Published in final edited form as:

Clin Pharmacol Ther. 2008 September ; 84(3): 412–416. doi:10.1038/clpt.2008.98.

Genetic Variation in Drug Transporters in Ethnic Populations

Cheryl D. Cropp¹, Sook Wah Yee¹, and Kathleen M. Giacomini¹

¹Department of Biopharmaceutical Sciences, University of California, San Francisco, San Francisco, California, USA

Abstract

Drug-metabolizing enzymes and membrane transporters work in concert to play crucial roles in drug absorption, distribution, and elimination. It is well recognized that genetic variation in drug-metabolizing enzymes contributes substantially to interindividual differences in drug response. With the notable exceptions of *CYP1A1* and *CYP2E1*, genes encoding cytochrome P450s, which are involved in the metabolism of >80% of all drugs used in clinical practice, are highly polymorphic.

¹ Interethnic variation in the distribution and frequency of occurrence of variant alleles in drug-metabolizing enzymes is known to alter the rate of drug metabolism *in vivo*, resulting in interethnic variation in drug disposition and response.

Introduction

In contrast to our understanding of the effects of ethnicity on drug metabolism, little is known about ethnicity-related differences in the disposition and effects of drugs that are substrates of membrane transporters. Recent pharmacogenomic studies of membrane transporters describe the discovery and functional characterization of variant transporters in ethnically diverse populations.² To our knowledge, there have been no reviews describing ethnic differences in allele frequencies, functional activities, or the clinical effects of genetic variants of membrane transporters. In this short review, we summarize findings from recent pharmacogenomic studies of transporters in two major superfamilies—adenosine triphosphate (ATP)-binding cassette and solute carrier (SLC)—that are responsible for the influx and efflux of numerous clinically important drugs. Our review focuses on transporters in the liver and kidney (see Table 1) that work together with drug-metabolizing enzymes to mediate drug absorption and disposition. In particular, we focus on ethnicity-related differences in allele frequencies and describe the functional activities of nonsynonymous variants that differ in their allele frequencies among various ethnic groups. Finally, we describe the limited studies that have directly compared drug disposition and response among ethnic groups. Clearly, there is a need for more studies examining interethnic differences in the absorption and disposition of drugs that are substrates of polymorphic transporters.

In the liver, transporters on the sinusoidal membrane of the hepatocyte (e.g., OCT1, OAT2, OATP1B1, and OATP1A2) play key roles in the hepatic uptake of drugs and thereby control access to hepatic drug-metabolizing enzymes (Figure 1a). These influx transporters also work in concert with efflux transporters on the canalicular membrane (e.g., MRP2, BSEP, BCRP, and P-gp) to excrete drugs and their metabolites into the bile (Figure 1a). Because of their critically important roles in drug absorption and disposition, identification of genetic variants in hepatic influx and efflux transporters has been the subject of many studies. Such studies have centered primarily on genetic variation in the coding region of the transporter genes, with

Correspondence: KM Giacomini, (kathy.giacomini@ucsf.edu).

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

a particular focus on nonsynonymous single-nucleotide polymorphisms, which have a high propensity to produce functional changes in the encoded transporter proteins. In Table 2, for each hepatic and kidney drug transporter, we show the most common nonsynonymous variant in each of three populations (African Americans, European Americans, and Asians). Frequencies of occurrence of nonsynonymous variants vary widely among the different transporter proteins. Noteworthy are the low allele frequencies of nonsynonymous variants in the organic anion transporter OAT2 ($\leq 2\%$), suggesting a high degree of purifying selection on the gene, *SLC22A7*. In contrast, OCT1 has a common nonsynonymous variant, with the allele frequency $>20\%$ in the three populations. Also noteworthy is that there may be large interethnic differences in allele frequencies of particular transporter variants. For example, for the MRP4 variant Lys304Asn, the allele frequency ranges from 8.7% in European Americans to 22.5% in Asians. If this allele were associated with functional changes in MRP4, the frequency differences could result in interethnic differences in drug disposition and response.

Similarly, in the kidney, the basolateral uptake transporters (e.g., OAT1, OAT3, and OCT2) are responsible for transporting drugs from blood into renal proximal tubule cells, whereas apical efflux transporters (e.g., MRP2, MRP4, and P-gp) transport drugs into the urine for excretion (Figure 1b). In addition, the uptake transporters on the apical membrane of proximal tubules (e.g., OCTN1 and OCTN2) may reabsorb xenobiotics filtered through glomeruli back into tubule cells, whereas basolateral efflux transporters (e.g., MRP1, MRP3, and MRP6) transport these reabsorbed chemicals back into the blood. Some transporters, e.g., OCTN1 and OCTN2, have a bifunctional role, transporting selected xenobiotics in the secretory direction into the tubule lumen and particular endogenous compounds (and xenobiotics) in the reabsorptive direction.

