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Applications of Pharmacogenetics in Revealing Variations in Pharmacodynamics

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In the past two decades many drugs were discovered through the developments taking place in molecular biology techniques. Drug action is now more defined. In addition to known pharmacogenetic variations on drug metabolism, variations in drug targets are also emerging. These targets include receptors, transporters, enzymes, channels and intracellular coupling processes. This review article presents the latest findings of genetic variations in pharmacological targets related to disorders of major systems such as central nervous system, cardiovascular system, and the respiratory system especially in relation to asthma and the HLA antigen genotype in hypersensitivity reactions.

INTRODUCTION

The past 20 years have witnessed a dramatic change in the way in which dugs are discovered and developed. The process of new therapeutic targets identification has been enhanced by what has been termed the 'genomic rush' which involves the principles of pharmacogenetics. Pharmacogenetics is the discipline that analyses the genetic basis for the inter-individual variation in the body disposition of drugs. One of its main goals is to give grounds to individualized treatment [1]. The demand to understand the specificity in drug action and associated benefits is a primary force behind the current drug industry towards the application of pharmacogenetics in drug discovery and development [2].

Research in pharmacogenetics is currently evolving in two directions. Firstly, to identify genes and gene products associated with certain diseases, which may serve as targets for new drugs and secondly to identify genes and allelic variants of genes that affect the expected and adverse responses to current and future drugs and to advice safer therapeutics [3]. Even with identical plasma concentrations of a drug across subjects, the variability in drug response is considerable [4]. In addition to pharmacogenetic effects on drug metabolism, therapeutically promising examples of genetic variations in pharmacological targets are also beginning to emerge. These pharmacodynamic effects include physiological and biochemical effects of drugs at macromolecular and subcellular targets such as receptors, transporters, enzymes, channels and intracellular coupling processes that modulate pharmacodynamic responses [3].

It has now become evident that polymorphisms of pharmacological targets (pharmacodynamic polymorphisms) may in fact be given more importance in addressing variations associated with drug therapy [3]. In a study of 270 cancer patients who were given antiemetic therapy with 5-HTR_{3B} receptor antagonists, approximately 30% suffered from nausea or vomiting despite taking these drugs. In this study, ultra rapid metabolism of tropisetron (and to a lesser extent for ondansetron) was shown to predispose patients to poor efficacy [5]. In a pharmacogenetic study that compared paroxetine and mirtazapine in 246 elderly patients with major depression, discontinuations due to paroxetine-induced

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side effects were strongly associated with the 5-HTR_{2A} C/C, rather than CYP2D6, genotype [6]. There was a significant linear relationship between the number of C alleles and probability of discontinuation.

The severity of side effects in paroxetine-treated patients with C/C genotype was also greater [6]. Thus, although paroxetine is metabolized by CYP2D6, polymorphism of 5-HTR_{2A} is a more important determinant of paroxetine-induced ADRs.

The variability in pharmacodynamic targets are more drug-specific than in the enzymes responsible for drug metabolism because many drugs are metabolized by the same enzyme but often have different drug targets such as enzymes or ion channels [7].There is certainly less information available for genetic polymorphisms of drug targets than for drug metabolizing enzymes and the knowledge on how mutations in genes coding for drug targets would affect the susceptibility for adverse drug reactions is even more limited [8]. Nevertheless, the area of pharmacogenetics is growing rapidly and its applications have revealed some of the variations associations with drug therapy of systems, diseases and conditions as described herein after.

Among the most widely studied are the pharmacological targets related to disorders of the central nervous system (CNS), cardiovascular system (CVS), respiratory system and the HLA antigen genotype in hypersensitivity reactions.

CNS DISORDERS

Psychiatric conditions

Considerable variability exists in efficacy and toxicity of antipsychotic medications. In the case of mood disorders, approximately 30-40% patients do not completely respond to treatment [9]. Serotonin transporter promoter length polymorphism has been implicated in the pathogenesis of mood disorders as well as in the therapeutic response to serotonergic drugs [10]. In patients with schizophrenia treated with antipsychotics, the TaqI polymorphism in the dopamine D2 receptor gene has been strongly associated with greater improvement in positive, but not negative symptoms after treatment [11, 12]. Carriers of the A-214G allele have been shown to exhibit fast time response to the antipsychotics resperidone and olanzepine while the -141C carriers exhibit longer response times [13]. Similarly, Gly 9 allele (Ser9Gly) of the dopamine D3 receptor gene and His 452 Tyr polymorphism in the 5-hydroxytryptamine 2A receptor (5-HT2A) gene are associated with response to clozapine. Weight gain induced by antipsychotics seems to be associated with the -759C allele of the 5-HT2C receptor. Additionally, the Gly9 variant of dopamine D3, the 102C variant of the 5-HT2A and the Ser 23-variant of the 5-HT2C receptors (in females) seem to increase the susceptibility to tardive dyskinesia [14, 15, 16].

