A Single-nucleotide Polymorphism in SCN9A May Decrease Postoperative Pain Sensitivity in the General Population

Guangyou Duan, M.S.,* Guifang Xiang, M.S.,† Xianwei Zhang, M.D.,‡ Ruimei Yuan, M.S.,* Huiming Zhan, M.S.,* Dongmei Qi, M.S.*

ABSTRACT

Background: This study aimed to explore the role of a non-synonymous single-nucleotide polymorphism, 3312G>T, in SCN9A, which was identified in probands with congenital indifference to pain, but which is also present in normal controls, in the prediction of individual baseline pain perception, and postoperative pain sensitivity in the general population.

Methods: Preoperative pressure pain thresholds and tolerance were measured in 200 patients undergoing pancreatectomy, and the postoperative pain sensitivity and analgesic demand were recorded. These variables were compared according to the SCN9A 3312G>T alleles. Logistic regression analysis was used to test the role of preoperative variables in the prediction of postoperative inadequate analgesia.

Results: The 3312T allele was present in 22 individuals, and the 3312T allele frequency was 5.5% (22/200). The average patient-controlled analgesia pressing frequency and opioid consumption in 3312G patients was significantly higher than those in 3312T patients (2.70 [SD: 0.84] vs. 2.05 [SD: 0.43], P < 0.001; 100.8 [SD: 40.7] vs. 74.8 [SD: 20.8] ml, P = 0.006). The incidence of inadequate analgesia in 3312G patients was significantly higher than that of patients carrying the 3312T allele (29.2% vs. 4.5%; P = 0.013). Carrying the 3312T allele and having a higher pressure pain threshold predicted a lower risk of postoperative inadequate analgesia, with an odds ratio of 0.10 (95% CI: 0.01 to 0.76, P = 0.026) and 0.32 (95% CI: 0.13 to 0.82, P = 0.018), respectively.

Conclusion: Patients carrying the SCN9A 3312T allele presented with lower postoperative pain sensitivity in the presence of a similar surgical pain stimulus, and had a lower likelihood of developing inadequate analgesia than those carrying the 3312G allele.

SURGERY is the most common and predictable source of pain.1 Although numerous measures have been developed for the management of postoperative pain, a recent survey shows that 30–71% of patients undergoing surgery experience moderate to severe postoperative pain,2 suggesting that postoperative pain treatment is not yet adequate. Implementation of appropriate preoperative screening methods may facilitate more aggressive pain therapies, specifically targeted at individuals at a high risk of experiencing severe postoperative pain. This, in turn, may translate into an improvement in postoperative rehabilitation and a reduction in short- and long-term morbidity.3 In some studies, several factors including demographics, psychological variables, quantitative sensory test results, the level of preoperative pain, and the type of surgery, have been identified as predictors of postoperative pain.4–7 Predicting postoperative pain at the gene level has not been investigated much and may be more challenging;1 however, human genome analysis allows us to investigate interindividual differences in pain thresholds and pain perception at the genetic level.8,9 SCN9A encodes the voltage-gated sodium-channel type IV-α subunit (Nav1.7) and is predominantly expressed in dorsal root ganglion neurons and sympathetic ganglion neurons.10

What We Already Know About This Topic

- Genetic determinants of pain and the analgesic need after surgery are poorly defined.
- Polymorphisms of the gene SCN9A, which codes for the NaV1.7 sodium channel, are associated with certain chronic pain conditions, but whether they are important to postoperative pain is not known.

What This Article Tells Us That Is New

- In 200 patients having pancreatic surgery, the presence of the 3312T allele of SCN9A was rare (10% of the population), and was associated with 30% less opioid use and a sixfold less risk of inadequate analgesia.
- The NaV1.7 sodium channel function is important in postoperative pain and analgesia.

* Research Assistant, † Senior Resident, ‡ Professor, Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

† Senior Resident, ‡ Professor, Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Submitted for publication February 16, 2012. Accepted for publication November 7, 2012. Support was provided solely from institutional and/or departmental sources. Guangyou Duan and Guifang Xiang contributed equally to this work.

