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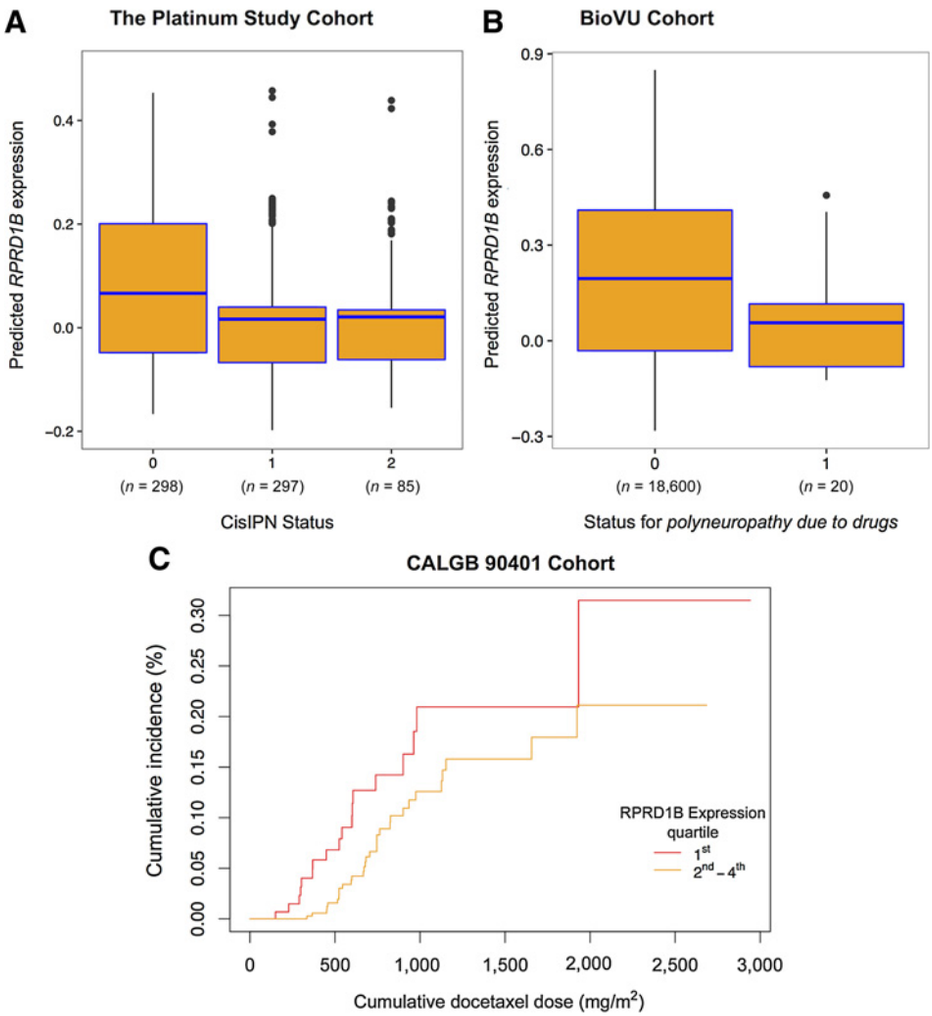

Figure 4.

Association of lower *RPRD1B* expression and CisIPN. Box and cumulative incidence plots of PrediXcan-predicted *RPRD1B* expression by neuropathy status reveal that lower expression correlates with neuropathy in (**A**) the Platinum Study's TCS cohort ($P = 3.6 \times 10^{-6}$), and (**B**) Vanderbilt's BioVU cohort (one-tailed $P = 0.021$) and (**C**) the CALGB 90401 docetaxel trial (one-tailed $P = 0.055$). In **A** and **B**, the centers of the boxplots indicate means, the hinges indicate interquartile regions (IQR), the whiskers indicate points within 1.5 × IQR. Data beyond the end of the whiskers are outliers plotted as points. In **B**, logistic regression was performed in BioVU to assess the association between PrediXcan expression and the code for polyneuropathy due to drugs—1 for cases ($n = 20$), 0 for controls ($n = 18{,}600$). In **C**, Cox proportional hazards regression was performed to assess the association between PrediXcan expression and a dose-to-grade 3 or higher neuropathy event in the CALGB. An arbitrary cutoff is used to illustrate the association between the continuous gene expression variable and the dose-to-event phenotype: Individuals were ranked according to gene expression as determined by PrediXcan and the first quartile refers to the 25% with the lowest genetically determined *RPRD1B* expression and second to fourth refer to the remaining individuals. Replication was assessed by the Fisher combined *P* value of both replications (BioVU and CALGB) and met significance ($P = 0.0089$).

variables. The cross-sectional design prevents conclusions as to whether these associated variables are risk factors or consequences of CisIPN which would require a prospective design. We found significant heritability, indicating that genetic variants could explain a large proportion of variability in the phenotype. Aggregating SNP effects using PrediXcan (31), a gene-level test imputing genetically regulated expression from genotypes, revealed lower expression of *MIDN* in skin and *RPRD1B* in whole blood, as well as higher expression of *THEM5* in tibial nerve as genome-wide significant. Using two independent datasets, we replicated the finding that lower *RPRD1B* predicted expression is associated with drug-induced neuropathy using predictors from whole blood, investigating a docetaxel-induced neuropathy phenotype and a broader drug-induced polyneuropathy phenotype in EHR.

