

Supplementary Information

Structures of a P4-ATPase lipid flippase in lipid bilayers

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Supplemental results and discussion

Results

In both E1-ATP and E2P structures, ctCdc50p has extensive interactions with ctDnf1p. On the cytoplasmic side, the N-terminal peptide (residues 23-46) of ctCdc50p runs along one face of ctDnf1p, interacting with the cytosolic loops of ctDnf1p, including the segment connecting TM4 and the P domain, the loop between TMs 6 and 7 (L6/7), L8/9, and a C-terminal amphipathic helix that was suggested to undergo conformational changes upon PI4P activation in scDrs2p^{1,2} (Fig. S10). The C-terminal tail of ctCdc50p (residues 384-398), which is invisible in the scCdc50p and hCDC50a structures, could be traced to run towards ctDnf1p. Thus, the C-terminal tail and the N-terminal peptide of ctCdc50p are in such a conformation that sandwiches the C-terminal amphipathic helix of ctDnf1p (Fig. S10). The two TMs of ctCdc50p form hydrophobic interactions with TM7 and TM10 of ctDnf1p. The ectodomain of ctCdc50p has the largest interfaces with ctDnf1p, interacting with all the exoplasmic loops except L1/2 (Fig. 1a). Thus, ctCdc50p acts as a 3-way clamp to hold TMs 3-10 of ctDnf1p in a relatively fixed conformation in both E1-ATP and E2P structures.

The E1-ATP and E2P structures have a lipid-binding site in common in a cavity formed by TMs 7, 8, and 10, on the opposite side of TMs 2, 4, and 6 (Fig. S11). Phospholipid density is observed at the cytoplasmic border of the membranes. The cavity was suggested to be a PI4P binding site for scDrs2p activation¹. However, in our structures, the head group does not insert as deep as PI4P in scDrs2p E2P^{inter} or E2P^{active}. Instead, it is likely to be the head group of PS as modeled in scDrs2p E2P^{inhib}¹.

Discussion

Phospholipid flipping coupled with the E1-E2 transition

Four lipid-binding sites are identified in the groove formed by TMs 2, 4, and 6, two from E1-ATP and two from E2P. The four sites arranged in such a way that they could relay the phospholipid substrates through the groove during the E1-E2 transition (Fig. S12). Conformational changes of TM1 and TM2 guide the phospholipids to move from the exoplasmic leaflet to the cytoplasmic leaflet. ATP binding to the lipid flippase in the E1-ATP state detaches the A domain from the N and P domains. The large motion of the A domain increases the flexibility of TMs 1 and 2 and exposes a negatively charged patch formed by the residues from TMs 2 and 4. The local lipid bilayers are distorted and the membranes are thinned by almost a half. In the distorted membranes, the phospholipid molecules are more likely to tilt parallel to the

membrane plane. The lipid head groups are in an inward-facing orientation, ready to enter the groove via E1-site2 (Fig. S12a). In the E2P state, the A domain is associated with the P and N domains tightly, leading to a relatively rigid conformation of TMs 1 and 2. The local lipid bilayer structures are restored. TMs 2, 4, and 6 create a cavity (E2-site1) in the exoplasmic leaflet for shielding the polar head group of the phospholipid that has been picked up from E1-site2 (Fig. S12b). E2-site1 is disrupted in the E1-ATP state as TM2 moves towards TMs 4 and 6 and two polar residues of TM4 (Q549 and N550) lean towards the membranes. The lipid head group is likely to be squeezed out and to move forward to the cytoplasmic leaflet via E1-site1, a shallow hydrophilic cleft (Fig. S12c). Finally, the phospholipid reaches E2-site2 and is held by a clamp between TMs 2 and 4 in a flipped conformation (Fig. S12d). The phospholipid substrate is ready to be laterally released into the cytoplasmic leaflet when the clamp is disrupted in the E1-ATP state. In the scenario proposed above, it takes two E1-E2 cycles to flip one phospholipid substrate, but costs one ATP molecule per phospholipid on average because two phospholipids are present at the same time in each state. However, as we are missing several intermediate states, e.g. E2 and E1P, the exact cycle number and ATP cost per substrate need further investigation. During lipid transport, the hydrophilic head group of the phospholipid substrate is constantly protected from the hydrophobic environment by sliding through the binding sites in the positively charged groove (Fig. 2b, d). The groove provides the only continuous hydrophilic pathway in the M domain during the E1-E2 transition (Compare Fig. 2b, d and Fig. S11c). The positive charges are mainly contributed by K174, R181, and K1121 on the TMs. The highly conserved K1121 has been shown to be important for substrate binding and ATPase activity³. Consistent with biochemical data³, the groove has high affinity to the lipid substrate in the E2P state as evident by the strong phospholipid density, whereas the groove shows weak lipid binding to facilitate lipid entry and exit in the E1-ATP state as indicated by the fragmented lipid density in the structure. Similarly, a hydrophilic membrane-traversing groove is also present in the TMEM16F scramblase⁴.

The “hydrophobic gate” model suggests that TMs 1 and 2 move away from TMs 3 and 4 during lipid transport⁵. Indeed, our structures show that TM1 and TM2 becomes flexible in E1-ATP. The key residue, I364 of the “hydrophobic gate” (I554 in ctDnf1p), is at the interface between TMs 1, 2, and 4 (Fig. S13). Thus the mutations of the residue may disrupt the E1-E2 equilibrium and hamper lipid flipping as observed in the mutagenesis studies⁵. The “two-gate” model suggests that the flippases recognize the phospholipid substrates by interacting with the head groups. Residues other than the classical ion binding residues in ion-pumping P-type ATPases are involved in recognition⁶⁻⁹. Consistent with the model, the four distinct binding sites in our structures mainly interact with the lipid head groups. However, the sites do not seem to provide a discrimination mechanism for different phospholipid substrates. As shown in the phospholipid-dependent ATPase activity assays, ctDnf1p may have different

substrate specificity from scDrs2p and hATP8A1. The amino acids that interact with the polar head group of the phospholipid substrate at E2-site1 are similar to those in the structures of scDrs2p and hATP8A1. The corresponding residues are Q549 and N550 of ctDnf1p, S503 and N504 of scDrs2p, and N352 and N353 of hATP8A1 (Fig. S1). The clamp residues of E2-site2 consist of both hydrophilic and hydrophobic residues, but are not conserved among P4-ATPases (Fig. S1). The serine residues at E1-site1 are highly conserved among P4-ATPases, and E1-site2 only provides a steric opening. Further studies on other intermediate states may provide clues on the substrate specificity.

Materials and methods

Protein expression and purification

Protein BLAST search identified three P4-ATPases in *C. thermophilum*, including one *S. cerevisiae* Drs2p homolog (ctDrs2p), one Dnf1p and Dnf2p homolog (ctDnf1p), and one Dnf3p homolog (ctDnf3p) (Fig. S1). Only one CDC50 protein was found in the *C. thermophilum* genome (ctCdc50p). After initial screening, ctDnf1p was chosen to co-express with ctCdc50p in yeast. The genes of ctDnf1p and ctCdc50p were cloned from the cDNA library of *Chaetomium thermophilum* (var. *thermophilum* strain: DSM1495, a gift from Dr. Stefan Schoebel). Superfolder green fluorescence protein (sfGFP)¹⁰, a Twin-Strep tag and a 3C protease cleavage site were fused to the N-terminus of ctDnf1p. sfGFP, a His₉ tag, and a 3C protease cleavage site were fused to the N-terminus of ctCdc50p. The expression plasmids pRS426-sfGFP-twinStrep-3C-ctDNF1 and pRS424-sfGFP-His₉-3C-ctCDC50 were co-transformed into *S. cerevisiae* strain BJ5465 using the LiAc/SS carrier DNA/PEG method¹¹. Yeast cells were cultured in synthetic drop-out medium supplemented with 2% raffinose at 30 °C for about 24h to reach an optical density (OD₆₀₀) of about 5. The culture was induced by the addition of 2% galactose and continued for 20 h at 25°C. The cells were harvested and stored at -80 °C until use.

The cells were suspended in the membrane extraction buffer (20 mM Tris-HCl pH 7.4, 150 mM NaCl, 5mM MgCl₂, 1mM DTT, and protease inhibitor cocktails) and lysed by high pressure homogenization. The crude lysate was clarified by centrifugation (20,000×g, 25 min, 4°C). The membrane fraction was pelleted by ultracentrifugation (200,000×g, 1 h, 4°C) and washed once with the membrane extraction buffer. The membrane pellets were solubilized in 2% lauryl maltose neopentyl glycol (LMNG, Anatrace) in the membrane solubilization buffer (20 mM Tris-HCl pH 7.4, 150 mM NaCl, 5mM MgCl₂, 1mM DTT, 10% glycerol, and protease inhibitor cocktails). After incubation at 4 °C for 1 h, the solution was clarified by ultracentrifugation (200,000×g, 1 h, 4°C). The supernatant was mixed with avidin (Sigma) and loaded onto a column pre-packed with StrepTactin resin (IBA

Lifesciences). The eluents were concentrated and incubated with 3C protease at 4 °C overnight. The protein solution was then loaded onto a Superdex 200 10/300 column (GE Healthcare). The peak fractions were pooled and concentrated (Fig. S2). The purified protein was either reconstituted into nanodiscs or flash-frozen in liquid nitrogen and stored at -80 °C.

The purified protein was mixed with MSP1D1¹² and yeast polar lipids (Avanti Lipids, 40 mg/ml dissolved in 1% DDM) at a molar ratio of 1:2:25. Bio-beads SM2 (Bio-Rad) were then added to the mixture and incubated at 4 °C overnight to remove detergents. The complex was further purified by size-exclusion chromatography on a Superdex 200 10/300 column. The peak fraction had a protein concentration of 1.0 mg/ml (Fig. S2). It was immediately used for cryo-EM sample preparation without concentrating.

Cryo-EM sample preparation and data collection

The freshly prepared samples were incubated with 1mM BeF₃ or 1mM AMPPCP on ice for 30min before vitrification. The cryo-grid preparation was performed at 4 °C and 100% humidity in an FEI Vitrobot Mark IV. 4 µl sample was applied to each freshly glow-discharged grid (Quantifoil, R1.2/1.3). The grids were then plunge-frozen in liquid ethane. The cryo-grids were screened with a 200 kV FEI Talos Arctica microscope equipped with a FEI Ceta camera. The data were collected on a 300 kV FEI Titan Krios TEM with a K2 summit camera and GIF Quantum energy filter (Gatan). The images were collected at a magnification of 130,000× with a calibrated pixel size of 1.055 Å. The dose rate was set at 8 e⁻/s/pixel and the exposure time was 8 s, corresponding to a total dose of 57.5 e⁻/Å². Movie stacks (32 frames each) were recorded with the software SerialEM¹³ under low-dose conditions with defocuses ranging from -1 to -2 µm.

Image processing

The movie stacks were subject to motion correction and electron-dose weighting by using MotionCor2¹⁴ (Fig. S3a, S4a). The program Gctf¹⁵ was used to estimate the contrast transfer function (CTF) parameters. Images of high quality were selected for further image processing on the basis of the CTF power spectra of the corrected images. The following calculations are performed with RELION3.0¹⁶. Particles of high quality were selected according to 2D classification (Fig. S3b, S4b) and 3D classification results. The selected particles were subject to several rounds of CTF refinement and polishing. After mask-based post-processing, the final maps had resolutions of 3.40 Å and 3.48 Å for the AMPPCP and BeF₃⁻ samples, respectively (Fig. S3, S4). All the resolution estimations were based on gold-standard Fourier Shell Correlation (FSC) 0.143 criteria.

The model for the E2P (BeF₃⁻) structure was built manually in Coot¹⁷, with the guidance of the scDrs2p structures. The model was refined in real space using Phenix¹⁸. For the model building of E1-ATP (AMPPCP), the E2P model was fit in the E1-ATP density map. Each domain is subject to rigid body refinement. Due to the local resolution limits, the A and N domains were not refined further. The rest parts of the E1-ATP model were refined in real space with Phenix. Model validation was done with MolProbity¹⁹. The cryo-EM maps have been deposited in the Electron Microscopy Data Bank under accession numbers 0872 (BeF₃⁻) and 0873 (AMPPCP). The atomic structure coordinates have been deposited in the Protein Data Bank under the accession number 6LCP (BeF₃⁻) and 6LCR (AMPPCP). All other data can be obtained from the corresponding author upon reasonable request.

ATPase activity assay

The ATPase activity assays were carried out by using BIOMOL® Green (Enzo) to measure the free phosphate concentrations. The reaction solutions consisted of 0.05mg/ml protein, 0.01% LMNG, 0.02% C₁₂E₉ (Anatrace), 150 mM NaCl, 20 mM HEPES-NaOH pH 7.5, 5mM MgCl₂, 1mM DTT, 2.5mM ATP, and lipids at the indicated concentrations. The reactions were carried out at 30 °C for 20 min, and then immediately diluted 10 times for color development. 100 µl reagent was added to 50 µl sample and the mixture was incubated at room temperature for 20 min. The absorbance at 650 nm was measured in a microplate reader (BioTek Cytation5). The phosphate concentration was determined by calibration with the phosphate standard (BML-KI102).

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Supplementary Figures

Fig. S1 Sequence alignment of selected P4-ATPases.

