Second genetic risk factor for late-onset Alzheimer's disease found

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Researchers have discovered the second, strong genetic risk factor for developing late-onset Alzheimer's disease, according to a new report in the June 27th issue of the journal *Cell*, a Cell Press publication.

The newly discovered gene, which previously had no known function, is predominantly active in a region of the brain that is hit early in the disease, where it acts as a channel for calcium, they show. Called calcium homeostasis modulator 1 (CALHM1), their evidence shows that different variants of the gene also influence the levels of amyloid-ß peptides. Those peptides make up the plaques that form in the brains of those with Alzheimer's.

"We are very excited about the idea that CALHM1 could be an important target for anti-amyloid therapy in Alzheimer's disease," said Philippe Marambaud of The Feinstein Institute for Medical Research and Albert Einstein College of Medicine. CALHM1's presence at the cell surface should ease the process of drug design, he explained. And because its activity is restricted to the brain, drugs aimed at CALHM1 are less likely to have peripheral side effects.

The possibility for side effects is a "big question mark" for other drugs now under clinical study, Marambaud said. Those drugs primarily target enzymes responsible for producing amyloid-ß peptides, he noted, but those enzymes are also found in other parts of the body.

The new findings come just as another group has reported the

identification of an imbalance of calcium in early-onset Alzheimer's disease, linked to a calcium release ion channel. Those results appear in the June 26th issue of Neuron, also a Cell Press publication.

Alzheimer's disease is a progressive neurodegenerative disorder characterized by a massive loss of neurons in several brain regions and by the presence of amyloid-ß plaques. While the rarer, early-onset form of the disease has been tied to a few dominant mutations, the vast majority of late-onset cases are thought to result from complex interactions among different genetic variants and environmental factors.

Previously, the only susceptibility gene unambiguously demonstrated worldwide is a particular variant of the gene known as APOE, found on chromosome 19. Other evidence suggested a second gene could be found on chromosome 10. However, despite intensive research efforts to characterize the genetic factor or factors located, no gene within the chromosome 10 region had been conclusively linked to late-onset Alzheimer's risk, Marambaud said.

Marambaud's team suspected that susceptibility to late-onset Alzheimer's disease might stem from genes active primarily in affected brain regions, such as the hippocampus. Following that logic in the new study, the researchers screened for genes expressed predominantly in the hippocampus that also fell within the Alzheimer's-linked chromosomal region.

That exercise led them to CALHM1, a gene of unknown function. Indeed, they found, a variant of CALHM1 is found more frequently in people with Alzheimer's disease than in those without. They estimate that a single copy of that variant, which results in a proline-to-leucine amino acid substitution (designated as p86L because it occurs at codon 86), increases one's chance of getting late-onset Alzheimer's disease by 1.44-fold. The risk for those with two copies of the p86L variant would

be higher still, Marambaud said.

" We quickly found that this variant was associated with the disease," Marambaud said. "The problem was it was a variant in a gene with no known function. We had no idea what it was."

Further study showed that CALHM1 is a calcium channel. They also found evidence that the CALHM1 variant more often found in those with Alzheimer's disease increases amyloid-ß levels by interfering with the passage of calcium into cells.

Several groups had proposed before that calcium dysregulation could be causative for Alzheimer's disease, but the notion had not been proven, Marambaud said.

" The present work provides strong support for the calcium hypothesis of Alzheimer's disease and is also an important step toward understanding the potential pathological cross talk between calcium signaling disturbances and pathways of amyloid-ß accumulation," the researchers concluded. "Moreover, the identification of CALHM1 as a key modulator of calcium homeostasis will allow us to further dissect the precise mechanism by which cytosolic calcium modulates amyloid precursor protein metabolism."

Source: Cell Press