

Differential Expression and Network Architecture of Inflammasome-Related Genes in the Alzheimer's Disease Hippocampus

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BACKGROUND

Inflammasomes are key drivers of neurodegeneration in AD, linking amyloid and tau pathologies with neuroinflammation¹. They promote inflammation through caspase-1 activation, IL-1 β B and IL-18 release and pyroptosis². The hippocampus, critical for memory, shows early inflammasome-related changes in AD. RNA-Seq analysis can identify DEGs, hub genes, and signaling pathways linked to inflammasome activation. This approach may reveal biomarkers and therapeutic strategies for AD.

OBJECTIVES

- To investigate DEGs associated with inflammasome activation in AD, with a focus on the human hippocampus, as identified through RNA-Seq and gene expression profiles.
- To AD. identify major signaling pathways, hub genes, and potential biomarkers or therapeutic targets linked to the inflammasome in

METHODOLOGY

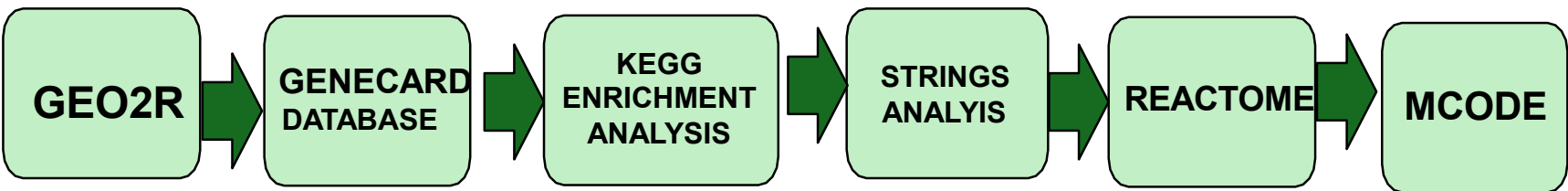


Figure 1. Bioinformatics Workflow for Differential Gene Expression and Pathway Analysis.

1. Biological pathway enrichment analysis: revealed key convergent pathways linked to inflammasome regulation in AD, including NF- κ B, TNF, NOD-like receptor, apoptosis, TLR, and AD signaling.

