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ORIGINAL ARTICLE

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Gamma-aminobutyric acid transaminase genetic polymorphism is a candidate locus for responsiveness to opioid analgesics in patients with cancer pain: An exploratory study

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Abstract

Aim: Cancer pain impairs not only physical functions but also social functions and roles. Consequently, the overall health-related quality of life of patients with cancer pain deteriorates. Opioid analgesics are recommended for treating moderate to strong cancer pain. Advances in human genome research have fueled a growing interest to understand individual differences in responsiveness to opioid analgesics. This study aimed to explore and identify novel loci for genes predisposing an individual to opioid analgesic responsiveness.

Methods: A total of 71 cancer patients rated their pain on an 11-point numerical rating scale twice before and after increasing opioid analgesics. A genomewide association study focusing on single nucleotide polymorphisms (SNPs) was conducted to associate pain decrease with increased dosage of opioid analgesics based on weight (ie, responsiveness to opioid analgesics). A genomewide significance ($P < 5E\text{-}8$) was set for multiplicity of analyses to control for false positives.

Results: Two SNPs passed the genomewide threshold for significance. One exonic SNP (rs1641025) was located in the *ABAT* [4-aminobutyrate aminotransaminase (GABA transaminase)] gene on chromosome 16. The other SNP (rs12494691) was located on chromosome 3, which was not associated with any known genes. These SNPs were not associated with opioid-related adverse effects.

Conclusions: Our results preliminarily suggest that both SNPs might be potential candidate loci for responsiveness to opioid analgesics, and GABA transaminase might be a possible target for developing adjuvant pharmacotherapy with opioid analgesics in adjuvant pharmacotherapy. Our results should be validated in a large-scale study with a larger sample size.

[a]See Appendix for the Japanese TR-Cancer Pain Research Group.

KEYWORDS
genetics: human, pain: basic/clinical, pharmacogenetics: basic/clinical, responsiveness to opioid analgesics

1 | INTRODUCTION

Pain is one of the most frequent symptoms among patients with terminal cancer, and the pain-associated distress experienced by those with cancer pain can cause anxiety, depression, and changes in social functions. Indeed, not only physical functions but also social functions and roles have been found to be lower in patients with cancer pain than in the general population; as a result, their overall health and quality of life (QOL) are severely impaired.[1] As anticancer treatments (ie, chemotherapy, radiotherapy, and surgery) become aggressive, the time patients spend with advanced stage disease increases; thus, the treatment of cancer pain is a chronic process. In addition to the advanced and terminal cancer periods in which the prevalence rate of cancer pain is 64%, pain has been reported in 33% of patients just after curative treatment and 59% of patients during anticancer treatment.[2] However, apart from patients with cancer who are terminally ill, sufficient analgesic supplementation is still not provided to more than half of patients with cancer who have received and just completed anticancer treatment.[3] A systematic review on barriers hindering adequate cancer pain management revealed inadequate assessment of pain and pain management as well as inadequate knowledge of pain management of healthcare professionals.[4] In particular, inadequate knowledge of opioid analgesics (eg, effective dose, upper limits, and the likelihood of addiction or tolerance) has been reported by many physicians and nurses.

Anecdotal variation in opioid analgesia seems to be a likely factor contributing to inadequate pain management. Some variations can be explained by genetic predisposition affecting either pain perception/processing or analgesic responses.[5] For example, among genetic polymorphisms associated with altered pain perception and processing, a mu-opioid receptor single nucleotide polymorphism (SNP) [*OPRM1* 118A>G (rs1799971)] has been shown to be associated with a 0.8-fold decrease in pressure pain intensity among carriers.[6] A previous study on *OPRM1* 118A>G has demonstrated the association between genetic polymorphisms and opioid analgesic responsiveness; patients with the minor allele homozygosity were found to require higher morphine doses (more than twofold) to achieve pain control.[7] Associations between human pain-related genotypes and variability in opioid analgesia have been well investigated.[8] Nevertheless, as most previous studies were based on Caucasian populations, this study aimed to explore and identify novel loci for genes predisposing an individual with cancer pain to opioid analgesic responsiveness in a non-Caucasian population. The results of this study will be useful in developing not only potential testing panels for specific patients who require higher opioid doses but also targeted pharmacotherapy for all cancer pain patients.

