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A significant association between rs2295190 polymorphism of the *ESR1* gene and fibromyalgia syndrome

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ABSTRACT

Fibromyalgia syndrome (FMS) is a multifactorial disease characterized by chronic diffuse pain. Genetic factors are also involved in the etiology. However, there is not enough information on the genetic factors that play a role in the pathogenesis of FMS. This study aims to investigate the relationship between estrogen receptor 1 gene (*ESR1*) 594G>A (rs2228480) and 325C>G (rs2295190) polymorphisms and FMS. A total of 294 women, 146 of who were FMS patients and 148 of whom were healthy controls, were enrolled in the study. The instruments used to collect data from patients included patient follow-up forms, Visual Analog Scale (VAS), and Fibromyalgia Impact Questionnaire (FIQ). Genotyping of *ESR1* 594G>A and 325C>G polymorphisms in the extracted DNA samples was performed using an RT-PCR device and TaqMan hydrolysis probes. It was found that, for rs2295190 polymorphism, patients with CG and GG genotypes versus CC genotypes showed a decreased risk for FMS (OR: 0.442; 95% CI: 0.234-0.833). But there were no significant differences were found in the genotype distribution of rs2228480 polymorphism between the FMS patients and controls. The intragroup evaluation of FMS patients revealed no significant association between symptoms, pain score, FIQ score, and polymorphisms ($p>0.05$). We believe that there is a significant association between *ESR1* rs2295190 polymorphism and FMS and that this polymorphism may be protective against FMS. However, there is a need for comprehensive studies on different populations to obtain clearer data as well as further studies to elucidate the possible mechanism of association.

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Introduction

Fibromyalgia Syndrome (FMS) is a chronic musculoskeletal disease accompanied by diffuse body pain, fatigue, tenderness, and sleep disturbance (1). FMS frequently affects women aged 30-50 years, with a reported prevalence of 1-4% in the entire population, ranging between 0-4% in men and 2.5-10.5% in women (2-4).

A higher prevalence of FMS in women is observed from young adulthood, suggesting the influence of sex hormones on the pathophysiology of this condition. However, the roles and possible mechanisms of action of sex hormones in the pathogenesis of FMS are still unknown and remain a matter of debate. Steroid hormones, particularly estrogen, affect the inflammatory process and the transmission of central pain through both peripheral and central nervous system (CNS) receptors (estrogen receptor-a [Era] and estrogen receptor-b [ERb]). For instance, estrogen is known to act directly on monocytes and macrophages to regulate the production of cytokines such as the estrogen hormone Interleukin-1 (IL-1), IL-6, and tumor necrosis factor-a (5).

Patients with FMS have an increased incidence of headaches. Migraine and non-migraine headaches have been reported in the range of 28-58% in patients with FMS (6). Likewise, a study on 33 FMS patients found current migraine in 45% and a lifetime migraine history in 55% of patients (7). As in FMS, the frequency of migraine has been reported to be approximately 2 times higher in women of reproductive age than in men, with the severity of migraine attacks being stronger in women (8). Studies investigating the relationship between sex hormone

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levels and polymorphisms in individuals with migraine have found a significant association between migraine attacks and especially estrogen receptor-alpha gene (*ESR1*) 594G>A (rs2228480) and 325C>G (rs2295190) polymorphisms (9-10).

The more frequent occurrence of fibromyalgia and migraine in women of reproductive age and their quite high co-occurrence suggests that these two diseases may have a common genetic basis and that genes associated with sex hormones play a role in the etiology of these two diseases. However, to our knowledge, there is no study examining the association between FMS and *ESR1* rs2228480, and rs2295190 polymorphisms so far. Therefore, this study investigated the association between FMS and *ESR-1* gene 594G>A (rs2228480) and 325C>G (rs2295190) polymorphisms, which have been found to increase the risk of migraine.

