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Review

Solute carrier transporters: Pharmacogenomics research opportunities in Africa

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Membrane transporters play a critical role in drug response as they provide the targets for many commonly used drugs and are major determinants of drug absorption, distribution, and elimination. Most of them belong to one of the two major super-families of membrane transport proteins, the ATP-binding cassette (ABC) transporters, and the solute carrier (SLC) transporters. They are subject to both genotypic and phenotypic polymorphisms, and variation in drug transporters may be the reason for inter-individual variability in pharmacokinetic disposition, efficacy, and toxicity of drug transporter substrates. The growing number of publications reporting genetic population data for the solute carrier transporters in particular shows their importance, as well as the increased interest in investigating them in most recent pharmaco-genetics/genomics research projects. These publications range from reporting baseline frequency distributions of SNPs of genes important in drug transport, discovering new genetic variants of these genes, and/or describing genotyping projects to identify probable responders or non-responders to therapy, or to predict exposure levels in different patients. This paper reviews the solute carrier transporters and highlights the fact that there is much to be learnt from characterizing human genomic variation in South Africa and sub-Saharan Africa, especially with regards to health applications. Genomic diversity in this region is indeed relatively under-studied despite being home to significant portion of human genomic diversity.

Key words: Solute carrier transporters, pharmacogenomics, pharmacogenetics.

HUMAN GENETIC VARIATION

Human genetic variation has implications on a broad range of biological and medical disciplines. For this reason, the study of human genetic diversity is relevant to a variety of research areas including human and population genetics, molecular biology, evolutionary biology, biological anthropology, health sciences and clinical medicine. The vast extent of inherited variation in the human genome only recently became apparent after almost the complete DNA sequences of the human genome became available (Brockmoller and Tzvetkov, 2008). One can extrapolate that very soon several human individuals will be entirely sequenced and that this will provide a more clear understanding of inter-individual variation in human genomes (Brockmoller and Tzvetkov, 2008). At the present time about 12 million single nucleotide polymorphisms (SNPs) have been identified in the human genome (Brockmoller and Tzvetkov, 2008). In addition, there are probably more than 100,000 insertions and deletions. There is also a large class of genetic variations summarized as variable number of tandem repeat polymorphisms (VNTR) (Brockmoller and Tzvetkov, 2008). These VNTRs include variable numbers of dinucleotide repeats, such as a variable number of TA in the TATA box in the core promoter of bilirubin glucuronyltransferase

Abbreviations: ABC, ATP-binding cassette; **SNPs,** single nucleotide polymorphisms; **VNTR,** variable number of tandem repeat polymorphisms; **PGx,** pharmacogenomics; **PGt,** pharmacogenetics; **MDR,** multidrug resistance; **SLC,** solute carrier; **OCTs,** organic cation transporters; **OATs,** organic anion transporters; **OCTNs,** organic zwitterion/cation transporters; **MATE,** multidrug and toxin extrusion.

UGT1A1 and larger repeat units, such as the 16 amino acid (48 bp) repeat in the dopamine D4 receptor (Brockmoller and Tzvetkov, 2008). It was only recently that we have learned that there are at least 1500 large genomic segments occurring interindividually in variable copy numbers (Brockmoller and Tzvetkov, 2008).

Variation in the human genome has a wide variety of medical and health implications. Genomic variation is believed to be the most important cause of variable response to drugs and other xenobiotics. Susceptibility to almost all diseases is also determined to some extent by genetic variation (Brockmoller and Tzvetkov, 2008). For this reasons, and driven by the advances in molecular biology, pharmacogenetics has evolved within the past 40 years from a niche discipline to a major driving force of clinical pharmacology, and it is currently one of the most actively pursued disciplines in applied biomedical research in general (Bhathena and Spear, 2008; Brockmoller and Tzvetkov, 2008; Kroetz et al., 2010; Meyer, 2004; Urban, 2010).

