

Supplementary Materials for

Structure of the STRA6 receptor for retinol uptake

Yunting Chen[†], Oliver B. Clarke[†], Jonathan Kim, Sean Stowe, Youn-Kyung Kim, Zahra Assur, Michael Cavalier, Raquel Godoy-Ruiz, Desiree C. von Alpen, Chiara Manzini, William S. Blaner, Joachim Frank, Loredana Quadro, David J. Weber, Lawrence Shapiro, Wayne A. Hendrickson and Filippo Mancia

correspondence to: fm123@cumc.columbia.edu

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Other Supplementary Materials for this manuscript includes the following:

Movies S1 to S3

Dataset	Danio rerio STRA6-CaM
Pixel size (Å)	1.255
Number of grids	2
Number of micrographs (total)	2613
Number of micrographs (final)	1657
Number of picked particles	317416
Final number of particles	56615
Box size (pixels)	200
Symmetry	C2
Resolution, overall	3.9
Est. accuracy rotations (degrees)	2.49
Est. accuracy translations (pixels)	0.72
Applied B-factor (sharpening)	-113.68
Molprobity clashscore	5.23
Ramachandran favored (%)	94.03
Ramachandran allowed (%)	5.28
Ramachandran outliers (%)	0.69
Rotamer outliers (%)	0.16

Table S1: Data collection and validation statistics for STRA6-CaM cryo-EM structure.

are given in parentitieses.	
Wavelength	0.97919
Resolution range	25.37 - 1.739 (1.801 - 1.739)
Space group	C 1 2 1
Unit cell	156.5, 37.2, 35.7; 90, 94.4, 90
Total reflections	67579 (3076)
Unique reflections	21134 (2084)
Multiplicity	3.2 (2.6)
Completeness (%)	98.8 (97.8)
Mean I/sigma(I)	6.7 (1.2)
Wilson B-factor	18.29
R-merge	0.095 (0.658)
R-meas	0.131 (0.882)
CC1/2	0.986 (0.609)
Reflections used in refinement	21098 (2083)
Reflections used for R-free	1026 (115)
R-work	0.2279 (0.3448)
R-free	0.2672 (0.4032)
Number of non-hydrogen atoms:	1504
macromolecules	1364
ligands	10
Protein residues	172
RMS(bonds)	0.007
RMS(angles)	0.88
Ramachandran favored (%)	100
Ramachandran allowed (%)	0
Ramachandran outliers (%)	0
Rotamer outliers (%)	0
Molprobity clashscore	2.97
Average B-factor:	32.35
macromolecules	32.06
ligands	30.25
solvent	35.52
Number of TLS groups	5

Table S2: Data collection and refinement statistics for CaM-CaMBP2 complex crystal structure. Values in the highest resolution shell (1.801-1.739) are given in parentheses.

Mutation	zSTRA	Structural	Reference
	equivalent	element	
	position		
P90L	P77	TM1TM2L	Pasutto, F. et al., Am. J. Human Gen. 2007
P293L	P272	JM1TM6L	Pasutto, F. et al., Am. J. Human Gen. 2007
T321P	T300	TM6	Pasutto, F. et al., Am. J. Human Gen. 2007
T644M	T613	CaMBP2	Pasutto, F. et al., Am. J. Human Gen. 2007
R655C	R626	αCT	Pasutto, F. et al., Am. J. Human Gen. 2007
G217E	A194	TM5	White, T. et al., Mol. Vis. 2008
Q438R	Q417	TM8	Chassaing, N. et al., Human Mut. 2009
R638P	R609	CaMBP2	Chassaing, N. et al., Human Mut. 2009
D560H/R655H	D539/R626	JML/ aCT	Segel, R. et al., Am. J. Med. Gen. 2009
G304K	F283	TM6	Casey, J. et al., Human Mut. 2011
R408Q	R387	TM7TM8L	Slavotinek, A.M. et al., Clin. Genet. 2015
G339S	G318	TM6TM7L	Kawaguchi, R., et al., J. Biol. Chem. 2008
		(lid helix)	

Table S3: STRA6 MWS missense mutations



Fig. S1. Purification and biochemical characterization of zebrafish STRA6. (A) Elution profile from size exclusion chromatography of STRA6 purified in buffer containing LMNG and CHS. (B) Denaturation curves of STRA6 purified in βDDM (black circles), LMNG (MNG, white circles) and LMNG/CHS (MNG+CHS, black triangles). The fraction of folded protein remaining is plotted against a control sample maintained at 4 °C. (C) Purified STRA6 analyzed on SDS-PAGE denaturing gel, stained by Coomassie blue. (D) Immunoblot of STRA6-CaM complex purified from transiently transfected HEK cells. Probed with anti-CaM antibody. Lanes as follows: (1): zebrafish STRA6-CaM purified from insect cells and reconstituted in amphipol; (2): Pulldown from HEK cells transfected with control plasmid pFM1.2; (3): Pulldown from HEK cells transfected with expression plasmid for zebrafish STRA6; (4): Empty; (5):

Purified recombinant human CaM (5ng). (E) Immunoblot of STRA6-CaM complex immunoprecipitated using an anti-STRA6 antibody from native zebrafish tissue. Probed with anti-CaM antibody. Lanes as follows: (1): zebrafish STRA6 immunoprecipitated using antibodies against the recombinant protein purified from insect celle; (2): Immunoprecipitation using control antibody; (3): Empty; (4) Purified recombinant human CaM; (5): Supernatant from immunoprecipitation (5µg total protein). (F) Oligomerization state of STRA6 in a solution containing β DDM, determined by multi angle light scattering coupled to refractive index and UV measurements. The estimated molecular weight of the protein component is ~200 kDa (left peak), consistent with STRA6 being a dimer in solution associated with two molecules of CaM. The peak to the right corresponds to excess β DDM in micelles of ~100 kDa.









Fig. S2. Cryo-EM analysis of Danio rerio STRA6. (A) Orientation distribution of particles in the final C2-symmetric reconstruction. The reconstruction is positioned in the center of a sphere as reference, and a histogram displaying the frequency of each unique orientation is represented on the surface of the sphere, with the length of each cylindrical bar proportional to the population size of particles in the final reconstruction with that angular orientation. (B) Final reconstruction colored by local resolution, calculated using ResMap (68), viewed from the extracellular region. A central vertical slab through the TM region is represented at right. (C) As B, viewed parallel to the membrane, with a slab taken through the TM region displayed in the inset. (D) Fourier Shell Correlation plot of the final refined reconstruction. The resolution at which the curve drops below 0.143 is indicated, and a thumbnail of the mask used for FSC calculation is inset, overlayed on the atomic model. (E) Four representative 2D class averages (upper panels) with maximum intensity projections of the final reconstruction in matching orientations (lower panels) (F) Power spectrum of a representative stack, calculated as an average of the power spectra of the frames in the stack with a window size of 3 frames. The contrast transfer function, fit using CTFFIND4 to a resolution of 3.0 Å, is displayed in the upper left quadrant. (G) Representative micrograph with particles picked using relion autopick (prior to 2D and 3D classification) circled and colored by the autopick figure of merit. A magnified view of an indicated section of the micrograph is represented below the main panel.



