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The association of gene polymorphisms in catechol-O'methyltransferase (COMT) and β2-adrenergic receptor (ADRB2) with temporomandibular joint disorders

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ABSTRACT

Objective: Temporomandibular disorder (TMD) has a multifactorial etiology that includes environmental, psychological, and genetic factors. This study aimed to evaluate the possible relationship between polymorphisms in *Catechol-O-methyltransferase (COMT)* and *β2-adrenergic receptor (ADRB2)* genes with TMD.
Design: This observational case-control study included 80 patients and 70 healthy controls. The diagnosis of TMD was made using the diagnostic criteria for TMD and the following TMD categories were used for the case group: muscular TMD and articular TMD (disc displacement and arthralgia). A genotyping study of gene polymorphisms in *COMT* (rs 9332377) and *ADRB2* (rs20530449) was performed from genomic DNA isolated from blood. The chi-square test was used to analyze the relationships. $P < 0.05$ was accepted as a significant difference.
Results: The polymorphic TT and CT genotype for COMT (rs rs9332377) was significantly higher in the articular TMD group while the non-polymorphic CC genotype was significantly lower in the articular TMD group ($P < 0.05$). Regarding ADRB2 (rs20530449), the polymorphic GG genotype was similarly considerably more common in the articular TMD group ($p < 0.05$). In addition, the T allele in the COMT (rs rs9332377) gene was found to be significantly higher in the articular TMD group ($p < 0.05$).
Conclusions: In the Turkish population, gene polymorphisms in *COMT* (rs9332377) and *ADRB2* (rs2053044) were associated with articular TMD. This study supports the hypothesis that changes in *COMT* and *ADRB2* genes may play a role in temporomandibular joint pain and predisposition to TMD.

1. Introduction

According to the American Oropasial Pain Academy, temporomandibular disorders (TMDs) are defined as a group of disorders with masticatory muscles, temporomandibular joint (TMJ), and associated structures. TMDs are the second most common state of chronic muscle pain (Leboeuf-Yde et al., 2009). Pain is mostly seen in the masticatory muscles and anterior ears and may be exacerbated in chewing or other jaw activities. Other findings include joint sounds, asymmetric jaw movement, masticatory muscle hypertrophy, muscle fatigue, headache, bruxism, palpation sensitivity, and limited jaw movement due to the difficult opening of the mouth (Tjakkes et al., 2010). Pain, functional, and psycho-social disorders associated with TMD affect the quality of life more negatively than other oral conditions (Dahlstrm & Carlsson, 2010). However, the mechanisms in the pathophysiology of chronic pain caused by TMDs are not fully understood and this makes it difficult to implement accurate diagnosis and appropriate treatment protocols (Arendt-Nielsen et al., 2015). The existing evidence shows that approximately 50%of the risk of the development of chronic pain is affected by genetic and epigenetic changes in pain-reduced systems and sensitizing processes of peripheral and central nervous systems (Diatchenko et al., 2013).

It has been reported that heredity for nociceptive and analgesic sensitivities in mice is estimated to be between 28% and 75% and as one

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of the candidate pain genes, the single-nucleotide polymorphisms (SNPs) in Catecholamine-O-Metiltransferase (*COMT*) gene (Mogil, 1999). There are two types of this enzyme: soluble-*COMT* (*S-COMT*) containing 221 amino acids and membrane-bound -*COMT* (*MB-COMT*) containing 271 amino acids. Both enzymes are coded by the *COMT* gene in the 22nd chromosome. The specific location is in the long arm in 22q11.21 (Gen ID 1312). The *COMT* consists of 27222 nucleotides and contains six exons, five introns, and two promoter zones (P1 and P2) (Nissinen & Männistö, 2010). *COMT* neutralizes a wide variety of catechol substrates, including catecholamines and catechol estrogens, and acts as a key modulator of dopaminergic and adrenergic/noradrenergic neurotransmission, including ascending and descending pain pathways (Tenhunen et al., 1994). At an early date like 1965, Marbach and Levitt showed the increased levels of urine catecholamine metabolites in patients with jaw joints and facial pain, and that it refers to decreased erythrocytic *COMT* activity, revealing that it could play a role in chronic pain (Marbach & Levitt, 1976). Low *COMT* activity in central regions produces a high dopaminergic tone with contrasting antinociceptive effects. It has been shown that polymorphisms in the *COMT* gene are often associated with the sensitivity processes and hyperalgesia and allodynia of the central nervous system in previous studies, and are significantly associated with increased TMD development risk (Mladenovic et al., 2016; Younger et al., 2010).

