B6-hHTT130-N

Strain Name: B6/JGpt-Tg(hHTT-CAG130)90/Gpt

Strain Type: Transgene

Strain Number: T054804

Background: C57BL/6JGpt

Description

Huntington's disease (HD) is a relatively rare type of chronic progressive chorea, mostly occurring in the middle-aged and elderly. The main manifestations are dance-like movements, mental disorders, and progressive dementia called the "triple sign". Pathologically, HD shows atrophy of the basal ganglia and neuron loss, among which caudate nucleus and lenticular nucleus lesions are Lord, these lesions can cause severe whole brain atrophy [1].

Huntington's disease is caused by a mutation of the Huntingtin (HTT) gene on chromosome 4. HTT is widely expressed in various organs throughout the body, including the central nervous system, and contains a polymorphic triple nucleotide repeat near the N-terminal of its gene coding region. That is, cytosine-adenine-guanine (CAG), which is translated into polyglutamine (poly Q) [2]. When the CAG repeats are greater than 35, it will cause abnormal polyQ amplification, while poly Q amplification directly leads to the misfolding of HTT protein fragments, which abnormally interact with a large number of proteins, and accumulate in the nucleus and nerve terminals, resulting in a variety of nerve cell functions. Damage affects a wide area of the brain [3]. In HD mice brains, there is a mass of N-terminal fragments containing amplified polyQ repeats, and these fragments can be translated into full-field mutant HTT (mHTT) endogenously. Consistent with this, the transgenic mice expressing mutant exon 1 or other N-terminal HTT fragments carrying the mutation showed a more severe and progressive disease phenotype than the mice expressing the mHTT [4-6].

Currently, there is no effective treatment or drug that can prevent or reverse Huntington's disease. Deutetrabenazine approved by the FDA can only be used to relieve motor symptoms and has not achieved the fundamental therapeutic effect. Therefore, the development of effective drugs for treating Huntington's disease still has enormous economic benefits. GPT independently developed the B6-hHTT CAG130 model, which was transferred into a human HTT gene fragment carrying 130 CAG

repeat expansions. It is expected that this model can simulate the pathological features and dysfunction phenotype of Huntington's disease, and can be used for the screening and safety evaluation of drug treatments for Huntington's disease.

Strategy

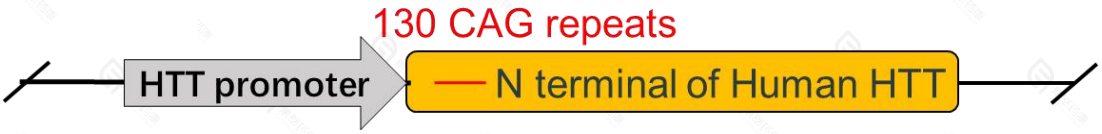

Fig.1 Schematic diagram of B6-hHTT130-N model stratery.

CAG repeat monitoring:

In the B6-hHTT130-N transgenic lines, the CAG repeat number is affected by genetic instability and may expand or contract. The phenotype of mice may change with the change of CAG repeat size. To avoid excessive individual differences, it is strongly recommended the CAG repeat number be quantified before the experiment to ensure the consistency of the phenotype of the enrolled mice.

Applications

1. Screening and safety evaluation of therapeutic drugs for Huntington's disease
2. Study of Huntington's disease mechanism

