İstanbul Med J 2018; 19: 39-42
DOI: 10.5152/imj.2018.58751

Effect of the IL-17F rs763780 Variant on Chronic Lymphocytic Leukemia and Multiple Myeloma Risk in a Turkish Cohort

IL-17F Rs763780 Varyantının Türk Grubunda Kronik Lenfositik Lösemi ve Multipl Miyelom Üzerine Etkisi

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Abstract / Öz

Introduction: Chronic lymphocytic leukemia (CLL) is one of the most common leukemias in developed countries. Multiple myeloma (MM), a clonal plasma cell disease, is the second most prevalent hematological cancer. Interleukin-17 (IL-17) can facilitate the secretion of numerous proinflammatory cytokines. The goal of the present study was to evaluate the effect of IL-17F rs763780 on CLL/MM susceptibility in a Turkish cohort.

Methods: The study included 37 patients with CLL, 21 patients with MM, and 100 healthy controls. The IL-17F rs763780 variant was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The frequencies of the alleles and genotypes in patient and control groups were compared by the χ^2 test.

Results: No significant difference was found in the distribution of genotypes and alleles frequencies for IL-17F rs 763780 between the patients and the healthy controls (P>0.05).

Conclusion: Our results suggest that IL-17 rs763780 variant may not contribute to CLL and MM pathogenesis.

Keywords: Chronic lymphocytic leukemia, multiple myeloma, interleukin-17F, variant

Amaç: Kronik lenfositer lösemi (KLL) gelişmiş ülkelerde en yaygın görülen lösemi tipleri arasındadır. Klonal plazma hücre hastalığı olan Multipl miyelom ikinci en sık görülen kan kanseridir. İnterlökin-17 (IL-17) birçok pro-enflamatuar sitokinin salınımını kolaylaştırabilir. Bu çalışmanın amacı Türk topluluğunda IL-17F rs763780 varyantının KLL/MM'a yatkınlığına olan etkisini incelemektir

Yöntemler: Çalışmaya 37 KLL/21 MM hastası ve 100 sağlıklı kontrolü dahil edildi. IL-17F rs763780 varyant genotip analizi polimeraz zincir reaksiyon-restriksiyon parça uzunluğu polimorfizmi (PZR-RFLP) ile yapıldı. Hasta ve kontrol gruplarında allel ve genotip sıklıkları χ^2 testi ile karşılaştırıldı.

Bulgular: IL-17 rs763780 varyant genotip dağılımı ve allel sıklığında hasta ve kontrol grubu arasında arasında önemli bir fark bulunmadı (P>0.05).

Sonuç: Sonuçlarımız IL-17 rs763780 varyantının KLL ve MM patogenezine katkıda bulunmayabileceğini desteklemektedir.

Anahtar Kelimeler: Kronik lenfositik lösemi, multipl miyelom, interlökin-17F, varyant

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in developed countries with an incidence of 4.1 per 100,000 persons per year (1). This disease is characterized by accumulation of mature B cells in lymphoid tissues, bone marrow, and peripheral blood (2). Pathogenesis of CLL has been associated with immune system abnormalities. Multiple myeloma (MM), a clonal plasma cell disease, is the second most frequent hematological cancer. It is still an incurable disease with poor survival rates (3). The pathogenesis of MM is complicated and multifactorial, in which numerous genetic and immunological changes play a role. Several abnormalities of T cell number or function have been reported in patients with MM. Nevertheless, the exact mechanisms and biologic ground for these abnormalities are still unknown (4).

The interleukin 17 (IL-17) family constitutes a subgroup of recently described proinflammatory cytokines. The IL-17 family includes six members, i.e., IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F, with regard to structure resemblance and order of discovery (5). IL-17A and IL-17F share 50% amino acid identity (6) and have a similar function (7) in the IL-17 family. Specialized T cells, named Th17 cells, serve as the major production site of IL-17A and IL-17F in several types of adaptive immunity. Growing evidence has shown that Th cells are crucial in the occurrence and progression of inflammatory disorders, autoimmune diseases, and malignant tumors. Recently, IL-17 has been reported to stimulate inflammatory processes. IL-17 can induce the secretion of proinflammatory cytokines to increase the inflammatory response, and its binding to the receptor would activate the neutrophils to regulate the inflammation in tissues (8).

The rs763780 variant of the IL-17F gene can result in a His to Arg substitution at amino acid position 161, and thereby hinder the function of wild-type IL-17F. This may lead to a higher risk of many malignant tumors such as bladder and gastric cancer (9, 10). Thus, the goal of the present

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This study was presented at Erciyes Medicine Days (11-13 May, 2017) as verbal presentation.

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Geliş Tarihi/Received: 04.05.2017

Kabul Tarihi/Accepted: 14.10.2017

study was to evaluate the effect of IL-17F rs763780 on CLL/MM susceptibility in a Turkish cohort.

