

Supporting Information

Mapping Co-regulation Pathways among Ligand Binding sites in RyR1

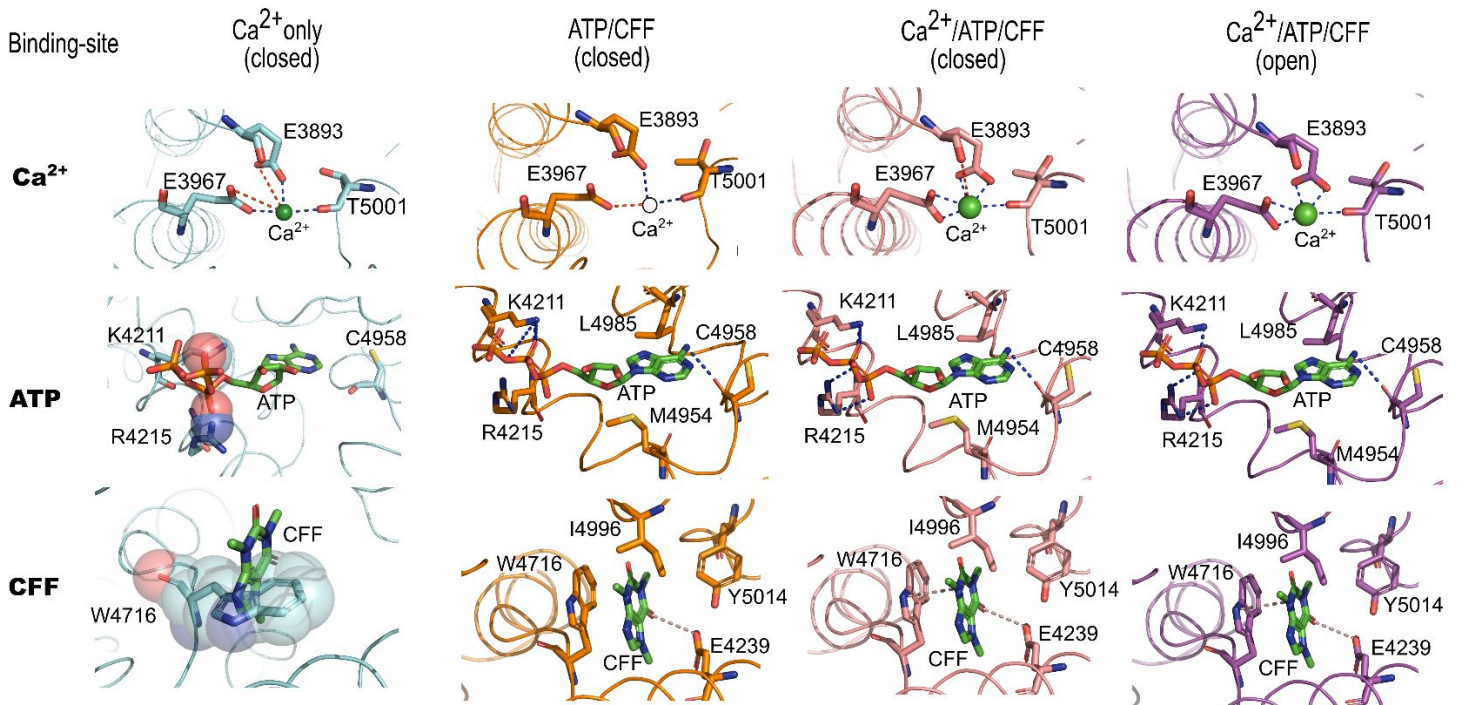


Fig S1. Interactions of Ca^{2+} , ATP, and CFF in different functional states of RyR1s. Residues displaying electrostatic, van der Waals, and stacking interactions with Ca^{2+} , ATP, and CFF in Ca^{2+} bound - closed RyR1 (PDB ID:5T15), ATP/CFF bound - closed RyR1 (PDB ID:5TAP), Ca^{2+} /ATP/CFF bound - closed RyR1 (PDB ID:5TAQ) and Ca^{2+} /ATP/CFF bound – open RyR1 (PDB ID:5TAL) are depicted in licorice representation. Backbone of RyR1 is shown as ribbon. Ca^{2+} is shown as a green or white sphere. ATP and CFF are shown in licorice representation. To depict closed conformations of ATP and CFF binding pockets in Ca^{2+} bound - closed RyR1, we docked ATP and CFF in respective pockets and represented residues exhibiting steric clashes in van der Waals representation. Strong electrostatic interactions ($<3.2 \text{ \AA}$) are shown as blue dashed lines and weak electrostatic interactions ($<4 \text{ \AA}$) as red dashed lines. repulsive interactions ($<3.5 \text{ \AA}$) are depicted as dashed lines in salmon color.

