INTRODUCTION
Peripheral neuropathy is a common and often dose-limiting toxicity associated with cancer chemotherapy treatment. Paclitaxel is a chemotherapeutic agent in the taxane family and functions by inhibiting microtubule assembly and inducing apoptosis. It is commonly prescribed in the treatment of carcinomas of the breast, ovary, lung and head and neck.1 Sensory peripheral neuropathy induced by paclitaxel is dose-dependent and is the most common toxicity associated with this microtubule inhibitor. Severe toxicity (Grade 3 or higher) generally occurs in 5–10% of patients although rates as high as 30% have been reported for certain dosage regimens.2 Known risk factors for paclitaxel-induced neuropathy include previous exposure to a neurotoxic agent or medical conditions associated with peripheral neuropathy, such as diabetes.2,4–6 Though most patients who suffer from paclitaxel-induced neuropathy do not have an identifiable predisposition. The pathogenesis of paclitaxel-induced peripheral neuropathy is unclear. Paclitaxel treatment may target axons, myelinating Schwann cells, or the dorsal root ganglion and neuron cell bodies of peripheral nerves.2 At any of these sites, damage may be mediated by microtubule stabilization or mitochondrial disruption.8 At very high single or cumulative doses almost all patients will experience some degree of peripheral neuropathy, but in certain susceptible patients neuropathy will occur at lower cumulative doses or with greater severity. Interindividual susceptibility to paclitaxel-induced peripheral neuropathy may be driven by an overall increase in exposure to paclitaxel or an increased sensitivity to damage or decreased capacity for repair at any of the putative targets of paclitaxel in the peripheral neuron.

Given the wide interindividual variability in incidence and severity of the toxicity independent of any known risk factors, it is likely that there is an underlying genetic basis for susceptibility to paclitaxel-induced neuropathy. Small candidate gene studies focusing on genes involved in paclitaxel pharmacokinetics and pharmacodynamics (for example, ABCB1, CYP2C8) or paclitaxel targets (for example, β-tubulin) have had mixed results, with some identifying variants associated with neuropathy9–11 and others failing to replicate previous results.12,13 Recently, a genome-wide association study from this group14 identified several single-nucleotide polymorphisms (SNPs) with moderate effect size in FZD3, FGD4 and EPHA5 associated with severity or dose at onset of paclitaxel-induced sensory peripheral neuropathy. An independent genome-wide study identified SNPs in RWD3 and TECTA associated with onset of paclitaxel-induced neuropathy,15 but...
these findings were not replicated by others.\textsuperscript{16} The large number of putative causative variants identified, many with small effect size, and the discrepancies from study to study suggest a complex polygenic etiology for susceptibility to paclitaxel-induced neuropathy.

Pharmacogenomic studies, especially those involved in the study of drug toxicities, come with their own particular set of challenges. Sample sizes are often limited, and phenotype definitions can be imprecise.\textsuperscript{17} This is compounded in cases where the toxicity does not appear to be driven by one or a few polymorphisms with large effect size, such as CYP2D6 polymorphisms and morphine toxicity,\textsuperscript{18} but rather by a number of variants each with small potential contribution to disease, as we propose is the case for paclitaxel-induced peripheral neuropathy. For these phenotypes, determining the extent to which genetic variability contributes to a particular toxicity can be challenging. Traditional heritability studies require large numbers of siblings or family structures that are not practicable, especially when studying potentially toxic drugs. Even when evidence for a heritable component to toxicity is available, candidate gene/candidate variant studies or traditional genome-wide association studies will likely be unable to identify variants with small effects that together explain a large portion of the expected heritability.

Recently, a method has been developed to estimate additive genetic variation or narrow-sense heritability driven by common SNPs (that is, those typically captured on genotyping platforms) in unrelated individuals using linear mixed models.\textsuperscript{16,20} This approach was applied to genome-wide SNP data in breast cancer patients treated with paclitaxel to determine the extent to which paclitaxel-induced sensory peripheral neuropathy is heritable and to identify causal SNPs driving this heritability.