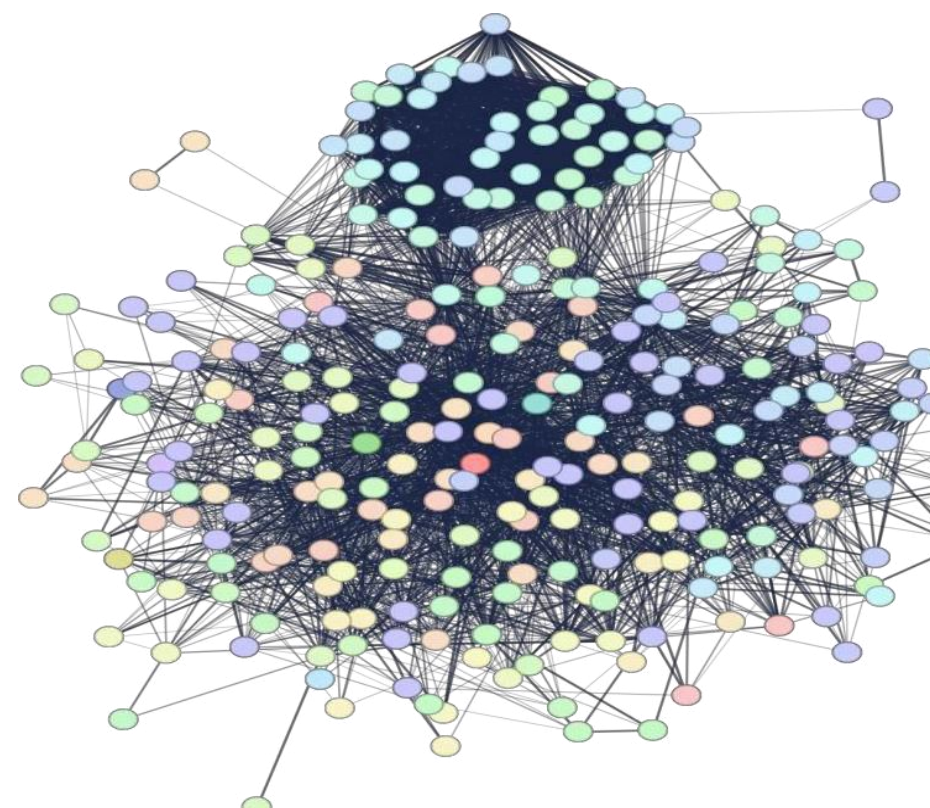
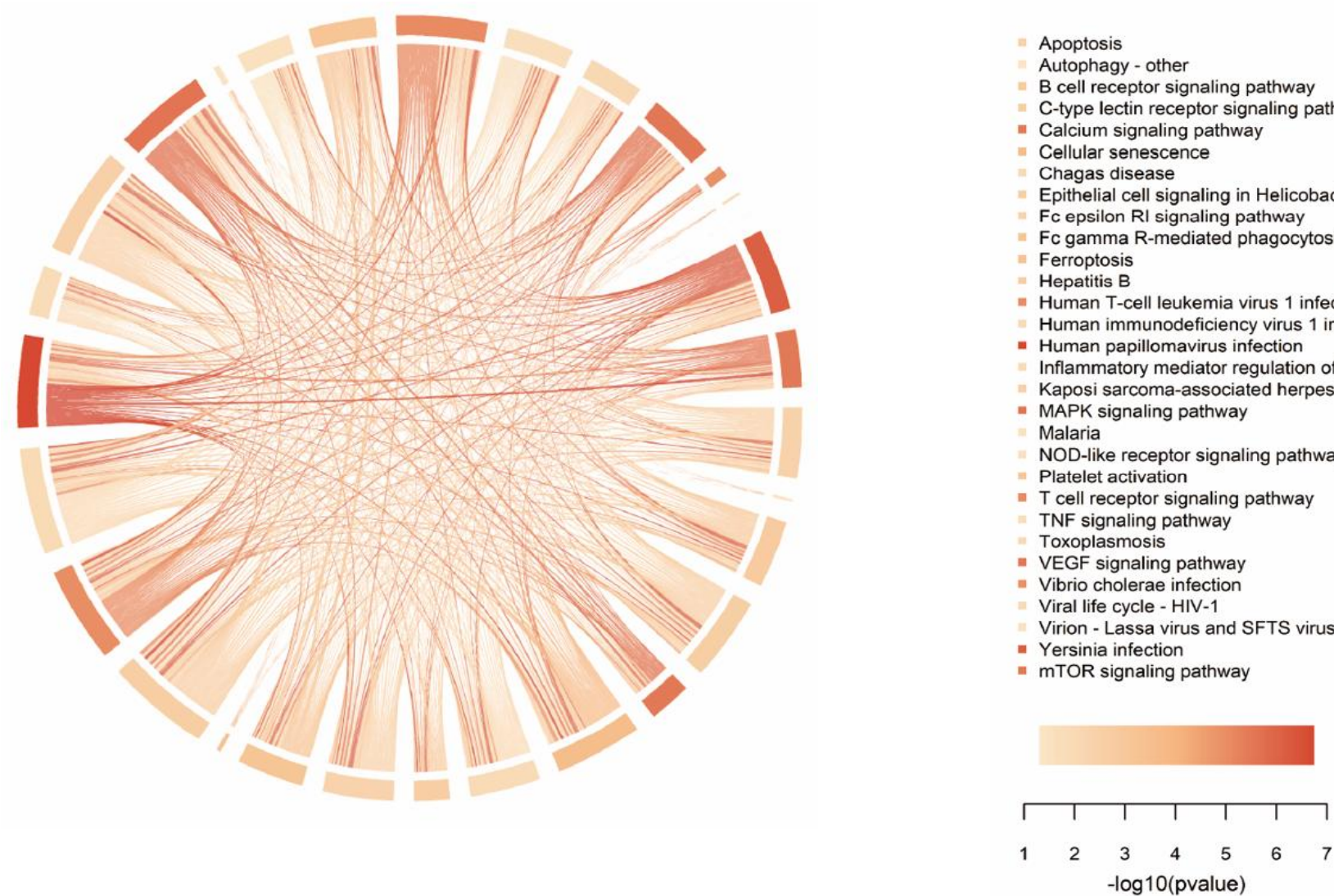


Figure 2. KEGG enrichment analysis showing the top TWENTY-NINE Inflammation-related and inflammasome-related pathways identified from hippocampal DEGs

2. Network Topology of DEGs Linked to Inflammasome Activation

A The architecture that highlights the functional specialization within the inflammasome network: hub proteins likely bottleneck proteins stabilize core signaling units, whereas between modules, coordinate crosstalk including oxidative stress, and cytokine release.

