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MINIREVIEW

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Genetic diversity and new therapeutic concepts

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Abstract The differences in medicinal drug responses among individuals had been known for quite some time. Some patients exhibit a life-threatening adverse reaction while others fail to show an expected therapeutic effect. Intermediate responses between the above two extreme cases are also known. In fact, it has been recently reported that approximately 100,000 deaths and more than 2 million hospitalizations annually in the United States are due to properly prescribed medications. This interindividual variability could be due in part to genetically determined characteristics of target genes or drug metabolizing enzymes. This has now been substantiated by a variety of studies. We know that "one size fits all" is not correct. Therefore, the application of pharmacogenetic concepts to clinical practice is an excellent goal in the postgenomic era. The successful completion of the human genome project provided necessary molecular tools, such as high-throughput SNP genotyping, HapMap, and microarray, that can be applied to develop proper therapeutic options for individuals. Recently, there have been considerable scientific, corporate, and policy interest in pharmacotherapy. However, identification of causal variations in a target gene is only a starting point, and the progress in this rapidly developing field is slower than expected. One major drawback could be due to the multigene determinant of drug response that requires a genome-wide screening. Additionally, application of pharmacogenetic knowledge into clinical practice requires a high level of accuracy, precision (risk/benefit ratio), and strict regulations. This is because the pharmacogenetic approach raises several ethical, moral, and legal questions. It is also necessary that both health professionals and the general public must be urgently educated. Despite these limitations, translation of pharmacogenomic data into clinical practice would certainly provide better opportunities to increase the safety and efficacy of medicine in the future.

Keywords Pharmacogenetics · Pharmacogenomics · Polymorphism · Gene · Medicine

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Introduction

It has been known for quite some time that there is a large variation in drug response among individuals (Meyer 2004). Some patients exhibit a life-threatening adverse reaction while others fail to show an expected therapeutic effect. Intermediate responses between the above two extreme cases are also possible (Evans and McLeod 2003). For instance, some schizophrenic patients treated with clozapine react adversely while others fail to show therapeutic response. Similarly, there is an association between clozapine response and polymorphism in dopamine receptors 3 (D3) and 4 (D4) as well as 5-hydroxytryptamine 2A and 5A genes. In fact, it has recently been reported that approximately 100,000 deaths and more than 2 million hospitalizations annually in the United States are due to properly prescribed medications (Muehlberger et al. 1997; Lazarou et al. 1998; Gandhi et al. 2003; Dormann et al. 2004). Hence, adverse drug reactions represent an important clinical problem and a leading cause of death (Ament et al. 2000).

The successful completion of the human genome sequence has provided a unique opportunity to understand drug efficacy and toxicity in the postgenomic era. As a result, new excitement has been generated in biomedical science and two related fields, namely, pharmacogenetics and pharmacogenomics, gained popularity in late 1990s. Pharmacogenetics is the study of the relationship between an individual's genetic makeup (mostly heritable variation in a single gene or a group of genes) and the response to medicinal drugs whereas pharmacogenomics investigates a large number of

clinically important genes (entire genome) and their expression that underlie the response to drugs (Hakonarsson and Stefansson 2004; Hall et al. 2004). The overall goal of these fields is to understand the relationships between heritable changes and interindividual variation to drug response. In many cases, adverse drug reactions are due to the poor metabolism of drugs in some individuals compared with others, and this leads to an elevated and harmful drug level in those individuals. This type of metabolic difference could be due in part to polymorphism in genes encoding drug-metabolizing enzymes (Weinshilboum 2003). As discussed below, accumulated evidence does support this notion, and the hypothesis is that an understanding of the genetic makeup of an individual may provide an opportunity to design safer and more efficient drugs suitable for each person.

