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The Distribution of HLA Alleles in Patients with Beta Thalassemia †

Yasin Yilmaz *, Zeynep Karakas, Ayse Erol Bozkurt, Demet Kivanc, Mediha Suleymanoglu, Hayriye Senturk Ciftci, Cigdem Kekik Cinar and Fatma Savran Oguz

Department of Pediatric Hematology and Oncology, Istanbul Medical Faculty, Istanbul University, 34098 Istanbul, Turkey; oguzsf@gmail.com (F.S.O.)

* Correspondence: dryasinyilmaz@gmail.com

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Abstract

Background: It has been shown that human leucocyte antigen (HLA) alleles are related to certain diseases. Some alleles were associated with alloimmunization in individuals with thalassemia. In this study, we studied the distribution of HLA alleles among beta thalassemia (BT) patients compared to healthy controls. Material and Methods: The HLA results of 100 patients with BT and 100 healthy controls were obtained for the study. The HLA-A, -B and -DRB1 tissue typing were performed at the laboratory. The low-resolution sequence-specific primer (SSP)–polymerase chain reaction (PCR-SSP) (Olerup HLA-A,B,DR typing kit, USA) and sequence-specific oligonucleotide (SSO)–PCR (LABType HLA-A,B,DR kit, ABD) methods were performed using the Luminex genotyping kits. All related data were retrospectively analyzed. Results: One in five patients (21%) underwent hematopoietic stem cell transplantation (HSCT). Patients with HSCT had significantly lower frequency of HLA-B *14, HLA-DRB1 *11 and HLA-DRB1 *16 alleles and had a higher frequency of HLA-A *66, HLA-B *41, HLA-B *55, HLA-DRB1 *3 alleles compared to patients without HSCT ($p < 0.05$). The HLA-A *3, HLA-B *41 and HLA-B *55 alleles were more commonly seen in HSCT patients compared to the healthy group ($p = 0.04$). Female patients showed a higher frequency of HLA-B *58 and HLA-DRB1 *4 alleles ($p = 0.04$). Conclusions: This study demonstrated that HLA-B *41 and -B *55 alleles were closely related to HSCT among BT patients. It might be considered that the variance in certain HLA-B alleles in BT patients might cause difficulty in finding a matched donor in this limited population.

Keywords: beta thalassemia; hematopoietic stem cell transplantation; HLA alleles

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1. Introduction

Beta thalassemia is one of the most frequent genetic diseases and is characterized by mild to severe anemia. According to requirement of transfusion, the disease is classified as non-transfusion-dependent (NTDT) or transfusion-dependent (TDT) thalassemia [1]. Patients with TDT receive regular blood transfusion throughout their life.

The prevalence of beta thalassemia carriers is 1.5% worldwide. The mostly affected regions like the Mediterranean region, the Middle East, Africa, Southeast Asia and India have a β-thalassemia carrier prevalence of between 1% and 20%. The incidence of TDT varies from 1 in 25.000 neonates to 1 in 100.000 neonates in European countries. The incidence rate of TDT is 1 in 55.000 newborns in the USA [2]. The prevalence of beta

thalassemia carriers is about 2% in Turkey and there are a total of 5500 patients with thalassemia and other hemoglobinopathies and approximately 1.5 million thalassemia traits in Turkey [3]. The most commonly seen beta thalassemia mutations in Turkey are [IVS-I-110 (G>A)] (52%), [IVS-I-6 (T>C)] (14%) and [IVS-II-1 (G>A)] (8%) [4].

Blood transfusions are the first milestone for patients with thalassemia. However, alloimmunization, viral transmission and iron overload are the main issues for patients receiving regular transfusions. One of the most important complications in transfusion-dependent patients is iron accumulation. Iron can accumulate in endocrine organs, leading to organ dysfunction, and in the heart and liver, leading to heart failure and fibrosis. Excess iron causes oxidative damage at the cellular level. In beta thalassemia patients, defects in iron metabolism, erythroid differentiation and antioxidant metabolism increase transfusion-related iron accumulation damage [1].

After chelation therapy was released on the market, iron-related complications of transfusion were usually reversed. These chelation therapies (deferoxamine, deferasirox, deferiprone) were the second milestone for beta thalassemia.

The third milestone for thalassemia treatment is hematopoietic stem cell transplantation. The first successful hematopoietic stem cell transplantation (HSCT) in patients with beta thalassemia major was performed by Thomas et al. in Seattle (USA) in 1981. This case, a 14-month-old male patient who had never received transfusions, underwent HSCT from his HLA-matched sister, and a long, disease-free life was achieved. Since then, many patients with TDT have been undergone HSCT. This is the only curative therapy for thalassemia so far [5]. Human leukocyte antigens (HLAs) are the main target for transplantation, and only some patients have HLA-identical siblings. Therefore, the remaining patients need to find matched unrelated donors from the Bone Marrow Registry [6].