Fig. S3. Analysis of heterogeneity by 3D classification. The eight classes obtained from 3D classification with Relion 1.3 are viewed parallel to the membrane with the resolution where the SSNR of the class drops below 2.0, as well as the number of particles in each class, labeled above each panel. Class 6, which was chosen for high-resolution refinement, is enclosed within a dashed red box.



Fig. S4. STRA6 fold and global quality of the cryo-EM density map. All panels are represented in stereo, as indicated. All density maps are contoured at 6

X R.M.S. (A & B) Two views of the density maps are shown, together with the C α trace of the entire structure, in which one STRA6 protomer is displayed in dark red, and one CaM in yellow. (C) STRA6-CaM is depicted in licorice representation. One protomer of STRA6 is represented in spectral coloring, from violet N-terminus to red C-terminus. One protomer of CaM is colored cyan. (D) The TM1-TM5 bundle (residues 31-209) is depicted in licorice representation, in spectral coloring from violet (31) to red (209). The viewpoint is parallel to the membrane and to the IM helix axis. The N-terminal segment of STRA6, preceding TM1 is adjacent to the TM4-5 loop. The relative position of these two segments is consistent with the presence of a predicted disulfide bond between C31 and C171 (*15*). A distinctive feature of the NTD is that TM3 has a two-proline kink in the middle of the membrane, separating it into two segments (TM3a and TM3b) with an interhelical angle of 17°



Fig. S5 Domain representation of the STRA6-CaM complex. Ribbon representation of the STRA6-CaM complex colored by domain, and labeled. Residue ranges are provided in parenthesis.



Fig. S6. Quality of the cryo-EM density map. (A) Two views of the STRA6-CaM complex are represented in the center and three insets are arranged around it, showing density quality in specific regions of the structure, with the structure represented as a C α trace with side chains in stick representation. (B) Model-map FSC curves calculated for the full map used for initial model building (gray); the test half-map withheld from the cross-validation refinement run (orange) and the

half-map used in the cross-validation refinement (blue). For details of model-map FSC calculations see Materials & Methods. Stereo views of two of the insets from (A) are shown in panel (C). Density maps are contoured at 6 X R.M.S.

D.rerio(A41GB6)/1-670 H.sepiens(09EX79)/1-667 L.oculatus(09EX79)/1-667 C.oculatus(X5XCL1)/1-668 C.niloticus(13KE07)/1-658 F.cormosa(A0A087XK69)/1-665 A.mexicanus(N5LF12)/1-668 G.gallus(FINSC4)/1-671 F.abicollis(U3KCH6)/1-670 M.domestica(F6X9H5)/1-645 M.musculus(07043)1/1-670 M.musculus(07043)1/1-670 H.glaber(G5BR62)/1-662 C.porcellus(H0VUR2)/1-671 C.familiaris(J39WH10)/1-655 L.africans(G3F6S3)/1-669 O.garnetti(H0X180)/1-707 P.anubis(A0A96NM01)/1-659 M.mulatta(F7GR1)/1-667 M.fascicularis(G7P935)/1-667 G.Gorilla(G3K6X2)/1-707 P.abelli(G3K6X2)/1-707 P.abelli(G3K6X2)/1-707 P.abelli(G3K6X2)/1-707 P.abelli(G3K6X2)/1-707

D.rerio(A41GB6)/1-670 H.sapiens(09BX79)/1-667 L.coulatus(W5NCL1)/1-664 O.niloticus(13KE07)/1-658 X.maculatus(H4ANR4)/1-665 P.formosa(A0A087KK69)/1-665 A.mexicanus(W5LF12)/1-670 M.domestica(F5XH5)/1-664 M.domestica(F5XH5)/1-664 M.domestica(F5XH5)/1-664 M.musculus(070491)/1-670 H.glaber(G5BR62)/1-662 C.porcellus(H0VUR2)/1-671 C.familiaris(370NF10)/1-655 L.africans(G37663)/1-669 O.garnetti(H0XI80)/1-707 P.anubis(A0A096NW1)/1-659 M.mulatu(F7GR11)/1-667 M.fascicularis(G7P935)/1-667 G.Gorilla(G3R6X2)/1-707 P.abelli(G3R6X2)/1-707 P.abelli(G3R6X2)/1-707 P.abelli(G3R6X2)/1-668 P.alecto(L5JW03)/1-688 E.caballus(F626X7)/1-667

D.rerio(A41GB6)/1-670 H.sapiens(09BX79)/1-667 L.oculatus(W5NCL)/1-664 O.niloticus(IJKE07)/1-658 X.maculatus(M4AN84)/1-665 P.formosa(A0A087XK69)/1-666 G.gallus(FINSC4)/1-667 H.admesticanus(W5LF12)/1-668 G.gallus(FINSC4)/1-671 H.admestica(F6X9H5)/1-645 M.musculus(070491)/1-670 H.glaber(G5BR62)/1-662 C.porcellus(H0VUR2)/1-671 C.familiaris(J9WWI0)/1-655 L.africans(G3F682)/1-665 O.garnettii(H0X180)/1-707 P.anubis(A0A986MW2)/1-667 M.fascicularis(G7P935)/1-667 G.Gorilla(G3R6K2)/1-707 P.abelli(G3RK62)/1-707 P.abelli(G3RK62)/1-707 P.abelli(G3RK62)/1-707

D.rerio(A4IGB6)/1-670 H.sapiens(098X79)/1-667 L.oculatus(WSNC11)/1-664 O.niloticus(IJKR07)/1-658 X.maculatus(MANR4)/1-665 P.formosa(A0A087XK69)/1-665 A.mexicanus(MSLF12)/1-668 G.gallus(FINSC4)/1-671 F.albicollis(UJ3KC4)/1-670 H.glaber(GSBRC2)/1-684 K.norvegicus(040R93)/1-670 H.glaber(GSBRC2)/1-662 C.porcellus(H0VUR2)/1-671 C.familiar(J3WR0)/1-665 L.africana(G3FGS3)/1-669 O.garnetti(H0XIB0)/1-677 H.malatca(F7GR1)/1-657 H.malatca(G3FGC2)/1-667 H.fascicularis(G7P935)/1-667 G.Gorilla(G3FGK2)/1-67 B.taurus(G1R4A)/1-667 B.taurus(F1NQ6)/1-667 B.taurus(F1NQ6)/1-668 P.alecto(L5JN03)/1-668 E.caballus(F6Z6X7)/1-667

