Original Article

Analysis of *CYP2D6* Gene Variant Frequencies in Iranian Population

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What's Known

- The *CYP2D6* gene variants, which impact the metabolism of several drugs (atomoxetine, opioids, tamoxifen, Selective Serotonin Reuptake Inhibitors (SSRIs), and tricyclic antidepressants), are identified based on guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group. Phenotypes are determined by diplotype and diagnosed variants.

What's New

- This study uncovers new insights into the frequency of *CYP2D6* gene variants in the Iranian population, revealing a high frequency of normal alleles for *CYP2D6**31, *55, *113, and *135.
- Our findings suggest that homozygous and heterozygous genotypes for these variants were absent in this study, indicating that these variants likely have no significant impact on the Iranian population. These results offer new insights into the advancement of personalized medicine.

Abstract

Background: The cytochrome P450 (P450s or CYPs) enzyme family, particularly *CYP2D6*, significantly influences drug metabolism, handling approximately 20-25% of prescribed medications. Understanding genetic polymorphisms is crucial for personalized medicine and optimizing drug therapy in specific geographic and racial contexts. Given the complex nature of studying *CYP2D6* genotypes, this study aimed to assess the prevalence of rare *CYP2D6* star alleles, including rs267608319 (*CYP2D6**31), rs1931013246 (*CYP2D6**55), rs569439709 (*CYP2D6**113), and rs747089665 (*CYP2D6**135), within the Iranian population.

Methods: Blood samples were obtained from 389 individuals across several ethnic groups in Tehran, Iran, from May to December 2022. PCR was used to amplify the region containing the desired variant. Genotyping was performed using the Sanger sequencing method.

Results: Our analysis revealed a high frequency of normal alleles for all four studied variants, indicating the absence of the risk allele in the Iranian population. These findings suggest that the studied alleles have no apparent effect on various ethnic groups in Iran.

Conclusion: The Iranian population has a typical genetic makeup for *CYP2D6* variations, impacting medication prescribing. Understanding genetic differences is crucial for personalized drug therapies. Further research into Iranian genetic variations is essential for advancing personalized medicine.

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Keywords ● Pharmacogenetics ● Polymorphism, genetic ● Precision medicine

Introduction

Pharmacogenomics has attracted increasing attention in healthcare as it addresses the critical issue of genetic variability in drug response. Such variability can significantly affect drug efficacy and lead to adverse drug reactions (ADRs), ultimately affecting patients' overall well-being.[1] Pharmacogenomics applies genetic data to personalized drug therapies to reach more effective and safer treatments.[2] One of the key players in this field is the Cytochrome P450 2D6 (*CYP2D6*) gene. This gene is a crucial component of drug absorption, distribution, metabolism, and excretion (ADME) that regulates the processing of approximately 20-25% of commonly prescribed drugs. These medications include tricyclic antidepressants, selective serotonin reuptake inhibitors, antipsychotics, opioids (e.g., codeine and

tramadol), antiarrhythmic, beta-blockers, anti-neoplastic agents such as tamoxifen and gefitinib, and a diverse array of other pharmaceuticals.[3-5]

CYP2D6 is known for its extensive polymorphism, with more than 140 documented genetic variants.[6] These variants can be categorized into several groups, including null alleles (resulting in a complete lack of enzymatic activity), reduced-function alleles (leading to diminished functional products; normal function alleles that maintain typical activity), and increased function alleles associated with augmented *CYP2D6* activity. Additionally, there are alleles with uncertain or unknown functional implications.[7, 8] The Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have developed comprehensive guidelines for classifying individuals based on their *CYP2D6* metabolic activity. This classification categorizes patients into different phenotypes based on activity scores (AS).[9-13] These phenotypes include ultrarapid metabolizers (UM, AS>2.25), extensive or normal metabolizers (EM, 1.25≤ AS≤2.25), intermediate metabolizers (IM, 0.25≤AS≤1), and poor metabolizers (PM, AS=0), reflecting the diverse *CYP2D6* metabolizer groups.[13, 14]

