

Benoît De Hertogh · Elvira Carvajal  
Emmanuel Talla · Bernard Dujon · Philippe Baret  
André Goffeau

## Phylogenetic classification of transporters and other membrane proteins from *Saccharomyces cerevisiae*

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**Abstract** On the basis of functional and phylogenetic criteria, we have identified a total of 229 subfamilies and 111 singletons predicted to carry out transport or other membrane functions in *Saccharomyces cerevisiae*. We have extended the Transporter Classification (TC) and created a Membrane Classification (MC) for non-transporter membrane proteins. Using the preliminary phylogenetic digits X, Y, Z (for new families, subfamilies, and clusters, respectively), we allocated a five-digit number to 850 proteins predicted to contain more than two transmembrane domains. Compared with a previous TC of the yeast genome, we classified an additional set of 538 membrane proteins (transporters and non-transporters) and identified 111 novel phylogenetic subfamilies.

**Keywords** Phylogenetic classification · Yeast · Membrane proteins · Transporters

### Introduction

In 1993, Milton Saier identified a large phylogenetic superfamily of secondary transporters that he called the “Major Facilitators” (MFS). This observation pioneered the use of phylogenetic tools to characterize the evolu-

tion pattern of transporter proteins. Phylogeny can also be used for predictions of mechanistic and functional features of transporters (Marger and Saier 1993; Saier 1999).

Generalization of this approach combining mechanistic, functional, and phylogenetic analyses led to the Transporter Classification (TC) system (Saier 2000), which in January 2002 identifies 824 transporters subfamilies (<http://www-biology.ucsd.edu/~msaier/transport/>).

The first use of phylogenetic tools to generate an inventory of the transporters, from a given species, based on genome sequence data was reported in 1995 (André 1995; Nelissen et al. 1995). Both papers examined the partial (70%) *Saccharomyces cerevisiae* genome sequence available at that time.

The inventory of yeast transporters was first updated in 1997 (Nelissen et al. 1997) after the complete yeast genome became public (Goffeau et al. 1996). A second update was performed in 1998 (Paulsen et al. 1998a), when the use of the TC nomenclature had been validated by the phylogenetic analysis of all predicted transporters from the first sequenced bacterial genomes (Paulsen et al. 1998b). These data have been edited on different web sites (Table 1). Peculiar phylogenetic features of the yeast transporters were recently reviewed (Van Belle and André 2001).

These phylogenetic analyses have resulted in the discovery of numerous new families and subfamilies of yeast transporters. Major examples are the identification of two large putative drug: proton antiporter families (Goffeau et al. 1996; Sa Correa and Tenreiro 2002), of six P-type ATPase families (Catty et al. 1997), of eight ABC transporters subfamilies (Decottignies and Goffeau 1997), of a yeast-specific subfamily of the MFS, which was first considered as of unknown function and later identified as the siderophore transporter subfamily (Goffeau et al. 1997; Lesuisse et al. 1998), of the large amino acids and ammonium transporter families (Jack et al. 2000; Marini et al. 1997; Regenbergh et al. 1999; Young et al. 1999), of the large sugar porters family

B. De Hertogh · P. Baret  
Unité de Génétique, Faculté d’Agronomie,  
Université Catholique de Louvain,  
Louvain-la-Neuve, Belgium

E. Carvajal  
Instituto de Biologia Roberto Alcântara Gomes,  
Universidade Estado Rio de Janeiro, Brazil

E. Talla · B. Dujon  
Unité de Génétique Moléculaire des Levures,  
Institut Pasteur and Université Pierre et Marie Curie,  
Paris, France

A. Goffeau (✉)  
Chaire Internationale de Recherche Blaise Pascal,  
Laboratoire de Génétique Moléculaire,  
Ecole Normale Supérieure, Paris, France  
e-mail: goffeau@fysa.ucl.ac.be

**Table 1** Websites for classification of *Saccharomyces cerevisiae* membrane ORFs products (TMS transmembrane spans)

Reference	ORFs	Sub-families	Single-tons	Comments
Nelissen et al. (1997)	186	22	21	All membrane proteins, TMS $\geq$ 10
Paulsen et al. (1998a, b)	312	54	2	Only transporters, TMS $\geq$ 6, TC nomenclature (4 digits)
André (2000)	217	45	6	Only transporters, TMS $\geq$ 6
Ward (2001)	1,593	370	763	All membrane proteins, TMS $\geq$ 2
De Hertogh et al. (2002)	856	231	114	All membrane proteins, TMS $\geq$ 3, TC nomenclature (5 digits)

(Kruckeberg 1996; Ozcan and Johnston 1999), of the large mitochondrial carrier family (Belenkiy et al. 2000; el Moulaj et al. 1997; Nelson et al. 1998), and of the anion:cation symporter subfamily (Llorente and Dujon 2000).

In the early classifications, only established transporter families with six or more predicted transmembrane spans were considered, even though more than 800 yeast proteins are predicted to contain one or two transmembrane spans (TMS) and more than 500 proteins are predicted to contain three to five TMS (Goffeau et al. 1993a, b).

In this review, we have classified phylogenetically all *S. cerevisiae* membrane proteins with more than two predicted TMS, be they transporters or not. We therefore extended the TC nomenclature to include new families, subfamilies, and clusters of putative transporters. In addition, based on similar functional and phylogenetic principles, we introduced the MC nomenclature for membrane proteins that are known to be non-transporters.

## Materials and methods

A defined set of 6,256 protein sequences predicted from *S. cerevisiae* (Blandin et al. 2000) was used as the starting material for this study. This data set comprises: (1) some modifications relative to the yeast new chromosome III (MIPS, <http://mips.gsf.de>), (2) new genes found in the hemiascomycetous random sequence tag (RST) project (Blandin et al. 2000) or by ORF fusion, and (3) a list of overlapping spurious ORFs based on homology criteria with RST sequences from hemiascomycetous yeast species (Talla and Dujon, unpublished results).

The transmembrane domains were predicted using Alom 2 (<http://www.psort.nibb.ac.jp/>) and TMHMM (<http://www.cbs.dtu.dk/services/TMHMM/>). A total of 630 ORF products of more than two-helical transmembrane domains predicted by either of the two softwares were further analyzed. All members of identified phylogenetic objects (family, subfamily, and cluster) were included when at least one of their members was predicted to contain more than two TMS. All members (membranous or not) of large membrane complexes were also included. These two sets amounted to 220 additional proteins.

Each of the 630 membrane-containing ORFs was analyzed manually using the Blast alignments provided by the December 2001 (or later) releases of YPD (<http://www.proteome.com/>

databases/YPD/), ExPasy (<http://www.expasy.ch/sprot/>), or NCBI (<http://www.ncbi.nlm.nih.gov/>).

The phylogenetic families were classified according to the TC system. The TC nomenclature comprises five digits. The two first digits correspond to mechanistic classes and subclasses. The third corresponds to phylogenetic families (or superfamilies, when large). The fourth digit defines phylogenetic subfamilies with closely related proteins. The fifth is defined either by the transported substrate or by high sequence identity.

ORF products with similarity scores (expected value or E value) lower than  $10 e^{-65}$  were empirically considered to belong to the same phylogenetic cluster corresponding to the fifth TC digit. ORF products with an E value lower than  $10 e^{-35}$  were empirically considered to belong to the same phylogenetic subfamily corresponding to the fourth TC digit. ORF products with an E value lower than  $10 e^{-20}$  were empirically considered to belong to the same phylogenetic subfamily corresponding to the third TC digit.

Common sense based on examination of phylogenetic trees (ClustalW, <ftp://ftp.ebi.ac.uk/software/unix/clustalw/>; Phylip, <http://evolution.genetics.washington.edu/phylip.html>) was used to discriminate marginal cases (e.g., when E values are distorted by the length parameter).

When possible, the TC digits were obtained from the specific "Blast search against TCDB" (<http://tcdb.ucsd.edu/tcdb/>) or "Web transport proteins prediction tool" (<http://cancer.lbi.ic.unicamp.br/transport/>). For the new ORF products with no established full TC numbers, the letters "X, Y, and Z" were used as third, fourth, and fifth digit, respectively. The different phylogenetic members of such new families, subfamilies, or clusters were distinguished by numeric indexes (e.g., Z1, Z2, Z3...).

