【Grant-in-Aid for Scientific Research (S)】

Integrated Disciplines (Complex Systems)

Title of Project： Integrative Biology of Autism Spectrum Disorder

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Research Area：Brain Sciences
Keyword：Autism, CNV, Cell model, Neural circuit, Brain gut axis

【Purpose and Background of the Research】

Psychiatric diseases were thought to be psychologically disturbed without any morphological abnormality in the brain and different from neurological diseases. However, recent advance in neuroscience provides a general concept of mental diseases as a biological disorder that is equivalent to other neurological and complex diseases. The same or similar pathological mechanisms as other diseases may underlie at the spine/synapse where classical neuropathology was unable to reach and detect its anomaly.

In Japan autism spectrum disorders (ASD) has been mainly studying in an aspect of educational psychology such as how to educate kids with autisms. Now research on ASD can lead the field on neuropsychiatric disorders as a spectrum, partly because the genetic contribution of ASD is higher than that of other psychiatric diseases.

We generated a mouse model for human chromosome 15q11-q13 duplication by using a chromosome-engineering technique based on Cre-loxP system as the first CNV (copy number variant) mouse model of ASD. The duplication of 15q11-q13 is the most frequently associated with cytogenetic abnormality of ASD. Recent advance in genome science has provided thousands of CNV and hundreds of those closely linked to ASD.

【Research Methods】

(Cell, Synapse) We have developed a next-generation chromosome engineering technique using CRISPR/Cas9 system. Using the next-generation chromosome engineering technique, we develop ES cell models with CNV seen in ASD. After neural differentiation from ES cells, we characterize them by transcriptome analysis such as RNA-seq and by morphological analysis.

(Circuit, Behavior) We examine neural circuits for social behavior by using virtual reality system or in vivo freely moving mice combined with optogenetics.

(Environment) To see brain-gut axis, we examine microbiota of patients with ASD and mouse model of ASD.

【Expected Research Achievements and Scientific Significance】

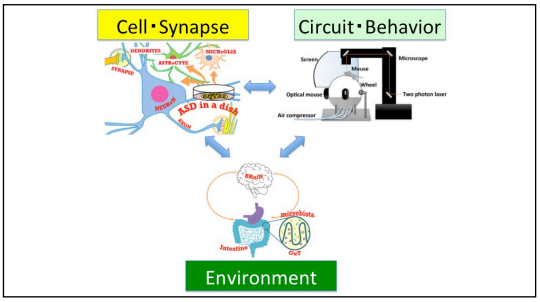

Figure 1　ASD

This study consists of three different approaches. PI attempts to understand the complex ASD pathophysiology by combination of the results of these different approaches.

Research achievements by this study will be expected not only to develop new diagnosis and treatment of ASD but also to contribute the understanding of social brain development.

【Publications Relevant to the Project】

・Nakatani, J., et al. Abnormal behavior in a chromosome-engineered mouse model for human 15q11-13 duplication seen in autism. ***Cell*** 137, 1235-1246, 2009.
・Isshiki, M., et al. Enhanced synapse remodeling as a common phenotype in mouse models of autism. ***Nat. Commun.*** 5, 4742, 2014.

【Term of Project】 FY2016-2020

【Budget Allocation】 139,200 Thousand Yen

【Homepage Address and Other Contact Information】

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