FAD$^{3T(APP/PS1/Tau)}$

Strain Name： C57BL/6JGpt-Tg(Thy-APP/Thy-PSEN1/Thy-MAPT)17/Gpt
Strain Type： Tg
Strain Number： T049751
Background： C57BL/6JGpt

Description

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder that severely impairs patients' ability to perform daily activities. AD is progressive and typically manifests in individuals over 65, with age being a significant risk factor. Symptoms of AD include memory loss, aphasia, identity loss, executive dysfunction, and alterations in personality and behavior. Pathological studies indicate that AD progression is closely linked to the accumulation of amyloid-beta (Aβ) protein fragments and Tau protein tangles (paired helical filaments) [1-2].

The underlying causes of AD are not yet fully understood, but genetic mutations are thought to be significant risk factors. Genes such as amyloid-beta precursor protein (*APP*), Presenilin 1 (*PSEN1*), and Presenilin 2 (*PSEN2*) are commonly mutated in familial cases of AD. These mutations impact pre-amyloid cleavage, leading to elevated production of Aβ42 and subsequent formation of amyloid plaque [3-4].

Tau, a microtubule-associated protein encoded by the *MAPT* (Microtubule-Associated Protein Tau) gene, primarily stabilizes microtubules within the axons of nerve cells. Tau plays a key role in the polymerization and stabilization of microtubules, axonal transport, signal transduction, and adult neurogenesis. *MAPT* gene mutations have been shown to induce hyperphosphorylation of Tau, resulting in neurofibrillary tangle formation within neurons - a feature linked to frontotemporal dementia and highly correlated with AD progression [5].

To date, no drug fully prevents or reverses AD progression, underscoring the critical need for new and effective treatments. GemPharmatech has developed a novel transgenic model, FAD$^{3T\ (APP/PS1/Tau)}$, which expresses the human *APP* gene with the Swedish mutation, *PSEN1* with the M146V mutation, and *MAPT* with the P301L mutation. In this model, Aβ plaque deposition appears in the cortex and hippocampus at two months of age, and elevated phosphorylated Tau levels are detectable in 1-month-old mice, with levels increasing over time. Additionally, female FAD3T (APP/PS1/Tau)

mice exhibit spatial learning and memory deficits at three months of age, with similar deficits appearing in males at four months.

In summary, the FAD$^{3T\ (APP/PS1/Tau)}$ model is capable of detecting diagnostic markers, pathological characteristics, and neurobehavioral phenotypes associated with Alzheimer's disease. This model closely mimics the disease progression observed in clinical AD patients and can be utilized for screening potential therapeutic agents and evaluating their safety.

Strategy

Fig 1. Schematic diagram of FAD^{3T} mouse transgenic strategy.

Application

1. Evaluating therapeutic candidates for Alzheimer's disease.
2. Investigating dementia-related pathology and interventions.
3. Exploring the biological mechanisms underlying aging.

Data support

1. Survival curve comparing FAD^{3T} male and female mice

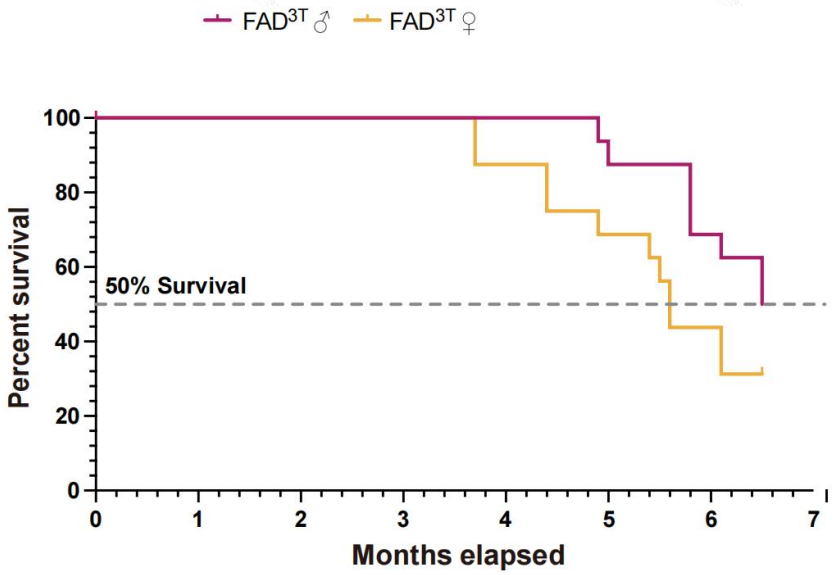


Fig 2. Survival curve of FAD^{3T} male and female mice

Survival curve comparing FAD^{3T} male and female mice over 7 months (n=12 per group). FAD^{3T} mice exhibit a reduced survival rate after 4 months, consistent with the progression of Alzheimer's disease.

