with amnestic mild cognitive impairment (MCI) were examined by gender and genotype. **Results:** In early AD, male gender and butyrylcholinesterase (BuChE)-K carrier status, if accompanied by apolipoprotein E (APOE) ϵ4 carrier status, results in prominent damage to grey and white matter in the medial temporal region and cognitive decline due to direct toxic effects of aggregated Aβ on cholinergic synapses, neurons, myelin and oligodendrocytes. Symptoms can be attenuated by increasing synaptic acetylcholine (ACh) in damaged, but still functional, cholinergic synapses. Conversely, chronic glial overactivation, that is more likely in females and due, at least in part, to extracellular ACh deficits, can also drive neurodegenerative processes. In females with wild-type BuChE, glial overactivation may be the main driver from MCI to AD. Females are more likely than males to have accelerated age-related myelin breakdown, more widespread white matter loss, loss of neural network connectivity, whole brain atrophy and functional decline. Damage to neural network connectivity can be attenuated by increasing extracellular ACh and this is disease-modifying. **Conclusions:** Identification of phenotypes is important to appropriately target dementia therapy and interpret biomarker data. Preservation of the functional integrity of the neural network may be an important component of strengthening cognitive reserve and significantly delaying the onset and progression of dementia, particularly in females. Prospective confirmation of these hypotheses is required.

P1-086 BRAIN SIZE GENES AND RISK OF DEMENTIA

Deniz Erten-Lyons[1], Beth Wilmot[2], Pavana Anur[2], Patricia Kramer[2], Shannon McWeeney[2], Shawn Westaway[2], Jeffrey Kaye[1], *[1]Portland Veterans Affairs Medical Center, Portland, OR, USA; [2]Oregon Health & Science University, Portland, OR, USA. Contact e-mail: ertenlyo@ohsu.edu*

Background: Alzheimer disease (AD) may have its origins in early life. Prenatal and early life exposures have been suggested to affect one's risk of AD. Early life brain development may be one of these events through its effect on brain reserve. We set out to determine if variations in 3 genes which have been associated with prenatal brain development are associated with increased risk of AD. **Methods:** Ninety-six tag single nucleotide polymorphisms (SNPs) from three brain-size related genes (*microcephalin*, CDK5 regulatory subunit-associated protein 2 (*CDKRAP2*) and centromeric protein J (*CENPJ*)) were genotyped in 187 cases with AD and 170 controls using the Illumina Bead Station. Subjects and controls over the age of 65 years old with no first-degree relatives with AD were selected from longitudinal studies of aging. PLINK, JMP (v5.01, SAS) and R (v 2.9) were used for data analysis. Eleven SNPs were excluded due to a minor allele frequency less than 0.05. Four subjects were removed due to poor sample quality. Logistic regressions were performed to determine if there was a relationship between genotypes and disease risk. Sex, cohort, dementia-free survival (defined as age at onset of dementia for cases or age at last evaluation for controls), *APOE* status (coded as presence of one or more e4 allele vs. none) were added as covariates. An additive genetic model was used. Permutation tests were done to account for multiple comparisons. Significance was set at $p < 0.05$. **Results:** Two SNPs, rs2442607 ($p = 0.0002$, OR = 3.74, CI = 1.84, 7.05) and rs17553089 ($p = 0.02$, OR = -2.33, CI = -1.13, -3.68) in *microcephalin* were found to be significantly associated with AD. After permutation testing with the covariates, only rs244277 remained significantly associated with disease status ($p = 0.007$). rs244277 is an intronic SNP in *microcephalin*. Its function is unknown. **Conclusions:** Genes which play a role in early brain development need to be further studied as mediators of cognitive/brain reserve.

