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LINE-1 expression and ORF1p interactome in the brain under physiological and pathological conditions

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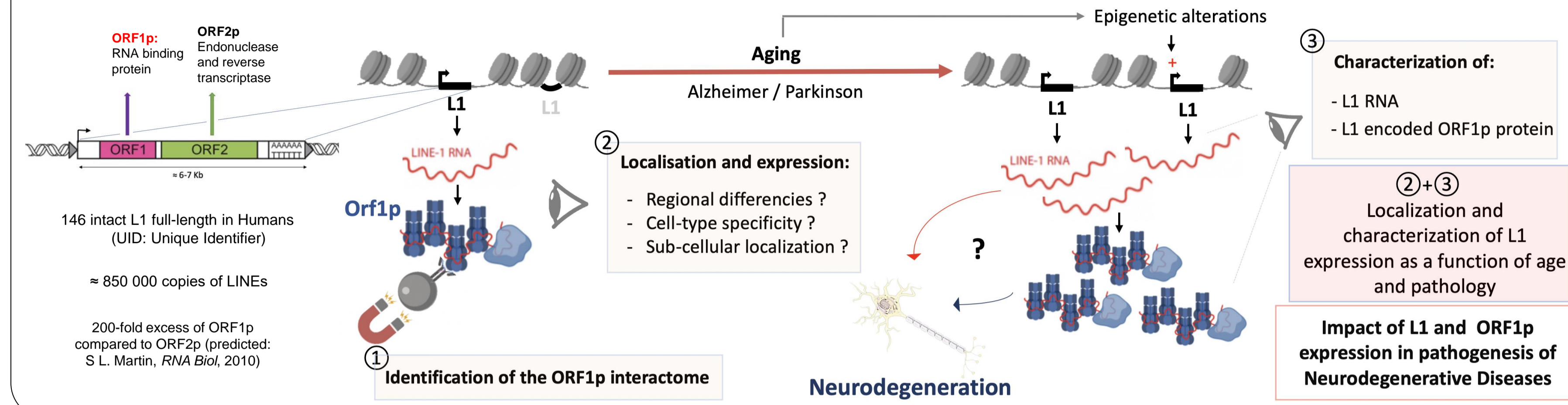
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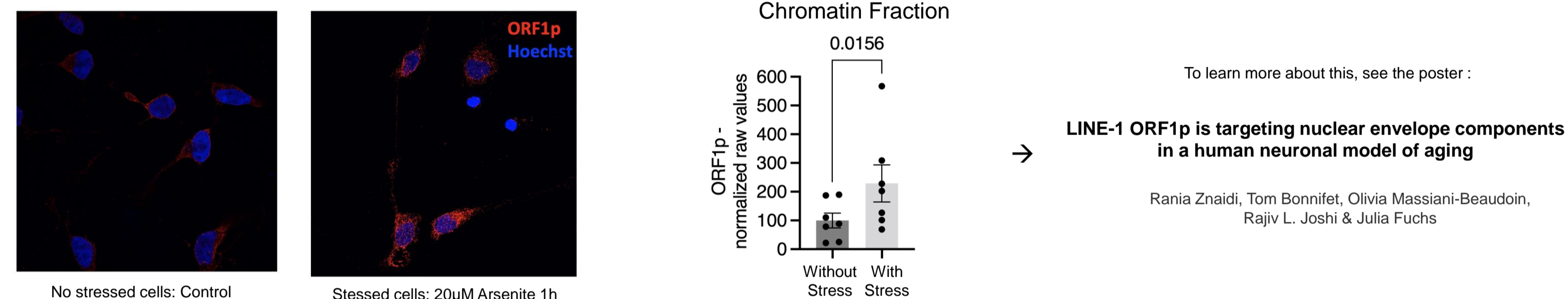
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A role of transposable elements in neurodegenerative diseases ?

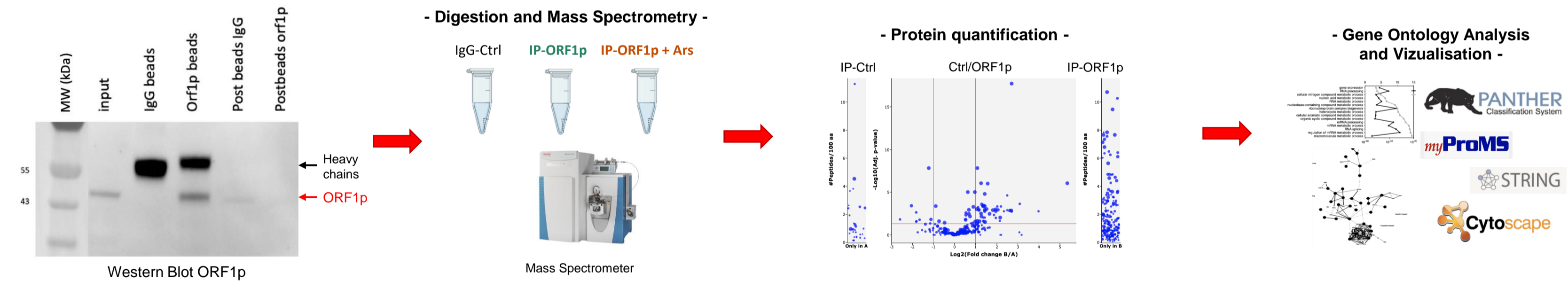


Interactome of the endogenous ORF1p protein in human dopaminergic neurons *in vitro*

