Researchers identify novel genetic variants associated with Alzheimer's disease

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Identifying genetic variants and the role they play in predisposing people to Alzheimer's disease can help researchers better understand how to treat the neurodegenerative condition for which there is currently no cure.

A new study led by Boston University School of Public Health (BUSPH)

and UTHealth Houston School of Public Health has identified several genetic variants that may influence Alzheimer's disease risk, putting researchers one step closer to uncovering biological pathways to target for future treatment and prevention.

Published in the journal *Alzheimer's & Dementia*, the study utilized whole genome sequencing and identified 17 significant variants associated with Alzheimer's disease in five genomic regions. This data enables researchers to pinpoint rare and important genes and variants, building upon genome-wide association studies, which focus only on common variants and regions.

The findings underscore the value of whole genome sequencing data in gaining long-sought insight into the ultimate causes and risk factors for Alzheimer's disease, which is the fifth leading cause of death among people 65 and older in the United States. As the most common form of dementia, Alzheimer's disease currently affects more than 6 million Americans and that number is expected to skyrocket to nearly 13 million by 2050.

"Prior genome-wide association studies using common variants have identified regions of the genome, and sometimes genes, that are associated with Alzheimer's disease," says study co-senior author Dr. Anita DeStefano, professor of biostatistics at BUSPH.

"Whole genome sequence data interrogates every base pair in the human genome and can provide more information about which specific genetic change in a region may be contributing to Alzheimer's disease risk or protection."

For the study, the researchers conducted single variant association analyses and rare variant aggregation association tests using whole genome sequencing data from the Alzheimer's Disease Sequencing

Project (ADSP), a genetics initiative that the National Institutes of Health developed in 2012 as part of the National Alzheimer's Project Act's goal to treat and prevent the disease. The ADSP data include more than 95 million variants among 4,567 participants with or without the disease.

Among the 17 significant variants that were linked to Alzheimer's disease, the KAT8 variant was one of the most notable, as it was associated with the disease in both the single and rare variant analyses. The researchers also found associations with several rare TREM2 variants.

"By using whole genome sequencing in a diverse sample, we were able to not only identify novel genetic variants associated with Alzheimer's disease risk in known genetic regions, but also characterize whether the known and novel associations are shared across populations," says study co-lead and corresponding author Dr. Chloé Sarnowski, assistant professor in the Department of Epidemiology at UTHealth Houston School of Public Health.

The ADSP includes ethnically diverse participants, and the population-specific assessments focused on White/European-ancestry, Black/African-American, and Hispanic/Latino subgroups, as well as a multi-population meta-analysis. Historically, Black and and Latino populations have been underrepresented in genetic studies of Alzheimer's disease despite having a higher prevalence of the disease than other ethnic groups.

"Including participants that represent diverse genetic ancestry and diverse environments in terms of social determinants of health is important to understanding the full spectrum of Alzheimer's disease risk, as both the prevalence of the disease and the frequencies of genetic variants can differ among populations," says Dr. DeStefano.

The sample sizes in the population-specific analyses were small, so the team had limited ability to detect associations, she says, "but we replicated known population differences for the APOE gene, which is one of the best-known and strongest risk genes for Alzheimer's disease."

In future studies, the researchers hope to examine the population-specific variants they identified in much larger sample sizes, as well as explore how these variants affect biological functioning.

"We are currently working on expanding this research to be able to use whole genome sequencing with larger sample sizes in the ADSP to be able to look at the full array of genetic variants, not only within known Alzheimer's disease genetic regions, but across the whole genome," says co-senior author Dr. Gina Peloso, associate professor of biostatistics at BUSPH.

The study was also co-led by Yanbing Wang while she was a Ph.D. student in biostatistics at BUSPH.

More information: Key variants via the Alzheimer's Disease Sequencing Project whole genome sequence data, *Alzheimer's & Dementia* (2024). DOI: 10.1002/alz.13705

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