[BIOINFO 2024]

Exploring Neuronal and Astrocytic Dysregulation in Phelan-McDermid Syndrome Using Single-Cell Transcriptomics

Chae Youn Kim[1], Jihye Choi[2], Seunghee Hong[1] and Chul Hoon Kim[2]

[1]*Department of Biochemistry, Yonsei University*
[2]*Department of Pharmacology, Graduate School of Medical Science, Brain Korea 21 Project, Yonsei University College of Medicine, Republic of Korea*
**Corresponding author: seungheehong@yonsei.ac.kr: , KIMHOON@yuhs.ac*

Phelan-McDermid syndrome (PMS) is a rare genetic disorder primarily caused by deletions or mutations in the SHANK3 gene located on chromosome 22. Despite ongoing research, detailed studies on PMS remain limited, hindering a comprehensive understanding of the disease. To elucidate the molecular mechanisms of PMS, we utilized human pluripotent stem cell-derived forebrain organoid models and conducted single-cell RNA sequencing analysis at developmental stages of 120 and 200 days.

Our analysis revealed significant differences in the proportions of excitatory neurons, inhibitory neurons, and astrocytes—key cell types involved in synapse composition—between normal and PMS samples at each timepoint.

Differentially expressed genes (DEGs) and Gene Set Enrichment Analysis (GSEA) indicated that synapse organization-related terms were notably downregulated in the PMS samples compared to normal samples. Comparative analysis showed that genes involved in synapse assembly were more highly expressed in normal neurons, LGE-derived inhibitory striatal projection neurons (ISPN), and astrocytes. In contrast, PMS samples showed a higher expression of developmental process, particularly in astrocytes, suggesting delays in synaptic formation and developmental processes.

Further analysis of astrocytes, including trajectory mapping, revealed distinct disease-related developmental paths, especially in A2 and reactive astrocyte states. These findings highlight key differences in synapse-related development across cell types and suggest critical mechanisms underlying PMS progression.