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BIOMARKERS

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BIOMARKERS (NON-NEUROIMAGING)

Integrative Multi-Omics Analysis Reveals Rac GTPase Pathway Dysregulation Driving Lipid Metabolic Alterations in Vascular Cognitive Impairment

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Abstract

Background: Vascular cognitive impairment (VCI) encompasses a spectrum of cognitive disorders linked to vascular dysfunction, with underlying mechanisms remaining poorly understood. Traditional single-omics approaches often fail to capture the complex biological networks driving VCI, necessitating integrative multi-omics methodologies.

Method: Brodmann area 7 brain tissue samples from 19 VCI cases and 21 controls were analyzed using a variety of "omics" platforms and were used to identify associations between metabolites, methylation, gene expression levels, and metabolic pathways associated with VCI.

Result: Genomic analysis highlighted the Rac GTPase pathway in VCI pathogenesis, supported by widespread epigenetic alterations upregulating pathway-associated genes. Further, transcriptomic data revealed dysregulation of lipid metabolism, oxidative stress, and GTPase activity, while our metabo-epigenomics analyses highlighted disruption of diacylglycerol and phosphatidylethanolamine metabolism driven by Rac GTPase. This comprehensive approach identified association gains, losses, and reversals in disease states, providing a comprehensive understanding of VCI-specific omics interactions.

Conclusion: This study underscores the value of integrative multi-omics in elucidating VCI mechanisms, revealing Rac GTPase-driven lipid metabolic disruptions as a potential hallmark of the disease. These findings provide new insights into the molecular underpinnings of VCI, paving the way for biomarker development and targeted therapeutic strategies.