

## **The Converging Pathologies of COVID-19 and Alzheimer's Disease**

**Course Code: CBIO311/ CBIO310**

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## 1. Introduction

The intersection of the COVID-19 pandemic and the global burden of Alzheimer's disease (AD) represent a critical frontier in modern biomedical research. Emerging evidence has redefined COVID-19 as a multi-organ disease with several neurological implications that share an array of risk factors and pathophysiological mechanisms with Alzheimer's disease (Shajahan et al., 2024).

The relationship between these two conditions appears to be bidirectional. Individuals with dementia encounter a higher risk of infection, while the covid-19 infection can trigger cognitive deficits ("brain fog") that acts as early-stage neurodegeneration (Amadoro et al., 2023; Shabani et al., 2023). This convergence is driven by overlapping molecular mechanisms, primarily neuroinflammation which is the "cytokine storm" in severe COVID-19 that affects the blood-brain barrier, activating microglia cells and creating a toxic environment similar to the chronic neuroinflammation seen in AD (Mayer & Fischer, 2025). Moreover, vascular and adrenergic signaling dysfunction which is apparent in both conditions (Miliotou et al., 2025). Furthermore, the body's stress response includes protease inhibitors that face an imbalance in AD patients which contributes to plaque formation that links acute viral responses to long-term neurodegeneration.

This report details a differential gene expression analysis aimed at identifying specific biomarkers that may drive these shared pathological pathways.

## 2. Project Objective

The primary aim of this analysis is to identify and visualize differentially expressed genes (DEGs) by integrating transcriptomic data from two different sources with these accession numbers GSE188847 and GSE104704. The study aimed to identify significant biomarkers based on the analysis done to be able to establish links between covid-19 and AD.

## 3. Methodology

The data processing pipeline was executed using the R programming environment and Geo2R. The specific workflow included

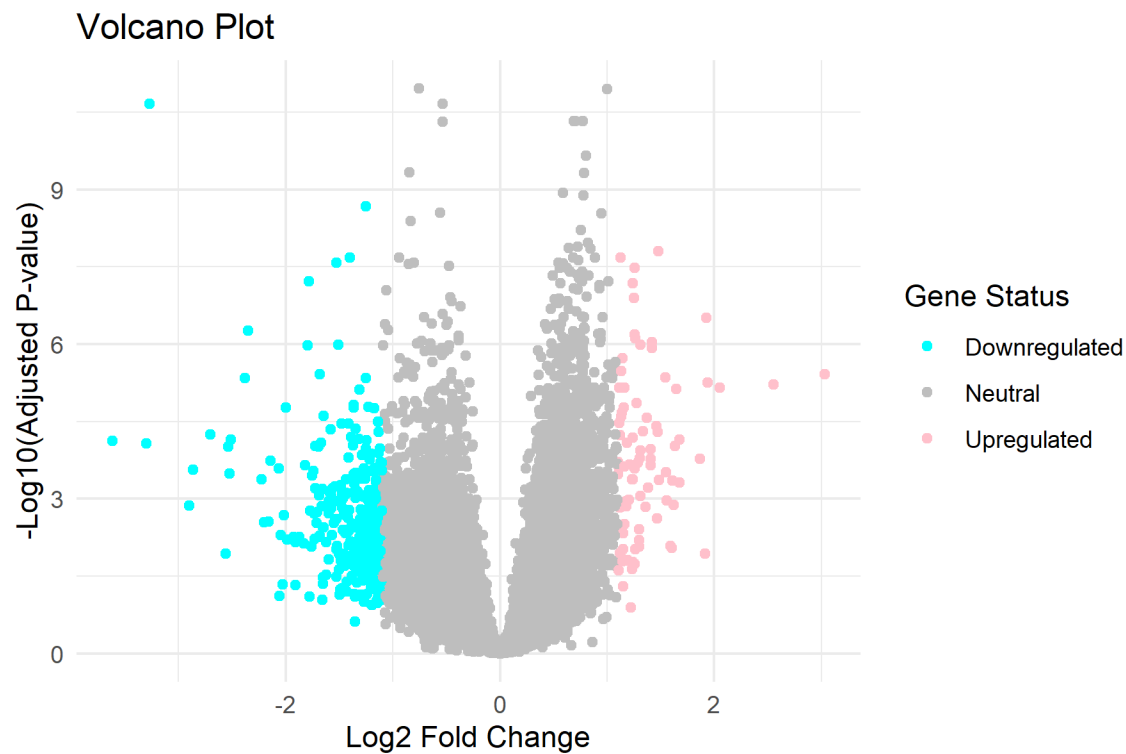
**Data Integration:** The two transcriptomic datasets were imported on Geo2R and analyzed afterwards they were standardized in R. Key identifiers were aligned (renaming GeneID to Gene), and statistical metrics such as Log2 Fold Change (log2FC) and adjusted p-values (padj) enabled the datasets to be merged into a single analytical framework based on common Gene IDs.

