TITLE: Identification of splicing changes causative of central nervous system defects in Myotonic Dystrophy

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RESEARCH PROJECT DESCRIPTION

Myotonic Dystrophy (dystrophia myotonica, DM) is the most common form of muscular dystrophy in adults. However, DM can affect individuals of all ages, from fetus to the elderly; furthermore, disease symptoms are multi-systemic, with profound central nervous system effects, including challenges with learning/memory, executive functioning, and regulation of sleep. A well-established model for disease pathogenesis is that expanded CTG repeats in DM1 are transcribed into RNA, sequestering members of the Muscleblind-like RNA binding proteins (MBNL), causing functional depletion of MBNL and mis-splicing of MBNL's endogenous targets, including numerous genes important for synapse function. Using RNAseq, we have performed transcriptome profiling of human DM1 brains and mouse models of DM1. While transcriptome profiling yields extensive information about all the splicing changes that occur in a given tissue or animal, a major challenge will be to identify the splicing changes that are responsible for particular phenotypes.

In this project, the student will identify splicing events whose perturbation may alter synaptic plasticity, synapse maintenance, or synapse formation. They will use neuronal culture to validate their dependency on CTG repeat expression, as well as MBNL function. These splicing events will then be perturbed in neuronal culture using genetic methods or splice site-switching oligonucleotides, and specific cellular phenotypes will be measured, such as synapse formation, dendritic spine density, and axonal growth. Techniques include neuronal culture, RNA isolation, RT-PCR, imaging, and other standard molecular & cell biological techniques. Computational analysis of RNAseq data may also be possible.