



Involvement of inhibitory neurons in amyotrophic lateral sclerosis and frontotemporal dementia linked to Fused in Sarcoma protein

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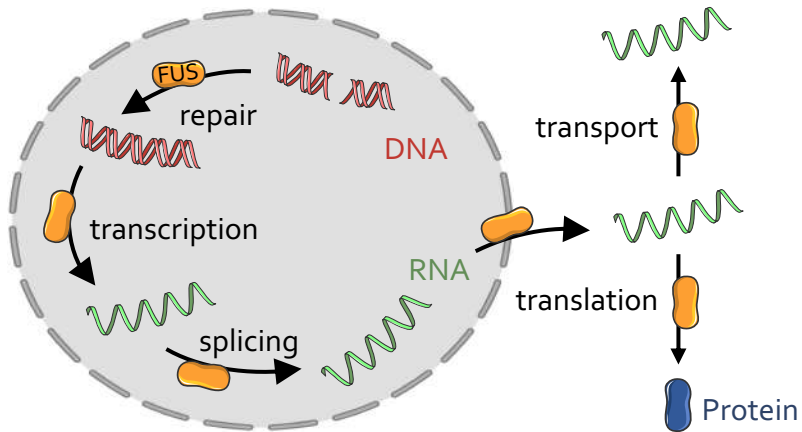
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INTRODUCTION

Fused in Sarcoma (FUS) is an ubiquitous and multifunctional **RNA/DNA-binding protein** involved in cellular functions (see below).



Mutations truncating its nuclear localisation signal (NLS) lead to its **cytoplasmic mislocalisation** in severe and juvenile forms of **amyotrophic lateral sclerosis** (ALS). This delocalisation is also observed in ALS and **frontotemporal dementia** (FTD) patients devoid of *FUS* mutations.

Our laboratory generated mice displaying constitutive and ubiquitous FUS truncation, and subsequent FUS delocalisation. This drove a **mildly progressive motor neurons disease** and **phenotypic features of FTD**². Moreover, **cortical hyperactivity** was associated with molecular and ultrastructural **alterations in cortical inhibitory neurons**^{1,2}.

**WHAT ARE THE ROLE OF INHIBITORY NEURONS
IN ALS-*FUS* AND FTD-*FUS*?**

TWO NEW MOUSE MODELS

We used a Cre-Lox recombination technology to manipulate the **GABAergic system** in *Fus* knock-in mice. These new models will be validated and used to understand the underlying mechanisms linked to FUS truncation.

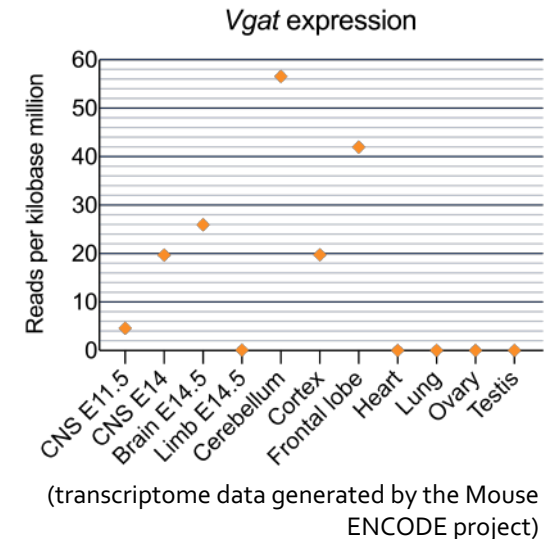
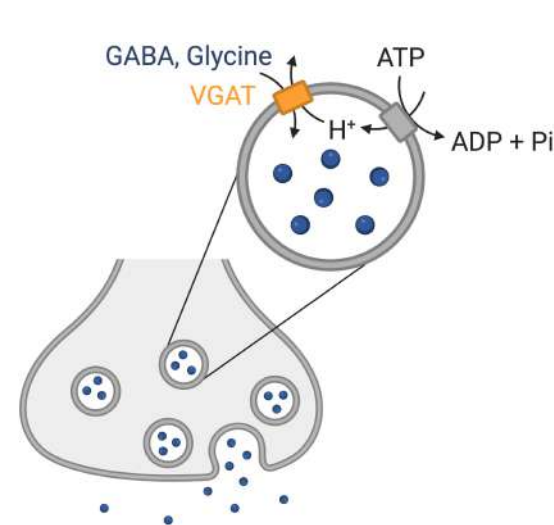
1/ Targeting Cre expression in inhibitory neurons