**MATERIALS AND METHODS**

**Patient data and study design**

The patient cohort for this study was taken from the paclitaxel arm of CALGB 40101 (Alliance), a Phase III trial studying adjuvant therapy for patients with breast cancer; all patients in the current study were also enrolled in CALGB 60202 (Alliance), the pharmacogenomic companion study, and signed an IRB (Institutional Review Board)-approved, protocol-specific informed consent for use of their specimens. Paclitaxel was administered every 2 weeks over 3 h at 175 mg m\textsuperscript{-2} for four or six cycles. A total of 1040 paclitaxel-treated individuals were included in the cohort; after quality control, including principal component analysis, call rate (>98%) and clustering performance, 859 Caucasian patients were retained for further analysis. Germline DNA was genotyped on the HumanHap610-Quad Genotyping BeadChip (Illumina) platform. SNP quality control measures for minor allele frequency (≥0.01), genotyping call rate (>99%) and Hardy–Weinberg equilibrium in controls (exact test \(p \geq 0.001\)) were applied using PLINK (v1.07). Genotyped data was imputed to call genotypes of untyped SNPs using MACH\textsuperscript{1.21} (1.0) and the 1000 Genomes\textsuperscript{21} Pilot I (June 2010) data from unrelated Caucasian (CEU) individuals as a reference; imputed data were filtered for \(r^2 \geq 0.9\). Recent publications describe further details regarding the pharmacogenomic\textsuperscript{14} and clinical\textsuperscript{24} studies. Details regarding patient selection, SNP quality control and imputation are outlined in Supplementary Figure S1.

**Phenotype**

Two phenotypes are of interest in studying paclitaxel-induced neuropathy—severity of the neuropathy and cumulative dose at onset of neuropathy. These outcomes may be driven by distinct or overlapping sets of genes. Peripheral neuropathy was graded on a scale of 0–5 according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2.0. The distribution of neuropathy grades in our cohort (Figure 1) matches expected numbers from previous clinical trials.\textsuperscript{25,26} Because the linear mixed modeling approach requires a continuous quantitative or binary phenotype, both severity of neuropathy and dose at onset of neuropathy were treated as continuous variables. Severity of neuropathy was modeled using the highest grade of neuropathy over the course of treatment with log-transformed cumulative dose administered at highest grade of neuropathy (mg m\textsuperscript{-2}) as a covariate. For patients who did not experience the toxicity, cumulative dose administered over the course of the study was used as the covariate. Onset of neuropathy was modeled using deviance residuals from a time-to-event analysis as a continuous phenotype. The deviance residuals are a normalized transform of the martingale residuals, which estimate the difference at a particular cumulative dose \(t\) between observed (incidence of grade 2 or higher peripheral neuropathy, 0 or 1) and expected events (predicted hazard for neuropathy at dose \(t\) for a given patient. Residuals from survival models have been previously used to model time to onset of various phenotypes as a quantitative trait when it is not possible to apply a survival model directly.\textsuperscript{27–29} The time-to-event analysis was conducted using a null Cox proportional hazards model without predictors, with time defined as cumulative paclitaxel dose and event defined as first instance of grade 2 or higher peripheral neuropathy.\textsuperscript{30} For patients who did not experience grade 2 or higher neuropathy, cumulative dose administered over the course of the study was used, producing right-censored dosage date. Deviance residuals from the Cox score test were calculated using the survival package in R.\textsuperscript{30,31}

**Pathway definitions**

Pathways evaluated were selected based on putative pathology for paclitaxel-induced neuropathy. Five Gene Ontology\textsuperscript{32} (GO Release 2012-09-15) Biological Process terms were included: Axonogenesis (GO: 0007409), Myelination (GO: 0042552), Transmission of Nerve Impulse (GO: 0019226), Microtubule-Related Processes (GO: 0007017), and Mitochondrial Organization and Transport (GO: 0006839 and 0007005), along with a manually curated set of genes associated with congenital peripheral neuropathy\textsuperscript{33} and a set of genes in the paclitaxel pharmacokinetic/pharmacodynamic pathway.\textsuperscript{34} For GO terms, all possible genes (regardless of evidence code) were included. For each pathway, gene boundaries for the largest isoform of each gene were extracted from the UCSC Table Browser using UCSC gene annotations from human genome build 37 (hg19). These gene boundaries (plus an additional 10 kb upstream and downstream) were used to extract all dbSNP135\textsuperscript{35} SNPs in the gene regions. Pathway SNP lists were used to extract the pathway-specific portion of the genome in PLINK (v1.07).\textsuperscript{36}

