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IL17F Gene Polymorphism in Egyptian Adult Patients with Acute Myeloid Leukemia

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Abstract: *Background:* Interleukin-17 (IL-17) is a cytokine pivotal in inflammation, autoimmune disorders, and cancer. This cytokine family comprises six members, including IL-17A to IL-17F, and five receptors, namely IL-17RA to IL-17RD and SEF. Several clinical studies have shown an increased expression of IL-17 in neoplastic disorders. Additionally, single nucleotide polymorphisms (SNPs) can impact gene functions and protein expression, which can in turn affect cellular proliferation and ultimately increase the risk of developing cancer. *IL17F rs763780 gene polymorphism* is linked to an increased risk of several malignancies and immunological disorders. The present study investigated the association between *IL17F* rs763780 gene polymorphism and susceptibility, clinicopathological features, and prognosis in adult Egyptian patients with AML. *Patients and method:* 102 AML patients (68 males and 34 females) and 106 healthy individuals were genotyped for the *IL17F rs763780* gene using a polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) assay. *Results:* Homozygous mutant GG genotype and G allele were significantly higher in AML patients than in the healthy control. However, no significant correlation was found between the gene polymorphism and disease characteristics or prognosis in different genotypes. *Conclusion:* mutant genotypes and alleles of the IL17F rs763780 gene polymorphism may be associated with an increased risk of AML among Egyptian patients.

Keywords: AML, *IL17F* rs763780, Prognosis

1. Introduction

Acute myeloid leukemia (AML) is a complex genetic disorder that accounts for 80% of acute leukemia in adults. It has a diverse clinical presentation, response to treatment, and prognosis [1]. The etiology of AML is multifactorial including both genetic and environmental factors. Additionally, an impaired immune system significantly contributes to the disease pathogenesis [2].

Interleukin-17 (IL-17) is a cytokine secreted by Th17 that bridges the adaptive and innate immune systems [3]. The human IL-17 gene is located on chromosome 6p12 and comprises 1874 base pairs [4]. The IL-17 family includes six pro-inflammatory cytokines, including IL-17A to IL-17F [5]. Previous studies have shown that IL-17 has a role in altering immune responses during cancer pathogenesis [6, 7].

IL-17F is one of the effector cytokines produced by activated CD4+T cells, monocytes, basophils, and mast cells. IL-17F (rs763780) gene polymorphism has been shown to influence the risk of human diseases such as bronchial asthma and inflammatory bowel disease [8-11]. Moreover, several studies reported that such polymorphism is associated with numerous malignancies such as pancreatic, gastric, colorectal, breast, and bladder cancer [12-16]. A recent meta-analysis confirms that IL-17F (rs763780) gene polymorphism is strongly associated with a higher risk for multiple cancers,

particularly colorectal cancer [17].

Despite being connected to various malignancies, limited data exist about the role of IL-17F (rs763780) polymorphism in AML. Some research explored the IL-17 level in AML [18-21], however, its association with clinical features and impact on the prognosis of AML patients remains uncertain.

The studies conducted on IL17 polymorphism in Egyptian AML patients showed conflicting results. While some studies indicated that there was no significant relationship between IL-17F (rs763780) mutant genotypes and AML incidence [22, 23], others found a statistically significant increase in IL-17F GG mutant genotype among AML patients compared to the control group [24].

2. Aim of the Study

The study's objective is to examine the impact of polymorphic variants of IL-17F (rs763780) on the susceptibility, clinical characteristics, and prognosis of AML in adult Egyptian patients.

3. Patients and Methods

3.1. Study Population

The current study is a retrospective case-control study. It was conducted on 102 adult newly diagnosed AML patients who attended Oncology Center, Mansoura University (OCMU) in the period between February 2012 and December 2015.

The diagnosis was established based on the WHO classification of myeloid neoplasms and acute leukemias [25]. Inclusion criteria comprised patients with normal karyotypes and no structural or numerical abnormalities. Acute promyelocytic leukemia (APL) and therapy-related AML (t-AML) were excluded from the study.

3.2. Control Group

The study included 106 healthy subjects (67 males and 39 females) with ages ranging from 22 to 72-year-old as a healthy control group and genotyped for the IL17F rs763780 gene.

3.3. Ethical Approval

The Mansoura University IRB approved the present work (R.23.08.2292) and informed consent was obtained from all research participants.

3.4. Method

The study involved the extraction of genomic DNA from both control participants and AML patients, with the latter group providing samples from the peripheral blood and/or the bone marrow. The samples were collected using EDTA and underwent DNA extraction according to the specific instructions provided by the manufacturer (Qiagen, Hilden, Germany).

