Unified inventory of established and putative transporters encoded within the complete genome of *Saccharomyces cerevisiae*

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Abstract We present the complete inventory of currently recognized and putative transporters encoded within the genome of *Saccharomyces cerevisiae*. These 258 transporters are classified into 42 families according to phylogenetic and substrate specificity criteria. Twelve of these yeast families are found only in eukaryotic organisms, and four are so far unique to yeast. Putative yeast-specific families transport heavy metals, arsenite and calcium. The phylogenetic analyses reported allow classification of 139 functionally uncharacterized yeast transporters into families of known functions. The relative proportions of yeast transporters specific for different classes of substrates differ only slightly from those reported for *Escherichia coli*. However, the ratio of secondary transporters (uniporters, cation symporters and antiporters) to primary ATP-driven transporters is much higher for yeast than for bacteria.

Key words: Yeast transporter; Phylogenetic classification; Genome analysis

1. Introduction

All living cells communicate with their environments, and eukaryotic cells additionally require communication between the cytoplasmic and intraorganellar compartments. Transmembrane communication is in part effected by solute-specific transport systems of several distinct types [1,2]. In a previous communication from one of our laboratories we analyzed prokaryotic microbial genomes for genes encoding established and putative transport systems [3]. Several additional publications have dealt with the description of specific types of transporters in *Saccharomyces cerevisiae*. For example, three publications have considered secondary carriers of *S. cerevisiae*, but two of these were published prior to the completion of the genome sequencing project [4,5], and the third did not apply strict phylogenetic criteria for the subclassification of the major facilitator superfamily [6]. Phylogenetic criteria have been used for the description of sugar porters [7], multidrug:H^+ antiporters [8], ATP-binding cassette transporters [9], and P-type ATPases [10]. The large family of yeast mitochondrial carriers was described in a distinct publication [11]. Global phylogenetic analyses of bacterial and eukaryotic members of the major facilitator, ABC and P-type ATPase superfamilies have also been reported [12–16].

In recent publications, we have devised a systematic approach to transporter classification based on both phylogeny and function [1,2]. This system has the advantage of being applicable to all transporter types found in nature. We initially classify transport systems on the basis of transport mode and energy coupling mechanism; the second level of classification is based on phylogenetic family; the third level of classification is based on phylogenetic subfamily or cluster, and the final level is based on substrate specificity. This system, termed the 'Transport Commission' (TC) system, resembles that of the 'Enzyme Commission' (EC) [17] except that phylogenic parameters have been introduced. In this paper we apply the TC system of classification to all recognized transporters encoded within the *S. cerevisiae* genome [18,19], and compare the relative proportions of the various transporter types to those of the prototypical bacterium, *Escherichia coli*.

2. Methods

The computational methods used for genome analysis have been described previously [3]. These approaches were confirmed using the methods described by Nelissen et al. [6]. Family designations used in the present publication are those described by Saier [1,2] (see our web site: http://www-biology.ucsd.edu/~msaier/transport/titlepage.html). Criteria for family assignment have been described in detail and will not be reported here ([1,2]; see above-mentioned web site). Detailed descriptions of yeast transporter representation in these various families are presented in a separate web site (http://www-biology.ucsd.edu/~ipaulsen/transport/titlepage.html). Previously published web sites specifically describing yeast transporters are available (http://www.mips.biochem.mpg.de/mips/yeast/yeast_main.htmlx). Attempts are currently being made to unify nomenclature and classification methods among web sites in accordance with those recommended by the transport commission and described here.

Table 1
Abundance of proteins of differing predicted membrane topologies encoded within the genomes of *S. cerevisiae* and *E. coli*

# TMSs	# Proteins		% of Total	
	Yeast[b]	*E. coli*[a]	Yeast[b]	*E. coli*[a]
0	4364	2861	70.8	66.8
1	937	655	15.3	15.3
2–3	390	220	6.5	5.1
4–6	185	211	3.1	4.9
7–9	144	153	2.3	3.6
>10	121	182	2.0	4.3
Total	6141	4282	100.0	100.0

[a] From Paulsen et al. [3].
[b] From the present study using the same prediction algorithm as in Paulsen et al. [3].

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3. Comparative hydropathy analyses of yeast and bacterial open reading frames

Table 1 summarizes the abundance of recognized yeast transport proteins of differing predicted membrane topologies. Approximately 71% of the proteins are predicted to be soluble. Of the remaining 29%, about half are predicted to span the membrane only once. These proteins include many with putative N-terminal signal peptides [20,21]. The remaining 14% exhibit two or more predicted transmembrane spanners (TMSs) and represent the most likely candidates for transmembrane solute transporters (Table 1). Approximately 850 proteins fall into this category. As noted below, we have identified 258 of these proteins as established or putative transporters and have assigned them to recognized families. Table 1 also reveals a general similarity in the numbers and distribution of proteins with various predicted TMSs in *S. cerevisiae* and *E. coli*. The only significant difference is a lower number of proteins with two or three TMSs and a higher number of proteins with four or more TMSs in *E. coli*.

