CYP2D6 gene polymorphisms and predicted phenotypes in eight indigenous groups from northwestern Mexico

Aim: Polymorphisms in *CYP2D6* impact the interindividual and interethnic variability of drug efficiency; therefore, we determined the *CYP2D6* allele distribution in eight Amerindian groups from northwestern Mexico and compared them with the frequencies in Mexican Mestizos. **Materials & methods:** A total of 508 Amerindians were studied. Genotyping of *CYP2D6*5* and multiplication alleles was performed by long-range PCR, while *CYP2D6*2*, **3*, **4*, **6*, **10*, **17*, **29*, **35*, **41* and copy number were evaluated by real-time PCR. **Results:** The most frequent alleles were *CYP2D6*2* (0.05–0.28), *CYP2D6*4* (0.003–0.21) and multiplications (0.043–0.107). *CYP2D6*5*, **6*, **10* and **41* were not observed in the majority of Amerindians, and *CYP2D6*3*, **17*, **35* and **29* were not detected. The poor metabolizer genotype (**4/*5*) was lower (0.2%) in Amerindians than in Mestizos (5%); conversely, the ultrarapid metabolizer genotype was higher (12.6%) in indigenous groups than in Mestizos (7%). **Conclusion:** Our data show a lower frequency of *CYP2D6* inactive alleles and a higher frequency of duplication/multiplication of *CYP2D6* active alleles in indigenous populations that in Mestizos.

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KEYWORDS: allele frequency ■ *CYP2D6* polymorphism ■ Mexican indigenous ■ pharmacogenetics ■ predicted phenotype

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CYP2D6 is an important member of the CYP450 family and is involved in the metabolism of many widely used drugs, including antidepressants, antipsychotics, antiarrhythmics, antiemetics, β-adrenoceptor antagonists (β-blockers) and opioids, which represent approximately 25% of all drugs metabolized by CYP450s [1–3]. In addition to the role of *CYP2D6* genetic polymorphisms in drug metabolism, their potential implication in the risk for certain diseases (i.e., psychiatric disorders and cancer) has been discussed [4,5].

The *CYP2D6* gene, located on chromosome 22q13.1, is highly polymorphic, with over 100 allelic variants identified to date [101]. Some of these alleles are associated with increased, decreased or absence of enzyme activity [6]. Among the alleles of *CYP2D6* that exhibit normal or increased activity are **1*, **2*, **35*, **1xN* and **2xN;* those with decreased activity are **10*, **17*, **29* and **41*. Furthermore, **3*, **4*, **5* and **6* are inactive [3]. All of the above alleles are of clinical relevance, as they often cause adverse drug effects or lack of drug effect in standard doses. Genotyping for the most frequent *CYP2D6* alleles in different populations can predict poor, extensive and ultrarapid metabolic phenotypes with some accuracy [7–10]. The most frequent nonfunctional alleles for Caucasians are *CYP2D6*4*, **5* and **3* and account for 95% of poor metabolizers (PMs) [11]. The ultrarapid metabolizer (UM) phenotype is found in 1–2% of Swedish Caucasians [12] and 29% of Ethiopians [13] with more than two functional copies of the gene.

Mexico is a country with high ethnic diversity. Currently, there are 68 Amerindian tribes representing 7% of the Mexican population [102]. These groups have particular social, cultural and genetic backgrounds that differ from the rest of the Mexican Mestizos (~93% of the total population). Therefore, it is predictable that Amerindian groups have a distinct drug response from populations with other genetic backgrounds.