Nonsynonymous variants of renal anionic transporters (OATs) appear to have low allele frequencies (OAT1, OAT2, OAT3, and OAT4, Figure 1b, Table 2), consistent with purifying selection on these transporters, and perhaps consistent with a low redundancy in their functions. As in the hepatocyte, ethnic differences in allele frequencies are apparent in renal transporters. For example, the most common nonsynonymous variant of the novel organic cation transporter, OCTN2, has an allele frequency of 10% in African Americans and $<1\%$ in European Americans. For more information on these transporter variants, see PharmGKB (<http://www.pharmgkb.org>) and dbSNP (<http://www.ncbi.nlm.nih.gov/projects/SNP/>).

Cellular Analysis of Variant Transporters

Ethnic differences in allele frequencies of nonsynonymous variants in membrane transporters may not translate into ethnic differences in drug disposition or response if the particular transporter variant is not functionally significant. To understand whether such variants may be functionally significant, cellular studies characterizing the functional activity of variant transporters are important. In cellular studies, variants are constructed by site-directed mutagenesis, expressed in cellular systems, and functionally characterized. Cellular systems for studies of drug transport include stably and transiently transfected mammalian cells: human embryonic kidney-293 and Madin–Darby canine kidney cells and oocytes from *Xenopus laevis*. Low or absent expression of endogenous transporters and ease of transfection are two of the reasons why these cell systems are optimal for drug transport studies. A drawback of these systems is that transfected cells may not reflect the actual *in vivo* situation.

Typical cellular analyses of the function of transporter variants include a functional screening followed by kinetic studies of interesting variants. An example of a functional screening of nonsynonymous variants of a transporter is depicted in Figure 2.³ In this functional scan, complementary DNAs of nonsynonymous variants of the transporter OATPIA2 were constructed by site-directed mutagenesis. Then equal amounts of complementary RNA (transcribed *in vitro*) of the reference OATPIA2 and its 11 nonsynonymous variants were

injected into individual oocytes from *X. laevis*. The extent of uptake of each of two known substrates of OATP1A2, estrone sulfate and methotrexate, was determined in the oocytes expressing OATP1A2 and its nonsynonymous variants. The results of this scan demonstrate that the Ile13Thr variant exhibited enhanced uptake of estrone sulfate and methotrexate as compared to the reference, OATP1A2. In contrast, OATP1A2-Arg168Cys, OATP1A2-Gln72Asp, and OATP1A2-Asn278DEL exhibited significantly reduced uptake of estrone sulfate and methotrexate as compared to the reference, OATP1A2. As noted in Figure 2, the allelic frequency of each of the variants of OATP1A2 exhibits interethnic differences among African-American, European-American, and Asian populations. If *in vitro* functional studies such as the one shown in Figure 2 are translated to the *in vivo* situation, significant interethnic population differences in the disposition of drugs that are substrates of OATP1A2 may be observed clinically. However, additional criteria for performing clinical studies to examine interethnic differences should include prior confirmation that the transporter plays a considerable role in the drug's response and/or disposition. The mere fact that a drug is a substrate of a transporter does not necessarily imply that the transporter will be important *in vivo*. Diffusional processes or other transporters with redundant functions should be considered.

Urban *et al.*⁴ conducted an analysis of cellular studies in 88 protein-altering variants (including nonsynonymous variants and insertions and deletions) of 11 membrane transporters identified in DNA samples from ethnically diverse populations including African Americans, European Americans, Asians, and Mexican Americans. Twenty-two of the variants showed reduced function and, of these, 5 were shared by two or more populations, whereas 17 were unique to a single ethnic group. Most of these reduced-function variants were found at low allele frequencies; however, some were associated with allele frequencies of >5%. Assuming that reduced-function variants are associated with variation in drug disposition and response, the interpopulation differences in the allele frequencies of reduced-function variants suggest that there will be important interethnic differences in drug disposition and response to substrates of these transporters.

Clinical Studies in the Pharmacogenomics of Membrane Transporters

Clinical differences among ethnic groups in the disposition and pharmacologic effects of drugs that are substrates of transporters may be attributed to differences in genetic and environmental factors that influence all aspects of the pharmacokinetic and pharmacodynamic pathway. For example, substrates of transporters may also be substrates of various polymorphic enzymes. These complexities make it difficult to understand the effects that genetic differences in transporter activity produce on drug disposition and response. Further, in contrast to the numerous clinical studies assessing the effects produced by polymorphisms in drug-metabolizing enzymes on drug disposition, there have been few clinical studies assessing the effects produced by genetic variants of membrane transporters. Most clinical studies involving the transport of drugs have been conducted in a single ethnic group. To our knowledge, only a single clinical study has directly assessed variations between ethnic groups in the disposition and/or pharmacologic effects of a transported substrate.⁵

Ho *et al.*⁵ compared the disposition of pravastatin, a substrate for OATP1B1, in European Americans and African Americans. Overall, they observed that pravastatin exposure (area under the curve and peak plasma concentration) was greater for European Americans than for African Americans. However, the observations were not explained by the presence of functional variants in OATP1B1 (i.e., 521T>C, 388A>G), which had been shown to have reduced function in *in vitro* assays. Clearly, other variants in *SLCO1B1* or other genes in the pravastatin pharmacokinetic pathway may account for the interethnic differences in response to exposure to pravastatin.

