

Table 1 Members of the EF-hand superfamily

Protein	Aliases	Function	Reference
CaM-like			
calmodulin	-CaM	-promiscuous Ca^{2+} sensor; regulates activity of kinases, phosphatases, ion channels, etc.	[1]
CLP	-human CaM-like protein	-expressed in mammary epithelial cells	[2]
CLSP	-calmodulin-like skin protein	-expressed in epithelial cells	[3]
yeast CaM		- Ca^{2+} -dependent processes in yeast	[4]
plant CaMs		- <i>Arabidopsis</i> has 9 identified variants	[5]
troponin C		-skeletal and cardiac muscle contraction	[6]
caldendrin	-calp (calmodulin-like protein), CaBP1; calbrain	-neuronal protein; three variants; modulates Ca^{2+} entry into the cytoplasm	[7]
myosin ELC	-myosin essential light chain	-molluscan muscle contraction; regulatory site	[8]
myosin RLC	-myosin regulatory light chain	-molluscan muscle contraction; structural site	[8]
squidulin		-light chain of myosin in axoplasm of squid	[9]
centrin	-caltractin	-cell cycle; four variants	[10]
CaVP	- Ca^{2+} vector protein	-from <i>Amphioxus</i> ; binds Ca^{2+} vector protein target (CaVPT)	[11]
calcineurin B	-CnB	-regulatory subunit of protein phosphatase calcineurin A	[12]
CHP	calcineurin B-homologous protein; p22	-exocytotic membrane traffic, inhibits GTPase-stimulated Na^+/H^+ exchanger; two variants	[13]
tescalin		-homologous to CHP	[14]
SOS3		-plant salt tolerance	[15]
AtCBL2	- <i>Arabidopsis thaliana</i> calcineurin B-like protein, SCaBP (SOS3-like CaBPs)	-nine variants	[16]
CIB	-calcium- and integrin-binding protein, calmyrin, KIP	-platelet aggregation; binds integrin and presenilins	[17]
cal glandulin		-snake venom gland protein	[18]
cal glandulin-like protein	CAGLP	-human protein of unknown function	[19]
CML24	-TCH2	-CaM-like <i>Arabidopsis</i> protein; functions in responses to abscisic acid, daylength, ion stress	[20]
SPEC-like			
SPEC	- <i>Strongylocentrotus purpuratus</i> ectodermal Ca^{2+} binding protein	-embryonic development	[21]
LPS	- <i>Lytechinus pictus</i> SPEC-resembling protein	-embryonic development	[22]
Sarcoplasmic CaBPs (SCPs) and SCP-like			
Invertebrate SCP	-including sarcoplasmic Ca^{2+} -binding proteins from <i>Nereis</i> and <i>Amphioxus</i>	- Ca^{2+} buffer	[23]
aequorin		-bioluminescence	[23]
obelin		-bioluminescence	[23]
calexcitin	-CE, cp20	-expressed in neuronal tissue; protein associated with learning; A and B isoforms	[24,25]
calerythrin		-prokaryotic CaBP; structurally similar to SCPs; from <i>Saccharopolyspora erythraea</i>	[26]
Polcalcins			
Aln g 4		-alder allergen	[27]
APC1	- <i>Arabidopsis</i> pollen calcium binding protein-1	- <i>Arabidopsis</i> allergen	[27]
Bet v 3 and 4		-birch pollen allergens	[27]
Bra n 1 and 2	-BPC1, <i>B. napus</i> pollen calcium binding protein-1	-oil seed rape allergens	[27]
Bra r 1 and 2		-turnip rape allergens	[27]
Cyn d 7		-Bermuda grass allergen	[27]
Jun o 4		-juniper allergen	[27]
Ole e 3 and 8		-olive allergen	[27]
Phl p 7		-timothy grass allergen	[27]
Syr v 3		-lilac allergen	[27]
Neuronal Ca^{2+} Sensors (NCS)			
NCS-1	-frequenin	-regulation of neurotransmission; learning; channel regulation	[28]
neurocalcin	-hippocalcin	-endocytosis	[28]
hippocalcin		-phospholipase D activation; anti-apoptotic; MAP kinase signaling	[28]
recoverin		-light sensitivity; regulates rhodopsin kinase activity in photoreceptors	[28]
visinin		-modulates adenylyl cyclase activity; four variants	[29]

