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Spectrum of Alpha-Thalassemia Mutations According to Immigration, Ethnicity in Bursa, Turkey and First Observing of SEA Double Gene Deletion

Bursa; Türkiye'de Göç, Etnik Kökene Göre Alfa-Talasemi Mutasyonlarının Spektrumu ve SEA Çift Gen Delesyonunun İlk Kez Gözlemlenmesi

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Abstract

Aim: Thalassemia syndromes are common in the Mediterranean region, including Turkey. Our aim is to investigate the genetic mutation diversity of alpha thalassemia cases in Bursa and to investigate the mutation diversity in relation to the cases' immigration status and ethnic origins.

Materials and Methods: Retrospective analysis was performed on 66 cases aged 1-18 years who were diagnosed as alpha thalassemia carriers by genetic mutation analysis. The patients' complete blood count, ferritin levels, hemoglobin electrophoresis, genetic mutations, immigration status, origin, whether they received iron therapy prior to the diagnosis were all evaluated.

Results: Of the 66 cases, 53% were female and 47% were male. The most common genetic mutation was the 3.7% deletion with a rate of 51.5%, followed by the heterozygous mutation with a deletion of 20.5 with a rate of 21.20%. SEA double gene deletion homozygous mutation 1.5% and, heterozygous mutation 1.5%. Eleven different genotypes of alpha thalassemia were discovered. While 3.7 deletion heterozygous mutation was most common in cases immigrating from Bulgaria, Syria, and Azerbaijan, FIL deletion mutation was most common in cases immigrating from Georgia, and alpha-2 polyA-2 heterozygous mutation was found in one case immigrating from Greece.

Conclusion: The most common mutation was 3.7 deletion and SEA double gene deletion was discovered, which had not been discovered in previous studies. With this study, we added to the literature the genetic mutation diversity in Bursa, which sees a lot of immigration

Keywords: SEA double gene deletion mutation; alpha thalassemia; immigration, ethnicity; Bursa; Turkey.

Öz

Amaç: Talasemi sendromları Türkiye'nin de dahil olduğu Akdeniz bölgesinde yaygındır. Amacımız Bursa'daki alfa talasemi olgularının genetik mutasyon çeşitliliğini araştırmak ve mutasyon çeşitliliğini vakaların göç durumu ve etnik kökenleri ile ilişkisini araştırmaktır.

Gereç ve yöntem: Genetik mutasyon analizi ile alfa talasemi taşıyıcısı tanısı alan 1-18 yaş arası 66 olgunun retrospektif analizi yapıldı. Hastaların tam kan sayımı, ferritin düzeyleri, hemoglobin elektroforezi, genetik mutasyonları, göç durumları, kökenleri, tanı öncesinde demir tedavisi alıp almadıkları değerlendirildi.

Bulgular: Çalışmaya alınan 66 olgunun %53'ü kadın, %47'si erkekti. En sık görülen genetik mutasyon %51,5 oranıyla %3,7 delesyon olurken, bunu %21,20 oranıyla 20,5 delesyon ile heterozigot mutasyon izledi. SEA çift gen delesyonu homozigot mutasyonu %1,5 ve heterozigot mutasyonu %1,5. Alfa talaseminin 11 farklı genotipi keşfedildi. Bulgaristan, Suriye ve Azerbaycan'dan göç eden olgularda en sık 3.7 delesyon heterozigot mutasyonu görülürken, Gürcistan'dan göç eden olgularda en sık FIL delesyon mutasyonu görüldü ve Yunanistan'dan göç eden bir olguda ise alfa-2 polyA-2 heterozigot mutasyonu saptandı.

Sonuç: En sık görülen mutasyon 3.7 delesyon olmuş ve daha önceki çalışmalarda keşfedilmemiş olan SEA çift gen delesyonu keşfedilmiştir. Bu çalışmayla yoğun göç alan Bursa'da genetik mutasyon çeşitliliğini literatüre kazandırdık.

Anahtar Kelimeler: SEA çift gen delesyon mutasyonu; alfa talasemi; göç; etnik köken; Bursa; Türkiye.

