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Original article

Killer immunoglobulin-like receptors and HLA C1/C2 genes diversities and susceptibility to acute myeloid leukemia in Saudi Arabian patients

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ABSTRACT

Objective: Natural Killer cells activation depends on the interaction with killer cell immunoglobin-like receptors (KIRs), which bind the peptide-binding region of several class-I Human Leukocyte Antigens (HLA class-I). In addition, KIR and HLA loci are highly polymorphic and display significant variation between individuals.

Methods: We attempted to investigate the association of 16 KIR complexes and the HLA-C1 and C2 ligands to the genetic predisposition and development of Acute Lymphoblastic leukemia (AML) in Saudi Arabian patients. We genotyped 16 KIR genes for 100 patients with Acute Lymphoblastic leukemia and 114 healthy controls, and all samples were considered for evaluating combined KIR-HLA C1/C2 associations.

Results: KIR genotype frequency differed significantly between AML patients and healthy controls. KIR2DL1, KIR2DL5, and KIR2DS2 increased significantly in patients than in controls. The 2DL5 gene contributed to the highest risk of AML (OR = 2.9906, $p < 0.00059$), followed by 2DS2 (OR = 1.8068; $p < 0.039$). However, the incidence of KIR 2DL3, KIR2DS4, and KIR2DL2 was significantly elevated in healthy controls compared to myeloid leukemia patients. The distributions of HLA-C1 and C2 ligands were not significantly different between patients and controls. Analyses of different combinations of KIR/HLA class I ligand profile show that the frequency of KIR2DL3 + in the presence of the allotype C1 was decreased among AML patients compared to controls. Similarly, KIR2DL3 and KIR2DL2/2DL3, when combined with their respective ligands, HLA-C2/C1, were significantly less prevalent in AML patients when compared to controls.

Conclusion: Our data suggested a potential predictive role for a specific KIR genotype, and HLA-I encoding genes to AML risk.

1. Introduction

Natural killer cells (NK cells) are part of innate immune system that serve as a first line of defense with the ability to eliminate virally infected cells and malignant transformations without previous sensitization. NK cells express receptors from several distinct families that regulate their killing activity. One receptor family that regulates the killing ability of NK cells is the Killer cell immunoglobulin-like receptor (KIR) family. The KIR receptors are a superfamily of immunoglobulin located at chromosomal region 19q13.4 within the leukocyte receptor complex (Caligiuri MA., 2008: Yokoyama et al., 2003).

Sixteen KIR receptors have been distinguished in humans: seven inhibitory receptors (3DL1–3, 2DL1–3, 2DL5), six activating receptors (3DS1, 2DS1–5), one (2DL4) with dual function as both inhibitory and activating potential and two genes (2DP1 and 3DP1) as pseudogenes that do not encode for a functional receptor (Al Omar et al., 2015: Xu et al., 2020).

The KIR gene cluster shows considerable variation due to gene-content diversity and haplotypic variation (Yawata et al., 2006). In

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addition to gene content diversity, allelic polymorphism + – extends KIR variations and accounts for differential expression levels of KIRs on the surface of NK cells (Middleton et al., 2010: Larki et al., 2022). KIR receptors are essential for acquiring the effector function of NK cells. KIR family consist of Ig-like domains that bind to HLA class-I molecules (major histocompatibility complex class-I (MHC class-I), also called human leukocyte antigen class-I), which aid the distinguish between "the self" and "the non-self." KIRs involve in education and selection during the process of NK cell maturation (Ljunggren et al. 1990; Sivori et al. 2019). The interaction between HLA class-I molecules expressed on normal tissue cells and KIRs on NK cells' surface shapes the autoimmune tolerance of the body (Xu et al., 2020). Accumulating evidence implied that different KIR/HLA gene combinations and the expression levels of HLA have the ability to influence cancer prognosis, treatment response, and immunotherapy strategy through several mechanisms (Xu et al., 2020; Muraro et al., 2022).

Hence, a growing body of literature has examined the relationship between KIR gene variations and different types of cancer. Several investigations have described KIR/HLA class I ligand compound genotypes which influences the susceptibility to various hematological malignancies. Data also suggested that the activity of NK cells as determined by inherited KIR/HLA class I ligand polymorphisms influences the susceptibility to myelogenous leukemia (Varbanova et al., 2019). However, just a few researches focusing on the relationship between KIR gene polymorphisms and the development of leukemia. To explore the relationship of KIR with leukemia development, the presents study aimed to investigate the contribution of KIR complex and HLA-I ligands to the genetic predisposition to Acute Myeloid Leukemia (AML) in the Saudi Arabian population, since this type of blood cancer is the most prevalent acute leukemia in adults and is responsible for the majority of cancer-related mortality (Alahmari et al., 2021).

