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Investigation of the Effects of Genetic Variations in CYP2C9 and VKORC1 on Warfarin Dose Requirements Among Iranian Patients from Khorramabad Province

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A B S T R A C T

Objective: Warfarin is a widely prescribed narrow therapeutic index anticoagulant. Determining proper warfarin dosage remains problematic due to its narrow therapeutic index and genetic variations from individual to individual. The administration of incorrect doses of warfarin can catastrophic adverse events. Observational studies have demonstrated single nucleotide polymorphisms in *CYP2C9* and *VKORC1* significantly affect warfarin dose requirements. The present study aimed to examine the influences of various genotypes on warfarin dose requirements among Iranian patients.

Methods: Blood samples were taken from 117 patients and stored in tubes containing EDTA. DNA extraction was performed on the blood samples and the different alleles and genotypes of the studied SNPs were identified and recorded by the PCR-RFLP technique.

Results: Of the 117 patients, no significant differences in the mean daily warfarin dose requirement were found among the genotypes of polymorphism *CYP2C9* * 3 (1075A> C). However, there were significant differences among the genotypes of *CYP2C9* * 2 (430C> T). The mean daily warfarin dose requirements were significantly different among wild genotypes, heterozygotes and mutants in the two polymorphisms of *VKORC1* (1173C> T) and *VKORC1*(1639G> A).

Conclusion: The results of our study demonstrated that *CYP2C9* and *VKORC1* polymorphisms have significant effect on warfarin maintenance dose requirements in iranian patients which would help improve the prediction of warfarin dose requirements and minimize the chance of over-anticoagulation or under-anticoagulation.

Keywords: CYP2C9, Genetic variations, VKORC1, Warfarin

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Introduction

Warfarin is an orally administered anticoagulant, which inhibits the production of vitamin K–dependent clotting factors such as II, VII, IX, and X, as well as proteins C and S. Blood tests should be performed to monitor warfarin activity based on the international normalized ratio (INR) to make sure the appropriate dose is being administered, because warfarin interacts with many commonly used medications and foods. An INR lower than the target range is indicative of an inadequate warfarin dose, increasing the risk of thromboembolic events, while bleeding risk increases sharply when INR is greater than the therapeutic range [1,2].

Warfarin inhibits the C1 subunit of vitamin K epoxide reductase enzyme, which is encoded by the *VKORC1* gene. *VKORC1* enzyme plays a key role in converting inactive vitamin K 2,3-epoxide to active vitamin K in the membrane of the endoplasmic reticulum. Vitamin K is required for the carboxylation of glutamic acid residues in blood-clotting proteins, including factors VII, IX, and X. Some alleles of this gene are associated with combined deficiency of vitamin K-dependent clotting factors-2 (VKFCD2) and increased resistance to warfarin. Moreover, its pseudogenes have been identified on chromosomes 1 and X [3-5].

The *VKORC1* G3673A polymorphism (or -1639 G > A; rs9923231) account for the potential low-dose phenotype, downregulates the gene and alters the factor binding site for the *VKORC1* transcription. Luciferase assays have shown that the G allele is more active than the A allele by 44%. Since a medium warfarin dose is adequate for heterozygotes, and the lowest doses of warfarin can produce the desired effects in homozygous A-allele carriers, patients with the A allele are most susceptible to the side effects of warfarin. Therefore, this SNP is the major factor in determining warfarin initiation dose [6,7].

The results of previous studies suggest the 1639 A allele is mostly observed in Asian populations with a frequency of approximately 92%, followed by Caucasian populations with a frequency of 40%, the lowest frequency being observed among African-Americans (13%), indicating minor allele reversal in Asian populations. The minor allelic frequencies of both rs9923231 and rs9934438 vary among racial groups. Nevertheless, the International Warfarin Pharmacogenetics Consortium (IWPC) studied the presence of the rs9923231 or rs9934438 variants, irrespective of race, concluding that these SNPs are linked with a decrease in warfarin dosage requirements in all three of the racial groups [8,9].

Located in the first intronic region of the *VKORC1* gene, the C6484T (1173C > T) SNP is associated with low warfarin dosage requirements, according to some studies. This variant is almost completely in linkage disequilibrium with the promoter region variant G3673A (rs9923231). Since both SNPs have very similar frequencies, the C6484T variant is thought to be functionally inert. However, C6484T is still generally utilized as an SNP marker for G3673A and for the haplotypes including this variant [10,11].

