J Surg Med. 2018;2(3):210-214.
DOI: 10.28982/josam.416309

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Determination of CYP2D6*3 and *4 allele frequency among Turkish population

Türk popülasyonunda CYP2D6*3 ve *4 allel frekansının saptanması

Zehra Okat [1,2], Kübra Yaman [1,2], Kezban Uçar Çiftçi [1,2], Selina Toplayıcı [1,2], Elif Kurt [1,2], Yavuz Taga [1,2]

[1] Department of Biochemistry, School of Medicine, Marmara University, Maltepe, Istanbul, Turkey
[2] Genetic and Metabolic Diseases Research and Implementation Centre, Marmara University, Maltepe, Istanbul, Turkey

ORCID ID of the authors
ZO: 0000-0002-9966-9884
KY: 0000-0002-4318-0529
KUÇ: 0000-0003-2448-6538
ST: 0000-0003-4221-7219
EK: 0000-0003-1956-575X
YT: 0000-0001-9450-5031

Corresponding author / Sorumlu yazar:
Zehra Okat
Address / Adres: Marmara Üniversitesi, Tıp Fakültesi, Biyokimya Anabilim Dalı, Maltepe, 34854, İstanbul, Türkiye
E-mail: zehraokat1980@gmail.com

Ethics Committee Approval: This project was approved by the Medical Faculty Ethics Committee of Marmara University (Number: B.30.2.MAR.0.01.02/AEK/207; Date: 01/03/2012).
Etik Kurul Onayı: Bu proje Marmara Üniversitesi Tıp Fakültesi Etik Kurulu tarafından onaylandı (Sayı: B.30.2.MAR.0.01.02 / AEK / 207; Tarih: 01.03.2012).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 17.04.2018
Accepted / Kabul Tarihi: 25.04.2018
Published / Yayın Tarihi: 25.04.2018

Abstract

Aim: CYP2D6 takes part in the family of cytochrome P450 enzymes, which is account for the detoxification of multifarious xenobiotics and various drug commonly used in medicine. CYP2D6 is a polymorphic gene encompassing more than 80 known polymorphism within the coding and promoter regions. The mutant CYP2D6*3 allele revealed with the deletion of A2637 found in exon 5 region. The other common mutant allele is CYP2D6*4 and this allele stem from a splice site defect of G1934A can be classified as the most typical mutations. The present study primarily aims to determine the CYP2D6*3 and *4 frequency defects among Turkish population.

Methods: Within the framework of the study, two critical alleles of CYP2D6 wild type allele, and CYP2D6*3 -CYP2D6*4 mutated alleles are genotyped on eighty healthy volunteers, who are unrelated, by the method of polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP).

Results: CYP2D6*4 allele frequency, which was identified as the loss of BstNI site, was determined as 13.16% on the examined reference group. Besides, the CYP2D6*4/CYP2D6*4 genotype ratio for the searched reference group was observed in only 2.63%. The heterozygous CYP2D6*3 allele frequency was determined as 1.32% on the examined reference group. Finally, CYP2D6*3/CYP2D6*3 genotype was not encountered in that searched reference group.

Conclusion: In the light of those findings, it can be clearly stated that the prevalence of CYP2D6*3 and *4 allelic variants in the Turkish population is the same with the other demographic groups in Turkey.

Keywords: CYP2D6 polymorphism, Xenobiotics, Turkish population, PCR-RFLP

Öz

Amaç: CYP2D6, çeşitli ksenobiyotiklerin ve ilaçların detoksifikasyonundan sorumlu sitokrom P450 enzim ailesi içerisinde yer almaktadır. CYP2D6, kodlama ve promotör bölgelerinde 80'den fazla bilinen polimorfizm içeren bir polimorfik gendir. En tipik mutasyonlar olarak sınıflandırılan, CYP2D6*3 mutant alleli, ekson 5'de A2637'nin delesyonuyla, CYP2D6*4 mutant alleli ise G1934A'nın splice site defektiyle meydana gelmiştir. Bu çalışmada öncelikle Türk toplumunda CYP2D6*3 ve *4 frekans defektlerinin belirlenmesi amaçlanmıştır.

