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ARTICLE

Pharmacogenetics of taxane-induced neurotoxicity in breast cancer: Systematic review and meta-analysis

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Abstract

Taxane-based chemotherapy regimens are used as first-line treatment for breast cancer. Neurotoxicity, mainly taxane-induced peripheral neuropathy (TIPN), remains the most important dose-limiting adverse event. Multiple genes may be associated with TIPN; however, the strength and direction of the association remain unclear. For this reason, we systematically reviewed observational studies of TIPN pharmacogenetic markers in breast cancer treatment. We conducted a systematic search of terms alluding to breast cancer, genetic markers, taxanes, and neurotoxicity in Ovid, ProQuest, PubMed, Scopus, Virtual Health, and Web of Science. We assessed the quality of evidence and bias profile. We extracted relevant variables and effect measures. Whenever possible, we performed random-effects gene meta-analyses and examined interstudy heterogeneity with meta-regression models and subgroup analyses. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and STrengthening the REporting of Genetic Association Studies (STREGA) reporting guidance. A total of 42 studies with 19,431 participants were included. These evaluated 262 single-nucleotide polymorphisms (SNPs) across 121 genes. We conducted meta-analyses on 23 genes with 60 SNPs (19 studies and 6246 participants). Thirteen individual SNPs (ABCB1-rs2032582, ABCB1-rs3213619, BCL6/-rs1903216, /CAND1-rs17781082, CYP1B1-rs1056836, CYP2C8-rs10509681, CYP2C8-rs11572080, EPHA5-rs7349683, EPHA6-rs301927, FZD3-rs7001034, GSTP1-rs1138272, TUBB2A-rs9501929, and XKR4-rs4737264) and the overall SNPs' effect in four genes (CYP3A4, EphA5, GSTP1, and SLCO1B1) were statistically significantly associated with TIPN through meta-analysis. In conclusion, through systematic review and meta-analysis, we found that polymorphisms, and particularly 13 SNPs, are associated with TIPN, suggesting that genetics does play a role in interindividual predisposition. Further studies could potentially use these findings to develop individual risk profiles and guide decision making.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Taxane-induced peripheral neuropathy (TIPN) is currently the main dose-limiting taxane adverse effect. Its large interindividual variability, independent of known risk factors, suggests that there could be an underlying genetic basis for susceptibility. Individual genes have been reported to be associated with TIPN, but the inconsistent replication of these findings, which thus far has not been quantified through meta-analysis, has impeded their validation for clinical use.

WHAT QUESTION DID THIS STUDY ADDRESS?

We aimed to assess the role of polymorphisms in taxane-induced neurotoxicity, by retrieving all the reported genetic markers through systematic review, and quantifying their effect through meta-analysis.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Results suggest that genetic polymorphisms do play a role in interindividual TIPN predisposition. We present 13 consistently reported single-nucleotide polymorphisms that could potentially be used to predict the individual risk for developing TIPN. We also collect a wide array of singly reported polymorphisms that seem to be associated, but warrant further replication. Factors such as ethnicity may influence the effect some of these polymorphisms have in the development of neuropathy.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Toxicities can have a huge effect on quality of life. The use of genetic markers, such as those presented in this work, may aid clinicians to assess TIPN risk and tailor chemotherapy for patients with breast cancer, to minimize toxicities and improve outcomes. The information gathered in this study brings us closer to a holistic approach to precision medicine.

INTRODUCTION

Breast cancer is currently the most commonly occurring malignancy in the world, accounting for 2,261,419 new cases in 2020 alone.[1] Currently, taxane-based chemotherapy regimens (e.g., paclitaxel and docetaxel) are used as first-line treatment in early-stage, locally advanced, and metastatic breast cancer.[2] However, their toxicities limit their use, often necessitating dose reduction and, sometimes, even treatment discontinuation.[3–5] Neurotoxicity, mainly manifested as peripheral neuropathy, is currently the main dose-limiting taxane adverse effect.[6]

Taxane-induced peripheral neuropathy (TIPN) has important interindividual variability.[7] Prevalence of neuropathy of any grade, clinically significant neuropathy (grade 2 or higher), and dose-limiting neuropathy are, respectively, estimated to be 81%, 27%, and 10%.[3–5] Some factors, such as increased dosage and age, are known to be associated with increased susceptibility of developing TIPN, and an augmented severity when it does develop.[8,9] Still, there is a large interindividual variability independent of known risk factors, which suggests that there could be an underlying genetic basis for susceptibility.[10]

There is evidence suggesting that some single-nucleotide polymorphisms (SNPs) and other genetic variants may aid in predicting individual predisposition. Multiple genes associated with the pharmacokinetics of these drugs, including ABCB1, CYP2C8, and CYP3A4, as well as genes likely involved in TIPN pathophysiological pathways, including TUBB2A and EphAs, have been studied.[11] Even though some SNPs in these genes have been found to be associated with neuropathy, the inconsistent replication of these findings, which thus far has not been quantified through meta-analysis, has impeded their validation for clinical use.[12,13]

In addition to neuropathy, taxanes can cause central nervous system (CNS) toxicity, mainly manifested as cognitive dysfunction. Although less clearly defined and common than TIPN, prediction of taxane-induced central neurotoxicity is an emerging need.[6]

Given that taxanes are currently used as a first-line treatment in breast cancer, it is necessary to have a pharmacogenetic toxicity panel. This could potentially guide decision making in oncologic clinical practice in the near future. Hence, in the present study, we aim to identify, by systematic review and meta-analysis, all pharmacogenetic

markers reported (until July 6, 2020) to be associated with developing taxane neurotoxic adverse effects in patients with breast cancer.

METHODS

Protocol and registration

We conducted a comprehensive systematic review and a meta-analysis following the STrengthening the REporting of Genetic Association Studies (STREGA) recommendations[14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] Our protocol was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020197199, http://www.crd.york.ac.uk/prospero).

Eligibility criteria

We included indexed publications that met the following criteria: (1) observational reports (case control, cohort, cross-sectional, and nested designs), (2) full text availability, (3) evaluated the association of genetic markers (including SNPs, miRNAs, copy number variants [CNVs], etc.) on the development of neurotoxicity (TIPN or CNS toxicity), (4) included patients with breast cancer (any stage) undergoing taxane-based chemotherapy (paclitaxel or docetaxel), and (5) genetic variation assessment as a function of neurotoxicity development. Full inclusion and exclusion criteria are shown in Text S1.

Information sources and search strategy

To identify all potential observational studies that met the above criteria, we conducted a systematic search in Ovid, ProQuest, PubMed, Scopus, Virtual Health, and Web of Science databases. The literature was searched from the first available article to July 6, 2020. Using key terms from the research question, we developed a comprehensive search matrix, including control vocabulary and Boolean/logic operators. Our strategy is included within the supplementary material (Text S2).

Study selection

The titles and abstracts of all retrieved studies were assessed for eligibility independently by two reviewers in duplicate (authors A.G. and A.A., or A.P.). Disagreements were taken to a field expert reviewer (authors F.E., R.E., or C.V.). Later, a single reviewer (author A.G.) screened full texts for inclusion, consulting a field expert reviewer when necessary.

Quality of evidence and risk of bias assessment

Two reviewers independently (authors A.G. and A.A., or M.O.) assessed the quality of evidence and risk of bias profile for every included study. Quality of evidence was graded as per STREGA guidelines.[14] Sixteen biases (Text S3) were selected by a field expert for risk assessment. Every bias was graded as high, intermediate, or low risk.

Data collection process and items

Data extraction for all included studies was carried out by two reviewers independently (authors A.G. and A.A.) using a data extraction form, which included: manuscript data (lead author name, year, journal, and impact factor), treatment data (taxane and concomitant drugs), methodological data (sample size, study design, genotyping method, neurotoxicity clinical diagnostic parameters, type of toxicity, and cancer types studied), and population characteristics (mean age, ethnicity, and country).

To identify all genetic markers being studied, two reviewers (authors A.G. and M.O.) extracted all genes and polymorphisms reported in the main text, figures, or tables, and a list was made (Table S1); we did not access supplementary material for the making of this list. For each SNP, the corresponding reference (rs) number was collected directly from the text when available, or from the Single Nucleotide Polymorphism Database[16] when not provided.

Based on the list that was made (Table S1), every polymorphism reported in more than one study was added to a second extraction form, for meta-analysis inclusion. This form compiled variables known to be relevant in genetic association studies,[17,18] specifically: polymorphisms' major/minor alleles, minor allele frequencies, Hardy-Weinberg equilibrium *p* values, allelic counts, genotypic counts, effect measures (odds ratio [OR], hazard ratio [HR], or risk ratio), and genetic model (additive, dominant, or recessive). These variables were obtained by two reviewers independently (authors A.G. and M.O.) both from the main text/figures/tables and from the supplementary material. Once all extractable data was obtained, ORs were calculated from allelic or genotypic counts whenever possible. All genes with polymorphisms whose effect measures were available

TABLE 1 Study characteristics and main findings

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Öfverholm 2010[54]	36	Paclitaxel	NCI-CTCAE grade ≥1 neuropathy	White/Sweden	Breast and ovarian cancer	ABCB1 (rs1045642, rs2032582) CYP2C8 (rs10509681) CYP3A4 (rs2740574)	No association with neuropathy
Park 2014[55]	21	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White/Australia	Breast cancer only	GSK3B (rs6438552) MAPT (rs242557)	GSK3β (rs6438552), C/C genotype (homozygous wild-type), increased risk of neuropathy (OR = 2, 95% CI 0.899–4.452, $p = \leq .05$).
Peila 2016[57]	49	Both (paclitaxel or docetaxel)	NCI-CTCAE (-)	White/Italy	Breast, Hodgkin's and non-Hodgkin's lymphoma, duodenal-rectal, lung, other	IL-1α (rs1800587) IL-1β (rs16944)	IL-1β (rs16944) minor allele (T) carriers had an increased risk of neuropathy ($p = 0.029$).
Rizzo 2010[38]	95	Both (paclitaxel or docetaxel)	NCI-CTCAE grade ≥1 neuropathy	White/Italy	Breast cancer only	ABCB1 (rs1045642, rs2032582, rs2032582, rs1128503) CYP2C8 (rs10509681, rs1058930, rs11572080, rs11572103) CYP1B1 (rs1056836)	No association with neuropathy
Rua 2018[39]	176	Both (paclitaxel or docetaxel)	NCI-CTCAE grade ≥1 neuropathy	White/France	Breast cancer only	KCNN3 (#CAG repeats)	A shorter CAG total sum in KCNN3 (sum of CAG repeats < 37) increased risk of neuropathy (RR = 1.51; 95% CI 1.02–2.3; $p = 0.036$). Carrying two KCNN3 short alleles (<19 CAG repeats each) increased risk of neuropathy compared to patients with two long alleles (≥19 CAG repeats each) (RR = 2; 95% CI 1.2–8.1; $p = 0.016$).
Schneider 2015[24]	*ECOG-5103*: 3431 *EA subset from ECOG-5103*: 1357 *ECOG-1199 Validation Study*: 2407 *EA subset from ECOG-1199 Validation Study*: 789	*ECOG-5103*: Paclitaxel *EA subset from ECOG-5103*: Paclitaxel *ECOG-1199 Validation Study*: Both (paclitaxel or docetaxel) *EA subset from ECOG-1199 Validation Study*: Both (paclitaxel or docetaxel)	NCI-CTCAE grade ≥2 or grade ≥3 neuropathy	*ECOG-5103*: White, Black, and Other/USA *EA subset from ECOG-5103*: White/USA *ECOG-1199 Validation Study*: White, Black, and other/USA *EA subset from ECOG-1199 Validation Study*: White/USA	Breast cancer only	*ECOG-5103*: GWAS *ECOG-1199*: 120 SNPs	*EA subset from ECOG-5103* 120 SNPs had a p value of $<1\times10^{-4}$ for grade ≥3 neuropathy. 65 SNPs had a p value of $<1\times10^{-4}$ grade ≥2 neuropathy. *EA subset from ECOG-1199* rs3125923 variant (G) allele increased risk of grade ≥3 neuropathy after correction of multiple comparisons (OR = 1.8, $p = 1.7\times10^{-3}$). rs9862208 variant (A) allele increased risk of grade ≥3 neuropathy (OR = 1.9, $p = 5.9\times10^{-3}$).

