

# Phenotypes and Clinical Genotypes of Bruxism Patients: A Systematic Review

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## ABSTRACT

**Background.** Bruxism is a phenomenon where psychological and exogenous biological factors act in greater percentage. Several genetic polymorphisms have been described in GABAA receptors, and some have been associated with motor limitations, such as the rs1805057 polymorphism of the GABRB1 gene (GABAA), which found a haplotype associated with a lower limitation in movement in acute pain processes. The aim to identify the clinical phenotypes in bruxism patients.

## Methods

Eligibility criteria were as follows: observational studies, case control studies, odds ratios, bruxism, patients, and a keyword search that included [[bruxism]], OR [[temporomandibular joint disorders]] OR [[sleep bruxism]], OR [[awake bruxism]], OR [[polymorphism]] or [[GABAA]], or [[serotonin]] , using the Boolean operators AND, OR and NOT.

## Results

Were included 210 identified records in databases; 50 records from other sources; 117 records were deleted after determining they were duplicates; 42 studies were included in qualitative synthesis ; finally, who met inclusion requirements 5 studies were included in synthesis. The comparison of global DNA methylation profiles in patients with bruxism shows a possible genetic influence on their etiology, indicating that patients with HTR2A rs2770304 alleles are at increased risk.

## Conclusion

the HTR2A rs2770304 allele leads to an increased risk of bruxism.

## Keywords

bruxism, temporomandibular joint disorders, phenotype, genotype, methylation.

## INTRODUCTION

Initial genetic evidence of bruxism is based on questionnaires and surveys, and evidence indicates that 20% to 50% of patients have at least one close family member reporting that there is a genetic relationship.<sup>1</sup> Several genetic polymorphisms have been described in GABAA receptors. Some have been associated with motor limitations, such as the rs1805057 polymorphism of the GABRB1 gene (GABAA), which found a haplotype associated with a lower limitation in movement in acute pain processes<sup>2</sup>; this subunit would act as an endogenous muscle relaxant with a greater inhibitory GABAergic action, reducing muscle spasm and allowing greater movement the chewing muscles.<sup>3</sup> Another case is the rs4906902 polymorphism of the GABRB3 gene (GABAA), which has been associated with the presence of a complex syndrome

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characterized by skeletal muscle pain.<sup>4</sup> Mishra *et al.*, postulated that at least 10–15 genes relate to phenotypes of anxiety. The most studied genes in this regard are serotonin transporter genes (receptors), and their relation to anxious personality ranges. The medium rafe brain serotonin system is related to mood modulation, anxiety, emotions, and cognition. In addition, the serotonergic system has been investigated in molecular genetics relating it to emotional behavior, variations in the SLC6A4 gene of the serotonin receptor (SERT) have been associated with more than twelve different traits of human behavior and other pathologies.<sup>4,5</sup> Bruxism is characterized by biological, psychological, and exogenous factors presenting as frequent clinical signs: repetitive movements of the jaw causing the teeth<sup>6</sup> to squeak, micro trauma to chewing muscles and cervical pain skull mandibular. The prevalence of bruxism was<sup>8</sup> to 31.4%, with the highest percentage in men<sup>7</sup>, neuromuscular activity accompanied by teeth grinding with three-dimensional mandibular movements. In 2017, the International Bruxism Assessment Council defined conceptual differences between sleep bruxism and awake bruxism. The new definitions are as follows. Masticatory muscle activity during sleep is characterized as rhythmic (phasic) or non-rhythmic (tonic), not a movement

disorder or a sleep disorder, in healthy individuals, which is known as sleep bruxism.<sup>8</sup> Awake bruxism is a masticatory muscle activity during wakefulness that is characterized by repetitive, sustained dental contact and mandibular hypermobility. An etiologically, emerging evidence suggests that psychology, biologic, and exogenous risk indicators have greater involvement than morphologic factors.<sup>9</sup> Having identified the HTR2A rs2770304 allele related to bruxism, a comprehensive evaluation system can be created to facilitate the diagnosis and subsequent clinical management of the patient.<sup>10</sup> Symptomatology found in patients with bruxism include the following: headache, neck pain, TMJ pain, limitation of mouth opening, joint noises, fatigue, and deviation in mouth opening. The following risk factors are considered as predisposing factors: macro and micro trauma<sup>11</sup>, skeletal changes of the face, occlusal contact, hyperactivity of chewing or cervical muscles, changes in TMJ<sup>12</sup>, hormonal and genetic factors, and psychological factors.<sup>13</sup> The aim to identify the clinical phenotypes in bruxism patients

### MATERIALS AND METHODS

This systematic review was registered with PROSPERO with the registration number CRD42020164836.

