Prediction of Genetic Predisposition to Isoniazid-Induced Hepatic Steatosis via Computational Analysis of Genetic Biomarkers

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Isoniazid (INH) is a first line drug for the treatment of Tuberculosis, a disease that causes 1.5 million deaths per year. This drug has high efficacy in TB-treatment, but can also lead to liver toxicity and hepatic steatosis. Many researchers have tried to identify reactive metabolite formations as an indicator of liver toxicity, however these only form after the drug has been taken. CYP2E1, NAT2 genotype, and acetylation rate have been investigated but are ineffective as predictive markers. Without pretreatment indicators, patients fear that they will develop steatosis from Isoniazid, leading to in-compliance with the medication, allowing M. tuberculosis to progress and become fatal. As such, biomarkers that can predict a patient's risk for such complications, pre-TB INH treatment, would be an invaluable clinical tool. This research identifies such biomarkers, through the analyses of gene expression levels between INH-treated mice that developed steatosis, versus those that did not. Using a treatment feature model, the expression levels of 18 genes that were most significant at predicting steatosis within a mice dataset (UNC School of Pharmacy) were identified. Thereafter, logistic regression, random forest, SVM, and gradient boosting classifier (GBC) models were attempted to predict INH-induced steatosis. GBC had the highest accuracy (0.83), f1 score (0.82), and ROC AUC score (0.83), with the following parameters: n estimators=250, learning rate=0.05, and max depth=2.5. From these newly-correlated 18 mouse genes, 16 human homologs were identified that possess cross correlation in cellular signaling pathways of liver function. As such, their expression can be measured in a patient, pre-INH TB-treatment, to predict whether the individual will develop INH-induced steatosis.