Sequence alignment of ctDnf1p, ctDrs2p and other P4-ATPases in yeast, bovine, human, and *A. thaliana*, aligned by T-coffee⁴⁸. The conserved domains and transmembrane helices of ctDnf1p are indicated above the sequences. The conserved residues are indicated in red letters. The amphipathic helix of TM1 is highlighted with a green bar above the alignment. The phosphorylation site of the P domain is highlighted with a green dot. The residues involved in the negatively charged patch are highlighted with red dots. The residues contribute to the positive charge of the groove are highlighted with blue dots. The residues involved in E1-site1 are highlighted with orange dots. The residues involved in E2-site1 are highlighted with magenta dots. The residues involved in E1-site2 are highlighted with purple dots. The key isoleucine residue in the hydrophobic gate model is highlighted with a grey dot. Ct, *Chaetomium thermophilum*; Sc, *Saccharomyces cerevisiae*; Bt, *Bos Taurus*; Hs, *Homo sapiens*; At, *Arabidopsis thaliana*. Uniprot accession numbers: ScDRS2, P39524; ScDNF1, P32660; ScDNF2, Q12675; BtATP8A2, C7EXK4; HsATP8A1, Q9Y2Q0; HsATP8A2, Q9NTI2; HsATP11A, P98196; HsATP11C, Q8NB49; HsATP8B1, O43520; HsATP8B2, P98198; HsATP10A, O60312; AtALA2, P98205; AtALA10, Q9LI83.

Fig. S2 Purification and characterization of the ctDnf1p-Cdc50p complex.

a, Flow chart of ctDnf1p-Cdc50p purification. **b**, Size-exclusion chromatography profile of the protein complex reconstituted into nanodiscs. The gray-shaded area (Fraction 27) was used for cryo-EM analysis. **c**, SDS-PAGE analysis of fractions from the SEC purification in **b**. **d**, ATPase activity of ctDnf1p-Cdc50p complex stimulated by phospholipids. Data points represent the mean \pm SEM of at least three experiments. POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine. POPS, 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-L-serine.

Fig. S3 Cryo-EM single particle analysis of ctDnf1p-Cdc50p with AMPPCP

a, Representative image after motion correction. **b**, Representative results of 2D classification. **c**, Workflow of the single particle analysis. **d**, Local resolution map of the final sharpened map, shown with (left) and without (right) the nanodisc. **e**, Fourier shell correlation (FSC) curve with estimated resolution according to the gold standard.

Fig. S4 Cryo-EM single particle analysis of ctDnf1p-Cdc50p with BeF₃.

a, Representative image after motion correction. **b**, Representative results of 2D classification. **c**, Workflow of the single particle analysis. **d**, Local resolution map of the final sharpened map shown with (left) and without (right) the nanodisc. **e**, Fourier shell correlation (FSC) curve with estimated resolution according to the gold standard.

Fig. S5 Examples of the fit of models into the density map.

a-g, Density map and model in selected regions of each domain and TMs. Residues at the beginning and end of each polypeptide segment are indicated. **h**, Density map and model of BeF_3^- , Mg^{2+} , and D606 in the E1-ATP structure. **i**, Density map and model of AMPPCP, Mg^{2+} , and D606 in the E1-ATP structure.

Fig. S6 Comparison of ctDnf1p-Cdc50p structures in the E1-ATP and E2P states.

a, Overlay of the E1-ATP and E2P structures by superimposing TMs 3-10 of ctDnf1p and ctCdc50p (grey). The A domain is yellow in E1-ATP and blue in E2P. The N domain is red in E1-ATP and cyan in E2P. TM2 is purple in E1-ATP and TMs 1 and 2 are green in E2P. **b**, same as **a**, except the N domains are omitted for clarity. The motion distance of the A domain between the E1-ATP and E2P states is labeled. **c**, same as **a**, except the A domains are omitted. The movement of the N domain between the E1 and E2 states is indicated. **d**, same as **a**, except rotating by 90 degrees and the A and N domains are omitted to show the movements of TMs 1 and 2 between the E1-ATP and E2P states.

Fig. S7 Comparison of AMPPCP in different E1-ATP structures

a-d, AMPPCP conformations from different P-type ATPases are shown as sticks. The protein structures from which AMPPCP are extracted are labeled.

Fig. S8 Comparison of phospholipid binding at E2-site1 in ctDnf1p and hATP8A1

a, Lipid binding at E2-site1 of ctDnf1p. The protein is shown as tan ribbon representation. The density of the lipid is shown as a grey mesh. The lipid (green) and its interacting residues (tan) are shown as sticks. **b**, Lipid binding in the E2Pi-PL structure of hATP8A1 (PDB ID: 6K7M, EMDB number: 9941). The protein is colored purple. The lipid is yellow. **c**, Superimposition of the two lipid binding sites. The yellow arrow and green arrow indicate the extension directions of the lipid acyl chains in hATP8A1 and ctDnf1p, respectively.

Fig. S9 Comparison of E1-site1 among P4-ATPase structures

a, E1-site1 in ctDnf1p. The density of the possible phospholipid substrate is shown as a grey mesh. The conserved serine residue is labeled. **b-c**, same as in **a**, except showing scDrs2p and hATP8A1, respectively.

Fig. S10 Interaction of the two terminal segments of ctCdc50p with ctDnf1p on the cytoplasmic side.

The N-terminal and C-terminal segments of ctCdc50p are colored yellow. The rest of ctCdc50p is pink. The ctDnf1p fragments that interact with ctCdc50p are colored red. The rest of ctDnf1p is tan. Interacting segments and TMs are labeled.

Fig. S11 A common lipid binding site in E1-ATP and E2P

a-b, Lipid binding site in E1-ATP (**a**) and E2P (**b**). The density of the lipid is shown as grey meshes. The lipid molecules are shown as sticks. **c**, Electrostatic potential surfaces of E1-ATP (left) and E2P (right), showing the lipid binding environment. The lipid molecules are shown as sticks. The surfaces showing here are on the opposite side of the surfaces showing in Fig. 2**b** and **d**.

Fig. S12 Model of phospholipid flipping by P4-ATPases

a, Cartoon drawing of E1-ATP. Domains are labeled and colored as in Fig 1**a**. The membrane is colored grey. The lipid molecules with light green heads are arranged to show the distortion of bilayers. The lipid molecule with the dark green head represents a substrate that is entering the transport pathway via E1-site2. **b**, Cartoon drawing of E2P. The lipid substrate is trapped in E2-site1. **c**, As in **a**, with the lipid bound at E1-site1. **d**, As in **b**, but the lipid substrate has been flipped to the cytosolic leaflet and waits at E2-site2 to be released.

Fig. S13 The “hydrophobic gate” residue I554 in cfDnf1p

a, Top view of the I554 and its interacting residues in E2P. The interacting residues are shown as sticks.
b, Top view of I554 in E1-ATP. TM4 is in the same orientation as it is in **a**.

Table S1 Cryo-EM data collection, refinement and validation statistics

	ctDnf1p-Cdc50p with AMPPCP (EMDB-0873) (PDB 6LCR)	ctDnf1p-Cdc50p with BeF ₃ ⁻ (EMDB-0872) (PDB 6LCP)
Data collection and processing		
Magnification	130,000	130,000
Voltage (kV)	300	300
Electron exposure (e-/Å ²)	57.5	57.5
Defocus range (µm)	-1.0 to -2.0	-1.0 to 2.0
Pixel size (Å)	1.055	1.055
Symmetry imposed	C1	C1
Initial particle images (no.)	2,397,258	2,820,251
Final particle images (no.)	272,912	249,694
Map resolution (Å)	3.40	3.48
FSC threshold 0.143		
Map resolution range (Å)	3.3-8.2	3.3-7.8
Refinement		
Model resolution (Å)	3.4	3.5
Map sharpening B factor (Å ²)	-94	-84
<u>Model composition</u>		
Non-hydrogen atoms	11590	12406
Protein residues	1420	1514
Ligands	17	18
<u>B factors (Å²)</u>		
Protein	41.2	50.0
Ligand	45.6	51.5
<u>R.m.s. deviations</u>		
Bond lengths (Å)	0.012	0.010
Bond angles (°)	1.055	1.088
<u>Validation</u>		
MolProbity score	2.16	2.35
Clashscore	15.5	18.1
Poor rotamers (%)	0.31	0.25
<u>Ramachandran plot</u>		
Favored (%)	89.8%	88.1%
Allowed (%)	10.2%	11.7%
Disallowed (%)	0%	0.2%

Fig S1

CtDNF1	MAPPQEEG-GG-----		10
CtDRS2	MSGRRPPG-AASSSHN-----P-NE-DLLLDLDN-DQPIYNSGQRSALTDLDDLMRSHNYDQDGLA-----		57
ScDRS2	MNDRETP-PK---RK-----P-GEDDTLFDIDFLDDTTSHSGSRSKVTNS-----HANANYIPPSHVLPEETIDLDADDDN		67
ScDNF1	MSGTFHGD-GH-----APMSP-FE-DTFQFEDN-SS---N-----EDTHIA-----		34
ScDNF2	MSSPSKPT-SPFVDDIEHESGSASNGLSSMSP-FD-DSFQFEK-SS---A-----HGNIEVA-----		51
BtATP8A2	MSRAT-----		5
HsATP8A1	MPTMRRTV-----S-----		9
HsATP8A2	MLNGAGLD-----KALKMSLPRRSRIRSS-----		24
HsATP11A	MDCSLVRTLVHR-----		12
HsATP11C	MQMVPSL-PPAS-----		11
HsATP8B1	MSTERDSE-TTFDEDSQ-----P-ND-EVVPYSDD-----ET-----		29
HsATP8B2	MTVPKEMP-EKWARAQA-----PPS-----WS-----		21
HsATP10A	MEREPAGT-EEP-----		11
AtALA2	MK-----		2
AtALA10	MAGPSRRR-RRLLH-----LS-----		14

CtDNF1	-----		-
CtDRS2	-----PSRPSVSYD-DFIGSSSSQPRHSAGRPPPS-----SGLSAPGSSSRPVGPY--STAIEINRQ		110
ScDRS2	IENDVHENLFMSNNHDDQTSWNANRFDSDAYQP-----QSLRAVKPPGLFARFGNGLKNAFTFKRKKGP--ESFEMNHY		139
ScDNF1	-----P-THFD-----DGATSNKYSRPQVSNFDETPKNKR-		63
ScDNF2	-----K-T-----GGSVLKRQSKPMKDI--STPDL SKV		76
BtATP8A2	-----		-
HsATP8A1	-----E--IRSRAEGYE-----		19
HsATP8A2	-----VGP--VRSS-LGYK-----		35
HsATP11A	-----Y-----		13
HsATP11C	-----E-----		12
HsATP8B1	-----		-
HsATP8B2	-----		-
HsATP10A	-----GPPGRR-----		17
AtALA2	-----		-
AtALA10	-----K--IYSYTCGKS-----		24

CtDNF1	-----		-
CtDRS2	-YSQT-SDLGNYQRYADDDYPDEGTSYYQHGGAGGEPSSGRANA---RQRNSVLSLGG-GFL-GRVKNRGLMGQYSEMDLPLTESRTGHR		196
ScDRS2	-NAVT-NNELDDNYLDS-----RNKFNI-----KILFNRYILR		170
ScDNF1	--EDA-EEFT-----FNDDTEYDNHSFQPTPKLNNGSGTFDDVE-LDNDSGEPH-TNY-DGMKFRFMGTG		122
ScDNF2	TFDGI-DDYSNDNDIND-DDELNGKKEIHE-----HENEVDDLHFSQATPMPNTG--GFEDVE-LDNEGSNNSDQADHKLKRVRFGTR		157
BtATP8A2	-----S-----		6
HsATP8A1	---KT-DDVSEKTS-----		29
HsATP8A2	---KAEDEMSRATS-----		46
HsATP11A	-----C-----		14
HsATP11C	-----C-----		13
HsATP8B1	---E---DEL D-----DQGS AVEP-----EQNRVNR-----EAEENREPFRR		59
HsATP8B2	-----R---KKPS-----		26
HsATP10A	---RR-R---EG-----		22
AtALA2	-----		-
AtALA10	---SF-Q--EDHSN-----		32

		A domain	
CtDNF1	RLTVKSGARKRLSLMTR-----AQAKNSATEKRQSGV--TDDGSPAADGD-QKEGSISSSNNGGSAPRKLKYFNLLPLPPE		96
CtDRS2	TDT-----GSGEIPAQPEKKKFDGPNFRFGFRS-----KPD-P-----STLGFRRIIYLNPP		243
ScDRS2	KN-----VGDAE-----GNGEPRVIHINDSL		191
ScDNF1	RNKKGN-----PIMGRSKTLK-----WARKNIPNPFED--FT--KDDIDPGAI--NRAQELRTVYVYNNMPLPKD		179
ScDNF2	RNKSGR-----IDINRSKTLK-----WAKKNFHNAIDE--FSTKEDSLENSAL--QNRSELETVYVYNNLPLED		217
BtATP8A2	-----		24
HsATP8A1	-----LAD-Q-----EEVRTIFINQPQ		45
HsATP8A2	-----VGD-Q-----LEAPARTIYLNQPH		64
HsATP11A	-----AGE-E-----NWVDSRTIYVGHREPP		34
HsATP11C	-----AGE-E-----KRVGTRTVFVGNH-PV		32
HsATP8B1	KE-----CTW-Q-----VKANDR-KYHEQPHEM		80
HsATP8B2	-----WG-----TEEERRARANDRE		41
HsATP10A	-----RTRTVRSNLLPPPG		36
AtALA2	-----RFVYINDDE		11
AtALA10	-----IGG-----PGFSRVVYCNPEGS		49

