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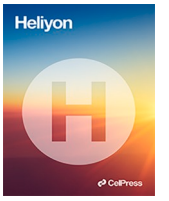

Research article

Genetic polymorphisms of CYP2C19 in ecuadorian population: An interethnic approach

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ABSTRACT

Introduction: *CYP2C19* is a highly polymorphic gene responsible for metabolizing commonly used drugs. *CYP2C19*2,*3* (loss of activity alleles) and **17* (increased activity allele) are the principal alleles included in clinical guidelines, however their prevalence varies among different ethnicities. Ecuadorian population is formed by Mestizos, Afrodescendants and Native Americans and frequency of *CYP2C19* alleles could be different among them. The objective of this study was to establish the frequency of these variants in the different populations of Ecuador and to compare them with other populations.

Materials and methods: DNA from 105 Afrodescendants, 75 Native Americans of the Kichwa ethnicity, and 33 Mestizos Ecuadorians was analyzed by nested-PCR to identify *CYP2C19*17* carriers. *CYP2C19*2* allele was analyzed in DNA from 78 Afrodescendants, 29 Native Americans of the Kichwa, and 16 Mestizos by TaqMan Allelic Discrimination Assay. *CYP2C19*3* was analyzed in 33 Afrodescendants by nested-PCR.

Results: The global frequencies of the alternate alleles were 14.22% (*CYP2C19*2*) and 2.10% (*CYP2C19*17*). No differences ($p > 0.05$) were observed among the subgroups. No *CYP2C19*3* carrier was identified. *CYP2C19*2* frequencies in Ecuador were similar to the ones reported in Europe, Africa and Middle East countries and to some American populations. Low *CYP2C19*17* frequencies, like the ones in our population, were also observed in East and South Asia and in Native American groups.

Discussion: Absence of differences in the ethnic groups in Ecuador for *CYP2C19*2* and **17* could be due to either a bias in sample selection (ethnic group was assed by self-identification) or to a high interethnic admixture in the Ecuadorian population that would had diluted genetic

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differences. In addition, *CYP2C19*2, *3,* and **17* alleles frequencies in our study suggest that Ecuadorians ancestry is mostly of Native American origin.

1. Introduction

CYP2C19 is an isoform of the cytochrome P450 2C subfamily that metabolizes up to 10% of commonly used drugs, including clopidogrel, proton pump inhibitors (PPIs), antidepressants, and benzodiazepines [1,2]. The drugs can treat conditions as common and serious as heart failure, which affects 26 million people worldwide and is most commonly caused by acute myocardial infarction [3]. To reduce the chances of heart failure, patients may undergo a percutaneous coronary intervention and receive antiplatelet therapy, including clopidogrel in 72% of the cases [3,4]. Unipolar depression has a prevalence of 16.2% and is the second leading cause of disability worldwide among other diseases treated with drugs that are substrates of the CYP2C19 enzyme [5]. Additionally, PPIs are prescribed to the 25% of the adult population, with 25% of these patients being prescribed for more than one year [6].

The gene encoding this enzyme is located on chromosome 10 (10q24.1–10q24.3). This highly polymorphic gene can contain up to 37 described variants [2,7]. Most alterations in CYP2C19 metabolic activity involve three of these variants: while *CYP2C19*2* (c.681G > A; rs4244285) and CYP2C19*3 (c.636G > A; rs4986893) lead to loss of function, *CYP2C19*17* (c.-806C > T; rs12248560) is associated with rapid metabolizers [1,7–9].

Individuals can be classified into ultrarapid (UM), rapid (RM), normal (NM), intermediate (IM), and poor metabolizers (PM) depending on the type of variant and its presence in one or both alleles [7,9]. All of these profiles would respond differently to standard doses of CYP2C19-metabolized drugs. In this regard, PM would result in increased plasma concentrations and decreased active metabolite formation, which is associated with a higher risk of toxicity. However, UM and RM would increase the risk of therapeutic failure [1,7]. The situation is reverse for treatment with prodrugs that require bioactivation by CYP2C19, such as clopidogrel. PM treated with standard doses of clopidogrel, increase the risk of therapeutic failure; in this case a cardiovascular event. However, UM and RM result in higher plasma concentrations of the active metabolite, although clinical guidelines still recommend the use of standard doses for UM and RM [9].

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) provides guidelines for phenotype prediction based on the combination of the different diplotypes [7,9].

- UM: carriers of two increased function alleles
- RM: carriers of one normal function allele and one increased function allele
- NM: carriers of two normal function alleles; intermediate metabolizers
- IM: carriers of one null allele with either one normal function allele or one increased function allele.
- PM: carriers of two null alleles [7,9].

Other pharmacogenetics implementation groups have also developed guidelines based on clinical evidence, such as the Dutch Pharmacogenetics Working Group (DPWG) and the French National Network of Pharmacogenetics (RNPGx). Although they use different terminology, they do not differ significantly in the clinical recommendations associated with the phenotypes [10].

The distribution of the different alleles of *CYP2C19* varies among different ethnic groups [1]. *CYP2C19*2* is the most common loss-of-function allele worldwide. The frequency of this haplotype is 15% in Europeans and Africans, 25–30% in Asians, and 60% in Oceanians. *CYP2C19*3* is the second most common loss-of-function allele [7]. This allele is present in 2–7% of Asians and in 15% of Oceanians, and rarely occurs in Europeans or Africans (allele frequency <1%). Finally, the gain-of-function allele, *CYP2C19*17*, is more common in Europeans (16–21%), Africans (16%), and Middle Eastern populations (~20%), as compared to Asians (3–6%) [1,7].

The Ecuadorian population is ethnically and culturally diverse [11,12]. During the European conquest and colonization, the Native American groups interacted with Europeans and Africans who arrived in the territory due to the slave trade. This interaction led to the establishment of the main groups of Ecuadorian inhabitants: Mestizos, Afro-descendants, and Native Americans [11–13]. According to the most recent Ecuadorian National Census (2022), 77.5% of the population identifies as Mestizos, European (mainly Spanish), Amerindian, and African descendants; 4.8% as Afro-descendants; and 7.7% as Native Americans [12,14]. Other ethnicities include Montubios (7.4%) and European descendants (6.1%), the former being a mixed population of Native American, European and African ancestry, like Mestizos, who inhabit the Pacific coast [12]. Due to the characteristics of the conquest and colonization, the Afro-descendant population is mainly located in the northern part of the country, while the Native American population is mainly located it the Andean region [12]. Among the Native Americans, the Kichwa are the most represented population [11,13]. They are an Andean population that can also be found in other countries, such as Bolivia and Peru [15].

Although several studies analyzed *CYP2C19* haplotype allele distribution in the Ecuadorian population, they were based only on the Mestizo population, or ethnicity was not even reported [8,16–18]. Only two studies reported analyses exclusively in Ecuadorians [8,16].

Given the interethnic variability in *CYP2C19* allele frequencies [1], and the lack of clear records of interethnic studies in the Ecuadorian population, the aim of this study is to analyze the frequencies of the main *CYP2C19* alleles involved in drug's metabolism in the different ethnic groups of Ecuador.

2. Material and methods

2.1. Participants

The study included 218 adult participants, 149 females, 68 males. In one sample, the sex was not reported. All participants were healthy and unrelated Ecuadorians, with no inbreeding or outbreeding among them. The sample included the three main ethnic groups of Ecuador, Mestizo [19], Native Americans of the Kichwa ethnicity [20], and Afro-descendant (109). Ethnicity was determined by self-identification and morphological characteristics, as is customary in the Ecuadorian National Census. They were all born and resident in Ecuador with at least 3 generations of Ecuadorian ancestry.

All subjects gave their written informed consent to participate in this study after being informed in detail about the purpose of this investigation. The study was approved by the Human Research Ethics Committee of the Universidad Central of Ecuador (Quito, Ecuador) (120-CE-UCE-2019, March 29, 2019) and was conducted in agreement with the Declaration of Helsinki and its subsequent revisions.

2.2. Genotyping

A dried blood spot on FTA Elute Card sample was collected from all participants. Genomic DNA was extracted from peripheral blood, blotted, and dried on filter paper using the Dried Blood Spot DNA Isolation Kit (Norgen Biotek corp™, ON, Canada).

