The Preliminary *COMT* rs4680 and *5HTR2A* rs6311 Polymorphisms in Patients with Bruxism

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Abstract

Aim: Bruxism, is a common oral condition characterised by teeth grinding and clenching and presents significant challenges in management due to its multifactorial nature. It is associated with stress, sleep quality, occlusion irregularities and genetic factors. Dopamine plays a crucial role in the central nervous system and peripheral organs. The catechol-O-methyltransferase (*COMT)* enzyme regulates dopamine metabolism and *COMT* rs4680 polymorphism has been associated with various mental disorders. Bruxism may also be association with the 5-Hydroxytryptamine Receptor 2A (5HTR2A) rs6311 polymorphism. The aim of this study was to investigate the association between these two gene polymorphisms in individuals with bruxism and healthy controls.

Method: The study included 10 participants with bruxism and age- and sex-matched healthy controls. Peripheral blood samples were obtained from all participants, and genomic DNA was isolated in the laboratory. Genotyping of the *COMT* rs4680 and 5HTR2A rs6311 polymorphisms was performed using real-time polymerase chain reaction (qPCR) with TaqMan Genotyping Assays.

Results: No statistically significant differences were observed between patients and controls in the genotype distribution or allele frequencies of the *COMT* rs4680 polymorphism. In contrast, for the *5HTR2A* rs6311 polymorphism, allele frequencies differed significantly between the bruxism and control groups (p=0.0267), with the T allele being more frequent among individuals with bruxism.

Conclusion: The findings suggest a potential association between the *5HTR2A* rs6311 polymorphism and bruxism, specifically implicating the T allele. Furthermore, particularly for the *COMT* rs4680 polymorphism, there have been no statistically significant differences found between control group and

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patient. However, due to the limited sample size, further research with larger sample sizes and comprehensive genetic analyses is warranted to validate our findings and elucidate the genetic factors contributing to bruxism.

Keywords: Bruxism, COMT, 5HTR2A, polymorphism.

Bruksizmli Bireylerde COMT rs4680 ve 5HTR2A rs6311 Polimorfizmleri

Öz

Amaç: Diş gıcırdatma ve sıkma ile karakterize, yaygın görülen bir oral durum olan bruksizm, multifaktöriyel yapısı nedeniyle yönetimi güç bir tablodur. Stres, uyku kalitesi, oklüzyon düzensizlikleri ve genetik faktörlerle ilişkilidir. Dopamin, merkezi sinir sistemi ve periferik organlarda kritik bir rol oynar. Katekol-O-metiltransferaz (*COMT*) enzimi dopamin metabolizmasını düzenler ve *COMT* rs4680 polimorfizminin çeşitli ruhsal bozukluklarla ilişkili olduğu bildirilmiştir. Bruksizmin ayrıca 5-Hidroksitriptamin Reseptör 2A (5HTR2A) rs6311 polimorfizmi ile de ilişkili olabileceği düşünülmektedir. Bu çalışmanın amacı, bruksizmi olan bireyler ve sağlıklı katılımcılarda bu iki gen polimorfizmi arasındaki ilişkiyi araştırmaktır.

Yöntem: Çalışmaya bruksizmi olan 10 birey ve yaş ile cinsiyet açısından eşleştirilmiş sağlıklı kontrol grubundaki katılımcılar dahil edildi. Tüm katılımcılardan periferik kan örnekleri alındı ve laboratuvarda genomik DNA izole edildi. *COMT* rs4680 ve *5HTR2A* rs6311 polimorfizmlerinin genotiplendirilmesi, TaqMan Genotipleme Kitleri kullanılarak gerçek zamanlı polimeraz zincir reaksiyonu (qPCR) ile gerçekleştirildi.

Bulgular: *COMT* rs4680 polimorfizminin genotip dağılımı ve allel frekansları açısından hasta ve kontrol grupları arasında istatistiksel olarak anlamlı bir fark saptanmadı. Buna karşın, *5HTR2A* rs6311 polimorfizmi için allel frekansları bruksizm ve kontrol grupları arasında anlamlı düzeyde farklı bulundu (p=0,0267) ve T allelinin bruksizmi olan bireylerde daha sık görüldüğü belirlendi.

