Abstract Title: DNA Methylation Biomarkers and Therapeutic Targets for Neurological Disorders

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Abstract: *Background:* Neurological disorders represent a significant health concern globally, contributing to both morbidity and mortality. They cover a broad spectrum, including neurodegenerative diseases, neurodevelopmental disorders, and neuropsychiatric conditions. They affect both the central and peripheral nervous systems, including the brain and spinal cord. The impact of neurological disorders extends beyond the burden of illness, as they can significantly diminish the quality of life for individuals affected. DNA methylation, crucial for gene regulation and genomic stability, involves adding methyl groups to DNA, often at cytosine residues in CpG dinucleotides. DNA methylation is a valuable biomarker in diverse disorders, providing insights into molecular signatures for diagnostics and prognostics. It is currently employed as a biomarker for various disorders.

Methods: We conducted genome-wide methylation analysis on several neurological disorders using the Illumina MethylationEPIC 850k array. The studied disorders include Autism, Huntington's Disease (HD), Alzheimer's Disease (AD), Parkinson's Disease (PKD), Dementia with Lewy bodies (DLB), and Chronic Traumatic Encephalopathy (CTE). At least 24 affected individuals were compared to 24 matched controls for each phenotype. Epigenetic and transcriptomic data was integrated using a series of analyses (bioinformatics, statistical, computational biology, Artificial Intelligence-based Deep Learning (AI DL), and pathway) to ascertain the role of epigenetic marks to the disease. Verification was conducted using pyrosequencing.

Results: The genome-wide methylation analysis uncovered significant methylation variations, showing both hyper and hypomethylation patterns throughout the genome (FDR $p<0.05$; AUC ROC > 0.90). Specific alterations related to the studied phenotypes were identified, offering valuable insights into the associated epigenetic landscape. We discovered methylation changes in specific gene groups related to circadian rhythm, glucose metabolism, cytokines, cytochromes, microRNAs, pain perception, transporters, autophagy, age-related factors, and noncoding RNAs within the present neurological disorders.

Conclusion: Current data unveils key insights into the epigenetic landscape, offering valuable information on the molecular mechanisms of these Neurological disorders. These findings pave the way for potential advances in diagnostics and therapeutics in the field.

Area of expertise: Epigenetic analysis expert in genetic diseases, pioneering biomarker discovery for precise diagnostics and targeted therapies. Transforming healthcare through research.