Cytochrome P450 2C9 polymorphisms (CYP2C9∗2 and CYP2C9∗3) have been found to reduce the metabolism of S-warfarin, decreasing warfarin degradation and clearance, and therefore, a lower dose would be needed to maintain the international normalized ratio (INR) at therapeutic levels. Thirty-two other SNPs have been found in the *CYP2C9* gene in addition to the wild-type protein CYP2C9*1, which produce the variant allozymes [12-15].

CYP2C9*2 and CYP2C9*3 are more frequently found in Caucasians than Asians. Therefore, CYP2C9 strikingly varies in its expression and catalytic activity across different individuals and ethnicities, resulting in either toxicity or therapeutic failure. In patients with at least one wild-type CYP2C9*1, (S)-warfarin clearance proceeds normally, while, in CYP2C9 polymorphisms with CYP2C9*2 and/or CYP2C9*3 alleles, the metabolism of (S)-warfarin is impaired. If treated with warfarin, these patients are twice to four times more likely to suffer adverse effects than patients with the wild-type allele, and therefore dosage adjustments are necessary for them [16,17].

Since sufficient data about a heterogeneous Iranian population could not be found, the objective of the present study was to identify the effects of genetic variations in CYP2C9*2, CYP2C9*3, *VKORC1*(1639G>A) and *VKORC1* (1173C>T) on warfarin dose requirements in patients referring to the Shahid Madani Hospital, Khorramabad, Iran, including inhabitants with diverse ethnic, cultural and genetic backgrounds, potentially representing the whole Iranian population.

Materials and Methods

Participants

This study included 117 patients referring to the cardiology clinic of the Shahid Madani Hospital in Khorramabad to whom

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warfarin was administered. The exclusion criterion was suffering from liver, kidney, and gastrointestinal diseases. Demographic and clinical variables were recorded, including age, sex, weight, mean daily warfarin dosage and mean INRs.

Ethics

This study has been approved by the Ethics Committee of the Lorestan University of Medical Sciences. Informed consent was obtained from all participants.

DNA extraction and genotyping

Blood samples were taken and stored in tubes containing EDTA. To extract DNA from blood samples, the Geno Plus Genomic DNA Extraction Midiprep System kit (Viogene, Taiwan) was used according to the manufacturer's instructions.

The PCR-restriction fragment length polymorphism (PCR-RFLP) technique was applied to determine the different alleles and genotypes of the studied SNPs. Primer sequences, conditions under which PCR reactions were carried out, and the restriction enzymes are presented in Table 1. Each PCR reaction was performed in 25 µL volumes containing approximately 100 ng of the template DNA, 10 picomoles of each primer, 12.5 µL of PCR 2X Master Mix and 9 µL of double-distilled water. Duplicated products at 37° C were treated with the enzymes listed in Table 1 (18,19). Fragments were separated on agarose gel and identified through a gel documentation system (Figure 1 and 2).

Table 1. PCR conditions for genetic analysis of CYP2C9 and VKORC1 variations (18). WT: wild type, Htz: heterozygous, Mut: homozygous mutant, bp: base pairs.

Variation	Primers	PCR product size	Restriction enzyme (RE)	RE digestion product size
CYP2C9*2 (430C>T) (rs1799853)	F-5'TCCTAGTTTCGTTTCTCTTCCTGT3' R5'ATAGTAGTCCAGTAAGGTCAGTGA3'	221 bp	Ava II	WT-122 + 99 bp Htz-221 + 122 +99bp Mut-221 bp
CYP2C9*3 (1075A>C) (rs 1057910))	F-5'CACGAGGTCCAGAGATGCATTG3' R-5'CTTCGAAAACATGGAGTTGCAGT3'	135 bp	Nsi I	WT-116 + 19 bp Htz-135 + 116 + 19bp Mut-135 bp
VKORC1-1639G>A (rs 9923231)	F5'GAGCCAGCAGGAGAGGGAAATAT3' R-5'GTTTGGACTACAGGTGCCTGCC 3'	291 bp	Msp I	WT-167 + 124 bp Htz-291 + 167 + 124bp Mut-291 bp
VKORC1 1173C>T (rs 9934438)	F5'CTAAGATGAAAAGCAGGGCCTAC3' R-5'CTGCCCGAGAAAGGTGATTTCC3'	201 bp	Sty I	WT-127 + 74 bp Htz-201 + 127 + 74bp Mut-201 bp

