HLA Genotypes in Turkish Hematopoietic Cell Recipients and Likelihood of Finding a Matched Donor Through Family Searches

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Abstract

Objectives: **Allogeneic hematopoietic stem cell transplant is a life-saving treatment, but donor numbers in Turkey do not meet the increasing demand for this procedure. Here, our objectives were (1) to assess the frequency of HLA-matched related donors in the Turkish population and (2) to identify the HLA antigens and haplotypes that are most frequent in Turkey.**

Materials and Methods: **The HLA genotypes of 841 consecutive recipients and 3071 family members were retrospectively reviewed.**

Results: **Matched related donors were identified for 368/841 recipients (44%). Extended family donor searches were performed for 111/181 pediatric recipients (61%), with nonsibling matched related donors found for 23 patients (21%). Matched related donors were found for a significantly higher proportion of pediatric patients (52%) than adult patients (41%) (odds ratio of 2.5; 95% confidence interval, 1.9-4.1; *P* = .02). The percentage of pediatric versus adult patients with 3 or more siblings was 13% versus 46% (odds ratio of 5.6; 95% confidence interval, 3.6-8.5; *P* = .001). The most frequent HLA class I antigens at each locus were HLA-A*02 (20.2%), HLA-B*35 (19.5%), and HLA-C*07 (19.8%). The most frequent HLA class II antigens at each locus were HLA-DRB1*11 (21.6%) and HLA-DQB1*03 (40.2%). The most common 3-locus haplotypes were HLA-A*24 B*35 DRB1*11 (F:0.020) and HLA-A*01 B*08 DRB1*03 (F:0.015). When adult and pediatric groups were combined, the most common locus haplotypes were found in 43/345 sibling donors (12%) and in 7/23 nonsibling pediatric donors (30%) (odds ratio of 2.7; 95% confidence interval, 1.2-6.4; *P* = .02).**

Conclusions: The results indicate that, in Turkey, it can be beneficial to revise donor search algorithms to include an extended family donor search before an unrelated donor search. This type of search can be effective because of the HLA haplotype diversity in Turkey, the frequency of consanguinity, and the country's limited donor pool.

Key words: *Extended family donors, Stem cell transplantation*

Introduction

Allogeneic hematopoietic stem cell transplant (allo-HSCT) can be a life-saving procedure for patients with certain malignant and benign conditions.[1] However, in Turkey, this treatment is not routinely available for all such patients because only one-third have an HLA-matched related donor (MRD). For the remaining two-thirds of these patients, it can be difficult to find a suitable matched unrelated donor due to the inadequate donor pool in Turkey.[2] One way to address the high demand for allo-HSCT is to find donors through extended family donor searches (EFDSs). To date, the reported experience with this type of search suggests that this strategy could potentially help accelerate donor recruitment in many developing nations that have high rates of consanguineous marriage. Turkey is one such country. Studies have indicated that the frequency of finding full MRDs in EFDS varies by population. For example, the chance of finding a family donor is high for patients of Turkish and Arabic origin, whereas it is rare in western countries.[3-7]

Limited data are available on the frequencies of HLA class I and class II antigens and haplotype profiles in small populations within Turkey.[8-13] Our aim was to assess the frequency of HLA-matched family donors in the Turkish population and to

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identify the HLA antigens and haplotypes that are most frequent in Turkey.

Materials and Methods

This retrospective study was carried out at the Gazi University Faculty of Medicine and was approved by the faculty's Institutional Review Board (approval code/reference number: 167).

We reviewed the clinical files of all patients (and corresponding donors) who underwent allo-HSCT for malignant or benign conditions between 2005 and 2014 and who had HLA results recorded by our HLA tissue-typing laboratory during that period. The patients and their donors were from all geographic regions of Turkey. Data on recipient-donor HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 typing were obtained. At our institution, HLA typing is performed at a low resolution using DNA-based methods; high-resolution allele typing is not available. Standard HLA nomenclature was used (http://hla.alleles.org/nomenclature/naming.html).

