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Association of CYP2C9 Single Nucleotide Polymorphisms with Warfarin Dose Requirements: A Study in Iraqi Patients

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Abstract

Objective: This study investigates the impact of two single nucleotide polymorphisms (SNPs) in the CYP2C9 gene—CYP2C9*2 (rs1799853) and CYP2C9*3* (rs1057910)—on warfarin metabolism. These variants affect the activity of the cytochrome P450 2C9 enzyme, which is responsible for warfarin clearance. We analyzed the genotypes and corresponding weekly warfarin doses in Iraqi patients, alongside demographic and clinical factors influencing dose variability.

Methods: The studied group consisted of 97 Iraqi individuals receiving stable warfarin treatment. Genotyping was performed by using Allele-Specific PCR for identifying the polymorphisms of the CYP2C9 gene, the CYP2C9*2 and CYP2C9*3 alleles since they are associated with warfarin clearance. The groups were categorized as wild type, heterozygous and mutant.

Result: The wild-type genotype (CC) of the CYP2C9*2 (rs1799853) was the most common in this study accounting for 73.2% of the participants. Heterozygous genotype (CT) was found in 24.7% while mutant type was (TT) at about 2.1%. CYP2C9*3 (rs1057910) the wild type (AA) was the most common in the population (89.7%), the Heterozygous (AC) was 10.3% but the (CC) homozygous mutants were not found in this study. A negative correlation was observed between warfarin dose requirements and the presence of genetic variants in the studied SNPs."

Conclusion: CYP2C9*2 and CYP2C9*3 polymorphisms significantly influence warfarin dose requirements by reducing drug clearance. These findings support the use of pharmacogenetic testing to guide personalized warfarin therapy, improving dose accuracy and patient safety.

Keywords: Warfarin, anticoagulation therapy, CYP2C9 gene, SNPs, rs1799853, rs1057910

Introduction

The application of warfarin in thromboembolic disorders management is expanding and includes risk factors such as deep venous thrombosis (DVT), pulmonary embolism (PE), and atrial fibrillation (AF).[1] Vitamin K-dependent clotting factors are blocked from production through the administration of warfarin which decreases the chances of undesirable altitude of blood clot.[2] Such an anticoagulant impact makes it possible to avoid troublesome and fatal consequences: stroke, pulmonary emboli or obstruction of an organ by means of clot. To contraindicate, however, is only a matter of time.[3] Due to the reasons, warfarin therapy is difficult to manage because of its narrow therapeutic range with a high interindividual variability. It is still challenging to reach and sustain an appropriate therapeutic dose that avoids the occurrence of both thromboembolic events and bleeding risks.[4]

Patient compliance is the biggest obstacle in the case of warfarin therapy. Some patients will achieve the desired anticoagulation levels with their lower doses; others, conversely, may require substantially higher doses to reach the desired therapeutic levels.[5] However, this level should not be exceeded as it would put the patient at risk of bleeding. This variation is the result of different genetic, as well as non-genetic factors, and increases the complexity of individualization in warfarin therapy. Identifying such factors is imperative for improving individual dosing to reduce the prevalence of adverse outcomes in patients.[4]

Factors include particulars on genetic basis for this variability, which are mainly polymorphisms in genes that code for proteins that are responsible for the metabolism as well as the action of warfarin.[6] In this case, one of the most notable is the CYP2C9 gene, which codes for the cytochrome P450 2C9 enzyme responsible for the metabolism of various drugs, including warfarin. This enzyme is responsible for the processes of hydroxylation of warfarin in the liver, which is one of the biotransformation steps of warfarin. As a medication, Warfarin shows a dose-dependent metabolism that is influenced by its pharmacokinetic and pharmacodynamic characteristics, which follow a first-order kinetic process in relation to its cytochrome P450 vitamin K-dependent metabolism, while pharmacodynamic activity is associated with target genes like CYP2C9.

