Original Article

Investigation of *MMP1* rs1799750 and *TGF-ß1* rs1800470 polymorphisms in individuals with different vertical facial patterns and temporomandibular joint disorder

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ABSTRACT

Objectives: To evaluate the effects of rs1799750 1G/2G polymorphism of the *MMP1* gene and rs1800470 T/C polymorphism of the *TGF-ß1* gene on temporomandibular disk displacement and vertical facial development.

Materials and Methods: Sixty-six individuals were examined radiographically prior to evaluation of the signs/symptoms of temporomandibular disorders according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). Class II, hyperdivergent individuals with TMD (+) were assigned to Group 1, and individuals with TMD (−) were included in Group 2; while Class I, normodivergent individuals with TMD (−) were included in Group 3. For genetic analysis, oral mucosa swab samples were collected, and genotype analysis was performed.

Results: The incidence of 2G alleles in Group 2 (72.7%) was significantly higher than the other groups ($P < .05$). ANB angle and mean Wits of the 1G/1G genotype of the *MMP1* gene were significantly lower than 1G/2G and 2G/2G. Mean Go-Gn of the 1G/1G genotype was significantly higher than that of 1G/2G. The mean SNB of the *TGF-β1* TT genotype was significantly higher than TC. The mean Co-Gn of TT was significantly higher than CC.

Conclusions: A relationship was found between the 2G allele of rs1799750 1G/2G polymorphisms of the *MMP1* gene and the risk of individuals developing disk displacement. Also, it was found that *TGF-ß1* gene rs1800470 29 T/C polymorphisms had a detrimental effect on mandibular development. (*Angle Orthod*. 2025;95:317–322.)

KEY WORDS: Temporomandibular joint disorders; *MMP1*; *TGF-β1*

INTRODUCTION

Temporomandibular joint disorder (TMD) is a complicated and multifactorial condition, typically characterized by joint dysfunction, joint and muscle pain, joint noise, mandibular hypomobility, and deviation of the mandible during mouth opening.[1] The temporomandibular joint (TMJ) consists of a complex structure of extracellular matrix (ECM) molecules. Collagens, which are found in the fibrocartilage of the articular surface of the temporal bone and mandibular condyle, are involved in the function of the articular disk, maintain the form of tissues, and make them resistant to tensile forces. Both enzymatic and nonenzymatic mechanisms are responsible for the degradation of the ECM of the TMJ.[2]

Other than those caused by environmental variables, genetic differences may potentially play a role in the development of TMD.[3] Individuals differ in their capacity to endure the same contributing risk factors, such as abnormal mechanical loading, aging, and gender impacts. Also, they may have varying degrees of sensitivity to TMD and different adaptive remodeling capacity during the degenerative phase, leading to various clinical outcomes.[4] Under the same conditions, individuals that are susceptible to TMD are more

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Accepted: January 7, 2025. Submitted: July 3, 2024.
Published Online: February 12, 2025

Table 1. Distribution of Age and Gender

Groups	Gender		Age	Total
	Female	Male	Mean	
Group 1: Class II high angle vertical pattern, TMD (+)	20	2	20.27 ± 0.65	22
Group 2: Class II high angle vertical pattern, TMD (−)	16	6	18.51 ± 0.59	22
Group 3: Class I normal vertical pattern, TMD (−)	15	7	22.25 ± 0.61	22

sensitive to maladaptive molecular responses mediated by proinflammatory cytokines, neuropeptides, free radicals, and matrix-degrading enzymes.[5]

The TMJ articular disk is primarily composed of proteoglycan aggregates and collagen fibers, the majority of which are types 1 and 2 collagen. Physiologic maintenance of the disk is achieved through a balance between collagen fiber degradation performed by matrix metalloproteinases (MMP) and their inhibitors.[6] Accelerated collagen breakdown has been linked to increased synthesis and overexpression of *MMP1* in the synovial fluid of the TMJ of osteoarthritic patients.[7,8] Previous researchers have demonstrated that the *MMP1* gene 1G/2G polymorphism enhanced local *MMP1* concentration, which contributed to quicker ECM degradation.[9,10] Patients with the *MMP1* rs1799750 polymorphism may show variable concentrations of *MMP1*, leading to higher collagen degradation and potentially increasing the risk of developing disk displacement (DD). Therefore, the primary aim of the present study was to evaluate the association between the 1607 1G/2G polymorphism of the *MMP1* gene and DD and skeletal development.

