



Human leukocyte antigens and adult acute myeloid leukemia: A first report from Lebanon

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ABSTRACT

Introduction: Acute Myeloid Leukemia (AML) represents the most common type of acute leukemia in adults and the second most common form of leukemia in general. AML has been associated with HLA alleles and these correlations have been widely investigated worldwide.

Objective: The aim of this study is to analyze the antigen frequency of HLA Class I (HLA-A, HLA-B, and HLA-C) and Class II (HLA-DRB1 and HLA-DQB1) among AML Lebanese adult patients.

Methods: This is a retrospective study reviewing all the HLA results of 121 adult patients admitted to the American University of Beirut Medical Center (AUBMC) from January 2017 to May 2022. Comparison of HLA frequency in AML patients to frequency in general Lebanese population published in previous studies was done.

Results: In HLA class I, an increased frequency of HLA-A*03 (OR, 1.61; 95% CI, 1.10 to 2.37; $P = 0.02$), HLA-A*25 (OR, 6.69; 95% CI, 1.78 to 25.07; $P = 0.01$), HLA-A*74 (OR, 8.33; 95% CI, 1.67 to 41.51; $P = 0.02$) was found in the AML group, whereas decreased frequency of HLA-B*15 (OR, 0.22; 95% CI, 0.05 to 0.93; $P = 0.03$) was noted. In HLA class II, DRB1*03 (OR, 0.27; 95% CI, 0.14 to 0.50; $P < 0.001$) was higher among the control group and DRB1*12 (OR, 15.71; 95% CI, 1.88 to 131.20; $P = 0.01$) among the AML group.

Conclusion: Findings revealed that three class I HLA antigens are predisposing to AML (HLA-A*03; HLA-A*25; HLA-A*74) and one class I HLA antigen is protective (HLA-B*15). Regarding class II HLA antigens, DRB1*03 was found to be protective whereas DRB1*12 was found to be predisposing to AML.

1. Introduction

The human major histocompatibility complex (MHC) system is also known as the human leukocyte antigen (HLA) system, since it is detected on the surface of leukocytes by specific alloantibodies (Terasaki and Dausset, 1990). The HLA system is divided into two classes: class I (HLA-A, B, and C) and class II (HLA-DP, DQ, and DR), with HLA genes located on the short arm of chromosome six. This system is important in transplant procedures to match incompatibility between donor and recipient (Corzo et al., 1995) and represents a well-established role in regulating the host's response to inflammation, infections, and 'non-self' antigens, as well as host's immune systems (i.e. innate, adaptive, and complement systems) (Shiina et al., 2009a).

The HLA genes represent the most studied polymorphic genes; they

are associated with more than fifty various diseases such as multiple sclerosis (MS) (Maghbooli et al., 2020), rheumatological diseases (van Drogenen and Holoshitz, 2017) and leukemias (Mishra et al., 2020). This strong relationship between MHC-H2k haplotype and susceptibility to leukemia development was discovered in mice first, which implied the possibility of similar associations in other species such as humans (Shiina et al., 2009b). Since then, the correlation between HLA and leukemia was widely investigated worldwide, especially for Acute Myeloid Leukemia (AML).

Acute Myeloid Leukemia (AML) is the most common type of acute leukemia in adults and the second most common form of leukemia (Siegel et al., 2020). AML prevalence rises with age, with a median age of 68 years at diagnosis in the United States (Siegel et al., 2020; Shallis et al., 2019). Its prognosis varies, with older patients having a lower rate

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of complete remission than younger patients (Shah et al., 2013). AML has been linked to a variety of environmental factors, including radiation, chemical exposure, and chemotherapy, but the reason of the somatic mutation remains unknown (Solanki et al., 2020). Seremetis et al., have reported an important correlation between AML and DRB loci (Seremetis et al., 1985). Additionally, another large study conducted using an international Bone Marrow Transplant Registry Data revealed the implication of HLA-C*3 and C*4 in AML (Bortin et al., 1987).

