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Genome-wide association studies for taxane-induced peripheral neuropathy (TIPN) in ECOG-5103 and ECOG-1199

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Abstract

Purpose—Taxane induced peripheral neuropathy (TIPN) is an important survivorship issue for many cancer patients. Currently, there are no clinically implemented biomarkers to predict which patients might be at increased risk for TIPN. We present a comprehensive approach to identification of genetic variants to predict TIPN.

Experimental Design—We performed a genome wide association study (GWAS) in 3431 patients from the phase III adjuvant breast cancer trial, ECOG-5103 to compare genotypes with TIPN. We performed candidate validation of top SNPs for TIPN in another phase III adjuvant breast cancer trial, ECOG-1199.

Results—When evaluating for Grade 3-4 TIPN, 120 SNPs had a p-value $<10^{-4}$ from patients of European descent (EA) in ECOG-5103. 30 candidate SNPs were subsequently tested in ECOG-1199 and SNP *rs3125923* was found to be significantly associated with Grade 3-4 TIPN

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($p=1.7\times 10^{-3}$; OR=1.8). Race was also a major predictor of TIPN, with patients of African descent (AA) experiencing increased risk of Grade 2-4 TIPN (HR=2.1; $p=5.6\times 10^{-16}$) and Grade 3-4 TIPN (HR=2.6; $p=1.1\times 10^{-11}$) compared with others. A SNP in *FCAMR*, *rs1856746*, had a trend toward an association with Grade 2-4 TIPN in AA patients from the GWAS in ECOG-5103 (OR=5.5; $p=1.6\times 10^{-7}$).

Conclusion—*rs3125923* represents a validated SNP to predict Grade 3-4 TIPN. Genetically determined AA race represents the most significant predictor of TIPN.

Keywords

Peripheral neuropathy; Taxanes; Single nucleotide polymorphisms (SNPs); Genome wide association study (GWAS); Genetic biomarker

INTRODUCTION

The taxanes are commonly used to treat patients with a variety of malignancies.(1, 2) While having improved outcomes, taxanes are not without toxicity. One of the most common toxicities is taxane-induced peripheral neuropathy (TIPN). TIPN can substantially impact quality of life, can be irreversible, and limit drug exposure; occasionally requiring cessation of treatment. The likelihood of TIPN depends on the type of taxane used, dose, and schedule.(3) However, there is also substantial inter-individual heterogeneity and it is difficult to predict which patients will be at greatest risk for TIPN prior to receipt. Several trials have previously been published evaluating the impact of germline genetic variation on likelihood of TIPN with variable results. These studies have varied widely in size, disease setting, phenotype definition, and genotype methodology.(4-12) Here we investigated genetic biomarkers of TIPN in two large, adjuvant breast cancer trials that incorporated taxanes; ECOG-5103(13) and ECOG-1199.(14)

METHODS

Genome wide association study (GWAS) for SNP discovery in ECOG-5103

ECOG-5103 (*Figure 1A*) was a phase III adjuvant breast cancer trial that randomized 4994 patients with node positive or high-risk node negative breast cancer to intravenous doxorubicin and cyclophosphamide every 2 or 3 weeks (at discretion of treating physician) for four cycles (AC) followed by 12 weeks of weekly paclitaxel (P; 80 mg/m²) alone (Arm A) or to the same chemotherapy with either concurrent bevacizumab (Arm B) or concurrent plus sequential bevacizumab (Arm C).(13) Germline (blood) DNA was available from 4033 patients. Genome-wide analyses were performed across all Arms to identify genotypes at single-nucleotide polymorphisms (SNPs) that were associated with TIPN.

ECOG-5103 case/control definitions for TIPN

Cases: Cases were defined as those experiencing Grade 2-4 TIPN (n=576 EA, 151AA) as assessed by the Common Toxicity Criteria Adverse Events (CTCAE) version 3.0. We separately assessed for those with the more extreme phenotype of Grade 3-4 (n=181 EA).

Cases included patients who received at least one dose of paclitaxel and the neuropathy event occurred during treatment or within 3 months of the last dose of therapy.

Controls: Controls (n=781EA, 62AA) included patients who met all the following: 1). Received all planned doses of paclitaxel; 2). Had follow-up for at least 3 months after the last dose of drug; 3). Did not meet any of the case definitions as outlined above; and 4). Had either paclitaxel or bevacizumab held or modified for any reason (i.e. disease progression or other toxicity) were excluded.

Genotyping and Statistical analysis—Genotyping was performed in two distinct study subsets as described previously.(15) Genotyping array data was obtained on Illumina products and extensive quality review was performed to assure SNP quality, develop principal components for race assignment and imputation (see **Supplemental Methods**). Analyses were performed in genetically defined EA and AA subsets of the E5103 samples.