Catecholamines are connected to two different receptors called α and β adrenergic receptors (*ADR*).

β2-adrenergic receptors (*ADB2*) are connected to a G protein and are also expressed in the regions of the central and peripheral nervous system in pain transmission (Hartung et al., 2014). Human *ADB2* is an intron-free gen on the 5q31–32.81 chromosome. Stimulation of this receptor leads to nociceptors that produce allodynia through activation of intracellular kinases. Also, the stimulation of these facilitates the transmission of pain through the release of proinflammatory molecules. It has been shown in a previous study that catecholamines increase their excitability by stimulating *ADRB2* receptors when they are present in primary afferent nociceptor nerve endings (Khasar et al., 2003). Due to the existence of different haplotypes encoding β-adrenergic receptors, more than a 10-fold risk of developing TMD has been found between individuals with higher and lower ADRB2 expression. These results show that both positive and negative imbalances in the *ADRB2* gene function increase vulnerability to chronic pain conditions such as TMD through different pathophysiological ways (Diatchenko et al., 2006). Therefore, it is seen that changes in the presence of polymorphisms in the *COMT* and *ADRB2* genes may be associated with permanent TMD conditions. There are few reports in the literature investigating the relationship between *COMT* and *ADRB2* gene polymorphisms and TMD, and different results have been presented (Bonato et al., 2021; Brancher et al., 2019a; de Souza Tesch et al., 2020; Michelotti et al., 2014). Although a recent meta-analysis study supports a significant relationship between genetic polymorphisms in the *COMT* gene and TMD, the authors stated that the results should be interpreted with caution due to the paucity of studies and population heterogeneity (Brancher et al., 2021). As far as we know, there is no study investigating the relationship between gene polymorphisms in *COMT, ADRB2,* and TMD in the Turkish population. This study aimed to evaluate the possible relationship between polymorphisms in *COMT* (rs9332377) and *ADRB2* (rs2053044) genes with TMDs. The h1 hypothesis to be tested is that *COMT* and *ADRB2* gene polymorphisms are associated with TMD.

2. Materials and methods

2.2. Study design and population

An observational, cross-sectional case-control study was designed. This study included consecutive patients with TMD and age/sex-matched healthy volunteers (controls) without TMD who applied to the Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey), between January 2022 and October 2022. The study was carried out according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (von Elm et al., 2008).

For the TMD group, those aged between 18 and 65 and diagnosed with "TMD" according to the -diagnostic criteria for TMD (DC /TMD) (Schiffman et al., 2014) were included in the study. For healthy controls, those aged between 18 and 65, without orofacial pain complaints, and Individuals who were healthy according to DC/TMD criteria were included in the study and were randomly selected over 9-month. The exclusion criteria of the study are:

(1) History of macro trauma and/or surgery in the orofacial region;
(2) Diagnosis of rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia, or other types of systemic joint disease;
(3) Prior treatments (surgical or conservative) for the TMD subgroup.

2.3. Clinical diagnosis of TMD

All participants were clinically evaluated by a researcher experienced in TMD using the DC/TMD-Axis I tool (Dworkin & LeResche, 1992), which has been validated for the physical diagnosis of TMD. All three subtypes of TMD (myofascial disorders, disc displacement, and arthralgia/arthroses) were included in the study according to DC/TMD diagnostic criteria. This is an approved tool for the physical diagnosis of TMD, allowing participants to be classified according to some of the following diagnostic subgroups: (0) No TMD; (I) myofascial pain; (II) common disk location changes; and (III) painful and/or degenerative TMJ conditions. The joint disorders diagnoses (subgroups II and III) were combined to form a single group called "articular TMD". Thus, three groups were eventually formed: (a) control (not diagnosed with TMD); (b) muscular TMD only; and (c) artıcular TMD only (de Souza Tesch et al., 2020). This process is non-mutually exclusive and allows each participant to belong to more than one diagnostic subgroup at the same time. Therefore, TMD patients who could enter both the muscular and articular groups were excluded from the study. Clinical examination findings of the patients were confirmed by radiological examinations when necessary. The diagnosis of disc displacement or degenerative joint disease was made by examining the MRI images taken from the patient.