4. Recognized families of transporters represented in *S. cerevisiae*

Tables 2 and 3 lists the transporter families represented within the yeast genome. Of the 21 currently recognized channel-type transporter families (category 1) only three are represented in yeast: the MIP family (TC# 1.1) which includes members specific for water and small neutral solutes [22], the VIC family (TC# 1.5) which includes a K^+-specific member [23] as well as a putative Ca^{2+}-specific member, and the ClC family in which all functionally characterized members transport Cl^- [15]. A total of seven recognized channel proteins, all included within these three families, are encoded within the yeast genome.

Table 2
Transporter families represented in the genome of *S. cerevisiae*[a]

Name of family	Abbreviation	TC#	# of members in *S. cerevisiae*	Systematic ORF name	Gene name	Substrate(s)/description	Occurrence[b]
Category 1. Channel-type transporters							
Major intrinsic protein	MIP	1.1	4	YFL054c	–[c]	Glycerol?	B, A, E
				YLL043w	*FPS1*	Glycerol; water	
				YLL052/053c	–	Water?	
				YPR192w	–	Water?	
Voltage-sensitive ion channel	VIC	1.5	2	YGL093c	*TOK1*	K^+	B, A, E
				YGR217w	*CCH1*	Ca^{2+} (α-subunit)	
Chloride channel	ClC	1.10	1	YJR040w	*GEF1*	Cl^-	B, A, E
Category 2. Carrier-type transporters							
Major facilitator[d]	MF	2.1	78				B, A, E
Subfamily							
Sugar porter	SP	2.1.1	33	YBR241c	–		B, A, E
				YBR298c	*MAL31*	Maltose/H^+ symporter (high-affinity)	
				YDL138w	*RGT2*	Glucose?	
				YDL194w	*SNF3*	Glycase? (high affinity)	
				YDL199c	–		
				YDL245c	*HXT15*		
				YDL247w	–		
				YDR342c	*HXT7*	Hexoses (high-affinity)	
				YDR343c	*HXT6*	Hexoses (high-affinity)	
				YDR345c	*HXT3*	Hexoses (low-affinity)	
				YDR387c	–		
				YDR497c	*ITR1*	Myo-inositol (major)	
				YDR536w	*STL1*		
				YEL069c	*HXT13*		
				YFL011w	*HXT10*	Hexoses	
				YFL040w	–		
				YGL104c	–		
				YGR289c	*AGT1*	α-Glucosides (general)	
				YHR092c	*HXT4/LGT1/RAG1*	Hexoses (moderate- to low-affinity)	
				YHR094c	*HXT1*	Hexoses (low-affinity)	
				YHR096c	*HXT5*		
				YIL170/171w	*HXT12*		
				YJL214w	*HXT8*		
				YJL219w	*HXT9*	Hexoses?	
				YJR158w	*HXT16*	Similar to hexose permeases	
				YJR160c	–		
				YLR081w	*GAL2/IMP1*	Galactose (and glucose)	
				YMR011w	*HXT2*	Hexoses (high-affinity)	
				YNL318c	*HXT14*		
				YNR072w	*HXT17*		
				YOL103w	*ITR2*	Myo-inositol (minor)	
				YOL156w	*HXT11/LGT3*	Glucose (low-affinity)	

Table 2 (*continued*)
Transporter families represented in the genome of *S. cerevisiae*[a]

