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Pulp Sensitivity: Influence of Sex, Psychosocial Variables, *COMT* Gene, and Chronic Facial Pain

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Abstract

Introduction: The purpose of this study was to evaluate the associations of variability in pulp sensitivity with sex, psychosocial variables, the gene that encodes for the enzyme catechol-O-methyltransferase (COMT), and chronic painful conditions (temporomandibular disorders [TMDs]). **Methods:** The study was composed of 97 subjects (68 women and 29 men aged 20–44 years). The electric (electric pulp tester) and cold (refrigerant spray) stimuli were performed on mandibular lateral incisors. The results were expressed as pain threshold values for electric pulp stimulation (0–80 units) and as pain intensity scores (visual numeric scale from 0–10) for cold stimulation. The Research Diagnostic Criteria for TMD were used to assess TMD, depression, and somatization. DNA extracted from peripheral blood was genotyped for 3 COMT polymorphisms (rs4680, rs6269, and rs165774) using the real-time TaqMan method. Multivariate linear regression was used to investigate the joint effect of the predictor variables (clinical and genetic) on pulp sensitivity (dependent variables). **Results:** Threshold responses to electric stimuli were related to female sex ($P < .01$) and the homozygous GG genotype for the rs165774 polymorphism ($P < .05$). Pain intensity to cold stimuli was higher in TMD patients ($P < .01$) and tended to be higher in women. Multivariate linear regression identified sex and the rs165774 COMT polymorphism as the determinants of electric pain sensitivity, whereas TMD accounts for the variability in the cold response. **Conclusions:** Our findings indicate that sex/a *COMT* gene variant and TMD as a chronic painful condition may contribute to individual variation in electric and cold pulp sensitivity, respectively. *(J Endod 2018;44:717–721)*

Key Words

Catechol-O-methyltransferase, chronic pain, dental pulp tests, pulp sensitivity, sex

Significance

When performing pulp sensibility testing, women and GG genotype carriers of the COMT rs165774 variant show a decreased pulp pain threshold to electric stimuli, whereas the presence of chronic facial pain increases pulp pain intensity to cold stimuli.

Pulp sensitivity testing is an essential part of the diagnostic process in the assessment of pulpal health. Thermal cold and electric tests are the most commonly used pulp sensitivity tests to assess pulp status from the sensory response. These tests have been proven to be accurate and reliable methods for the differentiation of vital and nonvital pulps (1), but uncertainty concerning the determination of pulpal disease/health may occur. Many factors may affect diagnostic accuracy and the use of these tests (2–5).

Sex has been proposed to be of relevance to nociception. Women show a higher risk for many pain conditions, including various acute and chronic clinical pain conditions, and response to pain treatment (6). There are data elements indicating that sex may contribute to the difference in pulp sensitivity (7, 8), but not all studies support these findings (4, 9). Stimulus perception has also been associated with a number of psychological factors, such as emotional distress, catastrophizing, psychosocial stress, anxiety, depression, and somatic awareness (10). Both depression and somatization might contribute to clinical pain measures in chronic pain populations (11); hence, their association with the pulp sensitivity response has not yet been elucidated. In the last decade, genetics has become a well-established factor that contributes to processing of nociceptive information and pain-related behavior (12, 13). Gene encoding for the catabolic enzyme catechol-O-methyltransferase (COMT), located in the chromosome 22q11, has been largely investigated in relation to pain sensitivity (14, 15). COMT inactivates dopamine, noradrenaline, and adrenaline, neurotransmitters involved in numerous physiological processes, including pain modulation (15). Single-nucleotide polymorphisms (SNPs) in the *COMT* gene may induce low COMT enzyme activity, produce an elevated level of catecholamines, and ultimately decrease tolerance to pain (14). It has also been confirmed that *COMT* genetic variants have modality- and sex-specific effects on pain sensitivity in both animal and human model studies (15). Regarding the potential role of genetic polymorphisms in tooth pain, 1 study has explored cyclooxygenase-2 gene variants associated with pain after endodontic treatment (16). However, there are no published data on genetic influence regarding individual variation in the pulp sensitivity response.