**Filtering Criteria:** To ensure biological relevance, genes were filtered based on expression thresholds significantly upregulated genes were defined by a positive Log2 Fold Change with a

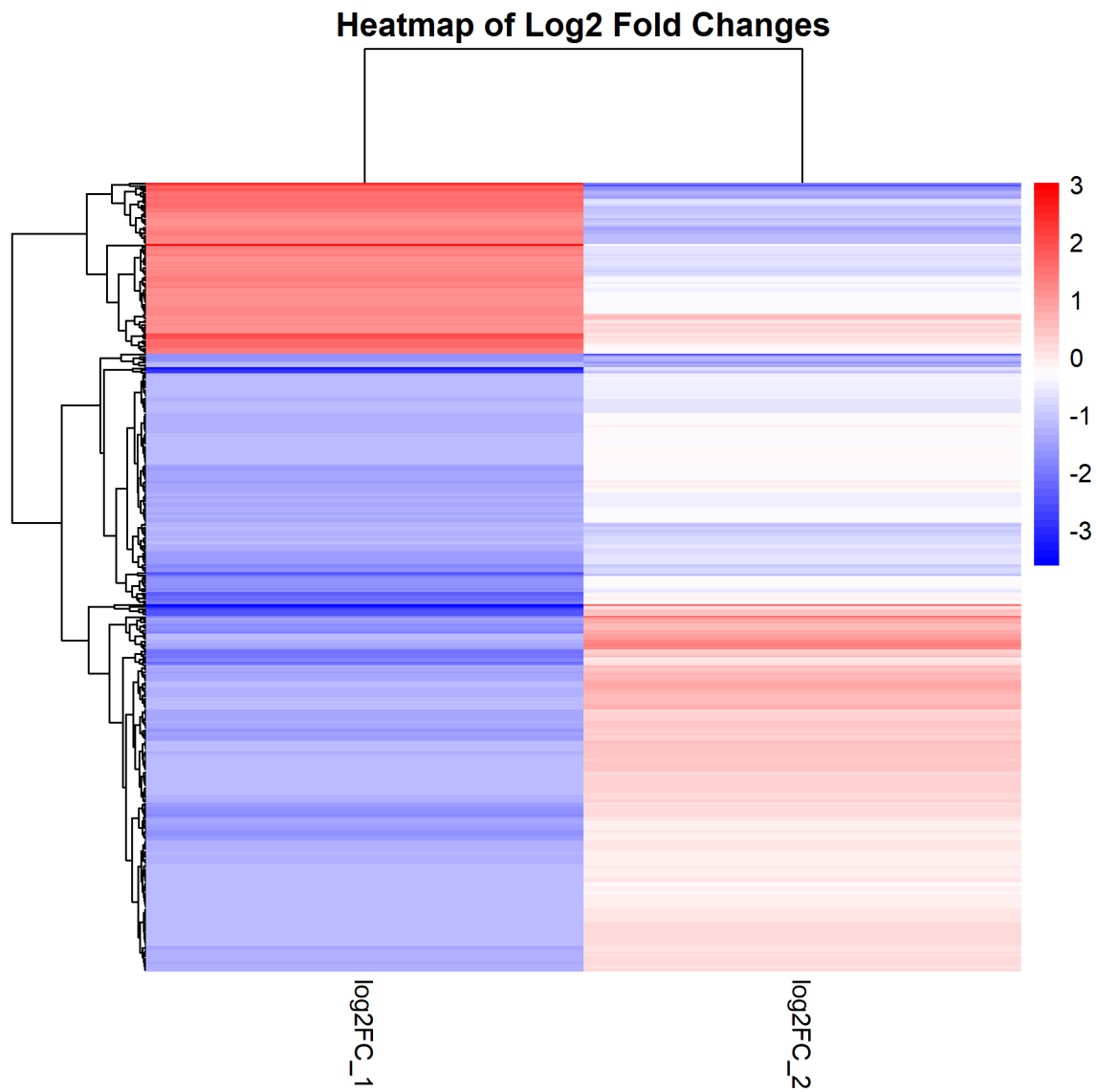
threshold  $> 1.1$  while significant downregulation was defined by a negative Log2 Fold Change with a threshold  $< -1.1$ .