Studies of the disposition of model substrates of transporters in single ethnic groups suggest that interethnic differences in drug disposition may be present. For example, BCRP-421C>A (Gly141Lys) is the most prevalent allele in Asians (40.80%), and its allele frequency in Asians is much greater than in other ethnic groups (Table 2). Zhang *et al.*⁶ conducted a pharmacokinetic study of rosuvastatin, a cholesterol-lowering drug in the same class as pravastatin, in 41 healthy Chinese subjects. They reported that subjects with the BCRP genotypes 421CA and 421AA showed a higher exposure to rosuvastatin (after receiving the same dose) than did subjects homozygous for 421C. The 421C>A variant is also found in Europeans, although at a much lower allele frequency (Table 2). It follows, therefore, that the population effect of this variant on rosuvastatin disposition in individuals with European ancestry would be much lower. In fact, the recommended starting dose for individuals of Asian descent is lower than that for Europeans.

Conclusions

In this brief review, we show that there are ethnic differences in the allele frequencies of transporter variants that are important in drug disposition in the liver and kidney. We also show that transporter variants that exhibit effects on function in cellular assays have notable interethnic differences in allele frequencies, suggesting that these reduced-function variants may be a source of variation in drug disposition among ethnic groups. Finally, there have been few clinical studies of the effects produced by genetic polymorphisms in transporters on drug disposition and response. These studies, largely carried out in single ethnic groups, suggest that there may be ethnic differences in the disposition and pharmacologic effects of drugs that are substrates for transporters. Clearly, to understand all the sources of interethnic differences in the disposition and effects of transported drugs, studies are needed that directly compare the pharmacokinetics and pharmacodynamics of transported drugs among ethnic groups.

Acknowledgments

We acknowledge National Institutes of Health grants including GM56847 for support of C.D.C. and GM61390 for support of the Pharmacogenomics of Membrane Transporters project. We acknowledge James E. Shima for his helpful discussions and advice on this manuscript.

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Figure 1. Distribution of the major influx and efflux drug transporters in **(a)** the liver and **(b)** the kidney.

Figure 2. Functional scan and allele frequencies of nonsynonymous variants of OATP1A2. Uptake of estrone sulfate (ES) and methotrexate (MTX) by *Xenopus laevis* oocytes expressing OATP1A2 and its nonsynonymous variants. The allele frequencies for African Americans (AA), European Americans (EA), and Asians (AS) are displayed for comparison. Variant positions were determined relative to the ATG start site and were based on the reference complementary DNA sequence of OATP1A2 (accession number NM_021094).

Table 1
Human liver and kidney transporters important in drug disposition

Gene symbol	Protein name	Full protein name	Representative substrates	References ^a
Influx transporters				
<i>SLC22A1</i>	OCT1	Organic cation transporter 1	Metformin, oxaliplatin	7, 8
<i>SLC22A2</i>	OCT2	Organic cation transporter 2	Metformin, amantidine	7, 8
<i>SLC22A4</i>	OCTN1	Novel organic cation transporter 1	Gabapentin	8
<i>SLC22A5</i>	OCTN2	Novel organic cation transporter 2	Carnitine	8
<i>SLC22A6</i>	OAT1	Organic anion transporter 1	Adefovir, tenofovir	9, 10
<i>SLC22A7</i>	OAT2	Organic anion transporter 2	Ganciclovir, allopurinol	9, 10
<i>SLC22A8</i>	OAT3	Organic anion transporter 3	Cimetidine, cefotaxime	9, 10
<i>SLC22A11</i>	OAT4	Organic anion transporter 4	Bumetanide, ketoprofen	9, 10
<i>SLC22A12</i>	URAT1	Urate anion exchanger 1	Uric acid, oxypurinol	11, 12
<i>SLCO1A2</i>	OATP1A2	Organic anion transporting polypeptide A	Methotrexate, fexofenadine	13, 14
<i>SLCO1B1</i>	OATP1B1	Organic anion transporting polypeptide C	Pravastatin, repaglinide	13–15
<i>SLCO1B3</i>	OATP1B3	Organic anion transporting polypeptide 8	Digoxin, paclitaxel	13, 14
<i>SLCO2B1</i>	OATP2B1	Organic anion transporting polypeptide B	Atorvastatin, benzylpenicillin	13, 16
<i>SLC47A1</i>	MATE1	Multidrug and toxin extrusion 1	Cimetidine, metformin	17, 18
<i>SLC47A2</i>	MATE2-K	Multidrug and toxin extrusion 2	Cimetidine, metformin	18, 19
Efflux transporters				
<i>ABCB1</i>	P-gp	P-glycoprotein	Etoposide, imatinib	20–23
<i>ABCB11</i>	BSEP	Bile salt export pump	Paclitaxel	15, 21, 24
<i>ABCC1</i>	MRP1	Multidrug resistance–associated protein 1	Methotrexate	20–22
<i>ABCC2</i>	MRP2	Multidrug resistance–associated protein 2	Doxorubicin, cisplatin	15, 20–22
<i>ABCC3</i>	MRP3	Multidrug resistance–associated protein 3	Etoposide, methotrexate	21
<i>ABCC4</i>	MRP4	Multidrug resistance–associated protein 4	Methotrexate	21
<i>ABCC6</i>	MRP6	Multidrug resistance–associated protein 6	Anthracyclines	21
<i>ABCG2</i>	BCRP	Breast cancer resistance protein	Mitoxantrone, doxorubicin	20, 23

