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Effect of single nucleotide polymorphism in the *SCN9A*, *SCN10A*, and *SCN11A* genes on postoperative pain

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Purpose: To investigate the association between postoperative pain intensity and single nucleotide polymorphisms (SNPs) in the *SCN9A*, *SCN10A*, and *SCN11A* genes.

Methods: Ninety-five patients were included in the study. All the participants recorded their preoperative percussion and preoperative pain levels on a visual analog scale (VAS) before root canal treatment. After the treatment, a form including the VAS was given to the patients to record their pain values and use of analgesics on the 1st, 2nd, 3rd, and 7th days after the treatment. DNA isolation and genotyping were performed and the association between polymorphisms and postoperative pain level was investigated.

Results: The AA genotype at the SNP rs6746030 and the CC genotype at rs4286289 of the *SCN9A* gene were significantly associated with higher postoperative pain levels. The CC genotype at SNP rs6801957 in the *SCN10A* gene was significantly associated with less postoperative pain.

Conclusion: The rs6746030 and rs4286289 SNPs in the *SCN9A* gene and rs6801957 in the *SCN10A* gene were associated with pain level after endodontic treatment.

Keywords: Postoperative pain, *SCN10A*, *SCN11A*, *SCN9A*, single nucleotide polymorphisms.

Introduction

Postoperative pain following endodontic treatment is a major concern for both patients and dentists, and it has been shown that it occurs in 3%–58% of patients (1). There are many factors that cause postoperative pain during root canal treatment (2). Chemical, mechanical, and microbial factors related to root canal preparation may contribute to periapical inflammatory processes that affect the severity and prevalence of post-treatment pain (3). Preoperative and postoperative pain are also strongly linked (4). Although individual differences in pain experience have been reported by dentists, the genetic basis of acute pain conditions such as postoperative pain after endodontic treatment has not been fully elucidated (5).

Variations that occur at a frequency of 1% or higher in particular DNA sequences of individuals in a population are called polymorphisms (6). Single nucleotide polymorphisms (SNPs) are the most common type of polymorphisms and occur in every 1000 base pairs in the human genome (7). It has been reported that SNPs in many genes have significant effects on sensitivity to pain (8). However, there is limited information in the literature about the effect of SNPs on pain intensity after root canal treatment. Applebaum et al. (5) reported that genetic variations in the *COX1* and *COX2* genes are associated with the level of postoperative pain following endodontic treatment. On

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the other hand, Karataş et al. (9) evaluated the effect of SNPs on the *OPRM1*, *COMT*, *5HTR3B, 5HT1A*, and *5HT2A* genes for postoperative pain intensity after root canal treatment, and reported no significant association between the evaluated SNPs and postoperative pain intensity.

The *SCN9A* gene, which encodes the Nav1.7 voltage-gated sodium channel (VGSC), the *SCN10A* gene, which encodes the Nav1.8 VGSC, and the *SCN11A* gene, which encodes the Nav1.9 VGSC, contribute significantly to pain signaling and formation (10–12). Genetic polymorphisms that contribute to pain phenotype risk or pain severity have been identified in the *SCN9A* gene (13,14). There is an association between human peripheral painful neuropathy and the Nav1.8 sodium channel, which is encoded by *SCN10A* (15). Previous research has shown that Nav1.8 expression plays an important role in various pain phenotypes such as neuropathic pain and inflammation (16,17). Moreover, the Nav1.9 sodium channel encoded by *SCN11A* is involved in pain transmission (18).

The effects of SNPs in the *SC9A*, *SCN10A*, and *SCN11A* genes on pain intensity have been clearly demonstrated (13,16,18). However, there is no study evaluating the possible association between polymorphisms in genes encoding VGSCs and postoperative pain following endodontic treatment. Therefore, the present study aimed to investigate the possible association between postoperative pain intensity following endodontic treatment and SNPs in *SCN9A*, *SCN10A*, and *SCN11A*. The null hypothesis was that there would be no association between SNPs in the *SCN9A*, *SCN10A*, and *SCN11A* genes and postoperative pain.