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INTRODUCTION

Thalassemias are hemoglobinopathies that occur of reduced or no roduction of the Hb

Thalassemias are hemoglobinopathies that occur as a result of reduced or no production of the Hb chain or chains called alpha (α), beta (β), gamma (γ), delta (δ) (1). The alpha globin gene, has a tetramer structure, is located on the short arm of the 16th chromosome and is called the 'alpha globin gene cluster' (2). Mutations on this gene cluster cause alpha thalassemia syndromes. There are four genes (αα/αα) controlling the synthesis of alpha globin, 12 of which are in homologous chromosomes. Mutations and or deletions in these genes reveal the disease clinic. While silent carriers are asymptomatic, alpha thalassemia intermedia and HbH diseases cause hemolytic anemia. Alpha thalassemia major, known as Hb Barts, usually results in fatal hydrops fetalis (3-5). Today, with the developments in genetics, it is possible to identify alpha thalassemia mutations and genetic diagnosis. In this way, it can be used for cases where genetic counseling is required.

According to research, the prevalence of alpha thalassemia carriers is 60% in the Middle East, 5-40% in Africa, 5-15% in the Mediterranean Region, and 5-15% in the Far East (3). The incidence of alpha thalassemia carriage was found to be 0.25-4.1% in multicenter studies conducted by various researchers in various centers throughout our country (6-10). Several single-center studies in southern Turkey, however, have found that the prevalence of alpha thalassemia ranges between 2.5% and 7.5% (11-16).

The aim of our study is to determine the genetic mutation diversity of the cases whose alpha thalassemia is considered and whose diagnosis is confirmed by genetics, to contribute to a prospective database throughout our country, and to evaluate the mutation diversity according to the immigration status and the migrated region in the city of Bursa, which receives a lot of immigration.

MATERIALS and METHODS

Sixty-six cases, aged 1-18 years, diagnosed with alpha thalassemia carrier and confirmed by genetic mutation analysis, who applied to the Pediatric Hematology Department in Bursa between January 1, 2015 and December 01, 2021 were included in the study. Approval for the study was obtained from the Clinical Studies Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital, with the protocol number 2011-KAEK-25 2021/12-10 on 06.05.2022. A retrospective descriptive study was conducted.

Patients were reviewed retrospectively. Complete blood count of the cases, ferritin levels, hemoglobin electrophoresis, genetic mutations were examined, the patients' immigration status, ethnic origin, whether they received iron therapy before the diagnosis of thalassemia carrier, how long they received iron therapy, parental consanguinity status, family history of alpha thalassemia carrier.

The age of diagnosis was learned by interviewing the families face-to-face and by phone.

For complete blood count, approximately 1 cc blood sample was taken from the patients in an EDTA tube and measured using a Beckman Coulter brand LH 780 model device. In the complete blood count of the patients; Hemoglobin (Hb), erythrocyte count (RBC), mean erythrocyte volume (MCV), erythrocyte distribution width (RDW), platelet count (PLT), leukocyte count (WBC), Mentzer index (MCV/RBC) values were used in the study. Anemia was diagnosed according to age and gender. Hemoglobin electrophoresis was studied in Aqilent brand 1100 model device by HPLC method. The MLPA method, which is based on the detection of copy number changes in target regions, was used to detect deletion type mutations (17). In this method, the probes are hybridized with DNA fragments related to alpha thalassemia. Probes hybridized with DNA are covalently linked to each other and amplified by Polymerase Chain Reaction (PCR). The amount of amplification is proportional to the number of copies in the target gene. In this way, a decrease in the signal of hybridized probes in the deletion regions and an increase in the probe signals in the duplication regions are observed (18). The genetic analysis of the cases in our study was carried out using the device named SALSA MLPA Probemix P140 HBA, which belongs to the brand of MRC Holland. An in vitro diagnostic or research-only semi-quantitative test was performed to detect deletions or duplications in the alpha-globin (HBA) gene cluster and its regulatory region in genomic DNA by means of this device. The P140 HBA is designed to confirm a potential cause and clinical diagnosis of alpha-thalassemia for molecular genetic testing of at-risk family

members and carrier screening in at-risk populations. Samples were isolated from human peripheral whole blood samples.

Statistical analyses

Demographic, clinical and genetic characteristics of alpha thalassemia cases were evaluated with descriptive statistical analyzes such as number, percentage, mean, standard deviation, median, minimum and maximum. The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test.

