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PharmGKB Submission Update: IV. PMT Submissions of Genetic Variations in ATP-Binding Cassette Transporters to the PharmGKB Network

TAN D. NGUYEN, JASON M. GOW, LESLIE W. CHINN, LIBUSHA KELLY, HOTCHERL JEONG, CONRAD C. HUANG, DOUG STRYKE, MICHIKO KAWAMOTO, SUSAN J. JOHNS, ELAINE CARLSON, TRAVIS TAYLOR, THOMAS E. FERRIN, ANDREJ SALI, KATHLEEN M. GIACOMINI, AND DEANNA L. KROETZ

Department of Biopharmaceutical Sciences (T.D.N., J.M.G., L.W.C., L.K., A.S., K.M.G., D.L.K.), Program in Human Genetics (K.M.G., D.L.K.), and Department of Pharmaceutical Chemistry (C.C.H., D.S., M.K., S.J.J., T.E.F.) and Genomics Core Facility, Program in Human Genetics (E.J.C., T.T.), University of California, San Francisco, San Francisco, California; and Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, California (H.J.)

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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 ATP-binding cassette (ABC) family of efflux transporters may result in altered expression and/or function of the encoded proteins. Resulting changes in intestinal absorption, intestinal, hepatic, and renal elimination, and tissue distribution of therapeutic agents can lead to alterations in drug response and drug toxicity profiles. In particular, loss-of-function variants may lead to accumulation of drugs in both target and nontarget tissues, resulting in toxicity.

Pharmacological Significance: ABC transporters are expressed in the basolateral (blood-facing) or apical (lumen-facing) membrane of polarized epithelial cells of the liver, intestine, and kidneys, where they play a role in the absorption, distribution, and elimination of bulky, neutral, or negatively charged compounds. Expression of ABC transporters in capillary endothelial cells of the blood-brain, blood-placenta, blood-cerebrospinal fluid, and blood-testes barriers is a major determinant of the access of many drugs into these restricted sites. The overexpression of some ABC transporters is associated with drug resistance in tumors.

Endogenous and Xenobiotic Substrates: See Table 3.

Functional Characteristics: ABC transporters are efflux transporters that are ATP-dependent. They facilitate the active efflux of compounds into either the lumen or blood for elimination or distribution.

Summary of Data Submitted:

Size of sample set assayed: *ABCB1*, *ABCB4*, *ABCB11*, *ABCC1*, and *ABCC2*: 247 (494 chromosomes); *ABCC3*, *ABCC4*, *ABCC5*, and *ABCG2*: 276 (552 chromosomes)
Number of gene regions assayed: 244
Total bases assayed: 68,585
Number of variant sites: 498
Polymerase chain reaction primers reported: 488

Publications:

Kroetz DL, Pauli-Magnus C, Hodges LM, Huang CC, Kawamoto M, Johns SJ, Stryke D, Ferrin TE, DeYoung J, Taylor T, et al. (2003) Sequence diversity and haplotype structure in the human *ABCB1* (*MDR1*, multidrug resistance transporter) gene. *Pharmacogenetics* **13:**481–494.

Pauli-Magnus C, Chinn L, Brett C, Feiner J, Lin E, and Kroetz DL (2003) No effect of MDR1 C3435T polymorphism on disposition and CNS effects of loperamide. *Clin Pharmacol Ther* **74:**487–498.

Article, publication date, and citation information can be found at http://pharmrev.aspetjournals.org.
doi:10.1124/pr.58.1.1.

