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Original Article

Genetic Heterogeneity of Beta Thalassemia Mutations in Kahramanmaraş Province in Southern Turkey: Preliminary Report

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Abstract

Introduction: Beta thalassemia is one of the most common autosomal single-gene disorders in the world. The prevalence of the disease is in the "thalassemia belt" which includes the Mediterranean region of Turkey. Throughout the country, the gene frequency is estimated to be 2.1%, but in certain regions, it increases up to 10%.

Aim: In this first study, we aimed to determine the frequency of β-thalassemia trait and distribution of mutations in Kahramanmaraş province located in the southern part of Turkey.

Materials and methods: In this study, 5-ml blood samples were taken from 14 thalassemic patients and their relatives who were taking care of them in Sutcu Imam University Hospital at Kahramanmaraş. Also, we collected blood samples from 245 adults for screening beta thalassemia trait. Haematological data were obtained by cell counter. HbA_2 was determined by HPLC. Ten common mutations were screened by the amplification refractory mutation system (ARMS) method. These β-thalassemia mutations are: -30 (T>A), Fsc8 (-AA), Fsc8/9 (+G), IVS1-1 (G>A), IVS1-5 (G>C), IVS1-6 (T>C), IVS1-110 (G>A), Cd 39 (C>T), IVS2-1 (G>A), IVS 2-745 (C>G). A rare mutation, Fsc44 (-C) was characterized by DNA sequencing.

Results: Ten patients were identified as homozygous for IVS1-110 (seven cases), Fsc 44 (two cases) and IVS1-5 (only one case). The rest of the 4 patients were double heterozygous (two: IVS1-110/IVS1-6, one: Fsc8/Fsc8-9, one: IVS2-1/IVS1-5). In 245 adult, five β-thalassemia trait carriers were detected by screening survey.

Conclusions: Sixteen alleles were detected as IVS1-110 in 57.1%. It was seen as the most common mutation in Kahramanmaraş. Seven different β-thalassemia mutations were found in this study. Each of 10 families had only one thalassemic patient, other two families had double thalassemic patient, 12 families in total. Furthermore, we found that the incidence of β-thalassemia trait was 2.04% in the province of Kahramanmaraş in southern Turkey.

Keywords

β-thalassemia mutations, Fsc44 (-C), Kahramanmaraş

INTRODUCTION

β-thalassemia is an autosomal recessive disorder characterized by microcytosis and hemolytic anemia, which is a result of the reduced synthesis of the β-globin chains of hemoglobin. β-thalassemia major is the most clinically significant of the thalassemias and requires lifelong transfusion therapy that will result in iron overload and subsequent clinical problems unless iron chelation therapy is undertaken.[1] β-thalassemia is much more common in the Mediterranean, West Africa, and large parts of Asia.[2] Turkey is a big country located both on the European and Asian continents. Due to the presence of various ancient civilizations, there is great genetic diversity. Therefore, 20% of the β-thalassemia mutations (42 of 200) and 5% of abnormal hemoglobins (52 of 1000) reported worldwide have been detected in Turkey.[3-5] Incidence of β-thalassemia trait is given as 2%, but at some regions this ratio increase as high as 10%. IVSI-110 is the most common beta thalassemia mutation in Turkey, and IVSI-6, Fsc 8, IVSI-1, IVSII-745, IVSII-1, Cd39, -30 and Fsc5 mutations follow this.[6] Therefore, it is important to make a screening strategy to clearly establish the prevalence of the β-thalassemia trait in a region and to develop a hemoglobinopathy control program that includes genetic counseling.

Beta thalassemia is a common disease in the Mediterranean region in Turkey.[2] The provinces of Hatay, Adana, Mersin, and Kahramanmaraş are in the east Mediterranean region of Turkey. The center of Kahramanmaraş and its eleven districts have a population of 1,112,634 as of 2019. Although there were several population screenings for beta thalassemia trait there is no information on β-thalassemia mutations in Kahramanmaraş province.