Vgat-Cre



B6J.129S6(FVB)-*Slc32a1*^{tm2(cre)Lowl} / MwarJ
Stock No: 028862 | Vgat-ires-cre knock-in (C57BL/6J)

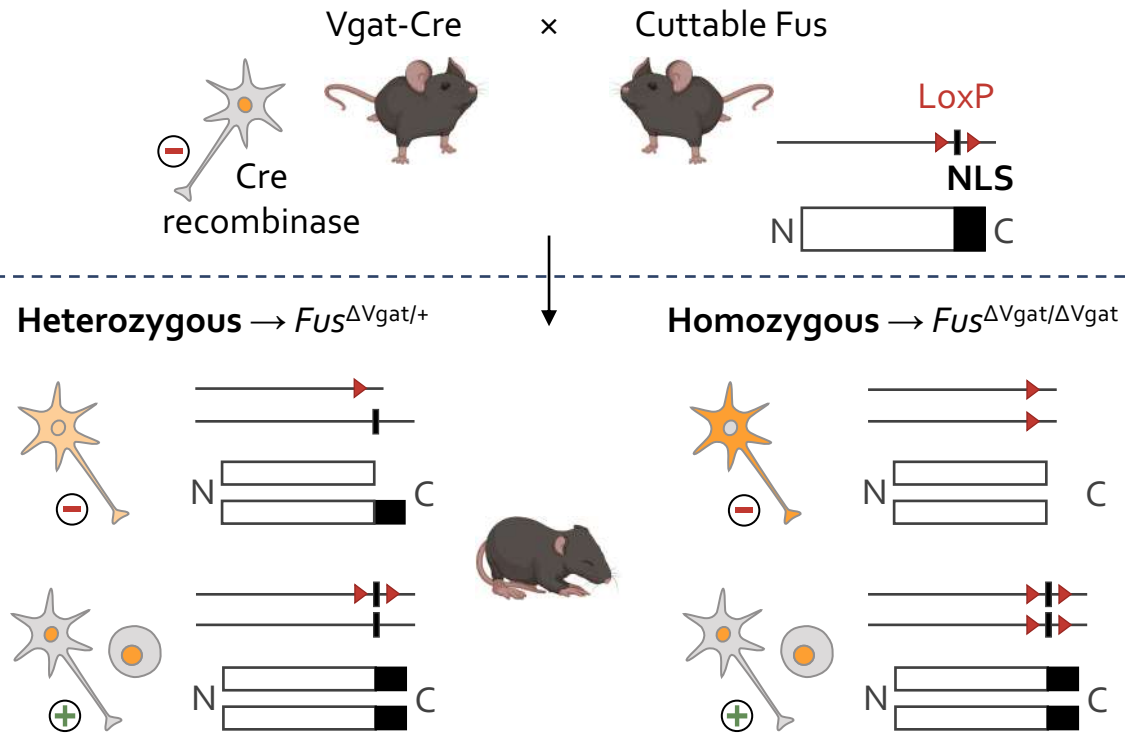
- Cre activity consistent with previous reports of *Vgat* expression
- *Vgat* expressed by a great majority of inhibitory neurons