TGF-β (transforming growth factor-β) regulates chondrocyte proliferation and differentiation as well as the formation and breakdown of the ECM.[11] *TGF-β1* signaling appears to be important in the development of the orofacial area by regulating palate development in both the epithelium and the mesenchyme.[12] Detamore and Athanasiou[13] performed an in vitro study to evaluate *TGF*-β in pig TMJ cultures and discovered that *TGF*-β considerably controlled the formation of ECM components such as collagen and glycosaminoglycan. Patients with different *TGF*-β*1* genotypes may show different concentrations of *TGF*-β*1*, leading to a growth-arresting effect and potentially increasing the likelihood of developing Class II skeletal relationships. Therefore, in the present study, we also aimed to evaluate the association between the T → C polymorphism of the *TGF*-β*1* gene and DD and skeletal development.

MATERIALS AND METHODS

The prospective study protocol was approved by Marmara University, Faculty of Medicine, Clinical Research Ethics Committee (09.2022.280, 11/02/2022, Istanbul, Turkey). The study sample consisted of 66 individuals, 15 males and 51 females (15–40 years). Informed consent was obtained from all patients included in the study. The sample size was determined using G-Power 3.1.9.4 (Heinrich-Heine-University, Düsseldorf, Germany) software based on a previous study.[14] A minimum of 22 participants was required for each group. Group 1 consisted of Class II hyperdivergent patients with TMD, Group 2 consisted of Class II hyperdivergent patients without TMD (ANB >4°, Go-MeSn >39°), and Group 3 consisted of Class I normodivergent patients without TMD (ANB <4°, Go-MeSn <39°; Table 1). Patients with previous orthodontic treatment or orthognathic surgery, cleft lip and palate, craniofacial syndromes, osteoarthritis of the TMJ, and rheumatic diseases were excluded from the study.

Cephalometric radiographs obtained from the patients prior to orthodontic treatment were traced with NemoStudio NX-Pro 10.4.2 (Software Nemotec, Madrid, Spain) by the same researcher (B.T.). After cephalometric examination, patients were clinically evaluated by an experienced orthodontist based on the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD).[15] Magnetic resonance imaging (MRI) was obtained for individuals in Group 1. During MRI examination, anterior DD without osteoarthritis was observed in at least one condyle of the patients as a finding.

Extraction and Analysis of Genomic Deoxyribonucleic Acid (gDNA)

Intraoral epithelial cells were collected with the help of DNA collection swabs. Then the DNA isolation process was completed using PureLink DNA isolation kit

Table 2. Evaluation of *TGF-β1* and *MMP1* Polymorphisms Among Groups

	No. (%)			*P* Value
	Group 1	Group 2	Group 3	
TGF-β*1*				
TT	3 (13.6%)	8 (36.4%)	9 (40.9%)	.113
TC	11 (50%)	5 (22.7%)	4 (18.2%)	
CC	8 (36.4%)	9 (40.9%)	9 (40.9%)	
TGF-β*1* (allele)				
T	17 (38.6%)	21 (47.7%)	22 (50%)	.526
C	27 (61.4%)	23 (52.3%)	22 (50%)	
MMP1				
1G/1G	6 (27.3%)	2 (9.1%)	9 (40.9%)	.058
1G/2G	11 (50%)	8 (36.4%)	6 (27.3%)	
2G/2G	5 (22.7%)	12 (54.5%)	7 (31.8%)	
MMP1 (allele)				
1G	23 (52.3%)	12 (27.3%)	24 (54.5%)	.017[a]
2G	21 (47.7%)	32 (72.7%)	20 (25.5%)	

[a] Chi-square test, $P < .05$.