2. Blood diagnostic biomarkers for AD detected in the FAD^{3T} mice

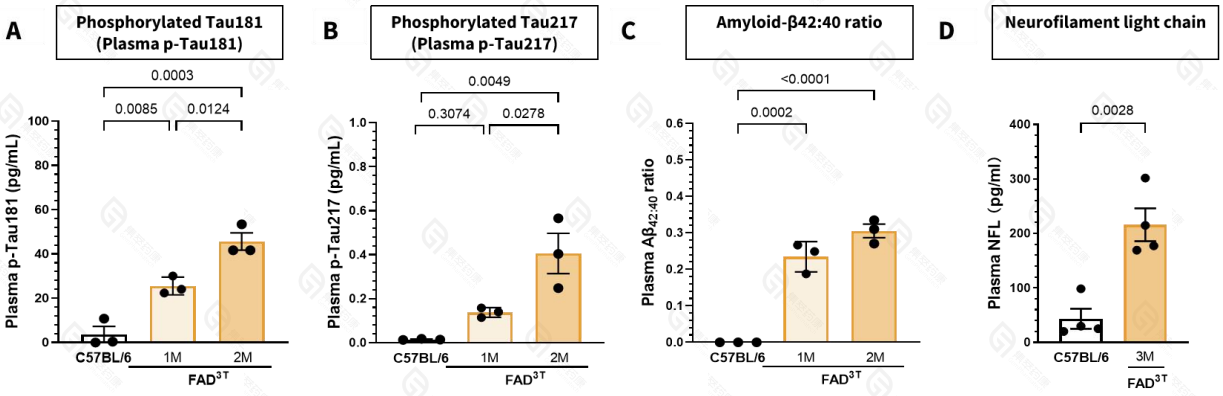


Fig 3. Detection of AD blood diagnostic biomarkers in FAD^{3T} mice

A. Plasma phosphorylated Tau181 (p-Tau181) levels in FAD^{3T} and C57BL/6 mice. FAD^{3T} mice show significantly elevated p-Tau181 levels compared to C57BL/6, with levels progressively increasing with age. **B.** Plasma phosphorylated Tau217 (p-Tau217) levels in FAD^{3T} and C57BL/6 mice. FAD^{3T} mice exhibit significantly higher p-Tau217

levels, which increase with age. **C.** Plasma Aβ42:40 ratio in FAD^{3T} mice and C57BL/6 mice. The Aβ42:40 ratio is significantly higher in FAD^{3T} mice at one month of age, with no further increase with age. **D.** Plasma neurofilament light chain (NfL) levels in FAD^{3T} mice at 3 months of age. NfL levels are significantly elevated in FAD^{3T} mice compared to C57BL/6.

