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Effect of a functional variant of tumor necrosis factor- β gene in temporomandibular disorders: A pilot study

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Abstract

Background: Temporomandibular disorders (TMD) are a group of conditions that cause chronic orofacial pain. The tumor necrosis factor β (TNF- β) is a proinflammatory cytokine that is involved in the various aspects of the inflammatory process including organization and maintenance, and in the arrangement of cells at the inflammation site. The purpose of this study was to evaluate the correlation between TNF- β +252A/G (rs909253) variant and susceptibility to TMD in a Turkish cohort.

Methods: The study included 104 patients (26 males, 78 females) with TMD and 126 healthy controls (44 males, 82 females). The TNF- β +252A/G variant analysis was based on Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP).

Results: There was no deviation from HWE for TNF- β +252A/G variant in patient and control groups. There was significant difference in genotype and allele frequencies between patient group and control group in terms of TNF- β +252A/G variant, respectively ($P = 0.010, 0.015$). A significant increase in the TNF- β +252 AG genotype and G allele frequencies were observed in TMD patients compared to healthy controls. The individuals with GG genotype and G allele had an increased risk of developing TMD. A statistically significant association was observed when the patients were compared with the controls according to AA genotype vs AG+GG genotypes ($P = 0.002$, OR: 2.23, 95% CI:1.31-3.82). TNF- β +252A/G genotype distribution was associated with chewing problems ($P = 0.046$).

Conclusions: In conclusion, our results provided evidence that TNF- β +252A/G variant may contribute to TMD development in a Turkish cohort. Further studies are needed to confirm this observation.

KEYWORDS

+252A/G, temporomandibular disorders, tumor necrosis factor β , variant

1 | INTRODUCTION

The temporomandibular joint (TMJ) is among the most complex and active joints in the human body and takes a crucial part in essential functions such as speaking, chewing, and swallowing.¹ The temporomandibular joint disorders (TMD) comprises set of musculoskeletal

and neuromuscular diseases that involve the TMJs, the masticatory muscles, and all adjacent tissues. The prevalence of TMD is estimated to be higher than 5% of the general population. The pathophysiological mechanism of the TMD is not clearly known, however the literature data suggest that the etiology of TMD involves inflammation, micro/macrotrauma, parafunctional habits, bruxism, and

stress.² The degenerative changes occurring in the TMJ are linked with osteoclastogenesis,³ however the molecular process associated with these changes remain unclear. It has been demonstrated that monocyte-macrophage derived cytokines levels are elevated in the synovial fluid of cases with TMD.⁴ Studies reported that cytokines including interleukin [IL]-1beta [β], IL-6 may induce the release of proteinases and facilitate the expression of degrading enzymes and inflammatory mediators, leading to TMJ inflammation and bone and cartilage breakdown.³ The tumor necrosis factor (TNF) is identified as a multifunctional pro-inflammatory cytokine that plays a role in various physiological processes as well as in pathological processes, such as inflammation, immunoregulation, proliferation, and apoptosis. The genes for TNF- α (OMIM 191160) and TNF- β (LT- α , MIM 153440), located within the major histocompatibility complex III region of chromosome 6, are closely linked with the genes for human leukocyte antigen (HLA) classes I (HLA-B) and II (HLA-DR).⁵ TNF- β promotes cell apoptosis and inflammatory responses as it binds to TNF receptor type 1 and 2, respectively. TNF- β is produced by lymphocytes and it resembles TNF- α structurally.⁵ These 2 substances bear 30% amino acid sequence similarity, have the same widely distributed corresponding cellular receptors and, thus share many of their functions.⁵ The presence of functional single nucleotide polymorphisms (SNPs) within these genes, modulate their expression, for example -308 G/A SNP in the TNF- α and +252 A/G SNP in the TNF- β gene. In a recent study, chance of having the TNF- α -308 GA genotype was 2.87 fold higher in subjects with TMD compared to the control group.⁶ SNP at position +252 within the first intron of TNF- β (transition guanine to adenine) (rs909253) that influences expression of both genes and plasma levels of TNF- α and TNF- β proteins.⁷ The presence of G at this position determines the mutant allele which is less frequent allele and is associated with higher TNF- α and TNF- β production.⁸ Changes in expression associated with polymorphic alleles of the TNF- β gene have been suggested in the pathogenic role of this cytokine in several chronic inflammatory and autoimmune disorders. Owing to relationship TMD and inflammation, we evaluated the association of TNF- β +252A/G variant with the risk to TMD in Turkish population.