A Kaplan-Meier curve was plotted to evaluate the time to first neuropathy event. The association between race and time to first neuropathy was evaluated with Cox proportional hazards model, and their associated hazard ratios and p-values are reported. In the subsequent genetic association analysis, a standard case-control association analysis (logistic regression) was performed to identify SNPs associated with the presence or absence of TIPN. Principal component (PC) (**Supplementary Figure 1**), age, body surface area (BSA), Arm of study, menopausal status, and ER/PR status were considered as potential covariates. The threshold was set at $p < 0.05$ for inclusion of a covariate in the logistic regression model. PC1, age and BSA were significant predictors and were used in subsequent association analyses. The individual SNP effect is reported as odds ratio (OR) and p-value. SNPs available on the HumanOmni1-Quad array were included in the statistical analysis. An additive model of SNP effect was used and the analysis was performed using SNPTEST v2.4.(16) To correct for multiple SNP comparisons, the p-value threshold for genome wide significance was set at 5×10^{-8} .(17)

Candidate SNP validation in ECOG-1199

ECOG-1199 (**Figure 1B**) was a phase III adjuvant breast cancer trial that randomized 5,052 patients to one of four treatment arms.(14) First, all patients received four cycles of AC every 3 weeks followed by P at 175 mg/m² every 3 weeks for four cycles, or P at 80 mg/m² weekly for 12 weeks, docetaxel (T) 100 mg/m² every 3 weeks for four cycles, or T at 35 mg/m² weekly for 12 weeks. Tumor derived DNA (formalin fixed paraffin embedded; FFPE) was available from 2906 patients. ECOG-1199 case and control designation were identical to that used for ECOG-5103 except CTC v2.0 definitions were used.

Top candidate SNPs (n=51) from the Grade 3-4 TIPN GWAS in ECOG-5103 were evaluated in ECOG-1199 (**Supplementary Table 1**). Only one SNP from each linkage disequilibrium (LD) block was selected to optimize coverage as well as to minimize corrections for multiple comparisons. Details regarding SNP selection, genotyping and quality review are available in the **Supplemental Methods**. Ancestry informative markers were not available, and thus analyses were performed separately for those of self-defined Caucasian race. The same logistic regression model used in the ECOG-5103 analyses was

employed in the ECOG-1199 statistical analysis. Both OR and p-value were reported. The p-value threshold for candidate SNP significance was set at 1.7×10^{-3} based on correction for the 30 successfully genotyped SNPs tested. All covariates used in ECOG-5103 were included in the ECOG-1199 analyses.

RESULTS

Rates of TIPN and clinical predictors

ECOG-5103—For the parent trial, depending on treatment arm 26-28% and 8-9% experienced TIPN of CTCAE v3.0 Grade 2-4 and 3-4 severity, respectively.(13) For the subset of 3169 patients who had analyzable genetic data, the risk of Grade 2-4 and Grade 3-4 TIPN was 27.6 % and 9.6 % respectively. Older age was a significant risk factor with a 13% increased risk per decade of life ($p=9.3 \times 10^{-4}$). Increased BSA was also significantly associated with an increased risk of neuropathy ($HR=2.8$; $p=7.1 \times 10^{-11}$). Race was genetically determined and those of African descent were markedly more likely to experience Grade 2-4 ($HR=2.1$; $p=5.6 \times 10^{-16}$) and Grade 3-4 ($HR=2.6$; $p=1.1 \times 10^{-11}$) TIPN compared to other races (**Figure 2**). This remained significant for both Grade 2-4 ($p=5.6 \times 10^{-14}$) and Grade 3-4 TIPN ($p=1.4 \times 10^{-11}$) when correcting for both age and BSA. Additionally, the degree of PC1 after correction for age and BSA was even more significantly associated with Grade 2-4 ($HR=0.5$; $p=9.4 \times 10^{-15}$) and Grade 3-4 ($HR=0.37$; $p=7.4 \times 10^{-13}$) TIPN.

ECOG-1199—For the parent trial, depending on treatment arm 16-27% and 4-8% experienced TIPN of CTC v2.0 Grade 2-4 and 3-4 severity, respectively.(14) For the subset of 2906 patients who had analyzable genetic data, the risk of Grade 2-4 and Grade 3-4 TIPN was 19.8% and 6.2% respectively. For the parent trial, race was determined by self-report and was not associated with risk of TIPN for the entire cohort but there was a strong trend for increased risk in the weekly paclitaxel arm with a similar odds ratio to that seen in ECOG-5103.(18) Age was not significant but was considered as a covariate to maintain consistency across trials. Increased BSA ($OR=1.9$; $p=0.0062$) was significantly associated with an increased risk of neuropathy.

GWAS results for TIPN in EA subset from ECOG-5103

The strength of association between genotype and Grade 3-4 TIPN (**Figure 3**) and Grade 2-4 TIPN are demonstrated in **Supplementary Table 2 and Supplementary Table 3**, respectively. 120 and 65 SNPs had a p-value $<1 \times 10^{-4}$ for the Grade 3-4 analysis and the Grade 2-4 analysis, respectively.

Evaluation of top EA SNPs in ECOG-1199

30 SNPs were evaluated in ECOG-1199 based on p-value and LD support (**Supplementary Table 4**). One SNP, *rs3125923*, was statistically significantly associated with increased risk of TIPN for Grade 3-4 severity after correction of multiple comparisons ($p=1.7 \times 10^{-3}$; $OR=1.8$). A second SNP, *rs9862208*, had a strong trend toward association with increased risk of TIPN for Grade 3-4 severity ($p=5.9 \times 10^{-3}$; $OR=1.9$); (**Table 1; Figure 4**).

GWAS results for TIPN in AA subset from ECOG-5103

Given the marked increased risk of TIPN among the AA subset, we performed an exploratory analysis for AA patients for Grade 2-4 TIPN (insufficient cases for Grade 3-4). The strength of association between genotype and TIPN are shown in **Figure 3** and **Supplementary Table 5**. 112 SNPs had a p-value $<1 \times 10^{-4}$. A SNP near *FCAMR*, *rs1856746*, had a trend toward a significant association ($p=1.6 \times 10^{-7}$; OR= 5.5).