Yöntemler: Çalışma çerçevesinde; CYP2D6'nın iki kritik alleli olan wild tip ve mutant CYP2D6*3-*4 allelleri, birbirleriyle ilişkisiz 80 sağlıklı kontrol üzerinde, Polimeraz Zincir Reaksiyonu (PZR) ve Restriksiyon Fragment Uzunluk Polimorfizmi yoluyla genotiplendirilmiştir (RFLP).

Bulgular: BstNI bölgesinin kaybı olarak tanımlanan CYP2D6*4 allel frekansı, incelenen referans grupta %13.16 olarak belirlenmiştir. Ayrıca; referans grupta araştırılan CYP2D6*4/CYP2D6*4 genotip oranının sadece %2.63 olduğu gözlemlenmiştir. Analiz edilen referans grupta; heterozigot CYP2D6*3 allel frekansı % 1.32 olarak tespit edilmiştir. Son olarak, CYP2D6*3/CYP2D6*3 genotipine araştırılan referans grubunda rastlanılmamıştır.

Sonuç: Bu bulgular ışığında, Türk populasyonunda CYP2D6*3 ve *4 allelik varyant prevalanslarının diğer demografik gruplarla aynı olduğu açıkça belirtilebilir.

Anahtar kelimeler: CYP2D6 polimorfizmi, Zenobiyotik, Türk popülasyonu, PZR-RFLP

How to cite / Atıf için: Okat Z, Yaman K, Çiftçi KU, Toplayıcı S, Kurt E, Taga Y. Determination of CYP2D6*3 and *4 allele frequency among Turkish population. J Surg Med. 2018;2(3):210-214.

Introduction

CYP2D6 enzyme is associated with the metabolism of currently used drugs, including antidepressants, antipsychotics, antiarryhythmics, anti-cancer, beta blockers, and beta-adrenoceptor [1,2]. In this respect, CYP2D6 locus is fairly polymorphic and recently, around 120 variant CYP2D6 alleles are included in that category (www.cypalleles.ki.se/CYP2D6.htm).

CYP2D6 alleles may be divided into these sub-items: alleles causing non-functional products refer as poor metabolizers (PMs); alleles induce a reduction at - metabolism ratio to be known as heterozygote extensive metabolizers (HEMs); alleles resulting in ultra-rapid metabolism ultra-rapid metabolizers (UMs) means individuals with genetically raised CYP2D6 activity and finally alleles who have minor functional effects called extensive metabolizers (EMs) [3]. In this respect, CYP2D6 gene is located in chromosome 22q13.1. CYP2D6*4 allele which is known as splice site G1934A transition induce truncated protein creation among Caucasians. And also, this mutation is one of the most prevalent mutations for this population group. Similarly, the transition from G to A at the intron 3/exon 4 boundary in CYP2D6 gene region accompanies inappropriate mRNA splicing. This defect leads to a frame shift and immature termination. In the same way, the transition from G to A was defined as a key defect at CYP2D6 locus, and it was presumed to represent 80-90% of the mutant alleles in PM [4]. Allele CYP2D6*3 is a frameshift mutation generated by a 1-bp deletion (2637delA) in exon 5. Those mutations result in the reduction of CYP2D6 isoenzyme activity or non-activity of CYP2D6 isoenzyme, which is finally sourced PM phenotype [5], hydroxylation deficiency of various classes of mostly used drugs, endogenous substances and environmental toxic chemicals [6,7] escalated risk of therapeutic failure or adverse side effects following a drug treatment [6]. Individuals who have two null CYP2D6 alleles are named as poor metabolizers (PMs) and researchers have found that PMs are seen in 5-10% of the Caucasians [8]. The CYP2D6*4 allele, subsequent to CYP2D6*5 and CYP2D6*3, is the most effective null allele in CYP2D6 allele group, resulting PM phenotype augmentation among Europeans (12-22%) [9].

