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REVIEW

Pharmacogenetics and the concept of individualized medicine

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Adverse drug reaction in patients causes more than 2 million hospitalizations including 100 000 deaths per year in the United States. This adverse drug reaction could be due to multiple factors such as disease determinants, environmental and genetic factors. In order to improve the efficacy and safety and to understand the disposition and clinical consequences of drugs, two rapidly developing fields – pharmacogenetics (focus is on single genes) and pharmacogenomics (focus is on many genes) – have undertaken studies on the genetic personalization of drug response. This is because many drug responses appear to be genetically determined and the relationship between genotype and drug response may have a very valuable diagnostic value. Identification and characterization of a large number of genetic polymorphisms (biomarkers) in drug metabolizing enzymes and drug transporters in an ethnically diverse group of individuals may provide substantial knowledge about the mechanisms of inter-individual differences in drug response. However, progress in understanding complex diseases, its negative psychosocial consequences, violation of privacy or discrimination, associated cost and availability and its complexity (extensive geographic variations in genes) may become potential barriers in incorporating this pharmacogenetic data in risk assessment and treatment decisions. In addition, it requires increased enthusiasm and education in the clinical community and an understanding of pharmacogenetics itself by the lay public. Although individualized medications remain as a challenge for the future, the pharmacogenetic approach in drug development should be still continued. If it becomes a reality, it delivers benefits to improve public health and allow genetically subgroup diseases thereby avoiding adverse drug reactions (by knowing in advance who should be treated with what drug and how).
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Introduction

Inter-individual variation in drug response among patients is well known and poses a serious problem in medicine. There are no biomarkers at present that can predict which group of patients responds positively, which patients are non-responders and who experiences adverse reactions for the same medication and dose. Physicians have to optimize a dosage regimen for an individual patient by a trail-and-error method. This kind of blind approach may cause adverse drug reactions in some patients. In fact, adverse reactions are found to occur in more than two million cases annually in the United States including 100 000 deaths.[1]

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Similarly, according to a German study, about 6% of adverse drug reactions are attributed to new hospital admissions.[2] This inter-individual variability in drug response could be due to multiple factors such as disease determinants, genetic and environmental factors and variability in drug target response (pharmacodynamic response) or idiosyncratic response. These factors affect drug absorption, distribution, metabolism and excretion.[3] An understanding of the variability in efficacy and toxicity of the same doses of medications in the human population, therefore, may provide safer and efficient drug therapy.

In this regard, pharmacogenetics that investigates the relationship between drug response and genetic differences and pharmacogenomics that uses a genome wide approach to study the entire spectrum of genes involved in drug response could provide the bases for a rational approach for prescription drugs. Towards this goal, after the completion of the human genome project, a haplotype map (HapMap) has been recently developed by the International HapMap Consortium with an intention of profiling DNA sequence variations across the human genome. This should provide a powerful tool to understand the genetic variants and drug responses (biomarkers). This knowledge may ultimately allow the development of personalized medications based on the genotype of each patient.[4] However, at present, its impact on medicine is minimum and the greatest challenge is to understand the genotype–environmental factor interactions, ethnicity and to optimize study design for the accuracy, high level of quality and consistency of technologies.[5] In the following sections, an attempt has been made to summarize some of the studies to demonstrate the relationship between gene variants and drug response. A wide range of systems has been discussed briefly to generalize the concept. In doing so, only data from the first half of this calendar year are reviewed because a huge amount of data has been previously published both in drug metabolism and drug target literature. The information discussed in this review should be taken as an example rather than an exhaustive discussion of the field. The reader is requested to consult other reviews for the detailed treatment of the subject.[3,5–10] The studies discussed below certainly do not suggest that pharmacological basis of drug development is a credible concept and become reality in the future, but they provide optimism for personalized medicine.

Drug metabolizing enzymes

A considerable body of evidence suggests that single-nucleotide polymorphism (SNP) in genes encoding drug transporters, drug-metabolizing enzymes, enzymes involved in DNA biosynthesis and repair might determine drug efficacy and toxicity. Among drug metabolizing enzymes, cytochrome *P*450 (CYP) proteins are heme-containing enzymes. They are well known for their oxidative degradation of endogenous chemicals present in the diet, environment and medications including immunosuppressive drugs such as cyclosporine and tacrolimus (Table 1), which have been extensively used to prevent acute rejection following solid organ transplantation.[11,12] There are as many as 57 CYP genes and among them three families of genes – CYP1, CYP2 and CYP3—are the major genes[7] contributing to the oxidative metabolism of various compounds (Table 1). The frequency of variant alleles of CYP families varies among populations according to the race and ethnic background.[13] For instance, there are 78 reported variants of CYP 2D6 that are associated with adverse drug reactions (Table 2). Many of these polymorphic genes encode inactive enzymes. These inactive enzymes may produce adverse drug reactions[14] among patients because of their poor metabolic activity (e.g. risperidone adverse effect). Similarly, several inactivating genetic polymorphisms have been reported in another member of the CYP family namely CYP2C19 (CYP2C19*2 and CYP2C19*3), which are also associated with adverse drug reactions (Table 2). This enzyme is responsible for the metabolism of proton pump inhibitors (e.g. omeprazole and lansoprazole). Approximately 2–4% of white and 4% of African Americans have poor metabolism.[7] Additionally, CYP2C9*2 and CYP2C9*3 alleles reduce the clearance of warfarin and increase the risk of bleeding[15] and CYP2C9*13