Materials and Methods

Participants

The study included 146 female patients aged >18 years who were newly diagnosed with FMS according to the criteria of the American College of Rheumatology (11) and 148 age-matched healthy women. In this study, all of the participants in the patient and control groups were selected to be female individuals, to eliminate the possible gender-related differences in genetic and clinical parameters and maintain homogeneity across the groups. All individuals were healthy and without any chronic diseases, such as diabetes, malignancy, endocrine, cardiovascular, autoimmune diseases, and Neuropsychiatric disease.

Before the study, ethics committee approval was obtained from the local Ethics Committee (Ethics committee decision no: 2018/555). Those who agreed to participate in the study provided a signed informed consent form. All human procedures were followed in accordance with the Helsinki Declaration of 1975 as revised in 2013.

The sociodemographic (age, height, weight, etc.) data of the participants included in the study were recorded in the patient follow-up form. Some clinical symptoms of FMS (such as sleep disorder, headache, irritable bowel syndrome, morning fatigue, paresthesia, and swollen soft tissues) and family history of FMS were questioned and recorded. Visual Analogue Scale (VAS) and Fibromyalgia Impact Questionnaire (FIQ) were administered to FMS patients and their scores were recorded.

Fibromyalgia Impact Questionnaire (FIQ)

Fibromyalgia Impact Questionnaire (FIQ) is an FMS-specific assessment scale that reflects the current health status of the patient by evaluating the functional status, disease severity, disability, and the effect of various parameters (12). The Turkish version of FIQ, the validity and reliability study of which was performed in the Turkish population, was administered and the scores were recorded (13). This scale assesses 10 different domains, including physical functioning, feeling well, work missed, job ability, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Other than the “feeling well” component, low scores indicate recovery or less impact of the syndrome. The maximum total score that can be obtained from the questionnaire is 100 points. A higher score indicates a greater impact of fibromyalgia on the patient.

Visual Analogue Scale (VAS)

The visual Analogue Scale (VAS) was developed by Price et al.(14) to measure the intensity of pain in the patient. VAS is a self-administered tool using a vertical or horizontal line of 10 cm in length, with each end labeled as 0=no pain and 10=most intense pain. The patient is asked to mark the point on this line that best corresponds to the intensity of pain he or she is experiencing. The distance from the marked point to the lowest end of the line (0=no pain) is measured in centimeters and the numerical value found indicates the severity of the patient's pain.

Polymorphism analysis

DNA isolation

Peripheral whole blood samples were collected from the participants into EDTA-containing tubes. Genomic DNA was extracted from peripheral blood lymphocytes using a genomic DNA isolation kit (GeneJET Genomic DNA Purification Kit, Thermo Scientific), following the manufacturer's instructions. The concentration and quality of the isolated DNA samples were measured using a microplate spectrophotometer (Epoch, Biotek, USA).

Genotyping of polymorphisms

ESR1 594G>A (rs2228480) and 325C>G (rs2295190) single-nucleotide polymorphisms (SNPs) were genotyped using a TaqMan™ SNP Genotyping Assay Human kit (Primerdesign Ltd., Southampton, UK) with TaqMan hydrolysis probes. The Real-time PCR protocol was as follows: initial denaturation (95°C, 8 min), 10 cycles of denaturation (95°C, 30 s), and then first extension (60°C, 60 s), followed by 35 cycles of second denaturation (95° C, 30 s) and second extension steps (68°C, 60 s). Fluorogenic data were collected through the ROX and VIC channels at the end of each cycle of the second extension.

The amplified PCR product was genotyped for *ESR-1* 594G>A and 325C>G polymorphisms by allelic discrimination assay, following the manufacturer's instructions. Genotyping was repeated twice for each patient and control subject.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 22.0 software was used for the statistical analysis of the study data. The correlation between fibromyalgia and *ESR1* gene polymorphisms, age, gender, height, weight, profession, sleep disorder, fatigue, headache, morning tiredness, dry mouth, restless leg, paresthesia, dry eye, concentration difficulty, the sensation of swollen soft tissues, family history of fibromyalgia, FIQ and VAS was determined using the chi-square ($\chi 2$) test. A logistic regression analysis was carried out by including the data of both groups. The degree of correlation was expressed as a 95% confidence interval (CI) and odds ratio (OR). The level of statistical significance was set at 0.05 in the tests.

