A Multi-Omics and Machine Learning Approach for Identifying Potential Salivary Biomarkers of and Treating Major Depressive Disorder

Lakkaraju, Ananya (School: Hamilton High School)

Major Depressive Disorder (MDD) negatively affects over 300 million people worldwide as the leading cause of disability, and suicide. Yet, current biomarkers fail to capture its biological heterogeneity and lack specificity. Thus, this study developed an end-to-end pipeline for MDD diagnostics and treatment incorporating biomarker identification and therapeutic testing. Specifically, publicly available metabolomics data (n=261) was analyzed using univariate (Spearman correlation and Mann-Whiteny U-tests) and multivariate (PCA, PLS-DA) analyses. An ensemble model with a tab transformer, multi-modal tab transformer, and MLP was developed, achieving a 97% AUC. Attention mechanisms enabled the model to capture complex interdependencies among metabolites. SHAP and permutation importance were applied to the model to determine top metabolite contributions for predictions. The top metabolites from global and local feature analysis were further analyzed through pathway and enrichment analysis, implicating disruptions in mitochondrial phospholipid metabolism, particularly the PEMT pathway responsible for PC biosynthesis, with PE(22:4) identified as a key biomarker ($p<0.05$). Global feature analysis on an external proteomics dataset identified ApoB, which is indirectly related to PE levels, as indicative of depression. Molecular docking software ChimeraX determined whether current treatments crossing the blood-brain barrier efficiently docked with PEMT, identifying Paliperidone (-9.31 kcal/mol) as an effective treatment compared to the control (-6.75 kcal/mol). In-vitro testing on a previously developed drug proved 2.5x more effective than the identified target protein's (ADCK3) original ligand. Future studies should evaluate phenotypic responses to novel therapeutics for MDD.

Awards Won: