COMBINING MACHINE LEARNING WITH AUTOMATED NEMATODE LIFESPAN ANALYSIS TO IDENTIFY MODIFIERS OF ALZHEIMER'S DISEASE

Joshua Russell,[1] and Matt Kaeberlein[1], *1. University of Washington, Seattle, Washington, United States*

Here we present new computational and experimental methods to leverage the gene expression and neuropathology data collected from several large-scale studies of Alzheimer's disease . These data sets include diverse data types, including transcriptomics, neuropathology phenotypes such as quantification of amyloid beta plaques and tau tangles in different brain regions, as well as assessments of dementia prior to death. This meta-analysis is a complex undertaking because the available data are from different studies and/or brain regions involving study-specific confounders and/or region-specific biological processes. We have therefore taken neural network and probabilistic computational approaches that reduce the data dimensionality, allowing statistical comparison across all brain samples. These approaches identify gene expression changes that are significantly associated with clinical and neuropathological assessment of Alzheimer's disease. We then conduct in vivo validation of the genes through genetic screening of C. elegans models of Alzheimer's disease utilizing our automated robotic lifespan analysis platform. This approach allows for the greater leverage of existing Alzheimer's disease biobank data to identify deep genetic signatures that could help identify new clinical gene-expression markers and pharmacological targets for Alzheimer's disease.

NEW APPROACH TO STUDYING COLLECTIVE EFFECTS OF GENETIC FACTORS ON ALZHEIMER'S DISEASE

Anatoliy Yashin,[1] Deqing Wu,[2] Konstantin Arbeev,[2] Igor Akushevich,[2] Arseniy Yashkin,[2] Matt Duan,[2] Eric Stallard,[1] and Svetlana Ukraintseva[1], *1. Duke University, Durham, North Carolina, United States, 2. Duke University, Durham, United States*

Despite the wide recognition of the multifactorial nature of Alzheimer's disease (AD), mechanisms of the collective influence of genetic and environmental factors on AD remain poorly understood. We used the Cardiovascular Health Study (CHS) and Framingham Heart Study (FHS) data to investigate the effects of genetic and gene-environment interactions on AD prevalence in the association analysis using logistic regression. Based on results of this analysis, we developed several new measures of integrated effects of SNPs, including for specific gene or group of genes, by constructing SNP-specific Interaction Polygenic Risk Scores (SIPRSs), Gene-specific Interaction Polygenic Risk Scores (GIPRS), and Trait-specific Interaction Polygenic Risk Scores (TIPRS), and tested them in the above data. We found strong interaction effects on AD among the SNPs in NRG3 gene and smoking, and among the SNPs in ATM and creatinine. In summary, we developed a new approach to measuring the collective impact of SNPs on complex traits, and discovered significant effects of the newly constructed SIPRS, GIPRS, and TIPRS on AD prevalence. The results of this study open a new opportunity of investigating the joint impacts of genetic and environmental factors on AD and other phenotypes of aging and health.

GERIATRIC TRAUMATIC BRAIN INJURY AND ALZHEIMER'S DISEASE SHARE SIMILAR PATTERNS OF WHITE MATTER DEGRADATION

ANDREI IRIMIA,[1] Kenneth Rostowsky,[1] Nikhil Chaudhari,[1] Maria Calvillo,[1] and Sean Lee[1], *1. University of Southern California, Los Angeles, California, United States*

Although mild traumatic brain injury (mTBI) and Alzheimer's disease (AD) are associated with white matter (WM) degradation, the nature of these alterations and the outcomes of their comparison have not been elucidated. Diffusion tensor imaging (DTI) has been utilized in both conditions, and has uncovered decreases in the fractional anisotropy (FA) of the corpus callosum and cingulum bundle, compared to healthy control (HC) volunteers [1, 2]. Despite mTBI being a potential risk factor for AD, no systematic quantitative comparison has been drawn between their WM degradation patterns. Here we investigated WM FA differences using DTI and tract-based spatial statistics (TBSS) between age- and sex-matched adults: 33 chronic mTBI patients, 67 AD patients and 81 HC participants. T1-weighted magnetic resonance imaging (MRI) and DTI were acquired at 3T. mTBI patients were scanned acutely and ~6 months post-injury. FSL software was used for artefact correction, FA computation and TBSS implementation. Statistical comparison of WM FA patterns between mTBI and AD patients was achieved by two one-sided t tests (TOSTs) of statistical equivalence, with equivalence bounds defined where Cohen's $d < 0.3$. A significant difference was found between the FA means of mTBI vs. HC groups, and the AD vs. HC groups ($p < 0.01$, corrected). Mean FA differences between mTBI and AD were statistically equivalent in the corpus callosum and in the inferior longitudinal fasciculus ($p < 0.05$, corrected). Future research should focus on clarifying the similarities between mTBI and AD, potentially leading to novel hypotheses and improved AD diagnosis.

NEURONAL-SPECIFIC PROTEASOME AUGMENTATION VIA EXTENDS LIFESPAN AND REDUCES AGE-RELATED NEURODEGENERATION

Andrew M. Pickering[1], *1. UT Health San Antonio, San Antonio, Texas, United States*

Cognitive function declines with age throughout the animal kingdom and increasing evidence shows that disruption of the proteasome system contributes to this decline. The proteasome has important roles in multiple aspects of the nervous system, including synapse function and plasticity, as well as preventing cell death and senescence. We report that augmentation of proteasome function, using overexpression of the proteasome β5 subunit, enhances proteasome assembly and function. Significantly, we go on to show neuronal-specific proteasome augmentation slows age-related declines in measures of learning, memory, and circadian rhythmicity. Surprisingly neuronal specific proteasome augmentation of proteasome function also produces a robust increase of lifespan in Drosophila melanogaster. Our findings appear specific to the nervous system; ubiquitous proteasome overexpression increases oxidative stress resistance but does not impact lifespan and is detrimental to some healthspan measures. These findings demonstrate a key role of the proteasome system in brain aging.