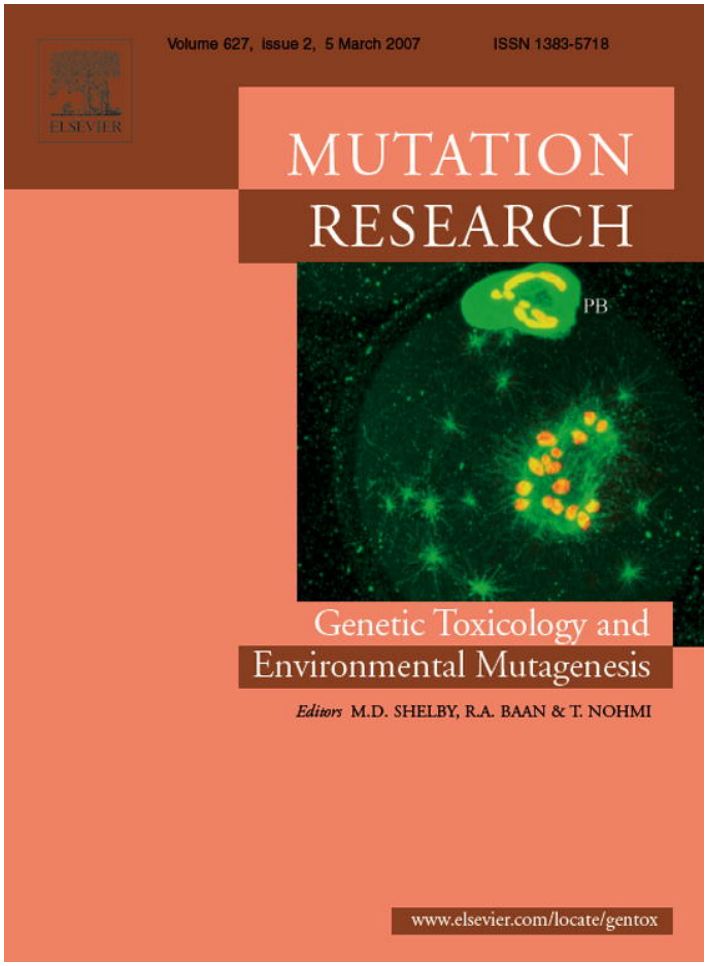

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Allele and genotype frequencies of metabolic genes in Native Americans from Argentina and Paraguay

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Abstract

Interethnic differences in the allele frequencies of CYP2D6, NAT2, GSTM1 and GSTT1 deletions have been documented for Caucasians, Asians, and Africans population. On the other hand, data on Amerindians are scanty and limited to a few populations from southern areas of South America. In this report we analyze the frequencies of 11 allele variants of CYP2D6 and 4 allele variants of NAT2 genes, and the frequency of GSTM1 and GSTT1 homozygous deleted genotypes in a sample of 90 donors representing 8 Native American populations from Argentina and Paraguay, identified as Amerindians on the basis of their geographic location, genealogical data, mitochondrial- and Y-chromosome DNA markers. For CYP2D6, 88.6% of the total allele frequency corresponded to *1, *2, *4 and *10 variants. Average frequencies for NAT2 *4, *5, *6 and *7 alleles were 51.2%, 25%, 6.1%, and 20.1%, respectively. GSTM1 deletion ranged from 20% to 66%, while GSTT1 deletion was present in four populations in less than 50%. We assume that CYP2D6 *2, *4, *10, *14; NAT2 *5, *7 alleles and GSTM1 and GSTT1 *0/*0 genotypes are founder variants brought to America by the first Asian settlers.

Keywords: CYP2D6 (MeSH ID D019389); *N*-Acetyltransferase 2; Human (MeSH ID C478900); Glutathione *S*-transferase M1 (MeSH ID C117740); GST theta 1 (MeSH ID C413545); American Native Continental Ancestry Group (MeSH ID D044467)

1. Introduction

Most drug-metabolizing enzyme genes show clinically relevant polymorphisms influencing the efficiency of phase I (modification of drug functional groups) or phase II (drug conjugation with endogenous moiety) reactions. *CYP2D6* gene has a role in phase I metabolism for more than 25% drugs [1], while *NAT2*, *GSTM1* and *GSTT1* gene products modulate phase II detoxification stages. Mutations or deletions of these genes give rise to alleles and eventually to genotypes with decreased or null gene expression. Since the therapeutic effectiveness, adverse effects, and carcinogenic potential of many drugs and environmental pollutants are associated with *CYP2D6*, *NAT2*, *GSTM1*, and *GSTT1* activity, the

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genotype characterization for these gene systems is of high clinical significance.

Interethnic differences in allele frequencies of *CYP2D6*, *NAT2*, *GSTM1* and *GSTT1* deletions are documented for Europeans, Asians, and Africans (see reviews in [2,3]). However, data on Native Americans are scanty and limited to a few populations. In this report we analyze the frequencies of 11 allele variants of *CYP2D6* gene, 4 allele variants of *NAT2*, and *GSTM1* and *GSTT1* homozygous deleted genotypes in a sample of donors representing 8 Native American populations from Argentina and Paraguay, identified as Amerindians on the basis of their geographic location, genealogical data, mitochondrial- and Y-chromosome DNA markers.

2. Material and methods

We analyzed 90 samples from Argentine and Paraguayan Native American populations with low level of endogamy and gene admixture. Donors in our series belonged to populations from geographic regions traditionally inhabited by Amerindian tribes. Genealogical records of each donor indicated Amerindian ancestry and lack of familial relationship with other donors from the same population. Biological samples, genealogical data and informed consents were obtained by Physical and Social Anthropologists that since long ago cohabit and work during different annual periods with the populations analyzed in this report. Biological samples were coded and submitted in anonymity for DNA testing. All cases showed a mitochondrial DNA haplogroup corresponding to one of the seven most frequent Amerindian-specific maternal lineages reported in Bailliet et al. [4]. Sixty-seven out of the 76 Y chromosomes analyzed showed the M3 T variant, characteristic of Native American paternal lineages [5]. A panel of seven Y-specific microsatellites (DYS19, DYS389a and b, DYS390, 391, 392, and 393) [5] allowed us to characterize the Y haplotypes. We found that each Amerindian Y chromosome corresponded to a different paternal lineage, indicating low endogamy for the donors included in our series. Argentine populations and individuals tested were: 18 individuals from Jujuy province (Andean region); 20 Wichi, 4 Chorote, and 7 Toba from Salta province (Gran Chaco region); 5 Mapuche from Río Negro province; and 8 Tehuelche from Chubut province (Patagonian region). The Paraguayan sample included 12 Ayoreo and 16 Lengua from Southern Paraguay (Gran Chaco region).

We identified *CYP2D6* alleles *1, *2, *3, *4, *6, *8, *10, *12, *14, and *15 using the nested PCR method [6] with a minor modification consisting in the use of *Hha*I restriction for the identification of the C2938T mutation; the wild allele has the site which generates two restriction fragments of 257 and 128 bp, while the C → T transition obliterates the *Hha*I site producing an unrestricted fragment of 385 bp. We testified the homozygous deletion of *CYP2D6*, *5 allele according to Nelson et al. [8]. For *CYP2D6* we use the nomenclature and gene metabolic activity indicated in http://www.imm.ki.se/CYPalleles/. *NAT2* *4, *5, *6, *7 alleles (nomenclature system indicated in http://www.louisville.edu/medschool/pharmacology/NAT.html) and *GSTM1* null form were detected as reported by Hou et al. [7]. The null form of *GSTT1* was determined according to Nelson et al. [8].

