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Combined *CYP2C9, VKORC1* and *CYP4F2* frequencies among racial and ethnic groups

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Abstract

Aims—*CYP4F2*3* (p.V433M) has been associated with higher warfarin dose requirements; however, its frequency, like other *CYP2C9* and *VKORC1* variants, has not been systematically assessed in major racial/ethnic populations. Thus, we determined the individual and combined frequencies of important *CYP2C9, VKORC1* and *CYP4F2* variants in several racial/ethnic groups.

Materials & methods—Healthy African–American, Asian, Caucasian, Hispanic and Ashkenazi Jewish (AJ) blood donors were genotyped for *CYP2C9 (*2, *3, *4, *5, *6, *8, *11* and **13*), *VKORC1* (g.-1639G>A) and *CYP4F2* (**3* [p.V433M] and rs2189784).

Results—The combined frequencies of variant *CYP2C9* alleles were 0.133, 0.078, 0.212, 0.178 and 0.212 among African–American, Asian, Caucasian, Hispanic and AJ individuals, respectively. *CYP4F2*3* frequencies were prevalent (0.233–0.342) among Asian, Caucasian, Hispanic and AJ individuals, while significantly less frequent among African–Americans (0.117; $p < 0.0001$). In addition, *CYP4F2*3* was in linkage disequilibrium with rs2189784, an allele recently associated with time-to-therapeutic international normalized ratio, among all studied populations. Importantly, 87–95% of Asian, Caucasian, Hispanic and AJ individuals had a variant *CYP2C9, VKORC1* and/or *CYP4F2*3* allele, compared with only 53% of African–Americans ($p < 0.0001$).

Conclusions—Compared with other racial/ethnic populations studied, only approximately one in 80 African– Americans were *CYP4F2*3* homozygous, indicating that this population would benefit less from dosing algorithms that include this variant. In addition, the unique allele frequency profiles identified among the different populations partly explain why genotype-guided warfarin dosing algorithms perform less well for African–Americans and suggest that other unidentified genetic and/or nongenetic factors that influence warfarin dosage may exist in this population.

Keywords

allele frequencies; *CYP2C9*; *CYP4F2*; pharmacogenetics; *VKORC1*; warfarin

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Ethical conduct of research
The authors state that they have obtained appropriate insti tutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Several studies on the genetic determinants of interindividual warfarin dose variability have identified polymorphisms and rare coding variants in cytochrome P450-2C9 (*CYP2C9*) and vitamin K epoxide reductase complex subunit 1 (*VKORC1*), which significantly influence warfarin dosage [1-3]. *CYP2C9* and *VKORC1* are involved in warfarin pharmacokinetics and pharmacodynamics, respectively, and when combined with other clinical (e.g., age and weight) and environmental (e.g., concomitant medication) factors, account for approximately 50% of interindividual warfarin dose varia tion [2-4]. Accordingly, these genetic and nongenetic variables have been modeled into regression algorithms to predict the therapeutic warfarin dose [3,5-7].

Recently, three genome-wide association studies using Caucasian patient cohorts identified a third gene implicated in warfarin dose variability, cytochrome P450-4F2 (*CYP4F2*) [8-10]. Although the newly identified variant allele (*CYP4F2*3* [rs2108622; c.1297G>A; p.V433M]) was only responsible for approximately 1–2% of the remaining variation in warfarin dose [8, 10], patients homo zygous for *CYP4F2*3* required 1–2.5 mg/day more warfarin to achieve stable anticoagulation then wild-type homozygotes [8,10,11]. Given that CYP4F2 is a vitamin K_1 oxidase and that *CYP4F2*3* has reduced capacity to metabolize vitamin K_1 [12], patients carrying this allele are predisposed to elevated hepatic levels of vitamin K_1, necessitating a higher warfarin dose for a therapeutic anticoagulant response. In addition, a noncoding *CYP4F2* variant (rs2189784) in linkage disequilibrium (LD) with *CYP4F2*3* has very recently been associated with time-to-therapeutic international normalized ratio [13], further supporting a role for CYP4F2 in vitamin K metabolism.

Although the association of *CYP4F2*3* with warfarin dose was recently confirmed in an Italian cohort [11] and elderly, frail Caucasian patients [14], the significance of this allele among racially diverse multi-ethnic patient populations is unclear. Furthermore, the frequencies of *CYP4F2*3* among major racial and ethnic groups, similar to other *CYP2C9* and *VKORC1* variants, have not been systematically established. Although smaller studies have previously reported variant *CYP2C9* and *VKORC1* allele frequencies among treated patient populations, few have surveyed healthy donors from multiple racial and ethnic groups, and no studies, to our knowledge, have investigated *CYP2C9, VKORC1* and *CYP4F2* altogether. Given that the frequencies of other important pharmacogenetic variants vary among racial and ethnic groups [2,15-17], we sought to determine and compare the allele frequencies of the three principal genes known to influence interindividual warfarin dose variability (*CYP2C9, VKORC1* and *CYP4F2*) in the African–American, Asian, Caucasian, Hispanic and Ashkenazi Jewish (AJ) populations.

