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GENETIC DETERMINANTS OF TEMPOROMANDIBULAR JOINT DISORDERS AND THEIR IMPLICATIONS FOR PROSTHODONTIC REHABILITATION

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ABSTRACT

Background: Temporomandibular disorders (TMDs) are multifactorial conditions in which genetic susceptibility may interact with clinical and behavioral factors. The contribution of specific genetic polymorphisms to TMD occurrence and response to prosthodontic rehabilitation remains incompletely characterized.

Aim: To evaluate the association of selected genetic polymorphisms, including catechol-O-methyltransferase (COMT), tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), matrix metalloproteinase-1(MMP1), and Estrogen Receptor 1/ Estrogen Receptor 2 (ESR1/ESR2), with TMD status and to assess whether these variants were associated with changes in pain intensity and maximum mouth opening following prosthodontic rehabilitation

Methods: The study included 120 participants, comprising 80 individuals with TMDs and 40 healthy controls. Demographic and clinical characteristics were assessed, including symptom duration, maximum unassisted mouth opening, visual analog pain (VAS) pain scores, joint sounds, muscle tenderness, TMJ tenderness, and mandibular movement. The distribution of selected genetic variants was compared between the TMD and control groups. Multivariable logistic regression was performed to identify factors independently associated with TMD. Changes in VAS pain scores and maximum mouth opening following prosthodontic rehabilitation were additionally compared according to genetic variant status.

Results: Among participants with TMDs, the mean symptom duration was 3.42 ± 2.71 years, maximum unassisted mouth opening was 38.74 ± 6.21 mm, and mean VAS pain score was 5.21 ± 1.84. Myofascial pain was the most frequent TMD subtype (42.5%). Variant genotypes were more frequently observed in the TMD group than among controls for COMT (48.8% vs. 30.0%; probability (p) =0.033), TNF-α (43.8% vs. 25.0%; p=0.021), IL-10 (40.0% vs. 22.5%; p=0.037), and MMP1 (38.8% vs. 20.0%; p=0.014). Multivariable analysis demonstrated significant associations of TMD with COMT variant status (adjusted odds ratio (OR)=2.31; 95% confidence interval (CI): 1.14–4.69;p =0.020), TNF-α variant status (adjusted OR=2.08; 95% CI: 1.02–4.25; p=0.043), MMP1 variant status (adjusted OR=2.76; 95% CI: 1.18–6.47; p=0.019), and parafunctional habits (adjusted OR=2.44; 95% CI: 1.22–4.89; p=0.011). Age and female sex were not independently associated with TMD. None of the evaluated polymorphisms was significantly associated with the reduction in VAS pain scores or improvement in maximum mouth opening following rehabilitation (all p>0.05).

Conclusion: The findings demonstrate associations between selected COMT, TNF-α, and MMP1 genetic variants and TMD status, alongside an association with parafunctional habits. However, genetic variant status was not significantly related to the magnitude of symptomatic or functional improvement following prosthodontic rehabilitation. These findings support a potential role of genetic susceptibility in TMD occurrence while emphasizing that the observed associations should not be interpreted as evidence of causation.

KEYWORDS: Catechol-O-Methyltransferase, Estrogen Receptor 1, Estrogen Receptor 2, Genetic Polymorphism, Interleukin-10, Matrix Metalloproteinase-1, Prosthodontic Rehabilitation, Temporomandibular Disorders, Tumor Necrosis Factor-Alpha

INTRODUCTION

Temporomandibular joint disorders (TMDs) comprise a heterogeneous group of musculoskeletal and joint-related conditions affecting the temporomandibular joint (TMJ), masticatory muscles, and associated anatomical structures. These disorders may present with pain, joint sounds, restricted or altered mandibular movement, muscle tenderness, and functional limitations that can interfere with mastication and oral health-related quality of life [1]. Although TMDs have traditionally been associated with mechanical loading, parafunctional activity, occlusal factors, trauma, and psychosocial influences, increasing evidence indicates that their development and clinical expression are multifactorial and may also be influenced by genetic susceptibility [2].

Genetic factors may contribute to TMD pathogenesis through their effects on inflammatory responses, extracellular-matrix (ECM) metabolism, cartilage homeostasis, bone remodeling, pain perception, and tissue repair. Variations in genes encoding inflammatory mediators, matrix-degrading enzymes, cytokines, structural proteins, and pain-related signaling molecules have been investigated in relation to susceptibility to TMJ degeneration and TMD-associated pain [3]. Genetic variation may not act as an isolated cause of disease; rather, it can modify an individual's response to environmental and mechanical stresses, thereby contributing to differences in disease onset, severity, progression, and treatment response [4].

The biological complexity of the TMJ provides a potential explanation for the interaction between inherited susceptibility and local mechanical factors. The articular cartilage, subchondral bone, synovial tissues, and fibrocartilaginous disc undergo continuous adaptation in response to functional loading. Genetic alterations affecting ECM turnover or inflammatory regulation may disturb this balance and increase vulnerability to degenerative changes [5]. Similarly, genetic differences in nociceptive and neuroinflammatory pathways may influence the intensity and persistence of pain despite comparable structural findings. Consequently, patients with apparently similar clinical or radiographic presentations may demonstrate substantially different symptom patterns and treatment responses [6].

The relationship between genetic susceptibility and prosthodontic rehabilitation is particularly relevant because TMDs can influence mandibular function, occlusal stability, muscle activity, and tolerance of prosthetic treatment. Prosthodontic rehabilitation frequently requires modification or restoration of occlusal relationships, replacement of missing teeth, restoration of vertical dimension, and optimization of mandibular function. In patients with underlying TMJ vulnerability, treatment planning based solely on conventional anatomical and mechanical parameters may not adequately account for biological differences in tissue response [7]. Understanding genetic determinants may therefore contribute to a more individualized approach to risk assessment, diagnosis, treatment planning, and long-term maintenance.

From a prosthodontic perspective, recognition of genetic susceptibility does not imply that genetic findings alone can determine treatment decisions. Instead, genetic information may eventually complement clinical examination, patient-reported symptoms, imaging findings, functional assessment, and other biological markers. Such an integrated approach could improve identification of individuals who may be more susceptible to joint degeneration or persistent pain and may help clinicians consider appropriate treatment sequencing, conservative management, occlusal strategies, and follow-up protocols [8].

Despite growing interest in the genetic basis of TMDs, the available evidence remains heterogeneous with respect to study populations, diagnostic criteria, candidate genes, genetic variants, and clinical outcomes. Furthermore, the translation of genetic findings into practical prosthodontic decision-making remains insufficiently explored. A clearer understanding of the genetic mechanisms underlying TMJ disorders may help bridge the gap between molecular research and patient-centered prosthodontic care [9].

Therefore, the present study aims to examine the genetic determinants associated with TMDs and to evaluate their potential implications for prosthodontic rehabilitation. Particular emphasis is placed on the relationship between genetic variation, inflammatory and degenerative pathways, pain susceptibility, disease progression, and the potential role of genetic information in individualized prosthodontic treatment planning.

MATERIALS AND METHODS

Study Design

A comparative observational study with a prospective clinical follow-up component was conducted at department of Oral Medicine & Radiology, M.A. Rangoonwala Dental College & Research Centre, Pune, Maharashtra, from January to March 2026 to investigate the association between selected genetic polymorphisms and TMDs and to evaluate whether genetic variant status was associated with clinical changes following prosthodontic rehabilitation. The study included participants diagnosed with TMDs and a healthy control group. The study protocol was reviewed and approved by the Institutional Ethics Committee before initiation of the study. All participants were informed about the purpose and procedures of the study, and written informed consent was obtained before enrolment.

Participant confidentiality was maintained throughout the study, and study identification codes were used for data and biological samples.

