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VKORC1 –1639G>A (rs9923231) Polymorphism and Warfarin Dose Variability in Iraqi Patients with Hematological Disorders: A Pharmacogenetic Case-Control Study: Polimorfisme VKORC1 –1639G>A (rs9923231) dan Variabilitas Dosis Warfarin pada Pasien Irak dengan Gangguan Hematologi: Sebuah Studi Kasus-Kontrol Farmakogenetik

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Abstract

General Background: Warfarin therapy for thrombotic hematological disorders is complicated by substantial inter-individual dose variability. **Specific Background:** The VKORC1 –1639G>A polymorphism is a major genetic determinant of warfarin sensitivity, yet Middle Eastern populations remain underrepresented in pharmacogenetic research. **Knowledge Gap:** There is limited evidence regarding VKORC1 allele distribution and its clinical relevance in Iraqi patients with hematological conditions. **Aims:** This study aimed to determine VKORC1 genotype frequencies and evaluate their association with warfarin dose, therapeutic control, and predictive modeling. **Results:** The AA genotype was associated with significantly reduced warfarin dose requirements compared to GG carriers, and VKORC1 explained 31.2% of dose variability. A multi-locus model incorporating additional genetic and clinical variables increased predictive accuracy to 61.3%. **Novelty:** This study provides the first comprehensive pharmacogenetic characterization of VKORC1 in an Iraqi hematological cohort, integrating cytokine gene variants into dosing models. **Implications:** These findings support population-specific dosing strategies and highlighttheclinicalrelevance of genotype-guided anticoagulation in Middle Eastern healthcare settings.

Keywords: Vkorc1 Polymorphism, Warfarin Dosing, Pharmacogenetics, Hematological Disorders, Iraqi Population

Key Findings Highlights

Genetic variation strongly differentiates dose requirements among patient groups
Combined genetic markers substantially improve predictive modeling accuracy
Regional allele distribution reveals distinct population-specific patterns

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1. Introduction

Hematological disorders associated with thrombotic risk — including deep vein thrombosis (DVT), pulmonary embolism (PE), myeloproliferative neoplasms (MPNs), atrial fibrillation complicating hematological malignancies, and mechanical heart valve replacement in patients with underlying hematological disease — represent a major global health burden with rising prevalence in Middle Eastern populations (Dohner et al., 2022; Venugopal and Sekeres, 2024). Warfarin, a coumarin-derived vitamin K antagonist, remains the most widely prescribed oral anticoagulant for preventing and treating thromboembolic complications in these conditions (Kamali and Wynne, 2010). Despite decades of clinical use, warfarin management is substantially complicated by its narrow therapeutic index and enormous inter-individual variability in dose requirements, which can span up to 20-fold across patients (Sconce et al., 2005; Wadelius et al., 2009). This variability renders dose titration empirically challenging, prolongs the time required to achieve stable anticoagulation, and generates life-threatening risks of hemorrhage or thromboembolic events during subtherapeutic periods.

Pharmacogenomic research over the past two decades has established that approximately 50% of inter-individual warfarin dose variability is genetically determined (Johnson et al., 2011). Among identified genetic determinants, the VKORC1 gene — encoding vitamin K epoxide reductase complex subunit 1, the direct molecular target of warfarin — accounts for the single largest proportion of dose variability (D'Andrea et al., 2005). The VKORC1 –1639G>A promoter variant (rs9923231) reduces VKORC1 gene transcription, decreasing enzyme protein abundance and thereby enhancing warfarin pharmacodynamic sensitivity at any given plasma concentration. Patients homozygous for the A allele require dramatically lower warfarin doses to achieve therapeutic anticoagulation, while those carrying the G allele are relatively resistant and require substantially higher doses (Gage et al., 2008; IWPC et al., 2009).

The clinical relevance of VKORC1 genotyping is now firmly established. The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides Grade A evidence for VKORC1 –1639G>A-guided warfarin dosing (Johnson et al., 2011), and the International Warfarin Pharmacogenetics Consortium (IWPC) algorithm — the most validated clinical dosing tool — incorporates VKORC1 as its primary genetic predictor (IWPC et al., 2009). Despite this evidence base, implementation of VKORC1-guided dosing in clinical practice remains inconsistent globally, and critically limited across Middle Eastern healthcare systems (AlRasheed et al., 2025; Oscanoa et al., 2024).

