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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## References

1. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med. 1995; 332:1004–1014. [PubMed: 7885406]
2. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. J Clin Oncol. 2006; 24:1633–1642. [PubMed: 16575015]
3. Donehower RC, Rowinsky EK, Grochow LB, Longnecker SM, Ettinger DS. Phase I trial of taxol in patients with advanced cancer. Cancer Treat Rep. 1987; 71:1171–1177. [PubMed: 2891441]
4. Postma TJ, Vermorken JB, Liefting AJ, Pinedo HM, Heimans JJ. Paclitaxel-induced neuropathy. Ann Oncol. 1995; 6:489–494. [PubMed: 7669713]
5. Rowinsky EK, Chaudhry V, Cornblath DR, Donehower RC. Neurotoxicity of taxol. J Natl Cancer Inst Monogr. 1993:107–115. [PubMed: 7912516]
6. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol. 1993; 20:1–15. [PubMed: 8102012]
7. Lipton RB, Apfel SC, Dutcher JP, Rosenberg R, Kaplan J, Berger A, et al. Taxol produces a predominantly sensory neuropathy. Neurology. 1989; 39:368–373. [PubMed: 2564647]
8. Flatters SJ, Bennett GJ. Studies of peripheral sensory nerves in paclitaxel-induced painful peripheral neuropathy: evidence for mitochondrial dysfunction. Pain. 2006; 122:245–257. [PubMed: 16530964]
9. Leandro-Garcia LJ, Leskela S, Jara C, Green H, Avall-Lundqvist E, Wheeler HE, et al. Regulatory polymorphisms in β-tubulin IIa are associated with paclitaxel-induced peripheral neuropathy. Clin Cancer Res. 2012; 18:4441–4448. [PubMed: 22718863]
10. Leskela S, Jara C, Leandro-Garcia LJ, Martinez A, Garcia-Donas J, Hernando S, et al. Polymorphisms in cytochromes P450 2C8 and 3A5 are associated with paclitaxel neurotoxicity. Pharmacogenomics J. 2011; 11:121–129. [PubMed: 20212519]
11. Sissung TM, Mross K, Steinberg SM, Behringer D, Figg WD, Sparreboom A, et al. Association of *ABCB1* genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia. Eur J Cancer. 2006; 42:2893–2896. [PubMed: 16950614]
12. Bergmann TK, Green H, Brasch-Andersen C, Mirza MR, Herrstedt J, Holund B, et al. Retrospective study of the impact of pharmacogenetic variants on paclitaxel toxicity and survival in patients with ovarian cancer. Eur J Clin Pharmacol. 2011; 67:693–700. [PubMed: 21327421]
13. Ofverholm A, Einbeigi Z, Manouchehrpour S, Albertsson P, Skrtic S, Enerback C. The *ABCB1* 3435 T allele does not increase the risk of paclitaxel-induced neurotoxicity. Oncol Lett. 2010; 1:151–154. [PubMed: 22966274]
14. Baldwin RM, Owzar K, Zembutsu H, Chhibber A, Kubo M, Jiang C, et al. A genome-wide association study identifies novel loci for paclitaxel-induced sensory peripheral neuropathy in CALGB 40101. Clin Cancer Res. 2012; 18:5099–5109. [PubMed: 22843789]
15. Schneider BP, Li L, Miller K, Flockhart DA, Radovich M, Hancock BA, et al. Genetic associations with taxane-induced neuropathy by a genome-wide association study in E5103. J Clin Oncol. 2011; 29(Suppl):1000.

