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RESEARCH

Frequency and relationship of HLA allele in Turkish patients with Fanconi anemia

Türk Fanconi anemili hastalarda HLA alellerinin sıklığı ve ilişkisi

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Abstract

Purpose: Fanconi anemia (FA) is a childhood disorder inherited in an autosomal recessive manner. It is characterized by bone marrow failure, a range of congenital physical abnormalities, increased susceptibility to cancer, chromosomal instability, and heightened sensitivity to cross-linking agents. The aim of this study was to determine the role of the HLA Class I and Class II alleles in genetic susceptibility to Fanconi anemia in Turkish patients.

Materials and Methods: In this study, we retrospectively evaluated the HLA-A, -B, and -DRB1 allele frequencies of patients with Fanconi anemia who underwent hematopoietic stem cell transplantation between 2010 and 2021. HLA-A, -B, -DR of all patients and healthy Turkish individuals were genotyped.

Results: The study included 86 patients with Fanconi anemia and 300 healthy controls. The most common antigens in patients with Fanconi were HLA-A*02, HLA-B*35 and DRB1*11. Moreover, in the patient group, the HLA-A*23 allele was significantly lower than the control group. When we evaluated the patient group according to gender the HLA-A*01 allele was significantly higher in the female patient group.

Conclusion: Our study provides valuable insights into the genetic susceptibility of Turkish patients with Fanconi anemia, focusing on the role of HLA Class I and Class II alleles. HLA-B*14 may be a risk factor and HLA-A*23 may be protective for Fanconi anemia. These results contribute to our understanding of the complex genetic factors underlying Fanconi anemia and may have implications for improved diagnosis, prognosis, and potential therapeutic interventions for affected individuals.

Öz

Amaç: Fanconi anemisi (FA), kemik iliği yetmezliği, çeşitli konjenital fiziksel anomaliler, kansere yatkınlık, kromozomal instabilite ve çapraz bağlayıcı ajanlara karşı aşırı duyarlılık ile karakterize otozomal resesif geçişli bir çocukluk çağı hastalığıdır. Bu çalışmanın amacı, Türk hastalarda HLA Sınıf I ve Sınıf II alellerinin Fanconi anemisine genetik yatkınlıktaki rolünü belirlemektir.

Gereç ve Yöntem: Bu çalışmada, 2010-2021 yılları arasında hematopoietik kök hücre nakli gerçekleşen Fanconi anemisi hastalarının HLA-A, -B, -DRB1 alel frekanslarını retrospektif olarak değerlendirdik. Tüm hastalara HLA tiplemesi yapıldı ve ayrıca sağlıklı Türk bireylerde de alelleri genotiplendirdik.

Bulgular: Çalışmaya 86 Fanconi anemili hasta ve 300 sağlıklı control dahil edilmiştir. Fanconi hastalarında en yaygın antijenler HLA-A*02, HLA-B*35 ve DRB1*11 idi. Ayrıca, hasta grubunda HLA-A*23 aleli kontrol grubuna göre anlamlı derecede düşüktü. Hasta grubunu cinsiyete göre değerlendirdiğimizde, HLA-A*01 aleli kadın hasta grubunda anlamlı olarak daha yüksekti.

Sonuç: Çalışmamız, HLA Sınıf I ve Sınıf II alellerinin rolüne odaklanarak, türk hastalarda Fanconi anemisi'nin genetik duyarlılığı hakkında değerli öngörüler sunmaktadır. HLA-B*14, Fanconi anemisi için bir risk faktörü olabilirken, HLA-A*23 koruyucu olabilir. Bu sonuçlar, Fanconi anemisi'nin karmaşık genetik faktörlerini anlamamıza katkıda bulunmakla beraber, etkilenen bireyler için daha iyi teşhis, prognoz ve potansiyel tedavi müdahaleleri açısından önemli olabilir.