PHARMCOGENOMICS AND PHARMACOGENETICS

Pharmacogenomics (PGx) is defined as 'The study of variations of DNA and RNA characteristics as related to drug response', and as a subset, pharmacogenetics (PGt) is 'The study of variations in DNA sequence as related to drug response' (Bhathena and Spear, 2008). It is widely expected that PGx will facilitate a trend toward improved patient outcomes by increasing our understanding at the molecular level of both the disease and treatment response. As such, PGx is central to personalized medicine strategies (Bhathena and Spear, 2008).

The term pharmacogenomics was introduced to reflect the recent transition from genetics to genomics and the use of genome-wide approaches to identify genes that contribute to a specific disease or drug response. A pharmacogenomics approach may allow a specific drug therapy to be targeted to genetically defined subsets of patients and may lead to a new disease and treatment classification at the molecular level (Eichelbaum et al., 2006).

Pharmacogenetics, on the other hand, is essentially the discipline which takes the patient's genetic information of drug transporters, drug metabolizing enzymes and drug receptors into account to allow for an individualized drug therapy leading to optimal choice and dose of the drugs in question (Holm, 2008). Observations implying that genetic variation was responsible for the diversity in some drug responses were already being made five decades ago (Meyer, 2004). Therapeutic failure of drugs as well as serious adverse side effects of drugs on individuals or subpopulations of patients can both have a genetic component. The toll that such variation takes in terms of individual suffering, high healthcare costs, and even lives, is increasingly being recognized (Meyer, 2004).

GENETIC POLYMORPHISMS AND VARIABILITY IN DRUG RESPONSE AND TOXICITY

A great deal of interindividual variability exists in drug responses and toxicity. This variation can result from genetic, environmental, physiological, and pathophysiological factors (Choi and Song, 2008). In general, genetic factors are estimated to account for 15 to 30% of interindividual variations in drug disposition and responses, but for certain drugs, genetic factors can account for up to 95% of the interindividual variability in drug disposition and effects (Avery et al., 2009; Choi and Song, 2008). Accounting for these differences would be highly beneficial, not only for the health care industry, but for patients themselves, decreasing the burden of treatment failures and adverse events on society (Avery et al., 2009).

Advances in genotyping technology in the last decade have led to the discovery of novel gene variations in drug transporters, drug targets, effect or proteins and metabolizing enzymes in the form of single-nucleotide polymorphisms (SNPs) that continue to provide insight into the biological phenomena that govern drug efficacy and toxicity (Avery et al., 2009).

It has long been recognized that genetic variations in drug metabolizing enzymes underlie the inter-individual differences in drug response. Certain single nucleotide polymorphisms in cytochrome P450 systems, such as CYP2D6, are well known to be related to altered drug metabolism, unexpected drug effect, and alterations of the clinical response and frequency of side effects (Sakata et al., 2004).

Molecular studies in pharmacogenetics have now been extended to numerous other human genes including those for several drug transport systems (Sakata et al., 2004). In addition to many drug-metabolizing enzymes, drug transport proteins have also consistently replicated associations between genetic variants and the clinical pharmacokenetics of at least one drug (Bhathena and Spear, 2008). It is estimated that there are approximately 170 genes whose products affect drug disposition, and that over half of these are polymorphic (Bhathena and Spear, 2008). For example, single nucleotide polynucleotides (SNPs) in the ABC (ATP-binding cassette) transporter multidrug resistance-1 (MDR1) genes were reported to influence the disposition of digoxin and fexofenadine. Furthermore, SNPs in the SLC (solute carrier) transporter OATP-C and OATP-B gene result in the decrease of drug transport activity (Sakata et al., 2004).

GENETIC POLYMORPHISM OF DRUG TRANSPORTERS

Membrane transporters play a critical role in a variety of physiological processes. They maintain cellular and organismal homeostasis by importing nutrients essential for cellular metabolism and exporting cellular waste

products and toxic compounds (Leabman et al., 2003). They are also important in drug response as they provide the targets for many commonly used drugs and are major determinants of drug absorption, distribution, and elimination (Leabman et al., 2003). Membrane transport proteins share a similar secondary structure, characterized by multiple membrane-spanning domains joined by alternating intracellular and extracellular segments (“loops”). Two of the major superfamilies of membrane transport proteins are the ABC (ATP-binding cassette) transporters, which include MDR1, a protein that pumps xenobiotics from cells, and the SLC (solute carrier) transporters, which take up neurotransmitters, nutrients, heavy metals, and other substrates into cells (Leabman et al., 2003).

