hTDP43^{wtxA315T}

Strain Name： B6/JGpt-Tg(hTARDBP A315T,hTARDBP)9/Gpt
Strain Type： Transgene
Strain Number： T054620
Background： C57BL/6JGpt

Description

Amyotrophic Lateral Sclerosis (ALS) is the third-largest neurodegenerative disease caused by the death of motor neurons in the brain and spinal cord. According to global ALS epidemiological statistics, the annual number of new ALS cases is 1 to 2.6 per 100,000 people. The incidence and prevalence increase with age and the average age of onset is 58 to 60 years old. Typical clinical symptoms are weakness of limbs, muscle paralysis, paralysis, etc. The pathological manifestations are degeneration of motor nerve cells in the brain and spinal cord, degeneration of the corticospinal tract and cortical medulla oblongata, and accumulation of toxic proteins [1].

TDP43 is encoded by the TARDBP gene and belongs to the heterogeneous nuclear ribonucleoprotein (hnRNP) family. In normal cells, TDP43 is mainly present in the nucleus and plays important roles in RNA regulation, such as transcriptional regulation, alternative splicing, and mRNA stabilization [2]. Under pathological conditions, cleavage, hyperphosphorylation, and ubiquitination of TDP43 can occur. These posttranslational modifications lead to cytoplasmic accumulation and aggregation of TDP43. The C-terminus of TDP43 is essential for the solubility and cellular localization of the TDP43 protein and regulates protein-protein interactions [3]. Mutations in the TDP43 have been identified in patients with familial ALS, and TDP43 aggregates are found in ALS patients, the TDP43 mutations including A315T, Q331K, M337V, Q343R, N345K, and N390D. TDP43 inclusions induce the mislocalization and aggregation of nucleoporins and transport factors. TDP43-induced impairment of the nuclear pore complex accelerates cytoplasmic mislocalization and accumulation of TDP43, subsequently contributing to neuronal dysfunction and toxicity [4].

At present, the development of effective drugs for the treatment of ALS has received widespread attention. GPT selected the A315T mutation site of the TDP43 protein to construct a hTDP43wtxA315T transgenic mouse model. This model can be used for the screening, safety evaluation, and pathogenesis of ALS therapeutic drugs.

Strategy

Fig.1 Schematic diagram of hTDP43^{wtxA315T} model stratery.

hTDP43^{wtxA315T} mice was established by co-overexpressing wt-human TARDBP cDNA and human TARDBP cDNA with A315T mutation.