## Results and discussion

### Global analysis

Four years ago 312 transporters from *S. cerevisiae*, containing at least six predicted transmembrane domains, were classified into 42 phylogenetic subfamilies using the three first TC digits (Paulsen et al. 1998a). We have now given five TC digit to every *S. cerevisiae* protein that is predicted to comprise three or more TMS. Therefore we classify 850 membrane proteins into 229 subfamilies and 351 clusters. In Table 2 we list all the members of each subfamily characterized by their ORF name and their four digits. The same information can be retrieved in a variety of fashions (such as alphabetical order, position on chromosomes,...) in our web site

**Table 2** Phylogenetic classification (TC and MC) of the *S. cerevisiae* membrane ORFs products

<b>Transport Classification (TC)</b>	<b>ORFs</b>	<b>Transport Classification (TC)</b>	<b>ORFs</b>
1.A The Alpha-Type Channels			
1.A.1 The Voltage-Gated Ion Channel (VIC) Superfamily			
1.A.1.7 The Outward Rectifier K <sup>+</sup> Channel Subfamily	YJL093c		YJR158w
1.A.1.11 The Voltage-gated Ca <sup>2+</sup> Channel Subfamily	YGR217w		YJR160c
1.A.4 The Transient Receptor Potential Ca <sup>2+</sup> Channel (TRP-CC) Family			YLR081w
1.A.4.7 The Vacuolar Voltage-gated Ca <sup>2+</sup> -activated Channel Subfamily	YOR088w		YMR011w
1.A.8 The Major Intrinsic Protein (MIP) Family			YNL318c
1.A.8.5 The Glycerol Efflux Facilitator Subfamily	YLL043w		YNR072w
1.A.8.6 The Aquaporin Subfamily	YLL053c		YOL103w
	YPR192w	2.A.1.2 The Drug: H <sup>+</sup> Antiporter-1 (12 Spanner) (DHA1) Subfamily	YOL156w
	YFL054c		YBR008c
	YJR040w		YBR043c
1.A.8.7 The Yeast Major Intrinsic Protein Subfamily			YBR180w
1.A.11 The Chloride Channel (ClC) Family			YGR138c
1.A.11.1 The Yeast Chloride Channel Subfamily			YHR048w
1.A.35 The CorA Metal Ion Transporter (MIT) Family	YOL130w		YIL120w
1.A.35.2 The CorA Metal Ion Transporter Type 2 Subfamily	YFL050c		YIL121w
	YKL064w		YLL028w
			YNL065w
1.A.X1 Undetermined Family	YBR086c		YNR055c
1.A.X1.Y1 Undetermined Subfamily			YOR273c
1.B The Beta-Barrel Porins			YPR156c
1.B.8 The Mitochondrial and Plastid Porin (MPP) Family		2.A.1.3 The Drug: H <sup>+</sup> Antiporter-2 (14 Spanner) (DHA2) Subfamily	YBR293w
1.B.8.1 The Mitochondrial and Plastid Porin (MPP) Type 1 Subfamily	YIL114c		YCL069w
YNL055c			YDR119w
2.A The Uni/Sym/Antiporters			YGR224w
2.A.1 The Major Facilitator (MFS) Superfamily			YKR105c
2.A.1.1 The Sugar Porter (SP) Subfamily			YML116w
			YMR088c
			YMR279c
			YOR378w
			YPR198w
		2.A.1.9 The Phosphate: H <sup>+</sup> Symporter (PHS) Subfamily	YCR098c
			YML123c
		2.A.1.12 The Sialate: H <sup>+</sup> Symporter (SHS) Subfamily	YKL217w
		2.A.1.13 The Monocarboxylate Porter (MCP) Subfamily	YDL054c
			YKL221w
			YNL125c
			YOL119c
			YOR306c
		2.A.1.14 The Anion: Cation Symporter (ACS) Subfamily	YAL067c
			YCR028c
			YGR065c
			YGR260w
			YIL166c
			YJR152w
			YLL055w
			YLR004c
			YOL163w
		2.A.1.1.16 The Siderophore-Iron Transporter (SIT) Subfamily	YCL073c
			YEL065w
			YHL040c

Table 2 (continued)

Transport Classification (TC)	ORFs	Transport Classification (TC)	ORFs
2.A.1.16 The Siderophore-Iron Transporter (SIT) Subfamily	YHL047c YKR106w YOL158c YCL038c YBR220c	2.A.7.Y1 The Drug/Metabolite Transporter (DMT-Y1) Subfamily Type X1 2.A.9 The Cytochrome Oxidase Biogenesis (Oxa1) Family 2.A.9.1 The Cytochrome Oxidase Biogenesis Type 1 Family 2.A.17 The Proton-dependent Oligopeptide Transporter (POT) Family 2.A.17.2 The Peptide: H <sup>+</sup> Symporter 2.A.18 The Amino Acid/ Auxin Permease (AAAP) Family 2.A.18.5 The Amino Acid/ Auxin Permease (AAAP-5) Subfamily Type 5 2.A.18.6 The Amino Acid/ Auxin Permease (AAAP-6) Subfamily Type 6	YGL225w YPL244c YER154w YKR093w YJR001w YBL089w YEL064c YIL119c YIL088c YKL146w YNL101w YDL128w YNL321w YBR296c YHL016c YBL030c YBR085w YMR056c YLR348c YER053c YJR077c YJL133w YKR052c YBR291c YFR045w YOR271c YOR100c YOR130c YIL134w YJR095w YMR241w YOR222w YPL134c YPR021c YKL120w YDL119c YDR470c YBR104w YBR058w YEL006w YIL006w YPR011c YHR002w
2.A.1.24 The Unknown Major Facilitator-1 (UMF1) Subfamily 2.A.1.25 The Peptide-Acetyl-Coenzyme A Transporter (PAT) Subfamily 2.A.3 Amino Acid/Polyamine/Organocation (APC) Superfamily 2.A.3.4 The Amino Acid/Choline Transporter (ACT) Subfamily	YDL210w YGL077c YKL174c YNR056c YGR055w YHL036w YBR068c YBR069c YBR132c YCL025c YDR046c YDR160w YDR508c YEL063c YFL055w YGR191w YKR039w YLL061w YNL268w YNL270c YOL020w YOR348c YPL265w YPL274w	2.A.19 The Ca <sup>2+</sup> : Cation Antiporter (CaCA) Family 2.A.19.2 The Ca <sup>2+</sup> : Cation Antiporter (CaCA-2) Subfamily Type 2 2.A.20 The Inorganic Phosphate Transporter (PiT) Family 2.A.20.2 The Inorganic Phosphate Transporter (PiT-2) Subfamily Type 2 2.A.21 The Solute:Sodium Symporter (SSS) Family 2.A.21.6 The Solute:Sodium Symporter (SSS-6) Subfamily Type 6 2.A.29 The Mitochondrial Carrier (MC) Family 2.A.29.1 The Mitochondrial Carrier (MC-1) Subfamily Type 1 2.A.29.2 The Mitochondrial Carrier (MC2) Subfamily Type 2 2.A.29.4 The Mitochondrial Carrier (MC4) Subfamily Type 4 2.A.29.5 The Mitochondrial Carrier (MC5) Subfamily Type 5 2.A.29.7 The Mitochondrial Carrier (MC7) Subfamily Type 7 2.A.29.8 The Mitochondrial Carrier (MC8) Subfamily Type 8 2.A.29.9 The Mitochondrial Carrier (MC9) Subfamily Type 9 2.A.29.10 The Mitochondrial Carrier (MC10) Subfamily Type 10 2.A.29.13 The Mitochondrial Carrier (MC13) Subfamily Type 13	YHL047c YKR106w YOL158c YCL038c YBR220c YDL210w YGL077c YKL174c YNR056c YGR055w YHL036w YBR068c YBR069c YBR132c YCL025c YDR046c YDR160w YDR508c YEL063c YFL055w YGR191w YKR039w YLL061w YNL268w YNL270c YOL020w YOR348c YPL265w YPL274w YMR243c YOR316c YDR205w YGL255w YLR130c YOR079c YPL006w YDR438w YJL193w YML018c YML038c YOR307c YEL004w YER039c YER039ca
2.A.3.8 The L-type Amino Acid Transporter (LAT) Subfamily 2.A.3.10 The Yeast Amino Acid Transporter (YAT) Subfamily	YMR243c YOR316c YDR205w YGL255w YLR130c YOR079c YPL006w YDR438w YJL193w YML018c YML038c YOR307c YEL004w YER039c YER039ca	2.A.29.15 The Mitochondrial Carrier (MC15) Subfamily Type 15 2.A.29.Y1 The Mitochondrial Carrier (MCY1) Subfamily Type Y1 2.A.29.Y2 The Mitochondrial Carrier (MCY2) Subfamily Type Y2 2.A.29.Y3 The Mitochondrial Carrier (MCY3) Subfamily Type Y3 2.A.29.Y4 The Mitochondrial Carrier (MCY4) Subfamily Type Y4 2.A.29.Y5 The Mitochondrial Carrier (MCY5) Subfamily Type Y5 2.A.29.Y6 The Mitochondrial Carrier (MCY6) Subfamily Type Y6	2.A.4 The Cation Diffusion Facilitator (CDF) Family 2.A.4.2 The Cation Diffusion Facilitator (CDF-2) Subfamily Type 2 2.A.4.4 The Cation Diffusion Facilitator (CDF-4) Subfamily Type 4 2.A.5 The Zn <sup>2+</sup> /Fe <sup>2+</sup> Permease (ZIP) Family 2.A.5.1 The Zn <sup>2+</sup> /Fe <sup>2+</sup> Permease (ZIP-1) Subfamily Type 1 2.A.5.2 The Zn <sup>2+</sup> /Fe <sup>2+</sup> Permease (ZIP-2) Subfamily Type 2 2.A.6 The Resistance-Nodulation-Cell Division (RND) Superfamily 2.A.6.6 The Eukaryotic (Putative) Sterol Transporter Subfamily 2.A.7 The Drug/Metabolite Transporter (DMT) Superfamily 2.A.7.9 The Triose-Phosphate Transporter (TPT) Subfamily 2.A.7.10 The UDP-N-Acetylglucosamine: UMP Antiporter (UAA) Subfamily 2.A.7.13 The 10–12 TMS Nucleotide Sugar Transporter (NST) Subfamily

