RESEARCH ARTICLE

Human Leukocyte Antigen Alleles (HLA-A, HLA-B, and HLA-DRB1) are associated with Acute Lymphoblastic Leukemia (ALL) : A Case-Control Study in a Sample of Iranian Population

Mahdi Kohansal Vajari[1,2], Mohsen Ehsan[2,3], Saeedeh Ghiasi[2], Saba Fooladi[4,5], Najibe Karami[2,6], Gholamhossein Hassanshahi[2], Ahmad Fatemi[7]*

Abstract

Objective: This study seeks to elucidate the association between HLA-A, HLA-B, and HLA-DRB1 alleles and their relative risk contributions to ALL within an Iranian cohort. **Methods:** Utilizing a robust case-control design, this research involved 71 ALL patients and 71 age and sex-matched healthy individuals. Genotyping of specified HLA alleles was performed using the advanced PCR-SSP technique. **Results:** Our findings reveal a marked increase in the prevalence of the HLA-DRB1*04 allele among patients diagnosed with ALL compared to the control group (P<0.027). Conversely, the alleles HLA-A*26 (P=0.025), HLA-A*33 (P=0.020), and HLA-DRB1*03 (P=0.035) were observed at significantly reduced frequencies within the patient population. **Conclusion:** Our findings highlight HLA-DRB1*04 as a potential genetic marker for increased susceptibility to ALL, while HLA-A*26, HLA-A*33, and HLA-DRB1*03 emerge as protective factors.

Keywords: Acute Lymphoblastic Leukemia- HLA Alleles- Iranian Population- PCR-SSP.

Introduction

Acute lymphoblastic leukemia (ALL), the most prevalent cancer among children, sees about 75% of leukemia cases globally [1, 2]. Despite high survival rates exceeding 85% for those without relapse, those experiencing relapse face severe prognoses. This positions ALL as a significant pediatric oncological challenge [3, 4].

Emerging studies suggest a sophisticated interplay between genetics and environmental factors in ALL's development. The timing of viral exposures and subsequent immune responses are particularly critical. This context highlights the importance of the Human Leukocyte Antigen (HLA) system in genetic susceptibility to ALL. The HLA, or major histocompatibility complex, involves over 100 polymorphic genes on chromosome 6 that are pivotal in immune defense, making it a focal point in ALL research [5, 6].

The HLA system, also known as the major histocompatibility complex (MHC), comprises a set of highly polymorphic genes located on chromosome 6. This region spans approximately 4 million base pairs and contains over 100 genes, divided into three primary classes: Class I (HLA-A, -B, -C), Class II (HLA-DP, -DQ, -DR), and Class III [7, 8]. hese genes are essential for coordinating the immune response against pathogens by facilitating the formation of TCR/peptide/HLA complexes. Given its pivotal role in immune mechanisms and its status as one of the most polymorphic gene clusters in the human genome, the HLA system has been extensively studied for its association with various diseases, including ALL [3].

Research into the association between HLA genes and ALL susceptibility continues to reveal a range of diverse and occasionally contradictory outcomes [9]. Investigations conducted in Eastern China have shown the significant role of the HLA-DRB114 locus in ALL, although no significant disparities were observed in the HLA-A and HLA-B loci between affected individuals and control groups [7]. Further studies have identified the HLA-DRB104 allele as increasing susceptibility to childhood ALL among females, additionally affecting the age at which the disease manifests [1].

[1]Student of Research Committee, Faculty of Allied Medicine, Kerman University of Medical Sciences, Kerman, Iran. [2]Department of Hematology and Medical Laboratory Sciences, Faculty of Allied Medicine, Kerman University of Medical Sciences, Kerman, Iran. [3]Department of Hematology and Blood Banking, Faculty of Allied Medicine, Iran University of Medical Science, Tehran, Iran.[4]Department of Biochemistry, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran. [5]Student Research Committee, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran. [6]Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran. [7]Cellular and Molecular Research Center, Gerash University of Medical Sciences, Gerash, Iran. *For Correspondence: ahmad.fatemi2@gmail.com

Further examination within pediatric ALL populations has noted the prognostic implications of the HLA-DRB111 allele. Research in Turkey highlighted several alleles such as A03 and DRB104 as predisposing factors, with the DRB104 allele specifically linked to an increased risk of ALL, in contrast to the standard risk associated with the DRB107 allele [3]. More recent findings suggest that the MBL2 BB genotype, when combined with DRB107 or co-inherited with HLA-DRB104 and DRB107, could contribute to pediatric ALL, emphasizing the role of initial immune defense mechanisms [2].