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Tanabe 2017[40]	127	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	Asian/Japan	Breast cancer only	ABCB1 (rs1045642, rs203258, rs1128503) CYP2C8 (rs10509681) SLCO1B3 (rs4149117)	In the genotypic model no SNPs were significantly associated with neuropathy. In subgroup analysis, patients ≥60 years with ABCB1 (rs1128503), TT genotype (homozygous minor allele) had increased risk of neuropathy in the recessive model ($p = 0.027$). On multivariable analysis, ABCB1 (rs1128503), TT genotype (homozygous minor allele) had increased risk of neuropathy (OR = 2.404, 95% CI 1.067–5.419, $p = 0.034$).
Tanabe 2020[41]	135	Both (paclitaxel or docetaxel)	NCI-CTCAE grade ≥2 neuropathy	Asian/Japan	Breast cancer only	SCN9A (rs12994338, rs13017637, rs7607967) SCN10A (rs12632942, rs6795970)	SCN9A (rs13017637) increased risk of neuropathy in patients with breast cancer after correction for multiple comparisons (OR = 5.053, 95% CI 1.743–14.641, $p = 0.0029$).
Tolaney 2019[27]	230	Paclitaxel	(-) grade ≥2 neuropathy	White/USA	Breast cancer only	51 SNPs	LOC154449 (rs3012437), increased risk of neuropathy after correction for age and body surface area (OR = 2.1, $p = 0.024$).
Van Rossum 2017[28]	646	Docetaxel	NCI-CTCAE grade ≥2 neuropathy	White/Netherlands	Breast cancer only	GSTP1 (rs1695, rs1138272) RWDD3 (rs2296308) TECTA (rs1829)	TECTA (rs1829), TT genotype (homozygous minor allele), increased risk of neuropathy compared with homozygous major allele or heterozygous carriers (OR = 4.18, 95% CI 1.84–9.51, $p = 0.001$). GSTP1 (rs1138272), heterozygous and homozygous minor allele carriers, increased risk of neuropathy (OR = 2.04, 95% CI 1.13–3.68, $p = 0.018$).
Hertz 2013[42]	*Mixed-race cohort*: 411 *European-American cohort*: 209 *African American cohort*: 107	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White, Black, Other/USA	Breast cancer only	CYP2C8 (rs10509681)	*Mixed-race cohort*: CYP2C8*3 (rs10509681) variant allele, assuming an additive genetic effect, increased risk of neuropathy (HR [per allele] = 1.98, 95% CI: 1.25–3.13, $p = 0.004$). *European-American cohort*: CYP2C8*3 (rs10509681) variant allele, assuming an additive genetic effect, increased risk of neuropathy (HR [per allele] = 1.93, 95% CI: 1.05–3.55, $p = 0.032$). CYP2C8*3 (rs10509681) variant allele in multivariate analysis increased risk of neuropathy (HR [per allele] = 1.95, 95% CI: 1.06–3.58, $p = 0.031$). *African American cohort*: Patients carrying one CYP2C8*3 (rs10509681) variant allele had increased neuropathy risk than wild-type homozygous patients (HR = 3.30, 95% CI: 1.04–10.45, $p = 0.043$).

(Continues)

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Kober 2020[63]	50	Paclitaxel	-	White, Asian, Black, Hispanic, Other/USA	Breast cancer only	81 genes in the HIF-1 signaling pathway (methylation and expression)	Eight genes (TFRC, RBX1, PFKL, CUL2, MKNK1, EGLN1, LDHA, MAP2K2) were differentially methylated and expressed in patients with neuropathy compared to patients without neuropathy ($p = < 0.05$).
Komatsu 2015[25]	183	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	Asian/Japan	Breast, stomach, lung, esophageal, colorectal, prostate, ovarian, uterine, cervix, hematopoietic malignancy	Asian patient neuropathy: GWAS Asian lymphoblastoid cell lines cytotoxicity: GWAS	Four genome wide significant SNPs associated with neuropathy at $p = 5 \times 10^{-5}$. No genome wide significant SNPs associated with neuropathy at $p = 5 \times 10^{-8}$. Comparison of results from Asian lymphoblastoid cell lines cytotoxicity and Asian patient neuropathy at $p < 0.05$, had 32 overlap genes (HLA-DPA1, PTPMT1, ERAP2, GBP2, GBP7, CCDC121, AES, PILRB, TRAPPC1, MAML2, MAP3K8, DDX54, TRAF3IP2, WARS2, RILP, GSK3A, ANKDD1A, CMKLR1, SMARCD1, KIAA0748, TBKBP1, BBS2, C6orf145, CSTB, IFNGR1, ORMDL3, BCR, PVRIG, C22orf34, NFIC, C19orf6, STARD3NL).
Kus 2016[58]	219	Both (paclitaxel and docetaxel)	NCI-CTCAE grade ≥1 or grade ≥2 neuropathy	Middle Easterner/ Turkey	Breast cancer only	ABCB1 (rs1045642) CYP3A4 (rs2740574) ERCC2 (rs13181) CYP2C8 (rs1934951) ERBB2 (rs1136201) ERCC1 (rs3212935) FDGF4 (rs351855) P53 (rs1042522)	ABCB1 (rs1045642), TT genotype (homozygous minor allele) increased risk, compared to TC and CC genotype, of grade ≥2 neuropathy (OR = 2.759, 95% CI 1.172–6.493, $p = 0.017$). CYP3A4 (rs2740574), AA (homozygous major allele) and AG genotypes, increased risk, compared to GG genotypes, of grade ≥2 neuropathy. (OR = 2.259,95% CI 1.033–4.941, $p = 0.038$) compared to GG genotype. FDGF4 (rs351855), GG (homozygous major allele) and AG genotypes, increased risk, compared to AA genotype, for grade ≥1 neuropathy (OR = 1.879, 95% CI: 1.001–3.525, $p = 0.048$).
Lam 2016[29]	188	Paclitaxel	NCI-CTCAE grade ≥1 neuropathy	White/Netherlands	Breast cancer only	CYP2C8 (rs11572080) CYP3A4 (rs35599367) EPHA5 (rs7349683) TUBB2A (rs909964) FGD4 (rs10771973)	CYP2C8*3 (rs11572080) variant (A allele), in multivariate analysis (adjusting for age, body surface area, and total cumulative paclitaxel dose), increased risk of neuropathy (HR = 1.59, 95% CI 1.01–2.52, $p = 0.045$).
Leandro-García 2012[43]	214	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White/Spain, Sweden	Breast, ovary, lung, and others	TUBB2A (rs909964, rs909965, rs9501929)	TUBB2A-101C/-112G (rs909964/rs909965) haplotype decreased risk of developing neuropathy (HR = 0.60, 95% CI 0.41–0.90, $p = 0.012$). There was also increased risk in multivariate analysis, adjusting for treatment schedule (HR = 0.62; 95% CI 0.42–0.93; $p = 0.021$).

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Lee 2015[44]	343	Paclitaxel	-	White/Spain	Breast and ovarian	CYP2C8 (rs11572080)	No association with neuropathy
Lee 2013[45]	85	Paclitaxel	-	Asian/Korea	Breast cancer only	25 SNPs	RRM1 (rs9937) minor (G) allele carriers had a decreased risk of neuropathy in univariate analysis (OR = 0.328, 95% CI: 0.135–0.797, $p = 0.014$). RRM1 ATAA haplotype increased risk of developing neuropathy (OR = 3.281, 95% CI 1.230–8.756, $p = 0.018$). RRM1 ATGA haplotype decreased risk of developing neuropathy (OR = 0.328 95% CI 0.135–0.797, $p = 0.014$).
Leibovici 2018[46]	35	Paclitaxel	TNSr grade ≥2 neuropathy	Middle Easterner/ Israel	Breast cancer only	BDNF (rs6265)	BDNF (rs6265) Met allele carriers (minor allele) had an increased risk of neuropathy. No association with neuropathy after excluding the patients with pre-existing peripheral neuropathy.
Leskela 2011[59]	118	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White/Spain	Breast, lung, and ovarian	ABCB1 (rs1045642, rs2032582, rs1128503, rs9282564) CYP2C8 (rs11572080, rs1058930, rs1113129, rs7909236) CYP3A4 (rs2740574) CYP3A5 (rs776746) SLCO1B1 (rs4149056) SLCO1B3 (rs4149117, rs7311358)	CYP2C8*3 (rs11572080) increased risk of neuropathy (HR [per allele] = 1.72; 95% CI = 1.05–2.82; and $p = 0.032$) in multivariate analysis (adjusting for treatment schedule and age). CYP3A5*3 (rs776746) decreased risk of neuropathy (HR [per allele] = 0.51, 95% CI = 0.30–0.86, $p = 0.012$) in multivariate analysis (adjusting for treatment schedule and age). CYP2C8 (rs1113129) Haplotype C decreased risk of neuropathy (HR [per allele] = 0.55, 95% CI = 0.34–0.89, $p = 0.014$) in multivariate analysis (adjusting for treatment schedule and age).
Abraham 2014[30]	1303	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White/England, Scotland, Wales, Ireland, N Ireland	Breast cancer only	73 SNPs	CYP2C8 (rs1058930) minor (C) allele increased risk of neuropathy (OR = 1.48; 95% CI 1.02–2.15; $p = 0.04$). ABCB1 (rs2032582) minor (A) allele increased risk of neuropathy (OR = 1.22; 95% CI 1.03–1.45; $p = 0.02$). TUBB2A (rs9501929) minor (C) allele increased risk of neuropathy (OR = 1.80; 95% CI 1.20–2.72; $p = 0.005$). KIAA0146-PRKD (rs6473187) minor (G) allele increased risk of neuropathy (OR = 1.48; 95% CI 1.01–2.17; $p = 0.02$). EPHA6 (rs301927) minor (G) allele increased risk of neuropathy (OR = 1.35; 95% CI 1.07–1.70; $p = 0.01$).

(Continues)

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
							ABCB1 (rs1045642) minor (G) allele decreased risk of neuropathy (OR = 0.83; 95% CI 0.70–0.98; $p = 0.03$). ABCB1 (rs3213619) minor (G) allele decreased risk of neuropathy (OR = 0.47; 95% CI 0.28–0.79; $p = 0.004$). ABCC2 (rs8187710) minor (A) allele decreased risk of neuropathy (OR = 0.63; 95% CI 0.42–0.93; $p = 0.02$). ABCC2 (rs17222723) minor (A) allele decreased risk of neuropathy (OR = 0.66; 95% CI, 0.44–1.01; $p = 0.05$). CYP1B1 (rs1056836) minor (C) allele decreased risk of neuropathy (OR = 0.81; 95% CI, 0.68–0.96; $p = 0.02$). SLCO1B1 (rs3829306) minor (T) allele decreased risk of neuropathy (OR = 0.66; 95% CI 0.44–1.01; $p = 0.05$).
Apellaniz-Ruiz 2016[47]	Discovery series: 228 Validation cohort: 202	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White/Spain, Sweden	Discovery series: breast and ovarian Validation cohort: Breast, ovarian, and other	191 SNPs	*Discovery series*: EPHA5/6/8 low-frequency variants increased risk of neuropathy (HR = 14.60, 95% CI, 2.33–91.62, $p = 0.0042$). *Validation cohort*: EPHA5/6/8 low-frequency variants increased risk of neuropathy (HR = 2.07, 95% CI, 1.14–3.77; $p = 0.017$).
Arbitrio 2019[60]	Discovery set: 79 Validation set: 54	Both (paclitaxel or docetaxel)	NCI-CTCAE grade ≥2 neuropathy	White/Italy	Breast cancer only	1936 SNPs and 5 CNVs	*Discovery set*: UGT2B7 (rs743824) AA genotype (homozygous major allele) decreased risk of neuropathy ($p = 0.002$). UGT2B7 (rs7439366) TT genotype (homozygous major allele) decreased risk of neuropathy ($p = 0.002$). UGT2B7 (rs7662029) AA genotype (homozygous minor allele) decreased risk of neuropathy ($p = 0.002$). UGT2B7 (rs7668258) TT genotype (homozygous minor allele) decreased risk of neuropathy ($p = 0.002$). NR1I3 (rs11584174) GG genotype (homozygous minor allele) decreased risk of neuropathy ($p = 0.001$). *Validation set*: The AUC computed from the ROC-curve generated by testing these 5 SNPs in the Validation Set is equal to 0.676 offering clear validation.

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Baldwin 2012[31]	*Discovery Cohort (CALGB 40101)*: 855 *European Replication Cohort*: 154 *African American Replication Cohort*: 117	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	*Discovery Cohort*: White/USA European *Replication Cohort*: White/USA *African American Replication Cohort*: African American/ USA	Breast cancer only	GWAS	*Top SNPs from cumulative dose to event analysis*: EPHA5 (rs7349683) minor (T) allele increased risk of neuropathy in the discovery cohort (HR [per allele] = 1.63, 95% CI 1.34–1.98, $p = 9.6\times10^{-7}$) XKR4 (rs4737264) minor (A) allele increased risk of neuropathy in the discovery cohort (HR [per allele] = 1.68, 95% CI 1.36–2.09, $p = 1.9\times10^{-6}$), and European Replication Cohort (HR [per allele] = 1.84, 95% CI 1.02–3.3, $p = 0.021$) in the European Replication Cohort. FGD4 (rs10771973) minor (A) allele increased risk of neuropathy in the discovery cohort (HR [per allele] = 1.57, 95% CI 1.30–1.91, $p = 2.6\times10^{-6}$), in the European Replication Cohort (HR [per allele] = 1.72, 95% CI 1.06–2.80, $p = 0.013$) and the African American Replication Cohort: (HR [per allele] = 1.93, 95% CI 1.13–3.28, $p = 6.7\times10^{-3}$). PITPNA (rs16948748) minor (G) allele increased risk of neuropathy in the discovery cohort (HR = 2.37, 95% CI 1.63–3.44, $p = 2.7\times10^{-6}$). CACNB2 (rs16916932) minor (T) allele increased risk of neuropathy in the discovery cohort (HR = 2.08, 95% CI 1.51–2.87, $p = 4.3\times10^{-6}$). GRIP1/CAND1 (rs17781082) minor (T) allele increased risk of neuropathy in the discovery cohort (HR = 1.60, 95% CI 1.31–1.96, $p = 4.3\times10^{-6}$). BCL6/ (rs1903216) minor (A) allele increased risk of neuropathy in the discovery cohort (HR = 1.59, 95% CI 1.30–1.95, $p = 5.6\times10^{-6}$) and the African American Replication Cohort in the recessive model (HR = 1.59, 95% CI 1.30–1.95, $p = 0.016$). NDRG1 (rs2233335) minor (G) allele decreased risk of neuropathy in the discovery cohort (HR = 0.65, 95% CI 0.52–0.80, $p = 5.2\ 10^{-5}$). *Top SNPs from Ordinal Analysis*: FZD3 (rs7001034) minor (T) allele decreased risk of neuropathy in the discovery cohort (OR = 0.57, 95% CI 0.48–0.69, $p = 3.1\times10^{-9}$). /SHROOM2 (rs5934683) minor (T) allele increased risk of neuropathy risk of neuropathy in the discovery cohort (OR = 1.61, 95% CI 1.33–1.93, $p = 6.0\times10^{-7}$). /ZFPM2 (rs2941627) minor (G) allele increased risk of neuropathy in the discovery cohort (OR = 1.91, 95% CI 1.40–2.51, $p = 3.5\times10^{-6}$). /BCAT1 (rs7973533) minor (G) allele decreased risk of neuropathy in the discovery cohort (OR = 0.66, 95% CI 0.55–0.79, $p = 8.4\times10^{-6}$).

