Review TRENDS in Pharmacological Sciences Vol.26 No.4 April 2005

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Pharmacogenomics in admixed populations

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Personalized drug therapy proffered by pharmacogenomics must be based on the recognition of inherent genetic individuality, rather than relying on inter-ethnic differences in the frequency of polymorphisms that affect the pharmacokinetics and targets of drugs. This is particularly significant in admixed populations, in which the substructure created by inter-ethnic crosses further increases the fluidity of racial and/or ethnic labels. Inter-ethnic admixture is either common or increasing quickly in many, if not most, populations, and so extrapolation on a global scale of pharmacogenomic data from well-defined ethnic groups is plagued with uncertainty. To impact positively on global health, pharmacogenomics must broaden its scope of investigation with respect to both target and population diversity, and avoid the risk of contributing to the creation of a genomics divide between regions and nations. In this review, I examine the challenges and advantages of studying pharmacogenomics in admixed populations, drawing examples mainly from the tri-hybrid populations of the Americas.

Inter-ethnic pharmacogenomic differences

Pharmacogenetics and pharmacogenomics deal with variations in drug response caused by hereditary factors [1]. Their most enticing promise is to reduce this variation by tailoring drug therapy to the genetic make-up of individuals [2]. Genetic polymorphisms affect both pharmacokinetics and pharmacodynamics, and their prevalence varies across populations. However, rarely, if ever, is a given polymorphism present or absent exclusively in one of the three continental populations – African, Asian and European – that have been investigated most extensively. In most documented cases of inter-ethnic pharmacogenomic differences, the mean difference between two populations is substantially smaller than the variation between individuals that comprise the populations [3]. This is not surprising because human genetic diversity stems largely from individual rather than continental differences [4]. Regardless of whether human 'races' are social constructs with no biological meaning [4–9], there is ample evidence of genetic admixture (see Glossary) in many, if not most, populations. Significantly, 'mixture of dissimilar individuals' was recognized as a factor of individual 'varieties' by George Leclerc (1707–1788), one of the first naturalists to discuss human variation [4].

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Available online 3 March 2005

In this review I examine the impact of admixture on pharmacogenomics, taking examples mostly from the people of the Americas who have been studied extensively from a population genetics perspective and are represented highly in pharmacogenomic trials [2]. However, the influence of admixture on pharmacogenomics is also evident in other continental populations. In Africans, the allele frequency of genes that encode drug-metabolizing enzymes (DMEs) differs significantly: Egyptians resemble Europeans in the allelic frequencies of genes that encode cytochrome P450 enzymes [10], but have a distinct frequency distribution of sulfotransferase variants [11], whereas Ethiopians differ from sub-Saharan Africans and African–Americans with respect to the *CYP2D6* locus [12], and have a unique distribution of *CYP2C9* alleles [13]. These data reflect the admixture of European, African and Middle Eastern characteristics in the gene-pool of modern Egyptians [14], and the significant fraction of Caucasoid origin in Ethiopians, who have been described as 'similar to Caucasoids, but otherwise very different' [4].

Pharmacogenomic evidence of population heterogeneity across Asia is also documented. Arabs (95% Saudi Arabians) resemble Caucasians for some DME-encoding alleles and Africans for other alleles, but have little similarity in genotype and allele frequencies with East Asians (Chinese, Japanese and Koreans) [15]. The latter have a high prevalence (13–20%) of the poor-metabolizer phenotype of CYP2C19, which is associated with defective alleles *CYP2C19*2* and *CYP2C19*3*. This pattern is not observed in Saudi

Glossary

Ancestry informative markers: Genetic markers that occur with substantially different allelic frequencies in different population groups. They are used to investigate genetic ancestry.

Biparental autosomal markers: Variable sites in the autosomal chromosomes. They are inherited from both parents, each of whom provides one allelic copy.

Genetic admixture: The mixing of two or more genetically different populations.

Haplotype: A specific segment of DNA that is inherited as a unit.

Linkage disequilibrium: The non-random association of alleles at different polymorphic sites in the genome.

Population structure: The organization of a population into sub-populations that differ in allele frequencies because of non-random mating, finite population size and/or geographical barriers. This is also known as stratification.

Uniparental genetic markers: Variable sites in mitochondrial DNA that are inherited from the maternal side (matrilineage), and variable sites in the Y-chromosome that are inherited exclusively by the son from the father (patrilineage).

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Arabians and in Thais but it is present in other South-East Asians (Filipinos and Indonesians) [16,17].