CYP2D6 gene polymorphisms have been widely studied in several ethnic groups; however, they are less well known in the indigenous population. Until now the polymorphisms **2* (20%), **3* (0%), **4* (0.6%), **5* (0.5%), **6* (0%), **10* (0%), **35* (0%), **41* (1.0%) and duplications (1.0%) of *CYP2D6* have been evaluated in indigenous Tepehuanos from Durango (northwest, Mexico) [9]. The PM phenotype was absent in this Amerindian group when tested with dextromethorphan [14]. In addition, only *CYP2D6*4* was also detected in five Mexican Amerindian groups: Tarahumaras (north),

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Purépechas (center), Tojolabales, Tzotziles and Tzeltales (southeast) (range: 1.2–7.3%) [15]. Recently, 14 novel variants were identified in Mexican Mestizos, including *CYP2D6*82*, which was hypothesized to be Amerindian origin because its identification in three Mexican Amerindian groups, Mixtecos (5%), Tepehuanos (3.3%) and Mayas (1.67%) [16]. A predicted CYP2D6 PM phenotype was lacking in the Mexican Amerindian population, while the frequency in Mexican Mestizos is 2–3.6% [14,15,17]. Little is known about the genetic variation of *CYP2D6* in indigenous populations northernmost from Mexico, which shows larger genetic distances from the rest of the Mexican populations [18]. Therefore, the aim of this work was to determine the allelic variants of *CYP2D6* and the predicted phenotype in indigenous populations from northwest Mexico. This study will allow for the generation of pharmacological therapy strategies adapted to the indigenous populations of Mexico.

Materials & methods

Subjects

A total of 508 unrelated individuals belonging to eight different indigenous groups of northwest Mexico were studied. The sample included 129 Tepehuanos, 107 Huicholes and 39 Mexicaneros from the state of Durango; 74 Tarahumaras from the state of Chihuahua; 81 Coras from the state of Nayarit; and 19 Seris, 15 Guarijíos and 44 Mayos from the state of Sonora. Individuals identified themselves as belonging to an ethnic group by stating that their grandparents, their parents and they themselves belonged to that ethnic group. Moreover, Amerindian ancestry was confirmed in all the groups studied, through the analysis of 15 short tandem repeats loci [19].

The research was authorized by the ethics committee of the Durango General Hospital of the Mexican Health Ministry (year 2007). All subjects signed an authorized informed consent form. TABLE 1 shows general characteristics of the studied groups.

Genotyping

For genotyping, the CEIBA.FP Consortium methodology was followed [20]. All biological samples were taken from volunteers in the respective communities. A total of 5 ml of peripheral blood was drawn in a tube with EDTA, and DNA was extracted using the QIAamp® DNA blood kit (Qiagen, Hilden, Germany) and evaluated for integrity and concentration through 1% agarose electrophoresis and spectrophotometry.

To detect the presence of allelic variants harboring a *CYP2D6*5* gene deletion or gene duplication, long-range PCR was performed as previously described [21,22]. Subjects positive for a duplication were further characterized for gene copy number. Genotype analysis for the *CYP2D6*2, *3, *4, *6, *10, *17, *29, *35, *41* and *CYP2D6* copy number variants was performed by quantitative real-time PCR using TaqMan® assays in a StepOne™ system (Applied Biosystems, CA, USA). PCR amplification for all SNPs was performed in a 20 µl final volume with 20 ng of template DNA, 1X TaqMan genotyping Master Mix (Applied Biosystems), 1X-specific TaqMan probe and water. Thermal cycling conditions were as follows: initial denaturation step of 10 min at 95°C followed by 40 cycles of denaturation at 92°C for 15 s and annealing at 60°C for 1 min. The identification of genotypes was carried out using allelic discrimination software (Applied Biosystems). The TaqMan probes used to recognize the *CYP2D6*2, *3, *4, *6, *10, *17, *29, *35, *41* and *CYP2D6* copy number variants were C_32407252_30, C_32407232_50, C_27102431_D0, C_32407243_20, C_11484460_40, C_2222771_40, C_34816113_20, C_34816116_20, C_27102444_80 and Hs00010001_cn, respectively (specifically targets *CYP2D6* exon 9 sequences and will not amplify *CYP2D7* or *CYP2D8* pseudogenes, or *CYP2D6* alleles having *CYP2D7* sequences in exon 9, e.g., *CYP2D6*36*).

The results of the allelic variants of *CYP2D6* were compared with a Mestizo population previously studied [9].

