**NEWS**

# Mouse model mimics mosaic mutation in tuberous sclerosis

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3 JUNE 2013

Deleting both copies of a gene linked to tuberous sclerosis complex (TSC), an autism-related disorder, in only a subset of brain cells recapitulates many ofthe disorder's symptoms in mice, according to a study published 9 May in *Neuron*[1].

The study also traces the disorder's origins to embryonic development, suggesting that introducing the mutation early, rather than later, in gestation causes more severe symptoms.

**Giant cells:** Mouse neurons lacking both copies of the TSC1 gene (right) are larger and have more of the chemical messenger parvalbumin (green) than do controls (left).

TSC is characterized by benign tumors, called tubers, throughout the brain and body. Nearly all individuals with TSC have **epilepsy** and **about half of them have autism**. The disorder is caused by a mutation in one copy of either TSC1 or TSC2. In mice, however, deleting one copy of either gene leads to only some of the symptoms of the disorder; deleting both copies is lethal. The mice in the new study are the first have both spontaneous seizures and **repetitive behaviors**.

People with the disorder also have variable symptoms of different severity. Some severe cases of TSC may be the result of a spontaneous mutation in the second copy of the gene. This is a so-called 'somatic' or mosaic mutation, affecting only random clusters of neurons in the brain.

"Mosaicism is one of the really interesting, relevant and largely unexplored cellular mechanisms that may contribute to complex diseases," says lead investigator **Mark Zervas**, assistant professor of biology at Brown University in Providence, Rhode Island.

One 2010 study found that most tubers in people with the disorder seem to lack both copies of either TSC1 or TSC2[2]. Another study, published laterthat year, found a second hit in tubers from only 1 of 34 people with the disorder[3].

In previous studies, researchers have deleted both copies of TSC1 in certain cell types or in certain brain regions. Deletion in the cerebellum leads to **repetitive behaviors** and social deficits. Deleting both copies of TSC1 in astrocytes — support cells in the brain — and in progenitor cells that develop into neurons **leads to seizures**.

The new study is the first to introduce a mosaic mutation in a TSC gene in a specific brain region. “People have written about this, but no one has really experimentally tested the idea,” says Zervas. “We wanted to start to unravel this cellular mechanism.”

## Mosaic model:

In the new study, the researchers used an experimental system that would delete both copies of TSC1 inconsistently across neurons in the thalamus — a brain region that relays sensory and motor information to the cortex. Most studies of TSC have focused on the cerebral cortex, which regulates higher-order brain function. The effects seen by mutating thalamic neurons suggest that many brain circuits are involved in the disorder.

When the researchers activated the mutation at embryonic day 12.5 (E12.5), equivalent to the first trimester in people, 91 percent of the mice had spontaneous seizures within two months after birth. They also had severe repetitive behaviors, grooming themselves so often that they cut their own skin.

“As a child neurologist, I found it particularly exciting that these animals seem to recapitulate the epilepsy phenotype quite nicely just by losing TSC1 in a subset of cells in the thalamus,” says **Mustafa Sahin**, assistant professor of neurology at Boston Children’s Hospital, who was not involved in the work. “If we think of autism as a circuit, we can probably perturb that circuit at different places.”

The mice may be a powerful model in which to test treatments for epilepsy in people with TSC, he adds. If people with the disorder have a mosaic mutation, then the models may also help test the effect of drugs on that mutation.

About 70 percent of neurons in the thalamus of these E12.5 mice had the mutations, and were enlarged, suggesting the bulk of the TSC tubers. (No mouse models of the disorder have formed actual tubers.) The mutant neurons also fired more readily than those of controls and contained high levels of parvalbumin. Parvalbumin helps control the amount of calcium in neurons, which regulates how readily neurons fire.

In contrast, when the researchers switched on the mutation at embryonic day 18.5 —equivalent to early second trimester in people — the mice had milder symptoms than those perturbed at E12.5. The E18.5 mice did not have repetitive behaviors and only 4 of the 17 mice had seizures, and only after they were handled.

Some of the E18.5 mutant neurons were also enlarged, but less so than the E12.5 neurons. They had normal levels of parvalbumin. However, only about 30 percent of the neurons in the thalamus had the mutation.

"It's not clear from the paper whether [these differences are] due to the timing or the subsets of neurons that lose the TSC allele," says Sahin.

Both these variables might influence the nature and severity of TSC in people, depending on when in gestation they develop a second TSC mutation.

The new study also suggests that the mutant neurons can alter the developmental path of normal neurons. For example, in the E12.5 mice, the mutant neurons in the thalamus make excessive projections into certain regions of the cortex, leading to changes in the organization of the cortex.

"The study is nice because you can see that part of the effect of the mutation can be traced back to very early in development," says **Alcino Silva**, professor of behavioral neuroscience and psychology at the University of California, Los Angeles, who was not involved in the study.

## References:

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3: Qin W. *et al. Brain Path.* **20**, 1096-1105 (2010) **PubMed**