e-ISSN: 2637-0611

Available online at
https://journal.uitm.edu.my/ojs/index.php/COS

Compendium of Oral Science 12 (2) 2025, 176 - 194

Compendium of Oral Science

Genetic and Epigenetic Contributions to Psychosomatic Conditions in Temporomandibular Disorder: A Systematic Review

Jamil Ahsan Kazi[1], Nur Fatihah Azman[1], Nur Asma Hashim[1], Nik Mohd Mazuan Nik Mohd Rosdy[1], Noor Azliza Wani Abd. Aziz[1*]

[1]*Faculty of Dentistry, Universiti Teknologi MARA Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia*

ARTICLE INFO

Article history:
Received 05 November 2024
Revised 11 January 2025
Accepted 10 March 2025
Online First
Published 01 September 2025

Keywords:
temporomandibular disorder
genetic
epigenetic
pain
psychological stress

DOI:
10.24191/cos.v12i2.8837

ABSTRACT

Objectives: Temporomandibular disorder (TMD) is a complex condition with unclear causes and an uncertain diagnosis. Evidence suggests that genetic and epigenetic factors contribute to its pathogenesis and influence psychosomatic conditions. Understanding these genotype-phenotype interaction is crucial for improving diagnosis and developing targeted therapies. This systematic review aims to (i) examine the genetic and epigenetic factors involved in TMD and (ii) assess their association with psychosomatic manifestations.

Methods: This review was registered in International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42024583915) and conducted in accordance with PRISMA guidelines. A systematic search of PubMed, MEDLINE, Scopus, ScienceDirect, Web of Science and Wiley databases identified studies published between 2019 and 2024. Eligible studies were selected based on predefined inclusion criteria. Extracted genomic and epigenomic data were analysed to identify predictive and diagnostic markers associated with TMD. A decision matrix analysis was performed to determine the most significant factors.

Results: Ten studies met the inclusion criteria. Genetic variations associated with TMD encode for structural, transporter, regulatory, receptor, enzymatic and ion channel proteins, while epigenetic modifications affected genes encoding extracellular protein, enzyme and transcription factor. Among these, COMT rs4680 was the most

[1*] Corresponding author. *E-mail address*: norazlizawani@uitm.edu.my

extensively studied, showing strong associations with pain modulation and anxiety in TMD patients.
Conclusion: The COMT gene emerges as a promising therapeutic target in TMD. This review highlights the complex interplay between genetic predisposition, epigenetic regulation and psychosomatic influences on TMD. A deeper understanding of these interactions may facilitate early diagnosis and personalized treatment strategies for managing TMD-related pain and psychological comorbidities.

1. INTRODUCTION

Temporomandibular joint (TMJ) is a highly specialized synovial joint formed by the articulation between the mandibular condyle with the glenoid fossa and articular eminence of temporal bone (Murphy et al., 2013). It is composed of synovial cavity, TMJ disc and a capsule, and is classified as ginglymoarthrodial joint which provides both gliding and hinge movement (Bordoni & Varacallo, 2023). Histologically, the TMJ disc is a fibrocartilaginous tissue with a biconcave shape that allows it to fit the bony anatomy and divide the joint into a superior and inferior compartment (Stocum & Roberts, 2018).

Temporomandibular disorder (TMD) is defined as a set of diseases and disorders that are related to alterations in the structure, function, or physiology of the masticatory system and that may be associated with other systemic and comorbid medical conditions (Laskin et al., 1983). It is one of the most common causes of orofacial pain (Spotts, 2017). Clinically, TMD presents with jaw pain, jaw joint locking, muscle tenderness and difficulty in chewing, which significantly impact daily activities. Unfortunately, researchers have been facing multiple challenges in developing the effective therapy due to its complex and multifactorial aetiopathogenesis (Bond et al., 2020). Contributing factors include trauma, arthritis, bruxism, stress, hormonal influences, and genetic predispositions. Psychological distress such as anxiety, has been specifically linked to TMD (Santos et al., 2022; Warzocha et al., 2024), as well as pain-related and joint-related TMD symptoms (Yap et al., 2021). Patients with myofascial TMD, in particular, exhibit heightened pain sensitivity and emotional distress (Manfredini et al., 2020), underscoring the role of psychosomatic interactions in disease manifestation.

According to Diagnostic Criteria for TMD (DC/TMD) Axis I, TMDs are divided into Group I: muscle disorders (including myofascial pain with and without mouth-opening limitation; Group II: involving disc displacement with or without reduction and mouth-opening limitation; and Group III: arthralgia, arthritis, and arthrosis (Schiffman et al., 2014). Clinically, TMD case are referred to the specialists of oral and maxillofacial surgery and oral medicine. Treatment involves pain relief, anti-inflammatory medications, muscle relaxants, physical therapy, behavioural counselling, and in severe cases, surgical intervention. However, the absence of objective predictive biomarkers limits early diagnosis and personalized treatment approaches.

Structurally, TMD is classified as either intra-articular due to inflammation, internal derangement or degeneration, or extra-articular due to muscular dysfunction. Histopathologically, TMJ disc degeneration is characterized by fibrosis, sclerosis, collagen deposition, calcification and inflammatory infiltration (Nardini et al., 2021). Recent studies have identified inflammatory biomarkers such as TNF-α, TNF receptors, interleukin-8 (IL-8), IL-6, and IL-1 in TMD patients, corroborated by imaging techniques like cone-beam computed tomography, magnetic resonance imaging and arthroscopy (Zwiri et al., 2020). Additionally, genome-wide analyses have reported altered expression of miRNAs in synovial fibroblasts and cartilage, affecting degenerative processes (Xu et al., 2016; Zhang et al., 2020; Mao et al., 2021). However, the molecular pathways underlying these pathological changes remain unclear.

https://doi.org/10.24191/cos.v12i2.8837

Recent research has focused on the role of genetic factors in the development and progression of TMD (Sangani et al., 2015). With regards to genetic polymorphisms, several factors including serotonin, cathecolamine, estrogen, folate and human leukocyte antigen (HLA) have been shown to be associated with the risk for TMD. With regards to gene mutation, several genes have been reported to influence the susceptibility towards TMD, including oestrogen receptor alpha (ESR1) (Kim et al., 2010), tumour necrosis factor alpha (TNF-α) (Etőz et al., 2006) and monoamine oxidase-A (MAOA) (Mutlu et al., 2005).

