Table (*Continued*)
Self-reported Physical Activity and Hazard of Dementia: Results from the Johns Hopkins Precursors Study (N=676)

Predictor	Age	Hazard ratio (95 CI)	N
Carrying groceries, Any limitation, age 60,69 (zphys_c60)	60-69	1.15 (0.15, 8.71)	368
Climbing flights of stairs, Any limitation, age 60,69 (zphys_d60)	60-69	2.73 (0.95, 7.84)	369
Climbing flights of stairs, Any limitation, age 70,79 (zphys_d70)	70-79	1.46 (0.38, 5.57)	74
Climbing one flight, Any limitation, age 60,69 (zphys_e60)	60-69	2.49 (0.31, 20.02)	367
Bending, kneeling or stooping, Any limitation, age 50,59 (zphys_f50)	50-59	0.82 (0.10, 6.93)	235
Bending, kneeling or stooping, Any limitation, age 60,69 (zphys_f60)	60-69	2.50 (0.86, 7.25)	368
Bending, kneeling or stooping, Any limitation, age 70,79 (zphys_f70)	70-79	1.12 (0.30, 4.23)	74
Walking more than a mile, Any limitation, age 50,59 (zphys_g50)	50-59	1.87 (0.21, 16.89)	235
Walking more than a mile, Any limitation, age 60,69 (zphys_g60)	60-69	3.50* (1.13, 10.82)	369
Walking more than a mile, Any limitation, age 70,79 (zphys_g70)	70-79	1.66 (0.44, 6.28)	74
Walking several blocks, Any limitation, age 50,59 (zphys_h50)	50-59	5.38 (0.59, 48.85)	234
Walking several blocks, Any limitation, age 60,69 (zphys_h60)	60-69	1.67 (0.21, 13.19)	367
Walking one block, Any limitation, age 60,69 (zphys_i60)	60-69	3.52 (0.43, 28.76)	365
Bathing or dressing, Any limitation, age 60,69 (zphys_j60)	60-69	5.33 (0.68, 41.71)	368

MONDAY, JULY 25, 2016
ORAL SESSIONS
O2-06
GENETICS: EPIGENETICS AND GENE-EXPRESSION CHANGES IN AD

O2-06-01 THE HUMAN BRAINOME: HUMAN BRAIN GENOME, TRANSCRIPTOME, AND PROTEOME INTEGRATION

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Background: We hypothesize that changes expression are crucial to Alzheimer's disease (AD) development. Previously we examined how DNA alleles control downstream expression of RNA transcripts and how those relationships are changed in pathologically confirmed AD tissue. We present a new pipeline to examine how proteins are incorporated into those network relationships. **Methods:** Two separate sets of human brain tissues were used for analysis. Set 1 contains tissues from brain banks located in the US that are funded through ADRCs (n=345, 49% AD). Set 2 contains tissues from an epidemiologic cohort developed by the Rush ADRC (n=409, 35% AD, 28% MCI). Genome, transcriptome and proteome data was collected and analyzed to determine key drivers for Alzheimer's pathology. Differential expression was used to inform selection of specific transcriptomic and proteomic modules from co-expression analysis using WCGNA. The seeding set was expanded to include other targets within the known KEGG/GO pathways and an in-house literature-based knowledgebase for the enriched modules. These seeding sets were then further examined in top-down modeling Bayesian procedures to develop causal links. Further analysis involved using key driver analysis to predict the crucial members for each module. **Results:** Comparison of our two datasets yields several modules which had significant overlap considering clustering separately in AD and control populations (p-value=0 to 0.03 comparing AD datasets; p-value=0 to 0.03 comparing control datasets). We found several functional modules that were over-represented in our data, including immune system processes, which we had previously discovered in a similar approach (see Zhang et al). Of further interest, we found about 50 key

drivers within our data, approximately half of which are novel targets. **Conclusions:** We present a novel pipeline for the analysis of our existing Human Brainome data.

O2-06-02 GENOME-WIDE META-ANALYSIS OF TRANSCRIPTOME PROFILING IDENTIFIES NOVEL DYSREGULATED GENES IMPLICATED IN ALZHEIMER'S DISEASE

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Background: Gene expression is a fundamental mechanism in susceptibility to and manifestation of complex disease. Prior studies suggest that abnormal gene expression patterns may contribute to the onset and progression of late-onset Alzheimer's disease (LOAD). We performed genome-wide transcriptome meta-analysis and whole-brain cortical thickness analysis in LOAD using blood-based microarray gene expression profiles. **Methods:** 1,440 non-Hispanic Caucasian participants (661 from the ADNI as a discovery sample and 674 and 105 from the AddNeuroMed and Mayo cohorts as