Address correspondence to Dr. Zhang: Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No.1095 Jie-Fang Road, Wuhan 430030, China. znpain@sina.com. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY’s articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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Some recent genetic studies have identified mutations in \textit{SCN9A} as contributory in three pain disorders: primary erythermalgia, paroxysmal extreme pain disorder, and congenital indifference to pain (CIP).\textsuperscript{11–19} These disorders are characterized by different pain phenotypes, ranging from complete absence of pain to extreme sensitivity to pain, and they occur rarely. Two very recent studies revealed that patients with mutations in \textit{SCN9A} develop a partial loss of pain perception.\textsuperscript{20,21} The pain perception in these patients ranged between complete absence of pain and normal sensitivity to pain.

Our research group has previously identified a novel, nonsynonymous single-nucleotide polymorphism (SNP), c.3312G>T, within exon 16 of \textit{SCN9A}, leading to the amino acid substitution V1104L in human Nav1.7, in a proband affected with CIP; this SNP was also present in normal controls.\textsuperscript{21} Given that this nonsynonymous SNP results in an amino acid change in a region of Nav1.7 that is responsible for gating, we hypothesized that this SNP may be involved in different levels of pain perception in the general population.

Thus, the present study assessed the association between the 3312G>T SNP in \textit{SCN9A} and preoperative pain perception, as well as postoperative pain sensitivity, and explored the role of this \textit{SCN9A} SNP in the prediction of individual baseline pain perception and postoperative pain sensitivity in the general population.

\section*{Materials and Methods}

\subsection*{Patients}

We had designed an overall study to explore the association between three different \textit{SCN9A} SNPs (one indentified in Chinese, two in European) and individual baseline pain perception, as well as postoperative pain sensitivity in the general population. The study protocol was approved by the Institutional Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, and the total sample size of recruited subjects was 800. The designed sample of 200 patients in the current study was one portion of the overall study and was used to investigate \textit{SCN9A} 3312G>T SNP (indentified in Chinese). Informed consent was obtained from all patients prior to study enrollment. The study was registered on ClinicalTrials.gov (ID: NCT 01507493) after completion of this portion of the overall study.

From January 2011 to October 2011, a total of 200 patients, aged 20–70 yr, who had undergone pancreatectomy under general anesthesia, were recruited into the present study. These patients were grouped based on the American Society of Anesthesiologists physical status I–II. All patients were Han Chinese and voluntarily received intravenous patient-controlled analgesia (PCA) treatment. The exclusion criteria included a known history of chronic pain, psychiatric diseases, communication disorders, diabetes mellitus, severe cardiovascular diseases, kidney or liver diseases with compromised hepatic function, alcohol or drug abuse, heavy smoking, pregnancy, or lactation.

\subsection*{Preoperative Management and Assessment of Pain Perception}

On the day before the operation, patients received information to minimize their anxiety related to the surgery. All patients were also trained to use the analgesic pump and the pain visual analog scale (VAS, 0 = no pain, 100 = unbearable pain) for postoperative pain assessment.

An electronic pressure algometer (YISIDA-DS2, Hong Kong, China) was used to measure the pressure pain threshold (PPT) and pressure pain tolerance (PTO) before surgery. A probe with a surface area of 1 cm$^2$ was applied to the lateral brachioradialis of the right elbow joint,\textsuperscript{22} and the pressure was increased at a speed of 1 kg/s. Patients were asked to inform the operators when they started to feel pain, and when pain became intolerable; these values were recorded. This procedure was repeated 10 min later, and the average of the two measurements was calculated.