Materials and methods

Study population

Eighty healthy donor volunteers, 54 males (72%) (Mean age=35.88 years SD± 12.78) and 22 females (28%) (Mean age=34.00 years SD=±11.66), four volunteers excluded who have participated in genotype study. They were referred from Haydarpaşa Numune Training and Research Hospital (Turkey). Healthy volunteers who are not related any disorder and have no medical history created the control group. This project was approved by the Medical Faculty Ethics Committee of Marmara University (Number: B.30.2.MAR.0.01.02/AEK/207; Date: 01/03/2012). All controls approvals were obtained after fully described the nature of the procedures to be applied in the investigation.

Molecular analysis

A total of eighty Genomic DNA were extracted using commercial kit for the genomic DNA extraction procedure using the salting out method from 200 µl of whole blood. Four samples could not be realized due to the inadequate amount of DNA. At the examination of the intron 3 polymorphism, 355 bp region of the CYP2D6 (CYP2D6*4) gene was amplified using primers PF: 5'-GCC TTC GCC AAC CAC TCC G-3', and PR: 5' AAA TCC TGC TCT TCC GAG GC-3'). PCR was conducted with a master mix (a total volume of 25 µl). PCR program requires the following conditions: first of all initial denaturation at 94 °C for 5-minutes, 30 cycles of denaturation at 94 °C for 1 minute, annealing at 60 °C for 1 minute, extension at 72 °C for 1.5 minutes, and final extension at 72°C for 10 minutes [10]. Amplified product which made up of PCR method was digested during overnight with 10 U of the restriction endonuclease *Bst* NI (*Mva* I) at 60 °C. Figure 1 illustrates the restriction patterns and classification of the genotypes.

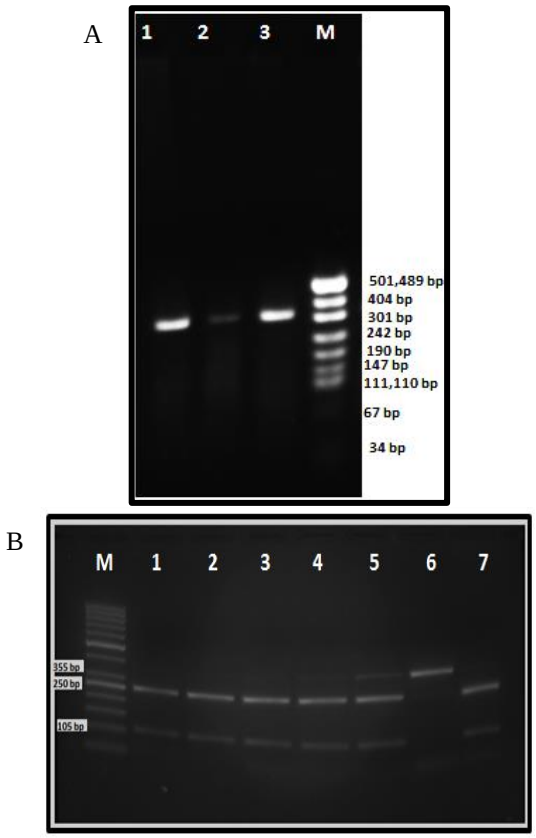

Figure 1: PCR products and RFLP Pattern of CYP2D6 Intron 3 Polymorphism.
A: PCR products of CYP2D6 Intron 3 Polymorphism, 355 bp (Line 1, 2, 3), Marker: pUC19/Msp I DNA ladder (Base pair ranges involve; 501, 489, 404, 331, 242, 190, 147, 111, 110, 67, 34 bp)
B: RFLP Pattern of CYP2D6 Intron 3 Polymorphism. Marker: 50 bp DNA Ladder (Base pair ranges involve; 1000, 900, 800, 700, 600, 500, 400, 300, 250, 200, 150, 100, 50 bp)