Allele frequencies were estimated by gene counting in 90 samples. We were able to typify complete genotypes in 84 individuals for *CYP2D6* and *NAT2*, 88 for *GSTM1*, and 79 for *GSTT1*. Statistical analyses for testing Hardy–Weinberg (H–W) equilibrium were carried out with a modified version of the exact test described by Guo and Thompson [9], using Arlequin software Version 2.0 [10]. Gene diversity was measured [11] in order to quantify the degree of total (Ht) and intrapopulation (Hs) genetic variability, and to estimate the coefficient of gene differentiation (GST) among populations. Genetic similarities among populations based on polymorphisms distribution for the four genetic systems were explored by means of Principal Component Analysis (PCA), using the NTSYS 2.11S software (Exeter Software). This technique simultaneously allows to compare objects (in this case populations) and variables (here genetic markers) in a dimensionally reduced geometric space.

3. Results

Allelic frequencies for *CYP2D6*, *NAT2*, *GSTM1* and *GSTT1* genes, along with Nei's estimates of gene diversity are presented in Table 1.The combined frequencies of *CYP2D6* *1, *2, *4 and *10 alleles represent 88.6% of the total. Alleles *1 and *2 were present in all populations, with 39.9% and 23.8% average frequency respectively. Allele *4 was third in average frequency (17.8%), with a wide range of variation among populations (6.2–37.5%). Allele *10 showed frequencies between 2.5% and 14.3%.

Most populations showed more than 40% frequency of allele *4 for *NAT2* (42.9–80%); Patagonian (Mapuche and Tehuelche) and Paraguayan (Lengua and Ayoreo) populations showed high incidence of allele *5 (31.2–50%). Allele *6 was present in 3% Wichi and in more than 12% Jujuy, Mapuche and Tehuelche populations, and absent in the rest of the populations. Frequency for allele *7 showed high variability among populations (4.5–42.9%) (Table 1).

Frequencies for GSTM1 deletion ranged from 20% to 66%, while GSTT1 deletion was present in four populations, 50% Mapuche, 33.3% Wichi, 25% Toba and 23.5% Jujuy (Table 1).

The highest Hs was observed for samples from Mapuche, whereas the lowest Hs value corresponded to Ayoreo. The amount of genetic variation attributable to interpopulation diversity (GST) was 0.131, a very high estimate if compared with those usually found among

Table 1
CYP2D6 and *NAT2* allele frequencies; *GSTM1*and *GSTT1* *0/*0 genotype frequencies; and gene diversity values

