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## Genetic Variation in Drug Disposition

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### 1. Introduction

Genetic variation is an important source of pharmacokinetic variability and leads to modification of drug response. It is one of the several factors contributing to variability in drug disposition. Any alteration in drug disposition, influences circulating drug concentrations, as well as the concentrations at the sites of action. Drug disposition is mainly affected by drug metabolizing enzymes, drug transport proteins, plasma protein binding and transcription factors. The knowledge about the factors influencing drug disposition is useful in predicting potential drug interactions and pharmacokinetic variations. Among the above factors the most important mechanism by which genetic variation modifies drug response is by altering drug metabolizing enzymes that in turn alter drug metabolism. These enzymes are proteins that catalyse the chemical alteration of drugs and other molecules inside the body. Metabolism converts most of the drug to inactive product but few others to more toxic product. The main organ for drug metabolism is liver; kidney, GI mucosa and lungs play smaller role. The drug metabolizing enzymes can either be functionalizing (oxidation, reduction, and hydrolysis) or conjugating (glutathione, glucuronide). Genetic variation in drug metabolizing enzymes can either increase or decrease drug metabolism. For example some individuals have genetically determined insufficiency to metabolise succinylcholine, a short-acting neuromuscular-blocking drug, widely used as muscle relaxant and in anaesthesia. It is normally rapidly hydrolysed by plasma cholinesterase. If succinylcholine is administered to such individual, he/she fails to inactivate succinylcholine rapidly and experiences prolonged neuromuscular block. This is because a recessive gene gives rise to an abnormal type of plasma cholinesterase and this abnormal enzyme has a modified pattern of substrate and inhibitor specificity.

Plasma binding proteins often bind a large fraction of a drug in circulation Binding varies from drug to drug. Sometimes drug bind more than 99%. Albumin is main plasma protein to which drug bind and mostly acidic drug bind with plasma albumin. Other drug binding plasma proteins are globulin, alpha acid glycoprotein etc. Protein binding affects pharmacology of drug. It alters unbound drug concentration in circulation and only unbound (free) drug can enter tissues. So any genetic variation in plasma protein brings about variation in drug response. Similarly, transcription factors are proteins that regulate gene expression. When bound to exogenous chemicals, certain transcription factors induce the expression of drug metabolizing enzymes and modify drug response. Some genetically

determined drug response based on factor other than pharmacokinetic variation. Consider an example of the individuals having red blood cells deficient in an enzyme called glucose-6-phosphate dehydrogenase. Deficiency of this enzyme increases the risk of hemolysis, if certain drugs such as aspirin and sulfonamides are administered.

Differences in metabolism, transportation, plasma protein binding of drugs are significant factors affecting drug disposition and results modification of drug action. This chapter summarizes the reviews of the findings on genetic variation related with drug disposition.

Genetic variation is an important source of pharmacokinetic as well as pharmacodynamic variability and leads to modification of drug response. It is one of several factors contributing to variability in drug disposition. The branch of science that deals with individual variation in drug response is termed pharmacogenetics. It deals with the genetic basis of variability of drug response in an individual and is a useful parameter for individualization of drug therapy. It is a rapidly emerging branch in which thousands of studies are carried out annually. Besides, it has important role in clinical practice and on drug development.

Recently, pharmacogenetic deals with the study of drug response in unrelated individuals. The difference in drug response is due to the variation of genotype, that encodes for drug-metabolizing enzymes, receptors for the drug, drug transport proteins, transcription factors and various ion channels. A change in genotype or a mutation in gene sequence may increase quantity and/ or activity of a protein or an essential enzyme. In some cases, such a change results in an exaggerated or reduced therapeutic response to a drug. In general, variation in genotype account for 15%–30% of inter-individual differences in drug metabolism and response, but for some drugs, genetic factors are of most common and account for up to 95% of inter-individual variability in drug disposition and effects.

The important drugs under different therapeutic categories are shown in Table 1.

