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Cumulative Genetic Risk Predicts Platinum/Taxane-Induced Neurotoxicity

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Abstract

Purpose—The combination of a platinum and taxane are standard of care for many cancers, but the utility is often limited due to debilitating neurotoxicity. We examined whether single nucleotide polymorphisms (SNPs) from annotated candidate genes will identify genetic risk for chemotherapy-induced neurotoxicity.

Patients and Methods—A candidate-gene association study was conducted to validate the relevance of 1261 SNPs within 60 candidate genes in 404 ovarian cancer patients receiving platinum/taxane chemotherapy on the SCOTROC1 trial. Statistically significant variants were then assessed for replication in a separate 404 patient replication cohort from SCOTROC1.

Results—Significant associations with chemotherapy-induced neurotoxicity were identified and replicated for four SNPs in *SOX10, BCL2, OPRM1*, and *TRPV1*. The Population Attributable Risk for each of the four SNPs ranged from 5-35%, with a cumulative risk of 62%. According to the multiplicative model, the odds of developing neurotoxicity increase by a factor of 1.64 for every risk genotype. Patients possessing 3 risk variants have an estimated odds ratio of 4.49 (2.36-8.54) compared to individuals with 0 risk variants. Neither the four SNPs nor the risk score were associated with progression free survival or overall survival.

Conclusions—This study demonstrates that SNPs in four genes have a significant cumulative association with increased risk for the development of chemotherapy-induced neurotoxicity, independent of patient survival.

INTRODUCTION

Combination chemotherapy with a platinum-containing drug (cisplatin, carboplatin, oxaliplatin) and a taxane (docetaxel, paclitaxel) have demonstrated improved outcomes for many malignancies including ovarian and lung cancer.(1-3) However, the efficacy of this therapy is often compromised because of debilitating toxicities, especially neurotoxicity. Despite initial tumor control, cancer patients treated with chemotherapy often must discontinue therapy due to peripheral neuropathy. There has also been the suggestion that

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presence of neuropathy may be associated with better progression-free survival in ovarian cancer.(4)

There have been many attempts to circumvent or minimize the neurotoxic effects of the chemotherapeutic agents.(5) Interventions using neuroprotectant agents including the administration of reduced glutathione(6), magnesium and calcium(7, 8), vitamin E(9), and xaliproden(10) are of interest, but require further studies to determine if there is a reproducible reduction of neurotoxic symptoms and no adverse effect on tumor control. In the absence of a modulator of neurotoxicity, prospective identification of the specific patients at greatest risk for this adverse event would allow informed decisions on therapy selection.

Previous studies designed to identify clinically-relevant genetic factors associated with chemotherapy-induced neurotoxicity have typically explored variation in genes related to the drug disposition or other drug related pathways.(11-14) The lack of a replication strategy has limited the utility of the study results.(15)

The purpose of this study was to evaluate the association of genetic variants in prespecified candidate genes with chemotherapy-induced neurotoxicity. The results of this study provide a pharmacogenetic model for predicting risk of chemotherapy-induced neurotoxicity and identify potential targets for therapeutic intervention.

METHODS

Patients and Clinical Data

The Scottish Randomized Trial in Ovarian Cancer (SCOTROC1) trial randomized 1077 patients with locally advanced or metastatic ovarian cancer to treatment with either docetaxel-carboplatin (n=539) or paclitaxel-carboplatin (n=538).(16) Correlative science studies, including germline DNA, were prospectively obtained and available from 914 individuals.(11) All patients provided written informed consent. Details of the SCOTROC1 trial (NCT00003998), patient characteristics, treatment outcomes, and toxicities for each treatment arm were previously described(16). Of particular relevance to this report, the presence of sensory neuropathy was graded prior to each cycle of chemotherapy, using the NCI-CTC ordinal assessment system that continues to be the standard for large oncology clinical trials. Data was not collected on the degree and timing of reversibility of the peripheral neuropathy phenotype. Patients had not received previous chemotherapy and did not have clinically detected peripheral neuropathy prior to initiation of therapy.

Candidate-Gene Association Study Design

A total of 60 candidate genes were chosen from three categories: nerve-related genes, inherited peripheral neuropathy genes, and drug-related genes (Supplemental Table 1). These genes were derived from studies of platinum/taxane pharmacology, dorsal root ganglia biology, inherited peripheral neuropathy discovery, or genome-wide association literature conducted in human subjects.(5, 17, 18) An Illumina GoldenGate custom SNP array (Illumina, San Diego, CA) with 1536 SNPs was designed based on linkage disequilibrium, putative function, and prior literature evidence of effect on gene function. (Supplemental Table 2).

