0031-6997/06/5801-3–4$7.00
PHARMACOLOGICAL REVIEWS
Vol. 58, No. 1
50415/3090565
Printed in U.S.A

Pharmacol Rev 58:3–4, 2006

PharmGKB Submission Update: V. PMT Submissions of Genetic Variation in SLC22 Family Transporters

YAN SHU, THOMAS J. URBAN, MAYA K. LEABMAN, TOMOE FUJITA, ANDREW R. ERDMAN, LEAH L. LAGPACAN, CHALINE BROWN, RICHARD A. CASTRO, CONRAD C. HUANG, DOUG STRYKE, MICHIKO KAWAMOTO, SUSAN J. JOHNS, TRAVIS R. TAYLOR, WENDY CHAN, MELANIE DE LA CRUZ, ELAINE J. CARLSON, THOMAS E. FERRIN, CLAIRE M. BRETT, ESTEBAN G. BURCHARD, IRA HERSKOWITZ, DEANNA L. KROETZ, AND KATHLEEN M. GIACOMINI

Departments of Biopharmaceutical Sciences (Y.S., T.J.U., M.K.L., T.F., A.R.E., L.L.L., C.B., R.A.C., E.G.B., D.L.K., K.M.G.) and Pharmaceutical Chemistry (C.C.H., D.S., M.K., S.J.J., T.E.F.), Genomics Core Facility (T.R.T., W.C., M.D.L.C., E.J.C.), and Departments of Anesthesiology (C.M.B.) and Biochemistry and Biophysics (I.H.), University of California, San Francisco, San Francisco, California

Supported by National Institutes of Health Grants GM61390 and GM36780
First published on December 1, 2005

Category: genotype

Project: Pharmacogenetics of Membrane Transporters

Table 1 provides HUGO Gene Nomenclature Committee (HGNC) symbols, PharmGKB submission URLs, submission dates, and release dates. Table 2 provides HGNC symbols, HGNC names, synonyms, GenBank accession numbers, and locus IDs.

Pharmacogenetic Significance: Genetic variation in the SLC22 family of solute transporters may result in altered expression and/or function of transporter proteins that play an important role in pharmacokinetics, such as intestinal absorption, biliary and renal excretion, and tissue distribution of therapeutic agents. Pharmacokinetic variability may lead to variation in clinical drug response and drug toxicity.

Pharmacological Significance: SLC22 transporters are generally expressed in the basolateral (blood-facing) or apical (lumen-facing) membrane of polarized epithelial cells of the important organs such as liver, intestine, and kidneys that are responsible for drug absorption, disposition, and elimination. SLC22 transporters may play an important role in determining pharmacokinetics of zwitterions as well as organic cationic or anionic compounds. Expression of SLC22 transporters in a specific tissue may be a major determinant of the access of many drugs into the tissue.

Endogenous and Xenobiotic Substrates: See Table 3.

Functional Characteristics: SLC22 transporters are multispecific transporters of organic ions localized to the plasma membrane of epithelial and endothelial cells of various tissues. Transport of solutes by SLC22 transporters can occur via facilitated diffusion (SLC22A1, SLC22A2, and SLC22A3), Na^+ cotransport or H^+ antiport (SLC22A4 and SLC22A5), or dicarboxylate exchange (SLC22A6 and SLC22A8). They facilitate the uptake and/or efflux of compounds into either the lumen or blood for elimination or distribution.

Summary of Data Submitted:

Size of sample set assayed: SLC22A1, SLC22A2, and SLC22A3: 247 (494 chromosomes); SLC22A4, SLC22A5, SLC22A6, and SLC22A8: 276 (552 chromosomes)
Number of gene regions assayed: 70
Total bases assayed: 21,740
Number of variant sites: 193
Polymerase chain reaction primers reported: 140

Publications:

Fujita T, Brown C, Carlson EJ, Taylor T, de la Cruz M, Johns SJ, Stryke D, Kawamoto M, Fujita K, Castro R, et al. (2005) Functional analysis of polymorphisms in the organic anion transporter, SLC22A6 (OAT1). *Pharmacogenet Genomics* **15:**201–209.

Leabman MK and Giacomini KM (2003) Estimating the contribution of genes and environment to variation in renal drug clearance. *Pharmacogenetics* **13:** 581–584.

Leabman MK, Huang CC, DeYoung J, Carlson EJ, Taylor TR, de la Cruz M, Johns SJ, Stryke D, Kawamoto M, Urban TJ, et al. (2003) Natural variation in human membrane transporter genes reveals evolutionary and functional constraints. *Proc Natl Acad Sci USA* **100:**5896–5901.