Materials and Methods

No studies evaluating the association between SNPs and pain following endodontic treatment using a visual analog scale (VAS) had been published when the study was planned. Therefore, data from previous studies could not be used for sample size calculation. A pilot study with 24 participants was conducted to determine the required sample size. The sample size calculation, which was conducted using the GPower program (GPower; Franz Faul, University of Kiel, Kiel, Germany) using the data of the pilot study, revealed that 12 patients were sufficient with an effect size of 0.95, an error of alpha of 0.05, and a power of 1.56. Ethical approval was obtained from the Ethics Committee of the Faculty of Dentistry of University of Atatürk.

Patients with a minimum preoperative pain level of 50, according to the VAS, were included in the study. Molar teeth and patients without any genetic disease were included. Exclusion criteria were patients with a history of systemic disease or allergies, psychiatric and mental problems, swelling, sinus tract or preoperative palpation pain, bruxism, resorption in the involved tooth, and presence of a periodontal pocket of more than 3 mm in the involved tooth. Patients who had used analgesics or anti-inflammatory drugs in the last 12 hours, who had root canal-treated teeth or teeth with root fracture, as well as ankylosis and pathological mobility, and pregnant or lactating patients were excluded from the study.

After signed consent forms were obtained from all participants, gender, age, and tooth number were recorded. All patients recorded their preoperative percussion and preoperative pain levels on a VAS. To test percussion sensitivity, the occlusal surface of the tooth was tapped with a blunt instrument. Before starting the treatment, saliva samples required for genetic analyses were collected into Eppendorf tubes containing at least 1 mL of saliva and the tubes were then stored at –80°C.

Treatment Protocol

Anesthesia was performed using 2 mL of articaine HCl containing 1:100,000 epinephrine. Following rubberdam isolation, an access cavity was prepared and canal orifices were determined. The coronal part of the root canal was prepared with Reciproc R25 (VDW, Munich, Germany) instruments. The working length was determined using a 10 K-file (Mani Inc.; Utsunomiya, Tochigi, Japan) with an electronic apex locator (Raypex 6; VDW GmbH, Bayerwaldstr, Munich, Germany). Then, the root canal preparation was performed using Reciproc (R25, R40, or R50) instruments at full working length. When a 20 K-type file could not passively reach working length, the canal was considered to be narrow and an R25 file was used. When a 20 K-type file, but not a 30 K-type file, could passively reach working length, a R40 file was used since the canal was considered medium. When a 30 K-type file could passively reach working length, the canal was considered to be wide and a R50 file was used. During root canal preparation, the root canals were rinsed with 1 mL of 1% NaOCl between three pecking motions. Each canal was irrigated with 5 mL of 1% NaOCl followed by 5 mL of 10% citric acid as final irrigation. Then, the canals were dried with paper points and root canals were obturated with a lateral condensation technique using tapered gutta-percha cones and a root canal sealer (Sealapex™; Kerr-Sybron, Orange, CA, USA). Permanent restoration (Single Bond Universal Adhesive; 3M ESPE, Neuss, Germany) was performed after bonding, using flowable composite and composite resin materials (3M ESPE, Kerr, TX, USA).

Table 1. Details of the SNPs investigated

Gene	Chromosome	SNP ID	Base pair position*	SNP function	Alleles*
SCN9A	2	rs6746030	166242648	Missense variant	A/**G**
	2	rs4286289	166305201	Intron variant	C/**A**
SCN10A	3	rs6801957	38725824	Intron variant	T/**C**
SCN11A	3	rs13080116	38865732	Intron variant	**T**/C

SNP: Single nucleotide polymorphisms; ID: Identification. *According to National Center for Biotechnology Information GRCh38.p12 assembly. *Ancestral allele in bold.

A form including VAS was given to the patients to record their pain values and use of analgesics on the 1st, 2nd, 3rd, and 7th days after the treatment. The participants were called for the control session at the end of the 7th day. The patients were clinically examined and asked to mark the percussion pain value in the treated tooth on the VAS form. All the treatment procedures were performed by one clinician.

Candidate Genes and SNP Selection

Four SNPs of three genes, *SCN9A*, *SCN10A*, and *SCN11A*, were examined. Genes and SNPs were selected after the literature search. The national biotechnology information center dbSNP (http://www.ncbi.nlm.gov/SNP/) and genome databases (https://www.ensembl.org/index.htmL) were used to obtain information on these genes (Table 1).

