A genetic variant that protects against Alzheimer's disease promotes immune cell functions

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A new study conducted by researchers at the University of Eastern Finland found that the PLCG2-P522R genetic variant, which protects

against Alzheimer's disease, enhances several key functions of immune cells. The results obtained in the study highlight the importance of immune cells as a target of future development of new therapies for Alzheimer's disease.

Alzheimer's disease is the most common form of dementia with more than 40 million affected people worldwide. To this day, there are no existing therapies for the effective prevention or treatment of the disease. Many recently identified Alzheimer's disease-associated risk genes are expressed preferentially or exclusively in microglia, the immune cells of the brain. A study conducted in collaboration with the University of Eastern Finland and the German DZNE institute investigated the role of the microglia-specific Plcg2-P522R genetic variant in Alzheimer's disease and found that it enhances several immune cell-specific functions. The results were published in *Molecular Neurodegeneration*.

A genome-wide association study from 2017, which included a Finnish cohort of Alzheimer's disease patients and healthy controls, identified Alzheimer's disease-associated risk loci in three genes, TREM2, ABI3 and PLCG2, which are mainly expressed in microglia. Several genetic variants of the TREM2 gene have been found to increase the risk for Alzheimer's disease. These TREM2 variants lead to a partial loss of function of the receptor and impair the activation of microglia. Consequently, the removal of β-amyloid, which accumulates in the brain during Alzheimer´s disease, is reduced. Recently, it has been shown that the phospholipase C gamma 2 (PLCγ2) enzyme is involved in the signaling pathway initiated by TREM2. The PLCG2-P522R variant reduces the risk of developing Alzheimer's disease, but its effects on immune cell functions have not been previously described.

"It is interesting how several Alzheimer's disease-associated risk genes affect microglial cell functions through the same signaling pathway. It

shows that targeting this pathway and the cellular functions it regulates may have significant therapeutic potential in the future," says Postdoctoral Researcher Mari Takalo from the Institute of Biomedicine of the University of Eastern Finland.

Protective variant sensitizes and activates immune cells

For this study, a mouse model carrying the Plcg2-P522R genetic variant was developed using the CRISPR-Cas9 gene editing technique in collaboration with the research group of German Professor Christian Haass at the DZNE Institute. The researchers found that the Plcg2-P522R variant increases PLCγ2 enzyme activity and enhances cell viability, phagocytic activity, and immune response in peripheral macrophages as well as in microglia-like cells. The results are in line with a recently published study in which deletion of the PLCG2 gene in microglial cells produced from human-induced stem cells had opposite effects.

"It is intriguing that results generated from cells of different origins that have been exposed to different methods of genetic modification, all point in a similar direction. Although this is just the beginning of research related to the role of PLCγ2 in the context of Alzheimer's disease, these results encourage to continue with further studies," Early Stage Researcher Rebekka Wittrahm says.

The study also looked at the effects of the protective Plcg2-P522R variant in the brain of mice. The changes observed in both the RNA expression analysis and the PET imaging study measuring microglial cell activity suggest increased microglial cell activity in Plcg2-P522R mice.

"Microglial cells with the protective genetic modification seem to be

more sensitive to various environmental stimuli and thus, may become more efficient at removing material harmful to the brain, such as β-amyloid. Further research is needed to find out exactly how sensitized microglial cells react in the presence of Alzheimer's disease-related changes in the aging brain," Takalo sums up.

"It is pivotal that we are able to study the role of genes associated with Alzheimer's disease comprehensively at the University of Eastern Finland, from the identification of the risk gene to further functional studies in animal models and patient cohorts," says Professor Mikko Hiltunen, who spearheads the research group.

More information: Mari Takalo et al. The Alzheimer's disease-associated protective Plcγ2-P522R variant promotes immune functions, *Molecular Neurodegeneration* (2020). DOI: 10.1186/s13024-020-00402-7

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