HLA is known for its high degree of polymorphism and diversity among populations. Till date, no previous study among Lebanese patients has been conducted to determine whether the Lebanese patients are predisposed to AML due to the genetic make-up of their HLA system or not. Keeping this in view, this study is aimed at analyzing the allele frequencies of HLA Class I (HLA-A, HLA-B, and HLA-C) and Class II (HLA-DRB1 and HLA-DQB1) among Lebanese adult AML patients as well as comparing them to a control group.

2. Methodology

2.1. Study population

In this study, we reviewed the charts of all AML patients diagnosed at or referred to the American University of Beirut Medical Center (AUBMC) between January 2017 and May 2022. AUBMC is one of the leading hospitals in Lebanon. It is located in the capital city Beirut, which is reachable by different districts within a few hours. It is the largest hospital in Lebanon and is considered a major referral center in the country and in the Middle East. Out of all AML patients, 121 adults (>18 years old) were tested for HLA at the molecular diagnostic laboratory prior to the hematopoietic stem cell transplant as part of their AML workup and were included in the study accordingly. All patients were referred by different oncologists from all different geographical areas and communities.

Data was obtained by accessing the Laboratory Information System of the Department of Pathology and Laboratory Medicine. The control group consisted of healthy hematopoietic stem cell and kidney potential donors tested for HLA at AUBMC, whose results were compared to those of several populations with interesting and common findings such as Moroccan, Jordanian, Tunisian etc..., the results of which have been published previously (Khansa et al., 2012; Khansa et al., 2013).

This study was retrospective, with no patient contact or consent, and carries no risk to the population studied. It was approved by the Institutional Review Board (IRB) committee at AUBMC on May 16, 2022 (ID number: BIO-2022-0121).

2.2. HLA testing

The Luminex reverse sequence-specific oligonucleotide (SSO) DNA typing system (LABScan 3d, xPONENT, powered by Luminex xMAP Technology, USA) that uses SSO probes linked to color-coded microspheres was used to determine the HLA alleles. The amplification is verified by electrophoresis on a 2% agarose gel stained with ethidium bromide. The PCR product is biotinylated, allowing for its detection using streptavidin coupled to R-phycoerythrin (SAPE). Readings on the Luminex analyzer were then performed following the manufacturer's instructions.

2.3. Statistical analysis

The fact that we included all patient in the study period, we did not carry out statistical sample size calculation. All loci were tested individually for Hardy-Weinberg equilibrium (HWE) and the gene frequencies of HLA-alleles of patients and control groups were compared using chi-square analysis via 2×2 contingency tables. In settings where the sample size was small, instead we carried out non-parametric test, specifically Fisher exact test. *P* values <0.05 were considered

statistically significant.

3. Results

Findings in Table 1 and Table 2 revealed the difference in the frequency of HLA alleles Class I and Class II respectively between the control group and adults AML Lebanese patients. Among the HLA class I (HLA A, HLA B and HLA C), there were no statistically significant difference between the two groups except for HLA-A*03 (Control = 9.78% vs. AML = 14.87%; (OR, 1.61; 95% CI, 1.10 to 2.37; *P* = 0.02), HLA-A*25 (control = 0.24% vs. AML = 1.65%; (OR, 6.69; 95% CI, 1.78 to 25.07; *P* = 0.01), HLA-A*74 (control = 0.16% vs. AML = 1.24%; (OR, 8.33; 95% CI, 1.67 to 41.51; *P* = 0.02), which were found to be higher in the AML group, whereas, HLA-B*15 (control = 3.59% vs. AML = 0.83%; (OR, 0.22; 95% CI, 0.05 to 0.93; *P* = 0.03)) was found to be higher among the control group as compared to AML patients. (See Table 3.)

In HLA class II antigens (HLA-DQB1 and HLA-DRB1), there were no statistically significant difference between the two groups except for HLA-DRB1*03 (control = 16.316% vs. AML = 4.96%; (OR, 0.27; 95% CI, 0.14 to 0.50; *P* < 0.001)) which is higher among the control group and HLA-DRB1*12 (control = 0.161% vs. AML = 2.48%; (OR, 15.71; 95% CI, 1.88 to 131.20; *P* = 0.01)) which is higher in the AML group.

