KASTAMONU MEDICAL JOURNAL

Original Article

DOI: 10.51271/KMJ-0125

Kastamonu Med J. 2023;3(4):192-197

ESR1 rs2234693 might be associated with TMD risk in the Turkish population, but not rs9340799

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Received: 31/08/2023 ◆ **Accepted**: 24/10/2023 ◆ **Published**: 17/12/2023

ABSTRACT

Aims: The gender and age distribution of temporomandibular disorder (TMD) suggest a possible role for the female hormonal axis in the pathogenesis. The goal of this study was to evaluate if estrogen receptor (ESR1) gene variants contribute to TMD susceptibility in the Turkish population.

Methods: A total of 270 people, 130 of whom were TMD patients and 140 healthy controls, were included in the study. The ESR1 PvuII (rs2234693) and Xbal (rs9340799) variants were genotyped using the polymerase chain reaction based restriction fragment length polymorphism (PCR-RFLP). The results were evaluated statistically.

Results: There were 110 women (81.48%) and 25 men (18.52%) in the patient group. We found there was a significant association between rs2234693 T/C, C/C genotypes and TMD (p=0.007). Also, the C allele was more prevalent in patients compared to controls (p=0.002). A statistically significant association was observed when the patients were compared with the controls according to TT versus TC+CC (p=0.002). There was no statistical significance between the patient and control groups in terms of rs9340799 genotype and allele distribution. Then we evaluated the relationship between genotype distributions and clinical characteristics. Both males and females had the highest rs2234693 T/C genotype (p=0.049). The majority of people with bruxism, bruxomania, and bruxism plus bruxoma carried the rs2234693 T/C genotype (p=0.025).

Conclusions: Our results showed that ESR1 rs2234693 might be associated with TMD risk in the Turkish population, but not rs9340799.

Keywords: Temporomandibular disorder, estrogen receptor alpha, variant, PCR-RFLP

INTRODUCTION

Temporomandibular disorder (TMD) covers clinical conditions affecting the temporomandibular joint (TMJ) and related structures. Preauricular pain, masticatory muscles, limitation of mandibular range of motion, noise during mandibular movement, headache, and facial pain are common symptoms.[1] Although the exact etiology of TMD is not fully elucidated, trauma, occlusal imbalances, psychological factors, parafunctional habits (e.g., bruxism), and systemic factors [e.g., rheumatoid arthritis (RA)] may be involved in TMD. It is a disorder that affects approximately 7-15% of the adult population. TMD is 1.5-2 times more common in women than in men.[2] Other inflammatory diseases, such as RA and osteoarthritis, are more common in women than men. The fact that women were more sensitive to experimental pain than men suggested that gender differences might play a role in pain sensation. TMD pain, which tends to occur after puberty, is more prominent during the reproductive years.[3] According to gender and age distribution, a possible link between the female hormonal axis, or estrogen level, and the pathogenesis of TMD is considered.[4]

Estrogen, the main female hormone, is produced endogenously during reproductive age. Estrogen acts through estrogen receptors, estrogen receptor-alpha (ERα), and beta (ERβ), which are encoded by the *ESR1* and *ESR2* genes, respectively. These receptors, which directly affect the expression of many target genes, are called dependent transcription factors.[5] Many data points suggest that this pathway plays a crucial role in several immune-related responses.[6] Estrogen receptors are highly expressed in bone and bone marrow. Wang et al.[7] demonstrated with a three-dimensional (3D) culture model that mechanical overload significantly suppressed the level of ERα in chondrocytes. This pressure and mechanical loading increased hypertrophy and osteogenic transition. In animal studies, it

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Cite this article as: Nursal AF, Yiğit S, Keskin A, Tümer MK. ESR1 rs2234693 might be associated with TMD risk in the Turkish population, but not rs9340799. *Kastamonu Med J.* 2023;3(4):192-197.

has been shown that estrogen deficiency causes structural changes in the TMJ.[8] Expression of *ESR1* in chondrocytes, stromal cells, and osteoblasts indicates that bone and cartilage can be regulated by the ESR1 gene.[5] The *ESR1* gene located on the long arm of chromosome 6 (6q25.1). There are many polymorphisms in this gene. Especially PvuII (rs2234693) and Xbal (rs9340799) variants, which are frequently seen in intron 1 of the *ESR1* gene, can affect ERα gene expression through changes in the binding and action of transcription factors.[9] In studies examining the relationship of these variants with osteoarthritis, the findings are controversial.[10, 11]

Therefore, we aimed to evaluate whether *ESR1* gene variants (rs2234693 and rs9340799) contribute to TMD susceptibility in the Turkish population.

