each individual, and used to estimate pathway-specific heritability in GCTA. Empirical p-values were generated by calculating the probability of obtaining a heritability estimate greater than that estimated from observed data.

PLINK Set Test

Briefly, the PLINK Set test as implemented in this study calculates the mean of all significant ($p < 0.05$) per-SNP p-values after filtering for SNPs in linkage disequilibrium ($r^2 \geq 0.5$). An empirical p-value is applied to each set test by permuting phenotype labels across individuals. SNP p-values for severity and onset of neuropathy were calculated in PLINK by linear regression of residuals from regression of grade of neuropathy on number of minor alleles, with log cumulative dose of paclitaxel and principal components as covariates in both initial regression and PLINK set test.

Results

The variance explained by common (MAF > 1%) SNPs for paclitaxel-induced neuropathy was estimated in a cohort of 845 unrelated Caucasian breast cancer patients treated with single agent paclitaxel. Two outcomes were of interest – severity of neuropathy (measured on a grade of 0 to 5) and cumulative dose administered at onset of neuropathy (≥ grade 2), both treated as 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 (Supplemental Table 1). For onset of peripheral neuropathy, no significant signal of heritability was detected in any of the pathways tested (Supplemental Table 2).

"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 ten 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 standard error (data not shown). For the GO Axon Extension and GO Regulation of Axonogenesis sets, the heritability signal from each 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 versus intergenic regions for the severity of peripheral neuropathy (Supplemental Table 3) and in the GO Axonogenesis set for severity of peripheral neuropathy (Supplemental Tables 4 – 6).

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[40], 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 (data not shown), 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 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[41–44]. 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 (Supplemental Table 7), a number have been implicated in neuropathy, including hereditary neuropathy genes (*MAP1B*[46], *NGF*[47],*FXN*[48]), *genes with variants or expression signatures associated with diabetic or HIV-induced peripheral neuropathy (APOE*[49, 50], *MAPT*[51], *CDH4*[51]), *genes involved in neurological pain pathways (MT3*[52], *TRPV2*[53], *CCR5*[54], *CXCL12*[55]), *and genes involved in response to or repair/prevention of peripheral nerve damage (RYK*[56], *SLIT1*[57], *NTRK3*[58], *NGF*[59, 60], *TRPV2*[53], *NTN1*[61], *NDEL1*[62]). 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 the GO Axonogenesis term was identified as an overrepresented pathway in a differential expression analysis in the *db/db* vs *db/+* mouse sciatic nerve[51]. Similarly, the GO Regulation of Axonogenesis term was identified as an overrepresented set in genes up-regulated in sural nerve biopsies from patients with advanced progression of diabetic neuropathy[63]. 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]. While 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 are in high LD 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. Gene Ontology terms are annotated using a combination of experimental evidence and computational analyses, and can be both manually and electronically annotated[32, 65]. The extensive set of sources for term annotation makes Gene Ontology 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 Gene

Ontology 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 (Supplemental Table 8).

The standard errors for the whole-genome heritability analyses are high due to the limited sample size. Large sample sizes are difficult to obtain in genomic studies of drug toxicities, since 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 analysis. 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 (Supplemental Figure 3) or onset of neuropathy modeled as a linear phenotype or time-to-event analysis (Supplemental Figure 4) 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 percent of variance explained by a 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[40] 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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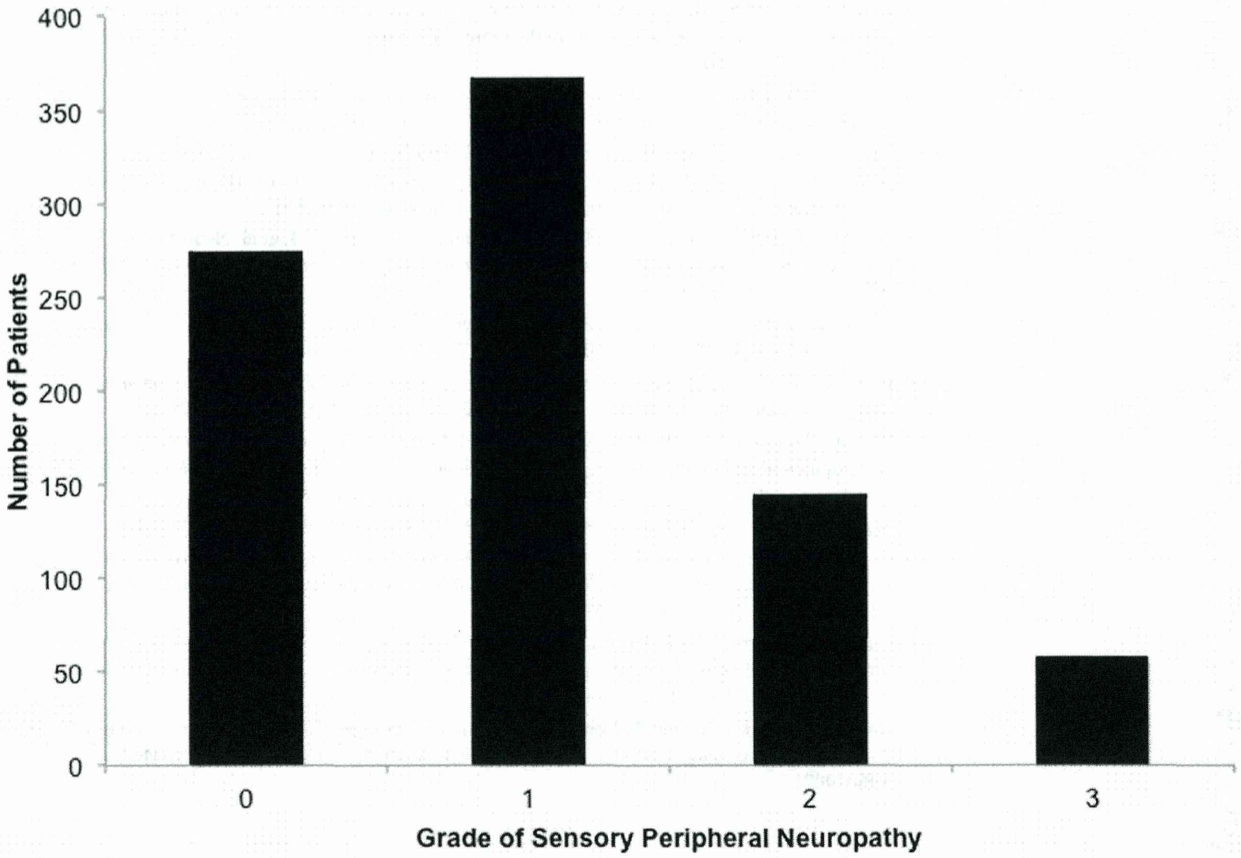