All recipients and donors gave signed informed consent before HLA studies. Donor searches were conducted by HLA typing of full sibling donors (ie, those who have the same parents) first. If a match was not found, parents and other willing related family members were HLA typed at the clinician's request. We defined match as a 6 of 6 match at HLA-A, HLA-B, and HLA-DRB1 antigens in sibling donor-recipient pairs and a 10 of 10 match at HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 antigens for nonsibling related donor-recipient pairs. Genomic DNA was isolated from each patient and healthy control (ie, their donor) using 200-µL aliquots of peripheral venous blood and the Biorobot EZ1 magnetic bead-based workstation (Qiagen, Hilden, Germany). For each individual, genotyping of HLA class I and II antigens was performed with use of the polymerase chain reaction with sequence-specific oligonucleotide probe hybridization method and Luminex technology (Gen-probe Lifecodes, Stanford, CA, USA).

Statistical analyses

Data were statistically analyzed using Statistical Package for Social Sciences software (SPSS version 15.0, Chicago, IL, USA). Descriptive statistics were generated for demographic data. Differences between donors and recipients were evaluated by chi-square analysis using odds ratio (OR) values and 95% confidence intervals (CI). Antigen frequencies for each locus were estimated by the direct counting method using Excel software. We used the software HAPLOTYPE ANALYSIS version 1.05 (University of Göttingen, Göttingen, Germany) to estimate haplotype frequencies.[14]

Results

Frequency of matched family donors

HLA reports were recorded for 841 recipients (660 adults and 181 children) and 3071 family members. HLA-identical donors were identified for 368 recipients (44%). Sibling donor rates were 41% (275/660) for adult patients and 38% (70/181) for pediatric patients. Per clinicians' decisions, nonsibling donor searches were performed for a median of 25 family members (range, 2-30) for the 111 pediatric patients (67%) who had consanguineous parents (first cousins). The probability of finding an HLA 10/10 identical nonsibling donor through the EFDS was 21% (23/111). Of the 23 nonsibling donors, 13 donors (56%) were parents and 10 donors (44%) were close relatives (5 uncles, 4 aunts, and 1 cousin).

Frequency of HLA class I and class II

Frequencies of HLA-A, HLA-B, and HLA-DRB1 are shown in Table 1. In total, 23 HLA-A antigens, 41 HLA-B antigens, 16 HLA-C antigens, 17 HLA-DRB1 antigens, and 9 HLA-DQB1 antigens were identified. The 2 most frequent HLA class I antigens at each locus were HLA-A*02 (20.2%) and HLA-A*24 (14.9%), HLA-B*35 (19.5%) and HLA-B*51 (15.9%), and HLA-C*07 (19.8%) and HLA-C*04 (18.6%). The 2 most frequent HLA class II antigens at each locus were HLA-DRB1*11 (21.6%) and HLA-DRB1*04 (13.8%) and HLA-DQB1*03 (40.2%) and HLA-DQB1*05 (23.1%). The most common 3-locus haplotypes (in order of ranking) were HLA-A*24,B*35,DRB1*11 (F:0.020) and HLA-A*01,B*08,DRB1*03 (F:0.015). The most common 5-locus haplotypes (in order of ranking) were HLA-A*02,B*35,C*04,DRB1*04,DQB1*03 (F:0.014) and HLA-A*24,B*35,C*04,DRB1*11,DQB1*03 (F:0.011) (Table 2). The most frequent 3-locus haplotypes in the sample of nonsibling donors were (in order) HLA-A*24,B*35,DRB1*11 (F:0.043) and HLA-A*01,B*08,DRB1*03 (F:0.021).

