J Surg Med. 2022;6(4):428-431.
DOI: 10.28982/josam.929820

Research article

Journal of Surgery and Medicine
e-ISSN = 2602-2079

Interleukin-1 beta gene polymorphisms in patients with fibromyalgia syndrome

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Ethics Committee Approval
Ethics approval for the study was obtained from Ethics Committee of Erenköy Psychiatric and Neurological Diseases Training and Research Hospital (Date: 14.07.2014, Number: 13/160). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2022 April 1

Abstract

Background/Aim: Fibromyalgia syndrome (FMS) has been linked to a genetic background. Although there are conflicting results, it has been suggested that cytokines play a role in FMS etiology. Interleukin (IL)1β is a cytokine that has been linked to FMS symptoms and has been detected in the skin of FMS patients. We aimed to determine the possible relationship between IL1β -31 and IL1β -511 polymorphisms in FMS.
Methods: In this cross-sectional study, we included patients who were diagnosed with FMS according to the American College of Rheumatology classification criteria. IL1β -31 (rs 1143627) and IL1β -511 (rs 16944) polymorphism genotyping was conducted in FMS patients (n = 33) and healthy controls (n = 41) using real-time polymerase chain reaction (RT-PCR).
Results: IL1β -511 variations in patients with FMS and control groups were significantly different (P = 0.010). The frequency of the IL1β -511 heterozygote AG genotype was significantly higher in controls (P = 0.028). Additionally, the frequency of the IL1β -511 wild type A allele was significantly higher in the control group (P = 0.003). The IL1β -31 genotypes and allele frequencies were not significantly different between the groups.
Conclusion: The IL1β -511 wild type A allele could be a risk-reducing factor for FMS. The present study suggests that genetic variations of the IL1β gene could play an important role in FMS etiology.

Keywords: Interleukin-1β, Polymorphism, Fibromyalgia syndrome

How to cite: Çetin B, Yılmaz SG, Güleç H, Ulutaş Ö, İsbir T. The interleukin-1 beta gene polymorphisms in patients with fibromyalgia syndrome. J Surg Med. 2022;6(4):428-431.

Introduction

Fibromyalgia syndrome (FMS) is a chronic, painful disorder that is characterized by widespread musculoskeletal pain, tenderness, fatigue, sleep disorders, mood disorders, and cognitive problems [1]. The prevalence of FMS is between 2% and 8%. First-degree relatives of patients with FMS are more likely to have FMS and other chronic pain states than relatives of individuals without FMS. Because of this familial aggregation, FMS is considered to have a genetic background [2]. Genes associated with the frequency of chronic pain conditions or pain sensitivity are involved in the regulation of neurotransmitters and other inflammatory pathways that modulate pain sensitivity [3].

FMS was shown to have a 50% heritability. Serotonin transporter gene (SLC6A4), catechol-O-methyltransferase (COMT) short nucleotide polymorphism rs4818, dopamine receptor D4, monoamine oxidase, β-2 adrenergic receptor, and guanosine triphosphate cyclohydrolase are candidate genes that are associated with FMS pathogenesis [4]. However, Feng et al. [5] reported two nonsense mutations associated with high specific cytokine levels.

Despite the controversies about FMS etiology, it has been proposed that cytokines may play a role in the syndrome's etiology. Several studies showed increased interleukin (IL)1β, IL6, IL8, and tumor necrosis factor (TNF)-α levels in FMS [6-10]. However, other studies showed no significant differences in IL1β in FMS patients [11-13].

IL1β is a somnogenic cytokine that is normally produced in response to infection, injury, or immunologic challenge [14], and it has influences on the neuroendocrine, autonomic, limbic, and cortical areas of the central nervous system (CNS) that regulate sleep [15]. IL1β is associated with hyperalgesia, fatigue, fever, sleep, and myalgias that may be relevant to FMS [16]. IL1β is detected in the skin of FMS patients, suggesting an inflammatory background for pain induction [17].

Because IL1β polymorphism has not been investigated adequately in FMS, we aimed to determine the relationship between IL1β -31 and IL1β -511 polymorphisms and FMS in a Turkish sample.

