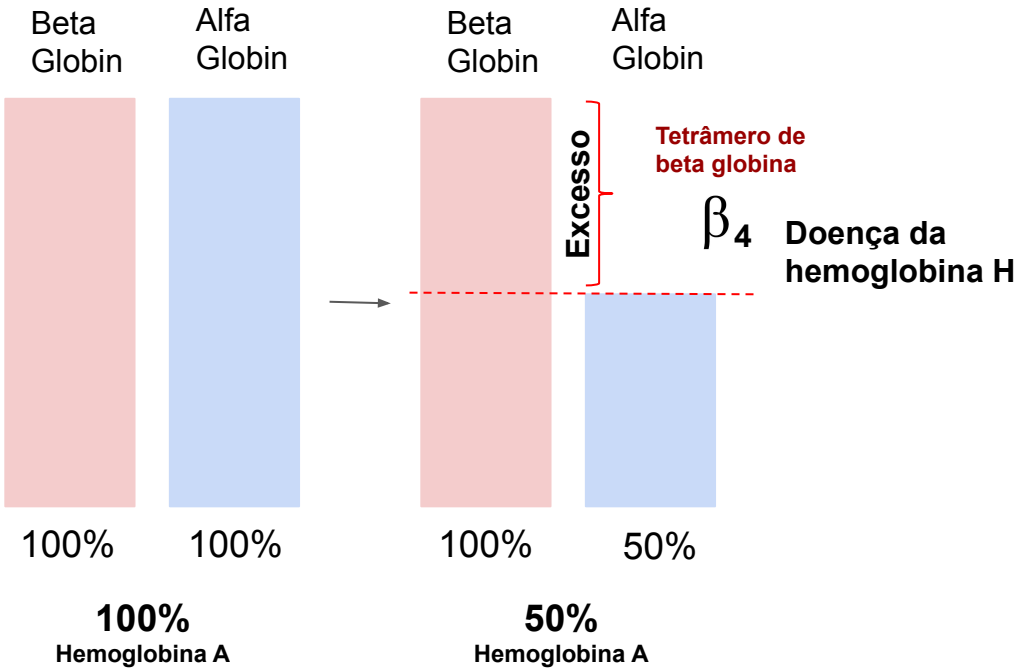
Beta Talassemias

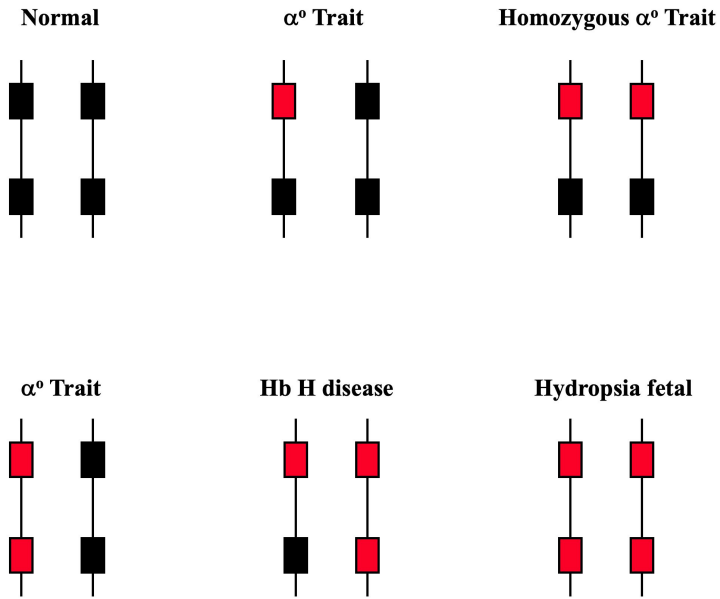
β Talassemias no Brasil e na região do Mediterrâneo

Mutação	Brasil		Mediterrâneo		
	Cromossomos	%	Sicília	Espanha	Grécia
CD39 C → T	110	56,7	36%	64%	17%
IVS-1 nt110 G→ A	43	22,2	27%	8%	43%
IVS-1 nt6 T → C	26	13,4	29%	15%	7%
IVS-1 nt1 G → A	7	3,6	3%	3%	13%
Outras	8	4,1	5%	10%	20%
Total	194				

