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MOSAIC

Molecular and circuits bases of epileptogenic mosaic cortical malformations

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The human brain is a genetic mosaic resulting from frequent somatic mutations during development. Somatic mosaicism can cause Focal Cortical Dysplasia (FCD), a cortical malformation that manifest in young children as drug-resistant focal seizures amenable to surgery resection. FCD are characterized by cortical disorganization secondary to abnormal migration and differentiation of neurons. Brain somatic mutations in genes of the mTOR signaling pathway are a frequent cause of FCD; however genetic etiology remains unidentified in many cases. Our consortium aims at understanding the genetic, molecular and circuit bases of FCD by combining in vitro and in vivo approaches in mouse and human. In Aim 1, using an in vivo genome-wide screen, we will identify genes and enhancers involved in neuronal mismigration in the mouse neocortex. In Aim 2, we will functionally investigate how candidate may cause abnormal circuit activity and seizures. In Aim 3, we will identify mosaic somatic mutations in a patient cohort and use human iPSCs-derived cortical organoids to identify the developmental mechanisms at play in FCD. Hence, ultimately, this proposal will pinpoint potentially druggable targets for this childhood neurodevelopmental disorder.