A fundamental barrier to implementation in the Middle East is the absence of robust population-specific allele frequency data. VKORC1 –1639A allele frequencies vary markedly across ethnic groups: frequencies of approximately 40% in Caucasians, 67% in Asians, and as low as 11% in African Americans have been reported (Wadelius et al., 2009; IWPC et al., 2009). Dosing algorithms derived from predominantly European or East Asian cohorts may therefore be poorly transferable to Iraqi and broader Arab populations, where the ancestral admixture background occupies an intermediate position in the global human genetic landscape. Studies from Saudi Arabia (AlRasheed et al., 2025), Egypt (Selim et al., 2018), and Peru (Oscanoa et al., 2024) confirm this population-level heterogeneity, yet no study has characterized VKORC1 –1639G>A specifically in Iraqi patients with warfarin-requiring hematological disorders.

Furthermore, patients with hematological conditions — particularly those with concurrent inflammatory states such as MPNs, lymphomas, or hematological malignancies — present additional pharmacodynamic complexity not captured by VKORC1 and CYP2C9 pharmacogenetics alone. Inflammatory cytokines modulate hepatic synthesis of clotting factors, vitamin K-dependent protein production, and CYP enzyme expression, suggesting that inflammatory genetics may independently contribute to warfarin pharmacodynamics in these patients (Evangelidis et al., 2025; Li et al., 2025).

The present study was designed to: (1) characterize VKORC1 –1639G>A allele and genotype frequencies in a well-defined Iraqi cohort of patients with hematological disorders compared to healthy controls; (2) quantify the effect of VKORC1 genotype on warfarin daily maintenance dose and TTR; (3) assess VKORC1 genotype contributions to bleeding and thromboembolic outcomes; and (4) evaluate the independent and combined predictive performance of VKORC1 within a multi-locus pharmacogenetic-cytokine dosing model. These findings address a critical knowledge gap and provide the foundational data necessary for precision anticoagulation implementation in hematological clinical practice across Iraq and the wider Middle Eastern region.

2. Materials and Methods

2.1. Study Design and Participants

This prospective case-control study was conducted between January 2023 and December 2024 at Al-Sadder Teaching Hospital and the University of Kufa Medical Center, Najaf, Iraq. Ethical approval was granted by the Institutional Review Board of the University of Kufa, College of Medicine (Protocol No. KUF-IRB-2022-047), and all participants provided written informed consent in accordance with the Declaration of Helsinki.

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Cases (n = 320) comprised adult patients (≥18 years) with established hematological conditions requiring chronic warfarin anticoagulation, including: DVT/PE (n = 128), myeloproliferative neoplasms with thrombotic complications (n = 74), atrial fibrillation associated with hematological disorders (n = 68), and mechanical heart valve replacement in patients with underlying hematological disease (n = 50). Eligibility required stable warfarin therapy — defined as a consistent dose maintaining INR within the target range of 2.0–3.0 for ≥3 consecutive clinic visits over a minimum of 3 months. Exclusion criteria included hepatic or renal dysfunction (ALT >3× ULN; creatinine >1.5× ULN), use of medications with known warfarin pharmacokinetic interactions, or refusal to provide genetic consent.

Controls (n = 280) were age- and sex-matched healthy Iraqi volunteers without personal or family history of hematological disorders, thromboembolism, or cardiovascular disease, and not receiving any anticoagulant, antiplatelet, or immunosuppressive therapy.

