

Pharmacogenetics and its Role in HIV Therapy

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ABSTRACT

Humans exhibit considerable genetic variations (polymorphism) within their DNA sequence, and HLA is the most polymorphic human gene known, leading to a wide allelic variation in humans among different ethnicities, and populations. This wide variation in the human genes is responsible for the inter-individual variation in the amount and the amino acid sequences of the proteins that function as drug targets and also pharmacokinetic parameters such as absorption, distribution, metabolism, and elimination. The overall effect of the polymorphisms is how it can modify ways in which an individual metabolize, distribute, eliminate, and respond to a particular drug. Since its introduction, pharmacogenetics studies have begun identifying these differences in drug dispositions and effects, to improve both the safety and efficacy of drugs based on patients' genetic constitution. Pharmacogenetic testing for antiretroviral drugs are now available as a screening method to allow for a more individualized therapy, thereby minimizing toxicity and enhancing treatment success. These genetic screenings have been integrated into clinical practice in antiretroviral therapy. This paper reviews the history, concept, and role of pharmacogenetics in HIV therapy, including advancement in Antiretroviral therapy.

Key Words: Antiretroviral therapy, Pharmacogenetics, & Polymorphism

INTRODUCTION

Pharmacogenetics refers to the study of inherited differences (variation) in drug response and metabolism allowing a tailor-made drug prescription to match an individual genotype. This term was first coined by Friedrich Vogel in 1959^[1]. Genetic variability can affect both the pharmacokinetics and pharmacodynamics of a

drug. Furthermore, the variability is also known to be associated with the likelihood of adverse drug reaction following drug metabolism (Figure 1). Pharmacogenomics has been introduced for several years. Pharmacogenomics and pharmacogenetics terms have been used interchangeably. Today, 'pharmacogenomics' refers to the investigation of the genetic variants to identify those involved in



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affecting drug metabolism, through the use of genome-wide association studies and RNA expression assays, followed by correlating the gene expression or single nucleotide^[2-5]. As such pharmacogenomics is the whole genome application of Pharmacogenetics. Therapeutic response and safety profile to drugs are often genetically predetermined, this is why some medications require genetic screening before they are prescribed to avoid toxicity. Genetic makeup is the major determinant of inter-individual variations in drug effects seen in clinical practice^[2-5]. This review focus on describing pharmacogenetics and the role it plays toward the prediction of reactions associated with HIV therapy especially immune-mediated hypersensitivity which could provide a means of allowing a more individualized therapy into clinical practice for the management of HIV patients

Overview of Pharmacogenetics and Pharmacogenomics

Pharmacogenetics and pharmacogenomics studies present an enormous opportunity to researchers working in various fields of pharmacology and toxicology, molecular biology and human genetics, genomics, internal medicine, endocrinology, physiology, epidemiology, statistics, bioinformatics, and computational biology^[6] towards improvement in drug developments, to provide an improving drug treatment options, safer dosing and also reduction in drug related morbidity and mortality in patients all over the world^[7].

It has been long recognized that different individuals differ in their susceptibility to diseases as well as their response to drugs. The Greek philosopher and mathematician, Pythagoras- who lived in Croton, southern Italy around 510 B.C, was

believed to be the first to recognize the dangers of developing adverse haemolytic anaemia, after ingestion of fava beans by some individuals, which was later found to be associated with deficiency of glucose 6- phosphate dehydrogenase (G6PD) enzyme in such individuals. Others still believed that the dawn of pharmacogenetics was the result of an original study by Snyder in 1932 concerning the 'phenylthiourea nontaster', phenotype inherited as an autosomal recessive trait. However, three important discoveries made in the 1950s gave rise to the discipline of pharmacogenetics. These include the presence of prolonged apnoea after administration of muscle relaxants, succinylcholine in individuals with an inherited deficiency of pseudocholinesterase enzyme deficiency^[8]. Secondly the primaquine sensitivity in an individual with G6PD deficiency^[9] in addition to an adverse response to fava beans. Thirdly is the slow metabolism of isoniazid in some individuals treated for tuberculosis, as a result of polymorphism of acetylating enzymes^[10]. Since then various examples of polymorphisms in genes encoding drug-metabolizing enzymes, drug transporters and drug targets (enzymes, receptor) have been described^[11,12] (Figure 2).