3. Aβ deposition in 2-month-old FAD^{3T} mice

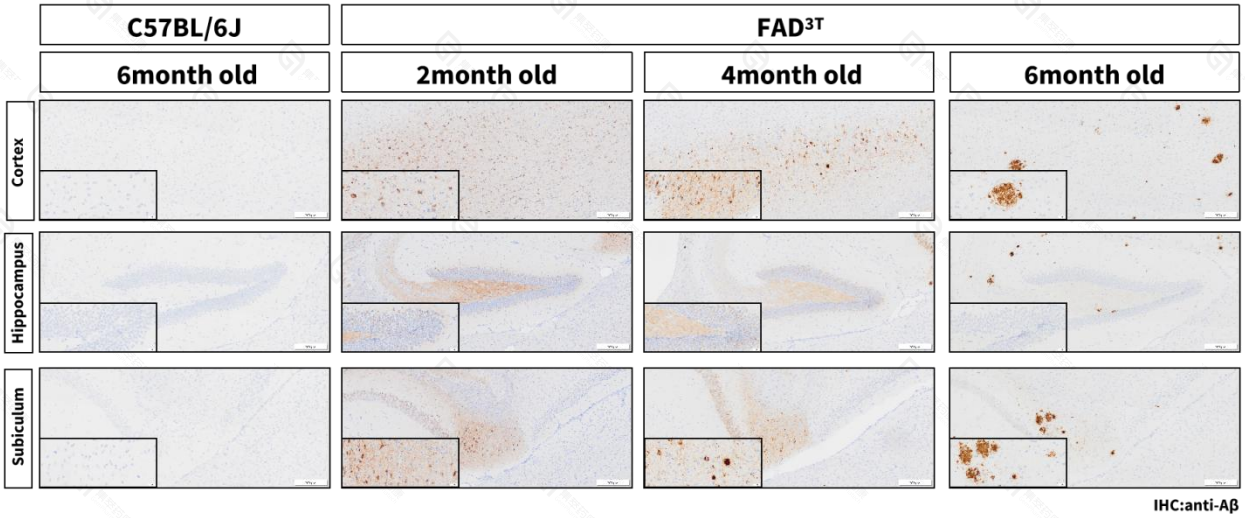
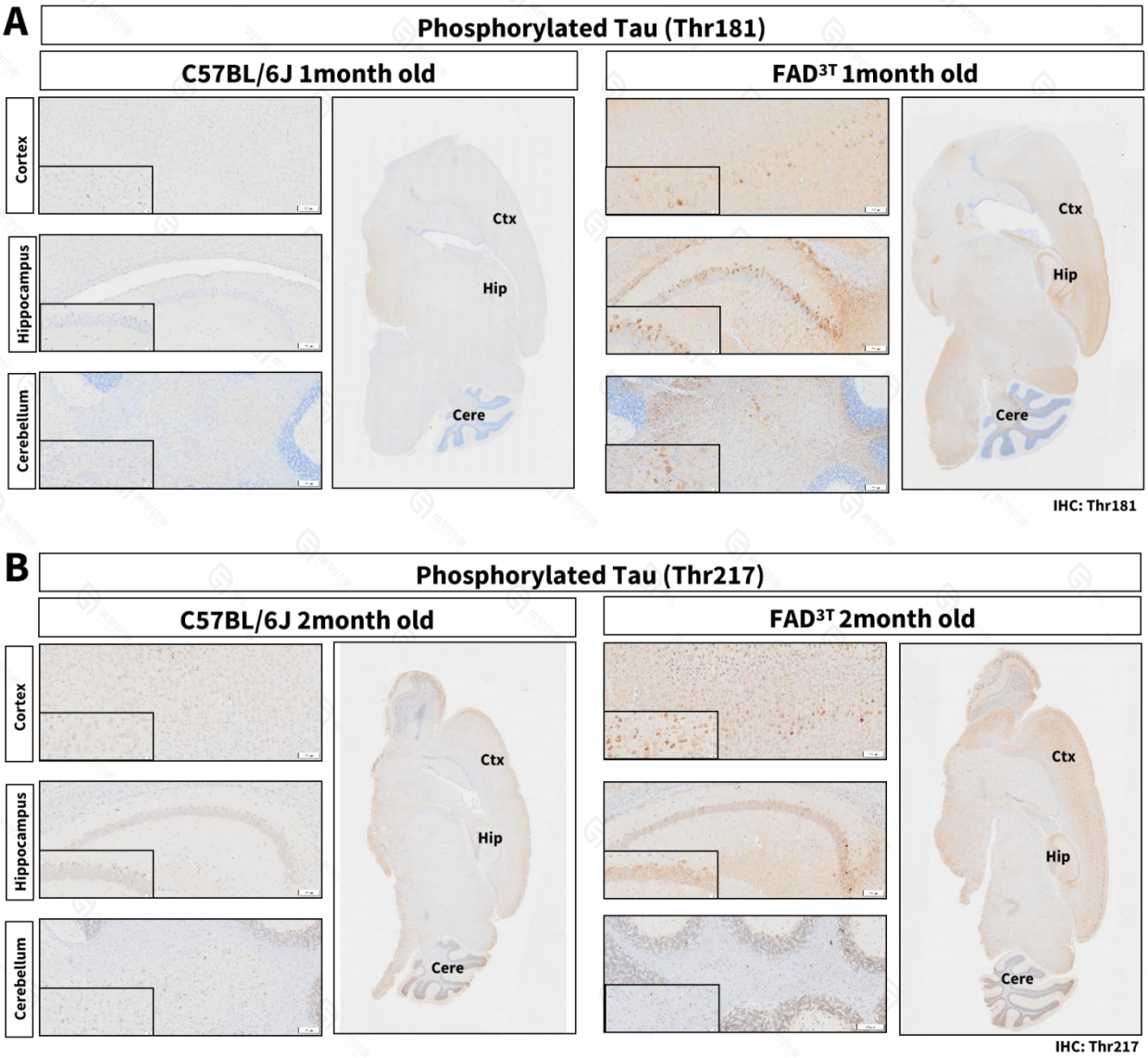
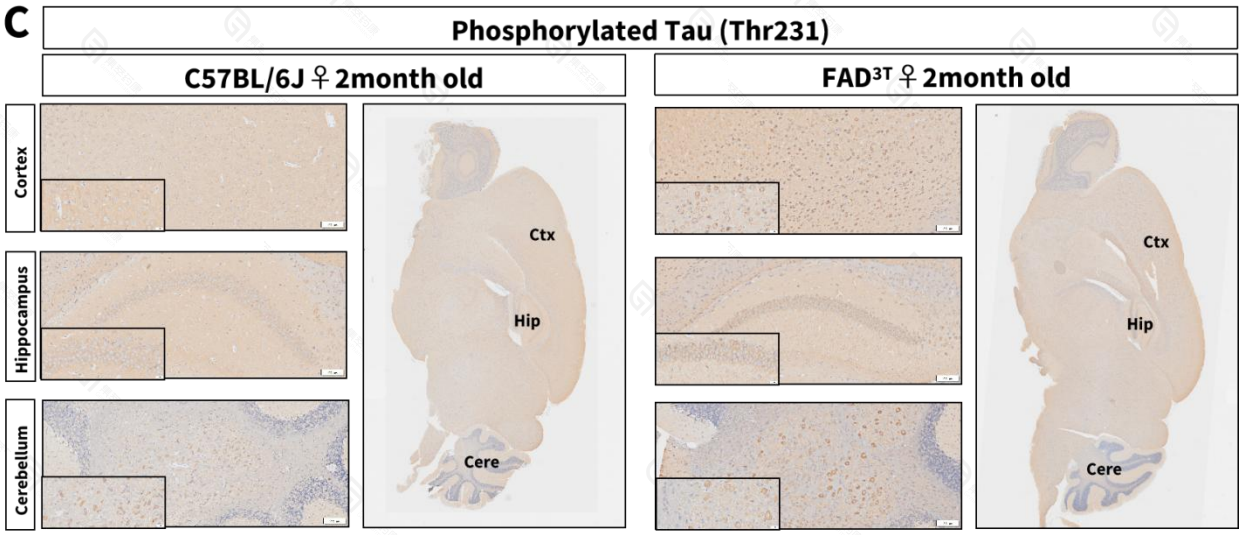