Beyond genetic variations, an interaction between the internal and external environment has been shown to lead to a localised change in DNA molecule that initiates a dramatic change in gene expression patterns and cell phenotype, termed as epigenetic mechanism (Turner, 2009). The epigenetic processes that are known to be capable of altering the gene expression patterns include i. cytosine methylation, ii. post-translational modification of histone proteins, and iii. RNA-based mechanisms. Notably, Dnmt3b deficiency has been shown to lead to TMJ osteoarthritis-like conditions (Zhou et al., 2019), while miRNA-140 has been identified as a key regulator of bone homeostasis and articular remodeling in the TMJ (Antolis et al., 2021).

Despite growing evidence of genetic-epigenetic interplay in TMJ and TMD, its role in psychosomatic manifestations such as pain, anxiety, and depression in TMD remains poorly understood. Therefore, this systematic review aims to: (i) Identify genetic and epigenetic factors influencing TMD development and progression, and (ii) Explore the relationship between molecular mechanisms and psychosomatic factors including pain, anxiety and depression, to enhance our understanding of TMD pathophysiology. By integrating these perspectives, this review seeks to provide insights into potential early diagnostic markers, risk stratification and targeted therapeutic strategies for TMD patients.

2. MATERIALS AND METHODS

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), ID: CRD42024583915.

2.1 Search strategy

The articles were systematically searched in accordance with the PRISMA 2020 guidelines. It was conducted in three stages involving article i. identification, ii. screening, and iii. included, in parallel with the predefined inclusion criteria. In identification stage, articles were searched through PubMed, MEDLINE, Scopus, ScienceDirect, Web of Science and Wiley databases, from the year 2019 to 2024, based on Booleans: 'genetic' OR 'epigenetic' AND 'temporomandibular disorder' AND 'anxiety' OR 'stress' OR 'depression'. The articles obtained from all databases were downloaded and transferred to the reference management software EndNote to ease the tracking of articles, in terms of the number of articles identified and the number of duplicates removed, as well as for the purpose of sharing the access of EndNote library between the reviewers at the end of article screening.

2.2 Procedure for study selection

Two independent reviewers were involved in the identification phase, which included article search through databases. The same two independent reviewers were then responsible for the screening phase, where articles with titles, abstracts and full texts were evaluated against predefined inclusion criteria. In the included phase, an additional independent reviewer was added, bringing the total number of reviewers to three. These three reviewers assessed the articles that focused on predictive markers for prospective studies, or diagnostic markers for retrospective studies. To evaluate the methodological quality of the included

https://doi.org/10.24191/cos.v12i2.8837

articles, the Risk of Bias (RoB) tool was applied. The CAMARADES checklist was used, assessing criteria such as randomization, use of controls, sample size calculation, peer-reviewed publication, outcome measures and declarations of potential conflicts of interest. Any discrepancies between reviewers' assessments were resolved through inter-examiner calibration, involving a fourth independent reviewer. The selection criteria included (i) Type of study, (ii) Type of report, (iii) Publication date and (iv) Language. The inclusion and exclusion criteria for selecting studies are summarized in Table 1.

Table 1. Inclusion and exclusion criteria.

	Inclusion criteria	**Exclusion criteria**
i. Type of study	a. Prospective studies that analyse progression of TMD with long-term follow-up outcomes. b. Retrospective studies comparing the groups with and without TMD.	Case reports.
ii. Type of report	Studies that report on: a. Predictive markers (prospective studies). b. Diagnostic markers (retrospective studies).	Studies that do not report on molecular markers.
iii. Publication date	Articles between 2019 - 2024.	Articles published before 2019, and after 2024.
iv. Language	Articles in English language.	Articles in other languages.

2.3 Strategy for data synthesis

2.3.1 Details of demographic characteristic of the study patients

The details of demographic characteristics of the study patients involving age, gender, country of origin, any parafunctional habits like excessive gum chewing and bruxism habit were recorded to assess potential influences on TMD outcomes.

2.3.2 Determination of outcome determinant

Outcome parameters focused on genetic and epigenetic factors and their risk for TMD conditions. Additionally, psychosomatic factors such as pain, anxiety and depression were examined in correlation with these genetic/epigenetic changes. The outcomes were summarised in a table, based on authors and their findings.

2.3.3 Genetic and epigenetic risk factors for TMD

The groups of the predictive and diagnostic markers and the risk for TMD conditions obtained from patients of each study were described. The biomarkers were grouped according to their association with psychosomatic conditions (painful TMD, anxiety and depression). These findings were summarized in a table to visualize the correlations between genetic/epigenetic factors and psychosomatic conditions.

https://doi.org/10.24191/cos.v12i2.8837

2.3.4 Identification of the Potential Genetic and Epigenetic Factors Contributing to TMD

The potential factors for TMD conditions were identified using the decision matrix analysis. The analysis began with a simple decision matrix, followed by weighted decision matrix, as described by Chang (2015). In simple decision matrix, the targets were scored against each criteria (outcome), based on the number of articles which reported the outcomes. This was followed by the weighted decision matrix, where scoring was done by having 1 – 4 points from the least mentioned outcome to the most mentioned. The target with the highest score represents the most investigated target with the most reported outcome.

3.0 RESULTS

3.1 Articles selection

839744 articles were obtained during the Identification stage following searching through the databases. At the end of Screening stage, the duplicates were removed, and research articles in English language with full text available, which reported the findings on prospective and/or retrospective studies in human were chosen, where 82 articles were obtained. During the Included stage, only research articles which concluded on the predictive markers (for prospective studies), or diagnostic markers (for retrospective studies) were chosen, where 26 articles were obtained. At the end of the Included stage, inter-examiner calibration was done to finalise selected articles based on evaluation of methodological quality, as summarised in Table 2, where 10 research articles were finally selected for the present systematic review, as summarised in Figure 1.

Table 2. Summary of the details of Risk of Bias (RoB) evaluation based on CAMARADES checklist.