(Continues)

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Bayraktar 2020[48]	719	Both (paclitaxel or docetaxel)	NCI-CTCAE grade ≥1 neuropathy	White, Black, Hispanic, other/USA	Breast cancer only	BRCA1 (Pathogenic variants) BRCA2 (Pathogenic variants)	No association with neuropathy.
Boora 2016[61]	119	Paclitaxel	CIPN20	- / USA	Breast, ovarian/ fallopian, lung, head and neck, endometrial, other	22 SNPs	EPHA5 (rs7349683) minor (T) allele increased the risk of neuropathy (OR = 2.07, 95% CI 1.08–4.10, $p = 0.02$) in the additive model. ABCB1 (rs3213619) minor (G) allele decreased the risk of neuropathy (OR = 0.12, 95% CI 0.00–1.11, $p = 0.03$) in the additive model.
Bosó 2014[49]	113	Both (paclitaxel or docetaxel)	NCI- CTCAE grade ≥2 neuropathy	White/Spain	Breast cancer only	47 SNPs	ERCC1 (rs3212986) T allele carriers (minor allele) had increased risk of neuropathy ($p = 0.039$), in multivariate analysis adjusting for (age, metastatic disease, and chemotherapy protocol) for the 43 patients treated with paclitaxel. SOD2 (rs4880) C allele carriers (minor allele) had decreased risk of neuropathy ($p = 0.039$), in multivariate analysis adjusting for (age, metastatic disease, and chemotherapy protocol) for the 43 patients treated with paclitaxel.
Chang 2009[50]	103	Paclitaxel	-	-	Breast cancer only	ABCB1 (rs2032582, rs1045642)	No association with neuropathy
Ciruelos 2019[32]	60	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White/Spain	Breast cancer only	ABCB1 (rs1045642) CYP2C8 (rs11572080) CYP3A4 (rs35599367, s67666821) EPHA5 (rs7349683) EPHA6 (rs301927) EPHA8 (rs209709)	*Univariate analysis*: EPHA5 (rs7349683) variant (A) allele increased risk of peripheral neuropathy (HR = 3.08, 95% CI 1.34–7.08, $p = 0.008$) in the recessive model. EPHA8 (rs209709) variant (G) allele increased risk of peripheral neuropathy (HR = 2.43, 95% CI 1.17–5.05, $p = 0.017$). *Multivariate analysis*: EPHA5 (rs7349683) variant (A) allele increased risk of peripheral neuropathy (HR = 2.96, 95% CI 1.27–6.91, $p = 0.012$) in the recessive model. EPHA6 (rs301927) variant (G) allele increased risk of peripheral neuropathy (HR = 3.69, 95% CI 1.34–10.18, $p = 0.012$) in the dominant model. EPHA8 (rs209709) variant (G) allele increased risk of peripheral neuropathy (HR = 2.89, 95% CI 1.32–6.33, $p = 0.008$)

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
De Graan 2013[33]	*Exploratory cohort*: 261 *Validation cohort*: 239	Paclitaxel	NCI-CTCAE grade ≥1 neuropathy or grade ≥3 neuropathy	White/Netherlands	Breast, esophagus, ovary, cervix, endometrial, lung, head/neck, adenoma/adenocarcinoma of unknown origin, other	ABCB1 (rs1045642) CYP2C8 (rs10509681) CYP2C8 (rs1058932) CYP3A4 (rs35599367)	*Exploratory cohort*: CYP3A4 (rs35599367), CYP3A4*22 allele increased risk of peripheral neuropathy ($p = 0.043$) in women. *Validation cohort*: CYP3A4 (rs35599367), CYP3A4*22 allele increased risk of grade ≥3 peripheral neuropathy (OR = 19.1, 95% CI 3.3–110, $p = 0.001$) in women.
Di Francia 2017[7]	35	Both (paclitaxel or docetaxel)	NCI-CTCAE grade ≥1 neuropathy	White/Italy	Breast, genitourinary, gastric, other	ABCB1 (rs1045642, rs2032582) CYP2C8 (rs10509681) CYP3A4 (rs2740574) CYP3A4 (rs35599367) GSTP1 (rs1695) SLCO1B1 (rs4149056) ERCC2 (rs13181) ABCG2 (rs2231137) XRCC3 (rs1799794)	The XRCC3 (rs1799794), G allele (minor allele) increased risk of neuropathy (OR = 2.61, 95% CI 0.91–7.61, $p = 0.03$) in the dominant model
Dorling 2016[23]	1279	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White/UK	Breast cancer only	94 genetic variants known to increase the risk of breast cancer	No association with neuropathy
Eckhoff 2014[62]	150	Docetaxel	NCI-CTCAE grade ≥2 neuropathy	White/Denmark	Breast cancer only	22 SNPs	GSTP1 (rs1138272) T allele (minor allele) carriers had an increased risk of neuropathy. After adjustment in a multivariate analysis rs1138272 retained its significance (OR = 3.85, 95% CI 1.34–11.09). GSTP1 (rs1138272) T allele (minor allele) carriers association with increased risk of neuropathy was confirmed in the time-to-neuropathy analysis (HR = 1.90, 95% CI 1.11–3.26, $p = 0.02$).
Hertz 2012[51]	109	Paclitaxel	NCI-CTCAE grade ≥3 neuropathy	White, Black, other/USA	Breast cancer only	CYP1B1 (rs1056836), CYP2C8 (rs11572080, rs10509681), CYP3A4 (rs2740574), CYP3A5 (rs776746), ABCB1 (rs1045642, rs2032582, rs1128503).	No statistically significant association with neuropathy

(Continues)

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Hertz 2014[52]	*White cohort*: 285 *Non-White cohort*: 124	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White, Black, other/ USA	Breast cancer only	CYP2C8 (rs11572103, rs10509681, rs1058930) and 564 genetic markers in the DMET Discovery analysis	CYP2C8 low-metabolizer phenotype group; patients carrying CYP2C8*2, *3 or *4 (rs11572103, rs10509681 or rs1058930) alleles had an increased risk of neuropathy (HR = 1.722, 95% CI 1.10–2.70, $p = 0.018$). In the DMET Discovery analysis, the variants with strongest association with neuropathy occurrence in the White patients were ABCG1 (rs492338) with $p = 0.0008$, CYP4A11 (rs11211402) with $p = 0.0010$, CYP4B1 (rs4646487) with $p = 0.0015$, GSTA5 (rs4715354) with $p = 0.0018$, ABCG1 (rs3788007) with $p = 0.0033$, CBR1 (rs998383) with $p = 0.0037$, ABCC1 (rs246221) with $p = 0.0039$, GSTA1 (rs4715332) with $p = 0.0049$, SLC16A1 (rs1049434) with $p = 0.0056$ and CYP17A1(rs6163) with $p = 0.0066$. ABCG1 (rs492338) minor (T) allele increased the risk of neuropathy, and surpassed the exploratory significance threshold for association in the White cohort ($p = 0.0008$). Values for the C/T genotype were OR = 1.70, 95% CI, 0.63–5.37, $p = 0.38$ compared to homozygous wildtype and for T/T genotype OR = 4.70, 95% CI: (1.64–15.57) $p = 0.002$. In the cumulative dose at onset of neuropathy (HR [per allele] = 2.11, 95% CI: 1.36–3.29, $p = 0.0008$). No association was found in the non-White cohort.
Marcath 2019[53]	60	Paclitaxel	CIPN8 score ≥30	White/United States	Breast cancer only	EPHA4 (rs17348202, rs768964879) EPHA5 (rs7349683, rs33932471, rs36050417) EPHA8 (rs144329757, rs45498698, rs62618734, rs999765, rs147795823, rs149515751, rs200304246, rs569320402)	EPHA5 (rs7349683) minor allele increased risk of neuropathy (β-coefficient = 0.39, 95% CI 0.11–0.67, $p = 0.007$). Carrying a greater number of EPHA genes missense variants (rs45498698, rs144329757, rs999765, rs569320402, rs62618734, rs147795823, rs149515751, rs200304246, rs768964879, rs36050417, rs33932471) was associated with decreased risk of neuropathy (β-coefficient = −0.42, 95% CI −0.72 to −0.12, $p = 0.006$).

TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Schneider 2016[26]	*AA patients from ECOG-5103*: 213	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy or NCI-CTCAE grade ≥3 neuropathy	African American/ USA	Breast cancer only	8958 genes for the grade ≥2 analysis, 7260 genes for the grade ≥3 analysis	Three genes (SBF2, OR51B6, LRP3) had a p value $< 10^{-4}$ for grade ≥2 neuropathy. Five genes (SBF2, OR51B6, SLCO2A1, ABCA2, MSH5) had p value $< 10^{-4}$ for grade ≥3 neuropathy. For grade ≥3 neuropathy, the top association was with SBF2 and was statistically significant for an increased risk ($p = 4.35 \times 10^{-6}$). Patients carrying any of the five deleterious variants in SBF2 (rs149501654, rs117957652, rs141368249, rs146987383, rs7102464) had an increased risk of grade ≥2 neuropathy (OR = 3.26) and grade ≥3 neuropathy (OR = 5.09).
Sucheston 2011[34]	888	Paclitaxel	NCI-CTCAE grade ≥3 neuropathy or FACT-TAX score >64	White, Black, Asian, Other/USA	Breast cancer only	39 SNPs	FANCD2 (rs7648104, rs7637888, rs6786638, rs6442150) increased risk of NCI-CTCAE grade ≥2 neuropathy by approximately twofold ($p < 0.001$). The four FANCD2 SNPs also increased risk of developing >64 score neuropathy in relation to FACT-TAX (rs7637888, (OR = 1.47, 95% CI 1.00–2.15), rs6786638 (OR = 1.47, 95% CI 1.00–2.15), rs6442150 OR = 1.4,7 95% CI = 1.00–2.15) and rs7648104 (OR = 1.53, 95% CI, 1.05–2.25). FANCD2 haplotype (rs3846177-rs9849434) increased risk of neuropathy (OR = 1.8, 95% CI 1.3–2.5, $p = 0.005$) FANCD2 haplotype (rs1552244-rs12152512) increased risk of neuropathy (OR = 1.7, 95% CI 1.2–2.4, $p = 0.007$) In Black patients FANCD2 haplotype (rs7648104-rs7637888) increased of neuropathy (OR = 1.6, 95% CI 11.1–2.4, $p = 0.03$)
Sucheston 2018[35]	1408	Paclitaxel	NCI-CTCAE grade ≥3	White, Black/USA	Breast cancer only	1M Chip	*European Americans (n = 1269)*: GNGT1(rs1858826) minor (G) allele decreased risk (OR = 0.21, 95% CI 0.10–0.46, $p = 8.2 \times 10^{-7}$). NXN (rs910920) minor (A) allele decreased risk (OR = 0.44, 95% CI 0.32–0.61, $p = 1.3 \times 10^{-7}$).

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TABLE 1 (Continued)

Taxane-induced peripheral neuropathy							
Author	***N***	**Taxane**	**Definition of neuropathy**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
							MIR5684 (rs1857798) minor (C) allele decreased risk (OR = 0.73, 95% CI 0.56–0.95, $p = 0.01$). FGD2 (rs12202642) minor (T) allele increased risk (OR = 2.98, 95% CI 1.6–5.4, $p = 0.02$). *African Americans (n = 139)*: GNGT1 (rs1858826) minor (G) allele decreased risk (OR = 0.26, 95% CI 0.07–0.95, $p = 0.04$). MIR5684 (rs1857798) minor (C) allele decreased risk (OR = 0.33, 95% CI 0.11–0.99, $p = 0.04$). FGD2 (rs12202642) minor (T) allele increased risk (OR = 13.7, 95% CI 1.06–175.7, $p = 0.04$).
Wheeler 2012[36]	855	Paclitaxel	NCI-CTCAE grade ≥2 neuropathy	White/USA	Breast cancer only	*CALGB 40101*: GWAS *European lymphoblastoid cell lines cytotoxicity assays*: GWAS	Comparison of results from lymphoblastoid cell lines cytotoxicity ($p < 0.001$) and CALGB 40101 patient neuropathy ($p < 0.05$), had 24 overlap SNPs (rs285428, rs1470558, rs7612941, TMEM44-rs7642318, TMEM44-rs10933663, rs6897671, rs9313818, rs1422857, KCNIP1-rs4868011, rs1624675, rs1796502, rs331455, rs724095, C12orf42-rs10778237, C12orf42-rs11111539, C12orf42-rs7306825, rs1782808, DIS3-rs8002545, XYLT1-rs4782010, RICH2-rs8069856, KIAA1328-rs323285, RFX2-rs7254081, rs2364513, rs10403813)

Taxane-induced Central neurotoxicity							
Author	***N***	**Taxane**	**Toxicity measurement and definition**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Ng 2016[37]	145	Both (paclitaxel or docetaxel)	*Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog)*: Cognitive Impairment was defined as a reduction of ≥10.6 points in the FACT-Cog summation score 6 weeks after the start of treatment or at the end of chemotherapy (3 months after the start of treatment) compared with the baseline value.	Asian/Singapore	Breast cancer only	BDNF (rs6265)	*(FACT-Cog): Cognitive Impairment*: After adjusting for clinically documented confounders and working status, BDNF (rs6265) homozygous minor allele (T = Met) genotype decreased risk of developing cognitive decline compared to homozygous major allele (C = Val) genotype (OR = 0.26, 95% CI: 0.08–0.92, $p = 0.036$).

TABLE 1 (Continued)

Taxane-induced Central neurotoxicity							
Author	***N***	**Taxane**	**Toxicity measurement and definition**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/ variant)[a]**	**Main findings[b]**
			Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog): Cognitive impairment in a particular cognitive domain was defined as a 15% score reduction at 6 weeks after the start of treatment or at the end of chemotherapy compared with the baseline value. Must have been at least 15% lower than his or her baseline score. *Headminder* (neuropsychological battery for examining patients' cognitive function in 4 domains): A reliable change index was calculated based on the repeated normative mean and standard error of the difference to adjust for the practice effect. Cognitive Impairment was defined as having a reliable change index score lower than -1.5. Fatigue and anxiety were measured and accounted as confounders.				*(FACT-Cog)*: *Cognitive Domains*: BDNF (rs6265) heterozygous genotype decreased risk of developing impairment in the multitasking ability domain compared with the homozygous major allele (C = Val) genotype (OR = 0.34, 95% CI 0.13–0.90, $p = 0.030$). BDNF (rs6265) homozygous minor allele (T = Met) genotype decreased risk of developing impairment in the verbal fluency domain compared with the homozygous major allele (C = Val) genotype (OR = 0.26, 95% CI: 0.07–0.96, $p = 0.043$) Overall, BDNF (rs6265) minor allele (T = Met) carriers were less likely to experience impairment in the domains of verbal fluency (OR = 0.34, 95% CI 0.12–0.90, $p = 0.031$) and multitasking ability (OR = 0.37, 95% CI 0.15–0.91, $p = 0.030$) compared with the homozygous major allele (C = Val) genotype. *Headminder*: No association with cognitive impairment.
Peila 2016[56]	49	Both (Paclitaxel or Docetaxel)	Mini Mental State Examination (MMSE): cognitive impairment when <24 score. Hospital Anxiety and Depression Scale (HADS): ≥8 indicates case of clinical anxiety and depression.	White/Italy	Breast, Hodgkin's and non-Hodgkin's lymphoma, duodenal-rectal, lung, other	IL-1α (rs1800587) IL-1β (rs16944)	No association with cognitive impairment, anxiety or depression

(Continues)

TABLE 1 (Continued)

Taxane-induced Central neurotoxicity							
Author	***N***	**Taxane**	**Toxicity measurement and definition**	**Ethnicity/country**	**Cancer types**	**Gene (SNP/variant)[a]**	**Main findings[b]**
Small 2010[57]	72	Both (paclitaxel or docetaxel)	Cognitive performance was assessed using a battery of neuropsychological tests: The National Adult Reading Test (NART) for overall intellectual ability assessment Three items from California Verbal Learning Test (CVLT) and three items from the Visual Reproduction subtest of the Wechsler Memory Scales-III (WMS-III) for episodic memory assessment Digit Span, Spatial Span subtests of the WAIS-II and trial 1 from the Color Trails Test for attention assessment Digit Symbol subtest of the WAIS-III and trial 2 of the Color Trails Test for complex cognition assessment Controlled Oral Word Association (COWA) test for verbal fluency assessment The Finger Oscillation Test (dominant and nondominant hands) for Motor speed assessment	White/USA	Breast cancer only	COMT (rs4680)	COMT (rs4680) minor allele carriers (A = Met) exhibited superior performance on tests across cognitive domains relative to major allele carriers (G = Val) (d = 0.46; 95% CI 0.20–0.73). COMT (rs4680) minor allele carriers (A = Met) exhibited superior performance on tests of attention relative to major allele carriers (G = Val) ($p < 0.001$; d = 0.96).

Note: This table describes the included studies' most relevant retrieved variables, stratified by type of neurotoxicity (peripheral or central). Spared variables can be reviewed in Table S2. EA: European American, -: not reported, a: genes and variants were not reported whenever an article assessed more than 20, instead the total SNP/variant number was reported. b: statistically significant findings of genetic associations with neurotoxicity are shown.

Abbreviations: CI, confidence interval; CNV, copy number variant; ECOG, Eastern Cooperative Oncology Group; GWAS, genomewide association study; HR, hazard ratio; NCI-CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events; OR, odds ratio; RR, risk ratio; SNP, single-nucleotide polymorphism.

TABLE 2 Meta-analyses results

Gene	SNP	Neuropathy Risk	Major Allele	Minor Allele	OR (95% CI)	I^2	N	Reference Genes
ABCB1	All SNPs				1.07 (0.96–1.20)	46%		Apellaniz-Ruiz 2017, Ciruelos 2019, Leskela 2011, Abraham 2014, Boora 2016, Hertz 2012, Kus 2016, De Graan 2013, Eckhoff 2014, Öfverholm 2010, Tanabe 2017
ABCB1	rs1045642		C	T	1.08 (0.89–1.30)	41%	2543	Ciruelos 2019, Leskela 2011, Abraham 2014, Boora 2016, Hertz 2012, Kus 2016, De Graan 2013, Eckhoff 2014, Öfverholm 2010, Tanabe 2017
ABCB1	rs1128503		C	T	1.33 (0.90–1.95)	37%	506	Leskela 2011, Hertz 2012, Tanabe 2017, Eckhoff 2014
ABCB1	**rs2032582**	**Increased**	**G**	**T**	**1.22 (1.07–1.40)**	**0%**	**1926**	Leskela 2011, Abraham 2014, Boora 2016, Hertz 2012, Eckhoff 2014, Tanabe 2017
ABCB1	rs9282564		T	C	0.70 (0.40–1.22)	0%	346	Leskela 2011, Apellaniz-Ruiz 2017
ABCB1	rs2229109		C	T	0.51 (0.17–1.56)	NA	228	Apellaniz-Ruiz 2017
ABCB1	**rs3213619**	**Decreased**	**A**	**G**	**0.46 (0.28–0.77)**	**0%**	**1422**	Abraham 2014, Boora 2016
ABCB1	rs55852620		T	G	1.01 (1.00–1.03)	NA	228	Apellaniz-Ruiz 2017
ABCC2	All SNPs				1.04 (0.44–2.48)	50%		Boora 2016, Abraham 2014
ABCC2	rs17222723		T	A	1.94 (0.39–9.58)	NA	119	Boora 2016
ABCC2	rs8187710		G	A	0.91 (0.32–2.63)	60%	1422	Boora 2016, Abraham 2014
BCL6/	All SNPs				1.56 (1.07–2.26)	44%	BCL6	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
BCL6/	**rs1903216**	**Increased**	**G**	**A**	**1.56 (1.07–2.26)**	**44%**	**1245**	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
CACNB2	All SNPs				0.91 (0.37.2.24)	72%		Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
CACNB2	rs16916932		C	T	0.91 (0.37.2.24)	72%	1,245	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
/CAND1	All SNPs				1.32 (1.01–1.73)	39%		Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
/CAND1	**rs17781082**	**Increased**	**C**	**T**	**1.32 (1.01–1.73)**	**39%**	**1245**	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
CYP1B1	All SNPs				0.81 (0.68–0.96)	0%		Abraham 2014, Hertz 2012
CYP1B1	**rs1056836**	**Decreased**	**G**	**C**	**0.81 (0.68–0.96)**	**0%**	**1414**	Abraham 2014, Hertz 2012

(Continues)

TABLE 2 (Continued)

Gene	SNP	Neuropathy Risk	Major Allele	Minor Allele	OR (95% CI)	I^2	N	Reference Genes
CYP2C8	All SNPs				1.12 (0.91–1.39)	48%		Leskela 201, Abraham 2014, Ciruelos 2019, Lam 2016, Lee 2015, Kus 2016, Hertz-E 2013, Hertz-A 2013, Apellaniz-Ruiz 2017, Boora 2016, Hertz 2012, DiFrancia 2017, DeGraan 2013
CYP2C8	**rs10509681**	**Increased**	**T**	**C**	**1.48 (1.08–2.03)**	**13%**	**909**	Hertz-E 2013, Hertz-A 2013, Apellaniz-Ruiz 2017, Boora 2016, Hertz 2012, DiFrancia 2017, DeGraan 2013
CYP2C8	rs1058930		G	C	0.69 (0.32–1.50)	75%	1768	Leskela 2011, Apellaniz-Ruiz 2017, Boora 2016, Abraham 2014
CYP2C8	rs1113129		G	C	0.55 (0.34–0.89)	NA	118	Leskela 2011
CYP2C8	**rs11572080**	**Increased**	**C**	**T**	**1.37 (1.09–1.73)**	**0%**	**858**	Ciruelos 2019, Lam 2016, Lee 2015, Leskela 2011, Apellaniz-Ruiz 2017, Boora 2016
CYP2C8	rs7909236		G	T	0.86 (0.49–1.51)	NA	118	Leskela 2011
CYP2C8	rs1934951		C	T	0.97 (0.33–2.87)	NA	89	Kus 2016
CYP2C8	rs41286886		C	T	0.74 (0.01–56.51)	NA	228	Apellaniz-Ruiz 2017
CYP2C8	rs1058932		C	G	0.52 (0.20–1.36)	NA	98	Apellaniz-Ruiz 2017
CYP3A4*	All SNPs	Increased*			1.53 (1.10–2.11)*	0%		Leskela 2011, Kus 2016, Eckhoff 2014, Ciruelos 2019, DiFrancia 2017, DeGraan 2013, Apellaniz-Ruiz 2017
CYP3A4	rs2740574		A	G	1.60 (0.98–2.62)	3%	487	Leskela 2011, Kus 2016, Eckhoff 2014
CYP3A4	rs35599367		C	T	1.37 (0.86–2.18)	0%	307	Ciruelos 2019, DiFrancia 2017, DeGraan 2013
CYP3A4	rs67666821		T	TT	2.48 (0.66–9.31)	0%	285	Ciruelos 2019, Apellaniz-Ruiz 2017
CYP3A5	All SNPs				0.83 (0.33–2.07)	72%		Leskela 2011, Eckhoff 2014
CYP3A5	rs776746		A	G	0.83 (0.33–2.07)	72%	268	Leskela 2011, Eckhoff 2014
EPHA5*	All SNPs	Increased*			1.50 (1.15–1.95)*	28%		Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Ciruelos 2019, Boora 2016, Apellaniz-Ruiz 2017
EPHA5	**rs7349683**	**Increased**	**C**	**T**	**1.55 (1.13–2.14)**	**46%**	**1302**	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Ciruelos 2019, Boora 2016
EPHA5	rs33932471		T	G	1.34 (0.53–3.42)	NA	228	Apellaniz-Ruiz 2017
EPHA5	rs36050417		C	T	0.86 (0.24–3.12)	NA	228	Apellaniz-Ruiz 2017

TABLE 2 (Continued)

