Case-Control Study

Identification of Candidate Genes Associated with Postherpetic Neuralgia Susceptibility

Xiufang Xing, MD, Yongyu Bai, MD, Kai Sun, MD, Qunshan Chen, MD, Hao Huang, MD, Weidong Qiu, MD, and Min Yan, MD

From: Department of Anesthesiology and Pain Medicine, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Address Correspondence:
Min Yan, MD
Department of Anesthesiology and Pain Medicine, Second Affiliated Hospital, Zhejiang University School of Medicine
No. 88 Jiefang Rd
Hangzhou, China 310009
E-mail: zryanmin@zju.edu.cn

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 09-12-2019
Accepted for publication: 11-07-2019

Free full manuscript: www.painphysicianjournal.com

Background: Postherpetic neuralgia (PHN) is one of the most common complications of herpes zoster (HZ). Heritable factors have been found to play a role in various clinical pain symptoms. However, the effect of gene variability on the susceptibility of PHN remains poorly understood.

Objectives: The aim of this study was to evaluate whether genetic variation in pain pathway genes was associated with PHN susceptibility in the Chinese population.

Study Design: Case–control study.

Setting: Department of Anesthesiology and Pain Medicine in a university hospital.

Methods: Seventy patients with PHN and 111 patients with HZ without developing PHN were enrolled. All patients received standardized antiviral agents and analgesics as needed during the acute phase of HZ. Twenty-four candidate genetic polymorphisms in 12 genes (IL1B, SCN9A, KCNK9, TRPV1, P2RX7, HTR1A, HTR2A, ADRB1, ADRB2, BDNF, COMT, and OPRM1) were genotyped in all patients. Multivariable logistic regression analyses were used to identify genetic variations associated with PHN susceptibility while controlling for potential confounders.

Results: Our results suggested that only variation in P2RX7 gene was associated with PHN susceptibility. The P2RX7 rs7958311 AG heterozygous genotype carriers had a decreased risk for PHN in the overdominant model (odds ratio [OR], 0.40; 95% confidence interval [CI], 0.21–0.77; $P = 0.005$), and codominant model (OR, 0.44; 95% CI, 0.20–0.98; $P = 0.045$). The P2RX7 rs7958311 GG homozygote genotype was associated with an increased risk for PHN under a recessive model (OR, 2.15; 95% CI, 1.01–4.56; $P = 0.046$). There were no significant associations between the other 23 single-nucleotide polymorphisms and PHN susceptibility.

Limitations: Lack of validation cohort to verify the findings.

Conclusions: In the present study in the Chinese population, we found purinergic receptor P2X7 rs7958311 may contribute to PHN development after HZ. Future larger independent cohorts are warranted to replicate these initial findings.

Key words: Herpes zoster, postherpetic neuralgia, polymorphisms

Pain Physician 2020: 23:E281-E288

Postherpetic neuralgia (PHN) is a chronic neuropathic pain syndrome after an outbreak of shingles (1). The pain is characterized by constant burning or stabbing sensation, paroxysmal lancinating pain, allodynia, and hyperalgesia (2). This painful condition can persist for months or even years and profoundly cause physical disability, emotional distress, and interference with daily activities (3).

Although little is known about the pathogenesis of PHN, it is certain that varicella zoster virus affects the peripheral and central nervous systems, subsequently leading to the occurrence of PHN (4). Injury to sensory

nerves induces plasticity changes in afferent and central neurons. Alteration of gene expression is a key factor of neurons biochemical, physiological, and anatomic modifications (5). Recent studies have shown that heritable factors play a role in experimental pain and various clinical pain symptoms (6-9).

The genes encoding voltage-gated sodium channels (SCN9) (10-12), potassium voltage-gated channels (KCNK9) (9,13), transient receptor potential vanilloid 1 (TRPV1) (14,15), and P2X purinoceptor 7 (PTRX7) (16,17) are involved in the modulation of nociceptive processing and their variants associated with several pain phenotypes. The gene involved in inflammatory signaling (IL1B) was associated with the intensity of pain (18). Moreover, the serotonergic and adrenergic system are receiving increasing attention due to their known role in nociceptive pathway (19). The genetic variability related to the enzyme catechol-O-methyltransferase (COMT) (20), brain derived neurotrophic factor (BDNF) (21), and opioid receptor mu 1 (OPRM1) (22) influence pain sensitivity and analgesic requirements.

Proposed risk factors for PHN include older age, greater acute pain severity, greater rash severity, perceptual processes, and genetic background (2,23-25). Sato-Takeda et al (26) reported the human histocompatibility leukocyte antigens (HLA), A33 and B44, and the HLA-A33-B44 haplotype were associated with the development of PHN. The frequency of HLA-A33-B44 haplotype was significantly higher in the patients with PHN than in the healthy controls. Chung et al (27) found the similar positive association of HLA-B*44:03 with PHN in Koreans. The aforementioned genetic analyses were all focused on the immune system, however, the effect of gene variability involved in pain perception, and modulation on the susceptibility of PHN remains poorly understood.Thus we hypothesized that the pain-related genes identified for other common pain syndromes would also play a role in PHN susceptibility.

