alertness and sleep process of brain and ChAT is also associated deeply with that process. This study was to explore effects of ChAT polymorphism into treatment outcome of acetylcholineesterase inhibitors(AchEIs) in the Alzheimer's disease(AD) **Methods:** Total 82 AD patients and 121 normal controls who were recruited with similar age and sex were assessed with ChAT 2384G>A(rs3810950) genotype and Korea-MMSE(K-MMSE) for responses of AchEIs during 26 weeks. 69 AD patients only finished this process among total 82. **Results:** The findings showed that ChAT genotypes and A allele distributions were significant statistically in the responders. ChAT A allele carriers(G/A, A/A) were increased in the responders more than the non-responders($x2 = 6.176$, $p = 0.013$), and ChAT A allele distributions were also higer in the responders($x2 = 5.658$, $p = 0.020$). K-MMSE changed scores between baseline and 26 week were improved in the ChAT A allele carriers(G/A, A/A) more than the A allele non-carriers(G/G)($p = 0.043$) **Conclusions:** This study suggests that the ChAT 2384G>A(rs3810950) is associated with treatment outcome of acetylcholine esterase inhibitors in AD patients

P1-070 CANDIDATE GENE STUDY IN THE ENDOSOME-TO-GOLGI RETRIEVAL PATHWAY REVEALS ASSOCIATION OF RETROMER GENES WITH ALZHEIMER'S DISEASE

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Background: Retromer complex plays a critical role in the endosome-to-Golgi retrieval pathway of various membrane proteins. Recent genetic and cell biological studies have implicated the retromer complex in regulating the localization and processing of amyloid precursor protein (APP), establishing it as a key player in the pathogenesis of Alzheimer disease (AD). **Methods:** We tested association of AD with eight genes in the endosome-to-Golgi retrieval pathway which displayed significant differential expression in a siRNA knockdown experiment: RAB7A, TBC1D5, FKBP15, SNX3, IQCE, FAM21B, EHD1 and KIAA1096. Association of SNPs in these genes was analyzed in five Caucasian GWAS datasets, genotyped in our laboratory or available publicly, containing 3275 AD cases and 3063 age-matched controls. Missing and novel genotypes were imputed using the Markov Chain Haplotyping (MaCH) software and the Hapmap CEU and YRI samples as reference haplotypes. Association was evaluated assuming an additive genetic model using generalized estimating equations. Results from individual datasets were combined by meta-analysis using the inverse variance approach implemented in the METAL software. We established statistical significance for SNPs by considering every gene as an independent hypothesis. Multiple-testing correction of individual p-values was done by accounting for the linkage disequilibrium (LD) in each gene. **Results:** Two SNPs in KIAA0196 yielded extremely promising results ($p = 0.0002$ and $p = 0.006$), but data for these SNPs were available in two datasets only. One SNP in IQCE revealed modest evidence of association ($p = 0.007$). Six SNPs in different LD blocks in FKBP15 were nominally significant. Nine SNPs in RAB7A were associated with AD (most significant $p = 0.0009$), three of which remained significant after correction for multiple testing. TBC1D5 showed most consistent evidence of association; the most significant SNP with $p = 0.0055$ exhibited the same direction of effect in all five datasets and almost reached the significance threshold of 0.005. Of interest, a non-synonymous coding SNP in this gene was marginally significant ($p = 0.014$). **Conclusions:** Recently, we showed that the cargo-selective subcomplex of the retromer requires Rab7 for its recruitment to the endosome and TBC1D5 negatively regulates VPS35/39/36 recruitment causing Rab7 to dissociate from the membrane (Seaman et al, 2009). These findings further support a role for retromer complex proteins in AD pathogenesis.