The knowledge about the factor influencing drug disposition is useful in predicting potential drug interaction and pharmacokinetic variation.

The genetic mechanisms for variation of drug response are variation in gene sequence. It includes changes in the primary nucleotide sequence of coding, regulatory, and splice regions of a gene. Less common forms are variability in the structure and function of the genome. Among these are sequence variation in microRNA (miRNA) binding sites, which affects the ability of miRNA to regulate translation; pharmacoepigenetics, which examines heritable chromatin modifications; and copy number variation.

## 2. Pharmacokinetic variability

The effectiveness of the medication is determined by how much of the drug is present at its site of action and how long sufficient concentrations of the drug remain at the site. Pharmacokinetics is the quantitative study of the time course of drug concentration in the body. It is the term used to describe the disposition of a drug throughout the body – that is, the drug's absorption, distribution, metabolism, and excretion (ADME). Pharmacokinetic variability is the variation in drug movement throughout the body. Drugs produce an effect

CYP2D6		CYP2C9	CYP2C19
<b>Analgesica, Antitussives</b>	<b>Antiemetics</b>	<b>Angiotensin II blockers</b>	<b>Anticonvulsants, hypnosedatives, muscle relaxants</b>
Codeine	Ondansetron	Irbesartan	Diazepam
Dextromethorphan	Tropisetron	Losartan	Phenytoin
Ethylmorphine			
Tramadol	<b>Antiestrogen</b>	<b>Anticonvulsant</b>	<b>Antidepressants</b>
	Tamoxifen	Phenytoin	Amitriptyline
<b>Antiarrhythmics</b>			Citalopram
Flecainide	<b>Antipsychotics</b>	<b>Antidiabetics</b>	Clomipramine
Mexiletine	Haloperidol	Glibenclamide	Imipramine
Propafenone	Perphenazine	Glimepiride	Moclobemide
	Risperidone	Glipizide	
<b>Antidepressants</b>	Thioridazine	Nateglinide	<b>Anti-infectives</b>
Amitriptyline	Zuclopenthixol		Proguanil
Doxepin		<b>Anti-inflammatories</b>	Voriconazole
Fluoxetine	<b>β-blockers</b>	Celecoxib	
Fluvoxamine	Metoprolol	Diclofenac	<b>Proton pump inhibitors</b>
Imipramine	Propranolol	Ibuprofen	Omeprazole
Maprotiline	Timolol	Piroxicam	Lansoprazole
Mianserin		Tenoxicam	Pantoprazole
Nortriptyline			Rabeprazole
Paroxetine		<b>HMG-CoA reductase inhibitor</b>	
Venlafaxine		Fluvastatin	<b>β-blocker</b>
		<b>Oral anticoagulant (S)-Warfarin</b>	Propranolol

Sistonen J.Pharmacogenetic variation at CYP2D6, CYP2C9, AND CYP2C19. Population Genetic and Forensic Aspects Department of Forensic Medicine University of Helsinki Finland 2008

Table 1. Common drug substrates of CYP2D6, CYP2C9, and CYP2C19 according to therapeutic Categories

only if they can reach its physiological target(s) in sufficient concentration. These processes determine the fate of a drug in the body. A combination of metabolism and excretion constitutes drug elimination. Following factors are the sources of individual variation in drug disposition.

- 1. Drug-metabolizing enzymes,
- 2. Drug transport proteins,
- 3. Receptors for the drug,
- 4. Various ion channels

## 2.1 Drug-metabolizing enzymes

Metabolism is biochemical reaction that takes place inside body. Almost all tissues are capable to metabolize drugs but the liver is the major site of metabolism. Besides liver, GI tract, kidney and lungs also metabolize certain fraction of drug. The main objective of metabolism is to convert lipophilic to hydrophilic so that drug is easily excreted from the body. In general, metabolites lack pharmacological activity and are more water soluble than the parent substance. But in few conditions, active metabolites are formed from inactive parent drugs; such parent drugs are termed as *prodrug*. The chemical reactions that involve in drug metabolism are categories into two types – Phase 1 reactions and – Phase 2 or *conjugation* reactions.

