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Global Distribution of CYP2C9*2, *3 and VKORC1 –1639G>A Risk Variants and Their Clinical Implications

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ABSTRACT

Genetic variations in CYP2C9 and VKORC1 can significantly influence the safety and effectiveness of certain medications. Individuals carrying the CYP2C92 (rs1799853), CYP2C93 (rs1057910), or VKORC1 c.-1639G>A (rs9923231) alleles are at higher risk of adverse effects, particularly bleeding complications. Allele frequencies for CYP2C92, CYP2C93, and VKORC1 c.-1639G>A were sourced from Phase III of the 1000 Genomes Project, adhering to Fort Lauderdale data-sharing principles. Risk phenotypes were determined based on established pharmacogenomic (PGx) guidelines, classifying carriers of these variants accordingly. Approximately 17.8% (95% CI: 16.3%–19.3%) of the global population are predicted to be intermediate or poor metabolizers due to CYP2C9*2 and/or *3 variants, placing them at increased risk. This prevalence was highest in Europeans (35%; 95% CI: 30.8%–39.2%), followed by South Asians (26.8%; 95% CI: 22.9%–30.7%), Admixed Americans (25.9%; 95% CI: 21.3%–30.5%), East Asians (6.7%; 95% CI: 4.5%–8.9%), and Africans (2.1%; 95% CI: 1%–3.2%). When combining CYP2C9 and VKORC1 c.-1639G>A variants, 33.1% (95% CI: 31.3%–35%) of individuals were classified as sensitive or highly sensitive responders. This combined risk phenotype was most common in East Asians (79.6%; 95% CI: 76%–83.1%), followed by Europeans (38.6%; 95% CI: 34.3%–42.8%), Admixed Americans (30%; 95% CI: 25.2%–34.8%), South Asians (25.2%; 95% CI: 21.3%–29%), and Africans (1.2%; 95% CI: 0.4%–2%). Differences across populations were highly statistically significant ($p < 0.05$; χ^2 test, $p = 1.94 \times 10^{-175}$). According to PharmGKB, at least 29 widely used drugs have their safety or efficacy affected by CYP2C9 and/or VKORC1 c.-1639G>A polymorphisms. Of these, at least 23 carry pharmacogenomic labeling information, and the Clinical Pharmacogenetics Implementation Consortium (CPIC) has issued dosing recommendations for at least 11 drugs based on these genetic variants. The study indicates that roughly one in five people worldwide carries CYP2C9 risk alleles that may compromise the safety of certain medications, while approximately one-third are at risk when VKORC1 variation is also considered. These findings highlight the potential value of routine pharmacogenomic testing to improve drug safety, particularly for the 11 drugs with existing CPIC guidelines. Further research is needed to assess the real-world clinical impact of implementing PGx-guided prescribing.

Keywords: Genetic polymorphisms, Clinical practice, CYP2C9, VKORC1, Efficacy, Safety

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Introduction

Variations in DNA sequence that occur in at least 1% of the population are termed genetic polymorphisms [1, 2]. A person's response to a medication depends largely on its pharmacokinetic and pharmacodynamic properties, both of which can be profoundly altered by inherited differences in drug-metabolising enzymes [3]. Precision (or personalised) medicine aims to maximise benefit and minimise harm by selecting treatments according to a patient's genetic makeup. Within this field, cytochrome P450 (CYP) enzymes are especially important because they perform roughly 80% of all phase I oxidative drug metabolism [4-9]. CYP2C9 is one of the major hepatic CYP isoforms, constituting about 20% of total CYP protein in the liver when measured by mass spectrometry

[10]. It metabolises many widely used medicines, including oral anticoagulants (e.g., warfarin), several statins, NSAIDs, phenytoin, and sulfonylurea antidiabetic agents [11-16].

The CYP2C9 gene is highly polymorphic; more than 85 allelic variants have been catalogued to date [17]. The two best-characterised loss-of-function alleles are *2 (p.R144C, rs1799853) and *3 (p.I359L, rs1057910). The *2 allele reduces enzyme activity by 30–40%, whereas *3 causes a much larger decrease of approximately 80% [11]. For warfarin, these variants slow the clearance of the more potent S-enantiomer by 30–40% (*2) and 80–90% (*3), dramatically raising bleeding risk [18, 19]. Because of these effects, both the FDA and EMA now list CYP2C9 genotyping recommendations in the labelling of 19 drugs [20], and the CPIC has published dose-adjustment guidelines for several high-use medications [11, 13, 14, 21].

VKORC1, located on chromosome 16, codes for vitamin K epoxide reductase, the molecular target of warfarin and other coumarin anticoagulants [13, 22]. The promoter polymorphism c.-1639G>A (rs9923231) lowers VKORC1 expression; individuals homozygous for the A allele typically need about 70% less warfarin than GG homozygotes [23-28]. This observation prompted the FDA to update the warfarin label in 2007 [25]. Algorithms that combine CYP2C9 and VKORC1 c.-1639G>A genotypes are now routinely used to select starting doses and reduce bleeding complications, with strong supporting evidence from multiple clinical trials [29-36].

