

Genetic Variation in Prediction of Drug Efficacy and Toxicity

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Personalized medicine is currently transitioning from its maturation into the clinical practice [1]. The individual response difference to the drug is attributable to the pharmacogenomics make up of each individual, or to the pharmacokinetic difference in its ADME property as absorption, distribution, metabolism and excretion. The pharmacogenomics make up and genetic variation can be categorized into single nucleotide polymorphisms (SNPs), insertion, deletion, translocation or duplication of the genome sequence. Extensive work has been carried out to test the effect of gene SNPs on the drug disposition, efficacy or toxicity of the drug, and there are successful examples in the drug regulation in terms of appreciable pharmacogenomics on the drug dosage and effect. For example, the United States Food and Drug Administration (FDA) has modified the dosage of irinotecan in the population of homozygous UGT1A1*28 allele with reduced UGT1A1 activity. The patients' plasma concentration of isoniazid which is an anti-tuberculosis drug had a bimodal distribution pattern. The difference in genomic make up of N-acetyltransferase gene differentiated the population into rapid vs. slow acetylators. The slow acetylators had higher isoniazid drug concentration, and the rapid acetylators had lower plasma drug concentration which in turn leads to diverse response/toxicity in these different populations [2].

However, individual SNPs often fail to predict the response variability between individuals. To understand these more complicated scenarios, the concept of haplotype is important. In contrast to a single marker, a haplotype contains a set of genetic variants in linkage disequilibrium that together provide more information than a single SNP. The haplotype can be inferred from genotype information using statistical methods such as parsimony algorithm [3]. The influence of haplotype is now considered more carefully during drug development, and clinical studies have demonstrated the usage of haplotype in the pharmacokinetic disposition, drug effect and toxicity. SNPs in drug metabolizing enzymes, targets and drug transporters are often correlated with the individual response differences. The SNPs and haplotypes of drug metabolizing enzymes can alter the disposition of the drug and correspondingly the concentration of the drug, resulting in varied response. Several examples from the literature show how these concepts have proven to be useful. For instance, the impaired function of CYP2D6 in its ability to metabolize opioids and antidepressants is due to the haplotype of CYP2D6*72 and CYP2D6*49 in the Japanese population [4]. Similarly, the 677C-1298C haplotype of 5, 10-methylenetetrahydrofolate reductase gene predisposes patients to a lower exposure to methotrexate whereas 677T-1298A haplotype patients possess a higher toxicity to methotrexate [5]. MHC class II HLA haplotype (HLA-DRB1*1501-HLA-DQB1*0602-HLA-DRB5*0101-HLA-DQA1*0102) has been shown in association with drug induced liver toxicity, and these individuals were excluded from the treatment of lumiracoxib to increase its safety profile [6]. OATP-C variant haplotype*5 delayed the uptake of pravastatin, and the total exposure to the drug (measured as the pharmacokinetic Area under the Curve) was decreased compared with the control haplotype. In a lot of scenarios, the SNPs and haplotype in association with drug effect variation driven by pharmacokinetic variation still needs to be proved. Most of our knowledge of how SNPs and haplotypes influence treatment comes from the response to small molecules, but similar

concepts are likely to influence the ADME properties and effectiveness of monoclonal antibody treatments whereas FcγRIIIa receptor polymorphism influenced the monoclonal antibody anti-CD20 response is an example [7]. This is an area that needs to be explored in future research.

As technologies for quantitative data collection in biological systems continue to advance, interactions between drugs, drug targets and secondary targets can be studied more systemically. The pharmacodynamics response to drug perturbations can be predicted and studied using mathematical models and differential equations in a quantitative manner. Models allow the different response of each individual to a drug to be quantitatively attributed to different amounts of enzymes, receptors, targets and off-target molecules. SNPs and haplotype with different mRNA expression leads to altered protein amount or enzyme activity levels. Thus the drug target and off target signaling network is changed which in turn leads to the biological systems response difference. These changes can be predicted and simulated by the computational tools as quantitative pharmacokinetic and pharmacodynamics models.

Epidemiology often uses environmental and genetic interactions in order to predict the risk or the susceptibility to disease. The pharmaceutical field is clearly moving in a similar direction. For instance, demographic information such as age, sex and body weight has been successfully applied as covariates in the prediction of individual variation in the drug concentration. In a similar rationale, the drug efficacy and toxicity difference can be due to interaction of drug concentration, individual pharmacogenomics make up and other internal and external environmental variables such as drug-drug interactions, food intake and disease status. A point that requires additional emphasis, however, is the ethnicity of the target population which has inherited different SNPs and haplotypes genomic compositions. The complexity of drug efficacy and safety needs to be addressed using interdisciplinary knowledge and information. Due to the social, economic, ethic and regulatory issues, the advancement and enforcement of pharmacogenomics and individualized medicine is on its way to daily practice like warfarin "prothrombin time" and dose adjustment.

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