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BRIEF REPORT

Implications of Polymorphisms in the *BCKDK* and *GATA-4* Gene Regions on Stable Warfarin Dose in African Americans

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VKORC1 **and** ***CYP2C9*** **genotypes explain less variability in warfarin dose requirements in African Americans compared with Europeans. Variants in** ***BCKDK*** **and** ***GATA*****-4 gene regions, purported to regulate** ***VKORC1*** **and** ***CYP2C9*** **expression, have been shown to play an important role in warfarin dose requirements in Europeans and Asians, respectively. We sought to determine whether rs56314408 near** ***BCKDK*** **or** ***GATA-4*** **rs2645400 influence warfarin dose requirements in 200 African Americans. Unlike the strong linkage disequilibrium (LD) between rs56314408 and** ***VKORC1*** **rs9923231 in Europeans, they were not in LD in African Americans. No associations were found on univariate analysis. On multivariable analysis, rs56314408 was associated (*P* = 0.027) with dose in a regression model excluding** ***VKORC1*** **rs9923231, and** ***GATA-4*** **rs2645400 was associated (*P* = 0.032) with dose in a model excluding** ***CYP2C*** **(*CYP2C9*2*, **3*, **5*, **6*, **8*, and **11*, *CYP2C* rs12777823) variants. Neither variant contributed to dose in the model that included both** ***VKORC1*** **rs9923231 and** ***CYP2C*** **variants. Our results do not support contributions of the studied variants to warfarin dose requirements in African Americans. However, they illustrate the value of studies in African descent populations, who have low LD in their genome, in teasing out genetic variation underlying drug response associations. They also emphasize the importance of confirming associations in persons of African ancestry.**

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The literature is limited in warfarin pharmacogenomic studies in African Americans. *VKORC1* and *CYP2C9* genotypes explain less variability in warfarin dose requirements in African Americans compared with those of European ancestry. Variants in *BCKDK* and *GATA*-4 gene regions, purported to regulate *VKORC1* and *CYP2C9* expression, have been studied in Europeans and Asians, respectively, but not in African Americans.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We sought to determine whether rs56314408 near *BCKDK* or *GATA-4* rs2645400 influence warfarin dose requirements in African Americans.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Our results do not support major contributions of studied variants to warfarin dose requirements in African Americans. However, our findings illustrate the value of studies in African descent populations, who have low linkage disequilibrium in their genome, in teasing out genetic variation underlying drug response associations. They also highlight the importance of confirming associations in persons of African ancestry.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Results do not support the inclusion of rs56314408 near *BCKDK* or *GATA-4* rs2645400 in pharmacogenomic dosing algorithms for African Americans.

Warfarin remains commonly prescribed despite the availability of direct-acting oral anticoagulants.[1] It is, however, a challenging drug to dose because of its narrow therapeutic index and pronounced interpatient variability in dose requirements. Warfarin dose requirements are influenced by *VKORC1* and *CYP2C9* genotypes and clinical factors.[2] *VKORC1*-1639G>A (rs9923231) and *CYP2C9*2* and **3* are the variants most commonly included in pharmacogenetic dosing algorithms and explain more than 30% of dose variability in Europeans, but only about 10% of the variability in African Americans.[3–6] The *CYP2C9*5*, **6*, **8*, and **11* and the rs12777823 variant in the *CYP2C* cluster explain an additional 11% of the dose variability in African Americans.[4,7,8]

Pharmacogenomic studies on warfarin are mostly done in Europeans and Asians. There is, therefore, a gap in the literature on warfarin pharmacogenomic studies in minorities

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like African Americans who show differences in minor allele frequencies (MAF) and have a lower linkage disequilibrium (LD) pattern.[9]