2 | MATERIALS AND METHODS

2.1 | Subjects

Temporomandibular disorders patients and healthy controls were recruited from the Department of Oral and Maxillofacial Surgery at the Dental Faculty at Gaziosmanpasa University, Tokat, Turkey. A total of 104 unrelated patients (26 males, 78 females; mean age \pm SD years 34.78 \pm 13.110) with a clinical diagnosis of TMD and 126 ethnically matched healthy controls (44 males, 82 females; mean age \pm SD years 36.52 \pm 10.903) were genotyped for the TNF- β +252A/G variant. All individuals, patients and healthy controls, were of Turkish origin, from the central region of Turkey. The healthy controls matched for age and gender with TMD patients

TABLE 1 The demographical characteristics of TMD patients and healthy controls

	Patients (n = 104)	Controls (n = 126)	P
Age, mean \pm SD (y)	34.78 \pm 13.110	36.52 \pm 10.903	0.272
Gender, n (%)			
Male	26 (25.0)	44 (34.9)	0.104
Female	78 (75.0)	82 (65.1)	

SD, standard deviation.

Data were analyzed by analysis of variance and χ^2 test.

(Table 1) ($P > 0.05$). TMD was diagnosed based on the criteria described by Schiffman et al.⁹ TMD patients with any other autoimmune/inflammatory disease were excluded from the study. A detailed medical history was taken, followed by a complete oral examination. The subjects were interviewed using a standard questionnaire including demographics, duration of disease, family history, history of systemic disease, bruxism, chewing problems, sound in TMJ, TMJ blocking, pain severity, and clinical characteristics of pain. Pain intensity in patients was measured using the numeric pain rating scale (NPRS).¹⁻¹⁰ A "numeric pain" score ranging from 0 (no pain) to 10 (maximum pain) was constructed. The protocol of this study was approved by the Institutional Ethics Committee, and all individuals gave written informed consent before entering the study.

2.2 | Genotyping

Blood samples were collected in ethylene diamine tetra-acetic acid (EDTA)-coated tubes from the patients with TMD and control subjects. Genomic DNA was isolated using commercial kit according to manufacturer protocol, and stored at -20°C until use. The TNF- β +252A/G variant was analyzed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) assays. The segment was replicated using the following forward and reverse PCR primers: 5'-CCG TGC TTC GTG GTT TGG ACT-3' and 5'-AGA GGG GTG GAT GCT TGG GTT C-3', respectively. Then, the 782 bp PCR products were cut with NcoI restriction endonuclease at 37°C overnight. The RFLP products were loaded on 3% agarose gels, stained with the ethidium bromide and monitored on an ultraviolet transilluminator. While the product form A allele remained uncut, 2 fragments (586 and 196 bp) were observed for G allele.

2.3 | Statistical analysis

Analyses of data were performed using the Statistical Package Program for the Social Sciences (SPSS, version 20.0, Chicago, IL, USA) and the OpenEpi Info software package version 2.3.1. Continuous data were given as mean \pm standard deviation (SD). Allele and genotype frequencies of patients and controls were compared with chi-square (χ^2) test. Odds ratio (OR) and 95% confidence interval (CI) were used for the assessment of risk factors.

