Network-Based Approach for Targeting Human Kinases commonly associated with Amyotrophic Lateral Sclerosis and Cancer

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a rare progressive and chronic motor neuron degenerative disease for which at present no cure is available. In recent years, multiple genes encode kinases and other causative agents for ALS have been identified. Kinases are enzymes that show pleiotropic nature and regulate several signal transduction processes and pathways. Our study showed 32 ALS associated kinases interacting with multiple disorders including cancers and we prepared a kinase-disease interaction network. Further, the hub genes in the disease-causing network were identified by calculating the network topological properties. Drug and miRNA repurposing was also done against the hub genes in the network to identify the potential drug target to disrupt the disease-causing network. Our study expands the current knowledge and understanding of the role of kinases in ALS and cancers indicating the link between both the disease and suggested some drug to repurpose to improve the situation.

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, characterized by the progressive degeneration of upper and lower motor neurons in the brain, in the brainstem, and in the spinal region. It is a heterogeneous disease where several pathophysiological processes have been demonstrated to induce neuronal death, including oxidative stress, mitochondria impairment, growth factor deficiency, neuro-inflammation, defective axonal transport, RNA metabolism, aberrant stimulation of kinase activity, impaired brain energy metabolism, autophagy, and stress-induced cell death . Recent studies also reported several other causative genes that encodes for kinases and involved in ALS and other neurodegenerative diseases . Kinases are enzymes that function as transferases to catalyze almost every signal transduction process and pathway by adding a phosphate group (PO_4^{3-}) to hydroxyl groups of substrates such as amino acids, nucleic acids, as well as lipids. The phosphorylation of protein via kinases stimulates the majority of the cell life processes, while the abnormal phosphorylation leads to the consequences of diseases, such as human cancer initiation and progression.

Methodologies

Identification of ALS associated Kinases

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Preparing Disease-kinase interaction network

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Preparing protein-protein interaction network

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Identification of hub genes in the network

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Gene Ontology and Pathways enrichment analysis

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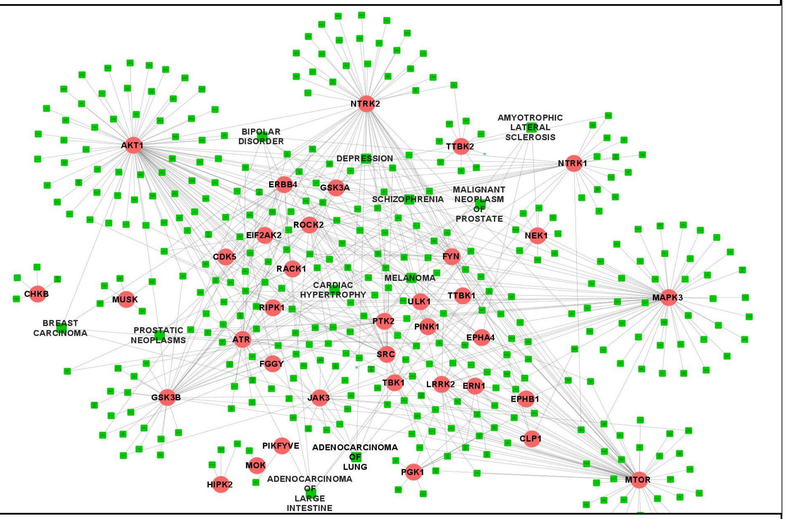
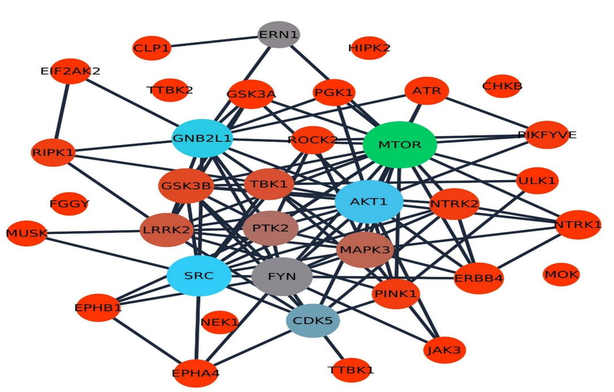
Chemical and miRNA based drug repurposing