- *Vgat* expressed during the embryonic development

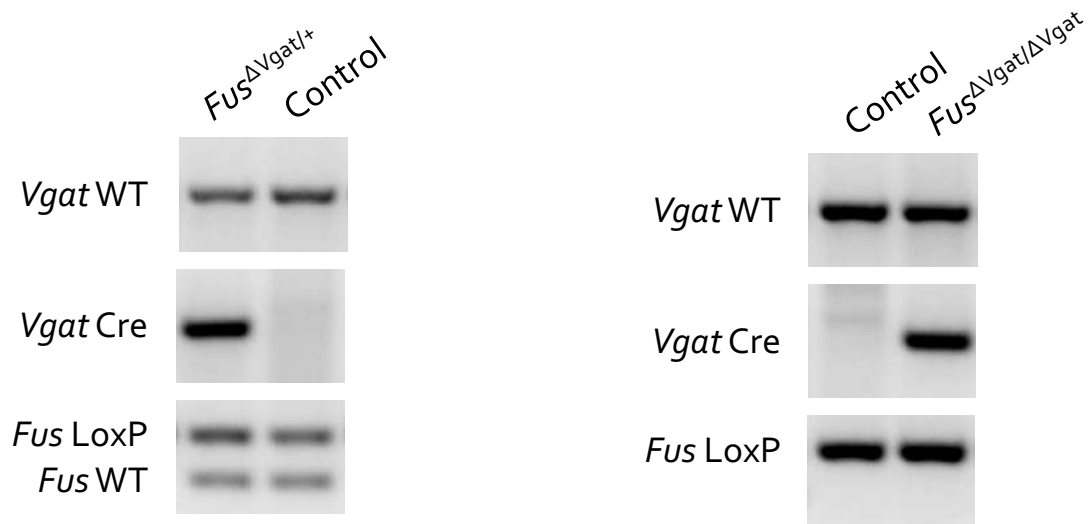
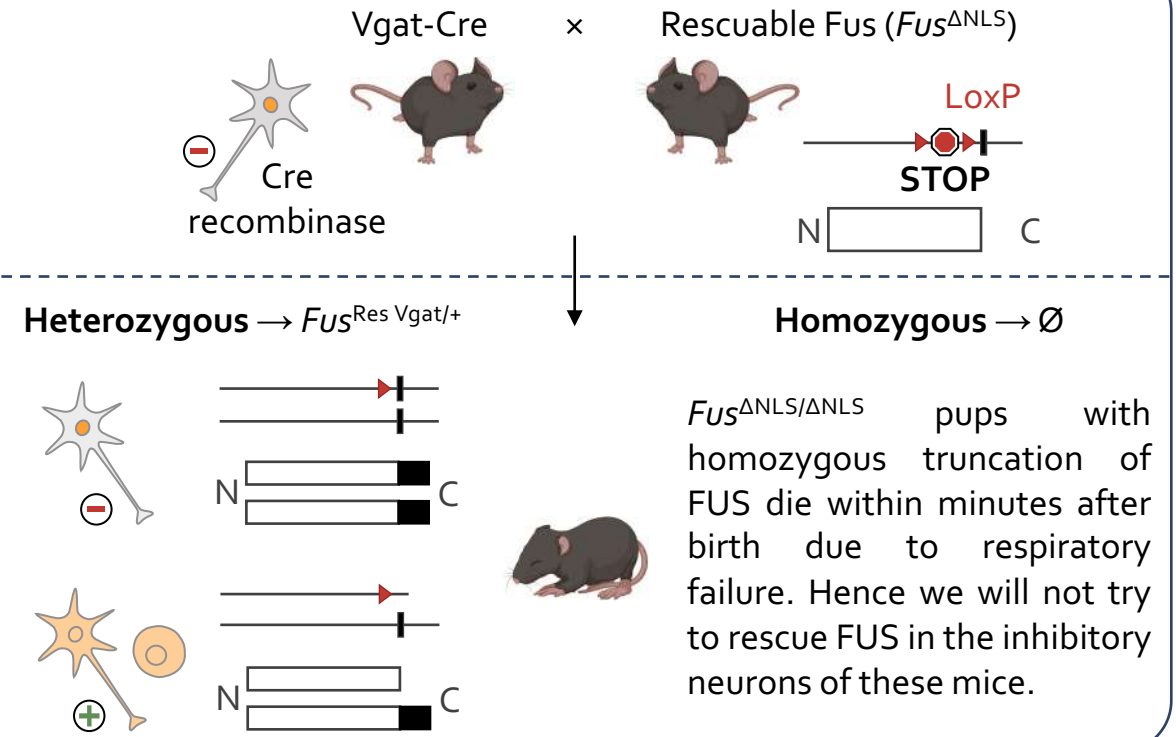


2/ Truncate FUS in inhibitory neurons



VS

3/ Truncate FUS in every cell except inhibitory neurons



MODELS VALIDATION

- Recombination efficiency
- Subcellular localisation of FUS



- Cre expression → Vgat-Cre x Cre Reporter (Rosa Td Tomato)

Preliminary results: Tomato expression is visible on the external surface of the olfactory bulbs and cerebellum while it is not the case for other tissues.