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Anahtar kelimeler: Fanconi anemisi, HLA, genotipleme, homozigotluk

INTRODUCTION

Fanconi anemia (FA) is a rare bone marrow disorder inherited in an autosomal recessive manner. On average, approximately 1 in 136,000 newborns are affected by FA, with incidence rates ranging from 1 in 100,000 to 250,000 births[1]. Individuals with FA frequently experience hematopoietic failure, leading to progressive pancytopenia. This condition results in a deficiency of functional bone marrow stem cells needed to maintain blood cell counts during cell turnover. In severe instances, FA patients may develop acute myeloid leukemia, a type of bone marrow cancer marked by an abundance of abnormal myelocytes. These myelocytes can impair the development of white blood cells, red blood cells, and platelets[2]. To date, 19 genes have been identified that encode proteins associated with the Fanconi anemia complementation groups. These genes are alternatively referred to with the root symbol "FANC". The proteins from the Fanconi anemia subtype (FANC) collectively participate in a vital DNA repair mechanism known as the Fanconi anemia pathway (FA pathway). This pathway plays a critical role in maintaining genomic integrity[3]. These genes encode proteins that comprise the FA core complex, two substrates (FANCD2 and FANCI Heterodimer), and multiple downstream interacting proteins, including FANCD1/BRCA2, FANCJ/BRIP1, FANCN/PALB2, and RAD51C[4,5]. Bone marrow failure, physical abnormalities, and organ defects occur in FA patients, who also face an elevated susceptibility to the onset of leukemia and solid tumors[6]. While gene therapy trials for FA are currently underway, allogeneic hematopoietic stem cell transplantation (allo-HSCT) continues to be the only established curative treatment for hematologic malignancies associated with FA. Furthermore, it has been suggested that graft versus host disease (GvHD) occurring after allo-HSCT may contribute to the increased risk of developing solid tumors in these patients[7].

FA develops because of mutations in genes that function in the FA pathway responsible for DNA repair. Hypersensitivity to DNA cross-linking agents and chromosomal instability are seen in FA patients due to DNA repair defects[8].

Human leukocyte antigen (HLA) molecules are important markers of health and disease. Our current understanding recognizes HLA molecules as the fundamental platform for immune responsiveness. Exploiting HLA-ligand interactions is thought to be effective in clinically personalized antigen-specific disease prevention[9].

Polymorphism in HLA has been associated with susceptibility to many diseases such as determinant of tissue or organ rejection[10,11]. This significance stems from their ability to present antigenic molecules to immune system cells. This study on Fanconi anemia and its relationship with HLA allele frequencies will contribute valuable insights to the literature. MHC molecules play a critical role in graft rejection and GvHD. Individuals expressing the same HLA molecules can accept each other's tissue grafts. Graft rejection develops among individuals with dissimilar HLA alleles[12]. Determination of common HLA alleles in these patients is important for the course of the disease. It also plays a role in better elucidating the pathogenesis of FA.

In Turkey, where consanguineous marriages are common, the prevalence of FA may differ from global estimates. HLA molecules play pivotal roles in immune response modulation and disease susceptibility. Polymorphisms in HLA alleles have been implicated in various diseases, including their influence on organ transplant outcomes.

This study aims to retrospectively analyze the frequencies of HLA Class I and Class II alleles in Turkish patients with Fanconi anemia. By identifying prevalent HLA alleles associated with FA, we seek to elucidate their potential role in disease susceptibility and provide insights into the genetic factors contributing to its pathogenesis.

MATERIALS AND METHODS

Sample

The power analysis was conducted using the website http://clincalc.com/stats/SampleSize.aspx. To detect a 20% difference between two groups (patient and control) with a 0.05 alpha error and 80% power, 86 adult patients with Fanconi anemia, who were followed between 2010-2021, and 300 healthy

individuals for the control group were included in the study. The patients were followed by Istinye University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology/Oncology, and Yeditepe University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology/Oncology.

The study protocol was approved by the ethical committee of Istanbul Faculty Medicine (No: 2021/38, date: 05/02/2021). All procedures were performed in compliance with the Declaration of Helsinki of 1975, as received in 2008.

HLA typing

HLA genotyping was performed at the Istanbul Faculty of Medicine, Department of Medical Biology, Tissue Typing Laboratory for Hematopoietic Stem Cell Transplantation (HSCT). We retrospectively evaluated the HLA-A, -B, -DRB1 allele frequencies of Fanconi anemia patients that are typed with Polymerase Chain Reaction (PCR)-Sequence Specific Primer (SSP) with Olerup SSP ABDR kits (Saltsjöbaden, Sweden) or Sequence Specific Oligonucleotide (SSO) method with commercial kits.

DNA isolation

Peripheral blood samples were collected into EDTA tubes from both patient and control groups. DNA was isolated using the sodium chloride salting-out method.

PCR-SSP method

The PCR-SSP (Polymerase Chain Reaction - Sequence-Specific Primers) method involved preparing a mastermix consisting of distilled water and Taq polymerase enzyme, to which the DNA samples were added. Amplification was performed using a Perkin Elmer cycler device. Post-amplification, the samples were electrophoresed on agarose gels, and the results were visualized under UV light.

