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Distribution of Cytochrome P450 2D6 (*4, *9, *10, *41) alleles in healthy population from north-west of Iran

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Abstract

BACKGROUND: The CYP2D6 gene locus is complex and highly polymorphic. Given the clinical importance of the CYP2D6 enzyme in liver xenobiotic metabolism, genotyping its significant alleles among different ethnic groups is essential for evaluating the efficacy of certain drugs. In this study, we assessed the frequency of the *CYP2D6*4, *9, *10, and *41* alleles in a healthy population from northwestern Iran.

METHODS: Fifty unrelated healthy individuals from West Azerbaijan Province, Iran, were studied using PCR-RFLP and ARMS-PCR techniques.

RESULTS: *CYP2D6*9* (rs5030656) allele was not detected. The frequency (%) of *CYP2D6*4* (rs3892097), *CYP2D6*10* (rs1065852) and *CYP2D6*41* (rs28371725) alleles were 10%, 13% and 8%, respectively.

CONCLUSION: Our findings indicate that the frequencies of "non-functional" and "reduced function" alleles are relatively high in this population. Determining Cytochrome P450 2D6 allele variations can contribute to risk assessment and patient management regarding adverse or poor drug responses, ultimately aiding in the prevention of increased mortality risks among different populations.

Keywords: CYP2D6; Polymorphism; Iranian; Healthy Population; Allele Frequency

Introduction

The cytochrome P450 (CYP) superfamily is a large and diverse group of enzymes found in living organisms, including eukaryotes and prokaryotes. These enzymes are named for their ability to absorb light at a wavelength of 450 nm when reduced and bound to carbon monoxide (CO)[1]. *CYP*s are fundamental catalytic proteins involved in drug detoxification, facilitating oxidation reactions during phase I of drug metabolism[2].

Among the P450 enzymes*, CYP2D6* is one of the most extensively studied due to its crucial role in hepatic metabolism, processing approximately 25% of commonly used lipophilic drugs, including tricyclic antidepressants, chemotherapeutics, antipsychotics, beta-blockers, and many other essential medications [3].

The *CYP2D6* gene family contains a large number of single nucleotide variants (SNVs), and the gene product plays a significant role in the biotransformation of xenobiotics[4,5]. The human *CYP2D6* gene locus spans approximately 4.3 kilobase pairs (Kbp) on chromosome 22q13.2 and is encoded by nine exons[1]. This gene is translated into the CYP2D6 protein, a heme-containing enzyme composed of 497 amino acids[1-6].

They are membrane-associated and accessible only through specific channels[7]. Although CYP enzymes are expressed in various organs, such as the kidneys, gonads, adrenal glands, and others, they are primarily localized in the endoplasmic reticulum of the liver and intestines[2]. They are also found in neuronal cells within the brain[8].

Due to genetic polymorphisms, hepatic *CYP2D6* protein levels vary significantly among populations worldwide[9]. More than 100 variant alleles of the *CYP2D6* gene have been identified to date, highlighting its considerable genetic variability. While many of these variants are rare, several polymorphisms alter enzyme function—rendering it inactive or affecting enzymatic activity by either increasing or decreasing its efficiency[10,11].

Approximately 109 distinct *CYP2D6* alleles and nearly 507 SNPs have been identified, with about 10% classified as nonsynonymous, meaning they modify the enzyme's structure and function. These polymorphisms arise from point mutations, deletions, insertions, gene rearrangements, or full-gene duplications[12].

CYP2D6 alleles are categorized into three functional classes: normal function, non-functional, and reduced function alleles[13]. These variant "star (*) *alleles" are documented in the Human CYP450 Allele Nomenclature Database[14]. CYP2D6*1 is the reference allele, signifying normal enzyme activity. Several other alleles, such as *2, exhibit similar functionality to the reference allele[3]. Other commonly identified CYP2D6 alleles include *3, *4, *9, *10, *17, *29, and *41[15].

According to the classification of CYP2D6 alleles, *1 and *2 are normal function alleles, *3 and *4 are non-functional, while *9, *10, *17, *29, and 41 are categorized as reduced function alleles[13]. Each individual carries two CYP2D6 haplotypes one on each chromosome which together form a diplotype. For example, the CYP2D64/41 diplotype indicates that one chromosome carries the polymorphisms associated with CYP2D64, while the other chromosome carries the polymorphisms linked to CYP2D6*41.

