Céspedes-Garro, Carolina; Rodrigues-Soares, Fernanda; Jiménez-Arce, Gerardo; Naranjo, María-Eugenia G.; Tarazona-Santos, Eduardo; Fariñas, Humberto; Barrantes, Ramiro; Llerena, Adrián; CEIBA.FP Consortium of the Ibero-American Network of Pharmacogenetics & Pharmacogenomics RIBEF

Relevance of the ancestry for the variability of the Drug-Metabolizing Enzymes CYP2C9, CYP2C19 and CYP2D6 polymorphisms in a multiethnic Costa Rican population

Revista de Biología Tropical, vol. 64, núm. 3, septiembre, 2016, pp. 1067-1076

Universidad de Costa Rica
San Pedro de Montes de Oca, Costa Rica

Available in: http://www.redalyc.org/articulo.oa?id=44946472012
Relevance of the ancestry for the variability of the Drug-Metabolizing Enzymes CYP2C9, CYP2C19 and CYP2D6 polymorphisms in a multiethnic Costa Rican population

Carolina Céspedes-Garro¹,²†, Fernanda Rodrigues-Soares³†, Gerardo Jiménez-Arce², María-Eugenia G. Naranjo¹, Eduardo Tarazona-Santos³,⁴, Humberto Fariñas¹, Ramiro Barrantes²*, Adrián Llerena¹ & CEIBA.FP Consortium of the Ibero-American Network of Pharmacogenetics & Pharmacogenomics RIBEF²

1. CICAB Clinical Research Center, Extremadura University Hospital and Medical School, 06080 Badajoz, Spain; carolina.cespedesgarro@ucr.ac.cr, megonzalez@unex.es, humberto.farinas@ses.juntaextremadura.net, allerena@unex.es
2. Genetics Section, School of Biology, University of Costa Rica, 2060 San Pedro, San José, Costa Rica; carolina.cespedesgarro@ucr.ac.cr, gerardo.jimenez@ucr.ac.cr, ramiro.barrantes@ucr.ac.cr
3. Departamento de Biología Geral. Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte, Brazil; fernandasoares@ufmg.br, edutars@icb.ufmg.br
4. Asociación Benéfica PRISMA, Lima 32, Lima, Perú; edutars@icb.ufmg.br
† Co-first authorship  •  * Correspondence

Received 18-IX-2015.  Corrected 08-II-2016.  Accepted 09-III-2016.

Abstract: CYP2C9, CYP2C19 and CYP2D6 metabolize around 40 % of drugs and their genes vary across populations. The Costa Rican population has a trihybrid ancestry and its key geographic location turns it into a suitable scenario to evaluate interethnic differences across populations. This study aims to describe the diversity of CYP2C9, CYP2C19 and CYP2D6 polymorphisms in Costa Rican populations in the context of their ancestry. A total of 448 healthy individuals were included in the study: Bribri (n= 47), Cabécar (n= 27), Maleku (n= 16), Guaymí (n= 30), Huetar (n= 48), Chorotega (n= 41), Admixed/Mestizos from the Central Valley/Guanacaste (n= 189), and Afro-Caribbeans (n= 50) from Limón. CYP2C9 (alleles *2, *3, *6) and CYP2C19 (*2, *3, *4, *5, *17) genotypes were determined by Real-Time PCR. African, European and Native American ancestry were inferred using 87 ancestry informative markers. The frequency of the decreased activity allele CYP2C9*2 is lower in the self-reported Amerindian groups compared to the admixed population, and the highest frequencies of CYP2C19*2 (null activity) and CYP2C19*17 (increased activity) were found in the self-reported Afro-Caribbean population. Moreover, a frequency of 0.7 % CYP2C9 gPMs in the Admixed population and a variable frequency of CYP2C19 gUMs (0.0-32.6 %, more prevalent in Afro-Caribbeans) in Costa Rican populations, was found. Finally, the following alleles were positively correlated with genomic African ancestry and negatively correlated with genomic Native American ancestry: CYP2D6*5 (null activity), CYP2D6*17 (decreased activity), CYP2D6*29 (decreased activity) and CYP2C19*17 (increased activity). No correlation for CYP2C9 polymorphisms and genomic ancestry was found. Further studies assessing the CYP2C9 and CYP2C19 sequence in these populations, preferentially by sequencing these genes, are warranted. Rev. Biol. Trop. 64 (3): 1067-1076. Epub 2016 September 01.

