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TITLE: Genetic variation underlying traumatic brain injury (TBI) and Late Onset Alzheimer's Disease (LOAD)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Age-related changes in memory function are not uniform even in the absence of dementia and contributing factors are unclear. Characterization of non-disease associated cognitive changes is crucial to gain a more complete understanding of brain aging.
Episodic memory was investigated in 13,979 ethnically diverse elderly (ages 72 to 85 years) with two to 15 years of follow-up, and with known dementia status, age, education and APOE genotypes at baseline. Adjusted trajectories of episodic memory performance over time were estimated using Latent Class Mixed Models. We also calculated the age-specific annual incidence rates of dementia in the non-demented elderly (n=10,659).
Two major episodic memory trajectories were estimated within each of the study groups: 1) Stables - consisting of individuals exhibiting a constant or improved memory function over time and 2) Decliners - consisting of individuals with a decline in memory performance over time. Compared with the individuals in the Stable trajectory, Decliners were more likely women, older, less educated, from non-White ancestry population and APOE-ε4 carriers. The highest annual incident rates of dementia were observed in the oldest age group (85 years old), among those of Caribbean-Hispanics ancestry and among Decliners who exhibited rates of incident dementia five times higher than those with Stable trajectories (rates= 15 per 100 person per year versus 3 per 100 person-per year).
Episodic memory can be preserved over time among elderly regardless of ethnic group. Age, gender, education and APOE genotype influence the maintenance of episodic memory over time. Declining memory over time is one of the strongest predictors of incident dementia.

15. SUBJECT TERMS

None listed

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1. **INTRODUCTION:**

There is a significant deficit in the literature investigating the possible association between TBI and increased susceptibility to develop LOAD later in life. We hypothesize that Traumatic Brain Injury interferes with aging process by accelerating individual's memory decline and possibly accelerating LOAD like neuro-degeneration. In addition, genetic risk factors including non-coding and highly penetrant coding variants interact with exposure to TBI to modify risk of LOAD. We will first characterize trajectories of memory change in subjects stratified by LOAD and TBI status using the longitudinal data from multiple cohorts including NIA-LOAD, ADGC, RADC, WHICAP and CHAP using growth mixture modeling (GMM) approaches and latent class approaches. We hypothesize that we will observe 4 major trajectories in the four groups of samples- Group 1 (rapid- decliners) corresponding to subjects with TBI and Alzheimer's Disease (LOAD), Group 2 corresponding to subjects with TBI but not LOAD, Group 3 corresponding to subjects with LOAD but not TBI and Group 4 (plateaus) corresponding to subjects without TBI and without LOAD. We will then test the interaction of genes with TBI in conferring risk of LOAD using genome-wide SNP data. We will validate the nominally significant genes ($p<0.001$) in the extreme-phenotype sub-sample including Group 1 and Group 4 individuals. After replicating the top genes in publicly available cohorts-RADC, CHAP and WHICAP, we will use whole exome sequencing data in WHICAP and NIA-LOAD to find rare variants that underlie these signals.

2. **KEYWORDS**

Episodic memory trajectories (EMTs), longitudinal evaluations, Alzheimer's Disease, Traumatic Brain Injury (TBI), dementia

3. **ACCOMPLISHMENTS**

- **What were the major goals of the project?**

Please see below our approved SOW for the project for the first two years. We have completed our tasks for Year 1 (marked in red) and have begun working on SA2 for year 2. We want to emphasize that we obtained longitudinal on all the datasets proposed in our grant which allowed us to increase our sample size to ~14,000 from 4878 as proposed in the project.

