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The Transporter Classification (TC) System, 2002

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ABSTRACT: The Transporter Classification (TC) system is a functional/phylogenetic system designed for the classification of all transmembrane transport proteins found in living organisms on Earth. It parallels but differs from the strictly functional EC system developed decades ago by the Enzyme Commission of the International Union of Biochemistry and Molecular Biology (IUBMB) for the classification of enzymes. Recently, the TC system has been adopted by the IUBMB as the internationally acclaimed system for the classification of transporters. Here we present the characteristics of the nearly 400 families of transport systems included in the TC system and provide statistical analyses of these families and their constituent proteins. Specifically, we analyze the transporter types for size and topological differences and analyze the families for the numbers and organismal sources of their constituent members. We show that channels and carriers exhibit distinctive structural and topological features. Bacterial-specific families outnumber eukaryotic-specific families about 2 to 1, while ubiquitous families, found in all three domains of life, are about half as numerous as eukaryotic-specific families. The results argue against appreciable horizontal transfer of genes encoding transporters between the three domains of life over the last 2 billion years.

KEY WORDS: transport, proteins, classification, membranes, channels, carriers.

I. INTRODUCTION

Transport systems comprise an essential feature of every living cell. They (1) allow the entry of all essential nutrients into the cell and its compartments, (2) regulate the cytoplasmic concentrations of metabolites by excretion mechanisms, (3) prevent toxic effects of drugs and toxins by mediating active efflux, (4) provide physiological cellular concentrations of ions that can differ by several orders of magnitude from those in the external medium, (5) export macromolecules such as complex carbohydrates, proteins, lipids and DNA, (6) catalyze export and uptake of signaling molecules that mediate intercellular communication, and (7) participate in biological warfare by exporting biological active agents that insert into or permeate the membranes of target cells. In fact, transport is an essential aspect of all life endowing processes: metabolism, communication, biosynthesis, and reproduction.

This article provides an update of the recently developed transporter classification

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(TC) system (Saier, 1998, 1999, 2000a), which was formally adopted by the International Union of Biochemistry and Molecular Biology (IUBMB) in June 2002. The development of a classification system for transport proteins has allowed us to gain a comprehensive overview of transport from structural, functional and evolutionary standpoints (Saier, 1999, 2000b, 2001). This development has been strongly influenced by recent progress in genome sequencing and the field of computational biology. Since our last description of the TC system (Saier, 2000a), we have expanded the transporter classification system by (1) introducing new families and classes of transporters (2) expanding the memberships of preexisting families, (3) providing more detailed annotation of these families and proteins, (4) updating reference citations relevant to proteins described in the TC system, and (5) creating an interactive database, which we have named TCDB. The results of our analyses, made possible by these updates, are reported here.

A. The TC System

The properties of the different hierarchical units that comprise the TC system are described briefly below and illustrated in Figure 1. The families within each class are presented in Table 1, and Table 2 provides descriptions of these families as well as at least one well-characterized member of each family. For more extensive descriptions please visit our websites and database (http://tcdb.ucsd.edu).

B. Classes of Transporters

1. Class 1. Channels/Pores

This class consists of channel-type facilitators. Transmembrane channel proteins span the lipid bilayer as either α-helices or β-strands. The transport mode of these systems generally involves the unencumbered passage of molecules across membranes by a process related to passive diffusion. Thus, channel-mediated transport usually occurs by facilitated diffusion, an energy-independent process in which the substrate passes through the transmembrane aqueous pore or channel without coupling of the translocation process to another chemical or vectorial process.

a. α-Type Channels

Transmembrane channel proteins of this subclass usually consist of bundles of transmembrane α-helices that form α-helical aqueous pores or channels. Rarely, β-strands contribute to the channel. These channels are found ubiquitously in the membranes of all types of organisms.

b. β-Barrel Porins

The transmembrane pores of these proteins consist exclusively of β-strands that form β-barrels. These channels are found in the outer membranes of bacteria, mitochondria, and plastids. They may be monomeric or oligomeric structures where the pore may be formed from just one or several polypeptide chains. Interactions with other proteins may control their activities.

c. Pore-Forming Toxins

These polypeptides attack target cells other than the producer cell by inserting into the target cell membrane, usually form-

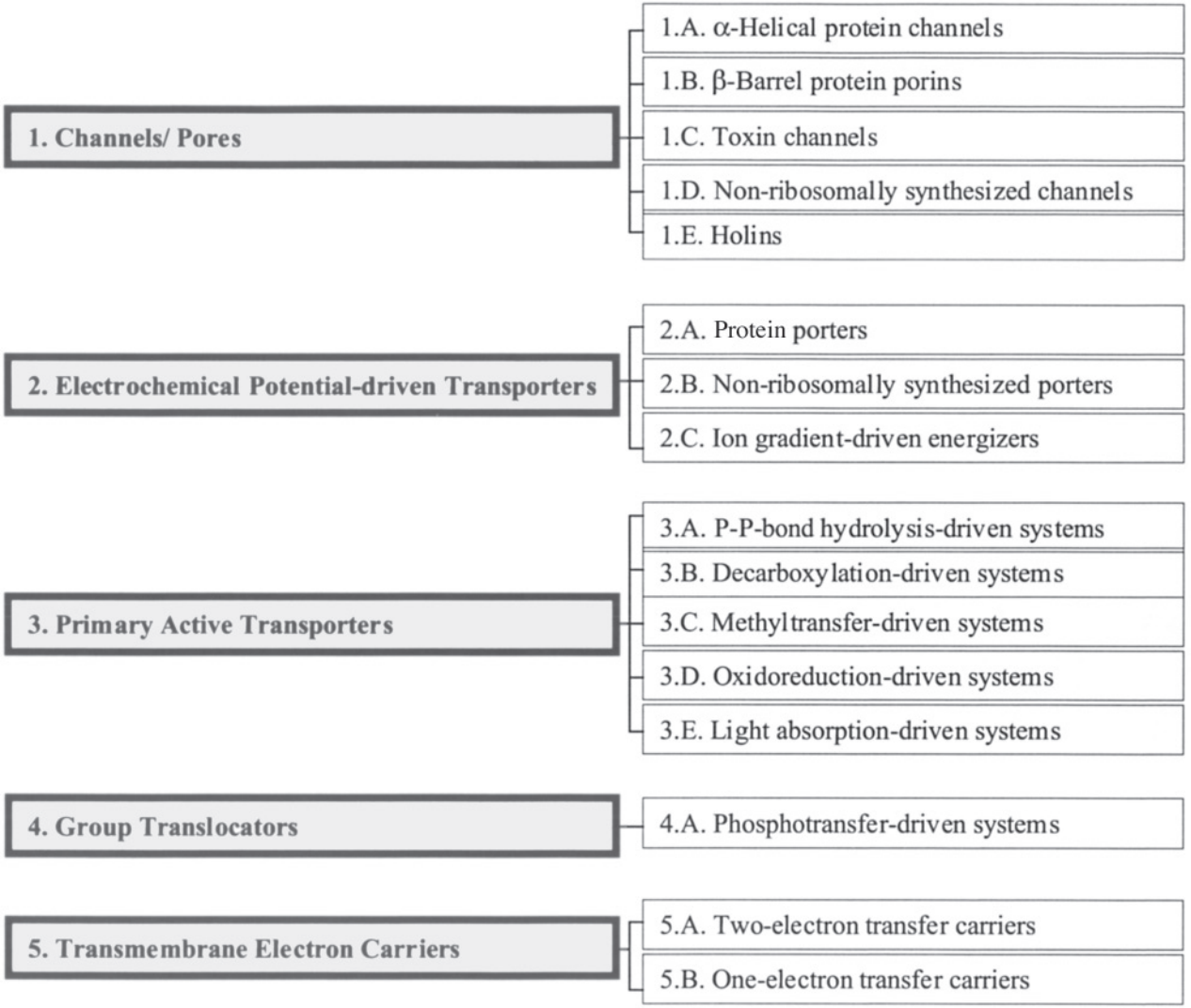

FIGURE 1. Schematic depiction of the hierarchical system for classifying families of transporters of defined function in the TC system. Classes are provided on the left while subclasses are provided on the right.

TABLE 1
Famlies of Transporters Found in the TC System

TC #	Family
1.A. α-Channels	
1.A.1	The Voltage-gated Ion Channel (VIC) Superfamily
1.A.2	The Animal Inward Rectifier K^+ Channel (IRK-C) Family
1.A.3	The Ryanodine-Inositol 1,4,5-triphosphate Receptor Ca^{2+} Channel (RIR-CaC) Family
1.A.4	The Transient Receptor Potential Ca^{2+} Channel (TRP-CC) Family
1.A.5	The Polycystin Cation Channel (PCC) Family
1.A.6	The Epithelial Na^+ Channel (ENaC) Family
1.A.7	ATP-gated Cation Channel (ACC) Family
1.A.8	The Major Intrinsic Protein (MIP) Family
1.A.9	The Ligand-gated Ion Channel (LIC) Family of Neurotransmitter Receptors
1.A.10	The Glutamate-gated Ion Channel (GIC) Family of Neurotransmitter Receptors
1.A.11	The Chloride Channel (ClC) Family
1.A.12	The Organellar Chloride Channel (O-ClC) Family
1.A.13	The Epithelial Chloride Channel (E-ClC) Family
1.A.14	The Non-selective Cation Channel-1 (NSCC1) Family
1.A.15	The Non-selective Cation Channel-2 (NSCC2) Family
1.A.16	The Yeast Stretch-Activated, Cation-Selective, Ca^{2+} Channel, Mid1 (Mid1) Family
1.A.17	The Chloroplast Outer Envelope Solute Channel (CSC) Family
1.A.18	The Chloroplast Envelope Anion Channel-forming Tic110 (Tic110) Family
1.A.19	The Influenza Virus Matrix-2 Channel (M2-C) Family
1.A.20	The gp91phox Phagocyte NADPH Oxidase-associated Cytochrome b558 (CytB) H^+-channel Family
1.A.21	The Bcl-2 (Bcl-2) Family
1.A.22	The Large Conductance Mechanosensitive Ion Channel (MscL) Family
1.A.23	The Small Conductance Mechanosensitive Ion Channel (MscS) Family
1.A.24	The Gap Junction-forming Connexin (Connexin) Family
1.A.25	The Gap Junction-forming Innexin (Innexin) Family
1.A.26	The Plant Plasmodesmata (PPD) Family
1.A.27	The Phospholemman (PLM) Family
1.A.28	The Urea Transporter (UT) Family
1.A.29	The Urea/Amide Channel (UAC) Family
1.A.30	The H^+- or Na^+-translocating Bacterial Flagellar Motor 1ExbBD Outer Membrane Transport Energizer (Mot/Exb) Superfamily
1.A.31	The Annexin (Annexin) Family
1.A.32	The Type B Influenza Virus NB Channel (NB-C) Family
1.A.33	The Cation Channel-forming Heat Shock Protein-70 (Hsp70) Family
1.A.34	The Envelope Virus E1 Channel (EVE1-C) Family
1.A.35	The CorA Metal Ion Transporter (MIT) Family
1.A.36	The Intracellular Chloride Channel (ICC) Family
1.B. β-Barrel porin	
1.B.1	The General Bacterial Porin (GBP) Family
1.B.2	The Chlamydial Porin (CP) Family
1.B.3	The Sugar Porin (SP) Family
1.B.4	The Brucella-Rhizobium Porin (BRP) Family
1.B.5	The Pseudomonas OprP Porin (POP) Family
1.B.6	The OmpA-OmpF Porin (OOP) Family
1.B.7	The Rhodobacter PorCa Porin (RPP) Family
1.B.8	The Mitochondrial and Plastid Porin (MPP) Family
1.B.9	The FadL Outer Membrane Protein (FadL) Family

TABLE 1 (continued)

1.B.10 The Nucleoside-specific Channel-forming Outer Membrane Porin (Tsx) Family
1.B.11 The Outer Membrane Fimbrial Usher Porin (FUP) Family
1.B.12 The Autotransporter (AT) Family
1.B.13 The Alginate Export Porin (AEP) Family
1.B.14 The Outer Membrane Receptor (OMR) Family
1.B.15 The Raffinose Porin (RafY) Family
1.B.16 The Short Chain Amide and Urea Porin (SAP) Family
1.B.17 The Outer Membrane Factor (OMF) Family
1.B.18 The Outer Membrane Auxiliary (OMA) Protein Family
1.B.19 The Glucose-selective OprB Porin (OprB) Family
1.B.20 The Two-Partner Secretion (TPS) Family
1.B.21 The OmpG Porin (OmpG) Family
1.B.22 The Outer Bacterial Membrane Secretin (Secretin) Family
1.B.23 The Cyanobacterial Porin (CBP) Family
1.B.24 The Mycobacterial Porin (MBP) Family
1.B.25 The Outer Membrane Porin (OPr) Family
1.B.26 The Cyclodextrin Porin (CDP) Family
1.B.27 The Helicobacter Outer Membrane Porin (HOP) Family
1.B.28 The Plastid Outer Envelope Porin of 24 kDa (OEP24) Family
1.B.29 The Plastid Outer Envelope Porin of 21 kDa (OEP21) Family
1.B.30 The Plastid Outer Envelope Porin of 16 kDa (OEP16) Family
1.B.31 The *Campylobacter jejuni* Major Outer Membrane Porin (MomP) Family
1.B.32 The Fusobacterial Outer Membrane Porin (FomP) Family
1.B.33 The Vibrio Chitoporin/Neisserial Porin (VC/NP) Family
1.B.34 The Corynebacterial Porin (PorA) Family

1.C. Pore-forming toxins

1.C.1 The Channel-forming Colicin (Colicin) Family
1.C.2 The Channel-forming δ-Endotoxin Insecticidal Crystal Protein (ICP) Family
1.C.3 The α-Hemolysin Channel-forming Toxin (αHL) Family
1.C.4 The Aerolysin Channel-forming Toxin (Aerolysin) Family
1.C.5 The Channel-forming ε-toxin (ε-toxin) Family
1.C.6 The Yeast Killer Toxin K1 (YKT-K1) Family
1.C.7 The Diphtheria Toxin (DT) Family
1.C.8 The Botulinum and Tetanus Toxin (BTT) Family
1.C.9 The Vacuolating Cytotoxin (VacA) Family
1.C.10 The Pore-forming Haemolysin E (HlyE) Family
1.C.11 The Pore-forming RTX Toxin (RTX-toxin) Family
1.C.12 The Cholesterol-binding, Thiol-activated Cytolysin (TAC) Family
1.C.13 The Channel-forming Leukocidin Cytotoxin (Ctx) Family
1.C.14 The Cytohemolysin (CHL) Family
1.C.15 The Whipworm Stichosome Porin (WSP) Family
1.C.16 The Magainin (Magainin) Family
1.C.17 The Cecropin (Cecropin) Family
1.C.18 The Melittin (Melittin) Family
1.C.19 The Defensin (Defensin) Family
1.C.20 The Nisin (Nisin) Family
1.C.21 The Lacticin 481 (Lacticin 481) Family
1.C.22 The Lactococcin A (Lactococcin A) Family
1.C.23 The Lactocin S (Lactocin S) Family
1.C.24 The Pediocin (Pediocin) Family
1.C.25 The Lactococcin G (Lactococcin G) Family

TABLE 1 (continued)

1.C.26 The Lactacin X (Lactacin X) Family
1.C.27 The Divergicin A (Divergicin A) Family
1.C.28 The Bacteriocin AS-48 Cyclic Polypeptide (Bacteriocin AS-48) Family
1.C.29 The Plantaricin EF (Plantaricin EF) Family
1.C.30 The Plantaricin JK (Plantaricin JK) Family
1.C.31 The Channel-forming Colicin V (Colicin V) Family
1.C.32 The Amphipathic Peptide Mastoparan (Mastoparan) Family
1.C.33 The Cathilicidin (Cathilicidin) Family
1.C.34 The Tachyplesin (Tachyplesin) Family
1.C.35 The Amoebapore (Amoebapore) Family
1.C.36 The Bacterial Type III-Target Cell Pore (IIITCP) Family
1.C.37 The Lactococcin 972 (Lactococcin 972) Family
1.C.38 The Pore-forming Equinatoxin (Equinatoxin) Family
1.C.39 The Complement Protein C9 (CPC9) Family
1.C.40 The Bactericidal Permeability increasing Protein (BPIP) Family
1.C.41 The Tripartite Haemolysin BL (HBL) Family
1.C.42 The Channel-forming *Bacillus anthrax* Protective Antigen (BAPA) Family
1.C.43 The Earthworm Lysenin Toxin (Lysenin) Family
1.C.44 The Plant Thionine (PT) Family
1.C.45 The Plant Defensin (PD) Family
1.C.46 The C-type Natriuretic Peptide (CNP) Family
1.C.47 The Insect Defensin (Insect Defensin) Family
1.C.48 The Prion Peptide Fragment (PPF) Family
1.C.49 The Cytotoxic Amylin (Amylin) Family
1.C.50 The Amyloid β-Protein Peptide (AβPP) Family
1.C.51 The Pilosulin (Pilosulin) Family
1.C.52 The Dermaseptin (Dermaseptin) Family
1.C.54 The Shiga Toxin B-Chain (ST-B) Family
1.C.55 The Agrobacterial VirE2 Target Host Cell Membrane Anion Channel (VirE2) Family
1.C.56 The *Pseudomanas syringae* HrpZ Target Host Cell Membrane Cation Channel (HrpZ) Family
1.C.57 The Clostridial Cytotoxin (CCT) Family
1.C.58 The Microcin E492/C24 (Microcin E492) Family