The necessary techniques are now available to carry out this challenging task. For instance, many genes contain multiple single nucleotide polymorphisms (SNPs), and there is a large collection of SNPs now available from the human genome project (http://www.ncbi.nlm.nih.gov/SNP/snp_summary.cgi). There are also several methods, such as high-throughput SNP genotyping, tagging SNPs, HapMap, automated statistical tools, and microarray, which can be applied to search for genes that underlie disease susceptibility or influence the response to drugs. Readers are requested to consult the recent reviews for further discussion on these methods (Gut 2001; Rodi et al. 2002; Goldstein et al. 2003; Shastry 2003, 2004; Freimuth et al. 2004; Hakonarsson and Stefansson 2004; Lavedan et al. 2004; Ahmadi et al. 2005). If we were to be successful in developing genotype-based medicine, it may have a maximum benefit for patients. In order to be successful, however, it is crucial to find the functionally relevant variation in genes encoding drug-metabolizing enzymes and drug targets.

In order to achieve this goal, pharmacogenomics is now focusing its interest in generating information that can be useful in clinical development. This strategy involves a comprehensive collection of epidemiological, genetic, clinical, and genealogical information. By collecting this type of information, it is possible to uncover genes more effectively that predispose to disease, enrich the population that is likely to respond to the study drug, and eliminate the nonresponder (Hakonarsson and Stefansson 2004). In this short report, I have attempted to outline some of these aspects focusing primarily on interindividual differences in drug responses that are attributed to variants in certain drug-metabolizing genes, most notably, CYP 450 alleles. Some examples are also given for certain cancer and antiviral drugs that are metabolized by these enzymes and are known to have different responses among individuals. The aspects discussed are not exhaustive, and they only serve as examples. These studies show that application of pharmacogenetics may significantly improve safer drug development.

Genomic variation and drug metabolizing genes

Interindividual variation in drug metabolism is an important aspect of drug therapy. This variability in drug response and toxicity could be due to genetic factors, inhibitors, inducers, and dietary factors (lifestyle). Genetic polymorphism (SNPs) in genes encoding drug-metabolizing enzymes, drug transporters, and DNA repair enzymes are present in populations (Table 1) and have been shown to influence drug pharmacokinetics (Thomas et al. 2004). For instance, cytochrome P450 (CYP) proteins are heme-containing enzymes that are responsible for the oxidative metabolism of a variety of endogenous and exogenous compounds (Ozdemir et al. 2000; Caraco 2004; Van Schaik 2004). While there are as many as 57 CYP genes in humans, three of these are the major isoforms (CYP3A4, CYP2D6, and CYP2C9) that contribute to drug metabolism (Daly 2004; Smith et al. 2004). Among the members of the CYP3A subfamily, the CYP3A5 gene is found to have extreme interpopulational variability in allele frequency and haplotype structure (Hustert et al. 2001; Kuehl et al. 2001; Lamba et al. 2002; Thompson et al. 2004). This enzyme is expressed in the prostate, kidney, liver, and intestine and metabolizes environmental carcinogens, endogenous substrates, and prescription drugs. In some patients, it may have a severely reduced activity (Table 1). Hence, it is likely that it may contribute to the differential drug responses among different individuals (Lamba et al. 2002). Because genetic polymorphism may predict variable gene expression and hence variable drug response, such an understanding of gene activity could improve therapies with personalized dose adjustments (Wojnowski 2004) and help to preclude nonresponders, toxic effects, and related hospitalization.

Additionally, among the members of CYP family, the CYP2C9 and CYP2C19 gene polymorphisms have a dramatic influence on the disposition of compounds such as warfarin (coumadin), phenytoin (antiepileptic) and sulfonylureas (antidiabetic). The most widely studied alleles are CYP2C9*2 (Arg144Cys) and CYP2C9*3 (Ile359Leu). Their frequencies also vary in different populations (Llerena et al. 2004). Individuals carrying CYP2C9*2 and CYP2C9*3 alleles have a lower daily dose requirement of warfarin and are more susceptible to adverse events (Aithal et al. 1999; Evans and Johnson 2001). This suggests that CYP2C9-genotype-based dosing may be beneficial (Hung et al. 2004; Lee 2004; Kirchheiner and Brockmoller 2005). Similarly, ethnic variations in CYP2A6 have been associated with slow nicotine metabolism in certain populations (Schoedel et al. 2004), and deficiency in CYP2D6 may cause nonresponse to antidepressant treatment (Haller-Gloor et al. 2004), indicating again that individualized treatment is clinically useful. In the northern European population, for instance, there exist three forms of CYP2D6 called poor, extensive, and ultrarapid metabolizers. There are more than 70 polymorphisms and 70

