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Ethnic differences in drug therapy: a pharmacogenomics perspective

Expert Rev. Clin. Pharmacol. 1(3), 337–339 (2008)



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“...when treating individual patients, the focus must be shifted from populations, ethnicities or races to the inherent genetic individuality that results from unique mosaics of variable haplotypes.”

“Pharmacogenetics deals with pharmacological responses and their modification by hereditary influences.” This definition, offered by Werner Kalow in the first book dedicated to pharmacogenetics, highlights the three pillars of this discipline: pharmacology, genetics and human diversity [1]. Pharmacogenetics has evolved greatly over the 50 years since Kalow’s book was published, and was rechristened pharmacogenomics (PGx) in the fashion of the ‘omics’ revolution, but its conceptual development and praxis remain contingent upon a better understanding of human genomic diversity and its impact on drug pharmacokinetics and pharmacodynamics. Ethnic specificity has become an integral part of pharmacogenetics/PGx research to the extent that, at the writing of this editorial, the PubMed database lists over 400 entries, including 141 reviews, for a query combining the terms ‘pharmacogen* and ethnicity’. The accumulated data reveal that allele, genotype and haplotype frequency of polymorphisms in ‘pharmacogenes’ (genes of pharmacological relevance) may differ significantly among populations categorized by ‘race’, ethnicity or continental origin. Such differences may be large (>50%) as is the case, for example, of the *CYP3A5*3* and *GSTM3*B* allele frequency between Europeans and sub-Saharan Africans. However, equally large or even larger intraethnic PGx variability is also evident, such as the fivefold range of *CYP3A5*3* frequency among sub-Saharan Africans or the 17-fold range of *CYP2C19*2* frequency within Europeans [2,101]. Two other facts conflict with the notion of race-based drug therapy in the context of PGx-informed

clinical pharmacology: first, only rarely, if ever, is a PGx polymorphism absent or common (>5%) exclusively in one specific population. Although large-scale resequencing studies of PGx candidate genes are more likely to identify low-frequency polymorphisms that are ‘private’ to a given population group, the implications of these findings on the praxis of PGx are still debatable. Second, data from a worldwide analysis of *CYP2D6* polymorphisms disclosed that the patterns of variation within and among populations are best described as a broad geographic cline, with no continental structure, similar to those shown by neutral markers [3].

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Collectively, the aforementioned observations should caution against the use of continental labels to lump together heterogeneous populations, as is often done in the PGx literature. The Asian category, for example, is applied to individuals of distinct ethnicity and/or living in different countries or regions of the vast continent of Asia. Not surprisingly, significant variation in the distribution of PGx polymorphisms is detected among ‘Asians’. Singapore provides a remarkable example of PGx diversity across different ethnic groups (Chinese, Malay and Indian) within a single country: the *CYP3A5*3* allele is nearly twice as frequent in Indians and Malays than in Chinese, whereas the functional haplotype *SLCO1B1*15* gene that encodes the liver-specific OATP1B1

drug transporter is rare in Indians (~2%) but occurs in approximately 10% of both Chinese and Malays [4]. Furthermore, intra-ethnic differences among the people of Asia are known to occur, for example, the 12-fold higher frequency of the duplicated *CYP2D6* genotype in Indians from Singapore [4] compared with Indians from Malaysia [5].

“The picture that emerges from the worldwide distribution of genetic polymorphisms in pharmacogenes is consistent with the pivotal studies of Lewontin, which established that interindividual differences account for most of all human variation.”

