Effect of Genetic Polymorphisms on Pain Sensitivity in the Orofacial Region: A Systematic Review

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Aims: To systematically review the literature to assess whether genetic polymorphisms affect orofacial pain sensitivity in healthy individuals and in patients with chronic orofacial pain disorders. **Methods:** Electronic searches were conducted to identify observational studies and clinical trials investigating the association between genetic polymorphisms and orofacial pain sensitivity in healthy individuals and/or patients with chronic orofacial pain disorders. Searches were carried out in PubMed, Embase, and Scopus databases using Medical Subject Headings and free terms. **Results:** Seven studies fulfilled the eligibility criteria: four analyzed healthy subjects, two included chronic orofacial pain patients, and one included samples of healthy subjects and patients with neuropathic pain. The results showed that genes associated with mechanical and thermal pain sensitivity were mostly related to opioid, catecholaminergic, inflammatory, and dopaminergic pathways. **Conclusion:** Genetic polymorphisms related to opioid, catecholaminergic, inflammatory, and dopaminergic pathways were associated with sensitivity to thermal and pressure stimuli in the orofacial region. Therefore, genetic factors should be taken into account for an accurate interpretation of orofacial pain sensitivity. These results will allow for a better understanding of the etiopathogenesis of chronic pain affecting the orofacial region, and consequently for finding new therapeutic targets. *J Oral Facial Pain Headache 2020;34:353–363. doi: 10.11607/ofph.2641*

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Pain sensitivity is a complex phenotype reflecting the contribution of several biologic, psychologic, and environmental risk factors.[1–4] Notwithstanding, there is considerable disparity in an individual's pain sensitivity, of which only about half may be explained by genetic effects.[2–7] Comprehension of genetic influences on normal and pathologic pain processing would improve knowledge of the neurobiologic underpinnings of pain perception in both general pain and chronic pain in particular.

Pain evoked by various stimuli (eg, pressure or heating in normal conditions), or even in clinical pathologies like musculoskeletal disorders, is acknowledged to vary markedly. It is known that a collection of aspects, including expectation, personality, and emotional state, can modulate the perception of pain, and that these aspects are also genetically mediated.[8]

In this context, efforts to assess pain sensitivity in humans in a standardized manner have led to the development of sophisticated sensory testing methods that can provide a comprehensive functional evaluation of the somatosensory system.[8,9] These methods, widely known as quantitative sensory testing (QST), can be applied in different ways for psychophysical testing of the mucosa, skin, and muscle tissue to assess sensory and pain perception pathways, including thermal and/or mechanical.[8,9] Thus, QST might be a useful tool to complement the understanding of the role of genetics in pain sensitivity in healthy individuals and in those with chronic pain, especially in the orofacial area. As orofacial chronic pain encompasses a vast area on the somatosensory cortex, painful stimuli in the orofacial area are highly perceived by the sensory system.

Several studies have shown the participation of single-nucleotide polymorphisms (SNPs) in the maintenance of pain states.[10–14] To date,

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the most comprehensive study investigating genetic risk factors for orofacial pain, particularly for TMD, has been the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study.[15] Of the thousands of genes surveyed, OPPERA showed a significant genetic influence—specifically of SNPs—on essential biologic pathways in the processing of noxious stimuli and pain perception.[15] However, not all outcomes were reproducible and validated by other studies, and there are conflicting data regarding what genetic variants really are associated with orofacial pain sensitivity.[16–20]

To date, there are many studies indicating the role of genetic polymorphisms on the variability of pain sensitivity,[10–12,14,21] but no studies have aimed to cover an overall account of this relationship. Therefore, the aim of this study was to conduct a systematic review of the literature to summarize the effects of genetic polymorphisms on orofacial pain sensitivity in healthy individuals and in patients with chronic orofacial pain disorders.

Materials and Methods

The present systematic review methodology was approved and registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD-42018094732) and carried out according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Review Question

The PECO strategy (Population, Exposure, Comparison, Outcomes) was used to formulate the focus question in this systematic review, in which the components were: Adults (P), presence of polymorphisms (E), absence of polymorphisms (C), and orofacial pain sensitivity (O).

