Elucidation of the molecular mechanisms associated with early onset primary dystonia (DYT16) caused by mutations in PACT

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Dystonia is an inherited neuromuscular movement disorder that has been shown to result from mutations in more than 25 different genes. The resultant phenotype consists of both agonist and antagonist muscles firing simultaneously. Consequently, patients suffer from inability to control their dystonic, often sustained repetitive movements, and have a compromised posture. One type of primary dystonia, the early onset dystonia 16 (DYT16), has been shown to be result from various mutations in the PACT (also known as PRKRA) gene that has been well characterized for its role in regulating apoptosis in response to cellular stress.

Under conditions of viral, oxidative, or endoplasmic reticulum stress, the cellular apoptosis has been shown to be regulated by prolonged translation inhibition resulting from kinase activity targeting the eukaryotic translation initiation factor 2 alpha. Events leading to eIF2 alpha phosphorylation in response to cell stress are attributed to interactions between three double stranded RNA binding proteins: PACT, TRBP, and PKR. These three proteins interact with each other forming homo- and heterodimers to impact cellular fate in response to stress signals. PACT is a **p**rotein **act**ivator of PKR, a serine-threonine kinase involved in innate immunity. PACT-PKR interaction is essential for facilitating apoptosis; whereas, **t**ransactivation **R**NA **b**inding **p**rotein (TRBP) serves as a PKR inhibitor via PACT-TRBP and TRBP-PKR heterodimerization. These three proteins share evolutionarily conserved double stranded RNA binding motifs that also facilitate protein-protein interactions and regulate the cell survival and apoptosis.

We have investigated the altered protein-protein interactions between PACT, PKR, and TRBP that result from various mutations reported in DYT16 patients, and for the first time in a mouse model of DYT16. Using various biochemical techniques, we characterized how these mutations influence PACT's function during stress response to regulate apoptosis. By utilizing DYT16 patient samples as well as an analogous mouse model with dystonia we are attempting to better understand how PACT mutations may lead to early onset dystonia. Our research highlights the insight obtained by applying biochemical, and molecular analysis to patient cells and mouse models to understand the etiology and pathophysiology of dystonia.