4. Discussion

Correlation between HLA polymorphisms, susceptibility and resistance to disease began soon after serological techniques for HLA class I typing were standardized. In fact, the first association of HLA to leukemia in humans was first reported in 1967 which demonstrated an increased expression of HLA A02 in patients with ALL compared to healthy individuals (Turkan and Haluk, 2015). Our findings suggest that HLA-A*03, HLA-A*25 and HLA-A*74 have a predisposing effect in AML patients as compared to general population. In Chinese population, HLA-A*01 was a predisposing allele whereas HLA-A*33 represented a protective role in AML (Li et al., 2005). In addition, HLA-A*11 allele was previously found to have a protective role among both Indian and Turkish population (Solanki et al., 2020; Ozdilli et al., 2010).

In our study an increased frequency of HLA-B*15 was detected in the general population as compared to patients with AML which was consistent with a previously published paper among Mexican population (Fernández-Torres et al., 2013). Other HLA-B alleles were found to have a protective role such as HLA-B*51 in Indian and Chinese population (Solanki et al., 2020; Li et al., 2005), HLA-B*38/18 in Turkish population (Ozdilli et al., 2010) and HLA-B*40 in the Mexican population (Fernández-Torres et al., 2013). Moreover, some alleles detected in the literature and predisposing to AML were HLA-B*07 in Brazilian population (Barion et al., 1992), HLA-B*21/35/49 in Turkish population (Ozdilli et al., 2010), HLA-B*39 in both Indian and Venezuelan population (Solanki et al., 2020; Villalobos et al., 2003) and HLA-B*37 in Chinese population (Li et al., 2005).

No HLA-C alleles were significantly associated with AML in our study. However, in the literature HLA-C*03 was detected as a predisposing allele among Koreans (Yoon, 2015) and HLA-C*07 among Indian population (Solanki et al., 2020). On the other hand, HLA-C*01 was found to have a protective function among Indians (Solanki et al., 2020). Studies have also shown a strong positive association of HLA-C*3 and HLA-C*4 with AML which supports the possibility that these antigens, or the genes encoding them are closely linked together, but the exact mechanism behind the theory is still unknown (Bortin et al., 1987).

Association between HLA Class II alleles and AML was found in our study with DRB1*03 having a protective effect and DRB1*12 having a predisposing role both of which were not previously found in previous studies. In contrast to our current result, DRB1*03 was one the most observed haplotype in AML patients in ethnic Turkish population (Turkan and Haluk, 2015). In the literature, DRB1*11 was found to be a protective allele in India and Iran (Solanki et al., 2020; Sarafnejad et al.,

Table 1
HLA Class I Antigen frequency in adults AML patients and healthy controls

Allele	Controls (N = 1994)	AML cases (N = 242)	OR (95%CI)	P value
A* 01	245 (12.3%)	25 (10.3%)	0.82 (0.53–1.27)	0.38
A* 02	374 (18.8%)	50 (20.7%)	1.13 (0.81–1.57)	0.48
A*03	195 (9.8%)	36 (14.9%)	1.61 (1.10–2.37)	0.02*
A*11	100 (5%)	17 (7%)	1.43 (0.84–2.44)	0.19
A*23	83 (4.2%)	12 (5%)	1.20 (0.65–2.23)	0.56
A*24	330 (16.7%)	37 (15.3%)	0.91 (0.63–1.32)	0.62
A*25	5 (0.2%)	4 (1.7%)	6.69 (1.78–25.07)	0.01*
A*26	104 (5.2%)	10 (4.1%)	0.78 (0.40–1.52)	0.47
A*29	65 (3.2%)	7 (2.9%)	0.88 (0.40–1.95)	0.76
A*30	133 (6.7%)	12 (5%)	0.73 (0.40–1.34)	0.31
A*31	23 (1.1%)	2 (0.8%)	0.71 (0.17–3.05)	1
A*32	90 (4.5%)	9 (3.7%)	0.82 (0.41–1.64)	0.57
A*33	78 (3.9%)	4 (1.7%)	0.41 (0.15–1.14)	0.10
A*34	4 (0.2%)	0	NA	NA
A*66	14 (0.7%)	1 (0.4%)	0.59 (0.08–4.48)	1
A*68	103 (5.1%)	8 (3.3%)	0.63 (0.30–1.31)	0.21
A*69	44 (2.2%)	5 (2.1%)	0.94 (0.37–2.38)	1
A*74	3 (0.2%)	3 (1.2%)	8.33 (1.67–41.51)	0.02*
A*80	1 (0.1%)	0	NA	NA
Total	1994 (100%)	242 (100%)		