CYP2C9 polymorphisms also affect warfarin's pharmacokinetics behaviours and such polymorphisms have pleotropic effects on CYP2C9 enzymes.[7] They mediate the metabolism of warfarin and such are hydrolytic enzymes – which have high enzymatic concentrations and activity. Lower concentrations of hydrolytic enzymes result in lower concentrations of warfarin in the systemic veins, and so in cardiac veins as well. Such conditions would necessitate the availability of lower doses of warfarin in the vascular system.[8]

CYP2C9 gene addresses many variants, and CYP2C9*2 *(rs1799853) and CYP2C9*3 (rs1057910) alleles are the most studied concerning warfarin dose. These single nucleotide polymorphisms (SNP) are referred to as the cause of activity decrease of the CYP2C9 isoenzyme, and therefore, the clearance of warfarin is reduced. Such persons may have one or two copies of the CYP2C9*2 *or CYP2C9*3 alleles which are associated with slow metabolism and hence lower doses are required to achieve and maintain effective levels of anticoagulation. The same studies suggest that patients with these variants may require more than 30% lower doses of warfarin than patients harboring wild-type CYP2C9 allele. These genetic variations are very important in an individualized warfarin therapy approach and these negative polymorphic variants have been included in dosage calculation algorithms.[6,9]

Nevertheless, the variances in warfarin response cannot be attributed solely to genetic markers. Many other factors are also important in determining how much treatment with warfarin will be required. These span basic population characteristics such age and sex that are important, as well as clinical factors, such as liver and kidney function, and the presence of other diseases. For instance, elderly patients have lesser metabolism rate than the younger patients which can lead to the delayed metabolism of warfarin. This is the same case with patients who are low in body weight, they may have a different volume of distribution and therefore require a different dose. As well as, liver or kidney dysfunction will interfere in the drug metabolism and clearance, therefore, the warfarin dose should also be adjusted in people with liver disease or kidney diseases. In addition to the above, certain drugs taken by the patients can influence warfarin metabolism and warfarin has the tendency to affect the anticoagulant activity positively or negatively. Other drugs such as antibiotics, antifungals and cardiovascular medications make this task even harder.[10–12]

Considering these aspects, the objectives of this study are twofold: 1) to explore the genetic and non-genetic factors associated with warfarin dose requirements in an Iraqi patient population. In this way, by analyzing the occurrence of the CYP2C9*2 *and CYP*2C9*3 SNPs, genetic predisposition, and some demographic as well as clinical variables, the authors aim to provide a broader picture of warfarin dose variability in this population. The study will assess the impact of genetic polymorphisms on warfarin metabolism and dosage requirements and evaluate the effects of age and weight. All goals of the study employ a combined strategy in order to highlight the complexity of warfarin dose determination and create conditions for more effective treatment in the future.

The fact that this study should improve safety for the patients concerned due to the use of genetic testing and dosing characteristics to optimize warfarin therapy for Iraqi patients would potentially be the more realistic approach. With this advancement, it may be possible to prevent adverse drug events and complications such as bleeding or clotting, thus ensuring better outcomes of treatment. Genetic polymorphism would make personalized warfarin therapy more secure and effective; hence, every patient would be ensured that they do not receive an excessive or insufficient amount of the drug relative to their specific genetics and clinical conditions.

Materials and Methods

The studied cohort included 97 Iraqi patients, 38 of whom were male, and 59 female, averaging 49.6 years of age and weighing 77.82 kg, all on stable warfarin therapy. Average INR levels were 2.6, within therapeutic range, while average weekly warfarin consumption was 31.6 mg. Patients were interviewed from various outpatient anticoagulation centers throughout the south and central regions of Iraq, including Karbala and bordering regions, to improve geographic representation and inclusivity for the Iraqi population. The group was ethnically homogeneous with majority Arab ancestry, which was representative of the population in these regions. Every participant had adhered to a stable warfarin therapy for a minimum of three consecutive clinic appointments while ensuring no dosage changes and no interfering medications had been taken, achieving stable pharmacokinetic equilibrium. The cohort size of 97 was selected from a combination of logistical and ethical constraints and estimated CYP2C9 polymorphisms prevalence in the chosen population, which ensured adequate statistical power to detect meaningful associations.

Inclusion criteria consisted of both men and women 18 years or older who required stable warfarin therapy (defined as no dose adjustment and INR within range) for three or more consecutive clinic visits. Patients were required to have no recent changes in any concomitant medications that would interact with warfarin.

Exclusion criteria consisted of active liver or renal dysfunctions, active malignancy, pregnancy, recent surgery, and any other warfarin metabolizing conditions that could affect INR stability. These criteria were applied in order to achieve a stable sample that possessed stable pharmacokinetic and pharmacodynamic characteristics.