Genotyping

DNA was extracted from whole blood samples obtained prior to the start of therapy. Genotyping of the 1536 SNP array was performed by the Duke University Center for Human Genetics Molecular Genetics core facility using methods that have been previously

described(19) and was analyzed used the Illumina Beadstudio software. An additional 33 SNPs that were not suitable for the Illumina array were genotyped using pyrosequencing (Biotage, Uppsala, Sweden).(11) Two SNPs were assessed using Taqman® Allelic Discrimination assays (Applied Biosystems) as previously described. (17)

Data Analysis

Patients that had less than 90% overall complete genotype information were removed (101 patients), as were patient with a lack of neurotoxicity information (5 patients), for a final n=808. SNPs that had less than 90% overall complete patient information or demonstrated significant deviations from Hardy-Weinberg equilibrium ($p<.05$ based on the results of a chi-square test for independence after Bonferroni corrections) were removed (resulting in 1261 final SNPs).

In order to prevent confounding due to population stratification, Principle component analysis was performed on these 1261 high quality SNPs.(20) Principle component analysis confirmed the homogeneity of the SCOTROC1 patient cohort. Subsequently, logistic regression with step-wise selection was utilized to determine clinical covariates that were associated with neurotoxicity: ECOG performance status, grade of GI toxicity, and treatment arm. Time to the first cycle at which ≥ grade 2 neuropathy was experienced was included as a covariate in the discovery phase only to reduce variability and improve power to detect genetic variations associated with toxicity (no matter how long it took to experience the toxicity). Only the clinical covariates of ECOG performance status and treatment arm were included in all subsequent association analyses (Table 1); the full distributions of all clinical characteristics can be seen in Supplemental Table 3.

In order to assess which SNPs were associated with moderate to severe neurotoxicity, we compared individuals with moderate to severe neurotoxicity (NCI-CTC grade 2-4) to those with mild or no neurotoxicity (NCI-CTC grade 0-1) under a case/control framework. From the overall available population, test and replication datasets were created by randomization to contain 50% of the cases and 50% of the controls. Each cohort had 404 patients, with cases (grades 2/3/4 neurotoxicity) = 91 and controls (grades 0/1 neurotoxicity) = 313. All SNPs were first evaluated in the testing cohort, and those declared nominally significant were evaluated in the replication cohort. To determine single-locus association with case/control status, logistic regression was utilized for each SNP including important clinical covariates using genotypic encoding rather than assuming an additive genetic model. Logistic regression was first performed on the test cohort, and SNPs with nominal p-values <0.05 were assessed in the replication cohort and were considered significant replications if $p<0.05$ in the replication set. To further reduce potential false positive findings, only the SNPs which met these criteria and were consistent in direction of the risk effect for each genotype (positive vs. negative estimated odds ratio) were considered true replications. For each replicating SNP, we selected the most likely genetic model for risk by fitting additive, dominant, recessive and genotypic models and selecting the model which maximized the likelihood, or equivalently minimized the model deviance. From this model we were able to determine the risk genotypes for each SNP.

To correct for the multiple comparisons made and to account for the possibility of false positive findings and the multistage analysis procedure, we carried out permutation testing to obtain a distribution of joint p-values for our initial association analysis and a distribution of p-values for the subsequent analysis of risk genotype score (described below), and corrected p-values were calculated from these distributions. A total of 1000 permuted data sets were generated by permuting neurotoxicity case/control status and repeated our entire analysis procedure including our two-stage association analysis, our determination of risk genotype, and analysis of risk genotype score on each of the 1000 datasets. Only SNPs with

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corrected p-values corresponding to a family-wise error rate of 0.05 were considered statistically significant.

Once the significant SNPs and most plausible genetic model were determined, we further quantified the effect due to each SNP using Population Attributable Risk (PAR). PAR is the proportion of the incidence of severe neurotoxicity in the population that is due to the risk genotype (the reduction in incidence of severe neurotoxicity that would be observed if the risk genotype were not present). The PAR for each SNP as well as the cumulative PAR for all significant SNPs can be calculated as follows:

$$PAR_i = \frac{p_i(OR_i - 1)}{p_i(OR_i - 1) + 1}$$
$$PAR = 1 - \left(\prod_{i=1}^{n} (1 - PAR_i) \right)$$

where OR_i is the odds ratio of the risk genotype for SNP i and p_i is the prevalence of the risk genotype for SNP i (21, 22).