ORF1p is present at steady-state and increases upon stress with a dynamic localization to chromatin

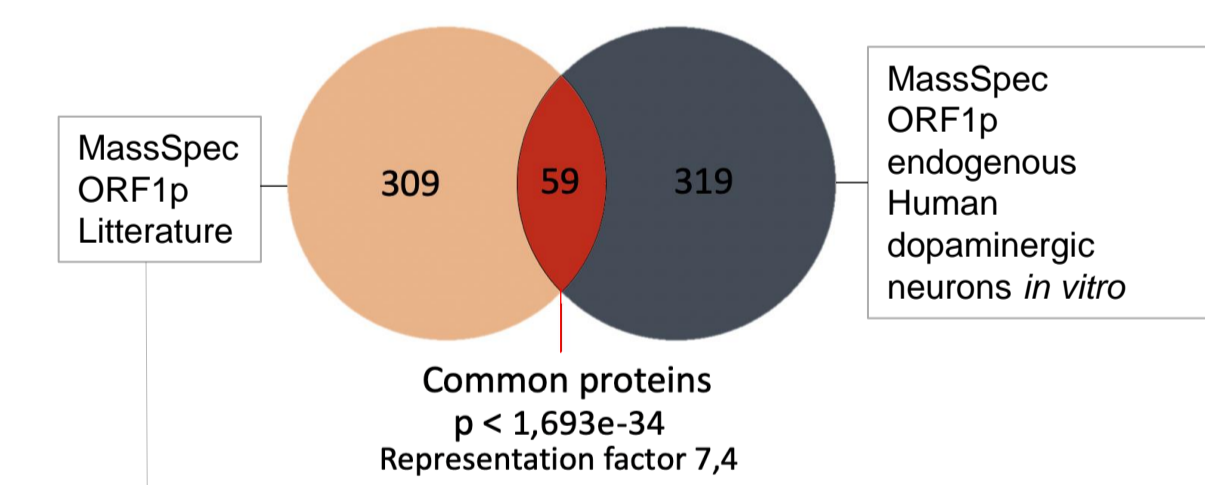


Identification of ORF1p binding proteins upon cellular stress



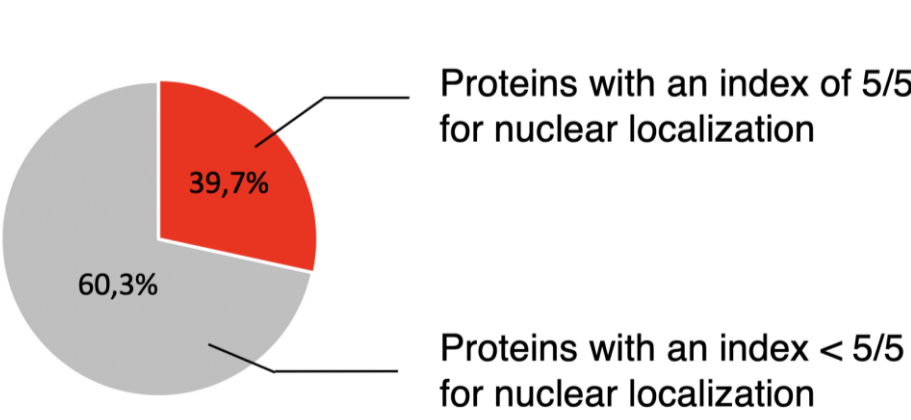
Identification of novel, potentially neuron-specific endogenous ORF1p binding proteins

Comparison with known protein partners of ORF1p in human cancerous cells lines



• J.L. Goodier et al. *Nucleic Acids Res.* 2013
• Taylor et al. *Cell*, 2013
• Moldovan and Moran. *PLoS Genet.* 2015

Proportion of nuclear proteins (COMPARTMENT database)

