e-JR7 SLA MNM

7èmes Journées de la Recherche SLA/MNM

Identifying motor unit specific alterations in a FUS deletion mutant zebrafish model

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FILSLAN Filière de Santé Maladies Rares Sclérose Latérale Amyotrophique et Maladies du Neurone Moteur — filière de santé maladies rares

ARSLA Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres Maladies du Motoneurone

AGENCE NATIONALE DE LA RECHERCHE ANR

Inserm

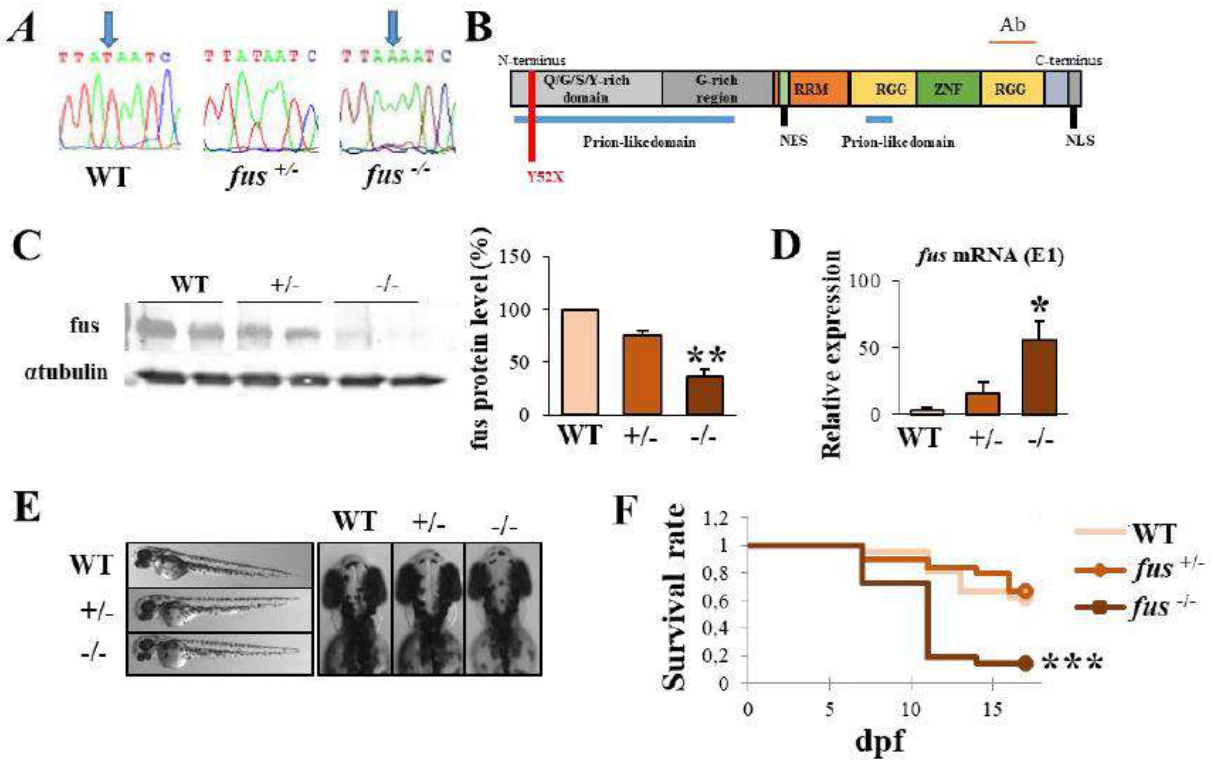
imagine INSTITUT DES MALADIES GÉNÉTIQUES

