B6-hSNCA A53T

Strain Name: B6/JGpt-Tg(hSNCA-A53T)62/Gpt

Strain Type: Transgene

Strain Number: T054329

Background: C57BL/6JGpt

Description

Parkinson's disease (PD) is a progressive degenerative disease of the central nervous system. The clinical manifestations are mainly motor system disorders such as resting tremors, muscle stiffness, and postural changes, and some are accompanied by cognitive impairment and mental retardation, dementia, etc., which is the second most common neurodegenerative disease in the world [1]. Theathological features of Parkinson's disease are mainly manifested as progressive loss of dopaminergic neurons (DA) in the substantia nigra pars compacta (SNpc) and the inclusion of Lewy bodies in the cytoplasm. Studies have shown that PD is related to a series of mechanisms such as oxidative stress, mitochondrial dysfunction, ubiquitin-proteasome system dysfunction, and excitotoxicity [2].

α-Synuclein (α-syn) is ubiquitous in the brain and is the main filamentous component of the characteristic pathological changes of PD, Lewy bodies, and the cause of some family forms of PD. At the same time, it has potential effects on synaptic plasticity, vesicle dynamics, and dopamine synthesis. Therefore, α-syn is considered a molecular marker of some neurodegenerative diseases. In PD, these inclusion bodies are distributed in the medulla oblongata, olfactory bulb, locus coeruleus, substantia nigra, and to a lesser extent in various areas of the cortex. SNCA, the gene encoding α-synuclein, has three main gene mutation sites: A53T (Ala-Thr), A30P (Ala-Pro), and E46K (Glu-Lys). These mutations can destroy the original molecular spatial structure of the protein, causing α-synuclein to fail to be degraded normally, and abnormally aggregate to form amyloid structures, thereby causing neuronal degeneration [3].

At present, therapeutic drugs targeting the clearance of α-synuclein have entered clinical trials one after another, and the development of effective drugs for the treatment of PD continues to receive widespread attention. GPT independently developed the B6-hSNCA A53T model for the A53T mutation sites of SNCA, which can be used for the screening, safety evaluation, and pathogenesis of Parkinson's disease drugs.

Strategy

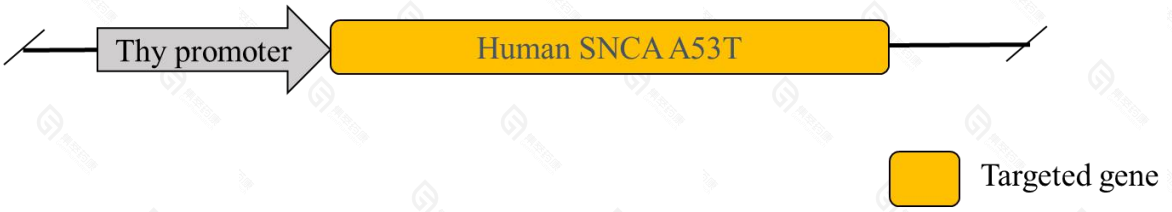

Fig.1 Schematic diagram of B6-hSNCA A53T model stratery.

Applications

1. Study on the pathogenesis and efficacy of Parkinson's disease
2. Study on pathogenesis of dementia with Lewy bodies
3. Studies on synaptic signal transduction and transport

Data support

1. Detection of a-Synuclein protein expression

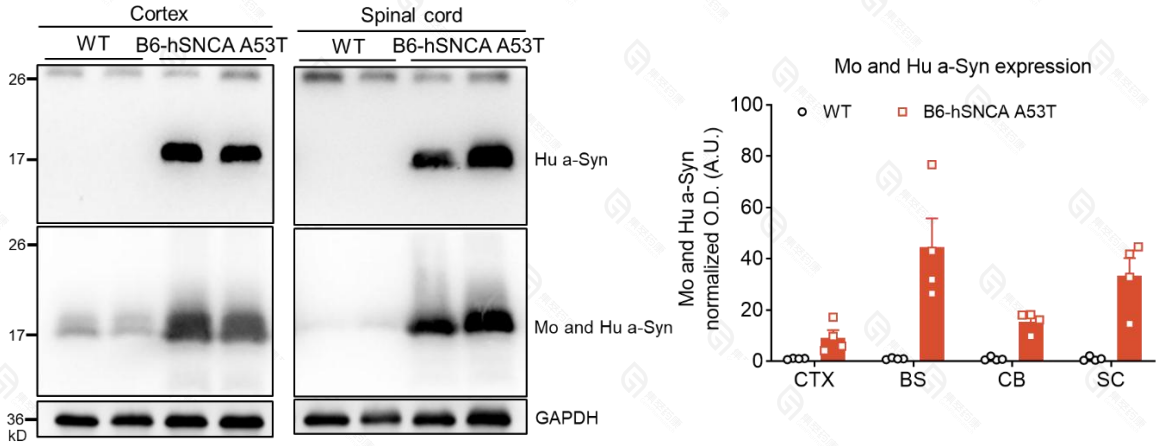

Fig 2. Expression of a-Synuclein protein.

