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Research Article

Frequency of *CYP2D6*3* and *4 and metabolizer phenotypes in three mestizo Peruvian populations

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Abstract

Wild type genotypes (*CYP2D6*) and their allelic variants have been described in a sample of a Peruvian mestizo population. The global allele frequency was 0.015 for *CYP2D6*3* and 0.051 for *CYP2D6*4*. The percentages of genotypes described were 97% *CYP2D6*1/*1* and 3.0% *CYP2D6*1/*3*; 90.60% for *CYP2D6*1/*1*, 8.55% *CYP2D6*1/*4* and 0.85% *CYP2D6*4/*4*. The allelic frequencies of *CYP2D6*3* in the Lima subpopulations were 0.022 and 0.010 for Junin; *CYP2D6*4* of 0.048, 0.060, and 0.050 for residents of Lima, Junín, and Tacna, respectively. The Hardy-Weinberg equilibrium test for the studied population showed that both frequencies are in equilibrium, $p < .05$. The metabolizer phenotype was inferred according to the genotypes: 11.54% were classified as intermediate metabolizers (*1/*3 or *1/*4) and 0.85% as poor metabolizers (*4/*4). It is concluded that the frequencies of the *CYP2D6*3* and *CYP2D6*4* alleles are low for the Peruvian mestizo population compared to the Latin American and tricontinental population, due to their natural population evolution, which is manifested by their decreased metabolic activity, the same that is relevant in clinical practice.

Keywords

Genetic polymorphism, Pharmacogenetics, Metabolic phenotype, Peruvian mestizo population

Introduction

Genetics is one of the main factors that determine the inter-ethnic variability in the pharmacological response, and this is explained by the differences in the population frequencies of genetic polymorphisms, which have clinical implications, therefore, the doses of a drug for a certain population, are not necessarily applicable to other populations or ethnic groups (Bertilsson, 1995); this polymorphism lies in the genes that encode various enzymes and among them, the family of the cytochrome P450 system, being the isoenzyme CYP2D6 (Debrisoquine 4-hydroxylase), the most representative in liver tissue (6% of all CYP450: CYP3A4, CYP2C9, and others) (Leitão et al. 2020; Saravia et al. 2021), and is involved in the phase I metabolism of almost 25% of clinically important drugs (Zanger and Schwab 2013; Ray et al. 2019; Jessurun et al. 2020) and in the metabolism of carcinogens (Bradford 2002; Da Silva et al. 2009).

The CYP2D locus is made up of a gene cluster, a *CYP2D6* gene, and two pseudogenes (*CYP2D7* and *CYP2D8*), with 97% and 92% similarity, respectively (Kimura et al. 1989; Zhou 2009). The autosomal *CYP2D6* gene is located on the long arm of chromosome 22 fragment q 13.1 (22q13.1), it consists of 4383 bp (Ur Rasheed et al. 2017) grouped in nine exons and eight introns that produces an mRNA of 1655 bp (Zanger et al. 2004; Dorado et al. 2017), with a 1383 bp open reading frame encoding a 497 amino acid protein (Salyakina et al. 2019; Leitão et al. 2020). More than 100 allelic variants have been described for this gene (https://www.pharmvar.org/gene/CYP2D6). Genes that have two functional alleles are called *CYP2D6*1* and *CYP2D6*2*, which encode an enzyme with extensive functional activity or wild type (Flores-Angulo et al. 2015); the most frequent alleles in the different populations are *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*6* (Rasheed et al. 2017) and *CYP2D6*10* (Flores-Angulo et al. 2015), of which the most Common are *CYP2D6*3* and * 4 (Da Silva et al. 2009) that express isoenzymes lacking activity (Johansson and Ingelman-Sundberg 2011; Flores-Angulo et al. 2015; Leitão et al. 2020). The *CYP2D6*3* variant consists of a deletion of an adenine base at position 2549 (g.2549delA; rs35742686) of exon 5, causing a truncated protein (Kagimoto et al. 1990; Dorado et al. 2017; Ur Rasheed et al. 2017), *CYP2D6*4* (g.1846G > A, rs3892097) is characterized by a single nucleotide polymorphism (transition from guanine to an adenine) at position 1846 (first nucleotide) of exon 4, causing a truncated protein due to a defect in splicing (Lu et al. 2013; De Andrés et al. 2017; Quiñones et al. 2017). Figure 1 describes the location of the CYP2D locus with its two pseudogenes and the *CYP2D6* gene with its 9 exons, at the same time indicating the location of the two alleles in the present study.