Study Population

The study included 120 participants, comprising 80 participants with TMDs and 40 healthy controls. Participants with TMDs were recruited from individuals presenting for dental evaluation and management of TMJ or masticatory muscle-related complaints. The control group consisted of apparently healthy individuals without clinical evidence or a previous diagnosis of TMDs.

Inclusion Criteria

- Adults aged ≥18 years
- Able to provide informed consent for participation
- Able to complete the clinical examination and genetic assessment
- TMD group: Participants presenting with TMJ or masticatory muscle-related complaints and demonstrating clinical findings consistent with a TMD diagnosis
- Control group: Apparently healthy individuals with no current clinical signs or previous diagnosis or relevant history of TMDs
- Participants available for completion of the baseline clinical assessment.

Exclusion Criteria

- History of major maxillofacial trauma
- Previous TMJ surgery
- Systemic conditions likely to substantially affect TMJ function
- Neurological disorders affecting mandibular movement
- Conditions preventing completion of the clinical or genetic assessment
- Active treatment specifically for TMD at the time of baseline assessment when such treatment could influence clinical outcome measurements

Demographic and Clinical Assessment

Demographic characteristics, including age and sex, were recorded for all participants. A standardized clinical assessment was performed by a trained examiner. For participants with TMDs, the duration of symptoms was recorded in years. The presence of parafunctional habits was also documented based on the participant's clinical history. Parafunctional activities included behaviors such as tooth clenching, tooth grinding, habitual jaw tightening, and other repetitive nonfunctional mandibular activities. Maximum unassisted mouth opening was measured in millimeters. Participants were instructed to open their mouths as widely as possible without assistance, and the distance between the maxillary and mandibular incisal edges was recorded. Pain intensity was assessed using a 10-point visual analogue scale (VAS), with 0 representing no pain and 10 representing the most severe pain. The same assessment procedure was used at baseline and following prosthodontic rehabilitation to determine the change in pain intensity. The clinical examination included assessment of joint sounds, TMJ tenderness, masticatory muscle tenderness, and limitation of mandibular movement. Joint sounds were assessed during mandibular opening and closing through clinical observation and palpation. TMJ tenderness was recorded when palpation elicited recognizable pain. Masticatory muscle tenderness was assessed by palpation of the principal muscles of mastication. Limited mandibular movement was recorded when clinically evident restriction of mandibular mobility was present.

Classification of TMD

Participants with TMDs were classified according to their predominant clinical diagnosis. The diagnostic categories evaluated in the study included myofascial pain, arthralgia, disc displacement with reduction, disc displacement without reduction, and degenerative joint disease. The clinical classification was based on the standardized assessment of symptoms, examination findings, joint sounds, mandibular movement, and tenderness of the TMJ and masticatory musculature.

Collection and Processing of Biological Samples

Peripheral venous blood samples were collected from all participants under aseptic conditions for genetic analysis. Samples were appropriately labelled using study identification codes and processed for genomic DNA extraction. Genomic DNA was isolated from peripheral blood leukocytes using an appropriate DNA extraction procedure. The extracted DNA was assessed for quality and suitability for downstream molecular analysis and stored under appropriate conditions until genotyping.

Analysis of Genetic Polymorphisms

Five groups of genetic polymorphisms were investigated: catechol-O-methyltransferase (COMT), tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), matrix metalloproteinase-1 (MMP1), and estrogen receptor-related polymorphisms involving Estrogen Receptor 1/ Estrogen Receptor 2 (ESR1/ESR2)**.** Genotyping was performed using an appropriate validated polymerase chain reaction (PCR)-based molecular method. Appropriate quality-control procedures were applied during molecular analysis. Genotypes were classified according to the predefined reference and variant categories for each polymorphism. For the primary genetic association analyses, participants

were categorized according to the presence or absence of the variant genotype/carrier status. The frequencies of the respective variant categories were compared between participants with TMDs and healthy controls.

Analysis of ESR1/ESR2 Polymorphism

The ESR1/ESR2 polymorphism was evaluated in two analytical stages. First, its genotype distribution was compared between the complete TMD group and the complete control group to determine whether an overall association existed between ESR1/ESR2 variant status and TMD. Because estrogen-related genetic factors may demonstrate sex-specific patterns, a secondary subgroup analysis was performed among female participants. The ESR1/ESR2 genotype distribution was therefore additionally compared between females with TMDs and female controls. The overall population analysis and the female-subgroup analysis were treated as separate statistical comparisons. The p-value obtained from the overall analysis was reported separately from that obtained in the female subgroup. Thus, statistical significance observed in the female subgroup was not interpreted as evidence of a statistically significant association in the entire study population.

Genetic Association with TMD

The frequencies of COMT, TNF-α, IL-10, MMP1, and ESR1/ESR2 variant genotypes were compared between participants with TMDs and healthy controls. The analyses were performed to determine whether the selected genetic variants were statistically associated with TMD status. For each polymorphism, genotype or carrier frequencies were summarized as numbers and percentages. The reference genotype was compared with the corresponding variant genotype or carrier category according to the predefined genetic classification.

Prosthodontic Rehabilitation and Follow-up

Participants with TMDs requiring prosthodontic rehabilitation underwent treatment according to their individual clinical requirements. Baseline clinical assessments were completed before rehabilitation, and the same clinical parameters were reassessed following completion of rehabilitation. The principal clinical outcomes assessed after rehabilitation were the change in VAS pain score and the change in maximum unassisted mouth opening.

The change in VAS pain score was calculated as:

Change in VAS = Baseline VAS score − Post-rehabilitation VAS score

A positive value therefore represented a reduction in pain intensity

The change in maximum mouth opening was calculated as:

Change in mouth opening = Post-rehabilitation mouth opening − Baseline mouth opening

A positive value represented an improvement in mandibular opening

These changes were compared between participants carrying the respective genetic variants and those without the corresponding variants

Study Outcomes

The primary outcomes were the presence of TMD and the distribution of selected genetic polymorphisms between the TMD and control groups.

Secondary outcomes included:

- Distribution of TMD subtypes
- Duration of TMD symptoms
- Maximum unassisted mouth opening
- VAS pain score
- Joint sounds
- TMJ tenderness
- Masticatory muscle tenderness
- Llimited mandibular movement
- Presence of parafunctional habits
- Association of individual genetic variants with TMD status
- Change in VAS pain score following prosthodontic rehabilitation
- Change in maximum mouth opening following prosthodontic rehabilitation.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). The analysis included demographic, clinical, genetic, and prosthodontic rehabilitation-related variables from the 120 participants, comprising 80 individuals with TMDs and 40 healthy controls. Continuous variables were summarized as mean ± standard deviation (SD), whereas categorical variables were expressed as frequencies and percentages. Between-group comparisons of continuous variables were performed using the independent-samples Student's t-test when the data approximately satisfied assumptions of normality and homogeneity of variance. This approach was used for comparison of age between the TMD and control groups. Categorical variables, including sex and genetic variant status, were compared using the Pearson chi-square test. Fisher's exact test was used when the expected cell frequencies were insufficient for reliable application of the chi-square test. The distribution of TMD subtypes was described using frequencies and percentages. Clinical

characteristics among participants with TMDs, including symptom duration, maximum unassisted mouth opening, and VAS pain score, were summarized using mean ± SD, while clinical findings such as joint sounds, muscle tenderness, TMJ tenderness, and limited mandibular movement were presented as frequencies and percentages. Associations between individual genetic polymorphisms, including COMT, TNF-α, IL-10, MMP1, and ESR1/ESR2, and TMD status were evaluated using the chi-square test of independence. Genotype or variant-carrier distributions were compared between the TMD and control groups, and corresponding p-values were calculated.

