Genetic polymorphisms of drug eliminating enzymes and transporters

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Abstract
The inter-individual variability in drug metabolism is considered as one of the most important factors that influence drug response i.e. efficacy and toxicity. This variability in drug response could be due to inhibition of the metabolic enzymes or transporters of drug elimination, co-administration of other drugs or the genetic variation in the metabolizer or transporter genes. When a given genetic variant is found in a certain population with a frequency of more than 1%, it is defined as polymorphic variant that results in an altered protein function. Based on the genetic polymorphism of drug metabolizing enzymes, a given population may be classified into three groups viz., (i) extensive metabolizers, carrying normal-function metabolic enzymes wherein levels of drug efficacy and drug elimination are balanced, (ii) ultra-extensive metabolizers, having extraordinary-function metabolic enzymes wherein drug elimination is enhanced, and (iii) poor-metabolizers with less active or no metabolic enzymes wherein drug accumulation is likely to occur due to reduced elimination. In the recent decade, several comprehensive studies have been conducted to investigate the genetic polymorphism of the metabolic enzymes and transporters in different ethnic groups. Such studies have enhanced our understanding of the mechanisms of drug toxicity in a given population as well as the ability to predict individuals who are predisposed to drug toxicity, reduced efficacy or environmental exposure-linked diseases. The present article reviews and discusses the genetic variants of genes that are heavily involved in drug elimination and transport.

Introduction
In general, prior to approval for the clinical use of a drug, extensive studies or trials have to be done to evaluate its efficacy and safety. The safety of drug treatment is a major concern since the toxicity and adverse drug reaction (ADR) have been identified as a significant factor in patient mortality. ADR can be defined as ‘an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medical product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regiment, or withdrawal of the product’ [1]. In the United States, drug toxicity and ADR occur in 1 out of 15 patients and represent the fourth to sixth leading cause of approximately 140,000 fatalities per year [2,3]. This forced the withdrawal of 10% of approved drugs from the market between 1975-1999 [4]. The economic burden resulting from drug-related morbidity and mortality in the US alone exceeded $177.4 billion in year 2000 [5]. Therefore, a better understanding of the underlying mechanism of ADR is necessary to prevent the significant outcomes of such a major health concern.

The pharmacologic or toxicological effect of a drug is related to the persisting level of the drug within the body where any modification in that level might alter body’s biochemical and/or physiological homeostasis. Any change in the processes of absorption, metabolism, distribution, or excretion affects the pharmacokinetic of drugs and their effects (Figure 1). Several polymorphisms that have been linked to variations in drug response involve genes that code for drug metabolizing enzymes and transporters.

Drug metabolism is an essential process by which human body gets rid of foreign lipophilic molecules usually via their conversion to more hydrophilic molecules that can be easily eliminated. Drug metabolism can be divided into two phases: phase-I (functionalization reactions) in which certain metabolic enzymes (mainly cytochrome P450 enzymes) metabolize drugs mainly via oxidation and to a lesser extent via reduction, hydrolysis and hydration, and Phase-II (conjugation reactions) in which sets of enzymes, such as UDP glucuronosyltransferases (UGTs), N-acetyl transferases (NATs), and esterases metabolize drugs via addition of large endogenous hydrophilic moieties (Figure 2).

Figure 1. The pathways most of drugs undergo in order to express their activities.
pro-carcinogens are activated by CYP1A1 and CYP1A2 [29]. CYP1A2 induce mutation [25-28]. It has been speculated that 90% of all known (PAHs), and aflatoxin B1 into intermediates that can bind DNA and for activation of nitrosamines, arylamines, polycyclic aromatic amines also been detected in the lungs and intestines. CYP1A is responsible expressed almost exclusively in the liver, although low expression has been identified in humans, among them only the first three families are divided into families and subfamilies [53-55]. UGT family 1 isoforms are derived from a single gene locus which spans more than 500 kb on chromosome 2q37. UGT1A comprises at least 12 promoters and first exons, which within the CYP2D subfamily in humans, CYP2D6 is the only active gene which is located in chromosome 10 [43]. CYP2D6 is expressed in the liver and to lesser extent in the intestines and brain. It is responsible for metabolizing a wide variety of prescribed drugs such as dextromethorphan and debiroside [40]. The CYP2D6 gene is characterized by its high genetic polymorphism and its resistance to induction [41,42].