The aim of this study was to examine the association of genetic variability in 12 genes related to inflammation, neuronal regulation, ion channel, serotonin, adrenaline, catecholamine, and opioid pathway with the susceptibility of PHN in the Chinese population.

Methods

Study Population

The study protocol was reviewed and approved by the institutional review boards of the Second Affiliated Hospital of Zhejiang University, School of Medicine, and the protocol was registered in the ClinicalTrials.gov Registry (NCT03708653). The study patients were recruited from consecutive patients with a clinically proven herpes zoster (HZ) or PHN diagnosis presenting to the Department of Dermatology or Pain Clinic between April 2018 and February 2019. Other inclusion criteria for the study included age ≥ 50 years, pain intensity of at least 4 on a 0 to 10 Numeric Rating Scale (NRS-11; 0 = no pain, 10 = the worst imaginable pain), and nontrigeminal herpetic rash. We excluded patients who did not receive appropriate antiviral therapy during the acute phase of HZ, or who had malignant tumor, or who were currently receiving or have recently received immunosuppressive or cytotoxic treatment. All patients had written informed consent prior to participation.

Data Collection and Outcome Measure

At baseline, demographic and clinical variables including age, gender, prodromal signs and symptoms, localization and severity of the herpetic rash, pain intensity, and comorbid diseases were recoded. Acute pain intensity was defined as the most severe pain from the prodromal phase to the first 2 weeks after rash onset (25).

Patients with HZ were followed up for at least 3 months to determine whether they developed PHN or not. PHN was defined as the presence of pain with NRS-11 ≥ 3 after 90 days of rash onset. A patient with pain intensity of NRS-11 < 3 or a patient whose treatment is terminated owing to pain disappearance was defined as non-PHN (28).

Genotyping

Approximately 2 mL of saliva was collected from patients using an Oragene DNA sample collection kit (Oragene DNA Self-Collection Kit, tube format OG-500; DNA Genotek Inc., Kanata, Ontario, Canada). Samples were stored at room temperature (approximately 5–10 weeks). Genomic DNA was extracted from saliva for genetic analysis by using Rapid saliva DNA Kit (Biomed Corporation, Shanghai, China) according to the manufacturer's recommendations. Single-nucleotide polymorphisms (SNPs) were genotyped using a KASP genotyping assay (Rui Biotechnology, Beijing, China) as previously described (29,30).

Quality control was performed to ensure the robust genetic association: SNPs with call rates of < 95%, minor allele frequency (MAF) < 0.05, or Hardy-Weinberg equilibrium (HWE) of $P < 0.05$ were excluded. Linkage disequilibrium (LD) was calculated from the patients'

genotypes. When strong LD ($r^2 > 0.9$) was present in one gene, we only included one SNP from each pair of SNP in the association study. Finally, there were 24 SNPs among the 12 candidate genes that passed all quality control filters (Table 1).

Statistical Analyses

Statistical analyses were completed with the SPSS 24.0 (IBM Corporation, Armonk, NY). Continuous variables were expressed as means and standard deviations or as medians and interquartile range, and categorical variables as counts and percentages. Differences between 2 groups were evaluated by the Student t-test or the Mann–Whitney U test was used to comparequantitative variables, and the chi-squared test or the Fisher exact test was used to compare categorical variables. For analyzing the association between SNPs and PHN susceptibility, odds ratios (ORs) and 95% confidence intervals (CI) were calculated by logistic regression analysis adjusted for potential risk factors including age, gender, and rash severity. Four genetic models (codominant, dominant, recessive, and overdominant) were evaluated for association of polymorphisms with risk of PHN. HWE, pairwise LD, and SNP haplotype analyses was assessed by SNPStats software (free web-based tool found online at http://bioinfo.iconcologia.net/SNPstats) (31). *P* values < 0.05 were considered significant.

Table 1. *Description of all SNPs analyzed.*

Gene	SNP	Chr.	Function	Position	Alleles	MAF	HWE *P*-value
COMT	rs4680	22	Missense	19951271	G>A	0.25	0.24
BDNF	rs6265	11	Missense	27679916	C>T	0.47	0.77
OPRM1	rs1799971	6	Intron	154039662	A>G	0.35	0.41
HTR1A	rs6295	5	Near-gene	63962738	C>G	0.22	0.19
HTR2A	rs6313	13	Intron	46895805	G>A	0.39	0.76
	rs2070037	13	Intron	46892935	T>C	0.33	0.50
	rs985933	13	Intron	46881728	A>G	0.33	0.87
	rs927544	13	Intron	46881916	G>A	0.28	0.58
	rs12584920	13	Intron	46890902	G>T	0.08	1.00
	rs9316233	13	Intron	46859220	C>G	0.23	0.68
	rs17289394	13		46899085	G>A	0.10	0.67
ADRB2	rs1042714	5	Missense	148826910	G>C	0.12	0.48
	rs11959113	5		148848933	G>A	0.28	1.00
ADRB1	rs1801253	10	Missense	114045297	G>C	0.25	0.85
TRPV1	rs8065080	17	Missense	3577153	T>C	0.37	1.00
	rs222747	17	Missense	3589906	C>G	0.40	0.21
SCN9A	rs4286289	2	Intron	166305201	C>A	0.41	0.76
	rs11898284	2	Intron	166325017	A>G	0.22	1.00
	rs16851778	2	Intron	166204799	A>G	0.38	0.53
KCNK9	rs2014712	8	Intron	139628391	C>T	0.28	0.27
	rs3780039	8	Intron	139664421	A>C	0.16	0.41
	rs11166921	8	Intron	139695512	A>C	0.38	0.75
IL1B	rs1143627	2	Coding-synon	112832813	G>A	0.45	0.77
P2RX7	rs7958311	12	Intron	121167552	G>A	0.49	0.14

