Analysis and update of the human solute carrier (SLC) gene superfamily

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Abstract
The solute-carrier gene (SLC) superfamily encodes membrane-bound transporters. The SLC superfamily comprises 55 gene families having at least 362 putatively functional protein-coding genes. The gene products include passive transporters, symporters and antiporters, located in all cellular and organelle membranes, except, perhaps, the nuclear membrane. Transport substrates include amino acids and oligopeptides, glucose and other sugars, inorganic cations and anions (H\(^+\), HCO\(_3\)\(^-\), Cl\(^-\), Na\(^+\), K\(^+\), Ca\(^{2+}\), Mg\(^{2+}\), PO\(_4\)\(^{3-}\), HPO\(_4\)\(^{2-}\), H\(_2\)PO\(_4\)\(^-\), SO\(_4\)\(^{2-}\), C\(_2\)O\(_4\)\(^{2-}\), OH\(^-\), CO\(_3\)\(^{2-}\)), bile salts, carboxylate and other organic anions, acetyl coenzyme A, essential metals, biogenic amines, neurotransmitters, vitamins, fatty acids and lipids, nucleosides, ammonium, choline, thyroid hormone and urea. Contrary to gene nomenclature commonly assigned on the basis of evolutionary divergence (http://www.genenames.org/), the SLC gene superfamily has been named based largely on transporter function by proteins having multiple transmembrane domains. Whereas all the transporters exist for endogenous substrates, it is likely that drugs, non-essential metals and many other environmental toxicants are able to ‘hitch-hike’ on one or another of these transporters, thereby enabling these moieties to enter (or leave) the cell. Understanding and characterising the functions of these transporters is relevant to medicine, genetics, developmental biology, pharmacology and cancer chemotherapy.

Keywords: human genome, transporters, solute carrier gene superfamily, uncoupling proteins, mitochondrial proton carriers, evolutionary genomics

Introduction
The period between the 1980s and the early 1990s might be considered the era of ‘the cloning of genes encoding enzymes and transcription factors’, whereas that between the early 1990s and the present day could be regarded as focusing on ‘the cloning of genes coding for transporters’. One conceivable reason for the earlier spotlight on many of the enzymes and transcription factors is that those gene products were more abundant and/or could be more easily isolated and antibodies generated against them (compared with transporters). Transporters are embedded within membranes and generally have multiple transmembrane domains. Another reason might be that the mRNA transcripts for enzymes are usually shorter than those for transporters, and early reverse transcription activities starting at the 3’ end were tedious and less efficient, meaning that longer mRNA transcripts were often unsuccessful.

Proteins with transport functions (http://www.tcdb.org/tcdb/) can roughly be divided into three categories: ATP-powered pumps, ion channels and transporters. ATP-binding cassette (ABC) pumps...
and other ATP-binding pumps use energy released
by ATP hydrolysis to move substrates across mem-
branes and out of cells or into cellular vesicles
against their electrochemical gradient. These pumps
have two states — open and closed. By contrast,
ion channels in most cases exist in the closed state.
Substrates (ions or water) are transferred down their
electrochemical gradient at extremely high effi-
ciency \((10^8 \text{s}^{-1})\). There are 49 ABC-related
functional genes in the human genome (including
the genes encoding the cystic fibrosis transmem-
brane conductance regulator \([\text{CFTR}]\) and the trans-
porter associated with antigen processing \([\text{TAP}] 1
and TAP2\). Aquaporins (AQPs) are water-channel
proteins, encoded by each of 13 \(AQP\) functional
genes in the human genome (http://www.gene-
names.org/).

Transporters facilitate the movement of a specific
substrate — either with or against its concentration
gradient. It is generally believed that conformational
change of the transporter protein is important in
this transfer process. Transporters move molecules
at only about \(10^2\) to \(10^4 \text{s}^{-1}\), a rate considerably
slower than that associated with channel proteins.
Many of these transporters belong to the solute-
carrier (\(\text{SLC}\)) gene superfamily — and include
passive transporters, symporters and antiporters, as
well as mitochondrial and vesicular transporters.
Passive transporters (or uniporters or facilitative
transporters) transport one molecule at a time down
a concentration gradient. By contrast, active trans-
porters (or co-transporters) couple the movement
of one type of ion or molecule against its concen-
tration gradient, to the movement of another ion
or molecule down its concentration gradient.
(Like ATP pumps, co-transporters mediate coupled
reactions in which an energetically unfavourable
reaction is coupled to an energetically favourable
reaction.) When the transported molecule or ion
and the co-transported molecule or ion move in
the same direction across a membrane, the trans-
porter is called a symporter; when they move in
opposite directions, the transporter is called an
antiporter (or exchanger). If the intracellular net
charge becomes negative, the process is termed
electronically; if the resulting intracellular net
charge remains unchanged, the process is termed
electroneutral.

