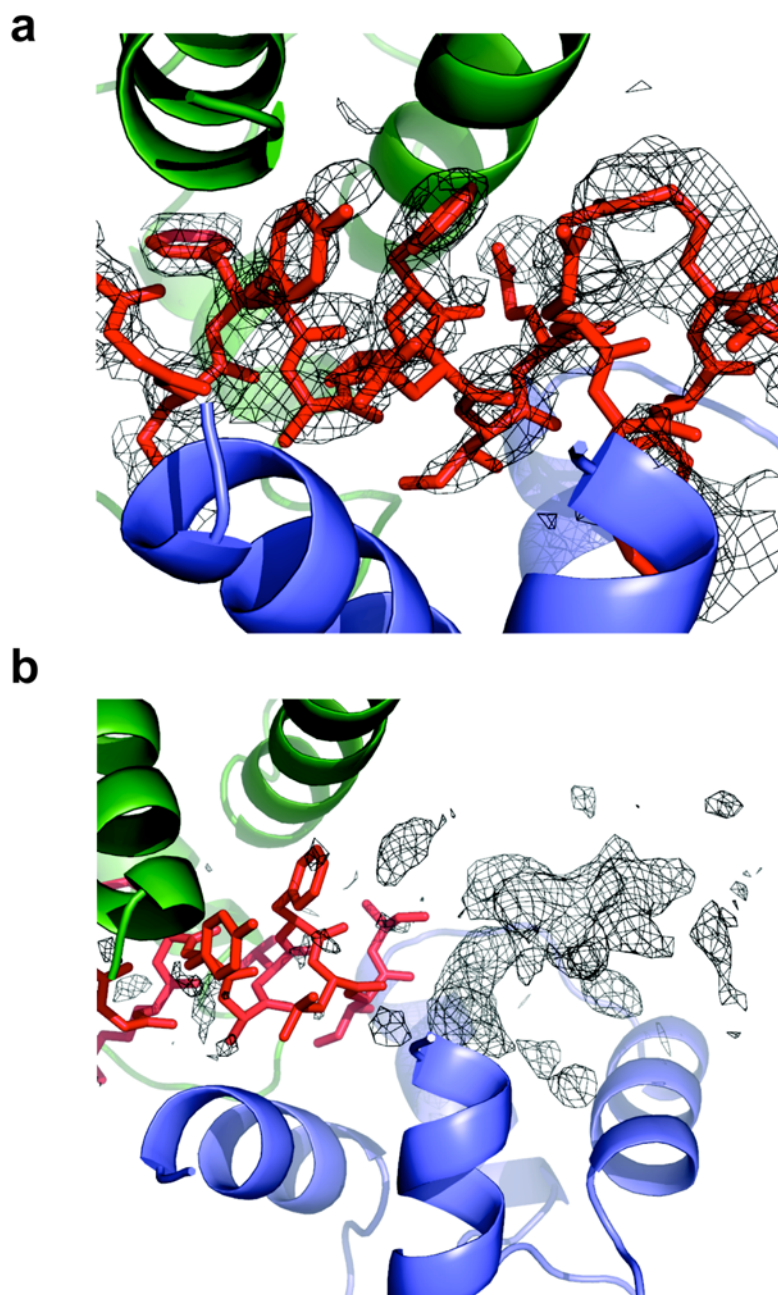
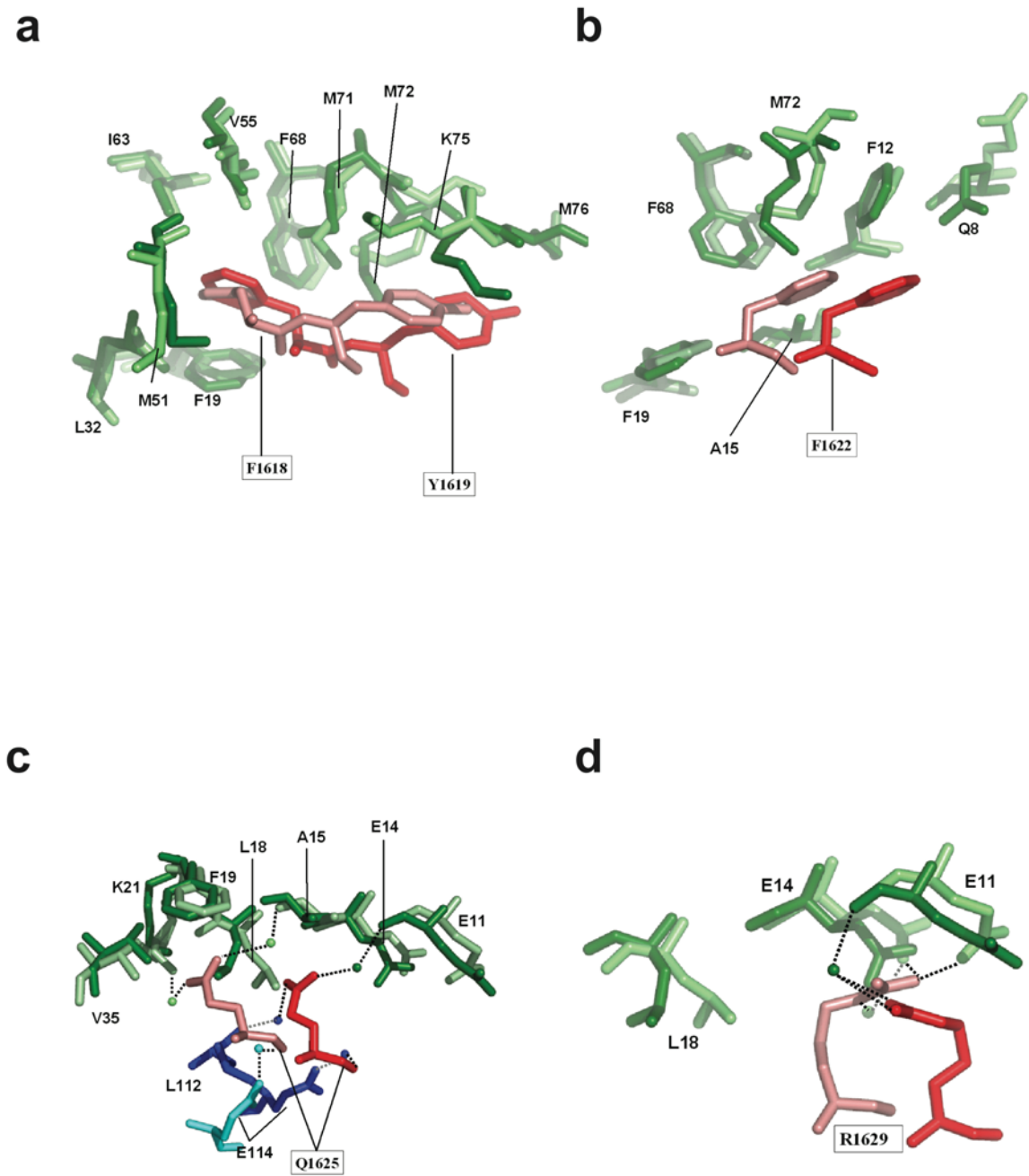
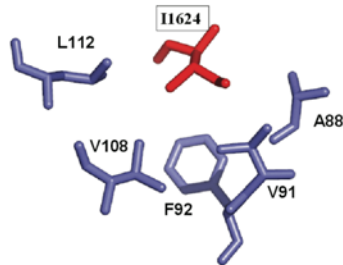