Abbreviations: ADRB1 = adrenoceptor beta 1; ADRB2 = adrenoceptor beta 2; BDNF = brain derived neurotrophic factor; Chr. = chromosome; COMT = catechol-O-methyltransferase; HTR1A = 5-hydroxytryptamine receptor 1A; HTR2A = 5-hydroxytryptamine receptor 2A; HWE = Hardy-Weinberg equilibrium; IL1B = interleukin 1 beta; KCNK9 = potassium two pore domain channel subfamily K member 9; MAF = minor allele frequency; OPRM1 = opioid receptor mu 1; P2RX7 = purinergic receptor P2X 7; SCN9A = sodium voltage-gated channel alpha subunit 9; SNP = single nucleotide polymorphism; TRPV1 = transient receptor potential cation channel subfamily V member 1.

Results

Characteristics of Study Population

The study population comprised 181 patients, including 111 patients with HZ without subsequent PHN and 70 patients with PHN. The overall demographic and clinical characteristics are shown in Table 2. The baseline cohort comprised 95 women (52.5%) and 86 men (47.5%), aged 50 to 86 years (mean 65.5 years). Compared with non-PHN, patients with PHN were significant older, more men, and more likely to suffer from severe rash. These variables were included as covariates in the regression model.

Genotypic and Allelic Frequencies in Patients With and Without PHN

The genotyping of 2 SNPs, rs6432896 (SCN9A), and rs2053044 (ADRB2), did not meet the HWE criterion. In addition, the rs6314 (HTR2A), rs6746030 (SCN9A), and rs1143634 (IL1B) had a very low MAF ($P < 0.05$). Strong LDs in HTR2A, SCN9A, and IL1B (Supplemental Fig. S1) were identified in our sample, and we included only one SNP from each pair of SNPs in the association study. Thus 24 SNPs were assessed for further association analysis.

The distribution of the allele and genotype frequencies for the remaining 24 SNPs in patients with and without PHN is summarized in Supplemental Table S1. The frequencies of rs7958311 (P2RX7) genotypes in patients with PHN (AA 27.1%, AG 42.9%, and GG 30%) differed significantly from those in patients without PHN (AA 19.8%, AG 64%, and GG 16.2%) ($P = 0.016$). The other 23 SNPs were not significantly different between patients with and without PHN (all $P > 0.05$).

Table 2. *Demographic and clinical data of patients with or without PHN.*

Characteristics	Non-PHN (n = 111)	PHN (n = 70)	*P*-value
Age	64.2 ± 8.6	67.7 ± 9.7	0.012
Male, n (%)	46 (41.4)	40 (57.1)	0.039
Prodromal pain, n (%)	89 (80.2)	49 (70.0)	0.117
Duration of prodromal pain, day	3 (1.8-4.0)	3 (0-4)	0.856
Intense of prodrome	4.3 ± 2.8	3.8 ± 3.1	0.313
Delay in diagnosis	2 (1-4)	2 (1-4)	0.872
Rash location, n (%)			0.698
Cervical	20 (18.0)	10 (14.3)	
Thoracic	74 (66.7)	52 (74.3)	
Lumbar	11 (9.9)	6 (8.6)	
Sacral	6 (5.4)	2 (2.9)	
Severe rash, n (%)	53 (47.7)	48 (68.6)	0.006
Pain intensity	5.7 ± 2.5	6.0 ± 2.8	0.392
Diabetes Mellitus	12 (10.8)	12 (17.1)	0.221

Abbreviations: PHN = postherpetic neuralgia

Genotypes of SNPs and the Risk of PHN

The potential associations between polymorphisms and PHN were examined based on different genetic models. After adjustments for age, gender, and rash severity, only rs7958311 (P2RX7) out of 24 SNPs were significantly associated with PHN. Compared with the AA and GG genotypes, the heterozygous genotype AG appeared to decrease the risk for PHN in the overdominant model (OR, 0.40; 95% CI, 0.21–0.77; $P = 0.005$), and dominant model (OR, 0.44; 95% CI, 0.20–0.98; $P = 0.045$). However, the genotype GG may be associated with a higher risk for PHN under a recessive model (OR, 2.15; 95% CI, 1.01–4.56; $P = 0.046$) compared with the AA and AG genotypes (Table 3).