Table 1 A partial list of genetic polymorphism and drug response. *5-FU* 5-fluorouracil

Gene	Name	Allele[a]	Phenotypic effect
Drug-metabolizing enzymes			
CYP3A4*17	Cytochrome P450	F189S	Reduced activity
CYP3A4*18A	Cytochrome P450	L293P	Increased activity
CYP3A5*3A-3J	Cytochrome P450	Splicing defect	Severely reduced activity
GSTP1	Glutathione *S*-transferase	I105V	Increased survival for 5-FU
UGT1A1	UDP-glucorono-syltransferase1A1	UGT1A1*28	Side effect for irinotecan
DPYD	Dihydropyrimidine dehydrogenase	DPYD*2A	Severe toxicity for 5-FU
TPMT	Thiopurine methyl transferase	TPMT*2, TPMT*3A TPMT*3C	Homozygotes are at higher risk for thiopurine treatment
Drug-pathway protein			
TYMS	Thymidylate synthase	TSER*2/*3	*3/*3 genotype requires higher dose of 5-FU
LIPC	Hepatic lipase	C514T	C/C genotype shows increased response to statin
MTHFR	Methylene tetrahydrofolate reductase	C677T	T/T genotype shows increased toxicity for methotrexate
ADRB1	Beta1 adrenergic receptor	R389G	R/R individuals have greater response to beta-adrenergic receptor antagonists
AGT	Angiotensinogen	M235T	Reduction of blood pressure
DRD3	Dopamine D3 receptor	S9G	Intermediate response to clozapine
HTR2A	Serotonin receptor 2A	H452Y	Reduced response to clozapine
ACE	Angiotensin converting enzyme-1	Ins/del	Del/Del genotype shows decreased proteinuria in response to ACE inhibitor
ALOX5	Arachidonate 5-lipoxygenase	Promoter VNTR	Homozygotes show decreased response to enzyme inhibitor
Drug transporter			
ABCB1	P-glycoprotein-1 (MDR1)	C3435T	T/T patients may have less drug-resistant epilepsy
Others			
XRCC1	DNA repair protein XRCC1	R399Q	Q/Q individuals less likely to develop therapy-related myeloblastic leukemia
IL 10	Interleukin 10	A1082G	G/G individuals have better response to prednisone
ADD1	Adducin 1 (alpha)	G460W	Hypertensives' show increased response to diuretics

[a] Types of mutations that are responsible for the alleles

haplotypes that have been identified within the exonic and promoter region of the CYP2D6 gene, and many of these variations decrease CYP2D6 activity. Approximately 5–10% of the Caucasian population is deficient in CYP2D6 activity. In certain other populations, duplication of this gene is associated with an ultrarapid metabolic state (Johansson et al. 1993; Lovlie et al. 1996). Patients carrying the ultrarapid allele do not show the expected therapeutic response (Weinshilboum and Wang 2004). For instance, when a patient was treated with small doses of codeine, life-threatening intoxication developed, which is reported to be associated with ultrarapid CYP2D6 metabolism (Gasche et al. 2004). Additionally, interindividual differences in the metabolism of the antiretroviral agent efavirenz and its central nervous system side effects have been shown to be associated with allelic variant of CYP2B6. This variant (G516T) is more common in African Americans than in European Americans (Haas et al. 2004a).