2.4. Genotyping analysis

Blood collection was performed from each participant's arm (cephalic vein) who met the study criteria in a 5cc ETDA2 tube and blood samples were stored in the refrigerator (+4 C). Genomic DNA was obtained from peripheral blood samples using the relevant DNA isolation procedures (Invitrogen™ PureLink™ Genomic DNA Mini Kit, Cat No: K182002, USA), the amount and purity were determined by Promega QuantiFluor E6090 (Promega, Madison, USA) and stored at − 20 °C until use. The single nucleotide polymorphism (SNP) rs9332377 in the *COMT* gene and rs2053044 in the *ADRB2* gene were selected for the study. The characteristics of the polymorphisms examined in *COMT* and *ADRB2* were given in Table 1.

A genotyping study of *COMT* and *ADRB2* polymorphisms from genomic DNA isolated from blood was performed using the Applied Biosystems 3130XL Genetic Analyzer (USA). MyTaq™ HS DNA Polymerase (Bioline, Meridian Bioscience, Tennessee, USA) was used in the reaction mixture and the relevant primers were designed by Sentebiolab (Ankara, Turkey).

2.5. Statistical analysis

All data were analyzed using IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software. The sample size was calculated as a total of 133 individuals, taking into account the 95% confidence interval and using

Table 1
Characteristics of the polymorphisms studied in the *COMT* and *ADRB2*.

Gene name	Position	Base pair position	SNP	SNP type	MAF	Base change
COMT (Catechol-O methyltransferase)	22q11.21	22:19968169	rs9332377	Intragenic	0.17	C/T
ADRB2 (Adrenoceptor beta 2)	5q31–32.81	5: 148825809	rs2053044	Intragenic	0.34	A/G

SNP: Single nucleotide polymorphism; MAF: Minor allele frequency.

80% statistical power to detect a 30% difference between study groups. (G*Power version 3.1.9.2 program, Heinrich-HeineUniversity, Dusseldorf, Germany). Considering the possibility of dropping patients out of the study, 150 volunteers were included in the study. Statistical differences in genotype and allele frequency between groups were analyzed using the χ^2 test after testing for Hardy-Weinberg equilibrium. P values < 0.05 were considered statistically significant and the risks associated with individual alleles and genotypes were calculated as odds ratio (OR) with a 95% confidence interval (CI).

3. Results

All participants were between the ages of 18–65 (mean age was 31.8 ± 11.57 years), 124 female and 26 male. The TMD group consisted of 69 female and 11 male individuals between the ages of 18–63 (mean age: 33.68 ± 12.05 years). The control group consisted of 55 females and 15 males between the ages of 18–65 (mean age: 29.64 ± 10.69 years). There was no significant difference between the TMD and control groups in terms of age and gender ($p = 0.332$ and $p = 0.115$, respectively).

DNA analysis from peripheral blood samples could be performed on 148 participants, 80 from the TMD group and 68 from the control group. DNA analysis results could not be obtained in 2 volunteers belonging to the control group. The example genotype sequence curve of *COMT* gene rs rs9332377 polymorphism was presented in Fig. 1, and the example genotype sequence curve of *ADRB2* gene rs2053044 polymorphism was presented in Fig. 2.

Genotype frequency comparison between groups for COMT and ADRB2 genes was presented in Table 2. When the articular TMD group was compared with the control group in terms of *COMT* gene rs9332377 polymorphism, a significant difference was observed in terms of genotype frequencies ($p < 0.05$). The TT genotype (homozygous mutant) and CT genotype (heterozygous mutant) were significantly higher in the articular TMD group than in the control group ($p = 0.034$, and $p = 0.045$, respectively). On the other hand, the CC genotype (homozygous wild) was significantly lower in articular TMD groups than in the control group ($p = 0.020$). Regarding the *ADRB2*, the GG genotype (homozygous mutant) was significantly higher in the articular TMD group than in the control group ($p = 0.048$).

Allele frequency comparison between groups for COMT and ADRB2 genes was presented in Table 3. The T allele in the *COMT* (rs rs9332377) gene was found to be significantly higher in the articular TMD group than in the control group ($p = 0.000$). When gene allele frequencies for *ADRB2* rs2053044 were compared, a significant difference was not observed between the groups.