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

HGNC Symbol	PharmGKB Submission	Submission Date	Release Date
ABCB1	http://www.pharmgkb.org/views/index.jsp?objId = PS203119&objCls = Submission	2/26/03	6/15/03
	http://www.pharmgkb.org/views/index.jsp?objId = PS204595&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204596&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204597&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204598&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204599&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204600&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204601&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204602&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204603&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204604&objCls = Submission	10/28/04	12/11/04
	http://www.pharmgkb.org/views/index.jsp?objId = PS204605&objCls = Submission	10/28/04	12/11/04
ABCB4	http://www.pharmgkb.org/views/index.jsp?objId = PS202961&objCls = Submission	2/26/03	6/15/03
ABCB11	http://www.pharmgkb.org/views/index.jsp?objId = PS203479&objCls = Submission	8/14/03	11/10/03
ABCC1	http://www.pharmgkb.org/views/index.jsp?objId = PS203004&objCls = Submission	2/26/03	6/15/03
ABCC2	http://www.pharmgkb.org/views/index.jsp?objId = PS203864&objCls = Submission	2/6/04	4/5/04
ABCC3	http://www.pharmgkb.org/views/index.jsp?objId = PS203567&objCls = Submission	9/15/03	11/10/03
ABCC4	http://www.pharmgkb.org/views/index.jsp?objId = PS203572&objCls = Submission	9/16/03	11/10/03
ABCC5	http://www.pharmgkb.org/views/index.jsp?objId = PS204064&objCls = Submission	7/9/04	10/27/04
ABCG2	http://www.pharmgkb.org/views/index.jsp?objId = PS204867&objCls = Submission	5/4/05	9/30/05

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

HGNC Symbol	HGNC Name	Synonyms	GenBank Accession No.	Locus ID
ABCB1	ATP-binding cassette, subfamily B (MDR/TAP), member 1	P-glycoprotein, multidrug resistance protein 1 (MDR1)	AF016535, M14758	5243
ABCB4	ATP-binding cassette, subfamily B (MDR/TAP), member 4	MDR3	M23234, Z35284	5244
ABCB11	ATP-binding cassette, subfamily B (MDR/TAP), member 11	Bile salt export pump (BSEP), sister of P-glycoprotein (P-gp)	AF091582	8647
ABCC1	ATP-binding cassette, subfamily C (CFTR/MRP), member 1	Multidrug resistance-associated protein 1 (MRP1)	L05628, U91318	4363
ABCC2	ATP-binding cassette, subfamily C (CFTR/MRP), member 2	MRP2, canalicular membrane organic anion transporter (cMOAT)	U63970	1244
ABCC3	ATP-binding cassette, subfamily C (CFTR/MRP), member 3	MRP3, cMOAT2	AF009670, AF085690	8714
ABCC4	ATP-binding cassette, subfamily C (CFTR/MRP), member 4	MRP4	AF071202	10257
ABCC5	ATP-binding cassette, subfamily C (CFTR/MRP), member 5	MRP5	AF104942	10057
ABCG2	ATP-binding cassette, subfamily G (WHITE), member 2	Mitoxantrone resistance transporter (MXR), breast cancer resistance protein (BCRP)	AF103796	9429

TABLE 3
Endogenous and xenobiotic substrates

Transporter	Substrates
P-gp	Daunorubicin, doxorubicin, vinblastine, vincristine, irinotecan, topotecan, etoposide, colchicine, paclitaxel, ritonavir, indinavir, digoxin, fexofenadine, cortisol, morphine, loperamide, ivermectin
MDR3	Phosphatidylcholine, digoxin, vinblastine, paclitaxel, aureobasidin A
BSEP	Bile salts
MRP1	Glutathione-, glucuronate-, and sulfate-conjugated organic anions; estradiol 17-β-D-glucuronide ($E_2$17βG), leukotriene C_4 (LTC_4), *S*-(2,4-dinitrophenyl) glutathione (DNP-SG)
MRP2	Glutathione-, glucuronate-, and sulfate-conjugated organic anions; $E_2$17βG, LTC_4, bilirubin glucuronide, DNP-SG, pravastatin, SN-38 glucuronide, irinotecan
MRP3	Epipodophyllotoxins, methotrexate, vincristine, etoposide, $E_2$17βG, LTC_4, glycocholate, glycochenodeoxycholate, taurodeoxycholate, taurochenodeoxycholate, glucuronides
MRP4	Steroid and bile acid conjugates, nucleoside analogs, 6-mercaptopurine (6-MP), 9-(2-phosphonylmethoxyethyl)adenine (PMEA), cAMP, cGMP
MRP5	6-MP, PMEA, low affinity for cyclic nucleotides
MXR	Anthracyclines, mitoxantrone, bisantrene, topotecan, SN-38