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GENETIC RISK VARIANTS AND BASELINE BRAIN PHENOTYPE JOINTLY PREDICT LONGITUDINAL SYMPTOM CHANGE IN SPORADIC PD: VALIDATION FROM PPMI TO PDBP

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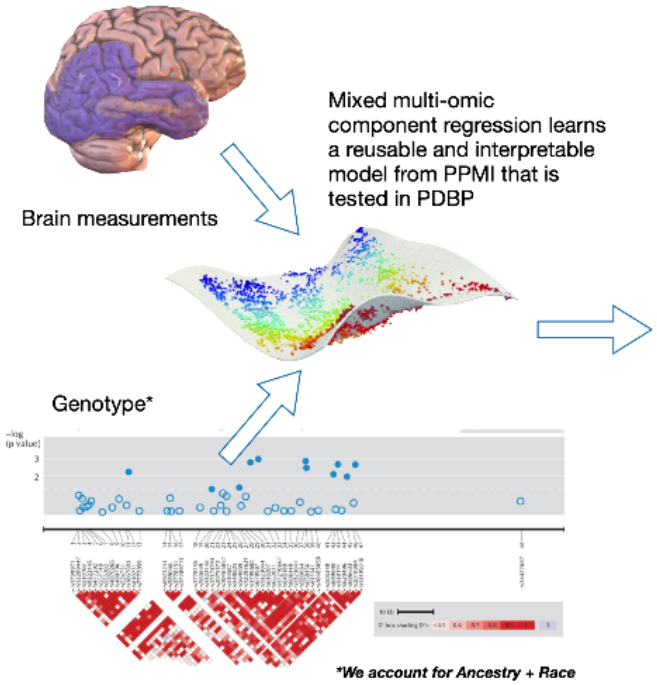
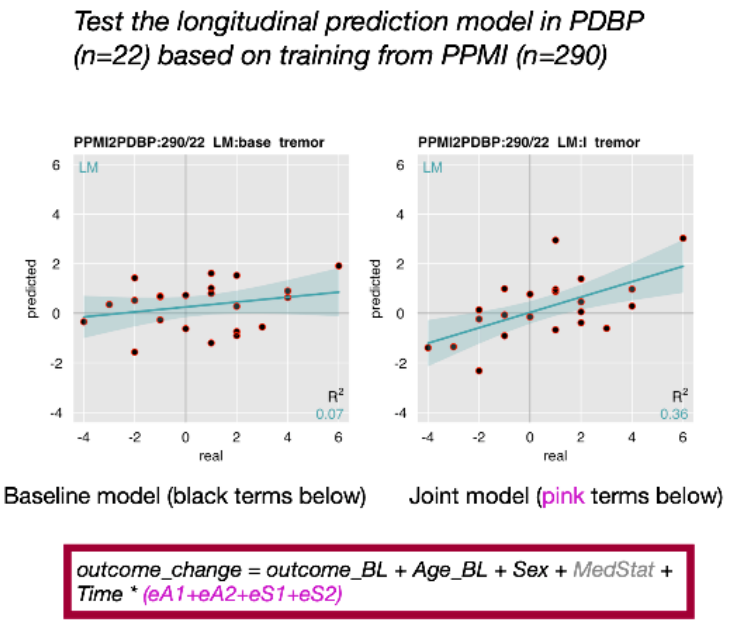
Aims: Multi-omic covariation between clinical scores, Parkinsons's Disease (PD) risk SNPs and neuroanatomy may encode differences in PD clinical progression. We demonstrate that multi-omic variations in sporadic PD improve prediction of longitudinal change in clinical measurements from baseine data.
Methods: PD risk SNPs (n=120 based on prior GWAS), baseline demographic and longitudinal clinical data were assembled from Accelerating Medicines Partnership PD (AMP-PD). Model training used Parkinson's Progression Markers Initiative (PPMI) data with evaluation in PD Biomarkers Program (PDBP) data. Early stage sporadic PD subjects were selected for consistent ancestry/race. T1-weighted (T1w) neuroimaging was processed via ANTsX [1] yielding tabular measurements of cortical thickness and volume**.** PPMI data (n=295, two time points minimum per subject) was used to cross-validate/tune a novel multi-omic prediction approach [2] that identifies a low-dimensional space linking baseline (first visit) brain structure, genetics and baseline clinical scores. The top two SNP-related and anatomy-related latent variables were then included with baseline clinical scores, age, sex and treatment status (on/off) in a regression model predicting change from baseline in a 1-4 year timeframe. The model was evaluated in independent PDBP data (n=22).
Results: Of 16 clinical outcomes in PDBP, 7 demonstrate Bonferroni-corrected significance beyond the clinical model. R^2 increases by 4% to 16% (improvement ratio 2% to > 50%) due to joint value from imaging and genetics; tremor prediction particularly
benefits.





Conclusions: Baseline multi-omic models improve prediction of clinical scores longitudinally including tremor, rigidity and UPDRS part 1 patient scores. Such a model may enhance patient selection & enable end users to target subjects that progress more rapidly in motor, cognitive symptoms or both. These results further suggest a complex interaction between genotype, phenotype and clinical progression. [1] doi: 10.1038/s41598-021-87564-6 [2] doi: 10.1038/s43588-021-00029-8