Understanding KCNQ2-encephalopathy: Leveraging human stem cell-derived neuronal models to uncover disease mechanisms and develop therapeutic solutions

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KCNQ2-encephalopathy caused by pathogenic gain-of-function variants in the KCNQ2 gene, is a severe neurological disorder that manifests in early childhood. It is characterized by developmental delay, intellectual disability, difficulties in movement and speech and autism spectrum disorder, significantly impacting the quality of life for both affected children and their families. Currently, the mechanisms by which these genetic changes lead to neurodevelopmental disorders remain largely unexplored and there are no specific treatments available for these patients. Therefore, this project aims to investigate how KCNQ2 gain-of-function variants lead to these severe neurological conditions. By integrating state-of-the art human induced pluripotent stem cell (hiPSC)-derived neuronal cell cultures with multi-electrode array recordings, we demonstrate that mutant KCNQ2 neurons exhibit delayed electrical maturation and reduced neuronal network activity compared to controls. Additionally, we aim to combine the power of these hiPSC-derived neurons and electrophysiological read-outs together with transcriptome sequencing and computational predictions to develop a drug screening platform to repurpose well-characterised clinically-approved drugs. This approach will offer new perspectives on the pathology of KCNQ2-encephalopathy and drive the discovery of novel therapeutic candidates.