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PHARMACOGENETICS: DOES A PERSONAL THERAPY EXIST?

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SUMMARY

Pharmacogenetics is a powerful tool to improve drug response and to maximize therapeutic efficacy and safety using genetic information of each individual. This review collects the available literature understanding the influence of heritability on an individual's drug metabolism.

Key words: *genetic factors - pharmacogenetic*

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INTRODUCTION

The history of pharmacogenetics comes up in the 510 B.C. when Pythagoras noted that ingestion of fava beans resulted in a potentially fatal reaction in some, but not all, individuals, later characterized to be due to deficiency of Glucose-6-phosphate dehydrogenase enzyme (Nebert 1999).

Subsequently, the concept of "personalized medicine" was anticipated in the late 1800s by Canadian physician Sir William Osler who noted "the great variability among individuals" (Issa 2007, Stuart 2011).

However, the term "pharmacogenetics" was first published by the German physician Friedrich Vogel only in the 1959 (Vogel 1959, Stuart 2011). Infact, in the late 1950s, the concept of pharmacogenetics originated from some clinical observations and genetic variation in humans was recognized as an important determinant of individual variability of drug response (Kalow & Staron, 1957; Kalow & Gunn, 1959, Evans et al. 1960). In these cases, patients with very high, and others very low, plasma or urinary drug concentrations that correspond to a specific phenotype of a drug response were identified, and the biochemical traits leading to the variation of drug concentrations were found to be inherited. On the other hand, the observation that individual variation of a drug response is often larger among members in a population (population variability) than within the same person at different times (intrapatient variability) further supports inheritance as a major determinant of drug response (Vesell 1989, Kalow et al. 1998, Ma & Lu 2011).

Currently, the majority of medicines are taken in dosages determined by patient age, weight, and other clinical factors. In most cases, these criteria are proving to be inadequate to ensure that a medicine will be safe and effective for a particular individual and drug response still often varies among patients, ranging from positive outcomes to fatal adverse reactions (Ni et al. 2013, Ventola 2013).

Although these clinical parameters are continuing to be used to guide drug treatment, they do not directly consider genetic factors, which can account for 20% to 40% of inter-individual differences in drug metabolism and response (Karczewski et al. 2012). In fact, for certain drugs or drug classes, genetic factors have been shown to be the most important influence on drug treatment outcomes (Ventola 2013).

Genetic mutations of proteins involved in drug targeting and drug metabolism and transport are likely to be the most important sources of individual variability in drug efficacy. Genetic variations can change the structure of a target protein via mutations in the coding region of the gene or the amount of the protein expressed by modulating gene regulation, both of which ultimately alter the function of the protein or the rate and kinetic constants in the case of an enzyme. Structural changes of receptors or enzymes may affect drug-receptor or drug-enzyme interaction and, consequently, drug response by affecting the absorption, distribution, metabolism, and elimination of drugs and thereby modulate their plasma and target tissue concentrations (Ma & Lu 2011).

The continued identification of relevant genes, sequence variants, and associated drug response phenotypes is evidenced by the paralleled increase in pharmacogenetics literature, particularly in relation to the completion of the Human Genome Project. The availability of genome-wide sequence data at that time also helped launch the related field of "pharmacogenomics" (Stuart 2011). Although frequently used interchangeably, these two fields do differ.

Pharmacogenomic research involves scanning the whole genome to find single-nucleotide polymorphisms (SNPs) that might be associated with drug response without necessarily knowing the specific function of the identified SNPs (Howland 2012). Whereas pharmacogenomics involves the study of genes in all chromosomes, pharmacogenetics is the study of specific SNPs in distinct genes with known functions that are plausibly connected to drug response (Ventola 2013).

