SUPPLEMENTAL MATERIAL

Yan et al., https://doi.org/10.1085/jgp.201611721

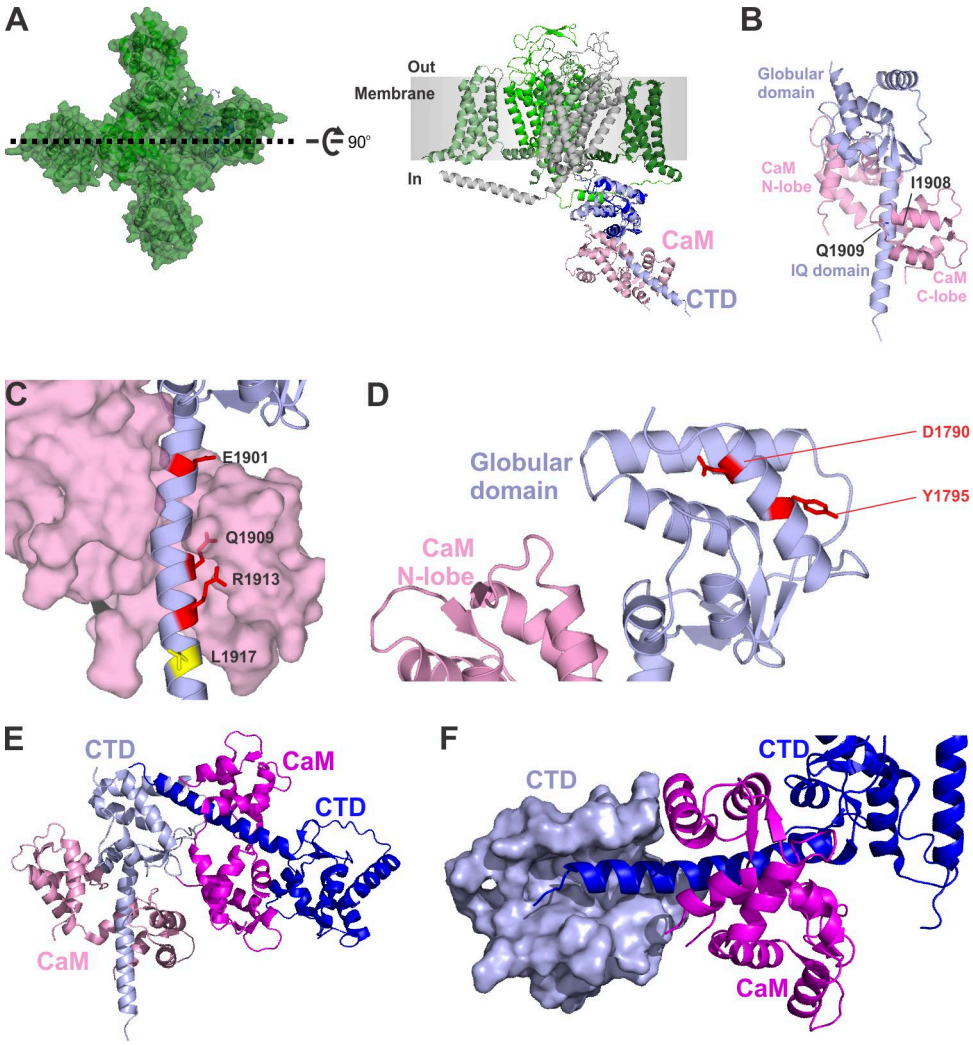


Figure S1. **CaM interaction with the $Na_V$ CTD.** (A) CaM (pink) binds to the cytoplasmic CTD of $Na_V$ channels (blue). Left panel shows the $Ca_V1.1$ α1 subunit structure viewed from the top (PDB accession no. 5GJV; Wu et al., 2016). The right panel is rotated 90° and provides a possible orientation of the intracellular CTD ($Na_V1.5$) in complex with CaM (PDB accession no. 4OVN; Gabelli et al., 2014). (B) The isolated heterodimer of CaM associated with the $Na_V1.5$ CTD. The globular domain and the IQ domain are indicated, along with the location of its signature Ile and Gln residues (Ile1908 and Gln1909). (C) Focus on LQT3 residues that interact with the CaM C-lobe, which wraps around the IQ domain to bury Gln1909 and Arg1913. Glu1901 interacts with the top of the CaM C-lobe. (D) Focus on LQT3 residues in the globular domain. (E and F) Proposed interaction between two $Na_V1.5$ CTD–CaM heterodimers based on arrangement of heterodimers observed in the crystal unit cell (PDB accession no. 4OVN).