- CYP2D6*4/*4 genotype; Poor metabolizer (PM); it carries inactive in two alleles; 355 bp (Line 6)
- CYP2D6 wt/*4 genotype; Heterozygote extensive metabolizer (HEM); carries one functional allele; 355, 250,105 bp (Line 5)
- CYP2D6 wt/wt genotype; Homozygote extensive metabolizer (EM); carries two functional alleles; 250,105 bp (Line 1,2,3,4 and 7)

270 bp region of the (CYP2D6*3) gene was amplified using primers PF: 5'-GAT GAG CTG CTA ACT GAG CCC-3', PR: 5'-CCG AGA GCA TAC TCG GGA C-3' for the examination of the exon 5 polymorphism. PCR was conducted via master mix. PCR program requires the following conditions: firstly initial denaturation at 94 °C for 5 minutes, 40 cycles of denaturation at 94 °C for 1 minute, annealing at 62 °C for 1

minute, extension at 72°C for 1.5 minutes, and the final extension at 72 °C for 10 minutes [10]. Amplified PCR product was digested during overnight with 10 U of the restriction endonuclease Hpa II (Msp I) at 37 °C. Figure 2 indicates the restriction patterns and classification of the genotypes.

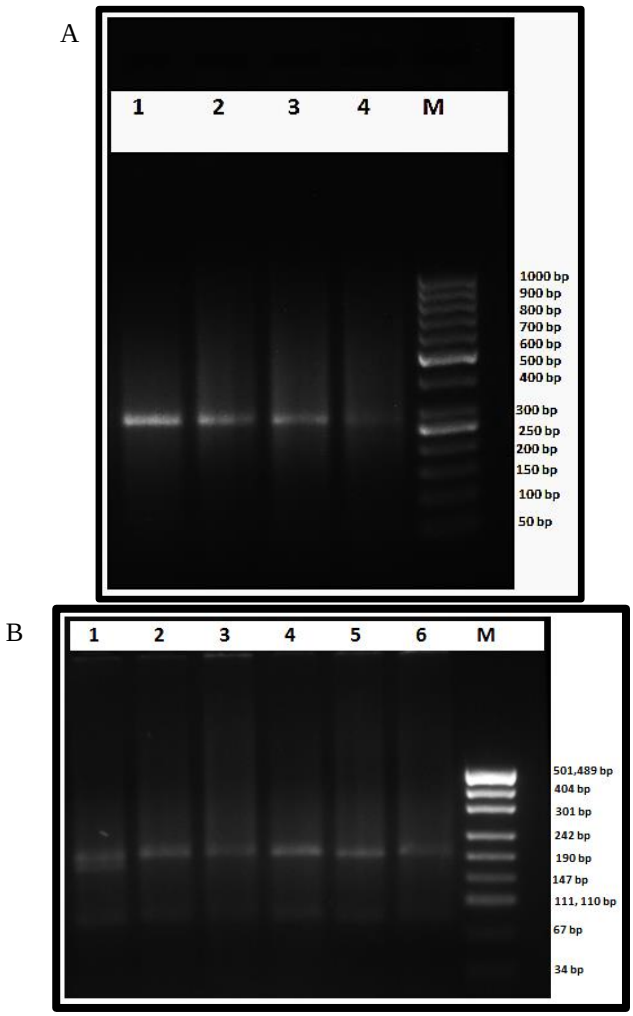

Figure 2: PCR products and RFLP Pattern of CYP2D6 Exon 5 Polymorphism.
A: PCR products of CYP2D6 Exon 5 Polymorphism, 270 bp (Line 1, 2, 3, 4)
Marker: 50 bp DNA Ladder (Base pair ranges involve; 1000, 900, 800, 700, 600, 500, 400, 300, 250, 200, 150, 100, 50 bp)
B: RFLP Pattern of CYP2D6 Exon 5 Polymorphism
Marker: pUC19/Msp I DNA ladder (Base pair ranges involve; 501, 489, 404, 331, 242, 190, 147, 111, 110, 67, 34 bp)

