News Release

Title

The SYNGAP1 3'UTR variant in ALS patients causes aberrant SYNGAP1 splicing and dendritic spine loss by recruiting HNRNPK

Key Points

・The novel *SYNGAP1* 3'UTR variant was identified from Japanese ALS cohort.

・This variant caused aberrant splicing of SYNGAP1 and dendritic spine loss via excessive recruitment of RNA-binding proteins.

・Excessive recruitment of RNA-binding proteins could be the novel therapeutic target of ALS.

Summary

A group of researchers, Dr. Satoshi Yokoi, Prof. Masahisa Katsuno (Department of Neurology, Nagoya University Graduate School of Medicine), Dr. Gen Sobue (President, Aichi Medical University) and Prof. Yohei Okada (Division of Neural iPSC, Research Institute for Medical Science of Aging, Aichi Medical University) and have revealed novel pathogenic mechanism of amyotrophic lateral sclerosis (ALS) by using induced pluripotency stem cell (iPSC)-derived motor neurons.

The novel Synaptic Ras-GTPase activating protein 1 (*SYNGAP1*) 3'UTR variant was identified from a multicenter cohort in Japan. Human induced pluripotent stem cell (hiPSC)-derived motor neurons with the *SYNGAP1* variant showed aberrant *SYNGAP1* splicing and dendritic spine loss. Moreover, the *SYNGAP1* variant excessively recruited RNA-binding proteins. Antisense oligonucleotides blocking RNA-binding proteins altered aberrant splicing and ameliorated dendritic spine loss. These data suggest that excessive recruitment of RNA-binding proteins is crucial for spine formation in motor neurons and could be the novel therapeutic target for ALS.

This work was published online in Journal of Neuroscience on October 19, 2022.

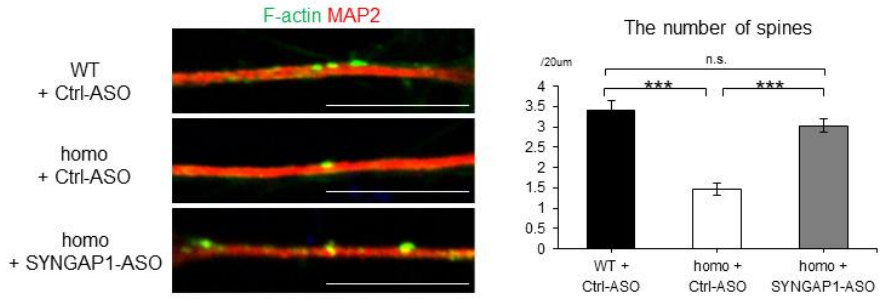
Research Background

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by rapid progression of upper and lower motor neuron loss, which causes paralysis and death within an average of 3-4 years from disease onset. There is no curative treatment for ALS. While RNA-binding proteins have been elucidated to be pathogenic factors of ALS, it is not yet known which RNAs cause the pathogenesis of ALS. We previously reported that Fused in sarcoma (FUS), a pathogenic RNA-binding protein in ALS, stabilizes Syngap1 mRNA at its 3'UTR and maintains dendritic spine maturation. The aim of this study is to elucidate whether this mechanism is crucial for ALS.

Research Results

The novel *SYNGAP1* 3'UTR variant was identified from a multicenter cohort in Japan. Human induced pluripotent stem cell (hiPSC)-derived motor neurons with the *SYNGAP1* variant showed aberrant splicing, increased isoform α1 levels, and decreased isoform γ levels, which caused dendritic spine loss. Moreover, the *SYNGAP1* variant excessively recruited Fused in sarcoma (FUS) and heterogeneous nuclear ribonucleoprotein K (HNRNPK), and antisense oligonucleotides blocking HNRNPK altered aberrant splicing and ameliorated dendritic spine loss (Figure 1).

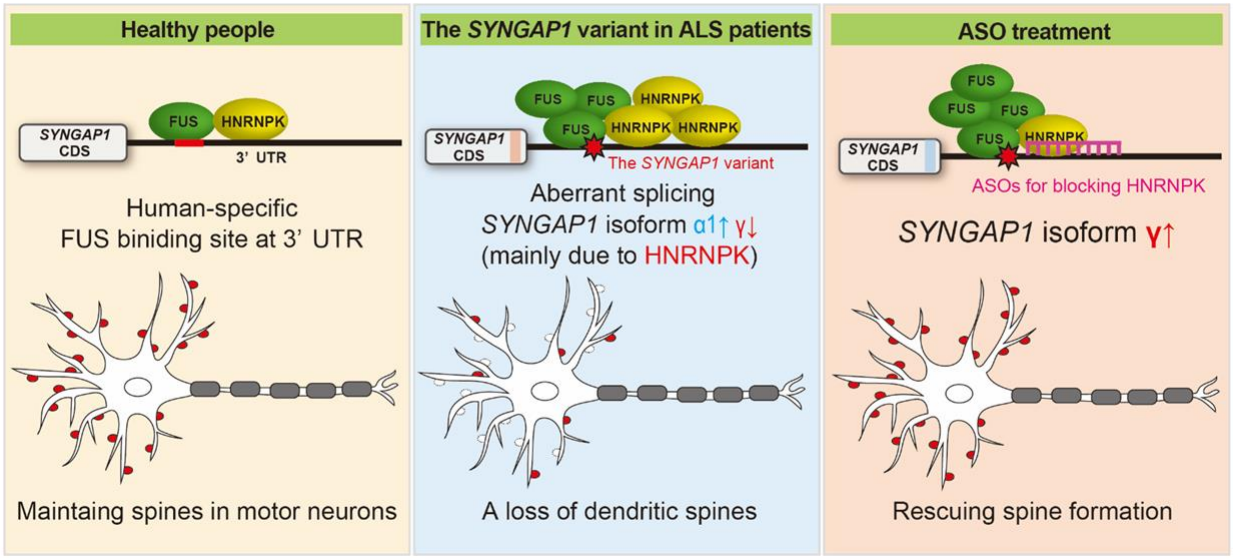
Figure 1:
Antisense oligonucleotides blocking HNRNPK could ameliorate dendritic spine loss in iPSC-derived motor neurons with SYNGAP1 variant.



Research Summary and Future Perspective

Our findings that dendritic spine loss is due to excess recruitment of RNA-binding proteins provide a basis for the future exploration of ALS-related RNA-binding proteins (Figure 2). This precise mechanism could be useful to generate curative treatment for ALS.

Figure 2: A graphical summary of this study



Publication

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