The complexity of HLA interactions is further evidenced by findings suggesting a link between ALL and the HLA-A11 and DRB101 alleles, alongside a noted negative association with the DRB113 allele [10]. Complementary research in Hong Kong has highlighted specific HLA markers in high-risk pediatric ALL cases, where HLA-B67 emerged as a male-specific marker linked to increased susceptibility to relapse, and HLA-A29 and HLA-B07 were identified as indicators of poor prognosis [6]. Additionally, the predictive potential of HLA class II expression in determining the efficacy of treatment for adult T-cell leukemia/lymphoma has been discovered, further illustrating the critical role of HLA gene expression in cancer progression and treatment response [11].

This backdrop of varying global research outcomes sets the stage for our case-control study, which aims to deepen understanding of the associations between specific HLA alleles and ALL development within an Iranian population [5] By contextualizing our research within global findings, we aim to contribute uniquely to the broader genetic narrative of ALL.

Materials and Methods

Participants

The present case-control study enrolled 71 individuals diagnosed with ALL, in accordance with the 2016 World Health Organization diagnostic criteria, alongside an equivalent number of healthy, non-related participants matched by age and sex. Sample size determination utilizing the PGA program aimed for a statistical power of 80% with a two-sided alpha error set at 5%. Despite exhaustive efforts to collect all available samples, the calculated target sample size was not achieved [12].

Ethics statement

This project was approved by the ethical committee of Kerman University of Medical Sciences (Ethical approval code: IR.KMU.REC.1398.131). Before initiating the collection of samples, all participants formally acknowledged and consented to their involvement by signing informed consent forms, thus upholding the study's ethical standards.

DNA extraction

Genomic DNA was isolated from whole blood samples that had been treated with EDTA (Ethylene-Diamine-Tetra-Acetic-Acid), which served as an anticoagulant, utilizing the EZ1 DSP DNA Blood Kit (QIAGEN, Netherlands). This protocol employed magnetic-particle technology and required sample volumes of either 200 or 350 μL. The extraction process commenced with the addition of chaotropic salts to the lysates, enhancing the DNA's affinity for the kit's magnetic particles and allowing for efficient, single-step extraction. Subsequent magnetic separation facilitated the isolation of DNA-bound particles. The samples were then subjected to a washing process using an elution buffer to eliminate residual impurities. The purity and concentration of the isolated DNA were quantitatively assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Post-extraction, the DNA samples were preserved at -20°C to ensure their stability for subsequent genotyping analyses.

HLA Typing

HLA allele genotyping was performed using the sequence-specific primer-polymerase chain reaction (SSP-PCR) technique, leveraging low-resolution typing kits supplied by Olerup, Sweden. This technique capitalizes on oligonucleotide primers designed to accommodate 3'-end mismatches, ensuring efficient amplification when there is near-perfect match to the target DNA. Following amplification, the PCR products were resolved using agarose gel electrophoresis, which separates DNA fragments by size. These fragments were visualized, photographed, and analyzed to assess the allelic diversity. Figure 1 presents a typical result from the SSP-PCR analysis, illustrating the specificity and precision of this genotyping approach.

Statistical Analysis

In this study, the Pearson's Chi-square test was strategically applied to discern variations in allele frequencies between the subject groups. Advanced multivariate logistic regression analyses were then conducted to probe the relationship between individual alleles and the risk of acute lymphoblastic leukemia (ALL), incorporating the derivation of odds ratios (ORs) and 95% confidence intervals (CIs) to enhance predictive accuracy. These statistical analyses were adeptly handled using the SPSS 22 software (IBM/SPSS Inc., New York, USA), configured to ensure rigorous data integrity. Statistical significance was established at a P-value of 0.05 or less, adhering to stringent analytical standards.

