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# The Effect of *SCN9A* Variation on Basal Pain Sensitivity in the General Population: An Experimental Study in Young Women

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**Abstract:** ***SCN9A* is a key player in various rare monogenic pain disorders, including absence of pain or extreme pain, indicating that *SCN9A* is critical in human pain perception. This study aimed to investigate the association between the single-nucleotide polymorphisms (SNPs) in *SCN9A* and basal pain sensitivity variability in the general population. We used a combined tag and candidate SNP approach to explore possible associations between *SCN9A* SNPs and basal pain sensitivity in 309 healthy female Chinese undergraduates. Mechanical and heat pain sensitivity were measured, and a total of 28 SNPs were included in the final correlation analysis. Four candidate SNPs (rs6746030, rs7595255, rs12622743, and rs11898284) and 10 tag SNPs were associated ($P < .05$) with different pain perception phenotypes and exhibited opposite effects, resulting in either hypersensitivity or hyposensitivity. Furthermore, of all these SNPs, rs16851778 showed the strongest significant ($P = .003$) association with lower mechanical pain sensitivity, which was strengthened in a subsequent replication sample with 260 young patients scheduled for elective gynecological surgery. These findings provided evidence that the variability of basal pain sensitivity was associated with *SCN9A* polymorphisms in the general population.**

***Perspective:** This study demonstrated that several candidate and tag* SCN9A *SNPs were associated with hypersensitivity or hyposensitivity to basal experimental pain stimulation. Moreover, we identified a novel SNP, ie, rs16851778, that was associated with lower mechanical pain sensitivity and that was strengthened in a subsequent replication sample.*



***Key words:*** SCN9A*, single-nucleotide polymorphisms, pain perception, variability, general population.*

A high degree of interindividual differences in pain sensitivity and reporting of pain have been observed in the clinical setting.[24,40] This variability in pain perception, whereby some patients are hypersensitive and others are hyposensitive, could contribute to the varying efficacies of clinical pain treatment[1] and susceptibility to chronic pain.[28] Moreover, such differences in individual pain perception are likely caused by the complex interactions among environmental and demographic factors.[3,12,20,36] However, even when accounting for the variability explained by these factors, individual differences remain; genetic variation has been shown to explain a significant portion of this remaining variability.[4,25,44] Understanding the effect of genetic variation on human pain perception may lead to more individualized pain treatment for patients.[44]

*SCN9A* encodes the voltage-gated sodium-channel type IV-$\alpha$ subunit (Nav1.7) and is predominantly expressed in dorsal root ganglion neurons and sympathetic ganglion neurons.[5,39] Genetic and functional studies have shown that Nav1.7 is a major contributor to pain signaling and pain disorders in humans.[12,29] Inactive mutations in *SCN9A*, which cause loss of function of Nav1.7, result in congenital insensitivity to pain,[8,45] whereas gain-of-function mutations in this gene produce distinct pain syndromes, such as inherited erythromelalgia and paroxysmal extreme pain disorder.[7,9]

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Furthermore, some genetic polymorphisms in *SCN9A* have recently been shown to contribute to the risk or severity of common pain phenotypes.[15,34,35] For example, our research group previously found that a nonsynonymous single-nucleotide polymorphism (SNP), rs4369876 (c. 3312G>T), may decrease postoperative pain sensitivity in patients undergoing surgery.[15] In contrast, another study[34,35] reported that rs6746030 (c. 3789G>A) was associated with increased pain in patients with chronic pain syndrome. Based on these findings, we hypothesized that *SCN9A* polymorphisms may contribute to the observed varying states of basal pain perception, ie, reducing or enhancing pain sensitivity in the general population.

Although some studies have recently investigated the association between *SCN9A* SNPs and the pain phenotype,[15,22,34,42] most of these studies have focused on only 1 or certain SNPs, and the participants in these studies often had underlying diseases or chronic pain, which made it difficult to investigate the effects of *SCN9A* on participants' original pain sensitivity. Thus, in the current study, we used a combined candidate and tag SNP approach to explore possible associations between *SCN9A* SNPs and basal pain perception, as evaluated by experimental methods in healthy female undergraduates. The novel findings were then replicated in an independent sample in patients scheduled for elective gynecological surgery using similar entry criteria. Through this study, we aimed to assess the potential effects of *SCN9A* SNPs on the variability of basal pain sensitivity in the general population.