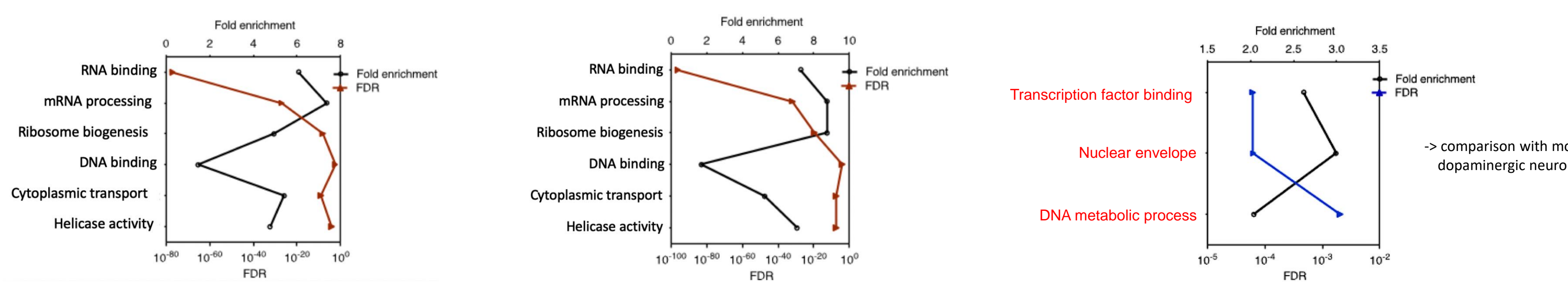


Upon stress, ORF1p recruits proteins related to novel GO categories

GO analysis of the ORF1p network without stress

GO analysis of the ORF1p network with stress

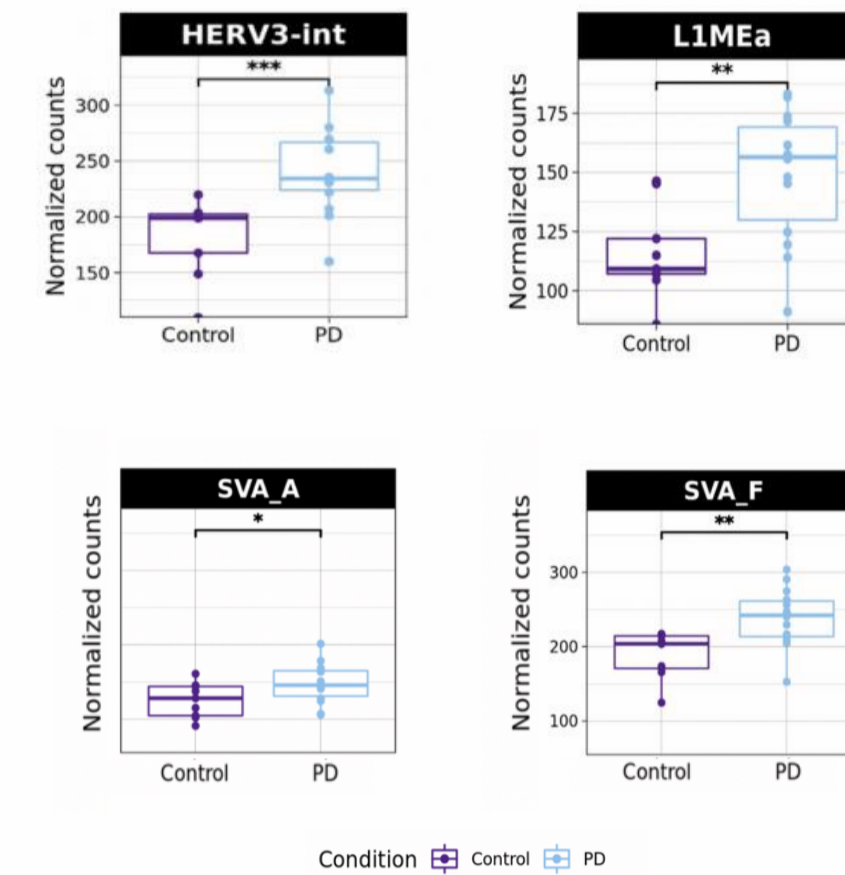
SLIM GO terms emerging upon stress



Differentially Expressed Transposable Elements (DE-TEs) in Parkinson (PD) and Alzheimer's Disease (AD)

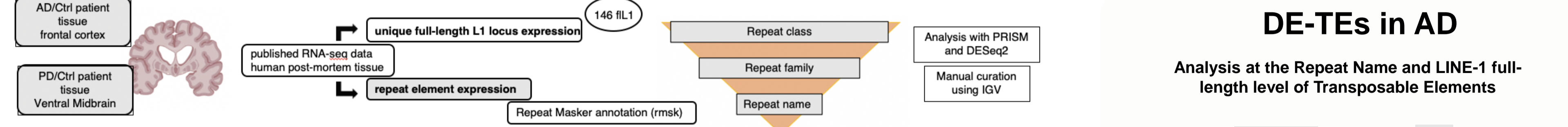
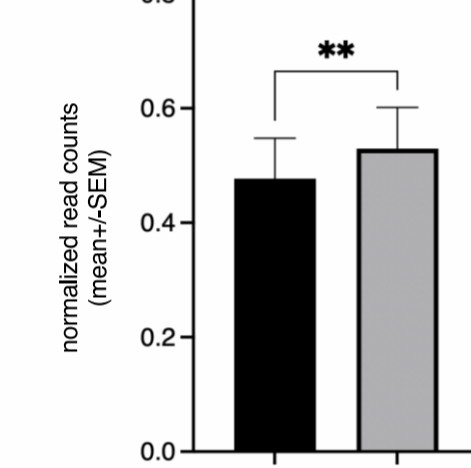
DE-TEs in PD

Analysis at the Repeat Name level of Transposable Elements.