To explore the cumulative effect of all significant SNPs, we calculated a neurotoxicity risk genotype score for each individual which was equal to the number of risk genotypes across all significant SNPs. We fitted a logistic regression model on the number of risk genotypes, as well as the important clinical covariates to reduce possible confounding effects of the covariates on toxicity. A significant result for risk genotype score would indicate a trend in the number of risk genotypes; as number of risk genotypes increases, the odds for developing severe neurotoxicity also increase. We performed the assessment with only the variables that would be known prior to the start of therapy (including ECOG status and treatment arm) to assess a clinical prediction model. The strength of the clinical prediction model was evaluated using area under the curve (AUC) analysis, comparing a model with clinical predictors only to a model also including SNPs.

We also investigated whether the individual SNPs significantly associated with neurotoxicity and the composite risk genotype score were associated with both survival time and progression free survival time in the full cohort using a Cox Proportional Hazards model which included the significant clinical covariates to control for confounding. All data analysis was performed in R-software (http://www.r-project.org/).

RESULTS

ECOG performance status (OR=1.42, p=0.006) and grade of GI toxicity (OR=1.42, p=0.001) were associated with increased risk of grade 2+ neurotoxicity, and docetaxel treatment (OR=0.30, p=7E-11) was associated with reduced risk of grade 2+ neurotoxicity, independently of SNP associations (See Table 1, Supplementary Table 3 for distributions of clinical characteristics).

From the 1261 SNPs which passed quality control standards, 69 SNPs were significantly associated with grade 2+ neurotoxicity in the test patient cohort at the $p<0.05$ level (Figure 1; Supplemental Table 4). Of those significant in the test cohort, five were also significant in the replication cohort. Four of these SNPs were consistent in the direction of clinical effect in the independent test and replication analyses (Table 2). The variants were in *BCL2, SOX10, OPRM1*, and *TRPV1*. All four SNPs reside on different chromosome, and there was no long-range linkage disequilibrium between these four SNPs, indicating that these are independent genetic effects ($R^2<0.0023$ for all pairwise combinations of SNPs). Furthermore, none of the four SNPs were associated with ECOG performance status or

treatment arm (p>0.05). The Population Attributable Risk (PAR) for each of the four SNPs varied from 5 to 35% (Table 3). Individuals with 0 risk genotypes have a reduction in incidence of neurotoxicity of 62% compared to individuals with all 4 risk genotypes (Table 3), although only four patients had all 4 genotypes (Table 4).

After calculating a risk genotype composite score for each individual (equal to the number of risk genotypes that individual carries), a strong association between the number of risk genotypes and neurotoxicity was observed (Figure 2A). The number of risk genotypes was associated with a multiplicative increase in the odds of developing neurotoxicity, with the odds of developing neurotoxicity estimated to increase by an average of 1.64 for every subsequent risk variant (p=0.007 after permutation correction) (Table 5). Patients with a composite score of 4 had an estimated odds ratio for neurotoxicity of 7.41 (3.14-17.46) compared to individuals with a composite score of 0. Incorporating the genotype risk score improved the strength of our predictive model, measured by the AUC with clinical predictors only (Discovery=0.685; Replication=0.664) as compared to the addition of the genotype risk score (Discovery=0.726; Replication=0.694).

Patients with a high risk genotype score (3-4 risk genotypes) had the same progression free survival (p=0.75) and overall survival (p=0.54) as patients with the lower risk composite score (0-2 risk genotypes) (Figure 2B and 2C, respectively). Additionally, Cox proportional hazards analysis for both survival time and progression-free survival for each individual genotype indicate no association with progression-free or overall survival.

DISCUSSION

An association study of biologically annotated candidate genes identified and replicated four variants that confer a cumulative risk for chemotherapy-induced neurotoxicity. The percent population attributable risk calculation for all 4 SNPs indicates a significant reduction in incidence of neurotoxicity of 62.0% for individuals with no risk genotypes compared to individuals with all 4 risk genotypes, although possessing all four risk genotypes is very rare (expected frequency=0.0065). Furthermore, there is a clear cumulative effect of the four SNPs, with an estimated odds ratio of 7.41 for risk of neurotoxicity in individuals with 4 risk genotypes in a model that also includes patient ECOG status and discerns between taxanes. This suggests an ability to determine a heightened risk of neurotoxicity from platinum/taxane combination chemotherapy prior to administration of therapy. Minimally, this information would allow an individual patient to make a more informed decision of the risks and benefits of therapy, including alternate chemotherapy regimens. This is especially important in the context of advanced disease, where the goal is palliation of the patient and risk of severe neurotoxicity may be detrimental.