Table 2 (continued)

Transport Classification (TC)	ORFs	Transport Classification (TC)	ORFs
2.A.29.Y7 The Mitochondrial Carrier (MCY7) Subfamily Type Y7	YNL083w	2.A.53.Y1 The Sulfate Permease (SulP-Y1) Subfamily Type Y1	YLR092w
2.A.29.Y8 The Mitochondrial Carrier (MCY8) Subfamily Type Y8	YGR096w	2.A.55 The Metal Ion (Mn <sup>2+</sup> -iron) Transporter (Nramp) Family	YPR003c
2.A.29.Y9 The Mitochondrial Carrier (MCY9) Subfamily Type Y9	YNL003c	2.A.55.1 The Metal Ion (Mn <sup>2+</sup> -iron) Transporter (Nramp-1) Subfamily Type 1	YGR125w
2.A.29.Y10 The Mitochondrial Carrier (MCY10) Subfamily Type Y10	YBR192w	2.A.57 The Equilibrative Nucleoside Transporter (ENT) Family	YHR050w
2.A.29.Y11 The Mitochondrial Carrier (MCY11) Subfamily Type Y11	YPR128c	2.A.57.3 The Equilibrative Nucleoside Transporter (ENT-3) Subfamily Type 3	YLR034c
2.A.29.Y12 The Mitochondrial Carrier (MCY12) Subfamily Type Y12	YDL198c	2.A.59 The Arsenical Resistance-3 (ACR3) Family	YOL122c
2.A.29.Y13 The Mitochondrial Carrier (MCY13) Subfamily Type Y13	YMR166c	2.A.59.1 The Arsenical Resistance-3 Type 1 Subfamily	YAL022c
2.A.29.Y14 The Mitochondrial Carrier (MCY14) Subfamily Type Y14	YGR257c	2.A.66 The Multi Antimicrobial Extrusion (MATE) Family	YPR201w
2.A.30 The Cation: Chloride Cotransporter (CCC) Family	YBR235w	2.A.66.3 The Multi Antimicrobial Extrusion (MATE-3) Subfamily Type 3	YDR338c
2.A.30.Y1 Undetermined Name	YNL275w	2.A.67 The Oligopeptide Transporter (OPT) Family	YHR032w
2.A.31 The Anion Exchanger (AE) Family	YDR456w	2.A.67.1 The Oligopeptide Transporter (OPT-1) Subfamily Type 1	YJL212c
2.A.31.1 The Anion Exchanger (AE-1) Subfamily Type 1	YLR138w	2.A.67.Y1 The Oligopeptide Transporter (OPT-Y1) Subfamily Type Y1	YPR194c
2.A.36 The Monovalent Cation:Proton Antiporter-1 (CPA1) Family	YJL094c	3.A The P-P Bond Hydrolysis – Driven Transporters	YGL114w
2.A.36.2 The Monovalent Cation:Proton Antiporter-1 (CPA1-2) Subfamily Type 2	YJL129c	3.A.1 The ATP Binding Cassette (ABC) Superfamily	YKL188c
2.A.36.4 The Monovalent Cation:Proton Antiporter-1 (CPA1-4) Subfamily Type 4	YKR050w	3.A.1.203 The Peroxysomal Fatty Acyl CoA Transporter (FAT) Subfamily	YPL147w
2.A.37 The Monovalent Cation:Proton Antiporter-1 (CPA2) Family	YER056c	3.A.1.204 The Eye Pigment Precursor (EPP) Transporter Subfamily	YCR011c
2.A.37.5 The Monovalent Cation:Proton Antiporter-1 (CPA2-5) Subfamily Type 5	YER060w	3.A.1.205 The Pleiotropic Drug Resistance (PDR) Subfamily	YDR011w
2.A.38 The K+ Transporter (TRK) Family	YER060wa		YDR406w
2.A.38.2 The K+ Transporter (TRK-2) Subfamily Type 2	YGL186c		YIL013c
2.A.39 The Nucleobase: Cation Symporter-1 (NCSI) Family	YIR028w		YNR070w
2.A.39.2 The Nucleobase Permease (NCS1-2) Type 2	YBR021w		YOL075c
2.A.39.3 The Nucleobase Permease (NCS1-3) Type 3	YBL042c		YOR011w
2.A.39.4 The Nucleobase Permease (NCS1-4) Type 4	YLR237w		YOR153w
	YOR071c		YOR328w
	YOR192c		YPL058c
	YMR177w		YKL209c
	YPL224c		YDR135c
2.A.42 The Hydroxy/Aromatic Amino Acid Permease (HAAAP) Family	YHL008c		YHL035c
2.A.42.4 The Yeast Cation Diffusion Facilitator (CDF-4) Subfamily Type 4	YCR037c		YKR103w
2.A.44 The Formate-Nitrite Transporter (FNT) Family	YIL047c		YKR104w
2.A.44.4 The Formate-Nitrite Transporter (FNT-4) Subfamily Type 4	YJL198w		YLL015w
2.A.47 The Divalent Anion: Na+ Symporter (DASS) Family	YNR015c		YLL048c
2.A.47.2 The Divalent Anion: Na+ Symporter (DASS-2) Subfamily Type 2	YGR121c		YGR281w
2.A.49 The Ammonium Transporter (Amt) Family	YNL142w		YLR188w
2.A.49.3 The Ammonium Transporter (Amt-3) Subfamily Type 3	YPR138c		YPL270w
	YBR294w		YMR301c
2.A.53 The Sulfate Permease (SulP) Family			Q0080/ATP8
2.A.53.1 The Sulfate Permease (SulP-1) Subfamily Type 1			Q0085/ATP6
			Q0130/ATP9

Table 2 (continued)

