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Supplementary information for:

Metal transport mechanism of the cation diffusion facilitator (CDF) protein family – structural perspective on human CDF (ZnT)-related diseases

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	4			
hZnT1			MG CWGRNRGRLLCMLALTFMFMV	L E
TtCzrB MgMamM			MRKSGCAVCSRSIGWVGLAVSTVLMV	L K M K
hZnT-8			E C C C C C C C C C C C C C C C C C C C	A E
hZnT-10	M =			A E
EcYiiP			MNOSYGR - LVSRAAIAATAMASLLLL	I K
hZnT-3	MEPSPA CLET RLVS R - A SL SL F		K TITLE HECKIDP PEPGLTPERLHARRQLYAACAVCFVFMA	G E
				-
hZnT1	V V V S R V T S S L A M L S D S F H M L S D V L A L V V A L V A E R F	ARRTHATQKNTFGWIRAEVN	MGALVNAIFLTGLCFAILLEAI <mark>E</mark> RFIEPHEMQQP L VVLGVGVA-	GL
TtCzrB MgMamM	A F A Y L L T G S V A L L S D A L E S L V N V A A A L A A L L A L A V A F V G L I G G S Q A M L A D A M Y S L K D M L N A L M V I I G T T I	A R K P P - D Q N H P F G H T K A B Y V S S K P L - D A E H P Y G H G K V E F I	V SAVLEG V LV V LAALWIAREAL PRILH PV PLEGLGLGLGUSLL- ILSMVVSVVFIVLTGYLLVHAVQILLDESLHRTPHLIVLWAALV	AS SI
hZnT-8	VVGGHIAGSLAVVTDAAHLLIDL <mark>T</mark> SFLLSLFSLWL	S S K P P - S K R L T F G W H R A E I I	LGALLSILCIWVVTGVLVYLACERLLYPDYQIQATVMIIVSSC-	A V
hZnT-1(UVSGYLGNSIALLSDSFNMLSDL <mark>I</mark> SLCVGLSAGYI	A R R P T R G F S A T Y G Y A R A E V V	VGALSNAVFLTALCFTIFVEAVLRLARPERIDDPELVLIVGVL-	GL
EcYiiP hZnT-2	I F A W W Y T G S V S I L A A L V D S L V D I <mark>G</mark> A S L T N L L V V R Y V	S L Q P A - D D N H S F G H G K A E S I V E I I	LAALAOSMFISGSALFLFLTGIOHLISPTPMTDPGVGVIVTIV-	A L A V
hZnT-3	V V G G Y L A H S L A I M T D A A H L L A D V <mark>G</mark> S M M G S L F S L W L	STRPA - TRTMTFGWHRSETI	LGALASVVSLWMVTGILLYLAFVRLLHSDYHIEGGAMLLTASI -	A V
	←			
hZnT1	LVNVLGLCLFHHHSGFSQD <mark>S</mark> GHGHSHGGH	- G H G H G L P K G P R V K S T R P G S	S S D I N V A P G E Q G P D Q E E T N T L V A N T S N S N G L K L D P A D P E N P R S G I	т
MgMamM	L L N - G L L A Y H L L K E G R R H R S P A			
hZnT-8	A A N I V L T V V L H Q R C L G H N H K E			
hZnT-10	VVN IIMAVLLGHDHGHSHGHGHGHGHGHDHHNHS LVNVVGLLIFQDCAAWFACCLRGRSRRLQQRQQLA	HGVTVTTHHHHHD EGCVPGAFGGPQGAE - DPRR		A T
EcYiiP	ICT-IILVSFQRWVVRRTQSQA			
hZnT-3	CANLLMAFVLHQAGPPHSHGSRGAEY		λP	
hZnT1	VEVQVNGNLVREPDHMELEEDRAGOLNMRGVF	LHVLGDALGSVIVVVNALVE	F - Y FSWKGCSEGDFCVNPCFPDPCKAFVEIINSTHASVYEAGPC	W V
TtCzrB MgMamM		YHVLSDVLTSLGVVLGVGLA KHHHGDATASGAVALGIIGA	A G L T G	- L - М
hZnT-8		VHALGDLFQSISVLISALII	I - Y F K P E	- Y
hZnT-1) VFANVAGDSFNTQNEPEDMMKKEK <mark>KSE</mark> ALNIRGVL	LHVLGDSIQSVGVMIGGAII LHVMGDALGSVVVVITAIIE	F - Y V L P L K	- w W Q
EcYiiP		L H Y Q S D V M M N G A I L L A L G L S	S - WYG	- W
hZnT-3	L-EGPEEPLPLGNTSVRAAF	VHVLGDLLQSFGVLAASILI		- Y
hZnT1	LYLDPTLCVVMVCILLYTTYPLLKESALILLQTVP	KQIDIRNLIK <mark>E</mark> LR		
TtCzrB MgMamM	W V LD P L LA LA V A G Q I L F L G Y R I V R E S V G G L M D E G L P W I D P A V A L W E T I D L L L L G K V V F M D A Y R G L M D H T A	PPEEVERIRAFLQER GEAVONRIVEAAER -		