Key words: CYP2C9, CYP2C19; CYP2D6, Costa Rica, Amerindian, Afro-Caribbean, genomic ancestry.

aCEIBA Consortium of authors (*group coordinator):

Group 1 Authors: Graciela E. Moya*, Verónica Ferreiro. Institutions: Pontificia Universidad Católica, Buenos Aires, Argentina; Argentina & Fundación GENOS, Buenos Aires, Argentina.
Cytochrome P450 enzymes (CYPs) are involved in the phase I metabolism of endobiotics and xenobiotics (i.e. drugs). Thus, the activity of these enzymes is related to the plasmatic levels of active drug in patients, as well as to their therapeutic effect. In the CYP2C subfamily of drug-metabolizing enzymes (DMEs), CYP2C9 and CYP2C19 are encoded by the CYP2C gene cluster in 10q24, and are polymorphic, presenting interethnic variability (CYP2C19 allele nomenclature, 2015; Sistonen et al., 2009).

CYP2C9 is involved in the metabolism of drugs such as warfarin, losartan, fluoxetine and non-steroidal anti-inflammatory drugs. Around 60 CYP2C9 gene variants have been described (CYP2C9 allele nomenclature, 2015), which explain a considerable proportion of variability in the drug metabolism. Some CYP2C9 alleles have been related to a null or decreased hydroxylation capacity, such as CYP2C9*3 allele that dramatically reduces the enzyme activity (Ingelman-Sundberg, Sim, Gomez, & Rodriguez-Antona, 2007). Thus, the carriers of two CYP2C9*3, as well as, alleles with null capacity are predicted to be poor metabolizers (gPMs) and to suffer adverse drug reactions (ADRs) (Yang et al., 2013).

CYP2C19 is responsible for the metabolism of antidepressants and proton pump inhibitors, among other drugs. A total of 34 CYP2C19 allelic variants that affect enzyme activity have been described, from null (i.e. CYP2C19*2, *3, *4, *5) to increased activity (i.e. CYP2C19*17) (CYP2C19 allele nomenclature, 2015). Individuals carriers of two inactive CYP2C19 alleles are predicted to be gPMs, while carriers of *1/*17 or *17/*17 genotypes are predicted ultrarapid metabolizers (gUMs). In pharmacological treatment, ADRs for both metabolic groups have been shown. Drug Regulatory Agencies report CYP2C19 as a pharmacogenetic biomarker for 16 drugs (Center for Drug Evaluation and Research, 2015) and that CYP2C19 status of patients might predict clinical outcomes (Altar et al., 2015; Niu et al., 2015; Tabata et al., 2015).
CYP2D6 metabolizes a wide range of drugs such as antidepressants, antiarrythmics, antipsychotics, and antihistamines. More than 100 allelic variants have been described for this gene, some of which have been related to null, decreased, normal and increased enzyme activity (CYP2D6 allele nomenclature, 2015). CYP2D6 gPMs and gUMs have been related to clinical outcomes in pharmacological therapy (Rolla et al., 2014; Seripa et al., 2015; Youngster et al., 2014) and Drug Regulatory Agencies report CYP2D6 as a pharmacogenetic biomarker for forty drugs (Center for Drug Evaluation and Research, 2015).

Interethnic differences in such cytochrome P450 genetic polymorphisms are partially responsible for the variations among populations in drug disposition. The trihybrid ancestry of the Costa Rican population (Segura-Wang, Raventós, Escamilla, & Barrantes, 2010), and the key geographic location of the country makes Costa Ricans fairly representative of the human genetic diversity in Central America.

The CEIBA.FP Consortium of the Ibero-American Network of Pharmacogenetics & Pharmacogenomics (RIBEF) has carried out studies in different Latin American populations (Dorado et al., 2012a; Dorado, Gallego, Peñas-Lledó, Terán, & Llerena, 2014), contributing to increase the pharmacogenetic knowledge of these neglected populations. Nevertheless, this is the first report of the CYP2C subfamily in a Costa Rican population including groups from different ethnic backgrounds. The present study aims to estimate the allele frequencies of CYP2C9, CYP2C19 and CYP2D6 polymorphisms in Costa Rican populations with different ancestry backgrounds.