a-Synuclein (mouse and human) and human a-Synuclein protein was detected in brain, spinal cord, cerebellum and brainstem from 8-week-old wild type and B6-hSNCA A53T male mice by Western Blot. Female mice were similar.

All data represent as MEAN ± SEM.

2. Dopaminergic neuron loss

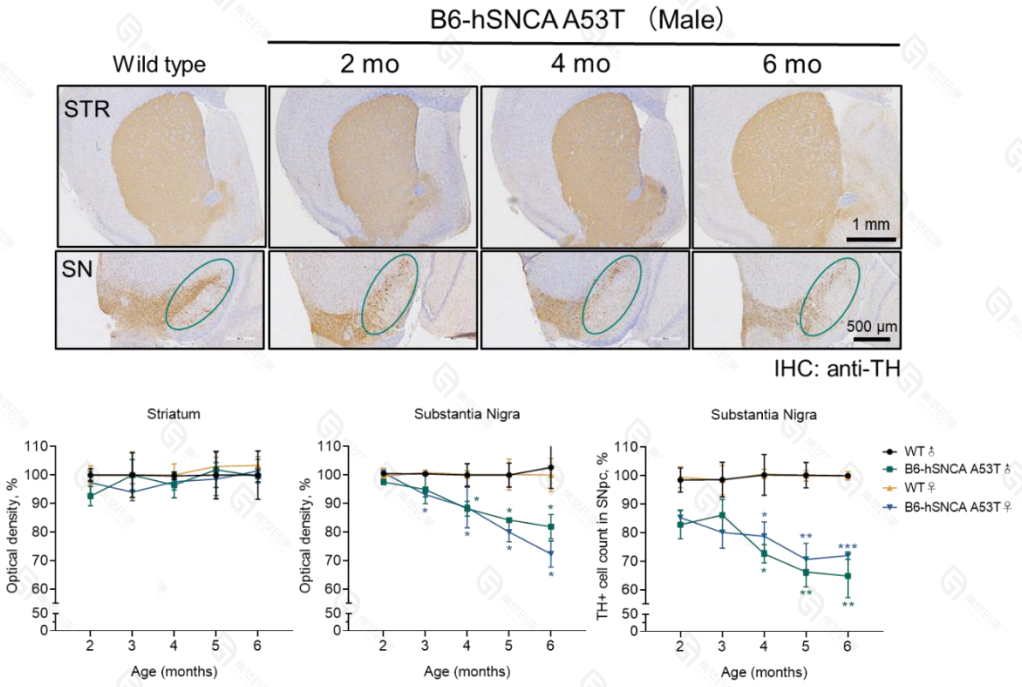

Fig 3. Dopaminergic neuron loss.

Representative images of TH^+ neruons in the striatum and substantia nigra of 2 to 6-month-old wild type and B6-hSNCA A53T male mice. Dopaminergic neurons were detected by the immunohistochemistry staining of the sections using Tyrosine Hydroxylase Antibody. Scale, 1 mm, 500 μm.

All data represent as MEAN ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001; two-way ANOVA, Tukey's post hoc analysis.