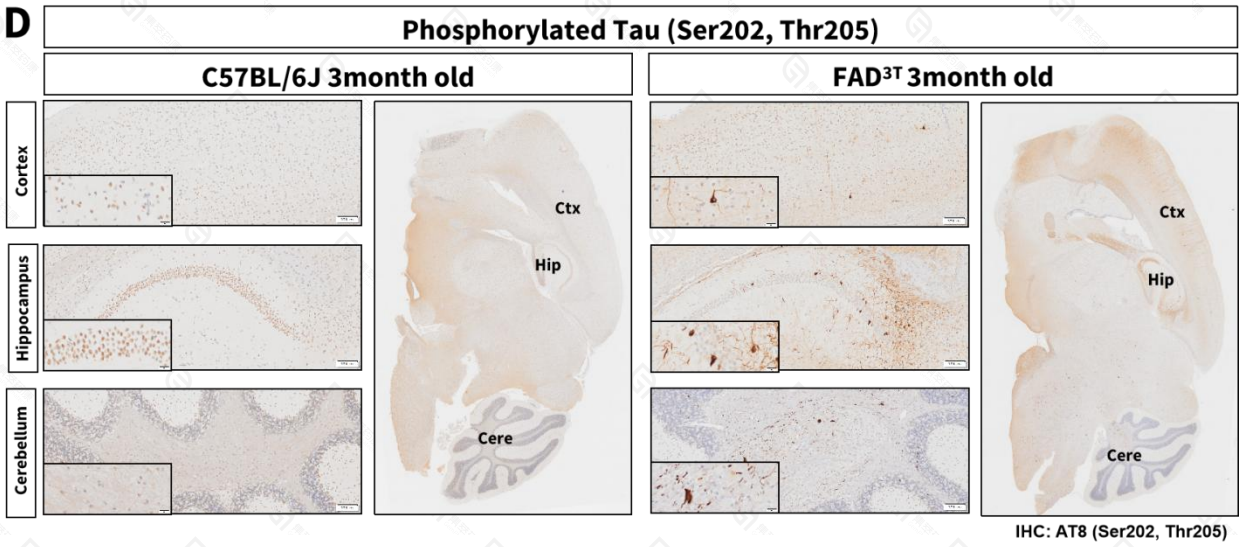
Fig 4. Detection of Aβ deposition in the brain of FAD^{3T} mice