Table 1. Frequency of HLA Antigens in the Turkish Study Patients (N = 841)

Antigen	%	Antigen	%	Antigen	%	Antigen	%	Antigen	%
A*01	12.2	B*04	0.1	C*01	4.8	DRB1*01	5.5	DQB1*01	0.3
A*02	20.2	B*06	0.1	C*02	4.1	DRB1*03	7.7	DQB1*02	15.3
A*03	12.5	B*07	5.1	C*03	5.4	DRB1*04	13.8	DQB1*03	40.2
A*11	8.4	B*08	3.7	C*04	18.6	DRB1*05	0.1	DQB1*04	2.2
A*18	0.1	B*12	0.1	C*05	2.6	DRB1*07	7.3	DQB1*05	23.1
A*21	0.1	B*13	3.4	C*06	9.7	DRB1*08	2.4	DQB1*06	18.8
A*23	3.5	B*14	2.0	C*07	19.8	DRB1*09	1.1	DQB1*08	0.1
A*24	14.9	B*15	3.0	C*08	2.4	DRB1*10	2.7	DQB1*11	0.1
A*25	0.3	B*16	0.1	C*11	0.1	DRB1*11	21.6	DQB1*14	0.1
A*26	5.5	B*18	5.6	C*12	13.0	DRB1*12	1.7		
A*28	0.3	B*27	3.2	C*14	5.2	DRB1*13	11.6		
A*29	2.1	B*35	19.5	C*15	7.9	DRB1*14	7.7		
A*30	3.2	B*37	1.5	C*16	4.3	DRB1*15	11.0		
A*31	2.5	B*38	3.9	C*17	1.9	DRB1*16	4.3		
A*32	6.2	B*39	1.0	C*18	0.3	DRB1*17	1.4		
A*33	3.1	B*40	2.9	C*57	0.1	DRB1*41	0.1		
A*34	0.1	B*41	2.5			DRB1*52	0.1		
A*36	0.1	B*44	6.5						
A*61	0.1	B*45	0.3						
A*66	0.4	B*46	0.2						
A*68	3.6	B*47	0.4						
A*69	0.7	B*48	0.1						
A*74	0.1	B*49	4.1						
		B*50	1.8						
		B*51	15.9						
		B*52	3.4						
		B*53	0.4						
		B*54	0.3						
		B*55	2.8						
		B*56	0.2						
		B*57	2.5						
		B*58	1.6						
		B*60	0.4						
		B*61	0.5						
		B*62	0.3						
		B*63	0.3						
		B*65	0.3						
		B*71	0.1						
		B*73	0.1						
		B*78	0.1						
		B*95	0.1						

Table 2. Haplotype Frequencies in the Turkish Study Patients (N = 841)

Three-locus Haplotype	Frequency	Five-locus Haplotype	Frequency
HLA-A*24 B*35 DRB1*11	0.020	HLA-A*02 B*35 C*04 DRB1*04 DQB1*03	0.014
HLA-A*01 B*08 DRB1*03	0.015	HLA-A*24 B*35 C*04 DRB1*11 DQB1*03	0.011
HLA-A*02 B*35 DRB1*04	0.014	HLA-A*02 B*35 C*04 DRB1*11 DQB1*03	0.009
HLA-A*02 B*35 DRB1*11	0.014	HLA-A*11 B*52 C*12 DRB1*15 DQB1*06	0.009
HLA-A*03 B*35 DRB1*11	0.013	HLA-A*03 B*35 C*04 DRB1*11 DQB1*03	0.008
HLA-A*01 B*35 DRB1*04	0.013	HLA-A*02 B*08 C*07 DRB1*03 DQB1*02	0.008
HLA-A*02 B*08 DRB1*03	0.011	HLA-A*01 B*35 C*04 DRB1*04 DQB1*03	0.008
HLA-A*11 B*52 DRB1*15	0.011	HLA-A*02 B*35 C*04 DRB1*03 DQB1*02	0.007
HLA-A*24 B*51 DRB1*11	0.010	HLA-A*02 B*35 C*04 DRB1*01 DQB1*03	0.007
HLA-A*02 B*44 DRB1*04	0.010	HLA-A*03 B*07 C*07 DRB1*11 DQB1*03	0.005

Comparison of pediatric and adult groups

Matched-related donors were found for a significantly higher proportion of pediatric patients (52%) than adult patients (41%) (OR of 2.5; 95% CI, 1.9-4.1; $P = .02$). Regarding the adult and pediatric groups combined, the most common 3-locus haplotypes were found in 43 (12%) of the 345 sibling donors, whereas these haplotypes were found in 7 (30%) of the 23 nonsibling pediatric donors (OR of 2.7; 95% CI, 1.2-6.4; $P = .02$). Findings for number of siblings also differed significantly between the pediatric and adult groups, with only 13% of pediatric patients having 3 or more siblings versus 46% of adult patients (OR of 5.6; 95% CI, 3.6-8.5; $P = .001$).

