NEWS

Autism gene PTEN plays vital role in neural stem cells

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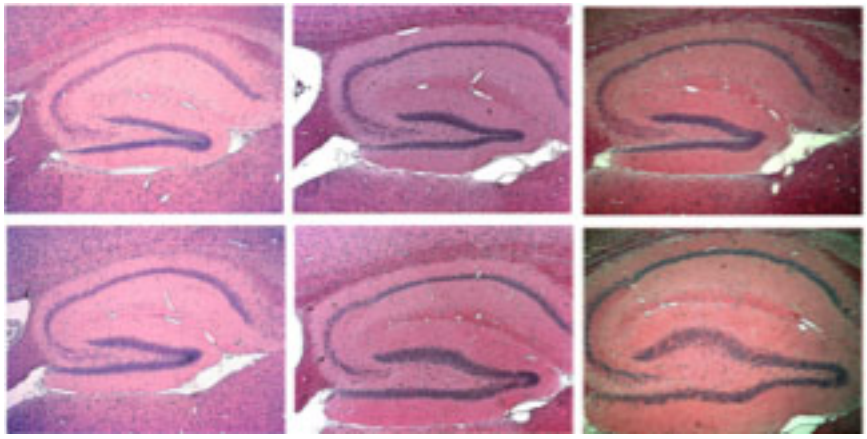

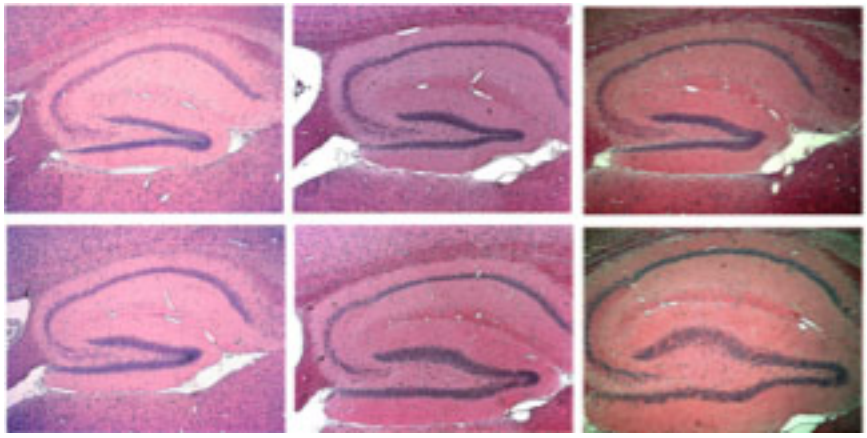

Brain disarray: At 7 months of age, the dentate gyrus, which helps form new memories, is larger and more disorganized in mice that lack PTEN in their neural stem cells (bottom row) than in controls (top row).

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Knocking out an autism-linked gene called **PTEN** only in neural stem cells in the hippocampus, a brain region central to learning and memory, throws the development of new neurons off course in adult mice, according to research published in April in the *Journal of Neuroscience*[1].

At first, new neurons are born more rapidly in these mice than in control animals. By the time the mice are 7 months old, which approximates middle age in a lab mouse, they have a larger and more disorganized dentate gyrus — part of the hippocampus — than controls do.

The findings show that “perturbation in just a small number of neurons can have profound effects on behavior and morphology,” says lead investigator **Luis Parada**, professor of developmental biology at the University of Texas Southwestern Medical Center in Dallas. “It leads one to speculate that PTEN loss in any small group of neurons could have profound consequences.”

PTEN is best known for its role in suppressing different types of cancer. Mutations in the gene have also been linked to **enlarged head, seizures and autism**. One 2010 study found PTEN mutations in about two percent of children with autism, and in seven percent of those who have both enlarged heads and autism[2].

PTEN is part of the PI3 kinase pathway, which comprises a set of enzymes that regulate cell growth, proliferation and differentiation.

“One of the critical questions we’re interested in trying to understand using mouse models is how PTEN mutations or mutations in the PI3 kinase pathway could lead to an autism-like phenotype,” says Parada.

Narrow knockout:

In 2009, Parada’s team showed that knocking out PTEN in the hippocampus and cortex in mice generates larger-than-normal neurons and leads to seizures and **macrocephaly**, or an enlarged head[3]. Others have found that neurons lacking PTEN are hyperconnected to other brain cells, both

near and far[4]. All of these features have some overlap with autism, which is often hypothesized to be a **disorder of neural connectivity**.

To hone in on PTEN's specific function, researchers genetically engineered mice so that the gene was turned off only in neural stem cells of the hippocampus beginning when the mice were 4 weeks old, the equivalent of young adulthood.

The result was "quite remarkable," says Parada. The birth of new neurons ramped up in the mutant animals, he says. "Over time, many more new neurons were made in the hippocampus than would be made under normal conditions."

The mutant neurons look outwardly functional and connect with other cells. But they are larger than normal, with more neural projections — the long, thin fingers that connect brain cells. As the mice age, the pool of neural stem cells shrinks.

It's like the stem cells "got burned out early," says Parada. "The implication is that there is a finite number of new neurons that can be made in the hippocampus, which we are very interested in looking into further."

The study is the first to find a role for PTEN in neurogenesis, or the birth of neurons, notes **Moses Chao**, professor of cellular biology at New York University, who was not involved in the study. "That makes a lot of sense, because PTEN is in a pathway that regulates cell proliferation and differentiation."

The research also helps to define one of PTEN's roles in the body.

"The findings are important because we know that in people, the protein is reduced from birth and probably has an effect on multiple populations of cells," says **Huda Zoghbi**, professor of molecular and human genetics at Baylor College of Medicine in Houston, Texas, who was not involved in the study.

The mice show some social impairment, though both Parada and Zoghbi say this is not an essential part of the findings. "It was clear the mice behaved abnormally, but it's not clear it is consistent with autism," says Parada.

Parada speculates that the stem cell finding might help explain why some postmortem studies of autism have found abnormalities in brain structure and others have not.

"It might be sufficient for perturbation to occur in a small number of neurons in the brain to have a substantial outcome," he says. "In humans, it might be even fewer."

The researchers plan to explore PTEN's function by using viruses to block the gene in an even

smaller subset of neurons.

They also plan to try to reverse the symptoms using drugs that block the function of the PI3 kinase family of enzymes. “We have done that a little bit and showed we could reverse many morphological phenotypes,” says Parada. “But it was much more difficult to alter behavioral phenotypes.”

References:

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