Université de Paris

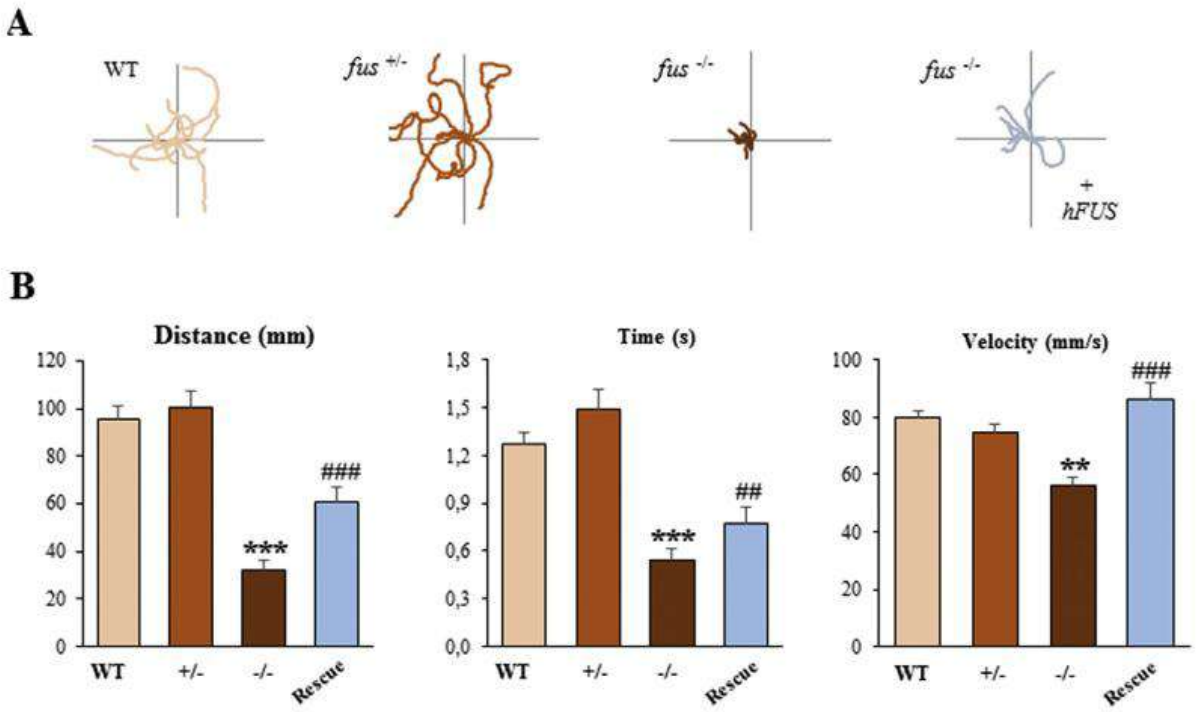
Chiara Guerrera ,**Proteomic Platform Necker**

Ivan Nemazanyy, **Plateforme d'étude du métabolisme Necker**

❑ Characterization and phenotypic analysis of a deletion mutant of the unique FUS orthologue in zebrafish



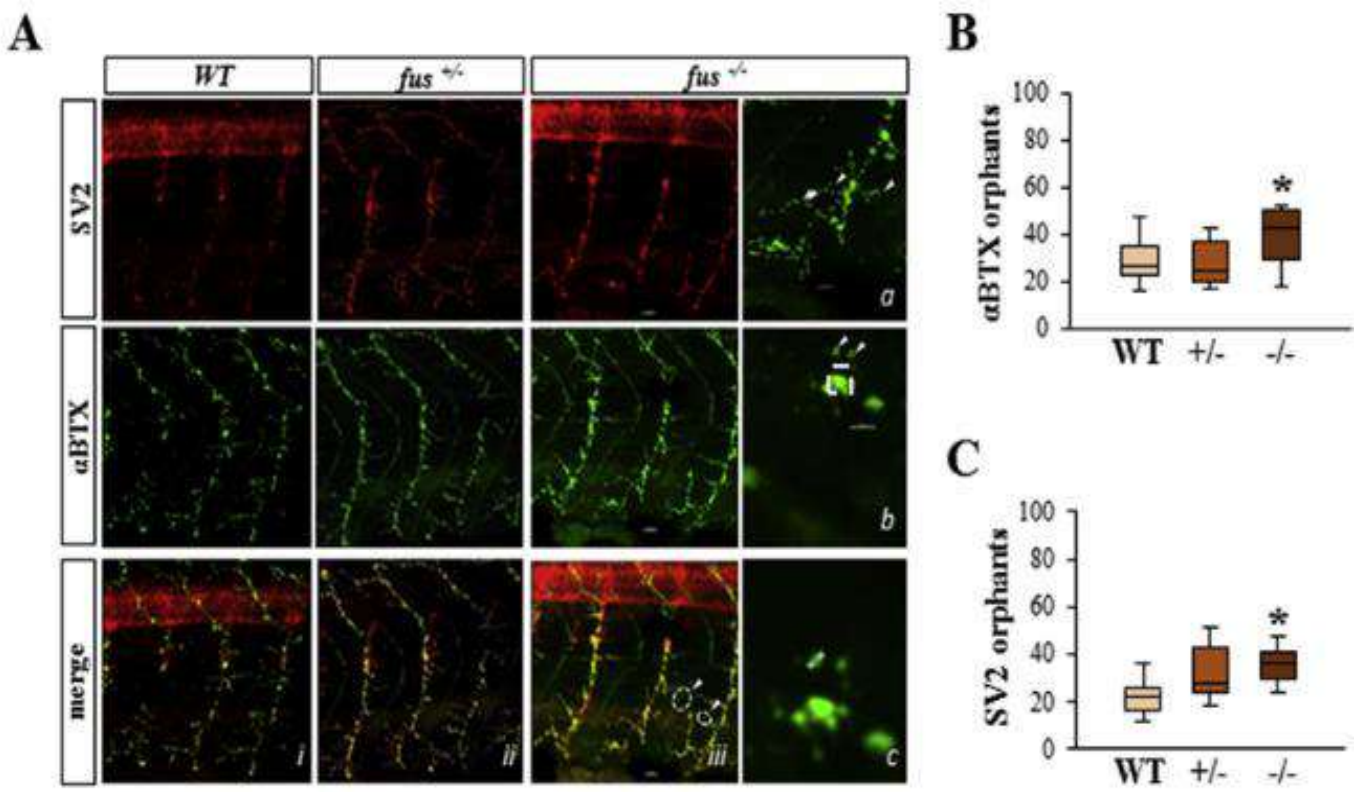
❑ fus deletion causes zebrafish mobility defects at the touch-evoked escape response