	A domain	TM1	TM2	
CtDNF1	LKDE-----EGHP IQQFPRNKIRTAKYTPLSFEPKKNLWFQFHNIANIFLFLVILVIFPIFGVNPGLNSVPLIVITVTAIKDAIED			179
CtDRS2	-----ANAANKYVDNHVSTAKYNFAFLPKFLFEQFSKFAFIFFLFTAGLQQIPGLSPTNRYTTIGPLIVLLVSAKDELVED			321
ScDRS2	-----ANSSFGYSDNHISTTKYNFAFLPKFLFEQFSKYANLFFELCTSAIQQVHVSPTNRYTTIGPLIVLLVSAKMECIED			269
ScDNF1	MIDE-----EGNPIMQYPRNKIRTKYTPLTFEPKNILFQFHNFANVYFLVLIILGAFQIFGVNTPGLSAVPLVVIVITAIKDAIED			262
ScDNF2	MLDE-----DGLPLAVYPRNKIRTKYTPLTFEPKNILFQFHNFANVYFLVLIILGAFQIFGVNTPGFASVPLIVIVITAIKDGIED			300
BtATP8A2	-----LNKFCDNQISTAKYSVVVTELRFLYEQRRAANAFELFIALLQQIPDVSPTRGRYTLVPLIIILTIAGIKEIVED			99
HsATP8A1	-----LTKFCNNHVSTAKYNIITFLRFLYEQFRRAANSEFLFIALLQQIPDVSPTRGRYTLVPLIFLAVAAIKEIIED			120
HsATP8A2	-----LNKFRDNQISTAKYSVLTFLRFLYEQRRAANAFELFIALLQQIPDVSPTRGRYTLVPLIIILTIAGIKEIVED			139
HsATP11A	-PGA-----EAYIPQRYPDNRIVSSKYTFWNEIPKNLFEQFRVANFVFLIIFLVQLI-IDTPSPVTSGPLFFVITVTAIKQYED			115
HsATP11C	-SET-----EAYIAQRFCDNRIVSSKYTLWNEIPKNLFEQFRRIANFVFLIIFLVQVT-VDTPSPVTSGLPLFFVITVTAIKQYED			113
HsATP8B1	-NTKFL-----CIKESKYANNAIKTYKYNFAFTFIMNLFEPQFRANLFLALLLQAVPQISTLAWYTLVPLVVVLGVTAIKDLVD			163
HsATP8B2	-----YNEKFQYASNCIKTSKYNILTFELVNLFEQFQEVANTYFLFLLILQLIPQISSLSWFTTIVPLVGLVLTITAVKDATD			119
HsATP10A	AEDPAAGAAGKERRRRRGCQHLADNRLKTKYTLLESFEPKKNLFEQFRPANVYFVFIALLNFVPAVNAFQPLALAPVLFILATAFRDLWED			130
AtALA2	-----ASKELCCDNRI SNRKYTLWNEIPKNLFEQFRFMNQYFLLIACLQLWSLITPVNPASTWGPLIFIFAVSASKEAWD			88
AtALA10	-----PAAERRNYAGNYVRSTKYTVASFEKSLFEQFRVANFVFLVITGIIISL-TDLSPYGAVSALLPLALVISATMVKEGIED			127

	TM2 cont.	A domain	
CtDNF1	YRRITLIDIELNNA	PVHRLQGWENNVNVEKDNVSLWRRFFKANSRFFGSIWHL-IERLWKEDAQSMR-----QR-FASADPRMSIETRTAPW	262
CtDRS2	YRKQADKALNMSKTRVLRG-		341
ScDRS2	IKRANSDEKELNNSAEIFSE-		289
ScDNF1	SRRTVLDELVNNTKTHILEGVENENVSTDNISLWRRFFKANSRLLFKFIQYCKEHLTEGKKRMRQRKHELVRVQKTVGTSGPRSSLDSID---		353
ScDNF2	SRTVLDELVNNTRTHILSGVKNENAVDNLWRRFFKANRALIKIFEYFSENLTAAAGREKQLQKKREELRRKRNSRSFSGPRGSLDSIG---		391
BtATP8A2	FKRHKADNAVNKKKTIIVLRN-		119
HsATP8A1	IKRHKADNAVNKKQTOVLRN-		140
HsATP8A2	FKRHKADNAVNKKKTIIVLRN-		159
HsATP11A	WLRHKADNAMNQCVPVHFIOH-		135
HsATP11C	CLRHRADNEVNKSTVYIIEEN-		133
HsATP8B1	VARHKMDKEINNRTECEVIKD-		183
HsATP8B2	YFRHKSQDNQVNNRQSQVLIN-		139
HsATP10A	YSRHRSDHKINHLGCLVFSRE-		151
AtALA2	YHRYLSDKKAKEKVVIVKQ-		108
AtALA10	WRKQQDIEVNNRKVKVHGD-		147

	A domain	
CtDNF1	DPSHRRSVASHTTEIEIQMTVPVSPVPHDPDPTVSSAIENEATLLQ--NLKGLDINHEIPVSGKA--RFHKDANKNLVVGDFVRIYNDDELPA	351
CtDRS2		369
ScDRS2		319
ScDNF1	--SYR-----VSADYGRPSLDYDNLEQGAG-----EANIVDRSLPRTDC--KFAKNYKGVKVGDIVRIHNDEIPAD	418
ScDNF2	--SYR-----MSADFGRPSLDYENLNQMTSQANRYNDGENIVDRTLQPNPEC--RFAKDYKNNVVGDIVRVHNDDEIPAD	463
BtATP8A2		147
HsATP8A1		168
HsATP8A2		187
HsATP11A		163
HsATP11C		161
HsATP8B1		211
HsATP8B2		167
HsATP10A		180
AtALA2		136
AtALA10		176

	A domain	
CtDNF1	IILLATSDDPDGACYVEETKLNLDGETNLKVRQALRCGRITLK-HA-RDCERAQVIESEPPQPNLYKYNGAIRWKQRPVWDPHPGEPREMSEPIGIDN	443
CtDRS2	LVLASSEPEGLCYIETANLDGETNLKIKQALPETASLV-SS-TELSRLGRLRSEQVNSLSLYTYEATLTLQGTGG-----GEKELPLNPEQ	453
ScDRS2	TIIILSSSEPEGLCYIETANLDGETNLKIKQSRVETAKFI-DV-KTLKNMNGKVVSEQVNSLSLYTYEGTMTLN-----DRQIPLSPDQ	399
ScDNF1	IILLATSDDPDGACYVEETKLNLDGETNLKVRQSLKCTNTIR-TS-KDIARTKFWIESEGEHSNLYTYQGNMKWRNLA---DG--EIRNEPITINN	504
ScDNF2	MILLATSDDPDGACYVEETKLNLDGETNLKVRQSLKCSKIIK-SS-RDITRTKFWIESEGEHANLYSYQGNFKWQDTQ---NG--NIRNEPVNINN	549
BtATP8A2	VVLLSSSEPEQAMCYIETANLDGETNLKIRQGLSHADMQ-TR-EVLMKLSGTIECEGPNRHLYDFTGNLNLGD-----KSPVALGPDQ	228
HsATP8A1	LISLSSEPEQAMCYIETANLDGETNLKIRQGLPATSDIK-DV-DSLMRISGRIESESNRHLYDFVGNIRLDG-----HGTVPLGADQ	249
HsATP8A2	VVLLSSSEPEQAMCYIETANLDGETNLKIRQGLSHADMQ-TR-EVLMKLSGTIECEGPNRHLYDFTGNLNLGD-----KSLVALGPDQ	268
HsATP11A	LIFLSSNRDGTGHVTHASLDGESSRHTHYAVDQTGKGFH-TE-EDIGGLHATIECEGQPPDLYKFGVGRINYSYL---N---DPVVRPLGSEN	248
HsATP11C	LILLSSCTDPTDGTGYVTASLDGESSRHTHYAVRDTIALC-TA-ESIDTLRAAIECEGQPPDLYKFGVGRINISYNS---L---EAVARSLGPEEN	246
HsATP8B1	LILLSSSEPNLSQYVEETAEALDGETNLKRFKMSLEITDQYLORE-DTLATFDGFIECEGPNRDLKFTGTLFWR-----NTSFPLDADK	292
HsATP8B2	LILLSSSEPEGLCYIETAEALDGETNMMVQAIPTSELG-DI-SKLAKFDGCEVIECEGPNRDLKFTGTLFWR-----ENKFPLSNQN	247
HsATP10A	LILLSSSDPDGLGHITAEALDGETNLKRRQVVRGFSELV-SE-FNPLTFSSVIECEGPNRDLKFTGTLFWR-----GKKAGLYKEN	261
AtALA2	LVLGTSDDPDGACYVEETAEALDGETDLKTRVIPSAC-VGI-DL-ELLHKMGVIECEGPKDKDIRFDANMRLFPF---I---DNDVCSLTIKN	220
AtALA10	LLLSSSYEDSVQYVEETAEALDGETNLKRVKQGLEATSSLL-NQSDSDFDKFRGVVRCEDPNVNLVYVFGTLALEE-----ERFPLSIQQ	257

	A domain	TM3	
CtDNF1	LLRGRGHLRNTAEWALVVVFTGHDTKIMMNAAGTIPSSRRARIARELNFNVICNFGILLIMCLIAAIAANGIAW--G--KTDASL-AWFEYGSIGG-		531
CtDRS2	LLRGTALRNTAWIHVVVFTGHDTKIMRNATAAPIKRTVKEKQNLKLVMLVGMVLSVISTAGDLIMR--G--V-AGRS-FEYLDLGDIT-		540
ScDRS2	MIRGTALRNTAWIFGLVIFVFTGHDTKIMRNTATAPIKRTAVEKIIINRQIIALFTVLIVLILISSIGNVIMS--T--A-DAKH-LSYLYLEGTN-		486
ScDNF1	VLRGCTLRNTKAWMGVVFVFTGHDTKIMLNSGITPTPKSRISRELNFVSVINFLVLLFICLVFSGIANGVYY--D--KGRSR-FYFEGTITAG-		592
ScDNF2	LLRGTALRNTKAWMGVVFVFTGHDTKIMINAGVPTPKSRISRELNFVSVILNVLVLLFICLVFAGIANGVYY--K--QKPRSR-DYFEGTITAG-		637
BtATP8A2	ILRGTALRNTQVWGFVVFVFTGHDTKIMQNSTKAPLRSNVEKVTNVQIILVLFGLLVMALVSSVAGALYWN--G--S-QGGK-NWYIKKMDAT-		315
HsATP8A1	ILRGAQLRNTQVWGFVVFVFTGHDTKIMQNSTSPPLRLSNVERITNVQIILILFCILIAMSLVCSVSGAIWN--R--R-HSGK-DWYLNLYGG-		336
HsATP8A2	ILRGTALRNTQVWGFVVFVFTGHDTKIMQNSTKAPLRSNVEKVTNVQIILVLFGLLVMALVSSVAGALYWN--R--S-HGK-NWYIKKMDT-		355
HsATP11A	LLRGTALRNTKTEKIFGVAIYTGEMTKMALNYQSKSQRRSAVESKSMNAFLIVLYLCILISKALINTVLKYMWQ--S--EPPFRDE-PWYNQKTESER		337
HsATP11C	LLMKGATLRNTKTEKIFGVAIYTGEMTKMALNYQSKSQRRSAVESKSMNAFLIVLYLCILISKALINTVLKYMWQ--S--TPYNDL-PWYNQKTKER		335
HsATP8B1	ILRGCVIIRNTDFCHGLVIFACADTKIMKNSGKTRFRRTKIDYLMNMYVYTFVVLVLLSAGLAIGHAYWE--A--Q-VGNS-SWYLYDGE-D-		378
HsATP8B2	MLRGCVLRNTEWCFGLVIFAGPDTKIMQNSGRTKFRRTSIDRLMNTLVLWIFGLVCMGVILAIGNAWE--H--E-VGMRFOVYLPWDEAV-		335
HsATP10A	LLRGTALRNTDAVVGIVYAGHETKALLNNSGPRYRSKLERQMNCDVLCVLLVCMMSLFSAVGHGLIWRYY--Q--EKKS-LFYVPKSDGSS		351
AtALA2	TLRQSCYLNRNTEWACVSVYTGNTKLGMSRGAEPRLTAMDAMDKLGTGAIFFVQIVVVLVLAGIANGVWK--D--T-EARK-QWYVQYPEEA-		307
AtALA10	ILLRDSKLRNTEVYVCAVVFVFTGHDTKVIQNSTDPSSRSRRIERTMDKIYLMFGLVFLMSVFGSIFGVETREDKVKNGRTE-RWYLKPDADI		350