Genotyping of *CYP2C19*17* was performed using a nested polymerase chain reaction (PCR) on 3 μL of extracted DNA as described by Baldwin et al. [21]. A 473 base pair (bp) product, containing the site were the *CYP2C19*17* variant site was obtained by the first PCR. This product was amplified by the second PCR to yield a final product of 143 bp, which still contained the *CYP2C19*17* site. The 143 bp product was digested with the Eco T22 I restriction enzyme at 37 °C for 8 h, containing: 15 μL PCR reaction, 2 μL sterile purified water, 2 μL 10x H buffer, and 1 μL Eco T22 I (*Ava*III) (Takara Bio, Shiga, Japan). The Eco T22 I restriction enzyme recognizes and cleaves an ATGCAˆT site. This restriction site disappears in individuals carrying the variant allele (T) of *CYP2C19*17*, resulting in a 143 bp band instead of the 116 bp band that appears with the wild-type allele (C). The products were electrophoresed on a 3 % agarose gel and stained with ethidium bromide. The fragments were visualized by exposing the gel to ultraviolet radiation (260–300 nm). A single band at 116 bp would appear in wild-type homozygote individuals, a single band at 143 bp would appear in mutant homozygote individuals and both bands would appear in heterozygote individuals.

In order to validate the method, all carriers of the T allele (heterozygotes and homozygotes) and 20 homozygotes of the C allele were confirmed by the specific TaqMan Allelic Discrimination Assay (Applied Biosystems, Foster City, CA, USA) C_469857_10 on a QuantStudio12KFlex Detection System (Applied Biosystems). The procedure was performed on the nested PCR products according to the manufacturer's recommendations. The Thermofisher Connect platform was used to upload and analyze the results (https://apps.thermofisher.com/apps/spa/#/dashboard) [22].

Genotyping of *CYP2C19*2* was performed using the specific TaqMan Allelic Discrimination Assay (Applied Biosystems, Foster City, CA, USA) C_25986767_70 on a QuantStudio12KFlex Detection System (Applied Biosystems) according to the manufacturer's recommendations. Results were uploaded and analyzed using the Thermofisher Connect platform [22]. Filter paper blood samples required an initial amplification using nested PCR in order to ensure the adequate DNA concentration and quality. Briefly, the protocol used 3.0 μL of extracted DNA, 2.5 μL of 1xPCR buffer, 0.2 mM dNTPs, 1.25 units of Taq DNA polymerase, 3.0 mM $MgCl_2$ and 0.3 μM of forward primer (5′-TTTGAGCCCCTCCCACTT-3′) and reverse primer (5′-CCTCCTGTGCTGATCTCAC-3′) for the first PCR. Primers for the second PCR were those previously described by Lakhan R et al. [23]. The PCR protocol followed the specifications of Itoh K et al. [24].

Detection of the *CYP2C19*3* allele was performed as described previously [24] with minor modifications. The first PCR required 5′-ATCCTGGGCTGTGCTCC-3′ and 5′-CACGCTTTGGGGCTGTC-3′ as forward and reverse primers, respectively. The forward primer for the second PCR reaction was 5′-ATTGAATGAAAACATCAGGATTG-3′ and the reverse primer was 5′-ACTTCAGGGCTTGGTCAATA-3′ (21). Thermocycling conditions followed the protocol described by Itoh k et al. [24]. A 435 bp product, containing the site where the *CYP2C19*3* variant is located, was obtained from the first PCR. This product was amplified by the second PCR to yield a final product of 132 bp, which still contains the *CYP2C19*3* site. The 15 μL PCR of the resulting product was digested by the *Bam*HI restriction enzyme (Takara Bio, Shiga, Japan) according to the manufacturer's recommendations. The *Bam*HI restriction enzyme recognizes and cleaves a GˆGATCC site. This restriction site disappears in individuals carrying the variant allele (A) of *CYP2C19*3*, resulting in a 132 bp band instead of the 96 bp band that appears with the wild-type allele (G). The products were electrophoresed on a 3% agarose gel and stained with ethidium bromide. The fragments were visualized by exposing the gel to ultraviolet radiation (260–300 nm). A single band at 96 bp would appear in wild-type homozygote individuals, a single band at 132 bp would appear in mutant homozygote individuals and both bands would appear in heterozygote individuals.

2.3. Predicted phenotype

A predicted phenotype was established for participants who were genotyped for both *CYP2C19*2* and **17* alleles according to The Clinical Pharmacogenetics Implementation Consortium (CPIC®) guidelines [9].

2.4. Statistics

Hardy–Weinberg equilibrium was assessed using contingency tables and the X^2 test with one degree of freedom. Contingency tables and X^2 test calculated with the Jamovi software version 1.6 were also used to establish differences in allele frequencies (four degrees of freedom) or phenotypes (eight degrees of freedom) between populations. Values were considered significant at $p<0.05$.

3. Results

The frequency distribution of the loss-of-function allele *CYP2C19*2* and gain-of-function allele *CYP2C9*17* in 123 and 214 individuals respectively is shown in Table 1. The *CYP2C19*2* allele was studied in 78 Afro-descendants, 29 Kichwas and 16 Mestizos, whereas *CYP2C19*17* was genotyped in 105 Afro-descendants, 75 Kichwas, and 33 Mestizos. Hardy-Weinberg equilibrium was followed in both Kichwa ethnic subgroups and also in the Mestizos genotyped for *CYP2C19*2*. However it could not be calculated in the Mestizos genotyped for *CYP2C19*17*, as they were all homozygotes for the wild-type allele. Regarding Afro-descendants, Hardy-Weinberg equilibrium was not observed in any subgroup.

Additionally, a group of 34 Afro-descendants were genotyped for the *CYP2C19*3* allele, but it was not found in any of them.

The frequency of the alternative allele, *A (rs4244285)*, which defines the *2 haplotype, was similar in the Kichwa (13.79%) and Afro-descendant (12.18%) populations, whereas it was more frequent in Mestizos (25%), however, there were no significant differences between groups ($p = 0.169$). The global frequency of the *A* allele was 14.22%. Regarding the alternative allele, *T* (rs12248560), of the *CYP2C19*17* haplotype, occurred with a frequency below 5% in all groups with a global frequency of 2.10% and, as for *CYP2C19*2*, there were no significant differences between groups ($p = 0.241$).

The 109 individuals who were genotyped for both *CYP2C19*2* and **17* alleles and their predicted phenotype (according to CPIC guidelines) is shown in Table 2. Normal metabolizer is the most common phenotype in all interethnic subgroups, followed by intermediate and poor metabolizers. No statistical differences were observed between the subgroups ($p = 0{,}809$).

The frequencies obtained in our study were also compared with those previously reported in other studies worldwide (Tables 3 and 4). We found statistically significant differences with the frequencies reported in Ecuadorians by Vicente et al. for both *CYP2C19*2* and **17* and with the frequencies reported by *de Andrés* et al. for *CYP2C19*17*, but not for *CYP2C19*2* [8,16]. Regarding other ethnicities, the frequencies we found for *CYP2C19*2* were similar to those reported in Europe, Africa and Middle East countries, while higher frequencies were found in Eastern and Southern Asian countries, and there is a great variability in American populations, (Table 3). However, the opposite circumstance is observed for *CYP2C19*17*, the low frequency observed in our population is more similar those reported in East and South Asia and also in Native American groups (Table 4).

4. Discussion

No significant differences were found in the frequencies of the *CYP2C19*2* and *CYP2C19*17* haplotypes among the different Ecuadorian subgroups analyzed in this study. This lack of difference could be attributed to an internal bias in sample selection. It is possible that either all the interethnic groups could include Mestizos, or there was a high rate of admixture in the interethnic subgroups, diluting their previous genetic differences. The study did not consider the interethnic diversity of CYP2C19*3 as only Afro-descendants were genotyped for this haplotype. Furthermore, it appears that the Afro-descendant population did not adhere to the Hardy-Weinberg equilibrium. This equilibrium is dependent on several conditions, including large populations, random mating, and the absence of mutation, migration, and selection. Given that the Afro-descendant population is the largest in our study, it is possible that the absence of random mating or migration may be the most likely causes of the observed disequilibrium. However, as no differences were found between the groups, it appears that the Hardy-Weinberg equilibrium did not have an impact on our results.

According to our results, the majority of Ecuadorians (78%) would be NM for the CYP2C19 isoenzyme. RM and UM are very rare in

Table 1
Allele and genotype frequencies for *CYP2C19*2* and **17*.