Haplotype Analysis

We analyzed haplotypes effects in HTR2A, SCN9A, ADRB2, TRPV1, KCNK9, but did not find any statistically significant results for PHN susceptibility (data not shown).

Discussion

Although a few studies have been conducted to identify the contribution of genetic variants to PHN risk, data of genetic variants in the pain pathways on the susceptibility of PHN are still lacking. We investigated 24 SNPs in 12 pain-related genes that are associated with other pain syndromes to increase the knowledge of genetic influences on PHN. After multivariable logistic analysis, associations between P2RX7 and persistent herpetic pain were identified.

The P2X7 receptor is a trimeric ion channel activated by extracellular adenosine 5′-triphosphate (17). P2RX7 is expressed in peripheral and central nervous systems and the immune system, which mediates and modulates pain (gene atlas, http://biogps.org). Normally, P2X7 receptors only allow small ions, such as K+ or Ca^{2}+, to pass. However, with prolonged activation, P2RX7 can switch to pore function, allowing passage of larger molecules (32). Recently, P2RX7 function has been found to be associated with chronic neuropathic and inflammatory pain. In patients with neuropathic

Table 3. *Logistic regression analyses of associations between P2RX7 rs7958311 and risk of PHN.*

Polymorphism	Genotype	Non-PHN n (%)	PHN n (%)	Adjusted OR[a] (95%CI)	*P*-value
Codominant	AA	22 (19.8%)	19 (27.1%)	1.00	
	AG	71 (64.0%)	30 (42.9%)	0.44 (0.20-0.98)	0.045
	GG	18 (16.2%)	21 (30.0%)	1.22 (0.48-3.09)	0.674
Dominant	AA	22 (19.8%)	19 (27.1%)	1.00	
	AG+GG	89 (80.2%)	51 (72.9%)	0.60 (0.28-1.27)	0.180
Recessive	AA+AG	93 (83.8%)	49 (70.0%)	1.00	
	GG	18 (16.2%)	21 (30.0%)	2.15 (1.01-4.56)	0.046
Overdominant	AA+GG	40 (36.0%)	40 (57.1%)	1.00	
	AG	71 (64.0%)	30 (42.9%)	0.40 (0.21-0.77)	0.005

[a] Adjusted for age, sex, rash severity

Abbreviations: CI = confidence interval; OR = odds ratio; PHN = postherpetic neuralgia; P2RX7 = purinergic receptor P2X 7.

pain, P2RX7 upregulated in both injured nerves and dorsal root ganglia (33). In neuropathic and inflammatory pain models, the hypersensitivity to both mechanical and thermal stimuli was completely absent in mice lacking p2x7 receptor (33).

Human P2RX7 variants can change protein expression or functionality, leading to loss-of-function (LOF) (34,35) and gain-of-function phenotypes (36,37). The SNP rs7958311 changes G to A, resulting in the alteration of arginine to histidine at position 270 of P2X7 receptor. A recent report showed carriers of the LOF His270 allele at rs7958311 (R270H) reported less pain intensity than carriers of the Arg270 allele in patients with chronic pain (38). Kambur et al (17) found that minor allele homozygotes (AA) reported lower pain intensity compared with the main allele homozygotes (GG) (AA vs. GG: $P = 0.027$). Heterozygous carriers did not differ from main allele homozygotes (AG vs. GG: $P = 0.98$) in postoperative pain during the first postoperative week. In the present study, our results suggested that the heterozygous carriers had lower risk of PHN compared with the homozygotes of AA and GG genotypes (AG vs. AA/GG, $P = 0.005$). However, we did not compare the pain intensity between different genotypes of rs7958311.

A mechanism-based, pharmacodynamic response study found that patients with PHN who carried the common Nav1.7 R1150W polymorphism responded better to TV-45070 (an inhibitor of the sodium channel Nav1.7) than the wild type carriers (39). Because of the small number of patients who provided a DNA sample for genetic analysis, no inferential analyses were performed in the study. Although it has been reported that the receptors associated with pain upregulated and the proportion of potassium voltage-gated channels and voltage-gated sodium channels increased in patients with PHN (40), no relationship between genetic variability in these genes and PHN susceptibility was observed in our study.

In the present study, the statistical power to detect an OR of 0.44 with a type 1 error rate of 0.05 was 95% for rs7958311 under codominant inheritance mode. Power estimates were calculated using QUANTO (University of Southern California, Los Angeles, CA). For multiple tests, the *P* value thresholds should be adjusted by Bonferroni correction. However, because of the exploratory nature of this study and the modest sample size, the association *P* value would not be likely to exceed the adjusted threshold ($P < 0.002$). We believe the genes investigated herein are strong biologic candidates, and further replication of these genes in other cohorts is needed to confirm the details.

There are some limitations in the present study. First, we did not analyze psychological aspects, which may have influenced the transition to PHN (41,42). Second, the candidate genes investigated herein were common functional SNPs. Other SNPs that have potential effects on the susceptibility of PHN may have not been studied. Further genome-wide association studies may provide a more comprehensive understanding of PHN susceptibility. Finally, although the sample size in the present study provides a sufficient statistical power to detect significant associations, it is still too small to avoid false-positive findings caused by multiple tests. We now are replicating the study in a validation cohort to confirm our findings.

