Medical Xpress

Researchers discover a gene's key role in building the developing brain's scaffolding

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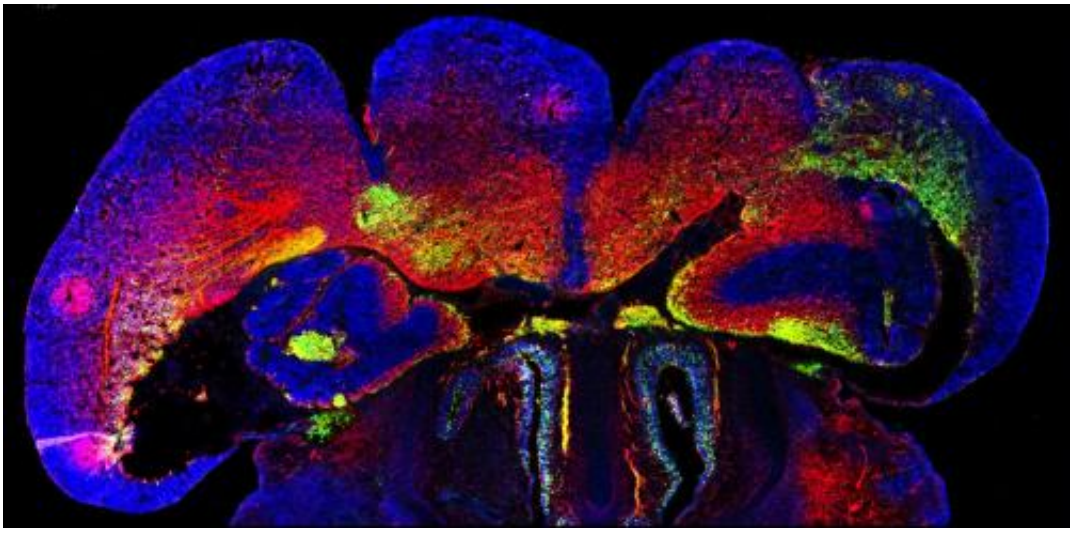

A mutated Arl13b gene caused neurons (red, green) to form clusters and other malformations in this mouse brain.

(Medical Xpress)—Researchers have pinpointed the role of a gene known as Arl13b in guiding the formation and proper placement of neurons in the early stages of brain development. Mutations in the gene could help explain brain malformations often seen in neurodevelopmental disorders.

The research, led by a team at the University of North Carolina School of Medicine, was published June 30 in the journal *Nature Neuroscience*.

"We wanted to get a better sense of how the cerebral cortex is constructed," said senior study author Eva Anton, PhD, a professor in the Department of Cell Biology and Physiology and a member of the UNC Neuroscience Center. "The cells we studied—radial glial cells—provide a scaffolding for the formation of the brain by making neurons and guiding them to where they have to go. This is the first step in the formation of functional neuronal circuitry in the brain. This study gives us new information about the mechanisms involved in that process."

The researchers became interested in the Arl13b gene because of its expression in a part of the cell called primary cilium and its association with a rare neurological disorder known as Joubert syndrome. The syndrome is characterized by brain malformations and autism like features.

"In addition to helping us understand an important cellular mechanism involved in normal brain development, this study may offer an explanation for some of the malformations seen in Joubert syndrome patients," said Anton. Although there is no immediate clinical application for these patients, the study does help illuminate the factors behind the disease. "It shows what may have gone wrong in some of those patients that led to the malformations," said Anton.

The cerebral cortex, the brain's "gray matter," is responsible for higher-order functions such as memory and consciousness. Like the scaffolding builders use to move people and materials during construction, radial glial cells provide an instructive matrix to create the basic structural features of the cerebral cortex. Mistakes in the formation and development of radial glial cells can translate into structural problems in the brain as it develops, said Anton.

Both mice and humans have the Arl13b gene. The researchers generated

a series of mice with mutations on the Arl13b gene at different developmental stages to track the mutations' effects on brain development. They discovered that the gene is crucial to the radial glial cells' ability to sense signals through an appendage called the primary cilium. Without this signaling capability, the radial glia were unable to organize into an instructive scaffold capable of orchestrating the orderly formation of cerebral cortex. "The cilia in these cells play an important role in the initial setup of this scaffolding," said Anton. "Without a functioning Arl13b gene, the cells were not able to determine polarity and formed haphazardly. As a result, they formed a malformed cerebral cortex with ectopic clusters of neurons, instead of the orderly layers of neurons with appropriate connectivity that would be expected, in the developing brain.

More information: Arl13b-regulated cilia activities are essential for polarized radial glial scaffold formation, DOI: 10.1038/nn.3451

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