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-}, $H_2PO_4^-$, SO_4^{2-}, $C_2O_4^{2-}$, 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 membranes 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 efficiency (up to $10^8 \, s^{-1}$). There are 49 *ABC*-related functional genes in the human genome (including the genes encoding the cystic fibrosis transmembrane conductance regulator [*CFTR*] and the transporter associated with antigen processing [*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 $10^4 \, s^{-1}$, a rate considerably slower than that associated with channel proteins. Many of these transporters belong to the solute-carrier (*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 transporters (or co-transporters) couple the movement of one type of ion or molecule against its concentration 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 transporter is called a symporter; when they move in opposite directions, the transporter is called an antiporter (or exchanger). If the intracellular net charge following transport becomes negative, the process is termed electronegative; if the intracellular

net charge becomes positive, the process is called electropositive; 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 possible exception of nuclear membranes (which have pores). 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 *SLC* superfamily have been reviewed during the past year or two, an overview of the entire gene superfamily has not been attempted since Hediger's publication[1] and the special 2004 issue of *Pflugers Archives*, which was devoted entirely to most of the *SLC* gene families. Such an update at the present time is deemed important because the number of genes now known to be in the *SLC* superfamily has changed considerably since then (http://www.tcdb.org/hgnc_explore2.php?stem=SLC).

Currently, there are 55 families in the human *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 *SLC* gene 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 *SLC35*, *SLCO1*, *SLCO2* and *SLCO4* families contain two or more subfamilies, whereas the remaining 51 families have no subfamilies (Table 1). In most families where more than one member is present, the first member was

Table 1. Human *SLC* gene superfamily, including description of the gene products

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
			PF00955	HC03_cotransp	
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 transporter family	14; 1 pseudo	PF00324	AA_permease	NP_003036
SLC8	Na^+/Ca^{2+} exchanger family	3	PF03160	Na_Ca_ex	NP_066920
			PF01699	Calx_eta	
SLC9	Na^+/H^+ exchanger family	11; 4 pseudo	PF00999	Na_H_Exchanger	
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
			PF08403		
SLC13	Na^+/SO_4^{2-}/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

Table 1. 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	Folate_carrier	NP_919231
SLC20	Type-III $Na^+/H_2PO_4^-$ 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_tran	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^+/HPO_4^{2-} 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–PO_4^{3-}/PO_4^{3-} 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 (M^{2+}) ion transporter family	14	PF02535	Zip	NP_055252
SLC40	Basolateral iron transporter family	1	PF06963	FPN1	NP_055400
SLC41	MgtE-like Mg^{2+} transporter family	3	PF01769	MgtE	NP_776253
SLC42	Rh-associated glycoproteins; NH_4^+ 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
			PF03137		
SLCO2 (A,B)	Prostaglandin and steroid sulphate transporter family	2	PF07648	OATP	NP_005621

Continued

Table 1. Continued

Protein family	Description	Number of members	Pfam	Domain	GenBank accession number
			PF03137		
SLCO3	Drug and organic anion transporter activity	1	PF07648	OATP	NP_037404
			PF03137	KAzal_2	
SLCO4 (A,C)	Thyroid hormone transmembrane transporter activity	2	PF07648	OATP	NP_057438
			PF03137		
SLCO5	Drug and organic anion transporter activity	1	PF07648	OATP	NP_112220
			PF03137		
SLCO6	Drug and organic anion transporter activity	1	PF07648	OATP	NP_775759
			PF03137	Kazal_2	
UCP1	Oxidative phosphorylation uncoupling activity (proton carrier)	1	PF00153	Mito_carr	NP_068605
UCP2	Oxidative phosphorylation uncoupling activity (proton carrier)	1	PF00153	Mito_carr	NP_003346
UCP3	Oxidative phosphorylation uncoupling activity (proton carrier)	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.[2]

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).