Our aim was to examine the possible factors for warfarin dose adjustment, with the aim of identifying the polymorphisms of the CYP2C9 gene, in particular, the CYP2C9*2 *and* CYP2C9*3 alleles since they are associated with warfarin clearance. Electrophoresis was conducted to analyze the PCR products. (The primers used, provided by Dr. Hassan Mahmood Mousa Abo Almaali, are listed in Tables 1 and 2) Genotyping was performed by using Allele-Specific PCR which is able to amplify DNA only if a specific allele exists. Primers were designed to the polymorphisms of the CYP2C9 gene, and the conditions of PCR were standardised out for effective amplification. After amplification, PCR products were viewed under the gel plate to visualize the amplified fragments bands to determine the different genotypes of the participants. This procedure is very sensitive and appropriate for the assessment of polymorphisms of genes that encode drug metabolic enzymes, therefore, it was possible to determine the effects of CYP2C9 polymorphisms on warfarin dosing among Iraqi patients. The results are expected to advance the objective of individualized anticoagulation procedure by increasing the therapeutic effect, as well as minimizing the side effects of warfarin. The PCR cycling conditions for rs1799853 and rs1057910 genotyping are summarized in Table 3. The distribution of patients according to CYP2C9 gene polymorphisms is presented in Table 4.

Table 1. **Genotyping of rs1799853 variants - primer sequences and other features**

rs1799853 C>T	Sequence (5′–>3′)	Template strand	Length	Start	Stop	Tm
Allele C	GGAAGAGGAGCATTGAGGACC	Plus	21	419	439	60.13
Allele T	GGAAGAGGAGCATTGAGGACT					
Reverse primer	CCCGCTTCACATGAGCTAACA	Minus	21	619	599	60.68
Product length	201					

Table 2. **Genotyping of rs1057910 variants - primer sequences and other features**

rs1057910 A>C	Sequence (5′–>3′)	Template strand	Length	Start	Stop	Tm
Allele A	GCACGAGGTCCAGAGATACA	Plus	20	1082	1101	58.90
Allele C	GCACGAGGTCCAGAGATACC	Plus	20	1082	1101	60.90
Reverse primer	ACATGGAGTTGCAGTGTAGGAG	Minus	22	1209	1188	60.03
Product length	128					

Table 3. **PCR cycling conditions for rs1799853 and rs1057910 genotyping**

	Rs1799853	
	Temperature	**Time**
Initial denaturation	95	5 min
Denaturation	95	20 sec
Annealing	57	30 sec
Extension	72	30 sec
Final extension	72	5 min
	Rs1057910	
	Temperature	**Time**
Initial denaturation	95	5 min
Denaturation	95	20 sec
Annealing	56	30 sec
Extension	72	30 sec
Final extension	72	5 min

Table 4. **Distribution of patients in the study sample according to SNPs in the CYP2C9 gene**

SNP (CYP2C9)		N (%)	Warfarin weekly dose (mg) Mean ± SD
rs1799853	**CC**	71 (73.2%)	33.64 ± 7.81
	CT	24 (24.7%)	26.32 ± 3.33
	TT	2 (2.1%)	23.5 ± 2.12
rs1057910	**AA**	87 (89.7%)	32.61 ± 7.4
	AC	10 (10.3%)	23.05 ± 2.67

SNP *2 (rs1799853) carriers (CT, TT) require 21%–30% lower doses compared to CC; SNP *3 (rs1057910) AC carriers require 29% lower doses compared to AA.

Table 5. **Distribution of patients in the study sample according to the diplotype of the CYP2C9 gene**

SNP (CYP2C9)	N (%)	Warfarin weekly dose (mg) Mean ± SD
***1/*1**	63 (64.9%)	34.88 ± 7.4
***1/*2**	22 (22.7%)	26.94 ± 2.7
***1/*3**	8 (8.2%)	23.94 ± 2.15
***2/*2**	2 (2.1%)	23.5 ± 2.12
***2/*3**	2 (2.1%)	19.5 ± 0.71

Table 6. **Study of the association of warfarin weekly dose with SNPs in the CYP2C9 gene**

		rs1799853	rs1057910	Diplotype
Warfarin weekly dose (mg)	r	–0.483**	–0.419**	–0.659**
	P. value	**<0.0001**	**<0.0001**	**<0.0001**

: Correlation is significant at the 0.01 level. *: Correlation is significant at the 0.05 level. *r* represents the Pearson correlation coefficient between weekly warfarin dose and the genetic variants (rs1799853, rs1057910, and Diplotype); all correlations are statistically significant with *P*-values < 0.0001, where "" indicates significance at the 0.01 level and "*" indicates significance at the 0.05 level.