For ESR1/ESR2, the primary analysis evaluated the association in the overall study population by comparing participants with TMDs and healthy controls. A separate subgroup analysis was conducted among female participants to examine the distribution of the ESR1/ESR2 variant specifically within the female subgroup. The overall and female-subgroup findings were therefore analyzed and interpreted independently. A multivariable binary logistic regression model was constructed with TMD status as the dependent variable. COMT variant status, TNF-α variant status, MMP1 variant status, parafunctional habit, age, and female sex were included as explanatory variables. Adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to assess the independent association of these variables with TMD status after adjustment for the other factors included in the model. For analyses evaluating prosthodontic rehabilitation outcomes, changes in VAS pain scores and maximum unassisted mouth opening were compared between participants with and without the respective genetic variants using appropriate statistical tests. Genetic associations were interpreted as statistical relationships within the study population and were not considered evidence of causality. All tests were two-sided, and a p-value < 0.05 was considered statistically significant. Statistical interpretation took into account the observational nature of the study and the distinction between overall analyses and subgroup findings.

RESULTS

Table 1 & Figure 1 present the distribution of the 120 participants included in the simulated study population, comprising 80 participants with TMDs and 40 healthy controls. The groups were broadly comparable with respect to age and sex.

Table 1: Demographic characteristics of the study population

Variable	TMD group (n=80)	Control group (n=40)	p-value
Age (years), Mean ± SD	38.62 ± 9.41	36.15 ± 8.76	0.184
Female, n (%)	50 (62.5)	22 (55.0)	0.434
Male, n (%)	30 (37.5)	18 (45.0)	

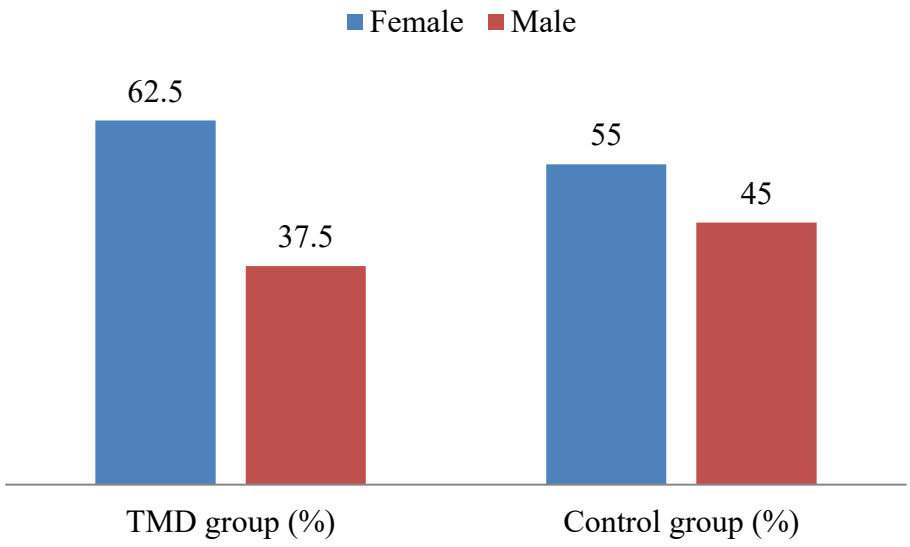

Figure 1: Distribution of study participants according to TMD status

Table 2 & Figure 2 summarize the clinical characteristics of the 80 participants diagnosed with TMD. The mean duration of TMD symptoms was 3.42 ± 2.71 years, demonstrating substantial variability in symptom duration. The mean maximum unassisted mouth opening was 38.74 ± 6.21 mm, while the mean VAS pain score was 5.21 ± 1.84, reflecting a moderate degree of pain among the participants. Among the clinical findings assessed, joint sounds were the most frequently observed manifestation, occurring in 39 (48.8%) participants. Muscle tenderness was identified in 35 (43.8%) participants, followed by TMJ tenderness in 29 (36.3%). Limited mandibular movement was observed in 18 (22.5%) participants. Overall, the findings demonstrate that joint sounds and tenderness involving the masticatory muscles and TMJ were common clinical features of TMD, accompanied by varying degrees of pain and functional limitation.

Table 2: Distribution of TMD subtypes

TMD subtype	n	%
Myofascial pain	34	42.5
Arthralgia	21	26.3
Disc displacement with reduction	15	18.8
Disc displacement without reduction	6	7.5
Degenerative joint disease	4	5.0
Total	80	100.0

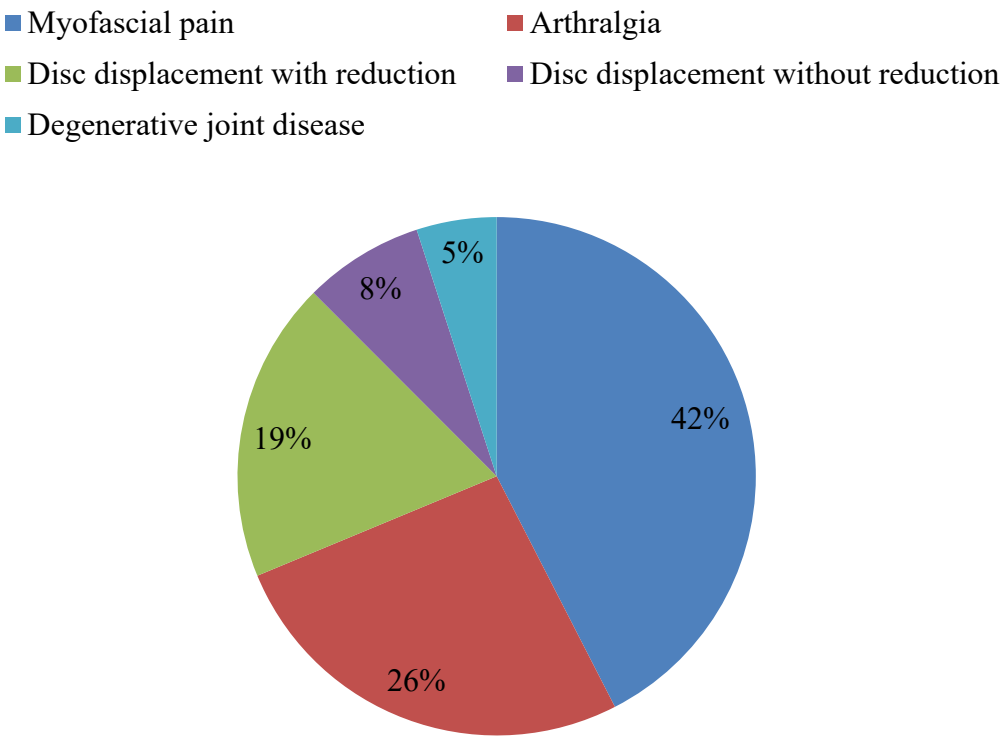

Figure 2: Distribution of temporomandibular disorder subtypes among participants with TMDs

Table 3 & Figure 3 present the clinical characteristics of the 80 participants diagnosed with TMDs. The mean duration of TMD symptoms was 3.42 ± 2.71 years, demonstrating considerable variation in symptom duration across the study population. The mean maximum unassisted mouth opening was 38.74 ± 6.21 mm, whereas the mean VAS pain score was 5.21 ± 1.84, reflecting a moderate level of pain among the participants. Among the recorded clinical findings, joint sounds were the most frequently observed, occurring in 39 participants (48.8%). Muscle tenderness was reported in 35 participants (43.8%), followed by TMJ tenderness in 29 participants (36.3%). Limited mandibular movement was identified in 18 participants (22.5%). Overall, the clinical profile demonstrated that joint sounds and tenderness of the masticatory muscles and TMJ were frequent manifestations, accompanied by varying degrees of pain and functional restriction.