3. a-Synuclein aggregation

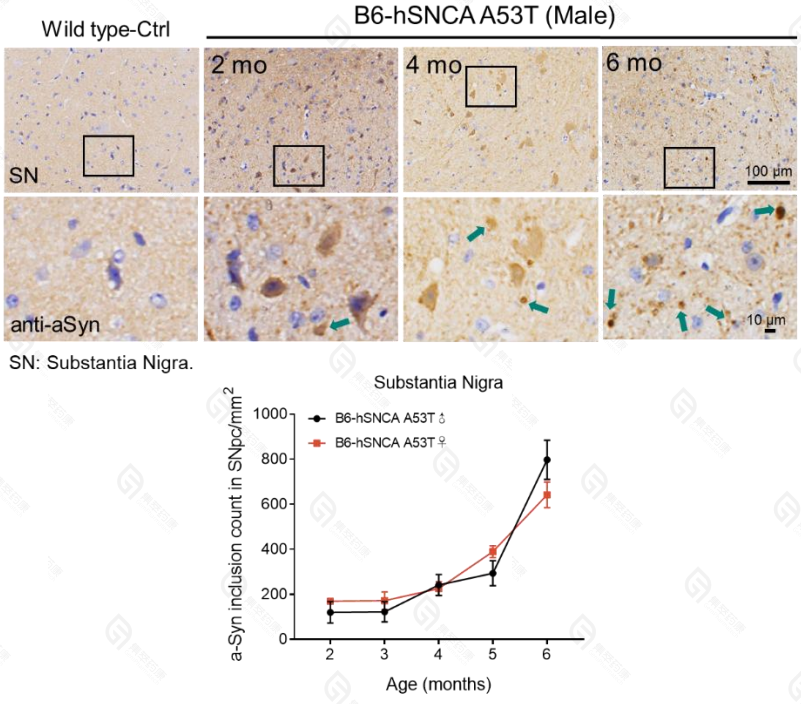

Fig 4. a-Synuclein aggregation.

Representative images of a-Synuclein inclusion in the substantia nigra of 2 to 6-month-old wild type and B6-hSNCA A53T male mice. a-Synuclein aggregation were detected by the immunohistochemistry staining of the sections using alpha Synuclein Monoclonal Antibody. Scale, 100 μm/10 μm.
All data represent as MEAN ± SEM.

4. Serine 129 phosphorylated a-synuclein expression

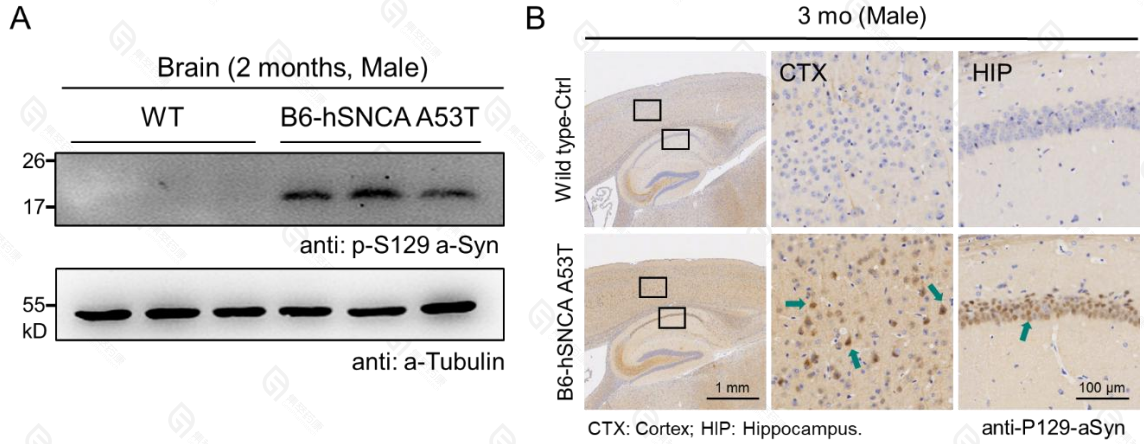

Fig 5. Expression of Serine 129 phosphorylated a-synuclein.

(A) Serine 129 phosphorylated a-synuclein protein was detected in brain from 2-month-old wild type and B6-hSNCA A53T male mice by Western Blot. (B) Representative images of serine 129 phosphorylated a-Synuclein in the cortex and hippocampus of 3-month-old wild type and B6-hSNCA A53T male mice. Scale, 1 mm/100 μm. Female mice were similar.