Sonuç: Bulgular, özellikle T allelini vurgulayarak, *5HTR2A* rs6311 polimorfizmi ile bruksizm arasında olası bir ilişkiye işaret etmektedir. Ayrıca *COMT* rs4680 polimorfizmi açısından hasta ve kontrol grupları arasında istatistiksel olarak anlamlı bir fark gösterilememiştir. Bununla birlikte, örneklem büyüklüğünün sınırlı olması nedeniyle, bulgularımızın doğrulanması ve bruksizme katkıda bulunan genetik faktörlerin daha iyi aydınlatılması için daha büyük örneklemlere sahip çalışmalar ve kapsamlı genetik analizler gerekmektedir.

Anahtar Sözcükler: Bruksizm, COMT, 5HTR2A, polimorfizm.

Introduction

Bruxism, as defined by the American Academy of Orofacial Pain, is a parafunctional activity involving teeth grinding, gnashing or clenching, occurring either during the day or at night[1]. The etiology of bruxism remains multifactorial and is not yet fully understood. Factors such as morphological conditions, central nervous system disorders, psychosocial elements, childhood bruxism, drug use and genetic predispositions have been identified as contributing factors[2].

Several diagnostic methods for bruxism exist, including questionnaires, clinical examinations, wear assessments via oral devices, portable electromyographic (EMG) recording, and polysomnography (PSG). In the present study, bruxism was defined at the “probable” level, based on self-reported symptoms and clinical examination. According to the bruxism diagnostic grading system, bruxism is classified into three categories: 'possible,' 'probable,' and 'definite.' A 'possible' diagnosis is based on self-

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reported data from questionnaires or anamnesis. A 'probable' diagnosis combines self-reporting with clinical examination, while 'definite' bruxism requires more comprehensive evaluations, such as clinical assessment, patient testimonials, EMG, and PSG[3].

Serotonin (5-HT) has 14 different receptor types, grouped into seven subfamilies. Except for the 5-HT3 receptor, which belongs to the ion channel receptor family, all others are G-protein-coupled receptors (GPCRs)[4]. Polymorphic variations in the *5HTR2A* gene, such as single nucleotide polymorphisms (SNPs), can impact receptor expression and function, potentially influencing the pathophysiology of neuropsychiatric disorders like schizophrenia and affective disorders. These variations are also linked to antidepressant therapy outcomes. In studies examining seasonal affective disorder, the rs6311 polymorphism of the *5HTR2A* promoter region (*HTR2A -1438C/T*) has produced inconsistent findings[5].

Dopamine, norepinephrine and epinephrine are catecholamines, neurotransmitters, and hormones that play key roles in physiological regulation, contributing to the development of neurological, psychiatric, endocrine, and cardiovascular disorders. Dopamine, synthesized from L-DOPA, is involved in motor function, respiration, blood pressure, intuition, and focus, while norepinephrine, released mainly from the adrenal medulla, affects circulation by inducing vasoconstriction and stimulating arteriole contraction, impacting cardiovascular function[6].

The rs4680 polymorphism of the *COMT* gene is a functional variant that influences over 40% of *COMT* enzymatic activity[7]. This non-synonymous SNP (val158met) results from a G-to-A substitution, leading to the replacement of valine with methionine at codon 158. This variation increases the thermolability of the *COMT* enzyme, reducing its activity by up to 75%. Found in 48% of Caucasians, the val158met polymorphism has been widely studied in various mental disorders, including bipolar disorder, schizophrenia, anxiety disorders, addictions, and attention deficit hyperactivity disorder[8].

The hypothesis of the present study is that the *COMT* rs4680 and *5HTR2A* rs6311 polymorphism are associated with susceptibility to bruxism. To our knowledge, this is one of the first studies to simultaneously examine both *COMT* rs4680 and *5HTR2A* rs6311 polymorphism in relation to bruxism, providing preliminary data on the genetic background of this condition.

Material and Methods

Participants

This study included 10 consecutive unrelated cases of patients with bruxism from Marmara University Faculty of Dentistry in Türkiye. The participants were selected based on the following criteria: aged 18-60 years, residing in Turkey, having natural dentition, no genetically transmitted disease in their first-degree relatives, not known or declared systemic disease, and not using regular medication. Individuals who did not meet the age criteria (not between 18-60 years), were not diagnosed with bruxism, had a

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genetic inherited disease in themselves or their first-degree relatives, had a known or declared systemic disease, had a history of taking or taking regular medications that affect sleep-wake regulation or are used to treat movement disorders, were pregnant, or had alcohol or drug addiction were excluded from the study. In addition, a control group of 10 age and sex matched healthy volunteers without a history or clinical signs of bruxism was recruited from individuals attending the same faculty for routine dental care. Control participants met the same inclusion and exclusion criteria as the patient group, except for the absence of bruxism.