METHODS

Subjects

One hundred thirty patients with TMD (110 females and 25 males: mean age: 30.97±11.59) were included in the present study. Patients were chosen from those who were diagnosed with TMD in the Department of Medical Genetics in the Giresun University. The diagnosis of TMD was made according to the diagnostic criteria published in 2014.[12] Subjects with TMJ surgery and trauma, RA, fibromyalgia, or other systemic musculoskeletal disorders, past or present neurological and/or psychiatric disorders, investigational drug or device use, opioid drug use, or pregnancy were excluded from either group. A total of 140 unrelated healthy age-matched controls (88 females and 52 males: mean age: 34.48±10.43) were included in the study. These control cases had no previous history of TMD. Both groups were of Turkish origin. The principles outlined in the Declaration of Helsinki were followed. The Kanuni Training and Research Hospital Ethics Committee approved the study (Date: 13.01.2016, Decision No: 2016/09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Genotyping

DNA extraction was performed using a commercial kit from two mL of venous blood taken from the groups. Genotyping of *ESR1* rs2234693 and rs9340799 variants was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis using the method described previously.[13] After amplification, the 1374 bp PCR product was digested with PvuII and XbaI restriction enzymes. Digestion products were separated on a 2% agarose gel. 982 and 392 bp fragments were detected when the G allele was present at position -351, and 937 and 437 bp fragments were detected when the C allele was present at position -397. 25% of samples were reworked to avoid inconsistencies in results.

Statistical Analysis

Statistical Package for the Social Sciences 22.0 IBM (NY, USA) was used for statistical analysis in the evaluation of the data in the study. The percentage frequency of categorical variables was used. The mean standard deviation was used to express continuous variables. In group comparisons, the chi-square test for categorical variables, the independent sample t-test for continuous variables, and the one-way Anova test were used.

RESULTS

In our study, we compared 135 patients [110 females (81.48%), 25 males (18.52%)] and 140 controls in terms of *ESR1* rs2234693 and rs9340799. The genotype and allele distribution of ESR1 rs2234693 and rs9340799 in the patient and control groups are shown in Table 1.

Table 1. Genotype distribution and allele frequencies of rs223493 and rs2234693 in patients and controls

rs2234693 (PvuII)	Patient group n:135 (%)	Control group n:140 (n)	p	OR (95%Cl)
Genotypes				
T/T	45 (33.33)	72 (51.43)	**0.007**	
T/C	62 (45.93)	51 (36.43)		
C/C	28 (20.74)	17 (12.14)		
TT: TC+CC	45 (33.33): 90 (66.67)	72 (51.43): 68 (48.57)	**0.002**	2.12 (1.30-3.45)
TT+TC: CC	107 (79.26): 28 (20.74)	123 (87.86): 17 (12.14)	0.097	1.73 (0.90-3.34)
Alleles				
T	152 (56.30)	195 (69.64)	**0.002**	1.75 (1.24-2.49)
C	118 (43.70)	85 (30.36)		
rs9340799 (Xbal)	**Patient group n: 135 (%)**	**Control group n: 140 (n)**	**p**	**OR (95%Cl)**
Genotypes				
A/A	59 (43.70)	52 (37.14)	0.137	
A/G	58 (42.96)	76 (54.29)		
G/G	18 (13.33)	12 (8.57)		
AA: AG+GG	59 (43.70): 76 (56.30)	52 (37.14): 88 (62.86)	0.268	0.76 (0.47-1.23)
AA+AG: GG	117 (86.67): 18 (13.33)	128 (91.43): 12 (08.57)	0.205	0.61 (0.28-1.32)
Alleles				
A	176 (65.19)	180 (64.29)	0.825	1.04 (0.73-1.48)
G	94 (34.81)	100 (35.71)		

Statistically significant values are shown in bold.

ESR1 rs2234693

The *ESR1* rs2234693 genotype distribution was statistically different between TMD patients and controls. The rs2234693 T/C and C/C genotypes were higher in the patient group compared to the control group (p=0.007). The T/T genotype was more prevalent in controls than in patients. A statistically significant association was observed when the patients were compared with the controls according to TT versus TC+CC [p=0.002, OR (CI 952.12 (1.30-3.45)]. Also, the C allele frequency was more prevalent in patients compared to controls (p=0.002, OR=1.78, 95% CI=1.24-2.49).