TABLE 2 Genotype and allele frequencies of TNF- β +252A/G variant in groups

TNF- β +252A/G	Patients n = 104 (%)	Controls n = 126 (%)	P	OR (CI 95%)
Genotypes				
AA	42 (40.4)	76 (60.3)	0.010	
AG	54 (51.9)	42 (33.3)		
GG	8 (7.7)	8 (6.3)		
AG: AA	54:42	42:76	0.002	2.31 (1.33-4.05)
GG: AA	8:42	8:76	0.396	1.80 (0.61-5.32)
AG+GG: AA	62 (59.6) : 42 (40.4)	50 (39.7):76 (60.3)	0.002	2.23 (1.31-3.82)
AA+AG: GG	96 (92.3) : 8 (7.7)	118 (93.7):8 (6.3)	0.697	1.23 (1.32-3.51)
Alleles				
A	138 (66.3)	194 (77.0)	0.015	0.59 (0.39-0.89)
G	70 (33.7)	58 (23.0)		1.69 (1.12-2.55)

Data were analyzed by χ^2 test. The results that are statistically significant are shown in boldface.

TABLE 3 Clinical and demographical characteristics of patients and controls according to TNF- β +252A/G variant genotypes

Characteristics	Total (n = 104)	AA (n = 42)	AG (n = 54)	GG (n = 8)	P
Age, mean \pm SD (y)	34.78 \pm 13.110	37.62 \pm 13.363	31.07 \pm 11.243	44.88 \pm 16.462	0.003
Gender, n (%)					
Male	26 (25.0)	9 (21.4)	13 (24.1)	4 (50.0)	0.226
Female	78 (75.0)	33 (78.6)	41 (75.9)	4 (50.0)	
Duration of disease, n (%)					
<1 y	26 (25.0)	6 (14.3)	18 (33.3)	4 (50.0)	0.112
1-5 y	38 (36.5)	18 (42.9)	19 (35.2)	1 (12.5)	
> 5 y	38 (36.5)	18 (42.9)	17 (31.5)	3 (37.5)	
Family history of TMD, n (%)					
Yes	52 (50.0)	20 (47.6)	27 (50.0)	5 (62.5)	0.743
No	52 (50.0)	22 (52.4)	27 (50.0)	3 (37.5)	
History of systemic disease, n (%)					
Yes	38 (36.5)	15 (35.7)	18 (33.3)	5 (62.5)	0.276
No	66 (63.5)	27 (64.3)	36 (66.7)	3 (37.5)	
Bruxism, n (%)					
Yes	58 (55.8)	24 (57.1)	30 (55.6)	4 (50.0)	0.932
No	46 (44.2)	18 (42.9)	24 (44.4)	4 (50.0)	
Chewing disorder, n (%)					
Yes	35 (33.7)	20 (47.6)	13 (24.1)	2 (25.0)	0.046
No	69 (66.3)	22 (52.4)	41 (75.9)	6 (75.0)	
Sound in TMJ (jaw joint clicking or popping), n (%)					
Yes	77 (74.0)	33 (78.6)	39 (72.2)	5 (62.5)	0.578
No	27 (26.0)	9 (21.4)	15 (27.8)	3 (37.5)	
TMJ locking (open or closed), n (%)					
Yes	8 (7.7)	3 (7.1)	5 (9.3)	0	0.647
No	96 (92.3)	39 (92.9)	49 (90.7)	8 (100)	

SD, standard deviation; TMD, Temporomandibular disorders; TMJ, Temporomandibular joint.

Data were analyzed by analysis of variance and χ^2 test. Mean plus standard deviation values are presented for age. The results that are statistically significant are shown in boldface.

All *P* values were 2-tailed and *P* values < 0.05 were considered as significant. The Hardy-Weinberg Equilibrium (HWE) was evaluated by χ^2 test.

3 | RESULTS

The demographical characteristics of the patients with TMD and controls are presented in Table 1. Age and gender distributions were not different between patient and control groups (*P* > 0.05).