1.D. Non-ribosomally synthesized channels

1.D.1 The Gramicidin A (Gramicidin A) Channel Family
1.D.2 The Syringomycin Channel-forming (Syringomycin) Family
1.D.3 The Syringopeptin Channel-Forming (Syringopeptin) Family
1.D.4 The Tolaasin Channel-forming (Tolaasin) Family
1.D.5 The Alamethicin Channel-forming (Alamethicin) Family
1.D.6 The Complexed Poly 3-Hydroxybutyrate Ca^{2+} Channel (cPHB-CC) Family
1.D.7 The Beticolin (Beticolin) Family
1.D.8 The Saponin (Saponin) Family
1.D.9 The Polyglutamine Ion Channel (PG-IC) Family
1.D.10 The Ceramide-forming Channel (Ceramide) Family

1.E. Holins

1.E.1 The P21 Holin S (P21 Holin) Family
1.E.2 The λ Holin S (λ Holin) Family
1.E.3 The P2 Holin TM (P2 Holin) Family
1.E.4 The LydA Holin (LydA Holin) Family
1.E.5 The PRD1 Holin M (PRD1 Holin) Family
1.E.6 The T7 Holin (T7 Holin) Family

TABLE 1 (continued)

1.E.7 The HP1 Holin (HP1 Holin) Family
1.E.8 The T4 Holin (T4 Holin) Family
1.E.9 The T4 Immunity Holin (T4 Immunity Holin) Family
1.E.10 The *Bacillus subtilis* ϕ29 Holin (ϕ29 Holin) Family
1.E.11 The ϕ11 Holin (ϕ11 Holin) Family
1.E.12 The ϕAdh Holin (ϕAdh Holin) Family
1.E.13 The ϕU53 Holin (ϕU53 Holin) Family
1.E.14 The LrgA Holin (LrgA Holin) Family
1.E.15 The ArpQ Holin (ArpQ Holin) Family
1.E.16 The Cph1 Holin (Cph1 Holin) Family
1.E.17 The BlyA Holin (BlyA Holin) Family
1.E.18 The *Lactococcus lactis* Phage r1t Holin (r1t Holin) Family
1.E.19 The *Clostridium difficile* TcdE Holin (TcdE Holin) Family

2.A. Porters: uniporters, symporters and antiporters

2.A.1 The Major Facilitator Superfamily (MFS)
2.A.2 The Glycoside-Pentoside-Hexuronide (GPH):Cation Symporter Family
2.A.3 The Amino Acid-Polyamine-Organocation (APC) Family
2.A.4 The Cation Diffusion Facilitator (CDF) Family
2.A.5 The Zinc (Zn^{2+})-Iron (Fe^{2+}) Permease (ZIP) Family
2.A.6 The Resistance-Nodulation-Cell Division (RND) Superfamily
2.A.7 The Drug/Metabolite Transporter (DMT) Superfamily
2.A.8 The Gluconate:H^+ Symporter (GntP) Family
2.A.9 The Cytochrome Oxidase Biogenesis (Oxa1) Family
2.A.10 The 2-Keto-3-Deoxygluconate Transporter (KDGT) Family
2.A.11 The Citrate-Mg^{2+}:H^+ (CitM) Citrate-Ca^{2+}:H^+ (CitH) Symporter (CitMHS) Family
2.A.12 The ATP:ADP Antiporter (AAA) Family
2.A.13 The C4-Dicarboxylate Uptake (Dcu) Family
2.A.14 The Lactate Permease (LctP) Family
2.A.15 The Betaine/Carnitine/Choline Transporter (BCCT) Family
2.A.16 The Telurite-resistance/Dicarboxylate Transporter (TDT) Family
2.A.17 The Proton-dependent Oligopeptide Transporter (POT) Family
2.A.18 The Amino Acid/Auxin Permease (AAAP) Family
2.A.19 The Ca^{2+}:Cation Antiporter (CaCA) Family
2.A.20 The Inorganic Phosphate Transporter (PiT) Family
2.A.21 The Solute:Sodium Symporter (SSS) Family
2.A.22 The Neurotransmitter:Sodium Symporter (NSS) Family
2.A.23 The Dicarboxylate/Amino Acid:Cation (Na^+ or H^+) Symporter (DAACS) Family
2.A.24 The Citrate:Cation Symporter (CCS) Family
2.A.25 The Alanine or Glycine:Cation Symporter (AGCS) Family
2.A.26 The Branched Chain Amino Acid:Cation Symporter (LIVCS) Family
2.A.27 The Glutamate:Na^+ Symporter (ESS) Family
2.A.28 The Bile Acid:Na^+ Symporter (BASS) Family
2.A.29 The Mitochondrial Carrier (MC) Family
2.A.30 The Cation-Chloride Cotransporter (CCC) Family
2.A.31 The Anion Exchanger (AE) Family
2.A.32 The Silicon Transporter (Sit) Family
2.A.33 The NhaA Na^+:H^+ Antiporter (NhaA) Family
2.A.34 The NhaB Na^+:H^+ Antiporter (NhaB) Family
2.A.35 The NhaC Na^+:H^+ Antiporter (NhaC) Family
2.A.36 The Monovalent Cation:Proton Antiporter-1 (CPA1) Family

TABLE 1 (continued)

2.A.37 The Monovalent Cation:Proton Antiporter-2 (CPA2) Family
2.A.38 The K^+ Transporter (Trk) Family
2.A.39 The Nucleobase:Cation Symporter-1 (NCS1) Family
2.A.40 The Nucleobase:Cation Symporter-2 (NCS2) Family
2.A.41 The Concentrative Nucleoside Transporter (CNT) Family
2.A.42 The Hydroxy/Aromatic Amino Acid Permease (HAAAP) Family
2.A.43 The Lysosomal Cystine Transporter (LCT) Family
2.A.44 The Formate-Nitrite Transporter (FNT) Family
2.A.45 The Arsenite-Antimonite (ArsB) Efflux Family
2.A.46 The Benzoate:H^+ Symporter (BenE) Family
2.A.47 The Divalent Anion:Na^+ Symporter (DASS) Family
2.A.48 The Reduced Folate Carrier (RFC) Family
2.A.49 The Ammonium Transporter (Amt) Family
2.A.50 The Glycerol Uptake (GUP) Family
2.A.51 The Chromate Ion Transporter (CHR) Family
2.A.52 The Ni^{2+}-Co^{2+} Transporter (NiCoT) Family
2.A.53 The Sulfate Permease (SulP) Family
2.A.54 The Mitochondrial Tricarboxylate Carrier (MTC) Family
2.A.55 The Metal Ion (Mn^{2+}-iron) Transporter (Nramp) Family
2.A.56 The Tripartite ATP-independent Periplasmic Transporter (TRAP-T) Family
2.A.57 The Equilibrative Nucleoside Transporter (ENT) Family
2.A.58 The Phosphate:Na^+ Symporter (PNaS) Family
2.A.59 The Arsenical Resistance-3 (ACR3) Family
2.A.60 The Organo Anion Transporter (OAT) Family
2.A.61 The C4-dicarboxylate Uptake C (DcuC) Family
2.A.62 The NhaD Na^+:H^+ Antiporter (NhaD) Family
2.A.63 The Monovalent Cation (K^+ or Na^+):Proton Antiporter-3 (CPA3) Family
2.A.64 The Twin Arginine Targeting (Tat) Family
2.A.65 The Bilirubin Transporter (BRT) Family
2.A.66 The Multi Antimicrobial Extrusion (MATE) Family
2.A.67 The Oligopeptide Transporter (OPT) Family
2.A.68 The p-Aminobenzoyl-glutamate Transporter (AbgT) Family
2.A.69 The Auxin Efflux Carrier (AEC) Family
2.A.70 The Malonate:Na^+ Symporter (MSS) Family
2.A.71 The Folate-Biopterin Transporter (FBT) Family
2.A.72 The K^+ Uptake Permease (KUP) Family
2.A.73 The Inorganic Carbon (HCO3-) Transporter (ICT) Family
2.A.74 The 4 TMS Multidrug Endosomal Transporter (MET) Family
2.A.75 The L-Lysine Exporter (LysE) Family
2.A.76 The Resistance to Homoserine/Threonine (RhtB) Family
2.A.77 The Cadmium Resistance (CadD) Family
2.A.78 The Branched Chain Amino Acid Exporter (LIV-E) Family
2.A.79 The Threonine/Serine Exporter (ThrE) Family
2.A.80 The Tricarboxylate Transporter (Tct) Family

2.B. Non ribosomally synthesized porters

2.B.1 The Valinomycin Carrier (Valinomycin) Family
2.B.2 The Monensin (Monensin) Family
2.B.3 The Nigericin (Nigericin) Family
2.B.4 The Macrotetrolide Antibiotic (MA) Family
2.B.5 The Macrocyclic Polyether (MP) Family
2.B.6 The Ionomycin (Ionomycin) Family

TABLE 1 (continued)

2.C. Ion gradient-driven energizers

2.C.1 The TonB-ExbB-ExbD/TolA-TolQ-TolR (TonB) Family of Auxiliary Proteins for Energization of Outer Membrane Receptor (OMR)-mediated Active Transport

3.A. Diphosphate bond hydrolysis-driven transporters

3.A.1 The ATP-binding Cassette (ABC) Superfamily
3.A.2 The H^+- or Na^+-translocating F-type, V-type and A-type ATPase (F-ATPase) Superfamily
3.A.3 The P-type ATPase (P-ATPase) Superfamily
3.A.4 The Arsenite-Antimonite (ArsAB) Efflux Family
3.A.5 The Type II (General) Secretory Pathway (IISP) Family
3.A.6 The Type III (Virulence-related) Secretory Pathway (IIISP) Family
3.A.7 The Type IV (Conjugal DNA-Protein Transfer or VirB) Secretory Pathway (IVSP) Family
3.A.8 The Mitochondrial Protein Translocase (MPT) Family
3.A.9 The Chloroplast Envelope Protein Translocase (CEPT or Tic-Toc) Family
3.A.10 The H^+-translocating Pyrophosphatase (H^+-PPase) Family
3.A.11 The Bacterial Competence-related DNA Transformation Transporter (DNA-T) Family
3.A.12 The Septal DNA Translocator (S-DNA-T) Family
3.A.13 The Filamentous Phage Exporter (FPhE) Family
3.A.14 The Fimbrilin/Protein Exporter (FPE) Family

3.B. Decarboxylation-driven active transporters

3.B.1 The Na^+-transporting Carboxylic Acid Decarboxylase (NaT-DC) Family

3.C. Methyl transfer-driven transporters

3.C.1 The Na^+ Transporting Methyltetrahydromethanopterin:Coenzyme M Methyltransferase (NaT-MMM) Family

3.D. Oxidoreduction-driven active transporters

3.D.1 The Proton-translocating NADH Dehydrogenase (NDH) Family
3.D.2 The Proton-translocating Transhydrogenase (PTH) Family
3.D.3 The Proton-translocating Quinol:Cytochrome c Reductase (QCR) Superfamily
3.D.4 The Proton-translocating Cytochrome Oxidase (COX) Superfamily
3.D.5 The Na^+-translocating NADH:Quinone Dehydrogenase (Na-NDH) Family
3.D.6 The Putative Ion (H^+ or Na^+)-translocating NADH:Ferredoxin Oxidoreductase (NFO) Family
3.D.7 The H_2:Heterodisulfide Oxidoreductase (HHO) Family
3.D.8 The Na^+- or H^+-Pumping Formyl Methanofuran Dehydrogenase (FMF-DH) Family
3.D.9 The H^+-translocating F420H2 Dehydrogenase (F420H2DH) Family

3.E. Light absorption-driven active transporters

3.E.1 The Ion-translocating Microbial Rhodopsin (MR) Family
3.E.2 The Photosynthetic Reaction Center (PRC) Family

4.A. Phosphotransfer-driven group translocators

4.A.1 The PTS Glucose-Glucoside (Glc) Family
4.A.2 The PTS Fructose-Mannitol (Fru) Family
4.A.3 The PTS Lactose-N,N'-Diacetylchitobiose-β--glucoside (Lac) Family
4.A.4 The PTS Glucitol (Gut) Family
4.A.5 The PTS Galactitol (Gat) Family
4.A.6 The PTS Mannose-Fructose-Sorbose (Man) Family

5.A. Transmembrane 2-electron transfer carrier

5.A.1 The Disulfide Bond Oxidoreductase D (DsbD) Family
5.A.2 The Disulfide Bond Oxidoreductase B (DsbB) Family

TABLE 1 (continued)

5.B. Transmembrane 1-electron transfer carrier

5.B.1 The Phagocyte (gp91phox) NADPH Oxidase Family

8.A. Auxiliary transport proteins

8.A.1 The Membrane Fusion Protein (MFP) Family
8.A.2 The Secretin Auxiliary Lipoprotein (SAL) Family
8.A.3 The Cytoplasmic Membrane-Periplasmic Auxiliary-1 (MPA1) Protein with Cytoplasmic (C) Domain (MPA1-C or MPA1+C) Family
8.A.4 The Cytoplasmic Membrane-Periplasmic Auxiliary-2 (MPA2) Family
8.A.5 The Voltage-gated K^+ Channel β-subunit (VICβ) Family
8.A.6 The Auxiliary Nutrient Transporter (ANT) Family
8.A.7 The Phosphotransferase System Enzyme I (EI) Family
8.A.8 The Phosphotransferase System HPr (HPr) Family
8.A.9 The rBAT Transport Accessory Protein (rBAT) Family
8.A.10 The Slow Voltage-gated K^+ Channel Accessory Protein (MinK) Family
8.A.11 The Phospholamban (Ca^{2+}-ATPase Regulator) (PLB) Family
8.A.12 ABC Bacteriocin Exporter Accessory Protein (BEA) Family
8.A.13 The Tetratricopeptide Repeat (Tpr1) Family

9.A. Transporters of unknown classification

9.A.1 The Polysaccharide Transport (PST) Family
9.A.2 The MerTP Mercuric Ion (Hg^{2+}) Permease (MerTP) Family
9.A.3 The MerC Mercuric Ion (Hg^{2+}) Uptake (MerC) Family
9.A.4 The Nicotinamide Mononucleotide (NMN) Uptake Permease (PnuC) Family
9.A.5 The Peroxisomal Protein Importer (PPI) Family
9.A.6 The Intracellular Nucleoside Transporter (INT) Family
9.A.7 The MerF Mercuric Ion (Hg^{2+}) Uptake (MerF) Family
9.A.8 The Ferrous Iron Uptake (FeoB) Family
9.A.9 The Low Affinity Fe^{2+} Transporter (FeT) Family
9.A.10 The Oxidase-dependent Fe^{2+} Transporter (OFeT) Family
9.A.11 The Copper Transporter-1 (Ctr1) Family
9.A.12 The Copper Transporter-2 (Ctr2) Family
9.A.13 The Colicin J Lysis (Cjl) Family
9.A.14 The Nuclear Pore Complex (NPC) Family
9.A.15 The YhaG Putative Tryptophan Uptake Permease (YhaG) family
9.A.16 The Lysosomal Protein Import (LPI) Family
9.A.17 The Lead (Pb^{2+}) Uptake Porter (PbrT) Family
9.A.18 The Peptide Uptake Permease (PUP) Family
9.A.19 The Mg^{2+} Transporter-E (MgtE) Family
9.A.20 The Low Affinity Cation Transporter (LCT) Family
9.A.21 The ComC DNA Uptake Competence (ComC) Family
9.A.22 The NhaE $Na^+(K^+)$:H^+ Antiporter (NhaE) Family
9.A.23 The Ferroportin (FP) Family

9.B. Putative uncharacterized transporters

9.B.1 The Metal Homeostasis Protein (MHP) Family
9.B.2 The Ca^{2+} Homeostasis Protein (CHP) Family
9.B.3 The Putative Bacterial Murein Precursor Exporter (MPE) Family
9.B.4 The Putative Efflux Transporter (PET) Family
9.B.5 The KX Blood-group Antigen (KXA) Family
9.B.6 The Toxic Hok/Gef Protein (Hok/Gef) Family
9.B.7 The Putative Bacteriochlorophyll Delivery (BCD) Family

TABLE 1 (continued)

9.B.8 The Canalicular Bile Acid Transporter (C-BAT) Family
9.B.9 The Urate Transporter (UAT) Family
9.B.10 The 6TMS Putative MarC Transporter (MarC) Family
9.B.11 The Mitochondrial mRNA Splicing-2 Protein (MRS2) Family
9.B.12 The (Salt or Low Temperature) Stress-induced Hydrophobic Peptide (SHP) Family
9.B.13 The Putative Pore-forming Entericidin (ECN) Family
9.B.14 The Putative Heme Exporter Protein (HEP) Family
9.B.16 The Putative Ductin Channel (Ductin) Family
9.B.17 The Putative Fatty Acid Transporter (FAT) Family
9.B.18 The SecDF-associated Single Transmembrane Protein (SSTP) Family
9.B.19 The Mn^{2+} Homeostasis Protein (MnHP) Family
9.B.20 The Putative Mg^{2+} Transporter-C (MgtC) Family
9.B.21 The Frataxin (Frataxin) Family
9.B.22 The Putative Permease (PerM) Family
9.B.23 The Digestive Vacuole Transporter (DVT) Family
9.B.24 The Testis-Enhanced Gene Transfer (TEGT) Family
9.B.25 The YbbM (YbbM) Family
9.B.26 The PF27 (PF27) Family
9.B.27 The YdjX-Z (YdjX-Z) Family
9.B.28 The YqaE (YqaE) Family
9.B.29 The YebN (YebN) Family
9.B.30 The Hly III (Hly III) Family
9.B.31 The YqiH (YqiH) Family
9.B.32 The Putative Vectorial Glycosyl Polymerization (VGP) Family
9.B.33 The YaaH (YaaH) Family
9.B.34 The Putative Membrane Peptide Cation Channel (PMP3) Family
9.B.35 The Putative Thyronine-Transporting Transthyretin (Transthyretin) Family
9.B.36 The Putative SgaT Transporter (SgaT) Family
9.B.37 The HlyC/CorC (HCC) Family
9.B.38 The Stationary-phase Anti-death (SAD) Family
9.B.39 The Long Chain Fatty Acid Translocase (lcFAT) Family

9.C. Functionally characterized transporters with unidentified sequences

9.C.1 The Endosomal Oligosaccharide Transporter (EOT)
9.C.2 Volume-sensitive Anion Channels (VAC)
9.C.3 The *Rhodococcus erythropolis* Porin (REP) Family
9.C.4 Nucleotide Sulfate (PAPS) Transporters (PAPS-T)
9.C.5 The Endoplasmic Reticulum/Golgi ATP/ADP or AMP Antiport Transporters (ATP-T)
9.C.6 The T7 Phage DNA Uptake Translocator (T7-T)

TABLE 2
Properties of Families of Transport Systems Included Within the TC System

TC #[a]	Family	Substrates[b]	Size range[c]	# TMSs[d]	Organisms[e]	#[f]	Examples
1.A. α-Type Channel-forming Proteins and Peptides							
1.A.1	VIC	Na^+; K^+; Ca^{2+}; multiple cations	Widely varied	$(2)_4$; $(4)_2$; $(6)_4$; $(8)_2$; $(12)_2$; $(24)_1$; often hetero-oligomeric	A, B, E	3	Voltage-gated Na^+ channels; voltage-gated Ca^{2+} channels; K^+ channels sensitive to voltage, Ca^{2+} or cyclic nucleotides of *Homo sapiens*
1.A.2	IRK-C	K^+	350-500	$(2)_4$	E (An)	2	Inward rectifier K^+ channels (ATP-activated or G-protein regulated) of *Homo sapiens*
1.A.3	RIR-CaC	Ca^{2+}	5000 or 2500	$(6)_4$	E (An)	2	Ryanodine receptor Ca^{2+} channels; inositol 1,4,5 triphosphate receptor Ca^{2+} channels of *Homo sapiens*
1.A.4	TRP-CC	Ca^{2+}, other cations	800-1500	$(6)_4$	E (An)	3	Transient receptor potential Ca^{2+} channel, TRP of *Drosophila melanogaster*
1.A.5	PCC	Na^+, K^+, Ca^{2+}	4000	$(7\text{-}11)_n$ $(6)_m$	E (An)	1	Polycystins 1 and 2 of *Homo sapiens*
1.A.6	ENaC	Na^+; cations	600-700	$(2)_4$ (e.g., $\alpha_2\beta\gamma$) (homo- or heterooligomeric	E (An)	2	Epithelial Na^+ channels; degenerins; peptide-gated ionotropic receptors of animals
1.A.7	ACC	Cations (monovalent cations, Ca^{2+})	350-600	$(2)_n$	E (An)	2	ATP-gated cation channel, $P2X_1$ of *Homo sapiens*
1.A.8	MIP	H_2O; H_2O, urea; glycerol, polyols; cations; anions	80-700	$(6)_4$	A, B, E	3	Aquaporins; Aqp1 of *Homo sapiens*; glycerol facilitators; GlpF, of *E. coli*
1.A.9	LIC	Cations or anions	400-700	$(3\text{-}5)_5$; often heterooligomeric	E (An)	3	Acetyl choline or serotonin-activated cation channels; glycine, glutamate or GABA-regulated Cl^- channels of *Homo sapiens*
1.A.10	GIC	Monovalent cations and Ca^{2+}	250-1500	$(3 \text{ or } 5)_5$	B, E (An)	2	Glutamate-regulated ionotropic channels of *Rattus norvegicus*
1.A.11	ClC	Cl^-, anions	400-1000	12	A, B, E	2	Voltage-gated Cl^- channel, ClC1 of *Homo sapiens*
1.A.12	O-ClC	Cl^-, anions	250-450	$(2)_n$	E (An)	2	Organellar voltage-sensitive Cl^- channels of *Bos taurus*

1.A.13	E-ClC	Cl^-, anions	900	$(4)_n$	B, E (An)	1	Ca^{2+}-activated Cl^- channel-2 of *Homo sapiens*
1.A.14	NSCC1	Monovalent cations: Na^+, Li^+, K^+	~450	$(4)_n$	E (An)	0	Non-selective cation channel, NSC1 of *Mus musculus*
1.A.15	NSCC2	Monovalent cations: Na^+, K^+, Cs as well as Ca^{2+} (slow)	250-400	$(2)_n$	E (An, F)	1	Non-specific channel translocation protein-1, NS1, of *Homo sapiens*; Sec62 of *Saccharomyces cerevisiae*
1.A.16	Mid1	Ca^{2+}	450-550	1 or 2	E (Y)	1	Mid1 of *Saccharomyces cerevisiae*
1.A.17	CSC	Ions, solutes	150-200	β-structure?	E (Pl)	1	Chloroplast outer envelope solute channel, CSC of *Pisum sativum*
1.A.18	Tic110	Anions, proteins	1000	2	E (Pl)	1	Protein import-related anion-selective channel, Tic110
1.A.19	M2-C	H^+	~100	$(1)_4$	V	0	Matrix protein, M2 of influenza virus
1.A.20	CytB	H^+	450-750	6 (heterooligo-meric)	E (An, Pl)	2	$gp91^{phox}$ phagocyte NADPH oxidase-associated cytochrome b558 H^+ channel of *Homo sapiens*
1.A.21	Bcl-2	Protein (cytochrome c)	100-350	$(1\text{-}5)_n$ (N=2?)	E (An), V	2	Apoptosis regulator, Bcl-X(L) of *Homo sapiens*
1.A.22	MscL	Proteins, ions (slightly cation selective)	100-200	$(2)_5$	A, B, E	1	Large mechanosensitive ion channels; MscL of *E. coli*
1.A.23	MscS	Ions (slightly anion selective)	200-1150	3-14	A, B, E	2	Small conductance mechanosensitive ion channel, KefA of *E. coli*
1.A.24	Connexin	Small molecules (no discrimination)	200-600	$(4)_n$	E (An)	2	Vertebrate connexin 43 (gap junction α-1 protein), CX43 of *Rattus norvegicus*
1.A.25	Innexin	Small molecules (no discrimination)	300-600	$(4)_n$	E (An)	2	Invertebrate innexin UNC-7 of *Caenorhabditis elegans*
1.A.26	PPD	Small molecules	~300	1	E (Pl)	1	Gap junction protein CX32 of *Arabidopsis thaliana*
1.A.27	PLM	Cl^- (anion-selective), taurine, lactate, glutamate, isethionate, gluconate	80-100	$(1)_n$	E (An)	1	Phospholemman; Cl^- conductance inducer protein, Mat-8 of *Mus musculus*
1.A.28	UT	Urea, water	350-400	10	E (An), B	1	Kidney vasopressin-regulated urea transporter, UT2 of *Rattus norvegicus*
1.A.29	UAC	Urea, amides	150-250	6	B	1	UreI protein of *Helicobacter pylori*

TABLE 2 (continued)

1.A.30	Mot/Exb						
1.A.30.1	Mot	H^+; Na^+	200-350 (MotA)	4	B	2	MotA and MotB of *E. coli*
			200-500(MotB)	1			
1.A.30.2	Exb	H^+ (energy-transducing system)	150-400+150-350+100-200 (TonB ExbBD)	1+3+1	B (G-)	2	TonB/ExbB/ExbD of *E. coli*
			350-450+200-300+100-200 (TolAQR)	1+3+1			
1.A.31	Annexin	Ions	250-700	4, 8	E	2	Hydra annexin XII
1.A.32	NB-C	Ions	~100	1	V	0	NB of influenza B virus
1.A.33	HSP70	Ions, polypeptides	500-750	0-2	A, B, E	3	Hsc70 protein of *Arabidopsis thaliana*
1.A.34	EVE1-C	RNA	1200-1300	5	V	1	HSFV structural polyprotein
1.A.35	MIT	Heavy metal ions	300-400	2-3	A, B, E	2	CorA of *E. coli*
1.A.36	ICC	Anions	500-600	4	E	0	MCLC of *Homo sapiens*
1.B. Outer Membrane Porins (β-structure)							
1.B.1	GBP	Ions, small molecules	250-450	16 stranded anti-parallel β-barrels	B (G-), V	2	OmpF of *E. coli*
1.B.2	CP	Ions, small molecules	300-400		B	1	Omp1 of *Chlamydia psittaci*
1.B.3	SP	Sugars, oligosaccharides	250-550	18 stranded anti-parallel β-barrels	B	1	LamB of *E. coli*
1.B.4	BRP	Ions, small molecules	300-400		B	0	Omp2 of *Brucella abortus*
1.B.5	POP	Ions, small molecules	400-450		B	1	OprP of *Pseudomonas aeruginosa*
1.B.6	OOP	Ions, small molecules	350-450	8 β-strands	B	2	OmpA of *E. coli*
1.B.7	RPP	Ions, small molecules	250-350	16-stranded β-barrels	B	0	PorCa porin of *Rhodobacter capsulatus*
1.B.8	MPP	Anions, small proteins	250-350	1 α-helix and 12 or 13 β-strands	E	2	Mitochondrial outer membrane VDAC of *Saccharomyces cerevisiae*
1.B.9	FadL	Fatty acids	400-500		B	1	FadL of *E. coli*
1.B.10	Tsx	Nucleosides	250-300	14 stranded β-barrels	B	1	Tsx of *E. coli*

1.B.11	FUP	Fimbrial protein subunits	750-950	24 β-strands	B	2	FacD of *E. coli*
1.B.12	AT	N-terminal protein domains	250-300	14 β-strands	B (G-)	2	AidA of *E. coli*
1.B.13	AEP	Alginate	~500	18 β-strands	B (G-)	0	AlgE of *Pseudomonas aeruginosa*
1.B.14	OMR	Iron-chelate complexes, colicins, vitamin B_{12}, etc.	350-1100	22 antiparallel β-strands	B (G-)	2	FepA of *E. coli*
1.B.15	RafY	Small molecules, oligo-saccharides	450-500		B (G-)	1	RafY of *E. coli*
1.B.16	SAP	Short chain amides, small molecules	~400		B (G-)	0	FmdC of *Methylophilus methylotrophus*
1.B.17	OMF	Proteins; lipooligosac-charides; drugs, dyes, signaling molecules; heavy metal ions, etc. (some OMFs can accommodate multiple substrate types)	400-550	$(4)_3$ β-strands	B (G-)	2	TolC of *E. coli*
1.B.18	OMA	Complex carbohydrates	350-600		B (G-)	2	ExoF of *Rhizobium meliloti*
1.B.19	OprB	Ions; small molecules	400-500		B (G-)	1	OprB of *Pseudomonas aeruginosa*
1.B.20	TPS	Proteins	550-600		B (G-)	2	ShlB of *Serratia marcescens*
1.B.21	OmpG	Ions, small molecules	~300	16	B (G-)	0	OmpG of *E. coli*
1.B.22	Secretin	Proteins	400-800	$(x)_{12}$	B, V	2	PulD of *Klebsiella oxytoca*
1.B.23	CBP	Ions, small molecules	400-950	14-16	B (G-)	1	SomA of *Synechococcus sp.*
1.B.24	MBP	Ions, small molecules	200-250		B	1	MspA of *Mycobacterium smegmatis*
1.B.25	Opr	Ions, small molecules	~450		B (G-)	0	OprD2 of *Pseudomonas aeruginosa*
1.B.26	CDP	Cyclodextrins	~350		B (G-)	0	CymA of *Klebsiella oxytoca*
1.B.27	HOP	Ions, small molecules	200-600	18	B (G-)	1	HopE of *Helicobacter pylori*
1.B.28	OEP24	Ions, small molecules	~200	7	E (P)	1	OEP24 of *Pisum sativum*
1.B.29	OEP21	Organic anions	~200		E (P)	1	OEP21 of *Pisum sativum*
1.B.30	OEP16	Organic cations	~150	$(2\beta, 1\alpha)_4$	E (P)	1	OEP16 of *Pisum sativum*
1.B.31	MomP	Ions, small molecules	~400		B (G-)	1	MomP of *Campylobacter jejuni*
1.B.32	FomP	Ions, small molecules	~400	$(16)_3$	B (G-)	0	FomA of *Fusobacterium nucleatum*

TABLE 2 (continued)

1.B.33	VC/NP	Acetylated chitooligomers; ions, small molecules	300-400		B (G-)	1	ChiP of *Vibrio furnissii*
1.B.34	PorA	Ions, small molecules	~50		B	0	PorA of *Corynebacterium glutamicum*
I.C. Toxins							
1.C.1	Colicin	Ions, small molecules	400-700 (150-180 for the channel domain)	2	B	2	Colicin Ia of *E. coli*
1.C.2.	ICP	Ions, small molecules	600-1400	6	B	2	CryIAa of *Bacillus thuringiensis*
1.C.3.	α-HL	Ions, small molecules	300-350	$(2)_7$ β-strands	B	1	α-hemolysin of *Staphylococcus aureus*
1.C.4	Aerolysin	Ions, small molecules	450-500	$(2)_7$ β-strands	B, E (Pl)	1	Aerolysin of *Aeromonas hydrophila*
1.C.5	ε-toxin	K^+; ions, small molecules	~350	1	B	1	ε-toxin of *Clostridium perfringens*
1.C.6	YKT-K1	Cations, ATP, small molecules	~300	$[2(\alpha\text{-subunit}) + 1(\beta\text{-subunit})]_n$	E	0	Yeast killer toxin of *Saccharomyces cerevisiae*
1.C.7	DT	DT, A-chain (protein)	550-600	$(2)_n$ (n=variable)	Bp	0	Diphtheria toxin (DT) of corynebacteriophage
1.C.8	BTT	BTT, L-chains	1150-1350	$(2)_n$	B	1	Botulinum and tetanus toxin channels of *Clostridium* species
1.C.9	VacA	Ions, small molecules	1250-1350	$(3)_n$ (n=6 or 12)	B	0	VacA of *Helicobacter pylori*
1.C.10	HlyE	Ions (moderately cation-selective)	~300	$(2)_n$	B	0	HlyE of *E. coli*
1.C.11	RTX-toxin	Ions, small molecules	250-1850	$(3)_n$	B	2	HlyA of *E. coli*
1.C.12	TAC	Ions, metabolites, proteins	450-600	$(2\ \beta\text{-hairpins})_n$ (n=30-60)	B	2	Perfringolysin O of *Clostridium perfringens*
1.C.13	Ctx	Ions	~300	$(?)_5$	Bp	0	Leucocidin cytotoxin, Ctx of *Pseudomonas aeruginosa* phage phiCTX
1.C.14	CHL	Ions and other solutes	450-750	$(0\text{-}1)_{5?}$	B	1	HlyA of *Vibrio cholera*
1.C.15	WSP	Small molecules	~400	$(0)_n$	E (An)	0	Whipworm stichosome porin of *Trichuris trichiura*
1.C.16	Magainin	Small solutes, electrolytes, water	80-300	$(2)_n$	E (An)	1	Magainin precursor of *Xenopus laevis*

1.C.17	Cecropin	Small solutes, electrolytes, water	30-65	$(0\text{-}1)_n$	E (An)	2	Cecropin A, B and C precursors of *Hyalophora cecropia*
1.C.18	Melittin	Small solutes, electrolytes, water	25-70	$(0\text{-}2)_n$	E (An)	0	Melittin major precursor of *Apis mellifera*
1.C.19	Defensin	Small solutes, electrolytes, water	30-100	$(0)_n$	E (A)	2	Neutrophil defensin GP-CS1 of *Cavia porcellus*
1.C.20	Nisin	Small solutes, electrolytes, water	55-60	$(0)_n$	B (G+)	1	Nisin precursor of *Lactococcus lactis*
1.C.21	Lacticin 481	Small solutes, electrolytes, water	~50	$(0)_n$	B (G+)	1	Lacticin 481 of *Lactococcus lactis*
1.C.22	Lactococcin A	Small solutes, electrolytes, water	65-75	$(0\text{-}1)_n$	B (G+)	1	Lactococcin A precursor of *Lactococcus lactis*
1.C.23	Lactocin S	Small solutes, electrolytes, water	25	$(1)_n$	B (G+)	0	Lactocin S of *Lactobacillus sake* LA5
1.C.24	Pediocin	Small solutes, electrolytes, water	40-70	$(0)_n$	B (G+)	1	Pediocin PA-1 precursor of *Pediococcus acidilactic*
1.C.25	Lactococcin G	Small solutes, electrolytes, water	~ 40+35	$(0)_n$	B (G+)	0	Lactococcin G of *Lactococcus lactis*
1.C.26	Lactacin X	Small solutes, electrolytes, water	~75+65	$(2)_n$	B (G+)	0	LafA and LafX of *Lactobacillus johnsonii*
1.C.27	Divergicin A	Small solutes, electrolytes, water	~75	$(2)_n$	B (G+)	0	DvnA of *Carnobacterium divergens*
1.C.28	Bacteriocin AS-48	Small solutes, electrolytes, water	70 (cyclic); (precursor: 105)	$(1)_n$	B (G+)	0	Bacteriocin AS-48 of *Enterococcus faecalis* S-48 plasmid pMB2
1.C.29	Plantaricin EF	Small solutes, electrolytes, water	~55+50	$(0)_n$	B (G+)	0	PlnE, F of *Lactobacillus plantarum*
1.C.30	Plantaricin JK	Small solutes, electrolytes, water	~55+55	$(0)_n$	B (G+)	0	PlnJ, K of *Lactobacillus plantarum*
1.C.31	Colicin V	Ions, small molecules	~100	$(1\text{-}2)_n$	B	0	Colicin V of *E. coli*
1.C.32	Mastoparan	Small molecules	~15	Barrel stove $(1)_n$	E (An)	1	Mastoparan of *Vespa xanthoptera*
1.C.33	Cathilicidin	Small molecules	90-250	$(1)_n$	E (An)	2	Pre-myeloid cathilicidin 1 of *Equus caballus*
1.C.34	Tachyplesin	Small molecules	~80	$(1)_n$	E (An)	1	Tachyplesin I of *Tachyplesus tridentatus*

TABLE 2 (continued)

