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Abstract Topic:- Rare disease therapeutics

Abstract Title:- Exploring molecular mechanisms of FSHD pathology by weighted gene co-expression network analysis

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Aims:-Facioscapulohumeral dystrophy, commonly known as FSHD is prevalent as one of the most common types of muscular dystrophy. It is a rare complex disorder without any disease-modifying treatments. Double homeobox 4 (DUX4) has been identified as a key player in FSHD pathology, however, the molecular mechanisms associated with aberrant expression of DUX4 are not completely understood. The current study is aimed at the identification of coexpressed genes significantly associated with FSHD pathology. The second objective is to find significantly associated genes in male and female FSHD subjects.

Methods:- Weighted gene co-expression network analysis (WGCNA) was performed on the publicly available RNAseq dataset GSE115650 to identify gene modules associated with FSHD-affected individuals. The modules were correlated with disease state, male and female FSHD subjects. Gene expression correlation with disease status was performed using Pearson correlation to identify significantly associated genes. Modules significantly associated with disease state were selected for downstream analysis. Genes significantly associated with male and female subjects were identified using in-built WGCNA functions. Downstream analysis was performed to investigate hub genes associated with disease state. Gene ontology was performed for biological interpretation of results affected in the diseased state, male, and female FSHD subjects.

Results:- We found certain modules in the gene regulatory network as significantly associated with FSHD diseased state. Genes in four modules were positively correlated with FSHD, while genes in two modules were negatively correlated. Gene ontology analysis of these modules evinced specific clusters of genes with roles in FSHD pathophysiology. Hub genes such as MYBPC1, PRAMEF26, DDX3Y, CGB2, GUSBP3 were identified from the networks and evaluated for potential to act as possible targets for treatment of FSHD. Further, we found that differences in genes significantly associated with either gender.

Conclusions:- This study presents a bioinformatics based approach to understand the molecular mechanism of FSHD and more generally other rare diseases with similar pathophysiology. We were able to identify key regulatory pathways and genes that may be playing a crucial role in the FSHD phenotype. These need to be explored further using experiments.

Keywords:- Facioscapulohumeral dystrophy, rare disease, WGCNA, muscular dystrophy, DUX4