The diagnosis of bruxism in the patient group was based on patient history and clinical examination. Patients reported frequent tooth grinding or clenching during sleep, and clinical signs such as tooth wear facets, linea alba, tongue or cheek indentations, and masticatory muscle tenderness were observed. No polysomnography (PSG) or electromyography (EMG) recordings were performed; therefore, all cases were classified as probable bruxism according to the international grading system. All clinical examinations were performed by a single prosthodontist who was blinded to the genetic analysis results.

Method

Peripheral blood samples were obtained from all participants by venipuncture and were transported at 4°C to the laboratory of the Department of Basic Medical Sciences, Medical Biology and Genetics Unit, Marmara University, for genetic analysis. DNA isolation was performed according to the manufacturer's instructions using the Canvax DNA isolation kit (Canvax Reagents S.L., C. Luis de Mercado, Boecillo, Valladolid, Spain). The quantity and purity of genomic DNA were assessed spectrophotometrically using the OD260/280 ratio, and samples were stored at −20°C until analysis. Genotyping of the *COMT* rs4680 and *5HTR2A* rs6311 polymorphisms was carried out by real-time polymerase chain reaction (qPCR) on a StepOnePlus™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) using TaqMan® Genotyping Assays (Applied Biosystems). PCR amplification was performed with an initial denaturation at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 15 s and annealing/extension at 60 °C for 1 min.

Ethical Statement

This research was conducted at Marmara University, Department of Prosthodontics. Ethical approval was obtained by Marmara University Clinical Research Council's Ethics committee numbered 2023/132 and 2023/133.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Genotype and allele frequencies were compared between the bruxism and control groups using chi-square or Fisher's exact tests, as appropriate. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for allele and genotype comparisons between groups. Hardy–Weinberg equilibrium (HWE) in the control group was

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evaluated using the chi-square test. Because only two loci were tested, no correction for multiple comparisons (e.g., false discovery rate or Benjamini–Hochberg procedure) was applied. A p value of <0.05 was considered statistically significant.

Results

The genotype and allele distributions of the COMT rs4680 and HTR2A rs6311 polymorphisms in patients with bruxism and controls are presented in Tables 1 and 2. For COMT rs4680**,** genotype frequencies did not differ significantly between the bruxism and control groups (p_genotype=0.3646), and allele frequencies were also similar (p_allele=0.7515). The G allele frequency was 50.0% in patients and 45.0% in controls (OR_G=1.22, 95% CI 0.35–4.24). Hardy–Weinberg equilibrium was satisfied in the control group (p_HWE =0.19).

For HTR2A rs6311, genotype distribution showed a trend toward a difference between groups (p_genotype=0.1014). The T allele was more frequent in the bruxism group than in controls (65.0% vs 30.0%; p_allele=0.0267; OR_T=4.33, 95% CI 1.15–16.32). Hardy–Weinberg equilibrium was also satisfied in the control group (p_HWE = 0.88).

Table 1. Genotype distribution and allelic frequencies of the COMT rs4680 polymorphism in patients with bruxism

Genotype	**Patients (n=10)**	**Controls (n=10)**	**OR (95% CI)***	**p (genotype)**
AA	3 (30.0%)	2 (20.0%)	1.00 (reference)	0.3646
AG	4 (40.0%)	7 (70.0%)	0.38 (0.004-3.34)	
GG	3 (30.0%)	1 (10.0%)	2.00 (0.11-35.81)	
Allele	**Patients**	**Control**	**OR_G (%95 CI)****	**p (allele)**
A	10 (50.0%)	11 (55.0%)	-	0.7515
G	10 (50.0%)	9 (45.0%)	1.22 (0.35-4.24)	

* Odds ratio for each genotype compared with AA.

** Odds ratio for the G allele versus the A allele.

Hardy–Weinberg equilibrium p value in controls: 0.19.