Conclusions

We found a protective role of the variant genotype (AG) in P2RX7 gene to PHN. Our findings will help improve the understanding of the pathogenesis of PHN and may contribute to the prognosis of whether a HZ patient will develop PHN, and thus perform appropriate individual treatment.

Acknowledgments

Authors' contributions: Drs. Xiufang Xing and Yongyu Bai had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Dr. Min Yan designed the study protocol. Drs. Xiufang Xing and Kai Sun managed the literature searches and summarized previous related work and wrote the first draft of the manuscript. Drs. Qunshan Chen, Hao Huang, and Weidong Qiu collected the data. Dr. Min Yan provided revision for intellectual content and final approval of the manuscript.

Supplemental Figure and Tablesavailable at www.painphysicianjournal.com

Supplemental Figure 1

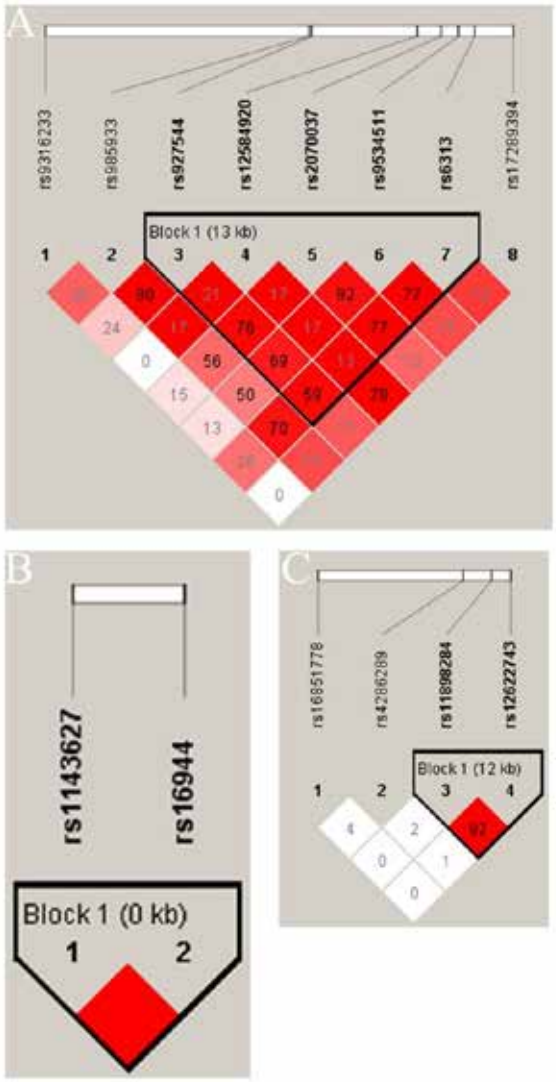
Supplemental Table 1

References

1. Dworkin RH, Schmader KE. Treatment and prevention of postherpetic neuralgia. *Clin Infect Dis* 2003; 36:877-882.
2. Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016; 157:30-54.
3. Johnson RW, Bouhassira D, Kassianos G, Leplège A, Schmader KE, Weinke T. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. *BMC Med* 2010; 8:37.
4. Jeon YH. Herpes zoster and postherpetic neuralgia: Practical consideration for prevention and treatment. *Korean J Pain* 2015; 28:177-184.
5. Garry EM, Delaney A, Anderson HA, et al. Varicella zoster virus induces neuropathic changes in rat dorsal root ganglia and behavioral reflex sensitisation that is attenuated by gabapentin or sodium channel blocking drugs. *Pain* 2005; 118:97-111.
6. Somogyi AA, Sia AT, Tan EC, Coller JK, Hutchinson MR, Barratt DT. Ethnicity-dependent influence of innate immune genetic markers on morphine PCA requirements and adverse effects in postoperative pain. *Pain* 2016; 157:2458-2466.
7. Sato H, Droney J, Ross J, et al. Gender, variation in opioid receptor genes and sensitivity to experimental pain. *Mol Pain* 2013; 9:20.
8. Okamoto N, Okumura M, Tadokoro O, Sogawa N, Tomida M, Kondo E. Effect of single-nucleotide polymorphisms in TRPV1 on burning pain and capsaicin sensitivity in Japanese adults. *Mol Pain* 2018; 14:1744806918804439.
9. Langford DJ, Paul SM, West CM, et al. Variations in potassium channel genes are associated with distinct trajectories of persistent breast pain after breast cancer surgery. *Pain* 2015; 156:371-380.
10. Duan G, Guo S, Zhang Y, et al. The effect of SCN9A variation on basal pain sensitivity in the general population: An experimental study in young women. *J Pain* 2015; 16:971-980.
11. Vargas-Alarcon G, Alvarez-Leon E, Fragoso JM, et al. A SCN9A gene-encoded dorsal root ganglia sodium channel polymorphism associated with severe fibromyalgia. *BMC Musculoskelet Disord* 2012; 13:23.
12. Reimann F, Cox JJ, Belfer I, et al. Pain perception is altered by a nucleotide polymorphism in SCN9A. *Proc Natl Acad Sci U S A* 2010; 107:5148-5153.
13. Langford DJ, West C, Elboim C, et al. Variations in potassium channel genes are associated with breast pain in women prior to breast cancer surgery. *J Neurogenet* 2014; 28:122-135.
14. Binder A, May D, Baron R, et al. Transient receptor potential channel polymorphisms are associated with the somatosensory function in neuropathic pain patients. *PLoS One* 2011; 6:e17387.
15. Valdes AM, De Wilde G, Doherty SA, et al. The Ile585Val TRPV1 variant is involved in risk of painful knee osteoarthritis. *Ann Rheum Dis* 2011; 70:1556-1561.