## RESULTS

Table 1: Summary of the risk of bias for in-vitro studies according to Consolidated Standards of Reporting Trials

Item	Oporto G <sup>15</sup> 2018	Oporto G <sup>16</sup> 2016	Hoashi, Y <sup>17</sup> 2017	Oporto G <sup>19</sup> 2018	Cruz, N <sup>21</sup> 2018
1 Abstract	Yes	Yes	Yes	Yes	Yes
2a Background and objectives	Yes	Yes	Yes	Yes	Yes
2b Background and objectives	Yes	Yes	Yes	Yes	Yes
3 Intervention	Yes	Yes	Yes	Yes	Yes
4 Outcomes	Yes	Yes	No	No	Yes
5 Sample size	No	No	Yes	No	Yes
6 Randomization: sequence generation	No	No	No	No	No
7 Allocation concealment mechanism	No	No	No	No	No
8 Implementation	No	No	No	No	No
9 Blinding	No	No	No	No	No
10 Statistical methods	Yes	Yes	Yes	No	Yes
11 Results: outcomes and estimation	Yes	Yes	No	Yes	Yes
12 Discussion: limitations	Yes	No	Yes	Yes	Yes
13 Other information: funding	No	No	No	Yes	Yes
14 Protocol	Yes	No	Yes	Yes	Yes

Table 2: Summary of the risk of bias

Item	Oporto G <sup>15</sup> 2018	Oporto G <sup>16</sup> 2016	Hoashi, Y <sup>17</sup> 2017	Oporto G <sup>19</sup> 2018	Cruz, N <sup>21</sup> 2018
Random sequence generation	Low	Low	Low	Low	Unclear
Allocation concealment	Low	Low	Low	Unclear	Unclear
Selective reporting	Low	Low	Low	Low	Low
Blinding (participants and personnel)	High	high	high	High	High
Blinding (outcome assessment)	High	High	High	High	High
Incomplete outcome data	Low	Low	Low	Low	Low

Table 3: Structural summary Systematic Review

Study (Year)	Object of Research	Intervention	Evaluation methods	Result
Oporto G <sup>15</sup> 2018	Compare global DNA methylation level in patients under bruxism treatment and control group.	SB (32 patients),WB (42),W&SB (42) patients and control group (CTR) (42) individuals	ELISA kit Methyl Flash Methylated DNA Quantification Kit	Significant differences were found in the amounts of methylated DNA in all circadian manifestations of BRX compared with the control group (SB 0.95 % ±) AB 0,87% ± 2.1 % Sleep and awake. = 0.17% ± 0.25%; Control = 1.69% ± 1.6%; Kruskal–Wallis test [p =.0001] followed by Dunn's test [p < .05]).
Oporto G <sup>16</sup> 2016	Evaluate the frequency of genetic polymorphisms in the HTR1A (rs6295), HTR2A (rs1923884, 4941573, 6313 2770304), HTR2C (rs17260565 and SLC6A4, rs 63749047) genes in subjects undergoing BRX treatment	130 patients were recruited to cases groups. Randomized controlled clinical trial contact areas	Diagnosis of circadian manifestations of BRX was reached using clinical criteria. Criteria in probable awake and/or sleep bruxism. Blood samples were obtained and genomic DNA was extracted from blood leukocytes using a salting out method as describe Genotypes were determined using TaqMan® SNP genotyping assay (Applied Biosystem, USA) 2× TaqMan® SNP genotyping master mix (Applied Biosystem, USA), and using	Suggested that polymorphisms in serotonergic pathways are involved in sleep bruxism. Further research is needed to the understanding of the increase of the physiopathology of BRX
Hoashi, Y <sup>17</sup> 2017	Generate neural cells using SB patient- specific induced pluripotent stem cells (iPSCs) Randomized controlled clinical trial	Two primary SB patients and two age- matched healthy controls were selected from SB and control group	Four lines of iPSCs, two from SB patients' controls, were established from peripheral and two from blood. The following iPSC clones were selected for detailed analysis: three from patient SB1 (SB1–1, SB1–2, and SB1–10), three from patient SB2 (SB2–2, SB2–7, and SB2–10), three from control 1 (C1-6, C1–12, and C1–18), and three from control 2 (C2–1, C2–2, and C2–4).	Patient-specific iPSCs were successfully differentiated into neurons expressing 5-HT2A.
Oporto G <sup>19</sup> 2018	Evaluate the frequency of single nucleotide polymorphisms (SNPs) in dopaminergic pathway genes (DRD1, DRD2, DRD3, DRD4, DRD5, and MAOB) in patients undergoing bruxism treatment and controls. Cross- sectional study	130 patients nonrelated Chilean patients (41 males and 89 females) were included in case groups	Bruxism diagnosis was reached using clinical criteria. Genotypes Bruxism diagnosis was reached using clinical polymerase chain reaction (PCR) of polymorphism rs63749047 (5-HTTLPR) of the SLC6A4 gene was determined using conventional	The G allele of DRD2 rs1800497 SNP was associated with significant risk reduction of awake- sleep bruxism (p = 0.041), while the C allele of DRD3 rs6280 SNP was associated with increased risk of sleep bruxism (p=0.02) and the C allele of DRD5 rs6283 SNP. was associated with decreased risk of awake bruxism (p = 0.01).

