Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e45; doi:10.1038/psp.2013.17

www.nature.com/psp

PERSPECTIVE

Pharmacogenetics in Africa, an Opportunity for Appropriate Drug Dosage Regimens: on the Road to Personalized Healthcare

C Masimirembwa[1] and JA Hasler[1]

The modern human appeared in Africa around 200,000 years ago with subsequent later migrations to populate Europe, Asia, and North America.[1] As humans adapted to various diets, diseases, climates, and so on, inherited traits emerged that gave rise to distinct population groups with physical and physiological differences, including the response to xenobiotic challenges (Figure 1). This *Perspective* highlights the interpopulation differences in response to drugs focusing on Africa and implications for global pharmacometric studies.

CPT: Pharmacometrics & Systems Pharmacology (2013) **2,** e45; doi:10.1038/psp.2013.17; advance online publication 29 May 2013

VARIATION IN DRUG METABOLISM AND DISPOSITION

Approximately 60 years ago, the metabolism and disposition of isoniazid, an antituberculosis drug, was one of the earliest demonstrations of pharmacogenetic differences in drug handling that resulted in clinical consequences.[2] There were marked differences in excretion of the drug among individuals who were then classified into slow acetylators (SA) and rapid acetylators of isoniazid with SA individuals being more prone to suffer from isoniazid-induced peripheral neuropathy. After the cytosolic enzyme, *N*-acetyltransferase 2 was cloned, many genetic variants were found that explained the rapid acetylators and SA status, and epidemiological studies showed that the SA status could vary from 5 to 95% depending on the population studied.[2] Since the discovery of differences in extent of excretion of isoniazid, a vast literature has developed documenting many other genetic polymorphisms for drug metabolizing enzymes and drug transporters. Many of these genetic polymorphisms are known to have clinical effects and to exhibit interethnic differences (**Table 1**). Studies are now including pharmacogenetic variables in optimizing the clinical use of some drugs; for example, Azuma *et al.*[3] recently conducted a randomized controlled trial for pharmacogenetics-based therapy and showed that a NAT-2 genotype–guided regimen reduces isoniazid-induced liver injury and early treatment failure in tuberculosis patients. To ensure translation of research to the bedside, the Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network is working to establish guidelines for clinical use of pharmacogenetic data.[4]

The clinical importance of pharmacogenetic traits has made major drug regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency develop policy documents and guidelines on the subject that can be found through a search of their world-wide websites. The pharmaceutical industry has also formed the Industry-Pharmacogenomics Working Group (www.i-pwg.org) to work on research and ethical guidelines on the integration of pharmacogenetics in drug discovery, development, and clinical use of medicines. Many drugs now carry pharmacogenetics information in their labels or leaflets, and the US Food and Drug Administration has since approved a number of pharmacogenetics tests that could be used to improve the use of these drugs (www.pharmgkb.org).

AFRICA'S GENOMIC DIVERSITY, OPPORTUNITY FOR ADVANCES IN APPROPRIATE DOSING REGIMENS, AND PERSONALIZED HEALTHCARE

The discovery of most pharmacogenetic traits was at the interindividual level followed by studies that also demonstrated interpopulation differences, reflecting the genomic diversity of populations. These observations create an interesting link between genomic medicine and recent molecular evolution arising from population/environmental factors unique in time and geography and which have implications for the safe and efficacious use of drugs in different populations (**Figure 1**). Most dosing regimens are recommended on the basis of clinical trials that have been done in Caucasian or Asian populations and that may not be appropriate for African populations.

The first major observation of clinical relevance for a genetic difference for Africans in safety and efficacy of a drug was for the deficiency of glucose-6-phosphate dehydrogenase, which is common in African populations and which is postulated to have arisen due to pressure from malaria infection. People with glucose-6-phosphate dehydrogenase deficiency are more resistant to malaria infection. However, should such people succumb to malaria, treatment with primaquine triggers hemolysis, as the deficiency of this enzyme compromises their ability to detoxify reactive metabolites generated from this drug (reviewed in ref. 2).