16. Bergmann TK, Vach W, Feddersen S, Eckhoff L, Green H, Herrstedt J, et al. GWAS-based association between *RWDD3* and *TECTA* variants and paclitaxel induced neuropathy could not be confirmed in Scandinavian ovarian cancer patients. Acta Oncol. 2013; 52:871–874. [PubMed: 22877241]
17. Motsinger-Reif AA, Jorgenson E, Relling MV, Kroetz DL, Weinshilboum R, Cox NJ, et al. Genome-wide association studies in pharmacogenomics: successes and lessons. Pharmacogenet Genomics. 2010; 23:389–394.
18. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet. 2006; 368:704. [PubMed: 16920476]
19. Lee SH, Wray NR, Goddard ME, Visscher PM. Estimating missing heritability for disease from genome-wide association studies. Am J Hum Genet. 2011; 88:294–305. [PubMed: 21376301]
20. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, et al. Common SNPs explain a large proportion of the heritability for human height. Nat Genet. 2010; 42:565–569. [PubMed: 20562875]
21. Li Y, Willer C, Sanna S, Abecasis G. Genotype imputation. Annu Rev Genomics Hum Genet. 2009; 10:387–406. [PubMed: 19715440]
22. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genet Epidemiol. 2010; 34:816–834. [PubMed: 21058334]
23. Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, et al. A map of human genome variation from population-scale sequencing. Nature. 2010; 467:1061–1073. [PubMed: 20981092]
24. Shulman LN, Cirrincione CT, Berry DA, Becker HP, Perez EA, O'Regan RO, et al. Six cycles of doxorubicin and cyclophosphamide or paclitaxel are not superior to 4 cycles as adjuvant chemotherapy for breast cancer in women with 0–3 positive axillary nodes: CALGB 40101. J Clin Oncol. 2012; 30:4071–4076. [PubMed: 22826271]
25. Muggia FM, Braly PS, Brady MF, Sutton G, Niemann TH, Lentz SL, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. J Clin Oncol. 2000; 18:106–115. [PubMed: 10623700]
26. Perez EA, Vogel CL, Irwin DH, Kirshner JJ, Patel R. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol. 2001; 19:4216–4223. [PubMed: 11709565]
27. Bouzigon E, Ulgen A, Dizier MH, Siroux V, Lathrop M, Kauffmann F, et al. Evidence for a pleiotropic QTL on chromosome 5q13 influencing both time to asthma onset and asthma score in French EGEA families. Hum Genet. 2007; 121:711–719. [PubMed: 17473937]
28. Dickson MR, Li J, Wiener HW, Perry RT, Blacker D, Bassett SS, et al. A genomic scan for age at onset of Alzheimer's disease in 437 families from the NIMH Genetic Initiative. Am J Med Genet B Neuropsychiatr Genet. 2008; 147B:784–792. [PubMed: 18189239]
29. Hunt KJ, Lehman DM, Arya R, Fowler S, Leach RJ, Goring HH, et al. Genome-wide linkage analyses of type 2 diabetes in Mexican Americans: the San Antonio Family Diabetes/Gallbladder Study. Diabetes. 2005; 54:2655–2662. [PubMed: 16123354]
30. Therneau TM. A package for survival analysis in S. 2012
31. Therneau, TM.; Grambsch, PM. Modeling Survival Data: Extending the Cox Model. Springer-Verlag: New York; 2000.
32. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet. 2000; 25:25–29. [PubMed: 10802651]
33. Timmerman, V. Inherited peripheral neuropathies Mutation database. 2011. http://www.molgen.ua.ac.be/cmtmutations/Home/Default.cfm
34. Oshiro C, Marsh S, McLeod H, Carrillo M, Klein T, Altman R. Taxane Pathway. Pharmacogenet Genomics. 2009; 19:979–983. [PubMed: 21151855]
35. Smigielski EM, Sirotkin K, Ward M, Sherry ST. dbSNP: a database of single nucleotide polymorphisms. Nucleic Acids Res. 2000; 28:352–355. [PubMed: 10592272]

36. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81:559–575. [PubMed: 17701901]
37. Pruitt KD, Harrow J, Harte RA, Wallin C, Diekhans M, Maglott DR, et al. The consensus coding sequence (CCDS) project: Identifying a common protein-coding gene set for the human and mouse genomes. Genome Res. 2009; 19:1316–1323. [PubMed: 19498102]
38. Bush WS, Dudek SM, Ritchie MD. Biofilter: a knowledge-integration system for the multi-locus analysis of genome-wide association studies. Pac Symp Biocomput. 2009:368–379. [PubMed: 19209715]
39. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. Am J Hum Genet. 2011; 88:76–82. [PubMed: 21167468]
40. Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM, et al. Genome partitioning of genetic variation for complex traits using common SNPs. Nat Genet. 2011; 43:519–525. [PubMed: 21552263]
41. Chaudhry V, Rowinsky EK, Sartorius SE, Donehower RC, Cornblath DR. Peripheral neuropathy from taxol and cisplatin combination chemotherapy: clinical and electrophysiological studies. Ann Neurol. 1994; 35:304–311. [PubMed: 7907208]
42. Letourneau PC, Ressler AH. Inhibition of neurite initiation and growth by taxol. J Cell Biol. 1984; 98:1355–1362. [PubMed: 6143759]
43. Melli G, Jack C, Lambrinos GL, Ringkamp M, Hoke A. Erythropoietin protects sensory axons against paclitaxel-induced distal degeneration. Neurobiol Dis. 2006; 24:525–530. [PubMed: 17010629]
44. Sahenk Z, Barohn R, New P, Mendell JR. Taxol neuropathy. Electrodiagnostic and sural nerve biopsy findings. Arch Neurol. 1994; 51:726–729. [PubMed: 7912506]
45. Roytta M, Raine CS. Taxol-induced neuropathy: chronic effects of local injection. J Neurocytol. 1986; 15:483–496. [PubMed: 2427662]
46. Allen E, Ding J, Wang W, Pramanik S, Chou J, Yau V, et al. Gigaxonin-controlled degradation of MAP1B light chain is critical to neuronal survival. Nature. 2005; 438:224–228. [PubMed: 16227972]
47. Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, Solders G, et al. A mutation in the nerve growth factor beta gene (*NGFB*) causes loss of pain perception. Hum Mol Genet. 2004; 13:799–805. [PubMed: 14976160]
48. Becker E, Richardson DR. Frataxin: its role in iron metabolism and the pathogenesis of Friedreich's ataxia. Int J Biochem Cell Biol. 2001; 33:1–10. [PubMed: 11167127]
49. Bedlack RS, Edelman D, Gibbs JW 3rd, Kelling D, Strittmatter W, Saunders AM, et al. *APOE* genotype is a risk factor for neuropathy severity in diabetic patients. Neurology. 2003; 60:1022–1024. [PubMed: 12654974]
50. Corder EH, Robertson K, Lannfelt L, Bogdanovic N, Eggertsen G, Wilkins J, et al. HIV-infected subjects with the E4 allele for *APOE* have excess dementia and peripheral neuropathy. Nat Med. 1998; 4:1182–1184. [PubMed: 9771753]
51. Pande M, Hur J, Hong Y, Backus C, Hayes JM, Oh SS, et al. Transcriptional profiling of diabetic neuropathy in the BKS *db/db* mouse: a model of type 2 diabetes. Diabetes. 2011; 60:1981–1989. [PubMed: 21617178]
52. Zurowski D, Nowak L, Machowska A, Wordliczek J, Thor PJ. Exogenous melatonin abolishes mechanical allodynia but not thermal hyperalgesia in neuropathic pain. The role of the opioid system and benzodiazepine-gabaergic mechanism. J Physiol Pharmacol. 2012; 63:641–647. [PubMed: 23388480]
53. Hori K, Ozaki N, Suzuki S, Sugiura Y. Upregulations of P2X(3) and ASIC3 involve in hyperalgesia induced by cisplatin administration in rats. Pain. 2010; 149:393–405. [PubMed: 20378247]
54. Padi SS, Shi XQ, Zhao YQ, Ruff MR, Baichoo N, Pert CB, et al. Attenuation of rodent neuropathic pain by an orally active peptide, RAP-103, which potently blocks CCR2- and CCR5-mediated monocyte chemotaxis and inflammation. Pain. 2012; 153:95–106. [PubMed: 22033364]

