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Pharmacogenetic polymorphisms in Brazilian-born, first-generation Japanese descendants

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Abstract

Brazil hosts the largest Japanese community outside Japan, estimated at 1.5 million individuals, one third of whom are first-generation, Brazilian-born with native Japanese parents. This large community provides a unique opportunity for comparative studies of the distribution of pharmacogenetic polymorphisms in native Japanese versus their Brazilian-born descendants. Functional polymorphisms in genes that modulate drug disposition (*CYP2C9, CYP2C19* and *GSTM3*) or response (*VKORC1*) and that differ significantly in frequency in native Japanese versus Brazilians with no Japanese ancestry were selected for the present study. Healthy subjects (200 native Japanese and 126 first-generation Japanese descendants) living in agricultural colonies were enrolled. Individual DNA was genotyped using RFLP (*GSTM3*A/B*) or TaqMan Detection System assays (*CYP2C9*2* and **3*; *CYP2C19*2* and **3*; *VKORC1* 3673G>A, 5808T>G, 6853G>C, and 9041G>A). No difference was detected in the frequency of these pharmacogenetic polymorphisms between native Japanese and first-generation Japanese descendants. In contrast, significant differences in the frequency of each polymorphism were observed between native or first-generation Japanese and Brazilians with no Japanese ancestry. The *VKORC1* 3673G>A, 6853G>C and 9041G>A single nucleotide polymorphisms were in linkage disequilibrium in both native and first-generation Japanese living in Brazil. The striking similarity in the frequency of clinically relevant pharmacogenetic polymorphisms between Brazilian-born Japanese descendants and native Japanese suggests that the former may be recruited for clinical trials designed to generate bridging data for the Japanese population in the context of the International Conference on Harmonization.

Key words: Japanese; Brazil; *CYP2C9*; *CYP2C19*; *GSTM3*; *VKORC1*

Introduction

Myrand et al. (1) reported that native Japanese and Japanese descendants born and living outside Japan display strikingly similar drug metabolic profiles for major cytochrome P450 (CYP) enzymes. It has been suggested that pharmacokinetic data from Japanese recruited outside Japan may be used to bridge foreign clinical data between Caucasians and Asians, in the context of the International Conference on Harmonization (ICH). The ICH is a tripartite body composed of the regulatory authorities and the industry associations of the European Community, Japan and the United States with observers from the World Health Organization, Health Canada and European Free Trade Area countries, charged with developing guidelines to harmonize global drug development and thus facilitate availability of new medicines efficiently. Brazil hosts the largest Japanese community outside Japan, estimated to be 1.5 million individuals, 4% of whom are native Japanese (2) and ca. one third are first-generation, Brazilian-born individuals with native Japanese parents (3). This large community provides a unique opportunity for comparative studies of the distribution of pharmacogenetic polymorphisms among native Japanese, their Brazilian-born descendants and Brazilians with no Japanese ancestry. For the present study, we selected functional polymorphisms in genes that modulate drug disposition (*CYP2C9*, *CYP2C19* and *GSTM3*) or response to drugs (*VKORC1*) and that differ significantly in their frequencies in native Japanese versus Brazilians with no Japanese ancestry (4-8). Recruitment of Brazilian-born

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individuals with Japanese ancestry in relatively isolated agricultural colonies minimized the impact of genetic admixture on the frequency of the chosen polymorphisms, and also increased the likelihood of providing pharmacogenetic data to support the proposal that Japanese descendants living outside Japan may be enrolled in clinical trials designed to generate bridging data for the Japanese population, in the context of the ICH (1).

Material and Methods

Study population

The study enrolled 200 native Japanese (median age 64 years, range 32-88) and 126 Brazilian-born, first-generation Japanese descendants (42 years, range 25-74), all living in agricultural colonies in Brazil's South (Ivoti, 29°37'23.63" S, 51°08'16.25" O and Gravataí 29°56'56.22" S, 50°59'29.62" O) and North regions (Tomé-Açu, 2°2'59.92" S, 48°07'10.54" O). The study was approved by the Ethics Committee of Pontifícia Universidade Católica do Rio Grande do Sul, and each subject provided written informed consent and information regarding Japanese ancestry. Data from Brazilians living in Rio de Janeiro, with no Japanese ancestry, previously genotyped in our laboratory for polymorphisms in *CYP2C9* (6)*, CYP2C19* (Suarez-Kurtz G, unpublished data), *GSTM3* (7), and *VKORC1* (8) were used for comparison.

