

# Pharmacogenetics: Role in Modifying Drug Dosage Regimens

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## Abstract

*With the advent of new molecular biology and scientific techniques, there is better understanding of genetic polymorphisms in oxidative drug metabolism systems today. These systems are important in pharmacogenetic studies which genotype polymorphic alleles encoding drug metabolising enzymes to enable the individual's drug metabolising phenotype to be found. Once found, the knowledge can be used to tailor drug dosage regimens to an individual to maximise therapeutic efficacy and minimise adverse drug reactions (ADRs). The knowledge could also be used to optimise drug development programmes so that all the subgroups within a target population are adequately represented in clinical trials.*

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## Introduction

Synder in 1932 wrote the first report on the Mendelian inheritance of the inability to taste phenylthiourea.<sup>1</sup> Twenty-five years later, Arno Motulsky suggested hereditary factors might be the explanation to inter-individual differences in drug responses.<sup>2</sup> Following this, Friedrich Vogel was the first to coin the term "pharmacogenetics".<sup>3</sup>

Pharmacogenetics can be defined as the study of the linkage between the individual's genotype and that individual's response to a foreign substance.<sup>4</sup> This could be due to genetic influences on either the pharmacokinetics or the pharmacodynamics of the xenobiotic. This is closely related to the field of pharmacogenomics, which is the use of advanced genetic tools to discover how variations in DNA of patients influence their phenotype and susceptibility to disease and responses to drugs.<sup>5</sup>

As far as the pharmacokinetics of a drug are concerned, pharmacogenetic studies aim to genotype polymorphic alleles encoding drug-metabolising enzymes in order to identify a person's drug metabolising phenotype.<sup>4</sup> Once identified, this can be used to tailor drug selection and dosing regimens to an individual, in the hope of minimising serious adverse drug reactions or therapeutic failure. Using this approach, it is anticipated that therapeutic efficacy and risk/benefit will be greatly optimised.<sup>4</sup>

The field of pharmacogenetics has been expanding

exponentially over the past two decades with the advent of advance molecular biology techniques and newer genetic analysis methods. Inevitably, this has caused the field of pharmacogenetics to infiltrate into areas of medicine, therapeutics and drug development.<sup>6</sup>

In therapeutics, genetic differences among individuals might be the key to how and what drugs are prescribed in the future. The knowledge of how genetically unique individuals react to certain drugs will help to significantly minimise the occurrence of life-threatening adverse reactions to drugs and will minimise the economic burden from having to deal with the consequences of these adverse reactions. It is estimated that adverse drug reactions caused more than two million hospitalisations and 100,000 deaths in 1994.<sup>5</sup> Clinical trials can also concentrate on characterising specific groups of individuals who are capable of responding favourably or unfavourably to a certain compound.<sup>5</sup>

As scientists become more aware of the inadequacy of the concept of "one-medicine-fits-all" approach in treating all patients, they are focusing their research on achieving the goal of individualised medicine<sup>7</sup> and the role of pharmacogenetics in this. In this regard, ethnicity per se has little relevance when it becomes possible to individualise therapy. The significance of conducting studies in one ethnic population for the data to be used in another becomes

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important when the frequency of genetic variations, responsible for unusual drug responses, are significantly different. Only when these frequencies are significantly different or unknown does ethnicity become an important issue in drug development and therapeutics.

### Ethnic Differences in Drug Effects

Variability among individuals of different ethnic groups in drug response often causes either over or under-treatment problems, with the danger of lack of therapeutic efficacy or drug toxicity.<sup>8</sup> Besides differences relating to diet and culture, the presence of mutant alleles within a population may be the most significant factor resulting in the inter-individual and inter-ethnic variability in observed responses to drugs. Genetic mutations in drug metabolising enzymes result in variants that have either higher, lower or no activity, and in extreme cases, the enzyme is completely absent.<sup>9</sup> The global heterogeneity in the frequency of these mutant alleles, and consequently the percentage of population with impaired or absent drug metabolism accounts for most of the inter-ethnic differences in pharmacokinetics and pharmacodynamics of drugs.<sup>10</sup>

The rest of this article will review a few major examples of genetic polymorphisms in drug metabolising enzymes important in metabolic elimination of drugs and their consequences for clinical efficacy and safety and their implications for drug development. These are the ones involving enzyme systems CYP2D6 and CYP2C19<sup>8</sup>, acetylation by N-acetyltransferase (NAT2)<sup>11</sup>, as well as S-methylation by thiopurine methyltransferase (TPMT).<sup>12</sup>

### Genetic Polymorphisms

Genetic polymorphism may be defined as the existence of more than one allele competing at a single gene locus,<sup>13</sup> causing a condition to be recognised when the least common phenotype occurs at a frequency of 1% or more.<sup>10</sup> Presence of multiple alleles at a specific gene locus commonly arises as a result of mutations in the wild type allele. These multiple alleles responsible for coding of proteins, such as enzymes, are either dominant, co-dominant or recessive.<sup>10</sup> As a result, depending on the co-segregation and combination of these alleles, the protein formed may be so defective that it is functionless.

