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Association between 5-Hydroxytryptamine Receptor 2A Gene (rs6313 and rs4941573) Polymorphism and Sleep Bruxism: A Meta-analysis

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Abstract

Genetic factors may influence sleep bruxism's pathogenesis. Even though the association between the, 5-hydroxytryptamine 2A (5-HTR2A) serotonin receptor gene polymorphism and sleep bruxism has been investigated, inconsistent findings have been discovered. As a result, meta-analysis was performed to gather complete results on this topic. PubMed, Web of Science, Embase, and Scopus databases were searched for all papers containing English abstracts until April 2022. Medical Subject Heading (MESH) terms plus unrestricted keywords were used in the searches. The Cochrane test and the I^2 statistic were used to determine the heterogeneity percentage in numerous researches. Comprehensive Meta-analysis v.2.0 software was used to conduct the analyses. Five properly fitting papers were chosen for meta-analysis from the 39 articles acquired during the initial search. The meta-analysis revealed that the 5-HTR2A polymorphism has no link with sleep bruxism susceptibility across the models studied (P-Value > 0.05). The combined odds ratio analysis revealed no statistically significant association between the 5-HTR2A gene polymorphism with sleep bruxism. Nonetheless, these findings require confirmation through researches with large sample sizes. Identifying genetic markers for sleep bruxism may help clarify and expand our current knowledge of bruxism physiopathology.

Keywords
- Polymorphism
- Genetic
- Sleep Bruxism
- Receptors
- Serotonin
- Meta-Analysis

Introduction

Marie Pietkiewicz coined the term "la bruxomania" in 1907, which came to be known as bruxism, which refers to the act of teeth grinding for no apparent reason. Repetitive and rhythmic teeth movement occur in conjunction with gradually rising masseter muscle tone and commonly happens without the patient being aware.[1] International consensus on the assessment of bruxism defines sleep bruxism (SB) as "a masticatory muscle activity during sleep that is

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characterized as rhythmic (phasic) or non-rhythmic (tonic) and is not a movement disorder or a sleep disorder in otherwise healthy individuals"[2].

In a recent review Lavigne et al. discussed the standardization of sleep bruxism metrics. Usually, the diagnosis of SB which is a multi-factorial condition is based on dental and medical histories and clinical manifestations. However, many new technologies and approaches can be used to make the diagnosis more objective. Developing a SB metrics that can make a difference in clinical settings will be beneficial to patients suffering from SB.[3]

Previous studies had shown a positive association between SB with TMD pain,[4] although more recent studies didn't confirm this.[5–7]

Several therapeutic and pharmacological data have shown serotonin or 5-hydroxytryptamine's (5-HT) role, which is the neurotransmitter responsible for maintaining circadian rhythm, muscular tone modulation, and breathing in the development of sleep bruxism.[8] For instance, selective serotonin reuptake inhibitors (SSRIs), provided to patients suffering from depression, have been linked with sleep bruxism in some circumstances, raising the notion that the 5-HT transporter is involved in this disease.[9] Additionally, it has been observed that 5-HT 1A receptor agonists can effectively treat SSRI-induced sleep bruxism.[10] Additionally, some research indicates that the 5-HT transporter serves as a control center for regulating serotonin neurotransmitters tone in the brain.[11]

5-hydroxytryptamine 2A (5-HTR2A) serotonin receptor gene is found on chromosome 13q14-q21 and comprises two introns and three exons.[12] Single nucleotide polymorphism (SNP) databases consisting of 230 SNPs are found within this gene region.[13] The 5HTR2A polymorphism has been investigated for its ability to control sleep and alertness, and findings indicate it is associated with sleep disturbances.[14]

Although no clear gene markers for sleep bruxism are established to date, clinical studies have revealed that 21-50% of people suffering from sleep bruxism had the disease in infancy. The consistency of sleep bruxism conditions between monozygotic twins is significantly greater than between dizygotic twins.[15] Additionally, recent investigations have indicated a substantial likelihood of genetic contribution to the development of this condition.[16–18] Castroflorio et al. in a study conducted in 2017 observed that patients experiencing sleep bruxism possessed a greater frequency of genetic variants than controls.[19]

Given the significance of sleep bruxism for oral health plus the fact that conflicting findings have been collected in this field, the importance of synthesizing the results of previous research on this disease, and the fact that small sample sizes result in low statistical power plus false-positive results, the focus shifted to meta-analysis. The study's purpose is to review data from studies examining the serotonin receptor gene polymorphism (5-HTR2A) in sleep bruxism.