	TM4	P domain	N	
CtDNF1	-----T-PAL-T-GFTFFWAAVIVFQNLVLEISLVSISLEIVRTLQAFETIYSYVGMYYEKIQPCIPKSNWISDDVQVQIEYIFSDKGTGLTQNVM			617
CtDRS2	-----GA-IAVFKIFIKDMVTYVWVLFSSLVLEISLVTLEMVYWHGILINDELIDYVDVTPANCRTSSLVEEIGMVEYVFSDKGTGLTQNME			629
ScDRS2	-----KA-GLF---FKDFTLFWLFSNLVLEISLFTVELIKYYQAFMINDSGLDLYYEKDTPTVVRTSSLVEEIQVIEYIFSDKGTGLTQNME			571
ScDNF1	-----S-AAT-N-GFVSFWVAVILYQSLVLEISLVSISVEIKTAQAAYFYGVLLYNAKLDYPTPKSNWISDDVQVQIEYIFSDKGTGLTQNVM			678
ScDNF2	-----S-AST-N-GFVSFWVAVILYQSLVLEISLVSISVEIKTAQAAYFYGVLLYNAKLDYPTPKSNWISDDVQVQIEYIFSDKGTGLTQNVM			723
BtATP8A2	-----S-DN---FGYLLTFIILYNNLLEISLVLTVLEVVKYTQALFINWDTMYIYGNTPAMARTSNLNEEQVYIFSDKGTGLTQNIMN			399
HsATP8A1	-----A-SN---FGLNFLTFIILFNNLLEISLVLTVLEVVKYTQAFINWDLDMHYEPTDTAAMARTSNLNEEQVYIFSDKGTGLTQNVMQ			420
HsATP8A2	-----S-DN---FGYLLTFIILYNNLLEISLVLTVLEVVKYTQALFINWDTMYIYGNTPAMARTSNLNEEQVYIFSDKGTGLTQNIMN			439
HsATP11A	-----QRNLF-L-K-AFTDFLAFMVLFNFIIVFSVMVTVEMQKFLGSFFITWEDMDEETGEGPLVNTSDLNEEQVYIFSDKGTGLTQNIMV			425
HsATP11C	-----ETLKV-L-MFTDFLSFMVLFNFIIVFSVMVTVEMQKFLGSFFITWEDMDEETGEGPLVNTSDLNEEQVYIFSDKGTGLTQNIMV			423
HsATP8B1	-----DT-PSY-R-GFLIFWGYIIVLNTMVEISLVSVEVIRLQSHFINWDLQMYAEDTPAKARTTTLNEEQVYIFSDKGTGLTQNIMT			465
HsATP8B2	-----DS-AFF-S-GFLFSWYIILNLTVEISLVSVEVIRLGHSEFINWDLQMYAEDTPAKARTTTLNEEQVYIFSDKGTGLTQNIMV			422
HsATP10A	-----LS-PVT-A-AVYSFLTMIIVLQVLEISLVSVEIVKACQVYFINWDMQLYDEETDSQLQCRALNITEDIQVYIFSDKGTGLTQNIMV			438
AtALA2	-----PWY-E-LLVIPLRFELLCSTMIETISIKVSLDLVGLYAKETIENWDMIDQETGTASAAANTAISEDQVYIFSDKGTGLTQNIMV			392
AtALA10	FFDPER-APM-A-AIYHFFATMLYSYFIETISLVSVEIVKVLQYKFINRDIHMYYEETDKPAQARTSNLNEEQVYIFSDKGTGLTQNIMV			441

	N domain	
CtDNF1	FKKATINGQFYGEAYTEAQAG--M--DRRRGINVEEEA-----KVIREEIAAAKVR-----AIRGL	669
CtDRS2	FKACSTAGVMYAESVPEDR-V--A--TIEDGV-----	656
ScDRS2	FKSCSITAGHCYIDKIPEDK-T--A--TVEDGI-----	598
ScDNF1	FKKCTINGVSYGRAYTEALAG--L--RKRQGIDVETEG-----RREKAEIAKDRDT-----MIDEL	730
ScDNF2	FKKCTINGVSYGRAYTEALAG--L--RKRQGVVVESEG-----RREKEEIAKDRDT-----MIDEL	775
BtATP8A2	FKKCSITAGVTYGHFPELTR-E--P--SSDDFS--R-----	427
HsATP8A1	FKKCTIAGVAYGHVPEPEDYD--C--SPDEWQ-----	448
HsATP8A2	FKKCSITAGVTYGHFPELAR-E--P--SSDDFC--R-----	467
HsATP11A	FKKCCIEGHVYVPHVICNGQV--L--PESSGID-----	454
HsATP11C	FIECCIDGHKYKGVTO--EVDG--L--SQTDTL-----	451
HsATP8B1	FKKCCINQIYGDHRDASQ-H--NH--NKIEQVDFS-----	496
HsATP8B2	FNKCSINCHSYGDVDFDLG-HKAELGERPEPVDFS-----	456
HsATP10A	FRRCTVSGVEYSHDANAQR-L---ARYQEADSEEEVVPRGGSVSRQSGISGSG---HQSVRVVHRTQSTKSHRRTGSRAEAKRASMLSKH	520
AtALA2	FRRCIGIFYGNENGD-----	410
AtALA10	FKKCSITAGKAYGRGITFEVERA--M--AVRSGGS-----PLV-----NEDLDV-----VVD--	482

	N domain	
CtDNF1	RELHDNPFYLHDEDMTFTA-PDFVEDLAGK-----NGPEQQQATEHFMALALALCHTVVAEKQ-----	724
CtDRS2	-----EVGIHDFKRLKDNLNK-----GHPTAQAIIDHFLTLTATCHTVIPEQK-----	698
ScDRS2	-----EVGYRKFDDLKKNLND-----PSDEDSPIINDFLTLTATCHTVIPEFQ-----	641
ScDNF1	RALSGNSQFYPEEVTFVS-KEFVRDLKGA-----SDEVQQRCEHFMALALALCHSVLVEAN-----	785
ScDNF2	RMSDNTQFCPEDLTFVS-KEIVEDLKGS-----SGDHQQKCEHFMALALALCHSVLVEPN-----	830
BtATP8A2	-----IPPPSDSCDFDD-PRLLKNIED-----NHPTAPCIQEFLLTLAVCHTVVPERD-----	475
HsATP8A1	-----NS-QFGDEKTFDD-SLLENLQN-----NHPTAPIICEFLTMMAVCHTAVPERE-----	495
HsATP8A2	-----MPPPCSDSCDFDD-PRLLKNIED-----RHPTAPCIQEFLLTLAVCHTVVPEKD-----	515
HsATP11A	-----MID-----SSPS-----V-NGREREELFRALCLCHTVQVKDDSDVDPG-----	492
HsATP11C	-----TYFD-----K-----VDKNREELFRALCLCHTVVEIKTNDAVD-----	484
HsATP8B1	-----WNTYADGKLAFYD-HYLIEQIQS-----G--KEPEVRFEFLLAVCHTVMVDR-----	541
HsATP8B2	-----FNPLADKKFLFWD-PSLLEAVKI-----G--DPHTHEFRLLSLCHTVMSEEK-----	501
HsATP10A	TA-----FSSPM-EKDI TPD-PKLLKVSCEDKSLAVARHQEHLLAHLSPELSDFDFEIALITICNTVVTSPDQ---PRTKVRVRFELKSPVKTI	606
AtALA2	-----LKD-AQLLNLAITS-----GSTDIVRFELTVMAICNTVLPVQ-----	444
AtALA10	-----QSGPKVKGFNFED-ERVMMGNWV-----RQPEAAVLQKFRLLAVCHTAVIPETD-----	530

	N domain	
CtDNF1	-----	738
CtDRS2	-----DSGEIKYQASSP	710
ScDRS2	-----SDGSIKYQASSP	653
ScDNF1	-----PDNPKKLDLKAQSP	799
ScDNF2	-----KDDPKKLDIKAQSP	844
BtATP8A2	-----GDSIVYQASSP	486
HsATP8A1	-----GDKIYQASSP	506
HsATP8A2	-----GDNIYQASSP	526
HsATP11A	-----RKSPDGGKSCVYISSP	509
HsATP11C	-----G--ATESAELTYISSP	499
HsATP8B1	-----TDGQLNYQASSP	553
HsATP8B2	-----NEGELYKAQSP	513
HsATP10A	EDFLRRFTPSCLTSGCSIGSLAANKSSHKLGSSFPSTPSSDGMLLRLEERLGOPTSAIASNGYSSQADNASELAQE--QESERELRYEASSP	698
AtALA2	-----SKAGDIVYKAQSQ	457
AtALA10	-----EESGNVSYEASSP	543

	N domain	
CtDNF1	DEAALVATARDMGFTVLGMSDGGIN--VNV-----MGKDMHFVLSIIEFNSSRKRMSSTIVRM-P-----DGRILLFCCKGADSVIYRSLKKG	817
CtDRS2	DEGALVEGAVQLGYRF LARKPRAVI--ITV-----NGQLEYELLAVCFENSTRKRMSSTIYRC-P-----DGKIRIYCKGADTVILERLNDQ	789
ScDRS2	DEGALVQGGADLGKFIIRKPNVSVTLLEE-----TGEEKEYQLNICEFNSTRKRMSAIFRF-P-----DGSIKLFCCKGADTVILERLDDE	734
ScDNF1	DEAALVATARDVGFSGVFKTKKGLI--IEM-----QGIQKEFEILNLEFNSSRKRMSCVKI-PGLNPGDEPRALILCKGADSIYRSLRSQ	884
ScDNF2	DESAALVSTARQLGYSFVGSSKGLI--VEI-----QGVQKEFOVLNVLEFNSSRKRMSCI IKI-PGSTPKDEPKALLICKGADSVIYRSLDRT	929
BtATP8A2	DEAALVKGARKLGFVFTARTPYSVI--IEA-----MGQEQTFGILNVLEFNSSDRKRMSVIVRT-P-----SGQLRLYCKGADNVI FERLSKD	565
HsATP8A1	DEGALVRAAKQLNFVTGRTPDSVI--IDS-----LGQEERYELNLVLEFNSTRKRMSVIVRT-P-----SGKLRLYCKGADTVIYDRLAET	585
HsATP8A2	DEAALVKGAKKLGFVFTARTPFSVI--IEA-----MGQEQTFGILNVLEFNSSDRKRMSVIVRT-P-----SGRLRLYCKGADNVI FERLSKD	605
HsATP11A	DEVALVEGQVRLGFTYLRKLDNYME--ILN-----RENHIERFELLEILSDFSRRRMSVIVKS-A-----TGEIYLFCKGADSSIFPRVIEG	589
HsATP11C	DEHALVKGAKRYGFTPLGNRNGYMR--VEN-----QRKEIEEYELLHTLNDAVRRRMSVIVKT-Q-----EGDILLFCCKGADSAVFPVRQNH	579
HsATP8B1	DEGALVNAARNFGFAFLAR TQNTIT--ISE-----LGTERTYVNLAILDNSTRKRMSIIVRT-P-----EGNIKLYCKGADTVIYERLHRM	632
HsATP8B2	DEGALVTAARNFGFVFRSRTPK TIT--VHE-----MGTAITYQLLAILDNSTRKRMSVIVRN-P-----EGKIRLYCKGADTILLDRLHHS	592
HsATP10A	DEAALVYAARAYNCVLERLHDQVS--VEL-----PHLG-RLTFELHTLCLDSVRRRMSVIRH-PL-----TDEINVYTKGADSVVMDLQPC	779
AtALA2	DEDAALVIAASKLHMVFVGKNNALLE--IRF-----NGSVIRYEVLEILFETSRRKRMSVVKDCQ-----NGKILLSCGADSAILPYARA	536
AtALA10	DEAAAVVAAREFGFEFNRTQNGIS--FREL DVS GEKVERVYRLNLVLEFNSTRKRMSVIVRD-D-----DGKLLLSCKGADNVMFERLAKN	628

