

Defects in brain cell migration linked to mental retardation

21 June 2013, by Michael C. Purdy

(Medical Xpress)—A rare, inherited form of mental retardation has led scientists at Washington University School of Medicine in St. Louis to three important "travel agents" at work in the developing brain.

The agents—two individual proteins and a tightly bound cluster of four additional proteins—make it possible for [brain neurons](#) to travel from the area where they are born to other [brain regions](#) where they will reside permanently and integrate into [neuronal circuits](#). Inhibiting any of these proteins in embryonic mice reduces the ability of neurons, which process and transmit information, to reach their final destinations and, presumably, to hardwire the brain.

"That kind of misplacement of brain cells is likely to seriously disrupt mental functions," said Azad Bonni, MD, PhD, the Edison Professor and chairman of the Department of Anatomy and Neurobiology. "This is just one of many ways that [brain development](#) can go awry. To understand [intellectual disability](#) and develop treatments, we need to understand the many problems that can arise as the brain develops and its circuitry is established."

The results appeared June 19 in *Neuron*.

The new work began as an inquiry into PHF6, a gene that is mutated in patients with Börjeson-Forssman-Lehmann syndrome. This disorder causes mental retardation, [developmental delays](#) and skeletal abnormalities. More than a decade ago, scientists identified a link between the condition and PHF6, but they did not know what the gene did in the brain.

Bonni's laboratory added [green fluorescent protein](#) to brain cells to track their development and movement in embryonic mice. Then the researchers inhibited PHF6 in some mice.

In normal mice, as expected, brain neurons migrated from the ventricular zone, where they were born, to the cortical plate, the precursor site of the [cerebral cortex](#). In the mature brain, the cerebral cortex is responsible for higher brain functions such as processing of [sensory data](#), attention and decision-making. In mice whose brain cells lacked PHF6, many brain cells either stayed in the ventricular zone or only completed part of their journey.

In a series of additional experiments, Bonni's research group showed that the PHF6 protein operates in the nucleus of brain neurons, the command center of the cell. The scientists found that the PHF6 protein interacts with the PAF1 complex, a tightly bound cluster of four proteins that regulates programs of gene expression. This cluster then turns on a cell surface protein called neuroglycan C in brain neurons.

If any of these factors were inhibited, mouse brain neurons were unable to complete their normal migration. The researchers could "rescue" the neurons by restoring the missing protein, allowing the cells to complete their journey.

Disrupting proper brain structure and organization may not be the only problem caused by the PHF6 mutation. A portion of patients with Börjeson-Forssman-Lehmann syndrome also have epilepsy.

In tests in mice, Bonni's group found that the misplaced brain neurons were more excitable. This might result from changes in the activity of other proteins regulated by PHF6 and could make the brain more susceptible to seizures.

The researchers also learned that increasing the production of neuroglycan C in brain neurons overcomes the harmful effects of PHF6 loss on the migration of neurons.

"Cell surface proteins such as neuroglycan C are in

good position to help cells move through their environment," Bonni said. "The protein's position on the cell surface of neurons also one day might make it an accessible target for drug treatments for developmental cognitive disorders."

Bonni suspects there might be additional problems in [brain cells](#) that develop without normal PHF6 and that errors in the gene might even impair function in neurons that make it to their final destinations. Further studies are underway.

More information: Zhang, C. et al. The X-linked intellectual disability protein PHF6 associates with the PAF1 complex and regulates neuronal migration in the mammalian brain, *Neuron* (2013), [dx.doi.org/10.1016/j.neuron.2013.04.021](https://doi.org/10.1016/j.neuron.2013.04.021)

Provided by Washington University School of Medicine in St. Louis

APA citation: Defects in brain cell migration linked to mental retardation (2013, June 21) retrieved 12 November 2019 from <https://medicalxpress.com/news/2013-06-defects-brain-cell-migration-linked.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.