The use of isoniazid for the treatment of tuberculosis is widespread in Africa where this disease is the leading cause

[1]African Institute of Biomedical Science and Technology, Harare, Zimbabwe. Correspondence: C Masimirembwa (collen.masimirembwa@aibst.com)
Received 28 January 2013; accepted 9 March 2013; advance online publication 29 May 2013. doi:10.1038/psp.2013.17

Table 1 Interpopulation differences in pharmacogenetic traits with potential clinical relevance[a,b]

Gene/ protein	Allele	Functional status	Allele frequency in different populations[a]			Some drugs affected	Clinical PK and PD effects	Interpopulation differences
			African	Asian	Caucasian			
CYP2D6	*4	No activity	1–8	1	12–21	β-Blockers, antide pressants, dextromethorphan codeine	Tardive dyskinesia from antipsychotics, narcotic side effects, loss of therapeutic effect	African and Asian populations have lower rates of metabolism of CYP2D6 substrate drugs than caucasians
	*5	No activity	1–7	6	4–6			
	*10	Reduced	2–6	50	1–2			
	*17	Reduced	14–34	0	0			
CYP2C9[b]	*2	Reduced	1	0	8–13	Warfarin, tolbutamide, Losartan, acenocoumarol	Hemorrhage	*2 and 3 not diagnostic in Africans and Asian
	*3	Reduced	0	2–3	7–9			Possible lower doses required in Africans with these alleles
	*5, *6, 8, *9 and *11	Reduced	–	–	–			
CYP2C19	*2	No activity	13–25	23–32	13	Omeprazole, proguanil diazepam	Increased efficacy of omeprazole, potential reduced effects of proguanil	Asians require lower doses of substrate drugs & risk reduced efficacy of proguanil
	*3	No activity	0	6–10	0			
CYP2B6	*6	Reduced	34–49	16–21	15–21	Efavirenz, artemisinin, nevirapine, cyclophosphamide	Increased CNS side effects to efavirenz	Increased ADRs reactions in African populations
CYP3A5	*3	No activity	20–27	80	93	Ticagrelor, quinine atazanavir	No data	Africans could metabolize these drugs faster
NAT-2	*5	SA	20–58	5	20–58	Isoniazid	Hypersensitivity to sulfonamides, isoniazid neurotoxicity	Frequency of SA in African, Asians, and Caucasians is 50, 20, and 50%, respectively
	*6	SA	8–29	19–31	27–28			
	*7	SA	2–6	10–16	2–4			
	*14	SA	3–13	0	0			
OATP1B1	*1B	increased	77	63	26	Statins	Myopathy and rhabdomyolysis	Asians use lower dose of rosuvastatin than Caucasians
	*5, *15	decreased	2	10–15	15–20			
BCR	C421A	decreased	2–5	35	11–14			
G6PDH	Many variants	Reduced to no activity	15–38	8	0–10	Primaquine, chloroquine	Hemolytic anemia	African people more susceptible to primaquine toxicity
HLA	HLAB*5701	Human leukocyte antigen	0.26–3.6	0.26–3.6	5–8	Abacavir	Predicts abacavir hypersensitivity	Validity not tested in Africans
VKORC1	1173 C>T	Vitamin K regeneration	9–24	74–89	36–42	Warfarin	Predicts warfarin dose	Most important for Asians

ADR, adverse drug reaction; CNS, central nervous system; G6PDH, glucose-6-phosphate dehydrogenase; OATP1B1, organic anion-transporter polypeptide 1B1; PD, pharmacodynamic; PK, pharmacokinetic; SA, slow acetylator.
[a]Allele frequency data obtained from ref. 5. [b]CYP2C9 reviewed in ref. 10.

