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Association Between COMT Gene Polymorphism (rs4680) and Familial Incidence of Temporomandibular Disorders (TMD): A Case Control Study

Naila Zakria[1], Amena Rahim[2], Mohammad Afzal[3], Saadia Sadiq[4], Syeda Sameen Zehra Rizvi[5], Aamir Rafiq[6]

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ABSTRACT

Objectives: Temporomandibular disorders (TMD) are a growing public health concern affecting the individual's quality of life. The aim of the study was to determine the genetic associations of *COMT* gene polymorphism *(rs4680)* in patients with family history of TMD with different etiologies.

Materials and Methods: It was a case control study. Cases included 63 Male and female patients aged 17-45 years and presented with TMD and reported a family history of TMD. Controls included 63 age, gender, and ethnicity matched healthy individuals having no TMD and with no family history of TMD. After getting an informed consent from the patients, Peripheral blood was taken to extract DNA and genotyped for *COMT* polymorphism *(rs4680)* by Tetra-ARMS PCR. The association was determined by calculating odds ratio and 95% confidence interval.

Results: The genotypic and allelic frequencies were computed using a 2*2 contingency table to find out the association between genetic polymorphism and family history of TMD we found a significant *p* value for AA genotype $p = (0.0002)$ and for A allele $p = (0.00004)$, however the GA genotype did not reach the level of statistical significance.

Conclusion: In the current study, we found that *COMT* gene polymorphism *(rs4680)* i.e., AA genotype and A allele is significantly associated with the risk of development TMD.

Key Words: COMT (rs4680), Family history, Polymorphism, Risk factor, Temporomandibular Disorders (TMD)

[1]Assistant Professor, Department of Biochemistry, HITEC- IMS Dental College, Taxila, Pakistan.

[2]Professor, Department of Biochemistry, Islamic International Medical College, Islamabad, Pakistan.

[3]Assistant Professor, Department of Biological and health science, Pak-Austria Fachhochschule Institute of Applied Sciences and Technology, Haripur, Pakistan.

[4]Associate Professor, Department of Biochemistry, Abbottabad International Medical College, Abbottabad, Pakistan.

[5]Assistant Professor, [6]Professor, Department of Prosthodontics, HITEC- IMS Dental College, Taxila, Pakistan.

Corresponding author:

Naila Zakria, Department of Biochemistry, HITEC- IMS Dental College, Taxila, Pakistan.

Email: nailazakria@gmail.com

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INTRODUCTION

"Temporomandibular disorders (TMD) are characterized as a collective term for a variety of clinical conditions involving the masticatory muscles, the temporomandibular joint, and related tissues"[1] Among orofacial pain conditions of nondental origin TMD is found to be the most common, with 2-4-fold higher prevalence in women as compared to men especially between ages 25-45 years.[2] This higher incidence is attributed to multiple factors of biological, social, physiological, hormonal, and genetic origin.[3] Various studies conducted in different countries showed different prevalence of severe TMD such as Sweden has 6.3%[2], India 9.1%[2], USA 16%[4], Lebanon 19.9%.[5] In Pakistan the prevalence of severe TMD is between 5% to 8.6%.[6,7]

The temporomandibular joint is a bilateral synovial joint that is formed by two bones, the mandible and the temporal bone. Each movement is synchronized to maximize functionality while minimizing harm to any structure.[8]one condition that possess a significant global health problem is temporomandibular disorder (TMD).

The fact that TMD is complex motivates researchers to identify genetics as a risk factor for TMD.[9] A type of gene sequence variation known as genetic polymorphism is present in more than 1% of the world's population.[10]These are locations in the human genome where one significant portion of human population has one nucleotide, while another substantial fraction has another.[10] Single nucleotide polymorphisms are well-thought-out the most useful biomarkers for disease diagnosis or prognosis because to their widespread occurrence, simplicity of analysis, affordable genotyping, and ability to conduct association analyses using statistical and bioinformatics tools.[11]therefore, they may have direct implications over the phenotype of susceptibility to infections affecting the productive sector. In this study, a set of immune-related genes (cc motif chemokine 19 precursor [ccl19], integrin β2 (itβ2, also named cd18

The *COMT* gene is specifically located at 22q11.21 (gene ID 1312) on the long arm of the 22nd chromosome.[12]rendering an enzyme with reduced activity that has been associated with psychiatric disorders and estrogen-related cancers. A new method for the detection of this polymorphism is described, based on the tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR It belongs to the dopaminergic system gene family and is crucial for the breakdown of dopamine in the brain's prefrontal cortex[12] rendering an enzyme with reduced activity that has been associated with psychiatric disorders and estrogen-related cancers. A new method for the detection of this polymorphism is described, based on the tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR It contributes to bodily processes including pain perception, stress response, and mood modification.[10] The *COMT* gene's fourth exon has a guanine-to-adenine substitution *(rs4680),* which causes the enzyme's methionine at position 158 to be replaced with a valine residue. (Val[158]Met).[10]

Joint conditions such as TMD may cluster in families through mechanisms like hereditary or genetic factors and psychological influences.[13] The current investigation is a controlled examination to see weather *COMT (rs4680)* is associated with an increased risk of TMD in individuals with family history of TMD as compared to controls . The research findings will identify genetic markers of TMD especially those with family history of TMD, aiding early management through awareness, minimal interventions like splints and medications and potentially avoiding the need for surgical procedures.