Phase 1 reactions occur in the cytosol, mitochondria, microsomes of cells of the liver and other organs. It includes oxidation, reduction, hydrolysis, cyclization and decyclization reactions. Much phase I drug metabolism is performed by polymorphic enzymes, particularly various forms of cytochrome P450 (CYP). The influence of genetic polymorphisms of drugs metabolized by CYP2C9, CYP2C19, and CYP2D6 indicates polymorphisms and affects the metabolism of 20%–30% drugs.

In Phase 2 reaction drugs or metabolites combine with other substances and results in increased water solubility of the substance, which decreases the amount that is reabsorbed through renal tubules and thereby increases the fraction that is excreted in the urine. It is also known as conjugation. The most common conjugation reaction is glucuronide, glycine, glutathione, glutamate and sulfate conjugation.

The cytochrome P450s are a multigene family of enzymes found predominantly in the liver, that are responsible for metabolism. Genetically determined variability in the level of expression or function of these enzymes has a profound effect on drug efficacy. Genetic polymorphisms for many drug-metabolizing enzymes and drug targets have been identified. Polymorphisms refer to sequence variations with an allele frequency of greater than or equal to 1%. Polymorphism in any one of many genes—including those encoding drug receptors, drug transporter are important determinants of clinical response. Polymorphisms have now been identified in more than 20 human drug metabolizing enzymes. Important examples are polymorphisms in the cytochrome P450 enzymes and in thiopurine methyltransferase. Polymorphism not only affects drug disposition but can also be important in the conversion of prodrugs into their active form. For example, codeine is metabolized into the analgesic morphine by CYP2D6, and the desired analgesic effect is not achieved in CYP2D6 poor metabolizers.

Cytochrome P450 system refers to a family of enzymes (usually hepatic) which are located on the endoplasmic reticulum, which performs oxidative metabolism of broad array of substances. Cytochrome P450 comprises the most important group of phase I enzymes. The most important CYP 450 enzymes are:

CYP3A4 (50% of P450 metabolism) followed by  
CYP2D6 (20%),  
CYP2C9 and CYP2C19 (together 15%)  
Others: CYP2E1, CYP2A6, and CYP1A2.



2.1.1 Some common drug metabolizing enzymes and genetic polymorphisms

*CYP2D6*– The notable substrates for this enzyme include the tricyclic antidepressants amitriptyline, clomipramine, desipramine, amphetamines,  $\beta$ -blockers, imipramine, and nortriptyline. Metabolism of these drugs is influenced by the polymorphism in gene that code *CYP2D6*. Polymorphism in gene that code *CYP2D6* may either reduce the rate of the metabolism and increased plasma concentrations of above mentioned drugs when given in recommended doses, or it may enhance the rate of metabolism and results into therapeutic failure because the drug concentrations at normal doses are far too low.

*CYP 3A4*- The notable substrates for this enzyme include alprazolam, triazolam, carbamazepine, methadone, pimozide, quetiapine, risperidone, zolpidem.

