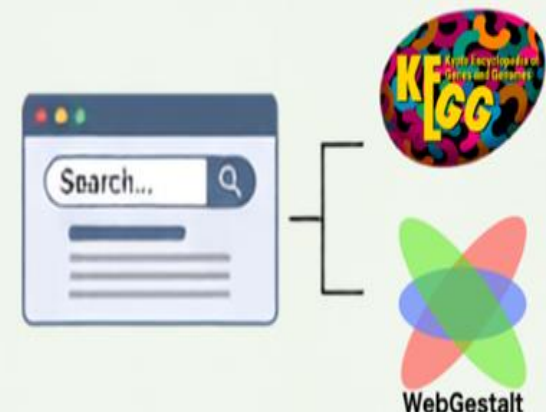
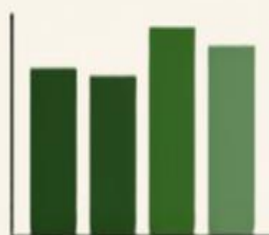
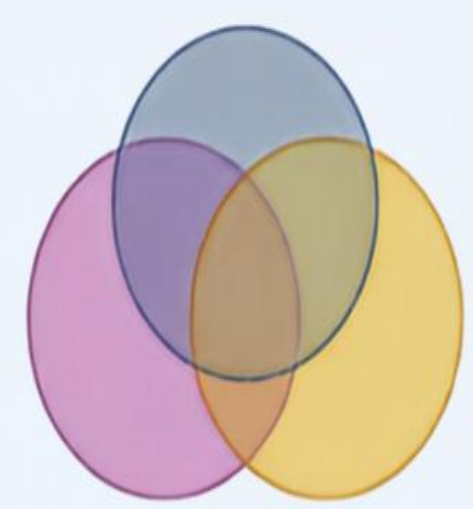
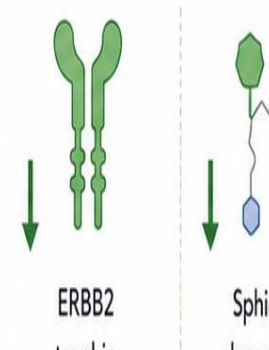
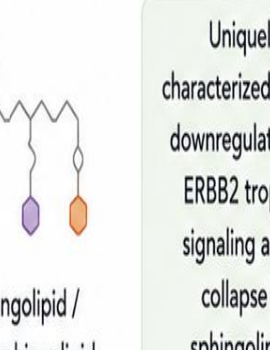
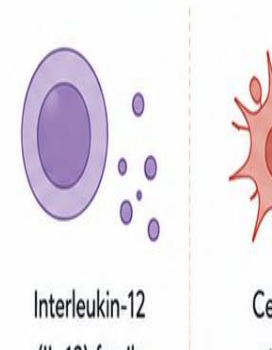
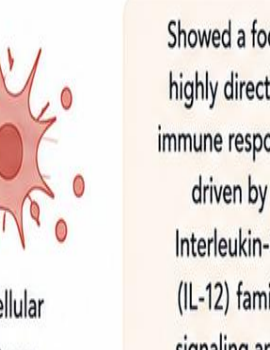
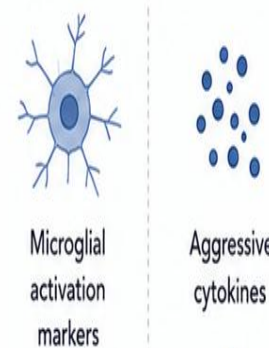
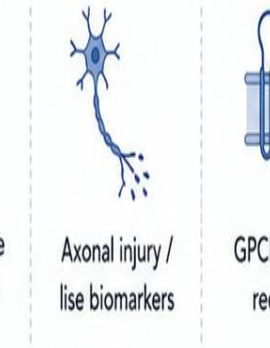
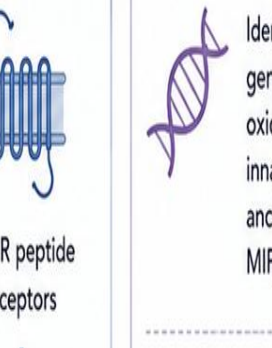
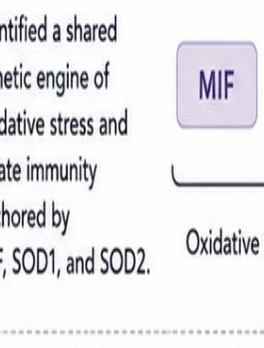
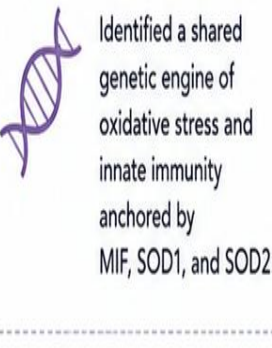
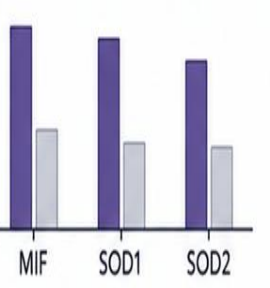
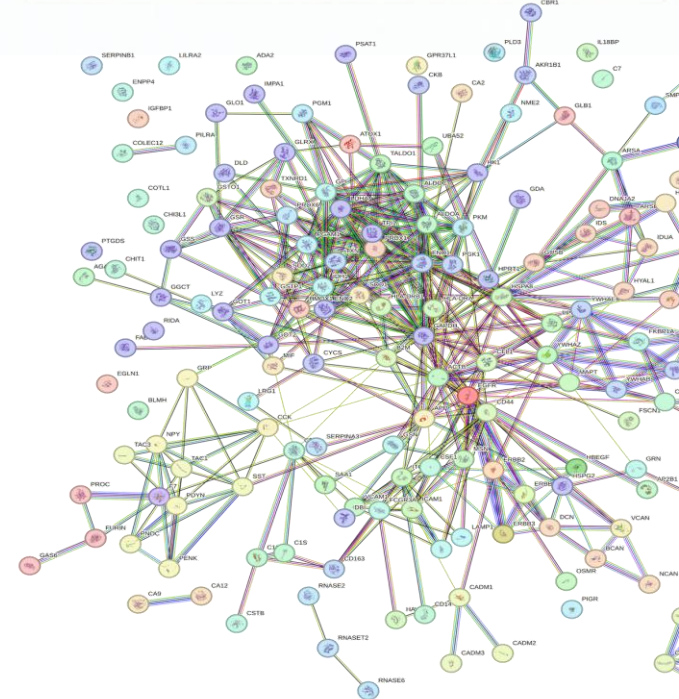


