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Genetic polymorphisms of *CYP2C8, CYP2C9* and *CYP2C19* in Ecuadorian Mestizo and Spaniard populations: a comparative study

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Abstract This study was designed to investigate the potential differences between Spaniards and Ecuadorian Mestizo people regarding *CYP2C8*, *CYP2C9*, and *CYP2C19* genetic polymorphisms. DNA from 282 Spaniard and 297 Ecuadorian subjects were analyzed by either a previously reported pyrosequencing method (*CY2C8*3, CYP2C9*2, CYP2C9*3, CYP2C19*2* and *CYP2C19*3*) or a nested PCR technique (*CYP2C19*17*). Whereas *CYP2C19*17* allele distribution was higher in Ecuadorians than in Spaniards ($P < 0.001$) and the frequency of *CYP2C19*3* was similar in these two populations ($P > 0.05$), the other allelic variants were detected at significantly lower frequencies in Ecuadorians than in Spaniards ($P < 0.05$). According to the diplotype distributions, the prevalence of the presumed CYP2C9 and CYP2C8 extensive metabolizers was higher in Ecuadorians than in Spaniards ($P < 0.05$). Individuals genotyped *CYP2C19*1/*17* and **17/*17* who were considered as ultrarapid metabolizers were overrepresented in Ecuadorians in relation to Spaniards ($P < 0.001$). By contrast, among Ecuadorians no poor metabolizers (PMs) of either CYP2C8 or CYP2C9 were found and only two individuals were CYP2C19 PMs. These data are compatible with a higher CYP2C8, CYP2C9, and CYP2C19 activity in Mestizo Ecuadorians as opposed to Spaniards, which could imply differences in dosage requirements for drugs metabolized by these cytochromes and should also be considered in allele-disease association studies.

Keywords *CYP2C8* · *CYP2C9* · *CYP2C19* · Polymorphism · Spaniards · Ecuadorians

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Introduction

Cytochrome P450 2C (CYP2C) subfamily of enzymes metabolizes around 20–30 % of all pharmaceutical drugs used today [1]. The main CYP2C isoforms, namely CYP2C8, CYP2C9, and CYP2C19 are homologous and share more than 80 % aminoacid sequence identity [1, 2]. The genes encoding for these enzymes are located together on chromosome 10q24 and exhibit genetic polymorphism [3]. This genetic variation gives rise to abolished, reduced, or increased catalytic activity towards the respective substrate drugs [3, 4]. The *CYP2C8, CYP2C9*, and *CYP2C19* allele frequencies are variable among different populations, thus implying potential interethnic differences in drug response in terms of either efficacy or likelihood of developing ADRs.

CYP2C9, the most abundant CYP2C isoform (50 % of the total CYP2C subfamily) [5], is involved in the metabolism of an elevated number of clinically important drugs including (S)-warfarin, losartan, tolbutamide, phenytoin, numerous NSAIDs and many antidepressants [1, 6, 7]. The main *CYP2C9* detrimental alleles, *CYP2C9*2* and **3*, cause defective CYP2C9 catalytic activity (10–40 and 5–15 %, respectively) [7]. CYP2C8 constitutes 26 % of the CYP2C isoforms. It is the main enzyme in the metabolism of several therapeutically important drugs such as amiodaquine,

paclitaxel, amiodarone, repaglinide, rosiglitazone and troglitazone [8] and also contributes to the metabolism of some NSAIDs [9]. The *CYP2C8*3* polymorphism causes decreased catalytic activity (50 % reduction for paclitaxel metabolism) [10]. CYP2C19 represents 16 % of the CYP2C subfamily [5] and is responsible for the metabolism of a range of clinically important drugs, namely proton pump inhibitors, diazepam, imipramine, fluoxetine, tolbutamide, voriconazole or clopidogrel [11–13]. *CYP2C19*2* and *CYP2C19*3* are the best characterized alleles responsible for the poor metabolizer phenotype (PM). In comparison with the wild type allele (*CYP2C19*1*), the *CYP2C19*3* variant causes the largest reduction in metabolic capacity for many CYP2C19 substrates, followed by the *CYP2C19*2* variant that is associated to an intermediate reduction [1].