The human CYP2E subfamily contains a single gene, CYP2E1, which is located in chromosome 7 [48]. CYP3A4 is highly expressed in the liver and intestines and to a lesser extent in the lungs. CYP3A4 is responsible for metabolism of a wide variety of drugs including nifedipine and erythromycin [49,50] and activation of many carcinogens such as polycyclic hydrocarbons (PAH) and aflatoxin B1 [25,27]. CYP3A4 is the most highly inducible CYP gene, and numerous pharmaceutical compounds, including rifampicin and dexamethasone, are able to enhance the expression of this gene [51,52].

UDP glucuronosyltransferase (UGT) enzyme

Conjugation with glucuronic acid is responsible for the elimination of a diverse range of xenobiotics and endogenous compounds in humans and other mammalian species. Glucuronidation serves as a clearance mechanism for drugs from almost all therapeutic classes, including dietary chemicals, environmental pollutants and chemical carcinogens, and phase-I oxidation products. Endogenous compounds metabolized by glucuronidation include bile acids, bilirubin, hydroxy-steroids and thyroid hormones. Although a number of bioactive glucuronides are known, glucuronidation is primarily considered a detoxification process. Glucuronidation reactions are catalyzed by UGT, the microsomal enzyme with a broad substrate profile. UGT genes have been classified into families and subfamilies based on evolutionary divergence, with all known UGT being included in the 1A, 2A and 2B subfamilies [53-55]. UGT family 1 isoforms are derived from a single gene locus which spans more than 500 kb on chromosome 2q37. UGT1A1 comprises at least 12 promoters and first exons, which are spliced separately to common exons 2-5 resulting in transcripts which encode enzymes with unique amino termini preceding an active gene which is located in chromosome 22 [39]. CYP2D6 is expressed in the liver and to lesser extent in the intestines and brain. It is responsible for metabolizing a wide variety of prescribed drugs such as dextromethorphan and debiroside [40]. The CYP2D6 gene is characterized by its high genetic polymorphism and its resistance to induction [41,42].

The human CYP3A subfamily consists of four genes, CYP3A4, CYP3A5, CYP3A7, and CYP3A43, which are located in chromosome 7 [48]. CYP3A4 is highly expressed in the liver and intestines and to a lesser extent in the lungs. CYP3A4 is responsible for metabolism of a wide variety of drugs including nifedipine and erythromycin [49,50] and activation of many carcinogens such as polycyclic hydrocarbons (PAH) and aflatoxin B1 [25,27]. CYP3A4 is the most highly inducible CYP gene, and numerous pharmaceutical compounds, including rifampicin and dexamethasone, are able to enhance the expression of this gene [51,52].

or proteins in human body can vary from one to another due to environmental factors, genetic variation also has a major impact.

**Cytochrome P_{450} (CYP) enzyme**

CYP are heme-containing, membrane-bound, and endoplasmic reticulum-located proteins [7,8] that catalyze the initial step in the oxidative metabolism of a plethora of endogenous (steroids, bile acids, fatty acids, prostaetlandins, leukotrienes, and biogenic amines) and exogenous (drugs, carcinogens, dietary supplements, pollutants, pesticides, and environmental chemicals) substances [9-14]. The name was derived from the cytochrome pigment (P) having a 450 nm ultraviolet spectral peak when reduced and bound to carbon monoxide [15-18].

Based on similarities in their protein sequences, CYP enzymes have been divided into families and subfamilies [10,19]. Enzymes with ≤40% sequence similarity are grouped into different families, designated by an Arabic number (e.g. CYP2). The enzymes with 40-55% similarity are grouped into different subfamilies, designated by an English alphabet (e.g. CYP2C). Enzymes with ≥55% similarity are classified as members of the same subfamily, and suffixed with Arabic number (e.g. CYP2C9). So far, fifty seven functional CYP genes and eighteen families have been identified in humans, among them only the first three families are involved in drug metabolism [15,20-23]. Of these CYP3A4 followed by 2D6, 2C8, and 2C19 contribute predominantly in metabolism of commonly used drugs (Figure 3).

The human CYP1A subfamily consists of two members, CYP1A1 and CYP1A2, which are located in chromosome 15 [24]. CYP1A2 is expressed almost exclusively in the liver, although low expression has also been detected in the lungs and intestines. CYP1A1 is responsible for activation of nitrosoamines, arylamines, polycyclic aromatic amines (PAHs), and aflatoxin B1 into intermediates that can bind DNA and induce mutation [25-28]. It has been speculated that 90% of all known pro-carcinogens are activated by CYP1A1 and CYP1A2 [29]. CYP1A2 is responsible for metabolism of some food supplements and drugs such as caffeine and theophylline [30,31], and is highly inducible by nicotine, charbroiled foods, and cruciferous vegetables [32,33].

