Elucidating the role of FUS mutant oligodendrocytes in the pathophysiology of ALS using induced pluripotent stem cells

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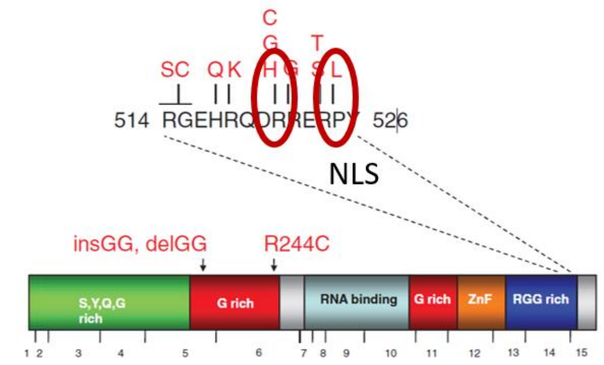
INTRODUCTION

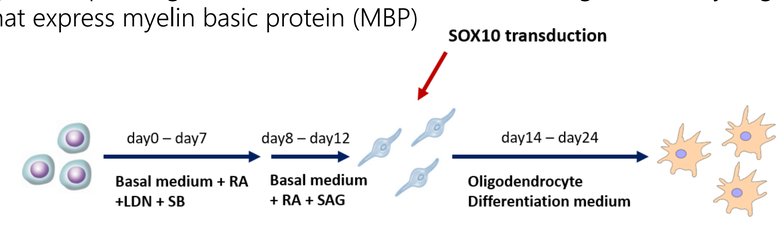
- FUS-linked ALS causes an aggressive form of the disease associated with a juvenile onset and short survival
- Most ALS-linked mutations are found in the nuclear localization signal (NLS) of the FUS protein causing cytoplasmic mislocalization
- Oligodendrocytes are known to play a role in the ALS pathogenesis as oligodendrocyte degeneration and myelin defects are observed in post mortem spinal cord tissue of ALS patients
- How do FUS mutant oligodendrocytes contribute to the ALS pathology?

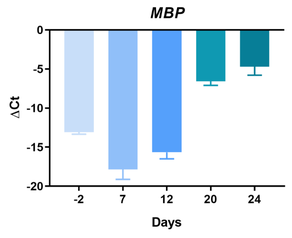


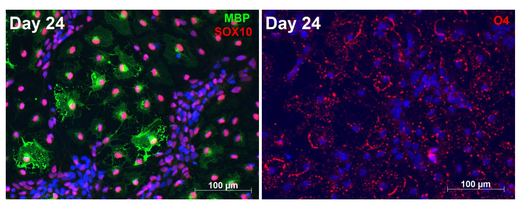
METHODS

Differentiation

By overexpressing SOX10 at neural stem cell (NSC) stage, O4$^+$ early oligodendrocytes are generated that express myelin basic protein (MBP)