Furthermore, the analysis of allelic frequencies revealed that the G allele and A allele were both present at a frequency of 50%. This suggests that the G and A alleles are equally represented in the genotypes and in our participant group with bruxism.

However, the higher prevalence of the AG genotype indicates a potential link between moderate dopamine metabolism disruptions and bruxism. Dopamine, as a key neurotransmitter, plays a critical role in motor activity, and imbalances in it signaling may lead to increased jaw muscle activity, which is characteristic of bruxism.

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For *COMT* rs4680, the genotype distribution among the 10 participants were as follows: 30% carried the GG genotype, 40% carried the AG genotype, and 30% carried the AA genotype. Allelic frequency analysis revealed equal representation of the G and A alleles, each with a frequency of 50%. These results indicate no statistically significant differences between the genotypes in the bruxism group, as reflected by a p-value of 0.3646. However, the higher prevalence of the AG genotype (40%) may suggest a link between moderate dopamine metabolism disruptions and bruxism.

In the control group, the GG genotype was less frequent (10%), the AG genotype more common (70%), and the AA genotype found in 20% of individuals. The allelic frequencies in the control group were 55% for the A allele and 45% for the G allele, with no significant differences (p=.7515).

The genotypes observed in the sample were CC (10%), CT (50%), and TT (40%), indicating the presence of genetic variation at the *5HTR2A* rs6311 locus among patients with bruxism. The CT genotype was the most prevalent, followed by TT and CC genotypes. The allelic frequencies revealed that the T allele had a frequency of 65%, while the C allele had a frequency of 35% in the sample. The genotype distribution and allelic frequencies of *5HTR2A* rs6311 polymorphism is summarized in Table 2. These findings suggest that the T allele may be more common among individuals with bruxism in our sample.

Table 2. Genotype distribution and allelic frequencies of the 5HTR2A rs6311 polymorphism in Patients with *Bruxism*

Genotype	**Patients (n=10)**	**Controls (n=10)**	**OR (95% CI)***	**p (genotype)**
AA	1 (10.0%)	5 (50.0%)	1.00 (reference)	0.1014
AG	5 (50.0%)	4 (40.0%)	6.25 (0.50–77.50)	
GG	4 (40.0%)	1 (10.0%)	20.00 (0.93–429.93)	
Allele	**Patients**	**Control**	**OR_G (%95 CI)****	**p (allele)**
A	7 (35.0%)	14 (70.0%)	–	0.0267
G	13 (65.0%)	6 (30.0%)	4.33 (1.15–16.32)	

* Odds ratio for each genotype compared with CC.

** Odds ratio for the T allele versus the C allele.

Hardy–Weinberg equilibrium p value in controls: 0.88.

For the *5HTR2A* rs6311 polymorphism, 10% of bruxism patients carried the CC genotype, 50% carried the CT genotype, and 40% carried the TT genotype. The T allele had a frequency of 65%, while the C allele was less frequent at 35%. In contrast, the control group exhibited a higher frequency of the CC genotype (50%), followed by CT (40%) and TT (10%). The allelic frequencies in the control group were 70% for the C allele and 30%

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for the T allele, showing a significant difference between the patient and control groups (p = .0267).

These findings suggest potential genetic contributions of the *COMT* rs4680 and *5HTR2A* rs6311 polymorphisms to bruxism. However, it is important to note that the sample size was small, and further studies with larger sample sizes are needed to confirm these results and establish the significance of this polymorphism in the development of bruxism.

Discussion

The findings of this study contribute to the growing body of literature exploring the genetic factors underlying bruxism, with a particular focus on the *COMT* rs4680 and *5HTR2A* rs6311 polymorphisms. The results align with previous studies that have demonstrated the significant role of *COMT* polymorphisms in a range of neurological and psychiatric conditions. For instance, the *COMT* rs4680 variant has been associated with schizophrenia, tardive dyskinesia, and working memory impairment in Parkinson's disease[9]. This suggests that the *COMT* enzyme, which modulates dopamine metabolism, could be a critical mediator in neuropsychiatric disorders involving dopaminergic dysfunction, which may also extend to sleep bruxism.