HLA tissue typing can play an important role in hematological disease. In this study, we aimed to investigate the HLA typing of patients with TDT and compare it with the healthy Turkish population. The rationale behind this aim is the low rate of HSCT among patients with TDT. The primary research question was why TDT patients have a low chance of finding a suitable donor. Our secondary aim was to show how thalassemic patients differ from healthy individuals.

2. Materials and Methods

2.1. Participants

Transfusion-dependent thalassemia patients who were followed up at Istanbul Medical Faculty Thalassemia Center were evaluated for this study. This study included patients registered to the center within the last twenty-five years. A total of 110 patients were evaluated and the HLA data of one hundred patients were available in the tissue bank of the study center. All participants were fully informed about the objectives of the study, and each provided written informed consent prior to participation. All personal data were anonymized to ensure confidentiality. A total of 48 female and 52 male patients with transfusion-dependent β-thalassemia [mean (±SD) age = 17.7 ± 7 years] were recruited into the study. The median age of diagnosis was 11 months and the median follow-up duration was 15 years. Furthermore, 25% of patients' parents had consanguineous marriage. Most patients (75%) were using deferasirox as a chelator.

Twenty-one patients (21%) underwent bone marrow transplantation. Thirteen of them (62%) received a transplant from a matched sibling donor, five of them (24%) from a matched unrelated donor and three of them (14%) from a matched related donor.

2.2. HLA Genotyping

DNA-based HLA-A, -B and -DRB typing of 100 patients with TDT and 100 healthy controls (randomly selected from the registry) was conducted at the Istanbul University Department of Medical Biology HLA typing laboratory. DNA samples were isolated from whole blood, and stored at −20 °C [7]. DNA samples were measured by a spectrophotometer. Samples with concentration 35–40 ng/mL and purity 260/280 = 1.8–2 were accepted for the study. The low-resolution sequence-specific primer (SSP)–polymerase chain reaction (PCR-SSP) (Olerup HLA-A,B,DR typing kit, Olerup SSP AB, Stockholm, Sweden) and sequence-specific oligonucleotide (SSO)–PCR (LABType HLA-A,B,DR kit, One Lambda, Los Angeles, CA, USA) methods were performed using the Luminex genotyping kits. LABType™ SSO uses sequence-specific oligonucleotide probes (SSO) bound to fluorescently coded microspheres to determine alleles encoded by the sample DNA. Target DNA was amplified with biotinylated, locus-specific primers. The assay was performed in a single well of a 96-well PCR plate. The incorporation of a step to amplify the target DNA by polymerase chain reaction (PCR), coupled with hybridization and detection in a single reaction mixture, renders this method suitable for both small- and large-scale testing. The PCR product is denatured and then allowed to re-hybridize to complementary DNA probes conjugated to fluorescently encoded microspheres. A flow analyzer, the LABScan™ 100 (Luminex® 100/200, One Lambda, Los Angeles, CA, USA), was used to determine the fluorescent intensity of PE (phycoerythrin) on each microsphere. The determination of the HLA typing was dependent on the correlation of reaction patterns with patterns related to published HLA gene sequences.

2.3. Statistics

The SPSS 23.0 (IBM Corp, Armonk, NY, USA) program was used for statistical analysis. For the categorical variables, the chi-square test was run. The odds ratio was used to compare the relative odds of the occurrence of the allele. A value of $p < 0.05$ indicated significance.

3. Results

3.1. HLA-Class I Allele Distribution

The most commonly seen alleles were the HLA-A*02 and A*03 alleles. There was no significant difference between thalassemic patients and healthy controls in the HLA-A locus. The HLA-B allele was also similar to the healthy group. HLA-B*35 and -B*51 alleles were the most commonly seen alleles in patients with thalassemia. HLA-B*13 was found to be low in thalassemia patients compared to the healthy population ($p = 0.04$). The HLA-B*53 allele was not seen in our patient population. The HLA-B*14 and -B*52 alleles were four times more frequently observed in thalassemia compared to the healthy group ($p = 0.05$ and $p < 0.01$).

3.2. HLA-Class II Allele Distribution

There is no significance in the frequency of HLA-DRB1 alleles between thalassemia patients and the healthy group. The most commonly seen allele was HLA-DRB1*11. The HLA-DRB1*9, -DRB1*10 and -DRB1*12 alleles were not found in the patient population.

