Haplotypes of Multidrug Resistance-Associated Protein 2 (MRP2) Affect the Pharmacokinetics of Tacrolimus in Kidney Transplant Recipients

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Background: The Immunosuppressive agent, tacrolimus *exhibits a narrow therapeutic index and* a large pharmacokinetic variability. Tacrolimus is metabolized by cytochrome P450 (CYP) 3A and effluxed via P-glycoprotein, but the involvement of other efflux transporters in tacrolimus disposition is uncertain.

Objective: To investigate the effects of genetic polymorphisms of CYP3As and efflux transporters on tacrolimus pharmacokinetics.

Methods: Population pharmacokinetic analysis was carried out using a total of 500 blood concentrations of tacrolimus from 102 adult kidney transplant recipients. For multidrug resistance-associated protein 2 (MRP2) gene, haplotype analysis was performed.

Results: Analysis revealed that CYP3A5 expressers and MRP2 high activity group (H2/H2 and H1/H2; H1, wild type; H2, 1249GA) decreased the dose-normalized trough concentration of tacrolimus by 2.3-fold (p0.001) and 1.5-fold (p=0.007), respectively. In the population pharmacokinetic analysis, CYP3A5 expressers and MRP2 high activity groups were identified as the significant covariates for tacrolimus apparent clearance (CL/F) expressed as $20.8 * (Age/50)^{-0.78} * 2.03$ (CYP3A5 expressers) * 1.40 (MRP2 high activity group). These findings suggest that in addition to CYP3A5 genotype, MRP2 genotype significantly affect the clearance of tacrolimus in a haplotype specific manner.

Conclusion: Determination of MRP2 as well as CYP3A5 genotype may be useful for more accurate tacrolimus dosage adjustment and may help in finding the tacrolimus dose faster and more accurately.

Supervised Machine Learning in the Personalized Assessment of the Risk of Breast Cancer

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Breast cancer is the most common form of cancer in women. Breast cancer comprises 22.9% of invasive cancers in women and 16% of all the female cancers. Currently, treatment decisions are based primarily on clinical parameters, with little use of genomic data. Our study takes into consideration the data of postmenopausal women of European descent and their single nucleotide polymorphism (SNP) information to assess the risk of developing breast cancer. We used various supervised machine learning and data mining techniques to generate a model for predicting risk of breast cancer using only genomic data. In this paper we propose an approach to select 9 best SNPs using various feature selection algorithms and evaluate binary classifiers performance. The machine learning model generated without the domain knowledge yields poor prediction results. We have evaluated the performance of a binary classifier by adding the domain knowledge of 11 SNPs into the training set and performing classification based on most informative features obtained from the feature selection technique. Our observations revealed that the machine learning model generated using both the domain knowledge and the feature selection technique performed slightly better compared to the naive approach of classification.

In this study we have used various data mining and supervised machine learning techniques for generating a prediction model capable of distinguishing between cases and controls for initial screening. We have statistically analyzed 3 different methods: *Naive SNP Selection Approach*, *Feature Selection Approach* and *Domain Knowledge Integration Approach*. We have demonstrated the benefit of the addition of domain knowledge of SNPs in machine learning procedures.

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