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Molecular Basis And Population Features Of B-Talassemia

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Annotation: The article highlights the basic ideas about β-thalassemia accumulated to date. The main characteristics of this pathology, the genetic basis and characteristics of mutant alleles of β-thalassemia are given. Data on mutations in β-thalassemia obtained by sequencing and the role of mutations in the development of this pathology are provided.

β-thalassemia is an autosomal recessive disease characterized by hypochromic hemolytic anemia and dependence on blood transfusions for life-saving reasons [4, 10].

Key words: *β-thalassemia, genetic, mutations, sequencing.*

The purpose of this review was to uncover and illuminate the genetic basis of β-thalassemia.

Characteristics of β-thalassemia alleles

A number of factors contributed greatly to the discovery of β-thalassemia alleles. First, β-globin mRNA is very abundant in reticulocytes and other erythroid precursors.

Because globin messenger RNAs account for about 90% of the messenger RNA in these cell types, globin cDNAs were the first human cDNAs synthesized, cloned, and sequenced [7–9]. In 1978, the β-globin gene was one of the first human genes to be cloned in bacteria. [5] It was fortunate that the gene was unusually small and simple for a human gene: it is 1.5 kilobases in size and contains only two introns.

The polymerase chain reaction method allowed the sequencing of genomic amplified β-globin genes and rapid characterization of unusual alleles. [3, 6]

We currently know of 51 point mutations in the β-globin gene and three deletions that cause β-thalassemia simplex. Deletions affecting other genes in the β-globin gene cluster in addition to the β gene cause thalassemias with a more complex developmental mechanism. For example, mutations in the distal element of the ACACCC promoter at the level of –90 nt. Surprisingly, no mutations have been observed so far in the CCAAT box at −70 nt.

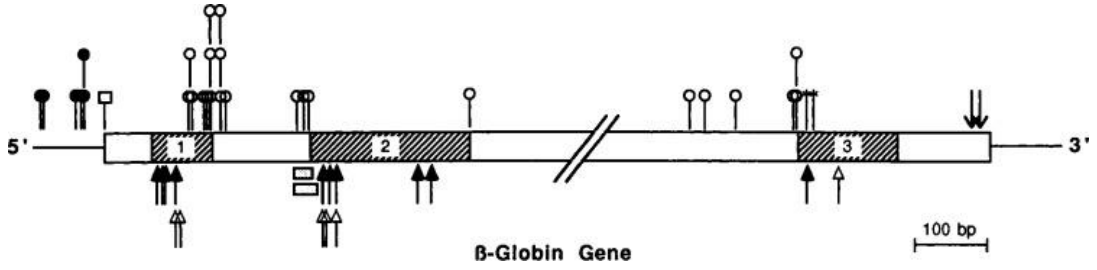

Figure 1. Point mutations in β-thalassemia.

As shown in Figure 1, the β-globin gene is shown by numbered shaded regions representing the coding regions of the exons.

The open regions between exons are introns, and the open regions at the 5' and 3' ends of the gene are untranslated regions that appear in the messenger RNA. Different types of mutations are represented by different symbols. For example, 22 of the 51 mutations affect RNA splicing and are shown as ⚲. (⚲), transcription; (⚲), site header; (↓) – RNA cleavage; (⚲),frame shift; (⚲), nonsense codon; (⚲), unstable globin; (▭), small deletion.

Table 1 .

Point mutations in β-thalassemia (total number = 51, April 1988)

Mutant Class	Type*	Source
1. Non-functional mRNA		
Stupid mutants		
1. Codon 17 (AT)	0	Chinese
2. Codon 39 (CT)	0	Mediterranean, European †
3. Codon 15(GA)	0	Asian Indian
4. Codon 121 (AT)	0	Polish
5. Codon 37 (GA)	0	Saudi Arabia
6. Codon 43 (GT)	0	Chinese
Frameshift mutants		
7. –2 Codon 8	0	Mediterranean
8. –1 Codon 16	0	Asian Indian
9. –1 Codon 44	0	Kurdish
10. +1 codons 8/9	0	Asian Indian
11. –4 codons 41/42	0	Asian Indian, Chinese
12. –1 codon 6	0	Mediterranean
13. +1 codons 71/72	0	Chinese
14. +1 codons 106/107	0	American black
15. –1 codon 76	0	Italian
16. –1 codon 37	0	Kurdish
II. RNA processing mutants		
Changes at the splice site		
1. IVS-1 position 1 (GA)	0	Mediterranean

Mutant Class	Type*	Source
2. IVS-1 position 1 (GT)	0	Asian Indian, Chinese
3. IVS-2 position 1 (GA)	0	Mediterranean, Тунисский, American black
4. IVS-1 position 2 (TG)	0	Tunisian
5. IVS-1 3' end –17 bp.	0	Kuwaiti
6. IVS-1 3' end –25 bp.	0	Asian Indian
7. 3' end of IVS-2 (AG).	0	American black
8. IVS-2 3' end (AC).	0	American black
Consensus changes		
9. IVS-1 position 5 (GK)	+	Asian Indian, Chinese, Melanesian
10. IVS-1 position 5 (GT)	+	Mediterranean, European
11. IVS-1 position 5 (GA)	+	Algerian
12. IVS-1 position 6 (TK)	+	Mediterranean
13. IVS-1 position is 1 (GC) (codon 30).	?	Tunisian
14. IVS-1 position is 3 (CT) (codon 29).	?	Lebanese
15. IVS-2 3'- end CAG-AAG.	+	Iranian, Egyptian
16. IVS-1 3'- end TAG-GAG	+	Saudi Arabia
Internal changes to the temporary detention facility		
17. IVS-1 position 110 (GA)	+	Mediterranean
18. IVS-1 position 116 (TG)	0	Mediterranean
19. IVS-2 position 705 (TG)	+	Mediterranean
20. IVS-2 position 745 (TG)	+	Mediterranean
21. IVS-2 position 654 (KT)	0	Chinese

Mutant Class	Type*	Source
Замены областей кодирования, влияющие на обработку		
22. Codon 26 (GA)	Hb E	Southeast Asia, European
23. Codon 24 (TA)	+	American black
24. Codon 27 (GT)	Hb	Mediterranean
III. Transcription mutants		
1. –88 КТ	+	American black, Asian Indian
2. –87 З g	+	Mediterranean
3. –31 g.g.	+	Japanese
4. –29 g.m.	+	American black, Chinese
5. –28 alternating current	+	Kurdish
6. –28 g.g.	+	Chinese
IV. RNA cleavage + polyadenylation mutants		
1. AAAAA-AAAAAA	+	American black
2. AATAAA-AATAAГ	+	Kurdish
V. Cap site mutants		
1. +1 alternating current	+	Asian Indian
VI. Unstable globins		
1. β Indianapolis (codon 112)	+	European
2. β Shoue-Yakushiji (codon 10)	+	Japanese

† Note: *: O, b ; +, b + .

†If two or more ethnic origins are reported, the evidence strongly suggests that the mutation occurred independently in each ethnic group.

Some mutant alleles responsible for the synthesis of beta globin lead to a moderate impairment of its production and are quite often identified as one of 2 genes in patients with diagnosed intermediate beta thalassemia. Mutations -87, -88 and -29 (AG) in black Americans and promoter mutations -28, cap-site mutation +1, β E and β Knoss mutations and IVS- Mutation 1 nt

6 have similar properties [1, 2, 11, 8]. Other mutations may also be associated with β-thalassemia intermedia, but the association has not yet been proven.

Conclusion

To date, a sufficient number of different mutations have been described that are responsible for the development of various forms of beta thalassemia, however, due to the fact that methods of treating this pathology continue to develop, this problem requires further study.

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