Data support

1. Detection of *HTT* mRNA expression

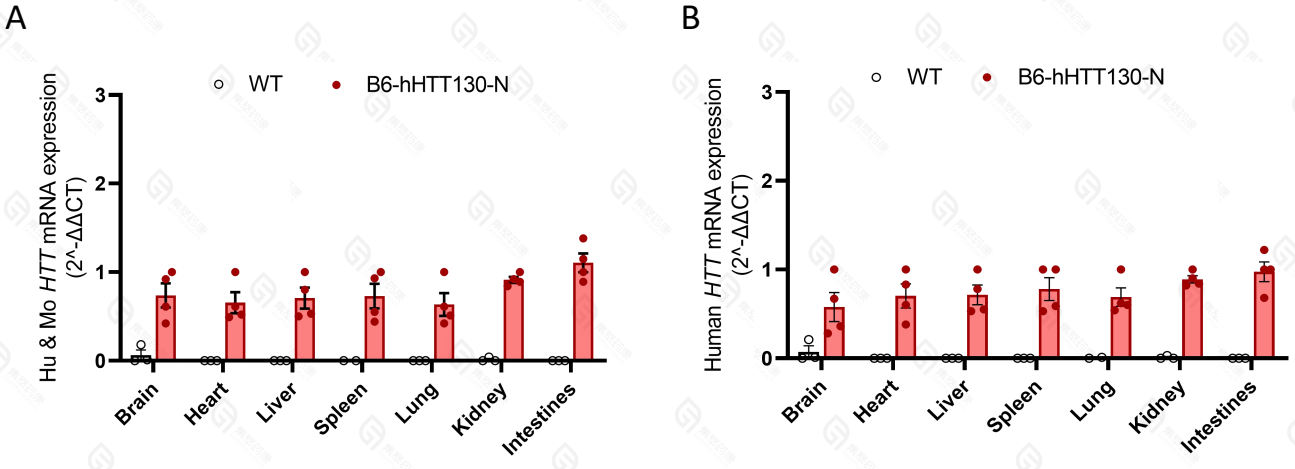

Fig 2. Expression of *HTT* mRNA.

HTT (mouse and human) and human *HTT* mRNA was detected in different organs from 20-week-old wild type and B6-hHTT130-N mice by QPCR. All data represent as MEAN ± SEM.

2. Mutant HTT (mHTT) aggregation in B6-hHTT130-N mice

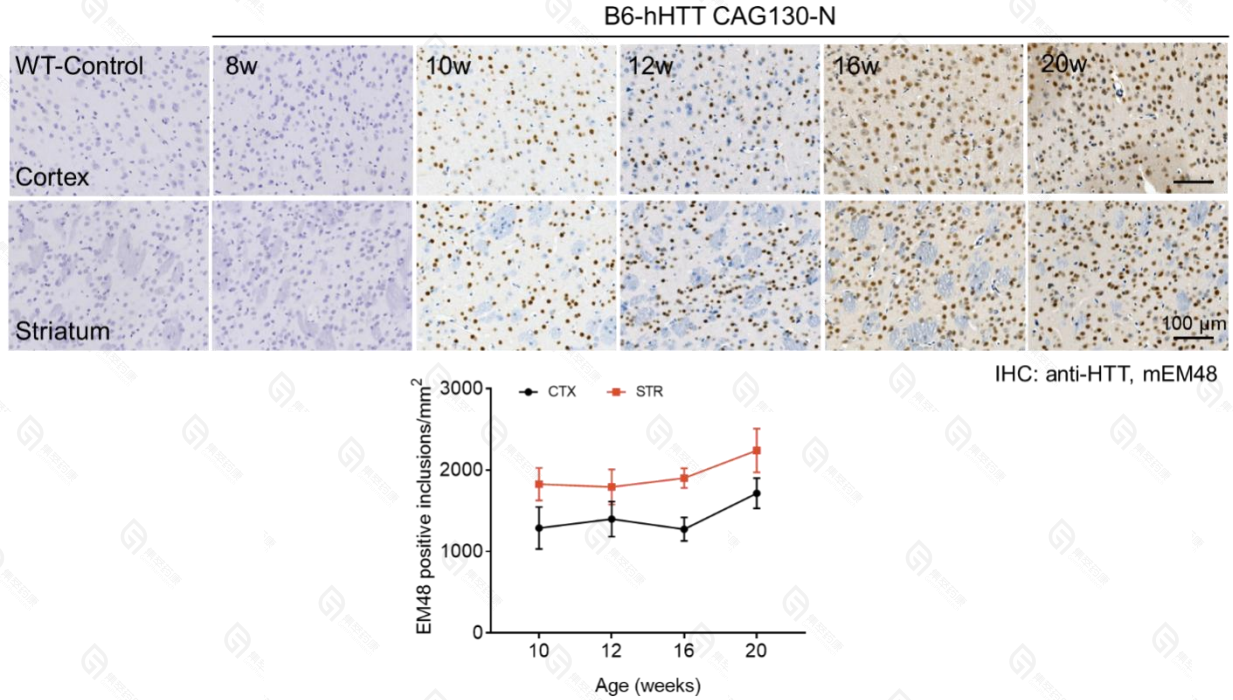

Fig 3. mHTT aggregation in B6-hHTT130-N mice.