Another notable pharmacogenetic association is with the drug pravastatin. This drug has been efficiently and widely used to reduce cardiovascular risk by lowering the cholesterol level. It is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme involved in cholesterol synthesis. This cholesterol-lowering therapy also exhibits a wide range of interindividual variability. The variable individual response has been attributed to the genetic difference between individuals in genes involved in cholesterol synthesis and statin metabolism. Recently, it was shown that two linked common polymorphisms in the HMG-CoA reductase gene are associated with reduced lipid-lowering activity. Heterozygous individuals may have a significantly reduced efficacy of pravastatin therapy (Chasman et al. 2004). The two SNPs are in the intronic sequence, and they may not affect the gene expression but mRNA stability in the cell instead. This study provides further clinical evidence of the impact of genetic variation. It also shows that genetic screening and genotype-based medicine has pathophysiological significance.

It must be noted, however, that all polymorphism in a gene does not need to have an influence on drug metabolism. For instance, CYP3A is expressed in the

kidney and extensively metabolizes cyclosporin, but CYP3A5*1 allele expression is not involved in cyclosporin dosing, long-term renal graft survival, and blood pressure regulation in the Caucasian population (Kreutz et al. 2004). Similarly, multi-drug-resistant transporter gene (MDR1) haplotypes in exons 21 and 26 do not influence the pharmacokinetics of the immunosuppressant drug tacrolimus (Lee et al. 2004; Mai et al. 2004). Additionally, the ATP-binding cassette transporter (ABCG2—breast-cancer-resistant protein) allele does not have any effect on the disposition of irinotecan in the European population (De Jong et al. 2004). Irinotecan is a prodrug that has been widely used in the treatment of advanced cancers and is activated by human carboxylesterase 2. Although its gene presents several polymorphisms and an intronic SNP is found to be associated with reduced carboxylesterase 2 mRNA expression in colorectal tumor (Marsh et al. 2004), none of the variations in the carboxylesterase 2 gene are found to be associated with protein activity (Charasson et al. 2004). Similarly, the polymorphism in the histamine- *N*-methyltransferase gene is not associated with gastric ulcer (Chen et al. 2004). Conversely, some genetic variants in nontarget genes may also be involved in producing adverse effects of drug treatment (Napolitano et al. 2000; Psaty et al. 2002). Thus, it is not only genetic variability of drug metabolism and drug target genes, but environmental factors, nontarget genes, and enzyme induction and inhibition that may also play a role in drug disposition (Root et al. 2004).

Gene polymorphism and immunosuppressive drugs

Azathioprine is an immunosuppressive prodrug that is metabolized by the thiopurine *S*-methyltransferase (TPMT) enzyme. This drug is used to treat autoimmune disorders and those receiving organ transplants. The enzyme TPMT contains three nonfunctional mutant alleles (TPMT*2, TPMT*3A, and TPMT*3C) that determine about 80–90% of low enzyme activity. TPMT*3A is the most common allele in the Caucasian population whereas in African American, Asian, and African populations, TPMT*3C is the most prevalent allele (Krynetski and Evans 2003). These alleles also predict azathioprine-induced myelotoxicity in kidney transplant recipients (Fabre et al. 2004) that can be life threatening because of adverse drug responses. Those patients homozygous for TPMT*3A may develop life-threatening myelosuppression with a normal dose of thiopurine drugs (Table 1). This suggests that if thiopurine doses are lowered according to the genotype, it is possible to treat patients without adverse effects. Thus, application of pharmacogenetic knowledge may help in optimization of immunosuppressive drug therapy as well as reducing drug toxicity (Formea et al. 2004). Recently, there has been considerable interest in the use of pharmacogenetic testing of TPMT prior to therapy (Balis and Adamson 1999). This is the only example of pharmacogenetic testing that has been integrated into clinical practice to date. However, its broader application is not possible at present because a set of functional variants described in the Caucasian population have different frequencies in different populations (McLeod and Siva 2002; Van Aken et al. 2003).