Allele frequencies of CYP2C9*2, *3 and VKORC1 c.-1639G>A differ markedly between continental populations and ethnic groups [30, 37-42]. Although the clinical importance of these variants is well recognised, comprehensive global surveys that include VKORC1 c.-1639G>A and link resulting risk phenotypes to the full range of affected prescription drugs are still scarce and often limited to regional subpopulations [20, 37, 43, 44]. To date, no published work has systematically connected these pharmacogenetic risk profiles to the number of commonly prescribed medicines whose safety or efficacy they influence.

Objectives

Most studies on genetic variant frequencies are restricted to subpopulations within limited geographic regions, which reduces their global applicability. This study aimed to estimate the worldwide prevalence of clinically relevant CYP2C92, CYP2C93, and VKORC1 c.-1639G>A polymorphisms using genetic data from the 1000 Genomes Project (2,504 individuals representing 26 populations). We sought to derive predicted pharmacogenetic phenotypes and associated risk categories on a global scale and to link these risk phenotypes to commonly prescribed medications whose efficacy and safety are influenced by these genetic variants.

Materials and Methods

Study population

Genotype data for CYP2C9*2, *3, and VKORC1 c.-1639G>A were analyzed from the 1000 Genomes Project Phase 3, covering five major continental ancestries: Africa (AFR), America (AMR), East Asia (EAS), Europe (EUR), and South Asia (SAS) [45, 46]. The dataset included:

- America (AMR): 347 individuals from four populations (Mexican Ancestry in Los Angeles [MXL], Colombians in Medellín [CLM], Puerto Ricans [PUR], Peruvians in Lima [PEL]).
- Europe (EUR): 503 individuals from five populations (Finnish [FIN], Utah residents with Northern/Western European ancestry [CEU], British [GBR], Toscani in Italy [TSI], Iberians [IBS]).
- Africa (AFR): 661 individuals from seven populations (African Ancestry Southwest US [ASW], African Caribbean in Barbados [ACB], Esan in Nigeria [ESN], Luhya in Webuye, Kenya [LWK], Gambian [GWD], Yoruba in Ibadan, Nigeria [YRI], Mende in Sierra Leone [MSL]).
- South Asia (SAS): 489 individuals from five populations (Gujarati Indians in Houston [GIH], Bengali in Bangladesh [BEB], Indian Telugu in UK [ITU], Sri Lankan Tamil in UK [STU], Punjabi in Lahore [PJL]).
- East Asia (EAS): 504 individuals from five populations (Han Chinese in Beijing [CHB], Chinese Dai in Xishuangbanna [CDX], Southern Han Chinese [CHS], Kinh in Ho Chi Minh City, Vietnam [KHV], Japanese in Tokyo [JPT]).

Genetic data extraction

In accordance with Fort Lauderdale principles, allele and genotype frequencies for CYP2C9*1, *2 (rs1799853), 3 (rs1057910), and VKORC1 c.-1639G>A (rs9923231) were obtained from the 1000 Genomes Project Phase 3

dataset for all 2,504 participants across the 26 populations. Individuals were assigned specific genotypes (e.g., CYP2C93/*3 for homozygous carriers of the *3 allele) based on the combination of alleles detected.

Assignment of predicted phenotypes and risk categories

CYP2C9 phenotypes were classified according to Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines [11, 14, 21]:

- Normal metabolizers (NM): CYP2C9*1/*1
- Intermediate metabolizers (IM): CYP2C9*1/*2, *1/*3, *2/*2
- Poor metabolizers (PM): CYP2C9*2/*3, *3/*3

For warfarin response, combined CYP2C9 and VKORC1 c.-1639G>A genotypes were used to define three response categories based on updated FDA labeling [19]:

- Normal responders (NR): e.g., CYP2C9*1/1 with VKORC1 G/G or A/G; CYP2C91/*2 with VKORC1 G/G
- Sensitive responders (SR): e.g., CYP2C9*1/*1 with VKORC1 A/A; various *1/*2 or *1/*3 combinations with A/G or A/A; *2/*2 with G/G
- Highly sensitive responders (HSR): combinations involving *1/*3 or *2/*2 with A/A, any *2/*3 or *3/*3 genotype regardless of VKORC1 status

These categories are summarized in **Table 1**.

Table 1. Predictive phenotypes based on the combined genotypes of *CYP2C9*2*, *CYP2C9*3*, and *VKORC1 c.-1639G>A* genetic variants.