P1-071 MOLECULAR SIGNATURES IN POST MORTEM BRAIN TISSUE OF INDIVIDUALS AT HIGH RISK FOR ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is a neurodegenerative condition characterized pathologically by neuritic plaques and neurofibrillary tangles. The objective in the present transcriptional profiling study was to identify both neurosusceptibility *and* intrinsic neuroprotective factors at the molecular level, not confounded by the downstream consequences of pathology. **Methods:** We thus studied post-mortem cortical tissue in 28 cases who were non-APOE4 carriers (called the APOE3 group) and 13 cases who were APOE4 carriers. Because APOE genotype is the major genetic risk factor for late onset AD, the former group was at low risk for development of the disease and latter group was at high risk for the disease. Mean age at death was 42 years and none of the brains had histopathology diagnostic of AD at time of death. We first derived interregional difference scores in expression between cortical tissue from a region relatively invulnerable to AD (primary somatosensory cortex, BA 1/2/3) and an area known to be susceptible to AD pathology (middle temporal gyrus, BA 21). We then contrasted the magnitude of these interregional differences in between-group comparisons of the APOE3 (low-risk) and APOE4 (high-risk) genotype groups. **Results:** We identified 70 transcripts that differed significantly between the groups and several Kyoto pathways that were disrupted in the APOE4 group, including those involved in mitochondrial function, calcium regulation, and cell-cycle re-entry. Using RT-qPCR, we validated multiple findings. Using pathway analyses we then found that these molecules comprised a network with multiple connections with each other and with APP and MAPT. **Conclusions:** Our results indicated that the abnormalities that we observed in single transcripts and in signaling pathways were not the consequences of diagnostic plaque and tangle pathology, but preceded it and thus may be a causative link in the long molecular prodrome that results in clinical AD.

P1-072 USING APOE TO PREDICT "IMMINENT" RISK OF ALZHEIMER'S DISEASE CONVERSION AMONG PATIENTS WITH MCI: THE REVEAL STUDY

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Background: The REVEAL Study is a series of randomized controlled trials evaluating the impact of disclosing *APOE*-based risk for Alzheimer's disease (AD). A Specific Aim of the fourth funding cycle of REVEAL is to develop a risk communication protocol to disclose three-year *APOE*-based risk of AD conversion to individuals with a diagnosis of amnestic-Mild Cognitive Impairment (MCI). **Methods:** Data was obtained from the Memory Impairment Study (Petersen et al. 2005), a clinical trial involving 769 amnestic-MCI patients, which provided three-year conversion data stratified by *APOE* genotype. Three-year AD conversion risk curves were created using Kaplan-Meier estimates by plotting the estimated risk (1 - survival function) for AD conversion by each *APOE* $\epsilon 4$ category (*APOE* $\epsilon 4$ positive vs. negative) as well as for all amnestic-MCI patients regardless of genotype, stratified by age. Cox proportional hazards regression was used to determine whether conversion rates differed by gender, age, and the presence or absence of an *APOE* $\epsilon 4$ allele. **Results:** Cox proportional hazards regression revealed

a significant difference in AD conversion risk by age and the presence of at least one *APOE* ϵ4 allele, but no significant difference was observed for gender. As a result, separate curves were created for different age groups (split by the median at 73.5 years, providing a ''younger'' and an ''older'' group) to demonstrate the risk of AD conversion based on amnestic-MCI diagnosis and *APOE* genotype (*APOE* ϵ4 positive or negative). Three-year risk of AD conversion across all groups ranged from 8.5% to 53.1%. Three-year AD conversion risk among individuals who are *APOE* ϵ4 positive was 40.0% for the younger age group and 53.1% for the older age group, and among individuals who were *APOE* ϵ4 negative, the risks were 8.5% (younger) and 27.7% (older). **Conclusions:** The resulting curves will be employed as part of a risk education and counseling protocol in an upcoming randomized controlled clinical trial, which aims to understand the impact of disclosing this type of risk information. Understanding the implications of communicating imminent risk is important as both *APOE* and MCI status represent means of identifying higher-risk individuals for future therapeutic opportunities.

P1-073 ANGIOTENSIN-CONVERTING ENZYME GENE AND PROTEIN TO ALZHEIMER'S DISEASE IN TAIWANESE ELDERLY

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Background: Angiotensin converting enzyme (ACE) gene insertion/deletion (indel) polymorphism has been considered a biomarker for Alzheimer's disease (AD); however, associations between ACE gene and protein level to AD are still undetermined in Taiwanese. **Methods:** We investigated 257 Taiwanese cases with AD and 137 ethnically matched controls using allele and genotype association methods, and logistic regression adjusting for the effects of age, education, gender, and Apolipoprotein E epsilon 4 allele status. After genotyping, 65 out of 257 AD patients, 11 with D/D genotype, 28 with I/I genotype, and 26 with I/D genotype, were recruited and measured their ACE protein level by radio-immune assay (RIA) and analyzed by analysis of variance (ANOVA) with post-hoc analysis for the differences of ACE protein level with regard to their corresponding ACE indel polymorphism. **Results:** Our AD patients with ACE I/I homozygote, compared to I/D and D/D genotype, were less likely to be associated with AD (OR:0.601; 95% CI:0.372-0.969; $p = 0.037$) .Consistently, ACE I/I homozygote, compared to the ACE I/D heterozygote, was less likely to be associated with AD (OR:0.584; 95%CI:0.349-0.976; $p = 0.040$). In allele analysis, D allele was significantly associated with the possibility of AD (OR: 1.665; 95%CI: 1.032-2.688; $p = 0.037$).In ACE protein level, the significant differences were found among these three groups ($p = 0.023$). The concentration of ACE protein level was 164.07 ± 86.36 (mean $\pm$ SD) ng/mL for D/D, 114.79 ± 31.32 ng/mL for I/I, and 141.45 ± 51.50 ng/mL for I/D genotype. After post-hoc analysis, we have found the significant difference between D/D and I/I genotype ($p = 0.010$). **Conclusions:** ACE I/I homozygote with its lower ACE protein level is independently less likely to be associated with AD. The findings signal the importance of ACE indel polymorphism and its corresponding protein level with regard to AD among Taiwanese.

