[BIOINFO 2023]

Assessing adult neurogenesis activity and validating association to Alzheimer's disease

Seungseok Kang[1,¶], Saehoon Jung[2,¶], Young-soo Chung[1,¶], Yoo-Jin Ha[1], Joonho Kim[1], Jeong Ho Lee[2,*], and Sangwoo Kim[1,*]

[1] *Department of Biomedical Systems Informatics, Brain Korea 21 Project, Yonsei University College of Medicine, Seoul, 03722, Republic of Korea*

[2] *Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, 34141, Republic of Korea*

[¶] *These authors contributed equally.*

**Corresponding author*

Alzheimer's disease (AD) is a type of dementia caused by the excessive aggregation of beta-amyloid protein. Recent research suggests that genomic alterations may contribute to sporadic AD, which accounts for 95% of all cases. However, the direct involvement of somatic variants and their potential origin such as adult hippocampal neurogenesis (AHN) in AD brain remains unclear. In particular, decrease in AHN in AD patients has gained recognition in recent years, prompting extensive research.

In this study, we employed laser capture microdissection to collect monoclonal-level specimens from the subgranular zone (SGZ) of the human dentate gyrus, aiming to isolate neuronal stem cells associated with AHN. We amplified low input DNA from the microdissected samples using the primary template-directed amplification (PTA) and performed whole-genome sequencing from 53 AD patients and 12 non-dementia individuals.

Although, no significant difference in mutation number between the AD and non-dementia group was observed, signature analysis revealed distinct mutational process. In the non-dementia group, we observed a significantly higher frequency ($p<0.0004$) of the reactive oxygen species (ROS)-related signature SBS36 compared to the AD group that might arise due to sustained metabolism in normal neuronal stem cells. Whereas, a significant NER deficiency signature SBS30 was observed in the AD group compared to non-dementia group ($P=0.016$). Furthermore, we found AD-significant GO terms associated with neurogenesis, generation of neuron, and axon development. In conclusion, our study provides evidence indicating impaired differentiation of neuronal stem cells related to AHN within the SGZ in AD patients.