When these genetic mutations equilibrate within a population, the phenotype they express display polymorphic distribution in that population.<sup>4</sup> Broadly, this genetic polymorphism can result in at least 2 main phenotypic classes based on the capacity to effect drug metabolism. The majority in the population belongs to the extensive metaboliser (EM) phenotype. However, in an autosomal recessive trait, both alleles involved can be deleted or mutated, leading to a phenotype that is recognised by the accumulation of the substrate drug concerned. This is the

poor metaboliser (PM) phenotype.<sup>4</sup> Sometimes, however, the gene concerned may be amplified, giving rise to an increased expression of enzyme leading to accelerated drug metabolism. This is then recognisable as an ultrarapid metaboliser (URM) phenotype.<sup>4</sup>

Patients can be differentiated into these 3 classes of metabolisers by genotyping (or sometimes by phenotyping) techniques and allowing the most appropriate therapy to be applied. In the phenotyping method, a specific test or probe drug metabolised by the pathway in question is given, after which the metabolic ratio (MR) is calculated. MR is the ratio of drug unchanged to its metabolite measured in the serum or urine.<sup>4</sup> Once a person's phenotype is found relative to the probe drug, drug metabolism phenotypes for other substrates of that enzyme can be predicted.<sup>14</sup>

Genotyping is the identification of specific genetic mutations such as gene duplication, null allele or inactivating allele that give rise to a defined drug metabolism phenotype.<sup>4</sup> A useful method in screening for specific mutations is amplification of a specified length of the genome concerned by polymerase chain reaction (PCR), then digesting the amplified DNA products with restriction endonucleases. The result is the generation of restriction fragment length polymorphism (RFLP) fragments whose differing size can be visualised and analysed by agarose gel electrophoresis with ethidium bromide staining and ultraviolet (UV) transillumination.<sup>4</sup> Another similar method is allele-specific PCR amplification when oligonucleotides that hybridise to specific alleles are utilised. In this latter method, only a small quantity of blood and tissue is required<sup>15</sup> and the genotyping process is unaffected by patient's disease or other concurrent medications which may influence drug metabolism. Thus, this is an efficient method of screening, giving results within 2 to 3 days, therefore allowing for rapid therapeutic decisions to be made.

More recently, DNA chips have been developed that can screen larger number of genes and mutations concurrently. Although currently limited by cost, this new technology holds great promise for genotyping as a routine clinical tool.

*CYP enzymes:* Genetic polymorphisms of the enzyme system cytochrome P450 are well researched in humans, especially the CYP2D6 responsible for debrisoquine 4-hydroxylation<sup>16</sup> and the CYP2C19 isoform responsible for S-mephenytoin hydroxylation.<sup>17</sup>

The clinical significance of CYP2D6 polymorphism is that it catalyses the oxidation of many drugs like antiarrhythmics, antidepressants and neuroleptics (Table II). Critically, these are the cardiovascular and psychoactive drugs that are intended to be administered long-term and many of them have narrow therapeutic index, producing concentration-related adverse drug reactions. In any

TABLE I: FREQUENCY OF SLOW ACETYLATORS IN DIFFERENT ETHNIC POPULATIONS<sup>8,10</sup>

| Population        | Percentage |
|-------------------|------------|
| African Americans | 42 to 51   |
| US White          | 52 to 58   |
| Chinese           | 22         |
| Eskimo (Canada)   | 5 to 6     |
| US Japanese       | 10         |
| Japanese (Japan)  | 7 to 12    |
| Korean            | 11         |
| Thais             | 28         |
| Filipinos         | 28         |
| Burmese           | 38         |
| South Indians     | 61         |

population, individuals are identified as either poor (PM) or extensive (EM) metabolisers of debrisoquine. Individual differences in the metabolism of these drugs result in increased incidence of adverse reactions for poor metabolisers to failed therapy for those ultrarapid metabolisers. Ultrarapid metabolism of drugs has been attributed to the duplication or even multiplication of the CYP2D6 gene. Toxicity to codeine in ultrarapid metabolisers is well-known. In these individuals, there is a rapid production of morphine which leads to epigastric pain. They also require very high doses of nortriptyline for effective antidepressant efficacy.

