CLDN5 Downregulation and Albumin: Investigating Hallmarks of Blood-Brain Barrier Breakdown as Novel Biomarkers of Suicide Neuropathology

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Over 1 million deaths annually can be attributed to suicide, yet no biomarkers exist. This study investigated blood-brain barrier (BBB) disruption by examining claudin-5 (CLDN5) epigenetic alterations, immunoglobulin-g (IgG), and albumin as biomarkers for suicide. DNA-methylation and RNA-sequencing de-identified data from the New York Psychiatric Institute were aligned to perform differential methylation and pathway enrichment analyses. Human de-identified postmortem brain tissue (n=80) of the dorsolateral prefrontal cortex (dlPFC) was stratified based on suicide as a cause of death. ELISA assays assessed IgG and albumin. Results indicated that CLDN5 ($p<0.05$) and two CpG sites on the CLDN5 promoter, namely cg06315607 ($p<0.05$) and cg20486569 ($p<0.05$), were downregulated in suicide decedents. 1,130 differentially expressed genes were identified with downregulated pathways in gene ontology categories of adherens junction (FDR=3.7 x 10-2, logFC=3.0), basal plasma membrane (FDR=2.8 x 10-3, logFC=2.9), and basolateral plasma membrane (FDR=1.1 x 10-2, logFC=2.4). Upregulation of pathways of extracellular matrix (FDR=2.9 x 10-2, logFC=2.5) and cell-cell junction (FDR=2.4 x 10-2, logFC=2.3) degradation were identified. Albumin was identified to be higher in the dlPFC of suicide decedents ($p<0.01$). CLDN5 downregulation and albumin could serve as pre-markers for suicide risk. The identified differentially expressed pathways could serve as targets for therapeutics to modulate claudin-5 levels to restore BBB integrity. Further quantitative proteomics studies should be employed to determine parameters for feasible serum-based albumin biomarkers to determine suicide risk.

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