Table 1 A partial list of drugs metabolized by various cytochrome *P*450 (CYP) and other enzymes

Enzyme	*Drug*
CYP1A2	Imipramine, Tacrine, Propranolol
CYP2C9	Cyclosporine, Nefazodone, Losartan
CYP2C19	Omeprazole, Lansoprazole
CYP2D6	Desipramine, Amitriptyline, Imipramine, Metoprolol, propranolol
CYP3A	Amitriptyline, Cyclosporine, Erythromycin, Imipramine, Losartan, Midazolam, Nefazodone, Omeprazole, Tacrolimus, Lovastatin, Triazolam
Glucuronosyl transferase	Labetalol, Morphine, Naloxone
TPMT	6-mercaptopurine
S-methyltransferase	Caprtopril

Table 2 A partial list of proteins associated with individual variations in drug response

Proteins	*Proteins*
CYP 1A2	Multidrug resistant protein 1
CYP 2A6	Serotonin transporter
CYP 2B6	Thiopurine *S*-methyltransferase
CYP 2C8	Glutathione *S*-transferase
CYP 2C9	UDP Glucuronosyl transferase
CYP 2C18	Catechol *O*-methyl transferase
CYP 2C19	Sulfonylurea receptor
CYP 2D6	Dihydropyrimidine dehydrogenase
CYP 2E1	Epoxide hydrolase
CYP 3A4	ATP binding cassette
CYP 3A5	Dopamine receptor
CYP 3A7	Multidrug resistance associated protein 1

allele is associated with reduced metabolism of lornoxicam.[16] Similarly, CYP2C8 plays a role in the disposition of therapeutic drugs.[17]

The intestinal epithelium and liver contain the most abundant member of the CYP family namely CYP3A and these enzymes are responsible for the metabolism of more than half of the therapeutic drugs. Its activity also varies among members of a given population. In addition, this enzyme may undergo induction (rifamycins) and inhibition (calcium channel blockers) depending on the drug administration, which may account for its poor or higher metabolic activity. The inter-individual variation in the immunosuppressive drugs cyclosporine and tacrolimus could be due to inter-individual differences in the expression of CYP 3A4 and 3A5 and the drug transporter P-glycoprotein.[12] However, genetic variants identified in the CYP3A4 and CYP3A5 genes have only a limited impact on the CYP3A mediated drug metabolism,[18] and hence the identification of the genotype for the ABCB1 gene may provide further clues for the individualization of immunosuppressive drug therapy.

Drug transporters

Genetic variability in drug transporters plays a role in the resistance of malignant cells to anticancer agents (Table 2). For instance, polymorphism in the ABC-binding cassette (ABC) gene may affect the function and expression of proteins.[19] This may cause certain drug induced side effects and uncertainty in treatment efficacy. One notable example is that in certain patients the reduced rate of methotrexate metabolism produced a severe methotrexate overdosing and nephrotoxicity. This defect is attributed to the heterozygous mutation (R412G) in the highly conserved amino acid arginine[20] of the ABCC2 gene, which encodes the human multidrug resistant protein-2 (MRP2). Interestingly, this mutated region is associated with substrate affinity and hence the mutant protein has a reduced rate of methotrexate elimination. In some other cases, a long-term use of methotrexate induces pancytopenia (which is determined by white blood cells and platelet counts.)[21] However, it is also known that polymorphisms always need not have to produce functionally defective proteins. For example, in the multidrug resistant gene (MDR1), certain polymorphisms may not have any effect on the drug response.[22] However, this could be due to nonsignificant statistical power. Thus, pharmacological studies on drug transporters (another target) are beneficial for predicting patients who are at risk in some cases at least.