**Visualization:** The dataset was visualized using volcano plots to display the global distribution of gene significance against the change in expression represented by the log fold change. In addition, heatmaps were used to perform clustering of the top differentially expressed genes.

#### 4. Key Findings



*Figure 1: A volcano plot effectively separating the significant DEGs. The "upper corners" high  $\log_{10} \text{padj}$  and high absolute  $\text{Log}_2\text{FC}$  with blue dots representing downregulated genes and pink ones upregulated genes.*



*Figure 2: A heat map utilizing a blue-white-red color gradient to visualize expression patterns. Hierarchical clustering separated samples into distinct groups, confirming that this gene set consistently differentiates the experimental conditions.*

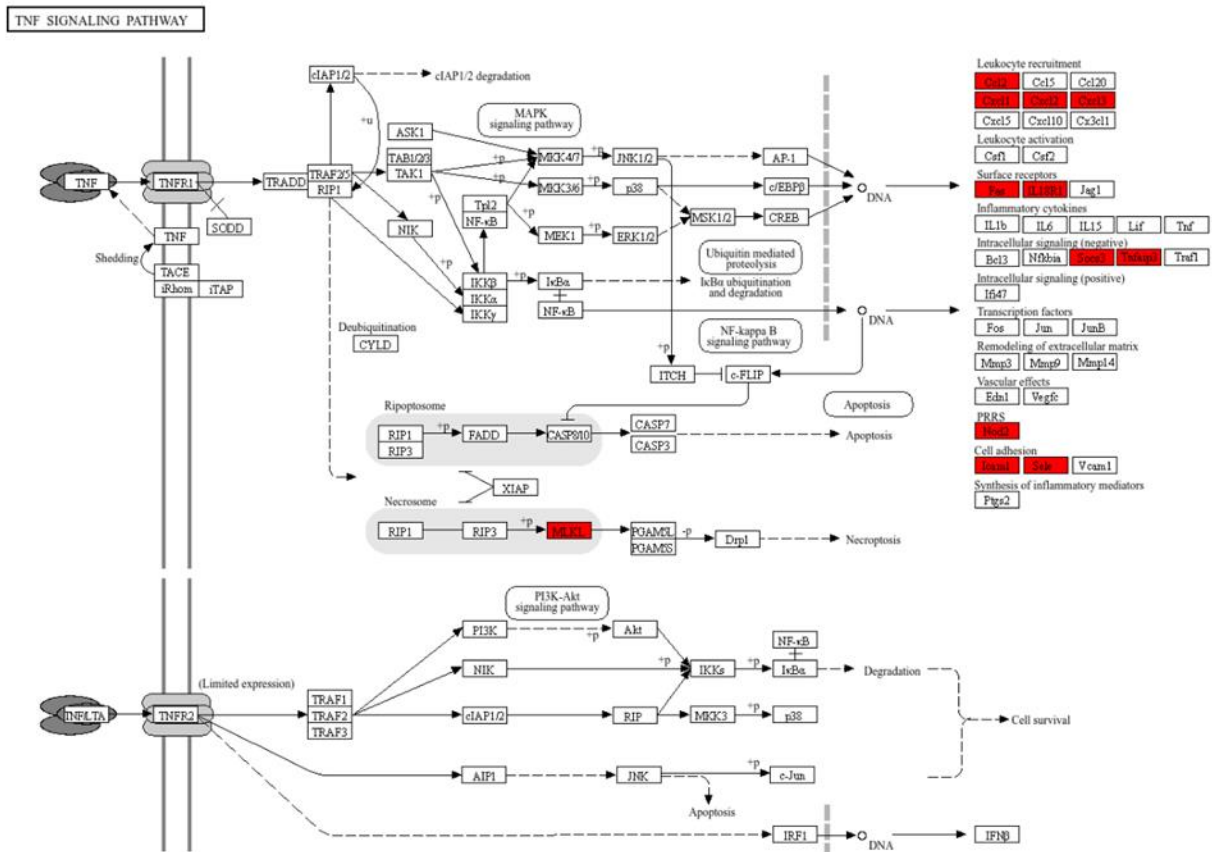


Figure 3: The TNF signaling pathway with red color indicating high expression.

