

Painful Temporomandibular Joint Clicking: A Genetic Point of View

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Aims: To determine whether there is an association between gene polymorphisms and patients with painful temporomandibular joint (TMJ) clicking when compared to patients with painless TMJ clicking and a healthy control group.

Methods: In this pilot study, the genotypic and allelic frequencies of candidate single-nucleotide polymorphisms (SNP) were compared among 60 individuals divided equally into three groups: patients with painful TMJ clicking (n = 20); patients with painless TMJ clicking (n = 20); and healthy controls (n = 20). Participants were genotyped for the following SNPs using real-time polymerase chain reaction: *MMP1* -16071G/2G, *COMT* Val158Met, *TNFα* -308, *IL1β* +3954, *IL6* -174, and *IL10* -1082. The pressure pain threshold (PPT) of the TMJ was also assessed. All variables were compared among groups.

Results: Patients with painful TMJ clicking had a significant association and a higher frequency of *MMP1* -16071G/2G ($P = .042$), *COMT* Val158Met ($P = .030$), and *TNFα* -308 ($P = .016$) when compared to the other groups, as well as a lower frequency of *IL10* -1082. Considering PPT values, a progressively lower mean was found in individuals with painful TMJ clicking, followed sequentially by the painless TMJ clicking and the control groups. **Conclusion:** This pilot study showed that patients with painful TMJ clicking had a significant association with mutant genotypes related to degradation of extracellular matrix components, pain, proinflammation, and anti-inflammation. Furthermore, these patients also had significantly lower TMJ PPT values in all comparisons. *J Oral Facial Pain Headache* 2022;36:229–235. doi: 10.11607/ofph.3115

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Temporomandibular joint (TMJ) clicking is usually related to internal derangements, such as disc displacement with reduction (DDWR), which is a sound produced when the condyle impacts against the disc when the disc is moved and repositioned through mandibular movements.^{1–3} TMJ clicking accounts for 30.7% of the clinical signs of temporomandibular disorders (TMDs) and is one of the most common complaints in patients.^{2,4} Although TMJ clicking is typically painless, in some cases, DDWR is accompanied by TMJ pain that occurs or is intensified at the clicking moment, which is called painful TMJ clicking.⁵ Some hypotheses have been raised to explain why this phenomenon happens, such as compression of the bilaminar zone and TMJ inflammation such as arthralgia.⁶

Several studies have investigated which clinical factors are important in patients with painful TMJ clicking, showing that the presence of awake bruxism and specific oral behaviors that create pressure on the jaw, a somatosensory profile that is more sensitive to mechanical pain tests, a less efficient pain modulation system, poor sleep quality, and higher levels of hypervigilance, pain catastrophizing, and kinesiophobia are key factors in these patients.^{5–7} These data confirm the complex and multifactorial nature of TMJ clicking and pain, indicating that investigations including factors other than clinical should also be performed.⁸

Dynamic and somatosensory TMJ profiles are also regulated by genetic aspects.⁹ Some genetic association studies have investigated

whether genetic polymorphisms are involved in TMJ clicking and pain.¹⁰ Their findings indicate that individual genetic background plays a role, contributing to the course and outcome of TMJ clicking and pain individually.^{9,10} A single-nucleotide polymorphism (SNP) in specific genes related to the degradation of extracellular matrix components (such as matrix metalloproteinase 1 [MMP1]),¹¹ pain sensitivity (such as catechol-O-methyltransferase [COMT]),¹² proinflammation (such as tumor necrosis factor alpha [TNF α], interleukin 1 beta [IL1 β], and interleukin 6 [IL6])^{13–15} and anti-inflammation (such as interleukin 10 [IL10])¹⁶ have already been associated with several internal derangements of the TMJ. However, no previous study has investigated the genes and genetic polymorphisms involved in patients with painful TMJ clicking.

Therefore, the present study aimed to determine whether there is an association between gene polymorphisms and painful TMJ clicking when compared to painless TMJ clicking and healthy control groups. The null hypothesis was that there would be no difference among these patient groups.