4. Discussion

Over the past decade, worldwide genetic studies have shown that genetic background strongly contributes to the etiology of TMD in the development of TMD (Melis & Di Giosia, 2016; Michelotti et al., 2014; Mladenovic et al., 2016; Slade et al., 2015; Smith et al., 2011). The development of chronic pain in patients with TMD, as well as its frequent association with other diseases such as musculoskeletal pain states, suggests the effect of genetic changes on the nociceptive process. Chronic and persistent pain states in TMD are associated with

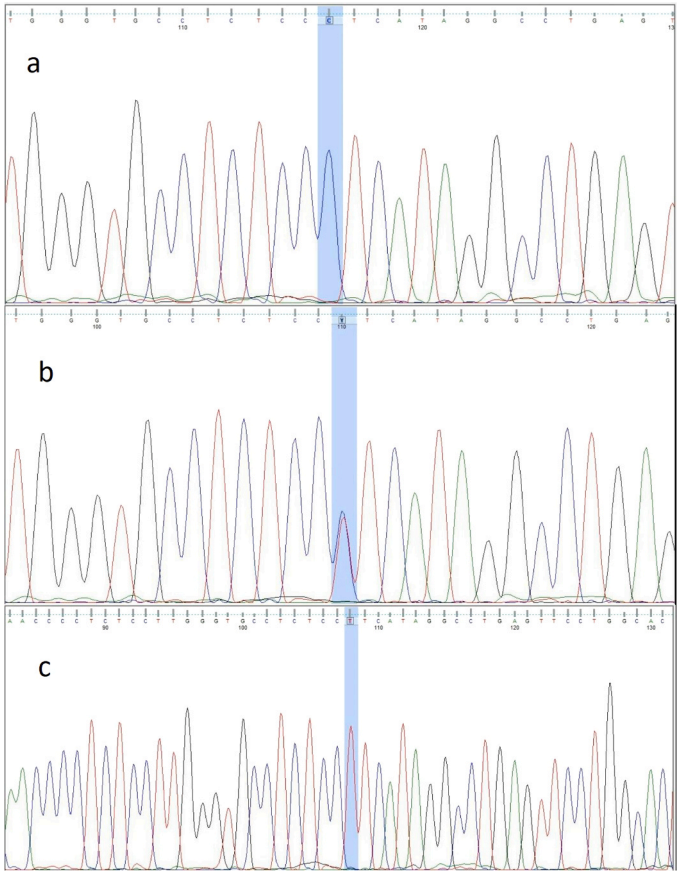

Fig. 1. a.Example CC genotype sequence curve of the COMT gene rs rs9332377; b. Example CT genotype sequence curve of the COMT gene rs rs9332377; c. Example TT genotype sequence curve of the COMT gene rs rs9332377.

catecholamine physiology and COMT enzyme (Nackley et al., 2007). Polymorphisms in the *COMT* and *ADRB2* genes greatly affect orofacial pain sensitivity (Diatchenko et al., 2005). This study evaluated the possible association of the *COMT* and *ADRB2* genes with TMDs and compared patients with muscular and articular TMD with asymptomatic controls. The observed results showed that polymorphisms in the *COMT* and *ADRB2* genes are associated with articularTMD.

COMT is an enzyme that breaks down catecholamines, including epinephrine, norepinephrine, and dopamine. Thus, it represents a critical protein that contributes to a variety of biological functions, including pain perception, mood, cognition, and responses to physical and emotional stress (Belfer et al., 2013). In this study, regarding the COMT gene rs9332377 polymorphism, significant differences were observed between the articular TMD and the control group in terms of both genotype and allele frequencies. According to the results of the research, it was revealed that the CC genotype had a protective effect against articular TMD, while the CT and TT genotypes increased the risk of articular TMD. Particularly, those with the TT genotype were more