ESR1 rs9340799

The prevalence of genotypes A/A, A/G, and G/G, profiles for the rs9340799 was 43.70%, 42.96%, and 13.33%, respectively, in patients, and 37.14%, 54.29%, and 8.57%, respectively, in the control group. We found no statistical significance between the patient and control groups in terms of rs9340799 genotype distribution (p=0.137). There was no significant difference in terms of rs9340799 allele frequency (p=825, OR=1.22, 95%CI=0.73-1.32).

Then we analyzed the relationship between the *ESR1* rs2234693 and rs9340799 genotype distribution and clinical characteristics,

including age, gender, disease age, family history, pain, teeth grinding or bruxism, increased pain when chewing or talking, pain severity, eating difficulties, a click sound from the chin, jaw locking, loudness, pain region, pain persistance, TMJ disorder, musculatory muscle symptoms, headache, Schiffman associated structure, and TMD criteria. Both males and females had the highest rs2234693 T/C genotype (p=0.049). In the subjects with bruxism, bruxomania, and bruxism plus bruxomania, there was mostly the rs2234693 T/C genotype (p=0.025). Results are presented in Table 2 and Table 3.

Table 2. The relationship between rs2234693 (PvuII) genotype distribution and patient characteristics

Characteristics		Total n=135 (%)	T/T n=45 (%)	T/C n=62 (%)	C/C n=28 (%)	p
Age, X±SD		30.97± 11.59	32.40± 12.81	31.11±11.50	28.36± 9.52	0.350
Gender, n (%)	Male	25 (18.52)	5 (20.00)	17 (68.00)	3 (12.00)	**0.049**
	Female	110 (81.48)	40 (36.36)	45 (40.91)	25 (22.73)	
Disease age, n (%)	0-1 year	63 (46.67)	19 (30.16)	31 (49.21)	13 (20.63)	0.211
	1-5 years	39 (28.89)	10 (25.64)	18 (46.15)	11 (28.21)	
	5 years and above	33 (24.44)	16 (48.48)	13 (39.39)	4 (12.12)	
Family history, n (%)	Yes	79 (58.52)	29 (36.71)	35 (44.30)	15 (18.99)	0.594
	No	56 (41.48)	16 (28.57)	27 (48.21)	13 (23.21)	
Presence of pain, n (%)	Yes	117 (86.67)	42 (35.90)	52 (44.44)	23 (19.66)	0.266
	No	18 (13.33)	3 (16.67)	10 (55.56)	5 (27.78)	
Teeth grinding or bruxism, n (%)	No	55 (40.74)	21 (38.18)	24 (43.64)	10 (18.18)	**0.025**
	Bruxism	11 (08.15)	3 (27.27)	8 (72.73)	0 (00.00)	