The term "genotype" is often used interchangeably with "diplotype" when characterizing an individual's genetic profile for the CYP2D6 gene. Based on an individual's CYP2D6 genotype, four distinct CYP2D6 metabolism phenotypes can be identified: ultrarapid metabolizer (UM), normal metabolizer (extensive metabolizer, NM or EM), intermediate metabolizer (IM), and PM[16,17].

Individuals with PM, IM, and UM phenotypes may experience pharmacokinetic variations compared to normal metabolizers due to differences in the CYP2D6 enzyme gene[18]. PMs either lack catalytic enzyme activity or possess two non-functional alleles, preventing them from effectively metabolizing or bioactivating drugs through the CYP2D6 pathway[9]. Consequently, PMs are prone to adverse drug

effects and treatment failures due to increased plasma drug levels. Conversely, UMs possess multiple functional alleles, leading to increased enzymatic activity, which can also present challenges[12,18].

Among the global population, the most prevalent CYP2D6 phenotype is the NM, accounting for approximately 78% of individuals, followed by IM phenotypes (12%) and PM phenotypes (8%). Ultrarapid metabolizers represent the smallest percentage of the population[19]. According to previous research, PM phenotypes are predominantly found in European populations, UM phenotypes are more common among North African individuals, and IM phenotypes are frequently observed in Asian populations[12].

CYP2D6 gene polymorphisms can result in metabolic function ranging from absent to increased activity, impacting drug metabolism and pharmacokinetic profiles across various drug classes, including beta-blockers[20].

Up to 80% of the hepatic metabolism of the beta1-blocker drug metoprolol is mediated by *CYP2D6* enzymes, with a smaller portion processed by CYP3A4[21]. Beta1-blocker drugs are widely used in the treatment of various cardiovascular diseases, including hypertension and other heart conditions, which are leading causes of early mortality and rising healthcare costs globally[22].

Determining a patient's *CYP2D6* genotype is a rational approach to mitigating the risk of adverse drug events (e.g., bradycardia, hypotension, or weakness) while maximizing the therapeutic benefits of beta-blockers[23]. As clinical pharmacogenetic testing becomes more widely available, selecting an appropriate strategy for predicting *CYP2D6* phenotypes is crucial for optimizing drug responses and determining the most effective dosage in treatment plans[24].

Since pharmacogenetics-guided therapeutic recommendations are based on *CYP2D6* phenotypes, translating genotype data into clinically relevant phenotypes is an efficient method for shaping medical treatment strategies[23]. Pharmacogenetics examines the influence of genetic variations on drug response, acknowledging that medication effects can differ among individuals[25]. Furthermore, calculating CYP2D6 enzymatic function based on diplotype analysis can help personalize medication strategies. The activity score system was introduced in recent years to facilitate CYP2D6 genotype-to-phenotype translation[26].

According to allele function, each allele is assigned a value to estimate enzyme activity within the activity score (AS) system. In this system, non-functional alleles (e.g., CYP2D6*4, 5) are assigned a value of 0, while decreased function alleles receive a value of either 0.25 (e.g., CYP2D610) or 0.5 (e.g., CYP2D6*9, *17, *41). Extensive function alleles (e.g., CYP2D6*2) are assigned a value of 1, whereas increased function alleles are allocated a value of 2 or higher, depending on the number of gene copies [3,26].

The AS system is used clinically to predict CYP2D6 metabolizer enzyme phenotypes. Poor metabolizers have an AS of 0, while ultrarapid metabolizers are characterized by an AS > 2.25[24]. Additionally, normal (extensive) metabolizers have an activity score between 1.25 and 2.25, while intermediate metabolizers fall within a range of 0.25 to 1.3.

Several key CYP2D6 alleles are described as follows:

- **CYP2D6*4 (rs3892097):** This allele results from a splicing defect that leads to non-functional enzyme activity due to the substitution of guanine (G) with adenine (A) at position 1846. This single base change alters the consensus acceptor splice site, producing a spliced mRNA with an extra base[27].
- **CYP2D6*9 (rs5030656):** This allele is characterized by the deletion of the K281 amino acid due to a three-base-pair deletion (AAG codon) in exon 4 at positions 2615–2617. This polymorphism leads to reduced or non-functional CYP2D6 enzyme activity[25]. It has a low prevalence in global populations, with a frequency ranging from 1% to 2%[26].
- **CYP2D6*10 (rs1065852):** This allele arises from a cytosine (C) to thymine (T) substitution

at nucleotide 100, resulting in the replacement of proline with serine at codon 34. This polymorphism is prevalent among Asians and is associated with reduced CYP2D6 enzyme metabolism[27]. The *10 allele frequency is 43% in East Asians, 20% in Central and South Asians, and up to 7% in other populations[26].