\subsection*{Anesthetic and Analgesia Technique}

After patients entered the operating room, electrocardiography, mean arterial pressure, and pulse oxygen saturation were monitored. Standardized general anesthesia was performed on all patients, using 0.05 mg/kg midazolam, 2 mg/kg propofol, 0.5 μg/kg sufentanil, and 0.6 mg/kg rocuronium for anesthesia induction. Central venous pressure and arterial pressure were monitored invasively. Anesthesia was maintained with a combined intravenous and inhalation anesthesia approach: inhalation of 1% sevoflurane, infusion of remifentanil (0.2–0.4 μg·kg$^{-1}$·min$^{-1}$) and propofol (6–10 mg·kg$^{-1}$·h$^{-1}$), and intravenous boluses of 0.2 mg/kg rocuronium. The depth of anesthesia was maintained using Narcotrend (MonitorTechnik, Bad Bramstedt, Germany).

Fifteen minutes before incision, 40 mg of parecoxib sodium and 2 mg of tropisetron hydrochloride were given intravenously for postoperative pain management and prevention of postoperative nausea and vomiting, respectively. PCA was started immediately after surgery, with sufentanil at 0.5 μg/ml and tramadol 5 mg/ml, using a controlled infusion pump (BCM, BCDB-200, Shanghai, China). The pump was programmed to use a loading dose of 2 ml, background infusion at 1.5 ml/h, PCA dose of 1 ml, lockout period of 10 min, and maximal dose of 12 ml within a 1-h period.

The average duration of surgery was 300 min (SD: 60 min), and the mean amount of blood loss was 500 (250) ml. Patients were monitored for 30 min in the postanesthesia care unit.

\subsection*{Assessment and Management of Postoperative Pain}

In the first 48 h after surgery, all patients received PCA. VAS scores were recorded 6, 12, 24, and 48 h after surgery. When inadequate analgesia (defined as VAS >40)\textsuperscript{23} was present at these time points, patients were given timely treatment...
with 40 mg of parecoxib sodium. At the same time, adverse effects, such as postoperative nausea and vomiting, pruritus, respiratory depression, and sedation, were also recorded. At the end of analgesic therapy, the data of PCA pressing frequency and opioid consumption from PCA pump were also recorded.

**Genetic Analysis**

Heparin anti-coagulated blood (2 ml) was collected from a central venous catheter during the operation, and all blood samples were stored at −80°C. Genomic DNA was extracted from the blood samples using the guanidinium isothiocyanate method.

Exon 16 of SCN9A was amplified from this genomic DNA by polymerase chain reaction with primers: 5′-TTC-GTTGCTGGTTGATTTG-3′ (forward) and 5′- CTA-CATGCAATGGTTAGAAC-3′ (reverse).

Polymerase chain reaction was performed on a Gene Amp PCR System 9700 (Applied Biosystems, Foster City, CA). Thereafter, the products of polymerase chain reaction were purified, and genotyping of the SCN9A 3312G>T SNP was accomplished by direct sequencing using an ABI PRISM 377 automatic sequencer (PE Applied Biosystems, Utrecht, Netherlands).

**Statistical Analysis**

All variables were summarized using standard descriptive statistics, such as the mean, SD, and frequency. The data were grouped according to the SCN9A alleles (3312G or 3312T), and an independent-sample t test was employed to compare the differences in age, weight, height, body mass index, PPT, PTO, VAS scores, and PCA opioid consumption between the 3312G group and 3312T group. The PCA pressing frequency data was abnormally distributed; thus, t tests were performed after a natural logarithm transformation. Differences in sex, adverse effects, and inadequate analgesia between the two groups were analyzed using Pearson Chi-square tests.

An exploratory logistic regression analysis was used to evaluate the role of SCN9A 3312G>T SNP in the prediction of inadequate analgesia; for these analyses, patients were classified by age (<45 yr, 45–59 yr, ≥60 yr), sex, body mass index (underweight, normal weight, overweight), PPT (absence or presence of high PPT), and PTO (absence or presence of high PTO). The criterion for inclusion into the regression equation was \( P < 0.05 \). Odds ratios (OR), with 95% CI, were determined based on the logistic regression analysis. Statistical analyses were performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL), and a two-tailed \( P \)-value less than 0.05 was considered statistically significant.

**Results**

In total, 200 patients (113 men and 87 women), with a mean age of 52.3 (SD: 9.0) yr were recruited according to the inclusion and exclusion criteria. All patients completed the study. The demographics of the patients are shown in table 1.

