

The Role of *MEN1* in Neurodegeneration: Insights from Postmortem Human Brains with Alzheimer’s Disease

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Increased Expression of *MEN1* and Related Cholinergic and Synaptic Genes in Alzheimer’s Disease Tissue

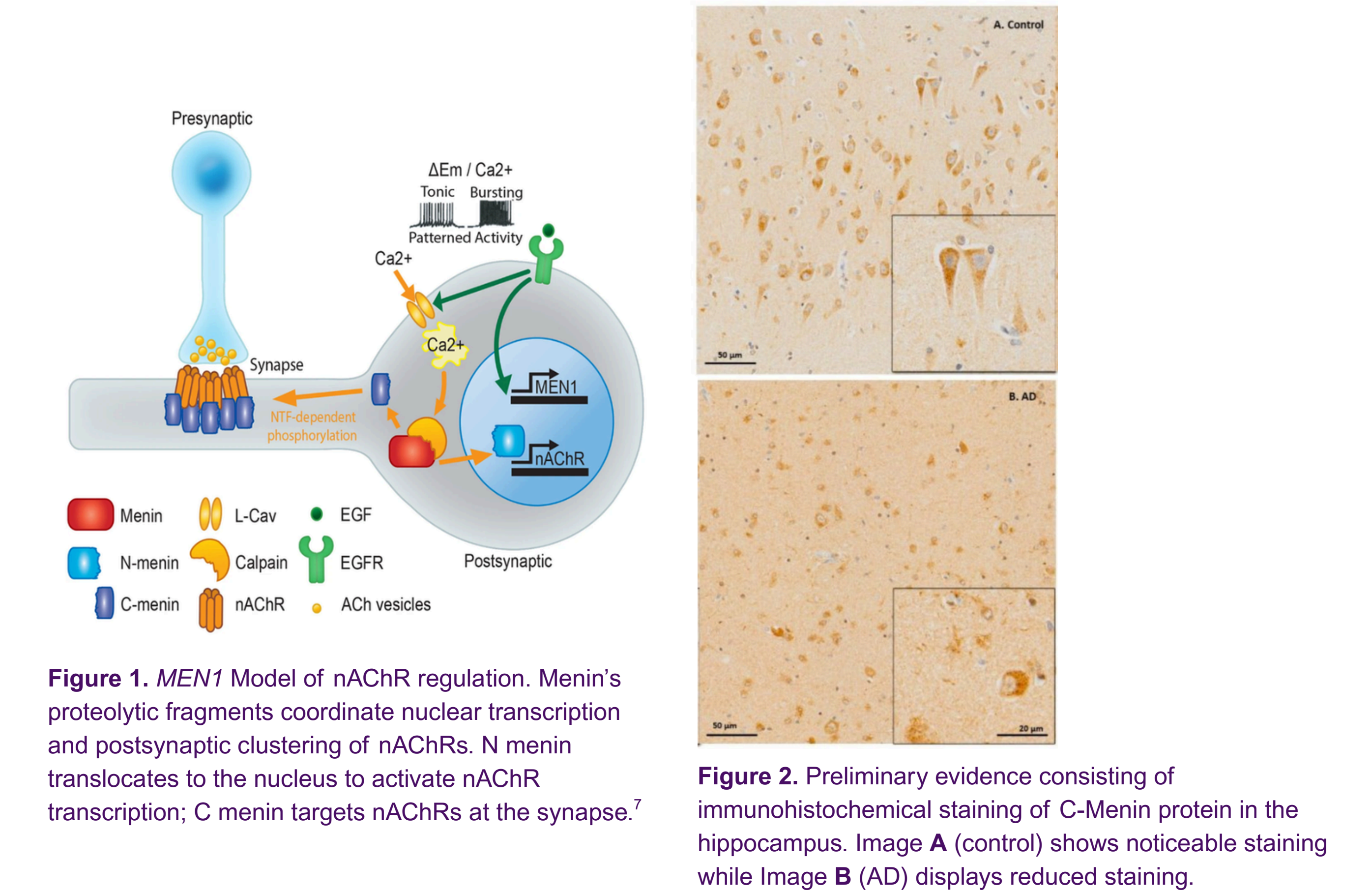
Introduction

- 155 million people live with dementia globally: **Alzheimer's disease (AD)** accounts for **60-70%** of these cases. Currently, no cure or truly preventative treatment exists.¹
- 2Despite significant progress in understanding tau and amyloid pathology (Tau and Amyloid hypotheses), AD's fundamental mechanisms remain elusive.
- 3The **Cholinergic Hypothesis** of AD: implicates impaired cholinergic synaptic function underlying learning, memory and cognition where **nicotinic acetylcholine receptors (nAChRs)** play an important role.²

