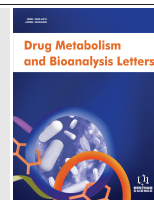**MINI-REVIEW ARTICLE**

CYP2D6 and CYP2C19 Genes Associated with Tricontinental and Latin American Ancestry of Peruvians

Angel T. Alvarado[1,2,*], María Saravia[1], Ricardo Losno[1], Ricardo Pariona[1], Ana María Muñoz[3], Roberto O. Ybañez-Julca[4], Berta Loja[1], María R. Bendezú[5], Jorge A. García[5], Felipe Surco-Laos[5], Doris Laos-Anchante[5], Haydee Chávez[5], Priscilia Aguilar[6] and Mario Pineda[7]

[1]*International Research Network in Pharmacology and Precision Medicine, Human Medicine School, San Ignacio de Loyola University, USIL, Lima, 15024, Peru;* [2]*Latin American Network for the Implementation and Validation of Clinical Pharmacogenomics Guidelines (RELIVAF-CYTED), Madrid, 28001, Spain;* [3]*Institute of Food Science and Nutrition, ICAN, San Ignacio de Loyola University, USIL, Lima, 15024, Peru;* [4]*Faculty of Pharmacy and Biochemistry, National University of Trujillo, Trujillo, 13001, Peru;* [5]*Faculty of Pharmacy and Biochemistry, San Luis Gonzaga National University of Ica, Ica, 11001, Peru;* [6]*Human Medicine, Continental University, 15304, Lima, Peru;* [7]*Pharmacy and Biochemistry, FCS, Scientific of the South University, UCSUR, Lima, 15067, Peru*

Abstract: Precision medicine seeks to individualize the dose from the beginning of pharmacological therapy based on the characteristics of each patient, genes involved in the metabolic phenotype, ethnicity or miscegenation, with the purpose to minimize adverse effects and optimize drug efficacy. The objective was to review studies that describe the association of the *CYP2D6* and *CYP2C19* genes with the tricontinental and Latin American ancestry of Peruvians. A bibliographic search was carried out in PubMed/Medline and SciELO, with various descriptors in Spanish and English.

The results of this review confirm that the ethnic origin of Peruvians is tricontinental due to European (mainly Spanish), African and Asian migration, in addition to Latin American migration, being 60.2% mixed, 25.8% Amerindian, 5.9% white, 3.6% African descent, 1.2% Chinese and Japanese descent, and 3.3% unspecified. Studies on *CYP2C19*3*, *CYP2D6*2, *3* and *6* have been reported in Peruvians, and the frequency is similar to that studied in Ecuadorians and Colombians. The *CYP2C19*3*, *CYP2D6*3*, and *CYP2D6*6* alleles found in Peruvians are common in Europeans, Africans, and Asians; while *CYP2D6*4* in Africans and *CYP2D6*2* related to Asians. In some studies, the ethnic/gene association has not been demonstrated; while others have shown a significant association, which is why further investigation is warranted. It is concluded that the studies on *CYP2D6* and *CYP2C19* genes associated with the tricontinental and Latin American ancestry of Peruvians are little, and according to what has been investigated, the *CYP2C19*3*, *CYP2D6*2, *3, *4* and *6* alleles have more related to their ancestry.

Keywords: CYP2D6, CYP2C19, pharmacogenetics, ethnicity, peruvians, alleles.

1. INTRODUCTION

Precision medicine seeks to individualize the dose from the start of pharmacological therapy based on the character-istics of each patient, ethnicity, and genotype/phenotype, with the aim of minimizing adverse effects and optimizing drug efficacy [1, 2]. The *CYP2C19* and *CYP2D6* genes are highly polymorphic and express drug-metabolizing enzymes, and have an impact on drug efficacy and safety [3, 4]. Gene CYP2D6 is located on chromosome 22q13.1, and consists of nine exons and eight introns with more than 135 alleles [4-8], including single nucleotide polymorphisms (SNPs) [9, 10].

*CYP2D6*1* (wt; rs16947), *CYP2D6*2* (G2850T; rs1135840), *CYP2D6*33* and *CYP2D6*35* [11-14] are the wild type alleles; while *CYP2D6*3, *4, *5,* and *6* express isoenzymes with no activity, and *CYP2D6*10, *17, *29,* and *41* encode enzymes with reduced activity [6, 11, 12]. The most common alleles are *CYP2D6*3* (2549A>del; rs 35742686) [6, 15, 16], *CYP2D6*4* (1846G>A, rs1065852) [12, 17-22], *CYP2D6*5* (CYP2D6del) [22, 23], *CYP2D6*6* (1707T>del; rs5030655) [12, 20], *CYP2D6*10* (rs1065852, 100C<T) [10, 21, 22], and *CYP2D6*17* (T107I, R296C, and S486T) [21]. The *CYP2D6* gene encodes monooxygenase proteins that participate in the phase I metabolism of approximately 25% of drugs in clinical use, such as antivirals, opioid analgesics (codeine, tramadol), beta-blockers, antidepressants (amitriptyline, citalopram, clomipramine, desipramine, doxepin, duloxetine,

*Address correspondence to this author at the International Research Network in Pharmacology and Precision Medicine, Human Medicine School, San Ignacio de Loyola University, USIL, Lima, P.O. Box: 15024, Peru; Tel: +51-01-3171000; E-mail: eaa.alvarado@hotmail.com

escitalopram, fluoxetine, fluvoxamine, paroxetine and nortriptyline), antipsychotics (aripiprazole, brexpiprazole, clozapine, flupenthixol, fluphenazine, olanzapine), antiarrhythmics (amiodarone, disopyramide, flecainide), antihistamines and β blockers (Atenolol, bisoprolol, carvedilol), cytostatic and statins [10, 22, 24-28]. Gene *CYP2C19* is located on chromosome 10q24; it has more than 35 allelic variants [25, 29, 30]. The most important are *CYP2C19*1* (wild type allele), *CYP2C19*2* (rs4244285, c.681G>A) [28, 31], *CYP2C19*3* (636G >A) [25, 29-32], *CYP2C19*4* (A>G at start codon), *CYP2C19*5* (1297C>T), *CYP2C19*6* (395G>A), *CYP2C19*7* (T>A at 5′ donor splice site of intron 5), *CYP2C19*8* (358T>C), *CYP2C19*16* (1324C>T) [31], and *CYP2C19*17* (rs12248560, g.-806C>T and -3042C>T) [28, 31]. The *CYP2C19* enzyme metabolizes nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants (clopidogrel), antidepressants (citalopram, escitalopram, sertraline, amitriptyline, clomipramine, doxepin, imipramine, and trimipramine), proton pump inhibitors (PPIs), and other drugs [3, 4, 25, 28, 32]. The combination of alleles of a person determines their genotype (and diplotype), and depending on the allele, a value is assigned to calculate the diplotype activity score; in turn, the diplotype provides a prediction of the metabolic phenotype and its clinical implication [28]. An individual with *CYP2D6*1/*1* diplotype is assigned an activity score of 1.0, and is classified as a normal metabolizer (NM); in them, the plasma level of the drug is within the therapeutic index, that is, above the minimum effective plasma concentration (C_{mE}) and below the minimum toxic concentration (C_{MT}). *CYP2D6*1/*9* diplotype with a score of 0.50 is classified as an intermediate metabolizer (IM), with *CYP2D6*3/*3* diplotype of score 0 being a poor metabolizer (PM); in individuals with *CYP2D6*3/*3* diplotype, plasma levels are observed that exceed the minimum toxic concentration (C_{MT}) with risk of presenting adverse effects. Gene duplication has a score of 2.0 and is considered an ultra-rapid metabolizer (UM), with the drug being rapidly metabolized so it does not exceed the minimum effective concentration, which translates into therapeutic failure (tricyclic antidepressants) or generates adverse effects (due to its rapid conversion of codeine into morphine) [1, 4, 8, 33, 34]. Previously, a bibliographic search was carried out on the CYP450 genes in the Peruvian population, and the same one was carried out in the Medline (PubMed) and SciELO databases; these investigations are scarce, so it is worth encouraging their realization. Despite the limited literature on Peru, a review of the *CYP2D6* and *CYP2C19* genes was proposed because they metabolize most of the drugs used in clinical practice (>25%) [10, 22], as both genes are highly polymorphic (135 allelic variants of *CYP2D6* and 35 allelic variants of *CYP2C19*) [4, 25, 29, 30] because they differ within and between populations [4], being the most frequent in European, African, Asian and Latin American populations that have a direct relationship with the Peruvian population [9], and being involved in the variations of the plasmatic levels of the drugs that are metabolized in the different ethnic groups and admixed populations [24]. Peruvians present genetic diversity due to their tricontinental, Latin American ethnic origin and their regional stratification (Coast, Andes and Jungle) [3, 35], which is another justification for reviewing the literature and integrating it into a single manuscript to increase scientific evidence and enabling it to be used in experimental, descriptive and observational studies on pharmacogenes (*CYP2C19/ CYP2D6*) associated with their ethnicity. The objective was to review studies that describe the association of the *CYP2D6* and *CYP2C19* genes with the tricontinental and Latin American ancestry of Peruvians, which allows explaining the variability of plasma drug levels and initiating the implementation of precision medicine in Peru.

2. *CYP2D6*, *CYP2C19* AND ETHNIC ANCESTRY OF PERUVIANS

Genetic ancestry is the information on the biological descent of an individual, including genetic relationships and historical information on the origin and experience of the remote ancestors of the individual. In the case of Peruvians, different levels of genomic ancestry have been reported in 25 regions of Peru; 83% are of American origin and 17% of European origin, and autochthonous genomic inheritance in Peru is around 80%, which corresponds to a very high prevalence of pre-Columbian genes in the current population [13]. Other studies have shown the ethnic origin of Peruvians, which is tricontinental due to European (mainly Spanish), African and Asian (Chinese and Japanese) migration, to which Latin American migration is added [7, 12, 14, 15], being 60.2% admixed (mixed Amerindian and white), 25.8% Amerindian, 5.9% white, 3.6% African descent, 1.2% Chinese and Japanese descent, and 3.3% unspecified [16]. The population of Lima is predominantly admixed (71%) with tricontinental ancestry (European, African and Asian) [2]; for this type of admixture, pharmacogenetic data from other populations are not applicable, so it is vital to have studies on Peruvians [36]. Table **1** [37-40] summarizes the ethnic origin of Peruvians according to the geographical regions admixed (Coast and Andes), Shimaa (Cusco, Andes), Aymara (Andes of Moquegua, Puno and Tacna) and Ashaninka (Jungle).

3. STUDIES ON *CYP2D6* AND *CYP2C19* IN PERUVIAN POPULATION

In this review, we have searched for various studies that associate ethnicity/gene (*CYP2C19* and *CYP2D6*) in the Peruvian population according to their ethnic origin. In this sense, 4 theses have been found to obtain the title of a pharmacist in the study carried out by Vera M.; the presence of the *CYP2D6* gene with the allelic variants *CYP2D6*1, *3, *4* and *6* was detected in 20 patients with tuberculosis from the city of Arequipa, Peru [40]. Later, Ortiz conducted a study on 20 patients diagnosed with schizophrenia in the city of Ayacucho; in the said study, he used the same technique and with the same reagent limitations as reported by Vera [41]. Valdivia described the *CYP2D6*4* allele in the mestizo population of Lima city, Huarochirí province (Lima), Calca province (Cusco) and Puno city (Puno) [42]. While Valdivia reported the genotypic frequency of *CYP2C19*2* (*1/*1: n = 70, 87.5%; *1/*2: n = 6, 7.5%, *p* = 0.42; *2/*2: n = 4, 5.0 %, *p* = 0.21) and *CYP2C19*3* (*1/*1: n = 66, 82.5%; *1/*3: n = 14, 17.5%, *p* = 0.51; *3/*3: n = 0, 0.0%) for patients with epilepsy and for admixed volunteers from the city of Arequipa [43].

