2005-492 Novel BAC Transgenic Model for Huntington's Disease

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Technology description

BACKGROUND

Huntington's disease (HD) is a neurodegenerative disease characterized by the adult-onset of abnormal movement, psychiatric disturbances, and cognitive impairment. The disease usually progresses relentlessly and results in the patients death within 15-20 years of its onset. Currently, there is no effective treatment for HD. HD is caused by a mutation in the first exon of the huntingtin gene (htt), which encodes a 350kD, ubiquitously expressed protein of unknown function. Mutant htt (mhtt) is thought to acquire dominant toxicities through the expansion of polyglutamine repeats. However, the precise mechanism by which various forms of mhtt cause HD is not clear. Transgenic mice have been a very useful genetic tool to study gene regulation and the effect of gene overexpression in vivo. Although several mouse models of HD have been generated to study HD, they either lack robust and selective neurodegeneration or have a relatively slow and mild disease process. Therefore, the need exists for transgenic mice that exhibit robust motor deficits and neuropathology phenotypes which make them more suitable to examine HD pathogenesis and to test candidate therapeutics.

INNOVATION

UCLA researchers have generated novel mouse models of HD using Bacterial Artificial Chromosome (BAC) transgenic technology. Western blot analyses demonstrate that the transgenic mice broadly express full length mhtt in the brain at approximately the same level as the endogenous murine wildtype htt. These mice exhibit progressive and robust motor deficits demonstrated by Rotarod and open field tests. These mice accumulate mhtt aggregates and inclusions in a brain and subcellular distribution pattern similar to that of HD patients. Neuropathological studies demonstrated that these mice exhibit highly selective brain atrophy and neurodegeneration in the cortex and striatum, but not in other brain regions spared in HD. Therefore, these mice represent a robust full length mouse model suitable to study HD pathogenesis and to test therapeutic compounds and strategies for HD.

Application area

- Transgenic HD mice can be used to study the pathogenesis of HD.
- Transgenic HD mice can be utilized to test therapeutic compounds and strategies for HD.

Advantages

- BAC transgenic system can consistently produce high levels of and endogenous-like transgene expression in vivo.
- Transgenic HD mice exhibit progressive and robust motor deficiencies as compared to other mouse models.
- Transgenic HD mice display neuropathology which is strikingly similar to HD patients.

Institution

University of California, Los Angeles

Inventors

Xiangdong Yang
Professor in Residence
PSYCHR&BEHAV

联系我们

叶先生

电 话：021-65679356
手 机：13414935137
邮 箱：yeyingsheng@zf-ym.com