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Computational Drug Repurposing and MicroRNA Identification Pipeline for Alzheimer's Disease Using RNA Sequencing Data Analysis

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects at least 27 million individuals worldwide. This condition significantly impacts the lives of patients and their families, as well as imposing substantial financial burdens on society. Currently, no definitive disease-modifying treatment exists, and various treatments have been developed to manage the symptoms of AD. Drug repurposing is a valuable alternative to uncovering new indications of approved or investigational drugs beyond their original medical indication. RNA sequencing (RNA-seq) is one practical approach to finding the heterogeneous gene expressions of diseases. Therefore, our study applied a computational drug repurposing pipeline to explore the candidate drugs based on AD differential gene expression signatures derived from RNA-seq data.

Methods and Materials: The expression profiles of 10 controls and 8 AD postmortem human hippocampus brains under the accession code GSE173955 were obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). The differentially expressed genes (DEGs) between AD and normal tissues were identified using GEO2R. Next, the LINCS database was used to identify potential candidate drugs for AD disease. Then, the top-ranked FDA-approved drugs were selected through considerable literature review and drug studies. Conversely, the DEGs were imported into the STRING database to identify the interactive association between the proteins. Then, all interactions with a significant combined score of 0.7 were selected for further analysis. The appropriate genes with the highest degrees of connectivity were selected as hub genes. The target scan database is a specialized collection of microRNA-mRNA targeting relationships. These databases were used to obtain hub gene-associated miRNA.

Results: This study identified 1,878 genes with $|\log2FC| \geq 1$ and p value of ≤ 0.05 as DEGs: 909 were upregulated, and 969 were downregulated. The significantly altered drug profiles that can reverse the expression pattern of AD include osapride, Momelotinib, and Enzastaurin. Furthermore, S100A8 has been identified as one of the most prominent hub genes in Cytoscape, which can be suppressed by miR-98-5p in the context of AD.

Conclusion and Discussion: In this study, we proposed several potentially repurposable candidates, Mosapride, Momelotinib, and Enzastaurin, as well as miR-9-5p for the treatment of AD progression. Mosapride is currently used to treat type 2 diabetes, functional dyspepsia, functional constipation, and epigastric pain syndrome. Momelotinib is a Janus kinase 1 and 2 inhibitor utilized in the treatment of myelofibrosis. Enzastaurin has been employed in the treatment of relapsed glioblastoma multiforme. Our findings may guide further repurposing studies tailored to different stages of disease progression. Moreover, we report S100A8 acts as an inflammatory mediator, with levels increasing as the brain ages. MiR-98-5p has the potential to suppress S100A8 expression in AD.

Keywords: Alzheimer disease, Drug repurposing, MicroRNA, RNA sequence analysis