		- TM1a (+	
1	1MSAETVN-NYDYSDWYENAAPTKAPVEVIPP	DPTADEGI	39
1	1MSSOPA-GNOTSPGATE-DYSYGSWYIDEPOGGEEL-OPEGEVPS	HTSIPPGI	5
1	1KAMASIDVPKDDYSYEYYDVOLEPTTSPEDTILO	DPTVDDRL	4
1	1MDYDYPE-LDPLPSKIEPEVIPPC	DPTADDRI	3
1	1MDKDALV-DYEYPD-LDPLPSKIETETIPP(DPTADDMI	3
1	1MDKDALV-DYEYPD-LDPLPSKIETETIPP(DPTADDMI	3
1	MSAETGKDYYDYSDWYENALPTKPPIEVIPP	DPTADDGI	.40
1	1MAANNSGAAHGSLIDDSEGDDLLSDWY I YETAEPAAP-ODDMEPSTIPEC	DPTVSPRI	5
1	DWYIYESTESTP-ODDLFPEAIPE	HPTISPRM	13:
1		OHSEPPSI	7
1	IMESOASENGSÖTSSGVTD-DYSSWYTEEPLGAEEV-OPEGVNPL	OPTVPPAL	5
1	MESOASENGSOTSSGVTD-DYSSWYLEEPLGAEEV-OPEGVLPL	OLTAPPAL	5
1	IMSLSOAAGNOTSSGGAD-DYSSWYIDEPOGNKEL-OPEGEVPS	OPSVPPAL	.50
1	IMSLSOAA-ENOTSSBAAD-DYSSWYIDEPLEDKEL-OPEGEVPS	OPSVPPAL	5
1	IMSSOAA-GNOTASGAAD-DYS-DWYLDEPODGOEL-PAEGAVES	HPSVLSGI	.4
1	IMSSOAA-GNOTS-GATE-DYSYGSWYIDEPPGGEEP-KPERPVSL	OTSIPPSI	5
1	1 - IGODGTGGDTRGPSPPPCOPAWDLSPSRAFSRELKARVKGEGLKMSSOAAGNOTS-STG-DFE-DNWYIDEPOGDEGL-OPDGTVPS	HPSVPPGI	9
1	MCMCECAAPLRAHPELTGPHEVDFLGCLENDSOGDWAAOEEKGRMSSOPA-GNOTSPGATE-DYSYGSWYIDEPOGGEEL-OPEGEVPSY	HTSVPPGI	.9
1	IMSSOPAGNOTSPGATE-DYSYGSWYIDEPOGGEEL-OPEGEVPS	HTSVPPGI	5
1	MSSOPA-GNOTSPGATE-DYSYGSWYIDEPOGGEEL_OPEGEVPS	HTSVPPGI	5
1	MSSOPA-GNOTSPGATE-DYSYGSWYIDEPOGGEEL_OPEGEVPS	HTSVPPGI	5
1	MGGKGGGGDTRGPVLFPCOLAOALSPRRAFPRELKEKGORMSSOPA-GNOTSPGATE-DYSYGSWYIDEPOGGEEL-OPEGEVPSY	HTSVPPGI	9
1	IMSSOPA-GNOTSPGPTE-DYSYGSWYIDEPOGGEEL-OPEGEVPS	HTSTPPSI	5
1		OPNUPPSI	5
1		HPSVPPCI	5
1		HDRVDDGI	5
	DIDIGSWIDDLEGGÖRD-ÖLEGAALL-GWÖLDDÖWNIDDLEGGÖRD-ÖLEGAALL	CITE IS A LE COL	

TM1b	O		TM2	0	(TM3a
40 FHICIAAISLVVMLVL	AILARROKL-SDNORG	LTGLLSPVNFLDHT(HKGLAVAVYGVLF	CKLVGMVLSHHPLPF	TKEVANKE	FWMILALLYY 13
52 Y <mark>H</mark> ACLASL <mark>S</mark> ILVLLL	AMLVRRRQLWPDCVRG	RPGLP <mark>SP</mark> VDFLAGDF	RPRAVPAAVFMVLLS	SS <mark>LCLLLPDEDAL</mark> PF	LTLASAPSQDGKTEAPRO	AWKILGLFYY 154
44 YHTCIAAISIIVLLVL	AS <mark>F</mark> TRRKR <mark>L</mark> AQDCFKG	I PG <mark>LL<mark>SP</mark>VN<mark>F</mark>LDHTF</mark>	RHKGLAVAVFGVLFO	CKLCVLVLAENPL <mark>P</mark> F	TKNSTQEHRE	YWKIVSLFYY 138
32 YHICITVISLVVMLIL	AVLARRMKV-GDRQKG	LPGLLSPVNFLDHT(0HKGLAVAVFGVLLO	CKLWGLLISPNPLPF	TTDTVNKQ	NWVILGVFFY 123
38 YHICITAISLVIMLIL	AILARRTKV-GKRQKG	LPGLLSPVNFLDHT(HKGLAVAVFGVLLC	KLWGLLISTNPLPF	TTDSTNKQ	INWVILGVEYY 129
41 VHICTAATSLVVMLTL	AVLARROKV-GDSLKG	PGLLSPVNFLDHT(HKGLSVAVFGVLEC	KITGLVLASNPLPF	TTDSINKC	WWITLALFVV 13
58 YHTCMAPISLAVLLGL	SLLVKRRHLHRDCWNG	IPGLLSPANFLEEEC	SNRGLMAAVFGILFS	SLCVLVLDADPLPL	ITHSSOHSRE	YWKILALLYY 152
33 Y <mark>H</mark> TIMAPISLAVILAL	SFLVKRRRLYRNCWNG ^V	VPGLLSPGNFLEEDO	GHRGLAAAVFGILFS	SS <mark>LCQLVLDKDPLP</mark> L	AAPSSPSARE	FWKILALFYY 127
73 YHTCLAPLSLVAILL	SLLVKRRRLCLGCCHG	FFGLP <mark>SP</mark> LDFLAEES	GRLVPVAVFGILF?	rk <mark>l</mark> cvlaleedp <mark>lp</mark> f	LPISSPAGQG	YWKTLALLYY 167
52 HHACLASLSLLALLL	ALLVRRRRLWPHCAHCI	RPGLP <mark>SP</mark> VDFLAGNF	RSWTVPTAVFVALFS	SNLCLLLPDENPL <mark>P</mark> F	LNRTAASSPDGEPETSRC	PWKLLALLYY 154
52 LHACLASLSFLVLLLL	ALLVRRRRLWPRCGHR	GLGLP <mark>SP</mark> VDFLAGDI	SWTVPAAVFVVLF	SNLCLLLPDENPLPF	LNLTAASSPDGEMETSRC	PWKLLALLYY 154
51 CHACLAVLSMLVLLLL	AWLVLHRRLRPGCRRG	RPSLPSPVDFLAGH	RPSPVPAAVFMVLF:	SALCLLLPSEDPLPF	LALASTPG======PG	PWKMLALLYY14:
50 LHTCLAVLSHLVLLLL	AVI MEREOL PRECENCY	SPREPSPVDFLAGH	ATWINDD AVENULF	SICLUPSEDPLPF	LPLTITPGPVQRMSLCPG	PWKMLALLII 153
51 SHACLASLSVLVLLLL	AVLVRRROLWPRCGHGI	RPGLPSPVDFLAED	SRTVPTAVEMVLFS	SLCLLLPDEDPLPF	LTLIWTPSOVKEPEOEHE	PWKMLALLYY 15
93 HHACLASLSILALLL	AMLVRRRQLWPDCGRGI	RPGLP <mark>SPVDF</mark> LAGDF	RPRTVPVAVFMVLFS	SSLCLLLPDKDPLPF	LSLALPPSQGNDNKV-VC	POKMLGLLYY 194
97 Y <mark>H</mark> ACLASL <mark>S</mark> ILVLLL	AVLVRRRQLWPDCVHG	RPGLP <mark>SP</mark> VDFLAGDF	RPQTVPAAVFMVLFS	SS <mark>LCLLLPDEDPLP</mark> F	LTLASVPSQG	AWKMLGLFYY 191
52 YHACLASLS ILVLLL	AVLVRRRQLWPDCVRGI	RPGLP <mark>SP</mark> VDFLAGDF	RPQTVPAAVFMVLFS	SSLCLLLPDEDPLPF	LTLASAPSQG	AWKMLGLFYY 146
52 YHACLASLSILVLLL	AVLVRRRQLWPDCVRG	RPGLP <mark>SPVDF</mark> LAGDF	(PQTVPAAVFMVLFS	SSLCLLLPDEDPLPF	LTLASAPSQGGKTEAPRW	IAWKMLGLFYY 154
52 YHACLASLSILVLLLL	ALLVRRRQLWPDCVRG	RPGLPSPVDFLAGD	(PQTVPAAVFMVLFS	SSLCLLLPDEDPLPF	LTLASAPSQGGKTEAARW	AWKMLGLFYY 154
52 VHACLASESILVEELE	AVLVRRRQLWPDCVRG		PRAVPAAVPNULF:	SICLLPDEDPLPF	LTLASAPSQUGKTEAPRO	AWKILGLEYY 15/
53 YHTCLAVISILVIFIL	AMLVRRROLWPRCGHGI	RPGLPSPVDFLTGDF	PRTVPAAVFMVLFS	SICLLPTEDPLPF	LSLASPPGRDGEAETSRC	PWKTLALLYY 15
51 LHACLAVLSILVLLL	AMLVKRROLWPRCGHG	RPGLPSPVDFSAGDO	PRTVPAAIFMVLFS	SSLCLLLPAEAPLPF	LTLASPPSGG	PWKMLALLYY 145
52 L <mark>H</mark> TCLAVL <mark>S</mark> ILVLLLL	AMLVRRRRLWPHCGRG	RPGLP <mark>SP</mark> VD <mark>F</mark> SAGDH	(PWTVPAAVFMVLFS	SSLCLLLPAEDPLPF	LTLASPPSPDGETETPRG	PWRMLALLYY 154