Isoform	Examples of drug substrates	Nature of polymorphism	Effect on activity
<i>CYP1A2</i>	Clozapine, olanzapine theophylline and caffeine	Polymorphisms in non-coding sequences may affect expression or induction.	No absence of activity reported. Some effects on expression or induction.
<i>CYP2A6</i>	Coumarin and nicotine	Non-synonymous mutations, large deletion and upstream polymorphisms.	Absence of activity seen at low frequency. Ultrarapid metabolizers may also occur.
<i>CYP2B6</i>	Cyclophosphamide and efavirenz	Non-synonymous and upstream polymorphisms.	No absence of activity reported. Variation in activity common.
<i>CYP2C8</i>	Paclitaxel, retinoic acid, rosiglitazone and repaglinide	Non-synonymous and upstream polymorphisms.	No absence of activity reported. Variation in activity common.
<i>CYP2C9</i>	Warfarin, ibuprofen, diclofenac, tolbutamide and phenytoin	Non-synonymous polymorphisms common. Also upstream polymorphisms.	Very low activity in some individuals.
<i>CYP2C19</i>	Omeprazole, diazepam, clobazam and clopidogrel	Splice site, initiation codon, non-synonymous and upstream polymorphisms.	Absence of activity common. Some ultrarapid metabolizers.
<i>CYP2D6</i>	Codeine, amitriptyline, nortriptyline, tamoxifen, metoprolol, timolol, tropisetron, dextromethorphan, atomoxetine, venlafaxine thioridazine, zuclopenthixol, perphenazine, risperidone and haloperidol.	Splice site, small and large deletions and non-synonymous polymorphisms. Duplication and other amplifications.	Absence of activity common. Some ultrarapid metabolizers.
<i>CYP2E1</i>	Ethanol and Isoniazid	Non-synonymous polymorphisms rare. Upstream polymorphisms common.	No absence of activity reported. Some variation in activity.
<i>CYP3A4</i>	Midazolam, cyclosporine, tacrolimus, erythromycin, nifedipine, simvastatin, atorvastatin, diltiazem verapamil, vincristine and dapsone	Non-synonymous polymorphisms rare. Upstream polymorphisms common.	No absence of activity reported. Some variation in activity.
<i>CYP3A5</i>	Broadly similar to <i>CYP3A4</i> above	Non-synonymous polymorphisms rare. Splice site polymorphisms common.	Absence of activity common.

Daly AK. Pharmacogenetics and human genetic polymorphisms (2010). Biochem. J. 429: 435–449

Table 2. CYP genes and polymorphic drug metabolism

*CYP2C9* – The notable substrates for this enzyme include warfarin. tolbutamide, glipizide, and phenytoin.

The CYP genes (See Table 2) have well characterized roles in pharmacogenetic studies on drug metabolism. Other CYP genes also contribute to drug and xenobiotic metabolism or have physiological roles, but pharmacogenetic data is more limited.

2.2 Drug transport protein

In addition to metabolizing enzymes, drug transport proteins also contribute to alteration in drug disposition. Many drugs are transferred by active transporter systems, membrane proteins that maintain both inward and outward transport of drugs and their metabolites in cells. Variation in a drug transporter producing a clinical impact is less common than is

observed for other pharmacokinetic mechanisms. However, there are examples of variation in drug transport that can be attributed to adverse drug effects. One such example is the *SLCO1B1* gene that encodes a polypeptide, OATP1B1, which mediates hepatic uptake of anionic drugs, including most HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) inhibitors (statins). Although statins are the safest drugs, they sometimes develop myopathy in relatively small percentage of treated individuals. Variability in drug transporters also contributes to resistance to a variety of medicines, most commonly observed in the treatment of a variety of cancers.

Transport proteins are embedded in the cell membrane and responsible for transport of endogenous compounds or drugs into the cell or outside of the cell i.e. across the biological membranes. They are classified into either efflux or uptake proteins, depending on the direction of transport. The extent of expression of genes coding for transport proteins can have a profound effect on the bioavailability and pharmacokinetics of various drugs. Additionally, genetic variation such as single-nucleotide polymorphisms (SNPs) of the transport proteins can cause differences in the uptake or efflux of drugs. Genetic variants of transport proteins can cause or contribute to a number of diseases, such as anemia.

There are two superfamilies of transport proteins that have important effects on the absorption, distribution, and excretion of drugs. These are the ATP-binding cassette (ABC) and the solute-carrier (SLC) superfamilies.

ATP-binding cassette (ABC) transporters are present in cellular and intracellular membranes and can be responsible for either importing (influx) or removing (efflux) of substances from cells and tissues. They often transport substances against a concentration gradient by using the hydrolysis of ATP to drive the transport.