The frequencies of *CYP2D6*3* and *4 are high in Caucasian European and North American populations, very low in African populations, and in some regions of Asia, such as China and Japan (Bradford 2002; Llerena et al. 2014).

*CYP2D6*5* is the product of a deletion of the complete gene, *CYP2D6*6* by deletion of thymine at position 1707

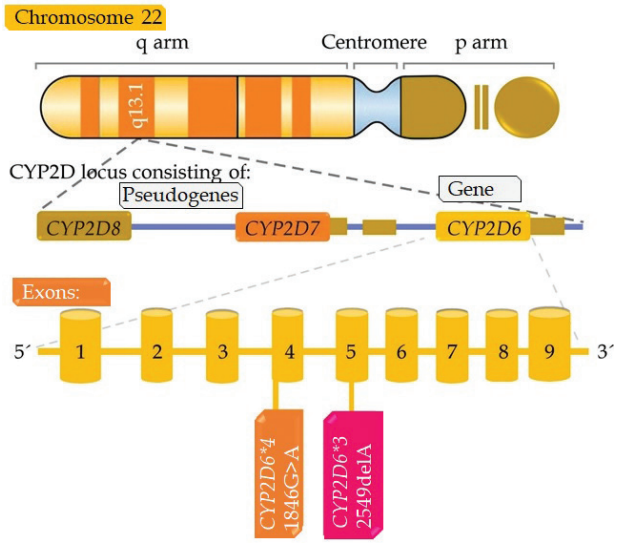

Figure 1. Location of the *CYP2D6* gene on the human chromosome, exons, *CYP2D6*3* and *4 alleles.

(1707delT) encoding a protein with null activity (Zhou 2009); *CYP2D6*10* is generated by a transition from guanine to an adenine (G > A, rs1065852), expressing a protein with reduced activity (Flores-Angulo et al. 2015). To describe the phenotypes, age, sex, and nutritional status must be taken into account, however, it is a study carried out by Lares-Asseff et al. (2005) determined that there is no effect of the mentioned parameters on the phenotypic expression of *CYP2D6* in Amerindian subjects of Tepehuan origin, using dextromethorphan as a metabolic marker, which may be due to the size of the population sample. Metabolic phenotypes can be obtained by extrapolating genotypes by putting the letter "g" in front of them to differentiate from phenotypes obtained with a test drug such as dextromethorphan (Llerena et al. 2014); thus we have genotypic extensive metabolizer (gEM), genotypic intermediate metabolizer (gIM), and genotypic poor metabolizer (gPM) (Gaedigk et al. 2008; Llerena et al. 2014).

After conducting a review in the PubMed-NCBI database on the studies of *CYP2D6* in Peruvian populations, it is evident that they are still scarce, being necessary to study them, due to their European migratory origin (Hunley and Healy 2011) (mainly Spanish) (Vilchez 2016), Latin American, African (Hunley and Healy 2011; Herrera-Paz 2013), and Asian (Chinese and Japanese) (Vilchez 2016), which have generated the current miscegenation of Peruvians, 68.3% Latin American (Homburger et al. 2015), 26–29% European (Ruiz-Linares et al. 2014), 3.2% African and 2.5% Asian (Homburger et al. 2015). A high percentage (> 50%) of the mestizo population was observed in Lima, Tacna, and Junin (INEI 2018). Due to these considerations, we have decided to study *CYP2D6*3* and *CYP2D6*4* in populations of the three aforementioned provinces, the alleles being selected, as they are the most frequent in Latin American populations (Muñoz et al. 1998) and in the world (Da Silva et al. 2009), due to their population and interethnic variability and because they metabolize more 25% of drugs for clinical use (Sa-