Given the key role of the *CYP2D6* enzyme in drug metabolism, it is important to understand the genetic diversity of this enzyme in different populations.[15] Not only are common alleles of interest, but rarer star alleles, particularly those with functional implications, are also crucial for accurately predicting a patient's drug response.[16-18] The *CYP2D6**31 (characterized by rs267608319, NC_000022.11: g.42126749C>T), *CYP2D6**55 (characterized by rs1931013246, NC_000022.11:g.42126956T>G), *CYP2D6**113 (characterized by rs569439709, NC_000022.11:g.42126752C>T), and *CYP2D6** 135 (characterized by rs747089665, NC_ 000022.11: g.42126926G>A) polymorphisms are of particular interest due to their potential impact on *CYP2D6* enzyme function. These alleles have been underrepresented in population genetics studies, particularly in Iranian populations. Investigating these variants will provide valuable insights into *CYP2D6* polymorphisms within this population and enhance our understanding of pharmacogenetic variability. The clinical significance of these variants lies in their potential to alter drug metabolism, resulting in individual differences in drug response and the risk of adverse reactions. Therefore, this study aims to determine the genotype frequencies of *CYP2D6* variants in the Iranian population.

Materials and Methods

Study Population

The study population encompassed various ethnic groups in Iran, including Persians (Fars), Azeris, Gilakis and Mazandaranis, Kurds, Arabs, Lurs, Baloches, Turkmen, and other ethnicities. A total of 389 individuals, consisting of 224 men and 165 women, were randomly selected for this study in the hospitals of Islamic Azad Tehran Medical Science University, Iran, from May to December 2022. The study's criteria for including and excluding participants were clearly defined in terms of ethnicity. In this process, individuals were assumed to be free of any pre-existing illnesses and not currently using specific medications. This study did not consider underlying medical conditions or participants' medication histories, which may be subjects of future follow-up. All participants signed the informed consent. All recruited patients completed the approved study questionnaire. The obtained data were compiled in an Excel file. The present investigation was approved using the Local Ethical Committee of Islamic Azad University, Tehran Medical Sciences (IR.IAU. PS.REC.1400.539, IR.IAU.PS.REC.1401.391). Peripheral blood sample (5 mL) anticoagulated with ethylenediaminetetraacetic acid (EDTA) was collected from all patients and stored at -20 □ before DNA extraction.

DNA Extraction and Sequencing

Genomic DNA was extracted from the 5 mL blood samples using the Roje DNA extraction kit (DNSol Midi Kit) based on salt deposition (ROJE Technologies, Iran) following the manufacturer's protocol. Primer design was conducted using Oligo7 software (Molecular Biology Insights, Inc., Cascade, Co., USA). The designed primers were Forward: 5′-GAAAGCAGGATTGAGCAGGG-3′ and Reverse: 5′-CTTCTCAGTCACACAGGCCT-3′ (table 1). The PCR reactions were prepared in a 28 µL volume, which included 10 µL of 2X Red master mix (Iran Pioneer Recombinant Company, Iran), 12 µL of double-distilled water (Samen Co., Iran), 4 µL of DNA, and 1 µL each of the forward and reverse primers. Amplification was performed under the following conditions: an initial denaturation at 95 °C for 5 min, followed by 45 cycles of 95 °C for 45 seconds, 58.5 °C for 45 seconds, 72 °C for 45 seconds, and a final extension at 72°C for 10 min. The resulting fragments were assessed for size and accuracy using 1% agarose gel electrophoresis. The Sanger sequencing method was employed to identify the nucleotides in the target sequence of the *CYP2D6* gene.