Methods & materials

Study population

Peripheral blood samples from healthy donors who indicated their racial background and gave informed consent for the use of their DNA for research were obtained from the New York Blood Center (NY, USA) with Institutional Review Board approval [18]. In addition, blood samples were obtained with informed consent from unrelated healthy 100% AJ individuals from the greater New York metropolitan area as previously defined [17,19]. All personal identifiers were removed, and isolated DNA samples were tested anonymously. Genomic DNA was isolated using the Puregene® DNA Purification kit (Qiagen, CA, USA) according to the manufacturer's instructions.

Genotyping

The *CYP450* allele designations refer to those defined by the Human Cytochrome P450 Allele Nomenclature Committee [20,101]. Genotyping of *CYP2C9* (**2, *3, *4, *5, *6, *8, *11* and

13*) and *VKORC1* (g.-1639G>A) was performed using the Tag-It™ Mutation Detection Kit (Luminex Molecular Diagnostics, ON, Canada) and PCR-restriction fragment length polymorphism assays as previously described [17,18]. The wild-type *CYP2C9* allele (1*) was assigned in the absence of other detectable variant alleles. *CYP4F2*3* and *CYP4F2*-rs2189784 were geno-typed using PCR-restriction fragment length polymorphism assays that employed forward (**3*: 5′-AGTCCCGGTCATCTCCCGCCAT-3′; rs2189784: 5′-GCTTTACTTACCTCACCCCC ACGC-3′) and reverse (**3*: 5′-CGCCAGCCTTGGAGAGACAGACA-3′; rs2189784: 5′-GGGGATGCAGCCGCACTCTAGAAA-3′) amplification primers and *Pvu*II and *Bss*SI, respectively (New England BioLabs, MA, USA USA).). PCR reactions were perperformed in 25 μl volumes containing approximately 100 ng of DNA, 1X PCR buffer, 1.5 mM (**3*) or 2.5 mM (rs2189784) $MgCl_2$, 0.2 mM of each dNTP, 0.4 μM of each primer and 1.0 unit of Platinum® Taq DNA Polymerase (Invitrogen, CA, USA). The amplifications consisted of an initial denaturation step at 94°C for 5 min followed by 35 amplification cycles (94°C for 30 s, 62°C for 30 s and 72°C for 30 s) and a final incubation at 72°C for 5 min. All digested PCR products were visualized by agarose gel electrophoresis, and representative controls were confirmed by bidirectional sequencing.

Of note, over 100–500 specimens per racial/ethnic group were analyzed for *CYP2C9* and *VKORC1*, and 300–500 specimens per racial/ethnic group for *CYP4F2*. Some of the *CYP2C9* and *VKORC1* data for the African–American and AJ populations were previously reported as noted [17-18].

Statistical analyses

Observed genotype frequencies were compared with those expected under Hardy–Weinberg equilibrium using the χ^2 test. The χ^2 test was also used to detect overall and pairwise differences in allele frequencies between all tested populations as implemented in SAS/Genetics (SAS Institute, Inc., NC, USA). Pairwise LD was estimated using Lewontin's D' and r^2 as implemented in Haploview [21].

Results

CYP2C9 allele & genotype frequencies

The *CYP2C9* allele and genotype frequencies are summarized in **T**ABLES 1 **&** 2. The overall difference in *CYP2C9* allele frequencies were highly significant ($p < 0.0001$), and significant pairwise differences were detected between all populations ($p < 0.01$) except between Caucasians and AJ ($p = 0.18$) and between Asians and Hispanics ($p = 0.06$). The combined frequencies of detected variant *CYP2C9* alleles were 0.078 (Asian), 0.133 (African–American), 0.178 (Hispanic) and 0.212 (Caucasian and AJ; Figure 1). All alleles were in Hardy–Weinberg equilibrium ($p > 0.05$), and no studied population carried the **4* (c.1076T>C, p.I359T) or **13* (c.269T>C, p.L90P) alleles. Based on their observed genotypes, the African–American, Asian, Caucasian, Hispanic and AJ predicted metabolic phenotypes [22] were distributed as extensive (75.7, 87.1, 66.0, 70.3 and 62.4%), intermediate (22.7, 11.8, 25.5, 23.8 and 32.9%) and poor (1.7, 2.0, 8.5, 6.0 and 5.0%) metabolizers, respectively.

VKORC1 allele & genotype frequencies

The *VKORC1* g.-1639G>A allele and genotype frequencies are summarized in **T**ABLES 1 **&** 3. The overall difference in *VKORC1* allele frequencies were highly significant ($p < 0.0001$), and African–Americans and Asians had significantly different *VKORC1* allele frequencies compared with all other populations ($p < 0.0001$). No significant differences between Caucasians, Hispanics and AJ individuals were observed. The g.-1639A frequencies ranged from 0.108 (African–American) to 0.667 (Asian; Figure 1). Consequently, the combined G/A

and A/A genotype frequencies ranged from 19.7% (African–American) to 77.5% (Asian). However, the Asian g.-1639G>A frequency significantly deviated from Hardy–Weinberg equilibrium ($p < 0.0001$), presumably as a result of subpopulation heterogeneity [23,24], as our Asian cohort was comprised of different ethnicities.