55. Benamar K, Geller EB, Adler MW. First in vivo evidence for a functional interaction between chemokine and cannabinoid systems in the brain. J Pharmacol Exp Ther. 2008; 325:641–645. [PubMed: 18281594]
56. Li X, Li YH, Yu S, Liu Y. Upregulation of Ryk expression in rat dorsal root ganglia after peripheral nerve injury. Brain Res Bull. 2008; 77:178–184. [PubMed: 18773946]
57. Yi XN, Zheng LF, Zhang JW, Zhang LZ, Xu YZ, Luo G, et al. Dynamic changes in Robo2 and Slit1 expression in adult rat dorsal root ganglion and sciatic nerve after peripheral and central axonal injury. Neurosci Res. 2006; 56:314–321. [PubMed: 16979769]
58. Gao WQ, Dybdal N, Shinsky N, Murnane A, Schmelzer C, Siegel M, et al. Neurotrophin-3 reverses experimental cisplatin-induced peripheral sensory neuropathy. Ann Neurol. 1995; 38:30–37. [PubMed: 7611721]
59. Apfel SC, Lipton RB, Arezzo JC, Kessler JA. Nerve growth factor prevents toxic neuropathy in mice. Ann Neurol. 1991; 29:87–90. [PubMed: 1705109]
60. Peterson ER, Crain SM. Nerve growth factor attenuates neurotoxic effects of taxol on spinal cord-ganglion explants from fetal mice. Science. 1982; 217:377–379. [PubMed: 6124041]
61. Wilson BD, Ii M, Park KW, Suli A, Sorensen LK, Larrieu-Lahargue F, et al. Netrins promote developmental and therapeutic angiogenesis. Science. 2006; 313:640–644. [PubMed: 16809490]
62. Toth C, Shim SY, Wang J, Jiang Y, Neumayer G, Belzil C, et al. Ndel1 promotes axon regeneration via intermediate filaments. PLoS One. 2008; 3:e2014. [PubMed: 18431495]
63. Hur J, Sullivan KA, Pande M, Hong Y, Sima AA, Jagadish HV, et al. The identification of gene expression profiles associated with progression of human diabetic neuropathy. Brain. 2011; 134:3222–3235. [PubMed: 21926103]
64. Lindquist KJ, Jorgenson E, Hoffmann TJ, Witte JS. The impact of improved microarray coverage and larger sample sizes on future genome-wide association studies. Genet Epidemiol. 2013; 37:383–392. [PubMed: 23529720]
65. Harris MA, Clark J, Ireland A, Lomax J, Ashburner M, Foulger R, et al. The Gene Ontology (GO) database and informatics resource. Nucleic Acids Res. 2004; 32:D258–D261. [PubMed: 14681407]

