

**P1-117** **BLOOD GENE EXPRESSION CHANGES IMPLICATED IN ALZHEIMER'S DISEASE**

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**Background:** Studies aimed at predicting risk for Alzheimer's disease (AD) are needed to improve the outcomes of clinical trials directed at treating this currently incurable disease. Brain expression studies have implicated transcriptional regulation as a functional mechanism important in AD etiology. Our hypothesis is that there may be gene expression changes that can be detected in peripheral blood prior to the onset of cognitive symptoms; we tested this in a cohort of subjects with clinically diagnosed AD dementia, amnesic MCI (aMCI) and clinically normal (CN) individuals with PiB-PET amyloid imaging. **Methods:** RNA was isolated from blood, using the PAXgene Blood RNA system, for 44 clinically diagnosed AD dementia, 56 aMCI, 82 CN-PiB-positive and 61 CN-PiB-negative subjects from the Mayo Clinic Study of Aging (MCSA). Gene expression measures were collected using the Illumina Whole-Genome DASL array. Transcript profiling analysis was performed in R using linear regression, including technical and biological covariates. Genome-wide genotypes are being imputed to the 1000 genomes reference set to facilitate eQTL analysis. The most significant genes were tested for replication in an independent cohort of 103 ADs and 213 Controls collected as part of the Alzheimer's disease Neuroimaging Initiative (ADNI). **Results:** Profiling analysis of the AD dementia vs CN PiB-neg groups identified 48 candidate genes (un-adjusted  $p < 5E-03$ ), of which 26 could be evaluated in the ADNI cohort. 9/26 achieved nominal significance, of which 7 were in a direction consistent with the discovery cohort. To identify disease relevant changes that occur prior to cognitive decline, we compared results from AD dementia vs PiB-neg and PiB-pos vs PiB-neg profiling analyses. We identified 90 genes that were nominally significant in both, 89 of which were in a consistent direction (31 down-regulated; 58 up-regulated). eQTL analysis will be performed to determine if the differentially expressed genes are associated with regulatory variants. **Conclusions:** Blood gene expression measures represent a feasible putative biomarker for AD dementia with tremendous potential. Analysis across two cohorts identified remarkable consistency in direction of association for genes with nominal significance. We identify a set of 89 genes that represent potential early, disease relevant, transcriptional changes that can be pursued further.

**P1-118** **ASSOCIATION OF LOW-FREQUENCY AND RARE CODING VARIANTS WITH INFORMATION PROCESSING SPEED**

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**Background:** Measures of information processing speed vary between individuals and decline with age. Studies of aging twins suggest there is a genetic component underlying the variation, with heritability estimates as high as 67%. We used the Illumina HumanExome BeadChip genotyping array to evaluate the association of rare coding variants with a neurocognitive test of this domain by performing a meta-analysis in the setting of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. **Methods:** The Digit Symbol Substitution Test (DSST) is a pencil and paper test that requires timed translation of numbers to symbols using a key. Test scores were available for 30,576 individuals of European ancestry and for 5,758 African-American individuals who were older than 45 years and free of dementia and clinical stroke. Linear regression models adjusted for age and gender were used to analyze the contribution of single variants using the seqMeta package; gene-based burden tests that either aggregate the total number of rare alleles by gene (T5, T1, and T01 tests) or sum weighted allele counts over rare variants in a locus (SKAT test) were also conducted within each cohort. Secondary analyses included adjustment for educational attainment. Meta-analyses to combine cohort-specific results were carried out separately for each ancestry group. **Results:** Low frequency variants in the *RNF19A* gene implicated in Parkinson's disease and amyotrophic lateral sclerosis reached the threshold for statistical significance ( $p = 2.01 \times 10^{-6}$ ) using the T01 test in individuals of European ancestry. Variants in *SLC22A7* ( $p = 3.91 \times 10^{-6}$ ), a transporter of guanine nucleotides, and *MTHFD1L* ( $p = 3.41 \times 10^{-6}$ ), involved in mitochondrial synthesis of tetrahydrofolate, were significantly associated with performance on the DSST in African-American individuals after adjustment for education using the T01 and SKAT tests, respectively. *MTHFD1L* single nucleotide polymorphisms were previously associated with plasma homocysteine levels and Alzheimer's disease risk. **Conclusions:** In this study, rare variants in novel genes were significantly associated with a test of processing speed in a large sample of community-dwelling adults. Replication efforts are ongoing.

**P1-120** **EXPLORING INTERNATIONAL GENOMICS OF ALZHEIMER'S PROJECT (IGAP) GENETIC MARKERS' EFFECT ON AGE AT ONSET OF DEMENTIA IN ALZHEIMER'S DISEASE PATIENTS**

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