Material and Methods

This systematic review study was accepted by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (ethical code: IR.TBZMED.VCR.REC.1400.166). The study protocol has been registered in PROSPERO (CRD42022332604).

Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 (PRISMA) guidelines was used to report systematic reviews in this article.[20]

Search Strategy

A targeted question was developed using the principles of PECO including Patient, Exposure, Comparison, and Outcome. The main purpose of this study was to determine whether the rate of polymorphism in the serotonin receptor gene is different in patients with sleep bruxism compared to healthy individuals.

A librarian searched the PubMed, Embase, Web of Science, and Scopus databases up to April 2022 for English-language published publications. No limitation was put on the start date. Additionally, relevant sources within the chosen studies were carefully searched, with our search being limited to human testing. The free and MESH (Medical Subject Headings) terms were combined in various ways to obtain data. The following keywords were used in the search: "bruxer" OR "sleep bruxism" OR "sleep brux" OR "bruxism" OR "bruxomania" OR "teeth grinding disorders" AND "Genetic susceptibility" OR "polymorphism" OR "single nucleotide polymorphism" OR "variant" OR "variants" OR "mutation" OR "SNP" AND "5-HT2A receptor" AND "5-HTR2A" OR "receptors serotonin2A".

Study Selection

Following the extraction of articles from databases, they were evaluated in three stages by two specialists. Two impartial reviewers (P.M and K.K) initially assessed titles and abstracts against eligibility criteria. Disagreements were settled through consultation through a third author (M.J). The full text of the related papers was then evaluated. The Newcastle-Ottawa scale was used to measure the study's quality, with the highest score as 9 for each article and a value equal to or greater than 7, indicating a solid research quality.[21] Microsoft Excel was utilized to obtain the study's characteristics. The form contained the author's name, the year of publication, country, the sample size, the method used to detect polymorphisms, and the source of controls. Cross-sectional and case-control studies reporting polymorphisms in the 5-HTR2A gene were included as the inclusion criteria in both cases and control groups. Case-report studies, review studies, and studies evaluating the polymorphism of alternative SNPs were excluded.

Meta- Analysis

Two distinct criteria, the odds ratio (OR) plus the 95% confidence interval (CI), were used to highlight gene polymorphism within control plus case populations. The odds ratio totals for allelic models, homozygous models, heterozygous models, dominant models, plus recessive models were measured. I^2 statistics and the Cochrane test were used to assess heterogeneity between studies. These statistics represent the variation percentage between trials. As per the fixed effect model, an I^2 of $< 50\%$ and a $P > 0.1$ suggested

no substantial heterogeneity between trials. Comprehensive Meta-analysis software v.2.0 was used to conduct the analyses. $P < 0.05$ was deemed statistically significant.

Results

Thirty-nine articles were identified through a comprehensive search of sources. Twenty-six articles were excluded due to duplication, and 8 studies were excluded after the titles and abstracts were reviewed. Five articles were included within the meta-analysis study after the entire content of the articles was reviewed.[17,18,22–24]

►**Fig. 1** depicts a flow chart of the articles identified and included. ►**Table 1** summarizes the studies considered in the study. The study quality used in the meta-analysis averaged 7.8, with most studies ranked as high (►**Table 2**).