Search Strategy

Electronic searches were conducted to identify articles assessing the association between polymorphisms and orofacial pain sensitivity in healthy individuals and/or patients with chronic orofacial pain disorders. Searches were performed in PubMed, EMBASE, and Scopus using Medical Subject Headings (MeSH) and free terms. An initial search was performed on PubMed with the following search strategy: ("Polymorphism, Genetic"[Mesh]) OR "Polymorphism, Genetic"[all]) OR "Polymorphism, Single Nucleotide"[Mesh]) OR "Polymorphism, Single Nucleotide"[all]) OR "Polymorphism"[all]) OR "Polymorphic Gene"[all]) OR "Allelic variant"[all] OR "Polymorphisms"[all]) AND ("Pain Threshold"[Mesh]) OR "Pain Threshold"[all]) OR "Pain Perception"[Mesh]) OR "Pain Perception"[all]) OR "Pain Measurement"[Mesh]) OR "Pain Measurement"[all]) OR "Psychophysics"[Mesh]) OR "Psychophysics"[all]) OR "Quantitative Sensory Testing"[all]) OR "Supra-threshold"[all]) OR "Suprathreshold"[all]) OR "Supra-threshold stimulus"[all]) OR "Suprathreshold stimulus"[all]). Searches were also performed in both Embase and Scopus with the respective search strategies tailored for these databases (see appendices in the online version of this article at www.quintpub.com/journals). No publication time or language restrictions were applied. Gray literature was examined by inspecting the first 200 items of a Google Scholar search, which included the key terms used for the search on PubMed. In addition, the references of the included papers were also searched for further studies.

Inclusion Criteria

Observational studies and clinical trials with baseline measures that investigated the association between polymorphisms and pain sensitivity in adults with or without chronic orofacial pain disorders (eg, TMD, trigeminal neuralgia, and orofacial neuropathic pain) were considered eligible for this systematic review. Diagnosis of TMD must have been based on the Research Diagnostic Criteria for TMD (RDC/TMD) and/or the Diagnostic Criteria for TMD (DC/TMD).

Exclusion Criteria

The following studies were excluded:

- Studies with samples including children or adolescents (< 18 years of age)
- Studies with samples including individuals with craniofacial anomalies, genetic syndromes, or neuromuscular diseases
- Studies that included cases with comorbidities such as tumor, cancer, fracture in the same area, fibromyalgia, migraine and other headaches, otalgia, sleep apnea, and rheumatoid arthritis
- Studies in which patients were receiving concomitant analgesics or anti-inflammatory drugs
- Studies without pain threshold or suprathreshold assessment in the orofacial region
- Studies that were abstracts, reviews, case reports, protocols, personal opinions, letters, and posters
- Studies with insufficient data after three attempts to contact authors

Data Collection and Assessment of Papers

Initially, records were screened based on title and abstract (Fig 1). The results from the database search were screened independently by two researchers (F.F.C.S. and R.L.P), and any disagreement between the reviewers was solved by a third researcher

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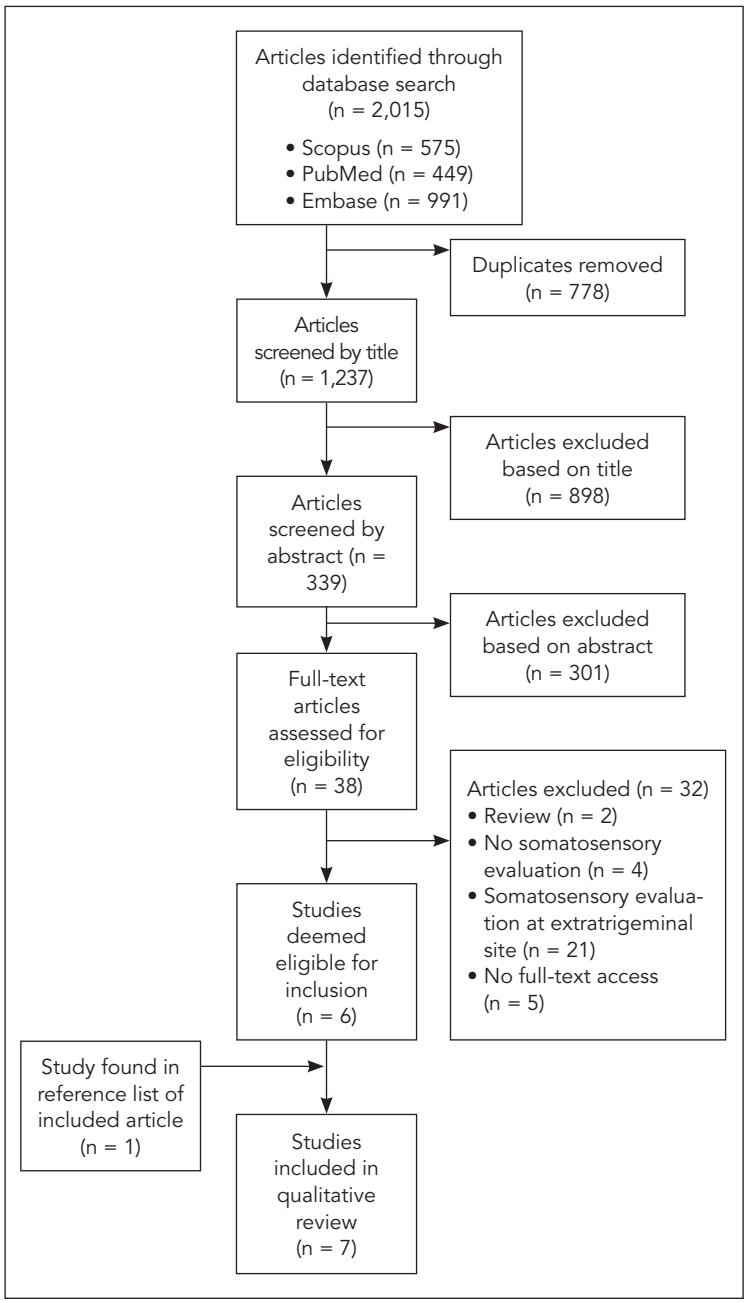