	CYP2C19*2					CYP2C19*17				
	Frequency n (%)					Frequency n (%)				
	*1/*1	*1/*2	*2/*2	HWE	A allele frequency (%)	*1/*1	*1/*17	*17/*17	HWE	T allele frequency (%)
Afrodescendants	63 (80.8%)	11 (14.1%)	4 (5.1%)	p<0.01	12.18	103 (97.2%)	2 (1.9%)	1 (0.9%)	p<0.01	1.8
Kichwas	21 (72.4%)	8 (27.6%)	0 (0%)	p = 0.39	13.79	70 (93.3%)	5 (6.7%)	0 (0%)	p = 0.77	3.3
Mestizos	10 (62.5%)	4 (25%)	2 (12.5%)	p = 0.18	25	33 (100%)	0 (0%)	0 (0%)	Incalculable	0
Total	94 (76.4%)	23 (18.7%)	6 (4.9%)	p<0.01	14.22	206 (96.2%)	7 (3.3%)	1 (0.5%)	p<0.01	2.1
X^2test X^2: 6.44(4df) p = 0.169						X^2test X^2: 5.49(4df) p = 0.241				

HWE: Hardy Weinberg Equilibrium.

Table 2
Predicted phenotype o individuals who had *CYP2C19*2* and **17* alleles genotyped.

	PM (*CYP2C19*2/*2*)	IM (*CYP2C19*1/*2*)	NM (*CYP2C19*1/*1*)	RM (*CYP2C19*1/*17*)	UM (CYP2C19*17/*17)	Total
Afrodescendants	4 (5.3%)	11 (14.5%)	59 (77.6%)	1 (1.3%)	1 (1.3%)	76
Kichwas	0 (0%)	2 (11.1%)	16 (88.9%)	0 (0%)	0 (0%)	18
Mestizos	2 (13.3%)	3 (20%)	10 (66.7%)	0 (0%)	0 (0%)	15
Total	6 (5.5%)	16 (14.7%)	85 (78%)	1 (0.9%)	1 (0.9%)	109
X^2test						
X^2: 4.51(8df), p = 0.809						

the population (1.8%), while a 20.2% of the population have a reduced enzyme activity (PM and IM), which must be taken into account when prescribing drugs metabolized by CYP2C19.

Comparing our results with other studies that reported the frequencies of *CYP2C19*2* and *CYP2C19*17* in the Ecuadorian population, we found some differences (Tables 3 and 4). Vicente et al. found frequencies of 7.8% for *CYP2C19*2*, and 24.9% for *CYP2C19*17* in a Mestizo population, whereas de Andres et al. found frequencies of 12.9% for *CYP2C19*2*, and 9.5% for *CYP2C19*17* in a non-ethnically specified Ecuadorian population, [8,16]. However, in our population, *CYP2C19*2* and *CYP2C19*17* alleles were present in 14.22% and 2.10% of individuals respectively. As mentioned above, the frequencies found in our study are in agreement with those from de Andrés et al. for the *CYP2C19*2* allele, but differ significantly from the data reported by Vicente et al. and also from the *CYP2C19*17* allele frequency of de Andrés et al. In this regard, different frequencies should be expected when comparing the three studies, since only interethnic variability only was the main objective of our study.

In order to compare our results with those reported in other populations worldwide, it is important to understand how it was the peopling of the American continent. Humans first arrived to America about 16,000 years ago through what is now the Bering Strait and spread to the rest of the continent. This explains the presence of "founding" lineages from Asian populations in Native Americans [90]. Focusing on the alleles analyzed in our study, *CYP2C19*2(A;* rs4244285*), *3(A; rs4983893),* and **17(T; rs12248560)* are considered as rare in Latin American populations, and their presence is negatively associated with Native American ancestry and the presence of *CYP2C19*2* and **17* in Latin American populations is positively associated with European ancestry [17,18]. Since ancestry is the main determinant of frequency variation, the presence of these alleles in Latin American individuals may be due to the colonization of the continent by foreign cultures, which may also explain the diversity of frequencies found in different regions of the continent [18].

*CYP2C19*3* is also a rare allele in European and African populations, and it is found almost exclusively in East Asian populations, suggesting a relatively recent origin of this variant, after the differentiation of these ethnic groups [7,34,46]. This is consistent with our results in the Afrodescendant subgroup and also with the absence of this allele in all of the different Latin American populations included in databases such as LDlink [91]. In this regard, we could predict that the *CYP2C19*3* frequency in the Mestizo and Kichwa subgroups should be zero, as in Afrodescendant individuals. However, this hypothesis needs to be tested in these populations in future studies.

On the contrary, *CYP2C19*2* is distributed in high frequency in ethnic groups of all Europe, Africa and Asia, suggesting that it is an old mutation that occurred before the Black, Oriental and Caucasian racial groups split and it can also be related to African ancestry [18,46], however, the higher frequencies are observed in East and Southeast Asian countries (Table 3).

In mixed American populations, there is a great variability in the presence of *CYP2C19*2*. The global frequency of the alternative allele, *A*, observed in mixed Americans in the LDlink database is 10.5%, with Puerto Ricans being the subpopulation where the allele is more frequent, 13%, and less frequent in Peruvians, 5.8% [91]. Analyzing the frequencies reported in different countries (Table 3), the highest frequency of the *A* allele in America is found in groups of East Asian and Southeast Asian descendants living in the United States (28.9% and 31.2% respectively) [36], in agreement with the higher rates of the allele in East and Southeast Asia, but it is also found in a Native American population from Mexico, the Tarahumaras (31%) [33]. On the other hand, the lowest frequencies of *CYP2C19*2* correspond to some Native American populations, Malek, Guaymí and Bribiri from Costa Rica [31], Purépechas, Tojolabales, Tzotziles and Tzeltales from Mexico [33]. The frequencies of Mestizos (6.9–26%) and Afrodescendants (16.5–21.9%) are variable and can be explained by the different degrees of miscegenation.

As previously mentioned, *CYP2C19*2* is negatively associated with Native American ancestry, but it can also be found in these populations (9.75%), more frequently in Northern Native Americans (11.36%) than in Central and Southern Native Americans (5.73% and 5.37% respectivly) [17]. Higher frequencies have been reported in Brazil (10.4%) [27] and in Chorotegans from Costa Rica (12.5%), although the latter group had a 22% of European ancestry [31]. Moreover, the *CYP2C19*2* allele differences of Native Americans with Mestizos, 10.77%, and Afrodescendants, 18.29%, are not particularly pronounced [17]. Comparing the results of our study, it was found that the frequencies observed in Ecuador are present throughout the American continent. These frequencies may correspond to a Mestizo population, although they can also be found in some Native American populations.

There are fewer studies genotyping *CYP2C19*17* because it is a more recently discovered allele. This allele is globally distributed with high frequencies in Europe, Africa, Middle East Asia and South Asia, but it is almost absent in East Asia (Table 4). In the mixed American populations included in LDlink, the global frequency of the *CYP2C19*17* rare allele, *T,* is 12%, although there are large differences among the subpopulations, ranging from 17.5% in Puerto Ricans to 4% in Peruvians [91]. The highest frequencies of *CYP2C19*17* in America (Table 4) are reported in populations with significant Caucasian or African ancestry, such as Mulattos and Afrodescendants (21.3 and 26.3%) from Brazil, but also in other interethnic Brazilian populations, including Native Americans (15.8%) [27,28], Colombians (20.9%) [30], Afro-Caribbean from Costa Rica (21.7%) [31], Caucasians (22%) and Afrodescendants

Table 3
Frequency comparison of *CYP2C19*2* allele with other populations.