3.3. HLA Distribution According to Bone Marrow Transplantation

TDT patients with bone marrow transplantation showed an increased frequency of HLA-A*66 ($p = 0.02$, $x^2 = 5.12$), HLA-B*41 ($p = 0.01$, $x^2 = 5.83$), HLA-B*55 ($p = 0.04$, $x^2 = 4.03$) and HLA-DRB1*03 alleles ($p = 0.01$; $x^2 = 6.36$). On the other hand, transplanted patients demonstrated a decreased frequency of HLA-B*14 ($p = 0.02$, $x^2 = 5.12$), HLA-

DRB1*11 (p = 0.03, x^2 = 4.50) and HLA-DRB1*16 alleles (p = 0.05, x^2 = 3.78) compared to non-transplanted patients (Table 1).

Table 1. Human leucocyte antigen (HLA) class I and II ratio among participants.

HLA Class	Transplanted Patients (n = 21)	Non-Transplanted Patients (n = 79)	Statistics
HLA-A*66	5%	0%	p **= 0.02**, x^2 = 5.12
HLA-B*14	0%	5%	p **= 0.02**, x^2 = 5.12
HLA-B*41	12%	3%	p **= 0.01**, x^2 = 5.83
HLA-B*55	10%	3%	p **= 0.04**, x^2 = 4.03
HLA-DRB1*3	19%	7%	p **= 0.01**, x^2 = 6.36
HLA-DRB1*11	14%	26%	p **= 0.03**, x^2 = 4.50
HLA-DRB1*16	2%	8%	p **= 0.05**, x^2 = 3.78

When compared to the healthy group, the HLA-B*13 allele was not shown in the transplanted group (p = 0.01, x^2 = 7.25). On the other hand, the HLA-A*03 (p = 0.04, x^2 = 4.01), HLA-B*41 (p = 0.03, x^2 = 4.34) and HLA-B*55 alleles (p = 0.04, x^2 = 4.03) were seen significantly more frequently in the transplanted patients (Table 2).

Table 2. Human leucocyte antigen (HLA) class ratio among participants.

HLA Class	Transplanted Patients (n = 21)	Healthy Group (n = 100)	Statistics
A3	24%	13%	p **= 0.04**, x^2 = 4.01
B13	0%	7%	p **= 0.01**, x^2 = 7.25
B41	12%	4%	p **= 0.03**, x^2 = 4.34
B55	10%	3%	p **= 0.04**, x^2 = 4.03

3.4. HLA Distribution by Gender

The HLA-B*58 allele was found significantly more frequently in female patients (p = 0.04). The HLA-DRB1*04 allele was twofold more frequently seen in female patients (p = 0.04, OR 2.25) (Table 3).

Table 3. Human leucocyte antigen (HLA) class I and II frequencies in Turkish patients with beta thalassemia (BT) according to gender.

HLA Class	Male (n = 52)	Female (n = 48)	Statistics	Odds Ratio (Female/Male)
HLA-B*58	0%	4%	p **= 0.04**, x^2 = 4.08	-
HLA-DRB1*4	10%	20%	p **= 0.04**, x^2 = 3.92	2.25

4. Discussion

In this study, we showed that patients with transfusion-dependent beta thalassemia were different from the healthy population in terms of HLA tissue typing. The HLA-B*13 allele was significantly lower in thalassemia patients, and the HLA-B*14 allele and HLA-B*52 allele were significantly higher in thalassemia patients compared to healthy controls. The HLA-B*44 and HLA-DRB1*04 alleles were found significantly more frequently in female patients.

HLA tissue typing can play important role in hematological disease. The incidence of the HLA-A28 allele increased in chronic ITP (immune thrombocytopenic purpura) patients [8]. HLA-DRB1*04 and DQB1*04 were regarded as predictive markers to assess the response to splenectomy [9]. In TTP (thrombotic thrombocytopenic purpura) patients, HLA-DRB1*04 was found to be a protective allele [10].

Regular transfusion is major treatment choice in patients with beta thalassemia major. Alloimmunization can occur in transfusion-dependent thalassemia and some patients are more prone to producing alloantibodies [11]. A recent study showed high antibody prevalence to HLA class I and II among patients receiving multiple blood transfusions [12]. It has been shown that some antibodies developed against HLA class I and II could cause rejection in HLA-matched donors [13–16]. Thus, screening of HLA alloimmunization is recommended before bone marrow transplantation. Some studies showed that the HLA-DRB1*15 allele was associated with alloantibody production in thalassemic patients [17]. In the same study, a relationship between HLA-DRB1*11 and the anti-K antibody was also revealed. Another study [18] showed a significant association between HLA-DRB1*11 and anti-K and anti-E antibody production.

Patients with TDT are at risk for hepatitis C infection due to chronic blood transfusion. The HLA-DRB1*03 allele was associated with viral clearance and the HLA-DRB1*07 allele was found to be related to chronic hepatitis C infection in beta thalassemia patients [19].