Results

Genotypic Distribution and Weekly Warfarin Dose

*SNP CYP2C9*2 (rs1799853)*

The wild-type genotype (CC) was the most common in this study, accounting for 73.2% of the participants. Patients bearing this genotype required the highest weekly dose of 33.6 ± 7.8 mg warfarin (Table 5). The heterozygous genotype (CT) was found in 24.7% of the population and was associated with a lower weekly dose requirement (26.3 ± 3.3 mg), while the homozygous variant genotype (TT) was rare, occurring in only 2.1% of participants, and required the lowest dose (23.5 ± 2.1 mg). Further analysis revealed a significant negative correlation between warfarin dose and the presence of the CYP2C9*2 variant ($r = -0.483$, $P < 0.0001$) (Table 6 and Figure 1), whereby an increase in the number of T alleles was associated with reduced dose requirements.

*SNP CYP2C9*3 (rs1057910)*

Similarly, for CYP2C93 (rs1057910), the wild-type genotype (AA) was the most frequent (89.7%) with a mean weekly dose of 32.6 ± 7.4 mg, while heterozygous (AC) individuals required a lower dose (23.0 ± 2.7 mg). No homozygous mutants (CC) were detected. A significant negative correlation between warfarin dose and CYP2C93 variant was also found ($r = -0.419$, $P < 0.0001$) (Table 6 and Figure 2).

Analysis of the Diplotypes

From the data obtained, it was observed that warfarin doses vary based on the genetic combinations of the individuals involved in the treatment.

- The most common diplotype, CYP2C9*1/*1, was located at 64.9% of patients and was related to the greater dose of 34.8 mg (± 7.4 mg)—the greatest weekly dosage.
- Patients carrying CYP2C9*1/*2 required a further reduced dosage of 26.9 ± 2.7 mg while on the other hand, CYP2C9*1/*3 patients required an even fewer dosage of about 23.9 ± 2.1 mg.

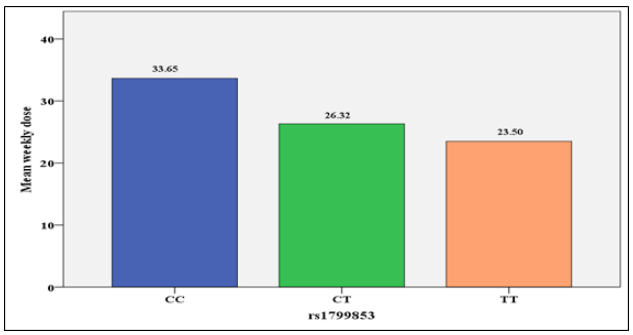

Fig. 1 **Association between rs1799853 genotypes and mean weekly warfarin dose.**

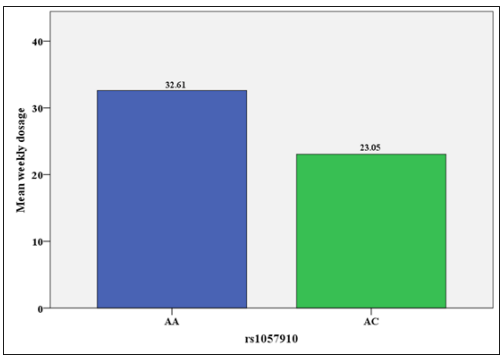

Fig. 2 **Mean weekly warfarin dose by rs1057910 genotypes.**

Table 7. **Predictors of warfarin dosage: results from univariate and multivariate analyses**

	Univariate analysis			Multivariate analysis*		
Predictor	**Coefficient (B)**	***P*. value**	**R^2**	**Coefficient (B)**	***P*. value**	**R^2 change**
Diplotype	–4.88	**<0.00001**	0.32	–3.65	**<0.00001**	0.32
Weight (kg)	0.49	**<0.00001**	0.24	0.16	**<0.00001**	0.124
Age (Year)	–0.228	**0.001**	0.11	–0.12	**0.026**	0.029
Sex	0.8	0.6	0.003	–	–	–
INR	–0.72	0.6	0.0025	–	–	–
PLT (x10^3 /µl)	–0.00046	0.96	0.0000	–	–	–

*Stepwise regression analysis. The table presents results from univariate and multivariate stepwise regression analyses predicting warfarin weekly dose; coefficients (B), *P*-values, and R^2 values are shown for each predictor, with multivariate analysis indicating the change in R^2 when variables are added to the model; predictors with a dash (–) were not included in the multivariate model.