1.C.35	Amoeba-pore	Small molecules	~100	$(1)_n$	E (Pr)	1	Amoebapore of *Entamoeba histolytica*
1.C.36	IIITCP	Proteins	300-600	$(2)_n$	B	1	Type III-protein secretion target cell pore protein, YopB of *Yersinia pseudotuberculosis*
1.C.37	Lactococcin 972	Small molecules	50-100	$(1)_n$	B	0	Lactococcin 972 of *Lactococcus lactis*
1.C.38	Equina-toxin	Small molecules	150-250	$(1)_{3 \text{ or } 4}$	E (An)	2	Equinatoxin of *Actinia tenebrosa*
1.C.39	CPC9	Ions, small solutes	500-600	$(1)_n$	E (An)	2	C9 of *Equus caballus*
1.C.40	BPIP	Cholesterol, lipopoly-saccharides	250-500	$(1)_n$	E (An)	2	BPIP precursor of *Homo sapiens*
1.C.41	HBL	Ions, small solutes	150-400	$(2)_n$	B	1	Hemolysin YhlA of *Edwardsiella tarda*
1.C.42	BAPA	Protein toxin, small molecules	150-800	$[3 \text{ (beta?)}]_n$	B (G+)	0	Iotatoxin Ib of *Clostridium perfringens*
1.C.43	Lysenin	Various solutes	~300	$(1)_n$	E (An)	0	Lysenin of *Eisenia foetida*
1.C.44	PT	Small molecules	45-47 (precur-sors: 70-140)	Two antiparallel α-helices and two antiparallel β-strands	E (Pl)	2	Viscotoxin B precursor of *Viscum album*
1.C.45	PD	Small molecules	45-54 (precur-sors:80-120)	Triple stranded antiparallel β-sheets and 1 α-helix	E (Pl)	2	γ-thionin of *Nicotiana tabacum*
1.C.46	CNP	Cations	Small peptides (precursors: 80-140)	$(0)_n$	E (An)	2	CNP precursor protein of *Homo sapiens*
1.C.47	Insect Defensin	Ions	Small peptides (precursors: 80-120)	$(0\text{-}2)_n$	E (An)	2	Phormicin precursor of *Protophormia terranovae*
1.C.48	PPF	Ions	200-300	1-3	E (An)	2	Major prion protein precursor Prp of *Ovis aries*
1.C.49	Amylin	Ions	25-150	0-1	E (An)	2	Amylin of *Canis familiaris*
1.C.50	AβPP	Ions	50-900	0-2	E (An)	2	AβPP of *Rattus norvegicus*
1.C.51	Pilosulin	Ions	~100	1	E (An)	1	Philosin I of *Myrmecia pilosula*

1.C.52	Derma-septin	Ions	70-80	1	E (An)	1	Brevinin-2EF of *Rana esculenta*
1.C.54	ST-B	Shiga toxin A	$(89)_5$	1-2	Bp	1	Verotoxin B-chain of *E. coli*
1.C.55	VirE2	Proteins, DNA, anions	500-600	β-structure (β-barrel?)	B	1	VirE2 of *Agrobacterium tumefaciens*
1.C.56	HrpZ	Cations, small molecules	~350	$(2)_n$	B	0	HrpZ cation-selective channel protein of *Pseudomonas syringae*
1.C.57	CCT	Toxin domain, ions, other solutes	2100-3200	2	B	0	Cytotoxin B of *Clostridium difficile*
1.C.58	Microcin E492	Monovalent cations	~100	$(0)_n$	B	0	Microcin C24 of *E. coli*
1.D. Nonribosomally-synthesized Channels							
1.D.1	Gramici-din A	Monovalent cations	15 L- and D-amino acids	0,5	B	0	Gramicidin A of *Bacillus brevis*
1.D.2	Syringo-mycin	Cations	Cyclic lipo-depsipeptide containing non-protein amino acids	1?	B	1	Syringomycin of *Pseudomonas syringae*
1.D.3	Syringo-peptin	Cations	Cyclic lipo-depsipeptide containing non-protein amino acids	1?	B	1	Syringopeptin SP22 of *Pseudomonas syringae*
1.D.4	Tolaasin	Cations	Lipodepsipep-tide (contains D-amino acids, hydroxy acids, and fatty acids)	1?	B	1	Tolaasin of *Pseudomonas tolaasii*
1.D.5	Alamethi-cin	Ions	20-21 amino acids including non-protein amino acids	1?	E (Fu)	1	Longibrachin I of *Trichoderma longibrachiatumn*
1.D.6	cPHB-CC	DNA (uptake)	PHB, Ca^{2+} and polyphosphate	-	B	1	Poly-(R)-3-hydroxybutyrate channel of *Streptomyces lividans*

TABLE 2 (continued)

1.D.7	Beticolin	Ions	Polycyclic		E (Fu)	0	Beticolin 0 of *Cercospora beticula*
1.D.8	Saponin	Various solutes	glycosylated triterpenoids, steroids and alkaloids		E (Pl)	0	Avenacoside A of *Avena sativa*
1.D.9	PG-IC	Ions	Polyglutamine ion channel ~60		E (An)	1	Polyglutamine
1.D.10	Ceramide	Small proteins	Lipids		E (An)	1	C_2-ceramide of *Glycine max*
1.E. Holins							
1.E.1	P21 holin	Endolysin, ions, small metabolites	70-100	2	B, Bp	1	Lysis protein S of *E. coli*
1.E.2	λ holin	Endolysin	100-150	3	B, Bp	1	Lysis protein S of phage λ
1.E.3	P2 holin	Endolysin	90-100	3	Bp	1	Lysis protein TM
1.E.4	LydA holin	Endolysin	~110	2	B, Bp	0	LydA protein of *E. coli*
1.E.5	PRD1 holin	Endolysin	90	1	Bp	0	Protein M of phage PRD1
1.E.6	T7 holin	Endolysin	45-70	1	Bp	1	Gb 17.5 phage T7
1.E.7	HP1 holin	Endolysin	70-90	1	B, Bp	1	Holin of *Haemophilus influenzae* phage HP1
1.E.8	T4 holin	Endolysin	200-250	1	Bp	1	Lysis protein of phage T4
1.E.9	T4 immunity holin	Endolysin	~80	2	Bp	1	Immunity protein of phage T4
1.E.10	ϕ29 holin	Protein	100-150	2	Bp	1	GP14 of Bacillus phage ϕ29
1.E.11	ϕ11 holin	Endolysin	50-200	2	B, Bp	1	Holin of Staphylococcus phage ϕ11
1.E.12	ϕAdh holin	Endolysin	114	1	Bp	0	Holin of *Lactobacillus gasseri* phage ϕAdh
1.E.13	ϕU53 holin	Endolysin	~66	1	Bp	0	Holin of *Lactococcus lactis* phage ϕU53
1.E.14	LrgA holin	Endolysin	100-150	4	B	1	LrgA of *Staphylococcus aureus*

1.E.15	ArpQ holin	Endolysin	~60	2	B	0	ArpQ of *Enterococcus hirae*
1.E.16	Cph1 holin	Endolysin	~135	3	Bp	0	Cph1 holin of *Streptococcus pneumoniae* phage Cp-1
1.E.17	BlyA holin	Endolysin	~70	1	Bp	0	BlyA of cp32 prophage from *Borrelia burgdorferi*
1.E.18	R1t holin	Lysin	75-80	2	Bp	0	Orf49 holin of *L. lactis* phage r1t
1.E.19	TcdE holin	Toxin	~160	3	B	0	TcdE of *Clostridium difficile*
2.A. Carrier-type Facilitators							
2.A.1	MFS	Numerous small molecules (also can serve as receptors)	300-1250	6, 12 or 14	A, B, E	3	Lactose permease, LacY of *E. coli*; drug efflux permease, EmrD of *E. coli*
2.A.2.	GPH	Sugars (glycosides)	250-650	12	A, B, E	2	Melibiose permease, MelB of *E. coli*
2.A.3	APC	Amino acids, polyamines, organocations (also can serve as receptors)	400-1250	10, 12, 14	A, B, E	2	Lysine permease, LysP of *E. coli*
2.A.4	CDF	Cd^{2+}, Co^{2+}, Ni^{2+}	300-750	6	A, B, E	2	Heavy metal uptake and efflux permeases of bacteria, eukaryotic plasma membranes and mitochondria (CzcD of *Ralstonia eutropha*)
2.A.5	ZIP	Zn^{2+}; Fe^{2+}	376	8	E	2	Zinc uptake transporter, Zrt1 of *Saccharomyces cerevisiae*
2.A.6	RND	Heavy metal ions; multiple drugs; oligosaccharides; organic solvents, fatty acids; phospholipids, cholesterol	800-1200	6, 12	A, B, E	3	Drug efflux pump, AcrA of *E. coli*
2.A.7	DMT	Multiple drugs; sugars and derivatives; nucleotides, nucleotide sugars	100-500	$(4)_2$, $(5)_2$, 10	A, B, E	3	Cationic drug efflux pump, Smr of *Staphylococcus aureus*
2.A.8	GntP	Gluconate, idonate	400-500	~12-14	A, B	2	Gluconate permease, GntP of *Bacillus subtilis*
2.A.9	Oxa1	Proteins	350-450	5	B, E	1	Oxalp of *Saccharomyces cerevisiae*

TABLE 2 (continued)

2.A.10	KdgT	2-keto-3-deoxygluconate	300-400	10-12	B	1	2-keto-3-deoxygluconate transporter, KdgT of *Erwinia chrysanthemi*
2.A.11	CitMHS	Citrate·Me^{2+}	400-450	12	B	1	Citrate:Me^{2+}:H^+ symporter, CitM of *Bacillus subtilis*
2.A.12	AAA	ATP, ADP	450-650	12	B, E (Pl)	1	ATP/ADP exchange translocase of *Rickettsia prowazekii*
2.A.13	Dcu	C_4-dicarboxylates	440	10, 12	B (G-)	1	Dicarboxylate uptake porter-A, DcuA of *E. coli*
2.A.14	LctP	Lactate	450-600	12	A, B	1	Lactate permease, LctP of *E. coli*
2.A.15	BCCT	Glycine; betaine; carnitine; choline; multiple organocations	450-700	12	B	2	Carnitine transporter, CaiT of *E. coli*
2.A.16	TDT	Tellurite; dicarboxylates	300-350	10	A, B, E	1	Tellurite uptake permease, TehA of *E. coli*
2.A.17	POT	Peptides; nitrate; amino acids	450-800	12	B, E	2	Dipeptide transporter, DtpT of *Lactococcus lactis*
2.A.18	AAAP	Amino acids and their derivatives	400-750	11	E	2	Amino acid/auxin:H^+ symporter, Aux-1 of *Arabidopsis thaliana*
2.A.19	CaCA	Ca^{2+}	350-400	10 or 11	A, B, E	2	Ca^{2+}:H^+ antiporter, ChaA of *E. coli*
2.A.20	PiT	Inorganic phosphate; sulfate	400-700	10-12	A, B, E	2	Phosphate transporter, PitA of *E. coli*
2.A.21	SSS	Sugars; amino acids; vitamins; nucleosides; inositols; iodide, organic and inorganic anions; urea; organocations (also can serve as receptors)	400-750	12-15	A, B, E	2	Pantothenate:Na^+ symporter, PanF of *E. coli*
2.A.22	NSS	Neurotransmitters (often amino acids); osmolytes; taurine; creatine	600-750	12	A, B, E (An)	3	Serotonin:Na^+ symporter of *Homo sapiens*
2.A.23	DAACS	C_4-dicarboxylates; acidic and neutral amino acids	400-600	8-10	A, B, E	2	Glutamate/aspartate permease, GltP of *E. coli*
2.A.24	CCS	Mono-, di- and tricarboxylates	400-450	12	B	1	Citrate:Na^+ symporter, CitS of *Klebsiella pneumoniae*

2.A.25	AGCS	Alanine, glycine	400-550	8-12	A, B	2	Alanine/glycine transporter, DagA of *Alteromonas haloplanktis*
2.A.26	LIVCS	Branched chain amino acids; Leu, Ile, Val	400-450	12	B	1	Branched chain amino acid transporter, BraB of *Pseudomonas aeruginosa*
2.A.27	ESS	Glutamate	~400	10	B	1	Glutamate:Na^+ symporter, GltS of *E. coli*
2.A.28	BASS	Bile acids	350-500	7	A, B, E (An)	1	Bile acid uptake system of *Rattus norvegicus*
2.A.29	MC	ATP/ADP/AMP; P_i; organic anions; H^+; carnitine/acyl carnitine; basic amino acids; FAD	300-750	6	E (mito)	3	ATP/ADP exchangers of *Homo sapiens* in mitochondria and peroxisomes
2.A.30	CCC	K^+, Na^+, Cl^-; KCl; NaCl	1000-1200	12	A, B, E	2	NaCl/KCl cotransporter of *Rattus norvegicus*
2.A.31	AE	Inorganic anions	900-1250	14	E	2	Anion exchanger, AE1 of *Homo sapiens*
2.A.32	Sit	Silicate	550	12	E	1	Sit1 of *Cylindrotheca fusiformis*
2.A.33	NhaA	Na^+/H^+	350-400	$(12)_2$	B	1	Na^+:H^+ antiporter, NhaA of *E. coli*
2.A.34	NhaB	Na^+/H^+	~520	9	B	1	Na^+:H^+ antiporter, NhaB of *E. coli*
2.A.35	NhaC	Na^+/H^+	~460	12	B	1	Na^+:H^+ antiporter, NhaC of *Bacillus firmus*
2.A.36	CPA1	Na^+/H^+; Na^+ or K^+/H^+	400-900	10-12	A, B, E	2	Na^+:H^+ antiporter, Nhe-1 of *Rattus norvegicus*
2.A.37	CPA2	Na^+/H^+ or K^+/H^+	250-650 + 150-300	10-14	A, B, E	2	K^+ efflux protein-C, KefC of *E. coli*
2.A.38	Trk	K^+	400-600	8	A, B, E	2	K^+ uptake permease, TrkH of *E. coli*
2.A.39	NCS1	Nucleobases; thiamine; nucleosides	400-650	12	A, B, E	2	Cytosine permease, CodB of *E. coli*
2.A.40	NCS2	Nucleobases; urate	400-600	12	A, B, E	2	Uracil permease, UraA of *E. coli*
2.A.41	CNT	Nucleosides	350-700	10; 13	A, B, E	2	Nucleoside:H^+ symporter, NupC of *E. coli*
2.A.42	HAAAP	Hydroxy and aromatic amino acids	400-450	11	B	2	Tyrosine permease, TyrP of *E. coli;* serine permease, SdaC of *E. coli*
2.A.43	LCT	Cystine	200-400	7	E	2	Lysosomal cystine transporter, cystinosin of *Homo sapiens*
2.A.44	FNT	Formate; nitrite	250-650	6 (6-8)	A, B, E	2	Formate efflux permease, FocA of *E. coli*
2.A.45	ArsB	Arsenite, antimonite	400-900	12	A, B, E	2	Arsenical resistance efflux pump of *Staphylococcus aureus*

TABLE 2 (continued)

2.A.46	BenE	Benzoate	~400	12	B	1	Benzoate:H^+ symporter, BenE of *Acinetobacter caleoaceticus*
2.A.47	DASS	Di- and tricarboxylates; phosphate; sulfate	400-950	11-14	A, B, E	2	Dicarboxylate translocator, SodiT1 of *Spinacia oleracea*
2.A.48	RFC	Reduced folate; TPP; thiamin	500-600	12	E (An)	2	Reduced folate carrier, RFC of *Mus musculus*
2.A.49	Amt	Ammonium	350-650	11; 12	A, B, E	2	Ammonium transporter, AmtB of *E. coli*
2.A.50	GUP	Glycerol	450-650	8-10	B, E	1	GUP1 of *Saccharomyces cerevisiae*
2.A.51	CHR	Chromate; sulfate (uptake or efflux)	~400	6; 10	A, B	2	The chromate transporter, ChrA of *Alcaligenes eutrophus*
2.A.52	NiCoT	Ni^{2+}, Co^{2+}; Ni^{2+}	300-400	8	B	2	Ni^{2+} uptake permease, HoxN of *Ralstonia eutropha*
2.A.53	SulP	Sulfate; sulfate, bicarbonate; anions	400-900	10-13	A, B, E	2	Sulfate permease, SulP of *Homo sapiens*
2.A.54	MTC	Di- and tricarboxylates	~290	5-6	E (mito)	1	Mitochondrial tricarboxylate carrier, MTC of *Rattus norvegicus*
2.A.55	Nramp	Divalent metal ions (uptake)	500-600	8-12	A, B, E	2	The divalent metal ion:H^+ symporter, Nramp2 of *Homo sapiens*
2.A.56	TRAP-T	C_4-dicarboxylates; acidic amino acids; sugars (?)	~1000 (three components)	12+4+0	A, B	2	Dicarboxylate transporter, DctPQM of *Rhodobacter capsulatus*
2.A.57	ENT	Nucleosides	~450	10-11	E	2	Equilibrative nucleoside transporter-1, hENT1 of *Homo sapiens*
2.A.58	PNaS	Inorganic phosphate	300-650	8	B, E	2	Renal Na^+-dependent phosphate transporter-2, NPT2 of *Rattus norvegicus*
2.A.59	ACR3	Arsenite	~400	10	A, B, E	1	Arsenical resistance-3 protein, ACR3 of *Saccharomyces cerevisiae*
2.A.60	OAT	Organic anions; prostaglandins; bile acids; bile conjugates; drugs; hormones	600-700	10-12	E (An)	2	Organic anion transporter, OATP1 of *Rattus norvegicus*; prostaglandin transporter, PGT of *Rattus norvegicus*
2.A.61	DcuC	Dicarboxylates	~460	10-12	B	0	C_4-dicarboxylate uptake porter, DcuC of *E. coli*
2.A.62	NhaD	Na^+/H^+	400-450	10-12	A, B	1	Na^+/H^+ antiporter, NhaD of *Vibrio parahaemolyticus*