Eligibility criteria were as follows: observational studies, case- control studies, odds ratios, bruxism, patients "with temporomandibular disorders , and a keyword search that included [[bruxism]], OR [[sleep bruxism]] , AND [[Sleep Bruxism]], , OR [[chewing]],OR [[oral parafunctional habits]], OR [[oral habits]] OR [[Facial pain]] or [[temporomandibular joint disorders]] AND [[Temporomandibular Joint Dysfunction Syndrome]] OR [[myofascial pain]] OR [[syndromes]] AND [[myalgia ]] AND [[osteoarthritis ]] OR [[arthralgia ]] OR [[orofacial pain]] OR [[TMD]] O [[temporomandibular disorder]]

OR[[polymorphism]] OR [[GABAA]],OR [[serotonin]], OR [[Case Control Studies ]],OR [[Odds Ratio Studies]] using the Boolean operators AND, OR and NOT. The Scopus, Ebsco, PubMed, Medline Embase, the Cochrane Library, the Web of Science databases were searched; alternate databases that were searched included Scielo, Latindex, and Redalyc. Using the Prisma research protocol, the flowchart sequentially explains the selected information. Complete articles published were included as follows: were included 210 identified records in databases; 50 records from other sources; 117 records were deleted

after determining they were duplicates; 42 studies were included in qualitative synthesis; finally who met inclusion requirements 5 studies were included in synthesis. (Fig. 1) The authors (BVVR, AZ, AU, LCH, BS.) independently selected the titles and summaries, excluded duplicates and irrelevant articles that did not contain keywords or fell within the inclusion criteria and considered only full text articles. The date and names of all authors were included in the final review article. If the articles did not meet the inclusion and exclusion criteria as complete articles, case controls, odds ratio were resolved by the third and fourth evaluator (VC, MR) those who considered the results obtained in the studies and the methodology to confirm or eliminate the articles. The data extraction procedure was evaluated according to the criteria of all authors. Articles are classified by the author/year, study objective, study type, methodology, results (standard mean and deviation) and conclusions.

