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GENETICS

Co-methylation network analysis of Psychosis in Alzheimer's disease

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Abstract

Background: Psychosis (broadly delusions and hallucinations) has a cumulative disease prevalence of around 40% in Alzheimer's disease (AD). The epigenomic, genomic, and neuropathological data provide powerful evidence that AD+P has a distinct neurobiological profile. Here, we used the weighted gene co-expression network analysis (WGCNA) method to investigate DNA methylation associated with AD+P in the dorsolateral prefrontal cortex of 153 post-mortem brain samples.

Method: Our primary analysis focused on applying WGCNA to the PITT-ADRC cohort, followed by subsequent replication of its findings in the BDR cohort. The genotype data from PITT-ADRC and the WGCNA results were further utilized to identify the most significant methylation Quantitative Trait Loci (mQTLs) associated with psychosis. Subsequently, we explored RNA sequencing data from PITT-ADRC to identify genes affected by the replicated findings uncovered in our primary analysis.

Result: We identified five AD+P-related modules in the PITT-ADRC cohort, with one of them being replicated in the BDR cohort. This replicated AD+P-related module exhibits a high enrichment in the T cell receptor signalling pathway. According to the colocalization analysis results, this module shares significant SNPs in some regions that are also significantly associated with Schizophrenia and Educational Attainment.

Conclusion: Understanding molecular differences between AD and Psychosis at the genetic and epigenetic levels could guide us in discovering appropriate treatments for AD+P cases. To this end, we initiated a comprehensive, large sample-sized network analysis study based on genetic and epigenetic data.