2. Materials and Methods

2.1. Subjects

2.1.1. Inclusion criteria for sample selection

Human whole blood samples of total 214 Individuals were collected for the study. Gender and age-matched controls and cases were selected for the study. The study included 100 patients (39 (39%) females and 61(61%) males) diagnosed with Acute Myeloid leukemia (AML) and having no other known pathologies or hematological disorders and previous cancer and 114 unrelated healthy individuals without any clinical signs of any type of cancer or other diseases of both genders (38 (33%) female and 76 (66%) male) served as controls. The average age of AML patients was 27.7 years, whereas the average age of healthy controls was 22.4 years.

2.1.2. Ethics approval

All procedures were in accordance with the Helsinki protocol and approved by the medical ethics committee in King Khalid University Hospital, Riyadh, Saudi Arabia. (Ref. No. E-21–5922).

2.1.3. Genomic DNA extraction and KIR and HLA-C typing

Three milliliters of blood samples were collected by venipuncture from each individual and then stored in ethylenediaminetetraacetic acid (EDTA)-containing tubes and stored at – 20 °C before analysis. Genomic DNA was extracted from blood samples using QIAamp DNA Blood Mini Kit (QIAGEN, GmbH, Hilden, Germany) following the recommendation of the manufacturer. DNA purity and concentrations were determined by spectrophotometric measurement of absorbance at 260 and 280 nm (A260/A280 ratio) using Nanodrop ND-2000c spectrophotometer (Thermo Scientific, Wilmington, DE, USA).

Genotyping of KIRs was performed for 16 genes and HLA-C1/C2 of the studied samples using the polymerase chain reaction-sequence-specific primer (PCR-SSP). All genotypes were determined as reported by (Tajik et al., 2009), which allows the detection of all known KIR genes.

The genotype analysis was performed to detect the 16 KIR and HLA-C1/C2 gene fragments via Thermocycler apparatus T100™ (Thermal Cycler from Bio-Rad Laboratories, Inc. Life Science Research, California 94547, United States). The amplified product was visualized under a UV transilluminator by BioDocAnalyze (Biometra GmbH, Germany) on 2% agarose gel containing ethidium bromide for the investigation of the presence or absence of gene-specific amplicons.

2.1.4. Statistical analysis

The frequency of each KIR, HLA-C ligand, and KIR/HLA-C ligand combination in the patient and control groups were determined by direct counting. Statistical analysis was performed using SigmaPlot version 11 software. The differences between the two groups in the distribution of each KIR gene, HLA-C genotype, and KIR/HLA-C combination were estimated using the two-tailed Fisher exact test with Bonferroni correction. The statistical significance was defined as $p < 0.05$. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the strength of the associations.

3. Results

3.1. The KIR gene frequencies and distribution in AML patients and healthy groups

In AML patients, a significant increase in the KIR2DL1, KIR2DL5 and KIR2DS2 frequencies were observed (OR = 0; P = 0.00023; OR = 0.35; P = 0.000059; OR = 1.806; P = 0.039) respectively. However, the frequency of KIR2DL2, KIR2DL3 and KIR2DS4 were significantly lower in AML patients (OR = 0.5512; P = 0.039; OR = 0.3062; P = 0.00023; OR = 0.2492; P = 0.000207) respectively. For the remaining loci, no significant differences were observed between groups (Table 1).

3.2. Distribution of the KIR ligand C1/C2 in AML patients and healthy groups

This study investigated the frequency of HLA-C allotypes, which are the main ligands of KIR receptors. The two main allotypes, HLA-C1 and –C2 frequency were determined for AML patients and healthy controls. However, significant differences in the frequency of either genotype and allotypes were not detected (Table 2).

3.3. Combinatorial analyses of selected KIR receptors in AML patients and healthy groups

In order to determine the relative contribution of effective genes that may be involved in the development of AML, various gene combinations were analysed and represented (Table 3). Because different KIR genes share the same ligand but differ in the strength of the inhibitory or activating signals, the frequency of some KIR gene combinations was performed.