mer et al. 2013; Salyakina et al. 2019; Leitão et al. 2020), mostly with a narrow therapeutic margin, so at standard doses with certain drugs, potential adverse effects (tricyclic antidepressants) can be observed, or absence of the pharmacological effect as in the case of codeine (Madadi and Koren 2008; Llerena et al. 2014).

Our objective was to identify the frequencies of the *CYP2D6*3* (rs35742686) and *CYP2D6*4* (rs3892097) variants to catalog the metabolic phenotypes of drugs in a sample of a Peruvian mestizo population, given their phenotypic importance as well as their high population and interethnic variability.

Materials and methods

Design, type of sampling and study population

Observational, descriptive, cross-sectional study, non-probabilistic convenience sampling and prospective recruitment between January 2017 and December 2020. The Peruvian inhabitants were summoned and informed about the objectives and importance of the study, after that, only those who signed the informed consent freely and voluntarily, were enrolled in the present investigation (Alvarado et al. 2019; Alvarado et al. 2021). A total of 234 Peruvian mestizo subjects (174, 74.36% men; 60 women, 25.64%) were recruited for this study; 184 were from the coastal zone of the Pacific Lima (n = 134; 57.26%) and Tacna (n = 50; 21.37%), and 50 subjects from the Andean zone of Junín (21.37%); and with an age of 19 to 53 years (mean of 24.68 years); both sexes [Lima: female 35 (26.12%); male 99 (73.88%). Tacna: female 9 (18%); male 41 (82%). Junín: female 16 (32%); male 34 (68%)] and with a mean age of 24.68 years (Lima: female, mean 26.63, SD ± 7.73; male, mean 23.72, SD ± 5.04. Tacna: female, mean 25.78, SD ± 2.33; male, mean 24.83, SD ± 3.04. Junín: female, mean 24.63, SD ± 1.63; male, mean 25, SD ± 0.65).

Inclusion and exclusion criteria

To include mestizo Peruvians in the present study, reports of the migratory pattern, native genes, and non-molecular markers of miscegenation (linguistic tree and surnames) were considered (Alvarado et al. 2021). Regarding the migratory pattern of Peruvians, this is a complex phenomenon, generated by the economic crisis, by the displacement of rural areas and the countryside towards the city, by natural disasters (Yamada 2010; Carrillo-Larco et al. 2017), and in the case of young people, it is due to the aspiration to pursue university studies, improve their social and economic level and living conditions, which contributes to the internal miscegenation of Peruvians (Carrillo-Larco et al. 2017), at the same time, said miscegenation, is due to migration of Latin Americans, Europeans, Africans (Hunley and Healy 2011), and Asians to Peru (Vilchez 2016); considering the linguistic tree and the ancestry surnames, which indicate the migratory patterns, population structure and historical phylogenetic relationships between populations (Herrera-Paz 2013). At the same time, it has been reported that 60%-70% of Peruvians have native genes that classify them as mestizos (Harris et al. 2018), observing in Lima 67.7% of the mestizo population and 2.8% of Afro-Peruvians; in Tacna (coastal border and commercial province) 49.3% are mestizo, 32.9% Aymara and 1.7% Afro-Peruvian; Junín (Andean zone) 52.4% are mestizo, 34.9% Quechua, 0.2% Aymara and 0.5% Afro-Peruvian (INEI 2018).

All of this allowed us to select mestizo Peruvians over 18 years of age and of coastal and Andean origin; at the medical examination, be in good health (systolic blood pressure of 110–139 mm Hg and diastolic of 60–89 mm Hg, abdominal circumference less than 95 cm in men and 82 cm in women and not having a diagnosis of diabetes); and by an explicit declaration of each volunteer not to consume alcoholic beverages or drugs of abuse, not to have a difficulty that prevents the taking of the biological sample and to give their consent in writing. All subjects, who belonged to an ethnic group, were not in a position to give their consent, and those who did not meet the inclusion criteria were excluded from the study (Alvarado et al. 2019; Alvarado et al. 2021).

