B6-hTTR V30M Tg

Strain Name: C57BL/6JGpt-Tg(h*TTR*-V30M)46/Gpt
Strain Type: Transgene
Strain Number: T059897
Background： C57BL/6JGpt

Description

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant hereditary disease caused by mutations in the transthyretin (*TTR*) gene, and characterized by the extracellular deposition of TTR amyloid fibrils predominantly in the peripheral nervous system[1].TTR is mainly synthesized in the liver and choroid plexus epithelium in the brain and is a transport protein of thyroxine (T4) in plasma and cerebrospinal fluid[2].TTR is found in biological fluids as a homotetrameric protein composed of 127 amino-acid polypeptide subunits. Disease-associated mutations have been shown to reduce the thermodynamic stability of the tetramer, cause TTR tetramers to dissociate and misfold into amyloid fibrils, which are typically rich in beta-sheets and resilient to proteasomal degradation[2-4].

To date, more than 100 *TTR* gene mutations have been reported, of which *TTR* Val30Met is the most common mutation. It is peculiarized by aberrant aggregation and deposition of misfolded amyloid forms of TTR protein in vital areas including the heart, autonomic and peripheral nervous system, kidneys, eyes, and other pertinent areas[2,5]. And, it is frequently predominated by progressive and tenacious nerve damage including autonomic axonal and sensorimotor polyneuropathy, which often exhibits multi-systemic manifestations.Regardless, the pathological ramifications could result in progressive organ failure and are even, considered life-threatening in certain situations.At present, liver transplantation is still the standard treatment to halt the progression of clinical symptoms in FAP, but new therapeutic strategies are emerging, including the silencing of messenger RNA to block the production of TTR protein, and stabilize the TTR tetramer structure to slow down the formation of amyloid deposition[2,4,5].

GemPharmatech selected the V30M mutation site of the TTR protein to construct a B6-h*TTR* V30M Tg transgenic mouse model. This model can be used for the screening, safety evaluation, and pathogenesis of FAP therapeutic drugs.

Strategy

Fig.1 Schematic diagram of B6-h*TTR* V30M Tg model stratery.

Applications

1. Studying the mechanism of familial amyloidotic polyneuropathy
2. Drug screening of familial amyloidotic polyneuropathy

Data support

1. Detection of Human *TTR* V30M

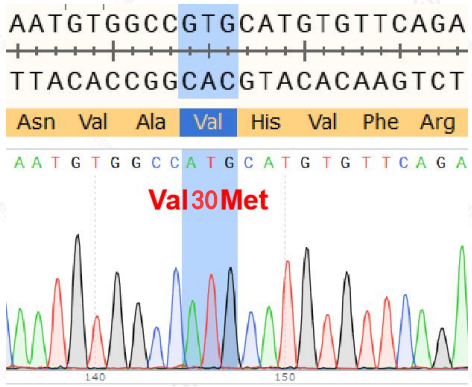

Fig.2 Human *TTR* V30M sequencing of B6-h*TTR* V30M Tg mice

Sanger sequencing confirmed the human TTR mutation in B6-h*TTR* V30M Tg mice, and the 30th amino acid in B6-h*TTR* V30M Tg mice was methionine (Met) marked in red.

2. Detection of human TTR protein expression

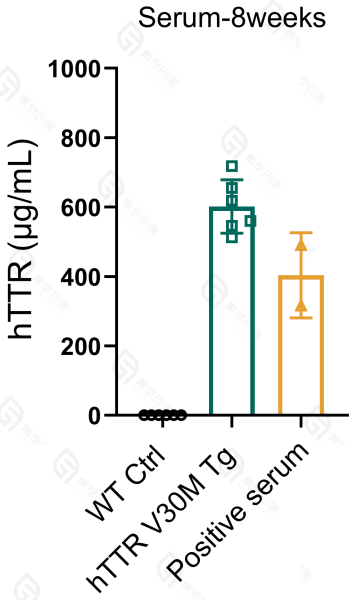

Fig.3 Detection of human TTR protein expression in B6-h*TTR* V30M Tg mice

Detection of human TTR protein expression in wild-type and B6-h*TTR* V30M Tg mice by ELISA kit.Human serum samples were used as positive control.The serum of B6-h*TTR* V30M Tg mice successfully expressed humanized TTR protein, while wild-type mice are not expressed. Data are presented as the MEAN ± SEM. n=3~5 of each group. T-test: *: *P* value ≤0.05, ns: no significant difference, *P* value > 0.05.

References

1. Sekijima Y, Wiseman RL, Matteson J, Hammarström P, Miller SR, Sawkar AR *et al*. The biological and chemical basis for tissue-selective amyloid disease. *Cell* 2005; 121: 73–85.
2. Batista,A.,Gianni,D.,Ventosa,M.*et al.*Gene therapy approach to FAP:*in vivo* influence of T119M in TTR deposition in a transgenic V30M mouse model. *Gene Ther* 21, 1041–1050 (2014).
3. Adams D, Theaudin M, Cauquil C, Algalarrondo V, Slama M . FAP neuropathy and emerging treatments. *Curr Neurol Neurosci Rep* 2014; 14: 435.
4. Chandrasekhar, G., Pengyong, H., Pravallika, G. *et al.* Defensin-based therapeutic peptide design in attenuating V30M TTR-induced Familial Amyloid Polyneuropathy. *3 Biotech* **13**, 227 (2023).
5. Paula G, Helena M, Susete C, Luis F. Maia & Maria Joao Saraiva (2016) Efficiency of silencing RNA for removal of transthyretin V30M in a TTR leptomeningeal animal model, *Amyloid*, 23:4, 249-253.