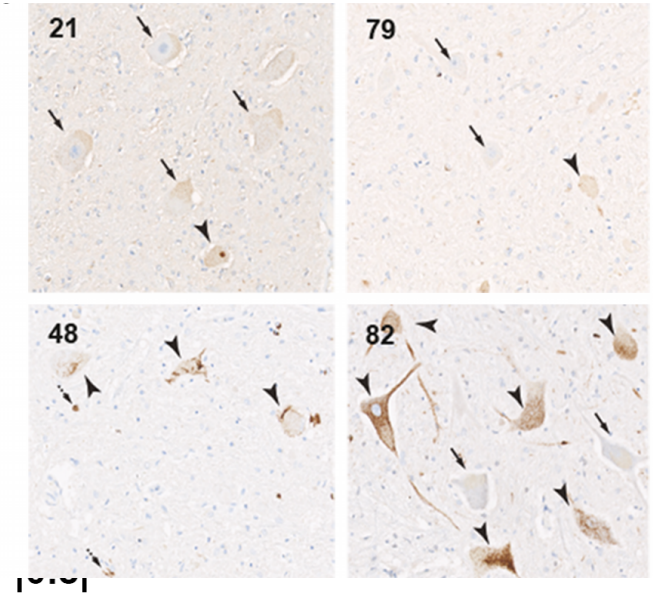
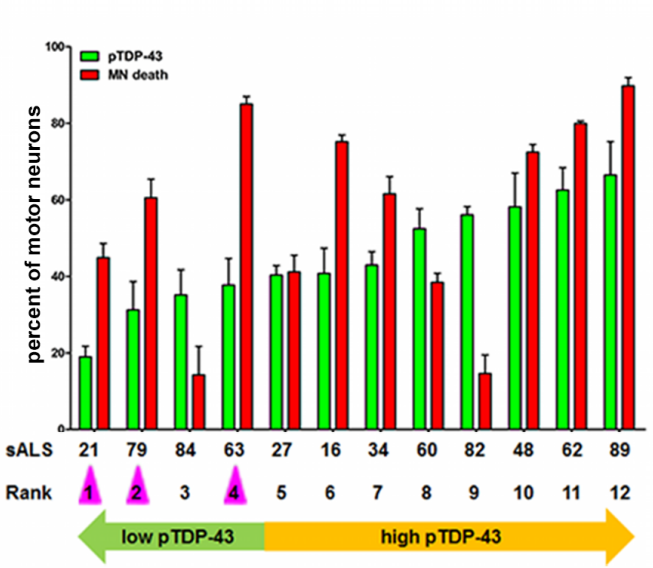
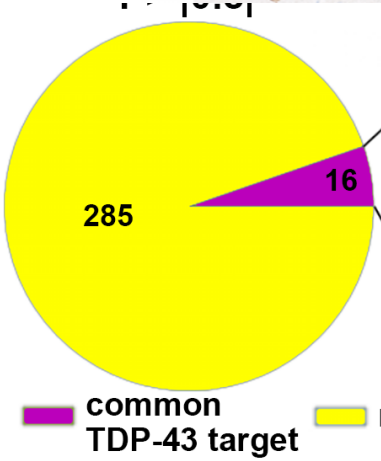
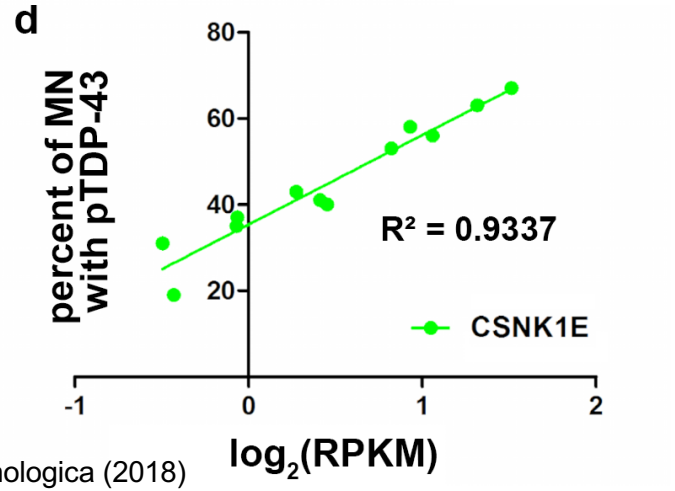
Pathology-guided transcriptome analysis





