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ORIGINAL RESEARCH

IL-10 rs1800896 Polymorphism: A Risk Factor for Adult Acute Lymphoblastic Leukemia

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Purpose: Single-nucleotide polymorphism (SNP) in the promoter region of the IL-10 gene can increase susceptibility to tumor development. The current study aimed to explore the genotypic frequency of interleukin-10 (IL-10) rs1800896 polymorphism in newly diagnosed adult patients with acute lymphoblastic leukemia (ALL) and validate whether this SNP is a risk factor for adult ALL.

Patients and Methods: This case–control study was based on a subset of newly diagnosed 154 adult patients with ALL recruited from the Radiation and Isotope Center in Khartoum (RICK) and 154 healthy controls from the same geographical area. Genomic DNA was used for the genotyping of rs1800896 polymorphism through allele-specific polymerase chain reaction (PCR) assays.

Results: The genotypic frequencies of rs1800896 showed a statistically significant association of AG and AA genotypes with adult ALL ($p<0.001$). Combined genotypes AG+GG vs AA also showed a positive association of rs1800896 with adult ALL (OR=4.89). The allelic frequencies of G and A did not show any significant difference in adult patients with ALL compared with the control group. AG rs1800896 genotype showed an increased risk of B and T ALL (OR=2.51 and 4.70, respectively). Age at diagnosis, gender, and immunophenotype (B vs T ALL) did not exhibit any association of rs1800896 with ALL in this patient group.

Conclusion: rs1800896 polymorphism is associated with an increased risk of ALL in adult patients irrespective of the age at diagnosis, gender, and immunophenotype of ALL.

Keywords: acute lymphoblastic leukemia, polymorphism, IL-10, –1082 (A>G), rs1800896

Introduction

Acute lymphoblastic leukemia (ALL) is a neoplastic disorder characterized by relentless proliferation with restricted differentiation of lymphoid cells and their accumulation in the bone marrow, circulation in the blood, and invasion of the extramedullary sites.[1,2] Although the exact pathophysiological agent/mechanism is unknown, inherited genetic susceptibility, certain environmental risk factors,[1] genetic polymorphisms in the oxidative stress enzymes,[3] and an altered immune microenvironment in the bone marrow have shown strong positive associations with ALL.[4] A growing body of literature is indicating the involvement of inflammatory processes in the development of malignancies.

Interleukin-10 (IL-10), also known as cytokine synthesis inhibitory factor (CSIF), is one of the most vital pleiotropic immunoregulatory cytokines secreted by the cells of lymphoid and myeloid lineages, including T helper cells (Th2 cells), CD4, CD8 T cells, natural killer cells, macrophages, monocytes, neutrophils, mast cells, eosinophils, and dendritic cells. IL-10 is also produced by tumor cells, which may lead to immunosuppression.[5]

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IL-10 regulates the functions of several cells. It inhibits macrophages and antigen-presenting cells (APCs) and robustly suppresses the immune system through transcriptional inhibition of cytokines, chemokines, major histocompatibility complex II molecules, and adhesion molecules. IL-10 also inhibits T-cell responses directly by acting on CD4 T cells and indirectly through APCs.[5] Contrary to its effect on CD4 T cells, IL-10 promotes the proliferation and cytotoxicity of CD8 T cells.[6] Furthermore, IL-10 suppresses the secretion of interferon gamma (IFN-γ) and IL-2.[7] As IFN-γ is pivotal in the activation of cellular immunity and stimulation of the antitumor response, its suppression would contribute toward the development of neoplasm.[8]

Similarly, IL-2, activates STAT5 transcription factors with the help of JAK tyrosine kinases through IL-2 receptors.[9] In addition to its role in immune regulation, IL-10 demonstrates two types of effects during tumor development, ie, cancer promoting (immunosuppressive) and cancer inhibitory (antiangiogenic).[10,11] Lymphoproliferation could be the underlying cause of a dysfunctional immune system. The pathogenesis and prognosis of lymphoid neoplasms have been attributed to the involvement of IL-10.[12–14]

