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I hypothesise, BACE1, a key β -secretase enzyme involved in amyloid precursor protein cleavage, may exhibit altered localization from postsynaptic to perisynaptic and endocytic regions in Alzheimer's disease, reflecting synaptic compartment-specific dysregulation of amyloidogenic processing.

Knowledge Graph Analysis Report: BACE1 Localization in Alzheimer's Disease

Conclusion: The knowledge graph model's results provide **strong computational support** for the hypothesis that BACE1 may exhibit altered localization from postsynaptic to perisynaptic and endocytic regions in Alzheimer's disease, reflecting synaptic compartment-specific dysregulation of amyloidogenic processing. The model identified numerous plausible new relationships connecting BACE1, amyloid precursor protein processing, and the context of Alzheimer's disease.

The Big Picture: Statistical Overview

The knowledge graph experiment evaluated the relationships between 97 unique biological entities. A total of 3,615 potential relationships (triples) were analyzed.

- **Confirmed Knowledge (Accepted):** 97 existing relationships were correctly identified and accepted by the model.
- **New Connection Discoveries (Accepted):** 585 novel relationships were predicted as plausible and accepted by the model, suggesting previously uncharacterized biological connections.
- **Rejected Ground Truth:** 4 known relationships were correctly identified as unlikely and rejected by the model.
- **Rejected New Triples:** 2,929 potential new relationships were filtered out as unlikely, indicating the model's ability to discern meaningful connections from noise.

Key Thematic Findings with Quantitative Support

The analysis reveals several key thematic connections that support the hypothesis, with scores closer to zero indicating higher confidence in the predicted relationship.

1. **BACE1 and Amyloid Precursor Protein (APP) Processing:**

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I hypothesise, The spatial distribution pattern of BACE1 within excitatory synapses may be conserved between transgenic APP/PS1 mouse models and sporadic human Alzheimer's disease cases, suggesting shared mechanisms of synaptic amyloid processing across species.

Based on the knowledge graph analysis, the results **partially support** the hypothesis. While the model identified existing relationships and generated some plausible connections related to BACE1, APP, and Alzheimer's disease, it did not extensively explore the specific context of "excitatory synapses" or directly link these to "sporadic human Alzheimer's disease cases" in a manner that definitively confirms conservation across models and human conditions. The rejected ground truth triples suggest limitations in the model's ability to identify nuanced functional relationships within the synaptic context.

The Big Picture: Statistical Overview

The knowledge graph model processed a total of 668 relationships. Of these, 15 known relationships were confirmed as true and accepted. Additionally, 46 new triple predictions were deemed plausible and accepted. A significant number of relationships, 605, were predicted as false and rejected. Finally, 2 known relationships were incorrectly rejected by the model.

Key Thematic Findings with Quantitative Support

1. **Established Links between BACE1, APP, and Alzheimer's Disease:**
 - BACE1 is linked to Alzheimer's disease via the **gene_disease** relationship with a score of **-0.0359**.
 - APP is also strongly associated with Alzheimer's disease through **gene_disease** with a score of **-0.0095**.
 - The **gene_gene** relationship between BACE1 and APP, crucial for amyloid processing, was confirmed with a score of **-0.0196**.
 - The link between APP and the Alzheimer's disease pathway (KEGG: map05010) was accepted with a score of **-0.0226**.
2. **Predicted Novel Associations and Potential Synaptic Relevance:**
 - While "excitatory synapses" is not directly present in the accepted triples, some predictions hint at processes relevant to synaptic function.
 - A new prediction links BACE1 to a phenotype related to **decreased synaptic glutamate release** with a score of **-0.4590**.
 - Predictions also connect BACE1 and APP to cell types associated with Alzheimer's disease, such as **"Alzheimer disease specific cell type"** (BTO:0000590) with scores of **-0.1778** for BACE1 and **-0.1402** for APP.

Supplementary Figure 8: EvoAge hypothesis generated for the asked questions.

(a) EvoAge response to the hypothesis of BACE1 relocation from postsynaptic to perisynaptic region. **(b)** EvoAge response to the hypothesis of BACE1 distribution in mouse and human models.