Table 1: Oligonucleotide sequence of primers in polymerase chain reaction (PCR)

Genes	Position	SNPs	Nucleotide changes	Primer (Sequence)
CYP2D6	chr22:42126749	rs267608319	g.42126749C>T	F: 5'- GAAAGCAGGATTGAGCAGGG-3'
	chr22:42126956	rs1931013246	g.42126956T>G	R: 5'-CTTCTCAGTCACACAGGCCT-3'
	chr22:42126752	rs569439709	g.42126752C>T	
	chr22:42126926	rs747089665	g.42126926G>A	

CYP2D6: Cytochrome P450 2D6; SNP: Single nucleotide polymorphism; F: Forward; R: Reverse

Table 2: The frequency of CYP2D6 SNPs in the Iranian population

SNP	Genotype	Diplotepe	Phenotype determination based on enzyme activity	Frequency
rs267608319	CC	*CYP2D6*1/1*	Normal Metabolizer	100%
	CT	*CYP2D6*1/31**	Intermediate Metabolizer	0
	TT	*CYP2D6*31/31**	Uncertain function	0
rs1931013246	TT	*CYP2D6*1/*1*	Normal Metabolizer	100%
	TG	*CYP2D6*1/*55*	Intermediate Metabolizer	0
	GG	*CYP2D6*55/*55*	Intermediate Metabolizer	0
rs569439709	CC	*CYP2D6*1/1**	Normal Metabolizer	100%
	CT	*CYP2D6*1/113**	Intermediate Metabolizer	0
	TT	*CYP2D6*113/113**	Unknown Function	0
rs747089665	GG	*CYP2D6*1/1**	Normal Metabolizer	100%
	GA	*CYP2D6*1/135**	Intermediate Metabolizer	0
	AA	*CYP2D6*135/135**	Unknown Function	0

Finally, sequence data were analyzed using Chromas version 2.6.6 software (Chromas Lite, Inc. of San Francisco, CA) to determine genotypes.

CYP2D6 Allele Determination

For *CYP2D6* allele determination, each sample's genotype and gene copy number were assessed. Following the nomenclature criteria established by the CPIC, the star alleles of each sample were determined based on their genotypes.[19] Homogeneous and heterogeneous sequences at each polymorphic locus were reported, and allelic categories were defined.

Determination of CYP2D6 Activity Score and Phenotype

The enzyme activity of each allele was determined through the CPIC standard protocol. Moreover, phenotypes were assigned based on the level of enzyme activity.[13, 19] After evaluating the genotype and star alleles of each sample, the enzyme activity was calculated using the CPIC-provided protocol, and phenotypes were assigned accordingly.

Results

In this study, we examined the genotypic frequencies of four rare polymorphisms within the *CYP2D6* gene (rs747089665, rs267608319, rs1931013246, and rs569439709) in the Iranian population (table 2). Figure 1 illustrates the amplicon size of the *CYP2D6* gene variants on agarose gel.

The following provides a summary of our findings:

Regarding the prevalence of the normal genotype for rs267608319, the risk allele was

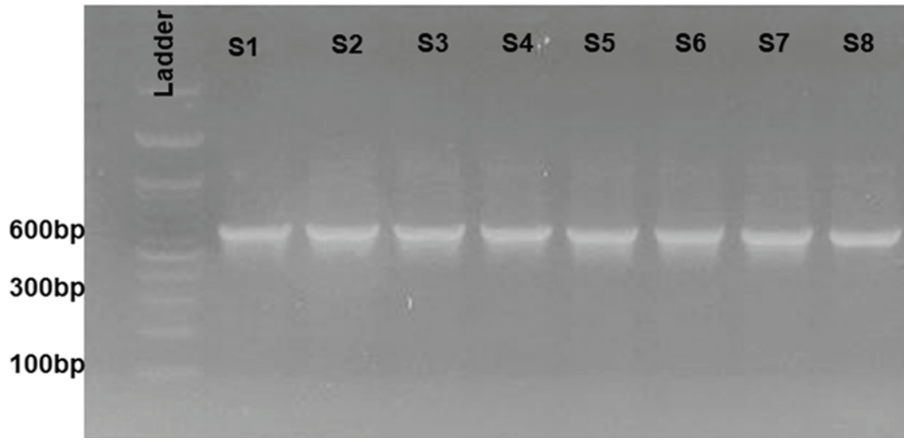

Figure 1: The results of the qualitative examination of the PCR products (626 bp) of CYP2D6 gene variants on 1% agarose gel.

