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Background: The use of biomarkers to identify individuals at risk for developing late-onset Alzheimer's disease (LOAD) is of interest for the design of therapeutic prevention or delay - of - onset clinical trials. A biomarker risk assignment algorithm (BRAA) based on APOE and TOMM40 '523 genotypes and age is being used to enrich an international phase 3, double-blind, randomized, placebo-controlled clinical trial. This presentation reports preliminary data on the performance of the BRAA, specifically precision of the BRAA as a function of the experimental variation of the genotype assays, predictive characteristics of the algorithm to identify MCI due to AD, and comparative data for CSF and imaging (fMRI) based biomarkers. **Methods:** A simulation study was performed to determine how the experimental variation of the APOE and TOMM40 '523 assays impacts the risk assignment by the BRAA. Performance of the BRAA (odds ratio, improvement in net reclassification rate vs. versions of the algorithm based only on age and/or APOE genotype) was calculated in a retrospective analysis of the Alzheimer's Disease Neuroimaging Initiative data (n = 660). Its performance (sensitivity and specificity) was compared to data from literature reports for proposed CSF and fMRI biomarkers. **Results:** The simulation study shows the expected precision of the BRAA to be >98%, based on the observed experimental variation of the TOMM40 '523 and APOE assays. The odds ratio for using the algorithm to predict MCI or LOAD ranges from 3 to 5, and comparison of the full algorithm to a version based on APOE and age alone shows a significant ($p < 0.0001$) improvement in the net reclassification rate. The performance of this informative genotype BRAA compares favorably (PPV, NPV 70-80%) with CSF and imaging (fMRI) biomarkers. **Conclusions:** The performance characteristics of the biomarker risk algorithm support its use as a pharmacogenetic enrichment tool for stratification of individuals at high or low risk for developing MCI due to AD in a phase 3 clinical trial. The data from this prospective trial will be used to support qualification of the BRAA by regulatory agencies.

P4-353 METHEMOGLOBIN CATABOLISM AND ALZHEIMER'S DISEASE

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Background: As a main aim we want to make a contribution to the establishment of sources of oxidants as key factors in understanding the role oxidants and oxidative stress play in the pathogenesis of neurodegeneration, namely as Alzheimer disease (AD) progression. Our original observation pointed out the main difference between the hemoglobin and methemoglobin degradation, do the heme oxygenation when a hemoglobin last products is Ferrous (Fe 2+) iron, but in the methemoglobin catabolism last products is Ferric (Fe 3+) iron. **Methods:** Abundant and permanent source of redox-active Ferric (Fe 3+) iron which without Ferrous-Ferric inversions, has "in situ" direct impact on the brain endothelial small vessels, accumulates and increases the r ate of capillary endothelial cell apoptosis and possibly crosses into brain parenchyma to the astrocytes, glia, neurons, and other neuronal cells (neurovascular unit). This postulated and made gain in understanding the transport and neuronal accumulation process of Ferric (Fe 3+) iron, and determines how iron is transported and accumulated intracellularly, identifiable as "Brain rust". **Results:** Previously obtained research found that the neonatal jaundice incidence (p=0.034), heart murmur at a later age (p=0.011) and children and adults mild disorders as dyslalia and learning/memory impairments (p=0.002) were significantly higher than in children and adult of control mothers without pregnancy methemoglobinemia. **Conclusions:** The consequence are performed as initial brain iron harmful effects from the mother-fetal pregnancy complication, and according to our hypothesis in humans could be followed with the neuronal death, and the disease aging process, and leading finally to the hard neurodegenerative disorders as AD, PD, MS and other neurodegenerative disease.

P4-354 BLOOD-BASED BIOMARKER DISCOVERY USING APTAMER CAPTURE (SOMASCAN) PLATFORM TECHNOLOGY

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Background: The search for peripheral protein biomarkers has utilized both mass spectrometry and capture technologies, the latter being multiplexed through platforms such as Luminex and Meso-scale discovery. These capture platforms are all antibody-dependent, representing a limitation in their scalability given the complexity of the human proteome. Here we report for the first time the use of aptamer capture platform measuring 1000 proteins using case-control study design as well as change over time and association with cognitive and non-cognitive phenotypes. **Methods:** A SOMAscan assay was used for quantifying proteins in blood samples from 321 Alzheimer's Disease (AD) patients, 209 normal elderly controls and 157 mild cognitive impaired (MCI) individuals (44 of which converted to AD within one year). For 104 of the AD patients, 83 of the healthy controls 43 of the stable MCI and 42 MCI converters we also measured plasma proteins at one year follow up. Each of the 1,001 measured proteins was tested for association with AD phenotypes including diagnosis, conversion to dementia, rate of decline, MRI measures of atrophy and non-cognitive symptoms. Furthermore, we assessed longitudinal changes of proteins. **Results:** we report here a number of novel associations with disease state including prostate specific antigen complexed with alpha1-antichymotrypsin, fetuin B, carbonic anhydrase I and III, as well as replicating previous associations such clusterin and pancreatic hormone. Using case-control design a signature of 13 proteins predicts disease with an accuracy (AUC) of 70%. We also report protein change over time and associations of protein with AD phenotypes including measures of pathology such as MRI and cognitive and non-cognitive symptoms. **Conclusions:** Using an innovative platform technology in a large series of subjects we find moderate associations between proteins in blood and disease state. This is now a very consistent finding and as we report both novel proteins and replicate previous associations this data moves closer to the goal of a peripheral biomarker for AD.

P4-355 FACTORS THAT INFLUENCE USE OF PLASMA BETA-AMYLOID AS A BIOMARKER OF ALZHEIMER'S DISEASE

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Background: Plasma β -amyloid (A β) peptide measurement is a candidate biomarker in Alzheimer's disease (AD), though studies have yielded conflicting results presumably related to methodological challenges. Factors that may influence peripheral peptide levels include disease stage and progression, Apolipoprotein (ApoE) genotype and lipid levels. We used banked