Genes from all these categories are ancient, having
members present in most, if not all, prokaryotes, as
well as all eukaryotes. Transporters in eukaryotic cells
move ions and other molecules across all cellular
membranes (cell surface, mitochondrial, endoplasmic
reticulum, Golgi and other vesicles), with the possi-
bility exception of nuclear membranes (which have
hores). The portion of the cell exposed to the lumen
is called its apical surface; the rest of the cell (ie its
sides and base) make up the basolateral surface.
Movement of ions or other molecules into the cell is
called influx; movement of ions or other molecules
out of the cell is termed efflux.

**SLC gene superfamily**

Although several specific families within the \(\text{SLC}\)
superfamily have been reviewed during the past
year or two, an overview of the entire gene super-
family has not been attempted since Hediger’s pub-
llication\(^1\) and the special 2004 issue of \(\text{Pflugers}
Archives\), which was devoted entirely to most of the
\(\text{SLC}\) gene families. Such an update at the present
time is deemed important because the number of
genes now known to be in the \(\text{SLC}\) superfamily
has changed considerably since then (http://www.
tcdb.org/hgnc_explore2.php?stem=SLC).

Currently, there are 55 families in the human
\(\text{SLC}\) gene superfamily, with a total of at least 362
putatively functional protein–coding genes. At least
20–25 per cent amino acid sequence identity (most
of which occurs in the consensus domain) is shared
by member proteins belonging to the same \(\text{SLC}\)
gen family. Table 1 includes the Pfam number
(http://pfam.sanger.ac.uk/), consensus sequence
(or domain) and GenBank accession number for
the first member of the 55 genes/gene products.
Note that the \(\text{SLC35}, \text{SLCO1}, \text{SLCO2}\) and
\(\text{SLCO4}\) families contain two or more subfamilies,
whereas the remaining 51 families have no sub-
families (Table 1). In most families where more
than one member is present, the first member was
| Protein family | Description                                                              | Number of members | Pfam   | Domain              | GenBank accession number |
|----------------|--------------------------------------------------------------------------|-------------------|--------|----------------------|--------------------------|
| SLC1           | High-affinity glutamate and neutral amino acid transporter family       | 7                 | PF00375| SDF                  | NP_004161                |
| SLC2           | Facilitative glucose transporter (GLUT) family                          | 14; 5 pseudo      | PF00083| Sugar_tr             | NP_006507                |
| SLC3           | Heavy subunits of the heteromeric amino acid transporters               | 2                 | PF00128| Alpha-amylase        | NP_000332                |
| SLC4           | Bicarbonate transporter family                                          | 10                | PF07565| Band_3_cyto          | NP_000333                |
|                |                                                                          |                   |        |                      |                          |
| SLC5           | Na⁺/glucose co-transporter family                                       | 12                | PF00474| SSF                  | NP_000334                |
| SLC6           | Na⁺- and Cl⁻-dependent neurotransmitter symporter family                | 19; 3 pseudo      | PF00209| SNF                  | NP_003033                |
| SLC7           | Cationic amino acid transporter/glycoprotein-associated amino acid      | 14; 1 pseudo      | PF00324| AA_permease          | NP_003036                |
|                | transporter family                                                       |                   |        |                      |                          |
| SLC8           | Na⁺/Ca²⁺ exchanger family                                               | 3                 | PF03160| Na_Ca_ex             | NP_066920                |
| SLC9           | Na⁺/H⁺ exchanger family                                                 | 11; 4 pseudo      | PF00999| Na_H_Exchange        |                          |
| SLC10          | Na⁺/bile salt co-transporter family                                      | 7                 | PF01758| SBF                  | NP_003040                |
| SLC11          | Proton-coupled metal ion transporter family                              | 2                 | PF01566| Nramp                | NP_000569                |
| SLC12          | Electroneutral cation/Cl⁻ co-transporter family                         | 9                 | PF00324| AA_permease          | NP_000329                |
| SLC13          | Na⁺/SO₄²⁻/carboxylate co-transporter family                             | 5                 | PF00939| Na_sulph_symp        | NP_071889                |
| SLC14          | Urea transporter family                                                 | 2                 | PF03253| UT                   | NP_056949                |
| SLC15          | Proton oligopeptide co-transporter family                               | 4                 | PF00854| PTR2                 | NP_005064                |