For SNP sets grouped by position in the genome (genic vs intergenic), gene and SNP annotations were extracted from the UCSC Table Browser using CCDS\textsuperscript{37} gene annotations from human genome build 37 (hg19) and SNP annotations from dbSNP135. Genic regions were defined as 10 kb upstream and downstream of transcription start and stop sites. For genes with multiple CCDS isoforms, the longest isoform was used. The Biofilter\textsuperscript{38} software (v2.0.0) was used to extract SNPs by genomic position.

**Linear mixed modeling heritability analysis**

Heritability estimates for the whole genome and for the pathways were generated using the Genome-Wide Complex Trait Analysis (GCTA)\textsuperscript{(v1.01)}
components as covariates in both initial regression and PLINK set test. The Pharmacogenomics Journal (2014), 336 – 342

Discussion of Polygenic Inheritance of Paclitaxel-Induced Neuropathy

The variance explained by all continuous quantitative variables. The variance explained by all genotyped SNPs across the genome was estimated as 41% for severity of neuropathy and 55% for onset of neuropathy but with high standard errors (44% and 47%, respectively) due to the small sample size. To narrow in on the causative SNPs driving heritability and reduce noise from non-causative SNPs, two methods were applied: (1) a genomic position based SNP selection, extracting SNPs in genic regions, and (2) a biological pathway-based selection that extracted SNPs that fall in biological pathways that are associated with putative mechanisms for susceptibility to paclitaxel-induced neuropathy.

When partitioning the genome in SNP sets by genomic location (Figure 2), a trend toward higher heritability was found in genic regions for severity ($h^2 = 49 \pm 37\%$, $P = 0.07$) and onset of peripheral neuropathy ($h^2 = 48 \pm 35\%$, $P = 0.08$). For severity of peripheral neuropathy, pathway-specific results show highest heritability estimates for the Axonogenesis gene set ($h^2 = 21 \pm 12\%$, $P = 0.040$; Table 1). A complementary pathway analysis approach, the PLINK set test, was used to further extend our pathway-based heritability results. Consistent with the GCTA analysis, only the Axonogenesis set is significant ($P = 0.012$) for severity of neuropathy using the set test (Supplementary Table S1). For onset of peripheral neuropathy, no significant signal of heritability was detected in any of the pathways tested (Supplementary Table S2).

'Children' of the GO Axonogenesis term, defined as terms with a 'is_a' or 'part_of' relationship with the Axonogenesis term, were subsequently tested for the severity of neuropathy phenotype (Table 2). Of the 10 terms tested, GO Regulation of Axonogenesis (GO: 0050770), GO Axon Extension (GO: 0048675) and GO CNS Neuron Axonogenesis (GO: 0021955) showed strong heritability signals ($h^2 = 13 \pm 6\%$ ($P = 0.009$), 10 \pm 5\% ($P = 0.020$) and 5 \pm 3\% ($P = 0.020$), respectively). To determine whether the signal from these three terms comes from independent genes in each set or overlapping genes in the three sets, heritability estimates were calculated using the pair-wise and three-way union or intersection of the GO Regulation of Axonogenesis, GO Axon Extension and GO CNS Neuron Axonogenesis sets. The union or intersection of the GO CNS Neuron Axonogenesis set with GO Axon Extension or GO Regulation of Axonogenesis sets resulted in lower heritability estimates than either independent set with high s.e. (data not shown). For the GO Axon Extension and GO Regulation of Axonogenesis sets, the heritability signal from the independent set and the union and intersection sets are very similar (Figure 3), suggesting that a large portion of the SNPs driving the heritability in the Regulation and Extension sets come from the 44 genes found in both gene sets.

