Study shows how common genetic variants in Black Americans increase Alzheimer's risk

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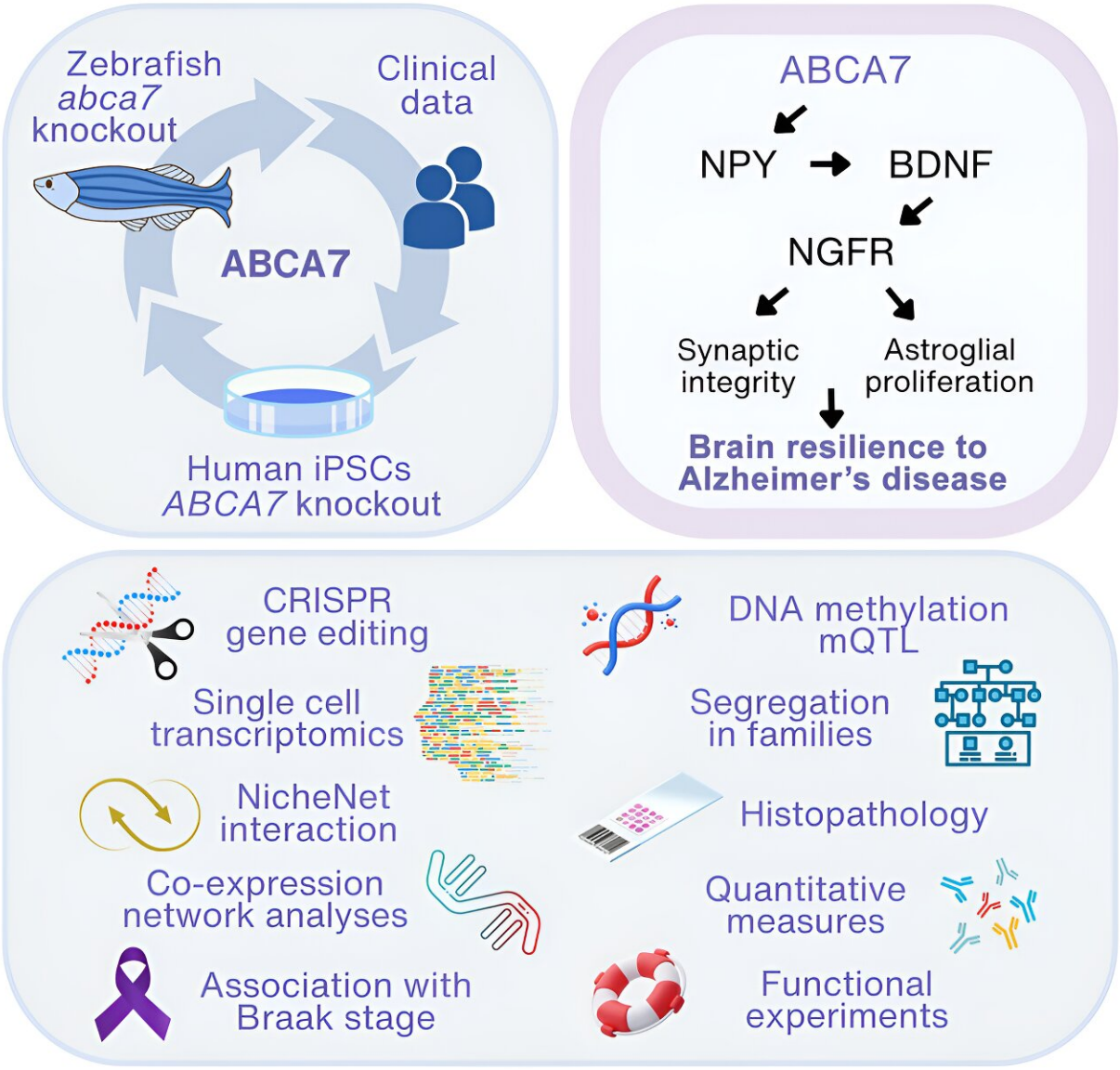

Graphical abstract. Credit: *Cell Genomics* (2024). DOI: 10.1016/j.xgen.2024.100642

Columbia University researchers have discovered how variants of the ABCA7 gene, which are common among Black Americans, increase the risk for Alzheimer's disease. The paper is published in the journal *Cell Genomics*.

The variants accelerate neurodegeneration by reducing the amount of neuropeptide Y, a protein essential for maintaining brain synapses and the resilience of brain neurons.

"Our findings not only enhance our understanding of Alzheimer's, but they also provide a new direction for developing treatments that could halt or reverse the progression of the disease," says study leader Caghan Kizil, Ph.D., associate professor of neurological sciences (in neurology and in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain) at Columbia University Vagelos College of Physicians and Surgeons.

Variants in the ABCA7 gene were first linked to a greater risk of Alzheimer's about a decade ago, but it has been unclear how the variants advance the disease.

ABCA7 variants have been linked to greater Alzheimer's risk in many racial and ethnic groups but are particularly significant among Black Americans. ABCA7 variants are more strongly linked to Alzheimer's disease in Black Americans than the well-known APOE4 gene, the most influential Alzheimer's gene among white Americans.

Understanding the molecular underpinnings of genetic risk factors like

ABCA7 is crucial for the development of new drugs.

Zebrafish as models for discovery

In the study, Kizil and his colleagues deleted one of two copies of the gene in zebrafish neurons (mimicking the gene's disruption in humans). Kizil's zebrafish allow his team to obtain information about Alzheimer's variants in weeks instead of months or years it can take with other animal models.

In the zebrafish, the researchers found that loss of the ABCA7 copy lowered the expression of neuropeptide Y in all regions of the brain but was most pronounced in the hippocampus, the brain's memory center.

"This disruption in neuropeptide Y levels impaired neurogenesis and reduced synaptic density, both of which are key factors in Alzheimer's pathology," Kizil says.

In human cells, the researchers found the same process in neurons derived from pluripotent stem cells and found signs that the protective neuropeptide Y pathway is compromised in the brains of people with Alzheimer's.

The researchers were able to rescue synaptic integrity in the zebrafish by restoring neuropeptide Y or other components in its pathway—highlighting a potential therapeutic target for Alzheimer's.

More information: ABCA7-dependent induction of Neuropeptide Y is required for synaptic resilience in Alzheimer's disease through BDNF/NGFR signaling, *Cell Genomics* (2024). DOI: 10.1016/j.xgen.2024.100642. www.cell.com/cell-genomics/ful … 2666-979X(24)00246-5

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