Applications

1. Screening and safety evaluation of therapeutic drugs for ALS disease
2. Study of ALS disease mechanism

Data support

1. Detection of TDP43 protein expression

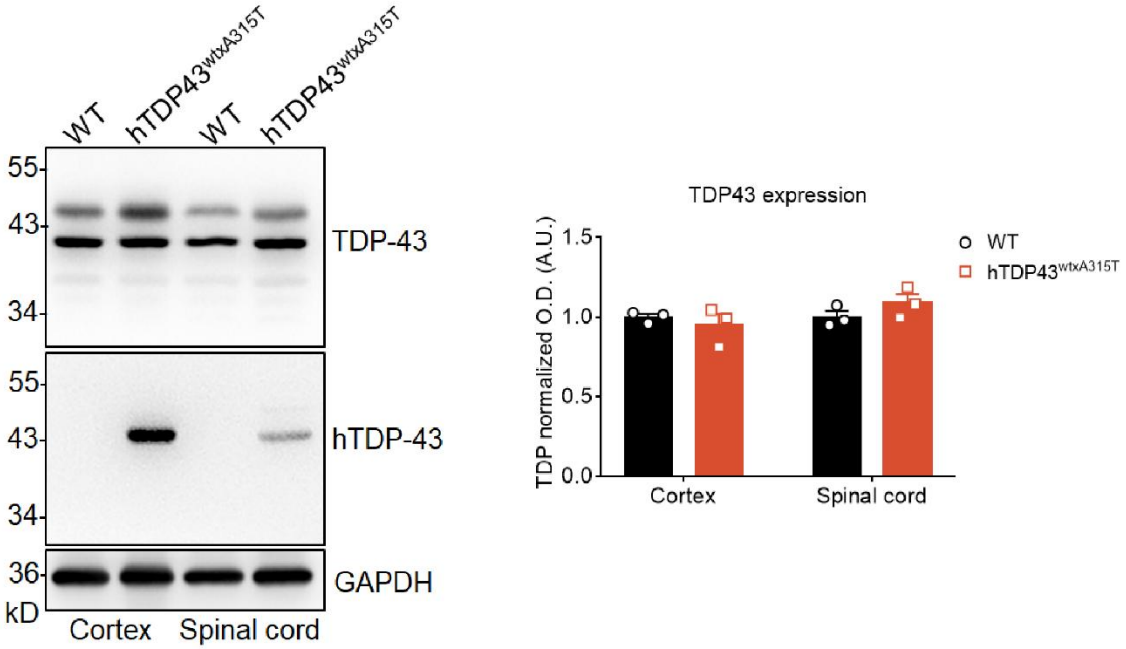

Fig 2. Expression of TDP43 protein

TDP43 (human and mouse) and human TDP43 protein was detected in brain and spinal cord from 8-week-old wild type and hTDP43^{wtxA315T} male mice by Western Blot.

All data represent as MEAN ± SEM. Unpaired two-tailed Student's t test.

2. TDP43 inclusions aggregation in hTDP43^{wtxA315T} mice

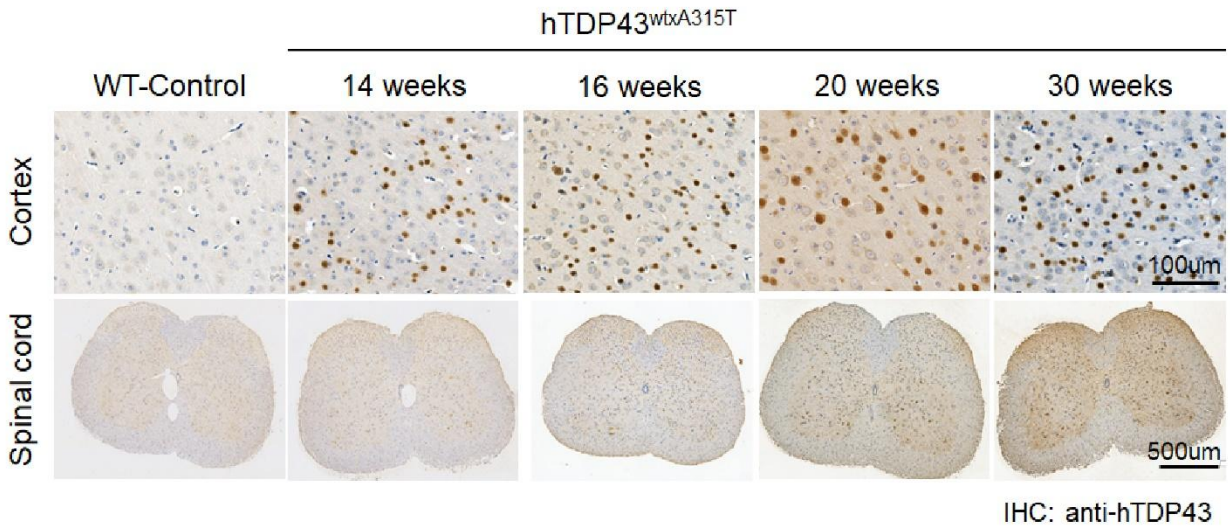

Fig 3. TDP43 inclusions aggregation in hTDP43^{wtxA315T} mice.

Representative images of TDP43 inclusions in the cortes and lumbar spinal cord of 14 to 30-week-old wild type and hTDP43^{wtxA315T} male mice. Female mice were similar. TDP43 inclusions were detected by the immunohistochemistry staining of the sections using TDP-43 (Human Specific) Monoclonal Antibody. Scale, Cortex, 100μm, Spinal cord, 500μm.