CYP4F2 allele & genotype frequencies

The *CYP4F2*3* and *CYP4F2*-rs2189784 allele frequencies are summarized in Table 4 and Figure 1. The *CYP4F2*3* (c.1297A) frequencies were significantly different ($p < 0.0001$) across all racial and ethnic groups studied, being prevalent among Hispanic (0.233), Asian (0.305), AJ (0.328) and Caucasian (0.342) individuals, while being less frequent among African–Americans (0.117). African–American and Hispanic frequencies were different from all other populations ($p < 0.0001$ and $p < 0.01$, respectively), and no significant differences between Asians, Caucasians and AJ individuals were observed. More common in all studied populations, the *CYP4F2*-rs2189784 frequencies were prevalent among Hispanic (0.355), Asian (0.357), Caucasian (0.447) and AJ (0.486) individuals, and statistically less frequent among African-Americans (0.302; $p < 0.05$). In addition, the Asian and Hispanic frequencies were different from Caucasians and AJ individuals ($p < 0.002$).

*CYP4F2*3* and *CYP4F2*-rs2189784 were in LD among all studied populations (D' = 0.80-0.96). In addition, *CYP4F2*3* and *CYP4F2*-rs2189784 were in Hardy–Weinberg equilibrium ($p > 0.05$) for all studied populations, and the identified genotype frequencies are summarized in Table 5. Notably, homozygosity for *CYP4F2*3* (c.1297A/A) was found among Hispanic (5.3%), Asian (9.0%), AJ (9.0%) and Caucasian (11.0%) individuals, whereas only 1.3% of African–Americans were homozygous for *CYP4F2*3* ($p < 0.0001$). Similarly, homozygosity for *CYP4F2*-rs2189784 was found among Hispanic (13.3%), Asian (11.7%), AJ (23.2%) and Caucasian (19.3%) individuals; whereas, only 8.7% of African–Americans were homozygous for *CYP4F2*-rs2189784.

Combined *CYP2C9*, *VKORC1* & *CYP4F2* frequencies

Table 6 **&** Figure 2 summarize the combined *CYP2C9, VKORC1*, and *CYP4F2*3* genotype frequencies for all of the studied populations. Notably, the vast majority of Hispanic (87.1%), Caucasian (87.7%), AJ (94.9%) and Asian (95.1%) individuals harbored a variant *CYP2C9, VKORC1* and/or *CYP4F2*3* allele, compared with only 52.5% of African-American individuals. When substituting *CYP4F2*-rs2189784 for *CYP4F2*3*, Hispanic (91.0%), Caucasian (92.4%), AJ (95.2%) and Asian (97.1%) individuals harbored a variant *CYP2C9, VKORC1* and/or *CYP4F2* allele, compared with only 69.0% of African–American individuals.

Discussion

The limited availability of combined allele frequency data in the African–American, Asian, Caucasian, Hispanic and AJ populations prompted our investigation into the three principal genes known to influence interindividual warfarin dose variability (i.e., *CYP2C9, VKORC1* and *CYP4F2*) in these racial and ethnic groups. Although smaller studies have previously reported variant *CYP2C9* and *VKORC1* allele frequencies among treated patient populations, few studies have surveyed healthy donors from multiple racial and ethnic groups, and no studies, to our knowledge, have investigated *CYP2C9, VKORC1* and *CYP4F2* together. Importantly, when examining alleles known to influence warfarin dosage (i.e., *CYP2C9*2, *3, *4, *5, *6, *8, *11* and **13*; *VKORC1* g.-1639G>A; *CYP4F2*3*), our data indicate that the vast majority (~90%) of Asian, Caucasian, Hispanic and AJ individuals harbored at least one variant allele, compared with only approximately half of African–Americans.

Although the African–American population has largely been under-represented in studies devoted to the genetic contribution of warfarin dose variability, they have similar frequencies of unstable anticoagulation compared with Caucasians [25], and the highest incidence rates of thromboembolism [26,27]. In addition, African–Americans typically require higher doses of warfarin than other racial groups [25,28,29]. Interestingly, several studies have found that pharmacogenetic warfarin dosing algorithms perform less well for African–Americans than Caucasians, even when race/ethnicity is included as a variable [5,7,30,31]. This is partly explained by the markedly lower frequencies of variant *CYP2C9* and *VKORC1* alleles identified in the African–American population compared with the other populations in our study, particularly as most dosing algorithms currently only incorporate *CYP2C9*2, *3* and *VKORC1* g.-1639G>A (or g.1173C>T). However, even when using a more extensive *CYP2C9* genotyping panel, only half of African-Americans harbored a variant *CYP2C9, VKORC1* and/or *CYP4F2*3* allele. In addition, other genetic (e.g., *APOE* [32]) and/or nongenetic (e.g., poor adherence [25]) factors may play a significant role in interindividual warfarin dosing variability among African–Americans.

Similar to the African–Americans [18], the Hispanic population carried several variant *CYP2C9* alleles (**2, *3, *5, *6, *8* and **11*), indicating that this ethnic group would also benefit from expanded genotyping panels beyond *CYP2C9*2* and **3*. However, in contrast to African–Americans, their *VKORC1* g.-1639A frequency was more consistent with individuals of European descent. In addition, none of the tested populations carried a *CYP2C9*4* or **13* allele, indicating that these alleles, originally identified in Japanese (**4*) [33], Chinese [34] and Koreans [35] (**13*), may be too rare to warrant inclusion into cost-effective clinical genotyping panels. Alternatively, our heterogeneous Asian population may have included other South East Asian subpopulations.

