David Kaplan and Freda Miller

Non-technical Title:
How alterations in translation of proteins in stem cells contributes to aberrant brain development and neurodevelopmental disorders

Non-technical summary:
A paradox of how neurodevelopmental disorders (NDD) arise is why there are so many genes associated with these conditions. NDDs in only some cases involve alterations in a single gene and more often involve dysregulation of many genes and therefore brain development. How can this occur? One mechanism is by mutation of genes such as MECP2 that perturbs the expression of many other genes important for cognition, culminating in Rett Syndrome. We propose a second mechanism, that alterations in the expression of key proteins in stem cells that build the brain contributes to some types of NDDs. We have found that in some cases leading to NDD, the expression of important genes is not altered, but there is aberrant expression of the proteins encoded by those genes. The expression or translation of proteins is controlled in part by "translational repressors", proteins that keep the production of key proteins silent until they are needed to produce the various cell types of the CNS. Alterations in the activity of translational repressors in the stem cells that build the brain can perturb the brain circuitry required for proper cognition. Our hypothesis is that a "master repressor" called 4E-T complexes with and regulates the translation of NDD-associated proteins that themselves regulate dozens of other NDD-associated genes. Perturbation of 4ET target or its protein partners such as occurs in NDDs would therefore dysregulate the expression of many proteins involved in determining when and how the brain is built. Our proposed studies, if successful, will identify a new layer of regulation of brain cell biology that if perturbed, will result in global alterations in brain development and function.