### MATERIALS AND METHODS

**Subjects:** The study comprised 448 healthy individuals, of which 385 were previously studied for the CYP2D6 gene (Céspedes-Garro, Jiménez-Arce, Naranjo, Barrantes, & Llerena, 2014). The following Native American Chibchan populations were analyzed: Bribri (n= 47), Cabécar (n= 27), Maleku (n= 16), Guaymí (n= 30) and Huetar (n= 48). An Oto-Manguean Mesoamerican Amerindian group: Chorotega (n= 41) was also included. Moreover, Admixed/Mestizos from the Central Valley and Guanacaste (n= 189), and Afro-Caribbeans (n= 50) from Limón were included (Céspedes-Garro et al., 2014a). The number of analyzed subjects varied according to the CYP2C gene and genomic ancestry analyses (Table 1, Table 2 and Table 3).

All DNA samples were obtained from a DNA biobank of the School of Biology of the University of Costa Rica. The samples were collected and stored after approval from review boards of the University of Costa Rica. Further information of collection and demographic data is available elsewhere (Azofeifa et al., 2004; Barrantes et al., 1990; Barrantes, Smouse, Neel, Mohrenweiser, & Gershowitz, 1982). The inclusion criteria of individuals in each group were previously defined (Céspedes-Garro et al., 2014a).

**Methods:** The strategy followed in the study has been designed by the CEIBA-MESTIFAR Project (Sosa-Macias et al., 2015).

**Genomic ancestry:** A total of 87 ancestry informative markers (AIMs) selected from

### TABLE 1
Mean of the genomic ancestry for different Costa Rican ethnic groups

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>European ancestry</th>
<th>African ancestry</th>
<th>Native American ancestry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admixed</td>
<td>32</td>
<td>0.429</td>
<td>0.168</td>
<td>0.403</td>
</tr>
<tr>
<td>Bribri</td>
<td>12</td>
<td>0.182</td>
<td>0.072</td>
<td>0.745</td>
</tr>
<tr>
<td>Chorotega</td>
<td>26</td>
<td>0.220</td>
<td>0.090</td>
<td>0.690</td>
</tr>
<tr>
<td>Guaymí</td>
<td>18</td>
<td>0.030</td>
<td>0.027</td>
<td>0.943</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>11</td>
<td>0.093</td>
<td>0.863</td>
<td>0.044</td>
</tr>
</tbody>
</table>

n: number of subjects.
103 previously proposed (Yaeger et al., 2008) were genotyped to infer African, European and Native American ancestry at individual and population levels. The Sequenom iPLEX platform (San Diego, CA, USA) genotyping (Pereira et al., 2012) was performed at the Centro Nacional de Genotipado (CEGEN, Santiago de Compostela, Spain). In the analyses, data from 119 Yoruba unrelated individuals from Ibadan, Nigeria (YRI) and 60 Utah residents with European ancestry from the CEPH collection (CEU) from The International HapMap Consortium (2010) were included as parental populations. The Expectation Maximization method implemented in the software Admixture (Alexander, Novembre, & Lange, 2009) was used to estimate ancestry, assuming three parental populations (k=3).

### CYP2C9 and CYP2C19 genotyping:

Genotyping for the CYP2C9*2 (rs1799853), *3 (rs1057910), *6 (rs9332131) and CYP2C19*2 (rs4244285), *3 (rs4986893), *4 (rs28399504), *5 (rs28399504) and *17 (rs12248560) alleles was carried out on genomic DNA using TaqMan assays as previously described (Dorado et al., 2012b; Llerena et al., 2014a; Peñas-Lledó et al., 2014). Chromosomes lacking the above-mentioned alleles/SNPs were classified as CYP2C9*1 and CYP2C19*1.

### CYP2D6 genotyping:

Data on CYP2D6*2 (rs1080985), *3 (rs35742686), *4 (rs1065852, rs3892097), *6 (rs5030655), *10 (rs1065852), *17 (rs28371706), *29 (rs59421388), *35 (rs1080985 and rs769258), *41 (rs28371725), CYP2D6*5, CYP2D6*1xN, *2xN, *4xN and