The human CYP2C subfamily consists of four genes, CYP2C8, CYP2C9, CYP2C18, and CYP2C19, which are located in chromosome 10 [34]. CYP2C9 is the most abundant CYP2C protein expressed in the liver. Lower levels of CYP2C9 expression have been detected in the kidneys and intestines. CYP2C9 is responsible for metabolizing many drugs such as tolbutamide and S-warfarin [35,36]. Its expression is subjected to induction by many drugs including phenobarbital and rifampicin [37,38].

Within the CYP2D subfamily in humans, CYP2D6 is the only active gene which is located in chromosome 22 [39]. CYP2D6 is expressed in the liver and to lesser extent in the intestines and brain. It is responsible for metabolizing a wide variety of prescribed drugs such as dextromethorphan and debiroside [40]. The CYP2D6 gene is characterized by its high genetic polymorphism and its resistance to induction [41,42].

The human CYP2E subfamily contains a single gene, CYP2E1, which is located in chromosome 7 [43]. CYP2E1 is expressed mostly in the liver and to a lesser extent in the kidneys and lungs. It is responsible for metabolism of many compounds including ethanol and chlorzoxazone [44,45]. CYP2E1 expression is subject to induction by a variety of compounds such as ethanol and isoniazid [45-47].

The human CYP3A subfamily consists of four genes, CYP3A4, CYP3A5, CYP3A7, and CYP3A43, which are located in chromosome 7 [48]. CYP3A4 is highly expressed in the liver and intestines and to a lesser extent in the lungs. CYP3A4 is responsible for metabolism of a wide variety of drugs including nifedipine and erythromycin [49,50] and activation of many carcinogens such as polycyclic hydrocarbons (PAH) and aflatoxin B1 [25,27]. CYP3A4 is the most highly inducible CYP gene, and numerous pharmaceutical compounds, including rifampicin and dexamethasone, are able to enhance the expression of this gene [51,52].

**Cons of microwave heating**

- Causes water displacement.
- Leads to uneven cooking.
- Can result in nutritional loss.
- Increases the risk of foodborne illness.

**Pros of microwave heating**

- Efficient and energy-saving.
- Uniform cooking.
- Preservation of nutrients.
- Reduces cooking time.

**Cons of conventional cooking**

- More time-consuming.
- Uneven cooking.
- Higher risk of overcooking.
- May result in loss of nutrients.

**Pros of conventional cooking**

- Allows for Broiling, Grilling, Roasting, and Baking.
- Full control over temperature and cooking time.
- Can enhance flavor.
- May lead to crispy or seared textures.

**Cons of roasting**

- Requires preheating.
- Can lead to overcooking if not monitored.
- May result in dryness.

**Pros of roasting**

- Results in Juicy and tender meats.
- Full control over temperature and cooking time.
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followed by UGT1A1 contributes predominantly in drug metabolism [57].

**Drug transporter proteins**

Many prescribed medications or their metabolites exist as organic anions at physiological pH. These compounds are ultimately handled by the organic anion transport systems of the kidney, liver, and choroid plexus, perhaps the best studied of which is the ‘classic’ multispecific organic anion secretory pathway of the renal proximal tubule. The organic anion transporter (OAT) comprises OAT1 (slc22a6), the prototypical OAT, OAT2 (slc22a7), OAT3 (slc22a8), OAT4 (slc22a11), and OAT5. Substrates of this secretory pathway are strikingly diverse and include such clinically important pharmaceuticals as beta-lactam antibiotics, probenecid, loop and thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAID), and methotrexate, among others, as well as various endogenous compounds, including cyclic nucleotides, prostaglandins, folate, neurotransmitter-metabolites, and hormone-conjugates [58].