Discussion

The literature contains little information about the probability of finding an HLA-identical family donor for a patient in a developing country who requires allo-HSCT.[3-7] Our main finding was that the likelihood of finding an MRD in Turkey is significantly higher

for children than for adults (52% vs 41%). This difference could be explained by the fact that 21% of the pediatric patient donors were nonsiblings who were identified via EFDS. Similar results for pediatric patient MRDs identified via EFDS were reported in previous studies from Turkey (23%) and Jordan (18%).[3,4] The frequency of findings MRDs via EFDS varies among populations.[3-7] According to the report in Israel, this was achieved for 80% of patients with Arabic origin and for 40% of Jewish patients in an Israeli donor search program.[5] High proportions of HLA-identical donors found by all search types (ie, range, 60% to 80%) have been reported for Saudi Arabia, Jordan, and Pakistan,[4,15,16] and the overall rate that we observed in our pediatric group (52%) was comparable. This may be explained by the high rate of consanguineous marriages in Middle Eastern countries (22% in Turkey).[17]

The probability of finding an HLA-identical unrelated donor in national and international donor registries is highly dependent on the presence of at least 1 common haplotype in the index case.[18] The rate of a matched unrelated donor transplant among all allo-HSCT is low (9%) in Turkey, mainly because of difficulties recruiting volunteers, economic barriers, and HLA haplotype diversity.[2,19-21] Consistent with these findings, data from the German donor program have indicated that the probability of finding matching donor-recipient pairs is 49% for a person of German descent but only 10% for a person of Turkish descent.[9,19] This underlines the importance of knowing the most frequent HLA antigens and haplotypes in different ethnic populations.

Our current study investigated HLA antigens and haplotype frequencies in a large sample of the Turkish population, which were compared with findings for other populations (Table 3). The distributions of the most frequent HLA-A, HLA-B, and HLA-C antigens were similar to those observed in previous studies of the Turkish population by Uyar and associates[13] (n = 142) and Kayhan and associates[8] (n = 408) and in Mediterranean countries such as Bulgaria, Macedonia, Albania, Greece, and Italy, but these results were higher than those reported in Asian populations. Only the frequency of HLA-B*51 in our study was different from that noted by Arnaiz-Villena and colleagues[10] in a report on the HLA class I allelic distribution in a Turkish population (n = 228). Our much larger sample size (841 patients) might explain this discrepancy. Among class II genotypes, HLA-DRB1*11, HLA-DRB1*04, and HLA-DRB1*13 were the most frequent antigens detected in our study, similar to that previously reported by Saruhan-Direskeneli and associates.[12] Those authors identified HLA-DRB1*11 as the major allele for Mediterranean countries, with the highest frequencies reported in Macedonia, Greece, Croatia, Albania, and Bulgaria.[12]

The most frequent HLA haplotypes have been well established for donors who were registered with the German bone marrow donor center, which includes parentage from 17 different countries.[9] However, similarly, the combination HLA-A*24 B*35 DRB1*11 haplotype was found to be at low frequency in people in Germany who were of Italian, Greek, and Turkish descent, and this is close to the value

