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Novel SNP in *CYP2C9* is associated with changes in warfarin clearance and *CYP2C9* expression levels in African Americans

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Abstract

Warfarin is a widely used anticoagulant whose active *S*-enantiomer is primarily metabolized by the *CYP2C9* enzyme. The *CYP2C9**2 and *CYP2C9**3 alleles are associated with lower warfarin dose requirement and decreased enzyme activity. In contrast, we previously identified a novel SNP (rs7089580 A>T) in *CYP2C9* that is associated with higher warfarin dose requirement in African Americans. In this study, we examine the effect of rs7089580 on warfarin pharmacokinetics and *CYP2C9* expression in 63 African American patients and 32 African American liver tissues, respectively. We found oral clearance of *S*-warfarin to be higher among carriers of the minor rs7089580 allele (T) compared to wild type homozygotes (3.73 ± 1.46 ml/min vs. 2.95 ± 1.39 ml/min, $p=0.04$). *CYP2C9* mRNA expression in liver tissue was also higher among A/T and T/T genotypes compared to A/A ($p<0.02$). Our findings indicate that rs7089580 is associated with higher *S*-warfarin clearance and *CYP2C9* expression and may help explain the higher dose requirement of warfarin in African Americans. Furthermore, rs7089580 is in complete linkage disequilibrium with the promoter SNP rs12251841 in African Americans which may provide a biologically plausible explanation for the observed effect on *CYP2C9* expression levels. Given the many clinically relevant substrates of *CYP2C9*, identifying polymorphisms that affect expression levels and metabolism across ethnicities is essential for individualization of doses with a narrow therapeutic index.

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Keywords

Warfarin; anticoagulant; African American; CYP2C9; oral clearance; SNP; rs7089580; pharmacokinetics

Introduction

Identifying ethnic-specific polymorphisms in drug-metabolizing enzymes is essential in bridging therapeutic doses and efficacy of drugs between ethnic groups. Warfarin is an anticoagulant used for the prevention or treatment of thromboembolic diseases. It is clinically supplied as a racemic mixture of equal amounts with the more potent *S*-enantiomer being responsible for the drug's anticoagulant effect.^{1, 2} CYP2C9 metabolizes >90% of *S*-warfarin thus playing an integral role in its clearance, and studies have identified several coding variants in *CYP2C9* that affect warfarin dose requirement.¹ Among these, *CYP2C9**2 (rs1799853) and *CYP2C9**3 (rs1057910) have been well-established as predictive of lower warfarin dose requirement and shown to reduce enzymatic activity by up to 30% and 80%, respectively, compared to the wild type enzyme.² However, both *CYP2C9**2 and *CYP2C9**3 are found at low frequencies in African Americans (AAs) and explain much less of the variation in dose as compared to Caucasian and Asian populations.³ A recent study reported *CYP2C9**8 (rs7900194), found almost exclusively in AAs, is also associated with lower warfarin doses and has been shown to decrease *CYP2C9* gene expression.⁴

Previously, we have shown a novel SNP located in intron 3 of *CYP2C9* (rs7089580) to be predictive of higher warfarin dose requirement in AAs, independent of other known genetic variants (*VKORC1* -1639G>A, *CYP2C9**2, *3, and *8).⁵ Bioinformatics analysis indicates that the presence of the A allele abolishes the site for several transcription factors (Nkx-2, PR B, PR A, and Max) which are present with the T allele. In addition, rs7089580 appears to be in complete linkage disequilibrium (LD, $r^2=1$) with rs12251841 which is located in the promoter region of *CYP2C9*.⁶ While there are population differences in the distribution of the rs7089580 T allele, the most striking difference is observed among Asian populations at 2% compared AAs at 19% according to HapMap (Supplementary Table 1). The incorporation of rs7089580, along with other genetic and clinical factors, into an African American-specific warfarin dosing algorithm explained a greater proportion of the variability in warfarin dose and showed greater accuracy in predicting high warfarin dose requirement in AAs as compared to the International Warfarin Pharmacogenetics Consortium (IWPC) pharmacogenomics and clinical algorithms.⁷ In this study, we evaluate the impact of rs7089580 on warfarin clearance in AAs on stable warfarin dose and *CYP2C9* gene expression in livers procured from healthy African American (AA) donors.