In an investigation carried out by Alvarado *et al.*, the frequencies of the allelic variants *CYP2D6*3* and *CYP2D6*4*

were identified in a sample of the Peruvian admixed population stratified by region, 184 subjects from the coast (Lima, n = 134; Tacna, n = 50) and 50 subjects from the Andes (Junín, n = 50) [12]. Continental ancestry and admixture of Old World (Africa, Asia, and Europe), geographic and ethnic diversity of Native American populations contribute to variation in *CYP2D6* [3]. Table **2** describes the studies of *CYP2C19* and *CYP2D6* genes carried out in Peruvians.

4. CYP2D6, CYP2C19 AND TRICONTINENTAL ANCESTORS OF PERUVIANS

In the European population, the *CYP2C19*2* allele accounts for 93% [44] and 21% *CYP2C19*17* [30]; 17% *CYP2C19*17* in Africans [30]; in Eastern Asians (China, South Korea and Japan), the prevalence of *CYP2C19*2* is 75%, and 25% *CYP2C19*3* [44] is specific to Asian individuals and is not found outside of Asian populations [21]. The frequency of the *CYP2C19*2* allele is variable in European and Asian populations, and in Hispanics, it is lower (12.6%) [45]. The distribution of *CYP2D6* allelic variants is wide in ethnic groups throughout the world [9]; in the European Caucasian population, *CYP2D6*2*, *3 *4, *5* and *6*, and *41* predominate [8, 28, 34]; in Caucasian Spanish, *CYP2D6*1* represents 31% [46], *CYP2D6*4* around 25% [7], 2.0-2.38% for *CYP2D6*9* [32, 46]; and in Africans, *CYP2D6*17* represents 25-40%, especially in sub-Saharan African blacks [21]. In Asians, *CYP2D6*10* represents between 47-70% [3, 8, 10, 11, 21, 27, 34], 1.5% *CYP2D6*36* [32], while *CYP2D5*5* and *CYP2D6*14* are exclusive to these populations [8].

The most relevant studies related to the tricontinental ancestry of Peruvians are described below: Wang *et al.* studied *CYP2C19* polymorphism in two provinces (Uygur and Han) of China. A frequency of 5.5% was found for *CYP2C19*2/*2* and 30.4% for *CYP2C19*1/*2*. The metabolic phenotypes are NM in Han 37.7% and in Uygur 40.6%; IM in Han 45.2% and Uygur 34.0%; PM 15.4% in Han and 6.8% in Uygur [47]. Biswas describes that the allele frequencies of *CYP2C19*2, *3* and *17* are different in ethnic groups. Africans (37.2%) and Europeans (35.4%) have a higher risk of presenting subtherapeutic effects or adverse effects, which is why they suggest carrying out pharmacogenomic studies of *CYP2C19* and evaluating clinical results [48]. (Fig. **1**) describes the frequency in the percentage of the *CYP2C19* alleles of Peruvians related to tricontinental ancestry.

Menoyo *et al.* studied the CYP2D6 genotype in 105 Spanish-Caucasian volunteers. The percentage is variable for various alleles. *CYP2D6*7, *8, *12, *14, *15*, and *21* have

not been observed [46]. Bousmann *et al.* indicate that *CYP2C19*35* alleles are found among African and American ethnic groups (2-9%). They observed the presence of the *CYP2D6* alleles *3*, *4*, *5*, *6*, *10*, *17*, *41*. The *CYP2D6*29* allele is present in African descendants (6-9%). The frequency of the *CYP2D6*12* allele in Peruvians, Colombians, Mexicans, and Puerto Ricans is 2% [32]. Naranjo *et al.* observed wild-type *CYP2D6*1* and *CYP2C19*1, CYP2D6*41* and *CYP2C19*17* (less frequent) alleles in the Native American population [49]. Rodrigues-Soares *et al.* reported that the *CYP2D6*2* and *CYP2D6*5* alleles are not correlated to continental ancestry. The *CYP2D6*35* and *CYP2D6*10* alleles are correlated to European ancestry; the *CYP2D6* alleles *17*, *29* and *41* have a greater association with continental ancestry. *CYP2D6*41* in Ibero-America (0-16.2%) is pre-established in European ancestors [3]. Leitão *et al.* conducted a review of the *CYP2D6* gene in Amerindian populations from Argentina, Costa Rica, Chile, Mexico, Paraguay, Peru, and the United States. The *CYP2D6* allele *17* and *29* were found to be present in Afro-descendant populations [11].

Fig. **2** describes the frequency in the percentage of the *CYP2D6* alleles of Peruvians related to tricontinental ancestry.

Regarding the frequency of metabolizers, it has been reported that poor metabolizers (PM) for *CYP2C19* in Caucasian European populations account for 2-5% [27], 4-7% in black Africans [44], 12-23% in Asians [27], specifically 15-17% in Chinese, 18-23% in Japanese, and 12-16% in Koreans [44]. This suggests that the PM phenotype is an autosomal recessive trait that is inherited [44]. Ultra-rapid metabolizers (UM) for *CYP2C19*17* are associated with a high risk of bleeding, such as clopidogrel, due to greater exposure to the active metabolite, which inhibits platelet aggregation [30]. PM for *CYP2D6* in Europeans represents between 5-10% [21, 22, 44], 2-5% in African American population, and 0.2%-1.0% in the Asian population [7, 9, 21]. The UM percentage for *CYP2D6* (at least three functional gene copies) in Caucasians is 10%, 3% in African Americans, and 1% in Hispanics, Chinese, and Japanese [34]. Ingelman-Sundberg and Rodríguez-Antona indicate that PMs for *CYP2D6* require 30-50 mg of nortriptyline, and UMs require 500 mg of the drug to achieve the same.

Plasma concentrations. Intermediate metabolizers (IMs) are mainly located in Asia due to the high frequency of *CYP2D6*10* [33]. In Amerindian populations from Argentina, Costa Rica, Chile, Mexico, Paraguay, Peru, and the United States, normal metabolizers (NM) for CYP2D6 are the most frequent, followed by IM, PM, and UM in that order [11, 22].

Table 1. Ethnic ancestry of Peruvians by European, African, Asian, and Native American migration.

Peruvian population	European (%)	African (%)	Asian (%)	Native American (%)	References
Admixed	24.1-17.0	4.9-3.6	1.2	71.1-83.0	[3, 37, 38, 39]
Shimaa	1.8	0.8	-	97.4	
Aymara	3.2	0.6	-	96.2	
Ashaninka	2.4	0.4	-	97.2	

Note: [39] Ethno-linguistic classification of the Peruvian native population; [3] Individuals genotyped for CYP 450 and ancestry.

Table 2. Studies of genes associated with ethnic groups and their stratification by regions of Peru.

Ethnic descent	CYP2C19		CYP2D6		References
	Genotype/Nucleotide (n) %	Allele (%)	Genotype/Nucleotide (n) %	Allele (%)	-
Admixed Ayacucho city, Ayacucho	ND	-	*1/*1 A/A (17) 85.0 *1/*4 G/A/G *1/*6 A *1/*3 A/del (3) 15.0	*1 *4 *6 *3	[40][A]
Admixed Ayacucho city, Ayacucho	ND	-	*1/*1 A/A (18) 90.0 *1/*4 G/G *1/*6 A *1/*3 A/del (2) 10.0	*1 *4 *6 *3	[41][A]
Admixed Lima city	ND	-	*1/*1 G/G (83) 83.0 *1/*4 G/A (16) 16.0 *4/*4 A/A (1) 1.0	*1 91.0 *4 9.0	[42]
Admixed Huarochiri, Lima	ND	-	*1/*1 G/G (19) 95.0 *1/*4 G/A (1) 5.0 *4/*4 A/A (0) 0.0	*1 97.5 *4 2.5	-
Admixed Calca, Cusco	ND	-	*1/*1 G/G (18) 78.3 *1/*4 G/A (5) 21.7 *4/*4 A/A (0) 0.0	*1 89.1 *4 10.9	-
Admixed Puno city, Puno	ND	-	*1/*1 G/G (22) 75.9 *1/*4 G/A (6) 20.7 *4/*4 A/A (1) 3.4	*1 86.2 *4 13.8	-
Admixed Arequipa city, Arequipa	*1/*1 G/G (70) 87.5 *1/*2 G/A (9) 11.3 *2/*2 A/A (1) 1.3 *1/*1 (69) 86.3 *1/*3 (11) 13.8 *3/*3 (0) 0.00	*1 93.0 *2 7.0 *1 93.0 *3 7.0	ND	-	[43]
Admixed Lima city	ND	-	*1/*1 A/A (128) 95.5 *1/*3 A/del (6) 4.5 *3/*3 del/del (0) 0.0 *1/*1 G/G (121) 90.3 *1/*4 G/A (13) 9.7 *4/*4 A/A (0) 0.0	*1 97.8 *3 2.2 *1 95.2 *4 4.8	[12]
Admixed Tacna city, Tacna	ND	-	*1/*1 A/A (50) 100.0 *1/*3 A/del (0) 0.0 *3/*3 del/del (0) 0.0 *1/*1 G/G (45) 90.0 *1/*4 G/A (5) 10.0 *4/*4 A/A (0) 0.0	*1 100.0 *3 0.0 *1 95.0 *4 5.0	-
Admixed Huancayo city, Junin	ND	-	*1/*1 A/A (49) 98.0 *1/*3 A/del (1) 2.0 *3/*3 del/del (0) 0.0 *1/*1 G/G (44) 88.0 *1/*4 G/A (4) 8.0 *4/*4 A/A (2) 4.0	*1 99.0 *3 1.0 *1 94.0 *4 6.0	-

Note: [A]It was not discriminated if they were *CYP2D6*1, *4* or *6*; ND: Undetermined.
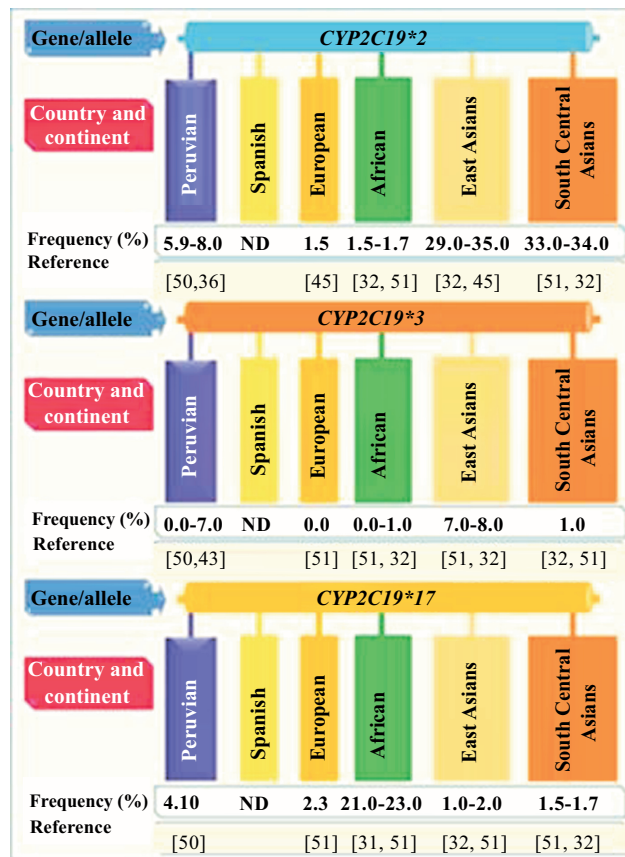
Fig. (1). *CYP2C19* allelic frequency of Peruvians and its relationship with their tricontinental ancestry. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Fig. (2). *CYP2D6* allelic frequency of Peruvians and its relationship with their tricontinental ancestry. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table **3** summarizes the genes, alleles, diplotype, phenotype, and activity score.