Genetic variants		*CYP2C9*					
		**1/*1*	**1/*2*	**1/*3*	**2/*2*	**2/*3*	**3/*3*
VKORC1 c.-1639G>A	*G/G*	Normal responder	Normal responder	Sensitive responder	Sensitive responder	Highly sensitive responder	Highly sensitive responder
	A/G	Normal responder	Sensitive responder	Sensitive responder	Highly sensitive responder	Highly sensitive responder	Highly sensitive responder
	A/A	Sensitive responder	Sensitive responder	Highly sensitive responder	Highly sensitive responder	Highly sensitive responder	Highly sensitive responder

According to Clinical Pharmacogenetics Implementation Consortium (CPIC) dosing guidelines, individuals classified as CYP2C9 intermediate metabolizers (IM) or poor metabolizers (PM) are at increased safety risk for numerous clinically important CYP2C9 substrate drugs; thus, these IM and PM groups were designated as risk phenotypes in this study [11, 14, 21].

The association between CYP2C92, CYP2C93, and VKORC1 c.-1639G>A variants and increased bleeding risk during warfarin therapy has been consistently demonstrated across multiple studies [30, 32, 39, 47-53]. Sensitive and highly sensitive responders exhibit a 2- to 5-fold higher risk of major hemorrhage [19, 53, 54]. Accordingly, warfarin sensitive responders (SR) and highly sensitive responders (HSR) were also classified as risk populations in the present study.

Linking risk phenotypes to medication safety and effectiveness

Clinical pharmacogenomic annotations and prescribing information for CYP2C92, CYP2C93, and VKORC1 c.-1639G>A were obtained from internationally recognized sources including FDA-approved drug labels, European Medicines Agency (EMA)-approved labels, Health Canada/Santé Canada (HCSC)-approved labels, and PharmGKB curated evidence [15, 55]. Actionable dosing recommendations were derived from published CPIC guidelines for the relevant drugs [11, 13, 14, 21].

Human ethics approval

All genetic data used in this study were sourced from Phase 3 of the 1000 Genomes Project, which complies with the Fort Lauderdale principles. No additional institutional ethics approval was required, as explicitly permitted for secondary use of these publicly available, previously published data [45, 46].

Statistical analysis

Descriptive statistics were used to calculate allele frequencies, genotype distributions, and risk phenotype prevalence. All analyses and graphical representations were performed using Microsoft Excel. Inter-population differences were assessed for statistical significance using the chi-square test. Results are presented as line charts.

Validation of data analysis

Raw variant data from the 1000 Genomes Project were independently categorized into genotype groups by two researchers using the COUNTIFS function in Microsoft Excel. All results were subsequently cross-verified and reconciled by the corresponding author to ensure accuracy and resolve any discrepancies.

Results and Discussion

Prevalence and distribution of CYP2C92, CYP2C93, and VKORC1 c.-1639G>A alleles and genotypes across 26 populations

- CYP2C9*2 allele: Global frequency 4.8% (95% CI 4.0%–5.6%). Highest in Europeans (12.4%; 95% CI 11.1%–13.7%), followed by Americans (9.9%; 95% CI 8.8%–11.1%), South Asians (3.5%; 95% CI 2.8%–4.2%), Africans (0.8%; 95% CI 0.5%–1.2%), and East Asians (0.1%; 95% CI 0%–0.2%).
- CYP2C9*3 allele: Global frequency 4.9% (95% CI 4.0%–5.7%). Highest in South Asians (10.9%; 95% CI 9.7%–12.2%), followed by Europeans (7.3%; 95% CI 6.2%–8.3%), Americans (3.7%; 95% CI 3.0%–4.5%), East Asians (3.4%; 95% CI 2.7%–4.1%), and Africans (0.2%; 95% CI 0%–0.4%).
- VKORC1 c.-1639A allele: Global frequency 35.6% (95% CI 33.7%–37.4%). Markedly highest in East Asians (88.5%; 95% CI 87.2%–89.7%), followed by Americans (41.1%; 95% CI 39.1%–43.0%), Europeans (38.8%; 95% CI 36.9%–40.7%), South Asians (14.5%; 95% CI 13.1%–15.9%), and Africans (5.4%; 95% CI 4.6%–6.3%).
- VKORC1 c.-1639G>A genotypes:
    - Heterozygotes (A/G) were most frequent in Americans (47.6%; 95% CI 42.3%–52.8%) and Europeans (46.1%; 95% CI 41.8%–50.5%), with the lowest frequency in Africans (10%; 95% CI 7.7%–12.3%). South Asians and East Asians showed intermediate frequencies of 24.1% (95% CI 20.3%–27.9%) and 19.4% (95% CI 16.0%–22.9%), respectively.
    - Homozygous A/A was predominant in East Asians (78.8%; 95% CI 75.2%–82.3%), followed by Americans (17.3%; 95% CI 13.3%–21.3%) and Europeans (15.7%; 95% CI 12.5%–18.9%). Prevalence was low in South Asians (2.5%; 95% CI 1.1%–3.8%) and extremely low in Africans (0.5%; 95% CI 0%–1.0%).
- CYP2C9 predicted genotypes (global frequencies):
    - *1/*1: 82.2% (95% CI 80.7%–83.7%) – most common
    - *1/*3: 8.5% (95% CI 7.4%–9.6%)
    - *1/*2: 7.7% (95% CI 6.7%–8.7%)
    - *2/*3: 0.8% (95% CI 0.5%–1.1%)
    - *2/*2: 0.6% (95% CI 0.3%–0.9%)
    - *3/*3: 0.2% (95% CI 0%–0.4%)

