Engineering autism: Mice with extra chromosome region show many autistic signs

June 25 2009

Mice who inherit a particular chromosomal duplication from their fathers show many behaviors associated with human autism, researchers report in the June 26th issue of the journal *Cell*, a Cell Press Publication. The duplicated chromosomal region in mice is the equivalent of human chromosome 15q11-13, the most frequent cytogenetic abnormality observed in autism, accounting for some five percent of all cases.

The engineered mice validate the human chromosome abnormality as one cause of the disease, the researchers said. They will also serve as an invaluable tool for therapeutic development.

"We know several mice as 'putative' models of autism, which show face validity that they are similar to human patients," said Toru Takumi of Hiroshima University in Japan. "In addition to these similar phenotypes, our mice have construct validity," meaning that their symptoms are traced to the same biological cause.

Autism is a common and heterogeneous neuropsychiatric disorder with manifestations of impaired social interaction and communication as well as repetitive behavior or restricted interest, the researchers explained. It is also one of the most heritable of all mental disorders, suggesting that genetic factors play an important role in development of the disease.

Scientists have studied many gene candidates, and mice carrying some of those mutations do show some signs. Still the molecular pathways underlying autism remain largely mysterious.

Chromosomal abnormalities are thought to account for 10 to 20 percent of cases and duplication of chromosome 15q11-13 is the only recurrent aberration so far linked to the disease.

In the new study, Takumi's team generated mice with a duplication of a region on their chromosome 7, mirroring the autism-linked abnormality seen in humans. Mice who inherit that abnormality from their fathers show poor social interaction, behavioral inflexibility, abnormal ultrasonic vocalizations and indications of anxiety, the results of extensive behavioral testing now show.

For instance, when given the option of spending time alone or in the presence of a stranger mouse, normal mice will often choose to hang out with the stranger, Takumi said. Mice with the chromosomal abnormality, on the other hand, more often choose to spend time with inanimate objects over fellow mice.

In tests of spatial memory, in which mice are trained to swim to a hidden platform, animals with the paternally inherited duplication were less able to adapt to changes in the platform's location than normal mice were. Another test, in which mice have to locate the correct hole to exit a box, showed similar results.

"We were honestly surprised to see behavioral inflexibility in two different reversal tests of learning and two different backgrounds," Takumi said. "Higher ultrasonic calls from pups with paternal duplication were unexpected" too. It's also hard to say exactly what those unusual calls mean for the mice, given scientists' limited understanding of mouse communication.

In other tests, the mice showed more signs of fear or anxiety, a feature common in autistic individuals.

The researchers also found molecular-level evidence that the duplication can lead to changes in a receptor for serotonin, a nerve messenger that acts as a growth factor in the immature brain. Those changes stem from different levels of one brain-specific small nucleolar RNA (snoRNA), known as MBII52, a molecule that is known to be involved in physiologically important "edits" to the receptor.

Because the gene that encodes MBII52 is "maternally imprinted," its expression in mice with the inherited duplication from their father was double that of normal mice or those who inherited the same abnormality from their mothers, they report. (Imprinted genes are chemically modified to prevent their expression.) Studies in cultured neurons showed that those changes to MBII52 are associated with an altered neural response, suggesting that changes in serotonin signals might underlie the aberrant behaviors exhibited by the animals.

In addition to those insights, the mice may yet hold many more clues for understanding autism and potential for new treatments.

"The link between social behaviors in rodents and social behavior in humans is difficult to establish," the researchers concluded. "Our model mouse will be valuable not only for therapeutic studies but also provides a starting point for more detailed genetic analysis directed toward understanding the etiology of developmental brain disorders."

Source: Cell Press (news : web)