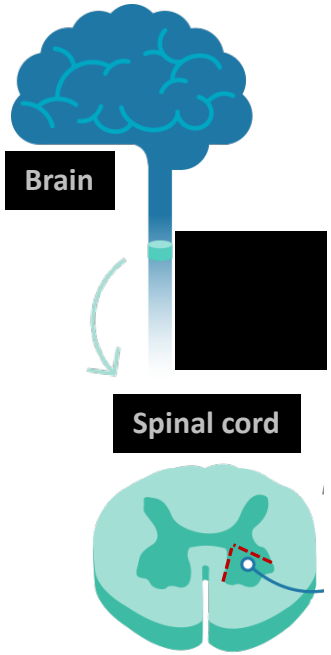


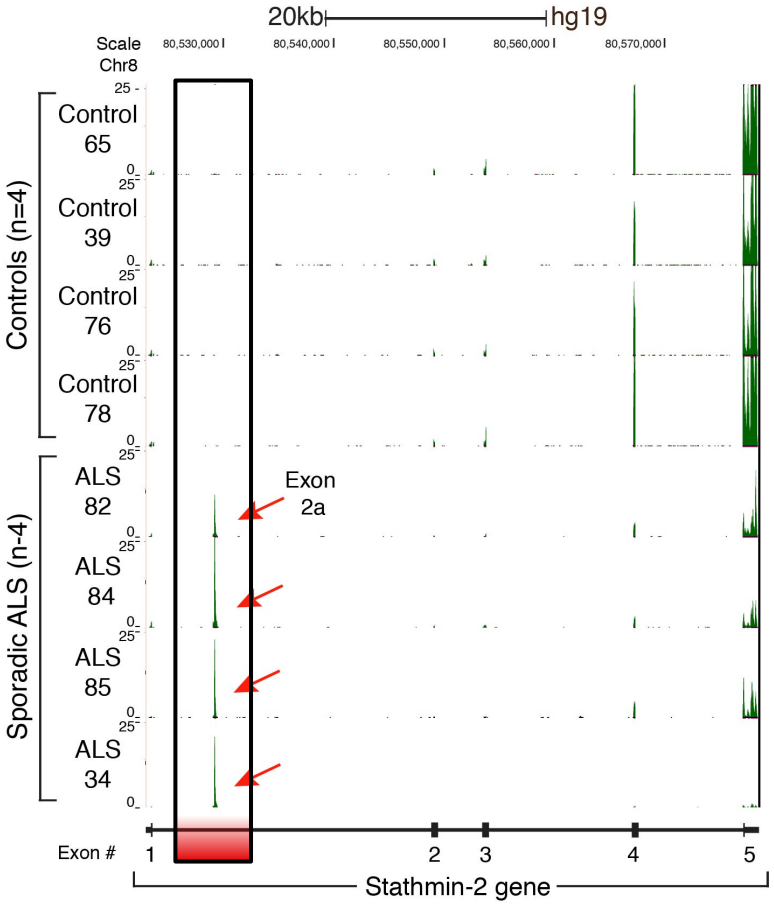
gene	r	gene	r
CSNK1E	0.96	SPTBN1	0.84
SETD5	0.90	PHC3	0.83
CLMN	0.88	SRRM2	0.82
ACTN1	0.87	MYH9	0.81
PNN	0.86	WSB1	0.81
LUC7L	0.86	RERE	0.80
PTGDS	0.85	DAAM2	0.80
NAV1	0.84	HSP90AB1	-0.85



Krach F, Batra R et al, Acta Neuropathologica (2018)