Gene	SNP	Neuropathy Risk	Major Allele	Minor Allele	OR (95% CI)	I^2	N	Reference Genes
EPHA6	All SNPs				1.22 (0.90–1.64)	77%		Ciruelos 2019, Abraham 2014, Apellaniz-Ruiz 2017
EPHA6	**rs301927**	**Increased**	**A**	**G**	**1.42 (1.05–1.92)**	**9%**	**1360**	Ciruelos 2019, Abraham 2014
EPHA6	rs4857276		C	T	1.01 (1.00–1.03)	NA	228	Apellaniz-Ruiz 2017
ERCC1	All SNPs				1.77 (0.35–8.90)	77%		Eckhoff 2014, Bosó 2015
ERCC1	rs3212986		C	A	1.77 (0.35–8.90)	77%	162	Eckhoff 2014, Bosó 2015
ERCC2	All SNPs				0.93 (0.30–2.88)	73%		
ERCC2	rs13181		T	G	0.93 (0.30–2.88)	73%	254	DiFrancia 2017, Kus 2016
FGD4	All SNPs				1.38 (0.95–2.03)	61%		Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016, Apellaniz-Ruiz 2017
FGD4	rs10771973		G	A	1.39 (0.93–2.07)	70%	1275	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
FGD4	rs144693221		C	A	0.74 (0.01–56.51)	NA	228	Apellaniz-Ruiz 2017
FZD3	All SNPs				0.81 (0.59–1.11)	78%		Baldwin-D 2012, Baldwin-E 2012, Boora 2016
FZD3	**rs7001034**	**Decreased**	**G**	**A**	**0.65 (0.43–0.99)**	**52%**	**974**	Baldwin-D 2012, Boora 2016
FZD3	rs7833751		G	T	1.03 (0.49–2.15)	87%	1829	Baldwin-D 2012, Baldwin-E 2012, Boora 2016
GSTP1*	All SNPs	Increased*			1.56 (1.07–2.26)*	37%		DiFrancia 2017, Van Rossum 2017, Eckhoff 2014
GSTP1	**rs1138272**	**Increased**	**C**	**T**	**2.34 (1.42–3.85)**	**0%**	**792**	Eckhoff 2014, Van Rossum 2017
GSTP1	rs1695		A	G	1.21 (0.86–1.70)	0%	823	DiFrancia 2017, Van Rossum 2017, Eckhoff 2014
NDRG1	All SNPs				0.90 (0.63–1.30)	60%		Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
NDRG1	rs2233335		T	G	0.90 (0.63–1.30)	60%	1245	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
PITPNA	All SNPs				1.56 (0.81–2.99)	51%		Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
PITPNA	rs16948748		T	G	1.56 (0.81–2.99)	51%	1,245	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
SBF2	All SNPs				0.96 (0.64–1.44)	0%		
SBF2	rs117957652		G	C	0.93 (0.12–6.96)	35%	405	Apellaniz-Ruiz 2017, Schneider 2016
SBF2	rs12574508		G	C	0.81 (0.43–1.51)	NA	228	Apellaniz-Ruiz 2017

(Continues)

TABLE 2 (Continued)

Gene	SNP	Neuropathy Risk	Major Allele	Minor Allele	OR (95% CI)	I^2	N	Reference Genes
SBF2	rs7102464		C	T	1.12 (0.59–2.12)	6%	405	Apellaniz-Ruiz 2017, Schneider 2016
SBF2	rs149501654		C	G	1.01 (0.04–25.17)	NA	177	Schneider 2016
SBF2	rs141368249		G	A	3.09 (0.16–58.18)	NA	177	Schneider 2016
SLCO1B1*	All SNPs	Decreased*			0.80 (0.65–0.98)*	0%		
SLCO1B1	rs4149056		T	C	1.02 (0.71–1.48)	0%	381	Leskela 2011, Apellaniz-Ruiz 2017, DiFrancia 2017
SLCO1B1	rs11045819		C	A	0.71 (0.40–1.26)	NA	228	Apellaniz-Ruiz 2017
SLCO1B1	rs2306283		A	G	0.79 (0.53–1.17)	NA	228	Apellaniz-Ruiz 2017
SLCO1B1	rs34671512		A	C	0.67 (0.28–1.59)	NA	288	Apellaniz-Ruiz 2017
SLCO1B1	rs3829306		C	T	0.66 (0.44–1.00)	NA	1303	Abraham 2014
SLCO1B3	All SNPs				1.07 (0.85–1.34)	0%		Leskela 2011, Apellaniz-Ruiz 2017, Tanabe 2017, Eckhoff 2014
SLCO1B3	rs4149117		T	G	1.26 (0.74–2.15)	39%	473	Leskela 2011, Apellaniz-Ruiz 2017, Tanabe 2017
SLCO1B3	rs7311358		A	G	1.06 (0.71–1.58)	0%	346	Leskela 2011, Apellaniz-Ruiz 2017
SLCO1B3	rs60140950		G	C	0.76 (0.43–1.34)	NA	228	Apellaniz-Ruiz 2017
SLCO1B3	rs11045585		A	G	1.24 (0.65–2.35)	NA	150	Eckhoff 2014
TUBB2A	All SNPs				1.28 (0.99–1.65)	1%		Abraham 2014, Eckhoff 2014
TUBB2A	**rs9501929**	**Increased**	**T**	**C**	**1.68 (1.15–2.45)**	**0%**	**1453**	Abraham 2014, Eckhoff 2014
TUBB2A	rs13219681		G	A	1.30 (0.47–3.60)	NA	150	Eckhoff 2014
TUBB2A	rs3734492		G	A	0.50 (0.04–5.53)	NA	150	Eckhoff 2014
TUBB2A	rs909964		C	T	1.11 (0.66–1.84)	NA	150	Eckhoff 2014
TUBB2A	rs909965		A	G	0.93 (0.55–1.57)	NA	150	Eckhoff 2014
XKR4	All SNPs				1.48 (1.12–1.95)	31%		Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016
XKR4	**rs4737264**	**Increased**	**A**	**C**	**1.48 (1.12–1.95)**	**31%**	**1245**	Baldwin-D 2012, Baldwin-E 2012, Baldwin-A 2012, Boora 2016

Note: Synthesis of the 23 gene meta-analysis results, stratified by SNP, of the association of minor alleles (the less common alleles) with taxane-induced peripheral neuropathy (TIPN). SNP meta-analyses that met statistical significance are in bold. Gene meta-analyses (overall SNPs' effect) that met statistical significance are marked with an asterisk (*). Odds ratios above 1 indicate that the variant is associated with increased neuropathy. Odds ratios below 1 indicate that the variant is associated with decreased neuropathy. *I* denotes heterogeneity (>75% highly heterogeneous, 25–75% moderately heterogeneous and <25%, comparable). Baldwin-D: Baldwin Discovery Cohort, Baldwin-E: Baldwin European-American Replication Cohort, Baldwin-A: Baldwin African-American Replication Cohort, Hertz-E: Hertz European-American Cohort, Hertz-A: Hertz African-American Cohort.

Abbreviations: CI, confidence interval; NA, not applicable; SNP, single-nucleotide polymorphism.

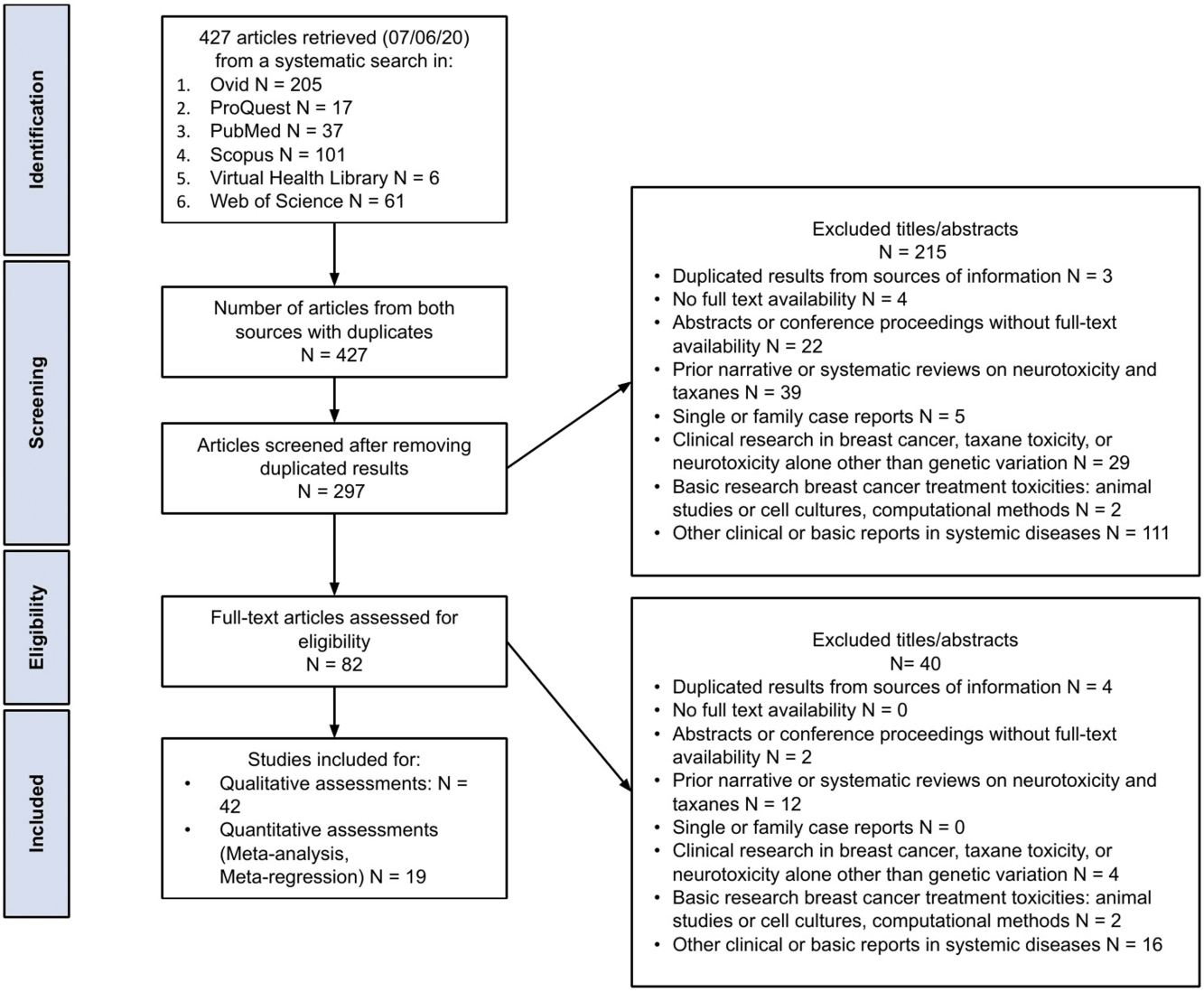

FIGURE 1 PRISMA flow diagram. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram showing the selection process for study inclusion.

from at least two studies (directly or by our calculation) were selected for meta-analysis. For each of these selected genes, polymorphisms with data available from only one study were also added to our second extraction form, to perform a gene-level meta-analysis stratified by polymorphism. It should be noted that polymorphisms that were *not* in Hardy-Weinberg Equilibrium were excluded from our meta-analysis. All data was reviewed by author Anric C. Perez-Ortiz, and any disagreements were consulted with a third field expert reviewer.

Synthesis of results

For every included study, the most relevant variables and all main and statistically significant findings of genetic associations with neurotoxicity were summarized in a table (Table 1). The rest of the extracted clinical variables were presented in Table S2. Estimated mean age was calculated whenever articles reported the median age, using the quantile estimation method.[19] Extracted variables known to be relevant in genetic association studies are summarized in Table S3.

Meta-analysis

We performed a Random-Effects-Model meta-analysis (utilizing reported or calculated ORs and HRs) for each selected gene using the "dmetar"[20] and "meta"[21] packages in R studio version 4.0.4.[22] Every meta-analysis was performed as a subgroup analysis, stratified by SNP. We drafted forest plots to visually display the individual effect of each SNP and the global effect of each gene. These meta-analysis results were then synthesized in a table (Table 2).

Last, we performed a meta-analysis for every included SNP, stratifying by the reported genetic model (additive,

dominant, and recessive) to examine the change in effect size across the different modes of inheritance.

Minor and major allele carriers were respectively considered as exposed and unexposed. Patients who did and did not develop taxane-induced neurotoxicity were respectively regarded as cases and controls.

Assessment of heterogeneity

To assess heterogeneity, I^2 and a chi-square test were used. I^2 values greater than 75% were considered highly heterogeneous, those between 25% and 75%, moderately heterogeneous, and those below 25%, comparable. For moderately and highly heterogeneous polymorphisms, a subgroup analysis was conducted stratifying by the following variables: ethnicity, administered taxane, and approach (genomewide association study or candidate gene approach). Moreover, for moderately and highly heterogeneous polymorphisms included in more than five studies in the meta-analysis, we performed a meta-regression to analyze the impact of various predefined characteristics on the effect estimates. The natural logarithm of the effect size was the dependent variable, and the number of participants, ethnicity, country, STREGA score, journal's impact factor, approach, administered taxane, cancer type, mean age, genotyping method, year, cut-off point for case definition, and neurotoxicity scale were entered as explanatory factors. Because we had limited power due to the small number of studies in each meta-analysis, we carried out a meta-regression of each variable singly and assumed a true relationship when $p < 0.05$.