# Methods

## Participants

The study protocol was approved by the institutional ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (registration ID 20121201). Written informed consent was obtained from all participants before the study.

As shown in Fig 1, the primary sample was used to explore the potential effects of tag and candidate *SCN9A* SNPs on pain sensitivity. A total of 319 pain-free, unrelated women (age range, 18–29 years), who were all Han Chinese, were recruited in the primary study population. All participants were healthy undergraduates at Tongji Medical College, Huazhong University of Science and Technology. Participants were included in the study if they met the following inclusion and exclusion criteria. The inclusion criteria were 1) right-hand dominant and 2) nonsmokers. The exclusion criteria were 1) use of any analgesic medication within the 4 weeks before the study; 2) alcohol or drug abuse; 3) pregnancy or lactation; 4) presence of dermatitis or damaged, red, or swelling skin at the selected testing locations.

To verify the findings of the primary study population, we included an independent sample using similar entry criteria. In the replication sample, 266 Han Chinese women (age range, 18–29 years) who were scheduled for elective gynecological surgery were recruited. All the patients in the current sample were restricted to American Society of Anesthesiologists physical status I.

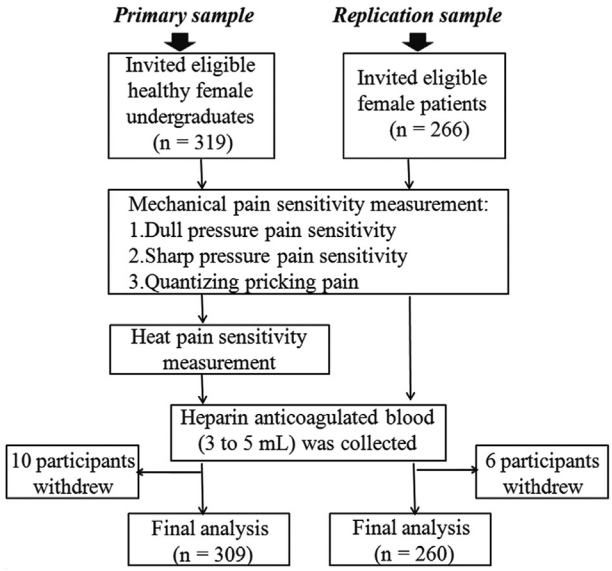


**Figure 1.** Flow diagram of the study.

## Design

In this study, the primary sample population was designed to validate the effects of candidate *SCN9A* SNPs and to explore the effects of tag SNPs on basal pain sensitivity; an independent sample population was included to replicate the results of the primary population. In the primary study population, we detected the pain perception of all participants through experimental pain measurement in a sequential manner as follows. Mechanical pain sensitivity, including dull pressure pain sensitivity, sharp pressure pain sensitivity, and quantizing pricking pain (QPT), were examined. Heat pain sensitivity was analyzed through withdrawal latency time (WLT) for heat radiation. These 2 measurements were determined by different investigators (S.G., Y.Y., L.Z., and P.H.), and standardized instruction and an initial trial of the mechanical and heat pain sensitivity measurements were performed at the outset of each testing session to familiarize the participants with the testing procedure.

Because the results of the primary study showed that the tag SNP rs16851778 was associated with 1 type of mechanical pain sensitivity with the strongest significance, the association between this SNP and mechanical pain sensitivity was preferentially examined in the replication cohort. The strongest $\beta$ weights for the associations with experimental pain sensitivity were found in candidate SNPs. Therefore, in the current study, the replication sample was used only for detection of the tag SNP rs16851778 and testing of mechanical pain sensitivity. The same standardized procedure for mechanical pain measurement used in the primary study population was performed for all patients before surgery.