SLC classification: an update

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Sequence-based similarity networks

A sequence similarity network is made up of links corresponding to pairwise relationships that score better than a defined cutoff[1,2] (Fig. 1). Pairwise sequence alignment scores, including percent sequence identity and Expectation Value (E-Value), were computed using SALIGN[3]. The E-value of a match is the number of sequences in the queried database that are expected to match by chance the query sequence at least as well as the assessed match; smaller values indicate more statistically significant alignments[3]. The E-value cutoffs for the final similarity networks were selected manually, similarly to our previous analysis[1,2]. Because of the small database that was used for the analysis (i.e., 386 sequences), E-value cutoffs that typically do not represent meaningful relationship among sequences when using large databases (e.g., E-value of 1) were also considered. Finally, the graphs representing the similarity networks were visualized using Cytoscape 2.8.1[4]. We used the yFiles organic layout algorithm, which maintains all the connections between the nodes to illustrate relationships. Groups of nodes that are inter-connected usually cluster together in the network.

Sequence similarity between human SLC sequences and PDB structures

For each transporter structure, we retrieved the amino acid sequence from the UniProt database[5]. We then ran the alignment server HHpred[6] against the human proteome, using the default parameters. Finally, we selected the alignment between the query sequence of known structure and the human transporter protein with the highest sequence identity, and also retrieved the E-value for the alignment (Table 1 and Supplementary Table 1).

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Atomic structures of homologs of drug ADME SLC transporters

The structures described in Table 1 are of the amino acid antiporter AdiC from *Escherichia coli*[7], the, homolog of the apical sodium-dependent bile acid transporter from *Neisseria meningitidis* (ASBT$_{NM}$)[8], the peptide transporter from *Shewanella oneidensis* (PepT$_{SO}$)[9], the high-affinity phosphate importer PiPT from *Piriformospora indica*[10], the concentrative nucleoside transporter from *Vibrio cholera* (vcCNT)[11], and the multidrug and toxic compound extrusion transporter NorM from *Vibrio cholera*[12].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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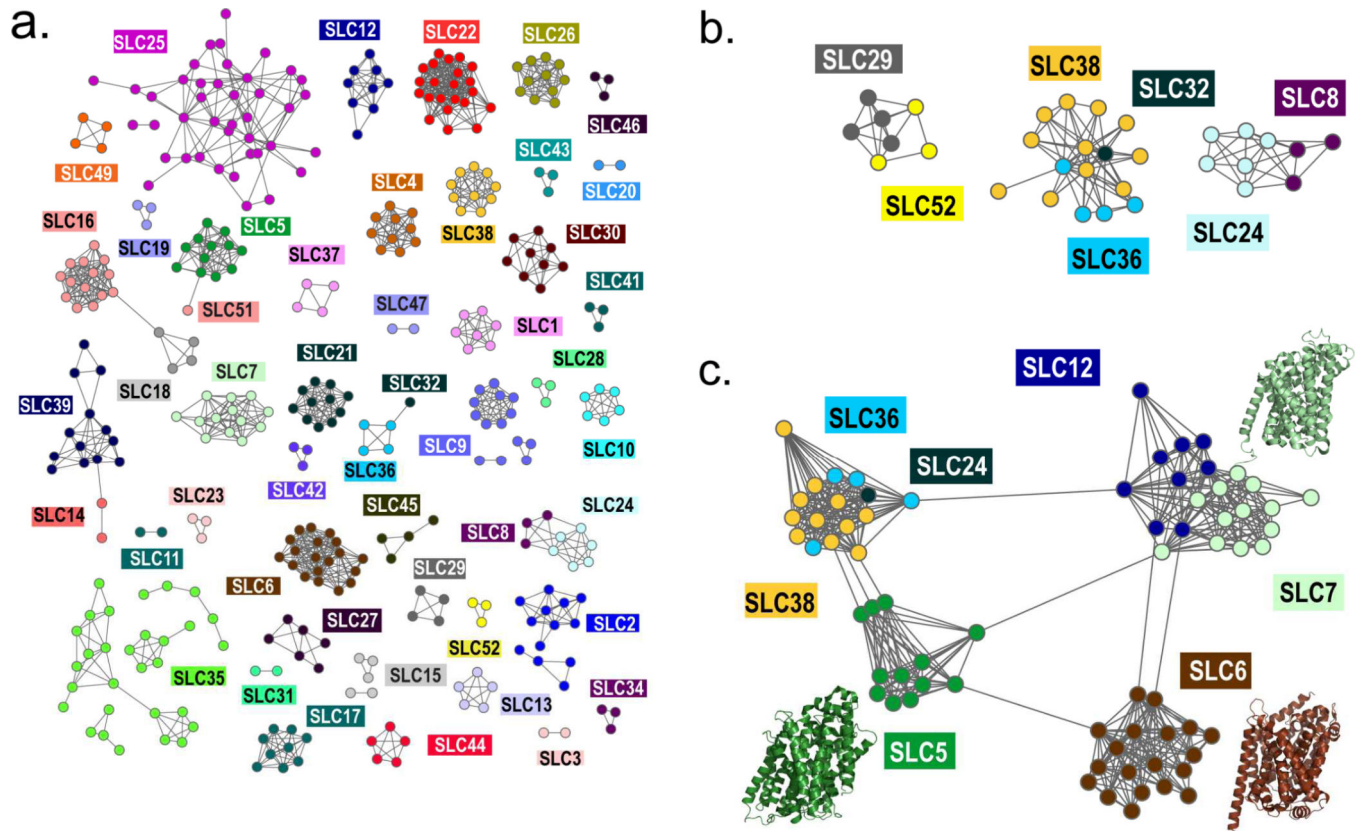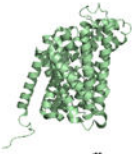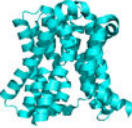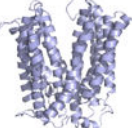
Figure 1.

