“Detecting SNP-SNP interactions in drug sensitivity screens via endophenotypes”

PI: Guan-Hua Huang (National Chiao Tung University)

Role: Principal investigator

Ministry of Science and Technology of Taiwan: 08/01/2020-07/31/2022

A growing body of evidence has indicated that SNP-SNP interactions are probably ubiquitous in the drug responding mechanism. Most current studies of drug sensitivity analysis evaluate one SNP at a time. This simplified approach often fails to identify SNPs that are weakly related to the drug response by itself but can have a considerable impact on the variability of drug sensitivity when combined with other SNPs. This study advocates an approach involving endophenotypes to facilitate the identification of the effects of genetic interaction. Endophenotypes are more closely associated with the underlying genotype than the phenotype in the natural progression of the drug response, thereby increasing the chances of identifying culprit genes. This study demonstrates how gene expression endophenotypes can assist in identifying candidate SNPs without displaying marginal SNP-drug association for further analysis of interactions. Methodologically, we will formulate the endophenotype in the causal mediation analysis framework and develop a formal statistical approach for validating endophenotypes. We will also develop a Bayesian formulation of a clustering procedure to identify SNP-SNP interactions. Using the cancer cell line data from the Genomics of Drug Sensitivity in Cancer Web portal, we will demonstrate the functionality of the proposed gene expression endophenotype-based approach.

Keywords: causal inference; drug sensitivity; endophenotype, gene expression; mediation analysis; SNP-SNP interaction