- Such rare types as CYP2C9*2/*2 and CYP2C9*2/*3 needed significantly less amount of doses, ie. 23.5 ± 2.1 mg and 19.5 ± 0.7 mg respectively.

The results also allowed the concluding of strong correlations of the dose variability with the diplotype variability ($r = –0.659$, $P < 0.0001$) indicating the important contribution of this variable as a factor affecting warfarin dose adjustment for the individual patient rather for the population.

Regression Analysis

Univariate Regression Analysis

Univariate regression analysis revealed that weight, age, and diplotype were significant predictors of weekly warfarin dose. These variables were then entered into a multivariate stepwise regression model, which confirmed their significant contributions to dose variability. Specifically, body weight was positively associated with warfarin dose (B = 0.16, P <0.0001), age was negatively associated (B = –0.12, P = 0.026), and certain diplotypes were linked with dose reductions compared to the CYP2C9*1/*1 diplotype (Table 7).

Multivariate Regression Analysis

The multivariate model revealed the following key relationships:

- Body weight: Each kilogram of weight added to the weekly warfarin dose of 0.16 mg ($P < 0.0001$).
- Age: Dose decreased by 0.12 mg for every year of age increased ($P = 0.026$).
- Diplotype:
  - Use of CYP2C9*1/*2 and CYP2C9*1/*3 was associated with dose reductions of 3.65 mg and 7.3 mg respectively compared to dose required by subjects using CYP2C9*1/*1.
  - There was also a need for dose reduction of 10.95 mg and 14.6 mg by carriers of CYP2C9*2/*2 and CYP2C9*2/*3 respectively. This analysis highlights how genetic and demographic variables interact in warfarin dosing and suggests that such variables should always be incorporated in personalized therapy aimed at improving the efficacy of anticoagulation.

Discussion

Our findings are consistent with previous studies showing that CYP2C9 polymorphisms significantly influence warfarin dosing across diverse populations and settings. CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) alleles are commonly known for being loss-of-function alleles and negatively affect the CYP2C9 enzyme activity, which contributes significantly to the metabolism of warfarin metabolization. Therefore, lower amounts of the drug are required to maintain therapeutic International Normalized Ratio (INR) levels due to diminished activity and slower clearance of the drug.[7,13]

These polymorphisms cause amino acid changes that modify the structure and catalytic efficiency of CYP2C9. More specifically, the *2 allele (Arg144Cys) and *3 allele (Ile359Leu) both antagonistically diminish substrate binding and metabolic function. The combination of these factors slows down the hepatic clearance of S-warfarin which is the more active enantiomer, thereby extending the drug's half-life and increasing its concentration in the bloodstream at consistent dosing intervals. Therefore, as we noted in our observations, carriers of these alleles attained therapeutic anticoagulation at sub-therapeutic doses of warfarin. These mechanistic effects have been consistently demonstrated in vitro and in clinical studies of the drug's pharmacokinetics.

Our results support prior studies in European populations, which found that carriers of CYP2C9*2 and *3 alleles require 17–37% lower warfarin doses than non-carriers, depending on diplotype configuration (Sconce et al., 2005; Wadelius et al., 2007). These variants were similar to trends seen in Asian populations, who had a lower allele frequency than their European counterparts (Higashi et al., 2002). Results from our cohort regarding the prevalence as well as dose adjustments very much correlate with the findings in the Middle Eastern cohort while indicating global patterns on genetic heterogeneity and the impact on the practice of medicine (Al-Eitan et al., 2021).[14–17]

The moderate negative correlations between CYP2C9 variants and warfarin dose (CYP2C9*2: $r = –0.483$; CYP2C9*3: $r = –0.419$) align with findings from other studies. Additionally, the lack of homozygous CYP2C9*3 mutants in our sample adheres to literature observations that this genotype is scarce in many populations. Such findings advocate for the consideration of such genetic factor differences when warfarin is prescribed in order to enhance the effectiveness of the anticoagulation therapy.[15,18–20]

The study successfully demonstrated that the combined effect of CYP2C9*2 and CYP2C9*3 diplotypes significantly reduces warfarin dose requirements. For example, in patients with the CYP2C9*2*3 diplotype, the lowest doses were required, which suggests the additive effect of both variants was present. Considering both polymorphisms together enhances the predictive value, as analyzing a single variant may lead to ambiguous interpretations regarding metabolism and therapy. Such kinetic attributes explain the recognition of the inclusion of diplotype analysis in pharmacogenetic dosing algorithms: we note that doses and diplotypes were closely related, the correlation in 63.9% of patients was significant ($r = –0.659$, $P < 0.0001$). The Clinical Pharmacogenetics Implementation Consortium (CPIC) has previously recommended the genotyping of the CYP2C9 variants for tailored warfarin therapy.