The addition of the risk genotype score improved the predictive ability of our model over the use of clinical predictors alone (AUC=0.67 vs. 0.71 in the full cohort); it should be noted that our risk predictive model relies on the assumption that all four SNPs have equal effects, which may not be the case. To assess this assumption, we investigated a model where the score was weighted by the odds ratio of each SNP, with little change to the AUC (0.71). Relatedly, it is unclear whether the classification of risk genotype for each SNP (which was wild-type homozygous in two cases and heterozygous in two cases) optimally describes the true nature of the genotype-phenotype relationship or if the use of an assumed genetic model could outperform this system.

None of the 4 significant SNPs were associated with progression-free survival or overall survival. This decouples the theoretical link between neurotoxicity and tumor control and does not support the worry that reducing neurotoxicity risk might also reduce anticancer

effect. The unlinking of neurotoxicity and response was also recently corroborated in breast cancer.(23) Indeed, this data suggests that intervention or prevention strategies for platinum/taxane neurotoxicity based on these four genetic variants are not likely to adversely influence the efficacy of the chemotherapeutic agent. Knowledge of genetic risk may serve as a valuable prediction tool so that a patient's level of acceptance of risk can be calibrated with approximate level of risk of neurotoxicity based on the number of risk genotypes.

While the overall goal of the current study was discovery and validation of genetic associations, several interesting covariates that would not be known prior to treatment, and could not be used in a predictive model, such as time to first cycle of grade 2 neurotoxicity and grade of gastrointestinal toxicity were identified. These endpoints likely reflect underlying biological risk that is not captured by the variants assessed in this study. Analysis of the variants with only treatment arm as a covariate yielded similar results, with similar effect size estimates and directions, and similar conclusions regarding association with toxicity and a lack of association with overall survival. This supports future work in additional cohorts to focus on testing and refining such a predictive pharmacogenomics model.

BCL2, SOX10, OPRM1, and *TRPV1* encompass a broad spectrum of functionalities including a role in apoptosis, a transcription factor, an opioid receptor, and therapeutic targets of pain management, respectively. These genes were amongst 58 candidate genes, all with biologic plausibility for impact on chemotherapy-induced peripheral neuropathy in humans. However, the mechanism by which the SNPs or genes we identified influences the development of neurotoxicity is yet to be defined. The variants identified in this study are not known to have direct functional consequence, as those in *BCL2, SOX10*, and *OPRM1* are intronic and the *TRPV1* variant lies outside of the coding region. Additionally, because these SNPs were chosen as "tagging" SNPs based on the linkage disequilibrium structure, it is likely that these SNPs are not directly responsible for biological effect, but act as markers for the important genomic regions. Future studies should try to refine these association signals through more fine mapping. For example, TRPV family members have recently been proposed to have effects on chemotherapy-associated neurotoxicity via glutathione pathway modulation, and using data from Caucasian individuals from the HapMap, we know that the SNP in *TRPV1* is in strong linkage disequilibrium (r2>.8) with several expression quantitative trait loci (according to data provided in SCANdb, www.scandb.org)).(24, 25) While functional understanding is desired, the replication of these SNPs in this study prepares the way for clinical intervention studies.

All patients in this study were treated with either docetaxel-carboplatin or paclitaxel-carboplatin combination therapy, with approximately equal numbers randomized to both the discovery and replication cohorts; however, paclitaxel and docetaxel may have different genetic markers of neurotoxicity. To evaluate this possibility, we separately examined each of the four SNPs stratified by treatment group, which yielded similar results (although less stable due to the reduced sample size), suggesting that the identified SNPs are general markers of platinum/taxane-induced neurotoxicity. Furthermore, because our full patient cohort was treated with combination platinum/taxane chemotherapy and both drug classes independently have been shown to cause neurotoxicity, it is possible that the neurotoxicity could result from either or both of the drugs. The genes identified in this study are not unique to the mechanism of action of either platinum (DNA adduct formation) or taxanes (inhibit microtubule dynamics), therefore, it cannot be assumed that this genetic risk model for neurotoxicity will be predictive in other contexts. Indeed, the recently replicated associations of *FGD4* and *CYP2C8**3 with paclitaxel-associated neurotoxicity(17, 26) were not observed in SCOTROC1 patients receiving the combination of carboplatin and

paclitaxel, suggesting that predictive biomarkers may be unique to the drug combinations being deployed.(11)