Alfa Talassemias







Alfa Talassemias

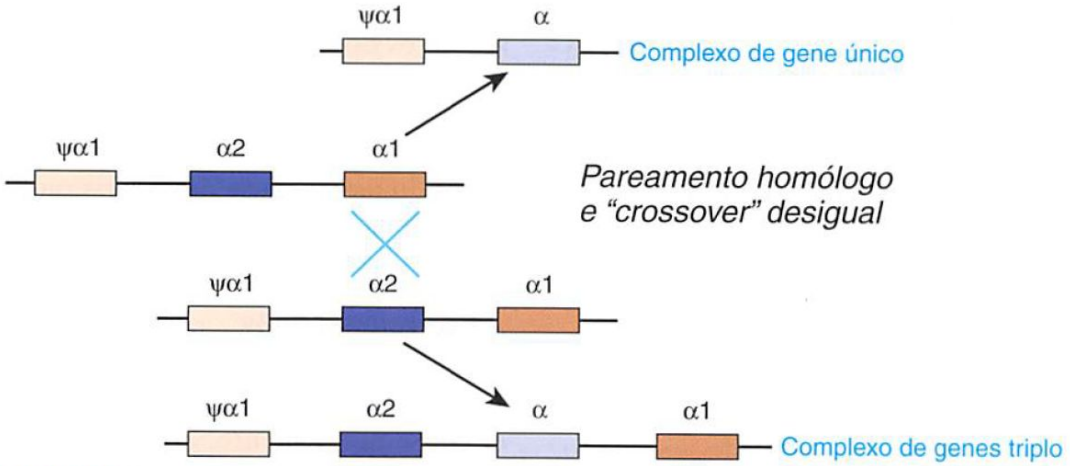
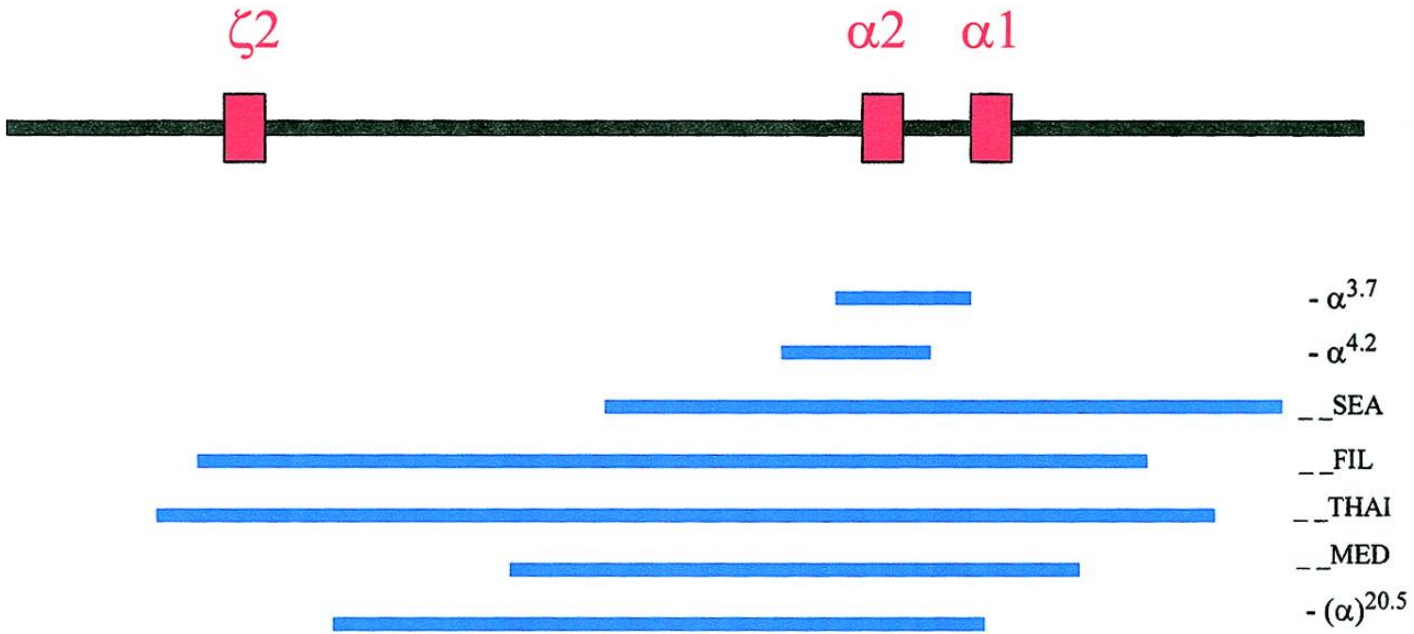