Results

Study samples

In this research, the demographic and clinical profiles of 71 healthy individuals (47 males and 24 females, average age 23.26 ± 12.5) were rigorously analyzed alongside those of 71 patients diagnosed with ALL (48 males and 23 females, average age 21.63 ± 13 years), as detailed in Table 1. Advanced statistical matching was employed to ensure comparability between groups, with the cohorts demonstrating no significant differences in age and gender (P-values of 0.12 and 0.72, respectively). This methodological precision enhances the reliability of subsequent findings, setting a robust foundation for exploring the specific impacts of ALL, independent of
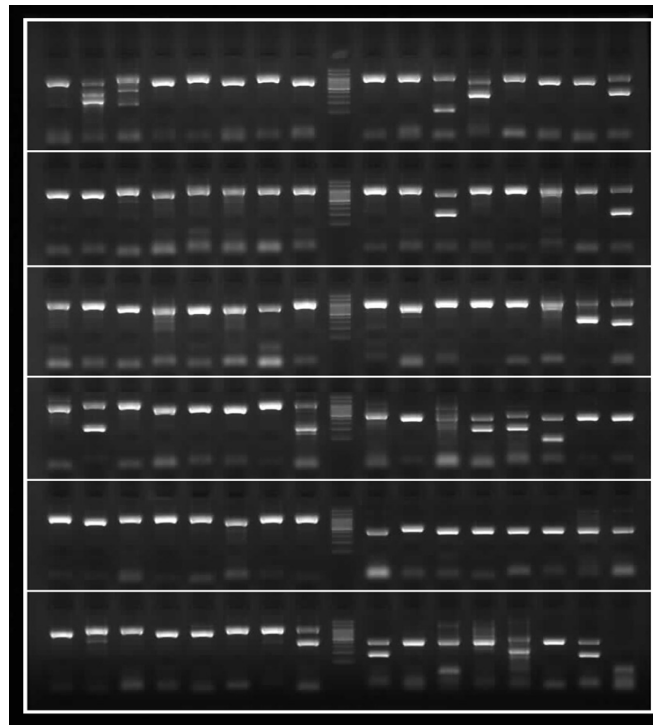
Figure 1. Representative Result of PCR-SSP for HLA Typing.

demographic variances.

HLA-A allelic associations with ALL

In the analysis of HLA-A alleles among both healthy subjects and patients with ALL, distinctive differences in statistical significance were observed. Notably, the alleles HLA-A*26 and HLA-A*33 demonstrated a correlation with decreased risk of ALL, exhibiting p-values of 0.025 and 0.02, respectively. Conversely, other HLA-A alleles did not show significant associations with ALL risk. Detailed data on the frequency of HLA-A alleles and

their correlations with ALL are systematically presented in Table 2.

HLA-B allelic associations with ALL

The analysis of this study clearly delineates the absence of an association between the prevalence of HLA-B alleles and ALL incidence among both patients and healthy controls. Detailed in Table 3, these findings are systematically presented.

HLA-DRB1 allelic associations with ALL

The results of our investigation identified statistically significant differences in the frequencies of the HLA-DRB1*03 and DRB1*04 alleles between the healthy controls and individuals diagnosed with ALL, evidenced by p-values of 0.035 and 0.027, respectively. These findings, including the specific allele frequencies and their relationships with ALL incidence, are comprehensively detailed in Table 4.

Discussion

Genetic and environmental factors are intricately linked in the pathogenesis of ALL [1]. While the precise biological mechanisms initiating ALL remain largely undefined, extensive research has illuminated the critical involvement of specific HLA alleles in the disease's onset and progression [6, 13, 14]. Detailed analysis of these alleles in ALL patients promises to unlock valuable insights into prognosis, therapeutic response, and the likelihood of relapse [15, 16, 5]. In this context, the current investigation is designed to rigorously assess the associations between HLA-A, HLA-B, and HLA-DRB1 alleles and the susceptibility to ALL within a distinct cohort of Iranian patients.

Table 1. Demographic and Clinical Characteristics of ALL Cases and Healthy Controls

	ALL Cases N = 71 (%)	Controls N = 71 (%)	P-Value
Gender			
Male	48 (67.6)	47 (66.2)	0.72
Female	23 (32.4)	24 (33.8)	
Age (Mean ± SD)	21.63 ± 13	23.26 ± 12.5	
<20	36 (50.7)	32 (45)	0.12
≥20	35 (49.3)	39 (55)	
Type of ALL			
B-ALL	71 (100)	-	
T-ALL	0	-	
Molecular subtype			
BCR/ABL t(9;22), p190 kD	0	-	
Outcome			
Complete Remission	14 (19.7)	-	
Relapse	12 (16.9)	-	
Dead	45 (63.4)	-	

Table 2. Association of HLA-A Alleles and Relative Risk of ALL Incidence (*P<0.05 is in bold).

