Form 1-5-2

Japan-U.S. Brain Research Cooperation Program
Researchers Dispatched to the U.S. Program FY2018: Report

Field: Neurobiology of disease

1. Researcher

Name: Shinichi HIROSE and Atsushi ISHII
Title: Professor and Associate Professor, respectively
Affiliation: Department of Pediatrics, Fukuoka University.

2. Research Title:

Characteristics of *KCNQ2* variants causing either benign neonatal epilepsy or developmental and epileptic encephalopathy

3. U.S. Joint Researchers/Institutes

Please give the name, title and affiliation.

Edward C. Cooper, Associate Professor
Department of Neurology, Baylor College of Medicine, Houston, Texas

4. Research Period, from/to (04/01/2018 to 03/31/2019):

Because of schedules of the participating researchers in the US and Japan, no exchange of the researchers could be done in this fiscal year. However, with the aid of extensive internet communication, we have completed the planned study and obtained the research outcomes shown below.

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

Objective: Pathogenic variants of *KCNQ2*, which encode a potassium channel subunit, cause either benign (familial) neonatal epilepsy—B(F)NE)—or *KCNQ2* encephalopathy (*KCNQ2* DEE). We examined the characteristics of *KCNQ2* variants.
Methods: *KCNQ2* pathogenic variants were collected from in-house data and two large disease databases with their clinical phenotypes. Nonpathogenic *KCNQ2* variants were collected from the Genome Aggregation Database (gnomAD). Pathogenicity of all variants was reevaluated with clinical information to exclude irrelevant variants. The cumulative distribution plots of B(F)NE, *KCNQ2* DEE, and gnomAD *KCNQ2* variants were compared. Several algorithms predicting genetic variant pathogenicity were evaluated.
Results: A total of 259 individuals or pedigrees with 216 different pathogenic *KCNQ2* variants and 2967 individuals with 247 different nonpathogenic variants were deemed eligible for the study. Compared to the distribution of nonpathogenic variants, B(F)NE and *KCNQ2* DEE missense variants occurred in five and three specific *KCNQ2* regions, respectively. Comparison between B(F)NE and *KCNQ2* DEE sets showed that B(F)NE missense variants frequently localized to the intracellular domain between S2 and S3, whereas those of *KCNQ2* DEE were more frequent in S6, and its adjacent pore domain, as well as in the intracellular domain between S6 and helix A. The scores of Protein Variation Effect Analyzer (PROVEAN) and Percent Accepted Mutation (PAM) 30 prediction algorithms were associated with phenotypes of the variant loci.
Significance: Missense variants in the intracellular domain between S2 and S3 are likely to cause B(F)NE, whereas those in S6 and its adjacent regions are more likely to cause *KCNQ2* DEE. With such regional specificities of variants, PAM30 is a helpful tool to examine the possibility that a novel *KCNQ2* variant is a B(F)NE or *KCNQ2* DEE variant in genetic analysis.

6. Other (Research concerns, particular points of note):

Both researchers in the US and Japan need enough independent grants to pursue the collaborative studies.

*Please attach any reference materials as necessary.