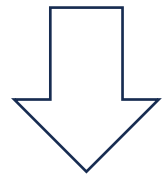


mGluR5 as a therapeutic target for TDP-43-related ALS

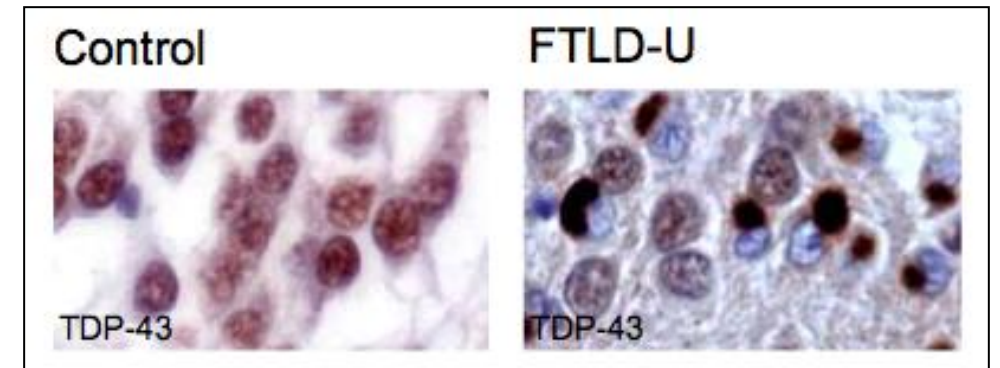
Focusing on TDP-43 abnormalities, a key pathology of amyotrophic lateral sclerosis (ALS), this study explored a novel therapeutic strategy targeting the glutamate receptor mGluR5. Single-nucleus RNA sequencing (snRNA-seq) analysis revealed significant upregulation of mGluR5 in the dorsal root ganglia (DRG) of ALS patients. Furthermore, in a TDP-43 model exhibiting neurite outgrowth impairment, mGluR5 inhibition demonstrated neuroprotective effects. These findings suggest that mGluR5 is involved in TDP-43-related pathology and highlight its potential as a disease-modifying therapeutic target for ALS.

Evidence Supporting mGluR5 as a Therapeutic Target in ALS

- In ~97% of ALS cases, TDP-43 protein mis-localizes from nucleus to cytoplasm and aggregates in neurons and glia
- Some ALS cases show mutations in the TDP-43 gene
- High mGluR5 gene expression observed in ALS lesions with TDP-43 pathology
- Pharmacological studies using TDP-43 model cells confirm neuroprotective effects of mGluR5 inhibition

