Genome-wide association study (GWAS) using phenotypes estimated from a kinetic-pharmacodynamic model of chemotherapy-induced peripheral neuropathy (CIPN)


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Objectives: Variability in CIPN may be partially explained by germline genetic variation. A kinetic-pharmacodynamic model was previously developed to quantitate the dose-CIPN relationship using data on patient-reported neuropathy\(^1\). We aimed to determine associations between single nucleotide polymorphisms (SNPs) and the variability of model-estimated parameters.

Methods: Data were extracted from CALGB 40502 (Alliance), a randomized phase III trial of paclitaxel, nab-paclitaxel or ixabepilone in patients with metastatic breast cancer. Phenotype parameters (BASE, SLOPE, KIN, KDE) and their variability (ETA) were estimated from the model (n=653). Whole genome genotyping of germline DNA was done on 964,055 markers using the Illumina HumanOmniExpressExome8 chip. Patients of European ancestry were selected by principal component analysis (n=408). GWAS was conducted with 625,445 markers using PLINK. The Genome Tissue Expression (GTEx) portal was used to select 66,577 SNPs mapped to expression quantitative trait loci (eQTLs) in tibial nerve tissue.

Results: ETA of BASE and SLOPE were associated with rs949262 at chromosome 18 (p=7.45x10^{-8}) and with rs4240447 at chromosome 9 (p=1.05x10^{-6}). Associations (p<1.79x10^{-7}) were also found with ETA of KIN and KDE. Of the eQTLs in tibial nerve, only rs4240447 was associated with ETA of BASE and SLOPE. Furthermore, rs4240447 is an intron variant of NCS1 (neuronal calcium sensor 1), which modulates synaptic transmission and may play a role in neuron differentiation.

Figure 1. Manhattan (A) and QQ (B) plots of ETA (BASE, SLOPE)

Conclusions: This study is novel because we conducted GWAS using model-estimated parameters as phenotypes. The model describes longitudinal drug-related toxicity, which facilitated discovery of relevant SNPs. We plan to validate our findings and incorporate rs4240447 as a covariate in the model.