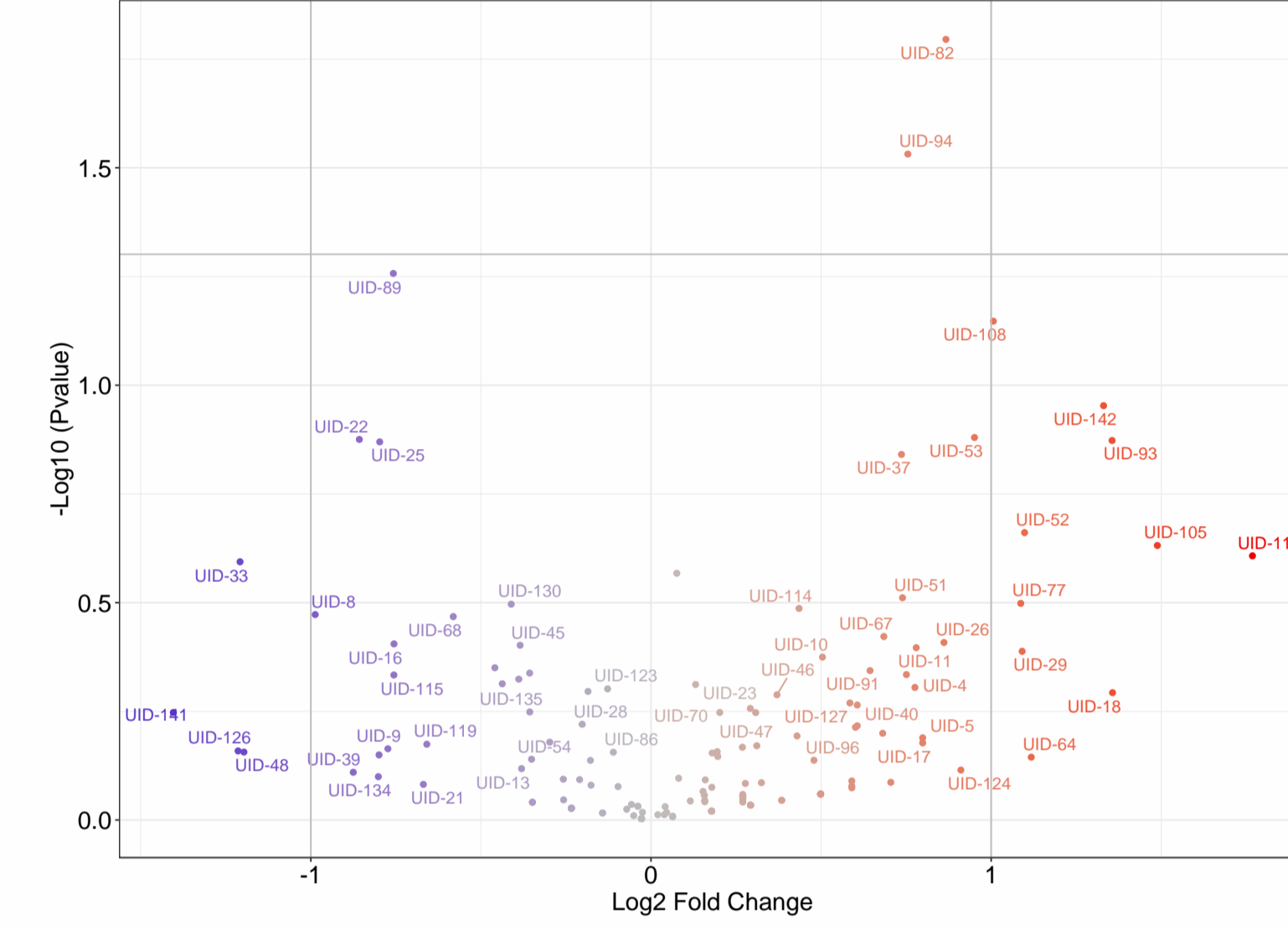
Several TE are up-regulated at the Repeat Name level in the context of Parkinson's Disease.

LINE-1 full-length expression in Control Vs Parkinson



Analysis at the LINE-1 full-length (UID) level of Transposable Elements.