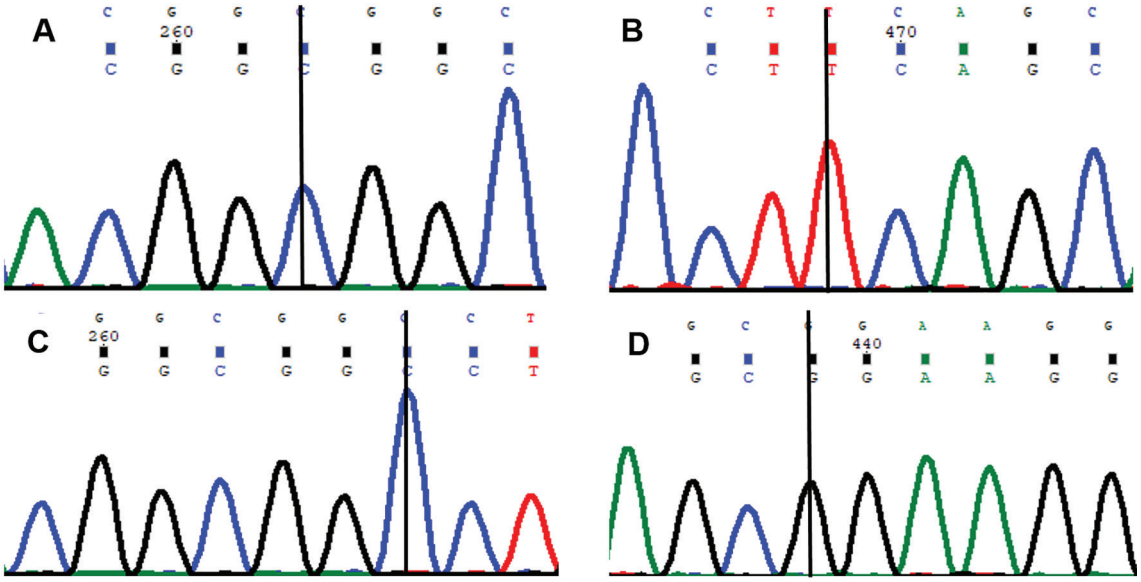

Figure 2: The DNA sequence chromatogram displays nucleotide changes at specific positions in the CYP2D6 gene. (A) A missense nucleotide transition C>T in g.42126749 of CYP2D6 gene, a wild-type sample for CYP2D6*31 (rs267608319) polymorphism. (B) A missense nucleotide transition T>G in g.42126956 of CYP2D6 gene, a wild-type sample for CYP2D6*55 (rs1931013246) polymorphism. (C) A missense nucleotide transition C>T in g.42126752 of CYP2D6 gene, a wild-type sample for CYP2D6*113(rs569439709) polymorphism. (D) A missense nucleotide transition G>A in g.42126926 of CYP2D6 gene, a wild-type sample for CYP2D6*135(rs747089665) polymorphism.

not present in the current study. The analysis results revealed the presence of a normal genotype for rs1931013246 in all members of the study population. Analysis of rs569439709 also revealed that the normal genotype was present consistently. Consistent with our previous findings, we observed that all individuals investigated for rs747089665 exhibited the wild-type genotype, signifying the absence of the variant allele within the Iranian cohort.

Overall, our results indicate a high prevalence of normal alleles for all four studied variants of the *CYP2D6* gene within the Iranian population (figure 2).