Genetic polymorphism and the metabolism of other drugs

Genetic factors also play a role in the individual response to antihypertensive agents (Huang et al. 2004), vascular disease agents(Nabel 2003; Yee and Bray 2004), asthmatic drugs (Pelaia et al. 2004), antipsychotic medication (Scharfetter 2004), medication for human behavioral disorders (Akio 2003), and drugs to treat diabetes (Rosmond 2004). For instance, an SNP in the catechol-*o*-methyltransferase results in about a three- to four-fold reduction in its activity and is associated with a number of neuropsychiatric disorders (Doyle et al. 2004). Similarly, in the case of asthma, homozygous patients with a variant in the 5-lipoxygenase-promoter region (Table 1) respond less well to the lipoxygenase inhibitor (Drazen et al. 1999). Although hypertension biology is very complex, potentially promising associations between angiotensin-converting enzyme insertion/deletion variant (Table 1) and drug treatments have been reported (Arnett and Claas 2004). It is for this purpose, typing of genes of an individual may provide a better way of predicting the "at-risk" genotype that may facilitate therapy (Ferraccioli et al. 2004).

Genetic variation and cancer chemotherapy

A purely speculative and an incomplete understanding of the metabolism of many drugs administered simultaneously to treat diseases such as cancer and the interaction between drugs (e.g., warfarin plus ciprofloxacin; phenytoin plus cimetidine) are also the leading causes of adverse drug toxicity in a large percentage of patients (Ament et al. 2000). Because anticancer drugs have a narrow therapeutic index, the individual differences in drug efficacy is particularly important. Therefore, pharmacogenetics can play a role in cancer chemotherapy as well (Smith et al. 2004). Interindividual, population-specific and age-related responses to chemotherapeutic agents are also well known. Methotrexate, for example, has been used in the treatment of number of malignancies. However, some patients develop resistance and others could have toxic side effects. This could be due to polymorphic difference in several genes, such as thymidylate synthase, methylenetetrahydrofolate reductase (Table 1), and thiopurine *S*-methyltransferase. In support of this is the finding that several genetic variants in methylenetetrahydrofolate reductase and thymidylate synthase genes have a predictive role (Krajinovic and Maghrabi 2004). Similarly,

genetic variants have been identified in 14 genes that are involved in gemcitabine metabolism. This drug shows a significant variability in the antitumor response and toxicity in cancer patients (Fukunaga et al. 2004). The anticancer drug 5-fluorouracil (5-FU) has been widely used to treat a variety of cancers. This drug is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). To date, 39 different mutations and polymorphisms have been reported for DPD, and 14 of them were found to be associated with 5-FU toxicity (Table 1). Patients with DPD deficiency may have a risk of developing a life-threatening toxicity (Van Kuilenburg 2004). Thus, genotype identification of an individual prior to therapy may help reduce the severe toxicity of 5-FU.

By measuring direct enzyme activity, genotype, gene expression, and designing an individualized chemotherapy, it may be possible to eliminate tumor cells from the host (Donnelly 2004). However, numerous genes are likely to influence chemotherapy response or cytotoxicity. It is difficult to predict which genes are involved in chemotherapy cytotoxicity using a candidate-gene approach. This may require genome-wide linkage analysis to map the trait loci influencing the cellular effect of chemotherapy cytotoxicity. One such approach (CEPH family) has recently been reported for the chemotherapy agents 5-FU and docetaxel (Watters et al. 2004). This type of approach is faster, widely applicable, requires a single blood sample, and does not require a prior knowledge of a small number of candidate genes (Roses 2004). Alternatively, the DNA microarray technique can also be used for studying drug response by genotyping selected candidate genes (Weinshilboum and Wang 2004). For instance, a specific chip for the rapid detection of CYP2D6 alleles has already been developed (Evans and Relling 2004) and is awaiting FDA approval in the US. Gene-expression profiling is another powerful technique that can be useful in all stages of drug development, including preclinical testing and predicting potential toxic effects. It is particularly valuable in the case of cancer treatment, but whether this technology helps predicting treatment success remains to be seen (Van de Vijver et al. 2002; Sotiriou et al. 2003). Although this procedure has several limitations, such as errors in the manufacturing of chips, low specificity, and discrepancy in differential gene expression data, by carefully selecting genes, it is possible to gain insight into the variation in drug response (Lorenzi et al. 2004).