Sensitivity analysis

Because we combined ORs and HRs in our meta-analyses, we conducted a sensitivity analysis to examine if there was

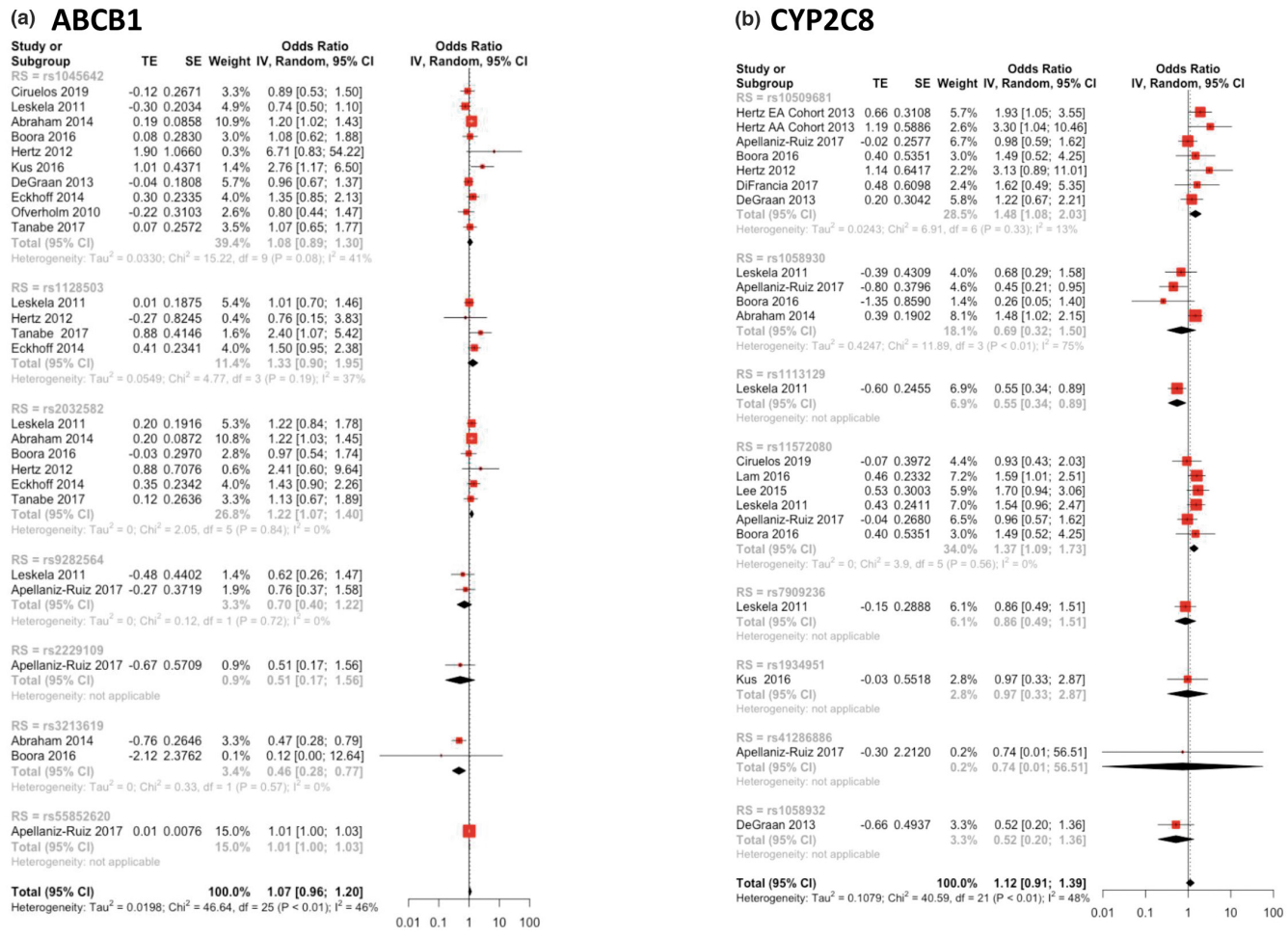

FIGURE 2 ABCB1 and CYP2C8 meta-analysis. Forest plots for the two largest gene-level meta-analyses (ABCB1 and CYP2C8) of single-nucleotide polymorphisms (SNPs) associated with taxane induced peripheral neuropathy (TIPN). (a) ABCB1 meta-analysis (7 SNPs analyzed). ABCB1-rs2032582 and ABCB1-rs3213619 are statistically significantly associated with TIPN. (b) CYP2C8 meta-analysis (8 SNPs analyzed). CYP2C8-rs10509681 and CYP2C8-rs11572080 are statistically significantly associated with TIPN. CI, confidence interval.

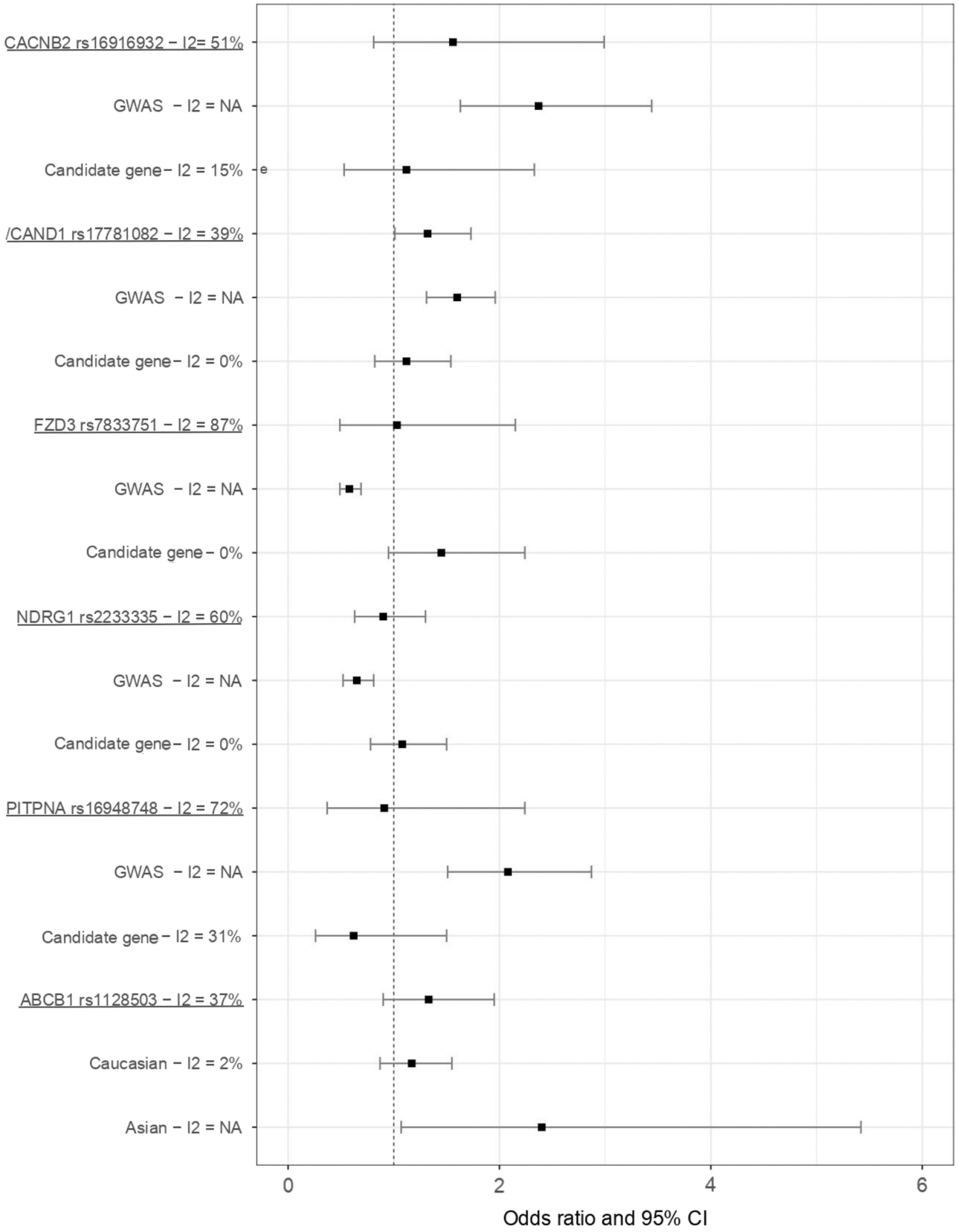

FIGURE 3 Subgroup analyses for moderately and highly heterogeneous SNP meta-analyses ($I^2 \geq 25\%$). Visual display of subgroup analyses for six SNPs associated with taxane-induced peripheral neuropathy. I^2 values for the original meta-analysis and for each subgroup are presented. For CACNB2-rs16916932, /CAND1-rs17781082, FZD3-rs7833751, NDRG1-rs2233335, and PITPNA-rs16948748, heterogeneity was significantly decreased when stratifying by approach: genome-wide association study (GWAS) vs. candidate gene approach. For ABCB1-rs1128503, heterogeneity was decreased when stratifying by ethnicity. CI, confidence interval; NA, not applicable; SNP, single-nucleotide polymorphism.

a difference between the two. Furthermore, we conducted a second sensitivity analysis to assess the effect of the studies that did not exclusively include patients with breast cancer on the main outcome. We performed an analysis of variance F-test for every meta-analysis to assess the effect of these variables on the main outcome ($p \leq 0.05$).

Risk of bias across studies

For every polymorphism assessed in at least five studies in the meta-analyses, publication bias was evaluated using funnel plots and the Egger regression asymmetry test.

RESULTS

Study selection

As represented in Figure 1, our systematic search identified, after removing duplicates, 297 studies. After screening abstracts and later full texts, 255 studies were excluded for the reasons listed in Figure 1. We retrieved 42 studies, which included 19,431 participants.

Study characteristics

The characteristics of the included studies are presented in Table 1. Fifteen of them were nested designs coming from randomized controlled trials (5 case controls[7,23–26] and 10 cohorts[27–36]), 17 were cohort studies,[37–53] and 10 were case-control studies.[54–63] The studies were conducted in the United States (15 studies[24,26,27,31,34–36,42,48,51–53,57,61,63]), Italy (4 studies[7,38,56,60]), Spain (4 studies[32,44,49,59]), Japan (3 studies[25,40,41]), and the Netherlands (3 studies[28,29,33]), among others. Three studies involved more than one country.[30,43,47] Studied patients were most commonly White (22 studies[7,23,27–30,32,33,36,38,39,43,44,47,49,53,54,55,56,59,60,62]), followed by Asians (5 studies[25,37,40,41,45]), Middle Easterners (2 studies[46,58]) and African Americans (1 study[26]). Ten studies included patients of more than one ethnicity,[24,31,34,35,42,48,51,52,61,63] and two did not report ethnicity.[50,57]

Thirty-two studies reported exclusively on patients with breast cancer,[23,24,26–31,34–53,55,57,58,60,62,63] whereas 10 studies also included some patients with other malignancies,[7,25,33,43,44,47,54,56,59,61] ovarian cancer being the most common (7 studies[33,43,44,47,54,59,61]). Most studies focused on patients treated with paclitaxel (29 studies[23–27,29,30–36,40,42–47,50–55,59,61,63]) or docetaxel (2 studies[28,62]), whereas 11 studies included patients exposed to either one of these two drugs.[7,37,38,39,41,48,49,56–58,60] Reported mean ages ± SDs ranged from 49.43 ± 8.35 to 60.7 ± 11.5 years. As for genotyping, most studies used microarray methods (20 studies[23–27,30–36,40,42–44,52,58–60,63]), followed by the use of Taqman probes (9 studies[7,29,33,38,41,53,57,61,62]) and DNA sequencing (5 studies[37,46,47,50,51]). Other methods, such as mass arrays (3 studies[28,45,49]) and PCR-RFLP (2 studies[54,56]) were also used.

Nearly all retrieved articles (39 studies[7,23–36,38–55,58–63]) studied taxane-induced peripheral neuropathy, whereas only two analyzed CNS toxicity.[37,57] One article examined both types of toxicity.[56] For neuropathy assessment (40 st udies[7,23–38,39–56,58–63]), the most used scale was National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE; 33 studies[7,23–36,38–43,47–52,54–60,62]), and the most common case definition was a grade 2 neuropathy or higher (21 studies[23,25,26,28,30–32,36,40–43,47,49,52,55,58–60,62]), followed by grade 1 or higher (6 studies[7,29,33,38,48,54]) and grade 3 or higher (4 studies[24,34,35,51]). Other scales were also used, such as CIPN20 (2 studies[53,61]), TNSr (1 study[46]), and FACT-TAX (1 study[34]). Four studies did not report the scale used.[27,44,45,63] Other methods apart from clinical assessment of neuropathy were also used. Eight studies included patients that were either previously or concomitantly treated with neurotoxic agents (i.e., platinum age nts).[38,42,47,48,52,54,56,59] For CNS toxicity (3 studies[37,56,57]), measurement and definition of toxicity varied widely. All three articles included "cognitive impairment" in the toxicity definition; however, the tests utilized for its assessment were different. Some studies measured cognitive domains individually, whereas others combined them into a unique score.[56] One study included anxiety and depression as a definition for toxicity.[56] Only one study accounted for confounders (fatigue, anxiety, and cancer stage).[37]

Quality of evidence and risk of bias assessment

We used STREGA to assess all included studies. Figure S1 summarizes their quality. The resulting rating range was 41% to 92% with a median of 71% and an interquartile range of 64%–77.5%. The results of the assessment of our predefined biases (Text S3) are shown in Figure S2. The most prevalent were intermediate risks for the domain of "observer" and "valid phenotype, breast cancer" bias. In addition, we found a high risk of "multiple comparison" bias.

