Altered neuronal connectivity in a conditional knockout mouse model with PCDH19 mosaic expression

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Developmental and Epileptic Encephalopathy 9 (DEE9, OMIM # 300088) is a debilitating neurological condition with no effective cure, characterized by early-onset seizures, intellectual disability and autism. DEE9 is due to mutations in the X-chromosome gene *PCDH19* that encodes protocadherin-19 (PCDH19), a calcium dependent cell-cell adhesion molecule highly expressed in the limbic system and cortex.

To investigate DEE9 pathogenic mechanisms, we generated a *Pcdh19* conditional knockout (cKO) mouse model by exploiting the Cre-LoxP technology. We delivered the Cre recombinase in *Pcdh19* floxed mice by either crossbreeding with hSyn1-Cre transgenic mice or intracerebroventricular (ICV) injection of adeno-associated vectors (AAVs) in order to obtain a mosaic expression of PCDH19 in the brain.

Pcdh19 mosaic mice, which recapitulate behavioral traits of DEE9, display an altered density of hippocampal synapses, with altered structure and function.

Functionally, patch-clamp experiments on acute hippocampal slices revealed that the hippocampus of mosaic mice is characterized by the presence of a population of hyperexcitable neurons, corresponding to PCDH19-negative neurons.

At network level, we observed altered firing rate and neuronal synchronization, as inferred from multielectrode array (MEA) recordings.

Altogether, these results indicate that PCDH19 mosaic expression profoundly affects circuit wiring and functioning, and provide new key to interpret DEE9 pathogenesis.