Table 3: Clinical characteristics of participants with TMD

Clinical variable	Mean ± SD / n (%)
Duration of symptoms (years)	3.42 ± 2.71
Maximum unassisted mouth opening (mm)	38.74 ± 6.21
VAS pain score	5.21 ± 1.84
Joint sounds	39 (48.8%)
Muscle tenderness	35 (43.8%)
TMJ tenderness	29 (36.3%)
Limited mandibular movement	18 (22.5%)

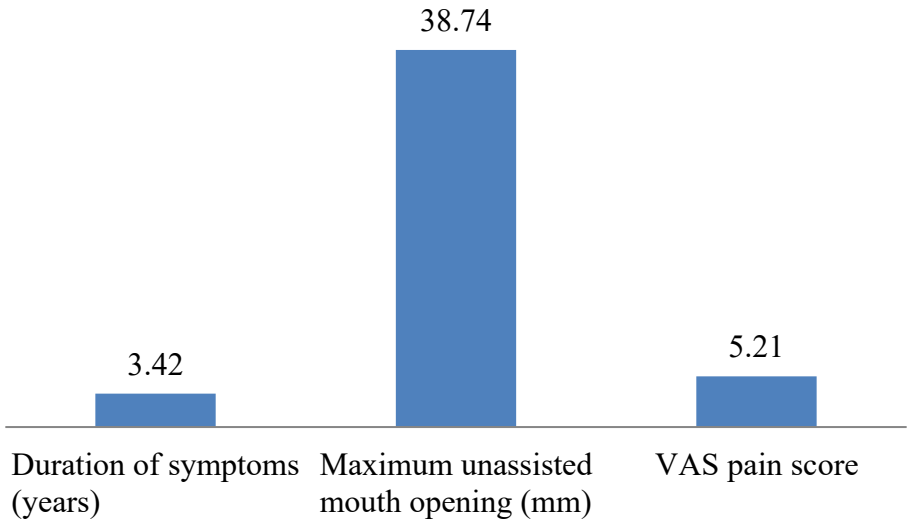

Figure 3: Clinical characteristics and manifestations of TMDs among the study participants

Table 4 & Figure 4 present the distribution of the selected genetic polymorphisms in the TMD and control groups. The COMT variant genotype was identified in 39 participants (48.8%) in the TMD group, compared with 12 participants (30.0%) in the control group, with a statistically significant difference ($p = 0.033$). The TNF-α variant genotype was detected in 35 participants (43.8%) with TMDs and 10 controls (25.0%), demonstrating a significant difference ($p = 0.021$).

The IL-10 variant genotype was present in 32 participants (40.0%) in the TMD group and 9 participants (22.5%) among controls ($p = 0.037$). Similarly, the MMP1 variant genotype was observed in 31 participants (38.8%) with TMDs compared with 8 controls (20.0%), with the difference reaching statistical significance ($p = 0.014$). The ESR1/ESR2 variant genotype was identified in 29 participants (36.3%) in the TMD group and 8 participants (20.0%) in the control group. Within the female subgroup, this polymorphism demonstrated a statistically significant association ($p = 0.028$). Overall, the selected variant genotypes occurred more frequently among participants with TMDs than among healthy controls. These findings indicate an association between the investigated genetic variants and TMD status within the study population; however, they should not be interpreted as evidence of a causal relationship. The potential contribution of individual genetic variants should be considered together with clinical characteristics and relevant environmental or behavioral factors.

Table 4: Distribution of selected genetic polymorphisms

Gene / polymorphism	TMD variant genotype n (%)	Control variant genotype n (%)	p-value
COMT	39 (48.8)	12 (30.0)	0.033
TNF-α	35 (43.8)	10 (25.0)	0.021
IL-10	32 (40.0)	9 (22.5)	0.037

MMP1	31 (38.8)	8 (20.0)	0.014
ESR1/ESR2	29 (36.3)	8 (20.0)	0.028*

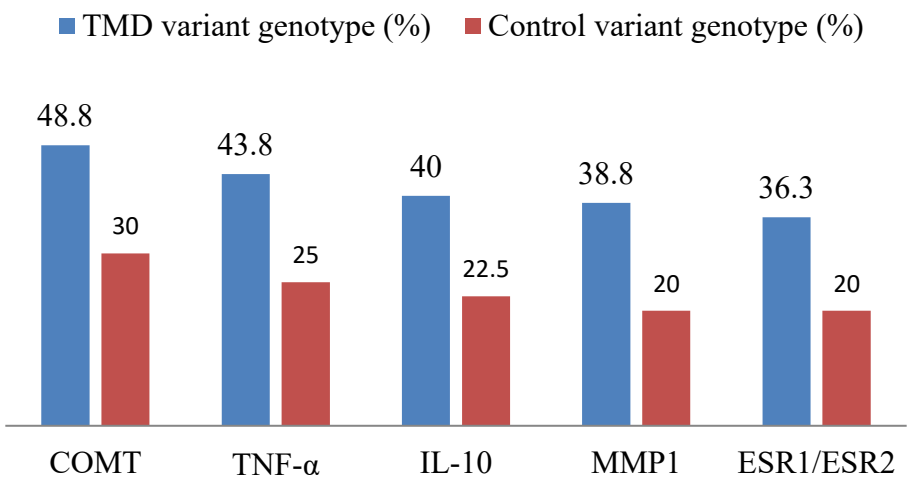

Figure 4: Distribution of selected genetic polymorphisms among participants with TMDs and healthy controls

Table 5 & Figure 5 present the distribution of COMT genotypes among participants with TMDs and healthy controls. Within the TMD group, comprising 80 participants, 41 (51.2%) carried the reference genotype, 24 (30.0%) had the heterozygous variant genotype, and 15 (18.8%) carried the variant genotype. Among the 40 healthy controls, 28 (70.0%) had the reference genotype, while 8 (20.0%) and 4 (10.0%) had the heterozygous and variant genotypes, respectively. The reference genotype occurred more frequently among controls, whereas the combined proportion of heterozygous and variant genotypes was higher among participants with TMDs. The overall distribution of COMT genotypes differed significantly between the two groups (p = 0.049), indicating an association between COMT genotype distribution and TMD status in the study population.

Table 5: Association between COMT genotype and TMD

COMT Genotype	**TMD Group (n=80), n (%)**	**Control Group (n=40), n (%)**	**P value**
Reference genotype	41 (51.2%)	28 (70.0%)	0.049
Heterozygous variant	24 (30.0%)	8 (20.0%)	
Variant genotype	15 (18.8%)	4 (10.0%)	
Total	80 (100.0%)	40 (100.0%)	

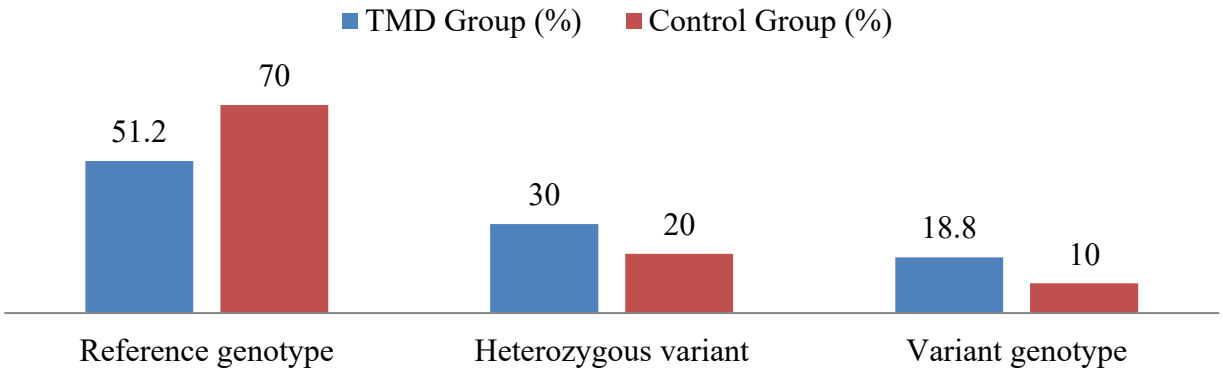

Figure 5: Distribution of COMT genotypes among participants with TMDs and healthy controls

Table 6 & Figure 6 present the relationship between the TNF-α polymorphism and TMD status. In the TMD group, 45 of 80 participants (56.2%) carried the reference genotype, whereas 35 (43.8%) carried the variant genotype. Among the 40 healthy controls, the reference genotype was present in 30 participants (75.0%), while the variant genotype was identified in 10 participants (25.0%). The variant genotype was consequently more common among participants with TMDs (43.8%) than among controls (25.0%). The observed difference in genotype distribution was statistically significant (p = 0.045), suggesting an association between the TNF-α polymorphism and TMD status within the study population.

