A new approach to modeling ALS based on TBK1 mutation in mice

https://neurodegenerationresearch.eu/survey/a-new-approach-to-modeling-als-based-on-tbk1-mutation-in-mice-3/

Principal Investigators

XU, ZUOSHANG

Institution

UNIV OF MASSACHUSETTS MED SCH WORCESTER

Contact information of lead PI
Country

USA

Title of project or programme

A new approach to modeling ALS based on TBK1 mutation in mice

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

422591.7431

Start date of award

01/07/2016

Total duration of award in years

2

Keywords

TBK1 gene, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia, Recombinant adeno-associated virus , novel strategies

Research Abstract
PROJECT SUMMARY Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are progressive neurodegenerative diseases. ALS causes motor neuron degeneration and paralysis. FTD causes cortical neuron degeneration leading to personality changes and loss of executive function. Both diseases are unstoppable ending in death. Increasing number of causal gene mutations are being identified and many of these can cause both diseases. To capitalize

on the newly discovered ALS/FTD genes for understanding the disease mechanism and developing therapies, animal models are needed. However, the conventional transgenic technologies of gene overexpression and knockout are slow and expensive, thus becoming a bottleneck constraining new model development. Additionally, there is a growing recognition that some patients have multiple gene mutations. This has led to the hypothesis that some ALS/FTD cases are caused by an oligogenic mechanism. Thus, it will be important to investigate how different mutations interact to cause the disease in animals. Currently this is done by intercrossing different mutant transgenic mouse strains. However, this process is slow because of the low yield of double or triple transgenic mice and the multigenerational crosses that are necessary to bring different transgenic lines to the same genetic background. To solve these problems, we propose a rAAV-intrathecal gene delivery approach for construction of transgenic mouse models for ALS. This approach is capable of delivering gene transduction throughout the spinal cord by a single injection of rAAV into the cerebrospinal fluid. We plan to deliver rAAV targeting the newly discovered ALS gene TBK1 for knockdown. Loss-of- function mutations in one allele of TBK1 gene causes dominantly inherited ALS in humans. However, this is difficult to model in mice because loss of one TBK1 allele in mice does not cause an overt phenotype but a complete knockout of this gene causes embryonic lethality. RNAi knockdown approach can silence gene expression to below 50% of the normal level and our previous work has demonstrated that knockdown of specific genes can achieve gene hypomorphic phenotypes in vivo. In this proposal, we will use rAAV to deliver TBK1 gene silencing in the spinal cord. We will inject the rAAV into several mouse strains including the normal wild type and mutant transgenic mice that develop ALS phenotype. We will determine whether this approach can induce ALS phenotypes in the wild type mice and/or modulate the disease phenotypes and pathology in the mutant ALS transgenic mice. If successful, this experiment will establish a new mouse model for ALS and a new method that is faster than the conventional gene knockout approach for construction of mouse models for ALS and for studying mutant gene interactions in vivo.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A