THE HARTWELL FOUNDATION

2021 Individual Biomedical Research Award

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Epigenetic Diagnosis and Targeted Treatment for Improving Cognitive Outcomes in Neurodevelopmental Disorders

Neurodevelopmental disorders (NDD) are cognitive disabilities associated with the function of the brain and nervous system. They include, principally, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), as well as developmental delays and other forms of intellectual disability. Such disabilities are often complex in nature and origin and can create a significant burden to families. While some combination of genetic, biological, psychosocial and environmental risk factors may contribute to the diagnosis, genetics plays a prominent role. Because the symptoms and behaviors of NDD may evolve as a child develops and many children have more than one condition, diagnosis may be difficult. Moreover, some disabilities are permanent. Sadly, despite general advances in prenatal and pediatric medical care, over the last 40 years the prevalence of pediatric ADHD and ASD in the United States have been increasing at an alarming rate, leaving the challenge as to how neurodevelopmental disorders can be specifically manipulated to improve cognitive outcomes. Recognizing that altering the DNA or genes of a child safely and effectively is not yet possible, a more reasoned alternative is the next closest target – 'epi-genetics'. Without any change in the underlying DNA, epigenetics determines the activation and deactivation of genes in tightly controlled patterns that determine heritable changes and manifest as a phenotype (e.g., caterpillar-butterfly transition). Based upon my discovery of a novel, single histone gene mutation that accounts for a pediatric neurodegeneration syndrome, I offer a new paradigm. I hypothesize that computational methodology can identify latent histone genes that contribute to pediatric NDD, and that the epigenetics of affected children can be specifically manipulated to improve their cognitive outcomes. The strategy I will use to identify putative histone genes will be derived from understanding how histone proteins get modified after they are made and how the incipient mutations alter downstream epigenetic processes. Most histone mutations result from an error in the DNA that causes the wrong amino acid to be incorporated into the protein and have a dominant negative effect. Fortunately, such missense variants are amenable to highly specific manipulation by small interfering RNA (siRNA) that will silence the gene. Through computational analysis of large existing datasets, I have now identified six additional histone proteins that affect development, including more than 25 children with these mutations who have overlapping NDD. Using a model test system, I propose to quantify how such histone mutations trigger neurologic dysfunction and will evaluate the effectiveness of siRNA therapy to turn off the mutated histone genes to make the cells function properly. If I am successful, clinical translation of a treatment for these histone-related neurodevelopmental syndromes will have a profound effect on improving the quality of life of affected children and their families.