Analysis of Cytochrome P450 2C9 Gene Polymorphism in a Sample of Iraqi Hypertensive Patients

Ali Hassan Ijam[1], Bahir Abdul-Razzaq Mshimesh[1], Ahmed Sahib Abdulamir[2], Shokry Faaz Alsaad[3]

[1]Department of Pharmacology and Toxicology, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq, [2]Department of Microbiology, College of Medicine, Al-Nahrain University, Baghdad, Iraq, [3]Department of Internal Medicine, College of Medicine, University of Babylon, Babil, Iraq

Abstract

Background: According to the literature review, there is little knowledge about CYP2C9 genetic variants in Iraqi hypertensive patients. **Objectives:** Evaluate and compare the distribution of important cytochrome CYP2C9 genetic variants within the Iraqi population in relation to other populations. **Materials and Methods:** After DNA extraction and subsequent polymerase chain reaction (PCR), the PCR products were subjected to Sanger sequencing to determine the CYP2C9 genetic variants in Iraqi hypertensive patients. The mutant alleles of the identified CYP2C9 genetic variants were compared to those of other countries. The study of linkage disequilibrium (LD) was conducted using the SHEsis program. **Results:** In the Iraqi population, a total of nine CYP2C9 polymorphisms were found with different frequencies. The comparative analysis of major variant rs1799853 C<T and rs1057910 A<C across different populations showed that the frequency of rs1799853 single nucleotide polymorphism (SNP) was significantly ($P < 0.05$)greater in Iraqis compared to both Asian and African–American populations. The allele frequency of rs1799853 and rs1057910 SNPs was comparable with other countries as Europe, Kuwait, Egypt, Jordan, Lebanon, Oman, Saudi Arabia, and Iran. The allele frequency of rs1057910 SNP was determined to be significantly ($P < 0.05$) greater in the Iraqi population in relation to the African–American population. Moreover, there was a very strong linkage among the studied CYP2C9 SNPs, except for rs555206628 SNPs; there was a weak linkage with CYP2C9 rs28371676 and rs1057910. **Conclusions:** This study provides insights into the prevalence of CYP2C9 polymorphisms among Iraqi populations. This knowledge has the potential to enhance the efficacy of pharmacotherapy through the use of personalized medicine strategies tailored specifically to this ethnic population.

Keywords: CYP2C9, genetic polymorphism, Iraqi populations, linkage disequilibrium

Introduction

The human genome comprises a total of 57 functional cytochrome P450 (CYP) genes, along with 58 pseudogenes. Those genes are categorized into 18 families and 43 sub-families based on their similarity in DNA sequences.[1]

The cytochrome P450 superfamily is a prominent class of phase I drug-metabolizing enzymes responsible for oxidizing a diverse range of endogenous compounds and xenobiotics, accounting for approximately 70–80% of currently utilized therapeutic drugs.[2] The CYP2C9 enzyme, belonging to the CYP450 superfamily, plays a pivotal role in the hydroxylation process of many different drugs. It is estimated to participate in the metabolism of approximately 15–20% of medications, such as losartan (for high blood pressure), warfarin (for blood clotting), ibuprofen (for pain), and tolbutamide and glimepiride (for diabetes).[3]

The CYP2C9 gene comprises a total of 50,708 nucleotides and is located within a group of CYP450 genes arranged as CYP2C18-CYP2C19-CYP2C9-CYP2C8 and covering an area of 500 kilobases on chromosome 10q24. This

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_1650_23

Address for correspondence: Dr. Ali Hassan Ijam, Department of Pharmacology and Toxicology, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.
E-mail: ahzajam84@gmail.com

Submission: 06-Nov-2023 **Accepted:** 15-Dec-2023 **Published:** 24-Sep-2024

How to cite this article: Ijam AH, Mshimesh BA-R, Abdulamir AS, Alsaad SF. Analysis of cytochrome P450 2C9 gene polymorphism in a sample of Iraqi hypertensive patients. Med J Babylon 2024;21:653-8.

