

## Prevalence of $\beta$ -Thalassemia Trait in Kutahya: A City in the Eastern part of Aegean Region in Turkey

Sayit Altikat<sup>\*1</sup>, Halil İsa Kuru<sup>2</sup>, Rümeysa Günay<sup>3</sup>, Kamil Türkmen<sup>4</sup>, Murat Seyit<sup>5</sup>

<sup>1</sup>Dumlupınar University, Medical Faculty, Biochemistry Department, Kutahya, Turkey, 43010

<sup>2</sup>Dumlupınar University, Simav Vocational High School, Kutahya, Turkey, 43010

<sup>3</sup>Health Directorship of Kutahya, Hemoglobinopathy Screening Center, Kutahya, Turkey, 43010

<sup>4</sup>Health Directorship of Kutahya, Director, Kutahya, Turkey, 43010

<sup>5</sup>Evliya Çelebi Training and Research Hospital, Emergency Department, Kutahya, Turkey, 43010

### \*Corresponding author

Sayit Altikat

Email: [saitaltikat@hotmail.com](mailto:saitaltikat@hotmail.com)

**Abstract:** The aim of present study was to report the frequency of  $\beta$ -Thalassemia trait and other hemoglobinopathies in Kutahya province, which is located in the eastern part of Aegean Region in Turkey, as part of the premarital screening program. To determine the prevalence of carriers for  $\beta$ -thalassemia, we screened patients sent on suspicion thalassemia by doctors and the premarital couples in 2008, 2009 and 2010. Haemoglobin variant analysis was performed with high-performance liquid chromatography (HPLC) technique. The subjects with HbA<sub>2</sub> >3.5 were accepted as  $\beta$ -thalassemia trait. In results a total of 14815 people were screened. The prevalence of patients with the  $\beta$ -thalassemia trait was 5.02% (744/14815). In conclusion such a high prevalence requires that screening efforts should be increased; the society should be educated and made aware of the matter. Major methods to be used to eradicate the disease are genetic consultation and prenatal diagnosis.

**Keywords:** Kutahya,  $\beta$ -Thalassemia Trait, Prevalence, Premarital Screening, Turkey

### INTRODUCTION

Thalassemia is a global hereditary blood disease caused by almost 200 gene mutations with a prenatal diagnosis and screening [1]. Despite their heterogeneity, the common feature of thalassemia is that one or more of the globin chains composing a normal person's haemoglobin molecule are not formed or synthesized deficiently [2].

It is a major global public health matter, which is prevalent especially in all Mediterranean countries including Turkey [3].  $\beta$ -thalassemia is a preventable blood disease inherited from mother and father to the infant [4]. Carriers are generally healthy in diseases regarded as autosomal recessive [5]. However, this disease is seen in their infants at certain rates, when they get married to carriers like themselves [6]. Therefore, prevention of a thalassemia infant is primarily possible by determining the carriers first [7]. Several simple tests can determine thalassemia trait [8]. Although it is a preventable disease through determining the carriers, genetic consultation and prenatal diagnosis, at least 315.000 thalassemia sufferers are born and receive treatment globally every year [9]. According to the World Health Organisation (WHO) data, its global carriage rate is 5.1%, which shows discrepancies according to by countries and the

regions in the countries [1]. In Turkey, thalassemia carriage is prevalent in Çukurova, along the Mediterranean coast, in Aegean and Marmara regions [5, 10]. There are almost 1,400,000 thalassemia carriers and 5,000 thalassemia patients in Turkey [6].  $\beta$ -thalassemia carriage prevalence is 4,3% in Turkey, according to the survey results of Turkish National Haemoglobinopathy Council conducted in 16 different cities [11].

In Turkey, determination of the thalassemia carriers and training and consultation efforts of the Ministry of Health through "Thalassemia Diagnosis and Treatment Centres" have recently accelerated. However, thalassemia births haven't been able to be prevented in Turkey yet due to frequent kin marriages, high birth rate, inadequate team work and register system, low number of infants upon whom prenatal diagnosis is conducted and insufficient training and consultation efforts on the subject. Since determination of the carriers is the first step in prevention of thalassemia, screening tests prior to marriage are crucial. This study was carried out to determine the  $\beta$ -thalassemia prevalence in and around Kutahya, to raise awareness about the matter in the society and to decrease the prevalence of the disease.