2.2. Clinical and Laboratory Data Collection

All patients underwent standardized clinical assessment covering demographic characteristics, comorbidities, concomitant medications, anticoagulation indication, and duration of warfarin therapy. Laboratory parameters including complete blood count (CBC), INR, liver function tests (LFTs), and renal function tests were recorded at baseline and at each follow-up visit. Warfarin daily maintenance dose was defined as the stable dose maintaining INR within the therapeutic target range (2.0–3.0). TTR was calculated using the Rosendaal linear interpolation method over a minimum 6-month follow-up period (Rosendaal et al., 1993). Bleeding events were classified by International Society on Thrombosis and Haemostasis (ISTH) criteria as major or clinically relevant non-major bleeding. Thromboembolic events were documented as objectively confirmed new or recurrent venous or arterial thromboembolism.

2.3. DNA Extraction and VKORC1 Genotyping

Genomic DNA was extracted from 5 mL of EDTA-anticoagulated peripheral venous blood using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) per the manufacturer's protocol. DNA quantity and purity were assessed by NanoDrop spectrophotometry (A260/A280 ratio 1.8–2.0; Miller et al., 1988).

VKORC1 –1639G>A (rs9923231) was genotyped using tetraprimer amplification refractory mutation system PCR (T-ARMS-PCR) with outer primers (outer forward: 5'-GCCAGCAGGAGAGGGAAATA-3'; outer reverse: 5'-AGTTTGGACTACAGGTGCCC-3') and inner allele-specific primers. The T-ARMS-PCR generated a 247-bp fragment for the G allele and a 184-bp fragment for the A allele, with an outer control band of 399 bp. PCR products were resolved on 2% agarose gels stained with ethidium bromide and visualized under UV illumination. A random 15% subset of samples was re-genotyped by a blinded second operator; concordance was 99.6%. All genotyping was performed blinded to clinical data (Perrey et al., 1999).

2.4. Statistical Analysis

Hardy-Weinberg equilibrium (HWE) was assessed for VKORC1 –1639G>A in control subjects using chi-square goodness-of-fit test. Allele and genotype frequencies between cases and controls were compared using chi-square or Fisher's exact tests. Associations between VKORC1 genotype and warfarin daily dose requirements were analyzed by one-way ANOVA with post-hoc Bonferroni correction. Logistic regression models (unadjusted and adjusted for age, sex, BMI, indication for anticoagulation, and concomitant medications) were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for bleeding and thromboembolic outcomes. Multiple linear regression was performed to construct pharmacogenetic and multi-locus dosing models, with the coefficient of determination (R^2) as the explained variance metric. Linkage disequilibrium between VKORC1 and co-studied cytokine polymorphisms was assessed using D' and r^2 statistics. All analyses were conducted using SPSS version 26.0 (IBM Corp.) and R version 4.3.1; statistical significance was set at $p < 0.05$ (two-tailed).

3. Results

3.1. Baseline Characteristics

The clinical characteristics of the 320 cases and 280 healthy controls are summarized in Table 1. Cases and controls were well-matched for age (mean 47.2 ± 14.8 vs. 46.9 ± 13.5 years; p = 0.83) and sex (55.3% male in cases, 53.9% male in controls; p = 0.73). The mean warfarin daily maintenance dose was 4.6 ± 1.9 mg/day (range: 1.0–12.0 mg/day). Mean TTR over the follow-up period was 61.4 ± 16.2%. During follow-up, 48 patients (15.0%) experienced at least one major or clinically relevant bleeding event, and 29 patients (9.1%) experienced a new or recurrent thromboembolic event.

Table 1. Baseline Clinical Characteristics of Cases and Controls

Characteristic	Cases (n = 320)	Controls (n = 280)	p-value
Age, years (mean ± SD)	47.2 ± 14.8	46.9 ± 13.5	0.83
Male sex, n (%)	177 (55.3)	151 (53.9)	0.73

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BMI, kg/m² (mean ± SD)	27.1 ± 4.2	26.8 ± 3.9	0.41
DVT/PE, n (%)	128 (40.0)	---	---
MPN, n (%)	74 (23.1)	---	---
AF + hematological, n (%)	68 (21.3)	---	---
Mechanical valve, n (%)	50 (15.6)	---	---
Mean warfarin dose, mg/day (± SD)	4.6 ± 1.9	---	---
TTR, % (± SD)	61.4 ± 16.2	---	---
Major bleeding, n (%)	48 (15.0)	---	---
Thromboembolic events, n (%)	29 (9.1)	---	---

DVT: deep vein thrombosis; PE: pulmonary embolism; MPN: myeloproliferative neoplasm; AF: atrial fibrillation; TTR: time in therapeutic range; SD: standard deviation.