Heritability estimates were also calculated using imputed data; as with the genotyped SNPs, whole-genome estimates of heritability with imputed SNPs had very high standard errors. For genomic position and pathway analyses, results from imputed data were similar to those described above for genotyped data, with a trend to higher heritability estimates in genic vs intergenic regions for the severity of peripheral neuropathy (Supplementary Table S3) and in the GO Axonogenesis set for severity of peripheral neuropathy (Supplementary Tables S4–S6).
DISCUSSION

These results suggest that a portion of variation in severity and onset of paclitaxel-induced sensory peripheral neuropathy is captured by additive effects of common SNPs in this clinical trial population. Previous studies have indicated that heritability is driven primarily by SNPs in genic regions, and a similar trend is found in our study. Within genic regions, we also noted a higher proportion of variance in severity and onset of peripheral neuropathy captured by SNPs in intronic regions, but it is unclear whether this is due to a bias in the design of the genotyping chip or true bias in the genomic location of SNPs associated with paclitaxel-induced neuropathy. If real, the enrichment of heritability signal in introns suggests that the majority of causal SNPs have subtle biological effects—for example, small changes in expression or stability that may be regulated by intronic SNPs, rather than overt changes in protein structure or function caused by variation in exons. This is consistent with a polygenic model in which many small, additive effects together contribute to the phenotype.

Further, a set of genes was identified that drive a substantial portion of the heritability of severity of paclitaxel-induced peripheral neuropathy, implicating axonogenesis and, more specifically, the regulation of axon outgrowth, in the pathophysiology of this adverse event. These results are supported by evidence from human biopsies, electrophysiological studies and

| Table 1. Heritability estimates for severity of paclitaxel-induced sensory neuropathy using SNPs in biological pathways implicated in the toxicity |
|---|---|---|---|---|---|
| Pathway | Heritability estimates | Pathway characteristics |
| | V(G)/V(p) | s.e. | pB | Padj | Empirical pD | No. of genes | Size (Mb) | No. of SNPs |
| GO Axonogenesis | 0.213 | 0.120 | 0.040 | 0.28 | 0.011 | 502 | 78.0 | 17,581 |
| GO Impulse Transmission | 0.000 | 0.122 | 0.500 | 1 | 0.999 | 746 | 106 | 22,886 |
| GO Myelination | 0.029 | 0.035 | 0.200 | 1 | 0.255 | 75 | 6.86 | 1336 |
| Congenital Peripheral Neuropathy | 0.000 | 0.030 | 0.500 | 1 | 0.999 | 40 | 4.03 | 947 |
| Paclitaxel Pharmacokinetics/Pharmacodynamics | 0.011 | 0.017 | 0.300 | 1 | 0.221 | 10 | 1.20 | 402 |
| GO Mitochondrial Transport and Organization | 0.012 | 0.055 | 0.400 | 1 | 0.545 | 274 | 19.7 | 3668 |
| GO Microtubule-Related Processes | 0.000 | 0.072 | 0.500 | 1 | 0.999 | 34 | 3.55 | 5775 |

Abbreviations: GO, Gene Ontology; SNP, single-nucleotide polymorphism. *Heritability was estimated for sets of SNPs within ±10 kb of genes in biological pathways implicated in the pathophysiology of paclitaxel-induced sensory peripheral neuropathy. The congenital neuropathy and paclitaxel pharmacokinetics/pharmacodynamics pathways were manually constructed from the literature. pB-value from GCTA (genome-wide complex trait analysis). Software upper limit for P-value is 0.5; maximal values are noted as 1. P-value corrected for seven observations. P-value from permutation analysis.

