Understanding the Role of CDKL5 C-Terminal Domain in CDD through Proximity Proteomics and Cross-Vertebrate Analysis

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CDKL5 deficiency disorder (CDD) is a severe neurological condition caused by mutations in the CDKL5 gene. While some mutations clearly disable the gene, many others – especially in a large, poorly understood region called the C-terminal domain — cannot be classified as harmful or harmless. This directly affects families: without clear diagnosis, patients may be excluded from emerging gene therapy trials. This project investigates what the C-terminal domain does at the molecular level. We identified a conserved segment, HCR6, that overlaps with patient mutations of uncertain significance. We will use proteomics to discover which proteins interact with HCR6, and test whether losing these interactions disrupts synapse formation in neurons. To confirm cross-species relevance, we will test HCR6 function in zebrafish brain circuits and mouse behavior. The results will provide a framework for interpreting patient mutations — converting variants of uncertain significance into actionable diagnoses — and may reveal new therapeutic targets.