PrediXcan

PrediXcan is a recently developed gene-based method that tests the genetically determined component of gene expression in a given tissue for association with a phenotype (31). The use of genetically determined gene expression to identify trait-associated genes is supported by evidence that SNPs associated with chemotherapeutic drug susceptibility (42) and complex traits (43) are more likely to be sites that associate with gene

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expression. Furthermore, an observed association with the genetic component proposes a causal direction of effect because the phenotype does not alter the germline genetic profile. We theorized that tibial nerve, skin, and whole blood best represent neuronal tissue and the microenvironment surrounding nerves and their endings, a potentially important source of variability in CIPN. Because genetic regulation of gene expression can be non-tissue specific, the Bonferroni correction (correcting for the total number of tests across the tissues) is conservative. In three of the four tissues tested, lower expression of *RPRD1B* is associated with CisIPN at $P < 10^{-4}$, illustrating substantial tissue-shared genetic regulation. Vanderbilt's BioVU identified lower predicted gene expression of *RPRD1B* in the discovery tissue (DGN whole blood) as associated with drug-induced polyneuropathy. However, the analysis could not distinguish drug classes. Further suggestive association of neuropathy with lower expression of *RPRD1B* in the CALGB 90401 may indicate that the mechanism for the association is not drug-specific, as that trial investigated neuropathy induced by docetaxel, another neurotoxic chemotherapeutic agent with a distinct mechanism of cytotoxicity. Therefore, *RPRD1B* might have broad implications in CIPN.

RPRD1B

Twenty SNPs in four distinct linkage disequilibrium blocks ($R^2 < 0.5$) 36 to 37.5 kb into chromosome 20 predict *RPRD1B* expression. *RPRD1B* codes for Kub5-Hera, a protein regulating the binding of RNA polymerase II to *CCND1* gene (cyclin D1), and regulating the transcription of several genes involved in the cell cycle (44). Emerging data indicate that *RPRD1B* plays an important role in several DNA repair mechanisms, including double-strand breaks (DSBs) repair through the association with core nonhomologous end-joining (NHEJ) proteins (45) and mismatch repair (46). Defects in *RPRD1B* expression or knockdown cause a deficiency in DNA repair mechanisms known to be critical in resolving cisplatin-induced lesions (47). Consistent with our data indicating low levels of *RPRD1B* being associated with CisIPN, knockdown of this gene in a breast cancer cell line, MDA-123, results in increased sensitivity to cisplatin (45). However, the suggestive association of *RPRD1B* with docetaxel-induced neuropathy indicates that other mechanisms may be important. *RPRD1B* functions as a coactivator of the ß-catenin–TCF complex to enhance the transcriptional activity of Wnt signaling (48). Wnt signaling is critical for initial neural cell-fate determination, patterning and synapse formation of sensory neurons of the dorsal root ganglia. This signaling pathway is also active in adult sensory neurons and modulates sensitivity to nociceptive stimuli (49, 50). Mechanistic insights into the function of RPRD1B are warranted to assess its role in the pathophysiology of neurotoxicity, possibly revealing novel targets.

Demographic and clinical factors and health behaviors

Our study identified age, smoking, excess alcohol use, and hypertension as associated with CisIPN. The relationship with age is consistent with several previous reports of taxane-induced neuropathy, including ECOG 5103 (4, 8, 36). In contrast, a number of studies of oxaliplatin-treated patients did not find an association with age (6, 7).

Tobacco and alcohol use. Few studies have addressed the role of tobacco use in CIPN. The authors of one study that found a correlation between smoking and CIPN postulated that long-term heavy smoking reduces peripheral blood flow, likely exacerbating paclitaxel-induced neuropathy (5). Conversely, a study of 730 TCS given platinum-based chemotherapy (9) and another of 62 patients with colon cancer receiving oxaliplatin reported no association (7). Among 169 patients given oxaliplatin-based chemotherapy, alcohol consumption was associated with neuropathy (6). In contrast, two studies in patients with breast cancer found no such relation of CIPN (10, 11). Alcohol-related peripheral neuropathy is a complication affecting up to half of alcoholic individuals (51). Excess alcohol use also plays a role in the development and progression of diabetic neuropathy (52).

Hypertension. In our study, the association between hypertension and CIPN was of borderline significance in multivariate analyses. Hypertension was not significantly associated with CIPN in the studies by Hershman and colleagues (4) and Glendenning and colleagues (9). One could postulate that microvascular complications associated with hypertension may contribute to CIPN, but our findings remain to be confirmed in other studies.

