FlyMALS
A multi-disciplinary project to identify common RNA-dependent pathways related to ALS and SMA using fly models

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Despite decades of research, the pathomechanisms underlying motor neuron diseases (MND) remain unclear. Given the clear phenotypic and genotypic differences, the abundance of evidence supporting common molecular pathways in Spinal Muscular Atrophy (SMA) and Amyotrophic Lateral Sclerosis (ALS) is striking. Among these, the preponderance of mutations in genes linked to RNA metabolism suggests it is central to MND, raising the question of how ubiquitous, housekeeping genes trigger tissue-specific alterations.

The FlySMALS consortium aimed to identify common RNA-dependent mechanisms underlying ALS and SMA by the combination of transcriptomic and proteomic studies in fly models. Three ALS and SMA models presenting knock-down of the causal disease gene orthologues Tbph, Caz (ALS) and Smn (SMA) were generated to identify common differentially expressed transcripts. We further generated models to map the direct interactions of these proteins with neuronal mRNAs, providing a detailed view of underlying regulatory networks and insights into the mechanisms leading to gene expression changes.

Although hundreds of transcripts were commonly altered in the KD models, providing evidence for common molecular pathways, none were found to be physically bound by the three proteins. This suggests that the phenotypic convergence occurs downstream of processes directly regulated by these proteins, requiring an integrative approach to distinguish cause from consequence. For this purpose, we developed a computational strategy to integrate our experimental datasets over the fly protein-protein interactome, taking advantage of network theory approaches to identify critical protein complexes collaborating as functional units. This approach led to the selection of 27 complexes and 29 proteins that specifically link Smn, Tbph and Caz to their commonly induced molecular dysfunctions. Translation of this disease network to the human counterpart revealed a significant functional conservation and overlap with a computationally derived human MND network. Conserved functional interactions included critical links between RNA processing and DNA damage pathways, whose relevance has been experimentally validated for the TDP-43 disease causing mutation N390D.

Our results suggest novel mechanisms for MND that explains the phenotypic convergence of independent disease genes into a neuronal pathology with great potential to contribute to the identification of common drug targets and biomarkers for asymptomatic disease states.