Immunohistochemistry staining for Aβ in the cortex, hippocampus, and subiculum of C57BL/6 (6-month-old) and FAD^{3T} mice at 2, 4, and 6 months of age. FAD^{3T} mice show progressive Aβ accumulation with age.

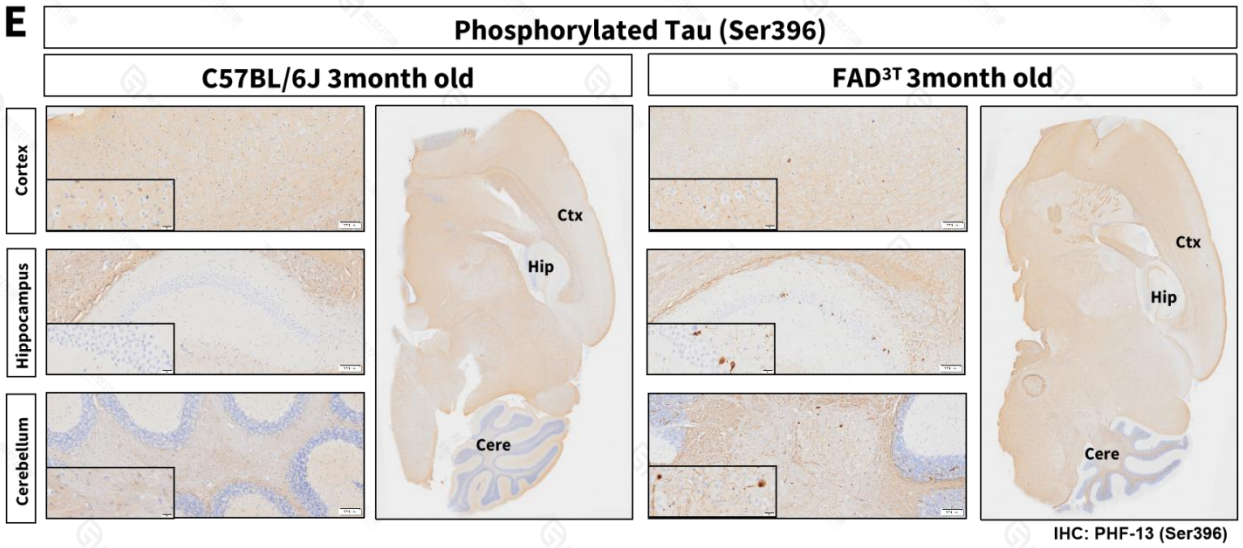
4. Tau pathology in FAD^{3T} mice







IHC: AT8 (Ser202, Thr205)



IHC: PHF-13 (Ser396)

Fig 5. Detection of phosphorylated Tau expression in FAD^{3T} mice

A. Immunohistochemistry staining for phosphorylated Tau (p-Tau181) in the cortex, hippocampus, and cerebellum of C57BL/6 and FAD^{3T} mice at 1 month of age. FAD^{3T} mice show Tau hyperphosphorylation compared to controls. **B.** Immunohistochemistry staining for phosphorylated Tau (p-Tau217) in the cortex, hippocampus, and cerebellum of C57BL/6 and FAD^{3T} mice at 2 months of age. FAD^{3T} mice show Tau hyperphosphorylation compared to controls. **C.** Immunohistochemistry staining for phosphorylated Tau (p-Tau231) in the cortex, hippocampus, and cerebellum of C57BL/6 and FAD^{3T} mice at 2 months of age. FAD^{3T} mice show Tau hyperphosphorylation compared to controls. **D.** Immunohistochemistry staining for phosphorylated Tau (Thr205/Ser202) in the cortex, hippocampus, and cerebellum of C57BL/6 and FAD^{3T} mice at 3 months of age. FAD^{3T} mice show Tau hyperphosphorylation compared to controls. **E.** Immunohistochemistry staining for phosphorylated Tau (p-Tau396) in the cortex, hippocampus, and cerebellum of C57BL/6 and FAD^{3T} mice at 3 months of age. FAD^{3T} mice show Tau hyperphosphorylation compared to controls. (The above-mentioned ages represent the earliest months at which different phosphorylated tau protein expressions were detected.)