Fig 1 Flowchart of study protocol.

(G.D.T.C). The full texts of articles selected for potential inclusion were obtained and carefully read by the same reviewers. The data of each study were extracted and analyzed independently by the two researchers according to the items presented in Table 1.

Quality assessment of the included cohort studies was based on the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and performed by two researchers (F.F.C.S. and R.L.P). Even though all included articles evaluated the association between genetic polymorphisms and orofacial pain sensitivity, the outcomes were extremely diverse. For instance, while the study by Jääskeläinen et al[22] evaluated thermal sensitivity, the study by Jounger et al[23] evaluated pain sensitivity after induction with hypertonic saline solution. Additionally, as *z* score values were not reported in most articles, it was not possible to combine different stimuli into a comparable dimension for pooling the results. Another heterogenous aspect relates to the analytical approaches, which also varied among the studies, resulting in different result estimates. For instance, results were given, among others, as median (with respective interquartile range), mean (and respective SD), regression coefficient (with respective 95% CI), and odds and hazard ratios (with respective 95% CI). Therefore, the heterogeneity of outcomes and result estimates precluded the performance of a meta-analysis to pool data from this systematic review.

Results

Literature Search

The search strategy yielded 2,015 results, 778 of which were duplicate articles. Thus, the titles and abstracts of 1,237 studies were screened for eligibility (Fig 1). Based on application of the inclusion criteria, the full texts of 38 papers were read. Five full texts could not be accessed, and 27 did not meet the inclusion criteria (2 were review papers; 4 did not evaluate somatosensory function; and 21 did evaluate somatosensory function, but at an extratrigeminal innervation site). Therefore, 32 studies were excluded from this review. Detailed reasons for study exclusion are displayed in Appendix 2.

Six studies, plus another obtained from the reference list of an included article, were finally included in this systematic review for a total of seven studies. All studies had an observational cross-sectional design. An update of the search in March of 2020 did not provide new relevant papers.

Included Studies

Of the seven included studies, four analyzed only healthy subjects, two presented TMD patients, and one had a sample that included healthy subjects and patients with neuropathic pain (Table 1). The NIH

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Table 1 Characteristics of the Included Studies Based on PECO Structured Reading

