CYP450s Genes in Eight Major Ethnicities of Iran

Subjects: Others

Contributor: Navid Neyshaburinezhad, Hengameh Ghasim, Mohammadreza Rouini, Youssef Daali, Yalda H. Ardakani

Genetic polymorphisms in cytochrome P450 genes can cause variation in metabolism. Thus, single nucleotide variants significantly impact drug pharmacokinetics, toxicity factors, and efficacy and safety of medicines. The distribution of CYP450 alleles varies drastically across ethnicities, with significant implications for personalized medicine and the healthcare system.

Keywords: Iranian ethnicities ; CYP450 genotype ; polymorphism

1. Introduction

Personalized medicine is one of the highly advanced fields of medical sciences. This branch of science delves into the patient's physiologic and pathophysiologic features and selects and carries out an appropriate and specific therapeutic approach for the patient [1]. Concentrating on the patient as the focal point rather than the disease augments the treatment effectiveness and decreases the probable side effects [2]. Despite the positive aspects of this system, achieving such an extent of knowledge of the patient's features to implement personalized medicine necessitates a tremendous amount of detailed information about patient physiology and pathophysiology [3][4]. So far, there have been numerous studies regarding the matter at hand. Primarily, an effort has been made to genetically assess the specific populations, such as the people of a country, and compare them to other countries [5][6][7]. Following that, the ethnicities of various countries have been studied and compared [8][9][10]. Such assessments/studies greatly help access the required information and individualized therapies.

Cytochrome p450 (CYP450) is one of the most potent metabolizing enzymes in the body. It metabolizes many endogenic and exogenic substances [11][12][13]. Differences in genotype and phenotype alter the enzyme's activity. Aside from intra-individual changes in these enzymes' activity by several physiological, pathological, and environmental factors [14][15][16][17][18][19][20], any change in the enzyme activity may alter pharmacotherapeutic efficiency and decrease or increase adverse drug reactions [21][22][23][24]. Hence, in personalized medicine, the enzyme family is one of the parameters that increase the specificity of pharmacotherapy in patients under investigation. A genetic assessment of CYP450 enzymes reveals that they fall into four categories: poor, intermediate, extensive, and ultra-rapid metabolizers, which have low, moderate, usual, and high activity, respectively [25]. As previously stated, the patient's response to therapy is not always consistent with his genotype. For instance, the patient's genotype indicates that the CYP450 enzyme is normal, but the pharmacotherapy response indicates the enzyme's decreased activity [26]. In such cases, it has been demonstrated that an enzyme's activity and phenotype are not concordant with the corresponding genotype for various reasons, such as diseases, medication use, diet, and the like. This phenomenon is known as phenocoversion. Nonetheless, the primary assessment of personalized medicine begins with genotyping [27][28].

In recent years, several studies have been conducted on the genotype of some cytochrome 450 enzymes in the Iranian population. In these studies, one cytochrome was investigated in one group of patients or a specific ethnicity [10][29][30][31]. However, no study has comprehensively investigated the important cytochromes P450 across various ethnicities in Iran's population. Results revealed that, while there are some similarities, there are many genotype differences between the cytochrome P450 enzyme of the Iranian population and the other populations mentioned above [32]. These findings highlighted the importance of conducting additional individual studies on the Iranian population to gain more information. Such data can advance personalized medicine, improve pharmacotherapy efficiency, and reduce probable unintended adverse effects in Iranian patients (concerning the genetic profile of cytochrome P450 enzymes).

2. CYP1A2

A previous study demonstrated that the frequency of the *1 allele in the Iranian population was 39.8% [32]. The only SNP with a frequency greater than 1% in the Iranian population is the *1F allele, which has a frequency of 59.9%. The Persian

(66.8%) and the Persian Gulf Islander (50%), among the eight Iranian ethnicities, have the highest and lowest frequency, respectively.

