reporter assays and Western blot analysis of human cell lines, neural progenitor cells and mouse primary corital neurons that over-expressed miRNAs, miRNA inhibitors and/or reporter constructs was used to assess miRNA mediated regulation of APP expression. Human subjects were recruited following IRB approved protocol, DNA was isolated from blood and sequencing based genotyping was utilized. **Results:** We demonstrate that six human, brain expressed miRNAs (miR-17-5p, 106a, 106b, 153, 324-5p, and 495) repress APP expression and used in situ hybridization of post-mortem human brain tissue to confirm brain expression and localization of these six miRNAs. We identified a SNP, rs45455403, that is located just outside of the miR-495 target site seed sequence. We tested the functional consequences of this SNP's minor allele using luciferase reporter assays. Introduction of the minor allele into the 3'UTR results in elimination of miR-495 repression of APP expression observed in the wild-type 3'UTR. rs45455403 is present in 6% of the African American (AA) community and therefore we are recruiting AA patients and controls to determine if this SNP increases the risk of developing AD. **Conclusions:** Our data demonstrates that the minor allele of rs45455403 eliminates miR-495 mediated repression of APP expression. Given the functional consequences of the minor allele of rs45455403 it is possible that this allele may alter risk of developing AD. We are in the process of testing this hypothesis.

FEATURED RESEARCH SESSIONS: F3-01 DISCLOSING RISK INFORMATION TO INDIVIDUALS AT IMMINENT RISK OF ALZHEIMER'S DISEASE

F3-01-01 DISCLOSURE OF APOE GENOTYPE TO PERSONS WITH MILD COGNITIVE IMPAIRMENT (MCI)

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Methods: We generated risk estimates using data obtained from a clinical trial involving 769 aMCI patients, which provided three-year conversion data stratified by APOE genotype (Petersen et al. 2005). We used an evidence-based approach in risk communication to develop graphics and language to communicate APOE genotype and a numerical risk estimate. Patients with aMCI are being recruited at four university medical centers (Harvard, Univ Michigan, Univ Penn and Howard) and randomized in a 2:1 ratio to either disclosure or non-disclosure arms. Scales of participant and caregiver distress, health behavior change and insurance/lifestyle change are measured at 6 weeks and 6 months. **Results:** Three-year risks for each age-group were: 8.4% for APOE-ε4 negative and 42.0% for APOE-ε4 positive individuals (ages 55-70), 20.5% for APOE-ε4 negative and 47.4% for APOE-ε4 positive (ages 71-77), and 30.7% for APOE-ε4 negative and 57.1% for APOE-ε4 positive (age 78 or older). Estimates based on MCI diagnosis and age alone (excluding genotype information) were 25.2% (ages 55-70), 34.0% (ages 71-77) and 43.9% (ages 78 or older). Educational materials were created to describe the possible APOE genotypes, an individual's APOE genotype result and three-year AD conversion risk. **Conclusions:** An evidence based procedure for risk estimation and an experimental trial of APOE genotype disclosure in aMCI patients has been designed and implemented. Preliminary results will be presented and discussed.

F3-01-02 DEVELOPMENT OF A STANDARDIZED APPROACH TO DISCLOSING AMYLOID IMAGING RESULTS IN MCI

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Background: Amyloid imaging is increasingly recognized as a powerful tool for predicting clinical outcomes in mild cognitive impairment (MCI). As this technology moves from the research setting into clinical practice, an emerging concern is that patients with MCI may have difficulty comprehending their test results. Given the lack of research on disclosing non-genetic biomarker information to cognitively impaired patients, the purpose of this two-phase study is to develop a standardized procedure for effectively communicating amyloid imaging results in the context of MCI. **Methods:** For phase 1, we convened a panel of experts in neuroimaging, neuropsychology, risk communication, regulatory affairs, and bioethics to determine the content and process for disclosing positive, negative, and inconclusive PiB-PET scan results to persons affected by MCI. The panel critically reviewed a series of outlines and scripted text for results disclosure in an iterative fashion. Visual aids were subjected to the same process of critique. Phase 2 remains in progress and aims to evaluate MCI patients' and family members' satisfaction with and comprehension of the materials developed in phase 1. Two out of a proposed sample of ten MCI dyads, including both amnestic and nonamnestic subtypes, have undergone mock (hypothetical) amyloid imaging results disclosure sessions and completed post-disclosure interviews. **Results:** Disclosure scripts for positive, negative, and inconclusive results, with accompanying visual aids, were developed. Each script was sequenced to review the purpose of amyloid imaging, disclose a hypothetical result, and interpret that result in terms of dementia risk and recommendations for clinical follow up. Scripts ranged from 245 to 300 words long with Flesch-Kincaid reading levels of 8th to 9th grade. All four participants agreed or strongly agreed with statements indicating that the session was "easy to follow," "included just about the right level of detail," and was "just about right" in length. All four rated the information as "clearly presented," and adequately restated, in their own words, the results that were disclosed. **Conclusions:** These preliminary findings support the feasibility of presenting amyloid imaging results in a manner that is satisfying to, comprehended by, patients with MCI and their families.