Name of family	Abbreviation	TC#	# of members in *S. cerevisiae*	Systematic ORF name	Gene name	Substrate(s)/description	Occurrence[b]
Drug:H^+ antiporter (14 spanner)	DHA14	2.1.2	10	YBR293w	–		B, A, E
				YCL069w	–		
				YDR119w	–		
				YGR224w	–		
				YKR105c	–		
				YML116w	*ATR1*/*SNQ1*	Aminotriazole and 4-nitroquinoline resistance	
				YMR088c	–		
				YMR279c	–		
				YOR378w	–		
				YPR198w	*SGE1*/*NOR1*	Crystal violet resistance	
Drug:H^+ antiporter (12 spanner)	DHA12	2.1.3	14	YBR008c	*FLR1*	Fluconazole resistance	B, E
				YBR043c	–		
				YBR180w	–		
				YCR023c	–		
				YGR138c	–		
				YHR048w	–		
				YIL120w	–		
				YIL121w	–		
				YJR124c	–		
				YLL028w	–		
				YNL065w	–		
				YNR055c	*HOL1*	Histidinol and Na^+ resistance	
				YOR273c	–		
				YPR156c	–		
Phosphate:H^+ symporter	PHS	2.1.9	2	YCR098c	*GIT1*	Involved in inositol metabolism	B, A, E
				YML123c	*PHO84*	Phosphate (high-affinity)/ H^+ symporter	
Sialate:H^+ symporter	SHS	2.1.12	1	YKL217w	*JEN1*	Lactate	B, E
Monocarboxylate porter	MCP	2.1.13	4	YKL221w	–		
				YNL125c	*ESBP6*	Monocarboxylates?	E
				YOL119c	–		
				YOR306c	–		
Anion:cation symporter	ACS	2.1.14	8	YAL067c	*SEO1*	Suppressor of sulfoxide ethionine resistance	E
				YCR028c	*FEN2*	Involved in fenpropimorph resistance	
				YGR065c	–		
				YGR260w	–		
				YIL166c	–		
				YJR152w	*DAL5*/*UREP1*	Allantoate and ureido-succinate	
				YLL055w	–		
				YLR004c	–		
Unknown major facilitator	UMF	2.1.15	6	YCL070/73c	–		E (Y)
				YEL065w	–		
				YHL040c	–		
				YHL047c	–		
				YKR106w	–		
				YOL158c	–		
Amino acid-polyamine-choline[e]	APC	2.3	24	YBR068c	*BAP2*	Branched-chain amino acids (leucine, valine and isoleucine)	B, A, E
				YBR069c	*VAP1*/*TAT1* *TAP1*	Valine, leucine, isoleucine, tyrosine and tryptophan	
				YBR132c	*AGP2*	Amino acids (general)	
				YCL025c	*YCC5*	Asparagine; glutamine	
				YDL210w	*UGA4*	GABA (high-affinity)	
				YDR046c	*PAP1*	Isoleucine, valine	
				YDR160w	–		
				YDR508c	*GNP1*	Glutamine (high-affinity)	
				YEL063c	*CAN1*	Arginine, lysine, ornithine and canavanine	

Table 2 (*continued*)
Transporter families represented in the genome of *S. cerevisiae*[a]

Name of family	Abbreviation	TC#	# of members in *S. cerevisiae*	Systematic ORF name	Gene name	Substrate(s)/description	Occurrence[b]
				YFL055w	*AGP3*	Amino acids (general)	
				YGL077c	*HNM1/CTR1*	Choline	
				YGR055w	*MUP1*	Methionine (high-affinity)	
				YGR191w	*HIP1*	Histidine	
				YHL036w	*MUP3*	Methionine (low-affinity)	
				YKL174c	*YKL174c*	Choline?	
				YKR039w	*GAP1*	Amino acids (general) [naturally occurring L-amino acid, γ-aminobutyrate, ornithine, citrulline, some D-amino acids and some toxic analogues]	
				YLL061w	–		
				YNL268w	*LYP1*	Lysine (high-affinity)	
				YNL270c	*APL1/ALP1*	Basic amino acids	
				YNR056c	*BIO5*	Involved in biotin synthesis	
				YOL020w	*TAT2/SCM2/ TAP2/LTG3*	Tryptophan (high-affinity)	
				YOR348c	*PUT4*	Proline and γ-aminobutyrate (high-affinity)	
				YPL265w	*DIP5*	Dicarboxylic amino acids	
				YPL274w	–		
Cation diffusion facilitator	CDF	2.4	5	YDR205w	–		B, A, E
				YMR177w	*MMT1*	Metal ions (Fe^{2+}) (mitochondrial)	
				YMR243c	*ZRC1*	Zn^{2+}/Cd^{2+}	
				YOR316c	*COT1*	Co^{2+}	
				YPL224c	*MMT2*	Metal ions (Fe^{2+}) (mitochondrial)	
Zinc (Zn^{2+})-iron (Fe^{2+}) permease	ZIP	2.5	2	YGL255w	*ZRT1*	Zn^{2+}	E
				YLR130c	*ZRT2*	Zn^{2+}	
Tellurite-resistance/ dicarboxylate transporter	TDT	2.16	1	YPL092w	*SSU1*	Sulfite?	B, A, E
Proton-dependent oligopeptide transporter	POT	2.17	1	YKR093w	*PTR2*	Peptides	B, E
Amino acid/auxin permease	AAAP	2.18	7	YBL089w	–	Amino acids?	E
				YEL064c	–	Amino acids?	
				YER119c	–	Amino acids?	
				YIL088c	–	Amino acids?	
				YJR001w	–	Amino acids?	
				YKL146w	–	Amino acids?	
				YNL101w	–	Amino acids?	
Ca^{2+}:cation antiporter	CaCA	2.19	4	YDL128w	*VCX1*	H^+/Ca^{2+} antiporter (vacuolar)	B, A, E
				YDL206w	–	Na^+/Ca^{2+} antiporter?	
				YJR106w	*ECM27*	Na^+/Ca^{2+} antiporter?	
				YNL321w	–	H^+/Ca^{2+} antiporter?	
Inorganic phosphate transporter	PiT	2.20	1	YBR296c	–	Phosphate	B, A, E
Solute:sodium symporter	SSS	2.21	1	YHL016c	*DUR3*	Urea	B, A, E
Mitochondrial carrier[f]	MC	2.29	34	YBL030c	*AAC2*	ADP/ATP antiporter	E
				YBR085w	*AAC3*	ADP/ATP antiporter	
				YBR104w	*YMC2*		
				YBR192c	*RIM2*		
				YBR291c	*CTP1*	Citrate	
				YDL119c	–		
				YDL198c	*YHM1*		
				YEL006c	–		
				YER053c	–		
				YFR045w	–		
				YGR096w	–		
				YGR257c	–		
				YHR002w	–		
				YIL006w	–		
				YIL134w	*FLX1*	FAD	
				YJL133w	*MRS3*		
				YJR095w	*ACR1*		