Region	Country	Ethnic group	*CYP2C19*2* (%)	N	Reference
America	Ecuador	Interethnic	14.22	123	Present study
	Ecuador	Mestizo	7.8**	297	[8]
	Ecuador	NS	12.9	132	[16]
	Ibero-American countries	North Native American	11.36	823	[17]
		Central Native American	5.73**	96	
		South Native American	5.37**	214	
		Admixed	10.77	1898	
		Afrodescendants	18.29	82	
		Caucasian	10.11	267	
		Argentinean Ashkenazi Jews	13.50	163	
	Bolivia	NS	7.8**	778	[25]
	Brazil	Caucasian	25*	38	[26]
	Brazil	Native American	10.4	183	[27]
		Caucasian	16.9	615	
		Mulatto	16.5	315	
		Afrodescendant	20.2	99	
	Brazil	White: North	9	156	[28]
		White: Northeast	12.5	176	
		White: Southeast	12.5	176	
		White: South	13.6	176	
		Brown: North	9.8	174	
		Brown: Northeast	13.1	174	
		Brown: Southeast	10.3	174	
		Brown: South	20.5*	176	
		Black: North	17.6	174	
		Black: Northeast	11.6	172	
		Black: Southeast	16.7	170	
		Black: South	10.5	164	
	Chile	NS	8.3*	167	[29]
	Colombia	NS	8.6*	239	[30]
	Costa Rica	Admixed	7.1**	141	[31]
		Bribri	4.3	23	
		Chorotega	12.5	36	
		Guaymí	0**	24	
		Maleku	0*	12	
		Afro-Caribbean	19.6	46	
	Mexico	Mestizo	9.3*	697	[32]
	Mexico	Mestizos	6.9**	125	[33]
		Tarahumaras (Native Americans)	31**	88	
		Purépechas (Native Americans)	5.4**	85	
		Tojolabales (Native Americans)	3.6**	43	
		Tzotziles (Native Americans)	5.6**	56	
		Tzeltales (Native Americans)	0**	19	
	United States	Cuban	19.6*	1965	[34]
		Dominican	15.6	942	
		Puerto Rican	13	1863	
		Central American	9**	1182	
		Mexican	11.7	4670	
		South American	11.6	772	
	United States	Oglala Sioux (Native American)	11	98	[35]
	United States	Mexican Americans	9.7	346	[36]
		African Americans	18.2	236	
		Caucasians	12.7	273	
		East Asians	28.9**	161	
		South East Asians	31.2**	80	
	Venezuela	Caucasian (88% European)	16.9	59	[37]
		Mestizo (75% European. 17% Native American)	16.7	51	
		Mestizo (40% Native American. 33% European. 27% African)	26*	48	
		Afrodescendant and Mestizo (38% African and Amerindian. 24% European)	17	82	
		Afrodescendant (59% African. 26% Native American. 15% European)	21.9	41	
Europe	Belgium	NS	9.1	121	[38]
	Bosnia & Herzegovina	Caucasian	16.2	216	[39]
	Cyprus	NS	21	40	[38]
	Croatia	Caucasian	14.8	1002	[40]

(*continued on next page*)

Table 3 (*continued*)

Region	Country	Ethnic group	*CYP2C19*2* (%)	N	Reference
	Denmark	NS	15	276	[41]
	Faroe Islands (Denmark)	NS	18.7	311	[41]
	France	NS	18	359	[42]
	Germany	Caucasian	15.2	423	[43]
	Greece	NS	13.1	283	[44]
	Hungary	Roma	20.5*	500	[45]
		Non-Roma Hungarian	12.6	370	
	Italy	NS	11	360	[46]
	Kosovo	Caucasian	13.03	234	[47]
	Lithuania	NS	19	20	[38]
	Malta	NS	20	41	[38]
	Netherlands	NS	15.8	215	[48]
	Norway	Caucasian	15.2	328	[41]
	Orkney Islands (Scotland)	NS	10.8	88	[38]
	Poland	NS	14.83	304	[49]
	Serbia	NS	16.3	500	[50]
	Spain	Caucasian	12.8	282	[8]
	Spain and Portugal	Caucasian	13.64	1521	[17]
Europe and Asia	Russia	Tartars	16	141	[51]
		Balkar	5.5**	200	
		Russian	11.38	290	
	Russia	Ulan-Ude (Buryat)	12.8	109	[52]
		Irkustk	10.2	118	
	Turkey	NS	15.2	347	[53]
Asia	Bahrain	NS	14.6	75	[54]
	Bangladesh	NS	24.06**	320	[55]
	China	NS	35.78**	109	[56]
	China	Han	30**	831	[57]
		Hui	30.6**	85	
		Uygur	22**	352	
		Kazak	18.8	69	
	China	Han	29.7**	214	[58]
		Hui	32.4**	108	
		Mongolian	18.2	129	
	China	Lin	35.6**	163	[59]
	China	Hakka	31.06**	6686	[60]
	China	Han	38.6**	136	[61]
		Uyghur	32.48**	214	
		Hui	49.39**	164	
		Mongolian	41.46**	158	
	India	NS	22**	308	[62]
	South India	NS	40.2**	87	[63]
	South India	Telugu language	33**	115	[64]
		Kannada language	39**	108	
		Malayalam language	31**	118	
		Tamil language	38**	112	
	Iran	NS	12.3	691	[65]
	Iran	Fars	15.3	180	[66]
		Turk	25**	110	
		Caspian	9.6	73	
		Lure	35**	80	
		Kurd	26.3**	95	
	Israel	Yemenite Jew	12.5	36	[67]
		Sephardic Jew	13.8	47	
		Ethiopian Jew	19.6	28	
		Bedouin(Arabian)	12	50	
	Japan	NS	26.7**	134	[68]
	Jordan	NS	12.3	158	[69]
	Korea	NS	28.4**	271	[70]
	Kuwait	NS	22*	100	[54]
	Lebanon	NS	13.4	161	[71]
	Malaysia	Malay	23*	53	[72]
		Chinese	23*	68	
		Indian	38**	20	
	Palestine	NS	15.5	110	[73]
	Saudi Arabia	NS	11.2	201	[20]

(*continued on next page*)

Table 3 (*continued*)

Region	Country	Ethnic group	*CYP2C19*2* (%)	N	Reference
	Singapore	Chinese	28**	100	[74]
		Malay	31**	100	
		Indians	32.5**	100	
	Thailand	Thai	29**	774	[75]
		Burmese	30**	127	
		Karen	28**	131	
	Tunisia	NS	9*	258	[54]
	Vietnam	Kinh	20.5**	100	[76]
		Tay	38.3**	103	
		Muong	33.8**	99	
		H'Mong	53.75**	40	
		Nung	43.9**	33	
Africa	Egypt	NS	10.9	247	[77]
	Ghana	NS	6**	204	[78]
	South Africa	NS	21.7	76	[79]
	Tanzania	NS	17.7	192	[79]
	Zimbabwe	NS	13.1	84	[79]

*p<0,05, **p<0.01, NS: Not specified.

(21%) from the United States [19] and Ashkenazi Jews from Argentina (20.55%) [17]. The lowest frequencies correspond to Native American populations, Bribiri, Chorotega, Guaymí and Maleku from Costa Rica, all below 5% [31] and North Native American from the Sioux tribe (9%) [35], also, there is an outlier of 0.4% in the population of Cuban origin from the United States [34]. In a study that included a much larger Latin American population, researchers found *CYP2C19*17* in 12.33% of Mestizos, 21.34% of Afro-descendants, and 1.59% of Native Americans. However, no *CYP2C19*17* allele carriers were found in Southern Native Americans, who are of Peruvian origin [17]. This information suggests that, the frequency of 2.1% of the *CYP2C9*17* allele in the individuals of our analyzed population corresponds predominantly to Native American ancestry.

Ancestry analysis can explain the frequencies we found for the *CYP2C19*2* (14.22) and *17 (2.10) alleles. Ecuadorian mestizos exhibit a ratio of 61.5% of Native American ancestry, 32.9% of European ancestry, and 5.6% of African ancestry [18]. This could explain the frequencies of our population, especially those for the *CYP2C19*17* allele, whose frequency is strongly correlated with a Native American population. Another interesting comparison could be made between our data and those of the Peruvian population within different databases. Peruvian mestizos have a higher percentage of Native American ancestry (71.1%) than Ecuadorians (61.5%) [18]. In the LDlink database, they have the lowest frequency of *CYP2C19*2* and **17* alleles in all the subgroups of Latin Americans, although the database includes only admixed populations [91]. As Peru and Ecuador are border countries, they may both have similar frequencies of these two alleles. Ecuadorians may have a higher frequency of those alleles due to their lower Native American ancestry, which is consistent with our data for *CYP2C19*2*. However, our data suggest a higher Native American component for *CYP2C19*17*. Therefore, further studies would be required to better understand these differences in *CYP2C19*17*.

4.1. Perspectives

The frequency of the most pharmacogenetically relevant alleles of *CYP2C19* in Latin America is strongly influenced by the rate of admixture between Native Americans, Europeans, and Africans during the colonization. The *CYP2C19*2, *3,* and **17* alleles are almost non-existent in Native American populations and their higher frequencies are linked to more admixed populations. There is a strong component of Native American ancestry in Ecuador, which may explain the lower *CYP2C19*2* and **17* frequencies found in our study as compared to European and African populations.

Pharmacogenomics aims to use a patient's genetic data to enable safer and more effective drug prescribing. However, Latin American populations have been largely underrepresented in genomic studies of drug response and disease susceptibility [92]. Therefore, this study provides valuable genetic data for the healthcare system and determines the frequencies of actionable alleles in ancestrally diverse populations. Studies like ours emphasize the significance of establishing dependable and up-to-date allele frequencies. This enables the application of pharmacogenetic guidelines not only to the general population but also to specific populations of mixed ancestry.

