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Original Research Article

Effect of CYP2C9 and VKORC1 genetic polymorphisms on warfarin dose requirement in Central China Han populations

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Abstract

Purpose: *To investigate the frequency of CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) and determine the effect of these genetic factors on weekly warfarin dose requirement in Central China Han populations.*
Methods: *A total of 333 hospitalized patients with deep venous thrombosis after minimally invasive surgery were enrolled in this study. Genotypes of VKORC1 and CYP2C9 were analyzed by polymerase chain reaction (PCR)-DNA Chip method. Multiple linear regression analysis was used to explore the impact on weekly warfarin dose requirement.*
Results: *The allele frequencies of VKORC1 -1639 G and VKORC1 -1639 A were 0.105 and 0.895, respectively, whereas no genotype of CYP2C9*1*2, CYP2C9*2*2 and CYP2C9*3*3 were found, and the allele frequencies of CYP2C9*1, CYP2C9*2 and CYP2C9*3 were 0.943, 0.015 and 0.042, respectively. Multiple linear regression analysis indicated that several factors including VKORC1 -1639 G>A, CYP2C9*2, CYP2C9*3, age, body mass index (BMI) and amiodarone use may explain the 47.2 % of individual variations in the weekly warfarin doses requirement.*
Conclusion: *There is no significant difference in the frequency of VKORC1 (-1639 G>A), CYP2C9*2 and CYP2C9*3 compared to those of Asian populations, but there is significant difference when compared with those of Europeans and Caucasians. Considering VKORC1 -1639 G>A, CYP2C9*2, and CYP2C9*3 genetic polymorphisms as well as age, BMI and amiodarone use may explain the 47.2% of individual variations in the weekly warfarin doses requirement..*

Keywords: *Warfarin, CYP2C9, VKORC1, Polymorphism, Body mass index, International normalized ratio*

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INTRODUCTION

Warfarin, a vitamin K antagonist, is a highly effective and commonly oral anticoagulation therapy, but it has a narrow therapeutic index. Under-anticoagulation or over-anticoagulation increased the risk of thrombosis and bleeding, respectively [1]. The international normalized ratio (INR) plays an important role in the efficacy and safety of warfarin treatment, thus, dosage

adjustments are often necessary [2]. The variability in warfarin therapy is a multifactorial issue. Clinical and environmental variables, and genetic variation play important roles in the warfarin response [3]. The FDA requires manufacturers to revise the warfarin label based on genetic polymorphisms in vitamin K epoxide reductase subunit C1 (VKORC1) and CYP2C9 in January 2010 [4].

Warfarin is a racemic mixture including S- and R-enantiomers. The S-warfarin enantiomer is metabolized by CYP2C9, whereas R-warfarin enantiomer is metabolized by various CYPs, such as CYP1A1, CYP1A2, CYP3A4 [3]. S-warfarin plays a more important role than R-warfarin [5]. CYP2C9*2 and CYP2C9*3 are common variants with reduced activity, and result in decrease warfarin doses requirement [6]. Both R- and S-warfarin inhibit the VKORC1 and prevent the activation of coagulation factors, thus exerting its anticoagulant effect [7]. VKORC1 (-1639 G>A) reduces the expression of VKORC1, resulting in sensitivity to warfarin and resistance of warfarin [3].

CYP2C9 and VKORC1 mutations, as well as age and body mass index (BMI) can explain 40~63% of individual variations in warfarin doses requirement [2]. However, genetic effects on warfarin dosing vary among different ethnic groups, live regions, lifestyle, culture, and dietary habits. Till date, no studies have been performed in the Central China Han population. The aim of this study was to determine the prevalence of allelic variants of VKORC1, CYP2C9 and their effect on warfarin dosage in Central China Han populations, providing a helpful clinical indicator for the safe dosage of warfarin.

MATERIALS AND METHODS

Patients

From December 2015 to October 2017, 333 patients were recruited from the Hospital of Hubei with deep venous thrombosis after the minimally invasive surgery, with an average age of 43 years. They were receiving stable weekly doses of warfarin, within a stable INR from 2 and 3.0 for at least 3 weeks. Mean weekly warfarin requirement was from 7 to 36 mg. Patients had no hepatic or renal diseases. Exclusion criteria included: hematological disease or hemorrhagic tendencies. The Ethics Committee of the Hospital of Hubei approved this study (approval no. 20151201). All participants signed an informed consent in compliance with the guidelines of Declaration of Helsinki [8].

Data collection

The medical variables were collected including gender, age, BMI, warfarin dose, INR values, alcohol drinking, and smoking status, medication history, concomitant diseases.