 TMB
 TM4
 TM5
 Cambro

 132
 PTLYYPLIACGTLHNKVGYULGSLISWTHFGILVWQKVDCPKTPQIYKYYALFGSL®QIACLAFLEFQYPLLLFKGLQNTETANASEDLSSSYYRDYVKKILK234

 155
 AALYYPLAACATAGHTAAHLLGSTLSWAHLGVQVWQRAECPQVPKIYKYYSLLASLPLLUGLGTLSUM PVQLWRSFSRRTC-AGSKGLQSSYSESULANLC256

 139
 PALYYPLIACGTHSWQYUGSLLSWTHFGILWQVVDCPKTTEIYKYYSLLSLEDLUGLGTLSUM PVQLWRSFSRRTC-AGSKGLQSSYSESULAX1LC256

 124
 PALYYPLIACGTHSWQYUGSLLSWTHFGILWQVUCDPKTTEIKYSSLTSLEQOICLAFLSTQVPLLFKRKGGTYASEDLJSSYKDVVKLIK231

 130
 PALYYPLIACGTHSWQYUGSLLSWTHFGULWQUDQPKTPIHKHSYLSSLEQOICLAFLSTQVPLLFKRKGLKGTEKNNATEDLSSSYKDVVKLIK231

 130
 PALYYPLIACGTHSWUGYUGSLLSWTHFGULWQUDQPKTPIHKHSSLSSLEQOIACLAFLSTQVPLLFKRKGLKGTEKNNATEDLSSYKDVVKKILK233

 133
 PALYYPLIACGTHSWUGYUGSLLSWTHFGULWQUDQPKTPIHKHSSLSSUFDIACLAFLSTQVPLLFKRKGLKGTEKNNATEDLSSYKDVVKKILK235

 133
 PALYYPLIACGTHSWUGYUGSLSWTHGUWWQUDQPKTPODYWYLWYLSLSSUFDIACLAFLSTQVPLLKKRKGRGENNATEDLSSYKDVVKKILK235

 153
 PALYYPLIACGTHSWUGYUGSLSWTHGUWWQUDQPKTPODYWLWYLSLSSUFSUFUKUK1LK235

 154
 PULYPLIACGTHSWUGYUGSLSWTHGUWWQUDQPCPTDIKYLWYLSLLSSUFJLSGLGTLSUFUKUKSUSSUFNOVUKUSL235

 155
 PALYYPLIACGTHSWUGYUGSLSWTHGUWWQUDQPCPTDIKYLWYLSLLSSUFJLSGLGTLSUFUKUKSUSSUFNOVUKUSL235

 156
 PALYPLIACGTARHGVAHUGYUGSLSWTHGUWWWQUQAPCPODPYLIKYLYSLLSSUFJLSUFUKUSSUSSUSSUSSUSSUFNOVUKUSL235

 157
 PALYPLIACGTARHGVAHUGYUGGLSWTHWWWWWWWWWWWWWWWWWWWWWUWWDQUDQUUWSUSTAFTUSSU

				\frown						,	
235	KKEPTKIS-SSTSKE	KLFDRLRDAVKSYI	YTPEDVFRFF	LKLAI	VVVAFIAL	MALLLISGV	LPTLHIV	RGVDI	ENIAFLLAG	NIIL	NDROEV 330
257	RKKLGS-S-YHTSKH	GFLSWARVCLRHC1	YTPOPGFHLF	LKLVL	ATLTGTAIY	OVALLLLVGV	VPTIOKV	RAGVT	TDVSYLLAG	GIVLS	EDKOEV 351
242	KKPSKN-S-SCTAEA	TLSARILESLRSYI	YTPEEVFRFF	LKLAI	AVVSFISVY	OVALLLVTFV	VP TLOKV	RAGVNI	EDIAFLLAG	NIHLS	EDRAEV 336
227	KKKSTKISTSSTDKF	KLPORITDAVKSYI	YTPEDAFRFF	LKLAI	GVVSFITLY	OMGLLLISAV	VPSLOTA	RL <mark>G</mark> VNI	EDVANLLAG	RIMLS	PDKHEV 323
233	EKTSSKVSTSSTDKF	KLPORVTDAVRSYI	YTPEEAFRFF	LKLAI	CVVSFITLY	OMGLVLISAV	VPTMOKA	RF <mark>G</mark> VDI	EDIANVLAG	OIIL	PDRKEV 329
233	EKKSNKVSKSSTDKF	KLPORVTDAVRSYI	YTPEEAFRFF	LKLAI	CVVSFITLY	OMGLVLISAV	VPTMOKA	RF <mark>G</mark> VDI	EDIANVLAG	OIIL	PDRKEV 329
236	KKKPSOASSRF	KLSERISDAFKSYI	YTPEEVFRFF	LKLAI	LVVAFIAL	OMALLLVTGI	VPTLOIV	RRGVDI	EDIAFLLAG	NIHLS	DDRKEV 328
256	RRLQKG-S-TPKLEE	SLVSRLRAYLCSYI	YAPEEGFOLF	LKLVL	MTTSVIAVY	OVALLLLVAF	VPTIQIV	RAGMTI	KDVVVLLVQ	GLVP	ENPGMPGDMEKE 356