- **CYP2D6*41 (rs28371725):** This allele is caused by the substitution of guanine (G) with adenine (A) at position 2988 in intron 6, leading to aberrant mRNA splicing. The resulting enzyme has reduced metabolic function[25]. This single nucleotide variant (SNV) is the most abundant reduced function CYP2D6 allele in European populations, with a frequency of up to 7%[26].

Given the impact of CYP2D6 enzyme activity on drug metabolism, evaluating allele frequencies in different populations is essential for understanding genetic variations across ethnic groups[28]. Previous studies have explored the frequency of various CYP2D6 polymorphisms, providing valuable insights into interethnic differences. However, the significance of these studies is somewhat limited due to small sample sizes[5].

Additionally, comparative data on CYP2D6 allele frequencies among different Iranian population groups remain limited[11]. Given the significant influence of CYP2D6 genotypes on catalytic protein activity and hepatic drug metabolism, determining allele frequencies across diverse populations is crucial for advancing genotype-guided drug response predictions[6].

For individuals concerned about CYP2D6 metabolism, genetic testing provides valuable information to guide drug dosage adjustments [3]. The aim of this study was to assess the allelic frequency of Cytochrome P450 2D6 (*4, *9, *10, *41) alleles in a healthy population from northwestern Iran.

Materials and Methods

Subject group and DNA extraction method

A group of fifty unrelated healthy individuals (aged 18–60) from West Azerbaijan Province, Iran, was included in our study. Venous blood samples (3–4 mL) were obtained from each participant and collected into tubes containing 500 µL of 0.5 mM EDTA (ethylenediaminetetraacetic acid). Genomic DNA was extracted using the salting-out method[29].

Primers sequences and genotyping method

Details on primers, PCR conditions, and methods used for allele investigation are provided in Table 1[30,31].

PCR reactions were performed in a 30 µL volume, consisting of 50 ng of DNA, 1× reaction buffer, 10 pmol of each primer, 200 µmol of each dNTP, 0.2 units of Taq DNA polymerase, and 1.5 mmol $MgCl_2$. The amplified PCR products were digested using 0.5 µL of Thermo Scientific™ ER0551 MvaI (BstNI) restriction enzyme (10 U/µL) at 37°C for 2 hours, specifically for the CYP2D6*4 allele.

Fragment analysis was conducted via electrophoresis on a 2% agarose gel stained with 0.2 µL of CinnaGen DNA Safe Stain (CinnaGen Co., Tehran, Iran).

Statistical Analysis

Allele and genotype frequencies were determined using the counting method and tested for Hardy-Weinberg equilibrium. All frequencies were expressed as percentages. A chi-square test was performed to compare frequency distributions between populations, with a p-value < 0.05 considered statistically significant

Results

Representative images of agarose gel electrophoresis for CYP2D6*4, CYP2D6*9, CYP2D6*10, and CYP2D6*41 alleles are shown in Figures 1-4. Genotype frequencies were counted and calculated based on the total number of samples.

Overall, among the study population, CYP2D6*9 had the lowest frequency (0%), while CYP2D6*10 was the most abundant allele (13%), followed by CYP2D6*4 (10%) and CYP2D6*41 (8%).

The most prevalent phenotype observed in this research was Intermediate Metabolizer (IM), with **12% of cases exhibiting the CYP2D6*4/*10