Allele	Identified mutations	Activity[a]	Total[b]	Jujuy	Wichi	Toba	Chorote	Lengua	Ayoreo	Mapuche	Tehuelche
CYP2D6 *1	No change	EM	**0.399** (0.50–0.29)	**0.438** (0.21–0.67)	**0.550** (0.33–0.77)	0.083 (0.00–0.29)	**0.500** (0.01–0.99)	0.344 (0.11–0.58)	0.274 (0.02–0.53)	**0.625** (0.20–1.05)	**0.500** (0.15–0.85)
*2	C100T, C2850T	EM	0.238 (0.15–0.33)	0.219 (0.03–0.41)	0.100 (0.00–0.23)	**0.584** (0.22–0.95)	0.125 (0.00–0.45)	0.125 (0.00–0.29)	**0.545** (0.26–0.83)	0.125 (0.00–0.41)	0.143 (0.00–0.85)
*4	C100T, G1846A	PM	0.178 (0.09–0.26)	0.062 (0.00–0.17)	0.250 (0.06–0.44)	0.083 (0.00–0.29)	0.375 (0.00–0.85)	0.282 (0.06–0.50)	0	0	0.143 (0.00–0.85)
*6	Del T1707	PM	0.042 (0.00–0.08)	0.094 (0.00–0.23)	0	0.250 (0.00–0.57)	0	0.031 (0.00–0.11)	0	0	0
*8	G1758T, C2850T	PM	0.006 (0.00–0.02)	0	0	0	0	0.031 (0.00–0.12)	0	0	0
*10	C100T	IM	0.071 (0.02–0.12)	0.125 (0.00–0.28)	0.025 (0.00–0.09)	0	0	0.095 (0.00–0.24)	0.045 (0.00–0.16)	0.125 (0.00–0.41)	0.143 (0.00–0.85)
*12	G124A, G1661C, C2850T	PM	0.042 (0.00–0.08)	0.031 (0.00–0.11)	0.075 (0.00–0.19)	0	0	0.031 (0.00–0.12)	0.091 (0.00–0.25)	0	0
*14	C100T, G1758A, C2850T	PM	0.018 (0.00–0.04)	0.031 (0.00–0.11)	0	0	0	0	0.045 (0.00–0.16)	0	0.071 (0.00–0.25)
*15	Ins T 138	PM	0.006 (0.00–0.02)	0	0	0.	0	0.031 (0.00–0.12)	0	0	0
NAT2 *4	No change	EM	**0.512** (0.41–0.61)	**0.445** (0.21–0.67)	**0.589** (0.36–0.79)	**0.429** (0.06–0.80)	**0.800** (0.41–1.00)	**0.469** (0.22–0.71)	**0.637** (0.36–0.91)	0.250 (0.00–0.63)	0.250 (0.00–0.55)
*5	C481T	IM	0.250 (0.16–0.34)	0.222 (0.03–0.41)	0.147 (0.00–0.30)	0.142 (0.00–0.40)	0.100 (0.00–0.39)	0.312 (0.08–0.54)	0.318 (0.05–0.58)	**0.500** (0.06–0.94)	**0.333** (0.01–0.66)
*6	G590A	PM	0.061 (0.01–0.11)	0.139 (0.00–0.29)	0.029 (0.00–0.10)	0	0	0	0	0.125 (0.00–0.41)	0.250 (0.00–0.55)
*7	G857A	PM	0.201 (0.12–0.28)	0.194 (0.01–0.38)	0.235 (0.04–0.42)	0.429 (0.06–0.80)	0.100 (0.00–0.39)	0.219 (0.02–0.42)	0.045 (0.00–0.16)	0.125 (0.00–0.41)	0.167 (0.00–0.43)
GSTM1 *0/*0	Null	PM	0.398 (0.29–0.49)	0.444 (0.21–0.67)	0.474 (0.25–0.69)	0.571 (0.20–0.94)	0.666 (0.20–1.00)	0.375 (0.14–0.61)	0.250 (0.01–0.50)	0.200 (0.00–0.55)	0.250 (0.00–0.55)
GSTT1 *0/*0	Null	PM	0.164 (0.09–0.24)	0.235 (0.04–0.43)	0.333 (0.13–0.54)	0.250 (0.00–0.57)	0	0	0	0.500 (0.06–0.94)	0
Sample size			90	18	20	7	4	16	12	5	8
Hs				0.550	0.545	0.499	0.395	0.570	0.393	0.588	0.479
Ht			0.543								
Gst			0.131 var = 0.0004, S.E. = 0.02								

Hs: intrapopulational; Hr: total gene diversity; GST: interpopulational gene diversity [11]. Bold values represent the most frequent allele variants for *CYP2D6* and *NAT2*.

[a] EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer. http://www.imm.ki.se/CYPalleles/.

[b] The values within parentheses denotes 95% confidence limit.