The heterogeneity among the studies that evaluated the association of 5-HTR2A polymorphism and sleep bruxism disease was significant ($I^2 > 50$, *P-value* <0.1) across all models, hence the random-effect model was utilized to consolidate the results. In ►**Fig. 2** and ►**Fig. 3**, the forest plots show the extent of the consolidated effect derived from the selected research. No significant difference between the ORs of the 5-HTR2A gene polymorphism was identified between case and control groups in all models ($P > 0.05$).

Discussion

The serotonergic system within the CNS exhibits decreased activity throughout sleep, most notably during rapid eye movement (REM) sleep, and is involved in maintaining arousal, controlling muscle tone, and various phasic events

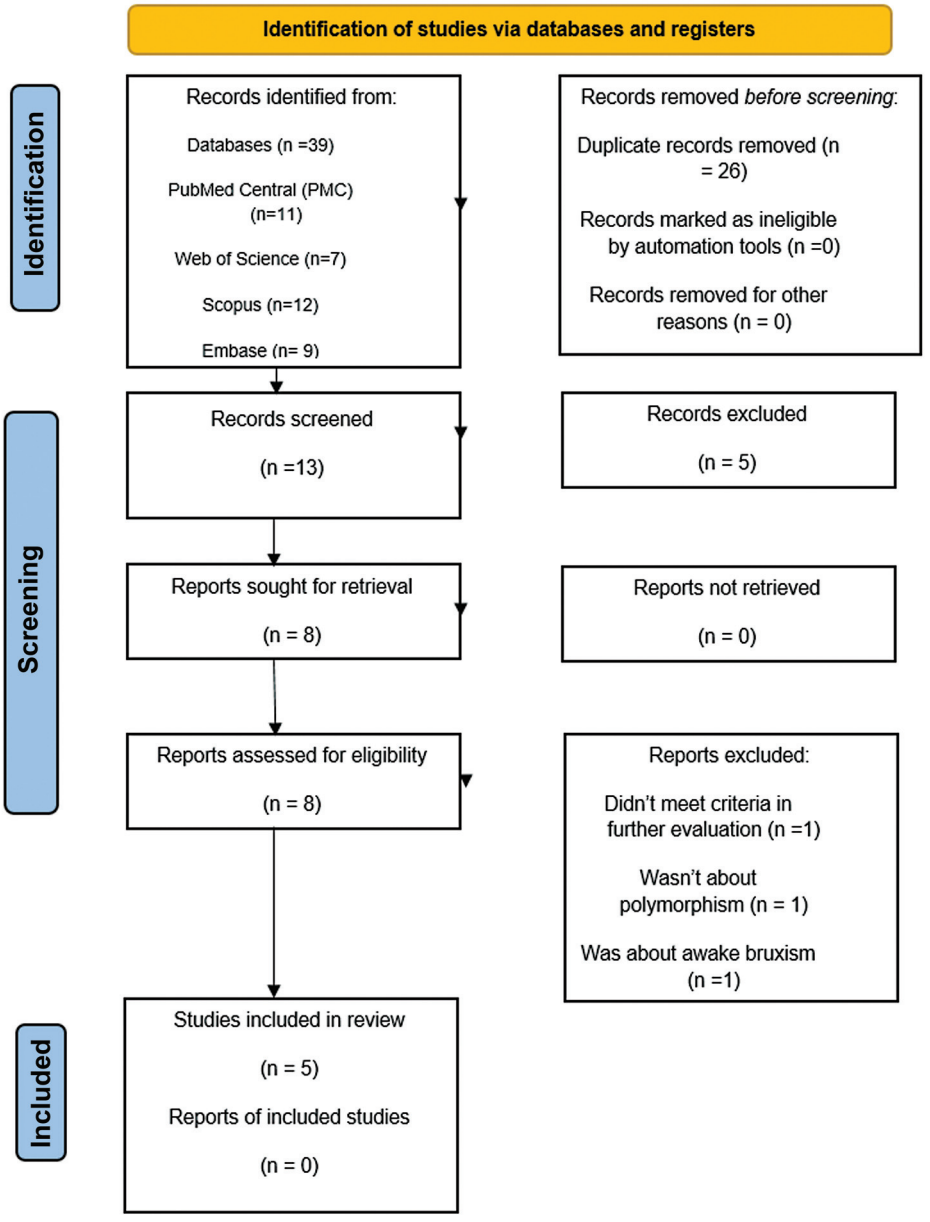

Fig. 1 The flowchart of the study selection using the Preferred Reference Items for Systematic Reviews (PRISMA) 2020.

