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Traumatic Brain Injury and Alzheimer's Disease

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14. ABSTRACT

There is growing evidence that individuals with TBI are at increased risk for AD/ADRD. However, TBI survivors don't invariably develop dementia in life and patients with dementia usually don't have a history of head injury indicating that more work is needed to understand the relationship between TBI and AD/ADRD. Beyond the E4 allele of apolipoprotein E (APOE E4), we have integrated common genetic variants into a 'polygenic hazard score' (PHS) for predicting AD dementia age of onset. Among APOE E3/3 cognitively normal individuals, who constitute the majority of all US individuals with AD, Alzheimer's Disease PHS (adPHS) predicts a) longitudinal cognitive decline and b) amyloid and tau pathology. Integrating common genetic variants jointly associated with vascular risk factors and AD, we have recently developed a vascular PHS (vPHS) to identify people who may be at high risk for both vascular and Alzheimer's pathology. In this proposal, our objective is to examine whether adPHS and vPHS predict cognitive decline, vascular and AD pathology among non-demented individuals with a history of TBI. By using two different polygenic scores, we will evaluate the unique contribution of Alzheimer's and vascular associated pathways to TBI. We hypothesize that among people with high genetic risk, TBI will accelerate Alzheimer's neurodegeneration, directly or through vascular disease.

Despite COVID-19 related slowdowns, we have obtained approval to access NACC and ROSMAP databases, and have obtained preliminary results showing differences in age-of-onset for dementia in individuals with high Alzheimer's disease risk who had a TBI versus those with a low Alzheimer's disease risk who had a TBI, at least for the ROSMAP cohort. We are currently quality-checking the PHS calculated for the NACC cohort, where we've encountered variable results depending on the program version used for PHS generation. We are thus engaged in quality-checking and ascertaining the source of this variability so that a final PHS calculation can be generated for the NACC cohort. We are thus in the preliminary analytic stage of the project, and plan to have submitted our findings for publication by the end of the next annual report. William G. Mantyh, MD accepted a position at University of Minnesota and we continue in our efforts to setup a subcontract, although progress has been slow.

15. SUBJECT TERMS

NONE LISTED

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1. Introduction:

There is growing evidence that individuals with TBI are at increased risk for AD/ADRD. However, TBI survivors don't invariably develop dementia in life and patients with dementia usually don't have a history of head injury indicating that more work is needed to understand the relationship between TBI and AD/ADRD. Beyond the E4 allele of apolipoprotein E (APOE E4), we have integrated common genetic variants into a 'polygenic hazard score' (PHS) for predicting AD dementia age of onset. Among APOE E3/3 cognitively normal individuals, who constitute the majority of all US individuals with AD, Alzheimer's Disease PHS (adPHS) predicts a) longitudinal cognitive decline and b) amyloid and tau pathology. Integrating common genetic variants jointly associated with vascular risk factors and AD, we have recently developed a vascular PHS (vPHS) to identify people who may be at high risk for both vascular and Alzheimer's pathology. In this proposal, our objective is to examine whether adPHS and vPHS predict cognitive decline, vascular and AD pathology among non-demented individuals with a history of TBI. By using two different polygenic scores, we will evaluate the unique contribution of Alzheimer's and vascular associated pathways to TBI. We hypothesize that among people with high genetic risk, TBI will accelerate Alzheimer's neurodegeneration, directly or through vascular disease.

2. Keywords

Head injury, Alzheimer's disease, genetic risk, traumatic brain injury, concussion, TBI, polygenic risk, dementia

3. Accomplishments

Major goals:
Assess whether Alzheimer's disease polygenic risk score predicts cognitive decline in non-demented people with TBI.

Assess whether Alzheimer's disease polygenic risk score is associated with amyloid, tau and vascular pathology in postmortem brains of non-demented people with TBI.