Data analysis

Hardy–Weinberg equilibrium was determined by comparing the genotype frequencies with the expected values using a contingency table χ^2 statistic with Yates's correction. The allele and genotype frequencies were compared with χ^2 and Fisher's exact tests. Phenotype prediction from genotype was evaluated using the activity score [23]. A value of 1 was assigned to reference alleles *CYP2D6 *1, *2* and **35*; a value of 0 to *CYP2D6*3, *4, *5* and **6*; a value of 0.5 to *CYP2D6*10, *17, *29* and **41;* and a value of 2 to multiplications of active *CYP2D6* alleles (**1×N* or **2×N*). The predictive phenotype was based on considering the individual activity score: subjects with activity score values of 0.5 or 1.0 were defined as intermediate metabolizers (IMs), which predicts considerably larger numbers of IMs than were actually observed by

Table 1. General characteristics of the studied Amerindians.

Groups	n	Age† (years)	Gender (%)		BMI† (kg/m²)	Ancestry‡ (%)
			Women	*Men*		
Mexicaneros	39	40.94 ± 12.53	64.1	35.9	24.74 ± 4.14	94.50
Tepehuanos	129	36.65 ± 13.45	66.1	33.9	22.21 ± 3.31	96.40
Huicholes	107	40.06 ± 16.55	60.8	39.2	22.32 ± 5.62	96.30
Coras	81	42.22 ± 21.42	64.5	35.5	25.64 ± 5.25	93.90
Guarijíos	15	57.4 ± 14.28	73.3	26.7	27.16 ± 6.72	81.60
Seris	19	53.84 ± 14.98	73.7	26.3	26.34 ± 5.11	88.00
Mayos	44	46.53 ± 17.44	74.4	25.6	27.96 ± 4.08	65.60
Tarahumaras	74	43.53 ± 13.10	67.6	32.4	24.03 ± 4.54	92.10

†*Information is expressed as average ± standard deviation.*
‡*Amerindian ancestry* [19].

phenotyping [23]; participants with values of 1.5 or 2.0 were considered as extensive metabolizers (EMs), subjects with an activity score of 0 were considered PMs, and individuals with activity scores >2 were classified as UMs. Statistical analyses were carried out using Sigma Plot v11 software (Systat Software, IL, USA).

Results

Allele frequencies

General characteristics of the Amerindians groups are summarized in Table 1. *CYP2D6* allele frequencies for all the Amerindian populations included in the study are reported in Table 2.

The allele frequencies of *CYP2D6*4* showed a wide variability between the studied Amerindian groups (range: 0–21%). Figure 1 shows a comparison of *CYP2D6*4* alleles between our studied populations, other Amerindians groups, Mexican Mestizos, Spaniards, Asians and Africans. The frequency of this allele was similar (~14%) between Mestizos from different states of Mexico and showed high variability among different indigenous groups. The Tepehuanos showed the lowest *CYP2D6*4* frequency (0.385%), similar to that reported in Asians [24], and the frequency in Coras was similar to that reported in Tojolabales from Chiapas, Mexico [15].

The Guarijío group had a similar *CYP2D6*4* allele frequency (3.3%) to the ones reported for Tzotziles of Chiapas, Mexico (2.7%) and Purépechas of Michoacán, Mexico (2.9%) [15] and a lower frequency than reported for Mapuches from Chile (3.6%) [25] and Tzeltales from Chiapas (5.3%) [15].

In our study, the frequency of *CYP2D6*4* in the Tarahumara and Tepehuano groups (10.1 and 0.385%, respectively) was different than previously reported for these groups (7.3 and 0.6%, respectively) [9,15].

The frequency of *CYP2D6*4* in the Mayo group (7.95%) was similar to that reported previously in the Canadian Inuit population (6.7–8.3%) [26]. The Seri group presented the highest frequency of this allele (21%), similar to that reported previously in Spaniards (18.5%) [22].

