Newly identified rare Alzheimer's disease gene mutation more common in Icelandic people

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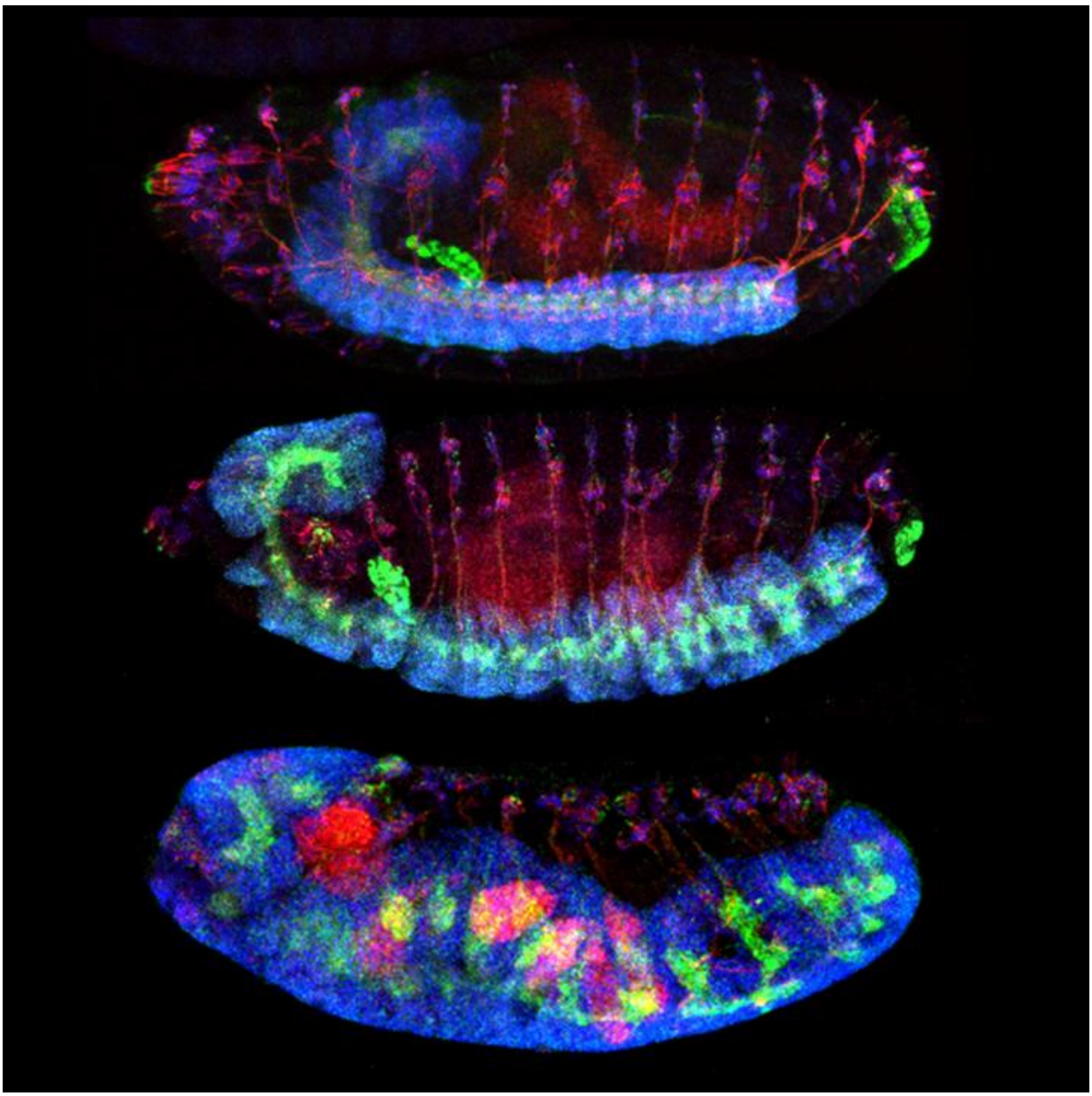

In fruit fly studies, the authors found that the P155L variant causes a loss-of-function in TM2D3, in the context of Notch-Presenilin signal transduction. Credit: Shinya Yamamoto, Baylor College of Medicine

People with Icelandic heritage are more likely to carry a novel rare mutation in the TM2D3 gene, which leads to greater risk for Alzheimer's disease, based on a new study published October 14th, 2016 in *PLOS Genetics* by Johanna Jakobsdottir of the Icelandic Heart Association, Sven van der Lee of Erasmus University in Rotterdam, and colleagues.

Alzheimer's disease is the most common form of dementia, affecting about 30% of adults above the age of 85. While scientists have already identified many common genetic variants that contribute to the disease, rare mutations with significant effects in the population have been more difficult to discover, except in rather isolated families. To find such rare variations, a collaboration of Alzheimer's researchers throughout the U.S. and Europe performed an analysis covering more than 11,000 genes in 1,393 late-onset Alzheimer's disease patients. They identified a variant in the TM2D3 gene that is associated with both a higher risk and earlier age of onset of Alzheimer's disease.

Interestingly, the TM2D3 genetic variant is about 10 times more common in Icelanders compared to the European population in general. Nevertheless, the variant remains quite rare and is present in fewer than 1% of the Icelandic population, and the prevalence of Alzheimer's disease in Iceland is comparable to that seen elsewhere in the world. The researchers also performed experiments in a fruit fly model, in which human TM2D3 was substituted for an equivalent fly gene, demonstrating that the discovered variant interferes with the Notch signaling pathway.

Other Notch signaling factors have previously been shown to participate in the generation of amyloid plaque brain pathology in Alzheimer's disease.

Jakobsdottir, van der Lee and colleagues have identified a rare genetic variant associated with Alzheimer's risk, and propose a possible function to explain its role in the disease. The TM2D3 gene has not previously been linked to Alzheimer's, and thus may have importance for understanding the mechanisms that contribute to the late-onset form of the disease.

Johanna adds "We have found a rare variant in the TM2D3 gene that correlates with risk of late-onset Alzheimer's disease and showed that it likely interferes with the Notch signaling pathway, which has relevance for Alzheimer's disease as other Notch signaling factors play a role in amyloid plaque pathology. However, we have not proven causality and further study is needed, including additional experiments in the fly, DNA sequencing to identify additional variants, and RNA sequencing to study effects on gene expression."

More information: Johanna Jakobsdottir et al, Rare Functional Variant in TM2D3 is Associated with Late-Onset Alzheimer's Disease, *PLOS Genetics* (2016). DOI: 10.1371/journal.pgen.1006327

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