Study links gene mutation to learning deficits in 'Clueless' mice

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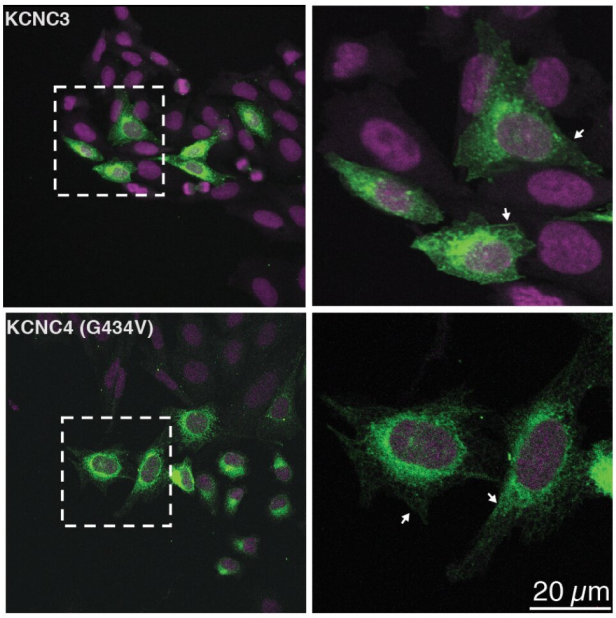

Credit: *Proceedings of the National Academy of Sciences* DOI: 10.1073/pnas.2204901119

A single mutation in a gene, Kcnc3, which encodes a potassium channel in neurons, causes learning deficits in mice, UT Southwestern researchers report in a new study in *PNAS*. The novel mutation decreases the activity of neurons in the hippocampus, the area of the brain important for learning and memory, and highlights a new role for potassium channels.

"Learning and memory are very complex at the genetic level. Unbiased searches for genes underlying learning and memory have not been successfully conducted in mice before," said Joseph Takahashi, Ph.D., Professor and Chair of Neuroscience at UT Southwestern and a Howard Hughes Medical Institute Investigator.

The discovery of the Kcnc3 mutation came out of an extraordinary effort by Dr. Takahashi and colleagues to conduct a large-scale mutagenesis screen in mice. Using a highly potent mutagen called ENU, the researchers induced random mutations in the mouse genome. The progeny of ENU-treated mice were then screened for neural and behavioral traits that could be mapped to specific genes to identify the causal mutation. This approach to unbiased gene discovery is called forward genetics.

From the mutagenesis screen, Dr. Takahashi and his team isolated a mutant mouse with spatial learning defects, which they named Clueless. In fear-conditioning tests, the mutants exhibited reduced freezing (a natural fear response in mice) as well as defects in long-term and short-term memory. The defects in Clueless mice mapped to a mutation in the Kcnc3 gene, which encodes a subunit of a special type of potassium channel called a voltage-gated potassium channel.

This is the first study to implicate Kcnc3 in learning, explained Dr. Takahashi, an investigator in UTSW's Peter O'Donnell Jr. Brain Institute. The full Kcnc3 knockout mouse model shows only mild gait issues with no defects in learning and memory, which could be due to developmental compensation or functional redundancy with other voltage-gated potassium channel subunits. Future research will help to answer some of these outstanding questions.

More information: Pin Xu et al, A missense mutation in Kcnc3 causes hippocampal learning deficits in mice, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2204901119

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