Genotype frequencies

CYP2D6 allele and genotype frequencies were in Hardy–Weinberg equilibrium for all the studied populations. Genotype frequencies, activity score and predictive phenotype in the Amerindian populations and a previously studied Mexican Mestizo group [9] are displayed in Table 3. The second most frequent genotype after **1/*1* was **1/*2*, with the highest value in the Cora population (35.8%). The predictive EM phenotype was more frequent in the Tepehuanos, Coras and Mexicaneros (range: 82.06–93.07%), and only the first two groups showed a higher EM phenotype frequency than the Mexican Mestizos ($p < 0.001$ and $p = 0.014$, respectively; Table 3). The predictive IM phenotype was significant between Mestizos and Mexicaneros, Seris, Tepehuanos and Tarahumaras (p-values <0.001–0.043). The predictive UM phenotype was more frequent in the Amerindian groups (except the Tepehuano group) than in Mexican Mestizos, but only the Huichol group displayed a statistically significant difference when compared with the Mestizos ($p = 0.009$). The Tarahumara group was the only Amerindian group that presented the predictive PM phenotype (**4/*5* genotype), with a frequency of 1.35%. No significant difference was found between the estimated frequencies of EM, IM and UM among Mexican Mestizos and the Amerindians; however, the frequency of the PM phenotype was statistically higher in

Table 2. *CYP2D6* allele frequencies among Mexican–Amerindian populations.

CYP2D6 alleles	Mexicaneros (n = 39)	Seris (n = 19)	Guarijíos (n = 15)	Tepehuanos (n = 129)	Mayos (n = 44)	Huicholes (n = 107)	Tarahumaras (n = 74)	Coras (n = 81)
**1*	0.697	0.69	0.64	0.739	0.67	0.61	0.523	0.648
**2*	0.22	0.05	0.23	0.2	0.1	0.21	0.21	0.28
**4*	0	0.21	0.03	0.003	0.08	0.07	0.115	0.01
**5*	0.013	0	0	0.004	0	0	0.034	0.012
**6*	0	0	0	0	0.03	0	0	0
**10*	0	0	0	0	0	0	0.007	0
**3*, **17*, **35* and **29*	0	0	0	0†	0	0	0	0
**41*	0	0	0	0.004	0.03	0	0.041	0.01
Multifunctional alleles	0.077	0.053	0.1	0.054	0.09	0.107	0.067	0.043

†CYP2D6*29 *nonevaluated for this ethnic group.*

the Mexican Mestizos that in the Amerindians ($p < 0.001$).

Discussion

Our results demonstrate a low frequency (<1%) of indigenous subjects with the PM genotype, in contrast to that observed in Mexican Mestizos (5%; $p < 0.001$); these data are consistent with the absence of PMs described in Cunas and Tepehuanos. Instead, the UM genotype was more frequent in indigenous populations (12.6%) than in Mestizos (7%). The PM genotype was identified only in the Tarahumara group, while the UM genotype was observed in all indigenous groups with considerable variation.

The low allelic diversity found in most of the studied ethnic groups could be masked because the small population sample of some of them (Guarijíos, Mayos and Seris), which is explained by the low response rate in these isolated communities, and the missing evaluation of the variant *CYP2D6*82* recently described in Mexican Amerindians [16].

We identified a low frequency of nonfunctional *CYP2D6* alleles in the indigenous groups studied, with the exception of the *CYP2D6*4* allele, which was found with a relatively high frequency in Seris (21.05%), similar to that in the Ngawbe (17.1%) and Embera (14.0%) groups of Panama and Colombia, Mexican Mestizos (13.1–11.2%), and other indigenous groups from Mexico (1.2%–7.3%) Supplementary Table 1 (see www.future-medicine.com/doi/suppl/10.2217/pgs.13.203) [9,10,15–17,25–33]. The *CYP2D6*4* allele is of clinical significance and often causes altered drug clearance and drug response accounting for 97% of all the PM phenotypes in Caucasians [11]. The inactive *CYP2D6*3* allele was detected in neither of these groups nor in other Amerindians [15,25–27,30] and is present at low frequencies in Asians and other studied populations [11].