HLA-A	Patient (n=71)		Control (n=71)		Odds Ratio	Confidence Interval 95%	P-value
	Allele (2n=142)	Frequency	Allele (2n=142)	Frequency	OR	CI	P*
A*01	11	7.75	5	3.5	0.462	0.149-1.428	0.172
A*02	37	25.9	26	18.25	0.588	0.299-1.158	0.123
A*03	9	6.25	10	6.95	1.291	0.478-3.489	0.614
A*11	18	12.9	19	13.8	1.076	0.508-2.277	0.848
A*23	3	2.1	1	0.7	-	-	-
A*24	20	14.4	15	10.55	0.672	0.306-1.475	0.32
A*26	7	4.85	17	11.9	0.317	0.116-0.867	**0.025**
A*29	3	2.1	5	3.5	1.717	0.394-7.475	0.467
A*30	10	6.95	15	10.55	1.498	0.616-3.642	0.37
A*31	2	1.4	5	3.5	2.614	0.490-13.94	0.245
A*32	11	7.75	8	5.55	0.775	0.287-2.093	0.614
A*33	2	1.4	11	7.75	0.182	0.042-0.791	**0.02**
A*68	9	6.25	5	3.5	0.47	0.135-1.639	0.228

Building upon prior research, our findings suggest that the HLA-DRB1*13 allele, which occurs less frequently among ALL patients, may exert a protective effect against the disease, while the HLA-DRB1*04 allele, which shows a moderate increase in prevalence among affected individuals, could be a susceptibility factor for childhood ALL [17]. This study supports these observations by demonstrating a significant association between the frequencies of HLA-DRB1*03 and DRB1*04 alleles and the incidence of ALL. Corroborating our results, a seminal study from Turkey in 2002 identified a positive correlation between the HLA-DRB1*04 allele and ALL,

Table 3. HLA-B allele Frequencies and association with Relative Risk of ALL Incidence.

HLA-B	Patient (n=71)		Control (n=71)		Odds Ratio	Confidence Interval 95%	P-value
	Allele (2n=142)	Frequency	Allele (2n=142)	Frequency	OR	CI	P
B*03	-	-	1	0.7	-	-	-
B*07	8	5.55	9	6.55	1.143	0.414-3.154	0.796
B*08	12	8.45	7	4.9	2.203	0.778-6.243	0.137
B*13	6	4.35	5	3.5	1.218	0.354-4.191	0.754
B*14	1	0.7	1	0.7	-	-	-
B*15	5	3.5	3	2.1	1.717	0.394-7.475	0.471
B*18	11	7.65	13	9.55	0.818	0.339-1.973	0.655
B*27	2	1.4	1	0.7	-	-	-
B*35	26	18.5	29	20.45	0.835	0.422-1.649	0.603
B*37	2	1.4	-	-	-	-	-
B*38	7	4.9	5	3.5	1.218	0.354-4.191	0.754
B*39	2	1.4	1	0.7	-	-	-
B*40	14	10.2	16	11.1	0.837	0.365-1.916	0.673
B*41	1	0.7	1	0.7	-	-	-
B*42	-	-	1	0.7	-	-	-
B*44	1	0.7	1	0.7	-	-	-
B*49	1	0.7	-	-	-	-	-
B*50	3	2.1	3	2.1	-	-	-
B*51	16	11.1	17	11.9	-	-	-
B*52	6	4.2	6	4.2	-	-	-
B*53	3	2.1	8	5.55	0.403	0.100-1.627	0.202
B*55	7	4.85	5	3.45	1.444	0.436-4.784	0.548
B*56	1	0.7	-	-	-	-	-
B*57	5	3.45	1	0.7	4.179	0.455-38.35	0.201
B*58	2	1.4	8	5.55	0.228	0.047-1.116	0.068

Table 4. Association of HLA-DRB1 Alleles and Relative Risk of ALL Incidence (*P<0.05 is in bold).