Cancer drugs

Drugs such as azathioprines, mercaptopurines and thioguanine have been used extensively to treat childhood acute lymphoblastic leukemia and inflammatory bowel disease. Thiopurine *S*-methyltransferase (TPMT) is a cytosolic enzyme that is involved in the metabolism of thiopurines (Table 1). Genetic polymorphism in this enzyme has been reported and the variant enzyme was shown to misfold and subsequently form aggresome.[23] It has been reported that the TPMT genotype has a substantial impact on the mercaptopurine treatment response.[24] Previous studies also have shown that patients with homozygous mutant TPMT alleles exhibit very low enzyme activity and develop a severe hematopoietic toxicity after treatment with standard doses of thiopurines.[25–27] Similarly, the response rate of 5-fluorouracil (5-FU) based treatment of advanced colorectal cancer is significantly linked to 677 C→T polymorphism in the methylenetetrahydrofolate reductase gene.[28]

Antihypertensive drugs and receptors

Hypersensitivity drug reactions may be potentially life threatening and result in a socioeconomic burden. They represent approximately one-third of all adverse drug reactions.[29] Although there are several risk factors, their clinical importance has not been understood. Most of the studies to date have failed to show any link between polymorphism in tumor necrosis factor alpha and both cardiomyopathy and coronary artery disease.[30] However, variation in two genes encoding angiotensin-converting enzyme and endothelial nitric oxide synthase influence the effects of standard therapies.[31] In addition, polymorphism in the sodium channel gamma-subunit promoter region is significantly associated with blood pressure response to hydrochlorothiazide.[32] Similarly, SNPs in angiotensinogen (T1198C), apolipoprotein B (G10108A) and adrenoreceptor alpha 2A (A1817G) significantly predict the change in left ventricular mass during antihypertensive treatment.[33] Although common variants may influence the blood pressure response to a given class of antihypertensive medication, studies of polymorphisms have generally provided conflicting results.[34] For instance, polymorphism in the alpha 2B adrenergic receptor gene does not show any association with azepexole response.[35] However, patients with Gly 389 variant and Ser 49 homozygous of the beta-adrenergic receptor require increases in heart failure medication.[36,37] Similarly, in the case of asthma that causes substantial economic burden, morbidity and mortality, patients exhibit an extensive inter-individual variation in the response to beta-agonists acting at beta 2 adrenergic receptors. This could be due to one nonsynonymous polymorphism (I772M) of adenylyl cyclase type 9 (AC 9) gene. This variation results in decreased catalytic activity (M772) and, therefore, alters albuterol responsiveness in the presence of a corticosteroid.[38] Additionally, in an Indian population, response to salbutamol treatment of asthmatic patients depends on polymorphisms of the beta 2 adrenergic receptor.[39]

Antipsychotic drugs and their receptors and transporters

There also exists a considerable variability in efficiency and toxicity of antipsychotic drugs. For instance, in the case of mood disorder, approximately 30–40% patients do not

completely respond to pharmacological treatment.[40,41] However, serotonin transporter promoter length polymorphism has been implicated (Table 2) in the pathogenesis of mood disorders as well as in the therapeutic response to seretonergic drugs.[42] In patients with schizophrenia, Taq I polymorphism in the dopamine D2 receptor is associated with greater improvement of symptoms after treatment. Similarly, Gly 9 allele (Ser 9 Gly) of the dopamine D3 receptor and His 452 Tyr polymorphism in the 5-hydroxytryptamine 2A receptor (5-HT2A) are associated with response to clozapine. The side effect (weight gain) induced by antipsychotics seems to be associated with the –759C allele of the 5-HT2C receptor. Additionally, Gly 9-variant of dopamine D3, the 102C-variant of the 5-HT2A and the Ser 23-variant of the 5-HT2C receptors (in females) seem to increase the susceptibility to tardive dyskinesia.[43,44]

The disorder epilepsy is a difficult disease to treat because different patients require different ranges of doses and some patients may even experience side effects such as increase in seizures, depression and double vision. In order to control epilepsy, drugs such as phenytoin and carbamazepine have been extensively prescribed throughout the world. At present, evaluation of the allelic variation between individuals relies on the prior identification of candidate genes and their therapeutic effects of antiepileptic drugs.[45] Recently, variants in the CYP2C9 and SCN1A (encodes a brain protein) genes are found significantly more often in patients treated with the highest doses of both phenytoin and carbamazepine.[46] Moreover, pharmacoresistant epilepsy is a major clinical problem in epilepsy. This could be due to multiple factors, but multidrug transporters may play a key role in resistance phenotypes. However, studies on one variant in the ABCB1 gene, so far provided inconclusive evidence.[47] Similarly, a long-term treatment of patients of Parkinson disease with L-Dopa exhibits L-Dopa induced dyskinesis in some patients and this could be due to genetic polymorphisms among patients.[48] Therefore, pharmacogenetic studies may provide an explanation of neuronal plasticity among Parkinson patients.

