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PharmGKB Submission Update: VI. PMT Submissions of Genetic Variations in Neurotransmitter Transporters (SLC6, SLC17, and SLC18) to the PharmGKB Network

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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 SLC6, SLC17, and SLC18 families of neurotransmitter transporters may result in altered expression and/or function of proteins (Tables 1 and 2). Since neurotransmitter transporters are involved in the regulation of signaling among neurons in the central and peripheral nervous system, genetic variation in these transport proteins has important pathophysiological and pharmacotherapeutic implications. In addition, many of these transporters are linked to various neurological disorders in humans (e.g., epilepsy, schizophrenia, depression, anxiety, and drug addiction). Furthermore, these transporters are the sites of action of various drugs of abuse [e.g., cocaine and amphetamines, including methylenedioxymethamphetamine (MDMA)] and are targets of several clinically approved drugs (e.g., desipramine, tiagabine, nisoxetine, benztropine, and reserpine).

Pharmacological Significance: Neurotransmitter transporters in the SLC6, SLC17, and SLC18 families are primarily expressed in neurons of the central and peripheral nervous system as well as in neuroendocrine tissues. Some of these transporters are also found in many non-neuronal tissues, such as kidney, liver, and intestine. A principal role of neurotransmitter transporters of the SLC6 family, which are expressed on the plasma membrane, is sequestration of extracellular solutes. Members of the SLC17 and SLC18 transporter families are instead expressed on the membrane of secretory vesicles and are primarily involved in the transport of neurotransmitters from the cytosol into secretory vesicles. Many clinically used drugs and abused substances are inhibitors or substrates of the SLC6, SLC17, and SLC18 families of neurotransmitter transporters. In particular, antidepressant and antiepileptic drugs target these neurotransmitter transporters as part of their primary mechanism of action. Therefore, the SLC6, SLC17, and SLC18 transporter families play an important role in the efficacy of such drugs.

Endogenous and Xenobiotic Substrates/Inhibitors: See Table 3.

Functional Characteristics:

SLC6: Synaptic signaling is terminated by a rapid accumulation of neurotransmitters into presynaptic terminals. The reuptake occurs via a cotransporter system, with the energy for transmitter transport provided by the Na^+ electrochemical gradient.

SLC17: This family of transporters is primarily driven by the electrical membrane potential but also by the pH gradient (i.e., proton exchange), and several members mediate the uptake of glutamate in light membrane vesicles.

SLC18: The vesicular monoamine transporters accumulate cytosolic monoamines into synaptic vesicles using the H^+ gradient generated by the vacuolar H^+ pump. This family of transporters is responsible for uptake of acetylcholine and biogenic amines into storage vesicles.

Article, publication date, and citation information can be found at http://pharmrev.aspetjournals.org.
doi:10.1124/pr.58.1.3.

Summary of Data Submitted:

Size of sample set assayed: DAT, NET, GAT1, VMAT1, and VACHT: 494 chromosomes; VGLUT3: 552 chromosomes; VMAT2: 898 chromosomes

Number of gene regions assayed: 81
Total bases assayed: 21,671
Number of variant sites: 167
Polymerase chain reaction primers reported: 162

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

HGNC Symbol	PharmGKB Submission	Submission Date	Release Date
SLC6A1	https://www.pharmgkb.org/views/index.jsp?objId = PS203182&objCls = Submission	2/26/03	6/16/03
SLC6A2	https://www.pharmgkb.org/views/index.jsp?objId = PS202962&objCls = Submission	2/26/03	10/17/03
SLC6A3	https://www.pharmgkb.org/views/index.jsp?objId = PS202783&objCls = Submission	2/26/03	6/16/03
SLC17A8	https://www.pharmgkb.org/views/index.jsp?objId = PS203552&objCls = Submission	9/9/03	10/17/03
SLC18A1	https://www.pharmgkb.org/views/index.jsp?objId = PS203862&objCls = Submission	2/6/04	4/5/04
SLC18A2	https://www.pharmgkb.org/views/index.jsp?objId = PS203574&objCls = Submission	9/17/03	10/17/03
SLC18A3	https://www.pharmgkb.org/views/index.jsp?objId = PS202880&objCls = Submission	2/26/03	6/16/03

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

HGNC Symbol	HGNC Name	Synonyms	GenBank Accession No.	Locus ID
SLC6A1	Solute carrier family 6 (neurotransmitter transporter, GABA), member 1	γ-Aminobutyric acid transporter, GABA transporter, GAT1, GABATR, GABATHG	X54673	6529
SLC6A2	Solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2	NET, NAT1, NET1, SLC6A5	M65105	6530
SLC6A3	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	DAT, DAT1	L24178	6531
SLC17A8	Solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 8	VGLUT3	NM_139319	246213
SLC18A1	Solute carrier family 18 (vesicular monoamine), member 1	CGAT, VAT1, VMAT1	U39905	6570
SLC18A2	Solute carrier family 18 (vesicular monoamine), member 2	SVAT, SVMT, VAT2, VMAT2	L23205	6571
SLC18A3	Solute carrier family 18 (vesicular acetylcholine), member 3	VACHT	U09210	6572

TABLE 3
Endogenous and xenobiotic substrates/inhibitors

Substrates are shown in bold.

Transporter	Substrates/Inhibitors
SLC6A1 GAT1	**GABA**, ACHC, DABA, nipecotic acid, NO-711, SKF89976A, SKF100330A, tiagabine
SLC6A2 NET	**Norepinephrine, dopamine > sympathomimetic amines, amphetamines**, nisoxetine, desipramine, cocaine, mazindol
SLC6A3 DAT	**Dopamine > norepinephrine, sympathomimetic amines, amphetamines, MPTP**, phenylpiperazine, cocaine, mazindol, benztropine, methylphenidate, nomifensine
SLC17A8 VGLUT3	**L-Glutamate > D-Glutamate > aspartate**, Evans blue, Chicago sky blue, Rose Bengal, quinoline-2,4-dicarboxylic acids, DIDS
SLC18A1 VMAT1	**Serotonin, dopamine, epinephrine, norepinephrine, histamine**, reserpine
SLC18A2 VMAT2	**Serotonin, dopamine, epinephrine, norepinephrine, histamine**, tetrabenazine, reserpine
SLC18A3 VACHT	**Acetylcholine**, vesamicol

ACHC, *cis*-1,3-aminocyclohexanecarboxylic acid; DABA, diaminobutyric acid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; DIDS, 4,4′-diisothiocyanatostilbene-2,2′-disulfonic acid; NO-711, 1-[2-[[(diphenylmethylene)imino]oxy]ethyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride; SKF89976A, *N*-(4,4-diphenyl-3-butenyl)-3-piperidine carboxylic acid; SKF100330A, *N*-(4,4-diphenyl-3-butenyl)-1,2,5,6,-tetrahydro-3-pyridine carboxylic acid.