Table 1 Summary of the data extracted from included studies in this review.

Authors (publication year)	Country	Control	Case	Location of polymorphism (5-HTR2A)	Method of polymorphism detection	Source of control
Duarte et al (2022)	Brazil	31	17	rs 6313 rs 4941573	PCR	Population-based
Wieckiewicz et al (2020)	Poland	125	100	rs 6313	PCR	Population-based
Cruz-Fierro et al (2018)	Mexico	59	112	rs 6313	PCR	Population-based
Oporto et al (2016)	Chile	59	130	rs 6313 rs 4941573	PCR	Population-based
Abe et al (2012)	Japan	48	66	rs 6313 rs 4941573	PCR	Hospital-based

PCR: Polymerase chain reaction.

Table 2. The quality score based on the Newcastle-Ottawa Scale (NOS) of each study included.

Authors / publication year	Selection				Comparability		Outcome				
	Case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Main factor*	Additional factor†	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Total score	Quality‡
Duarte et al (2022)	+	+	+	+	+	+	+	+	+	9	Good
Wieckiewicz et al (2020)	+	+	+	+	+	−	+	+	+	8	Good
Cruz-Fierro et al (2018)	+	+	+	+	−	+	+	+	+	8	Good
Oporto et al (2016)	+	+	+	+	−	−	+	+	+	7	Good
Abe et al (2012)	−	+	−	+	+	+	+	+	+	7	Good

*Age was matched between 2 groups.
†Sex was matched between 2 groups.
‡Good quality (score: ≥7) and fair quality (score: 5-7).