DNA Isolation and Genotyping

DNA from saliva was isolated using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Nanodrop (ND-1000; Thermo Fischer Scientific, Wilmington, DE, USA) was used to measure the quality of the DNA. Allele-specific SNP type assays were loaded on the Fluidigm 96.96 Dynamic Array™ IFC (Fluidigm Corp., San Francisco, CA, USA) and data collection software on the BioMark system (Fluidigm Corp.) was used to analyze the SNPs genotyping data with calculating FAM and HEX signals.

Statistical Analysis

The IBM SPSS Statistics 20 (USA) software was used to analyze the data. Intergroup comparisons (genotype variables, alleles, and haplotypes) were performed using non-parametric tests (Kruskal–Wallis and Mann–Whitney U tests). Since the data did not exhibit normal distribution, the Pearson's chi-square test was used to analyze the distribution of the data for gender, tooth number, and analgesic intake between groups. The tests were conducted using 95% confidence intervals ($p = 0.05$).

Results

The study included 95 patients (60 females and 35 males) aged 15–52 years (Fig. 1). None of the patients participating in the study requested an extra appointment due to postoperative pain, swelling, or sinus tract formation.

The rs6746030 and rs4286289 SNPs in *SCN9A*, rs6801957 in *SCN10A*, and rs13080116 in *SCN11A* were evaluated. Three different genotypes were detected for rs6746030 (AA, AG, and GG) and rs4286289 (AA, AC, and CC) in *SCN9A*, and for rs6801957 (CC, CT, and TT) in *SCN10A*; only the CT genotype was detected for rs13080116 in *SCN11A* in all individuals. Therefore, statistical evaluation could not be performed for the latter SNP. No statistically significant difference was found between the genotypes (rs6746030, rs4286289, and rs6801957) in terms of age, gender, and tooth number according to the groups ($p > 0.05$) (Table 2).

The genotype distribution of a population in large, independent, and random mating cases is described by the Hardy–Weinberg equilibrium (19). The rs4286289 and rs6801957 SNPs in the *SCN9A* and *SCN10A* genes evaluated in the study did not deviate from the Hardy–Weinberg equilibrium, suggesting that the study's genotyping is representative of general population (20). However, *SCN9A*'s rs6746030 SNP deviated from the Hardy–Weinberg equilibrium. To investigate the association of deviations from this equilibrium with genotyping error, systematic laboratory examination of raw genotype data was performed, and no evidence of error was found. High linkage equilibrium between *SCN9A*'s rs6746030 and rs4286289 was detected ($D' = 0.99–1$) according to the 1000 Genomes Project (https://www.ensembl.org/index.htmL).

Postoperative Pain Levels for Genotypes

A statistically significant difference was found between the AA, AG, and GG genotypes for rs6746030 in *SN9A* in terms of pain level on the 1st and 2nd postoperative days ($p < 0.05$). Individuals with the AA genotype had higher pain values than those with the AG and GG genotypes. There was no significant difference between genotypes in terms of analgesic use ($p > 0.05$) (Table 3).