Continued
| Protein family | Description                           | Number of members | Pfam    | Domain | GenBank accession number |
|---------------|---------------------------------------|-------------------|---------|--------|-------------------------|
| SLC16         | Monocarboxylate transporter family     | 14                | PF07690 | MFS_1  | NP_003042               |
| SLC17         | Vesicular glutamate transporter family | 8                 | PF07690 | MFS_1  | NP_005065               |
| SLC18         | Vesicular amine transporter family     | 3                 | PF07690 | MFS_1  | NP_003044               |
| SLC19         | Folate/thiamine transporter family     | 3                 | PF01770 |        | NP_919231               |
| SLC20         | Type-III Na\(^+\)/H\(_2\)PO\(_4\)\(^-\) co-transporter family | 2; 1 pseudo | PF01384 | PH04   | NP_006740               |
| SLC22         | Organic cation/anion/zwitterion transporter family | 23 | PF07690 | MFS_1  | NP_003048               |
| SLC23         | Na\(^+\)-dependent ascorbic acid transporter family | 4 | PF00860 | Xan_ur_permease | NP_005838 |
| SLC24         | Na\(^+\)/Ca\(^{2+}\) and Na\(^+\)/K\(^+\) exchanger family | 6 | PF01699 | Na_Ca_ex | NP_004718 |
| SLC25         | Mitochondrial carrier family          | 43; 4 pseudo      | PF00153 | Mito_carr | NP_005975 |
| SLC26         | Multifunctional anion exchanger family | 11 | PF01740 | Sulfate_transp | NP_998778 |
|               |                                       |                   | PF00916 | STAS   |                         |
| SLC27         | Fatty acid transport protein family   | 6                 | PF00501 | AMP-binding | NP_940982 |
| SLC28         | Na\(^+\)-coupled nucleoside transport family | 3 | PF07670 | Gate   | NP_004204               |
|               |                                       |                   | PF07662 | Nucleos_tra2_C |               |
|               |                                       |                   | PF01773 |        |                         |
| SLC29         | Facilitative nucleoside transporter family | 4 | PF01733 | Nucleoside_transp | NP_001071642 |
| SLC30         | Zn\(^{2+}\) efflux family            | 10                | PF01545 | Cation_efflux | NP_067017 |
| SLC31         | Copper transporter family              | 2; 1 pseudo       | PF04145 | Ctr    | NP_001850               |
| SLC32         | Vesicular inhibitory amino acid transporter family | 1 | PF01490 | Aa_trans | NP_542119 |
| SLC33         | Acetyl coenzyme A transporter family   | 1                 | IPR004752 | 2A0125 | NP_004724               |