Genotyping

A single blood sample (3 mL) was drawn from each subject and DNA was extracted using the GFX™ Genomic Blood DNA Purification Kit (Amersham Biosciences, USA). Validated TaqMan® assays (Applied Biosystems, USA) were used to discriminate the *VKORC1* 3673G>A (rs9923231), *VKORC1* 5808T>G (rs2884737), *VKORC1* 6853G>C (rs8050894), *VKORC1* 9041G>A (rs7294), *CYP2C9*2* (rs1799853), *CYP2C9*3* (rs1057910), *CYP2C19*2* (rs4244285), and *CYP2C19*3* (rs4986893) alleles. Polymerase chain reaction amplification for all single nucleotide polymorphisms was performed in 10-µL reactions with 30 ng template DNA, 1X Taqman Universal Master Mix (Applied Biosystems), 1X each primer and probe assay, and H_2O qsp. Thermal cycling was initiated with a first 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 allele detection process was performed for 1 min at 60°C on a Fast 7500 Real-Time System (Applied Biosystems) to determine the allelic discrimination. The *GSTM3*A/B* polymorphism, a 3-bp insertion/deletion in intron 6 (rs1799735), was genotyped by RFLP

Table 1. Allele frequencies and genotype distribution of *CYP2C9* and *CYP2C19* polymorphisms.

Single nucleotide polymorphisms		Native Japanese[a]	First-generation[a]	Non-Japanese Brazilian[b]	P
CYP2C9	*1/*1	84 (94.4%)	63 (98.4%)	239 (72.2%)	
	*1/*2	0	0	48 (14.5%)	
	*1/*3	5 (5.6%)	1 (1.6%)	36 (10.9%)	
	*2/*2	0	0	3 (0.9%)	<0.0001
	*2/*3	0	0	3 (0.9%)	
	*3/*3	0	0	2 (0.6%)	
	*2	0	0	57 (8.6%)	<0.0001
	*3	5 (2.8%)	1 (0.8%)	43 (6.5%)	
CYP2C19	*1/*1	27 (33.8%)	24 (40.7%)	195 (74.7%)	
	*1/*2	31 (38.8%)	15 (25.4%)	61 (23.4%)	
	*1/*3	9 (11.3%)	7 (11.9%)	1 (0.4%)	
	*2/*2	5 (6.3%)	5 (8.5%)	4 (1.5%)	<0.0001
	*2/*3	8 (10.0%)	7 (11.9%)	0	
	*3/*3	0	1 (1.7%)	0	
	*2	49 (30.6%)	32 (27.1%)	69 (13.2%)	<0.0001
	*3	17 (10.6%)	16 (13.6%)	1 (0.2%)	

Data are reported as number with percent in parentheses. [a]Individuals from Brazil's South region. [b]N = 331 for *CYP2C9* (Ref. 4) and N = 261 for *CYP2C19* (Suarez-Kurtz G, unpublished data). Chi-square test or, when appropriate, Fisher exact test for comparisons of allele frequencies or genotype distribution across the three groups.

as described previously (9) and *CYP2C9*, *CYP2C19* and *VKORC1* allele frequencies and genotype distribution were derived by gene counting. The *VKORC1* haplotypes were statistically inferred by the haplo-stats software, version 1.3 (10), available at http://mayoresearch.mayo.edu/mayo/research/schaid_lab/software.cfm. This software attributes a posterior probability value to the diplotype configuration for each individual based on estimated haplotype frequencies. Diplotypes were inferred with probabilities >0.98, for all individuals.

Statistical analysis

Deviations from Hardy-Weinberg equilibrium were accessed by the goodness-of-fit chi-square test. Allele and genotype frequencies were compared using the chi-square test or, when appropriate, the Fisher exact test. Statistical significance was set at $P < 0.05$.

Results

The *GSTM3*A/*B* polymorphism was monomorphic in native (N = 89) and in first-generation Japanese (N = 64) living in Brazil's South region, the variant **B* allele not being detected in either group. *CYP2C9*2* and **3* were absent or infrequent in these two groups, whereas *CYP2C19*3* and, especially, *CYP2C19*2* were common in both Japanese groups (Table 1). The genotype frequencies of the *CYP2C9* and *CYP2C19* polymorphisms did not deviate from expected Hardy-Weinberg proportions. No significant difference was detected between native Japanese and first-generation Japanese born in Brazil with respect to allele frequencies or genotype distribution of the *CYP2C9* and *CYP2C19* polymorphisms. In contrast, highly significant ($P < 0.0001$) differences in allele frequencies and genotype distribution of the *CYP2C9* and *CYP2C19* polymorphisms were observed between native Japanese or first-generation Japanese and Brazilians with no Japanese ancestry. These differences resulted from the higher frequency of the *CYP2C9*2* and **3* alleles, and the lower frequency of the *CYP2C19*2* and **3* alleles in Brazilians with no Japanese ancestry compared to native Japanese or first-generation Japanese (Table 1).

