Extensive network-based approach to identify the potential biomarkers of Amyotrophic Lateral Sclerosis

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Abstract

The prevalence of neurodegenerative diseases especially those affecting the ability of bodily control are prevailing in population worldwide and are predicted to increase rapidly in coming decades. Amyotrophic Lateral Sclerosis (ALS) is one such diseases with the rise in reported cases each year past. It is a motor neuron degenerative disorder, which degenerates both the upper and the lower motor neurons. In our study, we have analyzed 50 RNA-Seq samples of cerebellum region of control and ALS patient respectively to identify the differentially expressed genes in ALS patients. A total of 157 differentially expressed genes having fold-change greater than equal to 2 and less than equal to -2 and FDR <= 0.01 were identified. The GSEA analysis was done to identify the role of the identified DEGs at biological, cellular and molecular levels, further we prepared a protein-protein interaction network to identify the key regulatory genes in the disease-causing network to target those key regulatory genes using drugs and miRNA to disrupt the disease causing network.

Introduction

Amyotrophic lateral sclerosis (ALS) is a chronic age-of-onset neurodegenerative disorder characterized by the progressive degeneration of upper motor neurons (UMN) and lower motor neurons (LMN) within the motor cortex, brainstem, and spinal cord, ultimately leading to paralysis and death usually by a respiratory failure within 2–5 years of symptom onset. ALS is a multifactorial disease with several genetic, epigenetics, and environmental risk factors. More than 50 potentially causative or disease-modifying genes have been associated with ALS; however, pathogenic variants in SOD1, C9ORF72, FUS, and TARDBP are the most common. Although phenotypically indistinguishable from one another, 10% of cases are familial (fALS), usually with an autosomal dominant inheritance pattern, whilst the remaining 90% are sporadic (sALS), defined as having no family history of the disease. Recent studies reported the incidence of ALS between 0.6-3.8 per 100,000 persons/year. In Europe, the incidence of ALS is higher, ranging from 2.1-3.8 per 100,000 persons/year. Several genes and pathophysiological processes contribute to the disease, and it will be necessary to understand this heterogeneity to find effective treatments.

Methodologies

Collection and mapping of RNA-Seq data of ALS

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Gene count preparation and identification of DEGs

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Preparing protein-protein interaction network

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Identification of key regulatory genes in network

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Genome wide association study

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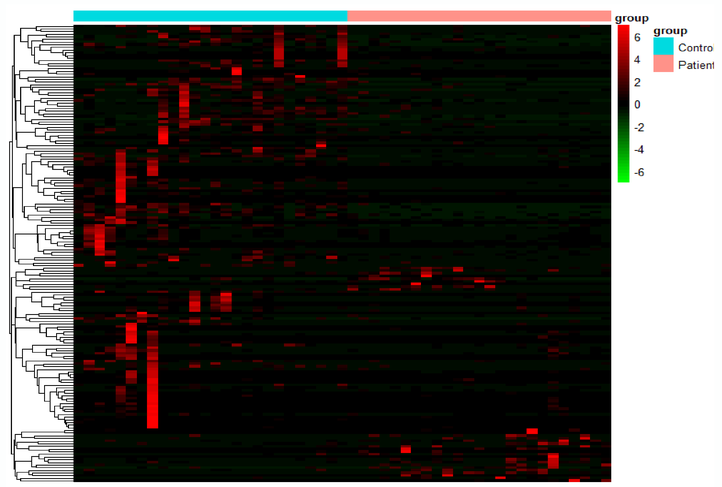
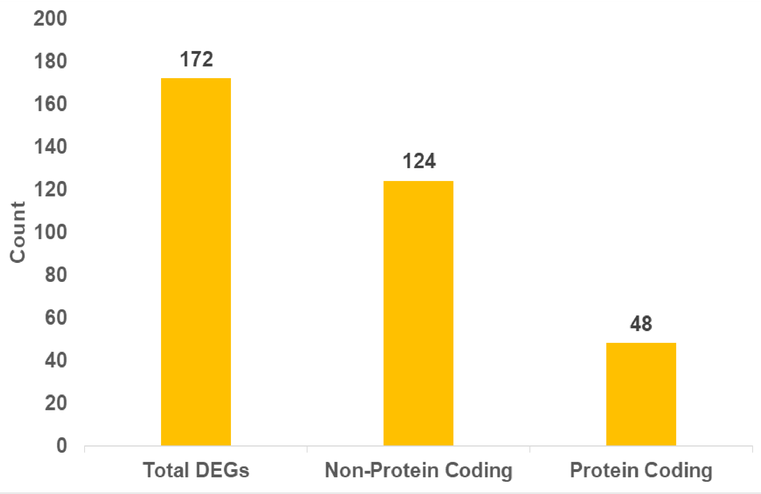
Chemical and miRNA based drug repurposing

