



Mutant Tau knock-in mice display frontotemporal dementia relevant behaviour and histopathology



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ABSTRACT

Models of Tau pathology related to frontotemporal dementia (FTD) are essential to determine underlying neurodegenerative pathologies and resulting tauopathy relevant behavioural changes. However, existing models are often limited in their translational value due to Tau overexpression, and the frequent occurrence of motor deficits which prevent comprehensive behavioural assessments. In order to address these limitations, a forebrain-specific (CaMKII α promoter), human mutated Tau (hTau_{P301L + R406W}) knock-in mouse was generated out of the previously characterised PLB1_{Triple} mouse, and named PLB2_{Tau}. After confirmation of an additional hTau species (~60 kDa) in forebrain samples, we identified age-dependent progressive Tau phosphorylation which coincided with the emergence of FTD relevant behavioural traits. In line with the non-cognitive symptomatology of FTD, PLB2_{Tau} mice demonstrated early emerging (~6 months) phenotypes of heightened anxiety in the elevated plus maze, depressive/apathetic behaviour in a sucrose preference test and generally reduced exploratory activity in the absence of motor impairments. Investigations of cognitive performance indicated prominent dysfunctions in semantic memory, as assessed by social transmission of food preference, and in behavioural flexibility during spatial reversal learning in a home cage corner-learning task. Spatial learning was only mildly affected and task-specific, with impairments at 12 months of age in the corner learning but not in the water maze task. Electroencephalographic (EEG) investigations indicated a vigilance-stage specific loss of alpha power during wakefulness at both parietal and prefrontal recording sites, and site-specific EEG changes during non-rapid eye movement sleep (prefrontal) and rapid eye movement sleep (parietal). Further investigation of hippocampal electrophysiology conducted in slice preparations indicated a modest reduction in efficacy of synaptic transmission in the absence of altered synaptic plasticity.

Together, our data demonstrate that the transgenic PLB2_{Tau} mouse model presents with a striking behavioural and physiological face validity relevant for FTD, driven by the low level expression of mutant FTD hTau.

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1. Introduction

The excessive phosphorylation and reduced microtubule (MT) association of the Tau protein leads to the formation of insoluble inclusions that are prominent cellular pathologies in many types of frontotemporal dementia (FTD) (Goedert et al., 1988; Crowther, 1991). Tau

gene mutations underlie ~5% of familial FTD cases with as many as 40% of all tauopathies, both sporadic and familial, presenting with Tau positive fronto-temporal lobar degeneration (see Neumann et al., 2009; Goedert et al., 2012 for reviews). Functionally, the majority of exonic FTD Tau variants lead to the promotion of phosphorylation, decreased phosphatase association, diminished MT binding and an increased propensity for protein self-aggregation (Goedert and Spillantini, 2000).

Despite a degree of shared common pathology between FTD tauopathies and Alzheimer's disease (AD), both dementias differ significantly in terms of early symptomatic presentation due to the divergent anatomical loci of neurodegeneration (Rabinovici et al., 2007). FTD can be broadly subdivided into behavioural variant FTD (bvFTD), associated with degeneration of the prefrontal cortex, and semantic variant FTD (svFTD), in which temporal lobe degeneration is primary (Ghosh and Lippa, 2015). Although executive dysfunction is common in both, svFTD is associated with varying language-based deficits, whilst bvFTD

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Table 1
Overview of transgenic hTau expressing mouse models. Model name, Tau mutation, isoform, promoter, expression level ('Expression'), regional expression ('Region'), histopathology and behavioural/cognitive phenotypes are shown, and listed in order of publication year. For onset, age in months (m) is given either for earliest report of histopathology (a) or behaviour (b). For behavioural/cognitive phenotypes, specific aspects affected are given in brackets, arrows indicate decline or enhancement. Abbreviations: B.S. = brain stem, CaMKII = Ca^{2+} /Calmodulin Kinase II, CNS = central nervous system, E.C. = entorhinal cortex, EPM = elevated plus maze, Endo. = endogenous, F.B. = forebrain, L/D box = light/dark box, NFTs = neurofibrillary tangles, N.R. = not reported, OF = open field, P-Tau = phospho-Tau, PDGF- β = platelet-derived growth factor β , PrP = prion protein promoter, PPI = pre-pulse inhibition, S.C. = spinal cord, STFP = social transmission of food preference, Tet = tetracycline inducible, and WM = water maze.