Methods

Patients

Among the AA patients on warfarin recruited from the University of Chicago and University of Illinois, Chicago, we were able to obtain plasma for 63 patients. Inclusion criteria were

self-described as AA ethnicity, age 18 years, international normalized ratio (INR) target of 2–3, and treatment with a stable dose of warfarin defined as the same dose for at least three consecutive clinic visits that produced an INR within the therapeutic range. None of the 63 patients reported missed warfarin doses within two weeks of enrollment. Biochemical and hematologic tests performed before the study ruled out evidence of hepatic impairment but indicated renal impairment in 8 patients (i.e., creatinine clearance ≤ 30 mL/min). Patients were not taking potent CYP2C9 inducers or inhibitors. The study protocol was approved by the respective Institutional Review Boards and informed consent was obtained from each patient. Patient characteristics are summarized in Table 1.

Measurement and analysis of warfarin pharmacokinetics

A venous blood sample was collected from each participant 12 to 16 hours after the last warfarin dose. The total and free warfarin plasma concentrations were determined by a stereoselective HPLC method and plasma unbound fractions by an ultra-filtration technique.⁸ Previously described analytical methods were used to determine plasma concentrations of respective warfarin enantiomers average $C_{p,ss}(R)$ and average $C_{p,ss}(S)$.⁹ The oral clearance (CL_{po}) values of both enantiomers were calculated according to the following equation:

$$CL_{po}(S \text{ or } R) = \left(D/2\tau / C_{p,ss} \right)$$

and unbound oral clearance ($CL_{po,u}$) of *S*-warfarin only was calculated as follows:

$$CL_{po,u}(S) = \left(D/2\tau / C_{u,ss} \right)$$

where *D* is the daily dose of racemic warfarin, a mixture of equal amounts of *R*- and *S*-warfarin thus *D*/2 is the daily dose of either *S*-warfarin or *R*-warfarin for CL_{po} ; τ is the dosing interval (i.e., 24 hours); $C_{p,ss}$ is the average total (bound plus unbound) plasma concentration of each enantiomer at steady state and $C_{u,ss}(S)$ is the average unbound plasma concentration of *S*-warfarin at steady state. $C_{u,ss}$ was calculated as the product of $C_{p,ss}(S)$ and plasma unbound fraction of *S*-warfarin. The $C_{p,ss}(R/S)$ describes the ratio of $C_{p,ss}$ of *R*- to *S*-warfarin. This formula assumes that plasma concentration measured 12–16 hours after dosing at steady state is very close to the average $C_{p,ss}$ value.⁹

CYP2C9 Liver Expression

Tissues from 34 AA adult livers were obtained from Life Technologies (Carlsbad, CA). *CYP2C9* mRNA levels were determined as previously described.¹⁰ The relative mRNA expression of *CYP2C9* was determined by comparing it against an arbitrarily chosen liver tissue after normalization of the *CYP2C9* gene expression levels to GAPDH using the 2^{-Ct} method.¹¹ The studies were performed in triplicate and the data was summarized as mean $\pm$ standard error (SE) values of all values.

Genotyping

All patients and liver samples were genotyped for *CYP2C9**2, *CYP2C9**3, *CYP2C9**8 using previously described methods.^{12, 13} For rs7089580, patients were genotyped through direct sequencing by PCR amplification of 1Kb overlapping fragments using a previously published method and primers.⁵ In addition, a panel of 105 ancestry informative markers (AIMs) was also genotyped for all patients to determine West African ancestry.¹⁴ Genotyping of AIMs was performed with the MassArray 7K HT genetic analysis system (Sequenom, Inc.)

Statistical analyses

Ancestry estimates were obtained from STRUCTURE 2.3.3 as previously described.¹⁵ Continuous variables were tested for normality as determined by the Kolmogorov–Smirnov normality test and only $CL_{po}(R)$ and $CL_{po,u}(S)$ were log-transformed to obtain normality prior to analysis. Warfarin clearance and plasma concentration between different genotypes were compared using univariate analysis. Comparisons between *CYP2C9* gene expression levels by genotype were determined by one-way analysis of variance. Demographic and clinical variables (Table 2) significantly associated with a pharmacokinetic parameter were adjusted for in the analysis. We corrected for body surface area (BSA) since physiologic parameters relevant to drug metabolism and elimination (e.g., renal and hepatic function) are proportional to BSA.¹⁶ Correlations between continuous clinical variables and pharmacokinetic parameters were assessed by means of linear regression analysis. For the association of variables between $CL_{po}(R)$ and $CL_{po,u}(S)$ parameters, we report the $\exp(\beta)$ which is the multiplicative term used to estimate the increase or decrease in $CL_{po}(R)$ and $CL_{po,u}(S)$.