The genotype distribution and allele frequencies of TNF- β +252A/G variant in patients and control groups are presented in Table 2. The genotype distribution of TNF- β +252A/G variant showed statistically significant difference between patients and controls, (*P* = 0.010). The patients had apparently higher frequencies in genotype AG of TNF- β +252 variant compared with the control group. There was statistically significant difference in the allele frequency of the TNF- β +252A/G variant between

patients with TMD and the controls (*P* = 0.015, OR: 0.59, 95% CI: 0.39-0.89).

The individuals with TNF- β +252A/G G allele had an increased risk of developing TMD. Also, a more statistically significant association was observed when the patients were compared with the controls according to AA genotype vs AG+GG genotypes (*P* = 0.002, OR: 2.23, 95% CI: 1.31-3.82). There was no deviation from HWE for TNF- β +252A/G variant in both patient and control groups. Furthermore, we also analyzed if any differences existed in clinical and demographical characteristics of patients according to genotype distribution. There was statistically significant difference between TNF- β +252A/G genotype distribution and chewing problems (*P* = 0.046) (Table 3). The homozygous AA genotype frequency was higher in patients with chewing problems.

Table 4 shows the clinical characteristics of pain of TMD patients stratified according to TNF- β +252A/G variant. Twelve patients who had no pain were not evaluated. No correlation was not observed between genotype distribution of TNF- β +252A/G variant and clinical

TABLE 4 Clinical characteristics of pain of TMD patients stratified according to TNF- β +252A/G variant

Characteristics	Total (n = 92)	AA (n = 38)	AG (n = 47)	GG (n = 7)	<i>P</i>
The severity of pain [The Numeric Pain Rating Scale (1-10)], mean \pm SD	3.96 \pm 1.983	4.24 \pm 2.136	3.64 \pm 1.870	4.57 \pm 1.718	0.269
Pain during sleep, n (%)					
Yes	51 (55.4)	21 (55.3)	26 (55.3)	4 (57.1)	0.996
No	41 (44.6)	17 (44.7)	21 (44.7)	3 (42.9)	
Pain during chewing and speaking, n (%)					
Yes	58 (63.0)	23 (60.5)	31 (66.0)	4 (57.1)	0.827
No	34 (37.0)	15 (39.5)	16 (34.0)	3 (42.9)	
The localization of pain, n (%)					
Muscle	11 (12.0)	6 (15.8)	3 (6.4)	2 (28.6)	0.290
Joint	69 (75.0)	29 (76.3)	36 (76.6)	4 (57.1)	
Muscle and joint	12 (13.0)	3 (7.9)	8 (17.0)	1 (14.3)	
Period of pain, n (%)					
Chronic	28 (30.4)	15 (39.5)	10 (21.3)	3 (42.9)	0.147
At regular intervals	64 (69.6)	23 (60.5)	37 (78.7)	4 (57.1)	
Factors that trigger pain					
Movement	55 (59.8)	21 (55.3)	30 (63.8)	4 (57.1)	0.845
Cold	17 (18.5)	7 (18.4)	8 (17.0)	2 (28.6)	
Movement and cold	20 (21.7)	10 (26.3)	9 (19.1)	1 (14.3)	
Types of pain					
Blunt	45 (48.9)	19 (50.0)	23 (48.9)	3 (42.9)	0.566
Sharp	44 (47.8)	18 (47.4)	23 (48.9)	3 (42.9)	
Pulse type	3 (3.3)	1 (2.6)	2 (2.1)	1 (14.3)	
The duration of pain					
<1 h	40 (43.5)	17 (44.7)	20 (42.6)	3 (42.9)	0.468
\geq 1 h	41 (44.6)	14 (36.8)	24 (51.1)	3 (42.9)	
Constant	11 (12.0)	7 (18.4)	3 (6.4)	1 (14.3)	

SD, standard deviation; TMD, Temporomandibular disorders.