of death among HIV/AIDS patients. Southern Africa is the epicenter of the HIV/AIDS pandemic and of the tuberculosis epidemic with >50% of people with tuberculosis also being HIV positive according to WHO estimates (http://www.who.int/hiv/topics/tb/data/en/index.html). The genetic polymorphism of NAT-2 resulting in the SA and rapid acetylators status has implications for the use of isoniazid in Africa. As ~50% of African people are SA, the burden of peripheral neuropathy can be very high if the doses of the drug are not titrated against the patient's capacity to remove the drug.[5] A further genetic polymorphism affecting the pharmacokinetics of a drug for tuberculosis, rifampicin, is that for the organic anion-transporter polypeptide 1B1 coded for by the gene *SLCO1B1*, which has a C/T variation (rs4149032) associated with reduced rifampicin blood levels. Pharmacometric modeling and simulation showed that for patients bearing this variant, an increase in rifampicin dose would be necessary to achieve therapeutic concentrations in the blood.[6] The polymorphisms of NAT-2 and SCLO1B1 are therefore important for efficacious treatment of tuberculosis since isoniazid and rifampicin are components of the combination therapy for the disease.

Genetic variants in the *CYP2B6* gene (e.g., CYP2B6*6) cause slower rates of metabolism than the expected "normal" rates for several drugs, including efavirenz. Slower metabolism predisposes to central nervous system adverse drug reactions that cause reduced compliance and possible emergence of drug resistance in the treatment of HIV/AIDS. The abundance of the slow allele, CYP2B6*6, is higher in African populations than that in Caucasians, probably contributing to more common problems with efavirenz-based chemotherapy of HIV infections than elsewhere. Nyakutira *et al.*[7] predicted

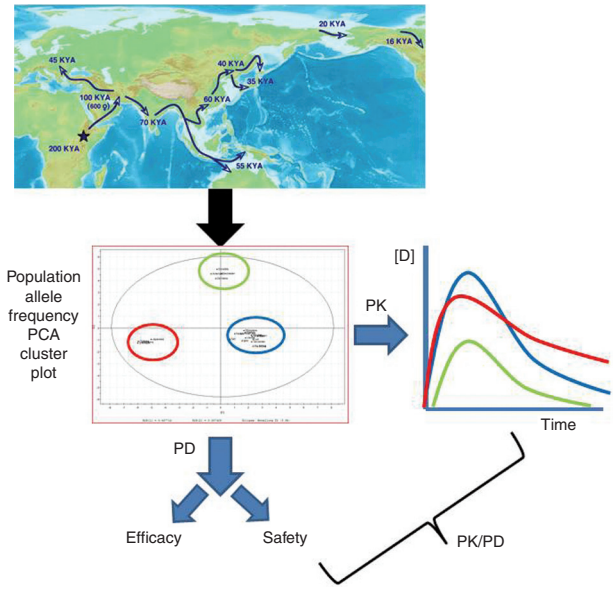

Figure 1. A schematic representation of possible pharmacokinetic (PK) and pharmacodynamic (PD) implications of population variability arising from human origin and migration. The scheme shows the postulated human population migration across the world (migration time given in kya (thousand years ago)) and a typical principal component analysis (PCA) observed in studies of genetic variations that affect drug pharmacokinetics. Each cluster indicates the similarity of studied populations with respect to 16 single-nucleotide polymorphisms of nine genes important for drug metabolism and transport (Matimba *et al.*, 2008). Red circle: Asian populations, Blue circle: African populations, and Green circle: Caucasian populations.

that patients homozygous for the low enzyme activity CYP2B6 variant would require a third of the current standard dose of 600 mg a day. Anecdotal clinical reports of patients whose central nervous system sides effects resolved upon dose reduction to 200 mg a day support this predicted safe dose. With 20% of the African people being homozygous for the slow allele, CYP2B6*6, use of a dosing algorithm guided by inclusion of pharmacogenetic data could translate to a significant clinical intervention for the safe use of efavirenz in Africa.[8]

The enzyme CYP2D6 metabolizes over 20% of drugs that are subject to metabolism by P450 and is of particular importance for the metabolism and disposition of psychoactive drugs and β-blockers. Early phenotyping studies showed a generally reduced enzyme activity in African populations. Molecular genetic studies led to the discovery of the CYP2D6*17 genetic variant as the major cause of this diminished enzyme activity.[9] There is a need for clinical studies in African populations to understand the implications of using Caucasian-based dose regimens for CYP2D6 substrate drugs in patients of African origin.