The extracted DNA was subject to genotyping for IL17F rs763780, utilizing polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Amplification of a specific section of the promoter region was achieved using primers with a forward sequence of 5′-GTT CCC ATC CAG CAA GAG AC-3′ and a reverse sequence of 5′-AGC TGG GAA TGC AAA CAA AC-3′.

PCR conditions entailed a preliminary denaturation step for 3 minutes at 94◦C, followed by 35 cycles of denaturation for 30 seconds at 94◦C, annealing for 30 seconds at 60◦C, and extension for 30 seconds at 72◦C, ending with a final extension step of 7 minutes at 72◦C. Amplified products were visualized through UV transillumination on 1% agarose gel that was stained with ethidium bromide. Subsequently, the amplified products underwent digestion using the NlaIII restriction endonuclease, produced by Thermo SCIETIFIC, following the manufacturer's instructions.

The digested products were separated by electrophoresis on 1% agarose gel and stained with ethidium bromide. The separation revealed three distinctive patterns: homozygous wild 'AA' presenting two bands at 288 and 124 bp, heterozygous 'AG' presenting three bands at 412, 288, and 124 bp, and homozygous mutant 'GG' featuring a single band at 412 bp.

3.5. Statistical Analysis

The statistical analysis utilized Medcalc version 15. Group comparisons were executed employing Chi-square with Yates's correction. The adherence of alleles and genotypes in the studied groups to the Hardy-Weinberg equilibrium was appraised by comparing observed and expected frequencies of genetic variants. The association between AML and IL17F rs763780 genotypes was assessed by computing odds ratios and their 95% confidence intervals via logistic regression analyses. Survival analysis was carried out using the Kaplan–Meier test. A significance threshold of ≤ 0.05 in a two-tailed test was considered indicative of statistical significance.

4. Results

4.1. Clinical Characteristics of the Studied Patients

The patients' clinical characteristics and outcome are summarized in Table 1. The study included 102 AML patients; 68 (66.7%) males and 34 (33.3%) females with a mean age of 43.5±14.1 years. Three patients were (M0), 18 patients were (M1), 21 patients were (M2), 33 patients were (M4), 15 patients were (M5), 9 patients were (M6) and 3 patients were (M7). Sixty-two patients (60.2%) achieved complete remission (CR) following induction therapy, 25 patients (24.5%) succumbed to induction death (ID) and 15 patients (14.7%) were refractory to induction chemotherapy. 12.7% relapsed after initial complete remission and 34.3% died during the study period. The healthy control group included 106 healthy subjects: 67 (63.2%) males and 39 (36.8%) females with a mean age of 45.6±13.1 years. Both patients and healthy control groups were age and sex-

matched.

Table 1. *Clinical and laboratory characteristics of the studied AML patients.*

Parameter		AML (N=102)
Age (years); mean±SD (min, max)		43.5±14.1 (16, 72)
Males; N (%)		68 (66.7)
Females; N (%)		34 (33.3)
Fever; N (%)		75 (73.5)
Pallor; N (%)		94 (92.2)
Bleeding tendency; N (%)		72 (70.6)
Splenomegaly; N (%)		59 (57.8)
Hepatomegaly; N (%)		72 (70.6)
Lymphadenopathy; N (%)		53 (52)
Total leucocytic count ($X10^9$/L); median (range)		17.5 (0.9-213)
Hemoglobin concentration (g/dL); median (range)		8.1 (4.2-13.4)
Platelets count ($X10^9$/L); median (range)		40.5 (6-335)
Peripheral blasts (%); median (range)		80 (9-95)
Bone marrow blasts (%); median (range)		79 (22-95)
FAB; N (%)	M0	3 (2.9)
	M1	18 (17.6)
	M2	21 (20.6)
	M4	33 (32.4)
	M5	15 (14.7)
	M6	9 (8.8)
	M7	3 (2.9)
Complete remission; N (%)		62 (60.8)
Induction death; N (%)		25 (24.5)
Refractory; N (%)		15 (14.7)
Relapse; N (%)		13 (12.7)
Total mortality; N (%)		35 (34.3)

4.2. IL17F (rs763780) Genotype and Allele Frequencies in Both AML Patients and Control

According to the results of the study, IL17F (rs763780) genotypes in AML patients and healthy control subjects were found to be independent when the HW equation was applied. The distribution of IL17F (rs763780) alleles and genotypes was shown in Table 2 for both AML patients and healthy control subjects. The study found that there was a significant difference in genotypic and allele frequencies between AML patients and healthy controls. Specifically, AML patients showed higher mutant G allele and GG genotypes compared to healthy control subjects (P = 0.017 for both).