The ATP binding cassette (ABC) is a ubiquitous and important family of such transporter proteins. Members of this super family are present in mammals as well as in prokaryotic organisms and use ATP as the energy source to activate the extrusion process. P-glycoprotein (P-gp) is the most important and widely studied member of ABC super family. P-gp is anatomical localized in several normal human tissues with excretory (liver, kidney, adrenal gland) and barrier (intestine, blood-brain barrier, placenta, blood-testis and blood-ovarian barriers) functions. Recently, it has been found that P-gp has an important physiological role in detoxification and protection of the body against toxic xenobiotics and metabolites. Its detoxification role is carried out by secreting toxic compounds into bile, urine, and the intestinal lumen and by preventing their accumulation in human body. Additionally, clinically important ADR were reported when digoxin (a good P-gp substrate) used with other drugs, such as quinidine, verapamil, talinolol, clarithromycin, itraconazole, erythromycin, and propafenone [59].

Multidrug and toxin extrusion (MATE) proteins (METAE1, MATE2, MATE2-K and MATE2-B) are the recently identified transporter that mediates the final excretion step for organic cations [60,61]. The MATE-mediated transport is driven by oppositely directed proton gradient, and are therefore, considered secondary active transporters. MATE proteins are involved in physiological and/or pharmacological processes such as pharmacokinetics, resistance in tumor tissues, and hormone secretion. Because of its importance, drug regulatory authorities are considering incorporation of MATE enzymes into their guidelines.

**Regulation of drug metabolizer and transporter genes**

The Level of any given protein is primarily regulated via controlled gene expression, a process in which the gene produces protein via transcription followed by translation.Modulation (inhibition or induction) of the activity of a given protein could be due to direct effect on the protein its modulator or through alteration in gene expression [62]. For instance, it has been found that the induction of CYP450 enzymes was attributed to elevation in the transcriptional activity of CYP genes [63,64]. Many CYP subfamilies including CYP1A, CYP2B, CYP2C, and CYP3A, are highly inducible by xenobiotics [21]. Therefore, the outcome of enzyme induction depends on the pharmacological activity of the parent compounds and their metabolites.

When the parent compound is the active therapeutic agent, then the net effect of enzyme induction could be loss of the pharmacological efficacy. For example, rifampicin increases the CYP3A4-dependent metabolism of cyclosporine resulting in rejection of the transplanted organ by the body [65]. On the other hand, when the metabolite is more active than the parent compound or toxic, then the induction will increase the chance for toxicity. For example, ethanol increases the CYP2E1-dependent metabolism of acetaminophen resulting in formation of its hepatotoxic metabolite (N-acetyl-p-benzoquinoneimine) [66]. The examples mentioned as well as many others all reveal the clinical consequences of Drug elimination enzymes induction and suggest that more studies are required in order to fully understand the mechanisms underlying their regulation.

In the recent decade, extensive efforts have been made to understand the molecular mechanisms underlying the expression of CYP enzymes. It has been found that the induction of CYP enzymes is primarily regulated by a group of orphan nuclear receptors. They are called orphans because they were identified without knowing their endogenous or exogenous ligands [67]. These receptors share two essential functional domains that include the N-terminal DNA-binding domain (DBD) and the C-terminal ligand-binding domain (LBD) [68]. The conserved DBD acts to link the receptor to specific 5′-flanking region (5′-FR) element in its target gene called the xenobiotic responsive element (XRE) [67]. The less conserved LBD has at least four functions: ligand binding, binding of co-activators or co-repressors, dimerization, and transactivation [69]. Nuclear receptors were considered prime candidates for mediating hepatic drug induction for several reasons [21]. First, their ligands are small and lipophilic similar to those of CYP enzymes. They bind to specific DNA elements similar to those found in the 5′-flanking sequences (5′-Fs) of CYP genes. Furthermore, they are expressed in specific tissues where most CYP enzymes are expressed. Finally, they play key roles in many physiological processes in which P<sub>450</sub> enzymes are involved.

The most studied nuclear orphan receptor is the pregnane X receptor (PXR). PXR was isolated and identified as a key regulator in CYP3A expression in 1998 [70-72], although recent studies have disclosed its regulatory role for other CYP genes such as CYP2C and CYP2B [73,74]. PXR is expressed predominantly in the liver and intestines and to a lesser extent in the kidneys and lungs [75]. Many chemicals including prescription drugs, steroids, and environmental factors are able to bind and activate PXR [70,76]. For example, the antibiotic rifampicin and the antidepressant herbal product hyperforin are potent PXR activators [77,78]. The biochemical process of PXR activation has been illustrated [68]. Upon ligand binding, a conformational change in the LBD creates a co-activator (e.g. steroid receptor coactivator-1, SRC-1) binding surface; and transcriptional activation occurs after recruitment of co-activator to the receptor [69]. Subsequently, PXR regulates gene expression by forming a heterodimer with the retinoid X receptor (RXRα) and then regulation is achieved by binding of the PXR-RXRα heterodimer to XRE present in the 5′-FR of the target gene (Figure 4). The unique feature of PXR-mediated induction is its species specificity, primarily due to the differences in LBD [70]. For example, rifampicin is a potent activator for human PXR but not the rodent isofrom, whereas pregnenolone-16α-carbonitrile (PCN), an anti-glucocorticoid, is a rodent-specific activator. PXR-humanized mice have been generated [79] and in these transgenic mice the profile of PXR-based induction was similar to the human profile.