The role of genetic factors in the development of bruxism has received increasing attention in recent years. In our study, we specifically investigated the *COMT* rs4680 polymorphism, which has been extensively studied in relation to various mental disorders and neuropsychiatric conditions. The *COMT* gene is 22.27 kb long and located in the 22q11.2 region. Three genotypes (GG/GA/AA) are formed as a result of the val158met (rs4680) polymorphism occurring in this gene and considering the involvement of dopamine and *COMT* enzyme in the regulation of neurotransmitters, it can be assumed that the rs4680 polymorphism may also have an effect on the formation of bruxism. In our study, *COMT* rs4680 polymorphism genotype and allele analysis were performed in individuals with bruxism.

The present study's results suggest that *COMT* genotype could influence sleep patterns, corroborating the findings of Valomon et al.[10] where homozygous Val/Val and Met/Met individuals showed a significant increase in sleep duration on rest days compared to workdays. This differential sleep response highlights a potential link between *COMT* genotype and sleep regulation, which could also play a role in the manifestation of sleep bruxism. Additionally, studies have shown an association between *COMT* polymorphisms and symptoms of temporomandibular disorders (TMD), particularly in regulating pain perception and stress response[11]. These findings suggest a shared genetic basis for both bruxism and TMD, further underscoring the relevance of the *COMT* rs4680 polymorphism in pain-related sleep disorders.

The genetic component of bruxism has been suggested in a systemic review by Lobbezoo et al.[3], though the specific genetic mechanisms remain unclear. While our study highlights the potential role of *COMT* rs4680, it is important to note that other genetic factors or gene-gene interactions may contribute to the development of bruxism. Indeed,

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some studies, such as that conducted by Wieckiewicz et al.[12], did not find significant associations between *COMT* polymorphisms and bruxism, reflecting the complexity and multifactorial nature of this condition.

In addition to *COMT*, a significant relationship between the *5HTR2A* rs6311 polymorphism and bruxism have also been found in the present study. The *5HTR2A* gene encodes the 5-HT2A receptor, which is involved in various physiological and behavioral processes, including mood regulation, cognition, and sleep. The distribution of CT, TT, and CC genotypes in our sample, with the T allele showing a higher frequency, indicates a genetic variation at the *5HTR2A* rs6311 locus that may predispose individuals to bruxism. These findings are consistent with previous studies that have linked *5HTR2A* polymorphisms to disorders involving serotonin dysregulation, such as obstructive sleep apnea and nocturnal enuresis[13,14]. The 5-HT2A receptor has also been implicated in the regulation of mood and anxiety, conditions that are often comorbid with bruxism[15].

The role of *5HTR2A* polymorphisms in sleep regulation has been well-documented, particularly in relation to serotonin's influence on sleep disorders. Our findings suggest that disruptions in serotonin signaling, potentially caused by polymorphisms at the *5HTR2A* rs6311 locus may lead to abnormal muscle activity during sleep, characterized as bruxism. This is consistent with previous research linking serotonergic dysfunction to both sleep disorders and motor activity during sleep[16,17].

Despite these important findings, several limitations of our study should be acknowledged. First, the small sample size of 10 patients limits the generalizability of our results. Larger cohort studies are necessary to confirm these associations and further elucidate the role of *COMT* and *5HTR2A* polymorphisms in bruxism. Second, our study focused on specific polymorphisms, rs4680 within the *COMT* gene and rs6311 within the *5HTR2A* gene; while other genetic variants that may contribute to bruxism were not examined. Future research should adopt a broader genetic approach, potentially utilizing genome-wide association studies (GWAS) to identify other relevant polymorphisms and gene-gene interactions.

Moreover, while this study highlights a potential link between serotonin-related and dopaminergic pathways in bruxism, the precise neurobiological mechanisms remain speculative. Further investigations using neuroimaging and electrophysiological techniques could help clarify the pathways through which these genetic variations influence bruxism pathophysiology.

Conclusion

In conclusion, this study explored the relationship between both the *COMT* rs4680 and *5HTR2A* rs6311 polymorphisms and bruxism, highlighting potential genetic influences on its development. Our findings suggest an association between the *5HTR2A* rs6311 polymorphism, particularly the T allele, and bruxism, while also reinforcing previous research on the role of the *COMT* rs4680 polymorphism. However, given the small sample size and the complexity of genetic interactions, these results should be interpreted with caution. Further research involving larger, more diverse populations

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and comprehensive genetic analyses is necessary to confirm these associations and better understand the genetic mechanisms behind bruxism.

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