A Twist in the Tail: Investigating the Impact of a Novel Epilepsy Mutation on Kv7.3 Protein Structure and Tetramerisation

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Epilepsy is one of the most prevalent neurological disorders, affecting approximately 65 million people globally. It is characterised by recurrent seizures, the severity of which is influenced by genetic, environmental, or often unknown factors. Critically, one in three individuals with epilepsy do not respond to existing treatments, highlighting the need to identify new therapeutic targets and develop more effective treatments.

The Kv7 family of voltage-gated potassium channels (Kv7.1 to Kv7.5), encoded by the KCNQ genes, plays a central role in epilepsy. The neuronal M-channel, primarily composed of Kv7.2 and Kv7.3 heterotetramers, regulates neuronal excitability by generating the M-current, a stabilising potassium current that helps prevent excessive neuronal firing.

Mutations in the KCNQ genes, particularly in the transmembrane and regulatory domains of Kv7.2 and Kv7.3, are strongly associated with epilepsy. A novel mutation has been identified in Kv7.3, located in the proposed assembly domain Helix D, replacing glutamine with leucine (Q653L) It lies in the distal half of the C-terminal tail, a flexible region with limited structural data, and may reveal a novel mechanism affecting channel function and assembly.

While Helix D in Kv7.1 and Kv7.4 drives tetramer formation, the same region in Kv7.3 uniquely favours monomer and dimer formation. Due to the lower conservation of Helix D in Kv7.3 compared to other Kv7 subtypes, as well as its crucial role in channel assembly, further investigation is required to elucidate its role in M-channel formation.

Preliminary findings suggest that wild-type Kv7.3 Helix D forms a mix of monomers and tetramers, while the Q653L mutant appears to favour tetramer formation, potentially disrupting channel function at the membrane by altering heteromeric channel stability. Ongoing investigations will focus on determining the specific structural and functional impacts of this mutation, aiding in the understanding of the structure-function relationship of Kv7 channels and paving the path towards developing more effective treatments.