HLA-DRB1	Patient (n=71)		Control (n=71)		Odds Ratio	Confidence Interval 95%	P-value
	Allele (2n=142)	Frequency	Allele (2n=142)	Frequency	OR	CI	P*
DRB1*01	24	16.9	16	11.2	1.67	0.784-3.58	0.181
DRB1*03	19	13.4	32	22.5	0.464	0.228-0.946	**0.035**
DRB1*04	14	10	4	2.8	3.75	1.16-12.15	**0.027**
DRB1*07	11	7.8	9	6.3	1.129	0.429-2.971	0.805
DRB1*08	2	1.3	1	0.7	-	-	-
DRB1*09	2	1.3	-	-	-	-	-
DRB1*10	3	2.1	6	4.2	0.478	0.115-1.991	0.311
DRB1*11	13	9.2	19	13.5	0.54	0.234-1.246	0.148
DRB1*12	2	1.3	-	-	-	-	-
DRB1*13	11	7.8	14	9.8	0.812	0.340-1.980	0.66
DRB1*14	13	9.2	5	3.5	2.685	0.893-8.072	0.079
DRB1*15	13	9.2	11	7.7	1.109	0.454-2.711	0.82
DRB1*16	15	10.5	25	17.8	0.547	0.253-1.183	0.125

and also noted the protective properties of HLA-DRB1*13 [18]. Additionally, subsequent research within the Turkish context pointed to HLA-DRB1*04 and DRB1*07 as alleles that potentially elevate ALL risk [19, 3]. Contrarily, research conducted by Fernandes et al. in Brazil observed a decrease in the prevalence of the DRB1*04 allele among ALL patients, presenting a divergence from our findings [20]. Consistently, further investigations have linked the HLA-DRB1*04 allele to various solid tumors, including cervical, breast, and lung cancers, and suggested its role as a risk factor in other hematological disorders such as chronic myelogenous leukemia (CML) [21-26]. Moreover, evidence indicates that the DRB1*04 and DRB1*07 alleles vary in their risk association with ALL, with DRB1*04 often correlating with a higher risk and DRB1*07 with a standard risk [3]. These findings collectively advocate for a deeper exploration of HLA-DRB1*04's role across different cancer types.

The results of this investigation elucidate that the presence of HLA-A*26 and HLA-A*33 alleles is significantly associated with the incidence of ALL. Comprehensive analyses have delineated a spectrum of HLA-A alleles, with A*33, A*01, A*03, and A*26 exhibiting protective effects, whereas A*24, A*31, A*23, A*30, A*68, and A*74 are identified as predisposing factors, collectively accounting for half of the alleles analyzed within populations at high risk for ALL [14]. This nuanced understanding challenges and expands upon previous findings, such as those reported by William Klitz and collaborators, who posit that A*26 and A*33 alleles act as protective agents in the incidence of childhood ALL [27].

The current investigation found no significant correlation between HLA-B alleles and ALL. This lack of association is consistent with findings from Zhou et al., who also did not observe notable differences in HLA-B allele frequencies between ALL patients and a control group from Eastern China. In contrast, a comprehensive study in Northern China involving ALL patients and healthy controls reported a different pattern [7]. This study identified a higher frequency of HLA-B*13:01 and B*40:02, along with a lower frequency of B*46:01 in ALL patients compared to the control population [28].

Several significant constraints have impacted the robustness of this study. Primarily, the small sample size restricts our ability to definitively conclude the associations between the identified HLA alleles and ALL. Despite over two years of diligent efforts to collect a comprehensive dataset, the research team was unable to secure a larger cohort. Additionally, the scope of the study was confined to a particular geographical region, which might have introduced a geographical bias affecting the generalizability of the findings. Considering the known variability of HLA alleles among different ethnic groups, it is imperative for future studies to expand their participant base to include a more diverse array of global populations.

In conclusion, our study identifies HLA-DRB1*04 as a potentially pivotal susceptibility factor for ALL, while HLA-A*26, HLA-A*33, and HLA-DRB1*03 emerge as likely protective elements. This delineation paves the way for groundbreaking approaches in the stratification of genetic risk factors, enabling more precise predictions of ALL susceptibility across various demographic landscapes.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

Ethics Approval and Participant Consent

This study was sanctioned by the ethics committee of Kerman University of Medical Sciences under the approval code IR.KMU.REC.1398.131. Written informed consent was obtained from all participants, with parents or legal guardians providing consent for individuals under the

age of 16. All research activities were conducted strictly adhering to the applicable guidelines and regulations to ensure ethical compliance and integrity.

