RESEARCH MODELS

APPswe/PSEN1dE9 (C57BL6)

Synonyms: APP/PS1, C57BL/6J APPswePsen1de9, B6.APB[Tg]

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Species: Mouse
Genes: APP, PSEN1
Mutations: APP KM670/671NL (Swedish), PSEN1: deltaE9
Modification: APP: Transgenic; PSEN1: Transgenic
Disease Relevance: Alzheimer's Disease
Strain Name: B6.Cg-Tg(APPswe,PSEN1dE9)85Dbo/Mmjax
Genetic Background: C57BL/6J
Availability: Available from the Jackson Laboratory, JAX MMRRC Stock# 034832 (formerly Jackson Lab Stock #005864)

Summary

APPswe/PSEN1dE9 mice carry two transgenes with AD-linked mutations: a chimeric mouse/human APP with the Swedish mutation and human PSEN1 lacking exon 9 (dE9), both under the control of the mouse prion protein promoter. This popular model was originally created on a hybrid C57BL/6 x C3H background (mice on this background are described elsewhere). However, some investigators preferred to use mice on a C57BL/6J background, and have since generated their own congenic lines through backcrossing. APPswe/PSEN1dE9 mice on a C57BL/6J background are commercially available through Jackson Labs.

Neuropathology

Amyloid plaques begin to emerge in the cortex at about 4 months of age and in the hippocampus at about 6 months, and increase in size and number with age (Minkeviciene et al., 2008; Jackson et al., 2013). There are regional differences in plaque burden, with plaque density in the cortex greater than those in the hippocampus and amygdala; occasional plaques have also been observed in the thalami of some mice (Minkeviciene et al., 2009). Plaque-associated astrogliosis (Malm et al., 2007; Minkeviciene et al., 2008; Jackson et al., 2013), microgliosis (Malm et al., 2007; Jackson et al., 2013), and dystrophic neurites (Malm et al., 2007; Jackson et al., 2013) are seen in APPswe/PSEN1dE9 mice.

Sex differences in amyloid deposition have been reported, although differences in methods make it difficult to integrate the information from different laboratories. The number of Thioflavin S-positive cortical plaques was found to be greater in 8-month females than males (Onos et al., 2019), while the percent area occupied by 6E10-immunoreactive plaques was greater in males than females, when a region containing hippocampus and overlying cortex was examined at 9 months (Ordóñez-Gutiérrez et al., 2015). In the latter study, plaque burden plateaued by 9 months in males, but not until about 12 months in females.

The retinas of APPswe/PSEN1dE9 mice also contain amyloid deposits, which are primarily associated with the vasculature. Consistent with the presence of amyloid angiopathy, microhemorrhages have also been observed in the retinas of these mice (Chintapaludi et al., BioRχiv, 2019). Cerebral amyloid angiopathy was not observed in the cortex (Onos et al., 2019).

Immunoreactivity for phospho-tau epitopes was seen in the cell bodies of CA3 hippocampal neurons of 16-month mice, in addition to dystrophic neurites surrounding plaques (Malm et al., 2007).

Synapse loss in the hippocampus occurs by 4 months: Compared with non-transgenic mice, APPswe/PSEN1dE9 mice had approximately 50 percent fewer puncta co-labeled for pre- and postsynaptic markers (synaptotagmin and homer in dentate gyrus, synaptophysin and PSD95 in CA1 stratum radiatum) (Hong et al., 2016).

Cognitive function/Behavior

By 6 months of age, APPswe/PSEN1dE9 mice are hyperactive, compared with non-transgenic littermates (Onos et al., 2019). Deficits in the Morris water maze emerge between 6 and 10 months and worsen with age: By 10 months transgenic mice appear unable to remember the location of an escape platform, and by 15 months mice have difficulty even learning the location of the platform (Minkeviciene et al., 2008).

Transcriptomics

Transcriptomic analyses revealed differences between APPswe/PSEN1dE9 and wild-type mice as early as 2 months of age (Chintapaludi et al., BioRχiv, 2019). Transgene-related differences in expression have been reported for genes related to protein translation, oxidative phosphorylation, hormonal signaling, proteolysis, and myeloid-cell function, among others (Jackson et al., 2013; Onos et al., 2019; Chintapaludi et al., BioRχiv, 2019). In addition, both wild-type and transgenic mice show age-related changes in brain transcriptomes; genes differentially expressed at 4 and 6 months, regardless of genotype, include those related to mRNA processing/protein translation and oxidative phosphorylation (Jackson et al., 2013).

Other

A substantial proportion of APPswe/PSEN1dE9 mice exhibit seizures. Electrographic seizures were recorded in 25 percent of 3-month transgenic mice, with that number increasing to 55 percent by 5 months. Almost 70 percent of mice exhibiting seizure activity on EEG also experienced behavioral seizures, with half of these having at least one generalized seizure (Minkeviciene et al., 2009).