5. Glial cells pathology

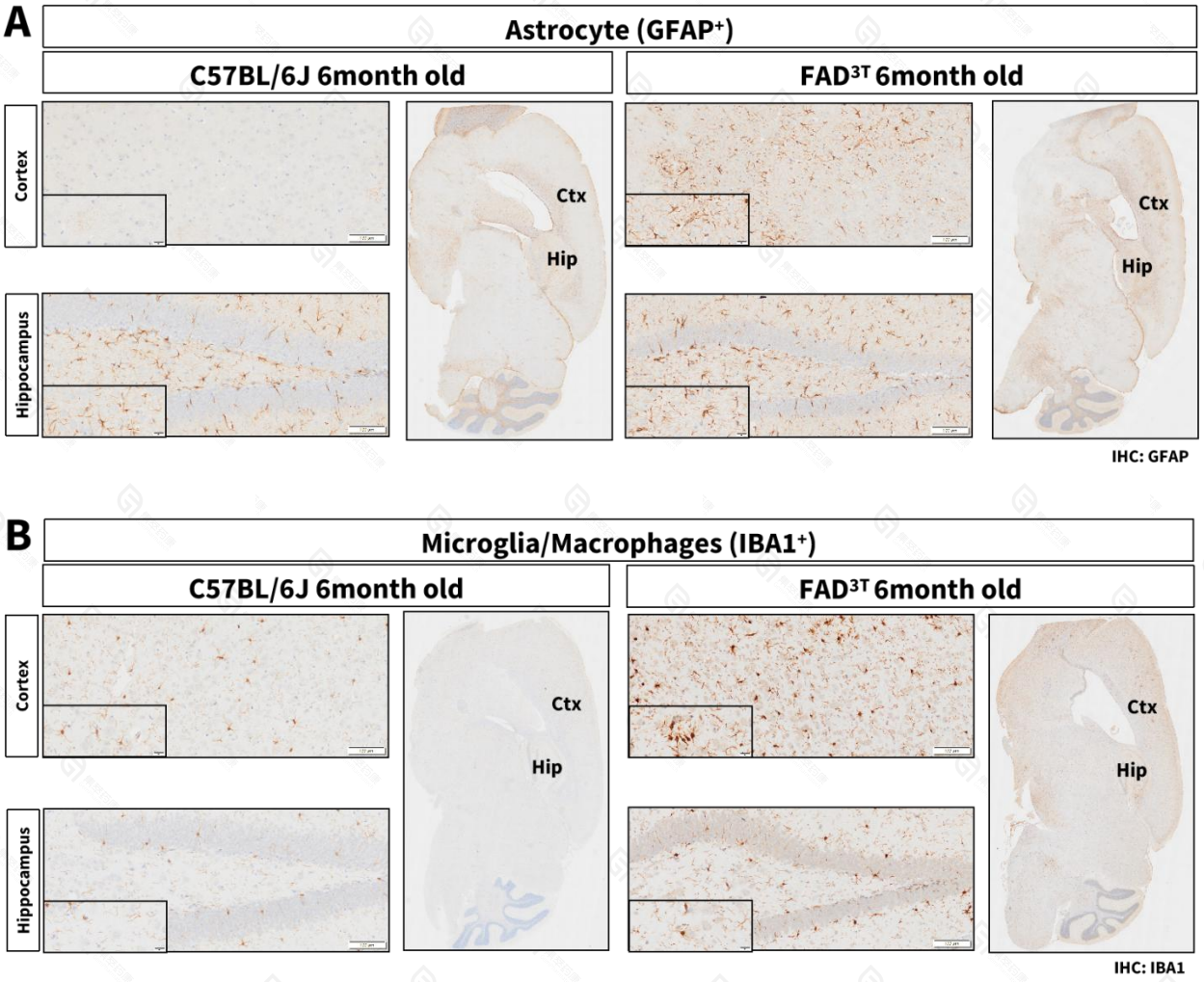


Fig 6. Detection of glial cells in FAD^{3T} mice

A. Immunohistochemistry staining for GFAP^{+} astrocyte in the cortex and hippocampus of C57BL/6 and FAD^{3T} mice at 6 months of age. FAD^{3T} mice display increased GFAP^{+} astrocyte density. **B.