Results

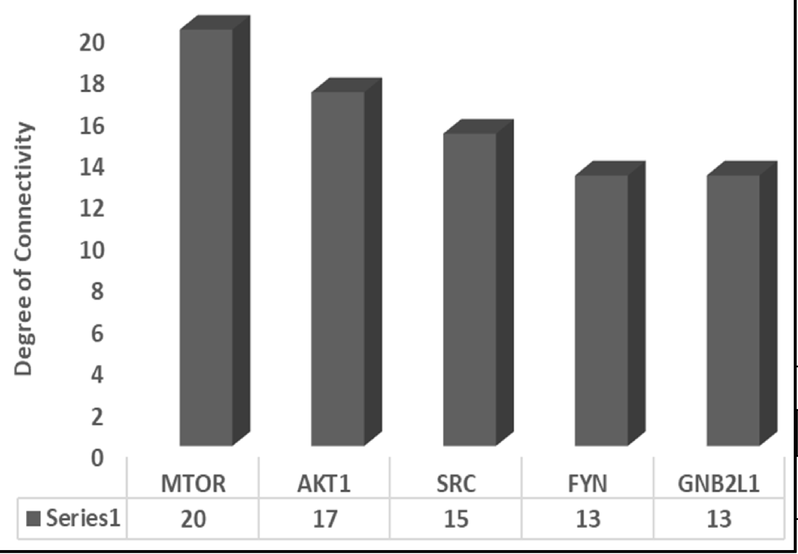
Disease-Kinase Interaction Network



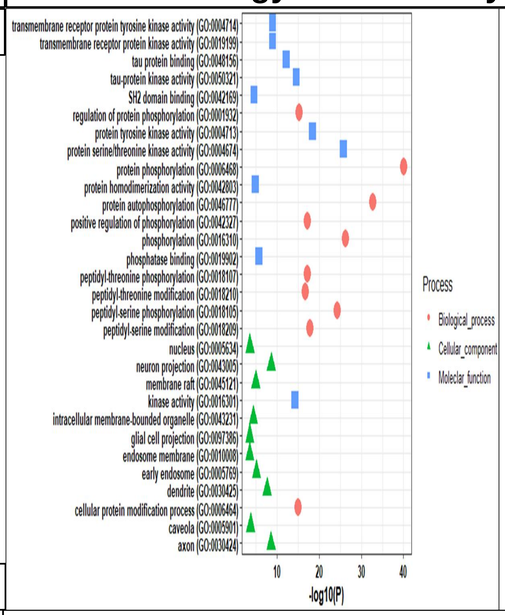
Protein-Protein interaction network

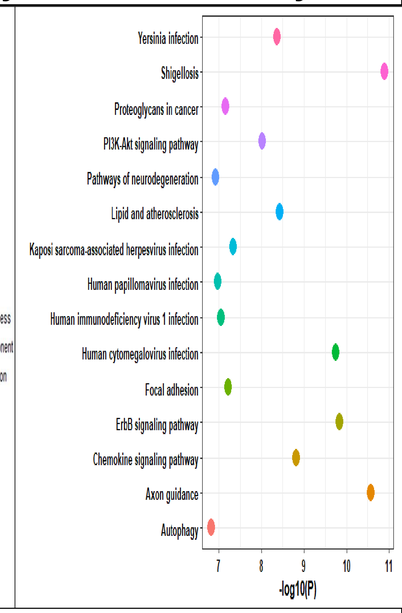


Identified Hub genes

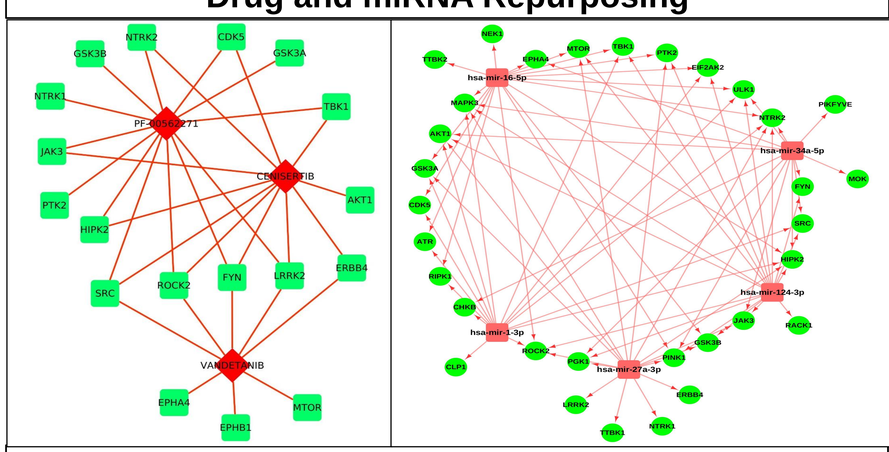


Gene Ontology and Pathway Enrichment Analysis





Drug and miRNA Repurposing



Conclusion

In this study, we have used a network-based system biology approach to investigate the kinase-based molecular interplay between ALS and other human diseases including cancer. We constructed the disease-kinase interactome that demonstrates the significant involvement of kinases in several human diseases including ALS, schizophrenia, bipolar disorder, depression, and different cancers. Here, from PPI network the resulting hub genes including AKT1, GNB2L1, SRC, FYN, and mTOR showing high degree of interactions between the kinases. Moreover, we also identified 28 kinases including hub genes, that are involved in ALS as well as various human cancers. We believe that this study will help in developing a better understanding of kinases role in neurodegeneration as well as in cancer

Acknowledgment

F.K sincerely thank the Amity University, Noida, for providing facilities.