Continuous variables using mean ± standard deviation or median (minimum: maximum) values; categorical variables were expressed as n (%).

Analyzes were performed using SPSS (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

RESULTS

Of the 66 cases included in the study, 53% were female and 47% male. 60.6% of the cases were Turkish, 15.2% Arab, 12.10% Kurdish, 6.1% Azeri, 4.5% Georgian and 1.5% Circassian ethnicity. 36.4% of the cases were immigrants, 37.5% of them were from Bulgaria, 29.2% from Syria, 16.7% from Azerbaijan, 12.5% from Georgia and 4.2% from Greece. Table 1 shows the mean values of the current age, age at diagnosis and laboratory measurements of the participants in the study.

Table 1. Descriptive statistics for current age, age at diagnosis, and laboratory measurements

n= 66	Descriptive statistics
Current Age	8.60±5.02
Age of diagnosis	6.01±4.83
Hemoglobin (g/dl)	10.69±1.48
MCV (fL)	62.89±6.79
RBC (x1012/L)	6.01±4.83
RDW	11.94±2.45
Mentzer Index	18.10±5.52
WBC (x109/L)	8551±2750
PLT (x109/L)	389310±136320
Ferritin (ng/ml)	43.90±129.70

*Data are expressed as median mean±max. deviation. (MCV: mean corpuscular volume, RBC:red blood cell, RDW:red cell distribution width, WBC:white blood cell, PLT:platelet).

Hemoglobin electrophoresis results of all participants were within normal limits. The rate of patients who were given iron therapy before diagnosis was 75.80% and the rate of those who were not given iron therapy was 24.20%. While the rate of cases who did not need transfusion before diagnosis was 98.50%, the rate of cases who needed transfusion was determined as 1.50%. In the genetic mutation analysis of the case who needed blood transfusion, Alpha-2 PolyA-1 heterozygous mutation and Alpha-1 cd 59G>A heterozygous mutation were found together. The median value calculated for the duration of iron treatment was determined as 6 months (minimum:1- maximum:60 months).

Among the patients included in the study, the rate of those whose parents were related was 21.20%. The rate of those with alpha thalassemia in siblings is 34.80%, those with both siblings and mothers are 4.5%, those with cousins 4.50%, mothers with 3%, those with fathers 1.5%, those with both fathers and uncles 1.5%, those with both uncles 1.5%, those with an uncle 1.5%, and those with an uncle 1.5%, and the rate of cases without a family member with a genetic diagnosis of alpha thalassemia was 47%.

When the distribution of genetic mutations of the cases is examined, the rate of those with 3.7 deletion heterozygous mutation is 51.5%, 20.5 deletion heterozygous mutation 21.2%, 3.7 deletion homozygous mutation 7.6%, med deletion heterozygous mutation 6.1%, alpha-2 polyA-1 heterozygous mutation 4.5%, FIL deletion heterozygous mutation 3%, alpha-1 cd 59 G>A heterozygous mutation 1.5%, alpha-2 polyA-2 heterozygous mutation 1.5%, 4,2 deletion heterozygous mutation was determined as 1.5%, SEA double gene deletion heterozygous mutation was determined as 1.5% and SEA double gene deletion homozygous mutation was determined as 1.5%. 90.9% of the cases had heterozygous genetic mutation and 9.1% had homozygous genetic mutation. There is no individual with alpha thalassemia genetic mutation in the family of those with homozygous genetic mutations (Table 2).

When Table 2 is examined, the rate of nine cases with a history of immigration from

Bulgaria with 20.5 deletion heterozygous mutations was 11.1%, 3.7 deletion heterozygous mutation 44.4%, alpha-2 polyA-1 heterozygous mutation 22.2%, med deletion heterozygous mutation was determined as 11.1% and SEA double gene deletion heterozygous mutation was determined as 11.1%. While the rate of those with 3.7 deletion heterozygous mutation in seven cases with a history of migration from Syria is 85.7%, the rate of those with alpha-1 cd 59 G>A heterozygous mutation was 7.15% and alpha-2 polyA-1 heterozygous mutation was 7.15%. In four cases with a history of immigration from Azerbaijan, the rate of those with 20.5 deletion heterozygous mutations was 25%, while the rate of those with a 3.7 deletion heterozygous mutation was 75%. In three cases with a history of immigration from Georgia, the rate of those with FIL deletion mutation was 66.7%, while the rate of those with med deletion heterozygous mutation was determined as 33.3%. In one case who migrated from Greece had alpha-2 polyA-2 heterozygous mutation. Table 3 shows genetic mutation analysis by ethnicity.

