Regulation of the alternative splicing of Dp71, the major brain dystrophin transcript, by splicing factors

Chelsea Wood[1]; Karen Anthony[1]

[1]Centre for Physical Activity and Life Sciences, Faculty of Arts, Science and Technology, University of Northampton, University Drive, Northampton, UK, NN1 5PH

Duchenne muscular dystrophy (DMD) is a fatal childhood genetic disorder, caused by the absence of dystrophin throughout the body. Parallel to muscle degradation, loss of dystrophin in the brain can lead to cognitive impairments and intellectual disabilities. Such DMD brain co-morbidities are linked to the loss of dystrophin protein 71 (Dp71). Dp71 is the most predominant dystrophin protein in the brain, and alternative splicing at exons 71 and 78 produces several Dp71 isoforms with different subcellular locations and functions.

Splicing factors regulating *DMD* alternative exons in skeletal muscle have recently been identified but it is not known what complement of splicing factors regulate *DMD* alternative splicing in the brain. Given the importance of Dp71 in the brain, we aim to assess the neuronal splicing factors regulating the alternative splicing of Dp71 exons 71 and 78 in the brain and whether this is disrupted in DMD.

We have generated *DMD* minigenes to study the alternative splicing of exons 71 and 78. These are being used to assess the activity of neuronal splicing factors such as the CUG-BP and ETR-3-like factor (CELF) and muscleblind-like (MBNL) families on the alternative splicing of Dp71. Additionally, we are modelling the loss of Dp71 in neuronal and glial cell lines, and DMD patient-derived fibroblasts with distal *DMD* mutations and assessing the effect of Dp71 loss on the expression of CELF and MBNL splicing factors.

Data from this work will be presented which provides a preliminary understanding of the significance of *DMD* alternative splicing within the brain. The development of brain-targeting treatments is complicated by the added complexity of dystrophin biology in the brain. Our work aims to inform such work through increasing our understanding of Dp71.