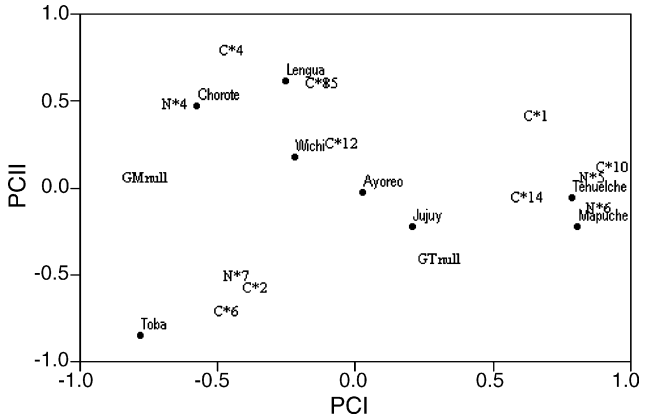

Fig. 1. Genetic similarities among Amerindian populations from Argentina and Paraguay based on *CYP2D6*, *NAT2*, *GSTM1*, and *GSTT1* polymorphisms distribution explored by means of the principal component analysis. PC: principal component; C: CYP2D6; N: NAT2; GMnull: GSTM1 null; GTnull: GSTT1 null.

South American populations using other genetic systems [12–14].

Genotypes distribution for *CYP2D6* and *NAT2* was consistent with H–W expectations in all the samples analyzed, with the exception of Wichi which presented a significant ($P < 0.001$) decrease of heterozygous genotypes for *NAT2* (data not shown). H–W equilibrium could not be tested for *GSTM1* and *GSTT1* due to the methodological difficulty for heterozygosity identification. *CYP2D6* 4 and *NAT2* *5, *6 and *7 alleles were associated with poor metabolizing (PM) genotypes (14.3% and 30.9%, respectively).

The Principal component analysis based on CYP2D6, NAT2, GSTM1, and GSTT1 polymorphisms is detailed in Fig. 1. The first and second vectors account for 34% and 21% of the total variation, respectively. Chorote, Lengua, Wichi, Ayoreo (from the Gran Chaco region), and Jujuy samples (from South-Central Andes) fall scattered in the center of the plot, without a clear clustering pattern. On the other hand, Mapuche and Tehuelche (from Patagonia) cluster together on the left side of the plot because of their high incidence on alleles *CYP2D6* *10, and *NAT2* *5 and *6. Toba (also from Gran Chaco region) appears as outlier of the arrange, at the bottom of the left extreme of the plot, because of the unusual high incidence of alleles *NAT* *7, *CYP2D*6, and principally *CYP2D*2.

4. Discussion

CYP2D6 *10 allele frequencies found for Amerindian populations ([2,15–17], and this report) are 3–10-fold lower than the average frequency (range 38–70%) detected in Chinese, Japanese, Singaporean, and Malaysian populations [2,18–22], and at least two-fold higher than those reported for African [23] and European [2] populations. Regarding allele *14 we found an average frequency of 0.18% for the three tribes that show this variant (Table 1), while it has been reported to occur at an average frequency of 2% in Chinese populations [24,25] and to be absent in Europeans and Africans [6,23]. Furthermore, Muñoz et al. [15] found a frequency of 3.6% of the *CYP2D6* *4 allele in a Chilean Mapuche population and assumed that this allele originally occurred in European populations (11.6–20.7%) [2,6] and was introduced into Amerindians via European gene introgression. The *CYP2D6* *4 allele was absent in the Argentine Mapuche population from our series and exhibit frequencies of 25%, 28% and 37.5%, respectively in Wichi, Lengua and Chorote populations which are known to have low gene admixture. Accordingly, we tentatively propose that *CYP2D6* *4, *10 and *14 allele variants in the Amerindian tribes analyzed here (Table 1) were already present in the ancestral Asian populations from which Native Americans derive (this assumption is more extensively discussed below).

CYP2D6 *3 allele was absent in Native Americans (Table 1) and present at low frequencies in Asians as well as all other geographic populations tested [2,6]. *CYP2D6* *6 (1.8%) [27], *8 (0.3%) [6], *12 (0.3%) [28], and *15 (0.08%) [6] alleles are rare for Europeans as well as for Native American populations ([26],and present results) (Table 1). We cannot conclude whether these alleles entered the Native American populations through recent genetic admixture or whether they were already present at low frequency in the founder groups.