Table 2 (*continued*)
Transporter families represented in the genome of *S. cerevisiae*[a]

Name of family	Abbreviation	TC#	# of members in *S. cerevisiae*	Systematic ORF name	Gene name	Substrate(s)/description	Occurrence[b]
				YJRO77c	*MIR1*	Phosphate	
				YKL120w	*PMT1*		
				YKR052c	*MSR4*		
				YLR348c	*DTP*	Dicarboxylates	
				YMR056c	*AAC1*	ADP/ATP antiporter	
				YMR166c	–		
				YMR241w	–		
				YNL003c	*PET8*		
				YNL083w	*YNG2*		
				YOR100c	–		
				YOR130c	*ARG11*		
				YOR222w	–		
				YPL134c	–		
				YPR011c	–		
				YPR021c	–		
				YPR058w	*YMC1*		
				YPR128c	–		
Cation-chloride cotransporter	CCC	2.30	1	YBR235w	–	Na^+-K^+-Cl^-?	B, E
Anion exchanger	AE	2.31	1	YNL275w	–	Anions?	E
Monovalent cation:proton antiporter-1	CPA1	2.36	2	YDR456w	*NHX1*	Na^+/H^+ antiporter	B, A, E
				YLR138w	*NHA1*	Na^+/H^+ antiporter	
Monovalent cation:proton antiporter-2	CPA2	2.37	1	YJL094c	–	Na^+/H^+ antiporter	B, A, E
K^+ transporter	Trk	2.38	2	YJL129c	*TRK1*	K^+/H^+ symporter	B, A, E
				YKR050w	*TRK2*	K^+/H^+ symporter	
Nucleobase:cation symporter-1	NCS1	2.39	9	YBL042c	*YBC2*	Uridine (nucleoside)	B, A, E
				YBR021w	*FUR4*	Uracil	
				YER056c	*FCY2*	Cytosine/purines	
				YER060w	*FCY21/22*	Cytosine/purines?	
				YGL186c	–	Cytosine/purines?	
				YIR028w	*DAL4*	Allantoin	
				YLR237w	*THI10*	Thiamin	
				YOR071c	–	Thiamin?	
				YOR192c	*THIY*	Thiamin	
Formate-nitrite porter	FNP	2.44	1	YHL008c	–	Acetate/H^+ symporter	B, A, E
Metal ion transporter	MIT	2.45	3	YKL050c	*ALR2*	Al^{3+}	B, A, E
				YKL064w	*MNR2*	Mn^{2+}	
				YOL130w	*ALR1*	Al^{3+}	
Divalent anion:Na^+ symporter	DASS	2.47	4	YCR037c	*PHO87*	Phosphate	B, A, E
				YIL047c	*SYG1*		
				YJL198w	–	Phosphate?	
				YNR013c	–	Phosphate?	
Ammonium transporter	Amt	2.49	3	YGR121c	*MEP1*	NH_4^+	B, A, E
				YNL142w	*MEP2*	NH_4^+	
				YPR138c	*MEP3*	NH_4^+	
Triose phosphate translocator	TPT	2.50	3	YJL193w	–	Triose-phosphates?	E
				YML038c	–	Triose-phosphates?	
				YOR307c	*SYL41*	Triose-phosphates?	
Sulfate permease	SulP	2.53	4	YBR294w	*SUL1*	SO_4^{2-}	B, E
				YGR125w	–		
				YLR092w	*SUL2*	SO_4^{2-}	
				YPR003c	–	SO_4^{2-}?	
Mitochondrial tricarboxylate carrier	MTC	2.54	1	YOR271c	–	Tricarboxylates	E
Acetyl-coenzyme A transporter	AcCoAT	2.55	1	YBR220c	–	Acetyl coenzyme A?	B, E
Arsenical resistance-3	ACR3	2.59	1	YPR201w	*ACR3*	Arsenite	E (Y)