Genotyping

DNA was extracted with TIANamp Blood DNA Kit (Tiangen, China). The polymerase chain reaction (PCR)- DNA Chip method was used to determine the polymorphisms in VKORC1 (rs9923231) and CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910). Sanger sequencing was used to confirm the above results.

Statistical analysis

Data was performed using SPSS 19.0 (SPSS, Inc, Chicago, IL, USA). Continuous variables were presented as means ± standard deviation (SD), and analyzed using independent-samples t-test, or ANOVA. Categorical variables were expressed as frequencies and percentages, and analyzed using Chi-square analyses. $P<0.05$ was accepted as statistically significant.

RESULTS

Clinical characteristics

A total of 333 patients with deep venous thrombosis were enrolled to this study, including 137 males (41.14 %) and 196 females (58.86 %), the age ranged from 21 to 78 years (a mean age of 43.26±12.56 years). Average body mass index (BMI) of the 333 patients was 24.68±4.69 kg/m^2. Average warfarin maintenance dose ranged from 7 to 36mg/week. Body surface area (BSA) of patients ranged from 1.26 to 2.43 m^2, with a mean of 1.65 ± 0.85 m^2. 333 patients had controlled their INR values ranged from 1.5 to 3.0. Patient characteristics are summarized in Table 1.

Table 1: Patient characteristics

Variable	Patients (n=333)
Age (mean±SD, years)	43.26±12.56
Gender (female, n, %)	196 (58.86)
BMI (kg/m^2)	24.68±4.69
BSA (m^2)	1.65 ± 0.85
Smoking (n, %)	84 (25.23)
Drinking (n, %)	41 (12.31)
Amiodarone use (n, %)	25 (7.51)
Enzyme inducers (n, %)	11 (3.30)
INR	2.35±0.78
Maintenance dose (mg/week)	20.65±12.26

Genotype, allele frequencies and ethnicity

Genotype frequencies did not reveal deviations from Hardy-Weinberg equilibrium. For the VKORC1 gene, frequencies of genotype GG, AG and AA were 0.015, 0.180 and 0.805, respectively, and allele frequencies of G and A were 0.105 and 0.895, respectively, the frequency of allele G was significantly lower than Caucasian, English, French, Brazil, Chinese Uygur and Greek, and similar to Thai, Taiwan and West China (Table 2).

For the CYP2C9 gene, frequencies of genotype, *1*1, *1*2, *1*3 *2*2, *2*3 and *3*3 were 0.916, 0, 0, 0.069, 0.015 and 0, respectively, and the allele frequencies of *1,*2 and *3 were 0.943, 0.015 and 0.042, respectively, which were significantly different among Khorasan, Gorgan, Tunisian, Caucasian and Egyptian, and similar to Japanese and Korean (Table 3).

Impact of *VKORC1* -1639 G/A, CYP2C9*2 and CYP2C9*3 SNPs on the weekly stable warfarin dose

The association of the mean weekly warfarin dosage in patients with various genotype is shown in Table 4 and Figure 1. The mean weekly warfarin dosage in patients with VKORC1 GA genotype was significantly higher than those of AA genotype (28.2±8.5 *vs* 18.9±6.8 mg/weekly; *P*< 0.001), while the wild type carrier of VKORC1 -1639 GG required a much higher dose than the GA or AA carriers (38.6±7.7 *vs* 28.2±8.5 mg/weekly, 38.6±7.7 *vs* 18.9±6.8 mg/weekly, respectively, all *P*< 0.001). The mean weekly warfarin dosage in patients with CYP2C9*1/*3 genotype was significantly higher than those of *2/*3 genotype (15.1±4.9 *vs* 9.1±3.2 mg/weekly; *P*< 0.001), while the wild type carrier required a much higher dose than the CYP2C9*1/*3 or CYP2C9*2/*3 carriers (23.2±8.6 *vs* 15.1±4.9 mg/weekly, 23.2±8.6 *vs* 9.1±3.2 mg/weekly, respectively, all *P*< 0.001).