gene consists of nine exons.[4] The CYP2C9 enzyme is mostly expressed in the hepatic tissue, with an estimated expression level ranking as the second highest among the many isoforms of the cytochrome P450 enzyme family. CYP2C9 constitutes approximately 20% of the hepatic CYP content.[5]

The expression of each cytochrome P450 enzyme is often affected by many processes and factors, including genetic polymorphisms, induction by xenobiotics, the presence of hormones, cytokines, and disease states. Additionally, factors such as sex, age, and other variables can also play a role in modulating CYP expression.[6]

The CYP2C9 gene in humans exhibits significant polymorphism in both its promoter and coding regions, resulting in allelic variations that differ in prevalence among various ethnic populations.[7] The presence of variants of the CYP2C9 gene is observed in a range of 5% to 30% throughout the population, and these variants have been linked to reduced or absent enzyme activity.[8,9] To date, approximately 85 alleles have been discovered in the regulatory and coding regions of CYP2C9.[10] Among these alleles, the most commonly observed variations are CYP2C9*2 (R144C, rs1799853) and CYP2C9*3 (I359L, rs1057910), which exhibit significantly lowered CYP2C9 enzyme activity compared to the wildtype allele (CYP2C9*1).[11] The presence of CYP2C9*2 leads to a replacement of the amino acid arginine with cysteine due to a C>T transition at position 430 (c.430C>T, p. Arg 144 Cys) in the CYP2C9 gene. The CYP2C9*3 variant is responsible for an alteration of the amino acid residue from isoleucine (Ile) to leucine (Leu) due to a transversion event, specifically an adenine (A) to thymine (T) substitution, in the CYP2C9 gene (c.1075A>C, p. Ile 359 Leu).[12]

The allelic variations CYP2C9*2 and CYP2C9*3 have a higher prevalence in European populations, while they are comparatively less common in African–American and Asian populations. Other polymorphisms of the CYP2C9 gene, including CYP2C9*5, *6, *8, and *11, are also responsible for decreased enzyme activity. These variants are more frequently observed in individuals of African–American origin.[13,14]

The most prevalent allelic variants of CYP2C9 in the Iraqi population were identified as CYP2C9*2 allele and CYP2C9*3 allele, with frequencies of 13.7% and 9.4%, respectively.[15] The frequencies of both mutations exhibit increased prevalence within Kurdish people.[16] A separate investigation conducted on a cohort of healthy Iraqi volunteers from various regions of Iraq, namely Arab, Kurd, and Turkmen populations, the presence of two prevalent alleles, CYP2C9*2 and CYP2C9*3, was observed. Additionally, a less frequent occurrence of the CYP2C9*5 allele was identified, whereas the CYP2C9*4 variant was not detected.[17]

Based on the available information, limited studies have been conducted on cytochrome P450 genotyping in Iraq. Thus, the purpose of this analysis was to assess the prevalence of "cytochrome CYP2C9" genetic variants in the Iraqi population in relation to that of other populations.

Materials and Methods

Patients

A total of 100 Iraqi hypertensive patients were recruited from the private clinic of an interventional cardiologist and diagnosed as hypertensive patients at stage I or II according to the ESH (2018) guideline.[18]

DNA sequencing of CYP2C9 gene

The DNA sequencing technique was employed to check for genetic variants of CYP2C9 within the Iraqi study group. In this study, 2 ml of venous blood was collected from each patient using a disposable plastic syringe. The blood samples were transferred to EDTA tubes designated for genetic analysis of CYP2C9 polymorphism.