Results

A total of 294 women, 146 of whom were FMS patients and 148 of whom were healthy controls, were enrolled in the study. As is seen in Table 1, the mean age of the patient and control groups was 47.49±10.0 and 45.63±8.9 years, respectively, with no statistically significant difference

Table 1. Sociodemographic and clinical characteristics of control and FMS group.

	Control (n=148)	FMS (n=146)	p-value
Age (X̄±SD)	45.63±8.9	47.49±10.0	0.096
Sleep Disorder (n(%))			
Yes	58(39.2)	119(81.5)	<0.001*
No	90(60.8)	27(18.5)	
Fatigue (n(%))			
Yes	120(81.1)	143(97.9)	<0.001*
No	28(18.9)	3 (2.1)	
Headache (n(%))			
Yes	85(57.4)	101(69.2)	0.037*
No	63(42.6)	45(30.8)	
Morning tiredness (n(%))			
Yes	85(57.4)	139(95.2)	<0.001**
No	63(42.6)	7(4.8)	
Dry mouth (n(%))			
Yes	81(54.7)	89(61)	0.280
No	67(45.3)	57(39)	
Paresthesia (n(%))			
Yes	66(44.6)	107(73.3)	<0.001**
No	82(55.4)	39(26.7)	
Dry eye (n(%))			
Yes	40(27)	52 (35.6)	0.112
No	108(73)	94(64.4)	
Concentration difficulty (n(%))			
Yes	79(53.4)	104(71.2)	0.002*
No	69(46.6)	42(28.8)	
Swollen soft tissue (n(%))			
Yes	62(41.9)	112(%76.7)	<0.001**
No	86(58.1)	34(23.3)	
Family history of FMS (n(%))			
Yes	13(8.8)	69(47.3)	<0.001**
No	135(91.2)	77(52.7)	

*p<0.05 ; ** p<0.001**;** SD, standard deviation; X̄, Mean. FMS, Fibromyalgia Syndrome.

Table 2. Genotype and allele frequencies of ESR-1 rs2228480, and rs2295190 polymorphisms in patients and controls.

	Control n (%)	FMS n (%)	*p*-value	OR (95% CI)
rs2228480				
GG	111 (%75)	120 (%82.2)		
AG+AA	37 (%25)	17.8 (%23)	0.134	0.650 (0.370-1.143)
rs2295190				
CC	114 (%77)	129 (%88.4)		
CG+GG	34 (%23)	17 (%11.6)	0.012*	0.442 (0.234-0.833)

OR, Odds Ratio; *Logistic regression analysis; p<0.05, significant value; FMS, Fibromyalgia Syndrome.

between the two groups (p>0.05). The distributions of professions in both groups were similar. The groups were also compared in terms of symptom frequencies. The frequencies of dry mouth and dry eye symptoms were similar (p=0.125, p=0.099, respectively). However, the frequencies of all other symptoms were statistically significantly higher in the patient group than in the controls (p<0.05). The frequency of familial history of FMS was 47.3% in the patient group, while it was 8.8% in the control group, with a significant difference between the two groups (p<0.05, Table 1).

