Alzheimer's Disease Differential Expression Analysis:

Control v. Incipient

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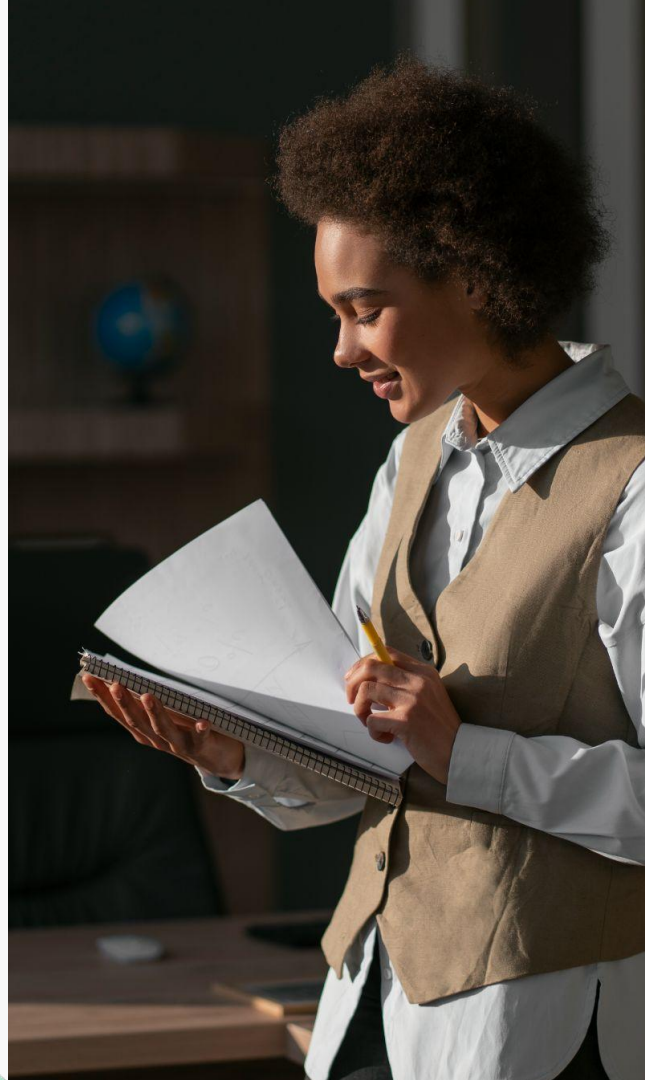
What is Alzheimer’s Disease

- **Alzheimer’s disease (AD):** The most common form of dementia, affecting millions worldwide.
- A progressive **neurodegenerative disorder** characterized by:
  - **Cognitive decline** (e.g., memory loss)
  - **Behavioral changes** impacting daily life
- Common symptoms:
  - **Early:** Mild memory loss, word-finding difficulties
  - **Progressive:** Poor judgment, confusion, apathy, depression

[17], [18]



Hallmark Pathologies of AD

- Amyloid-beta (Aβ) plaques: Extracellular protein deposits that interfere with neuronal communication.
- Neurofibrillary tangles (NFTs): Intracellular clumps of hyperphosphorylated tau protein.
- These pathologies contribute to:
  - Neuronal death and Brain tissue loss
  - Disrupted neuronal communication

[2]

01 Introduction about research problem

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Research Question

What biological pathways and differentially expressed genes are implicated in early AD pathology?

Methodology

Molecular Dataset: 43,135 Features
Clinical Dataset: 30 Patients

Data Source

2 Significant Pathways
4 DEGs

Top Results

Sample

15 Patients:
8 Control Group
7 Incipient Group

Analysis

Step 1: Exploratory Data Analysis
Step 2: Gene Expression Analysis
Step 3: Systems Biology Analysis