Alleles	Controls (N = 1309)	AML cases (N = 242)	OR (95%CI)	P value
B*07	53 (4%)	14 (5.8%)	1.46 (0.79–2.67)	0.22
B*08	29 (2.2%)	10 (4.1%)	1.90 (0.91–3.96)	0.09
B*13	42 (3.2%)	8 (3.3%)	1.03 (0.48–2.22)	0.94
B*14	62 (4.7%)	6 (2.5%)	0.51 (0.22–1.20)	0.12
B*15	47 (3.6%)	2 (0.8%)	0.22 (0.05–0.93)	0.03*
B*18	89 (6.8%)	18 (7.4%)	1.10 (0.65–1.86)	0.72
B*27	11 (0.8%)	4 (1.7%)	1.98 (0.63–6.28)	0.27
B*35	242 (18.5%)	50 (20.7%)	1.15 (0.82–1.61)	0.43
B*37	10 (0.7%)	2 (0.8%)	1.08 (0.24–4.97)	1
B*38	53 (4%)	11 (4.6%)	1.13 (0.58–2.19)	0.72
B*39	18 (1.3%)	4 (1.7%)	1.21 (0.40–3.59)	0.77
B*40	39 (3%)	5 (2.1%)	0.69 (0.27–1.76)	0.53
B*41	84 (6.4%)	18 (7.4%)	1.17 (0.69–1.99)	0.56
B*42	5 (0.4%)	0	NA	NA
B*44	97 (7.4%)	15 (6.2%)	0.83 (0.47–1.45)	0.5
B*45	12 (0.9%)	1 (0.4%)	0.45 (0.06–3.47)	0.70
B*46	1 (0.08%)	0	NA	NA
B*47	14 (1%)	1 (0.4%)	0.38 (0.05–2.93)	0.49
B*49	49 (3.7%)	7 (2.9%)	0.77 (0.34–1.71)	0.52
B*50	65 (5%)	17 (7%)	1.45 (0.83–2.51)	0.19
B*51	112 (8.5%)	20 (8.3%)	0.96 (0.59–1.58)	0.88
B*52	59 (4.5%)	12 (5%)	1.11 (0.59–2.09)	0.76
B*53	14 (1%)	1 (0.4%)	0.38 (0.05–2.93)	0.49
B*54	1 (0.08%)	0	NA	NA
B*55	38 (2.9%)	4 (1.7%)	0.56 (0.20–1.59)	0.39
B*56	2 (0.2%)	0	NA	NA
B*57	23 (1.8%)	5 (2.1%)	1.18 (0.44–3.13)	0.79
B*58	25 (1.9%)	3 (1.2%)	0.64 (0.19–2.15)	0.61
B*73	13 (0.9%)	4 (1.7%)	1.68 (0.54–5.18)	0.32
Total	1309 (100%)	242 (100%)		

Alleles	Controls (N = 1163)	AML cases (N = 242)	OR (95%CI)	P value
CW*01	32 (2.7%)	5 (2%)	0.75 (0.29–1.93)	0.66
CW*02	28 (2.4%)	3 (1%)	0.51 (0.15–1.69)	0.34
CW*03	54 (4.5%)	11 (4.6%)	0.98 (0.50–1.90)	0.95
CW*04	220 (18.8%)	51 (21.1%)	1.14 (0.81–1.61)	0.44
CW*05	27 (2.3%)	3 (1.2%)	0.53 (0.16–1.76)	0.46
CW*06	134 (11.5%)	30 (12.4%)	1.09 (0.71–1.66)	0.70
CW*07	182 (15.6%)	37 (15.3%)	0.97 (0.66–1.43)	0.89
CW*08	54 (4.7%)	6 (2.5%)	0.59 (0.25–1.39)	0.23
CW*12	188 (16.1%)	47 (19.4%)	1.25 (0.88–1.78)	0.22
CW*14	14 (1.3%)	5 (2.1%)	1.73 (0.62–4.85)	0.35
CW*15	103 (8.8%)	15(6.2%)	0.68 (0.39–1.19)	0.18
CW*16	68 (5.9%)	13 (5.4%)	0.91 (0.50–1.68)	0.77
CW*17	57 (5%)	16 (6.6%)	1.37 (0.77–2.44)	0.28
CW*18	2 (0.2%)	0	NA	NA
Total	1163 (100%)	242 (100%)		