Representative images of mHTT inclusions in the Cortex and Striatum of 8 to 20-week-old wild type and B6-hHTT130-N mice. mHTT inclusions were detected by the immunohistochemistry staining of the sections using huntingtin protein (mEM48) Antibody. Scale, 100μm.

N=6 each group. All data represent as MEAN ± SEM, two-way ANOVA, Tukey's post hoc analysis.

3. Loss of brain weight in B6-hHTT130-N mice

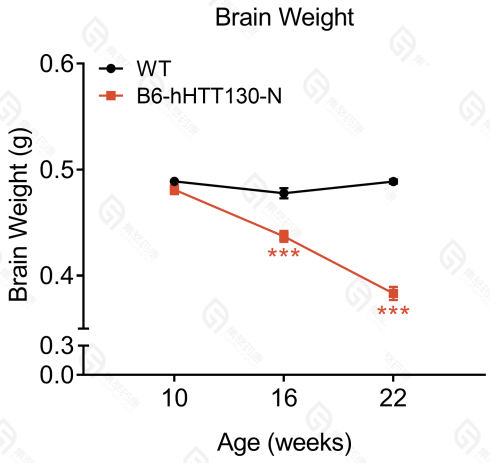

Fig 4. Loss of brain weight in B6-hHTT130-N mice.

Brain weight decrease in B6-hHTT130-N mice aged 10, 16 and 22 weeks.

N=6 each group. All data represent as MEAN ± SEM. ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis.

4. Loss of Medium spiny neurons in B6-hHTT130-N mice

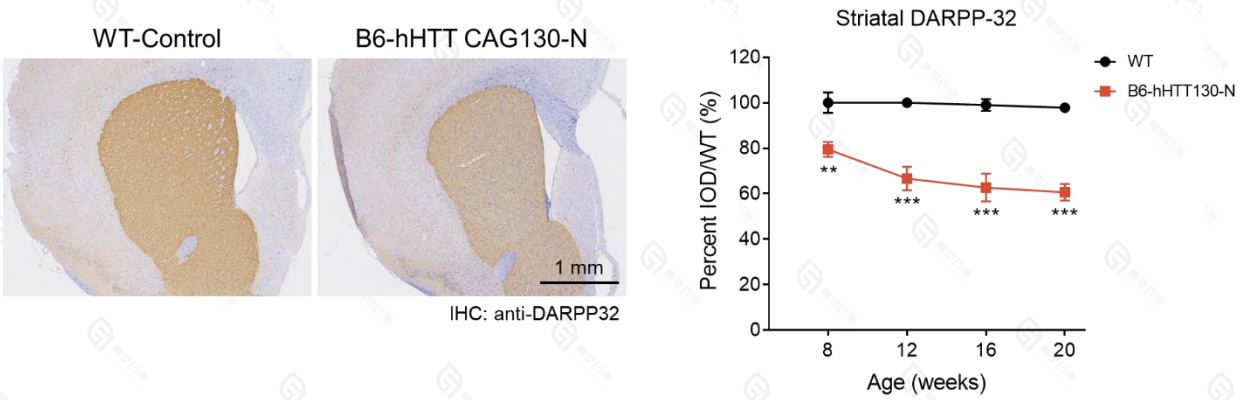

Fig 5. Medium spiny neurons in B6-hHTT130-N mice.

Representative images of DARPP32⁺ neurons in the Striatum of 8 to 20-week-old wild type and B6-hHTT130-N mice. DARPP32⁺ neurons were detected by the immunohistochemistry staining of the sections using DARPP-32 (19A3) Rabbit mAb Antibody. Scale, 1 mm.

N=6 each group. All data represent as MEAN ± SEM, **p < 0.01, ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis.