Availability of data and materials

Due to the risk of compromizing the privacy of participants, the datasets utilized and/or analyzed during the present research are not accessible to the public. The data would be provided upon reasonable request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

References

1. El Ansary MM, Mohammed LA, Hassan TH, Baraka A, Ahmed AA. Human leukocyte antigen-drb1 polymorphism in childhood acute lymphoblastic leukemia. Mol Clin Oncol. 2015;3(2):425-9. https://doi.org/10.3892/mco.2014.466.

2. Oguz R, Ciftci HS, Gokce M, Ogret Y, Karadeniz S, Pehlivan S, et al. The association of hla-drb1 alleles and mbl2 gene variant in pediatric acute lymphoblastic leukemia patients. Hematol Transfus Cell Ther. 2023. https://doi.org/10.1016/j.htct.2023.02.002.

3. Patiroglu T, Akar HH. The frequency of hla-a, hla-b, and hla-drb1 alleles in patients with acute lymphoblastic leukemia in the turkish population: A case-control study. Turk J Haematol. 2016;33(4):339-45. https://doi.org/10.4274/tjh.2016.0102.

4. Hunger SP, Raetz EA. How i treat relapsed acute lymphoblastic leukemia in the pediatric population. Blood, The Journal of the American Society of Hematology. 2020;136(16):1803-12. https://doi.org/10.1182/blood.2019004043.

5. Hosking FJ, Leslie S, Dilthey A, Moutsianas L, Wang Y, Dobbins SE, et al. Mhc variation and risk of childhood b-cell precursor acute lymphoblastic leukemia. Blood. 2011;117(5):1633-40. https://doi.org/10.1182/blood-2010-08-301598.

6. Ng MH, Lau K, Hawkins B, Chik K, Chan NP, Wong W, et al. Hla-b67 may be a male-specific hla marker of susceptibility to relapsed childhood all in hong kong chinese and hla-a33 or hla-b17 signifies a higher presentation leukocytosis: A retrospective analysis on 53 transplant candidates (1989–2003). Annals of hematology. 2006;85:535-41. https://doi.org/10.1007/s00277-006-0118-0.

7. Zhou M, Qiu H, Chen T, Xiao R, Yang J, Cen L, et al. Human leukocyte antigen (hla)-drb1* 14 is associated with a high incidence of acute lymphocytic leukemia. Oncology Research and Treatment. 2012;35(5):268-71. https://doi.org/10.1159/000338480.

8. Wieczorek M, Abualrous ET, Sticht J, Alvaro-Benito M, Stolzenberg S, Noe F, et al. Major histocompatibility complex (mhc) class i and mhc class ii proteins: Conformational plasticity in antigen presentation. Front Immunol. 2017;8:292. https://doi.org/10.3389/fimmu.2017.00292.

9. Ucar F, Sonmez M, Erkut N, Balci M, Yucel B, Yilmaz M, et al. Relation of hla-a, -b, -drb1 alleles and haplotypes in patients with acute leukemia: A case control study. Arch Med Res. 2011;42(4):305-10. https://doi.org/10.1016/j.arcmed.2011.06.003.

10. Uçar F, Sönmez M, Erkut N, Balcı M, Yücel B, Yılmaz M, et al. Relation of hla-a,-b,-drb1 alleles and haplotypes in patients with acute leukemia: A case control study. Archives of Medical Research. 2011;42(4):305-10.

11. Takeuchi M, Miyoshi H, Asano N, Yoshida N, Yamada K, Yanagida E, et al. Human leukocyte antigen class ii expression is a good prognostic factor in adult t-cell leukemia/lymphoma. Haematologica. 2019;104(8):1626-32. https://doi.org/10.3324/haematol.2018.205567.

12. Menashe I, Rosenberg PS, Chen BE. Pga: Power calculator for case-control genetic association analyses. BMC Genet. 2008;9(1):36. https://doi.org/10.1186/1471-2156-9-36.

13. Greaves MF, Maia AT, Wiemels JL, Ford AM. Leukemia in twins: Lessons in natural history. Blood. 2003;102(7):2321-33. https://doi.org/10.1182/blood-2002-12-3817.

14. Urayama KY, Thompson PD, Taylor M, Trachtenberg EA, Chokkalingam AP. Genetic variation in the extended major histocompatibility complex and susceptibility to childhood acute lymphoblastic leukemia: A review of the evidence. Front Oncol. 2013;3:300. https://doi.org/10.3389/fonc.2013.00300.