No.		**Randomization**	**Use of controls, sample size calculation**	**Peer-reviewed publication**	**Outcome measures**	**Declarations of potential conflicts of interest**
1	Rechia et al. (2020)	/	/	/	/	-
2	Jounger et al. (2021)	-	-	/	/	/
3	Vrbanović et al. (2023)	-	/	/	/	/
4	Zlendić et al. (2024)	/	/	/	/	/
5	Zlendić et al. (2024)	/	/	/	/	/
6	Ao et al. (2023)	/	/	/	/	/
7	Baratto et al. (2022)	/	/	/	/	/
8	Ekici & Söylemez (2024)	-	/	/	/	/
9	Brancher et al. (2019)	/	/	/	/	/
10	Meyer et al. (2024)	/	/	/	/	/

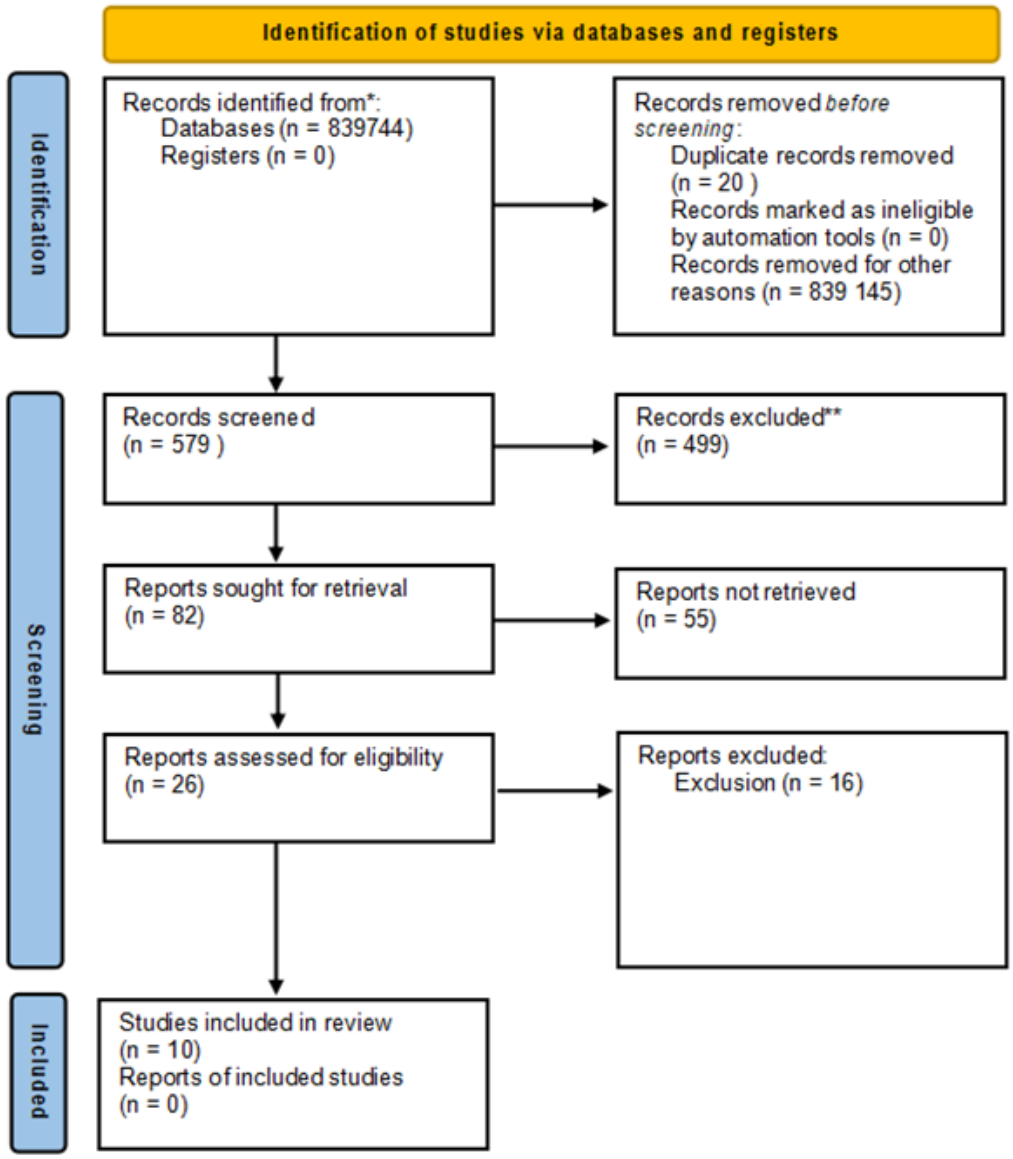

Fig 1. PRISMA 2020 flow diagram

The search and selection of the articles were carried out in three stages. In the first stage (Identification), the articles were searched based on Booleans, through databases. In the second stage (Screening), the duplicates were removed, and research articles in English language with full text available, which reported the findings on prospective and/or retrospective studies in human were chosen. In the third stage (Included), only research articles which concluded on the predictive markers (for prospective studies), or diagnostic markers (for retrospective studies) were chosen. At the end of the Included stage, inter-examiner calibration was done to finalize selected articles for the present systematic review.

https://doi.org/10.24191/cos.v12i2.8837

3.2 Demographic characteristic of study patients

The details of demographic characteristics of the study patients of TMD include the age, gender, country and hospital/ institute of sample origin, habit, and year of sample collection. Four-fifth (80%) of study patients were in the age range of more than 18 years old. Both genders were involved in the majority of the studies. The parafunctional habits like excessive gum chewing and bruxism habit were reported in only one-tenth of the studies. The details of demographic characteristics in the ten studies are summarised in Table 3.

Table 3. Summary of the details of demographic characteristics of the study patients of TMD.

No.	References	Age (year old)	Gender	Country	DNA isolated from	Habit	Sample taken (year)
1.	Rechia et al. (2020)	10 - 14	N/A	Brazil	Buccal cell	N/A	2016
2.	Jounger et al. (2021)	>18	Male & Female	Sweden	Blood or saliva	N/A	N/A
3.	Vrbanović et al. (2023)	⩾18	Male & Female	Croatia	Buccal swab	Bruxism	January 2020 - September 2022
4.	Zlendić et al. (2024)	⩾18	Male& Female	Croatia	Buccal swab	N/A	2020 - 2022
5.	Zlendić et al. (2024)	⩾18	Male& Female	Croatia	Buccal swab	N/A	2020 - 2022
6.	Ao et al. (2023)	18 - 44	Male & Female	United States	Blood	N/A	2006
7.	Baratto et al. (2022)	19-70	Male	Brazil	Saliva	N/A	2018 - 2019
8.	Ekici & Söylemez (2024)	18-65	Male & Female	Turkey	Blood	N/A	2023
9.	Brancher et al. (2019)	10-14	Girls & Boys	Brazil	Buccal cell	N/A	September 2014 - July 2016
10.	Meyer et al. (2024)	≥18	Male & Female	South Africa	Saliva	N/A	2020 - 2022

N/A: Information not available

3.3 Summary of Biomarkers of TMD and the Psychosomatic Association

The biomarkers of all the ten studies were described based on the genetic and epigenetic factors, in relation to the psychosomatic association. The psychosomatic association were investigated by more than four-fifth (90%) of the studies. The association between biomarkers of TMD with pain, anxiety and/or depression are summarized in Table 4.