CRediT authorship contribution statement

Alba Alonso Llorente: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Josefa Salgado Garrido:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Óscar Teijido Hermida:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Fabricio González Andrade:** Writing – review & editing, Resources, Investigation, Conceptualization. **Alberto Valiente Martín:** Writing – review & editing, Supervision, Resources. **Ana Julia Fanlo Villacampa:** Writing – review & editing, Formal analysis, Conceptualization. **Jorge Vicente Romero:** Writing – review & editing, Methodology, Formal analysis, Conceptualization.

Table 4
Frequency comparison of *CYP2C19*17* allele with other populations.

Region	Country	Ethnic group	*CYP2C19*17* (%)	N	Reference
America	Ecuador	Interethnic	2.10	214	Present study
	Ecuador	Mestizo	24.9**	297	[8]
	Ecuador	NS	9.5**	132	[16]
	Ibero-American countries	North Native American	1.88	823	[17]
		Central Native American	2.60	96	
		South Native American	0**	214	
		Admixed	12.33**	1898	
		Afrodescendants	21.34**	82	
		Caucasian	16.10**	267	
		Argentinean Ashkenazi Jews	20.55**	163	
	Brazil	NS	17**	50	[80]
	Brazil	White: North	11.5**	156	[28]
		White: Northeast	19.9**	176	
		White: Southeast	14.2**	176	
		White: South	21.6**	176	
		Brown: North	16.1**	174	
		Brown: Northeast	19.3**	174	
		Brown: Southeast	13.8**	174	
		Brown: South	18.8**	176	
		Black: North	17**	174	
		Black: Northeast	18**	172	
		Black: Southeast	16.7**	170	
		Black: South	20.4**	164	
	Brazil	Native American	15.8**	183	[27]
		Caucasian	18**	615	
		Mulatto	21.3**	315	
		Afrodescendant	26.3**	99	
	Colombia	NS	20.9**	239	[30]
	Costa Rica	Mestizo	10.3**	141	[31]
		Bribri	4.3	23	
		Chorotega	2.8	36	
		Guaymí	2.0	24	
		Maleku	0	12	
		Afro-Caribbean	21.7**	46	
	Mexican	Mestizo	14.3**	238	[81]
	United States	Caucasian	22**	107	[19]
		African American	21**	114	
		Hispanic	12**	108	
	United States	Native American	9**	98	[35]
	United States	Cuban	0.4**	1965	[34]
		Dominican	17.9**	942	
		Puerto Rican	16.5**	1863	
		Central American	11**	1182	
		Mexican	10.6**	4670	
		South American	10.9**	772	
Europe	Bosnia & Herzegovina	Caucasian	20.37**	216	[39]
	Cyprus	NS	11**	40	[38]
	Croatia	Caucasian	23.7**	1002	[40]
	Denmark	NS	20.1**	276	[41]
	Faroe Islands	NS	15.4**	311	[41]
	Germany	Caucasian	25.6**	423	[43]
	Greece	NS	19.61**	283	[82]
	Kosovo	Caucasian	19.01**	234	[47]
	Lithuania	NS	25**	20	[38]
	Malta	NS	26**	41	[38]
	Norway	Caucasian	22**	328	[41]
	Poland	Caucasian	27.2**	125	[83]
	Serbia	NS	22.2**	500	[50]
	Spain	Caucasian	14.9**	282	[8]
	Spain and Portugal	Caucasian	19.89**	1521	[17]
	Sweden	NS	18**	314	[84]
Europe and Asia	Russia	Tartar	27.3**	141	[51]
		Balkar	14**	200	
		Russian	26.84**	136	
	Russia	Ulan-Ude (Buryat)	10.1**	109	[52]
		Irkustk	23.3**	118	
	Turkey	NS	15.8**	347	[53]
Asia	Bangladesh	NS	11.7**	320	[55]

(*continued on next page*)

Table 4 (*continued*)

Region	Country	Ethnic group	*CYP2C19*17* (%)	N	Reference
	Bahrain	NS	27.3**	75	[54]
	China	Shanghai	0*	100	[85]
		Xi'an	1.5	100	
		Shenyang	2.08	100	
		Shantou	1.04	100	
	China	Han	1	831	[57]
		Hui	2.9	85	
		Uygur	3.1	352	
		Kazak	10.9**	69	
	Indian	NS	18**	55	[86]
	South Indian	NS	19.2**	206	[63]
	Iran	NS	21.60**	180	[87]
	Iran	Fars	28.2**	156	[66]
		Turk	26.9**	56	
		Caspian	17.1**	32	
		Lure	46.1**	13	
		Kurd	21.4**	14	
	Japan	NS	1.3	265	[88]
	Korea	NS	1.5	271	[70]
	Kuwait	NS	25**	100	[54]
	Saudi Arabia	NS	25.7**	201	[20]
	Singapore	Chinese	1	100	[74]
		Malay	2.5	100	
		Indian	16.5**	100	
	Tunisia	NS	21.3**	258	[54]
	Vietnam	Kinh	1	100	[76]
		Tay	1.4	103	
		Muong	1	99	
		H'Mong	0	40	
		Nung	0	33	
Africa	Egypt	NS	17**	190	[89]
	Ethiopia	NS	17.9**	190	[84]

*p<0,05, **p<0.01, NS: Not specified.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] C.F. Samer, K.I. Lorenzini, V. Rollason, Y. Daali, J.A. Desmeules, Applications of CYP450 testing in the clinical setting, Mol. Diagn. Ther. 17 (3) (2013) 165–184.
[2] S.F. Zhou, J.P. Liu, B. Chowbay, Polymorphism of human cytochrome P450 enzymes and its clinical impact, Drug Metab. Rev. 41 (2) (2009) 89–295.
[3] A.E. Berezin, A.A. Berezin, Adverse cardiac remodelling after acute myocardial infarction: old and new biomarkers, Dis. Markers 2020 (2020).
[4] N.L. Pereira, C.S. Rihal, D.Y.F. So, Y. Rosenberg, R.J. Lennon, V. Mathew, et al., Clopidogrel pharmacogenetics, Circ Cardiovasc Interv 12 (4) (2019) 1–21.
[5] S. Quaranta, J. Dupouey, R. Colle, C. Verstuyft, Pharmacogenetics of antidepressant drugs: state of the art and clinical implementation – recommendations from the French National Network of Pharmacogenetics, Therapie [Internet] 72 (2) (2017) 311–318, https://doi.org/10.1016/j.therap.2016.09.018. Available from:.
[6] L.G.T. Shanika, A. Reynolds, S. Pattison, R. Braund, Proton pump inhibitor use: systematic review of global trends and practices, Eur J Clin Pharmacol [Internet] 79 (9) (2023) 1159–1172, https://doi.org/10.1007/s00228-023-03534-z. Available from:.
[7] J.J. Lima, C.D. Thomas, J. Barbarino, Z. Desta, S.L. Van Driest, N. El Rouby, et al., Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing, Clin. Pharmacol. Ther. 0 (0) (2020) 1–7.
[8] J. Vicente, F. González-Andrade, A. Soriano, A. Fanlo, B. Martínez-Jarreta, B. Sinués, Genetic polymorphisms of CYP2C8, CYP2C9 and CYP2C19 in Ecuadorian Mestizo and Spaniard populations: a comparative study, Mol. Biol. Rep. 41 (3) (2014) 1267–1272.
[9] C.R. Lee, J.A. Luzum, K. Sangkuhl, R.S. Gammal, M.S. Sabatine, C.M. Stein, et al., Clinical pharmacogenetics implementation consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update, Clin. Pharmacol. Ther. 0 (0) (2022) 1–9.
[10] H. Abdullah-Koolmees, A.M. van Keulen, M. Nijenhuis, V.H.M. Deneer, Pharmacogenetics guidelines: overview and comparison of the DPWG, CPIC, CPNDS, and RNPGx guidelines, Front. Pharmacol. 11 (2021) 1–12.
[11] L. Poulsen, C. Børsting, C. Tomas, F. González-Andrade, R. Lopez-Pulles, J. González-Solórzano, et al., Typing of amerindian Kichwas and mestizos from Ecuador with the SNPforID multiplex, Forensic Sci Int Genet 5 (4) (2011) 105–107.
[12] R. Flores-Espinoza, E. Paz-Cruz, V.A. Ruiz-Pozo, M. Lopez-Carrera, A. Cabrera-Andrade, L. Gusmão, et al., Investigating genetic diversity in admixed populations from Ecuador, Am. J. Phys. Anthropol. 176 (1) (2021) 109–119.
[13] M. Baeta, C. Núñez, C. Sosa, M. Bolea, Y. Casalod, F. González-Andrade, et al., Mitochondrial diversity in amerindian Kichwa and mestizo populations from Ecuador, Int. J. Leg. Med. 126 (2) (2012) 299–302.
[14] Instituto nacional de estadísticas y censos (INEC), Censo de población y vivienda (CPV-2022) [Internet]. https://www.censoecuador.gob.ec/resultados-censo/, 2022.
[15] L. Rodriguez-Delfin, V. Rubin-de-Celis, M. Zargo, Genetic diversity in an andean population from Peru and regional migration patterns of amerindians in south America: data from Y chromosome and mitochondrial DNA, Hum. Hered. 51 (2001) 97–106.
[16] F. De Andrés, S. Terán, F. Hernández, E. Terán, A. Llerena, To genotype or phenotype for personalized medicine? CYP450 drug metabolizing enzyme genotype-phenotype concordance and discordance in the Ecuadorian population. Omi A, J Integr Biol. 20 (12) (2016) 699–710.

