Polymorphisms of CYP and ethnic differences

Tomonori Tateishi, MD
Pharmaceuticals & Medical Devices Agency, Chiyoda-ku, Tokyo, 100-0013 Japan.

Key words: CYP, polymorphism, ethnic differences, drug metabolism, antiepileptic drugs

Published online April 11, 2010

There is ample evidence for genetic polymorphisms of drug-metabolizing enzymes showing distinct subgroups in a population with or without the ability to transform certain drugs into polar metabolites before elimination. The polymorphic alleles lead to altered activity of these isoenzymes causing absent, decreased, or increased metabolism. An individual carrying two defective mutation alleles is categorized as a poor metabolizer (PM) and an individual carrying one or two wild-type alleles as an extensive metabolizer (EM). Like most other agents, many antiepileptic drugs (AED) are metabolized by a variety of enzymatic reactions, and the polymorphisms in the CYP family have attracted considerable attention. The CYP2D6, 2C9, and 2C19 polymorphisms account for the most frequent variations in phase I metabolism of drugs [1, 2].

Among these polymorphisms, CYP2D6 polymorphism was first discovered in the late 1970s [3]. CYP2D6 is responsible for the metabolism of drugs including beta-blockers, tricyclic antidepressants, and codeine which is metabolized to morphine. The in vivo activity of CYP2D6 is functionally absent [CYP2D6 poor metabolizers (CYP2D6 PM)] in 8% of Caucasians in Europe and North America, but
in fewer than 1% of Chinese or Japanese, contributing to the variability in drug concentrations and responses in these racial groups [4, 5]. The reason for the defect appears to be faulty expression of the cytochrome P450 protein, resulting in little or no isoform-catalyzed drug metabolism. Despite the low frequency of CYP2D6 PM in Asian populations, the mean distribution of the urinary metabolic ratio (MR) of debrisoquine / 4-hydroxydebrisoquine of EMs in a Chinese population is shifted towards higher values compared to a Swedish population, suggesting that a Chinese population has lower metabolic activity of CYP2D6 in vivo than a Swedish population [4]. Johansson et al. [6] investigated the molecular basis for the slow metabolism in Chinese EMs and reported that a variant of CYP2D6 (CYP2D6*10) was found at high frequency. This mutation in a Chinese results in lower enzyme activity both in vitro and in vivo compared to the wild type of CYP2D6 (CYP2D6*1). While CYP2D6*10 is the most frequent gene in the Chinese population (approximately 50%), its frequency in Caucasians (less than 2%) is much lower than that in Chinese [6] or Japanese [7] (approximately 40%). Among EMs in some Asian populations, the distribution of the in vivo CYP2D6 activity seems to vary. For instance, a previous phenotyping study reported differences in the frequency mode of the distribution histogram between Japanese and mainland Chinese populations, and a study of Taiwanese and mainland Chinese populations also indicated that there are inter-ethnic differences in the in vivo CYP2D6 activity between Asian populations [8]. As an extrem oppositie to CYP2D6 PM, the ultrarapid metabolizer phenotype can be caused by CYP2D6*2 allele, which is the second frequent CYP2D6 gene (allele frequency is around 30%) in Caucasians and is reported to be present in multiple (up to 13) gene copies in some persons (1-2% in Caucasians) resulting in extremely high in vivo CYP2D6 activities [9]. The frequency of CYP2D6*2 in Chinese and Japanese is around 10%, lower than that in Caucasians, and a person carrying CYP2D6*2 allele shows modest activity of CYP2D6 in vivo, suggesting that multiplicated CYP2D6*2 allele in a Japanese is unlikely. The allele frequencies of CYP2D6 in Japanese [7, 10], Chinese [6] and Caucasian [11] populations are summarized in Table 1.

The second polymorphism was discovered
in the 1980s in a study of the metabolism of the anticonvulsant drug mephenytoin, which has been known as the CYP2C19 polymorphism [12]. Population studies have shown that individuals can be categorized as EMs or PMs of this drug. The PM trait is inherited as an autosomal recessive trait, and the frequency of CYP2C19 PM is very low among Caucasians (less than 5% of the population) but more frequent in Asians (more than 10%) [13]. The PM phenotype is even more common throughout Polynesia and Micronesia with a very high frequency in certain Vanuatu islands of Eastern Melanesia [14]. This polymorphism has been shown to be due to genetic polymorphisms in CYP2C19. Among several variant alleles reported to date, two alleles with separate mutations have been associated with the defective enzyme in Caucasian and Asian populations (Table 2) [15]. The first is CYP2C19*2, which has a mutation in exon 5 causing an aberrant splice site. The other variant allele is CYP2C19*3 with a point mutation in exon 4 producing a premature stop codon. The most commonly mutated allele is CYP2C19*2 in both Asian and Caucasian PMs. The second discovered mutation, CYP2C19*3, is rare among Caucasian subjects but accounts for the remaining defective alleles in Asian subjects. Carriers of two CYP2C19 defective alleles have a severely impaired capacity to metabolize drugs that are substrates for this enzyme and are hence designated PMs. CYP2C19 is responsible for the metabolism of several therapeutically important drugs including omeprazole, lansoprazole, propranolol, imipramine, mephenytoin, chloroguanide, hexabarbitone and diazepam. Diazepam is metabolized to desmethyl diazepam and temazepam by CYP2C19 and 3A, respectively. In CYP2C19 PMs, the apparent oral clearance of diazepam is reduced and the elimination half-life is prolonged, compared to CYP2C19 EMs [16].

