Pharmacogenetics: an Emerging Therapeutic Option for Bangladesh

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ABSTRACT: From socioeconomic point of view adverse drug reactions (ADRs) present a challenging and expensive public health problem worldwide. Most important factors involved in this life threatening events are false diagnosis, failure of treatment, lack of proper patient counseling, lack of knowledge regarding medication use and polypharmacy. Pharmacogenetic research explores genetic variability between patients to explain observed differences in effectiveness of a drug therapy as well as adverse event profile. Thus pharmacogenetic testing could help to prevent treatment failure and adverse drug reaction in patients. It also allows the detection and prediction of ADRs and is a tool that can reduce the risks associated with ADRs. In this particular review we will discuss how genetic variation can influence drug response and how personalized medicine can be achieved as well as some recent pharmacogenetics works carried out in Bangladesh. The aim of this review is to increase awareness of the physicians and other health care practitioners and professionals about the variation of drug response due to genetic variation. This review can help the physicians to identify genetic factors associated with ADRs with all drugs and effectively incorporate pharmacogenetics into the practice of pharmacovigilance.

Key words: Pharmacogenetics, adverse drug reactions, pharmacovigilance, pharmacokinetics, pharmacodynamics

Pharmacogenetics. Despite its profound progress, modern pharmacotherapy still faces many challenges such as adverse drug reactions, sometimes serious or even lethal, and non response to standard therapy. The observed prominent variability in individual response to pharmacotherapy, in part, depends on well-known factors easily assessable, like age, sex, weight, liver and renal function, comedication, heterogeneity in the disease, nutritional state or smoking.[1] Furthermore, inherited variants in drug-metabolizing enzymes (DMEs), transporters, receptors and molecules of signal transduction cascades may have a major impact on drug response. We now know that the therapeutic failure of drugs as well as serious adverse side effects of drugs on individuals or subpopulations of patients can both have a genetic component.[2]

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Pharmacogenetics is the study of the heritable basis of individual differences in response to pharmaceutical agents.[3,4] These variations underlie the response to therapy, including possible adverse effects. It also deals with the assessment of clinical efficacy and the pharmacological phenotype. These are the central tenets of pharmacogenetics. Some health care leaders view pharmacogenetics as providing the potential to create personalized prescriptions; with the opportunity to improve patient compliance, reduce adverse events, and reduce the cost of managing chronic disease. Up to 90% of the variability in drug response between individuals can be explained by genetics. Pharmacogenetic information is now included in the labeling of about 10% of drugs approved by the FDA. Inherited variants in the cytochrome P450 drug metabolism genes contribute significantly to an individual's drug response. The variation that exists in all genes causes different members of a population to express different forms of proteins, including those that metabolize drugs or are the sites of drug action. This can lead to different responses to these drugs.

Measuring the DNA differences can thus predict the variation in response to the medicine.[5]

Genetic polymorphism. Polymorphism is a term which literally conjures up an image of variability of form, shape, size, structure and composition and it has a currency in a wide variety of disciplines in science and art. Genetic polymorphism is a much more specific term and describes frequent variation at a specific locus in a genome. A useful practical definition says that a locus is polymorphic when there are two or more allelic forms in the same population and the commonest allele has a frequency of 0.99 or less.[6] A genetic polymorphism occurs if, within a population, a single gene responsible for producing a metabolizing enzyme has a variant allele with the arbitrary frequency of 1%.[7] For many such genes single nucleotide polymorphisms (SNP) exist and an allelic site may have more than one SNP. Genotype is the detailed gene structure of an individual whereas the more commonly measured phenotype is the outcome of metabolism of a drug in an individual. Mutation is one of the factors causing DNA polymorphisms, and which therefore contributes to disease onset. DNA polymorphisms may be due to the deletion, insertion, or substitution of a nucleotide, may occur at coding or non-coding regions of the DNA and may or may not alter gene function. The occurrence of DNA polymorphism makes it possible to associate a person's response to drugs with particular DNA regions, for example, by correlating the occurrence of the polymorphism with the response. This is the basis of current phamacogenetics, which is the study of the impact of individual genetic variants on drug response.