The aim of the study was to determine the genetic associations of *COMT* gene polymorphism *(rs4680)* in patients with family history of TMD with different etiologies and the objective is to determine the genotypic and allelic frequency of *COMT* gene polymorphism *(rs4680)* in patients having a family history of TMD.

Several studies have been conducted in Pakistan focusing on various risk factors of TMD, but none considered the role of family history and genetics together.

In this study, the severity of TMD was assessed by using Fonseca's questionnaire.[14]

MATERIALS AND METHODS

It was a Case-control study. The study was carried out in the Multidisciplinary Laboratory in Islamic International Medical College Trust in collaboration with dental section of Railway Hospital Rawalpindi and dental college of Heavy Industries Taxila Educational City (HITEC), after taking approval from the Institutional Research Board

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and Ethics Committee (Ref: Riphah/IRC/22/2092) on 11 November 2022.

The duration of the study was 01 year after from September 2022 to August 2023. Sample size was calculated by Cochran's formula taking 95% confidence interval and 5% margin of error. The expected portion was obtained form the previously published literature. The sample size was 126 which was equally divided into cases and controls. Sampling was done by Non-Probability Convenient sampling. Sample was grouped as cases and controls. The inclusion criteria for cases was 63 Male and female patients between 17-45 years of age who gave an informed consent and presented with TMD and reporting a family history of TMD. Inclusion criteria for controls was 63 Age, gender, and ethnicity matched healthy individuals who gave an informed consent and had no TMD and also with no family history of TMD. The exclusion criteria was that the patient were not willing to participate in the study or those who were below the age of 17 and above 45 were excluded from the study. After getting informed consent from the patients, 3ml blood samples were collected by venipuncture, after proper antiseptic measures. Blood was then transported to the laboratory in Na. EDTA containing vacutainers and was preserved at 4-8°C until further analysis. DNA was extracted by the Chelex method. *COMT* gene *(rs4680)* was genotyped by Tetra-ARMS PCR using set of primers given in Table 1.[16]multiple COMT variants have been associated with the development of psychiatric disorders. Notably, select single-nucleotide polymorphisms (SNPs

Table 1: Sequence of Primers for COMT **(**rs4680)

Primer Name	Primer Sequence (5'-3')
RS4680-WG	CGGATGGTGGATTTCGCTGACG
RS4680-MA	TCAGGCATGCACACCTTGTCCTTTAT
RS4680-FO	CCAACCCTGCACAGGCAAGAT
RS4680-RO	CAAGGGTGACCTGGAACAGCG

PCR amplification began with an initial denaturation at 94˚C for 4 min followed by 30 amplification cycles which consisted of denaturation at 94˚C for 30 sec, annealing at 62˚C for 30 sec, and then extension at 72˚C for 20 sec. The final extension was carried out at 72˚C for 5 min and the cycle was terminated to hold at 4˚C for 30 min. PCR reaction was performed in a Veriti 96 well thermal cycler. To confirm reliability DNA extraction and PCR amplification were carried out under uniform conditions using authenticated protocols. Negative controls were included in each PCR cycle to screen contamination. In addition, a subset of samples was randomly selected, and re-genotyped, and consistent results were obtained, confirming the reproducibility of the assay. The PCR products were be visualized on 2% agarose gel

Statistical analysis was carried out using commercial statistical software package, SPSS version 27.0. Possible associations between the *COMT* gene polymorphism *(rs4680)* and family history of TMD were determined by computing odds ratio (OR) and 95% confidence interval (CI) by using chi-square test.

Frequencies and percentages were calculated for descriptive statistics. $p < 0.05$ was considered to indicate a statistical significance.

RESULTS

As shown in table 2 out of 126 subjects, 63 were included in cases and 63 subjects were controls. In cases the average age of subjects was 31.03 years with Mean ± SD (6.533) and the range was 20-45 years and in controls the average age was 30.98 years with Mean ± SD (7.286) years and range was 17-45 years. There were 34 (53.96%) females and 29 (46.03%) males in cases while in controls there were 31 (49.21%) females and 32(50.79%) males.