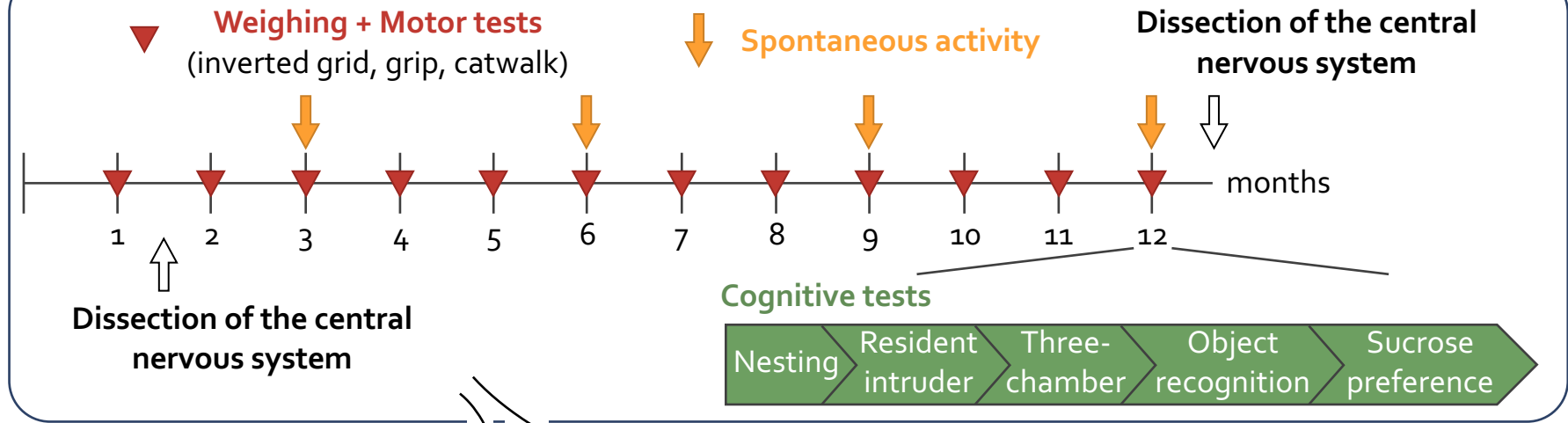
EFFECTS OF FUS TRUNCATION IN HETEROZYGOUS MICE

Preliminary results

Fus^{ΔVgat/+} and *Fus*^{Res Vgat/+} mice are **viable**. Our older mice are 6 months old. For the moment, they do not exhibit obvious physical abnormalities.

Fus^{ΔVgat/+} are **fertile** and show a mean productivity index of seven pups per female.

Perspectives - Longitudinal study



Molecular level

- Alterations of genes transcription

Cellular level

- Loss of neurons and/or functional synapses
- ALS pathological hallmarks
- Neuronal activity (Dr Sabine LIEBSCHER)

EFFECTS OF FUS TRUNCATION IN HOMOZYGOUS MICE

Preliminary results

Fus^{ΔVgat/ΔVgat} are born without obvious physical abnormalities but the vast majority of them **die before weaning**. We are currently defining the average age at death and will then investigate the death's cause.



REFERENCES

¹Sahadevan, *et al.* (2021) Synaptic FUS accumulation triggers early misregulation of synaptic RNAs in a mouse model of ALS. *Nature Communications* 12, 3027.

²Scekic-Zahirovic, Sanjuan-Ruiz, *et al.* (2021) Cytoplasmic FUS triggers early behavioural alterations linked to cortical neuronal hyperactivity and inhibitory synaptic defects. *Nature Communications* 12, 3028.