**SUPPLEMENTARY METHODS**

**Standard Protocol Approvals, Registrations, and Patient Consents**

All subjects included in ADNI project provided written informed consent, according to Helsinki Declaration, at the time of enrolment for imaging and genetic sample collection and completed clinical symptom assessments approved by each participating sites' Institutional Review Board. Following ADNI’s policies, the principal investigator of the present study has accepted ADNI Data Use Agreement and is authorized to use ADNI data.

Rush ROS and MAP cohort studies were approved by the Institutional Review Board of Rush University Medical Center. Each participant signed an informed consent and an Anatomic Gift Act.

**Phenotype – Imaging processing**

For our analysis, the pre-processed imaging data was downloaded from ADNI (a detailed description of the imaging acquisition protocol can be found online at the ADNI website) and linearly registered to the respective T1-MRI. Images were then registered to the MNI ICBM 152 reference space, using composite transformations, built using PET native to MRI native transformations, MRI native to MNI ICBM 152 linear and non-linear transformations. Subsequently, SUVR maps were produced using the cerebellar grey matter as the reference region and normalized with a probabilistic white matter mask (Figure 1). Both global and voxel-wise SUVR measures were used in the analyses.

**Phenotype – Cognitive scores**

For ADNI, the global cognition scores were developed by making a z-score of the sum of the memory and the executive function composite scores based on the mean and standard deviation of the controls. In Rush-ROS/MAP, the global cognitive scores were based on 17 cognitive performance tests. Briefly, raw scores for each test were first standardized using baseline mean and standard deviation of the entire cohorts. Standardized z-scores of individual tests were then averaged to derive a composite score for global cognition.

**Phenotype – Gene expression**

The ADNI cohort used the Affymetrix Human Genome U219 Array (Affymetrix, Santa Clara, CA) for expression profiling. Total RNA from peripheral blood was extracted using using the PAXgene Blood RNA Kit. Samples were then randomized to plates and all the posterior procedures such as hybridization, washing, staining, and scanning were performed in an Affymetrix GeneTitan system. Quality control and normalization of the data is described elsewhere1.

 In Rush-ROS/MAP cohorts, RNA expression was obtained using RNA sequencing performed on the Illumina HiSeq with 101 bp paired-end reads. For that, RNA was extracted from samples collected in the dorsolateral prefrontal cortex. RNA sequencing library preparation was performed by the Broad Institute Genomics Platform using the strand specific dUTP method. Quality control and further details of sample processing have already been described elsewhere2.

**Genotyping, imputation and gene selection**

DNA from ADNI participants was extracted from blood and genotyped using the Illumina HumanOmni2.5 BeadChip (Illumina, Inc., San Diego, CA) as described by 1. PLINK software (version 1.07) 3 was used to perform quality control, in which Single Nucleotide Polymorphisms (SNPs) with a genotyping efficiency <95%, a MA (MA) frequency of <5%, or deviation from Hardy-Weinberg equilibrium <1 x10-6 were excluded. Individuals were excluded if they had a call rate <95%. From initial over 2370 thousand SNPs, approximately 1274 SNPs remained after quality control (QC). Genetic relatedness was detected in 5 pairs of participants (PI\_HAT > 0.4), and one subject of each pair was randomly excluded.

For Rush-ROS/MAP cohorts, DNA was extracted, genotyped, imputed, and quality controlled according to procedures described elsewhere 4. In summary, genotyping was performed using the Affymetrix Genechip 6.0 platform at the Broad Institute’s Center for Genotyping or the Translational Genomics Research Institute and the Illumina HumanOmniExpress (Illumina, Inc, San Diego, CA, USA) at the Children’s Hospital of Philadelphia. These two sets of data were pooled after undergoing the same QC analysis in parallel: SNPs with a genotyping efficiency <95%, a MAF of <5%, or deviation from Hardy-Weinberg equilibrium <1 x10-4 were excluded, as well as individuals with call rate <95% were excluded. The dosage-values were obtained for each imputed SNP and recoded accordingly to match analysis performed with the discovery data. The subjects genotyped using the Affymetrix Genechip 6.0 platform had their rs4388808 genotype imputed, with an overall imputation score >0.9.

**REFERENCES**

1. Saykin AJ, Shen L, Yao X, et al. Genetic studies of quantitative MCI and AD phenotypes in ADNI: Progress, opportunities, and plans. Alzheimer's & dementia : the journal of the Alzheimer's Association 2015;11:792-814.

2. Lim AS, Srivastava GP, Yu L, et al. 24-hour rhythms of DNA methylation and their relation with rhythms of RNA expression in the human dorsolateral prefrontal cortex. PLoS genetics 2014;10:e1004792.

3. Purcell S, Neale B, Todd-Brown K, et al. PLINK: A tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559-575.

4. Keenan BT, Shulman JM, Chibnik LB, et al. A coding variant in CR1 interacts with APOE-epsilon4 to influence cognitive decline. Human molecular genetics 2012;21:2377-2388.