Deciphering the effect of FUS mutations on motor neuron axonal pathology in ALS

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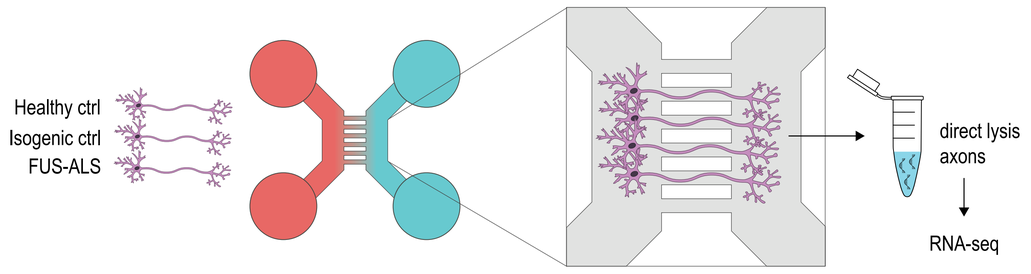
Background

- The **most aggressive form of amyotrophic lateral sclerosis** (ALS) is caused by mutations in ***Fused in Sarcoma (FUS)***
- FUS is a **RNA binding protein** involved in RNA metabolism
- **Pathological hallmarks** of FUS-ALS are **mislocalization** of FUS from the nucleus to the cytoplasm and **FUS-positive inclusions**
- **Functional consequences** of mutations in *FUS* **are still poorly understood**

Aim To reveal the effect of FUS-ALS mutations on the motor neuron axonal transcriptome

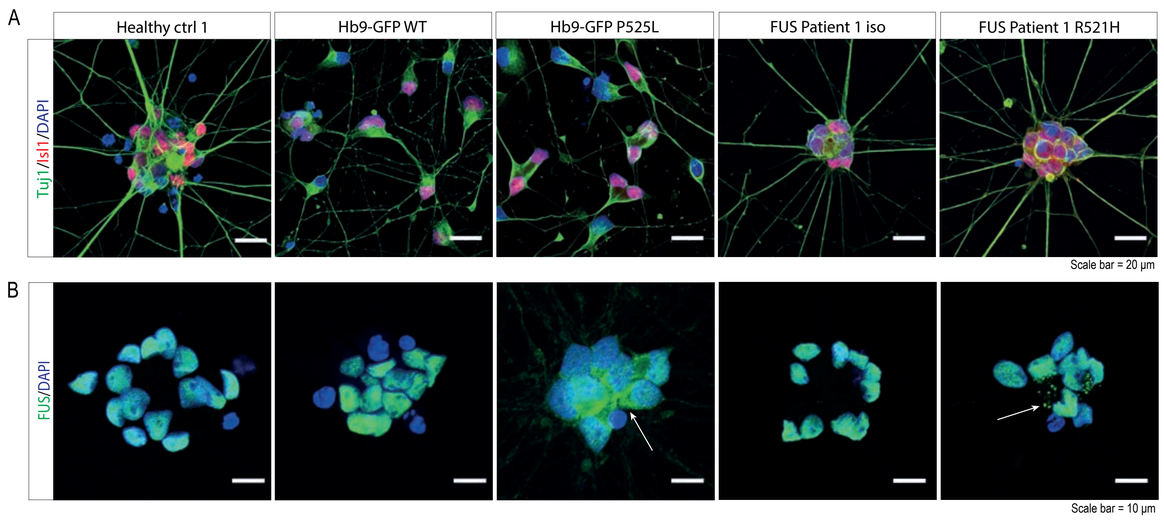
Method

- Motor neurons are generated from **FUS-ALS patient- and healthy ctrl-derived induced pluripotent stem cells** (iPSCs)
- ALS vs ctrl motor neurons are cultured in **compartmentalized microfluidic devices**
- **Axonal RNA** is isolated and sequenced