Leabman MK, Huang CC, Kawamoto M, Johns SJ, Stryke D, Ferrin TE, DeYoung J, Taylor T, Clark AG, Herskowitz I, et al. (2002) Polymorphisms in a human kidney xenobiotic transporter, OCT2, exhibit altered function. *Pharmacogenetics* **12:**395–405.

Article, publication date, and citation information can be found at http://pharmrev.aspetjournals.org.
doi:10.1124/pr.58.1.2.

Shu Y, Leabman MK, Feng B, Mangravite LM, Huang CC, Stryke D, Kawamoto M, Johns SJ, DeYoung J, Carlson E, et al. (2003) Evolutionary conservation predicts function of variants of the human organic cation transporter, OCT1. *Proc Natl Acad Sci USA* **100:**5902–5907.

Urban TJ, Giacomini KM, and Risch N (2005) Haplotype structure and ethnic-specific allele frequencies at the OCTN locus: implications for the genetics of Crohn's disease. *Inflamm Bowel Dis* **11:**78–79.

TABLE 1
HGNC symbols, Pharm GKB submission URLs, and submission and release dates

HGNC Symbol	PharmGKB Submission	Submission Date	Release Date
SLC22A1	http://www.pharmgkb.org/views/index.jsp?objId = PS203001&objCls = Submission	2/26/03	6/16/03
SLC22A2	http://www.pharmgkb.org/views/index.jsp?objId = PS202784&objCls = Submission	2/25/03	5/30/03
SLC22A3	http://www.pharmgkb.org/views/index.jsp?objId = PS202860&objCls = Submission	2/26/03	6/16/03
SLC22A4	http://www.pharmgkb.org/views/index.jsp?objId = PS203548&objCls = Submission	9/9/03	10/17/03
SLC22A5	http://www.pharmgkb.org/views/index.jsp?objId = PS203550&objCls = Submission	9/9/03	10/17/03
SLC22A6	http://www.pharmgkb.org/views/index.jsp?objId = PS203570&objCls = Submission	9/16/03	10/17/03
SLC22A8	http://www.pharmgkb.org/views/index.jsp?objId = PS203546&objCls = Submission	9/9/03	10/17/03

TABLE 2
HGNC symbols, HGNC names, synonyms, GenBank accession numbers, and locus IDs

HGNC Symbol	HGNC Name	Synonyms	GenBank Accession No.	Locus ID
SLC22A1	Solute carrier family 22 (organic cation transporter), member 1	OCT1	U77086	6580
SLC22A2	Solute carrier family 22 (organic cation transporter), member 2	OCT2	X98333	6582
SLC22A3	Solute carrier family 22 (extraneuronal monoamine transporter), member 3	EMT, OCT3	AJ001417	6581
SLC22A4	Solute carrier family 22 (organic cation transporter), member 4	OCTN1, ETT	NM_003059	6583
SLC22A5	Solute carrier family 22 (organic cation transporter), member 5	OCTN2	NM_003060	6584
SLC22A6	Solute carrier family 22 (organic anion transporter), member 6	OAT1	AF097490	9356
SLC22A8	Solute carrier family 22 (organic anion transporter), member 8	OAT3	NM_004254	9376

TABLE 3
Endogenous and xenobiotic substrates

Transporter	Substrates
OCT1	MPP^+, 5-hydroxytryptamine, buformin, choline, cimetidine, clonidine, debrisoquine, dopamine, epinephrine, norepinephrine, metformin, phenformin, pindolol, procainamide, ranitidine, serotonin, TEA, tyramine
OCT2	Cimetidine, creatinine, dopamine, epinephrine, guanidine, histamine, norepinephrine, memantine, metformin, MPP^+, phenformin, pindolol, procainamide, ranitidine, serotonin, TEA
OCT3	Dopamine, epinephrine, histamine, MPP^+, norepinephrine
OCTN1	L-Ergothioneine, L-carnitine, TEA, betaine, quinidine, pyrilamine, verapamil
OCTN2	L-Carnitine, L-lysine, L-methionine, cephaloridine, TEA, pyrilamine, verapamil, choline, quinidine
OAT1	*p*-Aminohippurate, acetylsalicylate, acyclovir, adefovir, cidofovir, didanosine, ochratoxin A, tetracycline, zidovudine
OAT3	Estrone sulfate, *p*-aminohippurate, urate, methotrexate, cAMP, cimetidine, ochratoxin A, salicylate, tetracycline

MPP^+, 1-methy-4-phenypyridinium; TEA, tetraethylammonium.