Taxane-induced sensory peripheral neuropathy is associated with an SCN9A single nucleotide polymorphism in Japanese patients

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Abstract

Background: Sodium channels located in the dorsal root ganglion, particularly Nav1.7 and Nav1.8, encoded by SCN9A and SCN10A, respectively, act as molecular gatekeepers for pain detection. Our aim was to determine the association between TIPN and SCN9A and SCN10A polymorphisms.

Methods: Three single nucleotide polymorphisms (SNPs) in SCN9A and two in SCN10A were investigated using whole-genome genotyping data from 186 Japanese breast or ovarian cancer patients classified into two groups as follows: cases that developed taxane-induced grade 2–3 neuropathy (N = 108) and controls (N = 78) with grade 0–1 neuropathy. Multiple logistic regression analyses were conducted to evaluate associations between TIPN and SNP genotypes.

Results: SCN9A-rs13017637 was a significant predictor of grade 2 or higher TIPN (odds ratio (OR) = 3.463; P = 0.0050) after correction for multiple comparisons, and precision was improved when only breast cancer patients were included (OR 5.053, P = 0.0029). Moreover, rs13017637 was a significant predictor of grade 2 or higher TIPN 1 year after treatment (OR 3.906, P = 0.037), indicating its contribution to TIPN duration.

Conclusion: SCN9A rs13017637 was associated with the severity and duration of TIPN. These findings are highly exploratory and require replication and validation prior to any consideration of clinical use.

Keywords: Breast and ovarian cancer, rs13017637, SCN9A, SCN10A, Taxane-induced peripheral neuropathy

Background

Taxanes, such as paclitaxel and docetaxel, are used to treat a variety of tumor, especially breast and ovarian cancer [1, 2]. The common non-hematologic toxicity associated with these drugs is peripheral neuropathy. Taxane-induced peripheral neuropathy (TIPN) can be dose limiting, which would affect treatment efficacy, and can worsen quality of life. As susceptibility to TIPN differs greatly among patients [3, 4], predicting patient risk could improve therapeutic efficacy and quality of life by personalizing treatment.

To date, several genes have been reported as potential risk factors for TIPN, including those associated with transport (e.g. ABCB1) [5–7], metabolism (e.g. CYP3A4, CYP3A5, and CYP2C8) [5, 8–10], development and regeneration in the nervous system (e.g. EPHA4 and EPHA5) [11], myelination in peripheral nerve (FGD4) [11], and β-
tubulin (TUBB2A) [12]. Thus, many pharmacogenetic studies have attempted to identify polymorphisms that contribute to variations in susceptibility to TIPN; however, current data are insufficient to make genetic testings routine for these variants.

Many different hypotheses regarding the mechanisms of sensory TIPN have been generated, including excessive microtubule assembly which causes the abnormal accumulation of disorganized microtubules disrupting normal cellular activities such as axonal transport and Schwann cell function; however, this process is still unclear [13, 14]. Voltage-gated sodium channels (VGSCs) located in the dorsal root ganglion (DRG), particularly Nav1.7 and Nav1.8, encoded by SCN9A and SCN10A, respectively, have important roles in the pathogenesis of human neuropathic pain [15–17]. VGSC mutations were reported to be associated with diseases of both the central and peripheral nervous systems [18]. Especially, mutations in SCN9A play a significant role in nociception signaling and have been associated with channelopathy-associated insensitivity to pain and paroxysmal extreme pain disorder, whereas the protein encoded by SCN10A is a tetrodotoxin-resistant sodium channel (SCNA) subunit that might be involved in painful peripheral neuropathy (PN) [15, 16]. Moreover, dorsal ganglionic Nav1.7 is up-regulated in rats and humans administered paclitaxel. Blocking the function of Nav1.7 was found to partially attenuate paclitaxel-induced hyperalgesia in rats. This suggests that this protein is involved in paclitaxel-induced neuropathic pain [19, 20]. However, no pharmacogenetic studies have focused on the association between TIPN and SCNA in a clinical setting. Therefore, we investigated the effects of SNPs in genes encoding VGSC using a prospective cohort of well-characterized breast or ovarian cancer patients treated with taxanes.