	N domain	P	
CtDNF1	E-----QADMRRETAQHLEMFV EGLR TLCAIERELSEEYERWRREHDLAATAL-ENREKLEEVADKIERDLTLLEGGTAIEDRLQDQVP		902
CtDRS2	N-----PHVDQTLRHLEEYASEGLR TLCLAFREVPQE FQEWYQVYDKAQTTVGGTRAQELDKAAEIEPKDFYLLGATAIEDRLQDQVP		873
ScDRS2	A-----NQVVEATMRHLEDYASEGLR TLCLAMRDISGEYEWNSIYNEAATTL-DNRAEKLDEAANLIEKNLILIGATAIEDRLQDQVP		818
ScDNF1	SG-----SNSEAI LEKTALHLEQYATEGLR TLCAIQRELSWSEYKWKNEYDIAAASL-ANRDELEVVADSIRELILLEGGTAIEDRLQDQVP		972
ScDNF2	QN-----DATALLEKTALHLEEYATEGLR TLCLAQRELTSWSEYERWVKYVDVAASV-TNREELDKVTDVIRELILLEGGTAIEDRLQDQVP		1015
BtATP8A2	S-----KYMEETLCHLEYFATEGLR TL CVAYADLSERDYEELWLVQEA STIL-KDRAQRLEECY EIEKNL LLLGATAIEDRLQDQVP		648
HsATP8A1	S-----KYKEITLKHLEQFATEGLR TL CFAVAEISESDFQEWRAVYQRASTSV-QNRLLKLEESYELIEKNLQLLGGATAIEDRLQDQVP		668
HsATP8A2	S-----KYMEETLCHLEYFATEGLR TL CVAYADLSENEYEWLVQEA STIL-KDRAQRLEECY EIEKNL LLLGATAIEDRLQDQVP		688
HsATP11A	-----KVDQIRARVERNAVEGLR TL CVAYKRLIQEYEGICCKLQAAKVAL-QDREKLLAEAYEIEKNL LLLGATAIEDRLQKAA		670
HsATP11C	-----EIELTKHVVERNAMDGYR TL CFAVKEIAPDDYERINRQLIEAKMAL-QDREKMEKVFDDEITNMNLIGATAIEDRLQDQAA		660
HsATP8B1	N-----PTKQETQDALDIFANETL TL CLCYKEIEKEFTEWNNKFMAASVAS-TNRDEALDKVYEEIEKDLILLLGGATAIEDRLQDQVP		715
HsATP8B2	T-----QELLNVTMDHLNEYAGEGLR TL VLAYKDLDEEYEWAEARLQASLAQ-DSREDRLASIYEEVENNMMLLGGATAIEDRLQDQVP		676
HsATP10A	SSVDARGRHQKIRSKTQNYLVNVAEGLR TL CIAKRVLSKEYBACWVLSHLEAESSL-ENSEELLFQSAIRLETNLHLLGATGIEDRLQDQVP		872
AtALA2	-----GQQ-TRTIGDAVEHYSQLGLR TL CLAWRELEENEYLEWSVKFKEASSLL-VDRWRIRAEVQCQRLEHDIYILGVTAIEDRLQDQVP		619
AtALA10	-----GRQFEAKTQEHVNQYADAGL R TL VLAYREVDENEYIEFNKSFNEAKASVSEDRREALIDETDKMIRDLILLLGGATAIEDRLQDQVP		713

	P domain	
CtDNF1	DTIALADAGIKIWLVTGDKVETA INIGFSCNLLNNDMD--LLRL-QVNESDAST-E--DDYLQLA-----E-----EQLKTN	969
CtDRS2	ETIHTQOEAGIKVWVLTGRQETA INIGMSCKLLSDDMM--LLII-NEETAFAATR---DNIQ-----D-----KK	931
ScDRS2	ETIHTQOEAGIKIWLVTGDRQETA INIGMSCRLLSDDMN--LLII-NEETRDDTE---RNLL-----D-----EK	876
ScDNF1	DCIELAEAGIKIWLVTGDKVETA INIGFSCNLLNNDME--LLVI-KTTGDDVKEFG--SEPSEIV---D-----ALLSKY	1040
ScDNF2	DSIALAEAGIKIWLVTGDKVETA INIGFSCNLLNNDME--LLVV-RASGEDVVEEFG--SDPIQVV---N-----NLVTKY	1083
BtATP8A2	ETIATLLKAEIKIWLVTGDKQETA INIGYSCRLVSQNMMA--LILL-KEDSLDATR---AAIT-----D-----QH	706
HsATP8A1	ETIETMKADIKIWLVTGDKQETA INIGHSCKLLKKNMG--MIVI-NEGSLDGRTR---ETLS-----D-----RH	726
HsATP8A2	ETIATLLKAEIKIWLVTGDKQETA INIGYSCRLVSQNMMA--LILL-KEDSLDATR---AAIT-----D-----QH	746
HsATP11A	DTIEALQKAGIKVWVLTGDKMETAAATCYACKLFRRTNQ--LLEL-TTKRIEESQ----LH-----D-----DVLFEFSKTVLRH	737
HsATP11C	ETIEALHAAAGLVWVLTGDKMETAKSTCYACRLFQNTTE--LLEL-TTKTIEESE--RKEDRLH-----E-----ELLIEYRKKLLHE	732
HsATP8B1	ETIETMKADIKIWLVTGDKQETA ENIGFACELLTDETT--IC-YGE-DI-N-----SL-----L-----HARMEN	771
HsATP8B2	ETIATLLANIKIWLVTGDKQETA AVNIGYSCKMLTDDMT--EVFIVTGHVTVLEVR--EELRKA-----R-----EKMMDS	742
HsATP10A	ETISKRRQAGLQIWLVTGDKQETA VNIAYACKLLDHDEE--VITL-NATSQEACA---ALLDQCLCYVQSRGLQRAPEKTK-----GKVSMR	953
AtALA2	ETIETERRAGINWVLTGDKQNTAIQIALSCNFISSPEPKGQAIQIAL--DGKTEEDVS---RSLERLV-----D-----HARMEN	680
AtALA10	ECIDKLAQAAGIKIWLVTGDKMETAA INIGFASSLLRQEMK--QII-NLETPQIKSLEKSGGKDEIE-----LASR-----ESVVMQ	786

	P domain	
CtDNF1	L-ERFNMGTGDEELK--RARKDHNAPSPTYALVLDGFTLRWVL-----S-----DSLKQKFL	1018
CtDRS2	LDAIR-----AQEHGTVEMGTLALVLDGKSLTYAL-----E-----RDLEKMFLL	970
ScDRS2	INALN-----EHQLSTHDMNTLALVLDGKSLGFAL-----E-----PELEDYLL	915
ScDNF1	LKEYFNLTGSEEEIF--EAKKDHEFPKGNVAIVLDGDAKLLAL-----YG-----EDIRKFFL	1091
ScDNF2	LREKFGMSGSEBELK--EAKREHGLPQGNFAVLDGDAKVAL-----NG-----EMRRKFFL	1134
BtATP8A2	CADL-----GSLLGKENDAALLDGHTLKYAL-----S-----FEVRRSFL	742
HsATP8A1	CTTL-----GDALRKENDFALLIDGHTLKYAL-----T-----FCVRRYFL	762
HsATP8A2	CTDL-----GNLLGKENDVALLDGHTLKYAL-----S-----FEVRRSFL	782
HsATP11A	SGSLT-----R-----DNLSGLSADMDQYGLLDGCAALSLIM-----K-----KPREDDSGSGNYRBLFL	785
HsATP11C	FP-KS-----T-----RSFKKAWTHEQEYGLLDGHTLKYAL-----S-----NSSQDSSSNYKSLFL	779
HsATP8B1	QRNRGGVY--AKFAPPV--QESFFPPGGNRAILDTGSLWNEILLEKTKRKNILKLFKPRTEEBERRMTQSKRRLEAKK-----E-----EQRQKNFV	854
HsATP8B2	SRSVGNQFTYQDKLSSKLSVLEAVAGEYALVINGHSLLAHAL-----E-----ADMELEFL	794
HsATP10A	FSSLC-----P--PSTSTASGRRPSLVDIGRSLAYAL-----E-----KNLEDKFL	992
AtALA2	-----L-----LTMTRITASEPKDVAFVLDGWALEIAL-----K-----H-HRDKFV	714
AtALA10	LQEGK-----ALLAASGASSEAFALLIDGKSLTYAL-----E-----DEIKKMFLL	826

	P domain	TM5	
CtDNF1	LLCKQCKSVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		1111
CtDRS2	DLAAMCKAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		1064
ScDRS2	TVAKLCKAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		1008
ScDNF1	LLCKNCKAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		1184
ScDNF2	LLCKNCKAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		1227
BtATP8A2	DLALSCKAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		835
HsATP8A1	DLALSCKAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		855
HsATP8A2	DLALSCKAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		875
HsATP11A	EICRSCAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		879
HsATP11C	QICCMKTAFLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		873
HsATP8B1	DLACECAVILCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		947
HsATP8B2	ETACACKAVLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		887
HsATP10A	ANMLVYFYFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL		1085
AtALA2	ELAILSRATLCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		806
AtALA10	DLATSCASVILCCRVSPKQAAAVVSMVKNGL-DVMTLSIGDGDANDVAMIQEADVGVGIGAGEEGRQAVMSSDFAIGQFRFLRQLRVLVHGRWSVRRLL		919

	TM5 cont.	TM6	TM7	
CtDNF1	AETISNFYFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			1205
CtDRS2	SKTILFVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			1158
ScDRS2	SVAILYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			1102
ScDNF1	AEMIPQFVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			1278
ScDNF2	AEMIPQFVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			1321
BtATP8A2	TKCILYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			929
HsATP8A1	SKCILYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			949
HsATP8A2	TKCILYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			969
HsATP11A	SELVQYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			973
HsATP11C	AHLVQYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			967
HsATP8B1	CKFLRYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			1041
HsATP8B2	CKFLCYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			981
HsATP10A	ANMLVYFYFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			1179
AtALA2	AELSQVYFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			899
AtALA10	ASMICYVFNKNVLYLIIELWFAFVNGFSGQLILFERWCIGLYNVIFLTPPTLGFIFERSCSQESMLRFPQLYKITQNAEGFNKTVFWGHGINAL			1013

	TM7 cont.	TM8	TM9	
CtDNF1	YQSVMSFFLFFIFVVLTPAAAGNDVSRTRLGAYIAHPAVITINGYLINTYRWDLWMLLSIVLSVDFIFF----W-TGV-Y-TATTYSAG			1291
CtDRS2	YHSILLYIGGSLFF-LGVQ-NABGFPAG-KWVWGTYMGAVLLTVLGKAALVTNNWTKWHVVGIPGSMLFVLV-FVGVY-GTV-A-PKLGFSME			1245
ScDRS2	FHSADVIFIGTILYRYGFALNMHGELAD-HWSVGVVYVTSVIIIVLKGAAALVTNQWTKFTLIAIPGSLFLWLI-FFPIY-ASI-F-PHANIARE			1191
ScDNF1	YQSVIICFFFPYLIVYHKMNVTSTNGLGDHRYFVGVVYVTTAVISCNVYVLLHQYRWDFWGLFIALSCLVFA----W-TGI-W-SSAIASRE			1364
ScDNF2	YQSVIICFFFPYLIVYHKMNVTSTNGLGDHRYFVGVVYVTTAVISCNVYVLLHQYRWDFWGLFIALSCLVFA----W-TGI-W-TSSSSNE			1407
BtATP8A2	VHSLLILFWFPMKALEHDT-VLANGHATD-YLFVGNVYVTVVVVVCLKAGLETWTAWTKFHSILAVWGSMLIWLW-FFGIY-STI-W-PTIPIAPD			1017
HsATP8A1	FHSVILFWFPMKALQYGT-AFGNGKTSY-DYLLGNVYVTVVVVVCLKAGLETWYWTWFSHIAIWGSIALWVW-FFGIY-SSL-W-PAIPMAPD			1037
HsATP8A2	VHSLLILFWFPMKALEHDT-VLANGHATD-YLFVGNVYVTVVVVVCLKAGLETWTAWTKFHSILAVWGSMLTWLW-FFGIY-STI-W-PTIPIAPD			1057
HsATP11A	FDALVFFFGAYFVEENT-VTSNQIFG-NWTFGTIVTVMVVFVCLKAGLETWYWTWFSHIAIWGSIALWVW-FFGIY-SSL-W-PAIPMAPD			1061
HsATP11C	FEGTVFFFGTYFLFQTAS-LEENGKVG-NWTFGTIVTVMVVFVCLKAGLETWYWTWFSHIAIWGSIALWVW-FFGIY-SSL-W-PAIPMAPD			1055
HsATP8B1	LTSMLIFLFFLGAYLQTV-QGGEAPS-D-YQSPAVTASALVITVNVQIGLDTSYWTFVNAFISFGSIALYFGIMDFHSAHG-H-VLFPFSAFQ			1131
HsATP8B2	YTSVMEFFFPYGVFADAT-RDDGTQLAD-YQSPAVTASALVITVNVQIGLDTSYWTFVNAFISFGSIALYFGIMDFHSAHG-H-VLFPFSAFQ			1071
HsATP10A	FQSLVCFSPYLLAYYDSN-----VD-LFTWGTPIVITIALTFLHLGIEIKTWTLNWTICGFSVLLFET-VALIY-NAS-CATCYPP-SN			1260
AtALA2	FHAIIVFVITIHAYAEK-----SE-MEELGMVALSGCIWQAFVVAQETNSFTVVLQHLSIWGNLVGFYA-INFLF-SA-----IPS-SG			975
AtALA10	ISALATIFFLCKESLKHQL-FDPPDGKTAG-REILGGTMYTCVVVWVNLQMALISISYFTWVQHVIVWGSIAFWYI-FLMIY-GAM-T-PSF-S-TD			1099