Divergent Neuroinflammatory Pathways In Alzheimer's Disease And Down Syndrome: Multifactorial Mechanisms Vs. Genetic Overexpression

Wednesday-0148

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CSF proteomics reveals that sporadic AD (LOAD) is driven by chronic trophic and lipid homeostatic failure, whereas genetic forms (ADAD and 21AD) are fueled by acute oxidative stress and neuroinflammation.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Alzheimer's Disease (AD) exhibits distinct clinical and genetic trajectories across different etiologies, including Late-Onset AD (LOAD), Autosomal Dominant AD (ADAD), and AD associated with Down Syndrome (21AD). Cerebrospinal fluid (CSF) proteomics provides a critical window into these pathological variations. This study aims to compare the functional CSF proteomic landscapes across LOAD, ADAD, and 21AD to delineate shared core pathways and etiology-specific molecular signatures.	1. GSEA USING WEBGESTALT (KEGG & REACTOME)  Gene Set Enrichment Analysis (GSEA) performed on input gene sets against KEGG and Reactome pathway databases. 2. STANDARDIZED INTERGROUP COMPARISON TOP 4 INCREASED PATHWAYS (HIGHEST POSITIVE NES)  TOP 4 DECREASED PATHWAYS (LOWEST NEGATIVE NES)  A standardized intergroup comparison was performed by selecting the top 4 increased and decreased pathways per cohort, using WebGestalt Normalised Enrichment Score (NES). 3. GENE TRIAGE  Identify unique and overlapping genes across three cohorts. 21AD Genes ADAD Genes LOAD Genes 4. PROTEIN-PROTEIN INTERACTION (PPI) NETWORK A high confidence (0.7) protein-protein interaction (PPI) network was constructed using STRING-DB.  STRING-DB Threshold: 0.700 Hiding disconnected nodes 1. LOAD (13 exclusive genes)  ERBB2 trophic signaling  Sphingolipid / glycosphingolipid metabolism Uniquely characterized by the downregulation of ERBB2 trophic signaling and a collapse in sphingolipid / glycosphingolipid metabolism. 2. ADAD (22 exclusive genes)  Interleukin-12 (IL-12) family signaling  Cellular stress responses Showed a focal, highly directed immune response driven by Interleukin-12 (IL-12) family signaling and cellular stress responses. 3. 21AD (137 exclusive genes)  Microglial activation markers  Aggressive cytokines  Axonal injury / lise biomarkers  GPCR peptide receptors Exhibited an expansive, massive neuroinflammatory signature, dominated by microglial activation markers, aggressive cytokines, and active biomarkers of axonal injury/lise, alongside suppressed GPCR peptide receptors 4. Core Genetic Axis (5 shared genes between ADAD and 21AD)  Identified a shared genetic engine of oxidative stress and innate immunity anchored by MIF, SOD1, and SOD2. Oxidative stress and innate immunity MIF SOD1 SOD2 Significantly higher abundance scores in the 21AD cohort compared to ADAD.  Abundance scores 21AD ADAD  Figure 6: Enriched proteins pathways in 21AD, ADAD and LOAD.(enrichment p-value <10×10⁻¹⁶)	CSF proteomics diverges between LOAD (slow lipid homeostatic failure) and genetic forms of AD (acute inflammation and oxidative stress). Furthermore, 21AD displays a major inflammatory cascade compared to a focal response in ADAD. A reflex of the increased genetic expression inherent of the trisomic condition.	van der Ende EL, In 't Veld SGJG, Hanskamp I, et al. CSF proteomics in autosomal dominant Alzheimer's disease highlights parallels with sporadic disease. Brain. 2023;146(11):4495-4507. doi:10.1093/brain/awad213 LOAD Dataset: syn36848078 21AD Dataset: syn61339659	
				SUPPORTERS  MEDICINA  IPq INSTITUTO DE PSIQUIATRIA HCFMUSP  ALZHEIMER'S ASSOCIATION  AAIC 26