Methods

Patients

Japanese women with breast or ovarian cancer receiving taxane regimens were enrolled in a prospective observational study to evaluate taxane-related toxicity and to explore gene variants associated with TIPN by performing a genome-wide association study (UMIN000005294) [7]. The eligibility criteria are shown in previous study [7]. All patients provided written informed consent for adjuvant treatment and DNA collection for genetic analysis. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local institutional review board (protocol number: 2013–199).

Treatment

Breast cancer patients were treated with 4 cycles of cyclophosphamide (600 mg/m²) and doxorubicin (60 mg/m²) (AC) or cyclophosphamide (500 mg/m²) with epirubicin (100 mg/m²) and 5-fluorouracil (500 mg/m²) (CEF) every 3 weeks. Subsequently, paclitaxel (80 mg/m², weekly) or docetaxel (75 mg/m², every 3 weeks) was administered for 12 weeks. In addition, 4 cycles of cyclophosphamide (600 mg/m², day1) and doxorubicin (75 mg/m², day1) every 3 weeks (CPA + DTX) was also an option for breast cancer treatment. Patients positive for HER2 by immunohistochemistry or gene amplification analysis received trastuzumab concurrently with paclitaxel (weekly or every 3 weeks). Ovarian cancer patients were treated with 6 cycles of paclitaxel (175 mg/m²) and carboplatin (AUC6, day 1) every 3 weeks (Tri TC), or paclitaxel (80 mg/m², day 1, 8, 15) and carboplatin (AUC6, day 1) every 3 weeks (dose-dense TC).

TIPN evaluation

Neuropathy was prospectively evaluated at baseline before paclitaxel treatment, at week 7, within 3 weeks at or after the final dose, and 1 year after the last dose of paclitaxel, based on the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0 [21]. Evaluators of PN are five medical oncologists who are trained in toxicity assessment. One patient was evaluated by the same physician.

Genotyping

A 10-mL blood sample was collected from each patient upon enrollment. Genotyping assays were performed for eligible patients with sufficient DNA in the sample. DNA was extracted from whole-blood samples using standard procedures. The extracted DNA was dissolved in TE buffer (10 mM tris-HCl and 1 mM EDTA, pH 8.0) and the concentration was adjusted to 100 ng/ml for whole-genome genotyping using a NanoDrop ND-1000 Spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). To analyze polymorphisms within and around the SCN9A and SCN10A gene regions, whole-genome genotyping data were used. Whole-genome genotyping was performed using the Infinium assay II and the iScan system (Illumina, San Diego, CA) according to the manufacturer’s instructions. The OmniExpressExome-8 v1.1 BeadChip was used to genotype entire samples. The BeadChip included a number of probes that was specific to copy number variation markers, but most were for SNP markers on human autosomes or sex chromosomes. Approximately 900,000 SNP markers were included in the BeadChip. After whole-genome genotyping, data were analyzed using GenomeStudio Genotyping module v1.6.3 (Illumina) to evaluate the quality of results, and genotype data for SNPs with SCN9A and SCN10A gene annotations were extracted. The analyzed SNPs were SCN9As (rs7607967, rs12994338, and rs13017637) and SCN10A (rs12632942 and rs6795970), which were evaluated in previous reports [17, 22–25].
Statistical analysis
The primary objective was to evaluate the association between TIPN grade and SCN9A and SCN10A variants. The association between genetic variants and the risk of grade 2–3 TIPN was assessed by logistic regression analysis with adjustments for confounding clinical covariates. The dependent variable was maximum TIPN grade (grades 0–1 or 2–3), and the independent variables were type of cancer (breast cancer vs. ovarian cancer), age (< 60 vs. ≥ 60 years), TIPN latency, and genotype data for each SNP; alternatively, the dependent variable was TIPN grade 1 year after treatment, and the independent variables were maximum TIPN grade, TIPN duration, and genotype data for each SNP. TIPN duration is defined as time from onset of PN until disappearance of PN or at 1 year of treatment. We preliminarily planned to dichotomize age at 60 years and compare TIPN, referring to our previous study [3]. For the selected polymorphisms, we considered either an additive, dominant, or recessive model. Odds ratios (ORs) and their 95% confidence intervals (95% CIs) were used to estimate relative risk. SCN9A and SCN10A frequencies were assessed for concordance with expectations based on the Hardy-Weinberg equilibrium (HWE), using the chi-square test and Fisher’s exact test. Given the sample size of cases (108 patients with grade 2–3 TIPN) and controls (78 patients with grade 0–1 TIPN) and assuming a power of 85%, the level of significance was 0.1. Power calculations were performed using G^power software v3.1.9.2. All analyses were performed using the highest grade of treatment-related sensory peripheral neuropathy. Patients for whom taxane-based chemotherapy was discontinued due to adverse events, except neuropathy, were excluded from the analyses. Multiple comparisons were accounted for by using Bonferroni adjustment α = 0.05 (corrected alpha (α = 0.05/5 = 0.01)). A two-sided adjusted P-value of < 0.05 was considered statistically significant, and all analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC, USA).