The DNA extraction process involved the use of the Relia Prep™ Blood gDNA Miniprep system (Promega, USA) as per the manufacturer's procedures.[19] Subsequently, the extracted DNA served as the template for amplification by polymerase chain reaction (PCR). The primers utilized for the purpose of PCR amplification and DNA sequencing were specifically designed to target two distinct regions of the CYP2C9 gene. The first region, denoted as region 1, encompasses "intron 1, exon 2, intron 2, exon 3, and a portion of intron 3." The second region, referred to as region 2, encompasses "intron 6, exon 7, and a portion of intron 7." The specific sequences of these primers can be found in Table 1. PCR settings utilized for the amplification of CYP2C9 gene involved a single cycle of initial denaturation at a temperature of

Table 1: Primer sequences

Primer	Sequence 5`-3`	Annealing temp. (°C)	Product size (bp)
CYP2C9-F1	GCCTGTGTGGCTGAATAAA	63	990
CYP2C9-R1	CTGGTGACATGTTCTGGAATAG		
CYP2C9-F2	TTCAGCCTATGTGTGTCTTTAT		942
CYP2C9-R2	CTAAGAGTAGCCAAACCAATCT		

F1: forward primer for region one, F2: forward primer for region two, R1: reverse primer for region one, R2: reverse primer for region two

95°C for 5 min. This was followed by denaturation (30 cycles) at 95°C for 30 s, annealing at 63°C for 30 s, and extension at 72°C for 1 min. The final extension step was performed at 72°C for 7 min.[20] The PCR products were visualized using a UV transilluminator on a 1.5% agarose gel treated with ethidium bromide to validate their purity and assess their mobility. The PCR results were sent to Macrogen Corporation, Korea for Sanger sequencing to identify SNPs.[21] The sequencing was performed using an ABI3730XL, an automated DNA sequencer.

Linkage disequilibrium (LD)

Linkage disequilibrium (LD) is a measure used to assess the degree to which an allele of a certain genetic variation is inherited or associated with a neighboring allele within a population. LD is crucial for biomedical research in many fields.[22]

The LD between two loci was measured using the SHEsis software. The D′ value was used to determine the level of LD between two SNPs loci; this value was most reliable for minor allele frequency (MAFs) ≤ 5%.[23]

Ethical approval

This study was initiated after receiving approval from scientific committee in the College of Pharmacy/University of Mustansiriyah. Additionally, the agreement of the Babylon Health Directorate was achieved according to the Ministry of Health's Ethical Committee (73 on 14/6/2022). All participants in this study signed a written consent form.

Statistical analysis

The statistical analyzes were conducted using the software SPSS version 26. The chi-square (2) test was used to analyze the difference with Hardy-Weinberg equilibrium (HWE) and to evaluate variations in allele frequencies between the Iraqi population and other populations. The assessment of LD between two loci was conducted using the SHEsis program.[24] The level of $P > 0.05$ was chosen as the cutoff for significance.

Results

Patient's demographic characteristics

A total of 100 Iraqi hypertensive patients were included in the study. The distribution was 48 males (48%) and 52 females (52%). The mean age was 50.58 years, and the average BMI was 32.21 kg/m^2. Mean systolic and diastolic blood pressures were 154 mm Hg and 93.85 mm Hg, respectively.

Genetic variants of CYP2C9 gene

Among the 100 hypertensive patients, nine allelic variants were detected in two specific regions of CYP2C9 gene, including three coding SNPs and other noncoding (intronic) SNPs, as shown in [Table 2].

Table 2: The detected SNPs of CYP2C9 gene and their location

No.	Coding SNPs ID	Location
1	rs555206628 G<A	10:94942223/Exon 3
2	rs1799853 C<T	10:94942290/Exon 3
3	rs1057910 A<C	10:94981296/Exon 7
No.	**Noncoding SNPs**	**Location**
1	rs2860905 G<A	10:94942538/Intron 3
2	rs9332120 T<C	10:94942093/Intron 2
3	rs9332119 G<C	10:94941844/Intron 1
4	rs28371675 C<T	10:94942580/Intron 3
5	rs28371676 T<C	10:94942606/Intron 3
6	rs9332197 T<C	10:94981151/Intron 6

rs: reference sequence

Genotype and allele frequencies

All discovered SNPs' genotype and allele frequencies were in agreement with HWE ($P > 0.05$), except for rs555206628, which deviated from HWE ($P > 0.05$). Table 3 displays the genotypic and allelic frequencies of the CYP2C9 gene's discovered SNPs among 100 individuals with essential hypertension.