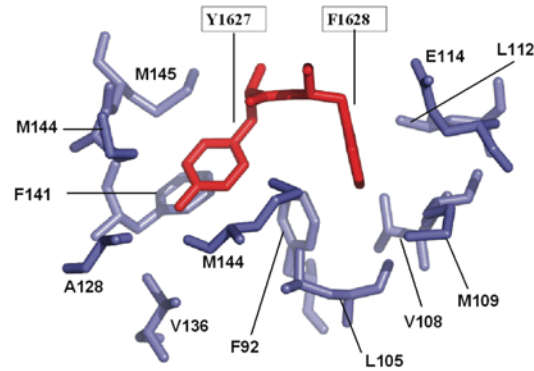
Supplementary Fig. 1 **a**, Experimentally phased and density modified electron density map, contoured at 1.2 σ , shown for the IQ domain in complex A. **b**, Residual difference electron density map contoured at 2 σ for the IQ domain in complex B. N-lobe and C-lobe are displayed in green and blue, respectively. IQ domain residues are shown as red sticks.



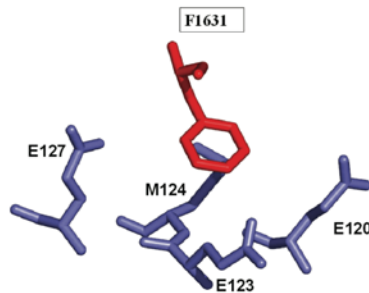
e



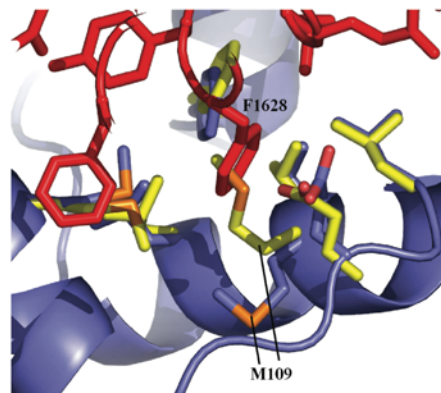
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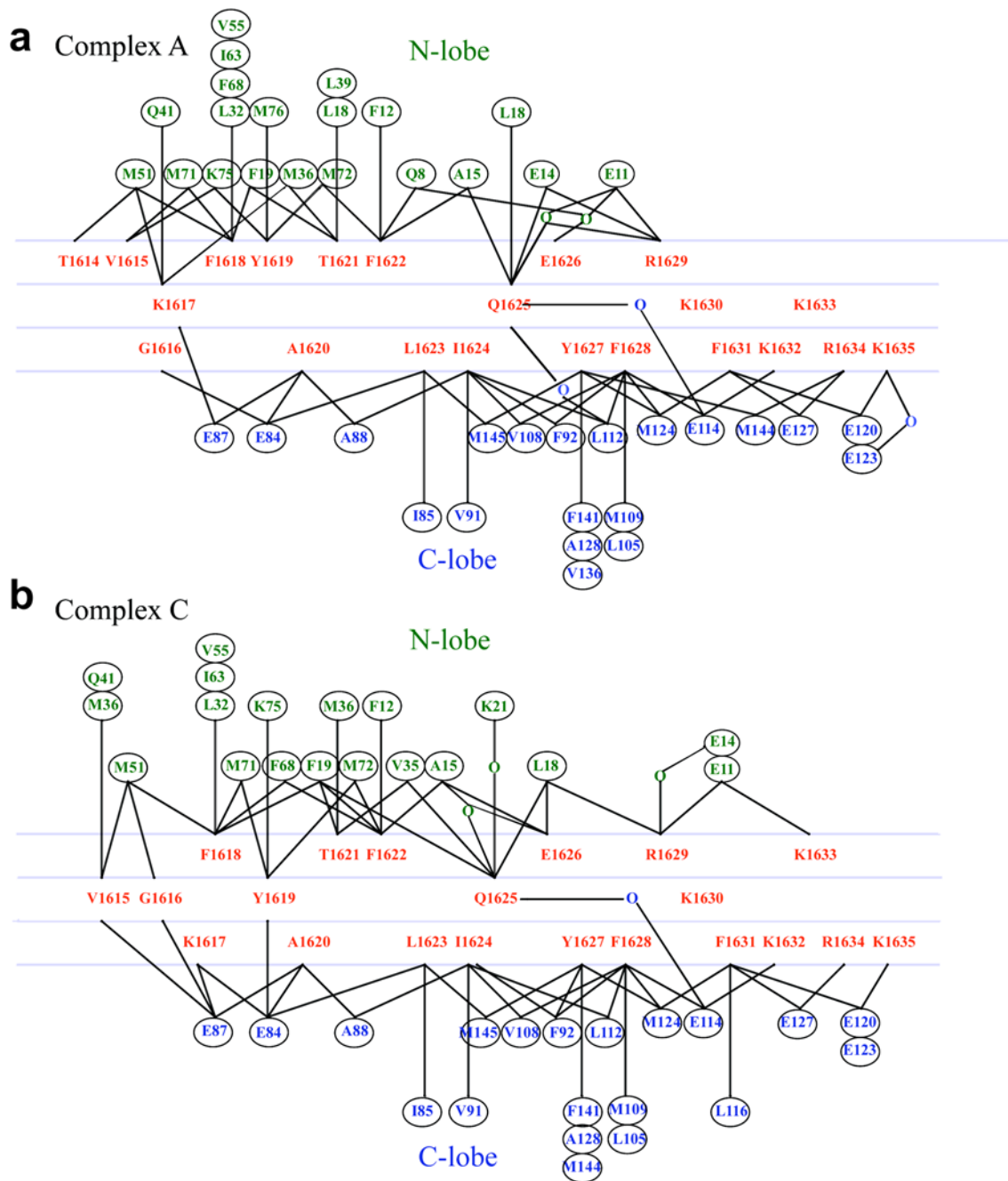
g



