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Review Articles

THE SPECTRUM OF BETA - THALASSEMIA MUTATIONS IN IRAN

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INTRODUCTION

Thalassemias are the world's most widespread genetic disorder known in man.[22] According to a WHO report,[25] thalassemia carriers are estimated to exceed 100 million persons and some 100 thousand affected babies are born each year. The incidence, prevalence and clinical forms of thalassemia vary in different parts of the world. However, the most common clinical forms of thalassemia vary in different parts of the world. However, the most common clinical presentation observed is thalassemia trait or the heterozygous state of either beta or alpha thalassemia. Beta-thalassemia is highest in prevalence in the Mediterranean area and parts of Africa and Asia, whereas alpha-thalassemia is highest among Asian populations in which 3.5% of the people are alpha-thalassemia carriers.[4] Thalassemias produce a massive public health problem in many countries but occur at a very high frequency in a broad belt stretching from the Mediterranean basin through the Middle East, India, Burma and Southern Asia.[22] Thalassemia is a hereditary hemolytic disease accompanied by hypochromic microcytic anemia. It is inherited as an autosomal recessive trait and encompasses a broad range of clinical manifestations. In all thalassemias, there is a reduction in the rate of synthesis of the globin chains that form normal hemoglobins. Thus, if there is a reduction in alpha chain synthesis the condition is an alpha-thalassemia. If the reduction is in beta chain synthesis the condition is a beta thalassemia. When the mutation leads to a complete lack of the alpha or beta chain the thalassemia is classified as alpha-0 or beta-0 respectively. If there is reduced alpha or beta chain synthesis they are called alpha$^+$ or beta$^+$ thalassemias.[21]

Defective hemoglobin production and damage to the red blood cells or their precursors result from globin subunits that are produced in excess. Beta-thalassemias result from mutations within the beta globin gene and affect beta globin production. Most alpha-thalassemias are the result of deletions of one or more alpha globin genes.

Five mutations, IVSII - 1(G-A), IVSI-5 (G-C), IVSI - 110, codon 39 (C-T) and codon 8/9 (+G) causing beta-thalassemia appear to have rather high frequencies in Iran. However, Noori-Daloii et al.[12] found four mutations, codon 39 (C-T), frameshift codon 8 (-AA), IVSI-6 (T-C) and IVSI-110 with frequencies of 60.3%, 9.5%, 4.8% and 1.6%, respectively.

An effective prevention program should aim at public education, population screening for heterozygotes, genetic counselling for carrier couples, antenatal diagnosis and premarital screening.

BETA THALASSEMIA IN IRAN

Iran is located on the thalassemia belt and a high frequency of the disease is known to exist in certain regions of the country, although most areas are believed to be affected. The disease has been reported to be particularly frequent around the Caspian and Oman Sea including Mazandaran and Gilan provinces in the North and Khuzestan, Fars, Booshehr, Hormozgan, Sistan-Baluchestan and Kerman provinces in the South.[27] Several extensive surveys in 1993 aiming at the distribution of thalassemia major in various regions of the country[28] indicated that Mazandaran, with 5422, and Fars, with 4662 patients are the two provinces with the highest prevalence of the disease. These are followed by Khuzestan with 3817, and Gilan with 2030 cases. Lower prevalences were reported in other provinces. Some 10% of the population in the south of the country are estimated to be the carrier for a beta thalassemia gene. Based on the surveys

Table Reported mutations causing β-thalassemia in Iran.

Mutation	Origin	Reference
A. Transcriptional Mutants		
-88(C- -A)	Kurdish	17
-101(C- -T)	Turkish	9
B. RNA Processing Mutants: Splice Junction		
IVSI-1(G--A)	Mediterranean	9
IVSI-1(G--C)	Tunisian, American Black	3
IVSII-1(G--A)	Mediterranean, Tunisian Afro -American	14
IVSII-1(G--C)	Iranian	14
Consensus Sequence		
IVSI- 5 (G--C)	Asian Indian ; Chinese	13
IVSI -6 (T--C)	Mediterranean	17
Other IVS Changes		
IVSI- 110 (G--A)	Mediterranean	13
IVSII - 745 (C--G)	Mediterranean	9
IVSII - 848 (C--A)	Iranian; Egyptian Afro - American	24
IVSII - 654 (C-T)	Chinese	2
C. Nonsense and Frameshift Mutations		
Nonsense		
Codon 39 (C--T)	Mediterranean	11,13
Frameshift		
Codon 5 (-CT)	Mediterranean	7,8
Codon 8 (-AA)	Mediterranean	15
Codons 8/9 (+G)	Asian; Indian	13,24
Codons 36/37 (-T)	Iranian; Kurdish	7
Codon 44 (-C)	Kurdish	13
D. Deletional Mutants		
-290 bp*	Iranian	5
-25 bp**, 3 IVS-1	Indian	9
-2bp*** + 11 bp	Iranian	6
E. Initiation Codon		
Codon 26 (G--A)	Southeast Asia	16

* Origin in the 5 untranslated region and removing the mRNA cap.