Despite the limited statistical contribution of *CYP4F2* to warfarin dose variability [8-11,13], homozygous *CYP4F2*3* patients may require 1–2.5 mg/day more warfarin than wild-type homozygous patients [8,10,11]. The high frequencies of this allele among Asian, Caucasian, Hispanic and AJ individuals were contrasted by the much lower frequency observed among African–Americans. Consequently, homozygosity for *CYP4F2*3* was statistically more frequent among Asian, Caucasian, Hispanic and AJ populations compared with African–American populations. Based on these frequencies, approximately one in ten Asian, Caucasian and/or AJ and approximately one in 20 Hispanic individuals are *CYP4F2*3* homozygotes who may benefit from the incorporation of this allele into pharmacogenetic-based dosing algorithms. By contrast, only approximately one in 80 African-American individuals are *CYP4F2*3* homozygotes, indicating that this population would benefit less from dosing algorithms that include this pharmacogenetic variant.

Although no published dosing algorithms currently include *CYP4F2*3* [3], this variant has been modeled into more extensive online dosing algorithms [102]. As *CYP4F2* continues to be studied in other racial and ethnic groups, it is possible that other algorithms will be generated that incorporate this allele as a variable. However, our data indicate that although *CYP4F2*3* may improve the predictability of pharmacogenetic-guided warfarin dosing for Asian, Caucasian, Hispanic and AJ individuals, it would be likely to have little benefit for the African–American population. This is evidenced by the very recent lack of association of *CYP4F2*3* with therapeutic warfarin dose requirements among an African–American patient cohort [36]. Further studies on *CYP4F2* are necessary to determine if **3* (p.V433M), or another variant allele in LD with **3* and/or rs2189784 [13], are causally involved in warfarin dose variability in non-Caucasian populations.

Conclusion

Our data support the modeling of *CYP4F2*3* into pharmacogenetic algorithms for improved warfarin dosing in most major racial and ethnic groups, but not African–Americans. Given that *CYP4F2*3* has recently been associated with acenocoumarol dose variability [37,38], our findings also have important implications for genotype-guided dosing of other coumarinderived anticoagulants. Furthermore, the combined *CYP2C9, VKORC1* and *CYP4F2* frequency data partly explain why current genotype-guided warfarin dosing algorithms perform less well for African–Americans and suggest that other unidentified genetic and/or nongenetic factors that influence warfarin dose variability exist in this population. Future genome-wide association studies directed specifically at this racial group are necessary to investigate other common variants that may significantly influence warfarin dosing among African–Americans. In addition, for all racial and ethnic groups, deep sequencing for novel and/or rare variants and studies devoted to epigenetic and/or copy number variation may elucidate other important genetic components of interindividual warfarin dose variability.

Future perspective

The majority of published candidate gene and genome-wide association studies have primarily investigated Caucasian patient populations. This has prompted an increasing number of studies that seek novel genetic variants that influence warfarin dosage in specific racial and ethnic subpopulations. It is important that these studies continue, as it has already been shown in some ethnicities that certain variants with significant influence on warfarin dosage occur at appreciable frequencies (e.g., *VKORC1* p.D36Y in the AJ population). As large ongoing clinical trials test the clinical validity and feasibility of pharmacogenetic-guided warfarin dosing, forthcoming studies should focus on the continued identification of ethnic-specific genetic and nongenetic factors for more refined, population-specific and personalized genotype-phenotype predictions. This is particularly pertinent given that many published warfarin dosing algorithms include alleles that are not common to all racial and ethnic groups and, therefore, may not be optimal for specific patient cohorts.

Executive summary

Background

- In addition to *CYP2C9* and *VKORC1*, a third gene, *CYP4F2*, has recently been implicated in warfarin dose variability.
- The limited availability of combined allele frequency data in the African–American, Asian, Caucasian, Hispanic and Ashkenazi Jewish (AJ) populations prompted our investigation of the three principal genes known to influence interindividual warfarin dose variability (*CYP2C9, VKORC1* and *CYP4F2*) in these racial and ethnic groups.

CYP2C9 & VKORC1 *frequencies*

- The combined frequencies of variant *CYP2C9* alleles (**2, *3, *4, *5, *6, *8, *11* and **13*) were 0.133, 0.078, 0.212, 0.178 and 0.212 among African–American, Asian, Caucasian, Hispanic and AJ individuals, respectively.
- The *VKORC1* g.-1639G>A frequencies were 0.108, 0.667, 0.406, 0.436 and 0.467 among African–American, Asian, Caucasian, Hispanic and AJ individuals, respectively.

CYP4F2 *frequencies*

- The CYP4F2*3 (p.V433M; rs2108622) frequencies were significantly different across all populations ($p < 0.0001$), being prevalent (0.233–0.342) among Asian, Caucasian, Hispanic and AJ individuals, while significantly less frequent among African–Americans (0.117; $p < 0.0001$).