3.2. VKORC1 –1639G>A Genotype and Allele Frequencies

The VKORC1 –1639G>A polymorphism was in Hardy-Weinberg equilibrium in controls (p = 0.41). Genotype and allele frequencies are presented in Table 2. In cases, the GG, GA, and AA genotype frequencies were 43.1%, 38.5%, and 18.4%, respectively. In controls, GG: 47.9%, GA: 39.3%, AA: 12.9%. The VKORC1 –1639 AA genotype was significantly more prevalent in cases compared to controls (OR = 1.59; 95% CI: 1.00–2.54; p = 0.048). The A allele frequency in cases (37.7%) was significantly higher than in controls (32.1%; OR = 1.28; 95% CI: 1.02–1.60; p = 0.031).

Table 2. VKORC1 –1639G>A Genotype and Allele Frequencies in Cases and Controls

Genotype/Allele	Cases n (%)	Controls n (%)	OR (95% CI)	HWE p	p-value
GG	138 (43.1)	134 (47.9)	**Reference**	0.41	---
GA	123 (38.5)	110 (39.3)	1.08 (0.75–1.56)	---	0.66
AA	59 (18.4)	36 (12.9)	1.59 (1.00–2.54)	---	0.048
G allele	62.3%	67.9%	**Reference**	---	---
A allele	37.7%	32.1%	1.28 (1.02–1.60)	---	0.031

OR: odds ratio; CI: confidence interval; HWE: Hardy-Weinberg equilibrium.

3.3. Effect of VKORC1 Genotype on Warfarin Dose Requirements

VKORC1 –1639G>A genotype exerted a highly significant dose-gene effect on warfarin maintenance dose requirements (Table 3). Patients with the AA genotype required the lowest mean daily dose (2.8 ± 0.9 mg/day), compared to GA heterozygotes (4.4 ± 1.3 mg/day) and GG homozygotes (5.7 ± 1.4 mg/day; p < 0.001 for all pairwise comparisons by ANOVA with Bonferroni correction). This represents a 51% dose reduction in AA vs. GG carriers. In multiple linear regression incorporating age, sex, BMI, warfarin indication, and CYP2C9 genotype alongside VKORC1 genotype, VKORC1 was the single largest contributor to explained variance (partial R^2 = 0.312), with the overall model explaining 48.7% of dose variability (R^2 = 0.487). Addition of cytokine gene polymorphisms (TNF-α, IL-6, IL-10) to this pharmacogenetic-clinical model increased total explained variance to 61.3% (R^2 = 0.613).

Table 3. VKORC1 –1639G>A Genotype and Warfarin Daily Maintenance Dose

VKORC1 Genotype	n	Mean Daily Dose (mg ± SD)	p-value vs. GG Reference
GG (reference)	138	5.7 ± 1.4	---
GA	123	4.4 ± 1.3	<0.001
AA	59	2.8 ± 0.9	<0.001

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p-values by ANOVA with post-hoc Bonferroni correction. SD: standard deviation.

3.4. VKORC1 Genotype and Clinical Outcomes

VKORC1 AA genotype carriers demonstrated a significantly lower mean TTR compared to GG carriers (58.1 ± 15.3% vs. 63.7 ± 16.4%; p = 0.031), potentially reflecting the heightened challenge of dose titration at ultra-low maintenance doses. In adjusted logistic regression, VKORC1 AA genotype was associated with a non-significant trend toward increased major bleeding (OR = 1.38; 95% CI: 0.79–2.40; p = 0.26), though this did not reach statistical significance after correction for multiple comparisons. No significant association was observed between VKORC1 genotype and thromboembolic events independent of CYP2C9 and cytokine covariates.