Tasks	YEAR 1				YEAR 2				YEAR 3			
	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4
SA1. To characterize trajectories of memory change in subjects stratified by AD and TBI status using the longitudinal data in 4,715 samples from the National Institute of Aging Late-Onset Alzheimer's Disease (NIA-LOAD) and Alzheimer's Disease Genetic Consortium (ADGC) cohorts.												
Task 1. Prepare and harmonize longitudinal phenotype data on memory performance from NIA-LOAD and ADGC cohorts												
a) Compute demographically adjusted z-scores of Logical Memory IA and IIA (sex,aged and education adjusted)												
Task 2. Prepare and harmonize the NIA-LOAD and ADGC GWAS datasets												
a) Quality control of genome-wide genotype data in both ADGC and NIA-LOAD cohorts (missingness, HWE etc)												
b) Quality control of sample level data in the two cohorts (relationship and sex checks, missingness etc)												
c) Joint imputation of the two datasets												
d) Joint Population substructure analyses of the two datsets												
Task 3: Implement GMM nested models to compute trajectories of memory decline in the joint NIA-LOAD and ADGC GWAS datasets												

SA2a. To identify genome-wide TBI-interacting genes that predict risk of AD using the non-stratified sample from the NIA-LOAD and ADGC cohorts.												
Task 1. Implement SREBIA on the NIA-LOAD and ADGC GWAS datasets												
Task 2. Implement special cases on the SREBIA algorithm (case-online and enhanced version)												
Task 3. Explore novel set based GXE gene-based methods to be applied on genome-wide data												
SA2b. To assess nominally significant TBI-interacting genes identified in SA2a in the stratified sample from the NIA-LOAD and ADGC cohorts.												
Task 1: To select the genes that are nominally significant at P<10e-03 for TBI genotype interaction in predicting LOAD risk												
Task 2: Select the most homogenous sample of rapid decliners and stable pleateaus (Group 1 and 4) as determined in Aim 1												
Task 3: Test TBI genotype interaction comparing rapid decliners and plateaus in nominally significant genes (SA2, Task1)												
SA2c.To validate the TBI-interacting genes identified in SA2b using independent cohorts with genome-wide SNP data available.												
Task 1. Prepare and harmonize longitudinal phenotype data on memory performance from RADC, CHAP and WHICAP												
Task 2. Prepare and harmonize the GWAS data from RADC, CHAP and WHICAP												

a) Quality control of genome-wide genotype data in the cohorts (missingness, HWE etc)												
b) Quality control of sample level data in the cohorts (relationship and sex checks, missingness etc)												
c) Joint imputation of the datasets												
d) Joint Population substructure analyses of the datsets												
Task 3. Validate the TBI interacting genes identified in SA2a and SA2b												
Task 4. Report results and evaluate potential manuscripts/conference presentations etc												
SA3. To investigate whether rare coding variants in the loci identified in SA2 interact with TBI in predicting risk of AD												
Task 1. Prepare WES from WHICAP and NIA-LOAD												
a) Alignment, variant calling and subsequent to determine high quality variant calls												
b) Harmonize variant data in the two datasets depending on capture kits, depth of coverage etc												
Task 2. Apply set based TBI genotype interaction analyses to determine genes with rare coding variants associated with LOAD in genes that were significant in SA2c												
Task 3. Conduct genotyping in samples without WES in both cohorts and re-assses TBI-genotype interaction in WES and genotype data												
Task 4. Explore other available WES datasets for replication												

Task 5. Report results and evaluate potential manuscripts/conference presentations etc												
Task 6. Explore possible collaborations with groups with functional expertise (RNA-seq, cell-based methods etc) to functionally characterize the genes and variants identified in Aims 1 through 3												

100% completed
25% completed
Planned

What was accomplished under these goals?

- *Major activities, Specific objectives and significant results*

  SA1. To characterize trajectories of memory change in subjects stratified by AD and TBI status using the longitudinal data in 4,878 samples from the National Institute of Aging Late-Onset Alzheimer's Disease (NIA-LOAD) and Alzheimer's Disease Genetic Consortium (ADGC) cohorts.

  Task: Implement GMM nested models to compute trajectories of memory decline in the joint NIA-LOAD and ADGC GWAS datasets.