Results
Patient characteristics
We analyzed 186 of 221 Japanese women enrolled between February 2011 and October 2013 at the two study sites. Thirty-five patients were excluded, including patients lost to follow-up (N = 16), patients not treated with taxane (N = 9), patients with a history of prior taxane use (N = 5), patients for whom chemotherapy was discontinued due to adverse events other than peripheral neuropathy (N = 1), and other reasons (N = 4). The demographic and clinical characteristics of patients are listed in Table 1. The median age was 52 years (range, 25–81 years). The number of breast and ovarian cancer patients was 135 and 51, respectively. One hundred and seventy-seven patients received paclitaxel treatment, whereas nine patients received docetaxel. Among 186 patients studied, for 38 (20%) and 16 (8%), the dose was reduced or treatment was terminated because of neuropathy or reasons other than neuropathy, respectively. Maximum grades of TIPN were 0 (N = 2, 1%), 1 (N = 76, 41%), 2 (N = 91, 49%), and 3 (N = 17, 9%).

Distribution of SCN9A and SCN10A genotypes
Genotypes in each SNP are listed in Table 1. Genotyping call rates by SNP and patient were estimated. We confirmed that both call rates (by SNP and patient) were ≥ 0.95 and all SNPs and samples were included in the analyses. The distributions of the SCN9A (rs7607967, rs12994338, and rs13017637) and SCN10A (rs12632942 and rs6795970) polymorphisms were all in accordance with the HWE (data not shown).

Association between SNPs and maximum TIPN grade
Results of dominant genetic model were reported in text and tables. Results of other models were not shown because they were not statistically significant. Of the five SNPs evaluated, SCN9A-rs13017637 was significantly associated with grade 2 or higher TIPN in all patients (OR, 3.463, P = 0.0050; Table 2). In addition, SCN9A-rs13017637 was significantly associated with grade 2 or higher TIPN among the 135 breast cancer patients (OR, 5.053, P = 0.0029; Table 2).

Association between SNPs and TIPN grade 1 year after taxane
Of the five SNPs evaluated, SCN9A-rs13017637 was significantly associated with grade 2 or higher TIPN in all patients (OR, 3.906, P = 0.0050; Table 2). However, no SNPs were significantly associated with grade 2 or higher TIPN among the 135 breast cancer patients.

Discussion
We evaluated the effect of sodium channel-related genes on TIPN development in breast or ovarian cancer patients treated with taxane. Multiple logistic regression revealed that SCN9A-rs13017637 was significantly associated with grade 2 or higher TIPN. It was also significantly associated with grade 2 or higher TIPN 1 year after the completion of taxane-based therapy. To our knowledge, this is the first study demonstrating that SNPs of sodium channel-related genes are associated with increased TIPN severity in Japanese patients treated with taxane.