Methods

Patients

This study consisted of 58 patients (37 CLL and 21 MM) and 100 healthy controls (51 males and 49 females). Clinical characteristics, peripheral blood morphologies, immuno-phenotype, and B-lymphocytes count of higher than 5.0×10^9/L confirmed the diagnosis of CLL (11). Subjects were defined by a definitive diagnosis of MM based on the International Myeloma Working Group criteria (12). We evaluated healthy volunteers (as control group) without CLL and MM matched for age and sex with case group. Consent for participation in the study was provided by the subjects. This research protocol was approved by Scientific and Ethics Committee of the University and the study was conducted according to the ethical guidelines of the Declaration of Helsinki.

Genotype Determination

About 5 mL peripheral blood was collected; ethylene diamine tetraacetic acid was used as anticoagulant for the analysis of the IL-17F gene variant. DNA was extracted from leukocytes according to the established protocol (13). The IL-17F variant was genotyped by polymerase chain reaction using primers described by Marwa et al. (14), followed by an enzymatic cleavage with the restriction enzyme NlaIII (restriction fragment length polymorphism). Then, digested fragment were checked using 2% agarose gel electrophoresis.

Statistical Analysis

Data analysis was done by SPSS version 22.00 for Windows (SPSS Inc.; Chicago, IL; USA). The results are presented as mean ± SD or number of cases (%). The genotype distribution and allele frequency of this variant in the control and patient groups were compared using Chi-squared tests. The Hardy-Weinberg equilibrium (HWE) was calculated using the de Finetti program (Online HWE and Association Testing-Institut für Humangenetik, Munich, Germany). P value $p<0,05$ was considered statistically significant.

Results

In this study, a total of 158 subjects, including 37 patients with CLL, 21 patients with MM, and 100 adult healthy controls were genotyped for the IL-17F rs763780 variant. The detailed data of the allele frequency and genotype distribution of the IL-17F rs763780 variant as well as HWE from each study are shown in Table 1. The frequency of the GG, GA, and AA genotypes of the IL-17F rs763780 variant in patients with CLL were 2.7%, 13.5%, and 83.8%, respectively, and in controls, the frequency was 0%, 13%, and 87%, respectively. There was no significant difference in genotype distribution of the IL-17F rs763780 variant between patients with CLL and controls ($p>0.05$). The IL-17F rs763780 variant G and A alleles were observed in 9.5%, and 90.5% of patients with CLL, 6.5% and 93.5% in controls, respectively. No significant difference was found in the IL-17F rs763780 variant allele frequencies between patients with CLL/MM and controls ($p>0.05$).

Regarding the distribution of IL-17F rs763780 genotypes in patients with MM, 0% were GG, 14.3% GA, and 85.7% AA when compared to 0%, 13%, and 87% in controls. The genotype distribution of the IL-17F rs763780 variant showed no statically significant difference between patients and controls. No significant difference was observed in the IL-17F rs763780 variant allele frequencies between patients and control group. In groups, the genotype distribution of this variant investigated in this study did not deviate from HWE.

Table 1. Genotype and allele distributions of IL-17F rs763780 variant

		IL-17F rs763780	
IL-17F rs763780	**CLL patients**	**Controls**	**p**
Genotypes	Na (%)	Nb (%)	
AA	31 (83.8)	87(87)	0.097
GA	5 (13.5)	13 (13)	0.089
GG	1 (2.7)	0 (0)	0.098
Alleles			
A	67 (90.5)	187 (93.5)	
G	7 (9.5)	13 (6.5)	0.403
HWE-p	0.199	0.486	
IL-17F rs763780	**MM patients**	**Controls**	**p**
Genotypes	Nc (%)	Nb (%)	
AA	18 (85.7)	87(87)	0.874
GA	3 (14.3)	13 (13)	1.000
GG	0 (0)	0 (0)	1.000
Alleles			
A	39 (92.6)	187(93.5)	
G	3 (7.4)	13 (6.5)	0.758
HWE-p	0.724	0.486	

Na: 37 Patients with chronic lymphocytic leukemia (CLL); Nb: 100 Healthy Control Groups; Nc: 21 Patients with multiple myeloma (MM); HWE: Hardy-Weinberg equilibrium

Discussion

CD4+T cells can be divided into four subsets such as T helper 1 (Th1), Th2, Th17, and CD4+ CD25+ T regulatory (Treg) cells according to the cytokines released and functions. The Th17 cell is a crucial mediator of cancer, chronic inflammation, and autoimmune disorders through secretion of proinflammatory cytokines, including IL-17A, IL-17F, IL-22, IL-21, and IFN-γ. Th17 cells have been studied in several solid tumors and a few of hematological malignancies such as monoclonal gammopathy of undetermined significance (15), acute myeloid leukemia (16), and non-Hodgkin lymphoma (17). In previous studies, it was shown that Th17 cells were significantly higher in peripheral blood from patients with acute myeloid leukemia (AML) (18) and MM (4), whereas lower in cases with chronic myeloid leukemia (CML) (19).