Gene polymorphism and antiviral therapy

Genetic factors also influence the efficacy and toxicity of antiviral therapy. For instance, CYP and drug transporters influence the disposition of human immunodeficiency virus (HIV) protease inhibitor and nucleotide and nonnucleotide analog reverse transcriptase inhibitor drugs (administration of multiple drugs is needed) (Martin et al. 2004). However, it involves variability in host alleles and drug–drug interaction; hence, it is a significant challenge to devise a pharmacotherapy. Despite this limitation, considerable effort has been made to understand the contribution of genetic factors for the development of toxicity and response that may have potential in the future. One interesting example in this respect is the association between abacavir hypersensitivity reactions and specific HLA and hsp70-hom genotypes (Haas 2004b). The finding that a nonfunctional deletion mutant of the HIV receptor CCR5 gene protected against infection may also help drug development.

Drug transporter gene polymorphism

As mentioned earlier, polymorphism in drug transporter genes also determines drug response. There are 48 known drug transporters. One of the best-characterized drug transporters is the MDR1 gene, which is also called ABCB1 and is known to transport a broad range of drugs. Little is known about other drug transporters. To date, there are 28 SNPs that have been reported in the MDR1 gene, and a silent SNP (C3435T) in exon 26 is found to be a risk factor for diseases such as Parkinson's, renal epithelial tumor, inflammatory bowel disease, and drug-resistant epilepsy (Sakaeda et al. 2004). This polymorphism is associated with different expression levels of the MDR1 gene, and a difference in allele frequency has also been reported between different population groups (Ostrovsky et al. 2004). Patients resistant to antiepileptic drugs are more likely to be associated with CC genotype at 3,435 of the ABCB1 gene than with the TT genotype (Siddiqui et al. 2003). This evidence also justifies the clinical use of pharmacogenetic tests for drug-dosage recommendation.

Concluding remarks

From the foregoing evidence, it is clear that there are striking examples of allelic frequency differences in drug-related genes that predispose individuals to different drug responses in different populations (Cha et al. 2004). DNA-based tests may, therefore, identify optimal dosing, maximize drug efficacy, reduce the risk of toxicity and related hospitalization, and improve drug selection (Oscarson 2003; Evans and McLeod 2003). However, before individualized medication makes its way to the clinic, we need to know the functions of polymorphism, gene–gene interaction rather than the individual gene effect, environmental factors (lifestyle of an individual), and how these affect phenotypes (Xie et al. 2001; Goldstein et al. 2003). In addition, a high level of accuracy, precision, and collection of a comprehensive set of data and their interpretation are needed to allow proper judgment for clinical applications (Hildebrandt 2004). We may also have to think about expanding our efforts to

include proteomic and metabonomic studies along with the genomic approach to achieve this challenging goal of personalized medicine (Nebert and Vesell 2004).

The goal of individualized medicine may also overcome the traditional trial-and-error method of treatment that is inefficient and expensive. In addition, we also have to consider social and ethical issues, such as discrimination, privacy protection, and public confidence (Breckenridge et al. 2004; Sankar et al. 2004). Its integration into clinical practice is also an important aspect (Fierz 2004; Lesko and Woodcock 2004), and all health care professionals must be urgently directed to genomic education as applied to medicine. Moreover, its integration into society must be of importance (Webster et al. 2004). Translation of pharmacogenetics and pharmacogenomics data into clinical practice would certainly provide significant opportunities to increase the safety and efficacy of medicine. Such data will ultimately allow clinicians to avoid drugs that adversely affect patients or select doses on the basis of genotype of an individual.

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