DISCUSSION

TIPN is considered one of the most important survivorship concerns for cancer patients.(19) There are established predictors of TIPN such as type and schedule of taxane.(18) Other demographic variables such as obesity and age are recognized to predispose as well.(18) Despite this, it is very difficult to predict which patients will ultimately develop neuropathy and which are at greatest risk for severe or irreversible TIPN. The heterogeneity of TIPN cannot be explained by differences in demographic variables alone suggesting the contributions of genetic variability. Several prior studies have demonstrated common SNP associations with TIPN,(4-9) although the clinical relevance is unclear.

In our analysis confined to EA patients, the more extreme phenotype data (Grade 3-4) provided the most impressive associations in terms of statistical significance despite smaller sample size. This suggests that there is an advantage to use of clearly defined, extreme phenotypes.(20) Although none of the SNPs in ECOG-5103 met genome wide significance, there were 120 SNPs with modest association and p-values $<1.0 \times 10^{-4}$. In our validation study from ECOG-1199, 58.8% of SNPs genotyped had an acceptable call rate 95% which is similar to previously reported data on FFPE samples.(21) We identified a SNP, *rs3125923*, that was associated with a statistically significant increased risk for TIPN. *rs3125923* is a variant in a gene desert on chromosome 1 and had LD support in our analysis (**Supplementary Figure 2**). While understanding the functional implications of predictive SNPs is important, more than 80% of prior GWAS identified trait loci are in the non-coding regions of the genome,(22) as was the case here. Prior work has demonstrated that SNPs in gene deserts can have substantial consequences for regulation through alterations in gene expression, RNA splicing, transcription factor binding, chromatin openness as measured by DNase I hypersensitivity, DNA methylation and histone modification.(22) Recent expression quantitative trait loci (eQTL) mapping has shown that *rs3125923* alters *GPR177* (G-Protein couple receptor gene) expression via trans-regulatory elements.(23) *GPR177*, also called the Wntless gene, encodes a receptor for Wnt proteins in Wnt secreting cells. Wnt, which is essential for neuronal development,(24) can sensitize peripheral sensory neurons via distinct noncanonical pathways.(25) These studies suggest downstream work should examine the impact of *rs3125923* on expression of *GPR177* in neurons and the impact of differential *GPR177* expression on taxane induced neuronal damage.

Prior studies (**Table 2**) have evaluated the role of genetic variation on likelihood of TIPN. Several have taken a candidate SNP-based approach with focus on metabolism,(5) transport,(10) paclitaxel binding site,(6, 10) and DNA repair genes.(7) Hertz et al.(5) demonstrated a trend toward greater likelihood of TIPN for those who carry the *CYP2C8*3* variant. Apellaniz-Ruiz et al. performed whole exome sequencing on 8 patients with severe TIPN

and found two with rare CYP3A4 variants that resulted in reduced enzyme expression.(11) Although not seen in any of the larger genome wide studies, the high-throughput panels are not optimally designed to evaluate for many of the CYP P450 metabolism enzymes and thus these findings should be further explored. Sucheston et al(7), Leandro-Garcia et al(6), and Abraham et al,(10) all identified associations between TIPN and SNPs from candidate genes with plausible biological rationale. Unfortunately, these did not include an independent validation cohort and were not reported as significant in the large genome wide data sets. Baldwin et al.(4) performed a GWAS in a large phase III adjuvant clinical trial. The top associations were SNPs in the genes *FDG4*, *EPHA5*, and *FZD3*, although the first two did not meet genome wide significance. They subsequently performed validation in a smaller cohort of patients and found an association with *FDG4*. Leandro-Garcia et al.(8) also performed a GWAS on 144 patients and found a modest association with a SNP in *EPHA4* although no validation was performed. They did, however, perform a meta-analysis combining their data with the CALGB40101 trial(4) and found a significant p-value with a SNP in *EPHA5*. Although provocative, the SNP in *EPHA5* did not validate in the independent validation cohort from the CALGB40101 trial and was not significant in our trial. Beutler et al.(9) performed massively parallel sequencing of 49 genes important for Charcot-Marie-Tooth in 119 patients. In this study, several SNPs in *ARHGEF10* had modest association with high odds ratio. Unfortunately validation of rare SNPs is difficult using the standard GWAS platforms, which are traditionally built to evaluate common variants.

While each of the prior data sets has identified provocative genomic associations with TIPN, there has been little to no overlap to date by independent groups. The top two SNPs from ECOG-1199 were not reported in prior studies.(4, 8) Additionally, our study did not provide support for the previously identified SNPs as outlined in **Table 2**.(4-9) There have been signals, however, of potentially important susceptibility pathways. Perhaps the most provocative associations to date have been in the *EPHA* family of genes, although clearly not reproducible across all studies. As Wntless (this study) and Frizzled (*FZD3*; CALGB40101 study (4)) are in the same pathway, our validated SNP may support the importance of the Wnt pathway in TIPN.