Table 6: Association between TNF-α polymorphism and TMD

TNF-α Genotype/Status	TMD Group (n=80), n (%)	Control Group (n=40), n (%)	P value
Reference genotype	45 (56.2%)	30 (75.0%)	0.045
Variant genotype/carrier	35 (43.8%)	10 (25.0%)	
Total	80 (100.0%)	40 (100.0%)	

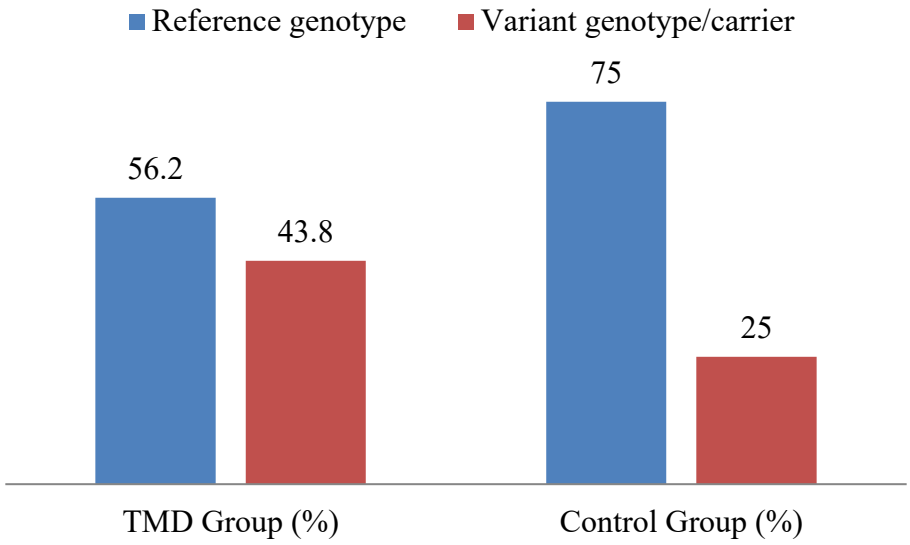

Figure 6: Association of TNF-α polymorphism genotype distribution with TMD status

Table 7 & Figure 7 present the association between the IL-10 polymorphism and TMD status. Among the 80 participants diagnosed with TMDs, 48 (60.0%) carried the reference genotype, whereas 32 (40.0%) carried the variant genotype. In the control group, comprising 40 participants, 31 (77.5%) had the reference genotype and 9 (22.5%) carried the variant genotype.

The variant genotype was observed in a greater proportion of participants with TMDs (40.0%) than in the control group (22.5%). However, the difference in genotype distribution between the two groups did not reach statistical significance (p = 0.057). Although the TMD group showed a higher proportion of IL-10 variant genotype carriers, the present findings do not provide statistically significant evidence of an association between the IL-10 polymorphism and TMD status in this study population.

Table 7: Association between IL-10 polymorphism and TMD

IL-10 Genotype/Status	TMD Group (n=80), n (%)	Control Group (n=40), n (%)	P value
Reference genotype	48 (60.0%)	31 (77.5%)	0.057
Variant genotype/carrier	32 (40.0%)	9 (22.5%)	
Total	80 (100.0%)	40 (100.0%)	

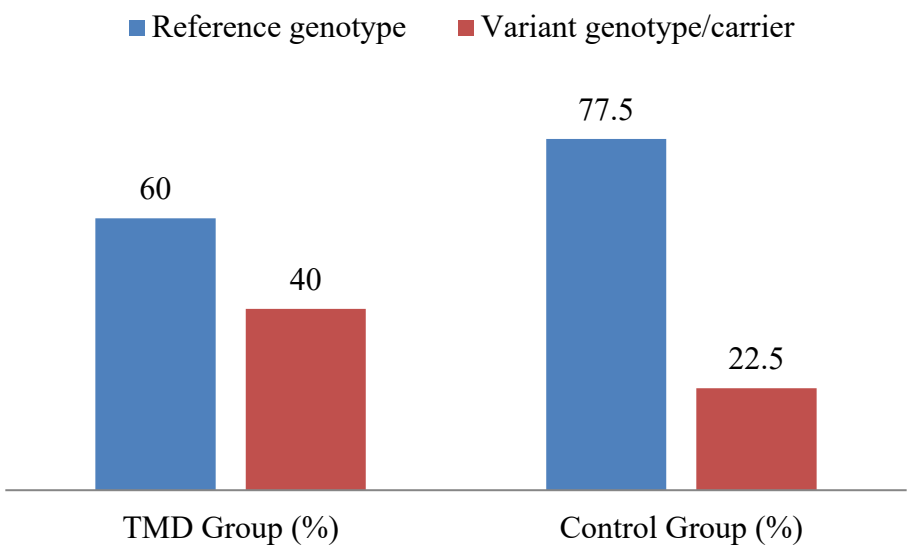

Figure 7: Distribution of IL-10 polymorphism genotypes among participants with TMDs and healthy controls

Table 8 & Figure 8 present the association between the MMP1 polymorphism and TMD status. Among the 80 participants with TMDs, 49 (61.2%) carried the reference genotype, whereas 31 (38.8%) carried the variant genotype. In the control group, consisting of 40 participants, 32 (80.0%) had the reference genotype and 8 (20.0%) carried the variant genotype. The MMP1 variant genotype was observed more frequently among participants with TMDs (38.8%**)** than among healthy controls (20.0%**).** The difference in genotype distribution between the two groups was statistically significant (p = 0.039), indicating an association between the MMP1 polymorphism and TMD status in the study population.

Table 8: Association between MMP1 polymorphism and TMD

MMP1 Genotype/Status	TMD Group (n=80), n (%)	Control Group (n=40), n (%)	P value
Reference genotype	49 (61.2%)	32 (80.0%)	0.039
Variant genotype/carrier	31 (38.8%)	8 (20.0%)	
Total	80 (100.0%)	40 (100.0%)	

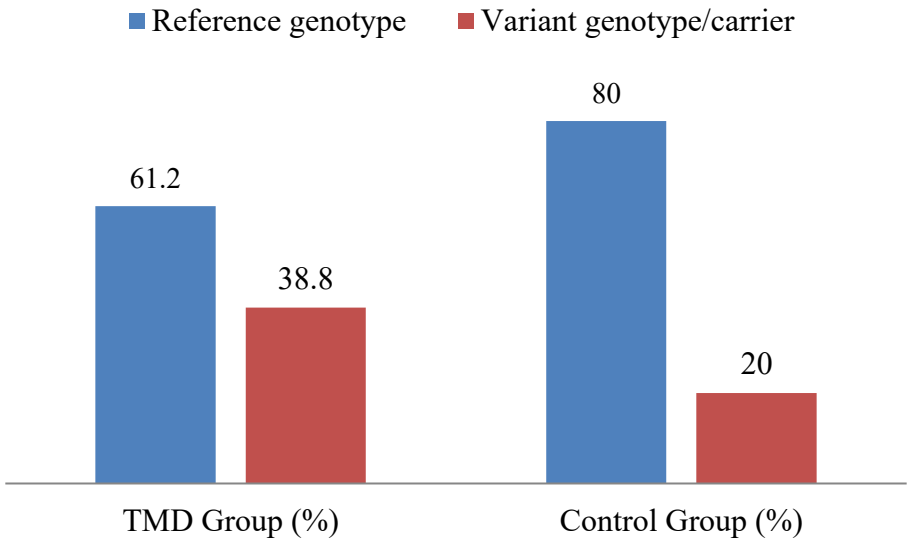

Figure 8: Distribution of MMP1 polymorphism genotypes among participants with TMDs and healthy controls

Table 9 & Figure 9 present the association between the ESR1/ESR2 polymorphism and TMD status. Of the 80 participants with TMDs, 51 (63.7%) carried the reference genotype, whereas 29 (36.3%) carried the variant genotype. Among the 40 healthy controls, 32 (80.0%) had the reference genotype and 8 (20.0%) carried the variant

genotype. The ESR1/ESR2 variant genotype was more frequently observed in the TMD group (36.3%) than in the control group (20.0%). However, the difference in genotype distribution between the two groups was not statistically significant (p = 0.067). Therefore, despite the higher proportion of ESR1/ESR2 variant genotype carriers among participants with TMDs, the present findings do not demonstrate a statistically significant association between this polymorphism and TMD status.