The IL-10 gene, located on chromosome 1q31–32, spanning 4.8 kb, contains five exons and four introns and encodes 178 amino acids. The promoter region of the IL-10 gene contains a large number of polymorphic sites that alter gene transcription.[15,16] Studies have shown that IL-10 gene polymorphisms increase the susceptibility to tumor development, eg, cancers of the head and neck,[17] laryngeal squamous cell carcinoma,[12] gastric cancers,[16,18,19] and hematological neoplasms, including chronic myeloid leukemia[20] and acute myeloid leukemia.[21–24]

One such single-nucleotide polymorphism (SNP) of the IL-10 gene is –1082 [G to A single base pair substitution (rs1800896)] in the promoter region that is associated with increased IL-10 expression and susceptibility to lymphoproliferative disorders, including lymphoma[12–14,25] and childhood acute lymphoblastic leukemia,[15,26,27] and several other malignancies[28] [reviewed by Trifunović et al[29]].

Although the role of rs1800896 SNP in the IL-10 gene as a risk factor for childhood ALL has been investigated,[15,27] studies are lacking addressing its susceptibility in adult ALL. This study aimed to 1) evaluate the frequency of IL-10 rs1800896 in newly diagnosed adult patients with ALL and 2) assess whether this SNP is a risk factor for adult ALL.

Materials and Methods

This case–control study included 154 newly diagnosed Sudanese adult patients with ALL, aged 19–75 years (93 men and 61 women), and 154 normal healthy age- and gender-matched controls (101 men and 53 women). The newly diagnosed patients were recruited from the Radiation and Isotope Center in Khartoum (RICK) between December 2019 and January 2022 before the initiation of the treatment. Al-Neelain University's ethical committee approved this study (project number 5/20). Each participant signed an informed consent form following the guidelines of the Declaration of Helsinki. The patients recruited to this study had no previous history or diagnosis of other malignancy. Patients were evaluated at the RICK according to the WHO guidelines. Complete blood counts, bone marrow examination, and flow cytometric analysis were carried out to establish the diagnosis of the patients by hemato-oncologists. A control group with no prior history of cancer was selected from the same geographic area as the patients, to represent the same age group and ethnicity as the patients. The clinical and demographic data were collected through a structured questionnaire. To perform the polymerase chain reaction (PCR) analysis, 3–5 mL of EDTA-anticoagulated venous blood samples were collected from the studied participants.

DNA Extraction

Isolation of DNA from peripheral blood samples was performed as per the manufacturer's protocol using a commercially available whole blood genomic DNA purification kit (QIAamp® DNA Mini Kit; Qiagen, Hilden, Germany). A GeneQuant device (Amersham Biosciences–Biochrome, Cambridge, UK) was used to verify the quantity and quality of extracted DNA. Until analysis, aliquots of the extracted DNA samples were maintained at –20°C.

Molecular Analysis

The genomic DNA was used for the genotyping of rs1800896 polymorphism through an allele-specific PCR assay using β-globin gene-amplified product as an internal positive control following previously described methods.[22] The PCR for

rs1800896 polymorphism was carried out utilizing a total volume of 20 µL, which was prepared by adding 14 µL distilled water, 4 µL of genomic DNA, and 0.5 µL of each primer. The following sets of specific primers were used: 5′-TACTAAGGCTTCTTTGGGAG-3′ (allele G forward), 5′-CTACTAAGGCTTCTTTGGGAA-3′ (allele A forward), and 5′-TCTCGGTTTCTTCTCCATCG-3′ (reverse). The thermocycling conditions started with one cycle at 94°C for 5 minutes, followed by 32 cycles at 94°C for 30 seconds, annealing at 58°C for 30 seconds, extension at 72°C for 40 seconds, and a final extension at 72°C for 5 minutes.

For each sample, 2.0% agarose gel electrophoresis was used to examine the banding patterns of the amplified products stained with ethidium bromide. A PCR product with 268 bp indicated successful amplification. Based on the presence or absence of a band at 550 bp, the rs1800896 allelic genotype was identified.