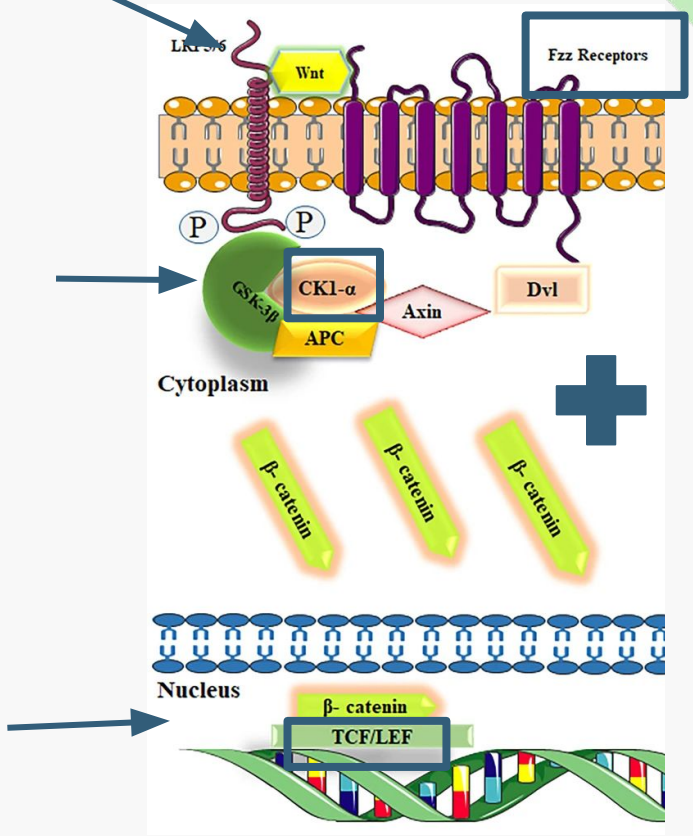
Top Pathway Results

Term	Results	Biological Relevance to AD
Wnt signaling pathway	Appeared consistently across databases	Regulates neuronal development, differentiation, and survival [1]
Interleukin-6-Mediated signaling pathway	Appeared consistently across databases	Implicated in inflammatory responses and neuronal apoptosis [5]
Neuronal System	High overlap in Reactome	Major organ system affected by AD [2]
cAMP signaling pathway	High overlap in KEGG	Implicated in neuronal apoptosis [4]
Adherens Junction pathway	Appeared consistently across databases	Supports neuronal connections [3]

Wnt / β-catenin Signaling Pathway in Brain

Wnt signaling promotes synaptic plasticity and provides neuroprotective effects

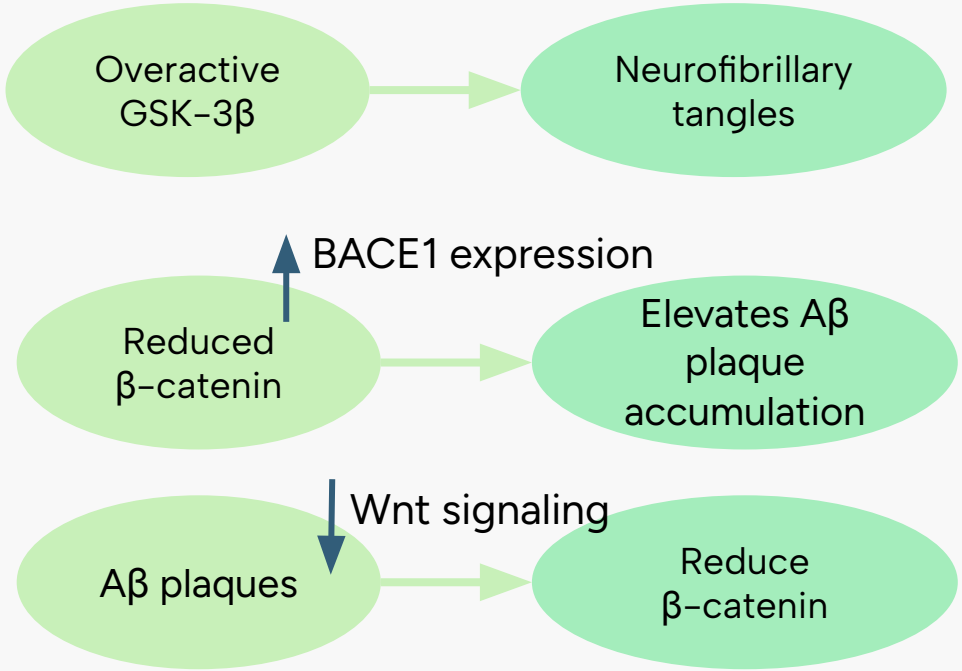
1. Wnt ligand binds to Frizzled receptors on cell surface
2. Destruction complex is inhibited, allowing β-catenin to accumulate in the cytoplasm
3. β-catenin translocates to the nucleus and interacts with TCF/LEF to regulate target genes