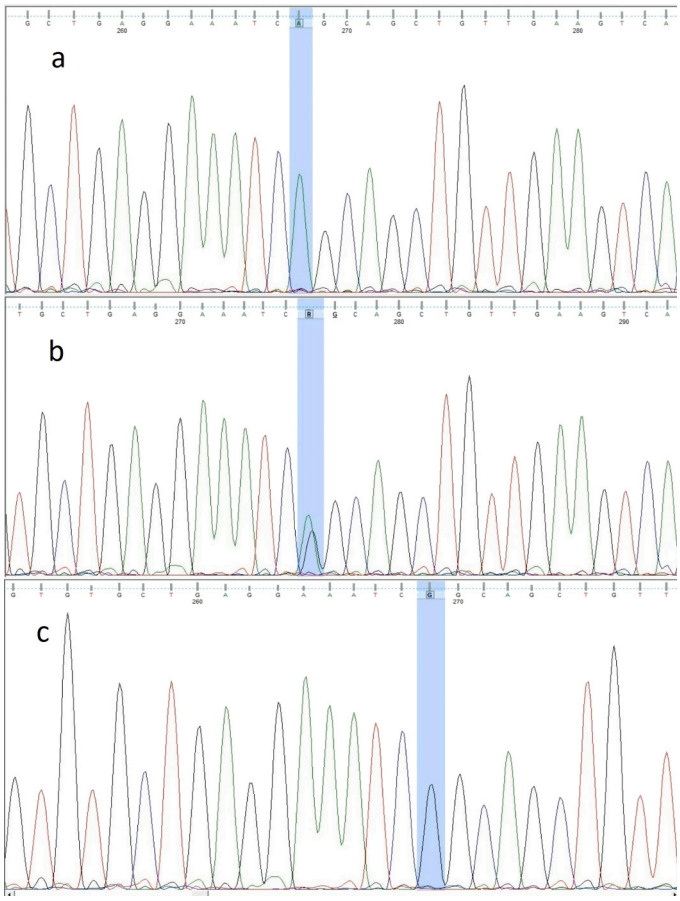

Fig. 2. a. Example AA genotype sequence curve of the ADRB2 gene rs2053044; b.Example AG genotype sequence curve of the ADRB2 gene rs2053044; c. Example GG genotype sequence curve of the ADRB2 gene rs2053044.

prone to articular TMD than those with the CT genotype (OR: 8.59; and OR: 2.15 respectively). This was associated with the risk allele (T allele) being significantly higher, especially in the articular TMD group ($P < 0.000$). These results support previous studies revealing the relationship between the *COMT* gene and TMD. The *COMT* gene rs9332377 polymorphism has been associated with an increased risk of developing chronic pain in a cohort of Australian adolescents followed over a 17-years. According to the authors, modifications in the gene may alter the regulation of adrenergic receptors, resulting in increased sensitivity to pain (Skouen et al., 2012).

A meta-analysis study analyzing the TMD association with the *COMT* gene, published in 2021, showed that two genetic polymorphisms in *COMT* (rs6269 and rs9332377) were significantly associated with TMD. Both polymorphisms were associated with myofascial pain. Rs9332377 was also associated with painful TMD (Brancher et al., 2021). In a study conducted in a Brazilian population, three regions of the *COMT* gene were analyzed (rs165774, rs6269, and rs9332377) and a statistically significant difference emerged between the study groups only for the rs9332377 region. In this study, the presence of the TT genotype was associated with a diagnosis of muscular TMD compared with individuals without this disorder (de Souza Tesch et al., 2020). In this study conducted in the Turkish population, unlike the study conducted in the Brazilian population, the joint TMD group instead of muscular TMD was associated with the presence of the polymorphic TT genotype. These results suggest that the TT genotype may be associated with different TMD subgroups in different populations.

Studies have shown that increased T allele in the *COMT* gene may be associated with TMD risk. In this study, two T alleles (CT and TT) were found to be significantly higher in the articular TMD subgroup than in the control group. These results are in agreement with the results of previous studies in the literature. In a previous study, the presence of one or two C alleles (CC or CT) for the COMT gene rs9332377 was associated with a greater than 50% reduction in the risk of belonging to the group of women who experience high levels of fatigue after cancer surgery (de Souza Tesch et al., 2020). Thus, the T allele appears to be associated with pain, while the C allele appears to be associated with protection against pain. This result indicates that the presence of the T allele for the *COMT* gene rs9332377 poses a risk for TMD, while the C allele may be associated with protection against TMD.

Changes in the *ADRB2* gene may alter the pain sensitivity of individuals, associated with symptoms of somatization, depression, anxiety, and low blood pressure, which are phenotypic features commonly found in individuals with extensive chronic pain, including TMD (Diatchenko et al., 2006). This occurs either by influencing the level of receptor expression or by determining the response to the stimulation agonist, thus directly related to catecholamines and indirectly to the COMT enzyme (Light et al., 2009). Therefore, the risk of phenotypic changes resulting from polymorphisms in the *ADRB2* gene is believed to be significantly higher than other risk factors such as fluctuations in estrogen levels, history of chronic pain, and even genetic variations in *COMT* (Diatchenko et al., 2005). In a previous study, a significant association was observed between *COMT* and *ADRB2* genes in groups with myofascial pain (Smith et al., 2011). These findings support previous

Table 2
Distribution of genotypes of the *COMT* and *ADRB2* genes.