- CYP2D6 wt/ wt genotype; Homozygote extensive metabolizer (EM); carries two functional alleles; 188,82 bp (Line 2,3,4,5,6)
- CYP2D6 wt/*3 genotype; Heterozygote extensive metabolizer (HEM); carries one functional allele; 188, 168, 82, 20 bp (Line 1)
- ***In this study CYP2D6*3/*3 genotype (PM) was not present; it carries inactive in two alleles; 168, 82, 20 bp.

Statistical Analysis

Our data were collected from the standpoint of range, frequencies (number of controls), mean± standard deviation ± SD and relative frequencies (percentages) where applicable. In these analyses, SPSS Version 14 was employed. Online Encyclopedia for Genetic Epidemiology (OEGE) software (2006) was used for calculating chi-square Hardy-Weinberg equilibrium test. In order to contrast the main categorical variables this test was used. In chi-squared test, the probability value (*p*- value) below 0.05 was accepted as statistically significant.

Results

Chi-square Hardy-Weinberg equilibrium was calculated for CYP2D6*3 and CYP2D6*4 (CYP2D6*3 $\chi 2$: 0.0135, P value: 0.9075, CYP2D6*4 $\chi 2$: 0.4718, P value: 0.4922). For CYP2D6*4 allele, individuals with one normal (250, 105 bp) and one mutated allele (355 bp) named as heterozygous. But homozygous individuals express 355 bp band while normal individuals show only 250, 105 bp fragments. When the results were evaluated, 76.32 % of the volunteers (n=58) had wild-type 'WT' allele. And also, 2.63 % of the cases (n=2) had two *4 (mutated) alleles, and they were homozygous for CYP2D6. 21.05% of the subjects (n=16) had one *4 allele, and they were heterozygous for CYP2D6*4. CYP2D6*4 mutant (MUT) allele frequency was 13.16%, wild-type 'WT' allele frequency was 86.84% in this group (Table 1).

For CYP2D6*3 allele, heterozygous individuals indicate 188, 168, 82 and 20 bands, homozygous individuals show 168, 82, 20 bp bands, while normal individuals demonstrate only 182, 82 bp fragments. 97.37% of the volunteers (n=74) had WT allele. 0% of cases (n=0) had two *3 (mutated) alleles, and they were homozygous for CYP2D6. 2.63% of the subjects (n=2) had one *3 allele, and they were heterozygous for CYP2D6*3. CYP2D6*3 MUT allele frequency was 1.32 %, wild-type 'WT' allele frequency was 98.68% in this group (Table 1).

Table 1: Genotype and allele frequency of CYP2D6*4 and CYP2D6*3 among Turkish population.

	Genotype Frequency (n=76)			Allele Frequency (n=152)	
	PM (%)	EM (%)	HEM (%)	WT (%)	MUT (%)
CYP2D6*4	2 (2.63%)	16 (21.05%)	58 (76.32%)	86.84%	13.16%
CYP2D6*3	0 (0%)	2 (2.63%)	74 (97.37%)	98.68%	1.32%

N: total number, MUT: mutant allele, WT: wild type allele, PM: homozygous mutant status, EM: homozygous normal status, HEM: heterozygote

Discussion

CYP2D6 polymorphism's susceptibility to different diseases had been inspected, including certain cancers, systematic pituitary adenomas, lupus erythematosus, Parkinson's disease, Balkon nephropathy and ankylosing spondylitis [11,12]. In cancer supportive treatment, 25% of all medicines is metabolized by CYP2D6 enzyme, involving tamoxifen, cytotoxic drugs and other drugs used [1,2]. Furthermore, CYP2D6 gene is liable for the detoxification of various carcinogens including polycyclic aromatic hydrocarbons (PAHs), and nitrosamines [2]. Therefore, CYP2D6 expression variation may have a role in drug-drug interaction and the susceptibility of cancers. However, in the various types of cancer, the significance of CYP2D6 allelic variants stays as a challenging and controversial issue. In that scope, some of the researches proposed CYP2D6 to have a role in cancer development; but some of the studies did not support this suggestion.