230	KRGRKE-S-SAKIEE	SLWSRIRSYLLSYI	YVPEEGFRIF	LKLVV	LTVAVIAVY	QVALLLLVAV	VPTIQIV	RAGMTI	KDVVVLLVQ	GLVPS	DNPAVPGDMEKE 330
271	. GKRSKS-S-SSVANF	SFPSRILFYFLSHI	YSPQRGFRLF	LKLIL	STLAAITIY	QEVLLLLVAF	VPNLQKA	RE <mark>GIT</mark> I	EEVTYMLAG	GLVL	EDKLEV365
257	PKKLDSCS-HPASKR	SLLSRAWAFSQHSI	YTPEPGFCLF	LKLVI	ATLTGTATY	QVALLLLVSV	VPTVQKV	RA <mark>G</mark> IT'	TDVSYLLAG	GIVL	EDRQEV352
257	PKKLDSCS-HPASKR	SLLSRAWAFSHHSI	YTPQPGFRLF	LKLVI	ATLTGTATY	QVALLLLVSV	VPTVQKV	RA <mark>G</mark> IN'	TDVSYLLAG	GIVL	EDRQEV352
248	RKQPGG-R-SYHTKQ	DFLSRAWDYSRRYI	YIPQPGFRLF	LKLVI	ATLTGTATY	QVALLLLASV	VPTLQKV	RA <mark>G</mark> LT'	TDVSYLLAG	GLVL	KDRQEV 342
256	RKKPGGWS-CHTSKQ	GFLSRAWDCSQRYI	YTPQPGFRLF	LKLVI	ATLTGTATY	QVALLLLASV	VPALQKV	RA <mark>G</mark> IT'	TDVSYLLAG	GVVL	EDRQEV351
255	RKKLAS-S-SRASKH	IG <mark>F</mark> LSRAWVSYRNYI	YTPQRGFRLF	LKLVL	ATLTGSAIY	QVALLLLVGV	/VPTIQRM	RA <mark>G</mark> IT'	TDICYLLAG	GILL	EDKQEV349
256	RKKLQS-S-SHTSKH	GFLSQAWICFRHHI	YTPQQGFRLF	LKLVL	AALTGTAIY	QVALLLLVGV	VPTIQKV	RA <mark>G</mark> IT <i>i</i>	ADVSYLLAG	GIVL	EDRQEV350
295	RKKLET-S-SHSPKH	IG <mark>F</mark> LSWAWICFRQYI	YTPQRGFRLF	PLKLVL	ATLTGTAIY	QVALLLLVGV	/VPTIQKV	RA <mark>G</mark> VT'	TDVSYLLAG	GIML	EDRQEV389
294	RKKLGS-S-SHTSKH	IGFLSWARVCLRHCI	YTPQPGFRLF	PLKLVL	ATLTGTAIY	QVALLLLVGV	VPTIQKV	RA <mark>G</mark> VT'	TDISYMLAG	GIVL	EDKQKV 388
249	RKKLGS-S-SHTSKH	IGFLSWARVCLRHCI	YTPQPGFRLF	PLKLVL	ATLTGTAIY	QVALLLLVGV	/VPTIQKV	RA <mark>G</mark> VT'	TDVSYMLAG	GIVL	EDKQEV 343
257	RKKLGS-S-SHTSKH	IGFLSWARVCLRHCI	YTPQPGFRLF	PLKLVL	ATLTGTAIY	QVALLLLVGV	VPTIQKV	RA <mark>G</mark> VT'	TDVSYMLAG	GIVL	EDKQEV351
257	RKKLGS-S-SHTSKH	IGFLSWARVCLRHCI	YTPQPGFRLF	PLKLVL	ATLTGTAIY	QVALLLLVGV	/VPTIQKV	RA <mark>G</mark> VT'	TDVSYMLAG	GIVL	EDKQEV351
297	RKKLGS-S-YHTSKH	IGFLSWAWVCLRHCI	YTPQPGFRLF	LKLVL	ATLTGTAIY	QVALLLLVGV	VPTIQKV	RA <mark>G</mark> VT'	TDVSYLLAG	GIVL	EDKQEV 391
257	RKKLGS-S-SHTSKH	IGFLSWAWVCLRHCI	YTPQPGFRLF	LKLVL	ATLTGTAIY	QVALLLLVGM	IVPNIQKV	RA <mark>G</mark> VT'	TDVSYLLAG	GIVL	EDKQEV351
258	QKKLKS-S-SHTCKR	GFASQAWMYFRHSV	YIPQQGFRLF	LKLVL	VTLTGTAIY	QVALLLLVGV	VPTIQKV	RAGIT	TDVSYLLAG	GIVL	EDRQEV352
248	RKKLGS-S-SHTSKH	IGFLLRAWICFRHYI	YTPQQGFRLF	LKLVL	ATLTGTAIY	QVGLLLLVSV	IPTIQKV	RAGIT'	TDVSYLLAG	GIVL	ENRQEV 342
157	OKKLES-R-SRTSKR	GFLSOAWICFROHT	YTPORGERLE	T.KT.MT.	ATLTGTATY	OVALLLLVGV	VPTTOKV	AGTT'	TDVSYLLAG	GLVLS	EDROEV 351

