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The association of HLA-A, -B gene polymorphisms with acute lymphoblastic leukemia (ALL) in Iranian patients

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ABSTRACT

Leukemia was the first disease in which the involvement of the major histocompatibility complex (MHC) was reported. MHC is a polygenic and polymorphic system containing the loci for genes coding class I, II and III of HLA (Human Leukocyte Antigen) genes which are one of the most polymorphic loci in the human genome, located on the short arm of chromosome 6 (6p23). In the present study, the relation between HLA-A,-B various alleles and ALL disease was investigated in Iranian patients. Eleven ALL cases who referred to bone marrow transplantation department of Taleghani Hospital and fifty healthy controls were randomly selected. DNA extraction was performed by salting out method followed by HLA-A, -B typing based on PCR-SSP technique using HLA-READY GENE of Inno-Train kits. DNA analysis demonstrated that the frequency of HLA-A*11 (pc= 0.009; OR: 9.510; 95% CI: 2.077- 43.537) was significantly higher in ALL patients than controls. According to these results, the HLA –A alleles may lead to susceptibility to ALL in Iranian patients. The results suggest that there is contribution between HLA-A*11 gene and ALL developing in Iranian patients. But, large sample size should be study to achieve more reliable outcomes.

Key words: acute lymphoblastic leukemia (ALL), HLA, polymorphism

1. INTRODUCTION

Blood cancer is a malignant progressive disease of hematopoietic organs that is introduced as uncontrollable proliferation of hematopoietic cells. The precursors of bone marrow cannot evaluate to normal cells and as a result, premature cells exceed the blood circulation. The abnormal blood cells are insufficient, so, at the end stage, it leads to patient death (1). Human leukocyte antigen (HLA) genes which are one of the most polymorphic loci in the human genome are located on the short arm of chromosome 6. HLA genes play a main role in the control of immune response (2-5). 75% of acute leukemia cases are ALL (acute lymphoblastic leukemia). The disease is more prevalent among children and the age of onset is about 3 -7 years. Caucasians are infected twice more than African- Americans (6). ALL mainly infects

children and youth. It is uncommon that middle-aged adult develop to ALL, but the risk of infection increases among elders. Leukemia was the first disease in which the involvement of the major histocompatibility complex (MHC) was reported (7). Wide studies about the association between leukemia and HLA genotype have been done. According to previous studies, HLA region can influence the susceptibility to or protection against ALL. Murine model was the first investigation of probable association MHC and leukemia (8). Walford et al. were the first researchers who studied the association of HLA and ALL (9). We had studied the association of HLA-DRB1 gene polymorphisms and ALL in Iranian patients (10). Also, we had evaluated the association of different alleles of HLA or other genes with some autoimmune disorders such as diabetes type 1 and MS disease (11-16). Reviewing of cancers in children demonstrated a high outbreak of leukemia (49.2%) and ALL was the most frequent type of leukemia (38.2%) in the Kermanshah province of Iran (17). According to the findings of a research that was performed in south part of Iran, ALL was the third prevalent cancer in men of this region (18). Also the findings of same study in Fars province of Iran showed that ALL is the first common cancer in men and the second common cancer in women of this province (19). Exposure to some industrial materials, agricultural chemicals (such as herbicides) and smoking may lead to ALL developing in adults. HLA genotypes may have a principal effect on the modification of environmental risk factor and can affect the ALL developing. In the present study, the association of HLA-A, -B alleles and ALL disease was investigated in 11 Iranian patients with ALL.

2. MATERIALS AND METHODS

2.1. Patients and controls

This study was performed as a case-control study. Peripheral blood samples were collected from 11 Iranian ALL patients and 50 healthy individuals as control group. The case and control groups were age and gender-matched. None of the control individuals had personal or familial history of cancer or autoimmune disease. The blood samples were collected from Taleghani Hospital of Tehran. The individuals were given informed consent form.

2.2. DNA extraction and HLA genotyping

The 5 ml blood samples were preserved in EDTA-imbued tubes and then DNA extraction was done by salting out method. The genotyping was performed at the Tehran Medical Genetics laboratory. HLA-A , -B typing was performed based on PCR-SSP technique (polymerase chain reaction – sequence specific primers) by using HLA-READY GENE KIT (Inno-Train Diagnostic GmbH, Germany). The cycling program involved the initial denaturation at 96 °C for 2 min followed by 10 cycles of denaturation at 96 °C for 15 s, annealing at 65 °C for 60 s, and followed by 20 cycles of denaturation at 96 °C for 15 s, annealing at 61 °C for 50 s, and elongation at 72 °C for 30 s. The electrophoresis using 2% agarose gel was done. After PCR, created bands in each well, were interpreted based on standard protocol available in the kit, using its specific software. The genotype of each individual was typed specifically.