Recently, the mutation of CYP2C19 causing ultrarapid metabolism was found by a Swedish group, and this allele (CYP2C19*17) was identified in the allele formerly categorized as the wild type allele [17]. The allele frequency of this mutation was reported to be 18% in both Swedes and Ethiopians and 4% in Chinese. An individual homozygous for this mutation has lower metabolic ratio of omeprazole and mephenytoin, meaning higher metabolic activity, that results from an increased transcriptional activity of this allele. Omeprazole total body clearance is reported to be around 50% increased, and the increase is

Table 2. Allele frequencies of CYP2C19 in Japanese, Taiwanese and Caucasian populations (numbers in brackets are numbers of references).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19*1</td>
<td>0.592</td>
<td>0.670</td>
<td>0.630</td>
<td>0.871</td>
</tr>
<tr>
<td>CYP2C19*2</td>
<td>0.279</td>
<td>0.230</td>
<td>0.320</td>
<td>0.129</td>
</tr>
<tr>
<td>CYP2C19*3</td>
<td>0.128</td>
<td>0.104</td>
<td>0.055</td>
<td>0</td>
</tr>
</tbody>
</table>
considered to be not as striking as in a ultra-rapid metabolizer of CYP2D6 [10]. We also studied this allele frequency, and only 3 heterozygous subjects were found out of 97 wild type homozygous subjects, and their metabolic activity was not striking. In 265 subjects, 7 heterozygous subjects were found, resulting in an allele frequency of 1.3%. In a Japanese population, low CYP2C19*17 allele frequency and the absence of homozygote suggest that this mutation has a minor role in CYP2C19 activity of the Japanese population [18].

CYP2C9 is another clinically significant drug metabolizing enzyme that demonstrates genetic variants defined as CYP2C9*2 and *3. The frequencies of CYP2C9*2 and *3 alleles vary among different ethnic populations: they are present in approximately 10-15% and 5-10%, respectively, of white populations, and are even less frequent (0% and 1%, respectively) in black and Asian populations [13]. CYP2C9 is responsible for the metabolism of clinically important drugs including phenytoin, warfarin, and certain antidiabetic drugs. The low frequency of defective CYP2C9*3 allele, however, contributes to the rarity of CYP2C9 PMs in the Japanese population and an individual heterozygous for CYP2C9*3 has fairly reduced metabolic activity. An individual carrying the CYP2C9*3 allele has lower daily dose requirement of phenytoin, a substrate of CYP2C9, and appears more susceptible to adverse events during the initiation of therapy. In a retrospective analysis of epileptic patients in the UK, the clinical dosage of phenytoine was reported to be different depending on the number of the CYP2C9*3 allele. Patients heterozygous for CYP2C9*3 needed 13% reduction of dosage and a homozygous patient required 29.4% reduction [19]. Another retrospective study from Taiwan reported the pharmacokinetic parameters calculated from a population analysis of the measured plasma concentrations of phenytoin for different CYP2C9 and 2C19 polymorphisms, and the authors recommended reducing the normal dosage of phenytoin (5–7 mg/kg/day) to 2–4 mg/kg/day for patients heterozygous for CYP2C9*3, but no adjustment for patients without CYP2C9*3 even if they carry defective alleles of CYP2C19. Their study suggests that CYP2C9 plays a greater role in phenytoin metabolism than CYP2C19 does [20].

In conclusion, polymorphic CYPs such as CYP2C9 or CYP2C19 partly contribute to the metabolism of some antiepileptic drugs such as diazepam, mephenytoin, and phenytoin, but genetic variation involving genotypes of drug metabolism has limited clinical impact on the treatment of epilepsy, because the elimination of most antiepileptic drugs is not affected by polymorphic enzymes. Nevertheless, it is useful to know that genetic variation may play a role in a patient developing side effects when treated with hepatically metabolized antiepileptic drugs, even though it seems to be rare.

References


