

Impact of CYP2C19 genetic polymorphisms on voriconazole exposure and safety in a Uruguayan hemato-oncologic cohort

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Research Article

Keywords: voriconazole, genotyping, CYP2C19, therapeutic drug monitoring, adverse drug reactions

Posted Date: October 6th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11133295/v1>

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Additional Declarations: No competing interests reported.

Abstract

Purpose

To evaluate the impact of CYP2C19 genetic polymorphisms on voriconazole exposure and the occurrence of adverse drug reactions in a Uruguayan hematology-oncology population treated with voriconazole.

Methods

Oncohematologic patients treated at a university hospital in Uruguay were enrolled between December 2021 and December 2024. CYP2C19 genotyping classified patients as normal, intermediate, or rapid metabolizers. Trough concentrations, clinical and paraclinical outcomes, including adverse drug reactions, were analyzed.

Results

Nearly half (46%) of trough concentrations fell outside the recommended therapeutic range: 27% were subtherapeutic and 19% were supratherapeutic. Genotypic distribution was 60% normal, 28% intermediate and 12% rapid metabolizers. Rapid metabolizers showed lower voriconazole exposure than normal metabolizers. While exposure did not differ significantly between intermediate and normal metabolizers, dose-dependent adverse events, including hallucinations and arthralgia, occurred in intermediate metabolizers. Elevated liver enzymes were observed in 60% of patients but were generally mild and frequently influenced by co-administration of other hepatotoxic agents.

Conclusion

CYP2C19 genetic polymorphisms significantly influence VCZ plasma levels and the risk of toxicity. CYP2C19 genotyping enables early identification of patients at risk of suboptimal drug exposure and adverse effects but is insufficient as a standalone strategy. Integrating preemptive genotyping with routine therapeutic drug monitoring is essential to personalize treatment, particularly in high-risk patients and complex clinical scenarios involving significant drug-drug interactions. Careful liver function monitoring remains crucial, especially in patients receiving other hepatotoxic agents.

Introduction

The administration of antifungals for therapeutic and, especially, prophylactic purposes is a constant in patients requiring hematology-oncology treatment. Although there have been major improvements in the past few years in the diagnosis and treatment of invasive fungal infections (IFIs), such as aspergillosis and candidiasis, they remain among the most common causes of infectious morbidity and mortality in

these patients. Voriconazole (VCZ) is a second-generation triazole with broad-spectrum antifungal activity used as a first-line treatment for IFIs [1–3].

VCZ exerts its antifungal activity by inhibition of 14- α -lanosterol demethylation, which is mediated by fungal cytochrome P450 enzymes [4]. It is rapidly and almost completely absorbed after oral administration, reaching peak plasma concentrations within 1–2 hours. Absolute bioavailability after oral administration is estimated to be 96%. Absorption is not affected by gastric pH, but food delays absorption and reduces bioavailability by 22%. The volume of distribution of VCZ at steady state is 4.6 L/kg, indicating extensive tissue distribution. Plasma protein binding is estimated to be 60%. It is eliminated by hepatic metabolism, with less than 2% of the dose found unchanged in urine. It exhibits nonlinear pharmacokinetics, with concentrations increasing disproportionately indicating dose-dependent metabolism. The elimination half-life is dose-dependent and is approximately 6 hours for 200 mg (oral administration). *In vivo* studies have suggested that VCZ is mainly metabolized by the hepatic cytochrome P450 isoenzyme CYP2C19 to VCZ- N-oxide [4–7].

VCZ is effective and generally well tolerated. However, it has a narrow therapeutic index and high variability in pharmacokinetics that can lead to unpredictable plasma levels. Plasma concentrations of VCZ show high interindividual variability, which may be due to the action of numerous factors (e.g. age, sex, weight, liver disease). Among these factors, genetic variations in *CYP2C19* (main hepatic cytochrome P450 enzyme responsible for its metabolism) gene play a predominant role in the drug's response [8, 9].

The *CYP2C19* gene is extensively polymorphic. According to the Pharmacogene Variation (PharmVar) Consortium, thirty-nine different alleles have been identified [10].

