A Multi-Modal AI/ML Platform for Neurodegenerative Risk Prediction: Integrating Epigenetic Signatures Through cfDNA Methylation and Functional Mobility Data

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Neurodegenerative diseases, including Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), are typically diagnosed after 50-80% neuronal loss, reflecting a critical failure of early detection. I developed a cross-modal AI platform integrating quantitative gait biomechanics with cell-free-DNA (cfDNA) methylomic and fragmentomic profiling for preclinical neurodegenerative risk stratification. Under IRB Pro00086054, a prospective cohort (n=100; 206 gait assessments) underwent standardized single- and dual-task locomotor testing via markerless motion capture. Forty-seven spatiotemporal and kinematic features were extracted following signal denoising, gait-cycle segmentation, and z-score normalization. Six architectures were benchmarked via stratified 5-fold cross-validation. A Transformer attention model achieved superior discrimination (accuracy 93.4%, sensitivity 91.2%, specificity 94.8%, AUC 0.962), capturing executive-motor interference signatures of early ND. In parallel, a cfDNA pipeline was trained on genome-wide methylation data (Illumina EPIC, >850,000 CpG loci) with functional normalization, bumphunter DMR detection (FDR<0.05), and fragmentomic extraction (sub-nucleosomal ratios, end-motif entropy, nucleosome-footprint scores). An SVM-RBF achieved 94.0% accuracy, AUC 0.978. SHAP attribution revealed progressive CpG hypermethylation gradients and short-fragment cfDNA enrichment in disease phenotypes. Cross-modal attention fusion yielded peak performance (accuracy 96.7%, AUC 0.991), confirming that biomechanical and epigenetic signals provide orthogonal yet synergistic biomarkers. This non-invasive framework establishes a scalable pathway toward pre-symptomatic ND screening and precision longitudinal risk modeling

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