Statistical analysis

SPSS version 18 was used for statistical analysis. To estimate the differences of allele distributions frequencies between groups the X2 test was emloyed to compare with the predictions of the Hardy-Weinberg equilibrium model. Different genotypes were compared in terms of the average daily warfarin dose requirements by the Mann-Whitney and Kruskal-Wallis tests.

Results

The patients had undergone the mitral valve replacement or aortic dissection in the Shahid Madani Hospital of

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Khorramabad. Of the 117 patients, 53 (45.3%) were male and 64 (54.7%) were female. The age range was 17-89 years old with an average age of 58.27 years and an average weight of 70.17 kg. The patients received other medications including metoprolol or propranolol and triamterene. The therapeutic dose of warfarin depends on the Patient, ranging from 25 mg to 8 mg per day. Patients warfarin use ranged from three months to twenty years. The INR ranged from 1 to 6.13 and the mean INR of the population was 2.547 with a standard deviation of 0.760.

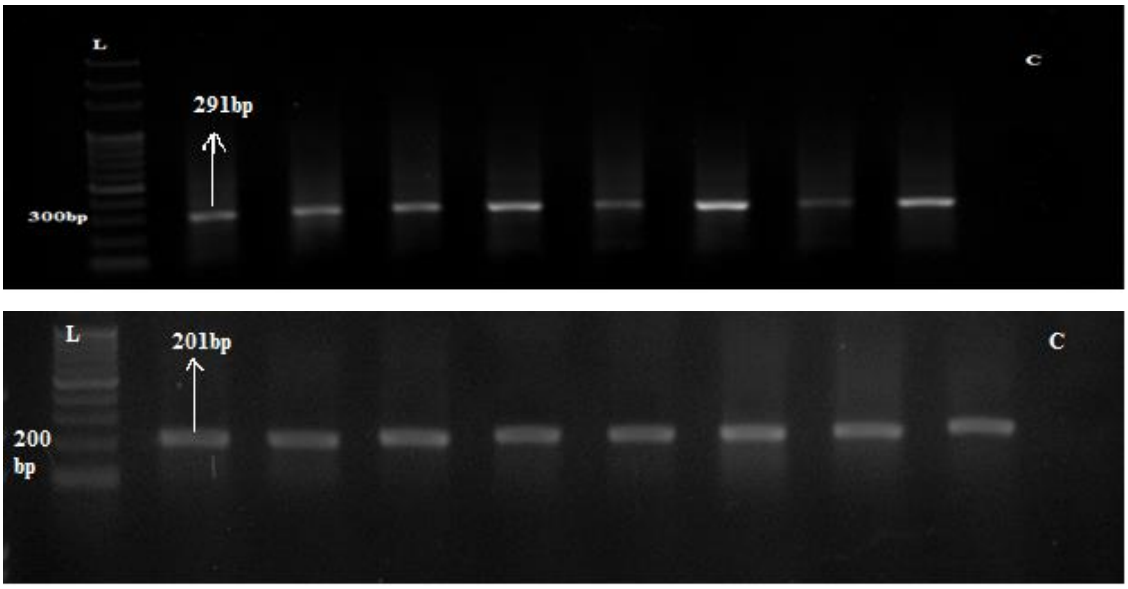
All variations, except for the variation in *CYP2C9* * 3 (1075A> C), were in accord with the Hardy-Weinberg equilibrium. The genotypic frequencies of *CYP2C9* * 2 (430C> T) W, H and M were 76.9%, 21.4%, and 1.7, respectively. The frequencies of *CYP2C9* * 3(1075A> C) were 84.6%, 12.0%, and 3.4%. Those of *VKORC1* (1173C> T) were 29.1%, 44.4%, and 26.5%. The genotypic frequencies of *VKORC1*- 1639G> A were 29.9%, 50.4%, and 19.7% (Figures 1 and 2).