* Statistically significant.

Table 2
HLA Class II Antigen frequency in adults AML patients and healthy controls.

Allele	Controls (N = 560)	AML cases (N = 242)	OR (95%CI)	P value
DQB1*02	90 (16.2%)	30 (12.4%)	0.74 (0.47–1.15)	0.18
DQB1*03	291 (51.9%)	143 (59.1%)	1.34 (0.98–1.81)	0.06
DQB1*04	17 (3%)	5 (2.1%)	0.67 (0.25–1.85)	0.64
DQB1*05	88 (15.8%)	39 (16.1%)	1.03 (0.68–1.55)	0.89
DQB1*06	73 (13%)	25 (10.3%)	0.77 (0.47–1.24)	0.28
DQB1*15	1 (1%)	0	NA	NA
Total	560 (100%)	242 (100%)		

Allele	Controls (N = 619)	AML cases (N = 242)	OR (95%CI)	P value
DRB1*01	26 (4.2%)	11 (4.6%)	1.09 (0.53–2.23)	0.82
DRB1*03	101 (16.3%)	12 (5%)	0.27 (0.14–0.50)	< 0.001*
DRB1*04	84 (13.6%)	44 (18.2%)	1.42 (0.95–2.11)	0.09
DRB1*07	56 (9%)	23 (9.5%)	1.06 (0.63–1.76)	0.83
DRB1*08	7 (1.1%)	3 (1.2%)	1.10 (0.28–4.28)	0.44
DRB1*09	0	1 (0.4%)	NA	NA
DRB1*10	17 (2.7%)	12 (5%)	1.85 (0.87–3.93)	0.11
DRB1*11	186 (30%)	79 (32.6%)	1.13 (0.82–1.55)	0.46
DRB1*12	1 (0.2%)	6 (2.5%)	15.71 (1.88–131.20)	0.01*
DRB1*13	65 (10.5%)	22 (9.1%)	0.85 (0.51–1.42)	0.54
DRB1*14	26 (4.2%)	8 (3.3%)	0.78 (0.35–1.74)	0.55
DRB1*15	39 (6.3%)	16 (6.6%)	1.05 (0.58–1.92)	0.87
DRB1*16	11 (1.8%)	5 (2.1%)	1.17 (0.40–3.39)	0.78
Total	619 (100%)	242 (100%)		

* Statistically significant.

2006), DRB1*15/4 were shown as predisposing alleles to AML in Turkey, whereas, DRB1*13 as protective allele (Ozdilli et al., 2010). In Brazil, both DRB1*102 and DRB1*107 were detected as susceptible alleles to AML (Fernandes et al., 2010).

As mentioned before, no HLA-DQB1 alleles were significantly associated with AML in our study. However, DQB1*03:03 and DQB1*104 were both negatively associated alleles in Iran and Brazil respectively (Sarafnejad et al., 2006; Fernandes et al., 2010). On the other hand,

DQB1*102 was found to be positively associated in the Brazilian population (Fernandes et al., 2010).

There are few reports in the literature describing a link between HLA and AML and while some of the current findings are compatible with earlier mentioned studies, other results are contradictory. This can be easily interpreted by the variation in antigen frequencies and case numbers between population and studies (Ozdilli et al., 2010). Additionally, variable disease outcomes were caused by the interaction of peptide antigens with the major histocompatibility complex (MHC), its differential binding, and the stability of the MHC/peptide connection, which in part was influenced by the individual's specific and unique HLA composition (Klitz et al., 2012).