** Immunohistochemistry staining for IBA1^{+} microglia in the cortex and hippocampus of C57BL/6 and FAD^{3T} mice at 6 months of age, demonstrating microglia activation in FAD^{3T} mice.

6. Spatial learning and memory deficits in FAD^{3T} mice in the Morris Water Maze

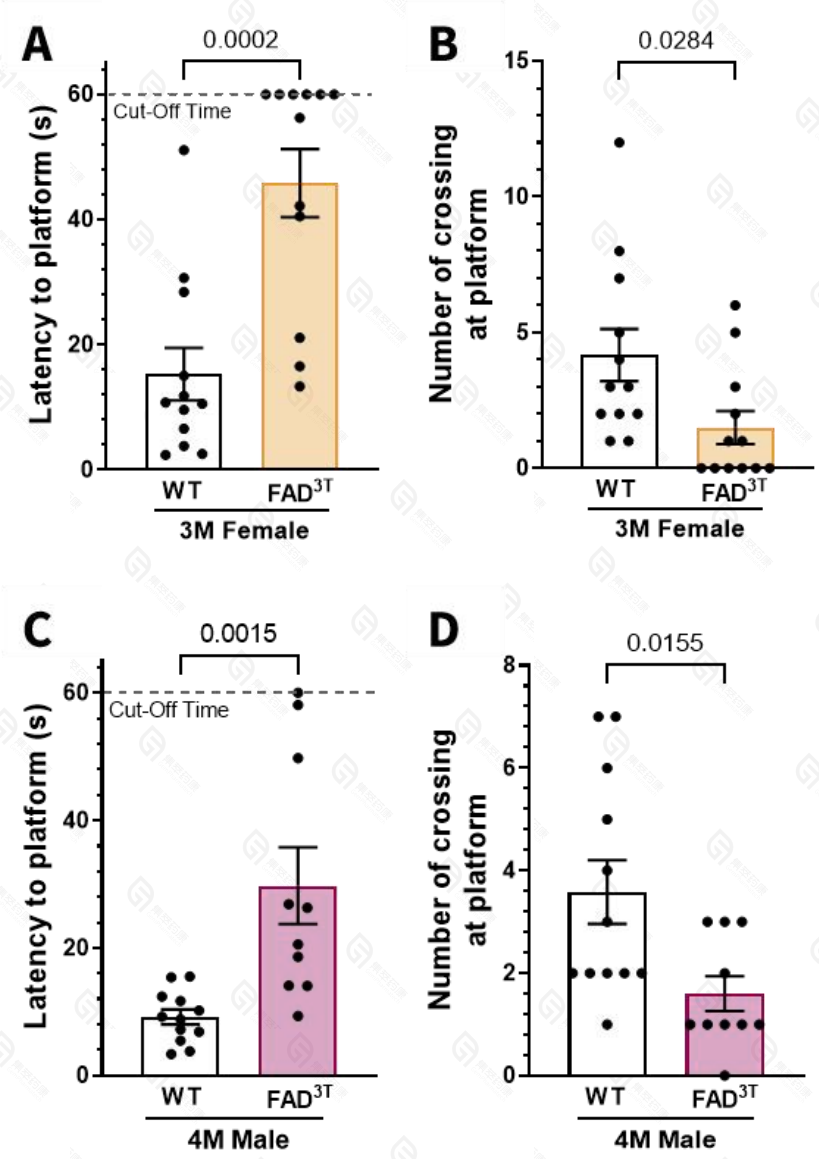
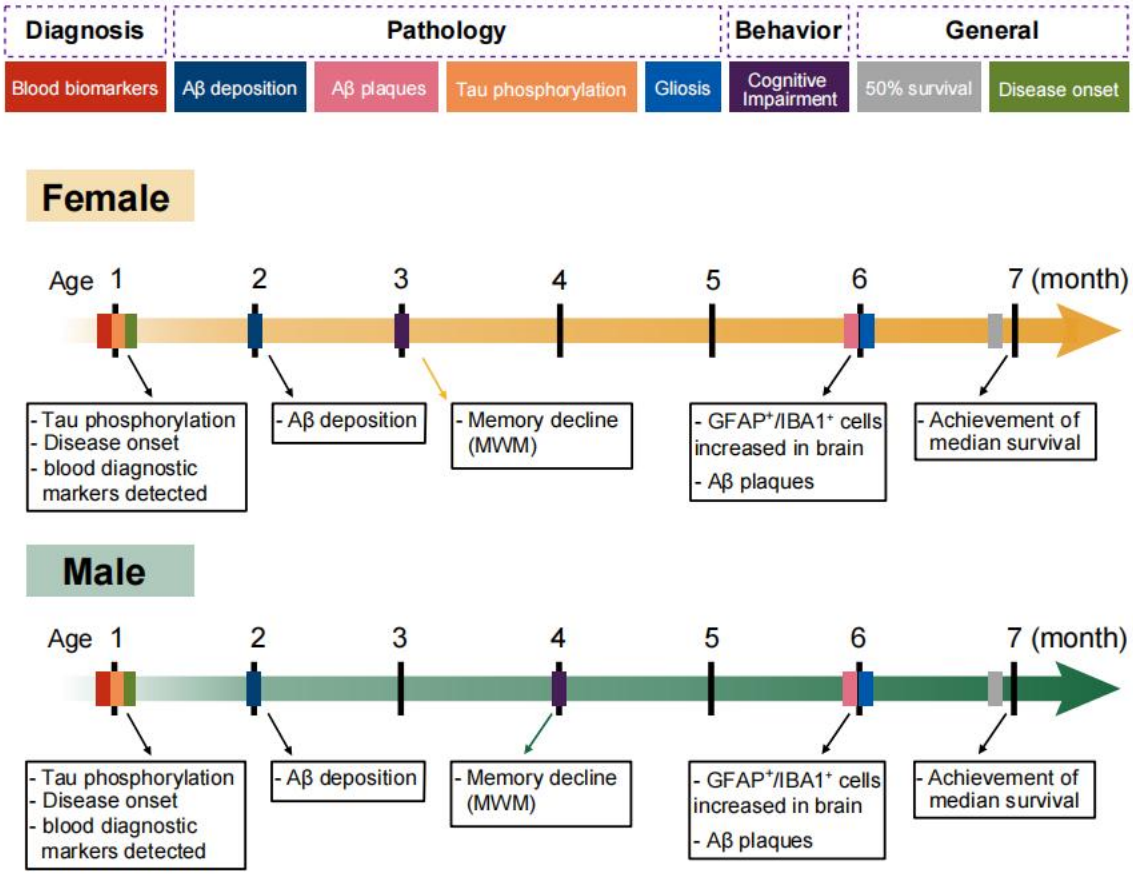