Initial analyses were focused in the optimization of the Latent Class Mixed Models (LCMM) algorithm using the Washington Heights Columbia Aging Project (WHICAP) as training dataset. The optimized algorithm was subsequently applied to all the original proposed study cohorts: The National Institute of Aging Late-Onset Alzheimer's Disease Family Study (NIA-LOAD) and The Alzheimer's Disease Genetic Consortium (ADGC), The Rush Alzheimer's Disease Center Cohorts (RUSH) and The Chicago Health and Aging Project (CHAP).

Episodic memory was investigated in 13,979 elderly (ages 72 to 85 years) with two to 15 years of follow-up, and with known dementia status, age, education and APOE genotypes. Adjusted trajectories of episodic memory performance over time were estimated using Latent Class Mixed Models. Analysis using two different study groups: i) only non-demented individuals at baseline evaluation and ii) all individuals at baseline evaluation regardless of dementia status at baseline. We also calculated the age-specific annual incidence rates of dementia (per 10 people) in the non-demented elderly sample (n=10,976).

The LCMM analysis has been adjusted for sex, age, education, total years of follow-up and scores of episodic memory at the baseline evaluation. When study cohort consisted of different ethnic groups, analysis were performed independently within each of the ethnicities (i.e., WHICAP and CHAP).

Two major episodic memory trajectories were estimated within each of the study cohorts: Stable comprising individuals exhibiting a constant or improved memory function and Decliner comprising individuals exhibiting memory decline. Interestingly, majority of the individuals cluster into the Stable trajectory of memory performance. Compared to the individuals with Stable trajectory, Decliners were more likely females and *APOE*-ε4 carries, older and slightly less educated. The highest incident annual rates of dementia (100 persons per year) were observed in

the oldest age group (≥85 years old), with slightly higher rates for women compared to males (rates= 4.0 versus 3.8) and the highest rates achieved by subjects with a Caribbean-Hispanic ancestry (rate=5.5). The rate of incident dementia was the strongest factor differentiating the two trajectories: subjects within Decliner trajectory had rates of dementia five times higher compared to those within Stable trajectories (rates= 14.9 versus 2.9).

Our results suggest that Episodic memory can be preserved over time among elderly regardless of ethnic group. Age, sex, education and APOE genotype influence the maintenance of episodic memory over time. Declining memory over time is one of the strongest predictors of incident dementia.

Figure 1A) Episodic memory trajectories (EMTs) considering only non-demented subjects at baseline within each of the study cohorts