Synthesis of results – Genetic analysis

The 42 included studies (19,431 participants) evaluated 121 genes and 262 SNPs. The five most prevalent genes

for these SNPs were ABCB1 (38 studies), CYP2C8 (32 studies), FANCD2 (22 studies), BRCA1 (18 studies), and CYP3A4 (15 studies). The five most prevalent SNPs were ABCB1-rs1045642 (14 studies), ABCB1-rs2032582 (12 studies), CYP2C8-rs10509681 (10 studies), CYP2C8-rs11572080 (8 studies), and CYP3A4-rs2740574 (7 studies).

Nineteen studies (6246 participants) were included in our meta-analysis,[7,26,28–33,40,42,44,47,49,51,54,58,59,61,62] by means of which we analyzed 23 genes with 60 SNPs. Forest plots of our two largest meta-analyses are shown in Figure 2. The 23 individual meta-analyses are shown in Figures S3–S25 and are summarized in Table 2. Thirteen individual SNPs, located in or near 11 genes, were statistically significantly associated with TIPN (bolded in Table 2). Most of these SNPs (9) were only studied in patients receiving paclitaxel, one SNP (GSTP1-rs1138272) was evaluated only in patients receiving docetaxel, and three SNPs (CYP2C8-rs10509681, ABCB1-rs2032582, and TUBB2A-rs9501929) were evaluated in studies of patients receiving either paclitaxel or docetaxel. In this latter group, the association was consistent across taxanes. In addition to these 13 SNPs, the overall effect of all evaluated SNPs in each of the four genes (CYP3A4: rs2740574/rs35599367/rs67666821, EphA5: rs7349683/rs33932471/rs36050417, GSTP1: rs1138272/rs1695, and SLCO1B1: rs4149056/rs11045819/rs2306283/rs34671512/rs3829306) was significantly associated with TIPN.

For 18 SNPs (those where genetic models were combined in the first meta-analysis), a subsequent genetic model stratified meta-analysis was conducted (Table S4). When stratifying by model, it was shown that ABCB1-rs1045642 in the dominant model was associated with an increased risk of neuropathy (OR = 3.14, 95% confidence interval [CI] 1.42–6.93), as compared to the additive model, where no association was found (OR = 1.06, 95% CI 0.92–1.22). A similar change in effect was seen in ABCB1-rs2032582 and

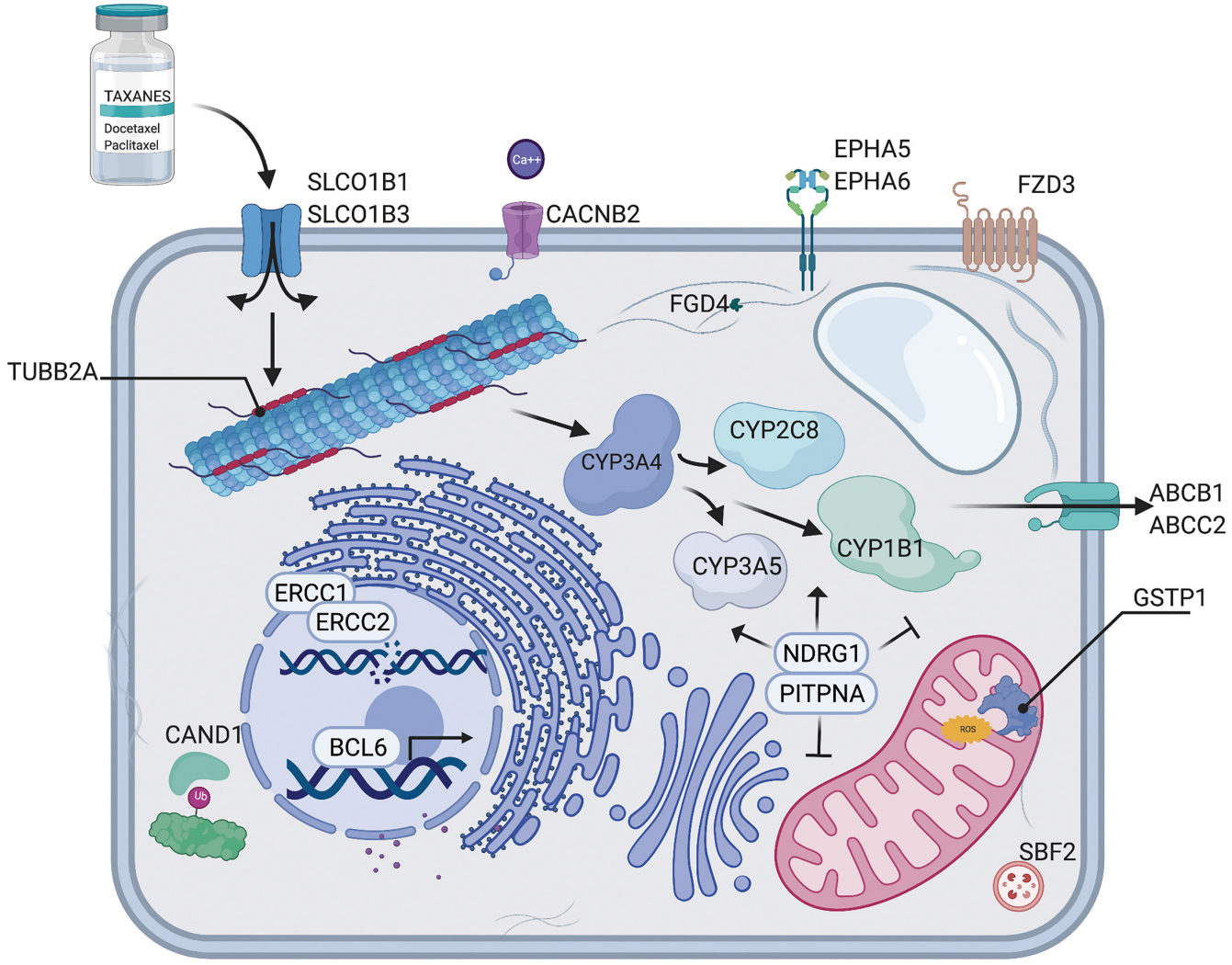

FIGURE 4 Subcellular location and function of proteins coded by the 23 genes included in our meta-analysis. These candidate genes might be involved in taxane induced-peripheral neuropathy (TIPN). XKR4 is not depicted.

SLCO1B3-rs4149117. In the additive model, these SNPs were associated with increased risk, and in the studies that used a dominant model, this effect was further increased. Therefore, for these three SNPs, further analysis was carried out separately. As for the rest of the SNPs, stratification through genetic models had no effect on the interpretation.

Assessment of heterogeneity

To address heterogeneity, we performed subgroup analyses (Figure 3; Figures S26–S31) for the moderately and highly heterogeneous SNP meta-analyses ($I^2 \geq 25\%$), whenever at least two studies could be included in a subgroup (12 SNPs). Notably, for five of these SNPs (CACNB2-rs16916932, /CAND1-rs17781082, FZD3-rs7833751, NDRG1-rs2233335, and PITPNA-rs16948748), heterogeneity was significantly decreased when stratifying by approach: genomewide association study (GWAS) versus candidate gene approach. GWAS found a strong association with neuropathy, whereas replication of these findings via the candidate gene approach found weaker or null associations. For ABCB1-rs1128503, heterogeneity was decreased when stratifying by ethnicity. An association with neuropathy was found in the Asian-based population study, whereas no association was found in the White-based population studies. For the rest of the SNPs, heterogeneity was not decreased when stratifying by approach, taxane, or ethnicity.

Furthermore, in the moderately and highly heterogeneous polymorphisms ($I^2 \geq 25\%$) evaluated in greater than or equal to five studies (only EPHA5-rs7349683 met this criterion), we carried out a meta-regression for each of the following variables singly: ethnicity ($p = 0.4976$), country ($p = 0.1210$), number of participants ($p = 0.9748$), STREGA score ($p = 0.2024$), journal's impact factor ($p = 0.1117$), approach ($p = 0.9200$), administered taxane ($p =$ not applicable [NA]), cancer type ($p = 0.4853$), mean age ($p =$ NA), dose frequency ($p = 0.4853$), genotyping method ($p = 0.4853$), year ($p = 0.065$), cutoff point for case definition ($p =$ NA), and neuropathy scale ($p =$ NA; Table S5). With a significance level at $p < 0.05$, no variable was found as a significant predictor.

Risk of bias across studies – Reporting biases

Funnel plots and p values from Egger's regression asymmetry test were performed for every SNP evaluated in greater than or equal to five studies in the meta-analysis (ABCB1-rs1045642, ABCB1-rs2032582, EphA5-rs7349683, CYP2C8-rs10509681, and CYP2C8-rs11572080). The evaluated SNPs showed no such indication of publication bias (Figures S32–36). However, these results could be limited, because the power of Egger's test to detect bias is low when there is a small number of studies.

Sensitivity analyses

We performed sensitivity analyses to assess the *effect type* (OR vs. HR) and *cancer type* (breast cancer exclusively vs. breast cancer and others) impact on the main outcome, for every polymorphism evaluated in greater than or equal to five studies. Results are summarized in Table S6. Results suggested that these variables have little or no effect on meta-analysis results. However, as for the variable "cancer type" in CYP2C8-rs10509681, the effect differed significantly in the "breast cancer exclusively" group (OR = 2.30, 95% CI 1.40–3.77) when compared to "breast cancer and others" group (OR = 1.15, 95% CI 0.81–1.63), with a p value of 0.01.

DISCUSSION

Summary of evidence

To the best of our knowledge, this is the first systematic review which included a meta-analysis to explore genetic predictors for taxane-induced neurotoxicity in patients with breast cancer. Numerous polymorphisms have been studied on this topic, of which many have attained statistically significant associations. However, these studies have often gotten contradictory results, probably attributable to differences in populations and methodological designs. As suggested by our study, factors such as type of cancer being studied, ethnicity, and approach may influence the effect some polymorphisms have in the development of neuropathy.

By far, the most studied markers are SNPs, followed by CNVs and differential methylation patterns. For the selection of SNPs, the candidate gene approach centered on taxane pharmacokinetics has been the most sought-after. However, with the advent of GWAS and an increasing understanding of TIPN pathophysiological pathways, numerous new genes have been studied in the last few years.

The variants found to be associated with neuropathy in our study are in accordance with a previous systematic review by Frederiks et al.,[11] which looked for genetic polymorphisms associated with taxane-induced toxicities. Our systematic search identified all the TIPN studies with breast cancer included in the Frederiks et al. review. For

these studies, the same main findings were extracted and reported in our Table 1.

However, because the study of the genetic polymorphisms associated with TIPN is a topic with increasing interest, more than half of our included studies were published after the search date of Frederiks et al. (September 6, 2015). This enabled us to identify new pharmacogenetic markers with a potentially larger effect on neuropathy (all of which can be reviewed in Table 1). For instance, the SCN9A gene, which codes for the α subunit of NaV1.7 channels and is associated with pain perception disorders,[64] was examined in a study published in 2020[41] and included in our systematic review. Here, it was found that SCN9A (rs13017637) minor allele was significantly associated with TIPN (OR = 5.053, 95% CI 1.743–14.641, $p = 0.0029$).

Moreover, our study, unlike the Frederiks et al. systematic review, included meta-analysis performance and subgroup analysis, whenever possible. This enabled us to quantify and examine inconsistent results across studies. Frederiks et al. noted that ABCB1 (rs1045642) minor allele had frequently been associated with TIPN, however, results had also been negative in some studies. Our meta-analysis found that ABCB1 (rs1045642) is significantly associated with increased risk of neuropathy in studies through a dominant genetic model, but not when using other genetic models.

As mentioned previously, 23 genes (Figure 4) with 60 SNPs were included in our meta-analysis, and 13 of these SNPs met statistical significance. These 13 identified SNPs could potentially be implemented in clinical practice, as their association with neuropathy has been replicated and quantified through meta-analysis. However, further assessment of these SNPs in predictive models is needed. Discussion on the genes with significant SNPs follows below.

ABCB1 gene

ABCB1 encodes for P-glycoprotein (P-gp), a transmembrane active efflux pump that mediates taxane cellular clearance[65] and excretion,[66] the latter being mainly biliary through feces.[67]

In our meta-analysis, the rs2032582 minor allele significantly increased the risk of neuropathy (OR = 1.22, 95% CI 1.07–1.40). This SNP codes for a missense variant which has been associated with P-gp loss of function, although findings remain unclear[68,69].