In some studies, it is stated that EM genotype may cause the tendency to various cancers whereas in other researches it is claimed that PM genotype may lead to the same tendency. The relationship between PM and EM genotypes, and tendency to cancer is still not explicit. It is considered that the individuals with PM genotype are less exposed to carcinogenic and genotoxic xenobiotic metabolites in comparison to those with EM genotype, but they are exposed to unmetabolized xenobiotics and toxic effects, which are stemmed from undetermined countless factors [13]. It is thought that mentioned toxic effects might promote to the development of carcinogenesis in PMs

[14]. Most of the variant alleles comprising of CYP2D6*3,*4, and *5 led to the production of the nonfunctional enzyme and those related variants were mostly evaluated as the PM phenotype [15]. Among European Caucasians, the PM is predicted among 7 to 10 % [16-20]. In that framework, CYP2D6*4 is a well- known defective allele among 21 % of the Caucasian population. In a different analyses it was shown that, CYP2D6*4 mutant allele frequency was rare in the Chinese, Japanese, Korean, and its deficiency or incidence had been reported about 1-3% [15, 18]. CYP2D6*4 allele frequencies in various populations were indicated as follows, 21% in Germans, 18% in Americans, and 8% in African Americans [19]. In a study which was performed in Turkey, CYP2D6*4 homozygote mutation rate was found as 4%, and allele frequency was 21% [20]. In addition to these analyses, Aydın et al. reported the CYP2D6*4 allele frequency as 15.4% in Turkey [19]. In the present study, the number of volunteers carrying CYP2D6*4 mutation turned out to be 18 (23.68%): 16 (21.05%) were heterozygous, and 2 (2.63%) were homozygous. Within the entire of control group, CYP2D6*4 allele frequency was measured as 0.13 (13.16%). As we compared our results with the study of Aynacıoğlu et al. [21], Aydın et al. [19], Sahin et al. [22], we determined that the frequencies of allele and homozygous mutations were nearly close.

If we talk about the inability of this study, in our analyses the main failure is to determine the other nonfunctional defective alleles (3*) in Turkish population. But this mutant allele is rare in most of white populations and also in Turkish populations: the detected allele frequency for *3 is 0.00 [21] or 0.025 [19]. In this study, the number of volunteers with CYP2D6*3 mutation was 2 (2.63%): 2 (2.63%) were heterozygous and 0 (0%) were homozygous. In all volunteers, CYP2D6*3 MUT allele frequency was 0.01(1.32%). In a different study, Antunes et al. [23], investigated the association between phenotypes and genotypes in patients with breast cancer in Brazil. They found the allelic frequencies as 2%, 18.1%, and 1% for the mutated alleles *3,*4, and *10, respectively. Another study which was performed by Jardim et al. [24] studied the presence of polymorphic alleles of CYP2D6*3,*4,*5,*6 and *10 in southern and southeastern regions of Brazil. Moreover, they also reported the allelic frequencies as 33%, and 38% for the polymorphic alleles *4 and*10, respectively. The polymorphic alleles *5 and *6 turned out to be heterozygous in one patient, and allele *3 was not observed in the reference population. The results of this study resemble to those reported by Antunes et al. [23] and Jardim et al. [24]. When they are compared to the results of Aynacıoğlu et al. [21], allele frequencies and homozygous mutations turns out to be similar. This study's results were close to the ones found in previous studies in Asia, Sweden, Denmark, India, Malaysia, China, Japan, Europe [25-28].