Inter-population comparison

A comparative analysis was conducted to examine the distribution diversity of the CYP2C9 variant alleles between the Iraqi population and populations from diverse nations. The two prominent SNPs, namely rs1799853 and rs1057910, were examined within the respective study. It was shown that the allele frequency of the rs1799853 SNP exhibited a statistically significant ($P > 0.05$) increase among individuals of Iraqi origin compared to those of Asian and African–American origin. The allele frequencies of the rs1799853 and rs1057910 SNPs were found to be comparable to those observed in several countries, including European nations, Kuwait, Egypt, Jordan, Lebanon, Oman, Saudi Arabia, and Iran. The allele frequency of the rs1057910 SNP was found to be considerably greater ($P > 0.05$) among individuals of Iraqi descent compared to the African–American community, as shown in [Table 4].

Linkage disequilibrium (LD)

Haplotype analysis identified one haplotype block with a very strong linkage among the studied CYP2C9 SNPs, except for rs555206628 SNPs, which showed weak linkage with CYP2C9 rs28371676 and rs1057910, [Figure 1].

Discussion

Genetic polymorphisms of CYP2C9 affect the metabolism of several therapeutically prescribed medications and endogenous compounds, thus affecting

Table 3: Allele and genotype frequency for the identified SNPs of CYP2C9 gene

Coding SNPs			
No.	**Genotype frequency *N*(%)**	**Allele frequency *N*(%)**	**HWE *P* value**
1	rs555206628 G<A		
	GG 40 (40%)	G 140 (70%)	0.0002*
	GA 60 (60%)	A 60 (30%)	
2	rs1799853 C<T		
	CC 73 (73%)	C 169 (84.5%)	0.67
	CT 23 (23%)	T 31 (15.5%)	
	TT 4 (4%)		
3	rs1057910 A<C		
	AA 86 (86%)	A 183 (91.5%)	0.06
	AC 11 (11%)	C 17 (8.5%)	
	CC 3 (3%)		
Noncoding SNPs			
No.	**Genotype frequency**	**Allele frequency**	**HWE *P* value**
1	rs2860905 G<A		
	GG 52 (52%)	G 139 (69.5%)	0.29
	GA 35 (35%)	A 61 (30.5%)	
	AA 13 (13%)		
2	rs9332120 T<C		
	TT 63 (63%)	T 158 (79%)	0.88
	TC 32 (32%)	C 42 (21%)	
	CC 5 (5%)		
3	rs9332119 G<C		
	GG 70 (70%)	G 167 (83.5%)	0.98
	GC 27 (27%)	C 33 (16.5%)	
	CC 3 (3%)		
4	rs28371675 C<T		
	CC 73 (73%)	C 169 (84.5%)	0.67
	CT 23 (23%)	T 31 (15.5%)	
	TT 4 (4%)		
5	rs28371676 T<C		
	TT 85 (85%)	T 182 (91%)	0.11
	TC 12 (12%)	C 18 (9%)	
	CC 3 (3%)		
6	rs9332197 T<C		
	TT 91 (91%)	T 191 (95.5%)	0.80
	TC 9 (9%)	C 9 (4.5%)	

Data presents as a number (*N*) of patients and percentage (%) * Statistically significant (chi-square test). HWE: Hardy-Weinberg equilibrium

patient responsiveness and adverse drug responses.[32] Many studies have examined CYP2C9 genetic variations globally, but few have examined Iraqi populations. The current findings improve our interpretation of CYP2C9 genetic variants and might be used to promote customized therapy in Iraqi patients.

The primary objective of the current study was to investigate the genotype and allele frequency of the CYP2C9 gene in the Iraqi population. Subsequently, these findings were compared to the previous research conducted on other populations.