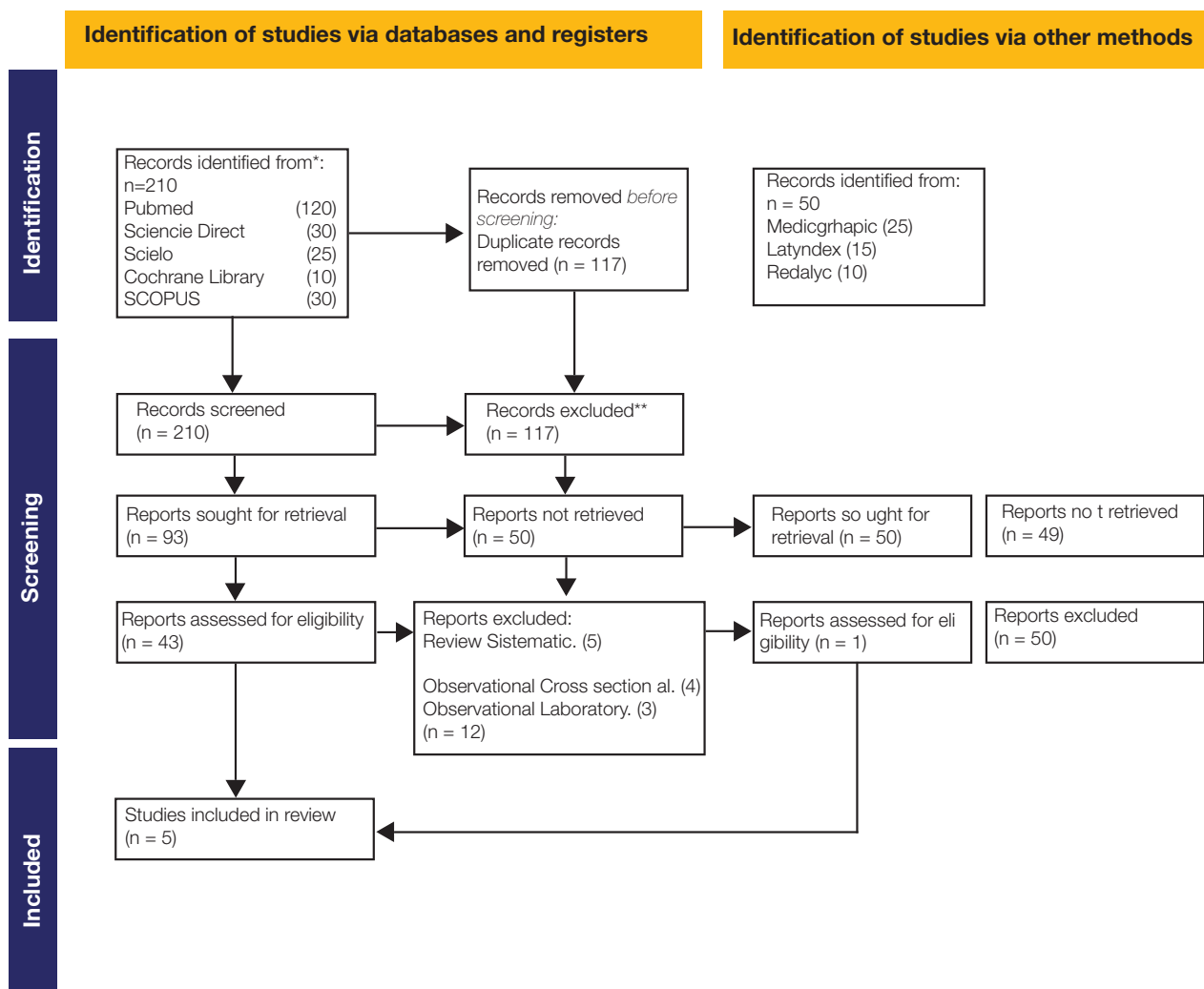
### DISCUSSION

The circadian manifestations of bruxism are associated with characteristic personality traits (stress)<sup>13,14</sup> as well as alterations in neurotransmitters and their pathways.<sup>15</sup>

Therefore, the neurotransmitters of the central nervous system as its genes are related to bruxism<sup>16,18</sup> considering its pathogenesis by serotonin, which is responsible for

the circadian rhythm, maintaining arousal, and regulating the response to stress, muscle tone and respiration, the typical manifestations associated with BRX.<sup>19</sup> Abe *et al.*,<sup>20</sup> studied the polymorphisms (HTR1A (rs6295), HTR2A (rs1923884, rs4941573, rs6313, rs2770304) and HTR2C) relating them to serotonergic transmission produced in sleep bruxism, finding three SNPs within the HTR2A gene (rs6313, rs2770304 and rs4941573) associated with SB in Japanese individuals, but did not explore other circadian manifestations.<sup>21,23</sup> The process of selecting patients with SB included screening, clinical examination, and the nightly use of an electromyography device for masseter muscle. We could not determine whether in the study control group people had signs of Bruxism. In the review carried out, evaluations were observed that coincided with the selection process of the SB individuals used, there were some differences in the general diagnostic method.