- FUS, mutated in ALS patients, encodes for **an RNA-binding protein,** involved in multiple aspects of RNA metabolism
- The majority of FUS mutations are localized in exon 15, which encodes for NLS (**nuclear localization signal**), **causing FUS redistribution into the cytoplasm**
- Our team report for the first time the **generation and phenotypic characterization of a stable zebrafish line mutant for the unique FUS orthologue in zf**
- In this model, **we demonstrated that the loss of its function reduces lifespan of homozygous individuals and leads to motor deficits**

A.-R. Bourefis, et al. Neurobiology of Disease 142 (2020) 104935

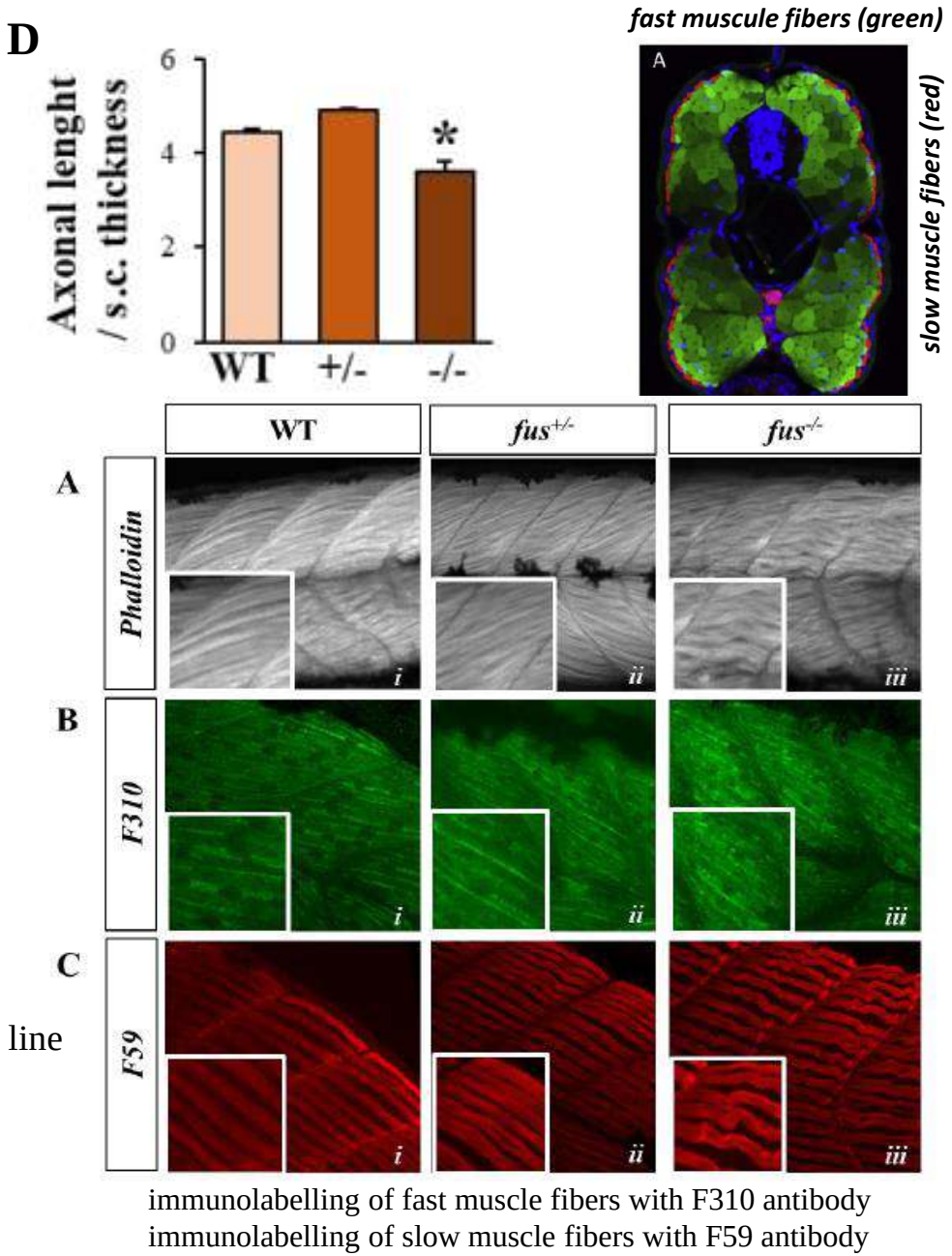
❑ fus LoF (loss of function) causes defects at the zebrafish NMJs