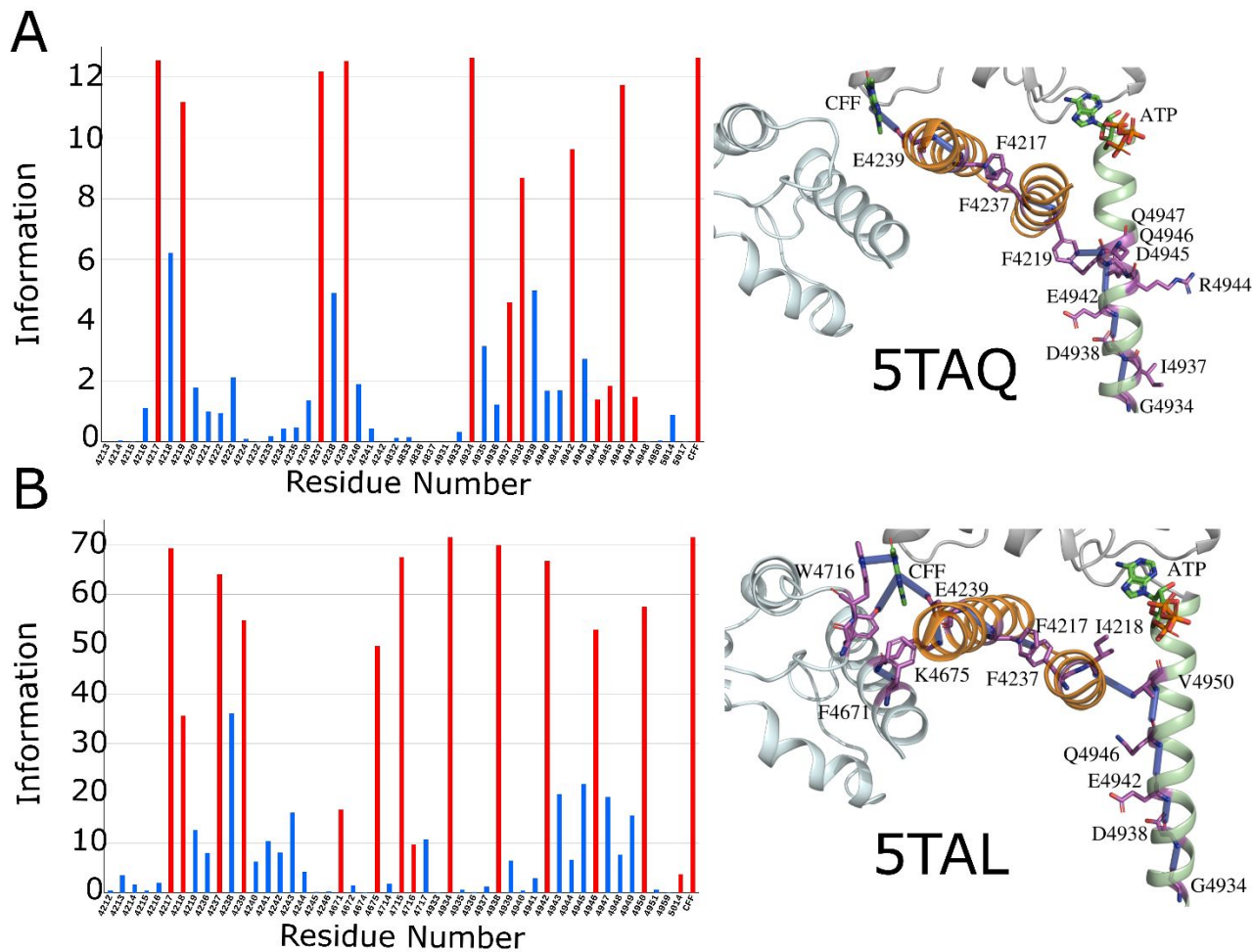


Fig S2. Allosteric communication between CFF binding site and pore region in A) Ca^{2+} /ATP/CFF bound - closed and B) Ca^{2+} /ATP/CFF bound - open RyR1 structures. Bars corresponding to residues participating in most optimal allosteric pathway between CFF binding site and pore region are highlighted in red. Bars for residues participating in other possible but least significant pathways are colored in blue. The height of bars in each chart represents the extent of allosteric information transmitted through the corresponding residue. Most prominent allosteric communications between CFF binding site and pore region are rendered as blue cylinders. Color code for RyR1 domains participating in allosteric communication among the ligand sites is as follows: TaF domain (4175–4253) in orange, Helical-bundle domain between S2 and S3 (4666–4786) in cyan, channel pore domain (4820–4956) in green, and CTD (4957–5037) in gray. ATP and CFF are shown in green licorice representation.