Since the inclusion of *CYP2C9**2, *3, and *8 was to determine if our analysis should be conditioned on these variants, the threshold for statistical significance was set at $p < 0.05$ since we are testing one SNP. Statistical analysis was carried out using IBM SPSS Statistics version 19.0.0 (SPSS, Inc., Chicago, IL). LD between rs7089580 and rs12251841 was obtained *in silico* using the 1000 Genomes panel for Americans of African Ancestry in SW USA (ASW).⁶

We conducted all research according to The Code of Ethics of the World Medical Association (Declaration of Helsinki), written informed consent was obtained from all participants, and institutional review board was obtained from all participating institutions.

Results

Patient demographic and clinical characteristics are summarized in Table 1. The major indication for warfarin therapy was deep vein thrombosis and/or pulmonary embolism (70%) and the mean daily dose was 6.5 mg. While most patients were female (86%), after adjusting for BSA, sex was not found to be significantly associated with warfarin dose requirement nor warfarin clearance. The mean age was 56.7 (± 13.5) years and mean BSA was 2.02 m² (± 0.28) (Table 1). The minor allele frequencies (MAF) for rs7089580, *CYP2C9**2, *3, and *8 are also shown in Table 1. There were no homozygotes for the T

allele identified. Age was found to be inversely correlated with all warfarin kinetic parameters except $CL_{po}S$, which may be due to the sample size (Table 2). There was no significant correlation between percent West African ancestry and warfarin concentration and clearance levels (Table 2).

Genetic association with pharmacokinetic measures

Warfarin dose requirement was higher in rs7089580 T allele carriers compared to non-carriers, as previously reported.⁵ For patients carrying the A/T genotype, the daily warfarin dose (7.5 ± 3.0 mg) was significantly higher compared to patients carrying the A/A genotype (6.15 ± 2.5 mg), $p=0.03$ (Table 3). The effect of rs7089580 genotype on plasma *R*- and *S*-warfarin concentrations [$C_{pss}(R)$ and $C_{pss}(S)$, respectively] and clearance is also shown in Table 3. Among A/T carriers, $C_{pss}(R)$ levels were significantly higher (1.21 ± 0.43 $\mu\text{g/mL}$, $p=0.03$) and $C_{pss}(S)$ levels were also higher, though not significant, (0.82 ± 0.33 $\mu\text{g/mL}$) compared to A/A carriers (1.18 ± 0.58 $\mu\text{g/mL}$ and 0.79 ± 0.35 $\mu\text{g/mL}$, respectively). We found statistically significant differences in *S*-warfarin clearance between genotypes (Table 3). Oral clearance of *S*-warfarin [$CL_{po}(S)$ (ml/min)] was 26.4% higher in patients with the A/T genotype compared to A/A genotype patients. An increase in unbound oral *S*-warfarin clearance [$CL_{po,u}(S)$ (ml/min)] for A/T carriers was also found (Table 3). Our results suggest that a higher *S*-warfarin clearance rate may lead to higher warfarin dose requirement. Furthermore, rs7089580 was not associated with *R*-warfarin clearance (Table 3). The *CYP2C9**2, *3, and *8 SNPs were not found statistically significant to dose or any pharmacokinetic measure which may be due to our sample size (data not shown) nor are they in LD with rs7089580.

Gene expression association with genotype

The effect of rs7089580 genotype on *CYP2C9* gene expression was compared among 34 adult AA liver samples. Demographic and genotypic characteristics are found in Table 4. Most of the liver samples are from female donors (64.7%) and the mean age for all liver donors is 57.6 (± 10.8) years (Table 4). Figure 1 shows that *CYP2C9* expression levels were significantly different between genotypes. The *CYP2C9* mRNA expression levels for A/T (20.34 ± 27.4 ; $p=0.02$) and T/T (17.25 ± 19.8 ; $p=0.01$) genotypes were significantly higher compared to A/A (4.90 ± 4.4) genotype (Figure 1).

