# **Epigenetics and Bruxism: Possible Role of Epigenetics in the Etiology of Bruxism**

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Bruxism is defined as a repetitive jaw muscle activity characterized by clenching or grinding of the teeth and/or bracing or thrusting of the mandible. There are two distinct circadian phenotypes for bruxism: sleep bruxism (SB) and awake bruxism, which are considered separate entities due to the putative difference in their etiology and phenotypic variance. The detailed etiology of bruxism so far remains unknown. Recent theories suggest the central regulation of certain pathophysiological or psychological pathways. Current proposed causes of bruxism appear to be a combination of genetic and environmental ( $G \times E$ ) factors, with epigenetics providing a robust framework for investigating G×E interactions, and their involvement in bruxism makes it a suitable candidate for epigenetic research. Both types of bruxism are associated with certain epigenetically determined disorders, such as Rett syndrome (RTT), Prader-Willi syndrome (PWS), and Angelman syndrome (AS), and these associations suggest a mechanistic link between epigenetic deregulation and bruxism. The present article reviews the possible role of epigenetic mechanisms in the etiology of both types of bruxism based on the epigenetic pathways involved in the pathophysiology of RTT, PWS, and AS, and on other epigenetic disruptions associated with risk factors for bruxism, including sleep disorders, altered stress response, and psychopathology. Int J Prosthodont 2015;28:594-599. doi: 10.11607/ijp.4126

Bruxism is defined as a repetitive jaw muscle activbity characterized by clenching or grinding of the teeth and/or bracing or thrusting of the mandible.<sup>1</sup> There are two distinct circadian phenotypes of bruxism: sleep bruxism (SB) and awake bruxism, which are considered separate entities due to the putative difference in their etiology and phenotypic variance.<sup>1,2</sup> The prevalence of bruxism is high, with approximately 8% of the general population estimated to suffer from SB and 20% from awake bruxism.<sup>2</sup> The detailed etiology of bruxism so far remains unknown.<sup>3</sup>

Recent theories of the etiology of bruxism point to the central regulation of certain pathophysiological or psychological pathways.<sup>4,5</sup> Stress and anxiety are the risk factors most commonly proposed to influence these pathways in awake bruxism,<sup>6-8</sup> while

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psychoactive substances<sup>3,9,10</sup> and sleep disorders, such as sleep apnea, periodic limb movement syndrome, and snoring,<sup>11-14</sup> represent the risk factors most commonly associated with SB. SB is associated with an event in sleep physiology called the arousal response.<sup>15</sup> It may be an exacerbation of the existing motor status during sleep caused by the risk factors.<sup>15</sup> Recent genetic studies indicate that the etiology of SB involves the interaction of environmental and genetic factors.<sup>16</sup> An indirect genetic effect, such as altered genetic sensitivity to environmental factors, most likely underlies the development of bruxism.<sup>3,13</sup>

Quantitative genetic modeling of twin data has shown that a combination of an additive genetic effects model (A) and a unique environmental effects model (E), the AE-model, constitutes the best fitting genetic model for SB, which means that genes and environmental factors interplay in the etiology of SB.<sup>3,16</sup> The study of mechanisms of genetic and environmental interactions (G×E) in diseases calls for the use of specific research methodologies.<sup>16,17</sup> Epigenetics provides a robust framework for investigating G×E interactions, and their involvement in bruxism makes it a suitable candidate for epigenetic research.<sup>16,18</sup> Further, both types of bruxism are associated with a group of epigenetically determined neurodevelopmental

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disorders, including Rett syndrome (RTT), Prader-Willi syndrome (PWS), and Angelman syndrome (AS),<sup>19,20</sup> which suggests that a mechanistic link may exist between epigenetics and bruxism. SB is closely associated with sleep and circadian alterations,<sup>11</sup> which have also been linked to RTT, PWS, and AS, and to epigenetic deregulation.<sup>21-24</sup>

The present article seeks to determine the possible role of epigenetic mechanisms in the etiology of both types of bruxism based on the epigenetic pathways involved in the pathophysiology of RTT, PWS, and AS, and on other epigenetic disruptions associated with risk factors for bruxism, such as sleep disorders, altered stress response, and psychopathology.