5. Body weight change and survival curve

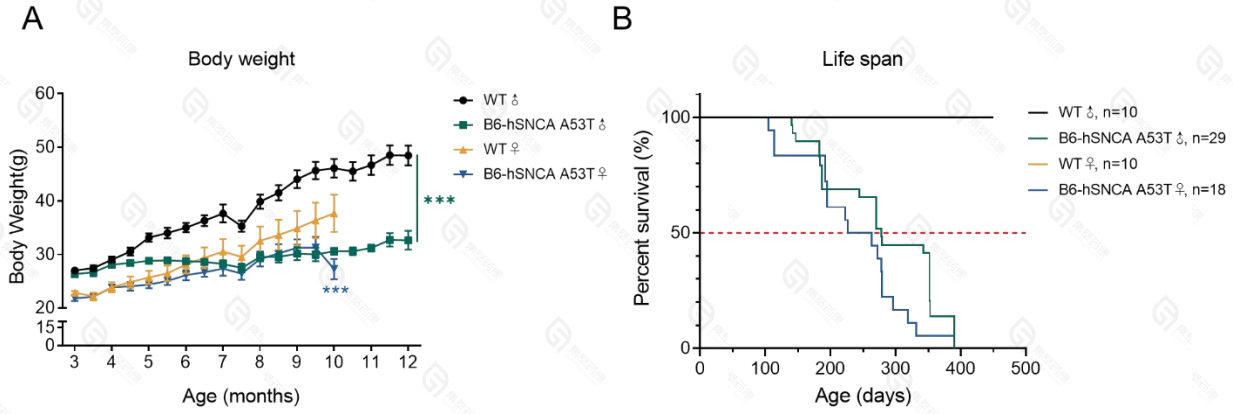

Fig 6. Body weight change and survival curve.

Weight changes and survival curve in B6-hSNCA A53T mice aged 3 to 12 months. The male mice began to die at the age of 5 months, and the median survival time reached at the age of 9-month-old. Female mice began to die at 3-3.5 months of age, and the median survival time was reached at 7.5-months-old. (A) N=10 each group. All data represent as MEAN ± SEM. ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis. (B) N>10 each group.

6. Deficiency in balance and coordination

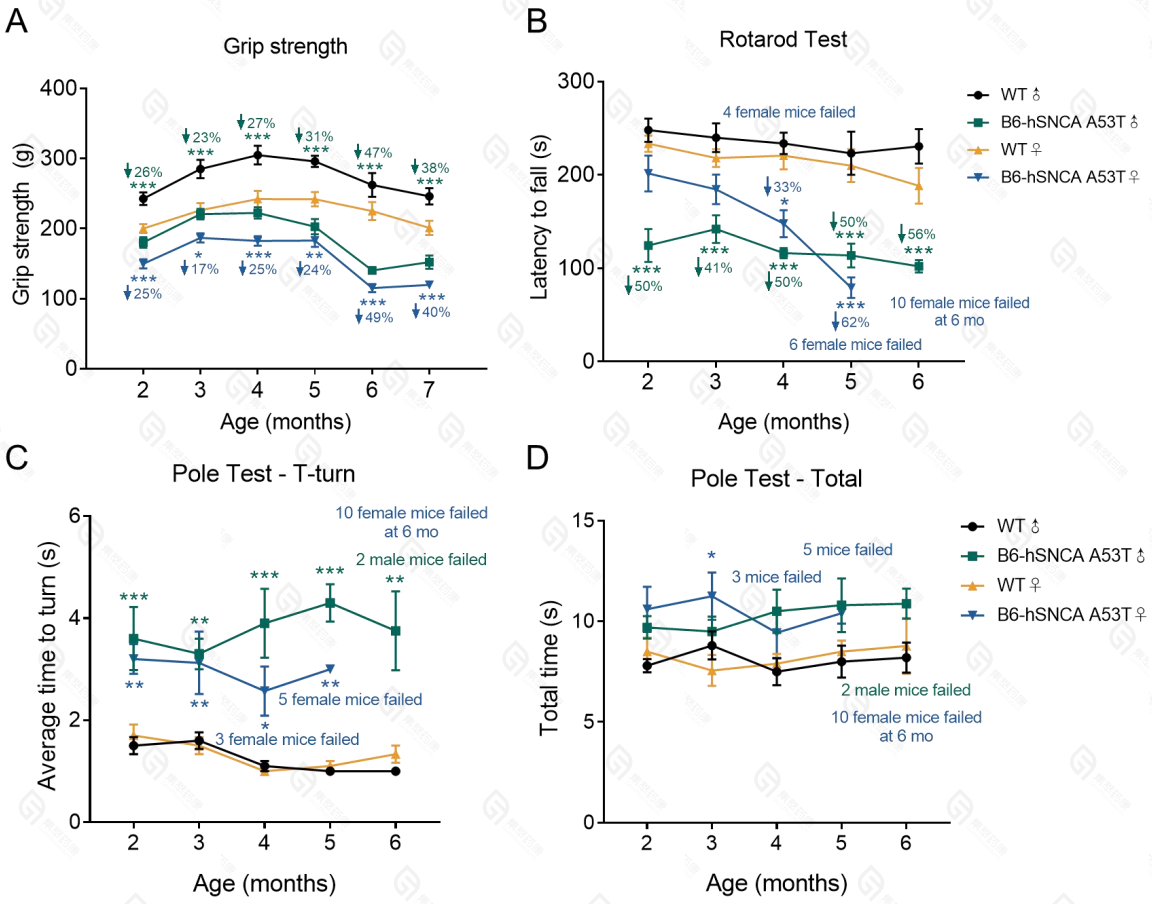

Fig 7. Deficiency in balance and coordination.