Furthermore, drug addictions are major social and medical problems and therefore impose a significant burden on society. Epidemiological, linkage and association studies have shown a significant contribution of genetic factors to the addictive diseases. Studies of polymorphisms in the mu opioid receptors and transporter genes have contributed significantly to the knowledge of genetic influence on opioid and cocaine addiction and the efficacy of opioid therapy in pain management.[49–52]

Environmental factors

Environment–genotype interactions play a major role in drug therapy. For instance, inter-individual variability has been seen in human liver UDP-glucuronosyltransferase 1A6 (UGT1A6) enzyme activity that glucuronidates various drugs and toxins (Table 1). Its expression is associated with polymorphisms in the 5′-regulatory and exon 1 regions. The three most common nonsynonymous polymorphisms are S7A, T181A and R184S. However, it did not explain the inter-individual variability in glucuronidation and alcohol consumption which suggests that environmental factors may have a significant role in alcohol consumption.[53,54] Similarly, alcohol dependence is not associated with single-nucleotide polymorphisms in the corticotropin releasing hormone receptor 1 (CRHR 1) gene.[55]

Ethnicity

In order to use genomic knowledge to develop drugs and to improve health, we need to consider ethnical differences in different populations.[56,57] There exists inter-ethnical differences in polymorphisms of genes encoding drug-metabolizing enzymes, transporters and disease associated proteins.[58,59] A population genetics-based method to calculate the probability value for a variation in the gene is recently developed.[60] Genetic differences are greater within socially defined racial groups than between groups.[61] Additionally, it has been found that genetic diversity decreases in noncoding regions whereas diversity of coding nonsynonymous SNPs is lower in regions containing a known protein sequence motif in individuals of European origin.[62]

Drug treatment may be tailored for greater effect if important genetic variation exists between racial and ethnic groups. By knowing these variants, patients can be classified into low, intermediate and high dose groups.[63,64] For instance, warfarin therapy shows a wide variation among patients of different ancestries. This variation could be due to polymorphisms in the gene encoding vitamin K epoxide reductase complex 1. Accordingly, Chinese patients require lower dosages of heparin and warfarin than those usually recommended for white patients.[65,66] Additionally, BiDil (combination of two generic drugs, isosorbide dinitrate and hydralazine) treatment of heart failure in African-Americans heart patients reduced mortality by 43%, claiming that African Americans and white Americans differentially respond to the treatment. This is claimed to be due to genetic differences in the pathophysiology of heart failure between the two groups.[67] In other words, there are biological differences between the two racial groups. However, in this study, there is no comparison population and hence results should be interpreted cautiously. Nevertheless, these results have opened the debate on the biological basis of race and ethnicity and pharmacogenetics may provide a useful understanding of ethnic and racial differences. Even in this case, however, we are still ignoring several important parameters such as diet, economic, environmental and psychosocial factors. Pharmacogenetics study on race and ethnicity is worthwhile because these are useful indicators of genetic variation. However, this kind of race and ethnicity classification for medical treatment leads to discrimination.

Concluding remarks

Inter-individual difference in the efficacy and toxicity of medication is common among patients. This difference in

drug response could be due to genetic, environmental factors and dose–response curve of a drug (pharmacokinetic and pharmacodynamic). Knowledge of an individual genetic variability in drug response is, therefore, clinically and economically important. Pharmacogenetics and pharmacogenomics are the two recent developments to investigate inter-individual variation and drug response. This type of genetic profiling of the population provides benefits for future medical care by predicting the drug response, or developing DNA based tests. However, these studies certainly do not suggest that pharmacological basis of drug development is a credible concept and become reality in the future because drug response can be modulated by a number of nongenetic factors such as comedication and concurrent diseases. These nongenetic factors may increase the complexity in prescribing the medication appropriately. Although in some cases polymorphism in a gene is associated with poor efficacy and adverse drug reactions, their clinical relevance remains to be understood. Moreover, it may not be applicable to all diseases and all treatments.[68]

Additionally, this kind of approach may require a genome-wide linkage analysis rather than genotyping of single genes and increased enthusiasm and education in the clinical community.[69] In addition, its negative psychosocial consequences, violation of privacy or discrimination by pharmacogenetic testing, knowledge on the variant and disease disposition (e.g. apolipoprotein E4 allele in statin treatment and Alzheimer disease), associated cost and availability and its complexity (extensive geographic variations in genes) and understanding or explaining the test results may pose a challenge in its public acceptance.[70] It is not clear at present whether data from one ethnic population can be extrapolated to another population. It is also necessary to bring pharmacogenetics itself to the lay public and explain how they influence drug response.[6,71,72] Therefore, incorporation of the pharmacogenetic data into clinical practice (risk assessment and treatment decision) is a challenge for the future.

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