Contribution of demographic characteristics and genotype variation to the weekly stable warfarin dose

Multiple linear regression analysis for variables (demographic characteristics and genotype) responsible for the weekly stable warfarin doses. Our data indicated that several factors including VKORC1 -1639 G/A, CYP2C9*2, CYP2C9*3, age, BMI and amiodarone use could explain 47.2% of individual variations in warfarin doses

Table 2: Genotype distributions and allele frequencies of *VKORC1* -1639 G/A in different races

Race	*VKORC1*–1639 G/A Genotype			*VKORC1*–1639 G/A Alle frequency	
	GG	AG	AA	G	A
Caucasian population [9]	0.39	0.47	0.14	0.72	0.38
English population [10]	0.19	0.56	0.25	0.53	0.47
French population [11]	0.22	0.35	0.43	0.58	0.42
Brazil population [12]	0.495	0.411	0.094	0.70	0.30
Thai [13]	0.028	0.280	0.692	0.168	0.832
Chinese Uygur population [8]	0.09	0.58	0.33	0.38	0.62
Taiwan Han population [9]	0.00	0.18	0.82	0.09	0.91
West China Han populations [14]	0.004	0.19	0.80	0.10	0.90
Greek-Cypriot population [15]	0.230	0.473	0.297	0.466	0.534
Present study	0.015	0.180	0.805	0.105	0.895

Table 3: Distribution of genotype frequencies of CYP2C9*2 and CYP2C9*3 in different races

Race	CYP2C9 genotype frequency					
	*1*1	*1*2	*2*2	*1*3	*2*3	*3*3
Southern Khorasan population [16]	0.641	0.158	0	0.175	0.025	0
Sistani Ethnic Group in Gorgan [17]	0.539	0.221	0.029	0.114	0.043	0
Uruguayan Caucasian population [18]	0.68	0.22	0.02	0.08	0	0
Bangladeshi population [19]	0.92	0	0	0.046	0	0.034
Iranian Baluch Ethnic Group [20]	0.709	0.118	0.455	0.818	0.273	0.182
Ghanaian population [3]	1.00	0	0	0	0	0
Tunisian population [21]	0.616	0.194	0.027	0.132	0.031	0
Japanese [22]	0.87	0	0	0.13	0	0
Korean [22]	0.86	0	0	0.14	0	0
Caucasian [22]	0.67	0.17	0.03	0.13	0	0
Egyptian population [23]	0.664	0.19	0.024	0.117	0	0.04
Present study	0.916	0	0	0.069	0.015	0

Table 4: Weekly doses of warfarin in patients with various genotypes

Genotype	Number (%)	Weekly doses (mg, mean±SD)
VKORC1 -1639 G/A		
Genotype		
GG	5 (1.5)	38.6±7.7
GA	60 (18.5)	28.2±8.5
AA	268 (80.0)	18.9±6.8
CYP2C9		
Genotype		
*1/*1	305 (91.6)	23.2±8.6
*1/*2	0 (0)	-
*1/*3	23 (6.9)	15.1±4.9
*2/*2	0 (0)	-
*2/*3	5 (1.5)	9.1±3.2
*3/*3	0 (0)	-

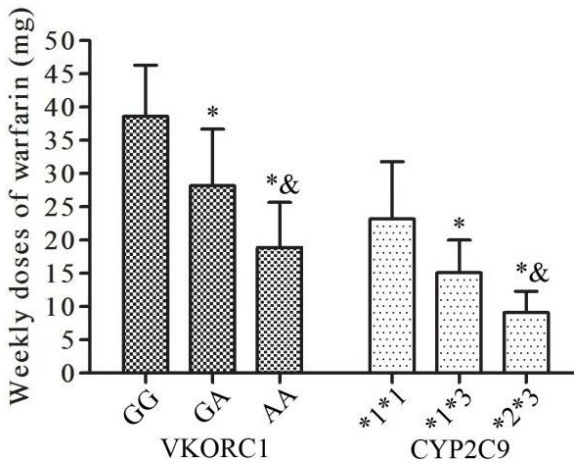

Figure 1: Weekly doses of warfarin (mean ± SD, mg) in patients with various genotypes. The differences in warfarin dose between the various genotypes were analyzed by one-way ANOVA; for VKORC1, compared with GG, $^{*}p < 0.001$, compared with GA, $^{\&}p < 0.001$; for CYP2C9, compared with *1*1, $^{*}p < 0.001$, compared with *1*3, $^{\&}p < 0.001$

Table 5: Demographic and genetic variables responsible for stable weekly warfarin dose by multiple linear regression

Variable	Standardized coefficient	Contribution (%)	*P*-value
Age	-0.162	8.6	< 0.001
BMI	0.035	2.6	< 0.001
VKORC1 (-1639 G/A)	-16.529	25.2	< 0.001
CYP2C9*2	-9.582	2.2	< 0.001
CYP2C9*3	-12.85	5.1	< 0.001
Amiodarone use	-6.905	3.5	< 0.001

requirement (Table 5). Age, amiodarone use, genotypes of VKORC1 -1639 G>A, CYP2C9*2, CYP2C9*3 were negatively associated with weekly stable warfarin doses; VKORC1 -1639 G/A contributed the most (25.2 %) to individual variations in warfarin doses requirement.