https://doi.org/10.24191/cos.v12i2.8837

Table 4. Summary of Biomarkers of TMD

9 studies assessed genetic factors	1. Rechia et al. (2020), COL2AI gene polymorphisms are not associated with myofascial pain and arthralgia in adolescents in Brazil, but rs2276454 is involved in the disc displacement. 2. Jounger et al. (2021), HTR3A gene polymorphisms rs1062613 contribute to increased pain intensity in TMD myalgia. 3. Vrbanović et al. (2023), GPX1 gene polymorphisms were not found to be significant risk factors for painful TMD, but rs1050450 linked to increased oral behaviours in patients, suggesting a relationship between daytime bruxism and stress. 4. Zlendić et al. (2023), OPRPN gene polymorphisms rs1387964 and COMT gene polymorphisms rs4680 and rs4818 are associated with higher pain intensity in TMD and are predictive of psychological factors like anxiety and depression. 5. Zlendić et al. (2024), COMT gene polymorphisms SNP rs4646310 and rs4680 and OPRM1 gene polymorphisms SNP rs1799971 have poorer treatment outcomes, including less pain reduction and less improvement in jaw function, suggesting genetic factors influence treatment response. 6. Baratto et al. (2022), DRD2 gene polymorphisms (rs6276) is associated with chronic pain in construction workers, suggesting a genetic influence on TMD severity. 7. Ekici & Söylemez (2024), T102C polymorphism in HTR2A gene (rs6313) is not a significant risk factor for TMD in Turkish population, but high anxiety is associated with CC genotype of HTR2A gene. 8. Brancher et al. (2019), 5HTT gene polymorphisms (rs1042173) is associated with painful TMD, COMT gene polymorphisms (rs4818) is associated with myofascial pain, while rs6269 is associated with anxiety in adolescents. 9. Meyer et al. (2024), highlighted gender disparities with women more affected by TMD, and COMT gene polymorphisms SNP's rs165656, rs9332377, rs4646310, rs6269, rs165774 are associated with pain perception in TMD patients in South Africa.
1 study assessed epigenetic factors	1. Ao et al. (2023), Epigenetic contributions to chronic painful TMD through methylation of the genes FMOD, PM20D1, ZNF718, ZFP57 and RNF39 following the development of acute painful TMD, indicating that they may influence tissue changes that determine whether the pain persist or resolve.

3.4 Genetic and epigenetic risk factors for TMD

Genetic and epigenetic factors significantly influence TMD susceptibility. Various genetic variants contribute to the functionality of structural protein, receptor, transporter protein, enzyme, regulatory protein, ion channel and hormone, while epigenetic mechanisms impact gene expression related to extracellular protein, enzyme and transcription factor. The findings of the ten studies examining the genetic and epigenetic factors associated with TMD and psychosomatic conditions are described and summarized in Table 5.

https://doi.org/10.24191/cos.v12i2.8837

3.4.1 Structural protein

Collagen provides strength and elasticity to TMJ connective tissues, supporting cartilage and joint stability. It absorbs mechanical stress, preventing damage and ensuring smooth jaw movement.

Research by Rechia et al. (2020) suggests that variations in Collagen Type II Alpha 1 (COL2A1), particularly rs2276454, may be linked to TMJ disc displacement, possibly contributing to joint instability in TMD subtypes. Although no strong links were found between TMD (including myofascial pain, arthralgia, and disc displacement) and the studied genetic variations, rs2276454 showed a borderline association in genotype distribution and a significant association in allelic distribution. In the recessive model, rs2276454 was significantly associated with disc displacement. Interestingly, the C allele was more common in unaffected individuals, suggesting it may help protect against TMD.

3.4.2 Receptor

Receptor proteins transmit signals between neurons, and enable neural communication. In TMJ, they regulate pain perception by modulating neurotransmitter activity. Their role in processing pain, emotions and muscle control makes them essential in TMD.

HTR2A (rs9316233) and HTR3A (rs1062613) are associated with higher pain intensity, with HTR3A also linked to jaw functional limitations (Jounger et al., 2021). HTR3B (rs1176744) is connected to pain influenced by stress, anxiety and depression, as well as self-reported oral behaviours and jaw function, with notable differences in genotype distribution between men and women (Jounger et al., 2021). Another HTR2A variant (T102C, rs6313) is linked to higher anxiety in TMD patients (Ekici & Söylemez, 2024). The opioid receptor Opioid Receptor Mu 1 (OPRM1) (rs1799971) is associated with worsening pain-free mouth opening, increased pain intensity, and anxiety, though AA carriers showed improvement while AG carriers worsened (Zlendić et al., 2024). The dopaminergic receptor DRD2 (rs6276) has been linked to chronic TMD pain (Baratto et al., 2022). These findings suggest receptor-related genetic variations contribute to pain sensitivity and psychosomatic factors in TMD.

3.4.3 Transporter

Transporter proteins regulate neurotransmitter levels by facilitating their reuptake from the synaptic cleft, ensuring efficient neural communication. In the context of TMD, this balance is essential for maintaining proper pain modulation and emotional regulation. Disruptions in neurotransmitter transport may contribute to altered pain perception and increased psychological distress

The serotonin transporter gene SERT (5-HTTLPR) is linked to psychological distress, jaw function, and pain (Jounger et al., 2021), while 5HTT (rs1042173) is associated with painful TMD conditions like arthralgia and myofascial pain (Brancher et al., 2019). These findings suggest transporter proteins play a role in TMD-related pain and its connection to mental health.

https://doi.org/10.24191/cos.v12i2.8837

3.4.4 Enzyme

Enzymes play a crucial role for neurotransmitters, ensuring proper signal transmission in the nervous system. They also help regulate oxidative stress, which can contribute to cellular damage. Variations in genes encoding enzymes may influence pain sensitivity, stress responses and overall susceptibility to TMD.

Variants of the catechol-O-methyltransferase (COMT) gene, including rs4680, rs4818, rs4646310, rs6269, rs165774, and rs9332377, have been linked to increased pain intensity, pain sensitivity, anxiety, depression, stress regulation, and reduced pain reduction in TMD patients (Jounger et al., 2021; Zlendić et al., 2023, Zlendić et al., 2024; Meyer et al., 2024; Brancher et al., 2019). COMT rs4680 is associated with higher pain intensity and somatic symptoms, particularly in individuals with the GG genotype (Jounger et al., 2021). COMT rs4646310 has been linked to worsening pain-free mouth opening, increased anxiety, and reduced pain relief (Zlendić et al., 2024), while rs6269 is associated with myofascial pain and disc displacement (Brancher et al., 2019). Additionally, oxidative stress-related enzymes, such as CAT (rs1001179), SOD2 (rs4880), GPX1 (rs1050450), and NQO1 (rs689452), have been investigated for their role in TMD. Among them, CAT rs1001179 is associated with higher depression scores, while GPX1 rs1050450 has been linked to increased waking-state oral behaviours and high-frequency parafunction (Vrbanović et al., 2023). These findings highlight the influence of enzyme-related genetic variations on TMD-related pain, psychological distress, and functional impairment.