Materials and Methods

This pilot cross-sectional case-control study was conducted following the Helsinki Declaration and the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹⁷ The present study was approved by the Research Ethics Committee of the Bauru School of Dentistry, University of São Paulo, Bauru, São Paulo, Brazil (protocol 118/2010).

The sample formation strategy was not randomized. The sample was obtained from 214 Brazilian individuals over 18 years of age who consecutively presented to the Bauru School of Dentistry from September 2012 to September 2013 requesting regular dental treatment (control group) or presenting with complaints of clicking and/or pain in the TMJ area. Recruitment of individuals was done through several advertisements placed on the university campus and in city locations, posts on social media, and radio ads. Participants were allocated to one of the groups according to clinical examination based on the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis 1.¹⁸ The sample formation and study design were based on a previous investigation.⁸ G*Power software, version 3.1.9.2, was used for sample size calculation. The following parameters were considered: test power of 0.8; significance level of .05; and effect size of 0.4 for analysis of variance (ANOVA) with one intersubject factor (group

[$n = 3$]). Thus, the sample size was calculated to be 60 individuals, homogenous as to race and social status, equally divided into three groups:

- Group 1 was composed of 20 patients (18 women, 2 men, mean age of 33.50 ± 10.33 years) with unilateral painful TMJ clicking (DDWR plus arthralgia in the same TMJ). The mean pain intensity measured during the first appointment with a 0 to 10 visual analog scale was 7.01 ± 1.09 ; however, no minimum intensity was established as an inclusion criterion. The patients in this group reported having complaints about TMJ clicking/pain for an average range of 15.20 ± 6.53 months.
- Group 2 was composed of 20 patients (20 women, mean age of 32.50 ± 12.81 years) with unilateral painless TMJ clicking (DDWR only). There was no report or complaint of any previous significant TMJ pain. The patients in this group reported having complaints about TMJ clicking for 22.28 ± 8.64 months.
- Group 3 (control group) was composed of 20 asymptomatic individuals (17 women, 3 men, mean age of 34.15 ± 11.60 years) with no TMJ clicking and no arthralgia.

Individuals were excluded due to pain other than arthralgia, TMJ sounds other than clicking (ie, crepitation or terminal thud due to TMJ hypertranslation), having had previous surgical intervention in the TMJ, or having systemic conditions such as fibromyalgia or any degenerative joint disease.

DNA Collection and SNP Analysis

DNA was extracted from each participant's saliva using a QIAamp DNA Mini Kit (Qiagen) following the manufacturer's instructions. DNA integrity was checked as previously described.¹³ For this investigation, SNPs of specific genes already reported in the literature to be related to several internal derangements of the TMJ were selected.^{11–16} Allelic discrimination of variants *COMT* Val158Met (rs4680), *MMP1* -16071G/2G (rs1799750), *TNF α* -308 (rs1800629), *IL10* -1082G>A (rs1800896), *IL1 β* +3954 (rs1143634), and *IL6* -174 (rs1800795) were performed in 3-mL reactions using TaqMan (Applied Biosystems) chemistry, as previously described.¹⁰ Real-time polymerase chain reaction (RT-PCR) was performed utilizing a 10-ng sample of DNA, $\times 1$ concentration TaqMan SNP genotyping assays, $\times 1$ concentration TaqMan Universal MasterMix, and H₂O q.s. 5 μ L. The RT-PCR cycle conditions were 60°C for 30 seconds, 95°C for 10 seconds, 40 cycles at 92°C for 15 seconds, 60°C for 60

Table 1 Comparison of Gene Polymorphisms Among Groups (n = 20 each)