There are no similarities in the frequency of the *1F allele between Iranian ethnicities and any other studied populations (Caucasian, European, Middle Eastern) (difference more significant than 1%) [33][34][35]. Additionally, genotypic analysis of these ethnicities revealed that the Kurds (51.5%) and the Persian Gulf Islanders (31.6%) have the highest and lowest frequency of homozygote genotype of CYP1A2*1F, respectively. In comparison, the Baloch (42.4%) and Kurds (28.8%) had the highest and lowest heterozygote genotype frequencies, respectively. In the Iranian population, the mean frequency of CYP1A2 homozygous and heterozygous genotypes based on the *1F allele were 41.5% and 36.6%, respectively.

3. CYP2B6

The *1 allele was found in 54.7% of the Iranian population [32]. The *9 allele had the highest prevalence (26.6%) in the Iranian population, ranging from 30.5% in the Lur to 24.0% in the Persian. The frequency of this allele among the Iranian Arabs was similar to the Caucasian race [36], the Persian similar to the European population, and the Lur to the Middle Eastern population [37][38][39]. Additionally, genotypic investigation of these ethnicities revealed that the Lur (9%) and Persian (5%) had the highest and lowest frequency of homozygote genotypes, respectively. In comparison, the Lur (43%) and the Persian (38%), respectively, had the highest and lowest frequency of heterozygote genotypes. In the Iranian population, the mean frequency of CYP2B6 homozygous and heterozygous genotypes based on the *9 allele were 6.2% and 40.6%.

The *5 allele was the second most prevalent allele (8.5%) among the Iranian population, ranging from 10% in the Arab and Baloch to 6.5% in the Persian. This allele frequency among Arab and Baloch of the Iranian population was similar to the Caucasian race [36]. In contrast, none of the Iranian ethnicities were similar to the European population or the Middle Eastern population [37][38][39]. Furthermore, genotypic analysis of these ethnicities revealed that the Baloch (2%) had the highest frequency of homozygote genotype, while Turkmen, Lur, Far, and Persian Gulf Islander did not. On the other hand, among the Iranian population, Arab and Turkmen (18%) and Persian (13%) had the highest and lowest frequency of heterozygote genotype, respectively. The mean frequency of CYP2B6 homozygous and heterozygous genotypes based on the *5 allele were 0.6% and 15.7% in the Iranian population, respectively.

Among Iranian ethnics, the *2 allele prevalence ranged from 8.5% in the Persian to 1.5% in the Turkmen. The frequency of the *2 allele among Baloch and Lur of the Iranian populations was similar to the Caucasian race and the European populations [36]. Moreover, the Arabs were similar to the Middle Eastern population in terms of the *2 allele frequency [37][38][39]. Additionally, a genotypic investigation of Iranian ethnics revealed that Fars, Arab, Kurd, and Baloch had a 1% frequency of homozygote genotype, whereas other ethnicities did not have this genotype. On the other hand, among the Iranian population, the Persian (15%) and the Turkmen (3%) had the highest and lowest frequency of heterozygote genotype, respectively. Mean frequency of CYP2B6 homozygous and heterozygous genotype based on the *2 allele was 0.5% and 9.6% in the Iranian population.

The *22 allele had a 2.6% frequency in the Iranian population. It ranged from 4.5% among the Persians to 1% among the Persian Gulf Islanders. This allele's frequency was similar to that of the Caucasian race, except for Persian and Persian Gulf Islanders [40]. Moreover, the frequency of this allele was similar to the European population of Kurd, Lur, and Persian Gulf Islanders. Furthermore, a genotypic investigation of these ethnicities revealed that the homozygote genotype was not found among any of the Iranian ethnicities. The Persian (95) and the Persian Gulf Islander (2%), on the other hand, had the highest and lowest frequency of heterozygote genotype among the Iranian population, respectively. In the Iranian population, the mean frequency of CYP2B6 homozygous and heterozygous genotypes based on the *9 allele was 0 and 5.2%, respectively.

The *3 allele had the lowest prevalence (1.3%) in the Iranian population, ranging from 4% in the Persians to 0% in the Baloch. The frequency of this allele in the Azeri, Persian Gulf Islander, and Turkmen populations was similar to that of the Caucasian race and the European population [36]. Similar to the *22 allele, genotypic analysis of these ethnicities revealed that the homozygote genotype was not found among any Iranian ethnicity. On the other hand, the Persian race (8%) had the highest frequency of heterozygote genotype. In comparison, the Baloch showed no heterozygote genotype. In the Iranian population, the mean frequency of CYP2B6 homozygous and heterozygous genotypes based on the *3 allele was 0 and 2.6%, respectively.