Continued
Table 1. Continued

| Protein family | Description                                                                 | Number of members | Pfam    | Domain         | GenBank accession number |
|----------------|------------------------------------------------------------------------------|-------------------|---------|----------------|--------------------------|
| SLC34          | Type-II Na⁺/HPO₄²⁻ co-transporter family                                     | 3                 | PF02690 | Na_Pi_cotrans  | NP_003043                |
| SLC35 (A,B,C,D,E,F) | Nucleoside-sugar transporter family                                           | 23                | PF04142 | Nuc_sug_transp | NP_006407                |
| SLC36          | Proton-coupled amino acid transporter family                                 | 4                 | PF01490 | Aa_trans       | NP_510968                |
| SLC37          | Sugar–PO₄³⁻/PO₄³⁻ exchanger family                                           | 4                 | PF07690 | MFS_1          | NP_061837                |
| SLC38          | System A & N, Na⁺-coupled neutral amino acid transporter family              | 11                | PF01490 | Aa_trans       | NP_109599                |
| SLC39          | Metal (M²⁺) ion transporter family                                          | 14                | PF02535 | Zip            | NP_055252                |
| SLC40          | Basolateral iron transporter family                                         | 1                 | PF06963 | FPN1           | NP_055400                |
| SLC41          | MgtE-like Mg²⁺ transporter family                                           | 3                 | PF01769 | MgtE           | NP_776253                |
| SLC42          | Rh-associated glycoproteins; NH₄⁺ transporter family                         | 3                 |         |                |                          |
| SLC43          | Na⁺-independent system-L-like amino acid transporter family                  | 3                 |         |                | NP_003618                |
| SLC44          | Choline-like transmembrane transporter activity                              | 5                 | PF04515 | DUF580         | NP_536856                |
| SLC45          | Putative sugar/H⁺ symporter activity                                         | 4                 | PF07690 | MFS_1          | NP_001073866             |
| SLC46          | Folic acid transporter (heme-containing) activity                           | 3                 | PF07690 | MFS_1          | NP_542400                |
| SLC47          | Polyspecific H⁺/organic cation exporter                                     | 2                 | PF01554 | MatE           | NP_060712                |
| SLCO1 (A,B,C)  | Drug, organic anion transporter family                                       | 4                 | PF07648 | OATP           | NP_602307                |
| SLCO2 (A,B)    | Prostaglandin and steroid sulphate transporter family                        | 2                 | PF07648 | OATP           | NP_005621                |

Continued
chosen to represent that entire family for the global amino acid alignment of the 55 proteins to generate a nearest-neighbour-joining (NNJ) dendrogram (Figure 1).

What had originally been named the ‘SLC21 (organic-anion transporting) family’ has now been changed to six highly divergent SLCO families. Also, the SLC42 family has its genes named RHAG, RHBG and RHCG, because they were first characterised as members of the blood Rh factor antigen family (Table 1).

### Table 1. Continued

| Protein family | Description                                      | Number of members | Pfam   | Domain       | GenBank accession number |
|----------------|--------------------------------------------------|-------------------|--------|--------------|--------------------------|
| SLCO3          | Drug and organic anion transporter activity      | 1                 | PF07648| OATP         | NP_037404                |
| SLCO4 (A,C)    | Thyroid hormone transmembrane transporter activity| 2                 | PF07648| OATP         | NP_057438                |
| SLCO5          | Drug and organic anion transporter activity      | 1                 | PF07648| OATP         | NP_112220                |
| SLCO6          | Drug and organic anion transporter activity      | 1                 | PF07648| OATP         | NP_775759                |
| UCP1           | Oxidative phosphorylation uncoupling activity    | 1                 | PF00153| Mito_carr    | NP_068605                |
| UCP2           | Oxidative phosphorylation uncoupling activity    | 1                 | PF00153| Mito_carr    | NP_003346                |
| UCP3           | Oxidative phosphorylation uncoupling activity    | 1                 | PF00153| Mito_carr    | NP_003347                |

The numbers of documented pseudogenes (‘pseudo’), to date, are noted in the ‘Number of members’ column; these numbers are likely to be gross underestimates, however, because if one does a BLAST search with each exon, numerous ‘bits and pieces’ of the gene plus detritus exons will probably be discovered.

### Evolution of the SLC genes

We examined the SLC superfamily by the NNJ method (Figure 1); we included two functionally unrelated ‘outlier’ genes (SOD1, encoding a soluble protein, and CYP1A1, encoding a membrane-bound protein) and two ‘internal controls’ within the same subfamily (SLC39A2 and SLC39A3, together with SLC39A1). SOD1 and CYP1A1 appeared to be ‘evolutionarily related’ to SLC7 and SLC3, respectively (Figure 1). Thus,
Figure 1. Dendrogram of a representative member of each of the 55 human SLC gene families, developed using Clustal W software, to test for evolutionary readiness. To avoid clutter, we have selected only the first member of each family, although most families have two or more members. We also added two unrelated ‘outlier’ genes (SOD1 and CYP1A1) and two additional members of the SLC39 family (SLC39A2 and SLC39A3) as ‘internal controls’. This nearest neighbour-joining (NNJ) method uses only global alignments of the entire protein sequences. In this case, although the NNJ method appears to gives various branches of different lengths, reflecting the presumed time since evolutionary divergence of the various branches of the gene tree, this tree is largely an artefact because the superfamily has mainly been pulled together by nomenclature experts who based this superfamily on function, rather than evolutionary divergence (see text).
whereas the three SLC39 family members are clustered, the unrelated ‘outliers’ did not fall outside the superfamily tree (as they should). From these findings, we conclude that — although the NNJ method of analysis suggests an evolutionary tree — one cannot detect sufficient evolutionary relatedness for the vast majority of the 55 SLC families making up this superfamily.