- VKORC1 c.-1639G>A genotypes (global frequencies):
    - G/G: 50.9% (95% CI 48.9%–52.9%)
    - A/G: 27.1% (95% CI 25.4%–28.8%)
    - A/A: 22.0% (95% CI 20.4%–23.6%)

Table 2. Frequency of genotypes associated with carrying either *CYP2C9*2*, *CYP2C9*3*, or *VKORC1 c.-1639G>A* genetic variants in the world populations participating in the 1000 Genomes Project.

Population	Genotype								
	CYP2C9						*VKORC1 c.-1639G>A*		
	**1/*1*	**1/*2*	**2/*2*	**1/*3*	**3/*3*	**2/*3*	*G/G*	*A/G*	*A/A*
AFR	97.9	1.7	0.0	0.5	0.0	0.0	89.6	10.0	0.5
AMR	74.1	17.9	0.6	6.6	0.0	0.9	35.2	47.6	17.3

EAS	93.3	0.2	0.0	6.3	0.2	0.0	1.8	19.4	78.8
SAS	73.2	5.3	0.2	19.4	0.6	1.2	73.4	24.1	2.5
EUR	65.0	18.5	2.2	12.1	0.2	2.0	38.2	46.1	15.7
All populations	82.2	7.7	0.6	8.5	0.2	0.8	50.9	27.1	22.0

Entries in bold represent the average prevalence in all populations.

Distribution of predicted CYP2C9 metabolizer phenotypes across populations

Using the genotype-to-phenotype translation rules outlined in the Methods and displayed in **Figure 1**, individuals were categorized into normal (NM), intermediate (IM), and poor metabolizers (PM).

Across the entire dataset, normal metabolizers accounted for 82.2% of participants (95% CI 80.7–83.7%). This phenotype was nearly universal in African-ancestry groups (97.9%; 95% CI 96.8–99.0%), very common in East Asians (93.3%; 95% CI 91.1–95.4%), and progressively less frequent in admixed American (74.1%; 95% CI 69.5–78.7%), South Asian (73.2%; 95% CI 69.3–77.1%), and European populations (65.0%; 95% CI 60.8–69.2%).

Intermediate metabolizers represented 16.8% of the global sample (95% CI 15.3–18.3%). They were most common among Europeans (32.8%; 95% CI 28.7–36.9%), followed closely by admixed American (25.1%; 95% CI 20.5–29.6%) and South Asian groups (24.9%; 95% CI 21.1–28.8%). The frequency dropped sharply in East Asians (6.5%; 95% CI 4.4–8.7%) and was rare in Africans (2.1%; 95% CI 1.0–3.2%).

Poor metabolizers were uncommon overall (1.0%; 95% CI 0.6–1.3%). The highest proportions were seen in Europeans (2.2%; 95% CI 0.9–3.5%) and South Asians (1.8%; 95% CI 0.6–3.0%), with lower rates in admixed Americans (0.9%; 95% CI 0–1.8%) and East Asians (0.2%; 95% CI 0–0.5%). No individuals with a poor-metabolizer genotype were identified in any of the African-ancestry populations.

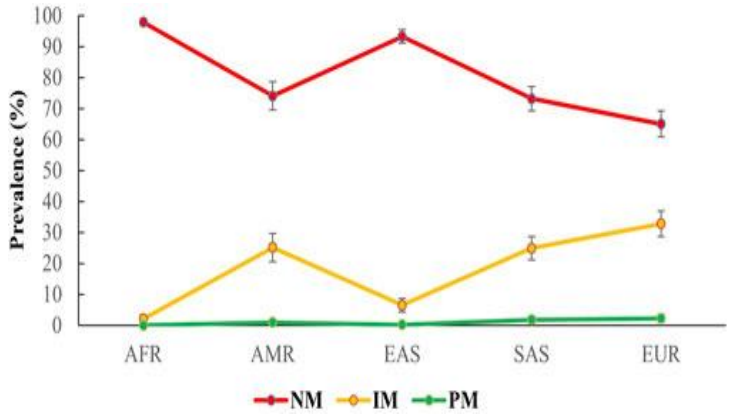

Figure 1. Predicted prevalence of CYP2C9 metabolic phenotypes (NM: normal metabolizer; IM: intermediate metabolizer; PM: poor metabolizer) across populations from the 1000 Genomes Project (AFR: African, AMR: Admixed American, EAS: East Asian, SAS: South Asian, EUR: European). Phenotypes were assigned based on carriage of the CYP2C9*1, *2, and *3 alleles according to international guidelines.