[a]The complete description of these families can be found on our web site (see Section 1).
[b]B, bacteria; A, archaea; E, eukaryotes; (Y), yeast only.
[c]Dashed lines (–) indicate that a gene designation is not available.
[d][4–6,13].
[e][5,6].
[f][11]

Secondary carriers (category 2) represent the major type of transporter found in yeast. One hundred and ninety-five of the 258 recognized transporters are secondary carriers, and of these, 78 belong to the major facilitator (MF) superfamily (TC# 2.1) [6,13]. Within this large superfamily, eight of the 18 currently recognized families [13] are represented in yeast. The members in these eight families are listed in Tables 2 and 3.

Twenty-five additional secondary carrier families are represented in yeast (TC# 2.3–2.59). Among these families are the large mitochondrial carrier (MC) family with 34 yeast members [11] and the amino acid-polyamine-choline (APC) family [24] with 24 yeast members (TC# 2.29). The next largest family, the amino acid/auxin permease (AAAP) (TC# 2.18) (Young et al., manuscript in preparation) has seven recognized yeast members. All of the 22 remaining families have between one and four members.

Three families of ATP-dependent primary carriers (category 3) are represented in Table 3. These include the ABC superfamily (TC# 3.1) with 22 members encoded within the yeast genome [9], and the P-ATPase family (TC# 3.3) with 16 members [10]. The F-ATPase family (TC# 3.2) includes just one mitochondrial (F-type) member and one vacuolar (V-type) member. These H^+ transport complexes contain 12 and 13 subunits, respectively [25].

Two remaining active transporters are electron flow-driven proton carriers, one within the coenzyme Q:cytochrome *c* reductase (QCR) family (TC# 6.3) and the other within the cytochrome oxidase (COX) family (TC# 6.4). These two yeast protein complexes are present in mitochondria and have 10 and 12 subunits, respectively [25].

Three genes apparently encode homologous mitochondrial outer membrane porins. These three porins are members of the mitochondrial and plastid porin (MPP) family (TC# 9.8). POR1 has been shown to be the principal porin in *S. cerevisiae*. POR2 and TOM40 are probably expressed at low levels [26–28].

Five of the remaining families presented in Table 3 include recognized transporters of unknown transport mode or energy coupling mechanism. They consequently belong to category 99 [1,2]. Each of the last two families listed in Table 3 includes a single putative transporter. Evidence that these proteins are transporters is substantial but not compelling. These two proteins are therefore assigned to category 100 (see our www site). The members of all seven of these ill-defined families are believed to transport di- and trivalent cations, mostly heavy metals.

Of the 42 transporter families that we have identified as a result of the *S. cerevisiae* genome analyses reported, a majority (24) have representation in the three kingdoms of life: bacteria, archaea, and eukaryotes (Tables 2 and 3). Moreover, six more families are represented in both bacteria and eukaryotes, and these may prove to be present in archaea as well. Twelve of the 42 families are eukaryotic-specific, and four of these are at present restricted to *S. cerevisiae*. One family, the unknown major facilitator (UMF; TC# 2.1.15), within the major facilitator superfamily (TC# 2.1) has similarly been identified only in yeast (Table 2). The families that are found only in eukaryotes may have arisen in eukaryotes or may alternatively have diverged from their prokaryotic counterparts beyond recognition. We anticipate that like the mitochondrial carrier family (TC# 2.29; see [29]), many of these

Table 3
Transporter families represented in the genome of *S. cerevisiae*[a] (continued)