2 | METHODS

2.1 | Participants

This study was approved by the appropriate institutional review boards of the respective hospitals, and written informed consent was obtained from all participants. The inclusion criteria were as follows: (a) diagnosis of cancer pain (irrespective of the organ and pathology of malignant lesions), (b) measurable pain intensity on an 11-point numerical rating scale (NRS) (0 = no pain, 10 = worst possible pain), (c) pain duration >1 week (recorded at inclusion), and (d) age >20 years. Both opioid-naïve patients and patients in opioid use (irrespective of duration of opioid medication and single dosages and daily times of on-demand opioid use) could participate in this study. The exclusion criteria were as follows: (a) patients with slight or more severe cognitive dysfunction, (b) patients with clinically relevant brain metastases, and (c) suspicion of an origin of pain other than from cancer. We evaluated their pain intensity (NRS) and opioid-induced complications (ie, nausea, vomiting, constipation, and somnolence) on a 5-point Likert scale (responses were scored as 0 = absence of symptoms, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe) twice before and after prescribing firstly or increasing opioid analgesics. There were no protocols how to increase opioid dosages, and the attending physicians who have expertise in cancer pain management increased opioid dosages for individual patients at their discretion. The second survey was conducted a day after increasing opioid dosages. Decreases in pain intensity and respective complications from the first survey to the second survey were expressed in percentage terms. We recorded the increased and total daily dosage of opioid analgesics based on weight [mean intravenous fentanyl-equivalent dose (mg/kg/day)] on the days of pain evaluation. We did not discriminate opioid-naïve patients from patients having opioid medication and analyzed them together.

In the first evaluation, 90 patients [age, 58.4 ± 13.4 years (mean ± SD); female, 50; pain duration, 11.2 ± 18.8 months] were enrolled, and 71 of these patients participated in the second evaluation. Therefore, we analyzed these 71 patients in this study.

2.2 | Genotyping

Venous blood samples were collected from all of the participants. Genomic DNA was isolated from peripheral blood lymphocytes using a standard salting-out method. The DNA was whole-genome amplified, fragmented, denatured, and hybridized to a prepared Omni1-Quad BeadChip (Illumina, San Diego, CA, USA), which contained 1 140 419 markers. All 71 patients were genotyped using the Omni1-Quad BeadChip. Normalized bead-intensity data obtained for

each sample were loaded into GenomeStudio software (Genotyping module ver. 1.8.4; Illumina), which converted fluorescence intensities into SNP genotypes. We excluded SNPs with a call rate of less than 95%, with a deviation from Hardy-Weinberg equilibrium at an error level of less than 10^{-3} and with a minor allele frequency less than 10^{-3}, which resulted in 771 433 SNPs.

2.3 | Statistical analysis of individual genotype data

Statistical calculations for individual genotyping data were performed using plink version 1.07,[9] R package version 2.14.1 (http://www.r-project.org; R Development Core Team 2011), EIGENSOFT package version 3.1,[10] and Haploview version 4.2.[11] The extent to which observed genotype frequencies for each SNP deviated from those expected under the Hardy-Weinberg equilibrium was assessed by Fisher's exact test. SNPs showing deviation from the Hardy-Weinberg equilibrium ($P < 0.001$) were excluded from the analysis. Individual SNP associations with responsiveness to opioid analgesics were estimated using a linear regression model for (a) additive (each copy of the minor allele has an equivalent additional additive value, ie, 0, 1, 2), (b) dominant (1 or 2 copies of the minor allele vs. 0 copies of the minor allele), and (c) recessive (2 copies of the minor allele vs. 0 or 1 copy of the minor allele) models. In the linear regression model, we set responsiveness to opioid analgesics as the dependent variable, and age, sex, and adding intravenous fentanyl-equivalent dosage and respective SNPs were set as covariates ($y = \beta_0 + \beta_1 \times \text{Age} + \beta_2 \times \text{Sex} + \beta_3 \times \text{Adding fentanyl dose} + \beta_4 \times \text{SNPs} + \varepsilon$). Both pain duration and duration of opioid medication did not enter the model as covariates, because to our best knowledge, no evidence was confirmed that neither pain duration nor opioid duration affects opioid analgesic responsiveness in cancer pain patients. Possibly not to obtain a significant statistical result by chance alone (false-positive results), we set the genomewide significance (ie, $P < 5E\text{-}8$).