The combination frequencies of some KIR genes 2DS2+/2DS3-, 2DS2-/2DS3+, 2DS2+/2DS3-/2DL5+,2DS2-/2DS3+/2DL5+, 2DS2-/2DS3-/2DL5+, 2DL2+/2DS2- and 2DL2-/2DS2 + were significantly higher in AML patients than Control group. In contrast, the higher frequencies in the healthy control were found statistically

Table 1
Comparison of KIR gene frequencies between AML patients and healthy groups.

Genes	AML patients n = 100		Controls n = 114		X^2	OR	CI 95%	*P*-value
	Count	%	Count	%				
3DL2	100	100%	114	100%	–	NaN	NaN	1
3DL3	100	100%	114	100%	–	NaN	NaN	1
2DL4	100	100%	111	97%	2.669	Infinity	NaN - Infinity	0.2497
3DP1	98	98%	114	100%	2.301	0	0-NaN	0.2172
2DL1	100	100%	101	89%	12.141	Infinity	NaN - Infinity	**0.0002**
2DL3	59	59%	94	82%	14.382	0.306	0.1637–0.572	**0.0002**
3DL1	92	92%	106	93%	0.0743	0.867	0.3133–2.405	0.8006
2DS4 dl	70	70%	103	90%	14.245	0.249	0.1172–0.53	0.0002
2DL2	44	44%	67	59%	4.6562	0.551	0.320–0.948	**0.0396**
2DL5	81	81%	67	59%	12.34	2.990	1.603–5.578	**0.0006**
2DS1	24	24%	35	31%	1.198	0.712	0.388–1.308	0.2875
2DS2	55	55%	46	40%	4.587	1.806	1.049–3.111	0.8910
2DS3	45	45%	51	45%	0.0015	1.011	0.589–1.7342	1
2DS5	31	31%	33	29%	0.1071	1.103	0.6137–1.981	0.7665
3DS1	26	26%	24	21%	0.7282	1.318	0.6987–2.485	0.4214
2DP1	100	100%	114	100%	–	NaN	NaN	1

AML: Acute Myeloid Leukemia; OR: odds ratio; CI: confidence interval; n, number of individuals; Boldfaced values indicate a significant difference at the P ≤ 0.05 level.

Table 2
The frequencies of KIR ligands C1-C2 in AML patients and healthy groups.

Gene /genotype	AML patients n = 100		Controls n = 114		X2	OR	CI 95%	*P*-value
	Count	%	Count	%				
C1	70	70%	83	73%	0.2060	1.1475	0.6334–2.078	0.7616
C2	71	71%	81	71%	0.0001	1.0026	0.5547–1.812	1
C1C2	41	41%	50	44%	0.1782	1.1242	0.6527–1.936	0.680
C1C1	29	29%	33	29%	0.0001	0.9974	0.5518–1.803	1
C2C2	30	30%	31	27%	0.2060	0.8715	0.481–1.5789	0.7616

AML: Acute Myeloid Leukemia; OR: odds ratio; CI: confidence interval; n, number of individuals; Boldfaced values indicate a significant difference at the P ≤ 0.05 level.

Table 3
Combinatorial analyses of selected KIR receptors among AML patient and control groups.

KIR Ligand	AML patients n = 100		Controls n = 114		X^2	OR	CI 95%	*P*-value
	Count	%	Count	%				
2DS2+/2DS3+	21	21%	43	38%	7.1037	2.2783	1.235–4.2031	**0.0106**
2DS2+/2DS3-	34	34%	21	18%	6.7707	0.4383	0.2337–0.8221	**0.0119**
2DS2-/2DS3+	24	24%	8	7%	12.081	0.239	0.1019–0.5607	**0.0005**
2DS2-/2DS3-	21	21%	43	38%	7.1037	2.2783	1.235–4.203	**0.0106**
2DS2+/2DS3+/2DL5+	14	14%	40	35%	12.556	3.3205	1.6765–6.576	**0.0004**
2DS2+/2DS3+/2DL5-	7	7%	3	3%	2.2821	0.3591	0.0903–1.4277	0.194
2DS2+/2DS3-/2DL5+	30	30%	11	10%	14.245	0.2492	0.1172–0.53	**0.0002**
2DS2-/2DS3+/2DL5+	18	18%	5	4%	10.293	0.209	0.074–0.586	**0.0016**
2DS2-/2DS3+/2DL5-	6	6%	3	3%	1.5003	0.4234	0.103–1.739	0.3099
2DS2+/2DS3-/2DL5-	4	4%	10	9%	1.984	2.3077	0.7005–7.6028	0.17846
2DS2-/2DS3-/2DL5+	20	20%	11	10%	4.6074	0.4272	0.1936–0.9428	**0.03431**
2DS2-/2DS3-/2DL5-	1	1%	31	27%	28.739	36.9759	4.9414–276.684	**0.0000000322**
2DL2+/2DS2+	22	22%	56	49%	16.918	3.4232	1.8807–6.2307	**0.0000588**
2DL2+/2DS2-	22	22%	11	10%	6.2305	0.3786	0.1733–0.8271	**0.014122**
2DL2-/2DS2+	33	33%	8	7%	23.219	0.2676	0.1132–0.6326	**0.002603**
2DL2-/2DS2-	23	23%	39	34%	3.2534	1.7409	0.9502–3.1896	0.096266