Transport Classification (TC)	ORFs	Transport Classification (TC)	ORFs
3.A.2.1 The H <sup>+</sup> -translocating F-type ATPase Subfamily	YBL099w YBR039w YDL004w YDR298c YJR121w YKL016c YLR295c YPL078c YPL271w YBR127c YDL185c YEL027w YEL051w YGR020c YHR026w YHR039c YKL080w YLR447c YMR054w YOR270c YOR332w YPL234c YPR036w	3.A.8.2 The Inner Mitochondrial Membrane Protein Translocase (TIM) Subfamily	YNL131w YOR045w YPR133wa YBR091c  YDL217c YDR322ca YEL020wa YGR181w YHR005ca YIL022w YIL054w YJL143w YJR135wa YNR017w YOR297c
3.A.2.2 The H <sup>+</sup> -translocating V-type ATPase Subfamily	YGL006w YGL167c YGL008c YPL036w YBR295w YDR270w YAL026c YDR093w YER166w YIL048w YMR162c YDR038c YDR039c YDR040c YEL031w YOR291w	3.D The Oxidoreduction-driven Active Transporters 3.D.3 The Proton-translocating Quinol: Cyt <i>c</i> Reductase (QCR) Superfamily 3.D.3.3 The Mitochondrial Ubiquinol: Cytochrome <i>c</i> Oxidoreductase Subfamily	Q00105/COB1  YBL045c YDR529c YFR033c YGR183c YHR001w YJL166w YOR065w YPR191w
3.A.3 The P-type ATPase (P-ATPase) Superfamily	YER166w YIL048w YMR162c YDR038c YDR039c YDR040c YEL031w YOR291w	3.D.4 The Proton-translocating Cytochrome Oxidase (COX) Superfamily 3.D.4.8 The Mitochondrial Cytochrome Oxidase Subfamily	Q0045/COX1 Q0250/COX2 Q0275/COX3 YDL067c YGL187c YGL191w YHR051w YIL111w YLR038c YLR395c YMR256c YNL052w
3.A.3.2 The Ca <sup>2+</sup> -ATPase (CaA) Subfamily	YDR457w YGR082w YHR117w YMR060c YMR203w YNL004w YNL070w YNL121c	9.A The Transporters of Unknown Classification 9.A.9 The Low affinity Family Fe <sup>2+</sup> -Transporter (FeT) Family 9.A.9.1 The Low-affinity Family Fe <sup>2+</sup> -Transporter (FeT-1) Subfamily Type 1 9.A.10 The Oxidase-dependent Fe <sup>2+</sup> -Transporter (OFeT) Family 9.A.10.1 The Oxidase-dependent Fe <sup>2+</sup> -Transporter (OFeT-1) Subfamily Type 1	YMR319c  YBR207w  YER145c YFL041w YMR058w
3.A.3.3 The H <sup>+</sup> -ATPase (PMA) Subfamily			
3.A.3.5 The Heavy Metal-ATPase (HMA) Subfamily			
3.A.3.8 The Aminophospholipid-ATPase (PLA) Subfamily			
3.A.3.9 The Na <sup>+</sup> Efflux-ATPase (ENa) Subfamily			
3.A.3.Y1 The ATPase of Non Assigned Specificity (NAS) Subfamily			
3.A.8 The Mitochondrial Protein Translocase (MPT) Family 3.A.8.1 The Outer Mitochondrial Membrane Protein Translocase (TOM) Subfamily			

Table 2 (continued)

Transport Classification (TC)	ORFs	Transport Classification (TC)	ORFs
9.A.11 The Copper Transporter-1 (Ctr1) Family	YPR124w	9.A.14.X4 The Nuclear Pore Complex (NPC-4) Subfamily Type X4	YMR153w YGL097w YGR163w YLR293c YMR235c YOR185c YDL207w YER009w YKL186c YKR095w YML031w YOR257w YPL169c
9.A.11.1 The Copper Transporter-1 (CTR1-1) Subfamily Type 1	YHR175w	9.A.14.X5 The Nuclear Pore Complex (NPC-5) Subfamily Type X5	YPL092w
9.A.12 The Copper Transporter-2 (Ctr2) Family	YAR002w		YBR290w YBR036c YOR334w
9.A.12.1 The Copper Transporter-2 (CTR2-1) Subfamily Type 1	YBL079w		YPL060w
9.A.14 The Nuclear Pore Complex (NPC) Family	YBR170c		YJL151c
9.A.14.X1 The Nuclear Pore Complex (NPC-1) Subfamily Type X1	YDL116w		YAL054c YBR041w YBR222c YLR054c
	YDR192c		YCR010c YNR002c YDR384c
	YER105c		YBR004c YBR040w YBR075w YBR187w YBR201w YCL002c YCR017c YCR023c YCR044c YCR075c YDL133w YDL180w YDL231c
	YER107c		
	YFR002w		
	YGL092w		
	YGL100w		
	YGL172w		
	YGR119c		
	YIL063c		
	YIL115c		
	YIL149c		
	YJL039c		
	YJL041w		
	YJL061w		
	YJR042w		
	YKL057c		
	YKL068w		
	YKR082w		
	YLR018c		
	YLR335w		
	YML103c		
	YMR047c		
	YMR129w		
	YMR255w		
	YOR098c		
	YNL189w		
	YBR017c		
	YDR335w		
	YDR395w		
	YER110c		
	YGL016w		
	YGL238w		
	YGL241w		
	YGR218w		
	YJR132w		
	YKL205w		
	YLR347c		
	YMR308c		
	YOR160w		
	YPL125w		
	YDL088c		
9.A.14.X2 The Nuclear Pore Complex (NPC-2) Subfamily Type X2		9.B.33 The YaaH (YaaH) Family	
9.A.14.X3 The Nuclear Pore Complex (NPC-3) Subfamily Type X3		9.B.33.1 The YaaH (YaaH-1) Subfamily Type 1	
		9.B.33.2 The YAAH (YAAH-2) Subfamily Type 2	
		9.B.X1 The Singletons	
		9.B.X1.Y1 The Singletons, nuclear DNA	
		9.B.11 Undetermined Family	
		9.A.X1.Y1 Undetermined Subfamily	
		9.B The Putative Uncharacterized Transporters	
		9.B.1 The Metal Homeostasis Protein (MHP) Family	
		9.B.1.1 The Metal Homeostasis Protein (MHP) Subfamily Type 1	
		9.B.2 The Ca <sup>2+</sup> Homeostasis Protein (CHP) Family	
		9.B.2.1 The Ca <sup>2+</sup> Homeostasis Protein (CHP) Subfamily Type 1	
		9.B.11 The Mitochondrial mRNA Splicing-2 Protein (MRS2) Family	
		9.B.11.1 The Mitochondrial mRNA Splicing-2 Protein (MRS2-1) Subfamily Type 1	
		9.B.11.Y1 The Mitochondrial mRNA Splicing-2 Protein (MRS2-Y1) Subfamily Type Y1	
		9.B.12 The Stress-induced Hydrophobic Peptide (SHP) Family	
		9.B.12.3 The Stress-induced Hydrophobic Peptide (SHP) Subfamily Type 3	
		9.B.17 The Putative Fatty Acid Transporter (FAT) Family	
		9.B.17.1 The Putative Fatty Acid Transporter (FAT-1) Subfamily Type 1	

Table 2 (continued)

Transport Classification (TC)	ORFs	Transport Classification (TC)	ORFs
9.B.X1.Y1 The Singletons, nuclear DNA	YDR084c		YKL034w
	YDR089w		YKL051w
	YDR090c		YKL100c
	YDR100w		YKL175w
	YDR105c		YKL207w
	YDR182w		YKR030w
	YDR319c		YKR051w
	YDR367w		YKR088c
	YDR411c		YLL014w
	YDR414c		YLR050c
	YEL045c		YLR065c
	YER083c		YLR220w
	YER118c		YLR242c
	YER140w		YLR443w
	YER187wa		YLR459w
	YFL007w		YML048wa
	YFL034w		YML059c
	YFR042w		YML066c
	YGL010w		YMR034c
	YGL041c		YMR071c
	YGL140c		YMR155w
	YGL161c		YMR187c
	YGR016w		YMR221c
	YGR026w		YNL080c
	YGR062c		YNL115c
	YGR089w		YNL257c
	YGR101w		YNL279w
	YGR149w		YNL294c
	YGR168c		YNL305c
	YHR078w		YNR039c
	YHR133c		YNR062c
	YHR140w		YOL073c
	YIL023c		YOL129w
	YIL030c		YOL137w
	YIL037c		YOL162w
	YIL049w		YOR030w
	YIL067c		YOR093c
	YIL090w		YOR161c
	YIL004c		YOR175c
	YIL051w		YOR228c
	YIL059w		YOR311c
	YIL091c		YOR363c
	YIL097w		YPL162c
	YIL108c		YPL246c
	YIL109c		YPR153w
	YIL163c		Q0010/ORF6
	YJR044c		Q0032/ORF8
	YJR085c		Q0144
	YJR118c		YLL005c
	YJR124c		YLR241w
			9.B.X1.Y2 The Singletons, Mito DNA
			9.B.X1.Y2 The Singletons, Mito DNA
		9.B.X1.Y2 The Singletons, Mito DNA	
		9.B.X2 The Uncharacterized Family X2	



Table 2 (continued)