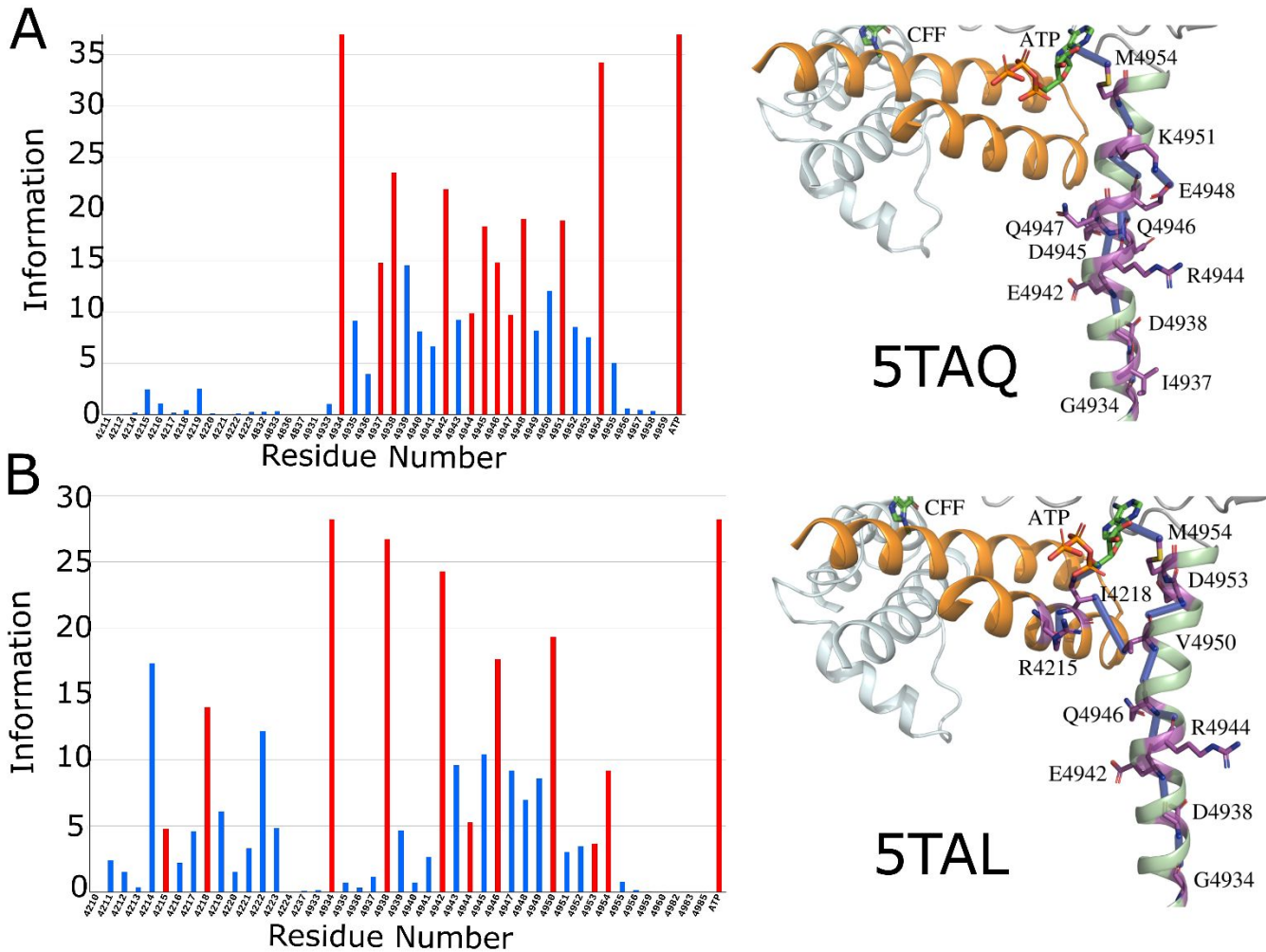


Fig S3. Allosteric communication between ATP binding site and pore region in A) Ca^{2+} /ATP/CFF bound - closed and B) Ca^{2+} /ATP/CFF bound - open RyR1 structures. Bars corresponding to residues participating in most optimal allosteric pathway between ATP binding site and pore region are highlighted in red. Bars for residues participating in other possible but least significant pathways are colored in blue. The height of bars in each chart represents the extent of allosteric information transmitted through the corresponding residue. Most prominent allosteric communications between ATP binding site and pore region are rendered as blue cylinders. Color code for RyR1 domains participating in allosteric communication among the ligand sites is as follows: TaF domain (4175–4253) in orange, Helical-bundle domain between S2 and S3 (4666–4786) in cyan, channel pore domain (4820–4956) in green, and CTD (4957–5037) in gray. ATP and CFF are shown in green licorice representation. ATP is shown in green licorice representation.