Through a genomewide association study (GWAS), we identified the loci for genes predisposing an individual to opioid analgesic responsiveness (ie, pain decrease corresponding to increased opioid analgesics). Then, we analyzed the associations between three variables (genotypes, decreases in pain intensity, and opioid-induced complications) and increased and total opioid dosages using the Kruskal-Wallis test. Bonferroni test was performed for post hoc analysis. The criterion for significance was set at $P < 0.05$. In addition, linkage disequilibrium patterns of the relevant SNPs were plotted using Haploview,[11] and the locus zoom around the relevant SNPs was demonstrated by LocusZoom version 1.1,[12] as supplementary figures.

3 | RESULTS

We conducted a GWAS by evaluating the association between SNPs and opioid analgesic responsiveness. Table 1 shows the characteristics of participants with cancer pain. Figure 1 shows the distribution of the *P* values of each SNP for all chromosomes (Manhattan plot). Two SNPs passed the genomewide significance ($P = 5E\text{-}8$) in the additive model, but no SNPs were found under both dominant and recessive models. One SNP (rs1641025, $P < 0.0204 \times 10^{-6}$) was located in the *ABAT* [4-aminobutyrate amino transaminase (GABA transaminase)] gene on chromosome 16 (locus 8777531). The other SNP (rs12494691, $P < 0.0392 \times 10^{-6}$) was located on chromosome 3 (locus 16658827), which was not associated with any known genes. For the rs1641025 SNP of the *ABAT* gene (Table 1), the increased dosage and total daily dosage at the first survey of opioid analgesics based on weight were comparable among the three groups according to the genotype of the SNP (Kruskal-Wallis test, $P = 0.11$ and 0.11, respectively; Table 1). The pain intensity before increasing opioid analgesics was similar among the three groups (Kruskal-Wallis test, $P = 0.93$). The Kruskal-Wallis test and subsequent post hoc Bonferroni test revealed a significant association between genotypes and opioid responsiveness for cancer pain (Kruskal-Wallis test, $P < 0.001$; Figure 2A). Opioid-induced complications were not associated with increased opioid analgesics among the three groups (Kruskal-Wallis test: nausea, $P = 0.79$; vomiting, $P = 0.83$; constipation, $P = 0.54$; somnolence, $P = 0.12$). The linkage disequilibrium pattern and the locus zoom of the rs1641025 SNP are demonstrated in Supporting Information Figure S1.

For the rs12494691 SNP (Table 1), decreases in pain intensity were significantly different (Kruskal-Wallis test, $P < 0.0001$; Figure 2b). In comparison with patients with major allele homozygosity and heterozygosity, those with minor allele homozygosity demonstrated a lower decrease in pain intensity after increasing opioid analgesics. Patients with major allele homozygosity improved more than those with heterozygosity. Among patients with the three genotypes, increased opioid dosage, total opioid dosage before increasing opioid analgesics, and pain intensity before increasing opioids were not significantly different. Opioid-induced complications were not associated with increased opioid analgesics among the three groups (Kruskal-Wallis test: nausea, $P = 0.45$; vomiting, $P = 0.81$; constipation, $P = 0.85$; somnolence, $P = 0.39$).

The linkage disequilibrium pattern and the locus zoom of the rs12494691 SNP are demonstrated in Supporting Information Figure S2.

4 | DISCUSSION

The present exploratory investigation was, to our best knowledge, the first GWAS to investigate possible associations between SNPs and responsiveness to opioid analgesics for cancer pain in a non-Caucasian population. This exploratory study revealed the associations of the rs1641025 SNP (located on the *ABAT* gene encoding GABA transaminase) and rs12494691 SNP (which was not associated with any known genes). Our results preliminarily suggest that both SNPs might be potential candidate loci for responsiveness to opioid analgesics, and GABA transaminase might be a possible target for developing adjuvant pharmacotherapy with opioid analgesics.

