Multiomic analysis implicates Nuclear Hormone Receptor and Wnt/β-catenin signalling in Clustering Epilepsy.

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Clustering Epilepsy (CE) is caused by cellular mosaicism of the X chromosome gene PCDH19. CE is typified by seizures that onset in infancy, occur in clusters and are often pharmacoresistant. CE individuals often present with diverse comorbidities and with variable clinical expressivity. To gather a comprehensive overview of the impact and delve into the mechanisms of mosaic loss of PCDH19 function in CE pathogenesis, we have performed methylation array and RNA-sequencing analyses of CE patient-derived cells and PCDH19 interactome analysis of the mouse brain. Firstly, we identified differentially methylated regions in the blood of CE patients, with enrichment of genes regulated by transcription factors involved in the Wnt/β-catenin pathway. Further epigenetic and transcriptomic analysis identified differential methylation and expression of Wnt/β-catenin regulated genes and NHRs in CE patient skin fibroblasts. Secondly, we identified an interaction between PCDH19 and β-catenin and gathered evidence that β-catenin-mediated gene regulation is impacted by PCDH19 cytoplasmic domain and pathogenic missense variants. Finally, we observed that NHRs mediate regulation of PCDH19 itself, where estradiol represses PCDH19 expression through ERα and the coregulator FOXA1. Together, these results point to a novel mechanism of NHR and Wnt/β-catenin signaling in the pathogenesis of CE and which pathways could be explored for therapy.