15. Nourizadeh M, Masoumi F, Memarian A, Alimoghaddam K, Moazzeni SM, Yaghmaie M, et al. In vitro induction of potent tumor-specific cytotoxic t lymphocytes using tlr agonist-activated aml-dc. Target Oncol. 2014;9(3):225-37. https://doi.org/10.1007/s11523-013-0285-6.

16. El Karaaoui A, Tamim H, El Achkar H, Fermanian P, Abbas F, Keleshian S, et al. Association of human leukocyte antigens (hla) profile and acute lymphoblastic leukemia in lebanese pediatric patients: A first report from lebanon. Human Gene. 2022;33:201072. https://doi.org/10.1016/j.humgen.2022.201072.

17. Yari F, Sobhani M, Sabaghi F, Zaman-Vaziri M, Bagheri N, Talebian A. Frequencies of hla-drb1 in iranian normal population and in patients with acute lymphoblastic leukemia. Arch Med Res. 2008;39(2):205-8. https://doi.org/10.1016/j.arcmed.2007.09.009.

18. Dorak MT, Oguz FS, Yalman N, Diler AS, Kalayoglu S, Anak S, et al. A male-specific increase in the hla-drb4 (dr53) frequency in high-risk and relapsed childhood all. Leuk Res. 2002;26(7):651-6. https://doi.org/10.1016/s0145-2126(01)00189-8.

19. Ozdilli K, Oguz FS, Anak S, Kekik C, Carin M, Gedikoglu G. The frequency of hla class i and ii alleles in turkish childhood acute leukaemia patients. J Int Med Res. 2010;38(5):1835-44. https://doi.org/10.1177/147323001003800531.

20. Fernandes TA, Fukai R, Souza CA, Lorand-Metze I, Magna LA, Kraemer MH. Molecular identification of the hla-drb1-dqb1 for diagnosis and follow-up of acute leukemias. Blood Cells Mol Dis. 2010;44(2):69-73. https://doi.org/10.1016/j.bcmd.2009.10.006.

21. Barion LA, Tsuneto LT, Testa GV, Lieber SR, Persoli LBL, Marques SBD, et al. Association between hla and leukemia in a mixed brazilian population. Revista da Associação Médica Brasileira. 2007;53:252-6. https://doi.org/10.1590/s0104-42302007000300024.

22. Amirzargar AA, Khosravi F, Dianat SS, Alimoghadam K, Ghavamzadeh F, Ansaripour B, et al. Association of hla class ii allele and haplotype frequencies with chronic myelogenous leukemia and age-at-onset of the disease. Pathol Oncol Res. 2007;13(1):47-51. https://doi.org/10.1007/BF02893440.

23. Alaez-Verson C, Berumen-Campos J, Munguia-Saldana A, Flores-Aguilar H, Guardado-Estrada M, Rodriguez-Gomez A, et al. Hpv-16 and hla-drb1 alleles are associated with cervical carcinoma in mexican mestizo women. Arch

Med Res. 2011;42(5):421-5. https://doi.org/10.1016/j.arcmed.2011.07.002.

24. Madeleine MM, Brumback B, Cushing-Haugen KL, Schwartz SM, Daling JR, Smith AG, et al. Human leukocyte antigen class ii and cervical cancer risk: A population-based study. J Infect Dis. 2002;186(11):1565-74. https://doi.org/10.1086/345285.

25. Gun FD, Ozturk OG, Polat A, Polat G. Hla class-ii allele frequencies in turkish breast cancer patients. Med Oncol. 2012;29(2):466-71. https://doi.org/10.1007/s12032-011-9873-4.

26. Yang L, Wang LJ, Shi GL, Ni L, Song CX, Zhang ZX, et al. Analysis of hla-a, hla-b and hla-drb1 alleles in chinese patients with lung cancer. Genet Mol Res. 2010;9(2):750-5. https://doi.org/10.4238/vol9-2gmr735.

27. Klitz W, Gragert L, Trachtenberg E. Spectrum of hla associations: The case of medically refractory pediatric acute lymphoblastic leukemia. Immunogenetics. 2012;64(6):409-19. https://doi.org/10.1007/s00251-012-0605-5.

28. Qi J, Chen L, Wang T, Wang M, Wang X, Wu J, et al. Association of hla-a,-b,-drb1 alleles and haplotypes with acute lymphoblastic leukemia among ethnic hans from northern china. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2017;34(5):737-42. https://doi.org/10.3760/cma.j.issn.1003-9406.2017.05.026.