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Research Article

CYP1A1 and CYP2E1 polymorphism frequencies in a large Brazilian population

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Abstract

The enzymes encoded by the polymorphic genes *CYP1A1* and *CYP2E1* play an important role in the activation and inactivation of xenobiotics. These enzymes have been associated with xenobiotic-induced diseases, such as cancer, therapeutic failure and adverse effects of drugs. The aim of the present study was to determine the allelic and genotypic frequencies of these polymorphisms in a large, ethnically mixed Brazilian population sample from Rio de Janeiro. Polymorphisms CYP1A1 and CYP2E1 were determined in 870 unrelated individuals by PCR-RFLP analysis in peripheral blood DNA. The observed allelic frequencies were 0.90 for *CYP1A1*1A* and 0.95 for *CYP2E1*1A*, in the total sample. The allelic frequency of *CYP1A1*2C* in "pardos" (0.13) and Brazilian whites (0.11) was higher than in Caucasians (0.05), which may be a result of the Amerindian genetic component, that presents the highest frequency of this allele observed up to now. The genotype distributions for both polymorphisms were in Hardy-Weinberg equilibrium and were statistically different between males and females, and among ethnic groups.

Key words: cytochromes P450, CYP1A1, CYP2E1, Brazil.

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Introduction

Cytochromes P450 (P450 or CYP) constitute the most important phase I enzyme group responsible for the metabolism of endogenous and exogenous (xenobiotics) substances. These detoxification enzymes are essential to the maintenance of an individual's health and well-being. CYP1A1 plays a key role in phase I metabolism of polycyclic aromatic hydrocarbons to their ultimate DNA-binding forms (McManus *et al*., 1990), and CYP2E1 is an ethanol-inducible enzyme important for the metabolism of ethanol, paracetamol, N-nitrosamines and a number of organic solvents (Guengerich *et al*., 1991). A great part of the current research focuses on the role that P450 plays in the metabolism of chemical compounds, due to its importance in pharmacogenetics and in the susceptibility to environment-related diseases (Hasler, 1999).

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A great part of the interindividual and interethnic differences in relation to xenobiotic effects is now attributable to genetic differences in their metabolism. Mutations in a gene coding for an enzyme that metabolizes these substances can give rise to enzyme variants with higher, lower or no activity, or may have no effect at all on enzyme activity (Hasler, 1999). Thus, individuals with elevated activation and low detoxifying potentials could be expected to be more susceptible to cancer (Ingelman-Sundberg, 2002). Many studies have produced conflicting results (d'Errico *et al*., 1996; Agundez, 2004), which is probably in part because of the low penetrance of this class of susceptibility genes (Garte *et al*., 2001). In addition, other studies have demonstrated that allele frequencies of metabolic genes are not randomly distributed throughout the human population, but follow specific ethnic and geographic patterns (Garte, 1998; Quinones *et al*., 1999; Garte *et al*., 2001; Roy *et al*., 2001). A small number of studies using large database has allowed for a more precise estimate of the population-specific frequency for these polymorphisms in normal control samples (Garte *et al*., 2001). These polymorphisms

are well characterized in some populations, especially Caucasians, but little is known about them in other ethnic groups. Brazilians form one of the most heterogeneous populations in the world, basically the result of a mixture between Caucasians, Africans and native Amerindians (Krieger *et al*., 1965; Carvalho-Silva *et al*., 2001). Besides the fact that the ethnic mixture is very pronounced in Brazil, it can vary a lot from region to region. In Rio de Janeiro, for example, the population derives from the mixture of 40% Caucasians, 52% Africans, and 8% Amerindians (Lopez-Camelo *et al*., 1996), whereas Caucasians are predominant in the Brazilian South (Marrero *et al*., 2005).

We present here a descriptive analysis of two polymorphic genes of the cytochrome P450 group of enzymes, *CYP1A1* (exon 7) and *CYP2E1* (RFLP *PstI*), in a large sample of the Rio de Janeiro population.