Parkinsonism

Treatment of Parkinson's disease with L-dopa may induce dyskinesia in some patients and this could be due to DRD2 gene polymorphisms among patients [17, 16]. Positive associations have been demonstrated between L-dopa-induced dyskinesia and DRD2 gene polymorphisms whereby the CAn-STR 13 and 14 copy alleles were protective while the 14 copy was a risk factor), the DAT gene and the OPRM1 G-allele [18]. Wang *et al*. (2001) have shown that the motor fluctuations may be associated with the DRD2 TaqIA polymorphism [19]. Studies linking hallucinations and genetic polymorphisms have mostly been non-consistent. Although significant positive associations have been demonstrated for polymorphisms in the DAT gene, the CCK gene and the APOE gene, these findings have not been consistent. The DRD2, DRD4, COMT and HCRT gene polymorphisms have been

associated with sleep attacks without warning signs [18].

Epilepsy

Epilepsy is a difficult disorder to treat because different patients require different ranges of doses and some patients may even experience side effects such as depression and double vision [16]. In order to control epilepsy, drugs such as phenytoin and carbamazepine have been extensively prescribed throughout the world. At present, evaluation of the allelic variation between individuals relies on the prior identification of candidate genes and their therapeutic effects of antiepileptic drugs [20]. Recently, variants in the SCN1A genes are found significantly more often in patients treated with the highest doses of both phenytoin and carbamazepine [21]. Moreover, drug resistant epilepsy is a major clinical problem, this could be due to multiple factors but multidrug transporters may play a key role in resistance phenotypes. However, studies on one variant in the ABCB1 gene, so far provided inconclusive evidence [22, 16].

Drug addiction

Drug addiction is a major social and medical problem and imposes a significant burden on society. Epidemiological studies have shown a significant contribution of genetic factors to the addictive diseases [16,23]. Studies of polymorphisms in the mu-opioid receptors have contributed significantly to the knowledge of genetic influence on opioid and alcohol addiction [24,25]

Naltrexone hydrochloride binds to the mu-opioid receptor (OPRM1) and has been shown to be effective in the management of alcohol dependence [26]. A variant of OPRM1, in which the amino acid asparagine is substituted for aspartate at position 40 (Asn40Asp) caused by the A118G SNP in the gene encoding OPRM1 alters β-endorphin binding, function and receptor levels [26]. Studies have shown that patients carrying at least one copy of this 40Asp allele have better treatment responses to naltrexone [27,28]. They showed lower rates of relapse, longer time to return to heavy drinking [26], lower alcohol induced high state [27], increased percentage of abstinent days, a decreased percentage of heavy drinking days and better clinical outcomes [28,29].

Dopamine D3 receptor genes

Tardive dyskinesia is a potentially irreversible movement disorder that occur after long term treatment with antipsychotic drugs. The Ser9Gly polymorphism in the dopamine D_3 receptors gene has been associated with an increased risk of tardive dyskinesia [30]. A higher predictive value can be achieved when mutations in genes coding for other receptors, such as the serotonin 5-HT2A and 5-HT2C receptors occur [31, 32]. Such combination testing would make sense for a pharmacological point of view, since the serotonin system is known to modulate dopaminergic effects on antipsychotic drugs. [8]

Polymorphism of the serotonin transporter

Genetic polymorphism in the promoter region of the serotonin transporter (5-HTT) gene is reportedly a determinant of response to fluvoxamine, a selective serotonin re-uptake inhibitor. The efficacy of fluvoxamine in the treatment of delusional depression has been shown to correlate with 5-HTT genotypes [29].