4. CYP2C8

According to the previous study, the frequency of the *1 allele was 95% in the Iranian population [32]. The *4 allele prevalence ranged from 5.5% in the Kurds to 0.5% in the Persians among Iranian ethnicities. None of the Iranian ethnicities had a frequency of the *4 allele similar to the Caucasian race [41]. The frequency of this allele among the Kurds was similar to the European population. Moreover, Arab, Lur, and Turkmen populations were similar to the Middle Eastern population regarding the *4 allele frequency [42]. Additionally, a genotypic study of Iranian ethnicities revealed that only the Azeri race had a 1% frequency of homozygote genotype, whereas the homozygote genotype was not found in other ethnicities. On the other hand, the Kurds (11%) and the Persian Gulf Islanders (1%) had the highest and lowest frequency of heterozygote genotype among the Iranian population, respectively. In the Iranian population, the mean frequency of CYP2C8 homozygous and heterozygous genotypes based on the *4 allele was 0.1% and 5.1%, respectively.

The prevalence of the *2 allele ranged from 6% in the Persian Gulf Islanders to 0% in Turkmen. The frequency of the *2 allele among the Lur was similar to the Caucasian race and the European population [43]. Additionally, a genotypic study of Iranian ethnics revealed that only Persian Gulf Islanders and Baloch had a 1% frequency of the homozygote genotype. Other ethnicities, on the other hand, did not have the homozygote genotype. In the Iranian population, the mean frequency of CYP2C8 homozygous and heterozygous genotypes based on *2 allele was 0.2% and 4.2%, respectively.

5. CYP2C9

According to the previous study [32], the *1 allele had a 78.1% prevalence. Among Iranian ethnicities, the *2 allele prevalence ranged from 15% in Lur to 7% in Arab. None of the Iranian ethnicities had the same frequency of the *2 allele as the Caucasian race. However, the frequency of this allele among Azeris was similar to the European population [35]. Moreover, regarding *2 allele frequency, the Azeri and Turkmen were similar to the Middle Eastern population [37][44][45][46]. Additionally, a genotypic study of Iranian ethnics revealed that Persian and Persian Gulf Islanders had the highest homozygote genotype (2%), while Lur, Turkmen, Kur, and Baloch did not.

Among Iranian ethnicities, the *3 allele prevalence ranged from 14.5% in Baloch to 7% in Arabs. None of the Iranian ethnicities had a frequency of the *2 allele similar to the Caucasian race. However, the frequency of this allele among the Azeri and Arab populations was similar to the European population [35]. Moreover, except for Baloch and Persian Gulf Islanders, all Iranian ethnicities were similar to the Middle Eastern population in terms of the *3 allele frequency [37][44][45][46]. Additionally, a genotypic study of Iranian ethnicities revealed that Baloch had the highest frequency of homozygote genotype (5%), while Arab and Azeri did not. On the other hand, the Persian Gulf Islanders (21%) and Arab and Kurds (14%) had the highest and lowest frequency of heterozygote genotype among the Iranian population, respectively.

6. CYP2C19

The frequency of the *1 allele in the Iranian population was 85.8% [32]. The only allele with a frequency of more than 1% among the Iranian population was the *2 allele. Its prevalence ranged from 18% in the Baloch to 11% in the Azeri, Lur, Kurd, and Persian Gulf Islanders. The frequency of the *2 allele was similar in the Arabs and Caucasians. However, among the Persian and Turkmen, its frequency was similar to the European population [35]. Moreover, the Baloch was similar to the Middle Eastern population regarding the *2 allele frequency [37][38][46][47]. Additionally, genotypic analysis of these ethnicities revealed that the Baloch (4%) and Fars, Arab, and Lur (2%) had the highest and lowest frequency of homozygote genotypes, respectively. In comparison, the Persian (29%) and Persian Gulf Islander (16%) populations had the highest and lowest frequency of heterozygote genotype, respectivel. In the Iranian population, the mean frequency of CYP2C19 homozygous and heterozygous genotypes based on the *2 allele was 2% and 22.3%, respectively.