The mean PPT and PTO were 3.66 (SD: 1.75) kg/cm² and 6.45 (SD: 2.60) kg/cm², respectively. Mean PPT was 4.10 (SD: 2.08) kg/cm² in men and 3.10 (SD: 0.96) kg/cm² in women \( (t = 4.565, P < 0.001) \). The mean PTO was 7.31 (SD: 2.80) kg/cm² in men and 5.44 (SD: 1.84) kg/cm² in women \( (t = 5.687, P < 0.001) \).

Patients were divided into two groups based on the presence of SCN9A alleles: 178 patients were homozygous for the major 3312G allele, while 22 patients were heterozygous for the minor 3312T allele (fig. 1). Thus, the frequency of the SCN9A 3312T allele was 5.5% (22/200) in the present study. There were no significant differences in weight, height, body mass index, sex, PPT, and PTO between the two groups (table 1). The patients in the 3312T group were older than those of the 3312G group \((55.6 \text{ [SD: 9.3]} \text{ vs. } 51.9 \text{ [SD: 9.3]}, P = 0.008; \text{table 1})\). However, the proportion of patients in different age groups was comparable between the 3312G and 3312T groups \(<45 \text{ yr: } 23.6\% \text{ vs. } 27.3\%; 45–59 \text{ yr: } 9.0\% \text{ vs. } 0.0\%; \geq 60 \text{ yr: } 67.4\% \text{ vs. } 72.7\%; \chi^2 = 2.12, P = 0.347\).

There were no significant differences in the VAS scores 6, 12, 24, and 48 h after surgery between the two groups (table 1). The distribution of data from PCA pump was shown in figure 2. Statistical analysis showed that the average PCA pressing frequency and opioid consumption within 48 h after surgery in the 3312G group were significantly higher than those of the 3312T group \((2.70 \text{ [SD: 0.84]} \text{ vs. } 2.05 \text{ [SD: 0.43]}, P = 0.001; 100.8 \text{ [SD: 40.7]} \text{ vs. } 74.8 \text{ [SD: 20.8]} \text{ ml}, P = 0.006; \text{table 1})\).

No respiratory depression or pruritus was found in the present study. Postoperative nausea and vomiting was noted in 17 patients \((17/200, 8.5\%\), including 15 \((15/178, 8.4\%\) in the 3312G group and 2 \((2/22, 9.1\%\) in the 3312T group. There was no significant difference in the incidence of adverse effects between the two groups \((8.4\% \text{ vs. } 9.1\%, P = 0.842; \text{table 1})\).

Postoperative inadequate analgesia was observed in 53 patients \((53/200, 26.5\%\), including 50 \((50/53, 94.3\%\) at 6 h, 2 \((2/53, 3.8\%\) at 12 h, and 1 \((1/53, 1.9\%\) at 24 h after surgery. Among these patients, 52 \((52/178, 29.2\%\) carried homozygous 3312G allele and 1 \((1/22, 4.5\%\) carried heterozygous 3312T allele. The incidence of inadequate analgesia in the 3312G group was significantly higher than that of the 3312T group \((29.2\% \text{ vs. } 4.5\%; P = 0.013; \text{table 1})\).

To determine which factors could be used in postoperative pain prediction, univariate logistic regression analysis was performed using the 3312G>T SNP, sex, age, PPT, PTO and body mass index as independent variables, and inadequate analgesia as the dependent variable. Results of this analysis are shown in table 2. Only the 3312G>T SNP and PPT were significant predictors of inadequate analgesia \((P = 0.037 \text{ and } 0.034, \text{ respectively; table 2})\).

