STOCK Tg(Camk2a-tTA)1Mmay Fgf14 Tg( tetO-MAPBP301)4510Kha/J

Stock No: 024854 | rTg4510

Transgenic

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Overview

Also Known As: rTg4510

These bitransgenic mice have tau\textsuperscript{P301L} expression in forebrain, and that expression can be greatly reduced by administration of the tetracycline analog doxycycline. The transgenes are the same as those in the “rTg4510” mouse line. They may be useful for studying the formation of neurofibrillary tangles associated with Alzheimer’s disease, neurodegenerative tauopathies and frontotemporal dementia.

The CaMK2a-tTA transgene integrated into chromosome 12 causing a 508 Kb deletion that spans the 3’ half of Vipr2, the entire Wdr60, Esyt2, D430020J02Rik and Ncapg2 loci and the first two exons of Ptpn2. Homozygous mice will therefore have a functional knock-out of the deleted loci, and altered or null expression of Vipr2 and Ptpn2. Founder line 1 has >20 transgene copies [Goodwin et al. 2019 Genome Res. 29:494].

The tetO-MAPT*P301L transgene integrated into chromosome 14 causing a 244 kbp deletion in the fibroblast growth factor 14 locus (Fgf14) - creating a Fgf14 null allele [Goodwin et al. 2019 Genome Res. 29:494]. Furthermore, Gamache et al. 2019 Nat Commun.
The CaMK2a-tTA transgene has the tetracycline-controlled transactivator protein (tTA) under regulatory control of the forebrain-specific calcium-calmodulin-dependent kinase II (CaMK2a) promoter. The tetO-MAPT*P301L transgene has the Tet-responsive element (TRE or tetO) and mouse prion protein promoter sequences (PrP or Prnp) directing expression of the P301L mutant variant of human four-repeat microtubule-associated protein tau (4R0N tau\textsuperscript{P301L}). As such, these bitransgenic mice (also called rTg(tau\textsuperscript{P301L}, 4510 bitransgenic mice) have tau\textsuperscript{P301L} expression in the forebrain, and that expression can be greatly reduced by
administration of the tetracycline or its analog doxycycline (dox).

The CaMK2a-tTA transgene integrated into chromosome 12 causing a 508.12 Kb deletion that spans the 3’ half of Vipr2 (vasoactive intestinal peptide receptor 2), the entire Wdr60 (WD repeat domain 60), Esyt2 (extended synaptotagmin-like protein 2), D430020J02Rik (RIKEN cDNA D430020J02 gene) and Ncapp2 (non-SMC condensin II complex, subunit G2) loci and the first two exons of Ptpn2 (protein tyrosine phosphatase, receptor type, N polypeptide 2). Homozygous mice will therefore have a functional knock-out of the deleted loci (Wdr60, Esyt2, D430020J02Rik, Ncapp2), and altered or null expression of Vipr2 and Ptpn2. Founder line 1 has a copy number of greater than 20 [Goodwin et al. 2019 Genome Res. 29:494].

The tetO-MAPT*P301L transgene was discovered to have integrated into chromosome 14 causing a 244 kbp deletion in the fibroblast growth factor 14 locus (Fgf14) - creating a Fgf14 null allele [Goodwin et al. 2019 Genome Res. 29:494]. Furthermore, Gamache et al. 2019 Nat Commun. 10:2479 identified there were ~70 transgene copies integrated.

Similarly made bitransgenic mice are described with tau^{P301L}_{P301L} expression levels approximately 13-fold greater than endogenous murine tau. This high tau^{P301L} expression in forebrain results in age-independent behavioral and pathological abnormalities, as well as age-dependent functional and structural abnormalities, associated with the progression of Alzheimer’s disease. Learning and memory tests performed on bitransgenic mice indicate impairments in the hippocampus and amygdala dysfunction. In addition, significant tau burden is observed in the amygdala. The behavioral and amygdala pathologies mimic the neurodegenerative tauopathy, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). After bitransgenic mice are administered dox, neuronal death ceases and the ability to acquire and retain new spatial memories is restored.

When maintained under doxycycline conditions, these bitransgenic mice may be expected to have the same phenotype as mice singly transgenic for tetO-MAPT*P301L: the untranslated sequence from Pnnp results in moderate levels of tau_{P301L} expression in brain before Tet-induction, but do not result in tauopathies. When hemizygous for each transgene, bitransgenic mice are viable and fertile.

Of note, bitransgenic mice on the hybrid FVBx129S6 background exhibit a sex-dependent phenotype. Females develop an earlier and more aggressive phenotype than males, developing higher levels of hyperphosphorylated tau by 5.5 months. Higher tau levels result in more severe impairment in spatial learning and memory than is observed in age-matched males. The Jackson Laboratory colony is maintained on an FVBxC57BL/6 background, male and female phenotypes have not been compared on this background.

TetO-MAPT*P301L transgenic mice prove to be better breeders than CaMK2a-tTA transgenic mice. As such, The Jackson Laboratory breeds female TetO-MAPT*P301L transgenic mice to male CaMK2a-tTA transgenic, with no reciprocal crosses, to maintain a productive colony.

### Development

### Expression Data

### Control Suggestions

### Selected References

### Genetics

- Tg(Camk2a-tTA)1Mmay
- Fgf14^{Tg(tetO-MAPT*P301L)x510Kha}

### Disease/Phenotype

### Disease Terms
Genotyping Protocols
Probe: Generic tTA/rtTA
Probe: Tg(MAPT) cDNA- Probe
Standard PCR: Tg(tTA)
MELT: Tg(Camk2a-tTA)1Mmay
QPCR: Tg(MAPT) cDNA
MELT: Generic tTA
Genotyping resources and troubleshooting

Dietary Information
LabDiet® 5K52 formulation (6% fat)

Breeding Considerations
Transgene carrier mice from Stock No. 015815 FVB-Tg(tetO-MAPT-P301L)Kha/JlwsJ are bred every generation to transgene carrier mice from Stock No. 007004 B6.Cg-Tg(Camk2a-tTA)1Mmay/Dbod1. TetO-MAPT-P301L transgenic mice prove to be better breeders than CaMK2a-tTA transgenic mice. As such, The Jackson Laboratory breeds female TetO-MAPT-P301L transgenic mice to male CaMK2a-tTA transgenic, with no reciprocal crosses, to maintain a productive colony.

Additional Breeding and Husbandry Support

Mating System
See “Breeding Considerations”

Citation
When using this Tg(Tg) mouse strain in a publication, please cite the originating article(s) and include JAX stock #024854 in your Materials and Methods section.

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Tg(tetO-MAPT-P301L)Kha/Dbod1
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