Table 3. Evaluation of *MMP1* Polymorphisms Among Subgroups

	Mean ± SD						
	1G/1G	1G/2G	2G/2G	*P* Value	1G/1G-1G/2G	1G/1G-2G/2G	1G/2G-2G/2G
SNA (°)	78.35 ± 3.50	78.72 ± 3.2	79.92 ± 2.98	.25	.929	.279	.396
SNB (°)	75.35 ± 3.82	73.56 ± 3.39	74.88 ± 4.23	.281	.302	.918	.455
ANB (°)	3.18 ± 2.58	5.08 ± 2.48	5.13 ± 2.68	.036[a]	.046[a]	.042[a]	.998
Wits	−0.43 ± 2.26	2.32 ± 4.26	2.64 ± 2.67	.010[a]	.026[a]	.012[a]	.94
N per A	−2.17 ± 4.21	−2.0 ± 3.06	−0.98 ± 2.77	.437	.984	.495	.533
ACB	68.02 ± 4.05	65.69 ± 3.84	66.28 ± 3.84	.163	.147	.341	.86
Mandibular length	72.13 ± 7.33	67.84 ± 5.9	70.68 ± 7.49	.124	.126	.785	.326
Max depth (°)	88.0 ± 4.27	88.08 ± 2.9	88.96 ± 2.74	.551	.997	.624	.614
Σ	395.98 ± 7.8	400.14 ± 6.67	399.58 ± 7.67	.173	.177	.277	.961
Go-MeSn	38.76 ± 7.28	42.04 ± 6.53	41.42 ± 6.57	.286	.277	.434	.944
ANS Me/Nme	55.64 ± 2.09	54.46 ± 2.89	55.63 ± 2.44	.201	.311	1	.252
Jarabak	65.55 ± 4.93	63.4 ± 4.95	64.0 ± 4.57	.359	.334	.568	.899
FMA	28.76 ± 6.73	32.52 ± 5.64	32.42 ± 6.86	.128	.156	.177	.998
Max height (°)	61.82 ± 3.05	62.88 ± 3.35	62.54 ± 3.98	.633	.608	.797	.94
Gonial ratio	127.65 ± 8.31	131.24 ± 6.55	130.54 ± 9.66	.365	.354	.513	.953
Y axis angle	61.76 ± 4.58	64.8 ± 3.7	64.38 ± 4.68	.069	.072	.143	.936
Face axis angle (°)	84.53 ± 5.15	82.28 ± 5.3	82.54 ± 5.86	.388	.397	.49	.985
Go-Co	55.97 ± 6.75	53.13 ± 5.46	55.2 ± 6.58	.302	.32	.919	.48
Co-Gn	111.24 ± 6.96	106.23 ± 6.27	109.85 ± 9.03	.085	.096	.83	.222
Go-Gn	70.82 ± 5.38	66.16 ± 4.06	68.3 ± 6.63	.030[a]	.023[a]	.317	.36
S-Go	74.72 ± 8.59	71.9 ± 6.53	74.74 ± 7.3	.323	.446	1	.373

[a] One-way analysis of variance, $P < .05$.

(Invitrogen, Van Allen Way Carlsbad, Calif). The DNA samples were kept at −20°C until the relevant gene area analysis was finished.

Taqman SNP genotyping kits (cat. no. 4371355, Thermo Fisher Scientific Inc., Waltham, MA, USA) and Real-Time PCR on StepOnePlus (Thermo Fisher Scientific Inc.) were used for genotyping assays. Genotyping was performed according to the manufacturer's protocols.

Statistical Analysis

IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Genotype and allele frequency distributions between Class II hyperdivergent patients with TMD and control groups were analyzed by χ^2 test.

Conformity of the parameters to a normal distribution was evaluated by Shapiro-Wilk tests. One-way analysis of variance was used to compare parameters between treatment groups and between gene alleles, and Tukey HSD was used to determine the group causing the difference. Significance was evaluated at $P < .05$.

RESULTS

MMP1 Polymorphism

A statistically significant difference was found among the groups for distribution of *MMP1* alleles ($P = .017$). The rate of the 2G allele in Group 2 (72.7%) was significantly higher than in Group 1 (47.7%) and Group 3 (25.5%; $P < .05$; Table 2).

Statistically significant differences were found between *MMP1* subgroups (1G/1G, 1G/2G, and 2G/2G) for mean ANB angle and Wits value ($P = .036$ and .010, respectively). The means of the ANB angle and Wits value for the 1G/1G genotype were significantly lower than for 1G/2G and 2G/2G ($P < .05$; Table 3).

A statistically significant difference between *MMP1* subgroups was also found for mean Go-Gn ($P = .030$). The mean Go-Gn of 1G/1G was significantly greater than for 1G/2G ($P < .05$; Table 3).

TGF-β1 Polymorphism

Statistically significant differences were found between *TGF-β1* subgroups (TT, TC, and CC) in SNB and GoMe-SN angles ($P = .030$ and .041, respectively). While mean SNB of the TT genotype was higher than TC, the mean GoMe-SN of TT was lower than in the TC genotype ($P < .05$; Table 4).

A statistically significant difference between the *TGF-β1* subgroups was also found for mean facial axis angle ($P = .027$). The mean facial axis angle of the TC genotype was significantly lower than for CC ($P < .05$; Table 4).

Also, a statistically significant difference was found between *TGF-β1* subgroups in mean Co-Gn distance ($P = .030$), which showed significantly higher values in the TT genotype than in CC ($P < .05$; Table 4).