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Additionally, the presence of chronic pain conditions may modulate pain sensitivity. Temporomandibular disorders (TMDs) present a group of common chronic painful conditions involving masticatory muscles, temporomandibular joints, and adjacent structures. Sensitivity to various noxious stimuli (ischemic, pressure, heat, and electric) in TMD patients has been examined in remote regions as well as in the orofacial region, mainly by cutaneous stimulation (17). The majority but not all studies indicate greater sensitivity to experimental pain relative to pain-free subjects. Increased sensitivity to pain-evoking stimuli in TMD patients has been attributed to chronic hyperexcitability of secondary or higher nociceptive fibers in the central nervous system and to an impaired pain regulatory system (17, 18). The pulp response among patients with chronic pain has been explored in a single study. The obtained results showed similar electric pain thresholds in 11 patients with myofascial pain dysfunction and 12 normal healthy subjects, predominantly women (19).

The aim of the current study was to investigate the associations of sex, psychological factors, the human *COMT* gene, and TMD as a chronic painful condition with pulp sensitivity of normal human pulp to electric and cold stimuli.

Material and Methods

The research was approved by the ethics committee and conducted in accordance with accepted ethical standards for research practice (guidelines of the Helsinki Declaration). The participants received detailed information about the study and signed an informed consent form.

Participants

In the present study, 97 subjects from a previous investigation were included in the analysis (20). Subjects of both sexes were accepted for the present study if they met, besides the previous exclusion criteria (ie, no known medical condition, pregnancy, lactation, irregularity in menstrual cycle, intake of oral contraceptives, drugs on a regular basis, or medications that could alter pain perception for at least 24 hours preceding the test session), the following additional criteria: the presence of vital mandibular lateral incisors free of caries, restorations, crowns, veneers, and tooth wear; no signs or symptoms of pulp and periodontal disease (confirmed clinically and radiographically); no previous root canal treatment; and no recent history of orthodontic treatment, periodontal treatment, or trauma. In total, 97 subjects (ages 20–44 years, mean age = 28.21 ± 6.01 years), 68 regularly menstruating women (menstrual cycle defined as varying between 26 and 28 days) and 29 men, were recruited. Only 1 tooth (#32) per patient was included. Each subject was evaluated once.

Pulp Sensitivity Testing

Dental pulp sensitivity was tested by electric and thermal (cold) stimuli. Before the test, the tooth surface was isolated and dried using cotton rolls. The electric test was performed using a digital pulp tester (Analytical Technologies, Redmond, WA) with reads from 0 to 80 units. As a conducting medium, toothpaste was applied lightly to the electrode. The probe was placed on the incisal third of the buccal surface, and the current intensity was increased gradually. Participants were asked to raise a hand on the first detection of a painful sensation. The lowest current intensity that provoked a pulp response was considered the pain threshold.

Cold pulpal testing was performed using a refrigerant spray (Endo-Frost-50C; Coltene/Whaledent, Altstätten, Switzerland) applied to the incisal third of the buccal surface of the tooth using a cotton pellet for 15 seconds or until the participant indicated a response. The participant was asked to rate his or her pain on a 0 to 10 numeric rating scale, with 0 representing no pain and 10 indicating the worst pain the subject has ever experienced. The test was repeated once if there was no response. A 0 value was marked if no response was obtained. A recovery period of at least 2 minutes was allowed after each pulp test.

