NEWS

Mutant monkeys mimic features of autism, Rett syndrome

BY **NICHOLETTE ZELIADT**

19 JUNE 2017

Monkeys with a mutation in the Rett syndrome gene, **MeCP2**, show characteristics of the condition, such as sleep problems and sensory sensitivity, as well as social difficulties and **repetitive behaviors** reminiscent of autism[1].

The monkeys also show features that are difficult to assess in mouse models of Rett, such as trouble recognizing another monkey's facial expressions.

The findings suggest that the monkeys may help researchers understand the neural underpinnings of the syndrome, and test treatments for the condition.

"This data can't be gotten from rodents," says lead investigator **Yongchang Chen**, professor of developmental biology at Kunming University of Science and Technology in China.

Rett syndrome mainly affects girls because most boys with a MeCP2 mutation are stillborn or die shortly after birth. The girls develop typically for about 18 months and then regress, losing their language and motor skills. Roughly 60 percent have autism[2].

Male monkeys with a MeCP2 mutation are also stillborn, the study shows. Females show signs of Rett syndrome and autism, but it is not yet known whether they regress. In **eye-tracking** tests, they seem to have trouble recognizing the emotions of other monkeys — a key feature of primate social behavior that is absent in rodents. The results were published 18 May in *Cell.*

"Primate models are going to be very important for understanding how these disorders unfold," says **Michael Platt**, professor of neuroscience at the University of Pennsylvania in Philadelphia, who was not involved in the study. "You can measure how much time a mouse spends sleeping or next to another mouse, but here they have the opportunity to really look at one of the major behavioral impairments [of autism]."

Making monkeys:

Chen and his colleagues **described the first of their MeCP2 mutant monkeys** in 2014. That monkey, which is female, did not show any Rett-like features by 4 months of age. The researchers re-examined the behavior of this monkey, along with four new ones, starting when the monkeys were 5 months old.

The team made the mutant monkeys using a gene-editing tool called TALENs. They first collected eggs from adult female cynomolgus monkeys and fertilized them with sperm from males. They then used TALENs to insert mutations into one copy of MeCP2 in fertilized eggs.

They transplanted the resulting 123 embryos into 41 females, 14 of which became pregnant (two with twins). These monkeys gave birth to five mutant females, as well as two males and one female without mutations. Five male and two female fetuses with MeCP2 mutations spontaneously aborted.

TALENs snips genes at specific spots, but the repair process that inserts mutations is imprecise. As a result, each of the live mutant monkeys carries a different mutation. All of the mutations

decrease the amount of MeCP2 protein, according to an analysis of skin and placenta samples from the babies. Because the researchers used the technique after conception, the monkeys carry MeCP2 mutations in only about one-quarter to half of their cells.

The mutant monkeys have slower and more irregular heartbeats than do controls without MeCP2 mutations. They sleep less than controls do, and awaken more frequently. They also have an unusually high tolerance for painfully hot stimuli and loud noises.

These findings are reminiscent of the heart problems, sleep troubles and unusual sensory responses that people with Rett syndrome often have.

Social signs:

The mutant monkeys also have social difficulties and repetitive behaviors reminiscent of those seen in autism. They spend less time grooming their cagemates and approaching them to play than controls do. They also show more stereotypical behaviors, such as pacing, rocking, bouncing, lip-smacking and sucking on their fingers and toes.

The researchers used eye-tracking technology to track the monkeys' gaze as they looked at images of another monkey's face or objects on a computer screen. The mutant monkeys show the usual preference for looking at monkey faces over inanimate objects, but an unusual preference for neutral faces over ones that display emotions.

This finding suggests the mutant monkeys have trouble recognizing facial expressions.

Researchers should examine how much time the monkeys spend looking at the eyes and mouths of other monkeys, Platt says. They could also track gaze in response to videos of monkeys or during social interactions.

It is unclear whether the mutant monkeys develop typically at first and then regress, or show abnormalities from the start. Chen says although his team began monitoring the monkeys at 5 months old, some of the tests, including eye tracking, couldn't be completed until the monkeys were almost 2 years old because of the time needed to train them. "Maybe it's too late and we missed information at earlier stages," he says.

Derailed development:

Chen and his team used magnetic resonance imaging to scan the brains of the mutant monkeys when they were 8, 15 and 20 months old. He says this type of long-term brain analysis is difficult to do in children with Rett syndrome, who have trouble lying still in the scanner. Mouse brains are easy to scan but develop rapidly and are structurally different from primate brains.

The researchers found several unusually small brain regions in the mutant monkeys, including the amygdala and cingulate cortex — two structures involved in social behavior. Some of the structural abnormalities were not apparent until the monkeys were 20 months old.

These brain abnormalities “seem milder than expected,” says **Hideyuki Okano**, professor of physiology at Keio University in Tokyo, Japan, who was not involved in the study.

Most children with Rett syndrome have unusually small brains, a condition called microcephaly. Although certain regions in the monkey brains are unusually small, the monkeys do not have microcephaly. The mildness of their brain features could be due to the fact that MeCP2 mutations affect only a subset of cells, Okano says.

Chen notes that the monkeys do not have cognitive problems, seizures or breathing difficulties — common features of Rett syndrome seen in some mice with MeCP2 mutations.

He and his colleagues are making more monkeys and plan to monitor their behaviors from birth. They are also measuring the monkeys’ brain activity using functional brain imaging to better understand how the structural changes relate to behavior.

REFERENCES:

1. Chen Y. *et al. Cell* **169**, 945-955 (2017) **PubMed**
2. Richards C. *et al. Lancet Psychiatry* **2**, 909-916 (2015) **PubMed**