HLA-A*26 and Susceptibility of Iranian Patients with Non-Hodgkin Lymphoma

Arezou Sayad[1], Mohammad Taghi Akbari[2**], Mahshid Mehdizadeh[3,4], Mohammad Taheri[1], Abbas Hajifathali[3*]

[1]Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, [2]Department of Medical Genetics, Faculty of Medical Science, Tarbiat Modares University, [3]Taleghani Bone Marrow Transplantation Center, [4]Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Non-Hodgkin lymphoma (NHL) includes a wide range of diseases with different clinical and biological features. NHL is usually presented as localized or generalized lymphadenopathy. It has been suggested that the HLA class I and II are associated with susceptibility to NHL. Different ethnic groups have been found to have different HLA class I and II alleles which affect NHL. **Objective:** To evaluate the association of HLA class I and class II with Non-Hodgkin's lymphoma in Iranian patients. **Methods:** We performed a case-control genotyping study on 75 Iranian NHL patients who were selected from among the patients referred to the Bone Marrow Transplantation Department of Taleghani Hospital and 120 apparently healthy control subjects using the SSP-PCR by a commercial kit. **Results:** Our results demonstrated that the HLA-A*26 (p: 0.026; OR: 8.5) and HLA-B*35 (p: 0.022; OR: 0.375) alleles had positive and negative associations with NHL disease, respectively. HLA-DRB1*13 allele showed decrease of frequency in patients in comparison with the controls, but it did not remain significant after correction. **Conclusions:** Our results conclude that HLA-A*26 may represent as a genetic susceptibility factors in Iranian patients with Non-Hodgkin's lymphoma, a finding which generally supports contribution of genetic factors in the etiology of this disorder. In addition, these results may be useful in designing a peptide based vaccine for the Iranian NHL patients with HLA-A*26.

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*Corresponding author: Dr. Abbas Hajifathali, Taleghani Bone Marrow Transplantation Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, e-mail: ar.sayad@sbmu.ac.ir.

**Co-Correspondence: Mohammad Taghi Akbari, Department of Medical Genetics, Faculty of Medical Science, Tarbiat Modares University, Tehran, Iran, e-mail: mtakbari@modares.ac.ir.

INTRODUCTION

The NHL includes a wide range of diseases with different clinical and biological features. NHL is usually presented as localized or generalized lymphadenopathy; however, in about one-third of patients it may be primarily found in other sites (1). Human leukocyte antigens (HLA) are among the most polymorphic genes and result in variations of the peptide-binding cleft influencing the bound antigens and presented to T cells (2). In general, HLA class I molecules present foreign antigens to CD8+ cytotoxic T lymphocytes, and HLA Class II molecules present antigenic peptides to CD4+ T helper cells (3). HLA plays a critical role in human immunological diseases, transplantation, host defense against infections, and all known risk factors for non-Hodgkin lymphoma (4). However, the crucial roles of the HLA system for regulating the susceptibility to tumors have become more clear (5).

Genome wide association studies have implicated a number of immune-related genes with NHL risk. Specifically, there are alleles within several genes located in the 6p21.3 chromosomal region, which are associated with NHL risk, including HLA genes (6-9). One study indicated that HLA-A*33, HLA-B*51, HLA-B*44 and HLA-DRB1*09 alleles had associations with NHL while another study demonstrated that HLA-A*26, HLA-B*35 and HLA-DRB1*13 alleles were associated with NHL, significantly (10, 11). The studies on HLA class II polymorphism in Thai and Japanese NHL patients in comparison with the controls indicated that the frequencies of HLA-DRB1*0803, *0802 and *1502 alleles were increased and DRB1*1501 and *0405 alleles were decreased but none of DRB alleles had a significant positive or negative association with NHL in Japanese patients, whereas the frequencies of DRB1*1502 and *0901 alleles were increased and the DRB1*0404, *0803 and *1106 alleles were decreased in Thai NHL patients. In addition, when allele frequencies of NHL Japanese patients were compared to Thai patients, only the DRB1*0803 allele was significantly increased in Japanese patients (12,13). Therefore, different studies have shown that different HLA alleles are associated with a population of NHL. The aim of our study was to evaluate the association of HLA genes with NHL in Iranian patients.