16. Sorge RE, Trang T, Dorfman R, et al. Genetically determined P2X7 receptor pore formation regulates variability in chronic pain sensitivity. *Nat Med* 2012; 18:595-599.
17. Kambur O, Kaunisto MA, Winsvold BS, et al. Genetic variation in P2RX7 and pain tolerance. *Pain* 2018; 159:1064-1073.
18. Loncar Z, Curić G, Mestrović AH, Mićković V, Bilić M. Do IL-1B and IL-1RN modulate chronic low back pain in patients with post-traumatic stress disorder? *Coll Antropol* 2013; 37:1237-1244.
19. Khan A, Khan S, Kim YS. Insight of pain modulation: Nociceptors sensitization and therapeutic targets. *Curr Drug Targets* 2019; 20:775-788.
20. Kambur O, Kaunisto MA, Tikkanen E, Leal SM, Ripatti S, Kalso EA. Effect of catechol-O-methyltransferase-gene (COMT) variants on experimental and acute postoperative pain in 1,000 women undergoing surgery for breast cancer. *Anesthesiology* 2013; 119:1422-1433.
21. Tian Y, Liu X, Jia M, et al. Targeted genotyping identifies susceptibility locus in brain-derived neurotrophic factor gene for chronic postsurgical pain. *Anesthesiology* 2018; 128:587-597.
22. Estévez-López F, Camiletti-Moirón D, Aparicio VA, et al. Identification of candidate genes associated with fibromyalgia susceptibility in southern Spanish women: The Al-Andalus Project. *J Transl Med* 2018; 16:43.
23. Jung BF, Johnson RW, Griffin DR, Dworkin RH. Risk Factors for postherpetic neuralgia in patients with herpes zoster. *Neurology* 2004; 62:1545-1551.
24. Cho SI, Lee CH, Park GH, Park CW, Kim HO. Use of S-LANSS, a tool for screening neuropathic pain, for predicting postherpetic neuralgia in patients after acute herpes zoster events: A single-center, 12-month, prospective cohort study. *J Pain* 2014; 15:149-156.
25. Haanpää M, Laippala P, Nurmikko T. Allodynia and pinprick hypesthesia in acute herpes zoster, and the development of postherpetic neuralgia. *J Pain Symptom Manage* 2000; 20:50-58.
26. Sato-Takeda M, Ihn H, Ohashi J, et al. The human histocompatibility leukocyte antigen (HLA) haplotype is associated with the onset of postherpetic neuralgia after herpes zoster. *Pain* 2004; 110:329-336.
27. Chung HY, Song EY, Yoon JA, et al. Association of human leukocyte antigen with postherpetic neuralgia in Koreans. *APMIS* 2016; 124:865-871.
28. Curran D, Schmidt-Ott R, Schutter U, Simon J, Anastassopoulou A, Matthews S. Impact of herpes zoster and postherpetic neuralgia on the quality of life of Germans aged 50 or above. *BMC Infect Dis* 2018; 18:496.
29. Graves H, Rayburn AL, Gonzalez-Hernandez JL, Nah G, Kim DS, Lee DK. Validating DNA polymorphisms using KASP assay in prairie cordgrass (spartina pectinata link) populations in the U.S. *Front Plant Sci* 2015; 6:1271.
30. He C, Holme J, Anthony J. SNP Genotyping: The KASP assay. *Methods Mol Biol* 2014; 1145:75-86.
31. Solé X, Guinó E, Valls J, Iniesta R, Moreno V. SNPStats: A web tool for the analysis of association studies. *Bioinformatics* 2006; 22:1928-1929.
32. North RA. Molecular physiology of P2X receptors. *Physiol Rev* 2002; 82:1013-1067.
33. Chessell IP, Hatcher JP, Bountra C, et al. Disruption of the P2X7 purinoceptor gene abolishes chronic inflammatory and neuropathic pain. *Pain* 2005; 114:386-396.
34. Gu BJ, Zhang W, Worthington RA, et al. A Glu-496 to Ala polymorphism leads to loss of function of the human P2X7 receptor. *J Biol Chem* 2001; 276:11135-11142.
35. Gu BJ, Sluyter R, Skarratt KK, et al. An Arg307 to Gln polymorphism within the ATP-binding site causes loss of function

of the human P2X7 receptor. *J Biol Chem* 2004; 279:31287-31295.