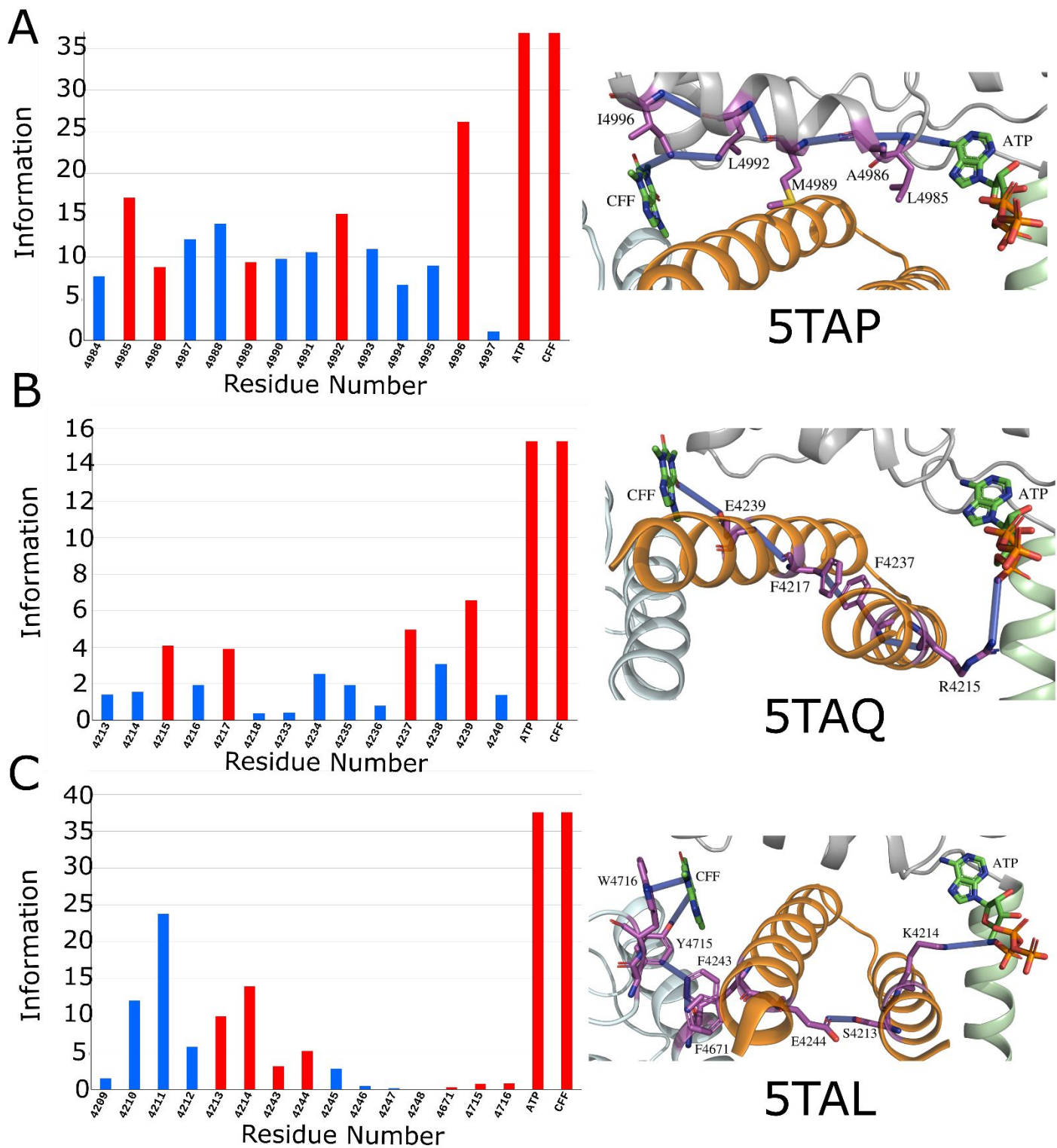


Fig S4. Allosteric communication between CFF and ATP binding sites in A) ATP/CFF bound - closed, B) Ca^{2+} /ATP/CFF bound - closed, and C) Ca^{2+} /ATP/CFF bound - open RyR1 structures. Bars corresponding to residues participating in most optimal allosteric pathway between CFF and ATP binding sites are highlighted in red. Bars for residues participating in other possible but least significant pathways are colored in blue. The height of bars in each chart represents the extent of allosteric information transmitted through the corresponding residue. Most prominent allosteric communications between ATP and CFF binding sites are rendered as blue cylinders. Color code for RyR1 domains participating in allosteric communication among the ligand sites is as follows: TaF domain (4175–4253) in orange, Helical-bundle domain between S2 and S3 (4666–4786) in cyan, channel pore domain (4820–4956) in green, and CTD (4957–5037) in gray. ATP and CFF are shown in green licorice representation.

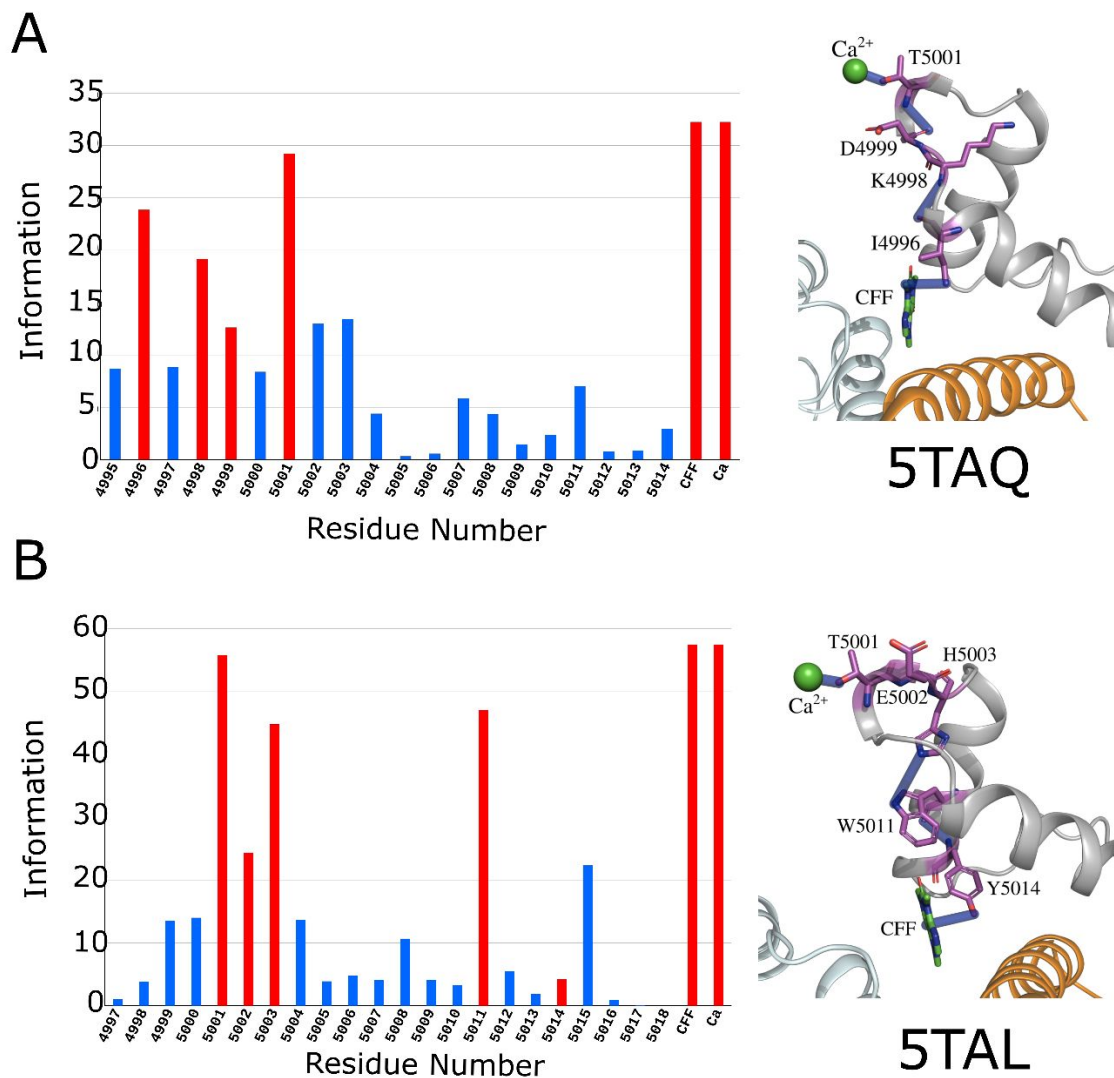


Fig S5. Allosteric communication between CFF and Ca^{2+} binding sites in A) Ca^{2+} /ATP/CFF bound - closed and B) Ca^{2+} /ATP/CFF bound - open RyR1 structures. Bars corresponding to residues participating in most optimal allosteric pathway between CFF and Ca^{2+} binding sites are highlighted in red. Bars for residues participating in other possible but least significant pathways are colored in blue. The height of bars in each chart represents the extent of allosteric information transmitted through the corresponding residue. Most prominent allosteric communications between CFF and Ca^{2+} binding sites are rendered as blue cylinders. Color code for RyR1 domains participating in allosteric communication among the ligand sites is as follows: TaF domain (4175–4253) in orange, Helical-bundle domain between S2 and S3 (4666–4786) in cyan, and CTD (4957–5037) in gray. CFF is shown in green licorice representation and Ca^{2+} is shown in green van der Waals representation.