ABC, adenosine triphosphate-binding cassette; SLC, solute carrier.

^aReview articles describing the pharmacological, physiological, and/or pharmacogenetics of the specific membrane transporters.

Table 2

The allele frequency of the most common non-synonymous variants for African Americans, European Americans and Asians.

Protein Name	African Americans (%)	European Americans (%)	Asians (%)
<i>Influx Transporters</i>			
OCT1	Val408Met (26.5)	Val408Met (40.2)	Val408Met (23.8)
OCT2	Ala270Ser (11.0)	Ala270Ser (15.8)	Ala270Ser (8.6)
OCTN1	Thr306Ile (26.9)	Leu503Phe (41.2)	Ile306Thr (35.8)
OCTN2	Pro549Ser (10.0)	Val481Phe (0.6)	Phe17Leu (1.7)
OAT1 ^a	Arg50His (3.2)	Ile226Thr (0.6)	
OAT2 ^a	Thr110Ile (2.3)	Arg227His (0.8)	
OAT3	Val281Ala (6.0)	Val448Ile (1.3)	Ile305Phe (3.5)
OAT4 ^a	Arg121Cys (2.3)	Arg48STOP (2.3)	
URAT1 ^b	Thr542LysfsX13 (1.5)		Arg342His (0.8)
OATP1A2 ^c	Thr668Ser (4.4)	Ile13Thr (16.3)	Ile281Val (0.8)
OATP1B1	Asp130Asn (27.2)	Asn130Asp (44.1)	Asp130Asn (19.9)
OATP1B3 ^d	Met233Ile (42.0)	Ala112Ser (19.0)	Ala112Ser (32.0)
		Ile233Met (19.0)	Ile233Met (32.0)
OATP2B1 ^e	Ser486Phe (40.5)	Arg312Gln (10.8)	Arg312Gln (38.9)
MATE1 ^b	Val338Ile (5.1)		Val480Met (0.8)
MATE2-K ^a	Pro162Leu (5.6)	Gly429Arg (0.9)	
<i>Efflux Transporters</i>			
P-gp	Ser1141Thr (11.1)	Ala893Ser (43.8)	Ala893Ser (45.0)
BSEP	Ala444Val (47.0)	Ala444Val (42.9)	Ala444Val (33.3)
MRP1 ^a	Cys1047Ser (4.5)	Val353Met (0.5)	
MRP2	Cys1515Tyr (19.6)	Val417Ile (17.0)	Val417Ile (11.7)
MRP3	Pro920Ser (11.3)	Ser346Phe (2.5)	Gly11Asp (0.8)
MRP4	Lys304Asn (18.1)	Lys304Asn (8.7)	Lys304Asn (22.5)
MRP6	Val614Ala (41.2)	Val614Ala (41.9)	Val614Ala (14.2)
BCRP	Val12Met (7.7)	Gln141Lys (8.1)	Gln141Lys (40.8)

^a No non-synonymous variants in Asians.

^b No non-synonymous variants in European Americans

^c Variant positions were determined relative to the ATG start site and were based on the reference complementary DNA sequence of OATP1A2 (accession number NM_021094)

^d Allele frequency obtained from dbSNP build 129 (<http://www.ncbi.nlm.nih.gov/projects/SNP>) using the submission number (ss#) ss38964433 or ss38884356

^e Allele frequency obtained from dbSNP build 129 (<http://www.ncbi.nlm.nih.gov/projects/SNP>) using the submission number (ss#) ss19226212 or ss48424042