Table 9: Association between ESR1/ESR2 polymorphism and TMD

ESR1/ESR2 Genotype/Status	TMD Group (n=80), n (%)	Control Group (n=40), n (%)	P value
Reference genotype	51 (63.7%)	32 (80.0%)	0.067
Variant genotype/carrier	29 (36.3%)	8 (20.0%)	
Total	80 (100.0%)	40 (100.0%)	

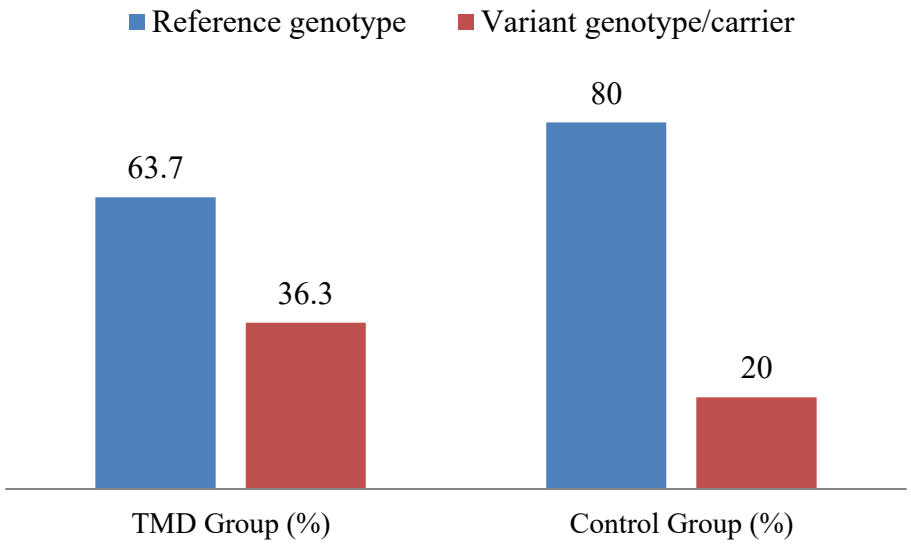

Figure 9: Distribution of ESR1/ESR2 polymorphism genotypes among participants with TMDs and healthy controls

Table 10 presents multivariable logistic regression was performed to identify independent predictors of TMD after adjustment for the other variables included in the model. COMT variant genotype was significantly associated with TMD, with an adjusted OR of 2.31 (95% CI: 1.14–4.69; p=0.020), indicating higher odds of TMD among participants carrying the COMT variant. Similarly, the TNF-α variant was independently associated with TMD (adjusted OR=2.08, 95% CI: 1.02–4.25; p=0.043). The MMP1 variant demonstrated a significant association with TMD, with an adjusted OR of 2.76 (95% CI: 1.18–6.47**;** p=0.019). Among the non-genetic factors, the presence of a parafunctional habit was also significantly associated with TMD (adjusted OR=2.44, 95% CI: 1.22–4.89; p=0.011). In contrast, age was not significantly associated with TMD (adjusted OR=1.02, 95% CI: 0.99–1.05; p=0.162), and female sex also did not show a statistically significant independent association (adjusted OR=1.38, 95% CI: 0.72–2.65; p=0.328). Overall, the multivariable model identified COMT, TNF-α, MMP1 variant status, and parafunctional habits as significant independent predictors of TMD, whereas age and sex were not statistically significant after adjustment for the other variables. These findings indicate an association rather than a causal relationship between the genetic variants and TMD.

Table 10: Multivariable logistic regression for TMD

Predictor	Adjusted OR	95% CI	p-value
COMT variant	2.31	1.14–4.69	0.020
TNF-α variant	2.08	1.02–4.25	0.043
MMP1 variant	2.76	1.18–6.47	0.019
Parafunctional habit	2.44	1.22–4.89	0.011
Age	1.02	0.99–1.05	0.162

Female sex	1.38	0.72–2.65	0.328

Table 11 & Figure 10 present the relationship between genetic variant status and the change in VAS pain scores following prosthodontic rehabilitation. Participants carrying the COMT variant demonstrated a mean reduction in VAS pain score of 2.48 ± 1.14, compared with 2.42 ± 1.09 among those without the variant; this difference was not statistically significant (p = 0.782). For the TNF-α polymorphism, the mean reduction in VAS score was 2.51 ± 1.16 among variant carriers and 2.46 ± 1.08 among participants without the variant (p = 0.841). The corresponding values for IL-10 were 2.45 ± 1.12 and 2.49 ± 1.10, respectively, with no statistically significant difference (p = 0.873). For MMP1, participants with the variant demonstrated a mean VAS reduction of 2.38 ± 1.13, compared with 2.51 ± 1.09 among those without the variant (p = 0.612). Similarly, the mean reduction associated with ESR1/ESR2 was 2.47 ± 1.15 among variant carriers and 2.44 ± 1.08 among non-carriers (p = 0.918). Overall, none of the evaluated genetic polymorphisms demonstrated a statistically significant association with the reduction in VAS pain scores following prosthodontic rehabilitation (all p > 0.05). Thus, within the study population, COMT, TNF-α, IL-10, MMP1, and ESR1/ESR2 variant status was not significantly associated with the magnitude of pain reduction after rehabilitation.

Table 11: Association between genetic variant status and reduction in vas pain score following prosthodontic rehabilitation

Genetic polymorphism	**Variant Present Mean ± SD**	**Variant Absent Mean ± SD**	**p-value**	**Significance**
COMT	2.48 ± 1.14	2.42 ± 1.09	0.782	Not significant
TNF-α	2.51 ± 1.16	2.46 ± 1.08	0.841	Not significant
IL-10	2.45 ± 1.12	2.49 ± 1.10	0.873	Not significant
MMP1	2.38 ± 1.13	2.51 ± 1.09	0.612	Not significant
ESR1/ESR2	2.47 ± 1.15	2.44 ± 1.08	0.918	Not significant

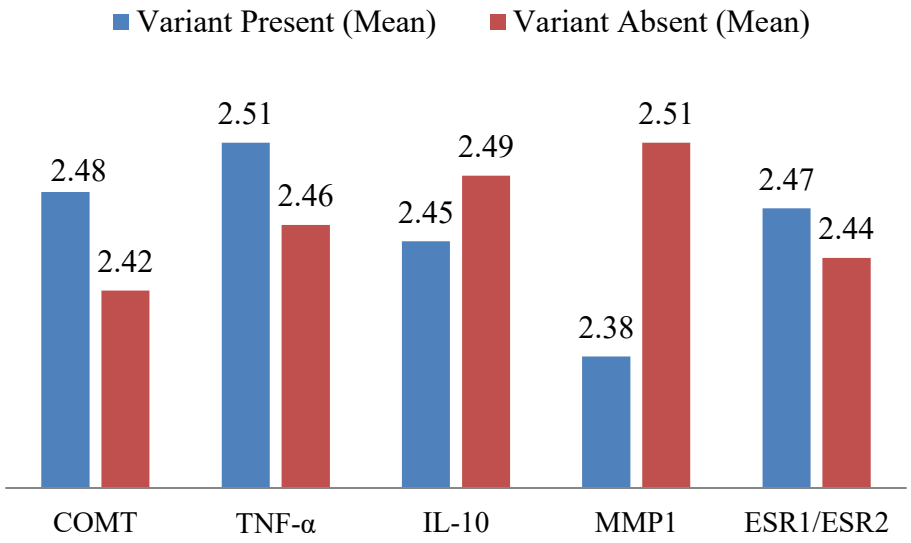

Figure 10: Association between genetic variant status and reduction in VAS pain scores following prosthodontic rehabilitation