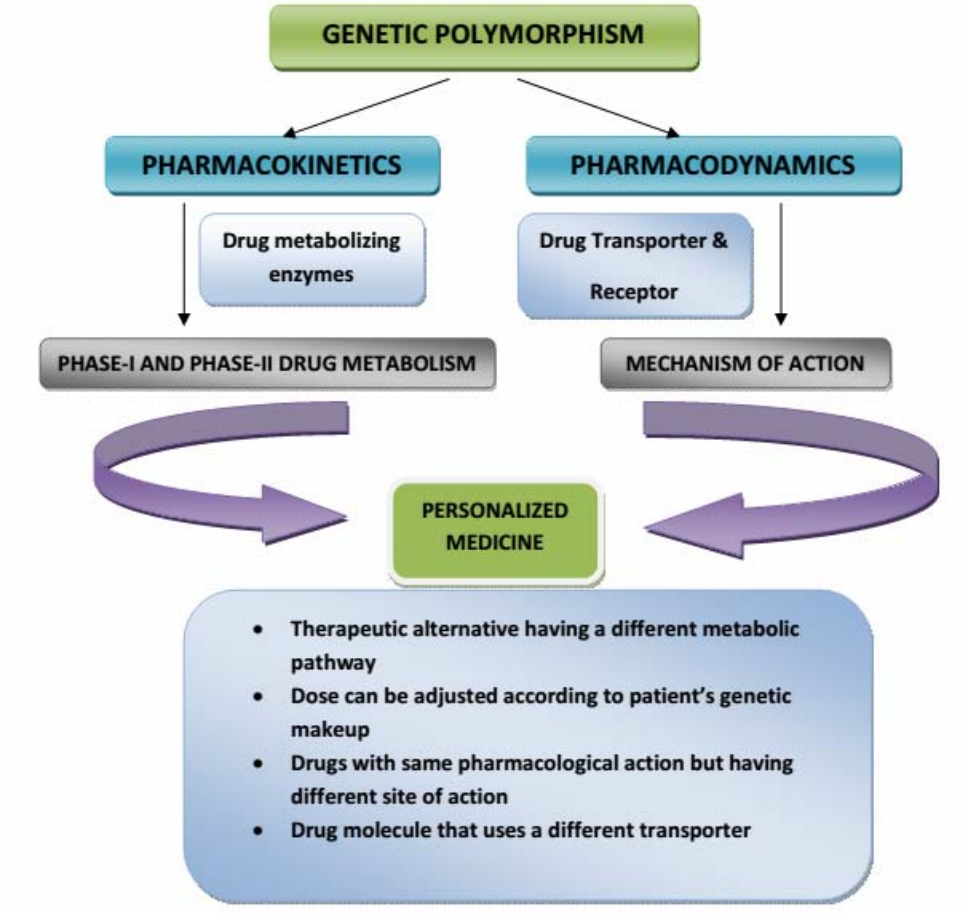

Figure 1. An overview of Pharmacogenetics: how variation in genetic makeup can influence the drug response (both pharmacokinetics and pharmacodynamics).

From Genotype to Phenotype. Predicting phenotype from genotype is a tool to personalize drug therapy, *i.e.*, to administer the optimal drug and dosage for each patient. Traditionally, information on an individual's metabolic capacity has been obtained through phenotyping, involving measurement and interpretation of drug concentrations. Genotyping is, however, becoming an increasingly important tool in clinical practice as well as in drug development, offering several advantages over traditional phenotyping: (i) results are not influenced by physiologic factors or concurrent medication; (ii) it can be performed less invasively without predisposing an individual to a drug and potential adverse effects; and (iii) it can provide predictive value for multiple drugs, rather than only a single drug.[8,9] Although the availability of various commercial genotyping platforms has made genotype information readily accessible, prediction of phenotype from genotype remains a challenge.[10]

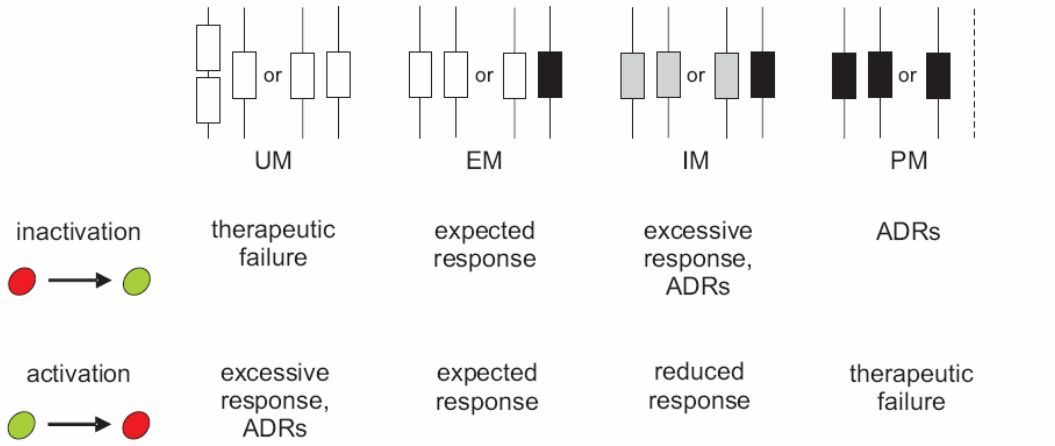

Figure 2. Scheme of the traditional classification of phenotypes based on genotypes and their clinical consequences depending on the type of reaction catalyzed by the polymorphic enzyme.