### Epigenetic Mechanisms

Broadly speaking, epigenetics is the study of all processes and features that contribute to the emergence of properties in the origin of the phenotype (somatic or behavioral) and its modifications in evolution.<sup>25,26</sup> It guides cell differentiation, growth, and development.<sup>27</sup> In a strict sense, molecular epigenetics represents a methodological approach to the search for epigenetic diagnostic markers and therapies for various diseases,<sup>27</sup> which could theoretically prove beneficial in the management of bruxism. It comprises molecular gene regulation and expression mechanisms at a critical control level that extend the DNA sequence.<sup>28,29</sup> At the same time, these molecular mechanisms represent the molecular techniques most frequently used in epigenetic research.<sup>30</sup>

In each cell, DNA is packaged in a very specialized structure called chromatin, which consists of DNA wrapped around the octamers of histone proteins.<sup>31</sup> While an open local chromatin configuration allows for the binding of transcription machinery to the gene promoters leading to gene activation, a closed chromatin configuration is not permissive for transcription.<sup>29</sup> Epigenetic modifications such as DNA methylation, histone modifications, and noncoding RNAs control the state of chromatin in the vicinity of gene regulatory regions and regulate gene expression.<sup>27,29</sup> DNA methylation occurs at the 5 position of cytosine residues, predominantly in the context of CpG dinucleotides. It is catalyzed by a family of enzymes called DNA methyltransferases (DNMTs), and is typically involved in gene silencing.<sup>27,29</sup> DNA methylation not only is responsible for single gene regulation but also plays an important role in global X chromosome inactivation and genomic imprinting.<sup>19</sup> The histone modifications described so far include acetylation, methylation, phosphorylation, ubiguitination, SUMOylation, and ADP-ribosylation.<sup>29</sup> Specific concerted combinations of DNA methylation and histone modifications can affect local chromatin configuration and mark specific genes or chromosomes for either enhanced activity or transcriptional repression.<sup>32</sup>

The epigenome is highly susceptible to environmental exposures during early prenatal development, when an extensive reprogramming of epigenetic marks takes place to establish cell- and tissue-specific gene expression.<sup>28,33</sup> Interferences with epigenetic reprogramming during early embryogenesis (eg, maternal stress, malnutrition, drug and alcohol abuse, toxins) hold significant potential to influence early gene programming in the developing embryo.<sup>34-36</sup> These mechanisms also influence DNA expression in specific cells in later life stages (eg, during neurogenesis, mandibular development).<sup>37,38</sup>

In summary, it seems likely that the whole developmental period is vulnerable to epigenetic disruption, and that any agent with the ability to affect the epigenome can cause adverse developmental effects.<sup>27</sup> Once established, DNA methylation patterns can be passed from one cell generation to another and persist into adulthood, thus providing the mechanism through which the early life environment can exert long-lasting effects on gene expression and phenotype.<sup>39</sup> These pattern changes can also be inherited.<sup>39</sup>

## Epigenetically Determined Diseases Associated with Bruxism

Both types of bruxism occur as symptoms of certain neurological disorders, caused by disruptions in the epigenetic DNA expression regulation, such as RTT and other methyl CpG binding protein 2 (MECP2)related disorders, PWS, or AS.<sup>19,20</sup>

RTT is a progressive neurodevelopmental disorder caused by mutations in a gene encoding a protein involved in epigenetic regulation.<sup>19</sup> Specifically, it is caused by de novo mutations in the MECP2 gene.<sup>20</sup> The mutation is detected in 90% of classic RTT phenotypes.<sup>40</sup> The MECP2 gene, located on the X chromosome, encodes a protein that binds to methylated sites of genomic DNA and facilitates gene silencing and genomic imprinting.<sup>21</sup> As mentioned, DNA methylation is one of the most important mechanisms of epigenetic control of DNA expression and the most intensely studied epigenetic mechanism.<sup>41</sup> MECP2 is essential for the normal development, maturation, and functioning of nerve cells.<sup>42</sup> Its alterations in RTT have serious deleterious effects on the developing nervous system, which express themselves in various motor function disturbances, including bruxism.43

Classic RTT predominantly affects girls and is characterized by a short period of developmental stagnation after the first 6 to 18 months of normal development, followed by a rapid retardation of acquired language and motor skills, and finally by a period of long-term stability.<sup>20</sup> Immaturity in brainstem mechanisms in RTT is expressed by the presence of early sleeping disorders such as sleep bruxism, nocturnal awakenings, and difficulty falling asleep.<sup>22</sup> Repetitive, stereotypic movement of limbs and jaws, sleep apnea, and cardiac abnormalities are a frequent finding in RTT patients.<sup>44</sup> Awake bruxism represents the second most frequent stereotypy in RTT (present in 90% of RTT phenotypes)<sup>44,45</sup> and is the main oral manifestation of this syndrome.43 Awake bruxism also seems to be highly indicative of the presence of an MECP2 mutation in RTT phenotypes.<sup>44</sup> It causes extensive tooth wear and muscular dysfunction in RTT patients and often requires dental treatment.<sup>43</sup>

