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Allele and phenotype frequencies of CYP2D6 in the Turkish population

Safa Can Polat[a], Muhammet Burak Batir[b], Fethi Sirri Cam[c,*]

[a] *Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Biology, Manisa, Türkiye*
[b] *Manisa Celal Bayar University, Faculty of Science and Letters, Department of Biology, Manisa, Türkiye*
[c] *Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, Manisa, Türkiye*

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Abstract

Aim: Cytochrome P450 is a hepatic enzyme system responsible for drug metabolism that comprises different iso-enzymes. The CYP2D6 enzyme, which composes 2-4% of all cytochrome enzymes, is responsible for 25% of the metabolisms of the drugs used in clinics. The genetic polymorphisms of this enzyme can change the efficiency and toxicity of the drugs used. In this study, the retrospective evaluation of CYP2D6 gene polymorphisms that influence enzyme activity in the Turkish population is targeted.

Materials and Methods: From the 192 patients sent from psychiatry, medical genetics, and neurology polyclinics to our laboratory, we determined CYP2D6 enzyme gene polymorphisms by multiplex polymerase chain reaction (PCR) and multiplex allele-specific primer extension (ASPE).

Results: Of all the cases, 82.29% were determined to be extensive, 12.5% intermediate, 2.08% poor, and 3.13% ultra-rapid metabolizers. In our population, the most frequent alleles were *1 (37.63%), *2 (24.75%), *41 (15.15%), *4 (9.85%), and *10 (4.29%), respectively.

Conclusion: Compared to previous studies conducted on Turkish society, the percentage of extensive metabolizers was higher in the current examined population. In contrast, the percentages of poor and ultra-rapid metabolizers were lower. In addition, the *41 allele, which has not been studied before in our population, that follows the decrease in enzyme function was detected as the most frequent allele in this study. The fact that the percentage of the cases in which changes were observed was 17.1% will help determine the CYP2D6 gene mutations in the pre-treatment cases.

Introduction

Belonging to the family of Cytochrome P450, liver isoenzymes are responsible for the metabolization of 90% of all drugs used clinically. Primary phase I enzymes have the highest strength among the Cytochrome P450 enzymes. Furthermore, among significant phase I enzymes, CYP2C9, CYP2C19, and CYP2D6 compose 40% of phase I hepatic drug metabolism [1]. In addition, CYP2D6 metabolizes clinically significant drugs like antidepressants, antipsychotics, antiarrhythmics, chemotherapeutics, and neuroleptics [2, 3].

Localized in 22q13.1 of the chromosome, the CYP2D6 gene region - with its more than 70 allelic variants, is the first defined gene at the molecular level and the most studied polymorphic cytochrome enzyme gene [4,5]. Many alleles of CYP2D6 encode enzymes that have reduced (*9, *10, *17, *29 and *41) or no-function (*3, *4, *5, *6, *7, *8, *11 and *15) compared to the wild-type (*1) enzyme. Among these allelic variants, the most important ones are CYP2D6*2, CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*17 and CYP2D6*41 [6]. Non-functional and reduced alleles can occur due to a missense mutation in the gene region, frameshift mutation, splicing defect, mutations causing premature stop codon and insertion, intragenic deletion, or total gene deletion. Individuals can also rearrange genes with more than two copies of the CYP2D6 gene (gene duplication) [7]. Therefore, depending on an individual's combination of alleles, drug-metabolizing phenotypes associated with the CYP2D6 enzyme can vary. On the other hand, among these derived allelic variants leading to null or inadequate metabolic activity, such as *4, *10, *17, and *41, could reach a relatively high frequency in Europe, East Asia, Africa, and Western Eurasia, respectively [8].