Non-genetic factors such as body weight and age also influence warfarin dosing. Heavier individuals may require higher doses due to a larger volume of drug distribution, as demonstrated by Schwarz et al (2008).[21] On the other hand older patients appeared to require lower dosages which may be due to lesser metabolic and renal clearance because of age. The studies by Limdi et al (2010).[22] provide support for this view as they showed warfarin continues to be dosed with a focus on age and weight as important parameters, regardless of any remote genetic factors. These positive factors argue for the inclusion of such non-genetic parameters into dosing algorithms so that dosages can be improved, hence minimizing negative outcomes.

This study highlights how both genetic and non-genetic factors influence warfarin dosing. Incorporating CYP2C9 genotyping alongside clinical predictors in dosing algorithms may improve therapeutic outcomes and reduce risks of bleeding or thromboembolism. Our findings especially emphasize the value of personalized therapy in populations with high genetic diversity.

It would, however, be helpful to broaden the scope of these results in future studies by including other genetic factors, such as polymorphisms within the VKORC1 gene, which is associated with warfarin resistance. Advanced techniques like next-generation sequencing can identify unique polymorphisms in Middle Eastern populations, aiding the development of improved dosing algorithms. Furthermore, evidence on the benefit of pharmacogenetic-guided therapy in anticoagulation treatment can be obtained from the prospective studies examining patients over a period of time.

Although this is a cross-sectional study, all patients had stable warfarin doses confirmed by at least three consecutive clinic visits with stable INR and no dose changes in the previous month. This provided a solid genotype-dose relationship assessment under equilibrium conditions. That said, we recognize that our understanding of how dose requirements may shift over time would be enriched by longitudinal data. Other prospective studies were encouraged to test our results and examine the enduring interplay of warfarin treatment and genetics in ethnically diverse populations.

To summarize the above, this research confirms the role of genetic polymorphism of the CYP2C9 gene and non-genetic factors such as the patient's body weight and age, in warfarin dose requirements. These results argue that pharmacogenetic testing should be conducted in the clinical practice in order to tailor the anticoagulation therapy and improve patient safety. The combination of genetic and non-gene predictors in dosage algorithms appears the most encouraging method for achieving precision in warfarin therapy.

These findings support the implementation of pharmacogenetic testing in clinical practice to personalize warfarin therapy, potentially reducing adverse events and improving patient outcomes. Incorporating such genetic information into dosing protocols can enhance precision medicine approaches, particularly in populations with diverse genetic backgrounds like Iraq.

Clinical Implications

On the other hand, the genetic polymorphisms of several candidate genes may be effective in predicting the warfarin dose needed in particular populations, which include the Arab population, as well as developing a strategy for its individualized input using pharmacogenetic data. The existing associations of CYP2C9 variants with extended range of doses make a case for including pharmacogenetic testing into the routine practice for a population with different genetic makeup as the Iraqi population.

Conclusion

This study demonstrates significant CYP2C9 genotype variability affecting warfarin dosing in the Iraqi population. These findings provide strong rationale for pre-treatment genetic

testing to guide individualized anticoagulation therapy. Incorporating such pharmacogenetic data into clinical practice could enhance precision medicine approaches, reduce adverse drug reactions, and improve treatment outcomes. Future studies including additional genetic markers and larger cohorts will further refine dosing algorithms and support broader clinical application.

Ethical Approval

This study was approved by the Ethics Committee of the College of Pharmacy/University of Karbala on August 5, 2024 (Ref:2024HU14). All patients provided informed consent before being enrolled in the study. The study was performed in accordance with the Declaration of Helsinki. The study adhered to all relevant ethical standards, and all inclusion/exclusion criteria were reviewed and approved by the institutional ethics committee.

Author Contributions

Alaa Ali Mohammad: Conducted all experimental and analytical work and wrote the manuscript. The primers were designed by Prof. Dr. Hassan Mahmood Mousa Abo Almaalii. Amal Umran Mosa: and Hassan Mahmood Provided supervision throughout the project and proofreading the manuscript.

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Conflicts of Interest

The authors advertise that they have no known competing financial interests or personal relationships that could have appeared to affect the work reported in this paper.

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