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An overall logistic regression model was fitted to the data based on these results, with the 3312G>T SNP and PPT as predictors; as summarized in table 3, this model was significant ($P = 0.001$). This indicated that the 3312G>T SNP and PPT could be used as predictors of inadequate analgesia ($\text{OR} = 0.10, 95\% \text{ CI}: 0.01 \text{ to } 0.76, P = 0.026; \text{OR} = 0.32, 95\% \text{ CI}: 0.13 \text{ to } 0.82, P = 0.018$; table 3). The ORs were determined based on the probability of the occurrence of inadequate analgesia in patients with different 3312G>T alleles or different PPTs. The likelihood of patients in the 3312T group presenting with inadequate analgesia was lower than in the 3312G group. Patients showing a higher PPT in the preoperative assessment of pain perception also had a lower chance of presenting with inadequate analgesia than those with a low preoperative PPT. The standard regression coefficients of the 3312G>T SNP and PPT in the model were 1.256 and 0.811, respectively.

### Discussion

The current study is the first to investigate the role of the novel SCN9A 3312G>T SNP in the modulation of postoperative pain sensitivity in patients from the general population. Our results demonstrate that postoperative PCA pressing frequency and PCA opioid consumption 48 h after surgery in patients carrying the 3312T allele were noticeably lower than in those carrying 3312G allele. We also demonstrate for the first time that patients carrying the 3312G allele had a higher incidence of inadequate postoperative analgesia than those carrying the 3312T allele.

Three hereditary pain disorders have been linked to mutations in the voltage-gated sodium-channel Nav1.7, which is encoded by SCN9A; however, patients with these pain syndromes are extremely rare. Diatchenko et al. suggested that the discovery of those genetic loci that produce quantitative rather than qualitative changes in gene function may clarify the causes of less severe but more frequent human pain conditions. We have previously identified a novel SCN9A 3312G>T variant in individuals in whom pain perception was partially ablated, as well as in 100 healthy controls. This led us to investigate whether there was any association between the SCN9A SNP and postoperative pain sensitivity. To control for other factors that may influence postoperative pain, all patients in this study underwent the same type of operation, viz., pancreatectomy, under general anesthesia, following a preoperative information session, and postoperative PCA, following the same analgesic protocol. The flexibility of PCA allows patients to titrate their own opioid dose, and generally provides adequate analgesia.
postoperative pain control. In addition, patients received timely treatment with 40 mg of parecoxib sodium when inadequate analgesia presented. Thus, the average postoperative VAS scores of all patients in the 3312G group and in the 3312T group were controlled at less than or equal to 30, and no statistically significant difference was observed in the VAS scores between the two groups.

However, we found that even with titration to the same approximate postoperative pain level, the PCA pressing frequency and opioid consumption of patients with the 3312T allele were less than those of patients with the 3312G allele. PCA is also an indirect pain assessment method; PCA pressing frequency reflects the patient's subjective analgesic requirements, while PCA opioid consumption corresponds to the patient's actual demand for relief of postoperative pain. Therefore, we conclude that the 3312G>T variant modulates patients' postoperative pain sensitivity; in particular, the 3312T allele is associated with a lesser degree of postoperative pain experience, following a similar surgical stimulus for pain.

Table 3. Overall Logistic Regression Model Based on 3312G>T SNP and PPT as Preoperative Predictors of Postoperative Inadequate Analgesia

<table>
<thead>
<tr>
<th>Preoperative Predictors</th>
<th>Chi-square</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>8.45</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3312G&gt;T SNP</td>
<td>4.93</td>
<td>0.026</td>
<td>0.10</td>
<td>0.01 to 0.76</td>
</tr>
<tr>
<td>PPT</td>
<td>5.61</td>
<td>0.018</td>
<td>0.32</td>
<td>0.13 to 0.82</td>
</tr>
</tbody>
</table>

OR = odds ratios; PPT = pressure pain threshold; SNP = single-nucleotide polymorphism.