This is the first report to our knowledge, on the frequency of CYP2C9 rs555206628 SNP in a sample of Iraqi hypertensive patients. It is of interest because it has a GA genotype frequency 60% and mutant (allele A) frequency (30%) compared to a low frequency of mutant (allele A) worldwide (0.0001).[31]

There is considerable variation in the allele and genotype frequency of CYP2C9 between populations, as shown by several studies on CYP2C9 variation.[14]

In this study, the two major allelic polymorphisms, CYP2C9 rs1799853 and rs1057910 SNPs, in Iraqi patients were compared to those of other populations. It was discovered that the prevalence of alleles in Iraqi was not significantly different from those in European and Middle Eastern countries. In contrast, the previous studies have

Table 4: CYP2C9 allelic frequency in diverse populations compared to those of Iraqis

Population	Total number of patients (*N*)	rs1799853 (allele T) frequency(%)	*P* value	rs1057910 (allele C) frequency(%)	*P* value
Iraq (current study)	100	15.5%		8.5%	
Iraq (other study)[15]	80	13.7%	0.84	9.4%	0.62
Kuwait[25]	108	14.0%	0.84	5.0%	0.38
Saudi Arabia[26]	131	13.3%	0.68	2.3%	0.05
Jourdin[27]	263	13.5%	0.68	6.8%	0.78
Lebanon[28]	161	12.2%	0.53	9.6%	0.62
Oman[29]	189	7.4%	0.07	2.9%	0.12
Iran[30]	800	10.5%	0.28	10.2%	0.62
Asian[31]	3216	0.1%*	0.0003	4.0%	0.23
African–American[31]	8616	2.0%*	0.0011	1.0%*	0.01
European[31]	107616	12.0%	0.53	6.0%	0.57

Chi-square test was used for statistical analysis. *$P > 0.05$ significant compared to current results

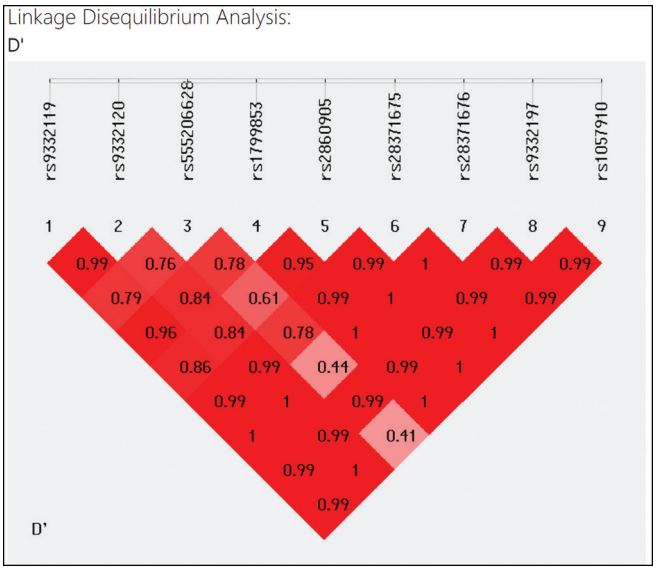

Figure 1: LD among the studied CYP2C9 SNPs

indicated a low prevalence of these SNPs within Asian and African–American populations, which was significantly different from the current results.

The influence of environmental factors on genetic polymorphisms is well-documented. The variations in allele frequency observed among populations can be attributed to various factors, including the ancestral origins, geographical isolation of different ethnic groups, dietary habits, lifestyles, and other relevant factors. These factors collectively have the potential to impact CYP2C9 polymorphisms.[33] This phenomenon might account for the observed variations in drug response among different ethnic groups.