Assessment of Chronic Facial Pain Condition (TMD), Depression, and Somatization

All subjects were previously investigated regarding the presence of painful TMD, depression, and somatization using the Research Diagnostic Criteria for TMD (RDC/TMD) (21). The RDC/TMD include completion of the history questionnaire and clinical examination and use a dual-axis approach. Axis I is composed to obtain the clinical diagnosis of TMD, whereas axis II assesses chronic pain and the level of psychosocial impairment. TMD diagnoses are defined in RDC/TMD by the presence of specific combinations of signs and symptoms gathered through subjective reporting by the patients and clinical examination. There are 3 major diagnostic categories recognized by the criteria. Only patients with common pain-related TMD diagnoses (myofascial pain and arthralgia) were included in the current study. Depression and somatization were assessed and classified with subscales of the Symptom Checklist 90R. Examination forms and specifications for examinations used in the current investigation were identical, as described in RDC/TMD. Somatization was calculated and analyzed as the presence of nonspecific physical symptoms including pain items. The RDC/TMD assessment and classification system for pain-related TMD, depression, and somatization is provided in Supplemental Table S1 (Supplemental Table S1 is available online at www.jendodon.com).

Genotyping

Genomic DNA was extracted from a total of 97 blood samples using the Blood Prep Isolation Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Three *COMT* SNPs, rs6269 (A > G, located in the 5′UTR), rs4680 (A/G, missense158Val/Met), and rs165774 (G > A, located in an intronic region), were genotyped using the TaqMan SNP Genotyping Assays (Applied Biosystems, Warrington, UK) according to the manufacturer's protocols. Allelic discrimination was performed using Real Time PCR 7500 (Applied Biosystems, Foster City, CA). All samples amplified sufficiently for allelic discrimination and were included in the final analysis.

To avoid interexaminer variability and bias, pulp sensitivity tests were performed by 1 investigator; TMD, depression, and somatization were assessed by another examiner; and genotype discrimination was performed by 2 experimenters blinded to patient status and outcomes.

Statistical Analysis

Data were analyzed using SPSS 20.0 (IBM Corp, Armonk, NY). The means and standard deviations for parametric data and the frequencies for nonparametric data were calculated. Univariate analyses were performed to screen for an association of individual clinical (sex, age, depression, somatization, and TMD) and genetic predictor variables (*COMT* SNPs) with the outcome variables (average pulp sensitivity scores). To compare the electric pain threshold between groups, 1-way analysis of variance and the independent samples *t* test were used. To compare the difference in intensity of pain induced by cold stimuli, intergroup analysis was performed using the Kruskal-Wallis and Mann-Whitney tests.

Factors with $P < .1$ on bivariate analysis were included in the multivariate modeling. Age was also included in the statistical modeling because it is known to influence pulp sensitivity. All reported *P* values were 2-sided, and the level of significance was assessed at $P < .05$.

Results

Values of electric stimuli thresholds and the intensity of pain to cold stimuli regarding sex, psychosocial variables, and the presence of TMD are given in Table 1. The pulp in women showed a lower threshold level to electric stimuli ($P < .01$), and pain intensity to cold stimuli tended to be higher compared with men. In comparison with healthy participants, subjects with TMD showed higher sensitivity to cold stimuli ($P < .01$) but not to electric stimuli. No relation was observed between the investigated pulp response for both electric and thermal stimuli and the level of depression or somatization.

Table 2 shows electric stimuli thresholds and the intensity of pain to cold stimuli with respect to *COMT* gene variants. Electric pain thresholds were lower, indicating greater pulp sensitivity, in subjects carrying the wild-type (GG) genotype for rs165774 *COMT* polymorphism in comparison with A allele carriers (AG/AA) ($P < .05$). No effects of genotype on cold pain rating were observed.

The results of the multivariate linear regression analysis are presented in Table 3. *COMT* gene polymorphism rs165774 and sex were retained as independent predictors of pain threshold values for electric pulp stimulation. TMD, but not sex, remained significant as an independent predictor of sensitivity to cold stimuli in regression analysis.

Discussion

The response of dental pulp to nociceptive stimuli varies between individuals and might be affected by a number of factors. Sex, psychosocial and genetic mechanisms, and a chronic pain condition may play a role in interindividual differences in pain responses. In order to clarify the possible influence of sex, depression, and somatization, *COMT* gene polymorphisms, and painful TMD on sensitivity of the pulp, the current study examined the association of these factors with dental pulp sensitivity by electric and thermal pulp testing. Predictive models of nociception suggest that sex and the rs165774 *COMT* polymorphism account for variability in electric sensitivity, whereas TMD accounts for variability in cold pulp sensitivity.