Material and Methods

Samples

Blood samples were collected from 663 unrelated blood donors at the Clementino Fraga Filho Hospital Blood Bank and from 207 healthy individuals from the Orthopedics and Traumatology Hospital of Rio de Janeiro, Brazil. Since these two groups of individuals were homogeneous in relation to the allelic and genotypic frequencies of *CYP1A1* and *CYP2E1*, and both were in Hardy-Weinberg equilibrium (HWE), they were joined into one group, totalizing 870 individuals (mean age = 40 years; 65% males). Of this total, 560 individuals were classified, by skin color and other physical traits, as whites (Caucasians, mainly Portuguese descendents); 181 as "pardos" (ethnic mixture of Europeans, Africans and Amerindians); and 129 as blacks (African descendants), based on the official Brazilian census categorization. The Ethics Committees of the institutions involved approved this study, and informed consent was obtained from all participating individuals.

Genotype analysis

Genomic DNA was isolated from peripheral blood according to the method described by Lahiri and Nurnberger (1991). Genotypes CYP2E1 (*Pst I*) and CYP1A1 (exon 7) were identified by PCR-restriction fragment length polymorphisms (PCR-RFLP), and the primer sequences were those reported by Sugimura *et al*. (1995) and Katoh *et al*. (1995), respectively. CYP1A1 polymorphism was detected in a *Hinc II* polymorphism assay, using a primer with a single base pair mismatch: 5'-GTCTCCC TCTGGTTACAGGA-3' (sense) and 5'GAAAGACCTC CCAGCGGTCA-3' (antisense). Amplicons (171 bp) were digested overnight (at 37 ºC) with endonuclease *Hinc II*, which allows the distinction between the restriction sites on alleles *CYP1A1*1A* (139 bp and 32 bp fragments) and *CYP1A1*2C* (120bp, 32bp and 19 bp fragments). The digestion product was analyzed by electrophoresis in a 10% polyacrylamide gel. For CYP2E1 genotyping, primers 5'-CCAGTCGAGTCTACATTGTCA-3' (sense) and 5'-TTCATTCTGTCTTCTAATGG-3' (anti-sense) were used to amplify a 410 bp fragment in CYP2E1, which includes a *Pst I* restriction site (Hayashi *et al*., 1991). PCR products were digested with *Pst I* (New England Biolabs™), according to the manufacturer's recommendations, and then subjected to electrophoresis in 3% agarose gel. A 410 bp non-digested fragment corresponds to the *CYP2E1*1A* allele, and two fragments of 290 and 120 bp correspond to the *CYP2E1*5B* allele.

Statistical analysis

The maximum likelihood method was used to estimate the allele frequencies, and the goodness of fit of the genotype distribution to the Hardy-Weinberg equilibrium was tested by chi-square. Comparisons between the different ethnic groups or sexes were performed through contingency tables analyzed by chi-square tests.

Results

The distribution of the 870 individuals according to sex, age, ethnicity and genotypes is presented in Table 1. In the total sample, the observed genotype frequencies of CYP1A1 were 80.3% for 1A/1A, 18.7% for 1A/2C, and 1.0% for 2C/2C mutant homozygotes, and for CYP2E1 they were 91.4% for 1A/1A, 8.4% for 1A/5B, and 0.2% for 5B/5B mutant homozygotes. In the total sample, the allele frequencies (± standard error) were 0.10 ± 0.007 for *CYP1A1*2C* and 0.04 ± 0.005 for *CYP2E1*5B*. The mean age was 39.58 ± 13.73, and there were no significant differences in genotype frequencies among the five age classes for both polymorphisms: CYP1A1, $p = 0.646$; and CYP2E1, $p = 0.960$ (Table 1). On the other hand, statistically significant differences were observed in the genotype frequencies for CYP1A1 and CYP2E1 in relation to ethnicity ($p = 0.015$), and between males and females for CYP1A1 ($p = 0.045$) and CYP2E1 ($p = 0.005$). In the total sample and within the three ethnic groups (whites, "pardos" and blacks), the genotype distribution was in Hardy-Weinberg equilibrium.

Table 2 shows the allelic frequencies of CYP1A1 and CYP2E1 stratified by ethnicity and compared with other Brazilian populations and different ethnic groups. The allelic frequency of *CYP1A1*1A* in the present study was 0.893 ± 0.009 in whites, 0.870 ± 0.017 in "pardos", and 0.953 ± 0.13 in blacks. For *CYP2E1*1A*, frequencies of 0.964 ± 0.005, 0.928 ± 0.013, and 0.957 ± 0.013 were observed in whites, "pardos" and blacks, respectively.

Discussion

The P450s of families 1-3, that include CYP1A1 and CYP2E1, are responsible for 70-80% of all phase I-dependent metabolism of clinically used drugs (Bertz and Gran-

Table 1 - Distribution of genotypes CYP1A1 and CYP2E1 according to sex, age and ethnicity in a Rio de Janeiro population sample.

