EXPRESSION OF TDP-43 CAUSES NEUROLOGICAL PHENOTYPES WITH AN ENHANCEMENT BY FALS MUTATIONS IN NOVEL DROSOPHILA MODELS OF ALS

N. Fujikake¹, Y. Saitoh¹, A. Yokoseki², O. Onodera³, K. Wada¹, Y. Nagai¹

¹Department of Degenerative Neurological Diseases, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, ²Department of Neurology, Brain Research Institute, Niigata University, ³Department of Molecular Neuroscience, Resource Branch for Brain Disease Research, Brain Research Institute, Niigata University, Niigata, Japan

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease which is characterized by selective motor neuron degeneration with ubiquitin-positive inclusions in the brain and spinal cord. Recently the TDP-43 protein has been identified as the main component of the inclusions in sporadic ALS, and moreover, mutations in the TDP-43 gene have been found to cause several types of familial ALS (FALS), suggesting that abnormalities of TDP-43 are involved in the pathogenesis of ALS. To elucidate the pathomechanism of TDP-43-induced neurodegeneration in vivo, we employed Drosophila melanogaster to model ALS because of its short life-span and abundant genetic information. We generated transgenic fly lines bearing the human wild-type or mutant TDP-43 (A315T and Q343R) genes. We found that expression of TDP-43 in the nervous system induces progressive locomotor dysfunction and premature death. In addition, TDP-43 expression in the eye caused severe compound eye degeneration. Importantly, these phenotypes were enhanced by TDP-43 FALS mutations. Immunohistochemical analyses revealed that the TDP-43 proteins are accumulated in both the nucleus and cytoplasm of neurons. Western blot analyses demonstrated that the TDP-43 proteins were abnormally fragmented and phosphorylated as seen in ALS patients. We conclude that our novel Drosophila models faithfully mimic the pathological and biochemical features of human ALS patients, and therefore are useful for genetic-modifier screening and drug screening to elucidate the pathomechanism and to develop therapies for ALS.