5. CYP2D6, CYP2C19 AND LATIN AMERICAN ASCEND-ANCE OF PERUVIANS

Allele frequencies and phenotypes of *CYP2D6* have been extensively studied in all African, European, East Asian, and South Asian populations, with very little in the East African and South Pacific regions [8]. In the Latin American population, it is evident that these studies are still scarce, specifically in Native Americans, despite the importance of pharmacogenetics to individualize pharmacological therapy. Next, a review of the studies carried out in admixed and Amerindian populations is made for the *CYP2C19* and *CYP2D6* genes. Auton *et al.* found in the Bolivian Amerindian population a lower frequency of *CYP2C19*2* compared to Caucasians, Asians, Oceanic, and Africans, which could be influenced by their being admixed [50-52]. Santos *et al.* reported the polymorphism of the *CYP2C19* gene according to the ethnic origin of 4 regions of the Brazilian population. *CYP2C19*3* and *CYP2C19*5* allelic variants were not detected. A frequency of 0.3% of allelic variants of CYP2C19*4 was found, and according to ethnicity, *CYP2C19*2* and *CYP2C19*17* were observed: Amerindian (10.4%, 15.8%); Caucasians (16.9%, 18.0%); mulattos (16.5%, 21.3%); and Afro-descendants (20.2%, 26.3%), respectively [53]. Salazar-Flores *et al.* observed in five groups of Mexican Amerindians *CYP2C19*2* (range 0-31%) and *CYP2D6*4* (range 1.2%-7.3%), and *CYP2D6*3* was detected exclusively in mestizos. *CYP2C19*4* and *5*, *CYP2D6*6*, *7* and *8* were not observed [54]. Favela-Mendoza *et al.* found *CYP2C19*2* and *CYP2C19*17* (14.29%) in the Mexican admixed population [55]. León-Moreno *et al.* observed the genetic variability of *CYP2C19* in populations from northern and southern Mexico. Frequencies were in the range of 5.9-19.3% for the *CYP2C19*2* allele for all populations studied; *CYP2C19*3* was not detected [56]. Céspedes-Garro *et al.* observed the presence of *CYP2C19*2* and *CYP2C9*17* (frequency of 2-10.3%) in mestizo and ancestral Costa Rican populations [24]. Hernandez-Suarez *et al.* reported alleles from the Puerto Rican population with a variable frequency of 14.1% for *CYP2C19*17*, 13.5% for *CYP2C19*2*, and 0.3% for *CYP2C19*4*. When stratifying by geographic region, *CYP2C19*2* has been observed with a frequency of 11.7%, 13.6%, and 15% in the central, western, and eastern regions, respectively; *CYP2C19*17* was 12.5% in the Central and West and 16% in the East [57]. Flores-Angulo *et al.* observed in the Aragüeño population of Venezuela a frequency of 4.4% of *CYP2D6*4*, 0.3% of *CYP2D6*6*, and 1% of *CYP2D6*10* [14]. Flores-Gutierrez *et al.* found in the ancestral Warao population a frequency of 0.022% of *CYP2C19*2* and 0.0% of *CYP2C19*3* [58]. De Andres *et al.* found an overlap in actual enzyme capacity between PM and NM for CYP2D6 (3.14%), and overlap of MU for CYP2C19 (11.48%) and NM for CYP2D6 (2.09%) in Nicaraguan mestizo population [59].

Table **4** describes the relationship of: CYP2C19/CYP2D6 genes of Peruvians with populations of Latin America.

6. CLINICAL IMPLICATION OF *CYP2D6* AND *CYP2C19*

Association studies between genotypes/plasma level and adverse drug effects are not conclusive; for example, Carlsson *et al.* reported that *CYP2C19*2* and *3* genotypes do not influence plasma levels of citalopram, N-desmethylcitalopram, and N,N-didesmethylcitalopram, detected at steady state. The study also concludes that *CYP2D6*3, *4, *6* and *2×2 do not influence the plasma levels of citalopram [69]. Thiem *et al.* found a correlation between *CYP2C19*1* and the N-demethylation (first nortriptyline, then N-desmethylnotriptyline) and hydroxylation (E-10-hydroxy-N-desmethylnortriptyline) of amitriptyline [70]. While, Aldrich *et al.* observed an association between the metabolic phenotypes and their clinical implication of citalopram and escitalopram [71]. Gasso *et al.* conducted a dose-escalation study of fluoxetine based on metabolic phenotype and found that it influences plasma levels [72]. Bousmann *et al.* indicate that *CYP2C19* poor metabolizers (PM) and *CYP2C19* ultra-rapid metabolizers (UR) require clinical monitoring [32]. Veldic *et al.* performed a retrospective analysis of *CYP2C19* genes in citalopram-treated patients of Caucasian (89.2%), African American (1.1%), Asian (0.7%), and other origins, indicating an association of poor metabolizers with adverse effects [73]. Findling *et al.* noted that clearance of paroxetine is related to *CYP2D6* [74]. While Cherma *et al.* found in two children (of four participants) *CYP2D6* alleles that predict poor metabolizers [75]. Maggo *et al.* carried out a case-control study in patients with depression and inhabitants of European origin (70%), Maori (11%), Asian (4%), and unspecified ethnic groups. PM was observed for *CYP2D6* (n = 15), *CYP2C19* (n = 6), and one individual as PM for *CYP2C19* [76]. Llerena *et al.* have described in Hispanics (excluding Amerindians) PM in a percentage ranging from 0-10%, and UM 0-5.3% [77]. Table **5** summarizes the main studies of genotypes, metabolic phenotype, and their clinical implications.

Fig. (**3**) shows the relationship of plasma concentration according to the metabolic phenotype of the patient.

Plasma concentration *versus* time curves of normal metabolizers (NM: *CYP2C19*1* and *CYP2D6*1*) that are within the therapeutic index; intermediate metabolizers (IM: *CYP2C19*1/*2* and *CYP2D6*1/*9*); ultrarapid metabolizers (UM: *CYP2C19*17* and *CYP2D6*1xN*); and poor metabolizers (PM: CYP2C19*2, *3 and CYP2D6*3, *4), is shown. Figure is made by the authors.

7. APPLICATION OF PHARMACOGENOMICS TO PRECISION MEDICINE IN PERU

The results of this review show that studies on *CYP2C19* and *CYP2D6* genes are scarce in Peruvian subpopulations, as pharmacogene association studies, and according to what has been found in the literature, the allelic variants *CYP2C19*3, CYP2D6*2* and *CYP2D6*3* have a similar frequency in Asians, while *CYP2D6*3* and *4* have a greater relationship with Africans. Regarding Latin American descent, there is a greater similarity between Ecuadorians and Colombians. Therefore, it is necessary to carry out studies with a larger number of samples and in the three geographical regions of Peru in order to associate gene allele frequency with the ethnic

origin of Peruvians (tricontinental and Latin American) and its influence on the response to drugs; this, at the same time, will allow to have genetic biomarkers typical of Peruvians, and shorten the distance with the other countries of Latin America, where there is more evidence of these studies. In this sense, the Latin American Network for the Implementation and Validation of Pharmacogenomic Clinical Guidelines (RELIVAF), of which Peru is a member, is promoting pharmacogenomic studies in Latin America, and especially in our country, which will allow for greater scientific evidence of the genes, Peruvian genotypes-phenotypes and their association with various drugs, to implement precision medicine in Peru.

Table 3. Alleles, phenotypes, and activity score value of *CYP2C19* and *CYP2D6* diplotypes.

Gene/ Chromosome: *CYP2C19*/10q24				References
Allele	**Diplotype**	**Phenotype**	**Activity**	
*CYP2C19*1*	*CYP2C19*1/*1*	NM	1	[24, 25, 29]
*CYP2C19*9* *CYP2C19*10* *CYP2C19*12* *CYP2C19*16* *CYP2C19*25* *CYP2C19*27*	*CYP2C19*1/*2*	IM	0.5	
*CYP2C19*2* *CYP2C19*3* *CYP2C19*4* *CYP2C19*5* *CYP2C19*6* *CYP2C19*7* *CYP2C19*8*	*CYP2C19*2/*2* *CYP2C19*2/*4* *CYP2C19*4/*4*	PM	0	
*CYP2C19*17*	*CYP2C19*1/*17* *CYP2C19*17/*17*	UM	2	
Gene/ Chromosome: *CYP2D6*/22q13.1				References
*CYP2D6*1* *CYP2D6*2* *CYP2D6*35*	*CYP2D6*1/*1* *CYP2D6*1/*2* *CYP2D6*1/*4* *CYP2D6*1/*5* *CYP2D6*1/*10* *CYP2D6*1/*35* *CYP2D6*2/*2*	NM	1	[4, 6, 11]
*CYP2D6*9* *CYP2D6*10* *CYP2D6*17* *CYP2D6*29* *CYP2D6*41*	*CYP2D6*1/*9* *CYP2D6*/*17* *CYP2D6*10/*10* *CYP2D6*6/*29* *CYP2D6*1/*41*	IM	0.5	
*CYP2D6*3* *CYP2D6*4* *CYP2D6*5* *CYP2D6*6* *CYP2D6*40*	*CYP2D6*3/*3* *CYP2D6*3/*4* *CYP2D6*4/*4* *CYP2D6*4/*5* *CYP2D6*6/*6*	PM	0	
*CYP2D6*1x2* *CYP2D6*2x2*	-	UM	2	

Table 4. *CYP2C19/CYP2D6* **genes and alleles of Peruvians compared to Latin American populations.**

Gene/Allele	Peru	Bolivia	Brazil	Colombia	Chile	Ecuador	Argentina	Venezuela	Mexico
CYP2C19 *2*	5.9 [50]	7.8 [52]	16.0 [53]	8.7 [60]	12.0 [63]	7.8 [65]	ND	0.14 [58] 0.07 [58]	8.6 [55]
3	0.0 [50]	0.1 [52]	0.0 [53]	0.0 [60]	0.0 [63]	0.4 [65]	ND	0.013 [58] 0.044 [58]	0.0 [55]
4	0.0 [50]	ND	0.3 [53]	0.0 [60]	ND	ND	ND	-	0.0 [55]
17	4.1 [50]	ND	20.4 [53]	12.8 [60]	ND	24.9 [65]	ND	-	14.3 [55]
CYP2D6 *2*	32.4 [50]	ND	ND	3.7 [60]	40.7 [64]	31.4 [66]	17.4 [67]	-	17.8 [68]
3	0.0 [50]	ND	ND	1.2 [61]	1.1 [64]	0.4 [66]	0.6 [67]	-	1.4 [68]
4	6.5 [50]	ND	ND	19.4 [61]	11.8 [64]	10.6 [66]	16.4 [68]	4.4 [14]	11.2 [68]
5	ND	ND	ND	0.8 [61]	ND	2.1 [66]	2.8 [68]	-	0.03 [68]
6	0.0 [50]	ND	ND	0.1 [62]	ND	0.0 [66]	0.4 [68]	0.3 [14]	ND
17	1.2 [50]	ND	ND	1.6 [61]	0.0 [64]	0.4 [66]	0.2 [68]	-	1.7 [68]
41	0.6 [50]	ND	ND	8.0 [62]	ND	2.5 [66]	7.7 [68]	-	2.2 [68]
*1xN or *2xN*	ND [50]	ND	ND	ND	0.3 [64]	0.8 [66]	3.4 [68]	-	5.0 [68]

Note: *CYP2C19/CYP2D6* genes of Peruvians with populations of Latin America.