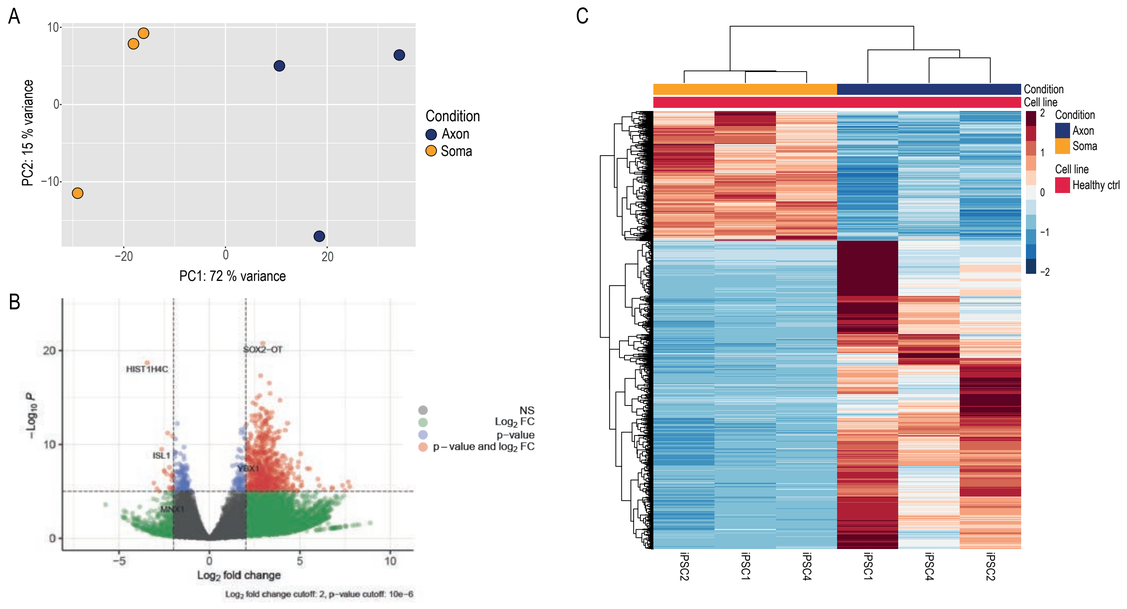


Results

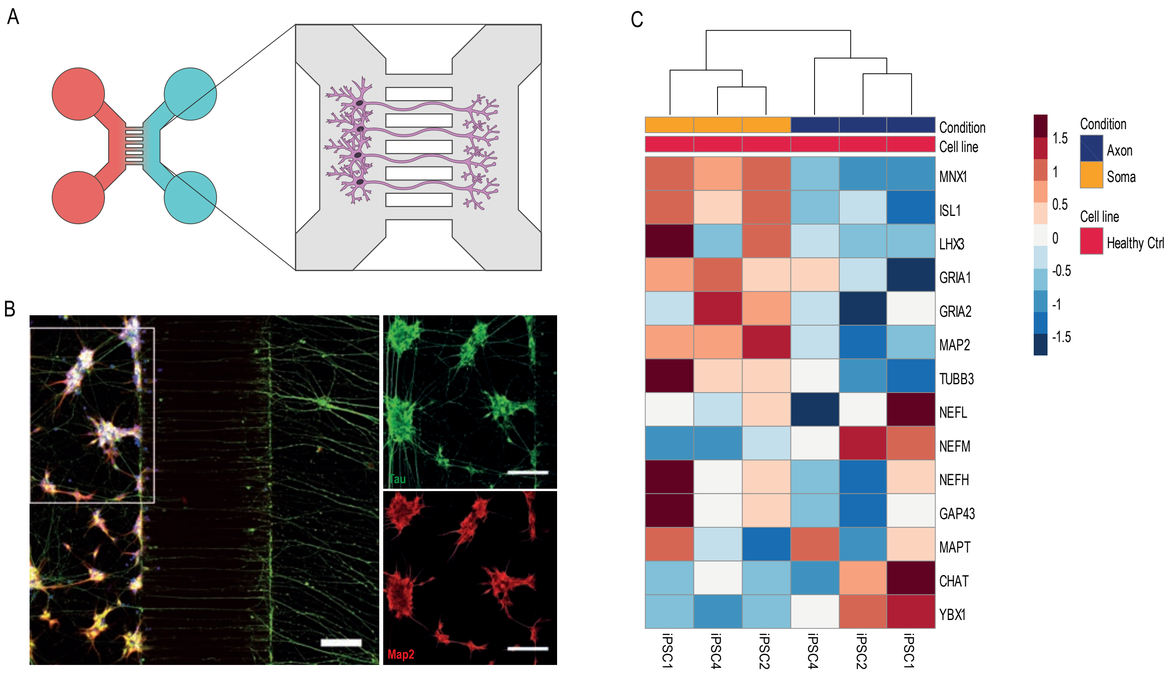
Mutant iPSC-derived motor neurons show cytoplasmic mislocalization of FUS