Inter-ethnic admixture in the American continent

Native Amerindians, European immigrants and Africans, who were originally brought in forcefully to the Americas, have contributed to different degrees and in a gender-specific manner to the formation of the trihybrid American population of the present time. Ancestry informative markers are a major asset in the study of the admixture process in the Americas. Thus, data from uniparental markers such as mitochondrial DNA (mtDNA) and the Y chromosome (for matrilineal and patrilineal ancestries, respectively) concur with historical evidence of asymmetrical mating in relation to sex and ethnicity that prevailed in the formation of both Latin American and North American populations. The most consistent finding is the introduction of European genes through males by the disproportionate number of unions of European males with African and Amerindian females [18]. Data from Brazil, which is the largest South American country and inhabited by a heterogeneous population of 180 million, illustrates this point: the mtDNA pool of white Brazilians reveals nearly equal amounts (30–40%) of Native American, African and European lineages, whereas <5% of the Y-chromosome pool is non-European. Conversely, an important European contribution is detected in the Y-chromosome pool of black Brazilians [18–21]. The admixture and, consequently, heterogeneity of the present-day populations of the Americas is also evident in autosomal genes that encode pharmacogenomic targets. Recent data from population-specific biparental autosomal markers estimate that the African ancestry in white Brazilians ranges from 13% to 32%, depending on the region of the country [22]. This agrees with previous results (7–34%) compiled from several sources [18]. By contrast, the European contribution to the genetic pool of 'African-derived' (black) Brazilians is estimated at 21–38%, whereas the Amerindian contribution to both white and black Brazilians varies from <10% in the south-east to 40–50% in the north (Amazon) [18]. Comparable results have been reported for other Latin American countries [18,23]. In the USA, the percentage of non-European alleles in European–Americans is, on average, <5%, whereas the European admixture in African–Americans is greater (19–26%) but varies widely, with some people having up to 70% of alleles associated with Caucasoids [24,25]. Genetic heterogeneity is also evident among Hispanics (defined as descendants of people from Latin American countries and other Spanish cultures), who represent 12% of the population of the USA, and share Amerindian, European and African ancestry. The Amerindian contribution is greater in the west (36–68%) than in the east (0–21%), at the expense of the European component, whereas the African contribution is similar in both regions (0–17%) [26].

Admixture introduces population structure

Admixture brings additional challenges to categorization based on continental origin, parental background and/or physical appearance. History shows that race and ethnic identification is not static but is flexible and responsive to the socio–political context in which it is deployed [27]. An example is the malleability of boundaries adopted by the United States Census Bureau, from the extreme 'one-drop rule' of the 1920s, whereby persons with even one ancestor of African origin were classified as black, to self-inclusion in either one or more ethnic groups, which prevails presently. Self-identification is also adopted by the Brazilian Census (http://www.ibge.gov.br/home/estatistica/populacao/censo2000/), in which six color/racial categories are proposed: white, black, Amerindian, intermediate ('pardo' in Portuguese, which encompasses admixture of white, black and/or Amerindian), yellow and other. Adopting the same categorization criteria does not eliminate cultural differences in racial and/or ethnic perception: a person who is 'black' in the USA might be 'white' in Brazil, where there is no racial-descent rule and it is possible for two siblings who differ in 'color' to be included in different racial and ethnic categories [18,22]. These drawbacks should be kept in mind when self-identified race information is adopted as a categorization criteria, and caution against interchangeably applying terms such as white, Caucasian and European on the one hand, and black, Negro and African on the other hand, when referring to persons of admixed ancestry. Regarding pharmacogenomics, it is hoped that better knowledge of genotype–phenotype associations will lead to the use of genetic markers alone to individualize therapy, thus obviating the controversial use of either race or ethnicity for this purpose.

A consequence of inter-ethnic crosses is variation in individual ancestry that generates distinct levels of population structure, depending on the extent and dynamics of the admixture process and the prevailing social environment in which this process develops. Thus, extrapolation of pharmacogenomic data from homogeneous (either little or no admixture) to admixed populations, and across admixed populations that share the same ancestral roots, might be misleading and unwarranted. The polymorphic *TPMT* gene can be used to support this assertion.