h



Supplementary Fig. 2 a-g, Details of interactions of Ca_v1.2 IQ domain residues with Ca²⁺/CaM. IQ domain residues are displayed in red, Ca²⁺/N-lobe residues in green, and Ca²⁺/C-lobe residues in blue. Dark colours correspond to complex A and light colours correspond to complex C. For the Ca²⁺/N-lobe interaction figures, the Ca²⁺/N-lobes of complex A and complex C have been superposed, outlining the differences in positions of IQ domain residues. For the Ca²⁺/C-lobe interactions, only chain A is shown, as the interactions in complex A and C are very similar. **h**, Superposition of complex A Ca²⁺/C-lobe (blue) with the Ca²⁺/C-lobe of CaM complexed to a CaMKII peptide (PDB entry 1CDM) (yellow), showing the different conformation of Met109 to produce a pocket for the deep anchor F1628. The CamKII peptide is not shown for clarity.



Supplementary Fig. 3 Overview of mainchain and sidechain interactions **a**, complex A and **b**, complex C. CaM residues ≤ 4 Å to the IQ domain are shown. IQ domain residues (red) are in three rows: contacts to Ca^{2+} /N-lobe only (upper), none or both (middle) or Ca^{2+} /C-lobe only (lower). Because contacts that are just below 4 Å in one complex but just above 4 Å in the other would appear only in one figure and hinder appreciation of the main differences, contacts ≤ 4.2 Å are included, provided they are ≤ 4.0 Å in the other complex. Water-mediated hydrogen bonds are indicated (o). Residues N-terminal or C-terminal to the interaction site with are not shown.

IQxxxRxxxxR
* * *

Ca_v1.2 GDDEVTVGKFYATFLIQEYFRKFKKRKEQGLVGKPSQRN
 Ca_v1.1 GDDEVTVGKFYATFLIQEHFRKFMKRQEYYGYRPPKDI
 Ca_v1.3 GDDEVTVGKFYATFLIQDYFRKFKKRKEQGLVGKYPKN
 Ca_v1.4 DEEEVTVGKFYATFLIQDYFRKFRRRKEKGLLGDAAPST
 Ca_v2.1 KSTDLTVGKIYAAMMIMEYYRQSKAKKLQAMREEQDRTP
 Ca_v2.2 KPDEMTVGKVYAALMIFDFYKQNKTTTRDQMQQAPGGLSQ
 Ca_v2.3 KASDLRVGKIYAAMMIMDYKQSKVKKQRQQLEEQKNAP

* * *

Na_v1.1 TTTLKRKQEEVSAVIIQRAYRRHLLKRTVKQASFTYNKN
 Na_v1.2 TTTLKRKQEEVSAIIIQRAYRRYLLKQKVKVSSIIYKKD
 Na_v1.3 TTTLKRKQEEVSAIIQARNYRCYLLKQRLKNISSKYDKE
 Na_v1.4 TTTLKRKHVEVCAIKIQRAYRRHLLQSRMKQASYMYRHS
 Na_v1.5 TTTLRRKHVEVSAMVIQRAFRRHLLQSLKHASFLFRQQ
 Na_v1.6 TTTLRRKQEEVSAVVLQRAYRGHLARRGFICKKTTSNKL
 Na_v1.7 TTTLKRKQEDVSATVIQRAYRRYRLRQNVKNISSIYIKD
 Na_v1.8 LSGPLRIPKPNQNILIQMDLPLVPGDKIHCLDILFAFTK
 Na_v1.9 VTTTKRKEEERGAAIIQKAFRKYMMKVTKGDQGDQNDLE

Supplementary Fig. 4 Sequence alignment of the IQ domains of Ca_v1, Ca_v2, and Na_v1 channels. Ca_v residues are coloured according to their corresponding contacts in complex A: green, Ca²⁺/N-lobe; cyan, Ca²⁺/C-lobe; purple, Ca²⁺/N-lobe and Ca²⁺/C-lobe. Na_v residues are coloured according to their degree of conservation: grey, identical; orange, conserved. Asterisks indicate principal aromatic anchor positions of the Ca_v1.2 IQ domain. The consensus IQ motif is indicated.