Genetic polymorphisms in drug transporter genes have increasingly been recognized as a possible mechanism accounting for variation in drug response (Shu et al., 2007). Genetic polymorphism of drug transporters has recently attracted interest because these transporters play important roles in the gastrointestinal absorption, biliary and renal elimination, and distribution to target sites of their substrates (Choi and Song, 2008). The aim of this research was to clarify the considerable inter-individual variability in the pharmacokinetics, efficacy, and toxicity of drugs (Choi and Song, 2008). There is emerging pharmacogenetic evidence now strongly suggesting those membrane transporters are subject to both genotypic and phenotypic polymorphism, and that variation in drug transporters may be the reason for interindividual variability in pharmacokinetic disposition, efficacy, and toxicity of drug transporter substrates (Choi and Song, 2008).

SOLUTE CARRIER TRANSPORTERS

The solute carrier (SLC) superfamily of transporters consists of more than 300 members subdivided into 47 families. They are expressed in most tissues, but primarily in the liver, lung, kidney, and intestine. Most solute carrier transporters are localized at either the basolateral or apical plasma membrane of polarized cells, but some are expressed in mitochondria and other organelles (Wojtal et al., 2009). Typical SLC transporters consist of several trans-membranes α-helices connected by intra- and extracellular loops and function as either monomers or hetero- or homodimers (Wojtal et al., 2009). SLC transporters are membrane-associated transporters that facilitate the passage of solutes, including peptides, bile acids, amino acids, ions, xenobiotics, drugs, and other biologically active compounds, across cell membranes in epithelial tissues, such as intestine and liver (Hediger et al., 2004; Koepsell et al., 2007). In the intestine, SLCs are critically involved in drug absorption, thus determining distribution and pharmacokinetic characteristics of many drugs (Meier et al., 2007).

Polyspecific organic cation transporters belong to the SLC22 family and the MATE family (Koepsell et al., 2007). Most transporters of the SLC22 family are polyspecific, transporting multiple different substrates, and are subdivided into three groups: organic cation transporters (OCTs), organic anion transporters (OATs), and organic zwitterion/cation transporters (OCTNs) (Meier et al., 2007). The OCTs include OCT1 (SLC22A1), OCT2 (SLC22A2) and OCT3 (SLC22A3). The OCTNs include OCTN1 (SLC22A4) that may be a proton cation exchanger, the Na+-carnitine cotransporter OCTN2 (SLC22A5) that can also operate as Na+ independent transporter for organic cations (Koepsell et al., 2007). OCTN1 and OCTN2 have attracted much attention as polymorphisms in the genes encoding them have been linked to inflammatory bowel disease (Meier et al., 2007).

The human organic cation transporters, also designated as hOCT1, hOCT2, and hOCT3, mediate electrogenic transport of small organic cations with different molecular structures, independent of sodium gradient. These organic cation substrates include clinically important therapeutics (e.g., metformin, procainamide, and cimetidine), endogenous compounds (e.g., dopamine and norepinephrine), as well as toxic substances [e.g., tetraethylammonium bromide (TEA)] (Kang et al., 2007). The genes encoding the three organic cation transporter isoforms (hOCT1, hOCT 2, and hOCT 3) are clustered together on the long arm of chromosome 6. Population genetics analyses identified numerous single-nucleotide polymorphisms (SNPs) in the three genes (Tzvetkov et al., 2009).

Human orthologs of the multidrug and toxin extrusion (MATE) family, members of which confer multidrug resistance on bacteria, were recently identified and named MATE1 (SLC47A1) and MATE2-K (SLC47A2). The SLC47A1 and SLC47A2 genes encode for the MATE1 and MATE2-K proteins, respectively. Both transporters are expressed mainly in the renal brush border membranes, and are H^+/organic cation antiporters involved in the transport of ionic drugs in the renal tubules (Kajiwara et al., 2009). It has been demonstrated that the antidiabitic drug metformin is an exceptional substrate for MATE1 and MATE2-K and that these proteins play a role in the elimination of metformin into the bile (MATE1) and urine [MATE1 and MATE2-K] (Avery et al., 2009). Recent studies suggest that interpatient variability in response to metformin therapy could be related to polymorphisms in the OCT genes and/or the MATE genes (Avery et al., 2009).