There are two clusters of gene families, however, that do show evolutionary relatedness (Figure 1). One is the mitochondrial-transport SLC25 family (of 43 members) clustered together with the three UCP families. This cluster is undoubtedly real because all members are concerned with transport across mitochondrial membranes. The other cluster is the group of six SLCO families. This is intriguing, especially because (vide infra) the substrates are fairly diverse (organic anions and drugs, prostaglandins, lipids and thyroid hormone).

Beyond those two clusters, we see no other statistically significant evolutionary relatedness. Therefore, with the exception of these two clusters, the remainder of the SLC gene families will be discussed on the basis of their common substrates. Many genes in the SLC superfamily are involved in paediatric inherited disorders and other human diseases (see Bergeron et al.3 and http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim). In addition, the functional properties of each family are often summarised on the basis of just a few members that have been thoroughly characterised. If that family has, say, 12 or 23 members, we should keep in mind that it is possible that some of the other members yet to be characterised will not adhere strictly to that specific moniker.

**Inorganic cation/anion transport**

Teleologically, one might argue that inorganic cation and anion transport would be, in evolutionary terms, among the oldest transport functions. Eight families comprise the group that transports exclusively inorganic cations and anions across membranes (Table 1): SLC4, with ten members, plays a pivotal role in mediating Na\(^+\)- and/or Cl\(^-\)-dependent transport of basic anions (e.g. HCO\(_3^-\), CO\(_3^{2-}\)) in various tissues and cell types (in addition to pH regulation, specific members of this family also contribute to vectorial transepithelial base transport in several organ systems, including the kidney, pancreas and eye);4 SLC8, with three members, is a group of Na\(^+\)/Ca\(^{2+}\) exchangers (SLC8A1 is known to exchange three extracellular Na\(^+\) ions for one intracellular Ca\(^{2+}\) ion and to be involved in cardiac contractility);5 SLC9, with 11 members, comprises Na\(^+\)/H\(^+\) exchanger proteins involved in the electroneutral exchange of Na\(^+\) and H\(^+\);6 SLC12, with nine members, functions as a Na\(^+\), K\(^+\) and Cl\(^-\) ion electroneutral symporter;7,8 SLC34, with three members, is an important type II Na\(^+\)/HPO\(_4^{2-}\) symporter.9,10 SLC20, with two members, originally identified as a viral receptor,11 functions as a type III Na\(^+\)/H\(_2\)PO\(_4^-\) symporter.10,11 SLC24, with six members, is a group of Na\(^+\)/Ca\(^{2+}\) or Na\(^+\)/K\(^+\) exchangers;12 and SLC26, with 11 members, is the transepithelial multifunctional anion (e.g. sulfate, oxalate, HCO\(_3^-\), Cl\(^-\)) exchanger family.13,14 also important in sound amplification in the cochlea.15

**Amino acid and oligopeptide transport**

Eight families are involved as transporters of amino acids and/or oligopeptides (Table 1): SLC1, with seven members, transports high-affinity glutamate and neutral amino acids;3,16 SLC3, with two members, encodes transporters of heavy subunits of heteromeric amino acids.3,17 The SLC3 family (along with other amino acid carrier SLC1, SLC6 and SCL7 families, plus the glucose carrier SLC2 and SLC5 families) is regarded as a collection of transporters that function mainly in ‘epithelial-derived’ cells;3 SLC7, with 14 members, represents cationic amino acid/glycoprotein transporters;3,18 SLC15, with four members, represents a family of proton-oligopeptide symporters;19,20 SLC17, with eight members, is involved in diverse processes ranging from the vesicular storage of the neurotransmitter glutamate to the degradation and metabolism of glycoproteins;21 SLC32, with one member only, transports amino acids across vesicle
membranes; SLC36, with four members (a mutation in the SLC36A1 gene was recently found to be associated with champagne dilution coat colour in horses), is involved in proton-coupled amino acid transport; SLC38, with 11 members, functions as a sodium-coupled neutral amino-acid transporter; and SLC43, with three members, represents the sodium-independent system-L-like (ie mediating the movement of bulky neutral amino acids across cell membranes) amino acid transporter family. It is worth noting that the SLC32, SLC36 and SLC38 families do appear to be evolutionarily related (Figure 1). SLC16 and SLC22 also transport amino acids, among other substrates, and are described later.