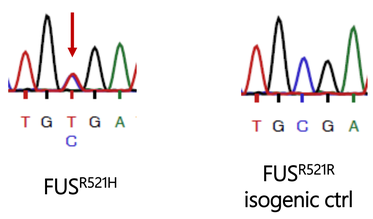


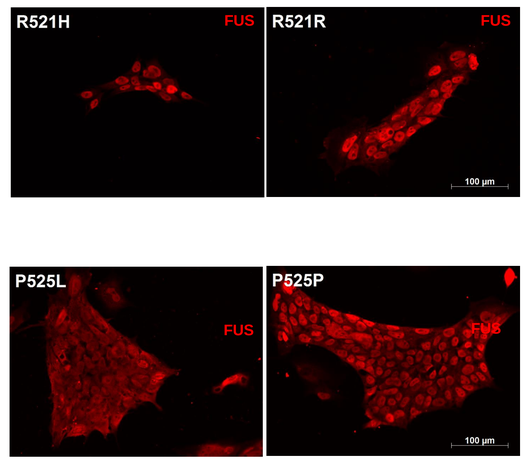




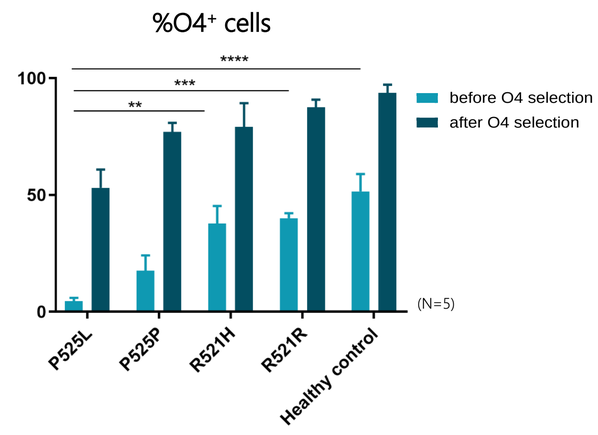
iPSC lines used

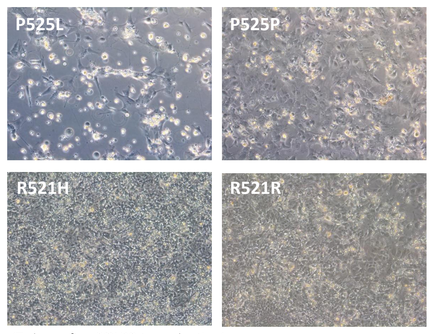
Cytoplasmic FUS mislocalization is observed for FUS^{P525L} iPSCs





FAILURE OF FUS^{P525L} MUTANT CELLS TO GENERATE O4$^+$ OLIGODENDROCYTES?

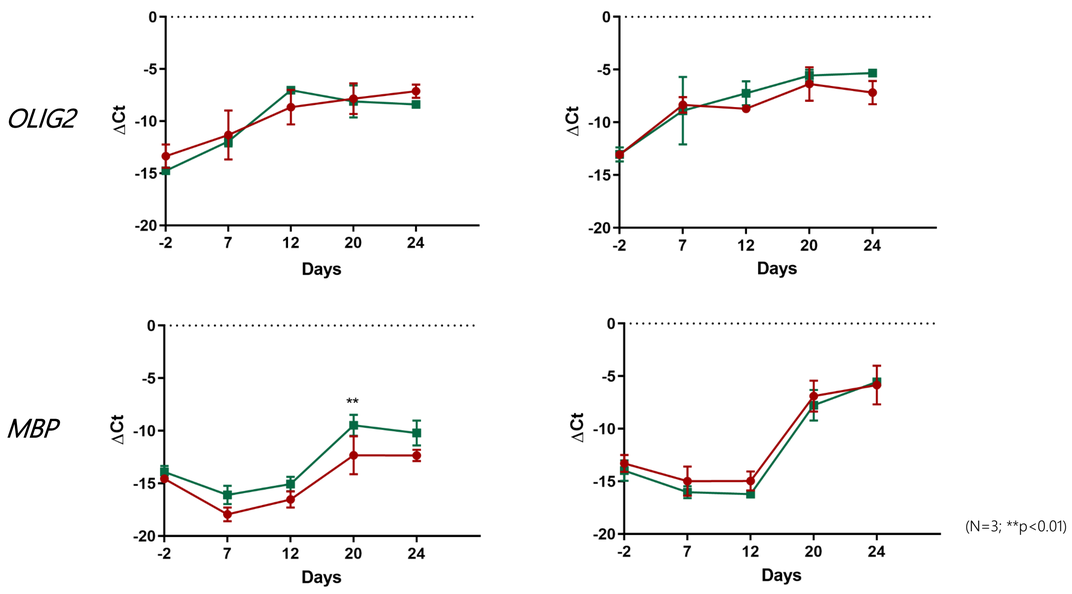




(7 days after SOX10 transduction)

qRT-PCR demonstrates that oligodendrocyte gene expression is similar in O4$^+$ cells from FUS^{P525L} and FUS^{P525P} iPSCs

qRT-PCR demonstrates that oligodendrocyte gene expression is similar in O4$^+$ cells from FUS^{R521H} and FUS^{R521R} iPSCs



(N=3; **p<0.01)