Figure 1. Distribution of sensory peripheral neuropathy in the study population

The distribution of the highest reported grade of sensory peripheral neuropathy is shown for 849 unrelated genetic Europeans from the paclitaxel arm of CALGB 40101. Toxicity is measured using the NCI-CTCAE Scale v2.

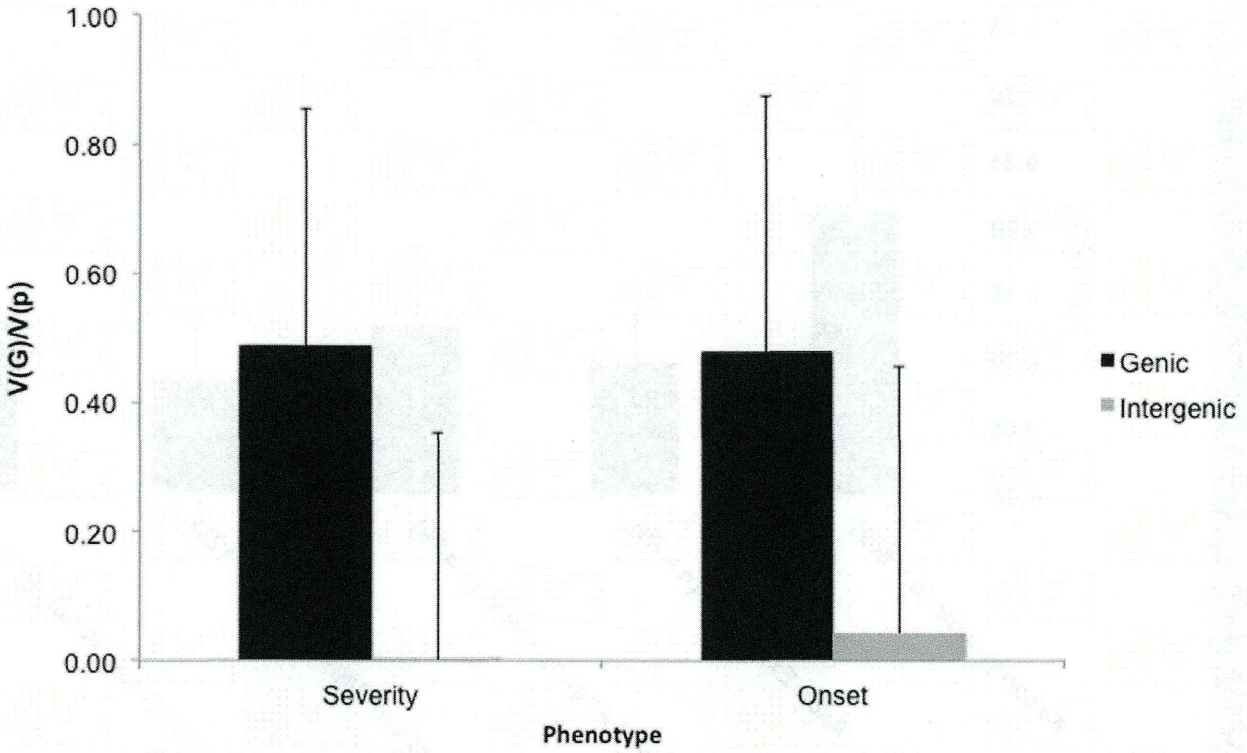

Figure 2. Heritability estimates for severity and onset of paclitaxel-induced sensory peripheral neuropathy for SNPs in genic and intergenic regions

Total genomic variance for both severity and onset of neuropathy was partitioned onto genic and intergenic regions. The error bars denote the SE for the heritability estimates.