Targeting ALS with Drug Repurposing: A Systems Biology Approach Validated in C. elegans Models

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive motor neuron loss and limited therapeutic options due to its complex, multifactorial pathology. Network-guided drug repurposing offers a promising strategy to identify novel therapeutic candidates by targeting dysregulated molecular pathways. In this study, we applied an integrative network-based approach to identify repurposable drugs for ALS. Transcriptomic data from human ALS patients were analyzed to identify differentially expressed genes and construct disease-associated molecular signatures. Protein-protein interaction (PPI) networks were generated using STRING and analyzed in Cytoscape to identify hub genes and key functional modules. Gene Ontology enrichment analysis revealed biological pathways implicated in ALS pathogenesis. Connectivity Map (CMap) analysis was then used to identify compounds predicted to reverse ALS-associated gene expression patterns, supported by compound-target associations from STRING and LINCS databases. Candidate drugs were prioritized based on network connectivity, mechanistic relevance, and translational potential. Top-ranked compounds were evaluated in an ALS Caenorhabditis elegans model to assess functional efficacy in vivo. Among the candidates, mozavapton demonstrated therapeutic potential by improving disease-associated phenotypes. Overall, this study establishes a network-guided drug repurposing framework that links ALS-associated genes to known drug targets and provides in vivo validation of a promising candidate, supporting further mechanistic investigation and preclinical development.

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