Table 2. *IL-17 polymorphisms genotype distribution and allele frequencies in the patients and healthy controls.*

Genotypes and alleles	Healthy control (n=106)		AML (n=102)		*P* value	OR (95%CI)
	No	%	No	%		
A allele	185	87.3	160	78.4	0.017	1.88 (1.12-3.18)
G allele	27	12.7	44	21.6		
AA genotype	80	75.5	66	64.7	-	Reference
AG genotype	25	23.6	28	27.5	0.341	1.21 (0.82-1.79)
GG genotype	1	0.9	8	7.8	0.017	3.82 (1.27-11.52)
AG+GG	26	24.5	36	35.3	0.090	1.38 (0.95-2.01)

4.3. Correlation of IL17F rs763780 Genotypes to Patients' Characteristics, Outcome, and Survival

The study results suggest that AML patients with different genotypes do not display significant differences in FAB subtypes, demographic, clinical, or laboratory characteristics (data not shown). Moreover, the study found no significant differences in response to therapy, total mortality, overall survival (OS), and disease-free survival (DFS) between AML patients with different genotypes as illustrated in Table 3 and Figures 1 and 2.

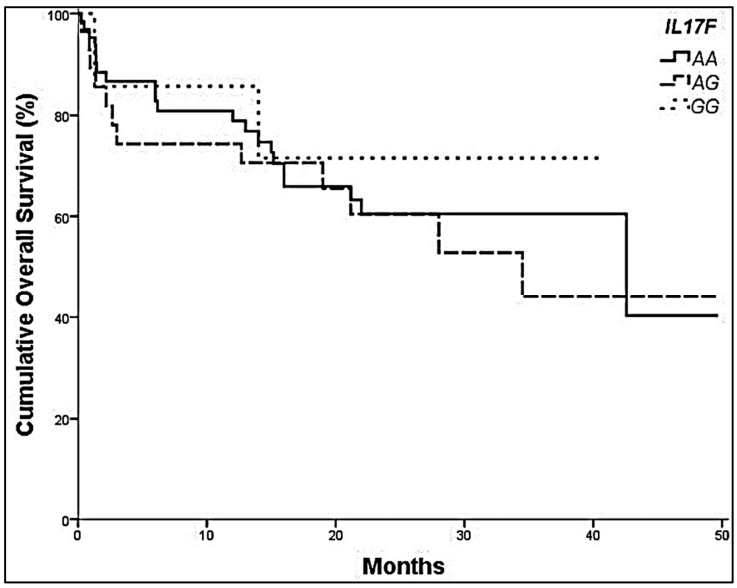

Figure 1. *Overall survival (OS) according to IL17F rs763780 genotypes: no significant difference was found between patients with different genotypes.*

Table 3. *Clinical outcome according to IL17F rs763780 genotypes of the studied AML patients.*

Clinical outcome	*IL17F* rs763780						*P* value
	AA (n=66)		AG (n=28)		GG (n=8)		
	N	%	N	%	N	%	
Complete remission (CR)	38	57.6	20	71.4	4	50	0.36
Induction death (ID)	18	27.3	5	17.9	2	25	0.66
Refractory (RD)	10	15.2	3	10.7	2	25	0.56
Relapse	7	10.6	5	17.9	1	12.5	0.57
Total mortality	21	31.8	12	42.9	2	25	0.57

