Novel gene for Alzheimer's disease in women identified

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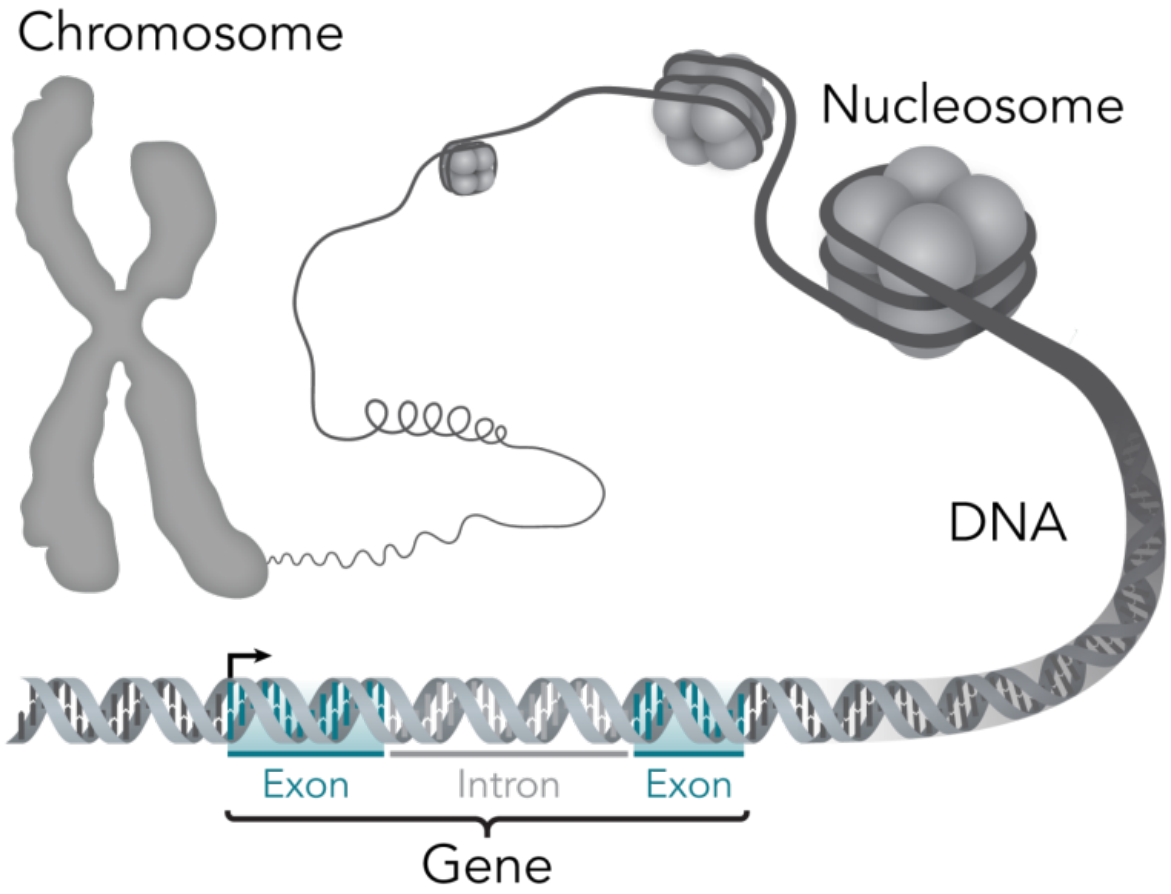

This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, affecting more than 5.8 million individuals in the U.S. Scientists have discovered some genetic variants that increase the risk for developing Alzheimer's; the most well-known of these for people over the age of 65 is the APOE ε4 allele. Approximately 60 percent of people from European ancestry with Alzheimer's carry this genetic variant, compared to just 26 percent of the general population, implying that other genes contribute to the genetic makeup of the disease.

In a new study published this week in *Alzheimer's Disease & Dementia: The Journal of the Alzheimer's Association*, researchers at the University of Chicago and Boston University School of Medicine (BUSM) have identified a new gene called MGMT that increases the risk of Alzheimer's in women.

The researchers conducted a genome-wide association study (GWAS) for Alzheimer's in two independent datasets using different methods. One approach focused on dementia in a large extended family of Hutterites, a founder population of central European ancestry who settled in the mid-west region of the country. Hutterites are often studied for genetic determinants of disease because they have a relatively small gene pool due to their isolated, insular culture. In this study, the individuals with Alzheimer's were all women. The second approach, predicated on evidence suggesting a link between Alzheimer's and breast cancer, analyzed genetic data from a national group of 10,340 women who lacked APOE ε4. In both datasets, MGMT was significantly associated with developing AD.

"This is one of a few and perhaps the strongest associations of a genetic risk factor for Alzheimer's that is specific to women," said Lindsay Farrer, Ph.D., chief of biomedical genetics at BUSM and a senior author of the study. "This finding is particularly robust because it was discovered independently in two distinct populations using different approaches. While the finding in the large dataset was most pronounced in women who don't have APOE ε4, the Hutterite sample was too small to evaluate this pattern with any certainty."

The researchers then further evaluated MGMT using multiple types of molecular data and other AD-related traits derived from human brain tissue. After thorough analysis, they found that that epigenetically regulated gene expression (i.e., one of the ways cells control gene activity without changing the DNA sequence) of MGMT, which has a role in repairing DNA damage, is significantly associated with the development of the hallmark AD proteins, amyloid-β and tau, especially in women.

"This study highlighted the value of founder populations for genetic mapping studies of diseases like Alzheimer's," said Carole Ober, Ph.D., Chair of Human Genetics at UChicago and a senior author of the study. "The relatively uniform environment and reduced genetic variation in Hutterites increases our power to find associations in smaller sample sizes than required for studies in the general population. The validation of our findings in the larger dataset used by the Boston University group was enormously gratifying and ultimately led to supportive epigenetic mechanisms that connected both sets of GWAS results to the MGMT gene."

According to the researchers, this study demonstrates the importance of searching for genetic risk factors for AD that may be specific to one gender. Further studies are needed to understand why MGMT influences AD risk greater in women than men.

More information: Genome-wide association and multi-omics studies identify MGMT as a novel risk gene for Alzheimer's disease among women, *Alzheimer's Disease & Dementia* (2022).

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