The prevailing principle for cancer pain treatment is the World Health Organization (WHO) three-step analgesic ladder, and strong opioids are recommended as the most potent analgesics for moderate

TABLE 1 Characteristics of participants with cancer pain treated with opioid analgesics

SNP	Gene	Location[a]	Major allele/minor allele	Minor allele frequency	Genotype	*N* [opioid-naïve] (male:female)	Age	Pain duration (months)	Total opioid dosage before increasing opioid analgesics (mg/kg/day)	Increased opioid dosage (mg/kg/day)	Cancer pain intensity		Decrease in pain intensity after increasing opioid analgesics (%)	Genomewide association study	
											Before increasing opioid analgesics	After increasing opioid analgesics		*P*-value	Effect size
rs1641025	ABAT	8777531, Chromosome 16	C/T	0.27	Major allele homozygosity	42 [15] (21:21)	59.3 ± 12.5	16.0 ± 24.7	1.9 ± 2.3	1.1 ± 1.5	6.0 ± 2.0	4.9 ± 1.9	15.8 ± 29.3	2.04E-08	0.36
					Heterozygosity	23 [7] (10:13)	56.1 ± 15.2	5.2 ± 9.5	6.5 ± 17.7	4.3 ± 16.4	5.9 ± 1.7	2.6 ± 1.7	56.7 ± 24.6		
					Minor allele homozygosity	6 [1] (1:5)	57.5 ± 16.2	6.7 ± 12.4	8.0 ± 9.5	55.2 ± 100.0	5.7 ± 1.4	3.2 ± 1.9	44.3 ± 29.7		
rs12494691	(no gene)	16658827, Chromosome 3	G/A	0.2	Major allele homozygosity	23 [10] (11:12)	61.0 ± 11.4	4.8 ± 8.0	0.77 ± 0.93	4.9 ± 17.2	6.2 ± 1.9	3.1 ± 1.7	49.9 ± 24.2	3.92E-08	0.01
					Heterozygosity	40 [10] (17:23)	55.6 ± 14/1	16.1 ± 25.4	4.0 ± 7.3	3.0 ± 11.9	5.9 ± 1.7	4.1 ± 2.1	26.8 ± 33.6		
					Minor allele homozygosity	8 [3] (4:4)	62.1 ± 16.0	10.0 ± 12.7	2.2 ± 1.6	32.3 ± 88.0	5.6 ± 2.4	5.6 ± 2.1	−4.4 ± 22.3		

[a]Base position was indicated in the Omni1-Quad BeadChip (Illumina, San Diego, CA, USA). Genotype data were defined by the Genome Reference Consortium human build 38.p7 (GRCh38.p7).

to severe pain.[13] However, in clinical practice, it is sometimes difficult to titrate opioid analgesics to achieve pain relief, possibly resulted by inadequate analgesic prescription relative to the pain level.[4] To address this clinical problem, the contribution of genetic variables to responsiveness to opioid analgesics has been investigated. Studies have revealed the significance of genetic variations such as common polymorphic variations in the mu-opioid receptor (*OPRM1*), catechol-*O*-methyltransferase (*COMT*), and other candidate genes.[8] Therefore, personalized medicine, which can be tailored to the genetic characteristics of each patient with cancer pain, is a promising field. Accordingly, our present GWAS suggests the identification of rs1641025 and rs12494691 SNPs could potentially contribute to the prediction of the dosage of opioid analgesics needed for pain decrease and the shortening of the titration period. There was a GWAS of opioid responsiveness in Japanese patients with acute postoperative pain, which identifies SNPs associated with the *METTL21A* and *CREB1* genes on chromosome 2.[14] These are quite different from our present findings, and different etiology between acute postoperative pain and chronic cancer pain might be a relevant reason.