The variant *CYP2D6*5* was detected in four of the eight Amerindian groups studied (Tarahumara, Cora, Tepehuano and Mexicanero) with a frequency similar to that reported in Mexican Mestizos (2.7–13.0%) [9,16,17]

The *CYP2D6*6* allele is mainly observed in the Caucasian population (0.4–1.4%) [34] and was not expected to be found in this study, however it was observed in only one Mayo subject, which leads to questions about its pure indigenous ancestry. This is in agreement with a previous study intended to evaluate the ancestry component of these indigenous groups, revealing a higher proportion of European alleles in the Mayo population [19].

*CYP2D6*10* is an allele associated with decreased enzyme activity; it was found in only one Tarahumara subject (0.7%) in this study. This is in agreement with the data reported by Salazar-Flores *et al.*, who did not detect this allele in the five Mexican indigenous populations they studied [15]. By contrast, this allele has been reported at varying frequencies in the indigenous populations of Argentina, Paraguay, Venezuela, Chile, Colombia and Canada (Supplementary Table 1) [25–27,31], with frequencies exceeding 50% in Asian populations [24].

Previous studies showed the presence of the *CYP2D6*35* allele in Caucasian populations with a frequency of 7.4% [35]. This allele has been found in Mexico with a frequency of 4.1% in Mestizo populations from the northwest [9,16,17]. We did not observe such alleles in any of the indigenous populations analyzed which makes them potentially useful markers for identifying Caucasian ancestry.

The range of frequencies of multiplications of functional alleles fluctuated between 4.3–10.7%

in the studied groups, which is similar to those reported in Mexican Mestizos (4.1–12.8%) [17].

Homozygosity for inactive alleles **4/*5* was found in only one Tarahumara subject (1.35%); a frequency similar to that reported in Japanese people (1%) [36] but lower than that reported for Embera (2.2%), Ngawbe (4.4%), Canadian Inuits (3.3%) [26] and Mexican Mestizos (6.8–10%) [14,17] populations. IMs are phenotypically tough to discriminate and are defined by the presence of genotypes with reduced function alleles. The high frequency observed in Seris (41.2%) and Mayos (22.7%) of such alleles is consistent with that observed in Asian (50%) [36,37] and indigenous populations of Venezuela (35%) [30]. The high frequency of IMs among the Seris and Mayos makes them more susceptible to presenting adverse events when they are medicated with CYP2D6 substrates, as has been reported in psychiatric patients with the PM or IM phenotype [38]. Moreover, several antiarrhythmic drugs, including metoprolol, timolol, propafenone and others, are metabolically inactivated by CYP2D6, leading to increased exposure and risk of adverse events for PMs and IMs [39–41]. CYP2D6 is involved in the metabolism of the parent drug into active metabolites (i.e., risperidone to 9-hydroxyrisperidone [42] or thioridazine to mesoridazine [43]); therefore, PMs might experience decreased activity of the active metabolite and a potential higher risk of drug–drug interactions [44].

The frequency of genotypes with duplication/multiplication of active *CYP2D6* alleles in Tepehuano subjects was the closest to those reported in Mexican Mestizos (7%) and white European populations (3–5%) [41] but higher than those for South American and Amerindian populations (0–1%) [9,10,32,45].

The likely cause for the gain of active genes in these indigenous populations is natural selection.