### 2.2.1 ABC transporters

There are at least 49 ABC transporter genes. These genes are particularly important for drug transport. Genetic polymorphisms affecting ABC transporter genes expression or changing their affinity for substrates and alter the absorption and elimination of drugs. It also alters drug concentrations at the site of action despite similar blood concentration. The majority of ABC transporters move compounds from the cytoplasm to the outside of a cell, although some of them move compounds into an intercellular compartment such as the endoplasmic reticulum, mitochondria, or peroxisome. ATP-binding transporters are responsible for the efflux of drugs and substrates, including bilirubin, several anticancer drugs, cardiac glycosides, immunosuppressive agents and glucocorticoids.

### 2.2.2 Solute Carrier Proteins

Solute carrier proteins (SLCs) are important in the transport of ions and organic substances across biological membranes in the maintenance of homeostasis. Members of the SLC superfamily consist of membrane channels, facilitative transporters, and secondary active transporters. Examples of some of the endogenous solutes that are transported include steroid hormones, thyroid hormones, and prostaglandins. Additionally, SLCs are important in the transport of a large number of drugs. In all, more than 40 families of transporters make up the SLC superfamily. Genetic variants of solute carrier proteins, such as *SLC6A3* gene encodes for the dopamine transporter DAT1, the *SLC6A4* gene codes for the serotonin transporter (SERT) that has been associated with variation in drug response.

### 2.3 Receptors for the drug

Receptors are the macromolecules that are located in cell membrane or inside cell or in organism to which drugs bind to initiate the series of biochemical reaction that leads to biological response. Most receptors are regulatory proteins (hormones, neurotransmitter), enzymes (dihydrofolate reductase), transport proteins ( $\text{Na}^+/\text{K}^+$  ATPase) and structural proteins (tubulin). Sequential variations in the receptor protein can affect target molecules or the structural integrity of the receptor and change ligand binding.

Genetic variation not only varies towards drug response by altering metabolism but also have important role in drug receptors. A growing number of drug targets (e.g., receptors) are known to exhibit genetic polymorphisms and alter drug response in humans. Many researches have been conducted to show polymorphisms in the gene encoding receptor/effectors contribute variation in drug response e.g.  $\beta$ 2-adrenergic receptor, is encoded by the gene ADRB2. This receptor interacts with endogenous catecholamines and various medications altering the effects of medications. Polymorphisms in the gene encoding this receptor have been associated with altered expression, down-regulation, and altered cell signaling and finally on clinical responses to endogenous and exogenous agonists.

### 2.4 Various ion channels

Ion channels are multimeric protein complexes and exert functionally overlapping control over excitability and signaling in both the plasma membrane and intracellular organelles. These channels control the electrical activity of muscles and nerves. There are various genes encoding the ion channels that have been identified.

Ion channel genes constitute about 1.2% of known protein coding genes. Mutations of these genes alter the functioning of ion channel resulting into a diverse array of clinical disorders in the body, especially in brain, nerve, muscle and heart. Predisposition of some common disorders like migraine and epilepsy might be mediated by genetic variation in ion-channel genes. Genetic variation in cellular ion transporter can also have a role in the alteration of drug response.

The most important ionic pores for generation and control of the action potential are voltage-dependent sodium and potassium channels. Specific genes coding for these channels are expressed in the central nervous system. So, it could be expected that a mutation in these genes may be at the origin of unbalance between excitation and inhibition and thus could cause epilepsy. Three types of epilepsies have been linked to mutations in human genes encoding subunits of:

- The neuronal nicotinic acetyl choline receptor (nAChR) ( $\alpha$ 4, *CHRNA4*, and  $\beta$ 2, *CHRNA2*, subunits),
- The voltage-gated potassium (*KCNQ2*, *KCNQ3*) channels and
- The voltage-gated sodium (*SCN1A*, *SCN1B*) channels.