Sodium channels in the DRG function as molecular gatekeepers of pain detection at peripheral nociceptors. Nineteen sodium channel subunits have been identified (Nav1.1–Nav1.9), each with a unique central and peripheral nervous system distribution. Gain-of-function (GOF) mutations in SCN9A, encoding Nav1.7, cause...
Table 1 Patient characteristics

| Cancer Type       | All patients (N = 186) | Cases TIPN Gr 2–3 (N = 108) | Control TIPN Gr 0–1 (N = 78) |
|-------------------|------------------------|------------------------------|------------------------------|
| Breast ca. a      | 135                    | 67                           | 68                           |
| Ovarian ca. a     | 51                     | 41                           | 10                           |
| Age (year) median (range) | 52 (25–81)   | 56 (25–81)                  | 48 (27–73)                  |
| Chemotherapy regimen b |                     |                              |                              |
| AC or CEF f/b wPTX | 126 (68%)              | 67 (62%)                    | 59 (77%)                    |
| AC or CEF f/b DTX  | 5 (3%)                 | 0                           | 5 (6%)                      |
| CPA + DTX         | 4 (2%)                 | 0                           | 4 (5%)                      |
| Dose dense TC     | 39 (21%)               | 34 (32%)                    | 5 (6%)                      |
| Tri TC            | 12 (6%)                | 7 (6%)                      | 5 (6%)                      |
| Maximum grade of TIPN c |                     |                              |                              |
| 0                 | 2 (1%)                 | 0 (0%)                      | 2 (3%)                      |
| 1                 | 76 (41%)               | 0 (0%)                      | 76 (97%)                    |
| 2                 | 91 (49%)               | 91 (84%)                    | 0 (0%)                      |
| 3                 | 17 (9%)                | 17 (16%)                    | 0 (0%)                      |
| Cumulative taxane dose (mg/m²) median (range) |                     |                              |                              |
| PTX               | 960 (560–1440) (N = 177) | 960 (560–1440) (N = 108) | 960 (688–1440) (N = 69) |
| DTX               | 300 (270–400) (N = 9)  | –                           | 300 (270–400) (N = 9)      |
| Time to develop TIPN (days) median (range) |                     |                              |                              |
|                  | 33 (7–79)              | 28 (7–79)                   | 35 (7–77)                   |
| Duration of TIPN (days) median (range) |                     |                              |                              |
|                  | 446 (0–1416)           | 455 (70–1395)               | 416 (0–1327)                |
| Grade of TIPN at 1 year after taxane |                     |                              |                              |
| 0                 | 44 (24%)               | 10 (9%)                     | 34 (44%)                    |
| 1                 | 74 (40%)               | 38 (35%)                    | 36 (46%)                    |
| 2                 | 41 (22%)               | 41 (38%)                    | 0 (0%)                      |
| 3                 | 2 (1%)                 | 2 (2%)                      | 0 (0%)                      |
| unknown           | 25 (13%)               | 17 (16%)                    | 8 (10%)                     |
| Full dose administration of taxane |                     |                              |                              |
|                  | 132 (71%)              | 63 (58%)                    | 69 (88%)                    |
| Dose reduction or termination of taxane due to TIPN |                     |                              |                              |
|                  | 38 (20%)               | 35 (32%)                    | 3 (4%)                      |
| Dose reduction or termination due to other reasons |                     |                              |                              |
|                  | 16 (8%)                | 10 (9%)                     | 6 (7%)                      |
| SCN9A rs7607967   |                       |                              |                              |
| GG                | 24 (13%)               | 15 (14%)                    | 9 (11%)                     |
| GA                | 84 (45%)               | 43 (40%)                    | 41 (53%)                    |
| AA                | 78 (42%)               | 50 (46%)                    | 28 (36%)                    |
| SCN9A rs12994338  |                       |                              |                              |
| TT                | 13 (7%)                | 9 (8%)                      | 4 (5%)                      |
| TC                | 80 (43%)               | 46 (43%)                    | 34 (44%)                    |
| CC                | 93 (50%)               | 53 (49%)                    | 40 (51%)                    |
| SCN9A rs13017637  |                       |                              |                              |
| TT                | 3 (2%)                 | 1 (1%)                      | 2 (3%)                      |
inherited erythromelalgia and paroxysmal extreme pain disorder, rare familial diseases associated with excruciating pain [26–28]. In contrast, loss-of-function mutations cause congenital pain insensitivity, a rare autosomal recessive disease [26, 27]. Rare missense variants have also been reported in SCN9A [29, 30] and SCN10A [30, 31] in patients with painful small fiber neuropathy. It is thought that enhanced Nav channel activity might directly contribute to pain experienced by these patients because several identified missense variants exerted GOF effects in cell-based electrophysiology assays [32]. Our findings indicate that SCN9A-rs13017637 is a risk factor for TIPN severity. However, the function of SCN9A-rs13017637 is not known. SCN10A-rs6795970 reportedly affects human pain sensitivity. A recent study suggested that SNPs in voltage-gated sodium channel genes (SCN9A-rs6746030 and SCN10A-rs12632942) can cause oxaliplatin-based peripheral neurotoxicity [24, 25, 33, 34]. A polymorphism in SCN9A (rs6746030) was also reported to be associated with decreased neurotoxicity [35]. However, these polymorphisms were not associated with TIPN in our study. Thus, there could be different predisposing polymorphisms for different ethnic groups. Moreover, a selective Nav1.7 channel blocker was shown to decrease firing frequency in the human DRG with spontaneous action potentials. This suggests that Nav1.7 might be a potential new target for TIPN treatment [19]. However, these results must be validated by larger and prospective studies.