Table 2: Demographic Characteristics of The Study Population

Total subjects N (%)	**Cases** n (%)	**Controls** n (%)
126(100)	63(50%)	63(50%)
Age (years)		
Mean± SD[a]	**31.03(±6.53)**	**30.98(±7.29)**
Gender n (%)		
Female	34(53.96)	31(49.21)
Male	29(46.03)	32(50.79)

[a] SD=Standard deviation

When we graded the cases according to Fonseca's questionnaire, we found that 20 (31.74%) subjects had mild TMD, 33 (52.38%) subjects had moderate TMD while 10 (15.87%) subjects had severe TMD.

The genotypic and allelic frequencies were computed using a 2*2 contingency table to find out the association

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between genetic polymorphism and family history of TMD and shown in table 3, we found a significant *p* value for AA genotype *p* = (0.0002) and for A allele *p* = (0.00004), however the GA genotype did not reach the level of statistical significance.

Table 3: Association of COMT gene polymorphism (rs4680) (G > A) with family history of TMD

Genotype	Cases n (%)	Controls n (%)	Odds Ratio (95% CI[b]) *p* value
GG	8(12.69)	24(38.09)	Ref 1[c]
GA	22(34.92)	23(36.50)	Ref 1 2.87(1.07-7.73) 0.06
AA	33(52.38)	16(25.39)	Ref 1 6.19(2.28-16.79) 0.0002*
Allele			
G	38(30.15)	71(56.35)	Ref 1
A	88(69.84)	55(43.65)	2.99 (1.79-5.02) 0.00004*

[b]CI=Confidence Interval

[c]Ref 1 means odd ratio is 1

DISCUSSION

The present work has focused on predisposing factor that influences susceptibility to TMD, the genetic component along with family history of TMD. In the developing field of genetic analysis, even a tiny bit of knowledge can have a significant impact on studies aimed at reducing the discomforts endured by TMD sufferers. The current study is an effort to determine if individuals with family history of TMD have a valine to methionine polymorphism of the *COMT* gene. Epinephrine and other catecholamines like dopamine and norepinephrine are degraded by the enzyme *COMT*.[17] Consequently, it represents a crucial protein that supports a number of biological processes, such as the sense of pain, mood, cognition, and reactions to physical and mental stress.[18]

The results show that AA genotype of COMT gene polymorphism (4680) is significantly associated with individuals having family history of TMD. These results are in accordance with a study by Eslamian et al in 2022.[19] But they are in contrast with the results by Karen et al who proved that myofascial pain does not run in families.[20]

It can be said that if a person has a family history of TMDs and he also has AA genotype of *COMT (4680)*, he is more likely to have symptoms of TMD as compared to an individual without a family history having same genotype. Low awareness of people about the family history of TMD in their 1st and 2nd degree relatives may attribute to an increased risk of developing TMD. In 2012, Plesh et al. conducted a study of twins and concluded that TMJ pain could be inherited.[21] Matsuka et al. also described the of family background as a predisposing factor of TMD.[13] Additionally, studies by Visscher et al disclosed that a specific genetic factor contributed to TMD pain was the presence of a specific protein encoding gene that is expressed in response to painful stimuli. That gene had been identified through genome sequencing in these individuals, suggesting a genetic predisposition to TMD.[22] All this knowledge can lead to personalized treatment plans for a particular high risk patient including specific medications, physical therapy and behavioral interventions. Educating families about the genetic aspects of TMD can help them understand the importance of compliance with treatment plans and preventive measures. Despite the associations we found the study has some limitations like this study considered only one genetic factor while TMD has diverse etiologies. Effect of additional genes and hormonal factors, were not considered, which could also contribute to the development of TMD.

CONCLUSION

In the current study, we found that *COMT* gene polymorphism *(rs4680)* i.e., AA genotype and A allele is significantly associated with the risk of development TMD in patients that have a family history of TMD. This highlights the importance of genetic factors in the development of TMD and suggests that genetic screening for COMT (rs4680) could help identify individuals at higher risk especially if the patient has a family history of TMD paving the way for more personalized treatment strategies. There were a few limitations of this study. Different etiologies of TMD need to be considered separately and effect of other genes and hormonal factors should also be considered. As TMD has diverse causes including genetic factors along with mechanical, psychological and environmental influences, it is important to consider different etiologies of TMD

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separately in future and in clinical practice.

DISCLAIMER
M. Phil research.

CONFLICT OF INTEREST
There is no conflict of interest among the authors.

ETHICAL STATEMENT
The ethical approval was taken from the Institutional Research Board and Ethics Committee (Ref: Riphah/IRC/22/2092) on 11 November 2022.

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AUTHORS CONTRIBUTION
Conception and design of the study: N. Zakria

Acquisition of data: A. Rahim, M. Afzal

Analysis and/or interpretation of data: M. Afzal

Drafting the manuscript: N. Zakria, S. Sadiq

Revising the manuscript critically for important intellectual content: S. S. Z. Rizvi, A. Rafiq

Approval of the version of the manuscript to be published: N. Zakria, A. Rahim, M. Afzal, S. Sadiq, S. S. Z. Rizvi, A Rafiq

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