Transgenic Ubiquitin (hUBQLN2) Mice Models of Amyotrophic Lateral Sclerosis with Frontotemporal Dementia (ALS-FTD)

Summary

ALS (or Lou Gehrig's disease) is a progressive neurodegenerative disorder associated with loss of upper and lower motor neurons. A majority of ALS patients (> 90%) die within 2 to 5 years of being diagnosed, usually because of upper respiratory failure. In addition to the hallmark of progressive muscle weakness, up to 15% of patients with ALS have a diagnosis of FTD, with up to 50% of patients showing some FTD symptoms. A common pathological feature in ~97% of all cases is a reduction in TAR-DNA binding protein 43 (TDP-43) in the nucleus and its accumulation in ubiquitin-positive inclusions in the cytoplasm of spinal motor neurons. UBQLN2 mutations have been linked to ALS and FTD, and UBQLN2 protein is found in cytosolic inclusions of both familial and sporadic ALS, suggesting it plays a central role in aggregate formation and proteasome impairment. Missense mutations in *UBQLN2* cause ALS-FTD but previous rodent models with *UBQLN2* mutations do not show motor neuron disease. As such, **these newly developed UBQLN2 mouse lines are unique in their ability to model ALS-FTD**. The WT *UBQLN2* non tansgenic mice are devoid of clinical and pathological signs of ALS and FTD. In contrast, the mutant *UBQLN2* mice develop motor neuron disease, TDP-43 pathology, show cognitive deficits and have shortened lifespans, recapitulating ALS-FTD clinical symptoms and pathology.

Key Investigator
Mervyn J. Monteiro

Field
Molecular Biology
Neuroscience
Genetics

Technology
Transgenic mice

Advantages
First UBQLN2 rodent models to recapitulate the central features of ALS-FTD (motor neuron disease and cognitive deficits)

Model recapitulates the clinical pathology of ALS

Analogous control/WT line also generated

Status
Available for licensing
Available for sponsored research

Patent Status
Tangible Research Property

UMB Docket Reference
MM-2017-037

External Reference
Le et al. (2016) *PNAS.* 113, E7580-E7589.

Market

Currently, there is no cure for ALS-FTD. Cognitive deficits such as FTD have a profound effect on the quality of life of ALS patients. The only FDA-approved therapy to slow down progression of ALS (riluzole, launched in 1995) does not improve motor symptoms and is not known to improve cognitive decline. Since ALS-FTD is a rare condition, it is challenging to enroll patients for clinical trials. Animal models that capture the ALS-FTD clinical disease pathology are likely to play a key role in development of novel treatments.

The most commonly used rodent models of ALS are superoxide dismutase (SOD1) and TDP-43 mutants. Most SOD1 ALS rodent models show motor neuron loss, paralysis and decreased life expectancy. However, these do not appear to show cognitive deficits. In contrast, some TDP-43 ALS rodent models show both motor neuron disease and cognitive phenotypes, but only some of these recapitulate the ubiquitin-positive neuronal cytosolic inclusions that characterizes the vast majority of ALS cases. Curently available UBQLN2 rodent models only show cognitive deficits and no motor phenotype. The newly generated UBQLN2 mutant lines stand out from SOD1, TDP-43, and previous UBQLN2 ALS models by expressing this motor-cognitive comorbidity in addition to the common TDP-43 pathology seen in ALS patients. They can therefore be valuable research tools to aid in the identification of new therapeutic targets for ALS. ALS is designated as an "orphan" disease and has a high unmet need for therapies. Therefore, potential therapies for ALS are eligible for market and regulatory incentives to facilitate and expedite their FDA approval.

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Technology

Two lines of mutant hUBQLN2 transgenic mice were established by cloning cDNA encoding human ALS-FTD P497S or P506T missense mutantations in the hUBQLN2 gene. The expression of hUBQLN2 is restricted to neurons, and lines overexpress hUBQLN2 to ~70-80% of the level of endogenous mouse UBQLN2. An additional line, called WT-358, expressing WT hUBQLN2 to ~20% the level of mUBQLN2 was also generated. P497S and P506T ALS-FTD mice all develop age-dependent pathological and clinical signs of motor neuron disease. Beginning at approximately 6 weeks of age, clinical signs progress, including muscle fiber denervation, muscle wasting, progressive difficulty in movement and decreased forelimb and hindlimb grip strength. At end-stage disease, these two lines of mice show age-dependent accumulation of uniquitinated inclusions in the brain and spinal cord, astrocytosis, a reduction in the number of hippocampal neurons, and recapitulate the common ALS pathological feature of reduced TDP-43 staining in the nucleus with a concomitant formation of ubiquitin-positive inclusions in the cytoplasm of spinal motor neurons. These two ALS-FTD lines also show memory deficits, as measured by novel object recognition, and massive neuronal loss in the hippocampus. While the WT non transgenic UBQLN2 mice do not develop motor neuron disease or show cognitive deficits, the WT-358 line also does not develop motor neuron disease, but does show mild cognitive defects.

Key Investigator
Mervyn J. Monteiro

Field
Molecular Biology
Neuroscience
Genetics

Technology
Transgenic mice

Advantages
First rodent models that display classic TDP-43 pathology that is seen in the vast majority of ALS cases.

Model recapitulates the clinical pathology of ALS

Analogous control/WT line also generated

Status
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Patent Status
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Technology Status

The motor symptoms, cognition, and cellular pathology of these three transgenic mouse lines have been well-characterized. The two mutant UBQLN2 lines, P497S and P506T, develop clinical signs of motor neuron disease such as decreased weight and grip strength, as well as age-dependent motor neuron and hippocampal neuron loss that is accompanied by a memory deficit. Lastly, characterization of TDP-43 phenotype reveals accumulation of inclusions in the cytoplasm of motor neurons in P497S and P506T, but not WT hUBQLN2 non transgenic mice, a classical pathological signature found in the vast majority of human ALS cases. However, the WT-358 line also develops the classic features of TDP-43 pathology, evidenced by clearance of TDP-43 from the nucleus and accumulation in ubiquitin+ cytoplasmic inclusions. Additionally, the WT-358 line does not manifest signs of motor neuron disease, thus providing an important control for drug screening studies. Together, the WT-358, P497S and P506T transgenic mice can be a great research tool for understanding the mechanisms by which UBQLN2 mutations cause ALS-FTD in humans, as well as for screening and testing of novel therapeutics to stop the progression of the disease.

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