Volcano plot: Differential expression of LINE-1 UID in Parkinson

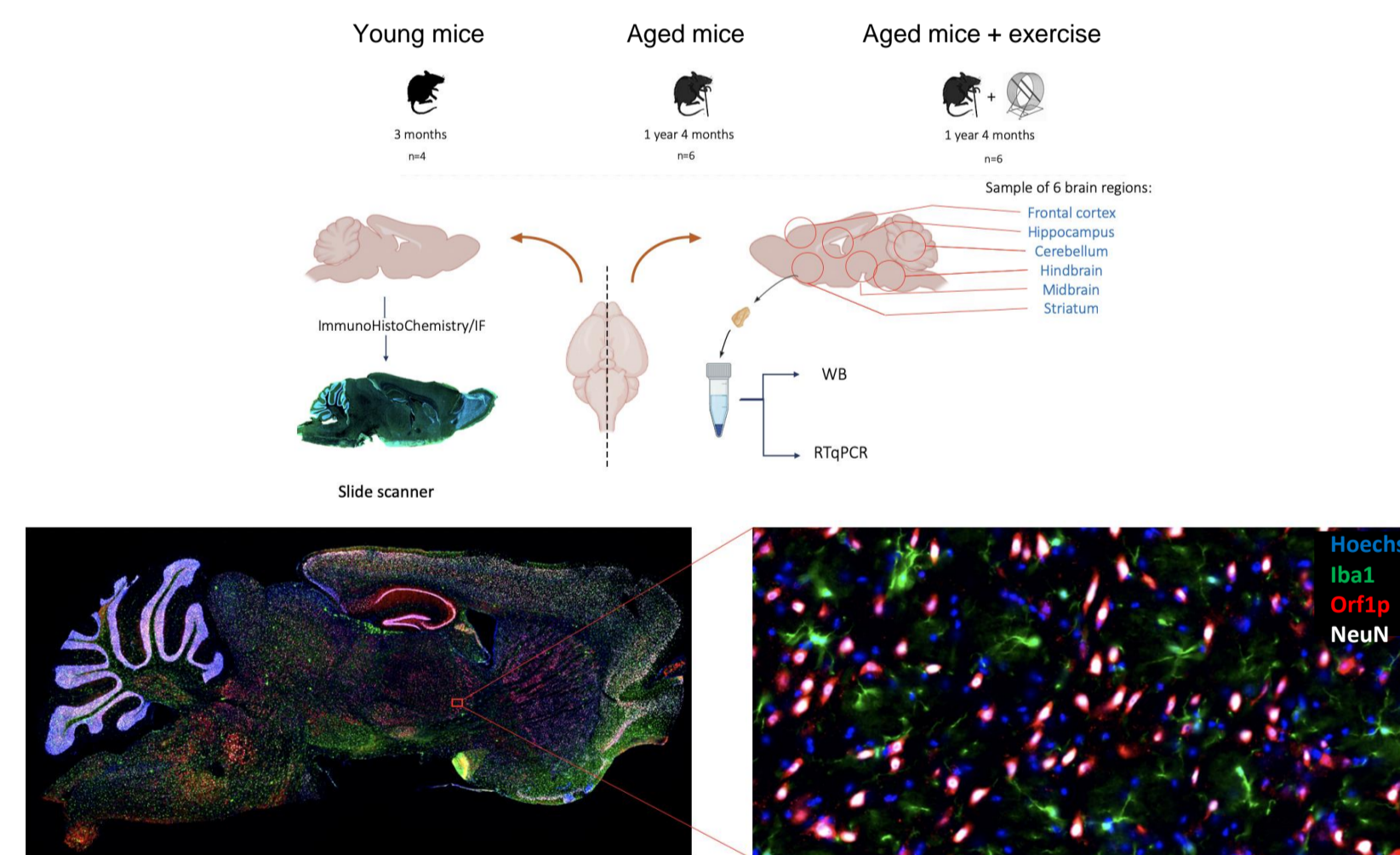


→ dysregulation of specific unique full-length LINE-1 elements in the context of PD.
→ Same conclusion on RNA-seq data from AD tissues with others dysregulated UIDs (see on the right).
→ Intronic UIDs expression is likely due to an autonomous expression of the LINE-1 element.
→ a disease-specific dysregulation of full-length L1 ?

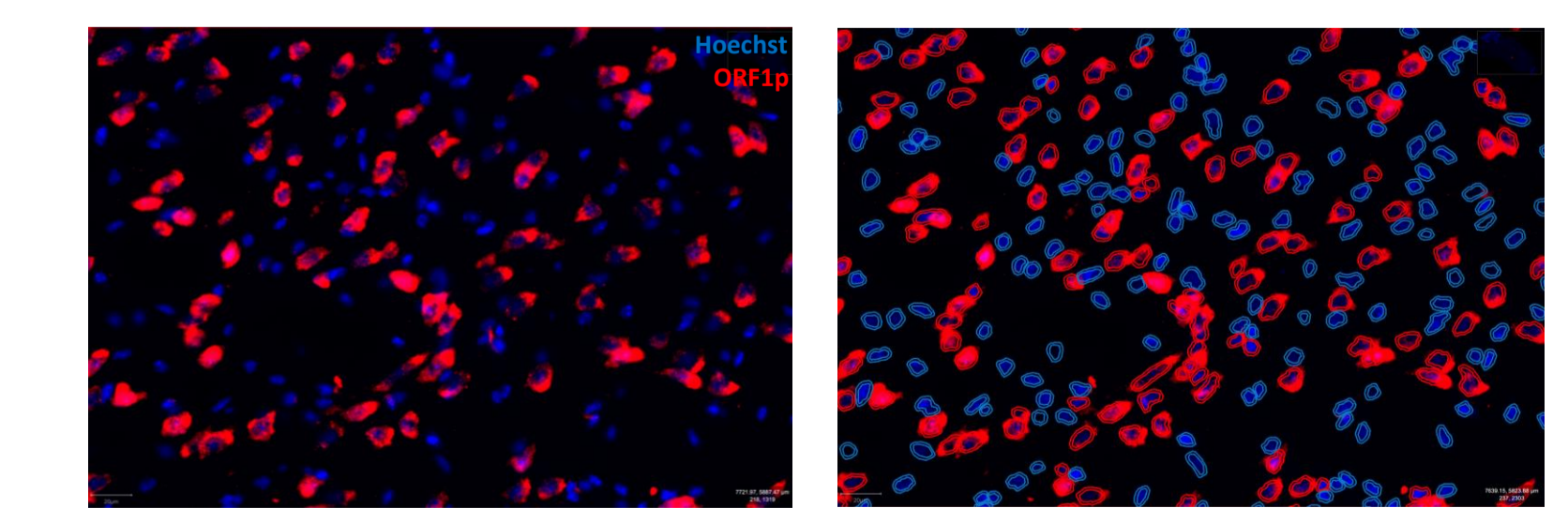
No expression correlation between the host gene (MAG1) and UID-89.