Patients recruited to participate in the study were referred by physicians and dentists in the community and at the university, with a presumptive diagnosis of bruxism. 25 Patients were then evaluated by a specialist in temporomandibular disorders<sup>26,28</sup> and classified into bruxism circadian manifestations (sleep bruxism, weak up bruxism, and sleep bruxism, weak up bruxism). This examination was performed in the control group as well to exclude the presence of bruxism.<sup>29</sup>



Therefore, to our knowledge, our work constitutes systematic review study that associated and examined the relationship between all circadian manifestations of bruxism and genetic polymorphisms within the serotonergic system.<sup>30</sup> We found significant differences in the rs27703045 SNP (HTR2A) between the SB group and the control group, where carriers of allele C showed an increased risk of SB compared to the control group. Grigoriadis, *A et al.*,<sup>31</sup> found differences in the rs27703045 SNP but compared genotypes of patients with SB with the control group. The HTR2A gene encodes 5-hydroxytryptamine (5-HT) 2A receptors. This family of receptors coupled with the G protein located in the brain involves physiological functions such as memory, sleep, nociception, eating and rewarding. However, these receptors have also been associated with depression<sup>32</sup> and epilepsy.<sup>33</sup> Serotonin receptors can directly or indirectly, depolarize or hyperpolarize, neurons by changing ion conductance and/or their concentrations within the cell; therefore, it is not surprising that serotonin is able to alter excitability in most serotonergic networks.<sup>34</sup> No information is available regarding the clinical importance of the Rs2770304 SNP, and this variant is known to be within the intrinsic regions of HTR2A. Previous reports have determined that inactivation of 5-HT2A receptors enhances depressive effects<sup>35</sup>, and in animal models, inactivation of these receptors increased susceptibility to epileptic chemicals and electrical products.<sup>36, 37</sup>

The findings show that the HTR2A rs6313 SNP was associated with an increased risk of SB in Japanese individuals. Therefore, it is possible that the HTR2A gene plays a role in SB physiopathology as well.<sup>38, 39</sup> HTR2A rs2770304 allele C studies showed an increased risk of patients with SB compared to the control group<sup>40, 41, 42</sup> whereas a decrease in the function of the 5-HT 2A receptor could be associated with depression and epilepsy.<sup>43</sup> Along with the intrinsic location of the rs2770304 SNP, it is noted that carriers of allele C<sup>44, 45</sup> showed receptor expression of 5-HT 2A; the function of receptors can also decrease in these individuals with episodes of BRX during sleep.<sup>46, 47</sup> Future research should be conducted to test this hypothesis, including functional studies and/or gene expression trials, to achieve a better understanding of the genetic basis of BRX circadian manifestations.<sup>48</sup> Although the diagnostic methods used in studies have limitations, they can be improved with the use of polysomnographic (PSG) and electromyography devices. Studies indicate that to recognize SB, the use of PSG is highly recommended by doctors and dentists within the gold standard of diagnostic research. Some authors note that the unstable nature of SB will also be reflected in fluctuations in the result variables of PSG recordings.<sup>49, 50</sup> In most studies, SB patients are asked to spend the night in a sleep monitoring laboratory. This action would detract from the validity of the procedure. The first night the patient will be adapting to, changes in the environment, which can alter the results. The recommendation is to first make a recording of only PSG to inhibit the patient to sleep under experiences and conditions different from their normal conditions. Observations indicate that variables associated with rapid eye movement take longer to stabilize<sup>51,52</sup> which appears to be a process extending to the fourth night. The PSG is described as a technique that is only suitable for small waiting times between diagnostic evaluation that takes between 5 and 6 months in the United States and

around the world, with noted limitations for the control policies and ethics committees that each country has. The etiology of bruxism is multifactorial; this SNP is one of the mechanisms involved in the circadian manifestations of BRX.<sup>53</sup>

## CONCLUSION

The clinical phenotype identified by the authors is the HTR2A rs2770304 allele the risk of bruxism patients.

## AUTHOR CONTRIBUTIONS

BVR, AZR, AUG, and ASA were involved in the conception and design of this study. BVR, LCHB, AMS, MRT were involved in the analysis and interpretation of the data. All authors were involved in drafting the manuscript. All authors reviewed and approved the final manuscript and agree to be held accountable for all aspects of the work

## ETHICAL APPROVAL

Approved by the Bioethics committee (CEISHSOLCAQ. OBS.19.125)

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## CONFLICT OF INTEREST

The authors have explicitly stated that there are no conflicts of interest in this article.

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## CPD questionnaire on page 52

The Continuing Professional Development (CPD) section provides for twenty general questions and five ethics questions. The section provides members with a valuable source of CPD points whilst also achieving the objective of CPD, to assure continuing education. The importance of continuing professional development should not be underestimated, it is a career-long obligation for practicing professionals.