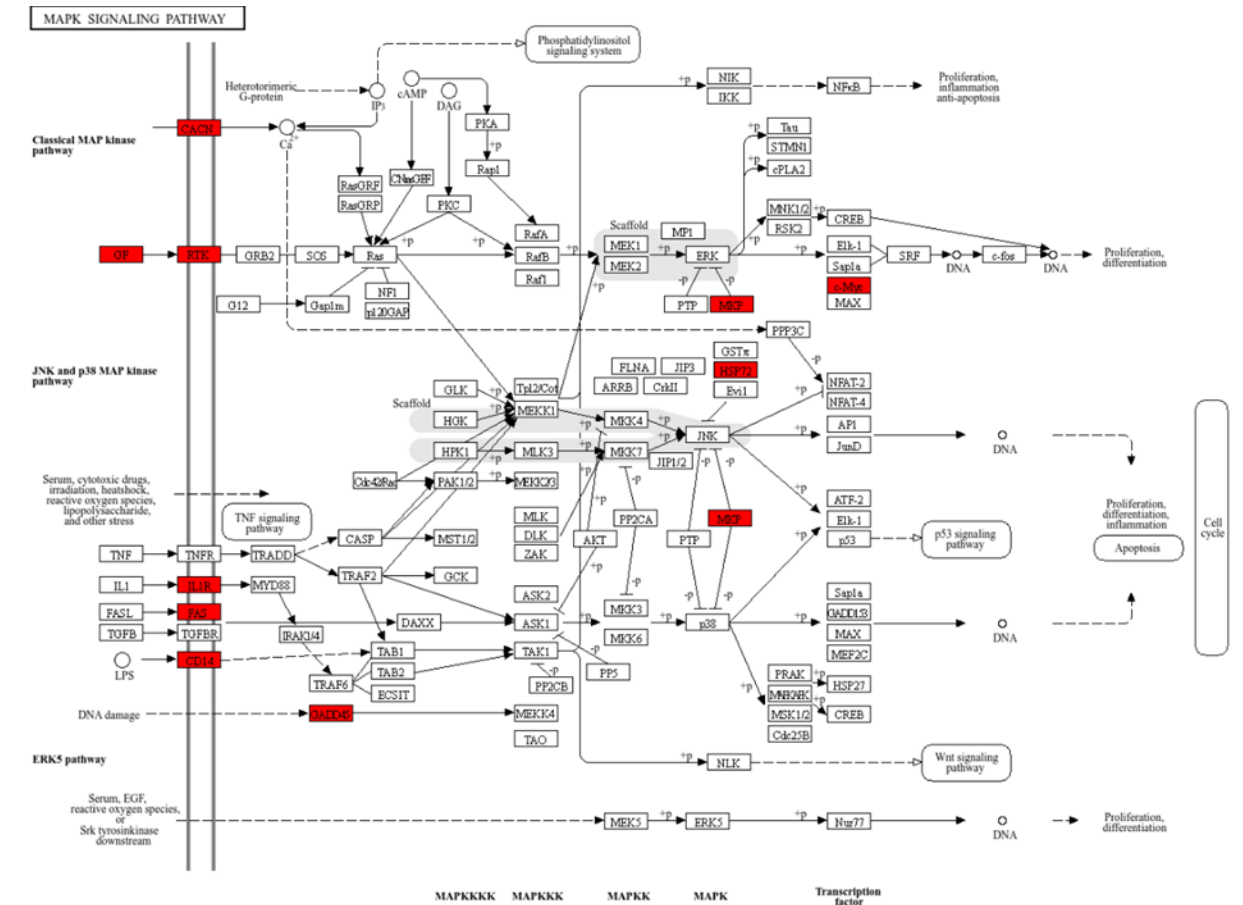


Figure 4: The MAPK signaling pathway with red color indicating high expression.

## 5. Analysis of the Findings

To contextualize the biological impact of the identified differentially expressed genes (DEGs), a pathway enrichment analysis was performed. The resulting pathway maps corroborate the functional roles of our top biomarkers, identifying a landscape of active neuroinflammation and vascular stress.

### 5.1. Vascular Dysfunction and Adrenergic Signaling

The upregulation of ADRA1D in our analysis indicates a disruption in adrenergic signaling, which is critical for vascular tone. This is substantiated by the MAPK Signaling Pathway visualization (fig 4), which highlights the upregulation of Voltage-dependent calcium channels (CACN). Since alpha-adrenergic receptors (ADRA1D) function by increasing intracellular calcium to trigger smooth muscle contraction, the upregulation of CACN provides a clear mechanistic link to

vascular constriction. This aligns with Akinaga et al. (2019), who confirm that the alpha-adrenoceptor subtype is predominant in large arteries and regulates vascular tone. Furthermore, they highlight the receptor's critical role in the hippocampus for memory consolidation, supporting our finding that ADRA1D upregulation may serve as a molecular bridge between the vascular complications of COVID-19 and the cognitive deficits of Alzheimer's.

## 5.2. TNF Signaling and Unchecked Inflammation

The downregulation of the protease inhibitor SERPINA3 in our analysis suggests a compromised ability to dampen the inflammatory response. This is visually confirmed by the TNF Signaling Pathway analysis, which reveals a robust upregulation of chemokines involved in