Transport Classification (TC)	ORFs	Transport Classification (TC)	ORFs
9.B.X3 The Uncharacterized Family X3	YMR266w YOL084w YAL018c YOL047c YOL048c YDL072c YKL065c YMR040w YCL065w YCR041w YCR097 <sup>wa</sup> YGR038w YLR350w YFR012w YMR063w YOL019w YDR492w YLR023c YOL002c YOL101c YAL053w YGL139w YOR365c YPL221w YBR147w YDR352w YMR010w YOL092w YBR168w YGR004w YLR324w YDR479c YHR150w YDL222c YML052w YNL194c YOR390w YPL279c YDL218w YNR061c YJR116w YPR114w YJR054w YML047c YMR253c YPL264c YCR061w YNL237w RTMI YER185w	9.B.X21 The Uncharacterized Family X21 9.B.X22 The Uncharacterized Family X22 9.B.X23 The Uncharacterized Family X23 9.B.X24 The Uncharacterized Family X24 9.B.X25 The Uncharacterized Family X25 9.B.X26 The Uncharacterized Family X26 9.B.X27 The Uncharacterized Family X27 9.B.X28 The Uncharacterized Family X28 9.B.X29 The Uncharacterized Family X29 9.D The Spurious and Dubious ORFs 9.D.1 The Spurious Overlapping	YGR213c YLR046c YOR049c YGR197c YJR015w YDL206w YJR106w YBR287w YLR152c YNL095c YOR092w YDR107c YER113c YLR083c YLR251w YOR292c YDL058w YOR165w YPR141c YGR049w YLR356w YLL023c YLR064w YER072w YFL004w YJL012c YPL019c  YAL016ca YAL031 <sup>wa</sup> YBR113w YBR219c YBR224w YCL041c YCR087w YDR053w YDR193w YDR413c YDR417c YDR491c YDR526c YEL018ca YEL053 <sup>wa</sup> YER079ca YER107 <sup>wa</sup> YGL024w YGL152c YGR114c YGR115c YGR228w
9.B.X4 The Uncharacterized Family X4			
9.B.X5 The Uncharacterized Family X5			
9.B.X6 The Uncharacterized Family X6			
9.B.X7 The Uncharacterized Family X7			
9.B.X8 The Uncharacterized Family X8			
9.B.X9 The Uncharacterized Family X9			
9.B.X10 The Uncharacterized Family X10			
9.B.X11 The Uncharacterized Family X11			
9.B.X12 The Uncharacterized Family X12			
9.B.X13 The Uncharacterized Family X13			
9.B.X14 The Uncharacterized Family X14			
9.B.X15 The Uncharacterized Family X15			
9.B.X16 The Uncharacterized Family X16			
9.B.X17 The Uncharacterized Family X17			
9.B.X18 The Uncharacterized Family X18			
9.B.X19 The Uncharacterized Family X19			
9.B.X20 The Uncharacterized Family X20			

Table 2 (continued)

Transport Classification (TC)	ORFs	Membrane Classification (MC)	ORF
9.D.1 The Spurious Overlapping	YHL019wa	10.A Lipids	YDR018c
	YHR028wa	10.A.1 Fatty Acids	YBR042c
9.D.2 The Spurious Associated to Ty Elements	YHR069ca	10.A.1.1 The Acyl Transferase Subfamily	YJL196c
	YIL047ca	10.A.1.2 The Fatty Acid Elongation Subfamily	YLR372w
9.D.3 The Spurious LTR Overlapping	YIL142ca		YCR034w
	YJL142c		YKL187c
9.D.4 The Dubious Non-overlapping	YJL175w		YLR414c
	YJL220w		YLR413w
9.D.5 The Spurious Associated to Ty Elements	YKL030w	10.A.1.3 The Stearoyl CoA Desaturase Subfamily	YGL055w
	YKL037w	10.A.1.4 The Diacylglycerol <i>O</i> -acyltransferase Subfamily	YGL084c
9.D.6 The Spurious Associated to Ty Elements	YKL053w		YPL189w
	YKL083w		YKR067w
9.D.7 The Spurious Associated to Ty Elements	YLR101c	10.A.2 Triacylglycerols	YBL011w
	YLR171w	10.A.2.1 The Triacylglycerol Synthesis Subfamily	YDR284c
9.D.8 The Spurious Associated to Ty Elements	YLR458w	10.A.2.2 The Lipid Phosphate Phosphatase Subfamily	YDR503c
	YMR052ca		YBR029c
9.D.9 The Spurious Associated to Ty Elements	YMR173wa	10.A.2.3 The Phosphatidate Cytidyltransferase Subfamily	YNL130c
	YNL109w	10.A.3 Phospholipids	YHR123w
9.D.10 The Spurious Associated to Ty Elements	YNL174w	10.A.3.1 The Phospholipid Synthesis Subfamily	YGR157w
	YNL228w		YDL142c
9.D.11 The Spurious Associated to Ty Elements	YOL079w	10.A.3.2 The PE N-methyltransferase Subfamily	YPR113w
	YOR082c	10.A.3.3 The Cardiolipin Synthase Subfamily	YGL126w
9.D.12 The Spurious Associated to Ty Elements	YPL238c	10.A.3.4 The Phosphatidylinositol Synthase Subfamily	YML075c
	YPR038w	10.A.3.5 The Inositol Phospholipid Synthesis Subfamily	YLR450w
9.D.13 The Spurious Associated to Ty Elements	YPR123c	10.A.4 Sterols	YCR048w
	YPR150w	10.A.4.1 The HMGD Subfamily	YNR019w
9.D.14 The Spurious Associated to Ty Elements	YIL029c	10.A.4.2 The Sterol Acyltransferase Subfamily	YGL012w
	YIL089w		YNL280c
9.D.15 The Spurious Associated to Ty Elements	YLR036c	10.A.4.3 The Sterol Reductase Subfamily	YLR056w
	YPL257w		YKL004w
9.D.16 The Spurious Associated to Ty Elements	YPR071w	10.A.4.4 The Sterol Desaturase Subfamily	YDR072c
	YCR018ca	10.A.4.5 Sphingolipids	YPL087w
9.D.17 The Spurious Associated to Ty Elements	YDR366c	10.A.5.1 The Ceramide Phosphoinositol Transferase Subfamily	YBR183w
	YER181c	10.A.5.2 The Alkaline Ceramidase Subfamily	YJL134w
9.D.18 The Spurious Associated to Ty Elements	YLR334c	10.A.5.3 The Sphingoid Phosphate Phosphatase Subfamily	YKR053c
	YOL013wa	10.A.5.4 The Sphingolipid-related Hydroxylase Subfamily	YMR297w
9.D.19 The Spurious Associated to Ty Elements	YOL106w	10.A.5.5 The Inositolphosphorylceramide Hydroxylase Subfamily	YDR272c
	YPR002ca	10.A.5.6 The Sphingolipid Elongation Subfamily	YDL015c
9.D.20 The Spurious Associated to Ty Elements	YHR181w	10.A.5.7 The Sphingolipid Mannosylation	YPL057c
	YAL064wb	10.A.5.8 The C26 Fatty Acid CoA/Sphingosine Transferase Subfamily	YBR161w
9.D.21 The Spurious Associated to Ty Elements	YBL048w	10.B Anchoring	YKL008c
	YCL058c	10.B.1 Prenylation/Transferase	YHL003c
9.D.22 The Spurious Associated to Ty Elements	YGR045c		
	YKR040c		
9.D.23 The Spurious Associated to Ty Elements	YML090w		
	YPL185w		

Table 2 (continued)

