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Prevalence of Cytochrome P-450 2C9 (CYP2C9) Alleles *2, and*3 among the Libyan Population of Tripoli Region

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Abstract
*The CYP2C9 gene encodes an enzyme that metabolizes a variety of drugs. Genetic variations in the CYP2C9 enzyme, particularly the CYP2C9*2 and CYP2C9*3 polymorphisms, can significantly impact enzyme activity, resulting in variations in drug metabolism and response among individuals who carry them. This study aimed to identify the prevalence of CYP2C9*2 and CYP2C9*3 alleles among the Libyan population in the Tripoli region and to compare the results with published data from other populations and ethnicities. This study included 300 randomly selected unrelated Libyan male blood donors, aged between 18 - 50 years. A high-resolution melting analysis (HRM) protocol was developed and employed as a screening tool for the detection of genetic variations, and direct DNA sequencing was used to confirm the presence of CYP2C9*2 and CYP2C9*3 polymorphisms. On one hand, 228 (73.33%) and 72 (24%) subjects were detected as wild-type and heterozygous CYP2C9*2, respectively, and on the other hand, 269 (98.66%), 29 (9.66%) and 2 (0.66%) subjects were detected as wild type, heterozygous, and homozygous mutant CYP2C9*3, respectively. In conclusion, CY2C9*2 and *3 is prevalent in Libyans residing in Tripoli region.*
Keywords. *CYP2C9 Polymorphism, CYP2C9*2, CYP2C9*3, High Resolution Melting (HRM), DNA Sequencing, Libya.*

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Introduction

Cytochrome P450 2C9 (CYP2C9) is a member of the human cytochrome P450 superfamily of enzymes, significantly involved in the metabolism of both xenobiotics (including drugs) and endogenous compounds. (1,2). Its function is to oxidize substrate molecules, leading to the production of many polar metabolites that are easily excreted from the body. CYP2C9 is responsible for the metabolic clearance of up to 25% of all drugs undergoing phase I metabolism (2–5). CYP2C9 is expressed primarily in the liver and is involved in the metabolism of many clinically relevant drugs, including phenytoin, losartan, tolbutamide, torsemide, warfarin, and NSAIDs (3,6–8). The human CYP2C9 gene is located on chromosome 10q24.2. It encodes a protein of 490 amino acid residues. Its overall length is about 55 kb, consisting of nine exons and eight introns (9,10). Several variants of the CYP2C9 gene have been described worldwide. CYP2C9*2 and CYP2C9*3 polymorphisms are the most common and well-studied (11).

CYP2C9*2 allele is a single base change that results in a C>T transition at position 430 in the coding sequence (C430T; rs1799853) of the CYP2C9 gene within exon 3, leading to an Arg-to-Cys substitution at residue 144 (Arg144Cys) (1,11,12), whereas the CYP2C9*3 allele is a single base change that results in an A>T transversion at position 1075 in the coding sequence (C1075T; rs1057910) of the CYP2C9 gene within exon 7, leading to an Ile-to-Leu substitution at residue 359 (Ile359Leu) (11,12).

These genetic polymorphisms affect the efficiency of the enzyme's metabolism. CYP2C9*2 allele leads to a decrease in enzyme activity by about 50–70% when compared to the wild-type allele, whereas CYP2C9*3 allele leads to a decrease of about 75-99% of the enzyme's activity, almost eliminating it when compared to the wild-type allele (6,13,14). Therefore, individuals carrying these alleles may affect the pharmacokinetics and pharmacodynamics of drugs metabolized by CYP2C9, potentially increasing the risk of side effects or reducing treatment effectiveness (1,3,4).

The prevalence of CYP2C9 genetic polymorphisms varies among different populations and ethnic groups. (6). Thus, understanding the prevalence of CYP2C9*2 and CYP2C9*3 alleles is important to predict drug efficacy and safety in clinical practice. In Libya, we could not find previous studies on the frequency of these polymorphisms among Libyans in the Tripoli region. Therefore, this study aimed to identify the prevalence of CYP2C9 gene CYP2C9*2 and CYP2C9*3 polymorphisms in Libyans living in the Tripoli region and to compare them with the results of other populations worldwide.