3.4.5 Regulator

Regulatory proteins play a crucial role in signalling pathways that influence how the body responds to pain and stress. Genetic variations in these proteins can alter their function, potentially increasing susceptibility to conditions like TMD.

The Opiorphin Precursor Protein (OPRPN) gene (rs1387964) has been linked to an increased risk of painful TMD, with the CC genotype being more common in affected individuals, suggesting a role in endogenous pain regulation (Zlendić et al., 2023). However, no significant association was found between this variant and pain intensity. Additionally, the ANKK1 gene (rs1800497), which regulates dopaminergic activity, has been associated with myofascial pain, indicating a potential link between dopamine signalling and TMD-related pain (Baratto et al., 2022). These findings highlight the influence of regulatory proteins on pain susceptibility in TMD.

3.4.6 Ion channel

Ion channels are essential for generating and transmitting electrical signals in the nervous system. They regulate the movement of ions across cell membranes, which is critical for nerve signal conduction and communication. In the context of pain perception, ion channel dysfunction can alter nociceptive processing, potentially contributing to conditions like TMD.

While variants in the Voltage-Gated Sodium Channel Genes (SCN1A) (rs6432860) and SCN2A (rs33985936) genes have been investigated for their association with TMD, neither showed a significant link to TMD pain or pain intensity (Zlendić et al., 2023). However, within the low pain intensity (LPI) group, individuals with the SCN1A rs6432860 AA genotype exhibited significantly higher depression scores compared to AG carriers, suggesting a potential role in psychological susceptibility related to TMD (Zlendić et al., 2023). These findings highlight the complex interplay between ion channel variants and emotional factors in TMD.

https://doi.org/10.24191/cos.v12i2.8837

3.4.7 Epigenetic modification

Epigenetic modifications alter gene activity without changing the DNA sequence. DNA methylation can regulate pain by turning genes on or off. In chronic TMD, these changes may influence inflammation, stress responses, and neural signalling.

The methylation of the genes FMOD, PM20D1, ZNF718, ZFP57, and RNF39 may also play a role in pain modulation associated with TMD, and has been linked to chronic painful TMD following the development of acute painful TMD (Ao et al., 2023). These findings highlight the importance of epigenetic mechanisms in TMD pathophysiology, offering potential targets for future therapeutic interventions.

Table 5. Genetic and epigenetic factors associated with TMD and psychosomatic conditions.

	Group	Gene Class	Gene	Genetic/ Epigenetic factor investigated	Genotype	Association with Psycho-somatic conditions	Authors
Genetic	Structural Protein	Collagen	COL2A1	rs2276454	TT	TMJ disc displacement	Rechia et al., 2020
				rs1793953		-	
	Receptor protein	Serotonergic system	HTR2A	rs9316233	C/G G/G	Higher pain intensity in TMD myalgia	Jounger et al., 2021
			HTR3A	rs1062613	C/T T/T	Higher pain intensity in TMD myalgia, limitation of lower jaw function	
			HTR3B	rs1176744	A/A	Pain intensity correlated with stress, anxiety, depression and associated with self-reported oral behaviours and jaw function	
	Trans-porter protein		SERT	5-HTTLPR	S/S	Higher levels of stress, anxiety, depression and somatic symptoms	
	Enzyme	Catecho-laminergic system	COMT	rs4680	A/G A/A	Increased somatic symptoms	

Enzyme	Antioxidant enzyme	CAT	rs1001179	CC	Associated with higher depression	Vrbanović et al., 2023
		SOD2	rs4880		-	
		GPX1	rs1050450	AA	Increased waking-state oral behaviours, high-frequency parafunction	
		NQO1	rs689452		-	
Enzyme	Catecho-laminergic system	COMT	rs4680	GG	Higher pain intensity, anxiety, depression	Zlendić et al., 2023
			rs4818	GG		
Regula-tory protein	Opioid system	OPRPN	rs1387964	CC	Increased risk for painful TMD	
Ion channel	Nociception	SCN1A	rs6432860	TT	Associated highest depression	
		SCN2A	rs33985936		-	
Receptor protein	Opioid system	OPRM1	rs1799971	AG	Worsening in pain-free mouth opening, poorer treatment response, pain intensity and anxiety	Zlendić et al., 2024
Enzyme	Catecho-laminergic system	COMT	rs4646310	AA AG	Worsening in pain-free mouth opening, less pain reduction, less reduction in anxiety, pain intensity and anxiety	
			rs4680	A allele (AA + AG)	Less pain reduction, pain intensity and anxiety	
			rs4818	G allele (GC or GG)	Pain sensitivity and stress regulation	
			rs6269	G allele (AG or GG)	Pain sensitivity and stress regulation	

https://doi.org/10.24191/cos.v12i2.8837

	Regulatory protein	Dopamine system	ANKK1	rs1800497	CT	Myofascial pain	Baratto et al., 2022
	Receptor protein		DRD2	rs6275	CT	-	
				rs6276	AG	Chronic pain in TMD	
	Receptor protein	Serotonergic system	HTRR2A	T102C (rs6313)	CC	Higher anxiety scores	Ekici and Söylemez, 2024
	Transporter protein	Serotonergic system	5HTT	rs1042173	AC	Painful TMD including arthralgia and myofascial pain	Brancher et al., 2019
	Enzyme	Catecholaminergic system	COMT	rs4818	CG	Myofascial pain, painful TMD, disc displacement	
				rs6269	AG	Myofascial pain, disc displacement, anxiety	
	Enzyme	Catecholaminergic system	COMT	rs165774	AG	TMD-related pain	Meyer et al., 2024
				rs9332377	CT	TMD-related pain, myofascial pain, myalgia	
				rs6269	GA	TMD-related pain	
				rs4646310	AG	TMD-related pain, myofascial pain, myalgia, disability related to TMD	
				rs165656	GC	TMD-related pain	
				rs4680	AG	Increased pain sensitivity	
Epigenetic	Extracellular protein		FMOD	methylation		Chronic painful TMD	Ao et al., 2023
	Enzyme		PM20D1				
	Transcription factor		ZNF718				
			ZFP57				
	Enzyme		RNF39				

- : no direct relation found

3.5 Potential Therapeutic Targets in TMD

Analysis from the simple decision matrix and further analysis from the weighted decision matrix (Table not shown) demonstrate that enzyme is the most investigated genetic factor with most reported association with psychosomatic conditions, mainly painful TMD. A well-established genetic factor in TMD is catechol-O-methyltransferase (COMT), which is linked to pain, anxiety and TMD, with multiple studies highlighting the importance of its polymorphisms.

