The aim of this study was to assess differences in the effect of traumatic brain injury (TBI) on the onset of Alzheimer’s disease (AD) and other dementias between veteran and non-veteran respondents of the Health and Retirement Study as well as to measure the sensitivity of these differences to the introduction of controls for groups of demographic, medical co-morbidity and polygenic risk scores reflecting AD hallmarks. Using the Fine-Gray proportional hazards model we found that TBI was a strong predictor of dementia in community dwelling residents age 65+: for AD associated risk was 181 % [Hazard Ratio (HR): 2.81; CI:2.05-3.86] sample-wide and 142% [HR: 2.42; CI:1.31-2.46] in veteran males. Effect magnitude decreased with the addition of risk-related control variables but remained associated with significantly increased risk. Large differences in risk were observed between veteran and non-veteran males for AD, vascular dementia, senile dementia, and dementia with Lewy Bodies.

GEOGRAPHIC DISPARITIES IN COUNTY-LEVEL PREVALENCE OF ALZHEIMER’S DISEASE ACROSS THE UNITED STATES
Mackenzie Fowler, Michael Crowe, and Richard Kennedy, University of Alabama at Birmingham, Birmingham, Alabama, United States

While national and state estimates of the prevalence and incidence of AD are available, estimates across finer geographic regions offer an opportunity to tailor programs to the needs of the local population. Previously, we estimated prevalence and incidence of AD at the county level across the continental United States and found that estimated prevalence of AD varied more than threefold across counties, predominantly in the Southeastern and Midwestern United States. We also observed “islands” of low AD within regions with high AD, and vice versa. We update these findings by examining changes in projected prevalence of AD over time, and comparing projected prevalence of AD to prevalence of AD diagnoses in Medicare. We also examine regional variation in provider specialty patterns and racial differences across counties as possible explanatory factors. Understanding small-area geographic disparities in prevalence will be critical for addressing practice variation in the prevention and diagnosis of dementia.

GEOGRAPHIC DISPARITIES OF COMORBIDITIES IN MORTALITY OF PATIENTS WITH ALZHEIMER’S DISEASE
Julia Kravchenko, Duke University, Durham, North Carolina, United States

Comorbidities can contribute to the gap in Alzheimer’s disease (AD) mortality between the East and West coast U.S. Using Multiple-Cause-Of-Death and 5%-Medicare data, we analyzed age-adjusted (65+) mortality rates from AD in two Health and Human Services (HHS) areas with opposed mortality patterns in 2010-2018: 150.9±0.6/100,000 in HHS2 (NJ,NY) and 363.1±1.5/100,000 in HHS10 (AK,ID,OR,WA). Co-existing diabetes, heart failure, cerebrovascular, digestive, and kidney diseases significantly contributed to this gap, while contribution of heart diseases reduced its magnitude. An unexpectedly strong effect (higher rate in HH10 by a factor of 3-5) was identified for symptoms/signs that are not from identified specific diseases, life-threatening injuries/falls and other external causes that are common among patients with AD. We concluded that although contributions of comorbidities with well-developed treatment guidelines (e.g., heart disease) to geographic disparities in AD mortality were small, the disparities can be generated by unexpected comorbidities including diseases with poorly defined conditions.

SESSION 7690 (SYMPOSIUM)
COMPLEMENTARY AND INTEGRATED STUDIES OF LONGEVITY AND HEALTHY AGING
Chair: Steven Cummings
Co-Chair: Thomas Perls
Discussant: Evan Hadley

Five NIH-funded studies, the Long Life Family Study (LLFS, U19), the Longevity Consortium (LC, U19), Longevity Genomics (U24), and Protective Omics Profiles in Centenarians (UH2) work together to triangulate on mechanisms of extreme longevity and healthy aging with the ultimate goal of discovering predictors and targetable pathways. Linkage analyses by LLFS identified extremely strong genetic linkage peaks for cross-sectional as well as longitudinal trajectory rates-of-change phenotypes. Deep sequencing suggests these peaks are driven by rare, protective variants in selected pedigrees. In cross-species studies (UH2, LC), genomics, metabolomics and proteomics are used to exploit many-fold variances in natural life spans to discover protective mechanisms that explain some of these differences. Proteome analysis reveals several longevity-related proteins such as Cip1/p21, FOXO3, TOP2A, AKT1, RICTOR, INSR and SIRT6 harboring post translational modification sites that preferentially appear in short- versus long-lived species. The U24 effort developed a tool using genetically-mediated gene expression to prioritize genes for longevity translational efforts. We found that BLOC1S1 was associated with longevity and protection from atrial fibrillation and hearing loss without being associated with adverse events. This novel target is undergoing functional characterization. A proteomic assay (4,131 proteins, Somascan) annotated by genome-wide association study results in a total of 1,797 centenarians and 3,685 controls divided into independent discovery and replication sets, discovered significant and replicated over-expression (thus, pro-longevity) of BIRC2 and under-expression of APOB in carriers of the APOE ε-2 allele. A novel protein signature of rs2184061 (CDKN2a/CDKN2B in chromosome 9) was also associated with slower aging.