TPMT encodes the enzyme thiopurine *S*-methyltransferase (TPMT), which degrades purine anti-metabolites (e.g. 6-mercaptopurine and azathioprine) that are used to treat childhood acute lymphoblastic leukemia (ALL) and used as immunosupressant agents. TPMT activity varies between individuals in all populations investigated, with a common trimodal-distribution pattern in which ∼89%, 11% and <0.5% of individuals have high, intermediate and either low or undetectable activity, respectively [28]. Adjusting the dose of 6-mercaptopurine according to the TPMT phenotype has had a major impact on the 5-year ALL-survival rate [29], and this is now performed routinely in many pediatric centers. This provides an outstanding example of the clinical value of pharmacogenomics. The variation in TPMT activity is caused largely by single nucleotide polymorphisms (SNPs), the three most common defective alleles being *TPMT*2* (G238G), *TPMT*3A* (G460A and A719G) and *TPMT*3C* (A719G) [30]. The frequency distribution of these alleles varies markedly across and within continental

Table 1. Distribution of the major variant alleles of *TPMT*[a]

Population group	*TPMT*2*	*TPMT*3A*	*TPMT*3C*
European	0.5	2.4–5.7	0.2–0.8
African:			
Kenyans and Ghanians	0	0	5.4–7.6
Egyptian	0	0.3	1.3
Asian:			
Chinese and Japanese	0	0	0.3–2.3
South-West Asian[b]	0	1.0	0
North American:			
European–American	0.2	3.2	0.2
African–American	0.4	0.8	2.4
South American:			
White Brazilian	0.6	1.8	1.8
Non-white Brazilian[c]	0.8	2.0	2.5
Argentinian	0.7	3.1	0

[a]As the % of total *TMPT* alleles. Data are from [31] and references therein.
[b]Includes people from India, Pakistan, Sri-Lanka and Nepal.
[c]Includes blacks and 'ethnically admixed'.

populations (Table 1). *TPMT*3A* is the most common allele in Europeans and South-West Asians, but has not been detected in either East Asians or West Africans, who also do not carry the *TPMT*2* allele. Nevertheless, *TPMT*2* and *TPMT*3A* are present in African–Americans, black Brazilians and Egyptians, which is consistent with European admixture in these three groups (see earlier). Notably, the relative frequencies of *TPMT*3A* and *TPMT*3C* in white and non-white Brazilians are not significantly different, which contrasts with the differences in the frequencies of these alleles in all other ethnic groups studied (Table 1). The extensive interethnic crossings and ensuing high level of genetic admixture in the Brazilian population have been suggested to account for this unique situation [31].

Pharmacogenomic studies in admixed populations

If not controlled for, the population structure created by admixture can affect gene mapping efforts and confound the association of other genetic and environmental factors with drug responses. This requires 'sifting through genetic noise' [3], which might not be necessary with non-admixed populations. Another perceived drawback of admixture is that the genetic variant that influences the response to a drug in one group might not have the same effect in another group because of different gene–gene and gene–environmental interactions. For example, a common polymorphism (C3435T) of the *ABCB1* (*MDR1*) gene, which encodes the *P*-glycoprotein drug transporter, is associated with inconsistent, opposite effects in drug pharmacokinetics (e.g. digoxin) and protein expression in different ethnic groups (reviewed in [32]). Ancestry-informative (population-specific) markers, which are used for genealogical studies and forensic genetics [33], might be valuable in pharmacogenomics as a tool to control the confounding effects of population admixture (see later).

Conversely, some characteristics of admixed populations might be advantageous for pharmacogenomic research: first, population admixture results in longer linkage disequilibrium (LD) segments than in the previously isolated populations, which enables fewer markers to be used in gene-association studies [34]. This property is valuable in investigating disease causality [35,36] and might be useful in pharmacogenomic research. The results of a recent study of the influence of *CYP2A6* polymorphisms on smoking behavior in Brazilians illustrate this point [37]. CYP2A6-mediated reactions account for ~80% of the catabolism of nicotine, the major culprit of tobacco dependence, and several studies have focused on the influence of *CYP2A6* polymorphisms on smoking habits and nicotine dependence [38–40]. A significant association between the variant *CYP2A6*1B* allele and smoking status has been verified in Brazilians in which individuals who have either one or two copies of *CYP2A6*1B* are over-represented among non-smokers compared with ever-smokers (i.e. smokers and ex-smokers) [31]. This association is influenced markedly by population structure: the risk of being smoking dependent is 14 times lower and 3 times lower, respectively, in white and intermediate Brazilians who have the *CYP2D6*1B* allele, compared with their wild-type homozygous counterparts. However, no such protective effect of the *CYP2D6*1B* allele is observed in self-identified black Brazilians. The latter result is confirmed by a subsequent survey of an isolated Amazon community of black persons in whom genetic admixture with European and Amerindian stocks is negligible (G. Vasconcelos *et al.*, unpublished). We intend to apply population-specific genetic markers that are validated for the Brazilian population [22] to explore the influence of individual genetic ancestry on the association of *CYP2A6*1B* with smoking dependence.

