The Novel Role of KRT Proteins as Biomarkers in the Dysregulated Neuroendocrine System of ALS for Early Diagnosis With PT150 as a Novel Multi-Target Neuroprotective Therapeutic

Sharma, Arnav (School: International Academy)
Das, Aryav (School: Park Tudor School)
Dunakhe, Samarth (School: Arizona College Prep High School)

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by motor neuron degeneration. Although biomarkers have been identified, they lack specificity. Combined with ALS heterogeneity, misdiagnosis reaches 40%. This paper proposes a Graph Neural Network (GNN) to diagnose ALS, identify an ALS-specific biomarker group, and develop a corresponding therapeutic. A whole blood transcriptome dataset was sourced. A kNN-based graph representation was built and used to train a GraphSAGE GNN. The model achieved an accuracy of 98% between ALS and control, and 85% between ALS patients and ALS mimics, outperforming existing diagnosis methods. The model was cross-validated on an Alzheimer's transcriptomic dataset, achieving an accuracy of 97%, surpassing prior approaches. Integrated Gradients quantified each gene's importance in the model's classification process, through which KRTAP3-1 and KRTAP9-8 emerged as significant genes. Gene ontology showed that these genes are involved in cytoskeletal integrity. In parallel, statistical analysis of an ALS proteomics dataset revealed the differential expression of KRT6A, KRT6B, and KRT4. UniProt analysis identified that these proteins are key for cytoskeletal integrity and cellular differentiation, both important in ALS pathogenesis. Neurospatial analysis showed that these KRT proteins are involved in the pituitary gland, suggesting that their downregulation may cause hormonal dysregulation in ALS. Hyperactivity of Glucocorticoid Receptor (GR) was identified as a contributor to KRT downregulation. Molecular docking identified PT150 as a therapeutic for ALS, deactivating GR and Cyclooxygenase 2 at -7.5kcal/mol. This regulates hormonal release and neuroinflammation in ALS potentially expanding patient lifespan by 20-30%.

Awards Won: