

Bioinformatics

Beta Thalassemia

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```

Beta globin gene

Uppercase characters:

- mature mRNA

Lowercase characters:

- introns
- flanking sequences

Red

- cat box
- tata box
- polyadenylation sequence

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Table 1 Types and Frequencies of β -Thalassemia Mutations and β -Globin variants in Lebanon

Mutation	Phenotype	Number of Chromosomes	Number of homozygotes/heterozygotes	Frequency (%)
IVS-1-110 (G>A)	β^*	178	65/48	34.2
IVS-1-1 (G>A)	β^*	78	29/20	15.0
IVS-1-6 (T>C)	β^*	75	28/19	14.4
cd 29 (C>T)	β^*	50	22/6	9.6
IVS-III-1 (G>A)	β^*	45	17/11	8.6
cd 5 (-CT)	β^*	26	9/8	5.0
cd 30 (G>C)	β^*	14	6/2	2.7
cd 8 (-AA)	β^*	13	5/3	2.5
cd 44 (-C)	β^*	8	3/2	1.5
IVS-II-745 (C>G)	β^*	6	3/0	1.1
β^0	β^*	5	0/5	1.0
-87 (C>G)	β^*	4	1/2	0.8
IVS-I-5 (G>C)	β^*	4	2/0	0.8
-88 (C>T)	β^*	3	1/1	0.6
290 bp deletion	β^*	3	1/1	0.6
25 bp deletion	β^*	2	1/0	0.4
β^0 -thalassemia (Sicilian type)	β^*	2	1/0	0.4
cd 8/9 (+G)	β^*	1	0/1	0.2
cd 36/37 (-T)	β^*	1	0/1	0.2
cd 39 (C>T)	β^*	1	0/1	0.2
Unknown		1	0/1	0.2
Total		520	194/132	100

"Genetic heterogeneity of beta thalassemia in Lebanon reflects historic and recent population migration" by N. J. Makhouli, et al.
"Annals of Human Genetics" in 2005 (issue 69, pages 55 to 66).

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Total		520	194/132	100

Six mutations are responsible for 86.8% of all beta thalassemias in Lebanon

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TABLE 2. FREQUENCY DISTRIBUTION OF THE MOST COMMON β -THALASSEMIA MUTATIONS IN MOROCCO AND IN ARAB AND MEDITERRANEAN COUNTRIES

Mutations	Morocco (160) ^a	Algeria (239)	Tunisia (233)	Portugal (561)	Spain (324)	Italy (325)	Egypt (337)	Lebanon (520)	Turkey (795)
Codon 39 (C→T)	26.58	27.6	40	36.8	36	40	1.5	0.5	3.8
F5C-8 (A→A)	13.91	-	0.9	-	0.4	0.1	1.8	2.5	5.4
IVS-II-745 (C→G)	7.6	0.9	2.5	-	-	5	5.6	1.2	5
-29 (A→G)	6.33	3.8	-	-	-	-	-	-	-
F5C-6 (A)	5.7	17	6.65	1	1	1.9	0.9	-	0.4
IVS-I-110 (G→A)	5.7	24.7	20.5	10	13	19.9	32.9	34.2	39.2
IVS-I-2 (T→C)	5.06	3.3	0.76	-	-	-	-	-	-
IVS-I-1 (G→A)	5.06	11.7	1	28	35	10.2	11.3	15	5
Total	76	89	72.3	75.8	85.4	77	54	53.4	58.8
References ^b	1	2.3	4	5.6	7	8	9	10	

^aValues in parenthesis indicate the total number of chromosomes studied.
^b1, Benami et al. (1994); 2, Fatoum et al. (1991); 3, Haj Khelil et al. (2004); 4, Faustino et al. (1999); 5, Anselem et al. (1988); 6, Ribeiro et al. (1997); 7, Rosatelli et al. (1992b); 8, Wayne et al. (1999); 9, Makhouli et al. (2005); 10, Tadmouri et al. (1998).

"Molecular basis of beta thalassemia in Morocco: possible origins of the molecular heterogeneity" by I. Agouti et al. In "Genetic Testing" Volume 12, Number 4, 2008.

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TABLE 2 Spectrum of Relative Frequencies (%) of β -Thalassemia Mutations in Tunisia, Algeria and Morocco

Mutation	Type	Origin	Tunisia	Algeria	Morocco
References			44	29	33
Codon 39, C>T	β^0	Mediterranean	48.76	43.78	49.00
IVS-I-110, G>A	β^*	Mediterranean	15.70	10.81	21.00
Codon 8, -AA	β^0	East European	-	0.54	0.20
Codon 6, -A	β^0	North African	1.65	7.02	2.60
IVS-I-6, T>C	β^*	West Mediterranean	2.48	0.54	0.60
IVS-I-1, G>A	β^0	Asian	3.31	4.32	4.50
Codon 5, -CT	β^0	Greek	-	0.40	-
Codon 44, -C	β^0	Kurdish Jews	1.65	1.62	3.80
IVS-I-2, T>C	β^0	Algerian; Russian	-	0.54	-
IVS-I-2, T>G	β^0	Tunisian	19.83	0.54	3.00
-30, T>A	β^*	Turkish	-	-	0.80
-29, A>G	β^*	Black	-	1.08	-

"Hemoglobinopathies in North Africa" by A. Haj Khelil et al. In "Hemoglobin, 34" Vol 34, Numb 1, 2010.

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Major Intermedia and Minor

- The alpha and beta loci determine the structure of the 2 types of polypeptide chains in adult hemoglobin, Hb A.
- Absence of beta chain causes beta-zero-thalassemia.
- Reduced amounts of detectable beta globin causes beta-plus-thalassemia.
- For clinical purposes, beta-thalassemia is divided into:
 - thalassemia major (transfusion dependent),
 - thalassemia intermedia (of intermediate severity), and
 - thalassemia minor (asymptomatic).