RESULTS

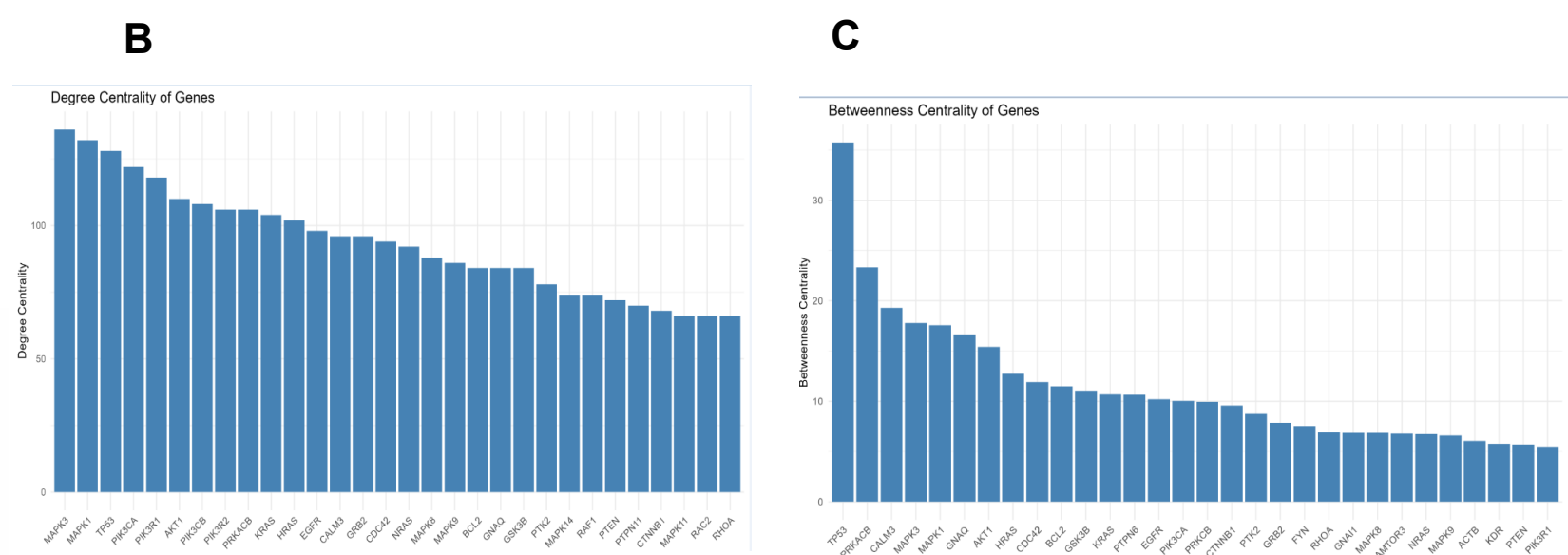


Figure 3. (A) Global architecture of the PPI network generated via STRING database (B) Ranking of the top 5% hub genes identified by degree centrality (DC) values. (C) Ranking of the top 5% bottleneck genes identified by betweenness centrality (BC) values.

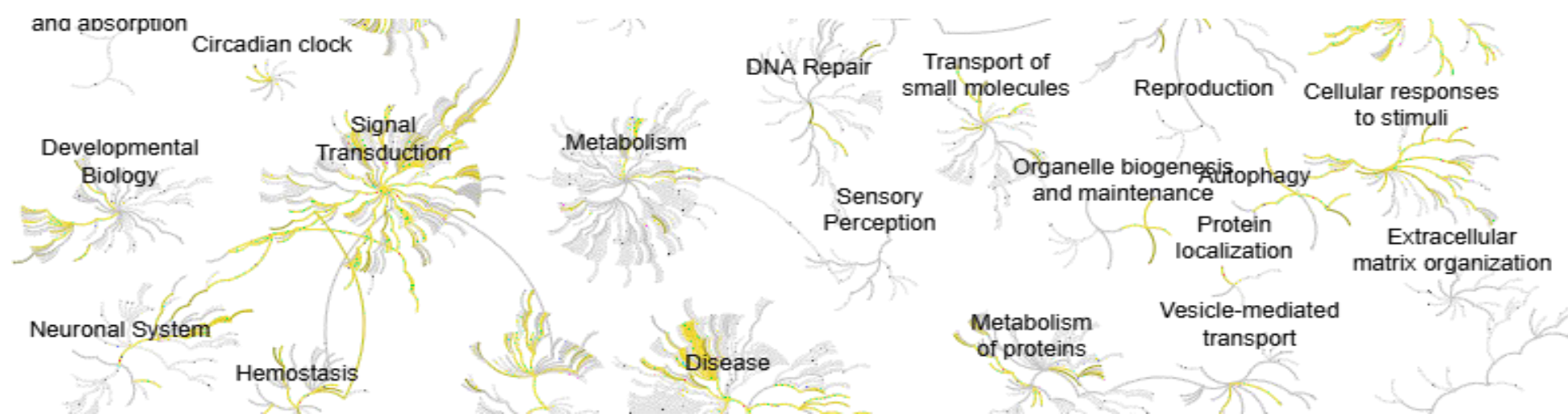


Figure 4. Reactome pathway enrichment analysis of all genes, (N=677) illustrating overlapping pathways. Pathways are ranked based on adjusted false discovery rate