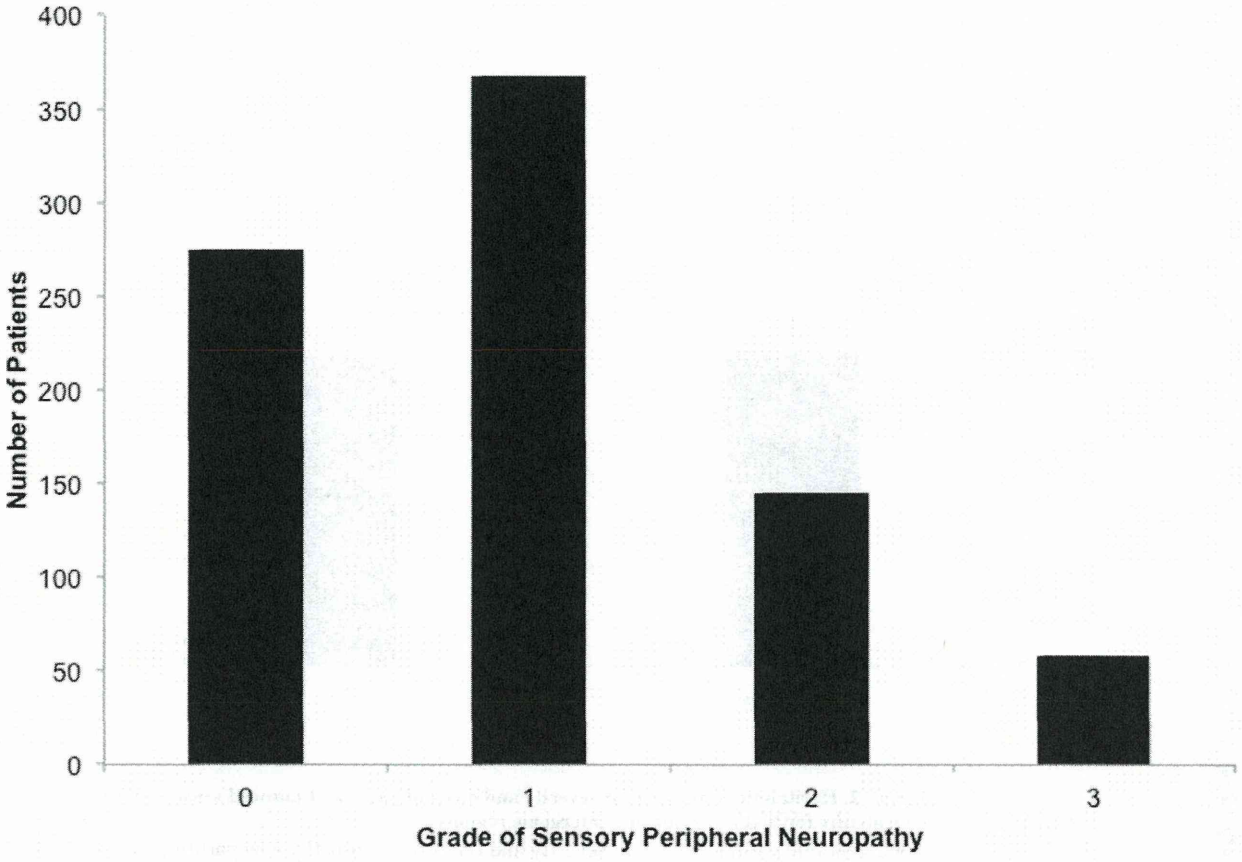


**Figure 1. Distribution of sensory peripheral neuropathy in the study population**

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.

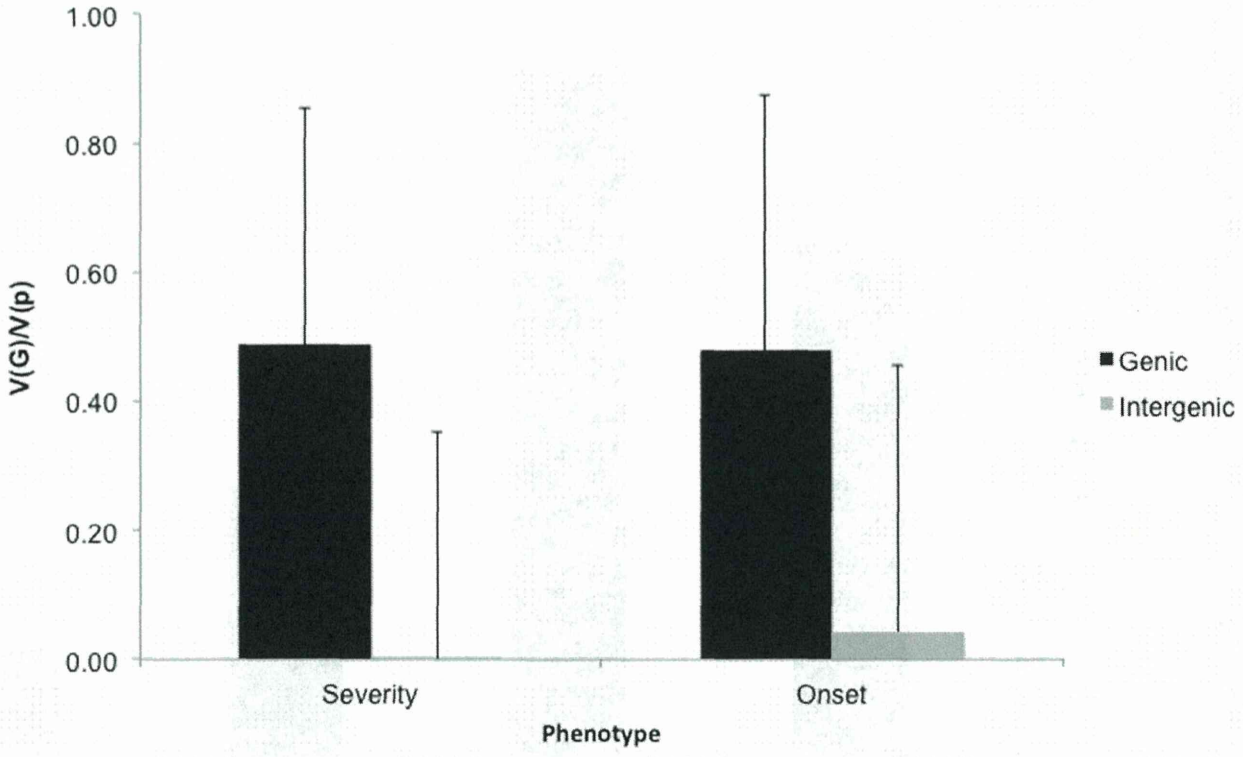


**Figure 2. Heritability estimates for severity and onset of paclitaxel-induced sensory peripheral neuropathy for SNPs in genic and intergenic regions**

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.