Materials and methods

Participants

Thirty-three patients with FMS and 41 control group participants were recruited from the Erenköy Physical Therapy and Rehabilitation Hospital outpatient polyclinic. All patients were diagnosed with FMS by their physiatrist, according to the American College of Rheumatology classification criteria [18]. Ethics approval for the study was obtained from the Ethics Committee of Erenköy Psychiatric and Neurological Diseases Training and Research Hospital (Date: 14.07.2014, Number: 13/160). After a detailed explanation of the study, written informed consent was obtained from all participants.

Genotyping

Genomic DNA was extracted from whole blood using an iPrep Purification Instrument (Invitrogen, Life Technologies, Carlsbad, CA, USA). Isolated DNA samples were analyzed spectrophotometrically using a NanoDrop 2000 (Thermoscientific, Waltham, MA, USA). IL1β -31 (rs 1143627) and IL1β -511 (rs 16944) were analyzed using Taqman assays (Thermoscientific). Allelic discrimination was performed using a 7500 Fast Real-Time Polymerase Chain Reaction (RT-PCR) (Applied Biosystems, Foster City, CA, USA) by interpreting the fluorescent data from hybridizing probes (VIC/FAM).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 23.0 version (IBM Corp., Armonk, NY, USA) was used for statistical analysis in the study. Patients and control group participants were compared, and differences in the serum levels were identified using a Student's *t*-test or a one-way ANOVA to compare the allele distributions and genotypes. The significance level was accepted as $P < 0.05$.

The goodness-of-fit test was used to check for deviations from the Hardy–Weinberg equilibrium (HWE) in all genotypic distributions. The Haploview bioinformatics software package 4.2 was used to measure linkage disequilibrium (LOD) between variants using D0 and r2 values (https://haploview.software.informer.com/4.2/).

The statistical power was evaluated using G*power software 3.1.9.4 version (G*power, University of Dusseldorf, Dusseldorf, Germany), and 55.9% sample power was obtained in the post hoc power analysis (effect size d = 0.5, alpha error probability = 0.05).

Results

We examined IL1β -511 (rs16944) and IL1β -31 (rs1143627) polymorphisms in FMS patients in the current research. The genotype and allele frequencies for IL1β polymorphisms in the patient and control groups are presented in Tables 1 and 2. Genotype and allele frequency distributions of the IL1β gene variations were consistent with the HWE.

Table 1: The distribution of IL1β -511 polymorphism and allele frequencies in the patient with fibromyalgia and control groups

SNP	Control (n = 41) n (%)	Fibromyalgia (n = 33) n (%)	*P*-value	Chi square	Odds Ratio	95% CI
IL1β -511(rs16944)						
Genotype			0.010*	9.253		
AA	10 (24.4%)	8 (24.2%)	0.988	0.000	0.992	0.341-2.888
AG	29 (70.7%)	15 (45.5%)	0.028*	4.846	0.345	0.132-0.901
GG	2 (4.9%)	10 (30.3%)	0.816	0.054	1.138	0.384-3.737
Allelle						
A	39 (47.56%)	31 (45.96%)	0.003*	8.699	0.118	0.024-0.596
G	33 (52.44%)	35 (53.04%)	0.988	0.000	1.008	0.346-2.935

n: Number of individuals, SNP: single nucleotide polymorphism, CI: confidence interval, * $P < 0.05$ was denoted as statistically significant

Table 2: The distribution of IL1β -31 polymorphisms and allele frequencies in the patient with fibromyalgia and control groups.

SNP	Control (n = 41) n (%)	Fibromyalgia (n = 33) n (%)	*P*-value	Chi square	Odds Ratio	95% CI
IL1β a -31 (rs1143627)						
Genotype			0.546	1.696		
GG	7 (17.1%)	8 (24.2%)	0.446	0.581	1.554	0.498-4.851
GA	24 (58.5%)	15 (45.5%)	0.263	1.255	0.590	0.234-1.489
AA	10 (24.4%)	10 (30.3%)	0.569	0.324	1.348	0.482-3.772
Allellic count						
G	51 (62.19%)	30 (45.45%)	0.198	1.660	0.590	0.214-1.380
A	31 (37.81%)	36 (54.55%)	0.446	0.643	0.643	0.206-2.008

n: Number of individuals, SNP: single nucleotide polymorphism, CI: confidence interval, * $P < 0.05$ was denoted as statistically significant

