Penn Medicine

the orphan disease center

CDKL5 Program of Excellence
2019 Pilot Grant Program

Project Title: "Plasma microtubule proteins as potential biomarkers for CDKL5 Deficiency Disorder (CDD)"

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CDKL5 Deficiency Disorder (CDD) is a rare brain disorder characterized by severe early-onset seizures in the first month of life, intellectual disability, motor and social impairment, and which mainly affects females. Currently, no therapies exist for CDD and only symptomatic pharmacological treatments are available. The use of animal models such as Cdkl-5null mice (lacking the CDKL5 gene) have shown to be an invaluable tool to gather insights into the molecular alterations underlining CDD. However, there is an urgent need for minimally invasive (i.e. peripheral fluid analysis) biomarkers of translational value to monitor disease progression. Microtubules are cytoskeletal elements playing vital roles in development of brain cells, supporting the formation, maintenance and remodeling of synapses, structures through which brain cells communicate. Dysfunction in microtubule dynamics leads to altered brain development and loss of synapses. Microtubule dynamics can be analyzed by measuring the post-translational modifications (PTMs) of the alpha-tubulin protein, the main building block of microtubules. We have recently discovered that alpha-tubulin PTMs can be detected in peripheral fluids, such as blood plasma and cerebrospinal fluid (CSF) in both animals and humans. Our human studies show that alterations in alpha-tubulin PTMs are evident in plasma of patients affects by neurodegenerative disorders such as Parkinson's disease (in collaboration with the Michael J Fox Foundation, MJFF). More recently, we have observed in a pilot study that behavioral alterations in Cdkl-5null male mice were accompanied by alpha-tubulin PTM changes in the brain and plasma of Cdkl-5null mice. Importantly, those behavioral and microtubular changes were rescued by a pharmacological treatment with a specific microtubule modulator. The objective of the current project is to confirm our preliminary observations in Cdkl-5null male mice extending them to include also Cdkl-5 heterozygous female mice since 80-90% of CDD patients are females. We will then to translate the assay into clinical settings by measuring alpha-tubulin PTMs in plasma of CDD patients sampled from Irish, Italian and US disease cohorts. If our hypothesis on altered plasma alpha-tubulin PTMs in CDD is correct, the results may have an immediate impact on the development of clinical diagnostic biomarkers and open new avenues for future original research, possibly leading to the discovery of innovative disease-modifying therapies.