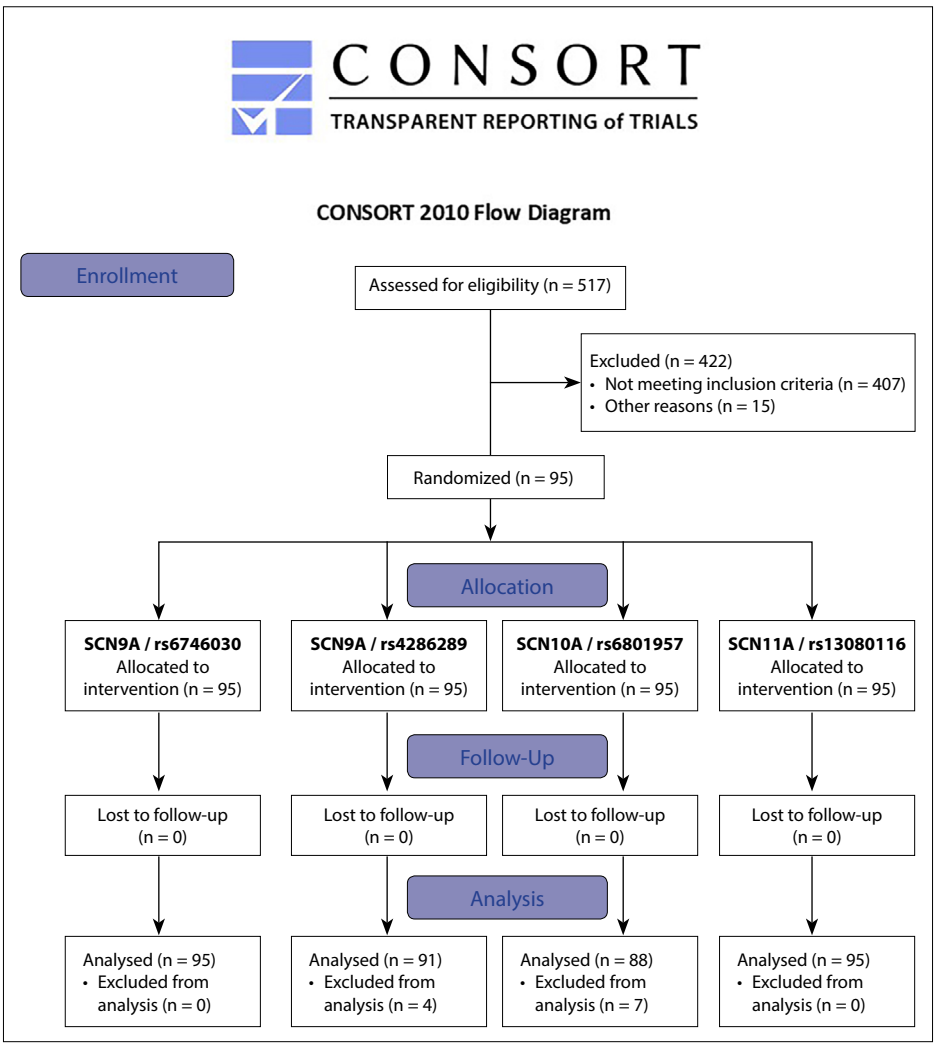

Fig. 1. Consort flow diagram.

Table 2. Distribution of age, gender, and jaw according to the *COMT*, *5HT1A*, and *5HT2A* genotypes

Genotypes	N	Mean Age	Gender		Maxillary molars	Mandibular molars
			Male	Female		
SCN9A rs6746030						
AA	7	34 ± 2.8	2	5	4	3
AG	21	32.2 ± 2	6	15	8	13
GG	67	30.7 ± 1	27	40	39	28
P value		0.496	0.558		0.267	
SCN9A rs4286289						
AA	52	30 ± 9.2	19	33	28	24
AC	35	32 ± 9.3	14	21	19	16
CC	4	36 ± 6.7	1	3	1	3
P value		0.308	0.827		0.524	
SCN10A rs6801957						
CC	32	30 ± 9.8	13	19	15	17
CT	42	32 ± 8.8	14	28	21	21
TT	14	31 ± 8.1	5	9	10	4
P value		0.591	0.810		0.284	

Table 3. Pain levels (median[range]) according to genotypes

Gene/ SNP	Genotype	Pre-operative pain level	Post-operative pain level on day 1	Post-operative pain level on day 2	Post-operative pain level on day 3	Post-operative pain level on day 7	Pre-operative pain on percussion	Post-operative pain on percussion	Analgesic intake
SCN9A/	AA	70 (50-90)	93 (45-100)	67 (23-98)	19 (0-96)	0 (0-28)	95 (71-97)	0 (0-46)	4
rs6746030	AG	70 (50-100)	46 (0-70)	21 (0-70)	0 (0-46)	0 (0-71)	71 (42-97)	0 (0-46)	5
	GG	80 (50-100)	23 (0-77)	11 (0-75)	0 (0-70)	0 (0-48)	72 (42-98)	0 (0-47)	18
P value		0.385	0.003	0.001	0.380	0.206	0.438	0.292	0.208
SCN9A/									
rs4286289	AA	72.5 (50-100)	23 (0-93)	20 (0-70)	0 (0-70)	0 (0-48)	71 (42-98)	0 (0-47)	15
	AC	70 (50-100)	46 (0-95)	21 (0-75)	0 (0-65)	0 (0-71)	72 (42-97)	0 (0-47)	11
	CC	80 (70-90)	85.5 (68-100)	77 (42-98)	61 (20-96)	12.5 (0-28)	84.5 (70-97)	14.5 (0-46)	1
P value		0.723	0.011	0.015	0.020	0.051	0.552	0.386	0.946
SCN10A/	CC	70 (50-100)	22 (0-75)	0 (0-51)	0 (0-51)	0 (0-71)	71 (42-98)	0 (0-23)	5
rs6801957	CT	70 (50-100)	46 (0-98)	22 (0-96)	20 (0-96)	0 (0-25)	94.5 (42-97)	0 (0-47)	16
	TT	80 (50-100)	47 (0-70)	21 (0-69)	0 (0-70)	0 (0-48)	70.5 (47-97)	0 (0-47)	5
P value		0.719	0.022	0.079	0.097	0.303	0.323	0.825	0.095