A recent study in a European population suggested that the rs56314408 C>T single nucleotide polymorphism (SNP), located on chromosome 16 in an enhancer upstream of the branched chain ketoacid dehydrogenase kinase (*BCKDK*) gene, could be a functional variant regulating *VKORC1* gene expression.[10] However, rs56314408 is in high LD with *VKORC1* rs9923231 in Europeans, and thus, whether this SNP influences warfarin dose independent of the *VKORC1* rs9923231 variant could not be determined in Europeans. Therefore, Cavalli *et al*. mentioned that it is warranted to genotype rs56314408 in warfarin-treated African Americans to see whether it improves warfarin dose predictions.[10] In another study, the GATA binding protein 4 (*GATA-4*) rs2645400 T>G variant was significantly associated with stable warfarin dose in Asians with prosthetic cardiac valves having the homozygous wild-type (i.e., **1/*1*) *CYP2C9* genotype. On multivariable analysis, rs2645400/rs4841588 combination increased contribution to the overall warfarin dose variability. This study, therefore, suggested that *GATA-4* plays a role in the regulation of *CYP2C9* gene expression and can be predictive of stable warfarin dose.[11]

Neither rs56314408 nor rs2645400 has been studied in African Americans. Therefore, this study aimed to determine whether the rs56314408 variant near *BCKDK*, which is in low LD with *VKORC1* rs9923231 in African Americans, and/or the *GATA-4* rs2645400 variant are associated with warfarin dose requirements in African Americans and explain additional variability in dose beyond that of the *VKORC1* and *CYP2C* (*CYP2C9*2*, **3*, **5*, **6*, **8*, and **11* and *CYP2C* rs12777823) polymorphisms. In our study, we are using these two SNPs as cases to illustrate the importance of carrying out pharmacogenomic studies in African Americans.

METHODS

Study population

This study included samples and data from a previously described cohort of warfarin-treated African Americans enrolled from the University of Illinois at Chicago who had reached a stable warfarin dose, defined as the dose that produced a therapeutic international normalized ratio for three consecutive clinic visits.[4] Only those for whom sufficient DNA was available to genotyping were included. As we have previously reported[4] and consistent with previous studies of genetic associations with warfarin response,[12,13] exclusion criteria included history of liver dysfunction or serum transaminase levels greater than 3 times the upper limit of normal, or liver cirrhosis; advanced malignancy; hospitalization within 4 weeks before the index visit, which is the third clinic visit where informed consent was obtained and data were collected; or febrile/diarrheal illness within 2 weeks of the index visit. In addition, patients with samples that did not genotype for at least one SNP were excluded, as well as patients requiring ≥ 90 mg/week, as doses ≥ 90 mg/week are often associated with warfarin resistance variants (e.g., *VKORC1* variants) that were not genotyped as part of this study.[14] The study was approved by the institutional review boards at the University of Florida and the University of Illinois at Chicago, and all patients provided written informed consent for the use of their samples and data. The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Data collection

As previously described, either a buccal cell or venous blood sample was collected from each patient for genotyping.[7,15] Clinical data were collected from the electronic medical record or through patient interview. Genotypes for *VKORC1* rs9923231 and *CYP2C* variants were available from previous efforts.[4]

Genotyping

Genomic DNA from clinical samples was isolated using the PureGene kit (Qiagen, Valencia, CA). Genotyping for rs56314408 and rs2645400 was carried out by polymerase chain reaction using HotStarTaq Plus Master Mix and followed by pyrosequencing on PSQ HS 96 system (Qiagen). The polymerase chain reaction and pyrosequencing primers are shown in **Table S1**.

Statistical analyses

The Hardy–Weinberg equilibrium (HWE) assumption was tested for each polymorphism of interest using the exact test on PLINK version 1.07.[16,17] The r^2 and D' values between rs56314408 and *VKORC1* rs9923231 were determined using Haploview.[18] Weekly warfarin dose was tested for normality using the Shapiro–Wilk test.