F3-01-03 DISCLOSURE OF AMYLOID STATUS IN SECONDARY PREVENTION TRIALS FOR ALZHEIMER'S DISEASE

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Background: As the field moves towards early intervention, there is increased reliance on biomarker evidence of preclinical Alzheimer's disease (AD) for inclusion into studies. There are a number of secondary prevention trial initiatives in the planning stages that will be conducted in asymptomatic individuals at-risk for AD on the basis of genetic and/or biomarker positivity. The disclosure of biomarker results with uncertain clinical implications in clinically normal older individuals raises important ethical issues. **Methods:** PET amyloid imaging and/or cerebrospinal fluid markers of Aß accumulation will be used to select eligible participants for the Anti-Amyloid treatment of Asymptomatic Alzheimer's disease (A4) trial being proposed by the Alzheimer's Disease Cooperative Study. This placebo-controlled trial will treat clinically normal amyloid-positive older subjects with a biologically active immunotherapeutic agent for 3 years to test the hypothesis that decreasing "upstream" amyloid accumulation will slow "downstream" neurodegeneration and rate of cognitive decline. Participants will be informed of their amyloid status, as only amyloid-positive individuals will be randomized to receive treatment or placebo, but a group of amyloid-negative individuals will participate in a natural history arm.

Results: Although converging evidence suggests that high amyloid burden is associated with an increased risk of cognitive decline, the impact of amyloid-positivity on the likelihood and timing of clinical progression to AD dementia on an individual basis remains unknown. We are developing safeguards based on the REVEAL study and consent language to convey the uncertainty of the clinical implications of amyloid-status in asymptomatic individuals. We also plan to imbed an ethics substudy in the A4 trial to evaluate the short and long-term impact of learning one's amyloid status (positive or negative). Alternative designs being considered by other prevention trial initiatives in genetic-risk subjects include randomizing non-mutation carriers to receive placebo only. **Conclusions:** The advent of secondary prevention trials in preclinical AD populations requires careful consideration of the issues of revealing biomarker results in asymptomatic populations. These trials provide an important research opportunity to evaluate the impact of learning one's amyloid status in the setting of incomplete knowledge regarding the future clinical implications, and the factors that influence the response to this information.

F3-01-04 DISCLOSING AMYLOID IMAGING RESULTS

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Background: Progress in Alzheimers disease diagnostics has revolutionized how clinicians and investigators define the disease. Central to this revolution are biomarkers, measures of pathophysiology that will allow investigators and clinicians to "see" Alzheimers disease prior to the onset of dementia. As promising as this revolution is, before clinicians can apply "preclinical Alzheimers disease" to diagnose and treat persons prior to disabling functional losses, investigators need to perform clinical trials. These investigators need best practices to safely, effectively and efficiently use amyloid imaging in clinical trials designed to prevent cognitive decline in cognitively normal older adults. The A4 Trial is an excellent opportunity to develop and test these practices. **Methods:** Literature review and structured Delphi interviews with experts in the fields of genetic testing and amyloid imaging, and analysis of the planned NIA supported A4 Trial. **Results:** Methods developed in the fields of genetic testing provide a template for how to disclose amyloid imaging results to asymptomatic older adults. Investigators need to develop methods to assess psychosocial well being prior to testing and monitor this after disclosure. Disclosure materials need to convey the uncertainty of both a positive and negative amyloid imaging scan. The A4 trial offers the first opportunity to roll out amyloid imaging in a real world context and to gather data to inform how best to translate amyloid imaging into clinical care. **Conclusions:** Successful recruitment and retention to clinical trials in persons with pre-clinical Alzheimers disease brings novel challenges related to participant informed consent and safety. The A4 Trial is an excellent opportunity to better understand how older adults make sense of biomarker results and how the results impact on health and well-being.