Name of family	Abbreviation	TC#	# of members in *S. cerevisiae*	Systematic ORF name	Gene name	Substrate(s)/description	Occurrence[b]
Category 3. Pyrophosphate bond hydrolysis-driven active transporters							
ATP-binding cassette[d]	ABC	3.1	22	YCR011c	*ADP1*		B, A, E
				YDR011w	*SNQ2*	4-Nitroquinoline and multiple drugs (efflux)	
				YDR135c	*YCF1*	Glutathione conjugates (uptake into vacuoles)	
				YDR406w	*PDR15*		
				YGR281w	*YOR1*	Oligomycin and multiple drugs (efflux)	
				YHL035c	–[c]		
				YIL013c	*PDR11*		
				YKL188c	*PXA2/PAL2*	Interaction with PXA1	
				YKL209c	*STE6*	a-factor peptide (efflux)	
				YKR103/104c	–	Frame shift or pseudo-gene	
				YLL015w	–		
				YLL048c	*BAT1*	Bile acids (uptake into vacuoles)	
				YLR188w	*MDL1*		
				YMR301c	*ATM1*	Hemehomeostasis (into mitochondria)	
				YNR070w	–		
				YOL075c	–		
				YOR011w	–		
				YOR153w	*PDR5/STS1*	Cycloheximide and multiple drugs	
				YOR328w	*PDR10*		
				YPL058c	*PDR12*		
				YPL147w	*PXA1/PAL1*	Very long chain fatty acyl CoA uptake (in peroxisomes)	
				YPL270w	*MDL2*		

Table 3 (*continued*)
Transporter families represented in the genome of *S. cerevisiae*[a] (continued)

Name of family	Abbreviation	TC#	# of members in *S. cerevisiae*	Systematic ORF name	Gene name	Substrate(s)/description	Occurrence[b]
H^+- or Na^+-translocating F-type, V-type and A-type ATPase[e]	F-ATPase	3.2.1	1			Twelve subunits of mitochondrial F-type ATPase	B, A, E
				mito DNA	*ATP6*		
				mito DNA	*ATP8*		
				mito DNA	*ATP9*		
				YBL099w	*ATP1*		
				YBR039w	*ATP3*		
				YDL004w	*ATP16*		
				YDR298c	*ATP5*		
				YJR121w	*ATP2*		
				YKL016c	*ATP7*		
				YLR295c	*ATP14*		
				YPL078c	*ATP4*		
				YPL271w	*ATP15*		
	V-ATPase	3.2.2	1			Thirteen subunits of vacuolar V-type ATPase	
				YBR127c	*VMA2*		
				YDL185c	*VMA1*		
				YEL027w	*CUP5*		
				YEL051w	*VMA8*		
				YGR020c	*VMA7*		
				YHR026w	*PPA1*		
				YHR039c	*VMA10*		
				YKL080w	*VMA5*		
				YLR447c	*VMA6*		
				YOR270c	*VPH1*		
				YOR332w	*VMA4*		
				YPL234c	*VMA11*		
				YPR036c	*VMA13*		
Cation-translocating P-type ATPase[f]	P-ATPase	3.3	16				B, A, E
				YAL026c	*DRS2*	Amino phospholipids	
				YBR295w	*PCA1*		
				YDR038c	*ENA5*	Na^+ (efflux)	
				YDR039c	*ENA2/PMR2b*	Na^+ (efflux)	
				YDR040c	*ENA1/PMR2a*	Na^+ (efflux)	
				YDR093w	–		
				YDR270w	*CCC2*	Cu^{2+}	
				YEL031w	*SPF1*	Involved in sensitivity to *Pichia* killer toxin	
				YER166w	–		
				YGL006w	*PMC1*	Ca^{2+} (vacuolar) uptake	
				YGL008c	*PMA1*	H^+ (efflux)	
				YGL167c	*PMR1*	Ca^{2+} (Golgi) uptake	
				YIL048w	–		
				YMR162c	–		
				YOR291w	–		
				YPL036w	*PMA2*	H^+ (efflux)	
Category 6. Oxidoreduction-driven active transporters							
Proton-translocating quinol:cytochrome *c* reductase[e]	QCR	6.3	1			Ten subunits of mitochondrial CoQ:cytochrome *c* reductase	B, E
				mito DNA	*COB*		
				YBL045c	*COR1*		
				YDR192c	*RIP1/NUP42*		
				YDR529c	*QCR7*		
				YFR033c	*QCR6*		
				YGR183c	*QCR9*		
				YHR001w	*QCR10*		
				YJL166w	*QCR8*		
				YOR065w	*CYT1*		
				YPR191w	*QCR2*		

Table 3 (*continued*)
Transporter families represented in the genome of *S. cerevisiae*[a] (continued)