DISCUSSION

Alpha thalassemia is fairly common in the Mediterranean basin, the Middle East, and tropical Africa, all of which are geographically close to Turkey. However, increased migration in recent returns has resulted in an increase in the incidence of thalassemia in these regions, making it a major global public health problem. Bursa is a city in western Turkey that sees a lot of immigration. As a result, prenatal diagnosis is critical for public health in terms of identifying and examining common genetic mutations in alpha thalassemia carriers and preventing hydrops fetalis caused by intrauterine fatal Bart's hemoglobinopathy.

Table 2. Mutation analysis by region of migration [n (%)]

Genetic Mutations	Bulgaria (n=9)	Syria (n=7)	Azerbaijan (n=4)	Georgia (n=3)	Greece (n=1)
Deletion 20.5 Heterozygous	1 (11.1%)	0 (0%)	1 (25%)	0(0%)	0 (0%)
Deletion 3.7 Heterozygous	4 (44.4%)	6 (85.%7)	3 (75%)	0 (0%)	0 (0%)
Alfa-1cd59G>AHeterozygous	0 (0%)	1 (7.15%)	0 (0%)	0 (0%)	0 (0%)
Alfa-2 PolyA-1 Heterozygous	2 (22.2%)	1 (7.15%)	0 (0%)	0 (0%)	0 (0%)
Alfa-2 PolyA-2 Heterozygous	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Fil Deletion Heterozygous	0 (0%)	0 (0%)	0 (0%)	2 (66.7%)	0 (0%)
Med Deletion Heterozygous	1 (11.1%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)

Table 3. Mutation analyzes by ethnicity (n (%)

Genetic Mutations	Turkish (n=40)	Arabic (n=10)	Kurdish (n=8)	Azerbaijan (n=4)	Georgian (n=3)	Circassian (n=1)
20.5 Deletion Heterozygous	12 (30%)	0 (0%)	1 (12.5%)	1 (25%)	0 (0%)	0 (0%)
3.7 Deletion Heterozygous	20 (50%)	9 (90%)	2 (25%)	3 (75%)	0 (0%)	0 (0%)
3.7 Deletion Heterozygous	1 (2.50%)	0 (0%)	3 (37.5%)	0 (0%)	0 (0%)	1 (100%)
4.2 Deletion Heterozygous	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Alpha-1cd59G>A Heterozygous	0 (0%)	1 (10%)*	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alpha-2 PolyA-1 Heterozygous	2 (5%)	1 (10%)*	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alpha-2 PolyA-2 Heterozygous	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fil Deletion Heterozygous	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (66.7%)	0 (0%)
Med Deletion Heterozygous	3 (7.5%)	0 (0%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)
Sea Double Gen Deletion Heterozygous	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sea Double Gen Deletion Heterozygous	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)

*alpha-1 cd 59 G>A heterozygous and alpha-2 polyA-2 heterozygous mutation was found in the same case of Arab origin and its rate was determined as 10%.

Altay et al. discovered 42 abnormal hemoglobin in the Turkish population (19,20). The rate of HbH hemoglobinopathy was reported to be 3.6% (19, 20). Canatan et al. discovered that 17.5% of patients had HbH disease (21). In studies conducted by various researchers in various centers throughout our country, the incidence of alpha thalassemia carrier was found to be 0.25-4.1% (7-10). Several single-center studies in southern Turkey, however, have found that the prevalence of alpha thalassemia carriers ranges between 2.5%-7.5% (11-16).