The absence of any language barrier has caused an important migratory influx of Ecuadorians to Spain over the last years and recently, the tendency has been for some groups of Spaniards to migrate to Ecuador. Ecuadorians are the biggest community of Latin Americans in Spain; Mestizos being the most representative and the largest group among Ecuadorians [14].

Understanding interethnic differences in allele frequencies opens the possibility to improve and optimize the clinical practice and the evaluation of the efficacy and safety of drugs for patients throughout the world. In this regard, data on the frequency distribution of the most common *CYP2C* variant alleles in Ecuadorians has not been documented so far. This information in Spaniards is based on studies of genetic polymorphisms of the CYP2C subfamily [9, 15–18] performed in populations from different geographic areas and mainly from the south of Spain. However, a geographic gradient according to latitude has been observed for some polymorphisms in Spain [19, 20]. Hence, the present study was designed to determine interethnic differences in pharmacologically-relevant *CYP2C8*, *CYP2C9* and *CYP2C19* variant alleles between a Spaniard and an Ecuadorian Mestizo population and also to compare their frequencies with those previously reported in other populations.

Materials and methods

The total study population consisted of 579 unrelated individuals. From these, 282 were white European subjects from Spain (137 males and 145 females) and 297 (147 males and 150 females) were subjects from Ecuador. Age ranges in years of the participants were 18–48 (mean: 27.5) and 18–52 (mean: 26.5) for Spaniards and Ecuadorians, respectively. The Spaniard subjects were people from the same geographical area (Northern Spain), and those from Ecuador were "Mestizo" (Amerindian and European descent), as assessed by the morphological traits, self-identification, and genotyping with a panel of ancestry-informative markers, AIM, (Power PlexR® 16 System kit, Promega Co, Madison, WI, USA). Individuals were randomly selected among students and personnel of the Medical School of the University of Zaragoza (Zaragoza, Spain) and the Metropolitan Hospital of Quito (Ecuador).

All individuals were healthy as assessed by medical history and physical examination. All subjects gave their written informed consent to participate in this study after detailed information about the purpose of this investigation which was approved by the Human Research Ethics Committee of Aragón (Zaragoza, Spain), and was conducted in accordance with the Declaration of Helsinki and its subsequent revisions.

Genotyping

Genomic DNA was extracted from peripheral blood, blotted and dried on filter paper using the QIAamp DNA Micro Kit (Izasa, Madrid, Spain).

Genotyping of *CY2C9*2* (430C > T, rs1799853), *CY2C9*3* (1,075 A > T, rs1057910), *CY2C8*3* (416 G > A, rs11572080 and 1,196 A > G, rs10509681), *CYP2C19*2* (681 G > A, rs4244285) and *CYP2C19*3* (636 G > A, rs4986893) was carried out following a previously described pyrosequencing method [21] with minor modifications. We used streptavidine-coated Sepharose beds (Amersham Biosciences, Uppsala, Sweden) to immobilize the PCR product. Sepharose beds were mixed with binding buffer, Milli-Q water, and PCR products to a volume of 70 µl per well. The plate was incubated for 20 min at 22 °C (1,300 rpm). The beds were washed using Vacuum Prep 5001 and released into 40 µl of annealing buffer containing 16 pmol of sequencing primer.

The *CYP2C19*17* allele was detected by a nested PCR. *CYP2C19**17 gene-specific primers were used to amplify a 476-bp fragment of the region of interest. This PCR product was diluted ten times and served as a template for the subsequent allele-specific PCR. The forward primer of this PCR was either 5′-TCTTCTGTTCTCAAAGC-3′ for identification of the *CYP2C19*1* allele or 5′-TCTTCTGTTCTCAAAGT-3′ for identification of the *CYP2C19*17* allele. The products were electroforesed on a 2 % agarose gel and stained with ethidium bromide. The accuracy of the method was validated by blind duplicates using the some genomic DNA. Every time PCR reactions were done a negative and a positive control was run simultaneously.

Predicted metabolic phenotype

Individuals were grouped into distinct predicted phenotypes according to the CYP2C genetic polymorphisms.