Data were analyzed by analysis of variance and χ^2 test. Mean plus standard deviation values are presented for the severity of pain.

parameters of pain such as pain severity, pain during sleep, chewing or speaking, pain localization, pain period, factors that trigger pain, pain type and pain duration.

4 | DISCUSSION

Temporomandibular disorders are characterized by pain in the masticatory muscles, in the TMJ, and in the adjacent hard and soft tissues. Approximately 80% of the patients with TMD present with signs and symptoms related to joint disease, such as disk displacement, arthralgia, osteoarthritis, and osteoarthritis, implying that a comprehension of the underlying pathobiology of diseases of the TMJ would be helpful to most of the patients with TMD. The pathophysiology of TMJ pain and dysfunction is not clearly established.

Balance between the synthesis and the destruction of various types of extracellular matrix collagens and aggrecan is impaired and this constitutes a characteristic of degenerative changes in TMJ. It has been shown that these events are related to the inflammatory process of TMJ since high levels of inflammatory modulators, including cytokines, nitric oxide, and cartilage matrix catabolites, and of proteinases including matrix metalloproteinases (MMPs), were seen in the synovial fluid.^{10,11} There are many studies in which MMPs polymorphisms are investigated in TMD cases. Planello et al¹² reported that there is a significant relationship between MMP1 2G/2G genotype and TMJ degeneration. Milosevic et al¹³ found that the subjects carrying MMP-9 gene C-1562T variant T allele had an approximately two-fold increased risk for TMD. Also, it was suggested that the -1607 1G/2G polymorphism of MMP-1 promoter was related to TMJ osteoarthritis.¹⁴ Pro-inflammatory cytokines are essential immune mediators that offer protection to the host, and the production of specific endogenous inhibitors, including soluble receptors or receptor antagonists, act as a mechanism to counterbalance the proinflammatory effects of the cytokines. Indeed, disease is believed to result when a cytokine imbalance occurs, either from persistent local elevation of pro-inflammatory cytokines or from deficient activity of natural anti-inflammatory mechanisms, resulting in tissue destruction.¹⁵

The degenerative changes in the TMJ are characterized by an imbalance in the synthesis and degradation of matrices, which are mediated by chondrocytes and fibrochondrocytes in the cartilage and fibrocartilage tissues of the TMJ, causing a progressive loss of cellular matrix components of the articular cartilage and/or subchondral bone. Cytokines can lead to cartilage degradation by upregulation of metalloproteinases gene expression, and blunting chondrocyte compensatory synthesis pathways. Although methodology differs, all articles reported that levels of pro-inflammatory cytokines were significantly higher in synovial fluid of TMD patients compared to in healthy control subjects.^{16,17} This finding suggests a proactive role of these cytokines in the pathogenesis of TMD and TMJ behaves similar to other synovial joints that are affected by osteoarthritis (OA) or rheumatoid arthritis (RA). It was found that cytokines like

interleukin-1 beta (IL-1 β), IL-6 and TNF- α may induce the release of proteinases and promote the expression of degrading enzymes and inflammatory mediators, ensuing TMJ inflammation and bone and cartilage degradation.^{3,4,18,19} In patients with chronic connective tissue disease involving-TMJ, TNF- α levels in TMJ synovial fluid were significantly elevated compared to plasma levels, suggesting the significant role of local cytokine production.²⁰

TNF- β is a cytokine that plays multiple roles in inflammatory and immunomodulatory processes. TNF- β is abundant in bone tissue and has been implicated as an important regulator of both bone formation and resorption which can stimulate osteoblastic proliferation and differentiation, as well as hinder mature osteoclasts and proliferation of mononuclear osteoclast precursors in vitro.²¹ Previous studies have demonstrated that TNF- β levels are increased in the serum and synovial tissue of RA and OA patients.^{22,23} A recent report showed that TNF- β promotes proliferation and inflammatory cascade signaling in fibroblastlike synovities, which constitutes a trigger and onset point of RA.²⁴ Even at low levels, TNF- β is more likely to increase the secretion of IL-6, IL-8, and MMP3 compared to TNF- α .²⁵