Several limitations of this post hoc analysis of a completed clinical study should be considered. The primary objective of the SCOTROC1 trial was not to assess peripheral neuropathy, and thus some potentially useful data is not as thoroughly established, including baseline incidence of neuropathy or other known clinical risk factors such as diabetes. Also, the neuropathy phenotype was collected exclusively by clinician reporting using the standard NCI-CTC scale. While this scale is still the industry standard for international cancer clinical trials, more sensitive scales that incorporate patient assessment have been developed to overcome this challenge.(27) Objective neuropathy measurement using nerve conduction or other surrogate metrics may be an even more sensitive technique for collecting this phenotype in future studies, should these methods be refined to use in the context of routine oncology practice. Unfortunately it is extraordinarily difficult and expensive to prospectively collect comprehensive toxicity data in large multicenter clinical trials and impossible to collect it retrospectively.

This study is a first step in defining a pharmacogenetic risk model for this treatment limiting side-effect of platinum-taxane chemotherapy.(28) This gives a basis for studies that further validate this risk model in independent patient cohorts to identify the power of this model to predict chemotherapy-induced neurotoxicity as well as to evaluate the utility of these genes as therapeutic targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STATEMENT OF TRANSLATIONAL RELEVANCE

The ability to predict which patients are at highest risk of chemotherapy-induced peripheral neuropathy would enable clinicians to make more informed treatment decisions. This association study of credentialed candidate genes found and replicated 4 single nucleotide polymorphisms that can categorize an ovarian cancer patients' risk of neuropathy when treated with platinum/taxane combination therapy. Patients possessing 3 risk variants have 4.5 times greater risk of neuropathy compared with individuals with no risk variants. The variants did not associate with overall survival. These variants are ready for confirmatory prospective studies to validate the utility in neuropathy risk stratification. Patients who are predicted to be at high risk could be offered alternative treatment options that are similarly effective but safer for those individuals.

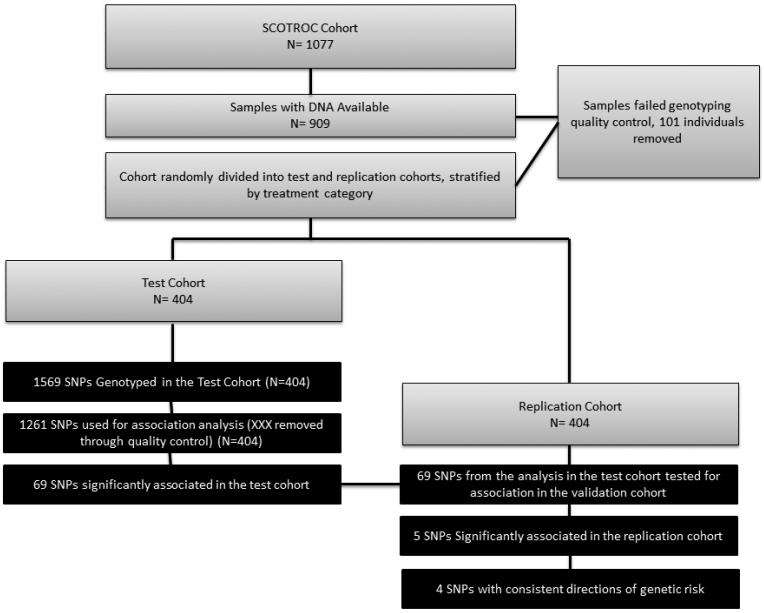

Figure 1.
Flowchart of the study design, including SNP QC and the narrowing number of SNPs per stage, in addition to patient characteristics.

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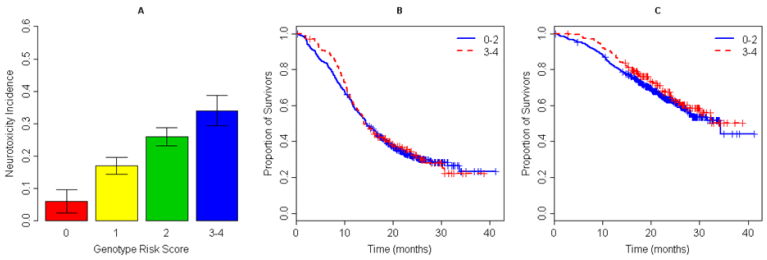

Figure 2.