The possible reasons for lack of complete overlap in results are multi-fold. First, some or all of these findings may be spurious. Second, the variable phenotype definition, taxane type/schedule, collection methodology, definition of race, and genomic strategy may have hampered reproducibility. The need to harmonize some of these confounding variables may be a reasonable expectation based on the underlying biology and pharmacology. For example, while the host tissue may broadly predispose a patient to a given drug or drug class that can cause neuropathy, there are biological and pharmacokinetic differences, that may make the identification of a universal predictive biomarker impossible to identify. The need to correct for all confounders, however, makes it difficult to use the marker in practice and begs the question as to which may be most valuable; a marker that is accurate for a very specific situation or a more generalizable marker with less statistical power. Regardless, novel genetic findings have the potential to unravel the underlying cause and potentially provide insight leading to novel drugs to prevent or treat TIPN. While our top SNP increased the risk, others with more modest associations decreased the risk. This speaks to

the potential genetic complexity of predisposition for TIPN and also explains what is seen clinically, with some patients experiencing early and severe neuropathy while others never experience neuropathy. Multi-genetic models will ultimately need to be developed but will require multiple massive data sets for operative statistical power. Given the discordance in the data, it is highly likely that the most efficient and statistically well-poised approach will include a meta-analysis across several of these large datasets. Also, use of more high-throughput technology, such as massively parallel sequencing might further shed light on the genetic contributions.(9)

The strengths of the current study include the non-biased evaluation of common variants across the genome in a discovery cohort from a large, adjuvant randomized phase III trial with attempted validation in a similarly sized and designed trial. Despite the lack of established functionality of the SNPs identified, this represents the highest level of clinical association for a biomarker.(26) One weakness of this study includes the use of FFPE tumor derived DNA in ECOG-1199. Thus, for ECOG-1199, genotypes might be impacted by somatic point mutations and loss of heterozygosity (LOH). This limitation was minimized by careful quality review of the genotypes including filtering of SNPs that did not meet stringent criteria for the rate of genotype calls, expected MAF, and deviation from HWE. Additionally, none of these sites represent areas of frequent LOH nor somatic mutations in breast cancer.(27) Thus, while isolated cases of LOH or mutations cannot be ruled out at the individual level, at the trial level this did not appear to be an issue. Although race and obesity were significant independent predictors of peripheral neuropathy, other potentially important variables such as Diabetes Mellitus could also play a role. Unfortunately comorbidities and co-medications were not formally collected in either ECOG-5103 or ECOG-1199 and the inability to include them in modeling is a limitation to this study. Another limitation is the use of CTCAE phenotype definitions. Recent work has demonstrated patient reported outcomes (PROs) might be more sensitive.(28) The use of PROs in large trials is beginning to be used to help enhance clinically relevant interpretation and is destined to augment correlative studies such as these. Finally, although ECOG-5103 and ECOG-1199 were similar in design and size, there were some important differences. Important to this correlative work was the variability in taxane implemented and schedule. SNPs that might be docetaxel-specific would not have been identified from the discovery cohort that included only paclitaxel. Further, confirmation of paclitaxel-specific SNPs may have been underpowered in the validation cohort where only half the patients received paclitaxel. As we set out on this project, however, our hope was to identify a marker(s) that would predispose to neuropathy from the taxanes broadly.

In the group genome-wide genotyped from ECOG-5103, there was also a substantial increase in the risk for TIPN in AA patients. Further, the degree of African American ancestry (determined by PC1; with higher values representing less African ancestry) was even more statistically significant than the binary analysis. For example, the hazard ratio of 0.5 seen in the Grade 2-4 analysis meant that a 1-unit change in PC1 (reflecting a decrease in African ancestry) reduced the neuropathy risk by 50%. This analysis further supports that this is a true genetic effect, rather than environmental. Based on these data, AA patients should also be counseled about the increased risk of TIPN. As previously described, self-defined race is often inaccurate and thus ECOG-5103 includes a truly unique cohort of

genetically defined AA patients from a trial with rigorous uniformity for phenotype collection. The GWAS confined to AA patients did identify an interesting group of SNPs that associated with TIPN on Chromosome 1, including *rs1856746*. This SNP, found at 1q32.2, is located within 20 Kb of *FCAMR*, a gene that encodes for the Fc receptor Fc α / μ R. Fc α / μ R is found in B Cells and lymphoid cells and is highly specific for IgM and IgA.(29) Though the mechanism of action for TIPN is not fully understood, there is evidence of a possible relationship with the immune system.(30) The *rs1856746* G allele is more common in AA than EA (96% vs. 44%) and may partially explain the differential genetic predisposition. Although intriguing, this finding should only be regarded as hypothesis generating. Because of the substantial risk for TIPN in the AA cohort, additional work from other large data sets is warranted to confirm or refute these findings.

As markers of other toxicities from competing regimens emerge, more personalized treatment regimens can be recommended. The ultimate goal, however, is to identify therapies that might treat or prevent these toxicities. The genetic findings for predisposition might serve nicely to help unravel the mechanistic underpinnings, an important first step in therapeutic development and improved patient care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STATEMENT OF TRANSLATIONAL RELEVANCE