Because *CYP2A6*1B* appears to code for a normal phenotype, its association with tobacco dependence cannot be explained by impaired nicotine metabolism, as proposed previously for *CYP2A6* alleles that encode enzymes with either no activity or reduced activity [38,40]. It has been suggested that *CYP2A6*1B* might be in gene linkage with other mutation(s) that are the true cause of the observed association with smoking behavior, and that this LD is sensitive to population structure [37]. Polymorphisms that might be protective in one population but not in others have been described previously. These include SNPs in the promoter region of the gene encoding cyclooxygenase 2, which have a different impact on the risk of developing prostate cancer in African–Americans compared with European–Americans [36]. Another example is the HEE haplotype of the gene that encodes the chemokine receptor CCR5, which is associated with delayed disease progression in European–Americans infected with HIV, but accelerated progression in African–Americans [41].

A second potential use of admixed populations in pharmacogenomics is to gather information on people, such as African and Amerindian groups, that are either excluded or under-represented in clinical drug trials. For example, the Brazilian population allows for genetic studies that are relevant to Africans from the west coast (present-day Angola, Zaire and Congo) and Mozambique, the major sources of the enslaved Africans trafficked into Brazil during the 16–19th centuries [42]. It is estimated that 94 million Brazilians (56% of the total population) have >50% African ancestry [43]. For comparison, the populations of Angola, Zaire and Mozambique are 11 million, 58 million and 18 million, respectively (http://www.infoplease.com/ipa/). These considerations indicate

that studies in Brazilians and other populations of admixed African ancestry might fill pharmacogenomic information gaps that are pertinent to African populations. A persuasive demonstration of this potential advantage of admixture is the identification in African–Americans of a *CYP2C9* variant (*CYP2C9*5*), which is derived from a C1080G transversion in exon 7 and encodes an enzyme isoform with reduced catalytic activity [44]. Subsequent studies revealed that this defective allele occurs in sub-Saharan Tanzanians and Beninese, but not in Ethiopians [45,46]. *CYP2C9*5* has not been detected in Europeans, European–Americans, Mexican–Americans and East Asians [44–47] and, therefore, appears to have a restricted distribution among sub-Saharan Africans and their descendants (Table 2). *CYP2C9*5* has a significant effect on the pharmacokinetics of the CYP2C9 substrate losartan in Africans [48], an observation that cautions against the indiscriminate extrapolation of genotyping panels across populations for the purposes of drug individualization. Clearly, panels based on the most frequent *CYP2C9* polymorphisms (*CYP2C9*2* and *CYP2C9*3)* in Europeans and European–Americans are of limited value for sub-Saharan Africans and their descendants, and Asians.

Concern over predictive pharmacogenomic tests might be extended to drug development because genetic differences in either admixed or homogenous populations might result in the preferential development of drugs that benefit one group more than another [49]. Although central to the impact of pharmacogenomics on societies, this issue is outside mainstream drug research and development, and has provided the impetus to create a collaborative network in Brazil, the Rede Nacional de Farmacogenética/farmacogenômica (REFARGEN) [50]. *CYP2C9* was one of the first clinically relevant pharmacogenomic targets investigated by REFARGEN's researchers, and the results indicate that the clearance of the CYP2C9 substrates tenoxicam and piroxicam is reduced significantly in Brazilians that are heterozygous for either *CYP2C9*2* or *CYP2C9*3* compared with wild-type homozygotes [51,52]. Notably, the two alleles affect the clearance of piroxicam and tenoxicam to the same extent, which contrasts markedly with data for other non-steroidal anti-inflammatory drugs (NSAIDs) studied in European, European–American and Japanese subjects (Figure 1). The latter studies detect significant effects of *CYP2C9*3* but not *CYP2C9*2* on the disposition and/or pharmacodynamics of celecoxib [53–55], flubirprofen [56] and ibuprofen [57,58]. However, neither variant allele affects the hydroxylation of diclofenac [59,60] (Figure 1). Considered together, these pharmacogenomic studies indicate that the influence of polymorphisms in *CYP2C9*