There were some limitations to this study. First, we focused on paclitaxel or docetaxel as taxane regimens. There might be possible differences between paclitaxel and docetaxel regarding the severity or duration of PN. Moreover, platinum added to taxane might influence PN because it was reported as a risk factor for chemotherapy-induced PN [36]. Second, although cumulative drug doses were different, no adjustments were made for multiplicity of inferences. However, differences in cumulative doses were small and would be less likely to influence TIPN development. Third, our study focused on SCN9A and SCN10A, which were evaluated based on previous studies; other

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**Table 1** Patient characteristics (Continued)

| Gene | SNP | All patients (N = 186) | Cases TIPN Gr 2–3 (N = 108) | Control TIPN Gr 0–1 (N = 78) |
|------|-----|------------------------|-----------------------------|-----------------------------|
| TC   |     | CC                     | 37 (20%)                    | 16 (15%)                    | 21 (27%)                    |
|     |     | CA                     | 146 (78%)                   | 91 (84%)                    | 55 (70%)                    |
| SCN10A rs12632942 |   |                       |                             |                             |
| GG   |     | 44 (24%)               | 28 (26%)                    | 16 (20%)                    |
| GA   |     | 87 (47%)               | 49 (45%)                    | 38 (49%)                    |
| AA   |     | 55 (29%)               | 31 (29%)                    | 24 (31%)                    |
| SCN10A rs6795970 |   |                       |                             |                             |
| AA   |     | 4 (2%)                 | 3 (3%)                      | 1 (1%)                      |
| AG   |     | 47 (25%)               | 25 (23%)                    | 22 (28%)                    |
| GG   |     | 135 (73%)              | 80 (74%)                    | 55 (71%)                    |

| Gene | SNP | All patients (N = 186) | Cases TIPN Gr 2–3 (N = 108) | Control TIPN Gr 0–1 (N = 78) |
|------|-----|------------------------|-----------------------------|-----------------------------|
| TC   |     | CC                     | 37 (20%)                    | 16 (15%)                    | 21 (27%)                    |
|     |     | CA                     | 146 (78%)                   | 91 (84%)                    | 55 (70%)                    |
| SCN10A rs12632942 |   |                       |                             |                             |
| GG   |     | 44 (24%)               | 28 (26%)                    | 16 (20%)                    |
| GA   |     | 87 (47%)               | 49 (45%)                    | 38 (49%)                    |
| AA   |     | 55 (29%)               | 31 (29%)                    | 24 (31%)                    |
| SCN10A rs6795970 |   |                       |                             |                             |
| AA   |     | 4 (2%)                 | 3 (3%)                      | 1 (1%)                      |
| AG   |     | 47 (25%)               | 25 (23%)                    | 22 (28%)                    |
| GG   |     | 135 (73%)              | 80 (74%)                    | 55 (71%)                    |