PMs are also at risk of some serious adverse drug reactions. These include perhexiline-induced neuropathy and/or hepatotoxicity, phenformin-induced lactic acidosis, bufuralol-induced vomiting and greater bradycardia due to B-blockers and central nervous system (CNS) toxicity due to nortriptyline. Propafenone-induced CNS effects and B-blockade are more frequent in PMs. The pharmacokinetic basis of this was provided by Siddoway et al<sup>18</sup> who studied the profile of this drug in 28 patients (22 EMs and 6 PMs) with chronic ventricular arrhythmias. They found that the steady-state plasma concentrations of propafenone were significantly higher in PMs than in EMs and were linked to a larger incidence of central nervous system adverse effects in the PMs (67%) compared to the EMs (14%).

Poor metabolisers are at risk of loss of metabolite-mediated pharmacological effects, for example, relative loss of analgesic effect of codeine or tramadol and antiarrhythmic effects of encainide.

There are substantial differences in the pharmacogenetics of debrisoquine hydroxylation between Caucasian and Chinese populations.<sup>19</sup> For example, the frequency of the PMs phenotype is higher (5% to 10%) among white Caucasians<sup>20</sup> than among Chinese (<1%).<sup>21</sup>

A recent study using long-range and nested PCR technology by Wong et al 1998<sup>22</sup> to characterise the polymorphisms in an Asian population comprising 230 Chinese, 60 Malays and 48 Indians showed that the frequency of the duplicated or multiplicated CYP2D6\*rep allele was 0.087, 0.075 and 0.25 in Chinese, Malays and Indians, respectively. In contrast, only 1% to 2% of some Oriental and European groups, and as much as 29% of an Ethiopian group were found to carry the CYP2D6\*rep allele. On the other hand, about 5% of Caucasians and 1% to 2% of Orientals were found to carry the CYP2D6\*5 deletion allele which lacks the entire CYP2D6 gene locus. Homozygous carriers of this allele show serious metabolic deficiency. In Chinese and other Oriental populations, the most common allelic variant found has been the CYP2D6\*10A,10B—an allele related to decreased CYP2D6 activity. As for the CYP2D6\*5 deletion allele, the frequency was 0.10, 0.12 and 0.08 in Chinese, Malays and Indians, respectively. The frequency of the CYP2D6\*10A,10B allele was 0.37, 0.38 and 0.22, respectively.<sup>22</sup>

CYP2C19, another cytochrome P450 isozyme showing genetic polymorphism, is associated with the 4'-hydroxylation of the S-enantiomer of mephenytoin.<sup>23</sup> Drugs metabolised by CYP2C19 are diazepam, omeprazole, propranolol, mephenytoin and proguanil.<sup>4</sup> In contrast to debrisoquine polymorphism, no ultrarapid phenotype has been found for CYP2C19. Inheritance of the PM phenotype is autosomal recessive<sup>24</sup> whereas the EM phenotype consists of homozygous dominant and heterozygous recessive genotypes.<sup>4</sup> There is inter-ethnic variation in PM phenotypes: 2% to 5% of Caucasian<sup>24</sup> and black Zimbabwean Shona populations,<sup>25</sup> and 18% to 23% in

TABLE II: CYP2D6 SUBSTRATES<sup>4</sup>

| Antiarrhythmics | Antidepressants | Beta-blockers | Neuroleptics | Miscellaneous    |
|-----------------|-----------------|---------------|--------------|------------------|
| Amiodarone      | Imipramine      | Propranolol   | Perphenazine | Codeine          |
| Encainide       | Amitriptyline   | Timolol       | Thioridazine | Debrisoquine     |
| Flecainide      | Nortriptyline   | Metoprolol    |              | Indoramin        |
| Mexilitine      | Desipramine     | Bufuralol     |              | Phenformin       |
| Propafenone     | Clomipramine    |               |              | 4-OH amphetamine |
| Sparteine       |                 |               |              |                  |
| N-propylamaline |                 |               |              |                  |

Oriental populations.<sup>26</sup> The frequency of poor metabolisers approaches as high as 70% on the two islands of Vanuatu in eastern Melanesia.