Null variants are represented by black boxes, decreased-function variants by gray boxes, and fully functional variants by white boxes. The dash line indicates a whole-gene deletion. Red represents an active drug molecule and green an inactive molecule. UM: ultra-rapid metabolizer; EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer (Adopted from Zanger *et al.*)[11]

Genetic Polymorphism and Pharmacokinetics. The biotransformation reactions catalyzed by drug metabolizing P450s result mostly in inactivation of a drug as they attenuate its biologic activity and accelerate its clearance from the body. However, these P450s also participate in bioactivation of some prodrugs to their clinically active form. In some of the biotransformation reactions catalyzed by P450s more reactive electrophilic metabolites are produced that may play a role in drug toxicity.

About 40% of Phase-I drug metabolazing enzymes has a large extent variability due to genetic polymorphism[12,13] that causes alteration in enzyme activity and may lead to inter-individual differences in the metabolism of drugs and could therefore influence pharmacokinetics and pharmacodynamics. Accroding to metabolic rate individuals can be grouped into four phenotype group: poor metabolizers (PMs) lacking functional enzyme due to mutation in both alelles, intermediate metabolizers (IMs) heterozygous for one defective allele and extensive metabolizers (EMs) with two normal alleles and ultra rapid metabolizers (UMs) carrying

gene duplication or multiple gene copies. The rate of metabolism for a certain drug can differ 1000-fold between the PMs and UMs. Such patients may require dose adjustments as a standard population based dosing may result in a higher risk for adverse effects due to high plasma levels in PMs or in unresponsiveness to treatment in UMs.[14,15]

A number of genetic predisposition cases due to deficient metabolism has been reported up to date including both Phase I and Phase II enzymes. The best example is the association of CYP2C9 polymorphisms with warfarin dose requirements and the risk of bleeding. Warfarin is widely used, perhaps the most common indication being the prevention of embolic complications in patients with atrial fibrillation. The major risk of warfarin treatment is hemorrhage; the incidence varies from 10 to 24 episodes per 100 patients for all bleeding complications and from 1.2 to 7.0 episodes per 100 patients for major bleeding complications.[16] Similar considerations also apply to Phase II enzymes. For example, slow acetylation has been associated with a number of adverse effects, including vomiting with sulfasalazine[17], peripheral neuropathy with isoniazid[18,19] and SLE with procainamide.[20] More recently, a large number of functionally relevant polymorphisms have been identified in the various glucuronosyl transferase isoforms.[21] A pharmacogenetic study of 12 candidate genes in patients who had developed hepatotoxicity with the anti-Parkinsonian drug tolcapone[22] showed an association only with the Ala181 and Ser184 variants in the UGT1A gene complex. Multiple copies of functional CYP2D6 genes[23,24] were identified in individuals resulting in extremely rapid metabolism of nortriptyline.[15]