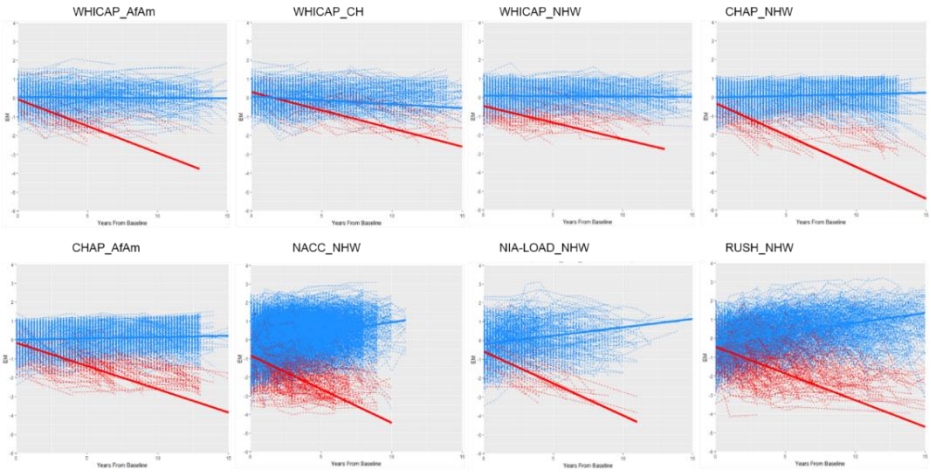
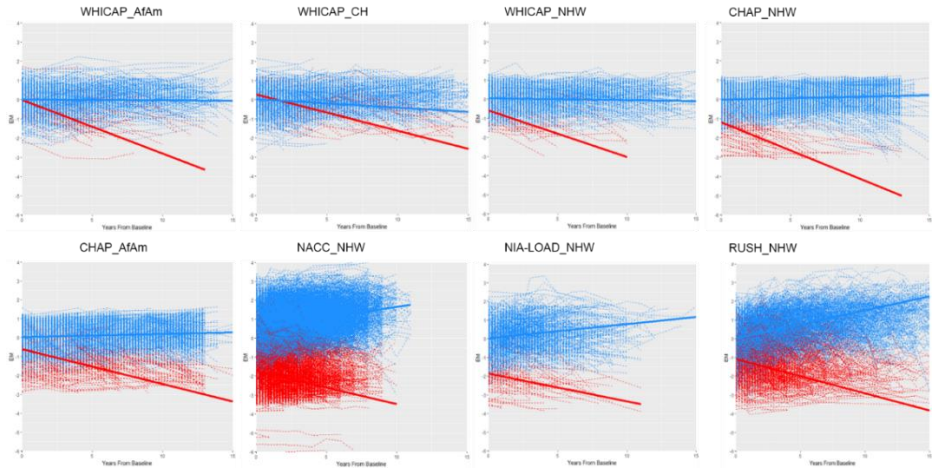


Figure 1B) Episodic memory trajectories (EMTs) considering all subjects at baseline within each of the study cohorts



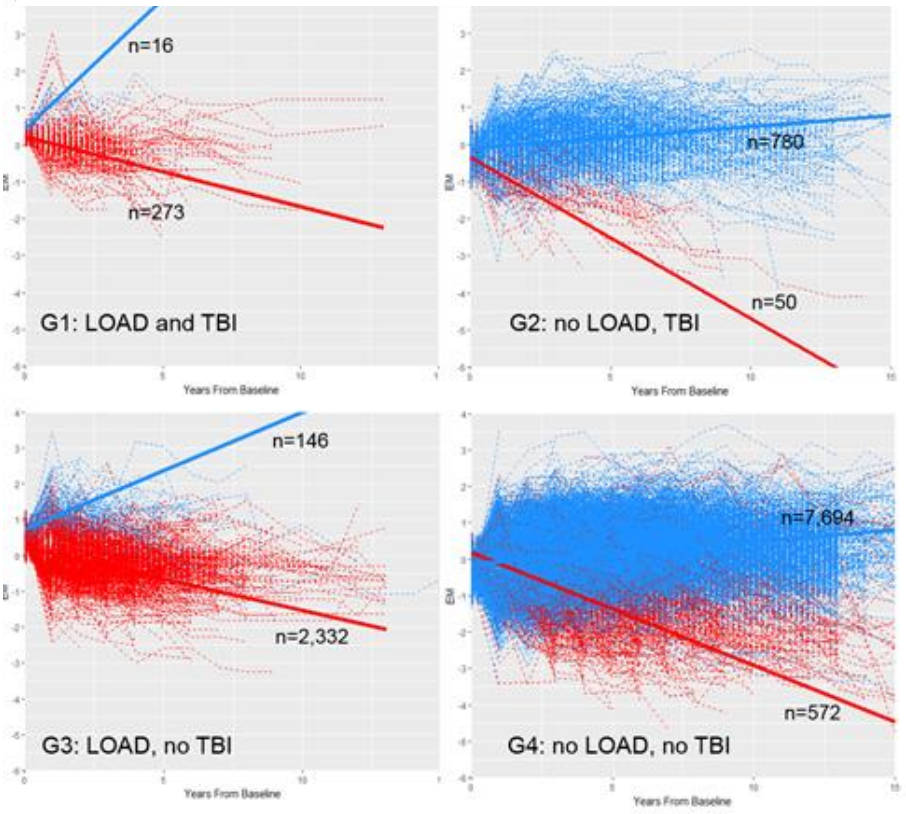
Subsequently, we have started to generate Episodic Memory Trajectories using a sample of 11,934 subjects from two of the proposed cohorts (NIA-LOAD and ADGC), supplemented with two additional cohorts, the Chicago Health and Aging project (CHAP) and Rush University (RUSH). Since our preliminary results (manuscript under submission for publication) have shown that episodic memory can be preserved over time among elderly regardless of ethnic group, the CHAP cohort includes participants from both African-American (n=1,977) and Non-Hispanic White ancestry (n=1,301). The rest of cohorts (n=8,656) are limited to participants of Non-Hispanic White ancestry.