TM10

CtDNF1 FYQA-APQVYQELTFWMLIVTPALCLLPRLLVVKCIQKQRFPYDVDIIREQAN--R--GDFAAAD-----AAAV-----AALGGPE 1362
 CtDRS2 FFEV-IPRLFSNPSFWLQMPTLAILCLARDFAWKFSKRLWKPEAYHHVQEIQK--Y--NI----- 1300
 ScDRS2 YYGV-VKHTYGSVFWLTLIVLPIFALVDRFLWKYKRMYPETVHYVQEMQK--Y--NI----- 1246
 ScDNF1 FFKA-AARIYGAPSFVAVFFVAVLFCLLPRFTYDSQKFFYPPTDVEIVREMWO--H--GHFDHYP-----PGYDPTDPRPKVTKAGQHGEK 1446
 ScDNF2 FYKG-AARVFAQPAYWAVLFGVGLFCLLPRFTIDCIRKIFYPKDIEIVREMWL--R--GDFDLYP-----QGYDPTDPSRPRINEIRPLT-D 1488
 BtATP8A2 MKGQ-ATMVLSSAHFWLGLFLVPTACLIEDVAWRAAKHTCKKTLLEEVQEM--K--SR----- 1072
 HsATP8A1 MSGE-AAMLFSGGVFWMGLLFIPVASLLLDVVYKVIKRTAFKTLVDEVQELEA--K--SQ----- 1092
 HsATP8A2 MRGQ-ATMVLSSAHFWLGLFLVPTACLIEDVAWRAAKHTCKKTLLEEVQELT--K--SR----- 1112
 HsATP11A MYVY-FIQMLSSGPAWLAIVLLVTISLLPDVLKVKLQRLWPTATERVQTKSQ--C--LSVE----- 1118
 HsATP11C MYFV-FAQMLSSVSTWLAIIILLIFISLFFPELLIVLKNVRRRSARRNLSCRRASDS--LSAR----- 1114
 HsATP8B1 FTGT-ASNALRQPYIWLTIILAVAVCLLPPVAIRFLSMTIWPESDKIQKHKR--R--LK----- 1186
 HsATP8B2 FVGN-AQNTLAQPTVWLTIVLTTVVCIMPVAVFRFLRLNLKPDLSDTVRYTQL--VRKKQK----- 1129
 HsATP10A PYWT-MQALLGDPVFYLTCLMTPVAALLPRLFFRSLOGRVFPPTQLQLARQLTR--K--SPRCSAPKETFAQGRLPKDS----- 1334
 AtALA2 MYTI-MFRLCSQPSYNTMFLIVGAGMGPIFALKYFRYTYRPSKINILQQAER--M--GGPIL-----TLG----- 1036
 AtALA10 AYMVFLEALAPAPSYWLTTLFVMIFFALIPYFVYKSVQMRFFPKYHQMIQWIRY--E--GHSN----- 1157

CtDNF1 RVEGESLG-SLSSSGKSGRSKSKKHQQYASVDEDRRPIYPPSIATHNTRAQNGSD-----GTT----- 1420
 CtDRS2 ----- 1420
 ScDRS2 ----- 1420
 ScDNF1 IIEGIALSDNL---GGSNYSR-----DSVVTTEEIPMTF-MH-----GED-----GSPSGYQKQETW-----M 1494
 ScDNF2 FKEPISLDTHF---DGVSHSQ-----ETIVTEEIPMSI-LN-----GEQ-----GSRKGYRVSTTLERRDQLSPVTTTN 1548
 BtATP8A2 ----- 1420
 HsATP8A1 ----- 1420
 HsATP8A2 ----- 1420
 HsATP11A ----- 1420
 HsATP11C ----- 1420
 HsATP8B1 ----- 1420
 HsATP8B2 ----- 1420
 HsATP10A ---GT---EHSSGR-----TV-KTSVPLSQPS-----WHTQQPVCSEASGEPSS----- 1371
 AtALA2 ---N---IETQPR-----TIEKDLSPISITQ-----PKNRSPVY----- 1064
 AtALA10 -----DPE----- 1160

CtDNF1 -----YIMQSRTS-----TELQQEMPFDREETPAVR-PSIERTRPSYDRIRR--SIDRVRPSEASNDFT 1480
 CtDRS2 -----QDYRP-----RME---QFQK---AIRKVR----- 1318
 ScDRS2 -----SDSRP-----HVQ---QFQN---AIRKVR----- 1264
 ScDNF1 TSPKETQDLLQSPQFQQAQTFG-----R-----GPSTNVRS--SLDRTREQMIATNQLD 1541
 ScDNF2 NLPRRSMASAR-----G--NKLRT--SLDRTREEMLANHQLD 1581
 BtATP8A2 -----VMGRAMLR-DSNGKRMNERDRLK--RLSRKTP----- 1102
 HsATP8A1 -----DPGAVVL-----GKSLTERAQLLK--NVFKKNH----- 1118
 HsATP8A2 -----VLGKAVLR-DSNGKRLNERDRLIK--RLGRKTP----- 1142
 HsATP11A -----QSTI----- 1122
 HsATP11C -----PSVR----- 1118
 HsATP8B1 -----AE-----EQWQRROQVFR----- 1199
 HsATP8B2 -----AQ-----HRCMR--RVGR----- 1140
 HsATP10A -----TVDMSPVREHTLLEGLSAP-APMSSAPGEAVLR-SPGGCPEESKVR-A--STGRVTP----- 1425
 AtALA2 -----EP-----LLSDSPN-ATR-----R--SFGPGTP----- 1084
 AtALA10 -----FV-----EMVRQR-SIRPTTVGYTARR-AA----- 1183

CtDNF1 SAARL-----SRIESTHSSL--GHTYSHQRESYAG--ESSGAQQGQEP--QORRFNLATVRKRGLSAFSSKKSIDTT--EGE----- 1548
 CtDRS2 -----QVQRM--RKQRGYAFSMA--DE-----SQTR--VLQAY-----DTT--RHR----- 1351
 ScDRS2 -----QVQRM--KKQRGYAFSQA--EEG-----GQEK--IVRMY-----DTT--QKR----- 1298
 ScDNF1 NRYSV-----ERARTSL-----DL-----PGVTN-----A-----ASL-----I--GTQ----- 1568
 ScDNF2 TRYSV-----ERARASL-----DL-----PGINH-----A-----ETL-----L--SQR----- 1608
 BtATP8A2 --PT-L-----FRGSSLQQSMPHGYAFSQE--EHGA--V-----TQEE--IVRAY-----DTT--KQK----- 1144
 HsATP8A1 --VN-L-----YRSESLQQNLLHGAYAFSQD--ENGI--V-----SQSE--VIRAY-----DTT--KQR----- 1160
 HsATP8A2 --PT-L-----FRGSSLQQGVPHGYAFSQE--EHGA--V-----SQEE--VIRAY-----DTT--KKK----- 1184
 HsATP11A --FML-S-----QTSSS-----LSF----- 1134
 HsATP11C --PLL-L-----RTFSD-----ESN-----VL----- 1132
 HsATP8B1 -----RGVST--RRSAYAFSHQ--RGYADLI-----SSGRSIRKKRS-----PLDAIVADGTAE-- 1244
 HsATP8B2 -----T-GSRRSGYAFSHQ--EGFGELI-----MSGKNMRLSSL-----ALSSFTTRSSSSWI 1185
 HsATP10A --LSSLFSLPTFSLNWISSWLVSRRLGSLVQLQFSRT--EQLADGQ--AGRG-----L-----PVQ--PHS----- 1477
 AtALA2 --FE-F-----FQSQSR--LSSSSGYTRNCK--D----- 1106
 AtALA10 -----SV-----RRS----- 1188

CtDNF1 ----PPREP-----PM----- 1555
 CtDRS2 ----GR-YGEMAS-----SRT-IGI-----AQ----- 1367
 ScDRS2 ----GK-YGELQDASANPFNDNGLGNSDFESAEPFIENPFADGNQNSNRFFSSSRDDI-----SF-DI--- 1355
 ScDNF1 ----Q-N-N----- 1571
 ScDNF2 ----S-RDR----- 1612
 BtATP8A2 ----SR-KK----- 1148
 HsATP8A1 ----PD-EW----- 1164
 HsATP8A2 ----SR-KK----- 1188
 HsATP11A ----- 1148
 HsATP11C ----- 1164
 HsATP8B1 --YR-R-TGD-----S----- 1251
 HsATP8B2 ESLRRK-KSDSAS-----SPS-GGA-----DK-PLKG- 1209
 HsATP10A ----GR-SG-----L-QGPDHRLLIASSRRSQ 1499
 AtALA2 -----N----- 1107
 AtALA10 ----AR-FHDQIY-----KDL-VGV----- 1202

