Which residues are important within the N-terminal helix of hERG PAS domain to maintain a functional channel?

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The hERG K^+ channel plays an important role in maintaining proper repolarisation in the heart. Dysfunctional hERG, caused either by drug block or genetic mutation, results in long QT syndrome characterised by a prolonged QT interval on the surface electrocardiogram and an increased risk of cardiac arrhythmias and sudden death.

The cystoplasmic N-terminal domain of hERG contains a 110 residues Per-Arnt-Sim (PAS) domain (S26 to K135). Deletion of the N-terminal 135 residues of hERG results in a significantly faster rate of deactivation. Further, the WT rate of deactivation can be restored by external application of a recombinant protein corresponding to the N-terminal 135 residues. Subsequent studies showed that the deletion of just the N-terminal tail (Δ2-26) had the same effect as deletion of M1 to K135 suggesting that it is the N-terminal tail rather than the PAS domain that is critical for the slow deactivation in hERG. In the previously solved crystal structure of the hERG PAS domain, the N-terminal tail (M1 to Q25) was disordered.

In this study, we have determined the structure of the PAS domain including the N-terminal tail using NMR spectroscopy. The NMR ensemble is very similar to the crystal structure except it exhibits an additional flexible N-terminal helix (T13 to E23). The functional role of this N-terminal helix is being explored through site-directed mutagenesis and two-electrode voltage clamp of *Xenopus* oocytes, which express the mutant hERG channels. Preliminary results show that this N-terminal helix is functionally important, in particular, T13A and D16A slow deactivation while F14A and R20A exhibit a faster deactivation compare to WT. Further investigation using a GGGS linkers displacement of the N-terminal helix shows a fast deactivation resembling the Δ2-26 hERG, indicating this N-terminal helix plays a role of positioning the first 9 residues in a correct orientation to regulate deactivation of the channels.