Figura 11-9 O mecanismo provável que determina a forma mais comum de α-talassemia, a qual se deve à deleção de um dos dois genes de α-globina no cromossomo 16. Alinhamento incorreto, pareamento homólogo, e recombinação entre o gene α1 em um cromossomo e o gene α2 no cromossomo homólogo resultam na deleção de um gene da α-globina.

Alfa Talassemias

Deleções associadas com alfa talassemia



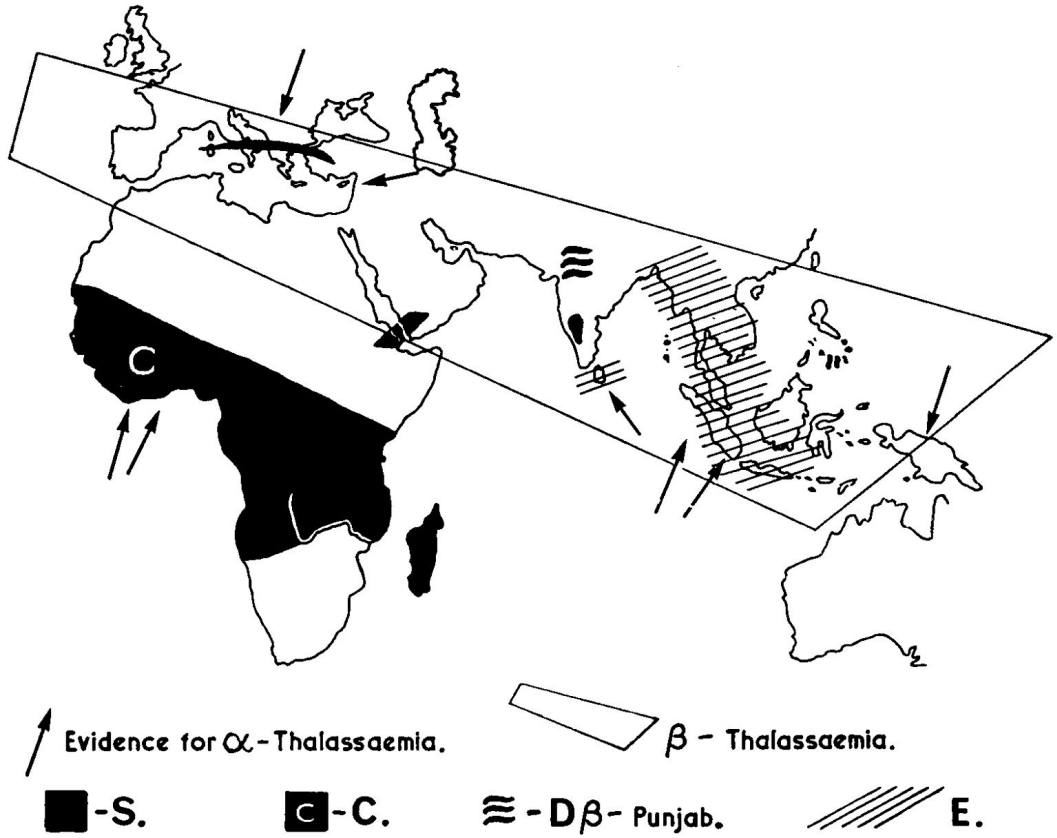


FIG. 36–1. Geographic distribution of Hb S, Hb C, Hb E, Hb D Punjab, and α- and β-thalassemia. (Specially prepared by Dr. Hermann Lehmann.)

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