Discussion

Our findings revealed that the Iranian population mostly had normal genotypes for all alleles studied, i.e., *CYP2D6*31*CC (100%), *CYP2D6*55* TT (100%), *CYP2D6*113* CC (100%), and *CYP2D6*135* GG (100%). These alleles affect the functions of the *CYP2D6* enzyme, which is important for drug breakdown in the body.[20, 21] Studying the frequency of rare *CYP2D6* alleles in different populations can help improve personalized medicine and drug therapy.[16] In other words, they had the Normal Metabolizer (NM) phenotype. The *CYP2D6*1* allele, known as a functional allele, was very prevalent in the Iranian population. This finding also supports the NM frequency in many populations.[15] The impact of genetic variations on individual responses to various drugs holds significant importance. This variation is especially important for the *CYP2D6* gene regarding its key role in drug metabolism.[20, 22-23]

Shiran and colleagues aimed to identify the *CYP2D6* oxidation phenotype with dextromethorphan as a probe drug in the Mazandarani ethnic group in Iran. In their study, 71 healthy volunteers were given dextromethorphan, and their *CYP2D6* activity was assessed by analyzing dextromethorphan and its metabolite. Results showed a 560-fold interindividual variation in dextromethorphan metabolic ratios, with 7.04% identified as poor metabolizers. The study suggests a need for further research in larger samples to better understand the pharmacogenetic basis for personalized medicine.[24] Bagheri and colleagues investigated *CYP2D6* gene polymorphisms in an Iranian population of different ethnicities, comparing allele frequencies with other populations. *CYP2D6**4 (G1846A) and *14 (G1758A) alleles were absent in Iranian populations, while they found significant differences in the frequencies of the T/T, C/T, and C/C genotypes of the *CYP2D6**10 allele across all Iranian ethnic groups. While the absence of the *CYP2D6**4 (G1846A) and *14 (G1758A) alleles in various Iranian ethnicities is noteworthy, the authors emphasized the importance of considering the presence of the *CYP2D6**10 allele in drug research and routine treatment. This information could be particularly

valuable for clinicians in optimizing therapy and identifying individuals at risk of adverse drug reactions before initiating clinical trials.[25] In a study conducted in Tabriz, Iran, researchers examined the genetic variations in the *CYP2D6* gene among 100 healthy individuals. They specifically focused on the frequencies of five major alleles: *CYP2D6**2, *CYP2D6**4, *CYP2D6**5, *CYP2D6**10, and *CYP2D6**17, which play a crucial role in drug metabolism. The study revealed differences in allele frequencies between the Iranian population and other ethnic groups, such as Orientals, Saudi Arabians, and Caucasians, while similarities were observed with the Mediterranean population and South Indians. The findings of this study contribute to the understanding of *CYP2D6* genetic polymorphism in the Iranian population and its implications for drug metabolism.[26]

The *CYP2D6**31 is a non-functional variant of the *CYP2D6* gene. People who have this allele are poor metabolizers of certain drugs. Based on the gnomAD database, the frequency of this allele is very low in different populations. The alternative allele (T) is found in 0.000271 of Africans (n=7372), 0.0002 of European Finns (n=14980), 0.000554 of Latinos (n=23474), and 0.0000458 of South Asians (n=832).[27] This result indicates that *CYP2D6**31 is an uncommon allele in several populations.[28-33] After reviewing the available information on *CYP2D6**31, we conclude that this allele is usually absent in various populations. However, investigations in the Spanish populations revealed the presence of the *CYP2D6**31 allele in 2% of the population.[32] The *CYP2D6**55 allele, one of the alleles with reduced function, was not observed in the Iranian population (n=389).

According to NCBI database, two studies conducted in the Japanese population (i.e., 14KJPN and 8.3KJPN with n=28186 and 16728, respectively), the allele frequencies were observed to be 0.00004 and 0.00006, respectively.[34] As a result, it is one of the rare alleles of the *CYP2D6* gene with a lower frequency than other alleles of the *CYP2D6* gene in different societies.[35-38] This claim can be supported by further investigations and using more extensive and more diverse statistical populations.

