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RESEARCH ARTICLE

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The *IL-1Ra* gene variable number tandem repeat variant is associated with susceptibility to temporomandibular disorders in Turkish population

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Background: Temporomandibular joint disorders (TMD) are a group of disorders involving temporomandibular joint and related structures. Interleukine-1 receptor antagonist (IL-1Ra) is an important anti-inflammatory molecule that competes with other interleukin-1 molecules. This study was designed to investigate the possible association of the *IL-1Ra* VNTR variant with the risk of TMD in the Turkish population.

Methods: Peripheral blood samples were collected from 100 patients with TMD (23 males, 77 females) and 110 healthy individuals (35 males, 75 females). Genotyping of *IL-1Ra* 86 bp VNTR variant was evaluated by gel electrophoresis after polymerase chain reaction (PCR).

Results: Our results show that there is a statistically significant difference between TMD patients and control group with respect to IL-1Ra genotype distribution and allele frequencies. 1.2, 1.4, and 4.4 genotypes were more common in patients, while 2.2 and 3.3 genotypes were rarer ($P<.000$). Frequency of alleles 1 and 4 was higher in patient groups ($P<.000$), whereas alleles 2 and 3 had a lower frequency in patients with TMD ($P<.000$).

Conclusions: This is the first correlation study that evaluates the association between *IL-1Ra* gene VNTR variant and TMD. The VNTR variant related to *IL-1Ra* gene showed a strong pattern of association with TMD that may have a potential impact on disease counseling and management. Larger studies with various ethnicities are needed to establish the impact of *IL-1Ra* VNTR variant on risk of developing TMD.

KEYWORDS
interleukine-1 receptor antagonist, temporomandibular joint disorders, VNTR variant

1 | INTRODUCTION

Temporomandibular disorders (TMD) involve alterations of the temporomandibular joint, masticatory muscles and related structures[1] and are accompanied by various symptoms such as facial pain, mandibular motion, clicking and grinding. It is estimated that the prevalence of TMD varies between 2% and 6% in developing countries.[2] The etiology of TMD includes micro/macro trauma, inflammation, parafunctional habits and bruxism, and stress.[3]

Interleukin-1 family consists of interleukin-1α (IL-1α), interleukin-1β (IL-1β) and interleukin-1 receptor antagonist (IL-1Ra). IL-1α and IL-1β are potent proinflammatory cytokines and act as agonist. *IL-1Ra* gene is an anti-inflammatory cytokine and acts as antagonist of other IL-1 molecules.[4] The *IL-1Ra* gene is localized on chromosome 2 (2q12.21), near the genes for *IL-1α* and *IL-1β*. *IL-1Ra* gene has a polymorphic site in the second intron, which is an 86-bp variable number tandem repeat (VNTR).[4] This variant contains five alleles which have been reported (1-5) corresponding to 4, 2, 5, 3 and 6 copies of 86-bp

sequence, respectively. The allele with two repeats has been reported to be associated with serum IL-1Ra levels and in vitro production of IL-1β.[5] *IL-1Ra* VNTR variant is found to be associated with various diseases. Although pro-inflammatory cytokines play important role in pain induction, their contribution to chronic pain conditions is not known yet. This study was designed to reveal whether VNTR variant of *IL-1Ra* gene is associated with TMD in Turkish patients.

2 | MATERIALS AND METHODS

2.1 | Patients

In our study, 100 patients with TMD diagnosis (23 males and 77 females) and 110 healthy volunteers (35 males and 75 females as control group) who were recruited from Tokat Gaziosmanpasa University, Dentistry Faculty, were included. The TMD diagnosis was based on the criteria as described by Schiffman et al.[6] The mean age was 34.92±13.34 and 37.52±11.46 in the patient and in the control group, respectively. Both the sample group and control group were recruited from the Turkish population. Subjects included in this study were older than 18 years. Written informed consent was obtained from all healthy individuals as well as patients with TMD, according to the Helsinki Declaration. This study was approved by the Clinical Research Ethical Committee.

2.2 | Molecular analysis

Genomic DNA isolated from whole blood collected from TMD patients and the control group using standard procedures (Sigma-Aldrich, St. Louis, MO, USA) was stored at −20°C. PCR reaction was performed in a 25 μL final volume containing 25 pmol/L of each primer, 0.1 mmol/L of dNTP, 0.5 μg of genomic DNA, 1.5 mmol/L of MgCl, 2 and 2.5 μL of PCR buffer, and 1.5 unit of Taq DNA polymerase according to the following protocols: initial denaturation at 94°C for 4 minutes; 30 cycles of denaturation at 94°C for 45 seconds, annealing at 51°C for 30 seconds, and extension at 72°C for 45; and final extension at 72°C for 5 minutes. The 86-bp VNTR polymorphism of *IL-1Ra* was analyzed using polymerase chain reaction (PCR) with 5′-CTCAGCAACACTCCTAT-3′ forward primer and 5′-TCCTGGTCTGCAGGTAA-3′ reverse primer as previously described.[7] PCR products were separated by electrophoresis on a 2% agarose gel and visualized by ethidium bromide staining. Five different alleles of *IL-1Ra* were defined as follows: allele 1, four repeats (410 bp); allele 2, two repeats (240 bp); allele 3, five repeats (500) bp; allele 4, three repeats (325 bp) and allele 5, six repeats (595 bp).

