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Structural and Thermodynamic Characterization of the Gating Pathway in a K^D Channel

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Structures of inwardly-rectifying (Kir) potassium channels are now available in many different crystallographic states. We now analyse these structures in the context of functional data for mutations at over 180 positions within the Kir1.1 (ROMK) channel. This reveals an extensive network of physically interacting residues which stabilise the pre-open and open-states of the channel, but which breaks down upon channel closure. This approach not only validates a struc- tural gating pathway for the Kir channel, but also provides insight into the structure of the transition state connecting these crystallographic states. This gating network also appears to be an important structural determinant of the thermodynamic stability of these different gating states as well as influencing the impact of mutations on channel function, and suggest that such state-dependent physical connectivity between residues may also be relevant to our understanding of other allosteric proteins.