**Table 2** SNPs correlate with severity of TIPN† (grade 0–1 vs. grade 2–3) in all patients and in breast cancer patients (subset analysis), and SNPs correlate with TIPN§ (grade 0–1 vs. grade 2–3) at 1 year after completion of taxane treatment in all patients

| Gene | SNP       | Odds ratio | Odds ratio (95% C.I. ‡) | P-value |
|------|-----------|------------|--------------------------|---------|
| SCN9A | rs7607967 | 1.749      | 0.889–3.441              | 0.1054  |
|      | rs1299438 | 0.952      | 0.492–1.841              | 0.8836  |
|      | rs13017637| 3.463      | 1.456–8.237              | 0.0050  |
| SCN10A | rs12632942 | 1.024      | 0.498–8.237              | 0.9491  |
|      | rs6795970 | 0.949      | 0.450–1.998              | 0.8894  |
| A subset analysis in Breast only | | | | | |
| SCN9A | rs7607967 | 1.822      | 0.864–3.842              | 0.1151  |
|      | rs1299438 | 0.913      | 0.442–1.888              | 0.8061  |
|      | rs13017637| 5.053      | 1.743–14.641             | 0.0029  |
| SCN10A | rs12632942 | 1.262      | 0.569–2.802              | 0.567   |
|      | rs6795970 | 1.135      | 0.515–2.501              | 0.7537  |

**Table 3** Patient characteristics (Continued)

| Analysis at 1 year after completion of taxane treatment in all patients | All patients (N = 186) | Cases TIPN Gr 2–3 (N = 108) | Control TIPN Gr 0–1 (N = 78) |
|----------------------------------------------------------|------------------------|-----------------------------|-----------------------------|
| SCN9A | rs7607967 | 0.735 | 0.313–1.728 | 0.4805 |
|      | rs1299438 | 0.952 | 0.418–2.167 | 0.9069 |
|      | rs13017637| 3.906 | 1.084–14.075 | 0.03719 |
| SCN10A | rs12632942 | 0.560 | 0.219–1.430 | 0.225 |
|      | rs6795970 | 1.834 | 0.697–4.826 | 0.2192 |

†TIPN taxane-induced peripheral neuropathy, ‡C.I. confidence interval
sodium channel subunits such as Nav1.9 were not evaluated. Fourth, there was a possible issue with type I error for this study because of multiple test.

**Conclusion**

TIPN was associated with SCN9A-rs13017637 in Japanese breast or ovarian cancer patients who received taxane. This finding is highly exploratory and requires replication and validation prior to any consideration of clinical use.

**Abbreviations**

TIPN: Taxane Induced Peripheral Neuropathy; VGSCs: Voltage Gated Sodium Channels; DRG: Dorsal Root Ganglion; SCN9A: Synuclein alpha; PN: Peripheral Neuropathy; AC: Doxorubicin and Cyclophosphamide; CEF: Cyclophosphamide and Epirubicin and 5-Fluorouracil; CPA: Cyclophosphamide; DTX: Docetaxel; TC: Carboplatin and Paclitaxel; ORs: Odds ratios; Cis: Confidence intervals; HWE: Hardy Weinberg Equilibrium; GOF: Gain Of Function

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**Authors’ contributions**

YT contributed to collecting data and writing the manuscript. YT, CS and DN was a major contributor in analyzing and interpreting the patient data. AS, YO, NT, MY, KY, TT, HK, KT contributed to collecting data. KH contributed the design of this work. SS was a major contributor in analyzing and interpreting the patient data. JH contributed to collecting data and writing the manuscript. YT, CS and DN were responsible for the final manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

All patients provided written informed consent for adjuvant treatment and DNA collection for genetic analysis. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of National Cancer Center Hospital and Toranomon Hospital.

**Consent for publication**

Not applicable.

**Competing interests**

The authors have no competing interests to declare.

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