P1-065 GENETIC VARIANTS ASSOCIATED WITH INCIDENCE OF LATE-ONSET ALZHEIMER'S DISEASE IN CAUCASIANS

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Background: A series of large genome wide association studies identified several variants that affect susceptibility of Alzheimer's disease including CR1, CLU, PICALM, BIN1, CD2AP, CD33, EPHA1, MS4A6A/MS4E4 and ABCA7 and more recently additional genes have been identified via a large mega-meta-analysis by the International Genomics of Alzheimer Project (IGAP). However, a large part of the genetic contribution to late-onset Alzheimer's disease (LOAD) remains to be explained. The aim of the present study was to identify novel genetic loci associated with incidence of LOAD in Caucasians and for previously identified genes assess their impact on 'when' in addition to 'whether' one developed AD. **Methods:** IGAP assembled a dataset of 13,863 subjects (mean age at baseline75.21±6.55, 61.1% female, 1,449 incident AD cases) from 6 independent sites representing studies in the Alzheimer's Disease Genetic Consortium (Washington Heights-Inwood Columbia Aging Project and Adult Changes in Thought studies), Cohorts for Heart and Aging Research for Genomic Epidemiology (CHARGE) consortium (Framingham Heart Study, Cardiovascular Health Study, Rotterdam Study) and European Alzheimer's Disease initiative (3 City study). Additional cohorts (Religious Orders Study, Rush Memory and Aging Project) will soon be included as well. Genome-wide associations with AD incidence were assessed using Cox proportional hazards models adjusted for baseline age, sex and where appropriate study-site and familial relationships. Inverse-variance meta-analysis was performed for SNPs present in at least 5 studies. **Results:** In preliminary analyses, no novel genome-wide significant findings were identified. Among previously implicated AD genes the most significant associations were observed for CD2AP (hazard ratio (hr) = 0.81, p=1.99xe-5), followed by SORL1 (hr=0.78, p=.0002) and BIN1 (hr=1.15, p= 0.00048) **Conclusions:** This preliminary study, which examines the impact of previously identified risk variants on age at onset of disease observed the most significant associations for genes involved in endocytosis and intracellular trafficking. While these findings need to be confirmed in the larger meta-analysis of the complete sample, it is biologically plausible to postulate that genes modulating intracellular enrichment of potentially pathogenic proteins are related to onset of AD.

P1-066 ORDERED SUBSET ANALYSIS CNV ASSOCIATION WITH ALZHEIMER'S DISEASE AAO PHENOTYPES

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Background: Alzheimer's disease (AD) is a devastating neurodegenerative disorder affecting approximately 5.4 million individuals in the US and is the most common cause of dementia in North America and Europe. Genetic factors play an important role in the pathogenesis of AD and contribute to the variance of age at onset (AAO). APOE4 has a strong effect on AAO and an additional 4-5 loci may contribute to the heritability of AAO. AAO is an important endophenotype and a potential therapeutic target for disease modifying therapy. Ordered subset analysis using AAO as a quantitative endophenotype may identify genetic risk that contributes to a subset of AD. This CNV association study with AAO of AD was designed to examine the role of these low-frequency variants with intermediate penetrance in relation to AAO of AD. **Methods:** 781 AD subjects and 200 normal controls enrolled in the Texas Alzheimer Research Consortium project were phenotyped for AAO and genotyped on the Genome-Wide Human SNP Array 6.0 (Affymetrix) array. The PCA corrected logR data was segmented to reduce the dataset to probes where any event occurred. Ordered subset analysis for the numeric array data means was performed by adding sequentially groups of subjects with the same AAO. **Results:** The ordered subset analysis using the univariate segmentated logR data identified 28 probes corresponding to 6 chromosomal regions, where the maximum p-value survived multiple testing correction. When using the multivariate segmented logR data, 41 probes survived multiple testing correction. Several of the gains and losses contributed to the young AAO subset (<60), but some of the dosage differences appeared to be contributing to the older AAO (>80). The APOE4 allele had its maximum effect at around AAO 74 consistent with previous reports. Replication on the NIA-LOAD familial dataset is ongoing. **Conclusions:** The genetic heterogeneity of AD has been demonstrated in multiple GWAS studies. Ordered subset analysis using AAO as a quantitative endophenotype

Table 1
Results from meta analysis of Cox proportional hazard analysis of AD incidence in 6 cohorts for known AD genes.

SNPID	Coded/non-coded allele	Coded allele frequency(SE)	Gene	Hazard ratio	P-value
chr1:207575967	T/C	0.9911 (0.0019)	CR1	0.590727766	0.01423
chr2:127892810	T/C	0.4024 (0.0378)	BIN1	1.147745978	0.0004753
chr6:47473274	A/G	0.2037 (0.0059)	CD2AP	0.80646079	1.99E-05
chr7:143117919	A/G	0.5522 (0.0193)	EPHA1	0.903210176	0.01072
chr8:27495342	T/C	0.0365 (0.0017)	CLU	1.247323431	0.0166
chr11:59851551	A/G	0.2514 (0.0987)	MS4A6A	1.100428886	0.03096
chr11:85673270	T/C	0.4427 (0.0244)	PICALM	1.096474464	0.01043
chr19:966693	T/C	0.8432 (0.1526)	ABCA7	0.84324309	0.02493
chr19:51828135	T/C	0.741 (0.0883)	CD33	0.868228804	0.0012
chr11:121267485	A/T	0.8974 (0.1258)	SORL1	0.781296937	0.0002141