Scientific studies on molecular biology have proposed that IL-17 is a key proinflammatory cytokine that induces the release of several cytokines and chemokines by various cell types, including mesenchymal cells and myeloid cells, to draft monocytes and neutrophils into the microenvironment of inflammation (20). Growing evidence shows that IL-17 acts as modulator of tumorigenesis and metastasis. Considering the essential role of Th17/Tc17 in immu-

nity, it is thought that IL-17 is involved in inflammation by promoting activation of several proinflammatory cytokines, like IL-1, IL-6, and interferon γ. The gene encoding IL-17F is localized on chromosome 6p12.2, which contains three exons and two introns (21). The IL-17F rs763780 variant is found within the coding region of the IL-17F gene and leads to a His to Arg substitution at amino acid 161. In vitro functional analysis showed that the IL-17 expression and function may be inhibited in carriers of the rare G allele (22). This variant was found to be related to the occurrence of several autoimmune diseases such as asthma (23), inflammatory bowel disease (24), and multiple sclerosis (25).

CLL is a multifaceted disease in terms of clinical manifestation, severeness, and prognosis of the disease. Complex immune disorders, occurring even in patients during early clinical stages, are among the characteristics of CLL and are believed to be involved in the pathogenesis. MM was among the most frequent hematological malignancies and characterized by clonal proliferation of plasma cells and overproduction of monoclonal immunglobins. MM is a genetically complex and heterogeneous disease. , Its precise pathogenesis has not been clarified. The imbalance of T lymphocyte subgroups and cytokine network may be involved in MM (26).

There are a few reports on the role of IL-17F in tumor development. It was reported that the IL-17F rs763780 variant showed no association in patients with breast cancer in Chinese Han women (27). In a meta-analysis, Liu et al. (28) reported that the IL-17F rs763780 variant was significantly related to higher gastric cancer risk. Additionally, in another meta-analysis, Dai et al. (29) suggested that the IL-17F rs763780 variant significantly increased cancer risk, particularly in gastric cancers. Subgroup analysis proposed the presence of an important relationship between the IL-17F rs763780 variant and cancer susceptibility in a Caucasian cohort. But in a meta-analysis, Zhao et al. (30) reported that this variant did not change cancer risk in all genetic models of Asian population.

Zhu et al. (31) demonstrated that the IL-17F rs763780 GG homozygous genotype showed higher correlation in patients with AML in Chinese population. Also, it was reported that the IL-17F rs 763780 GG genotype was higher in patients with AML (32). Although the significance of IL-17F in the etiopathogenesis of CLL and MM is uncertain, we evaluated that the IL-17F rs763780 variant may affect CLL/MM susceptibility in a Turkish cohort. There was no significant difference in the distribution of the genotypes and the frequencies of alleles of the IL-17F both in patients with CLL and MM. Some limitations are present in our study. First, we focused on only one variant involved in the pathway of IL-17, other regulatory genes in this family signalling pathway may also contribute to the pathogenesis of CLL and MM. Second, owing to the relatively small sample size, the frequencies of some homozygous variants were low in groups and therefore reduced the statistical power.

Finally, environmental factors are also crucial in the occurrence of malignancies. The potential interactions between genetic and environmental factors may also alter the development of hematological malignancies. These factors may change the effects of the IL-17F variant on susceptibility to CLL and MM, and they should be considered. Third, different genotyping modalities may also have an impact on the prevalence of the allele.

Conclusion

Our analysis is the first study to scrutinize whether the IL-17F rs763780 variant is a risk factor for CLL and MM development. Although these results do not support any major role of IL-17F rs763780 in CLL and MM pathogenesis, future case-controlled and population-based studies are necessary to study more precisely the association between the variant and potential gene-gene and gene-environment interactions.

Ethics Committee Approval: Ethics Committee approval was received for this study from the ethic committe of Gaziantep University Faculty of Medicine.

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.P., A.F.N.; Design - M.P., S.P.; Supervision - M.P., S.P.; Resource - M.P., S.K.; Materials - S.P., S.K.; Data Collection and/or Processing - A.F.N., S.K.; Analysis and/or Interpretation - S.P., S.K.; Literature Search - A.F.N., S.P.; Writing - A.F.N., M.P.; Critical Reviews - S.P., S.K., M.P.

Conflict of Interest: No conflict of interest declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite Gaziantep Üniversitesi Tıp Fakültesi Etik Kurulu'ndan alınmıştır.

Hasta Onamı: Hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - S.P., A.F.N.; Tasarım - M.P., S.P.; Denetleme - M.P., S.P.; Kaynaklar - M.P., S.K.; Malzemeler - S.P., S.K.; Veri Toplanması ve/veya işlemesi - A.F.N., S.K.; Analiz ve/veya Yorum - S.P., S.K.; Literatür taraması - A.F.N., S.P.; Yazıyı Yazan - A.F.N., M.P.; Eleştirel İnceleme - S.P., S.K., M.P.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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Cite this article as: Nursal AF, Pehlivan M, Kurnaz S, Pehlivan S. Effect of the IL-17F rs763780 variant on chronic lymphocytic leukemia and multiple myeloma risk in a Turkish cohort. İstanbul Med J 2018; 19: 39-42.