*Corresponding author:
Email address: sirri.cam@cbu.edu.tr (Fethi Sirri Cam)

CYP2D6 enzyme phenotypes have been classified into four groups, from the lowest level of metabolism to the highest: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra-rapid extensive metabolizers (UMs) [9]. Extensive metabolizers are defined as having regular enzyme activity and are homozygous or heterozygous for at least one functional or reduced functional allele. IMs have decreased enzyme activity relative to EMs and have two reduced functional alleles, one non-functional allele, and one reduced functional allele. PMs have little or no CYP2D6 catalytic activity and have two non-functional alleles. Finally, UMs have multiple functional alleles (CYP2D6*1XN and CYP2D6*1XN) of a single CYP2D6 gene, increasing enzyme activity [10].

Determining the genetic variations in the CYP2D6 enzyme gene is significant in cases where no drug effect is seen and various adverse effects exist. Individuals with PM, IM, and UM phenotypes that occur due to the variations in the CYP2D6 enzyme gene may display different pharmacokinetic interactions from normal individuals. In individuals with PM and IM phenotypes, drug toxicity may be increased depending on the decreased enzyme activity [11]. PM patients prescribed tricyclic antidepressants (TCA) who are homozygous for the CYP2D6*4 allele metabolize these drugs more slowly, which puts them at higher risk for adverse side effects. In users of tricyclic antidepressants (TCAs), the side effect risk of changing to another antidepressant was remarkably higher in poor metabolizers (PMs:*4/*4) compared with extensive metabolizers (EMs:*1/*1) [12]. Also, in CYP2D6 *4/*4 PMs, beta-blocker (metoprolol) users' adjusted heart rate was ~4 times lower compared with *1/*1 extensive metabolizers (EMs), causing an increased risk of bradycardia in PMs. Also, tamoxifen-treated patients with CYP2D6 alleles *4, *5, *10, *41 had worse survival rates than carriers of functional alleles because of the impaired tamoxifen metabolism [13]. In UMs, the inability to adequately respond to the standard doses of drugs is observed. On the other hand, UMs can suffer from parallel difficulties to PMs. Despite having opposite phenotypes, both can experience toxicities; however, UMs would encounter toxicities resulting from an increased metabolite level, whereas the PMs would encounter toxicities resulting from an increased level of the parent drug [14].

In today's world, it is expected that modern medicine has not only the function of aftercare but also prevention of the disease's occurrence and foresight. In this sense, genetic information is used primarily for this foresight. Determining the frequencies of alleles that cause variations in CYP2D6 enzyme activities in societies and their phenotypic effects will enable designing individualized treatment doses for the drugs metabolized with this enzyme. Therefore, in this study, the evaluation of the Turkish population's frequencies of alleles of the CYP2D6 enzyme gene and its phenotypic effects is targeted. For the sake of treatment efficacy, screening the genotypes in societies in which genotypes affecting enzyme activity are frequent is of vital importance.

Materials and Methods

DNA extraction from blood samples

The number of cases required for the groups was determined through the G*Power statistical analysis program, with an impact scale of 1.0, and the total number of cases required for the study was 192. Unrelated 192 patients (96 men and 96 women) from psychiatry and neurology polyclinics at Manisa Celal Bayar University are included as study participants. Approval from the Clinical Research Ethics Committee of Manisa Celal Bayar University was obtained for the study protocol (approval no. 20.478.486). DNA with sufficient purity (260/280 ratios: ≥1.7) and concentration (≥ 30 ng/µl) was obtained by QIAamp® DNA Mini Kit from the patient's peripheral venous blood samples in EDTA tubes. The DNA samples obtained by the patients were studied using the methods of multiplex polymerase chain reaction (PCR) and multiplex allele-specific primer extension (ASPE) on the Luminex 200 platform with a universal tag separation system.

Multiplex PCR

Genotyping of genomic DNA and amplicons of individual genes was performed with the Luminex-based xTag Mutation Detection Kit P450-CYP2D6 version 3 (Austin, Texas, USA). For each genomic specimen being sampled, two independent PCR reactions were performed. The primer mix of PCR-A and TaKaRa Taq™ HS Perfect Mix (Japan) was used to amplify fragments up to 3.8 kb and were used to detect the mutations as listed in Table 1, as well as a duplication amplicon (3.2 kb), which indicated the existence of the duplication genotype. The primer mix of PCR-B and TaKaRa Taq™ HS Perfect Mix (Japan) was used to amplify produced fragments up to 2.6 kb and were used to detect the mutations as listed in Table 1, as well as a deletion amplicon (3.5 kb) indicative of the deletion genotype. The thermal cycling conditions (SensoQuest, Gottingen, Germany) of the PCR program comprised an initial denaturation step of 3 min at 98 °C, then 35 cycles of 95 °C (60 s), 66 °C (30 s), 72 °C (210 s) pursued by a final extension step of 5 min at 72 °C.