NAT2 *5, *6 and *7 alleles showed marked frequency variations among populations: *5 was present in 60–50% Europeans [2,29], 4% Asians [30], 40% Oji-Cree Amerindians [31], <10% Central American Amerindians [17], and an intermediate frequency (∼25%, range 10–33.3%) for the populations included in this report (Table 1). On the other hand, the average frequency of *NAT2* *6 allele was lower in Amerindian populations (6%) (Table 1) than in Asians [30] or Europeans [3] (31% and 28.5%, respectively). The average frequency of the *7 variant was similar in Asian (16%) [30] and Amerindian populations ([17,31], and present results). Interestingly, previous studies have described 39% low processing isoniacid phenotypes in 166 admixed individuals from Jujuy province with predominant Amerindian genetic background [32]. In good agreement with those results the molecular analysis in our Jujuy samples showed 38.8% (7/18) low processing genotypes (data not shown).

The frequency of the *GSTM1* *0/*0 genotype in Amerindians was not significantly different from those found in Asian and European populations (53% for both geographic groups) [3]. GSTT1 *0/*0 genotypes in the four tribes of our series showing homozygous deletions ranged from 23% to 47% (Table 1). These figures start at the highest frequencies detected in European populations (10–26%) [3] and extend to overlap the Asian population frequencies of null/null *GSTT1* genotypes (32–50%) [3]. The Asian tracing of deleted *GSTT1* genotypes has been performed in extant Japanese, Korean and Singaporean populations [3]. On the other hand, it is generally accepted that the initial American settlers were a probably a small human group derived from ancestral south/central Siberian populations that crossed the Bering bridge approximately 30,000 years ago to colonize Beringia and thereafter to migrate south into America at variable timed episodes [33–35]. Accordingly, the rather intermediate rates between European and Asian frequencies of *GSTT1* null/null genotypes detected in our series of Amerindian populations might perhaps reflect the frequency of this genotype in ancestral Siberian or Beringian populations. Yet, the alternative possibility that initially high Asian-like frequencies of homozygous null *GSTT1* genotypes were lowered by relatively recent European Caucasian gene introgression into Amerindian populations should be also taken into consideration. All donors in our sample were considered Amerindians on the basis of geographic location, genealogical data and the presence of Amerindian-specific markers in mtDNA and Y chromosomes. Although the combination of all these characteristics does not totally preclude a European gene introgression, at least they strongly suggest that such introgression, if it existed, probably played a minor role influencing the frequencies of null/null *GSTT1* genotypes detected in our series of Amerindian populations. Moreover, the variable range of intertribal deleted genotypes detailed in Table 1 as well as those reported for the Brazilian-Paraguayan Amerindian populations reported by Gaspar et al. (6.5–30.3%) [16] may be due to the same causes, genetic drift, and low gene admixture, proposed above to explain the lack of GSTT1 *0/*0 in some Amerindian populations.

The frequency observed for *CYP2D6* and *NAT2* genotypes (Table 2) revealed that *CYP2D6* *4 allele was always related with PM genotypes; *10 and *14 alleles could be assigned as PM genotypes only when found in heterozygous state with allele *4. NAT2 *5, *6 and *7 alleles were usually associated with PM genotypes.

The Principal Component Analysis evidenced high degree of genetic differentiation among Gran Chaco populations, and close similarity between both Patagonian groups (Mapuche and Tehuelche) (Fig. 1). Wichi, Toba, and Chorote samples analyzed in this study belong to neighbor populations which shared the same habitat and a hunting/gathering based economy before the cultural influence of the European colonization [36]. Other authors that used various neutral DNA markers have also reported a high degree of genome differentiation [12,13,36–40]. Furthermore, although Mapuche and Tehuelche populations very likely settled the Patagonia in two different colonizing events, they share a long history of cultural contact and exhibit a high degree of genetic affinity [40]. It is worth noting that for measuring interpopulation genome affinities we favored the use of PCA instead of the genetic distance analysis because the former system may be used without any constraint of the evolutionary theory (i.e., it does not depend on the neutrality of markers) and simply shows graphically the relationship among *n* objects and *n* variables.