Bone marrow transplantation is the only curative treatment for patients with TDT. The 5-year overall survival (OS) was 92% in a recent study [2]. HLA tissue typing is the main criterion for a successful transplantation. Donor matching was defined as HLA-A, C, B, DRB1 and DQB1 allele-matched ("10/10") or -mismatched. The donor types are matched siblings, matched related donors and matched unrelated donors (9/10 or 10/10) [20].

A study from Turkey revealed, in terms of the proportion of donor types, that 70% of patients had a matched sibling donor (MSD), 17% a matched unrelated donor (MUD) and 13% a matched related donor (MRD) [2]. Another study from Turkey showed 56% MSD, 28% MUD and 16% MRD [21]. A study from China demonstrated a rate of 25% MUD [22] and a study from India showed 22% MUD [23].

The rate of matched unrelated donors (MUDs) for transplantation in beta thalassemia patients ranges from 15 to 30%. The different types of HLA in thalassemic patients can make it difficult to find an identical one. On the other hand, in terms of frequently used tissue typing in thalassemia patients, HLA-B*52 was also one of the most common (the third most common in our study). Conversely, in terms of frequent tissue typing in healthy patients, HLA-B*13 was also one of the most common (the fourth most common in our study). This discrepancy can also cause difficulties in finding a matched donor. Our data also showed that transplanted TDT patients had an increased frequency of the HLA-B*55 allele and HLA-DRB1*03 allele. However, the presented literature does not provide related information. This can be explained by donor availability or immunogenetic compatibility. It cannot be deduced that these alleles are more common since healthy patients had a decreased frequency of these alleles; however, at least it can be postulated that patients with these alleles had less challenges in finding a relevant donor. These discrepancies can be taken into consideration for future donor selection.

The position of HLA alleles in determining the risk of disease has recently been very well studied. The HLA-B*13, which we found to be very low in the thalassemia population, was found to be a predictive marker of dapsone-induced hypersensitivity [24]. On the other hand, the HLA-B*13 allele was shown to have protective effects in HIV-1 disease [25].

Another HLA allele that we found significantly more frequently in the thalassemia population is the HLA-B*14 allele. This allele was found to be related to sarcoid arthritis [26]. The HLA-B*52 allele was found to be very closely related to large vessel vasculitis [27]. These two alleles (B*14 and B*52) are both associated with rheumatologic disease and were found to be high in the thalassemia population as well. Long-term follow-up studies may indicate a tendency of the thalassemia population to develop these diseases; however, the scope of this research is not sufficient to draw this conclusion. Nevertheless, this study showed how different the HLA typing of the thalassemia population is from a healthy

population. This result can demonstrate that it might be challenging to find a matched donor for bone marrow transplantation.

Mishra et al., 2023 [28] investigated HLA alleles among thalassemia patients in India. The researchers showed a positive association between HLA-DRB1*15 and DQB1*06 and thalassemia and a negative association between HLA-A*31 and B*07 and thalassemia. In our study, these alleles were observed in both thalassemia patients and the healthy population. In another study (Asuar et al., 2019), it was revealed that the HLA-B*46 allele was positively associated with thalassemia in Malaysia, while the HLA-B*60 allele was negatively associated [29]. In our study, we did not find the B*60 allele among thalassemia patients and the B*46 allele was very rare. Scigliuolo et al., 2023 [30] examined HLA diversity between beta thalassemia and sickle cell anemia patients and found that the HLA-A*30-B*13 and HLA-A*68-B*53 haplotypes were associated with beta thalassemia. The researchers suggested that the extensive genetic diversity of HLA seen in sickle cell anemia patients is probably due to their African ancestry, whereas this diversity is less pronounced in beta thalassemia patients. They even concluded their study by discussing the practical difficulties that the genetic diversity of HLA in hemoglobinopathy patients creates in finding HLA-matched unrelated donors, as in our study.

The number of male and female participants was equal. The different alleles between males and females were not significant among transplanted and non-transplanted TST and healthy participants. Gender may not be a confounding factor; however, the limited size of our study is our most important limitation. There may be other confounding factor such as ethnogenetic variations that we could not evaluate in this study. This study was conducted in one of the largest thalassemia centers in our country and may serve as a representation of our population. Defining the difference in TDT from the healthy population can guide us on how we should approach HSCT for TDT patients. Some of the data in this study were presented orally at a previous conference [31].

5. Conclusions

In this study, we showed that patients with transfusion-dependent beta thalassemia were different from the healthy population in terms of HLA tissue typing. This can cause difficulty in finding a matched donor for bone marrow transplantation. Moreover, some rheumatologic disease-related HLA alleles were found at a high level in the thalassemia population. The rheumatological symptoms might be screened in clinical settings. Large-cohort studies and long-term follow-up studies are needed to draw specific conclusions.

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Data Availability Statement: Data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflicts of Interest: The authors declare that they have no conflicts of interest.

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