PWS and AS are neurological disorders caused by different epigenetic imprinting defects on chromosome 15 in the q11-q13 region.<sup>19</sup> Genomic imprinting is the expression of certain genes in specific regions of the genome, which is regulated by their parental inheritance.<sup>46</sup> This expression is regulated by epigenetic marks, specifically DNA methylation and histone modifications that are established on either the paternal or maternal chromosomes.<sup>19</sup> PWS is caused by a lack of paternal contribution in the 15q11-1q13 region (possibly the HBII-85 gene), while AS is due to a lack of maternal contribution (a defect in the UBE3A gene).<sup>19</sup> Patients with these diseases display a range of neurological findings, a delayed development of motor skills and speech, and intellectual disability.<sup>19,47</sup>

In PWS patients, the dysfunction of hypothalamicpituitary-adrenocortical axis (HPA) function leads to growth hormone deficiency, lack of satiety, hyperfagia, and excessive obesity.<sup>19</sup> Sleep disorders such as sleep bruxism, excessive daytime sleepiness, and sleep apnea are common in individuals with PWS.<sup>23</sup> Further, they show an excessive level of tooth wear due to both awake and sleep bruxism, possibly in combination with excessive acidic food intake, gastroesophageal reflux, and hyposalivation.<sup>48</sup> Most young adults with PWS need extensive prosthetic restorations because of bruxism and advanced tooth wear.<sup>48</sup>

In addition to severe psychomotor delay and speech problems, patients with AS display stereotypies, including awake bruxism, gait ataxia and/or tremulousness of the limbs, and a specific behavioral phenotype.<sup>49</sup> Seizures and an abnormal EEG are frequently found in AS patients.<sup>19</sup> Further, they exhibit a vast range of sleep disorders, including sleep bruxism, prolonged sleep latency, night awakenings and reduced total sleep time, enuresis, sleep terrors, somnambulism, nocturnal hyperkinesia, and snoring.<sup>24</sup>

## Epigenetic Disruptions Associated with the Pathophysiologic Events Involved in Bruxism

SB is strongly associated with the pathophysiology of sleep and breathing.<sup>50</sup> Sleep and breathing disorders are also a constant finding in RTT, AS, and PWS,<sup>22-24</sup> in which bruxism is the main oral symptom.<sup>43,48,49</sup> Like RTT, AS, and PWS, sleep and breathing pathologies (eg, sleep apnea) have also been associated with different DNA methylation disruptions, histone modulation mechanisms, noncoding RNAs, and genomic imprinting defects.<sup>21,51,52</sup> Data from human subjects reveal that the levels of DNA methylation and those of associated factors are connected with circadian rhythms and exhibit rhythmic oscillations.<sup>21</sup> Further, DNA methylation associated factors have been proven to be subject to modulation by external chronobiological cues (zeitgebers), specifically through MECP2 modulations in the central nervous system,<sup>21,53</sup> which is also the main mechanism involved in RTT. Animal studies confirm the association between MECP2 mutations and circadian alterations.<sup>21</sup> Bruxism also seems to be highly indicative of the presence of an MECP2 mutation in RTT phenotypes.44

Adverse prenatal environmental factors, such as maternal stress, malnutrition, and poor sleeping habits; in utero alcohol, nicotine, and drug exposure; premature birth; and low birth weight, influence these epigenetic mechanisms and have detrimental effects on the organization of the circadian rhythms, which can increase the risk of sleep disturbances and poor sleep quality.54-56 An altered function of the HPA axis has been suggested as a potential mechanism underlying these associations.<sup>35</sup> Cocaine inhibits the reuptake of monoamines at the presynaptic junction, leading to higher levels of activation in the catecholaminergic systems and higher concentrations of norepinephrine, serotonin, and dopamine in the synaptic cleft.<sup>57</sup> An altered function catecholaminergic system has been proposed as a possible pathophysiologic mechanism in both types of bruxism as well.<sup>58</sup>

