한국뇌연구원 Korea Brain Research Institute

Press Release

내일을 위한 정부혁신 보다 나은 정부

Haploinsufficiency of CYFIP2 Causes Lithium-Responsive Prefrontal Dysfunction

- Joint research work by Korea University, Seoul National University, and KBRI was published in a prestigious academic journal of brain neurology.
- The identified pathophysiological mechanisms of CYFIP2 deficiency are expected to advance the therapeutic development in intellectual disability and epilepsy.

□ Korea Brain Research Institute (KBRI headed by Suh Pann-ghill) announced on the 6th of July that joint research team led by Professor Kihoon Han (Korea University College of Medicine), Professor Se-Young Choi (Seoul National University, School of Dentistry), and Group Leader Kea Joo Lee (KBRI) successfully identified the structural and functional roles of CYFIP2 gene, an established genetic risk factor for intellectual disability and epilepsy, in the mouse prefrontal cortex.

<From left – Professor Kihoon Han of Korea University, Professor Se-Young Choi of Seoul National University, and Group Leader Kea Joo Lee of KBRI>

□ Intellectual disability, characterized by significant limitations in learning and problem solving, and epilepsy, characterized by unpredictable seizures and loss of awareness, are the two representative disorders caused by abnormal brain functions. Multiple genetic variants associated with the onset of

these two disorders have been reported. However, the specific mechanism through which they trigger brain dysfunction has not been identified clearly.

□ The research team led by Professor Kihoon Han focused on overseas research cases that revealed the repeated association of genetic variations of CYFIP2 with intellectual disability and epilepsy based on the analysis of patients' genomes. Thus, they first produced a mouse model with reduced CYFIP2 expression. Using this animal model, the team examined the structural and functional changes in the medial prefrontal cortex associated with memory, decision-making, and emotion and finally discovered that layer 5 (L5) neurons displayed selective changes in synaptic ultrastructure and excitability.

□ The L5 neurons of heterozygous CYFIP2 mice displayed enlarged synapses as well as excessive excitability compared to the same neurons of wild-type mice. Excess neuronal excitability is known as one of the main causes of epilepsy. Accordingly, the CYFIP2 mutant mice showed an increased seizure susceptibility in response to epilepsy-inducing substances.

□ The team also noticed the fact that lithium improved the symptoms of brain disorders such as bipolar disorder and Fragile X Syndrome, a type of intellectual disability caused by genetic abnormalities in the X chromosome. Therefore, they next examined the effects of lithium in the CYFIP2 mutant mice. The results revealed that hyperexcitability of L5 neurons within the medial prefrontal cortex, behavioral abnormalities, and seizure susceptibility have all been recovered to the normal level by lithium treatment.

□ Taken together, these results define the structural and functional roles of CYFIP2 gene and are expected to advance the development of treatment options for intellectual disability and epilepsy caused by the genetic variation of CYFIP2.

□ This study was published online in Annals of Neurology (June 20, 2020), an internationally renowned academic journal ranking among the top 5% in clinical neurology and among the top 10% in neuroscience.

□ This work was supported by National Research Foundation of Korea (NRF) grants and the KBRI basic research program funded by Ministry of Science and ICT.