Table 1. Primers and PCRs conditions of tested alleles in this study

Allele	Primers	PCR conditions	Method	Pattern of alleles after gel electrophoresis
*CYP2D6*4*	f: 5'–tgccgccttcgccaaccact–3' r: 5'–tcgccctgcagagactcctc–3'	94 °C/8 min 62 °C/2 min 30×72 °C/30 s 94 °C/30 s 62 °C/20 s 72 °C/5 min 22 °C/1 min	PCR-RFLP Using BstNI 37°C/2h	Wild-type/Wild-type: 201+108 bps Wild-type/Mutant-type: 309+201+108 bps Mutant-type/Mutant-type: 309 bp
*CYP2D6*9*	out f: 5′-caggtgaacgcagagcacag-3′ out r: 5′-ccggatgtaggatcatgagc-3′ wt f: 5′-ttcctggcagagatggagaa-3′ *9 f: 5′-ttcctggcagagatggaggt-3′	95°C/5 min 95°C/30 s Wild-type: 30×61°C/30 s Mutant-type: 31×60°C/30 s 72°C/1 min 72°C/10 min	ARMS-PCR	Internal control: 549 bp Mutant-type: 341 bp Wild-type: 341 bp
*CYP2D6*10*	out f: 5′-ggggcaagaacctctggagc-3′ out r: 5′-ctggtccagcctgtggtttc-3′ wt r: 5′-agtggcaggggcctggagg-3′ *10 f: 5′-acgctgggctgcacgcttct-3′	95°C/5 min 95°C/30 s Wild-type: 32×67°C/30 s Mutant-type: 29×60°C/30 s 72°C/1 min 72°C/10 min	ARMS-PCR	Internal control: 505 bp Mutant-type:192 bp Wild-type: 351 bp
*CYP2D6*41*	out f: 5′-ccgttctgtcccgagtatgc-3′ out r: 5′-cggccctgacactccttctt-3′ wt f: 5′-agtgcaggggccgagggtgg-3′ *41 f: 5′-agtgcaggggccgagggcga-3′	95°C/5 min 95°C/30 s Both wild/ mutant type: 32×65.5°C/30 s 72°C/1 min 72°C/10 min	ARMS-PCR	Internal control: 339 bp Mutant-type: 142 bp Wild-type: 142 bp

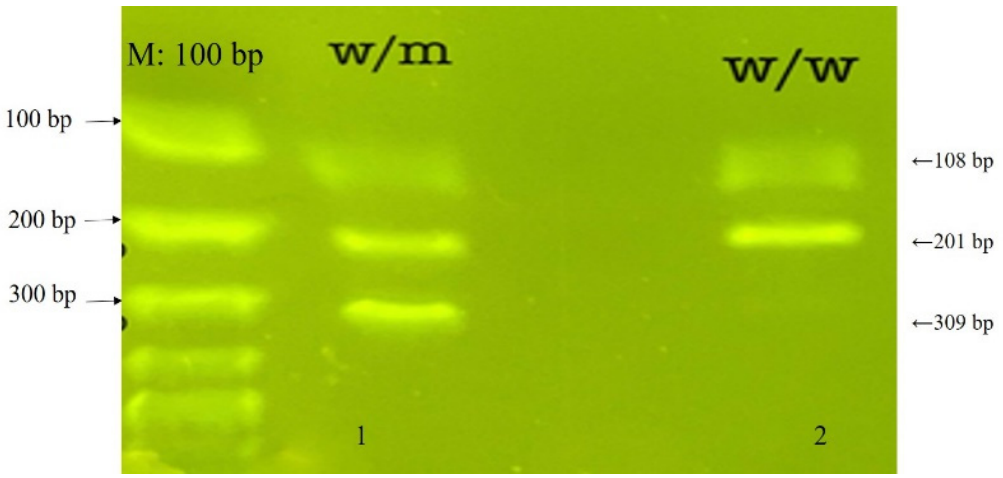

Figure 1. *CYP2D6*4* allele in our samples
M: 100 bp DNA ladder. w/m: heterozygous sample for mutant allele of *CYP2D6*4* (201bp+108 bp+309 bp); w/w: homozygous sample for normal allele of *CYP2D6*4* (201bp+108 bp)

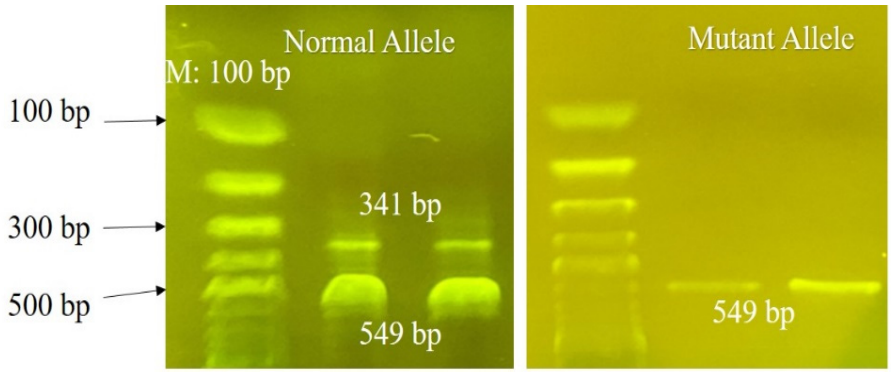

Figure 2. *CYP2D6*9* allele in our samples
M: 100 bp DNA ladder. Homozygous samples for normal allele of *CYP2D6*9* (341bp+549 bp) (left);
Mutant allele of *CYP2D6*9 was not found in this study* (549 bp: internal control without 341 bp) (right)