Combined* CYP2C9, VKORC1 & CYP4F2 *frequencies

- Importantly, 87–95% of Asian, Caucasian, Hispanic and AJ individuals had a variant *CYP2C9*, *VKORC1* and/or *CYP4F2*3* allele, compared with only 53% of African–Americans ($p < 0.0001$).

Conclusion

- The *CYP4F2*3* frequency predicts that approximately one in ten Asian, Caucasian and/or AJ and approximately one in 20 Hispanic individuals are *CYP4F2*3* homozygotes who may benefit from incorporation of this allele into pharmacogenetic-based dosing algorithms.
- Only approximately one in 80 African–American individuals are *CYP4F2*3* homozygotes, indicating that this population would benefit less from dosing algorithms that include this pharmacogenetic variant.
- The African–American, Asian, Caucasian, Hispanic and AJ populations have unique *CYP2C9*, *VKORC1* and *CYP4F2* allele frequency profiles that partly explain why genotype-guided warfarin dosing algorithms perform less well for African–Americans and suggest that other unidentified genetic and/or nongenetic factors that influence warfarin dosage exist in this population.

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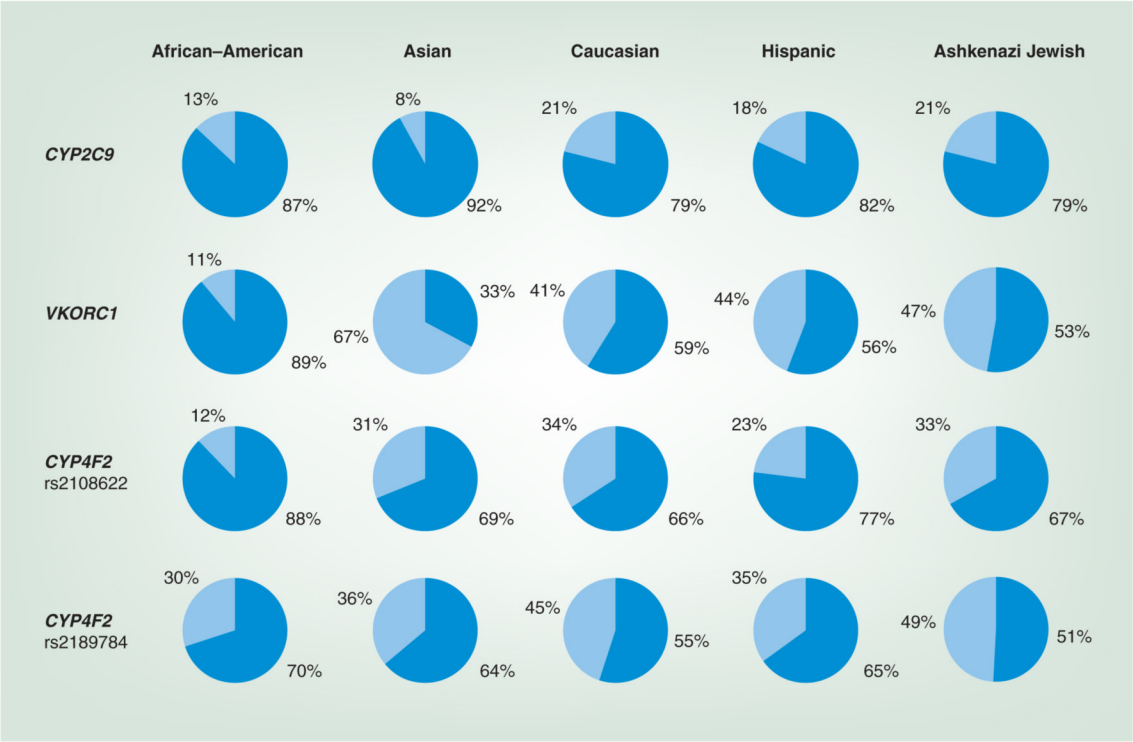

Figure 1. Variant *CYP2C9* (combined **2, *3, *5, *6, *8* and **11*), *VKORC1* (g.-1639G>A) and *CYP4F2* (3* [rs2108622] and rs2189784) allele frequencies in various racial and ethnic populations**

Wild-type and variant allele frequencies are represented by dark blue and light blue shading, respectively.