3. Muscle atrophy in hTDP43^{wtxA315T} mice

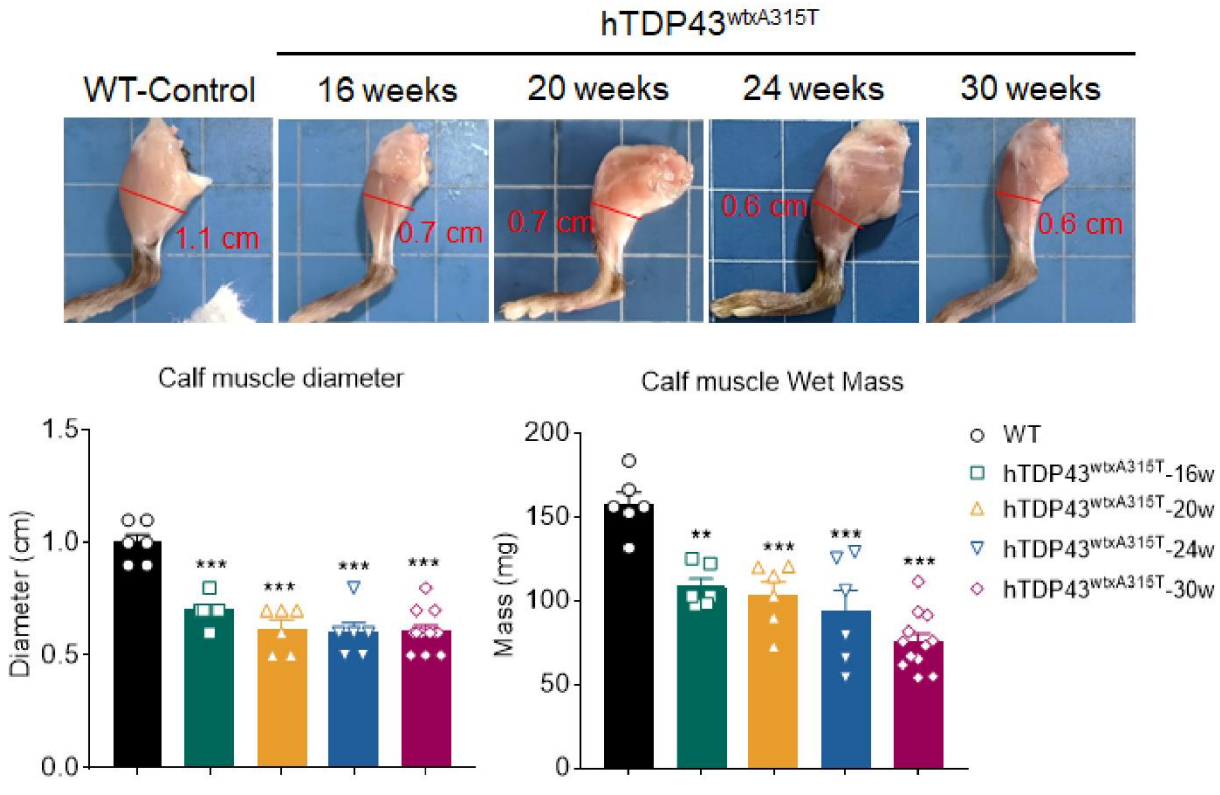

Fig 4. Diameter and wet mass of calf muscle in hTDP43^{wtxA315T} mice.

Representative photos of the hind-limb muscles of 16 to 30-week-old wild type and hTDP43^{wtxA315T} male mice. Female mice were similar. The red lines point to the measured sites of the muscle.
All data represent as MEAN ± SEM. **p < 0.01, ***p < 0.001; unpaired two-tailed Student's t test.