Univariate analysis using nonparametric Kruskal–Wallis and Mann–Whitney *U* tests was performed to determine genotype associations with weekly warfarin dose requirements. The Kruskal–Wallis test was performed for rs56314408 because an additive model was used for this polymorphism, and Mann–Whitney *U* test was used for *GATA-4* rs2645400 because only three patients were homozygous variant for this polymorphism, making a dominant model preferable. Multiple linear regression analysis was then conducted to test the association among each polymorphism and warfarin dose requirements, while adjusting for *VKORC1* rs9923231 and *CYP2C* variants, separately and in different combinations. Each regression model included clinical factors (age, body surface area, history of stroke or transient ischemic attack, and current smoking status) previously associated with warfarin dose requirements in African Americans.[4,8,19] The variability of warfarin dose explained, or R^2, was reported for each model. A *P* value of 0.05 was considered statistically significant. Given a previous association between the *GATA-4* rs2645400 SNP and warfarin dose specific to those with the *CYP2C9*1/*1* genotype,[11] subgroup analyses (univariate and multivariable) were also performed in this subset. Including at least 180 patients and using MAF of 0.09 provided 80% power to detect a difference in weekly warfarin dose by SNP of ≥ 8.7 mg with an alpha of 0.05. All analyses were conducted using SAS software version 9.4 Copyright 2013 (SAS Institute, Cary, NC).

RESULTS

A total of 200 patients were genotyped for rs56314408 and rs2645400, with at least 180 included in each

analysis. The majority (78%) was women, with a mean age of 55 ± 16 years, mean body surface area of 2.0 ± 0.3 m^2, and median weekly warfarin dose of 42.5 mg (interquartile range 34.5–56.1 mg). Twenty-six percent of patients had history of stroke or transient ischemic attack, and 19% were current smokers. The MAFs of rs56314408 and rs2645400 were 0.46 and 0.10, respectively, which is consistent with that reported in the 1000 genomes African ancestry in Southwest USA (ASW) population (0.45 and 0.11, respectively).[20] Both variants were in Hardy–Weinberg equilibrium. Rs56314408 and *VKORC1* rs9923231 were not in LD in our African American population (r^2 = 0.07, D' = 0.77). Weekly warfarin dose was not normally distributed. Therefore, values were natural log-transformed prior to regression analysis.

Neither variant was associated with warfarin dose requirements on univariate analysis (**Figure 1**). On multiple linear regression, including clinical factors and *CYP2C* variants, rs56314408 was associated with warfarin dose requirements (P = 0.027, R^2 = 33%; **Table 1**, model 1). However, this association was no longer evident when *VKORC1* rs9923231 was added to the model. Similarly, *GATA-4* rs2645400 was associated with dose in a model, including clinical factors and *VKORC1* rs9923231 (P = 0.032, R^2 = 31%; **Table 1**, model 2), but not after inclusion of the *CYP2C* variants into the model. A model including clinical factors plus *VKORC1* rs9923231 and *CYP2C* variants explained 38% of the variability in warfarin dose requirements in the study population but showed no association between rs56314408 or rs2645400 and dose (**Table 1**, model 3).

When limiting the analysis to those with *CYP2C9*1/*1* genotype, there was no statistically significant association between the *GATA-4* rs2645400 SNP and warfarin dose on univariate analysis (P = 0.100). It was marginally associated in a multiple linear regression model with clinical factors and *VKORC1* rs9923231 (P = 0.045, R^2 = 34%; **Table S2**, model 2a), but the association was no longer significant after adjusting for the *CYP2C* rs12777823 variant (P = 0.177, R^2 = 35%; **Table S2**, model 2b).

DISCUSSION

In our African American population, we found no association between rs56314408 near *BCKDK* or *GATA-4* rs2645400 and warfarin dose requirements. These data, therefore, do not support that either of these polymorphisms provides a major contribution to warfarin dose variability in African Americans.