DISCUSSION

VKORC1 and CYP2C9 genetic polymorphisms, age, BMI and concomitant drugs affect warfarin stable dose requirements, however, about 50 % of warfarin dose variation remaining unexplained [24]. Most studies mainly focused on the warfarin stable dose, but neglected the initial response to warfarin therapy, patients with over- or under-anticoagulation increase the risk of bleeding or thrombosis. 333 Central Chinese patients undergoing warfarin therapy participated in our present study, we monitored a wider range of outcomes of the patients from initiation to a 6-month follow-up. Our data indicated that several factors including VKORC1 -1639 G/A, CYP2C9*2, CYP2C9*3, age, BMI and amiodarone use could explain 47.2 % of individual variations in the weekly stable warfarin doses. Our study is the first to assess impact of genetic polymorphisms of CYP2C9, VKORC1, enzyme inhibitor (amiodarone) and BMI on warfarin dose requirements in Central China Han populations.

Our study showed that the frequencies of allele G and A of VKORC1 gene were 0.105 and 0.895, respectively, and the allele frequencies of *1, *2 and *3 of CYP2C9 were 0.943, 0.015 and 0.042, respectively. The allele frequencies of G of VKORC1, CYP2C9*2 and CYP2C9*3 were significantly different among European and Caucasian populations, but similar to Asian populations (Table 2 and Table 3). Furthermore, the weekly warfarin doses requirement of patients with VKORC1, CYP2C9 wild type were significantly higher than those of with the mutant types ($p < 0.001$).

In this present study, we found that VKORC1 (-1639 G>A), CYP2C9 *2 and *3 are the major genetic factors of warfarin dose which confirmed the previous findings [9]. Bourgeois *et al* found that beyond VKORC1 and CYP2C9, other genetic factors are unlikely associated with the variance in warfarin dose [24]. Our study found that VKORC1 -1639 G/A could explain 25.2 % of individual variations in the weekly stable warfarin doses which also confirmed the previous studies, and the VKORC1 -1639 G/A polymorphism contributed the most to individual variance [24].

In this present study, the contribution of VKORC1 (25.2 %) was greater than those of CYP2C9 (7.3 %), which confirmed the previous findings [13]. Until now, some previous studies reported that the contribution of CYP2C9*3 ranged from 1.7~6.0 % in Asians [13], however, the CYP2C9*3 explained 5.1 % of the weekly stable warfarin dose variance in our study, which was lower than Caucasian populations (12.9 %) [24]. In Asians, CYP2C9*2 mutation is rare and CYP2C9*3 mutation frequency is relatively lower [25], therefore, the CYP2C9*3 allele accounted for a lower proportion compared with Caucasians.

In the present study, we found that non-genetics factors including age, BMI and amiodarone use explained 14.7 % of individual variations in the weekly warfarin doses requirement, which were similar to the results previously reported [13]. Compared with genetic factors, the contribution of non-genetics factors to explain the warfarin dose variance is lower. In non-genetic factors, age accounted for the largest proportion (8.6 %) to the weekly warfarin doses variance, which was similar to previous report [13]. In addition, BMI and amiodarone explained 2.6 % and 3.5 % of the dose variance, respectively. Therefore, this results may help the clinicians in considering VKORC1 -1639 G >A, CYP2C9*2, and CYP2C9*3 genetic polymorphisms as well as age, BMI and amiodarone use for individual variations in the weekly warfarin doses requirement, and reduce the rate of complications.

CONCLUSION

There is no significant difference in the frequency of VKORC1 (-1639 G>A), CYP2C9*2 and CYP2C9*3 compared to those of Asian populations, but there is significant difference when compared with those of Europeans and Caucasians. Considering VKORC1 -1639 G>A, CYP2C9*2, and CYP2C9*3 genetic polymorphisms and age, BMI and amiodarone use may explain the 47.2% of individual variations in the weekly warfarin doses requirement.

DECLARATIONS

Acknowledgement

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Conflict of interest

No conflict of interest is associated with this study.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Conceived and designed the experiments: Zhi-Jiang Li and Xu Liu. Performed the experiments: Zhi-Jiang Li and Xu Liu. Analyzed the data: Xu Liu. Wrote the paper: Zhi-Jiang Li and Xu Liu.

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