Study, y	Population (P)	Exposure (E)
Jääskeläinen et al,[22] 2014	Healthy subjects (n = 29; 18 women, 26 right-handed), mean age 23 y, range 18–30 y Neuropathic orofacial pain patients (n = 16: trigeminal neuropathic pain after nerve injury [n = 7], burning mouth syndrome [n = 5], atypical facial pain [n = 4]; 14 women), mean age 60 y, range 39–74 y.	Participants were genotyped for the COMT SNP Val158Met and *DRD2* SNP 957C>T. CDT, WDT, CPT, and HPT were measured on the left infraorbital nerve distribution. G1: A_A (Met/Met) genotype for *COMT*. G2: A_G (Met/Val) genotype for *COMT*. G3: T_T genotype for *DRD2*. G4: T_C genotype for *DRD2*.
Jounger et al,[23] 2016	Healthy adults (n = 60; 30 men, 30 women), mean age 26.8 ± 3.9 y.	Participants were genotyped for HTR3A SNP rs1062613 (C178T) and HTR3B SNP rs1176744 (386A>C). The participants thereafter received bilateral injections of hypertonic saline into the masseter muscle to evoke pain. PPT was measured on the most prominent points of the masseter muscle (injection sites). G1: C_T genotype for *HTR3A*. G2: T_T genotype for *HTR3A*. G3: A_C genotype for *HTR3B*. G4: C_C genotype for *HTR3B*.
Hastie et al,[24] 2012	Healthy young adults (n = 247; 118 men, 129 women), age range 18–54 y.	Participants were genotyped for the A118G SNP of the *OPRM1* gene. PPT was measured on the masseter muscle bilaterally. G1: AA genotype.
Fillingim et al,[25] 2005	Healthy volunteers (n = 167; 96 women, 71 men).	Participants were genotyped for the A118G SNP of the *OPRM1* gene. PPT was measured on the right masseter muscle. G1: A_A genotype.
Diatchenko et al,[26] 2006	Healthy pain-free women (n = 187), age range 18–34 y.	Four *COMT* SNPs were genotyped: rs6269 (G>A), rs4633 (C>T); rs4818 (G>C); and rs4680/Val158Met (G>A). These were equivalent to the following haplotypes: LPS (G_C_G_G); APS (A_T_C_A); HPS (A_C_C_G), respectively. PPT was measured on the temporalis and masseter muscles, the TMJ, and the ventral surface of the wrist. TPT was measured on the skin overlying the masseter muscle, the forearm, and the dorsal surface of the foot. G1: LPS/LPS diplotype.
Furquim et al,[27] 2016	152 TMD patients (136 women and 16 men; mean age of 36.6 ± 11.00 y) and 91 sex- and age-matched healthy subjects in the control group (82 women)	Participants were genotyped for TNFα SNP rs1800629 (G308A). PPT was measured on the TMJ, the anterior fascicle of the temporal and masseter muscles, and the Achilles tendon (extratrigeminal site). G1: G_A genotype. G2: A_A genotype. G3: G_A + A_A genotypes.
Smith et al,[28] 2013	Cohort of 2,737 initially TMD–free individuals followed up for a median of 2.8 years, during which time 260 developed TMD.	Participants were genotyped for a panel of 3,295 SNPs representing 358 genes known to be involved in systems relevant to pain perception. PPT was measured on five body sites: overlying the masseter, temporalis, and trapezius muscles, the TMJ, and the lateral epicondyle. Cutaneous mechanical pain thereshold, ratings of suprathreshold stimuli, temporal summation, and aftersensations were assessed on the hand. HPT, heat pain tolerance, ratings of suprathreshold stimuli, temporal summation, and aftersensations were assessed on the forearm.

APS = average pain sensitivity; CDT = cold detection threshold; CPT = cold pain threshold; G1–G6 = group 1–6; HPS = high pain sensitivity; HPT = heat pain threshold; LPS = low pain sensitivity; MB-COMT = membrane-bound catechol-O-methyltransferase; PPT = pressure pain threshold; S-COMT = soluble isoform catechol-O-methyltransferase; SNP = single-nucleotide polymorphism; WDT = warm detection threshold; TPT = thermal pain threshold.

quality assessment for the included studies is displayed in Table 2.

Healthy subjects studies. The four studies in healthy subjects (Table 1) enrolled 690 individuals (460 women, 230 men; age range of 18 to 54 years). The total number of participants in each study varied from 29[22] to 247.[24] Most of the subjects were female, and only the study by Jounger et al[23] had an even sex