2.A.63	CPA3	K^+ or Na^+/H^+	>700; possibly multiple components	~17	B	1	K^+:H^+ antiporter, PhaA-G of *Rhizobium meliloti*; Na^+:H^+ antiporter, Nha1 of an alkalophilic *Bacillus* species
2.A.64	Ṭat	Proteins, mostly redox proteins	>600 (2-4 subunits)	9 (6+1+1+1)	A, B, E	2	Twin Arginine targeting and translocation TatABCE system of *E. coli*
2.A.65	BRT	Bilirubin	~350	5	E (An)	0	Bilirubin transporter of *Rattus norvegicus*
2.A.66	MATE	Drugs, dyes; nucleotides?	400-700	12	A, B, E	3	Norfloxacin and other drug efflux pump, NorM of *Vibrio parahaemolyticus*
2.A.67	OPT	Peptides	600-900	12-15	A, B, E	2	Oligopeptide transporter, OPT1, of *Candida albicans*
2.A.68	AbgT	Aminobenzoyl-glutamate	~500	12-13	B	1	Aminobenzoyl-glutamate transporter, AbgT, of *E. coli*
2.A.69	AEC	Auxin (efflux)	600-700	8-12	A, B, E	2	Auxin efflux carrier, PIN1 of *Arabidopsis thaliana*
2.A.70	MSS	Malonate	255+129	7+4	B	0	Malonate:Na^+ symporter, MadLM of *Malonomonas rubra*
2.A.71	FBT	Folate, biopterin, methotrexate	450-650	12	B, E	1	Folate-biopterin transporter of *Leishmania donovani*
2.A.72	KUP	K^+ (uptake)	400-800	12	A, B, E	2	The K^+:H^+ symporter, Hak1 of *Neurospora crassa*
2.A.73	ICT	HCO_3^-	350-500	10	B	1	HCO_3^-:Na^+ symporter of *Synechococcus* PCC7942
2.A.74	MET	Thymidine, drugs, steroids	200-300	4	E (An)	1	Lysosomal hydrophobe/amphiphile transporter, MTP of *Mus musculus*
2.A.75	LysE	Basic amino acids	150-250	5	A, B	1	Lysine/arginine exporter, LysE of *Corynebacterium glutamicum*
2.A.76	RhtB	Neutral amino acids and their derivatives	150-250	5	B	2	Neutral amino acid exporter, RhtB of *E. coli*
2.A.77	CadD	Cd^{2+}; cations	150-250	5	B	1	Cadmium resistance protein, CadD of *Staphylococcus aureus*
2.A.78	LIV-E	Leu, Ile, Val	~250 + ~110	7+4	A, B, E (Pr)	2	AzlC, AzlD of *Bacillus subtilis*
2.A.79	ThrE	Thr, Ser	450-600	10	A, B, E	2	Thr/Ser:H^+ antiporter of *Corynebacterium glutamicum*
2.A.80	Tct	Tricarboxylates	~500	12+4+0	B, (A?)	2	TctABC of *Salmonella enterica*

TABLE 2 (continued)

2.B Non-ribosomally Synthesized Porters							
2.B.1	Valino-mycin	K^+	12		B	0	Valinomycin of *Streptomyces fulrissimus*
2.B.2	Monensin	K^+, Na^+, H^+	No amino acids		B	0	Monensin A of *Streptomyces cinna-monensi*
2.B.3	Nigericin	K^+, H^+	No amino acids		B	0	Nigericin of *Streptomyces hygroscopicus*
2.B.4	MA	Monovalent cations	No amino acids		B	1	Nonactin of *Streptomyces griseus*
2.B.5	MP	Cations	No amino acids		B	2	Macrocyclic polyethers (crown com-pounds)
2.B.6	Ionomy-cin	Divalent cations	No amino acids		B	0	Ionomycin of *Streptomyces conglobatus*
2.C. Ion-gradient-driven energizers							
2.C.1	TonB-ExbB-ExbD/ TolA-TolQ-TolR		100-350	1+3+1	B	2	TonB system of *E. coli*
						2	TolA system of *E. coli*
3.A. P-P-Bond Hydrolysis-driven Transporters							
3.A.1	ABC	All sorts of inorganic and organic molecules of small, intermediate and large sizes, from simple ions to macro-molecules	1000-2000 (multidomain; usually multi-subunit)	$\underline{(5)_2; (6)_2; 12}$ variable	A, B, E	3	Maltose permease, MalEFGK of *E. coli*; multidrug resistance protein, MDR of *Homo sapiens*
3.A.2	F-ATPase	H^+; Na^+	>4000 (multiple subunits)	$(2)_{10}+(1)_2+(5)_1$	A, B, E (chloro; mito)	2	F_0F_1-ATPase of *E. coli*

3.A.3	P-ATPase	Cations (uptake and/or efflux): Na^+, K^+; H^+, K^+; Ca^{2+}, K^+; Na^+; H^+; K^+; Ca^{2+}; Ca^{2+}, Mn^{2+}; Mg^{2+}; Mn^{2+}; Cu^{2+}; Cu^+, Ag^+; Ag^+; Zn^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Pb^{2+} (some systems may be specific for one or only a few of these heavy metal cations). phospholipids (flipping)	600-1200 (sometimes multisubunit)	(6-12), 8, 10	A, B, E	3	KdpABC (K^+ uptake) of *E. coli*
3.A.4	ArsAB	Arsenite, antimonite, (tellurite?)	~1100 (multi-domain; two subunits)	12	A, B, E	2	The arsenite efflux pump, ArsAB of *E. coli*
3.A.5	IISP	Proteins	>2000 (multiple subunits)	SecY (10) SecE 1 SecG 1 or 2	A, B, E	2	The type II secretory pathway system, SecAYEG of *E. coli*
3.A.6	IIISP	Proteins	>2000 (multiple subunits)	≥10 integral membrane constituents	B	2	The type III secretory pathway system, YscNDRSTUC; LcrD of *Yersinia* species
3.A.7	IVSP	Proteins, protein-DNA complexes	>2000 (multiple subunits)	≥10 integral membrane constituents	B	2	The type IV secretory pathway system, VirB2-11 of *Agrobacterium tumefaciens*
3.A.8	MPT	Mitochondrial proteins	>2000 (multiple subunits)	≥9 integral membrane constituents	E (mito)	1	The mitochondrial protein translocase, Tom and Tim proteins of *Saccharomyces cerevisiae*
3.A.9	CEPT	Chloroplast proteins	>2000 (multiple subunits)	Several integral membrane constituents	E (chloro)	1	The chloroplast envelope protein trans-locase, IAP proteins of *Pisum sativum*
3.A.10	H^+-PPase	H^+	650-800	15	A, B, E (Pl vacuoles)	2	Vacuolar H^+-pyrophosphatase, V-PPase of *Arabidopsis thaliana*
3.A.11	DNA-T	Single-stranded DNA	>1000 (multiple subunits)	3 subunits	B	1	Competence-related DNA transformation transporter, ComEA-EC-FA of *Bacillus subtilis*
3.A.12	S-DNA-T	DNA, DNA-protein complexes	600-1350	2, 4, 6	B	2	Cell division protein FtsK of *E. coli*
3.A.13	FPhE	Viruses	109+348+476	1	Bp	1	F1 assembly/export channel

TABLE 2 (continued)

3.A.14	FPE	Proteins	320-420 + 350-570	3	B	1	Competence-related pilin exporter of *Bacillus subtilis*
3.B. Decarboxylation-driven Active Transporters							
3.B.1	NaT-DC	Na^+	~1000 (4 subunits)	10	A, B	2	Oxaloacetate decarboxylase of *Salmonella typhimurium*
3.C. Methyl Transfer-driven Active Transporters							
3.C.1	NaT-MMM	Na^+	~8 subunits; most integral membrane constituents	6-7 (A), 1 (B), 8 (C), 2-7 (D), 0-2 (E), 1 (F), 1 (G), 1 (H)	A	1	Na^+-transporting methyltetrahydromethanopterin: Coenzyme M methyltransferase of *Methanobacterium thermoautotrophicum*
3.D. Oxidoreduction-driven Active Transporters							
3.D.1	NDH	Na^+; H^+ (efflux)	14-41 subunits	Multiple integral membrane subunits	B, E (mito, chloro)	2	NDH of *E. coli*
3.D.2	PTH	H^+ (efflux)	~2000 (1-3 proteins; 3 domains; dimeric)	$(12\text{-}14)_2$	B, E (mito)	2	PTH of *E. coli*
3.D.3	QCR	H^+ (efflux)	2000-6000 multiple (3-11) subunits; dimeric	8 (C), 1 (D), 1 (G), 1 (J), 1 (K)	B, E (mito; chloro)	2	Cytochrome bc_1 complex of *Bos taurus*
3.D.4	COX	H^+ (efflux)	2000-6000 multiple (3-11) subunits; dimeric	E: 12 (I), 2 (II), 7 (III), 1 (IV), 1 (VIa), 1 (VIc), 1 (VIIa), 1 (VIIb), 1 (VIIc), 1 (VIII) B: 12 (I), 2 (II)	A,B,E, (mito)	3	Cytochrome c oxidase of *Bos taurus*
3.D.5	Na-NDH	Na^+ (efflux)	Multiple subunits	9(B); 1(C): 5(D); 6(E); 3(F)	B	1	Na^+-translocating NADH-quinol reductase of *Vibrio alginolyticus*
3.D.6	NFO	H^+ or Na^+ (efflux)	Multiple subunits	5+1+6+1+2-4 +9	B	1	H^+ or Na^+ translocating NADH:ferredoxin oxidoreductase, rnfA-H of *Rhodobacter capsulatus*
3.D.7	HHO	H^+ (efflux)	Multiple subunits	2 (D); 6 (E); 4 (G); 1 (A); 5 (C)	A,B	1	H_2:heterodisulfide oxidoreductase of *Methanosarcina mazei*

3.D.8	FMF-DH	H^+ or Na^+ (efflux)	Multiple subunits	2 (F); 1 (G)	A	1	Formyl methanofuran dehydrogenase Fwd A-G of *Methanobacterium thermo autotrophicum*
3.D.9	$F_{420}H_2DH$	Reduced donor, H^+	M_r of complex about 120,000	1 (F); 14 (N); 14 (M); 19 (L); 2 (K); 5 (J); 1 (I); 7 (H); 3 (A)	A	1	$F_{420}H_2DH$ of *Methanosarcina mazei*
3.E. Light-driven Active Transporters							
3.E.1	MR	H^+ (efflux); Cl^- (uptake)	~250	7	A, E B, E	2	Bacteriorhodopsin of *Halobacterium salinarum*
3.E.2	PRC	H^+ (efflux)	multiple subunits	5+5+1	B, E (chloro)	2	Reaction center and cytochrome b_6f complex of *Rhodobacter sphaeroides*
4.A. Phosphotransferase Systems							
4.A.1	Glc	Glucose; N-acetylglucosamine; α- and β-glucosides (i.e., maltose; trehalose; sucrose; arbutin; arbutin, cellobiose, salicin)	~2000 (3 domains; dimeric)	$(8)_2$	B	2	Glucose IICB-IIA of *E. coli*
4.A.2	Fru	Fructose; mannitol	~2000 (3 domains; dimeric)	$(6)_2$	B	2	Fructose IIB'BC-IIAMH of *E. coli*
4.A.3	Lac	Lactose; cellobiose, N,N'-diacetylchitobiose; lichenan oligosaccharides	~2000 (3 domains; dimeric)	~$(8)_2$	B	2	Lactose IICB-IIA of *Staphylococcus aureus*
4.A.4	Gut	Glucitol	~2000 (3 domains; dimeric)	$(8)_2$	B	1	Glucitol IICBC'-IIA of *E. coli*
4.A.5	Gat	Galactitol, D-Arabitol	~2000 (3 domains; dimeric)	~$(8)_2$	B	1	Galactitol IIC-IIB-IIA of *E. coli*

TABLE 2 (continued)

4.A.6	Man	Glucose, mannose, fructose; glucosamine, N-acetylglucosamine; sorbose; galactosamine; N-acetylgalactosamine	~2000 (4 domains; probably dimeric)	$\underline{(6\ (IIC)+1\ (IID))_2}$	B	1	Mannose IIAB-IIC-IID of *E. coli*
5.A. Transmembrane Electron Transfer Carriers							
5.A.1	DsbD	$2e^-$	150-800	6-9	A, B	2	DsbD of *E. coli*
5.A.2	DsbB	$2e^-$	150-200	4	B	1	DsbB of *E. coli*
5.B Transmembrane 1-Electron Transfer Carriers							
5.B.1	$Gp91^{phox}$	$1e^-$	450-750	$\underline{6}$	B, E	2	$Gp91^{phox}$ of *Homo sapiens*
8.A. Auxiliary Transport Proteins							
8.A.1	MFP	Proteins; peptides; lipo-oligosaccharides; drugs, dyes, signaling molecules; heavy metal ions, etc.	350-500	$\underline{1}$	B	2	EmrA of *E. coli*
8.A.2	SAL	Proteins, peptides	100-150	0-1	B (G-)	1	PulS of *Klebsiella pneumoniae*
8.A.3	MPA1	Complex polysaccharides	600-800	2	B	2	ExoP of *Rhizobium meliloti*
8.A.4	MPA2	Complex polysaccharides	300-400	2	B	2	KpsE of *E. coli*
8.A.5	VICβ	K^+	200-550	2	B, E	2	β1a of *Homo sapiens*
8.A.6	ANT	Nutrients	~3000	2	E	0	CSF1 of *Saccharomyces cerevisiae*
8.A.7	EI	Sugars	500-600	0	B	1	Enzyme I of *E. coli*
8.A.8	HPr	Sugars	60-95	0	B	1	HPr of *E. coli*
8.A.9	rBAT	Cationic and neutral amino acids uptake	500-700	4	E (An)	2	rBAT of *Oryctolagus cuniculus*
8.A.10	MinK	K^+	100-200	1	E (An)	2	MinK of *Rattus norvegicus*
8.A.11	PLB	Ca^{2+}	~50	1	E (An)	2	PLB of *Homo sapiens*
8.A.12	BEA	Bacteriocins	100-200	1	B (G+)	0	BrcD of *Brochothrix campestris*
8.A.13	Tpr1	K^+, alkali metal ions	~1040	1	A, B, E	2	Tpr1 of *Schizosaccharomyces pombe*

9.A. Transporters of Unknown Classification

9.A.1	PST	Polysaccharides (export)	400-500	12	A, B	2	Lipopolysaccharide exporter, RfbX1 of *E. coli*
9.A.2	MerTP	Hg^{2+} (uptake)	~200	3	B	2	Mercuric ion transporter, MerTP, encoded on the IncJ plasmid pMERPH of *Shewanella putrefaciens*
9.A.3	MerC	Hg^{2+} (uptake)	~140	4	B	1	Mercuric ion uptake transporter, MerC, encoded on the IncJ plasmid pMERPH of *Shewanella putrefaciens*
9.A.4	PnuC	Nicotinamide mononucleotide (uptake)	~320	7	B	1	The nicotinamide mononucleotide uptake permease, PnuC of *Salmonella typhimurium*
9.A.5	PPI	Peroxisomal proteins	Multimeric subunits	3-5 (10p) +2-4 (12p) +1-2 (13p) +0-1 (14p) +0-1 (5p) +0-2 (7p) +0-1 (4p)	E	1	PEX of *Homo sapiens*
9.A.6	INT	Nucleosides	200-300	4	E (An)	2	Intracellular nucleoside transporter, MTP of *Mus musculus*
9.A.7	MerF	Hg^{2+}	~80	2	B	2	MerF importer of *Pseudomonas aeruginosa* plasmid
9.A.8	FeoB	Fe^{2+} (uptake)	~800	8-13	A,B	2	The Fe^{2+} uptake transporter, FeoB of *E. coli*
9.A.9	FeT	Fe^{2+} (Co^{2+}, Cd^{2+}) (uptake)	~550	6	E (Y)	0	The Fe^{2+} transporter, Fet4p of *Saccharomyces cerevisiae*
9.A.10	OFeT	Fe^{2+} (uptake)	~400	6	A,B,E	2	The oxidase-dependent Fe^{2+} transporter, Ftr1p of *Saccharomyces cerevisiae*
9.A.11	Ctr1	Cu^{2+} (uptake)	~400	2-3	E (Y)	1	The copper transporter, Ctr1p of *Saccharomyces cerevisiae*
9.A.12	Ctr2	Cu^{2+} (uptake)	150-200	3	E	1	The copper transporter, Ctr2p of *Saccharomyces cerevisiae*
9.A.13	Cjl	Colicins Js	~65	0	B	0	Cjl of *Shigella sonnei*
9.A.14	NPC	RNA; proteins, small molecules, etc.	30-50 proteins		E	1	Nuclear pore complex of *Saccharomyces cerevisiae*
9.A.15	YhaG	Tryptophan	150-200	6	B	0	YhaG of *Bacillus subtilis*

TABLE 2 (continued)