Statistical Analysis

The statistical analyses, including descriptive statistics of the mean, standard deviation, and odds ratio (OR) with 95% confidence interval (CI), were performed using SPSS for Windows version 23 (IBM Corp, Armonk, NY, USA). The Pearson chi-squared test or Fisher's exact test was used to evaluate the significance of the difference in genotype distributions of patients and controls. In addition, quantitative variables were tested using an independent *t*-test. Statistical significance was judged by a p value less than 0.05.

Results

The gender and age of the patients with ALL and controls were well matched and did not show any statistically significant differences ($p>0.05$). The majority of the patients (83.1%) were B ALL (Table 1).

The genotypic and allelic frequencies of rs1800896 are presented in Table 2. AG and AA genotypes showed statistically significant associations with adult ALL (OR=3.1 and 0.20 respectively, $p<0.001$). Combination analysis of AG+GG versus AA also showed a positive association of rs1800896 with 4.89 odds ratio of ALL in patients compared with healthy controls (Table 2). The allelic frequencies of G and A rs1800896 did not show any significant difference in adult patients with ALL compared with the control group.

Based upon the immunophenotyping of ALL, the AG rs1800896 genotype showed an increased risk of B and T ALL (OR=2.51 and 4.70, respectively). However, the AA rs1800896 genotype showed a significant association with B ALL only (Table 3). Age at diagnosis, gender, and immunophenotype (B vs T ALL) did not exhibit any associations of rs1800896 and rs1800629 with ALL in the patient group (Table 4).

Table 1 Demographic Measures of the Studied Subjects

Category	Cases (n=154)	Controls (n=154)	*p*-Value
Gender			
Male, n (%)	93 (60.4%)	101 (65.6%)	0 0.345
Female, n (%)	61 (39.6%)	53 (34.4%)	
Age			
Mean±SD (years)	44.90±14.3	47.09±16.1	0.193
Range (years)	19–75	20–74	
< Mean age, n (%)	75 (48.7%)	86 (55.8%)	0.209
> Mean age, n (%)	79 (51.3%)	68 (44.2%)	
Immunophenotype			
B-ALL, n (%)	128 (83.1%)	–	–
T-ALL, n (%)	26 (16.9%)	–	–

Table 2 Genotype Distribution and Allele Frequencies of rs1800896 in Patient and Control Groups

SNP	Genotype	ALL (n=154)	Controls (n=154)	Odds Ratio (95% CI)	*p*-Value
rs1800896	GG	21 (13.6%)	26 (16.9%)	0.78 (0.42 to 1.45)	0.429
	AG	121 (78.6%)	83 (53.9%)	3.1 (1.90 to 5.16)	<0.001
	AA	12 (7.8%)	45 (29.2%)	0.20 (0.10 to 0.41)	<0.001
	AG+AA vs GG	133 (86.4%)	128 (83.1%)	1.29 (0.69 to 2.40)	0.429
	AG+GG vs AA	142 (92.2%)	109 (70.8%)	4.89 (2.47 to 9.687)	<0.001
Allele frequency					
rs1800896	G	163 (52.9%)	173 (56.2%)	1.14 (0.83 to 1.57)	0.419
	A	145 (47.1%)	135 (43.8%)		

Table 3 Genotype Distribution of rs1800896 in the B ALL/T ALL Cases and Control Groups

SNP	Genotype	B-ALL (n=128)	Controls (n=154)	Odds Ratio (95% CI)	*p*-Value	T-ALL (n=26)	Controls (n=154)	Odds Ratio (95% CI)	*p*-Value
rs1800896	GG	20 (15.6%)	26 (16.9%)	0.91 (0.48 to 1.72)	0.776	1 (3.8%)	26 (16.9%)	0.20 (0.03 to 1.52)	0.119
	AG	99 (77.3%)	83 (53.9%)	2.51 (1.48 to 4.26)	0.001	22 (84.6%)	83 (53.9%)	4.70 (1.55 to 14.30)	0.006
	AA	9 (7%)	45 (29.2%)	0.18 (0.09 to 0.40)	<0.001	3 (11.5%)	45 (29.2%)	0.32 (0.09 to 1.11)	0.071