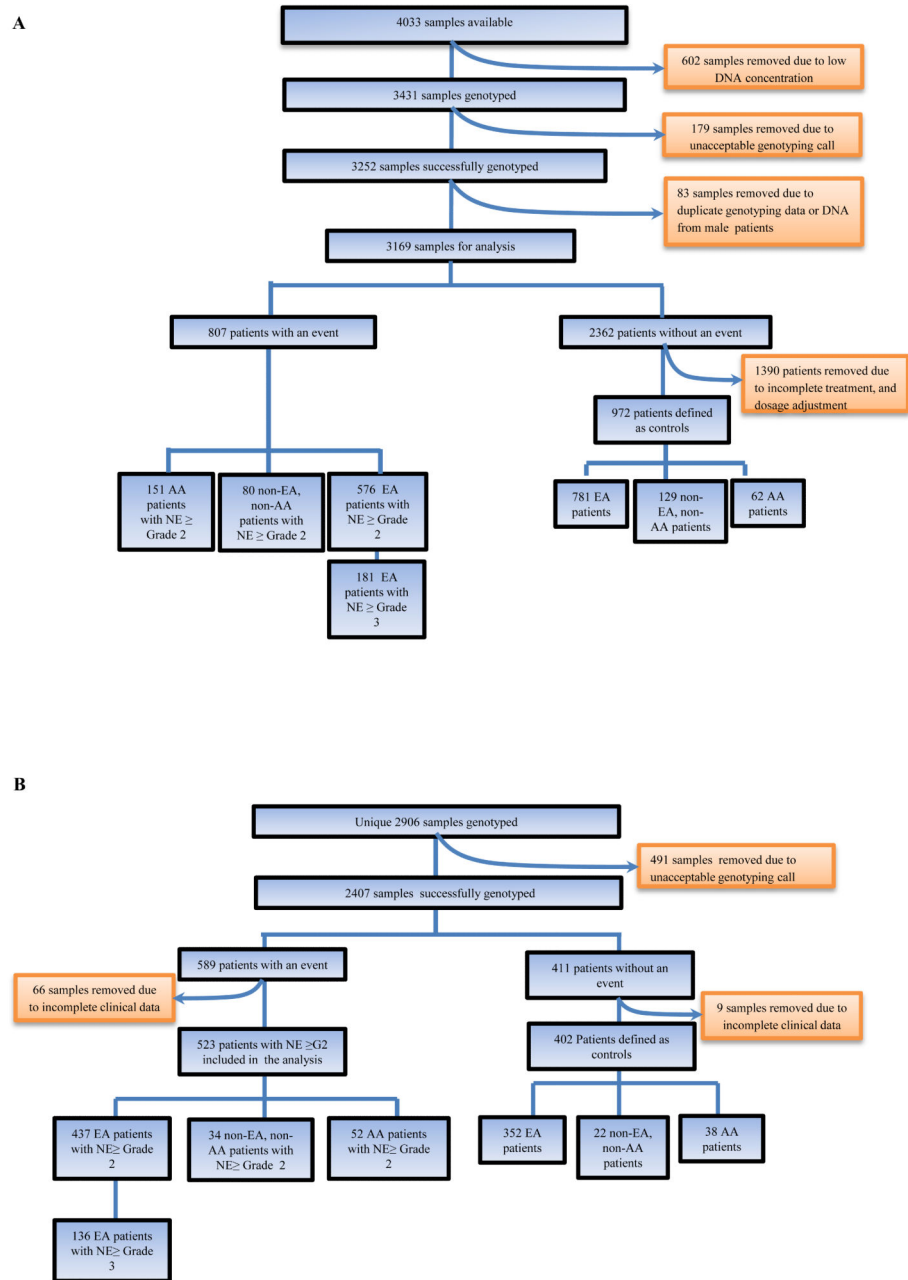
The optimal therapeutic index for any given drug is a function of efficacy as well as toxicity. While much work has focused on the identification of biomarkers that predict efficacy, the discovery of high quality biomarkers that predict toxicity are lacking. Inherited genetic variation is one important source for the heterogeneity in toxicity seen across a population. Drug-induced side effects can create unnecessary, serious medical morbidity and can impact the global quality of life experience for the patient. A significant toxicity can also limit the full-intended receipt of a potentially life-saving therapy. Taxane induced peripheral neuropathy is one of the most common and important toxicities across multiple disease types and settings. Herein we demonstrate that African American Race and a genetic variant (*rs3125923*) are important predictors for this toxicity.

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AA=African American; EA=European American; NE=Neuropathy event

Figure 1.
 CONSORT diagram
 (A) ECOG-5103 (the genome wide discovery cohort)
 (B) ECOG-1199-(the candidate SNP validation cohort)