36. Cabrini G, Falzoni S, Forchap SL, et al. A His-155 to Tyr polymorphism confers gain-of-function to the human P2X7 receptor of human leukemic lymphocytes. *J Immunol* 2005; 175:82-89.
37. Sun C, Chu J, Singh S, Salter RD. Identification and characterization of a novel variant of the human P2X(7) receptor resulting in gain of function. *Purinergic Signal* 2010; 6:31-45.
38. Ide S, Nishizawa D, Fukuda K, et al. Haplotypes of P2RX7 gene polymorphisms are associated with both cold pain sensitivity and analgesic effect of fentanyl. *Mol Pain* 2014; 10:75.
39. Price N, Namdari R, Neville J, et al. Safety and efficacy of a topical sodium channel inhibitor (TV-45070) in patients with postherpetic neuralgia (PHN): A randomized, controlled, proof-of-concept, crossover study, with a subgroup analysis of the Nav1.7 R1150W genotype. *Clin J Pain* 2017; 33:310-318.
40. Baron R, Binder A, Wasner G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; 9:807-819.
41. Opstelten W, Zuithoff NP, van Essen GA, et al. Predicting postherpetic neuralgia in elderly primary care patients with herpes zoster: Prospective prognostic study. *Pain* 2007; 132(Suppl 1):S52-S59.
42. Katz J, McDermott MP, Cooper EM, Walther RR, Sweeney EW, Dworkin RH. Psychosocial risk factors for postherpetic neuralgia: A prospective study of patients with herpes zoster. *J Pain* 2005; 6:782-790.



Supplemental Fig. S1. *LD plots of SNPs of the HTR2A, SCN9A, and IL1B genes. The top horizontal bar illustrates the location of SNPs on a physical scale. Colors indicate the level of D' (white = low D', red = high D'), while numbers represent the r^2 value (no number where $r^2 = 1$). (A) LD in 8 SNPs of HTR2A. The rs2070037 SNP was genotyped as a proxy ($r^2 > 0.9$) for rs9534511. (B) LD in 2 SNPs of IL1B. The rs1143627 SNP was genotyped as a proxy ($r^2 = 1$) for rs16944. (C) LD in 4 SNPs of SCN9A. The rs11898284 SNP was genotyped as a proxy ($r^2 > 0.9$) for rs12622743.*

Supplemental Table S1. *Genotype and allele distributions of polymorphisms in patients with and without PHN.*

Gene	SNP	Genotype/ allele	Non-PHN n (%)	PHN n (%)	*P*-value
COMT	rs4680	A/A	10 (0.09)	5 (0.07)	0.771
		G/A	36 (0.32)	26 (0.37)	
		G/G	65 (0.59)	39 (0.56)	
		G	166 (0.75)	104 (0.74)	0.917
		A	56 (0.25)	36 (0.26)	
BDNF	rs6265	C/C	22 (0.20)	16 (0.23)	0.844
		T/C	57 (0.51)	36 (0.51)	
		T/T	32 (0.29)	18 (0.26)	
		T	121 (0.55)	72 (0.51)	0.568
		C	101 (0.45)	68 (0.49)	
OPRM1	rs1799971	A/A	46 (0.41)	34 (0.49)	0.303
		A/G	47 (0.42)	30 (0.42)	
		G/G	18 (0.17)	6 (0.09)	
		A	139 (0.63)	98 (0.70)	0.150
		G	83 (0.37)	42 (0.30)	
HTR1A	rs6295	C/C	2 (0.02)	3 (0.04)	0.374
		G/C	39 (0.35)	29 (0.42)	
		G/G	70 (0.63)	38 (0.54)	
		G	179 (0.81)	105 (0.75)	0.204
		C	43 (0.19)	35 (0.25)	
HTR2A	rs6313	A/A	46 (0.42)	23 (0.33)	0.508
		A/G	49 (0.44)	35 (0.50)	
		G/G	16 (0.14)	12 (0.17)	
		A	141 (0.64)	81 (0.58)	0.282
		G	81 (0.36)	59 (0.42)	
HTR2A	rs2070037	C/C	12 (0.11)	5 (0.07)	0.405
		T/C	48 (0.43)	37 (0.53)	
		T/T	51 (0.46)	28 (0.40)	
		T	150 (0.68)	93 (0.66)	0.822
		C	72 (0.32)	47 (0.34)	
HTR2A	rs927544	A/A	56 (0.51)	36 (0.51)	0.925
		A/G	47 (0.42)	30 (0.43)	
		G/G	8 (0.07)	4 (0.06)	
		A	159 (0.72)	102 (0.73)	0.799
		G	63 (0.28)	38 (0.27)	
HTR2A	rs985933	A/A	11 (0.10)	9 (0.13)	0.741
		G/A	47 (0.42)	31 (0.44)	
		G/G	53 (0.48)	30 (0.43)	
		G	153 (0.69)	91 (0.65)	0.439
		A	69 (0.31)	49 (0.35)	
HTR2A	rs12584920	G/G	93 (0.84)	61 (0.87)	0.312
		G/T	18 (0.16)	8 (0.11)	