Our results with rs56314408 are inconsistent with those by Cavalli *et al*., who proposed that rs56314408, which is an allele-specific SNP in high LD with *VKORC1* rs9923231 in Europeans, could be a functional variant regulating *VKORC1* expression based on *in vitro* assays.[10] Given the strong LD between rs56314408 and *VKORC1* rs9923231 in Europeans, it is difficult to discern if the effects of rs56314408 on gene transcription result in important effects on warfarin response that are independent of the *VKORC1* variant in this population. However, our data from African Americans, in whom there is no LD between rs56314408 and *VKORC1* rs9923231, suggest that any effect of rs56314408 on transcription does not translate into clinically significant differences in warfarin dose requirements, at least in African Americans. Specifically, the loss of association between rs56314408 and warfarin dose when *VKORC1* rs9923231 was added to the model suggests that rs56314408 does not influence warfarin dose requirements independent of the *VKORC1* rs9923231 variant.

In a separate study of 201 Asian patients with prosthetic heart valves, none of 11 *GATA-4* variants tested, including the rs2645400 variant, was associated with warfarin dose in the population overall.[11] However, when limiting univariate analysis to those with the *CYP2C9 *1/*1* genotype, the rs2645400 G allele was associated with lower stable warfarin dose. On multivariable analysis, the rs2645400/rs4841588 combination accounted for 1.2% of the overall interindividual variability in warfarin dose requirements.[11] GATA-4 is a liver-specific transcription factor recently shown to play an important role in regulating *CYP2C9* gene expression.[21] Although we observed a marginally significant association between the *GATA-4* rs2645400 SNP and warfarin dose in the subpopulation of *CYP2C9*1* allele homozygotes on multiple linear regression, it was no longer associated after adjusting for *CYP2C* rs12777823, a SNP associated with warfarin clearance and dose requirements in African ancestry patients.[8] It is possible that the lower frequency of the SNP in African Americans vs. Asians contribute to the disparate findings between studies. Of note, we did not genotype for the rs4841588 SNP examined in the Jeong *et al*. study,

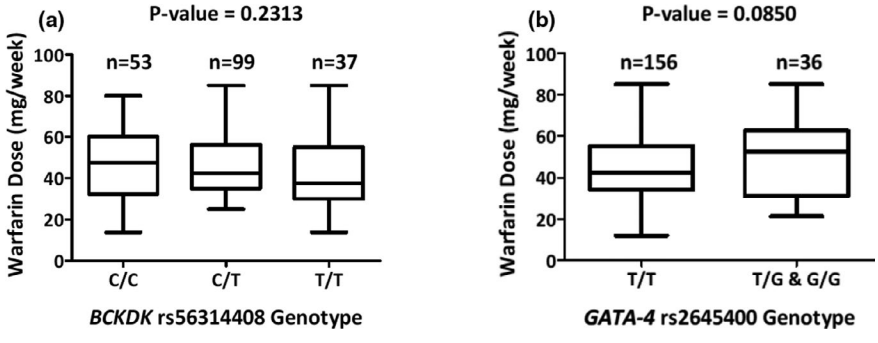

Figure 1 Warfarin dose requirements by (**a**) rs56314408 near the *BCKDK* gene and (**b**) *GATA-4* rs2645400. In the boxplots shown, horizontal lines within boxes represent medians. The lower and upper boundaries represent the 25th and 75th percentiles, respectively. The lower and upper whiskers represent the minimum and maximum warfarin doses that are not outliers, respectively.