The *CYP2C19* alleles, *CYP2C19**2 (c.681G > A) and *CYP2C19**3 (c.636G > A) are the most studied loss-of-function variants. *CYP2C19**2 causes an mRNA splicing defect, while *CYP2C19**3 creates a stop codon, resulting both in a non-functional enzyme. In contrast, the *CYP2C19* rs12248560 allele (*CYP2C19**17, c.-806C > T), the only described allele to be associated with increased enzyme activity, is due to a variation in the promoter region, resulting in increased transcription.

Depending on the co-existing alleles, patients are classified into different phenotypic categories such as:

- - normal metabolizer (NM): two copies of normal function alleles (without a *2, *3, or *17 allele)
- - poor metabolizer (PM): combinations of no function alleles and/or decreased function alleles (two copy of a *2 or *3 allele or combination of both)
- - intermediate metabolizer (IM): one normal/increased function allele and one decreased function allele (one copy of a *2 or *3 allele)
- - rapid metabolizer (RM): combinations of normal function and increased function alleles (*1/*17 genotype)
- - ultrarapid metabolizer (UM): Two increased function alleles are present (*17/*17 genotype)

The global frequencies of *CYP2C19**2, *CYP2C19**3, and *CYP2C19**17 are 15.2%, 0.3%, and 20.4%, respectively. However, they vary according to ethnicity. For example, in Europeans, *CYP2C19**2 and *CYP2C19**17 are highly represented (14.6% and 21.7%, respectively), whereas *CYP2C19**3 is relatively rare (0.02%). Other reduced, non-functional or increased *CYP2C19* alleles are rare [11].

In patients carrying *CYP2C19* alleles other than the wild-type allele, altered VCZ exposure is expected; therefore, these alleles are considered risk alleles and specific clinical recommendations apply. Influence of pharmacogenomics in VCZ pharmacokinetics has been explored, mostly on Caucasian or Asian populations. UM phenotypes have frequent sub therapeutic levels, and PM have more frequent supra therapeutic levels [12–15].

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has released VCZ dosing guidelines based on *CYP2C19* genotype for both pediatric and adult patients [16]. In adult UM and RM metabolizers the probability of achieving therapeutic concentrations with standard dosing is reduced, therefore alternative antifungal agents, not primarily metabolized by *CYP2C19*, are preferred. Conversely, IM and PM metabolizers exhibit higher dose-adjusted trough concentrations, with PM at increased risk of adverse events. For PM, alternative agents are recommended, but if VCZ is initiated, a preemptive dose reduction combined with stringent therapeutic drug monitoring is advised [16].

The great variability in exposure to VCZ together with the confirmation of a good correlation of the pre-dose concentration (C_0) with effectiveness and adverse reactions (ADRs), position therapeutic drug monitoring (TDM) as a valuable tool in optimizing treatment outcomes and minimizing adverse effects [17].

The Infectious Diseases Society of America [18, 19] recommends a trough level $> 1–1.5 \mu\text{g/mL}$ for treatment efficacy but $< 5–6 \mu\text{g/mL}$ to reduce the risk of neurotoxicity, while the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring recommend an upper limit of $4–5 \mu\text{g/mL}$ to reduce hepatotoxicity risk [20].

Common ADRs include gastrointestinal problems, hepatotoxicity, visual disturbances (photopsia and photophobia), periostitis, neurological toxicity (visual hallucinations, encephalopathies, and neuropathy), and phototoxicity [3, 21]. Hepatotoxicity and neurotoxicity—particularly visual hallucinations—are commonly associated with VCZ plasma concentrations above target levels [22, 23].

This study aimed to assess the impact of *CYP2C19* phenotypes on VCZ exposure within a Uruguayan cohort of hemato-oncology patients. Secondary objectives included the evaluation of potential associations between adverse events, phenotypes, and drug exposure, while also determining the prevalence of *CYP2C19* alleles in a group of healthy volunteers.

Materials and Methods

The study enrolled hospitalized patients treated by the Academic Hematology Unit of the Hospital de Clínicas Dr. Manuel Quintela, Montevideo, Uruguay during the period December 2021-December 2024. The inclusion criteria included: i. being under treatment with oral VZC and ii. patients over 18 years old. The study was approved by the Institutional Ethics Committee of Hospital de Clínicas and was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki and its subsequent amendments, the principles of Good Clinical Practice, and all applicable regulatory requirements. Written informed consent was obtained from all participants prior to their enrollment in the study.