Table 12 & Figure 11 present the relationship between genetic variant status and the change in maximum mouth opening following prosthodontic rehabilitation. Participants carrying the COMT variant demonstrated a mean

increase in mouth opening of 3.42 ± 2.81 mm, compared with 3.51 ± 2.76 mm among participants without the variant. This difference was not statistically significant (p = 0.874). Among participants with the TNF-α variant, the mean increase in mouth opening was 3.36 ± 2.79 mm, compared with 3.54 ± 2.77 mm in those without the variant (p = 0.761). For the IL-10 polymorphism, the corresponding mean increases were 3.45 ± 2.83 mm in variant carriers and 3.48 ± 2.75 mm in non-carriers, with no statistically significant difference (p = 0.956). Participants carrying the MMP1 variant showed a mean increase of 3.31 ± 2.82 mm, compared with 3.56 ± 2.73 mm among those without the variant (p = 0.684). For ESR1/ESR2, the mean increases were 3.44 ± 2.80 mm among variant carriers and 3.50 ± 2.74 mm among non-carriers (p = 0.924). Overall, none of the evaluated genetic polymorphisms demonstrated a statistically significant association with the improvement in maximum mouth opening following prosthodontic rehabilitation (all p > 0.05). Within the present dataset, the magnitude of improvement in mandibular opening was therefore not significantly different according to COMT, TNF-α, IL-10, MMP1, or ESR1/ESR2 variant status.

Table 12: Association between genetic variant status and increase in mouth opening following prosthodontic rehabilitation

Genetic polymorphism	**Variant Present Mean ± SD (mm)**	**Variant Absent Mean ± SD (mm)**	**p-value**	**Significance**
COMT	3.42 ± 2.81	3.51 ± 2.76	0.874	Not significant
TNF-α	3.36 ± 2.79	3.54 ± 2.77	0.761	Not significant
IL-10	3.45 ± 2.83	3.48 ± 2.75	0.956	Not significant
MMP1	3.31 ± 2.82	3.56 ± 2.73	0.684	Not significant
ESR1/ESR2	3.44 ± 2.80	3.50 ± 2.74	0.924	Not significant

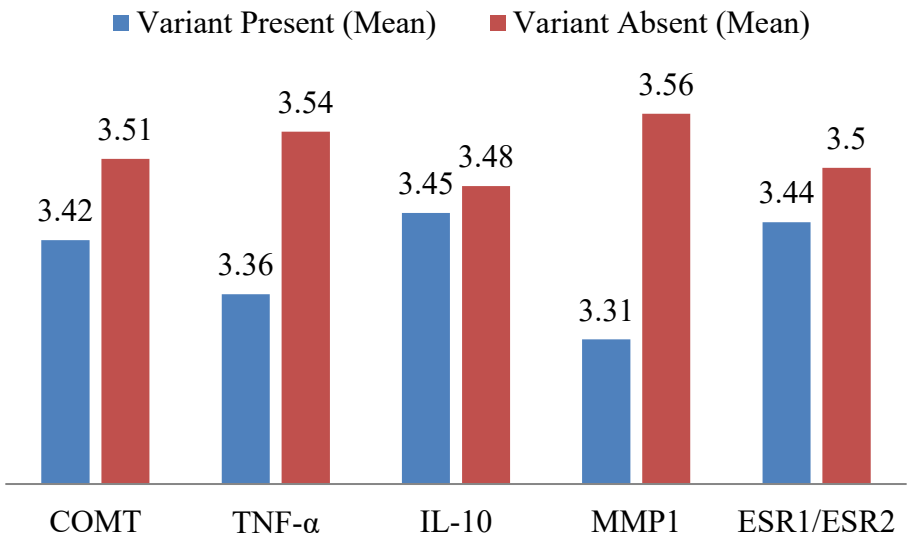

Figure 11: Association between genetic variant status and improvement in maximum mouth opening following prosthodontic rehabilitation

DISCUSSION

The present study demonstrated significant associations between selected genetic variants involving COMT, TNF-α, ESR1/ESR2 and MMP1 and TMD status, suggesting that inherited biological differences may contribute to individual susceptibility to TMDs. At the same time, the absence of a significant relationship between genetic variant status and the magnitude of symptomatic or functional improvement after prosthodontic rehabilitation

indicates that genetic susceptibility and treatment response may represent distinct clinical phenomena. These findings support a multifactorial model in which genetic, mechanical, behavioral, inflammatory, and functional factors interact in the development and clinical expression of TMD.

The relationship between dental occlusion and TMD has historically been an important consideration in prosthodontics. However, the available evidence does not support a simple direct causal relationship between occlusal characteristics and TMD. Manfredini et al. (2017) [10] reviewed association studies concerning dental occlusion and TMD and emphasized the complexity of the relationship, indicating that occlusal variables should not be regarded as isolated determinants of TMD. This perspective is consistent with the present findings, in which genetic susceptibility and parafunctional behavior were associated with TMD, while genetic status did not independently predict the extent of improvement following rehabilitation. Thus, TMD should be approached as a condition arising from multiple interacting determinants rather than from a single anatomical or genetic factor.

The genetic component identified in the present study is supported by previous molecular investigations. Aneiros-Guerrero et al. (2011) [11] reported associations between TMD and polymorphisms involving folate-pathway enzymes, dopamine receptor D4 (DRD4), and glutathione S-transferase M1 (GSTM1). Their findings demonstrated that genetic variation across biological pathways involved in neurotransmission, metabolism, and cellular responses may contribute to differences in TMD susceptibility. The present observation of associations involving COMT, TNF-α, and MMP1 similarly indicates that genetic variation affecting neurotransmitter metabolism, inflammatory regulation, and ECM remodeling may influence the likelihood of developing TMD.

The broader genetic evidence has also been synthesized using comparative approaches. Almeida et al. (2025) [12] conducted a network meta-analysis of genetic polymorphisms associated with TMD and demonstrated that multiple genetic pathways may be involved in TMD-related phenotypes. Their findings reinforce the concept that TMD genetic susceptibility is polygenic rather than attributable to a single gene or polymorphism. In this context, the associations observed in the present study should be interpreted as evidence of potential biological susceptibility rather than proof that any individual variant directly causes TMD. Genetic effects may be relatively modest and may become clinically relevant through interactions with environmental exposures, parafunctional activity, mechanical loading, inflammatory processes, and individual pain-processing characteristics.

Parafunctional habits represented another important factor associated with TMD in the present investigation. Repetitive activities such as tooth clenching, grinding, or other excessive mandibular muscle activity can increase functional loading of the masticatory system and may contribute to muscular fatigue, joint stress, and persistence of symptoms. The coexistence of parafunctional behavior and genetic susceptibility may therefore help explain why individuals exposed to apparently similar mechanical conditions can develop different clinical manifestations. Importantly, the present findings do not establish a causal relationship between parafunctional habits and TMD, but they support their consideration during comprehensive clinical assessment.