Fig S2

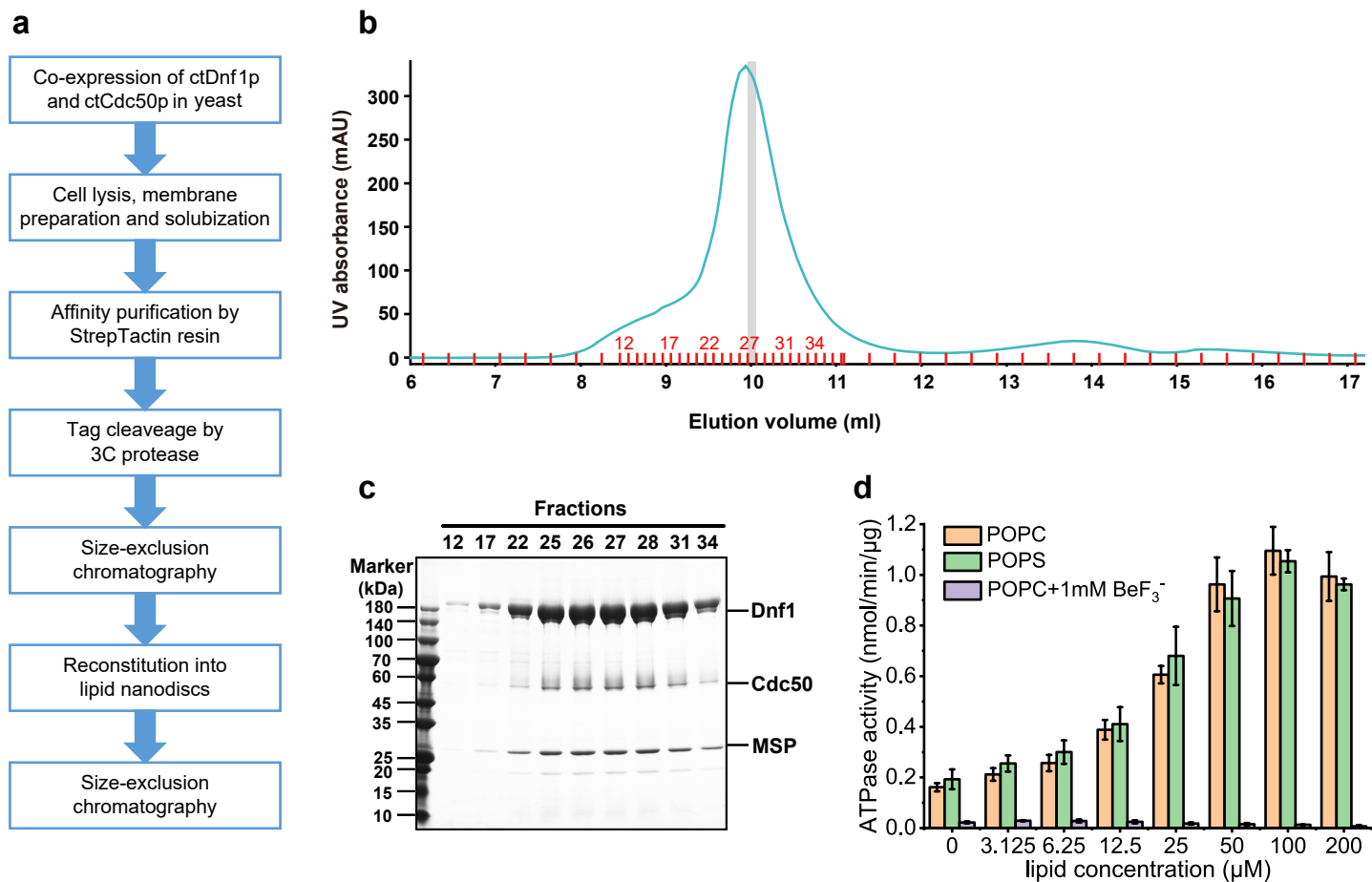


Fig S3

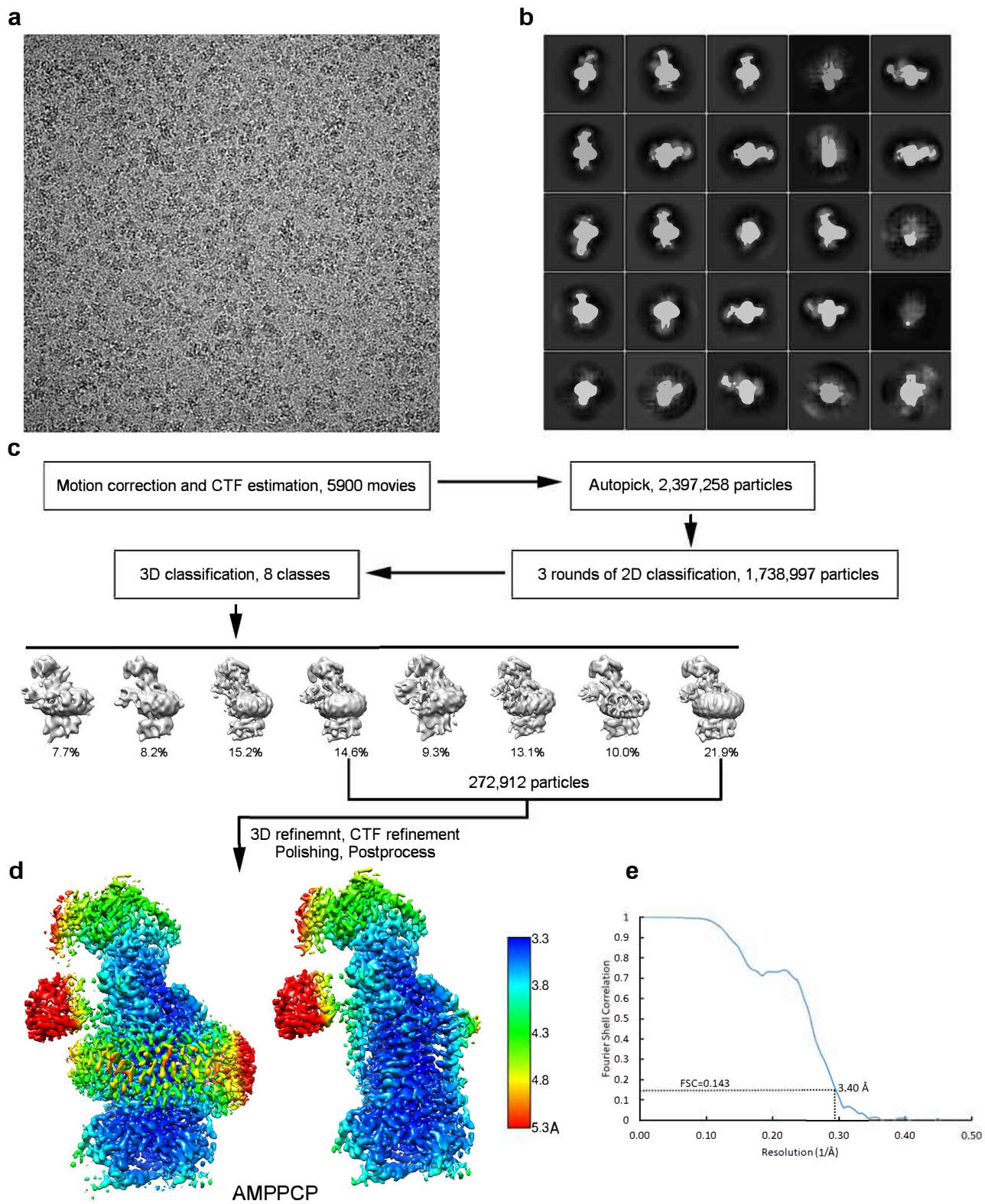


Fig. S4

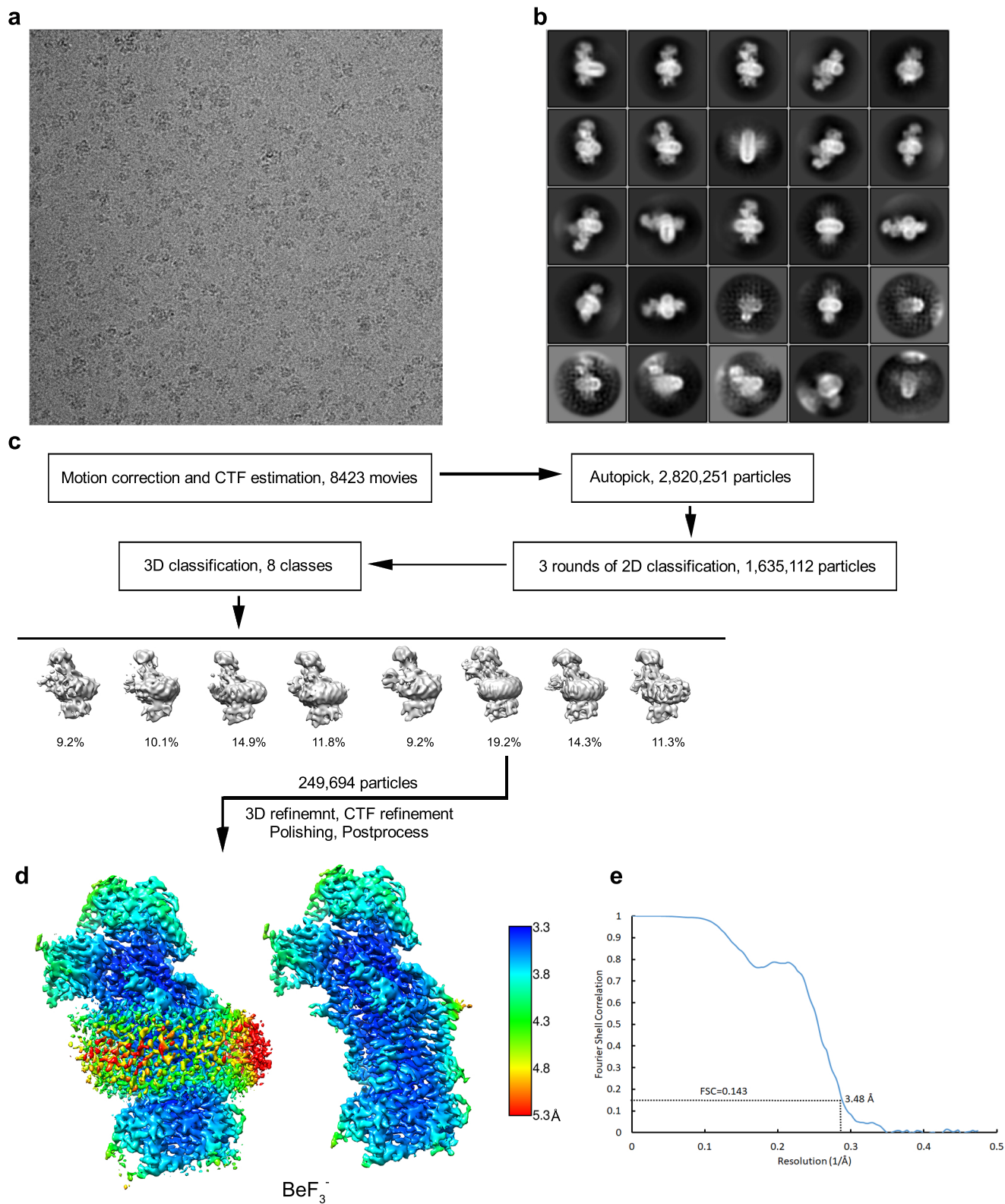


Fig. S5

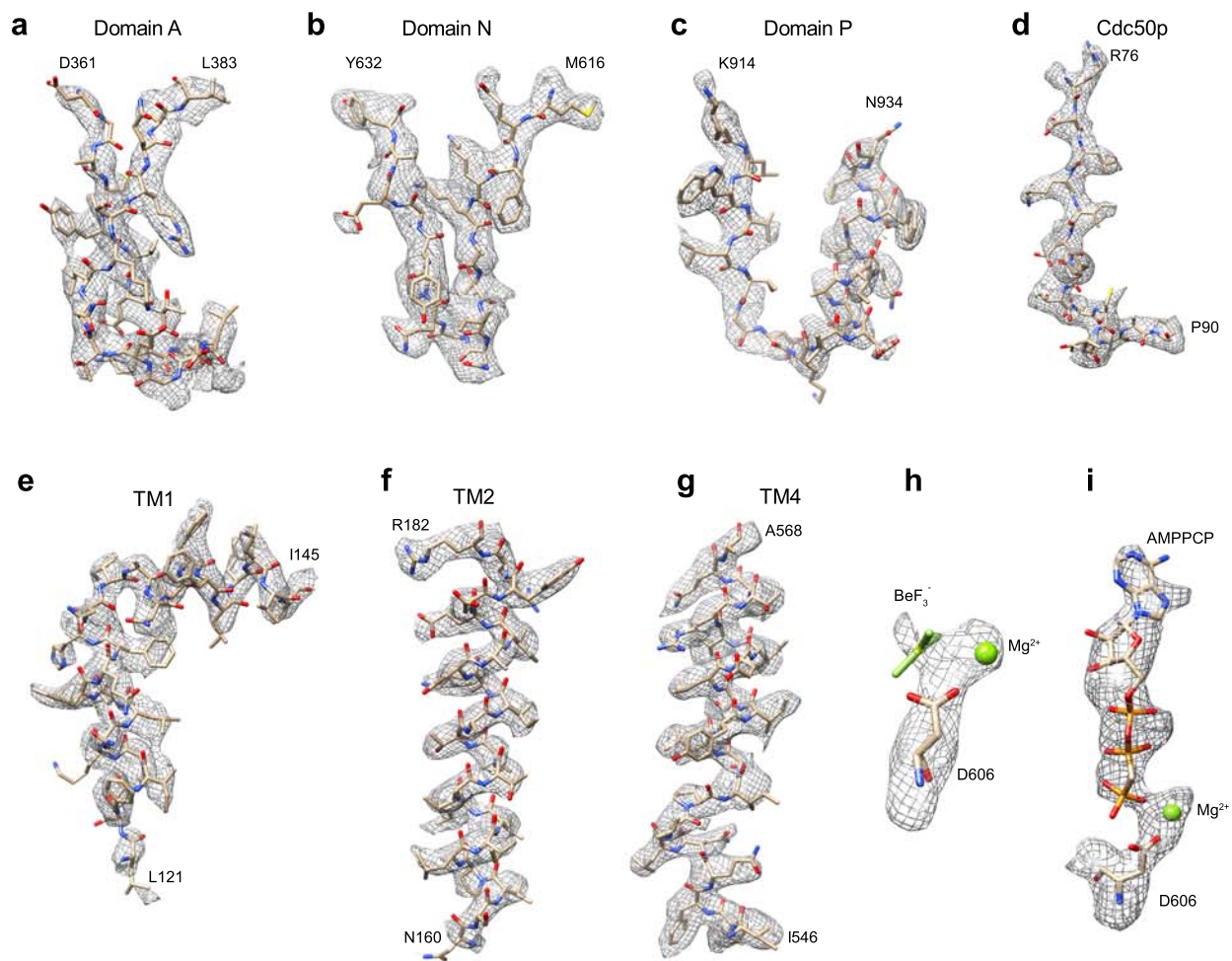


Fig. S6

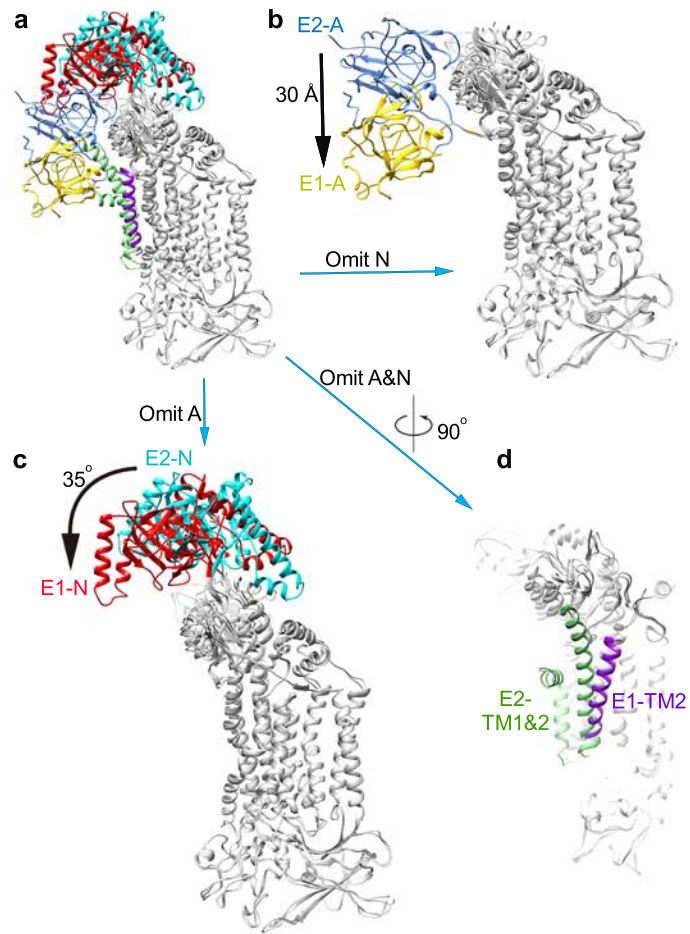


Fig. S7

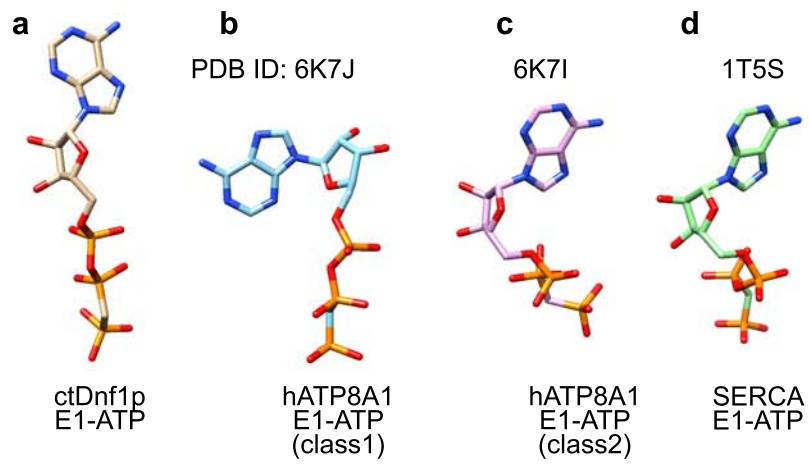