Gene	SNP	Genotype/ allele	Non-PHN n (%)	PHN n (%)	*P*-value
		T/T	0	1 (0.02)	
		G	204 (0.92)	130 (0.93)	0.738
		T	18 (0.08)	10 (0.07)	
HTR2A	rs9316233	C/C	64 (0.58)	43 (0.61)	0.363
		C/G	42 (0.38)	21 (0.30)	
		G/G	5 (0.04)	6 (0.09)	
		C	170 (0.77)	107 (0.76)	0.974
		G	52 (0.23)	33 (0.24)	
HTR2A	rs17289394	A/A	1 (0.01)	1 (0.01)	0.879
		G/A	20 (0.18)	11 (0.16)	
		G/G	90 (0.81)	58 (0.83)	
		G	200 (0.90)	127 (0.91)	0.845
		A	22 (0.10)	13 (0.09)	
ADRB2	rs1042714	C/C	85 (0.76)	53 (0.76)	0.707
		C/G	25 (0.23)	17 (0.24)	
		G/G	1 (0.01)	0	
		C	195 (0.88)	123 (0.88)	0.996
		G	27 (0.12)	17 (0.12)	
ADRB2	rs11959113	A/A	7 (0.06)	7 (0.10)	0.303
		G/A	50 (0.45)	24 (0.34)	
		G/G	54 (0.49)	39 (0.56)	
		G	158 (0.71)	102 (0.73)	0.728
		A	64 (0.29)	38 (0.27)	
ADRB1	rs1801253	C/C	60 (0.54)	41 (0.59)	0.196
		C/G	46 (0.41)	22 (0.31)	
		G/G	5 (0.05)	7 (0.10)	
		C	166 (0.75)	104 (0.74)	0.917
		G	56 (0.25)	36 (0.26)	
TRPV1	rs8065080	C/C	45 (0.41)	26 (0.37)	0.901
		C/T	51 (0.46)	34 (0.49)	
		T/T	15 (0.13)	10 (0.14)	
		C	141 (0.64)	86 (0.61)	0.690
		T	81 (0.36)	54 (0.39)	
TRPV1	rs222747	C/C	41 (0.37)	29 (0.41)	0.618
		C/G	51 (0.46)	27 (0.39)	
		G/G	19 (0.17)	14 (0.20)	
		C	133 (0.60)	85 (0.61)	0.879
		G	89 (0.40)	55 (0.39)	
SCN9A	rs4286289	A/A	37 (0.34)	25 (0.36)	0.947
		A/C	56 (0.50)	34 (0.48)	
		C/C	18 (0.16)	11 (0.16)	
		A	130 (0.59)	84 (0.60)	0.786
		C	92 (0.41)	56 (0.40)	

Gene	SNP	Genotype/ allele	Non-PHN n (%)	PHN n (%)	*P*-value
SCN9A	rs11898284	A/A	65 (0.58)	45 (0.64)	0.491
		A/G	42 (0.38)	21 (0.30)	
		G/G	4 (0.04)	4 (0.06)	
		A	172 (0.77)	111 (0.79)	0.685
		G	50 (0.23)	29 (0.21)	
SCN9A	rs16851778	A/A	47 (0.42)	21 (0.30)	0.220
		A/G	52 (0.47)	38 (0.54)	
		G/G	12 (0.11)	11 (0.16)	
		A	146 (0.66)	80 (0.57)	0.099
		G	76 (0.34)	60 (0.43)	
KCNK9	rs2014712	C/C	55 (0.50)	41 (0.59)	0.494
		C/T	44 (0.40)	23 (0.33)	
		T/T	12 (0.10)	6 (0.08)	
		C	154 (0.69)	105 (0.75)	0.248
		T	68 (0.31)	35 (0.25)	
KCNK9	rs3780039	A/A	4 (0.04)	2 (0.03)	0.525
		C/A	25 (0.22)	21 (0.30)	
		C/C	82 (0.74)	47 (0.67)	
		C	189 (0.85)	115 (0.82)	0.450
		A	33 (0.15)	25 (0.18)	
KCNK9	rs11166921	A/A	38 (0.34)	30 (0.43)	0.468
		A/C	56 (0.5)	32 (0.46)	
		C/C	17 (0.16)	8 (0.11)	
		A	132 (0.59)	92 (0.66)	0.233
		C	90 (0.41)	48 (0.34)	
IL1B	rs1143627	A/A	35 (0.32)	18 (0.26)	0.604
		A/G	56 (0.5)	36 (0.51)	
		G/G	20 (0.18)	16 (0.23)	
		A	126 (0.57)	72 (0.51)	0.321
		G	96 (0.43)	68 (0.49)	
P2RX7	rs7958311	A/A	22 (0.2)	19 (0.27)	0.016
		A/G	71 (0.64)	30 (0.43)	
		G/G	18 (0.16)	21 (0.3)	
		A	115 (0.52)	68 (0.49)	0.549
		G	107 (0.48)	72 (0.51)	