Three groups were established for both CYP2C8 and CYP2C9 activities: extensive metabolizer (EM: wild type homozygous), intermediate metabolizer (IM: heterozygous genotype for the loss-of function CYP2C alleles), and poor metabolizer (PM: homozygous or compound heterozygous genotypes for the loss-of-function CYP2C alleles). For CYP2C19, a fourth phenotypic group was defined as ultrarapid metabolizer (UM). The UM phenotype was that of individuals *CYP2C19*17* homozygous or heterozygous *CYP2C19*1 *17*. The group classified as "unknown phenotype" consisted of individuals heterozygous for *CYP2C19*17* and either *CYP2C19*2* or **3*.

Statistics

Differences in allele frequencies between populations were measured by the χ^2 goodness-of-fit with two degrees of freedom. Hardy–Weinberg equilibrium was assessed by comparing the genotype frequencies with the expected values using a contingency table by χ^2 test. Probability values of less than 0.05 were regarded as statistically significant.

Results

CYP2C8, CYP2C9 and *CYP2C19* genotype frequencies corresponded to those predicted by the Hardy–Weinberg law ($P > 0.05$ in all cases). Similarly, *CY2C8*, *CYP2C9* and *CYP2C19* allele frequencies were within the 95 % confidence interval.

Table 1 summarizes the *CY2C8*, *CYP2C9* and *CYP2C19* allele frequencies screened in this work. When the allele distributions between the two populations of Spaniards and Ecuadorians were compared it was found that, with the double exception of the alleles *CYP2C19*3* (that was similarly distributed in the two populations) and *CYP2C19 *17* (that was more frequent in Ecuadorians than in Spaniards), the other variant alleles (*CYP2C9*2*, *CYP2C9*3*, *CYP2C19*2*, and *CYP2C8*3*) were detected at much lower frequencies in Ecuadorians than in Spaniards (Table 1).

The *CYP2C9*2* allelic variant was the most common detrimental *CYP2C9* allele in Spaniards as opposed to Ecuadorians. In this latter population the *CYP2C9*2* allele was less prevalent than the *CYP2C9**3 allelic variant [0.5 and 3.7 %, respectively (Table 1)].

Table 2 shows the *CYP2C* expected phenotypes according to the diplotype distribution. The prevalence of the genotypes linked to high CYP2C8, CYP2C9 and CYP2C19 metabolic activity, that is extensive metabolizers (EMs), was higher in Ecuadorians than in Spaniards. By contrast, the predicted IM phenotype (Intermediate metabolizers) for CYP2C8, CYP2C9 and CYP2C19 resulted to be less frequent in Ecuadorians than in Spaniards and, at the extreme, poor metabolizers (PMs) for the cytochromes CYP2C8 and CYP2C9 were absent in Ecuadorians and only 0.7 % of individuals could be classified as CYP2C19 PM (Table 2). Individuals carrying the genotypes *CYP2C19*1/*17* or *CYP2C19 *17/*17*, with a predicted CYP2C19 ultrarapid metabolism (UM), were overrepresented in Ecuadorians in relation to Spaniards (41.4 and 26.9 %, respectively).

Discussion

In this work we have observed that the frequencies of the common *CYP2C8, CYP2C9* and *CYP2C19* allelic variants in Spaniards from Aragon (North-East of Spain) are not different to those previously found in other Spaniard groups as in other Caucasian populations [9, 16, 22, 23]. Nevertheless, there exist important differences between the major ethnic groups. In this regard, *CYP2C9**2, has been detected at a greater frequency in our sample of Spaniards (13.3 %), than in African American (3.3–4.3 %) or Asian populations [9, 23–25], to such an extent that, the *CYP2C9*2* allelic variant has not been found in different East Asian groups [25–27]. A similar profile of interethnic differences has been detected for the *CY2C9*3* and *CYP2C8*3* frequency distributions in our group of Spaniards (7.7 and 11.4 %, respectively), with a nearly selective presence of these allelic variants in Spaniards in this study as well as in other Caucasians [9, 28].