** A 25 base pair deletion that begins in the 3 portion of IVSI and includes the mRNA acceptor splice site.

***Insertion of 11 base pairs between positions 1 and 4, removing two bases at position 2 and 3 in IVS-II..

carried out by the Iranian National Blood Transfusion Center,[27] the number of patients with thalassemia major alone is estimated to be around 15,000 in the country.

More information is recently being published on beta-thalassemia in Iran [8-11, 13-15] with some screening projects on the distribution of mutations causing thalassemia in some provinces already on the way in the country. Alpha-thalassemia is found in the neighboring countries and therefore it probably exists in our population too; nevertheless it has not been reported. The bulk of the existing data on thalassemia in Iran came from the reports on clinically encountered Iranian thalassemic patients, published mostly

in the last decade, focusing on the nature of the mutations in the disease.

Merat and Nili in 1986[10] studied 22 clinically diagnosed thalassemic patients from Fars province by chain synthesis technique and found that all 22 randomly selected patients were beta-thalassemics. Table I shows 24 different mutations so far reported to be responsible for beta-thalassemia in Iran. Wong et al.[23,24] found two mutations, codon 8/9 (+G) and IVSII-848(C--A) causing beta thalassemia in Iranian patients. Baird et al.[1] reported an IVSII-1(G--A) mutation in an Iranian . Thein et al.[19,20] investigated a few beta thalassemia cases in Iranians. Nozari et al.[13] have studied eleven Iranian beta thalassemic families living in America and found six mutations, codon 39 (C--T), codon 8/9 (+G), IVS 1-5 (G - - A), IVSII-1 (G--A), IVSI-110 (G--A) and codon 44 (-C), with the first two each comprising 30.7% of the total mutations. Rund et al.[17] have investigated mutations in a few thalassemic Iranians, finding the codon 39 (C--A) mutation. Merat et al.[9] reported four mutations of Mediterranean, Indian and Turkish origin, first found in Iran (Table I), in 17 patients, mostly heterozygous, from Fars province. Mahboudi et al.[8] studied 50 homozygous, or compound heterozygous, beta-thalassemia cases from Fars province. They showed that IVSI-5 (G--C) comprised 37%, IVSI-110 (G--A) 17.8%, and IVSII-1 (G--A) 13.7% of the mutations among the chromosomes studied, while in another study [9] the IVSII-1 (G--A) was found to be the most frequent mutation (31%). A high incidence of beta thalassemia was reported in Iranian Jews.[27] Tadmouri et al.[18] found a codon 36/37 (-T) mutation in a Turkish patient which they suggest has originated from northern Iran. However, this mutation was later reported in Iranians.[14] Nozari et al.[14] studied 108 beta-thalassemic chromosomes from ethnic Iranian subjects and identified 20 different mutations. Seven of these mutations, codon 8 (-AA), IVSI II-1 (G--C), initiation codon (ATG--ATT), codon 19 (A--G), codon 26 (G--A), IVSI - 1 (G--C) and IVSII - 654 (C--T) of various origins, were first reported in Iranians. According to their results, IVSII - 1 (G--A) was the most frequent (13.8%) among the 20 mutations they identified.

There is evidence, based on general routine screening, that beta-thalassemia is widespread throughout Iran. But to determine the prevalence of various mutations requires additional data to be collected from different areas of the country. The frequencies of various mutations have been ranked on the basis of the limited number of chromosomes investigated in each study. Thus, by comparing these results, it is difficult to arrive at a conclusion regarding the prevalence of individual mutations in various parts of Iran. However, it is evident from the existing data that the five mutations IVSII - 1 (G-A), IVSI - 5 (G-C), IVSI - 110 (G-A), codon 39 (C-T) and codon 8/9 (+G) are present in Iran with rather high frequencies. Therfore, various mutations and their frequencies, reported by different investigators, could be representative of some of the beta thalassemia genes responsible for beta-thalassemia in the general population of Iran. However, even these limited studies reveal the fact that mutations causing beta-thalassemia in Iran are numerous and originate from those found primarily in Mediterranean, and also Asian - Indian and Afro-American populations. The occurrence of many mutations in Iran may reflect a high degree of genetic admixture resulting from the fact that this part of the world has been a route for the East-West migration along the Silk Road between Europe and Asia.

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