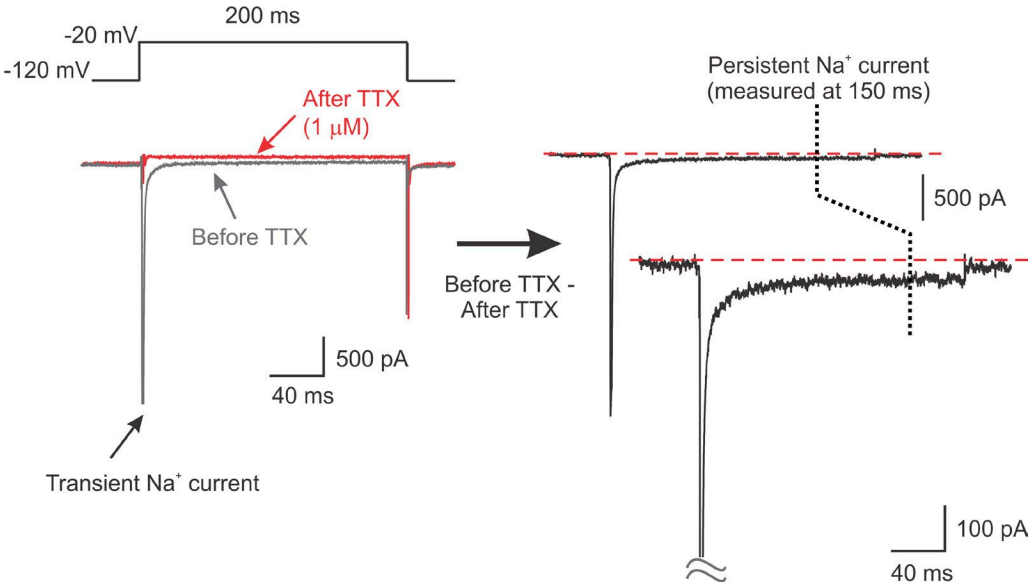


Figure S2. **Measurement of persistent $Na^+$ current from $Na_V1.5^{TTX-S}$.** (left) Exemplar traces of $Na_V1.5^{TTX-S}$ expressed in HEK293T cells before and after application of 1 μM TTX. (right) Subtraction of the TTX-sensitive background current leaves the TTX-resistant $Na^+$ channel current. (inset) At a magnified scale.

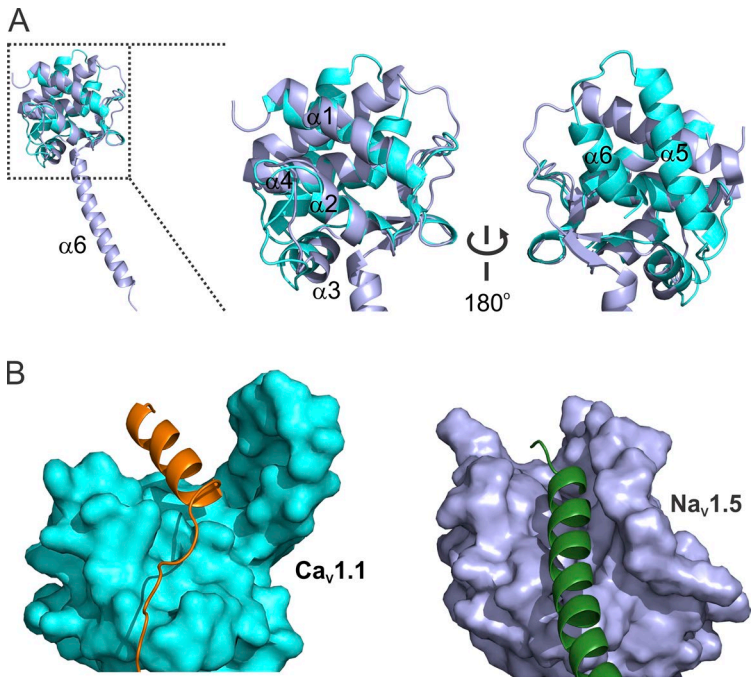


Figure S3. **Structural parallels between the $Na_V1.5$ and $Ca_V1.1$ CTDs.** (A) Overlay of the $Ca_V1.1$ (cyan) and $Na_V1.5$ (purple) CTDs. Note the structural homology from α helix α1 to α helix α4, but not for α helix α5 and α helix α6. (B) Structural homology showing the interaction of the III-IV linker (orange) with the globular domain of the $Ca_V1.1$ CTD; and a $Na_V1.5$ CTD IQ domain (α6) with the globular domain of a second $Na_V1.5$ CTD (see also Fig. 3, A and B).

## REFERENCES

Gabelli, S.B., A. Boto, V.H. Kuhns, M.A. Bianchet, F. Farinelli, S. Aripirala, J. Yoder, J. Jakoncic, G.F. Tomaselli, and L.M. Amzel. 2014. Regulation of the NaV1.5 cytoplasmic domain by calmodulin. *Nat. Commun.* 5:5126. http://dx.doi.org/10.1038/ncomms6126

Wu, J., Z. Yan, Z. Li, X. Qian, S. Lu, M. Dong, Q. Zhou, and N. Yan. 2016. Structure of the voltage-gated calcium channel Cav1.1 at 3.6Å resolution. *Nature.* 537:191–196. http://dx.doi.org/10.1038/nature19321