As a result, the present study shown that 2.63% of the Turkish individuals who are living in the city of İstanbul are the carriers of two nonfunctional mutated alleles, *4 being homozygous for CYP2D6*4 but there were no 0 (0%) homozygous for CYP2D6*3 in volunteer group. It is clinically crucial to be able to define those individuals who have altered pharmacokinetics for CYP2D6 substrates for preventing adverse drug reactions. Because CYP2D6 is capable of metabolize 25% of commonly prescribed drugs.

Although the population of this study is not broad as to be capable to reflect whole Turkish population, we believe that if the results to be obtained from here are evaluated with the results of other studies to be conducted in different regions of Turkey in this field, they may contribute to the determination of frequency of CYP2D6 gene variants in Turkish population. Consequently, the results obtained from different populations would contribute to the area of pharmacogenetics applications in medicine.

References

1. Brosen K, Gram LF. Clinical significance of the sparteine/debrisoquine oxidation polymorphism. Eur J Clin Pharmacol. 1989;36(6):537-47. PMID: 2570698.
2. Dahl ML, Bertisson L. Genetically variable metabolism of antidepressants and neuroleptic drugs in man. Pharmacogenetics. 1993;3(2):61-70. PMID: 8100166.
3. Cascorbi I. Pharmacogeneticist's of cytochrome P4502D6: genetic background and clinical implication. Eur J Cln Invest. 2003; 33(2):17-22. PMID: 14641552.
4. Gough AC, Miles JS, Spurr NK, Moss JE, Gaedigk A, Eichelbaum M, et al.. Identification of the primary gene defect at the cytochrome P450 CYP2D locus. Nature. 1990;347(6295):773-6. DOI: 10.1038/347773a0.
5. Van Der Weide J, Steinjns L. Cytochrome P450 enzyme system: genetic polymorphisms and impact o clinical pharmacology. Ann Clin Biochem. 1999;36(6):722-9. DOI: 10.1177/000456329903600604.
6. Lavandera JV, Parera VE, Batlle A, Buzaleh AM. CYP2D6 polymorphisms in patients with porphyrias. Mol Med. 2006;12(9-10):259-63. DOI: 10.2119/2005-00047.Lavandera.
7. Stamer UM, Bayerer B, Wolf S, Hoeft A, Stüber F. Rapid and reliable method for cytochrome P450 2D6 genotyping. Clin Chem. 2002;48(9):1412-7. PMID: 12194916.
8. Sistonen J, Sajantila A, Lao O, Corander J, Barbujani G, et al. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenet Genomics. 2007;17(2):93-101. DOI: 10.1097/01.fpc.0000239974.69464.f2 .
9. Fernandez-Santander A, del Saz M, Tejerina A, Bandres F. CYP2D6*4 allele and breast cancer risk: is there any association? Clin Transl Oncol. 2012;14(2):157-9. DOI: 10.1007/s12094-012-0776-4.
10. Schur BC, Bjerke J, Nuwayhid N, Wong SH. Genotyping of cytochrome P450 2D6*3 and *4 mutations using conventional PCR*. Clinica Chimica Acta. 2001;308(1-2):25-31. PMID: 11412814.
11. Lennard MS. Genetic polymorphism of sparteine/debrisoquine oxidation: a reappraisal. Pharmacology and Toxicology. 1990;67(4):273-83. PMID: 2077517.
12. Mayer UA. Pharmacogenetics- five decades of therapeutic lessons from genetic diversity. Nat Rev Genet. 2004;5(9):669-76. DOI: 10.1038/nrg1428.
13. Taninghera M, Malacarnea D, Ugolinia A, Parodia S. Drug metabolism polymorphisms as modulators of cancer susceptibility. Mutat Res. 1999 May;436(3):227-61. PMID: 10354524.
14. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE. Increased cell division as a cause of human cancer. Cancer Res. 1990;50(23):7415-21. PMID: 2174724.
15. Zanger UM, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemisry. Naunyn Schmiedebergs Arch Pharmacol. 2004;369(1):23-37. DOI: 10.1007/s00210-003-0832-2.
16. Alvan G, Bechtel P, Iselius L, Gundert-Remy U. Hydroxylation polymorphisms of debrisoquine and mephenytoin in European populations. Eur J Clin Pharmacol. 1990;39(6):533-7. PMID: 2151318.
17. Bradford LD. CYP2D6 allele frequency in European Caucasions, Asians, Africans and their descendants.Pharmacogenomics. 2002;3(2):229-43. DOI: 10.1517/14622416.3.2.229.
18. Bertilsson L, Dahl ML, Dalen P, Al-Shurbajı A. Molecular genetics of CYP2D6: clinical relevance with focus om psychotropic drugs. Br J Clin Pharmacol. 2002;3(2):111-22. DOI: 10.1046/j.0306-5251.2001.01548.x.
19. Aydin M, Hatirnaz O, Erensoy N and Ozbek U. CYP2D6 and CYP1A1 mutations in the Turkish population. Cell Biochem Funct. 2005;23(2):133-5. DOI: 10.1002/cbf.1222.
20. Koseler A, Ilcol YO and Ulus IH. Frequency of mutated allele CYP2D6*4 in the Turkish population. Pharmacology. 2007;79:203-6. DOI: 10.1159/000100959.
21. Aynacıoğlu, AS, Sachse C, Bozkurt A. Low frequency of defective alleles of cytochrome P450 enzymes 2C19 and 2D6 in the Turkish population. Clin Pharmacol Ther. 1999;66:185-92. DOI: 10.1053/cp.1999.v66.100072001.

