Pharmacogenomics and the genetic diversity of the Brazilian population

Brazilians represent one of the most heterogeneous populations in the world, as a result of five centuries of admixture between its three ancestral roots: autochthonous Amerindians, white Europeans, and sub-Saharan Africans. The heterogeneity and admixture of Brazilians has important implications for the design and interpretation of clinical trials, the implementation of pharmacogenetics/-genomics (PGx) knowledge in drug prescription, and the extrapolation of PGx data from other, more homogeneous populations. The population paradigm in PGx emerges from the observation that the frequency of several polymorphisms in "pharmacogenes" may vary widely among populations. One extreme example is provided by the *CYP3A5* gene, which encodes the drug-metabolizing enzyme CYP3A5, important for the elimination of several clinically useful drugs, such as the immunosuppressants tacrolimus and cyclosporine. The frequency of the variant *CYP3A5*3* allele, which encodes a non-functional CYP3A5 isoform, is less than 10% among sub-Saharan Africans but exceeds 90% among Europeans. However, the frequency of *CYP3A5*3* in healthy Brazilians living in Rio de Janeiro, self-identified as white ("branco") or black ("preto") according to the "color/race" categorization of the Brazilian census, was 78% and 32%, respectively (*Pharmacogenomics* 2007; 8:1299-306). Thus, the *CYP3A5*3* allele is three times more frequent among self-identified black Brazilians (32%) than black Africans (< 10%) and is considerably less common among self-identified white Brazilians (78%) than Europeans (> 95%). The African-European admixture of Brazilians provides an explanation for these discrepancies, since irrespective of "color/race" self-identification, most Brazilians share European and African genetic ancestries, and many have also a significant proportion of Amerindian ancestry (*Pharmacogenomics in Admixed Populations*. Landes Bioscience; 2007). It is reasonable to think that the sizeable contribution of European ancestry in self-identified black Brazilians accounts for the higher frequency of *CYP3A5*3* in this group, compared to black Africans. Similarly, the proportion of African ancestry in white Brazilians may account for the lower frequency of *CYP3A5*3* in the latter, compared to Europeans. The situation described for the *CYP3A5*3* polymorphism was reproduced in our studies on other PGx polymorphisms (*Pharmacogenet Genomics* 2007; 17:765-72; *Eur J Clin Pharmacol* 2008; 3:253-6). Collectively, these results indicate that extrapolation of PGx data from relatively homogeneous groups (e.g. white Europeans or North Americans) is clearly not applicable to the majority of Brazilians (*Trends Pharmacol Sci* 2005; 26:196-201).

Recognition of this fact prompted the creation of the Brazilian Pharmacogenetics Network (REFARGEN; http://www.refargen.org.br), a consortium of 18 research groups from Brazilian institutions, with the mission to provide leadership in PGx research and education in Brazil, with a population health impact. REFARGEN researchers developed logistic regression approaches to investigate the influence of individual ancestry – estimated with a panel of insertion/deletion polymorphisms validated as ancestry-informative markers (*Ann Human Genet* 2006; 70:658-65) – on the frequency distribution of PGx polymorphisms among Brazilians. The results showed that the heterogeneity of our population must be dealt with as a continuous variable, which cannot be adequately represented by arbitrary "race/color" categories. In a PGx-informed context, this implies that each person must be treated as an individual rather than as an "exemplar of a race", and that the notion of "race-targeted" drugs is unacceptable, especially in the case of admixed populations.

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