In these initial analyses, for the TBI phenotype, we have used a broad definition which includes TBI with and without loss of consciousness (brief or extended), brain trauma (chronic or with brief or extended loss of consciousness), head injury with and without loss of consciousness.
To characterize EMTs, described LOAD and TBI phenotype definitions were used to create four groups: Group 1 subjects corresponds to subjects with both disorders (TBI +LOAD), Group 2 corresponds to subjects with TBI but not LOAD, Group 3 corresponding to subjects with LOAD but not TBI and Group 4 corresponds to subjects without any disorder (no TBI and no LOAD). Since the diagnosis of TBI is available only at the baseline evaluation, each cohort participant' group membership was defined at baseline and keep it through the subsequent follow-ups. Table 1 summarizes the sample size for each of the study cohorts stratified by group membership.

As previously described, episodic memory trajectories (EMTs) were derived using Latent Class Mixed Models. Episodic memory scores were adjusted for gender, age, education, episodic memory scores at baseline and total years of follow-up (truncated to a maximum of 15 years) using a multivariate regression model. The residuals from the adjusted linear model were then used in the LCMM analysis.

As presented in Figure 2, and as previously hypothesized, our preliminary results show that majority of the subjects (93%) within the control group G4, non-demented subjects without TBI, exhibited a predominant sustained memory performance over time. As also previously hypothesized, the vast majority (~94%) of subjects in groups G1 (with both LOAD and TBI) and G3 (LOAD in the absence of TBI) exhibited decline in memory performance. Within this two groups (G1 and G3), we also observed that memory of subjects within the stable EMT seems to improve over time, which may be due to a practice effect. Interestingly, the majority of subjects within group G2, i.e., TBI in the absence of LOAD, were classified into a stable EMT. We have originally hypothesized that TBI subjects will exhibit a predominantly stable pattern of the memory decline

Figure 2: EMTs for each of the defined LOAD and TBI groups



- *Major accomplishments*

  1. Manuscript describing methodology to derive the episodic memory trajectories (EMTs) in the study cohorts and corresponding findings has been submitted for publication in Neurology journal.

  2. Characterization of EMTs in a sample of 13,979 subjects from different ethnic backgrounds with and without Late Onset Alzheimer's Disease and no Traumatic Brain Injury that can be use as reference for future analyses.

  3. Longitudinal trajectories of episodic memory performance (EMTs) for four groups defined based on Late Onset Alzheimer's Disease (LOAD) and Traumatic Brain Injury (TBI)

diagnoses: Group 1 subjects with TBI and LOAD, Group 2 subjects with TBI but not LOAD, Group 3 subjects with LOAD but not TBI and Group 4 subjects without TBI and without LOAD.

- **What opportunities for training and professional development has the project provided?**
  Nothing to Report

- **How were the results disseminated to communities of interest?**
  Manuscript describing the results of from the episodic memory trajectory analyses has been submitted to Neurology Journal

- **What do you plan to do during the next reporting period to accomplish the goals?**

Our Specific aim for the next reporting period of the grant is

SA2a. To identify genome-wide TBI-interacting genes that predict risk of AD using the non-stratified sample from the NIA-LOAD and ADGC cohorts.

