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

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ABSTRACT

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.

INTRODUCTION

- >60% of patients experienced CIPN during their course of treatment, with 30% continued 6 months after treatments[1,7].
- CIPN symptoms includes numbness, loss of proprioception sense, tingling, pins and needles sensation[5].
- A recent study of patients treated with paclitaxel on CALGB 40101 identified SNPs with moderate effect size in *FZD3*, *FGD4*, and *EPHA5* associated with severity or dose at onset of CIPN[2].
- A study in phase III adjuvant breast cancer trials, ECOG-5103 and ECOG-1199, showed 120 SNPs with modest association, and rs3125923 was found to be significantly associated with Grade 3-4 CIPN[8].
- A kinetic-pharmacodynamic (K-PD) model was developed to quantitate the dose-CIPN relationship for paclitaxel, nab-paclitaxel and ixabepilone in CALGB 40502[4].
- Large between-subject variability was estimated in the model (*Table 1*) and genetic variation may describe some of this variability.
- The objective of this study was to discover single nucleotide polymorphisms (SNPs) associated with the dose-CIPN score model-estimated parameters.

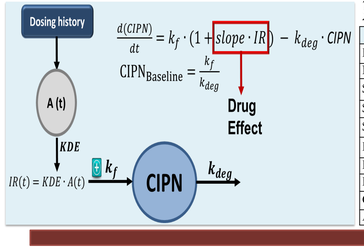


TABLE 1. Parameter estimates for the K-PD model (adapted from Mehrotra et al, 2017)

Parameter (units)	Estimate	%BSV
K_{in} (unit/day)	0.0084	118%
Baseline CIPN score (unit)	0.5	33%
Slope for paclitaxel (unit/mg/day)	0.882	34.2%
Slope for nab- paclitaxel (unit/mg/day)	0.826	
Slope for ixabepilone (unit/mg/day)	9.74	
KDE for paclitaxel (day^{-1})	0.0086	145%
KDE for nab- paclitaxel (day^{-1})	0.0122	
KDE for ixabepilone (day^{-1})	0.0047	
Covariance between baseline and slope		33.6%
Additive residual error (unit)	1.90	

METHODS

- Data were obtained from CALGB 40502 (Alliance), a randomized phase 3 trial of paclitaxel vs. nab-paclitaxel vs. ixabepilone in patients with metastatic breast cancer [6].
- *Phenotype data:*
  - CIPN parameters (BASE, IRG, KDE, KIN, and SLOPE) were estimated from a dose-CIPN score model[4] (n=653). The model was developed using NONMEM (Ellicott City, MD) from extracted data of dose and patient-reported CIPN scores.
- *Genotype data:*
  - DNA extraction was performed from peripheral blood samples (n=635). 964,055 SNPs were genotyped on the Illumina Human Omni Express (Illumina, San Diego, CA)
  - SNPs with call rate =0 and autosomal SNPs were excluded, leaving 882,023 SNPs (n=628).
  - 4,312 SNPs, 54,548 SNPs, and 262,328 SNPs were excluded due to 1% missing genotype data, Hardy-Weinberg equilibrium (HWE) $p < 1 \times 10^{-6}$, and minor allele frequency (MAF) > 0.05, respectively.
- Genome-wide association study (GWAS) were conducted in 560,835 SNPs using PLINK[3] version 1.9 and R version 3.3.2.

RESULTS

FIGURE 1. Principal component analyses (n=628)