Levels of peripheral Aβ show sex-dependent changes with age: Between 9 and 15 months of age, plasma concentrations of Aβ40 and Aβ42 rise in females but fall in males, so that females have approximately fourfold higher concentrations of plasma Aβ40 and 1.3-fold higher concentrations of Aβ42 than males at 15 months (Ordóñez-Gutiérrez et al., 2015).

Bladder dysfunction has been observed in some mice, with males affected from very young ages, while females do not show signs until about 10 months (Ordóñez-Gutiérrez et al., 2015).

Modification Details

These transgenic mice were made by co-injecting two vectors encoding mutant APP and mutant PSEN1 (Jankowsky et al., 2001). The APP sequence encodes a chimeric mouse/human APP (Mo/HuAPP695swe) that was "humanized" by modifying three amino acids. In addition, the Swedish mutation was introduced. The PSEN1 sequence encodes human presenilin-1 lacking exon 9 (dE9). Expression of both genes was directed to the CNS with the mouse prion protein promoter. The transgenes inserted at a single locus, Chr9:113003660 (Build GRCm38/mm10), causing a 1 bp duplication that does not affect any known genes (Goodwin et al., 2019). APPswe/PSEN1dE9 mice were originally created on a hybrid C57BL/6 x C3H background.

Related Strains

APPswe/PSEN1dE9 (line 85). This is the original APPswe/PSEN1dE9, on a hybrid C57BL/6 x C3H background.

CAST.APPPS1. These mice are among a set of three models created by backcrossing APPswe/PSEN1dE9 mice to different "wild-derived" strains—inbred strains created in the laboratory from subspecies of house mice caught in the wild less than 50 years ago (Onos et al., 2019). The CAST strain differs from C57BL6 at around 23 million sites in the genome. Compared with APPswe/PSEN1dE9 on a congenic C57BL/6J background, these mice are hyperactive and have fewer plaques, but more microglia surrounding each plaque. These mice also exhibit cerebral amyloid angiopathy. At 8 months, transgenic mice have fewer neurons in the hippocampus than do non-transgenic littermates, but whether this difference reflects a developmental problem or neurodegeneration has yet to be determined. Cognitive deficits are observed by 8 months in males.

WSB.APPPS1. This is the second line created by backcrossing APPswe/PSEN1dE9 mice to a "wild-derived" strain (Onos et al., 2019). The WSB strain differs from C57BL6 at around 7 million sites in the genome. Compared with APPswe/PSEN1dE9 on a congenic C57BL/6J background, these mice are hyperactive and have fewer plaques. These mice also exhibit cerebral amyloid angiopathy, with a compromised blood-brain barrier. Transgenic females have fewer neurons in the cortex and hippocampus than do non-transgenic littermates, but whether this difference reflects a developmental problem or neurodegeneration has yet to be determined. Cognitive deficits are observed by 8 months in females.

PWK.APP/PS1. This is the third of the lines created by backcrossing APPswe/PSEN1dE9 mice to a "wild-derived" strain (Onos et al., 2019). The PWK strain differs from C57BL6 at around 22 million sites in the genome. Compared with APPswe/PSEN1dE9 on a congenic C57BL/6J background, these mice are hyperactive and have fewer plaques. Neuron loss is not observed in cortex or hippocampus at 8 months. Working memory and short-term memory were intact at 6 to 8 months.

D2.APB[Tg]. These mice are on a D2 genetic background. They were generated by backcrossing B6.APBTg mice to stock D2 mice (DBA/2J; JAX Stock #000671). Mice on this background are more prone to spontaneous seizures than the B6 congenic. The seizures are lethal, and are thought to account for the premature death of D2.ABPTg mice; 70 percent die between two and three months of age. Those that survive to six months of age exhibit reduced amyloid pathology relative to B6 counterparts (Jackson et al., 2015).

PHENOTYPE CHARACTERIZATION

Plaques
Amyloid plaques begin to emerge in the cortex at about 4 months of age and in the hippocampus at about 6 months.

Tangles
Not observed.

Neuronal Loss
Neuron loss has not been observed in mice up to 12 months of age.

Gliosis
Plaque-associated astrogliosis and microgliosis are evident by 4 and 8 months, respectively.

Synaptic Loss
Synapse loss in the hippocampus occurs by 4 months.

Changes in LTP/LTD
No data.

Cognitive Impairment
Deficits in the Morris water maze emerge between 6 and 10 months and worsen with age.

Last Updated: 07 Oct 2019

COMMENTS / QUESTIONS

No Available Comments

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REFERENCES

Research Models Citations

APPswe/PSEN1dE9 (line 85)
WSB.APP/PS1
CAST.APP/PS1
PWK.APP/PS1

Paper Citations

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External Citations

JAX Stock #000671
JAX MMRRC Stock# 034832

FURTHER READING

No Available Further Reading

PRIMARY PAPERS

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ALZPEDIA

APP

Presenilin-1 (PSEN1)