NEWS

Feisty mice may reveal autism gene's link to aggression

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20 NOVEMBER 2014

Fight club: Male mice with extra copies of the UBE3A gene are so aggressive that they can't be housed with female mice.

Varying the number of copies of a single autism-linked gene modulates social behavior and aggression in mice, according to results presented yesterday at the **2014 Society for Neuroscience annual meeting** in Washington, D.C.

Researchers hope to use this association to identify other genes involved in both behaviors.

The gene, called **UBE3A**, is the driving factor in two neuropsychiatric disorders: **Angelman syndrome** and **duplication 15q syndrome**. The disorders result from a deletion or duplication, respectively, of the 15q11-13 chromosomal region, which includes UBE3A.

Children with Angelman syndrome lack one copy of the 15q11-13 region, whereas those with dup15q syndrome have one or two extra copies. (Children with two extra copies are more severely affected.)

The disorders share some symptoms, such as developmental delay and severe seizures. But social behavior is nearly opposite in the two disorders: Children with Angelman syndrome are especially social, whereas those with dup15q syndrome often have autism and are more withdrawn.

To better understand these symptoms, researchers have recapitulated the mutations in mice. A 2011 study found that mice with **two extra copies of UBE3A** prefer to investigate an object in their

cage rather than a novel mouse. The males also keep mum around females, making few vocalizations that might signal their interest in mating.

In the new study, **Matthew Anderson's** team tested the same behaviors in mice with a UBE3A deletion, which model Angelman syndrome. This is something that hasn't been done before, he says. His team found that these mice are especially social, spending most of their time with the other mouse in the cage. And they vocalize frequently.

In the course of this usual battery of tests, however, Anderson's team noticed something unusual: Male mice with UBE3A duplications kept attacking the females in their cage.

"The females kept getting separated because of injuries," says Anderson, associate professor of pathology and neurology at Beth Israel Deaconess Medical Center in Boston. "So we said, 'I wonder if these males are aggressive?'"

The standard mouse aggression test — introducing a new 'intruder' mouse for ten minutes — confirmed his hunch. Mice with a UBE3A duplication attack the intruder significantly more often than controls do. By contrast, Angelman mice attack intruders less often than controls do.

The results suggest that, as it does with social behavior, the amount of UBE3A modulates the amount of aggression. UBE3A is unlikely to be the only factor, however, as it regulates the expression of other genes.

Anderson's team has found that gene expression overall goes up with extra copies of UBE3A and down in the case of a deletion. The researchers also highlighted a group of genes that match UBE3A levels closely: Their expression is highest with two extra copies, a little lower with a single extra copy, lower still in control mice and lowest in mice with the deletion.

Anderson declined to reveal the names of these genes because the data are unpublished, but says they have other links to autism and, perhaps, to aggression.

"Aggression is sort of underappreciated in autism, but if you look at what brings families to the clinic to see a psychiatrist, it's aggression," he says. "It's a major issue and we can find a set of genes involved in that process."

*For more reports from the 2014 Society for Neuroscience annual meeting, please **click here**.*