[1, 6, 7, 8, 9]

Wnt / β-catenin Signaling Pathway in AD

Components of the Wnt / β-catenin signaling pathway are often disrupted in AD patients:



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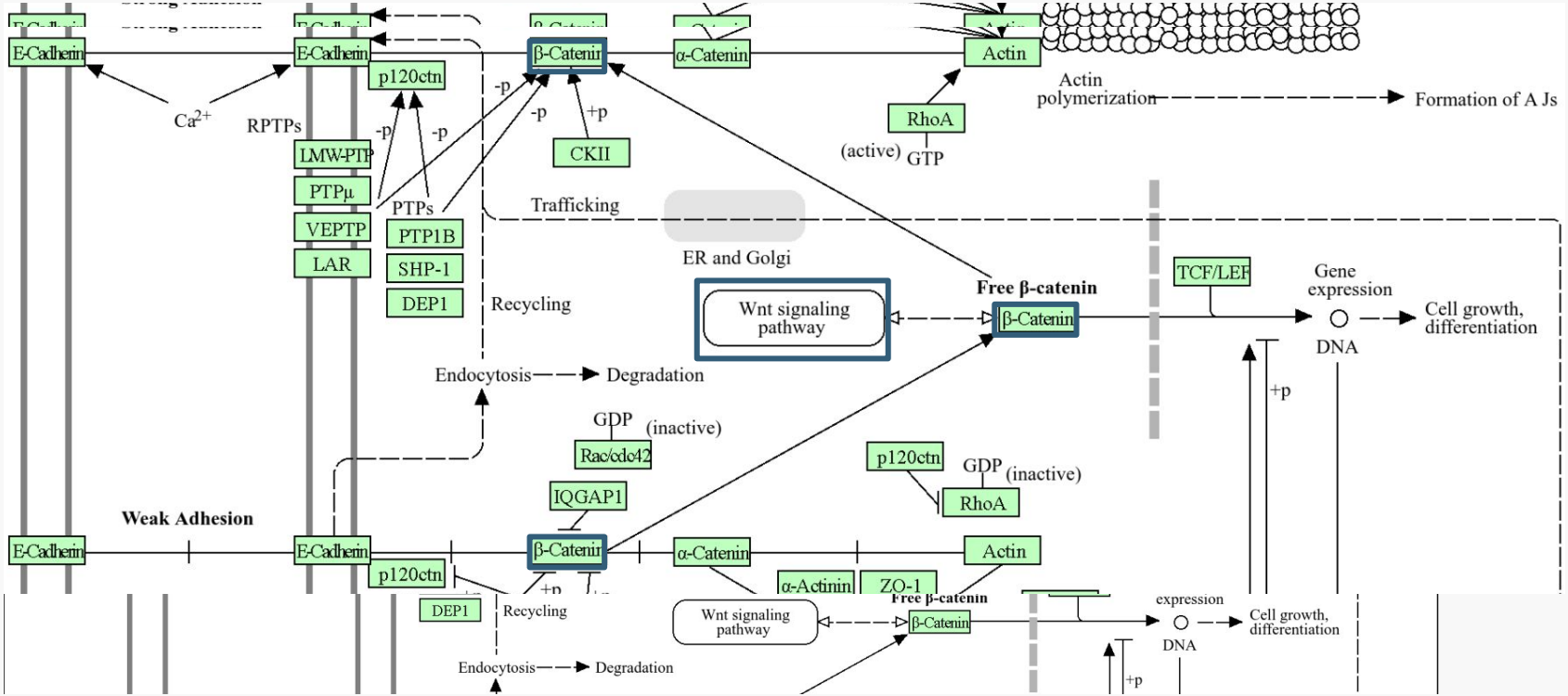
Adherens Junction Pathway