**N-Acetylation polymorphism:** This polymorphism was first reported by Evans et al<sup>27</sup> in 1960 when they studied the rate of elimination of isoniazid in tuberculous patients. Sulfamethazine, hydralazine, procainamide, dapsone and nitrazepam are metabolised by this system.<sup>11</sup> Table I shows the inter-ethnic distribution of slow acetylators. Blum et al<sup>28</sup> in 1990 discovered that the NAT2 gene was responsible for the polymorphic distribution of N-acetylation activity in humans.

Ethnic differences in acetylator phenotypes illustrate very well how genetic polymorphisms affect drug metabolism (Table I).<sup>8</sup> There is a higher incidence of fast acetylator phenotype in Asians, resulting in reduced concentrations of drugs undergoing acetylation and reduced drug effects. An example will be the reduced anti-tuberculous efficacy of isoniazid.<sup>8</sup> On the other hand, slow acetylator phenotypes can cause specific adverse drug reactions such as those associated with hydralazine-induced lupus, isoniazid-induced neuropathies and sulphonamide-induced hypersensitivity reactions. In all these adverse drug reactions, acetylation inactivates the compound concerned. There is also an increased risk of phenytoin toxicity in slow acetylators treated concurrently with phenytoin and isoniazid because isoniazid is an inhibitor of the metabolism of phenytoin.

In addition, as NAT2 is an important cytosolic enzyme for the detoxification and/or bioactivation of various carcinogenic arylamines,<sup>29</sup> it was hypothesised that the polymorphism of NAT2 gene is linked to the occurrence of bladder and colorectal carcinomas.<sup>30</sup> The relative risk of having bladder cancer in slow acetylators was 2 to 3 times compared to the rapid acetylators.<sup>31</sup> In Japan where the frequency of slow acetylators is only 11%, bladder cancer has a low (6.3 per 100,000) incidence. In contrast, the corresponding figures in the United States are 58% and 25.8/100,000, respectively.<sup>32</sup> The Japanese also have a very low incidence of colorectal cancer.<sup>33</sup>

**S-methylation polymorphism:** TPMT is a genetically-determined polymorphic cytoplasmic enzyme which catalyses the S-methylation of aromatic and heterocyclic sulfhydryl drugs like 6-mercaptopurine and its pro-drug azathioprine.<sup>9</sup> Azathioprine and 6-mercaptopurine are catalysed competitively by S-methylation and the metabolic route to form cytotoxic metabolite 6-thioguanine nucleotide (6-TGN) which may disrupt DNA.<sup>9</sup> Although TPMT activity is highest in the liver and kidneys, substantial activity can be detected in red blood cells.<sup>34</sup> The genetic polymorphism which controls TPMT activity in the human red blood cell has been shown to regulate the level of this

enzyme activity in hepatic tissue.<sup>35</sup>

Patients with low TPMT activity in erythrocytes treated with azathioprine and 6-mercaptopurine were highly susceptible to myelosuppression.<sup>36,37</sup> This is because low TPMT activity in these patients leads to the accumulation of 6-TGN in the blood and patients with high 6-TGN levels are more vulnerable to get thiopurine-induced myelosuppression.

In a white population, the frequency of phenotypes having high, intermediate, and low TPMT activities are 88.6%, 11.1%, and 0.3%, respectively. However, in a study of 119 healthy Chinese subjects, TPMT activity in the Chinese population in Singapore was lower than what might have been expected in a white population. In addition, no gender-based differences were discovered.<sup>34</sup>

### Conclusion: The New Millennium

As the explosion of new discoveries in medical, biological and technological expertise takes us into the new millennium, there are rapid advancements in the field of pharmacogenetics with respect to pharmacotherapy. New methodologies in receptor biology, enzymology, genetic recombination and cloning technology as well as biochemical toxicology have enhanced our insight into the molecular aspects of pharmacogenetics and an individual's susceptibility to disease. As more genetic polymorphisms of drug metabolism systems are discovered and characterised, their relevance and importance in the medical practice and the drug development process have become increasingly recognised.

The identification and isolation of genetic variants in humans are now being viewed as fundamental to the understanding of inter-individual variability in pharmacotherapy.

With the new DNA chip technologies, it will soon be possible to genotype every individual according to their disease susceptibility genes as well as drug metabolism phenotype. This knowledge will provide the clinician with the ability to prophylactically target specific molecular defects and to provide effective and optimal drug therapies that maximise therapeutic efficacy and minimise adverse drug reactions. The social and medical benefits to such an optimised process would be expected to be quite substantial. The ethics of such methods have, however, been inadequately addressed this far. It is hoped that the future will bring not only greater understanding but also greater wisdom in the use of these new technologies.

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