Clinically important Human Leukocyte Antigen (HLA) Alleles among Bahraini Population

Eman Farid, MD, PhD* Kannan Sridharan, MD, DM**

Background: Human Leukocyte Antigen (HLA) has been well associated with autoimmune and rheumatic disorders; HLA B27 with ankylosing spondylitis, HLA B5 with Behcet's disease, HLA DR3/DR4 with type I diabetes, HLA DR4 with rheumatoid arthritis, and HLA DR2/DR3 with systemic lupus erythematosus. Distribution of HLA alleles has been significantly influenced by ethnicity. Considering the dearth of data on distributions of HLA alleles in Bahraini population, the present study was carried out in healthy individuals.

Objective: To assess the prevalence of HLA B27, HLA B5, HLA DR2, HLA DR3 and HLA DR4 alleles in healthy Bahraini individuals.

Design: A Retrospective Cross-Sectional Study.

Setting: Department of Pathology-Immunology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain.

Method: Two-hundred and fifty unrelated Bahraini healthy individuals (donors for kidney/bone marrow transplantation that were assessed between 1 January 2017 and 31 March 2019) were included. The following HLA alleles were screened in this cohort: HLA B27 and B5 (Class I), and HLA DR2, DR3 and DR4 (Class II).

Result: Fifty-five (22%) individuals had HLA B5 (with its two splits 51 and 52), 50 (20%) had HLA DR2, 35 (14%) had DR3, 30 (12%) had DR4, and 4 (1.6%) had HLA B27. Fifty-five (22%) individuals had HLA B5 (with its two splits 51 and 52), 50 (20%) had HLA DR2, 35 (14%) had DR3, 30 (12%) had DR4, and 4 (1.6%) had HLA B27.

Conclusion: HLA B27 is a rare allele in the Bahraini population, while the other studied alleles are moderately distributed.

INTRODUCTION

Human Leukocyte Antigen (HLA) molecules, encoded by genes located in the short-arm of chromosome 6, is involved in transmembrane presentation of peptides to T-cells[1]. HLAs are classified into Class I (A, B, C, E, F and G) and Class II (DR, DQ, DM and DP)[2]. HLA system has been attributed in several autoimmune and rheumatologic disorders such as rheumatoid arthritis (RA), type 1 diabetes milletus (T1DM), ankylosing spondylitis, and systemic lupus erythematosus (SLE); infectious conditions such as human immunodeficiency virus (HIV) and hepatitis C virus; organ transplantation; and transfusion-related reactions[3-5]. Prevalence of HLA types vary between different ethnic populations[6]. Bahraini population is unique particularly with respect to consanguinity that ranges between 20 and 50%[7]. Previous studies have demonstrated association between certain HLA alleles with auto-immune disorders[8,9]. Up to date, there is a lack of data regarding the HLA distribution in healthy Bahraini population.

The aim of this study is to assess the prevalence of HLA B27, HLA B5, HLA DR2, HLA DR3 and HLA DR4 alleles among healthy Bahraini individuals.

METHOD

The study was initiated after obtaining approval from the Institutional Ethics Committee. The study was carried out in compliance to the World Medical Association Declaration of Helsinki guidelines. The design of the study was retrospective cross-sectional enrolling unrelated healthy donors for kidney/bone marrow transplantation that were assessed between January 2017 and March 2019. Participants were ascertained healthy from their medical history, physical examination, and laboratory tests.

HLA typing was done serologically by lymphocytotoxicity method, using immunomagnetic beads and immunofluorescence staining,

* Senior Consultant/ Head of Immunology
Department of Pathology
Salmaniya Medical Complex
Ministry of Health
Associate Professor
Department of Microbiology/Immunology
College of Medicine & Medical Sciences
Arabian Gulf University
** Associate Professor
Department of Pharmacology & Therapeutics
College of Medicine & Medical Sciences
Arabian Gulf University
Kingdom of Bahrain
E-mail: efareed@health.gov.bh

Biotest Co. Germany[10]. As a standard of care, five HLA alleles that were clinically important such as HLA B27 and B5 (Class I) and HLA DR2, DR3 and DR4 (Class II) were tested and the same has been captured in this study.

Descriptive statistics was used for representing the demographic variables as well as distributions of HLA alleles. Antigen frequency was estimated by direct count. Chi-square test of association was used to compare the proportions of patients with each of the alleles in the present study with that of other populations in the region.

RESULT

Two-hundred and fifty individuals were recruited. Mean (SD) age of the study participants was 35.4 (15.1) years. One-hundred and thirty-six (54.4%) were males.

Fifty-five (22%) individuals had HLA B5 (with its two splits 51 and 52), 50 (20%) had HLA DR2, 35 (14%) had DR3, 30 (12%) had DR4, and 4 (1.6%) had HLA B27.