Nevertheless, our findings revealed that there were no statistically significant differences in PPT or PTO between the 3312G group and the 3312T group. These findings indicated that the individuals carrying different SCN9A 3312 G>T alleles showed similar sensitivity to pressure stimulation. The experimental stimulation methods typically used for assessment of pain perception include mechanical stimulation, electrical stimulation, heat or cold stimulation, etc. Pressure stimulation, which is classified as mechanical stimulation, can be monitored, is easily applied for evaluating tenderness, and is typically a method more acceptable to patients. Thus, in our subjects, only the pressure algometer was chosen to evaluate preoperative individual basal pain perception. In addition, even those studies that have used several different experimental stimulation methods to investigate the basal pain perception of patients with CIP caused by SCN9A mutations found that not all painful stimulus tests showed differences between CIP and non-CIP individuals. Thus, further studies on healthy individuals, using additional experimental stimulation methods, may be required.

However, our logistic regression analysis data indicated that patients showing a high PPT had a lower likelihood of presenting with inadequate analgesia, with an OR of 0.32 (95%CI: 0.13 to 0.82). What is more, we found that the SCN9A 3312T allele can predict a lower risk of postoperative inadequate analgesia with an OR of 0.10 (95%CI: 0.01 to 0.76). Comparison of the standard regression coefficient of the two predictive factors (SCN9A 3312G>T SNP vs. high PPT, 1.256 vs. 0.811), indicates that the SCN9A 3312G>T SNP is more strongly predictive than the preoperative pain tests for predicting postoperative inadequate analgesia. Thus, our results also imply that predicting postoperative pain at the gene level may be more promising than conventional methods.
The current study demonstrated that patients with the 3312T allele required less analgesic use to control postoperative pain and had a lower risk of presenting with inadequate analgesia. This may allow us to implement a preoperative genetic screening to distinguish those individuals at high risk of experiencing postoperative excessive analgesia. Moreover, two recent studies found that a \( SCN9A \) SNP (rs6746030), with a frequency of about 10% in control subjects, was associated with increased pain perception; the functional effect of this SNP was confirmed in HEK293 cells by patch-clamp experiments.\(^{25,31}\) Thus, patients with this variant may be likely to experience postoperative inadequate analgesia, although in this study, we have not investigated the role of this particular SNP in postoperative pain.

On the basis of these previous findings and the results we present here, we speculate that, in the general population, there may be a "skewed state of pain perception," where the function of Nav1.7 is partially altered so as to decrease or increase the individual's sensitivity to pain. Further studies will be needed to clarify the effect of the V1104L substitution on the electrophysiological function of Nav1.7, as well as to confirm the association between SNP rs6746030 and postoperative pain. This may eventually lead to alternative methods for predicting the risk of experiencing postoperative excessive or inadequate analgesia.

In conclusion, a decrease in sensitivity to postoperative pain was associated with the SNP of \( SCN9A \) 3312G>T. Patients carrying the \( SCN9A \) 3312T allele presented here, we speculate that, in the general population, there may be a "skewed state of pain perception," where the function of Nav1.7 is partially altered so as to decrease or increase the individual's sensitivity to pain. Further studies will be needed to clarify the effect of the V1104L substitution on the electrophysiological function of Nav1.7, as well as to confirm the association between SNP rs6746030 and postoperative pain. This may eventually lead to alternative methods for predicting the risk of experiencing postoperative excessive or inadequate analgesia.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

“Summer of 1943” Class Portrait of “90-Day Wonders”

Necessity was certainly the mother of invention during World War II. Shortages of physicians with “militarily useful” surgical specialties, like anesthesiology, led to accelerated medical schooling and specialization. In Rochester, Minnesota, the Mayo Clinic sponsored one such program from June through September of 1943. Left-to-right above the class portrait are closeup photoportraits of Instructors J.S. Lundy and R.C. Adams, and then trainees identified as C. L. P. Hebert, W. R. Miller, J. G. Kurfees, W. F. Fitzpatrick, and D. D. Goldthwaite. Beneath the class picture are left-to-right portraits of trainees H. H. Hyndman, M. L. Berlowe, Conrad DeLateur, Harry Meyer, “W. D. Rhu Jr,” W. D. Futch, and R. F. Stappenbeck. A class view of a dozen of anesthesiology’s “90-day wonders”!

George S. Bause, M.D., M.P.H., Honorary Curator, ASA’s Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.