	CYP1A1 genotype frequencies N (%)			CYP2E1 genotype frequencies N (%)		
Sex	1A/1A	1A/2C	2C/2C	1A/1A	1A/5B	5B/5B
Male	442 (79)	116 (20)	3 (1)	500 (89)	59 (10)	2 (1)
Female	257 (83)	47 (15)	5 (2)	295 (95)	14 (5)	0 (0)
	$\chi^2_2 = 6.198$ p = 0.045			$\chi^2_2 = 10.488$ p = 0.005		
Age (years)						
18 - 27	157 (79.7)	39 (19.8)	1 (0.5)	180 (91.4)	16 (8.1)	1 (0.5)
28 - 37	184 (78.6)	46 (19.7)	4 (1.7)	212 (90.6)	21 (9.0)	1 (0.4)
38 - 47	169 (81.6)	36 (17.4)	2 (1.0)	190 (91.8)	17 (8.2)	0 (0.0)
48 - 57	97 (78.2)	27 (21.8)	0 (0.0)	115 (92.7)	9 (7.3)	0 (0.0)
≥58	92 (85.2)	15 (13.9)	1 (0.9)	98 (90.7)	10 (9.3)	0 (0.0)
	$\chi^2_8 = 6.009$ p = 0.646			$\chi^2_8 = 2.523$ p = 0.96		
Ethnic Group						
Whites	445 (79)	110 (20)	5 (1)	520 (93)	40 (7)	0 (0)
“Pardos”	137 (76)	41 (23)	3 (2)	157 (87)	22 (12)	2 (1)
Blacks	117 (91)	12 (9)	0 (0)	118 (91)	11 (9)	0 (0)
	$\chi^2_4 = 12.38$ P = 0.015			$\chi^2_4 = 12.272$ p = 0.015		
Total Sample						
	699 (80.3)	163 (18.7)	8 (1.0)	795 (91.4)	73 (8.4)	2 (0.2)
	χ^2_1 (HWE) = 0.197 p = 0.660			χ^2_1 (HWE) = 0.056 p = 0.810		

HWE = Hardy-Weinberg equilibrium.

Table 2 - Allele frequencies of *Cyp1A1* (*exon 7*) and *CYP2E1* (*Pst I*) in different ethnic groups.

			Allele frequencies		
Gene	Ethnic groups	N	*CYP1A1*1A*	*CYP1A1*2C*	Reference
CYP1A1	Whites	560	0.89	0.11	Present paper
	“Pardos”	181	0.87	0.13	Present paper
	Blacks	129	0.95	0.05	Present paper
	South Amerindians	257	-	(0.54-1.0)	Gaspar *et al*. (2002)
	Brazilians (RJ)	108	0.91	0.09	Sugimura *et al*. (1995)
	Brazilians (SP)	221	0.83	0.17	Burim *et al*. (2004)
	Caucasians	4790	0.95	0.05	Garte *et al*. (2001)
	Africans	481	0.97	0.03	Garte *et al*. (2001)
	Asians	1132	0.77	0.23	Garte *et al*. (2001)
CYP2E1			*CYP2E1*1A*	*CYP2E1*5B*	
	Whites	560	0.96	0.04	Present paper
	“Pardos”	181	0.93	0.07	Present paper
	Blacks	129	0.96	0.04	Present paper
	Brazilians (Caucasians)	206	0.95	0.05	Gattas & Soares-Vieira (2000)
	Brazilians (African descendants)	86	0.94	0.06	Gattas & Soares-Vieira (2000)
	Brazilians (RJ)	108	0.94	0.06	Sugimura *et al*. (1995)
	Brazilians (SP)	221	0.94	0.06	Burim *et al*. (2004)
	South Amerindians	257	0.58-0.98	(0.02-0.42)	Gaspar *et al*. (2002)
	Caucasians	1454	0.96	0.04	Garte *et al*. (2001)
	Asians	719	0.77	0.23	Garte *et al*. (2001)

neman, 1997; Evans and Relling, 1999) and participate in the metabolism of a huge number of xenobiotic chemicals (Ingelman-Sundberg, 2002). The metabolic activation of precarcinogens and drugs might have toxic or carcinogenic effects. The vast interindividual variation in human drug metabolism has been a major problem for the drug industry and for the physicians, because this variation can lead to a variety of outcomes, which include therapeutic failure, adverse effects, and toxicity in selected individuals undergoing treatment, that are difficult to foresee (Ingelman-Sundberg, 2002). The type and prevalence of allelic variants present in an individual or in a population can influence the pharmacological and toxicological effects of drugs, toxins and carcinogens, leading to interindividual and interethnic differences (Kalow and Bertilsson, 1994).