Another important nuclear receptor is the constitutive androstane receptor (CAR). CAR was first isolated in 1994, but its role in CYP2B induction was not appreciated until 1998 [80-82]. CAR also can
regulate other CYP genes such as CYP3A and CYP2C [83,84]. CAR is expressed predominantly in the liver and intestines and can be activated by many drugs such as phenobarbital and phenytoin. The mechanism of CAR activation is more complex than that of PXR. CAR is cytosolic protein and upon activation, it translocates into the nucleus and forms a heterodimer with RXRα. Similar to PXR, it is the heterodimer that binds to target gene sequence and activates transcription [85-87]. Phenobarbital activates CAR by facilitating its nuclear translocation through a phosphorylation-based mechanism [85,87,88]. The only molecules shown to directly bind CAR were androstane and clortalidione which are inverse agonists that deactivate the response [89]. Like PXR, CAR shows species differences in its induction profile, for example 1,4-bis[(3.5 dichloropyridyloxy)]benzene (TCPBOB) was found to be specific mouse CAR activator [88,90]. The broad role of CAR and PXR in regulating many metabolizing enzymes and transporters and cross-regulation of gene expression has been reported [91].

Perhaps the most well studied nuclear receptor is the aryl-hydrocarbon receptor (AhR). AhR has been known to be a CYP1A regulator [91-94]. AhR is a helix-loop-helix protein that belongs to the polycyclic aromatic hydrocarbon (PAH) family of transcription factors. Similar to CAR, AhR is a cytosolic protein and becomes activated once activated by its ligand. Consequently, the activated receptor translocates into the nucleus, forms a heterodimer with its nuclear translocator protein (ARNT), binds to XRE sequences upstream of CYP1 genes, and activates gene transcription [95,96]. AhR-dependent induction is conserved among many cell types and across animal species. A significant number of substances were found to be ligands for AhR including omeprazole as well as several important environmental carcinogens found in auto exhaust and cigarette smoke [97,98].

Other nuclear receptors are also known to involve in CYP regulation. For example, the peroxisome proliferator-activated receptor (PPARα) regulates CYP4A [99-101] and the vitamin D receptor (VDR) regulates CYP3A, CYP2B, CYP2C, and CYP24 [102-103]. The liver X receptor (LXR) and the farnesol X receptor (FXR) both regulate the expression of CYP7A [104-107]. Additionally, some transcriptional factors play crucial role in CYP regulation. For example, the hepatic nuclear factor (HNF1α) regulates the expression of CYP2E1, CYP1A2, CYP7A1, and CYP27 [108] and the HNF4α regulates CYP3A, CYP2C, CYP2D6, CYP2A6, and CYP2B [109-111]. Other transcriptional factors such as the HNF3γ regulates CYP2C [112] while the CAAT/ enhancer binding protein (C/EBP) regulates the expression of CYP2B, CYP2D, and CYP2C [113]. Similar to CYP450 genes, expression levels of P-gp, OAT, and of course UGTs were found to be greatly regulated by nuclear receptors, the pregnancy X receptor (PXR) particularly [114,115].

The mammalian MATE 1 is encoded by SLC47A1 gene. Polymorphisms in SLC47A1 genes may affect renal excretion of substrate drugs, such as metformin, resulting in inadequate pharmacotherapy or occurrence of toxic effects [116]. However, expression and function of MATE enzymes in tissues other than kidney and liver remain to be elucidated.

Conclusion

The efficacy as well as safety of therapeutic drugs is a major concern in patient management where inter-individual genetic variability in drug metabolizer and transporter genes greatly influences drug response. Ample of studies on molecular mechanisms of such the genetic polymorphism have enhanced our understanding of drug metabolism, and to predict its toxicity in a given population. Nevertheless, a comprehensive and better understanding of the drug toxicity is necessary to prevent the significant outcomes of such a major health concern.

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