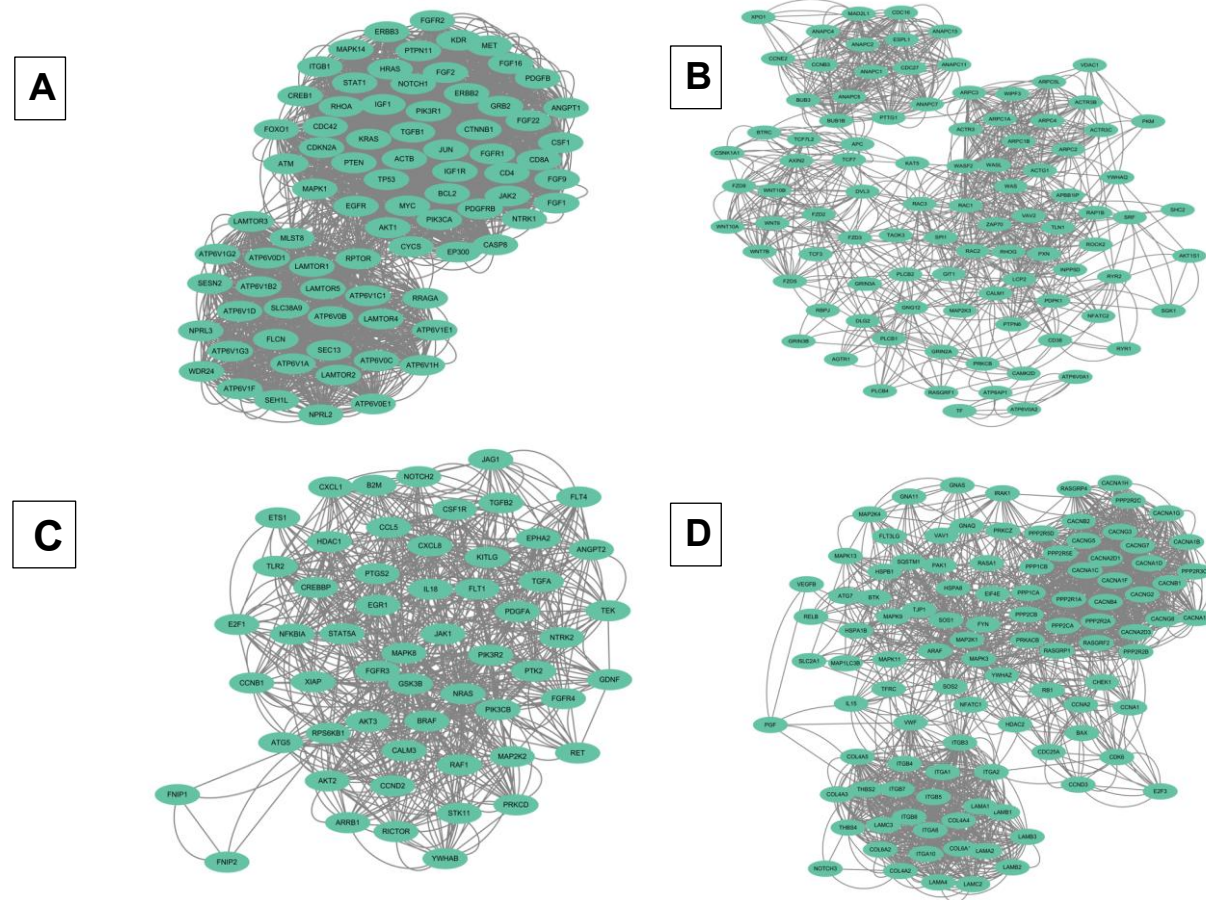


Figure 5. MCODE-derived functional modules in the inflammasome PPI network: **A.** Cluster 1 – Hub-enriched immune signaling **B.** Cluster 2 – Integrin–ECM adhesion and signaling (ITGA/ITGB, ECM, kinases)

CONCLUSION

In conclusion, this study highlights a systems-level framework in which multiple signaling pathways converge to modulate inflammasome activity in AD. The observed modular network structure, dominated by TLR, mitochondrial, and cytokine-related pathways, provides a genomic rationale for targeting upstream regulators of inflammasome activation rather than individual inflammasome genes themselves. Such an approach could enable the design of multi-target therapeutic strategies aimed at restoring immune balance in the AD brain.

REFERENCES

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2. Freeman, L., Guo, H., David, C.N., Brickey, W.J., Jha, S., Ting, J.P.-Y., 2017. NLR members NLRC4 and NLRP3 mediate sterile inflammasome activation in microglia and astrocytes. *Journal of Experimental Medicine* 214(5), 1351–1370.