Demographic data including sex, age, body weight, medication history, dosage regimen, time of last dose, sampling time, concentrations of VCZ, information on concomitant medications, genetic variants on *CYP19* gene as well as biochemical and hematological test results, and other relevant data were collected using a data collection form.

To define abnormal liver function tests, the results obtained during treatment were compared with baseline results (tests prior to starting VCZ). In addition, ADRs reported by the medical staff were recorded. Their causality was evaluated using the Naranjo algorithm [24], and severity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [25], a standardized classification widely used in hematology-oncology clinical practice. The severity of liver function tests according to the CTCAE is presented in Table 1.

Table 1
Liver function tests severity [25].

	ALT and AST		Blood bilirubin		ALP and GGT	
	baseline normal	baseline abnormal	baseline normal	baseline abnormal	baseline normal	baseline abnormal
Grade 1	>ULN – 3,0 x ULN	> 2,5–3,0 BV	>ULN – 1,5 x ULN	> 1,0–1,5 BV	>ULN – 2,5 x ULN	> 2,0–2,5 BV
Grade 2	> 3,0–5,0 x ULN	> 3,0–5,0 BV	> 1,5–3,0 x ULN	> 1,5–3,0 BV	> 2,5–5,0 x ULN	> 2,5–5,0 BV
Grade 3	> 5,0–20,0 x ULN	> 5,0–20,0 BV	> 3,0–10,0 x ULN	> 3,0–10,0 BV	> 5,0–20,0 x ULN	> 5,0–20,0 BV
Grade 4	> 20,0 x ULN	> 20,0 BV	> 10,0 x ULN	> 10,0 BV	> 20,0 x ULN	> 20,0 BV

ULN: upper normal limit; BV: baseline value; GGT: gamma-glutamyltransferase; ALP: phosphatase alkaline; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

VCZ Concentration Analysis

Pre-dose morning blood samples were withdrawn from the antecubital vein and placed in tubes with EDTA. Plasma was separated by centrifugation and stored at – 25°C until analysis. Plasma drug concentrations were determined using a validated high-performance liquid chromatography (HPLC) method performed at the Drug Monitoring Unit of Hospital de Clínicas, using an Ultimate 3000 Thermo Scientific HPLC system equipped with a UV DAD-3000 detector. Fifty microliters of internal standard (imipramine, 40 mg/L) were added to 1.0 mL of plasma. Then, 500 µL of sodium carbonate 1 M were added and the extraction was performed with 2.5 mL of ethyl acetate and vortex shaken for 1 minute. After centrifugation, the supernatant was separated and dried under a nitrogen stream at 37°C. Dry residue was dissolved with 200 µL of water: acetonitrile (60:40) and transferred to 250 µL polypropylene vials for injection into the HPLC. The separation of the compounds was performed on a Phenomenex C18 column (150 x 4.60 mm 5 µm). The mobile phase consisted of buffer phosphate 50 mM pH 4: acetonitrile (60:40) and was pumped at a flow rate of 0.8 mL/min. The column compartment was kept at 30°C and detection was performed at the wavelength of 254 nm. Under these conditions, the retention times of analytes were 7.5 and 10 minutes for imipramine and VCZ respectively. The HPLC method was linear between 0.4 and 9.8 mg/L. For concentrations located in the low, medium, and high portions of the calibration curve, intra- and interday coefficients of variation (precision) and relative errors (accuracy) below 15% were obtained.

CYP2C19 genotyping

Blood samples were withdrawn from the antecubital vein and placed in tubes with EDTA. DNA was isolated using the High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. DNA concentration was quantified in a NanoDrop ND-1000 UV-Vis Spectrophotometer (ThermoScientific, USA). The *CYP2C19*2* and *CYP2C19*3* alleles were determined by TaqMan® allelic discrimination assays (C__25986767_70 and C__27861809_10, respectively) in a Rotor Gene 6000 (Corbett Life Science, Qiagen, MD, USA) using the allelic discrimination interface. Direct sequencing was used to validate the corresponding controls for each genotype. The *CYP2C19*17* allele was determined by polymerase chain reaction (PCR) and Sanger sequencing. The amplification reaction was performed using the following primers: 2C19x17F (forward) 5'-CATCTCTGGGGCTGTTTTCC-3' / 2C19-x17R (reverse) 5'-CAAATGGGAAAAGGGAGACC-3'. Amplified fragments (316bp) were purified and analyzed by DNA sequencing on an ABI 3730xl System (Macrogen Inc service). *CYP2C19*1* was assigned if the *2, *3, or *17 allele was not detected.