The allele frequency also varies widely between studies. This may be due to some polymorphisms being linked to disease states; therefore, their frequency in patient groups may differ from healthy populations. Variations in observed allelic frequencies may also be explained, at least in part, by the large differences in sample sizes across these investigations.[34]

Conclusion

The characterization of allele distribution patterns among populations is a valuable tool in ensuring the safe administration of medications to patients worldwide. The frequency patterns of CYP2C9 variations among the Iraqi population display similarities to those reported in other populations of European and Middle Eastern origins. However, notable differences exist when comparing these distributions to those found in African–American and Asian populations. Moreover, the analysis of haplotypes revealed the presence of a single haplotype block exhibiting strong linkage among the investigated CYP2C9 SNPs, except for rs555206628 SNPs. There was a weak linkage seen with CYP2C9 rs28371676 and rs1057910 SNPs.

Acknowledgment

The authors would like to thank Mustansiriyah University(www.uomustansiriyah.edu.iq), Baghdad, Iraq, for its support in the present work.

Conflict of interest

There are no conflict of interest.

Data availability statement

All datasets generated or analyzed during this study are included in the manuscript.

Financial support and sponsorship

Nil.

References

1. Ingelman-Sundberg M. The human genome project and novel aspects of cytochrome P450 research. Toxicol Appl Pharmacol 2005;207:52-6.
2. Manikandan P, Nagini S. Cytochrome P450 structure, function, and clinical significance: A review. Curr Drug Targets 2018;19:38-54.