Multiple Endocrine Neoplasia Type 1 (*MEN1*)

MEN1 is mainly known as a tumor-suppressor gene: it functions in cell cycle signaling, DNA repair and transcriptional regulation. It encodes the scaffold protein **menin**.^{2,3}

- MEN1* knockdown blocks synapse development.⁴
- MEN1* regulates nAChR expression and function.^{4,5}
- Loss of *MEN1* impairs learning and memory in mice.⁶



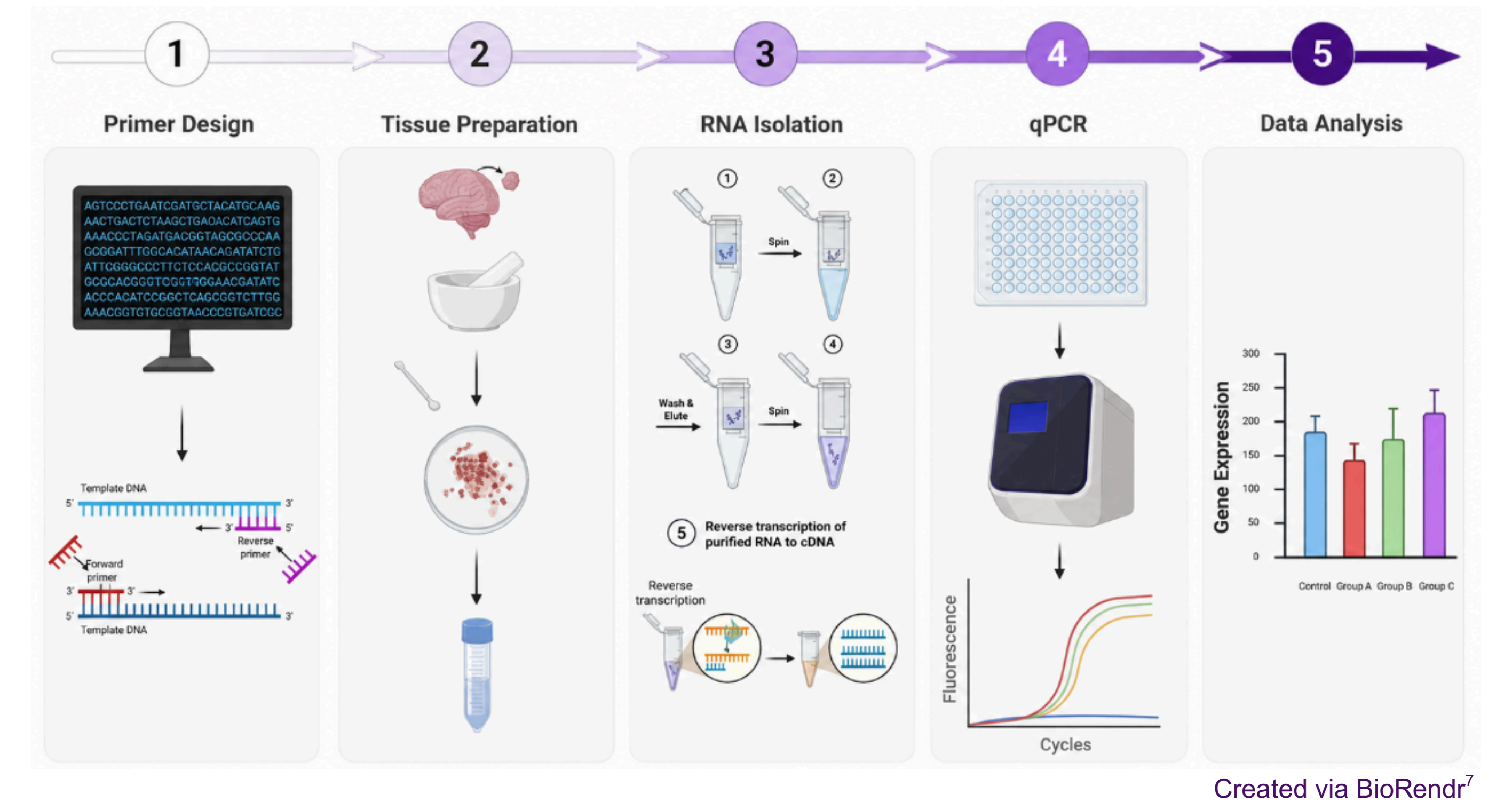
Research Question

Is ***MEN1* expression altered** in individuals with AD, and do related **cholinergic and synaptic genes** show similar directional changes?

Brain Samples: Entorhinal Cortex

Subject	RNA Integrity	Age	Sex	Race	Postmortem Interval (h)	Diagnosis	NeuroBioBank
1	6.1	83	Male	White	18.68	Control	Harvard
2	3.3	55	Female	White	21.66	Control	
3	1.5	58	Female	White	12.92	Early-onset AD	
4	5.7	59	Female	Unknown	21.67	Control	
5	3.4	57	Female	White	24.68	Early-onset AD	
6	2.9	57	Male	Unknown	20.47	Control	Mount Sinai
7	6.4	80	Female	Unknown	26.67	Control	
8	3	58	Male	White	4.83	Early-onset AD	
9	7.6	85	Female	White	8	Control	
10	6.9	83	Male	African-American	2.5	Late-onset AD	
11	5.9	84	Male	White	22.25	Late-onset AD	Miami
12	7.1	87	Female	White	6.5	Late-onset AD	
13	3.6	86	Female	White	5.1	Control	
14	5.3	59	Male	White	28.2	Control	
15	2.1	58	Male	White	27.3	Control	
16	6.3	58	Female	White	8.75	Control	Pittsburgh