THE LONG LIFE FAMILY STUDY: SEQUENCING EXCEPTIONAL PEDIGREES FOR RARE PROTECTIVE VARIANTS
Michael Province,1 Kaare Christensen,2 Stephanie Consentino,3 Joseph Lee,3 Anne Newman,4 Thomas Perls,5 Bharat Thyagarajan,6 and Joseph Zmuda,4 1. Washington University School of Medicine, SAINT LOUIS, Missouri, United States, 2. University of Southern Denmark, Odense C, Syddanmark, Denmark, 3. Columbia University, New York, New York, United States, 4. University of Pittsburgh, Pittsburgh, Pennsylvania, United States, 5. Boston University School of Medicine, Boston,
Massachusetts, United States, 6. University of Minnesota, Minneapolis, Minnesota, United States

The Long Life Family Study (LLFS) has longitudinally measured key aging phenotypes on 4,953 participants (539 pedigrees) in the USA and Denmark selected for exceptional familial longevity. On average, both generations of the LLFS sample are healthier than average for their age/sex, for many phenotypes. However, the pedigrees are heterogeneous, with different families showing familial clustering of protection for different phenotypes. Linkage analyses identified extremely strong genetic linkage peaks for many cross-sectional as well as longitudinal trajectory rates of change phenotypes. These peaks are NOT explained by GWAS SNPs (either measured or imputed). Pedigree specific HLODs and preliminary deep sequencing suggests that these peaks are driven by rare, protective variants running in selected pedigrees. Whole Genome Sequencing, a third longitudinal visit, and extensive OMICs (transcriptomics, epigenomics, metabolomics and proteomics) will help us resolve the mechanisms behind these protective genetically linked variants, and could illuminate new biology and enable new therapeutics.

OMICS OF LONG-LIVED MAMMALS AND LINKS TO HUMAN CENTENARIANS

Gregory Tombline,1 Jonathan Gigas,1 Matthew Simon,1 Yousin Suh,2 Andrei Seluanov,1 and Vera Gorbunova,1 1. University of Rochester, Rochester, New York, United States, 2. Columbia University, New York, New York, United States

Mammalian species differ up to 100-fold in their aging rates and maximum life spans. Long-lived mammals appear to possess traits that extend lifespan and healthspan. Pro-longevity mechanisms are complex traits afforded by connections between metabolism and protein functions that are unlikely to be predicted by genomic approaches alone. Thus, metabolomics and proteomics studies are required to understand the mechanisms of longevity. Sirtuin 6 will be presented as an example of a protein that evolved enhanced enzymatic function in long-lived species and also demonstrates enhanced activity and unique alleles in human centenarians. Proteome analysis reveal several longevity related proteins such as Cip1/p21, FOXO3, TOP2A, AKT1, RICTOR, INSR and SIRT6 harboring PTM sites that preferentially appear in either short- or long-lived species. The prospects of enhancing life expectancy and healthspan of humans by altering metabolism and proteoforms with drugs that mimic changes observed in long-lived species will be discussed.

IDENTIFYING TRANSLATIONAL LONGEVITY TARGETS WITH GENETICALLY MEDIATED TRANSCRIPTOME-WIDE ASSOCIATION STUDIES

Daniel Evans,1 Steven Cummings,1 and Nicholas Schork,2 1. California Pacific Medical Center, San Francisco, California, United States, 2. Translational Genomics Research Institute, Phoenix, Arizona, United States

We hypothesized that trait associations with genetically mediated gene expression could be used to screen for genes that are good candidates for translational studies of longevity. We compiled a collection of genetically-mediated transcriptome-wide association studies using 33 traits and outcomes from large-scale, publicly-available GWAS meta-analysis results. The traits/outcomes were grouped within eight categories (aging, anthropometric, cardiovascular, inflammation, lung function, metabolic, musculoskeletal, and neurological). To test the utility of this approach, we examined trait associations with the drug target of statins, and we correctly identified known therapeutic effects and adverse events of statins. Specifically addressing the hypothesis, we examined a collection of candidate longevity-associated genes and identified one gene associated with lifespan that appears to also be associated with protection from atrial fibrillation and hearing impairment without being associated with adverse events. This screening approach can be used to prioritize gene targets for longevity translational efforts.

EFFECT OF LONGEVITY GENETIC VARIANTS ON THE MOLECULAR AGING RATE

Paola Sebastiani,1 Anastasia Gurinovich,1 Zeyuan Song,1 William Zhang,2 Stefano Monti,1 Sofiya Millman,2 Nir Barzilai,1 and Thomas Perls,1 1. Boston University, Boston, Massachusetts, United States, 2. Albert Einstein College of Medicine, Bronx, New York, United States, 3. Boston University School of Medicine, Boston, Massachusetts, United States

We conducted a genome-wide association study of 1317 centenarians from the New England Centenarian Study and 2885 controls using >9M genetic variants. The most significantly associated variants were correlated to 4131 serum proteins in 224 study participants. The genetic and protein associations were replicated in a genome-wide association study of 480 centenarians and ~800 controls of Ashkenazy Jewish descent and a proteomic scan of approximately 1000 participants of the same study. The analysis replicated a protein signature associated with APOE genotypes and confirmed strong overexpression of BIRC2 (p < 5E-16) and underexpression of APOB in carriers of the APOE2 allele (p < 0.05). The analysis also discovered and replicated associations between longevity variants and slower changes of protein biomarkers of aging, including a novel protein signature of rs2184061 (CDK2a/CDK2B in chromosome 9). The analyses show that longevity variants correlate with proteome signatures that could be manipulated to discover healthy aging targets.

SESSION 7695 (SYMPOSIUM)

POLICY SERIES: INTERDISCIPLINARY PUBLIC POLICY DISCUSSION

Chair: Brian Lindberg
Discussant: Linda Harootyan

Aging and health care public policy in Washington can be driven and influenced by the work of GSA researchers, educators, and practitioners from across the nation. This session will examine and explore public policy priorities from an interdisciplinary perspective and consider opportunities for communicating these policies with key policymakers. This session is an interdisciplinary look at policy issues in aging with the speakers representing views from the six sections of GSA. This session, organized by the GSA Public Policy Committee, will provide both GSA section leadership and attendees an opportunity to have an open