Unravelling changes in transcription start and end in motor neuron disease models

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Abstract / MSc thesis project proposal

Motor neuron diseases like Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis are linked to mutation in proteins involved in RNA metabolism, including SMN and Fus. Although most of these proteins are generally considered to predominantly influence cellular events at the level of mRNA splicing, stability localisation and/or translation, several lines of evidence suggest they may also influence transcription start and termination sites, thereby altering the 5' and 3' UTRs of messenger RNAs. The impact of specific protein mutations on the cellular transcriptome can be assessed from mRNA-seq data. However, most data analysis pipelines are focused on performing differential expression analysis at the gene level or identifying alternative exon usage. Therefore, the characterisation of changes that affect the 5' and 3' untranslated regions go mRNA molecules is often overlooked. These sequence elements are however particularly critical in the context of neuronal function, which relies heavily in the control of mRNA localisation, which is dependent on these sequence elements. In this MSc project we will take advantage of multiple transcriptome datasets from SMA and ALS disease models available in the host lab to address this topic. The student will begin by performing a literature search on the latest methods available to specifically map 5' and 3' UTR changes, defining the strategy to best analyse the data. Improvements or new implementations to these methods will be established as needed. The student will then analyse the available datasets, first assessing the coverage or 5'-3' biases in mRNA-seq approaches. A detailed transcriptome map of mRNA variants will be established, including comparison of changes between neuronal and non-neuronal cells. Differential expression analysis focusing on 5' and 3' ends will be performed. The genomic loci encoding genes that are identified as being altered in the context of disease associated mutations will be analysed in search for specific sequence features that can explain the observed differences. This study will provide a deeper understanding of transcriptome changes linked to neuronal disorders.