2026 IMPACT CIRCLE

Project Title: Genetic risk for synapse decline in Alzheimer's disease and related dementias

Investigator: Tara Tracy, PhD

Unmet Need/Primary Question

People with diseases involving the protein tau, such as Alzheimer's disease, often experience memory and thinking problems. However, some individuals remain mentally sharp for longer than expected, even when tau builds up in their brains. Understanding why some people are more resilient to tau-related brain damage could help us to identify individuals who are at higher risk for Alzheimer's disease and to develop treatments that protect the brain.

Research from our group and others suggests that the health and function of synapses—the connections that allow brain cells to communicate—may play a key role in this resilience. Strong synaptic connections may help the brain continue to function even when harmful tau is present. What scientists do not yet understand is how genetic differences between people interact with synapse biology to protect these connections and slow cognitive decline. This gap in knowledge limits our ability to understand how resilience works at a biological level.

In this project, we will address this challenge by combining genetic, molecular, and cellular studies to understand how variations in the KIBRA gene influence synapse function and help the brain remain resilient to tau-related disease.

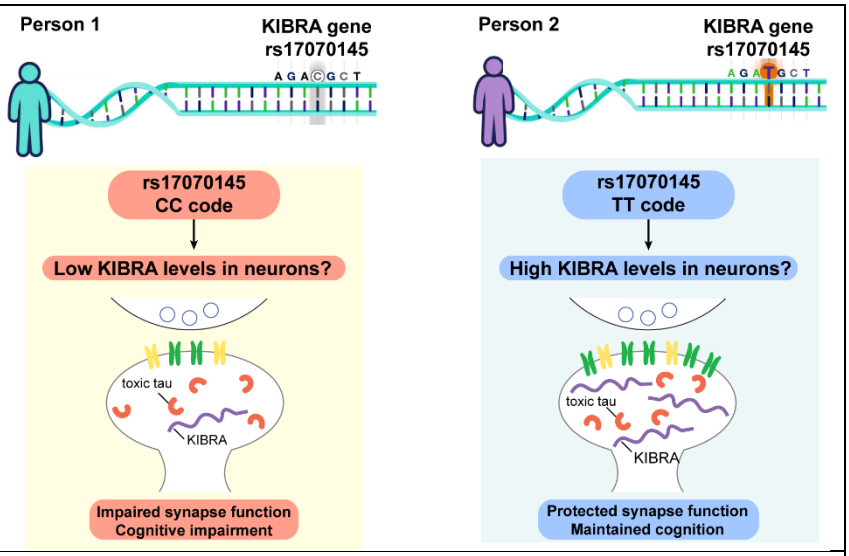
Novel Hypothesis: We hypothesize that a single variant in the gene for KIBRA regulates a person's susceptibility to synapse decline and cognitive impairment in Alzheimer's disease.

Project Proposal

A small genetic difference in the gene for KIBRA, called rs17070145, has been linked to memory and brain health. This genetic variation involves a single change in DNA, where one building block (T) can be replaced by another (C). Large genetic studies have shown that people who carry at least one T version of this variant tend to maintain better memory as they age. In contrast, people with two C versions (CC code) have a higher risk of developing late-onset Alzheimer's disease and may experience greater declines in thinking abilities over time. This suggests that the T version may help protect brain function.

The C version of this variant is very common, which means understanding how it affects the brain could have a major impact on public health. Although many studies have found links between this genetic variant and memory, these studies only show associations, meaning they cannot prove that the variant directly causes differences in brain function. They also cannot explain how

this genetic change affects neurons, the cells that allow the brain to process information. The biological role of this genetic variant in neurons and at synapses remains unknown. In this project, we will address this important gap in our knowledge by studying the rs17070145 variant directly in human neuron models of Alzheimer's disease and related dementias. This approach will allow us to determine how this genetic difference directly affects synapses and how it influences susceptibility to or protection against Alzheimer's disease related brain dysfunction.



Summary of our model: We hypothesize that Person 1 with the CC code in rs17070145 may have lower levels of KIBRA at synapses making them more vulnerable to synapse dysfunction leading to Alzheimer's disease. On the other hand, Person 2 with the TT code in rs17070145 may have higher levels of KIBRA at synapses which could make them protected against toxic tau proteins that accumulate in the brain in Alzheimer's disease.

Description of Potential Impact:

This project has the potential to transform how we understand and ultimately treat Alzheimer's disease and related dementias by identifying a concrete biological link between genetic risk and synapse health. By directly testing how the KIBRA rs17070145 variant affects human neurons, this work could reveal a causal mechanism underlying resilience or vulnerability to cognitive decline. Because the risk-associated C allele is highly prevalent in the population, even modest effects on synapse function could translate into substantial public health impact. Defining how this variant influences synaptic stability and function may also enable earlier identification of individuals at greatest risk for decline, opening the door to more precise patient stratification in clinical trials and, eventually, in clinical care.

More broadly, this project could shift the field toward targeting synapse dysfunction as a central and actionable driver of disease progression. If KIBRA-mediated pathways are shown to protect synapses from tau-related damage, they would represent promising targets for therapeutic development aimed at preserving or restoring cognitive function. Such approaches could complement existing strategies that focus on reducing tau or amyloid-β in the brain, addressing a critical gap in current treatment paradigms. Ultimately, uncovering genetic mechanisms of synaptic resilience could guide the development of first-in-class therapies that slow or prevent cognitive decline, with implications extending across multiple neurodegenerative diseases even beyond Alzheimer's disease.