P1-087 MICROARRAY ANALYSIS OF HUMAN NEUROBLASTOMA CELLS EXPOSED TO BETA-AMYLOID, ALUMINUM, AND THE BETA-AMYLOID-ALUMINUM COMPLEX

Valentina Gatta[1], Denise Drago[2], Stefano L. Sensi[3,4], Paolo Zatta[2], *[1]Functional Genomics Unit-Center of Excellence of Aging, Univ. G. D'Annunzio, Chieti Scalo, Italy; [2]CNR-Institute for Biomedical Technologies-Metalloproteins Unit, University of Padua, Padua, Italy; [3]Functional Neurology Unit-Center of Excellence of Aging, Univ. G. D'Annunzio, Chieti Scalo, Italy; [4]University of California-Irvine, Irvine, CA, USA. Contact e-mail: v.gatta@unich.it*

Background: Metal ion dyshomeostasis has been implicated in Alzheimer's disease (AD) and several evidences have shown that aluminum (Al) can have a role in promoting the disease by freezing beta-amyloid (Aβ) in a oligomeric state that is highly neurotoxic (reviewed in Zatta et al., TIPS, 2009). In this study, we employed a microarray assay to analyze changes in the gene expression profile of neuron-line SH-SY5Y cells exposed to Aβ, Al, or the Aβ-Al complexes **Methods:** SH-SY5Y cells were exposed for 24h to either Aβ, Aβ-Al, or Al alone, and 1 ug of total RNA was extracted, amplified, and coupled with either the Alexa Fluor 555 or Alexa Fluor 647 probes. Labeled aRNA was applied directly to microarray slides containing 35,129 spotted oligonucleotide sequences of human genes. The RNA of untreated SH-SY5Y cells was used as a control in each microarray experiment. The identified genes were then analyzed with Ingenuity Pathways Analysis (IPA) software in order to classify them on the basis of their biological functions and disclose functional networks and/or pathways. Finally, expression data were validated by quantitative real-time PCR. **Results:** When compared to Ab or Al exposures, the Aβ-Al complex determines a selective up-regulation of 1535 as well as a down-regulation of 1815 transcripts. Among the genes known to be AD-related 29 were up and 23 downregulated, respectively. Interestingly, the IPA study revealed that exposure to Ab-Al complexes changes expression of genes involved in functional areas related to neurological conditions, amino acid metabolism, cellular signaling and inflammatory responses. Pathways analysis indicates that the Ab-Al complex modulates changes in the expression of genes that can be involved in key AD-related pathways regulating glutamatergic transmission, mitochondrial function, and calcium homeostasis. **Conclusions:** In this study, we find that the Aβ -Al complex produces selective alterations in the expression profiles of genes that are key for synaptic functioning, energy production and homeostasis of calcium and therefore play an important role in both AD progression and/or neuroprotection.

P1-088 AN EXAMINATION OF APP, PSEN1, PSEN2 AND MAPT WITHIN A LARGE GENOME-WIDE ASSOCIATION DATASET

Amy Gerrish, Jade Chapman, Denise Harold, Rebecca Sims, Paul Hollingworth, Richard Abraham GERAD Consortium, Michael Owen, Julie Williams, *Cardiff University, Cardiff, United Kingdom. Contact e-mail: Gerrisha@cf.ac.uk*

Background: The neuropathological hallmarks of Late-Onset Alzheimer's Disease (LOAD) implicate both the tau gene *MAPT* and genes involved within the amyloid pathway as possible susceptibility loci. However, the role of *APP*, *PSEN1*, *PSEN2* and *MAPT* in LOAD remains unclear. **Methods:** We analysed *APP*, *PSEN1*, *PSEN2* and *MAPT* for association in a large GWAS dataset (GERAD1) which consisted of 3941 Alzheimer's cases and 7848 controls. All AD cases met criteria for either probable (NINCDS-AARDA, DSM-IV) or definite (CERAD) AD. Elderly controls were aged 60 years or over and were screened for cognitive decline or neuropathological signs of AD. Population controls were drawn from large existing cohorts with available GWAS data. Individuals were genotyped on either the Illumina 610-quad, 550k or 317k single-nucleotide polymorphism arrays. SNPs were tested for association with AD using logistic regression, assuming an additive model. Each locus was subjected to single marker and gene-wide analysis. Gene-wide analysis was performed in PLINK using variants within 20kb of each gene. In addition, samples that were genotyped on the Illumina 610 quad chip (n = 5715) were analysed for copy number variants (CNVs). Expression analysis was performed using publicly available eQTL datasets. **Results:** We observed a significant association to LOAD with *MAPT* after set based analysis ($P = 0.013$) plus a trend for significance with *APP* ($P = 0.053$). Detailed analysis of *MAPT* identified seven