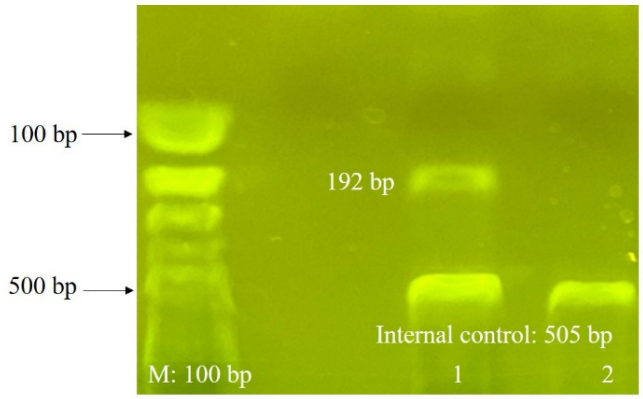

Figure 3. Mutant *CYP2D6*10* allele in this study. M: 100 bp DNA ladders
Lane 1: A sample with mutant *CYP2D6*10* allele; Lane 2: A sample without mutant *CYP2D6*10* allele;
Internal control: 505 bp and mutant allele: 192 bp

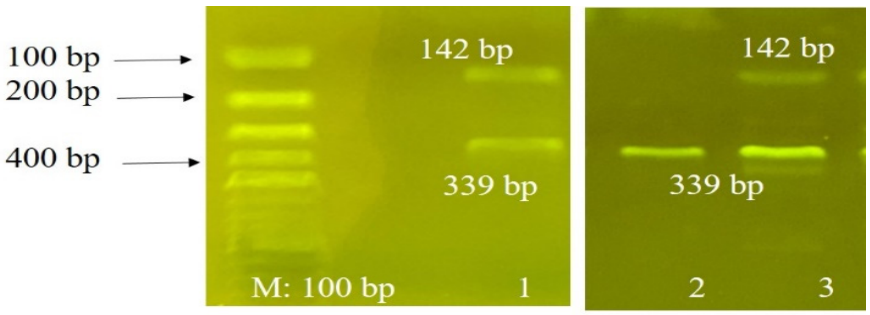

Figure 4. *CYP2D6*41* allele in our samples
M: 100 bp DNA ladder. Lane 1: a samples with normal allele of *CYP2D6*41* (142bp+339 bp) (left);
Lane 2: a sample without mutant allele of *CYP2D6*41*; Lane 3: a sample with mutant allele of *CYP2D6*41*(right)
Normal/mutant allele: 142 bp and internal control: 339 bp

genotype. Additionally, **2% of cases carried the CYP2D6*4/41 genotype*, and **homozygous CYP2D6*10/10 and CYP2D641/41 genotypes* were identified in 2% of tested samples.

No homozygous sample for the mutant allele CYP2D6*4 was detected in this study.

Discussion

In this study, we examined the CYP2D6*4, *9, 10, and 41 alleles in a healthy population from northwest Iran. Our findings indicated that the allelic frequency of **CYP2D6*9 (rs5030656) was zero. Additionally, the frequencies of CYP2D6*4 (rs3892097), CYP2D6*10 (rs1065852), and CYP2D6*41 (rs28371725) were 10%, 13%, and 8%, respectively.

Our results suggest that non-functional and reduced-function alleles are more prevalent in this population. To contextualize these findings, we compared the allele frequencies of **CYP2D6*4, *9, *10, and 41* from this study with those reported in other populations (Tables 2 and 3). The results indicate that allele frequencies in our study differ from those observed in several Asian populations.

Among the most frequently detected alleles in this study were **CYP2D6*4 and 10*. The frequency of the CYP2D6*41 reduced-function allele was similar among Caucasians[19], the United States[32], and this study, while it varied in African[5] and European[5] populations. Conversely, CYP2D6*41 was found to be more frequent in Turkey[18].