| Table 2. Heritability estimates for severity of neuropathy captured by SNPs in subsets of the GO Axonogenesis set |
|---|---|---|---|---|---|
| GO Axonogenesis children | Heritability estimates | Pathway characteristics |
| | V(G)/V(p) | s.e. | pB | Padj | Empirical Pd | No. of genes | Size (Mb) | No. of SNPs |
| Axonal Fasciculation | 0.000 | 0.025 | 0.5 | 1 | 0.999 | 15 | 2.89 | 922 |
| Peripheral Neuron Axonogenesis | 0.005 | 0.010 | 0.3 | 1 | 0.203 | 2 | 0.13 | 15 |
| Axon Guidance | 0.000 | 0.019 | 0.5 | 1 | 0.999 | 362 | 57.51 | 699 |
| Axonogenesis in Innervation | 0.011 | 0.015 | 0.2 | 1 | 0.146 | 3 | 0.15 | 19 |
| Axon Regeneration | 0.000 | 0.013 | 0.5 | 1 | 0.999 | 29 | 3.31 | 314 |
| CNS Neuron Axonogenesis | 0.051 | 0.031 | 0.020 | 2 | 0.028 | 26 | 6.32 | 935 |
| Axon Extension | 0.097 | 0.050 | 0.020 | 2 | 0.003 | 70 | 8.88 | 1862 |
| Regulation of Axonogenesis | 0.130 | 0.059 | 0.009 | 0.09 | 0.001 | 104 | 20.85 | 3239 |
| Axon Target Recognition | 0.012 | 0.019 | 0.3 | 1 | 0.26 | 13 | 3.10 | 396 |

Abbreviations: CNS, central nervous system; GO, Gene Ontology; SNP, single-nucleotide polymorphism. *Heritability was estimated for sets of SNPs within ±10 kb of genes in children (subsets) of the GO Axonogenesis set. pB-value from GCTA (genome-wide complex trait analysis). Software upper limit for P-value is 0.5; maximal values are noted as 1. P-value corrected for 10 observations. P-value from permutation analysis.

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Figure 3. Heritability estimates for severity of paclitaxel-induced sensory peripheral neuropathy for single-nucleotide polymorphisms (SNPs) in selected Gene Ontology (GO) biological pathways. Heritability was estimated for sets of SNPs within all pathways contained within the GO Axonogenesis pathway. Results are shown (heritability ± s.e.) for those pathways with significant (P<0.05) heritability signals. The heritability estimates for the intersection between and union of the Axon Extension and Regulation of Axonogenesis are also shown.
animal- and cell-based models that paclitaxel causes a distal axonopathy, in which the degeneration of axons occurs first at axon ends. This pattern of neuronal damage is consistent with a length-dependent neuropathy, targeting the long axons that extend into the hands and feet first, as typically occurs with paclitaxel-induced neuropathy.61 Further, there is evidence that demyelination and ganglionopathy, if they do occur, are secondary to axon damage.41,44,45 The current results suggest that susceptibility to paclitaxel-induced neuropathy is caused in part by heightened sensitivity to or reduced capacity to repair this distal axon damage.

Of the 44 genes in the GO Axon Extension and GO Regulation of Axonogenesis overlap set (Supplementary Table S7), a number of genes have been implicated in neuropathy, including hereditary neuropathy genes (MAPT,46 NGR,47 FXN48), genes with variants or expression signatures associated with diabetic or HIV-induced peripheral neuropathy (APOE,49,50 MAPT,51 CDH451), genes involved in neurological pain pathways (MT3,52 TRPV253,54 CCR5,54 CXCL1255) and genes involved in response to or repair/prevention of peripheral nerve damage (Ryk,56 SLIT1,57 NTRK3,58 NGR,59,60 TRPV253, NTN1,61 NDEL162). The majority (38) of these 44 genes fall in the GO term Regulation of Axon Extension (GO 0030516), which is a subset of both GO Regulation of Axonogenesis and GO Axon Extension.

The pathway results are also consistent with gene expression analyses in mouse and human studies of diabetic neuropathy. In a study examining the pathophysiology of diabetes-induced neuropathy in a mouse- and cell-based model, paclitaxel causes a distal axonopathy.51 Similarly, the GO Regulation of Axonogenesis term was identified as an over-represented pathway in a differential expression analysis in the mouse sciatic nerve.51 Although neuron damage is caused by different mechanisms in diabetes and following paclitaxel treatment, these results suggest that susceptibility to sensory peripheral neuropathy is driven by the same sets of genes.