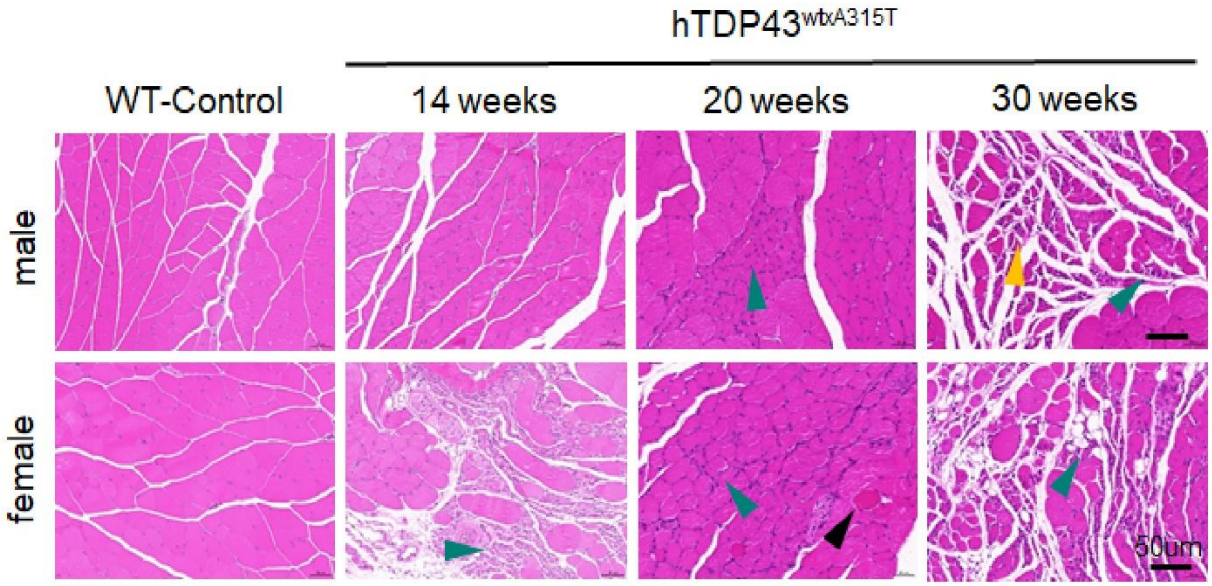

Fig 5. Muscle atrophy in hTDP43^{wtxA315T} mice.

Representative images of the hind-limb muscles of 14 to 30-week-old wild type and hTDP43^{wtxA315T} mice. The yellow arrow point to shrinking muscle cells, green arrow point to dense nuclei and black arrow represents increased eosinophilic acid. Scale, 50μm.

4. Loss of weight in hTDP43^{wtxA315T} mice

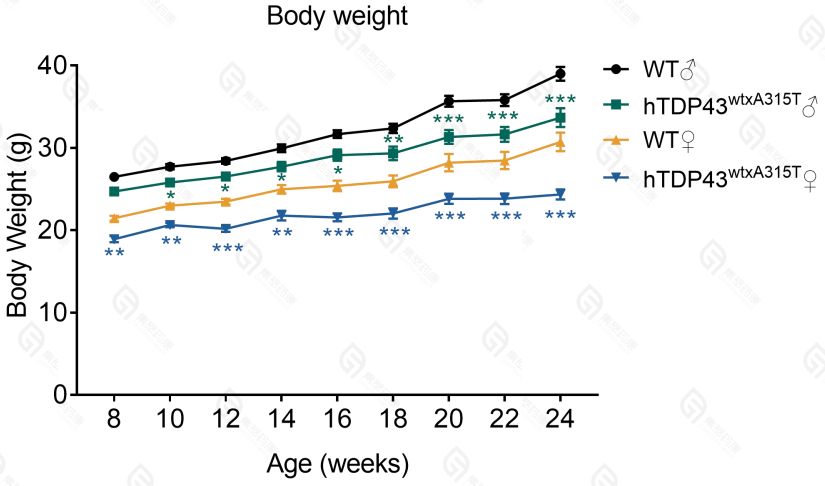

Fig 6. Loss of weight in hTDP43^{wtxA315T} mice.

Weight changes in hTDP43^{wtxA315T} mice aged 8 to 24 weeks.
N=10 each group. All data represent as MEAN ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001, Two-way ANOVA test.

