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Nature Publishing Group
Academic Journals Division,
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Nature Publishing Group
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345 Park Avenue South
New York 10010-1707, USA

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Pharmacogenomics in admixed populations: the Brazilian pharmacogenetics/pharmacogenomics network—REFARGEN

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Interethnic genetic differences in the prevalence of polymorphisms affecting drug-metabolizing enzymes, drug transporters, and receptors are well documented and must be considered within the perspective of individualized pharmacotherapy. Pharmacologically relevant genetic polymorphisms are rarely present or absent exclusively in one of the three major continental populations (African, Asian and European) that have been more extensively investigated. Possible examples are the *CYP2C9*2* allele, which has not been reported in Asians, and both *TPMT*2* and **3A*, which appear to be absent in Africans. In most cases of documented interethnic pharmacogenomic differences, it is the allelic frequency of polymorphic loci which vary across continental populations; the mean variation, however, remains substantially smaller than the variation between individuals comprising these populations. This is not surprising, since only ~10% of the total human genetic diversity stems from continental rather than individual differences. Irrespective of whether human 'races' are social constructs without biological meaning, there is overwhelming evidence for genetic admixture in people from different ancestries in most, if not all populations.

In the American continent, the autochthonous Amerindians, and people of European and African origin, contributed in different degrees and in a gender-specific manner to the formation of the tri-hybrid population of the present time. In the United States, the average European admixture in African-Americans has been estimated as ~19–26%, whereas the percentage of non-European alleles in Euro-Americans is less than 5%.¹ Brazil, the largest country in South America and the fifth largest in the world, is inhabited by a highly heterogeneous population of 180 million people. Estimates based on matrilineal ancestry (mitochondrial DNA (mtDNA) haplotypes) in Brazilians self-identified as white indicate similar contributions (30–40%) of Amerindian, African and European females, although significant regional differences were noted, with higher Amerindian contribution in the North region and predominance of European ancestry in the South. In contrast, less than 5% of the patrilineal ancestry (Y-chromosome) in white Brazilians was non-European. Conversely, in self-identified black Brazilians, European ancestry is higher in the Y chromosome as compared to the mtDNA.^{2–5} These observations are consistent with the evidence of asymmetrical mating in relation to sex and ethnicity, which occurred in the formation of the Brazilian population. The extensive admixture of Brazilians makes also ethnic classifications, based on continental origin, parental background or physical appearance rather relative. Furthermore, race identification is not a static characteristic—a person who is 'black' in the United States may be 'white' in Brazil, where no racial descent rule is operational, and it is possible for two siblings differing in 'color' to be included in diverse racial or ethnic categories.

Interethnic admixture introduces variation in individual ancestry, and results in distinct levels of population structure, depending on the extent and dynamics of the admixture process and the prevailing social environment where this process developed. Thus, extrapolation of pharmacogenomic data across admixed populations, even when the ancestral roots are shared, may be misleading if not unwarranted. Polymorphisms of the *TPMT* gene—which is an outstanding example of the clinical utility of pharmacogenomics—illustrate the marked differences that can be observed across populations in the Americas: In Brazilians, either white or non-white, the frequencies of the variant alleles *TPMT*3A* and *TPMT*3C* do not differ significantly,⁶ whereas in European-Americans *TPMT*3A* is 16 times more frequent and, conversely, in

African-Americans it is three times less frequent, than *TPMT**3C.⁷ Even within South America, significant differences in *TPMT* allele frequencies are observed between neighboring countries: *TMPT**3C, which occurs in 1.8% of white Brazilians, has not been detected in Argentinians.⁸

To deal with the specificities of pharmacogenomics in our heterogeneous population, Brazilian researchers from various institutions distributed over the five regions of the country established a collaborative network, named Rede Nacional de Farmacogenética/farmacogenômica or REFARGEN (Brazilian National Pharmacogenetics/pharmacogenomic Network). REFARGEN aims to promote close scientific interaction among its members, to establish a multi-centered repository of biological samples for pharmacogenomic studies, to create an archive of pharmacogenomic data for the Brazilian population, to provide a forum for public debate of topics pertaining to pharmacogenomics and to play an active role in educational programs directed to the health science students, professionals and public health officials. In 2004, REFARGEN's members have organized symposia in the annual national meetings of the Brazilian societies of Clinical Genetics, Genetics, and Pharmacology and Experimental Therapeutics, as well as in the Congress of the European Societies of Pharmacology (EPHAR2004). Pharmacogenomics in admixed populations, a motivation force behind the creation of REFARGEN, is the topic of a symposium scheduled for the 2005 annual meeting of the American Society for Clinical Pharmacology and Therapeutics. Additional information on REFARGEN's members, activities and organization can be accessed at www.refargen.org.br.

Pharmacology and genetics, the pillars of pharmacogenomics, have a long tradition in Brazil and are represented by national societies with many decades of activity and thousands of members. It is significant that three of the four Brazilian members of the USA National Academy of Sciences are either geneticists (Francisco M Salzano and Warwick E Kerr) or pharmacologists (Sergio H Ferreira), and all the three have been presidents of their respective national societies. Pharmacogenomic investigation raises important ethical questions. Brazil has a structured system for the approval of clinical protocols, based on institutional review boards (IRB), which must be accredited—and are reviewed at regular intervals—by an independent national ethics committee (CONEP) linked to the National Health Council (CNS). This guarantees proper ethical conduct for any project developed in the country. The guidelines for research in human genetics, encompassing pharmacogenomic studies, were updated by the CONEP-CNS system in August 2004 and provide a solid ethical background for Brazilian researchers to contribute data from our population, and meet the challenge of expanding on a global scale, pharmacogenomics' promise of individualized therapy—including in this process developing countries such as Brazil and its large and admixed population, who will now be in a position to benefit from the advances achieved in this field. In this context, REFARGEN's mission is to support Brazilian researchers and their international collaborators in this endeavor.

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G Suarez-Kurtz

Division of Pharmacology, Instituto Nacional de Câncer, Rio de Janeiro, RJ, Brazil
E-mail: kurtz@inca.gov.br