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Investigating the mechanisms underlying oligodendrocyte dysfunction in C9ORF72 ALS

Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease in which motor neurons degenerate. Oligodendrocyte dysfunction has also been shown to be a feature of ALS[1, 2]. Moreover, pathological ubiquitylated cytoplasmic inclusions (UCIs) are well documented in oligodendroglia in addition to neurones. Myelin basic protein (MBP) is translated in oligodendrocyte processes. MBP messenger RNA (mRNA) must therefore be transported to processes while inhibiting its translation. The C9ORF72 gene contains the expansion of an intronic GGGGCC repeat in many ALS cases (C9ALS)[3, 4]. The GGGGCC motif binds heterogeneous nuclear ribonucleoprotein A2 (hnRNPA2)[3], which is essential for the assembly of MBP mRNA transport granules[5]. This may lead to sequestration of hnRNPA2, reducing its availability to bind MBP mRNA, thereby causing myelin dysfunction in C9ALS. This project undertakes a characterisation of oligodendrocyte pathology in C9ALS.

Materials and methods: We used immunohistochemistry (IHC) for p62 to quantify oligodendroglial UCIs in motor (MCx) and frontal cortices and spinal cord (SC). IHC was used to quantify hnRNPA2, MBP, phosphorylated-TDP43 (pTDP43), dipeptide repeat-inclusions (DPRs) and oligodendrocyte precursor cells (OPCs) in the MCx white matter.

Results: C9ALS cases showed more glial UCIs in the cortex compared to sporadic ALS (sALS) and Ct cases. Both C9ALS and sALS cases show increased UCIs in the SC in comparison with Ct cases. These C9ALS cases also show that the number of glial UCIs in the white matter underlying the motor cortex correlates negatively with the amount of MBP, the proportion of cells expressing hnRNPA2, and the number of OPCs in the same area. These C9ALS cases rarely showed DPRs and did not show a specific pTDP43 pathology in the MCx WM.

Conclusions: MCx UCIs, but not SC UCIs, are specific of C9ALS. The lack of some myelination markers in the MCx WM of C9ALS could be related to proteins included in the UCIs which are still unknown, but not to DPRs, in the MCx WM.

References:
1. Lee et al. Nature 2012; **487:** 443-8.
2. Kang et al. Net neurosci 2013; **16:** 571-9.
3. DeJesus-Hernandez et al. Neuron 2011; **72**: 245-56.
4. Renton et al. Neuron 2011; **72**: 257-68.
5. Ainger et al. J Cell Biol 1997; **138:** 1077-87.

FOR SBTB OFFICE USE
Project no. 14/007

AUTHORISATION TO USE TISSUE RESOURCE FROM THE SHEFFIELD BRAIN TISSUE BANK (SBTB)

FOLLOWING CONSIDERATION BY THE SBTB MANAGEMENT BOARD:

Proposed Study Title

Glial pathology and RNA transport in ALS

SECTION A: PROJECT STAFF DETAILS

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SBTB PROJECT REQUEST NUMBER: 14/007

This project was reviewed by the SBTB Management Board and approval to release tissue under REC **08/MRE00/103** was granted.

Professor P G Ince
Director SBTB

Date: 26/8/14

FOR SBTB OFFICE USE
Project no. 14/006

AUTHORISATION TO USE TISSUE RESOURCE FROM THE SHEFFIELD BRAIN TISSUE BANK (SBTB)

FOLLOWING CONSIDERATION BY THE SBTB MANAGEMENT BOARD:

Proposed Study Title

An autopsy study of stress granule markers in ALS

SECTION A: PROJECT STAFF DETAILS

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Professor P G Ince
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