The growing number of publications reporting genetic population data for the solute carrier transporters shows their importance, as well as the increased interest in investigating them in most recent pharmacogenetics/genomics research projects (Kajiwara et al., 2009; Kang et al., 2007; Leabman et al., 2003; Meier et al., 2007; Sakata et al., 2004; Shu et al., 2007; Toh et al., 2010; Wojtal et al., 2009). These publications are

reporting baseline frequency distributions of SNPs of genes important in drug transport, discovering new genetic variants of these genes, and/or describing genotyping projects to identify probable responders or non-responders to therapy, or to predict exposure levels in different patients.

GENETIC ANCESTRY AND BEYOND: PHARMACO-GENETICS/GENOMICS FROM AFRICA FOR AFRICA

The concepts of race, ethnicity, and ancestry, have long had a strong influence on pharmacogenetic discovery and on our understanding of population level differences in drug response (Urban, 2010). Despite controversy surrounding the use of these terms, 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 (Suarez-Kurtz, 2005). Population based studies can help to establish baseline frequency distribution of SNPs of genes important in drug metabolism and/or transport. Extrapolations of possible clinical implications of the baseline frequency distribution of some of the alleles based on established phenotypic characteristics could guide doctors in drug prescription decision-making and/or provide explanations of ethnic-specific adverse effects in metropolitan medical practice (Matimba et al., 2008).

Genomic diversity within sub-Saharan Africa, and for that matter the entire African continent, is relatively under-studied, despite being home to significant portion of human genomic diversity (Hardy et al., 2008). There is thus much to be learnt from characterizing human genomic variation in this part of Africa, especially with regards to health applications (Hardy et al., 2008). South Africa in particular contains a wealth of different population groups. This fact was recognized in the National Biotechnology Strategy Report for South Africa (2002), and recommended that the country focus on documentting the genomic diversity contained within the local indigenous and immigrant populations (Hardy et al., 2008). The country is indeed home to the indigenous Khoisian, Xhosa, Zulu, Venda, and Sotho Pedi groups, the Afrikaners and the Cape Coloured, the latter being a uniquely admixed population of immigrant Europeans, Asians and the indigenous populations (Hardy et al., 2008). Admixed groups, such as Latinos, African Americans, or Cape Coloureds from South Africa, share varying proportions of different ancestral populations and their genetic complexity can potentially complicate biomedical research studies (Via et al., 2009). Their mixed ancestry, however, can provide the intrinsic variability needed to untangle complex gene-environment interactions, which may help to explain the population differences in the epidemiology of complex diseases (Via et al., 2009).

Since 2006, Prof. Benjeddou's research group, from the Department of Biotechnology at the University of the Western Cape (South Africa), has been investigating the genetic diversity and origins of the Cape local communities with a special focus on the Cape Muslim population (Abrahams et al., 2010; Benjeddou et al., 2006; Cloete et al., 2010). The feedback from the investigated communities showed that despite the enthusiasm about knowing their genetic ancestry, there is great interest in expanding the program to include the investigation of a variety of medical and health implications resulting from the genetic diversity of these populations. It is widely believed that this type of research will benefit the investigated communities as well as the country as a whole. The study of the genetic diversity of the solute carrier transporter genes and its pharmacogenetic implications within the South African and Sub-Saharan African populations can be the first step in that direction. It will contribute in filling the gap of missing important pharmacogenetics data from South Africa and Sub-Saharan Africa. It is an opportunity to produce original research in the area of pharmaco-genetics/genomics in Africa for Africa. It is also an excellent opportunity to forge balanced and meaningful international collaborations between African researchers and counterparts from the Western World and other developed and developing countries.

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