

Development of mouse models for ALS5 and SPG11

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Research Abstract

Amyotrophic lateral sclerosis (ALS) is a paralytic and usually fatal disorder caused by degeneration of motor neurons in the brain and spinal cord, eventually leading to respiratory failure and death. The pathogenic mechanisms of ALS remain to be largely unknown. Genetic and animal model studies have played a major role in understanding the disease mechanisms. We mapped an autosomal recessive form of ALS (designated as ALS5) to a 6cM region

between D15S146 and D15S123 on chromosome 15 using three inbred kindreds from Tunisia. We have now identified homozygous mutations in the gene KIAA1840 in the ALS5-linked families. Mutations in KIAA1840, which encodes spatacsin, have been previously linked to autosomal recessive spastic paraplegia 11 (SPG11). Our work, therefore, indicates that ALS5 and SPG11 are actually allelic motor neuron diseases caused by the same genetic defect. The disease mechanism by which mutations or loss of spatacsin causes motor neuron degeneration remains unknown. We found that spatacsin co-localizes with large dense core vesicle markers, suggesting that spatacsin may regulate the function of the large dense core vesicles, and dysfunction of the large dense core vesicles may underlie the pathogenic mechanisms of ALS5/SPG11. Indeed, we found a unique type of membrane-associated inclusion bodies in the motor neurons in the autopsy sample of an ALS5 patient. These inclusions are ubiquitin-, p62-positive, and also chromogranin A-positive, supporting the hypothesis that the dense core vesicles defects are involved in the formation of these unique inclusions, and in the pathogenesis of ALS5/SPG11. In this R21 application, we propose two specific aims. In Aim 1, we will develop ALS5-linked Spg11 knockin and knockout mouse models using CRISPR technique. In Aim 2, we will characterize the phenotype and pathology of the mouse models, especially the structural entity and pathological features of the unique membrane-associated inclusion bodies. Successful completion of the proposed studies will lead to the development of ALS5 and SPG11 mouse models, and may provide mechanistic insight into the pathogenesis of ALS, especially the spatacsin-related dense core vesicle defects and motor neuron degeneration in ALS5 and SPG11. Understanding the pathogenesis may facilitate the rational design of therapeutic strategies for spatacsin-linked motor neuron diseases, the most frequent forms of recessive motor neuron diseases. We will deposit the mouse models to the Jackson Laboratories for resources sharing as soon as the lines are established and preliminary characterized.

Further information available at:

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