The role of prosthodontic treatment in patients with TMD requires careful interpretation. Hagag et al. (2000) [13] discussed the relationship between occlusion, prosthodontic treatment, and TMDs and emphasized the importance of considering functional factors when planning prosthodontic care. Their observations are relevant to the present study because rehabilitation may modify occlusal contacts, mandibular function, and the distribution of functional forces. Nevertheless, improvement after rehabilitation cannot necessarily be attributed to correction of a specific genetic or occlusal abnormality. The clinical response is likely to reflect the combined effects of restoration of oral function, adaptation of the masticatory system, symptom management, behavioral modification, and individual biological characteristics.

The improvement observed following rehabilitation, despite the absence of a significant association between genetic status and treatment response, is particularly noteworthy. This finding suggests that patients carrying potentially susceptibility-associated variants may still experience clinically meaningful improvement after appropriate prosthodontic management. Consequently, genetic variation should not be interpreted as a determinant of poor treatment response. Instead, genetic information may have greater relevance for understanding baseline susceptibility than for predicting the degree of postoperative or post-rehabilitation improvement. This distinction is important because it prevents genetic findings from being overextended into clinical decision-making without adequate evidence.

Conservative and functional interventions may also influence TMD outcomes independently of genetic background. Zhang et al. (2021) [14] reported that exercise-based interventions and occlusal splint therapy can be beneficial approaches for painful TMD, highlighting the potential importance of functional rehabilitation and symptom-directed management. These observations support a multimodal treatment philosophy in which management is directed toward the patient's clinical presentation rather than determined solely by genetic characteristics. In patients undergoing prosthodontic rehabilitation, appropriate assessment of pain, mandibular movement, parafunctional behavior, muscle function, and joint symptoms may therefore remain essential regardless of genotype.

Sex-hormone-related genetic pathways may provide another dimension to the biological heterogeneity of TMD. La Rosa et al. (2025) [15] systematically examined polymorphisms in ESR1/ESR2 and their relationship with TMDs,

emphasizing the potential involvement of estrogen-related biological mechanisms in TMD susceptibility. Although the present study focused on COMT, TNF-α, and MMP1 rather than estrogen receptor polymorphisms, these findings reinforce the broader concept that genetic regulation of inflammatory, hormonal, and tissue-remodeling pathways may contribute to individual differences in TMD presentation. Such evidence further supports a multifactorial model rather than a single-gene explanation.

The association of MMP1 variants with TMD in the present study is biologically plausible because MMP-1 participate in ECM degradation and tissue remodeling. Altered regulation of matrix-degrading enzymes could potentially affect the equilibrium between tissue breakdown and repair within the TMJ Similarly, TNF-α is an important inflammatory mediator, and genetic variation affecting inflammatory signaling could modify the biological response to mechanical stress. COMT, through its role in catecholamine metabolism, may influence pain processing and individual differences in pain sensitivity. These pathways provide a possible biological framework linking genetic variation with TMD susceptibility, although functional confirmation of these mechanisms requires molecular and longitudinal investigations.

An important finding of the present study was the lack of a statistically significant association between genetic variant status and the magnitude of symptomatic or functional improvement after prosthodontic rehabilitation. This result indicates that the presence of a susceptibility-associated genotype should not automatically be considered a predictor of treatment outcome. Clinical improvement may be influenced by numerous factors, including baseline disease severity, duration of symptoms, parafunctional behavior, psychosocial factors, prosthetic design, adherence to treatment recommendations, neuromuscular adaptation, and follow-up duration. Therefore, genetic information should currently be considered complementary to, rather than a replacement for, conventional clinical assessment.

The findings also have potential implications for individualized prosthodontic care. Genetic testing could eventually contribute to risk stratification if specific variants are consistently validated across larger and ethnically diverse populations. However, the present results do not justify using individual genetic variants alone to determine whether a patient should receive a particular prosthodontic intervention. Instead, genotype information may eventually be integrated with clinical examination, TMD diagnostic criteria, imaging, parafunctional assessment, pain characteristics, and functional measurements. Such an approach could provide a more comprehensive understanding of individual biological variability while avoiding overinterpretation of isolated genetic associations.

Several limitations should be considered when interpreting these findings. The identification of statistical associations does not establish causality, particularly in a multifactorial disorder such as TMD. Genetic effects may also vary according to population characteristics, environmental exposures, sex, age, disease phenotype, and interactions among multiple variants. Furthermore, candidate-gene associations require replication in independent populations before their clinical utility can be established. The absence of an association between genotype and rehabilitation response should similarly be interpreted cautiously because treatment outcomes may be influenced by multiple clinical and behavioral variables.

Overall, the present findings add to the growing evidence that TMD susceptibility may involve interactions between genetic predisposition and behavioral or mechanical exposures. The observed associations involving COMT, TNF-α, and MMP1 are consistent with the involvement of pain-processing, inflammatory, and ECM pathways, while the association with parafunctional habits highlights the contribution of modifiable functional factors. At the same time, the lack of a significant relationship between genetic variant status and improvement following prosthodontic rehabilitation indicates that genetic susceptibility should not be equated with treatment prognosis. Further longitudinal and multicenter studies incorporating larger samples, comprehensive genetic profiling, and standardized TMD phenotyping are warranted to determine whether genetic information can eventually provide clinically useful risk stratification or treatment-response prediction.

LIMITATIONS

The present study has several limitations that should be considered when interpreting its findings. First, the study included a relatively small sample of 120 participants, comprising 80 individuals with TMDs and 40 healthy controls, which may limit the statistical power and generalizability of the findings. The assessment was based on a selected group of genetic polymorphisms, including COMT, TNF-α, IL-10, MMP1, and ESR1/ESR2**;** therefore, other genetic variants or gene–gene interactions that may contribute to TMD susceptibility were not evaluated. Second, TMDs are multifactorial conditions influenced by biological, mechanical, behavioral, and psychosocial factors. Although the analysis incorporated selected demographic and clinical variables, residual confounding by factors not included in the model cannot be excluded. The observed genetic associations should consequently be interpreted as statistical relationships rather than evidence of a direct causal effect. The study also relied on genotype or variant-carrier classifications, which may not fully reflect the functional consequences of individual genetic variants or their effects on gene expression and protein activity. Furthermore, the absence of significant differences in pain reduction and improvement in maximum mouth opening according to genetic variant status suggests that the clinical relevance of these polymorphisms for prosthodontic rehabilitation remains uncertain. Finally, the findings

were obtained within the specific study population and clinical context examined and may not be directly applicable to populations with different demographic or genetic characteristics. Larger, adequately powered studies incorporating broader genetic profiling, longer follow-up periods, and detailed assessment of environmental, behavioral, and psychosocial factors are required to clarify the clinical significance of genetic susceptibility in TMDs and its potential role in prosthodontic treatment planning.

CONCLUSION

The present study indicates that selected genetic polymorphisms may be associated with TMD status. In particular, COMT, TNF-α, and MMP1 variant status demonstrated significant associations with TMD in the multivariable analysis, while parafunctional habits also showed an independent association. In contrast, IL-10 and ESR1/ESR2 did not demonstrate statistically significant associations with TMD status in the overall analysis. Despite these associations, genetic variant status was not significantly related to the magnitude of pain reduction or improvement in maximum mouth opening following prosthodontic rehabilitation. The findings therefore suggest that, within the present dataset, these genetic polymorphisms may be relevant to TMD susceptibility but do not appear to independently determine short-term clinical improvement following prosthodontic rehabilitation. Overall, genetic factors may represent one component of the complex biological background underlying TMDs, rather than isolated determinants of disease or treatment outcome. Genetic information may eventually complement clinical examination, functional assessment, imaging, and evaluation of behavioral and environmental factors in individualized patient care. However, the present findings should be interpreted as evidence of association rather than causation. Further large-scale and longitudinal investigations are warranted to establish whether genetic profiling can provide clinically meaningful information for risk assessment and personalized prosthodontic rehabilitation.

Conflicts of Interest: Nil
Financial Support: None

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