

Supplementary Table S1

Major Eukaryotic Lineages
alveolata
amoebozoa
apusozoa
choanoflagellida
cristidiscoidea
cryptophyta
diplomonadida
euglenozoa
filasterea
fungi
haptophyceae
heterolobosea
ichthyosporea
metazoa
parabasalia
rhizaria
rhodophyta
stramenopiles
viridiplantae

Supplementary Table S2

Protein / protein family	Domain annotation
Calmodulin family	EF-hand_7+EF-hand_7
ERp57 (PDIA3)	Thioredoxin+Thioredoxin_6+Thioredoxin+Thioredoxin_8
SERCA	Cation_ATPase_N+TM+TM+E1-E2_ATPase+TM+TM+Cation_ATPase+Hydrolase+Hydrolase_3+TM+Cation_ATPase_C
CaMK / CDPK	Pkinase^
Calstabin	FKBP_c
PPP2R3	EF-hand_7*
Calcineurin A	Metallophos
Calcineurin B	EF-hand_7+EF-hand_7+EF-hand_6+EF-hand_4
TMX1	Thioredoxin+TM
Calreticulin	Calreticulin
Calnexin	Calreticulin+TM
TRIC	TRIC
Homer (WH1 dom.)	Evh1^
ERdj5	DnaJ+Thioredoxin+Thioredoxin+Thioredoxin+Thioredoxin
Sarcalumenin	EHD_N+Dynamin_N
IP3R	Ins145_P3_rec+MIR+RYDR_ITPR+RYDR_ITPR+RIH_assoc+TM+TM+TM+TM+TM+TM
ORAI	Orai-1
NCS1	EF-hand_7+EF-hand_7+EF-hand_7+EF-hand_6
Calcipressin	Calcipressin
STIM	EF-hand+SAM+TM+SOAR
ERp44	Thioredoxin+Thioredoxin_6
RyR	Ins145_P3_rec+MIR+RYDR_ITPR+SPRY+RyR+RyR+SPRY+SPRY+RYDR_ITPR+RyR+RyR+RIH_assoc+EF-hand_8+TM+TM+TM+TM+TM+TM
Sorcin	EF-hand_8+EF-hand_7
L-type VGCC (pore)	TM+GPHH+Ca_chan_IQ+CAC1F_C
TRPC	Ank_2+TRP_2+TM+TM+TM+TM+TM+TM

WFS2 (CISD2)	MitoNEET_N+zf-CDGSH
CREC family	EF-hand_7+EF-hand_7+EF-hand_7
Bcl2	BH4+Bcl-2+TM†
SelN	EF-hand_6
Wolframin	Sel1+Sel1+Sel1+wEF-hand+TM+TM+TM+TM+TM+TM+TM+TM+TM+wOB‡
Neurabin	PDZ*
Tespa1 (KRAP dom.)	KRAP_IP3R_bind
Calsequestrin	Calsequestrin
S100	S_100+EF-hand_7

^: Other domains vary

*: Other domains vary and are not very globular

†: Domain architecture varies between family members

‡: The domains wEF-hand and wOB refer to the wolframin-specific version of the EF-hand and OB-fold domains reported in this paper

Supplementary Table S3

Alignment Abbreviation	Scientific name	Common name	Clade
Hsapiens	<i>Homo sapiens</i>	Human	<i>Mammalia</i>
Mmusculus	<i>Mus musculus</i>	House mouse	<i>Mammalia</i>
Ggallus	<i>Gallus gallus</i>	Chicken	<i>Aves</i>
Drerio	<i>Danio rerio</i>	Zebrafish	<i>Actinopterygii</i>
Skowalevskii	<i>Saccoglossus kowalevskii</i>	Acorn worm	<i>Hemichordata</i>
Dmelanogaster	<i>Drosophila melanogaster</i>	Fruit fly	<i>Hexapoda</i>
Tcastaneum	<i>Tribolium castaneum</i>	Red flour beetle	<i>Hexapoda</i>
Dpulex	<i>Daphnia pulex</i>	Water flea	<i>Crustacea</i>
Lpolyphemus	<i>Limulus polyphemus</i>	Atlantic horseshoe crab	<i>Chelicerata</i>
Lgigantea	<i>Lottia gigantea</i>	Owl limpet	<i>Mollusca</i>
Obimaculodies	<i>Octopus bimaculodies</i>	California two-spot octopus	<i>Mollusca</i>
Hrobusta	<i>Helobdella robusta</i>	Leech	<i>Annelida</i>
Celegans	<i>Caenorhabditis elegans</i>		<i>Nematoda</i>
Epallida	<i>Exaiptasia pallida</i>	Brown glass anemone	<i>Cnidaria</i>
Tadhaerens	<i>Trichoplax adhaerens</i>		<i>Placozoa</i>
Aqueesnlandica	<i>Amphimedon queenslandica</i>	Sponge	<i>Porifera</i>
Srosetta	<i>Salpingoeca rosetta</i>		<i>Choanoflagellatea</i>
Smoellendorffii	<i>Selaginella moellendorffii</i>	Spikemoss	<i>Streptophyta</i>
Vcarteri	<i>Volvox carteri f. nagariensis</i>		<i>Chlorophyta</i>
Tpseudonana	<i>Thalassiosira pseudonana</i> CCMP1335		<i>Bacillariophyta</i>
Pinfestans	<i>Phytophthora infestans</i> T30-4	Late potato blight	<i>Oomycetes</i>
Tgondii	<i>Toxoplasma gondii</i> ME49		<i>Apicomplexa</i>
Slemnnae	<i>Stylonychia lemnae</i>		<i>Ciliophora</i>
EHuxleyi	<i>Emiliania huxleyi</i> CCMP1516		<i>Haptophyta</i>

Supplementary Table S4

Human wolframin repeat 1		Human wolframin repeat 2		Human wolframin repeat 3		Canonical SLR [^]	
Position	Residue	Position	Residue	Position	Residue	Position	Residue
65	A	102	A	141	A	3	A
69	R	106	V	145	L	7	L
70	S	107	G	146	R	8	G
73	R	110	Y	149	L	11	Y
76	G	113	L	154	G	14	G
83	D	123	S	158	E	28	D
87	P	126	A	162	E	32	A
94	R	133	A	169	E	39	A
95	A	134	A	170	T	40	A
98	G	137	G	173	E	43	G

[^]: From Mittl & Schneider-Brachert, 2007