leukocyte recruitment (Ccl2, Cxcl1, Cxcl2, Cxcl3). The diagram illustrates a hyper-inflammatory state called "cytokine storm." The suppression of SERPINA3, which normally acts as a "brake" on proteolytic cascades, likely contributes to this unchecked upregulation of inflammatory markers. Licastro et al. (2005) established that SERPINA3 is a critical genetic factor in Alzheimer's disease, directly linked to the regulation of neuroinflammation and amyloid plaque formation. Therefore, the suppression of this gene in our dataset indicates a compromised ability to control inflammation, potentially leading to the unchecked neurotoxicity observed in both COVID-19 and dementia.

## 6. Conclusion

This analysis elucidates the shared biomarkers between COVID-19 and Alzheimer's disease, identifying specific pathway dysregulations that indicate their bidirectional risk. The integration of differential gene expression with pathway enrichment reveals two critical mechanisms including vascular and adrenergic stress highlighted in the upregulation of ADRA1D that is highly linked to the increased calcium channel activity observed in MAPK signaling pathway of both conditions. Additionally, inflammatory dysregulation where the suppression of SERPINA3 correlates with a hyper-activated TNF signaling pathway, confirming that the loss of this protease inhibitor fuels the cytokine storm via Ccl2, Cxcl1. To summarize, these findings provide molecular evidence that SARS-CoV-2 infection increases neurodegenerative risks through specific, identifiable pathways, highlighting ADRA1D and SERPINA3 as potential therapeutic targets to mitigate post-infectious cognitive decline.

## References

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