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Materials and methods

Study population and samples

This study involved 300 unrelated male blood donors from Tripoli, aged 18-50 years (mean ± standard deviation = 31.38 ± 6.78 years), who were randomly selected at Al-Jalaa Maternity Hospital. Four millilitres of venous blood were collected in EDTA tubes for DNA isolation and molecular genetic studies. Donor information was obtained through personal interviews. Written informed consent was obtained, and the study was approved by the Scientific Ethics Committee of the Libyan Academy.

Genomic DNA extraction

Genomic DNA was extracted from whole blood samples of 200 µl EDTA-anticoagulated whole blood using the QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, USA). The manufacturer's instructions were followed. Extracted genomic DNA samples were stored at -20°C until use.

Primer's design

The occurrence of CYP2C9*2 and CYP2C9*3 variations in the study subjects was explored using high-resolution melting (HRM) analysis protocols, and direct DNA sequencing was used to confirm the results. The GenBank: NG_008385.1 sequence [https://www.ncbi.nlm.nih.gov/nuccore] was used to design the primers for CYP2C9*2 and CYP2C9*3 variations. Some primers were designed in this study, and others were reported in previous studies (Tables 1 and 2). The primers were designed using Oligo Analyser 1.5 software (Gene Link™) (Kuopio, Finland) and were ordered from Metabion (Metabion, Martinsried, Germany).
The accuracy of the designed primer sequences was verified by comparison with the GenBank database using the Basic Local Alignment Search Tool (http://www.ncbi.nlm.nih.gov/BLAST/).

Table 1: Sequences of the primers used for CYP2C9*2 and CYP2C9*3 polymorphism detection using HRM

Primer name	Primers 5'-3'	Tm	Amplicon size (bp)	Reference
CYP2C9*2F	CCTCATGACGCTGCGGAA	58.4˚C	90	(15)
CYP2C9*2R	CTCAACTCCTCCACAAGGC	59.5°C		Current study
CYP2C9*3F	CCACATGCCCTACACAGATG	60.5°C	87	(16)
CYP2C9*3R	TGCCCCATGCAGTGACCTG	61.6°C		(15)

Table 2: Sequences of the primers used for CYP2C9*2 and CYP2C9*3 polymorphism detection using Sequencing

Primer	Primers 5'-3'	Tm	Amplicon size (bp)	Reference
CYP2C9*2F	CCTGGGATCTCCCTCCTAGT	62.5	194	(17)
CYP2C9*2R	CCACCCTTGGTTTTTCTCAA	56.4		(18)
CYP2C9*3F	GAACGTGTGATTGGCAGAAA	56.4	208	(19)
CYP2C9*3R	CTGCAACTCCATGTTTTCGA	56.4		Current study

*Detection of CYP2C9*2 and CYP2C9*3 variations using HRM*

HRM analysis was carried out using a ready-to-use Type-it HRM PCR Kit (QIAGEN, Germany). The final volume of the reaction was 25 µL containing 8.5 µl de-ionized water, 0.5 µl of 10 pmol/µl primers to give a final concentration of 0.2 pmol of each primer, 12.5 µl 2X Type-it HRM PCR Master mix, and 3 µl (5–50 ng) genomic DNA. The reaction was carried out using the Rotor-Gene Q real-time PCR analyzer (QIAGEN GmbH). The thermo cycling profile consisted of one cycle of an initial Hot Taq polymerase activation at 95°C for 2 min, followed by 45 cycles of denaturation at 94°C for 15 s, annealing at 56°C for 20 s, and extension at 72°C for 20 s. Melting curves were produced by continuous collection of the fluorescence signal at the extension step using a green channel from 75°C to 85°C during the HRM phase. Each step was raised by 0.05°C per second. The decrease in fluorescence with rising temperature creates melting curves; accordingly, changes in nucleotides result in different curve patterns.