AIM

This is the first study in which we aimed to investigate the genetic heterogeneity of β-thalassemia mutations in the province of Kahramanmaraş in the southern part of Turkey.

MATERIALS AND METHODS

The present study was undertaken with the objective to determine the frequencies of β-thalassemia mutations and their distribution in Kahramanmaraş province of Turkey. This study was approved by the Ethics Committee of Sutcu Imam University. We scanned 245 people randomly in Kahramanmaraş and the district, and also 14 thalassemic patients and their relatives who were taking care of them in Sutcu Imam University Hospital at Kahramanmaraş. Haematological data were obtained by a cell counter. HbA_2 level was determined by HPLC. Genomic DNA was isolated from leukocytes by DNA extraction kit (Bioneer *AccuPrep* Genomic Kit). Ten different mutations were screened by ARMS method.[7,8] These common β-thalassemia mutations are: -30 (T>A), Cd 8 (-AA), Cd 8/9 (+G), IVS 1-1 (G>A), IVS 1-5 (G>C), IVS 1-6 (T>C), IVS 1-110 (G>A), Cd 39 (C>T), IVS 2-1 (G>A), IVS 2-745 (C>G). The primer sequences of mutations are listed in **Table 1**. After DNA extraction, PCR was set up in two separate tubes for each sample - one test tube for the amplification of the normal ARMS primer and another one for the amplification of the mutant ARMS primer. 20 μL of final PCR reaction volume was used for this purpose. The reaction volume was composed of 0.5 μg of the DNA template, 0.01 μg of each of the four primers (2 control primers: 5'-CAA TGT ATC ATG CCT CTT TGC ACC -3' and 5'-GAG TCA AGG CTG AGA GAT GCA GGA -3', one common primer 5'-ACC TCA CCC TGT GGA GCC AC -3' or 5'-CCC CTT CCT ATG ACA TGA ACT TAA -3', and 1 mutant/normal ARMS primer for the normal/mutant allele), 0.5 unit Taq DNA polymerase, and 0.2 mM of each dNTP in a solution of 10 mM Tris-HC1, 50 mM $MgCl_2$, and 1 mM spermidine. The PCR cycling was set for 5 minutes initial denaturation at 94°C, followed by 25 cycles at 94°C for 30 seconds, 1 minute at 65°C, and 72°C for 1 minute 30 seconds, and the final extension at 72°C for 10 minutes. Fifteen microliters of the PCR products were mixed with 3 μL of a loading buffer and then loaded on a 2% agarose gel. The gel was set at 100 volts for 1 hour and then stained with ethidium bromide. After staining, the bands could be seen under UV light. A rare β-thalassemia mutation (Fsc44) was characterized by DNA sequencing. The PCR process with the forward primers 5'-CTTAGAGGTTCATTGAAT CACGGCTGT-CATCACTTAGAC-3' and reverse primer 5'-TATGACA-TATTTCGGATC GCCTCCCCTTCCTATGACATGA-3', one denaturing cycle at 96°C for 5 minutes followed by 35 cycles including denaturation at 94°C for 30 seconds, annealing at 62°C for 40 seconds and extension at 72°C for 20 seconds, final extension was at 72°C for 10 minutes. The PCR products were then run on a 2% agarose gel containing ethidium bromide, and visualized under UV light. The polymerase chain reaction products were purified using the QIAquick PCR Purification kit (Qiagen GmbH). The sequencing was performed using forward primer with BigDye Terminator v3.1 Loop Sequencing kit and an ABI PRISMVR 3130 Genetic Analyzer (Applied Biosystems).

RESULTS

Five of 245 samples in Kahramanmaraş province were identified as having the β-thalassemia trait. MCV in the most detected β-thalassemia carriers was less than 70 fl and their A2 level was more than 3.7%. Other blood cell indices such as Hb, MCH, and MCHC were lower than normal range in these people. These indices can be found in β-thalassemia carriers. The results of β-thalassemia traits are shown in **Table 2**.

