Staff Writer
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Hussman Institute for Human Genomics Researchers Identify Novel Alzheimer's Disease Risk Pathways in African Americans

Alzheimer's disease is a major health concern in the U.S. – more than 5 million adults are impacted by the disease. It's the most common form of dementia and the sixth leading cause of death. Inherited factors are known to affect people's risk for developing the disease. But these factors can differ among individuals based on their ancestral backgrounds, which often have different genetic risks.

It's essential to identify the genetic factors that define these different disease risks across groups because they can offer critical insights into Alzheimer's disease etiology. It can give us a better understanding of the disease causes that are the same across populations versus those that are different and thus provide critical information to develop novel therapeutic measures that will benefit all. Unfortunately, in the United States, African Americans and Hispanics are often underrepresented in genomic studies.

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African Americans from the same community as non-Hispanic whites are approximately twice as likely to develop Alzheimer's disease. Despite this disparity, most Alzheimer's disease genetic studies – called Genome-Wide Association Studies (GWAS) – have been conducted in non-Hispanic whites. The studies aim to identify genetic factors for disease by searching an individual's genetic makeup for small variations that occur more (or less) frequently in people with a particular disease than in people without the disease. Each study can look at millions of variations simultaneously. Researchers use GWAS data to pinpoint genes that may contribute to a person's risk of developing a certain disease.

A group of researchers is determined to narrow the research gap in racially and ethnically diverse populations – and they recently led the largest GWAS on Alzheimer's disease in African Americans to date. The study, which combines and analyzes data collected from 8,006 African Americans (2,784 Alzheimer's disease patients and 5,222 unrelated cognitively intact controls), was published in the *Journal of the American Medical Association (JAMA) Neurology* on October 19.

The researchers include Brian Kunkle, Ph.D., M.P.H., a research assistant professor in the John P. Hussman Institute for Human Genomics (HIHG) and the Dr. John T. Macdonald Foundation Department of Human Genetics at the University of Miami Miller School of Medicine; Margaret A. Pericak-Vance,

Ph.D., director of the HIHG and Dr. John T. Macdonald Foundation Professor of Human Genetics; Christiane Reitz, M.D., Ph.D., assistant professor of neurology and epidemiology in the Gertrude H. Sergievsky Center and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University; and Richard Mayeux, M.D., M.Sc., Gertrude H. Sergievsky Professor of Neurology, Psychiatry and Epidemiology (in the Gertrude H. Sergievsky Center) and co-director of the Taub Institute.

Previously, the team connected the *APOE*, *ABCA7*, and *TREM2* genes, which are involved in lipid processing and immune response, as Alzheimer's risk loci in African Americans. These genes have also been found to increase risk in non-Hispanic white populations. The current study significantly increased the number of participants, allowing researchers to identify several new genetic risk factors for Alzheimer's disease in African Americans. These novel risk factors confirm immunity and lipid processing as important processes and implicate neuronal transport and processing pathways. Finding these new genes and the biological functions (pathways) they control provides for greater insights into the causes of Alzheimer's and allows for their targeting by clinicians with therapeutic interventions in the future.

While the major pathways involved in the origins of Alzheimer's disease in African Americans are similar to those in non-Hispanic whites, the authors note that many of the specific disease-associated genetic risk factors within these pathways are different among populations and could be important for developing population-specific therapeutics.

"These findings support the importance of studying Alzheimer's

in all human populations," said Dr. Kunkle, the lead author. "Because genetic risk variants can differ significantly across populations with different ancestries, we have the opportunity to make novel discoveries that will benefit the specific study population and people all across the globe."

The UM HIHG team and their collaborators have long advocated for an inclusive approach to biomedical research. They have implemented engagement and outreach strategies to strengthen the participation of diverse populations in their studies.

"We recognized early on the need to advance community-based participatory efforts to increase understanding of Alzheimer disease and the importance of participation," said Dr. Pericak-Vance. "Only by being inclusive in our approach and including all groups will we be able to develop targeted drug therapies, which would be universally beneficial."

The other collaborators at UM are Michael Schmidt, Ph.D.; Kara L. Hamilton-Nelson, M.P.H.; Melissa Jean-Francois, M.P.H.; Larry D. Adams; Jeffery M. Vance, M.D., Ph.D.; Michael L. Cuccaro, Ph.D.; and Eden R. Martin, Ph.D.

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For more information, or to participate in the African American Alzheimer's disease study, please contact the study's coordinator:

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