Research Use Statement for Application for Genomic Data from NIAGADS

Late-onset Alzheimer's Disease (LOAD) affects millions of Americans, yet there are no treatments that can meaningfully affect disease progression once symptoms have manifested, creating a serious unmet need for a widely-available genetic risk prediction model (GRPM) that can accurately predict patients' LOAD risk before neurodegeneration begins. Such a test would allow at-risk individuals to prepare for the future, enact lifestyle changes, undergo regular screenings, and/or enroll in clinical trials. A sufficiently accurate GRPM could also improve the outcomes of clinical trials by allowing pharmaceutical researchers to match treatment cohorts according to underlying disease risk, increasing the probability of detecting treatment effects. Despite recent advancements, GRPMs for LOAD lack sufficient discrimination ability to support these applications.

Under a Phase I SBIR award, we demonstrated that our GRPM approach achieves significantly greater accuracy than traditional risk factors by exploiting diagnostic heterogeneity and epistatic interactions among variants. First we will build models using genetic information to predict LOAD endophenotypes such as amyloid beta and tau levels, and volumes of different brain regions. Then the predicted endophenotypes will be combined into a final prediction model for clinical diagnosis. This model can then be applied to new subjects by predicting their endophenotype measurements and subsequently predicting clinical diagnosis at any given age. In this way, an individual's risk of LOAD can be predicted earlier in life before pathological changes begin.

The ADC data, with corresponding phenotypes obtained from the National Alzheimer's Coordinating Center (NACC), will be incorporated with data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), dbGaP, the UK Biobank and data to be generated under this project. The integrated dataset will be mined for individual and epistatic SNP associations with LOAD endophenotypes using Parabon's Crush-MDR software. Machine learning will be applied to the selected SNPs to build predictive models for each endophenotype and a final model for disease status.

Non-Technical Summary for Application for Genomic Data from NIAGADS

Late-onset Alzheimer's Disease affects millions of Americans, yet there are no treatments that can meaningfully affect disease progression once symptoms have appeared, creating a serious unmet need for a widely-available genetic test that can accurately predict a person's Alzheimer's Disease risk in middle age or earlier. Such a test would allow at-risk individuals to prepare for the future, enact lifestyle changes, undergo regular screenings, and/or enroll in clinical trials. A sufficiently accurate test could also improve the outcomes of clinical trials by increasing the probability of detecting treatment effects. However, despite recent advancements, genetic tests for Alzheimer's Disease lack sufficient accuracy to support these applications. In this project, we will address this need by creating a highly accurate genetic test able to predict a person's risk of developing Alzheimer's Disease at any age.