Table 5. Genotypes, metabolic phenotypes and clinical implications.

| Type of Study	Genotype/Metabolic Phenotype	Clinical Implications	References
Descriptive study	*CYP2C19*2* (G>A, Gly681Ala) *CYP2C19*3* (Gly636Ala)	Oral contraceptives may influence the metabolism of citalopram. This could be due to a contraceptive interaction with CYP2C19.	[69]
Descriptive study	*PM para CYP2C19*	In PM for CYP2C19, a significantly lower amount of demethylation was evidenced.	[70]
Retrospective study	Poor metabolizer (PM) *CYP2C19*2/*2* *CYP2C19*2/*4* Ultra-rapid metabolizers (UR) *CYP2C19*1/*17* *CYP2C19*17/*17*	PM patients present side effects, with citalopram and escitalopram being the most likely cause of discontinuing treatment. UR patients have fewer adverse effects and respond to treatment with citalopram and escitalopram.	[71]
Review study including gene-drug association studies	PM: *CYP2C19*2/*2* *CYP2C19*2/*4* UR: *CYP2C19*1/*17* *CYP2C19*17/*17*	Individuals with *CYP2C19*2/*2* and *CYP2C19*2/*4* alleles require lower doses (50% of the recommended dose), and patients with *CYP2C19*1/*17* or *17/*17* alleles require an antidepressant that is not metabolized by *CYP2C19*.	[32]
Retrospective study of depressed patients (2003-2013)	PM: *CYP2C19*2/*2* *CYP2C19*2/*4*	Significance in PM was observed for *CYP2C19*. Plasma levels of citalopram/escitalopram were increased with the risk of adverse effects.	[73]
Descriptive study	RM y UR para *CYP2D6*	These genotypes do not influence the plasma levels of citalopram and its two metabolites.	[69]
Descriptive study	*CYP2D6*	*CYP2D6* influences the clearance of paroxetine.	[74]
Open design study	PM: *CYP2D6*4/*4*	It was observed that it influences the plasmatic level; subsequently, fluvoxamine doses were personalized, being three times lower (75-100 mg) to achieve levels of 58 ng/mL. As it was a very small sample, this association was not statistically significant.	[75]
Descriptive study	*CYP2D6*	The fluoxetine/(S)-norfluoxetine ratio was found to be low in UR, and higher in IM and PM.	[72]
Cases and controls study	PM para CYP2D6 PM para CYP2C19	On 7/15 PM *CYP2D6* were dose intolerants of escitalopram, citalopram, or sertraline. PM *CYP2C19* tolerated escitalopram dose but not fluoxetine (minimally metabolized by CYP2C19).	[76]
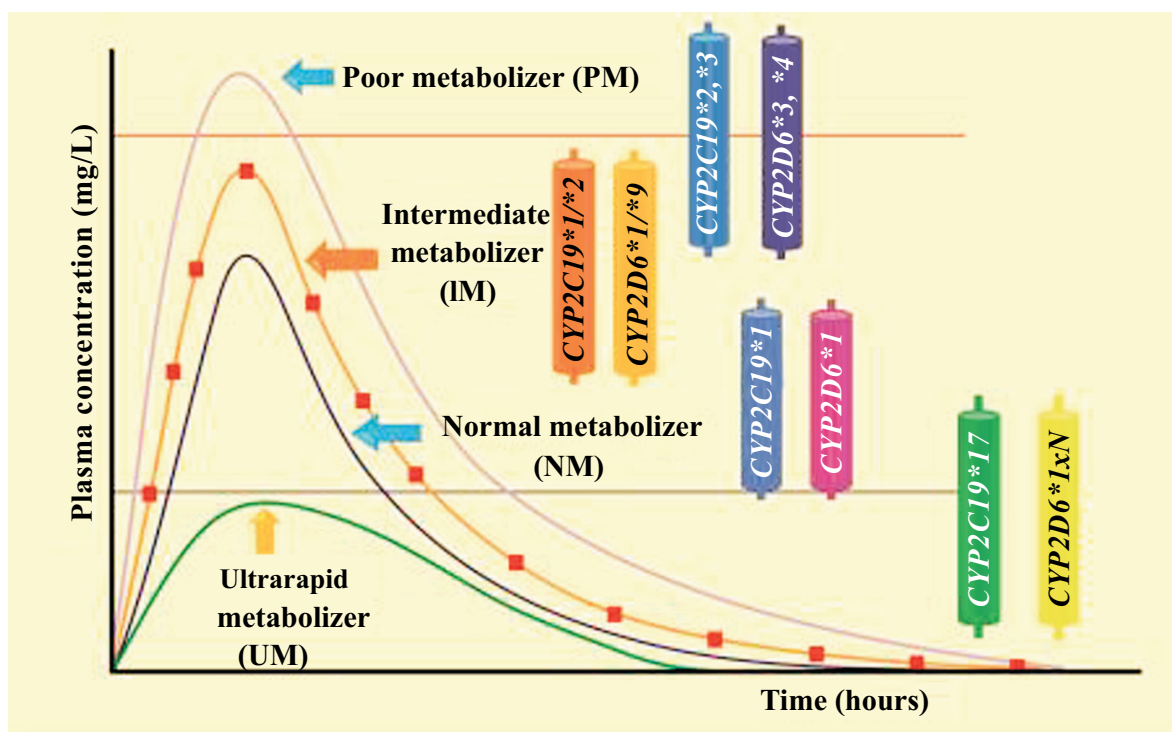
Fig. (3). Plasma drug concentration level according to the patient's metabolic phenotype and its clinical implication. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The limitations of this review are the few pharmacogenetic studies in patients and the Peruvian population in general, limited studies of the association of ethnicity/genes/drugs, and the heterogeneous design of the international studies that do not allow a significant association between ethnicity and pharmacogenes. Notwithstanding the foregoing, this study will form part of the scientific evidence for Peruvian doctors and researchers to carry out pharmacogenomic studies according to their specialty, and in the short term, it will be a routine clinical practice tool.

CONCLUSION

It is concluded that the studies on the *CYP2D6* and *CYP2C19* genes associated with the tricontinental and Latin American ancestry of Peruvians are little, and according to what has been investigated, the *CYP2C19*3, CYP2D6*2, *3, *4* and *6* alleles have a greater relationship with European, African and Asian populations. Association studies between genotypes/plasma level and adverse drug effects are not conclusive, which is why multicenter studies with a larger number of patients are warranted.

LIST OF ABBREVIATIONS

NM	=	Normal Metabolizers
NSAIDs	=	Nonsteroidal Anti-inflammatory Drugs
PM	=	Poor Metabolizers
PPIs	=	Proton Pump Inhibitors
UM	=	Ultra-rapid Metabolizer
UR	=	Ultra-rapid Metabolizers

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

REFERENCES

[1] Alvarado, A.T.; Muñoz, A.M.; Loja, B.; Miyasato, J.M.; García, J.A.; Cerro, R.A.; Quiñones, L.A.; Varela, N.M. Study of the allelic variants CYP2C9*2 and CYP2C9*3 in samples of the Peruvian mestizo population. *Biomédica,* **2019,** *39*(3), 601-610.
http://dx.doi.org/10.7705/biomedica.4636 PMID: 31584773

[2] Alvarado, A.T.; Paredes, G.; García, G.; Morales, A.; Muñoz, A.M.; Saravia, M.; Losno, R.; Bendezú, M.R.; Chávez, H.; García, J.A.; Pineda, M.; Sullón-Dextre, L. Serum monitoring of carbamazepine in patients with epilepsy and clinical implications. *Pharmacia,* **2022,** *69*(2), 401-406.
http://dx.doi.org/10.3897/pharmacia.69.e82425

[3] Rodrigues-Soares, F.; Peñas-Lledó, E.M.; Tarazona-Santos, E.; Sosa-Macías, M.; Terán, E.; López-López, M.; Rodeiro, I.; Moya, G.E.; Calzadilla, L.R.; Ramírez-Roa, R.; Grazina, M.; Estévez-Carrizo, F.E.; Barrantes, R.; LLerena, A.; Tinoco, C.A.; Álvarez, M.; Borbón, A.; Céspedes-Garro, C.; Cobaleda, J.; Andrés, F.; Delgado, R.; Dorado, P.; Fariñas, H.; Ferreiro, V.; Fricke-Galindo, I.; Galaviz-Hernández, C.; Garza-Ocañas, L.; Gilman, R.H.; Hernández, F.; Jiménez-Arce, G.;

Jung-Cook, H.; Lares-Aseff, I.; Lazalde-Ramos, B.P.; Michelin, L.; Monroy-Jaramillo, N.; Naranjo, M.E.G.; Ortega-Vázquez, A.; Ortiz-López, R.; Pérez, B.; Pérez-Páramo, Y.X.; Remirez, D.; Rojas-Martínez, A.; Sarmiento, A.P.; Scliar, M.; Terán, S.; Zamudio, R. Genomic ancestry, *CYP 2D6,CYP 2C9*, and*CYP 2C19* among latin Americans. *Clin. Pharmacol. Ther.,* **2020**, *107*(1), 257-268.
http://dx.doi.org/10.1002/cpt.1598 PMID: 31376146

[4] Kane, M. CYP2D6 Overview: Allele and phenotype frequencies. Medical Genetics Summaries. **2021**. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574601/

[5] Zanger, U.M.; Raimundo, S.; Eichelbaum, M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch. Pharmacol.,* **2004**, *369*(1), 23-37.
http://dx.doi.org/10.1007/s00210-003-0832-2 PMID: 14618296

[6] ur Rasheed, M.S.; Mishra, A.K.; Singh, M.P. Cytochrome P450 2D6 and Parkinson's Disease: Polymorphism, metabolic role, risk and protection. *Neurochem. Res.,* **2017**, *42*(12), 3353-3361.
http://dx.doi.org/10.1007/s11064-017-2384-8 PMID: 28871472

