Form 1-3

Japan-U.S. Brain Research Cooperation Program
Researchers Dispatched to the U.S. Program FY2024: Report

Field: Neurobiology of disease

1. Researcher

Name: Rei Yasuda
Title: Assistant Professor
Affiliation: Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

2. Research Title:
Identification of causative genes and development of therapy for undiagnosed and rare neurological diseases using *Drosophila* models

3. U.S. Joint Researchers/Institutes
Please give the name, title and affiliation.

Name: Shinya Yamamoto, DVM, PhD
Title: Assistant Professor
Affiliation: Department of Molecular & Human Genetics, Baylor College of Medicine

4. Research Period, from/to (yyyy/mm/dd): 2024/5/1-2024/9/17

5. Abstract, Results, and Research Significance (300 Words):

There are many undiagnosed or rare genetic diseases in the field of neurology. In the USA, the national research program, the Undiagnosed Disease Network (UDN), was organized to solve undiagnosed or rare diseases. In this project, the Model Organisms Screening Center (MOSC) has conducted functional analysis of candidate gene variants using model organisms, which has contributed to the identification of causative genes and the development of therapy. We focused on a rare genetic disease, *LAMB1*-related leukoencephalopathy. Although nonsense, missense, and late-truncating variants in *LAMB1* are associated with a diverse severity of symptoms, the functional consequences of these variants are largely unknown. In addition, while the function of *LAMB1* orthologs has been studied during development in various model organisms, the role of this gene in the mature nervous system has been ill-defined. We aimed to generate and evaluate the *Drosophila melanogaste*r (fruit fly) model of *LAMB1*-related leukoencephalopathy and to study the role of the fly ortholog in the post-developmental nervous system.

Drosophila LanB1 is orthologous to all four human *LAMB* family genes. First, we found that fly *LanB1* gene is expressed in a subset of glial cells in developing and mature fly brains. Second, we found that LanB1 protein was localized in the blood-brain barrier (BBB), and *LanB1* knockdown in the BBB resulted in short life span and impaired locomotor activity. Third, since the human *LAMB1* transgene did not function in the fly models, we used the fly *LanB1* transgene with analogous variants and found that the missense variant was a partial loss of function. Finally, we transfected *LAMB1* variants into human HEK293T cells and found that late truncated LAMB1 was uniquely secreted as a monomer, which might be the basis of a gain-of-function mechanism.

Our data contributes to the understanding of the ECM component of the fly BBB and lays the foundation to unravel the molecular consequences of different pathogenic variants in *LAMB1*.

6. Other (Research-related concerns, particular points to note):

There are no research-related concerns. I'm very grateful for the generous support from the Japan-U.S. Brain Research Cooperation Program.

*Please attach any reference materials as necessary.

Rei Yasuda, Hirokazu Hashimoto, Mikiko Oka, Jung-Wan Mok, Marium Waqar, Brigitte Dauwalder, Oguz Kanca, Toshiki Mizuno, Shinya Yamamoto. Functional analysis of pathogenic variants in *LAMB1*-related leukoencephalopathy reveals genotype-phenotype correlations and suggests its role in glial cells. Hum Mol Genet. 2025. Online ahead of print.