Table 1 Multiple linear regression models

	Model 1[a]		Model 2[b]		Model 3[c]	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Intercept	3.7308 (0.1690)	< 0.0001	3.6138 (0.1764)	< 0.0001	3.6301 (0.1674)	< 0.0001
rs56314408 (near *BCKDK*)	−0.0691 (0.0310)	0.0271	–	–	−0.0401 (0.0314)	0.2036
GATA-4 rs2645400	–	–	0.1224 (0.0565)	0.0317	0.0669 (0.0525)	0.2047
VKORC1 rs9923231	–	–	−0.2100 (0.0539)	0.0001	−0.1814 (0.0549)	0.0012
CYP2C9 star variants	−0.1800 (0.0512)	0.0006	–	–	−0.1830 (0.0497)	0.0003
CYP2C rs12777823	−0.0881 (0.0355)	0.0141	–	–	−0.0938 (0.0350)	0.0080
Age	−0.0062 (0.0013)	< 0.0001	−0.0072 (0.0014)	< 0.0001	−0.0058 (0.0013)	< 0.0001
BSA	0.2736 (0.0725)	0.0002	0.2914 (0.0727)	< 0.0001	0.3161 (0.0718)	< 0.0001
Stroke/TIA	−0.1491 (0.0490)	0.0027	−0.1591 (0.0511)	0.0021	−0.1676 (0.0479)	0.0006
Current smoking status	0.1116 (0.0533)	0.0378	0.0705 (0.0564)	0.2134	0.0991 (0.0529)	0.0628

BCKDK, branched chain ketoacid dehydrogenase kinase; BSA, body surface area; *CYP2C*, cytochrome P450 2C; *CYP2C9*, cytochrome P450 2C9; *GATA*-4, GATA binding protein 4; TIA, transient ischemic attack; *VKORC1*, vitamin K epoxide reductase complex subunit 1.
Weekly warfarin doses were natural log-transformed prior to regression analysis.
CYP2C9 star variants include **2*, **3*, **5*, **6*, **8*, and **11*.
An additive model was used for all SNPs except *GATA-4* rs2645400 and *CYP2C9* star variants, which were coded as binary variables (variant allele carrier vs. noncarrier).
[a]Model 1 showing association of rs56314408 (near *BCKDK*) with warfarin dose (R^2 = 33%, n = 182). [b]Model 2 showing association of *GATA-4* rs2645400 with warfarin dose (R^2 = 31%, n = 192). [c]Model 3 showing lack of association of rs56314408 and *GATA-4* rs2645400 with warfarin dose (R^2 = 38%, n = 180).

and, thus, cannot comment on its association in African Americans.

Our study with the rs56314408 variant further demonstrates the value of studies in African Americans in pinpointing the responsible variant underlying drug response associations within a haplotype block. This has been similarly demonstrated with polymorphisms within the *VKORC1* gene. Specifically, Rieder *et al*. identified five polymorphisms (–4931T>C, –1639G>A, 1173C>T, 1542G>C, and 2255C>T) in strong LD in a European ancestry population defining a *VKORC1* haplotype that conferred significant effects on warfarin dose requirements.[22] However, the specific polymorphism underlying the dose association was unknown and could not be determined from dose association studies in European ancestry populations. In subsequent studies in African Americans, in whom there is significantly lower LD in the *VKORC1* gene, we and others found that –1639G>A, but not 1542G>C, was responsible for observed associations between *VKORC1* genotype and warfarin dose requirements.[23,24]

Our findings with the *GATA-4* rs2645400 genotype emphasize that an association observed in one ethnic population should not be generalized to other ethnic populations, particularly those of African ancestry. This has been previously demonstrated with the *CYP4F2* genotype, which is associated with higher warfarin dose requirements in European and Asian ancestry populations, but not in African Americans.[13,25,26] As a result, recent guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC) make no recommendations regarding the *CYP4F2* genotype for persons of African ancestry, but recommend higher doses with the *CYP4F2* variant allele in non-African ancestry populations.[27]

In conclusion, our results do not support a major contribution of either the *BCKDK* rs56314408 or *GATA-4* rs2645400 variant to warfarin dose requirements in African Americans. However, we cannot rule out that these variants may provide smaller contributions to warfarin dose requirements that we were unable to detect because of our limited sample size. Importantly, our findings illustrate the value of studies in African descent populations in teasing out genetic variation underlying drug response associations. They also highlight the importance of confirming associations in persons of African ancestry.

Supporting Information. Additional supporting information may be found in the online version of this article at the publisher's web site:

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