Table2. Genotype frequency in subjects

Variation/ Genotypes	**W(%)**	**H(%)**	**M(%)**
*CYP2C9*2 (430C>T)*(rs1799853)	90(76.9)	25(21.4)	2(1.7)
*CYP2C9*3 (1075A>C)* (rs 1057910)	99(84.6)	14(12)	4(3.4)
VKORC1-1639G>A (rs 9923231)	35(29.9)	59(50.4)	23(19.7)
VKORC1 -1173C>T (rs 9934438)	34(29.1)	52(44.4)	31(26.5)

W: wild-type homozygous alleles, H: heterozygous alleles; M: mutant homozygous alleles.

The average daily warfarin dose requirements for different genotypes are presented in Fig. 3. Comparing the mean daily dose requirements of warfarin among wild genotypes (W) and genotypes containing at least one mutant allele (H and M), no significant differences were found among the genotypes of the *CYP2C9* * 3 (1075A> C) polymorphism (p-value = 0.422). However, there were significant differences among the genotypes of *CYP2C9* * 2 (430C> T) (p-value = 0.027). There were also significant differences in the mean daily dose requirements of warfarin among wild genotypes, heterozygotes and mutants in the two polymorphisms of *VKORC1* (1173C> T) (p-value = 0.001) and *VKORC1* (1639G> A) (p-value = 0.000).



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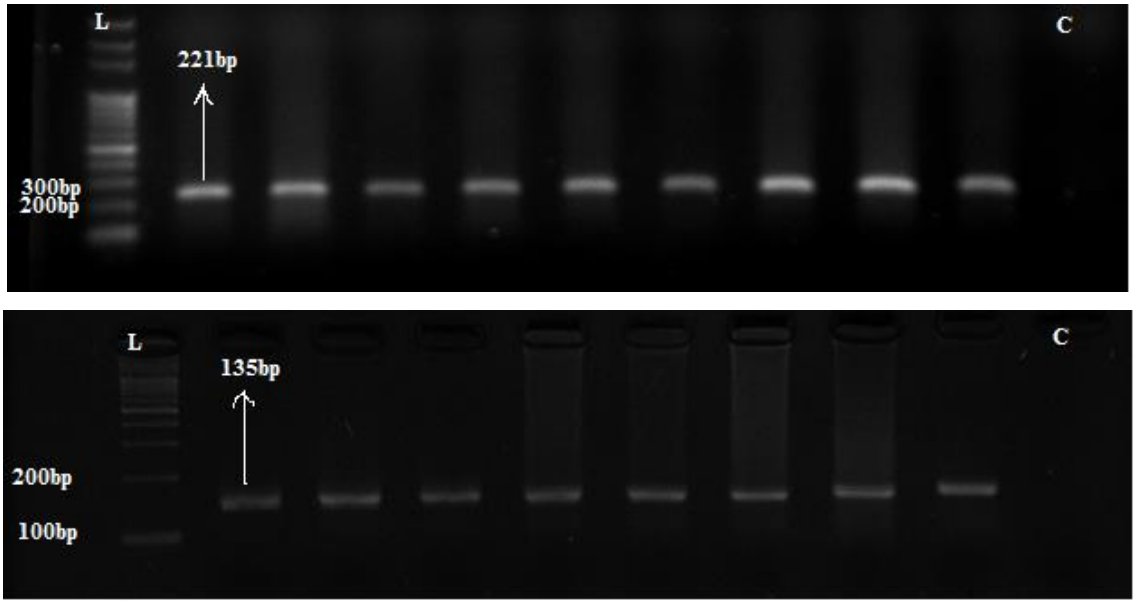
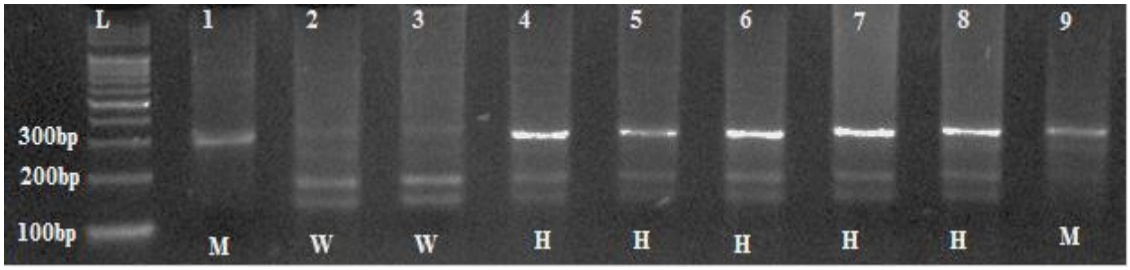
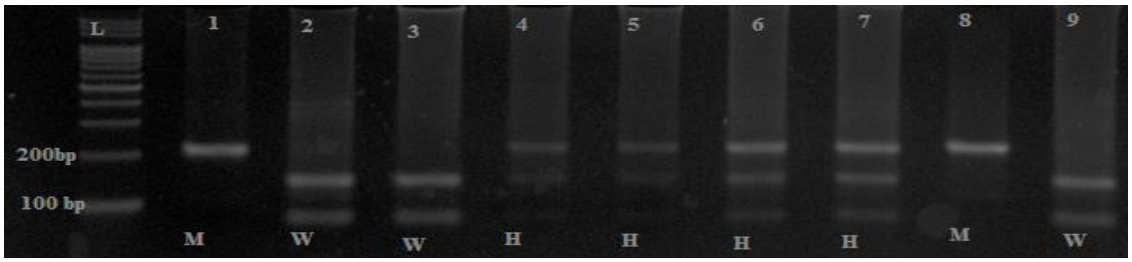


