

CASK-related disorders

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CASK-related disorders are genetically defined neurodevelopmental syndromes. There is limited information about the effects of CASK mutations in human neurons. Therefore, we sought to delineate CASK-mutation consequences and neuronal effects using induced pluripotent stem cell-derived neurons from two mutation carriers. One male case with autism spectrum disorder carried a novel splice-site mutation and a female case with intellectual disability carried an intragenic tandem duplication. We show reduction of CASK protein in maturing neurons from the mutation carriers, which leads to significant downregulation of genes involved in presynaptic development and of CASK protein interactors. Furthermore, CASK-deficient neurons showed decreased inhibitory presynapse size as indicated by VGAT staining, which may alter the excitatory-inhibitory (E/I) balance in developing neural circuitries. Using in vivo magnetic resonance spectroscopy quantification of GABA in the male mutation carrier, we further highlight the possibility to validate in vitro cellular data in the brain. Our data show that future pharmacological and clinical studies on targeting presynapses and E/I imbalance could lead to specific treatments for CASK-related disorders.