IL1β -511genotypic frequencies in FMS patients and in the control group were significantly different ($\chi2$ = 9.253, *P* = 0.010). The frequency of the IL1β -511 heterozygote AG genotype was statistically higher in controls compared to patients ($\chi2$ = 4.846, *P* = 0.028; odds ratio [OR] = 0.345, 95% confidence interval [CI] = 0.132–0.901). Although there was no significant difference in the variant G allele frequency between the study groups ($\chi2$ = 0.000; *P* = 0.988), the wild type A allele frequency was significantly higher in the control group ($\chi2$ = 8.699; *P* = 0.003). Our results established that carrying the A allele decreased the FMS risk 0.1-fold (OR = 0.118, 95% CI = 0.024–0.596). Thus, carrying the A allele could be a risk-reducing factor for FMS.

There were no significant differences between the groups regarding the frequency of the IL1β -31 genotype ($\chi2$ = 1.696, *P* = 0.546) or allele (G allele *P* = 0.198, A allele *P* = 0.446), and there were no significant differences in the homozygote mutant (AA) and homozygote wildtype (GG) genotype carriers between the groups (*P* = 0.114). However, allele frequency analysis showed that most of the individuals in the control group carried the wild type G allele (62.19%), while most of patients with FMS had the variant A allele (54.55%), but this difference was not statistically significant.

Table 3 shows the serum IL1β (pg/mL) levels according to IL1β -31and IL1β -511 genotypes and alleles in FMS patients. There were no statistically significant differences between the groups or concerning the IL1β genotypes. The small sample size may account for these results.

We showed that the distribution of the IL1β -511 (rs16944) genotype in the FMS and control groups (*P* = 0.010) is statistically significantly different in the current analysis. Thus, we analyzed the effect of the IL1β genotype polymorphism frequency on the somatization data before and after treatment (Table 4). There was a significant difference between the genotypes according to the somatization data (*P* = 0.039). Eighty percent of the patients with the GG genotype were in the "strong" group before treatment. Moreover, most of the individuals carrying the G allele were in the "strong" group (*P* = 0.024). Although the results are not statistically significant, those who carry the G allele seem to be less responsive to treatment.

Haplotype analysis for IL1β -31and IL1β -511 is shown in Table 5. However, the high-pairwise D′ value was 0.92 (Figure 1), and the frequency of the haplotype created by the risk alleles was not significantly different in FMS patients compared to controls.

Table 3: Serum IL1β (pg/mL) levels according to IL1β -31and IL1β -511 genotypes in the patients with fibromyalgia

Fibromyalgia (n = 30)	First	Second	Difference	*P*-value
IL1β -511(rs16944)				
Genotype				
AA	8.89	7.11	4.84	0.484
AG	6.03	5.83	0.744	0.744
GG	9.42	6.82	0.784	0.78
Allelle				
A	7.08	6.30	0.76	0.441
G	9.42	6.82	2.60	0.550
IL1β a -31 (rs1143627)				
Genotype				
GG	9.34	7.69	1.60	0.436
GA	6.04	5.66	0.30	0.527
AA	9.42	6.82	2.60	0.817
Allelle				
G	7.08	6.30	0.76	0.645
A	7.16	6.16	0.99	0.545

n: Number of individuals, SNP: single nucleotide polymorphism, CI: confidence interval, * *P* < 0.05 was denoted as statistically significant

Table 4: Comparison of Somatization data before and after treatment due to IL1β -511 genotypes in the patients with fibromyalgia

IL1β-511(rs16944) Genotype	AA	AG	GG	A Allele	G Allele
Phqsom					
none	0	0	0	0	0
low	4 (50%)	2 (33.3%)	0 (0%)	6 (26.1%)	2 (8%)
mild	2 (25%)	6 (60%)	2 (20%)	8 (34.8%)	8(32%)
strong	2 (25%)	7 (41.2%)	10 (80%)	9 (39.1%)	15 (60%)
P-value	0.039*			0.068	0.024*
Phqsom 2					
none	3 (42.9%)	1 (7.7%)	1 (16.7%)	4(20%)	2 (10.5%)
low	1 (14.3%)	5(38.5%)	0 (0%)	6 (30%)	5 (26.3%)
mild	1 (14.3%)	4 (30.8%)	3 (50%)	5 (25%)	7 (36.8%)
strong	2 (28.5%)	3(23.1%)	2(33.3%)	5(25%)	5(26.3%)
P-value	0. 284			0.410	0.266

