Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

Could the 3′UTR+101G>C Mutation Detected in Two Sibling Cases Be a Mutation Affecting the Clinical Presentation in Thalassemia Patients?

Keywords: 3'UTR+101G>C Mutation; Thalassemia.

Published: March 01, 2024 **Received: December 03, 2023** **Accepted: February 09, 2024**

Citation: Atas U., Karakus V., Kurtoglu E. Could the 3′UTR+101G>C mutation detected in two sibling cases be a mutation affecting the clinical presentation in thalassemia patients? Mediterr J Hematol Infect Dis 2024, 16(1): e2024023, DOI: http://dx.doi.org/10.4084/MJHID.2024.023

To the editor.

β-thalassemia is one of the most common recessive genetic diseases worldwide and is characterized by varying degrees of chronic anemia caused by the quantitative reduction or absence of structurally normal β-globin chains resulting from a series of mutations.[1] It is estimated that approximately 5.2% of the world's population carries a potentially pathogenic hemoglobin gene and that more than 330,000 newborns are affected by a serious hemoglobin disorder every year.[2] To date, more than 350 β-thalassemia mutations have been reported in the IthaGenes database.[3] Homozygous and compound heterozygous mutations can result in transfusion-dependent-β-thalassemia (TD-β-thalassemia).[4] Here, we report two siblings with a diagnosis of transfusion-independent-β-thalassemia (TI-β-thalassemia) caused by an unreported mutation, despite compound heterozygosity for previously identified mutations.

Case 1: A 68-year-old male patient diagnosed with TI-β-thalassemia has been under follow-up for the last 12 years due to transfusion requirements, chelation, and heart failure. The patient, whose parents had no clinical pathology, was first diagnosed with splenomegaly at the age of 7. However, without a clear diagnosis and follow-up, the patient was investigated for weakness and abdominal distension at the age of 35. At that time, microcytic anemia that did not require transfusion, hepatosplenomegaly, gallstones, and elevated HbF levels according to hemoglobin electrophoresis were detected, and the patient was diagnosed with thalassemia intermedia (TI-β-thalassemia) and put under follow-up. Starting at the age of 54, the patient began to receive regular transfusions for an unknown reason at an outside center and iron chelation due to transfusional iron accumulation. Despite chelation, the patient developed heart failure 4 years later. At the beginning of the follow-up, the patient's DNA analysis showed heterozygous mutations of c.92+6T>C (rs35724775) (IVS-I-6) and c.93-21G>A (rs35004220) (IVS-I-110), which can cause TD-β-thalassemia, as well as the 3′UTR+101G>C (+233 relative to termination codon) (rs12788013) mutation, which is suspected to cause β-thalassemia. In the additional genetic analysis, no α-globin chain mutation that could alleviate the disease was found. These results suggested that this new mutation detected was a mutation that caused the patient, who was expected to be TD-β-thalassemia, to become a TI-β-thalassemia patient for many years and alleviated the clinic.

Case 2: The patient's sister, who is one year younger than him and is being followed up for TI-β-thalassemia, was found to have the same mutations. However, unlike his brother, additional genetic analysis detected a heterozygous deletion in the α-globin chain gene. We thought that the fact that he had an α-thalassemia trait along with the 3′UTR+101G>C mutation explained his better clinical condition compared to his brother and that she was still transfusion-independent.

β-thalassemia is a molecularly heterogeneous disease with different mutations emerging in different ethnic backgrounds.[4-7] In the Turkish population, more than 40 mutations have been identified to date.[8,9] Guzelgul et al. detected 22 different β-thalassemia mutations in 52 pediatric TD-β-thalassemia patients in their study conducted in the Cukurova region. Homozygous mutations were identified in 36 patients (IVS-I-110 (58.0%), codon 8 (–AA) (HBB: c.25_26delAA) (5.6%), -30 (T>A) (HBB: c.-80T>A) (5.6%), IVS-I-6 (5.6%), and IVS-II-1 (%5.6)), while compound heterozygous mutations were found in 13 patients. Two of these patients were reported to have compound heterozygous mutations of IVS-I-110 and IVS-I-6, similar to our two siblings.[4] In Palestinian patients, IVS-I-6 was reported to be the most common mutation, followed by IVS-I-110.[5] Thalassemia is extremely present also in the very populous oriental Asiatic regions, like India, China, and Thailand, where frequently is prevalent the alfa

thalassemia, and different mutations have been described.[10-12] In India, the five more common mutations found in Kumar et al.'s study[10] were IVS1-5 (G>C) (47.0%), codon 41-42 (-TCTT) (9.3%), codon 8-9 (+G) (8.3%), codon 16 (-C) (8.3%) and 619bp del (6.0%). DNA sequencing revealed the less common mutations like; codon 15 (G>A) (5.6%), IVS1-1 (G>T) and codon 30 (G>C) (4.6%) each and Cap+1 (A>C) (1.7%). Other rare mutations comprised of 4.6%.

