Researchers identify mutation that alters Alzheimer's disease progression

March 15 2024

Researchers identify a mutation that alters Alzheimer's disease progression. The UMA coordinates this study, carried out by 100 multidisciplinary researchers from 50 different entities. Credit: University of Malaga

The scientist of the Faculty of Medicine of the University of Malaga

José Luis Royo has coordinated a study that summarizes eight years of research and brings together 100 multidisciplinary specialists, identifying a mutation that alters Alzheimer's disease progression.

The work, published in the *Journal of Alzheimer's Disease*, has characterized a genetic variant in SIRPβ1 gene, which affects the way in which the immune system fights against beta-amyloid deposits, the cause that leads to this pathology.

In conducting this work, a longitudinal study was carried out using epidemiological samples of more than 1,300 patients from Malaga and Barcelona, evidencing the role of this mutation in the cognitive decline of those affected. However, it was found that it does not represent a risk factor in itself for Alzheimer's disease.

"All human beings have the same genes, but there are variants of each one that make us different. Different external appearances and, also, different physiologies and metabolisms," explains José Luis Royo, Professor of the Department of Surgical Specialties, Biochemistry and Immunology.

The UMA scientist points out that an analysis of the presence of this variant in the SIRPβ1 gene showed that 30% of the general population has one mutation copy and 4% of the population has both copies affected. "Therefore, we are talking about a variant that is very present in the general population," he says.

Dual effect

The research, which involves scientists from more than 50 different entities, shows that the mutant variant changes the structure of the protein and how this alters the behavior of brain immune cells, called microglia.

"When we studied its role in the course of the disease, we found out that it has a dual effect depending on the disease stage: at the beginning, in patients with mild cognitive impairment, the mutation increases the conversion risk to Alzheimer's disease, so it has a detrimental effect in early stages; however, when dementia is established as such, those mutation carriers show slower cognitive decline, suggesting a beneficial effect among these patients," clarifies the UMA researcher.

Royo points out that, therefore, the mutation affects the immune system response to beta-amyloid deposits, probably to the neuroinflammation process, which is a physiological response in the early stages but harmful if it becomes chronic as the disease progresses.

Thus, this dual effect of the genetic variant, he says, suggests that this cell signaling pathway should be inhibited during the early stages of the disease, but it should be stimulated in patients in more advanced stages, to chemically mimic the effect generated by the mutation. "This finding opens the door to a new biochemical therapeutic target that, in the future, could be synthesized with a drug," he concludes.

Currently, researchers are working to characterize the effect of this mutation at a higher level of complexity and have designed a system to look for modifiers of this cell signaling pathway.

More information: José María García-Alberca et al, An Insertion Within SIRPβ1 Shows a Dual Effect Over Alzheimer's Disease Cognitive Decline Altering the Microglial Response, *Journal of Alzheimer's Disease* (2024). DOI: 10.3233/JAD-231150

Provided by University of Malaga