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HGG Adv. 2025 May 8;6(3):100450. doi: 10.1016/j.xhgg.2025.100450. Online ahead of print.

Pathogenic PPP2R5D variants disrupt neuronal development and neurite outgrowth in patient-derived neurons that are reversed by allele-specific knockdown

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PMID: 40340253 PMID: [PMC12148737](#) DOI: [10.1016/j.xhgg.2025.100450](#)

Abstract

A significant barrier to the treatment of neurodevelopmental disorders (NDDs) is a limited understanding of disease mechanisms. Heterozygous missense variants in PPP2R5D cause Hogue-Janssens syndrome 1, a rare NDD characterized by macrocephaly, developmental delay, intellectual disability, seizures, autism spectrum disorder, and early-onset Parkinson disease. This study investigated the impact of pathogenic PPP2R5D variants on neuronal development and evaluated allele-specific knockdown as a potential therapeutic strategy. Induced pluripotent stem cells derived from individuals carrying the E198K and E420K variants, along with CRISPR-corrected isogenic controls, were differentiated into neural progenitors and cortical glutamatergic neurons. Patient-derived neural progenitors were hyper-proliferative, and glutamatergic neurons differentiated from these cells exhibited increased neurite outgrowth. Notably, neuronal overgrowth phenotypes were not observed in neurons lacking PPP2R5D, suggesting the disorder does not result from loss of function. RNA sequencing (RNA-seq) of glutamatergic neurons derived from patient lines compared to their isogenic controls revealed disruptions in pathways critical for neuronal development, synaptic signaling, and axon guidance. To target pathogenic transcripts, antisense oligonucleotides (ASOs) were designed to selectively knock down the E198K allele, the most common disease-causing missense variant. The most effective ASOs reversed neurite outgrowth defects in patient-derived neurons. These findings uncover molecular mechanisms underlying PPP2R5D-related NDDs and support allele-specific knockdown as a potential therapeutic approach.

Keywords: Hogue-Janssens syndrome; PPP2R5D; RNA-seq; allele-specific knockdown; antisense oligonucleotides; iPSCs; induced pluripotent stem cells; neurite outgrowth; neurodevelopmental disorders; patient-derived neurons.

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Figures

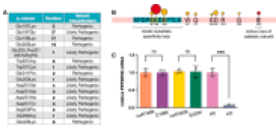


Figure 1 Overview of pathogenic *PPP2R5D* variants...

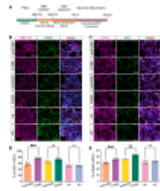


Figure 2 Induction of hPSCs revealed that...

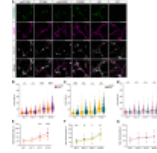


Figure 3 E198K and E420K patient-derived neurons...

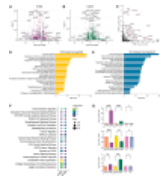


Figure 4 Transcriptional changes in patient-derived neurons...

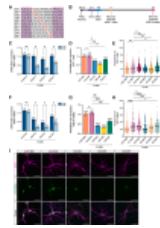


Figure 5 Selective ASO knockdown of the...

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[Eur J Hum Genet.](#) 2025 May 15. doi: 10.1038/s41431-025-01856-3. Online ahead of print.

Cell-type specific global reprogramming of the transcriptome and epigenome in induced neurons with the 16p11.2 neuropsychiatric CNVs

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PMID: 40374944 DOI: [10.1038/s41431-025-01856-3](#)

Abstract

Copy number variants (CNVs), either deletions or duplications, at the 16p11.2 locus in the human genome are known to increase the risk for autism spectrum disorders (ASD), schizophrenia, and several other developmental conditions. Here, we investigate the global effects on gene expression and DNA methylation using an induced pluripotent stem cell (iPSC) to induced neuron (iN) cell model system derived from 16p11.2 CNV patients and controls. This approach revealed genome-wide and cell-type specific alterations to both gene expression and DNA methylation patterns and also yielded specific leads on genes potentially contributing to some of the phenotypes in 16p11.2 patients. There is global reprogramming of both the transcriptome and the DNA methylome. We observe sets of differentially expressed genes and differentially methylated regions, respectively, that are localized genome wide and that are shared, and with changes in the same direction, between the deletion and duplication genotypes. The gene PCSK9 is identified as a possible contributing factor to symptoms seen in carriers of the 16p11.2 CNVs. The protocadherin (PCDH) gene family is found to have altered DNA methylation patterns in the CNV patient samples. The iPSC lines used for this study are available through a repository as a resource for research into the molecular etiology of the clinical phenotypes of 16p11.2 CNVs and into that of neuropsychiatric and neurodevelopmental disorders in general.

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