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Comparison (C)	Outcomes (O)
G5: C_C genotype for *DRD2*. G6: G_G (Val/Val) genotype for *COMT*.	Baseline QST measurements of healthy subjects revealed an allele-dependent main effect of the *DRD2* SNP 957C>T on all thermal thresholds (CDT, WDT, CPT and HPT). Healthy subjects in G3 showed the lowest detection thresholds for all 4 sensory modalities, while participants in G5 showed significantly higher sensory detection thresholds, indicative of relative thermal hypoesthesia compared to G3 (for all detection thresholds). The genotype effects on sensory thresholds were independent of the *COMT* SNP Val158Met; only for CPT was there an interaction effect between *DRD2* SNP 957C>T and *COMT* SNP Val158Met ($P = .0204$). The CPTs were lowest in G3 and G1 subjects, but post hoc pairwise comparisons did not reveal significant differences among the different genotype combinations. In neuropathic pain patients, G3 patients experienced on average more severe pain symptoms than G4 or G5 patients. Also, pain symptom severity was not associated with the *COMT* SNP Val158Met. These findings link both increased heat pain sensitivity and neuropathic pain to the homozygous 957TT form of the *DRD2* gene.
G5: C_C genotype for *HTR3A*. G6: A_A genotype for *HTR3B*.	Women in G5 had a larger pain area than men, and women in G3 reported higher pain intensity than men. There were no differences in pain intensity, pain duration, or pain area among the different *HTR3* alleles. There were no differences in PPT among groups.
G2: A_G/G_G genotypes.	Higher PPT scores were measured in G2 patients (in non-Hispanic white individuals, but not in Hispanic white or African American individuals); however, the associations among PPT, race/ethnicity, and gene were not statistically significant.
G2: G_G/A_G genotypes.	A significant main effect of genotype emerged for PPT ($P < .001$). G2 subjects had higher thresholds than G1 subjects. Women reported lower PPTs than men.
G2: HPS/APS diplotypes.	There was no significant association between the Val158Met SNP and global pain outcome. G2 individuals were strongly associated with measures of TPT ($P = .001$) and were more responsive to painful stimuli than G1 individuals ($P < .007$). Individuals who possess the Met-containing form of MB-COMT and/or haplotypes that produce reduced levels of *S-COMT* (G2) may have an increased risk of developing persistent pain conditions.
G4: G_G genotype.	For PPT, participants in G2 demonstrated decreased pain sensitivity for the TMJ and the anterior fascicle of the temporal muscle compared to G4. When participants in G3 were compared to G4, there was no statistical difference between groups in terms of pain response.
No comparison group.	No single SNP was significantly associated with risk of onset of TMD. One SNP (rs10809907, MPDZ) was associated with heat pain temporal summation in the lowest tertile of first-pulse responders. No SNPs were significantly associated with the PPT principal component.

distribution. Pressure pain threshold (PPT) was evaluated in all studies, especially in the masseter muscle. An effect of gender was reported only by Fillingim et al, where women presented lower PPTs than men.[25] In the same study, higher PPTs were found in individuals with GG/AG genotypes of the μ-opioid receptor gene *OPRM1*. One study considered the relationship between race/ethnicity and PPT, and no statistically

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Table 2 NIH Quality Assessment[a] of the Included Studies

Study, y (population of interest)	Item No.														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality rating
Jääskeläinen et al,[22] 2014 (healthy subjects and neuropathic pain patients)	Y	Y	N	N	N	NA	NA	Y	Y	NA	Y	NR	NA	N	Poor (inclusion nor exclusion criteria were reported)
Jounger et al,[23] 2016 (healthy subjects)	Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	Y	NR	NA	NR	Good
Hastie et al,[24] 2012 (healthy subjects)	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	NR	Fair
Fillingim et al,[25] 2005 (healthy subjects)	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	NR	Fair
Diatchenko et al,[26] 2006 (healthy subjects)	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	Y	Good
Smith et al,[28] 2013 (TMD subjects)	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	NR	Fair
Furquim et al,[27] 2016 (TMD subjects)	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	N	Fair

Y = yes; N = no; NA = not applicable; NR = not reported.
[a]NHLBI Quality Assesstment Tool for Observational Cohort and Cross-Sectional Studies.
Items:
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

significant association was found.[24] However, in the same study, higher PPTs were found in individuals with AG/GG genotypes of *OPRM1*.[24] Diatchenko et al found no significant association between the catechol-O-methyltransferase gene (*COMT*) SNP rs4680 (Val158Met) and global pain outcome.[26] Jounger et al reported no differences in pain intensity, pain duration, or pain area between different alleles of the serotonin ($5\text{-}HT_3$) receptor genes *HTR3A* and *HTR3B*.[23] Only Jääskeläinen et al evaluated cold detection, warm detection, cold pain, and heat pain thresholds.[22] The effects of *DRD2* genotype on traditional sensory thresholds were independent of *COMT* SNP Val158Met. In addition, baseline QST measurements of the healthy subjects revealed an allele-dependent main effect of the *DRD2* SNP 957C>T on all thermal thresholds.[22] The quality assessment of included studies is shown in Table 2.

