The intracellular domain of the epilepsy-related protein PCDH19 regulates spine density in cortical neurons

Mutations in the X-linked cell adhesion molecule Protocadherin 19 (PCDH19) lead to epilepsy with cognitive impairment in heterozygous females and post-zygotic mosaic males. A complete absence of functional protein does not elicit symptoms, indicating a complex physiopathology and a dependence on cellular mosaicism. It is believed that mosaic expression of PCDH19 on neuronal membranes leads to defective cell-cell communication in the brain, but whether further roles beyond cell adhesion are critical for PCDH19 function in the cortex is currently unknown. Here, we characterize the proteolytic processing of PCDH19 in mouse cortical-like embryonic stem cell derived neurons and cortical lysates and show that its intracellular domain interacts with importins to be transported into the nucleus. RNAseq analysis of neurons derived from an engineered mouse embryonic stem cell line further indicates that the intracellular domain of PCDH19 leads to broad changes in the transcriptional landscape that are related to neuronal differentiation processes. Finally, we use in utero electroporation to provide the first in vivo data about the role of this cleaved intracellular domain in upper layer cortical neurons, where it reduces spine density without affecting overall dendritic morphology. Because processing is activity dependent, our results suggest that PCDH19 could act as an activity sensor in a synapse to nucleus signaling pathway involved in synaptic homeostasis.