Investigating The Genetic Links Between Alzheimer's Disease And Cancer

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Background & Motivation

- There has been evidence in recent years of an inverse relationship between Alzheimer's disease (AD) and cancer, but whether the relation is causal, and if so, the precise causal mechanisms, are still unknown.
- Polygenic risk scores (PRS) are useful for disease genetic risk prediction and the colocalization approach is helpful for bidirectional causation.
- In this study, we will use pathway-specific PRS Analysis and colocalization analysis to discover pathways and overlapping loci that may be causally involved in the inverse relationship between AD and cancer.

Research Hypotheses and Aims

- We hypothesize (1) causal genetic variants contribute to the inverse relationship between AD and cancer; (2) specific types of cancer are negatively associated with AD pathogenesis; (3) specific biological pathways and genes are responsible for the inverse relationship.
- Therefore, we will carry out the following specific aims:

(1) To calculate PRSs to identify which biological pathways are involved in the inverse relationship

(2) To identify shared loci that are possibly functional for both AD and cancer

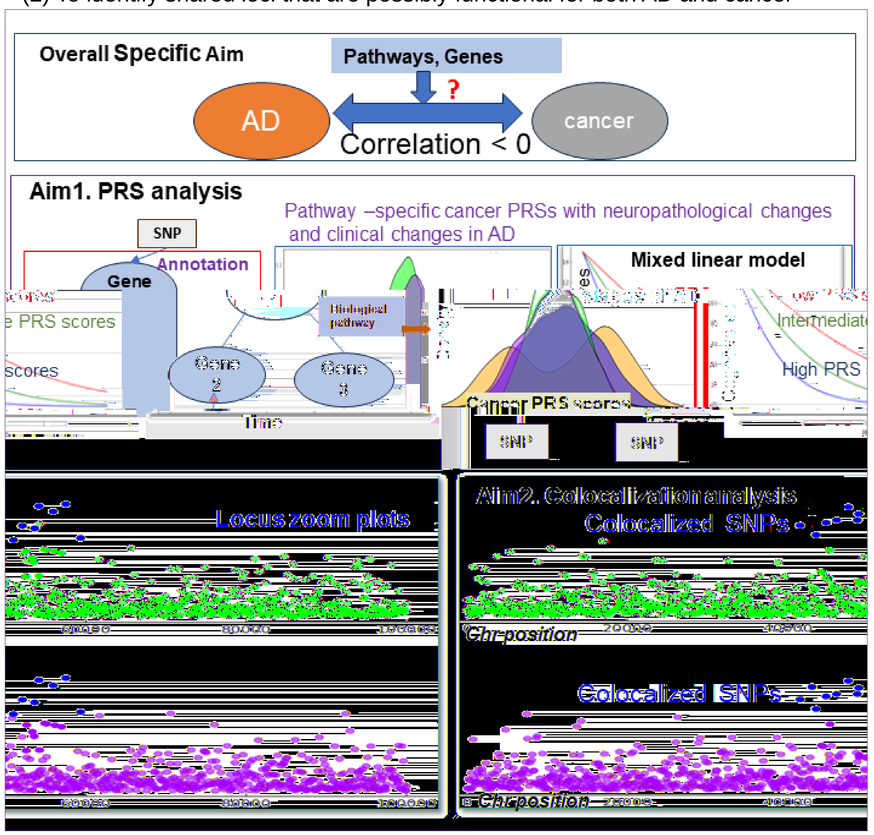

Fig 1. Flow chart of research aims and hypotheses

Materials & Methods

- Hypotheses will be tested using

a. the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and Neuropathology (NP) Data Set linked with whole genome sequencing (WGS) data in the Alzheimer's Disease Sequencing Project (ADSP) and

b. cancer-related summary statistics based on the results from the United Kingdom (UK) Biobank.