3.5. Multi-Locus Dosing Model

In the six-locus pharmacogenetic-cytokine multiple linear regression model (Table 4), VKORC1 genotype retained the largest standardized regression coefficient (β = −0.42; partial R^2 = 0.312; p < 0.001), followed by CYP2C9 genotype (partial R^2 = 0.119), age (partial R^2 = 0.073), body surface area (partial R^2 = 0.052), and inflammatory cytokine genotypes (TNF-α partial R^2 = 0.031; IL-10 partial R^2 = 0.026). VKORC1 was not in significant linkage disequilibrium with any cytokine polymorphism studied (D' < 0.15; p > 0.05), confirming independent predictive contributions.

Table 4. Multiple Linear Regression Model for Warfarin Daily Dose Prediction

Variable	β	SE	Standardized β	p-value	Partial R^2
Intercept	8.42	0.84	---	<0.001	---
VKORC1 genotype	-1.47	0.11	-0.42	<0.001	0.312
CYP2C9 genotype	-0.84	0.14	-0.22	<0.001	0.119
Age (years)	-0.032	0.006	-0.18	<0.001	0.073
Body surface area (m^2)	+0.61	0.18	+0.12	0.001	0.052
TNF-α genotype	-0.28	0.11	-0.09	0.013	0.031
IL-10 genotype	-0.22	0.09	-0.08	0.019	0.026
Overall model R^2				**<0.001**	**0.613**

β: unstandardized regression coefficient; SE: standard error.

4. Discussion

4.1. VKORC1 –1639G>A as the Dominant Pharmacogenetic Determinant

This study confirms that VKORC1 –1639G>A is the primary genetic determinant of warfarin dose requirements in Iraqi patients with hematological disorders, accounting for 31.2% of total dose variance as a single locus. The dose-gene gradient observed — GG (5.7 mg/day), GA (4.4 mg/day), AA (2.8 mg/day) — exhibits a clear codominant pattern consistent with the established mechanistic model of allele-dose-dependent VKORC1 promoter suppression. This is fully concordant with foundational pharmacogenomic studies (D'Andrea et al., 2005; Sconce et al., 2005; Wadelius et al., 2009) and with contemporary validation across multiple ethnic cohorts including Saudi (AlRasheed et al., 2025), Egyptian (Selim et al., 2018), and Peruvian (Oscanoa et al., 2024) populations. These findings provide the first such confirmation in an Iraqi hematological cohort, substantially reinforcing the universality of the VKORC1 pharmacogenetic effect.

The VKORC1 –1639A allele frequency of 37.7% in our patient cohort occupies a biologically and clinically meaningful intermediate position between the Caucasian (approximately 40%), Asian (approximately 67%), and African (approximately 11%) reference ranges (IWPC et al., 2009; Wadelius et al., 2009). This intermediate allele frequency directly implies that VKORC1 genotype-guided dosing will have significant clinical impact in the Iraqi population: a substantial proportion of patients carry the dose-reducing AA genotype and risk over-anticoagulation when initiated on standard Caucasian-derived empirical doses. Conversely, GG carriers may be under-anticoagulated on the same regimen. Existing CPIC dosing recommendations for VKORC1 are derived primarily from non-Arab populations and require recalibration using ethnic-specific allele frequency priors for maximal clinical utility (Johnson et al., 2011).

The VKORC1 –1639G>A molecular mechanism is well characterized. The variant disrupts a transcription factor binding site in the VKORC1 gene promoter region, reducing mRNA transcription rates in hepatic cells and thereby decreasing steady-state VKORC1 enzyme protein levels. With less target enzyme available, pharmacologically active S-warfarin achieves greater proportional inhibition of vitamin K recycling at lower plasma concentrations, shifting the warfarin dose-response curve leftward (D'Andrea et al., 2005; NCBI, 2018). This mechanistic clarity provides a strong rationale for genotype-guided dosing that is independent of ethnic background, and our Iraqi population data support extending this mechanistic principle to the Middle Eastern context.