Traditional adjuvant drugs include antidepressants, antiepileptics, neuroleptics, and corticosteroids. There has been growing interest in these adjuvant drugs, which have an opioid-sparing effect on cancer pain relief. The WHO analgesic ladder system recommends the concomitant use of adjuvant drugs, which can supplement and reduce the analgesic dosage at every step. The rs12494691 SNP was not located in any transcribed regions. Moreover, to our knowledge, there are no reports indicating its functional role. The most adjacent gene to this SNP is the deleted in azoospermia-like (*DAZL*) gene (Supporting Information Figure S2), which is known to relate with infertility.[15] Therefore, the rs12494691 SNP does not seem to have any associations with adjuvant analgesics for cancer pain at present. On the other hand, the rs1641025 SNP was located in the exonic region of the *ABAT* gene encoding GABA transaminase. GABA is the most abundant inhibitory neurotransmitter in the central nervous system, where it regulates many physiological functions including somatosensory and pain perception, anxiety, and reward-related processes. In the synapse, its action is mediated through GABA-specific receptors on postsynaptic membranes. GABA is degraded to succinic semialdehyde by GABA transaminase, consequently deactivating GABAergic transmission. Hence, GABA transaminase can modulate GABAergic transmission in the central nervous system. For example, independently of rs1641025, genetic variants of the *ABAT* gene are likely associated with somatosensory evoked potentials in families at high risk for affective disorders and autism.[16,17] In terms of GABAergic analgesia, GABAergic agonists themselves are classically known to have analgesic potency, and those can enhance opioid analgesia and attenuate opioid-related adverse effects.[18] Furthermore, the inhibition of GABA transaminase in the spinal cord can lead to antinociception and the potentiation of opioid analgesia.[19] In the periaqueductal gray region of the midbrain, opioids inhibit GABAergic interneurons, which tonically suppress the descending pain inhibitory system, and subsequently exert opioid analgesia. GABA transaminase inhibition in the midbrain can aggravate pain perception.[20] Although we did not

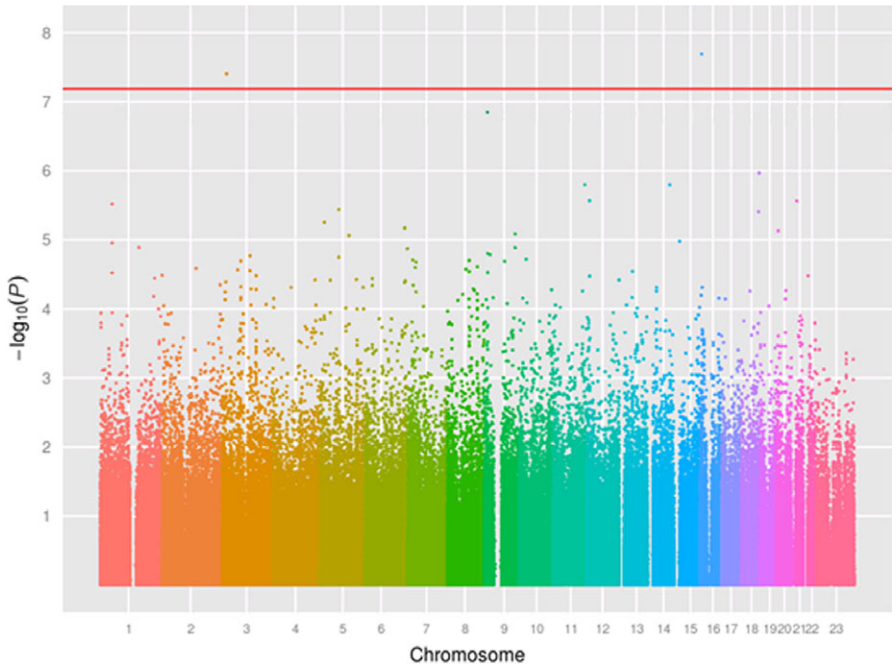

FIGURE 1 Manhattan plot of the association study of responsiveness to opioid analgesics in patients with cancer pain. The distribution of −log10(*P*) was obtained for the associations tested between the genotypes and responsiveness to opioid analgesics for all human chromosomes in the additive model (Manhattan plot). The horizontal red line indicates the genomewide significance ($P < 0.05 \times 10^{-6}$)