This study has few limitations. The main limitation is the small cohort size, as our sample does not represent all Lebanese AML patients. We are currently working at the AUBMC to create a public national database to address this issue. Furthermore, this paper serves as a baseline study for advanced research on HLA antigens and AML disease prognosis, which may help patients with risk stratification and treatment options. We will extrapolate these findings into allelic level of testing and association where HLA typing using Next Generation Sequencing (NGS) technology will add more to the discoveries of new alleles in any population. A recent study finding represented the potential for AML therapeutic translation (Narayan et al., 2019). NPM1 is mutated in approximately one-third of adult AML patients (The Cancer Genome Atlas Research Network, 2013), and 30 to 70% of patients with NPM1 have AML relapse within five years (Pratcorona et al., 2013). The ligands CLAVEEVSL and AVEEVSLRK are predicted to bind and have the correct anchor residues for HLA-A*02:01 and HLA-A*03:01 respectively. These findings can support future studies evaluating and targeting the endogenous HLA presentation of mutated NPM1 in order to stimulate an endogenous anti-AML response.

Finally, we concluded that three class I HLA alleles are predisposing to AML (HLA-A*03; HLA-A*25 and HLA-A*74), one class I HLA allele is a protective allele (HLA-B*15). Regarding class II HLA alleles (DRB1*03) was protective whereas, (DRB1*12) was predisposing to AML. Larger studies using additional technologies such as NGS are needed to discover more allelic characterization of the HLA genotypes that both patients and controls have and to shed light on the roles of HLA with killer immunoglobulin-like receptors (KIR) in the genetic predisposition to AML (Misra et al., 2016).

Table 3
Predisposing and protective HLA antigens for AML found in literature from different countries.

Risk of AML	HLA antigens				
	HLA-A	HLA-B	HLA-C	DRB1	DQB1
Predisposing	A*01; China (Li et al., 2005) A*03; Lebanon A*25; Lebanon A*74; Lebanon	B*07; Brazil (Barion et al., 1992) B*21; Turkey (Ozdilli et al., 2010) B*35; Turkey (Ozdilli et al., 2010) B*37; China (Li et al., 2005) B*39; India (Solanki et al., 2020) and Venezuela (Villalobos et al., 2003) B*49; Turkey (Ozdilli et al., 2010)	C*03; Korea (Yoon, 2015) C*07; India (Solanki et al., 2020)	DRB1*03; Turkey (Turkan and Haluk, 2015) DRB1*4; Turkey (Ozdilli et al., 2010) DRB1*12; Lebanon DRB1*15; Turkey (Ozdilli et al., 2010) DRB1*102; Brazil (Fernandes et al., 2010) DRB1*107; Brazil (Fernandes et al., 2010)	DQB1*102; Brazil (Fernandes et al., 2010)
Protective	A*11; Indian (Solanki et al., 2020) Turkey (Ozdilli et al., 2010) A*33; China (Li et al., 2005)	B*15; Lebanon, Mexico (Fernández-Torres et al., 2013) B*18; Turkey (Li et al., 2005) B*38; Turkey (Li et al., 2005) B*40; Mexico (Fernández-Torres et al., 2013). B*51; India (Solanki et al., 2020) China (Li et al., 2005)	C*01; India (Solanki et al., 2020)	DRB1*03; Lebanon DRB1*11; India (Solanki et al., 2020) Iran (Yoon, 2015) DRB1*13; Turkey (Ozdilli et al., 2010)	DQB1*104; Brazil (Fernandes et al., 2010) DQB1-03:03 Iran (Sarafnejad et al., 2006)

(): references.

CRedit authorship contribution statement

Hani El Achkar: Project administration, Supervision, Data curation, Writing – original draft. **Hani Tamim:** Formal analysis, Software. **AbdulKarim El Karaaoui:** Data curation, Methodology, Writing – original draft. **Puzant Fermanian:** Data curation, Methodology. **Sose Keleshian:** Data curation, Methodology. **Fatmeh Abbas:** Data curation, Methodology. **Rami Mahfouz:** Conceptualization, Formal analysis, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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