**Transport of glucose and other sugars**

Four families function as sugar transporters (Table 1): SLC2, with 14 members, is the well-studied facilitative glucose transporter (GLUT) family; SLC5, with 12 members, functions as a Na\(^+\)/glucose symporter; SLC37, with four members, is a group of sugar–PO\(_4\)\(^-\)/PO\(_4\)\(^2-\) exchangers, with glucose-6–PO\(_4\)\(^-\) transporter-1 being the most well characterised; and SLC45, with four members, appears to function as a sugar/H\(^+\) symporter. The SLC45A1 gene is located at 1p36.23. SLC45A2, associated with skin pigmentation and protection against malignant melanoma, is located at 5p13.3. SLC45A3, located at 1q32.1, is, curiously, one of several genes that have been found to be involved in recurrent gene rearrangements in prostate cancer. SLC45A4 was mapped to 8q24.3 (http://www.genenames.org/).

**Transport of bile salts and organic anions**

Four families participate as transporters of bile salts and organic anions (Table 1): SLC10, with seven members, is involved in bile acid transport; SLC13, with five members, is the Na\(^+\)/sulphate/selenate/thiosulphate/carboxylate symporter family. The di- and tri-carboxylates include succinate, citrate and alpha-ketoglutarate; SLC16, with 14 members, is involved in the proton-linked transport of monocarboxylate anions (eg lactate, pyruvate and ketone bodies) and aromatic amino acids; and SLC47, with two members, has so far only been characterised as a polyspecific H\(^+\)/organic cation exporter. The SLC47 genes have also been nicknamed ‘multidrug and toxicant extrusion-1 and -2’ (MATE1 and MATE2). The SLC47A1 and SLC47A2 genes both map to 17p11.2 (http://www.genenames.org/). Four of the SLCO families also participate in organic anion transport, and these are separately described later as an evolutionary cluster.

**Metal ion transport**

Six SLC families are involved in metal ion transport (Table 1): SLC11, with two members that function as proton-coupled metal ion influx transporters, also known as the ‘natural resistance-associated macrophage protein’ (NRAMP) homologues; SLC30, with ten members, is involved in Zn\(^2+\) efflux; SLC31, with two members, is a copper influx transporter family; SLC39, with 14 members, functions in the influx of essential metals such as Zn\(^2+\), Fe\(^2+\), Cu\(^2+\) and Mn\(^2+\), although non-essential toxic metals such as Cd\(^2+\), Pb\(^2+\) and Hg\(^2+\) can ‘hijack’ at least two of these transporters; SLC40, with one member only, is a basolateral iron transporter; and SLC41, with three members, is the ‘MgtE-like’ magnesium transporter family, which has been characterised principally in prokaryotes (also found in yeast, worm and fly), while their physiological role in eukaryotes remains unclear.

**Transport of urea, neurotransmitters and biogenic amines, ammonium and choline**

Five families participate in the transport of these molecules (Table 1): SLC6, with 19 members, represents Na\(^+\) and Cl\(^-\) ion-dependent neurotransmitter (gamma-aminobutyric acid [GABA], serotonin, dopamine and norepinephrine) transporters, having relatives even in prokaryotes; SLC14, with
two members, is involved in the transport of urea;49 SLC18, with three members, transports acetylcholine (by the vesicular acetylcholine transporter SLC18A3) and biogenic amines (by the vesicular monoamine transporters SLC18A1 and SLC18A2) into secretory vesicles, which are then discharged into the extracellular space by exocytosis;50 SLC22, with 23 members, is highly conserved in the fly and worm, functions in endogenous organic cation/anion/zwitterion (eg carnitine, betaines, amino acids) transport and thus is very important in drug transporter functions;51 SLC42, with three members52 that appear to be involved in NH₄⁺ transport (whereas their gene names are RHAG, RHBG and RHCG); and SLC44, with five members and homologues in yeast, fly and worm, appears to be involved in choline transport.53