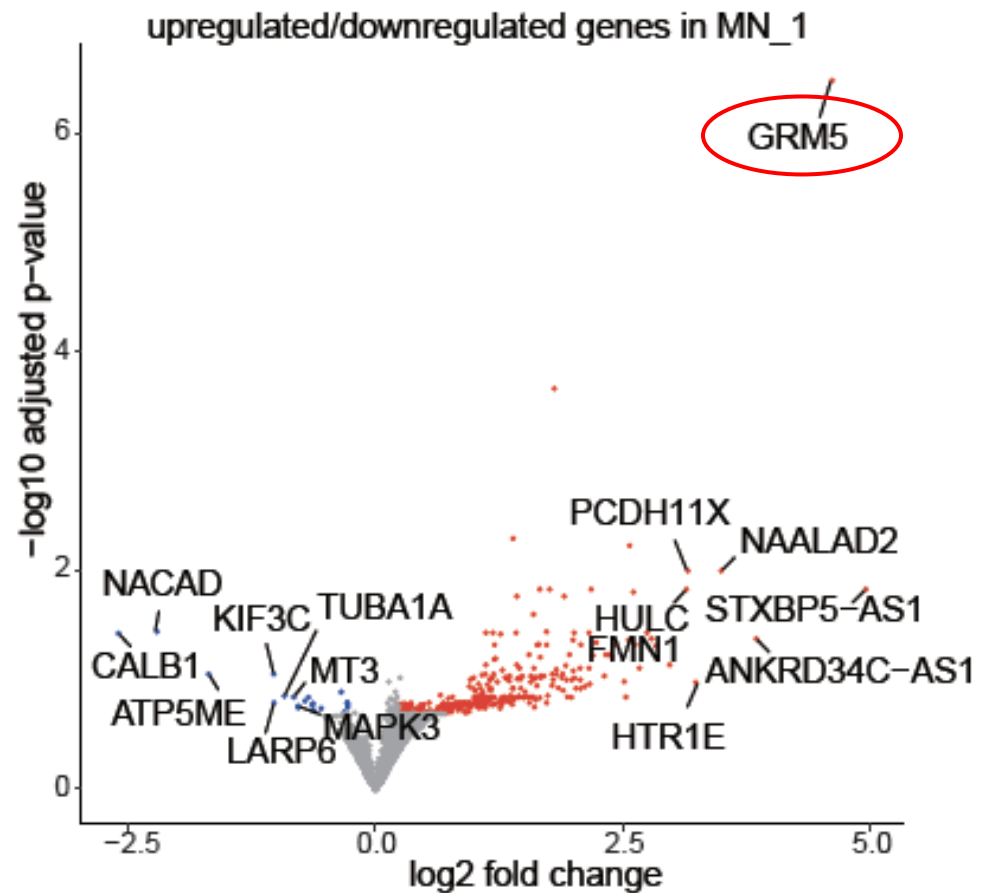


mGluR5: A New Disease-
Modifying Target from Our
Study
(Patent Pending)

