Genome Medicine

EDITORIAL

Pharmacogenomics: a key component of personalized therapy

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The goal of personalized medicine is to provide individualized treatment and to predict the clinical outcome of different treatments in different patients. Pharmacogenomics is one of the core elements in personalized medicine. The basic concept is that interindividual variability in drug response is a consequence of multiple factors, including genomics, epigenomics, the environment and a patient's characteristics, such as gender, age and/or concomitant medication [1]. Thirty years ago, drug response was found to be altered by genetic polymorphisms in drug-metabolizing enzymes (for example, the cytochrome P450 2D6 and the thiopurine *S*-methyltransferase) [2], yet valid and predictive biomarkers for therapeutic effects and/or for avoiding severe side effects are lacking for more than 90% of drugs currently used in clinical practice. Pharmacogenomics in recent years has used a new generation of technologies known as 'omics' approaches that has led to a revolution in the understanding of disease susceptibility and pathophysiology, providing enormous potential for novel therapeutic strategies.

It is beyond doubt that pharmacogenomics promotes the development of targeted therapies, as was demonstrated by the approval earlier this year of the drug ivacaftor by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of a subset of cystic fibrosis patients. Ivacaftor is approved only for cystic fibrosis patients bearing the specific G551D genetic variant in the cystic fibrosis transmembrane regulator (*CFTR*) gene, which encodes a protein that regulates chloride and water transport in the body and is defective in the disease. Ivacaftor targets the CFTR protein, increases its activity, and consequently improves lung function [3].

Although this and other examples (such as vemurafenib as an inhibitor of the BRAF V600E mutation in malignant melanoma [1]) suggest the demise of the blockbuster model of drug development, the concept of targeted therapy is in its early stages. One reason is that monogenic pharmacogenetic traits are mostly unable to explain the variations in a complex phenotype such as drug response [2]. There is evidence through drug-target network analyses that most currently used drugs have multiple targets and numerous off-target effects. Genome-wide approaches such as sequencing, epigenomic profiling and metabolomics will be essential for understanding the detailed molecular architecture of disease etiology and/or drug response. Genome-wide association studies (GWAS) have implicated many new biological pathways, but this approach has limitations because most of the variants that have been associated with clinical phenotypes, such as adverse drug reactions, are not necessarily causal.

There is reasonable hope that pharmacogenomic research will benefit from a combination of different omics technologies. Recently, multi-omics studies have shown their use in discovering potential novel therapeutic targets [1]. For instance, in one multi-omics study the integrative personal omics profile (iPOP), which combines genomic information with additional dynamic omics activities (that is, transcriptomic, proteomic, metabolomic and autoantibody profiles), from a single individual over a 14-month period demonstrated that iPOP data can be used to interpret healthy and diseased states, and can be helpful in the diagnostics, monitoring and treatment of diseased states [4].

The major challenge, however, is the bioinformatic analysis and valid interpretation of highly complex multi-omics data sets. A recent National Institutes of Health White Paper by the Quantitative and Systems Pharmacology Workshop Group [5] stated that: 'Genomics is, in and of itself, insufficient as a means to develop and study drugs: the operation of biological networks is strongly affected not only by changes in coding sequence or gene expression but also by transient responses to external signals at the level of protein activity, posttranslational modification, stochastic processes, etc.' Thus, with the help of an integrative systems pharmacology approach, multiple one-dimensional biomolecular-omics data sets,

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