We will be taking the following steps to fulfill the goals of SA2:

1. Narrow TBI phenotype definition based on severity

We will refine the definition of TBI by accounting for degree of severity. We will create four different categories: no history of TBI, mild TBI (head injury with loss of consciousness lasting less than 10 minutes), moderate TBI (head injury with loss of consciousness lasting between 10 to 30 minutes), and severe TBI (head injury with loss of consciousness lasting more than 60 minutes).

2. EMTs will be derived using the new TBI definition to update the qualitative description of the trajectories of memory performance within each of the defined groups

3. Quantify the degree of memory decline exhibited by subjects classified within the declining memory trajectories so we are able to statistically test our initial hypotheses, i.e., subjects within group G1 (affected by both LOAD and TBI) will exhibit the fastest decline on memory performance over time, i.e., rapid-decliners.

4. Incorporate additional study cohorts: WHICAP, which will increase final sample size (~4,000 subjects)

5. Explore final sample size gain by incorporating an additional cohort of Caribbean-Hispanic families with TBI and LOAD diagnosis, Estudio Familiar de la Influencia Genetica Alzheimer (EFIGA).

6. Conduct a genome-wide association analysis for TBI using study cohorts that at this time have both TBI diagnosis and imputed genome-wide genotype data available.

7. Explore novel set based GXE gene-based methods to be applied on genome-wide data to further elucidate the relationship between TBI and LOAD.

4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**

Characterization of EMTs in a sample of 13,979 subjects from different ethnic backgrounds with and without Late Onset Alzheimer's Disease and no Traumatic Brain Injury that can be use as reference for future analyses.

- **What was the impact on other disciplines?**

Nothing to Report

- **What was the impact on technology transfer?**

Nothing to Report

- **What was the impact on society beyond science and technology?**

Nothing to Report

5. CHANGES/PROBLEMS

- **Changes in approach and reasons for change**

Nothing to Report

- **Actual or anticipated problems or delays and actions or plans to resolve them**

Imputed genome-wide genotype data for some of the study cohort is currently being generated, i.e., ADGC cohort is finalizing imputation of their GWAS data using the Haplotype Reference Consortium (HRC), a reference panel of 64,976 human haplotypes constructed using whole genome sequence data from 20 studies of predominantly European ancestry. Although in the long

term, the use of HRC will significantly improve our ability to discover and refine causal loci, will delay the inclusion of ADGC cohort in the analysis for the immediate future analyses.

- **Changes that had a significant impact on expenditures**

Hiring of the post-doctoral research scientist is being more difficult than anticipated and it explains why there is large carryover into the second year. In an attempt to broader our options to find a suitable candidate, we have contacted the Division of Neurology Clinical Outcomes Research and Population Science (NeuroCORPS) at Columbia University Medical Center. NeuroCORPS receive requests from a number of data science/computer science students at Columbia University looking for analytic opportunities. Therefore, we will interview master students who have strong background in statistics or/and bioinformatics data analysis.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report

- **Significant changes in use or care of human subjects**

Nothing to Report

- **Significant changes in use or care of vertebrate animals**

Nothing to Report

- **Significant changes in use of biohazards and/or select agents**

Nothing to Report

6. PRODUCTS

- **Publications, conference papers, and presentations**

Manuscript describing methodology to derive the episodic memory trajectories (EMTs) in the study cohorts and corresponding findings has been submitted for publication in Neurology journal.