Results

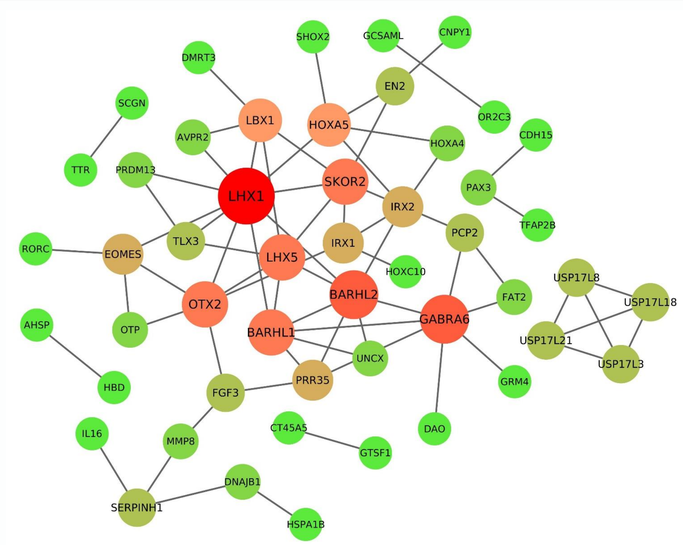
Heat-Map representing the identified DEGs



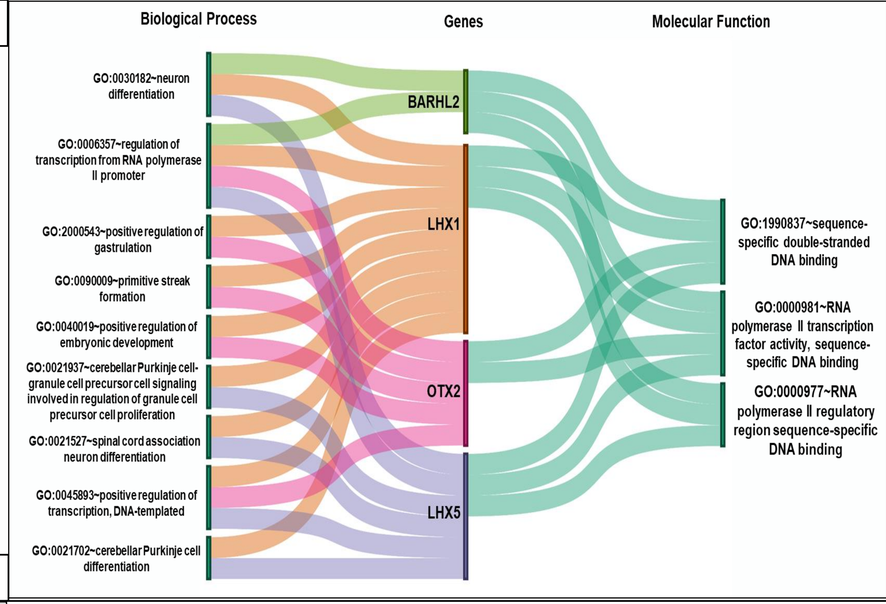
Count of Protein coding and Non-coding DEGs



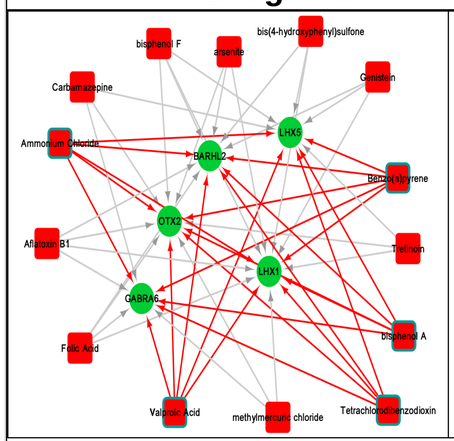
Identification of key regulatory genes

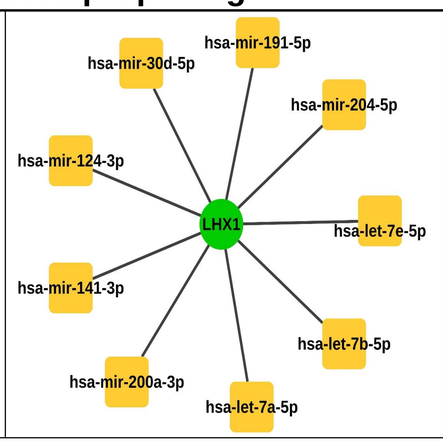


Genome wide association study



Drug and miRNA Repurposing





Conclusion

In this study, we have analyzed the RNA-Seq data of control and ALS patients to identify the differentially expressed genes in the ALS patients. We identified a total of 172 DEGs during our analyses, of which 48 genes were protein coding in nature. A network based analysis of the 48 DEGs revealed LHX1, BARHL2, GABRA6, BARHL1 and etc. as key regulatory genes in the disease causing network. Next we did the genome wide association study revealed the roles of key genes in neuron differentiation, regulation of transcription from RNA polymerase II promoter, spinal cord association neuron differentiation as well as cerebellar purkinje cell differentiation. Further, the drug and miRNAs repurposing was done against the identified key regulatory genes. We believe that our study will help to identify some new key biomarkers in the prognosis of ALS disease and helps adding some more information related to the Amyotrophic Lateral Sclerosis.

Acknowledgment

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