P1-074 GENETIC DEFICIENCY OF PLASMA LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 (LP-PLA_2) AND RISK OF ALZHEIMER'S DISEASE IN JAPAN

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Background: High plasma levels of lipoprotein-associated phospholipase A2 (Lp-PLA_2) are associated with an increased risk for cardiovascular disease, stroke and was implicated as a risk factor for dementia in the Rotterdam study, suggesting that pharmacological inhibition of this enzyme may protect from these diseases. An Asia-specific polymorphism, 994G>T (V279F) within the *PLA2G7* gene encoding Lp-PLA_2 is associated with absence of plasma enzyme activity. The objective of this study was to test the hypothesis that genetic deficiency of $LpPLA_2$ activity protects against Alzheimer's disease (AD). **Methods:** This was a genetic case-control study of 1,952 subjects with late-onset AD (by NINCDS-ADRDA criteria) and 2,079 independent-living non-demented controls (age > 60 years) recruited from the local community in Japan as part of the Japanese Genetic Study Consortium of AD. All subjects were Japanese. *PLA2G7* 994G>T (SNP RS16874954) was genotyped by Taqman. Association of the *PLA2G7* null mutation with AD was tested by logistic regression under an additive genotypic model adjusted for age/age of AD onset, gender, and number of apolipoprotein E (*APOE*) e4 alleles. **Results:** Mean (SD) age at onset of the AD subjects was 74.1 (5.0), and 71% were female. Mean age of the control subjects was 75.3 (6.1), and 58% were female. 53% of AD subjects carried the *APOE* e4 allele, compared to 17% of controls. The frequency of the *PLA2G7* null allele was 16.1% in AD subjects and 16.2% in control subjects. Genotypes were in Hardy-Weinberg equilibrium. The *PLA2G7* null polymorphism was not associated with risk of AD - OR 0.98 (95% CI 0.86-1.12, $p = 0.81$) per additional null allele, adjusted for age/age at onset, gender, and number of *APOE* e4 alleles. The null polymorphism was not significantly associated with risk of AD in *APOE* e4 negative subjects_OR 0.92 (CI 0.79-1.09, $p = 0.33$)_or in *APOE* e4 positive subjects_OR 1.12 (CI 0.88-1.42, $p = 0.35$). **Conclusions:** Genetic deficiency of Lp-PLA_2 activity due to carriage of 279F allele is not associated with a reduced risk of AD in Japan.

P1-075 ASSOCIATION OF GENETIC VARIATION IN THE ELECTRON TRANSPORT CHAIN AND ALZHEIMER'S DISEASE

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Background: Decreased functionality of enzymes comprising the mitochondrial electron transport chain has been reported for Alzheimer's disease and impaired mitochondrial function has been theorized as an Alzheimer's disease mechanism. Furthermore, polymorphisms in both the mitochondria and nuclear encoded genes of the electron transport chain are known to affect the functionality of mitochondrial energy production and other cellular processes. We theorize that polymorphisms with the electron transport chain have an association with risk for the development or progression of Alzheimer's disease. **Methods:** We used existing samples and genome-wide association scan (GWAS) data from a longitudinal study conducted by the Texas Alzheimer's Research Consortium (TARC) to test the hypothesis that genetic variation in mitochondrially encoded genes of the electron transport chain are associated with increased risk for development or more rapid progression of Alzheimer's disease. The TARC data and tissue banks contain rich longitudinal clinical data and DNA samples collected from over 500 individuals with a primary diagnosis of Alzheimer's disease and over 300 individuals diagnosed as cognitively normal. We plan to test associations between development or progression of Alzheimer's disease and candidate polymorphisms within mitochondrial encoded genes. **Results:**