**MATERIAL & METHOD**

In order to find  $\beta$ -thalassemia prevalence in Kütahya province, those who applied for marriage in 2008, 2009 and 2010, adults diagnosed anaemia and suspected of thalassemia by gynaecologists, internists and primary care physicians and children of all ages sent by paediatricians and primary care physicians were included into the study.  $\beta$ -thalassemia trait screening was done on hemoglobinopathy screening centre in Kütahya under the auspices of the Ministry of Health. Firstly, those who applied for marriage were informed about thalassemia and full cooperation was secured by emphasizing the importance of determination of the carriers and training of the families. They signed the "Informed Consent Form". The children, sent by paediatricians with anaemia diagnosis and thalassemia suspicion, and their families were also informed and their voluntary participation was maintained. The ethical approval was obtained from the Ethics Committee of Pamukkale University Faculty of Medicine, Denizli, Turkey.

2.5 ml venous blood sample was taken from the subjects into EDTA tubes and the analysis was done

in laboratory within an hour. The analyses were conducted using "Ultra<sup>2</sup> -215 Primus Resolution Assay Versions 5.1.5. Instrumental Serial Number: 100630/2010", which works upon HPLC (High-performance liquid chromatography) method and carries out Haemoglobin Chain analysis. The kits used in the study were Trinity Biotech Elution Reagent for Hemoglobin Variant Assay Mobile Phase1 and Trinity Biotech Elution Reagent for Hemoglobin Variant Assay Mobile Phase2.

**RESULTS**

Total 14815 individuals were involved in the screening study in Kütahya province. In the study,  $HbA_2 > 3.5$  values were accepted as  $\beta$ -thalassemia trait. Accordingly, it was determined that 744 of 14815 (5.02%) were  $\beta$ -thalassemia trait. In the 22 months period, 6,438 couples (a total of 12876 persons) were screened for hemoglobinopathies in the province of Kütahya. As a result of premarital screening was determined 7 carrier couples in total. The distribution of hemoglobinopathies is presented in Table 1.

**Table 1:  $\beta$ -thalassemia screening studies in Kütahya**

	n	Carrier Number	(%)
<b>2008</b> (2 months)	409	44	10.8
<b>2009</b> (12 months)	8676	498	5,74
<b>2010</b> (8 months)	5730	202	3,53
<b>Total</b> (22 months)	14815	744	5,02

**DISCUSSION**

In this study, it was found that  $\beta$ -thalassemia carriage prevalence in and around Kütahya is 5.02%. The rate of  $\beta$ -thalassemia carriage in Turkey is 2.1% in general, but this number can rise up to 10% in various places [12]. Different results have been obtained in various studies on  $\beta$ -thalassemia carriage prevalence in different parts of Turkey.  $\beta$ -thalassemia carriage prevalence was determined to be high in the southern coast of Turkey and in Western Thrace, while it was found to be low in Eastern and Northern Anatolia [5, 6, 13]. In the studies conducted in the Mediterranean Region, the rate of  $\beta$ -thalassemia carriage was found as follows: Antalya 10.2%, Muğla 4.8%, Hatay 7.9 %, Mersin 2.04% [5, 14, 15, 16]. In the studies conducted in South-eastern Anatolia, the rate of  $\beta$ -thalassemia carriage was found as follows: Van 2.08%, Elbistan 1%, Kahramanmaraş 2.35%, Adıyaman 1.91%, Gaziantep 1.84% [9, 17, 18, 19, 20] In the studies conducted in Central and Eastern Anatolia, the rate of  $\beta$ -thalassemia carriage was determined as follows: Elazığ 0.5%, Erzurum 0.68%, Konya 2%, Kayseri 1.71% [3, 21, 22, 23]. In the studies conducted in Thrace Region, the rate of  $\beta$ -thalassemia carriage was found as follows: Kırklareli 3.06%, Edirne 6.44%, Kocaeli 0.89% [6, 24, 25]. The city of Kütahya is located in the eastern part of Aegean Region in Turkey.