9.A.16	LPI	Protein	~400	2	E	1	LAMP of *Homo sapiens*
9.A.17	PbrT	Pb^{2+}	400-650	7	B	1	PbrT of *Ralstonia metallidurans*
9.A.18	PUP	Peptides, microcins, antibiotics (uptake)	~400	7	B	1	Microbin uptake permease, SbmA of *E. coli*
9.A.19	MgtE	Mg^{2+}, Co^{2+} (uptake)	300-500	4-5	A, B	2	Mg^{2+}-transporter MgtE of *Bacillus firmus*
9.A.20	LCT	Monovalent cations	~570	8-10	E (Pl)	0	Low affinity cation transporter, LCT1 of *Triticum aestivum*
9.A.21	ComC	DNA, proteins	1000-1250		B (G-)	1	Pilus assembly protein of *Neisseria meningitidis*
9.A.22	NhaE	Na^+, K^+	~250	7-9	B		NhaE of *Bacillus subtilis*
9.A.23	FP	Fe^{2+}; H^+	400-800	8-10	E (An, Pl)	1	Murine ferroportin IREG1
9.B. Putative Uncharacterized Transporters							
9.B.1	MHP	Me^{2+}	250-350	3	E (Y)	0	Bsd2 of *Saccharomyces cerevisiae*
9.B.2	CHP	Ca^{2+}	~400	9-10	E (Y)	0	Csg2 of *Saccharomyces cerevisiae*
9.B.3	MPE	Murein precursor	250-550	9-10	B	2	FtsW of *E. coli*
9.B.4	PET	?	500-1000	6	B, E	2	YccS of *E. coli*
9.B.5	KXA	Neutral amines and/or oligopeptide transporter	400-450	10	E (An)	1	The KX blood group antigen (putative amino acid transporter) of *Homo sapiens*
9.B.6	Hok/Gef	Ions; non-specific?	45-60	1	A, B	1	The toxic Gef protein of *E. coli*
9.B.7	BCD	Bacteriochlorophyll?	400-500	12	B	1	LhaA of *Rhodobacter capsulatus*
9.B.8	C-BAT	Bile acids?	~500	1	E	2	C-BAT (GP110) of *Rattus norvegicus*
9.B.9	UAT	Urate	~300	1	E (An)	2	UAT of *Rattus norvegicus*
9.B.10	MarC	Drugs? Peptides?	150-250	6	A, B	1	MarC of *E. coli*
9.B.11	MRS2	Mg^{2+}	350-500	2	E	1	MRS2 of *Saccharomyces cerevisiae*
9.B.12	SHP	Ions?	50-150	2	B, E	1	BLT101 of *Lophopyrum elongatum*
9.B.13	ECN	Ions; small molecules?	40-50	1	B	0	Entericidin B (EcnB) of *E. coli*
9.B.14	HEP	Heme?	500-1000	15	A, B, E	2	OccmF (Cel1) of *Rhodobacter capsulatus*
9.B.16	Ductin	Small molecules	100-200	4	B, E		Ductin of *Drosophila melanogaster*
9.B.17	FAT	Fatty acids?	500-600	0-4	A, B, E	3	FatP of *Mus musculus*
9.B.18	SSTP	Auxiliary protein?	50-200	1	B	2	YajC of *E. coli*
9.B.19	MnHP	Mn^{2+}	~300	7-8	E (Y)	0	ATX2 of *Saccharomyces cerevisiae*
9.B.20	MgtC	Mn^{2+}	150-250	5-6	B	1	MgtC of *Salmonella typhimurium*

9.B.21	Frataxin	Fe^{2+}?	100-250	0	B, E	2	Frataxin of *Homo sapiens*
9.B.22	PerM	?	300-500	7	A, B	2	PerM of *E. coli*
9.B.23	DVT	H^+? (vacuolar)	400-500	10	E	0	PfCRT of *Plasmodium falciparum*
9.B.24	TEGT	Amino acids?	200-250	7	B, E	1	TEGT of *Homo sapiens*
9.B.25	YbbM	?	200-300	7	A, B, E	0	YbbM of *E. coli*
9.B.26	PF27	?	200-400	5-7	B, E	1	Y615 of *Synechocystis* PCC6803
9.B.27	YdjX-Z	?	200-250	5	B, E	1	YdjX of *E. coli*
9.B.28	YqaE	Ions?	50-100	2	B, E	1	YqaE of *E. coli*
9.B.29	YebN	?	150-250	6	B, A	1	YebN of *E. coli*
9.B.30	Hly III	Ions? small molecules?	200-350	7	B, E	1	Hly III of *Bacillus cereus*
9.B.31	YqiH	?	150-300	5-6	B		YqiH of *E. coli*
9.B.32	VGP	Polysaccharides (export)	250-750	4	A, B, E	2	WbbF of *Salmonella enterica* serovar Borreza plasmid pWQ799
9.B.33	YaaH	?	150-400	4-6	A, B, E	1	YaaH of *E. coli*
9.B.34	PMP3	H^+? Cations?	50-550	2	A, B, E	1	Pmp3p of *Saccharomyces cerevisiae*
9.B.35	Trans-thyretin	Thyroxine	100-200	1	E, B	1	Transthyretin precursor of *Rattus norvegicus*
9.B.36	SgaT	Sugars?	450-700	12	B	1	SgaT (IIC) of *E. coli* SgaA (IIA) of *E. coli* SgaB (IIB) of *E. coli*
9.B.37	HCC	Ions?	250-500	3	B	2	HlyC of *Brachyspira hyodysenteriae*
9.B.38	SAD	?	200-300	7	B, E	2	Sad (YbhL) of *E. coli*
9.B.39	lcFAT	Fatty acids	~472	3	E	2	CD36 of *Mus musculus*

9.C. Functionally Characterized Transporters With Unidentified Sequences

9.C.1	EOT	Oligosaccharides
9.C.2	VAC	Anions
9.C.3	REP	Ions; small molecules
9.C.4	PAPS-T	Nucleotide sulfate
9.C.5	ATP-T	ATP/ADP/AMP
9.C.6	T7-T	Phage DNA

[a]TC#, number of the family according to the transporter classification system.

TABLE 2 (continued)

[b]Substrates of single transporters within a family are separated by commas; substrates transported by different protein members of the family are separated by semicolons.

[c]Size range (in number of amino acyl residues) when a single type of subunit is present, or for the entire complex when several types of subunits are present. In some cases the individual subunits in multisubunit systems are indicated separately.

[d]#TMSs, number of (putative) transmembrane α-helical segments, TMSs, (or β-strands in section 1.B) in a polypeptide chain. Underlined numbers indicate that the #TMSs is established by x-ray crystallographic data or that substantial experimental evidence suggests the proposed topology, usually as a result of the use of gene fusion technology. If not underlined, numbers indicate the numbers of TMSs predicted based on hydropathy analyses using available programs such as WHAT and AveHAS (see our Web site (http://www.biology.ucsd.edu/~yzhai/biotools.html)). In some cases, the numbers of predicted TMSs is zero, and hence a "0" is entered. In many such cases, the actual TMS(s) is (are) amphipathic, and hence the program does not predict TMSs correctly.

Subscripts refer to the number of polypeptide chains in the complex when known. "n" indicates an oligomeric structure of unknown or poorly defined number of subunits. If alternative structures are found for different transporters within a single family, these are separated by semicolons.

[e]The abbreviations used for organismal types, eukaryotic organelles and viruses are as follows: Organismal type: B, bacteria; A, archaea; E, eukaryote; G-B, Gram-negative bacteria; G+B, Gram-positive bacteria; Y, yeast; Fu, fungi; Pr, protozoans; Pl, plants; An, animals; Eukaryotic organelles: Mito, mitochondria; Chloro, chloroplasts; Plastids, nonphotosynthetic plastids of plants; Viruses: Bp, bacteriophage; V, Virus.

[f]The numbers represent the order of magnitude of members in this family as of November 2001. 0: between 0 and 5; 1: between 6 and 49; 2: between 50 and 499; 3: more than 500.

ing oligomeric transmembrane pores. The toxic effects are caused by allowing the free flow of electrolytes and other small molecules across the membrane. Polypeptides of this subclass are probably synthesized universally by all types of living cells.

d. Non-Ribosomally Synthesized Channels

These molecules often consist of small molecular building blocks such as L- and D-amino acids and hydroxy acids. The assembly of the molecular building blocks allows construction of oligomeric transmembrane ion channels. "Depsipeptides" and amino acid-free substances of this class usually provide a function related to biological warfare. Most of these substances are synthesized by bacteria and fungi.

e. Holins

The primary function of holins appears to be export of murein hydrolases across the cytoplasmic membranes of bacteria where the enzymes hydrolyze the cell wall polymer as a prelude to cell lysis. Holins may also facilitate leakage of electrolytes and nutrients from the cell cytoplasm, thereby promoting cell death. They are encoded within the genomes of Gram-positive and Gram-negative bacteria as well as those of the bacteriophage of these organisms. The many families of channel-forming holins do not exhibit significant sequence similarity between themselves but display common structural and functional characteristics.

2. Class 2. Electrochemical Potential-Driven Transporters

These transport systems are also called secondary carrier-type facilitators. Class 2 systems usually exhibit strict stereospecificity and are energy coupled to the proton motive force (pmf) or the sodium motive force (smf).

a. Porters

This subclass consists of transport systems that utilize carrier-mediated processes to catalyze uniport (a single species is transported either by facilitated diffusion or in a membrane potential-dependent process if the solute is charged), antiport (two or more species are transported in opposite directions in a tightly coupled process, not coupled to a direct form of energy other than chemiosmotic energy), and/or symport (two or more species are transported together in the same direction in a tightly coupled process, not coupled to a direct form of energy other than chemiosmotic energy). These systems are ubiquitous, being found in all living organisms.

b. Non-Ribosomally Synthesized Porters

Like nonribosomally synthesized channels, these molecules may be depsipeptides or non-peptide-like substances. They usually facilitate translocation by complexing an ion in their hydrophilic interior, exposing their hydrophobic exterior and moving from one side of the bilayer to the other. Transport can be electrophoretic if the free

porter can cross the membrane in the uncomplexed form, or it can be electroneutral if only the complex can cross the membrane. Most of these molecules are products of bacteria and fungi.

c. Ion-Gradient-Driven Energizers

These energizers use the proton or sodium motive force across the cytoplasmic membrane. The mechanism is poorly understood, but they undoubtedly couple proton (H^+) or sodium (Na^+) fluxes to the energized process. Currently, recognized energizers can drive bacterial flagellar rotation or active transport across the outer membranes of Gram-negative bacteria, but they belong to a single family.

3. Class 3. Primary Active Transporters

These transporters use a primary source of energy when compared with a secondary (chemiosmotic) source of energy to drive active transport of solutes against concentration gradients. Secondary energy sources must be generated by driving an active transport process at the expense of a primary energy source.

a. P-P-Bond Hydrolysis-Driven Transporters

Transport systems of this subclass hydrolyze the diphosphate bond of inorganic pyrophosphate or a nucleoside triphosphate to drive the active uptake and/or extrusion of a solute or solutes. The transport protein may or may not be transiently phosphorylated, but the substrate is not chemically modified. Members of this subclass are found in all domains of the living world.

b. Decarboxylation-Driven Transporters

Transport systems that drive solute uptake or extrusion by decarboxylation of a cytoplasmic substrate are included in this subclass. These multisubunit transporters are currently thought to be restricted to prokaryotes and belong to a single family.

c. Methyltransfer-Driven Transporters

A single characterized multisubunit protein family currently falls into this subclass, the Na^+-transporting methyltetrahydromethanopterin:coenzyme M methyltransferases. These transporter complexes have been found only in archaea.

d. Oxidoreduction-Driven transporters

This subclass is comprised of transport systems that drive transport of a solute (H^+ or Na^+) energized by the exothermic flow of electrons from a reduced substrate to an oxidized substrate. These multisubunit systems are distributed in all domains of the living world.

e. Light Absorption-Driven Transporters

Transport systems that utilize light energy to drive transport of an ion are included in this subclass. These systems and their homologues are distributed in all three domains of life.

4. Class 4. Group Translocators

This class includes transport systems that chemically alter the substrate during transport across a membrane so that the species released into the cytoplasm differs from the one that was taken up.

a. Phosphotransfer-Driven Group Translocators

Transport systems of the bacterial phosphoenolpyruvate:sugar phosphotransferase system are the only recognized group translocators. The product of the transport reaction, derived from extracellular sugar, is a cytoplasmic sugar-phosphate. The enzymatic constituents that catalyze sugar phosphorylation are superimposed on the transport process in a tightly coupled and highly sophisticated process.

5. Class 5. Transmembrane Electron Carriers

This class includes systems that catalyze electron flow across a biological membrane. The electrons are transferred from donors localized to one side of the membrane to acceptors found on the other side. These systems contribute to or subtract from the membrane potential, depending on the direction of electron flow.

a. Transmembrane 2-Electron Transfer Carriers

This subclass is restricted to systems that catalyse transfer of a pair of electrons across the membrane in one or more discrete steps without splitting the paired electrons.

b. Transmembrane 1-Electron Transfer Carriers

This subclass includes systems that catalyse the sequential transfer of single electrons across the membrane.

6. Class 8. Accessory Factors Involved in Transport

Proteins that function with or are complexed to known transport proteins are included in this category. In some cases, auxiliary proteins are considered to be an integral part of the transport system, and in such cases the proteins are classified with the transporter. Then no distinct entry in category 8 is provided.

a. Auxiliary Transport Proteins

This subclass consists of proteins that facilitate transport across one or more bio-

logical membranes, but themselves do not participate directly in transport. These proteins always function in conjunction with one or more established transport system(s). They may provide a function connected with energy coupling to transport, play a structural role in complex formation, serve a biogenic or stability function, or play a regulatory role.

7. Class 9. Incompletely Characterized Transport Systems

Transport protein families for which insufficient information is available to allow classification in a defined class (e.g., TC classes 1 to 5) belong to category 9.

a. Recognized Transporters of Unknown Biochemical Mechanism

Recognized families of transport proteins of unknown classification are grouped in this subclass. These families include at least one member for which a transport function has been established, but either the mode of transport or the energy coupling mechanism is not known. They will be classified elsewhere when the transport mode and/or energy coupling mechanisms are characterized.

b. Putative Uncharacterized Transport Proteins

Putative transport protein families are grouped into this subclass if a transport function has been suggested for one or more members of the family, but evidence for such a function is not yet compelling. They will either be classified elsewhere when the transport function of a member becomes established, or are eliminated from the TC system if the proposed transport function is disproven.

c. Functionally Characterized Transporters Lacking Identified Sequences

Transporters of particular physiological significance are included in this category even though a family assignment cannot be made. When their sequences are identified, they will be assigned to an established family. This is the only TC subclass that includes individual proteins rather than protein families.

C. The Significance of Transporter Family Association

Nearly 400 families are currently included in the TC system (see Table 1 and TCDB). Affiliation with a family requires satisfying rigorous statistical criteria of homology (Saier, 1994). Briefly, a protein must exhibit a region of 60 residues or more in comparable portions of the protein that exhibit a comparison score in excess of nine standard deviations (SD) with at least one established member of that family. Whereas the classes and subclasses distinguish functionally distinct types of transporters, the families and subfamilies provide a phylogenetic basis for classification. Thus, the TC system is a functional/phylogenetic system of classification. Families rarely cross class or subclass lines.

Recognition of a phylogenetic relationship based on sequence similarity allows certain conclusions regarding three-dimensional structural features. Any two proteins that can be shown to be homologous (i.e., that exhibit sufficient primary and/or secondary structural similarity to establish that they arose from a common evolutionary ancestor) can be expected to exhibit strikingly similar three dimensional structures although a few exception have been noted (Saier and Tseng, 1999). Therefore, extrapolation from one member of a family of known structure to all other members becomes justifiable. The extrapolation of structural data to other proteins should never be made if homology has not been established. Similar arguments apply to mechanistic considerations. Thus, the mechanism of solute transport is likely to be similar for all members of a permease family, and variations on a specific mechanistic theme are greatest when the sequence divergence is greatest. In contrast, for members of any two independently evolving permease families, the transport mechanism may be strikingly different. Extensive experimental work has established that phylogenetic data can also be used to predict substrate specificity, polarity of transport and even intracellular localisation depending on the family and the degree of sequence divergence observed within that family (Saier, 2000a,c).

The current TC system, summarized in Table 1, is available in database format on the World-Wide-Web (http://tcdb.ucsd.edu). It provides detailed descriptions of and reference citations for (1) TC classes, (2) subclasses, (3) families, (4) subfamilies, and (5) individual proteins. Additionally, relevant research tools can be found on our website, facilitating examination of the world of transport proteins. TCDB is equipped with a search tool that allows the user to search by key word, gene name, family, or protein sequence. Any protein demonstrably homologous to a TC family member can be identified using TC-BLAST. TCDB is interconnected with other useful databases and websites.

D. Characteristics of the Families

Key features of the transporter families currently recognized in TCDB, are summarized in Table 2. This table provides the TC number of the family, the substrates that are transported (substrates that are common to one transporter are separated by commas, whereas substrates of different transporters are separated by semicolons) and the size ranges of the individual protein members within each family. Additionally, the probable numbers of transmembrane segments in the integral membrane constituents of the family and sometimes the oligomeric structures are predicted. The organismal groups in which members of the family have been identified and the approximate sizes of the families (numbers of members expressed in orders of magnitude) are indicated. Finally, a well-characterized example is provided in the last column.

Several TC entries presented in Table 2 are superfamilies. In such cases, TCDB indicates the numbers of subfamilies currently recognized within that superfamily. The VIC (TC 1.A.1), MF (2.A.1), and ABC (3.A.1) superfamilies are the largest and most diverse transporter superfamilies currently recognized, but several other TC families have achieved superfamily status. The interested reader is referred to TCDB for further explanation and continual updates.

II. TOPOLOGIES OF VARIOUS TRANSPORT PROTEIN TYPES

As indicated in Table 2, the topologies of proteins within the different families of

the TC system were predicted using topological prediction programs such as WHAT (Zhai and Saier, 2001) and TOPPRED (Claros and von Heijne, 1994). In relatively few instances have protein topologies been experimentally established, but when this information is available it is provided (underlined values in Table 2).

We have proposed that channels and carriers are fundamentally different at both structural and functional levels, but that the former were the evolutionary precursors of the latter (Saier, 2000b). In Figure 2, the topologies of channel and carrier proteins are compared. The numbers of TMSs found in the protein constituent types within several subclasses are plotted. The average number of TMS ± S.D. for each of these subclasses is shown in Figure 3.