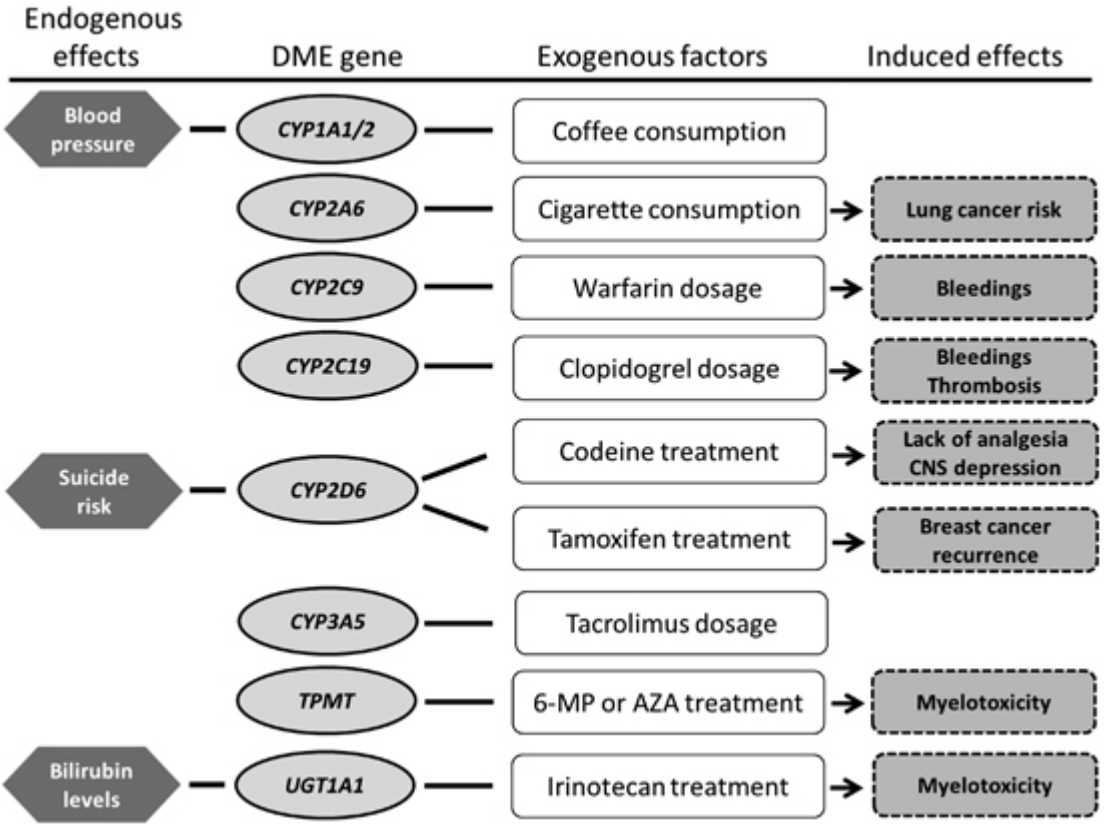

Figure 3. Summary of the major effects of DME polymorphism on clinical outcome of drug and exogenous exposure, as well as endogenous phenotypes. 6-MP: 6-mercaptopurine; AZA: azathioprine (Adopted from Sim *et al.*)[25]

Pharmacogenetics and drug safety. Interindividual variations in drug disposition are important causes for adverse drug reactions and lack of pharmacological action. The majority of phase I and phase II drug-metabolizing enzymes (DMEs) are polymorphic and considered as essential factors for the outcome of drug therapy. Genome-wide association (GWA) studies with a focus on drug response, as well as more targeted studies of genes encoding drug metabolizing enzymes (DMEs) have revealed in-depth information and provided additional information for variation in drug metabolism and drug response, resulting in increased knowledge of drug development and clinical therapeutics.

In general, variability in drug metabolism may lead to an ADR through one or more of the following mechanisms mentioned by Pirmohamed and Park.[26]

1. Increased concentration of the drug as a result of deficient metabolism leading to a dose dependent ADR;
2. Deficient enzyme activity results in rerouting of metabolism leading to an ADR;
3. Exaggerated drug response as a result of increased metabolism when the drug effect is dependent on the active metabolite rather than the parent drug;
4. Variability in the formation of the reactive metabolite leading to idiosyncratic drug toxicity; and
5. Decreased bio-inactivation of the reactive metabolite as a result of a deficiency in detoxification.

Although considerable challenges remain in predicting phenotype as well as in transforming this information into clinical guidelines for drug treatment of individual patients, there are already some promising examples of how genetic variation in drug metabolism can be taken into account in clinical practice to improve therapeutic outcome (Table 1).

Personalized medicine: An advanced and tailored therapy. Different people respond differently to the same therapy: while one treatment brings about the desired success in one group of patients with e.g., lung cancer, it does not change the condition of other groups at all, or even leads to adverse effects. The genetic makeup and metabolic profile of an individual patient influences the effect of a drug. Although genetic pretesting is not a clinical routine it can eliminate the serious side effects that supposed to be occur in a patient with abnormal gene function thus causing a bizarre metabolic pattern by a genetically variable enzyme. The adverse effects can be eliminated by giving the drug only when the patient's enzyme activity is normal or by reducing the drug dose if the activity is low.

Table 1. Examples of drugs for which pharmacogenomic information regarding DMEs is included in the drug label.