*Figure 1. PCR Products of the VKORC1 gene and the CYP2C9 gene polymorphism: (A) The SNP of VKORC1(1639G>A), (B) The SNP of VKORC1 (1173C>T), (C) The SNP of CYP2C9*2 (430C>T), (D) The SNP of CYP2C9*3 (1075A>C). Left: Ladder (L) 100bp, Right: Negative control (NC).*

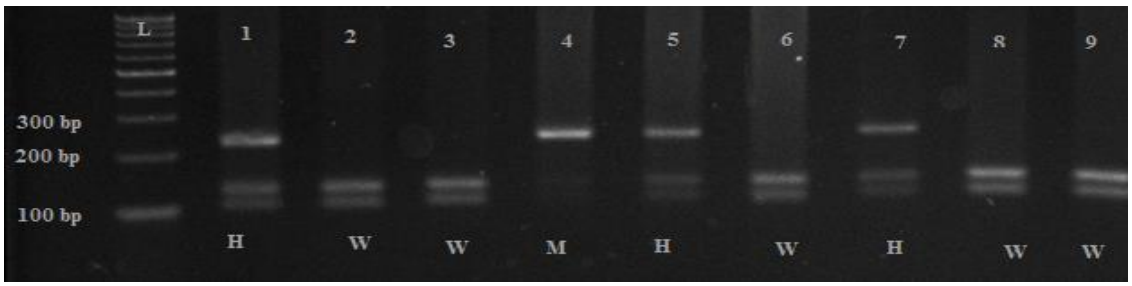
A



B



C



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D

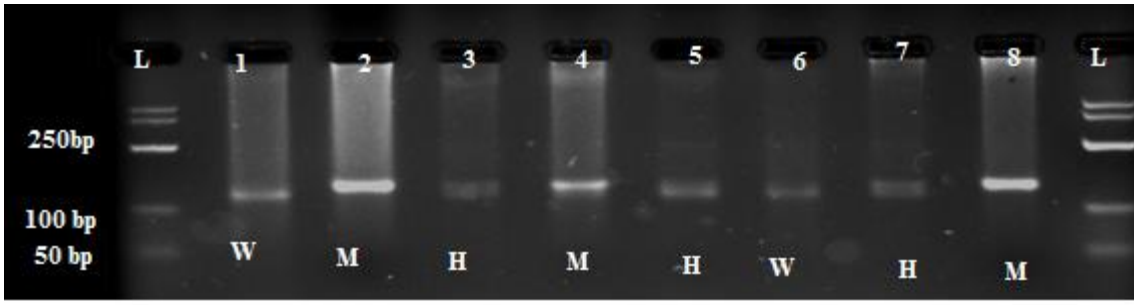
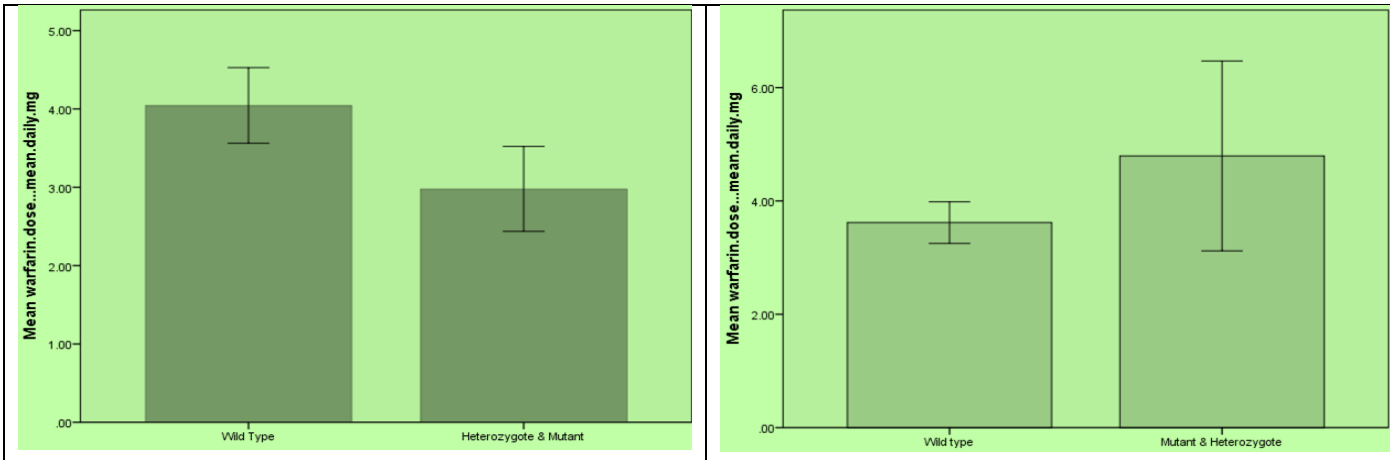
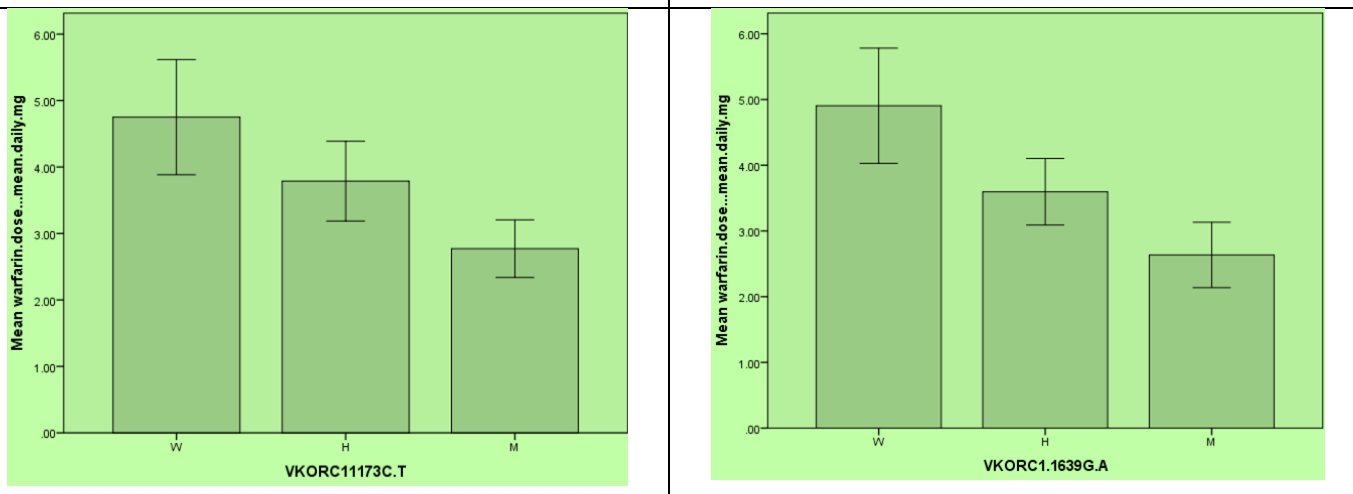