VILIP kChIPs	-visinin-like proteins -Kv channel-interacting proteins (KchIPs)	-three variants; guanylyl cyclase activation - K ⁺ -channels regulation; 4 variants; repression of transcription	[28] [28]
DREAM	-calsenilin, kChIP3	-transcriptional repressor; a member of the kChIPs; binds presenilin	[28]
GCAPs	-guanylyl cyclase activating protein;	-light sensitivity; eight variants	[30]
Parvalbumins			
parvalbumin oncomodulin	- α -parvalbumin - β -parvalbumin	-binds excess Ca ²⁺ -binds excess Ca ²⁺	[31] [31]
S100s and S100-like			
S100A1	- S100A($\alpha\beta$)	-regulation of energy metabolism; cardiac contractions	[32,33]
S100A2	-S100L, CaN19	-cytoskeleton organization; tumor repression	[33,34]
S100A3	-S100E	-disregulation associated with cancer	[32]
S100A4	-metastasin, calvasculin, CAPL	-cytoskeleton regulation; tumor promoting activity; cytokine-like when excreted	[32,33]
S100A5	-S100D	-cytoskeleton regulation	[33]
S100A6	-calcyclin, CAPY, CABP	-chemotactic agent	
S100A7	-psoriasin, PSOR1	-forms dimer with S100A9; cytoskeleton regulation; propagates inflammation; cytokine-like when excreted	[32,33]
S100A8	-calgranulin A, CAGA, MRP8, CGLA	-forms dimer with S100A9; functions same as S100A8	[32,33]
S100A9	-calgranulin B, CAGB, MRP14, CGLB	-cytoskeleton regulation; anti-inflammatory activity; acts independent of Ca ²⁺	[32,33]
S100A10		-cytoskeleton regulation	[32,33]
S100A11	-calgizzarin, S100C, MLN70	-cytokine-like when excreted	[33]
S100A12	-calgranulin C	-cytokine-like when excreted	[32,33]
S100A13		-cytokine-like when excreted	[32]
S100A14	-BCMP84		[32]
S100A15			[32]
S100A16	-S100F, DT1P1A7		[32]
S100B($\beta\beta$)	-S100 β	- regulation of energy metabolism; regulation of cell cycle; regulation of cytoskeleton; neuroprotective function; cytokine-like when excreted; Ca ²⁺ homeostasis	[32-34]
S100P		-tumor development; stimulation of cell proliferation and survival	[32,34]
calhepatin p26olf cabindin D _{9k}	-intestinal CaBP	-S100-like protein of <i>Lepidosiren paradoxa</i> liver -frog olfactory epithelium -binds excess Ca ²⁺ and functions in intracellular Ca ²⁺ transport	[35] [36] [33]
trichohyalin profilaggrin repetin EH domain		-multidomain: associates with keratin -multidomain: associates with keratin -associates with keratin -multidomain; used to form protein:protein interactions; involved in endocytosis and signal transduction; Ca ²⁺ serves a structural role	[37] [38] [33] [39]
Penta EF-Hand subfamily			
calpain		-intracellular cysteine protease; both domain VI of large subunit and domain IV of small subunit contain 5 EF-hands; forms heterodimer between domain IV and VI	[40]
sorcin	-soluble resistance-related calcium binding protein	-drug resistance; Ca ²⁺ homeostasis through channel modulation; forms homodimer	[40]
grancalcin		-granule membrane fusion and degranulation of neutrophils; forms homodimer	[40]
ALG-2	-apoptosis-linked gene 2	-apoptosis; can form heterodimers with peflin	[40]
peflin	-PEF protein with long N-terminal hydrophobic domain	-Ca ²⁺ signaling events in higher vertebrates; forms heterodimer with ALG-2	[40]
Hexa EF-hand subfamily			
calbindin D _{28k}	-1 α ,24-dihydroxy vitamin D ₃ -dependent CaBP	-found in intestinal epithelium and brain; possibly both buffer and sensor; neuroprotective agent	[41]
calretinin		-abundant in neuronal tissue; roles in both Ca ²⁺ buffering and as a Ca ²⁺ sensor	[41]