4. DISCUSSION

The findings from this review highlight the complex interplay of genetic and epigenetic factors that influence TMD. Given the integral role of the TMJ in essential functions such as mastication and speech, understanding its structural integrity and dysfunction is central to comprehending the pathophysiology of TMD. Among the various molecular factors, enzymes and receptor-related genes have emerged as critical determinants in modulating pain and associated psychosomatic conditions.

Enzymatic regulation plays a significant role in the pathophysiology of TMD, particularly in the modulation of pain sensitivity and oxidative stress. Catechol-O-methyltransferase (COMT), a key enzyme involved in neurotransmitter metabolism, has been widely studied for its role in pain perception and anxiety in TMD patients. Majority of studies have reported significant associations between COMT polymorphisms and myofascial pain, linking them to heightened anxiety and increased pain sensitivity. These findings support the hypothesis that COMT's role in pain regulation could contribute to the psychosomatic aspects of TMD, including the emotional and psychological distress often reported by patients. However, results across studies remain inconsistent, as some researchers have found no significant association between COMT variants and TMD-related pain or psychological factors. This variability suggests that other genetic or epigenetic factors may modulate COMT's influence on TMD, highlighting the complexity of its role in pain perception and psychosomatic conditions. Further research is needed to clarify these conflicting findings and determine the precise contribution of COMT to TMD pathophysiology.

Receptor-related genes are crucial in modulating pain perception and psychosomatic factors in TMD. Polymorphisms in serotonin and opioid receptor genes, such as HTR2A, HTR3A, and OPRM1, have been linked to increased pain intensity, heightened anxiety, and dysfunctional jaw movement. These findings suggest that receptor dysregulation, especially in pathways regulating pain and mood, may contribute to the chronic pain and psychological distress experienced by TMD patients. Given the opioid system's role in pain modulation and emotional regulation, these genetic variants may help explain why some TMD patients experience more severe symptoms and reduced responsiveness to treatments. The dopaminergic system, particularly genes like DRD2, has also been implicated in chronic pain in TMD, suggesting a potential interaction between dopamine signalling and pain modulation. These findings support the hypothesis that alterations in serotonin and dopamine pathways may contribute to the chronic pain and emotional distress commonly observed in TMD patients. These receptor-related genetic variations present promising targets for future therapeutic interventions aimed at mitigating both pain and the psychological aspects of TMD.

Epigenetic modifications further complicate the genetic landscape of TMD, with DNA methylation. These alterations may influence gene expression in response to environmental stimuli, contributing to pain modulation in TMD patients. This underscores the growing importance of epigenetics in TMD research and its potential role in personalized treatment strategies. While much attention has been given to genetic polymorphisms in TMD, the relatively limited exploration of epigenetic mechanisms calls for further investigation into how environmental factors interact with genetic susceptibility to influence TMD progression.

https://doi.org/10.24191/cos.v12i2.8837

The findings of this review align with and extend the current body of research on TMD. Studies by Alshahrani et al. (2024) confirmed that genetic polymorphisms significantly impact the development, onset, and progression of TMD, with similar conclusions drawn from neuroimaging studies (Yin et al., 2020) that identified structural and functional changes in pain-related brain regions. These neurobiological findings support the hypothesis that TMD pathophysiology is influenced not only by genetic factors but also by psychosocial components. Furthermore, the potential role of epigenetic modifications emphasizes the need for a more comprehensive understanding of how environmental factors, such as stress, parafunctional behaviours and lifestyle choices, interact with genetic susceptibility to influence both pain perception and emotional well-being.

5. CONCLUSION

The genes encoding the enzymes emerge as a promising therapeutic target in TMD. The COMT gene polymorphism was the most extensively studied, showing strong associations with pain modulation and anxiety in TMD. Besides, this review highlights the multifactorial nature of TMD, involving genetic predisposition, epigenetic regulation and psychosomatic influences. Future research should focus on elucidating the genetic-epigenetic interplay in TMD and how these mechanisms can be leveraged to develop personalized treatment strategies that address both the physical and psychological aspects of the disorder.

FUNDING

This research received no specific grant from any funding agency.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ACKNOWLEDGEMENT

We acknowledge the facility support for the databases by the Tun Abdul Razak Library, Universiti Teknologi MARA, Malaysia.

CONTRIBUTION OF AUTHORS

Noor Azliza Wani Abd. Aziz designed the study, performed the analysis, wrote the manuscript, main supervisor of this ERP project and corresponding author. **Jamil Ahsan Kazi** designed the study, wrote the manuscript, co-supervisor of this ERP project and first author. **Nur Fatihah Azman** collected data and performed the analysis. **Nur Asma Hashim** collected data and performed the analysis. **Nik Mohd Mazuan Nik Mohd Rosdy** co-supervisor of this ERP project.

REFERENCES

Alshahrani, A. A., Saini, R. S., Okshah, A., Alshadidi, A. A. F., Kanji, M. A., Vyas, R., Binduhayyin, R. I. H., Ahmed, N., Mosaddad, S. A., & Heboyan, A. (2024). The association between genetic factors and temporomandibular disorders: A systematic literature review. *Archives of Oral Biology, 166*(106032), 1-12. https://doi.org/10.1016/j.archoralbio.2024.106032.

Antolis, M., Langit, K. S., Gultom, F. P., & Auerkari, E. I. (2021). Molecular genetics and epigenetics of temporomandibular disorder. *Journal of Physics, Conference Series ISNPINSA 2020*, *1943*(2021), 1-9. https://doi.org/10.1088/1742-6596/1943/1/012085.

Ao, X., Parisien, M., Fillingim, R. B., Ohrbach, R., Slade, G. D., Diatchenko, L., & Smith, S. B. (2024). Whole-genome methylation profiling reveals regions associated with painful temporomandibular disorders and active recovery processes. *Pain, 165*(5), 1060–1073. https://doi.org/10.1097/j.pain.0000000000003104.

