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

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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

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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

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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

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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

e_2, with aptamer-based serum proteomics (SomaLogic technology) of 4783 human proteins corresponding to 4137 genes. We discovered a signature of 16 proteins that associated with different APOE genotypes, and replicated the signature in 3 independent studies. We show that the protein signature tracks with gene expression profiles in brains of late onset Alzheimer's disease vs. healthy controls. Finally, we show that seven of these proteins correlate with cognitive function changes. Therefore, targeting APOE e_2 molecularly may preserve cognitive function.

SESSION 3220 (PAPER)

PAIN AND PAIN MANAGEMENT

AN EMOTION REGULATION THERAPY FOR LATER-LIFE PAIN: EVIDENCE OF EARLY TREATMENT EFFECTS

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Chronic pain (CP) is a common, morbid, and costly disorder in older adults. Guidelines encourage clinicians to employ non-pharmacologic therapies for its management, but current psychological interventions (e.g., CBT for pain) have modest treatment benefits and their effects are largely unknown in older cognitively impaired adults. We developed PATH-Pain, an emotion regulation therapy focused on reducing negative emotions and augmenting positive emotions. PATH-Pain is appropriate for use by older adults with CP, negative emotions, and a wide range of cognitive functioning. Treatment consists of 8 weekly individual sessions followed by 4 monthly booster sessions. One hundred older adults (ages 60+) with CP (≥ 3 months) and at least mild-to-moderate levels of negative emotions (per the Positive and Negative Affect Schedule) were randomized to receive PATH-Pain versus Usual Care (UC). Cognitive screening revealed that 44 participants were cognitively intact (Montreal Cognitive Assessment (MoCA) score ≥26), while 56 evidenced mild-to-moderate cognitive impairment (MoCA=16-25). Participants completed follow-ups at 5 (n=89) and 10 weeks (n=84), while 24-week assessments are ongoing. Examination of the treatment × time interaction in a repeated-measures mixed model indicate the presence of treatment effects. PATH-Pain (vs. UC) participants experienced significant reductions in pain intensity ($p<0.044$) and pain-related disability ($p<0.003$). Reductions in pain-related disability score were more pronounced among cognitively impaired individuals. The PATH-Pain group also demonstrated significant reductions in emotional suppression ($p<0.019$) and depression ($p<0.009$) scores. These results suggest that PATH-Pain is an effective treatment for the management of pain in cognitively intact and cognitively impaired older adults.

CHRONIC PAIN CONTRIBUTES TO INJURIOUS FALLS IN COMMUNITY-DWELLING OLDER ADULTS

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Fall injuries are a leading cause of death among older adults, and chronic pain has been identified as a fall risk factor. However, the potential impact of chronic pain on injurious falls is unknown. This prospective study examined the relation between chronic pain and injurious falls in a 4-year follow-up of community-dwelling older adults. The MOBILIZE Boston study recruited 765 older adults aged ≥70y living in the Boston area. Pain characteristics, including pain severity, pain interference, and pain location, were measured at baseline using the Brief Pain Inventory subscales and a joint pain questionnaire. Musculoskeletal pain distribution was categorized as "no pain", "single site pain", or "multisite pain". Injurious falls were ascertained in telephone interviews following reports of falls on the monthly fall calendar postcards. The overall rate of injurious falls was 35/100 person-years. Negative binomial models, adjusting for sociodemographics, BMI, chronic conditions, mobility difficulty, analgesic and psychiatric medications, and depression, showed that pain interference and pain distribution, but not pain severity, independently predicted injurious falls. Participants in the highest third of pain interference scores had a 53% greater risk of injurious falls compared to those in the lowest pain interference group (adj. IRR=1.53, 95% CI: 1.15, 2.05). Older adults with multisite pain had a 50% higher risk of injurious falls than those without pain (adj.IRR=1.50, 95% CI: 1.16, 1.93). Risk of injurious falls related to pain was stronger among women than men. Research is needed to determine effective strategies to prevent fall injuries among older adults with chronic pain.

DEVELOPING A RAI-MDS 2.0 BEHAVIOR-BASED PAIN ASSESSMENT SCALE FOR LONG-TERM CARE RESIDENTS WITH ADVANCED DEMENTIA

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In Canadian and many international long-term care (LTC) facilities, pain assessment frequently relies on data from the Resident Assessment Instrument – Minimum Data Set 2.0 (RAI-MDS). The RAI-MDS produces a two-item scale, measuring both pain frequency and pain intensity. This scale correlates well with self-reported pain in cognitively intact LTC residents, but despite repeated testing, is less valid for use in residents with more advanced cognitive impairment who are unable to self-report their pain. In this study we aimed to develop and validate a behaviour-based pain assessment scale for long-term care residents using data available in the RAI-MDS. To construct our initial scale, we reviewed the literature and compiled a list of observable indicators of pain (e.g., grimacing) and linked these with 28 similar items available in the RAI-MDS. Using Delphi techniques, we further refined this to 20 items. We then evaluated the psychometric properties of our scale using two independent, representative samples, of urban LTC residents in Western Canada. Exploratory factor analyses were conducted in sample one (n=16,282) and confirmatory factor analyses (CFA) were then conducted in sample two (n=15,785) in order to test, and confirm, our model. A two-factor solution was identified grouping RAI-MDS items into subscales 1) change in status (e.g., new onset restlessness) and 2) behaviours (e.g., crying). Commonly recognized model fit indices were acceptable suggesting the adequacy of the two-factor solution. Results