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TITLE: Traumatic Brain Injury and Alzheimer's Disease

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CONTRACTING ORGANIZATION: University of California, San Francisco, CA

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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) genomic and clinical data after lengthy approval processes
2) Preliminary generation of Polygenic Hazard Score (PHS) for NACC data. We encountered a potential source of error with the generation of PHS scores within the NACC cohort due to a software issue. We are currently troubleshooting this issue and we are in the midst of performing quality-control.
3) Quality checking, organization of data, and preliminary analyses of ROSMAP 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 ROSMAP Cohort. Participants were excluded who had recent TBI (e.g. < 1 year), which we performed because falls can accompany dementing illness itself and thus confound cause-and-effect.

Patients with history of mild TBI converting to abnormal cognition (N=24)	Upper 25%ile (N=6)	Lower 25%ile (N=6)
Average age converting from normal to abnormal cognition (mean +/- standard deviation)	81 (7.6)	86 (8.2)
Sex (female/total)	4/6	4/6
Education (years)	18.3	17.8
Total number of visits (mean)	10	7.7
Non-APOE Polygenic Hazard Score (mean +/- standard deviation)	0.73 (0.14)	-0.67 (0.42)

Note that, for sex- and education-matched control participants (e.g. those participants without a history of head trauma or concussion), the mean age of converting from normal to abnormal cognition was 84 for the upper quartile and 87 for the lower quartile. These results support prior data that mild TBI decrease the age of onset of cognitive impairment. The increased gap in age-of-onset for cognitive impairment in the concussion group compared to the non-concussion group (5 years versus 3 year difference between upper and lower quartiles) supports our premise that Alzheimer's disease genetic risk, represented by the PHS, has a larger impact in TBI compared to non-TBI patients in decreasing the age-of-onset for cognitive impairment.

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 gaining approval, calculation of preliminary PHS for NACC, final calculation of PHS of ROSMAP, and preliminary ROSMAP data analysis. During the next reporting period goal, we plan on finalizing the PHS calculation for NACC patients and then performing the full, final analysis within ROSMAP and NACC of to understanding how Alzheimer's disease genetic risk (represented by the PHS) impacts dementia age-of-onset in patients with and without a history of traumatic brain injury history. 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 ROSMAP with what we find after final calculation of PHS within the NACC database. Should our preliminary data reflect what we find in the total analysis, this will be the first study to measure 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, 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.

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.

7. Participants & Other Collaborating Organizations

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

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 encountered administrative delays in establishing this 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