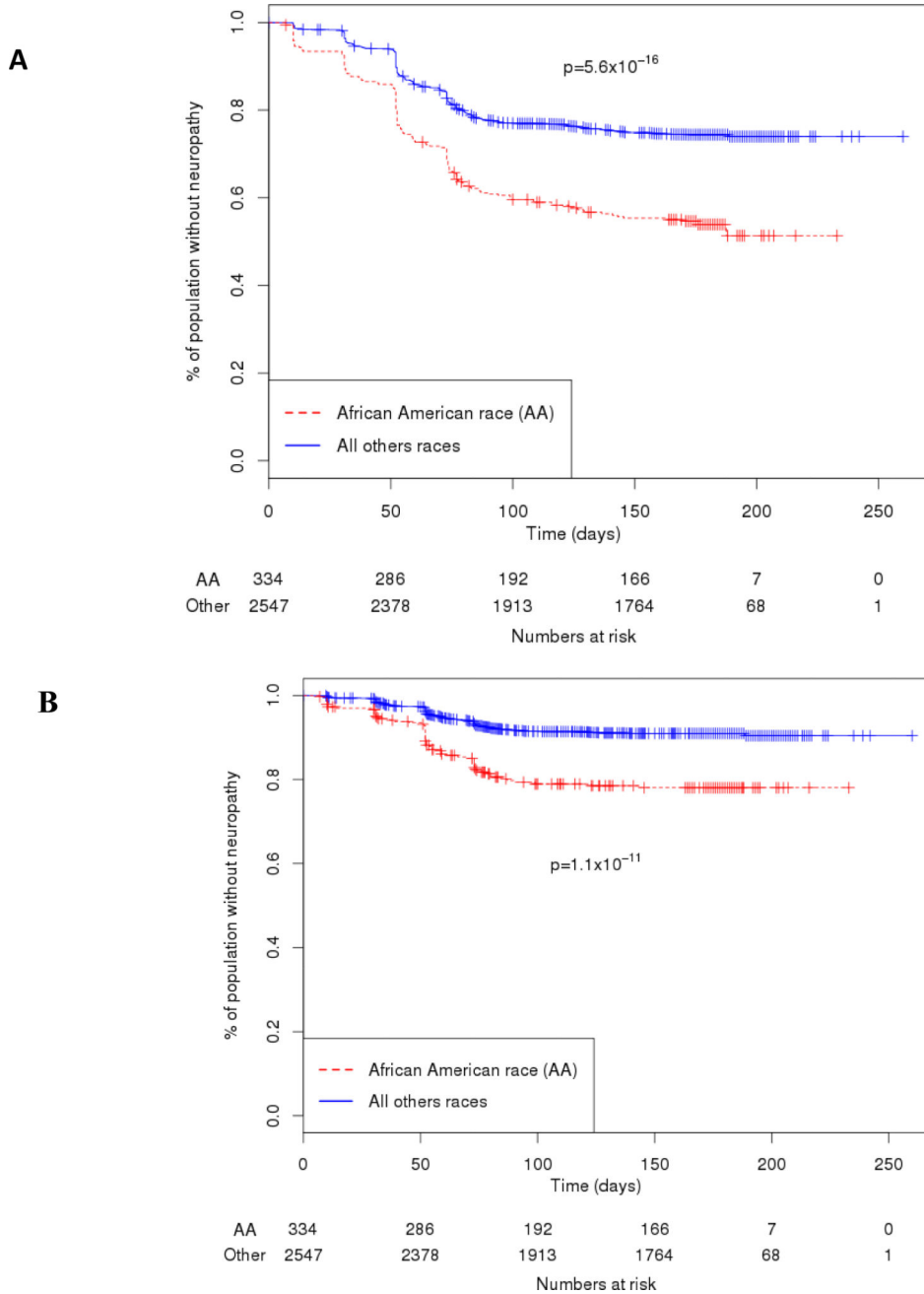


Figure 2. Comparison of Grade 2-4 and Grade 3-4 peripheral neuropathy by genetically determined race in ECOG-5103. (A) The frequency of Grade 2-4 peripheral neuropathy in the genotyped cohort was 43.3% for those of African descent vs. 24.6% for all other races combined (p-value= 5.6×10^{-16}). The number of patients that had follow-up data and were still at risk for neuropathy at each time point is displayed below. (B) The frequency of G3-4 peripheral neuropathy in the genotyped cohort was 18.4% for those of African descent vs. 8.1% for all other races combined (p-value= 1.1×10^{-11}). The

number of patients that had follow up data and were still at risk for neuropathy at each time point is displayed below.

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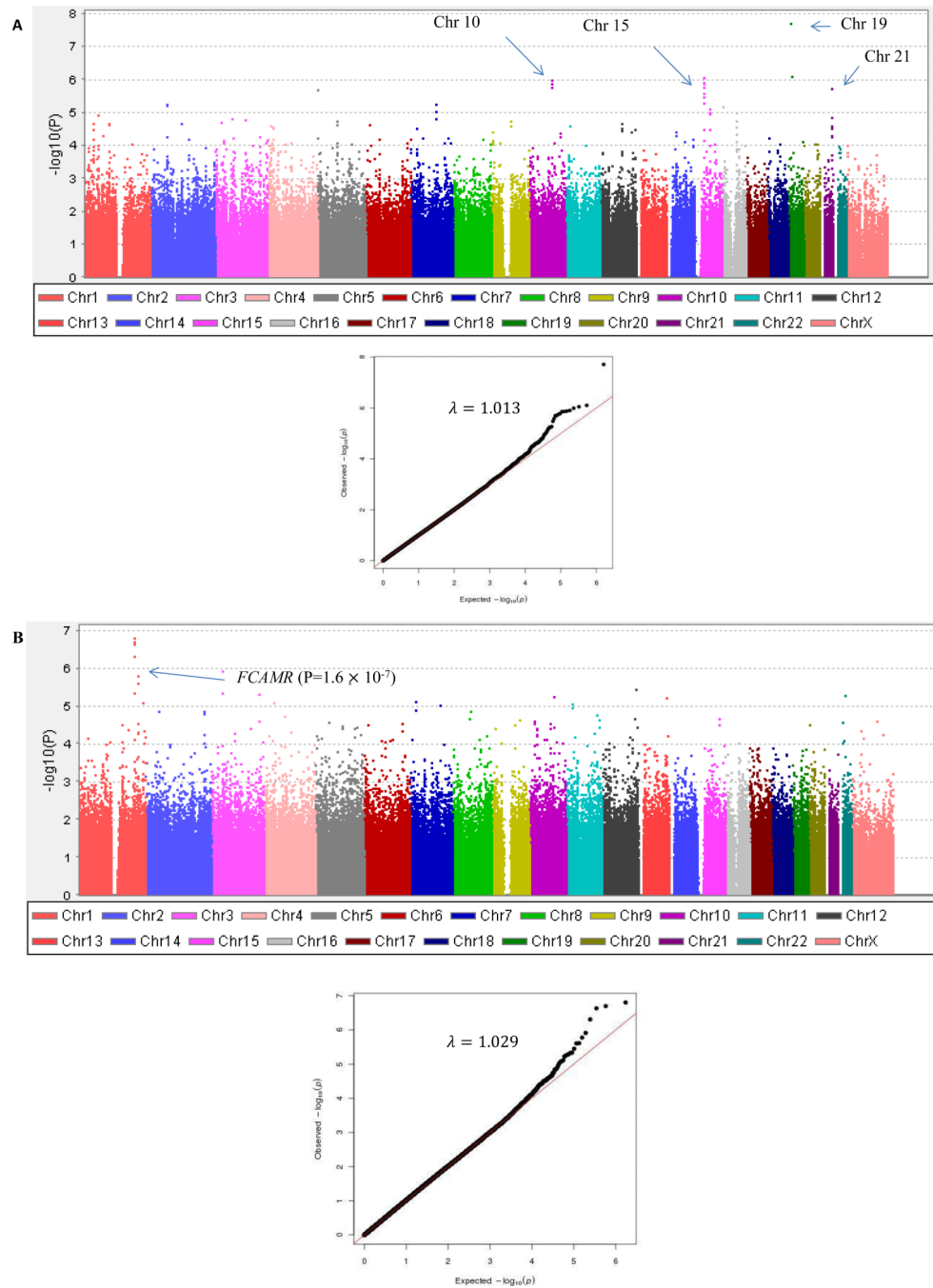