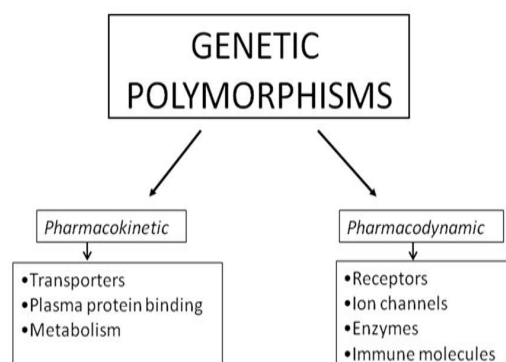


Figure 1. Schematic diagram illustrating the effect of genetic variations on both the pharmacokinetic and pharmacodynamics of a drug.

Genetic Variations/Polymorphisms

The sequencing of the human genome opens a broader opportunity for greater specificity and safety in therapeutics through the utilization of individual genetic information. HLA is the most polymorphic human gene known, leading to a wide allelic variation in humans among different ethnicities, and populations. Considerable genetic variations exist within the human genome as manifested by the differences in the DNA sequence^[13]. These sequence differences can be in coding regions, regulatory regions (i.e. promoter enhancers) introns, at 5' or 3' flanking regions, and also at the exons region, in form of nucleotide deletions, insertions, oligonucleotide repeats, and single nucleotide polymorphism (SNPs)^[14]. By far the inter-individual differences in human DNA sequence are predominantly the result of SNPs. The wide variation in the human genes is responsible for the variation in the quantity and the amino acid sequences of the proteins that function as drug targets and pharmacokinetic properties such as absorption, distribution, metabolism, and elimination.

Single Nucleotide Polymorphisms (SNPs)

A single nucleotide polymorphism is a nucleotide within a specific position in the genome, which varies in different individuals. The variation is said to be stable and discrete, occurring in at least 1% of a specific population. The sequence alteration, occurs in every 100-300 bases along with the three- billion base pairs within the human genome^[15], giving rise to over 2 million SNPs within the human genome^[6]. The frequency of this polymorphism varies often with race. Moreover, for a specific location within the genome, a small number of SNP patterns exist (Haplotype), which can account for about 80-90% of the human population. SNPs have numerous advantages over

microsatellite repeat in pharmacogenetics in that, SNPs occurrence are much frequent within the genome as mentioned earlier^[6]; furthermore, they exhibit a stable mode of inheritance as a result of becoming less prone to germline mutations. In addition to SNPs being bi-allelic^[16], the occurrence can also be either within coding or regulatory regions- as such making it to be directly responsible for the traits under study. It is worthy to note that, not all changes in DNA sequencing (genotype) affect the gene expression (phenotype). The two main types of SNPs include synonymous polymorphism (silent) and replacement polymorphism. Some SNPs are known to have a measurable effect on an individual, but the majority of these variations exert no effect. In pharmacogenetics, it is those polymorphisms (SNPs) with the measurable effect which are of primary interest and more so plays an important role in determining individual response to drug therapy^[17].

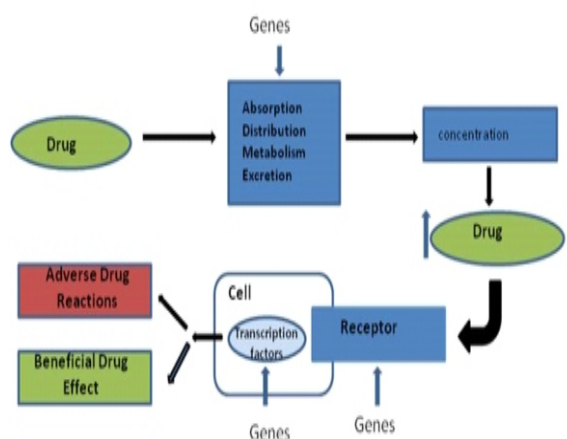


Figure 2. A Schematic diagram illustrating that genes are involved in determining the drug effect at various levels of both pharmacokinetics and pharmacodynamics. The blue arrows indicate levels in which the genes could be involve.

Genetic Variation and Drug Metabolism

During therapy, most drugs exert their effect by interacting with various proteins in form of receptors, enzymes, and intracellular signaling proteins, genetic variation in these proteins can affect sensitivity (efficacy and toxicity) to drugs in a patient^[18]. Genetic polymorphism in drug-metabolizing enzymes influences both toxicity and efficacy of a drug, and the two main enzymes broadly studied are, Phase I (cytochrome P450s) and phase II metabolizing enzymes^[18]. Variation in these enzymes could be in form of reduced, abolished, enhanced, or altered activity, being expressed as four major phenotypes. These phenotypes include poor metabolizers (lacking the functional enzyme), intermediate metabolizers (heterozygous for a defective allele), fast metabolizers (homozygous for the functional allele), and ultra-rapid metabolizers (having more than two functional gene copies)⁽¹⁹⁾.