	Bruxomania	21 (15.56)	9 (42.86)	11 (52.38)	1 (04.76)	
	Bruxism+ Bruxomania	48 (35.56)	12 (25.00)	19 (39.58)	17 (35.42)	
Increased pain when chewing or talking, n (%)	Evet	91 (67.41)	32 (35.16)	38 (41.76)	21 (23.08)	0.355
	No	44 (32.59)	13 (29.55)	24 (54.55)	7 (15.91)	
Pain severity, X±SD		4.36± 2.53	4.58± 2.26	4.29± 2.57	4.18±2.89	0.772
Eating difficulties n (%)	Yes	64 (47.41)	25 (39.06)	28 (43.75)	11 (17.19)	0.356
	No	71 (52.59)	20 (28.17)	34 (47.89)	17 (23.94)	
Click sound from the chin, n (%)	Yes	112 (82.96)	36 (32.14)	54 (48.21)	22 (19.64)	0.494
	No	23 (17.04)	9 (39.13)	8 (34.78)	6 (26.09)	
Jaw locking, n (%)	Yes	31 (22.96)	8 (25.81)	16 (51.61)	7 (22.58)	0.597
	No	104 (77.04)	37 (35.58)	46 (44.23)	21 (20.19)	
Loudness, X±SD		3.96± 2.46	4.07± 2.46	4.00± 2.33	3.68± 2.79	0.794
Pain region, n (%)	No pain	10 (07.41)	2 (20.00)	5 (50.00)	3 (30.00)	0.807
	Muscle pain	18 (13.33)	8 (44.44)	7 (38.89)	3 (16.67)	
	Joint region	44 (32.59)	15 (34.09)	22 (50.00)	7 (15.91)	
	Joint and muscle pain	63 (46.67)	20 (31.75)	28 (44.44)	15 (23.81)	
Pain persistance, n (%)	Continually	35 (25.93)	16 (45.71)	14 (40.00)	5 (14.29)	0.385
	Periodically	90 (66.67)	27 (30.00)	43 (47.78)	20 (22.22)	
	No	10 (07.41)	2 (20.00)	5 (50.00)	3 (30.00)	
Tmj disorder, n (%)	Yes	125 (92.59)	39 (31.20)	60 (48.00)	26 (20.80)	0.143
	No	10 (07.41)	6 (60.00)	2 (20.00)	2 (20.00)	
Masticatory muscle symptoms, n (%)	Yes	81 (60.00)	27 (33.33)	34 (41.98)	20 (24.69)	0.331
	No	54 (40.00)	18 (33.33)	28 (51.85)	8 (14.81)	
Headache, n (%)	Yes	67 (49.63)	26 (38.81)	30 (44.78)	11 (16.42)	0.296
	No	68 (50.37)	19 (27.94)	32 (47.06)	17 (25.00)	
Schiffman associated structure, n (%)	Yes	2 (01.48)	0 (00.00)	2 (100.00)	0 (00.00)	0.303
	No	133 (98.52)	45 (33.83)	60 (45.11)	28 (21.05)	
TMD criteria n (%)	TMD TMJ disorder	16 (11.85)	3 (18.75)	10 (62.50)	3 (18.75)	0.421
	Masticatory muscle	6 (04.44)	3 (50.00)	1 (16.67)	2 (33.33)	
	1 and 2 together	46 (34.07)	13 (28.26)	21 (45.65)	12 (26.67)	
	1 and 3 together	39 (28.89)	15 (38.46)	19 (48.72)	5 (12.82)	
	2 and 3 together	4 (02.96)	3 (75.00)	1 (25.00)	0 (00.00)	
	1, 2, and 3 together	24 (17.78)	8 (33.33)	10 (41.67)	6 (25.00)	