Table 2 compares the genotype frequencies of *ESR1* gene rs2228480 and rs2295190 polymorphisms between FMS and the control group. The genotype distribution of rs2295190 was found that 77% wild type (CC) and 23% polymorphic genotype (CG+GG) in the control group, and 88.4% CC and 11.6 CG+GG in the FMS group, and the genotype frequencies were significantly different between patients and controls. In addition, it was found that individuals with polymorphic genotypes of rs2295190 versus wild-type genotypes showed a decreased risk for FMS (OR: 0.442; 95% CI: 0.234-0.833). However, no signifi-

Table 3. Comparison of ESR1 gene rs2228480 and rs2295190 genotype distributions in FMS patients according to accompanying symptoms

	rs2228480		*rs2295190*	
	GG / AG+AA	***p***	**CC / CG+GG**	***p***
Sleep disorder *(n)*				
Yes	98/21	0.915	105/14	0.897
No	22/5		24/3	
Fatigue *(n)*				
Yes	117/26	0.415	126/17	0.525
No	3/0		3/0	
Headache (n*)*				
Yes	85/16	0.352	92/9	0.123
No	35/10		37/8	
Morning tiredness (*n)*				
Yes	115/24	0.446	123/16	0.823
No	5/2		6/1	
Dry mouth (*n)*				
Yes	71/18	0.340	79/10	0.848
No	49/8		50/7	
Paresthesia (*n)*				
Yes	86/21	0.342	96/11	0.395
No	34/5		33/6	
Dry eye (*n)*				
Yes	44/8	0.569	45/7	0.611
No	76/18		84/10	
Concentration difficulty (*n)*				
Yes	83/21	0.236	95/9	0.076
No	37/5		34/8	
Swollen soft tissue (*n)*				
Yes	89/23	0.118	99/13	0.980
No	31/3		30/4	
Family history of FMS (*n)*				
Yes	58/11	0.577	62/7	0.593
No	62/15		67/10	

FMS, Fibromyalgia syndrome; WT, Wild type; PM, Polymorphic type.

Table 4. Comparison of FIQ and VAS pain score levels according to ESR1 gene rs2228480 and rs2295190 genotype distributions in FMS patients.

	FIQ		**VAS pain**	
	Value	**p-value**	**Value**	**p-value**
rs2228480				
GG (n=120)	62.17 ± 12.0	0.767	6.71 ± 1.5	0.226
AG+AA (n=26)	61.39 ± 13.1		6.92 ± 1.5	
rs2295190				
CC (n=129)	61.68 ± 12.5	0.343	6.69 ± 1.5	0.226
CG+GG (n=17)	64.68 ± 8.4		7.17 ± 1.1	

FMS, Fibromyalgia syndrome; FIQ: Fibromyalgia impact questionnaire; VAS, Visual analog scale.

cant differences were found in the genotype distribution of rs2295190 polymorphism between the FMS and control group.

When we analyzed the distributions of the polymorphisms we examined according to the concomitant clinical symptoms in FMS patients, no significant difference was found in terms of genotype distributions (Table 3, p>0.05).

Similarly, when we compared FIQ and VAS score levels in FMS patients according to ESR1 gene rs2228480 and rs2295190 genotype distributions, no significant difference was observed between the groups (Table 4, p>0.05).

Discussion

The prevalence of FMS is known to be 8 times higher in women than in men. It has been suggested that the higher levels of anxiety in women, the incompatibility of coping methods with stress, and the effects of altered levels of hormones during the menstrual cycle on the central nervous system contribute to the higher prevalence of FMS in women than in men (15). Estrogen has been reported to have significant effects on pain duration and sensitivity (hyperalgesia), with its deficiency being a risk factor for the development of FMS (16). Another study investigating the relationship between the changes in estrogen and progesterone hormones during menstruation and pain in FMS showed a significant correlation between progesterone levels and pain severity only in the late luteal phase but no correlation between estrogen levels and pain in FMS (17). A recent study examining follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone levels, and serum G-protein coupled estrogen receptor (GPER/GPR30) activities in women with FMS found only higher GPER activity in women with FMS, regardless of disease severity (18).

