Recapitulates Features of ALS and FTD using a Patient Derived Human Transgene

Expansion of the number of repeats of a specific hexanucleotide sequence (GGGGCC, called G4C2) in the C9orf72 gene is the most common known cause of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). This C9-500 mouse model contains a mutation with 500 G4C2 repeats, the full human C9orf72 gene and substantial flanking sequence but no other known genes. Unlike other mouse models that overexpress G4C2 expansion mutations, or result in molecular but not pathological changes, our C9-500 mice recapitulate both the molecular and the clinical features of ALS and FTD, including progressive motor deficits and neurodegeneration.

Background

Amyotrophic Lateral Sclerosis, also known as Lou Gehrig's disease, is a degenerative neurological disorder leading to muscle weakness, paralysis, respiratory failure and death (Rowland and Shneider, 2001; Liu et al., 2016). In addition, the degenerative neurologic disorder FTD leads to degeneration of the frontal and anterior temporal lobes of the brain resulting in behavioral changes such as loss of empathy, apathy, and loss of inhibition (NIH, 2016). The most common known cause of both ALS and FTD is the G4C2 repeat expansion in the C9orf72 gene. The expanded repeats lead to the expression of sense G4C2 and antisense G2C4 expansion RNAs and the expression of six proteins that do not require the canonical ATG start signal previously thought to be essential for protein production (Cleary and Ranum, 2014). These six dipeptide proteins, glycine-alanine (GA), glycine-proline (GP) and glycine-arginine (GR) from the sense direction and proline-alanine (PA), proline-arginine (PR) and glycine-proline (GP) from the antisense direction, are expressed by a novel type of translation called repeat-associated non-ATG (RAN) translation. The accumulation of sense G4C2 and antisense G2C4 expansion RNAs in the cell nucleus and the accumulation of RAN proteins are consistently found in ALS/FTD patients (Zu et al. 2013, Liu et al., 2016).

Application

Mouse model that provides unique tool for studying the cause, progression and possible treatments for ALS and FTD

Advantages

- Unique model of the most common genetic forms of both C9orf72 ALS and FTD
- Endogenous human promotors drive transgene expression in a manner that accurately models human disease
• Mice develop classic features of both ALS and FTD including paralysis, motor neuron loss and behavioral changes thus providing a superior mouse model for studying these diseases
• Mice show accumulation of sense and antisense RNA foci and RAN proteins which are found in the human disease

Inventors

Laura Ranum, Ph.D., is a professor in the College of Medicine at the University of Florida. Over a three year period, she was awarded more than 7 million dollars in research funding from the National Institutes of Health, the Muscular Dystrophy Association (MDA), Target ALS, the ALS Association and the Packard Foundation for her research on repeat associated non-ATG translation in ALS/FTD and other repeat expansion diseases. Dr. Ranum’s research interests include the genetic mechanisms of ALS, FTD, muscular dystrophy, and ataxia.