SSO method

In the SSO (Sequence-Specific Oligonucleotide) method, hybridization was achieved by adding 15 µL of beads to 5 µL of amplified DNA samples. Subsequently, 170 µL of a dilution and streptavidin mixture was added. The evaluation of the samples was performed using a Luminex device.

Statistical analysis

Statistical analysis utilized the SPSS (version 28.0) software, while correlation analysis was conducted using the Pearson test. Chi-square analysis was performed for comparisons between nominal groups. The p values were corrected by the Bonferroni method multiplying the p-value by the number of alleles compared for each parameter.

RESULTS

Eighty-six patients (mean age: 28,73 years±7,59 (6-45 years)) with FA were included in the study. Thirty-two of the patients were female (mean age: 30,13 years±7,99 (6-42 years)) and 54 (mean age: 27,91 years±7,29 (11-45 years)) were male. Three-hundred healthy individuals (F/M:117/183, 36 years±4,16 (18-55) who were not related to each other were included in the study. No statistical significance was found in the patient group in terms of male and female gender.

The most common antigens in patients with FA were HLA-A*02 (21.5%), HLA-A*24 (16.9%), HLA-A*01 (13.4%), HLA-B*35 (20.9%), HLA-B*51 (13.9%), HLA-B*14 (8.1%) and DRB1*11 (21.4%), DRB1*04 (17.5%), DRB1*03 (11%). The most common antigens in controls were HLA-A*02 (25.3%), HLA-A*24 (15.7%), HLA-A*01 (12.5%), HLA-B*35 (17.1%), HLA-B*51 (13.6%), HLA-B*44 (22%) and DRB1*04 (17.2%), DRB1*11 (16.8%), DRB1*13 (11.8%) (Table 1).

In the patient group, the HLA-A*03 (9.9%) ($p=0.015$, OR:2.118 95% CI: 1.188-3.776, $p_c>0,05$), HLA-B*38 (7.0%) ($p=0.047$, OR:1.993 %95 CI: 1.001-3.969, $p_c>0,05$) and HLA-B*14 (8.1%) ($p>0.0001$, OR:3.757 %95 CI: 1.800-7.839, $p_c<0,05$) allele were markedly elevated in comparison to the control group, while the HLA-A*23 (% 10.7) ($p=0.001$, OR:0.169 95% CI: 0.054-0.531, $p_c<0,05$) and HLA-DRB1*07 alleles (4.5%) ($p=0.023$, OR:0.433 95% CI: 0.202-0.926, $p_c>0,05$) were found to be significantly higher in the control group.

When we evaluated the patient group according to gender the HLA-A*01 (n:16, 25%) ($p=0.001$, OR: 4.810 %95 CI: 1.856-12.465, $p_c<0,05$), HLA-A*29 (n:4, 6.3%) ($p=0.009$, OR: 1.067 %95 CI: 1.001-1.136, $p_c>0,05$) and HLA-B*14 (n:9, 14.1%) ($p=0.029$, OR: 3.371 %95 CI: 1.077-10.552, $p_c>0,05$) alleles were significantly higher in the female patient group. The HLA-A*03 (n:15, 13.9%) ($p=0.022$, OR:

0.200 %95 CI: 0.044-0.905, p_c>0,05) and HLA-B*38 (n:12, 11.1%) (p=0.004, OR: 0.889 %95 CI: 0.832-0.950, p_c>0,05) allele were significantly higher in the male patient group.

Table 1. The most common HLA class I and class II alleles in patients and controls