					P-value (OR (95% CI)			
Gene /rs	Genotype	Control (n = 68) n (%)	Muscular TMD (n = 36) n (%)	Articular TMD (n = 44) n (%)	Control vs Muscular P value OR (95% CI)		Control vs Articular P value OR (95% CI)	
COMT (rs9332377)	CC	49 (72.1)	27 (75)	19 (43.2)	0.469	1.16 (0.46–2.92)	0.020 *	0.39 (0.17–0.89)
	CT	18 (26.5)	9 (25)	20 (45.5)	0.349	0.74 (0.29–1.90)	0.045 *	2.15 (0.97–4.76)
	TT	1 (1.5)	0 (0)	5 (11.4)	0.654	1.02 (0.99–1.05)	0.034 *	8.59 (0.97–76.2)
ADRB2 (rs2053044)	AA	7 (10.3)	1 (2.8)	2 (4.5)	0.115	0.21 (0.03–1.78)	0.303	0.55 (0.14–2.19)
	AG	33 (48.5)	19 (52.8)	16 (36.4)	0.418	1.18 (0.53–2.66)	0.142	0.61 (0.28–1.31)
	GG	28 (41.2)	16 (44.4)	26 (59.1)	0.454	1.14 (0.50–2.58)	0.048 *	2.06 (0.95–4.46)

COMT: Catechol-O-methyltransferase; *ADRB2*: β2-adrenergic receptor; TMD: Temporomandibular disorder
OR: Odds ratio; CI: Confidence Intervals; n: Number, * : $P < 0.05$;

Table 3
Distribution of alleles of the *COMT* and *ADRB2* genes.

Gene /rs	Allele	Control (n = 68) n (%)	Muscular TMD (n = 36) n (%)	Articular TMD (n = 44) n (%)	P-value (OR (95% CI) Control vs Muscular P value	Control vs Muscular OR (95% CI)	Control vs Articular P value	Control vs Articular OR (95% CI)
COMT (rs9332377)	C	116 (85.3)	63 (87.5)	58 (65.9)	0.662	0.83	0.000 *	3
	T	20 (14.7)	9 (12.5)	30 (34.1)		(0.36–1,93)		(1.57–5.73)
ADRB2 (rs2053044)	A	47 (34.6)	21 (29.2)	20 (22,73)	0.431	1.28	0.059	1.79
	G	89 (65.4)	51 (70.8)	68 (77.27)		(0.69–2.38)		(0.97–3.3)

COMT: Catechol-O-methyltransferase; *ADRB2*: β2-adrenergic receptor; TMD: Temporomandibular disorder
OR: Odds ratio; CI: Confidence Intervals; n: Number, * : $P < 0.05$.

studies that have observed that the muscle pattern of these disorders is often associated with central nervous system sensitization and hyperalgesia (Younger et al., 2010). In the current study, the *ADRB2* gene rs2053044 polymorphism was analyzed and it was observed that the GG genotype was higher in the articular TMD subgroup than in the control group. In a study conducted in Brazil, *COMT* and *ADRB2* gene polymorphisms were investigated among TMD subgroups, and no significant difference was observed between sub-groups of TMD and the control group in terms of *ADRB2* (rs2053044) polymorphism (de Souza Tesch et al., 2020). In another study conducted in Brazil investigating the relationship between *COMT, ADRB2,* and *HTR1A* genes and TMD and other arthralgias, no relationship was found between *ADRB2* (rs2053044) polymorphism and TMD. In the *ADRB2* rs1042713, the AA genotype was found to be statistically associated with the absence of myofascial pain. In addition, genotype CG and polymorphic genotype CG + GG were statistically highly correlated with subjects with TMD and no other arthralgia (Bonato et al., 2021). These findings are similar to the height of the GG genotype in the articular TMD group in our study. This result showed that the GG phenotype may increase the risk of TMD by causing an increase in pain sensitivity.