Baratto, S. S. P., Meger, M. N., Camargo, V., Nolasco, G. M. C., Mattos, N. H. R., Roskamp, L., Stechman-Neto, J., Madalena, I. R., Küchler, E. C., & Baratto-Filho, F. (2022). Temporomandibular disorder in construction workers associated with ANKK1 and DRD2 genes. *Brazilian dental journal, 33*(4), 12–20. https://doi.org/10.1590/0103-6440202204963.

Bond, E. C., Mackey, S., English, R., Liverman, C. T., & Yost, O. (2020). Temporomandibular disorders: Priorities for research and care. National Academies of Sciences, Engineering, and Medicine. Washington, DC: *National Academies Press*. https://doi.org/10.17226/25652.

Bordoni, B., & Varacallo, M. (2023). Anatomy, Head and Neck, Temporomandibular Joint. Jul 17. In: StatPearls. Treasure Island (FL) *StatPearls Publishing*, Jan. PMID: 30860721.

Brancher, J. A., Spada, P. P., Meger, M. N., Fatturri, A. L., Dalledone, M., de Paiva Bertoli, F. M., Deeley, K., Scariot, R., Vieira, A. R., Küchler, E. C., & de Souza, J. F. (2019). The association of genetic polymorphisms in serotonin transporter and catechol-O-methyltransferase on temporomandibular disorders and anxiety in adolescents. *Journal of oral rehabilitation, 46*(7), 597–604. https://doi.org/10.1111/joor.12783.

Chang K-H. Decisions in engineering design. In: Chang K-H, editor. Design theory and methods using CAD/CAE. Amsterdam: Elsevier; 2015. p. 39–101. doi:10.1016/b978-0-12-398512-5.00002-5.

do Nascimento Rechia, B. C., Michels, B., Faturri, A. L., de Paiva Bertoli, F. M., Scariot, R., de Souza, J. F., Küchler, E. C., & Brancher, J. A. (2020). Polymorphisms in COL2A1 gene in Adolescents with Temporomandibular Disorders. *The Journal of clinical pediatric dentistry, 44*(5), 364–372. https://doi.org/10.17796/1053-4625-44.5.12.

Ekici, Ö., & Arıkan Söylemez, E. S. (2024). The association of T102C (rs6313) polymorphism in the 5-HT2A receptor gene with temporomandibular disorders and anxiety in a group of Turkish population. *Cranio: the journal of craniomandibular practice, 1–9*. Advance online publication. https://doi.org/10.1080/08869634.2024.2369729.

Etőz, O. A., Erdal, M. E., Herken, H., Bayazit, Y. A., & Mutlu, M. N. (2006). Lack of association between the 308GA polymorphism of the tumor necrosis factor alpha gene and temporomandibular dysfunction. *The Pain Clinic, 18*(2), 175-180. https://doi.org/10.1163/156856906776760443.

Kim, B. S., Kim, Y. K., Yun, P. Y., Lee, E., & Bae, J. (2010). The effects of estrogen receptor α polymorphism on the prevalence of symptomatic temporomandibular disorders. *Journal of Oral and Maxillofacial Surgery, 68*(12), P2975-2979. https://doi.org/10.1016/j.joms.2010.02.023.

Laskin, D. M., Greenfield, W., Gale, E., Rugh, J., Neff, P., & Alling, C. (1983). President's conference on examination, diagnosis, and management of TMD. Chicago, IL. *American Dental Association*.

Leppilahti, J. M., Knuutila, J., Pesonen, P., Vuollo, V., Männikkö, M., Karjalainen, M. K., Suominen, A. L., & Sipilä, K. (2025). Genome-Wide Association Study of Temporomandibular Disorder-Related Pain in Finnish Populations. *Journal of oral rehabilitation, 52*(2), 151–159. https://doi.org/10.1111/joor.13883.

Louca Jounger, S., Christidis, N., Hedenberg-Magnusson, B., List, T., Svensson, P., Schalling, M., & Ernberg, M. (2021). Polymorphisms in the HTR2A and HTR3A Genes Contribute to Pain in TMD Myalgia. *Frontiers in oral health, 2*, 647924. https://doi.org/10.3389/froh.2021.647924.

Manfredini, D., Bandettini Di Poggio, A., Cantini, E., Dell'osso, L., & Bosco, M. (2004). Mood and anxiety psychopathology and temporomandibular disorder: A spectrum approach. *Journal of Oral Rehabilitation, 31*(10), 933-940. https://doi.org/10.1111/j.1365-2842.2004.01335.x.

Mao, D., Wu, M., Wei, J., Zhou, X., Yang, L., & Chen, F. (2021). MicroRNA-101a-3p could be involved in the pathogenesis of temporomandibular joint osteoarthritis by mediating UBE2D1 and FZD4. *Journal of Oral Pathology and Medicine, 50*(2), 236-243. https://doi.org/10.1111/jop.13131.

Meyer, M. K., Ismail, E., & Chetty, M. (2024). Investigating the Association between Catechol-O-Methyltransferase Gene Activity and Pain Perception in South African Patients with Different Temporomandibular Disorders Diagnoses. *Biomedicines, 12*(10), 2331. https://doi.org/10.3390/biomedicines12102331.

Murphy, M. K, MacBarb, R. F, Wong, M. E, & Athanasiou, K. A. (2013). Temporomandibular disorders: A review of etiology, clinical management, and tissue engineering strategies. *The International Journal of Oral & Maxillofacial Implants, 28*(6), e393–e414. https://doi.org/10.11607/jomi.te20.

Mutlu, N., Erdal, M. E., Herken, H., Ozkaya, M., Erdal, N., Oz, G., & Bayazit, Y. A. (2005). Monoamineoxidase-A gene promoter polymorphism in temporomandibular joint pain and dysfunction. *The Pain Clinic, 17*(1), 39-44. https://doi.org/10.1163/1568569053421663.

Nardini, L. G., Meneghini, M., Guido, M., Baciorri, F., & Manfredini, D. (2021). Histopathology of the temporomandibular joint disc: Findings in 30 samples from joints with degenerative disease. *Journal of Oral Rehabilitation*, *48*(9), 1025-1034. https://doi.org/10.1111/joor.13218.

Sangani, D., Suzuki, A., VonVille, H., Hixson, J. E., & Iwata, J. (2015). Gene mutations associated with temporomandibular joint disorders: A systematic review. *OAlib, 2*(6), 1-13. https://doi.org/10.4236/oalib.1101583.

Santos, E. A., Peinado, B. R. R., Frazão, D. R., Né, Y. G. dS., Fagundes, N. C. F., Magno, M. B., Maia, L. C., Lima, R. R. & Souza-Rodrigues, R. D. (2022). Association between temporomandibular disorders and anxiety: A systematic review. *Frontiers in Psychiatry*, *13*(990430), 1-18. https://doi.org/10.3389/fpsyt.2022.990430.

