NEWS

Monkey models march into autism research arena

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Overcoming profound technical challenges, researchers may be well on their way to making a troop of monkey models for studying autism and related conditions. They presented glimpses of the progress in the past week at the **2015 Society for Neuroscience annual meeting** in Chicago.

For decades, mice have been the mainstay of autism research because of the ease with which scientists can alter their genes. But tiny rodents are severely limited in their potential to recapitulate a complex social disorder. For example, some drugs that make a mouse more sociable have had **little effect in children**.

With their genetic similarity to people, primates have always seemed a better choice for studying autism, but making monkey models has not been easy. Researchers have optimized the tools needed to engineer mutations into monkeys — from inserting transgenes into embryos to snipping genes out with **molecular scissors** — over the past few years. To breed monkeys, they also need patience: Monkeys do not reproduce as fast as rodents do.

Researchers presented findings on two new transgenic marmosets this past week. One marmoset lacks **MeCP2**, the gene mutated in Rett syndrome, an autism-related developmental disorder. The other carries an indicator in its neurons that flashes fluorescent light whenever the neurons fire. Eventually, researchers could combine these characteristics, creating monkeys whose glowing brains paint a real-time picture of the effects of an autism-linked mutation on the brain.

It will be fairly straightforward to combine different kinds of transgenic marmosets because they breed relatively quickly, says **Guoping Feng**, professor of brain and cognitive sciences at the Massachusetts Institute of Technology, who is not involved in any of the work presented at the meeting. In particular, he says, the monkeys with the indicator of neuron activity “will be very useful for studying circuit dysfunction in autism models in the future.”

Feng is setting up a large breeding colony with the aim of making several autism marmoset models, starting with ones that lack **SHANK3**, a leading autism gene.

Glowing brain:

To create monkeys with the activity indicators, one team of researchers injected germ cells with a virus that carries DNA encoding an enzyme called GCaMP. The enzyme is derived from GFP, the green fluorescent jellyfish protein beloved to researchers, and it glows only when exposed to calcium, which rushes into a neuron when it fires.

The researchers expressed the enzyme in all neurons, but they can also make monkeys that express the enzyme in only certain subtypes of neurons, such as those that inhibit brain activity, says Jung-Eun Park, a staff scientist at the National Institutes of Health, who presented the findings Saturday.

Park and her colleagues inserted engineered embryos into 20 monkeys that gave birth to three baby monkeys that express the enzyme in their neurons; one of the baby monkeys died shortly after birth. The other two are now several months old and express the enzyme in their spinal fluid. Cells from the spinal fluid glow as expected. In a few months, the older of the two marmosets will

be old enough to participate in invasive brain experiments, Park says.

Another team has engineered a marmoset that lacks one copy of MeCP2, the Rett syndrome gene. This monkey, **which researchers first described** at the 2014 Society for Neuroscience Annual Meeting, had her first birthday in August.

Outward signs:

Last year, another team of researchers announced a male rhesus macaque with mutated **MeCP2**. This monkey died shortly after birth, however, possibly as a result of side effects from the gene-editing technology used to insert the mutation[1].

At 1 year of age, the female marmoset is healthy and seems no different from her normal littermates, says Noriyuki Kishi, a postdoctoral researcher in **Hideyuki Okano**'s lab at Keio University in Minato, Japan, who presented the findings yesterday. People with Rett syndrome begin to show signs of the disorder starting at 2 years of age.

The researchers may be seeing the first indications of Rett-like symptoms, however. The mutant monkey's head grew at the same pace as those of her siblings until 6 months of age, but it is starting to shrink. At 1 year it was 15 percent smaller than that of a control monkey. Small head size is also seen in people with Rett syndrome.

Kishi and his team are videotaping the marmoset for five minutes each month, looking for any signs of problems with breathing, motor skills, social withdrawal and seizures, a few key symptoms of the syndrome.

*For more reports from the 2015 Society for Neuroscience annual meeting, please **click here**.*

REFERENCES:

1. Liu Z. *et al. Neurosci. Bull.* **30**, 381-386 (2014) **PubMed**