Table 4 Distribution of rs1800896 Among Patients According to Age Group, Gender, and Origin of ALL

Parameter	Category	rs1800896		
		GG	AG	AA
Age group	**< Mean (years)**	14	55	6
	> Mean (years)	7	66	6
Chi-square (*p*-value)		3.23 (0.198)		
Gender	**Male**	10	77	6
	Female	11	44	6
Chi-square (*p*-value)		2.51 (0.286)		
Origin	**B-ALL**	20	99	9
	T-ALL	1	22	3
Chi-square (*p*-value)		2.91 (0.234)		

Discussion

Inflammatory cytokines are among the instrumental players in the development of tumors, by inducing angiogenesis, hyperproliferation, DNA aberrations, and genetic mutations.[30] Polymorphisms in the promoter region of the genes can alter

the transcription and abnormal expression of proteins that may contribute to the development of neoplasia.[31,32] It is a well-known fact that these polymorphisms affect the production and function of IL-10 and result in hematological neoplasms.[33]

The current study evaluated polymorphisms in the promoter region of the IL-10 gene in adult patients with ALL. The findings show that AG and AA rs1800896 genotypes are associated with an increased risk for the development of ALL in adult patients [OR=3.1 (95% CI=1.90 to 5.16) and OR=0.20 (95% CI=0.10 to 0.41), respectively]. Comparable to the findings of this study, differences related to rs1800896 polymorphism in patients with childhood ALL and healthy controls have been reported in the literature.[33,34] However, the results of the current study are contradictory to some other studies, where no differences in the distribution of rs1800896 polymorphism between control and childhood ALL were reported.[15,27]

In the current study, the genotypic distribution of rs1800896 showed that AG+GG versus AA had 4.89 odds ratio of ALL compared to the control group (Table 2). Similar findings were reported in a meta-analysis of 18 case–control studies.[35] It has been reported that the GG genotype poses a decreased risk of leukemia in comparison to the AG+AA genotype.[35]

The current study shows that rs1800896 has no significant associations with age at diagnosis, gender, or subtype of ALL (Table 4). This finding is consistent with the literature.[33] Contradictory reports are available on the genotypic and allelic frequencies of rs1800896 and its association with lymphoid neoplasms. In one study, a high frequency of rs1800896 was found in patients with diffuse large B-cell lymphoma (DLBCL) compared with normal controls.[12] In contrast, another study found no significant differences in the distribution of the rs1800896 polymorphism between DLBCL patients and controls.[36] Similarly, in patients with myeloproliferative neoplasms, including chronic myeloid leukemia and acute myeloid leukemia, rs1800896 showed no association with genotypic and allelic frequencies.[20,23,24] The haplotype of rs1800896 may also affect the overall survival. It has been reported that patients with DLBCL who had high levels of IL-10 showed poor prognosis and disease outcome.[12] Hence, it was presumed that the G>A/G>A diplotype in patients with lymphoid neoplasms would result in a lower level of IL-10 and better overall survival.[37] Contrary to this, it has also been reported that the rs1800896 genotype is not associated with progression-free survival or overall survival in patients with Hodgkin's lymphoma.[38] These contradictory reports could be due to the stage of the disease, environmental or sociodemographic characteristics, geographic location, or ethnicity. The conflicting reports in the literature necessitate large-scale studies in different populations with all possible risk evaluations.

It is concluded that the AG, AA, and AG+GG versus AA genotypes of rs1800896 polymorphism are associated with an increased risk for adult ALL. Furthermore, the frequency of rs1800896 is not affected by the age of the patient at diagnosis, gender, or subtype of ALL.

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Disclosure

The authors declare no conflicts of interest in this work.

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