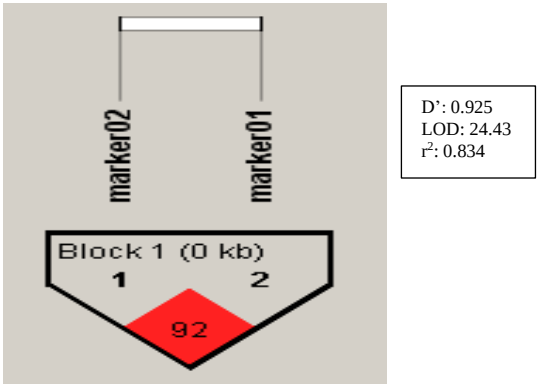
n: Number of individuals, * *P* < 0.05 was denoted as statistically significant

Table 5: The distribution of IL1β -511 polymorphism and allele frequencies in the patient with fibromyalgia and control groups

Haplotype Associations	Frequency	Case, Control Ratios	Chi Square	*P*-value
rs 1143627 A: rs 16944 G	0.499	0.530, 0.479	0.404	0.525
rs 1143627 G: rs 16944 A	0.457	0.469, 0.449	0.063	0.802
rs 1143627 A: rs 16944 A	0.025	0.000, 0.041	2.664	0.102
rs 1143627 G: rs 16944 G	0.019	0.000, 0.031	1.975	0.159

* *P* < 0.05 was denoted as statistically significant

Figure 1: Linkage disequilibrium plot of IL1β -511(rs16944) and IL1β a -31 (rs1143627) single nucleotide polymorphisms



Marker 01: rs16944, Marker 02: rs162601143627, Red represents a high-pairwise D' value, LOD: Linkage disequilibrium

Discussion

FMS pathophysiology is multifactorial, and it remains unclear. Altered pain processing, hormonal influences, autonomic dysautonomia, and immunological and genetic factors play a role in FMS pathogenesis [19]. Several studies have proposed that there is a relevance between pro-inflammatory cytokines and clinical FMS symptoms such as sleep disorders, hyperalgesia, and fatigue [20, 21].

Although pro-inflammatory cytokines are known to be related to inflammatory responses, there is no information about their function in FMS pathogenesis [22]. Most research has concentrated on pro-inflammatory cytokine serum levels and their receptors. Because epidemiological and molecular studies are not sufficient, the possible association between IL1β -31 and IL1β -511 polymorphisms in patients with FMS has, therefore, been investigated in the present research.

Salemi et al. [17] investigated the role of IL1β in neurogenic inflammation. They examined skin biopsies in patients with FMS using immunohistochemistry and RT-PCR. They found that IL1β mRNA and cytokine expression was increased in patients with FMS. Cytokines were detected in skin biopsies in

healthy individuals. Their study demonstrated the immunoreactivity of IL1β in FMS patients.

To understand the genetic basis of FMS, many single nucleotide polymorphisms (SNPs) in proinflammatory cytokine genes have been investigated [23]. However, in our study there were no significant differences between the groups regarding the IL1β -31 genotype frequency. Hall et al. [24] indicated that IL1β -31 promoter gene polymorphism could alter IL1β gene transcription and subsequently IL1β protein serum levels. The promoter region of the IL1β gene variant at the -31 position in the as IL1β -31 polymorphism has promoter sequences that have a potential source of polymorphisms that affect gene expression. The IL1β -31 gene mutant allele variant in the TATA box region promotes IL1β transcription and accelerates the inflammatory reaction.

Limitations

The small sample size in our study limits the generalizability of our results to the general population. To clarify and confirm this relationship, further studies with a larger sample size are required.

Conclusion

IL1β -511 genotype frequencies between the FMS and control groups were significantly different. Homozygote wildtype (AA) and heterozygote (GA) genotypes were significantly higher in the control group. Furthermore, wild type A allele was significantly higher in the control group. Our results indicates that carrying the A allele could be a risk-reducing factor for FMS. To the best of our knowledge, the present study established, for the first time, the association between IL1β gene polymorphism and FMS in a Turkish sample.

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