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## **iPS Cell Research Discovers Common Pathologies in Psychiatric Disorders Elucidation of the Pathogenesis of Bipolar Disorder and Schizophrenia May Find Application in Therapeutic Drug Development**

In a joint research study with Sumitomo Dainippon Pharma Co., Ltd. and Nagoya University, a research team at Keio University has successfully used iPS cells<sup>1</sup> derived from patients with bipolar disorder<sup>2</sup> and schizophrenia<sup>3</sup> who have copy number variation (CNV)<sup>4</sup> to show that abnormal neuron morphology is a common condition in both disorders. The Keio University research team was led by Professor Hideyuki Okano of the Keio University School of Medicine, Department of Physiology, and included joint researchers from the Department of Physiology. Sumitomo Dainippon Pharma team was led by Takaya Ishii of the iPS Cell-Based Drug Discovery, Drug Research Division. The Nagoya University team was led by Professor Norio Ozaki of the Department of Psychiatry and Child and Adolescent Psychiatry.

The aim of the research team was to elucidate the pathology of these psychiatric disorders and focus on the new CNVs thought to be involved in their onset. The research team first established a method for selectively and efficiently differentiating iPS cells taken from somatic cells of bipolar disorder and schizophrenia patients with different CNVs into two types of neurons (glutamatergic and GABAergic neurons<sup>5</sup>). Analysis of these neurons revealed that, in both disorders, the length of dendrites decreases in both types of neurons, and the number of synapses, which transmit neural information, also decreases.

The results of this research show the successful use of patient-derived iPS cells to reproduce pathological conditions common to psychiatric disorders and are expected to lead to further clarification of psychiatric disorders and the development of therapeutic drug candidates. The results of this study were published on September 20, 2019 (EDT) in the online journal *eNeuro*.

### **1. Research Background**

Both bipolar disorder and schizophrenia are major psychiatric disorders that affect ~1% of the worldwide population, but their cause and underlying molecular mechanisms remain to be elucidated. The pathologies of these kinds of disorders are complex, and their heterogeneity, along with diverse environmental factors, means that symptoms vary greatly from person to person even among patients diagnosed with the same disorder.

Animal models are important for the research and development of therapeutic drugs, but there are limits to the recapitulation of clinical characteristics of these disorders in animal models due to the large differences in the structure and function of human and animal brains. Therefore, there is a serious need for reliable models that functionally mimic the pathology of psychiatric disorders and can be applied to

the elucidation of their molecular mechanisms and the development of therapeutic drugs. Using iPS cell technology developed in 2006 by Professor Shinya Yamanaka at Kyoto University, we are now able to produce iPS cells from patient-derived somatic cells that can be differentiated into neurons for use in research. Keio University School of Medicine has reported the results of numerous research projects using iPS cells, in particular for neurodegenerative diseases including Parkinson's disease and amyotrophic lateral sclerosis (ALS) (Fujimori K, et al., *Nature Medicine*, 2018). But at the same time, the complex genetic background of psychiatric disorders still proves to be a big hurdle to research using iPS cells.

To solve this issue, in March 2012, Keio University School of Medicine and Sumitomo Dainippon Pharma began joint research using iPS cells derived from patients with psychiatric disorders, and together they have promoted industry-academia research collaboration that allows for technology and knowledge sharing.

We also worked together with the Nagoya University Graduate School of Medicine, through a program of the Japan Agency for Medical Research and Development (AMED), in order to elucidate part of the complex genetic background of these psychiatric disorders, and through genome analysis discovered new copy number variants that have pathological significance (deletion of the *PCDH15* gene in bipolar disorder patients and the *RELN* gene in schizophrenia patients<sup>6</sup>) (Kushima I, et al., *Cell Rep*, 2018).

In this study, by focusing on copy number variation as it relates to the development of bipolar disorder and schizophrenia, we conducted pathological analyses using neurons differentiated from patient-derived iPS cells and sought to establish a model that can reproduce the pathologies of psychiatric disorders while overcoming the challenge of variability caused by different genetic backgrounds.

## **2. Research Significance and Future Development**

In this study, we succeeded in using iPS cells derived from two bipolar disorder patients with *PCDH15* deletion and one schizophrenia patient with *RELN* deletion to selectively and efficiently induce glutamatergic neurons and GABAergic neurons, which have been shown to experience function decline or network failure in psychiatric disorders.