Discussion

The polymorphic *CYP2C9* enzyme is involved in metabolizing approximately 20% of all currently prescribed drugs.¹⁷ Polymorphisms within *CYP2C9* that affect enzymatic activity and lead to adverse response to *CYP2C9* substrates have been reported. Therefore, *CYP2C9* pharmacogenetics is important for maximal drug efficacy. We previously identified rs7089580 to be predictive of higher warfarin dose requirement in AAs.⁵ Here, we have replicated the association of rs7089580 with warfarin dose requirement in a separate AA population, where A/T patients required a higher daily dose compared to A/A patients (Table 3). Additionally, we found patients carrying the A/T genotype for rs7089580 had significantly higher oral clearance of *S*-warfarin (26.4%) compared to A/A carriers. The effect of rs7089580 on warfarin clearance is consistent with the effect on dose -- the T allele

of rs7089580 is predictive of higher warfarin dose requirement which may stem from a higher clearance rate. Furthermore, we found the T allele affects *CYP2C9* gene expression, where a significant increase in mRNA levels for A/T and T/T carriers is observed compared to A/A individuals (Figure 1). The effect observed of the T allele on *CYP2C9* expression levels is in accordance with the higher warfarin clearance found among patients carrying the T allele. As previously stated, rs7089580 is in LD with the promoter SNP rs12251841 and bioinformatics analysis for liver-specific *cis*-element clusters revealed rs12251841 is located in a *cis*-regulatory region for the transcription activator PXR/CAR.¹⁸ However, this remains to be experimentally validated and we recommend that both SNPs, rs7089580 and rs12251841, be genotyped to confirm LD. The estimation of steady state pharmacokinetics parameters for warfarin using a single plasma sample is a possible limitation. However, this model has been used previously and shown to estimate C_{ss} within 1–6% of the average concentration over a 24 hour period.¹⁹

In general, patients of African descent require higher mean warfarin doses of 6.7 mg/day and African American ethnicity has been found to be a predictor of warfarin doses 5 mg/day, whereas patients from the Far East (Chinese, Japanese, and Malay) require the lowest mean doses at 3.1 mg/day.^{20–25} In this study, we are the first to demonstrate that West African ancestry is not associated with warfarin pharmacokinetics in AAs but history of DVT/PE is significantly associated with a higher *S*-warfarin concentration ($\beta=0.21$, $p=0.03$) (Table 2). Furthermore, DVT/PE as an indication for taking warfarin is associated with higher dose requirement. This is not to say that different genetic variants, compared to other ethnicities, are not present in AAs and the genetic contribution to warfarin dose requirement in AAs needs to be further explored and identified. In conclusion, our study suggests that the rs7089580 T allele predicts an increased rate of warfarin metabolism, due to increased *CYP2C9* gene expression. These findings shed light on the mechanism underlying increased warfarin dose requirements in patients with the rs7089580 T allele.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

All authors have read the journal's authorship agreement. The manuscript has been reviewed and approved by all named authors. Editorial support for preparation of the manuscript was only provided by the authors.

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Background

Warfarin is the most commonly prescribed oral anticoagulant. We previously identified a novel SNP (rs7089580 A>T) in *CYP2C9* that is associated with higher warfarin dose requirement in African Americans. In this study, we examine the effect of rs7089580 in warfarin clearance and *CYP2C9* expression levels.

Translational Significance

The clinical implementation of pharmacogenetics by medical centers is growing. However, most of the available data are from people of European ancestry which poses challenges in the clinical translation for other populations. Our study is focused on African Americans and therefore, provides the opportunity to discover genetic contributions to drug response and metabolism that may be missed through European-only studies.

Figure 1. Effects of rs7089580 genotypes on CYP2C9 expression levels in human livers
Carriers of AT and TT genotypes had increased CYP2C9 expression levels. Box plots indicate 25th and 75th percentiles.

Table 1

Demographic, clinical, and genotypic characteristics of African American patients on stable warfarin dose.

