CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Novel CDKL5 complex partners and kinase substrate candidates

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Intellectual disability (ID) is characterized by significant limitations both in intellectual functioning and in adaptive behaviors. ID affects 1-3% of the general population and can be caused by a diverse spectrum of factors including genetic mutations. While the number of novel genes responsible for ID is rapidly increasing our current understanding of their functions and the underlying mechanisms that cause the disorder lacks far behind. One of the well-established ID genes is CDKL5 (cyclin-dependent kinase-like 5). It maps to the X chromosome and deleterious mutations of CDKL5 cause a severe syndromic neurodevelopmental disorder with early onset, mostly difficult to control, epileptic seizures, which start in the first months after birth. Other prominent clinical features include cognitive dysfunction, hypotonia and motor impairment. Our current knowledge of CDKL5's functions and the underlying pathophysiologic mechanisms of the CDKL5 disorder is scarce and there is currently no cure available. For the development of treatments it is necessary to better understand CDKL5's protein functions during normal brain development and the functional consequences of its deficiency. In this research project we will further investigate newly identified CDKL5 candidate protein complex partners and kinase substrate candidates on different levels and how the impact of CDKL5 deficiency on these proteins could contribute to the clinical phenotype. For this we will use in vitro and in vivo model systems. A clear knowledge of molecules and cellular processes that are involved in the CDKL5 disorder will hopefully pave the way towards the identification of novel targets that can be used for the development of drug therapies.