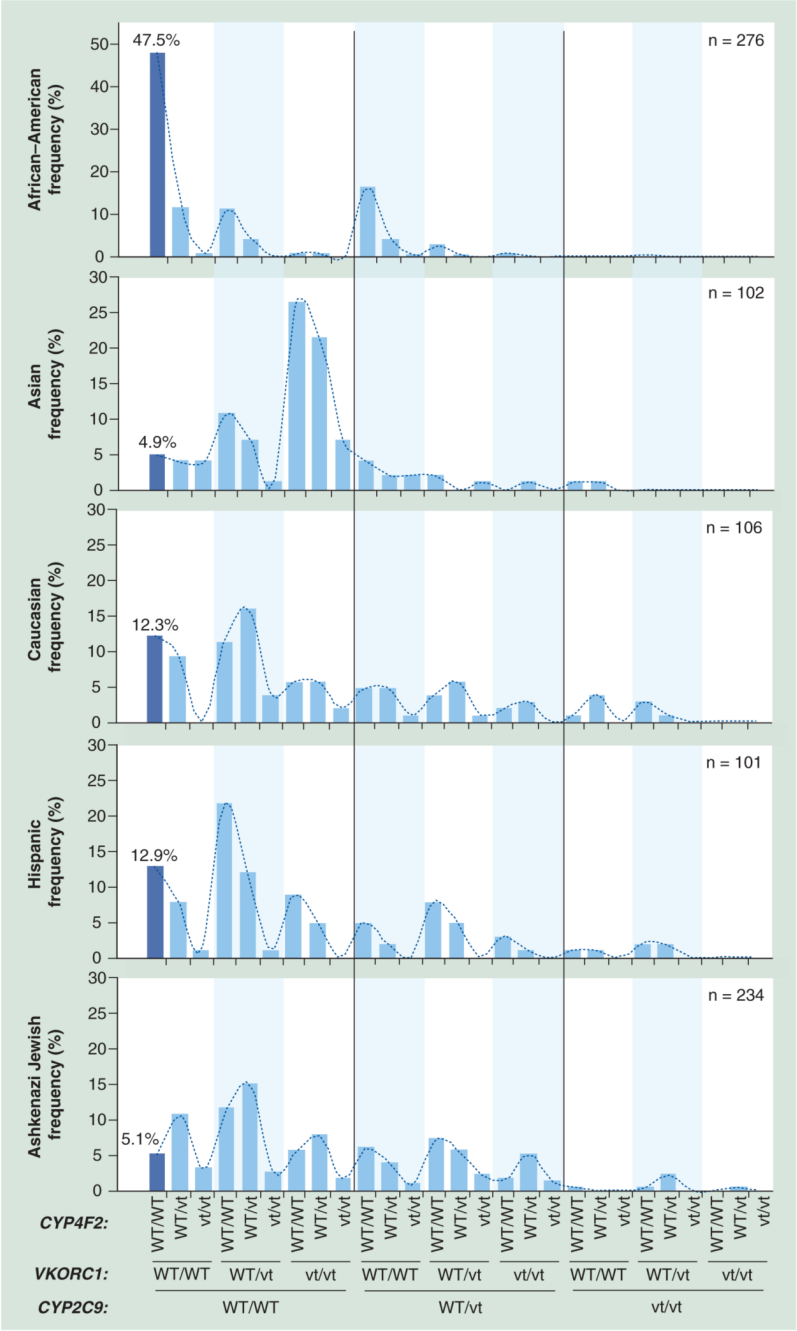

Figure 2. *CYP2C9, VKORC1* and *CYP4F2* genotype frequency profiles in various racial and ethnic populations

CYP2C9, VKORC1 and *CYP4F2* genotype frequencies were combined for a subset of subjects with available data. Frequencies were subdivided based on variant *CYP2C9* (**2, *3, *5, *6, *8* and **11*), *VKORC1* (g.-1639G>A) and *CYP4F2* (**3*; p.V433M) alleles. For each population studied, the frequency of homozygosity for a WT genotype at all three loci is highlighted by a dark blue bar, and a dotted line indicates the frequency profile trend. Note the high frequency (47.5%) of African–Americans with WT alleles compared with those in all other studied populations ($p < 0.0001$).

n: Number of subjects; vt: Variant allele; WT: Wild-type allele (*CYP2C9*: **1*; *VKORC1*: g.-1639G; *CYP4F2*: p.V433).

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Table 1

***CYP2C9* and *VKORC1* allele frequencies**

Allele	African–American† (n = 600)		Asian (n = 204)		Caucasian (n = 212)		Hispanic (n = 202)		Ashkenazi Jewish‡ (n = 1004)	
	Freq.	*95% CI*	*Freq.*	*95% CI*	*Freq.*	*95% CI*	*Freq.*	*95% CI*	*Freq.*	*95% CI*
CYP2C9										
**1*	0.867	0.839–0.894	0.922	0.885–0.958	0.788	0.733–0.843	0.822	0.769–0.875	0.788	0.763–0.813
**2*	0.028	0.015–0.042	0.029	0.006–0.053	0.151	0.103–0.199	0.069	0.034–0.104	0.128	0.108–0.149
**3*	0.020	0.009–0.031	0.039	0.013–0.066	0.057	0.025–0.088	0.064	0.031–0.098	0.083	0.066–0.100
**4*	0.000	0.000–0.000	0.000	0.000–0.000	0.000	0.000–0.000	0.000	0.000–0.000	0.000	0.000–0.000
**5*	0.015	0.005–0.025	0.000	0.000–0.000	0.000	0.000–0.000	0.015	0.000–0.032	0.001	0.000–0.003
**6*	0.010	0.002–0.018	0.000	0.000–0.000	0.000	0.000–0.000	0.005	0.000–0.015	0.000	0.000–0.000
**8*	0.047	0.030–0.064	0.010	0.000–0.023	0.000	0.000–0.000	0.015	0.000–0.032	0.000	0.000–0.000
**11*	0.013	0.004–0.023	0.000	0.000–0.000	0.005	0.000–0.014	0.010	0.000–0.024	0.000	0.000–0.000
**13*	0.000	0.000–0.000	0.000	0.000–0.000	0.000	0.000–0.000	0.000	0.000–0.000	0.000	0.000–0.000
VKORC1										
g.-1639G	0.892	0.867–0.917	0.333	0.269–0.398	0.594	0.528–0.660	0.564	0.496–0.633	0.533	0.490–0.576
g.-1639A	0.108	0.083–0.133	0.667	0.602–0.731	0.406	0.340–0.472	0.436	0.367–0.504	0.467	0.424–0.510

CI: Confidence interval; Freq.: Frequency; n: Number of alleles

†*Data from* [18].