5. Motor performances deficiency in hTDP43^{wtxA315T} mice

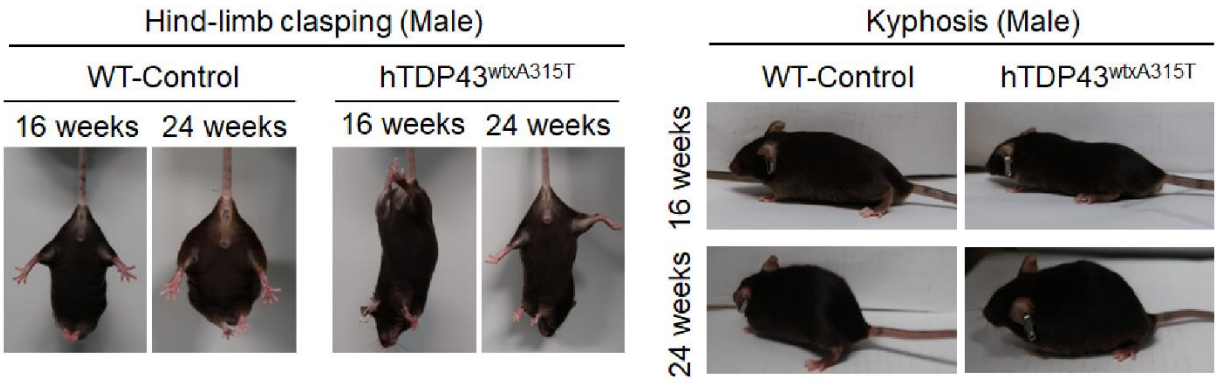

Fig 7. Motor performances deficiency in hTDP43^{wtxA315T} mice.

Hind-limb clasping and kyphosis of WT and hTDP43^{wtxA315T} male mice aged 16 and 24 weeks. Female mice were similar.

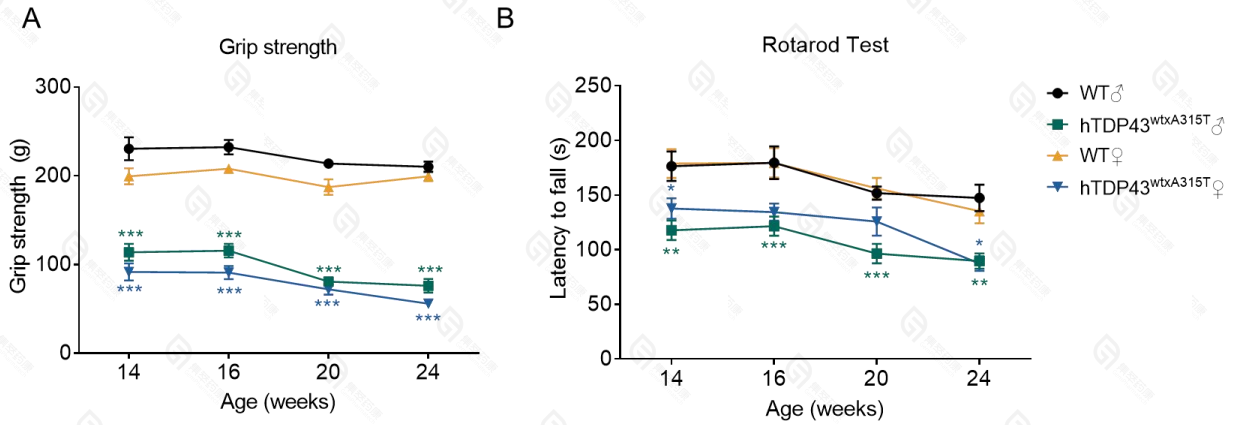

Fig 8. Motor performances deficiency in hTDP43^{wtxA315T} mice.

(A)Grip strength in hTDP43^{wtxA315T} mice. The hind limb grip strength at 14 to 24-week-old of male and female wild type and hTDP43^{wtxA315T} mice in grip strength test. (B) Rotarod test in hTDP43^{wtxA315T} mice. The latency (seconds fall in the rotarod) of 14 to 24-week-old of male and female wild type and hTDP43^{wtxA315T} mice in the rotarod test.