Amplicon treatment and multiplex allele-specific primer extension

The two reactions (PCR-A and PCR-B) were pooled following PCR amplification. To facilitate efficient incorporation of biotin-dCTP during the multiplex Allele-Specific Primer Extension (ASPE) reaction, the pooled PCR product was treated with Shrimp Alkaline Phosphatase to inactivate any remaining nucleotides (particularly dCTP) and with Exonuclease I to degrade any primers leftover from the PCR reaction in the thermal cycler (SensoQuest, Gottingen, Germany) with 30 min at 37 °C and 5 cycles of 99 °C conditions. ASPE was then carried out using xTAG 2D6 v3 ASPE Primer Mix and the 5X Platinum Tfi Reaction Buffer and Tfi 50 mM MgCl2 in the thermal cycler (SensoQuest, Gottingen, Germany) with 2 min at 96 °C, then 40 cycles of 94 °C (30 s), 56 °C (30 s), 74 °C (30 s) pursued by a final extension step of 15 min at 99 °C conditions.

Table 1. Mutations observed by xTAG CYP2D6 kit.

	Mutations and Polymorphisms detected by xTAG CYP2D6 Kit		Predicted Enzyme Activity
* Genotype[1]	PCR A	PCR B	Normal
*1	None	None	Normal
*2	-1584 C>G, 1661 G>C	2850 C>T, 4180 G>C	None
*3		2549 A>del	None
*4	100 C>T, 1661 G>C, 1846 G>A	2850 C>T, 4180 G>C	None
*5		Deletion	None
*6	1707 T>del	4180 G>C	None
*7		2935 A>C	None
*8	1661 G>C, 1758 G>T	2850 C>T, 4180 G>C	None
*9		2613-2615 delAGA	Reduced
*10	100 C>T	1661 G>C, 4180 G>C	Reduced
*11	883 G>C, 1661 G>C	2850 C>T, 4180 G>C	None
*14A	100 C>T, 1661 G>C, 1758 G>A	2850 C>T, 4180 G>C	None
*15	138 insT		None
*17	1023 C>T, 1661 G>C	2850 C>T, 4180 G>C	Reduced
*41	1661 G>C	2850 C>T, 2988 G>A, 4180 G>C	Reduced
DUP	Duplication		Enhanced

Bead hybridization and Data acquisition

A 2.5 µL aliquot of the ASPE reaction was hybridized with the universal array (BeadMix) in the presence of the hybridization buffer and incubated with streptavidin, R-phycoerythrin conjugate (reporter solution). Specimens were analyzed on the Luminex 100/200 instrument, and a signal was generated for each locus and the duplication and deletion amplimers if present. These fluorescence values were then examined to define whether each loci's wild-type/mutant allele was detected or whether the samples carried an allele(s) with the deletion or duplication.

Table 1 shows the duplications, deletions, polymorphisms, mutations, and related alleles. According to the obtained data, alleles were determined, and the phenotypes table identified patients' phenotypes.

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23 and are presented as medians. Allele and genotype frequencies were calculated by the counting method and were tested for Hardy-Weinberg equilibrium. The chi-square test was used to compare frequencies between populations.

Results

Of all the patients' phenotypes, 2.08% were determined as poor, 82.29% as extensive, 12.5% as intermediate, and 3.13% as ultra-rapid metabolizers (Table 2).

Table 2. Cases by Phenotypes.