There was no significant difference between male and female ratios in our study and the other two studies conducted with patients with alpha thalassemia mutations in our country (22,23). The autosomal recessive inheritance of the disease can be attributed to the lack of a significant gender difference. The mean age at the time of diagnosis of the cases participating in our study was determined as (6.01±4.83) years. When we scanned studies on alpha thalassemia in our country, the age at first diagnosis was reported as 9 months-5 years, 1.5-50 years, and 1-46 years (22-24). The cases in our study consisted of more pediatric age compared to other studies.

The mean value of RBC levels in our study was found to be higher than the upper limit of the laboratory reference range of 5x1012/L, consistent with thalassemia syndromes. Mentzer indices calculated for the cases in our study had a mean value of 11.94 ±2.45, which was found to be consistent with thalassemia syndromes (25). The mean RDW value and ferritin in our study was found to be at the upper limit of the laboratory reference. This was attributed to some of the individuals diagnosed with alpha thalassemia having concurrent iron deficiency at the time of diagnosis. Prior to diagnosis, 75.80% of our cases received iron

treatment (minimum 1 month-maximum 60 months, median six months).

All of the Hb electrophoresis findings in our study were within the normal range. Hemoglobin electrophoresis results from HbH patients in different centers in our country were found to be normal, supporting the data in our study (22,24).

In our study, we discovered that 21.20% of the cases had a close or distant consanguinity between their parents. In other publications dealing with alpha thalassemia cases in our country, we did not find any evaluation based on kinship. This is significant because individuals with alpha thalassemia genetic mutations may have symptomatic alpha thalassemia syndrome in their children, even if they have asymptomatic silent alpha thalassemia carriers and marry a silent alpha thalassemia carrier relative. In 53.7% of the cases in our study, there was a relative known to have a genetic mutation in terms of alpha thalassemia. In any study conducted with alpha thalassemia cases in our country, no information was found regarding the investigation and investigation of genetic mutations in relatives.

90.90% of the cases in our study were heterozygous and 9.10% had homozygous genetic mutations. Transfusion need developed before diagnosis in only one of 66 cases in our study. In the genetic mutation analysis of this patient, Alpha-2 PolyA-1 heterozygous mutation and Alpha-1 cd 59 G>A heterozygous mutation were found together. In a study conducted with HbH patients in Turkey, it was reported that patients who required blood transfusion were in the series with genetically homozygous mutations (26). Our findings also supported that the symptomatic severity of alpha thalassemia case increased as the number of mutated alleles from the four gene alleles involved in alpha chain synthesis increased, as in this study.

The most common mutations in our study were the 3.7% deletion heterozygous mutation with 51.50% and the 20.5 deletion heterozygous mutation with 21.20%. Deletion mutations were found in 94% of cases and non-deletion mutations in 6% of cases. Karakaş et al. found 69.3% deletion mutations and 30.6% non-deletion mutations, Sütçü et al. found 100% deletion mutations, Çelik et al. found 81.8% deletion mutations and 18.2% non-deletion mutations (15,23,27). We detected 11 different genetic mutations in the alpha thalassemia gene in our study. In studies conducted in different regions of Turkey, 14 different alpha thalassemia gene mutations were detected (22,24,26-29).

Çelik et al. found that the most common mutation in Antakya-Hatay was –α 3.7 with a rate of 57.3%, of which 43.81% was the -α 3.7 deletions (27). Ünal et al. found the most common mutation to be -α3.7 with a rate of 62.8%, and the most common genotype was found to be –α3.7/αα with a rate of 39.7% (22). Karakaş et al. found that the most common mutation was -α3.7 single gene deletion mutation in 39% of the cases (23). The most common mutation in the vicinity of Adana by Güvenç et al. was -α3.7 single gene deletion with a rate of 53.33% (28). Öner et al. reported that -a (3.7) kb deletion was the most common with a rate of 56% (26). Çürük et al. found 3.7 deletions with a rate of 29.6% in the Çukurova region and reported the flour as the most common mutation (29). However, in the study conducted by Sütçü et al. in the Isparta region, different from other studies conducted in our country, MED double gene deletion (heterozygous mutation) was detected in 5 of 9 children with alpha thalassemia genetic mutation. -3.7 single gene deletions was the third most common mutation in this study (15). In our study, 3.7 deletions were found in the heterozygous form (3.7 single gene deletions) in 34 cases (51.50%), and it was the most common mutation in our study. In our study, 3.7 deletions was found in homozygous form in 5 cases (7.60%), and the overall rate of 3.7 deletion was 59%. Our results were similar with other reports from our country.