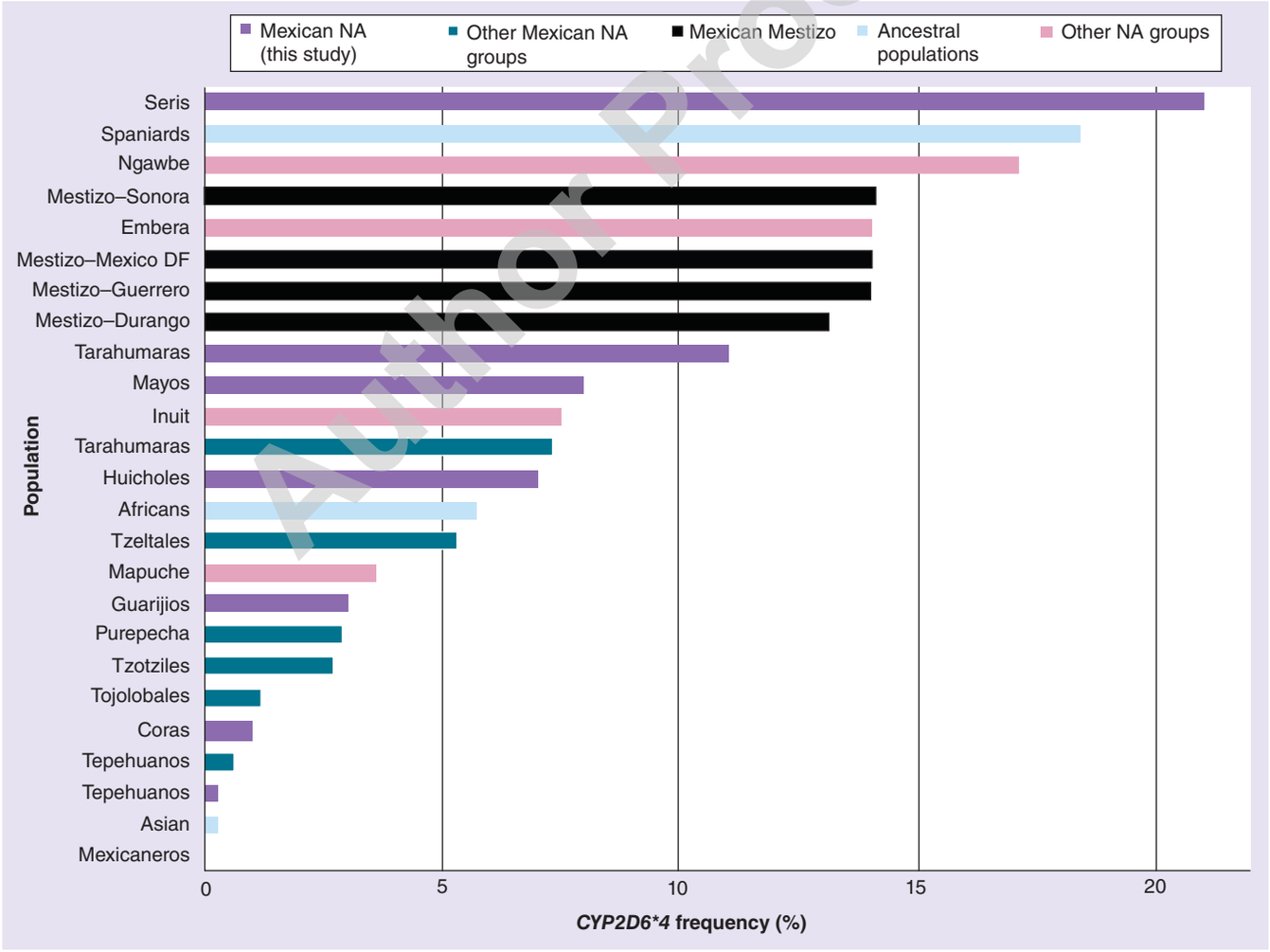

Figure 1. *CYP2D6*4* allele frequencies (%) in ancestral populations, Amerindian groups and Mestizos from Mexico.
DF: Distrito Federal; NA: Native Amerindians.
Data taken from [9,15,16,22,24–27].

Table 3. *CYP2D6* genotype frequencies (%) in Amerindian studied groups from Mexico and one group of Mestizos† previewed reported.