Methods



Results

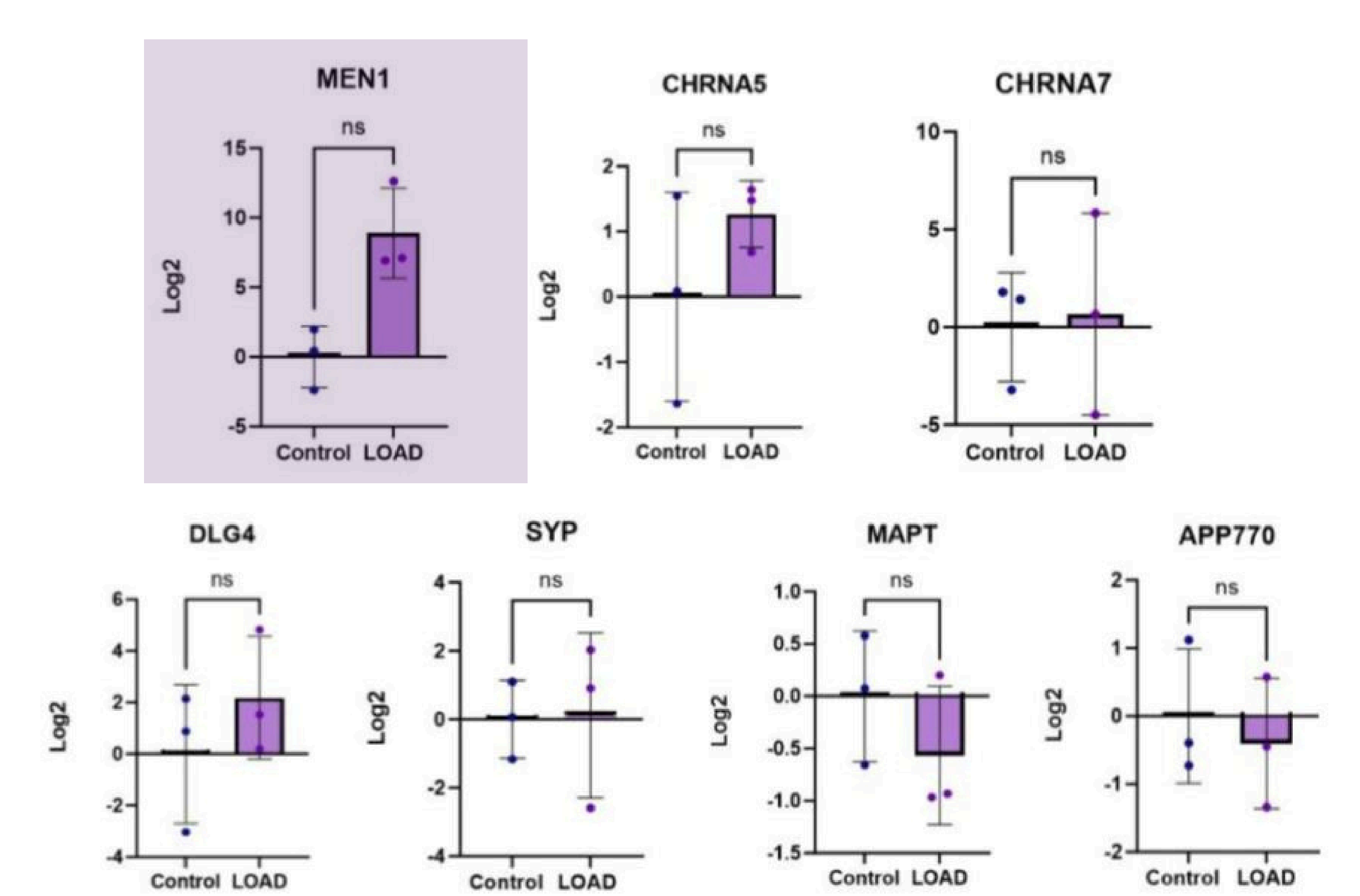


Figure 3. Summary data, gene expression fold change in late-onset Alzheimer's disease of *MEN1* and genes implicated in amyloid (*APP*), tau (*MAPT*), and cholinergic (nAChR5, nAChR7) pathology, as well as synaptic function (*DLG4*, *SYP*), from human entorhinal cortex samples (n = 3 per group) measured by qPCR. Expression levels were calculated using the $\Delta\Delta C_t$ method. Bars represent mean $\pm$ SEM. Statistical comparisons were conducted using the Mann-Whitney test: $p < 0.05$ was considered statistically significant.

GENE GROUP	GENE	DIRECTIONAL TREND IN LOAD
$\alpha 5$ nAChR subunit (regulated by menin)	<i>CHRNA5</i>	↑ Increased
$\alpha 7$ nAChR subunit (regulated by menin)	<i>CHRNA7</i>	↑ Increased
PSD-95 postsynaptic protein	<i>DLG4</i>	↑ Increased
Synaptophysin presynaptic protein	<i>SYP</i>	↔ No clear directional change
Microtubule-associated protein tau	<i>MAPT</i>	↓ Decreased
Isoform of amyloid precursor protein	<i>APP770</i>	↓ Decreased

LOAD = Late-onset Alzheimer's disease. Arrows summarize the direction of expression observed in the results graphs.

Conclusions

- ➔ *MEN1* expression in the entorhinal cortex was higher in late-onset AD group with an average 8.9 fold change
- ➔ Cholinergic genes associated with proteins menin regulates (*CHRNA5*, *CHRNA7*), and a postsynaptic protein menin co-localizes with (*DLG4*), showed similar upward directional trends.
- Together, these findings are consistent with a possible *MEN1*-associated cholinergic and postsynaptic compensatory response in response to AD pathology.
- Alternatively, increased *MEN1* expression may reflect broader cellular stress responses or a neuroprotective function with preferential survival of neurons with high *MEN1* expression.

Future Directions

- Integrate immunohistochemical and proteomic analysis to confirm menin expression and abundance between groups.
- ↓
- Replicate findings in a larger and more diverse cohort, including exploring differences with early-onset AD cases.
- ↓
- Determine whether *MEN1* expression tracks with $\alpha 5/\alpha 7$ nAChRs and PSD-95 at the protein level.

References

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