THE FUTURE OF PHARMACOGENETICS IN AFRICA

The few examples cited above illustrate the way in which particular common pharmacogenetic traits can influence the safety and efficacy of drugs in Africa and highlight the critical need to ensure that dosing recommendations are made with consideration of the pharmacogenetic profile of populations as a whole and of individuals. The clear differences among African, Asian, and Caucasian populations demonstrate the need for population-specific preclinical and clinical studies and trials.

There is currently a limited capacity for pharmacogenetics and pharmacogenomics research in Africa. Strategies and policies for development of science and technology must ensure a future where Africa can take an active role in harnessing the power of genomic research in addressing its healthcare challenges. Already very positive steps are being taken with the establishment of initiatives such as the Human Heredity and Health in Africa project (http://h3africa.org/) that aims at strengthening research capacity for genomics in Africa. Another such initiative, sponsored by WHO and United Nations Economic Commission for Africa, is the African Network for Drugs and Diagnostics Innovation (http://www.andi-africa.org/) whose primary objective is to promote and support health product research and development led by African institutions for diseases of high prevalence in the continent. Formation of the African Society of Human Genetics and the African Pharmacogenomics Consortium also demonstrate an increased interest and participation by African researchers in genomics research.

Pharmacogenetic/genomic studies require good pharmacological data to explore genotype and phenotype associations. To explore these associations and translate them to clinically relevant models, pharmacometric studies will play a crucial role. The challenge now is to educate and promote a cadre of trained young, energetic, and committed young scientists in Africa who will lead the continent in drug discovery and development in a global world, leading to population-appropriate pharmacology and personalized medicine. The future for exciting research in pharmacogenetics and pharmacometrics in Africa looks enticing and has great potential for translation into clinical applications in the treatment of major epidemics such as HIV/AIDS and tuberculosis, and for innovative treatment of the growing problem of noncommunicable diseases.

Conflict of interest. The authors declared no conflict of interest.

1. Campbell, M.C. & Tishkoff, S.A. African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. *Annu. Rev. Genomics Hum. Genet.* **9**, 403–433 (2008).
2. Meyer, U.A. Pharmacogenetics – five decades of therapeutic lessons from genetic diversity. *Nat. Rev. Genet.* **5**, 669–676 (2004).
3. Azuma, J. *et al.* NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy. *Eur. J. Clin. Pharmacol.* (2012); e-pub ahead of print 14 November 2012.
4. Relling, M.V., & Klein, T.E. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin. Pharmacol. Ther.* **89**(3), 464–467 (2011).
5. Matimba, A. *et al.* Establishment of a biobank and pharmacogenetics database of African populations. *Eur. J. Hum. Genet.* **16**, 780–783 (2008).
6. Chigutsa, E. *et al.* The SLCO1B1 rs4149032 polymorphism is highly prevalent in South Africans and is associated with reduced rifampin concentrations: dosing implications. *Antimicrob. Agents Chemother.* **55**, 4122–4127 (2011).

7. Nyakutira, C. *et al*. High prevalence of the CYP2B6 516G–>T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur. J. Clin. Pharmacol.* **64**, 357–365 (2008).
8. Nemaura, T., Nhachi, C., & Masimirembwa, C. Impact of gender, weight and CYP2B6 genotype on efavirenz exposure in patients on HIV/AIDS and TB treatment: implications for individualising therapy. *Afr. J. Pharm. Pharmacol.* **6**, 2188–2193 (2012).
9. Masimirembwa, C., Persson, I., Bertilsson, L., Hasler, J. & Ingelman-Sundberg, M. A novel mutant variant of the CYP2D6 gene (CYP2D6*17) common in a black African population: association with diminished debrisoquine hydroxylase activity. *Br. J. Clin. Pharmacol.* **42**, 713–719 (1996).
10. Daly, A.K. Optimal dosing of warfarin and other coumarin anticoagulants: the role of genetic polymorphisms. *Arch. Toxicol.* **87**, 407–420 (2013).