

## News Release

### **Title: Aberrant interaction between FUS and SFPQ in neurons of a wide-range of FTLD spectrum diseases**

#### **Key Points**

- Disruption of the FUS-SFPQ interaction was observed in a wide-range of FTLD spectrum diseases.
- Imbalanced ratio of tau isoforms regulated by FUS/SFPQ was observed in a wide-range of FTLD spectrum diseases as well.
- These results were not observed in Alzheimer disease, or Pick disease, indicating that impaired interactions of FUS/SFPQ is a common pathogenesis in FTLD spectrum diseases.

#### **Summary**

Fused in sarcoma (FUS) is genetically and clinicopathologically linked to frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). We have previously reported that intranuclear interactions of FUS and Splicing factor, proline- and glutamine-rich (SFPQ) contribute to neuronal homeostasis. Disruption of the FUS-SFPQ interaction leads to an increase in the ratio of 4-repeat tau (4R-tau)/3-repeat tau (3R-tau), which manifests in FTLD-like phenotypes in mice. Here, we examined FUS-SFPQ interactions in 142 autopsied individuals with FUS-related ALS/FTLD (ALS/FTLD-FUS), TDP-43-related ALS/FTLD (ALS/FTLD-TDP), progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD), Alzheimer disease (AD), or Pick disease (PiD) as well as controls. Immunofluorescent imaging showed impaired intranuclear colocalization of FUS and SFPQ in neurons of ALS/FTLD-FUS, ALS/FTLD-TDP, PSP, and CBD cases, but not in AD and PiD cases. Immunoprecipitation analyses of FUS and SFPQ revealed reduced interactions between the two proteins in ALS/FTLD-TDP and PSP cases, but not in those with AD. Furthermore, the ratio of 4R/3R-tau was elevated in cases with ALS/FTLD-TDP and PSP, but was largely unaffected in cases with AD. We concluded that impaired interactions between intranuclear FUS and SFPQ and the subsequent increase in the ratio of 4R/3R-tau constitute a common pathogenesis pathway in FTLD spectrum diseases.

#### **Research Background**

Fused in sarcoma (FUS), Transactive response (TAR) DNA-binding protein 43 (TDP-43), and tau are known pathologic proteins in the frontotemporal lobar degeneration (FTLD) spectrum, including FTLD, amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), and cortico-basal degeneration (CBD). TDP-43 and FUS are causative for ALS and FTLD, which collectively comprise a continuous disease spectrum of multisystem proteinopathies. Using a mouse model, we reported that FUS regulates alternative splicing of tau proteins in coordination with Splicing factor, proline- and glutamine-rich (SFPQ). Under normal conditions, the two proteins form a high-molecular-weight complex in the nucleus. Disease-associated mutations in FUS gene, however, disrupt formation of the complex resulting in unregulated

alternative splicing of tau, a disproportional increase in the 4R-tau/3R-tau ratio, and eventually neurodegeneration.

### **Research Results**

We examined FUS-SFPQ interactions in 142 autopsied individuals with FUS-related ALS/FTLD (ALS/FTLD-FUS), TDP-43-related ALS/FTLD (ALS/FTLD-TDP), progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD), Alzheimer disease (AD), or Pick disease (PiD) as well as controls. Immunofluorescent imaging showed impaired intranuclear colocalization of FUS and SFPQ in neurons of ALS/FTLD-FUS, ALS/FTLD-TDP, PSP, and CBD cases, but not in AD and PiD cases. Immunoprecipitation analyses of FUS and SFPQ revealed reduced interactions between the two proteins in ALS/FTLD-TDP and PSP cases, but not in those with AD. Furthermore, the ratio of 4R/3R-tau was elevated in cases with ALS/FTLD-TDP and PSP, but was largely unaffected in cases with AD.

### **Research Summary and Future Perspective**

Our results indicate that interactions between FUS and SFPQ are impaired in the neuronal nuclei of FTLD-spectrum disorders associated with FUS, TDP-43, and 4R-tau, but not in AD. This study provides evidence for impaired intranuclear FUS-SFPQ interactions in FTLD-spectrum diseases associated with FUS, TDP-43, and 4R-tau, but not in AD or PiD. The results suggest a specific and common pathogenic process across FTLD spectrum diseases other than neuronal inclusions.

### **Publication**

Ishigaki S, Riku Y, Fujioka Y, Endo K, Iwade N, Kawai K, Ishibashi M, Yokoi S, Katsuno M, Watanabe H, Mori K, Akagi A, Yokota O, Terada S, Kawakami I, Suzuki N, Warita H, Aoki M, Yoshida M, Sobue G. Aberrant interaction between FUS and SFPQ in neurons of a wide-range of FTLD spectrum diseases. *Brain*, published online on August 7th, 2020. DOI: 10.1093/brain/awaa196.

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