A statistically significant difference was found between the AA, AC, and CC genotypes for rs4286289 in *SCN9A* in terms of pain level on the 1st, 2nd, and 3rd postoperative days ($p< 0.05$). Patients with the CC genotype had higher pain values compared with those with the AA and AC genotypes. There was no statistically significant difference between the genotypes in terms of analgesic use ($p> 0.05$) (Table 3).

A statistically significant difference was found between the CC, CT, and TT genotypes for rs6801957 in *SCN10A* in terms of pain level on the 1st postoperative day ($p< 0.05$). It was shown that individuals with the CC genotype had lower pain levels than those with the CT and TT genotypes. No statistically significant difference was found between the genotype groups in terms of analgesic use ($p> 0.05$) (Table 3).

All individuals in the population examined for rs13080116 in *SCN11A* were found to have the heterozygous (CT) genotype. Therefore, statistical evaluation could not be made.

Postoperative Pain Levels for Alleles

Statistical analysis was performed to determine the distribution of postoperative pain values among allele groups. A statistically significant difference was found between the A and G alleles for rs6746030 in *SCN9A* in terms of postoperative pain level ($p< 0.05$) (Table 4). On postoperative day 1 and day 2, the A allele was associated with higher pain levels than the G allele.

A significant difference was also found between the A and C alleles for rs4286289 in *SCN9A* in terms of postopera-

Table 4. Pain levels (median[range]) according to alleles

	N	Pre-operative pain level	Post-operative pain level on day 1	Post-operative pain level on day 2	Post-operative pain level on day 3	Post-operative pain level on day 7	Pre-operative pain on percussion	Post-operative pain on percussion
SCN9A/rs6746030								
A Allele	35	70 (50-100)	47 (0-100)	23 (0-98)	0 (0-96)	0 (0-71)	71 (42-97)	0 (0-46)
G Allele	155	80 (50-100)	23 (0-77)	12 (0-75)	0 (0-70)	0 (0-71)	72 (42-98)	0 (0-47)
P value		0.158	0.047	0.001	0.559	0.048	0.755	0.079
SCN9A/rs4286289								
A Allele	139	70 (50-100)	23 (0-95)	21 (0-75)	0 (0-70)	0 (0-71)	71 (42-98)	0 (0-47)
C Allele	43	70 (50-100)	47 (0-100)	22 (0-98)	0 (0-96)	0 (0-71)	72 (42-97)	0 (0-47)
P value		0.824	0.047	0.102	0.364	0.017	0.392	0.453
SCN10A/rs6801957								
C Allele	106	70 (50-100)	22.5 (0-98)	18 (0-96)	0 (0-96)	0 (0-71)	72 (42-98)	0 (0-47)
T Allele	70	70 (50-100)	46.5 (0-98)	21 (0-96)	0 (0-96)	0 (0-48)	71 (42-97)	0 (0-47)
P value		0.418	0.010	0.085	0.140	0.220	0.685	0.587

Table 5. Pain levels according to haplotype results (median[range])

Haplotypes	N	Pre-operative pain level	Post-operative pain level on day 1	Post-operative pain level on day 2	Post-operative pain level on day 3	Post-operative pain level on day 7	Pre-operative pain on percussion	Post-operative pain on percussion
GAT	25	70 (50-100)	23[a,b,d] (0-70)	7[b] (0-70)	21 (0-70)	0 (0-48)	71 (42-97)	0 (0-47)
GCT	19	80 (50-100)	47[b,c] (0-77)	21[a,b] (0-75)	0 (0-65)	0 (0-43)	72 (42-96)	0 (0-47)
GAC	15	80 (60-100)	2[d] (0-75)	12[b] (0-51)	0 (0-51)	0 (0-0)	94 (47-98)	0 (0-23)
GCC	5	60 (50-90)	0[d] (0-67)	0[b] (0-46)	0 (0-49)	0 (0-8)	94.5 (47-97)	0 (0-21)
ACC	5	50 (50-90)	22[a,b,d] (0-52)	21[c,b] (0-23)	0 (0-21)	0 (0-71)	71 (47-94)	0 (0-21)
AAT	5	70 (60-80)	46[a,b,c] (22-93)	48[a] (21-68)	19 (0-47)	0 (0-20)	71 (47-97)	21 (0-46)
ACT	6	70 (70-90)	49[c] (42-98)	31.5[a,c] (21-96)	0 (0-96)	0 (0-25)	96 (71-97)	0 (0-46)
AAC	4	70 (50-80)	58[a,b,d,c] (22-69)	33.5[b] (0-46)	22.5 (0-45)	0 (0-19)	70.5 (47-95)	21 (0-22)
P value		0.367	0.019	0.043	0.736	0.459	0.211	0.313