Transport Classification (TC)	ORFs	Membrane Classification (MC)	ORFs
10.B.1.1 The Prenylation Transferase Type 1 Subfamily	YDR410c		YNL192w
10.B.1.2 The Prenylation Transferase Type 2 Subfamily	YPL172c		YBR023c
10.B.1.3 The Prenylation Transferase Type 3 Subfamily	YNR041c	10.C.2.2 The Beta-1,3-glucan Synthesis Subfamily	YLR342w
10.B.2 Prenylation/Protease			YGR032w
10.B.2.1 The Prenylation Protease Type 1 Subfamily	YJR117w		YMR306w
10.B.2.2 The Prenylation Protease Type 2 Subfamily	YMR274c		YNL322c
10.B.3 GPIinositoylation		10.C.2.3 The Beta-1,6-glucan Synthesis Subfamily	
10.B.3.1 The GPIinositoylation Type 1 Subfamily	YGR216c	10.D Trafficking	YPR149w
10.B.3.2 The GPIinositoylation Type 2 Subfamily	YLR088w	10.D.1 SEC	YGR131w
10.B.3.3 The GPIinositoylation Type 3 Subfamily	YJL062w	10.D.1.1 The Non-classical Secretion Subfamily	YGL054c
10.B.3.4 The GPIinositoylation Type 4 Subfamily	YKL165c	10.D.1.2 The ER Vesicles Subfamily	YBR210w
	YLL031c		YLR378c
	YGL142c	10.D.1.3 The Translocation into ER Subfamily	YBR283c
10.B.3.5 The GPIinositoylation Type 5 Subfamily	YOR149c		YCL001w
10.B.3.6 The GPIinositoylation Type 6 Subfamily	YMR281w	10.D.1.4 The COPII Components Subfamily	YGR284c
10.B.3.7 The GPIinositoylation Type 7 Subfamily	YPL076w		YFL025c
10.B.3.8 The GPIinositoylation Type 8 Subfamily	YDR302w		YNL263c
10.C Polysaccharides		10.D.1.5 The ER to Golgi Subfamily	YMR292w
10.C.1 Glycosylation	YDL093w		YGR172c
10.C.1.1 The Mannosyltransferase Subfamily	YGR199w		YBL102w
	YJR143c		YDR170c
	YAL023c		YEL022w
	YDL095w		YJR031c
	YOR321w	10.D.1.6 The ER Translocation Subcomplex Subfamily	YHR142w
	YDR307w		YPL094c
	YBL082c		YOR254c
	YNR030w		YBR171w
	YNL219c		YDR264c
	YJR013w	10.D.2 ENDO	YOR034c
	YGL065c	10.D.2.1 The ENDO Subfamily	YLR246w
	YOR002w		YDR126w
	YOR067c		YOL003c
	YGR227w		YNL326c
	YOL132w		YDR459c
10.C.1.2 The Glucosyltransferase Subfamily	YMR215w		
	YLR343w	10.D.3 MITO	
	YOL030w	10.D.3.1 The Mitochondrial Morphology Subfamily	YML104c
	YMR307w		YOL060c
	YBR243c	10.D.3.2 The Inner Membrane Assembly Subfamily	YER141w
10.C.1.3 The Acetyl-glucosamyltransferase Subfamily	YOR085w	10.D.4 VAC	
10.C.1.4 The Oligosaccharyltransferase Complex Subfamily	YMR149w	10.D.4.1 The Vacuolar Sorting Subfamily	YCR099c
	YOR103c		YNR065c
	YGL022w		YJL222w
	YML019w		YBL017c
10.C.1.5 The Dolichol Kinase Subfamily	YMR013c		YCR100c
10.C.1.6 The Dolichol Pyrophosphate Phosphatase Subfamily	YGR036c		YNR066c
10.C.1.7 The N-glycosylation Subfamily	YBL020w		YIL173w
10.C.2 Wall			YCR101c
10.C.2.1 The Chitin Synthesis Subfamily	YBR038w	10.D.4.2 The Autophagy Subfamily	YDL149w

Table 2 (continued)

Membrane Classification (MC)	ORFs	Membrane Classification (MC)	ORFs
10.D.5 RETRO GOLGI		10.G.2.1 The Permease Folding Type 1 Subfamily	YNL008c
10.D.5.1 The RETRO GOLGI to ER Subfamily	YBL040c	10.G.2.2 The Permease Folding Type 2 Subfamily	YMR119w YDL212w
10.E Signaling		10.G.3 Misfold Degradation	
10.E.1 G-Receptors	YHL017w YKL039w YKL178c YFL026w YDL055c	10.G.3.1 The Misfold Degradation Type 1 Subfamily	YOL013c
10.E.1.1 The Seven TMS Receptors Subfamily		10.H Subtelomeric Conserved	
		10.H.1 COS	
		10.H.1.1 The COS Subfamily	YML132w YGL263w YFL062w YNL336w YBR302c YGR295c YNR075w YDL248w YOR301w YJR161c YHL048w YKL219w
10.E.2 GTPases	YOL081w YBR140c		
10.E.2.1 The GTP RAS-dependent Subfamily			
10.F Oxidoreductases			
10.F.1 Iron Reductases	YOR381w YKL220c YLL051c YNR060w YOR384w YLR214w YOL152w YLR047c YGL160w YGL198w		
10.F.1.1 The Iron Reductase Type 1 Subfamily			
		10.X Others	
10.F.1.2 The Iron Reductase Type 2 Subfamily		10.X.1 The Short Chain Alcohol/Ribitol Dehydrogenase	
10.F.1.3 The Iron Reductase Type 3 Subfamily		10.X.1.1 The Short Chain Alcohol/Ribitol Dehydrogenase Type 1 Subfamily	YLR426w YDL114w
		10.X.1.2 The Short Chain Alcohol/Ribitol Dehydrogenase Type 2 Subfamily	YMR226c
10.F.2 NADH		10.X.1.3 The Short Chain Alcohol/Ribitol Dehydrogenase Type 3 Subfamily	YKL071w
10.F.2.1 The NADH Type 1 Subfamily		10.X.1.4 The Short Chain Alcohol/Ribitol Dehydrogenase Type 4 Subfamily	YIR036c
10.G Chaperones		10.X.1.5 The Short Chain Alcohol/Ribitol Dehydrogenase Type 5 Subfamily	YIR035c
10.G.1 Heat Shock		10.X.1.6 Short Chain Alcohol/Ribitol Dehydrogenase Type 6 Subfamily	YIL124w
10.G.1.1 The Heat Shock Type 1 Subfamily	YCR021c YDR033w YBR054w	10.X.2 Mit Succinate Deshydrogenase	
		10.X.2.1 The Succinate Deshydrogenase Type 1 Subfamily	YKL141w
		10.X.2.2 The Succinate Deshydrogenase Type 2 Subfamily	YMR118c

**Table 3** Phylogenetic classification (TC and MC) of the *S. cerevisiae* membrane ORF products

Subclasses	Family (X)	Subfamily (Y)	Cluster (Z)	ORF
<b>Transporter Classification (TC)</b>				
1.A The alpha-Type Channels	6	9	10	12
1.B The beta-Barrel Porins	1	1	1	2
2.A The Porters, Uniporters, Symporters and Antiporters	28	74	151	211
3.A The P-P Bond Hydrolysis-driven Transporters	4	18	28	88
3.D The Oxidoreduction-driven Active Transporters	2	2	2	21
9.A The Transporters of Unknown Classification	4	10	13	67
9.B The Putative Uncharacterized Transporters	36	36	40	202
9.D Spurious and Dubious	4	4	4	68
<b>Membrane Classification (MC)</b>				
10.A Lipids	5	21	21	42
10.B Anchoring	3	13	14	15
10.C Polysaccharides	2	10	22	36
10.D Trafficking	5	12	21	41
10.E Signaling	2	2	4	7
10.F Oxidoreductases	2	4	6	10
10.G Chaperones	3	4	5	7
10.H Subtelomeric Conserved	1	1	1	12
10.X Others	2	8	8	9
Total:	110	229	351	850
<b>Large Transport Complexes</b>				
3.A.2.1.3 The Yeast H <sup>+</sup> -translocating F-type ATPase Complex				12
3.A.2.2.3 The Yeast H <sup>+</sup> -translocating V-type ATPase Complex				14
3.A.8.1.1 The Yeast Outer Mitochondrial Membrane Protein Translocase Complex				11
3.A.8.2.1 The Yeast Inner Mitochondrial Membrane Protein Translocase Complex				12
3.D.4.8.1 The Yeast Cytochrome Oxidase Complex				12
3.D.3.3.1 The Yeast Ubiquinol: Cytochrome c Oxidoreductase Complex				9
9.A.14 The Nuclear Pore Complex Family				58
Total:				128
<b>Novel Phylogenetic Membrane Objects</b>				
The newly classified transporters	1	24	87	170
The predicted membrane singletons of unknown function	1	111	111	111
The spurious membrane ORFs	4	4	4	68
The non-transporters membrane proteins	25	80	112	179

(<http://www.genolevure>). The fifth digit of each ORF product is also available in this web site, as well as additional information, such as gene names, the number of predicted TMS, and the putative transported substrates.

Table 3 sums up the quantitative distribution of the major subdivisions of the *S. cerevisiae* transporters and other membrane proteins. As expected, the major classes are the secondary porters and the transport ATPases. Few channel and porin proteins are detected. The most-interesting feature of our classification is the large (190) number of ORF products of still unknown function.