Accomplishments:
COVID-19 has significant hindered forward progress of this research application. However, several key accomplishments have occurred despite the adversity of COVID-19. These include:

1) Acquisition of National Alzheimer's Coordinating Center (NACC) clinical and Alzheimer's Disease Sequencing Project (ADSP) genetic data after lengthy approval processes
2) Preliminary generation of Polygenic Hazard Score (PHS) for ADSP data. We encountered a potential source of error with the *APOE* calls within the ADSP cohort due to a software issue. We are currently troubleshooting this issue and we are in the midst of performing quality-control.
3) Approval, acquisition, and generation of Polygenic Hazard Score (PHS) for ROSMAP data after lengthy approval and procurement process. We encountered several errors in the generation of PHS scores involving *APOE* calls, but surmounted these issues with substantial investment in learning new troubleshooting techniques and training new study personnel (retaining study personnel was a particular challenge during COVID and the changing economic environment).
4) Training of investigators on the design, calculation and troubleshooting of polygenic risk scores, which led to study team members obtaining National Institutes of Health R01 funding (separate, non-overlapping project) and faculty positions at University of Minnesota (WGM) and University of California, San Diego (Iris Broce).
5) Preliminary results, albeit based on data that is questionable from the NACC/ADSP, are described in the pages below. We are currently double checking a descrepency in *APOE* calls that resulted (e.g. the higher PHS has paradoxically LESS *APOE4* carriers, which is clearly incorrect as *APOE4* provides higher PHS and therefore more risk for AD).

NACC TBI participants	PHS no *APOE* 25th percentile (N=21)	PHS no *APOE* 75th percentile (N=21)	P-value
PHS (without *APOE*)	-0.9741299 (0.3190419)	0.7689954 (0.3582729)	**<0.0001**
Age at first visit, years	72.52381 (6.779521)	70.57143 (7.24273)	0.37
Sex, % female	67 %	38%	0.06
Cardiovascular Summary Score* (median, interquartile range)	1 (0 - 1)	1 (1 - 2)	0.12
Formal education, years	16.19048 (2.731649)	16.19048 (2.731649)	1.0
Baseline MMSE (mean, interquartile range)	29 (27 – 29.5)†	28.5 (26 - 30)†	0.95
Total follow-up time, years	6.83 (3.84)	6.00 (3.46)	0.44
APOE ε4 carriers, %	52 %	14 %	**0.026**
APOE ε2 carriers, %	9.5%	9.5%	1.0
# participants crossing into dementia	3	7	0.15
Dementia age-of-onset, years	74.66667 (12.05543)	69.14286 (8.687703)	0.43

*Cardiovascular summary score = summation of presence or absence of diabetes, hypertension, hypercholesterolemia, coronary artery disease, prior stroke, and congestive heart failure (1 point for the presence of each condition).

† 1 MMSE score missing from each quartile group

NACC TBI participants *APOE3/APOE3* PHS too small to compute (total N = 57); lower quartile mean 70.7 (13.6) (3 participants); upper quartile mean 72 (14.1) (2 participants)

ROSMAP participants *APOE3/APOE3* PHS (total N=42); lower quartile mean 89.4 (6.66) (6 participants); upper quartile mean 83.4 (7.11) (5 participants)

Performed Shapiro Wilk testing of normality of continuous variables. Only two failing were MMSE and Cardiovascular Summary Score, which we report Median (Interquartile Range) and differences between these quartile groups were evaluated via Wilcoxon rank-sum non-parametric testing. Other continuous variables were tested with paired student's t-test. χ^2 test was utilized for assessing differences of sex, *APOE* carrier status, number of participants crossing into dementia between quartile groups.

Statistical comparisons were made via Wilcoxon rank-sum test (MMSE and vascular disease). Continuous normally distributed variables are tested via two way student's t-test. Categorical variables (sex, *APOE*, # participants who developed dementia) were tested via Chi-square testing.

NACC TBI participants	PHS with *APOE* 25th percentile (N=21)	PHS with *APOE* 75th percentile (N=21)	P-value
PHS (with *APOE*)	-0.9285089 (0.3632542)	1.304944 (0.4015747)	**<0.0001**
Age at first visit, years	71.47619 (7.480769)	70.95238 (7.324453)	0.82
Sex, % female	52%	39%	0.35
Cardiovascular Summary Score* (median, interquartile range)	1 (0 – 1.5)	2 (1 - 2)	**0.016**
Formal education, years	15.61905 (4.295069)	16.52381 (2.293884)	0.40
Baseline MMSE (mean, interquartile range)	29 (27 – 30)†	30 (28.5 - 30)†	0.056
Total follow-up time, years	7.321853 (3.904778)	7.274364 (3.108411)	0.97
APOE ε4 carriers, %	57 %	24 %	**0.028**
APOE ε2 carriers, %	9.5%	9.5%	1.0
# participants crossing into dementia	4	3	0.68
Dementia age-of-onset, years	77.25 (11.1168)	70.3 (10.40833)	0.44

*Cardiovascular summary score = summation of presence or absence of diabetes, hypertension, hypercholesterolemia, coronary artery disease, prior stroke, and congestive heart failure (1 point for the presence of each condition).