SNP is probably the most common variation. More than 90% of human genes contain at least one SNP, and nearly every human gene is marked by a sequence

variation. In the human genome, more than 14 million SNPs have been identified. Most SNPs seem to have no apparent effect on gene function but certain SNPs are known to be associated with significant changes in drug efficacy and drug disposition (McLeod & Evans 2001, Roden et al. 2006, Ma & Lu 2011). The identification of SNPs in each individual could be used to create an SNP profile that correlates with individual drug response. Currently, we prescribe drugs according to the model that "one dose fits all" (Marshall 1997). Using SNP profiling, it may be possible to tailor drug prescription and drug dosage to the individual, thereby maximizing efficacy and minimizing toxicity (Pirmohamed 2001).

Moreover, another kind of genetic variation can occur in "non-SNP" polymorphisms, known as structural variations (SVs) (Scott 2011). SVs consist of small (less than 10 base pairs) insertions or deletions (indels), copy number variations (CNVs), and inversions, that occur less frequently than SNPs but have greater repercussions because they encompass larger regions of genomic variation than SNPs do (Ventola 2013). Both SNPs and SVs are thought to play a role to varying degrees with respect to individual phenotypic drug response outcomes, such as drug sensitivity, resistance, and toxicity (Crews et al. 2012).

Thus, the availability of the complete human genome sequence has made it possible to analyze the impact of variations of the human genome sequence on the pathogenesis of important diseases and the response to drug therapy at an accelerating rate in recent years (Ma & Lu 2011). The purpose of this work is to report the papers that described the role of genetics in drug response.

HUMAN GENETICS IN DRUG RESPONSE

As mentioned before, genetic polymorphisms can affect the drug response at different levels. In fact, they can occur in drug targets, drug-metabolizing enzymes and drug transporters finally affecting drug reactions.

One of the most influential discoveries for pharmacogenetics and its potential clinical utility was the identification in 1977 of the hepatic cytochrome P450 oxidase (CYP450) that controls the metabolism of the majority of drugs (Scott 2011). In particular, one of the member family of CYP450, the CYP2D6 is now believed to be directly involved in the metabolism of ≈25% of all commonly used drugs. In fact, genetic variation in CYP2D6 and other genes that encode for drug-metabolizing enzymes, have been correlated with four general metabolism phenotypes: *poor metabolizers* that have two non-functional alleles and therefore have little enzyme activity; *intermediate metabolizers* have one non-functional allele and one normally functioning allele, and therefore have decreased enzyme activity; *extensive metabolizers* have two normally functioning alleles and therefore have normal enzyme activity; *ultra-rapid metabolizers* that have one or more alleles which result in increased enzyme activity compared to extensive metabolizers.

The impact of each metabolizer type on medication response depends on the role of the enzyme in the metabolism of the specific drug in question. For example, for a drug that is inactivated by the enzyme, an ultra-rapid metabolizer may need a higher dose of the drug to reach a therapeutic range, while for another drug, that is activated by the enzyme, ultra-rapid metabolizer status may be associated with increased exposure to the drug and therefore an increased risk of adverse drug reactions.

Now that DNA-based CY450 enzyme tests are clinically available, genetic screening can identify these metabolism phenotypes among individuals (Scott 2011).

Among the CYP450 enzyme family, of note are the polymorphic variant alleles of the two enzymes from the CYP2C subfamily: CYP2C9 and CYP2C19. CYP2C9 gene is highly polymorphic and metabolizes many clinically relevant drugs. For CYP2C19 around 27 variant alleles have been described of which the most recognized are CYP2C19*2 and CYP2C19*3 that determine a complete loss of enzyme activity (Ventola 2013, Scott 2011). However, other CYP2C19 alleles also result in a loss, reduced or increased metabolic enzyme activity (Ma et al. 2012).

In addition to the CYP450 genes, other polymorphic drug metabolism enzymes and their clinically relevant substrates include thiopurine *S*-methyltransferase, UDP-glucoronosyltransferase and dihydropyrimidine dehydrogenase, among others. However, drug efficacy is not influenced only by genetic variation in drug-metabolizing enzymes. In fact, polymorphisms in genes that encode for drug targets and drug transporters have also been shown to alter drug response (Scott 2011).

