ALS-induced Gene Dysregulation Increases Blood Glucose & Sodium Levels in Patients

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Introduction:
The most common form of Motor Neuron Disease (MND), Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder that affects nerve cells in the brain and spinal cord. ALS is characterized by muscle atrophy, loss of movement, and eventual paralysis. While a small proportion of ALS has been attributed to known genetic mutations, it is estimated that 90% of ALS cases occur without any family history or genetic cause [1]. Our research investigates gene dysregulation in ALS patients with no specific mutations to understand the changes at the gene level, its effect on biological pathways, and the cause of symptoms.

Materials and Methods:
From the NCBI Gene Expression Omnibus Dataset GSE68607, we selected 38 total gene profiles taken from lymphoblastoid tissue samples, with 23 ALS profiles with no known genetic mutations versus 15 healthy control profiles. We performed a t-test analysis using GEO2R and identified the top 400 up-regulated genes with p-values < 0.01. We then inputted these genes into the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) to identify enriched protein-association networks associated with our upregulated genes, cataloged in the Kyoto Encyclopedia of Genes and Genomes (KEGG).

Results:
In the top 400 upregulated genes found in ALS patients with p-value below 0.01, our analyses identified the following genes associated with the Carbohydrate Digestion and Absorption (CDA) and the Aldosterone-regulated sodium reabsorption (ASR) KEGG pathways (strength of 0.97 and 0.96 respectively): HK1, AMY2B, ATP1A3, ATP1B3, PIK3CD, PRKCB, and MAPK1. HK1 and AMY2B were found in the CDA pathway and MAPK1 was found in the ASR pathway. The other four genes were shared in both pathways.

Discussion:
The upregulated genes in the CDA pathway confirm previous research that ALS causes an increase in blood sugar levels and reduces glucose uptake from the bloodstream, while also rendering tissues unable to produce sufficient insulin for homeostasis [2]. The CDA pathway is also commonly linked to ALS symptoms such as constipation and nausea, caused by autonomic nervous system damage in regions that regulate activity in the intestinal tract [3]. The ASR pathway regulates sodium reabsorption using aldosterone, a corticosteroid secreted in the adrenal cortex [4]. In ALS, sodium reabsorption is likely impacted since the autonomic functions are affected. However, its specific impact is largely unknown and should be studied further. The goal is that this research can be used to identify targets for gene therapies that can help alleviate symptoms and minimize causes of ALS.

Keywords:
Amyotrophic Lateral Sclerosis, Carbohydrate Digestion, Aldosterone-Regulated Sodium Reabsorption, Blood Sugar, Glucose, Insulin, GEO

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