Mapping the sequence of conformational changes underlying selectivity filter gating in a potassium channel

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The potassium channel selectivity filter both discriminates between K^+ and sodium ions and contributes to gating of ion flow. Static structures of conducting (open) and non-conducting (inactivated) conformations of this filter are known, however the sequence of protein rearrangements that underlie interconversion between these two states is not. Using ϕ-value analysis we have studied the macromolecular rearrangements associated with selectivity filter gating in the human ether-a-go-go-related gene (hERG) K^+ channel, a key regulator of the rhythm of the heartbeat. We have found that closure of the selectivity filter gate is initiated by K^+ exit and then followed in sequence by conformational rearrangements of the pore domain outer helix, extracellular turret region, voltage sensor domain, intracellular domains and pore domain inner helix. In contrast to the simple linear models proposed for opening and closing of ligand-gated ion channels, a much more complex spatial and temporal sequence of widespread domain motions connects the open and inactivated states of the hERG K^+ channel.