Biomarker	Drugs
CYP2D6 variants	Atomoxetine, fluoxetine, tamoxifen, metoprolol
CYP2C9 variants	Celecoxib, warfarin
CYP2C19 variants	Esomeprazole, omeprazole, voriconazole
NAT variants	Isoniazid, rifampin
TPMT variants	Azathioprine, merceptopurine
MTHFR variants	Methotrexate
UGT1A1 variants	Irinotecan

Several dosing guidelines have been published by Clinical Pharmacogenetics Implementation Consortium (CPIC) and approved by Food and Drug Administration (FDA) according to patient's genotype.[27-29] Warfarin is a widely used anticoagulant with a narrow therapeutic index and large interpatient variability in the dose required to achieve target anticoagulation. Common genetic variants in the cytochrome P450-2C9 (CYP2C9) and vitamin K–epoxide reductase complex (VKORC1) enzymes, in addition to known non-genetic factors, account for ~50% of warfarin dose variability. CPIC guidelines for warfarin dosing (in mg) to achieve a therapeutic International Normalized Ratio (INR) based on CYP2C9 and VKORC1 genotype are summarized in table 2. Genotypes that constitute the * alleles for CYP2C9 are shown in Table 3.

Similar type of recommendation is also available for abacavir, phenytoin, clopidogrel and some other drugs. In individuals with the HLA-B*57:01 variant allele ("HLA-B*57:01-positive"), abacavir is not recommended and should be considered only under exceptional circumstances.[28] Phenytoin is contraindicated in individuals with the HLA-B*15:02 variant allele ("HLA-B*15:02-positive") due to significantly increased risk of phenytoin-induced cutaneous adverse reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Additionally, patients with the CYP2C9 poor metabolizer phenotype may require reduced doses of phenytoin.[29]

Table 2. Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on *CYP2C9* and *VKORC1* genotype using the warfarin product insert approved by the US Food and Drug Administration.[27]

VKORC1:-1639 G>A	CYP2C9*1/*1	CYP2C9*1/*2	CYP2C9*1/*3	CYP2C9*2/*2	CYP2C9*2/*3	CYP2C9*3/*3
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

Table 3. Genotypes that constitute the * alleles for CYP2C9 gene.[27]

Allele	Constituted by genotypes at:	Amino acid changes	Enzymatic activity
*1	reference allele at all positions	No change	Normal
*2	C>T at rs1799853	R144C	Decreased
*3	A>C at rs1057910	I359L	Decreased

Current Pharmacogenetics Practice in Bangladesh. Several studies have already been carried out and published on interindividual variation in disease prognosis and the pharmacological action of different drugs. In cardiovascular pharmacogenetics, variation in CYP2C19 has been studied in clopidogrel and prasugrel effectiveness and the article is under publication procedure.[30] Warfarin dose adjustment in different CYP2C9 and VKORC1 genotype in Bangladeshi population is also under publication process. Genotype-phenotype variability in human CYP3A locus has been extensively studied in both Bangladeshi population[31] and Nepalese population residing in Bangladesh.[32] Variability in human CYP3A locus has also been studied in tuberculosis patients of Bangladesh.[33] Lung cancer risk in relation to nicotinic acetylcholine receptor, CYP2A6 and CYP1A1 genotypes in the Bangladeshi population has been reported by Islam MS *et al.*[34] and TP53 codon 72 and codon 47 polymorphism to lung cancer relation has been reported by Mostaid *et al.*.[35] Association of CYP3A4, CYP3A5 polymorphisms with lung cancer risk in Bangladeshi population is also reported by Islam *et al.*.[36] Pharmacogenetics of Methotrexate induced mucositis (MTHFR gene), azathioprine induced myelosuppression (TPMT gene), atorvastatin induced myopathy (SLCO1B1 gene) is still under investigation. Some private and government hospital already started pharmacogenetics practice to maintain CPIC dosing guideline for Warfarin, Clopidogrel and Azathioprine etc.

CONCLUSION

Recent advances in DNA sequencing and genotyping have made it possible to identify variation in DNA sequence and structure rapidly and accurately. As a result, it is now possible to correlate genomic variation with drug response, which helps us to predict individual variation in responses to specific drugs, to optimize drug selection and dose and to avoid adverse effects associated with drug therapy. Now it is time to assess whether pharmacogenomics and pharmacogenetics research has provided important insights into a personalized approach to prescribing and dosing medications. Implementation of pharmacogenetics and pharmacogenomics in pharmacotherapeutics and pharmacovigilance will eliminate the traditional “One size-Fits all” type prescription pattern.

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