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,
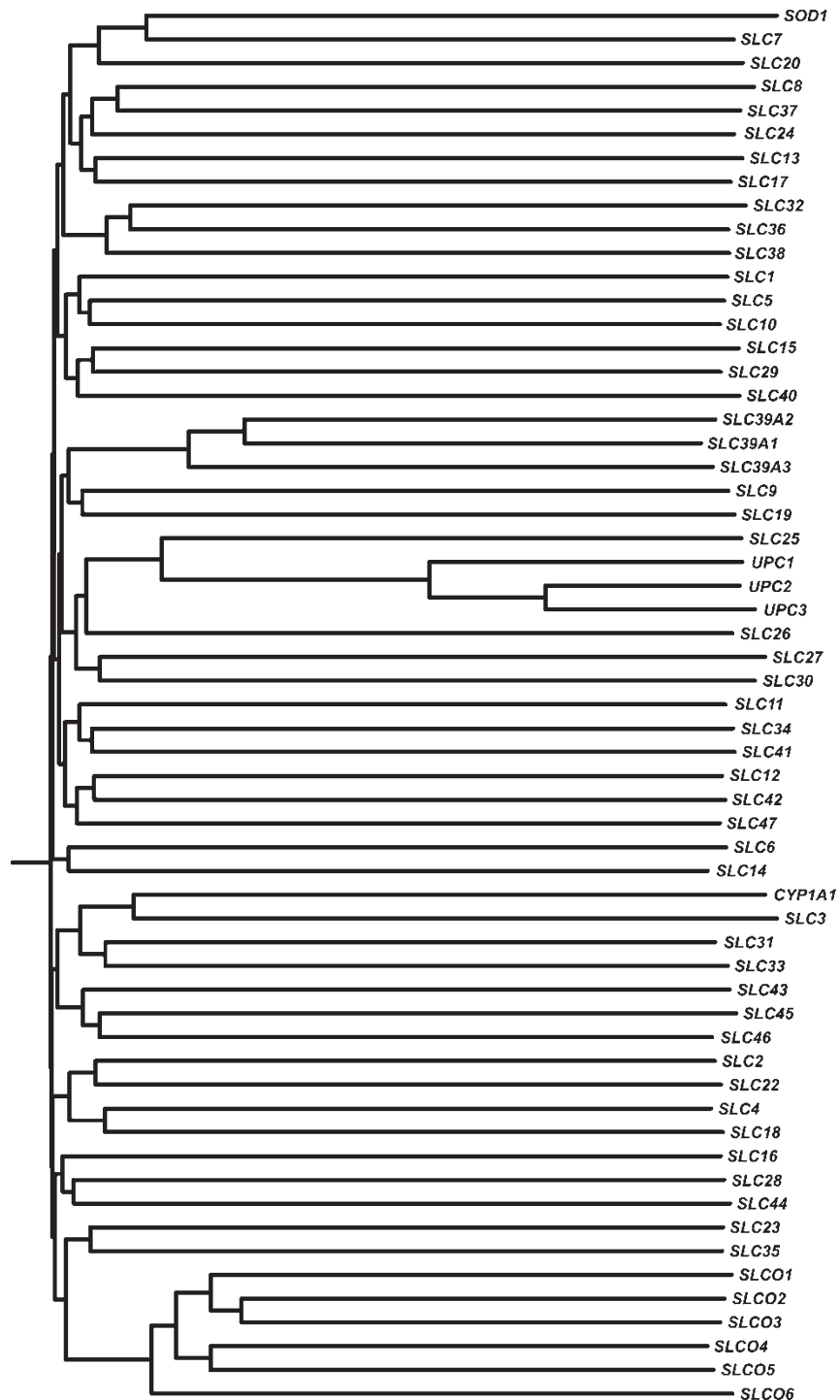
Figure 1. Dendrogram of a representative member of each of the 55 human *SLC* gene families, developed using Clustal W software, to test for evolutionary readiness. To avoid clutter, we have selected only the first member of each family, although most families have two or more members. We also added 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 (eg 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 $Na^+/(H_2PO_4)^-$ 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 (eg 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;[22] SLC36, with four members (a mutation in the *SLC36A1* gene was recently found to be associated with champagne dilution coat colour in horses[23]), is involved in proton-coupled amino acid transport;[24] SLC38, with 11 members, functions as a sodium-coupled neutral amino-acid transporter;[25] 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.[1,26] 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;[2,27] SLC5, with 12 members, functions as a Na^+/glucose symporter;[2,28] SLC37, with four members, is a group of sugar$-PO_4^-$/PO_4^- exchangers, with glucose-6$-PO_4^-$ transporter-1 being the most well characterised;[29] and SLC45, with four members, appears to function as a sugar/H^+ symporter. The *SLC45A1* gene is located at 1p36.23.[30] *SLC45A2*, associated with skin pigmentation and protection against malignant melanoma,[31] 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.[32] *SLC45A4*[33] 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;[34] SLC13, with five members, is the Na^+/sulphate/selenate/thiosulphate/carboxylate symporter family. The di- and tri-carboxylates include succinate,

citrate and alpha-ketoglutarate;[35] SLC16, with 14 members, is involved in the proton-linked transport of monocarboxylate anions (eg lactate, pyruvate and ketone bodies) and aromatic amino acids;[36] and SLC47, with two members, has so far only been characterised as a polyspecific H^+/organic cation exporter.[37] The *SLC47* genes have also been nick-named '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;[38] SLC30, with ten members, is involved in Zn^{2+} efflux;[39,40] SLC31, with two members, is a copper influx transporter family;[41] SLC39, with 14 members, functions in the influx of essential metals such as Zn^{2+}, Fe^{2+}, Cu^{2+} and Mn^{2+},[40,42] although non-essential toxic metals such as Cd^{2+}, Pb^{2+} and Hg^{2+} can 'hijack' at least two of these transporters;[43,44] SLC40, with one member only, is a basolateral iron transporter;[45] 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.[46]

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,[3,47] having relatives even in prokaryotes;[48] 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 members[52] that appear to be involved in NH_4^+ 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[58] maps to 9q32, and SLC46A3[33,59] to 13q12.3 (http://www.gene-names.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[64] 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 prostaglandins[65] 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[70] (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.

Acknowledgments

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 *SLC2A9* gene from dogs exhibiting hyper uricosuria and hyperuricaemia* underscores the importance of SLC289 as an additional uric acid transporter in mammals, which in all likelihood include humans.

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