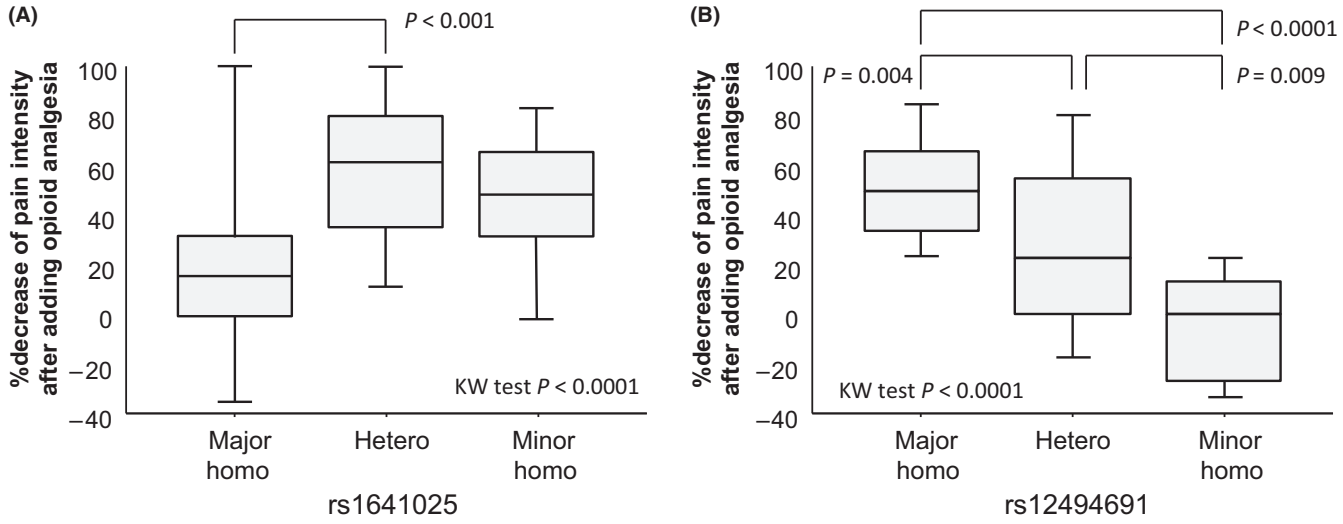

FIGURE 2 Associations of opioid responsiveness with the relevant single nucleotide polymorphisms (SNPs). The boxes represent the 25th to 75th percentiles with the horizontal line showing the median value of the percentage decrease in cancer pain intensity after increasing opioid analgesics. A, rs1641025 SNP—located in the *ABAT* gene; B, rs12494691 SNP—not located in known gene regions. The Kruskal-Wallis test revealed significant differences among the three groups (major allele homozygosity, heterozygosity, and minor allele homozygosity). Bonferroni post hoc tests were also conducted to examine associations (represented by *P* values)

specify whether the genetic variant of the *ABAT* gene upregulates or downregulates the function of GABA transaminase in the present study, GABA transaminase might be a possible target for developing adjuvant pharmacotherapy with opioid analgesics.

There are two major limitations of this study. One is, the number of enrolled patients was limited and the number of patients with homozygosity for the minor allele of these SNPs was also small. The other is, the peaks of the SNPs were stand-alone in both the Manhattan plot and the locus zooms (Supporting Information Figures S1 and S2), although they passed the genomewide threshold for significance to adjust for multiplicity of analyses. Both of these limitations could increase the possibility of false-positive results, and therefore, our results should be validated in a large-scale study with a larger sample size. Our present findings should be considered as exploratory or hypothesis-generating rather than hypothesis-testing, and we possibly suggest that genetic variants of the *ABAT* gene and

the other SNP are potential candidate markers for responsiveness to opioid analgesics for cancer pain, and GABA transaminase might be a suitable marker for concomitant use with opioids in adjuvant pharmacotherapy.

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CONFLICT OF INTEREST

Authors (M.S., D.N., K.I., Y.Y. and Japanese TR-Cancer Pain research Group) were supported by a Ministry of Health, Labour, and Welfare Science Research Grant (H21-Cancer-011 and H26-Cancer-060). The other authors declare no conflict of interest.

DATA REPOSITORY

The authors cannot make our data open to the public because of our institutional ethics committee policy.

APPROVAL OF THE RESEARCH PROTOCOL

This study was approved by our institutional ethics committee (G2804-3).

INFORMED CONSENT

We obtained written informed consent from all of the participants.

REGISTRY

This study has been registered in a public trial registry, University Medical Information Network (UMIN000008595).

ANIMAL STUDIES

N/A.

AUTHOR CONTRIBUTIONS

The manuscript has been read and approved by all authors. Yaeko Yokoshima analyzed data and wrote a manuscript. Masahiko Sumitani directed and conducted the whole study. Daisuke Nishizawa and Kazutaka Ikeda assisted the present genomewide association analyses. Makoto Nagashima and Ryoji Kato collected mainly collected samples of the patients and the Japanese TR-Cancer Pain research Group also collected samples. Jun Hozumi, Hiroaki Abe, Kenji Azuma, and Rikuhei Tsuchida assisted Yaeko Yokoshima and Masahiko Sumitani to analyze the data. Yoshitsugu Yamada supervised the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX

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