7. CYP2D6

A previous study found that the frequency of the *1 allele in the Iranian population was 10.6% [32]. The prevalence of the *2 allele was the highest in the Iranian population (47%), ranging from 53% in Baloch to 42% in Azeri. The frequency of the *2 allele among all Iranian ethnics was similar to the Caucasian race [35]. However, none were similar to the Middle Eastern population [48][49][50]. Furthermore, a genotypic analysis of these ethnicities revealed that the Baloch (32%) and Azeri (17%) had the highest and lowest frequency of homozygote genotype, respectively. In comparison, the Azeri (50%) and Lur (38.3%) had the highest and lowest frequency of heterozygote genotype, respectively. In the Iranian population, the mean frequency of CYP2D6 homozygous and heterozygous genotypes based on the *2 allele was 24.4% and 45.3%, respectively.

The *10 allele prevalence ranged from 22.5% in Azeris to 10% in the Arabs. None of the Iranian ethnics had the same frequency of the *10 allele as the Caucasian race, the European population [35] or the Middle Eastern population [48][49][50]. Additionally, genotypic analysis of these ethnicities revealed that the Azeri (7%) and Lur, Arab, and Persian Gulf Islander (1%) had the highest and lowest frequency of homozygote genotype, respectively. In comparison, the Azeri (31%) and Baloch (17%) had the highest and lowest frequency of heterozygote genotype, respectively. In the Iranian population, the mean frequency of CYP2D6 homozygous and heterozygous genotypes based on the *10 allele was 3.1% and 24%, respectively.

The *41 allele prevalence ranged from 18.5% in the Persian to 8.5% in the Persian Gulf Islander. The frequency of the *41 alleles among Turkmen and Persian Gulf Islander was similar to the Caucasian race and Turkmen to the European population [51]. Furthermore, except for Turkmen and Persian Gulf Islanders, the frequency of this allele was comparable to the Middle Eastern population [48][49][50]. Additionally, a genotypic analysis of these ethnicities revealed that Azeri, Kurd, Lur, and Baloch (4%) and Arab (1%) had the highest and lowest homozygote genotypes, respectively. In comparison, Azeri (29%) and Baloch (11%) had the highest and lowest frequency of heterozygote genotype, respectively. In the Iranian population, the mean frequency of CYP2D6 homozygous and heterozygous genotypes based on the *41 allele was 3.1% and 21.7%, respectively.

With a prevalence of more than 1%, the *4 alleles had the lowest frequency among CYP2D6 alleles. None of the Iranian ethnicities had the same frequency of the *4 allele as the Caucasian race or the European population [35]. However, the frequency of this allele among Kurds and Turkmen was similar to the Middle Eastern population [48][49][50]. Additionally, the Azeri (17%) and the Arab (7.5%) had this allele's highest and lowest frequency. According to the genotypic analysis of these races, Azeri (4%) and Lur lacked the homozygote genotype. In comparison, Azeri (26%) and Turkmen (12.1%) had the highest and lowest frequency of heterozygote genotype, respectively. In the Iranian population, the mean frequency of CYP2D6 homozygous and heterozygous genotypes based on the *4 allele was 1.7% and 19%, respectively.

8. CYP2E1

The *1 allele frequency in the Iranian population was 94.1% [32]. The *4 allele, with a 5.6% frequency in the Iranian population, is the only one with a frequency of more than 1%. None of the Iranian ethnicities had the same frequency of the *4 allele as the European population. At the same time, the Azeri was similar to the Middle Eastern population regarding the *4 allele frequency [46]. The Persian (8%) and the Azeri (3.5%) also had this allele's highest and lowest frequency, respectively. The homozygote genotype was found only in Kurds and Lurs (1%), with no other ethnicities having this allele. In addition, the Persian (16%) and the Azeri (7%) had the highest and lowest frequency of heterozygote genotype, respectively. In the Iranian population, the mean frequency of CYP2E1 homozygous and heterozygous genotypes based on the *4 allele was 0.3% and 10.7%, respectively.