Men and women differ in their responses to pain, with higher pain risk and sensitivity commonly observed among women. Sex differences in responses to experimental pain have been investigated using a wide variety of stimulus modalities; however, obtained data are inconsistent (6, 22). Regarding dental pulp sensitivity, the findings are conflicting as well. Although some studies found no sex variation in pulp sensitivity (4, 9), the present study showed significantly lower pulp sensory thresholds to electric stimuli and tendency toward higher pulp sensitivity to cold stimuli in women. This is in accordance to previous findings showing that women report a lower pulp electric sensory threshold (7, 8). Possible mechanisms contributing to sex variation in pulp sensory response are not fully understood. A larger crown diameter in males has been proposed to account for the difference. Also, some data provides evidence of biological and psychosocial mechanisms that may contribute to differences in pain between women and men (6).

Polymorphisms in the *COMT* gene may affect pain sensitivity through catecholaminergic (noradrenergic/adrenergic and dopaminergic) and opioid mechanisms (23). Catecholamines peripherally excite nociceptive C- and A-delta fibers (24), and both cold and electrically evoked acute pain are likely the result of A-delta stimulation. In the present study, we found associations only between the wild-type (GG) genotype of the intronic rs165774 *COMT* polymorphism and the threshold pain response to electric stimuli. Accordingly, A allele carriers of the SNP rs165774 have been previously associated with lower pain sensitivity in a female population (25). The authors reported that, among 22 various *COMT* polymorphisms, the rs165774 variant showed the strongest evidence of association with cutaneous heat pain sensitivity. According to a recent article (26), rs165774 was linked to individual variability in sensitivity to painful stimuli, with A allele playing a protective role against the risk of pressure pain sensitivity. In the current study, the rs165774 *COMT* variant was not related to cold pain intensity. This finding might be associated with differences between pain modalities in transmission through tooth structures and pain control mechanisms activated. Namely, it has been proven that pulp sensation to thermal stimuli is likely caused by a physical change in dentin rather than direct nerve stimulation (27). According to recent findings, SNP rs165774 encodes for a COMT isoform showing high affinity for dopamine and likely modulates pain perception through analgesic dopaminergic pathways (26). The G allele of rs165774 coincides with COMT of higher catabolic activity, which is related to lower dopamine levels and consequent nociceptive effects. Animal, clinical, and genetic data

TABLE 1. Mean (± Standard Deviation) of Electric Pain Threshold and Pain Response to Cold with Respect to Sex, Temporomandibular Disorder (TMD), Depression, and Somatization Scores (according to Research Diagnostic Criteria for Temporomandibular Disorders) in the Study Population ($N = 97$)

		Electrical pain threshold		Pain response to cold (0–10 numeric rating scale)	
Variables	*n*	Mean ± SD	*P* value	Mean ± SD	*P* value
Sex					
Female	68	14.55 ± 5.85	**.004**	3.73 ± 2.05	.055
Male	29	19.31 ± 9.82		2.86 ± 1.75	
Depression					
Normal	51	17.75 ± 8.78	.257	3.33 ± 2.10	.702
Moderate	25	14.20 ± 5.54		3.58 ± 2.03	
Severe	21	12.75 ± 3.15		3.68 ± 1.75	
Somatization					
Normal	57	16.81 ± 8.26	.389	3.29 ± 2.07	.134
Moderate	19	14.67 ± 3.79		3.13 ± 1.65	
Severe	21	12.17 ± 2.04		4.26 ± 1.97	
TMD					
With	50	15.56 ± 6.94	.575	4.04 ± 2.10	**.007**
Without	47	16.42 ± 6.94		2.86 ± 1.70	

Significant values ($P < .05$) are presented in bold.