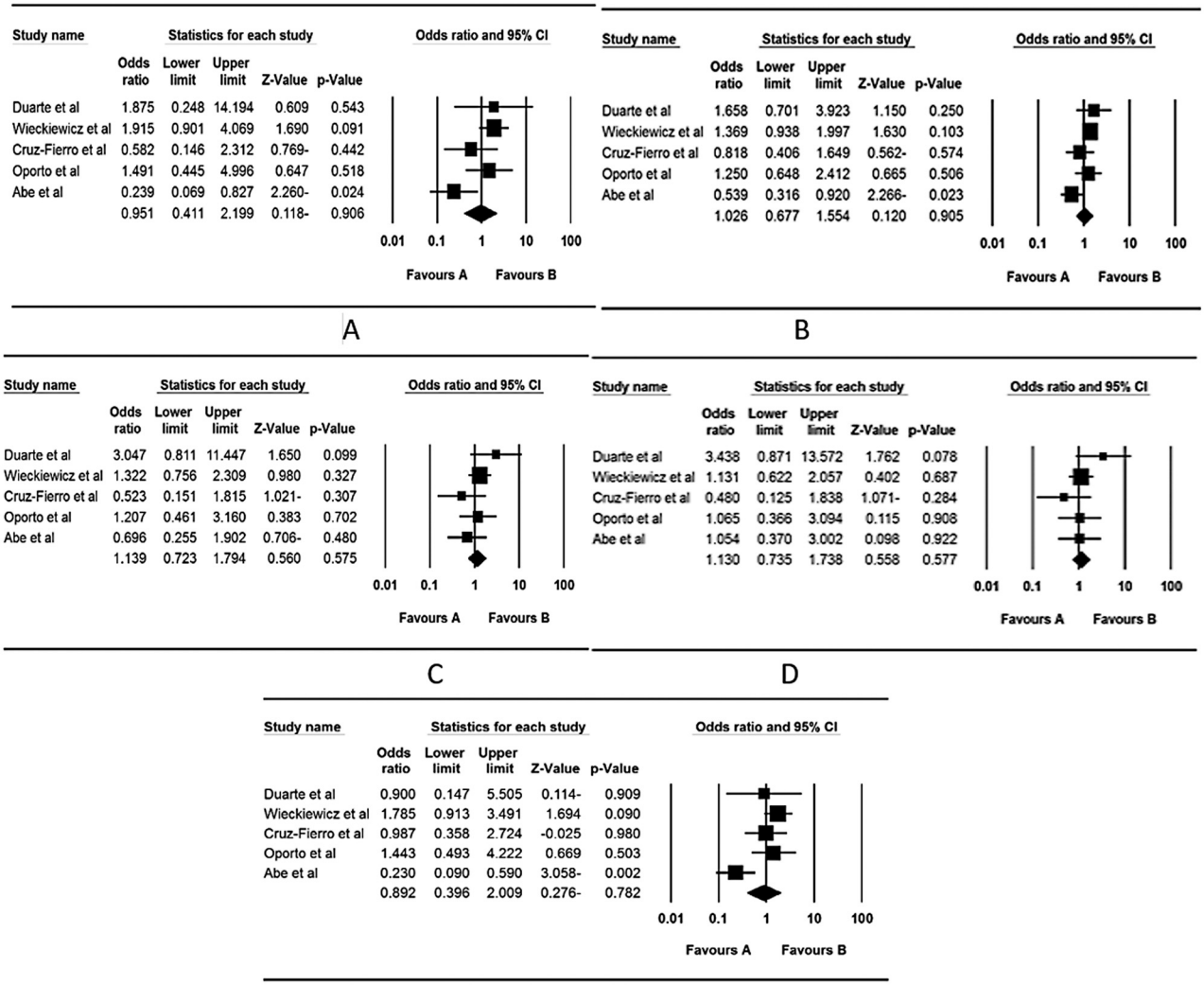

Fig. 2 Forest plot of the polymorphism of HTR2A rs6313 gene and sleep bruxism susceptibility in 5 genetic models. A) Allelic models (T vs. C), B) Homozygous models (TT vs. CC), C) Heterozygous models (TC vs. CC), D) Dominant models (CT + TT vs. CC), E) Recessive models (TT vs. CC + CT). CI = confidence interval, OR = odds ratio.

throughout sleep.[15] It has been shown that the levels of enzymes in serotonin synthesis pathway (tryptophan hydroxylase 1 and aromatic l-amino acid decarboxylase) do not have any effect on the occurrence and severity of SB[25]; however, SSRI usage has been linked to SB, and SSRI-induced SB has shown to be successfully treated with a 5-HT 1A receptor agonist.[10] Therefore, the reason for low serotonin levels in SB patients, which may be related not only to serotonin synthesis but also to processes associated with the serotonin neurotransmission pathway need to be investigated.[26] As a result, 5-HT-related polymorphisms for potential prospective linkage with SB were evaluated in this study.

The HTRA2 serotonin receptor is critical for adult mood regulation, and polymorphisms in the HTR2A gene are connected with various mental illnesses.[13] Additionally, these receptors' expression is a trait associated with anxiety. Compared with non-bruxers, those with bruxism demonstrated substantial variations in anxiety, aggression, and phobia anxiety.[27] According to a controlled lab study, SB patients contended and felt more worried than average people.[28] In case-control research conducted by Abe et al.,[17] subjects underwent masseter muscle electromyography for three nights to determine the link between genetic, psychological, plus behavioral variables and sleep bruxism within the Japanese population. Furthermore, 13 polymorphisms in four genes inscribing serotonergic neurotransmitters were investigated genetically, HTR1A, HTR1A, HTR2A, and HTR2C. Only the C allele harboring the HTR2A gene with the rs6313 single nucleotide polymorphism (T > 102C) significantly enhanced the incidence of sleep bruxism (odds ratio = 4.250, 95% confidence interval [CI]: 1.599-11.297, p = 0.004). The study results imply that the existence of the C allele, linked with an elevated risk of SB, may lead an individual to flawed 5-HT2A receptor creations, which, when combined with other risk factors, may predispose the patient to SB. A specific study drawback was the absence of laboratory-based polysomnographic recordings, the benchmark for SB evaluations. Another disadvantage of the study was that