Figure 3. Manhattan plot (A) for Grade 3-4 peripheral neuropathy from EA patients in ECOG-5103. X-axis indicates the chromosomal position of each SNP analyzed; Y-axis denotes magnitude of the evidence for association, shown as $-\log_{10}(\text{p-value})$. (B) Grade 2-4 peripheral neuropathy from AA patients in ECOG-5103. X-axis indicates the chromosomal position of each SNP analyzed; Y-axis denotes magnitude of the evidence for association, shown as $-\log_{10}(\text{p-value})$.

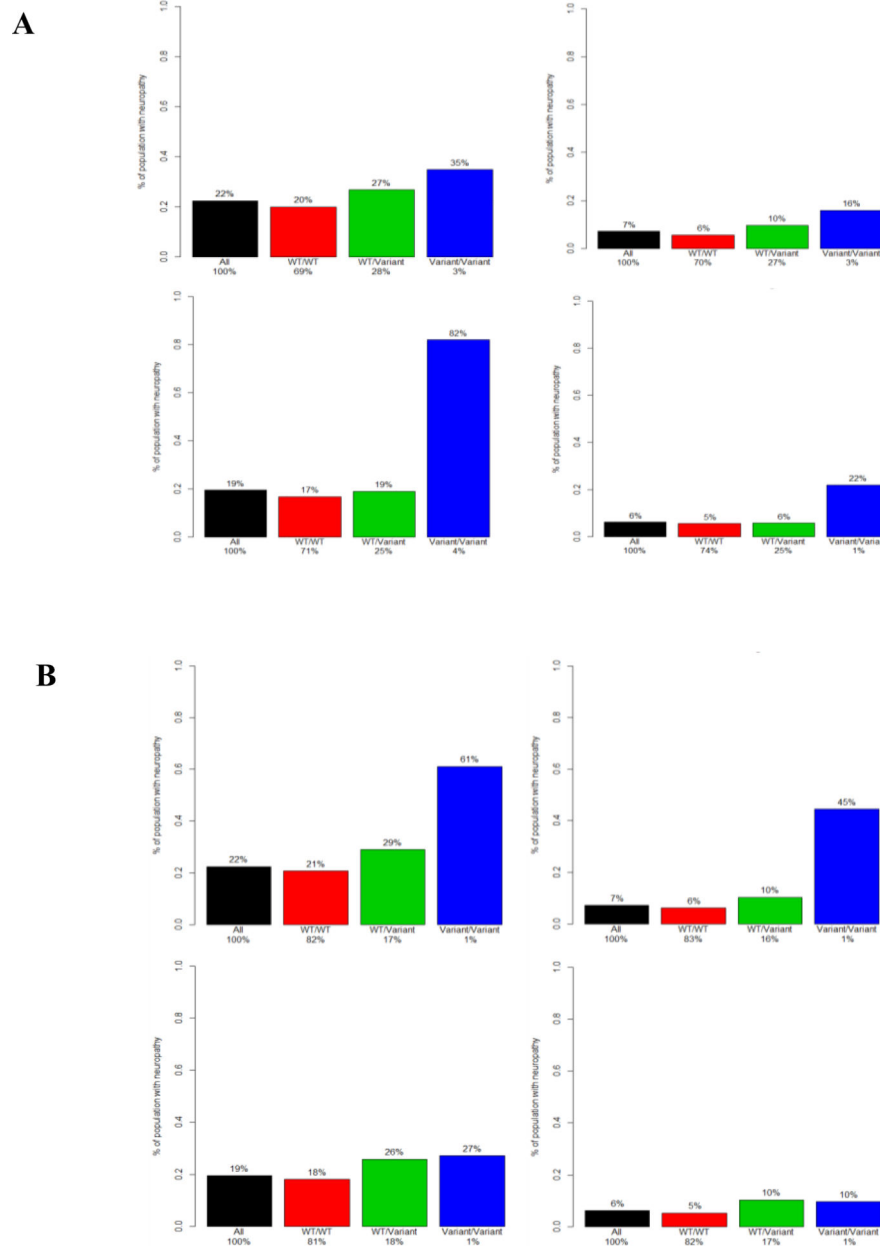


Figure 4.

Frequency of peripheral neuropathy by genotype for *rs3125923* and *rs9862208*. Each colored bar represents the estimated frequency of neuropathy based on the relative likelihood of an event derived from a genotype. The black bar represents the frequency of neuropathy in the entire E5103 genotyped cohort. The red, green, and blue bars represent an estimated frequency as determined by the odds ratio for the WT/WT, WT/Variant, and Variant/Variant genotypes, respectively. The percentage value above each bar represents the estimated likelihood of a patient with that genotype experiencing neuropathy. The percentage value on the x-axis represents the fraction of the population with that specific genotype. WT= wild type allele.