Besides, we investigated β-thalassemia mutation in 14 thalassemic patients and their relatives. While 10 families

Table 1. The Amplification Refractory Mutation System (ARMS-PCR) primers

Mutations	Primer sequences, 5'→ 3'
IVS1-110 (G>A) 40M	CTG ATA GGC ACT GAC TCT CTC TGC CTG TTA
IVS1-110 (G>A) 41N	ACC AGC AGC CTA AGG GTG GGA AAA TAC ACC
IVS1-1 (G>A) 42M	TTA AAC CTG TCT TGT AAC CTT GAT ACG AAT
IVS1-1 (G>A) 43N	TTA AAC CTG TCT TGT AAC CTT GAT ACG AAC
CD 39 (C>T) 47M	CAG ATC CCC AAA GGA CTC AAA GAA CCT GTA
CD 39 (C>T) 52N	TTA GGC TGC TGG TGG TCT ACC CTT GGT CCC
IVS1-6 (C>T)	TCT CCT TAA ACC TGT CTT GTA ACC TTC ATG
IVS1-6 (C>T)	TCT CCT TAA ACC TGT CTT GTA ACC TTC ATA
FSC8 (-AA) 54M	ACA CCA TGG TGC ACC TGA CTC CTG AGC AGG
FSC8 (-AA) 70N	ACA CCA TGG TGC ACC TGA CTC CTG AGC AGA
-30 (T>A) 57M	GCA GGG AGG GCA GGA GCC AGG GCT GGG CAA
-30 (T>A) 58N	GCA GGG AGG GCA GGA GCC AGG GCT GGG CAT
IVS2-1 (G>A) 49M	AAG AAA ACA TCA AGG GTC CCA TAG ACT GAT
IVS2-1 (G>A) 77N	AAG AAA ACA TCA AGG GTC CCA TAG ACT GAC
IVS2-745 (C>G) 50M	TCA TAT TGC TAA TAG CAG CTA CAA TCG AGG
IVS2-745 (C>G) 56N	TCA TAT TGC TAA TAG CAG CTA CAA TCG AGC
IVS1-5(G>C) 88M	CTC CTT AAA CCT GTC TTG TAA CCT TGT TAG
IVS1-5(G>C) 89N	CTC CTT AAA CCT GTC TTG TAA CCT TGT TAC
FSC8/9 (+G) 90M	CCT TGC CCC ACA GGG CAG TAA CGG CAC ACC
FSC8/9 (+G) 91N	CCT TGC CCC ACA GGG CAG TAA CGG CAC ACT

M: mutant; N: normal

Table 2. Haematological data of five β-thalassemia trait samples from population screening

Sex-Age	Rbc (10^{12}/L)	Hb (g/dl)	Hct (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)	HbA_2 (%)	Hb F (%)	Hb Type	Mutations
F-33	5.4	10.6	29.2	53.9	19.5	36.2	3.8	0.2	AA	IVS1-110
F-31	5.3	11.9	35.6	67.6	22.6	33.4	4.7	0.8	AA	IVS1-6
M-35	5.8	12.5	39.3	68.0	22.0	31.9	5.0	1.6	AA	IVS1-110
F-30	5.2	9.9	30.6	58.0	19.0	32.4	3.8	0.5	AA	IVS1-110
F-33	5.3	10.1	33.3	62.0	19.0	30.4	3.9	0.7	AA	Fsc44

F: female; M: male

had only one thalassemic patient, two families had double thalassemic patient, 12 families in total. Our results showed that ten patients were identified as homozygous; seven IVS1-110 (G>A), two Fsc 44 (-C) and one IVS1-5 (G>C). The rest of the 4 patients were characterized as double heterozygotes. Two of the cases were IVS1-110/IVS1-6, another was Fsc8/Fsc8-9 and still another was IVS2-1/IVS1-5. The list of patient results is presented in **Table 3**. Furthermore, 16 chromosomes were detected as IVS1-110 in 14 patients (57.14%). IVS 1-110 (G>A) was seen as the most common mutation in Kahramanmaraş. Seven different β-thalassemia mutations were found in this study. The distribution of β-thalassemia mutations detected in the present study is presented in **Table 4**.