Mutations in *CHRNA4* and *CHRNA2* are associated with some cases of familial epilepsies classified as autosomal dominant nocturnal frontal lobe epilepsies with an important intra and interfamilial clinical heterogeneity. Mutations in voltage-gated potassium channels *KCNQ2* and *KCNQ3* have been identified in benign familial neonatal convulsions.



The sodium channel is composed of four homologous domains that contain well-characterized voltage-sensing and pore regions. The four domains form a sodium-permeable pore within the membrane that is remarkably selective for the individual ion that it conducts. Each domain comprises six membrane-spanning segments, each of which has an  $\alpha$ -helical structure. And each sodium channel  $\alpha$  subunit associates with one or more different  $\beta$  subunits. This association of  $\alpha$  and  $\beta$  auxiliary subunits has an important influence on the voltage dependence, kinetics and cell-surface expression of most voltage-gated ion channels. Most neurological channelopathies associated with dysfunction of voltage-gated ion channels are caused by mutations in the gene encoding the pore-forming subunit.

Myotonia is a clinical disorder in which patients experience muscle stiffness because of a failure of normal electrical inactivation of activated muscle. Myotonia can result from mutations in either the *CLCN1* gene, that encodes the muscle voltage-gated chloride channel, or *SCN4A* encoding the voltage-gated sodium channel.

### 3. Pharmacogenetics and adverse drug reactions

Drug is any substance or product that is used or intended to be used to modify or explore the physiological system or pathological state for the benefit of the recipients. Interacting with receptors drugs not only produce desired effect but also produce undesired effect. Most undesirable effect associated with drugs is overdose/ poisoning, development of resistance, and adverse drug reaction (ADR). Amongst these effects ADR are important and leads to morbidity and mortality. Fortunately, when drugs are used properly, many ADR can be avoided or at least kept to a minimum. According to WHO 'ADR is any noxious, unintended and undesirable effect that occur at doses normally used in men for prophylaxis, diagnosis or therapy of the disease or modification of physiological function'. Adverse effect to drug may develop promptly or only after prolonged medication or even after stoppage of medications. Type B ADRs, which are not directly predictable from drug pharmacology and are unrelated to pharmacological actions of the drugs and often caused by immunological and pharmacogenetic mechanism, these effects are rare, but they are potentially very serious consequences for the patient. Type A (Predictable), can be predictable from drug pharmacology and is dose dependent. It is common and found to occur in 80%. It includes side effects, toxic effect, withdrawal symptoms.

Polymorphisms in the genes that code for drug-metabolizing enzymes, drug transporters, drug receptors, and ion channels can alter drugs pharmacokinetics as well as pharmacodynamics. Polymorphism results in individual's risk of having adverse drug reactions

Some pharmacogenetically determined adverse drug reactions include prolonged muscle relaxation after succinylcholine injection due to inherited deficiency of a plasma cholinesterase, resulting alteration of metabolism. Haemolysis is caused by antimalarials and sulfonamides due to glucose-6-phosphate dehydrogenase deficiency.

It was found that the genetic polymorphism of the drug-metabolising enzyme CYP2D6 due to the antiarrhythmic drug, sparteine, is responsible for adverse drug reactions such as nausea, diplopia, and blurred vision. Similarly, orthostatic hypotension after the antihypertensive agent debrisoquine is also due to genetic polymorphism. It was found that ticlopidine induced hepatotoxicity. The incidence of hepatotoxicity is more common among Japanese patients than Europeans because hepatotoxicity is associated with *HLA* (human

leucocyte antigen) genes. HLA gene is predominantly presented in Japanese. Carbamazepine, a widely used anticonvulsant, can cause hypersensitivity reactions but rarely showed Stevens–Johnson syndrome. Various study showed that Taiwanese have high incidence of CBZ-induced Stevens–Johnson syndrome because they have very strong association between the *HLA gene* and CBZ-induced SJS.