secretagogin	-suppresses cell growth	[42]	
calsymin	-prokaryotic CaBP; from <i>Rhizobium etli</i> ; role in nitrogen fixation	[26]	
CREC subfamily			
reticulocalbin	-regulated processes of ER	[43]	
calumenin	-regulated processes of ER	[43]	
ERC-55	-taipoxin-associated CaBP 49 (TCBP-49), E6-binding protein (E6BP)	-regulated processes of ER	[43]
crocalbin	-regulated processes of ER	[43]	
Cab45	-regulated processes of Golgi lumen	[43]	
Spectrins			
α -actinin	-multidomain; membrane cytoskeleton	[44]	
spectrin	-multidomain; membrane cytoskeleton	[44]	
dystrophin	-multidomain; membrane cytoskeleton	[44]	
EC-Domain-Containing Proteins			
BM-40	-SPARC, osteonectin	-multidomain; secreted glycoprotein; anti-adhesive; binds Ca^{2+} as a structural role	[45]
QR1		- multidomain; quail retina protein	[46]
SC1	-hevin	- multidomain; brain protein; adhesion modulator	[47,48]
testican	-SPOCKs	- multidomain; proteoglycan; three isoforms	[49]
tsc36		- multidomain; TGF- β -induced protein	[50]
Miscellaneous			
Iba1	-ionized Ca^{2+} -binding adaptor molecule 1	-membrane ruffling	[51]
TCBP-23	- <i>Tetrahymena pyriformis</i> CaBP	- Ca^{2+} sensitive changes in ciliary beating	[52]
Flagellar calcium-binding protein	-FCaBP	- <i>Trypanosoma cruzi</i> protein; associates with flagellar membrane in Ca^{2+} -dependent manner	[53]
CBP40	- Ca^{2+} binding protein 40, LAV1-2	-expressed in the amoebae and plasmodia of <i>Physarum polycephalum</i>	[54]
nucleobindin	- Ca^{2+} -binding 63 kDa bone protein; calnuc	-mineralized bone matrix component (extracellular); Ca^{2+} storage in the Golgi; binds DNA	[55-57]
NEFA	-DNA binding, EF-hand, Acidic amino acid rich region	-related to nucleobindin; DNA binding protein	[58]
80K-H		- Ca^{2+} channel modulator	[59]
calsensin		-small neuronal protein	[60]
<i>E. histolytica</i> CaBP		-from <i>Entamoeba histolytica</i>	[61]
CDPKs	- Ca^{2+} -dependent protein kinases	-multidomain protein; found in plants and protists	[62]
ryanodine receptor		-multidomain protein; sarcoplasmic reticulum Ca^{2+} channel	[63]
CaV1.2 channel		-multidomain; possibly involved in Mg^{2+} regulation	[64]
Cbl		-multidomain; adaptor protein that functions as a negative regulator of many signaling pathways; unknown if structural or regulatory	[65]
diacylglycerol kinase	-DGK	-multidomain; regulation of cellular functions; isoforms α , β , and γ show varying levels of Ca^{2+} sensitivity	[66]
phospholipase C		-multidomain; hydrolyzes phosphatidylinositol 4,5-bisphosphate to inositol-1,4,5-triphosphate and diacylglycerol	[67]
glycerol-3-phosphate dehydrogenase		-multidomain; FAD-dependent enzyme of the inner mitochondrial membrane	[68]
AIF-1	-allograft inflammatory factor-1	-multidomain; inflammation	[69]
AtCBG	- <i>Arabidopsis</i> Ca^{2+} -binding GTPase	-ABA-mediated salt stress signaling	[70]

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Table 2 Ca^{2+} -binding ability of members of the EF-hand superfamily¹