Phenotype	Number of Cases	Frequency (%)
Poor Metabolizer (PM)	2	2.08
Intermediate Metabolizer (IM)	24	12.5
Extensive Metabolizer (EM)	158	82.29
Ultra Rapid Metabolizer (UM)	6	3.13
Total	192	100

Table 3. Cases by the Frequencies of Alleles.

Variant Allele	Frequency (%)	95% Confidence Interval
CYP2D6 *1	37.63	37.55-37.71
CYP2D6 *2	24.75	24.36-25.14
CYP2D6 *41	15.15	15.08-15.22
CYP2D6 *4	9.85	9.81-9.89

Table 4. Genotypes by Extensive Metabolizers.

Genotype	Number of Cases	Observed (predicted) Frequency[a] (%)
*1/*2	39	20.31 (20.2)
*1/*1	27	14.06 (14.42)
*1/*41	22	11.46 (11.03)
*2/*41	13	6.77 (6.88)
*2/*2	11	5.73 (5.66)
*1/*4	11	5.73 (5.66)
*2/*4	11	5.73 (5.66)
*1/*10	7	3.65 (3.69)
*2/*10	4	2.08 (2.17)
*1/*5	4	2.08 (2.17)
*2/*5	3	1.57 (1.62)
*1/*9	2	1.04 (1.01)
*2/*17	1	0.52 (0.53)
*1/*17	1	0.52 (0.53)
*1/*6	1	0.52 (0.53)
*1/*3	1	0.52 (0.53)
Total	158	82.29

[a] Predicted frequencies calculated according to the Hardy–Weinberg equation.

Variant CYP2D6 alleles were within the 95% confidence interval (Table 3). Also, genotype frequencies of the

Table 5. Genotypes by Intermediate Metabolizers.

Genotype	Number of Cases	Observed (predicted) Frequency[a] (%)
*4/*41	8	4.16 (4.24)
*41/*41	6	3.13 (3.02)
*4/*10	3	1.57 (1.49)
*10/*41	2	1.04 (1.05)
*7/*41	1	0.52 (0.54)
*4/*9	1	0.52 (0.54)
*5/*41	1	0.52 (0.54)
*17/*41	1	0.52 (0.54)
*10/*11	1	0.52 (0.54)
Total	24	12.5

[a] Predicted frequencies calculated according to the Hardy–Weinberg equation.

Table 6. Genotypes by Poor Metabolizers.

Genotype	Number of Cases	Observed (predicted) Frequency[a] (%)
*4/*4	2	1.04 (1.0)
*4/*6 *	1	0.52 (0.54)
6/*6	1	0.52 (0.54)
Total	4	2.08

[a] Predicted frequencies calculated according to the Hardy–Weinberg equation.

Table 7. Genotypes by Ultra Rapid Metabolizers.

Genotype	Number of Cases	Observed (predicted) Frequency[a] (%)
*1/*1DUP	3	1.57 (1.66)
*1/*2DUP	2	1.04 (1.01)
*2/*2DUP	1	0.52 (0.46)
Total	6	3.13

[a] Predicted frequencies calculated according to the Hardy–Weinberg equation.

CYP2D6 were in equilibrium with the Hardy–Weinberg equation (Table 4-7).

The most frequent alleles in the CYP2D6 gene were determined as *1, *2, *41, *4, and *10, respectively (Table 3). While the percentage of the alleles with the normal function was 62.37%, and that of the non-functional was 13.64%, 8 and 14A alleles were not observed. Besides, the percentage of the reduced function alleles was 20.96%, and duplicative alleles were 3.03%.

In EMs, 16 different genotypes were determined, and *1/*2 was considerably frequent (Table 4).

The *41 allele, which causes a reduction in enzyme activity, was examined in all IMs except for allele *4. The *4/*41 genotype is the most frequent in these cases (Table 5).

The *4 allele, which causes enzyme inactivation, was observed in % 9.85 of the cases, and the genotypes of the PMs were *4/*4, *4/*6, *6/*6 and *10/*11 (Table 6).

In UMs, the duplication of *1 and *2 alleles was observed (Table 7).