Individuals from Japanese communities in the North and South regions of Brazil were genotyped for the *VKORC1* polymorphisms. There were no differences in allele of genotype frequencies between the two groups, and the combined data for the two regions are shown in Tables 2 and 3. Native and first-generation Japanese did not differ from each other with respect to the prevalence of the *VKORC1*

Table 2. Allele frequencies and genotype distribution of *VKORC1* polymorphisms in native Japanese, Brazilian-born first-generation Japanese and non-Japanese Brazilians.

Single nucleotide polymorphisms		Native Japanese[a] (N = 200)	First-generation[a] (N = 126)	Non-Japanese Brazilians[b] (N = 390)	P
3673G>A	GG	1 (0.5%)	3 (2.4%)	170 (43.5%)	
	GA	37 (18.5%)	24 (19%)	180 (46.2%)	<0.0001[c]
	AA	162 (81.0%)	99 (78.6%)	40 (10.3%)	
	G	39 (9.7%)	30 (11.9%)	520 (66.7%)	<0.0001[d]
	A	361 (90.3%)	222 (88.1%)	260 (33.3%)	
5808T>G	TT	198 (99.0%)	125 (99.2%)	243 (62.3%)	
	TG	2 (1.0%)	1 (0.8%)	129 (33.1%)	<0.0001[c]
	GG	0	0	18 (4.6%)	
	T	398 (99.5%)	251 (99.6%)	615 (78.8%)	<0.0001[d]
	G	2 (0.5%)	1 (0.4%)	165 (21.2%)	
6853G>C	GG	1 (0.5%)	3 (2.4%)	137 (35.1%)	
	GC	35 (17.5%)	23 (18.2%)	198 (50.8%)	<0.0001[c]
	CC	164 (82%)	100 (79.4%)	55 (14.1%)	
	G	37 (9.2%)	29 (11.5%)	472 (60.5%)	<0.0001[d]
	C	363 (90.8%)	223 (88.5%)	308 (39.5%)	
9041G>A	GG	161 (80.5%)	99 (78.6%)	146 (37.4%)	
	GA	38 (19%)	24 (19%)	194 (49.7%)	<0.0001[c]
	AA	1 (0.5%)	3 (2.4%)	50 (12.8%)	
	G	360 (90%)	222 (88.1%)	486 (62.3%)	<0.0001[d]
	A	40 (10%)	30 (11.9%)	294 (37.7%)	

Data are reported as number with percent in parentheses. [a]Pooled data for the North and South regions. [b]Data from Ref. 6. [c]Chi-square test or, when appropriate, Fisher exact test for comparisons of genotype distribution across the three groups. [d]Chi-square test or, when appropriate, Fisher exact test for comparisons of allele frequencies across the three groups.

Table 3. Haplotype distribution of *VKORC1* polymorphisms in native Japanese, Brazilian-born first-generation Japanese and non-Japanese Brazilians.

Haplotypes	Native Japanese (N = 400)	First-generation (N = 252)	Non-Japanese Brazilian[a] (N = 778)
ATCG	359 (89.8%)	220 (87.3%)	94 (12.1%)
GTGA	35 (8.8%)	27 (10.7%)	293 (37.6%)
GTCA	2 (0.5%)	2 (0.8%)	0
ATCA	2 (0.5%)	0	0
GGGA	1 (0.2%)	0	0
GGGG	1 (0.2%)	0	0
AGCG	0	1 (0.4%)	165 (21.2%)
ATGA	0	1 (0.4%)	0
GTGG	0	1 (0.4%)	178 (22.9%)
GTCG	0	0	48 (6.2%)

Data are reported as number with percent in parentheses. [a]Data from Ref. 6.

polymorphisms examined (Table 2). However, comparison of either group with Brazilians with no Japanese ancestry (Table 2) revealed highly significant differences in both allele frequencies and genotype distribution of each *VKORC1* polymorphism. Thus, the variant alleles 3673A and 6853C were two to three times more frequent, and the 9041A allele was three times less common in the two Japanese groups compared to Brazilians with no Japanese ancestry. The *VKORC1* 5808G allele was rare in the Japanese groups (0.4%), whereas it occurred in 21% of Brazilians with no Japanese ancestry (Table 2).