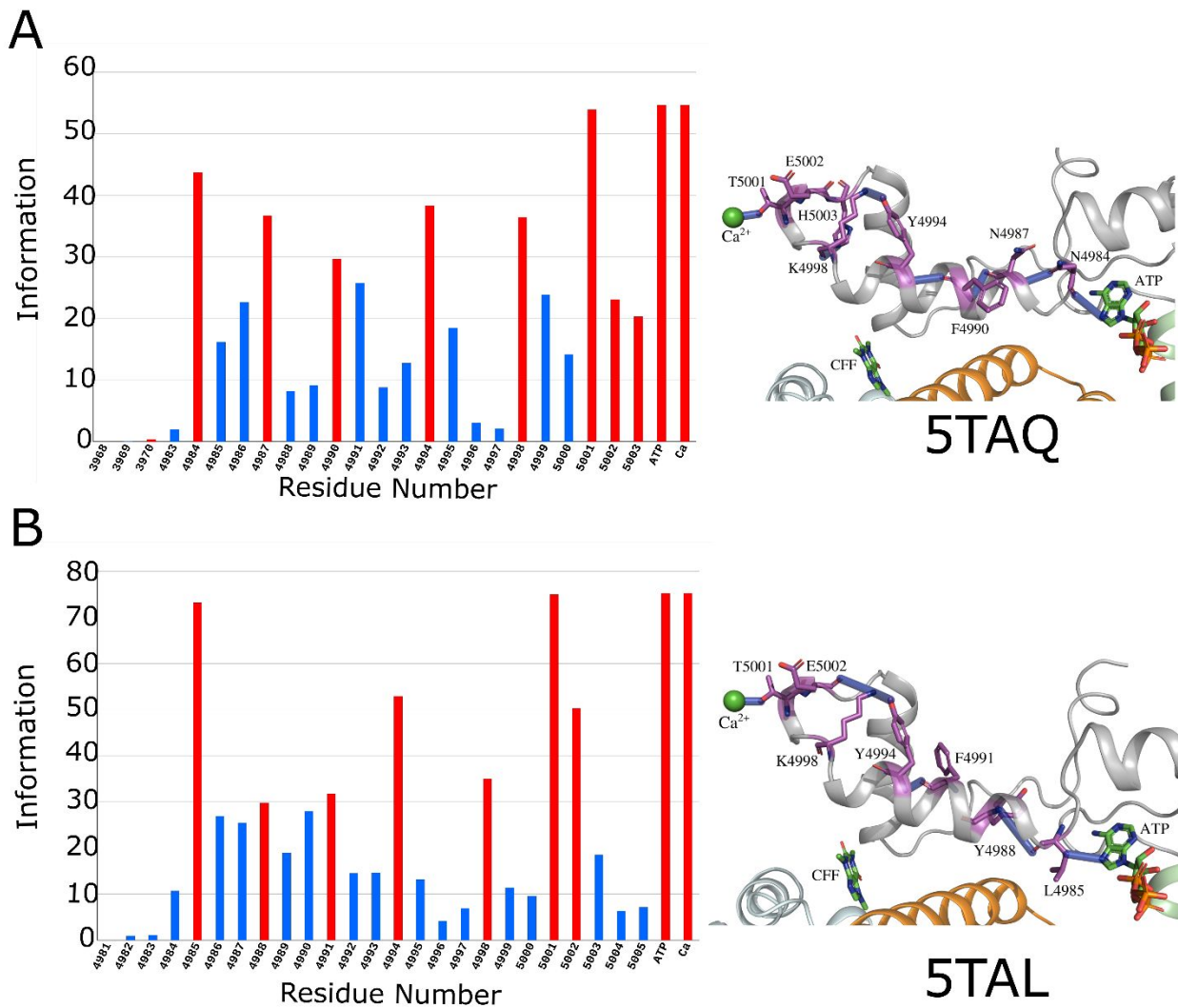


Fig S6. Allosteric communication between ATP and Ca^{2+} binding sites in A) Ca^{2+} /ATP/CFF bound - closed and B) Ca^{2+} /ATP/CFF bound - open RyR1 structures. Bars corresponding to residues participating in most optimal allosteric pathway between ATP and Ca^{2+} binding sites are highlighted in red. Bars for residues participating in other possible but least significant pathways are colored in blue. The height of bars in each chart represents the extent of allosteric information transmitted through the corresponding residue. Most prominent allosteric communications between ATP and Ca^{2+} binding sites are rendered as blue cylinders. Color code for RyR1 domains participating in allosteric communication among the ligand sites is as follows: TaF domain (4175–4253) in orange, Helical-bundle domain between S2 and S3 (4666–4786) in cyan, channel pore domain (4820–4956) in green, and CTD (4957–5037) in gray. ATP is shown in green licorice representation and Ca^{2+} is shown in green van der Waals representation.