Discussion

Depending upon CYP2D6 enzyme gene polymorphisms that vary by ethnicity and individual, enzyme phenotypes may be observed in different frequencies in different societies [15,16]. CYP2D6 enzyme is a cytochrome iso-enzyme important in 25% of the metabolism of medicines utilized in clinics, especially psychiatric ones. Therefore, allelic differences of this enzyme gene may affect enzyme activity and, depending upon the enzyme phenotype, may change the serum level of the medicines used [17, 18]. For this matter, for the CYP2D6 gene in Turkish society, 16 different frequencies of allele, phenotype, and genotype were specified with the help of Luminex and XMap analysis systems in this study.

Most PM phenotypes range from 0–2%, 5–10%, 0-2%, and 0-19% in Asians, Caucasians, Arabians, and African, respectively [19,20]. As for the current study, the frequency of PM phenotype was observed as ~%2,1. These cases constitute risky groups regarding drug intoxication and possible adverse effects. It was ascertained that this frequency is much lower than the ones (5-10%) reported in Europe [20]. With this study and others related to Turkish society, it has been observed that the prevalence of the PM phenotype ranges from 1% to 4%.

The PM phenotype is most commonly associated with a particular allele, the CYP2D6*4 allele, disrupting proper mRNA formation. The frequency of the CYP2D6*4 allele is 12-21% for Caucasian populations and 1-4% for Asians, Black Africans, and Saudi Arabians [20-22]. In particular, the PM phenotype in whites mainly results from the existence of the non-functional alleles CYP2D6*3 and CYP2D6*4. The frequency of the CYP2D6*4 allele was reported between 10,0-13,9% in previous studies on Turkish society [23-25]. As for this study, *4 alleles were found close to the numbers in the previous related studies on Turkish society and the highest (9,85%) among non-functional alleles. CYP2D6*4 alleles exist with a frequency of about 75% among non-functional alleles in the Caucasian populations, while that of CYP2D6*3, *4, *5, *6 alleles is 98% [20,26,27]. Similarly, in this study, the CYP2D6*4 allele exists with a frequency of about 72% among non-functional alleles in the Turkish populations, while that of CYP2D6*3, *4, *5, *6 alleles is 96%. Interestingly, in this study, despite the close similarity between the non-functional allele frequencies of CYP2D6 that causes PM phenotype in the Turkish and Caucasian societies, the Turkish PM phenotype frequency (~2%) was lower than that of the Caucasian (5-10%).

However, on the contrary, the frequency of IMs (12,5%) that follow a reduction in enzyme activity was monitored at a similar rate to the one that Serin et al. reported (12%) [24]. Nevertheless, the frequency of the IMs in Aynacıoğlu et al. was reported as 23,8% [23]. The CYP2D6 phenotype depends on environmental factors in addition to the CYP2D6 genotype. The co-administration of drugs metabolized by CYP2D6 or other drugs that can act as inducers or inhibitors of CYP2D6 also affects the drug-metabolizing phenotype. Other factors include the indi-

vidual's age, size and gender, renal and liver function, disease statuses, and lifestyle factors such as smoking, some foods, and alcohol consumption [28-30]. The presence of these other factors that influence phenotype is rather crucial for IMs. In IMs, combining other factors that affect enzymes, the drug may lead to toxications [31]. Therefore, the adverse effects of drugs on IMs should be sifted through, and patients should be informed about this situation.

An important finding of this study is that the *41 allele was the most frequent mutant allele in our population, which has not been studied before. Observed with a decrease in enzyme activity, this allele has been evaluated for the first time in Turkish society with a quite high frequency (15,15%). While it was seen at least in one allele of 82% of all the IMs, it was observed at least in one allele of 82% of all the EMs. The frequency of the *41 alleles was 69% in the reduced alleles of the Caucasian population and 20% in the general population. Besides, this variant represents 50-60% of IMs in Caucasian populations [32,33]. In our study, the frequency of the *41 alleles was 72% in the reduced alleles and 15,5% in the general population.