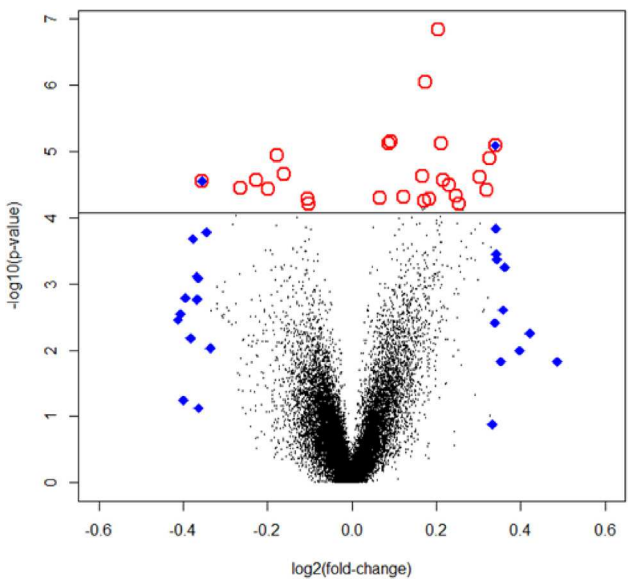

Figure 1. Volcano plot of transcriptome analysis results in the ADNI cohort (discovery sample). Red circles represent significantly differentially expressed genes in AD compared to CN.

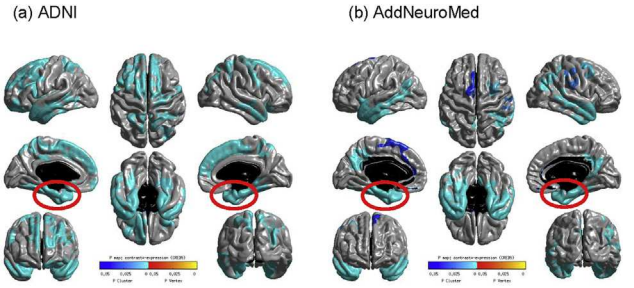

Figure 2. Association of *CREB5* gene expression levels with brain structure using whole brain surface-based analysis using two independent cohorts: (a) ADNI (discovery sample) and (b) AddNeuroMed (replication sample). Whole-brain cortical thickness analysis demonstrated the identification and replication of brain regions, especially entorhinal cortex, significantly associated with expression of *CREB5*. Statistical maps computed using SurfStat were thresholded using random field theory (RFT) as a multiple testing correction at p-corrected < 0.05.

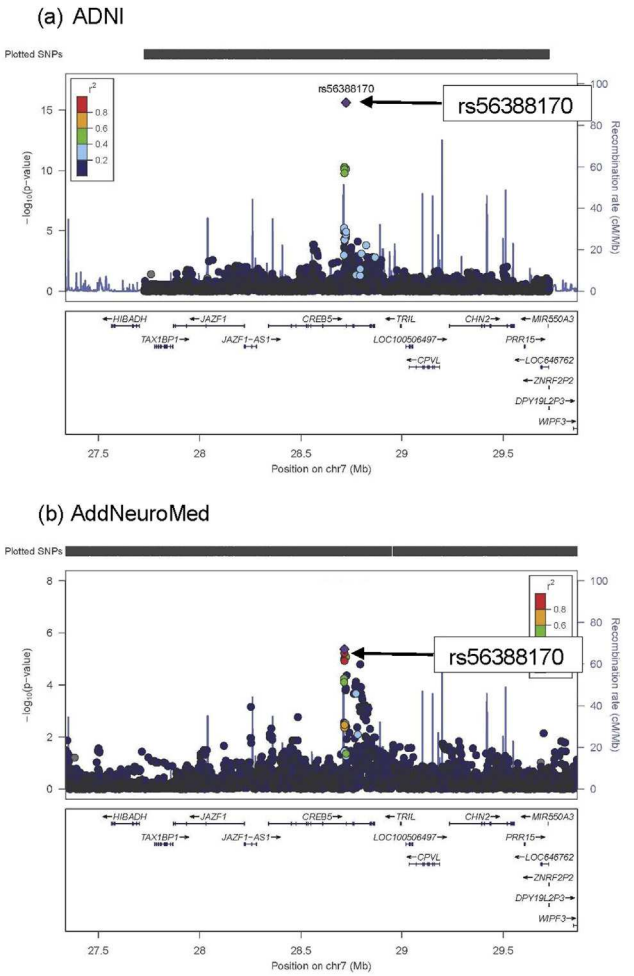

Figure 3. Results of *cis*-eQTL mapping analysis of *CREB5* using two independent cohorts: (a) ADNI (discovery sample) and (b) AddNeuroMed (replication sample). *cis*-eQTL mapping analyses of *CREB5* detected 5 significant associations with $p < 5\times10^{-8}$ in the ADNI. The most significant *cis*-eQTL SNP (rs56388170) in the ADNI was replicated in the AddNeroMed. All SNPs are plotted based on their -$\log_{10}$ p-values, NCBI build 37 genomic position, and recombination rates calculated from the 1000 Genomes Project reference data.