5. Body weight change and survival curve in B6-hHTT130-N mice

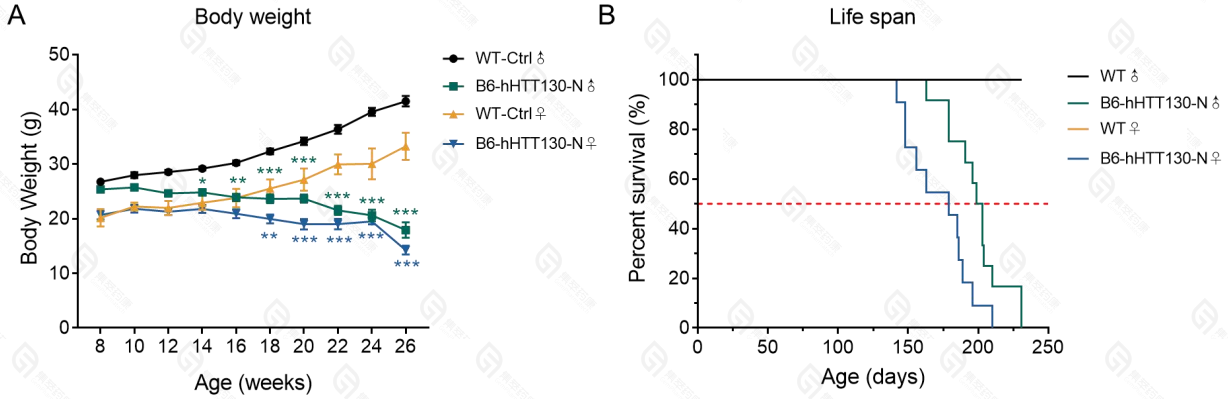

Fig 6. Body weight change and survival curve in B6-hHTT130-N mice.

Weight changes and survival curve in B6-hHTT130-N mice aged 8 to 26 weeks. Median survival time was reached at 26 weeks of age in males and 24 weeks in female mice. (A) 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. (B) N>10 each group.

6. Motor deficiency in B6-hHTT130-N mice

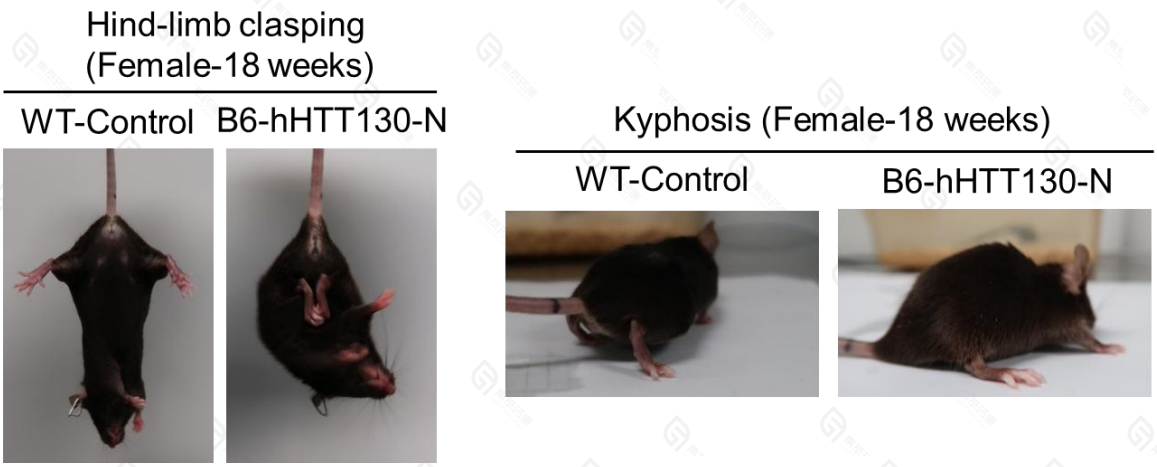

Fig 7. Motor deficiency in B6-hHTT130-N mice.

Hind-limb clasping and kyphosis of WT and B6-hHTT130-N female mice aged 18 weeks. Male mice were similar.