Throughout history, Turkey has served as a geographical bridge connecting the West, East, and Middle East. Therefore, the mutation spectrum in CYP2D6 reflects the diverse ethnic origins of the Turkish population, including African, Middle Eastern, and Asian populations. In our study, the frequency of the reduced *17 allele was 0,76%, while it was 1,11% in Aynacioğlu's study [23]. Considering our ancestors' Northern migration stops, Africa, Saudi Arabia, Europe, and Asia, it can be observed that the frequencies of *17 alleles are 20-35%, 3-9%, 0-1%, and 0%, respectively. Last, the reduced *10 allele frequencies in Africa, Saudi Arabia, Europe, and Asia are 6%, 3-9%, 1-2%, and 51%, respectively [8,11,19,20,34]. This study and the related others indicate that the frequency of the reduced *10 alleles is 4-6% [23-25].

The frequencies of non-functional CYP2D6*3 and reduced *9 alleles were restricted to Europe, although they did not reach polymorphic frequencies (>1%) [8,9,20]. Similarly, both in this study and in Ayanicioğlu's, the CYP2D6*3 and *9 alleles frequencies are below 1%. Moreover, the frequencies of the CYP2D6*7 and *11 alleles are below 0.25% [23].

The frequencies of EMs that include at least one of CYP2D6 *1 or *2 alleles, which are connected with functional enzyme-encoding, varies by region: Caucasian (84%), Arabian 76%), African (77%), and Asian (80%) [8,20,35]. However, in Caucasians, the frequency of EMs is higher than in other populations. In Serin et al.'s study on the Turkish population in Euro-Asia, the frequency of EMs is indicated as 63%, and Aynacıoğlu et al. reported this frequency as 66,1% [23,24]. In comparison, it is 82,29% in our study. These findings differ from the methods used and alleles observed. In our study, in addition to the alleles observed in Serin et al.'s research, CYP2D6 *1, *2, *7, *8, *11, *14A, *15, *17 and *41 alleles and in addition to the alleles observed in Aynacıoğlu et al.'s study, CYP2D6 *41 allele were examined. Moreover, as the patients from various parts of Turkey (Anatolia, Aegean, and Marmara) were the participants in this study, the variation between the previous related research may be due to regional differences.

The total frequency of the functional CYP2D6 *1 (~30%) and *2 (~25%) is ~55% in Caucasians [20,35]. On the other hand, in this study, the total frequency of the functional CYP2D6 *1 (37,6%) and *2 (24,8%) is 62,4% in Turkish society. This frequency in the Arabian, African, and Asian populations is ~60%, ~55%, and ~60%, respectively [20,35]. Despite the interaction among Turkish, Asian, and Middle Eastern societies, the frequency of CYP2D6 *1 and *2 alleles in the Turkish population is similar to that of Caucasians. The frequency of UMs in this study is 3.13%, similar to the frequency (2-3%) previously reported in most European countries [20,35]. However, Serin et al. reported the frequency of UMs in Turkish society as 4%, and Aynacıoğlu et al. reported this frequency as 8.66% [23,24]. As previously mentioned, dissimilarities between our study and previous ones may be due to regional or methodological differences.

Conclusion

This study determined the CYP2D6 phenotype and allele frequency in the Turkish population. Among the non-functional and reduced CYP2D6 alleles in Turkish society, the frequency distribution of *3, *4, *5, *6, *9, and *41 allelic variants was similar to that of Caucasians. Among the reduced and non-functional CYP2D6 alleles, the Turkish population exhibits the highest frequency of *41 and *4, respectively, comparable to the Caucasian population. In addition, the frequencies of PMs (2,08%) and IMs (12,5%) in Turkish society differ from the frequencies of PMs (7,5%) and IMs (6%) in Caucasians. For the Turkish population, determining the frequency distributions and allele frequencies of CYP2D6 phenotypes can guide the selection of suitable treatments for patients. Moreover, the near future will inform us about the clinical and practical utility of the studies on the family of Cytochrome P450 genes.

Ethical approval

This study was approved by the Clinical Research Ethics Committee of Manisa Celal Bayar University (approval no. 20.478.486). All methods were performed in accordance with the relevant guidelines and regulations.

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