DISCUSSION

Thalassemias, especially β-thalassemia, are a common genetic disorder in our country. Although the average rate of β-thalassemia trait is 2.1% in overall Turkey, this rate is up to 10% in the Mediterranean region and its surrounding areas.[3,4] The treatment to sustain life in thalassemia major is necessary regular blood transfusion with iron chelation but this requires much commitment on part of the family.[9] The treatment is also hampered by less of blood resources available and lack of motivated voluntary donors. The only cure for affected children is bone marrow transplantation whose management involves major financial inputs, there-

Table 3. Combination of β-thalassemia mutations for thalassemic patients

Case number	One of the alleles	The other allel
1	Fsc 44	Fsc 44
2	IVS 1-110	IVS 1-110
3	Fsc 8	Fsc 8/9
4	IVS 1-110	IVS1-6
5	IVS 1-110	IVS1-6
6	IVS 1-110	IVS 1-110
7	IVS 1-110	IVS 1-110
8	IVS II-I	IVS1-5
9	IVS 1-110	IVS 1-110
10	IVS1-5	IVS1-5
11	IVS 1-110	IVS 1-110
12	Fsc 44	Fsc 44
13	IVS 1-110	IVS 1-110
14	IVS 1-110	IVS 1-110

Table 4. Distribution of beta-thalassemia mutations in Kahramanmaraş

β globin gene mutations	Chromosome number	%
IVS 1-110 (G>A)	16	57.14
IVS II-I (G>A)	1	3.57
Fsc 44 (-C)	4	14.28
Fsc 8 (-AA)	1	3.57
IVS 1-5 (G>C)	3	10.71
IVS 1-6 (T>C)	2	7.14
Fsc 8/9 (+G)	1	3.57
Total	28	100

fore prevention is a priority. This is possible by targeted carrier detection, genetic counseling and prenatal diagnosis.

An increase in the incidence of β-thalassemia is noted in the following regions: Mediterranean countries (e.g. Italy, Turkey, Greece, and Malta), the Middle East region (including Iran, Iraq, Syria, Jordan, Palestine), and North African countries (including Egypt, Tunisia, Algeria, Morocco and some African countries).[10] In Cyprus, the estimated β-thalassemia carrier rate is around 12%–15% of the population.[11] The most common β-globin gene mutation is IVS1-110 (G>A), with a percentage of 74%–80%, followed by three other alleles, specifically IVS-2- 745 (C>G), IVS-1-6 (T>C), IVS-1-1 (G>A), with frequencies of 5%–8%.[12] Greece is a country of approximately 11 million people with a mean frequency of β-thalassemia carriers of 7.4%.[13] The molecular basis of β-thalassemia is very heterogeneous in Greece, and up to 30 β-thalassemia mutations have been observed. The molecular characterization of β-thalassemia was evaluated in three studies on 857 thalassemia patients (106 with thalassemia intermedia covering more than 25% of the 3241 patients with thalassemia major and thalassemia intermedia) registered in 2010.[14] The standard definition of the Arab world includes the 22 states and territories from the Atlantic Ocean in the west to the Arabian Sea in the east, and from the Mediterranean Sea in the north to the Horn of Africa and the Indian Ocean in the southeast. It has a combined population of around 350 million people, one-third of whom are under 15 years of age. β-thalassemia is encountered in polymorphic frequencies in almost all Arab countries with carrier rates ranging from 1 to 11%.[15] Among Arabs, the heterogeneity of these mutations varies from 44 different mutations in UAE to 10 in Eastern Saudi Arabia. The most widespread and common mutation among Arabs is IVS-1-110 (G>A). The latter mutation has its highest prevalence in Cyprus and Greece suggesting that it may be of Greek origin. In the Eastern Arabian Peninsula, the Asian Indian mutations (IVS-1-5 (G>C), codons 8/9 (+G) and IVS-1 (–25 bp del) are more common.[15] Furthermore, El-Hashemite et al. reported that of 1.5 million annual live births, approximately 1000 babies are born with β-thalassemia major. The most common mutations in Egyptian children with β-thalassemia are IVS-1-110 (G>A) - 48%, IVS-1-6 (T>C) - 40%, IVS-1-1 (G>A) - 24%, IVS-1-5 (G>C) - 10%, IVS-2-848 (C>A) - 9%, IVS-2-745 (C>G) - 8%, and IVS-2-1 (G>A) - 7%.[16] In the eastern Mediterranean region, Iran is one of the major centres for the prevalence of β-thalassemia. Due to the high consanguinity in the population, it is estimated that there are more than three million β-thalassemia carriers (4%-8%) and 20000 patients. In Jordan, published statistics indicate that there are 1500 major cases and about 150 000 to 200 000 carriers of the disease. Studies have shown that between 5% and 6% of the Lebanese people are carriers of thalassemia minor.[17] The number of affected people in Kuwait is 250-300 patients.[17] High prevalence of β-thalassemia trait in Iraq has been reported.[18-21] The Emirates, Palestine and Bahrain studies are compatible with the pooled prevalence.[22-25] The highest prevalence value of this study was reported by Pakistan.[26] As a general conclusion, Pakistan[26,27] and Iraq[22-25] have a higher prevalence of β-thalassemia trait values according to their premarital screening results.

