 Genome-wide Analyses Associate Variants in Rho GTPase Signaling Pathways With Microtubule Targeting Agent-Induced Sensory Peripheral Neuropathy

Katherina C. Chua1, Carol Ho2, Taisei Mushiroda3, Chen Jiang4, Flora Mulkey4, Hope S. Rugo5, Michiaki Kubo3, Kourosh Owzar4, Lawrence N. Shulman6, and Deanna L. Kroetz7

1Pharmaceutical Sciences and Pharmacogenomics Graduate Program, University of California San Francisco, San Francisco, CA, USA
2School of Pharmacy, University of California San Francisco, San Francisco, CA, USA
3Laboratory for Genotyping Development, Riken Center for Integrative Medical Sciences, Kanagawa, Japan
4Alliance Statistics and Data Center, Duke University, Durham, NC, USA
5Department of Medicine, University of California San Francisco, San Francisco, CA, USA
6Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
7Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, USA

Microtubule-targeting agents (MTAs) are commonly prescribed for breast cancer and other solid tumors. Sensory peripheral neuropathy (SPN) is the major dose-limiting toxicity for MTAs. This study aims to identify genetic components that influence the susceptibility for developing MTA-induced SPN. A genome-wide association was conducted with advanced breast cancer patients in CALGB 40502 (Alliance) receiving weekly paclitaxel, nab-paclitaxel, or ixabepilone treatment. Patients were genotyped on the Illumina HumanOmniExpressExome-8 BeadChip and 574,465 SNPs and 469 genetically estimated Europeans remained after quality control. A Cox regression model with cumulative dose to first instance of Grade 2 or higher SPN was used in the primary analysis. The GWAS in CALGB 40502 yielded no genome-wide significant results. These findings were combined with a previously published GWAS of CALGB 40101 for a meta-analysis, which included the addition of 859 European subjects. The top-ranking variant was downstream of S1PR1 (rs74497159; MAF = 0.07; HR = 1.89 (1.48-2.43); P = 3.62E-07). The gene S1PR1 encodes for sphingosine 1-phosphate receptor 1, a G-protein coupled receptor that signals reorganization of actin cytoskeleton and formation of lamellipodia via RAC1 activation, which has been previously implicated in paclitaxel-induced neuropathic pain. Bioinformatic analysis on rs74497159 suggests that this variant lies within a transcriptionally active regulatory region, potentially increasing S1PR1 expression and stimulating the development of MTA-induced SPN. Additionally, a previously reported variant in FGD4 (rs10771973; MAF = 0.31; HR = 1.39 (1.21-1.59); P = 2.15E-06), encoding for a guanine nucleotide exchange factor that activates Cdc42 GTPase to regulate actin cytoskeletal assembly for filopodia formation, remained associated with MTA-induced SPN in the meta-analysis. Overall, our pharmacogenomic study suggests that genomic perturbations in RhoGTPase signaling essential for neurite morphology may underlie MTA-induced SPN. Functional genomic studies in human iPSC-derived sensory peripheral neurons are ongoing to understand the role S1PR1 and FGD4 in this drug-induced toxicity.

Keywords: pharmacogenomics, taxane, peripheral neuropathy