‡*Combined data with* [17].

Table 2

CYP2C9 genotype frequencies

Predicted metabolizer phenotype/genotype	Observed (expected[†]) frequency (%)				
	African–American[‡] (n = 300)	*Asian (n = 102)*	*Caucasian (n = 106)*	*Hispanic (n = 101)*	*Ashkenazi Jewish[§] (n = 502)*
Extensive metabolizer					
**1/*1*	75.7 (75.1)	86.3 (84.9)	66.0 (62.1)	70.3 (67.5)	62.4 (62.1)
Intermediate metabolizer					
**1/*2*	4.3 (4.9)	3.9 (5.4)	15.1 (23.8)	9.9 (11.4)	20.7 (20.2)
**1/*3*	3.3 (3.5)	6.9 (7.2)	9.4 (8.9)	8.9 (10.6)	12.0 (13.0)
**1/*5*	2.7 (2.6)	0.0 (0.0)	0.0 (0.0)	2.0 (2.4)	0.2 (0.2)
**1/*6*	1.7 (1.7)	0.0 (0.0)	0.0 (0.0)	1.0 (0.8)	0.0 (0.0)
**1/*8*	8.7 (8.1)	1.0 (1.8)	0.0 (0.0)	1.0 (2.4)	0.0 (0.0)
**1/*11*	2.0 (2.3)	0.0 (0.0)	0.9 (0.7)	1.0 (1.6)	0.0 (0.0)
Total	22.7 (23.1)	11.8 (14.5)	25.5 (33.4)	23.8 (29.3)	32.9 (33.4)
Poor metabolizer					
**2/*2*	0.3 (0.1)	1.0 (0.1)	6.6 (2.3)	1.0 (0.5)	1.2 (1.7)
**2/*3*	0.3 (0.1)	0.0 (0.2)	1.9 (1.7)	1.0 (0.9)	2.6 (2.1)
**2/*8*	0.0 (0.3)	0.0 (0.1)	0.0 (0.0)	1.0 (0.2)	0.0 (0.0)
**3/*3*	0.0 (0.0)	0.0 (0.2)	0.0 (0.3)	1.0 (0.4)	1.0 (0.7)
**3/*5*	0.0 (0.1)	0.0 (0.0)	0.0 (0.0)	1.0 (0.2)	0.0 (0.0)
**3/*8*	0.0 (0.2)	1.0 (0.1)	0.0 (0.0)	0.0 (0.2)	0.0 (0.0)
**3/*11*	0.3 (0.1)	0.0 (0.0)	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)
**5/*6*	0.3 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
**8/*11*	0.3 (0.1)	0.0 (0.0)	0.0 (0.0)	1.0 (0.0)	0.0 (0.0)
Total	1.7 (1.0)	2.0 (0.6)	8.5 (4.4)	6.0 (2.5)	5.0 (4.5)

Extensive metabolizer: CYP2C9*1/*1*; Intermediate metabolizer:* CYP2C9*1/variant; Poor metabolizer:* CYP2C9 *variant/variant.*

n: Number of subjects.

[†]*Predicted Hardy–Weinberg frequencies.*

[‡]*Data from* [18].

§ *Combined data with* [17].

Table 3

VKORC1 genotype frequencies

VKORC1 g.-1639G>A genotype	Observed (expected[†]) frequency (%)				
	African–American[‡] *(n = 300)*	*Asian (n = 102)*	*Caucasian (n = 106)*	*Hispanic (n = 101)*	*Ashkenazi Jewish*[§] *(n = 260)*
G/G	80.3 (79.5)	22.5 (11.1)	36.8 (35.3)	30.7 (31.8)	29.2 (28.4)
G/A	17.7 (19.3)	21.6 (44.4)	45.3 (48.2)	51.5 (49.2)	48.1 (49.8)
A/A	2.0 (1.2)	55.9 (44.4)	17.9 (16.5)	17.8 (19.0)	22.7 (21.8)

n: Number of subjects.

[†] *Predicted Hardy–Weinberg frequencies.*

[‡] *Data from* [18].

[§] *Data from* [17].