In the studies conducted in the cities around Kütahya, the rate of  $\beta$ -thalassemia carriage was found as follows: Bursa (Mustafakemalpaşa) 2.78% and Denizli 2.2% [26, 27]. In this study, the rate of  $\beta$ -thalassemia carriage in Kütahya was found 5.02%. The result of this study is higher compared to both the result of those in nearby cities and the mean of those conducted countrywide.

Among the genetic diseases the most common disorders are hemoglobinopathies [28]. Beta-thalassemia is prevalent in Mediterranean countries, the Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa and in South America [4]. According to WHO data, the global carriage rate is 5.1% [1] Thalassemia syndromes cover a relatively wide genetic range. Thalassemias are named as  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\delta\beta$ ,  $\epsilon\gamma\delta\beta$  thalassemia according to globin chain with deficient synthesis [29]. According to this definition, deficient alpha chain construction causes  $\alpha$ -thalassemia, while deficient beta chain construction causes  $\beta$ -thalassemia. The most common types are  $\alpha$  and  $\beta$ -thalassemias.  $\alpha$ -thalassemia is mostly seen in the Far East, whereas  $\beta$ -thalassemia is more frequent in the Mediterranean countries and Turkey [30]. Contrary to sickle cell anaemia caused by uniform mutation,  $\beta$ -thalassemia is very heterogeneous at molecular level [31].

Thalassemia is an autosomal recessive heterogeneous group disease characterized by Hypochromic Microcytic Anaemia occurring when one or more haemoglobin (Hb) chains are synthesized defectively [32]. Thalassemia carriage can be determined through certain simple tests. Considering how hard the treatment is for the family and the child, one can grasp the importance of diagnosis and preventive treatment [3]. The most efficient methods of protection against such hereditary diseases are public training, screening of the carriers, genetic counselling and prenatal diagnosis. B-Thalassemia requires a regular control program in Turkey as in Italy, Greece and Cyprus [33, 34, 35]. Turkish Republic of Northern Cyprus (TRNC), Italy and Greece have succeeded in preventing thalassemia infants being born in the last decade thanks to society screening, pre-marriage carrier detection, effective genetic counselling, informing the public in various ways and prenatal diagnosis applications [1]. Considering that today, the neighbour Mediterranean countries have eradicated the disease almost completely, the facts that a screening program appropriate for the current conditions should be provided immediately and that public training should be boosted where carriage is prevalent are the first steps to be taken in the matter [18].

Because the rate of thalassemia carriage in Kütahya is high, it is crucial in determining the carriers to screen the relatives of patients and carriers through blood tests and analyse the couples who will get married in terms of carriage. The public should be informed about the disease and the risks involved in kin-marriage and in the marriage of carriers. The married couples both of whom carriage has been detected should be provided genetic counselling and the pregnant should be directed to genetic diagnosis centres for necessary tests. Prenatal diagnosis should be made by doing the necessary tests within the first two months of pregnancy to prevent the infants of carrier couples from being thalassemia. Kütahya showing high prevalence areas such as thalassemia screening program in addition to the improvement in educational programming, which is an important cause of morbidity and mortality reduction and eradication of thalassemia can be effective.

## CONCLUSIONS

Such a high prevalence requires that screening efforts should be increased; the society should be educated and made aware of the matter. Major methods to be used to eradicate the disease are genetic consultation and prenatal diagnosis.

Consequently, it is crucial that the importance of thalassemia which is a hereditary blood disease should be told to public, the public should be made aware and trained, and screening should be extended to determine carriers and to prevent diseased infants from being born.