hZnT-8	KIADPICTFIFSILVLASTITILKDFS <mark>I</mark> LLMEGVP	KSLNYSGVKE <mark>L</mark> IL		
hZnT-1	KIVDLICTLAFSVIVLGTTINMIRNILEVLMESTP)CYIDPSLTVLMVIIILSSAFPLIKETA <mark>A</mark> ILLQMVP	KEIDATKLEKGLL KGVNMEELMS <mark>K</mark> LS		
EcYiiP	HRADALFALGIGIYILYSALRMGYEAVQSLLDRAL	PDEERQEIID <mark>I</mark> VTSW		
hZnT-3	KAADPISTFLFSICALGSTAPTLRDVLRILMEGTP	RNVGFEPVRDT LL		
	2			
hZnT1	N V E G V E E V H E L H V W Q L A G S R I I A T A H I K C E D P T S Y	MEV AKTIKDVFHNH		
TtCzrB MgMamM	IRGRALEVHDLKTRR – AGPRSFLEFHLVVRGDTPV - VPGVRGVIHLRARY – VGODIWADMIIGVDPENTV	EEA HRLCDEL EOA HEICEAV		
hZnT-8	AVDGVLSVHSLHIWSLTMNQVILSAHVATAASRDS	Q V V REIAKALSKSF		
AtMTP1 hZnT-1(EMEEVVAVHELHIWAITVGKVLLACHVNIRPEADA AVPGI <mark>S</mark> SVHEVHIWELVSGKIIATLHIKYPKDRGY	DMV NKVIDYIRREY QDA STKIREIFHHA		
EcYiiP	PGVSGAHDLRTRQ-SGPTRFIQIHLEMEDSLPL	VQA HMVADQV		
hZnT-3	SVEGVEALHSLHIWALTVAQPVLSVHIAIAQNTDA SVPGVRATHELHLWALTLTYHVASAHLAIDSTADP	EAV AEASSRLOGRF		
b7pm1		C C G T I P O A P S G		
TtCzrB	ERAL	- AQAF PGLQATI		
MgMamM hZnT-8	TMHSLTIOMESPVDO PDCL C DPCD	- C G K I R R I E S L H		
AtMTP1	N I S H V T I Q I E R			
hZnT-10 EcYiiP) GIHNVTIQFENVDLKEPLEODLLLCGSPCISKG EQAI	C A K Q L C C P P G A L P L A - L R R F P G S D V I I		
hZnT-2	HFHTVTIQIEDYSEDKDCQCCGPSD			
nzni-3	GESSCILOVEDIQPE ACCLICELPEOA			
hZnT1		N T D N V - V T P T V N M		
TtCzrB		N I P A V - V I E I K N M		
MgMamM hZnT-8	VSAEAREIGDTTKPSFSDQPLSF	D E V M L S K V D N -		
AtMTP1				
nznr-1(EcYiiP	H V N G C A E H N G G P S L D T Y G - S D G L S R R D A R E V A I H Q D P C S V V P R E G K R S M L	E V S L D S C - L S D H G Q S S		
hZnT-2 hZnT-3				
h7rm1		Extended N-terminal	\sim	
nznr1 TtCzrB		Extended His-rich loop	\lor	
MgMamM		A/S _{TM} site		
AtMTP1		S _{IF} site	1 2 3 4 5 6 7 8 9	
hZnT-1(EcYiiP) LNKTQEDQCYVNRTHF	B site	Variable Average Conserved	
hZnT-2	2	S _{CDs} site	🛛 - Insufficient data	
nzn1-3		- U100	—	

Figure S1. Sequence conservation between bacterial (*Escherichia coli* YiiP, *Thermus thermophilus* CzrB and *Magnetospirillum gryphiswaldense* MSR-1 MamM), plant (*Arabidopsis thaliana* MTP1) and human (ZnT-1, ZnT-2, ZnT-3, ZnT-8 and ZnT-10) CDF proteins. Multiple sequence alignment was calculated by ClustalO¹. Conservation scores and colored structure were produced by ConSurf server^{2,3} and PyMol version 2.3.5 (Schrödinger, LLC); scale of conservation ranges from dark blue (variable positions) to dark red (highly conserved positions); yellow coded residues refer to incomplete data (calculation for these sites were performed on less than 10% of the sequences). Functional regions are marked as colored arrays, human ZnT-8 transmembrane helices as cylinders and metal binding sites in human ZnT-8 and *E. coli* YiiP as colored spheres. Human ZnT-8 structure (PDB code 6XPE⁴) is presented and colored by ConSurf conservation scores, with metal binding residues presented as sticks and zinc ions in yellow spheres.

Supplemental references

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