*Figure 2. Polymorphism analysis of the VKORC1 gene and the CYP2C9 gene by PCR followed by specific restriction enzyme digestion: (A) The SNP of VKORC1(-1639G>A), (B) The SNP of VKORC1 (1173C>T), (C) The SNP of CYP2C9*2 (430C>T), (D) The SNP of CYP2C9*3 (1075A>C). L: Ladder, W: wild-type homozygous alleles, H: heterozygous alleles, M: mutant homozygous alleles.*



(430C>T)CYP2C9*2 P value=.027 | (1075A>)CYP2C9*3 P value=.422



VKORC1 (1173C>T) P value=.001 | *VKORC1*(1639G>A) P value=.000

Figure 3. Mean warfarin dosage among CYP2C9*2, CYP2C9*3, *VKORC1* (1173C>T) and *VKORC1* (1639G>A) genotypes.

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Discussion

In the present study, the role of *CYP2C9* and *VKORC1* polymorphisms in warfarin dose requirements in Iranian patients undergoing warfarin treatment were characterized. Developing such a predictive ability that takes genetic characteristics into account may help improve dose adjustment and reduce the risk of over- or under-anticoagulation. The importance of these polymorphisms in the necessary dose of warfarin has been reported in several studies in different populations, however, it should be noted that, despite similar research in Iran, to the best of our knowledge there has never been a simultaneous analysis of these four polymorphisms in Iran.

As previous studies have shown variables, such as age, weight, and gender play a significant role in determining the warfarin dosage. Hence, the univariate logistic regression analysis was used to predict the effects of weight, age, and gender in this study [18-21].

As many other studies have pointed out the fact that race and ethnicity could play an important role in gene alteration and therefore warfarin dosage, it was attempted to conduct this study on Iranian peoples to determine the efficiency of standard INR. With the same purpose, Fatima Donia Mili *et al.* conducted a study on black patients in 2017 in which the results showed that participants with the *VKORC1*-1639G>A variant alleles required a lower mean daily warfarin maintenance dosage for therapeutic INR levels, which supports the findings of the present study [22].

The study and management of adverse reactions associated with the administration of warfarin is an important healthcare issue which has led many researchers to investigate how the dosage can be optimized via different techniques. Tao-Sheng Huang et al. conducted a study on 1285 Chinese patients about the effects of *VKORC1* and *CYP2C9* gene polymorphisms on variations in warfarin requirement in patients suffering from atrial fibrillation. Applying a new method involving electrochemical detection via a sandwich-type format, in which a 3′ short thiol capture probe and a 5′ ferrocene-labeled signal probe were used, they genotyped the three SNPs (*CYP2C9* *2, *3 and *VKORC1* c.-1639G > A). The results showed that most Chinese patients were more sensitive and responsive to warfarin since the majority of patients (99.4%) were found to be mutant-type and heterozygotes at locus c.-1639G > A (1). The results of the present study were also based on the finding that patients carrying *VKORC1* and *CYP2C9* gene polymorphisms (even single copies), required lower warfarin doses to achieve therapeutic ranges of INR [23].

It is already known that *VKORC1* and *CYP2C9* account for approximately 40% of the variability in warfarin dose requirements. Numerous studies have documented this fact, such as a study conducted by Fumihiko Takeuchi *et al.* in 2009, which assayed about 326,000 markers in 1,053 Swedish patients to identify genes that change the response to warfarin. In this study, Takeuchi and his colleagues investigated the association of each of the 325,997 SNPs with warfarin dose and found that SNPs clustering near *VKORC1* and *CYP2C9* showed the strongest statistical signals [12,24].

The results of the current study extend the known associations among the mean daily dose requirements of warfarin and wild genotypes, heterozygous and mutants in the two polymorphisms of *VKORC1* (1173C> T) and *VKORC1*(1639G> A) [6]. Elizabeth A. Sconce *et al.* studied 297 patients with stable anticoagulation and a target INR of 2.0 to 3.0. In this study, genetic analyses were undertaken to detect *CYP2C9* (*2 and *3 alleles) and *VKORC1* (1639 polymorphism). Venous INR and plasma concentrations of R- and S-warfarin were measured. The average warfarin daily dose requirement was highest in *CYP2C9* homozygous wild-type patients, when compared with patients carrying the variant *2 and *3 alleles ($P < .001$). In comparison with patients with the GA and the AA genotypes, the average daily dose requirement of warfarin was also highest in patients with the *VKORC1* (position -1639) GG genotype ($P < .001$) [25].