ORF1p expression and localization in the Mouse and Human brain

ORF1p is expressed at steady-state in neurons

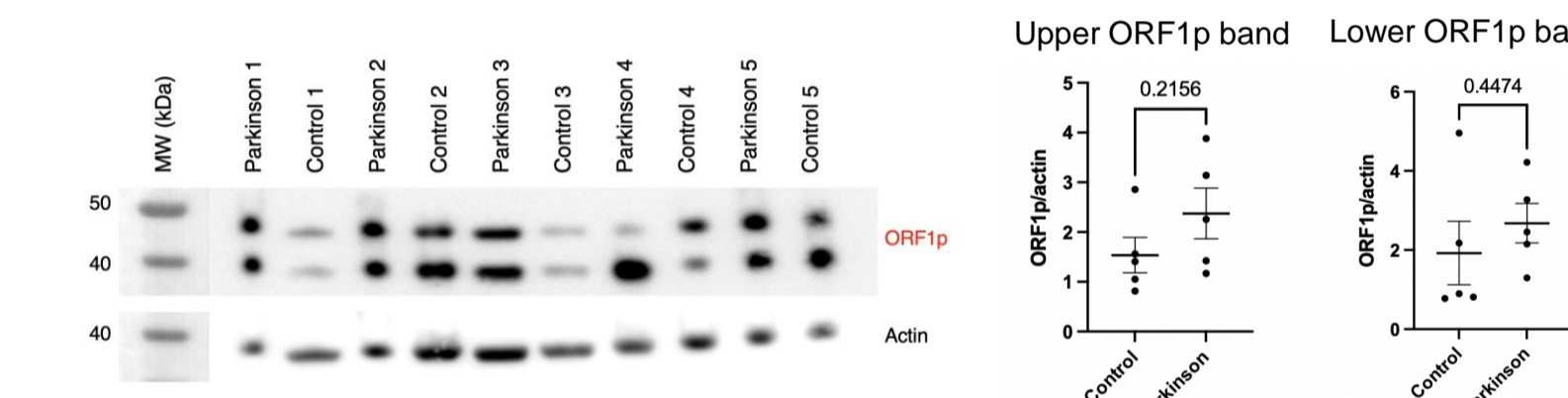


- A basal and widespread expression of ORF1p is observed in neurons across each brain region of young and aged mice (+/- voluntary exercise).
- Analyzing more than 2.5 million cells in total thanks to deep-learning analysis methods on large-scale image acquisition.
- Characterization of ORF1p distribution across neuronal (NeuN) and microglial (Iba1) cells in the mouse brain at the regional, the cell-type and sub-cellular levels in the context of aging.
- Decipher a potential shift/modification of ORF1p distribution in aging at multiple spatial scales.

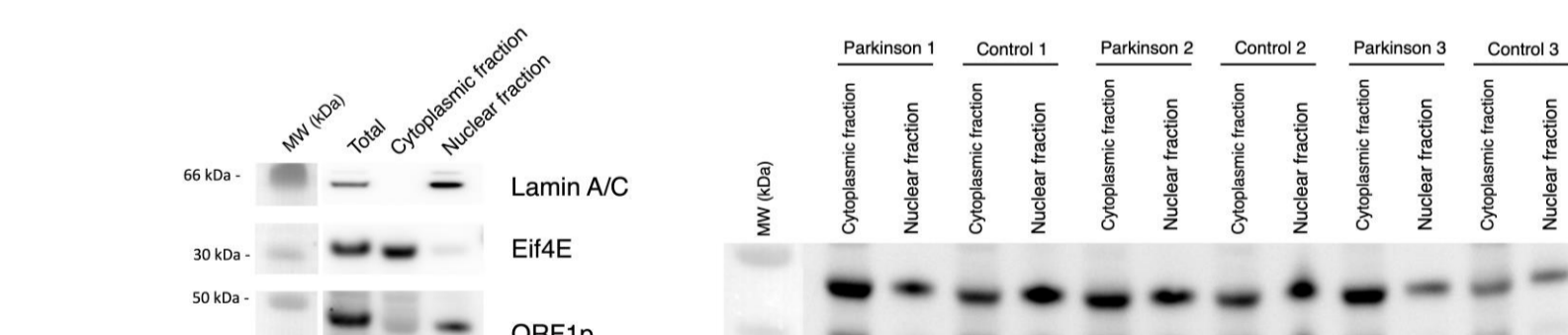


Example of automatic segmentation of each nucleus, and detection of ORF1p positives cells allowing to characterize each cell of the whole sagittal slice