TNF- β gene +252A/G variant within the first intron is also named as NcoI polymorphism and affects a phorbol ester-responsive element. Studies have demonstrated that this variant is particularly appealing since variations in the region responsible for transcriptional regulation may have implications for the TNF- α gene expression and variability on TNF- α synthesis.⁸ The interindividual variations in the capacity for producing TNF- α may be associated with the differences in the transcription rate, the regulation of messenger RNA stability, translocation efficiency, or processing of the mature proteins. The common allele A is related with enhanced TNF- α gene expression, because it is located within a phorbol ester-responsive DNA element with high affinity for the Activator protein 1(AP-1), c-jun and c-fos heterodimer transcription factor family.⁷ It was reported that TNF- β +252A/G variant is associated with various autoimmune disease including systemic lupus erythematosus,²⁶ Graves' disease,²⁷ systemic sclerosis,²⁸ and myasthenia gravis.²⁹ In addition, it was also reported that the TNF- β +252A/G G allele and GG genotype were correlated with breast cancer.^{30,31} Also, it was shown that GG genotype of TNF- β +252A/G variant was more common in RA patients compared to the controls.^{32,33} It was reported that there were significant differences in the percentages of alleles for TNF- β +252A/G between OA patients and the controls while there was not any significant difference in the genotypic distribution of TNF- β +252A/G variant.³⁴ However, TNF- β +252 variant showed no significant difference in patients with ankylosing spondylitis compared to the controls.

In present study, we investigated whether TNF- β +252A/G variant is associated with TMD susceptibility in a Turkish population sample. In our study, TNF- β +252A/G variant AG genotype was significantly higher in patients (heterozygous advantage) compared to controls while AA genotype was significantly over-represented in controls compared to the patients ($P = 0.010$) (Table 2). A more statistically significant association was observed when the patients

were compared with the controls according to AA genotype vs AG+GG genotypes (OR:2.23, 95% CI: 1.31-3.82; $P = 0.002$). There was a significant difference in the allele frequency of the +252 site of the TNF- β gene between TMD patients and controls ($P = 0.012$) (Table 2). G allele, associated with a higher production of TNF- α and TNF- β , was found to be linked with a higher risk in development of TMD. Meanwhile, G allele of TNF- β +252A/G variant was associated with the increased risk of TMD. There was no deviation from HWE for TNF- β +252A/G variant in both patient and control groups. In addition, it was found that TNF- β +252A/G variant is associated with chewing problems ($P = 0.046$) (Table 3). However, the presence of TNF- β +252A/G variation had no influence on the other clinical findings.

5 | CONCLUSION

The report clearly showed that the TNF- β +252A/G variant are significantly associated with the susceptibility to TMD in Turks. Immune hypotheses of TMD suits very well with the findings of this study performed on the TNF- β variant. This cytokine may contribute to the pathogenesis of synovitis and degenerative changes of cartilage and bone of the TMJ. This is an important issue in the context of pathogenesis of inflammatory diseases. These results provide a valuable reference for inflammatory diseases and future disease association studies. However, further studies involving other ethnic populations are required to confirm association of this variant with susceptibility of TMD.

AUTHOR'S CONTRIBUTIONS

Concept—S.Y., A.T., A.F.N.; Design—S.Y., K.Y., M.K.T.; Supervision—S.Y.; Materials—K.Y. M.K.T.; Data Collection and/or Processing—K.Y., M.K.T., S.Y.; Analysis and/or Interpretation—S.Y.; Literature Search—K.Y., A.F.N., A.T., N.K., M.K.T., S.Y.; Writing—A.T., A.F.N.; Statistics—A.T., N.K.; Critical Reviews—A.T., A.F.N., S.Y.

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