[7] Smith, E.C. Understanding CYP2D6 and its role in tamoxifen metabolism. *Oncol. Nurs. Forum,* **2013**, *40*(6), 547-548.
http://dx.doi.org/10.1188/13.ONF.547-548 PMID: 24161632

[8] Gutiérrez Rico, E.M.; Kikuchi, A.; Saito, T.; Kumondai, M.; Hishinuma, E.; Kaneko, A.; Chan, C.W.; Gitaka, J.; Nakayoshi, T.; Oda, A.; Saito, S.; Hirasawa, N.; Hiratsuka, M. CYP2D6 genotyping analysis and functional characterization of novel allelic variants in a Ni-Vanuatu and Kenyan population by assessing dextromethorphan O-demethylation activity. *Drug Metab. Pharmacokinet.,* **2020**, *35*(1), 89-101.
http://dx.doi.org/10.1016/j.dmpk.2019.07.003 PMID: 32037159

[9] Nguyen, H.H.; Ma, T.T.H.; Vu, N.P.; Bach, Q.T.N.; Vu, T.H.; Nguyen, T.D.; Nong, H.V. Single nucleotide and structural variants of CYP2D6 gene in Kinh Vietnamese population. *Medicine (Baltimore),* **2019**, *98*(22), e15891.
http://dx.doi.org/10.1097/MD.0000000000015891 PMID: 31145348

[10] Qiao, W.; Martis, S.; Mendiratta, G.; Shi, L.; Botton, M.R.; Yang, Y.; Gaedigk, A.; Vijzelaar, R.; Edelmann, L.; Kornreich, R.; Desnick, R.J.; Scott, S.A. Integrated *CYP2D6* interrogation for multiethnic copy number and tandem allele detection. *Pharmacogenomics,* **2019**, *20*(1), 9-20.
http://dx.doi.org/10.2217/pgs-2018-0135 PMID: 30730286

[11] Leitão, L.P.C.; Souza, T.P.; Rodrigues, J.C.G.; Fernandes, M.R.; Santos, S.; Santos, N.P.C. The metabolization profile of the *CYP2D6* Gene in Amerindian populations: A review. *Genes (Basel),* **2020**, *11*(3), 262.
http://dx.doi.org/10.3390/genes11030262 PMID: 32121156

[12] Alvarado, A.T.; Ybañez-Julca, R.; Muñoz, A.M.; Tejada-Bechi, C.; Cerro, R.; Quiñones, L.A.; Varela, N.; Alvarado, C.A.; Alvarado, E.; Bendezú, M.R.; García, J.A. Frequency of CYP2D6*3 and *4 and metabolizer phenotypes in three mestizo Peruvian populations. *Pharmacia,* **2021**, *68*(4), 891-898.
http://dx.doi.org/10.3897/pharmacia.68.e75165

[13] Johansson, I.; Ingelman-Sundberg, M. Genetic polymorphism and toxicology--with emphasis on cytochrome p450. *Toxicol. Sci.,* **2011**, *120*(1), 1-13.
http://dx.doi.org/10.1093/toxsci/kfq374 PMID: 21149643

[14] Flores-Angulo, C.; Villegas, C.; Mora, Y.; Martínez, J.A.; Oropeza, T.; Moreno, N. Variantes alélicas de CYP2D6: *4, *6 y *10 en una muestra de residentes del estado Aragua, Venezuela. *Rev. Peru. Med. Exp. Salud Publica,* **2015**, *32*(4), 746-751.
http://dx.doi.org/10.17843/rpmesp.2015.324.1767 PMID: 26732924

[15] Kagimoto, M.; Heim, M.; Kagimoto, K.; Zeugin, T.; Meyer, U.A. Multiple mutations of the human cytochrome P450IID6 gene (CYP2D6) in poor metabolizers of debrisoquine. Study of the functional significance of individual mutations by expression of chimeric genes. *J. Biol. Chem.,* **1990**, *265*(28), 17209-17214.
http://dx.doi.org/10.1016/S0021-9258(17)44890-3 PMID: 2211621

[16] Dorado, P.; González, I.; Naranjo, M.E.G.; de Andrés, F.; Peñas-Lledó, E.M.; Calzadilla, L.R.; LLerena, A. Lessons from Cuba for global precision medicine: *CYP2D6* genotype is not a robust predictor of CYP2D6 ultrarapid metabolism. *OMICS,* **2017**, *21*(1), 17-26.
http://dx.doi.org/10.1089/omi.2016.0166
PMID: 28271978

[17] Quiñones, L.; Roco, Á.; Cayún, J.P.; Escalante, P.; Miranda, C.; Varela, N.; Meneses, F.; Gallegos, B.; Zaruma-Torres, F.; Lares-Asseff, I. Farmacogenómica como herramienta fundamental para la medicina personalizada: Aplicaciones en la práctica clínica. *Rev. Med. Chil.,* **2017**, *145*(4), 483-500.
http://dx.doi.org/10.4067/S0034-98872017000400009
PMID: 28748996

[18] Lu, Y.; Mo, C.; Zeng, Z.; Chen, S.; Xie, Y.; Peng, Q.; He, Y.; Deng, Y.; Wang, J.; Xie, L.; Zeng, J.; Li, S.; Qin, X. El polimorfismo del alelo CYP2D6*4 aumenta el riesgo de enfermedad de Parkinson: evidencia de metanálisis. *PLoS One,* **2013**, *8*(12), e84413.
http://dx.doi.org/10.1371/journal.pone.0084413 PMID: 24376807

[19] de Andrés, F.; Sosa-Macías, M.; Ramos, B.P.L.; Naranjo, M.E.G.; LLerena, A. CYP450 Genotype/phenotype concordance in mexican amerindian indigenous populations–where to from here for global precision medicine? *OMICS,* **2017**, *21*(9), 509-519.
http://dx.doi.org/10.1089/omi.2017.0101 PMID: 28873029

[20] Saxena, R.; Shaw, G.L.; Relling, M.V.; Frame, J.N.; Moir, D.T.; Evans, W.E.; Caporaso, N.; Weiffenbach, B. Identification of a new variant CYP2D6 allele with a single base deletion in exon 3 and its association with the poor metabolizer phenotype. *Hum. Mol. Genet.,* **1994**, *3*(6), 923-926.
http://dx.doi.org/10.1093/hmg/3.6.923 PMID: 7951238

[21] Chen, P.Y.; Wang, S.C.; Poland, R.E.; Lin, K.M. Biological variations in depression and anxiety between East and West. *CNS Neurosci. Ther.,* **2009**, *15*(3), 283-294.
http://dx.doi.org/10.1111/j.1755-5949.2009.00093.x
PMID: 19691548

[22] Qi, G.; Yin, S.; Zhang, G.; Wang, X. Genetic and epigenetic polymorphisms of eNOS and CYP2D6 in mainland Chinese Tibetan, Mongolian, Uygur, and Han populations. *Pharmacogenomics J.,* **2020**, *20*(1), 114-125.
http://dx.doi.org/10.1038/s41397-019-0104-2 PMID: 31616043

[23] Gaedigk, A.; Blum, M.; Gaedigk, R.; Eichelbaum, M.; Meyer, U.A. Deletion of the entire cytochrome P450 CYP2D6 gene as a cause of impaired drug metabolism in poor metabolizers of the debrisoquine/sparteine polymorphism. *Am. J. Hum. Genet.,* **1991**, *48*(5), 943-950.
PMID: 1673290

[24] Céspedes-Garro, C.; Rodrigues-Soares, F.; Jiménez-Arce, G.; Naranjo, M.G.; Tarazona-Santos, E.; Fariñas, H.; Barrantes, R.; Llerena, A. 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.,* **2016**, *64*(3), 1067-1076.
http://dx.doi.org/10.15517/rbt.v64i3.20901 PMID: 29461783

[25] Maruf, A.A.; Greenslade, A.; Arnold, P.D.; Bousman, C. Antidepressant pharmacogenetics in children and young adults: A systematic review. *J. Affect. Disord.,* **2019**, *254*, 98-108.
http://dx.doi.org/10.1016/j.jad.2019.05.025 PMID: 31112844

[26] Taylor, C.; Crosby, I.; Yip, V.; Maguire, P.; Pirmohamed, M.; Turner, R.M. A Review of the Important Role of *CYP2D6* in Pharmacogenomics. *Genes (Basel),* **2020**, *11*(11), 1295.
http://dx.doi.org/10.3390/genes11111295 PMID: 33143137

[27] Lim, Y.J.; Cha, E.Y.; Jung, H.E.; Ghim, J.L.; Lee, S.J.; Kim, E.Y.; Shin, J.G. Genetic polymorphisms of CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 in Vietnamese-Koreans. *Transl. Clin. Pharmacol.,* **2014**, *22*(2), 70-77.
http://dx.doi.org/10.12793/tcp.2014.22.2.70

[28] Skadrić, I.; Stojković, O. Defining screening panel of functional variants of CYP1A1, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 genes in Serbian population. *Int. J. Legal Med.,* **2020**, *134*(2), 433-439.
http://dx.doi.org/10.1007/s00414-019-02234-7 PMID: 31858263

[29] Vargas, R.J.; Cobar, O. CYP450 y farmacogenética en Guatemala. Revisión narrativa. *Ciencia, Tecnología y Salud,* **2021**, *8*(2), 211-219.
http://dx.doi.org/10.36829/63CTS.v8i2.947

[30] Saeed, L.H.; Mayet, A.Y. Genotype-phenotype analysis of CYP2C19 in healthy saudi individuals and its potential clinical implication in drug therapy. *Int. J. Med. Sci.,* **2013**, *10*(11), 1497-1502.
http://dx.doi.org/10.7150/ijms.6795 PMID: 24046523

[31] Lee, S.J. Clinical application of CYP2C19 pharmacogenetics toward more personalized medicine. *Front. Genet.,* **2013**, *3*, 318.
http://dx.doi.org/10.3389/fgene.2012.00318 PMID: 23378847

[32] Bousman, C.; Maruf, A.A.; Müller, D.J. Towards the integration of pharmacogenetics in psychiatry. *Curr. Opin. Psychiatry,* **2019**, *32*(1), 7-15.

http://dx.doi.org/10.1097/YCO.0000000000000465 PMID: 30299306

[33] Ingelman-Sundberg, M.; Rodríguez-Antona, C. Pharmacogenetics of drug-metabolizing enzymes: implications for a safer and more effective drug therapy. *Philos. Trans. R. Soc. Lond. B Biol. Sci.,* **2005**, *360*(1460), 1563-1570.
http://dx.doi.org/10.1098/rstb.2005.1685 PMID: 16096104

[34] De, T.; Park, C.S.; Perera, M.A. Cardiovascular pharmacogenomics: does it matter if you're black or white? *Annu. Rev. Pharmacol. Toxicol.,* **2019**, *59*(1), 577-603.
http://dx.doi.org/10.1146/annurev-pharmtox-010818-021154 PMID: 30296897

[35] Vílchez, H. Hacia una nueva diversidad: Migraciones asiáticas en América Latina. *Tiempo y Espacio,* **2016**, *26*(65), 99-119.