Considering that the allelic and genotypic frequencies of metabolic genes vary throughout the human population according to specific ethnic and geographic patterns (Garte, 1998; Quinones *et al*., 1999; Garte *et al*., 2001), acquiring knowledge about them is an important task, not only for disease association studies, but also for the evaluation of chemotherapy and adverse drug reactions.

Here, we determined the allelic and genotypic frequency distribution of polymorphisms *CYP1A1* (*exon 7*) and *CYP2E1* (*Pst I*) in a large Brazilian population sample from Rio de Janeiro. The allelic frequency of *CYP1A1*2C* in the total sample (0.10) was similar to another one from Rio de Janeiro (0.09) studied by Sugimura *et al*. (1995), but lower than the results found in São Paulo (0.17) by Burim *et al*. (2004). When the total sample was stratified by ethnicity and compared with the results observed by Garte *et al*. (2001), the frequency in whites (0.11) was higher than in Caucasians (0.05), but in blacks (0.05) the frequency seemed similar to Africans (0.03). The highest *CYP1A1*2C* frequency (0.13) was observed in "pardos", and was probably influenced by the Amerindian genetic component, which presents the highest frequency of this allele observed up to now (Table 2). In fact, studies have shown that tri-hybrid miscegenation occurs in the Brazilian population in different proportions of the three main groups (Caucasians, Africans and Amerindians) around Brazil (Krieger *et al*., 1965; Lopez-Camelo *et al*., 1996; Carvalho-Silva *et al*., 2001; Parra *et al*., 2003), which could explain the geographic differences observed in the genetic frequencies.

The frequency observed in the present study for *CYP2E1*5B* (0.04) was equal to that of Caucasians (Garte *et al*., 2001) and similar to the results of Sugimura *et al*. (1995), Gattas and Soares-Vieira (2000) and Burim *et al*. (2004) in other Brazilian populations. After stratification, the *CYP2E1*5B* allele frequency was the same (0.04) in whites and blacks, and higher in "pardos" (0.7). Similarly to allele *CYP1A1*2C*, the higher frequency of allele *CYP2E1*5B* in "pardos" may have been influenced by Amerindian miscegenation, as this allele is also common in Amerindians (Muñoz *et al*., 1998; Gaspar *et al*., 2002). The genetic contribution of Amerindians in the population of Rio de Janeiro is relatively low (8%) (Lopez-Camelo *et al*., 1996), but the high frequency of these alleles in Amerindians (Muñoz *et al*., 1998; Gaspar *et al*., 2002) might have influenced significantly the final frequency. Nevertheless, we cannot forget that the allele frequency of *CYP2E1*5B* was very low, and that this result might have occurred by chance or due to a type I statistical error.

Ethnic differences in metabolic polymorphisms have been previously reported (Muñoz *et al*., 1998; Garte, 1998; Quinones *et al*., 1999; Garte *et al*., 2001) and our results corroborate the ethnic difference in the allelic frequency of *CYP1A1* (*éxon 7*) between Caucasians (or whites) and Africans (blacks). Polymorphisms CYP1A1 and CYP2E1 showed a good fit to Hardy-Weinberg's genetic equilibrium model in relation to the observed and expected genotype frequencies, both in the total sample and in the stratified ethnic sub-groups.

Age effects on the allelic and genotypic frequencies were not observed in the present study. On the other hand, sex differences were found for CYP1A1 and CYP2E1, and this effect has already been noted for CYP1A1 in cancer patients, but not in control populations (Dresler *et al*., 2000). The basis for the sex differences in the genotype frequency distributions of CYP1A1 and CYP2E1 is unknown, but their significance can be due to a type I statistical error.

This study provides basic information about the allele and genotype frequency distributions of two specific polymorphisms, *CYP1A1* (*exon 7*) and *CYP2E1* (*Pst I*), in the population of Rio de Janeiro. These frequencies may be useful as a reference for future studies about cancer susceptibility, therapeutic failure and/or adverse effects of drugs.

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