TAAT

		TM7	G)			TM8b	
D.rerio(A4IGB6)/1-670 H.sapiens(92BX79)/1-667 L.oculatus(1%DKC1)/1-664 O.niloticus(1%IXE07)/1-658 X.maculatus(MAXB4)/1-665 P.formosa(A0A087XK69)/1-665 A.mexicanus(WSLF12)/1-668 G.gallus(FINSC4)/1-671 F.albicollis(U3XCM6)/1-645 M.domestica(F6X915)/1-684 R.norvegicus(04QR8)/1-670 H.glaber(GSBR2)/1-670 H.glaber(GSBR2)/1-667 C.familaris(J9NWTO)/1-655 L.africana(G3T653)/1-669 O.garneti(1(H0XIB0)/1-707 P.anubis(A0A096NMG1)/1-704 C.sabaeus(A0A09FNUT)/1-659 M.mulatta(F7N11)/1-677 P.abelli(GSRC2)/1-667 B.taurus(F1N4Q6)/1-667 P.abelli(GSRC2)/1-667 B.taurus(F1N4Q6)/1-667 B.taurus(F1N4Q6)/1-668 F.acabalus(F626X7)/1-667	331 VRIVYYINCVIIC 352 VELVKHELALIVC 354 VRIVYYMCUVU 324 VRIVYYMCUVU 330 IRIVYYMCUVU 330 IRIVYYMCUVU 331 LETVKHILALIVC 357 LETVKHILALIVC 358 VELVKHELALIVC 358 VELVKHELALIVC 359 VELVKHELALIVC 359 VELVKHELALIVC 359 VELVKHELALIVC 360 VELVKHELALIVC 360 VELVKHELALIVC 370 VELVKHELALIVC 380 VELVKHELALIVC 380 VELVKHELALIVC 381 VELVKHELALIVC 382 VELVKHELALIVC 382 VELVKHELALIVC 383 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D.rerio(A4IGB6)/1-670 H.sapiens(09BX79)/1-667 L.oculatus(USK07)/1-664 O.niloticus(ISK07)/1-658 X.maculatus(MANR4)/1-665 P.formosa(A0A087XK9)/1-665 A.mexicanus(MSLF12)/1-664 f.albicolls(USXC0)/1-664 H.donvegicus(04OR82)/1-670 H.glaber(G5BRC2)/1-670 H.glaber(G5BRC2)/1-672 C.porcellus(H0VUR2)/1-670 L.africana(G37653)/1-665 U.africana(G37653)/1-665 D.garetti(H0XI80)/1-707 P.anubis(G7041)/1-670 M.mulactus(F7GR11)/1-667 M.fascicularis(G7P935)/1-667 G.Gorilla(G3R6X2)/1-707 P.abelli(G3R6X2)/1-707 P.abelli(G3R6X2)/1-707 B.taurus(F1N406)/1-707 P.abelli(G3R6X2)/1-707	536 EAP PGYRCXSHYI 557 ATL PGYYTKNET 542 EGF PGYRCAHYI 535 EAF PAYRCAHYI 535 EAF PAYRCAHYI 535 EAF PAYRCAHYI 534 EAF PGYRCAHYI 534 EAF PGYRCAHYI 534 EAF PGYRCAHYI 534 EAF PGYRCAHYI 558 ASL PGYRCAHY 558 ASL PGYRTYRNIT 558 ASL PGYRTYRNIT 557 ATL PGYRTYRNIT 557 ATL PGYRTYRNIT 557 ATL PGYRTYRNIT 558 ATL PGYRTYRNIT 557 ATL PGYRTYRNIT 558 ATL PGYRTYRNIT		LLQSSGODG LLQQSALPRTH LQSSALPRTH LQSSAGOT LLQSUQGS LLQSLOQES LLQSLOQES	LSAQRIRDAE G IAAPQDSLRPGED SAEQKIRDAE G 	TOEVQOEKKQ WOLLQVRDBM TELVQOEKKQ TOEVQOEKKL TOEVQOEKKL TOEVQOEKKL TOEVQOEKKL TOEVQOEKKL TOEVQOEKKL TOEVQOEKKL TOEVQOEKKL MOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM WOLLQVRDBM	NKVS NAKRAF KAGARPGASRG SKLS NSRRAF NKVS SARRAF NKVS SARRAF NKVS SARRAF NKVS SARRAF NKVS RLKRSF NKAGACHKGSOSF NKAGACHKGSOSF NKAGACHKGSOSF NKAGACHKGSOSF NKAGACHKGSOSF NKAGACHKGSOSF NKGACPRASHG NKGACPRASHG NKGACPRASHG NKGACPRASHG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKGACPRASSEG NKG	AHWQLLYTUVN ARWGLAYTLH ARWGLAYTLH MHQLYTUVN RHQLYTUVN MHQCLYTUVN ARWGLAYTUL ARWGLAYTUL ARWGLAYTUL ARWGLAYTULH ARWGLAYTULH ARWGLAYTULH ARWGLAYTULH	PSLVGSRM 628 PTLQVPR-556 PSLVASKH 634 PSLVASKH 634 PSLVASKH 634 PSLVASKH 637 PSLVASKH 637 PSLVASKH 637 PSLVASKH 637 PSLVASKH 637 PSLVASKH 637 PSLVASKH 649 PSLVASKH 649 PSLVASKH 649 PSLVASKH 649 PSLVASKH 649 PSLVASKH 649 PSLVASKH 649 PTLQVPRK 653 PTLQVPRK 648 PTLQVPRK 648 PTLQVPRK 655 PTLQVPRK 655 PSLQASKH 655 PSLQASKH 6554
D.rerio(A41GB6)/1-670 H.sapiens(09BX79)/1-667 L.oculatus(5%DC1)/1-654 O.niloticus(13KE07)/1-658 X.maculaus(MANE4)/1-665 P.formosa(A0A087XK69)/1-665 A.mexicanus(MSLF12)/1-664 H.domestica(F6X9H5)/1-664 H.domestica(F6X9H5)/1-664 H.domestica(F6X9H5)/1-664 H.glaber(GSH8C)/1-670 H.glaber(GSH8C)/1-670 H.glaber(GSH8C)/1-670 H.glaber(GSH8C)/1-667 D.garnethi(H0X100)/1-707 P.anubis(G7R43)/1-667 M.mulata(G7R6X1)/1-667 M.scicularis(G7P835)/1-667 M.scicularis(G7P835)/1-667 M.scicularis(G7P835)/1-667 M.scicularis(G7P835)/1-667 M.scicularis(G7P835)/1-667 M.scicularis(G7P835)/1-707 P.anubis(G3R6X2)/1-707 P.anubis(G3R6X2)/1-707 P.anubis(G7R454)/1-658 M.scicularis(G7P835)/1-667 M.fascicularis(G7P835)/1-667 M.fascicularis(G7P835)/1-667 M.fascicularis(G7P835)/1-667 M.fascicularis(G7P835)/1-667 P.atuely(F867K7)/1-667	629 FQCQSSESF INGAL 657 TAILGA- 635 FQCQSSESP INGSL 635 FQCQSSESP INGSL 628 FQLQTADNF INGSL 628 FQLQTADNF INGSL 628 FQLQTADNF INGSL 628 FQLQSSESF INGTL 654 TAILCPT 657	SRTSKEGSKKDGSVKEP NGAQP	NKEAESAAASN TTREAEAAAASN PREAEAAAASN SREAEGAATN SREAEGAATN SREAEGAATN					670 664 658 6663 6671 6454 680 670 6752 6757 6677 667 667 667 668 668 668 668 668 6

 M.mulatta(F70R11)/1-667
 657

 M.fascicularis(G7P85)/1-667
 657

 G.Gorilla(G3R682)/1-707
 697

 P.abelli(G3R682)/1-667
 697

 G.Gorilla(G3R682)/1-667
 697

 B.taurus(F1N406)/1-668
 656

 Fig. S7. STRA6 sequence alignment. Sequence alignment (generated using

 MUSCLE (64)) comprising 26 STRA6 sequences, where the intensity of the color is proportional to the degree of conservation, colored and visualized using Jalview

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(65). Residues are colored by their physicochemical properties using a modified version of the Zappo scheme: aliphatic residues (I, L, V, A & M) are in salmon, aromatics (F, W & Y) in orange, positively charged (K, R & H) in blue, negatively charged (D, E) in red, polars (S, T, N, Q) in green, G in magenta, P in cyan, C in yellow. Secondary structure elements are labeled and displayed above the alignment, in yellow. Solid and dotted indicate regions of the protein, which are visible and disordered in the structure, respectively.





and **D**) Two views of the STRA6-CaM atomic model, with one protomer colored by the local correlation of each residue, averaged over the atomic positions. The radius of the backbone trace is inversely proportional to the correlation, such that a thicker trace indicates lower correlation with the experimental map.