In Turkey, the distribution of β-thalassemia alleles displays a decreasing gradient of mutational heterogeneity from East to West Anatolia. Some authors report that 16 different cities in the Marmara, Aegean, and the Mediterranean region between 1995 and 2000, 380 000 healthy subjects were screened.[28] The 16 endemic cities are Adana, Antakya, Antalya, Aydin, Bursa, Denizli, Diyarbakir, Edirne, Isparta, Istanbul, Izmir, Kahramanmaraş, Kirklareli, Mersin, Mugla, and Urfa. Average prevalence of β-thalassemia trait was 4.3%. The highest prevalence of β-thalassemia was reported in the West Mediterranean and in the East Mediterranean, with a frequency of 13.1%.

We conducted the first molecular study in Kahramanmaraş province which is in the East Mediterranean region of Turkey. In our study, we scanned randomly 245 people (5 of 245 samples were identified as having the β-thalassemia trait), and found the incidence of β-thalassemia trait to be 2.04% in Kahramanmaraş. Also, in our study, 7 different mutations were detected, the most frequent being IVS1-110 (G>A) - 57.14%. Other mutations that were encountered include Fsc 44 (-C), IVS1-5 (G>C), IVS2-1 (G>A), IVS1-6 (C>T), Fsc 8 (-AA), and Fsc 8/9 (+G). These 6 mutations made up 42.86% of all detected mutations. In our study, IVS1-110 (G>A) mutation was identified in 57.14% which appears to be related to consanguineous marriages in Kahramanmaraş province. Also, there is one heterozygous person carrying this mutation in our screening study. This mutation is very common in Kahramanmaraş. In addition, the first screening studies in Kahramanmaraş were initiated by Yuregir et al. in 2001.[29] They scanned 1491 persons at random, and the incidence of β-thalassemia trait was found to be 0.93% in Kahramanmaraş. The other group made premarital screening of 1109 people in Kahramanmaraş -Elbistan in 2003 and they found the incidence of β-thalassemia to be 0.90%.[30] Kahramanmaraş Health Authorities organized premarital screening center, 48126 people were scanned between January 2006 and January 2009, the prevalence of β-thalassemia and sickle cell anemia was 2.8% and 0.4%, respectively.[31] After these comprehensive studies, premarital screening tests were made compulsory for all couples to marry by the government in Kahramanmaraş. Some research reported the results of prenatal diagnosis of sickle cell and β-thalassemia in Adana.[32,33] They found that 57.3% of the IVS1-110 mutation incidence was due to parents carrying β-thalassemia specificity. Fsc 44 was reported by Rund et al. to be a frequent mutation (31.2%) in the Jews of Kurdish in North Iraq.[34] Our study showed the second frequency for Fsc44 (14.28%) in Kahramanmaraş province. These results confirm that β-thalassemia mutations are highly heterogeneous, attributed to the ethnic characteristics in different parts of Turkey. This is the first study to determine the frequencies of β-thalassemia mutations in the city of Kahramanmaraş. When a patient is born with β-thalassemia, there is no effective treatment option except bone marrow transplantation. Therefore, the best method for dealing with β-thalassemia is prenatal diagnosis. In the current study, six families who carry the β-globin gene mutation were given genetic consultation for prenatal diagnosis based on DNA analysis.

