RESEARCH MODELS

3xTg

Synonyms: 3xTg-AD, The LaFerla mouse

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Species: Mouse
Genes: APP, PSEN1, MAPT
Mutations: APP KM670/671NL (Swedish), MAPT P301L, PSEN1 M146V
Modification: APP: Transgenic; PSEN1: Transgenic; MAPT: Transgenic
Disease Relevance: Alzheimer's Disease
Strain Name: B6;129-Psen1^{tm1Mpm} Tg(APPSwe,tauP301L)1Lfa/Mmjax
Genetic Background: C57BL/6;129X1/SvJ;129S1/Sv
Availability: The Jackson Lab; available through the JAX MMRRC Stock# 034830; Live

Summary

These widely-used mice contain three mutations associated with familial Alzheimer's disease (APP Swedish, MAPT P301L, and PSEN1 M146V). The mice are viable, fertile, and display no initial gross physical or behavioral abnormalities. Translation of the overexpressed transgenes appears restricted to the central nervous system, including the hippocampus and cerebral cortex. These mice display both plaque and tangle pathology. Aβ deposition is progressive, with intracellular immunoreactivity detected in some brain regions as early as three to four months of age. Extracellular Aβ deposits appear by six months in the frontal cortex and become more extensive by twelve months. Changes in tau occur later; by 12 to 15 months aggregates of conformationally-altered and hyperphosphorylated tau are detected in the hippocampus (Oddo et al., 2003; Billings et al., 2005).

Neuropathology

These mice develop age-related, progressive neuropathology including plaques and tangles. Extracellular Aβ deposits are apparent by six months in the frontal cortex, and become more extensive by twelve months. Although tau pathology is not observed at six months, it is evident by twelve months. Synaptic dysfunction, including LTP deficits, occur prior to plaques and tangles.

Cognition/Behavior

Cognitive impairment is observed by four months. Impairments first manifest as a retention/retrieval deficit and not as a learning deficit, and occur prior to plaques and tangles. Deficits are observed in both spatial and contextual based paradigms. At age 6.5 months, 3xTg mice displayed learning and memory deficits in the Barnes maze, but performed better than B6129SF2 wild-type mice in the Y maze and fear conditioning tasks (Stover et al., 2015). Clearance of intraneuronal Aβ by immunotherapy rescues the early cognitive deficits in a hippocampal-dependent task.

Modification Details

Single-cell embryos from mice with knock-in of PSEN1 with the PS1M146V mutation were injected with two human transgenes (APP with the Swedish mutation and MAPT with the P301L mutation, both under the control of the mouse Thy1.2 promoter). The transgenes integrated at a single locus, Chr2:87862466-87862463 (Build GRCm38/mm10), causing a 3 bp deletion that does not affect any known genes (Goodwin et al., 2017).

Note

This model was formerly available through The Jackson Lab as Stock# 004807.

Related Strains

3xTg-AD on C57BL/6J. 3xTg-AD mice on a congenic C57BL/6J background are expected to be available from The Jackson Laboratory (Stock# 008880) beginning in January 2019.

3xTg-AD congenic 129S4. 3xTg-AD mice on a congenic 129S4 background are expected to be available from The Jackson Laboratory (Stock# 031988) beginning in February 2019.

PHENOTYPE CHARACTERIZATION

Plaques
Extracellular Aβ deposits by 6 months in the frontal cortex, predominantly layers 4 and 5 and progress with age (Oddo et al., 2003).

Tangles
By 12 months extensive tau immunoreactivity in CA1 neurons of the hippocampus, particularly pyramidal neurons, later in the cortex. No tau pathology at 6 months (Oddo et al., 2003).

Neuronal Loss
Unknown.

Gliosis
Increased density of GFAP immunoreactive astrocytes and IBA-1 immunoreactive microglia compared with wild-type mice at 7 months (Caruso et al., 2013). Development of gliosis may occur earlier.

Changes in LTP/LTD
By 6 months decreased LTP compared with wild type controls. Impairment in basal synaptic transmission. No change at 1 month of age (Oddo et al., 2003).

Cognitive Impairment
Cognitive impairment manifests at 4 months as a deficit in long-term retention and correlates with the accumulation of intraneuronal Aβ in the hippocampus and amygdala, but plaques and tangles are not yet apparent (Billings et al., 2005).

Last Updated: 29 Nov 2018

COMMENTS / QUESTIONS

No Available Comments

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REFERENCES

Paper Citations

Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron*. 2003 Jul 31;39(3):409-21. PubMed.

Billings LM, Oddo S, Green KN, McGaugh JL, LaFerla FM. Intraneuronal Abeta causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. *Neuron*. 2005 Mar 3;45(5):675-88. PubMed.

Stover KR, Campbell MA, Van Winssen CM, Brown RE. Early detection of cognitive deficits in the 3xTg-AD mouse model of Alzheimer's disease. *Behav Brain Res*. 2015 Aug 1;289:29-38. Epub 2015 Apr 17 PubMed.

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External Citations

The Jackson Laboratory (Stock# 008880)

The Jackson Laboratory (Stock# 031988)

JAX MMRRC Stock# 034830

FURTHER READING

News

Mistakes Prompt Retraction of Controversial Paper, and Publication Ban 4 Mar 2015

Triple Trouble: AD Mice Decline Faster With Lewy Bodies 30 May 2010

Cholinergic Transmission and Aβ: Boosting M1 Receptors Treats Model 3 Mar 2006

Mitochondria Sag Early in AD Mouse Model 21 Aug 2009

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Intraneuronal Aβ: Was It APP All Along? 20 Jun 2011

Papers

Blázquez G, Cañete T, Tobeña A, Giménez-Llort L, Fernández-Teruel A. Cognitive and emotional profiles of aged Alzheimer's disease (3×TgAD) mice: effects of environmental enrichment and sexual dimorphism. *Behav Brain Res*. 2014 Jul 15;268:185-201. Epub 2014 Apr 15 PubMed.

Martin SA, Jameson CH, Allan SM, Lawrence CB. Maternal high-fat diet worsens memory deficits in the triple-transgenic (3xTgAD) mouse model of Alzheimer's disease. *PLoS One*. 2014;9(6):e99226. Epub 2014 Jun 11 PubMed.

Torres-Lista V, López-Pousa S, Giménez-Llort L. Marble-burying is enhanced in 3xTg-AD mice, can be reversed by risperidone and it is modulable by handling. *Behav Processes*. 2015 Jul;116:69-74. Epub 2015 May 6 PubMed.

PRIMARY PAPERS

Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron*. 2003 Jul 31;39(3):409-21. PubMed.

ALZPEDIA

APP

Tau (MAPT)

Presenilin-1 (PSEN1)

EXTERNAL RESOURCES

AlzPED (NIA Alzheimer's Disease Preclinical Efficacy Database) curated citations

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