CaMBP1

D.rerio(A4IGB6)	223 SYYRD <mark>YVK</mark> KILKKK	236
H.sapiens(Q9BX79)	245 SYSEE <mark>YLR</mark> NLLCRK	258
L.oculatus(W5NCL1)	230 SYYKD <mark>YVK</mark> EILKKK	243
O.niloticus(I3KE07)	215 SYYRD <mark>YVK</mark> KMLNKK	228
X.maculatus(M4AN84)	221 SYYRD <mark>YVK</mark> TILYEK	234
P.formosa(A0A087XK69)	221 SYYRD <mark>YVK</mark> SILYEK	234
A.mexicanus(W5LF12)	224 SYYRD <mark>YVK</mark> KILKK <mark>K</mark>	237
G.gallus(F1NSC4)	244 GYYKK <mark>YLK</mark> AVLSR <mark>R</mark>	257
F.albicollis(U3KCM6)	218 SYYRK <mark>YLK</mark> AVLSKR	231
M.domestica(F6X9H5)	259 SYYED <mark>YLR</mark> HILSGK	272
R.norvegicus(Q4QR83)	245 SYSEK <mark>YLR</mark> ALLCP <mark>K</mark>	258
M.musculus(070491)	245 SYSEK <mark>YLR</mark> TLLCPK	258
H.glaber(G5BRG2)	236 RDSKE <mark>YLR</mark> SLLCRK	249
C.porcellus(HOVUR2)	244 SDTEE <mark>YLK</mark> SLLCRK	257
C.familiaris(J9NWI0)	243 SYSED <mark>YLR</mark> TLLCRK	256
L.africana(G3T6S3)	244 SYSEE <mark>YLR</mark> YLLRRK	257
O.garnettii(HOXI80)	283 RYSEE <mark>YLR</mark> NLLCRK	296
P.anubis(A0A096NMQ1)	282 SYSEE <mark>YLR</mark> NLLCRK	295
C.sabaeus(A0A0D9RNU1)	237 SYSEE <mark>YLR</mark> NLLCRK	250
M.mulatta(F7GRI1)	245 SYSEE <mark>YLR</mark> NLLCRK	258
M.fascicularis(G7P935)	245 SYSEE <mark>YLR</mark> NLLCRK	258
G.Gorilla(G3R6K2)	285 SYSEE <mark>YLR</mark> NLLCRK	298
P.abelli(Q5R7B4)	245 SYSEE <mark>YLR</mark> NLLCRK	258
B.taurus(F1N4Q6)	246 SYSEE <mark>YLR</mark> TLLCQK	259
P.alecto(L5JW03)	236 SYPEE <mark>YLR</mark> TLLCRK	249
E.caballus(F6Z6X7)	245 SYSEE <mark>YLR</mark> TLLCQK	258

375 SHPVMKAFCGLLLQSS	390	59
396 SHPAMTAFCSLLLOAO	411	620
381 SHPVMKAFCGVLLQSP	396	60
368 SHPVMKAFCGMLLQSV	383	593
374 SHPVMKAFCGILLQSL	389	598
374 SHPVMKAFCGILLQSL	389	591
373 SHPVMKAFCGLLLQAP	388	59
401 SHPLMRAFCLLLLQPT	416	62
375 CHPLLKAFCFLLLQPG	390	599
410 SHPAMRAFCFLLLQLP	425	631
397 SHPGVIAFCALLLHVP	412	62
397 SHPGVIAFCALLLHAP	412	62
387 SHPAMTAFCALLLEVQ	402	61
396 SHPAVTAFCALLLGAR	411	621
394 SHPATTAFCTLLLRTR	409	61
395 SHPAVTAFCTLLLRGR	410	62
434 SHPAMTAFCTLLLQAR	449	66
433 SHPAMTAFCFLLLQAR	448	663
388 S <mark>HP</mark> AITA <mark>FC</mark> FLLLQAR	403	61
396 SHPAMTAFCFLLLQAR	411	62
396 SHPAMTAFCFLLLQAR	411	62
436 SHPAMTAFCSLLLQAQ	451	66
396 SHPAMTAFCSLLLQAR	411	62
397 SHPAATAFCALLLRTQ	412	62
387 SHPAMITFCALLLRTQ	402	61
396 SHPAMTTFCALLLRTQ	411	624

222	VAD-	-INAI	/KAK	АПУ	vQ.	ىلى	I.	LLV.		PD	L V	GD	KU	021
626	KGAR	PGAS	SRGR	AR <mark>V</mark>	IG.	LA	Y	LL	H <mark>N</mark>	РТ	'LÇ	VF	RK	656
605	KLS-	-NSF	RRAR	ARV	IL:	LL	F	LV	NN	PS	LV	AS	RK	633
592	KVS-	-IAF	KRAR	RHV	IQ:	LL	Y	LV	NN	PS	LV	GT	RK	620
598	KVS-	-SAF	KRAR	MH <mark>V</mark>	Q.	LL	Y	LV	NN	PS	LV	GT	RK	626
598	KVS-	-SAF	KRAR	MH <mark>V</mark>	IQ:	LL	Y	LV	NN	PS	LV	GT	RK	626
597	KPV-	SNG	KRAR	GHV	H.	LL	Y	LV	NN	PS	LV	GS	RK	626
625	GGG-	-RLF	KRSR	ARV	W.	LA	Y	LL	N <mark>N</mark>	PS	LM	IGC	RK	653
599	GRA-	-RIF	RRIR	AR <mark>V</mark>	W	VA	Y	LL	HN	PS	LI	AS	RK	627
638	NAT-	-RSF	RQSR	IRV	IG:	LA	Y	LI	R <mark>N</mark>	PS	LI	тF	RK	666
627	KGAG	PKGS	SRSR	AR <mark>V</mark>	IG:	LA	Y	LL	HN	PS	LÇ	AF	RK	657
627	KGAG	HKGS	SQSR	AR <mark>V</mark>	IG.	LA	Y	LL	HN	PS	LÇ	AF	RK	657
619	KAAG	LRAC	GRSW	ARV	I G'	VA	Y	LL	HN	PP	ΓK	AA	RK	649
628	KAAG	LHAC	GRSW	AR <mark>V</mark>	I G'	VA	Y	LL	HN	PA	ΓK	AA	RK	658
619	RGVG	SRAF	RQGR	ARV	IG:	LA	Y	LL	HN	PA	ТČ	AF	RK	649
626	KGAG	PRAS	SHGR	AR <mark>V</mark>	IG:	LA	Y	LL	HN	PA	ТČ	AF	RK	656
664	KGAG	PRVS	SRGR	ARV	IG:	LA	Y	LL	HN	PA	ТČ	AF	RK	694
663	KGAR	PRAS	SRCR	ARV	IG:	LA	Y	LL	HN	PΤ	'LÇ	VF	RK	693
618	KGAR	PRAS	SRCR	ARV	IG:	LA	Y	LL	HN	PΊ	LČ	VF	RK	648
626	KGAR	PRAS	SRCR	ARV	IG:	LA	Y	LL	HN	PΤ	ĽÇ	VF	RK	656
626	KGAR	PRAS	SRCR	AR <mark>V</mark>	IG:	LA	Y	LL	HN	PΤ	'LÇ	VF	RK	656
666	KGAR	PRAS	SRSR	ARV	IG:	LA	Y	LL	HN	PΤ	'LÇ	VF	RK	696
626	KGAR	PRAN	IRGR	ARV	IG:	LA	Y	LL	HN	PΤ	ĽÇ	VF	RK	656
625	KGAG	PRAF	RQGR	ARV	IG:	LA	Y	LL	HN	PA	ТČ	AF	RK	655
615	KGTG	PRAF	RQGR	ARV	IG:	LA	Y	LL	HN	PA	ТČ	AF	RK	645
624	KGAR	PRAF	IRGR	ARV	IG.	LA.	٧ſ	Т.Т.	ΗN	PΑ	T.C	AF	RK	654

NT 7 171

Fig. S10. Molecular details of the STRA6-CaM interaction. Separate views of the three CaM-binding peptides of STRA6 represented as C α traces with side chains shown in stick, overlaid over a hydrophobic surface colored according to the Kyte-Doolittle hydropathy scale (71) from white (-4.5, most polar) to black (4.5, most hydrophobic). For CaMBP0, CaMBP1 is also represented as part of the hydrophobic surface, as it forms part of the CaMBP0-binding cleft.