CARDIOVASCULAR DISORDERS

Cardiovascular pharmacogenetics has the potential for improvements in the use of cardiovascular drug therapy, through selection of the most appropriate drug therapy in an individual based on their genetic profile [33].

Hypertension

Hypertension is prevalent and affects approximately 1 in every 4 adults in the Western world. Although five drug classes are available for the first-line treatment of hypertension, only about a third of hypertensive patients have their blood pressure controlled to <140 /90 mm Hg with the available drugs [34]. Genetic variations are known to alter antihypertensive drug therapy [35]. The genetic determinants of response to two major antihypertensive drug classes, thiazide diuretics and beta-adrenergic receptor blockers would help in rationalizing the therapy in variant population. Polymorphism in the sodium channel γ-subunit promoter region has significantly altered blood pressure response to hydrochlorothiazide [36]. Recent studies have suggested that genetic variability influences the response to hydrochlorothiazide, a thiazide diuretic and many genes seem to contribute to the overall effect. For example, *GNB3*, *WNK1, AGTRI*, *SCNNIG*, and *NOS2* each seem to explain only a small portion (<5%) of the response [37-40]. A similar variability was found to be associated to treatment with beta-blockers. The β_1-adrenergic receptor (ADRB1) may explain up to 20% of the variable response to a beta-blocker [41]. Two of the four diplotype groups responded to metoprolol, but two did not [41]. As with thiazide diuretics establishing an algorithm that predicts poor or excellent response based on genotype would dramatically promote establishing an antihypertensive regimen tailored to a specific patient.

Polymorphism of cardiac potassium channels

Drugs prolonging the QT interval such as cisapride, astemizole, terfenadine and halofantrine, have attracted considerable attention recently. Excessive prolongation of QT interval, in the right setting, predisposes to torsade de pointes (TdP), a potentially fatal ventricular tachyarrhythmia [42]. The duration of this interval reflects the duration of ventricular action potential. The major determinant of the action potential duration is the potassium current mediated by the rapid component of the delayed rectifier potassium channels (IKr). Many drugs have been withdrawn as a result of their potential to prolong the QT interval and induce TdP. Following advances in molecular biology, genetics and pharmacology of ion channels, it has become evident that there is a great diversity of genes that control the expression of these potassium channels [44]. Mutations of the subunits that form these channels including IKr, are common and give rise to congenital long QT syndromes [3].

Polymorphism of angiotension converting enzyme

Variation in two genes encoding angiotensin converting enzyme (ACE) and endothelin nitric oxide synthase influence the effects of standard therapies [44]. Similarly, single nucleotide polymorphisms (SNPs) in angiotensinogen (T1198C), apolipoprotein B (G10108A) and adrenoceptor α-2A (A1817G) significantly alter the change in left ventricular mass during antihypertensive treatment [45].

Anticoagulant drug therapy

The emergence of pharmacogenetic-guided anticoagulant drug development has unraveled novel approaches in the management of hemorrhage and ensured individualized therapy. Through cheminformatics, decisions could be made in anticoagulant drug discovery [46]. It has long been recognized that CYP2C9 which is responsible for metabolism of oral anticoagulants is a subject of genetic polymorphism affecting activity. It has been estimated that as much as 30% variability in response to the oral anticoagulant warfarin may be explained by genetic variations in the VKORC1 gene encoding the oral anticoagulant target enzyme vitamin K epoxide reductase and the CYP2C9 genetic variant [47]. Polymorphisms in the non-

coding sequences of this gene affect the levels of gene expression, leading to interindividual variation in the amount of this protein present in the liver. Association between the G-1639A gene polymorphism (an allele in which the guanine reside is replaced with adenine at position 1639) and the dose of oral anticoagulants (warfarin, acenocoumarol and phenprocoumarol) has been reported [48-50].

Asthma

Asthma is a chronic inflammatory condition characterized by reversible airway narrowing and bronchial hyper-responsiveness. It is a multifactorial disease influenced by both genetic and environmental factors. An estimated 70 to 80% of variability in individual responses to asthma pharmacotherapy may be due to genetic variation [51]. Currently, asthma pharmacogenomic research has concentrated on three drug classes, the β-agonists, leukotriene antagonists and the corticosteroids. Individuals who carry Arg16/gly 16 or Gly16/Gly16 mutations of β_2-adrenoceptors have been shown to respond much less favourably to salbutamol-induced acute bronchodilatation [52]. Two studies comparing regular and as needed use of salbutamol [53, 54] have shown that patients who were homogynous for Arg at B16 (Arg16/Arg16), experienced worse outcomes with regular salbutamol compared to those carrying the gly16/gly16 variant. Patients who carry mutations of the core promoter of 5-lipoxygenase (ALOX-5) respond poorly to ALOX-5 inhibitors such as zileuton [55]. The IL4 589 T allele has been shown to be associated with increased IL-4 gene transcription and corticosteroid resistant asthma [56].