For the combined CYP2C9 and VKORC1 c.-1639G>A genotypes, individuals were classified into three warfarin-sensitivity phenotype categories (NR: normal response, SR: sensitive response, HSR: highly sensitive response) as outlined in the methods.

Geographic analysis of these combined predictive phenotypes revealed striking population differences:

- Normal response (NR) was most prevalent in Africans (98.8%, 95% CI 98.0–99.6%), followed by South Asians (74.8%, 95% CI 71.0–78.7%), Admixed Americans (70.0%, 95% CI 65.2–74.8%), Europeans (61.4%, 95% CI 57.2–65.7%), and was least common in East Asians (20.4%, 95% CI 16.9–24.0%).
- Sensitive response (SR) showed the opposite pattern, with the highest frequency in East Asians (73.8%, 95% CI 70.0–77.6%) and the lowest in Africans (1.2%, 95% CI 0.4–2.0%). Intermediate prevalences were observed in Europeans (33.2%, 95% CI 29.1–37.3%), Admixed Americans (27.1%, 95% CI 22.4–31.8%), and South Asians (22.7%, 95% CI 19.0–26.4%).
- Highly sensitive response (HSR) was most frequent in East Asians (5.8%, 95% CI 3.7–7.8%) and Europeans (5.4%, 95% CI 3.4–7.3%), followed by Admixed Americans (2.9%, 95% CI 1.1–4.6%) and South Asians (2.5%, 95% CI 1.1–3.8%). No individuals with HSR were identified in the African population.

The distribution of these combined phenotype groups across populations is illustrated in **Figure 2.**

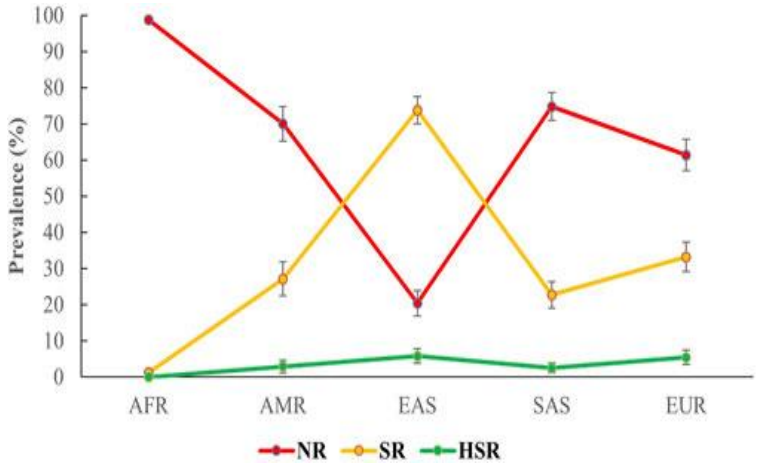

Figure 2. Predicted prevalence of combined CYP2C9 and VKORC1 c.-1639G>A phenotypes in populations from the 1000 Genomes Project (AFR: African, AMR: Admixed American, EAS: East Asian, SAS: South Asian, EUR: European). Phenotypes were categorized as normal responders (NR), sensitive responders (SR), and highly sensitive responders (HSR) according to international guidelines and the carrier status of CYP2C9 and VKORC1 c.-1639G>A variant alleles.

Prevalence of risk phenotypes across the 26 populations

As described in the Methods section, CYP2C9 risk phenotypes were defined by the presence of intermediate (IM) or poor metabolizer (PM) status. Among the 2,504 individuals in the 1000 Genomes Project, CYP2C9 risk phenotypes were present in approximately one-fifth of participants (17.8%; 95% CI 16.3%–19.3%). Marked geographic variation was observed: the highest prevalence occurred in Europeans (35.0%; 95% CI 30.8%–39.2%), followed by South Asians (26.8%; 95% CI 22.9%–30.7%), Admixed Americans (25.9%; 95% CI 21.3%–30.5%), East Asians (6.7%; 95% CI 4.5%–8.9%), and Africans, who showed the lowest frequency (2.1%; 95% CI 1.1%–3.2%).

For the combined CYP2C9 and VKORC1 c.-1639G>A genotypes, sensitive (SR) and highly sensitive (HSR) responders were considered risk phenotypes and accounted for roughly one-third of the cohort (33.1%; 95% CI 31.3%–35.0%). East Asians displayed the highest prevalence of these combined risk phenotypes (79.6%; 95% CI 76.0%–83.1%), whereas Africans had the lowest (1.2%; 95% CI 0.4%–2.0%). Europeans, Admixed Americans, and South Asians showed intermediate frequencies of 38.6% (95% CI 34.3%–42.8%), 30.0% (95% CI 25.2%–34.8%), and 25.2% (95% CI 21.3%–29.0%), respectively. The differences in risk-phenotype distribution across ancestral groups were highly statistically significant ($p < 0.05$; $\chi^2 = 1.94 \times 10^{-175}$).