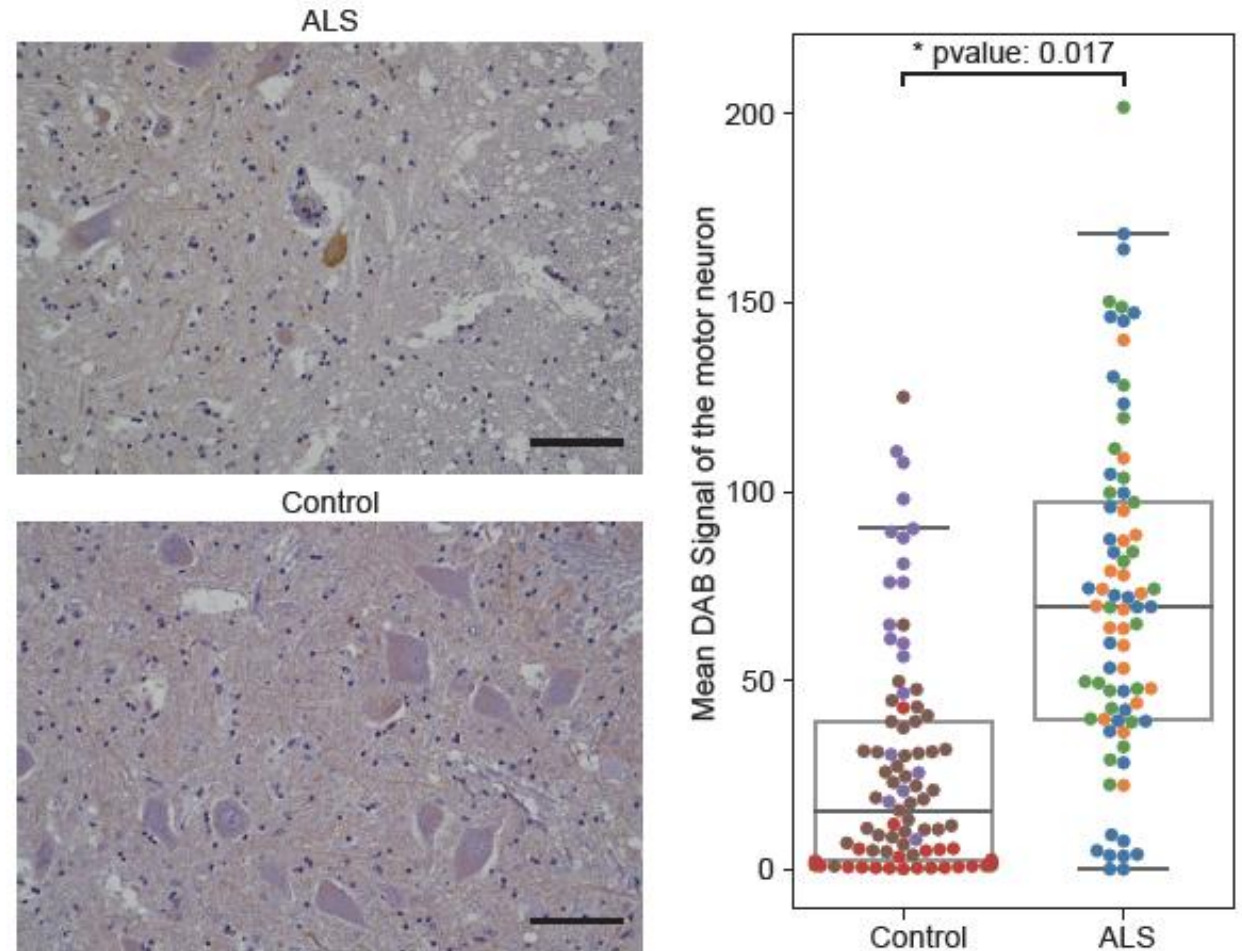


(Arai et al. BBRC, Neumann et al. Science 2006)

GRM5 (mGluR5) Upregulation in ALS Spinal Motor Neurons



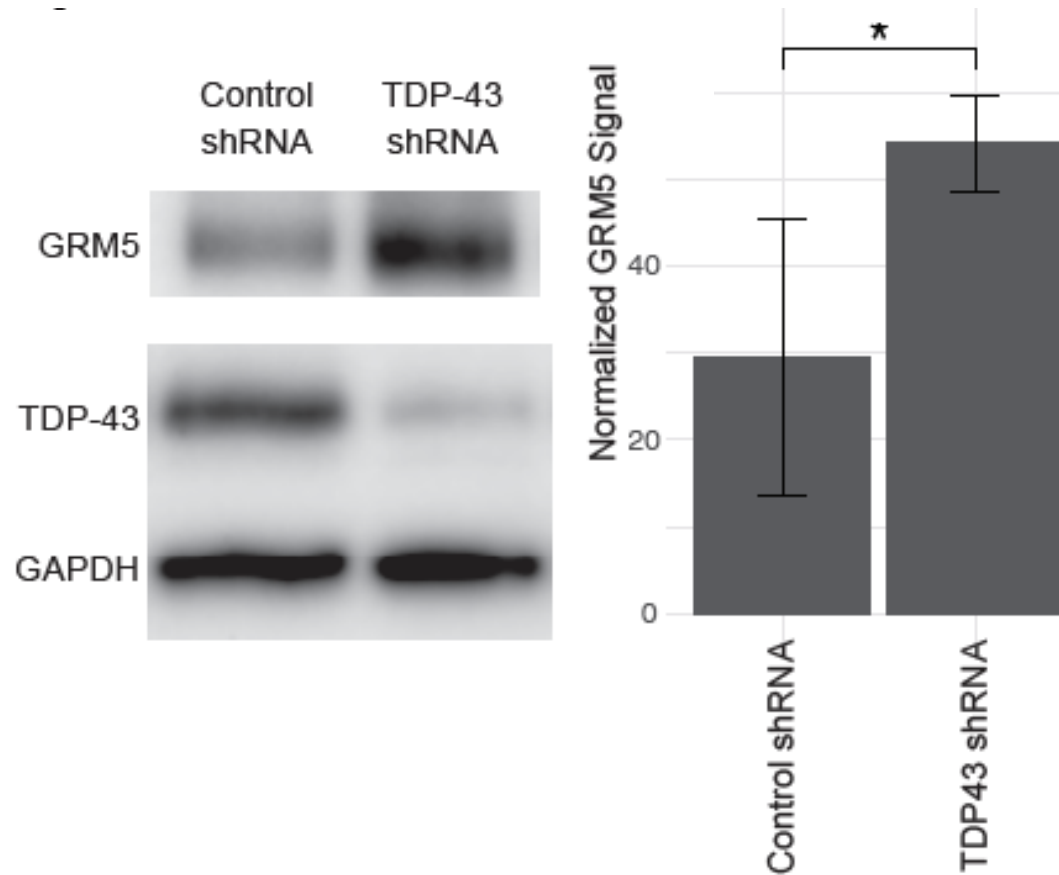
Volcano Plot: ALS vs Control (Spinal Motor Neuron snRNA-seq)