		Painful TMJ clicking	Painless TMJ clicking	Control group	P value
<i>MMP1</i> -1607	Present (1G1G)	16 (80) ^A	12 (60) ^B	8 (40) ^C	.042*
	Absent (2G2G)	4 (20) ^A	8 (40) ^B	12 (60) ^C	
<i>COMT</i> Val158Met	Present (GG, AG)	15 (75) ^A	13 (55) ^B	6 (30) ^C	.030*
	Absent (AA)	5 (25) ^A	7 (45) ^B	14 (70) ^C	
<i>TNFα</i> -308	Present (GG, GA)	12 (60) ^A	6 (30) ^B	3 (15) ^B	.016*
	Absent (AA)	8 (40) ^A	14 (70) ^B	17 (85) ^B	
<i>IL10</i> -1082	Present (CC, CA)	5 (25) ^A	9 (45) ^B	13 (65) ^B	.049*
	Absent (AA)	15 (75) ^A	11 (55) ^B	7 (35) ^B	
<i>IL6</i> -174	Present (GG, GC)	12 (60) ^A	7 (35) ^A	7 (35) ^A	.224
	Absent (CC)	8 (40) ^A	13 (65) ^A	13 (65) ^A	
<i>IL1β</i> +3954	Present (CC)	7 (35) ^A	7 (35) ^A	5 (25) ^A	.829
	Absent (CT)	13 (65) ^A	13 (65) ^A	15 (75) ^A	

Data are reported as n (%) unless otherwise indicated. *Statistically significant difference according to chi-square test. Different superscript capital letters represent significant differences among groups.

seconds, and 60°C for 30 seconds.¹³ For reaction quality control, a sample of the known genotype (positive control) and a no-DNA template sample (negative control) were included in the plate,¹³ and only genotypes with an automatic call rate > 95% were considered. Genotyping was performed blinded to group status.¹³

Pressure Pain Threshold of the TMJ

To investigate the somatosensory profile of the TMJ pain, the pressure pain threshold (PPT) was measured with a digital algometer (DDK-20 model, Kratos). The device had a rod at one end with a flat circular tip with a diameter of 1 cm² through which an increasing and constant pressure of approximately 0.5 kgf/cm² was applied. Before the examination, the individuals were instructed to press a button as soon as the painful sensation started. The PPT was determined as the arithmetic mean of three measurements (with a 10-minute interval between them). Tests were performed on the skin overlying the TMJ. In patients, the side of the complaint was selected as the test side. In healthy controls, the dominant side was chosen as the test side.^{5,19}

Statistical Analysis

Normal distribution of the data was assessed using Kolmogorov-Smirnov test. Chi-square test was used to assess deviations from the Hardy-Weinberg equilibrium and to compare the polymorphism prevalence among groups. Pearson chi-square test was performed for analysis of genotypes using the dominant model. One-way analysis of variance (ANOVA) followed by post hoc Tukey test was used to compare the PPT values of the TMJ. A 5% significance level was used for all tests. SPSS software version 25.0 (IBM) was used to analyze the data.

Results

Genotypes for all studied SNPs were in the Hardy-Weinberg equilibrium. In the comparison of the SNP prevalence among groups, patients with painful TMJ clicking had a significantly higher frequency of *MMP1* -16071G/2G, *COMT* Val158Met, and *TNFα* -308 and a lower frequency of *IL10* -1082G>A when compared to the other groups ($P < .05$). Also, these four SNPs presented a significant association with patients exhibiting painful TMJ clicking ($P < .05$). Patients with painless TMJ clicking presented a higher prevalence of and significant association with *MMP1* -16071G/2G and *COMT* Val158Met only when compared to the control group ($P < .05$). There was no difference between patients with painless TMJ clicking and control group individuals regarding *TNFα* -308 or *IL10* -1082 ($P > .05$). SNPs *IL1β*+3954 and *IL6* -174 presented no difference in any comparisons (Table 1).

Considering PPT values of the TMJ, significantly lower values (1.11 ± 0.39) were found in patients with painful TMJ clicking when compared to patients with painless TMJ clicking (1.55 ± 0.45). The painless TMJ clicking group also showed lower mean PPT values than the control group (2.05 ± 0.67 ; Table 2).

