[BIOINFO 2023]

Noncoding Rare Variant Association in Alzheimer's Disease Using Single-cell Chromatin Accessibility Data

Chanhee Kim[1,2], Yujin Kim[1,2], Joon-Yong An[1,2,3*]

[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]School of Biosystem and Biomedical Science, College of Health Science, Korea University, Seoul, 02841, Republic of Korea
**Corresponding author: joonan30@korea.ac.kr*

Over the last several years, research have identified dozens of common variants associated with Alzheimer's disease (AD) risk. However, research investigating the association between noncoding rare variants and AD still remains challenging. Utilizing cell type-specific chromatin accessibility datasets, we perform category-wide association study (CWAS) using whole genome sequencing (WGS) data to evaluate noncoding association in AD. We analyzed WGS data of 1,087 individuals from the Religious Orders Study and Rush Memory and Aging Project. We collected single-cell chromatin accessibility data from published papers to create cell type-specific functional annotation. We used CWAS-plus to detect noncoding variants associated with AD using various functional annotations. In CWAS-plus, variants are categorized into functional annotation combinations, referred to as categories. We computed risk score using lasso regression model to check predictive power of noncoding categories. To investigate the relationships among AD-associated categories, Detecting Association With Networks analysis (DAWN) was conducted. Our WGS study found that the risk score of rare variants is higher in noncoding regions compared to those in coding regions. This noncoding signal was driven by variants in the intergenic region. The strongest intergenic signal was driven by the regulatory regions of microglia. Lastly, through DAWN analysis, we identified core annotations and relationships among intergenic variants involved in AD risk. We suggest candidate AD risk noncoding rare variants which are microglial-specific regulatory elements in intergenic region.