#### Novel features

Compared with previous compilations (Table 1), a first novelty of the present inventory is to include the membrane proteins with three, four, and five predicted TMS. We have used two predictive softwares. For the 850 proteins analyzed, Alom 2 predicts a total of 3039 TMS while TMHMM predicts 4452 TMS. TMHMM is cur-

rently considered to be the best performing predictive transmembrane domains program, while ALOM 2 is considered to have the lower number of false positives (Möller et al. 2001). In the present survey, Alom 2 predicts 68% of the TMS predicted by TMHMM, while in a previous comparison of a set of diverse membrane proteins of known structure (Möller et al. 2001), Alom 2 predicted only 55%.

One of the consequences to reduce to three, the threshold for minimal number of predicted TMS, is the unraveling of 26 new families, 104 new subfamilies, and 199 new clusters (Table 3). In order not to interfere with future allocation of "official" TC numbers, we used the temporary digits X1, X2,..., Y1,..., Z1... to identify new families, subfamilies, or clusters respectively.

A second novel feature is the use of a new five-digit system (MC) to characterize 179 membrane proteins with non-transport function. Indeed, known enzymatic functions are carried out by membrane proteins. This includes enzymes involved in lipid metabolism, polysaccharide metabolism, subcellular membrane trafficking,

signaling, non-mitochondrial oxidoreductases, chaperones, and others. These enzymatic activities were grouped in the new class 10 (first digit). A second digit (subclass) has been given to each general function. Each subclass has been divided in specific metabolic pathways to which we have allocated a third digit and an acronym. The last two digits have been given according to the TC phylogenetic criteria, such as E value  $<10 e^{-35}$  for subfamilies and E value  $<10 e^{-65}$  for clusters. Even though EC numbers (which have no phylogenetic components) are usually associated with non-transporters activities, it is useful to use phylogenetic criteria, allowing comparative classification of these membrane proteins from other genomes.

A third novelty is the extension of subclass 9.B “the putative uncharacterized transporters,” which now comprises 202 members classified in six families (12 ORFs), 111 “singletons,” and 30 “uncharacterized families” (79 ORFs). In order to cast a wider net, the members of these 30 “uncharacterized families” were associated when their E value was below  $10 e^{-10}$  [a more-stringent E value ( $10 e^{-20}$ ) was used for all others families]. Most of the new members of this subclass have no described phenotype when mutated.

A fourth novel feature is the introduction of new subclasses 9.D, the spurious and dubious ORFs, which comprises a total of 68 ORF products subdivided into spurious overlapping (48 ORF products in 9.D.1), Ty-related (12 ORF products in 9.D.2), LTR-related (1 ORF product in 9.D.3), and dubious non-overlapping (7 ORF products in 9.D.4). The DNA sequences of the spurious overlapping ORFs overlap with another ORF on the other strand. They neither have a mutant phenotype in *S. cerevisiae* or an orthologue in other species. The dubious non-overlapping ORFs have the same properties, but they do not overlap another ORF.

Finally, one of the major contributions of our work is to provide a non-ambiguous phylogenetic marker (with the use of the X, Y, Z digits and the inclusion of non-transporter membrane proteins) to an additional set of 319 membrane proteins (179 membrane proteins plus 111 singletons, plus 79 uncharacterized family members, excluding spurious and dubious ORFs) that were not established transporters in our former classification (Paulsen et al. 1998a). This allows phylogenetic comparisons with related fungal genomes.

### Specific comments

It is worth mentioning that a total of 128 proteins belong to large transport complexes, such as the mitochondrial and vacuolar ATP synthase/hydrolase (26), the yeast cytochrome oxidase (12), and the yeast ubiquinol:cytochrome c oxidoreductase (9), the nuclear pore complex (58), the yeast outer mitochondrial membrane protein translocase (12), the yeast inner mitochondrial membrane protein translocase (11) (Table 3). These large numbers of components are due to the fact that associat-

ed non-membrane proteins are included in these complexes.

Most of the remaining 285 membrane proteins [856 total proteins minus 128 protein in large complex proteins, minus 111 uncharacterized singletons, minus 79 ORF products from new uncharacterized families (9.B.X), minus 68 spurious and dubious ORFs and minus 185 non-transporter membrane proteins] are likely to be true transporters, not associated with large complexes.

Among the novel or reclassified subfamilies, let us mention the following major features:

The unknown major facilitator subfamily (Goffeau et al. 1997), which is one of the few large subfamilies to be specific for yeasts, has been identified as siderophore-iron transporters (2.A.1.16, SIT) (Lesuisse et al. 1998).

The triose phosphate transporters are now included in a large new superfamily, the drug/metabolite transporter (2.A.7, DMT), which comprises nine yeast members involved in the transport of triose-phosphate, nucleotide sugar or unknown metabolites (Jack et al. 2001).

The incompletely characterized transport systems (9.B) have been totally reorganized and now comprise 38 subfamilies and 209 members, several of which are new, such as the putative fatty acid transporters family (9.B.17, FAT) and the YaaH family (9.B.33, YaaH), reported to drive ammonium efflux (Palkova, Devaux, Ricicova, Minarikova, Le Crom, Jacq, unpublished results). This class 9.B contains a large number of families and singletons of unknown function.

Several ORF products have been reclassified in new families or subfamilies according to the January 2002 version of the TC database. For instance, new subfamilies such as the unknown major facilitator (2.A.1.24, UMF1), the peptide-acetyl-CoA transporter (2.A.1.25, PAT), the eukaryotic (putative) sterol transporter (2.A.6.6, EST), the yeast cation diffusion facilitator (2.A.42.4, CDF-4), the equilibrative nucleoside transporter (2.A.57.3, ENT-3), the multi-antimicrobial extrusion (2.A.66.3, MATE-3), the oligopeptide transporter family (2.A.67, OPT), the undetermined families 9.A.X1 and 9.A.X2 now comprise one or several yeast members each.

One of the surprising outcomes of this classification is the unraveling of numerous metal transporters across the different cell and organelles membranes. Table 4 lists 40 members of 20 subfamilies possibly involved in metal transport. Another unexpected discovery is the diversification of 17 carboxylates transporters distributed in ten subfamilies (Table 5).

### Prospects

Two important analyses remain to be done. The first is the phylogenetic analysis of the about 800 proteins predicted to have only one or two TMS. This can only be done one by one, using human expertise, because too many false-positive predictions hinder this approach.

The second one is to develop a reliable semi-automatic software for classification of the membrane proteins from

