
Rare β -Thalassemia Mutation in a Turkish Patient: FSC-36/37 (-T)

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Abstract We describe the rare β -thalassemia mutation at codons 36/37 (-T) for the first time in Turkey. The propositus is a Turkish patient with β -thalassemia major who originated in Adana but now resides in Istanbul. Molecular analysis revealed a compound heterozygosity for the common eastern Mediterranean mutation IVS-I-110 (G-A) along with mutation FSC-36/37 (-T). The FSC-36/37 (-T) mutation could have arisen somewhere in the region, including northern Iran and the inaccessible mountainous region of eastern Anatolia. The mutation could have followed two migration routes during the time of Ottoman rule, the first being to Azerbaijan and the second, probably a more recent one, passing through southeastern Anatolia and reaching southern Bulgaria.

β -thalassemia is an autosomal recessive disorder characterized by microcytic and hemolytic anemia and by diminished (β^+) or absent (β^0) beta globin-chain synthesis (Weatherall and Clegg 1981). At present, nearly 180 mutations that produce β -thalassemia have been identified in the β -globin gene (Baysal and Carver 1995). However, in each ethnic group a much more specific collection of alleles accounts for the inactivation of most of the β -globin genes (Kazazian 1990). At least five of these mutations are exclusive to Kurdish Jews (Rund et al. 1991). Here, we describe one of those mutations, a frame shift at codons 36/37 (-T), in a Turkish patient.

Materials and Methods

The patient is a 5-year-old Turkish girl from Istanbul who was first seen in the hematology clinic of the Medical School of Adana. The first diagnosis was made at the age of 18 months. Her hematological data (Table 1) show classic signs of β -thalassemia major.

Blood samples were collected in tubes containing EDTA, and DNA was extracted from white blood cells according to the method of Poncz et al.

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Table 1. Hematological Data for the Propositus and Her Parents

Characteristic	Father	Mother	Propositus
	[Age 34, Born in Osmaniye (Adana)]	[Age 26, Born in Osmaniye (Adana)]	[Age 5, Born in Gebze (Kocaeli)]
Red blood cells ($10^{12}/L$)	—	3.54	—
Hemoglobin (g/dl)	13.9	7.3	7.9
Hematocrit (%)	46	22.9	24
Mean corpuscular volume (fl)	69.1	64.6	79.3
Mean corpuscular hemoglobin (pg)	20.9	20.6	25.7
Mean corpuscular hemoglobin concentration (g/dl)	30.2	31.9	32.4
Phenotype	β -thalassemia carrier	β -thalassemia carrier	β -thalassemia major
Genotype	IVS-I-110/N	FSC-36/37/N	IVS-I-110/FSC-36/37

(1982). In vitro amplification of genomic DNA was performed using the technique of Saiki et al. (1988). Screening for the presence of the common Mediterranean mutations was carried out by dot-blot hybridization of the β -globin gene region with allele-specific oligonucleotide (ASO) probes (Diaz-Chico et al. 1988). Further analysis was done by direct sequencing of the polymerase chain reaction (PCR) product, using the dideoxy chain termination method (Sanger et al. 1977) in combination with ^{35}S -dATP and Sequenase Version 2.0 (United States Biochemicals).

Results

ASO hybridization with 18 probes specific for Mediterranean countries revealed the presence of the IVS-I-110 (G-A) mutation on one chromosome of the child and of her heterozygous father. The mutation of the mother, thus the other allele of the child, could not be identified by this approach. Sequencing of the proband's DNA uncovered the presence of the rare FSC-36/37 (-T) mutation on her other chromosome (Figure 1). This mutation was confirmed to be present in the DNA of the mother.

Discussion

More than 180 mutations that affect the expression of the β -globin gene have been described so far. Several of these mutations are unique to Kurdish Jews. However, subsequent molecular analysis of β -thalassemia patients from different countries revealed the presence of some of these mutations else-

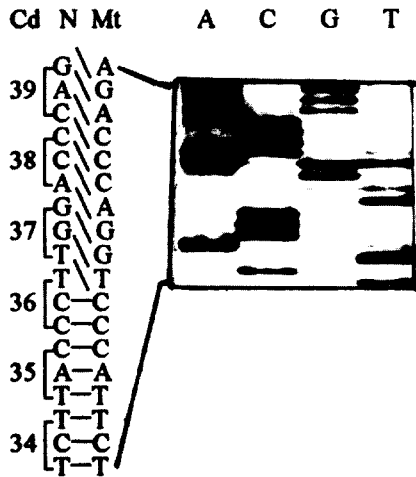


Figure 1 Part of the sequencing gel identifying the FSC-36/37 (-T) mutation in the propositus. The T in codon 36/37 is missing in the mutated (Mt) sequence, thus giving rise to a frame shift.

where as well. For example, the frame shift at codon 44 (-C), the polyadenylation mutation (AATAAA-AATAAG), and the TATA box mutation at -28 (A-C) have been described in 0.3–1.2%, 0.5%, and 0.1–0.4%, respectively, of β -thalassemia cases in Turkey (Altay and Basak 1995; Tadmouri et al. 1996).

Here, we record the additional finding of the FSC-36/37 (-T) mutation in a Turkish β -thalassemia patient originating from the city of Adana. A careful investigation of the origin of the mother (Table 1) revealed that at least three of her grandparents were from the city of Muş (eastern Anatolia) and had a Kurdish origin.

A search of the literature for previous records of the FSC-36/37 (-T) mutation uncovered its first description in an Iranian from Masjed Solaiman in the province of Khuzistan in northwestern Iran (Kazazian 1990). Later, the mutation was described in five Kurdish Jews (Rund et al. 1991; Filon et al. 1994), on at least four chromosomes in individuals from Azerbaijan (Çürük et al. 1992; Tagiev et al. 1993; Kuliev et al. 1994), and in some members of an Iranian family (Kim et al. 1994). Recently, Jankovic et al. (1994) reported the same mutation heterozygously inherited along with the rare mutation Cd 30 (G-C) in a thalassemic child of Turkish nationality who lived in southern Bulgaria. In some of these studies haplotype analysis was performed and the FSC-36/37 (-T) mutation was found exclusively on haplotype I, reflecting the same ancestral background for patients carrying this mutation.

From these results it can be concluded that the FSC-36/37 (-T) mutation could have arisen somewhere in the region, including northern Iran and the

inaccessible mountainous region of eastern Anatolia. These regions are mainly inhabited by a rural population of nomadic Kurdish tribes related to the Persians by language and genotype. Thus the mutation might have followed two migration routes during the time of Ottoman rule, the first being to Azerbaijan and the second, probably a more recent one, passing through southeastern Anatolia and reaching southern Bulgaria.

Acknowledgments Thanks are due to E.Y., the patient's father, who supplied us with the hematological data of the patient, and to Duru Malyalı, who referred the patient to our center. This research was funded by Boğaziçi University Research Funds through grant 95-B-104 and by the Technology Development Foundation of Turkey (through grant TTGV-086). G.O. Tadmouri is a fellow of the Scientific and Technical Research Council of Turkey (TÜBİTAK).

Received 6 June 1996; revision received 3 September 1996.

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