† 1 MMSE score missing from each quartile group

NACC Control participants	PHS no *APOE* 25th percentile (N=44)	PHS no *APOE* 75th percentile (N=44)	P-value
PHS (without *APOE*)	-0.902357 (0.3699209)	0.8125665 (0.2703812)	<**0.0001**
Age at first visit, years	74.49788 (7.930068)	75.5825 (9.325193)	0.5582
Sex, % female	66 %	55%	0.386
Cardiovascular Summary Score* (median, interquartile range)	1 (1 - 2)	1 (0.5 - 2)	0.9313
Formal education, years	15.36364 (2.382991)	15.11364 (3.577812)	0.7006
Baseline MMSE (mean, interquartile range)	28 (25 – 29)†	28 (25.5 - 29)†	0.8501
Total follow-up time, years	3.527148 (2.122251)	4.164446 (2.30909)	0.1812
APOE ε4 carriers, %	52 %	40 %	0.251
APOE ε2 carriers, %	2.3%	2.3%	1.0
# participants crossing into dementia	17	18	0.828
Dementia age-of-onset, years	74.93876 (11.32863)	76.69574 (11.8033)	0.6565

† 2 MMSE scores missing from 1st quartile group

NACC Control participants	PHS with *APOE* 25th percentile (N=44)	PHS with *APOE* 75th percentile (N=44)	P-value
PHS (with *APOE*)	-0.8749924 (0.3834057)	1.605378 (0.4156464)	<**0.0001**
Age at first visit, years	76.39284 (9.809415)	76.22042 (9.745519)	0.9343
Sex, % female	48 %	55%	0.522
Cardiovascular Summary Score* (median, interquartile range)	1 (1 - 2)	1 (0 - 2)	0.2157
Formal education, years	15.18182 (2.903668)	15.09091 (2.826932)	0.8821
Baseline MMSE (mean, interquartile range)	28 (25 – 29)†	27 (24.5 - 29)†	0.9534
Total follow-up time, years	3.774471 (2.395118)	3.611395 (1.819611)	0.7200
APOE ε4 carriers, %	45 %	52 %	0.522
APOE ε2 carriers, %	4.5%	4.5 %	1.0
# participants crossing into dementia	19	23	0.7288
Dementia age-of-onset, years	76.95573 (12.79184)	79.0542 (9.392059)	0.5437

† 2 MMSE scores missing from 1st quartile group

ROSMAP TBI participants	PHS no *APOE* 25th percentile (N=14)	PHS no *APOE* 75th percentile (N=14)	P-value
PHS (without *APOE*)	-0.7959729 (0.263209)	0.7750446 (0.1561728)	**<0.0001**
Age at first visit, years	77.88384 (6.275485)	76.23174 (8.428572)	0.5614
Sex, % female	57 %	43%	0.450
Cardiovascular Summary Score* (median, interquartile range)	1 (0 - 1)	1 (0 - 1)	0.8993
Formal education, years	17.21429 (2.359223)	18.21429 (3.984172)	0.4264
Baseline MMSE (mean, interquartile range)	29 (28 – 30)	29 (28 - 30)	0.7884
Total follow-up time, years	9.378508 (5.353156)	9.609074 (5.271792)	0.9095
APOE ε4 carriers, %	36 %	36 %	1.0
APOE ε2 carriers, %	7.1 %	7.1 %	1.0
# participants crossing into dementia	5	5	1.0
Dementia age-of-onset, years	87.37249 (7.279574)	82.50459 (7.65572)	0.3330