For Aim1

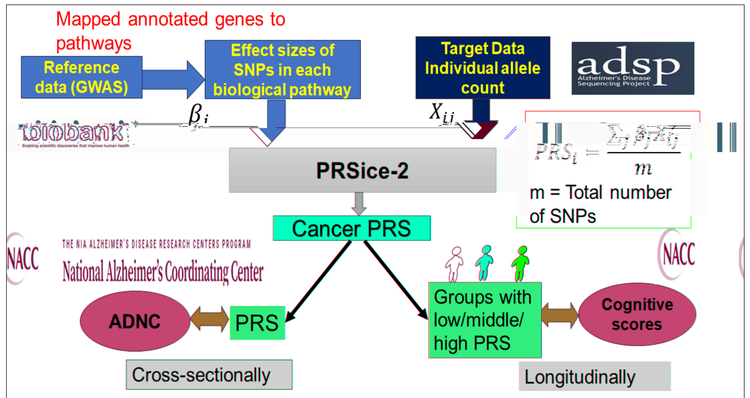

Fig. 2. Flow chart for pathway-specific polygenic risk score analysis

For Aim2

- We will perform Bayesian colocalization analyses using two summary statistics.
- The summary statistics related to AD will be generated by the NACC UDS and NP data and ADSP WGS.
- We will evaluate colocalizations in each combination between clinically diagnosed and autopsy-confirmed AD and each type of cancer of interest.

Results

- As preliminary results, we computed total PRS using the Alzheimer's Disease Genetic Consortium (ADGC) genotype data and UK Biobank summary statistics for five cancers (colorectal, breast, liver, lung, and prostate).
- We then compared the MMSE score changes between three groups based on cancer PRS (low, moderate, and high) using a linear mixed effects model (Fig.3), and no significant relationship was found between the three groups of total cancer PRS and MMSE scores over the time.

This study is supported by P01AG078116 and P30AG072946

Results

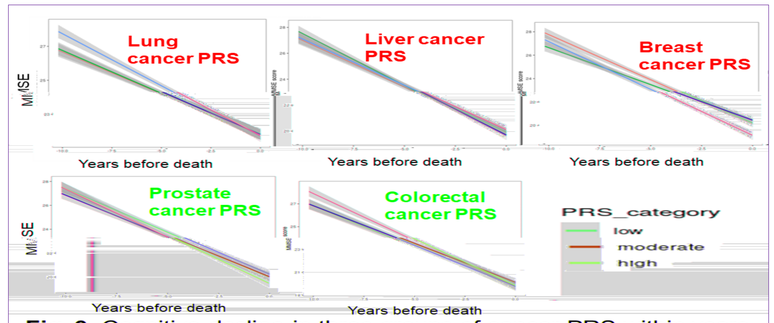

Fig. 3. Cognitive decline in three groups of cancer PRS within years before death

- However, another preliminary result in our study using pathway-specific cancer PRS with AD showed that individuals with higher biological pathway-specific cancer PRS were less likely to have AD/dementia-related traits.
- The most significant biological processes include cell cycle pathways, angiogenesis, and neurodevelopmental pathways (**Table 1**).
- Angiogenesis and atherosclerosis pathways are also important in TDP-43 and cerebrovascular diseases, respectively.

Table 1. Significant biological processes from preliminary analysis of cancer PRS scores with Alzheimer's disease neuropathologic changes

Traits	Biological pathways	Neuropathology
Prostate	Regulation of cyclin-dependent protein serine/threonine kinase activity	Neuritic plaques (C score)
Prostate	G1/S transition of mitotic cell cycle	Neuritic plaques (C score)
Breast	Angiogenesis	Atherosclerosis
Breast	Signal transduction	TDP-43 pathology
Liver	Apoptotic process	Braak stage (B score)
Liver	Apoptotic signaling pathway	Braak stage (B score)
Lung	Chromatin organization	Braak stage (B score)
Lung	Memory biological process	Neuritic plaques (C score)
Colorectal	Hippocampus development	Neuritic plaques (C score)
Colorectal	Hemopoiesis	Neuritic plaques (C score)

Discussion & Conclusion

- While selection and survival bias cannot be completely ruled out, disruptions of specific biological pathways may contribute to the observed inverse relationship between cancer and AD.
- We also expect to identify shared genetic loci to reveal biological underpinnings from colocalization analysis and details of specific biological pathways from PRS analysis using whole genome sequencing data.
- The implications of the study results could identify pathways and genetic factors that could pave the way for future studies to explore detailed risk assessment and breakthroughs in precision treatment for patients at risk of AD, cancer, or both.