DISCUSSION

TMDs are very common in society. Their prevalence and frequency in different populations, symptoms, and etiology have been the subject of studies.[16,17]

Table 4. Evaluation of *TGF-β1* Polymorphisms Among Subgroups

	Mean ± SD						
	TT	TC	CC	*P* Value	TT-TC	TT-CC	TC-CC
SNA (°)	79.7 ± 3.26	78.1 ± 2.79	79.31 ± 3.44	.26	.261	.911	.418
SNB (°)	75.95 ± 2.52	72.8 ± 4.02	74.69 ± 4.15	.030[a]	.024[a]	.49	.204
ANB (°)	3.8 ± 2.67	5.45 ± 2.86	4.58 ± 2.44	.15	.126	.586	.51
Wits	1.06 ± 3.49	1.58 ± 4.24	2.36 ± 2.79	.446	.883	.424	.733
N per A	−1.18 ± 2.85	−1.98 ± 3.53	−1.82 ± 3.49	.716	.725	.792	.986
ACB	68 ± 3.93	65.45 ± 4	66.17 ± 3.72	.106	.102	.257	.809
Mandibular length	72.09 ± 7.56	69.36 ± 6.49	68.83 ± 6.85	.267	.435	.265	.965
Max depth (°)	88.9 ± 2.67	87.95 ± 3.38	88.31 ± 3.56	.65	.629	.815	.928
Σ	396.59 ± 6.73	401.83 ± 7.71	398.34 ± 7.23	.072	.064	.695	.244
Go-MeSn	39.2 ± 6.19	44.1 ± 6.55	39.92 ± 6.78	.041[a]	.044[a]	.927	.088
ANS Me/Nme	55.58 ± 1.91	55.46 ± 2.15	54.69 ± 3.23	.442	.989	.483	.575
Jarabak	65.39 ± 4.47	62.42 ± 5.3	64.58 ± 4.46	.128	.125	.837	.28
FMA	29.95 ± 5.62	34.1 ± 5.47	30.73 ± 7.43	.094	.106	.91	.184
Max height (°)	63 ± 4.23	63.35 ± 3.23	61.42 ± 2.86	.131	.944	.278	.151
Gonial ratio	129.75 ± 9.95	129.6 ± 6.27	130.65 ± 8.44	.896	.998	.93	.906
Y axis angle	63.05 ± 3.91	65.3 ± 3.99	63.38 ± 4.96	.215	.243	.964	.312
Face axis angle (°)	84 ± 5.35	80.25 ± 5.18	84.23 ± 5.23	.027[a]	.069	.988	.035[a]
Go-Co	56.82 ± 5.67	53.7 ± 5.3	53.62 ± 7.07	.168	.254	.198	.999
Co-Gn	112.55 ± 7.09	107.85 ± 5.86	106.74 ± 8.65	.030[a]	.121	.029[a]	.87
Go-Gn	70.52 ± 5.94	67.56 ± 5.05	66.77 ± 5.54	.071	.215	.066	.882
S-Go	75.98 ± 6.77	72.97 ± 7.56	72.41 ± 7.59	.24	.403	.24	.965

[a] One-way analysis of variance, $P < .05$.

Genetic variants may contribute to the development of TMD and the pain experience. Authors of several studies have linked genetic polymorphisms to musculoskeletal conditions such as fibromyalgia[18] and lower back pain.[19] This strongly suggests that TMD pathophysiology may also be significantly influenced by genetic conditions.

Authors of most studies have reported that a Class II skeletal relationship and hyperdivergent growth pattern are conditions associated with a higher risk for the development of TMD.[20–22] Skeletal patterns associated with TMD include short ramus height and mandibular length, steep mandibular plane angle, increased profile convexity, and mandibular retrognathism.[23]

In this study, two of the groups had a Class II hyperdivergent skeletal pattern (Group 1 was TMD [+], and Group 2 was TMD [−]). Since these two groups both had a Class II skeletal relationship with hyperdivergent vertical pattern, skeletal relationship and vertical pattern alone, as a cause of joint disease, could be excluded. Additionally, the third group had a Class I skeletal relationship and normodivergent pattern without TMD. Group 3 was included in the present study to investigate the relationship between gene polymorphisms and skeletal relationships.

MMP1 Gene Polymorphism

In the present study, a statistically significant difference was found among the three groups in terms of allelic frequency of *MMP1* rs1799750 polymorphism. The rate of the 2G allele was higher in Group 2 than the other groups. Other researchers found a higher rate of the 2G allele in individuals with TMD in their studies.[14,24,25] In the current study, the heterozygous genotype 1G/2G was more common in Group 1, which agreed with Rosales et al.[14] and Luo et al.[25] Differences among the studies may have been due to inadequacies in TMD diagnosis. In the current study, patients were diagnosed based on clinical examination, panoramic radiography, and RDC/TMD due to ethical reasons. In some previous studies, advanced imaging techniques such as MRI and computed tomography images were used.