TRANSCRIPTOMIC ANALYSIS SUGGESTS LIPID AND CYTOSKELETAL DEFECTS IN FUS MUTANT O4$^+$ CELLS

Gene Ontology: biological process

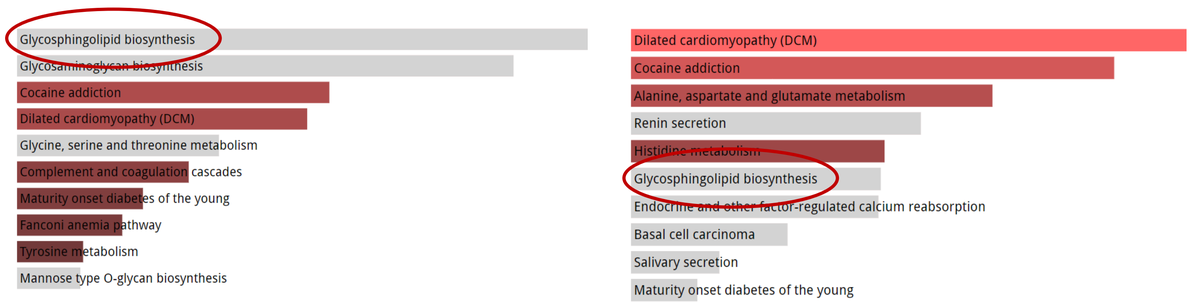
Differentially expressed genes between FUS^{P525L} mutant O4$^+$ cells and their isogenic control

Gene ontology ID	Biological Process	FDR
GO:0000226	microtubule cytoskeleton organization	5.1E-8
GO:0048285	organelle fission	5.9E-8
GO:0007017	microtubule-based process	1.5E-7
GO:0007417	CNS development	3.2E-7
GO:0007049	Cell cycle	4.1E-7

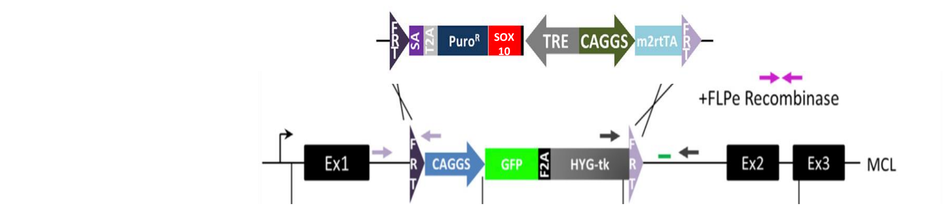
Differentially expressed genes between FUS^{R521H} mutant O4$^+$ cells and their isogenic control

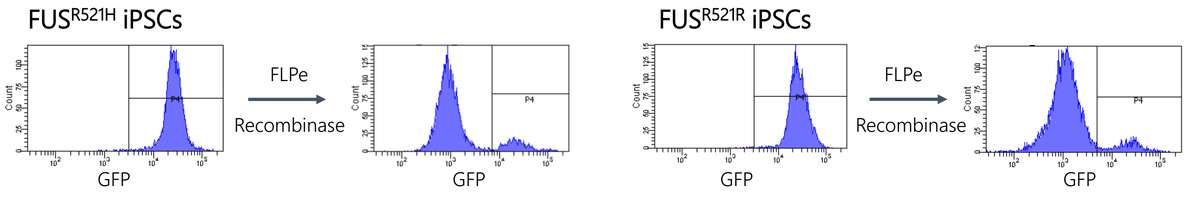
Gene ontology ID	Biological Process	FDR
GO:0040011	Locomotion	3.8E-12
GO:0048870	Cell motility	1.8E-9
GO:0007417	CNS development	3.8E-9
GO:0007155	Cell adhesion	6.3E-9
GO:0006928	Movement of cell/subcellular component	6.3E-9

KEGG Human 2019



SOX10 OVEREXPRESSION FROM AAVS1 LOCUS TO AVOID USE OF LENTIVIRAL VECTORS





FUTURE PERSPECTIVES

- Validate results from transcriptomic analysis which might uncover candidate novel drug targets
- Co-culture of FUS mutant oligodendrocytes with normal donor iPSC neurons are being performed to assess possible toxic/non-supportive effects of the oligodendrocytes