Statistical analysis

Data are presented as median and range or absolute values and percentages for quantitative and qualitative variables, respectively. Medians are compared using the Wilcoxon test, after assessing normality with the Shapiro–Wilk test, employing R software.

Results

This single-center study enrolled a cohort of 25 patients, yielding a total of 37 trough plasma concentrations. The clinical characteristics and the corresponding VCZ levels are summarized in Table 2. Additional information on these data, including the complete raw dataset, is provided in Online Resource 1.

Table 2

Population description and VCZ predose concentration stratified by treatment reason. Values are expressed as median (range) or number (%) as appropriate. BMI: body mass index; C₀: predose concentration. TR: population therapeutic range.

		Total (N = 25)	Prophylaxis (N = 15)	Infection treatment (N = 10)
Sex	Female	12 (48)	7 (54)	4 (40)
	Male	13 (52)	6 (46)	6 (60)
Age, years		53 (19–81)	56 (19–81)	48 (27–64)
BMI, kg/m ²		25 (15–35)	25 (15–34)	24 (16–35)
Dose, mg/day		400 (200–1200)	400 (200–400)	600 (200–1200)
C ₀ VCZ		37	21 (57)	16 (43)
	Below TR	< 1.0 10 (27)	7 (33)	3 (19)
	TR	1.0–5.5 20 (54)	10 (48)	10 (63)
	Above TR	> 5.5 7 (19)	4 (19)	3 (19)

Of the total VCZ pre-dose concentrations measured, 46% were outside the population therapeutic range (27% were below and 19% were above it).

To establish the prevalence of *CYP2C19* risk alleles among the Uruguayan Population, a cohort of 182 Uruguayan individuals (25 + 157 volunteers) was genotyped. The *1/*1 genotype was observed in 90 individuals (49%), followed by *1/*2 in 41 participants (23%). Both *1/*17 and *2/*17 genotypes were identified in 22 individuals each (12%), while the *2/*2 genotype was found in 7 participants (4%).

The frequency of *CYP2C19* phenotypes observed in our population is consistent with that reported for the American population according to ClinPGx/CPIC, marked by a high prevalence of NM and a low prevalence of PM, Fig. 1 [26].

According to international guidelines, *CYP2C19* genotype was translated into phenotypic categories based on the combination of *CYP2C19* alleles, as previously described. In this cohort, 12% were classified as RM, 60% as NM, 28% as IM and 0% as PM. VCZ plasma concentrations, stratified according

to phenotype, are presented in Table 3. Raw genotyping data for each patient are detailed in Online Resource 2. No statistically significant differences were observed between the NM and IM phenotypes (p for C_0 : 0.5573; p for normalized C_0 : 0.5574), and statistical comparison for RM was not feasible.

Table 3

VCZ plasma concentrations stratified by *CYP2C19* phenotype. N: number of patients; n: number of determinations; LOQ: lower limit of quantification; RM: rapid metabolizer; NM: normal metabolizer; IM: intermediate metabolizer. VCZ plasma concentration are reported as mean values and corresponding range. The reported ADRs included hallucinations (n = 2; causality: probable; severity: grade 1), arthralgia (n = 1; causality: probable; severity: grade 2) and elevated liver enzymes (n = 15; causality: 14 patients possible, 1 patient probable; severity: 11 patients grade 1, 2 patients grade 2 and 2 patients grade 3). The arthralgia case involved pain in the left shoulder, which worsened with abduction and palpation, and showed partial improvement with paracetamol. Detailed information on patients who experienced hallucinations and arthralgia are provided in Table 4.

CYP2C19 Genotype	CYP2C19 Phenotype	N	Genotype Prevalence	n	C_0 (mg/L)	C_0 normalized (kg/L)
*1/*17	RM	3	0.12	3	2.4 (1.1–3.9)	0.24 (0.20–0.30)
*1/*1	NM	15	0.60	24	2.9 (< LOQ-9.5)	0.53 (< LOQ-1.83)
*1/*2	IM	5	0.20	10	4.4 (< LOQ-16.5)	0.75 (< LOQ-2.78)
*2/*17		2	0.08			

Table 4

Patients who experienced hallucinations and arthralgia. DD: Daily dose; ND: normalized dose by body weight; IM: intermediate metabolizer; ADR: Adverse drug reaction.