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Detection of CYP2C9*2 and CYP2C9*3 variations using direct DNA sequencing

Sanger sequencing was used to confirm HRM results. The final volume of the reaction mix (25 µl) contained 5 µl of 5X Red Load Hot Taq Mix (Martinsried-Germany), 0.5 µl of 10 pmol/µl of each primer, 16 µl water, and 3 µl (5–50 ng) genomic DNA. Thermo cycling program for both (CYP2C9*2 and CYP2C9*3) polymorphisms was run on TC-412 thermocycler (Techne, Duxford, Cambridge) including one cycle Taq polymerase activation at 94°C for 2 min, followed by 45 cycles of denaturation at 94°C for 30 s, and annealing at 56°C for 30 s, and extension at 72°C for 30 s, with a final extension at 72°C for 2 min.

The amplified PCR product was cleaned using the QIAquick PCR purification kit (Qiagen, Chatsworth, CA) following the manufacturer's instructions. Then, sequencing was performed using the Big Dye Terminator v3.1 Cycle Sequencing Kit (BDT v3.1) (PE Applied Biosystems, Foster City, CA) on a TC-412 thermocycler (Techne, Duxford, Cambridge).

Forward and reverse DNA sequencing reactions were assembled separately using the following mixtures: 4 µl BDT v3.1 reaction mix, 4 µl 5X sequencing buffer, 1 µl 3.2pmol/µl primer, 1 µl purified PCR product, and 10 µl de-ionized water. The cycle sequencing was performed on 20 µl sequencing reaction in a TC-412 thermocycler (Techne, Duxford, Cambridge) under an initial denaturation at 94°C for 1 min, followed by 25 cycles of denaturation at 96°C for 10 s, annealing at 55°C for 5 s, and extension at 60°C for 4 min.

The cycle-sequencing product was purified by ethanol/EDTA precipitation. The precipitate was suspended in 20 µl of Hi Di formamide, denatured at 95°C for 2 min, pipetted into 96-well plates, and analyzed using an ABI PRISM® 3130 genetic analyzer (Applied Biosystems, Foster City, CA, USA) at the Department of Biochemistry of the University of Tripoli. The resultant sequences were edited, and the database analysis was done using BLAST (http://www.ncbi.nlm.nih.gov/BLAST).

Results

Genotyping of CYP2C9*2 polymorphism using HRM analysis

Figure .1 illustrates the normalised melting curve of HRM for CYP2C9*2 (C430T) polymorphism. This figure demonstrates that the HRM protocol effectively distinguished differences in the melting curve shapes linked to various genotypes, enabling differentiation between genotypes, such as wild-type (C430C) and heterozygous (C430T), by generating two distinct melting profiles. However, no homozygous mutant cases (T430T) were identified.

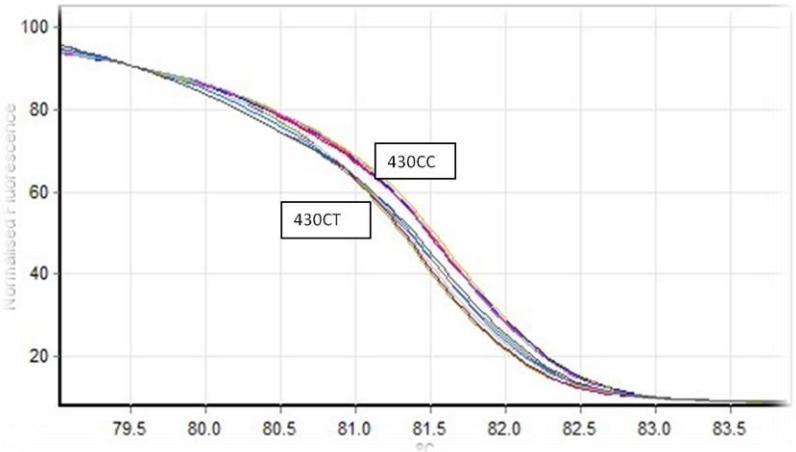

Figure 1: High-resolution melting analysis. Normalized melting curves for CYP2C9*2 polymorphism. The melting curves show two different patterns: wild-type (C430C) and heterozygous (C430T). Differences in genotypes of CYP2C9*2 polymorphisms. It shows that the heterozygote melts first, followed by the wild type.