Drug Metabolizing Enzymes and Pharmacogenetics

The process of drug metabolism is made of two phases. Phase I (oxidation), involved modification of drug functional group by either cytochrome or non-cytochrome enzyme. The cytochrome P450 however dominates this phase. Phase II, involves a process of drug conjugation, thereby making the drug generally water-soluble to enhance elimination of drug/metabolites. Although several enzymes are participating in this phase, the most predominant one is the glucuronyl transferases (UGT) (Figure 3). Moreover, most drug-metabolizing enzymes essentially involved in either phase I or Phase II are now known to demonstrate genetic polymorphisms clinically^[18]. Cytochrome P450 (CYPs) is a multigene superfamily encoding for a group of polymorphic

drug-metabolizing enzymes, found to be responsible for the metabolism of many compounds⁽²⁰⁾. At least 55 human CYP genes have been identified. These enzymes are often the rate-limiting for the fate of the drug in the body and their dysfunction may lead to undesired effects and toxicity^[21]. Polymorphisms of several P450s, such as CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 are the cause of different drug responses^[11, 12] Figure 3, which could be in form of decreasing the activity of some drugs and increasing the activity in others, thereby making it complex. Among the CYPs, the most thoroughly studied pharmacogenetics enzyme is CYP2D6. More than 75 alleles of CYP2D6 have been identified (description available at <http://www.immi.ki.se/cypallesles>), 9 of which affect the metabolism of approximately 25% of drugs including many over the counter drugs. Poor metabolizers have CYP2D6 genes that code for altered or missing protein due to common mutations, including splicing site, large and small deletion. The ultra-rapid metabolizers can have amplification of CYP2D6 up to about 13 times, such individuals have an inadequate therapeutic response to standard doses of the drugs metabolized by CYP2D6^[22]. The frequency of this variation varies among different populations and could be up to 29% in East Africans^[23]. Furthermore, in combined drug therapy one drug can influence the activity of the other through competitive inhibition of a P450 enzyme or by increasing gene expression or toxicity as in ritonavir (P450 inhibitor) and indinavir combination, during HIV treatment^[24]. Genetic variation of N acetyltransferase (NAT), a phase II enzyme was also identified during the late 1940s in patients treated for tuberculosis with isoniazid (INH). Two genes coding for N acetyltransferase (NAT1 & NAT2) were identified

in humans [25]. Furthermore, NAT2 polymorphism shows a striking ethnic variation [26], East Asian subjects are more often found to be rapid acetylators.

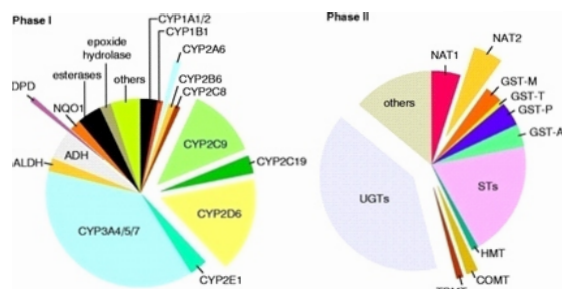


Figure 3. Drug metabolizing enzymes exhibiting relevant genetic polymorphisms, both belonging to phase I and phase II. Adopted from: Evans WE, Relling MV. Pharmacogenomics: Translating functional genomics into rational therapeutics. *Science* 286:487-491, 1999.

mediated through recognition of drug by variants of the human leukocyte antigen (HLA) gene [30]. The HLA is targeted by antigen-specific immune responses [31]. The drug and its metabolites may conjugate or bind to intracellular proteins, after which they become presented as either antigens or haptens by the major histocompatibility complex (MHC) I or II to the CD8+ or CD4+ T cells, thereby inducing drug-specific T cells response [32]. MHC is the most polymorphic of all human genes. Furthermore, MHC is subdivided into classes I, II, and III, with MHC I having 3 loci (HLA-A, B, and C). The HLA-B is the most variable. Recently HLA-B* 5701, HLA-DR7, and HLA-DQ3 haplotype has been associated with the patient's susceptibility to abacavir ADRs [33-35].