TMD studies. In the two TMD studies (Table 1), 412 patients were evaluated (only Furquim et al[27] described the gender and age distribution of their population; 136 women and 16 men, mean age of 36.6 ± 11.00 years, and 91 sex- and age-matched healthy subjects in the control group [82 women]). The total number of participants in each study varied from 260[28] to 152.[27] Most of the subjects were female, and no study had an even gender distribution or an evaluation of the effect of gender on pain sensitivity. PPT was measured in both studies at multiple locations (usually at the TMJ and the masseter and temporalis muscles as trigeminal sites, and the hand, forearm, and Achilles tendon as extratrigeminal sites). Other QST measurements, such as mechanical pain threshold, warm detection threshold, temporal summation, and aftersensations, were assessed only by Smith et al.[28] Participants were genotyped for the *TNF*α SNP rs1800629 (G308A) and for a panel of 3,295 SNPs representing 358 genes known to be involved in systems relevant to pain perception. In Smith et al[28] no single SNP was significantly associated with the risk of onset of TMD, but one (*MPDZ* rs10809907) was associated with heat pain temporal

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summation in the lowest tertile of first-pulse responders. No SNPs were significantly associated with the PPT principal component, but Furquim et al[27] found an association of the TNFα-308 SNP rs1800629 with decreased pain sensitivity for the TMJ and with PPT of the anterior fascicle of the temporalis muscle. Regarding quality assessment, both studies were classified as fair quality (Table 2).

Neuropathic pain studies. One study[22] included 16 patients (14 women, 2 men) with neuropathic orofacial pain (trigeminal neuropathic pain after nerve injury [n = 7], burning mouth syndrome [n = 5], and atypical facial pain [n = 4]) with a mean age of 60 years (range 39 to 74 years). Of the possible QST measurements, cold detection, warm detection, cold pain, and heat pain thresholds were evaluated in the left infraorbital nerve distribution. Participants were genotyped for the *COMT* SNP Val158Met and the *DRD2* SNP 957C>T. Pain symptom severity was not associated with the Val158Met SNP. Regarding quality assessment, this study was classified as poor quality (Table 2).

Discussion

The present study is the first, to the authors' knowledge, to summarize the effects of genetic polymorphisms on orofacial pain sensitivity in healthy individuals and in patients with chronic orofacial pain disorders. The main findings indicate that genes associated with pressure and thermal pain sensitivity are mostly related to opioid (*OPRM1*), catecholaminergic (*COMT*), inflammatory (*TNFα*), and dopaminergic (*DRD2*) pathways. The serotoninergic (HTR3A and HTR3B) pathway, surprisingly, did not show an association with mechanical pain or with deep pain sensitivity. Therefore, pain sensitivity in the orofacial region appears to be strongly related to the genes involved in neuromodulatory pathways, emphasizing the importance of neuronal signaling—specifically nociceptive upward and inhibitory descending signaling—in pain perception and chronicity.[18]

Two of the seven studies[24,25] evaluated the effect of the *OPRM1* SNP A118G on mechanical pain sensitivity using PPT. In both studies, the individuals carrying the polymorphic allele showed higher PPT values when compared to individuals with the ancestral allele. The *OPRM1* gene encodes the μ-opioid receptor, which is responsible for mediating the work of endogenous opioids and morphine drugs.[29] This SNP was evaluated only in studies on healthy subjects[24,25] and demonstrated a pain-protective role against mechanical pain sensitivity. On a similar note, experimental studies in human cell cultures have investigated the possible mechanisms behind the analgesic role of A118G, and this polymorphic receptor showed greater binding affinity for β-endorphin.[30] Therefore, it has been hypothesized that individuals with a rare allele could realize more effective endorphinergic endogenous pain inhibition.