[36] Marsh, S.; King, C.R.; Van Booven, D.J.; Revollo, J.Y.; Gilman, R.H.; McLeod, H.L. Pharmacogenomic assessment of Mexican and Peruvian populations. *Pharmacogenomics,* **2015**, *16*(5), 441-448.
http://dx.doi.org/10.2217/pgs.15.10 PMID: 25916516

[37] Sandoval, J.R.; Salazar-Granara, A.; Acosta, O.; Castillo-Herrera, W.; Fujita, R.; Pena, S.D.J.; Santos, F.R. Tracing the genomic ancestry of Peruvians reveals a major legacy of pre-Columbian ancestors. *J. Hum. Genet.,* **2013**, *58*(9), 627-634.
http://dx.doi.org/10.1038/jhg.2013.73 PMID: 23863748

[38] CIA World Factbook: Peru **2021**. Available from: https://www.cia.gov/the-world-factbook/countries/peru/

[39] Campbell, L. *American Indian Languages: The Historical Linguistics of Native America. Oxford Studies in Anthropological Linguistics*; Oxford University Press: New York, **1997**.

[40] Vera, M. *Molecular genetic profile of cytochrome CYP2D6 in patients with tuberculosis treated at the Regional Hospital of Ayacucho-2013*; Professional thesis San Cristobal de Huamanga National University: Ayacucho, **2014**.

[41] Ortiz, L. Metabolizing phenotypes of the CYP2D6 gene in schizophrenic patients treated with antipsychotic drugs. Ayacucho*,* professional training school of pharmacy and biochemistry: San Cristóbal de Huamanga National University, Ayacucho, **2017**.

[42] Ortiz, L. Distribution of the *4 allele of Cytochrome CYP2D6 in Peruvian subpopulations.*,* [Professional thesis]. National University of San Marcos.: Lima, **2018**.

[43] Valdivia, C. Identification of single nucleotide polymorphisms (SNP'S) of cytochrome P450, CYP2C9*2 AND CYP2C19*2 AND *3, in epileptic patients.*,* Catholic University of Santa Maria: Arequipa, **2018**.

[44] Tabari, R.G.; Marjani, A.; Ataby, O.A.; Mansourian, A.R.; Samai, N.M. Genetic polymorphism of cytochrome p450 (2C19) enzyme in Iranian Turkman Ethnic Group. *Oman Med. J.,* **2013**, *28*(4), 237-244.
http://dx.doi.org/10.5001/omj.2013.69 PMID: 23904915

[45] Mirzaev, K.; Zelenskaya, E.; Barbarash, O.; Ganyukov, V.; Apartsin, K.; Saraeva, N.; Nikolaev, K.; Ryzhikova, K.; Lifshits, G.; Sychev, D. *CYP2C19* polymorphism frequency in Russian patients in Central Russia and Siberia with acute coronary syndrome. *Pharm. Genomics Pers. Med.,* **2017**, *10*, 107-114.
http://dx.doi.org/10.2147/PGPM.S126305 PMID: 28442925

[46] Menoyo, A.; del Rio, E.; Baiget, M. Characterization of variant alleles of cytochrome CYP2D6 in a Spanish population. *Cell Biochem. Funct.,* **2006**, *24*(5), 381-385.
http://dx.doi.org/10.1002/cbf.1258 PMID: 16130179

[47] Wang, T.; Zhao, T.; Bao, S.; Jia, L.; Feng, J.; Yu, A.; Sun, L.; Guo, X.; Li, H.; Yu, L. CYP2C19, PON1, and ABCB1 gene polymorphisms in Han and Uygur populations with coronary artery disease in Northwestern Xinjiang, China, From 2014 Through 2019. *Medicine (Baltimore),* **2020**, *99*(29), e20582.
http://dx.doi.org/10.1097/MD.0000000000020582 PMID: 32702814

[48] Biswas, M. Global distribution of CYP2C19 risk phenotypes affecting safety and effectiveness of medications. *Pharmacogenom. J.,* **2021**, *21*(2), 190-199.
http://dx.doi.org/10.1038/s41397-020-00196-3
PMID: 33082528

[49] Naranjo, M.G.; Rodrigues-Soares, F.; Peñas-Lledó, E.M.; Tarazona-Santos, E.; Fariñas, H.; Rodeiro, I.; Terán, E.; Grazina, M.; Moya, G.E.; López-López, M.; Sarmiento, A.P.; Calzadilla, L.R.; Ramírez-Roa, R.; Ortiz-López, R.; Estévez-Carrizo, F.E.; Sosa-Macías, M.; Barrantes, R.; LLerena, A. 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,* **2018**, *22*(9), 575-588.
http://dx.doi.org/10.1089/omi.2018.0114 PMID: 30183544

[50] Auton, A.; Abecasis, G.R.; Altshuler, D.M.; Durbin, R.M.; Abecasis, G.R.; Bentley, D.R.; Chakravarti, A.; Clark, A.G.; Donnelly, P.; Eichler, E.E.; Flicek, P.; Gabriel, S.B.; Gibbs, R.A.; Green, E.D.; Hurles, M.E.; Knoppers, B.M.; Korbel, J.O.; Lander, E.S.; Lee, C.; Lehrach, H.; Mardis, E.R.; Marth, G.T.; McVean, G.A.; Nickerson, D.A.; Schmidt, J.P.; Sherry, S.T.; Wang, J.; Wilson, R.K.; Gibbs, R.A.; Boerwinkle, E.; Doddapaneni, H.; Han, Y.; Korchina, V.; Kovar, C.; Lee, S.; Muzny, D.; Reid, J.G.; Zhu, Y.; Wang, J.; Chang, Y.; Feng, Q.; Fang, X.; Guo, X.; Jian, M.; Jiang, H.; Jin, X.; Lan, T.; Li, G.; Li, J.; Li, Y.; Liu, S.; Liu, X.; Lu, Y.; Ma, X.; Tang, M.; Wang, B.; Wang, G.; Wu, H.; Wu, R.; Xu, X.; Yin, Y.; Zhang, D.; Zhang, W.; Zhao, J.; Zhao, M.; Zheng, X.; Lander, E.S.; Altshuler, D.M.; Gabriel, S.B.; Gupta, N.; Gharani, N.; Toji, L.H.; Gerry, N.P.; Resch, A.M.; Flicek, P.; Barker, J.; Clarke, L.; Gil, L.; Hunt, S.E.; Kelman, G.; Kulesha, E.; Leinonen, R.; McLaren, W.M.; Radhakrishnan, R.; Roa, A.; Smirnov, D.; Smith, R.E.; Streeter, I.; Thormann, A.; Toneva, I.; Vaughan, B.; Zheng-Bradley, X.; Bentley, D.R.; Grocock, R.; Humphray, S.; James, T.; Kingsbury, Z.; Lehrach, H.; Sudbrak, R.; Albrecht, M.W.; Amstislavskiy, V.S.; Borodina, T.A.; Lienhard, M.; Mertes, F.; Sultan, M.; Timmermann, B.; Yaspo, M-L.; Mardis, E.R.; Wilson, R.K.; Fulton, L.; Fulton, R.; Sherry, S.T.; Ananiev, V.; Belaia, Z.; Beloslyudtsev, D.; Bouk, N.; Chen, C.; Church, D.; Cohen, R.; Cook, C.; Garner, J.; Hefferon, T.; Kimelman, M.; Liu, C.; Lopez, J.; Meric, P.; O'Sullivan, C.; Ostapchuk, Y.; Phan, L.; Ponomarov, S.; Schneider, V.; Shekhtman, E.; Sirotkin, K.; Slotta, D.; Zhang, H.; McVean, G.A.; Durbin, R.M.; Balasubramaniam, S.; Burton, J.; Danecek, P.; Keane, T.M.; Kolb-Kokocinski, A.; McCarthy, S.; Stalker, J.; Quail, M.; Schmidt, J.P.; Davies, C.J.; Gollub, J.; Webster, T.; Wong, B.; Zhan, Y.; Auton, A.; Campbell, C.L.; Kong, Y.; Marcketta, A.; Gibbs, R.A.; Yu, F.; Antunes, L.; Bainbridge, M.; Muzny, D.; Sabo, A.; Huang, Z.; Wang, J.; Coin, L.J.M.; Fang, L.; Guo, X.; Jin, X.; Li, G.; Li, Q.; Li, Y.; Li, Z.; Lin, H.; Liu, B.; Luo, R.; Shao, H.; Xie, Y.; Ye, C.; Yu, C.; Zhang, F.; Zheng, H.; Zhu, H.; Alkan, C.; Dal, E.; Kahveci, F.; Marth, G.T.; Garrison, E.P.; Kural, D.; Lee, W-P.; Fung Leong, W.; Stromberg, M.; Ward, A.N.; Wu, J.; Zhang, M.; Daly, M.J.; DePristo, M.A.; Handsaker, R.E.; Altshuler, D.M.; Banks, E.; Bhatia, G.; del Angel, G.; Gabriel, S.B.; Genovese, G.; Gupta, N.; Li, H.; Kashin, S.; Lander, E.S.; McCarroll, S.A.; Nemesh, J.C.; Poplin, R.E.; Yoon, S.C.; Lihm, J.; Makarov, V.; Clark, A.G.; Gottipati, S.; Keinan, A.; Rodriguez-Flores, J.L.; Korbel, J.O.; Rausch, T.; Fritz, M.H.; Stütz, A.M.; Flicek, P.; Beal, K.; Clarke, L.; Datta, A.; Herrero, J.; McLaren, W.M.; Ritchie, G.R.S.; Smith, R.E.; Zerbino, D.; Zheng-Bradley, X.; Sabeti, P.C.; Shlyakhter, I.; Schaffner, S.F.; Vitti, J.; Cooper, D.N.; Ball, E.V.; Stenson, P.D.; Bentley, D.R.; Barnes, B.; Bauer, M.; Keira Cheetham, R.; Cox, A.; Eberle, M.; Humphray, S.; Kahn, S.; Murray, L.; Peden, J.; Shaw, R.; Kenny, E.E.; Batzer, M.A.; Konkel, M.K.; Walker, J.A.; MacArthur, D.G.; Lek, M.; Sudbrak, R.; Amstislavskiy, V.S.; Herwig, R.; Mardis, E.R.; Ding, L.; Koboldt, D.C.; Larson, D.; Ye, K.; Gravel, S.; Swaroop, A.; Chew, E.; Lappalainen, T.; Erlich, Y.; Gymrek, M.; Frederick Willems, T.; Simpson, J.T.; Shriver, M.D.; Rosenfeld, J.A.; Bustamante, C.D.; Montgomery, S.B.; De La Vega, F.M.; Byrnes, J.K.; Carroll, A.W.; DeGorter, M.K.; Lacroute, P.; Maples, B.K.; Martin, A.R.; Moreno-Estrada, A.; Shringarpure, S.S.; Zakharia, F.; Halperin, E.; Baran, Y.; Lee, C.; Cerveira, E.; Hwang, J.; Malhotra, A.; Plewczynski, D.; Radew, K.; Romanovitch, M.; Zhang, C.; Hyland, F.C.L.; Craig, D.W.; Christoforides, A.; Homer, N.; Izatt, T.; Kurdoglu, A.A.; Sinari, S.A.; Squire, K.; Sherry, S.T.; Xiao, C.; Sebat, J.; Antaki, D.; Gujral, M.; Noor, A.; Ye, K.; Burchard, E.G.; Hernandez, R.D.; Gignoux, C.R.; Haussler, D.; Katzman, S.J.; James Kent, W.; Howie, B.; Ruiz-Linares, A.; Dermitzakis, E.T.; Devine, S.E.; Abecasis, G.R.; Min Kang, H.; Kidd, J.M.; Blackwell, T.; Caron, S.; Chen, W.; Emery, S.; Fritsche, L.; Fuchsberger, C.; Jun, G.; Li, B.; Lyons, R.; Scheller, C.; Sidore, C.; Song, S.; Sliwerska, E.; Taliun, D.; Tan, A.; Welch, R.; Kate Wing, M.; Zhan, X.; Awadalla, P.; Hodgkinson, A.; Li, Y.; Shi, X.; Quitadamo, A.; Lunter, G.; McVean, G.A.; Marchini, J.L.; Myers, S.; Churchhouse, C.; Delaneau, O.; Gupta-Hinch, A.; Kretzschmar, W.; Iqbal, Z.; Mathieson, I.; Menelaou, A.; Rimmer, X.; Xifara, D.K.; Oleksyk, T.K.; Fu, Y.; Liu, X.; Xiong, M.; Jorde, L.; Witherspoon, D.; Xing, J.; Eichler, E.E.; Browning, B.L.; Browning, S.R.; Hormozdiari, F.; Sudmant, P.H.; Khurana, E.; Durbin, R.M.; Hurles, M.E.; Tyler-Smith, C.; Albers,