9. CYP3A4

In the Iranian population, the prevalence of the *1 allele was 99.7% [32]. The frequency of mutated alleles of the CYP3A4 enzyme was less than 0.5% among the Iranian population.

10. CYP3A5

According to the previous research, the prevalence of the *1 allele in the Iranian population was 3.8% [32]. The *3 allele, with a 96.1% frequency in the Iranian population, was the only one with a frequency of more than 1%. The frequency of the *3 allele among all Iranian ethnicities, except Persian, Turkmen, and Lur, was similar to the Caucasian race [35] while showing no similarity with the European or Middle Eastern populations [52][53]. The Persian (98.2%) and the Arab (94.8%) had this allele's highest and lowest frequencies, respectively. Genotypic analysis of these ethnicities revealed that the Persian (99%) and Arab (88%) had the highest and lowest frequency of homozygote genotypes, respectively. In comparison, the Arab (11%) and Persian (0%) had the highest and lowest frequency of heterozygote genotype, respectively. In the Iranian population, the mean frequency of CYP3A5 homozygous and heterozygous genotypes based on the *3 allele was 93.9% and 5.8%, respectively.

References

1. Akhoon, N. Precision Medicine: A New Paradigm in Therapeutics. Int. J. Prev. Med. 2021, 12, 12.

2. Mathur, S.; Sutton, J. Personalized medicine could transform healthcare. Biomed. Rep. 2017, 7, 3–5.
3. Goetz, L.H.; Schork, N.J. Personalized medicine: Motivation, challenges, and progress. Fertil. Steril. 2018, 109, 952–963.
4. Samer, C.F.; Lorenzini, K.I.; Rollason, V.; Daali, Y.; Desmeules, J.A. Applications of CYP450 testing in the clinical setting. Mol. Diagn. Ther. 2013, 17, 165–184.
5. Ganoci, L.; Bozina, T.; Mirosevic Skvrce, N.; Lovric, M.; Mas, P.; Bozina, N. Genetic polymorphisms of cytochrome P450 enzymes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 in the Croatian population. Drug Metab. Pers. Ther. 2017, 32, 11–21.
6. Serpe, L.; Canaparo, R.; Scordo, M.G.; Spina, E. Pharmacogenetics of drug-metabolizing enzymes in Italian populations. Drug Metab. Pers. Ther. 2015, 30, 107–120.
7. Zhou, Y.; Ingelman-Sundberg, M.; Lauschke, V.M. Worldwide Distribution of Cytochrome P450 Alleles: A Meta-analysis of Population-scale Sequencing Projects. Clin. Pharm. Ther. 2017, 102, 688–700.
8. Ahmed, S.; Gul, S.; Akhlaq, M.; Hussain, A.; Tariq Khan, S.; Rehman, H.; Hanif Bangash, M.; Al Mughairbi, F.; Hamid Hamdard, M. Estimation of polymorphisms in the drug-metabolizing enzyme, cytochrome P450 2C19 gene in six major ethnicities of Pakistan. Bioengineered 2021, 12, 4442–4451.
9. Korytina, G.; Kochetova, O.; Akhmadishina, L.; Viktorova, E.; Victorova, T. Polymorphisms of cytochrome p450 genes in three ethnic groups from Russia. Balkan Med. J. 2012, 29, 252–260.
10. Tabari, M.G.; Naseri, F.; Ataby, M.A.; Marjani, A. Genetic Polymorphism of Cytochrome p450 (2C9) Enzyme in Iranian Baluch Ethnic Group. Open Biochem. J. 2015, 9, 37–41.