The picture that emerges from the worldwide distribution of genetic polymorphisms in pharmacogenes is consistent with the pivotal studies of Lewontin [6], which established that interindividual differences account for most of all human variation. This paradigm extends further to the variation in drug-response phenotypes across populations/ethnicities. For example, the median metabolic ratio (MR) of the *CYP2D6* probe debrisoquine differs 2 to 2.4-fold between Europeans (Swedes, MR: 0.56) and either Africans (Ethiopians, Yorubas and Zimbabweans, MR: 1.14) or Asians (Chinese, MR: 1.32), whereas a tenfold range of variation is observed within each group [7]. Data from two widely prescribed therapeutic classes, namely lipid-lowering statins and coumadin anticoagulants, confirm this pattern. Thus, single-dose studies in healthy volunteers showed that Chinese and Malays from Singapore achieve higher plasma concentrations of rosuvastatin than white subjects living in the same environment [8], and that Koreans experience a higher plasma exposure to rosuvastatin than Europeans [9]. In both comparisons, the mean value of the pharmacokinetic parameters of rosuvastatin exposure was 2 to 3.5-fold greater in the Asian populations. However, the interindividual variation was several-times greater within each population sample. Warfarin (Coumadin®) is the most commonly prescribed drug for therapy and prevention of thromboembolic conditions. Warfarin has a narrow therapeutic window and displays broad variation in intra- and inter-individual drug requirements, demanding close clinical monitoring and repeated international normalized ratio (INR) measurements. Several studies have shown that the weekly dose of warfarin required to attain the INR target range (usually 2–3) is 15–20% lower in white (Caucasian American) than in black (African-American) patients [10–12]. We observed similar results (PERINI JA, SUAREZ-KURTZ G, UNPUBLISHED DATA) in a cohort of approximately 400 Brazilian patients self-identified as white or black, but it was also evident that the required weekly dose of warfarin to achieve the target INR varied over tenfold within each of our patient ‘color’ groups! In a multivariate analysis, black ‘race’ was found to explain 9% of the variability in warfarin dose among US patients [12]. However, the individual proportion of African ancestry, estimated by ancestry informative markers, varies widely among African-Americans (e.g., from 2.3 to 97.8%, in

the Coronary Artery Risk Development in Young Adults study cohort [13]) and, most importantly, in a continuous manner. Not surprisingly, the frequency of PGx polymorphisms in African-Americans may vary depending on the region of the USA in which the study was performed [14]. This pattern of intraethnic heterogeneity must be acknowledged in debates over race-targeted therapy for African-Americans and, by extension, other extensively admixed populations, such as Brazilians and US Hispanics [15]. It is reasonable to anticipate that the continuum in genetic ancestry within admixed populations of the Americas will be reflected in the frequency distribution of PGx polymorphisms. We used a logistic regression approach to verify that this is indeed the case for polymorphisms in several pharmacogenes (*CYP3A5*, *GSTM1*, *GSTM3*, *ABCB1* and *GNB3*) among Brazilians. This analysis showed that the distribution of the variant alleles/genotypes is best fit by continuous functions of the proportion of individual African ancestry, irrespective of self-reported color/racial categories [16–19]. There is evidence that, for at least one of the variants that we studied – *GSTM1-null* – a similar situation prevails among African-Americans [20].

The diversity in drug response across populations/ethnicities – population PGx – will probably continue to stimulate PGx research and receive greater attention from regulatory agencies than it has hitherto, with inevitable consequences on how drugs are developed, evaluated, approved, promoted and ultimately prescribed [21]. Recognition of interethnic differences in drug response might be useful in the establishment of public health policies, the design and interpretation of clinical trials, and possibly to help guide clinicians to prospectively evaluate those patients with the greatest probability of expressing a variant genotype. However, when treating individual patients, the focus must be shifted from populations, ethnicities or races to the inherent genetic individuality that results from unique mosaics of variable haplotypes [22]. In a PGx-informed context, this uniqueness implies that an individual cannot be treated as ‘an exemplar of a race’ [23], a notion particularly important for admixed populations, in which stratification further increases the fluidity of racial/ethnic labels. PGx has the potential to benefit people worldwide and to reduce the health disparity between developing and developed nations. This goal is unlikely to be achieved by relinquishing the notion of personalized drug therapy tailored to individual genetic characteristics in favor of models of population-based drug development and prescription, with all their potential pitfalls, especially when extended to admixed populations in developing or developed nations [24].

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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