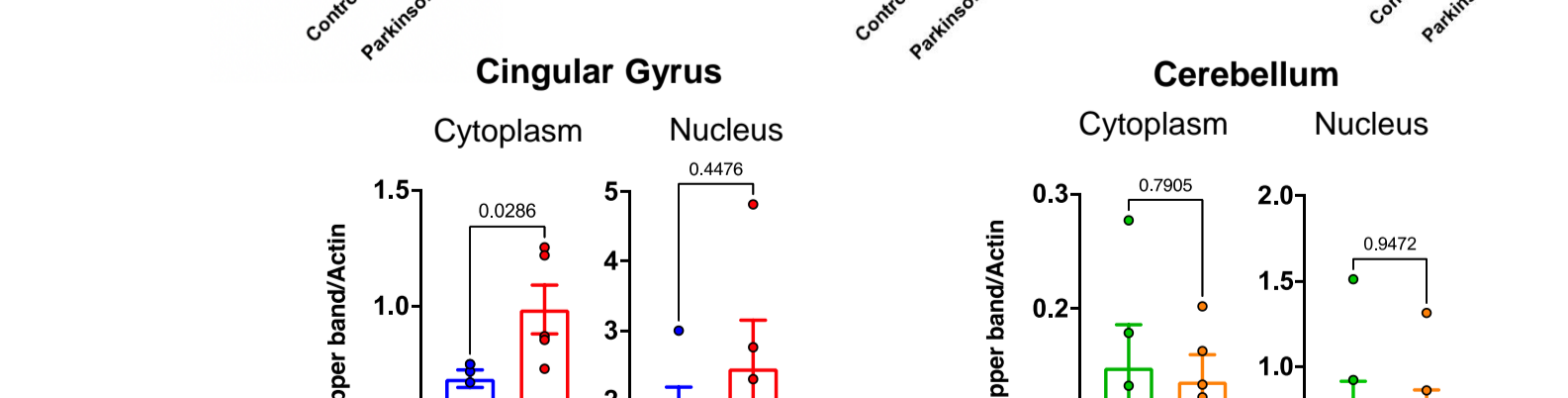
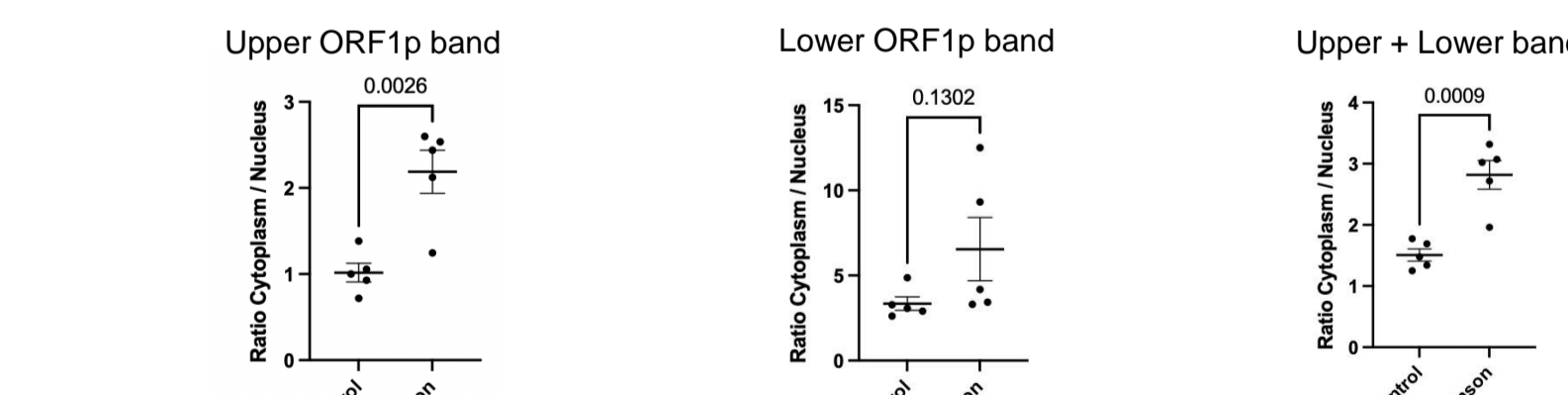
ORF1p expression in healthy and PD individuals