Table 3. HLA Haplotype Studies in the Turkish Population

Author	No. of Patients	Type of Study Group	HLA Haplotypes	HF
Arnaiz-Villena and associates (2001)[10]	228	Unrelated blood donors	A*24, B*51, DR*11, DQ*07	0.053
			A*23, B*49, DR*11, DQ*07	0.026
Uyar and associates (2004)[13]	142	Unrelated blood donors	A*0201, B*08, CW*07, DRB1*0301, DQA1*0501, DQB1*02	0.021
			A*24, B*35, CW*04, DRB1*1101, DQA1*0501, DQB1*0301	0.014
Schmidt and associates (2009)[11]	23 776	Unrelated Turkish bone marrow donors in Germany	A*11,24, B*35, 51, DR* 04, 11	0.063
			A*24, B*35, DR* 11	0.042
Kayhan and associates (2013)[8]	408	Dialysis patients	A*02, B*51*DRB1*11	0.014
			A*11, B*35*DRB1*11	0.012
			A*24, B*35*DRB1*11	0.011
Pingel and associates (2013)[9]	4856	Unrelated Turkish bone marrow donors in Germany	A*30:01, B*13:02, CW*06:02, DRB1*07:01, DQ*02:01	0.0098
			A*24:02, B*35:02, CW*04:01, DRB1*11:04	0.0092
Current study	841	Bone marrow patients in Turkey	A*02, B*35, C*04, DRB1*04, DQB1*03	0.014
			A*24, B*35, C*04, DRB1*11, DQB1*03	0.011
			A*24, B*35, DRB1*11	0.020
			A*01, B*08, DRB1*03	0.015

Abbreviations: HF, haplotype frequency

observed in our sample and to values in other reports on Turkish populations.[9,11,13] In contrast, we observed other common HLA haplotypes at completely different rankings and frequencies in comparison to studies by Kayhan and associates[8] and Arnaiz-Villena and associates.[10] Those investigations involved smaller sample sizes of Turkish patients and different types of donors (unrelated blood donors and dialysis patients); ours is the first study to have analyzed common HLA haplotype frequencies in a large sample of Turkish bone marrow patients.

Transplant physicians often face great challenges finding MRDs for patients who express rare HLA haplotypes. However, the frequency of the most common haplotype was significantly higher in the nonsibling donors than in the sibling donors in our study. These data indicate that, in cases where a patient's siblings have the rare haplotype, the other family members should be tested to identify whether they share a haplotype with the index case. Together, our results and other findings to date indicate that identifying the most common HLA genotypes in the Turkish population might improve the family donation rate in our country's national donor search program.

In parallel with a previous report,[4] we found a higher frequency of sibling donors in the adult group than in the pediatric group; therefore, physicians of adult patients who require allo-HSCT tend not to do routine screening for EFDS. Although this search strategy was only used for pediatric patients in our study, the results suggest that EFDS may be useful for finding HLA-compatible donors in Turkey, a country with a high rate of consanguinity and relatively diverse HLA haplotypes. How these factors might contribute to the observed difference in the use of an EFDS approach between the 2 age groups would require further study.

The HLA-A, HLA-B, and HLA-DRB1 typings of most donor registries are routinely performed by serologic and/or low-resolution techniques initially because these methods are cost-effective. This is followed by high-resolution typing for other loci if needed. High-resolution typing is not performed for nonsibling pairs in our institution. However, Kanda and associates[22] used the Japanese national HLA data library to classify nonsibling related donors as genotypically matched if the loci that were serologically matched and less than a 5% risk of genotype mismatch in the Japanese population. Such a comprehensive database is needed in the Turkish populations, although Uyar and associates[13] have shown that serologic data from the small sample size Turkish population corresponded well with genomic data at the HLA-A and HLA-B loci.

The major limitations of this study are its retrospective single center experience and the fact that allele-level HLA typing was not performed on nonsibling donors. Our study, although retrospective, provided HLA typing results on a large number of nonsibling related donors. A prospective multicenter study is needed to validate our findings.

Conclusions

For patients who require allo-HSCT and do not have a sibling donor, no universal agreement or standards are in place to govern the most appropriate method to select a donor. In Turkey, donor search algorithms can be revised to include an EFDS before an unrelated-donor search. This type of search can be effective because of the HLA haplotype diversity in our country, the frequency of consanguinity, and Turkey's limited donor pool.

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