Tau variant (name)	Isoform	Promoter	Expression (fold)	Region	Onset (m)	Histopathology	Behavioural/cognitive phenotype	Reference
P301L (JNPL3)	4R2N	mPrP	2	CNS + S.C.	4 ^b	P-Tau/NFTs in F.B. + S.C. + B.S. Spinal motor neuron loss (>8 m)	Motor deficits	Lewis et al. (2000)
P301L	4R2N	Thy 1.2	N.R.	CNS + S.C.	3 ^a	P-Tau/NFT in F.B. + S.C. + B.S.	No motor deficit	Gotz et al. (2001)
V337M	4R2N	PDGF- β	0.1	CNS: F.B.	12 ^b	P-Tau/NFTs in F.B.	No WM deficit Increase in EPM open arms ($\downarrow$ anxiety)	Tanemura et al. (2001, 2002)
P301S	4R0N	Thy 1	2	CNS + S.C.	3 ^b	P-Tau/NFTs in F.B. + S.C. Spinal neuron loss Muscle atrophy	Motor deficits WM deficits ($\downarrow$ memory) Increased time in OF centre ($\downarrow$ anxiety)	Allen et al. (2002) and Scattoni et al. (2010)
R406W	4R2N	CaMKII	0.2	CNS: F.B.	16 ^b	P-Tau/NFTs in F.B.	No motor deficits Cued/contextual fear conditioning ($\downarrow$ memory) No difference in L/D box ($-$ anxiety) PPI deficits ($\uparrow$ psychosis) Immobility in forced swim test ($\uparrow$ depression)	Tatebayashi et al. (2002) and Egashira et al. (2005)
R406W	4R2N	mPrP	10	CNS + S.C.	2 ^a	P-Tau/NFTs in F.B. + S.C.	N.R.	Zhang et al. (2004)
P301L (Tg4510)	4R0N	CaMKII (Tet)	13	CNS: F.B.	2–4 ^b	P-Tau/NFTs in F.B. Cortico-spinal neuron loss (>10 m)	Motor deficits WM deficits ($\downarrow$ memory) Contextual fear conditioning ($\downarrow$ memory) PPI deficits ($\uparrow$ psychosis)	Santacruz et al. (2005), Ramsden et al. (2005), Hunsberger et al. (2014), and Koppel et al. (2014)
P301S + G227V (THY-Tau22)	4R1N	Thy 1.2	5	CNS + S.C.	3 ^b	P-Tau/NFTs in F.B.	No motor deficits WM deficit ($\downarrow$ memory) STFP deficit ($\downarrow$ memory) Y-maze deficit ($\downarrow$ memory) Contextual fear conditioning ($\downarrow$ memory) Increase in EPM open arms ($\downarrow$ anxiety) Immobility in tail suspension test ($\uparrow$ depression) Reduced reward performance ($\uparrow$ anhedonia)	Schindowski et al. (2006) and Van Der Jeugd et al. (2011, 2013)
P301S (PS19)	4R1N	mPrP	5	CNS + S.C.	3 ^b	P-Tau/NFTs in F.B. + S.C. Spinal neuron loss Muscle atrophy	Motor deficits WM deficits ($\downarrow$ memory) Increase in EPM open arms ($\downarrow$ anxiety) PPI deficits ($\uparrow$ psychosis) Decreased hot plate threshold ($\uparrow$ nociception) No change in forced swim test	Yoshiyama et al. (2007) and Takeuchi et al. (2011)
K257T + P301S (DM Tau-tg)	4R0N	Tau	0.1	CNS + S.C.	6 ^b	P-Tau and NFTs in F.B.	No motor deficits WM deficits ($\downarrow$ memory) RAWM deficits ($\downarrow$ memory)	Rosenmann et al. (2008)
P301L (rTg TauEC)	4R0N	CAMKII/neurosin	N.R.	E.C. hippocampus	3 ^a	P-Tau and NFTs in E.C. and hippocampus Propagation of pathology via synaptic	Contextual fear conditioning deficit ($\downarrow$ memory)	De Calignon et al. (2012) and Polydoro et al. (2014)

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