MATERIALS AND METHODS

Patients and Controls. Seventy-five Iranian patients with NHL from the Bone Marrow Transplantation Department of Taleghani Hospital were selected. The diagnosis of NHL was made by the cooperating oncologist. Besides, one hundred twenty ethnically, age and sex-matched healthy individuals without any personal or familial history of diagnosed cancer or autoimmune disorders were randomly included as controls. The subjects gave an informed written consent agreeing to participate.

DNA Extraction and HLA Genotyping. Genomic DNA from venous peripheral blood samples was isolated by applying the salting out method. The HLA typing was carried out at the Tehran Medical Genetics Laboratory. HLA-A, -B, -DRB1 genotyping was performed based on SSP-PCR by HLA- READY GENE ABDR Kit (Inno-Train Diagnostic GmbH, Germany) according to the manufacturer's instructions. The electrophoresis using 2% agarose gel was applied on amplified PCR products.

Statistical Analysis. Comparisons between the various HLA-A, -B, -DRB alleles of patients with NHL and controls were made using the Fisher's exact tests. All the

analyses were done using SPSS version 18.0 for windows software. P values less than 0.05 was considered to be statistically significant.

RESULTS

Distributions of gender and age among patients with NHL and control individuals are shown in Table 1.

Table 1. Distributions of sex and age of NHL patient and control groups.

Variables	NHL Patients	Controls
Female	33 (44%)	48 (40%)
Male	42 (56%)	72 (60%)
Age (mean ± SD, years)	32 ± 3.8	31 ± 3.6
Age Range (years)	19-58	17-56

The allele frequencies of HLA-A, HLA-B, and HLA-DRB1 in patients and controls are demonstrated in Table 2. According to low resolution HLA typing, the NHL patients had an increase in the frequency of HLA-A*26 allele in comparison with the controls, significantly (7% vs. 1%; p: 0.026; OR: 8.5; Table 2). The HLA-B*35 allele was significantly more frequent in the control individuals than in NHL patients (11% vs. 24%; p: 0.022; OR: 0.375; Table 2). The HLA-DRB1*13 allele was more frequent in controls, but it did not remain significant after correction (p: 0.182; OR: 0.237; Table 2). We observed that HLA-A*26 and HLA-B*35 alleles had significantly positive and negative associations to NHL disease, respectively.

DISCUSSION

After description of serological technique for HLA typing, studies on the association of the HLA allele and the susceptibility to or protection against different disease started. In our research, we investigated the association of HLA class I and II with NHL in Iranian patients. In our study, the HLA-A*26, -B*35 alleles had significant positive and negative associations with NHL, whereas DRB1*13 allele showed decrease in NHL patients, but this difference did not remain significant after correction. Consistent to our study, in a research on the non-Hispanic white descent, it is reported that HLA-A*26:01 allele was associated with increased NHL risk and -B*35:03 was associated with decreased NHL risk (10).

Table 2. The allele frequencies of HLA-A, HLA-B, HLA-DRB1 in patients with NHL and control group.