AML: Acute Myeloid Leukemia; OR: odds ratio; CI: confidence interval; n, number of individuals; Boldfaced values indicate a significant difference at the P ≤ 0.05 level.

significant in combinations of 2DS2+/2DS3+, 2DS2-/2DS3-, 2DS2+/2DS3+/2DL5+, 2DL2+/2DS2 + and 2DL2-/2DS2- (Table 3).

3.4. Distribution of the frequencies of KIR genes in presence and absence of their HLA-C1 and HLA-C2 ligand

The combination frequencies of some KIR genes in the presence of their ligands 2DL2+/2DS2-/C1 + and 2DL2-/2DS2+/C1 + were found significantly higher in AML patients than control group. Although, the control group showed higher frequency in some KIR genes in the presence of their ligands 2DL3 + C1+, 2DL3 + C1 C2 + and 2DL2+/2DS2+/C1 +.

4. Discussion

Acute myeloid leukemia (AML) is an aggressive malignancy of the bone marrow blast cells. The uncontrolled proliferation of undifferentiated myeloid cells characterizes AML. It originates

Table 4
The distribution of the frequencies of KIR genes in presence and absence of their C1-C2 ligands between AML patients and healthy control groups.

KIR Ligand	AML patients n = 100		Controls n = 114		X2	OR	CI 95%	*P*-value
	Count	%	Count	%				
2DL2 + C1+	32	32%	50	44%	3.1701	1.6602	0.9485–2.9059	0.0909
2DL2 + C1−	12	12%	18	16%	0.6347	1.375	0.6268–3.0165	0.4391
2DL2 + C1C1+	15	15%	23	20%	0.977	1.4322	0.701–2.9264	0.3722
2DL2 + C1C2+	17	17%	27	24%	1.4572	1.5152	0.7697–2.9827	0.2406
2DL3 + C1+	42	42%	68	60%	6.6426	2.0414	1.183–3.5228	**0.013464**
2DL3 + C1−	17	17%	26	23%	1.1188	0.6932	0.3509–1.3696	0.3099
2DL3 + C1C1+	21	21%	26	23%	0.1015	1.1115	0.58–2.1298	0.8687
2DL3 + C1C2+	21	21%	41	36%	5.7974	2.1129	1.1426–3.907	**0.023078**
2DL2/3 + C1+	25	25%	38	33%	1.7809	1.5	0.8256–2.7253	0.2291
2DL2/3 + C1−	9	9%	13	11%	0.3336	1.3014	0.5313–3.1878	0.65467
2DL2/3 + C1C1+	11	11%	18	16%	1.0431	1.517	0.6792–3.3886	0.3252
2DL2/2DL3 + C1C2+	15	15%	20	18%	0.252	26.6333	12.823–55.317	0.6157
2DS2 + C1+	40	40%	49	43%	0.1951	1.1308	0.6553–1.9511	0.679
2DS2 + C1−	15	15%	15	13%	0.15	0.8586	0.3967–1.8583	0.8439
2DS2 + C1C1+	11	11%	20	18%	1.8415	1.7215	0.7807–3.7961	0.2425
2DS2 + C1C2+	15	15%	29	25%	3.5539	1.9333	0.9677–3.8625	0.0643
2DL1 + C2+	71	71%	76	67%	0.4651	0.8169	0.4567–1.4613	0.5554
2DL1 + C2−	29	29%	25	22%	1.4114	0.6877	0.3703–1.2774	0.2706
2DL1 + C2C2+	30	30%	30	26%	0.3584	0.8333	0.4586–1.5143	0.6475
2DL1 + C1C2+	41	41%	46	40%	0.0093	0.9735	0.5635–1.6816	1
2DS1 + C2+	16	16%	23	20%	0.6232	1.3269	0.6566–2.6818	0.4805
2DS1 + C2–	8	8%	12	11%	0.4013	1.3529	0.5296–3.4564	0.6399
2DS1 + C1C1+	8	8%	12	11%	0.4013	1.3529	0.5296–3.4564	0.6399
2DS1 + C1C2+	8	8%	15	13%	1.4774	1.7424	0.7057–4.302	0.2718
2DS1 + C2C2+	8	8%	8	7%	0.0743	0.8679	0.3133–2.4046	0.8006
2DL2+/2DS2+/C1+	17	17%	43	38%	11.334	2.9569	1.5518–5.6345	**0.000794**
2DL2+/2DS2-/C1+	15	15%	7	6%	4.5334	0.3707	0.1446–0.9502	**0.042121**
2DL2-/2DS2+/C1+	23	23%	6	5%	14.305	0.186	0.0723–0.4784	**0.000211**
2DL2+/2DS2+/C1-	5	5%	13	11%	2.8355	2.4455	0.8399–7.121	0.137
2DL2-/2DS2-/C1+	14	14%	27	24%	3.2256	1.9064	0.9363–3.8815	0.083