2.3 | Statistical analysis

All statistical analyses were performed using SPSS 16.0 (SPSS, Chicago, IL, USA) and Arlequin 3.11 software (University of Bern, Bern, Switzerland). Continuous data were presented as mean±SD (standard deviation) and (min-max). Chi-square test was used to test the significance of differences in the allele frequency and genotype distribution between the two study groups. Hardy-Weinberg equilibrium test was performed for both study groups using Hardy-Weinberg Equilibrium Calculator for 2 Alleles. Odds ratio (OR) with 95% confidence intervals (CIs) were estimated and a P value of <.05 was considered statistically significant.

3 | RESULTS

Two hundred and ten Turkish individuals (110 controls and 100 patients) participated in the study. There were 75 female and 35 male participants in the control group, and 77 female and 23 male participants in the patient group. The females constituted the majority of the cases in both patient and control groups. The baseline clinical and demographic characteristics of the study patients with TMD are shown in Table 1. Genotypic and allelic distributions of the *IL-1Ra* VNTR variant are presented in Table 2. Genotype frequencies of *IL-1Ra* VNTR variant were in a good agreement with Hardy-Weinberg equilibrium for 1.1, 1.2, and 2.2 genotypes in TMD patients, as there were no significant differences between observed [64 (64%), 23 (23%), 3 (3%)] and expected [63.34 (70.37%), 24.33 (27.03%) in 1.1, 1.2 and 2.2, respectively, 2.34 (2.6%) in 1.1, 1.2 and 2.2, respectively] genotype frequencies (P<.604). The 1.1, 1.2, 1.4, 2.2, 3.3, and 4.4 genotypes of the *IL-1Ra* VNTR variant were observed in 64%, 23%, 7%, 3%, 0%, and 3% of patients, respectively. The frequency of the 1.2, 1.4, and 4.4 genotype was higher in the TMD population compared with the

TABLE 1 Baseline clinical and demographics features of the patients with temporomandibular joint disorders

Characteristic	Control group (n:110)	Study group (n:100)
Gender, male/female	35/75 (31.81/68.18)	23/77 (23/77)
Age, mean±SD, y	37.52±11.46	34.92±13.34
Disease duration, n		
0-5 y	—	63
5 ↑ y	—	37
Family history, yes/no, n	—	49/51
Systemic diseases, yes/no, n	—	37/63
Pain, yes/no, n	—	74/26
Bruxism, yes/no, n	—	55/45
Chewing difficulties, yes/no, n	—	33/67
TMJ clicking or popping, yes/no, n	—	73/27
TMJ locking, yes/no, n	—	8/92
Pain duration, n		
1-60 min	—	41
60 ↑ min	—	39
Continuous	—	11

TMJ, temporomandibular joint; SD, standard deviation.

TABLE 2 Genotype and allele frequencies of IL-1Ra variable number tandem repeat gene polymorphisms in temporomandibular joint disorders patient and control groups

	Genotypes						
	1.1 (n)	1.2 (n)	1.4 (n)	2.2 (n)	3.3 (n)	4.4 (n)	*P*
IL-1Ra							
Patients (n:100)	64	23	7	3	0	3	<.000*
Controls (n:110)	60	5	1	36	8	0	
	Alleles						
	IL-1Ra 1 (±)		**IL-1Ra 2 (±)**		**IL-1Ra 3 (±)**	**IL-1Ra 4 (±)**	
Patients, n (%)	158 (79/42)		29 (14.5/85.5)		0 (0/100)	13 (6.5/93.5)	
Controls, n (%)	126 (57.2/42.7)		71 (32.2/67.7)		16 (7.2/92.7)	1 (0.45/99.5)	
P	<.000*		<.000*		<.000*	<.000*	
OR (CI 95%)	2.8 (1.82-4.34)		0.35 (0.21-0.57)		0.06 (0.00-0.37)	15.15 (2.61-328)	

*The results that are statistically significant.

control group, while the TMD group also showed a lower frequency of genotype 2.2 and 3.3 compared with the healthy controls. Genotype distribution showed statistically significant differences between the patients with TMD and the control subjects (*P*<.000). Four alleles were found in our study population, namely alleles 1 (four repeat), 2 (two repeats), 3 (five repeats), and 4 (three repeats). Allele 5 (six repeats) was absent. In the TMD patient group, the allele frequencies were *P*<.000 for alleles 1, 2, 3, and 4. We observed significant differences between the patients with TMD and the control population for allele frequency, as well as in genotype frequencies (*P*<.000). Frequency of alleles 1 and 4 was higher in the TMD patients as compared with the control group, while that of alleles 2 and 3 was lower in the patient group.