Alleles	Patients with NHL n=150(%)	Controls n=240(%)	PC Value [a]	OR(95%CI)
HLA-A*01	9(6%)	24(10%)	NS	-
HLA-A*02	35(23%)	65(27%)	NS	-
HLA-A*03	24 (16%)	50(21%)	NS	-
HLA-A*11	18(12%)	22(9%)	NS	-
HLA-A*23	9(6%)	10(4%)	NS	-
HLA-A*24	39(26%)	46(19%)	NS	-
HLA-A*26	10(7%)	2(1%)	0.026[b]	8.5(1.836-39.351)
HLA-A*29	3(2%)	7(3%)	NS	-
HLA-A*30	0(0%)	2(1%)	NS	-
HLA-A*31	0(0%)	2(1%)	NS	-
HLA-A*32	0(0%)	2(1%)	NS	-
HLA-A*33	0 (0%)	5(2%)	NS	-
HLA-A*68	3(2%)	3(1%)	NS	-
HLA-B*07	9(6%)	9(4%)	NS	-
HLA-B*08	3(2%)	7(3%)	NS	-
HLA-B*09	3(2%)	7(3%)	NS	-
HLA-B*13	6(4%)	7(3%)	NS	-
HLA-B*14	3(2%)	2(1%)	NS	-
HLA-B*15	3(2%)	4(2%)	NS	-
HLA-B*18	3(2%)	5(2%)	NS	-
HLA-B*27	6(4%)	9(4%)	NS	-
HLA-B*35	16(11%)	58(24%)	0.022[c]	0.375(0.206-0.68)
HLA-B*38	11(7%)	19(8%)	NS	-
HLA-B*39	6(4%)	7(3%)	NS	-
HLA-B*40	3(2%)	4(2%)	NS	-
HLA-B*41	3(2%)	2(1%)	NS	-
HLA-B*44	21(14%)	33(14%)	NS	-
HLA-B*49	3(2%)	9(4%)	NS	-
HLA-B*50	3(2%)	12(5%)	NS	-
HLA-B*51	33(22%)	36(15%)	NS	-
HLA-B*52	6(4%)	2(1%)	NS	-
HLA-B*54	3(2%)	0(0%)	NS	-
HLA-B*55	3(2%)	4(2%)	NS	-
HLA-B*57	3(2%)	2(1%)	NS	-
HLA-B*58	0(0%)	2(1%)	NS	-
HLA-DRB1*01	6(4%)	10(4%)	NS	-
HLA-DRB1*03	15(10%)	22 (9%)	NS	-
HLA-DRB1*04	9(6%)	14(6%)	NS	-
HLA-DRB1*07	12(8%)	24(10%)	NS	-
HLA-DRB1*08	3(2%)	2(1%)	NS	-
HLA-DRB1*09	12(8%)	10(4%)	NS	-
HLA-DRB1*10	9(6%)	12(5%)	NS	-
HLA-DRB1*11	54(36%)	82(34%)	NS	-
HLA-DRB1*12	3(2%)	2(1%)	NS	-
HLA-DRB1*13	3(2%)	19(8%)	0.182[d]	0.237(0.069-0.817)
HLA-DRB1*14	9(6%)	26(11%)	NS	-
HLA-DRB1*15	9(6%)	7(3%)	NS	-
HLA-DRB1*16	6(4%)	10(4%)	NS	-

a: p value of Chi-square or Fisher's exact test with bonferroni correction. b: p-value before correction: 0.002. c: p-value before correction: 0.001. d: p-value before correction: 0.014. n: number of alleles. NS: not significant. NHL: non-Hodgkin's lymphoma.

Moreover, HLA-DRB1*13 allele was inversely associated with NHL risk (p=0.03, OR: 0.71) (10). In a study on Korean patients with NHL, the HLA-DRB1*09 allele was significantly increased (p=0.006; RR=2.7). Also in their study HLA-B*51 allele and HLA-A*33 and HLA-B*44 alleles had susceptibility and protective effects on NHL, respectively (11). The HLA class II genes in Thai patients with non-Hodgkin's lymphoma showed that the frequencies of -DRB1*09:01 and *15:02 were increased while those of DRB1*04:04, *08:03 and *11:06 were decreased in NHL patients when compared with the normal population (12). The evaluation of HLA class II alleles frequencies in Japanese patients with non-Hodgkin's lymphoma demonstrated that whereas the frequencies of HLA-DRB1*08:03, *08:02 and *15:02 were increased and the DRB1*15:01 and *04:05 were decreased in NHL patients, none of these HLA class II alleles showed a significant positive or negative associations with NHL (13). Study on HLA class II polymorphism in Egyptian children with lymphomas showed that the HLA-DRB1*13:01 was significantly increased in patients with NHL in comparison with the controls (14).

In conclusion, HLA allele associations in our population demonstrated some differences from previous published researches on Hodgkin lymphoma disease (HD).

Variations amongst populations' backgrounds might be the reason behind these controversies. In addition, further studies with large sample sizes are needed to better define the associations of HLA genes in NHL patient and to confirm our preliminary findings.

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