(A) Frequency of neuropathy by genotypes of *rs3125923* in ECOG-5103 (top) and ECOG-1199 (bottom) for grade 2-4 neuropathy (left) and grade 3-4 neuropathy (right).
(B) Frequency of neuropathy by genotypes of *rs9862208* in ECOG-5103 (top) and ECOG-1199 (bottom) for grade 2-4 neuropathy (left) and grade 3-4 neuropathy (right).

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Table 1

SNPs with strongest statistical significance (based on p-value) from samples of European Ancestry in ECOG-1199 validation study

SNP	Chr	E5103 G3-4 P-value	OR	E1199 G3-4 P-value	OR	E5103 G2-4 p-value	OR	E1199 G 2-4 p-value	OR
<i>rs3125923</i>	1	5.0×10^{-5}	1.8	0.0017	1.8	0.0001	1.5	0.0013	1.6
<i>rs9862208</i>	3	8.5×10^{-5}	2.0	0.0059	1.9	0.0002	1.6	0.0174	1.5

SNP=single nucleotide polymorphism; Chr=chromosome; OR=odds ratio; G3-4=Grade 3-4; G2-4=Grade 2-4

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Table 2

Selected SNPs previously reported to be associated with taxane-induced peripheral neuropathy

Author	Number of patients	Clinical trial	Drugs	Phenotype	Genotypes	Genes of Top Associations	Validation
Sucheston (7)	888	SWOG S0221	Paclitaxel (variable schedule/dose): Adjuvant-predefined number of cycles	CTC v.3.0 peripheral neuropathy - Grade 0-2 (controls) vs. Grade 3-4 (cases)	Candidate <i>BRCA1</i> and <i>FANCD2</i>	<i>FANCD2</i>	None
Leandro-Garcia(6)	214	Prospective Cohort	Paclitaxel at variable dose +/- carboplatin, gemcitabine, bevacizumab, cisplatin, cetuximab, trastuzumab, or lapatinib. Metastatic setting-variable duration.	CTC v. 2.0 peripheral neuropathy - Grade 2-3 (Cases vs. Grade 0-1 (controls)	Candidate SNPs in <i>Beta-tubulin IIa</i>	<i>Beta-tubulin IIa</i>	None
Hertz(5)	111	Retrospective cohort	Paclitaxel containing regimens- variable schedule and dose +/- cyclophosphamide or trastuzumab. Neoadjuvant-predefined duration but variable	CTC v. 4.0 peripheral neuropathy Grade 3+ (cases)	Candidate metabolism SNPs: <i>CYP1B1*3</i> , <i>CYP2C8*3</i> , <i>CYP3A4*1B/</i> <i>CYP3A5*3C</i> , and <i>ABCB1*2</i> .	<i>CYP2C8*3</i>	None
Baldwin(4)	855	CALGB-40101	Paclitaxel 4-6 cycles: Randomized, phase III trial with planned number of cycles	CTC v. 2.0 Grade peripheral neuropathy Grade 2+ (cases)	GWAS	<i>FDG4</i> <i>EPHA5</i> <i>FZD3</i>	European American cohort (n=154) and African American Cohort (n=117): <i>FDG4</i> significant in EA (p=0.013) and AA subgroup; p=6.7 × 10 ⁻³
Leandro-Garcia(8)	144	Prospective cohort	Paclitaxel + carboplatin: variable Metastatic: duration variable and some with prior neurotoxic chemo	CTC v. 2.0 Grade peripheral neuropathy Grade 2+ (cases)	GWAS	<i>EPHA4</i>	No validation but <i>EPHA5</i> with significant p-value in meta-analysis with CALGB40101. (4)
Beutler(9)	119	Alliance N08C1	Paclitaxel at variable dose and schedule +/- carboplatin	CIPN20	Targeted sequencing of 49 candidate genes	<i>ARHGEF10</i>	None
Abraham (10)	1303	tAnGo & NeotAnGo	Paclitaxel at uniform dose, but variable schedule	CTC v.2.0	Genotyping 73 SNPs in 50 candidate genes	<i>ABCB1</i> <i>TUBB2A</i>	GWAS pending
Apellaniz-Ruiz (11)	8	Patients selected from hospital population	Paclitaxel at variable dose and schedule	CTC v.4.0	Whole exome sequencing	<i>CYP3A4</i>	Yes
Boso (12)	113	Patients selected from electronic medical records	Paclitaxel & Docetaxel	CTC v.4.0	Genotyping 47 SNPs in 20 candidate genes	<i>CYP3A4</i> <i>ERCC1</i> <i>CYP2C8</i>	None

Author	Number of patients	Clinical trial	Drugs	Phenotype	Genotypes	Genes of Top Associations	Validation
Schneider (Current study)	1357 (for Grade 2+ analysis) 962 for Grade 3+ analysis	ECOG-5103	Paclitaxel at uniform dose and schedule. Randomized, phase III trial with predefined number of cycles +/- bevacizumab	CTC v. 3.0 peripheral neuropathy, Grade 2+ and Grade 3+	GWAS	<i>See results section</i>	ECOG 1199 randomized phase III trial with paclitaxel or docetaxel at variable schedule and dose. Grade 3+ n=488. <i>rs3125923</i> p=5.9×10 ⁻³

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