Obtaining genomic DNA

Genomic DNA (gDNA) was obtained by buccal swabbing of non-keratinized stratified flat epithelial tissue, rubbing the inner cheek mucosa five to six times with the swab to ensure an adequate amount of scaly cells. Subsequently, the swab was immersed for 60s in 300 µL of lysis buffer and the resulting mixture was refrigerated at 4°C for a time not exceeding 18 hours. The DNAg was extracted using the innuPRE DNA Master kit (Analytik Jena), following the manufacturer's protocol, a procedure performed at the USIL Pharmacology Laboratory. Genomic DNA was quantified by spectrophotometry using Denovix equipment (model DS-11, FX, Spectrophotometer Series, USA). Samples with absorbance ratios of 260/280 nm and 260/230 nm equal to or greater than 1.8 were considered suitable for the study. The samples were stored at -20°C until analysis.

Genotypic analysis

The genotypes were determined using the real-time PCR technique (RT-PCR), using Buffer TE 1X reagents, for the identification of allelic variants, TaqMan probes capable of discriminating single nucleotide polymorphisms (SNPs) identified as *CYP2D6*3* (rs35742686) and *CYP2D6*4* (rs3892097) (TaqMan Genotyping Master Mix, catalog number 4371355-brand Thermo Fischer Scientific Inc.). The *CYP2D6*1* allele was not directly determined; All alleles that were negative for SNPs *CYP2D6*3* and *CYP2D6*4* were designated as *CYP2D6*1*, which is acceptable when the sequence variations corresponding to alleles are not determined, so it is not wrong to assume that No *X = *1.

In the standard protocol, the reaction mix was 20 ng gDNA, 5µL of 2X Genotyping Master Mix (Catalog No 4371355), 0.5 µL of 20X TaqMan SNP Genotyping AssayTM (containing the two probes and primers direct and reverse) and nuclease-free molecular biology grade water (HyPure HyCloneTM) in sufficient quantity for 10 µL of final reaction volume.

To determine *CYP2D6*3*, the TaqMan SNP Genotyping Assay catalog number 4362691 was used; C_32407232_50, which discriminates the g.2549delA deletion; and for *CYP2D6*4* the catalog number 4362691; C_27102431_D0, which discriminates the transition g.1846G > A.

For the amplification, the Stratagene Mx3000P equipment (Agilent Technologies, Waldbronn, Germany) was used, whose program consisted of an initial cycle of denaturation at 95°C for 10 min, and the second segment consisted of 50 cycles consisting of 15s of denaturation at 92°C, 90s of alignment at 60°C and 60s of elongation at 72°C.

Statistical analysis

To determine if the distribution of the studied genotypes was in Hardy-Weinberg equilibrium (HWE), the Chi-square (X^2) goodness-of-fit test was performed, considering a degree of freedom and a p-value <.05. X^2 values less than 3.88 in the comparison indicated acceptance of the null hypothesis, therefore, the observed frequencies did not differ significantly from those expected (Alvarado et al. 2019; Alvarado et al. 2021). *CYP2D6* allele frequencies predicted metabolic phenotypes (Zanger et al. 2004). The Statistical Software GraphPad Prism 9 was used. Version 9.1.2.

Ethical considerations

The study was carried out in strict compliance with good clinical practices (BCP), Code of Ethics of the World Medical Association (Declaration of Helsinki), the research protocol, and informed consent being approved by the Ethics Committee of Hospital Santa Rosa, by certificate No 16-19-CMI-HSR. Each volunteer was assigned a code number to guarantee their anonymity and confidentiality (Alvarado et al. 2019; Alvarado et al. 2021).