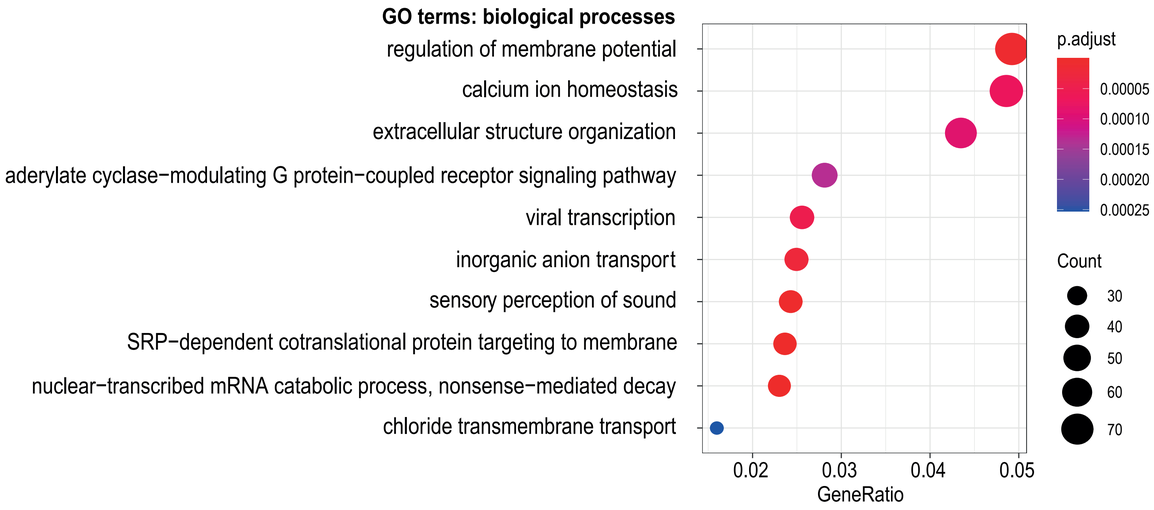
Motor neuron axons do have a distinct transcriptome from somas



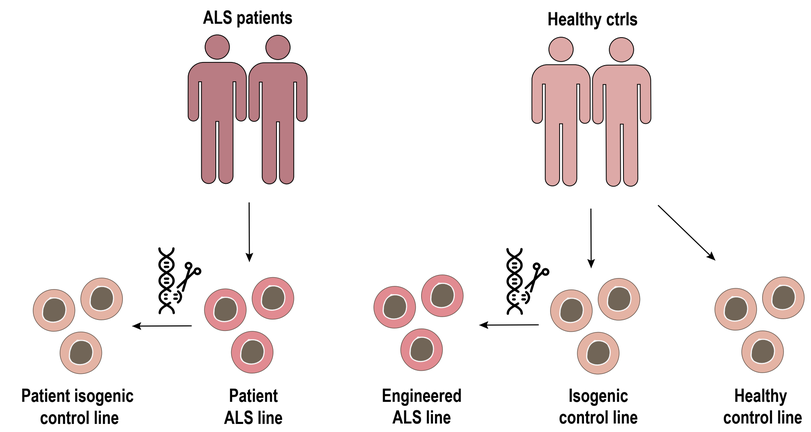
Microfluidic devices enable separation of motor axons from their somas



The axonal transcriptome is defined by ion transport related processes



Next: study design to investigate the axonal transcriptome of FUS-ALS vs ctrl



Conclusions

- **FUS mutant iPSC-derived motor neurons show ALS hallmarks** such as cytoplasmic mislocalization of FUS
- **Compartmentalized microfluidic devices** are a **great technology to study the axonal transcriptome**
- **The axonal transcriptome is distinct from the soma transcriptome** and is defined by **ion transport related processes**

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