Researchers have found that first-degree relatives of

patients with FMS have an 8-fold higher risk of developing FMS compared to the general population. Patients with a family history of FMS are more sensitive to pain and more prone to develop conditions such as irritable bowel syndrome (IBS), temporomandibular disorder (TMD), headache-migraine, restless legs syndrome, and other regional pain syndromes (19-20). This information supports the hypothesis that genetic factors may affect FMS. Setting forth on this hypothesis, many studies have been conducted to demonstrate specific genetic polymorphisms in FMS. Studies conducted to date have found a higher frequency of polymorphisms in the serotonin receptor, serotonin transporter, dopamine D4 receptor, and catechol-O-methyltransferase genes in FMS patients (21).

There are numerous polymorphism studies of some potential candidate genes such as serotonin transporter (*SLC64A4*), transient receptor potential vanilloid channel 2 (*TRPV2*), myelin transcription factor 1 like (*MYT1L*), and neurexin 3 (*NRXN3*), especially associated with pain and inflammation pathways in FMS. It was reported that there was a significant relationship between some polymorphisms of these genes and FMS (22). However, it was found that some polymorphisms in genes encoding μ-opioid receptor gene (*OPRM1*)(23), human serotonin-1A receptor (*5-HTR1A*)(24), and beta-2 adrenergic receptor (*ADRB2*) were not associated with FMS (25).

To our knowledge, there is only one study dealing with the relationship between FMS and polymorphisms of genes encoding estrogen hormone receptors, and the SNP region examined in this study differs from ours. In this study by Arslan et al. (26), 100 FMS and 119 healthy individuals were compared in terms of the frequencies of two *ESR1* gene variants named PuvII (rs2234693) and XbaI (rs9340799). They found that the frequency of PuvII CC genotype and C allele was significantly higher in the FMS patient group. In our study, the association between *ESR-1* gene rs2228480 and rs2295190 polymorphisms and FMS was examined and it was found that GG, CG genotype, and G allele of rs2295190 reduced the risk of FMS development (p=0.01, OR:1.973). However, such a relationship with rs2228480 has not been determined.

Consistent with previous studies (6,7) we found that the frequency of headaches in the FMS group was considerably higher than in the control group (69.2%, 57.4%, respectively, p=0.037*). However, no significant relationship was found between the frequency of headaches and the polymorphisms we examined. We found that the frequency of symptoms (headache, fatigue, sleep problems, paresthesia, etc.) accompanying FMS was not associated with the polymorphisms. Similarly, we found that FIQ and VAS pain score levels did not differ in terms of the polymorphisms we examined.

The limitations of this study are the non-inclusion of male FMS patients and healthy controls as a separate group, studying a small number of single nucleotide polymorphisms, the small sample size, and the inclusion of a single ethnic group. Another important limitation of our study is that headache types (such as migraine, tension, and cluster headache) were not evaluated separately.

In conclusion, this study demonstrated that *ESR1* 325C>G (rs2295190) gene polymorphism may cause a decrease in the risk of developing FMS. Our results showed no effect of *ESR1* polymorphisms on symptoms, FIQ, and VAS pain scores. The results of this study will contribute to studies investigating sex hormone polymorphisms for the pathogenesis and treatment of FMS. However, there is a need for further clinical studies including higher several participants and male patients as well as more different SNPs to elucidate the role of estrogen and its receptors in the pathogenesis of FMS.

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Conflict interest
None.

Author's contribution
EK and IS designed the study. EK and GYC collected data. IS, EO, and YS performed Genetic analyses. IS, EO, and YS performed the statistical analyses. EK, IS, EO and AT interpreted and discussed the results. EK and IS wrote the paper. EK, IS, GYC, and EH contributed to the final version of the manuscript.

Ethics approval and consent to participate
This study was approved by the Erciyes University Clinical Research Ethics Committee (Ethics committee decision no: 2018/555). Those who agreed to participate in the study provided a signed informed consent form. All human procedures were followed in accordance with the Helsinki Declaration of 1975 as revised in 2013.

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