Results

Table 1 shows that the frequency of the *CYP2D6*4* allele is higher than the *CYP2D6*3* allele (0.015), while the wild-type genotype and allele frequencies are the most frequent, for a sample of Peruvian mestizo inhabitants. No homozygous *3/*3 (del/del) genotypes were described in these populations.

Next, the genotype and allelic frequencies of the sub-samples corresponding to inhabitants of the coast and the Andes of Peru are exposed, which are low. For Lima residents, the frequency of *CYP2D6*1/*3* and *3/*3 is 0.022, and for Junín it is 0.01, but they were not observed in Tacna residents; while the frequency of *CYP2D6*1/*4* and *4/*4 was similar in the three provinces (Table 2).

Table 3 shows the phenotypes that can be extrapolated from the genotypes, observing in this group of the mestizo population 12.39% of metabolic phenotypes with decreased activity, of which 0.85% are poor metabolizers.

Figure 2 shows the percentages of extrapolated poor metabolizers (gPM) of CYP2D6 from the European, Af-

Table 1. Genotype frequencies for alleles *3 and *4 of the *CYP2D6* gene in a sample of a Peruvian mestizo population.

Reference ID	Genotype	Nucleotide	n	%	Allele	f	X^2
rs35742686	*1/*1	A/A	227	97.0	*1	0.985	
	*1/*3	A/del	7	3.0	*3	0.015	0.054
	*3/*3	del/del	0	0.0			
	Total		234	100.0			
rs3892097	*1/*1	G/G	212	90.60	*1	0.949	
	*1/*4	G/A	20	8.55	*4	0.051	3.46
	*4/*4	A/A	2	0.85			
	Total		234	100.0			

n: sample number, %: percentage, f: allelic frequency.

Table 2. Genotypic and allelic frequencies for the variants *3 and *4 of the *CYP2D6* gene in the three Peruvian mestizo populations included in the present study.

Genotype	*n* (%)			Allelic frequency		
	Lima	Tacna	Junín	Lima	Tacna	Junin
*CYP2D6*1/*1* A/A	128 (95.5)	50 (100.0)	49(98.0)	0.978	1.0	0.99
*CYP2D6*1/*3* A/del	6 (4.5)	0 (0.0)	1 (2.0)	0.022	0.0	0.01
*CYP2D6*3/*3* del/del	0 (0.0)	0 (0.0)	0 (0.0)			
Total	134 (100.0)	50 (100.0)	50(100.0)	1.00	1.00	1.00
*CYP2D6*1/*1*	121 (90.3)	45 (90.0)	44 (88.0)	0.952	0.95	0.94
*CYP2D6*1/*4*	13 (9.7)	5 (10.0)	4 (8.0)	0.048	0.05	0.06
*CYP2D6*4/*4*	0 (0.0)	0 (0.0)	2 (4.0)			
Total	134 (100.0)	50 (100.0)	50 (100.0)	1.00	1.00	1.00

n: sample number by province, %: percentage of genotypes by province.

Table 3. Extrapolated metabolic phenotypes in the Peruvian mestizo population, according to the combinations of *CYP2D6*3* and *4.

Extrapolated phenotypes	*CYP2D6*3*	*CYP2D6*4*	Activity	*n*	%	Genotypes
Extensive metabolizer (gEM)	*1/*1	*1/*1	2	205	87.61	*1/*1
Intermediate metabolizer (gIM)	*1/*3	*1/*1	0.5–1.5	7	11.54	*1/*3
	*1/*1	1*/*4		20		*1/*4
Poor metabolizer (gPM)	*1/*1	*4/*4	0	2	0.85	*4/*4
	*3/*3	*1/*1		0		*3/*3

n: sample number, %: percentage of metabolizers.

Table 4. Studies of *CYP2D6*3* and *4 in Latin American and tricontinental populations were used in the comparison with the Peruvian population studied.

