Human gene variant produces attention deficit disorder-like problems in mice

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Mutant mice are providing scientists with a new neurobiological framework to understand the brain changes observed in distractible humans who carry a common gene variant whose frequency has been associated with Attention Deficit Hyperactivity Disorder (ADHD). The scientists demonstrate that mice that express the variant adopt an inattentive phenotype similar to that seen in humans.

The study, led by researchers from the University of Michigan in collaboration with Florida Atlantic University, Temple University, and the National Institute on Deafness and Other Communication Disorders, National Institutes of Health, used genetically engineered mice to examine the neural and behavioral effects of a choline transporter (CHT) variant. Prior work by the team has shown that the variant associated with heightened distractibility in humans, though whether the variant was itself causal for inattention was unclear.

In the new study, researchers made a single change in the gene encoding the neuronal CHT and then searched for physiological changes in the brain, focusing on their ability to sustain production and release of the powerful brain chemical acetylcholine, which is synthetized from choline.

In humans, disruption of acetylcholine signaling impairs one's capacity to filter distractors and to perform focus-demanding tasks. A total loss of CHT function in mice and people leads to early death due to the role played by acetylcholine in muscle contraction, particularly the muscles that control breathing. Lesser reductions in CHT activity allow for normal growth and movement, but mice with these changes exhibit premature fatigue when made to run on a treadmill. Work from the new study reveals that the mice show signs of mental fatigue as well.

Results of the study, published in *The Journal of Neuroscience*, indicate that the CHT gene variant known as Val89 reduces the rate of choline uptake and the capacity to sustain acetylcholine production during attention-demanding conditions, effects that lead to diminished cognitive performance when the mice are faced with attentional challenges. Evidence from the mouse studies provides direct evidence that Val89 drives increased vulnerability to distraction and provides a mechanistic basis for the diminished frontal cortex activation observed in Val89-expressing humans.

"Our mouse studies, along with prior behavioral and brain imaging studies, indicate that a single copy of the variant is sufficient to change acetylcholine availability and its resulting cognitive effects," said Randy D. Blakely, Ph.D., co-author, executive director of the FAU Stiles-Nicholson Brain Institute and professor, FAU Schmidt College of Medicine. "Seeing effects from a single copy of Val89 suggests that choline transport may be mediated by a pair of CHT proteins such that one poorly functioning copy can impact the normal function of the other, leading to stronger effects than expected from simply having one copy compromised."

This finding has been reported before in people with neuromuscular disorder causing CHT mutations, but this also appears to be the case for brain function.

"Val89 mice lack cognitive flexibility in response to an attentional challenge," said Eryn Donovan, lead author and a graduate student in the Department of Psychology, University of Michigan. "Our findings from this mouse model suggest the potential for a more complete investigation of the effects of the CHT Val89 mutation in the brain as well as the development of therapeutic strategies for those with disrupted acetylcholine signaling."

According to the United States Centers for Disease Control and Prevention, the estimated number of children ever diagnosed with ADHD, according to a 2016 parent survey, is 6.1 million. This same survey shows that 6 in 10 children with ADHD had at least one other mental, emotional or behavioral disorder and 62 percent were taking ADHD medication. Although ADHD most often occurs in children, it also can be diagnosed in adulthood.

"We think that the CHT Val89 mouse can be a valuable model to study heritable risk for cognitive disorders that arise from cholinergic

dysfunction," said Blakely. "We now can gain much more insight into the brain effects of the Val89 variant in ways that cannot be done in humans and possibly lead to new ways to treat disorders associated with brain acetylcholine signaling that appear in childhood, such as ADHD, or during aging, as with Parkinson's disease and Alzheimer's disease."

In addition to new insights into a potential risk factor for psychiatric and neurological disorders, Martin Sarter, Ph.D., a professor of psychology and neuroscience at the University of Michigan and the communicating author of the study says that their findings explain why healthy humans expressing this genetic variant exhibit robust attentional vulnerabilities.

"As this genetic variant is quite common, occurring in about 9 to 10 percent of humans, we now understand exactly how this variant influences the brain mechanisms that are essential for paying attention," said Sarter.

More information: Eryn Donovan et al, Disrupted choline clearance and sustained acetylcholine release in vivo by a common choline transporter coding variant associated with poor attentional control in humans, *The Journal of Neuroscience* (2022). DOI: 10.1523/JNEUROSCI.1334-21.2022

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