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A Reachable Goal: Application of Pharmacogenomics Biomarkers to Improve Drug Efficacy and Safety

Chang CW[1] and Ning B[2*]

[1]Division of Bioinformatics and Biostatistics, National Center for Toxicological Research, FDA Jefferson, AR, USA
[2]Division of Systems Biology, National Center for Toxicological Research, FDA Jefferson, AR, USA

Introduction

Ensuring drug efficacy and safety are unremitting challenges for drug manufacturers and public health organizations worldwide. It has been estimated that, when all of the drugs in the market used to treat common diseases are considered, only 25% to 60% of patients exhibit the expected pharmacological response [1], while a small portion of patients could develop adverse reactions (ADRs). ADRs are one of the leading causes of illness and death associated with prescription medications, and ADRs are estimated to occur in 6.2-6.7% of all hospitalized patients, resulting in more than 2 million adverse drug reaction cases annually, including approximate 100,000 incidences of death in the United States [2].

ADRs can be divided into type A and type B categories. Type A reactions exhibit dose-dependent toxicity while the toxicity observed with type B reactions are dose-independent and occur only in susceptible individuals and are often referred as "idiosyncratic" [3]. Although the factors that predispose individuals to develop ADRs remain largely unknown for most cases, it is believed that genetic predisposition is involved in both type A and type B ADRs (especially the type B reaction). Various examples of genetic predisposition to ADRs have been reported during the last several decades, such as primaquine-induced hemolytic anemia, thioridazine-induced QT prolongation, warfarin-induced risk of bleeding, voriconazole-induced hepatotoxicity, statin-induced muscle toxicity, carbamazepine-induced skin injury and agranulocytosis caused by clozapine [3-6].

Generally, genetic variations in drug-metabolizing enzymes and transporters are major contributors for type A reactions. For example, genetic variants in *CYP2D6* and *VKORC1* genes can be used to estimate warfarin-related dose requirements among patients of different ancestries to reduce the risk of excessive bleeding [7]. In contrast, type B reactions are more complex and are usually associated with more than one gene. Notably, variations in genes coding cytokines and MHC are responsible for individual susceptibility to some idiosyncratic ADRs. For incidence, sulfamethoxazole and phenytoin may interact with drug-specific $CD4^+$ and $CD8^+$ T-cells through their T-cell receptors to induce allergic reactions in susceptible individuals [8] and a genome-wide association study showed that the *HLA-A*3101* allele was significantly associated with the clinical spectrum of carbamazepine-induced ADRs in Europeans [9].

On the other hand, the use of microRNAs (miRNAs) as biomarkers to predict drug effectiveness and/or toxicity provides a new avenue for individualized patient care which could have a tremendous impact on the optimization of drug therapy overall. As miRNA expression has been reported to be affected by drugs and since miRNAs themselves may affect drug metabolism and toxicity, the differential expression of miRNA species can be utilized as potential biomarkers of drug efficacy and safety. For example, accumulating evidence clearly indicates that higher expression of miR-21 is associated with resistance to a number of chemotherapeutic drugs. Higher expression of miR-21 is associated with cisplatin resistance in lung cancer patients [10], while miR-122 and miR-129 are thought to be valuable biomarkers for acetaminophen-induced liver injury [11].

A large body of patient response data has been gathered to address the relationship between genetic/genomics alterations and drug efficacy/safety. Moreover, the successful application of this approach in clinical studies has gradually raised the expectation for utilizing pharmacogenomics biomarkers to optimize drug use on a wider scale. In 2005, a "Guidance for Industry" (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073162.pdf)" was issued by the US Food and Drug Administration (FDA), which recommends the types of pharmacogenomics data that should be submitted to the regulatory agency during the drug development process.

A database of genetic variants that affect treatment outcomes for some drugs is maintained by the FDA to

promote drug efficacy and drug safety (http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). This database includes pharmacogenomic biomarkers in drug labeling and it provides special warnings/precautions for prescription and administration of certain drugs. Currently, over a hundred drugs are listed in the database together with pharmacogenomics biomarkers associated with drug exposure, variability in clinical response, risk for adverse events, genotype-specific dosing, mechanisms of drug action, or polymorphic drug targets.

Beside the FDA drug labeling database, the National Institute of Health Pharmacogenomics Research Network also provides a pharmacogenomics knowledge base, PharmGKB (www.pharmgkb.org). PharmGKB contains information concerning the impact of human genetic variation on drug responses, including gene variant annotations, drug-centered pathways, clinical annotations, pharmacogenomics-based drug-dosing, and drug labels, if available. In addition to the utility of the integrated information available in the database for clinical interpretation and implementation, the collected data from a variety of sources also provides a better opportunity to establish a global picture of pharmacogenomics and the use of these biomarkers to improve drug efficacy and safety.