3. Cho MA, Yoon JG, Kim V, Kim H, Lee R, Lee MG, *et al*. Functional characterization of pharmacogenetic variants of human cytochrome P450 2C9 in Korean populations. Biomol Ther 2019;27:577-83.
4. Van Booven D, Marsh S, McLeod H, Carrillo MW, Sangkuhl K, Klein TE, *et al*. Cytochrome P450 2C9-CYP2C9. Pharmacogenet Genomics 2010;20:277-81.
5. Soars MG, Gelboin HV, Krausz KW, Riley RJ. A comparison of relative abundance, activity factor, and inhibitory monoclonal antibody approaches in the characterization of human CYP enzymology. Br J Clin Pharmacol 2003;55:175-81.
6. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther 2013;138:103-41.
7. Xie HG, Prasad HC, Kim RB, Stein CM. CYP2C9 allelic variants: Ethnic distribution and functional significance. Adv Drug Deliv Rev 2002;54:1257-70.
8. Sistonen J, Fuselli S, Palo JU, Chauhan N, Padh H, Sajantila A. Pharmacogenetic variation at CYP2C9, CYP2C19, and CYP2D6 at global and microgeographic scales. Pharmacogenet Genomics 2009;19:170-9.
9. Shaw K, Amstutz U, Kim RB, Lesko LJ, Turgeon J, Michaud V, *et al*; CPNDS Clinical Recommendation Group. Clinical practice recommendations on genetic testing of CYP2C9 and VKORC1 variants in warfarin therapy. Ther Drug Monit 2015;37:428-36.
10. PharmVar Standards. Available from: https://www.pharmvar.org/genes.
11. Wei L, Locuson CW, Tracy TS. Polymorphic variants of CYP2C9: Mechanisms involved in reduced catalytic activity. Mol Pharmacol 2007;72:1280-88.
12. Parikh SJ, Evans CM, Obi JO, Zhang Q, Maekawa K, Glass KC, *et al*. Structure of cytochrome P450 2C9*2 in complex with losartan: Insights into the effect of genetic polymorphism. Mol Pharmacol 2020;98:529-39.
13. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide distribution of cytochrome P450 alleles: A meta-analysis of population-scale sequencing projects. Clin Pharmacol Ther 2017;102:688-700.
14. Zhou Y, Nevosadová L, Eliasson E, Lauschke VM. Global distribution of functionally important CYP2C9 alleles and their inferred metabolic consequences. Hum Genomics 2023;17:15.
15. Ali Saleh M, Kadhim HM, Sahib AS, Abdulamir AS, Altawil R. The effect of CYP2C9 and VKORC1 genetic polymorphism on warfarin dose requirements in a sample of Iraqi patients. J Kerman Univ Med Sci 2021;28:139-49.
16. Eissa AA. The effect of vitamin K epoxide reductase complex and cytochrome p450 gene polymorphisms on warfarin dose among Kurdish patients in Duhok-Iraq. Duhok Med J 2016;10:77-86.
17. AL-Tayie SR, Al-Awadi SJ, Al-Zaidi M. Genotype frequency of cytochrome P450 2C9 (CYP2C9) mutations in Iraqi ethnic groups. Indian J Forensic Med Toxicol 2021;15:4296-301.
18. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, *et al*. ESC/ESH guidelines for the management of arterial hypertension. Kardiol Pol 20182019;77:71-159.
19. Promega Corporation Website. Updated. Available from: http://www.promega.com.
20. Abdullah AM, Merza NS, Merza AS. Detection of Toxoplasma gondii oocysts in contaminated soils using polymerase chain reaction analysis in Duhok City Iraq. Med J Babylon 2022;19:271-74.
21. Al-Kaim HW, Al-Dahmoshi HO. Prevalence of AcrAB-TolC efflux pump among Proteus mirabilis isolated from cystitis patients in Hilla City, Iraq. Med J Babylon 2023;20:503-10.
22. Myers TA, Chanock SJ, Machiela MJ. LDlinkR: An R package for rapidly calculating linkage disequilibrium statistics in diverse populations. Front Genet 2020;11:157.
23. Goddard KA, Hopkins PJ, Hall JM, Witte JS. Linkage disequilibrium and allele frequency distributions for 114 single nucleotide polymorphisms in five populations. Am J Hum Genet 2000;66:216-34.
24. Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005;15:97-8.
25. Alrashid MH, Al-Serri A, Alshemmari SH, Koshi P, Al-Bustan SA. Association of genetic polymorphisms in the VKORC1 and CYP2C9 genes with warfarin dosage in a group of Kuwaiti individuals. Mol Diagn Ther 2016;20:183-90.
26. Alzahrani AM, Ragia G, Hanieh H, Manolopoulos VG. Genotyping of CYP2C9 and VKORC1 in the Arabic population of Al-Ahsa, Saudi Arabia. Biomed Res Int 2013;2013:315980.
27. Yousef AM, Bulatova NR, Newman W, Hakooz N, Ismail S, Qusa H, *et al*. Allele and genotype frequencies of the polymorphic cytochrome P450 genes (CYP1A1, CYP3A4, CYP3A5, CYP2C9, and CYP2C19) in the Jordanian population. Mol Biol Rep 2012;39:9423-33.
28. Djaffar-Jureidini I, Chamseddine N, Keleshian S, Naoufal R, Zahed L, Hakime N. Pharmacogenetics of coumarin dosing: Prevalence of CYP2C9 and VKORC1 polymorphisms in the Lebanese population. Genet Test Mol Biomarkers 2011;15:827-30.
29. Tanira MO, Al-Mukhaini MK, Al-Hinai AT, Al Balushi KA, Ahmed IS. Frequency of CYP2C9 genotypes among Omani patients receiving warfarin and its correlation with warfarin dose. Community Genet 2007;10:32-7.
30. Neyshaburinezhad N, Ghasim H, Rouini M, Daali Y, Ardakani YH. 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.
31. Available from: https://www.ncbi.nlm.nih.gov/snp/rs1799853,rs1057910,rs55520662.
32. Geng T, Zhang XY, Wang L, Wang H, Shi X, Kang L, *et al*. Genetic polymorphism analysis of the drug-metabolizing enzyme CYP1A2 in a Uyghur Chinese population: A pilot study. Xenobiotica 2016;46:542-7.
33. Ding Y, Yang D, Zhou L, He P, Yao J, Xie P, *et al*. Cytochrome P450 2C9 (CYP2C9) polymorphisms in Chinese Li population. Int J Clin Exp Med 2015;8:21024-33.
34. Ahmed S, Altaf N, Ejaz M, Altaf A, Amin A, Janjua K, *et al*. Variations in the frequencies of polymorphisms in the CYP2C9 gene in six major ethnicities of Pakistan. Sci Rep 2020;10:19370.