## REFERENCES

1. Yaprak I; Beta Talasemi Tanı ve Tedavisinde Güncel Yaklaşımlar. Sürekli Tıp Eğitim Dergisi 2004; 13(2): 58-59.
2. Borgna-Pignatti C, Galanello R; Thalassemias and related Disorders: Quantitative Disorders of Hemoglobin Synthesis. In: Greer JP, Rodgers GM, Foerster J, Paraskevas F, Lukens JN, Glader B eds. Wintrobe's Clinical Hematology. 11th Edn. Lippincott Williams & Wilkins, Philadelphia, 2004; 1319-1365.
3. Karakukcu C, Kocer D, Torun YA, Karakukcu M, Yokus O, Ozdemir MA *et al.*; Premarital Hemoglobinopathy Screening in Kayseri: A City in Middle Anatolia Region of Turkey. Journal of pediatric hematology/oncology. 2012; 34(2): e49-e52. doi:10.1097/MPH.0b013e3182370bdf
4. Galanello R, Origa R; Review: Beta-thalassemia. Orphanet J Rare Dis, 2010; 5(11): 1-15. doi: 10.1186/1750-1172-5-11
5. Arıca SG, Turhan E, Özer C, Arıca V, Şilfeler DB, Şilfeler D *et al.*; Evaluation of hemoglobinopathy screening results of a six year period in Turkey. International Journal of Collaborative Research on Internal Medicine & Public Health (IJCRIMPH), 2012; 4(2): 145-151.
6. Sarper N, Şenkal V, Güray F, Bayram J; Premarital hemoglobinopathy screening in Kocaeli, Turkey: a crowded industrial center on the north coast of Marmara Sea. Turkish Journal of Hematology, 2009; 26(2): 62-66.
7. Cao A, Furbetta M, Galanello R, Melis MA, Angius A, Ximenes A, *et al.*; Prevention of homozygous beta-thalassemia by carrier screening and prenatal diagnosis in Sardinia. American journal of human genetics, 1981; 33(4): 592-605.
8. Hashemizadeh H, Noori R; Premarital Screening of Beta Thalassemia Minor in north-east of Iran. Iranian Journal of Pediatric Hematology & Oncology, 2013; 3(1): 210-215.
9. Guler E, Celik M, Davutoglu M, Ekerbicer HC, Karabiber H; The evaluation of results of the premarital screening of hemoglobinopathies trait in Kahramanmaraş. TAF-Preventive Medicine Bulletin, 2008; 7(3): 243-244.
10. Altay Ç; The frequency and distribution pattern of  $\beta$ -thalassemia mutations in Turkey. Turk J Haematol, 2002; 19(2): 309-315.
11. Canatan D, Kose MR, Ustundag M, Haznedaroglu, D, Ozbas S; Hemoglobinopathy control program in Turkey. Community Genet. 2006; 9(2):124-126.
12. Altay Ç, Başak AN; Molecular basis and prenatal diagnosis of hemoglobinopathies in Turkey. Int. J. Pediatr. Hematol. Oncol 1995; 2: 283-290.
13. Yüregir GT, Donma O, Dikmen N, Isbir T, Cinar M; Population studies of hemoglobin S and other variants in Cukurova, the southern part of Turkey.