The comparison of the *CYP2C19*3* prevalence between populations further illustrates the almost exclusive presence of this variant in Asian populations [29, 30]. In fact,

Table 1 Polymorphism studied across the CYP2C cluster

Variant allele	Spaniard population		Ecuadorian Mestizo population	
	Frequency *n* (%)	95 % CI	Frequency *n* (%)	95 % CI
CYP2C8				
*CYP2C8*3*	32 (11.4)	7.6–16.2	19 (6.5)	3.8–10.2
CYP2C9				
*CYP2C9*2*	37 (13.3)	9–18	1 (0.5)	0.0–1
*CYP2C9*3*	22 (7.7)	4–11	11 (3.7)	1–6
CYP2C19				
*CYP2C19*2*	36 (12.8)	8.4–18.7	23 (7.8)	4.5–12.4
*CYP2C19*3*	1 (0.3)	0.0–1.9	1 (0.4)	0.0–2.5
*CYP2C19*17*	42 (14.9)	10.7–20.1	74 (24.9)	19.5–31.2

CI confidence interval

Table 2 Assignment of likely phenotypes based on CYP2C diplotypes

Gene	Observed genotypes	Predicted phenotype	Spaniards		Ecuadorians	
			Frequency *n* (%)	95 % CI	Frequency *n* (%)	95 % CI
CYP2C9						
	**1/*1*	EM	164 (58.1)	49.6–67.7	272 (91.6)	81.0–103.1
	**1/*2* or **1/*3*	IM	104 (36.9)	30.1–44.6	25 (8.4)	5.4–12.4
	**2/*2, *2/*3* or **3/*3*	PM	14 (5)	2.7–8.3	0 (0)	0–1.2
CYP2C8						
	**1/*1*	EM	226 (80.2)	70.0–91.3	261 (87.9)	77.5–99.2
	**1/*3*	IM	54 (19.1)	14.3–24.9	36 (12.1)	8.4–16.7
	**3/*3*	PM	2 (0.7)	0.0–2.5	0 (0)	0–1.2
CYP2C19						
	**17/*17* or **1/*17*	UM	76 (26.9)	21.2–33.7	123 (41.4)	34.4–49.4
	**1/*1*	EM	141 (50.0)	42.0–58.9	127 (42.8)	35.6–50.8
	**1/*2* or **1/*3*	IM	58 (20.6)	15.6–26.5	28 (9.4)	6.2–13.6
	**2/*2, *2/*3* or **3/*3*	PM	5 (1.8)	0.0–4.1	2 (0.7)	0.0–2.4
	**2/*17* or **3/*17*	Unkown	2 (0.7)	0.0–2.5	17 (5.7)	3.3–9.1

CI confidence interval, *UM* ultrarapid metabolizer, *EM* extensive metabolizer, *IM* intermediate metabolizer, *PM* poor metabolizer

whereas frequencies as high as 10 % have been detected in Oriental subjects [30, 31], in African and Caucasian populations the frequency was reported to be very low or even totally absent [23]. The *CYP2C19*17* allele frequency found here in Spaniards (14.9 %) was close to the lower limit of the range of values described in other European groups (18–27 %) [32, 33]; this magnitude in Spaniards being located between two extremes: the largest *CYP2C19*17* prevalence detected in African descent (32.3 %) [34] and the lowest frequency reported in Asians (1.3–4.4 %) [35]. These findings could suggest that the *CYP2C8*3, CYP2C9*2, CYP2C9*3*, *CYP2C19*3* and *CYP2C19*17* mutations could have a rather recent origin, probably after the split of Black, Oriental and Caucasian racial groups [28]. By contrast, *CYP2C19*2,* which is the most prevalent *CYP2C19* detrimental allele among Caucasians, has been detected in 12.8 % of our Spaniard population; this relatively high frequency is a common genotypic characteristic of the different ethnic groups, thus indicating that this mutation is relatively old and occurred before the differentiation of the three major racial groups.

