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Iqsec2 knockout mice recapitulate the intellectual disability and epilepsy phenotype of patients with loss-of-function mutations

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The IQ motif and SEC7 domain-containing protein 2 (IQSEC2) is an X-chromosome gene mutated in both males and females leading to Intellectual Disability (ID) and severe early-onset seizures. The pathogenesis underpinning these mutations remains unknown. Utilizing CRISPR/Cas9 targeted editing, we have generated an Iqsec2 KO mouse model to investigate the molecular and cellular deficits in this gene resulting in disease outcomes; a fundamental step towards the design and implementation of potential treatment options. We confirmed the loss of Iqsec2 mRNA expression and the lack of Iqsec2 protein detected within the brain of founder and progeny mice. Recapitulating the human setting, both male (48%) and female (45%) Iqsec2 KO mice present with frequent and recurrent seizures. There was an increased occurrence of seizures, reabsorption and unsuccessful nurturing of live young in breeding females. Developmentally, the KO mice exhibit significantly increased hyperactivity, altered anxiety and fear responses, decreased social interactions, delayed learning capacity and decreased memory retention/novel recognition; recapitulating the psychiatric issues, autistic-like features and cognitive deficits present in patients with loss-of-function IQSEC2 mutations. Interestingly, the loss of Iqsec2 function not only causes severe ID and seizures in KO male mice, but in agreement with the patient setting, similar severity is also noted in females despite being in a heterozygous state for this X-chromosome gene. We contend this newly generated mouse model provides a highly relevant biological tool required to interrogate IQSEC2/Iqsec2 function in the brain.

Biography

Cheryl Shoubridge is an Associate Professor of Human Genetics with a research focus on investigating the molecular pathogenesis underpinning genetic causes of intellectual disability and seizures. Her research utilizes numerous experimental models relevant to the associated clinical phenotypes, including rodent models, primary neurons in culture through to clinical specimens. Currently, she is working in the pre-clinical setting on identifying and validating treatments to improve disease outcomes. Her expertise in genetics, neuroscience and molecular biology underpin her more recent focus on investigating the pathogenic mechanisms contributing to disease outcomes of intellectual disability and seizures due to deficits in synaptic plasticity.

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