***Corresponding author:** Ning B, Division of Systems Biology, National Center for Toxicological Research, FDA, Jefferson, AR 72079, USA, Tel: 870-543-7129; Fax: 870-543-7773; Email: baitang.ning@fda.hhs.gov

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One successful example of the application of pharmacogenomics biomarkers to improve drug efficacy is found in the use of afatinib to treat patients with metastatic non-small cell lung carcinoma (NSCLC). Although the overall survival of NSCLC patients was not improved by afatinib in the general population during clinical trials, survival was significantly increased when using afatinib to treat NSCLC patients harboring genetic variants of the epidermal growth factor receptor (EGFR) gene exon 19 deletion or exon 21 (L858R) substitution mutation [12,13]. Afatinib, a drug specifically targeting genetic variants, now is considered as the first-line treatment for a specific subpopulation of NSCLC patients.

A genetic variant related to abacavir-induced hypersensitivity provides another successful example of using a pharmacogenomics biomarker to improve drug safety. Abacavir is an effective antiretroviral drug used to treat human immunodeficiency virus (HIV) infected patients. However, abacavir can induce serious, even life-threatening ADRs in certain individuals. Pharmacogenomics studies revealed that the genetic variant HLA-B* 57:01 is strongly associated with increased risk of abacavir-induced ADRs [14,15]. Immunological studies provided the evidence that the specific interaction of abacavir and HLA-B*57:01 altered binding affinity between the HLA molecule and the HLA-presented endogenous peptide repertoire, resulting in cytokine-mediated idiosyncratic ADRs [16,17]. Later, the implementation of HLA-B*57:01 screening in patients shows a significant predictive value and cost-effective impact on the decreasing the risk of abacavir-induced ADRs [18].

The emerging concept of precision medicine evokes the need of biomarkers to classify/stratify subpopulations by their differences in genetic makeups/epigenetic modifications/genomic alterations that are related to disease susceptibilities, prognoses of diseases, responses to a particular treatment, or the risks of drug ADRs. Clinical studies have successfully proved the concept of utilizing biomarkers to improve drug efficacy and safety. However, the number of useful pharmacogenomics biomarkers is still relatively small. The identification and the acceptance of novel biomarkers is constrained by many confounding factors, such as the complexity of pharmacological mechanisms, the quality of experimental results, the heterogeneity within a study population, the criterion of phenotype selection, and the limitation of the experimental sample size, and the various biomedical strategies used to identify and validate biomarkers. Currently, there is no guidance as to what pharmacogenomics studies would sufficiently and optimally assess genetic variants that are associated with drug efficacy or safety.

The challenges for developing effective pharmacogenomics-based patient therapy are significant, and new research strategies that are more comprehensive are required to identify and validate new biomarkers. Instead of a pure association study, the combination of multiple approaches might be more appropriate to categorize the causative genetic variants that are truly associated with drug efficacy or adverse reactions. Experimental approaches (*in vitro* or *in vivo* studies) may provide direct and strong support for the biological function of a genetic variant, while epidemiological studies, population genetics, evolutionary genetics and pharmacological intervention studies are also powerful tools to elucidate the relationship between genetic variants and pharmacological traits and to provide insight regarding the functional significance of various genetic traits. To facilitate the establishment of suitable pharmacogenomics biomarkers, the FDA Biomarker Qualification Program was established to provide a framework in qualifying biomarkers (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm). This qualification program not only offers a framework, but also integrates the information gathered for qualified biomarkers and encourages new biomarker identification and utilization. This program provides a formal process for the development and evaluation of biomarkers.

The acceptance and use of pharmacogenomic biomarkers in clinical practice will require long time frame, high costs, and close collaborations among biomedical researchers and clinical specialists with different types of expertise. Although the process is costly and time-consuming, the rigorous evaluation of the relationship between genetic variants and drug response is extremely valuable. The use of advanced experimental and analytical technologies, such us high-through put screening approaches, next-generation sequencing technology, and cloud data integration, should provide opportunities to discover new biomarkers and investigate their underlying mechanisms more efficiently. Combined with previous efforts to improve drug safety and efficacy, the use of pharmacogenic approaches offers hope that precision medicine is not just an idea, but a reachable goal.

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