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Dose Response Analysis in Cell Line Models for Cancer Pharmacogenomics

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Introduction

- Cancer patients undergoing traditional chemotherapy show a large amount of variability and severe adverse reactions in response to anti-cancer drugs.
- The variability in anti-cancer drug response is influenced by host and tumor DNA.

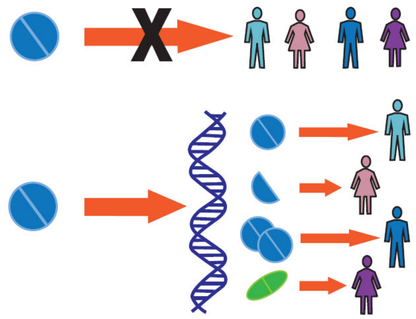

Fig 1. Use of pharmacogenetic markers to tailor drug therapy for patients

- Cancer pharmacogenomics = The study of the relationship between genetic variations and how our body responds to anti-cancer drugs.
- The goal of cancer pharmacogenomics is to tailor drug therapy for patients in order to :
  - ✓ Maximize efficacy
  - ✓ Minimize toxicity
  - ✓ Reduce healthcare cost

Objective

- Perform genome-wide association studies (GWAS) of 45 anti-cancer drugs in human cell lines to identify novel genetic predictors of anti-cancer drug response that can be used optimize cancer therapeutics for patients.

Materials and Methods

Cell lines

- Established model for drug response assays in pharmacogenomics
- Human immortalized lymphoblastoid cell lines
- Source: The 1000 Genomes Project
- Racially and ethnically diverse population
- Allows for the investigation of differential drug response in different populations

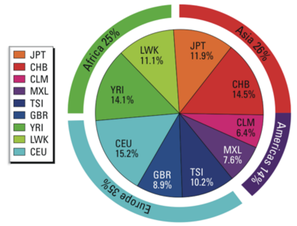

Fig 2. Ethnic diversity of the 1000G cell lines

Drugs

45 FDA-approved anti-cancer drugs

- 28 chemotherapy drugs
- 15 tyrosine kinase inhibitors
- 2 monoclonal antibodies
- Paclitaxel and Epirubicin combination

Dose response assays

- alamarBlue® cell viability assays
- 6 concentrations of each drug

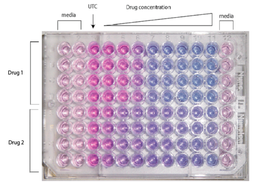

Fig 3. alamarBlue® cell viability assay

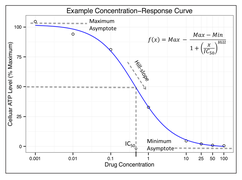

Fig 4. Dose-Response curve

Statistical analysis

- Used the MANCOVA model to model the entire dose response profile
- MAGWAS - **M**ultivariate **A**nalysis of covariance **G**enome-**W**ide **A**ssociation **S**oftware
- Model equation: $Y_{ij} = \boldsymbol{X}_{ij}\beta + \mu_i + \boldsymbol{e}_{ij}$, $\boldsymbol{e}_{ij} \sim N(\mathbf{0}, \boldsymbol{\Sigma})$, where

Y_{ij} is the vector of normalized responses across the six concentrations of the drug for the *jth* individual with genotype *i* at single-nucleotide polymorphism (SNP) *s*
X_{ij} is the covariate matrix which includes sex, experimental batch and the first 3 principal components
μ_i is the vector of parameters modeling the effects of genotype *i* at SNP *s*

Results

- 34 peak SNP-drug associations at the suggestive significance level, with p-value < 10^{-6}
- 4 peak SNP-drug association at the genome-wide significance level, with p-value < 10^{-8}
- 21 unique drugs with at least one suggestive association
- 15 unique genes identified
- **Top hit genes : NFAT5 and NQO1 on chromosome 16**

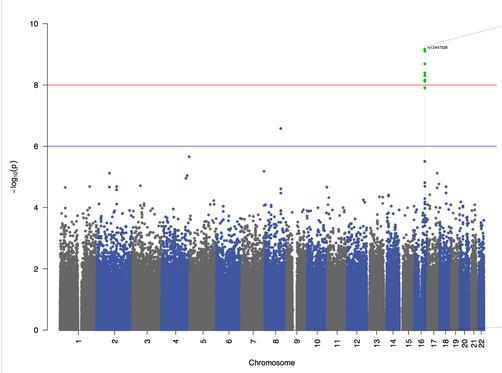

Fig 5. Manhattan plot depicting genome-wide SNPs associated with Erlotinib response

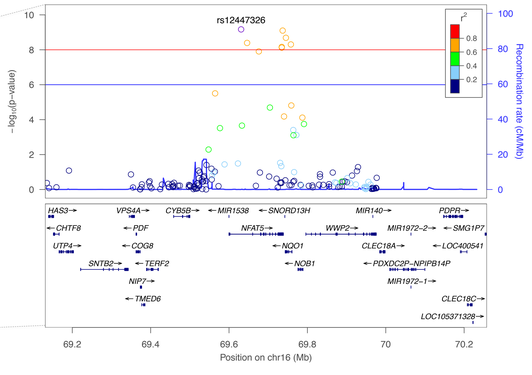

Fig 6. Detailed view of the regional genes +/-500 kilo base pairs around SNP rs12447326

Gene	Associated Drugs	Known role
NFAT5	Arsenic Trioxide Erlotinib Trametinib Paclitaxel + Epirubicin	Transcription factor that regulates the genes induced by osmotic stress. Associated with impaired cell proliferation in hyperosmotic stress conditions in mice.
NQO1	Arsenic Trioxide Erlotinib Paclitaxel + Epirubicin	Antioxidant enzyme involved in the detoxification of environmental carcinogens. Associated with adenocarcinoma of the gastrointestinal tract.

Table 2. Details for the two top hit genes from the GWAS

Summary

- We have identified multiple genome-wide variants (SNPs) associated with the differential response of several FDA-approved anti-cancer drugs.
- Several of the identified SNPs are in genes that are known to be involved in cancer-related pathways.
- These results provide promising candidate genes for functional follow-up studies.

Future directions

We will perform functional validation experiments to identify the biological mechanisms by which the associated variants influence drug response using:

- siRNA knockdown experiments
- Gene and Protein expression analysis

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