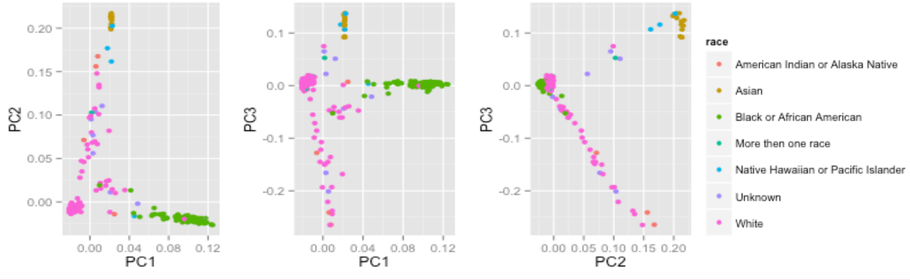
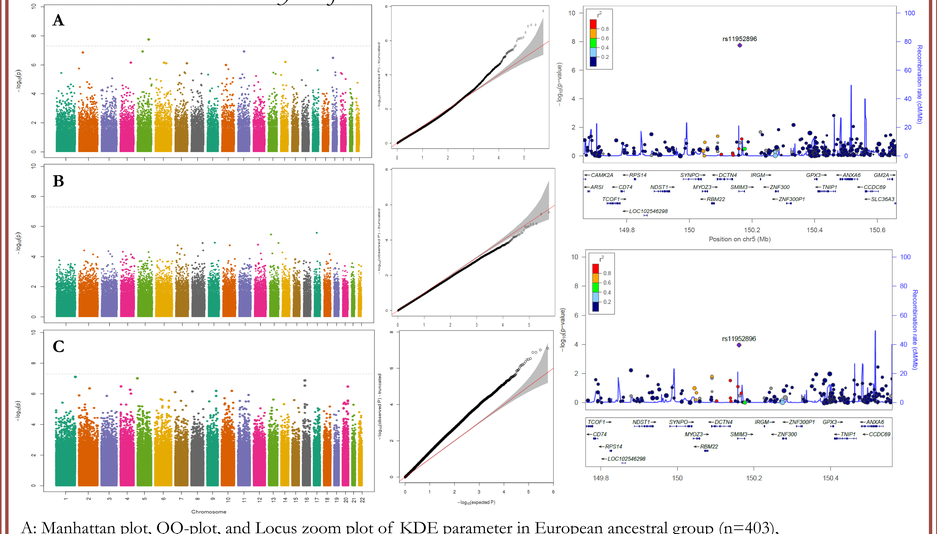


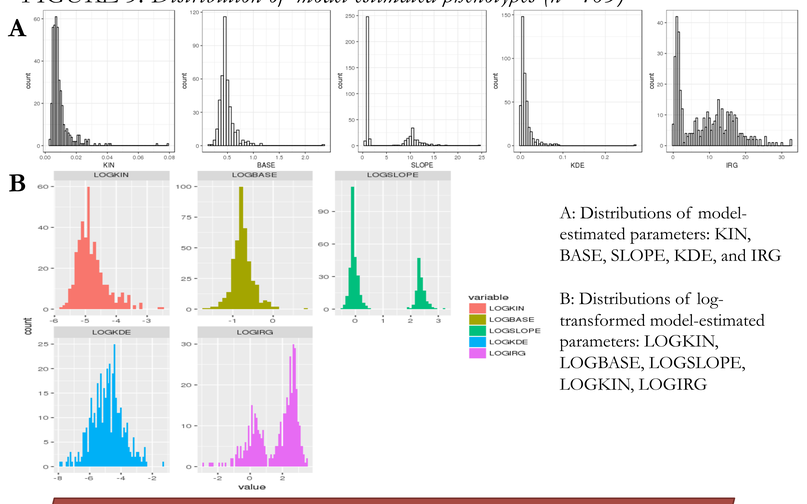
FIGURE 2. GWAS analyses of KDE



A: Manhattan plot, QQ-plot, and Locus zoom plot of KDE parameter in European ancestral group (n=403),
B: Manhattan plot, QQ-plot, and Locus zoom plot of Log-KDE parameter in European ancestral group (n=403),
C: Manhattan plot and QQ-plot of KDE in entire (admixed) population (n=524)

RESULTS

FIGURE 3. Distribution of model-estimated phenotypes (n=403)



A: Distributions of model-estimated parameters: KIN, BASE, SLOPE, KDE, and IRG

B: Distributions of log-transformed model-estimated parameters: LOGKIN, LOGBASE, LOGSLOPE, LOGKIN, LOGIRG

SUMMARY

- Genomic inflation was detected when data from all patients were used, indicating genetic admixture occurred (Figure 2C).
- KDE was significantly associated with rs11952896 in patients of European ancestry ($p < 5 \times 10^{-8}$), but was not significant with log-transformed KDE (Figure 2A and B).
- Although no SNPs reached genome wide significance, the top 10 SNPs for each parameter exhibited modest association at $p < 1 \times 10^{-4}$ (Figure 2B).
- Future directions are to explore associations of groups of SNPs and/or gene expression.

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