CYP2D6 genotype	Mexicaneros (n = 39)	Seris (n = 19)	Guarijíos (n = 15)	Tepehuanos (n = 129)	Mayos (n = 44)	Huicholes (n = 107)	Tarahumaras (n = 74)	Coras (n = 81)	Amerindians total (n = 508)	Mestizos† (n = 100)	Activity score	Predicted phenotype
**3/*4*	0	0	0	0	0	0	0	0	0	1	0	PM
**4/*4*	0	0	0	0	0	0	0		0	3	0	
**4/*5*	0	0	0	0	0	0	1.35	0	0.197	1	0	
Total	0	0	0	0	0	0	1.35	0	**0.197**‡	5		
**1/*4*	0	31.58	0	0.77	13.64	11.21	17.57	1.235	7.68	10	1	IM
**1/*5*	2.56	0	0	0.77	0	0	2.7	1.235	0.98	1	1	
**1/*6*	0	0	0	0	6.82	0	0	0	0.59	0	1	
**2/*4*	0	10.52	6.67	0	0	3.74	1.35	1.235	1.77	1	1	
**2/*5*	0	0	0	0	0	0	2.7	1.235	0.59	1	1	
**3/*41*	0	0	0	0	0	0	0	0	0	1	0.5	
**4/*10*	0	0	0	0	0	0	0	0	0	1	0.5	
**4/*41*	0	0	0	0	2.27	0	0	0	0.197	1	0.5	
**10/*10*	0	0	0	0	0	0	0	0	0	1	1	
**41/*41*	0	0	0	0	0	0	1.35	0	0.197	1	1	
Total	**2.56**§	**42.1**¶	6.67	**1.54**‡	22.73	14.95	25.67	**4.94**#	12.01	18		
**1/*1*	56.42	47.38	53.33	64.61	40.91	38.32	33.78	43.21	47.44	39	2	EM
**1/*2*	20.51	0	20	22.31	13.64	19.63	17.57	35.8	21.46	15	2	
**1/*10*	0	0	0	0	0	0	1 .35	0	0.197	1	1.5	
**1/*35*	0	0	0	0	0	0	0	0	0	7	2	
**1/*41*	0	0	0	0	2.27	0	5.4	2.47	1.38	2	1.5	
**2/*2*	5.13	0	0	5.38	0	5.61	2.7	4.94	3.94	2	2	
**2/*10*	0	0	0	0	0	0	0	0	0	1	1.5	
**2/*41*	0	0	0	0.77	2.27	0	0	0	0.39	0	1.5	
**35/*41*	0	0	0	0	0	0	0	0	0	1	1.5	
**1XN/*4*	0	0	0	0	0	0	0	0	0	1	2	
**2XN/*5*	0	0	0	0	0	0.93	1.35	0	0.39	1	2	
Total	82.06	47.38	73.33	**93.07**‡	59.09	64.49	62.15	**86.42**#	75.2	70		

Total = ∑ of frequencies.
†Data taken from [9].
Values in bold indicate statistical differences for the comparisons of Mexican Mestizo and ethnic group's proportions. p-values for these significant differences were ‡p < 0.001, §p = 0.035, ¶p = 0.043 #p = 0.014 and ††p = 0.009, respectively.
EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer; UM: Ultrarapid metabolizer.

Table 3. *CYP2D6* genotype frequencies (%) in Amerindian studied groups from Mexico and one group of Mestizos† previewed reported (cont).

CYP2D6 genotype	Mexicaneros (n = 39)	Seris (n = 19)	Guarijíos (n = 15)	Tepehuanos (n = 129)	Mayos (n = 44)	Huicholes (n = 107)	Tarahumaras (n = 74)	Coras (n = 81)	Amerindians total (n = 508)	Mestizos† (n = 100)	Activity score	Predicted phenotype
**1xN/*1*	5.13	10.52	0	1.54	13.64	14.95	4.05	3.7	6.69	2	3	UM
**1xN/*2*	7.69	0	20	1.54	4.54	4.67	5.4	2.47	4.13	3	3	
**2XN/*2*	2.56	0	0	2.31	0	0.94	2.7	2.47	1.77	2	3	
Total	15.38	10.52	20	5.39	18.18	**20.56**††	12.15	8.64	12.6	7		

Total = ∑ of frequencies.
†Data taken from [9].
Values in bold indicate statistical differences for the comparisons of Mexican Mestizo and ethnic group's proportions. p-values for these significant differences were ‡p < 0.001, §p = 0.035, ¶p = 0.043 #p = 0.014 and ††p = 0.009, respectively.
EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer; UM: Ultrarapid metabolizer.

