NEWS

Genetically modified monkeys show autism-like behaviors

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Monkeys engineered with multiple copies of a gene called MeCP2 show autism-like characteristics, including lack of social activity and **repetitive behaviors**. In a first for autism research, the monkeys pass the extra genes on to their offspring, which show social deficits too, according to a

report published 25 January in *Nature*[1].

People who carry an extra copy of MeCP2 have a rare disorder called **MeCP2 duplication syndrome**, characterized by severe intellectual disability, movement problems, seizures, anxiety and autism. People with two extra copies are more severely affected, and those with mutations in the gene typically have Rett syndrome, a disorder related to autism.

By inserting extra copies of this gene in monkeys, the researchers have taken a promising step toward a **primate model for autism**, experts say.

“We have all kinds of mouse models, but very few of them actually show similar symptoms to humans,” says lead investigator **Zilong Qiu**, principal investigator in the Institute of Neuroscience at the Chinese Academy of Sciences in Shanghai. “That made us to believe we should make a primate model.”

However, many scientists say that the model is imperfect and question its relevance to autism. Unlike people with the duplication syndrome, the monkeys have up to seven copies of MeCP2 and express high levels of it only in neurons; they also do not show all of the symptoms seen in people with the syndrome.

“It’s a model of some neurological abnormalities due to overexpression of MeCP2 in neurons, which is interesting, but I don’t think it really captures the key features of the duplication syndrome,” says **Huda Zoghbi**, director of the Jan and Dan Duncan Neurological Research Institute at Texas Children’s Hospital in Houston, who was not involved in the work.

Model behavior:

Qiu and his colleagues used a virus to insert the human MeCP2 gene into the genomes of 94 eggs collected from adult female macaque monkeys. The virus inserts the gene at random, but is designed so that the gene is expressed only in the brain.

The researchers then fertilized the eggs with sperm collected from male monkeys and transplanted the resulting 53 embryos into 18 female surrogates. Half of the females became pregnant and gave birth to a total of eight live monkeys.

Analyses of DNA from hair root samples revealed that the monkeys carry varying numbers of human MeCP2 copies. Based on the locations of the insertions, the researchers say the human genes are unlikely to disrupt the functions of any monkey genes.

By 18 months of age, the genetically modified monkeys spend more time than controls do repeatedly circling their cages. They also show **signs of anxiety**: They grunt more than controls do when a person stares into their eyes.

The monkeys tend to spend less time than controls interacting with cagemates — a behavior reminiscent of the social deficits characteristic of autism. Oddly, these deficits are only apparent when the researchers measure interactions between pairs of genetically modified monkeys; they do not occur when these monkeys are paired with controls.

“MeCP2 duplication people [having difficulty] interacting with other MeCP2 duplication people isn’t really what you’d think of as social deficit,” says **Jeffrey Neul**, chief of child neurology at the University of California, San Diego, who was not involved in the study. “I would say this is a subtle phenotype.”

Key differences:

The monkeys diverge from people with MeCP2 duplication in other important ways: They do not have seizures, and those with multiple copies of the human gene do not have more severe symptoms than those with only one. They also show few problems on tests of cognitive function. For example, they have little trouble learning to locate a piece of food hidden inside a particular box.

Zoghbi says these differences may be due to the human genes being expressed in the monkeys at different times and locations than they typically are in people.

Still, the researchers managed to clear some key technical hurdles. Because monkeys can take up to five years to become sexually mature, the researchers used a technical shortcut to breed a second generation of transgenic monkeys: They obtained a piece of testicular tissue from a 2-year-old monkey and grafted it onto a mouse, which then produced viable monkey sperm after 10 months.

Using this sperm, Qui’s team generated four additional monkeys. Like the previous generation, these monkeys carry extra copies of MeCP2. They also spend less time interacting than controls do.

The new monkeys are the first nonhuman primate autism model to pass their engineered genes on to their offspring. “The most important part about this is that they were able to start establishing that this is a viable genetic model that can be propagated,” Neul says.

One drawback of their technique, however, is that the virus randomly inserts copies of the gene, making it impossible to control the number of copies in the next generation[2]. Newer, **more precise genome-editing techniques** could overcome this limitation.

Primate debate:

In 2014, a group of Chinese researchers used these precision tools to engineer **macaques with a**

mutation in MeCP2 that is found in people with Rett syndrome. Similarly, a Japanese team reported last year that a female **marmoset lacking MeCP2** may be **showing early Rett-like symptoms**.

The new model is likely to **revive debates** about the advantages and limitations of using monkeys in research. “Ultimately, it’s a very expensive technology,” says **Alysson Muotri**, associate professor of pediatrics and cellular molecular medicine at the University of California, San Diego, who was not involved in the work. “It costs more to grow a colony of monkeys than a mouse. And the gestation time takes longer, so all the experiments take forever to be done.”

But Qiu, who also works with mouse models, says monkeys are better suited than mice for studying social interactions and complex cognitive skills. “Although it costs a lot regarding money and effort, it will give us insights the mouse models wouldn’t be able to provide,” he says.

Qiu says his team is scanning the monkeys’ brains to identify abnormalities tied to excess MeCP2.

“We hope to find particular brain regions or particular neural circuits that are responsible for, say, repetitive behaviors or defects in social interactions,” he says. “If we can establish the responsible neural circuits in our transgenic monkeys, then we can use available technologies such as gene-editing tools to try to intervene.”

REFERENCES:

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2. Lois C. *et al. Science* **295**, 868-872 (2002) **PubMed**