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

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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 lamellpodia 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.

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