- **Journals publications**

Nothing to Report

- **Books or other non-periodical, one-time publications**

Nothing to Report

- **Other publications, conference papers, and presentations**

Nothing to Report

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**
  - *Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."*

***Example**:*

Name:	Badri Vardarajan
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2.4

Contribution to Project:	Dr. Vardarajan has contributed to the preparation and harmonization of the data from the different study cohorts, and reviewed/edited the manuscript
Funding Support:	N/A

Name:	Sandra Barral
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2.4
Contribution to Project:	Dr. Barral performed the statistical analyses, supervised Ms. Zhao analyses, interpreted the data, and wrote the manuscript.
Funding Support:	N/A

Name:	Xingtao Zhao
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6 months
Contribution to Project:	Ms. Zhao integrated data from the study cohorts and performed the latent class mix models analyses
Funding Support:	N/A

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Vardarajan, Badri (PI): KL2TR000081 has ended. Dr. Vardarajan no longer contributes effort on P50AG008702 and W81XWH-12-1-0013. As his KL2 award has ended, Dr. Vardarajan contributes efforts to additional projects: New Investigator Research Grant (Alzheimer's Association), U54AG052427, RF1AG054023, and RF1AG054074.

  Barral, Sandra (PI): Dr. Barral contributes efforts to U54AG052427 in addition to active other support previously reported.

- **What other organizations were involved as partners?**

Nothing to Report

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS**

Nothing to Report

- **QUAD CHARTS**

Nothing to Report

9. **APPENDICES**

Nothing to Report

10. ***THE APPENDICES.***

List of abbreviations

Alzheimer's Disease (AD)
Alzheimer Disease Research Centers (ADCs)
Apolipoprotein E (APOE)
The Alzheimer's Disease Genetic Consortium (ADGC)
Binary Sequence Alignment/Map (BAM)
Bootstrap likelihood ratio test (BLRT)
Base pairs (bp)
Base Quality Score Recalibration (BQSR)
Burrows-Wheeler Aligner (BWA)
The Children's Hospital of Philadelphia (CHOP)
Combined Annotation Dependent Depletion (CADD)
The Center for Inherited Disease Research (CIDR)
Copy Number Variation (CNVs)
Database of Single nucleotide polymorphism (dbSNP)

Deoxyribonucleic acid (DNA)
The Department of Defense and Veterans Brain Injury Center (DVBIC)
Genome Analysis Toolkit (GATK)
Gigabites (Gb)
Glasgow Coma Scale (GCS)
Gene environment interaction (GXE)
Genomic Evolutionary Rate Profiling (GERP)
Growth mixture modeling (GMM)
Genome-Wide Association Studies (GWAS)
Human Gene Mutation Database (HGMD)
Hardy-Weinberg Equilibrium (HWE)
Identity-by-descent (IBD)
Latent Class Growth Analysis (LCGA)
Linkage disequilibrium (LD)
Late Onset Alzheimer's Disease (LOAD)
Minimum Allele Frequency (MAF)
Rush Memory and Aging Project (MAP)
Microtubule-Associated Protein Tau (MAPT)
The Minority Aging Research Study (MARS)
Megabases (Mb)
Maximum Likelihood Algorithms (MLE)
The National Alzheimer's Coordinating Center (NACC)
The National Heart, Lung, Blood Institute Grand Opportunity Exome Sequencing Project (NHLBI GO ESP)
National Insitutes of Aging (NIA)
The National Institute of Aging Late-Onset Alzheimer's Disease Family Study (NIA-LOAD)
The National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)
Nanograms (ng)
Online Mendelian Inheritance in Man (OMIM)
Polymorphism Phenotyping (POLYPHEN)
Principal Components (PCs)
Polymerase Chain Reaction (PCR)
Quality Control (QC)
The Rush Alzheimer's Disease Center Cohorts (RADC)
The Religious Orders Study (ROS)
Sorting Intolerant From Tolerant (SIFT)
Single nucleotide polymorphism (SNP)
Traumatic Brain Injury (TBI)
Uniform Data Set (UDS)
Variant Call Format (VCF)
The Washington Heights Inwood Columbia Aging Project (WHICAP)
Whole Exome Sequence (WES)
Whole Genome Sequence (WGS)

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