AML: Acute Myeloid Leukemia; OR: odds ratio; CI: confidence interval; n, number of individuals; Boldfaced values indicate a significant difference at the P ≤ 0.05 level.

from a hematopoietic stem cell that acquires genetic, epigenetic mutations and is able to self-renew to conserve the disease status. In the current study, we investigated the contribution of KIR gene content and their corresponding HLA-I ligands to AML in the Saudi Arabian population (see Table 4).

To our knowledge, this is the first study demonstrating that individual KIR genes and specific genotypes seem to be associated with susceptibility to AML. Therefore, we suggested that the interactions between KIR-HLA class I ligands can impact the NK cell dynamics and responses toward AML. The association between KIRs and KIR HLA class I ligand variants have been found with various tumors. However, we observed a significant association with some receptors and their ligands when considering the distribution in the combination of some KIR genes in the presence or absence of their ligands. Here, we investigated the associations of KIRs with their cognate HLA ligands C1 and C2 groups, individually or in a different combination, regarding AML susceptibility. Analysis of the distribution of 16 KIR genes between AML patients and healthy control groups demonstrated that two activating KIR genes (2DS4 and 2DS3) are significantly less frequent in AML patients. Our findings mainly identified the association between KIR2DL2 carriers and their activating counterpart 2DS2 with an increased risk of AML; similarly, 2DS2+/2DS3-/2DL5 + and 2DS2+/2DS3- were found to be associated with the increasing risk of having AML. On the other hand, a clear association was not identified considering genotypes of the HLA C1/C2 polymorphism in different combinations with the explored disease. KIR genotype frequency differed significantly between AML patients and healthy controls for KIR2DL1, KIR2DL3, KIR2DS4, KIR2DL2, KIR2DL5, KIR2DS2 KIR2DL5A. Nevertheless, the results of our study are not in line with previous findings in different types of blood cancers. A study conducted by Karabon et al. (2011) and Ozturk et al., (2012) showed that KIR2DL5 was less frequent in patients with onco-hematological diseases such as B-cell chronic lymphocyte leukemia and Hodgkin's lymphoma patients. Giebel et al. (2008) found a significant association between KIR2DS4 and leukemia, chronic myeloid leukemia (Zhang et al., 2010), and acute lymphoblastic leukemia (Misra et al., 2016) which is inconsistent with our present data.

5. Conclusions

In conclusion, KIR2DL1, KIR2DL3, KIR2DS4, KIR2DL2, KIR2DL5, KIR2DS2 and the combination of 2DL3 + C1 + and 2DL3 + C1C2+, 2DL2+/2DS2+/C1+, 2DL2+/2DS2-/C1+, 2DL2-/2DS2+/C1 + are associated with either susceptibility toward AML or protection against AML in the Saudi population.

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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Further reading

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