tive pain level ($p< 0.05$) (Table 4). On postoperative day 1, the C allele was associated with increased pain sensitivity compared with the A allele.

A significant difference was found between the C and T alleles for rs6801957 in *SCN10A* in terms of postoperative pain level ($p< 0.05$) (Table 4). The T allele was found to be associated with higher pain levels on postoperative day 1.

Postoperative Pain Levels for Haplotypes

Eight haplotype groups (GAT, GCT, GAC, GCC, ACC, AAT, ACT, and AAC) were formed based on minor alleles for rs6746030 and rs4286289 in *SCN9A* and for rs6801957 in *SCN10A* in the 3rd chromosome (Table 5). A statistically significant difference was found between these haplotypes in terms of postoperative pain levels on the 1st and 2nd postoperative days ($p < 0.05$). On postoperative day 1, individuals with haplotypes GCC and GAC reported less pain than those with haplotypes GCT, AAT, and ACT. Individuals with the ACT haplotype had more pain on the 1st postoperative day than those with the GAT and ACC haplotypes. On postoperative day 2, individuals with haplotypes GCC, GAC, and GAT reported less pain than those with the AAT and ACT haplotypes. In addition, the ACC haplotype group reported less pain than the AAT haplotype group.

Discussion

In this study, the association between two SNPs (rs6746030, rs4286289) in the *SCN9A* gene, one (rs6801957) in the *SCN10A* gene, and one (rs13080116) in the *SCN11A* gene and postoperative pain levels in endodontic patients were investigated. There was a significant association between rs6746030, rs4286289, and rs6801957 and postoperative pain following root canal treatment. Therefore, the null hypothesis was rejected.

There is no other study in the literature examining the relationship between the rs6746030, rs4286289, rs6801957, and rs13080116 polymorphisms and postoperative pain intensity after root canal treatment; therefore, direct comparisons could not be made. However, there are studies evaluating individual changes in pain transmission and pain sensitivity related to the examined SNPs.

Reeder et al. (14) investigated the relationship between rs6746030 and interstitial cystitis/bladder pain syndrome; and found that AA and AG genotypes were associated with pain syndrome in patients with interstitial cystitis/bladder pain syndrome. Additionally, another study reported that rs6746030 in patients with symptomatic disk herniation could be related to pain intensity (21). Moreover, a significant nominal relationship was found between the rs6746030 and the pain level in patients with Parkinson's disease (22). Both clinical and experimental pain studies have shown that the most pain is felt in individuals carrying the AA genotype in rs6746030, whereas the least pain intensity is felt in those carrying the GG genotype (23). In the present study, it was found that individuals with the AA genotype in rs6746030 experienced more pain on the 1st and 2nd postoperative days compared with individuals with the AG and GG genotypes. Therefore, the results of the present study are in accordance with those of previous studies. Reimann et al. (23) investigated different genotypes of the SCN9A gene in various chronic pain conditions such as osteoarthritis, sciatica, phantom pain, lumbar discectomy, and pancreatitis; the authors found an association between the A allele at the SNP rs6746030 and pain perception. In addition, Reeder et al. (14) showed that the A allele at the SNP rs6746030 is associated with increased risk of developing interstitial cystitis/bladder pain syndrome. In accordance, the results of the present study show that the A allele at the SNP rs6746030 is associated with higher pain levels on the 1st postoperative day.

Thus, the findings of the present study related to the SNP rs6746030 are corroborated by previous studies.