Environmental factors, such as diet, could have exerted a selective advantage on duplicated *CYP2D6* genes, increasing the survival rates of these individuals. It is believed that a similar phenomenon has occurred in Ethiopia and in Saudi Arabia [1], where the highest frequency of multiple *CYP2D6* active genes has been described [13,45]. In the indigenous populations, living conditions of extreme poverty have prevailed for generations, which have resulted in the restriction of food and inadequate caloric intake. This led to the search for alternative sources of food, such as some plant species. Therefore, long periods of starvation could exert a selection pressure, favoring the survival of subjects with the ability to detoxify plants toxins. The basis of this selection would be the ability of CYP2D6 to detoxify alkaloids [46].

One of the most commonly duplicated and multiplied *CYP2D6* active alleles is *CYP2D6*2*, which is the most frequent in the populations studied (5.26–26.5%). This isoform of the enzyme is likely to have more affinity towards certain plant products that have been traditionally consumed for many years by some Mexican indigenous groups.

Subjects with multiple active *CYP2D6* copies metabolize drugs more rapidly; therefore, the therapeutic effect of a drug at standard doses is not achieved. These individuals also may develop adverse reactions due to the formation of 10- to 30-fold higher amounts of metabolites [47]. Marked decreased drug concentrations have been observed in UMs with drugs such as tramadol [48], venlafaxine [49], morphine [50] and mirtazapine [51]. Additionally, the role of CYP2D6 in personality has been demonstrated in Latino Americans from Cuba, as analyzed with the Karolinska Scale of Personality [52,53], and a higher frequency of suicide attempts among UMs has been reported [54,55].

Conclusion

This study demonstrates a low frequency of inactive *CYP2D6* alleles in indigenous populations and a higher frequency of duplication/multiplication of active *CYP2D6* alleles than in Mexican Mestizos. The information obtained may be useful for generating drug therapy strategies aimed at the indigenous populations of Mexico.

Future perspective

CYP2D6 genotyping can partially predict enzyme activity; hence, the results obtained in the present work will complement further studies evaluating the relationship between genotype and phenotype (pharmacologic response)

in indigenous populations. The observed CYP450-mediated metabolism response also considers the effects of different ethnic and cultural factors. The knowledge of the pharmacogenetic characteristics in Mexican Amerindian groups will be relevant for the implementation of therapeutic strategies focused on indigenous populations.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- CYP2D6 is an important member of the CYP450 family; it is involved in the metabolism of many widely used clinical drugs.
- Genetic polymorphisms of the CYP2D6 enzyme can produce deep changes in enzyme activity, thus determining the individual response to a certain drug through poor, intermediate, extensive or ultrarapid metabolizer phenotypes.
- In this work, we determined the allelic variants of *CYP2D6* and the predicted phenotype in eight indigenous groups from northwest Mexico and compared them with Mexican Mestizos.

Results

- The *CYP2D6*1* wild-type was predominant in the groups studied. The more frequent allele variants were *CYP2D6*2* (range: 5–28%), *CYP2D6*4* (range: 1.0–21.0%) and multiplication of functional alleles (range: 4.3–10.7%).
- The *CYP2D6*3*, **17*, **35* and **29* variants were not detected in the Amerindian groups studied.
- Homozygosity for two inactive alleles, and thus a poor metabolizer phenotype, was detected in only one Tarahumara subject, and the **1xN/*1*, **1xN/*2* and **2xN/*2* genotypes (phenotypically ultrarapid metabolizers) were very frequent in the groups studied (5.5–20.5%).

Conclusion

- The present data show a low frequency of inactive alleles of *CYP2D6* and a higher frequency of duplication/multiplication of *CYP2D6* active alleles in indigenous populations compared with Mexican Mestizos.
- Our results support the idea that ethnic variability must be considered in pharmacological treatment, especially for drugs metabolized by CYP2D6 and/or with a narrow safety range.

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