DD (mg)	ND (mg/kg)	C_0 (mg/L)	Phenotype CYP2C19	ADR	Causality	Severity
800	5.94	16.5	IM	Hallucination	Probable	Grade 1
				Arthralgia	Probable	Grade 2
400	5.71	7.82	IM	Hallucination	Probable	Grade 1

The characteristics of liver enzymes alterations are detailed in Table 5. Among patients who experienced this adverse event, the *CYP2C19* genotypes were distributed as follows: 60% NM, 27% IM and 13% RM.

Hepatotoxic drugs were co-administered in all patients who experienced the ADR [25]. Notably, among the 16 patients with this ADR, 8 received hepatotoxic drugs metabolized by CYP3A4 (cyclosporine, atorvastatin, cytarabine, fluconazole and imatinib). It was found that only three of the fifteen patients with elevated liver enzymes exhibited VCZ plasma concentrations above the therapeutic range, and these patients were all classified as grade one in severity.

Table 5

Liver enzyme alterations during VCZ treatment. n: number of events. GGT: gamma-glutamyltransferase; ALP: phosphatase alkaline; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DB: Direct bilirubin; TB: Total bilirubin.

GGT	Grade 1, n	Grade 2, n	Grade 3, n	Total, n (%)
	9	2	1	12 (32)
ALP	9	1	0	10 (26)
ALT	7	0	1	8 (21)
DB	5	0	0	5 (13)
AST	6	0	1	7 (18)
TB	0	0	0	0 (0)

Discussion

The *CYP2C19* genotype distribution observed in the patient population of this study is consistent with that observed in the Uruguayan cohort of 182 individuals, supporting the representativeness of our study population. In addition, this distribution is consistent with that reported for the American population according to ClinPGx/CPIC.

The normalized C_0 values observed in RM patients appeared to be lower than those in NM and IM, suggesting a potential impact of this phenotype on drug exposure. In RM patients, increased *CYP2C19* activity, the main enzyme involved in VCZ metabolism, is expected, which may result in lower plasma concentrations [16]. However, these findings should be interpreted with caution, given that the small number of patients in each phenotype group limited the strength of the analysis.

Besides, various covariates beyond the *CYP2C19* genetic polymorphism significantly influence VCZ exposure. These include pathophysiological conditions (particularly inflammation and hepatic function), age, body weight, drug–drug interactions, and genetic variations in other isoenzymes such as *CYP3A4* and *CYP2C9*.

The high proportion of patients with plasma concentrations outside the therapeutic range (17/25) reinforces the importance of TDM to guide dose adjustments, with the aim of optimizing treatment efficacy and minimizing the risk of adverse events.

The ADRs observed in this study have been previously reported in association with VCZ [21]. An association between VCZ plasma concentrations and the occurrence of hallucinations has also been suggested [21, 27, 28]. Hallucinations, both visual and auditory, have been reported in post-marketing studies with frequencies ranging from 13% to 32%. The mechanism underlying this VCZ-related ADR remains unclear [29].

Regarding musculoskeletal ADRs, periostitis is commonly reported [23, 30]. Patients typically report myalgia and diffuse bone pain. The risk of periostitis increases with both dose and duration of treatment [30]. The only case of arthralgia in this study corresponded to the highest VCZ plasma concentration in the study. It is hypothesized that VCZ may lead to periostitis through the accumulation of fluoride in bodily tissues. Indeed, plasma fluoride levels in patients treated with VCZ have been shown to be higher than in patients treated with non-fluorinated azoles such as itraconazole [23, 30]. It is noteworthy that hallucinations and arthralgia, which were suggested to be dose-dependent, were observed in patients with a *CYP2C19* IM phenotype. This finding suggests that closer monitoring of adverse events may be warranted in patients with a *CYP2C19* IM phenotype.