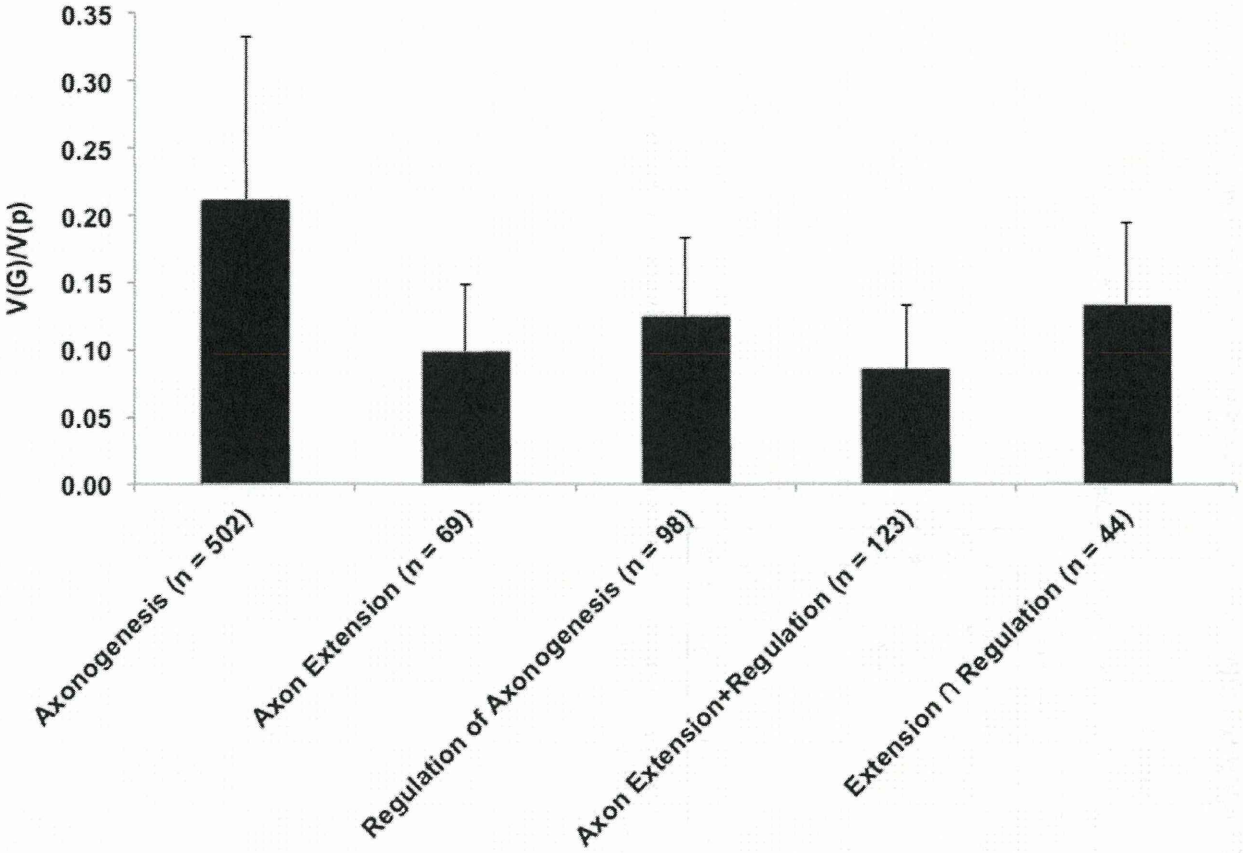


**Figure 3. Heritability estimates for severity of paclitaxel-induced sensory peripheral neuropathy for SNPs in selected GO biological pathways**

Heritability was estimated for sets of SNPs within all pathways contained within the GO Axonogenesis pathway. Results are shown (heritability ± SE) 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.

**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)[1] | SE | P[2] | Padj[3] | Empirical P[4] | # Genes | Size (Mb) | #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 | 1,336 |
| 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 | 3,668 |
| GO Microtubule Related Processes | 0.000 | 0.072 | 0.500 | 1 | 0.999 | 34 | 3.55 | 5,775 |

[1] 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.

[2] P-value from GCTA. Software upper limit for p-value is 0.5; maximal values are noted as 1.

[3] P-value corrected for seven observations.

[4] P-value from permutation analysis.