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Frequencies (%) of CYP2C9 alleles and phenotypes predicted from genotype in different Costa Rican ethnic groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported Ancestry</td>
<td>n</td>
</tr>
<tr>
<td>Admixed</td>
<td>137</td>
</tr>
<tr>
<td>Bribri</td>
<td>46</td>
</tr>
<tr>
<td>Cabécar</td>
<td>27</td>
</tr>
<tr>
<td>Chorotega</td>
<td>31</td>
</tr>
<tr>
<td>Guaymí</td>
<td>27</td>
</tr>
<tr>
<td>Huetar</td>
<td>48</td>
</tr>
<tr>
<td>Maleku</td>
<td>15</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>45</td>
</tr>
</tbody>
</table>

| Self-reported Ancestry | n | *1 | *2 | *3 | *4 | *5 | *17 | gPMs | gUMs |
| Admixed | 141 | 81.9 | 7.1 | 0.0 | 0.7 | 0.0 | 10.3 | 0.0 | 17.7 |
| Bribri | 23 | 91.3 | 4.3 | 0.0 | 0.0 | 0.0 | 4.3 | 0.0 | 8.7 |
| Chorotega | 36 | 84.7 | 12.5 | 0.0 | 0.0 | 0.0 | 2.8 | 0.0 | 5.6 |
| Guaymí | 24 | 98.0 | 0.0 | 0.0 | 0.0 | 0.0 | 2.0 | 0.0 | 4.0 |
| Maleku | 12 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Afro-Caribbean | 46 | 58.7 | 19.6 | 0.0 | 0.0 | 0.0 | 21.7 | 0.0 | 32.6 |

n: number of subjects; gPMs: predicted poor metabolizers from genotype; gUMs: predicted ultra-rapid metabolizers from genotype.

a P < 0.05 compared to the rest of populations with the exception of the Chorotega tribe; b P < 0.05 compared to the rest of populations.
*10xN alleles were published for the Costa Rican population (Céspedes-Garro et al., 2014a; Céspedes-Garro et al., 2014b).

**Predicted hydroxylation capacity group:**
To infer metabolic phenotype from the genotypes, zero value was assigned to CYP2C9*3 and *6 and CYP2C19*2, *3, *4 and *5 variants, 0.5 value to CYP2C9*2, one to CYP2C9/19*1, and two to CYP2C19*17 (Peñas-Lledó et al., 2014). Individuals with activity score values equal to zero were classified as gPMs, and individuals with activity score higher than two were classified as gUMs (for CYP2C19) (Peñas-Lledó et al., 2014). An activity score was adapted for CYP2D6 (Gaedigk et al., 2008; Llerena et al., 2012). Previously reported data on CYP2D6 have been analyzed together with original ancestry information of the subjects.

The differences in CYP2C9 and CYP2C19 allele frequencies among populations were compared using the Fisher’s exact test (alpha = 0.05). Hardy-Weinberg equilibrium for alleles was determined using a contingency table X² statistic with Yate’s correction. Statistical analyses were performed using the STATISTICA 4.3 (StatSoft, Tulsa, OK, USA) and GraphPad Prism 3.02 (GraphPad Software, San Diego, CA, USA).

The correlation between individual ancestry and the number of copies of a specific allele in each individual was estimated using the Spearman’s rank correlation, with the R cor.test command (R Foundation, 2015).

**RESULTS**

**Genomic ancestry:** The studied individuals and populations from Costa Rica encompass a wide spectrum of continental ancestry and self-reported admixed individuals from the Central Valley and Guanacaste showed many of the possible combinations of European, African and Native American admixture (Fig. 1). Moreover, the three self-reported

![Fig. 1. Barplots of individual continental ancestry, main CYP2C9 and CYP2C19 alleles and CYP2C19 predicted phenotypes frequency distributions in Costa Rican populations. The approximate location of populations is shown in the chart.](image)
Native groups mostly have Native American ancestry, with low African ancestry (<9%) and European ancestry that range from 3% in Guaymí to 22% in the Chorotega. The Afro-Caribbean population has a very high African ancestry (86%), with all the individuals showing more than 76% of African ancestry (Table 1 and Fig. 1).

**CYP2C9 and CYP2C19 alleles and predicted metabolic phenotypes:** CYP2C9 and CYP2C19 genotype frequencies fit the Hardy-Weinberg equilibrium for all the studied populations.

Consistently with previous studies, the wild-type CYP2C9*1 is modal in all populations (Table 2). The decreased-activity CYP2C9*2 allele frequency was higher in the Admixed and Huetar populations (7-8%) than in the Afro-Caribbean, Bribrí, Cabécar, Maleku and Guaymí (<1.1%; P <0.05). No differences were found in the frequency of the decreased-activity CYP2C9*3 allele across the different groups. The null-activity CYP2C9*6 variant was not detected in the Costa Rican populations. Moreover, only one admixed subject was a CYP2C9 predicted poor metabolizer (gPM).

