Differential gene expression to explore the up and down regulation of genes in the Hippocampus and Frontal Cortex of DM1 and DM2 patients

Megan Barber, Sawyer Hicks, and Andy Berglund
University at Albany, The RNA Institute, Albany, NY

Myotonic dystrophy type 1, also known as DM1, presents itself in adulthood as well as at birth at times, and is the most common form of muscular dystrophy. DM1 is known to be a multisystem disorder that can have a myriad of clinical symptoms. This autosomal dominate hereditary disease has a characteristic CTG expansion in the 3'-UTR region of the protein coding gene DM1 protein kinase (DMPK). The quantity of repeats can range from 50 repeats to greater than 1 thousand repeats. The more prevalent the repeats, i.e. the more repeats a patient has, the more severe the manifestations of this disease become. The age of onset also plays a major role in the severity of DM1. Myotonic Dystrophy 2, DM2, is much rarer than DM1 and is caused by a CCTG expansion in the gene CCHC-Type Zinc Finger Nucleic Acid Binding Protein (CNBP). Similar to DM1, the repeat expansion results in faulty RNA production and leads to an accumulation of sequestered proteins in the cell that interrupt normal cellular function. MBNL, also known as muscleblind-like proteins, have been determined to be sequestered by the repeat expansion leading to a diminished quantity of MBNL available. The lack of MBNL leads to the functional loss in the MBNL RNA-binding proteins which causes misregulation of alternative splicing events that results in clinical symptoms such as myotonia, insulin resistance, and weakness in muscles. DM2 patients are more prone to cognitive symptoms when compared to DM1 patients. As a summer research fellow in the Berglund lab, I aimed to explore the differential gene expression in the hippocampus and frontal cortex of DM1, DM2, and control patients by studying RNA-seq datasets. The goal was to explore the up and down regulation of genes to determine if there are any other genes that may be up and down regulated resulting in faulty cellular function and how this may result in clinical manifestations of Myotonic Dystrophy type 1 and 2. Finally, I wanted to determine if there was a substantial difference in differential gene expression between DM1 and DM2 patients that may explain why cognitive deficits tend to be more prevalent in DM2 patients. To begin this project, I used an SRA retrieval script (Goodwin et al DATE) which utilized the SRA tool fasterq-dump to download previously published frontal cortex and hippocampus sequencing data. Then I aligned the sequencing reads to the human reference genome hg38 and loaded the alignment files into RStudio where I used the differential expression software DMSeq2 to conduct my analysis. I compared the up and down regulation of genes between DM1 and DM2 patients compared to control samples. I predicted that since DM2 patients tend to suffer more from cognitive symptoms than DM1 patients, DM2 samples in the hippocampus and frontal cortex will be notably more disrupted in terms of down or up regulation in these regions of genes. Through my experiments, I determined this was not the case rather there was rather uniform up and down regulation of genes in both DM1 and DM2 brains compared to the control brains. In the future, I plan to conduct alternative splicing events analysis through RMATS as well as exploring other regions of the brain such as the temporal and occipital lobe.