Premature polyadenylation of stathmin-2 is a hallmark of sALS





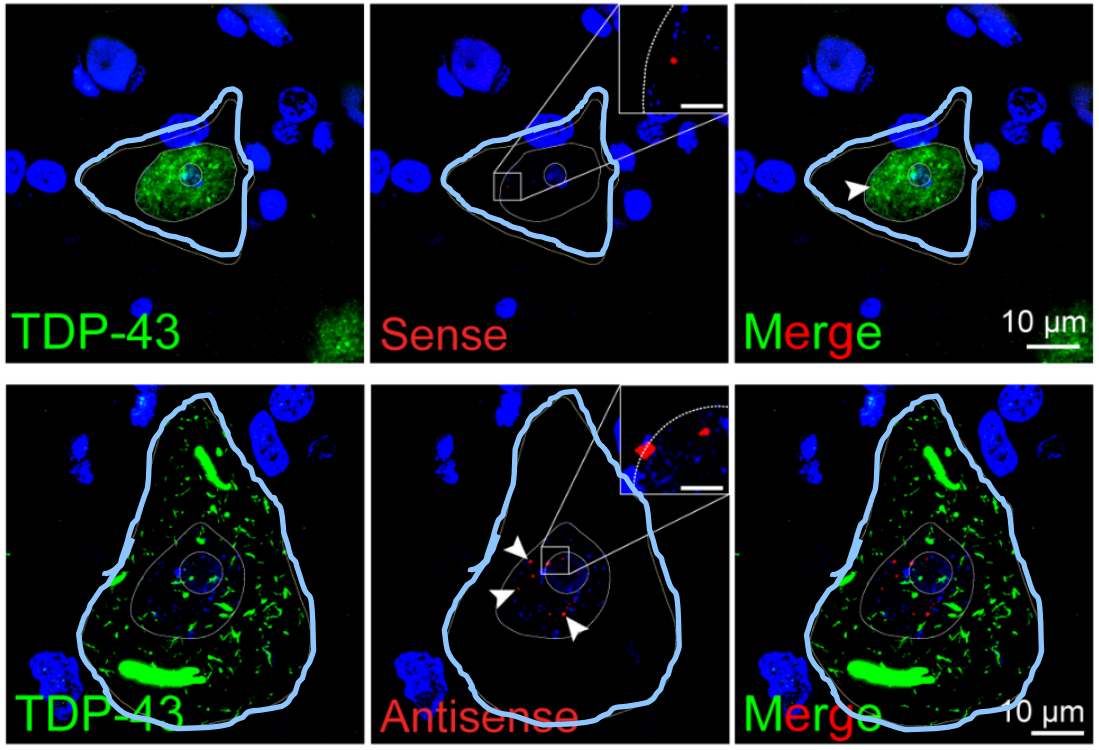
human spinal motor neurons

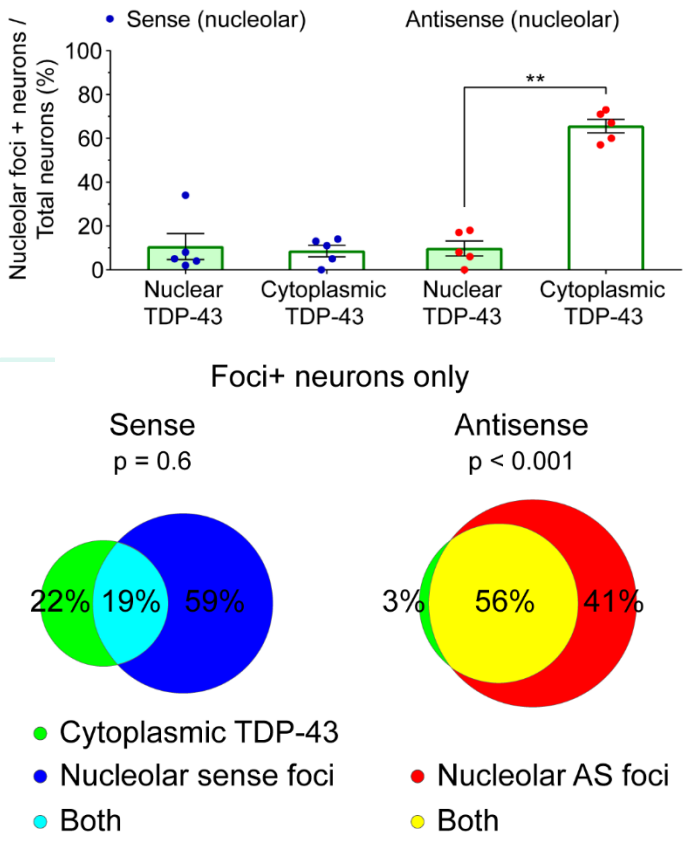
Sporadic ALS patients

1 2a

Zevic Melamud et al, 2019

Nucleolar antisense RNA foci correlate with TDP-43 mislocalization in C9 ALS

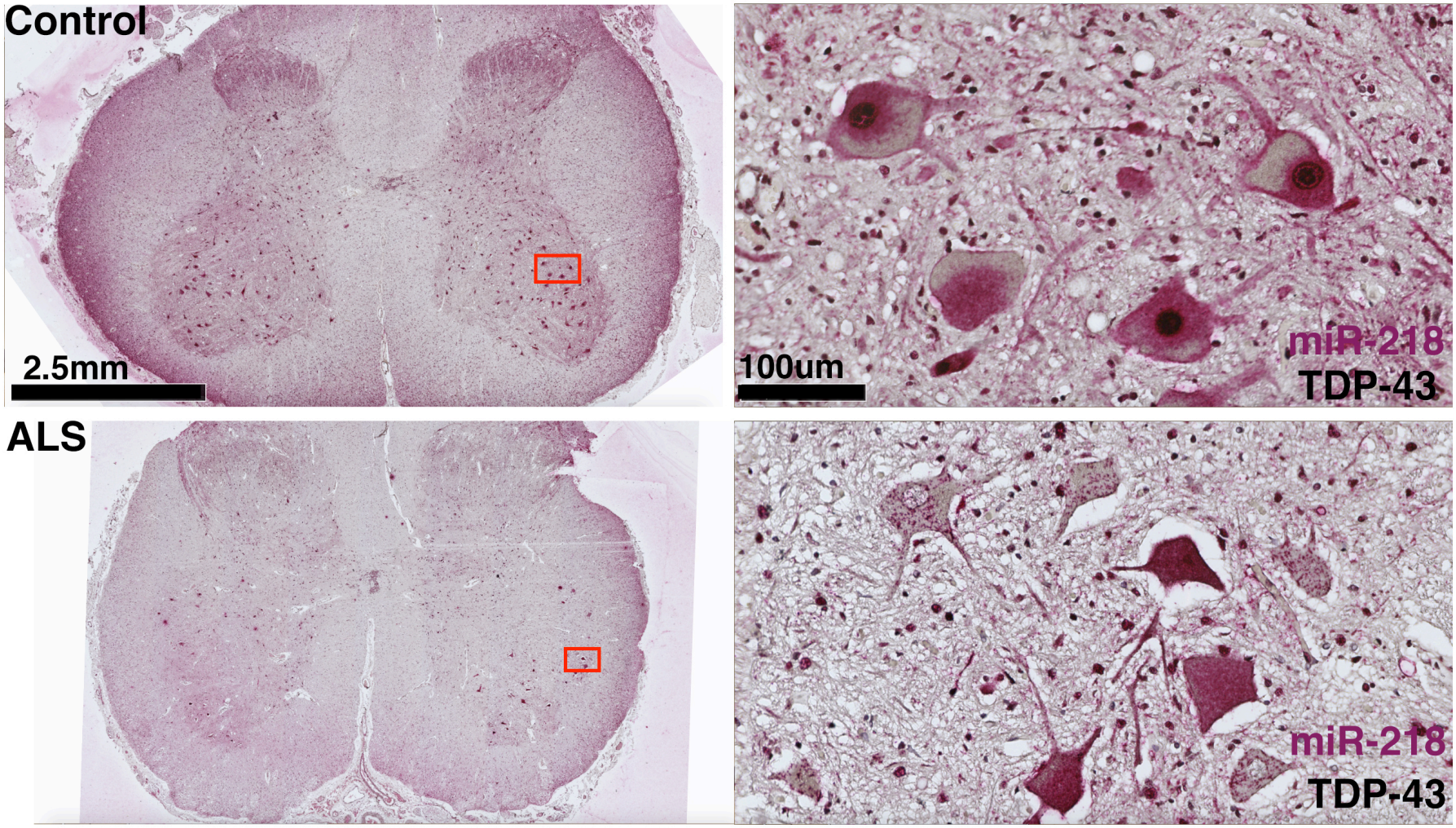




Aladesuyi, Stauffer, Saberi et al, 2018

- Aladesuyi et al., *ANP* 2019

Co-CISH-IHC shows TDP-43 mislocalization precedes miR-218 reduction



Summary and conclusions

1. Phenotypes reflect underlying anatomy of ALS pathobiology, which are "continuous" (not discrete);
2. Clinical progression reflects *in vivo* real time anatomy of neuropathology;
3. Phenotypes are not really useful in predicting biology;
4. Progression to respiratory neurons is a unique feature of ALS neurodegeneration;
5. ALS pathobiology desynchronizes, summates and saturates over time and space;
6. TDP-43 pathology in ALS has a "sweet spot"—that is, it translocates, aggregates and then disappears (at least in the spinal cord);
7. Readouts are loss of nuclear TDP-43 or cytoplasmic aggregation;
8. At the cellular level, the time course of neuron death is unknown;
9. Brain and spinal cord pathology should be looked at simultaneously;
10. The neuropathology literature is dominated by FTD-TDP-43, but ALS-TDP-43 has special attributes and opportunities;
11. Neuropathology can validate mechanistic predictions--Best opportunity is in spinal cord, and in bulbar and UMN predominant ALS.

Ravits Lab in Escape Room, Feb 21, 2020

Acknowledgements

Ravits Lab

Basic Research
Takuya Ohkubo, MD, PhD
Sandra Diaz Garcia, PhD
Marta Fernandez Bustamante, PhD
Maria Rodriquez
Amy Taylor
Bankole Aladesuyi
Ron Batra PhD
Florian Krach

Translational Research
Rosemarie Previte
Gil Gutierrez
Danielle Bussey

National Institute of Neurological Disorders and Stroke

ALS Association
Fighting Lou Gehrig's Disease
Create a world without ALS.

Target ALS

Microsoft Research

Collaborators

Don Cleveland, PhD, UCSD
Gene Yeo, PhD, UCSD

•Pamela Golden
•Richard Smith
•Wyckoff Family
• Friends & family of Greg Brooks
• Lois Caprille

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University of California, San Diego
School of Medicine