Protein	# of EF-hands (functional/total)	K_{dS} (M)	Positive Cooperativity	Notes	Reference
S100s and S100-like					
S100A1	1 ^w ,1 ^C /2	10^{-4e}	No		[1]
S100A2	1 ^w ,1 ^C /2	10^{-4g}	Yes		[2]
S100A3	1 ^w ,1 ^C /2	10^{-2g}	slightly negative	-Zn ²⁺ binding protein	[3]
S100A4	1 ^w ,1 ^C /2	10^{-4g}	Yes		[4]
S100A5	1 ^w ,1 ^C /2	$10^{-4}, 10^{-7g}$	Yes	-Cu ²⁺ binding impairs Ca ²⁺	[5]
S100A6	1 ^w ,1 ^C /2	10^{-4g}	Yes		[4]
S100A8	1 ^w ,1 ^C /2	?	?		[6]
S100A9	1 ^w ,1 ^C /2	?	?		[7]
S100A11	1 ^w ,1 ^C /2	10^{-4g}	Yes		[8]
S100A12	1 ^w ,1 ^C /2	$10^{-8}, 10^{-5a}$	Yes	-in absence of Zn ²⁺ binds 1 Ca ²⁺ with an affinity of 10^{-5} M	[9]
S100A13	1 ^w ,1 ^C /2	$10^{-6}, 10^{-5g}$	Yes		[10]
S100B($\beta\beta$)	1 ^w ,1 ^C /2	$10^{-6}, 10^{-5a}$	No	-Zn ²⁺ increases Ca ²⁺ affinity, two different affinity sites	[11]
S100P	1 ^w ,1 ^C / [*] /2	$10^{-7}, 10^{-4a}$	No		[12]
calhepatin	1 ^w ,1 ^C /2	$10^{-6}, 10^{-4a}$	No		[13]
calbindin D _{9k}	1 ^w ,1 ^C /2	10^{-7g}	Yes		[14]
S100A7	1 ^C /2	?	n/a		[15]
S100A16	1 ^C /2	10^{-4g}	n/a		[16]
EH domain	1 ^C /2	variant specific	n/a	-both low and high affinities reported	[17-19]
p26olf	2 ^w ,2 ^{p26olf} /4	10^{-5f}	Yes		[20]
Polecalcins					
Bet v 4	2 ^C /2	?	?		[21]
EC-domain-containing					
testican	2 ^C /2	10^{-5j}	?	-disulphide bond in canonical EF-hand	[22]
BM-40	1 ^N ,1 ^C /2	10^{-8j}	?	-disulphide bond in canonical EF-hand	[23]
Spectrins					
α -actinin	2 ^C /2	?	Yes	-EF2 has a significantly higher affinity than EF1	[24]
α -spectrin	2 ^C /4	10^{-4f}	Yes		[25]
Parvalbumins					
parvalbumin	2 ^C / [*] /3	10^{-8g}	No		[26]
oncomodulin	2 ^C / [*] /3	$10^{-8}, 10^{-7j}$	No		[27]
CaM-like					
calmodulin	4 ^C /4	$10^{-7}-10^{-5g}$	Yes		[28]
troponin C	4 ^C / [*] /4	$10^{-6}, 10^{-5f}$	Yes (high affinity) No (low affinity)	-structural and regulatory sites; structural sites can bind Mg ²⁺ ; EF1 in cardiac TnC is nonfunctional	[29]
CLSP	4 ^C / [*] /4	$10^{-6}, 10^{-4g}$	Yes (high affinity) No (low affinity)	-structural and regulatory sites; structural sites can bind Mg ²⁺	[30]
CLP	4 ^C /4	$10^{-5}, 10^{-4g}$	Yes (high affinity) No (low affinity)		[31]
calcineurin B	4 ^C /4	$10^{-7}, 10^{-5g}$	Yes		[32]
SOS3	4 ^N /4	?	?		[33]
centrin	1-4 [*] /4	$10^{-6}-10^{-3g}$	No	-several variants which bind differing numbers of Ca ²⁺ and with different affinities; some have Ca ²⁺ /Mg ²⁺ sites	[34-36]
yeast CaM	3 ^C /4	10^{-6f}	Yes		[37]
caldendrin	3 ^C / [*] /4	$10^{-6}, >10^{-4f}$	Yes (high affinity)	- two sets of sites; in presence of physiological [Mg ²⁺] Ca ²⁺ does not bind weak site; five variants	[38]
CaVP	2 ^C /4	$10^{-7}, 10^{-4f}$	No		[39]
CHP	2 ^C /4	10^{-8d}	No		[40]
CIB	1 ^N / [*] ,1 ^C /4	$10^{-7}, 10^{-6f}$	No		[41]
AtCBL2	2 ^N /4	?	most likely not	-EF-hands are unpaired	[42]
myosin RLC	1 ^N / [*] /4	10^{-6h}	n/a	-from chicken gizzard	[43]
myosin ELC	1 ^N /4	< 10^{-6a}	n/a		[44]
Neuronal Ca²⁺ sensors (NCS)					
Frq1	3 ^C /4	$10^{-7}-10^{-5f}$	Yes	-unmyristoylated form binds Ca ²⁺ with higher affinity and no apparent positive cooperativity	[45]
neurocalcin	3 ^C / [*] /4	$10^{-7}-10^{-6i}$	Yes	-unmyristoylated form binds Ca ²⁺ with higher affinity and no apparent positive cooperativity	[46]
GCAPs	3 ^C / [*] /4	10^{-7b}	Yes (some variants)		[47,48]
NCS-1	3 ^C / [*] /4	$10^{-8}-10^{-5f}$	Yes	-number of Ca ²⁺ bound and affinity dependent on state of myristylation; unmyristoylated form binds Ca ²⁺ with no apparent positive cooperativity	[49]
DREAM	1 ^N / [*] ,2 ^C /4	$10^{-6}, \text{low}^j$	Yes	-two sets of sites; high affinity sites display positive	[50]