Clinical implications of CYP2C9 and VKORC1 c.-1639G>A risk phenotypes for drug safety and efficacy

According to PharmGKB clinical annotations (PharmGKB, 2025a), genetic variation in CYP2C9 affects the safety or efficacy of at least 29 commonly prescribed drugs, with evidence levels ranging from 1A (high) to 4 (preliminary). Eleven drugs—warfarin, celecoxib, flurbiprofen, fluvastatin, ibuprofen, lornoxicam, meloxicam, phenytoin, piroxicam, siponimod, and tenoxicam—carry the strongest evidence (Level 1A). Acenocoumarol has Level 1B evidence, at least 14 drugs have Level 3 evidence, and at least three drugs have Level 4 (unsupported) evidence related to CYP2C9*2 or *3 alleles.

In contrast, VKORC1 c.-1639G>A is linked to altered response for at least three drugs (warfarin, acenocoumarol, and phenprocoumon), all supported by Level 1A evidence (PharmGKB, 2025b).

Pharmacogenomic (PGx) labeling information from the FDA, EMA, Health Canada (HCSC), Japan's PMDA, and Swissmedic exists for CYP2C9 variants in at least 23 drugs, primarily sourced from the FDA's Table of Pharmacogenomic Biomarkers in Drug Labeling. CYP2C9 testing is explicitly required for siponimod. Fifteen drugs are labeled "Actionable PGx," recommending dose adjustment or alternative therapy in individuals with known risk genotypes/phenotypes (although pre-treatment testing is not mandated). Three drugs (abrocitinib, rimegepant, and prasugrel) are categorized as "No Clinical PGx," providing genetic information without specific clinical recommendations (PharmGKB, 2025a).

For VKORC1 c.-1639G>A, warfarin is the only drug with formal drug-label PGx annotation; both the FDA and HCSC classify it as "Actionable PGx." A detailed list of affected drugs and corresponding evidence levels is presented in **Table 3.**

Table 3. The PharmGKB drug labels for the *CYP2C9* and *VKORC1 c.-1639G>A* genetic variants.

Drugs	FDA	EMA	HCSC	PMDA	Swissmedic	Genetic variants
Avatrombopag	Informative PGx	Actionable PGx	Actionable PGx	-	-	*CYP2C9*2, CYP2C9*3*
Celecoxib	Actionable PGx	-	Actionable PGx	Actionable PGx	Actionable PGx	*CYP2C9*2, CYP2C9*3*
Dronabinol	Actionable PGx	-	-	-	-	*CYP2C9*2, CYP2C9*3*
Erdafitinib	Actionable PGx	-	Actionable PGx	-	-	*CYP2C9*3*
Etrasimod	Informative PGx	Actionable PGx	Informative PGx	-	-	*CYP2C9*2, CYP2C9*3*
Flibanserin	Informative PGx	-	Informative PGx	-	-	*CYP2C9*2, CYP2C9*3*
Flurbiprofen	Actionable PGx	-	Actionable PGx	-	-	*CYP2C9*2, CYP2C9*3*
Fosphenytoin	Actionable PGx	-	Informative PGx	-	-	*CYP2C9*2, CYP2C9*3*
Glyburide	-	-	Actionable PGx	-	-	*CYP2C9*2, CYP2C9*3*
Lesinurad	Actionable PGx	Actionable PGx	-	-	Informative PGx	*CYP2C9*1, CYP2C9*3*
Meloxicam	Informative PGx	-	-	-	-	*CYP2C9*2, CYP2C9*3*
Nateglinide	Informative PGx	-	-	-	-	*CYP2C9*2, CYP2C9*3*
Phenytoin	Actionable PGx	-	Informative PGx	-	Actionable PGx	*CYP2C9*2, CYP2C9*3*
Piroxicam	Actionable PGx	-	-	-	Actionable PGx	*CYP2C9*2, CYP2C9*3*
Prasugrel	-	-	-	-	Informative PGx	*CYP2C9*
Siponimod	Testing required	Testing required	Testing required	-	-	*CYP2C9*1, CYP2C9*2, CYP2C9*3*
Warfarin	Actionable PGx	-	Actionable PGx	-	-	*CYP2C9*1, CYP2C9*2, CYP2C9*3, rs9923231*
Glimepiride	-	-	Actionable PGx	-	-	*CYP2C9*2, CYP2C9*3*
Losartan	-	-	-	-	Actionable PGx	*CYP2C9*3*
Acenocoumarol	-	-	-	-	Actionable PGx	*CYP2C9*2, CYP2C9*3*
Brivaracetam	-	-	-	-	Informative PGx	*CYP2C9*2, CYP2C9*3*

Here, FDA, Food and Drug Administration; EMA, European Medicines Agency; HCSC, Health Canada Santé Canada; PMDA, Pharmaceuticals and Medical Devices Agency; PGx, pharmacogenomics.

To date, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has published pharmacogenomic dosing guidelines for 11 drugs that are influenced by CYP2C9 genetic variation [11, 13, 14, 21]. For warfarin, CPIC provides a comprehensive dosing algorithm that incorporates CYP2C9 and VKORC1 variants, along with CYP4F2 and rs12777823, and takes patient ancestry into account [13].