SNP rs6746030 is located in exon 18 and affects the amino acid at position 1150 Nav1.7; while the G allele encodes the arginine, the A allele encodes tryptophan (23). Considering the information in the literature, the findings of the present study can be attributed to the amino acid change caused by the missense variant.

Duan et al. (24) found an association between postoperative pain intensity and the SNP rs4286289 in the *SCN9A* gene in female patients who underwent gynecological laparoscopic surgery. According to the results of the present study, there was a statistically significant difference between the genotypes of rs4286289 on the 1st, 2nd, and 3rd postoperative days in terms of postoperative pain level. It was shown that patients with the CC genotype had more pain than those with the AA and AC genotypes. In addition, the C allele was associated with increased pain sensitivity on postoperative day 1.

The functional impact of the rs4286289 polymorphism on pain phenotypes is unclear as it resides in an intronic region (24). Genetic and functional studies have shown that the Nav1.7 sodium channel encoded by the *SCN9A* gene has important roles in pain signaling and generation, especially that expressed in dorsal root ganglion neurons and sympathetic ganglion neurons (10). In addition, the *SCN9A* gene is responsible for pain disorders (23). Mutations in *SCN9A* that cause loss of function of Nav1.7 cause congenital insensitivity to pain (25), while gain-of-function mutations cause different pain syndromes such as hereditary erythromelalgia and paroxysmal extreme pain disorder (26,27). Based on this information, one can envision that the rs4286289 polymorphism affects pain sensitivity because it causes changes in the functions of the Nav1.7 channel encoded by the *SCN9A* gene.

Duan et al. (28) evaluated the experimental pain sensitivity of the rs6801957 variant in the *SCN10A* enhancer region including mechanical and heat stimuli; the authors showed that individuals with the AA minor homozygous allele at rs6801957 had significantly lower mechanical pain sensitivity compared with other individuals. In the present study, it was determined that patients with the major CC homozygous allele at rs6801957 had a lower level of pain on postoperative day 1 than those with the CT and TT genotypes. Although the AG genotype has been mentioned in the literature (28), in the present study, the polymorphism was CT. It has also been referred to as CT polymorphism in the genome browser (https://www.ensembl.org/index.htmL). These differences in bases may be due to the use of primers belonging to the forward strand of the DNA while genotyping. There was no study in the literature investigating the relationship between the *SCN10A*'s rs6801957 and postoperative pain sensitivity. While Duan et al. (28) used a hand-held electronic mechanical algometer to test the effect of the rs6801957 polymorphism on mechanical pain sensitivity, in our study, a VAS was used to measure the postoperative pain value. It is difficult to provide correlations between studies because the parameters shown by the two are different.

Several studies have shown the effect of *SCN10A* SNPs on pain sensitivity. Although the Nav1.8 sodium channel encoded by *SCN10A* is expressed in the nociceptive dorsal root ganglion and trigeminal ganglion neurons, this channel is also found in peripheral axons in the skin and cornea (29). The biophysical properties of Nav1.8, its critical role in repetitive conduction, and its presence in free nerve endings suggest that Nav1.8 may significantly affect nociceptor excitability, and thus, contribute to pain (11). Gain-of-function mutations in *SCN10A* have been shown to be associated with painful neuropathy (11).

The collection of biological specimens in epidemiology studies is increasing due to the increasing emphasis on the study of genetic factors and the simplicity of obtaining DNA from biological tissue (30). This requires specimen collection procedures that are appropriate and acceptable to both patients and clinicians (31). These procedures include the collection of biological samples such as saliva or blood (32). Taking saliva samples from patients for DNA isolation is simpler; it entails a lower risk of infection and is a less costly, painless, non-invasive technique compared with blood sample collection (31).

Conclusion

A significant association was found between the SNPs rs6746030, rs4286289 in *SCN9A*, and the SNP rs6801957 in *SCN10A* and postoperative pain intensity after root canal treatment. Postoperative pain was higher for the rs6746030 AA genotype compared with the AG and GG genotypes, and for the rs4286289 CC genotype compared with the AA and AC genotypes, and it was lower for the rs6801957 CC genotype compared with the CT and TT genotypes. The A allele at rs6746030, C allele at rs4286289, and T allele at rs6801957 were associated with higher postoperative pain values after root canal treatment. Studies with larger populations and different genes are needed to examine the relationship between endodontic postoperative pain intensity and genetic polymorphisms.

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Conflict of Interest: None declared.

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