Double labeling of SV2 and alpha_bungarotoxin

- These behavioral deficits were accompanied by **anatomical defects**, including reduced length of **motor neurons and neuromuscular junctions (NMJ) fragmentation**.

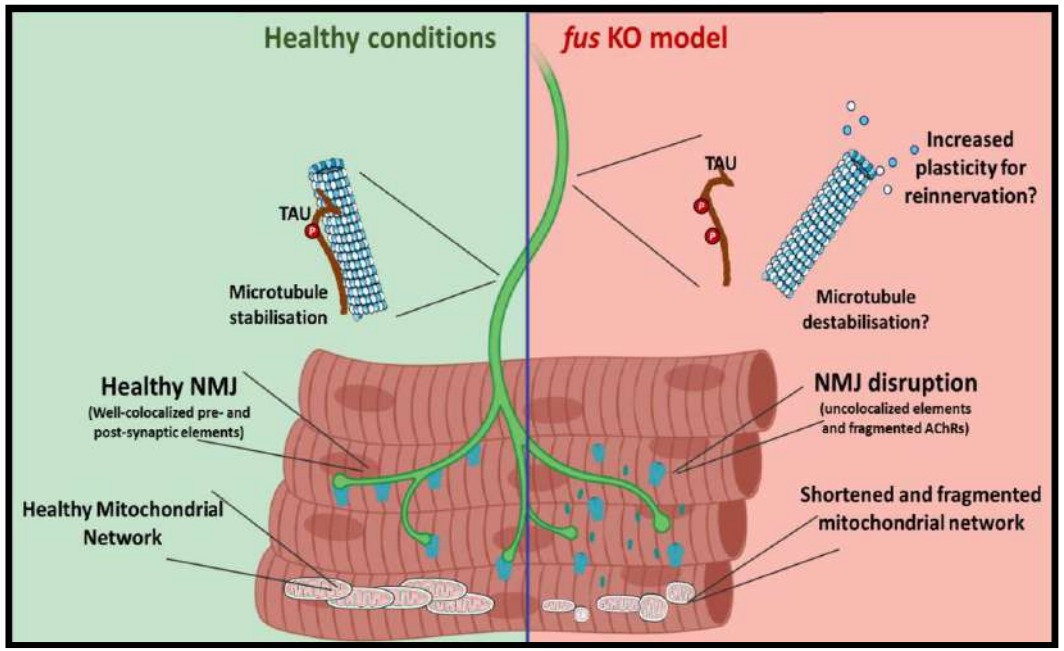
❑ Motor neuron and muscle structure in FUS mutants
fus KO causes slow muscle disorganization



immunolabelling of fast muscle fibers with F310 antibody
immunolabelling of slow muscle fibers with F59 antibody

- **WT and *fus*+/-** conditions displayed well organized muscle structures with typical parallel line pattern.
- ***fus*-/- conditions** showed a disorganized structure with curvy and non-parallel fibers

❑ *Hypothesis of ALS features occurrence in our us KO zebrafish model*



***fus* is KO in zebrafish**, pre- and post-synaptic elements fail to colocalize properly to form functional synapses, with AChRs presenting pathological fragmentations

*This plasticity could depend on enhanced cytoskeletal dynamics involving the microtubules and thus, **modulating tau function as well as tau-related kinases to ensure tau phosphorylation**.*

❑ Perspective and Future Directions

- **Transcriptomic and proteomic sequencing**

identify biomarkers candidates and therapeutic targets in FUS-ALS patients

- Generation **of a specific transgenic line** harboring the *fus* non-sense mutation on a ***hb9:GFP* background**.
- MNs express the GFP (green fluorescent protein) construct, as the *hb9* gene is involved in **MN differentiation**
- Sort through **FACS** (Fluorescence activated cell sorting) the MN and perform specifically the transcriptomic/proteomic analysis
- **Cross compare** our omics analysis with the transcriptomic analysis from FUS knock-out and knock-in mouse models (Luc Dupuis, Strasbourg) and iPSCs and biopises from ALS patients carrying FUS mutations (Alberto Catanese, Ulm University)