Name of family	Abbreviation	TC#	# of members in *S. cerevisiae*	Systematic ORF name	Gene name	Substrate(s)/description	Occurrence[b]
Proton-translocating cytochrome oxidase[e]	COX	6.4	1			Twelve subunits of mitochondrial cytochrome oxidase	B, A, E
				mito DNA	*COX1*		
				mito DNA	*COX2*		
				mito DNA	*COX3*		
				YDL067c	*COX9*		
				YGL187c	*COX4*		
				YGL191w	*COX13*		
				YHR051w	*COX6*		
				YIL111w	*COX5B*		
				YLR038c	*COX12*		
				YLR395c	*COX8*		
				YMR256c	*COX7*		
				YNL052w	*COX5A*		
Category 9. Outer membrane porins, β-type							
Mitochondrial and plastid porin	MPP	9.8	3	YNL055c	*POR1*	Mitochondrial outer membrane anion-selective porin 1	B, E
				YIL114c	*POR2*	Mitochondrial outer membrane anion-selective porin 2	
				YHR203w	*TOM40*	Putative mitochondrial outer membrane porin 3	
Category 99. Transporters of unknown transport mode or energy coupling mechanism							
Low-affinity Fe^{2+} transporter	FeT	99.9	1	YMR319c	*FET4*	Fe^{2+} (uptake; low-affinity)	E
Oxidase-dependent Fe^{2+} transporter	OFeT	99.10	2	YER145c	*FTR1*	Fe^{2+} (uptake; high affinity)	B, A, E
				YBR207w	–		
Copper transporter-1	Ctr1	99.11	1	YPR124w	*CTR1*	Cu^{2+} (uptake; high-affinity)	E (Y)
Copper transporter-2	Ctr2	99.12	2	YHR175w	*CRT2*	Cu^{2+} (uptake; low-affinity)	E
				YLR411w	*CRT3*	Cu^{2+} (uptake; high-affinity)	
Metal ion (Mn^{2+}-iron) transporter	Nramp	99.13	3	YHR050w	*SMF2*	Mn^{2+} (uptake; low-affinity)	B, A, E
				YLR034c	*SMF3*		
				YOL122c	*SMF1*	Mn^{2+} (uptake; high-affinity)	
Category 100. Putative transporters							
Metal homeostasis protein	MHP	100.1	1	YBR290w	*BSD2*	Heavy metal ions (Cu^{2+}, Co^{2+}, Mn^{2+} and Cd^{2+}; endoplasmic reticular membrane?)	E (Y)
Ca^{2+} homeostasis protein	CHP	100.2	1	YBR036c	*CSG2*	Ca^{2+} (endoplasmic reticular membrane?)	E (Y)

[a]The complete description of these families can be found on our web site (see Section 1).
[b]B, bacteria; A, archaea; E, eukaryotes; (Y), yeast only.
[c]Dashed lines (–) indicate that a gene designation is not available.
[d][9].
[e][25].
[f][10].

eukaryote-specific families will prove to have arisen after the three major kingdoms of life diverged from each other.

5. Inventory of transporters according to substrate specificities

Table 4 categorizes yeast transporters according to established or proposed substrate specificities. Transporters that comprise the largest percent of the complete complement of recognized yeast transporters (24%) function in the uptake of carbon compounds. Carbohydrate transporters (15%) are included within the MIP, MF and TPT families; transporters specific for carboxylates (8%) are found within the MC, MF and FNP families, and acyl CoA transporters (1.2%) occur within the AcCoAT and ABC families [1,2].

Nitrogenous compounds transported in yeast (19% of all recognized transporters) include amino acids (12%; APC and AAAP families), peptides (0.8%; POT and ABC families), as well as nucleotides, nucleosides, nitrogenous bases, urea and NH_4^+ (total of 6.6%; Table 4).

Transporters belonging to several distinct families function to maintain cation homeostasis (19% of all recognized transporters). Among these, 7% are concerned with monovalent cation transport (H^+, Na^+ and K^+), 3% are concerned with Ca^{2+} transport and 9% function in heavy metal ion transport. By contrast, only 7% function to transport inorganic anions (Table 4).