Fig 7. Spatial learning and memory deficits in FAD^{3T} mice

The Morris Water Maze (MWM) test in female FAD^{3T} and C57BL/6 mice at 3 months of age and male mice at 4 months of age (n=10-12). Comparison of latency to the platform **(A, C)**, and number of platform crossings **(B, D)** on the test day between FAD^{3T} and C57BL/6 female mice at 3 months of age and male mice at 4 months of age. FAD^{3T} mice exhibit significantly impaired performance in spatial memory tasks.

7. Summary



Risk warning:

1. **Mortality in Mice:** The mice, with death typically occurring at 3–4 months of age, exhibit a mortality rate of approximately 25%.
2. **Phenotypic Stability**: As a transgenic strain, requires adherence to a systematic genetic breeding strategy. Independent breeding may lead to changes in gene copy number, potentially resulting in phenotypic instability among individuals.

References

1. Oakley, Holly et al. “Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation.” *The Journal of neuroscience : the official journal of the Society for Neuroscience* vol. 26,40 (2006): 10129-40. doi:10.1523/JNEUROSCI.1202-06.2006
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5. Lester, Evan et al. “Tau aggregates are RNA-protein assemblies that mislocalize multiple nuclear speckle components.” *Neuron* vol. 109,10 (2021): 1675-1691.e9. doi:10.1016/j.neuron.2021.03.026