This is the first report providing data about genetic polymorphism of the *CYP2C* subfamily in an Ecuadorian Mestizo population and demonstrates that the distribution of the common *CYP2C8, CYP2C9* and *CYP2C19* allelic variants differs from that of Spaniards and other populations. Thus, on the one hand, the *CYP2C9*2* allele was less common in Ecuadorians than in Spaniards (Table 1) and close to the practical absence of this allelic variant found in Asians [25], and, on the other hand, the frequencies of the *CYP2C9*3* and *CYP2C8*3* alleles in Ecuadorians (Table 1) were between the values found in Spaniards in this study and those reported in Orientals [4, 9]. These results seem to be consistent with the ethnohistory of the Mestizo people. Indeed, Mestizos are characterized by a biracial admixture of populations with a gene pool derived from Native Amerindian groups (originating from Asia) with Caucasians coming from Spain and other European countries. Interestingly, the *CYP2C9*3* allele frequency in Ecuadorians (3.7 %) was similar to that reported in other Latin-American groups, such as Bolivians (3 %), Tepehuan-Mexicans (1.5 %) or Chilean (4 %) [36–38].

With regard to the *CYP2C19*3* allelic variant, its presence in Ecuadorians was as rare (0.4 %) as in Spaniards in this study (0.3 %), in contrast to the high frequencies reported in Orientals [30]. As a result of the genetic background of the Mestizo Ecuadorians, we would expect to find a higher CYP2C19*3 frequency. Since similar lower values of this variant allele frequency have been observed in other groups from the same geographical area, such as Colombia, Mexico or Bolivia [36, 37, 39, 40] we can only speculate about the possibility of the existence of a selection factor against CYP2C19*3 in the region. A negative selection factor has been suggested to explain the lower frequency of the CYP3A4*1B allele in non African population [41]. Although relatively high, the prevalence of the *CYP2C19*2* allele in Ecuadorians (7.8 %) was the lowest in comparison with Caucasians including Spaniards in this study (10–17 %), and also with Africans(18–20 %) or Asians (21–45 %) [28]. However, both *CYP2C19*2* and *CYP2C19**3* were found at a similar frequency in Ecuadorians as in other groups from the same geographical region [36, 37, 39, 40]. Consistently, in a previous study performed on Indians from Panama [42] no PMs of

S-mephenytoin were found, thus opening the possibility of the existence in this area of a common pre-colonial ancestry with similar genetic characteristics. The *CYP2C19*17* allele frequency in Ecuadorians was significantly higher in comparison with Spaniards in our sample (Table 1). By contrast, it was similar to that described in some European and African populations [32, 43–45] and also comparable to the frequency detected in an Amerindian group from Brazil (20.8 %) [34].

The genotype distribution detected in this study (Table 2) may derive in differential pharmacokinetic consequences in the two populations studied in this work with potential influence on either therapeutic response or toxicity. In fact, individuals with presumed phenotype linked to high CYP2C8, CYP2C9, and CYP2C19 (EMs and/or UMs) appears to be overrepresented in Ecuadorians in relation to Spaniards (Table 2). Accordingly, it could be expected that Ecuadorians, on average, could require a higher mean daily dose of CYP2C substrate drugs than Spaniards. Conversely, since PMs are more prevalent in Spaniards, dose-dependent adverse drugs reactions could be more common in this population. In addition, for pro-drugs needing to be bioactivated to elicit pharmacological activity, the predicted phenotypic distributions found here would indicate that more Ecuadorians could undergo increased therapeutic responses than Spaniards, thus being exposed to a greater risk for excessive drug effects.

Conclusion

In conclusion, our findings reinforce the notion about the existence of important interethnic differences in *CYP2C8*, *CYP2C9* and *CYP2C19* allele and genotype frequencies. The results clearly support the need for further investigations, including independent clinical trials, dealing with the clinical significance of the genotypic differences for optimal drug dosage and drug selection in the different populations. Since the scientific baggage to apply the pharmacogenetic knowledge to practical dose recommendations is increasingly growing, the results of the present study could be useful as a support to identify individuals with altered pharmacokinetics for CYP2C8, CYP2C9 or CYP2C19 substrates in order to adopt appropriate therapeutic strategies. The data should also be considered in allele-disease association studies to better understand the genetic risk factors affecting many conditions and also to predict them in the future.

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