TABLE 2. Mean (± Standard Deviation) of Electric Pain Threshold and Pain Response to Cold with Respect to Catechol-O-methyltransferase (COMT) Genotype Distribution ($N = 97$)

		Electric pain threshold		Pain response to cold (0–10 numeric rating scale)	
	n	Mean ± SD	*P* value	Mean ± SD	*P* value
rs4680					
wt (GG)	24	14.67 ± 7.11	.623	3.53 ± 2.26	.897
het (AG)	58	16.40 ± 8.02		3.38 ± 1.86	
mut (AA)	15	16.44 ± 6.37		3.71 ± 2.19	
rs6269					
wt (GG)	2	23.00 ± 24.04	.272	5.50 ± 3.55	.322
het (AG)	65	16.31 ± 7.44		3.30 ± 2.02	
mut (AA)	30	14.78 ± 6.38		3.71 ± 1.83	
rs165774					
wt (GG)	45	14.03 ± 6.27	.056	3.28 ± 2.13	.472
het (AG)	47	17.78 ± 8.33	**.017***	3.70 ± 1.94	
mut (AA)	5	16.52 ± 7.15		3.04 ± 1.19	

het, heterozygous; mut, mutant; SD, standard deviation; wt, wild type.

Significant values ($P < .05$) are presented in bold.

*GG genotype versus A allele carriers (wt vs het/mut).

TABLE 3. Factors Entered into the Multivariate Models ($P < .1$ on Bivariate Analysis) for Electric Pain Threshold and Pain Response to Cold

Electric pain threshold					
Model	**R^2**		**B (CI)**	**Beta**	***P* value**
1	0.140	Sex	−4.678 (−7.790 to −1.567)	−0.286	**.004**
		COMT rs165774 (AG/AA vs GG)	3.535 (0.682–6.395)	0.235	**.016**
2*	0.158	Sex	−4.395 (−7.514 to −1.275)	−0.268	**.006**
		COMT rs165774 (AG/AA vs GG)	3.273 (0.408–6.138)	0.218	**.026**
Pain response to cold					
1	0.113	Sex	0.707 (−0.135 to 1.552)	0.163	.100
		TMD	1.086 (0.312–1.860)	0.273	**.006**
2*	0.143	Sex	0.806 (−0.036 to 1.649)	0.186	.060
		TMD	1.071 (0.306–1.836)	0.269	**.007**

Beta, standardized regression coefficient; R^2, the proportion of variability in the electric pain threshold and pain response to cold/pulp sensitivity that may be explained by its association with the factors in the regression model.

Significant values ($P < .05$) are presented in bold.

*Adjusted for age.

suggest that dopamine has direct antinociceptive effects by dopaminergic receptors (23). Regarding dental pulp, it has been shown that the activation of the striatal dopamine D2 receptors inhibits a painful response of secondary trigeminal nociceptive fibers induced by suprathreshold pulp stimulation (28). On the other hand, recent findings suggest that the release of dopamine after an acute painful stimulus mediates the motivation to avoid or endure pain (29). Bearing in mind the fact that electric stimulation is aversive in nature and provokes a greater emotional reaction than other modalities (30), COMT-related differences in the pulp response to electric but not cold stimuli might be associated with an emotional component that affects dopaminergic modulatory mechanisms in controlling perceived pain intensity.

Furthermore, sex/genotype interactions of relevance to nociception have been proposed (15, 31). *COMT* polymorphisms showed a higher association with capsaicin-induced sensitivity in female mice, and pain perception in women (15) accounts for about 16% of variability in electric pulp sensitivity. Similar results on sex and genotype interactions and experimental pain were obtained previously for opioid receptor gene polymorphisms (31), suggesting sex and genotype interaction may play a role in heat pain ratings.