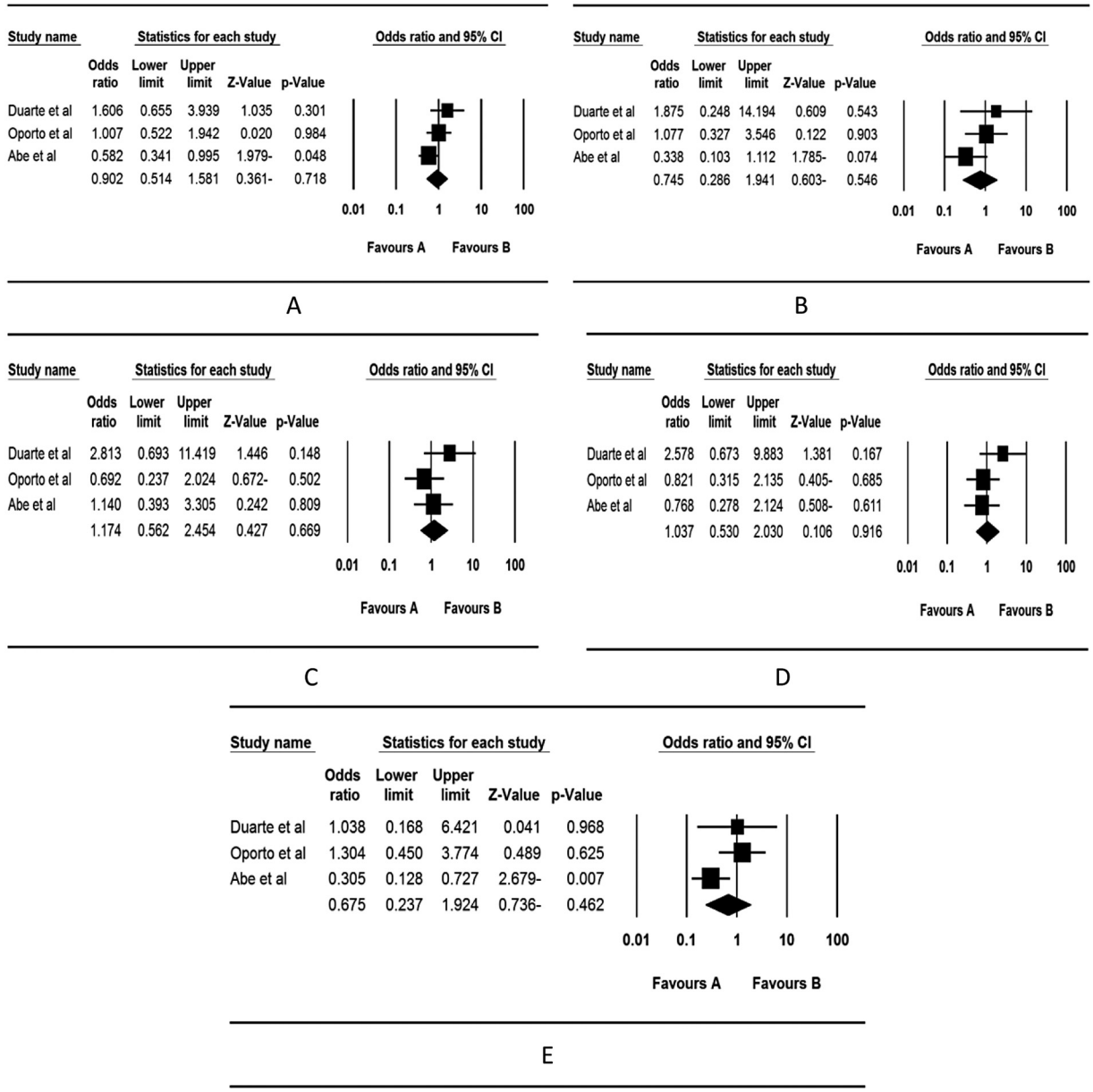

Fig. 3 Forest plot of the polymorphism of HTR2A rs4941573 gene and sleep bruxism susceptibility in 5 genetic models. A) Allelic models (G vs. A), B) Homozygous models (GG vs. AA), C) Heterozygous models (AG vs. AA), D) Dominant models (AG + GG vs. AA), E) Recessive models (GG vs. AG + AA). CI = confidence interval, OR = odds ratio.

they used dental patients plus academic staff; therefore, the results could not be generalized to the Japanese population. Oporto et al., conducted a study in 2016 on genetic polymorphisms within the serotonergic system plus their connection with circadian aspects in bruxism, and patients were grouped depending on the type of bruxism they experienced (awake, sleeping, or both), and a control group of healthy individuals was employed. SB patients were selected in this study through screening, medical examination, and the use of an overnight masseter electromyographic device, plus the link among all circadian expressions of bruxism plus a serotonergic system genetic polymorphism, was studied. The HTR2A C allele polymorphism (rs6313) was strongly related to an elevated chance of sleep bruxism.[18]

Cruz-Fierro et al. found no connection between the HTR2A gene polymorphism (rs6313) with sleep bruxism in a study conducted in 2018.[24] This study enrolled 59 healthy individuals plus 112 bruxism sufferers; no significant change in serotonin receptor gene polymorphism was observed between the groups. No significant genetic connections were found within the population of the study (north-eastern Mexico), which can be explained by a close connection between genetic factors plus the environment, as well as its influence on causing individual differences in genes associated with personality traits, cognitive abilities, and particularly, bruxism.[29,30]

Wieckiewicz et al., showed that there are associations between SNPs within the HTRA2 gene and Bruxism episode index values.[23] The bruxism episode index increased