Discussion

To the best of the authors' knowledge, this is the first pilot study to describe patients with painful TMJ clicking from a genetic point of view. The results showed that these patients had a significant association and a higher prevalence of mutant genotypes related to degradation of extracellular matrix components, pain, and proinflammation (*MMP1* rs1799750, *COMT* rs4680, and *TNFα* rs1800629, respectively), as well

Table 2 Comparison of PPT Among Groups

Group comparison	Difference in means (kgf/cm ²)	P value
Group 1 x Group 2	0.44	.024*
Group 1 x Group 3	0.94	< .001*
Group 2 x Group 3	0.50	.011*

*Statistically significant difference according to one-way ANOVA with Tukey post hoc test. Group 1 = painful TMJ clicking; Group 2 = painless TMJ clicking; Group 3 = control group.

as a lower frequency of anti-inflammation gene polymorphisms (*IL10* rs1800896). Furthermore, these patients also showed significantly lower TMJ PPT values when compared to the other groups. Thus, the null hypothesis was rejected.

In the present study, a significant association with and a higher prevalence of the mutant genotype *MMP1* -16071G/2G was found in the painful TMJ clicking group when compared to the other groups (Table 1). These results were expected due to several factors. First, it is already known that the *MMP1* -1607 polymorphism induces a higher local concentration of *MMP1*, which contributes to quicker degradation of the extracellular matrix of articular tissues.^{20,21} With this gene polymorphism, the physiologic balance of matrix metalloproteinases and their inhibitors in the articular disc is disrupted, which can create an environment susceptible to intra-articular disorders such as painful TMJ clicking.^{22–25} Second, it is interesting to note that, in the present study, this polymorphism was also more prevalent in the painless TMJ group when compared to the control group. Although this finding is in accordance with previous literature that has already investigated and found an association between *MMP1* SNP rs1799750 and simple DDWR,^{11,26,27} the present results indicate an important genetic role of *MMP1* in cases of worse prognosis of disc displacement, such as when accompanied by arthralgia. Future longitudinal studies should investigate whether people with painful TMJ clicking and *MMP1* SNP can evolve to degenerative disorders of the TMJ, since an association between these two variables has already been reported.²⁸

A similar result was found in the *COMT* SNP analysis. In the present study, there was a significant association and a higher prevalence of the mutant genotype *COMT* Val158Met in the painful TMJ clicking group compared to the other groups (Table 1). This was also an expected result, since it is well known that *COMT* polymorphisms, especially Val158Met, are strongly associated with increased pain sensitivity once the SNP causes an amino acid substitution in the enzymatic polypeptide chain, resulting in lower thermostability and consequently less *COMT* activity.^{29,30} The higher prevalence of *COMT* Val158Met in the painless TMJ group when compared

to the control group also makes sense, since *COMT* SNPs are described in the literature as involved in several TMD disorders, even when the pain is not the main characteristic.¹² Also, a TMJ with DDWR can present some level of sensitization regardless of the presence of significant clinical pain,⁵ which can be influenced by SNP rs4680.

Both SNPs related to proinflammation (*TNF α* -308) and anti-inflammation (*IL6* -174) were significantly associated with the painful TMJ clicking group, as these polymorphisms showed, respectively, higher and lower prevalence in these patients when compared to the other groups. However, there was no difference when these SNPs were compared between patients with painless TMJ clicking and the control group individuals (Table 1). These results are in line with the condition characteristics. Although the present study did not evaluate the TMJ synovial fluid to confirm the presence of inflammatory mediators, it has been demonstrated in the literature that clinical TMJ arthralgia is mediated by inflammatory mediators, and that in painful TMJ clicking due to arthralgia, the pain is related to TMJ inflammation.^{4–6} Also, it is known that *TNF α* -308 polymorphism induces a higher production of *TNF α* (a proinflammatory cytokine present in a TMJ with inflammatory processes),^{16,31–34} and that the *IL10* -1082 polymorphism is associated with high production of *IL10* (an anti-inflammatory cytokine).^{35,36} Therefore, the combination of a higher frequency of proinflammation SNPs and a lower frequency of anti-inflammation SNPs is expected in an arthralgia scenario, such as painful TMJ clicking. These findings agree with previous studies in which an association between these polymorphisms and TMD was reported.^{10,13,16} However, the present study is the only one so far to subdivide the TMD sample into groups according to diagnosis and clinical characteristics. This methodology allowed for better understanding of the pathophysiology of these conditions individually and not just in a large, heterogenous group of TMD patients.