2.3. Statistical analysis

Comparisons between the different HLA-A, -B alleles of ALL patients and controls were calculated using the Chi-square and Fisher's exact tests. SPSS V 18.0 was applied to analyze the obtained results. P-value <0.05 was considered to be statistically significant. Bonferroni correction, a method resolving the problem of multiple comparisons, was used to correct the p-value.

3. RESULTS AND DISCUSSION

In this research 11 ALL patients and 50 controls were involved who were gender and age-matched. In comparison between patients and control group, HLA-A*11(pc= 0.009; OR: 9.510 ; 95% CI: 2.077- 43.537) was significantly higher in ALL patients than controls. The allele frequency of HLA-A, -B in patient and control groups are shown in the Table 1.

Table 1. The allele frequencies of HLA-A, -B in ALL patient and control groups

Alleles	ALL patients n=22(%)	Controls n=100(%)	p-value a	pc-value b	OR(95%CI) c
HLA-A*01	1(4.5%)	6(6%)	0.791	NS 7.119	-
HLA-A*02	7(31.8%)	30(30%)	0.867	NS	-
HLA-A*03	3(13.6%)	18(18%)	0.624	NS	-
HLA-A*11	5(22.7%)	3(3%)	0.001	**0.009**	**9.510(2.077-43.537)**

HLA-A*23	1(4.5%)	7(7%)	0.674	NS	-
HLA-A*24	8(36.3%)	29(29%)	0.496	NS	-
HLA-A*26	2(9%)	4(4%)	0.295	NS	-
HLA-A*29	1(4.5%)	2(2%)	0.452	NS	-
HLA-A*33	1(4%)	1(1%)	0.329	NS	-
HLA-B*07	0(0%)	1(1%)	1	NS	-
HLA-B*08	1(4.5%)	2(2%)	0.452	NS	-
HLA-B*09	0(0%)	3(3%)	1	NS	-
HLA-B*13	1(4.5%)	3(3%)	0.554	NS	-
HLA-B*14	1(4.5%)	3(3%)	0.554	NS	-
HLA-B*18	0(0%)	3(3%)	1	NS	-
HLA-B*27	1(4.5%)	2(2%)	0.452	NS	-
HLA-B*35	5(22.7%)	22(22%)	0.941	NS	-
HLA-B*38	1(4.5%)	4(4%)	1	NS	-
HLA-B*39	1(4.5%)	4(4%)	1	NS	-
HLA-B*40	1(4.5%)	4(4%)	1	NS	-
HLA-B*41	0(0%)	4(4%)	1	NS	-
HLA-B*44	2(9%)	12(12%)	0.698	NS	-
HLA-B*49	1(4.5%)	2(2%)	0.452	NS	-
HLA-B*50	1(4.5%)	2(2%)	0.452	NS	-
HLA-B*51	5(22.7%)	25(25%)	0.823	NS	-
HLA-B*52	1(4.5%)	4(4%)	1	NS	-

The significant p-value after Bonferroni correction and OR are shown in bold. [a] Value of Chi-square or Fisher's exact test without correction. [b] adjusted Bonferroni p-value. [c] corrected 95% confidence interval for odds ratio. n, number of alleles; NS, not significant, ALL: Acute lymphoblastic leukemia. In the present study, the relation between HLA-A,-B various alleles and ALL disease in 11 Iranian patients was investigated. In 1967 the first study on HLA in leukemia showed an increased frequency of HLA-A2 in ALL patients (20). Our results that differ from some other populations, demonstrated significant increase in the frequency of HLA-A*11 allele in the ALL patients in comparison with controls. Inconsistent with our results, the study that was done on 35 ALL patients in Brazil, revealed

that frequency of HLA-B*45 and HLA-B*56 was significantly higher than control group. So these are susceptible alleles in Brazilian ALL patients (21). In 2010, a study was done in Turkey showed that HLA-A*23 and HLA-B*07 were significantly lower in patients than controls. So it can be inferred that mentioned alleles are probably protective alleles in Turkish population (7). According to the research which was done in Han nationality of china, HLA-B*58 appears to contribute to the genetic susceptibility of patients with ALL. In Han population, the phenotypic frequency of HLA-B*58 in ALL patients was significantly higher than that of control group, with the relative risk of 7.4 (22).

4. CONCLUSION

According to our results, HLA-A appears to contribute to ALL developing and HLA-A*11 has genetic susceptibility effect on ALL in the Iranian population. The number of studied cases was limited, so further cases are required to announce more reliable outcomes. Therefore, study on large sample size was suggested.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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