The CYP2D6*4 allele exhibits a distinct distribution pattern between Iranian and Caucasian populations; however, it remains one of the most prevalent alleles among Caucasians. The distribution of CYP2D6*4 was similar among Iranian, African, and Turkish populations.

The Chinese population[13] exhibits the lowest frequency of CYP2D6*4, in contrast to other global populations. The frequencies of CYP2D6*4 among European and United States populations are relatively similar. The frequency of CYP2D6*10 in our study closely resembles that found in South Indian populations[30]. Notably, CYP2D6*10 was absent in European populations [13], but is one of the most prevalent alleles in Chinese populations. Among United States populations, CYP2D6*10, a reduced-function allele, has a low frequency of under 2%.

The CYP2D6*9 allele was absent (0%) in the Iranian population, similar to findings in African[5] and Chinese[13] populations. Generally, CYP2D6*9 is a relatively rare allele across populations.

Table 3 presents the allele frequencies

Table 2. Comparison of *CYP2D6* allelic frequency among Iranian and some other major populations

Allele	Turkey (%)[18]	Caucasians (%)[19]	South Indians (%)[30]	Africans (%)[5]	Europeans (%)[5]	Chinese (%)[13]	US(%)[32]	West Azerbaijan of Iran (%)
4	9.85	20.7	7.3	11.9	15.5	<1	16.1	10.0
9	ND	2.0	ND	0.4	1.6	<1	2.4	0.0
10	ND	8.0	10.2	3.2	0.2	60	1.7	13.0
41	15.15	8.0	ND	3.0	3.0	ND	8.2	8.0

ND: Not Determined

Table 3. Comparison of *CYP2D6* allelic frequency between our results and the other Iranian groups

Allele	Neyshaburinezhad et al[4]	Kouhi et al[33]	Bagheri et al[27]	Our study
CYP2D6*4	11.2%	12.5%	0%	10.0%
CYP2D6*9	ND	ND	ND	0%
CYP2D6*10	15.10%	9.0%	31.9%	13.0%
CYP2D6*41	14%	ND	ND	8.0%

ND: Not Determined

of CYP2D6 among different Iranian ethnic groups. Notably, CYP2D6*4 was not detected in populations such as Fars, Lure, Kurd, and Mazani, which contrasts with our findings[27]. However, the frequency of CYP2D6*10 in this study aligns with previous studies, with rates reaching up to 32%. In contrast, the study by Kouhi et al. [33]. reported a CYP2D6*10 frequency lower than 10%, contradicting other studies.

Our results are consistent with findings from Neyshaburinezhad et al.[4], where CYP2D6*10 was one of the most frequent alleles. The high prevalence of homozygous T/T CYP2D6*10 in Iranian groups suggests a predisposition to adverse or poor drug responses, potentially increasing the risk of mortality.

CYP2D6 is a clinically significant pharmacogene involved in the metabolism of approximately 25% of commonly prescribed drugs across various medical disciplines. It is highly polymorphic, with numerous genetic variants that exhibit population-specific distributions and significantly influence its drug-metabolizing enzymatic activity.

Research indicates that CYP2D6 and its polymorphisms play a vital role in personalized dosing strategies for CYP2D6 drug substrates, particularly in opioid therapy, psychiatry, oncology, and cardiology[34]. Consequently, identifying individuals with altered pharmacokinetics for CYP2D6 substrates is essential to prevent adverse drug reactions.

Evaluating CYP2D6 polymorphisms in different ethnic populations provides valuable insights into personalized medicine and facilitates comparisons of pharmacogenetic variations across ethnic groups. Genetic testing to detect CYP2D6 alleles is a fundamental step in minimizing drug-related adverse effects.

This investigation serves as a pilot study and represents the findings of a master's thesis.At future, it is necessary to pay attention to more details including number of samples and the other CYP2D6 alleles.

Conclusion

Our findings demonstrated that the CYP2D6*9 allele had the lowest frequency. The most abundant alleles were *CYP2D6*10,* followed by CYP2D6*4 and *CYP2D6*41*, respectively. The most prevalent phenotype observed in our study was Intermediate Metabolizer (IM).

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: EB, AD, HS, MB
Data Acquisition: EB, NK, HS, MB
Data Analysis or Interpretation: EB, MB
Manuscript Drafting: EB, MB
Critical Manuscript Revision: AD, NK, HS, MB
All authors have approved the final manuscript and are responsible for all aspects of the work.

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