Population	*CYP2D6*3%(n)*	*CYP2D6*4%(n)*	Reference
Mestizo Peruvian	3.0(234)	9.4 (234)	Present study
Costa Ricans	1.4(139)	10.4(130)	Céspedes-Garro et al. 2014
Colombians	1.2(121)	10.4(121)	Isaza et al. 2000
Brazilians	3.4(89)	17.8(89)	Da Silva et al. 2009
Chileans	1.0(253)	12.0(253)	Roco et al. 2012
Ecuadorians	0.4	10.6(118)	Dorado et al. 2012
Africans	0	6.0	Quiñones et al. 2017
East Asians	0	0.0	Quiñones et al. 2017
South Asians	0	11.0	Quiñones et al. 2017
European	2	19.0	Quiñones et al. 2017
Spanish people	1(105)	13.8(105)	Menoyo et al. 2006

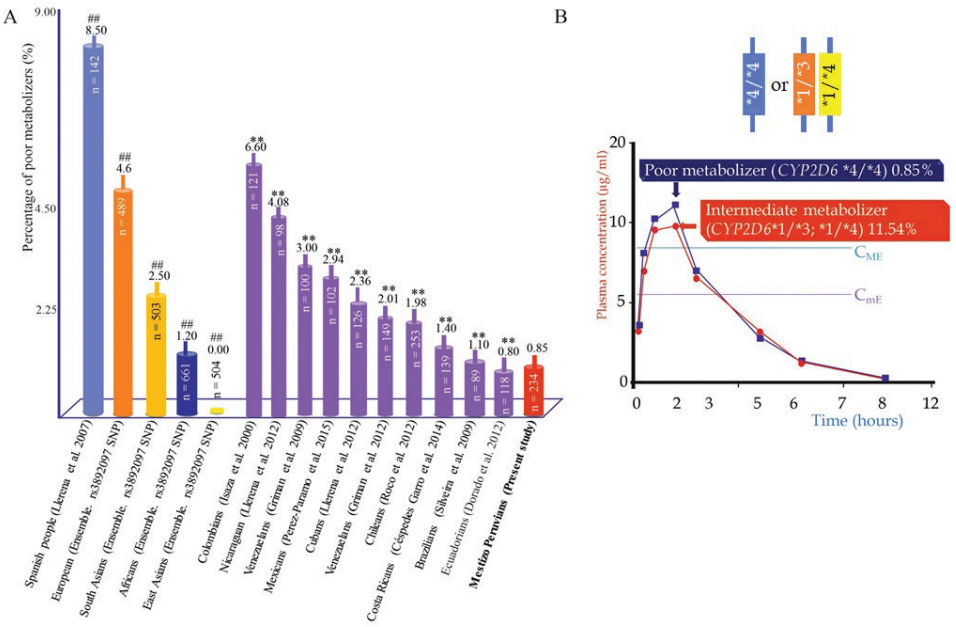

Figure 2. Percentages (%) of poor metabolizers (gPM) extrapolated from the genotype in different populations of the tricontinent and Latin America previously studied and their clinical implication. ##: tricontinental population, **: Latin American population.

rican, Asian, and Latin American populations, compared to the Peruvian mestizo population. In the Spanish, it is higher and in the East Asians it is not observed; in the Ecuadorian population, the metabolic phenotype is similar to that observed in the Peruvian population of the present study (Part A). Part B represents the plasma level that would occur in poor and intermediate metabolizers, whose clinical implication would be the generation of adverse reactions.

Table 4 shows the percentages of *CYP2D6*3* and *4 of the populations that originate the miscegenation of Peruvians, the same that is tricontinental (European, African, and Asian) and Latin American.