4 | DISCUSSION

Temporomandibular joint disorders are an important public health problem, since it causes chronic orofacial pain interrupting daily activities.[8] Epidemiological studies suggested that preexisting pain conditions, depression, and female sex are among the consistent risk factors for TMD.[9] The patients who suffer from chronic and painful TMD have several psychosocial characteristics in common with subjects who have other painful syndromes.[10] Chronic fatigue syndrome, fibromyalgia syndrome, chronic widespread pain, TMD and irritable bowel syndrome are some of conditions that currently lack a clear physical or biological etiology and have inconsistent laboratory abnormalities.[11] Some studies suggest that chronic pain conditions may be the result of augmented neurotransmitter activity of the central nervous system, a mechanism called central sensitization.[12] The hypothalamic-pituitary-adrenal axis (HPA axis) is one of the major stress systems, and it possibly initiates and bolsters this process.[13] The majority of previous studies reported a reduced activity and impaired feedback sensitivity of the HPA axis in conditions associated with chronic pain.[14,15] It has also shown that circulatory levels of proinflammatory cytokine increase in diseases with widespread pain.[16,17] Increased circulatory pro-inflammatory cytokine levels are associated with a high sensitivity to pain,[18] perceived stress,[19] and depressed mood,[20] which are among the phenotype characteristics of TMD and widespread pain. Current studies report that cytokines play a role in the pathophysiology of TMD. Furthermore, it has been reported that the level of proinflammatory cytokine increases in temporomandibular joint of the patients with TMD.[21,22]

IL-1 is one of the essential inflammatory mediators released from various types of cells, such as macrophages, monocytes, and synovial cells.[23] IL-1α and IL-1β act similarly through the IL-1 type 1 receptor, whereas IL-1Ra is a natural inhibitor of IL-1 and competes for the relevant receptor. It is known that the augmented expression of pro-inflammatory cytokines results in an immune response and activates the HPA axis.[24] IL-1β has been implicated in a wide range of actions. Early studies suggested that this cytokine acts in a specific behavioral complex such as various sleep disorders, anxiety, and reduced social interactions.[25] Evidence suggests that IL-1β is upregulated throughout the brain following an exposure to stress[26] and plays a crucial role in stress-induced HPA axis regulatory responses.[27] It was found that *IL-1β* variants are associated with major depression.[28]

IL-1Ra exerts a competitive inhibitory effect at the receptor site of *IL-1α* and *IL-1β* and down-regulates the immune response and inflammation.[29] McIntyre et al.[30] reported that the relative concentrations of IL-1β and IL-1Ra could modulate the initiation and termination of the pro-inflammatory response. The *IL-1Ra* intron 2 VNTR variant consists of three potential protein-binding sites: an interferon α silencer A, an interferon β silencer B, and an acute phase response element. It has been found that the control of cell proliferation activity was regulated by IL-1Ra production through these three binding sites.[7] The number of repeats in *IL-1Ra* varies from individual to individual and the frequency of each allele differs among various ethnic or geographic populations. Several studies have tried to establish a relationship between the *IL-1Ra* genotypes and concentration of the IL-1Ra protein.[31] *IL-1Ra* VNTR variant was examined in several distinct disease groups such as

pre-eclampsia, systemic lupus erythematosus, cancer, infertility and rheumatoid arthritis.[32-36] It has been reported that *IL-1Ra* VNTR variant differs markedly in patients with irritable bowel syndrome, a disease belonging to central sensitization group, compared with control cases.[37]

It was reported that the frequency of allele 2 increases in several auto-inflammatory or inflammatory diseases, such as in ulcerative colitis,[38] multiple sclerosis,[39] diabetic nephropathy,[40] and systemic lupus erythematosus.[41] Regarding the underlying pathophysiology, studies suggest that individuals with the allele2 (containing two repeats) of *IL-1Ra* have a more prolonged and more severe pro-inflammatory immune response compared with those having other IL-1Ra genotypes.[31] Besides, increased circulating IL-1Ra levels and higher IL-1β levels have been observed in persons with *IL-1Ra* allele2.[42]

In this study, we hypothesized whether the *IL-1Ra* VNTR variant plays a role in susceptibility on TMD. In this case-control study, we found that the *IL-1Ra* VNTR variant is significantly associated with TMD. In our study, frequency of the 1.2, 1.4, and 4.4 genotype was statistically higher in patients with TMD, while that of 2.2 and 3.3 genotype was lower in patients (P<.000; Table 2.). Also, a significant difference was observed in allelic distribution between TMD patients and the controls (P<.000). Frequency of alleles 1 and 4 was high in the patient group, whereas alleles 2 and 3 had a lower frequency. Frequency of allele 2, which is associated with several auto-inflammatory and inflammatory diseases, was found to be lower in patients with TMD. We believe that this might be the first report from Turkey on variant in encoding cytokine in patients with TMD. Reflecting its biological role, these results suggest that the *IL-1Ra* VNTR variant plays a major role in the development of TMD. Further studies are needed to establish the essential effect and possible interactions of *IL-1Ra* alleles, such as functional studies to clearly identify the effect of the allele 2 in various conditions.

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