Adverse Drug Reactions (ADRs) and Pharmacogenetics

ADRs are defined by the World Health Organisation as noxious and unwanted responses to a normal dose of a drug [27]. They constitute an important public health problem, as they can cause serious morbidity and also mortality in some patients. ADRs are the 4th -6th leading cause of death in the USA [28] and are also the cause of drug withdrawal from the market (4%, 1974-1994). In the UK, it accounts for 6.5% of hospital admission costing up to £500m. ADRs have been classified into two types (A & B). Type A (on-target effect), are dose dependant reactions and are also predictable. They are an exaggeration of the pharmacological effect. While type B (off-target or idiosyncratic) reactions are dose-independent and also unpredictable, comprise about 10- 15% of all ADRs [29]. Type B though less common, but is the most severe form of ADRs and it includes hypersensitivity drug reactions (HDRs) which is

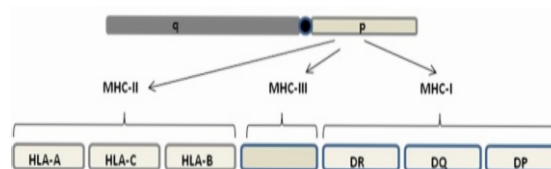


Figure 4. The diagram illustrates chromosome 6, with the short arm (p) bearing the major histocompatibility complex (MHC) I, II, and III.

Pharmacogenetics and Pathogenic Microorganisms

Pharmacogenetics studies also provide a means of studying the therapeutic response of microorganisms and their host, to overcome the

problem of decreased drug sensitivity or even resistance in some cases, as there is evidence of HIV resistance to saquinavir (antiproteases)^[36] and 3TC (nucleoside reverse transcriptase analogue)^[37]. Moreover, genes induced by INH in *Mycobacterium tuberculosis* have been identified through the use of microarrays, with many of the INH responsive genes encoding proteins that are relevant to the drug mode of action^[38]. Thereby providing new potential targets for an effective antituberculous agent

Pharmacogenetics in HIV Therapy

The causative pathogen of AIDS was first discovered during the early 1980s and since then efforts have been made to develop an effective therapy against HIV, with the first antiretroviral medication (zidovudine) being available by 1987^[39]. WHO estimated that by the end of 2007 about 33 million people were living with HIV in the world. Since 1987 over 20 antiretroviral drugs targeting HIV reverse transcriptase, protease, and viral entry have been approved for clinical use. Access to antiretroviral therapy (ART) has been increasing with the greatest in sub-Saharan Africa. The antiretroviral agents (ARV) administered in form of highly active retroviral regimens (HAART) reduce AIDS mortality by at least 70%^[39]. Six classes of ARV were available for the combination of HAART regimens. The use of these agents is often associated with substantial inter-individual variability in antiretroviral efficacy, plasma drug exposure, and tolerability^[40]. Several factors are found to be associated with variability in drug metabolism. These include host genetics, underlying disease, co-medication, patient compliance, and demographic factors such as gender, age, and race. Furthermore, the efficacy and tolerability of ARVs are often affected by both

immunogenetic factors (HLA/immune response genes) and pharmacogenetics factors (drug-metabolizing enzyme, drug transporter, and receptor genes)^[41-43].

The marked pharmacokinetic variability of antiretroviral drugs often depends on the factors modulating their metabolic pathway. CYP450 enzyme complex is the main metabolizer concerned in hepatic clearance of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PI). Numerous genetic polymorphisms at different CYP450 isoenzymes as mentioned earlier are known to influence drug metabolism resulting in altered plasma drug exposure^[11, 12]. Those CYP450 polymorphisms with potential relevance to antiretroviral therapy include CYP3A4 (PI), CYP286 (efavirenz, nevirapine), CYP3A5 (indinavir, saquinavir), CYP2C9 (nelfinavir)^[41, 44-48]. Furthermore, the activity and expression of phase II conjugative enzymes and drug transporters for instance P-glycoprotein (P-gp), the multidrug transporter multidrug resistance (MDR1) gene products^[11, 43, 49] are known to be modulated by the polymorphisms at the genes encoding for these proteins and thus affecting the disposition of both the conjugated and transported drugs. All the current antiretroviral agents belonging to the PI group are substrates for the P-gp efflux pump in the small intestine^[50]. Polymorphisms of these drug transporter proteins influencing antiretroviral therapy also include organic anion transporters (OATs) as in tenofovir in addition to P-gp (PIs, zidovudine, nevirapine)^[45, 51, 52]. Polymorphism of uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) enzyme, concerned with drug-bilirubin conjugation reactions has been associated with toxicity of certain antiretroviral agents during therapy (indinavir and atazanavir)^[46].

Protease inhibitors in HIV therapy

Single nucleotide polymorphisms (SNPs) have been shown to have a significant effect on the pharmacokinetic parameters of Lopinavir/ritonavir (LPV/r) influencing the immunovirological response or adverse effect^[53]. The most significant associations were seen between SNPs in the dopamine receptor D3 gene and the pharmacokinetic parameters of Lopinavir/ritonavir. The study identified patients who are at increased risk of achieving sub-therapeutic levels of LPV/r plasma concentrations leading to resistance, and also individuals at increased risk of toxicity^[53].