[12]

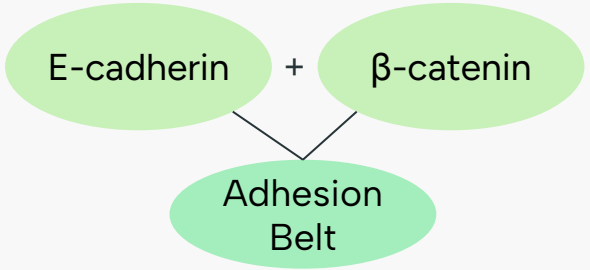


Adherens Junction Pathway in Brain

- Tissue Structure
- Permeability
- Cell Communication

[13]

"Down-regulation or deletion of E-cadherin is significantly related to ... poor prognosis."



- VE-cadherin expression reduced
- Binding with fibrinogen-Aβ related to cognitive disorders
- Affects blood flow to brain
- Affects permeability

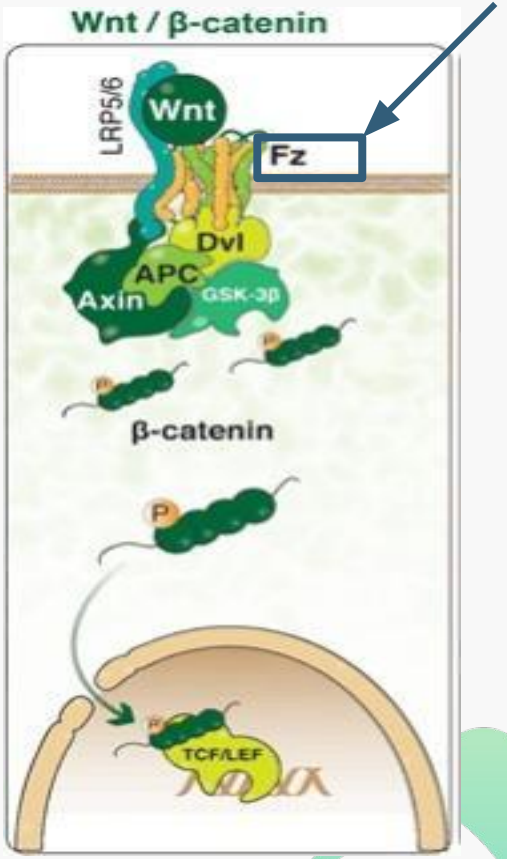
[3]

- Helps tissue structure of Blood-Brain Barrier
- Barrier = brain permeability
- “damage in the hippocampus, cortex, and cerebrospinal fluid” found in AD cases

[14]

Frizzled-8 (FZD8)

- What is it?
  - Member of the Frizzled Receptor family, classified as Wnt receptors that mediate diverse functions in neurons including **neurogenesis** [23]
  - Essential for **WNT activation and signal transportation** [22]
  - Plays a vital role in **stabilizing β-catenin** [21]
  - **Frizzled–Wnt signalling** is important for maintaining a **healthy nervous system** [22]



Frizzled-8 (FZD8)

- Relevance to Alzheimer's Disease:
  - Impaired frizzled receptors function may lead to disruptions in wnt signaling, linked to **neuronal damage**, **synaptic loss**, and **cognitive decline** in Alzheimer's. [25]

- Findings:
  - It was upregulated in **incipient AD** patients with a signed fold change of 1.49
    - P-Value 0.0062
    - CI (0.20, 0.96)
  - This upregulation could indicate an attempt to **counteract early AD pathology** or reflect **underlying changes in Wnt signaling activity**

SMAD4 (Mothers Against Decapentaplegic Homolog 4)

