to carriers of other genotypes. Dr Monti will present an association analysis of APOE genotype data with 4137 human proteins in serum of 222 New England Centenarian Study participants. The analysis discovered a signature of 16 proteins that associated with different APOE genotypes, and replicated in 3 independent studies. Dr. Ellerby will summarize her recent analyses that used transcription analysis of isogenic iPSCs with APOE2 and APOE4 homozygote genotypes differentiated into inhibitory GABAergic neurons to show that E2 inhibitory GABAergic neurons regulate genes involved in nuclear division, DNA integrity and DNA damage checkpoint.

SURVIVAL ADVANTAGE OF APOE2

Sudha Seshadri[1], *1. UT Health San Antonio, San Antonio, United States*

Apolipoprotein E is a glycoprotein mediator and regulator of lipid transport and uptake. The APOE-ε4 allele has been associated with higher risk of Alzheimer's disease and of mortality, but the effect of the less prevalent APOE-ε2 on survival remains elusive. We aggregated data of 38,537 individuals of European ancestry (mean age 65.5 years; 55.6% women) from six large population-based cohorts to determine the association of APOE-ε2, with survival in the general population. During a mean follow-up of 11.7 years, 17,021 individuals died. Compared with homozygous APOE-ε3 carriers, APOE-ε2 carriers were at lower risk of death (hazard ratio,95% confidence interval: 0.94,0.90-0.99; P=1.1*10-2), whereas APOE-ε4 carriers were at increased risk (HR 1.17,1.12-1.21; P=2.8*10-16). Risk was lowest for homozygous APOE-ε2 (HR 0.89,0.74-1.08), and highest for homozygous APOE-ε4 (HR 1.52,1.37-1.70). Results did not differ by sex. The association was unaltered after adjustment for baseline LDL or cardiovascular disease. Larger, multiethnic collaborations are ongoing.

REDUCED COGNITIVE DECLINE WITH THE APOE ε2/ε2 GENOTYPE IN THE LONG LIFE FAMILY STUDY AND NEW ENGLAND CENTENARIAN STUDY

Benjamin Sweigart,[1] Benjamin Sweigart,[2] Stacy L. Andersen,[3] Stephanie Cosentino,[4] Nicole Schupf,[5] Thomas T. Perls,[3] and Paola Sebastiani[2], *1. Boston University, Department of Biostatistics, Boston, Massachusetts, United States, 2. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, United States, 3. Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, United States, 4. Department of Neurology, Columbia University, New York, New York, United States, 5. Department of Epidemiology, Columbia University Mailman School of Public Health, New York, New York, United States*

A growing body of evidence has suggested a protective effect on cognition of the ε2 allele of APOE. To determine if APOE ε2 is associated with protection against cognitive decline, we analyzed repeated measures of the Telephone Interview for Cognitive Status (TICS) from 2,933 Long Life Family Study subjects and 679 New England Centenarian Study subjects using a multivariable linear mixed effects model. The median age at first TICS administration was 73 (interquartile range [IQR] 64, 83). Subjects had a median of 3 TICS assessments (IQR 2, 4) and a median follow-up time of 5.0 years (IQR 2.9, 7.0). Carriers of the ε2/ε2 genotype had a significantly slower rate of decline in TICS score compared to the ε3/ε3 reference group (-0.05 points per annum for ε2/ε2 carriers compared with -0.15 points for ε3/ε3 carriers, p-value for difference 0.017). These results support a protective effect of the ε2 allele.

GENOMIC ANALYSIS OF HUMAN ISOGENIC APOE IPSC-DERIVED INHIBITORY GABAERGIC NEURONS

Lisa Ellerby,[1] Sicheng Song,[2] Sean Mooney,[2] Stephen Scheeler,[3] and Swati Naphade[3], *1. The Buck Institute, Novato, California, United States, 2. University of Washington, Seattle, Washington, United States, 3. Buck Institute for Research on Aging, Novato, California, United States*

Isoforms of ApoE modify the risk for Alzheimer's disease (AD), cardiovascular disease and are also associated with exceptional longevity. Specifically, the ApoE E2 allele is associated with lower risk of AD-related neurodegeneration and with exceptional longevity, while the E4 allele is a major risk factor for AD and is associated with higher levels of Abeta deposition in the brain. The mechanisms modulating extended lifespan/healthspan mediated by E2 compared to E3 and E4 genotypes are not clear. One hypothesis is that the E2 allele is neuroprotective and compensates for neuronal dysfunction induced by misfolded protein expression in aging and disease. To understand the molecular basis of the protective effect of the E2 allele we performed transcriptomic analysis of isogenic iPSCs with E2E2 and E4E4 genotypes differentiated into inhibitory GABAergic neurons. Our analysis revealed that ApoE2 inhibitory GABAergic neurons regulate genes involved in nuclear division, DNA integrity and DNA damage checkpoint.

A SERUM PROTEIN SIGNATURE OF APOE GENOTYPES IN CENTENARIANS

Stefano Monti,[1] Stefano Monti,[2] Paola Sebastiani,[3] Anastasia Gurinovich,[4] Toshiko Tanaka,[5] Lori L. Jennings,[6] David J. Glass,[6] and Thomas T. Perls[7], *1. Boston University, Boston, Massachusetts, United States, 2. Division Of Computational Biomedicine, Boston University School of Medicine, Boston, Massachusetts, United States, 3. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, United States, 4. Bioinformatics Program, Boston University, Boston, Massachusetts, United States, 5. Translational Gerontology Branch, National Institute on Aging, Baltimore, Maryland, United States, 6. Novartis Institutes for Biomedical Research, Cambridge, Massachusetts, United States, 7. Geriatrics Section, Department of Medicine, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts, United States*

The discovery of treatments to prevent or delay Alzheimer's disease is a priority. The gene APOE is associated with cognitive change and late onset Alzheimer's disease, and epidemiological studies have shown that the e_2 allele of APOE has a neuroprotective effect, and it is associated with increased longevity. We correlated APOE genotype data of 222 New England Centenarian Study participants, including 79 centenarians, 84 centenarian offspring and 55 carriers of APOE