Table 1

Drug ADME SLC families that can be modeled based on atomic resolution structures from other organisms.

Family[a]	Function[b]	Template Structure[c]	Percent Sequence Identity[d]	Representative Drug Substrates[e]
SLC7 (14)	Cationic amino acid transporter/glycoprotein-associated family	AdiC[#]	21 (1.4 × 10^{-47})	Melphalan, gabapentin, levodopa, baclofen
SLC10 (7)	Na$^+$ bile salt co-transporters	ASBT$_{NM}$	26 (1.8 × 10^{-42})	Rosuvastatin, atorvastatin, fluvastatin
SLC15 (4)	Proton oligopeptide co-transporters	PepT$_{SO}$*	34 (2.2 × 10^{-28})	Valacyclovir, cephalexin, cefadroxil, enalapril, captopril
SLC22 (26)	Organic cation/anion/zwitterion transporters	PiPT*	20 (4.9 × 10^{-34})	Metformin, acyclovir, methotrexate, olmesartan, ipratropium, oxaliplatin, cimetidine
SLC28 (3)	Na$^+$-coupled nucleoside transporters	vcCNT	40 (6.4 × 10^{-130})	Fludarabine, gemcitabine, cytarabine
SLC47 (2)	Multidrug and toxin extrusion (MATE) transporters	NorM	23 (4.8 × 10^{-51})	Metformin, trospium, fexofenadine

[a] *Family* marks the human SLC family, as annotated by the Bioparadigms database[2]. The number of human protein sequences in the family is provided in parenthesis.

*b*Function gives the function of the human family, as described in the Bioparadigms database

*c*Template Structure describes the most related atomic structure to the family. Structures with the MFS and NSS folds are marked with '*' and '#', respectively. Detailed description of the structures, including the full name of the proteins and the corresponding references are described in the Supplementary Material.

*d*Percent Sequence Identity provides the percent sequence identity of the best scoring hit from each family; E-value is given in parenthesis (Supplementary Material)

*e*Representative Drug Substrates gives examples of key prescription drugs that are substrates of the transporter.