Regarding hepatotoxicity, VCZ is identified as the second triazole with the highest risk of drug-induced liver injury, showing a wide incidence of enzyme elevation (13–69%) influenced by *CYP2C19* polymorphism, comorbidities, and pharmacological interactions [32, 37]. Despite this frequency, hepatotoxicity is predominantly asymptomatic and reversible, with a low discontinuation rate (~ 1%) and clinical normalization typically occurring within one to three months post-withdrawal [38]. The underlying mechanism likely involves the competitive inhibition of hepatic oxidative metabolism, which may exacerbate the toxicity of co-administered drugs [32]. Furthermore, the relationship between VCZ C_0 and liver damage remains controversial; while some evidence suggests a toxicity threshold between 3.0 and 6.0 mg/L, the lack of a consistent correlation across studies underscores the complex, multifactorial nature of VCZ-induced hepatic injury [37, 39].

In this study, although a high number of patients presented elevated liver enzyme levels, most cases were mild (only two patients were grade 2 and two were grade 3). As previously noted, it is important to consider the co-administration of hepatotoxic drugs in all cases.

Furthermore, in patients receiving hepatotoxic drugs that are metabolized by *CYP3A4*, there is an added risk of potential pharmacokinetic interactions between VCZ as the precipitant drug (an inhibitor of this isoenzyme), which may lead to increased exposure to these agents [26, 40–42].

Although many drugs cause elevation of liver enzymes, these are often mild and reversible, and must be distinguished from severe hepatotoxicity. Therefore, a thorough analysis of ADRs (including causality and severity) during patient monitoring is crucial to assess clinical relevance and support patients' management.

Conclusions

Given the inherent complexity of this cohort characterized by a high prevalence of VCZ concentrations outside the therapeutic range, TDM is essential for treatment optimization. Concurrently, *CYP2C19* genotyping serves as a critical predictive tool, enabling early identification of high-risk patients and supporting individualized follow-up strategies.

The high prevalence of plasma concentrations outside the therapeutic range, coupled with the occurrence of hallucinations and arthralgia in CYP2C19 intermediate metabolizers, underscores the synergistic value of combining TDM and genotyping for clinical management. Although liver enzyme alterations in this population are often multifactorial, the inherent hepatotoxic potential of VCZ, particularly when co-administered with other hepatotoxic agents, warrants close hepatic monitoring to ensure patient safety.

Declarations

No funding was received to assist with the preparation of this manuscript.

The authors have no relevant financial or non-financial interests to disclose.

Author Contribution

B.J.P. and G.N. developed and validated the analytical technique for voriconazole quantification, collected the data, determined voriconazole concentrations, and performed data analysis. O.F. contributed to data analysis and the initial drafting of the manuscript. E.P. and V.M. performed the CYP2C19 genotyping and, together with M.C. and V.M.M contributed to the initial drafting of the manuscript and the interpretation of the results. B.M. and S.M. were responsible for patient referral and contributed to the interpretation of the results and the critical revision of the manuscript. All authors commented on previous versions of the manuscript, and read and approved the final version.

Data Availability

All data supporting the findings of this study are available within the paper and its Supplementary Information.

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Figures

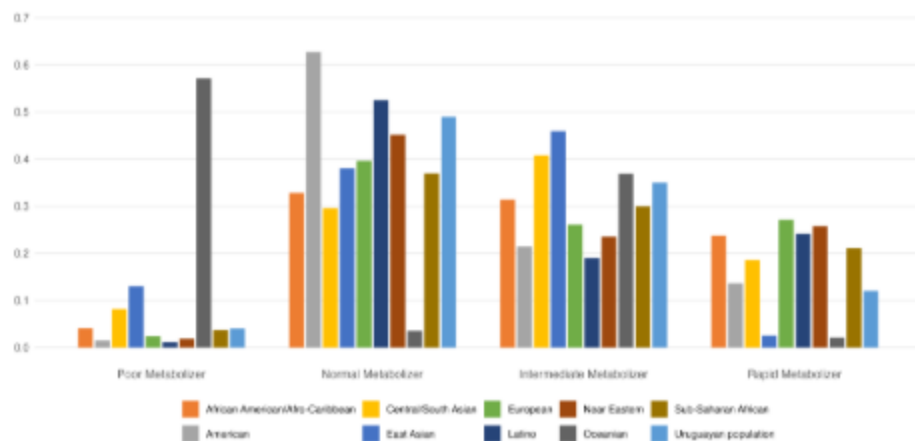


Figure 1

Frequencies of CYP2C19 phenotypes in biogeographical groups.

Supplementary Files

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