PgmNr 2042: Polygenic analysis of persistent cisplatin-induced peripheral neuropathy implicates immune-mediated processes.

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Cisplatin-induced peripheral neuropathy (CisIPN) is a debilitating, often irreversible outcome of platinum-based chemotherapy. No approved therapy exists and mechanisms remain elusive. We aimed to uncover the polygenic architecture of CisIPN using GTEx expression quantitative trait loci (eQTL)-based analyses from a GWAS of CisIPN in 680 genetically European testicular cancer survivors (TCS). **Methods**: TCS completed validated questionnaires to define a binary case-control CisIPN phenotype. Genotyping, quality control, and GWAS were performed. The enrichment of GTEx cis-eQTLs ($p < 10^{-6}$ in any tissue) was assessed by permutation resampling. Briefly, GWAS was performed with randomized phenotype labels adjusting for covariates (age, 10 genotype principal components) 500 times. The number of GTEx eQTLs with $p < 5 \times 10^{-3}$ in the shuffled-phenotype GWAS was computed for each permutation and the null empirical distribution of eQTL counts was used to approximate a normal distribution. A Z-score was computed from the observed overlap of GTEx eQTLs in the non-permuted GWAS to assess the significance. Protein-protein interactions (PPI) of protein-coding gene targets of enriched eQTLs and functional pathway enrichment were evaluated with KEGG using one-tailed Fisher's exact tests. **Results**: Out of 3485 genotyped SNPs with $p < 0.005$ in the CisIPN GWAS, 725 were eQTLs for 498 gene targets, indicating significant eQTL enrichment ($p = 0.0048$). We reassessed enrichment of eQTLs in each of the 44 tissues at the same threshold and another more stringent threshold (GWAS $p < 0.005$ and 0.001 respectively) to ensure robustness. Seven of 44 tissues displayed eQTL enrichment ($p < 0.05$ at both GWAS p-value thresholds): tibial nerve, tibial artery, subcutaneous adipose tissue, thyroid, pituitary, hypothalamus, and the nucleus accumbens. Protein-coding gene targets (349 of 498) provided the input for PPI, which displayed

significant interaction ($p = 2 \times 10^{-4}$), with 149/349 proteins forming a single network. KEGG pathway analysis implicated major immune functions, including autoimmunity pathways such as autoimmune thyroid disease (FDR $q = 1 \times 10^{-4}$), type I diabetes ($q = 2 \times 10^{-4}$) and rheumatoid arthritis ($q = 4 \times 10^{-4}$). **Conclusion**: Our analysis implicates regulatory regions of a 149-protein network in CisIPN. This network involves proteins functioning in immune processes, e.g., TLR2, TLR4 and MHC. Deeper analysis and functional studies are needed to validate our findings.

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