11. Chen, Q.; Zhang, T.; Wang, J.F.; Wei, D.Q. Advances in human cytochrome p450 and personalized medicine. Curr. Drug Metab. 2011, 12, 436–444.
12. Nebert, D.W.; Russell, D.W. Clinical importance of the cytochromes P450. Lancet 2002, 360, 1155–1162.
13. Testa, B.; Pedretti, A.; Vistoli, G. Reactions and enzymes in the metabolism of drugs and other xenobiotics. Drug Discov. Today 2012, 17, 549–560.
14. He, Z.X.; Chen, X.W.; Zhou, Z.W.; Zhou, S.F. Impact of physiological, pathological and environmental factors on the expression and activity of human cytochrome P450 2D6 and implications in precision medicine. Drug Metab. Rev. 2015, 47, 470–519.
15. Neyshaburinezhad, N.; Rouini, M.; Shirzad, N.; Esteghamati, A.; Nakhjavani, M.; Namazi, S.; Ardakani, Y.H. Evaluating the effect of type 2 diabetes mellitus on CYP450 enzymes and P-gp activities, before and after glycemic control: A protocol for a case-control pharmacokinetic study. MethodsX 2020, 7, 100853.
16. Neyshaburinezhad, N.; Seidabadi, M.; Rouini, M.; Lavasani, H.; Foroumadi, A.; Ardakani, Y.H. Evaluation of hepatic CYP2D1 activity and hepatic clearance in type I and type II diabetic rat models, before and after treatment with insulin and metformin. Daru 2020, 28, 479–487.
17. Neyshaburinezhad, N.; Rouini, M.R.; Entezari, H.; Lavasani, H.; Ardakani, Y.H. Evaluation of changes in cytochrome P450 2C19 activity in type 2 diabetic rats before and after treatment, by using isolated perfused liver model. Iran. J. Basic Med. Sci. 2020, 23, 629–635.
18. Neyshaburinezhad, N.; Rouini, M.; Lavasani, H.; Ardakani, Y.H. Evaluation of Cinnamon (Cinnamomum Verum) Effects on Liver Cyp450 2D1 Activity and Hepatic Clearance in Diabetic Rats. Jundishapur. J. Nat. Pharm. Prod. 2021, 16, e101797.
19. Rezai, S.; Neyshaburinezhad, N.; Rouini, M.; Lavasani, H.; Ardakani, Y.H. Can combination therapy with insulin and metformin improve metabolic function of the liver, in type I diabetic patients? An animal model study on CYP2D1 activity. J. Diabetes Metab. Disord. 2020, 19, 2049–2056.
20. Rouini, M.R.; Ghazi-Khansari, M.; Ardakani, Y.H.; Dasian, Z.; Lavasani, H. A disposition kinetic study of tramadol in rat perfused liver. Biopharm. Drug Dispos. 2008, 29, 231–235.
21. Rollason, V.; Lloret-Linares, C.; Lorenzini, K.I.; Daali, Y.; Gex-Fabry, M.; Piguet, V.; Besson, M.; Samer, C.; Desmeules, J. Evaluation of Phenotypic and Genotypic Variations of Drug Metabolising Enzymes and Transporters in Chronic Pain Patients Facing Adverse Drug Reactions or Non-Response to Analgesics: A Retrospective Study. J. Pers. Med. 2020, 10, 198.
22. Zanger, U.M.; Schwab, M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharm. Ther. 2013, 138, 103–141.
23. Lloret-Linares, C.; Rollason, V.; Lorenzini, K.I.; Samer, C.; Daali, Y.; Gex-Fabry, M.; Aubry, J.M.; Desmeules, J.; Besson, M. Screening for genotypic and phenotypic variations in CYP450 activity in patients with therapeutic problems

in a psychiatric setting, a retrospective study. Pharm. Res. 2017, 118, 104–110.