Although the A118G SNP is associated with lower pressure pain sensitivity in the orofacial region, similar findings have been found at other extratrigeminal sites.[29,31–35] However, ethnicity seems to be a confounding factor in the relationship between genes and pain sensitivity, and only one study took that into account. Hastie et al[24] evaluated four experimental pain modalities at trigeminal and extratrigeminal sites in three different ethnic groups. The results demonstrated an ethnic-dependent association of *OPRM1* genotype with thermal and ischemic pain modalities emerging only among non-Hispanic white individuals, regardless of sex. Nevertheless, some authors propose that functional effects of A118G variants diverge by ethnicity, possibly due to linkage to nearby other functional polymorphisms or gene-gene interactions (eg, a genetics-based difference in opioid metabolism). Certainly, other studies have previously shown interactive effects between *OPRM1* and *COMT.*[36,37] Subsequently, Val158Met, the most-studied *COMT* SNP, demonstrated diverse allele frequencies in ethnic groups, and this could hypothetically elucidate variances in associations of *OPRM1* with pain phenotypes.[24]

COMT encodes the enzyme responsible for the regulation of catecholamine levels in the body and was evaluated in two out of seven studies, one in a healthy population[26] and the other in a neuropathic pain population.[22] This gene is highly polymorphic, mainly resulting in functional polymorphisms that cause enzymatic hypoactivity. As a consequence, epinephrine levels increase, potentiating pain signaling through β-adrenergic receptors.[38] Some of these combinations result in three major haplotypes of *COMT*, designated as low pain sensitivity (LPS), average pain sensitivity (APS), or high pain sensitivity (HPS).[26] Therefore, depending on which one appears, *COMT* haplotype could also be related to hypo- or hyperalgesia.[26] In Diatchenko et al,[26] the nociceptive role was only associated with thermal pain threshold in the healthy population with the HPS/APS diplotype. Among neuropathic pain populations, *COMT gene* variations do not seem to contribute to pain sensitivity in the orofacial region. Notwithstanding, effects on the *COMT* gene on pain perception seem to be sex dependent, considering previous findings reporting that female individuals express less of the COMT enzyme due to estrogenic downregulation. Thus, women might be primed toward a more *COMT*-dependent pain sensitivity.[39,40] Unfortunately, none of the included studies assessed

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the interaction between *COMT* polymorphisms and sex, which may have influenced the studies' results.

The results of the present review revealed other genes, such as *MPDZ* (encodes MUPP1 protein), *DRD2* (encodes dopamine D2 receptor), and *TNFα* (encodes TNFα cytokine),[41–43] that might be involved in the nociceptive pathway. Nevertheless, only the *DRD2* gene with the 957C>T SNP was associated with neuropathic pain.[22] Among individuals with TMD, only the *MPDZ* SNP rs10809907 was associated with pain sensitivity; more specifically, with temporal summation.[28]

Regarding QST, the most-used test in the included studies was PPT, followed by thermal pain and detection tests. Measurement of PPT has been frequently applied to assess muscle and joint sensitivity, which are related to painful musculoskeletal conditions (eg, TMD).[1,44–46] However, only one included study evaluating PPT in the orofacial region among patients with TMD found an association with genetic polymorphisms.[27] Accordingly, the evidence to support this association is still very low. On the other hand, PPT in healthy participants was statistically significantly associated with pain sensitivity, but only when muscle pain was not experimentally induced. Jounger et al[23] was the only study that induced pain in the masseter muscle through saline injection and was also the only study that found no association with PPT or an influence of genetic polymorphism on pain sensitivity. Polymorphisms in serotonin receptor genes seem not to influence experimental pain (ie, muscle pain induced by injection of saline).[23] Nonetheless, other studies that evaluated chronic pain at extratrigeminal sites showed the participation of serotoninergic pathways in pain sensitivity.[47–49] It is possible that Jounger et al[23] was underpowered due to a small sample size and thus was not able to confirm the association.