Schiffman, E., Ohrbach, R., Truelove, E., Look, J., Anderson, G., Goulet, J.P., List, T., Svensson, P., Gonzalez, Y., Lobbezoo, F., Michelotti, A., Brooks, S. L., Ceusters, W., Drangsholt, M., Ettlin, D., Gaul, C., Goldberg, L. J., Haythornthwaite, J. A., Hollender, L., Jensen, R., John, M. T., De Laat, A.,

de Leeuw, R., Maixner, W., Meulen, M. V. D.,Murray, G. M., Nixdorf, D. R., Palla, S., Petersson, A., Pionchon, P., Smith, B., Visscher, C. M., Zakrzewska, J., & Dworkin, S. F. (2014). Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: Recommendations of the international RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. *The Journal of Oral & Facial Pain and Headache*, *28*(1), 6-27. https://doi.org/10.11607/jop.1151.

Spotts, P. H. (2017). Temporomandibular disorder: An underdiagnosed cause of headache, sinus pain, and ear pain. Letters to the editor. *American Academy of Family Physicians*, *95*(3), 142.

Stocum, D. L., & Roberts, W. E. (2018). Development and physiology of the temporomandibular joint. *Current Osteoporosis Reports*, *16*(4), 360-368. https://doi.org/10.1007/s11914-018-0447-7.

Turner, B. M. (2009). Epigenetic responses to environmental change and their evolutionary implications. *Philosophical Transactions of The Royal Society B, 364*(1534), 3403-3418. https://doi.org/10.1098/rstb.2009.0125.

Vrbanović, E., Zlendić, M., Trošelj, K. G., Tomljanović, M., Vuković Đerfi, K., & Alajbeg, I. Z. (2023). Association of Oxidative-Stress-Related Gene Polymorphisms with Pain-Related Temporomandibular Disorders and Oral Behavioural Habits. *Antioxidants (Basel, Switzerland), 12*(6), 1195. https://doi.org/10.3390/antiox12061195.

Warzocha, J., Gadomska-Krasny, J., & Mrowiec, J. (2024). Etiologic factors of temporomandibular disorders: A systematic review of literature containing Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) and Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) from 2018 to 2022. *Healthcare*, *12*(575), 1-31. https://doi.org/10.3390/healthcare12050575.

Xu, J., Liu, Y., Deng, M., Li, J., Cai, H., Meng, Q., Fang, W., Long, X., & Ke, J. (2016). MicroRNA221–3p modulates Ets-1 expression in synovial fibroblasts from patients with osteoarthritis of temporomandibular joint. *Osteoarthritis Cartilage, 24*(11), 2003-2011. https://doi.org/10.1016/j.joca.2016.06.011.

Yap, A. U., Marpaung, C., & Rahmadini, E. D. (2021). Psychological well-being and distress: Their associations with temporomandibular disorder symptoms and interrelationships. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *132*(2), 163-171. https://doi.org/10.1016/j.oooo.2021.02.012.

Yin, Y., He, S., Xu, J., You, W., Li, Q., Long, J., Luo, L., Kemp, G. J., Sweeney, J. A., Li, F., Chen, S., & Gong, Q. (2020). The neuro-pathophysiology of temporomandibular disorders-related pain: a systematic review of structural and functional MRI studies. The Journal of Headache and Pain, 21(78):1-20.

Zhang, A., Ma, S., Yuan, L., Wu, S., Liu, S., Wei, X., Chen, L., Ma, C., & Zhao, H. (2020). Knockout of miR-21-5p alleviates cartilage matrix degradation by targeting Gdf5 in temporomandibular joint osteoarthritis. *Bone and Joint Research, 9*(10), 689-700. https://doi.org/10.1302/2046-3758.910.BJR-2020-0140.R1.

Zhou, Y., Chen, M., O'Keefa, R. J., Shen, J., Li, Z., Zhou, X., & Mao, J. J. (2019). Epigenetic and therapeutic implications of dnmt3b in temporomandibular joint osteoarthritis. *American Journal of Translational Research*, *11*(3), 1736-1747.

Zlendić, M., Vrbanović, E., Trošelj, K. G., Tomljanović, M., Đerfi, K. V., & Alajbeg, I. Z. (2024). Genetic influence on treatment outcomes in patients with pain-related temporomandibular disorders. *Journal of oral rehabilitation, 51*(8), 1542–1554. https://doi.org/10.1111/joor.13730.

Zlendić, M., Vrbanović, E., Tomljanović, M., Gall Trošelj, K., Đerfi, K. V., & Alajbeg, I. Z. (2024). Association of oral behaviours and psychological factors with selected genotypes in pain-related TMD. *Oral diseases, 30*(3), 1702–1715. https://doi.org/10.1111/odi.14583.

Zwiri, A., Al-Hatamleh, M. A. I., Ahmad, W. M. A. W., Asif, J. A., Khoo, S. P., Husein, A., Ab-Ghani, Z., & Kassim, N. K. (2020). Biomarkers for temporomandibular disorders: Current status and future directions. *Diagnostics, 10*(5), 303. https://doi.org/10.3390/diagnostics10050303.

6. APPENDIX

A. About the Authors

Noor Azliza Wani Abd. Aziz, PhD is Senior Lecturer in the Centre of Preclinical Science Studies at the Faculty of Dentistry, Universiti Teknologi MARA. She has been a Lecturer of Anatomy since 2008 and involved in academic and research activities. Her main research activity is in the area of animal research, behavioural and molecular neuroscience and natural approach to oral health. She can be reached through her email at norazlizawani@uitm.edu.my.

Jamil Ahsan Kazi is Associate Professor at Centre of Preclinical Science Studies, Faculty of Dentistry, Universiti Teknologi MARA (UiTM) Sg. Buloh Campus, Malaysia.

Nur Fatihah Azman is involved as a student of Elective Research Project (ERP). Faculty of Dentistry, Universiti Teknologi MARA (UiTM) Sg. Buloh Campus, Malaysia.

Nur Asma Hashim is involved as a student of Elective Research Project (ERP). Faculty of Dentistry, Universiti Teknologi MARA (UiTM) Sg. Buloh Campus, Malaysia.

Nik Mohd Mazuan Nik Mohd Rosdy is Associate Professor at Centre of OMF Diagnostics & Medicine Studies, Faculty of Dentistry, Universiti Teknologi MARA (UiTM) Sg. Buloh Campus, Malaysia.