A comparison of the studied HLA alleles with other Gulf countries is present in table 1. The distributions of the HLA alleles assessed in the present study were similar across the regional populations except HLA DR2 and B5 that were significantly higher in Emiratis. HLA DR2 was also reported in significantly higher proportions in Omani population.

Table 1: Comparisons of Distributions of HLA Alleles in Various Populations in the Arabian Gulf Peninsula

HLA alleles	Frequency distribution (%)				
	Bahrain (Present study)	Kuwaiti	Omani	Saudi	Emirati
HLA DR2	20	10.4[11]	37.4[12]	13.6[14]	43[15]
HLA DR3	14	15.7[11]	14.57[12]	16.5[14]	14.3[15]
HLA DR4	12	14.4[11]	8.23[12]	3.5[14]	19.4[15]
HLA B5 (51)	22	15.3[11]	8.9[12]	16.1[14]	34.4[15]
HLA B27	1.6	0.8[11]	0.3[13]	0.7[14]	0.8[15]

DISCUSSION

We undertook the present study to assess the frequency of clinically important HLA alleles in Bahraini population. We observed that HLA B27 was the least frequent similar to other regional populations. HLA DR2 and B5 were less frequent compared to Emiratis and Omani populations[12,15].

The distribution of HLA alleles has been studied by various investigators in the Arab population. A recent meta-analysis compiling data from 100 populations in 16,000 patients revealed that the most common HLA alleles were HLA A01, A02, B35, B51, DRB1 and DQB1 in Arabs[16]. HLA class II alleles and haplotypes (DRB1 and DQB1) have been previously assessed in a small Bahraini population (n=72) and compared to Lebanese by Almawi et al[17]. The authors observed that the DRB1*160101-DQB1*050101 and DRB1*030101-DQB1*0201 haplotypes were more frequent among Bahrainis, while the DRB1*110101-DQB1*030101 and DRB1*040101-DQB1*0302 haplotypes were more frequent in Lebanese population. Another study from Bahraini population with multiple sclerosis (MS) has concluded that HLA antigens A2, A9, A19, B5, B35, B40, DR3, DR4 and DR16 is higher in patients[18]. A recent study by Hajjej et al in 175 Bahraini individuals revealed that the most common class I alleles were A*02:01:01, A*01:01:01, B*35:01:02, C*12:01:01, and C*04:01:01, while DRB1*03:01:01, DQB1*02:01:01, and DQB1*05:01:01 were the most frequent class II HLA alleles and haplotypes[19]. Farid et al observed that HLA B27 was prevalent in 2.7% of healthy Bahraini individuals (n=260) like that observed in the present study[20]. However, the authors have observed that HLA B27 is prevalent in 96% of those with ankylosing spondylitis (n=26)[20]. Similarly, HLA DR4 was observed to be prevalent in approximately 27% Bahraini patients with rheumatoid arthritis (in-house unpublished data) compared to 12% that we observed in healthy individuals. In our population, 66.7% of individuals with Behcet's disease were observed with HLA B5 allele[21].

The present study is the largest until now that has assessed the distributions of various HLA alleles in Bahraini population. However, population-based studies are needed. Population-based studies assessing the frequencies of HLA alleles and haplotypes are important for choosing the most appropriate donors. This is partly due to the recently established fact that patients with one or two frequently occurring haplotypes particularly HLA with non-HLA antigens that remain in linkage disequilibrium experience less risk of acute graft-versus-host-disease[22,23]. In the present study, the prevalence of HLA DR3/DR4 was observed at 26% and these alleles carry high risk for T1DM. T1DM has been reported in approximately 8.5 per 100,000 Bahraini population and 83% of Bahraini children with DM were observed with HLA DR3/DR4 alleles[24,25]. Considering the prevalence of various clinically important HLA alleles in our population, there is a clear-cut need for HLA screening to be initiated early in life for appropriate disease prevention strategies. We also observed subtle differences in the distributions of HLA alleles between Bahraini and regional groups. This could partly be attributed to the relatively smaller size of the samples evaluated in the clinical studies as well as higher prevalence of HLA alleles in Bahraini population.

The present study is limited in recruiting the individuals only from a single tertiary care hospital in Bahrain.

CONCLUSION

We have evaluated the prevalence of clinically important HLA alleles: HLA B27, B5(51), DR2, DR3, DR4 in Bahraini healthy population. HLA B27 is a rare allele in the Bahraini population. There is a need for HLA family screening to be initiated early in life to identify members carrying a higher risk, for appropriate prevention strategies of autoimmune/rheumatic disease.

The present study is limited in recruiting the individuals only from a single tertiary care hospital in Bahrain. Moreover, the data from this study will provide the background prevalence for basing future population-based assessment of HLA alleles and haplotypes in Bahraini population. We recommend setting up a national Bahraini registry based on HLA allele's distribution that can support organ transplantation centers in choosing appropriate donors.

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