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

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Chemotherapy-induced peripheral neuropathy (CIPN) is a common toxicity caused by exposure to anticancer agents that impairs quality of life. Recently, a kinetic-pharmacodynamic model has been developed to quantitate the dose-CIPN relationship using data on patient-reported CIPN in a randomized phase III trial of paclitaxel, nab-paclitaxel and ixabepilone in metastatic breast cancer. Five parameters (BASE, IRG, KDE, KIN, SLOPE) were estimated in this model. Parameter estimates had relatively large between-subject variability, and genetic variation is hypothesized to describe some of this variability. A genome-wide association study was done using the model-estimated parameters as phenotypes (n=524). KDE was significantly associated with rs11952896 in patients of European ancestry ($p < 5 \times 10^{-8}$), but was not significant with log-transformed KDE. Future directions are to explore whether groups of common variant SNPs and/or gene expression are associated with parameter estimates.

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