[BIOINFO 2023]

Dysregulation of the Wnt/β-catenin signaling pathway via Rnf146 upregulation in a VPA-induced mouse model of autism spectrum disorder

Seoyeon Kim[1,2,15], Gaeun Park[3,4,15], Wooyoung Eric Jang[5,15], Edson Luck Gonzales[6], Jungeun Ji[1,2], Seunghwan Choi[7], Yujin Kim[1,2], Ji Hwan Park[8], Hazara Begum Mohammad[8], Geul Bang[9], Minkyung Kang[3,4], Soobin Kim[3,4], Se Jin Jeon[6], Jin Young Kim[9], Kwang Pyo Kim[5,10],Chan Young Shin[6]*, Joon-Yong An[1,2,7]*, Min-Sik Kim[8,11,12]* and Yong-Seok Lee[3,4,13,14]*

[1]Department of Integrated Biomedical and Life Science, Korea University, Seoul 02841, Republic of Korea.
[2]BK21FOUR R&E Center for Learning Health Systems, Korea University, Seoul 02841, Republic of Korea.
[3]Department of Biomedical Science, Seoul National University College of Medicine, Seoul 03080, Republic of Korea.
[4]Department of Physiology, Seoul National University College of Medicine, Seoul 03080, Republic of Korea.
[5]Department of Applied Chemistry, Institute of Natural Science, Global Center for Pharmaceutical Ingredient Materials, Kyung Hee University, Yongin 17104, Republic of Korea.
[6]School of Medicine and Center for Neuroscience Research, Konkuk University, Seoul 05029, Republic of Korea.
[7]School of Biosystem and Biomedical Science, College of Health Science, Korea University, Seoul 02841, Republic of Korea.
[8]Department of New Biology, DGIST, Daegu 42988, Republic of Korea.
[9]Research Center for Bioconvergence Analysis, Korea Basic Science Institute, Ochang 28119, Republic of Korea.
[10]Department of Biomedical Science and Technology, Kyung Hee Medical Science Research Institute, Kyung Hee University, Seoul 02447, Republic of Korea.
[11]New Biology Research Center, DGIST, Daegu 42988, Republic of Korea.
[12]Center for Cell Fate Reprogramming and Control, DGIST, Daegu 42988, Republic of Korea.
[13]Neuroscience Research Institute, Seoul National University College of Medicine, Seoul 03080, Republic of Korea.
[14]Wide River Institute of Immunology, Seoul National University, Hongcheon 25159, Republic of Korea.
[15]These authors contributed equally: Seoyeon Kim, Gaeun Park, Wooyoung Eric Jang.
*Correspondence: chanyshin@kku.ac.kr; joonan30@korea.ac.kr; mkim@dgist.ac.kr; yongseok7@snu.ac.kr

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social behavior, communication difficulties, repetitive behaviors, and restricted interests. Various factors contribute to ASD development, including both genetic and environmental influences. One well-known environmental factor linked to ASD is valproic acid (VPA) exposure during pregnancy. Studies showed that prenatal VPA exposure disrupts neural development and differentiation in offspring, leading to autistic-like behaviors. This supports a causal link between maternal VPA exposure and ASD susceptibility, though its precise functional mechanisms in the brain remain unclear.

In this study, we used high-resolution mass spectrometry to conduct a quantitative proteomic analysis on the prefrontal cortex (PFC) of mice exposed to VPA in utero. We discovered a significant overlap of differentially expressed proteins (DEPs) in the PFC of VPA-exposed mice with ASD risk genes. We differentially expressed genes (DEGs) in the postmortem cortex of ASD patients. Among these DEPs, we observed notable upregulation of the RING-type E3 ubiquitin ligase RNF146 under

VPA exposure, a key regulator of the Wnt/β-catenin signaling pathway. Consistent with the effects of VPA exposure, overexpression of Rnf146 in the adult rodent PFC led to dysregulation of the Wnt/β-catenin signaling pathway and subsequent impaired social behaviors. Additionally, PFC neurons from Rnf146-overexpressing mice exhibited increased excitatory synaptic transmission, providing a mechanistic basis for the observed behavioral deficits.

Our findings demonstrate that Rnf146 plays a critical role in ASD development and contributes to behavioral impairments in response to VPA exposure. This result suggests Rnf146 as a potential therapeutic target for the intervention of ASD.