Despite success in estimating heritability for paclitaxel-induced neuropathy and identifying a subset of the genome driving this heritability, some limitations in available methods and data are noted. One of the primary limitations of any pathway or gene set-based analysis is the gene set definitions available. All available set definitions are limited by current knowledge about the pathway in question, and well-curated sets are restricted to those pathways of interest to researchers. Further, the number of SNPs captured per gene varies, either because of true differences between number of variants or haplotype structure between genes or because of differences in coverage between genes on the genotyping platform that was used. Such variability in local coverage is known to be a limitation in all commercial genotyping platforms.64 Although imputation of missing SNPs did increase SNP density in each set, heritability estimates with imputed data were close to those with just genotyped data; because of the high imputation quality threshold used (r\(^2\) > 0.9), it is likely that additional SNPs in high linkage disequilibrium with genotyped SNPs, adding little additional information. For onset of peripheral neuropathy, no significant signal of heritability was detected in any of the pathways tested, either because genes driving heritability of onset of neuropathy are in a pathway we did not select or because the use of deviance residuals from the Cox proportional hazards regression rather than a direct proportional hazards regression did not adequately model the data. It is also possible that one or more of the selected pathways is incompletely annotated. GO terms are annotated using a combination of experimental evidence and computational analyses and can be both manually and electronically annotated.32,52 The extensive set of sources for term annotation not only makes GO the most comprehensive source of annotated terms available but also contributes to significant noise (incorrectly assigned genes) being built into the terms. Unfortunately, highly accurate manually annotated gene sets are currently limited, and those that exist reflect the current body of knowledge regarding a given pathway. The GO was the only database that included gene sets for each of the peripheral neuropathy mechanisms of interest. For the GO set Axonogenesis, more restrictive set definitions were investigated, including limiting pathway genes to those annotated to Axonogenesis by experimental evidence and those that were direct associations. The GO Axonogenesis experimental set gave an estimate of heritability significantly lower than that derived from the complete gene set (8% vs 22% for the complete set), suggesting that using a more conservative gene annotation would result in loss of power (Supplementary Table S8). The standard errors for the whole-genome heritability analyses are high owing to the limited sample size. Large sample sizes are difficult to obtain in genomic studies of drug toxicities, as recruitment into these studies is often limited to existing clinical trials. However, by narrowing in on the ‘causative’ SNPs, signals of heritability were obtained even with relatively small sample sizes. In this study, constraints were also imposed by the linear mixed modeling method applied, which requires a continuous or dichotomous phenotype. Although severity of neuropathy is best modeled as an ordinal variable, it is treated as a continuous quantitative variable for the purpose of this study. Likewise, onset of neuropathy is best fit in a survival model, but deviance residuals from a survival model were used as a continuous trait in the current analyses. Despite these limitations, the results from the modified phenotype definitions are likely close to those that would be estimated from the application of non-linear phenotype definitions. For example, effect estimates for SNPs in biological pathways from severity of neuropathy modeled as a linear or ordinal variable (Supplementary Figure S2) or onset of neuropathy modeled as a linear phenotype or time-to-event analysis (Supplementary Figure S3) are highly correlated (r\(^2\) = 0.91 and 0.97, respectively). However, it is important to note that, because of the constraints on the phenotype definition, we treat heritability estimates obtained from our analyses simply as an indication of association between a certain sets of SNPs and our phenotypes of interest, rather than absolute measures of percentage of variance explained by particular SNP set. Finally, a gene boundary cutoff of 10 kb was selected to ensure that the SNPs are associated with the genes in our pathway (as opposed to a neighboring gene), though at the cost of losing potential causative SNPs in upstream and downstream regulatory regions of a gene. Because most genetic variability appears to be explained by SNPs in or near genes,65 our approach likely captures a significant fraction of the variability explained by the genes in a given set.

In summary, these results suggest that there is a heritable component to the severity and dose to onset of paclitaxel-induced sensory peripheral neuropathy. Further, genes involved in axon outgrowth may modulate the severity of paclitaxel-induced neuropathy. Understanding the mechanisms and pathways involved in susceptibility to paclitaxel-induced sensory peripheral neuropathy will help identify therapies that can mitigate the toxicity and guide future drug development.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the The Pharmacogenomics Journal website (http://www.nature.com/tpj)