Table 2
CYP2D6, *NAT2*, *GSTM1* and *GSTT1* genotype frequencies

Gene	*n*	Genotype	*n*	Frequency[a]	Predicted phenotype
CYP2D6	84	1/1	19	0.226 (0.14–0.32)	EM
		1/2	10	0.119 (0.05–0.19)	EM
		1/4	7	0.083 (0.02–0.14)	EM
		1/6	3	0.036 (0.00–0.08)	EM
		1/10	9	0.107 (0.04–0.17)	EM
		1/12	5	0.059 (0.01–0.11)	EM
		1/14	1	0.012 (0.00–0.04)	EM
		2/2	9	0.107 (0.04–0.17)	EM
		2/4	2	0.024 (0.00–0.06)	EM
		2/6	2	0.024 (0.00–0.06)	EM
		2/10	3	0.036 (0.00–0.08)	EM
		2/12	2	0.024 0.00–0.06)	EM
		4/4	6	0.071 (0.02–0.13)	PM
		4/6	1	0.012 (0.00–0.04)	PM
		4/8	1	0.012 (0.00–0.04)	PM
		4/10	1	0.012 (0.00–0.04)	IM
		4/14	2	0.024 (0.00–0.06)	PM
		12/15	1	0.012 (0.00–0.06)	PM
NAT	84	4/4	26	0.309 (0.21–0.41)	EM
		4/5	18	0.214 (0.13–0.30)	EM
		4/6	1	0.012 (0.00–0.04)	EM
		4/7	13	0.155 (0.08–0.23)	EM
		5/5	7	0.083 (0.02–0.14)	PM
		5/6	1	0.012 (0.00–0.04)	PM
		5/7	8	0.095 (0.03–0.16)	PM
		6/6	2	0.024 (0.00–0.06)	PM
		6/7	4	0.048 (0.00–0.09)	PM
		7/7	4	0.048 (0.00–0.09)	PM
GSTM1	88	0/0	35	0.398 (0.30–0.50)	PM
GSTT1	79	0/0	13	0.164 (0.08–0.25)	PM

[a] The values within parentheses denotes 95% confidence limit.

Conversely, the construction of population phylogenetic histories by using coding genome sequences has produced rather inconsistent information.

5. Conclusions

Information on the frequencies of xenobiotic metabolizing genes in Native American and Asian populations is based on a relative low number of geographic populations. Thus for instance, Japanese and Chinese are the two main Asian populations used as reference for the comparison of allele frequencies between Amerindians and Asians. Moreover, American aborigine rates are based on the allele and genotype frequencies obtained from the analysis of a total of 431 individuals representing 16 Amerindian populations from Argentina, Brazil, Chile, and Paraguay ([15,16], present report). We propose here that, at least for the series of tribes reported here, the influence of Caucasian gene admixture had low influence, or no influence at all in the frequencies depicted in Tables 1 and 2. Accordingly, we suggest that the allele and genotype variants detailed in these tables already existed in Siberian or Beringian ancestral populations from which extant Native Americans derive, and that interpopulation allele and genotype frequency variations detected probably resulted from the genetic drifts and the eventual genetic bottlenecks that probably occurred during the Native American colonization of the Continent. This assumption, however, is no more than a first approximation needing further corroboration through the study of allele and genotype variant frequencies in other Amerindian populations from northern South American regions, from Central and North America, from other linguistic groups of Native Americans (Nadene and Aleut-Eskimo), and from populations of central and south Siberia. Moreover, since we are dealing with xenobiotic gene frequencies in different geographic populations, an eventual variation resulting of selective pressures cannot be ruled out.

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