Patient-derived neurons exhibited dendrite shortening and decreasing synapse numbers when compared with neurons derived from healthy control subjects. These abnormalities were commonly observed regardless of disorder or neuron type. Similar abnormalities were also observed in neurons induced from iPS cells derived from healthy individuals in which *PCDH15* or *RELN* was artificially deleted using gene editing technology (see Fig. 1). Previous studies by other groups have reported similar results using postmortem human brains of bipolar disorder and schizophrenia patients. (Konopaske GT, et al., *JAMA Psychiatry*, 2014).

These results strongly suggest that the phenotypes observed in this study are general phenotypes of psychiatric disorders, and we can expect that pathology will be related to the functions of *PCDH15* and *RELN*.

These results have shown that it is possible to construct an *in vitro* model that reflects the pathologies of psychiatric disorders by using patient-derived iPS cells with pathological copy number variation. In addition, this model may lead to the analysis of pathological mechanisms common to psychiatric disorders and the development of new therapeutic drugs that could be widely effective in treating psychiatric disorders.

In the future, along with further analysis using the *in vitro* model obtained through this study, more accurate reproduction of the brain, including coculture of different types of neurons or coculture with glial cells<sup>7</sup> is expected to aid in the elucidation of pathological conditions and the further exploration of therapeutic targets.