For CYP2C19, both the null-activity CYP2C19*2 allele and the increased-activity CYP2C19*17 allele were more common in the Afro-Caribbean population than in the other Costa Rican groups (P <0.05) (Table 3). These allele distributions suggest that almost a third of the subjects in the Afro-Caribbean population (15 out of 46) are gUMs for CYP2C19, more than in any other Costa Rican group (P <0.05).

The frequency of CYP2C9*2 for the admixed Costa Rican population is similar to those reported for other Latin American admixed populations from Brazil, Chile, Ecuador, Mexico and Hispanics from United States of America (Céspedes-Garro et al., 2015).

**DISCUSSION**

This is the first study on CYP2C9 and CYP2C19 in a multiethnic Costa Rican population, and it has been contextualized estimating the genomic ancestry of these populations.

The observed low frequency of the decreased-activity allele CYP2C9*2 in the most Amerindian populations from Costa Rica (Bribri, Cabécar, Maleku and Guaymí) (Azofeifa, Ruiz, & Barrantes, 2001), is consistent with other studies on North- and South- Amerindians, which reported frequencies from 0 to 4.8% for this allele (Céspedes-Garro et al., 2015). Noteworthy, the high CYP2C9*2 frequency in the Huetar (8.3%) is similar to that of the Costa Rican admixed population (7.7%), in agreement with reports that estimate that the Huetar groups have European and African admixture as high as 3.9 to 32.9% (Barrantes, 1993; Santos, Ward, & Barrantes, 1994; Bieber, Bieber, Rodewald, & Barrantes, 1996; Azofeifa et al., 2001; Ruiz-Narváez et al., 2005).

The frequency of CYP2C9*2 for the admixed Costa Rican population is similar to those reported for other Latin American admixed populations from Brazil, Chile, Ecuador, Mexico and Hispanics from United States of America (Céspedes-Garro et al., 2015).

The very low frequencies of CYP2C9 gPMs in the Costa Rican populations (predicted by surveying the presence of the *3 and *6 allele), is also in agreement with other studies in diverse Latin American and Native American populations, including US-Hispanics (Céspedes-Garro et al., 2015). This frequency can indicate that Costa Rican populations are not susceptible to adverse reactions of CYP2C9-metabolized drugs (warfarin, losartan, diclofenac) due to genetic factors.
Regarding CYP2C19 in Native Costa Ricans, the frequency of the null-activity allele CYP2C19*2 varies from 0 to 12.5 %. The CYP2C19*2 frequency in the Chorotega tribe (12.5 %) was similar to that reported for Amerindian populations from Brazil (10.4 and 11.1 %) (Santos et al., 2011; Vargens, Petzl-Erler, & Suarez-Kurtz, 2012). The low frequencies for this allele in Bribri, Maleku and Guaymi populations (4.3, 0 and 0 %, respectively) are similar to those from the Purépechas, Tzotziles, Tojolabales and Tzeltales Mexican Amerindian tribes (5.4, 5.6, 3.6 and 0 %, respectively) (Salazar-Flores et al., 2012).

As previously reported, CYP2C19*3 frequency is rare outside Eastern Asia and Melanesia (Sistonen et al., 2009); for this reason, the lack of this allele in Costa Rican populations was expected.

The increased-activity CYP2C19*17 allele frequency of the Afro-Caribbean population is consistent with its high frequency in the West African Gambia population (23.0 %) (Janha et al., 2014), which is in accordance to the predominant Western African origin of the African diaspora to the Americas (Madrigal, 2006). The ascertainment of CYP2C19 gUMs by genotyping of the CYP2C19*17 allele has only been performed in other two Latin American admixed populations from Brazil and Ecuador (26.8 and 41.4 %, respectively) (Santos et al., 2011; Vicente et al., 2014), and both frequencies are higher than that of the Costa Rican admixed population (17.7 %; P<0.05). This result suggest that Costa Rican populations are less susceptible to therapeutic failure or adverse reactions in therapies based on drugs metabolized by CYP2C19, such as omeprazole and clopidogrel.

A correlation among CYP2D6*5, *17 and *29 alleles with ancestry was also found in this study, consistently with higher frequencies of *17 and *29 in African populations (Llerena et al., 2014b). The null-activity CYP2D6*4 allele is associated to European ancestry (Llerena et al., 2014b), and is supposed to be a marker of this ancestry. However, in our multiethnic sample of individuals, the CYP2D6*4 allele is also present in 23 individuals with more than 30 % of Native American ancestry and less than 60 % of European ancestry. Furthermore, the highest frequencies of CYP2D6*4 worldwide are in the Chibchan groups (e.g. Bari from Venezuela - 42.5 % - and Bribri and Cabécar from Costa Rica - 31.9 and 26.8 %, respectively) (Céspedes-Garro et al., 2014a; Céspedes-Garro et al., 2014b). Altogether, our results suggest that the *4 allele may be also common in Native American populations.