Ünal et al. discovered the 20.5 deletion as the second most common allele, with a rate of 51.4% (24). Other studies found that the second most common mutations were -20.5 deletions, -20.5 kb single gene deletion, 20.5 kb double gene deletion, and 20.5 gene deletions (15,23,26-29). The 20.5 deletion was found to be the second most common mutation among alpha thalassemia mutations in our study, which is consistent with many other studies in our country. Karakas et al. study, as well as two other studies, identified MED double gene deletion as the third most common alpha thalassemia mutation (23,26, 29). It was reported as the second most common mutation in Güvenc et al. and as the most common mutation in Sütcü et al. (15,28). In our study,

MED double gene deletion was the third most common deletion alpha thalassemia mutation, and similar results were obtained in terms of mutation frequency with other studies conducted in our country.

α2 polyA-1 is a non-deletion mutation, also known as AATAAA>AATAAG (Saudi type). It was found in three cases (4.5%) in our study and was the most common non deletion mutation. In studies conducted in different regions, this mutation was found with a frequency of 4.7%, 3.7%, 0.7%, and 0.5% (27, 21, 25, 26). In other studies conducted in our country with cases with alpha thalassemia mutation, it was reported that α2 polyA-1 mutation was not found.

FIL deletion was found in two cases in our study, with a frequency of 3%. Only two studies in our country found FIL deletion rates of 0.5% and 1% (23,27). The fact that we encountered this mutation, which is extremely rare in our country, in our study in Bursa can be explained by the fact that Bursa is a city that receives immigrants from all over the world. In our study, one (1.5%) patient had α1 cd 59 G>A heterozygous mutation. In the literature, this non-deletion mutation is referred to as Hb Adana. Its frequency was found to be 0.5%, 5.1%, 6.2% and in studies conducted in our country (23,24,29). The α2 polyA-2 non deletion mutation is known as AATAAA>AATGAA (Turkish type). In our study, we found this mutation in one (1.5%) case. Its frequency was found to be 10%, 7.8%, 2.5%, 2%, and 0.5% in different studies conducted in our country (23,26-29). In our study, we discovered 4.2 deletion mutations in one case, which was heterozygous, with a 1.5% frequency. Other studies in our country found its frequency to be 12%, 2.1%, 1.6%, 0.6%, and 0.5% (23,26,27-29). We discovered homozygous SEA double gene deletion in one case and heterozygous SEA double gene deletion in one case in our study, and the rate of this deletion among the mutations we discovered in our study was 3%. We found no other studies on alpha thalassemia in Turkey that showed SEA double gene deletion.

Unlike previous studies in our country, we evaluated the mutations of the cases based on the region they migrated to and their self-declared races in our study. The most common mutation was discovered 3.7 deletions heterozygous mutation in cases originating from Bulgaria, Syria, and Azerbaijan however FIL deletion mutation in cases from Georgia. We discovered SEA double gene deletion, which had not previously been discovered in Turkish studies, in one Bulgaria immigrant. There were no studies with alpha thalassemia carriers in Bulgaria, Georgia, or Syria that we could find. The genotyping of alpha thalassemia carriers in Azerbaijan revealed 9 different mutations. The most common mutation was discovered to be 20.5 gene deletions, followed by 3.7 gene deletions in the Azerbaijani population (30).

CONCLUSION

We conducted with alpha thalassemia patients in Bursa, is one of the most comprehensive genetic mutation analyses in Turkey. Due to ethnic heterogeneity caused by migrations, the diversity of alpha thalassemia mutations has increased. Individuals with alpha thalassemia mutations can be identified in advance and severe forms of the disease can be avoided by providing genetic counseling, emphasizing the importance of these studies in our society where thalassemia is common. The determination of mutational diversity may contribute to the establishment of a national database for Hb variants that we may encounter.

Author's Contribution

The authors declare no conflict of interest.

The authors disclose that no grants or support resources were used.

All authors declared their contribution to the study at all stages and approved the final version of the manuscript.

All authors declared that this manuscript has not been published before and is not currently being considered for publication elsewhere.

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