As seen in Figure 2, the topological types that comprise α-type channels (TC subclasses 1.A, 1.C, and 1.E) differ fundamentally from secondary carriers (TC subclass 2.A). Most families of α-helical channels

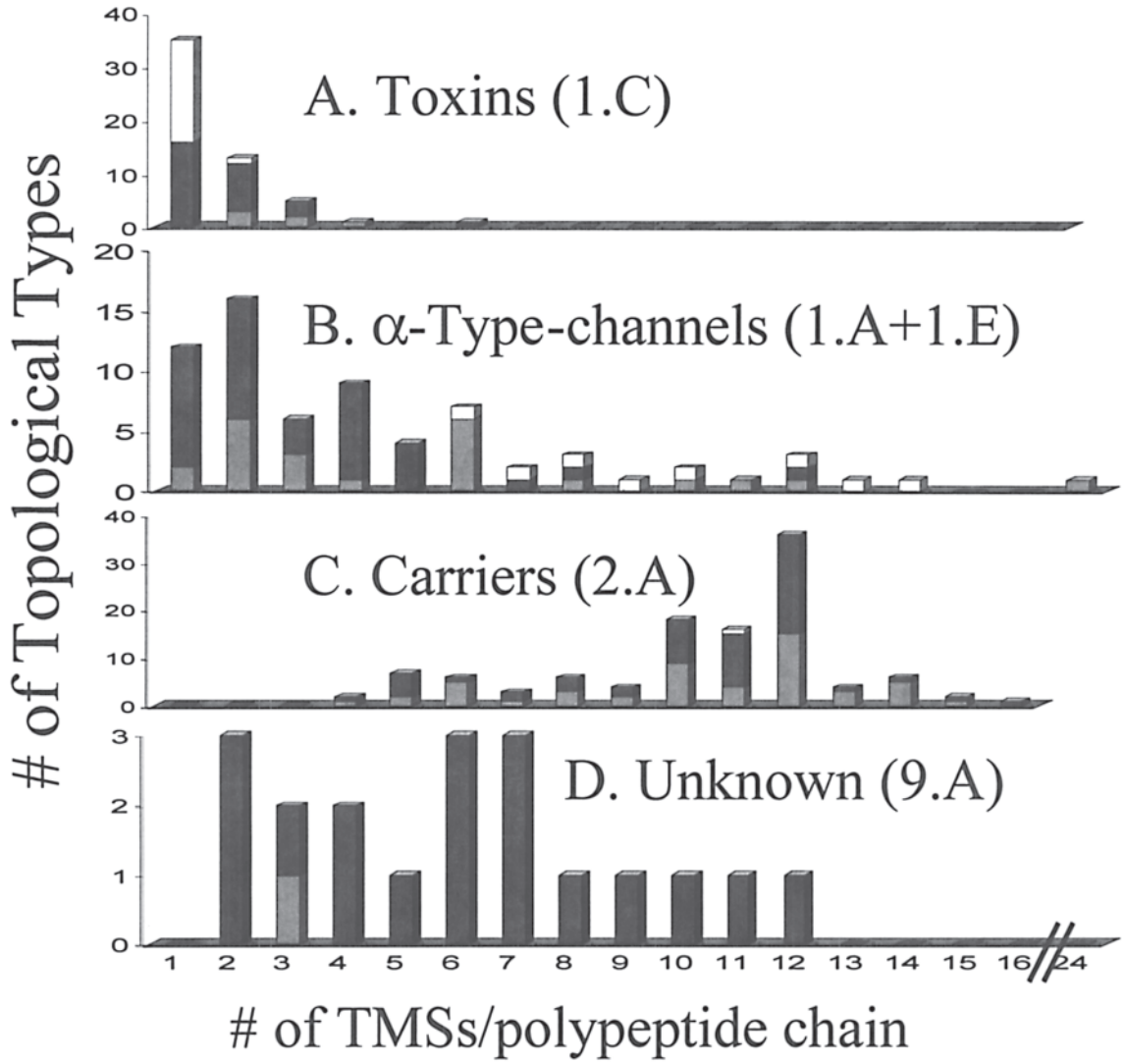

FIGURE 2. Distribution of the various topological types of transporters in four subgroups of the TC system. (A) channel-forming toxins (1.C); (B) α-type channels (1.A plus 1.E); (C) porters (2.A); (D) transporter types of unknown mechanism (9.A). Grey, established; black, putative; white, uncertain.

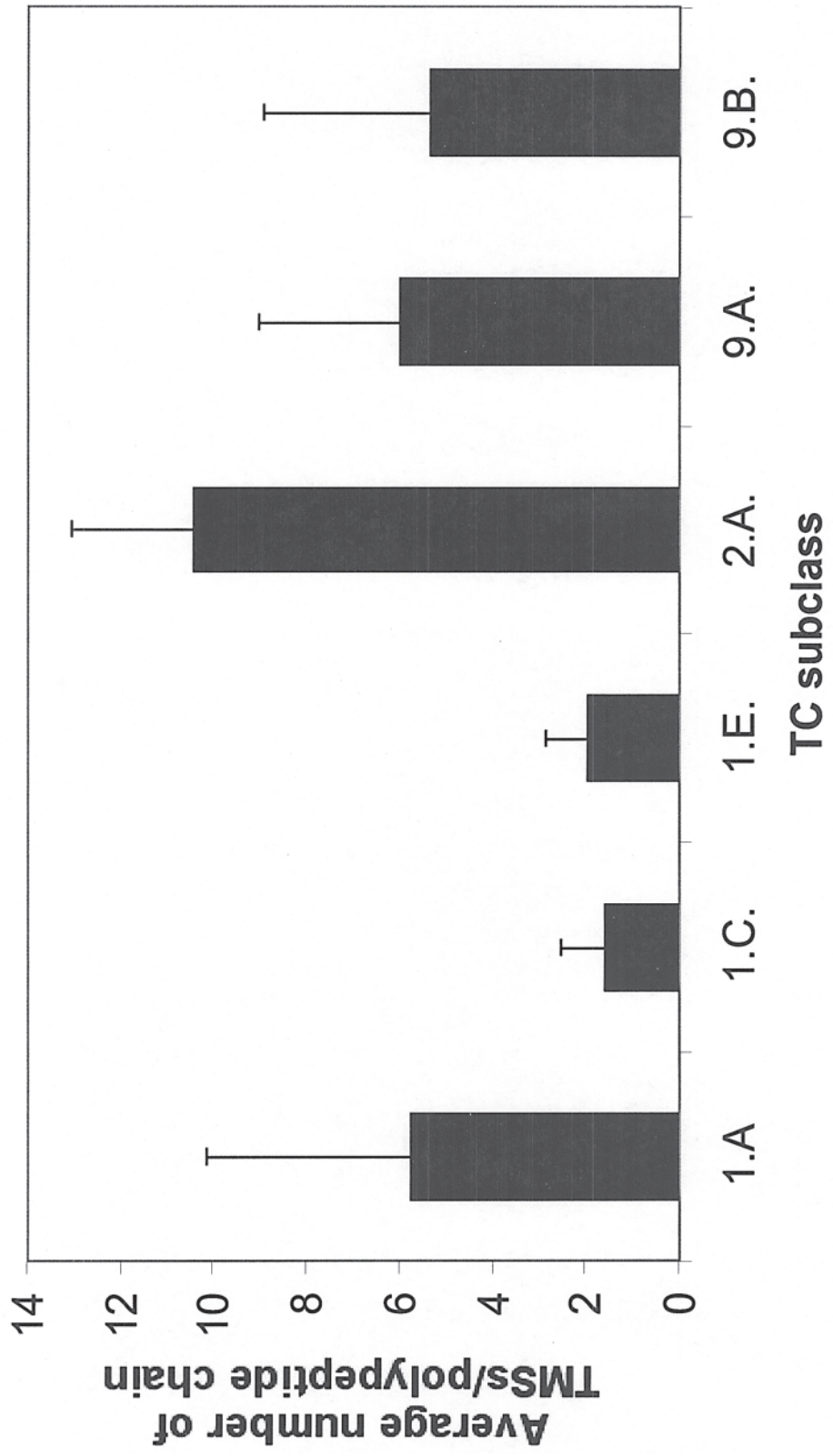

FIGURE 3. Average numbers of putative TMSs for transporter type polypeptide chains in six different subclasses of the TC system. The bars provide the variation within the subfamily expressed in standard deviations.

include proteins with one to six TMSs, whereas the vast majority of carrier-type families display 10 to 12 TMSs. Almost all proteins in subclasses 1.C and 1.E display just one or two TMSs, but channel proteins with up to 24 TMSs per polypeptide chain can be found in subclass 1.A.

These differences are displayed in a different way in Figure 3. Here the average number of TMSs for the various protein types in each subclass are presented ± S.D. Fundamental differences are apparent. These observations document the critical topological differences between the different classes of channels as well as between channels and porters. The small numbers of TMSs in most channel-forming proteins reflect their oligomeric structures, while the larger numbers of TMSs in the carriers reflect their basically monomeric constructions.

The average numbers of TMSs for subclasses 9.A and 9.B are more representative of channel-like proteins than carriers suggesting that the majority of these proteins that prove to be transporters may prove to be channels. However, some will undoubtedly prove to be carriers, and a few may prove to function by novel mechanisms. The data in Figures 2 and 3 allow one to predict which class 9.A families will prove to be members of TC class 1 or 2.

It has been proposed that large complex transport systems arose progressively from smaller simpler ones (Saier, 2000b). Subclass 1.A channels could have developed from toxin-like peptide channels of subclass 1.C or holin-like channels of subclass 1.E, while subclass 1.A channels might have been the evolutionary precursors of porters. The latter proteins have more TMSs, and by virtue of their increased structural and functional complexity it is reasonable to propose that carriers arose from channels in a process that involved internal gene duplication events (Saier, 1994). In fact, sequence analyses have revealed the presence of internal repeat sequences in many of the proteins that comprise families of secondary and primary active transporters (Saier, 1994, 1998, 2001). The repeat units of these complex transporters resemble the full-length sequences of the simpler channels (Saier, 2000c). It is important to note that very few families of transporters include homologues that function in a capacity other than transport. Arguments that primary active transporters and group translocators resulted from superimposing catalytic proteins such as enzymes onto channels and carriers have been presented (Saier, 2000b)

III. SIZE VARIATIONS IN TRANSPORTERS IN THE DIFFERENT TC SUBCLASSES

Figure 4A provides an evaluation of the size ranges observed for the families that comprise the different subclasses of the TC system. Most families in TC subclass 1.A are of intermediate size (100 to 1000 residues per polypeptide chain), but a few are less than 100 or more than 1000 residues. In contrast, most transporter types in TC subclasses 1.C and 1.E are much smaller, and all of the 1.E. subclass proteins are small. Proteins of subclass 2.A are never smaller than 100 residues in length, and most exceed 500 residues. Those of subclass 9.A. more closely resemble the channels of subclass 1.A. These size differences reflect the topological differences reported in Figures 2 and 3.

Size variance is presented in Figure 4B. Variance is minimal for channel-forming subclasses 1.C and 1.E but substantially greater for subclass 1.A. The variance for proteins of subclass 2.A is comparable to that of the channels of subclass 1.A. Interestingly, that in subclass 9.A is minimal.

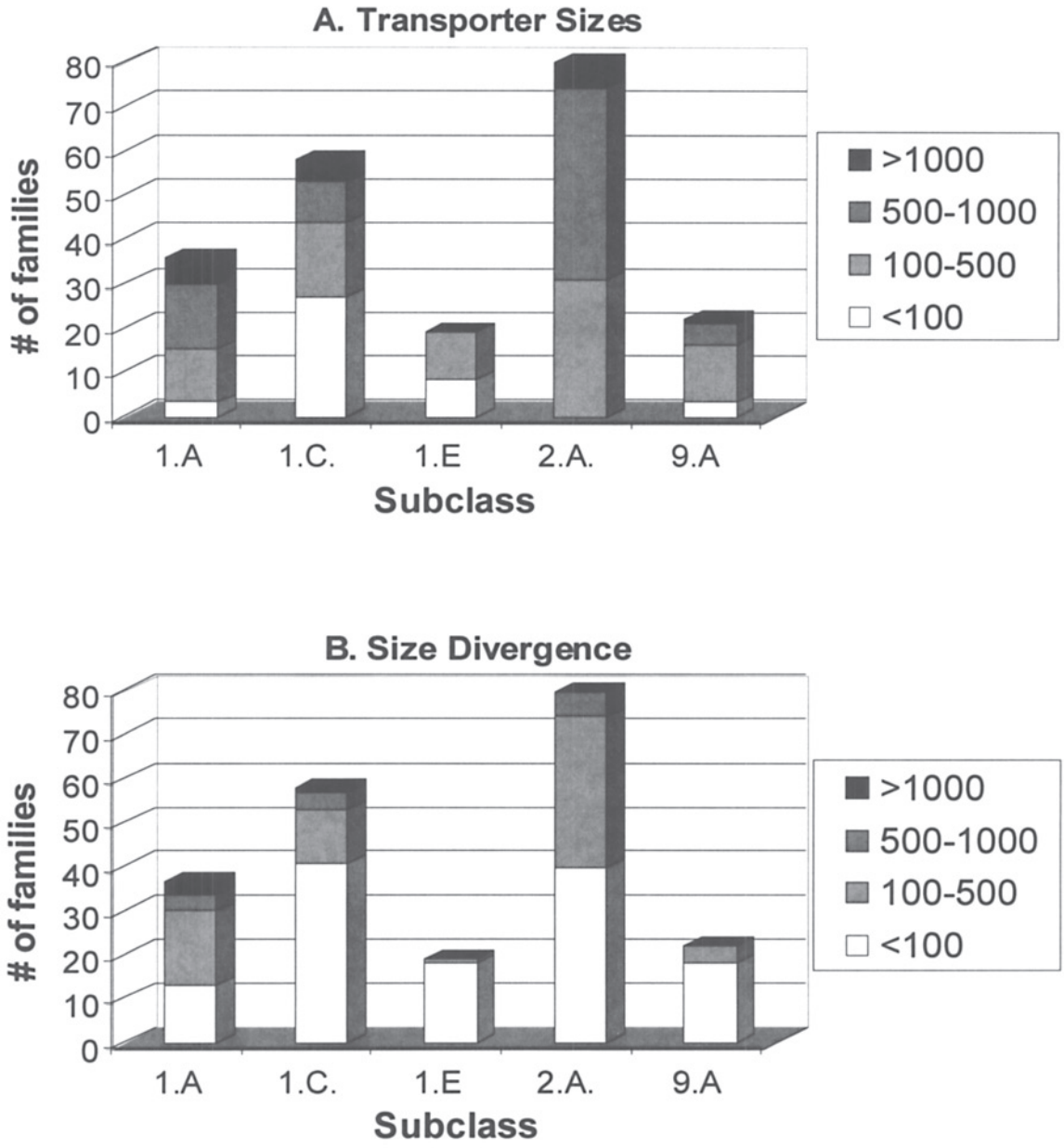

FIGURE 4. Schematic depiction of A, polypeptide sizes within the transporter families in selected TC subclasses, and B, the protein size variances observed for these same subclasses. (A) White (bottom) average size of <100 residues; light gray, average size between 100 and 500 residues; dark gray, average size between 500 and 1000 residues; black (top), average size greater than 1000 residues. B, white (bottom), variance <100 residues; light gray, variance between 100 and 500 residues; dark gray, variance between 500 and 1000 residues; black (top), variance greater than 1000 residues.

IV. CURRENT SIZES OF TRANSPORTER FAMILIES

As shown in Table 2, recognized transporter families differ over 3 orders of magnitude with respect to the numbers of currently sequenced proteins which comprise them. To examine the size distributions of the current transporter families, the data shown in figure 5 were compiled. The vast majority of the TC families are of intermediate size, having between 6 and 500 currently sequenced members. Only 66 families have five members or less. There are only 15 currently recognized families that include more than 500 sequenced protein members. Most of them are ubiquitous, having membership from all major domains of living organisms. Of the channels, the five largest families are the ubiquitous VIC, MIP and HSP70 families (TC#1.A.1, 1.A.8 and 1.A.33, respectively) as well as the eukaryotic-specific TRP-CC and LIC families (TC#1.A.4 and 1.A.9, respectively). Of the secondary active carriers, the MF (2.A.1), RND (2.A.8), DMT (2.A.7), NSS (2.A.22), MC (2.A.29), and MATE (2.A.68) superfamilies have the largest membership. Among the primary active carriers, the ABC (3.A.1), P-type ATPase (3.A.3) and COX families (3.D.4) have the greater family membership with decreasing numbers in this order. One putative transporter family (FAT (9.B.17)), the acyl-CoA synthase family, includes thousands of sequenced proteins, but a role of these proteins in transport is not well established (Saier and Kollmann, 1999). If these enzymes couple fatty acid uptake to coenzyme A thio-esterification, the process provides a second example of group translocation in which the substrate is modified during transport (Faergeman et al., 2001).

V. DISTRIBUTION OF TRANSPORTER FAMILIES IN THE THREE DOMAINS OF LIFE

The occurrence of transporter types in the three domains of life was evaluated by creating a plot which shows the representation of the members of a family in the three domains of living organisms, the bacteria, the archaea, and the eukaryotes. Table 3 provides compilations for each of the different subclasses within the TC system, while Figure 6 evaluates the entire TC system. Most ubiquitous families are found within subclass 2A. We propose that this fact reflects the larger polypeptide sizes of these usually monomeric proteins. The smaller oligomeric channel-forming proteins may have undergone more extensive sequence divergence leading to the appearance of multiple families exhibiting insufficient degrees of sequence similarity to allow establishment of homology. Larger protein size facilitates distant phylogenetic relationship detection, and requirements for retention of specific functional properties restrict the natural process of sequence divergence that occurs over evolutionary time.

Most of the channels in class 1 are restricted to specific organismal types. This fact may in part reflect the ease with which simple channel-like functions can be generated *de novo* from small peptides. It may also reflect the absence of strict constraints preventing sequence divergence.