According to the information in the literature, TD-β-thalassemia is expected to occur in cases with compound heterozygous mutations of IVS-I-110 and IVS-I-6. However, the 3'UTR+101G>C mutation, which was detected in the first case without any accompanying α-globin chain gene mutation, maybe the reason for TI-β-thalassemia for approximately 55 years. In the second case, which was still TI-β-thalassemia, a heterozygous mutation was detected in the α-globin chain gene, which was expected to alleviate the clinical condition, along with all three mutations. The presence of a previously unreported but detected 3′UTR+101G>C mutation in both patients raises the question of whether this mutation could be "a mutation that mitigates the clinical presentation." To confirm this theory, the presence of this mutation should be evaluated in TI-β-thalassemia with homozygous or compound heterozygous mutations.

Unal Atas, Volkan Karakus and Erdal Kurtoglu.

Health Sciences University, Antalya Training and Research Hospital, Department of Hematology, Antalya, Turkey.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Volkan Karakus, M.D. Antalya Training and Research Hospital, Department of Hematology, Antalya, Turkey. Tel: +90 5057656778. E-mail: dr_v_karakus@yahoo.com

References:

1. Thein PL. The molecular basis of beta-thalassemia. Cold Spring Harb Perspect Med. 2013;3:a011700. https://doi.org/10.1101/cshperspect.a011700 PMid:23637309 PMCid:PMC3633182
2. Modell B, Darlison M. Global epidemiology of hemoglobin disorders and derived service indicators. Bull World Health Organ. 2008 Jun; 86(6): 480-487. https://doi.org/10.2471/BLT.06.036673 PMid:18568278 PMCid:PMC2647473
3. Kountouris P, Lederer CW, Fanis P, Feleki X, Old J, Kleanthous M. IthaGenes: an interactive database for hemoglobin variations and epidemiology. PLoS One. 2014;9:e103020. https://doi.org/10.1371/journal.pone.0103020 PMid:25058394 PMCid:PMC4109966
4. Guzelgul F, Seydel GS, Aksoy K. β-Globin Gene Mutations in Pediatric Patients with β-Thalassemia in the Region of Çukurova, Turkey. Hemoglobin. 2020 Jul;44(4):249-253. https://doi.org/10.1080/03630269.2020.1792489 PMid:32664780
5. Samha L, Sirdah MM, Reading NS, Karmi B, Agarwal AM. Molecular Understanding of Severe Cases of β-Thalassemia in the Nablus Region, West Bank, Palestine. Hemoglobin. 2020 Mar;44(2):128-130. https://doi.org/10.1080/03630269.2020.1763398 PMid:32420772
6. Atroshi SD, Al-Allawi NAS, Eissa AA. Updated Molecular Spectrum of β-Thalassemia Mutations in Duhok Province, Northern Iraq: Ethnic Variation and the Impact of Immigration. Hemoglobin. 2021 Jul;45(4):239-244. https://doi.org/10.1080/03630269.2021.1984250 PMid:34794358
7. Farra C, Abdouni L, Souaid M, Awwad J, Yazbeck N, Abboud M. The Spectrum of β-Thalassemia Mutations in the Population Migration in Lebanon: A 6-Year Retrospective Study. Hemoglobin. 2021 Nov;45(6):365-370. https://doi.org/10.1080/03630269.2021.1920975 PMid:33947296
8. Nazı Başak A. The molecular pathology of β-thalassemia in Turkey: the Boğaziçi University experience. Hemoglobin. 2007;31(2):233-241. https://doi.org/10.1080/03630260701296735 PMid:17486506
9. Tadmouri GO, Başak AN. β Thalassemia in Turkey: a review of the clinical, epidemiological, molecular, and evolutionary aspects. Hemoglobin. 2001;25(2):227-239. https://doi.org/10.1081/HEM-100104031 PMid:11480784
10. Kumar R, Singh K, Panigrahi I, Agarwal S. Genetic Heterogeneity of Beta Globin Mutations among Asian-Indians and Importance in Genetic Counselling and Diagnosis. Mediterr J Hematol Infect Dis. 2013;5(1):e2013003. https://doi.org/10.4084/mjhid.2013.003 PMid:23350016 PMCid:PMC3552784
11. Zhu Y, Shen N, Wang X, Xiao J, Lu Y. Alpha and beta-Thalassemia mutations in Hubei area of China. BMC Med Genet. 2020 Jan 6;21(1):6. https://doi.org/10.1186/s12881-019-0925-5 PMid:31906886 PMCid:PMC6943895
12. Sinlapamongkolkul P, Surapolchai P, Viprakasit V. Justification of universal iron supplementation for infants 6-12 months in regions with a high prevalence of thalassemia. Mediterr J Hematol Infect Dis. 2023, 15(1): e2023056. https://doi.org/10.4084/MJHID.2023.056 PMid:37705528 PMCid:PMC10497306