Transport of vitamins and cofactors

Four families participate in vitamin or cofactor transport (Table 1): SLC19, with three members, transports folate and thiamine, energised by a transmembrane H⁺/OH⁻ gradient;54 SLC23, with four members, transports ascorbic acid;55 SLC33, with a single member, is an acetyl coenzyme A transporter, which serves as a substrate of acetyltransferases that modify the sialyl residues of gangliosides and glycoproteins;56 SLC46, with three members, is involved in proton-coupled folic acid transport. Homozygous mutations in the SLC46A1 gene, located at 17q11.2, are associated with hereditary folate malabsorption.57 SLC46A2 maps to 9q32, and SLC46A3 to 13q12.3 (http://www.genenames.org/).

Nucleoside/nucleotide transport

Three families carry out the transport of nucleosides and nucleotides (Table 1): SLC28, with three members, functions in Na⁺-coupled nucleoside transport and thus is a potentially important pharmacological target;60 SLC29, with four members, mediates (along with the SLC28 transporters) uptake of natural nucleosides (among them adenosine) — these members are major routes of entry for a variety of nucleoside analogues used in anticancer and antiviral therapies;61 SLC35, with 23 members, transports nucleotide sugars (pooled in the cytosol) into the lumen of the Golgi apparatus and endoplasmic reticulum, wherein occurs most of the synthesis of glycoconjugates.62

Transport of fatty acids, prostaglandins and steroid sulphates

Two SLC families are involved in these functions (Table 1): SLC27, with six members, participates in the transport of long-chain fatty acids;63 and SLCO2, with two members (detailed below), functions in prostaglandin and steroid sulphate transport.

SLCO gene families

The six SLCO gene families represent an evolutionary cluster (Figure 1); four of the families are involved in organic anion-transporting polypeptides (OATPs), which include 14 transmembrane-domain glycoproteins expressed in various epithelial cells (Table 1): SLCO1, with four members, is involved in drug transport; SLCO3, with a single member, transports unknown organic anions; SLCO5 and SLCO6, both families having a single member, also transport unknown organic anions and are believed to be important in drug transport, whereas SLCO2, with two members, functions in the transport of prostaglandins65 and steroid sulphates.66 SLCO4, with two members, functions in the transport of thyroid hormone.67 Most of the SLCO proteins have not yet been well characterised.

Transport across mitochondrial membranes

The four gene families involved in mitochondrial transport also represent an evolutionary cluster (Figure 1): SLC25, with 43 members (the largest of all SLC families), is known to comprise the ‘mitochondrial carriers’, shuttling a variety of metabolites across the mitochondrial inner membrane;68 and UCP1,69 UCP2,70,71 and UCP3 (located at chromosomes 4q28-q31, 11q13 and 11q13.4, respectively) function...
as ancient uncoupling proteins, or proton pumps involved in mitochondrial energetics (Table 1).

**Conclusions**

The SLC gene superfamily comprises 55 families, totalling at last 362 putatively functional protein-coding genes that encode multiple transmembrane transporters. Whereas all the transporters undoubtedly have endogenous substrates, drugs, non-essential metals and many other environmental toxicants in all likelihood are able to ‘hitch-hike’ on one or another of these transporters, thereby being able to enter (or leave) the cell. Understanding and characterising the functions of all these transporters should be relevant to medicine, genetics, pharmacology and cancer chemotherapy. Because more than half of these genes remain to be characterised, this field seems ripe — perhaps especially for young investigators who wish to choose a research topic with little or no competition at the present time.

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**NOTE ADDED IN PROOF:** The SLC22A12 gene is known to encode urate transporter-1. The very recent finding of an association of mutations in the SLC22A9 gene from dogs exhibiting hyperuricosuria and hyperuricaemia* underscores the importance of SLC289 as an additional uric acid transporter in mammals, which in all likelihood include humans.

*Ramsach, D., Safa, N., Young, A., Karmi, N., Schaible, R.S. and Ling, G.V. (2008), ‘Mutations in the SLC289 gene cause hyperuricosuria and hyperuricaemia in the dog’, *PLoS Genet.* 30 November; e1000246.

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