Function

- Found on chromosome 18
- Transmits signals from cell surface to nucleus
- Cell growth/division
- Transcription factor
- Tumor suppressor

[15]

Relevance to Alzheimer's

- Increased expression associated with AD
- Highly expressed SMAD4 leads to increasing gene transcription of genes associated with Alzheimer's
- SMAD4 alone not significant, found to be significant in TGF-β pathway which is present in both of our chosen pathways

[16]

SMAD4 (Mothers Against Decapentaplegic Homolog 4)

Results: Significant results from two probes

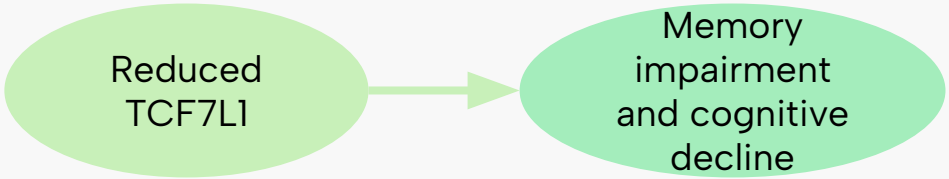
- Upregulated in **incipient AD** patients compared to controls with a signed fold change of 1.48
  - P-value: 0.0002
  - CI: (0.32, 0.80)

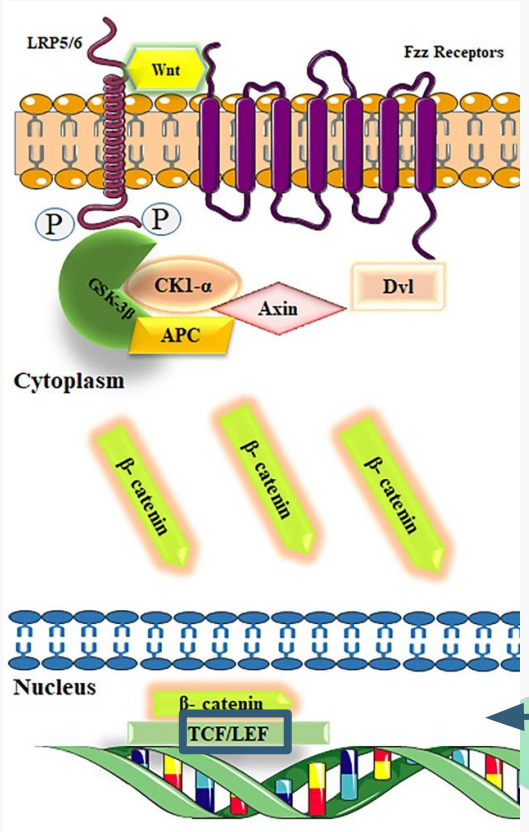
- Downregulated in **incipient AD** patients compared to controls with a signed fold change of -1.19
  - P-value: 0.005
  - CI: (-0.41, -0.09)

Could indicate different functions of SMAD4 may contribute to AD when over or under expressed

TCF7L1 (Transcription Factor 7 Like 1)

- What is TCF7L1?
  - Member of the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors
  - In Wnt signaling pathway, it acts as a **transcriptional activator** upon β-catenin accumulation [1]
- Relevance to Alzheimer's Disease:
  - TCF7L1 is **significantly reduced** in hippocampus of AD patients [10]





TCF7L1 (Transcription Factor 7 Like 1)

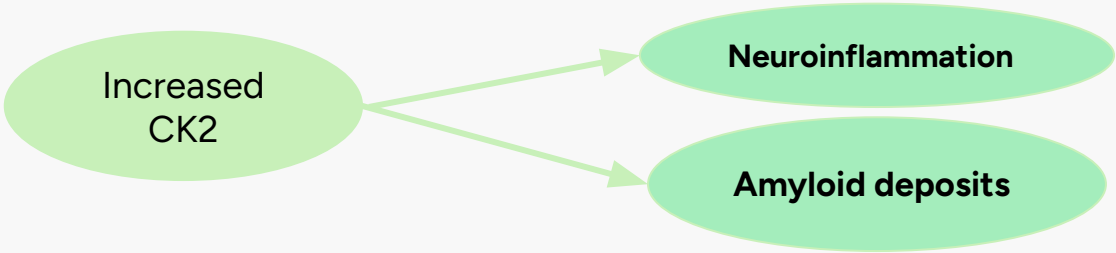
Results:

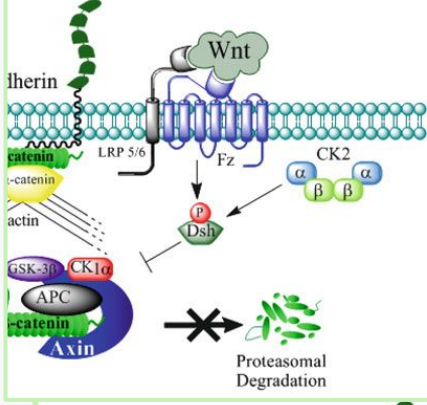
- We found TCF7L1 to be **upregulated in incipient AD** patients compared to controls with a signed fold change of 1.39
  - P-value: 0.009
  - CI: (0.14, 0.81)
- Might suggest a **compensatory response to early neurodegeneration**, though further research is needed to confirm this

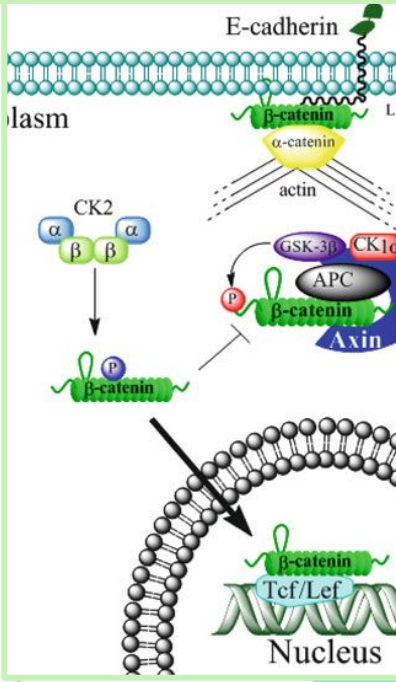
CSNK2A2 (Casein Kinase 2 Alpha 2)

- What is CSNK2A2
  - Constitutively active serine/threonine kinase
  - Member of protein kinases that regulates cell growth, DNA repair, and apoptosis inhibition.
  - Role In Wnt Signaling Pathway [19]:
    - CK2 stabilizing β-catenin, a critical component for activating Wnt target genes

- Relevance to Alzheimer's Disease
  - **CK2 levels increased** within the **hippocampus and temporal cortex** of AD patients [20]







CSNK2A2 (Casein Kinase 2 Alpha 2)

Results:

- We found **CSNK2A2 to be down regulated in incipient AD patients** compared to controls with a signed fold change of -1.40
  - P-value: 0.007
  - CI: (-0.81, -0.17)
- Might suggest compensatory mechanism to hyperphosphorylation of Tau by CK2 but need more research

Conclusions

- FZD8 gene was found to be upregulated, however, limited research links it directly to AD. The majority indicate that it may play a role in several types of cancer rather than Alzheimer's

- TCF7L1 results contradict literature, suggesting further research on compensatory mechanisms in early AD patients

- SMAD4 showed both downregulation and upregulation in some of the incipient group

Future Improvements

- **Expanded Cohort for Wnt/Adherens Pathway Biomarkers**
  - To validate the identified genes as biomarkers in larger and diverse patient cohorts.
- **Longitudinal Analysis of Wnt and Adherens Pathways**
  - To observe the progressive changes in the pathways from early to advanced stages of AD. This could reveal critical stages where pathway dysfunction accelerates AD progression.
- **Investigate Compensatory Mechanisms**
  - Exploring additional cohorts could help confirm or clarify the reasons behind the upregulation and downregulation of the genes, potentially revealing compensatory responses to neurodegeneration in the early stages of Alzheimer's disease.

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