#### 4. Clinical applications

The importance of genetic variation has been best illustrated by the approval of BiDil, a cardiovascular combination product of isosorbide dinitrate and hydralazine, by FDA for the Afro-American population in 2005. Similar race- or gene-specific drugs are likely to be marketed in near future as a response to need for safer and more effective drugs.

##### 4.1 Cancer treatment

Genetic variation at *CYP2D6* has important therapeutic implications in cancer treatment. Tamoxifen are used to treat breast cancer. It is a pro-drug, requiring metabolic activation to active metabolites endoxifen and 4-hydroxytamoxifen. These reactions are catalyzed by *CYP2D6*. Variation in gene coding *CYP2D6* enzyme activity has been shown to affect tamoxifen treatment outcomes. Besides, *CYP2D6* polymorphism can also affect the efficacy of antiemetic drugs, which are often used for nausea and vomiting induced by cancer chemotherapy. Serotonin type receptor antagonist ondansetron, is metabolized by enzyme *CYP2D6*. *CYP2D6*-related rapid metabolism decrease therapeutic effect (severe emesis) and dose adjustment is necessary.

##### 4.2 Oral anticoagulation therapy

Warfarin, as the most commonly used anticoagulation therapy, is indicated for the prophylaxis and/or treatment of thromboembolism. It is also indicated for treatment and prophylaxis of deep vein thrombosis, acute myocardial infarction, and stroke. Warfarine act as vitamin K antagonists by inhibiting the liver microsomal enzyme, vitamin K epoxide reductase, which is essential in the vitamin K cycle and formation of clotting factors.

Warfarin is administered as a racemic mixture of *R*- and *S*-enantiomers, the latter of which is predominantly responsible for the anticoagulant effect and metabolized by *CYP2C9*. Similar doses of warfarin given to different individuals can result in varied drug responses. Patients with a two genetic variants have a significantly increased occurrence of a serious or life-threatening bleeding incident. This is due genetic polymorphism of drug metabolizing enzyme *CYP2C9*.

##### 4.3 Proton Pump Inhibitor (PPI) therapy

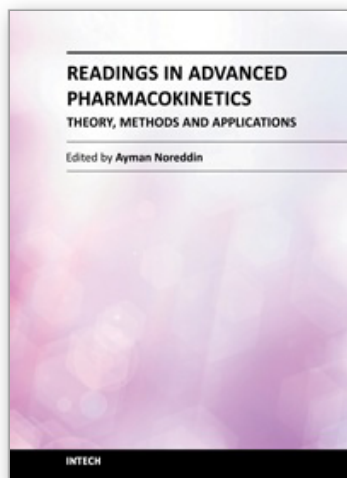
PPIs, such as omeprazole, lansoprazole, are widely used for the treatment of acid-related diseases, including gastroesophageal reflux disease and peptic ulcer, as well as for the eradication of *Helicobacter pylori* in combination with antibiotics. PPIs are mainly metabolized by *CYP2C19* in the liver, and the clinical outcome of drug therapy depends on genetic variation at the encoding gene *CYP2C19*. Ultra-rapid *CYP2C19*-related metabolism is an important factor contributing to therapeutic failures in drug treatment with PPIs, especially in European populations.

#### 4.4 Psychiatric drug therapy

Genetic variation is an important factor for the variation in psychiatric drug response. The meta-analysis conducted by Kirchheiner *et al.* showed that of 36 commonly used antidepressants, for 20 of those, data on polymorphic CYP2D6 or CYP2C19 were found and that in 14 drugs such genetic variation would require at least doubling of the dose in extensive metabolizers in comparison to poor metabolizers. They also showed that out of 38 antipsychotics, CYP2D6 and CYP2C19 genotype was of relevant in 13 drugs. Amitriptyline has relatively narrow therapeutic range and high toxicity at increased concentrations, leading to severe adverse effects. The main CYPs involved in amitriptyline metabolism are CYP2C19. Genetic variation of these enzymes has been shown to correlate with the serum concentrations of amitriptyline, as well as with the occurrence of side-effects related to amitriptyline therapy.

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