As illustrated in Figure 6, bacterial specific transport protein families are more prevalent than are those found only in eukaryotes (47% vs. 26%). This could be a reflection of evolutionary pressure forcing bacteria to maintain diversity in order to remain adaptive in response to a wide range of environmental stress conditions. Multicellular eukaryotes generally create internal

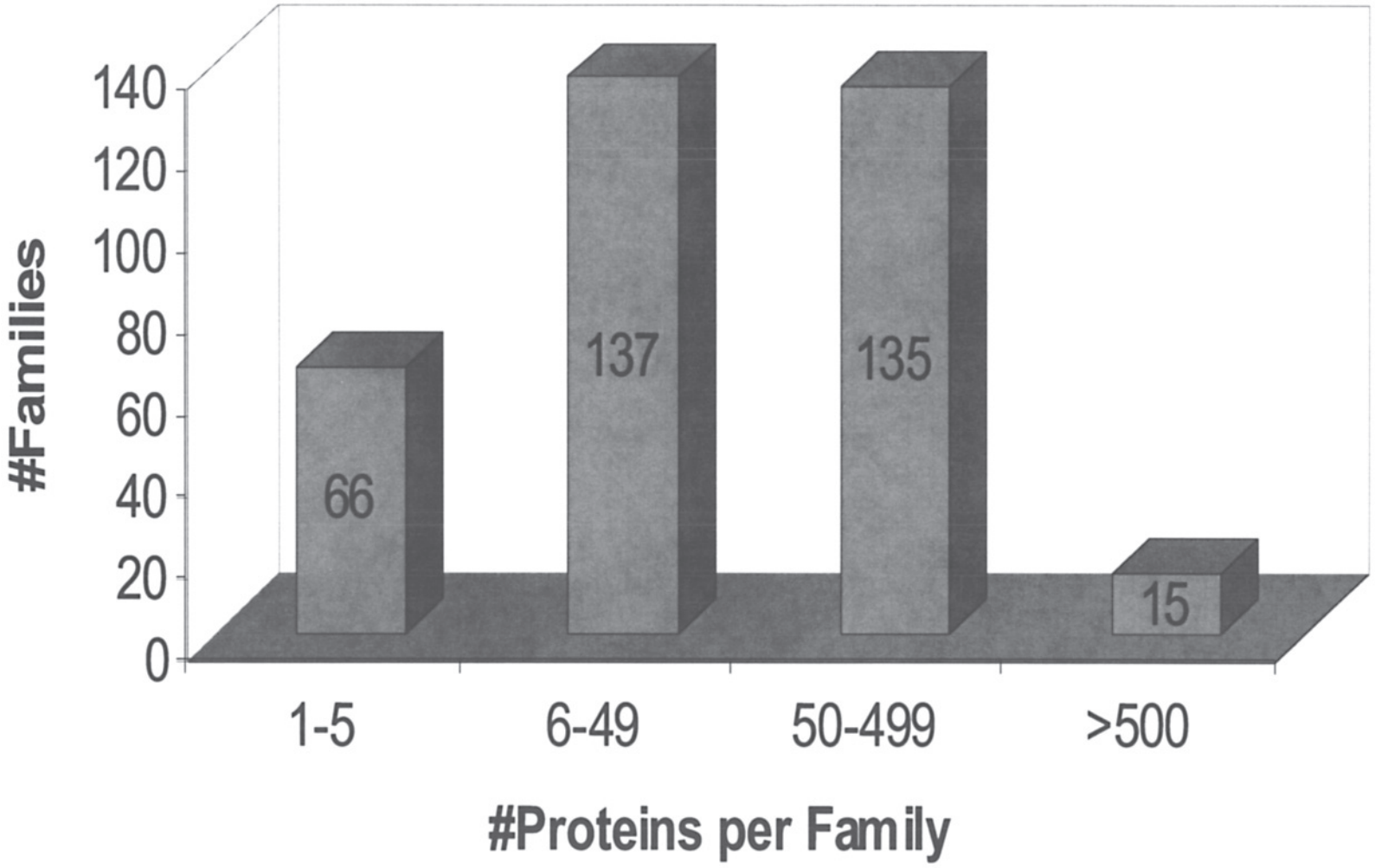

FIGURE 5. Family size distribution for all families found in the TC system. As of January, 2002, 66 families have five sequenced members or less; 137 families have between 6 and 49 members; 135 have between 50 and 499 members; and only 15 have over 500 sequenced members.

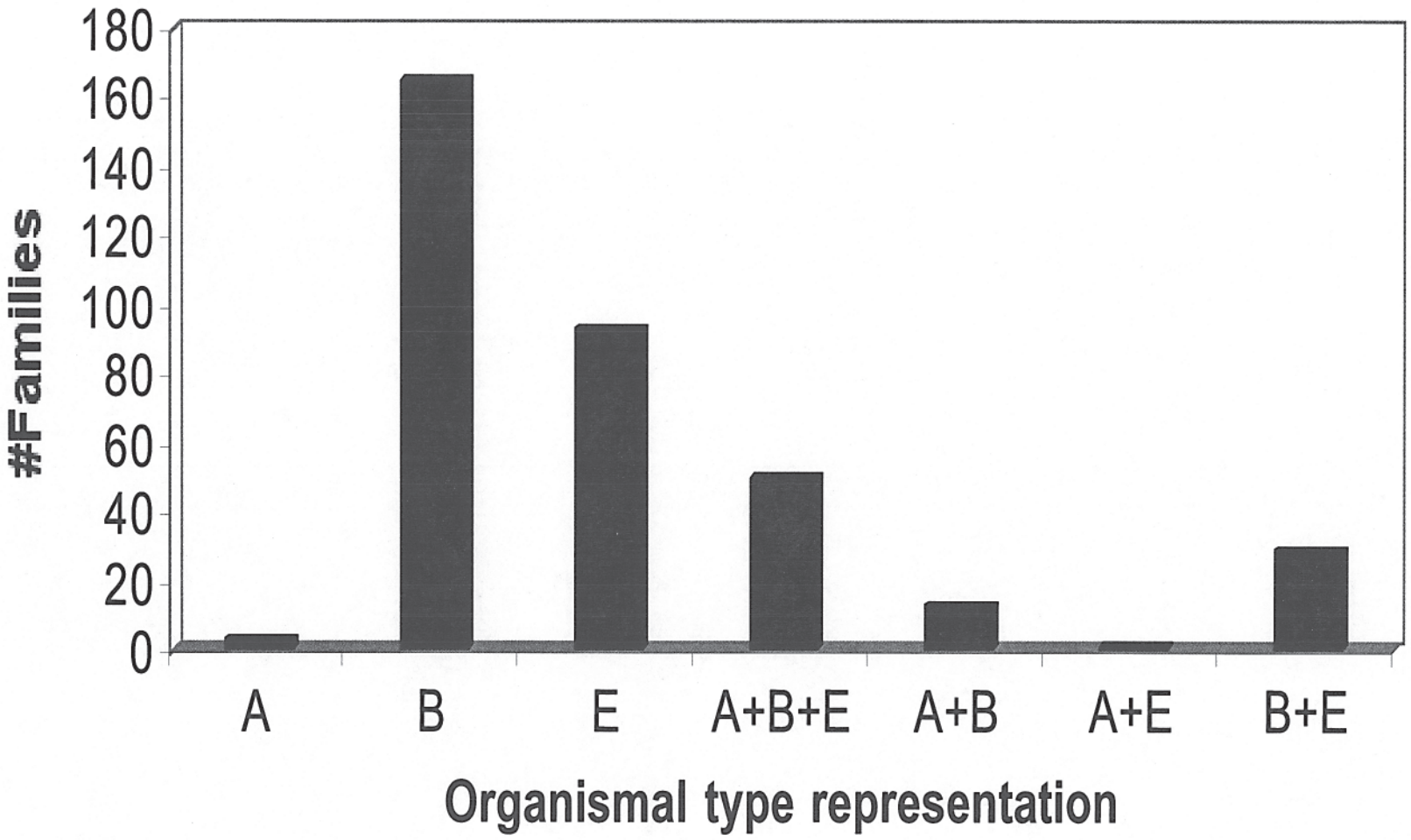

FIGURE 6. Distribution of family membership within the three domains of living organisms for all TC families. (A) archaea; (B) bacteria, and (E) eukaryotes.

TABLE 3
Distribution of Transporter Families in the Three Domains of Living Organisms[1]

TC Subclass	Organismal Distribution						
	B	E	A	B, E	B, A	E, A	B, E, A
1.A	5	25	0	2	0	0	5
1.B	30	4	0	0	0	0	0
1.C	34	23	0	1	0	0	0
1.D	5	5	0	0	0	0	0
1.E	18	0	0	0	0	0	0
2.A	25	12	0	8	4	0	31
2.B	7	0	0	0	0	0	0
3.A	6	2	0	1	0	0	5
3.B	0	0	0	0	1	0	0
3.C	0	0	1	0	0	0	0
3.D	2	0	2	4	1	1	1
4.A	6	0	0	0	0	0	0
5.A	1	0	0	0	1	0	0
5.B	0	0	0	1	0	0	0
8.A	7	4	0	1	0	0	1
9.A	11	9	0	0	2	0	1
9.B	8	9	0	11	4	0	6
Total	165	93	3	29	13	1	50
%	47%	26%	1%	8%	4%	0, 3%	14%

[1]B, bacteria; E, eukaryotes; A, archaea; B, E, bacteria and eukaryotes but not archaea; B, A, bacteria and archaea but not eukaryotes; E, A, eukaryotes and archaea but not bacteria; B, E, A, ubiquitous; found in all three domains. Note: Some entries in Table 2 were updated after the compilation presented here was completed.

homeostatic environments that obviate the need for extensive cellular stress response mechanisms. The greater diversity of prokaryotic transporters may also reflect the greater period of evolutionary time that these organisms have been on Earth. Eukaryotes may have evolved from a limited subgroup of primordial bacteria, and these bacteria may not have exhibited the full complement of prokaryotic transporter families. Alternatively, eukaryotes may have lost families that were present in the eukaryotic progenitor. Although eukaryotes exhibit fewer families than prokaryotes, they have proliferated tremendous numbers of paralogues within certain families, probably for very specific purposes involving tissue-specific and organelle-specific functions (*C. elegans* sequence consortium, 1998).

There are very few archaeal-specific transporter families. This may in part be a reflection of the fact that functional data are sparse for archaeal proteins. The focus of molecular biological research over the last 6 decades has been concerned almost exclusively with bacterial and eukaryotic systems. However, if archaea arose from primordial bacteria, they may have acquired a restricted subset of proteins from the ancestral bacterium, and they then would have had less time to diversify. This interesting postulate should be subject to empirical re-

search. It should be noted that recognition of a transporter family is facilitated by the availability of genomic sequence data only if functional data are available.

Ubiquitous families (A+B+E in Figure 6) represent 14% of the total, while those represented in just two of the domains of life are still less numerous with those shared by bacteria and eukaryotes (8%) exceeding those shared by archaea and bacteria (4%) by twofold. Only one family (0.3%) is found only in the archaeal and eukaryotic domains. Some of these families found in just two domains will undoubtedly prove to be ubiquitous when more sequence data and more sensitive search tools become available.

VI. TRANSPORT PROTEINS FOR WHICH THREE-DIMENSIONAL STRUCTURAL DATA ARE AVAILABLE

Detailed structural data on transport proteins will be necessary in order to gain an ultimate understanding of transport processes. Unfortunately, very few membrane proteins have yielded to the techniques of the X-ray crystallographer.

Despite the fact that integral membrane proteins comprise about one-third of all proteins, less than 2% of the available 3-D structures are for such proteins. These transporters are listed in Table 4.

VII. CONCLUSIONS AND PERSPECTIVES

The TC system displayed in TCDB (http://tcdb.ucsd.edu) allows any researcher to easily gain access to the extensive body of knowledge available for transport systems. With the tools we provide on our websites, one can convincingly view the relationships between the established transporters in the TC system and novel proteins that recently have been or will soon be sequenced or discovered. A valuable tool for this purpose is TC-Blast that performs a Blast search against TCDB, revealing the nearest homologues and the families in the TC system to which the query sequences belong. There are also a number of other programs available on our website which help to bring to light the features of newly discovered transporters (e.g., WHAT, AveHAS, BBF, TV, etc.). The interested reader is invited to view our web site to familiarize herself or himself with these tools.

Due to the nature of transporters as integral membrane proteins, we believe that computational approaches will prove useful particularly for their structural elucidation. Phylogenetic analyses should reveal structure/function relationships that greatly facilitate empirical research. With the availability of better tools, it will be easier to track phylogenetic relationships and the pathways by which proteins have evolved. Tracking the evolutionary pathways taken for the appearance of topologically dissimilar proteins within a family and for families of transporters exhibiting dissimilar mechanisms of action will prove to be a daunting but highly worthwhile endeavour. For this purpose it will be important to create new and more reliable topological prediction programs as well as programs that allow detection of very distant phylogenetic relationships (Pei and Grisham, 2001).

Another crucial aspect of analysing relationships between families, and even classes of families, will involve designing a broad-based dataset of proteins within each family in an accurate but automated way. We are currently designing such software for the TC system. If the datasets for the different families are sufficiently extensive

TABLE 4
Transport Proteins for Which High-Resolution 3-Dimensional Structural Data Are Available

TC Number	Protein	Family	Source	PDB code
1.A. α-type channels				
1.A.1.1.1	K^+ channel, KscA	VIC	*Streptomyces lividans*	1BL8
1.A.8.1.1	Glycerol Channel, GlpF	MIP	*E. coli*	1FX8
1.A.8.8.1	Aquaporin 1	MIP	*Homo sapiens*	1FQY
1.A.9.1.1	Acetylcholine receptor*	LIC	*Torpedo californica*	3MRA
1.A.11.5.1	ClC Chloride Channel	ClC	*E. coli*	1KPK
1.A.11.5.1	ClC Chloride Channel	ClC	*Salmonella typhimurium*	1KPL
1.A.21.1.1	Apoptosis regulator, Bcl-X(L)	Bcl-2	*Homo sapiens*	1MAZ
1.A.22.1.2	Mechanosensitive channel	MscL	*Mycobacterium tuberculosis*	1MSL
1.B. β-barrel porins				
1.B.1.1.1	Porin (OmpC)	GBP	*E. coli*	1IIV (Theo.)
1.B.1.1.2	Porin (PhoE)	GBP	*E. coli*	1PHO
1.B.1.1.3	Porin (OmpF)	GBP	*E. coli*	1OPF
1.B.3.1.1	Maltoporin (LamB)	SP	*Salmonella typhimurium*	1MAL
1.B.6.1.1	Porin (OmpA)	OOP	*E. coli*	1BXW
1.B.7.1.1	Porin (PorCa)	RPP	*Rhodobacter capsulatus*	2POR
1.B.14.1.4	FhuA ferrichrome receptor	OMR	*E. coli*	1BY5
1.C. Pore-forming protein and peptide toxins				
1.C.1.1.1	Colicin Ia	Colicin	*E. coli*	1CII
1.C.1.2.2	Colicin E1	Colicin	*E. coli*	1COL
1.C.1.2.2	Cry 1Aa	ICP	*Bacillus thuringiensis*	1CIY
1.C.2.2.1	Cry 3Aa	ICP	*Bacillus thuringiensis*	1DLC
1.C.3.1.1	α-Hemolysin	αHL	*Staphylococcus aureus*	7AHL
1.C.4.1.1	Aerolysin	Aerolysin	*Aeromonas hydrophila*	1PRE
1.C.18.1.1	Melittin	CAP	*Apis melifera*	2MLT
1.C.19.1.1	Defensin	CAP	*Homo sapiens*	1DFN
1.D. Non-ribosomally synthesized channels				
1.D.1.1.1	Gramicidin A	Gramicidin	*Bacillus brevis*	1GMK
1.D.5.1.1	Alamethicin	Alamethicin	*Trichoderma viride*	1AMT
3.A. P-P-bond hydrolysis-driven transporters				
	F_1F_0 ATP synthase subunit C	F-ATPase	*E. coli*	1A91, 1QO1
3.A.3.2.4	Ca ATPase, SR	P-ATPase	*Oryctolagus cuniculus*	1EUL
3.D. Redox-driven proton pumps				
3.D.3.2.1	Quinol:cytochrome c reductase	QCR	*Bos taurus*	1BGY, 1QCR, 1BCC
3.D.4.2.1	Cytochrome c oxidase	COX	*Thermus thermophilus*	1EHK
3.D.4.6.1	Cytochrome c oxidase	COX	*Paracoccus denitrificans*	1AR1
3.D.4.7.1	Cytochrome c oxidase	COX	*Bos taurus*	1QLE
3.E. Light-driven proton pumps				
3.E.1.1.1	Bacteriorhodopsin	MR	*Halobacterium salinarum*	1BRX, 2BRD, 1AP9, 1AT9, 1BRD
3.E.1.2.1	Halorhodopsin	MR	*Halobacterium salinarum*	1E12
3.E.1.3.1	Sensory rhodopsin	MR	*Halobacterium salinarum*	1HG8
3.E.2.1.1	Reaction center	RC	*Rhodobacter sphaeroides*	2RCR, 4RCR
3.E.2.1.1	Reaction center	RC	*Rhodopseudomonas viridis*	1PRC

*Only low-resolution structural data are available for this protein.

and reliable, we will be able to derive accurate sequence motifs and patterns that characterize a family and have structural/functional significance. New approaches for characterizing families will undoubtedly come to light.

Research into the molecular basis of transport processes can be greatly facilitated using *in silico* approaches. Such approaches are likely to reveal information present in primary protein sequences that are currently masked due to our limited understanding of proteins and the inadequacies of currently available computational technologies. Bioinformatic advances should facilitate, for example, the development of transport protein specific drugs, thereby providing a basis for a new class of antibiotic, antiprotozoan and antifungal substances. Many other unforeseen advances can be anticipated.

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