These guidelines are detailed in **Tables 4 and 5** and strongly emphasize the need for special caution in individuals with CYP2C9 intermediate metabolizer (IM) or poor metabolizer (PM) phenotypes to ensure both safety and

efficacy of many clinically important medications. For instance, in patients with IM or PM status, CPIC recommends preferring alternative agents that are not dependent on CYP2C9 metabolism, are not substrates of CYP2C9, or are CYP2C9 substrates but have a short half-life, rather than using piroxicam or tenoxicam.

Table 4. The CPIC dosing guidelines for drugs based on the *CYP2C9* genetic polymorphism.

Drugs	CYP2C9 phenotype	Recommendations	Classification of recommendations	References
Celecoxib, flurbiprofen, ibuprofen, lornoxicam	IM (AS-1)	CPIC guidelines recommend starting therapy at the lowest recommended initial dose for patients with CYP2C9 intermediate metabolizer (IM) status and an activity score (AS) of 1.0.	Moderate	[21]
	PM	CPIC recommends initiating therapy at 25%–50% of the lowest recommended starting dose in patients with CYP2C9 intermediate metabolizer status and an activity score (AS) of 1.0.	Moderate	[21]
Fosphenytoin, phenytoin	IM (AS-1)	CPIC notes that CYP2C9 intermediate metabolizers (IMs) with an activity score (AS) of 1.0 may require dose reduction because higher plasma concentrations increase the risk of toxicity.	Moderate	[14]
	PM	CPIC recommends that CYP2C9 poor metabolizers (PMs) receive substantially reduced doses (or consider an alternative agent when available) due to significantly increased plasma concentrations that markedly elevate the risk of toxicity.	Strong	[14]
Fluvastatin	IM	CPIC recommends avoiding doses >40 mg in CYP2C9 intermediate metabolizers (IMs). If higher doses are required to achieve therapeutic goals, an alternative statin (not metabolized by CYP2C9) should be considered.	Moderate	[11]
	PM	CPIC recommends avoiding doses >20 mg in CYP2C9 poor metabolizers (PMs). If higher doses are required to achieve therapeutic goals, consider an alternative statin that is not metabolized by CYP2C9.	Moderate	[11]
Meloxicam	IM (AS-1)	CPIC recommends initiating therapy at 50% of the lowest recommended starting dose in CYP2C9 intermediate metabolizers (IMs) with an activity score (AS) of 1.0.	Moderate	[21]
	PM	CPIC recommends avoiding meloxicam in CYP2C9 poor metabolizers (PMs) due to significantly prolonged half-life and markedly increased plasma exposure; an alternative NSAID (not metabolized by CYP2C9) should be used.	Moderate	[21]
Piroxicam, tenoxicam	PM/IM	CPIC recommends selecting an alternative NSAID for CYP2C9 poor metabolizers (PMs) and intermediate metabolizers (IMs) that is: not metabolized by CYP2C9, not substantially affected by CYP2C9 genetic variants in vivo, or metabolized by CYP2C9 but has a shorter half-life.	Moderate	[21]

Here, IM, intermediate metabolizers; PM, poor metabolizers; AS, activity score.

Table 5. The CPIC dosing guidelines for warfarin based on the *CYP2C9* and *VKORC1 c.-1639G>A* genetic polymorphisms.

Drugs	*CYP2C9* and *VKORC1 c.-1639G>A* combined phenotype	Recommendations	Classification of recommendations	References

Warfarin	HSR, SR	CPIC recommends that for non-African individuals carrying CYP2C9 *2 and/or *3 alleles and VKORC1 c.-1639G>A, dosing should be based on validated pharmacogenetic algorithms.	Strong	[13]
		CPIC recommends that, for African individuals carrying CYP2C9 *2 and/or *3 alleles and VKORC1 c.-1639G>A, dosing be determined using validated pharmacogenetic algorithms, with an additional 15%–30% dose reduction applied if the patient also carries CYP2C9 *5, *6, *8, or *11 variant alleles.	Moderate	

Here, SR, sensitive responders; HSR, highly sensitive responders.

This study demonstrated that 17.8% (95% CI: 16.3%–19.3%) of individuals in the 1000 Genomes Project possess CYP2C9 genotypes that increase the risk of toxicity for multiple clinically important drugs influenced by CYP2C9 genetic variation. Likewise, the combined effect of CYP2C9 and VKORC1 c.-1639G>A polymorphisms places 33.1% (95% CI: 31.3%–35.0%) of the cohort at elevated risk of adverse outcomes during warfarin therapy. South Asian and European populations exhibited the highest burden of clinically actionable CYP2C9 variants, whereas East Asian and European ancestries were most affected by the combined CYP2C9/VKORC1 c.-1639G>A genotype. These observations identify key populations for targeted pharmacogenomic research and personalized therapeutic strategies.