24. Marsousi, N.; Desmeules, J.A.; Rudaz, S.; Daali, Y. Prediction of drug-drug interactions using physiologically-based pharmacokinetic models of CYP450 modulators included in Simcyp software. Biopharm. Drug Dispos. 2018, 39, 3–17.
25. Tracy, T.S.; Chaudhry, A.S.; Prasad, B.; Thummel, K.E.; Schuetz, E.G.; Zhong, X.B.; Tien, Y.C.; Jeong, H.; Pan, X.; Shireman, L.M.; et al. Interindividual Variability in Cytochrome P450-Mediated Drug Metabolism. Drug Metab. Dispos. 2016, 44, 343–351.
26. Gloor, Y.; Lloret-Linares, C.; Bosilkovska, M.; Perroud, N.; Richard-Lepouriel, H.; Aubry, J.M.; Daali, Y.; Desmeules, J.A.; Besson, M. Drug metabolic enzyme genotype-phenotype discrepancy: High phenoconversion rate in patients treated with antidepressants. Biomed. Pharm. 2022, 152, 113202.
27. Klomp, S.D.; Manson, M.L.; Guchelaar, H.J.; Swen, J.J. Phenoconversion of Cytochrome P450 Metabolism: A Systematic Review. J. Clin. Med. 2020, 9, 2890.
28. Shah, R.R.; Smith, R.L. Addressing phenoconversion: The Achilles' heel of personalized medicine. Br. J. Clin. Pharm. 2015, 79, 222–240.
29. Azarpira, N.; Ashraf, M.J.; Khademi, B.; Darai, M.; Hakimzadeh, A.; Abedi, E. Study the polymorphism of CYP3A5 and CYP3A4 loci in Iranian population with laryngeal squamous cell carcinoma. Mol. Biol. Rep. 2011, 38, 5443–5448.
30. Hashemi-Soteh, M.B.; Hosseini, E.; Fazelnia, S.; Ghasemian-Sorbeni, F.; Madahian, S.; Shiran, M.R. Frequencies of CYP2B64,5, and 6 Alleles within an Iranian Population (Mazandaran). Genet. Res. 2021, 2021, 8703812.
31. Tabari, R.G.; Marjani, A.; Ataby, O.A.; Mansourian, A.R.; Samai, N.M. Genetic Polymorphism of Cytochrome p450 (2C19) Enzyme in Iranian Turkman Ethnic Group. Oman Med. J. 2013, 28, 237–244.
32. Neyshaburinezhad, N.; Ghasim, H.; Rouini, M.; Daali, Y.; Ardakani, Y.H. Frequency of Important CYP450 Enzyme Gene Polymorphisms in the Iranian Population in Comparison with Other Major Populations: A Comprehensive Review of the Human Data. J. Pers. Med. 2021, 11, 804.
33. Bilgen, T.; Tosun, O.; Luleci, G.; Keser, I. Frequencies of four genetic polymorphisms in the CYP1A2 gene in Turkish population. Genetika 2008, 44, 1133–1136.
34. Hamdy, S.I.; Hiratsuka, M.; Narahara, K.; Endo, N.; El-Enany, M.; Moursi, N.; Ahmed, M.S.; Mizugaki, M. Genotyping of four genetic polymorphisms in the CYP1A2 gene in the Egyptian population. Br. J. Clin. Pharm. 2003, 55, 321–324.
35. Myrand, S.P.; Sekiguchi, K.; Man, M.Z.; Lin, X.; Tzeng, R.Y.; Teng, C.H.; Hee, B.; Garrett, M.; Kikkawa, H.; Lin, C.Y.; et al. Pharmacokinetics/genotype associations for major cytochrome P450 enzymes in native and first- and third-generation Japanese populations: Comparison with Korean, Chinese, and Caucasian populations. Clin. Pharm. Ther. 2008, 84, 347–361.
36. Lang, T.; Klein, K.; Fischer, J.; Nussler, A.K.; Neuhaus, P.; Hofmann, U.; Eichelbaum, M.; Schwab, M.; Zanger, U.M. Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. Pharmacogenetics 2001, 11, 399–415.
37. Al-Mahayri, Z.N.; Patrinos, G.P.; Wattanapokayakit, S.; Iemwimangsa, N.; Fukunaga, K.; Mushiroda, T.; Chantratita, W.; Ali, B.R. Variation in 100 relevant pharmacogenes among emiratis with insights from understudied populations. Sci. Rep. 2020, 10, 21310.
38. Ellison, C.A.; Abou El-Ella, S.S.; Tawfik, M.; Lein, P.J.; Olson, J.R. Allele and genotype frequencies of CYP2B6 and CYP2C19 polymorphisms in Egyptian agricultural workers. J. Toxicol. Environ. Health A 2012, 75, 232–241.
39. Yuce-Artun, N.; Kose, G.; Suzen, H.S. Allele and genotype frequencies of CYP2B6 in a Turkish population. Mol. Biol. Rep. 2014, 41, 3891–3896.
40. Zanger, U.M.; Klein, K. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): Advances on polymorphisms, mechanisms, and clinical relevance. Front. Genet. 2013, 4, 24.
41. Bahadur, N.; Leathart, J.B.S.; Mutch, E.; Steimel-Crespi, D.; Dunn, S.A.; Gilissen, R.; Houdt, J.V.; Hendrickx, J.; Mannens, G.; Bohets, H.; et al. CYP2C8 polymorphisms in Caucasians and their relationship with paclitaxel 6 alpha-hydroxylase activity in human liver microsomes. Biochem. Pharmacol. 2002, 64, 1579–1589.
42. Sahinogullari, Z.U. Genetic polymorphism of CYP2C8*4 in a healthy Turkish population. Med. Sci. Int. Med. J. 2020, 9, 314–319.
43. Kudzi, W.; Dodoo, A.N.; Mills, J.J. Characterisation of CYP2C8, CYP2C9 and CYP2C19 polymorphisms in a Ghanaian population. BMC Med. Genet. 2009, 10, 124.
44. Alzahrani, A.M.; Ragia, G.; Hanieh, H.; Manolopoulos, V.G. Genotyping of CYP2C9 and VKORC1 in the Arabic population of Al-Ahsa, Saudi Arabia. Biomed. Res. Int. 2013, 2013, 315980.