The absence of more articles investigating the influence of genetic polymorphisms on pain sensitivity at trigeminal sites in populations with chronic orofacial pain was a limiting factor of the present study. Most of these studies focused on extratrigeminal sites for sensory testing, and that was one of the major reasons why some articles were not included in the present review. The relationships between pain thresholds in the trigeminal and extratrigeminal regions in patients with chronic pain is not yet clear. The presence of phenomena such as plasticity of the descending pain inhibitory pathways could influence pain thresholds beyond the neuroanatomical boundaries of the patient's pain complaint region to other body sites, like extratrigeminal areas.[50–55] In addition, when the relationship between mechanical sensory testing and genetic polymorphism was investigated, only PPTs were assessed.[23–28] The lack of evidence for other mechanical sensory tests, such as pinprick sensitivity or dynamic mechanical allodynia, may be due to the small number of studies evaluating that parameter in the orofacial region,[56–60] and the even lower number evaluating genetic influence. In this way, it is important that future genetic pain studies embrace all mechanical pain sensitivity parameters for a better understanding of human pain sensitivity. Therefore, the small number of eligible articles makes it unfeasible to draw more concrete conclusions for chronic pain, both musculoskeletal and neuropathic orofacial. In addition, the absence of systematic calibration between the two researchers (F.F.C.S. and R.L.P.) may have led to some subjective results. Moreover, a sex comparison, menstrual status of female subjects, ethnicity, and psychosocial profile could not be evaluated in all eligible studies, and these all are factors that might influence pain sensitivity independently of genetics.[39,40,61,62] On the other hand, studies evaluating genetic effects on extratrigeminal musculoskeletal chronic pain conditions like fibromyalgia, low back pain, and chronic widespread pain have provided some valuable insights into their pathophysiologies.[63–66] Additionally, musculoskeletal conditions were associated with polymorphisms of genes encoding the matrix metallopeptidase 1 enzyme (*MMP1*), proinflammatory cytokine interleukin 1α (*IL1A*), interleukin receptors (*IL1RN*, *IL18R1*, *IL18RAP*), β2-adrenergic receptor (*ADRB2*), μ-opioid receptor (*OPRM1*), catechol-O-methyltransferase (*COMT*), guanosine triphosphate cyclohydrolase (*GCH1*), dopamine D4 receptor (*DRD4*), monoamine oxidase A (*MAOA*), serotonin transporter (*SLC6A4*), serotonin receptor 2A (*HTR2A*), and estrogen receptor 1 (*ESR1*).[67–96]

Genetic studies conducted in the last decade have been of major importance for elucidating some of the molecular pathophysiologic mechanisms of pain sensitivity and their variations in healthy individuals and patients with chronic pain. Although some of these studies[23,24,28] occasionally presented insufficient statistical power to confirm the involvement of specific genes, the network of some causal mechanisms has begun to be demonstrated; eg, activation of the β-adrenergic nociceptive pathway and the protective role of *OPRM1* A118G on pain sensitivity. Despite the fact that many genetic variants contribute to interindividual differences, it is difficult to estimate to what extent genetic factors explain orofacial pain sensitivity. Current research from other fields has implicated epigenetics mechanisms that enable a gene-environment interaction dynamic as the most likely explanatory model.[97–101] Accordingly, future studies in the field of orofacial pain should include epigenetic factors in their evaluations.

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Conclusions

These findings indicate that genetic polymorphisms related to opioid, catecholaminergic, inflammatory, and dopaminergic pathways are significantly associated with the variability of somatosensory sensitivity in the orofacial region, and in particular with sensitivity to thermal and pressure stimuli. Therefore, genetic factors should be taken into account for an accurate interpretation of orofacial pain sensitivity.

Highlights

- To the authors' knowledge, this study is the first systematic review to assess the effects of genetic polymorphisms on pain sensitivity in healthy and chronic pain subjects.
- Genetic polymorphisms seem to impact pain sensitivity to thermal and mechanical stimuli.

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Appendix 1 Scopus and Embase Search Strategies

Scopus:
TITLE-ABS-KEY ("Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR "Polymorphism" OR "Polymorphic Gene" OR "Allelic variant" OR "Polymorphisms") AND TITLE-ABS-KEY ("Pain Threshold" OR "Pain Perception" OR "Pain Measurement" OR "Psychophysics" OR "Quantitative Sensory Testing" OR "Suprathreshold" OR "Suprathreshold" OR "Suprathreshold stimulus" OR "Suprathreshold stimulus")

Embase:
('polymorphism, genetic'/exp OR 'polymorphism, genetic' OR 'polymorphism, single nucleotide'/exp OR 'polymorphism, single nucleotide' OR 'polymorphism'/exp OR 'polymorphism' OR 'polymorphic gene' OR 'allelic variant' OR 'polymorphisms') AND ('pain threshold'/exp OR 'pain threshold' OR 'pain perception'/exp OR 'pain perception' OR 'pain measurement'/exp OR 'pain measurement' OR 'psychophysics'/exp OR 'psychophysics' OR 'quantitative sensory testing'/exp OR 'quantitative sensory testing' OR 'supra-threshold' OR 'suprathreshold' OR 'supra-threshold stimulus' OR 'suprathreshold stimulus')

Appendix 2 References Excluded and Reasons for Exclusion

Review article

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Without somatosensorial evaluation

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Somatosensorial evaluation at extra-trigeminal site

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