TMD: Temporomandibular disorder, TMJ: temporomandibular joint. Statistically significant values are shown in bold

Table 3. The relationship between rs9340799 (Xbal) genotype distribution and patient characteristics

Characteristics		Total n=135 (%)	A/A n=59 (%)	A/G n=58 (%)	G/G n=18 (%)	p
Age, X±SD		30.97± 11.59	30.31±11.49	31.64±12.14	31.00±10.61	0.826
Gender, n (%)	Male	25 (18.52)	11 (44.00)	11 (44.00)	3 (12.00)	0.976
	Female	110 (81.48)	48 (43.64)	47 (42.73)	15 (13.64)	
Disease age, n (%)	0-1 year	63 (46.67)	27 (42.86)	26 (41.27)	10 (15.87)	0.927
	1-5 years	39 (28.89)	17 (43.59)	17 (43.59)	5 (12.82)	
	5 years and above	33 (24.44)	15 (45.45)	15 (45.45)	3 (09.09)	
Family history, n (%)	Yes	79 (58.52)	34 (43.04)	38 (48.10)	7 (08.86)	0.132
	No	56 (41.48)	25 (44.64)	20 (35.71)	11 (19.64)	
Presence of pain, n (%)	Yes	117 (86.67)	48 (41.03)	53 (45.30)	16 (13.68)	0.268
	No	18 (13.33)	11 (61.11)	5 (27.78)	2 (11.11)	
Teeth grinding or bruxism, n (%)	No	55 (40.74)	24 (43.63)	25 (45.45)	6 (10.91)	0.249
	Bruxism	11 (08.15)	5 (45.45)	4 (36.36)	2 (18.18)	
	Bruxomania	21 (15.56)	14 (66.67)	6 (28.57)	1 (04.76)	
	Bruxism+	48 (35.56)	12 (25.00)	19 (39.58)	17 (35.42)	
Increased pain when chewing or talking, n (%)	Yes	91 (67.41)	37 (40.66)	41 (45.05)	13 (14.29)	0.587
	No	44 (32.59)	22 (50.00)	17 (38.64)	5 (11.36)	
Pain severity, X±SD		4.36± 2.53	4.14± 2.66	4.67±2.45	4.11±2.37	0.470
Eating difficulties n (%)	Yes	64(47.41)	30 (46.88)	27 (42.19)	7 (10.94)	0.663
	No	71 (52.59)	29 (40.85)	31 (43.66)	11 (15.49)	
Click sound from the chin, n (%)	Yes	112 (82.96)	46 (41.07)	50 (44.64)	16 (14.29)	0.383
	No	23 (17.04)	13 (56.52)	8 (34.78)	2 (08.70)	
Jaw locking, n (%)	Yes	31 (22.96)	15 (48.39)	11 (35.48)	5 (16.13)	0.618
	No	104 (77.04)	44 (42.31)	47 (45.19)	13 (12.50)	
Loudness, X±SD		3.96±2.46	3.71±2.57	4.17±2.41	4.06±2.31	0.592
Pain region, n (%)	No pain	10 (07.41)	5 (50.00)	4 (40.00)	1 (10.00)	0.340
	Muscle region	18 (13.33)	11 (61.11)	4 (22.22)	3 (16.67)	
	Joint region	44 (32.59)	18 (40.91)	23 (52.27)	3 (06.82)	
	Joint region and muscle pain	63 (46.67)	25 (39.68)	27 (42.86)	11 (17.46)	
Pain persistance, n (%)	Continously	35 (25.93)	18 (51.43)	15 (42.86)	2 (05.71)	0.467
	Periodically	90 (66.67)	36 (40.00)	39 (43.33)	15 (16.67)	
	No	10 (07.41)	5 (50.00)	4 (40.00)	1 (10.00)	
Schiffman TMJ disorder, n (%)	Yes	125 (92.59)	52 (41.60)	57 (45.60)	16 (12.80)	0.091
	No	10 (07.4)	7 (70.00)	1 (10.00)	2 (20.00)	
Schiffman masticatory muscles, n (%)	Yes	81 (60.00)	37 (45.68)	30 (37.04)	14 (17.28)	0.122
	No	54 (40.00)	22 (40.74)	28 (51.85)	4 (07.41)	
Schiffman headache, n (%)	Yes	67 (49.63)	30 (44.78)	29 (43.28)	8 (11.94)	0.891
	No	68 (50.37)	29 (42.65)	29 (42.65)	10 (14.71)	
Schiffman associated structure, n (%)	Yes	2 (01.48)	0 (00.00)	1 (50.00)	1 (50.00)	0.099
	No	133 (98.52)	59 (44.36)	57 (42.86)	17 (12.78)	
TMD criteria n (%)	TMJ disorder	16 (11.85)	6 (37.50)	9 (56.25)	1 (06.25)	0.500
	Masticatory muscle	6 (04.44)	5 (83.33)	0 (00.00)	1 (16.67)	
	1 and 2 together	46 (34.07)	18 (39.13)	20 (43.48)	8 (17.39)	
	1 and 3 together	39 (28.89)	17 (43.59)	19 (48.72)	3 (07.69)	
	2 and 3 together	4 (02.96)	2 (50.00)	1 (25.00)	1 (25.00)	
	1, 2, and 3 together	24 (17.78)	11 (45.83)	9 (37.50)	4 (16.67)	

TMD: Temporomandibular disorder, TMJ: temporomandibular joint.

DISCUSSION

One of the most common causes of chronic pain in the orofacial region is TMD.[14] Gender is an important determinant of health. It plays a role in the pathophysiology of various dental diseases, including TMD and pregnancy-associated gingivitis.[15] Although the results are controversial, it is reported that women are 2-3 times more likely to develop TMD than men.[16] It is considered that this difference is due to excessive

articular flaccidity, trauma, age, and behavioral, hormonal, genetic, anatomical, and psychosocial reasons. It was reported that subjective symptoms and clinical characteristics of TMD patients show distinct tendencies according to different age groups.[17] Hormonal fluctuations during pregnancy and during the menstrual cycle have been shown to cause painful sensations in patients with TMD.[18,19] Jedynak et al.[20] reported that TMD is common in women with menstrual disorders (92.3%). They declared that women with TMD symptoms should be questioned about female hormone disorders.

