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Editorial

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The Needs and Challenges in Assessing Genetic Variants for Drug Efficacy and Safety

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The views presented in this paper are those of the authors and do not necessarily represent those of the U.S. Food and Drug Administration.

Genetic variation, environmental stimulation, and their interaction introduce significant interindividual variability in disease susceptibility, drug efficacy and adverse drug reactions. A large body of data collected from studies during the last decade gradually raised the expectation of personalized medicine: a genotype-based prescription should benefit patients not only in maximizing overall drug efficacy and minimizing adverse drug reactions, but also in selection of appropriate drugs and their tailored dosages specifically matched to each individual's genotype. Unfortunately, genetic profile or single association studies alone will not be sufficient to validate/determine biomarkers for drug efficacy and drug safety in all instances, and limitations always exist in pharmacogenomics and association studies due to many factors, such as complexity of phenotypes (usually, multiple subsets of variants associate with the same phenotype with small to moderate effects on the phenotype); the quality of genotyping platforms; the reliability of the experimental system; the underline genetic heterogeneity within a study population; the criterion of sample selection; the experimental sample size; and whether the genetic-environmental interaction was taken into consideration. Therefore, there is an absolute need to answer the urgent and important questions: to what extent should genetic variants be considered as clinically significant in drug responses and how should we assess these variants?

There is no sufficient guidance for pharmacogenomics studies to optimally assess genetic variants that are associated with drug metabolism and action. However, the functional characterization of genetic variants is achievable by conducting studies with different research approaches, such as experimental investigation, evolution conservations, population genetics, epidemiological analyses, and intervention studies to provide evidences for the biological function of genes and variants [1].

Experiment-based studies to assess function can provide strong and direct evidence of biological roles for genetic variants; however, measurements from such studies may be influenced by experimental designs and limitations of experimental materials (such as tissue specificity, exposures, genetic background of the individuals, etc.). Thus, the results may not reflect the complexity of the biological-environmental interactions and may also be challenging to interpret in the context of complex human traits. Under "ideal" conditions, the conclusions from *in vitro* or *in vivo* studies using animal models might be directly applicable to the human situation. However, results from studies with the limitations outlined above will be difficult to translate into clinically useful information for patients, which limits the application of the identified biomarkers in drug development.

Population-based approaches (including epidemiology, population genetics, and evolutionary genetic and pharmacological intervention studies) are powerful tools that provide insights into the functional significance of genetic variants to a pharmacological trait. The strength of population-based approaches is highly dependent on the number of participants (sample size) included in the study. The larger the sample size, the more likely that a true significant association will be found between the genetic variant and the phenotype. However, the pursuit of the largest sample size is constrained by its feasibility, such as study cost and time limitations. The genetic heterogeneity among the study subpopulation, the classification of phenotypes, and the inclusion/exclusion criteria for subject selection can dramatically influence the quality of the study. Therefore, the strict definition of the ethnicity of participants and the accurate phenotyping of a trait must be achieved to assess functions of genetic variants in pharmacogenetics studies. The genome-wide association study (GWAS) is a valuable step towards better understanding the interactions between genetic factors and environmental factors that contribute to complex, low-penetrant phenotypes, including drug responses. It allows interrogation of the relationships between genetics and biological phenotypes in the whole genome at a resolution not unattainable previously, in thousands of unrelated individuals, and unconstrained by prior hypotheses. This approach has resulted in systematic, well-powered and genome-wide surveys that revealed susceptibility loci associated with different phenotypes. Up to the second quarter of 2011, 1,449 GWAS were published, among which 237 types of disease and drug responses were reported to be associated with genetic variants at $p \leq 5x10^{-8}$ level [2]. That said, this approach has provided insights to, in some extend, the biological functions of genetic variants related to phenotypic traits [3].

Identification, assessment and validation of the genetic variant in abacavir-induced hypersensitivity provide us a successful example. Abacavir, a potent HIV-1 reverse transcriptase inhibitor, has been reported to be associated with adverse reactions that are characterized by serious and even life-threatening symptoms including skin rash, fever, malaise, and gastrointestinal and respiratory symptoms. Epidemiological association studies have identified that the genetic variant HLA-B*57:01 allele is in a strong linkage with the abacavir-induced adverse reactions [4,5]. An immunological study has shown that the activation of CD8+ cells to produce cytokines was driven by abacavir-HLA-B*57:01 specific binding [6]. Recently, the mechanism has been further revealed to be that abacavir selectively interacts with HLA-B*57:01 inducing a conformational change which leads to altered binding between the HLA molecule and the HLA presented endogenous peptide repertoire. This results in cytokine production by T cells that induces an idiosyncratic adverse drug reaction [7,8].

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Despite some specific successes, there are challenges in the accurate and appropriate measurement of phenotypes, genotypes and environmental factors. The phenotypic heterogeneity should be minimized, and the genotyping accuracy and the purity of genetic ancestry should be optimized in both "control" and "case" subgroups. Experimental procedures should be improved to reveal the real interaction between drugs and genetic variants in the human body. To achieve such a goal, a systematic and comprehensive translational research system is needed to evaluate genetic variants and their interaction with drugs from benchside to bedside.

To promote drug efficacy and drug safety, the US Food and Drug Administration (FDA) maintains a database [9] of genetic variants that affect the treatment outcomes of some drugs. Included are genetic biomarkers and related advices/warnings that are listed on the drug labels that indicate efficacy differences and possible adverse reactions among patient with certain genotypes. Currently, over a hundred drugs are listed. In addition, the FDA Biomarker Qualification Program has been developed to "provide a framework for scientific development and regulatory acceptance of biomarker for use in drug development" [10].

We believe that a better functional characterization of causative genetic variants to screen and delineate drug-genetic interactions will help improve the selection of the best drug (i.e., in terms of high efficacy, low adverse reactions) for the individual thus empowering personalized medicine.

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