GRM5 Staining (DAB, Brown) and Quantification in Spinal Motor Neurons

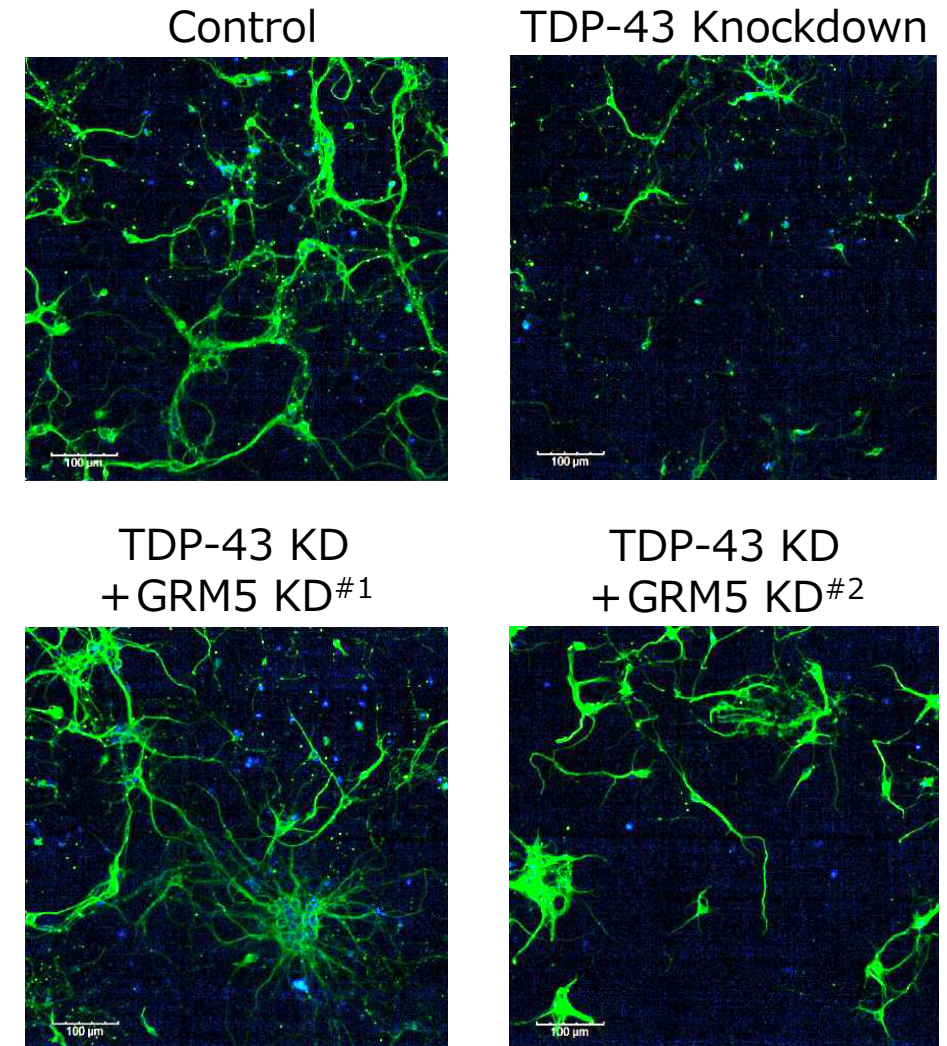
(Takeuchi et al. under revision)

mGluR5 Efficacy in TDP-43 Neurodegeneration Model



TDP-43 and GRM5 Expression in Control vs TDP-43-Knockdown Neurons

(Takeuchi et al. under revision, Patent Pending)



GRM5 Inhibition Rescues Neurite Outgrowth in TDP-43-Deficient Neurons