[17] M.E.G. Naranjo, F. Rodrigues-Soares, E.M. Peñas-Lledó, E. Tarazona-Santos, H. Fariñas, I. Rodeiro, et al., Interethnic variability in CYP2D6, CYP2C9, and CYP2C19 genes and predicted drug metabolism phenotypes among 6060 ibero-and native Americans: RIBEF-CEIBA consortium report on population pharmacogenomics, OMICS A J. Integr. Biol. 22 (9) (2018) 575–588.

[18] F. Rodrigues-Soares, E.M. Peñas-Lledó, E. Tarazona-Santos, M. Sosa-Macías, E. Terán, M. López-López, et al., Genomic ancestry, CYP2D6, CYP2C9, and CYP2C19 among Latin Americans, Clin. Pharmacol. Ther. 107 (1) (2020) 257–268.

[19] G.L. Kearns, J.S. Leeder, A. Gaedigk, Impact of the CYP2C19*17 allele on the pharmacokinetics of omeprazole and pantoprazole in children: evidence for a differential effect, Drug Metab. Dispos. 38 (6) (2010) 894–897.

[20] L.H. Saeed, A.Y. Mayet, Genotype-phenotype analysis of CYP2C19 in healthy saudi individuals and its potential clinical implication in drug therapy, Int. J. Med. Sci. 10 (11) (2013) 1497–1502.

[21] R.M. Baldwin, S. Ohlsson, R.S. Pedersen, J. Mwinyi, M. Ingelman-Sundberg, E. Eliasson, et al., Increased omeprazole metabolism in carriers of the CYP2C19*17 allele; a pharmacokinetic study in healthy volunteers, Br. J. Clin. Pharmacol. 65 (5) (2008) 767–774.

[22] Product pages for thermo Fisher Connect (TM) platform [internet]. https://apps.thermofisher.com/apps/spa/#/dashboard.

[23] R. Lakhan, R. Kumari, K. Singh, J. Kalita, U.K. Misra, B. Mittal, Possible role of CYP2C9 & CYP2C19 single nucleotide polymorphisms in drug refractory epilepsy, Indian J. Med. Res. 134 (9) (2011) 295–301.

[24] K. Itoh, K. Inoue, S. Yanagiwara, H. Kyoya, T. Suzuki, A rapid and simple detection of genetic defects responsible for the phenotypic polymorphism of cytochrome P450 2C19, Biol. Pharm. Bull. 22 (1) (1999) 77–79.

[25] H.V. Bravo-Villalta, K. Yamamoto, K. Nakamura, A. Bayá, Y. Okada, R. Horiuchi, Genetic polymorphism of CYP2C9 and CYP2C19 in a Bolivian population: an investigative and comparative study, Eur. J. Clin. Pharmacol. 61 (3) (2005) 179–184.

[26] R. Linden, A.L. Ziulkoski, P. Tonello, M. Wingert, A.A. Souto, Relation between CYP2C19 phenotype and genotype in a group of Brazilian volunteers, Brazilian J Pharm Sci 45 (3) (2009) 461–467.

[27] P.C.J.L. Santos, R.A.G. Soares, D.B.G. Santos, R.M. Nascimento, G.L.L.M. Coelho, J.C. Nicolau, et al., CYP2C19 and ABCB1 gene polymorphisms are differently distributed according to ethnicity in the Brazilian general population, BMC Med Genet [Internet] 12 (1) (2011) 13. Available from: http://www.biomedcentral.com/1471-2350/12/13.

[28] G. Suarez-Kurtz, J.P. Genro, M.O. De Moraes, E.B. Ojopi, S.D.J. Pena, J.A. Perini, et al., Global pharmacogenomics: impact of population diversity on the distribution of polymorphisms in the CYP2C cluster among Brazilians, Pharmacogenomics J [Internet] 12 (3) (2012) 267–276, https://doi.org/10.1038/tpj.2010.89. Available from:.

[29] J. Ruedlinger, Y. Prado, T. Zambrano, N. Saavedra, B. Bobadilla, M. Potthoff, et al., CYP2C19*2 polymorphism in Chilean patients with in-stent restenosis development and controls, BioMed Res. Int. 2017 (2017).

[30] A. Arévalo-Galvis, W.A. Otero-Regino, G.N. Ovalle-Celis, E.R. Rodríguez-Gómez, A.A. Trespalacios-Rangel, Prevalence of CYP2C19 polymorphism in Bogotá, Colombia: the first report of allele *17, PLoS One 16 (1 January 2021) (2021) 1–12.

[31] C. Céspedes-Garro, F. Rodrigues-Soares, G. Jiménez-Arce, G. Naranjo M-E, E. Tarazona-Santos, H. Fariñas, et al., Relevance of the ancestry for the variability of the Drug-Metabolizing Enzymes CYP2C9, CYP2C19 and CYP2D6 polymorphisms in a multiethnic Costa Rican population, Rev. Biol. Trop. 64 (3) (2016) 1067–1076.

[32] C. Hoyo-Vadillo, J. Garcia-Mena, A. Valladares, C.R. Venturelli, N. Wacher-Rodarte, J. Kumate, et al., Association of CYP2C19 genotype with type 2 diabetes, Health (Irvine Calif) 2 (10) (2010) 1184–1190.

[33] J. Salazar-Flores, L.A. Torres-Reyes, G. Martínez-Cortés, R. Rubi-Castellanos, M. Sosa-Macías, J.F. Muñoz-Valle, et al., Distribution of CYP2D6 and CYP2C19 polymorphisms associated with poor metabolizer phenotype in five Amerindian groups and western mestizos from Mexico, Genet. Test. Mol. Biomarkers 16 (9) (2012) 1098–1104.

[34] K. Melin, J.Y. Moon, Q. Qi, D.F. Hernandez-Suarez, J. Duconge, S. Hua, et al., Prevalence of pharmacogenomic variants affecting the efficacy of clopidogrel therapy in the Hispanic Community Health Study/Study of Latinos cohort, Pharmacogenomics 20 (2) (2019) 75–83.

[35] J.H. Oestreich, L.G. Best, P.P. Dobesh, Prevalence of CYP2C19 variant alleles and pharmacodynamic variability of aspirin and clopidogrel in Native Americans, Am Heart J [Internet] 167 (3) (2014) 413–418, https://doi.org/10.1016/j.ahj.2013.10.028. Available from:.

[36] H.R. Luo, R.E. Poland, K.M. Lin, Y.J.Y. Wan, Genetic polymorphism of cytochrome P450 2C19 in Mexican Americans: a cross-ethnic comparative study, Clin. Pharmacol. Ther. 80 (1) (2006) 33–40.

[37] De Guerra D. Castro, S. Flores, M.H. Izaguirre, Distribution of CYP2C19*2 and CYP2C19*3 polymorphisms in Venezuelan populations with different admixture, Ann. Hum. Biol. 40 (2) (2013) 197–200.

[38] J. Petrović, V. Pešić, V.M. Lauschke, Frequencies of clinically important CYP2C19 and CYP2D6 alleles are graded across Europe, Eur. J. Hum. Genet. 28 (1) (2020) 88–94.