Estrogen is important in development and homeostasis for both sexes, although relative levels vary. Estrogens do not only affect the female reproductive system, they can also affect the functioning of the whole body. Estrogens in the blood affect the metabolism of other tissues and organs by binding to plasma proteins. Estrogens can exert their effects on cells with a direct or indirect effect on gene expression through receptors located on cell membranes as well as nuclear estrogen receptors.[20] Estrogens have the ability to influence monocytes and macrophages by regulating the production of proinflammatory cytokines (interleukin-1, interleukin-2, and TNF-α). It has been reported that 10 nM estradiol treatment reduces the promoter activity and gene expression of proteoglycan 4, which is required for joint lubrication in baboon disc fibrochondrocytes.[21] 17-β estradiol induces the production and destruction of matrix metalloproteinases (MMP9 and MMP13) in TMJ fibrocartilage.[19,22] Abdrabuh et al.[23] demonstrated that some TMJ structures, including the articular disc and condylar cartilage layer, are disrupted after estrogen deficiency. In one study, the prevalence of TMD was found to be 2-3 times lower in pregnant women with reduced estrogen than in non-pregnant women.[24] In a study investigating the relationship between TMD pain and periods of the menstrual cycle, it was stated that TMD pain is highest at times when estrogen is lowest, but rapid estrogen change may also be associated with increased pain.[25] One method to assess the role of estrogen in TMD is to examine its prevalence in postmenopausal women taking hormone replacement therapy (HRT). A study observed a significant increase in the prevalence of TMD in postmenopausal women taking HRT.[26] However, other studies have found no significant difference in the prevalence of TMD in postmenopausal women taking HRT compared to those receiving no treatment.[27,28] Some studies have shown that TMD mostly affects women of childbearing age, suggesting that these high estrogen levels aggravate the disease.[29] Two studies showed that orofacial pain was significantly reduced during the third trimester of pregnancy[30] and increased postpartum.[18] This suggests that TMD pain is reduced by high estrogen levels.

Several single nucleotide polymorphisms (SNPs) have been identified in the *ESR1* gene. rs2234693 and rs9340799, two of the most studied SNPs, are located in the first intron of ESR and are in strong linkage disequilibrium with each other.[31] It has been suggested that these variants affect *ESR1* expression and activation and alter the action of estrogen. The rs2234693 C and rs9340799 G alleles in *ESR1* were associated with higher gene expression and more positive estrogen-induced effect.[32] In women, overexpression of the ESR in the TMJ indicates excessive joint laxity. The clinical picture is likely to be affected by ESR polymorphisms.[33] These variants appear to be markers for bone mineral density and cardiovascular disease in women.[34] Additionally, these variants are thought to play a role in estrogen-related diseases such as breast cancer, osteoporosis, endometriosis, and familial early ovarian dysfunction.[34] In our previous study, we showed that *ESR1* rs2234693 and rs9340799 are effective in the development of common fibromyalgia and some clinical features in women.[35] Quinelato et al.[36] reported that the *ESR1* rs2273206 T/T genotype was associated with an increased risk of developing TMJ pain. In an animal study, *ESR2* rs1256049 was associated with disc displacement and arthralgia in adult rats.[37] Bonato et al.[38] reported that the rs1676303 T/T and rs6574293 G/G genotypes were associated with TMD. The A/A genotype of *ESR1* rs1643821 was found to be a risk factor for dysfunctional worsening after orthognathic surgery.[39]

In this study, we investigated the effect of *ESR1* rs2234693 and rs9340799 on TMD development in the Turkish population. To the best of our knowledge, this is the first study to examine the relationship between TMD and *ESR1* gene variants in our country. We found that the rs2234693 C allele is a risk factor for the development of TMD. This suggested that patients were exposed to high *ESR1* expression. Also, there was a significant association in terms of TT vs. TC+CC (Table 1). We then compared the genotype distributions of these variants with the demographic and clinical characteristics of the patients. Homozygous genotypes were more common in females, while heterozygous genotypes were more common in males for rs2234693. The majority of our patients with bruxism, bruxomania, and bruxism plus bruxomania carried the rs2234693 T/C genotype (Table 2). However, the genotype distribution of both variants was not significantly associated with other clinical characteristics.

Our study has some limitations. It is important that female patients do not have hormone level information and that their menstrual cycle is not questioned.

CONCLUSION

TMD is a disease of complex origin. In this study, we showed for the first time in our country that *ESR1* rs2234693 is a factor that may predispose to joint degeneration. Determining the relationship between TMD and these variants is important for elucidating the molecular structure of TMD.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from Kanuni Training and Research Hospital Ethics Committee (Date: 13.01.2016, Decision No: 2016/09).

Informed Consent: Written informed consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

Financial Disclosure: We do not have any financial support for this study.

Author Contributions: All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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