Beyond plaques and tangles: Genetic variation may increase risk of cognitive decline

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A genetic variation in some people may be associated with cognitive decline that can't be explained by deposits of two key proteins associated with Alzheimer's disease, amyloid ? and tau, according to a study published in the September 16, 2020, online issue of *Neurology*, the medical journal of the American Academy of Neurology. The genetic variation leads to alterations in the metabolism of glutathione, an antioxidant, and may be associated with thinning of the cortex of the brain, the study says. The variation is found on the sixth chromosome.

Amyloid is a protein that forms into plaques, while tau is a protein that forms into tangles. Both are found in the brains of people with Alzheimer's disease but also in the brains of older people with normal cognition.

Genetic variations, called single nucleotide polymorphisms, are common and can act as biological markers, helping locate genes that are associated with disease.

"Our study identified one significant single nucleotide polymorphism related to cognitive decline independent of amyloid ? and tau protein deposits in the brain," said study author Yong Jeong, M.D., Ph.D of the Korea Advanced Institute of Science and Technology (KAIST), in Daejeon, South Korea. "We showed that this genetic variation negatively affects thinking and memory skills, partly because it's associated with thinning in the cortex of the brain."

The study involved data from 486 people who all had amyloid ? deposits in the brain, but some had normal thinking and memory skills, some had mild cognitive impairment, and some had Alzheimer's dementia. Researchers used genetic analysis to pinpoint gene variants that were associated with cognitive function independent of amyloid and tau.

The researchers estimated that 5% of the amount of variance in cognitive function was explained by the single nucleotide polymorphisms.

Although the people with the genetic variant had similar amounts of amyloid ? and tau protein deposits in their brains as those without the genetic variation, they performed worse on cognitive tests than those without the genetic variation. On a cognitive test where the highest score is 30, the people with the variant scored an average of 25 points, compared to 27 for those without the variant.

Among those with the variant, 11% had normal cognition, compared to 25% of those without the variant. Forty percent of those with the variant had mild cognitive impairment, compared to 46% of those without the variant; and 49% of those with the variant had Alzheimer's dementia, compared to 29% of those without the variant.

To measure the thickness of each person's brain cortex, a common measure of brain health, researchers looked at brain scans. People who did not have the genetic variation, on average, had a greater cortical thickness than the people who have the genetic variation.

"Deposits of amyloid ? and tau proteins in the brain may be required for a diagnosis of Alzheimer's disease, but the current thinking is that they are not by themselves enough to cause cognitive decline and dementia," Jeong said. "Understanding the genetic mechanisms underlying the development of Alzheimer's may lead to the development of new treatments for this devastating disease."

A limitation of the study is that because only people with certain levels of amyloid ? protein in their brains were included in the study, the sample size was small.

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