FEATURED RESEARCH SESSIONS: F3-02 NEUROFIBRILLARY DEGENERATION: WHO IS THE CULPRIT?

F3-02-01 SOLUBLE ABNORMALLY HYPERPHOSPHORYLATED TAU

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Background: Understanding mechanistically the foundation of synaptic withering and loss that precedes cell death in Alzheimer's disease (AD) and other neurodegenerative diseases is pivotal. Accumulation of hyperphosphorylated tau and the disruption of microtubules are correlated with synaptic loss and pathology of AD. One hallmark lesion of neurodegenerative disease in AD is the initial appearance of neurofibrillary tangles inside neurons. These tangles are composed mainly of hyperphosphorylated tau, a microtubule-associated protein (MAP), polymerized into paired helical and straight filaments (PHFs/SFs). Impaired cognitive function and pathology of AD is correlated with this lesion (PHFs/SFs). In in vitro assays, soluble hyperphosphorylated tau is disruptive to microtubule assembly, whereas tau, stimulates tubulin assembly and subsequent stabilization of microtubules. Microtubules are the "tracks" for axonal transport: disruption of the microtubules leads to compromised axoplasmic flow, dysfunction at the synaptic terminals, and eventually neuronal death. Microtubules are disrupted in AD. We have determined that Thr 212, Thr 231, and Ser 262 are critical sites in tau phosphorylation using pseudophosphorylated tau (Ps-tau) expressed in cultured cells. **Methods:** Our objective was to study the mechanism of neurodegeneration, cytoskeleton dynamics and its subcellular localization by expressing Ps-tau in cells and animal models. For dynamic studies, we performed time-lapse fluorescent microscopy with fluorescent-tagged tau constructs that we generated and co-transfected in CHO cells with fluorescent-tagged tubulin. We used site directed mutagenesis to study the mechanism of Ps-tau translocation in the nucleus and immunocytochemistry to analyze actin polymerization. **Results:** We found that Ps-tau disrupts the microtubules and the actin filaments, and it induces active process of exocytosis. Ps-tau translocates in the nucleus of the cells probably through binding to importins. Mutation of the putative importin binding site on Ps-tau prevented its nuclear localization. We are studying whether this change in subcellular localization changes Ps-tau toxicity. We have expressed Ps-tau in Droshophila neurons and in an inducible mouse model. We have found that the expression of Ps-tau has an effect on the cognitive abilities of the animals. **Conclusions:** These findings suggest that the combination of phosphorylation at Thr212, 231 and Ser262 in the same tau molecule can trigger toxic reaction. The mechanism of tau toxicity might involve not only the microtubule system but also the microfilaments.

F3-02-02 O-GLCNACYLATED TAU: A LINK BETWEEN IMPAIRED GLUCOSE METABOLISM AND NEURODEGENERATION IN ALZHEIMER'S DISEASE

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Background: Brain glucose metabolism is impaired in Alzheimer disease (AD), and this impairment starts before the onset of clinical symptoms, suggesting a causative role in neurodegeneration, but the exact molecular mechanism is unknown. A sensor of intracellular glucose metabolism is O-GlcNAcylation, a posttranslational modification of nucleocytoplasmic proteins by β-N-acetyl-glucosamine (GlcNAc). O-GlcNAcylation of tau affects its abnormal hyperphosphorylation, which is a key mediator of neurodegeneration in AD. **Methods:** The role of O-GlcNAcylation in converting normal tau into abnormally hyperphosphorylated tau was investigated by in vitro, cell culture and in vivo studies. These posttranslational modifications were also studied in postmortem human brain tissue from control and AD cases. **Results:** We found that O-GlcNAcylation regulated phosphorylation of tau inversely both in vitro and in vivo. In AD brain, O-GlcNAcylation was decreased, and the decrease correlated to hyperphosphorylation of tau. Abnormally hyperphosphorylated tau isolated from AD brain contained much less O-GlcNAc modification than the non-hyperphosphorylated tau. O-GlcNAc modified and regulated brain insulin signal transduction, which plays an important role in learning and memory. Decreased brain O-GlcNAcylation was found to lead to dysregulation of insulin signaling that contributes to neurodegeneration in AD. **Conclusions:** In AD, impaired glucose uptake/metabolism probably results in decreased O-GlcNAcylation and consequently hyperphosphorylation of tau, leading to neurofibrillary degeneration. Thus, O-GlcNAcylated Tau could be a link between impaired glucose metabolism and neurodegeneration in AD.