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Molecular Modeling of HC-HD Region in Kv7.1 Channel

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Kv7.1 is a voltage-gated potassium channel predominantly responsible for sustaining membrane potential by selectively allowing potassium permeates across the cell membrane and thus playing a significant role in regulating cell excitability and signaling[1]. Mutations in Kv7.1 reduce I_{Ks} and lead to Long QT syndrome 1 (LQTS1). Uniquely, Kv7.1 contains a long intracellular C-terminal domain that performs the physiological function of channel trafficking, tetramerization, degradation and phosphorylation. X-ray crystallography investigations showed that the CT region comprises four helical segments (helix A-D), and direct physical interaction between CT of Kv7.1 and that of KCNE1 constitutes an independent region that regulates the I_{Ks} channel deactivation[2]. According to UniProt, there are 28 mutations associated with LQT1 located in HC-HD region (residues 535-625) of Kv7.1 C-terminal. The structure of separate HC (535-568) and HD (585-625) regions is known but the linker structure between them remains obscure. Therefore, the main aim of this study is to model its structure. By performing molecular modeling in ColabFold (https://github.com/sokrypton/ColabFold), the structure of HC-HD region is obtained. Besides, protein with two single mutations (G589D and E596K) and wt protein were applied to 100 ns MD simulation with charmm27 force field using the Gromacs package. The simulation result shows that the HC-HD models are stable. However, cryo-EM data of Kv7.1 indicate that HD is weakly structured, which contradicts the stability of alone HD structure (PDB ID: 3bj4), so additional efforts are needed to clarify the structure of the HC-HD region.

References

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