considerably in homozygous HTR2A rs6313 TT patients compared to heterozygous patients. They evaluated the effect of a serotonin pathway gene polymorphism on sleep bruxism within this study via video polysomnography, considered the benchmark for evaluating bruxism. While polysomnography is regarded as the gold standard for diagnosing SB, it does have certain drawbacks. The next goal for SB evaluation is to develop a convenient tool that can be utilized in both clinical practice and research to evaluate ongoing bruxism activity directly, reliably, and promptly.[31]

According to the current meta-analysis, it is recommended that the influence of polymorphisms in alternative genes involved in SB be studied to establish a definitive conclusion concerning gene polymorphism function as a predictive marker for this disorder. It is worth mentioning that the 5-HT2A receptor can be expressed via various methods.[15] Furthermore, SB is a multifactorial disease. As a result, it may be difficult to identify the genetic role of the disorder, especially since families often share a common environment and may have a similar lifestyle, which makes it difficult to determine the risk of inheritance or transmission of the disorder in a person. Limitations of the present study include sample sizes were restricted for some groups. Secondly, our search was restricted to articles in English, which may have influenced our results. Thirdly, we could not adjust for confounding characteristics such as age, gender, plus mental status in research to analyze potential gene-environment correlations. For corroborating the results of this study, additional research should be conducted with more significant sample numbers in diverse populations and with clinical and personal characteristics recorded.

Conclusion

Combined odds ratio analysis revealed no statistically significant association between the 5-HTR2A polymorphism with sleep bruxism. For gaining a better understanding of cell activity, future research should focus on functional analyses or mechanistic studies, which may include evaluating protein or gene expression, collecting new data, and offering a broader evaluation of SNP effects at the cellular level. These discoveries may aid in the identification of one of SB's highly effective molecular mechanisms.

Source(s) of support
None.

Conflicting Interest
None.

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