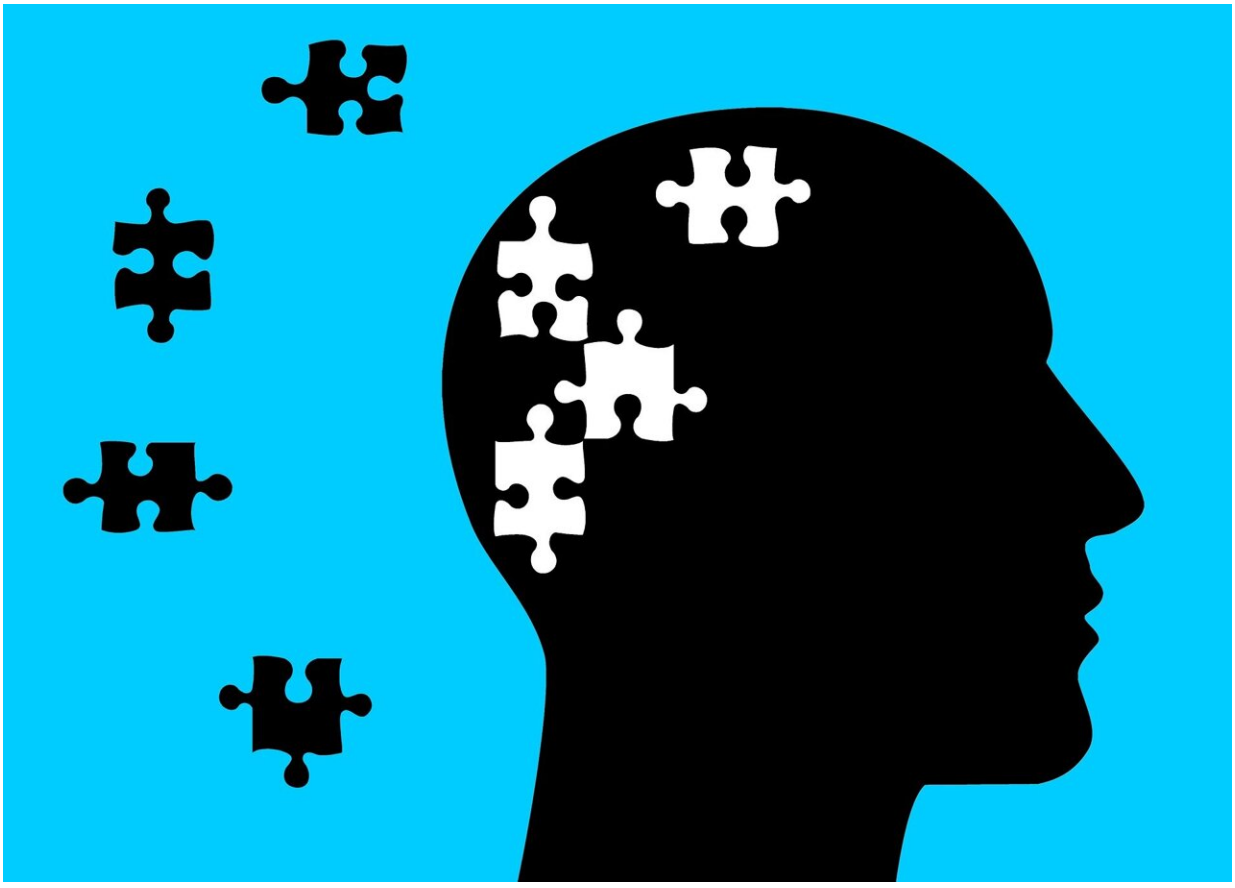
New study reveals dementia risks unique to people with African ancestry

December 22 2022



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In the largest-ever genetic study of dementia in people of African ancestry, VA researchers identified several genetic risks different from

those seen in people of European ancestry.

By using data from the VA Million Veteran Program (MVP), the team found multiple instances where gene variants may raise the risk of Alzheimer's disease and related dementias.

The findings appear in the December 22, 2022, issue of *Molecular Psychiatry*.

"MVP represents an incredible resource for examining the genetics of many diseases, including dementia," said study author Dr. Mark Logue, a statistician with the VA Boston Healthcare System and National Center for PTSD. "This study is one of the first Alzheimer's-disease-related studies to come out of MVP. My colleagues and I are working hard to ramp up dementia work in MVP and to team up with other large-scale Alzheimer's disease and dementia studies.

"The results signify a substantial increase in the knowledge of the genetic architecture of dementia risk in African ancestry populations," Logue said.

People of African descent and other minority groups are historically underrepresented in genetic research, which is why this study represents an important milestone, according to the research team.

In the United States, a greater proportion of African Americans have Alzheimer's disease than people of European ancestry; however, most large genetic studies of Alzheimer's disease study white participants. While there are genes implicated in Alzheimer's that are consistent across different populations, the researchers explained in the study that specific variants may differ by ancestry. That means study results using only one ethnic group may not apply to other groups, hindering dementia prevention and treatment. For example, studies have found that a gene

variant called APOE E4 carries the largest genetic risk for Alzheimer's disease in people with European ancestry, but the effect of APOE E4 is half as strong in people of African ancestry.

Increasing the representation of non-European ancestry populations in genome-wide association studies has been identified as a critical scientific and equity issue in genetic studies. The difference in sample sizes between European ancestry and non-European ancestry studies to date could even contribute to health disparities in minority populations, according to the study.

To address this disparity, Boston VA researchers compared the genomes of more than 4,000 MVP participants of African ancestry who had dementia with more than 18,000 veterans without dementia. The team also conducted a second analysis comparing 7,000 black MVP participants who reported that their parents had dementia with 56,000 others whose parents didn't have dementia. This sample is more than twice the size of the previous largest Alzheimer's genetic study of individuals of African ancestry.

The results showed an association between dementia risk and variants in six different genes, including APOE. While many of these genes have been linked to dementia in past genetic studies of people with European ancestry, only two of them had been identified as significant risk factors in people with African ancestry.

While many of the genetic variants identified in this study were linked to dementia in groups, the particular gene variants linked to dementia risk were different between people of African and European ancestry, meaning that different forms of the same gene may affect a person's dementia risk based on their race.

These new findings will help close the gap in knowledge of Alzheimer's

risk based on ancestry, the researchers said. Identifying population-specific genetic risk factors will lead to more accurate risk assessment in people of African ancestry and could also reveal new molecular targets to develop medications to treat Alzheimer's disease.

With over 900,000 participants to date, MVP is one of the world's largest genetic research programs. MVP researchers collect genetic data in addition to information on health, lifestyle, and military exposures to understand how genes affect health and illness.

MVP is also one of the most diverse genetic programs in the world. More than 150,000 African American veterans have volunteered to join MVP, making up 18% of all participants. This means MVP includes more people of African ancestry than any other biobank in the world. Thanks to its diversity and the altruism of the veterans who participate, MVP is working to close the racial gap in the link between genetics and disease.

"The sheer size of MVP as one of the world's largest genetic databases means that it can really push forward what is known about how genes influence dementia risk," Logue said. "Working on MVP data is an exciting opportunity for a researcher like me, and I'm grateful to all of the veterans who agreed to be in this study."

More information: African ancestry GWAS of dementia in a large military cohort identifies significant risk loci, *Molecular Psychiatry* (2022). DOI: 10.1038/s41380-022-01890-3

Provided by Veterans Affairs Research Communications

December 22) retrieved 18 February 2023 from https://medicalxpress.com/news/2022-12-reveals-dementia-unique-people-african.html