The *CYP2D6**113 allele has been described as an uncertain function allele. Research has shown that the *CYP2D6**113 haplotype contributes to Intermediate Metabolizer (IM). According to the frequencies of alternative allele (T) given in genomAD-Exomes for various subpopulations, the T allele was T=0.00337 in Asians (n=32898) and 0.00001 in non-Finnish Europeans (n=69848).[39] In the present study, the frequency of the allele T was 0, and no *CYP2D6**113 allele was discovered. The *CYP2D6**135 has been reported as an unknown function allele. The *CYP2D6**135 haplotype results in Poor Metabolizer (PM). According to the frequencies of alternative allele (A) related to various sub-populations that have been reported in genomAD-Exomes, the frequency of A allele in Latino/Admixed American (n=32946), East Asian (n=19144), and non-Finnish European (n=119172) was 0.0006678, 0.0005746, and 0.00002517, respectively.[40] The finding that all individuals investigated for the *CYP2D6**135 allele exhibited the wild-type genotype in our study confirms the absence of the variant allele within the Iranian cohort. The consistent presence of wild-type genotypes within the Iranian population, regardless of ethnicity, suggests normal enzyme activity in these specific loci of the *CYP2D6* gene. As can be inferred from this result, Iranians may generally exhibit normal enzyme activity for these *CYP2D6* gene star alleles, which play a critical role in the metabolism of a wide range of drugs. Our results are in line with the findings from previous studies on the frequency of *CYP2D6* variants across other global populations.[23, 36, 37] Understanding these specific genetic variations in different populations is crucial for the advancement and implementation of pharmacogenomics techniques in clinical practice.[41]

The prevalence of wild-type genotypes for the studied variants in the Iranian population facilitates the prediction of drug metabolism and therapeutic outcomes, as it indicates a lower occurrence of non-functional or reduced-function alleles that might affect *CYP2D6* enzyme activity. From this perspective, healthcare professionals can utilize this knowledge to optimize drug therapies for individuals of Iranian descent, thereby potentially reducing the incidence of adverse drug reactions and improving treatment efficacy. To ensure the safety and effectiveness of drug treatments for all individuals, it is crucial to emphasize the importance of conducting pharmacogenomics research and integrating it into various medical disciplines. Nonetheless, the impact of genetic variation on drug metabolism extends beyond the specific variants studied here. The highly polymorphic nature of the *CYP2D6* gene suggests that a more comprehensive investigation of genetic variations within the Iranian population is warranted.

This study presents some limitations that should be acknowledged. Firstly, the sample size may not adequately represent the genetic diversity of the broader Iranian population, potentially leading to biased allele frequency estimates. Secondly,

focusing only on four rare polymorphisms within the *CYP2D6* gene limits the generalization of findings to other variants that may also influence drug metabolism. Therefore, future research with larger, more diverse cohorts and a broader array of genetic variants is recommended to enhance the understanding of pharmacogenomic implications in the present population.

Conclusion

Based on the results of our study, it is clear that the Iranian population predominantly exhibits the wild-type genotype for the studied *CYP2D6* polymorphisms, including rs267608319, rs1931013246, rs569439709, and rs747089665. These findings have significant implications for clinical pharmacology, highlighting the importance of considering population-specific genetic variants when prescribing drug treatments to individuals of Iranian descent. By understanding the genetic diversity of *CYP2D6* variations within the Iranian population, we pave the way for developing more personalized and effective drug therapies. This, in turn, can contribute to improved patient outcomes and overall healthcare quality. Continuing research into genetic variations in drug metabolism within the Iranian population will be crucial for advancing personalized medicine and optimizing drug therapy.

Authors' Contribution

M.H: Methodology, Investigation, Validation, Formal Analysis, Visualization, and Writing-Original draft preparation. E.A: Resources, Investigation, formal analysis, and Writing-Original draft preparation. S.A.B and A.N: Methodology and Writing -Review & Editing. M.H.: Writing -Review & Editing, Supervision and Project administration. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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