Variable	N = 63
Warfarin dose, mg/d	6.5 ±2.7
Percent West African ancestry	82.1%
Female	85.7%
Male	14.3%
Age (years)	56.7 ±13.5
Weight (kg)	96.8 ±28.0
Height (cm)	165.22 ±8.4
Body surface area (m ²)	2.02 ±0.28
Creatinine clearance (ml/min)	59.02 ±22.51
Indication for warfarin	
Deep vein thrombosis/pulmonary embolism	69.8%
Stroke	14.3%
Atrial fibrillation	7.9%
Peripheral vascular disease	7.9%
Polymorphism	Minor Allele Frequency
rs7089580 (T allele)	15%
<i>CYP2C9</i> *2	5%
<i>CYP2C9</i> *33	0.08%
<i>CYP2C9</i> *83	11%

Values presented as mean ± SD

Table 2

Association of clinical and demographic variables to warfarin kinetic parameters (n=63).

Clinical Variable	C _{p,ss} R (µg/mL)	C _{p,ss} S (µg/mL)	C _{p,ss} R/S	CL _{po} R (mL/min)	CL _{po} S (mL/min)	CL _{po} S (mL/min)
BSA, m ²	nss	nss	nss	exp(β) = 1.97 p = 0.003	β = 1.27 p = 0.05	exp(β) = 2.46 p = 0.007
WAA	nss	nss	nss	nss	nss	nss
Age, years	β = -0.01 p = 0.009	β = -0.01 p = 0.003	nss	exp(β) = 1.01 p = 0.01	nss	exp(β) = 0.99 p = 0.03
Warfarin dose, mg/d	β = 0.14 p = <0.0001	β = 0.07 p < 0.001	nss	exp(β) = 1.06 p = 0.02	β = 0.18 p = 0.007	exp(β) = 1.01 p < 0.001
CrCl, ml/min	nss	β = 0.005 p = 0.02	nss	exp(β) = 1.01 p = 0.005	nss	exp(β) = 1.07 p = 0.07
DVT/PE	nss	β = 0.21 p = 0.03	nss	nss	nss	exp(β) = 0.69 p = 0.06

BSA, body surface area

WAA, West African ancestry

CrCl, creatinine clearance

DVT/PE, deep vein thrombosis/pulmonary embolism

nss, not statistically significant

exp(β) < 1 reflects a decrease

exp(β) > 1 reflects an increase

Table 3

Association of clinical pharmacokinetic parameters of warfarin to rs7089580 genotypes

Pharmacokinetic parameter	A/A Carriers (n=44)	A/T Carriers (n=19)	P-value
Warfarin daily dose, mg	6.15 $\pm$ 2.5	7.5 $\pm$ 3.0	0.03 [†]
C _{pss} (R) ^a (μg/mL)	1.18 $\pm$ 0.58	1.21 $\pm$ 0.43	0.03
C _{pss} (S) ^a (μg/mL)	0.79 $\pm$ 0.35	0.82 $\pm$ 0.33	0.18
C _{pss} (R/S)	1.53 $\pm$ 0.52	1.73 $\pm$ 0.78	0.24
CL _{po} (R) (mL/min)	2.01 $\pm$ 0.96	2.16 $\pm$ 0.60	0.09 ^a
CL _{po} (S) (mL/min)	2.95 $\pm$ 1.39	3.73 $\pm$ 1.46	0.04 ^b
CL _{po,u} (S) (mL/min)	218.94 $\pm$ 114.3	268.71 $\pm$ 132.6	0.02 ^b

Values presented as mean $\pm$ SD.[†] Adjusted for age, body surface area, and deep vein thrombosis/pulmonary embolism^a Adjusted for age, dose, body surface area, and creatinine clearance.^b Adjusted for age, dose, body surface area, and deep vein thrombosis/pulmonary embolism.C_{pss} = warfarin plasma concentrationC_{pss} (R/S) = ratio of R over S warfarin plasma concentration as steady stateCL_{po} = oral clearanceCL_{po,u} = unbound oral clearance

Table 4

Demographic and genotypic characteristics of livers from African American donors.

Variable	N = 34 (mean, $\pm$ SD)
Female	64.7%
Male	35.3%
Age, years	57.6 ($\pm$ 10.8)
Weight, kg	84.2 ($\pm$ 22.1)
Height, cm	170.3 ($\pm$ 8.9)
BSA (m ²)	1.98 ($\pm$ 0.29)
rs7089580	Frequency (n)
A/A	61.7% (21)
A/T	32.3% (11)
T/T	6% (2)