On the other hand, we found that rs3213619 significantly decreased neuropathy risk (OR = 0.46, 95% CI 0.28–0.77). This SNP is known to code for an intronic variant in the promoter region that has been correlated with increased P-gp expression in different tissues.[16,70] Meta-analysis of the studies which used a dominant genetic model, found rs1045642 to be associated with an increased risk of neuropathy (OR = 3.14, 95% CI 1.42–6.93). Some studies have shown that this variant decreases ABCB1 mRNA expression.[71,72]

All of our findings are consistent with the expectation that lower expression of P-gp may lead to decreased cellular clearance and excretion of taxanes, higher intracellular concentrations, and therefore greater toxicity, whereas a high expression could prevent toxicities.[65] One must bear in mind, however, that this same expectation might be taken to suggest that a low expression of P-gp could increase tumor response to taxanes.[65,71,72]

CYP2C8 gene

CYP2C8 is expressed mainly in the liver, where it accounts for ~7% of cytochrome P450 content.[73] CYP2C8 is the enzyme primarily responsible for paclitaxel's metabolism; however, it is not involved in docetaxel's metabolism, which is primarily due to CYP3A5. For both taxanes, there is also a contribution from CYP3A4.[74]

The activity of CYP2C8 is widely varied among individuals.[73] Two missense variants, rs10509681 and rs11572080, code for CYP2C8*3 and have been associated with a lower rate of paclitaxel metabolism.[75,76] In our meta-analysis, these two variants were found to increase the risk of developing TIPN (OR = 1.48, 95% CI 1.08–2.03 and OR = 1.37, 95% CI 1.09–1.73, respectively).

CYP1B1 gene

CYP1B1 encodes for a cytochrome enzyme that, unlike others, is not expressed in the human liver and therefore not involved in hepatic metabolism. CYP1B1 is expressed in the endoplasmic reticulum of extrahepatic organs.[77,78] Tumor cells have shown to express high levels of this enzyme, and this is associated with tumor progression.[38] CYP1B1 does not metabolize taxanes, but it binds to them, thereby reducing cellular availability.[79,80] The variant rs1056836 has been significantly associated with higher expression levels of CYP1B1 mRNA.[81] Consistent with this, in our meta-analysis, this variant was linked with a decreased risk of developing TIPN (OR = 0.79, 95% CI 0.68–0.94).

EphA genes

The Eph genes (9 EphA members and 5 EphB members) encode for the largest known family of receptor tyrosine

kinases.[82] EphA/ephrin-A signaling is crucial for nervous system development, neuroplasticity, axon guidance, tissue regeneration, angiogenesis, and tumor progression.[13] EphA5 has been shown to play a role in nerve injury repair and to be essential in the initiation of the early phases of synaptogenesis. Both EphA6 and EphA5 play an important role in the development of neuronal cytoarchitecture.[13,83] In our meta-analysis, EPHA5-rs7349683 and EPHA6-rs301927 were associated with an increased risk of TIPN (OR = 1.55, 95% CI 1.13–2.14 and OR = 1.42, 95% CI 1.05–1.92, respectively).

TUBB2A gene

The *TUBB2A* gene encodes for β-Tubulin, a protein that polymerizes with α-tubulins to form polarized filaments called microtubules.[84] Taxanes exert their chemotherapeutic effect by binding to the β-subunit of tubulin, promoting microtubule assembly and stabilization, leading to mitotic arrest, which results in apoptosis of cancer cells.[85] However, functional microtubules are essential for nutrient transport in neurons. For this reason, altered microtubule dynamics in axons caused by taxanes is postulated to be one of the main pathophysiological causes of TIPN.[6]

The rs9501929 variant is located in the TUBB2A promoter region. Only one study[43] has assessed this variant's effect on TUBB2A expression. Results from this study showed that lymphocytes carrying the rs9501929 minor allele had a significantly higher TUBB2A mRNA content. In addition, this study indicated that higher TUBB2A gene expression confers resistance to paclitaxel-induced apoptosis, which could consequently decrease neuropathy and response to paclitaxel in tumor cells.[43]

In our meta-analysis, rs9501929 was found to be significantly associated with an *increased* risk of neuropathy (OR = 1.68, 95% CI 1.15–2.45). It should be noted that only three included studies assessed this variant and its association with TIPN,[30,43,62] of which only two had the information needed for meta-analysis inclusion. The study left out was precisely the one discussed in the previous paragraph. There is still information missing regarding this variant's statistical association with neuropathy and its biological significance. These two factors should be further investigated to elucidate TUBB2A variants' true effect on TIPN.

GSTP1 gene

GSTP1 encodes for a glutathione S-transferase enzyme, responsible for the inactivation of various toxic compounds (including by-products of oxidative stress) by catalyzing their conjugation with reduced glutathione.[86] Evidence suggests oxidative stress is a fundamental factor of TIPN. Rat models have shown both an increase in reactive oxygen species and an accumulation of atypical mitochondria in neuron cell bodies when the rodents are treated with paclitaxel.[87,88] The GSTP1 rs1138272 variant has been related to changes in catalytic and regulatory functions of GSTP1 because this variant affects substrate specificity,[89] possibly hampering the enzyme's ability to inactivate oxidative stress by-products and other toxic compounds.[62] In our meta-analysis, rs1138272 was indeed correlated with an increased risk of TIPN (OR = 2.34, 95% CI 1.42–3.85).

Other gene variants

BCL6/-rs1903216, FZD3-rs7001034, /CAND1-rs17781082, and XKR4-rs4737264 are all top hits of a GWAS based on the clinical trial CALGB 40101m which additionally met statistical significance in our meta-analysis (respectively, OR = 1.56, 95% CI 1.07–2.26; OR = 0.65, 95% CI 0.43–0.99; OR = 1.32, 95% CI 1.01–1.73; and OR = 1.48, 95% CI 1.12–1.95). They have been scarcely studied elsewhere, and their effects on the encoded proteins are not yet known.

BCL6 is a zinc finger transcription factor which functions as a regulator of the germinal center and is associated with several lymphomas. However, its role in the nervous system and TIPN is not clear yet.[90] FZD3 is a member of the frizzled gene family and encodes a G-protein-coupled receptor involved in the Wnt signaling pathway, which is important for neurite outgrowth.[91] CAND1 codes for the cullin-associated and neddylation-dissociated protein 1 (CAND1), whose main function is to regulate cullin neddylation and ubiquitin ligase activity. This protein has been associated with developmental processes.[92,93] XKR4 codes for an XK-related protein expressed in the cerebellum. Its function has not been well-characterized, but it has been associated with addiction, substance abuse, cognitive deficits, and other memory, executive function, and neuropsychiatric symptoms.[13,94]

For /CAND1-rs17781082 heterogeneity, decreased when stratifying by approach. The effect was stronger in the original Baldwin et al.'s GWAS and weaker in the replications. This finding is consistent with the argument that GWAS are better at detecting associations than at quantifying them.[18]

Sensitivity analyses

In many studies, genotypic and allelic frequencies were not reported, so we had to extract the effect measures

directly from the articles, instead of being able to calculate them ourselves. This often precluded us from obtaining the desired effect measure (OR vs. HR) with the desired genetic model (additive, dominant, or recessive), which in turn implied that our first meta-analyses combined different effect measures as well as different genetic models. Therefore, we assessed any possible impact of these two combinations on our results.

Genetic model subgroup analyses showed that the effect did not differ significantly between models in most cases. Nonetheless, results should still be interpreted cautiously: when analyzing the effect of a particular SNP on neuropathy, one should consider both the combined and the stratified analysis that we reported.

Our sensitivity analyses suggested that combining ORs with HRs did not affect meta-analyses results. Extracted HRs were based on cumulative incidence and not incidence density, which makes them more suitable to be combined with ORs.

Along the same line, some of the retrieved studies did not focus exclusively on patients with breast cancer. This may have affected our results for at least one variant (Table S6). This could arise from the fact that different types of cancer involve different taxane dosage regimens, which may influence the incidence of neuropathy. It should be borne in mind, however, that this may also happen within the same type of cancer, among different stages and subtypes.

Chemotherapy induced peripheral neuropathy

Chemotherapy induced peripheral neuropathy (CIPN) is not limited to the use of taxanes. Common neurotoxic agents used for the treatment of breast cancer include platinum-based drugs, vinca alkaloids, ixabepilone, and eribulin.[95] Similarly to taxanes, it has been speculated that genetic differences account, at least partially, for CIPN interindividual variability during treatment with the aforementioned drugs. Efforts to elucidate genetic factors increasing the risk of developing CIPN have been carried out individually for each drug, as pharmacokinetics, pharmacodynamics, and pathophysiological pathways leading to neuropathy vary between drugs. Most genetic variants linked to CIPN vary per agent. However, variants in some genes, such as GSTP1, have been found to be linked to CIPN across drugs.[96]

In breast cancer, patients receiving a taxane drug are more likely to develop neuropathy, as compared to those who are receiving other chemotherapy.[97] Because taxanes (paclitaxel and docetaxel) behave similarly, they have been classically grouped in studies assessing peripheral neuropathy pharmacogenetics. Various genetic variants have been found to be consistently associated with both docetaxel and paclitaxel-induced neuropathy. However, because paclitaxel is the most commonly used taxane drug and the most neurotoxic, most studies have used this drug to assess pharmacogenetics.[6,11] Even though docetaxel may behave similarly in most cases, our results come mainly from paclitaxel-based studies, which highlights the need for more studies using docetaxel.

Novel drugs, such as eribulin, act similarly to taxanes, which might lead us to believe that pharmacogenetics might be similar.[98] However, to date, nearly no studies have assessed the genetic variants associated with neuropathy in patients receiving eribulin. A recently published abstract found NDRG1-rs2233335 to be associated with neuropathy in patients receiving eribulin.[99] This variant was also found to be associated with neuropathy in patients receiving taxanes in our meta-analysis.

Central neurotoxicity

Given that our systematic search found only three articles on genetic predictors for the development of taxane-induced central neurotoxicity in patients with breast cancer, it is clear that this is an area that has been scarcely studied. To date, this prevents us from identifying the usefulness of these predictors in the clinical setting.

BDNF-rs6265 and COMT-rs4680 minor alleles have been the only two variants reported to be associated with this toxicity (they have been linked to a decreased risk). These genes are widely expressed in the CNS, and they code respectively for a neurotrophin that regulates several neurological processes and an enzyme that catabolizes monoamine.[100,101] Both variants have been linked to a lessened cognitive decline in some systemic diseases.[102,103]

An important limitation is that each of the three articles used different tools for toxicity identification. To be able to study associated genetic markers more systematically, a universal definition of taxane-induced central neurotoxicity is needed.

Limitations

We found some potential limitations, both in our study and in the included studies. Limitations in our study arose mainly from the wide variety of studied polymorphisms in the retrieved articles. On the one hand, this complicated the task of systematically reviewing all variants in the desired depth. On the other hand, it entailed that each variant was studied and reported only in a small number of articles. In fact, this number was most often

just one, in which case, we were prevented from carrying out a meta-analysis altogether. Moreover, when the variant was reported in more than one article and a meta-analysis was performed, the number was often still small, limiting power, and sometimes precluding the undertaking of further analyses (meta-regression, publication bias assessment, sensitivity analyses, and subgroup analyses).

The extensiveness of the topic prevented us from discussing all genes. We discussed those with polymorphisms found to be statistically significant in our meta-analyses. It should be noted, most SNPs included in our systematic review could not be included in our meta-analyses.

There are also clear limitations within the included studies. Methodological constraints, such as inclusion of a heterogeneous population within a study, were common (different types of cancer, taxane, ethnicities, age, and dosage). This is particularly relevant when factors in the matter are known to be associated with neuropathy, such as age, dosage, and co-administration of neurotoxic agents.[8,9] There was also a frequent lack of thoroughness in reporting. Often only significant results were reported, and sometimes the studies neither calculated effect sizes nor provided the data needed for us to calculate them. In addition, individual studies were often small, which may have led to a lack of statistical power for detecting associations. One final observation is that nearly all studies analyzed White populations, and only a few of them assessed African Americans, Asians, and Middle Easterners. This limits the generalizability to other populations, such as Hispanics. Collectively, these and other limitations present us with opportunities for further exploration.

CONCLUSION

Our systematic review collects a large number of polymorphisms reported to be associated with taxane-induced peripheral neuropathy. These results suggest that genetics does play a role in interindividual predisposition.

Through meta-analysis, we present 13 SNPs that are significantly associated with TIPN. Their consistently reported effect on neuropathy suggests that they could potentially be used to predict the individual risk for developing TIPN. For their eventual implementation in clinical practice, prediction models should be developed and validated. In this way, these SNPs could have a role in tailoring chemotherapy treatment to minimize toxicities and improve patient outcomes.

There is still a vast number of SNPs that seem to be associated with neuropathy but have only been studied once. Further studies replicating these findings, using more rigorous methodological designs, are needed to develop a more complete pharmacogenetic toxicity panel, and concomitantly increase our understanding of TIPN.

In the context of taxane treatment for breast cancer, the information gathered in this study brings us closer to a holistic approach to precision medicine. Toxicities can have a huge effect on quality of life; hence, the continued elucidation of genetic markers predicting their development is an important outstanding challenge.

AUTHORS CONTRIBUTIONS

A.G. and A.P. designed research. A.G., A.F., A.P., A.A., M.O., C.V., R.E., and J.E. performed research. A.G., A.F., A.P., C.V., R.E., J.E., R.C., and B.A. analyzed data. A.G., A.P., C.V., R.E., and J.E. wrote the manuscript.

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DATA AVAILABILITY STATEMENT

All datasets used for the development of this work are available from the corresponding author upon request.

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SUPPORTING INFORMATION

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

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