ABCA7 gene associated with almost doubled Alzheimer's risk in African-Americans

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African-Americans with a variant of the ABCA7 gene have almost double the risk of developing late-onset Alzheimer's disease compared with African-Americans who lack the variant. The largest genome-wide search for Alzheimer's genes in the African-American community, the study was undertaken by the Alzheimer's Disease Genetics Consortium and led by neurologists from Columbia University Medical Center. It will be published in the April 10 issue of the *Journal of the American Medical Association*. The study was primarily funded by the National Institutes of Health (NIH).

"Our findings strongly suggest that ABCA7 is a definitive genetic risk factor for Alzheimer's disease among African-Americans," said study senior author, Richard Mayeux, MD, MS, professor and chair of Neurology at CUMC. "Until now, data on the genetics of Alzheimer's in this patient population have been extremely limited."

The ABCA7 gene is involved in the production of cholesterol and lipids, which suggests that lipid metabolism may be a more important pathway in Alzheimer's disease in African-Americans than in whites. Because cholesterol and lipid imbalances (which eventually lead to vascular disease and heart attacks and strokes) are more common in African-Americans, treatments that reduce cholesterol and vascular disease may potentially be an effective way to reduce or delay Alzheimer's in this population.

"While we need to conduct research to determine whether reducing

cholesterol will lower the chance of Alzheimer's in African-Americans, maintaining healthy cholesterol levels always has the benefit of lowering one's risk of heart attack and stroke," said Dr. Mayeux.

The study involved nearly 6,000 African-American participants, most of whom are volunteers from 18 NIH-funded Alzheimer's Disease Centers. The Centers and other researchers contributed samples to the Alzheimer's Disease Genetics Consortium, an NIH-supported research program led by Gerard D. Schellenberg, PhD, at the University of Pennsylvania. Approximately 2,000 of the volunteers were diagnosed with probable Alzheimer's disease and 4,000 were cognitively normal. The purpose of the study was to look for genetic variants among African-Americans, who are known to have a higher incidence of late-onset Alzheimer's than whites living in the same community. Ninety percent of all cases of Alzheimer's, which affect an estimated 5 million Americans aged 65 and older, are described as having the late-onset form of the disease.

"ABCA7 is the first major gene implicated in late-onset Alzheimer's among African Americans, and it has an effect on disease risk comparable to that of APOE-e4—which has been known for two decades to be a major genetic risk factor in whites," said Christiane Reitz, MD, PhD, assistant professor of neurology, who conducted the study's genetic analyses as first author on the paper. "Both genes raise the risk of Alzheimer's in this population twofold." The extent of the role of APOE-e4 in African-Americans had been uncertain because of inconsistent results from previous, smaller studies.

"Based on these results, we now know that both APOE-e4 and ABCA7 are major genetic risk factors for African-Americans, whereas for whites, only one of the two—APOE-e4—confers a similar degree of risk," said Dr. Mayeux, who is also co-director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain and the Gertrude

H. Sergievsky Center at CUMC. He is the Gertrude H. Sergievsky Professor of Neurology, Psychiatry and Epidemiology.

Several other genes that had recently been linked to Alzheimer's in white populations were also confirmed in the current study to play a role in African-Americans. "Because they cross ethnic groups, the likelihood increases that these genes are very important in the development of Alzheimer's," said Dr. Reitz, who is a member of both the Sergievsky Center and the Taub Institute. "And that gives us clues in our search for the cellular pathways associated with the disease."

"These findings suggest that the genetic underpinnings of Alzheimer's disease may vary among different populations—and so should not be treated homogeneously," said Dr. Reitz.

"One of the key research goals set forth in the National Alzheimer's Project Act of 2011 is to improve outcomes for ethnic and racial minority populations that are at higher risk for this devastating disease," said Neil Buckholtz, PhD, of the National Institute on Aging, which leads the NIH effort to find ways to treat, delay or prevent Alzheimer's. "These findings advance our understanding of genetic underpinnings that may play a role in disease onset and progression in African-Americans and suggest a novel target for therapeutic development."

ABCA7 also affects the transport of several important proteins, including amyloid precursor protein, which is involved in the production of amyloid—the major source of the plaques that develop in the brains of Alzheimer's patients. Thus, there are multiple ways that ABCA7 might contribute to an increased risk of late-onset Alzheimer's disease among African-Americans.

The most immediate impact of the new findings will be for scientists studying the causes of Alzheimer's and ways to prevent the disease. "Our

next step is to do more lab work and more genetic sequencing, to understand the biological reasons for the increased risk seen with ABCA7 and other genes implicated in late-onset Alzheimer's disease," said Dr. Mayeux.

While the study's discoveries may eventually lead to the development of genetic risk estimates specific to African-Americans, Dr. Mayeux cautions that the utility of genetic testing for Alzheimer's is still years away. "We are not yet at the point where we can take what we know about Alzheimer's genes and come up with an accurate risk assessment," he said.

The study's findings also must be replicated in independent groups of African-Americans.

"The participant data pooled together for this analysis basically represented all of the African-American samples from well-characterized individuals in the United States," said Dr. Buckholtz. "Because large sample sizes are needed to conduct reliable genetic analyses, it is vitally important that African-Americans and people of other racial/ethnic groups participate in genetic studies supported by NIA." He noted that broad collaboration and data-sharing efforts among researchers make such studies possible.

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