Poor and disturbed sleep has a wide spectrum of detrimental consequences, ranging from neuroendocrine and cardiovascular alterations to poor psychological well-being and psychiatric disorders.<sup>59–61</sup> The level of maternal anxiety possibly mediates the association between prenatal cocaine exposure and sleep difficulties.<sup>57</sup> The association of the development of psychopathology and altered stress response with DNA methylation disruptions and histone modifications has been extensively documented in the scientific literature.<sup>31,62</sup> Awake bruxism is also associated with psychological and psychiatric disorders, including altered stress responsiveness,<sup>58</sup> schizophrenia,<sup>63</sup> anxiety, and aggressive behavior.<sup>64–66</sup>

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Serotonin plays a crucial role in psychological and psychiatric disturbances, arousal response, circadian rhythm regulation, and muscle tone maintenance.<sup>67</sup> Psychiatric disturbances, including anxiety, suicidality, schizophrenia,68-71 and sleep disorders such as sleep apnea,72 show strong associations with the polymorphism of genetic markers that are part of the serotonin transmission system. Variation in serotonintransporter-linked polymorphic region 5-HTTLPR and its contribution to altered stress sensitivity represent one of the most extensively investigated fields of epigenetic neuropsychiatric research.<sup>17</sup> Serotonin transporter protein gene SLC6A4 has been shown to play an important role in the pathophysiology of mood disorders, and its expression is strongly influenced by altered DNA methylation statuses.73 DNA methylation profiles within the serotonin transporter gene also moderate the association of 5-HTTLPR and cortisol stress reactivity.<sup>74</sup> Serotonin alterations have been proposed to play a role in the pathophysiology of both types of bruxism.<sup>4</sup> A recent molecular genetic study has confirmed a strong correlation between the occurrence of the serotonin receptor gene HTR2A rs6313 polymorphism and increased risk for SB.<sup>13</sup>

### Conclusion

Bruxism is a complex disorder with a controversial etiology. Evidence from genetic studies indicates that bruxism is caused by a mix of genetic and environmental ( $G \times E$ ) factors, but the heritability of bruxism has still not been explored in detail. No studies have yet been conducted to investigate the association of bruxism with epigenetics, even though epigenetics specifically focuses on research modalities that investigate  $G \times E$  interactions. Further, both types of bruxism are associated with three representative neurodevelopmental disorders that are caused by epigenetic disruptions, including RTT, PWS, and AS, and these associations suggest a direct link between epigenetic deregulation and bruxism. There have been no studies of the association between sleep pathology, bruxism, and epigenetics, although SB is closely associated with sleep disturbances and the latter have been linked to similar epigenetic disruptions like RTT, PWS, and AS.

Future research focusing on the genes and mechanisms involved in the epigenetic pathophysiology of RTT, AS, PWS, and other risk factors for bruxism is warranted. The results of such investigations could help shed light on some of the etiologic and diagnostic dilemmas concerning both types of bruxism.

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#### Literature Abstract

#### Cross-Sectional Study on the Prevalence and Risk Indicators of Peri-Implant Diseases

This cross-sectional study assessed and identified the prevalence and risk indicators of peri-implant diseases in patients treated in a university setting. A total of 186 patients with 597 implants were included in the study. Personal data (age, gender, frequency of dental visit, history of periodontal treatment, causes of tooth loss, diabetes, osteoporosis, and head and neck radiotherapy), clinical data (plaque scores, presence of keratinized tissue, pocket probing depth, and bleeding on probing [BOP]), and radiographic data (vertical bone loss at mesial and/or distal surfaces of implants) were recorded. Peri-implant mucositis was defined when at least one site had positive BOP. Peri-implantitis was diagnosed when there was BOP at one surface and > 2 mm of radiographic bone loss. Results showed statistically significant associations between high plaque score and peri-implant mucositis, between history of periodontal disease and peri-implantitis compared to those placed in the mandible). The authors found that hard and soft tissue has a significant protective effect against peri-implant mucositis. No statistically significant association was found between peri-implant mucositis and smoking, diabetes, osteoporosis, head and neck radiotherapy, or frequency of dental visit. The authors concluded that history of periodontal disease and level of oral hygiene were the most important risk indicators for peri-implantitis and peri-implant mucositis, respectively. The study did not put types of prosthetic restoration and bone loss at buccal/labial and lingual surfaces of implant into consideration.

Konstantinidis IK, Kotsakis GA, Gerdes S, Walter MH. Eur J Oral Implantol 2015;8:75–88. References: 25. Reprints: Dr I Konstantinidis, Universitätsklinikum, Zahnärztliche Prothetik Fetscherstrabe 74, 01307 Dresden, Germany. Fax:+49 351 4585314. Email: Ioannis.Konstantinidis@uniklinikum-dresden.de—Huong Nguyen, Edmond, Oklahoma, USA

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