Discussion

In this study, the *CYP2D6*3* and *CYP2D6*4* alleles were characterized in samples of 234 mestizo inhabitants of the coastal zone (Lima and Tacna) and the Andean Province (Junín) of Peru. Observing 3% of the *CYP2D6*3* genotype and 9.4% of *CYP2D6*4*; with a frequency of the allele *CYP2D6*3* and *CYP2D6*4* of 0.015 and 0051, respectively. In previous Latin American studies on *CYP2D6*3* it has been reported that this genotype is rare and varies from 0.4% to 2.0%. In Europeans, it is 2% (Quiñones et al. 2017) and exclusively in the Spanish population, it is 1% (n = 105) (Menoyo et al. 2006); while, in Africans and Asians, the frequency is 0% (Quiñones et al. 2017). The X^2 for both polymorphisms indicates that the observed genotype frequencies did not differ significantly from those expected, so there is an HWE. This research shows a difference in frequencies with the Latin American populations, having a greater similarity with the Costa Ricans (Céspedes-Garro et al. 2014), Ecuadorians (Dorado et al. 2012), and Colombian populations (Isaza et al. 2000). The percentage is higher in Spanish populations (Menoyo et al. 2006), lower in Africans, and not expressed in East Asians (Quiñones et al. 2017). This is due to the natural evolution suffered by populations since more than 488 years have passed since the arrival of the first Spaniards (1532), Africans (1527), Chinese (1849), and Japanese (1899) (Vilchez 2016). Ingelman-Sundberg M (2005) explains that the difference in the distribution of *CYP2D6* alleles is due to the evolutionary peculiarities of the populations, which is evidenced by metabolic variability; also, it has been established that the frequencies of allelic variants are different in each ethnic group, but the effect of each allelic variant is identical in all populations (Zanger et al. 2004).

Regarding the extrapolated phenotypes, it is observed that 11.54% are genotypic intermediate metabolizers (gIM) with mutated heterozygous genotypes *1/*3 and *1/*4; while 0.85% are genotypic poor metabolizers (gPM) with a homozygous mutated genotype *4/*4, with an activity of 0.5–1.5 and 0, respectively (Gaedigk et al. 2008; Llerena et al. 2014); the gPMs of the present study have a greater similarity with those reported for Ecuadorians, followed by Brazilians, and in terms of continental ancestry, there is a greater similarity with Africans (Ensemble). In a study carried out by Sosa-Macías et al. (2006), it was shown that the frequency of the poor metabolizer phenotype in Mexican mestizos was 6.8%, and in Tepehuan Amerindians they were not observed.

These results are relevant in clinical practice for this group of the mestizo population, as they are susceptible to presenting side effects and even adverse reactions, since the drug not metabolized by the CYP2D6 protein, exceeds the maximum effective plasma concentration (C_{ME}), being necessary to adjust dose based on phenotype and follow pharmacotherapy.

The limitations of the present study are in the sample size and in the method of selection for convenience. Anoth-

er bias, which can lead to confusion, is not having studied the other allelic variants of *CYP2D6*, which are being considered in future studies by our research network. In our country, pharmacogenetic studies are still limited, although there is evidence in other Latin American countries that shows that they influence the safety and efficacy of drugs. Notwithstanding the foregoing, the results presented in this study are relevant, as they contribute to generating scientific evidence and encourage clinical studies in precision medicine, especially in patients who are treated with drugs with a narrow therapeutic margin such as antidepressants, analgesics. opioids, antihypertensives (metoprolol, propranolol), antiarrhythmics (propafenone and quinidine), neuroleptics, docetaxel, paclitaxel, tamoxifen, and tamsulosin (Zanger and Schwab 2013; Ray et al. 2019; Jessurun et al. 2020).

We recommend conducting more research on these and other *CYP2D6* alleles to complement the present study and promote them as biomarkers in precision medicine in underserved populations in Peru.

Conclusion

Our findings indicate that the average frequencies of the *CYP2D6*3* and *CYP2D6*4* alleles are low for the Peruvian mestizo population compared to the Latin American and tricontinental populations, due to their natural population evolution, which is manifested by their activity decreased metabolism, the same that is relevant in clinical practice, since CYP2D6 intervenes in the metabolism of a wide variety of prescription drugs.

The interpopulation variability reported in previous Latin American studies supports the need for large-scale pharmacogenetic studies in our country.

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