A limitation of this study is the low number of individuals in some of the populations, mainly Amerindians. However, considering that Amerindians are under-represented in pharmacogenetics surveys, important information is provided. Another limitation, shared with most pharmacogenetics studies, is that we genotyped specific SNPs that define specific alleles (haplotypes) and classified as wild type (CYP2C9*1 or CYP2C19*1) the individuals that do not carry these alleles. However, it is unknown if populations that are under-represented in pharmacogenetics studies, such as Native Americans, may present variants that were not genotyped, or that were even unknown and that may alter enzymatic activity. Thus, further studies assessing the CYP2C9 and CYP2C19 sequence in an unbiased fashion, preferentially by sequencing these genes, would be necessary.

ACKNOWLEDGMENTS

CCG was supported by a fellowship of the University of Costa Rica in the PhD program of the University of Extremadura. The study is part of the Research Program entitled “Genética, Ecología y Salud en los Amerindios de Costa Rica” (N°742-93-903) and the project N° 742-90-416 of the University of Costa Rica. The research was supported by a grant from Junta de Extremadura, Cooperación Extremena AEXCID 13IA001. ET-S and FRS were supported by the CAPES Agency of the Brazilian Ministry of Education. The project was coordinated in the CEIBA.FP Consortium of the
Relevancia de la ancestría para la variabilidad de polimorfismos de las enzimas metabolizadoras de fármacos CYP2C9, CYP2C19 y CYP2D6 en una población multiétnica de Costa Rica. CYP2C9, CYP2C19 y CYP2D6 metabolizan aproximadamente el 40 % de los fármacos y los genes que las codifican varían en las distintas poblaciones humanas. La población costarricense posee ancestria trihíbrida y su posición geográfica estratégica la convierten en un escenario idóneo para evaluar la variabilidad interétnica en sus poblaciones multiétnicas. El presente estudio tiene como objetivo describir la diversidad de polimorfismos CYP2C9, CYP2C19 y CYP2D6 en las poblaciones costarricenses en el contexto de su ancestría. Un total de 448 individuos sanos fueron incluidos: Bribri (n= 47), Cabécar (n = 27), Maleku (n= 16), Guaymi (n= 30), Huetar (n = 48), Chorotega (n = 41), mestizos del Valle Central y Guanacaste (n = 189) y afrocaribeños de Limón (n= 50). Los genotipos CYP2C9 (alelos *2, *3, *6) y CYP2C19 (*2, *3, *4, *5 y *17) fueron determinados mediante PCR tiempo real. Las ancestrías africana, europea y nativa americana fueron inferidas usando 87 marcadores informativos de ancestria. La frecuencia del alelo de actividad disminuida CYP2C9*2 fue menor en los grupos autodefinidos de amerindios que en la población mestiza y las frecuencias más altas de CYP2C19*2 (actividad nula) y CYP2C19*17 (actividad incrementada) se encontraron en la población autodefinida afrocaribeña. Asimismo, se encontró una frecuencia de gPMs CYP2C9 de 0.7 % en la población mestiza y una frecuencia variable de gUMs CYP2C19 (0.0 a 32.6 %, más prevalente en afrocaribeños) en las poblaciones costarricenses. Por último, los siguientes alelos fueron positivamente correlacionados con la ancestria africana y negativamente con la ancestoría nativa americana: CYP2D6*5 (actividad nula), CYP2D6*17, CYP2D6*29 (ambos de actividad disminuida) y CYP2C19*17 (actividad incrementada). No se encontró correlación entre los polimorfismos CYP2C9 y la ancestria. Se requieren estudios posteriores que evalúen la secuencia de CYP2C9 y CYP2C19 en estas poblaciones, preferiblemente mediante la secuenciación de estos genes.

**Palabras clave:** CYP2C9, CYP2C19, CYP2D6, Costa Rica, amerindios, afrocaribeños, ancestría genética.

**REFERENCES**


Distribution of CYP2D6 and CYP2C19 polymorphisms associated with poor metabolizer phenotype in five Amerindian groups and western Mestizos from Mexico. *Genetic Testing and Molecular Markers*, 16(9), 1098-1104.