Genotyping of CYP2C9*3 using HRM analysis

Figure 2. Shows the normalized melting curve of HRM of CYP2C9*3 (A1075C) polymorphism. Again, this figure demonstrates that the HRM protocol can reveal differences in the melting curve shapes associated with various genotypes, thereby differentiating between them, i.e., wild-type (A1075A), heterozygous (A1075C), and homozygous (C1075C) by producing three distinct melting profiles.

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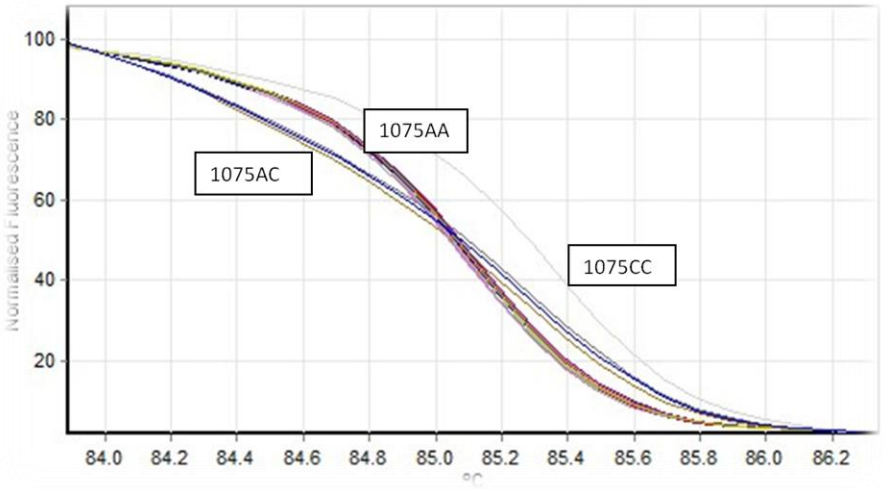

Figure 2: High-resolution melting analysis. Normalized melt curves for CYP2C9*3 polymorphism. The melting curves show three different patterns: wild-type (A1075A), heterozygous (A1075C) and mutant homozygous (C1075C). Differences in genotypes of the CYP2C9*3 polymorphism. It shows that the melting curves of the heterozygote melt first, followed by the wild type and homozygote, with the shape of the wild type and the homozygote being the same.

*Genotyping of CYP2C9*2 and CYP2C9*3 polymorphisms using direct DNA sequencing*

Samples displaying variation with HRM were subjected to direct DNA sequencing using Big Dye Terminator v3.1 Cycle, and the variations were confirmed.

*Frequencies of CYP2C9*2 and CYP2C9*3 polymorphisms in the study population*

Genotype frequencies were estimated in 300 people from Libyan men from the Tripoli region. A total of 600 chromosomes were analyzed for the presence of CYP2C9*2 and CYP2C9*3 polymorphisms in the CYP2C9 gene.

Regarding CYP2C9*2 polymorphism, 228 subjects (76%) were detected as wild-type (C430C), 72 subjects (24%) as heterozygous (C430T), and no subjects were detected as homozygous (T430T). Whereas CYP2C9*3 polymorphism, 269 subjects (89.66%) were detected as wild-type (A1075A), 29 (9.66%) as heterozygous mutant (A1075C), and 2 (0.66%) as homozygous mutants (C1075C).

The allele frequency of CYP2C9*2 (C430T) for (C) allele was 528 (88%) and for (T) was 72 (12 %). The allele frequency of CYP2C9*3 (A1075C) for (A) allele was 567 (94.5%) and for (C) was 33 (5.5%) (Table 3).

Table 3: Allele frequency of CYP2C9*2 and CYP2C9*3 polymorphisms in the CYP2C9 gene in the study population

Genotype					
CYP2C9*2 polymorphism, n (%)			**CYP2C9*3 polymorphism, n (%)**		
C/C	C/T	T/T	A/A	A/C	C/C
228 (73.33%)	72 (24%)	0 (0%)	269 (89.66%)	29 (9.66%)	2 (0.66%)