- Nihon Ketsueki Gakkai zasshi: journal of Japan Haematological Society 1987; 50(4): 757.
14. Bircan İ, Şişli S, Güven A, Çali Ş; Hemoglobinopathies in the district of Antalya, Turkey. *Pediatric Hematology and Oncology* 1993; 10: 289-291.
  15. Arcasoy A, Turan F, Yeşil N, Kemahlı S; Muğla ili ve çevresinde talasemi ve anormal hemoglobin sıklığının taranması. *Pediatride Yönelişler*, 1994; 1(2): 78-80.
  16. Tosun F, Bilgin A, Kizilok A, Arpacı A, Yüregir GT; Five-year evaluation of premarital screening program for hemoglobinopathies in the province of Mersin, Turkey. *Turk J Hematol* 2006; 23(2): 84-89.
  17. Gerçik F; Van İli Çevresinde Beta Talasemi Sıklığı. *Uzmanlık Tezi*, Yüzüncü Yıl Üniversitesi, Tıp Fakültesi, 2006; 86.
  18. Canatan D, Bor S, Arcasoy A, Yeşil N; Elbistan yöresinde anormal hemoglobin ve HbA2 yüksekliği ile karakterize beta-thalassemia taşıyıcı taraması. *Doğa Tr. J. Of Medical sciences* 1990; 14: 555-561.
  19. Genc A, Tastemir Korkmaz D, Buyukleyla M, Celiker M; Prevalence and molecular analysis of  $\beta$ -thalassemia in Adiyaman, Turkey. *Hemoglobin*, 2012; 36(2): 131-138.
  20. Gurbak M, Sivaslı E, Coskun Y, Bozkurt AI, Ergin A; Prevalence and hematological characteristics of  $\beta$ -thalassemia trait in Gaziantep urban area, Turkey. *Pediatr Hematol Oncol*. 2006; 23(5): 419-425.
  21. Acemoglu H, Beyhun NE, Vancelik S, Polat H, Guraksin A; Thalassaemia screening in a non-prevalent region of a prevalent country (Turkey): is it necessary?. *Public Health* 2008; 122(6): 620-624.
  22. Koç A, Kocabay K, Öncü T, Güvenç T; Elazığ yöresinde beta talasemi taşıyıcılığı ve anormal hemoglobin taraması. *T. Klin Pediatri* 1993; 2: 70-71.
  23. Guler E, Karacan M; Prevalence of Beta-thalassemia and sickle cell anemia trait in premarital screening in Konya urban area, Turkey. *J Pediatr Hematol Oncol*. 2007; 29(11): 783-785. doi: 10.1097/MPH.0b013e318159a570
  24. Vural Ö, Saltık A, Demir M, Akar N, Arcasoy A; A screening of Beta-thalassemia trait and the Frequency of Hemoglobinopathies in Edirne-Türkiye. *Int. J. Hematol* 1996; 64(1): 83.
  25. Demir M, Vural Ö, Yorulmaz F, Ozer H; Prevalence of  $\beta$ -thalassemia trait in Turkey. *Haema J Hellenic Soc Haematol* 1999; 2: 135-138.
  26. Bolaman Z, Enli Y, Köseoğlu M, Koyuncu H, Aslan D; Prevalence of beta thalassemia trait in Denizli. *Turk J Haematol* 2001; 18(2): 85-88.
  27. Akar N, Uysal Z, Yeşil N, İnce E, Arcasoy A, Ata Y; Mustafakemalpaşa ve köylerinde anormal hemoglobin ve HbA2 yüksekliği ile karakterize beta-talasemi taşıyıcılığı araştırması. *Doğa-Tr. J. Of medical Sciences*, 1990; 14: 551-554.
  28. Yılmaz B, Balım Z, Özknay F, Gündüz C, Altıntaş N, Aydınok Y, *et al.*; Molecular Genetic Analyses of Beta-Thalassemia Patients. *Ege journal of medicine* 2000; 39(3): 153-157.
  29. Jain R, Perkins J, Johnson ST, Desai P, Khatri A, Chudgar U *et al.*; A prospective study for prevalence and/or development of transfusion-transmitted infections in multiply transfused thalassemia major patients. *Asian journal of transfusion science*, 2012; 6(2): 151.
  30. Date last updated: february 1 2014. Date last accessed: february 1 2014. Başak Nazlı A., Talasemi ve Hemoglobinopatiler;  $\beta$ -Talasemi'de Moleküler Tanı ve Yöntemleri 49-60. <http://www.talasemifederasyonu.org.tr/pdf/tani/1cansinTani.pdf>
  31. Huisman THJ, Carver MFH, Baysal E; A syllabus of thalassemia mutations. Atlanta: Sickle Cell Anemia Foundation; 1997; 310.
  32. Rund D, Rachmilewitz E;  $\beta$ -Thalassemia. *New England Journal of Medicine* 2005; 353(11): 1135-1146.
  33. Cao A, Galanello R, Rosatelli MC, Argioli F, De Virgiliis S; Clinical experience of management of thalassemia: the Sardinian experience. In *Seminars in hematology*, January 1996; 33(1): 66.
  34. Telfer P, Coen PG, Christou S, Hadjigavriel M, Kolnakou A, Pangalou E, *et al.*; Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980-2004. *haematologica*, 2006; 91(9): 1187-1192.
  35. Bozkurt G; Thalassemia prevention and control program in the Turkish Republic of Northern Cyprus. 2nd International Thalassemia Summer School, 2002; 01-05.