C.A.; Ayub, Q.; Balasubramaniam, S.; Chen, Y.; Colonna, V.; Danecek, P.; Jostins, L.; Keane, T.M.; McCarthy, S.; Walter, K.; Xue, Y.; Gerstein, M.B.; Abyzov, A.; Balasubramanian, S.; Chen, J.; Clarke, D.; Fu, Y.; Harmanci, A.O.; Jin, M.; Lee, D.; Liu, J.; Jasmine Mu, X.; Zhang, J.; Zhang, Y.; Li, Y.; Luo, R.; Zhu, H.; Alkan, C.; Dal, E.; Kahveci, F.; Marth, G.T.; Garrison, E.P.; Kural, D.; Lee, W-P.; Ward, A.N.; Wu, J.; Zhang, M.; McCarroll, S.A.; Handsaker, R.E.; Altshuler, D.M.; Banks, E.; del Angel, G.; Genovese, G.; Hartl, C.; Li, H.; Kashin, S.; Nemesh, J.C.; Shakir, K.; Yoon, S.C.; Lihm, J.; Makarov, V.; Degenhardt, J.; Korbel, J.O.; Fritz, M.H.; Meiers, S.; Raeder, B.; Rausch, T.; Stütz, A.M.; Flicek, P.; Paolo Casale, F.; Clarke, L.; Smith, R.E.; Stegle, O.; Zheng-Bradley, X.; Bentley, D.R.; Barnes, B.; Keira Cheetham, R.; Eberle, M.; Humphray, S.; Kahn, S.; Murray, L.; Shaw, R.; Lameijer, E-W.; Batzer, M.A.; Konkel, M.K.; Walker, J.A.; Ding, L.; Hall, I.; Ye, K.; Lacroute, P.; Lee, C.; Cerveira, E.; Malhotra, A.; Hwang, J.; Plewczynski, D.; Radew, K.; Romanovitch, M.; Zhang, C.; Craig, D.W.; Homer, N.; Church, D.; Xiao, C.; Sebat, J.; Antaki, D.; Bafna, V.; Michaelson, J.; Ye, K.; Devine, S.E.; Gardner, E.J.; Abecasis, G.R.; Kidd, J.M.; Mills, R.E.; Dayama, G.; Emery, S.; Jun, G.; Shi, X.; Quitadamo, A.; Lunter, G.; McVean, G.A.; Chen, K.; Fan, X.; Chong, Z.; Chen, T.; Witherspoon, D.; Xing, J.; Eichler, E.E.; Chaisson, M.J.; Hormozdiari, F.; Huddleston, J.; Malig, M.; Nelson, B.J.; Sudmant, P.H.; Parrish, N.F.; Khurana, E.; Hurles, M.E.; Blackburne, B.; Lindsay, S.J.; Ning, Z.; Walter, K.; Zhang, Y.; Gerstein, M.B.; Abyzov, A.; Chen, J.; Clarke, D.; Lam, H.; Jasmine Mu, X.; Sisu, C.; Zhang, J.; Zhang, Y.; Gibbs, R.A.; Yu, F.; Bainbridge, M.; Challis, D.; Evani, U.S.; Kovar, C.; Lu, J.; Muzny, D.; Nagaswamy, U.; Reid, J.G.; Sabo, A.; Yu, J.; Guo, X.; Li, W.; Li, Y.; Wu, R.; Marth, G.T.; Garrison, E.P.; Fung Leong, W.; Ward, A.N.; del Angel, G.; DePristo, M.A.; Gabriel, S.B.; Gupta, N.; Hartl, C.; Poplin, R.E.; Clark, A.G.; Rodriguez-Flores, J.L.; Flicek, P.; Clarke, L.; Smith, R.E.; Zheng-Bradley, X.; MacArthur, D.G.; Mardis, E.R.; Fulton, R.; Koboldt, D.C.; Gravel, S.; Bustamante, C.D.; Craig, D.W.; Christoforides, A.; Homer, N.; Izatt, T.; Sherry, S.T.; Xiao, C.; Dermitzakis, E.T.; Abecasis, G.R.; Min Kang, H.; McVean, G.A.; Gerstein, M.B.; Balasubramanian, S.; Habegger, L.; Yu, H.; Flicek, P.; Clarke, L.; Cunningham, F.; Dunham, I.; Zerbino, D.; Zheng-Bradley, X.; Lage, K.; Berg Jespersen, J.; Horn, H.; Montgomery, S.B.; DeGorter, M.K.; Khurana, E.; Tyler-Smith, C.; Chen, Y.; Colonna, V.; Xue, Y.; Gerstein, M.B.; Balasubramanian, S.; Fu, Y.; Kim, D.; Auton, A.; Marcketta, A.; Desalle, R.; Narechania, A.; Wilson Sayres, M.A.; Garrison, E.P.; Handsaker, R.E.; Kashin, S.; McCarroll, S.A.; Rodriguez-Flores, J.L.; Flicek, P.; Clarke, L.; Zheng-Bradley, X.; Erlich, Y.; Gymrek, M.; Frederick Willems, T.; Bustamante, C.D.; Mendez, F.L.; David, P., G.; Underhill, P.A.; Lee, C.; Cerveira, E.; Malhotra, A.; Romanovitch, M.; Zhang, C.; Abecasis, G.R.; Coin, L.; Shao, H.; Mittelman, D.; Tyler-Smith, C.; Ayub, Q.; Banerjee, R.; Cerezo, M.; Chen, Y.; Fitzgerald, T.W.; Louzada, S.; Massaia, A.; McCarthy, S.; Ritchie, G.R.; Xue, Y.; Yang, F.; Gibbs, R.A.; Kovar, C.; Kalra, D.; Hale, W.; Muzny, D.; Reid, J.G.; Wang, J.; Dan, X.; Guo, X.; Li, G.; Li, Y.; Ye, C.; Zheng, X.; Altshuler, D.M.; Flicek, P.; Clarke, L.; Zheng-Bradley, X.; Bentley, D.R.; Cox, A.; Humphray, S.; Kahn, S.; Sudbrak, R.; Albrecht, M.W.; Lienhard, M.; Larson, D.; Craig, D.W.; Izatt, T.; Kurdoglu, A.A.; Sherry, S.T.; Xiao, C.; Haussler, D.; Abecasis, G.R.; McVean, G.A.; Durbin, R.M.; Balasubramaniam, S.; Keane, T.M.; McCarthy, S.; Stalker, J.; Chakravarti, A.; Knoppers, B.M.; Abecasis, G.R.; Barnes, K.C.; Beiswanger, C.; Burchard, E.G.; Bustamante, C.D.; Cai, H.; Cao, H.; Durbin, R.M.; Gerry, N.P.; Gharani, N.; Gibbs, R.A.; Gignoux, C.R.; Gravel, S.; Henn, B.; Jones, D.; Jorde, L.; Kaye, J.S.; Keinan, A.; Kent, A.; Kerasidou, A.; Li, Y.; Mathias, R.; McVean, G.A.; Moreno-Estrada, A.; Ossorio, P.N.; Parker, M.; Resch, A.M.; Rotimi, C.N.; Royal, C.D.; Sandoval, K.; Su, Y.; Sudbrak, R.; Tian, Z.; Tishkoff, S.; Toji, L.H.; Tyler-Smith, C.; Via, M.; Wang, Y.; Yang, H.; Yang, L.; Zhu, J.; Bodmer, W.; Bedoya, G.; Ruiz-Linares, A.; Cai, Z.; Gao, Y.; Chu, J.; Peltonen, L.; Garcia-Montero, A.; Orfao, A.; Dutil, J.; Martinez-Cruzado, J.C.; Oleksyk, T.K.; Barnes, K.C.; Mathias, R.A.; Hennis, A.; Watson, H.; McKenzie, C.; Qadri, F.; LaRocque, R.; Sabeti, P.C.; Zhu, J.; Deng, X.; Sabeti, P.C.; Asogun, D.; Folarin, O.; Happi, C.; Omoniwa, O.; Stremlau, M.; Tariyal, R.; Jallow, M.; Sisay Joof, F.; Corrah, T.; Rockett, K.; Kwiatkowski, D.; Kooner, J.; Tịnh Hiê'n, T.; Dunstan, S.J.; Thuy Hang, N.; Fonnie, R.; Garry, R.; Kanneh, L.; Moses, L.; Sabeti, P.C.; Schieffelin, J.; Grant, D.S.; Gallo, C.; Poletti, G.; Saleheen, D.; Rasheed, A.; Brooks, L.D.; Felsenfeld,

A.L.; McEwen, J.E.; Vaydylevich, Y.; Green, E.D.; Duncanson, A.; Dunn, M.; Schloss, J.A.; Wang, J.; Yang, H.; Auton, A.; Brooks, L.D.; Durbin, R.M.; Garrison, E.P.; Min Kang, H.; Korbel, J.O.; Marchini, J.L.; McCarthy, S.; McVean, G.A.; Abecasis, G.R. A global reference for human genetic variation. *Nature,* **2015**, *526*(7571), 68-74.
http://dx.doi.org/10.1038/nature15393

[51]   Koopmans, A. *CYP2D6 and CYP2C19 genotyping in psychiatry: bridging the gap between practice and lab*; ProefschriftMaken: Maastricht, **2021**.
http://dx.doi.org/10.26481/dis.20210512ak

[52]   Bravo-Villalta, H.V.; Yamamoto, K.; Nakamura, K.; Bayá, A.; Okada, Y.; Horiuchi, R. Genetic polymorphism of CYP2C9 and CYP2C19 in a Bolivian population: an investigative and comparative study. *Eur. J. Clin. Pharmacol.,* **2005**, *61*(3), 179-184.
http://dx.doi.org/10.1007/s00228-004-0890-5 PMID: 15776277