HLA-A	2n:172 Patients	AF	2n:600 Control	AF	HLA-B	2n:172 Patient	AF	2n:600 Control	AF	HLA-DR	2n:154 Patient	AF	2n:600 Control	AF
A*02	37	0.215	152	0.253	B*35	36	0.209	103	0.171	DRB1*11	33	0.214	101	0.168
A*24	29	0.169	94	0.157	B*51	24	0.139	82	0.136	DRB1*04	27	0.175	103	0.172
A*01	23	0.134	75	0.125	B*14	14	0.081	13	0.022	DRB1*03	17	0.11	52	0.087
A*03	17	0.099	28	0.047	B*07	13	0.076	30	0.05	DRB1*13	16	0.104	71	0.118
A*11	14	0.082	36	0.060	B*38	12	0.07	21	0.035	DRB1*01	13	0.085	41	0.068
A*68	10	0.058	20	0.033	B*39	7	0.041	20	0.033	DRB1*15	12	0.078	57	0.095
A*32	10	0.058	21	0.035	B*44	7	0.041	48	0.08	DRB1*14	9	0.058	26	0.043
A*26	7	0.041	37	0.062	B*18	7	0.041	36	0.06	DRB1*07	7	0.046	63	0.105
A*30	7	0.041	20	0.033	B*15	7	0.041	33	0.055	DRB1*16	7	0.046	43	0.072
A*33	5	0.029	16	0.027	B*49	6	0.035	18	0.03	DRB1*10	5	0.032	9	0.015
A*29	4	0.023	9	0.015	B*55	6	0.035	9	0.015	DRB1*12	4	0.026	16	0.027
A*23	3	0.017	62	0.103	B*57	5	0.029	19	0.032	DRB1*08	4	0.026	14	0.023
A*25	2	0.012	8	0.013	B*40	5	0.029	37	0.062	DRB1*09	0	0	4	0.007
A*69	2	0.012	6	0.010	B*08	5	0.029	26	0.043	-	-	-	-	-
A*31	1	0.005	12	0.020	B*41	3	0.017	16	0.027	-	-	-	-	-
A*80	1	0.005	0	0	B*13	3	0.017	16	0.027	-	-	-	-	-
A*66	0	0	3	0.005	B*52	3	0.017	16	0.027	-	-	-	-	-
A*36	0	0	1	0.002	B*50	3	0.017	17	0.028	-	-	-	-	-
-	-	-	-	-	B*27	2	0.012	13	0.022	-	-	-	-	-
-	-	-	-	-	B*73	2	0.012	0	0	-	-	-	-	-
-	-	-	-	-	B*47	1	0.006	0	0	-	-	-	-	-
-	-	-	-	-	B*71	1	0.006	0	0	-	-	-	-	-
-	-	-	-	-	B*58	0	0	8	0.013	-	-	-	-	-
-	-	-	-	-	B*37	0	0	7	0.012	-	-	-	-	-
-	-	-	-	-	B*53	0	0	7	0.012	-	-	-	-	-
-	-	-	-	-	B*48	0	0	3	0.005	-	-	-	-	-
-	-	-	-	-	B*56	0	0	2	0.003	-	-	-	-	-

Note: Allele frequencies were calculated using Gene [RATE] tools.; Abbreviations: AF, allele frequency; n, number of observed alleles.

When the homozygosity of alleles at each locus was compared in the patient and control groups, HLA-A*01, HLA-B*07, HLA-B*49, HLA-B*39 and HLA-B*55 allele homozygosity was significant in patients (Table 2).

Table 2. Homozygosity of HLA-A and HLA-B alleles

HLA-A, B	Patient	Control	p value
A2	8 (9.3%)	22 (7.3%)	p=0.548
A1	5 (5.8%)	5 (1.7%)	p=0.033
A11	1 (1.2%)	1 (0.3%)	p=0.396
A33	1 (1.2%)	0 (0.0%)	p=0.233
A24	3 (3.5%)	8 (2.7%)	p=0.686
A3	1 (1.2%)	0 (0.0%)	p=0.233
A26	0 (0.0%)	2 (0.7%)	p=0.998
A28	1 (1.2%)	0 (0.0%)	p=0.233
A30	0 (0.0%)	1 (0.3%)	p=0.999
A32	0 (0.0%)	1 (0.3%)	p=0.999
A23	1 (1.2%)	0 (0.0%)	p=0.233
B07	4 (3.5%)	0 (0.0%)	p=0.011
B35	6 (7.0%)	9 (3.0%)	p=0.093
B38	2 (2.3%)	2 (0.7%)	p=0.216
B15	1 (1.2%)	0 (0.0%)	p=0.223
B38	2 (2.3%)	2 (0.7%)	P=0.216
B49	2 (2.3%)	0 (0.0%)	p=0.049
B14	1 (1.2%)	1 (0.3%)	p=0.396
B51	4 (4.7%)	5 (1.7%)	p=0.116
B39	2 (2.3%)	0 (0.0%)	p=0.049
B55	2 (2.3%)	0 (0.0%)	p=0.049
B44	0 (0.0%)	4 (1.3%)	p=0.579
B41	1 (1.2%)	0 (0.0%)	p=0.223
B52	0 (0.0%)	1 (0.3%)	p=0.999
B50	0 (0.0%)	1 (0.3%)	p=0.999
B40	0 (0.0%)	1 (0.3%)	p=0.999

HLA-A homozygosity was found in 21 (24.4%) patients and 39 (13.0%) in controls p= 0.010; HLA-B homozygosity was found in 24 (27.9%) patients and 24 (8.0%) in controls p= 0.0001

DISCUSSION

Fanconi anemia is a disease characterized by various complications and frequent hematological abnormalities. Allogeneic HSCT from HLA-matched donor is currently the only effective method of restore normal hematopoiesis[13,14]. Prior studies indicated that HSCT is an effective treatment for Fanconi anemia. In this study, we performed genotyping of HLA-A, -B, and DRB1 in both Turkish individuals diagnosed with Fanconi anemia and in healthy subjects. This allowed us to assess the association between these alleles and the disease.