A surprisingly large percent of the recognized yeast transporters (estimated at 11%) are believed to transport drugs and other hydrophobic or amphipathic substances. The majority of both MF- and ABC-type drug efflux pumps are believed to

Table 4
Distribution of identified yeast transporters according to substrate specificity and comparison with those in *E. coli*

Substrate class	Estimated % transporters		Families represented in yeast[c]
	Yeast[a]	*E. coli*[b]	
Carbon compounds			
Carbohydrates	15	24	MIP, MF (SP), TPT
Mono/di/tri-carboxylates	8	4	MC, MF (SHS, MCP, ACS), FNP
Acyl-CoA	1.2	0	AcCoAT, ABC
Total carbon	24	28	
Nitrogen compounds			
Amino acids	12	14	APC, AAAP
Peptides	0.8	4	POT, ABC
Nucleosides/nucleotides/purines/pyrimidines/thiamin	5	4	NCS1, MC
Urea	0.4	0.4	SSS
NH_3	1.2	0.4	Amt
Total nitrogen	19	23	
Cations			
Monovalent	7	5	VIC, CCC, CPA1, CPA2, Trk, P-ATPase, F-ATPases, QCR
Ca^{2+}	3	1	VIC, CaCA, P-ATPase, CHP
Heavy metals	9	10	CDF, ZIP, MIT, ABC, P-ATPase, FeT, OFeT, Ctr1, Ctr2, MnT, MHP
Total cations	19	16	
Anions			
Cl^-/HCO_3^-	1.2	1	ClC, CCC, AE
SO_4^{2-}	1.6	1	SulP
HPO_4^{2-}	3.5	2	MFS (PHS), Pit, MC, DASS
AsO_3^{2-}	0.4	1	ACR
SO_3^{2-}	0.4	0	TDT
Total anions	7	5	
Drugs	11	13	MF (DHA14, DHA12), ABC
Unassigned	20	15	MC, ABC, P-ATPase

[a]Each yeast transporter represents about 0.4% of the total (258 recognized systems).
[b]Each *E. coli* transporter represents about 0.35% of the total (285 recognized systems [3]).
[c]Family abbreviations are indicated. Full family names and their TC#s are provided in Table 2.

lack specificity for a particular drug, and instead, function as multidrug resistance (MDR) determinants. Finally, about 20% of the recognized transporters are of unassigned substrate specificity. Most of these belong to the MC, ABC and P-ATPase families.

6. Perspectives and conclusions

The analyses reported in this communication provide guides for future biochemical analyses of transport function. We have noted that of the 258 recognized transporters in *S. cerevisiae*, 195 are probably secondary carriers, 42 are primary carriers, seven are channel proteins, three are porins in the outer mitochondrial membrane, and 11 function by unknown mechanisms. The largest families of yeast transporters are the MF superfamily with 78 members, the MC family with 35 members, the APC family with 24 members, the ABC superfamily with 22 members, and the P-type ATPases with 16 members. Even though a similar trend is observed for the distribution of transporters of specific substrates in *S. cerevisiae* and *E. coli* (Table 4), it is interesting to note that in yeast the secondary carriers represent 77% of all recognized transporters, and that nearly half of these belong to the MF superfamily. In *E. coli*, 62% of the recognized transporters are secondary carriers, and only 35% of these belong to the MF superfamily [3]. Of the yeast primary carriers, about half (56%) are ABC permeases, but in *E. coli* this percentage is much larger (88%) [3]. *S. cerevisiae* possesses almost five times as many secondary carriers as primary carriers and 3.6 times as many MF permeases as ABC permeases, but *E. coli* has just 2.5 times as many secondary carriers as primary carriers, and equal numbers of MF and ABC superfamily members. It is interesting to note that while these ratios clearly indicate a preponderance of secondary carriers in yeast, the same is apparently not true of bacteria in general as some prokaryotes such as *Mycoplasma genitalium* and *Synechocystis* PCC6803 exhibit about twice as many primary carriers as secondary carriers [3]. In fact, none of the prokaryotes analyzed to date exhibit as large a percentage of secondary carriers as does *S. cerevisiae*. We suspect that this situation will prove to reflect a common mode of transport characteristic of most if not all eukaryotic organisms. This property may in turn reflect the multiorganellar nature of eukaryotes, and the heavy dependence of these organisms on aerobic metabolism.

Among the 258 yeast transporters listed in Tables 2 and 3, a total of 139 lack genetic or biochemical names and thus lack either a demonstrated transport function or a recognizable physiological function as deduced from a mutant phenotype. The phylogenetic transport protein classification presented here often allows prediction of the nature of the transported substrate of the 'putative' or 'orphan' yeast transporters and therefore provides a guide to definitive biochemical and physiological experimentation for defining the functions of these proteins.

In addition to the 258 recognized transporters tabulated here, many yeast transporters are likely to be identified as a result of future biochemical, genetic, phylogenetic and physiological studies. Of the 850 predicted polytopic yeast proteins, we estimate that about half, or approximately 10% of all yeast proteins will prove to function in transmembrane solute transport. The same approximate percentage of prokaryotic genes encode transport proteins [3]. If one takes

into account macromolecular transporters as well, this percentage is likely to be still larger. The functional identification of these proteins will provide exciting challenges for future investigators.

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