The allele frequencies of CYP2C9*2 and *3 across 26 global populations, as well as VKORC1 c.-1639G>A, aligned closely with previously reported data, thereby validating earlier findings [37, 39, 43, 44, 56-58].

Although the results offer a solid foundation for estimating global pharmacogenetic risk, several limitations exist. Notably, the 1000 Genomes Project does not include samples from the Middle East, North Africa (MENA), or Oceania, which may bias overall prevalence estimates. Additionally, phenoconversion—where non-genetic factors such as comorbidities or drug interactions alter the expressed phenotype despite the underlying genotype—must be considered [59]. For example, co-administration of fluconazole (a CYP2C9 inhibitor) with flurbiprofen (a CYP2C9 substrate) showed that a 200 mg dose of fluconazole converts CYP2C9 normal metabolizers (NMs) to intermediate metabolizers (IMs) and IMs to poor metabolizers (PMs), while a 400 mg dose converts both NMs and IMs to PMs [60]. These interactions highlight the need for larger, more comprehensive studies that incorporate both genetic and non-genetic determinants of drug response.

Several international pharmacogenomics consortia are translating evidence into clinical practice. PharmGKB currently provides graded clinical annotations for at least 29 drugs associated with CYP2C9*2 and *3 and at least three drugs linked to VKORC1 c.-1639G>A. The U.S. FDA contributes the majority (~73.9%) of CYP2C9 pharmacogenomic labeling information, supplemented by agencies including the EMA, Health Canada (HCSC), PMDA, and Swissmedic [61].

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published genotype-based dosing guidelines for at least 10 drugs metabolized by CYP2C9 (primarily accounting for *2 and *3 alleles) and a detailed warfarin dosing algorithm that integrates both CYP2C9 and VKORC1 c.-1639G>A genotypes. Using CPIC-standardized phenotype assignments, this study represents the first global-scale analysis of predictive high-risk phenotypes for CYP2C9 alone and in combination with VKORC1 c.-1639G>A across diverse populations.

The observed prevalence—17.8% (95% CI: 16.3%–19.3%) at risk due to CYP2C9 variants and 33.1% (95% CI: 31.3%–35.0%) at risk due to the CYP2C9/VKORC1 combination—underscores the urgent need for widespread implementation of pharmacogenomic testing. For instance, meloxicam, which has a long half-life (15–20 h), carries heightened toxicity risk in impaired metabolizers; CPIC therefore recommends alternative therapy for CYP2C9 poor metabolizers and a 50% dose reduction in certain intermediate metabolizers (activity score 1.0) to prevent excessive exposure [21].

It should also be noted that CYP2C9 genetic variation does not account for all pharmacokinetic differences in affected drugs. Additional genetic factors frequently contribute to the efficacy or safety of the same medications. For instance, fluvastatin response is influenced by both SLCO1B1 and CYP2C9 variants, phenytoin metabolism is modulated by polymorphisms in CYP2C19, CYP1A1, and EPHX1, and warfarin safety is affected not only by CYP2C9 and VKORC1 but also by CYP4F2 and rs12777823 [11, 13, 14, 62, 63]. In such cases, constructing

pharmacogenomic polygenic response scores (PGxRS) that integrate multiple relevant variants could substantially improve the prediction of adverse reactions or therapeutic failure.

Despite active efforts by international pharmacogenomics consortia to implement genotype-guided prescribing, limited evidence and incomplete genotype–phenotype correlations remain major barriers to the routine adoption of precision medicine. Although guidelines and drug-label updates continue to emerge, clinical uptake is still restricted. The current study helps address this gap by delivering comprehensive, population-scale evidence that may inform regulatory bodies and healthcare stakeholders, particularly supporting the integration of pharmacogenomic testing for drugs with strong genetic associations.

Limitations

This analysis relies on predicted phenotypes derived from genotype combinations rather than direct measurement of CYP2C9 or VKORC1 enzyme activity, which may introduce some variability in risk estimates. Furthermore, the lack of representation from the Middle East, North Africa (MENA), and Oceania in the 1000 Genomes Project reduces the generalizability of the global prevalence figures.

Future directions

Having demonstrated the relevance of CYP2C9*2, *3, and VKORC1 c.-1639G>A variants to the safety of at least 11 widely used drugs, future research should prioritize large-scale, prospective, real-world studies evaluating pharmacogenomic-guided therapy and clinical outcomes. Additional efforts are also needed to generate high-level evidence for drugs currently classified under lower evidence categories in PharmGKB, thereby facilitating more definitive implementation recommendations.

Conclusion

To enhance the safety of at least 11 clinically important medications, this study shows that approximately one-fifth of the global population carries CYP2C9 genotypes conferring increased risk, whereas roughly one-third are at risk when CYP2C9 and VKORC1 c.-1639G>A variants are considered together. Large-scale, longitudinal investigations across diverse ethnic groups are now essential to confirm the clinical utility of routine pharmacogenomic testing and to advance the realization of precision medicine.

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