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P4-340 IS APOLIPOPROTEIN E EPSILON4 ALLELE A HIGHER RISK FACTOR FOR ALZHEIMER'S DISEASE THAN FOR VASCULAR DEMENTIA? A NEUROPATHOLOGICAL STUDY

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Background: Apolipoprotein E epsilon4 allele (APOEe4) is a genetic risk factor for late-onset Alzheimer's disease (AD). It is also associated with cardiovascular pathologies, such as coronary artery disease and hypercholesterolemia. Despite these well-known associations, the link between APOEe4 and VaD is still a matter of debate. Moreover, most of the studies regarding APOEe4 and AD or VaD association relied on groups determined by clinical criteria and lacking pathological confirmation. Aim: To compare the prevalence of APOEe4 in subjects with VaD and AD, defined by neuropathological examination in a sample sourced from a general autopsy service. **Methods:** 61 participants from the Human Brain Bank of the Brazilian Aging Brain Study Group were classified according to neuropathological examination, using international accepted criteria (AD = 40, VaD = 21). Mixed dementia cases (AD plus VaD) were excluded. APOE genotype was determined by Real Time PCR, in duplicates. Subjects were divided in APOEe4 carries (n = 25) and APOEe4 non carries (n = 36) and these frequencies were compared between AD and VaD groups. The groups were compared using Fisher's Exact test. **Results:** APOEe4 carries were more common among AD subjects than among VaD subjects (52.5% vs. 19.0%; p = 0.015). AD and VaD groups were similar regarding age and years of education. Female gender were more prevalent in AD group than in VaD group (70.0% vs 42.9%, p = 0.04). Multivariate logistic regression analysis, adjusting for gender, age and years of education, did not change the association between APOEe4 and AD or VaD. APOEe4 carriers had 4.7 times more chance to have AD than APOEe4 non carriers compared to VaD group (OR = 4.70, CI 95%. 1.34-16.45, p = 0,015). **Conclusions:** APOEe4 was a higher risk factor for neuropathologically-defined AD than for VaD. However, these preliminary results should be confirmed in larger groups.

P4-341 ALZHEIMER RISK VARIANT COMPLEMENT COMPONENT (3B/4B) RECEPTOR-1 (CR1) AND BRAIN FUNCTION DURING AGING

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Background: Recent studies have identified polymorphisms in the complement component (3b/4b) receptor-1 (CR1) gene to be associated with risk for Alzheimer's disease (AD). We previously identified complement proteins as plasma biomarkers of AD associated with brain atrophy in patients and amyloid burden in non-demented older individuals. We examined the effect of the rs3818361 single nucleotide polymorphism in the CR1 gene on longitudinal changes in resting state regional cerebral blood flow (rCBF) in cognitively normal older individuals in the Baltimore Longitudinal Study of Aging (BLSA). **Methods:** Longitudinal 15O-water PET measurements of rCBF were available at baseline and 7 annual follow-up visits in 85 BLSA participants (mean age at baseline; 69.3 ± 7.3 years), in whom genome-wide genotyping data were collected. Neuropsychological testing measured performance in six cognitive domains including memory. **Results:** Allele frequencies in the CR1 rs3818361 polymorphism were C/C in 60 subjects (70.6%) and C/T in 25 subjects (29.4%). The two groups (CC and CT) did not differ significantly in age at baseline, education or APOE e4 status. Mini-Mental State Examination scores and annual rates of change in domain-specific cognitive performance also did not differ significantly between groups. We observed significant longitudinal changes in rCBF in several brain regions in carriers of the AD risk allele (T) of rs3818361 relative to non-carriers. Longitudinal increments in rCBF were observed in the right and left insula, orbitofrontal cortex, medial frontal gyrus, brainstem and thalamus. Longitudinal decreases in rCBF were observed in the right and left middle frontal gyri, inferior parietal cortex and precuneus. These associations remained significant after co-varying for age, sex and APOE e4 status. **Conclusions:** The AD risk variant of CR1 influences longitudinal changes in rCBF in brain regions intrinsic to memory processes in cognitively normal older individuals. The regions involved are those vulnerable to accumulation of beta amyloid and include components of the default mode network known to be disrupted by amyloid deposition even in non-demented elderly. We propose that these observed changes in neuronal activity represent both perturbations in neural function as well as compensatory changes in key memory circuits that are required to maintain normal cognition in at-risk individuals during aging.

P4-342 MITOCHONDRIAL DNA SEQUENCE VARIATION IS ASSOCIATED WITH COGNITIVE FUNCTION IN THE ELDERLY

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Background: Energetic decline underlies a range of age-associated pathological conditions including neurological impairments and other changes generally associated with senescence. The vast majority of the energy needs (90%) of the human body are met by mitochondrial oxidative phosphorylation (OXPHOS); a system for producing the energy required to maintain the structure and function of the body. Hundreds of genes responsible for mitochondrial assembly, metabolism, growth, and reproduction are distributed throughout the nuclear and mitochondrial genomes. The genes of the mitochondrial DNA (mtDNA) are central to energy production, both to generate ATP and to generate heat to maintain body temperature. Human mtDNA has a mutation rate that is 10-20 times higher than that of nuclear DNA and approximately one-third of sequence variants may be functionally important. It is likely that most mtDNA variation that impacts function is rare in frequency and only detectable by direct sequencing. **Methods:** We comprehensively examined mitochondrial genomic variation by sequencing the ~16.5 kilobases of mtDNA from 138 participants from the Health, Aging, and Body Composition Study, a prospective cohort of 3,075 community-dwelling elders (> 70 years). Sequence-level genetic risk scores were assessed for associations with baseline measurements of the Teng mini-mental status exam (3MS) and the digit symbol substitution test (DSST). All analyses were adjusted for age, clinic site, sex and lean mass. **Results:** Genetic risk scores for OXPHOS complexes I and IV were highly significantly associated with both measures of cognitive function. Specifically, genetic risk scores for the ND2 (p = 10e-8), ND5 (p = 10e-6), and COI (p = 10e-8) genes were associated with 3MS.Genetic risk scores for the ND4 (p = 10e-11), ND5 (p = 10e-5), and COIII (p = 10e-5) genes were associated with DSST. Specific combinations of common and rare mtDNA variants were examined to identify sequences that underlie differences in cognitive functioning. **Conclusions:** These results from a population based study of aging directly link mtDNA variation with cognition in the elderly and possibly provide a mechanism by which specific mtDNA complexes and genes contribute to the maintenance of cognitive function. Identifying genetic variants that influence cognitive maintenance in the elderly could lead to interventions that prolong the productive and healthy years of human life.

P4-343 EARLY-ONSET ALZHEIMER'S DISEASE LIKELY HAS AUTOSOMAL RECESSIVE CAUSES

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Background: Alzheimer's disease (AD) occurring on or before 60 years, or early-onset AD (EOAD), accounts for only a small fraction of all AD cases