Table 3 shows the *VKORC1* haplotype distribution in the study cohort. Haplotype ATCG was by far the most common (87-90%) in both native and first-generation Japanese, followed by haplotype GTGA (8-11%). The other haplotypes accounted for <2% total genetic variability in these groups. This haplotype distribution differs markedly from that previously reported for Brazilians with no Japanese ancestry (6), in whom GTGA was the predominant haplotype (38%), followed by haplotypes GTGG (23%) and AGCG (21%). Not surprisingly, a highly significant difference ($P < 0.0001$, Fisher exact test) in *VKORC1* haplotype distribution was observed between Brazilians with no Japanese ancestry and either native or first-generation Japanese.

Discussion

The present results indicate that the frequency of genetic polymorphisms in four proteins involved in phases I (*CYP2C9* and *CYP2C19)* and II (*GSTM3*) of drug metabolism and in drug pharmacodynamics (*VKORC1*) does not differ between native Japanese and Brazilian-born Japanese descendants living in Brazil. These results are consistent with historical evidence that intermarriage between native Japanese who had emigrated to Brazil and Brazilians with no Japanese ancestry is unusual (3). Our data for both Brazilian-born, first-generation Japanese and (not surprisingly) for native Japanese living in Brazil are in excellent agreement with published data on individuals born and living in Japan regarding the frequency of polymorphisms in *CYP2C9* (4,11), *CYP2C19* (4,11) and *VKORC1* (5,12). To the best of our knowledge, there are no published data on the frequency of the *GSTM3*A/*B* polymorphism in Japanese. If so, our study is the first report of the absence of the *GSTM3*B* allele in native Japanese, consistent with results for other Asian populations (13,14).

The striking similarity in the frequency of clinically relevant pharmacogenetic polymorphisms between Brazilian-born Japanese descendants and native Japanese observed in the present study suggests that the former may be recruited for clinical trials designed to generate bridging data for the Japanese population in the context of the ICH (1). This possibility is all the more attractive in view of the expressive number (~1.5 million) of Brazilian-born individuals of Japanese ancestry (2). However, it should be acknowledged that the data obtained in the present study cohort, composed of first-generation Japanese descendants living in agricultural colonies, may not be extrapolated to the second- and third-generations of Brazilian-born subjects of Japanese ancestry, especially those individuals living in urban centers, because of the increasing impact of genetic admixture (3). Accordingly, the remarkable differences in the frequency of the studied pharmacogenetic polymorphisms between Brazilians with no Japanese ancestry and either native or first-generation Japanese are likely to be attenuated as the extent of admixture increases.

Among the genes investigated in the present study, *CYP2C9* and *CYP2C19* encode enzymes that are responsible for the hepatic metabolism of 20% of all prescribed drugs (15). The *CYP2C9*2*, *CYP2C9*3*, *CYP2C19*2*, and *CYP2C19*3* variant alleles are associated with reduced or null enzyme catalytic activity, which may affect drug disposition leading to an altered clinical response. For example, the intrinsic clearance of S-warfarin is reduced in carriers of *CYP2C9*2* and/or *CYP2C9*3*, who require lower warfarin maintenance doses to attain adequate anticoagulation (16,17). Genetic variation in *CYP2C19* has been found to modulate the efficacy of proton pump inhibitors such as omeprazole and lansoprazole: data from Japanese cohorts show that carriers of the *CYP2C19*2* or **3* variant alleles display higher cure rates for gastroesophageal reflux disease and *Helicobacter pylori* infection by proton pump inhibitor-based therapies than patients with the *CYP2C19*1/*1* genotype (18). The relatively high combined frequency of *CYP2C19*2* and **3* in Japanese individuals (confirmed in the present study) may account for these results, which have not been consistently repro-

duced in other populations (19,20).

The *GSTM3*A/*B* polymorphism, a 3-bp insertion/deletion in intron 6, which may affect regulation and ultimately the amount and activity of *GSTM3* (9), has been investigated as a risk factor for cancer, with contradictory results (21-23). The *GSTM3*A/*B* polymorphism was monomorphic in our study population suggesting that the increased risk associated with the variant *GSTM3*B* allele may not be relevant to the Japanese and other southeast Asian populations, in which this allele is absent or rare (14).

The *VKORC1* polymorphisms examined in the present study are major determinants of warfarin dose requirements in most populations, including the Japanese (5,12,24). The *VKORC1* gene encodes vitamin K epoxide reductase, which is the target for the anticoagulant effect of warfarin (25). Haplotypes including *VKORC1* 3673A, which largely predominate among Japanese and other eastern Asian populations (24), predict high sensitivity to the anticoagulant effect of warfarin. This is thought to account for the low-dose phenotype that predominates in these populations, and in view of the present results, may be anticipated to prevail among first-generation, Brazilian-born Japanese.

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