Identification of Cell-Free DNA Methylation Signatures as a Potential Genomic Biomarker of Alzheimer's Disease

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Alzheimer’s Disease (AD) is a progressive, neurodegenerative disease that leads to brain atrophy and neuronal apoptosis and is the leading cause of dementia worldwide. Minimal insight has been obtained regarding the use of circulating cell-free DNA (cfDNA) from liquid-based biopsy to analyze epigenetic signatures in the brain, which could allow for the establishment of nascent translational clinical tools through the identification of novel genes and mechanistic pathways involved in the etiology of AD and enable the early detection of the disease. cfDNA from one female AD patient and one female Control patient was extracted from plasma samples, bisulfite converted, and processed for Whole Genome Bisulfite Sequencing (WGBS) library construction. The WGBS libraries were sequenced with Illumina Next Generation Sequencing (NGS). The computational analysis of WGBS data was performed on the Human Genetics Compute Cluster (HGCC), and the following computational workflow was executed: FastQC Analysis, Quality Trimming, WGBS Reads Mapping, Methylation Calling, Differentially Methylated Region (DMR) Identification, and DMR Annotation. Finally, Gene Ontology (GO), Enrichment, and Pathway analysis was conducted to identify enriched biological pathways associated with the identified Differentially Methylated Loci (DML) in DMR Annotation. 10,848 DMRs, composed of 2,615 hypermethylated DMRs and 8,233 hypomethylated DMRs, were identified upon DMR Identification. The GO analysis revealed multiple enriched Central Nervous System (CNS)-related processes in the DML. These enriched biological processes indicate the methylation alteration of some critical genes involved in brain development and could be potential markers of AD but require further validation through larger sample sizes.

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