For patients with altered TMJ mechanisms caused by disc displacement and inflammation that can also sensitize the TMJ area^{37,38} and with a higher prevalence of mutant genotypes related to degradation of extracellular matrix components, pain, and proinflammation, as well as a lower frequency of protective

anti-inflammation gene polymorphisms, some level of somatosensory sensitization in proportion to the prevalence of the SNPs is expected to be found. This could explain the PPT results found in the present study. Patients with painful TMJ clicking presented lower PPT values when compared to patients with painless TMJ clicking, and patients with painless TMJ clicking showed lower PPT means compared to the control group (Table 2). This sequentially lower PPT is in agreement with previous studies, suggesting that there is a certain degree of sensitization in individuals with DDWR with a certain degree of modification in response to the pressure applied.⁵

It is also important to consider the female predominance in this study. The female to male ratio in the present sample was 11:1. Although this gender distribution is higher than in previous studies (1.9:1 to 3.5:1),^{5,6} it is not surprising, as women tend to seek TMD treatment more often than men. In addition, the literature has already showed that TMJ disc displacement and arthralgia are more prevalent in women.^{2,4} The greater occurrence of these pathologies in women could result from the influence of some female-specific characteristics, such as a smaller articular space, greater intra-articular pressure, greater joint laxity, and higher TMJ pain levels possibly caused by the influence of estrogen, which can increase inflammatory hyperalgesia in the TMJ area and present a peripheral/central action in the modulation of pain.^{39,40} Besides that, other TMJ genetic studies have also shown a higher prevalence of mutated genotypes related to tissue degradation, pain, and inflammation (such as *MMP1*, *COMT*, *TNF α* , and *IL10*) in women.^{10–13,41} Future gender comparison studies should help clarify the role of the gender-genetic relationship in TMJ conditions.

This pilot study reveals interesting genetic insights about the phenomena of painful TMJ clicking. Both results—the presence and the absence of specific gene polymorphisms related to degradation of extracellular matrix components, pain, proinflammation, and anti-inflammation—can help explain the occurrence of pain in only some cases of TMJ clicking. These data reveal the importance of undertaking a genetic study to elaborate a mechanism-based, personalized treatment plan once a genetic role has been identified in cases of worse prognosis of disc displacement, such as when accompanied by arthralgia. Nevertheless, caution is important when judging the present findings. The small sample of this pilot study prevents extrapolating the observed results beyond other populations different from the present one. Genome-wide association studies (GWAS) with larger samples are encouraged in the future. Additionally, the present investigation has other limitations, such as the

absence of synovial fluid analysis, gender comparison, the menstrual status of the female participants, ethnicity, and psychosocial profiles, which are factors that might influence pain sensitivity independent of genetics.

Conclusions

In view of the results and limitations of this pilot study, it can be concluded that patients with painful TMJ clicking had a significant association and a higher prevalence of mutant genotypes related to degradation of extracellular matrix components, pain, and proinflammation, and a lower frequency of anti-inflammation gene polymorphisms. Also, these patients had a higher TMJ pain sensitivity when compared to the other groups.

Key Findings/Clinical Implications

Painful TMJ clicking is linked to a higher frequency of mutant genotypes related to degradation of the extracellular matrix, pain, and proinflammation, as well as a lower frequency of anti-inflammation polymorphisms. The present results help explain the role of genetics in cases of worse prognosis of disc displacement, such as when accompanied by arthralgia. It is important to consider a genetic study to elaborate the treatment plan in painful clicking cases.

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