Several studies have evaluated genetic variants and their influence in the response to different drugs such as:

Opioid drugs. It has been shown that the opioid oxycodone is metabolized by CYP2D6 enzyme. One study demonstrated that poor metabolizers had a two-fold to 20-fold decrease, and ultra-rapid metabolizers had a 1.5-fold to 6-fold increase, in analgesic effects compared with extensive metabolizers. In addition, respect to adverse effects, the ultra-rapid metabolizers are also at an increased risk of toxicity. However, other studies have also analyzed the genetic variants involved in the metabolism of codeine (Ma et al. 2012, Ventola 2013).

Psychotropic drugs. It has been demonstrated an association of the dopamine D2-receptor gene with drug response and it has been confirmed in a systematic review (Ventola 2013).

The dopamine transporter gene, DAT, has been positively associated with clozapine response but negatively with risperidone (Reynolds 2012). In addition, an SNP in the 5-hydroxytryptamine (5HT or

serotonin) receptor 2A gene was found to affect antipsychotic treatment response (Ventola 2013).

Cardiovascular drugs. Warfarin is the most commonly used oral anticoagulant that acts on VKORC1 (vitamin K epoxide reductase complex subunit 1) enzyme. VKORC1 catalyzes the conversion of vitamin K epoxide to reduced vitamin K, which is required for post-translational modification of different coagulation factors. Several polymorphism in the coding region of VKORC1 have been identified such as A41S, V45A, R58G, V66M, L128R; all of them are associated with warfarin resistance that necessitates a daily dose greater than 15 mg/day (Ma & Lu 2011). However, studies on genetic variants and response to other cardiovascular drugs have been performed (Ventola 2013).

Anticancer drugs. In oncology, somatic genetic changes in tumors were found to have more of an effect on drug efficacy compared with variations in an individual's germline DNA (Salari et al. 2012, Ventola 2013). A key to the success in targeted cancer therapy is to separate responders from nonresponders in clinical practice, so that the drug is targeted to patients who have a particular molecular abnormality (Ma & Lu 2011). Somatic genetic mutations in tumors can also help predict resistance to treatment, as it has been observed in colorectal cancers, in which activating mutations in KRAS are known to be a predictive marker for resistance to the EGFR-specific monoclonal antibodies cetuximab and panitumumab (Salari 2012, Ventola 2013). On the other hand, one study estimated that genetic factors could determine more than 40% of the susceptibility to cisplatin-induced cytotoxicity (Ni et al. 2013).

Additional studies for genetic variants and response to *proton pump inhibitors, anti-infective drugs and anticonvulsant drugs* have been performed (Ventola 2013).

DISCUSSION AND CONCLUSION

Although the usefulness of genetic variance in drug response has been demonstrated from different researcher groups, its application in clinical practice has been weak. There are different factors preventing its application. There is a need for trained doctors and pharmacists with adequate expertise in interpreting pharmacogenetic test results (Madian et al. 2012). Another barrier is represented by the cost because many physicians consider the expense of genotyping as overbalancing its potential benefits (Ventola 2013). However, severe adverse drug reactions are one of the most common reasons for hospital admissions in the U.S., therefore using genetic tests will help to reduce the cost of hospitalization. Finally, while a considerable amount of pharmacogenetic data have been produced, most of them are low reproducible for other pharmacogenetic gene-drug association also because sometimes the pharmacogenetic allele frequencies can significantly differ between racial and ethnic populations (Scott 2011).

Multidisciplinary teams of laboratory, clinical, and computational researchers are working together to personalize drug treatment by incorporating an individual's genetic information (both germline and somatic) into existing prescribing models. A patient's genome needs to be identified only once in a lifetime, which makes pharmacogenetic screening a potentially very potent, cost-effective diagnostic tool (Ventola 2013).

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