No missing data

ROSMAP TBI participants	PHS with *APOE* 25th percentile (N=14)	PHS with *APOE* 75th percentile (N=14)	P-value
PHS (with *APOE*)	-0.9605346 (0.2925727)	1.11041 (0.4259154)	**<0.0001**
Age at first visit, years	79.59695 (7.718066)	75.67224 (6.4045)	0.1551
Sex, % female	57 %	50%	0.705
Cardiovascular Summary Score* (median, interquartile range)	1 (0 - 1)	1 (0 - 2)	0.8553
Formal education, years	16.92857 (2.894671)	18.78571 (3.468065)	0.1361
Baseline MMSE (mean, interquartile range)	29 (28 – 30)	29 (28 - 30)	0.9313
Total follow-up time, years	9.551384 (5.465419)	11.67732 (5.360927)	0.9095
APOE ε4 carriers, %	0 %	71 %	**0.001**
APOE ε2 carriers, %	43 %	7.1 %	**0.029**
# participants crossing into dementia	7	7	1.0
Dementia age-of-onset, years	90.64633 (6.911032)	85.79603 (7.424705)	0.2298

Next steps:

Same for ROSMAP control group (or maybe not since these are similar to previous published Desikan 2017 data)

Spreadsheets don't match APOE status (which makes sense since it looks like this is reversed on these tables – looking into our STATA ready sheet, there is a difference in this compared to PHS_apoe_wAgeCorrection_out). Does this latter sheet differ from the NACC database? Did I scramble the APOEs somehow?

Head trauma group showed substantial reductions relating both PHS no APOE and PHS w APOE in regards to disease age-of-onset. Both PHS no APOE and PHS w APOE performed similarly in regards to predicting who would have a lower age-of-onset. But this did not exceed the predictive ability of individuals without head trauma (see if true).

Training and professional development:
Dr. William G. Mantyh, MD was a neurologist and clinical fellow at the start of this project. This project allowed him to gain an understanding of the intersection of clinical behavioral neurology, large consortium based clinical research, and analysis of genetically complex disease such as TBI-induced head trauma and dementia. This work provided Dr. Mantyh invaluable experience to gain a faculty position as an Assistant Professor at University of Minnesota in the Department of Neurology. It also provided Dr. Mantyh the experience needed to successfully compete for an NIH R01 grant (in a non-overlapping research project)

Dr. Jennifer S. Yokoyama has provided invaluable mentorship in how to understand, interpret, and harness genetic data to better diagnose, predict and find targetable pathways for head-trauma associated dementia.

A study team member, Dr. Iris Broce, was able to harness the knowledge gained in this project to obtain a faculty position as an Assistant Professor at the University of California, San Diego.

Dissemination of results:
Nothing to report. We are in the midst of troubleshooting the PHS in the NACC group, and when this analysis is finished we plan on submitting for publication.

Next reporting period goals:
N/A

4. Impact

Our results are not yet interpretable due to software issues with our PRS, which we will complete in the near future.

5. Changes/Problems

The COVID-19 pandemic caused significant delays in the IRB, data use agreements, and transfer of data for this study. However, we have all genetic and clinical data in hand after lengthy approval and acquisition processes.

Elsewhere, we are double checking the results of the preliminary PHS calculations in the NACC database. This requires running the PHS-generating algorithm incorporating the Single Nucleotide Polymorphisms (SNPs) that comprise the PHS along with their associated weights. The program we were using had conflicting results depending on the version used, and thus we are performing an analytical "deep dive" to ascertain the source of this variability. This process is currently underway after several disheartening set backs.

We also experienced changes in the lab's personnel who helped with the computational aspects of this work, which requires re-hiring and re-training. This significantly delayed out project. Thankfully, we are able to re-initiate the PHS calculation process and hope for publishable results (we will publish negative or positive findings) by the end of 2023.

There were no changes relating to changes in approach, expenditures, use or care of human subjects, or use of biohazards.

6. Products

Name:	*Jennifer S. Yokoyama*
Project Role:	*PI*
~~Researcher Identifier~~ (e.g. ORCID ID):	0000-0001-7274-2634

Nearest person month worked:	*4*
Contribution to Project:	*Dr. Yokoyama has designed the study approach, performed genetic analysis, and performed administrative work to obtain study approval*

Name:	*William G. Mantyh*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	0000-0003-2096-2461
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Mantyh has identified clinical endpoints to measure, queried and coordinated data management with NACC and ROSMAP databases, and performed administrative work to obtain study approval*

Change in active other support of PD/PI or senior/key personnel since last reporting period

Nothing to report.

Organizations involved as partners

None

8. Special Reporting Requirements

Nothing to report. No inventions were created as part of this project.

9. Appendices

Nothing to report