22. Sahin S, Aydogan L, Benli I, Ozyurt H. Distribution of HLA-B27 and CYP2D6*4 mutations in the middle Black Sea area (Tokat) of Turkey. Genetics and Molecular Research 2011;10(4):3987-91. DOI: 10.4238/2011.December.2.3.
23. Antunes MV, Linden R, Santos TV, Wallemacq P, Haufrois V, Classen JF, et al. Endoxifen levels and its association with CYP2D6 genotype and phenotype: evaluation of a southern Brazilian population under tamoxifen pharmacotheraphy. Ther Drug Monit. 2012;34:422-31. DOI: 10.1097/FTD.0b013e318260b46e.
24. Jardim DLF, Katz A. Determination of the frequency of CYP2D6 polymorphisms in Brazilian women and literature review. Rev Bras Mastol. 2014;20:55.
25. Jonrit H, Petersen S, Dankier P, Flemming N, Grandjean P, Weihe P, et al. Polymorphism of CYP2D6, CYP2C19, CYP2C9 and CYP2C8 in the Faroese population. Eur J Clin Pharmacol. 2005 Aug;61(7):491-7. DOI: 10.1007/s00228-005-0938-1.
26. Adithan C, Gerard N, Naveen AT, Koumaravelou K, Shashindran CH, Krishnamoorthy R. Genotype and allele frequency of CYP2D6 in Tamilian population. Eur J Clin Pharmacol. 2003 Oct;59(7):517-20. DOI: 10.1007/s00228-003-0657-4.
27. Ling J, Shixiu P, Jacqueline M, Edgar H, Katharina R, Matin H. Single-Step Assays to Analyze CYP2D6 Gene Polymorphisms in Asians: Allele Frequencies and a Novel*I 4B Allele in Mainland Chinese. Clinical Chemistry. 2002;48:983-88.
28. Yamada H, Dahl ML, Lannfelt L, Viitanene M, Winbland B, S joqvist F. CYP2D6 and CYP2C19 genotypes in an elderly Swedish population. Eur J Clin Pharmacol. 1998;54(6):479-81. PMID: 9776439.