[39] S. Vidovic, R. Skrbic, M.P. Stojiljkovic, V. Vidovic, J. Becarevic, S. Stoisavljevic-Satara, et al., Prevalence of five pharmacologically most important CYP2C9 and CYP2C19 allelic variants in the population from the Republic of Srpska in Bosnia and Herzegovina Prevalencija pet farmakoloski najznacajnijih CYP2C9 i CYP2C19 alelenih varijanti u populaciji R, Arh. Hig. Rada. Toksikol. 72 (3) (2021) 129–134.

[40] L. Ganoci, T. Božina, N. Mirošević Skvrce, M. Lovrić, P. Mas, N. Božina, Genetic polymorphisms of cytochrome P450 enzymes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 in the Croatian population, Drug Metab Pers Ther 32 (1) (2017) 11–21.

[41] R.S. Pedersen, C. Brasch-Andersen, S.C. Sim, T.K. Bergmann, J. Halling, M.S. Petersen, et al., Linkage disequilibrium between the CYP2C19*17 allele and wildtype CYP2C8 and CYP2C9 alleles: identification of CYP2C haplotypes in healthy Nordic populations, Eur. J. Clin. Pharmacol. 66 (12) (2010) 1199–1205.

[42] C. Bertrand-Thiébault, H. Berrahmoune, A. Thompson, B. Marie, S. Droesch, G. Siest, et al., Genetic polymorphism of CYP2C19 gene in the stanislas cohort. A link with inflammation, Ann. Hum. Genet. 72 (2) (2008) 178–183.

[43] T. Geisler, E. Schaeffeler, J. Dippon, S. Winter, V. Buse, C. Bischofs, et al., CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation, Pharmacogenomics 9 (9) (2008) 1251–1259.

[44] K. Arvanitidis, G. Ragia, M. Iordanidou, S. Kyriaki, A. Xanthi, A. Tavridou, et al., Genetic polymorphisms of drug-metabolizing enzymes CYP2D6, CYP2C9, CYP2C19 and CYP3A5 in the Greek population, Fundam. Clin. Pharmacol. 21 (4) (2007) 419–426.

[45] C. Sipeky, A. Weber, M. Szabo, B.I. Melegh, I. Janicsek, G. Tarlos, et al., High prevalence of CYP2C19*2 allele in Roma samples: study on Roma and Hungarian population samples with review of the literature, Mol. Biol. Rep. 40 (8) (2013) 4727–4735.

[46] M.G. Scordo, A.P. Caputi, C. D'Arrigo, G. Fava, E. Spina, Allele and genotype frequencies of CYP2C9, CYP2C19 and CYP2D6 in an Italian population, Pharmacol. Res. 50 (2) (2004) 195–200.

[47] V. Krasniqi, A. Dimovski, H.Q. Bytyqi, A. Eftimov, L. Šimičevic, N. Božina, Genetic polymorphisms of CYP2C9, CYP2C19, and CYP3A5 in Kosovar population, Arh. Hig. Rada. Toksikol. 68 (3) (2017) 180–184.

[48] R. Ruiter, R.H.N. Schaik, Increased survival in breast cancer patients using tamoxifen R esearch A rticle, Pharmacogenomics 11 (10) (2010) 1367–1375.

[49] A. Sałagacka-Kubiak, M. Żebrowska-Nawrocka, A. Jeleń, M. Mirowski, E. Balcerczak, CYP2C19*2 polymorphism in Polish peptic ulcer patients, Pharmacol Reports [Internet] 71 (2) (2019) 272–275, https://doi.org/10.1016/j.pharep.2018.12.011. Available from:.

[50] I. Skadrić, O. Stojković, Defining screening panel of functional variants of CYP1A1, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 genes in Serbian population, Int. J. Leg. Med. 134 (2) (2020) 433–439.

[51] S.P. Abdullaev, K.B. Mirzaev, I.S. Burashnikova, A.A. Shikaleva, A.A. Kachanova, S.P. Abdullaev, et al., Clinically relevant pharmacogenetic markers in Tatars and Balkars, Mol Biol Rep [Internet] 47 (5) (2020) 3377–3387, https://doi.org/10.1007/s11033-020-05416-4. Available from:.

[52] E.M. Zelenskaya, G.I. Lifshits, K.Y. Nikolaev, O.S. Donirova, V.D. Altayev, K.A. Apartsin, et al., The frequency of the minor polymorphisms in the CYP2C19, VEGFR-2 genes, and clinical outcomes in Russian and buryat patients with acute coronary syndrome, Genet. Test. Mol. Biomarkers 24 (6) (2020) 338–342.

[53] F. Saydam, İ. Değirmenci, A. Birdane, M. Özdemir, T. Ulus, C. Özbayer, et al., The CYP2C19*2 and CYP2C19*17 polymorphisms play a vital role in clopidogrel responsiveness after percutaneous coronary intervention: a pharmacogenomics study, Basic Clin. Pharmacol. Toxicol. 121 (1) (2017) 29–36.

[54] R. Abdelhedi, N.A. Bouayed, S. Alfadhli, L. Abid, A. Rebai, N. Kharrat, Characterization of drug-metabolizing enzymes CYP2C9, CYP2C19 polymorphisms in Tunisian, Kuwaiti and Bahraini populations, J. Genet. 94 (4) (2015) 765–770.

[55] M.S. Bin Sayeed, M.N. Hasan Apu, M.T. Munir, M.U. Ahmed, M.S. Islam, M.M. Haq, et al., Prevalence of CYP2C19 alleles, pharmacokinetic and pharmacodynamic variation of clopidogrel and prasugrel in Bangladeshi population, Clin. Exp. Pharmacol. Physiol. 42 (5) (2015) 451–457.

[56] Y. Liu, N. Liu, W. Li, H. Shao, H. Zhi, J. Li, Relationship of CYP2C19*2 and CYP2C19*3 gene polymorphism with clopidogrel response variability and recurrent cardiovascular events in Chinese patients undergoing percutaneous coronary intervention, Pharmacology 91 (3–4) (2013) 165–172.

[57] L. Ma, Y. Yuan, J. Li, C. Yu, J. Zhao, Distribution of CYP2C19, ABCB1 and PON1 polymorphisms in Chinese Han, Hui, Uygur and Kazak patients with coronary atherosclerotic heart disease, Int. J. Immunogenet. 47 (6) (2020) 539–545.

[58] S.J. Yin, Y.B. Ni, S.M. Wang, X. Wang, Y.Q. Lou, G.L. Zhang, Differences in genotype and allele frequency distributions of polymorphic drug metabolizing enzymes CYP2C19 and CYP2D6 in mainland Chinese Mongolian, Hui and Han populations, J. Clin. Pharm. Therapeut. 37 (3) (2012) 364–369.

[59] J.H. Wang, P.Q. Li, Q.Y. Fu, Q.X. Li, W.W. Cai, CYP2C19 genotype and omeprazole hydroxylation phenotype in Chinese Li population, Clin. Exp. Pharmacol. Physiol. 34 (5–6) (2007) 421–424.

[60] Z. Zhong, J. Hou, B. Li, Q. Zhang, S. Liu, C. Li, et al., Analysis of CYP2C19 genetic polymorphism in a large ethnic Hakka population in southern China, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 23 (2017) 6186–6192.

[61] L.J. Zuo, T. Guo, D.Y. Xia, L.H. Jia, Allele and genotype frequencies of CYP3A4, CYP2C19, and CYP2D6 in han, uighur, hui, and Mongolian Chinese populations, Genet. Test. Mol. Biomarkers 16 (2) (2012) 102–108.

[62] S. Gulati, A. Yadav, N. Kumar, Kumar G. Kanupriya, N. Aggarwal, et al., Frequency distribution of high risk alleles of CYP2C19, CYP2E1, CYP3A4 genes in Haryana population, Environ Toxicol Pharmacol [Internet] 37 (3) (2014) 1186–1193, https://doi.org/10.1016/j.etap.2014.03.013. Available from:.

[63] D. Anichavezhi, U.S. Chakradhara Rao, D.G. Shewade, R. Krishnamoorthy, C. Adithan, Distribution of CYP2C19*17 allele and genotypes in an Indian population, J. Clin. Pharm. Therapeut. 37 (3) (2012) 313–318.

[64] R. Jose, A. Chandrasekaran, S.S. Sam, N. Gerard, S. Chanolean, B.K. Abraham, et al., CYP2C9 and CYP2C19 genetic polymorphisms: frequencies in the south Indian population, Fundam. Clin. Pharmacol. 19 (1) (2005) 101–105.

