Rare gene variants double risk for Alzheimer's disease

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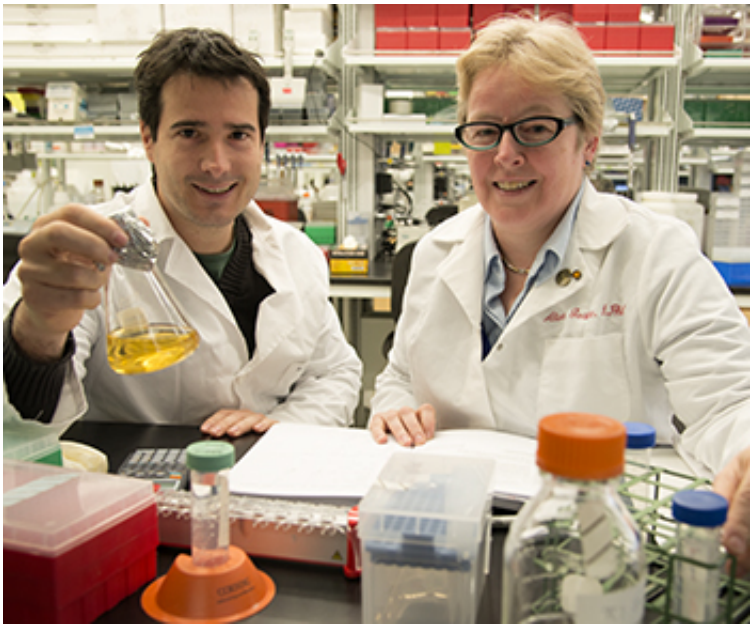

Carlos Cruchaga, Ph.D., (left) and Alison M. Goate, D.Phil., led a research effort that has identified rare variations in a gene that double a person's risk of developing Alzheimer's disease later in life. Credit: Robert J. Boston

A team led by researchers at Washington University School of Medicine in St. Louis has identified variations in a gene that doubles a person's risk of developing Alzheimer's disease later in life.

The research is published online Dec. 11 in the journal *Nature*.

Over the past two decades, scientists have discovered a number of common genetic variants linked to early-onset (which strikes before age 65) and the more common late-onset forms of Alzheimer's disease. But those variants account for only a fraction of Alzheimer's cases.

The newly identified variations, found in a gene never before linked to Alzheimer's, occur rarely in the population, making them hard for researchers to identify. But they're important because individuals who carry these variants are at substantially increased risk of the disease.

As part of the new research, the investigators focused on families with several members who had Alzheimer's.

As a practical matter, finding mutations linked to Alzheimer's disease means it may be possible to identify more people at risk years before they develop any symptoms. These patients could be monitored carefully for early signs of Alzheimer's and possibly even get treatments to slow the progression of the disease.

"We were very excited to be able to identify a gene that contains some of these rare variants," said lead author Carlos Cruchaga, PhD. "And we were surprised to find that the effect of the gene was so large. After adjusting for other factors that can influence risk for the disease, we found that people with certain gene variants were twice as likely as those who didn't have the variants to develop Alzheimer's."

As in many genetic studies of Alzheimer's, Cruchaga and his co-investigators analyzed DNA from people in families in which multiple members were affected by the disease.

"That allowed us to identify several families affected by the common mutations in genes we already knew about," Cruchaga explained. "We removed those families from the dataset and focused our efforts on

other families that were affected by Alzheimer's disease but did not have any known genetic variants that had been linked to the disease."

They sequenced all the protein-coding genes from several individuals in each of the 14 families, using a technique called whole exome sequencing. Some of these family members had an Alzheimer's diagnosis but others did not.

The investigators compared DNA from affected individuals in a family to those in the same family who didn't have the disorder. Eventually, they identified two families that carried the same variation in the phospholipase-D 3 gene (PLD3). The variation was present in affected family members but not in the elderly family members who did not have Alzheimer's disease.

"We then studied another 11,000 other people with and without the disease and found that a PLD3 gene variant doubled the risk for Alzheimer's disease," said Cruchaga, an assistant professor in the Department of Psychiatry. "This PLD3 variant, like the recently identified rare variant in the TREM2 gene, appears to confer more risk for Alzheimer's disease than other genes identified by the latest genome-wide association studies."

After the initial exome sequencing, researchers used more detailed sequencing to look closely at the PLD3 gene in another 4,000 people of the same age, some of whom had Alzheimer's disease. This experiment helped them identify additional variants in the gene that increased risk for Alzheimer's, indicating that the PLD3 gene clearly had a role in the development of late-onset Alzheimer's disease.

"The approach we've taken in this project is just as important as the discovery that this gene is involved in Alzheimer's," said co-investigator Alison M. Goate, DPhil. "By studying gene variants within families, we

were able to narrow down the number of variants that might cause disease. If we had been using unrelated individuals, we would not have had the statistical power to find these rare variants."

Additional experiments conducted in the laboratory showed that when the PLD3 gene is active, levels of amyloid-beta decline. This substance aggregates in the brains of Alzheimer's patients to form plaques. When the researchers decreased expression of PLD3, levels of amyloid-beta increased.

"That experiment strongly suggests that PLD3 is influencing Alzheimer's disease risk by regulating the activity of the gene that makes amyloid," said Goate, the Samuel and Mae S. Ludwig Professor of Genetics in Psychiatry.

The researchers don't completely understand how changes in the PLD3 gene are involved in Alzheimer's disease yet.

"Part of the beauty of genetics is that you don't need to know the function of a gene to know that it's involved in a disease," said Goate, also a professor of genetics and co-director of the Hope Center for Neurological Disorders. "But now that we've found that this gene is involved, we need to figure out its precise role in the body and how particular variants contribute to the development of Alzheimer's disease."

More information: Cruchaga C, et al. Rare coding variants in phospholipase D3 (PLD3) confer risk for Alzheimer's disease. *Nature*. Advance Online Publication, Dec 11, 2013.dx.doi.org/10.1038/nature12825