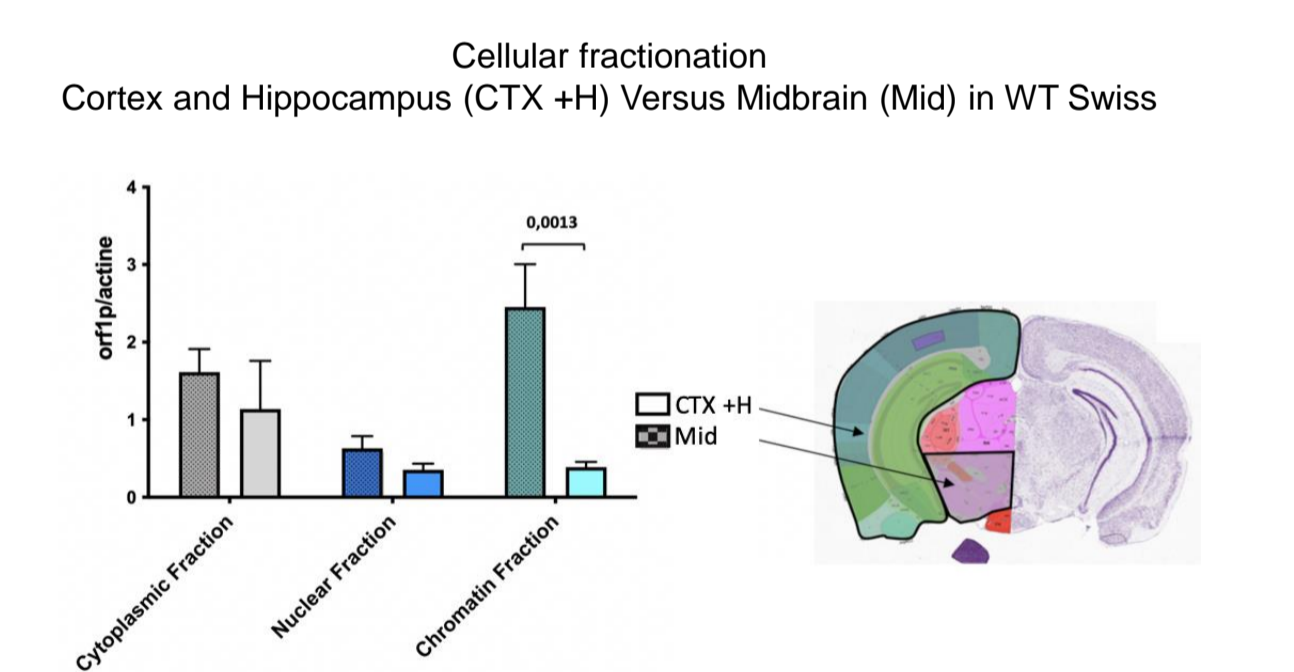
ORF1p is detected in the nucleus



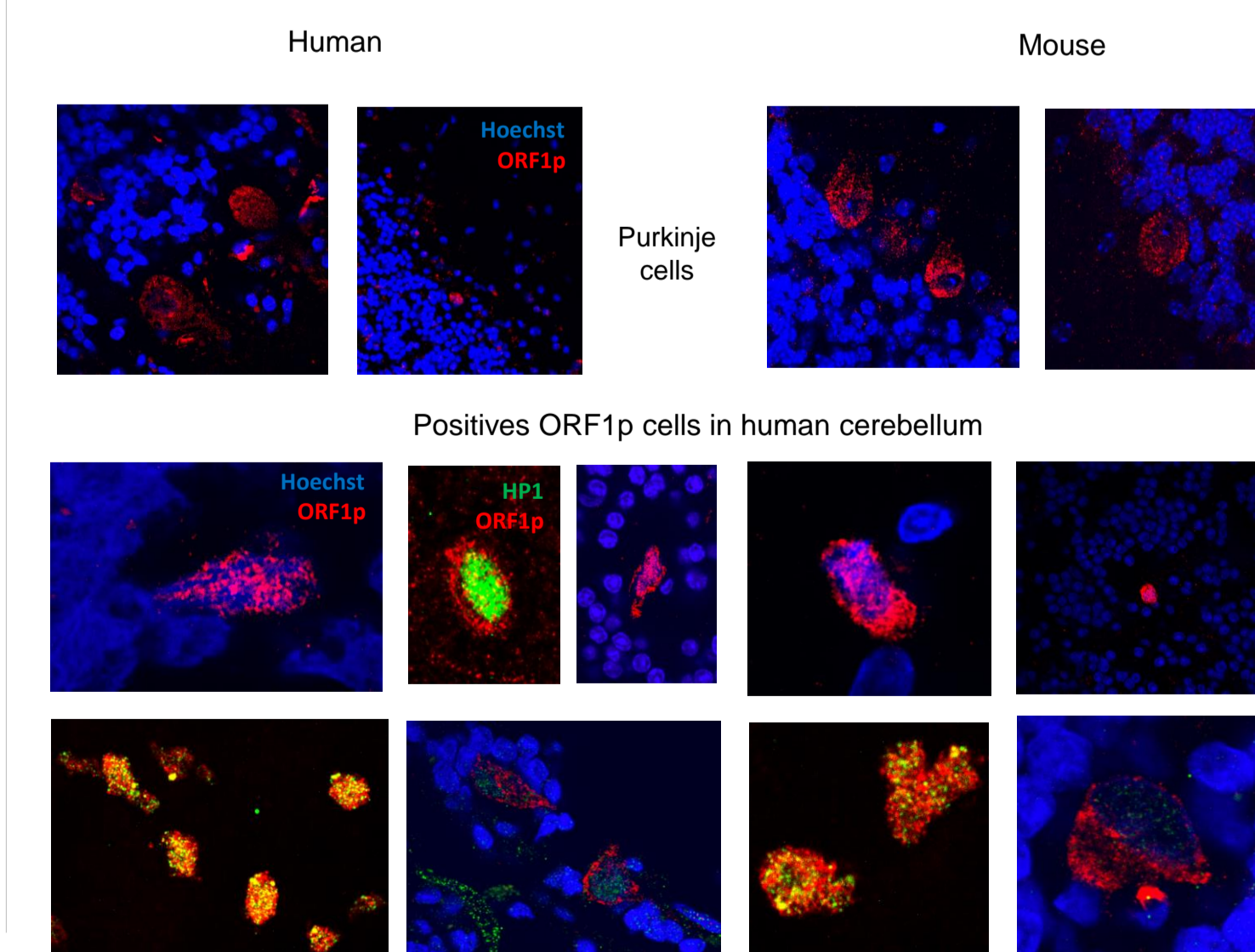
ORF1p is increased in the cytoplasmic fraction of PD individuals



A region-specific localization of ORF1p to chromatin



Orf1p expression in Human and mouse cerebellum



- Identification of endogenous ORF1p protein partners in human dopaminergic neurons, with novel potentially neuron-specific interacting proteins.
- Upon stress, ORF1p is relocalized to chromatin and recruits nuclear proteins associated with the nuclear envelope, transcription factors binding functions and DNA metabolic processes.
- In Alzheimer's and Parkinson's disease, we observe a disease-specific dysregulation of Transposable Elements
- We find a widespread ORF1p expression in the mouse and human brain, mostly in neurons. We are currently characterizing the impact of aging on ORF1p expression and localization at different scales. We observe regional specificity in the localization of ORF1p to chromatin in the mouse brain.
- ORF1p is found in the cytoplasm but also in the nucleus of human *post-mortem* brain tissues. A significant increase of cytoplasmic ORF1p is detected in the cingulate gyrus of PD individuals but not in the cerebellum.