Pathology-guided transcriptome analysis

- Images of immunohistochemistry showing different brain regions.
- Bar chart showing correlation between pTDP-43 and percent of motor neurons.
- Pie chart indicating the percentage of common TDP-43 targets.
- Table listing gene names and correlation coefficients.

Premature polyadenylation of stathmin-2 is a hallmark of sALS

Zevic Melamud et al, 2019
**Nucleolar antisense RNA foci correlate with TDP-43 mislocalization in C9 ALS**

Aladesuyi et al., 2018

![Image of cellular localization](image)

Aladesuyi, Stauffer, Saberi et al, 2018
Co-CISH-IHC shows TDP-43 mislocalization precedes miR-218 reduction
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.
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Therapies for ALS & Related Disorders