All data represent as MEAN ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001, Two-way ANOVA test.

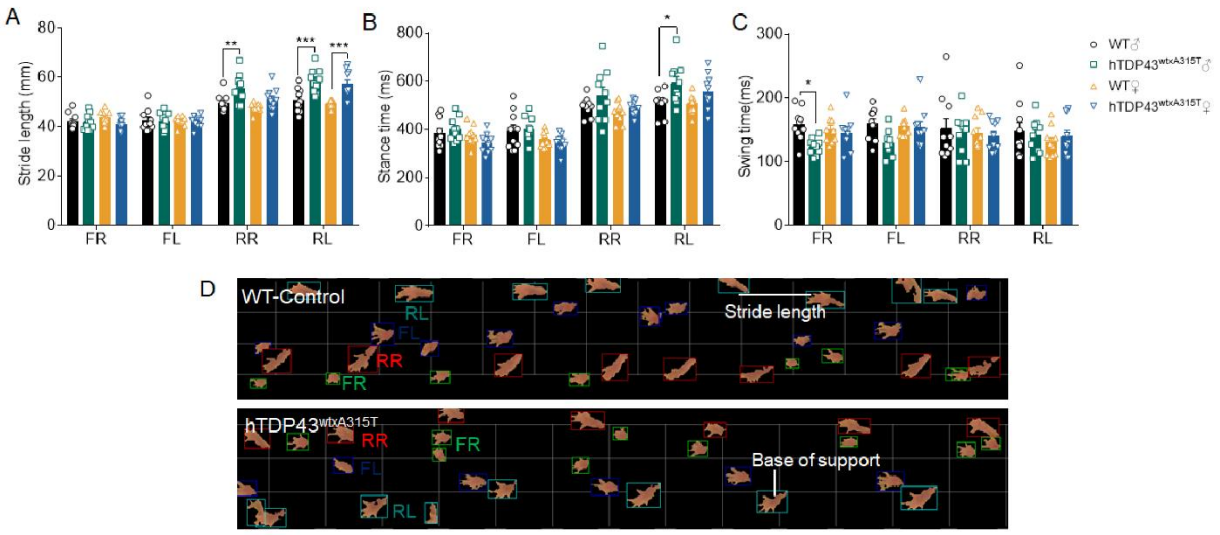

Fig 9. Abnormal gait in hTDP43^{wtxA315T} mice.

(A-C) Stride length, Stance time and Swing time in hTDP43^{wtxA315T} mice aged 16 weeks. (D) Representative images of wild-type (up) and hTDP43^{wtxA315T} strides (down) in the gait test. Left forepaw (FL, blue), right forepaw (FR, green), left hindpaw (RL, cyan) and right hindpaw (RR, red).
All data represent as MEAN ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001, Two-way ANOVA test.

References

1. Zhang F, Strom A L, Fukada K, et al. “Interaction between Familial Amyotrophic Lateral Sclerosis (ALS)-linked SOD1 Mutants and the Dynein Complex”. Journal of Biological Chemistry, 2007, 282(22):16691-16699.
2. Wegorzewska I, Bell S, Cairns NJ, Miller TM, Baloh RH. “TDP-43 mutant transgenic mice develop features of ALS and frontotemporal lobar degeneration”. Proc Natl Acad Sci U S A. 2009 Nov 3;106(44):18809-14. Epub 2009 Oct 15.
3. Jo, Myungjin, Shinrye Lee, Yu-Mi Jeon, Seyeon Kim, Younghwi Kwon, and Hyung-Jun Kim. “The role of TDP-43 propagation in neurodegenerative diseases: integrating insights from clinical and experimental studies”. Experimental & Molecular Medicine 52, no. 10 (2020): 1652-1662.
4. Philips T, Rothstein JD. “Rodent Models of Amyotrophic Lateral Sclerosis”. Curr Protoc Pharmacol. 2015 Jun 1;69:5.67.1-5.67.21.