A: Adenine, C: Cytosine, G: Guanine T: Thymine

Discussion

Across different ethnicities and populations worldwide, the frequencies of CYP2C9*2 and CYP2C9*3 alleles vary widely. A global study of 70 countries revealed that the highest frequency of the CYP2C9*2 allele was seen in the Middle East and Europe. The prevalence was highest in Iran (18.1%), followed by Croatia (16.5 %), Lebanon (15.4%), and France (15%). In other major population groups in the world outside these and surrounding areas, the frequency of the CYP2C9*2 allele is lower (6). CYP2C9*3 was most prevalent in the Emirates (21.3%), which is much higher than its prevalence in other Middle Eastern populations, where frequencies hover around 6% on average, and southern Asian populations (11.9%) in Pakistan, 11.6 in Bangladesh, followed by the southern European population (10.1%) in Spain. CYP2C9*3 is less common in some European, Middle Eastern, and other global populations (6). The prevalence of CYP2C9*2 and CYP2C9*3 alleles is generally low in Africa. CYP2C9*2 is absent in sub-Saharan Africa, and it has been detected at relatively high frequencies in some North African populations, up to 12% in Morocco (6,20,21). CYP2C9*3 is also absent or rare in sub-Saharan Africa (6). CYP2C9*2 allele was found to be 0.08% frequent in the Thai population, while CYP2C9*3 allele was found to be 5.27% frequent (22). In Chinese population research, no one was discovered to carry the CYP2C9*2 allele. (6).

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In our study, we found that the frequency of CYP2C9*2 allele is 12.0%, which is in a range comparable with Romania (11.3%) (11), Sweden (11.7%) (4), Egypt (12%) (14), Denmark (12.1%) (23), Serbia (12.3%), Saudi Arabia (12.4%), Italy (12.4%), Bulgaria (12.5%), Australia (12.8%) (6), Greece (12.9%), Spain (13.3%) (6), and Jordan (13.5%) (24). However, it is slightly higher compared with Brazil (10.7%), Turkey (10.6%), Morocco (9.5%), USA (9.0%), Chile (9.0%) (6), and Oman (7.2%) (25), and is lower compared with Iran (18.1%) (6), Croatia (16.5%) (26), Lebanon (15.4%) and France (15%) (6,27). In contrast, the frequency of CYP2C9*2 allele is very rare or absent in most Southeast and East Asia studied so far, with the highest frequency observed in the Malay (1.0%), and low in South Asia populations, with frequencies around (5%), and it is generally absent or rare in sub-Saharan African populations, especially in countries such as Benin (0.0%), Ghana (0.0%), Mozambique (0.0%), Nigeria (0.0%), and Gambia (0.4%) (6).
In addition, our results show that the frequency of the CYP2C9*3 allele in the Libyan population is 5.5%. This is similar to that in Denmark (5.3%) (23)], Thai (5.3%) (6), Egypt (6.0%) (20)Brazil (6.0%), Saudi Arabia (6.3%), Iran (6.5%), Sweden (6.5%) (6)Jordan (6.8%) (24), and Australia (6.9%) (6). However, it is slightly higher compared with the USA (4.4%), Chile (4.0%) (6). In contrast, the frequency of the CYP2C9*3 allele is lower compared with Bulgaria (7.5%), Lebanon 7.8%, and France (8.0%) (27), Greece (8.1%), Romania (9.3%) (11) Italy (9.4%) (6), Croatia (9.5%) (28), Turkey (9.8%), and Spain (10.1%) (6). The lowest frequency of the CYP2C9*3 allele was reported in East and Southeast Asian populations such as Japan (2.4%), Indonesia (2.4%), Venezuela (2.3%), and Malay (2.9%). Finally, in Africa, the allele is generally absent in sub-Saharan African populations, especially in countries such as Benin (0.0%), Gambia (0.0%), Ghana (0.0%), Nigeria (0.0%), and Mozambique (1.0%) (6).

Conclusion

For the first time, we investigated the prevalence of CYP2C9 polymorphisms CYP2C9*2 and CYP2C9*3 in the Libyan population residing in the Tripoli region, and we found that the frequencies of CYP2C9*2 and CYP2C9*3 alleles fall in a similar range to other North African populations, and it is relatively high compared to other African nations.

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Conflict of interest

The authors have no conflicts of interest to disclose

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