Previous studies have reported that TMD is associated with increased sensitivity to experimental pain (17). TMD patients not only show higher sensitivity to noxious stimuli but also have a diminished ability to modulate/reduce evoked acute orofacial pain regarding pain-free controls (18). The current results support these observations because the enhanced pulp sensitivity to cold stimuli has been observed among TMD subjects. Accordingly, TMD patients showed greater sensitivity to thermal, especially to cold stimuli, in the nearby neck region (32). Several neurobiological mechanisms implicated in the clinical pain phenotype might be involved in the cold hypersensitivity among TMD patients, including peripheral and central sensitization. These phenomena comprise an increase in the excitability of primary trigeminal nociceptive fibers and central nociceptive pathways, respectively, both producing pain hypersensitivity. The absence of an association with electric stimuli in the present study corresponds to the observation of Sharav et al (19) showing that the electric pulp threshold in myofascial pain dysfunction patients was lower but not significantly in comparison with the controls. These findings confirm the hypothesis that various types of experimental stimuli are not equally clinically relevant. In addition, TMD patients do not show an impairment in sensitivity to a small increase in the intensity of nociceptive stimuli (33), as is the case with gradual increments in current intensity when electric pulp testing is performed. The present findings support the observation of a review article that the increased sensitivity in TMD patients apparently does not seem to involve electrically evoked pain (17).

Various psychosocial mechanisms may play an important role in interindividual differences in pain. According to Klauenberg et al (34), depressive symptoms may exacerbate the experience of experimental pain in healthy individuals. In a female TMD population, depression was linked to behavioral measures of pain (ischemic pain threshold and tolerance), whereas somatization was related to the perception of clinically relevant pain (painful masticatory sites) (11). Using the same diagnostic criteria for the assessment of depression and somatization as Sherman et al (11), we found a lower electric threshold and higher cold pain intensity in participants with higher depression/somatization levels. However, the observed differences did not reach a level of significance. The relationship between somatization or depression and experimental pain perception is yet to be explored.

There are several methodological limitations in the current study. The first is related to the subjectivity of the thermal and electric tests, which is both patient and examiner dependent and thus may limit the predictive value of a test. The examination involving a corresponding contralateral intact tooth and 2 investigators, each performing 1 type of pulp sensitivity test, would complete the obtained results. Second, there appears to be variable pain sensitivity among various TMD subtypes. However, the total number of TMD patients was too small for classification according to RDC/TMD diagnosis. Furthermore, pain levels in female participants were investigated irrespective of the menstrual cycle phase. Namely, gonadal hormones, estrogen and progesterone, can express pronociceptive as well as antinociceptive effects depending on the overall hormonal profile. Finally, the data reported in the present study were obtained in a group of participants with a specific genetic background and should be validated in other populations.

Conclusions

The results of this study indicate an association of pulp sensitivity with sex, the rs165774 variant of the *COMT* gene, and chronic painful conditions (eg, TMD). The present findings also indicate that these variables may independently influence reported pulp sensitivity when a cold or electric test is applied to evaluate pulp status.

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Irena Mladenovic and Jelena Krunic contributed equally to this study.

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The authors deny any conflicts of interest related to this study.

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SUPPLEMENTAL TABLE S1. The Research Diagnostic Criteria for Temporomandibular Disorders (TMDs) Definition and Classification System for Pain-related TMD, Depression, and Somatization

	Assessment	Diagnostic categories	Criteria
Axis I			
TMD diagnosis*	Case history examination	Myofascial pain	Report of pain in temples, jaw, face, preauricular area, or ear Pain to palpation in ≥3 of 20 muscle sites
		Arthralgia	Report of pain in TMJ area Pain to palpation in one or both TMJ sites Absence of coarse crepitus
Axis II			
Depression	Case history (Depression subscale from SCL-90R)	Normal	<0.535
		Moderate	0.535–1.105
		Severe	>1.105
Somatization†	Case history (Somatization subscale from SCL-90R)	Normal	<0.500
		Moderate	0.500–1.000
		Severe	>1.000

SCL-90R, Symptom Checklist 90R; TMJ, temporomandibular joint.

*Note that patients may have 1 or more TMD diagnoses.

†Pain items included.