Table 4

***CYP4F2* allele frequencies**

Allele	African–American (n = 600)		Asian (n = 600)		Caucasian (n = 600)		Hispanic (n = 600)		Ashkenazi Jewish (n = 1000)	
	Freq.	95% CI	Freq.	95% CI	Freq.	95% CI	Freq.	95% CI	Freq.	95% CI
c.1297G>A										
G	0.883	0.858–0.909	0.695	0.658–0.732	0.658	0.620–0.696	0.767	0.733–0.801	0.672	0.643–0.701
A (p.V433M)	0.117	0.091–0.142	0.305	0.268–0.342	0.342	0.304–0.380	0.233	0.199–0.267	0.328	0.299–0.357
rs2189784										
G	0.698	0.662–0.735	0.643	0.605–0.682	0.553	0.514–0.593	0.645	0.607–0.683	0.514	0.483–0.545
A	0.302	0.265–0.338	0.357	0.318–0.395	0.447	0.407–0.486	0.355	0.317–0.393	0.486	0.455–0.517

CI: Confidence interval; Freq.: Frequency; n: Number of alleles.

Table 5

CYP4F2 genotype frequencies

CYP4F2 genotype	Observed (expected[†]) frequency (%)				
	African–American (n = 300)	*Asian (n = 300)*	*Caucasian (n = 300)*	*Hispanic (n = 300)*	*Ashkenazi Jewish (n = 500)*
c.1297G>A (p.V433M)					
G/G	78.0 (78.0)	48.0 (48.3)	42.7 (43.3)	58.7 (58.8)	43.4 (45.2)
G/A	20.7 (20.6)	43.0 (42.4)	46.3 (45.0)	36.0 (35.8)	47.6 (44.1)
A/A	1.3 (1.4)	9.0 (9.3)	11.0 (11.7)	5.3 (5.4)	9.0 (10.8)
rs2189784					
G/G	48.3 (48.8)	40.3 (41.4)	30.0 (30.6)	42.3 (41.6)	26.0 (26.4)
G/A	43.0 (42.1)	48.0 (45.9)	50.7 (49.4)	44.3 (45.8)	50.8 (50.0)
A/A	8.7 (9.1)	11.7 (12.7)	19.3 (20.0)	13.3 (12.6)	23.2 (23.6)

n: Number of subjects.

[†]*Predicted Hardy–Weinberg frequencies.*

Table 6

Combined *CYP2C9, VKORC1* and *CYP4F2*3* genotype frequencies

CYP2C9	*VKORC1* g.-1639G>A	*CYP4F2*3* (c.1297G>A; p.V433M)	African–American†		Asian		Caucasian		Hispanic		Ashkenazi Jewish‡	
			n	*Freq. (%)*	*n*	*Freq. (%)*	*n*	*Freq. (%)*	*n*	*Freq. (%)*	*n*	*Freq. (%)*
Extensive metabolizer	G/G	G/G	131	47.5	5	4.9	13	12.3	13	12.9	12	5.1
		G/A	31	11.2	4	3.9	10	9.4	8	7.9	25	10.7
		A/A	2	0.7	4	3.9	0	0.0	1	1.0	7	3.0
		G/A	11	4.0	7	6.9	17	16.0	12	11.9	35	15.0
		A/A	0	0.0	1	1.0	4	3.8	1	1.0	6	2.6
	A/A	G/G	2	0.7	27	26.5	6	5.7	9	8.9	13	5.6
		G/A	2	0.7	22	21.6	6	5.7	5	5.0	18	7.7
		A/A	0	0.0	7	6.9	2	1.9	0	0.0	4	1.7
Intermediate metabolizer	G/G	G/G	44	15.9	4	3.9	5	4.7	5	5.0	14	6.0
		G/A	11	4.0	2	2.0	5	4.7	2	2.0	9	3.8
		A/A	1	0.4	2	2.0	1	0.9	0	0.0	2	0.9
	G/A	G/G	7	2.5	2	2.0	4	3.8	8	7.9	17	7.3
		G/A	1	0.4	0	0.0	6	5.7	5	5.0	13	5.6
		A/A	0	0.0	1	1.0	1	0.9	0	0.0	5	2.1
	A/A	G/G	2	0.7	0	0.0	2	1.9	3	3.0	4	1.7
		G/A	0	0.0	1	1.0	3	2.8	1	1.0	12	5.1
		A/A	0	0.0	0	0.0	0	0.0	0	0.0	3	1.3
Poor metabolizer	G/G	G/G	0	0.0	1	1.0	1	0.9	1	1.0	1	0.4
		G/A	0	0.0	1	1.0	4	3.8	1	1.0	0	0.0
		A/A	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	G/A	G/G	1	0.4	0	0.0	3	2.8	2	2.0	1	0.4
		G/A	0	0.0	0	0.0	1	0.9	2	2.0	5	2.1
		A/A	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	A/A	G/G	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		G/A	0	0.0	0	0.0	0	0.0	0	0.0	1	0.4

CYP2C9	*VKORC1* g.-1639G>A	*CYP4F2*3* (c.1297G>A; p.V433M)	African–American†		Asian		Caucasian		Hispanic		Ashkenazi Jewish‡	
			n	*Freq. (%)*	*n*	*Freq. (%)*	*n*	*Freq. (%)*	*n*	*Freq. (%)*	*n*	*Freq. (%)*
		A/A	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Extensive metabolizer: CYP2C9*1/*1*; Intermediate metabolizer:* CYP2C9*1/*variant*; *Poor metabolizer:* CYP2C9 *variant/variant.*

Freq.: Frequency; n: Number of subjects.

†*Combined data with* [18].

‡*Combined data with* [17].