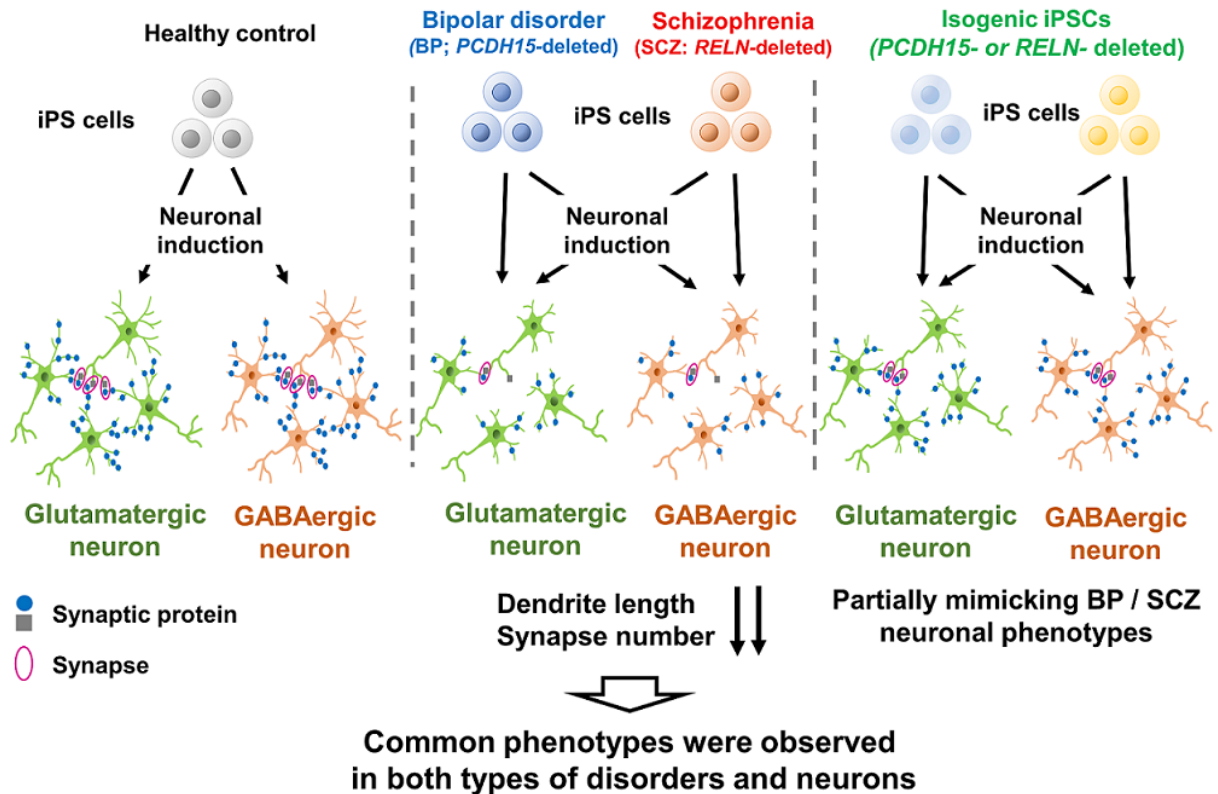


Fig. 1

### 3. Notes

This joint-research was conducted together with Sumitomo Dainippon Pharma and was supported by JSPS Grants-in-Aid for Scientific Research (KAKENHI) JP17K10083 and JP26830018 as well as the following programs of the Japan Agency for Medical Research and Development (AMED):

- Research Project for Practical Applications of Regenerative Medicine  
“Research for drug discovery using mental/neurological disease-specific iPS cells”
- Research Center Network for Realization of Regenerative Medicine  
“The Acceleration Program for Intractable Diseases Research utilizing Disease-specific iPS cells”
- Strategic Research Program for Brain Sciences (SRPBS)  
“Development of diagnostic and therapeutic methods with full use of the results from genome studies on schizophrenia and ASD”
- Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS)  
“Elucidation of pathological neural circuits of neurological and psychiatric disorders based on large-scale neuroimaging analysis and human/non-human primate “translatable” brain markers (Elucidation of pathological neural circuits by exploring rare genetic mutations in psychiatric disorders)”

## **4. Research Paper**

Title : In vitro modeling of the bipolar disorder and schizophrenia using patient-derived induced pluripotent stem cells with copy number variations of *PCDH15* and *RELN*

Authors : Takaya Ishii, Mitsuru Ishikawa, Koki Fujimori, Takuji Maeda, Itaru Kushima, Yuko Arioka, Daisuke Mori, Yuhki Nakatake, Bun Yamagata, Shintaro Nio, Takahiro A. Kato, Nan Yang, Marius Wernig, Shigenobu Kanba, Masaru Mimura, Norio Ozaki, Hideyuki Okano

Publication : *eNeuro*

### **[Glossary]**

#### **<sup>1</sup>iPS Cells**

An iPS (induced pluripotent stem) cell is a type of cell that, through the introduction of specific transcription factors into somatic cells such as blood cells, has acquired the ability to differentiate into various tissues and cells, with the capacity for self-renewal.

#### **<sup>2</sup>Bipolar Disorder**

Bipolar disorder is a type of psychiatric disorder that causes alternation between, or simultaneously exhibition, of manic and depressed states.

#### **<sup>3</sup>Schizophrenia**

Schizophrenia is a type of psychiatric disorder where people experience a combination of positive symptoms, such as hallucinations and delusions, and negative symptoms, such as decreased motivation and cognitive impairment.

#### **<sup>4</sup>Copy Number Variation(CNV)**

Copy number variation refers to a change in a part of the genome where a chromosome, instead of producing the usual two copies, produces one or fewer copies (deletion), or three or more copies (duplication). This study focuses on deletion events where just one copy is produced.

#### **<sup>5</sup>Glutamatergic Neurons and GABAergic Neurons**

Nerve cells can be broadly classified into two types. One is an excitatory neuron, a typical example of which is a glutamatergic neuron. These can increase neuronal activity by releasing the neurotransmitter glutamate. The other type is an inhibitory neuron, a typical example of which is a GABAergic neuron. These can suppress nerve activity by releasing glutamate and gamma-aminobutyric acid (GABA), another neurotransmitter.

#### **<sup>6</sup>*PCDH15* Gene & *RELN* Gene**

In this study, iPS cells were derived from patients with new copy number variations in each of these genes. Previous studies have suggested that these genes may be associated with multiple psychiatric disorders. Both genes are involved in cell adhesion and migration, and this function may be related to the phenomenon shown in this study.

#### **<sup>7</sup>Glial Cells**

Glial cells are a general term for non-neuronal cells that make up and support the nervous system, and the human brain is thought to have around 50 times as many glial cells as neurons.

\*Please direct any requests or inquiries to the contact information provided below.

\*The content of this research will also be published in a press release by Nagoya University.

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\*A color version of this press release is  
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