Calcium binding to the EF hand motif regulates polycystin 2 function

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Polycystin 2 (PC2) is one of the two proteins that when mutated result in polycystic kidney disease. PC2 is a calcium (Ca^{2+}) release channel that opens and closes in response to increasing intracellular Ca^{2+}. We have previously identified an EF hand motif on PC2 that controls the Ca^{2+} sensitivity of the protein. The EF hand motif is a well-conserved region for Ca^{2+} binding and is a typically found as a pair (EF hand domain). Mammalian PC2 differs from most EF domain containing proteins in that the first EF hand motif is non-canonical (site 1), and cannot bind Ca^{2+}, whereas the second EF hand motif (site 2) binds Ca^{2+}. However, the EF domain of PC2 proteins in evolutionary earlier organisms can bind two Ca^{2+} molecules, albeit with different affinity.

In this study, we sought to determine if the two EF motifs in mammalian PC2 are interchangeable, or if Ca^{2+} binding to site 2 only is essential and necessary for PC2 function. We created a series of mutants in the mammalian EF hand domain with one or two functional Ca^{2+} binding sites. Expression of these mutants in mammalian kidney cells revealed that binding of Ca^{2+} to site 2 was essential for function. However, the Ca^{2+} signal could be enhanced by the introduction of an additional Ca^{2+} binding site at site 1. We conclude that the position and affinity of the Ca^{2+} binding site in PC2 is critical for maintaining function.