The role of CYP2C9*3 variation has been long studied regarding warfarin therapy and in many of these studies, the CYP2C9*3 variation increases the risk of supratherapeutic INR and bleeding complications [26]. In the present study, no significant differences were found among the genotypes of polymorphism CYP2C9*3 which is consistent with earlier research on Asians indicating that reduced warfarin dose requirements may be mainly caused by *VKORC1* genetic variations because Asians are rarely carriers of *CYP2C9* gene variants, if at all [27,28].

The study of genetic variants in different parts of Iran is essential as it is located between both European and Asian populations. The ethnic and genetic diversity and variations in Iran could be due to migration and population flows. In a similar study

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conducted in 2018 on the Kurdish population in the Kermanshah province of Iran, 110 patients who had undergone cardiac surgery and took warfarin were genotyped for polymorphisms of *VKORC1*(1639 G>A), CYP2C9*2, and CYP2C9*3. The frequencies of the *VKORC1* (1639A) allele and the CYP2C9*2 and *3 alleles were 42.3%, 14% and 5.4%, respectively [29]. In another study conducted by Azarpira in 2010 on 150 Iranians residing in the southern provinces, the frequency of CYP2C9*3 among Iranians (9.8%) was found to be similar to Caucasians (9.7%), but was higher than Africans (1%), the Japanese (2.3%), and Iranians living in the northern provinces (0%). The frequency of CYP2C9*2 in the participants of the current study (25.3%) was quite different from Caucasian (10-13%), African (2%) and Asian (0%) populations. For *VKORC1*, the allelic frequency of -1639A (55.6%) was similar to that of Caucasians, but different from African-Americans (13%) and the Chinese (96%) [30]. The DNA samples, genotyped for *VKORC1*, using the PCR-RFLP of a study conducted in Kerman province, showed that from 112 patients, the most frequently observed genotype was *VKORC1* GA (48.2%). Genotype frequencies of *VKORC1* GG and AA among the participants were 39.3% and 12.5%, respectively. The results also demonstrated a significant relationship between the presence of *VKORC1* (1639G>A) and the daily dose requirement of warfarin (P = 0.011, R2 = 0.080). *VKORC1* (1639 A) alleles were less commonly detected than *VKORC1* (1639 G) alleles and required lower warfarin dosages [31]. These results are in line with the present study.

Finally, it should be mentioned that this study was conducted because of the necessity of identifying the significant role of genotype in drug dosage, which can vary among the races and geographical conditions. The present study confirms previous reports about the significance of pharmacogenetic testing in predicting high risks of bleeding or thrombosis before the initiation of anticoagulation with warfarin in patients carrying either the variants (1639A and 1173C) or the CYP2C9*2 (430C>T) alleles.

Abbreviations

bp: Base pair; CYP2C9: Cytochrome P450 complex subunit 2C9; DNA: Deoxyribose nucleic acid; DVT: Deep vein thrombosis; EDTA: Ethylenediaminetetraacetic acid; H: Heterozygous alleles; Htz: Heterozygous; INR: International normalized ratio; IWPC: International Warfarin Pharmacogenetics Consortium; L: Ladder; M: Mutant homozygous alleles; Mut: Homozygous mutant; NC: Negative control; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; PMs: Poor metabolizers; SNP: Single nucleotide polymorphism; SPSS: Statistical Package for the Social Sciences; VKFCD2: Combined deficiency of vitamin k-dependent clotting factors-2; VKORC1: Vitamin K epoxide reductase complex subunit 1; W: Wild-type homozygous alleles; WT: Wild type; µL: Microliter

Declarations

The authors have no relevant financial or non-financial interests to disclose.

The authors have no conflicts of interest to declare that are relevant to the content of this article.

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

The authors have no financial or proprietary interests in any material discussed in this article.

Ethics approval

This study has been approved by the Ethics Committee of the Lorestan University of Medical Sciences. Informed consent was obtained from all participants.

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