Relationship between genotype risk score (0-2 vs 3-4) and (A) incidence of neurotoxicity (+/− 2 standard errors), (B) progression free survival (p=0.75) or (C) overall survival (p=0.54) in the full dataset.

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Table 1

Clinical characteristics of patients from both the discovery and replication cohorts (for significant covariates).

		Full data		Discovery Cohort		Replication Cohort	
Variable	**Level**	**N**	**%**	**N**	**%**	**N**	**%**
Worst grade of sensory neuropathy	0	285	35.3%	142	35.1%	143	35.4%
	1	341	42.2%	171	42.3%	170	42.1%
	2	135	16.7%	66	16.3%	69	17.1%
	3	44	5.4%	23	5.7%	21	5.2%
	4	3	0.4%	2	0.5%	1	0.2%
Worst grade of GI toxicity	0	37	4.6%	18	4.5%	19	4.7%
	1	212	26.2%	116	28.7%	96	23.8%
	2	416	51.5%	201	49.8%	215	53.2%
	3	130	16.1%	62	15.3%	68	16.8%
	4	13	1.6%	7	1.7%	6	1.5%
ECOG performance status	0	268	33.2%	119	29.5%	149	36.9%
	1	426	52.7%	221	54.7%	205	50.7%
	2	114	14.1%	64	15.8%	50	12.4%
Treatment	Paclitaxel/Carboplatin	400	49.5%	206	51.0%	194	48.0%
	Docetaxel/Carboplatin	408	50.5%	198	49.0%	210	52.0%

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Table 2

SNPs significantly associated with moderate to severe neurotoxicity in the replication cohort. Estimates are adjusted for ECOG performance status and treatment status.

SNP	Gene	Base Change	Chromosome	Position	MAF	Permutation Corrected P-value	Odds Ratio	95% CI	Risk Genotype	Proportion cases per genotype
rs139887	SOX10	C->G	22	38371396	0.38	0.001	1.77	(1.21, 2.59)	CG	CC = 24/111 = 0.22
										CG = 98/355 = 0.28
										GG = 58/320 = 0.18
rs2849380	BCL2	A->G	18	60979360	0.21	0.013	2.82	(1.1608, 6.8761)	AA	AA = 10/26 = 0.38
										AG = 49/272 = 0.18
										GG = 123/506 = 0.24
rs544093	OPRM1	A->C	6	154457493	0.10	0.015	1.67	(1.017, 2.7328)	AA	AA = 157/653 = 0.24
										AG = 23/144 = 0.16
										GG = 2/10 = 0.20
rs879207	TRPV1	A->G	17	3466596	0.37	0.002	1.62	(1.1131, 2.3655)	AG	AA = 57/314 = 0.18
										AG = 103/383 = 0.27
										GG = 22/86 = 0.20

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Table 3

Percent population attributable risk (PAR) for each SNP and cumulative PAR based on OR estimates in Table 1, adjusted for ECOG status and treatment arm.

	rs139887	rs2849380	rs544093	rs879207	All SNPs
PAR (%)	19.6	5.6	35.2	22.8	62.0

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Table 4

Frequencies (percentages) of cases and controls in each genotype risk category.

Genotype Risk Score	0	1	2	3	4	Total
Cases	3 (6%)	41 (17%)	85 (26%)	48 (31%)	3 (75%)	180
Controls	45 (94%)	202 (83%)	244 (74%)	107 (69%)	1 (25%)	599
Total	48	243	329	155	4	779

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Table 5

Association between risk genotype and risk of neurotoxicity *

Genotype Risk Score	Proportion of cases with risk genotype	Proportion of controls with risk genotype	Model with only *a priori* covariates Odds Ratio	95% CI for *a priori* covariate model	Permutation Corrected P-value
0	0.06	0.94	-	-	-
1	0.17	0.83	1.64	(1.3313, 2.0442)	0.007
2	0.26	0.74	2.72	(1.7724, 4.1789)	-
3	0.31	0.69	4.49	(2.3597, 8.5427)	-
4	0.75	0.25	7.41	(3.1415, 17.4632)	-

* Both ECOG performance status and treatment arm were utilized as covariates and were determined to be associated with neurotoxicity. Neurotoxicity risk increases per ECOG performance category (OR=1.45, 95% CI 1.11-1.89, uncorrected p=0.00631) and patients undergoing docetaxel-carboplatin treatment were at a reduced risk of developing neurotoxicity (OR=0.30, 95% CI 0.21-0.43, uncorrected $p=8\times10^{-11}$).