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UM Researchers Head $18.8 Million NIH Grant to Discover How Race and Ethnicity Impact Alzheimer's Risk, Prevention

Scientists with the John P. Hussman Institute for Human Genomics at the University of Miami Miller School of Medicine are leading research to uncover how Alzheimer’s disease risk differs among races and ethnicities. Their goal is to analyze large amounts of available data to identify genetic targets for preventing progression of the neurological disease in diverse, at-risk populations.

Armed with an $18.8 million, five-year grant from the National Institute on Aging (NIA), principal investigator Jeffery M. Vance, M.D., Ph.D., professor of human genetics and neurology at the Miller School, is leading the Additional Sequencing for the Alzheimer's Disease Sequencing Project. Preventing Alzheimer’s disease progression before memory problems occur is an important focus of the research.

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“Rare variants are one of the real interests people have for looking at protective factors,” Dr. Vance said. “We’re not only looking for genetic changes that increase Alzheimer’s disease risk, we’re also looking at genetic changes that reduce risk. These are rare but tend to be good targets for prevention.”

The aim of the “Additional Sequencing for the Alzheimer's Disease Sequencing Project (ADSP),” also known as the ADSP follow-up studies (ADSP-FUS), is to harness information from existing clinical and genetic data with a focus on underserved and ethnically diverse populations. Hussman Institute researchers are funded to coordinate, adjudicate, blend or “harmonize,” and perform quality control metrics on phenotypic and sequencing data for more than 60,000 individuals from many diverse populations in an effort to develop globally applicable therapies and preventions.

Dr. Vance’s co-principal investigators at the Hussman Institute include Michael Cuccaro, Ph.D., associate professor of human genetics and psychology; and Brian Kunkle, Ph.D., a research assistant professor and head of the Genetic Epidemiology Division in the Center for Genetic Epidemiology and Statistical Genetics (CGESG) at the Hussman Institute.

HIHG Director Margaret A. Pericak-Vance, Ph.D., is overseeing the overall ADSP-FUS effort for the National Institute on Aging, and Eden Martin, Ph.D., director of CGESG, is

overseeing quality control of the ADSP-FUS sequencing data. Miller School researchers are working on the project with Columbia University, the University of Pennsylvania and Uniformed Services University Health System researchers.

Examining Data to Prevent Alzheimer's Progression

Hussman Institute researchers have long been at the forefront of studying Alzheimer's disease genetics in populations of people, including Caucasians, African Americans, and Hispanics, as well as smaller contained populations, such as the Amish. They led an international collaboration of the largest ever Alzheimer's disease study of more than 94,000 individuals and published their results last year in the journal *Nature Genetics*.

Studies show that races and ethnicities differ genetically based on their ancestral backgrounds when it comes to Alzheimer's disease risk. And within races, there are many influences that also impact whether a person will develop Alzheimer's disease.

Over the past several years, research has shown that the genetic contributions to Alzheimer's disease differ significantly among different populations. For example, the apolipoprotein e4 allele (*ApoE4*) is the major genetic risk factor for Alzheimer's disease in European and Asian populations but confers much less risk for the disease in Africans and African Americans, according to Dr. Pericak-Vance, who in 1993 discovered the first association of *ApoE4* to late-onset Alzheimer's disease. *ApoE4* remains the most important known Alzheimer's risk factor today.

In African Americans, researchers at the Hussman Institute and their collaborators showed that another gene, adenosine triphosphate-binding cassette, subfamily A, member 7 (*ABCA7*), has a similar effect on risk for Alzheimer's disease as does *ApoE4* in individuals of African ancestry. The risk for *ABCA7* and Alzhiemer's disease in the European population is much less compared with African American risk. These examples demonstrate the importance of including different ancestries in research, as each population has unique risks for Alzheimer's disease that must be known as scientists translate these findings to treatment and prevention, the ultimate goal of genetic studies.

"The ADSP-FUS aims to sequence people of all backgrounds in the U.S., taking into account the many ancestral diversities that exist in order to develop therapies that will be applicable to all," Dr. Pericak-Vance said.

The ADSP-FUS studies use datasets that already exist, including those with valuable cognitive data, collected DNA and even positron emission tomography (PET) brain imaging.

The current ADSP grant focuses on collecting clinical data and sequencing data on three groups: Hispanic/Latino populations who have been seen at NIA-funded Alzheimer's disease centers, including 1Florida ADRC, which the Miller School helps lead.

"The second group is a really interesting group from the Faroe Islands, which are north of Scotland. About 50,000 people live there," Dr. Vance said. "The important point is that this population, like the Amish, is a contained population which facilitates finding changes that occur in the genome."

The third group is from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, which has data, including PET images, on more than 1,100 people at risk for memory loss due to Alzheimer's but who had not yet experienced symptoms.

Dr. Vance is the corresponding principal investigator for the grant. Dr. Cuccaro is leading the effort to statistically harmonize studies that use different measures, so investigators can use all of the rich data for meaningful genetic analyses.

"Each of the datasets included has a variety of clinical-phenotype measures that they collect and use to characterize their participants, such as measures of cognition, vascular risk, etc. Information from these measures is crucial to helping understand the genetic data," Dr. Cuccaro said. "For instance, we can examine the relationship of genetic information and different patterns of cognitive performance, thus providing clues as to the role of specific genes in generating certain outcomes. This could inform efforts to develop much needed precision medicine strategies for Alzheimer's disease."

Dr. Kunkle is a leader on the NIA Alzheimer's Disease Gene Verification Committee that verifies the best gene candidates for follow-up. The genetic data from this grant will increase the diversity of populations needed to define the best gene candidates in the ADSP Gene Verification Committee.

"This will allow for more confidence in risk genes and biological mechanisms that overlap among populations and will also allow for discovery and assessment of additional gene candidates that may be specific to certain populations," Dr.

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Kunkle said. “Ultimately, these data will increase the Gene Verification Committee’s ability to identify the most promising genes for further assessment as therapeutic targets by the broader scientific community.”