(A) Grip strength in B6-hSNCA A53T mice. The limbs grip strength at 2 to 7-month-old of wild type and B6-hSNCA A53T mice in grip strength test. (B) Rotarod test in B6-hSNCA A53T mice. The latency (seconds fall in the rotarod) of 2 to 6-month-old of wild type and B6-hSNCA A53T mice in the rotarod test. (C-D) Pole test in B6-hSNCA A53T mice. the time required for the mice to orient themselves facing in a downward direction (time to T-turn) and to descend to the base of the pole (total time) of 2 to 6-month-old of wild type and B6-hSNCA A53T mice.

N=10 each group. All data represent as MEAN ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis.

7. The timeline of disease progression in B6-hSNCA A53T mice

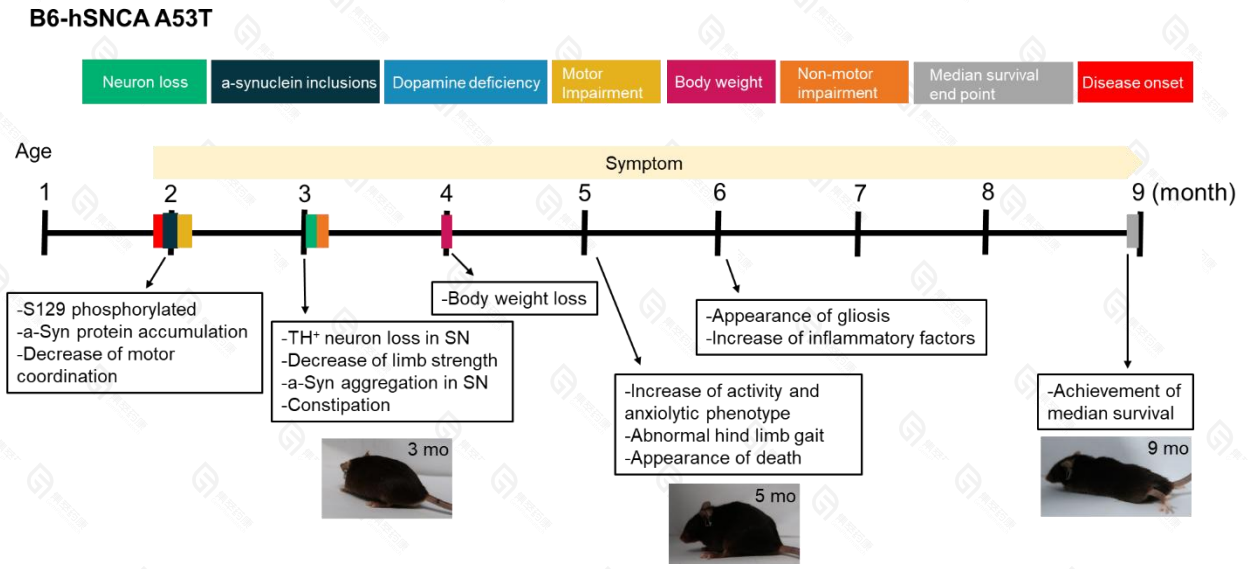

Fig 8. The timeline (month) of disease progression in B6-hSNCA A53T mice.

More data is in progress.

References

1. Fernagut PO, Chesselet MF. “Alpha-synuclein and transgenic mouse models.” Neurobiol Dis. 2004 Nov;17(2):123-30.
2. Yang W, Hamilton JL, Kopil C, Beck JC, Tanner CM, Albin RL, Ray Dorsey E, Dahodwala N, Cintina I, Hogan P, Thompson T. “Current and projected future economic burden of Parkinson's disease in the U.S.” NPJ Parkinsons Dis. 2020 Jul 9;6:15.
3. Conway KA, Rochet JC, Bieganski RM, Lansbury PT Jr. “Kinetic stabilization of the alpha-synuclein protofibril by a dopamine-alpha-synuclein adduct.” Science. 2001 Nov 9;294(5545):1346-9.