[53]   Santos, P.C.J.L.; Soares, R.A.G.; Santos, D.B.G.; Nascimento, R.M.; Coelho, G.L.L.M.; Nicolau, J.C.; Mill, J.G.; Krieger, J.E.; Pereira, A.C. CYP2C19 and ABCB1gene polymorphisms are differently distributed according to ethnicity in the Brazilian general population. *BMC Med. Genet.,* **2011**, *12*(1), 13.
http://dx.doi.org/10.1186/1471-2350-12-13 PMID: 21247447

[54]   Salazar-Flores, J.; Torres-Reyes, L.A.; Martínez-Cortés, G.; Rubi-Castellanos, R.; Sosa-Macías, M.; Muñoz-Valle, J.F.; González-González, C.; Ramírez, A.; Román, R.; Méndez, J.L.; Barrera, A.; Torres, A.; Medina, R.; Rangel-Villalobos, H. Distribution of CYP2D6 and CYP2C19 polymorphisms associated with poor metabolizer phenotype in five Amerindian groups and western Mestizos from Mexico. *Genet. Test. Mol. Biomarkers,* **2012**, *16*(9), 1098-1104.
http://dx.doi.org/10.1089/gtmb.2012.0055 PMID: 22913530

[55]   Favela-Mendoza, A.F.; Martinez-Cortes, G.; Hernandez-Zaragoza, M.; Salazar-Flores, J.; Muñoz-Valle, J.F.; Martinez-Sevilla, V.M.; Velazquez-Suarez, N.Y.; Rangel-Villalobos, H. 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.,* **2015**, *94*(1), 3-7.
http://dx.doi.org/10.1007/s12041-015-0477-1 PMID: 25846871

[56]   León-Moreno, L.C.; Saldaña-Cruz, A.M.; Sánchez-Corona, J.; Mendoza-Carrera, F.; García-Zapién, A.G.; Revilla-Monsalve, C.; Islas-Andrade, S.; Brito-Zurita, O.; Pérez-Vargas, A.; Flores-Martínez, S.E. Distribution of potential risk alleles and haplotypes of the CYP2C9 and CYP2C19 genes in Mexican native populations: A comparative study among Amerindian populations. *Meta Gene,* **2019**, *20*, 100565.
http://dx.doi.org/10.1016/j.mgene.2019.100565

[57]   Hernandez-Suarez, D.; Tomassini-Fernandini, J.; Cuevas, A.; Rosario-Berrios, A.; Nuñez-Medina, H.; Padilla-Arroyo, D.; Rivera, N.; Liriano, J.; Vega-Roman, R.; Renta, J.; Melin, K.; Duconge, J. Clinical relevant polymorphisms affecting clopidogrel pharmacokinetics and pharmacodynamics: Insights from the Puerto Rico newborn screening program. *Int. J. Environ. Res. Public Health,* **2018**, *15*(6), 1115.
http://dx.doi.org/10.3390/ijerph15061115 PMID: 29848980

[58]   Flores-Gutiérrez, S.; Rodríguez-Larralde, Á.; Vívenes de Lugo, M.; Castro de Guerra, D. Distribution of polymorphisms in the *CYP2C9* gene and *CYP2C19/CYP2C9* haplotypes among Venezuelan populations. *Ann. Hum. Biol.,* **2017**, *44*(2), 191-198.
http://dx.doi.org/10.1080/03014460.2016.1192218 PMID: 27230833

[59]   de Andrés, F.; Altamirano-Tinoco, C.; Ramírez-Roa, R.; Montes-Mondragón, C.F.; Dorado, P.; Peñas-Lledó, E.M.; LLerena, A. Relationships between CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 metabolic phenotypes and genotypes in a Nicaraguan Mestizo population. *Pharmacogenomics J.,* **2021**, *21*(2), 140-151.
http://dx.doi.org/10.1038/s41397-020-00190-9
PMID: 33024249

[60]   Isaza, C.; Henao, J.; Martínez, J.H.I.; Arias, J.C.S.; Beltrán, L. Phenotype-genotype analysis of CYP2C19 in Colombian mestizo individuals. *BMC Clin. Pharmacol.,* **2007**, *7*(1), 6.
http://dx.doi.org/10.1186/1472-6904-7-6
PMID: 17623107

[61]   Isaza, C.A.; Henao, J.; López, A.M.; Cacabelos, R. Isolation, sequence and genotyping of the drug metabolizer CYP2D6 gene in the Colombian population. *Methods Find. Exp. Clin. Pharmacol.,* **2000**, *22*(9), 695-705.
http://dx.doi.org/10.1358/mf.2000.22.9.802286
PMID: 11294012

[62] Botton, M.R.; Campos, K.C.; Duconge, J.; Scott, S.A. Pharmacogenomics in Latin American populations. *Pharmacogenomics,* **2019,** 329-368. http://dx.doi.org/10.1016/B978-0-12-812626-4.00012-7

[63] Roco, Á.; Quiñones, L.; Agúndez, J.A.G.; García-Martín, E.; Squicciarini, V.; Miranda, C.; Garay, J.; Farfán, N.; Saavedra, I.; Cáceres, D.; Ibarra, C.; Varela, N. Frequencies of 23 functionally significant variant alleles related with metabolism of antineoplastic drugs in the chilean population: Comparison with Caucasian and Asian populations. *Front. Genet.,* **2012,** *3,* 229. http://dx.doi.org/10.3389/fgene.2012.00229 PMID: 23130019

[64] Varela, N.; Quiñones, L.A.; Stojanova, J.; Garay, J.; Cáceres, D.; Cespedes, S.; Sasso, J.; Miranda, C. Characterization of the CYP2D6 drug metabolizing phenotypes of the Chilean mestizo population through polymorphism analyses. *Pharmacol. Res.,* **2015,** *101,* 124-129. http://dx.doi.org/10.1016/j.phrs.2015.07.020 PMID: 26211952

[65] Vicente, J.; González-Andrade, F.; Soriano, A.; Fanlo, A.; Martínez-Jarreta, B.; Sinués, B. genetic polymorphisms of CYP2C8, CYP2C9 and CYP2C19 in ecuadorian mestizo and spaniard populations: A comparative study. *Mol. Biol. Rep.,* **2014,** *41*(3), 1267-1272. http://dx.doi.org/10.1007/s11033-013-2971-y PMID: 24430292

[66] Machín, E. metabolic phenotypes of dextromethorphan and losartan, CYP2D6 and CYP2C9 genotypes in the ecuadorian population compared to the spanish.*,* [Doctoral thesis]. University of Extremadura: Badajoz, **2012**.

[67] Moya, G.; Dorado, P.; Ferreiro, V.; Naranjo, M.E.G.; Peñas-Lledó, E.M.; LLerena, A. High frequency of CYP2D6 ultrarapid metabolizer genotypes in an Ashkenazi Jewish population from Argentina. *Pharmacogenomics J.,* **2017,** *17*(4), 378-381. http://dx.doi.org/10.1038/tpj.2016.27 PMID: 27068265

[68] López, M.; Guerrero, J.; Jung-Cook, H.; Alonso, M.E. CYP2D6 genotype and phenotype determination in a Mexican Mestizo population. *Eur. J. Clin. Pharmacol.,* **2005,** *61*(10), 749-754. http://dx.doi.org/10.1007/s00228-005-0038-2 PMID: 16249913

[69] Carlsson, B.; Olsson, G.; Reis, M.; Wålinder, J.; Nordin, C.; Lundmark, J.; Scordo, M.G.; Dahl, M.L.; Bengtsson, F.; Ahlner, J. Enantioselective analysis of citalopram and metabolites in adolescents. *Ther. Drug Monit.,* **2001,** *23*(6), 658-664. http://dx.doi.org/10.1097/00007691-200112000-00011 PMID: 11802100

[70] Thieme, D.; Rolf, B.; Sachs, H.; Schmid, D. Correlation of inter-individual variations of amitriptyline metabolism examined in hairs with CYP2C19 and CYP2D6 polymorphisms. *Int. J. Legal Med.,* **2008,** *122*(2), 149-155. http://dx.doi.org/10.1007/s00414-007-0184-4 PMID: 17992535

[71] Aldrich, S.L.; Poweleit, E.A.; Prows, C.A.; Martin, L.J.; Strawn, J.R.; Ramsey, L.B. Influence of CYP2C19 metabolizer status on escitalopram/citalopram tolerability and response in youth with anxiety and depressive disorders. *Front. Pharmacol.,* **2019,** *10,* 99. http://dx.doi.org/10.3389/fphar.2019.00099 PMID: 30837874

[72] Gassó, P.; Rodríguez, N.; Mas, S.; Pagerols, M.; Blázquez, A.; Plana, M.T.; Torra, M.; Lázaro, L.; Lafuente, A. Effect of CYP2D6, CYP2C9 and ABCB1 genotypes on fluoxetine plasma concentrations and clinical improvement in children and adolescent patients. *Pharmacogenomics J.,* **2014,** *14*(5), 457-462. http://dx.doi.org/10.1038/tpj.2014.12 PMID: 24663076

[73] Veldic, M.; Ahmed, A.T.; Blacker, C.J.; Geske, J.R.; Biernacka, J.M.; Borreggine, K.L.; Moore, K.M.; Prieto, M.L.; Vande Voort, J.L.; Croarkin, P.E.; Hoberg, A.A.; Kung, S.; Alarcon, R.D.; Keeth, N.; Singh, B.; Bobo, W.V.; Frye, M.A. Cytochrome P450 2C19 poor metabolizer phenotype in treatment resistant depression: Treatment and diagnostic implications. *Front. Pharmacol.,* **2019,** *10,* 83. http://dx.doi.org/10.3389/fphar.2019.00083 PMID: 30837869

[74] Findling, R.L.; Nucci, G.; Piergies, A.A.; Gomeni, R.; Bartolic, E.I.; Fong, R.; Carpenter, D.J.; Leeder, J.S.; Gaedigk, A.; Danoff, T.M. Multiple dose pharmacokinetics of paroxetine in children and adolescents with major depressive disorder or obsessive-compulsive disorder. *Neuropsychopharmacology,* **2006,** *31*(6), 1274-1285. http://dx.doi.org/10.1038/sj.npp.1300960 PMID: 16319918

[75] Chermá, M.D.; Ahlner, J.; Bengtsson, F.; Gustafsson, P.A. Antidepressant drugs in children and adolescents: analytical and demographic data in a naturalistic, clinical study. *J. Clin. Psychopharmacol.,* **2011,** *31*(1), 98-102. http://dx.doi.org/10.1097/JCP.0b013e318205e66d PMID: 21192151

[76] Maggo, S.; Kennedy, M.A.; Barczyk, Z.A.; Miller, A.L.; Rucklidge, J.J.; Mulder, R.T.; Foulds, J.A. Common CYP2D6, CYP2C9, and CYP2C19 gene variants, health anxiety, and neuroticism are not associated with self-reported antidepressant side effects. *Front. Genet.,* **2019,** *10,* 1199. http://dx.doi.org/10.3389/fgene.2019.01199 PMID: 31850065

[77] LLerena, A.; Dorado, P.; Naranjo, M.E.G.; Peñas-Lledó, E. *CYP2D6 ethnic variability in Hispanics. CYP2D6: Genetics*; Pharmacology and Clinical Relevance, **2014,** pp. 54-66. http://dx.doi.org/10.2217/fmeb2013.13.139