COMT is a combination of an enzyme responsible for metabolizing catecholamine derivatives and promoting the inactivation of acetylcholine (Nackley et al., 2007). The promoter region of the *COMT* gene can play a regulatory role in the *COMT* gene and may predispose to pain-related diseases by affecting processes such as the number of SNPs, DNA transcription, RNA splicing, mRNA stability, and mRNA transport and translation (Nackley et al., 2006). This enzyme is a strong candidate for studying the etiology of many painful conditions, including many psychological and physiological painful conditions and modulation of pain (Lachman et al., 1996). In a recent study investigating the association between polymorphisms in the *COMT* and *HTR2A* genes and temporomandibular disorder and anxiety in adolescents, both genes were associated with TMD symptoms, regardless of gender or anxiety (Brancher et al., 2019b). Polymorphisms in the COMT gene may reduce the functions of the enzyme, resulting in elevated catecholamine levels that stimulate beta-adrenergic receptors responsible for pain sensation (Nackley et al., 2007). The fact that both the COMT gene and ADRB2 gene polymorphisms examined in this study were observed in the articular TMD group suggests that there may be a possible relationship between both polymorphisms. These results support previous study findings indicating that changes in the *COMT* gene may also increase pain sensitivity by affecting ADRB2 receptors. Knowing the genetic characteristics of a patient with chronic pain can assist the specialist concerning the patient's prognosis and thus influence the overall therapeutic approach. The use of ADRB2 blockers is effective in improving pain symptoms in individuals with genetic haplotypes that cause higher pain sensitivity. In a study using the non-selective β-adrenergic antagonist Propranolol, heterozygous patients with the COMT haplotype showed a reduction in pain, while no benefit was reported in homozygous patients. Therefore, *COMT* haplotypes may serve as genetic determinants of β-adrenergic antagonist therapy outcomes and identify a subset of TMD patients who would benefit from such therapy (Tchivileva et al., 2010).

This study has some limitations: 1) The fact that the study had a small sample size is a limitation that should be considered when interpreting and generalizing the findings. These study findings need to be confirmed with larger sample sizes and studies to be conducted in different populations. 2) Since temporomandibular joint disorders are predominantly seen in women, the fact that the majority of the participants are women should be taken into account when interpreting the results. In the study, the results were not adjusted by taking the "gender" factor into account. When divided by gender, the sample would become smaller and this could lead to random results. For this reason, it is suggested that new studies be done comparing genetic analysis between men and women. 3) To elucidate the pathophysiological mechanism of TMD, other types of genetic studies, such as specific miRNA analysis, gene expression, and tissue protein quantification, should be performed in patients undergoing TMJ surgery. Despite these limitations, this study is the first to investigate COMT and ADRB2 gene polymorphisms in the Turkish population and is relevant for pioneering the study of the genetic basis of individuals with TMD.

According to the results of the present study,; polymorphisms in the COMT (rs93323779 and ADRB2 (rs20530449) genes were significantly associated with artıcular TMD. It was observed that the CT and TT genotypes in the COMT gene rs9332377 polymorphism were associated with susceptibility to articular TMD, and the CC genotype was associated with protection against TMD. Similarly, it was observed that the GG genotype in the ADRB2 gene rs2053044 polymorphism may increase the risk of articular TMD. These results support previous studies showing the association of *COMT* and *ADRB2* gene polymorphism with TMD. *COMT* gene polymorphisms may be associated with TMD pain through their effects on peripheral and central neuronal pain thresholds and ADRB2 receptors. These data suggest that genetic variability in the *COMT* and *ADRB2* genes may play a role as a risk factor for the onset of temporomandibular pain. More cross-sectional, cohort, and case-control studies in different populations are needed to elucidate the relationship of catecholamine and its receptor gene polymorphisms with TMD and possibly their effects on pain processing mechanisms.

Ethical statement

This study was approved by Afyonkarahisar Health Sciences University, Clinical Research Ethics Committee (decision dated 03.09.2021 and numbered 10–454), and the Helsinki Declaration guidelines were followed in the study. Each volunteer to be included in the study was informed about the study protocol and an informed consent form was

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CRediT authorship contribution statement

Ömer Ekici: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing, Visualization, Supervision, Project administration, Funding acquisition. **Evrim Suna Arıkan Söylemez:** Methodology, Validation,Software, Formal analysis, Data curation, Writing – review & editing, Visualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This study was supported by Afyonkarahisar Health Sciences University Scientific Research Projects Commission under grant number (21. GENEL. 025).

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