Fig. S8

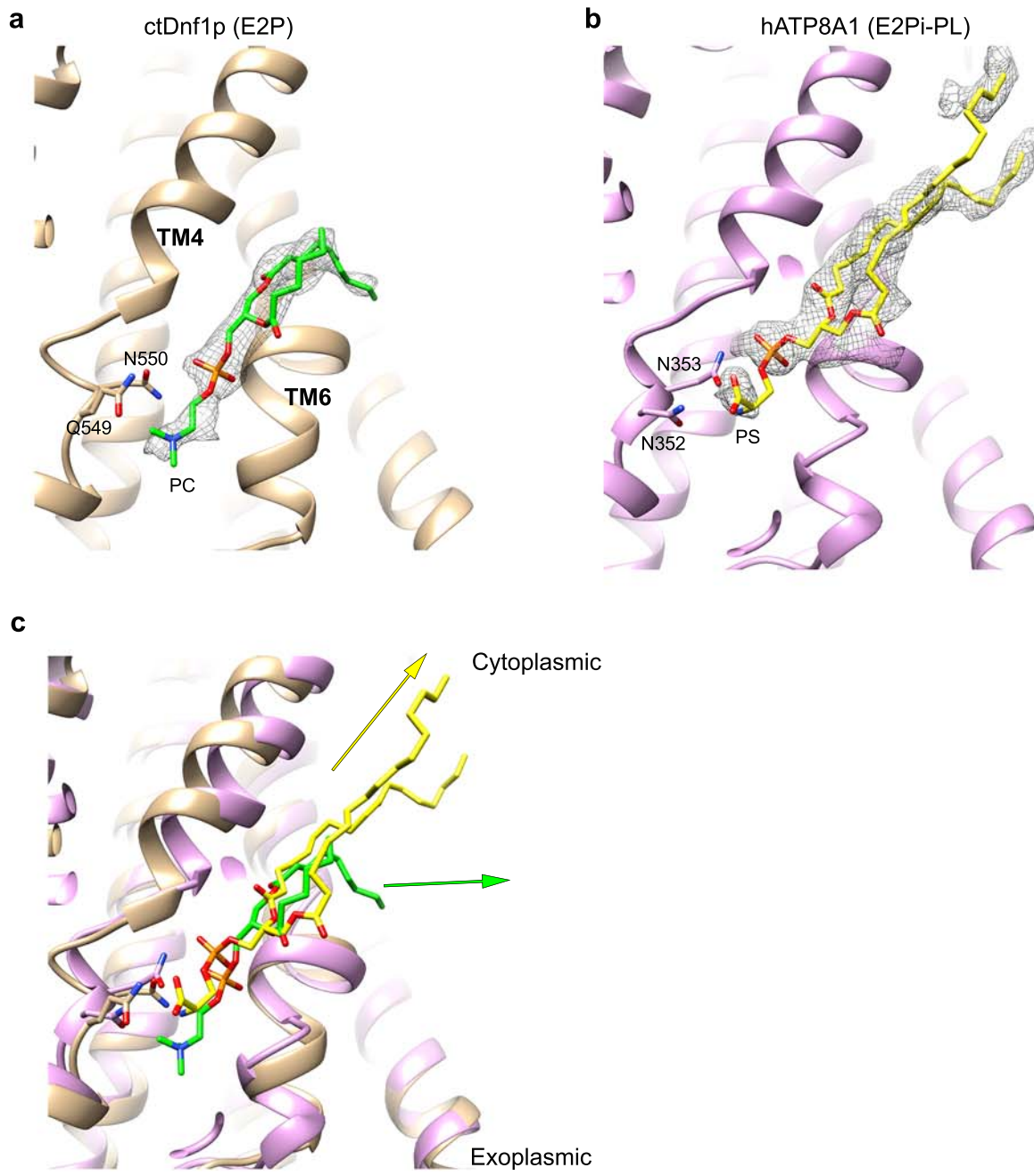


Fig. S9

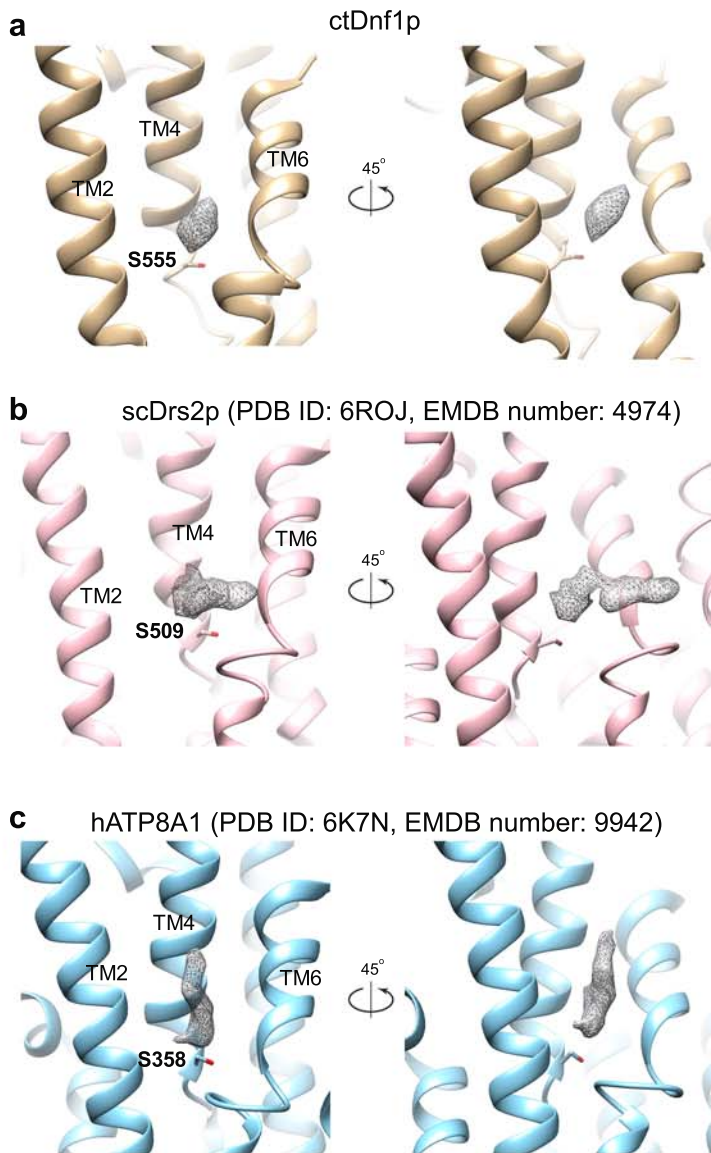


Fig. S10

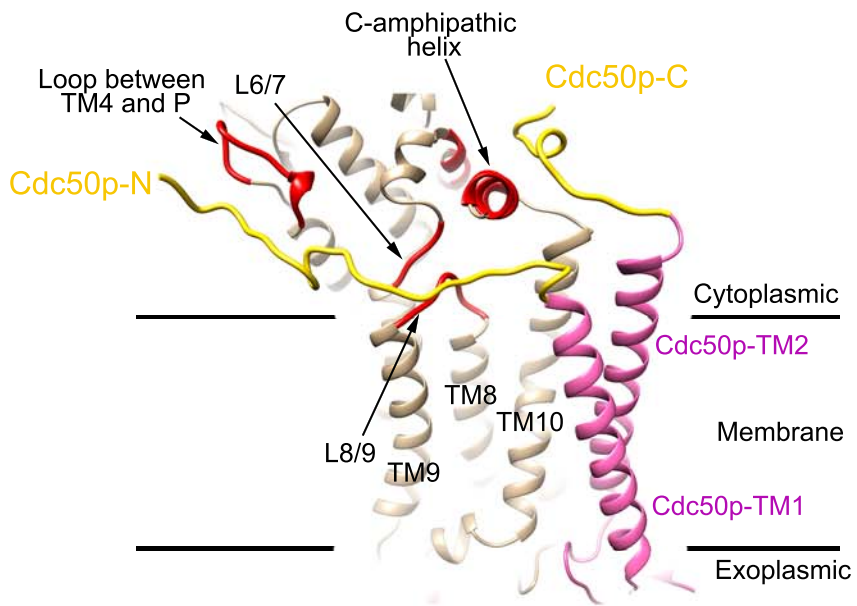


Fig. S11

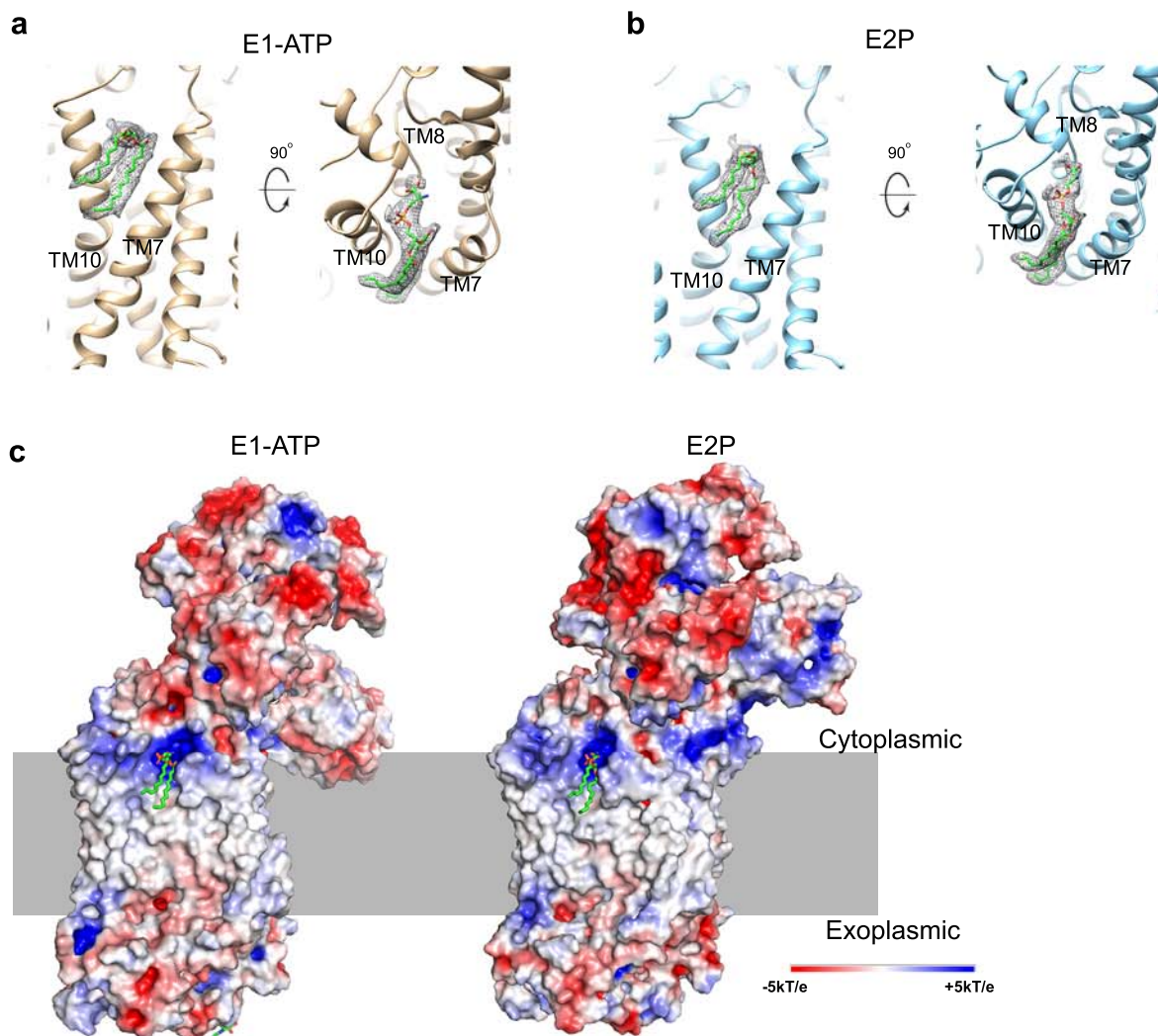


Fig. S12

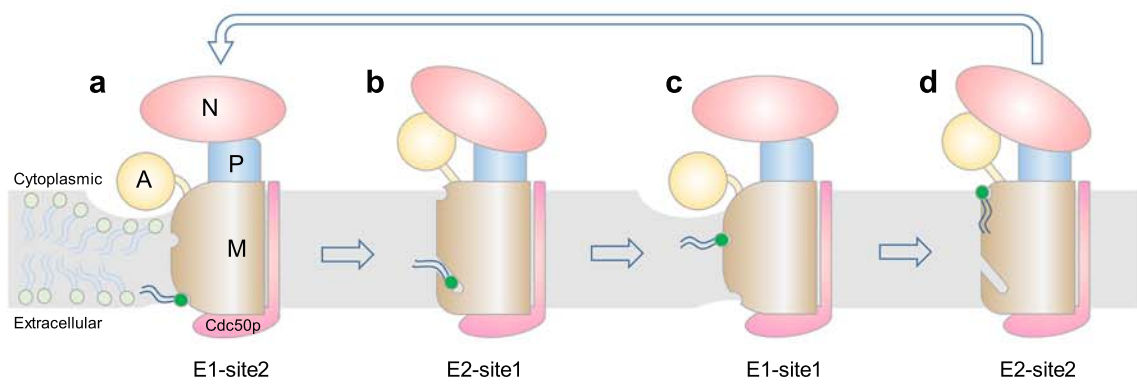


Fig. S13