kChIPs	2 ^C /4	?	?	cooperativity in presence of Mg ²⁺	[51]
VILIP recoverin	2 ^C /4 2 ^C /4	10 ⁻⁶ , 10 ^{-4g} 10 ^{-5f}	No Yes	-unmyristoylated form binds Ca ²⁺ with higher affinity and no apparent cooperativity	[52] [53]
SCPs and SCP-like					
NSCP calerythrin	3 ^{C*/4} 3 ^C /4	10 ⁻⁷ -10 ^{-6g} 10 ⁻⁹ -10 ^{-8a}	Yes Yes between paired sites	-two sets of sites	[54] [55]
aequorin	3 ^{C*/4}	10 ^{-5g}	?		[56]
obelin	3 ^{C*/4}	?	?		[57]
calexitin B	3 ^{C*/4}	10 ⁻⁷ -10 ^{-6f}	Yes		[58]
calexitin A	2 [*] /4	10 ^{-7c}	?	-may contain a third functional EF-hand	[59]
Penta EF-hand sub-family					
calpain domains IV and VI	1 ^{PEF} , 2 ^C /5	10 ^{-5a}	No	-Ca ²⁺ affinity sensitive to the activation state of calpain and the presence of a substrate	[60,61]
ALG-2	1 ^{N(EF5)} , 2 ^C /5	10 ⁻⁶ -10 ^{-4g}	Yes	-different variants have differing Ca ²⁺ binding abilities	[62,63]
sorcinc	1 ^{PEF} , 1 ^C /5	10 ^{-6a}	?		[64]
grancalcin	1 ^{PEF} , 1 ^C /5	10 ^{-5g}	Yes		[65,66]
Hexa EF-hand sub-family					
calbindin D _{28K}	4 ^{C*/6}	10 ⁻⁷ -10 ^{-6g}	Yes		[67]
calretinin	4 ^C /6	10 ⁻⁶ , 10 ^{-4g}	Yes		[68]
secretagogin	4 ^C /6	10 ⁻⁸ -10 ^{-4g}	Yes		[69]
CREC-subfamily					
calumenin	7 ^C /7	10 ^{-4g}	No		[70]
reticulocalbin	4 ^C /6	?	?		[71]
Miscellaneous					
<i>E. histolytica</i> CaBP	4 ^{C*/4}	10 ⁻⁶ -10 ^{-3g}	Yes	-no cooperativity observed in presence of Mg ²⁺	[72]
CDPK	3-4 ^C /4	10 ⁻⁶ -10 ^{-5f}	Isoform dependent	-various isoforms have different Ca ²⁺ -binding abilities; some isoforms display negative cooperativity	[73]
CBP40	4 ^C /4	10 ⁻⁸ -10 ⁻⁶ⁱ	Negative	-EF1 lacks the N-terminal helix	[74]
FCaBP	2 ^C /4	10 ⁻⁵ -10 ^{-4j}	No		[75]
nucleobindin	2 ^C /2	10 ^{-5a}	Yes		[76]
NEFA	2 ^C /2	10 ⁻⁸ -10 ^{-7f}	No		[77]
calsensin	2 ^C /2	?	?		[78]
ryanodine receptor	2 ^C /2	10 ⁻⁴ -10 ^{-3g}	Yes		[79]
tescalin	1 ^{C*/4}	10 ^{-7g}	n/a		[80]
Cbl	1 ^N /2	high	n/a		[81]
Iba1	1 ^N /2	weak	n/a		[82]
CaV1.2 channel	1 [*] /1	10 ^{-4a}	n/a	-binds Mg ²⁺	[83]

¹ Due to the fact that there is no standardization of methods and protocols used to determine Ca²⁺ affinities, only the magnitudes of the Ca²⁺ dissociation constants are indicated. As well, since ionic strength influences Ca²⁺ affinity the amount of salt used in each study is also included.

^C canonical EF-hand

^P pseudo EF-hand

^N noncanonical

* also binds Mg²⁺ with physiological significance

^a no salt

^b 40mM KCl

^c 50mM KCl

^d 60mM KCl

^e 90mM KCl

^f 100mM KCl

^g 150mM KCl

^h 50mM NaCl

ⁱ 100mM NaCl

^j 150mM NaCl

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