Lower physical activity and weight gain. We found CisIPN was associated with lower physical activity levels and greater weight gain since chemotherapy completion. Although a longitudinal study design would be best for establishing causal inferences, it is possible that CIPN symptoms could deter from physical activity and thereby promote weight gain. Known downstream effects of weight gain include obesity, diabetes, and other medical complications. Another long-term study in TCS has shown other comorbidities are associated with CIPN, including neuroticism (53), further emphasizing the clinical impact of CIPN symptoms and their effects on patient health.

Strengths and limitations

A major strength of our study consists of its comprehensive assessment of a variety of clinical and genetic factors associated with CisIPN. Other strengths include the homogeneity of cisplatin-based chemotherapy without the administration of other neurotoxic drugs, detailed data on cisplatin dose, and the high patient participation rate (93%). Patient reported outcomes were carefully considered, and for the CisIPN phenotype, the validated EORTC QLQ-CIPN20 questionnaire (20) was applied. Although a number of studies of CIPN (reviewed above) considered the influence of one or a few covariates on CIPN, the present investigation considered all variables taken together. In addition, to our knowledge, no other study has considered the impact of CIPN on self-reported health or reported associations with weight gain and physical activity. PrediXcan (31), a state-of-the-art gene-based method implicated *RPRD1B*, a gene known to play an important role in DNA repair mechanisms involved in cisplatin-induced damage, and shown to increase cisplatin sensitivity upon knockdown (45). Predictions are most helpful for variables known prior to treatment, yet as in previous studies (15, 18, 38, 39), baseline data before treatment were not collected. Any cross-sectional study design has potential inherent limitations and does not allow us to infer causation of other evaluated risk factors for CisIPN, but rather to report important associations.

Another limitation in this study is the underpowered statistical analyses, as only 85 out of 680 reported severe CisIPN,

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although a larger proportion reported moderate symptoms (297 of 680). A larger sample size would allow better estimation of the effects of clinical factors and SNPs and would enable making meaningful inferences about phenotype heritability which is limited by large standard errors here. Last, in replicating our study in a large set of EHR, we found lower predicted gene expression of *RPRD1B* to be associated with drug-induced polyneuropathy; however, this phenotype was not able to distinguish specific drug classes.

Conclusions

In view of the significant associations we found between smoking, excess alcohol use, decreased physical activity, and weight gain with CisIPN, health care providers should promote a healthy lifestyle among patients with CisIPN. The borderline significant association we observed for hypertension and CisIPN remains to be confirmed in other studies, but nonetheless, in view of the highly significant relationship we previously reported between hypertension and hearing loss in TCS (37), health care providers should carefully monitor blood pressure.

There are currently no agents available to prevent or treat CIPN (12), which in our cisplatin-treated population, and as reported by others (9), persists long term. This observation underscores the importance of identifying at-risk patients prior to the administration of chemotherapy, which is currently not possible. Significant heritability indicates that a large proportion of variability in toxicity could be explained by genetic variants, but larger samples are needed to reduce the standard error before variants can be used in clinical prediction. Future research efforts should continue to elucidate the genetic underpinnings of CIPN, with our investigation now showing the importance of using functional genomic information such as expression data in genome-wide analyses to improve power and provide mechanistic explanations. Such approaches are more robust than reporting single polymorphisms with small-to-moderate effect sizes, which require larger datasets and are less clinically impactful. In addition, future research efforts should continue to provide the underpinnings for the eventual development of risk prediction models for CIPN that take into account not only genetic influences but also clinical, demographic, and other important covariates. Our study provides one such example of a comprehensive approach. Future efforts will focus on independent replication in a similarly characterized TCS cohort and evaluation of the predictive power of the variables associated in this study to potentially translate models of CisIPN prediction into the clinic.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.E. Dolan, O.E. Charif, H.E. Wheeler, E.R. Gamazon, M. Kubo, N.J. Cox, L.B. Travis

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.E. Dolan, O.E. Charif, H.E. Wheeler, E.R. Gamazon, S. Ardeshir-Rouhani-Fard, D.R. Feldman, C.J. Beard, L.H. Einhorn, N.J. Cox, L.B. Travis

Writing, review, and/or revision of the manuscript: M.E. Dolan, O.E. Charif, H.E. Wheeler, E.R. Gamazon, S. Ardeshir-Rouhani-Fard, D.R. Feldman, R.J. Hamilton, D.J. Vaughn, C.J. Beard, C. Fung, S.D. Fossa, D.L. Hertz, L.H. Einhorn, N.J. Cox, L.B. Travis

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.E. Dolan, M. Kubo, L.H. Einhorn, L.B. Travis

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Other (contributed cases and was involved with all aspects of the study): L.H. Einhorn

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Clinical Cancer Research

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M. Eileen Dolan, Omar El Charif, Heather E. Wheeler, et al.

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