CONCLUSIONS

After we have identified the mutations in β-thalassemia patients living in the city of Kahramanmaraş, the number of cases of prenatal diagnosis will promptly increase. Therefore, this will provide important benefits to the population health and the national economy as well.

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Conflicts of interest

There are no conflicts of interest.

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Генетическая гетерогенность мутаций бета-талассемии в провинции Кахраманмараш в южной Турции: предварительный отчёт

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Резюме

Введение: Бета-талассемия – одно из наиболее распространённых аутосомных моногенных заболеваний в мире. Заболевание преобладает в т.н. «Поясе талассемии», который включает Средиземноморский регион Турции. По стране генетическая частота составляет 2.1%, но в некоторых регионах она увеличивается до 10%.

Цель: В этом исследовании нашей целью было определить заболеваемость β-талассемией и распространённость мутаций в провинции Кахраманмараш, расположенной на юге Турции.

Материалы и методы: Для исследования было взято 5 мл. кровь от 14 пациентов с талассемией и их родственников, которые заботились о них в университетской больнице Сутчу Имам, Кахраманмараш. Мы также взяли образцы крови у 245 взрослых для скрининга на бета-талассемию. Гематологические данные получали путем подсчёта клеток. HbA_2 измеряли с помощью высокоэффективных жидкостных хроматографических колонок (ВЭЖХ). Десять распространённых мутаций были проверены системой amplification refractory mutation system (ARMS). Эти мутации β-талассемии: 30 (T>A), Fsc8 (-AA), Fsc8/9 (+ G), IVS1-1 (G>A), IVS1-5 (G>C), IVS1-6 (T>C), IVS1-110 (G>A), Cd 39 (C>T), IVS2-1 (G>A), IVS 2-745 (C>G). Редкая мутация Fsc44 (-C) была определена путем секвенирования ДНК.

Результаты: Десять пациентов были идентифицированы как гомозиготные по IVS1-110 (семь случаев), Fsc 44 (два случая) и IVS1-5 (только один случай). Остальные 4 пациента были дважды гетерозиготными. (два: IVS1-110/IVS1-6, один: Fsc8/Fsc8-9, один: IVS2-1/IVS1-5). Путём скрининга у 2456 взрослых было выявлено пять носителей характерной черты β-талассемии.

Заключение: Для IVS1-110 обнаружено шестнадцать аллелей у 57.1%. Это считается самой распространённой мутацией в Кахраманмараше. В этом исследовании было идентифицировано семь различных мутаций β-талассемии. В каждой из 10 семей был только один пациент с талассемией, в двух других семьях был пациент с двойной мутацией талассемии, всего 12 семей. Кроме того, мы обнаружили, что заболеваемость β-талассемией составила 2.04% в провинции Кахраманмараш, расположенной на юге Турции.

Ключевые слова

мутации β-талассемии, Fsc44 (-C), Кахраманмараш