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TITLE: 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. We are currently in the 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 are trying 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) IRB and data use agreement approval by the National Alzheimer's Coordinating Center
2) Data has been transferred from the National Alzheimer's Coordinating Center
3) IRB and data use agreement approval by ROSMAP
4) Data has been transferred from ROSMAP, but several missing variables need to be re-requested to ROSMAP
5) Quality checking, organization of data, and preliminary analyses of National Alzheimer's Coordinating Center has completed (see Table 1 and 2). Table 1 shows that individuals in the upper 25% percentile for polygenic Alzheimer's disease risk (e.g. individuals who were in the 25% riskiest category for Alzheimer's disease genetic risk) developed, on average, dementia 6 years earlier than individuals in the lower 25% percentile. This preliminary data suggests that Alzheimer's disease risk influences which patients with TBI become demented sooner. Table 2 is almost identical to Table 1, however it examines only patients with "extensive" previous TBI, which means head trauma with loss of consciousness for > 5 minutes. Thus, unlike Table 1 that includes all patients with *any* remote TBI, Table 2 includes only patients with an "extensive" remote TBI. In other words, Table 2 excludes patients with mild TBI. Similar to the results shown in Table 1, Table 2 demonstrates that patients at higher genetic risk for Alzheimer's disease – namely those patients in the upper 25% percentile for Alzheimer's disease genetic risk – are, on average, 2 years younger at age of dementia diagnosis than those with lower Alzheimer's disease genetic risk.

TABLE 1: Comparison of individuals with a history of **any** remote TBI who converted to dementia during the study. Data obtained from the National Alzheimer's disease Coordinating Center (NACC).

Patients with ANY severity remote TBI	Lower 25%le (N=82)	Upper 25%ile (N=82)	P-value
Converters	22	22	
Average age at dementia	80	74	P=0.022
Sex (female/total)	34/82	28/82	
Education	18 years	17 years	
Initial CDR Global	0.2	0.2	
Age at first visit	74	71	

Age is reported in years

TABLE 2: Comparison of individuals with a history of **extensive** (e.g. > 5 minutes loss of consciousness) remote TBI who converted to dementia during the study. Data obtained from the National Alzheimer's disease Coordinating Center (NACC).

Patients with 'extensive' remote TBI	Lower 25%le (N=29)	Upper 25%ile (N=29)	P-value
Converters	9	11	
Average age at dementia	78	76	0.56
Sex (female/total)	10/29	7/29	
Education	18	19	
Initial CDR Global	0.3	0.3	
Age at first visit	80	81	

Age is reported in years

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. 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.

Dissemination of results:
Nothing to report.

Next reporting period goals:
We have accomplished a critical goal despite COVID-19 related slowdowns, which is obtaining data from NACC and ROSMAP, two large databases that have clinical and genetic information regarding patients with previous head trauma. This approval process, including the IRB approval and data use agreements, represented a significant amount of time and delay. With this data in hand, we plan on further analyzing the association between Alzheimer's disease genetic risk and the development of dementia in individuals with a history of head trauma. We expect to have results in publication format and submitted for publication by next year.

4. Impact

Results remain preliminary, and we hope to replicate our preliminary results in the NACC database with what we find using the ROSMAP database. Should our preliminary data reflect what we find in the total analysis, this will be the first study to study polygenic risk of TBI and lead to new insights regarding why certain individuals with TBI develop dementia and why others with the same degree of TBI do not. This is a first step to uncovering disease pathways that can be targeted with disease modifying drugs, helping to treat TBI in American's military and civilian personnel.

5. Changes/Problems

The COVID-19 pandemic caused significant delays in the IRB, data use agreements, and transfer of data for this study. However, these "road blocks" have been overcome and we are now on track to meeting the grant timeline.

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

6. Products

Nothing to report. We are still in the preliminary analysis phase, and plan to have publications submitted during next year's annual report.

7. Participants & Other Collaborating Organizations

Individuals working on the project

Name:	*Jennifer S. Yokoyama*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	

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):	
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

Dr. William G. Mantyh completed his fellowship at University of California, San Francisco and accepted a position of Assistant Professor at University of Minnesota. We are currently working with Department of Defense assigned personnel to organize a subcontract. These efforts were initiated July 1 2020 and we have not yet heard back from the Department of Defense about how to move forward with a subcontract.

Information for Dr. William G. Mantyh's current institution:
Organization Name: University of Minnesota
Location: Minneapolis, MN
Partner's contribution to the project: Dr. William G. Mantyh's contributions are listed above.

8. Special Reporting Requirements

Nothing to report

9. Appendices

Nothing to report