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New Insight into the Cause of Common Dementia

Researchers at the Mayo Clinic campus in Florida have found a clue as to how some people develop a form of dementia that affects the brain areas associated with personality, behavior, and language.

In the Nov. 17 online issue of the American Journal of Human Genetics, the scientists write that they discovered a link between two proteins -- progranulin and sortilin -- that might open new avenues for the treatment of Frontotemporal Lobar Degeneration (FTLD), which occurs in the frontal lobe and temporal lobe of the brain. This form of dementia, which is currently untreatable, generally occurs in younger people, compared to other common neuro-degenerative disorders such as Alzheimer's disease.

"We now can look for a direct link between these two proteins and the development of FTLD," says the study's lead author, neuroscientist Rosa Rademakers, Ph.D. "The hope is that if we do find a strong association, it might be possible to manipulate levels of one or both of these proteins therapeutically."

Coincidentally, a research group from Yale University led by Stephen Strittmatter, M.D., Ph.D., has also pinpointed sortilin's association with progranulin -- thus confirming Mayo's results. Their study is being published in Neuron, also on Nov. 17.

FTLD is a family of brain diseases that are believed to share some common molecular features. One is the presence of mutations in the gene that produces tau protein in neurons. The other is mutations in the progranulin gene that Mayo Clinic researchers and their colleagues discovered in 2006. They found that 5 to 10 percent of patients with FTLD have a mutation in this gene, and that these mutations lead to a substantial loss of normal progranulin protein production, and development of FTLD.

The protein made by the progranulin gene is found throughout the body, and performs different functions according to the type of tissue (organ) it is located in. But in the brain, it is believed to support neurons and keep them healthy.

Still, researchers do not really know how normal progranulin protein functions in the brain what other proteins it interacts with and so in this study they sought to uncover clues about progranulin biology by conducting a Genome-Wide Association Study (GWAS).

Based on their previous findings that a simple blood test is able to measure progranulin levels in plasma and could be used to identify patients with progranulin mutations, they tested blood from 518 healthy individuals in a GWAS to look for genetic variants that could explain some of the normal variability of progranulin levels in plasma. They found very strong association with two genetic variants in the same region of chromosome 1 and confirmed this finding in a second group of 495 healthy individuals.

By reviewing the scientific literature, they further ascertained that the same genetic variant found to be associated with plasma progranulin levels also affects the levels of the protein sortilin. Like progranulin, sortilin is found throughout the body and is involved in different tasks. In the brain, it is known to be important for survival of brain neurons.

"So, using a genetic approach, we identified a previously unknown connection between sortilin and progranulin," Dr. Rademakers says.

The researchers then studied the two proteins in cell culture and showed that the amount of sortilin in cells determines how much progranulin is taken inside or remains outside of a cell. "Our study shows that changes in the levels of sortilin result in different levels of progranulin available to cells. Given that we found FTLD patients often have less progranulin than they should, we believe that if you can manipulate levels of progranulin and/or sortilin in the brain, you might have a way to treat this disorder," says Dr. Rademakers.

"Our study and the study led by the Yale researchers describe completely independent and unbiased screens which both identified this protein sortilin as being important in the regulation of progranulin," Dr. Rademakers says. "This obviously opens new avenues for treatment for patients with progranulin mutations and perhaps dementia patients in general."

Researchers from the National Institutes of Health, University College London, the University of British Columbia, and Mayo Clinic in Minnesota also participated in this study.

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