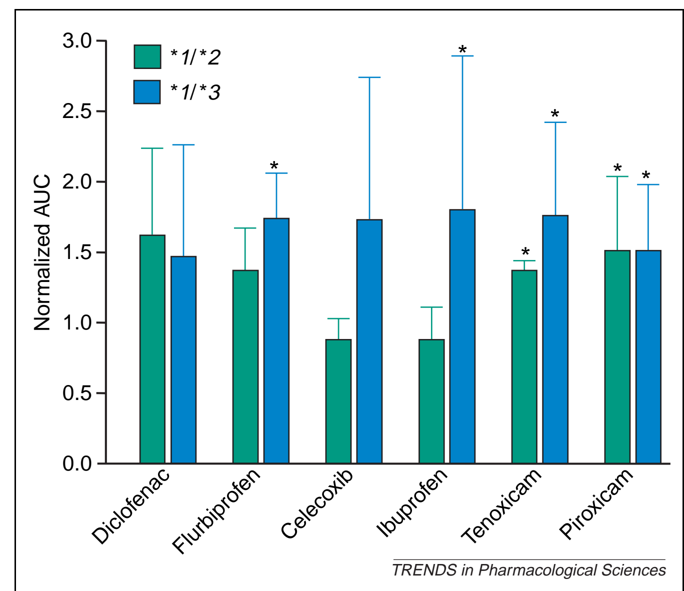

Figure 1. Influence of the defective alleles *CYP2C9*2 and CYP2C9*3* on the area under the plasma concentration versus time curves (AUC) of non-steroidal anti-inflammatory drugs (NSAIDs). Data for heterozygotes [**1/*2* (green) and **1/*3* (blue)] are expressed as mean+SD, normalized to the respective mean value in homozygous wild-type (*CYP2C9*1/CYP2C9*1*) individuals. Studies were selected with a minimum of three people in each heterozygous group. Diclofenac [59], flurbiprofen [56], ibuprofen [58], tenoxicam [51] and piroxicam [52] were administered as single doses. Celecoxib [54] was applied twice daily for 15 days, and the data shown refer to the last dose. $^*P<0.05$ for differences between heterozygotes and the corresponding wild-type homozygous group.

Table 2. Distribution of major *CYP2C9* alleles[a]

Population group	*CYP2C9*1*	*CYP2C9*2*	*CYP2C9*3*	*CYP2C9*5*
European[b]	74–82	11–16	7.4–9.8	0
African:				
West Africa[c]	95	0	0	0.8–1.8
Ethiopian	93	4.3	2.3	0
Egyptian	82	12	6	–
Asian:				
East Asian[d]	95–98	0	1.1–4.9	0
Turkish	79	11	10	–
North-American:				
European–American	78–86	8–15	4.3–7.0	0
African–American	95–98	1.0–2.5	0.5–1.3	1.7
Mexican–American	86	8	6	0
Canadian Indian	91	3	6	–
South American:				
White Brazilian	80	12	8.1	–
Intermediate Brazilian	86	7.2	6.8	–
Black Brazilian	92	4.5	3.2	–

[a]As the % of total *CYP2C9* alleles. Data from [44–47,51,65], and references therein].
[b]British, Italian, Spanish and Swedish.
[c]Beninese and Tanzanian.
[d]Chinese, Japanese, Korean and Taiwanese.

on the disposition and effects of NSAIDs is substrate-, variant-allele- and population-specific.

Concluding remarks

The recognition of inter-ethnic differences in drug response might be useful in establishing public health policies, designing and interpreting clinical trials and, possibly, guiding clinicians to evaluate prospectively which patients have the greatest probability of expressing a variant genotype. A practical example of these possibilities is the recent effort to target the heart failure drug BiDil® exclusively to African–Americans, under controversial claims of a distinctive 'patho-physiology found primarily' in this group (http://www.nitromed.com/BiDil.asp) [27]. However, personalized drug therapy, the promise of pharmacogenomics, must be based on the recognition of the inherent genetic individuality. This uniqueness implies that 'each person must be treated as an individual…rather than as an exemplar of a race' [9], a notion that is particularly important for admixed populations in which substructure increases further the fluidity of racial and ethnic labels. Because inter-ethnic admixture is either common or increasing quickly in many, if not most, populations, global extrapolation pharmacogenomic data from well-defined ethnic groups is plagued with uncertainty. Nevertheless, the relevance of population admixture was not addressed in a recent issue of *Nature Review Genetics* [61] that focused on pharmacogenomics. To impact positively on global health, pharmacogenomics must broaden its scope with respect to target and population diversity [62], and include admixed populations, with their perceived challenges and advantages. This goal is unlikely to be achieved simply by mandates to include subjects from ethnic minorities in clinical trials [63,64], particularly when these groups are represented in relatively small numbers and are labeled by phenotypes that do not reflect accurately genetic ancestry.

Acknowledgements

G.S-K. is a Senior Investigator of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and work in his laboratory is supported by grants from CNPq, Fundação Ary Frauzino (FAF), Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) and Swiss Bridge Foundation.

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