[65] M.M. Saber, M. Boroumand, M. Behmanesh, Investigation of CYP2C19 allele and genotype frequencies in Iranian population using experimental and computational approaches, Thromb Res [Internet] 133 (2) (2014) 272–275, https://doi.org/10.1016/j.thromres.2013.11.005. Available from:.

[66] M. Dehbozorgi, B. Kamalidehghan, I. Hosseini, Z. Dehghanfard, M.H. Sangtarash, M. Firoozi, et al., Prevalence of the CYP2C19*2 (681 G>A), *3 (636 G>A) and *17 (-806 C>T) alleles among an Iranian population of different ethnicities, Mol. Med. Rep. 17 (3) (2018) 4195–4202.

[67] H.R. Luo, V. Aloumanis, K.M. Lin, D. Gurwitz, Y.J.Y. Wan, Polymorphisms of CYP2C19 and CYP2D6 in Israeli ethnic groups, Am. J. PharmacoGenomics 4 (6) (2004) 395–401.

[68] H. Fukushima-Uesaka, Y. Saito, K. Maekawa, S. Ozawa, R. Hasegawa, H. Kajio, et al., Genetic variations and haplotypes of CYP2C19 in a Japanese population, Drug Metabol. Pharmacokinet. 20 (4) (2005) 300–307.

[69] A.M. Yousef, N.R. Bulatova, W. Newman, N. Hakooz, S. Ismail, H. Qusa, et al., Allele and genotype frequencies of the polymorphic cytochrome P450 genes (CYP1A1, CYP3A4, CYP3A5, CYP2C9 and CYP2C19) in the Jordanian population, Mol. Biol. Rep. 39 (10) (2012) 9423–9433.

[70] K.A. Kim, W.K. Song, K.R. Kim, J.Y. Park, Assessment of CYP2C19 genetic polymorphisms in a Korean population using a simultaneous multiplex pyrosequencing method to simultaneously detect the CYP2C19*2, CYP2C19*3, and CYP2C19*17 alleles, J. Clin. Pharm. Therapeut. 35 (6) (2010) 697–703.

[71] I.D. Jureidini, N. Chamseddine, S. Keleshian, R. Naoufal, L. Zahed, N. Hakime, Prevalence of CYP2C19 polymorphisms in the Lebanese population, Mol. Biol. Rep. 38 (8) (2011) 5449–5452.

[72] Y.S. Yang, L.P. Wong, T.C. Lee, A.M. Mustafa, Z. Mohamed, C.C. Lang, Genetic polymorphism of cytochrome P450 2C19 in healthy Malaysian subjects, Br. J. Clin. Pharmacol. 58 (3) (2004) 332–335.

[73] B.M. Ayesh, I.R. Al-Astal, M.M. Yassin, The clinical effects of CYP2C19 *2 allele frequency on Palestinian patients receiving clopidogrel after percutaneous coronary intervention, Int J Clin Pharm [Internet] 41 (1) (2019) 96–103, https://doi.org/10.1007/s11096-018-00782-3. Available from:.

[74] M.Y. Chan, H. Tan, R Esearch A Rticle CYP2C19 and PON1 Polymorphisms Regulating Clopidogrel Bioactivation in Chinese , Malay and Indian Subjects R Esearch A Rticle, 2012, pp. 533–542.

[75] W. Tassaneeyakul, W. Mahatthanatrakul, K. Niwatananun, K. Na-Bangchang, A. Tawalee, N. Krikreangsak, et al., CYP2C19 genetic polymorphism in Thai, Burmese and Karen populations, Drug Metabol. Pharmacokinet. 21 (4) (2006) 286–290.

[76] N.P. Vu, H.T.T. Nguyen, N.T.B. Tran, T.D. Nguyen, H.T.T. Huynh, X.T. Nguyen, et al., CYP2C19 genetic polymorphism in the Vietnamese population, Ann Hum Biol [Internet] 46 (6) (2019) 491–497, https://doi.org/10.1080/03014460.2019.1687750. Available from:.

[77] S. Hamdy, M. Hiratsuka, K. Narahara, M. El-Enany, N. Moursi, M. Ahmed, et al., Allele and genotype frequencies of polymorphic DCP1, CETP, ADRB2, and HTR2A in the Egyptian population, Eur. J. Clin. Pharmacol. 58 (1) (2002) 29–36.

[78] W. Kudzi, A.N.O. Dodoo, J.J. Mills, Characterisation of CYP2C8, CYP2C9 and CYP2C19 polymorphisms in a Ghanaian population, BMC Med. Genet. 10 (2009) 8–13.

[79] C. Dandara, C.M. Masimirembwa, A. Magimba, J. Sayi, S. Kaaya, K. De Sommers, et al., Genetic polymorphism of CYP2D6 and CYP2C19 in East- and Southern African populations including psychiatric patients, Eur. J. Clin. Pharmacol. 57 (1) (2001) 11–17.

[80] E.R. de Abreu Netto, R.L.A. Netto, M.F. Santana, J.P. de Moura Neto, L.C. de Lima Ferreira, Variants *1, *2, *3 and *17 of CYP2C19 cytochrome among Helicobacter pylori carriers from manaus, amazonas state, Brazil, Asian Pac. J. Cancer Prev. APJCP 22 (7) (2021) 2289–2294.

[81] A.F. Favela-Mendoza, G. Martinez-Cortes, M. Hernandez-Zaragoza, J. Salazar-Flores, J.F. Muñoz-Valle, V.M. Martinez-Sevilla, et al., Genetic variability of CYP2C19 in a Mexican population: contribution to the knowledge of the inheritance pattern of CYP2C19*17 to develop the ultrarapid metabolizer phenotype, J. Genet. 94 (1) (2015) 3–7.

[82] G. Ragia, K.I. Arvanitidis, A. Tavridou, V.G. Manolopoulos, Need for reassessment of reported CYP2C19 allele frequencies in various populations in view of CYP2C19*17 discovery: the case of Greece, Pharmacogenomics 10 (1) (2009) 43–49.

[83] M. Kurzawski, B. Gawrońska-Szklarz, J. Wrześniewska, A. Siuda, T. Starzyńska, M. Droździk, Effect of CYP2C19*17 gene variant on Helicobacter pylori eradication in peptic ulcer patients, Eur. J. Clin. Pharmacol. 62 (10) (2006) 877–880.

[84] S.C. Sim, C. Risinger, M.L. Dahl, E. Aklillu, M. Christensen, L. Bertilsson, et al., A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants, Clin. Pharmacol. Ther. 79 (1) (2006) 103–113.

[85] L. Chen, S. Qin, J. Xie, J. Tang, L. Yang, W. Shen, et al., Genetic polymorphism analysis of cytochrome P4502E1 (CYP2E1) in Chinese Han populations from four different geographic areas of Mainland China, Pharmacogenomics 9 (6) (2008) 671–702.

[86] P.K. Chawla, S.R. Nanday, A.J. Dherai, R. Soman, R.V. Lokhande, P.R. Naik, et al., Correlation of CYP2C19 genotype with plasma voriconazole levels: a preliminary retrospective study in Indians, Int. J. Clin. Pharm. 37 (5) (2015) 925–930.

[87] M. Payan, N. Tajik, M.R. Rouini, M.H. Ghahremani, Genotype and allele frequency of CYP2C19*17 in a healthy Iranian population, Med. J. Islam. Repub. Iran 29 (1) (2015) 872–980.

[88] K. Sugimoto, T. Uno, H. Yamazaki, T. Tateishi, Limited frequency of the CYP2C19*17 allele and its minor role in a Japanese population, Br. J. Clin. Pharmacol. 65 (3) (2008) 437–439.

[89] B. Khalil, M. Shahin, M. Solayman, T. Langaee, M. Schaalan, Y. Gong, et al., Genetic and nongenetic factors affecting clopidogrel response in the Egyptian population, Clin Transl Sci 9 (1) (2016) 23–28.

[90] R. Bisso-Machado, N.J.R. Fagundes, Uniparental genetic markers in Native Americans: a summary of all available data from ancient and contemporary populations, Am. J. Phys. Anthropol. 176 (3) (2021) 445–458.

[91] M.J. Machiela, S.J. Chanock, LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants, Bioinformatics 31 (21) (2015) 3555–3557.

[92] G. Sirugo, S.M. Williams, S.A. Tishkoff, T. Therapeutics, Q.H. Sciences, The missing diversity in human genetic studies, Cell. 177 (1) (2019) 26–31.