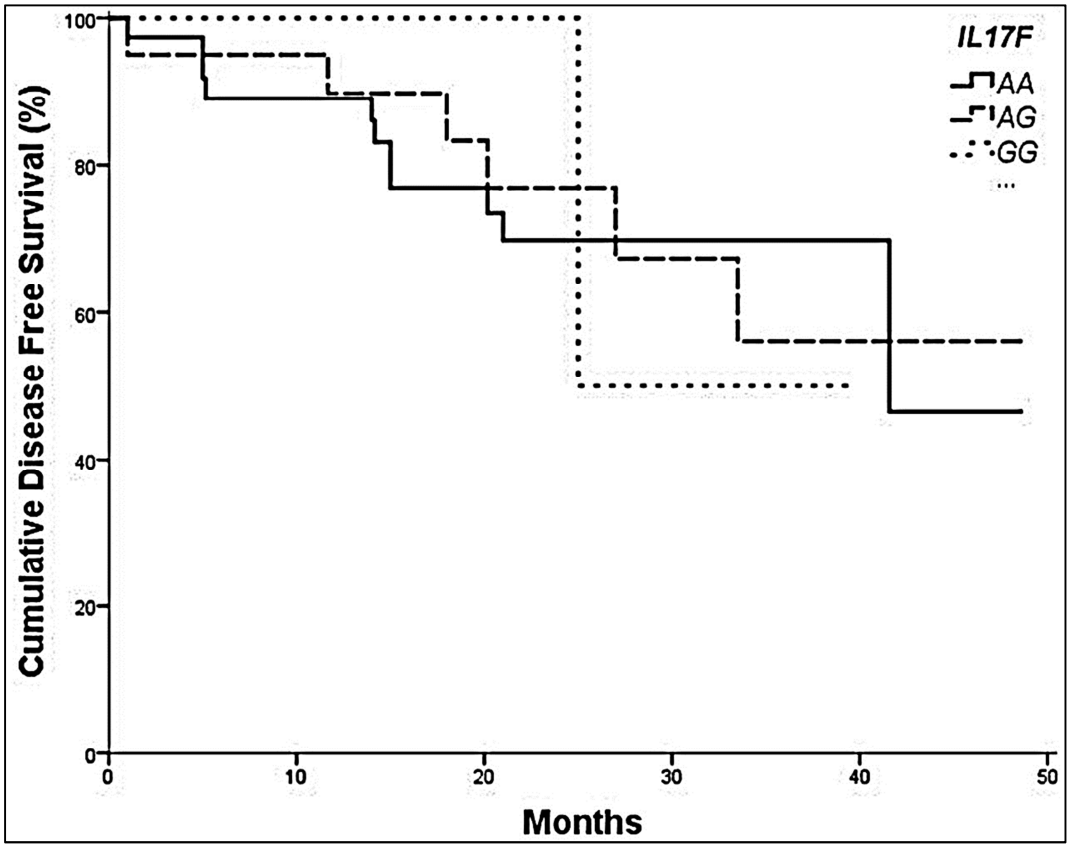

Figure 2. *Disease-Free Survival (DFS) according to IL17F rs763780 genotypes: no significant difference was found between patients with different genotypes.*

5. Discussion

Several studies suggested that Th17 cells and their cytokines may play a role in AML development [18-20]. IL-17 is involved in a variety of conditions including inflammatory and autoimmune disorders [6, 26, 27], as well as in various tumors, including gastric cancer, breast cancer, and multiple myeloma [28-30].

In the current study, we aimed to investigate the involvement of IL-17F genetic polymorphism in susceptibility to AML, as well as its relation to clinical features and prognosis in AML patients. Our finding showed that the mutant GG genotype and G allele were significantly higher in Egyptian AML patients compared to healthy individuals, indicating the impact of polymorphic variants in predisposing for AML development. This observation re-enforces a previous finding by Wrobel et al. who conducted a study including 62 AML patients and 125 healthy controls in a Polish population and reported that the IL-17F polymorphism appeared to be correlated with susceptibility to AML. In their study, the presence of the IL-17F G allele was more frequent among AML patients (32.3%) than healthy controls (8.8%) (RR = 4.76, P < 0.001) [31].

More evidence supporting the role of IL-17 in higher susceptibility to AML comes from studies that examined the kinetics of IL-17-producing cells (Th17 cells). It has been reported that patients with acute leukemias had significantly higher levels of circulating Th17 cells than healthy controls. Moreover, Th17 cell levels decreased significantly in patients achieving CR after induction therapy [19, 32].

Our study revealed that IL17F polymorphic variants did not exhibit any correlation with the clinicopathological features, response to therapy, or survival (overall and disease-free survival) in our patient population. This comes in agreement with the research conducted by Wrobel et al. who also did not observe any association between the studied polymorphisms and response to therapy or patient survival

[31]. Contradicting data was reported by Han et al. who found that the increase of Th17 cell number and IL-17 level was associated with poor prognosis of AML patients [33].

Our research was limited due to the relatively small number of participants we recruited. Furthermore, we believe that the examination of IL-17F serum levels would have helped to better understand the relationship between the genetic polymorphism we studied and its serum levels. Therefore, we recommend enrolling more patients in a larger study to validate the role of IL-17F polymorphism as a molecular contributor to the development of AML.

6. Conclusion

The current research suggests that the G mutant allele of the IL17F is a potential contributor to AML development. However, its impact on the response to treatment or overall survival rates remains insignificant. More studies are needed to determine its impact on treatment response and overall survival rates. Additionally, the examination of IL-17F serum levels could provide a valuable insight into the relationship between the genetic polymorphism we studied and its serum levels. It is crucial to conduct more extensive research with larger sample sizes and diverse backgrounds to establish a concrete association between IL17F genetic polymorphism and AML development and outcome.

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Conflicts of Interest

The authors declare no conflicts of interest.

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