Mice with 'mohawks' help scientists link autism to two biological pathways in brain

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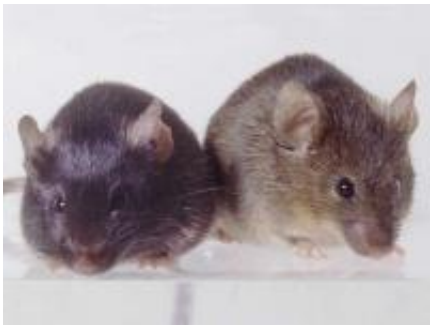

"Aha" moments are rare in medical research, scientists say. As rare, they add, as finding mice with Mohawk-like hairstyles. But both events happened in a lab at NYU Langone Medical Center, months after an international team of neuroscientists bred hundreds of mice with a suspect genetic mutation tied to autism spectrum disorders.

Almost all the grown mice, the NYU Langone team observed, had sideways,"overgroomed" hair with a highly stylized center hairline between their ears and hardly a tuft elsewhere. Mice typically groom each other's hair.

Researchers say they knew instantly they were on to something, as the telltale overgrooming—a repetitive motor behavior—had been linked in other experiments in mice to the brain condition that prevents children

from developing normal social, behavioral, cognitive, and motor skills. People with autism, the researchers point out, exhibit noticeably dysfunctional behaviors, such as withdrawal, and stereotypical, repetitive movements, including constant hand-flapping, or rocking.

Now and for what NYU Langone researchers believe to be the first time, an autistic motor behavior has been traced to specific biological pathways that are genetically determined.

The findings, says senior study investigator Gordon Fishell, PhD, the Julius Raynes Professor of Neuroscience and Physiology at NYU Langone, could with additional testing in humans lead to new treatments for some autism, assuming the pathways' effects as seen in mice are reversible.

In the study, to be published in the journal *Nature* online May 25, researchers knocked out production in mice of a protein called Cntnap4. This protein had been found in earlier studies in specialized brain cells, known as interneurons, in people with a history of autism.

Researchers found that knocking out Cntnap4 affected two highly specialized chemical messengers in the brain, GABA and dopamine. Both are so-called neurotransmitters, chemical signals released from one nerve cell to the next to stimulate similar sensations throughout the body. GABA, short for gamma-aminobutyric acid, is the main inhibitory neurotransmitter in the brain. It not only helps control brain impulses, but also helps regulate muscle tone. Dopamine is a well-known hormonal stimulant, highly touted for producing soothing, pleasing sensations.

Among the researchers' key findings was that in Mohawk-coiffed mice, reduced Cntnap4 production led to depressed GABA signaling and overstimulation with dopamine. Researchers say the lost protein had opposite effects on the neurotransmitters because GABA is fast acting

and quickly released, so interfering with its action decreases signaling, while dopamine's signaling is longer-acting, so impairing its action increases its release.

"Our study tells us that to design better tools for treating a disease like autism, you have to get to the underlying genetic roots of its dysfunctional behaviors, whether it is overgrooming in mice or repetitive motor behaviors in humans," says Dr. Fishell. "There have been many candidate genes implicated in contributing to autism, but animal and human studies to identify their action have so far not led to any therapies. Our research suggests that reversing the disease's effects in signaling pathways like GABA and dopamine are potential treatment options."

The U.S. Centers for Disease Control and Prevention estimate that one in 68 American children under age 8 has some form of autism, with five times as many boys as girls suffering from the spectrum of disorders.

As part of their study, researchers performed dozens of genetic, behavioral, and neural tests with growing mice to isolate and pinpoint where Cntnap4 acted in their brains, and how it affected chemical signaling among specific interneuron brain cells, which help relay and filter chemical signals between neurons in localized areas of the brain.

They found that Cntnap4 in mature interneurons strengthened GABA signaling, but did not do so in younger interneurons. When researchers traced where Cntnap4 acted in immature brain cells, Dr. Fishell says tests showed that it stimulated "a big bolus of dopamine."

As part of testing to confirm the hereditary link among Cntnap4, the two pathways, and grooming behaviors, researchers exposed young mice with normal levels of Cntnap4, who did not groom each other, to mature mice with and without Cntnap4. Only mature mice deficient in Cntnap4

preened the hairstyle on other mice. Further tests in young mice without Cntnap4 showed that other, mature mice with normal amounts of Cntnap4 largely let them be, without any particular grooming or hairstyle.

Dr. Fishell and his team plan further analyses of how GABA and dopamine production changes as brain cells mature, and precisely what cellular mechanisms are involved in autism. Their goal is to control and rebalance any biological systems that go awry, as a possible future therapy for the disease.

More information: Cntnap4 differentially contributes to GABAergic and dopaminergic synaptic transmission, DOI: 10.1038/nature13248

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