Fig. S11. Crystal Structure of CaM-CaMBP2. (A) Stereo representation of an overlay of the CaM-CaMBP2 crystal structure (in purple and magenta, respectively) and the corresponding region of the STRA6-CaM cryo-EM structure (in dark red, and gold, respectively). **(B)** Representative region of the 2Fo-Fc electron density map of the CaM-CaMBP2 crystal structure contoured at 1 x R.M.S.



Fig. S12. ITC thermograms of STRA6 peptides – CaM interactions. Representative ITC thermograms for the reversed titrations used to observe CaM interactions with STRA6 peptides: CaM interaction with (A) CaMBP0, (B) CaMBP1, (C) CaMBP2, and (D) CaMBP1.2 under calcium-loaded conditions. All experiments were performed in 20 mM HEPES, pH 7.4, 50 mM NaCl, 10 mM CaCl₂, 5 mM MgCl₂, and 0.5 mM TCEP at 37°C. CaMBP1 titrations into CaM were not performed, because the peptide aggregated at concentrations greater 0.1 mM in aqueous solutions due to its hydrophobicity, preventing its use as a titrant.



Fig. S13. Conservation of STRA6 within the outer cleft and pockets. (A) Slab in the membrane plane of the STRA6 conservation surface using the Consurf server, viewed from the extracellular region. The STRA6 molecular surface is colored from cyan (least conserved) to maroon (most conserved). (B) Ribbon representation of the NTD, IMa and IMb colored by conservation as in (A), with conserved residues represented in stick, and the bounding surfaces of each pocket shown in purple and pink transparent surfaces for the outer and inner pockets, respectively. (C) Molecular details of conserved interactions within the outer pocket. (D) Molecular details of interactions within the outer pocket.

		(TM1) TM1b		TM2
D.rerio(A4IGB6)/1-670 H.sapiens(92BX79)/1-667 L.oculatus(WSNC1)/1-664 O.niloticus(IXEX07)/1-658 X.maculatus(MANN84)/1-665 A.mexicanus(MSJE12)/1-666 A.domestica(FCPP12)/1-666 A.domestica(FCPP12)/1-620 R.norvegicus(Q4ORB4)/1-621 B.taurus(FLMV07)/1-618 O.arise(KSPNV9)/1-618 M.putorius.furo(M3Y493)/1-622 C.familiaris(E2RC24)/1-618		PVEVIPPCOPTADEGLPHICIAAISUVVML PEGEVPSCHTSIPEGLYHACLASLSILVUL PEGEVPSCHTSIPEGLYHACLASLSILVUL PEGEVPSCHTADEGLYHICITVISUVVML EFEVIPPCOPTADEKLYHICITVISUVVML EFEVIPPCOPTADEKLYHICITVISUVVML ETETIPPCOPTADEKLYHICITVISUVVML ETETIPPCOPTADEKLYHICITAISUVIN ETETIPPCOPTADEKLYHICITAISUV ETETIPPCOPTADEKLYHICITAISUP TCVISUVELELLYSLIPSPFILM TCVISUVELELLYSLIPSFFILM TCVSSVDELELFLYSLIPSFFILM TCVSSVDELELFLYSLIPSFFILM TCVSSVDELELFLYSLIPSFFILM TCVSSVDELELFLYSLIPSFFILM	LAILARR QKLSDNQRGLTGLSPV LLAILVRR RQLWPDCVRGRPGLPSV ULSPTRRRKLADCCFKEIFGLSV ULSPTRRRKUGDRQKGLFGLSV LLAILARRTRVGRRQKGLFGLSV ULAILARRTRVGRRQKGLFGLSV ULSPCRR-HRKQDDKYLLGSRFGIVMEL USFLORRWHKQLDDKSYLLGSRFGIVMEL USFLORRBFRSDT-YLLNNRFGHIVEL USFLORRBFRSDT-YLLNNRFGHIVEL USFLORRBFRSDT-YLLNNRFGHIVEL USFLORRBFRSDT-YLLNNRFGHIVEL USFLORRBFRSDT-YLLNNRFGHIVEL USFLORRBFRSDT-YLLNNRFGHIVEL USFLORRBFRSDT-YLLNNRFGHIVEL	FLDHTOHKGLAVAVGVLPCKLVGWULS 10 FLAGDRFRAVPAVFWULSSLCLLED 120 FLDHTRHKGLAVAVGVLPCKLVGUVLSSLCLLED FLDHTRHKGLAVAVFGVLPCKLWGLLIS 105 FLDHTCHKGLAVAVFGVLLCKLWGLLIS 105 FLDHTCHKGLVAVFGVLLCKLWGLLIS 105 FLDHTCHKGLVAVFGVLPCKLWGLLSS 105 FLDHTCHKGLVAVFGVLPCKLWGLLSS 105 FLDHTCHKGLVAVFGVLPCKLWGLLSS 105 FLDHTCHKGLVAVFGVLPCKLWGLLSS 105 FLDHTCHKGLVAVFGVLPCKLWGLSS FLGTFNNHSVGIACATANKV-HELFS 95 FVGTFSNHSVGVAPGATANKV-HELFS 95 FVGTFSNHSVGGLAFGATANKV-HELFS 95 FVGTFS
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Fig. S14. Sequence alignment between STRA6 and RBPR2. Sequence alignment (generated using MUSCLE (64)) comprising seven STRA6 sequences and seven putative RBPR2 sequences, where the intensity of the color is proportional to the degree of conservation, colored and visualized using Jalview (65). Residues are colored by their physicochemical properties using a modified version of the Zappo scheme: aliphatic residues (I, L, V, A & M) are in salmon, aromatics (F, W & Y) in orange, positively charged (K, R & H) in blue,

negatively charged (D, E) in red, polars (S, T, N, Q) in green, G in magenta, P in cyan, C in yellow. Secondary structure elements are labeled and displayed above the alignment, in yellow. Solid and dotted indicate regions of the protein, which are visible and disordered in the structure, respectively.

Movie S1. Density quality of STRA6. The STRA6-CaM complex is depicted in ribbon representation with one STRA6 protomer in spectral coloring (violet N-terminus to red C-terminus). The associated protomer of CaM is colored cyan. The density map is represented as blue mesh and contoured at 7 X R.M.S.

Movie S2. STRA6-CaM interactions. CaM is represented as a molecular surface colored by hydrophobicity according to the Kyte-Doolittle scale (71) from -4.5 (most polar) in light blue to 4.5 (most hydrophobic) in orange. The N-lobe of CaM is initially at the top of the screen. CaMBP0, 1 and 2 are depicted in ribbon representation with side chains shown in stick. The CaMBPs are colored by conservation from cyan (least conserved) to maroon (most conserved), based on the alignment presented in **Fig. 2** and **Fig. S7**.