OTHER DISORDERS

Ryanodine receptor gene

If an individual with certain mutations in the gene coding for the skeletal muscle ryanodine receptor (RYR2) is exposed to halogenated inhalational anaesthetics or suxamethonium during anaesthesia, the life-threatening condition malignant hyperthermia may arise [57]. Traditionally, patients in whom such a reaction has been suspected have been diagnosed by a phenotyping method, the caffeine halothane contracture test [58]. As numerous mutations in the RYR2 gene are known to cause susceptibility to malignant hyperthermia [57], genetic testing would be expected to be helpful tool in this respect.

Abacavir-induced hypersensitivity reactions and HLA genotype

Hypersensitivity reactions to abacavir which limits its clinical utility occur in about 5% of patients who receive the drug for HIV-1 infection [59]. This reaction clinically present in a variety of ways including high fever, chills, sore throat, cough, dyspnea, tachypnea, nausea, vomiting, diarrhea, loss of appetite, abdominal pain, arthralgia, myalgia, malaise, fatigue, dizziness and a generalized macular rash [60]. It usually develops within the first few weeks of therapy and does not appear to be dose-related. If therapy is stopped, symptoms usually subside within a few days. But, when therapy is continued symptoms tend to worsen, typically involving multiple organ systems, and may include hypotension, respiratory distress, anaphylaxis and even death [60]. Restarting therapy may cause severe reactions within hours of drug administration. Therefore, re-challenge with the drug is contraindicated in patients who have developed the condition [60]. This reaction is more common in women than in men, is much less common in the black population and tends to present within families [61]. For these reasons, a genetic basis was suspected shortly after the initial description, and a role for the major histocompatibility complex (MHC) was investigated.

A study identified an association between HLA-B*5701 and hypersensitivity to abacavir in patients of Caucasian ancestry

[62]. The sensitivity of HLA-B* 5701 ranged from 46-94%. Other recent studies have shown that the reaction can be reliably prevented by genetic screening of patients [1,63]. For that reason, guidelines now recommended HLA-B*5701 testing prior to initiating abacavir therapy and the positive status is considered an absolute contraindication for the use of the drug [64].

CONCLUSION

It is now becoming evident that polymorphisms of pharmacological targets may in fact be given more importance in addressing variations associated with drug therapy. Such process of targets identification has been enhanced by the application of molecular biology techniques. These targets include receptors, transporters, enzymes, channels and intracellular coupling processes. It is possible to identify the reason for 30% nonresponders of antiemetic drug therapy. Serotonin transporter promoter length polymorphism has been implicated in the pathogenesis of mood disorders as well as in the therapeutic variation to serotonergic drugs. Studies of polymorphisms in the mu-opioid receptors have contributed significantly to the management of opioid and alcohol addiction. Drug resistant epilepsy could be due to multiple factors but multidrug transporters may play a key role in resistance phenotypes.

The genetic determination of response to two major drug classes, thiazide diuretics and beta-receptor blockers would help in rationalizing the antihypertensive therapy in variant population. It has become evident that there is a great diversity of genes that control the expression of rectifier potassium channels involved in prolongation QT interval by certain drugs to induce torsade de pointes.

An estimated 70 to 80% of variability in individual responses to asthma pharmacotherapy may be due to genetic variation. Mutations in the gene coding for the skeletal muscle ryanodine receptor (RYR2) when exposed to halogenated inhalational anaesthetics or suxamethonium may cause the life-threatening malignant hyperthermic condition. Hypersensitivity reactions to abacavir occur in about 5% of HIV-1 infected patients who had associated with HLA-B*5701 allele. As the concepts of pharmacogenetics evolve to fine-tune the process of individualized drug selection, better pharmacologic options may become available to patients which at least devoid of severe adverse drug reactions.

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