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Researchers find gene that protects against dementia in high-risk individuals

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Neuroscientists had assumed that a mutation in the progranulin gene, which makes the progranulin protein and supports brain neurons, was sufficient to produce a kind of dementia known as frontotemporal lobar degeneration (FTLD). But now an international team of scientists led by researchers at Mayo Clinic's campus in Florida have found another genetic factor they say appears to protect against the disorder in progranulin mutation carriers.

In an article published in the Dec. 22, 2010, issue of Neurology, the medical journal of the American Academy of Neurology, the researchers report that people with a mutated progranulin gene who also inherited two copies of a specific variant of the TMEM106B gene are significantly less likely to develop FTLD or they have their disease onset delayed.

"This was an unexpected but very exciting finding because it suggests that if we could understand what TMEM106B is, and how it and its variants work, this could provide a new avenue for development of an agent that protects against FTLD," says the study's lead author, neuroscientist Rosa Rademakers, Ph.D.

The study was a follow-up to a genome-wide association study led by researchers from the University of Pennsylvania School of Medicine, which included 45 centers around the world and was published in March 2010 in *Nature Genetics*. This study used postmortem brain tissue to pinpoint variation in the TMEM106B gene as a risk factor for FTLD.

What these patients all had in common was that they had lesions of misfolded TDP-43 proteins inside brain neurons. Researchers found that TMEM106B variants also played a role in FTLD patients with a progranulin mutation who invariably have these brain lesions.

"This research was designed to confirm the findings of the earlier study and to expand it to see if TMEM106B could modulate progranulin levels," Dr. Rademakers says. To do this, the researchers looked for the TMEM106B variant in a new set of patients, including 82 FTLD patients who had progranulin mutations, 562 FTLD patients without mutations, as well as a group of 822 healthy controls.

In the group as a whole, they did not see a significant association with TMEM106B, but there was a very significant association between TMEM106B variants and the development of FTLD in individuals with progranulin mutations.

The researchers found that individuals with a progranulin mutation who also inherited two copies of the protective TMEM106B allele did not develop FTLD or developed it at a much later age than is typical, which is normally around age 60, Dr. Rademakers says. "Since progranulin mutation carriers produce 50 percent less progranulin protein, we believe TMEM106B may affect progranulin levels and therefore specifically works in people with progranulin mutations," she says.

In support of their hypothesis, they found that individuals carrying the protective TMEM106B allele have more progranulin in their blood plasma, suggesting that the TMEM106B allele works to increase progranulin protein levels.

"The protective form of TMEM106B leads to higher levels of progranulin in the blood. Whether it also increases the levels of progranulin in the brain has not yet been studied and will be the focus of

our future research," Dr. Rademakers says.

Not only could the beneficial TMEM106B allele be the basis of a novel therapy for individuals with a progranulin mutation, it might also help others who are at risk, for dementia she adds. "Subtle changes in progranulin levels have been linked to an increased risk for the development of FTLD, so now we have an interesting new lead to explore."

Provided by Mayo Clinic