Efavirenz and Niverapine in HIV Therapy

Efavirenz (EFV) and nevirapine are NNRTI and important components of first-line antiretroviral therapy accepted worldwide. Efavirenz is often administered with emtricitabine and tenofovir once daily, as a fixed-dose combination, while nevirapine is usually in combination with lamivudine and zidovudine. EFV works by directly binding and inhibiting the HIV reverse transcriptase enzyme thereby blocking the reverse transcription of the virus' RNA into DNA, and effectively preventing viral replication. Strong associations have been demonstrated between the HLA-B*40 and HLA-C*15 alleles and nevirapine and efavirenz-induced skin rash^[54]. Screening for the HLA-B*40 and HLA-C*15 alleles can be utilised before placing patients of nevirapine or efavirenz to avoid a subset of hypersensitivity reaction^[54].

EFV is metabolized in the liver by CYP2B6. EFV administration is often associated with central nervous system side effects from mild to severe. This enzyme is highly polymorphic, exhibiting both inter-individual variability and also

functional differences between genetic variants^[55, 56]. CYP2B6 (516>G) polymorphism is associated with elevated plasma level concentration and also an increase in the neurotoxicity of EFV^[57]. This polymorphism is known to be higher in sub-Saharan Africans and African Americans compared to European, Asian, and Hispanic populations^[57,58].

Abacavir Drug Hypersensitivity Reaction

Abacavir (ABC), a nucleoside analogue reverse transcriptase inhibitor (NRTI) has been used for the treatment of human immunodeficiency virus (HIV) infection as part of a combination therapy, highly active antiretroviral therapy (HAART) regimen. It has been available as a single drug co-formulation with either NNRTIs or PIs^[59]. ABC is metabolized primarily through alcohol dehydrogenase or glucoronyl transferase. Although ABC generally is well tolerated with proven efficacy in treating HIV, about 8% of patients on initial ABC are known to develop an immune-mediated hypersensitivity reaction (HSR) that necessitates immediate discontinuation of ABC and replacing it with an alternative antiretroviral regimen. Hypersensitivity reaction occurs usually within the first six weeks, in form of a rash, lethargy, abdominal and acute respiratory symptoms^[60]. A recent study using transgenic mice to understand the mechanism of abacavir-induced hypersensitivity demonstrated a strong association between the reaction and HLA-B*57:01 allele^[61]. The severity and rapidity of these ADRs increase on re-exposure to the drug. ABC hypersensitivity has been associated with MHC. Moreover, recent studies described an association between the presence of HLA-B*5701, HLA-DR7, HLA-DQ3 with patients' predisposition to ABC allergic reactions^[33-35]. As such currently HLA-B*5071

screening before ABC treatment is now recommended in international HIV treatment guidelines(62). Despite its efficacy in treating HIV, approximately 5% of individuals that receive abacavir develop an immune-mediated hypersensitivity reaction (HSR) that warrants immediate discontinuation of abacavir and switching to an alternative antiretroviral regimen. Pharmacogenetic testing, like the genetic testing for abacavir HSR, has been integrated into clinical practice.

However, it is worth noting that despite the strong association between abacavir-induced hypersensitivity and HLA-B*57:01 allele, not all abacavir-related side effects are due to the HLA-B*57:01-mediated hypersensitivity reaction, as other adverse reactions occur in allele (HLA-B*57:01) non-carriers⁽⁶³⁾. Another showed that in clinically suspected abacavir HSR rates were low (1.3%) or less in HLA-B*5701-negative patients^[64], therefore screening for HLA-B*5701 is now standard care in resource-rich settings, and patients should be confirmed HLA-B*5701-negative to be eligible for abacavir-based regimen^[64].

CONCLUSION

Pharmacogenetics provides a powerful means of investigating variable responses to drugs within different individuals. Advances in genetics and molecular biology now allow for associations of genetic traits and patient outcomes. Thereby providing delivery of individualized therapy, based on race/ethnicity and gender as in the case of HIV therapy. Genetically determined reactions associated with HIV therapy especially immune-mediated hypersensitivity reactions have been documented with abacavir, and this and other severe reactions necessitate immediate

discontinuation of the implicating drug and switching to an alternative regimen. These reactions can now be predicted using pharmacogenetic testing, allowing a more individualized therapy. This prediction and the treatment adjustment have been integrated into clinical practice in the management of HIV.

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