4.2. VKORC1 Genotype and Time in Therapeutic Range

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The lower mean TTR observed in VKORC1 AA carriers (58.1% vs. 63.7% in GG; p = 0.031) warrants careful clinical consideration. While pharmacogenetic dosing algorithms are designed to minimize supratherapeutic INR events in sensitive patients, our data suggest that practical TTR is lower in AA carriers despite stable dosing, potentially reflecting the heightened consequence of any dietary vitamin K fluctuation, concurrent medication change, or illness episode in a patient on ultra-low warfarin doses (2.8 mg/day mean). Even small absolute dose changes represent proportionally larger relative dose adjustments at the lower end of the warfarin dosing range, increasing INR volatility. This underscores that VKORC1 genotyping must be complemented by more frequent INR monitoring protocols for AA carriers, particularly during the initiation phase and following any clinical perturbation (Hamberg and Wadelius, 2014).

4.3. Contribution to the Multi-Locus Dosing Framework

The central clinical contribution of this study is the demonstration that VKORC1 –1639G>A serves as the anchor locus for a six-gene pharmacogenetic-cytokine dosing algorithm achieving $R^2 = 0.613$ — substantially exceeding VKORC1 and CYP2C9 alone ($R^2 = 0.487$), which already outperforms clinical-factor-only models (Pirmohamed, 2023; Ma and Lu, 2011). The additional 6.2 percentage points of explained variance contributed by cytokine gene polymorphisms (TNF-α, IL-6, IL-10) represents clinically meaningful precision improvement. Each percentage point of unexplained dose variance may translate to periods of subtherapeutic or supratherapeutic anticoagulation in individual patients, with attendant risks of thromboembolism or hemorrhage (Hamberg et al., 2010; Kitzmiller et al., 2011). In patients with hematological disorders — who may already carry elevated baseline thrombotic or hemorrhagic risk from their underlying condition — these precision increments are particularly consequential.

Our findings support several evidence-based clinical recommendations. First, VKORC1 –1639G>A genotyping should be implemented as a standard pre-prescription pharmacogenetic test for Iraqi patients commencing warfarin therapy for hematological indications, consistent with CPIC Level A guidance (Johnson et al., 2011). Second, patients identified as AA carriers should be initiated on doses at the lower range of evidence-based recommendations (approximately 2–3 mg/day initiation), with INR monitoring within 3–5 days of initiation. Third, the IWPC and pharmacogenetic dosing algorithms should be prospectively validated and ethnicity-recalibrated using Iraqi population allele frequency data. Fourth, future implementation studies should evaluate whether genotype-guided warfarin initiation improves TTR, reduces time to stable anticoagulation, and decreases bleeding and thromboembolic event rates in this population compared to standard empirical initiation.

Several limitations of this study should be acknowledged. Although sample size was adequate for the primary pharmacogenetic outcomes, the study was conducted at a single center in Najaf, potentially limiting generalizability across the geographic and ethnic diversity of the Iraqi population. CYP4F2 (V433M) genotype, which contributes modestly to warfarin dose variability particularly in vitamin K-enriched diets common in the Middle East, was not assessed. Serum cytokine levels were not measured in all participants, preventing direct genotype-phenotype functional correlation. Dietary vitamin K intake was estimated but not precisely quantified, representing a residual confounding variable. Finally, the cross-sectional assessment of stable warfarin dose does not capture intra-individual dynamic variability during disease flares (Metzger et al., 2006).

5. Conclusions

This study establishes that VKORC1 –1639G>A (rs9923231) is the dominant pharmacogenetic determinant of warfarin dose requirements in Iraqi patients with hematological disorders, explaining 31.2% of total dose variance as a single locus. The intermediate A allele frequency of 37.7% — distinct from both Caucasian and Asian reference populations — demonstrates the necessity of population-specific pharmacogenetic characterization and algorithm recalibration for the Middle Eastern clinical context. Integration of VKORC1 within a six-locus pharmacogenetic-cytokine model further enhances predictive accuracy to 61.3% of dose variance, supporting a precision anticoagulation framework that extends beyond conventional pharmacogenetics. These data provide the strongest yet evidence base for urgent clinical implementation of VKORC1-guided warfarin dosing in hematological practice across Iraq and the wider Middle Eastern region.

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