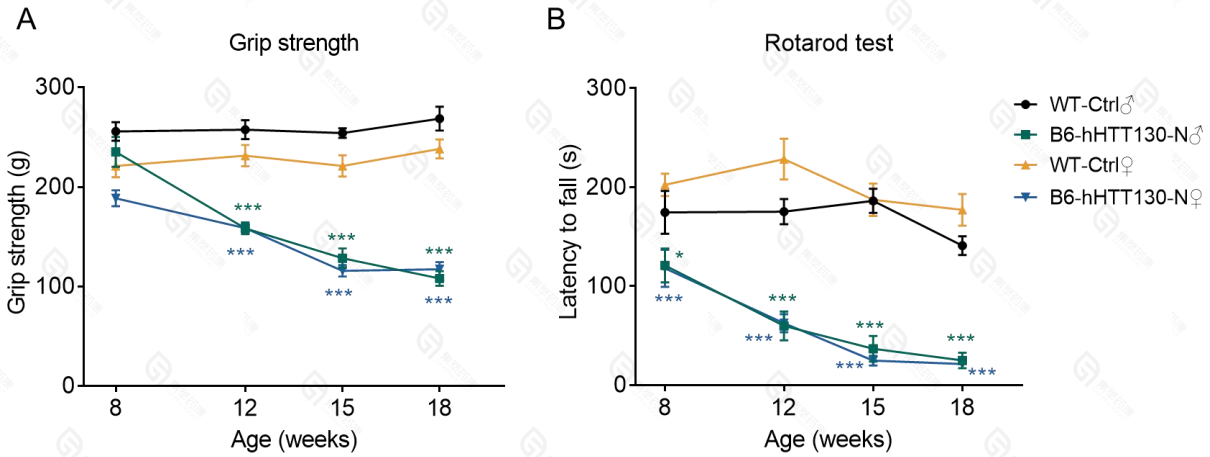

Fig 8. Motor deficiency in B6-hHTT130-N mice.

(A) Grip strength in B6-hHTT130-N mice. The limbs grip strength at 8 to 18-week-old of wild type and B6-hHTT130-N mice in grip strength test. (B) Rotarod test in B6-hHTT130-N mice. The latency (seconds fall in the rotarod) of 8 to 18-week-old of wild type and B6-hHTT130-N mice in the rotarod test.

N=12 each group. All data represent as MEAN ± SEM. *p < 0.05, ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis.

7. The timeline of disease progression in B6-hHTT130-N mice

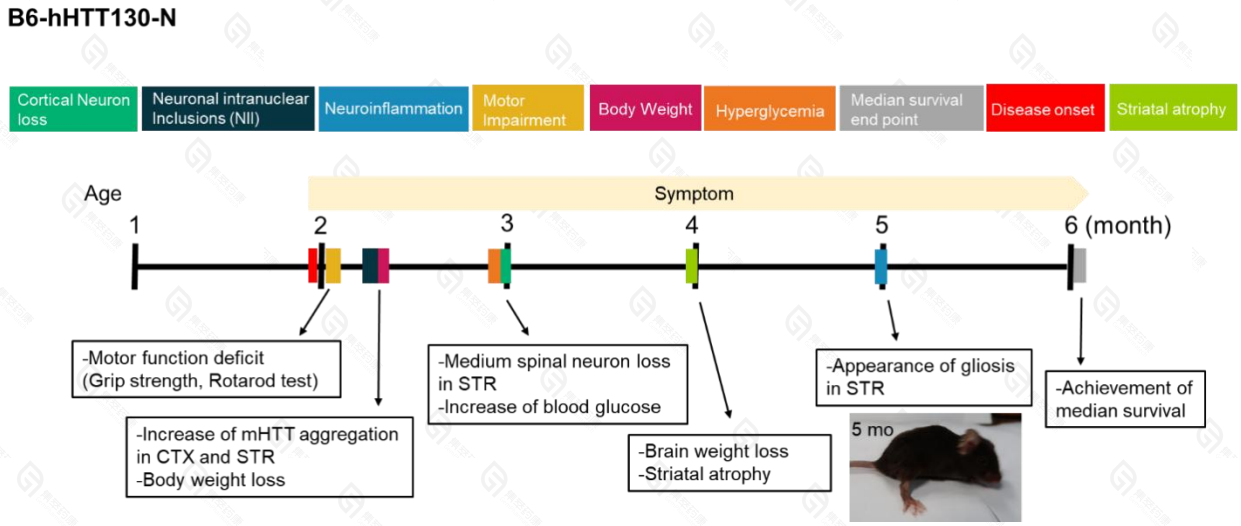

Fig 9. The timeline (month) of disease progression in B6-hHTT130-N mice.

References

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