45. Aynacioglu, A.S.; Brockmoller, J.; Bauer, S.; Sachse, C.; Guzelbey, P.; Ongen, Z.; Nacak, M.; Roots, I. Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin. Br. J. Clin. Pharm. 1999, 48, 409–415.
46. Hamdy, S.I.; Hiratsuka, M.; Narahara, K.; El-Enany, M.; Moursi, N.; Ahmed, M.S.; Mizugaki, M. Allele and genotype frequencies of polymorphic cytochromes P450 (CYP2C9, CYP2C19, CYP2E1) and dihydropyrimidine dehydrogenase (DPYD) in the Egyptian population. Br. J. Clin. Pharm. 2002, 53, 596–603.
47. Sabırli, R.; Köseler, A.; Yilmaz, A.; Doğu Kılıç, İ. CYP2C19*1 and CYP2C19*2 Polymorphism in Turkish Patients Being Diagnosed with Stable Coronary Artery Disease and Using Clopidogrel. Bagcilar. Med. Bull. 2021, 6, 53–60.
48. Alali, M.; Ismail Al-Khalil, W.; Rijjal, S.; Al-Salhi, L.; Saifo, M.; Youssef, L.A. Frequencies of CYP2D6 genetic polymorphisms in Arab populations. Hum. Genom. 2022, 16, 6.
49. Khalaj, Z.; Baratieh, Z.; Nikpour, P.; Khanahmad, H.; Mokarian, F.; Salehi, R.; Salehi, M. Distribution of CYP2D6 polymorphism in the Middle Eastern region. J. Res. Med. Sci. 2019, 24, 61.
50. Taskin, B.; Percin, F.E.; Ergun, M.A. Investigation of CYP2D6 Gene Polymorphisms in Turkish Population. Psychopharmacol Bull. 2016, 46, 67–72.
51. Del Tredici, A.L.; Malhotra, A.; Dedek, M.; Espin, F.; Roach, D.; Zhu, G.D.; Voland, J.; Moreno, T.A. Frequency of CYP2D6 Alleles Including Structural Variants in the United States. Front. Pharm. 2018, 9, 305.
52. Abd El Wahab, N.; Shafik, N.F.; Shafik, R.E.; Taha Sh, A.; Shafik, H.E.; Darwish, A.D. Association of CYP3A5*3 and CYP1A1*2C Polymorphism with Development of Acute Myeloid Leukemia in Egyptian Patients. Asian Pac. J. Cancer Prev. 2017, 18, 747–752.
53. Arıcı, M.; Özhan, G. The evaluation of CYP3A4 and CYP3A5 genetic profiles in Turkish population. J. Fac. Pharm. Istanbul 2016, 46, 15–22.