**Table 4** Phylogenetic classification of metal transporters in *S. cerevisiae*

	ORF	Gene	TMS Psort	TMS TMHMM	Putative substrate
The Alpha-Type Channels					
The CorA Metal Ion Transporters					
1.A.35.2.1 The Aluminum Resistance Protein	YOL130w	<i>ALR1</i>	1	1	Mn <sup>2+</sup> / Mg <sup>2+</sup> /Al <sup>2+</sup> /Co <sup>2+</sup>
1.A.35.2.2 The Manganese Resistance Protein	YKL064w	<i>MNR2</i>	2	2	Mn <sup>2+</sup>
1.A.35.2.2 The Manganese Resistance Protein	YFL050c	<i>ALR2</i>	0	0	Mn <sup>2+</sup>
The Secondary Carriers					
The SIT Transporters					
2.A.1.16.1 The Ferrioxamine: H <sup>+</sup> Symporter	YEL065w	<i>SIT1</i>	10	14	Ferrioxamine
2.A.1.16.2 The Ferric Enterobactin: H <sup>+</sup> Symporter	YOL158c	<i>ENB1</i>	6	11	Ferric enterobactin
2.A.1.16.3 The Ferric Triacetylfusarinine C: H <sup>+</sup> Symporter	YHL047c	<i>TAF1</i>	8	14	Ferric triacetylfusarinine
2.A.1.16.Z1 The Ferrichrome: H <sup>+</sup> Symporter	YHL040c	<i>ARN1</i>	7	13	Ferrichrome
2.A.1.16.Z2 Undetermined Substrate	YCL073c		8	12	Unknown
2.A.1.16.Z2 Undetermined Substrate	YKR106w		8	12	Unknown
The CDF Transporters					
2.A.4.2.1 The Mitochondrial Co <sup>2+</sup> /Zn <sup>2+</sup> Uptake Permease	YOR316c	<i>COT1</i>	3	6	Co <sup>2+</sup> and others
2.A.4.2.2 The Mitochondrial Zn <sup>2+</sup> /Cd <sup>2+</sup> Uptake Permease	YMR243c	<i>ZRC1</i>	5	6	Zn <sup>2+</sup> /Cd <sup>2+</sup>
2.A.4.4.1 The Nuclear/ER Zn <sup>2+</sup> Uptake Permease	YDR205w	<i>MSC2</i>	12	14	Zn <sup>2+</sup>
The ZIP Transporters					
2.A.5.1.1 The High-affinity Zinc Uptake Transporter	YGL255w	<i>ZRT1</i>	5	8	Zn <sup>2+</sup>
2.A.5.1.1 The High-affinity Zinc Uptake Transporter	YLR130c	<i>ZRT2</i>	6	7	Zn <sup>2+</sup>
2.A.5.2.1 The Golgi Mn <sup>2+</sup> Homeostasis Protein	YOR079c	<i>ATX2</i>	4	8	Mn <sup>2+</sup>
The CaCA Transporters					
2.A.19.2.2 The Vacuolar Mn <sup>2+</sup> /Ca <sup>2+</sup> : H <sup>+</sup> Antiporter	YDL128w	<i>VCX1</i>	7	11	Ca <sup>2+</sup> (Mn <sup>2+</sup> )
2.A.19.2.Z1 Undetermined Substrate	YNL321w		11	13	Ca <sup>2+</sup>
The MC Transporters					
2.A.29.5.1 The MRS Protein	YJL133w	<i>MRS3</i>	0	0	Unknown
2.A.29.5.1 The MRS Protein	YKR052c	<i>MRS4</i>	0	0	Unknown
The Nramp Transporters					
2.A.55.1.1 The High-Affinity Me <sup>2+</sup> (Fe <sup>2+</sup> /Mn <sup>2+</sup> ) Uptake Transporter	YOL122c	<i>SMF1</i>	9	11	Mn <sup>2+</sup> (H-aff) and others
2.A.55.1.2 The Putative Low-affinity Mn <sup>2+</sup> Uptake Transporter	YLR034c	<i>SMF3</i>	8	10	Mn <sup>2+</sup> / Fe <sup>2+</sup>
2.A.55.1.2 The Putative Low-affinity Mn <sup>2+</sup> Uptake Transporter	YHR050w	<i>SMF2</i>	7	11	Mn <sup>2+</sup> (L-aff)
The P-P Hydrolysis-Driven Transporters					
The ABC Transporters					
3.A.1.207.1 The Vacuolar Metal Resistance Protein	YLL015w	<i>BPT1</i>	8	14	Bilirubin
3.A.1.207.1 The Vacuolar Metal Resistance Protein	YDR135c	<i>YCF1</i>	12	14	Cd <sup>2+</sup> conjugates
The P-ATPase Transporters					
3.A.3.5.3 The Cu <sup>2+</sup> /Ag <sup>+</sup> Efflux ATPase	YDR270w	<i>CCC2</i>	5	8	Cu <sup>2+</sup>
3.A.3.5.3 The Cu <sup>2+</sup> /Ag <sup>+</sup> Efflux ATPase	YBR295w	<i>PCAI</i>	7	7	
The Transporters on Unknown Mechanism					
9.A.9.1.1 The Low-affinity Fe <sup>2+</sup> Transporter	YMR319c	<i>FET4</i>	4	7	Iron
9.A.10.1.1 The High-affinity Fe <sup>2+</sup> Uptake Transporter Complex (Oxidase)	YFL041w	<i>FET5</i>	2	0	Iron
9.A.10.1.1 The High-affinity Fe <sup>2+</sup> Uptake Transporter Complex (Oxidase)	YBR207w	<i>FTH1</i>	5	7	Iron
9.A.10.1.1 The High-affinity Fe <sup>2+</sup> Uptake Transporter Complex (Oxidase)	YMR058w	<i>FET3</i>	2	1	Iron
9.A.10.1.1 The High-affinity Fe <sup>2+</sup> Uptake Transporter Complex	YER145c	<i>FTR1</i>	6	7	Iron
9.A.11.1.1 The High-affinity Copper Transporter	YPR124w	<i>CTR1</i>	2	3	Cu <sup>2+</sup>
9.A.12.1.3 The Low-affinity Copper Uptake Transporter	YHR175w	<i>CTR2</i>	2	2	Cu <sup>2+</sup>
9.A.12.1.4 The High-affinity Copper Uptake Transporter	YLR411w	<i>CTR3</i>	3	3	Cu <sup>2+</sup>
The Putative Uncharacterized Transporters					
9.B.1.1.1 The Metal Homeostasis Protein (ER)	YBR290w	<i>BSD2</i>	2	3	Cu <sup>2+</sup> /Co <sup>2+</sup> /Mn <sup>2+</sup> /Cd <sup>2+</sup>
9.B.11.1.1 The MRS2 Protein	YOR334w	<i>MRS2</i>	0	0	Mg <sup>2+</sup>
9.B.11.1.Z.1 Undetermined Substrate	YPL060w	<i>LPE10</i>	0	2	Mg <sup>2+</sup>
9.B.X1 The Singletons	YDR182w	<i>CDC1</i>	1	3	Mn <sup>2+</sup> ?
9.B.X1 The Singletons	YLR220w	<i>CCC1</i>	5	3	Iron (vacuolar)
9.B.X1 The Singletons	YNR039c	<i>ZRG17</i>	4	6	Zinc

**Table 5** Phylogenetic classification of organic acids transporters in *S. cerevisiae*

	ORF	Gene	TMS Psort	TMS TMHMM	Putative Substrate
The Secondary Carriers					
The SHS Transporters					
2.A.1.12.2 The Lactate/Pyruvate: H <sup>+</sup> Symporter	YKL217w	<i>JEN1</i>	8	12	Lactate
The MCP Transporters					
2.A.1.13.Z1 The Monocarboxylate Porter Subfamily 1	YOR306c		8	12	Unknown
2.A.1.13.Z1 The Monocarboxylate Porter Subfamily 1	YOL119c		7	12	Unknown
2.A.1.13.Z2 The Monocarboxylate Porter Subfamily 2	YNL125c	<i>ESBP6</i>	7	11	Unknown
2.A.1.13.Z3 The Monocarboxylate Porter Subfamily 3	YKL221w		7	11	Unknown
2.A.1.13.Z4 The Monocarboxylate Porter Subfamily 4	YDL054c		8	11	Unknown
The ACS Transporters					
2.A.1.14.4 The Allantoate Porter	YJR152w	<i>DAL5</i>	6	12	Allantoate/ureidosuccinate
The MC Transporters (Mitochondrial)					
2.A.29.2.3 The Dicarboxylate: Pi Antiporter	YLR348c	<i>DIC1</i>	0	0	Dicarboxylate
2.A.29.7.Z1 The Citrate Transporter	YBR291c	<i>CTP1</i>	0	0	Citrate
2.A.29.13.1 The Succinate/Fumarate Antiporter	YJR095w	<i>SFC1</i>	2	2	Succinate/fumarate
2.A.29.13.Z1 The OxoDiCarboxylate Transporter	YPL134c	<i>ODC1</i>	0	1	2-Oxodicarboxylate
2.A.29.13.Z1 The OxoDiCarboxylate Transporter	YOR222w	<i>ODC2</i>	0	0	2-Oxodicarboxylate
2.A.29.13.Z3 The Citrate/Ketoglutarate/Succinate Transporter	YMR241w	<i>YHM2</i>	0	0	Citrate/ketoglutarate/succinate
2.A.29.15.1 The Oxaloacetate/Malonate/Sulfate/Thiosulfate Transporter	YKL120w	<i>OAC1</i>	2	1	Oxaloacetate
The FNT Transporter					
2.A.44.4.1 The Acetate: H <sup>+</sup> Symporter	YHL008c		5	6	Acetate
The P-P Hydrolysis-driven Transporters					
The ABC Transporters					
3.A.1.205.3 The Weak Acid Exporter	YPL058c	<i>PDR12</i>	8	11	Weak acids
The Transporters on Unknown Mechanism					
9.A.X2.Y1.Z1 Weak similarity to Sulfate/Malate Porters	YPL092w	<i>SSU1</i>	6	9	Sulfate/malate?

other yeast species. Indeed, the sequence of numerous fungal genomes has been recently disclosed (Gaillardin et al. 2000; Souciet et al. 2000; Tekaiia et al. 2000; Wood et al. 2002) and many others are expected in the near future. The use of such automatic analysis tools has been thus far disappointing, because of the lack of a non-ambiguous reference database such as the one we have developed. Development of new softwares should be greatly facilitated by the present inventory carried out manually.

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