Human Leukocyte Antigen genes are one of the most polymorphic genes in humans and play an important role in the regulation of the host's immune response. In an epidemiological study conducted in 2021, researchers determined the effect of the HLA-A*03 allele in patients with various cancer types as a biomarker to predict the response to immunotherapy. Their findings indicated a link between the presence of HLA-A*03 alleles and diminished overall survival as well as progression-free survival across multiple tumor types. Additionally, their findings demonstrated the interaction of HLA-A*03 with treatment across four extensive randomized controlled trials focusing on renal cell carcinoma. Moreover, it was predictive of poorer progression-free survival following immunotherapy[15].

In our study, our results revealed that HLA-A*03, HLA-B*14, HLA-B*38 was significant but after Bonferroni test results HLA-B*14 may be a risk factor for Fanconi anemia. However, whether HLA-B*14 has the potential to be a biomarker in patients with Fanconi anemia requires further investigation. On the other hand, the difference in the HLA-A*23 and HLA-DRB1*07 ratios in the patient and control groups were significant. However, after Bonferroni test results DRB1*07 lost its significance. HLA-A*23 may be a protective factor for Fanconi anemia. HLA-A*01, HLA-A*29, and HLA-B*14 alleles in the female patients and HLA-A*03 and HLA-B*38 alleles in the male patients were significantly higher. According to our Bonferroni test HLA-A*01 could be consider as risk factor in female patients group with Fanconi anemia.

A research finding has highlighted an increased prevalence of HLA-A2 and HLA-A2 homozygosity among individuals diagnosed with aplastic anemia and Fanconi anemia within the French population[16]. In another study, researchers did not find any association between HLA-A alleles and Fanconi anemia in the Iranian population[17]. In our comparison results of homozygosity in Fanconi patients and controls, homozygosity in the HLA-A1 allele was found in %5.8 of patients and in %1.7 of

controls. However, we did not find significant homozygosity for the HLA-B and DR alleles in patients and controls.

HLA also plays a role in better elucidating the pathogenesis of FA. At the same time, it will enable the creation of new options for donor selection for hematopoietic stem cell transplantation of FA, immunosuppressive therapy, directing prophylactic treatments for micro-organisms, graft rejection and applications for the prevention of graft versus host disease (GvHD)[8,18]. Fu RT et al. have documented a relationship between HLA alleles and the effectiveness of immunosuppressive (IS) therapy in aplastic anemia (AA) patients across various regions. Their findings suggest that in children with severe AA, those expressing certain alleles such as HLA-B*15:02, B*40:02, B*48:01, DRB1*09:01, C*01:02, C*03:04, DQB1*03:03, and DQB1*06:02 may experience superior efficacy of IS therapy. Conversely, efficacy may be diminished in children with severe AA expressing alleles like HLA-A*29:01, B*15:11, B*38:01, B*39:05, DRB1*15:01, C*01:02, and C*08:22[19]. Twelve of the 86 patients included in the study were transplanted from HLA full-match siblings. 12 patients received the same immunosuppressive regimen. Therefore, we could not evaluate the effect of HLA alleles and immunosuppressive therapy on GVHD. This is the limitation of our study. Since the HLA region is polymorphic, having a large sample size will strengthen the statistical significance. Therefore, the small number of patients is a limitation of the study. Additionally, the inadequacy of information on the immunosuppressive treatment received by the patients has also limited the determination of the relationship between the disease, HLA, and treatment.

In summary, our study revealed varying frequencies of HLA-A, HLA-B, and HLA-DRB1 alleles between patients with Fanconi anemia and healthy controls. These results not only hold practical significance for hematopoietic stem cell transplantation in these patients but also suggest a potential involvement of dysregulated immune responses in their condition. Further investigations need to be performed to better demonstrate the relationship between HLA-A/B/DRB1 alleles underlying molecular mechanisms of these findings.

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