Many hypotheses have been formed regarding the causes of TMD. However, the multifactorial etiologic approach proposed by De Boever[26] remains valid today due to the lack of scientific resources to support alternate hypotheses, which may have created differences between the study groups in the present study.

In the current study, although it was not statistically significant, 27.3% of Group 1 had the 1G/1G genotype, 9.1% of Group 2, and 40.9% of Group 3. Since Group 3 had Class I individuals with normal vertical dimensions, the homozygous 1G/1G genotype may be more common in individuals with normal skeletal development and a healthy TMJ.

A significant difference was found between *MMP1* genotype subgroups for ANB angle and Wits value averages in the present study. The mean ANB angle and Wits value of 1G/1G were significantly lower than for 1G/2G and 2G/2G. These values provide information about the direction of skeletal development in

individuals, and high values indicate the presence of a Class II skeletal relationship. The fact that these values were low in individuals with 1G/1G homozygous genotype suggests that *MMP1* may provide information about skeletal development. The *MMP1* 1G/1G homozygous genotype increases the development of a skeletal Class I relationship.

Additionally, the Go-Gn distance of 1G/1G was significantly greater than for 1G/2G. Looking at the Go-Gn linear value, which provides information about mandibular corpus length, it could be speculated that the mandibular corpus length is longer in individuals with a homozygous 1G/1G genotype than in individuals with a heterozygous 1G/2G genotype.

This present study is the first one to examine *MMP1* polymorphism and TMD in a small sample of the Turkish population. Additionally, we were the first to classify patients according to cephalometric values and to examine *MMP1* polymorphism. In the future, further studies on this subject with larger sample sizes and using more accurate diagnostic tools or TMD will contribute more to the finalization of the results and the elucidation of this topic in the literature.

TGF-β1 Polymorphism

In the present study, heterozygous TC and homozygous CC individuals were more common in Group 1 than in the other groups, although the difference was not statistically significant. In the literature, Jiao et al.[27] suggested that *TGF-β1* may be an important marker for the development of TMJ osteoarthritis. No authors in the literature have investigated the relationship between *TGF-β1* rs1800470 polymorphism and joint disorders. However, the presence of the C allele has been reported to cause diseases such as osteoarthritis, hip dysplasia, and rheumatoid arthritis.[28,29] Therefore, the greater percentage of the C allele in Group 1, which had TMD patients, may support these findings.

In the *TGF-β1* genotype subgroups, some of the skeletal values showed significant differences. While the SNB angle in the TT subgroup was greater than in TC, the Co-Gn distance was greater in the TT subgroup than in CC. Since these values are both related to mandibular growth, it may be concluded that the presence of the C allele negatively affects mandibular growth.

Additionally, while GoMe-SN in the TC subgroup was significantly higher than TT, the facial axis angle was significantly lower in TC. Although the other differences were not statistically significant, it can be speculated that higher ratios of vertical height were seen in the heterozygous TC subgroup.

In the literature, this article is the first one relating *TGF-β1* rs1800470 polymorphism and craniofacial development. Although the results were not statistically significant, it might be suggested that the presence of the C allele negatively affects mandibular growth. To reach statistically significant results, increasing the sample size and looking at these linear and angular values may contribute to the literature on mandibular development. In the future, having more information about genetic skeletal deformities in individuals may provide further information to guide growth during treatment.

CONCLUSIONS

- In the present study, the 1G/2G genotype, which is the heterozygous genotype in *MMP1* rs1799750 polymorphism, may be a risk factor for the development of TMD, and the 1G/1G genotype is thought to be a genotype that protects individuals from TMD.
- The *TGF-β1* TC heterozygous genotype was found more frequently in Group 1 individuals with TMD than in healthy individuals. The TC genotype, which is the heterozygous genotype in the *TGF-β1* rs1800470 polymorphism, may be a risk factor for the development of TMD.
- Patients with the 1G/1G genotype were more prone to having a Class I skeletal relationship. The presence of 2G in *MMP1* rs1799750 polymorphism is thought to negatively affect mandibular growth.
- Finally, the *TGF-β1* rs1800470 29 T/C polymorphisms may have a detrimental effect on mandibular development, and heterozygous TC genotype may increase vertical growth in individuals.

ACKNOWLEDGMENTS

This study was funded by Marmara University, Scientific Research Projects Department (Project code TDH-2022-10523). It was presented at 18th International Turkish Orthodontic Society Symposium and received first prize in oral presentations.

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