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ATG GTG CAT CTG ACT CCT GAG GAG AAG TCT GCC GTT
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ACC CAG AGG TTC TTT GAG TCC TTT GGG GAT CTG TCC
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GCT CAT GGC AAG AAA GTG CTC GGT GCC TTT AGT GAT
GGC CTG GCT CAC CTG GAC AAC CTC AAG GGC ACC TTT
GCC ACA CTG AGT GAG CTG CAC TGT GAC AAG CTG CAC
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IVS-1-6 (T > C)

IVS-1-1 (G > A)

IVS-1-110 (G > A)

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ATG GTG CAT CTG ACT CCT GAG GAG AAG TCT GCC GTT
ACT GCC CTG TGG GGC AAG GTG AAC GTG GAT GAA GTT
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GCT CAT GGC AAG AAA GTG CTC GGT GCC TTT AGT GAT
GGC CTG GCT CAC CTG GAC AAC CTC AAG GGC ACC TTT
GCC ACA CTG AGT GAG CTG CAC TGT GAC AAG CTG CAC
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cd 5 (-CT)

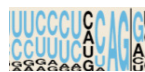
cd 29 (C > T)

IVS-II-1 (G > A)

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GCC ACA CTG AGT GAG CTG CAC TGT GAC AAG CTG CAC
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YYYYYYNYAGIG

IVS-1-110 (G > A)

```

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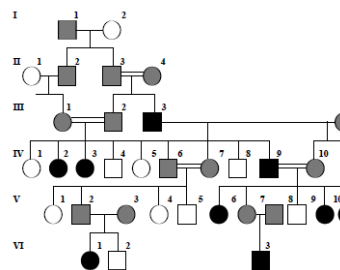
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Mutation: TGCCTATTAG | T

Wild Type: TGCCTATTGG | T

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Consanguineous Family

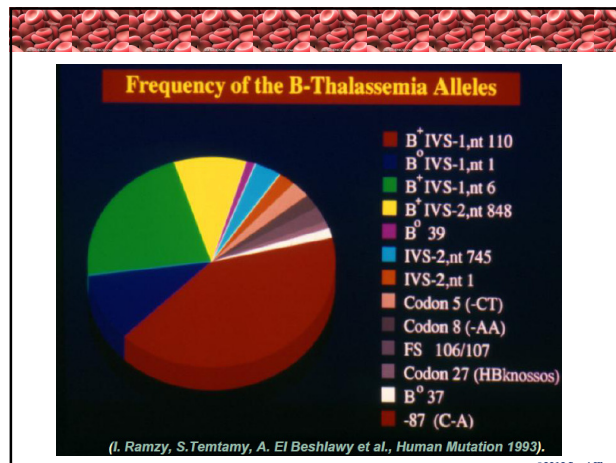
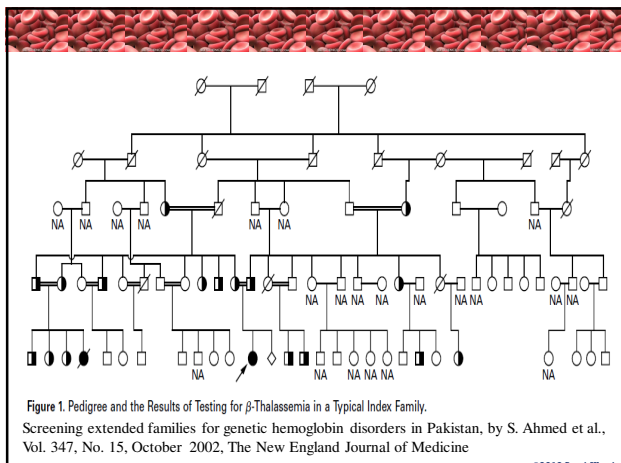


In the **Western family**:
 * Mutation carriers are usually scattered throughout the general population.
 So the genetic basis for their disease predisposition is missed

In the **Arab family**:
 * Arab society mutation carriers mostly remain concentrated within the extended family, so the genetic nature of their disease predisposition may be obvious.

Genetic Disorders in the Arab World: United Arab Emirates
 The Arab World by Ghazi Omar Tadmouri

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Prevention of Thalassemia

Problems with the prevention of thalassemia in Egypt

- > National screening for thalassemia not yet available.
- > Centers for genetic counseling and premarital examination are lacking.
- > Prenatal diagnosis centers are few and not yet well equipped.
- > Prenatal diagnosis conducted on a limited and voluntary basis.
- > Population awareness is improving.

UAE Genetic Diseases Association

UAE free of Thalassemia 2012

مركز الخليج للعلاج
 Gulf Genetic Centre

مركز أمراض الدم الوراثية بمنطقة جازان
 Hereditary Hematological Disease Center

Free Of Thalassemia by 2012

- The first project of the UAE GDA (Emirates Free Of Thalassemia by the year 2012) is aimed at identifying the Beta-Thalassemia and Sickle-cell carriers in the UAE pre-marital population.
- UAE GDA seeks to step up the fight against Thalassemia, in line with the UAE federal government's vision to make the country free from the new births of children with Thalassemia major by the year 2012.

Molecular Defects in Thalassemia

The molecular defects identified in thalassemias:

- gene deletion, e.g., of the terminal portion of the beta gene
- chain termination (nonsense) mutations
- point mutation in an intervening sequence
- point mutation at an intervening sequence splice junction
- frameshift deletion
- fusion genes, e.g., the hemoglobins Lepore; and
- single amino acid mutation leading to very unstable globin,
 - Example: Hb Vicksburg (beta 75 leu-to-0).