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Researchers find that 2 proteins are key for normal-sized brains

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In work that may one day correct or prevent genetic conditions tied to smaller-than-normal brains and shed light on the evolution of human head size, researchers at MIT's Picower Institute for Learning and Memory analyzed the interaction of two proteins key to brain development.

Neurogenesis is the process through which neurons are created during prenatal development to populate the growing brain. Li-Huei Tsai, director of the Picower Institute and Picower Professor of Neuroscience, found that two proteins--Cdk5rap2 and pericentrin—work together to regulate neural growth in the developing brain. Loss of function of these proteins results in human disorders such as primary autosomal recessive microcephaly (MCPH) and Majewski osteodysplastic primordial dwarfism, type II (MOPDII), genetic conditions characterized in part by abnormally small head circumference.

An understanding of these rare genetic disorders may offer insight into one of the most striking differences between us and our closest living relatives: brain size and cognitive ability.

The researchers show that Cdk5rap2 and pericentrin interact with one another to regulate proliferation of neural progenitor cells that give rise to the brain layer called the neocortex. Pericentrin recruits Cdk5rap2 to structures within the neural progenitor cells, and loss of Cdk5rap2 results in decreased cell proliferation.

"Given the link between head circumference, intelligence deficits and psychiatric disorders, these findings have implications for our understanding of how abnormalities in brain development can play a role in a number of diseases," said Tsai, a Howard Hughes Medical Institute investigator and the director of the neurobiology program at the Broad Institute's Stanley Center for Psychiatric Research. In addition to leading to potential treatments for MCPH and MOPDII, the work may also shed light on the increase in brain size during human evolution.

How They Did It: To examine the role of CdkSrap2 in neurogenesis, the researchers knocked out Cdk5rap2 in mouse embryos during brain development. Effects included an altered distribution of cells among the cortical layers of the brain.

Next Steps: The researchers are now exploring how these proteins and others mutated in individuals with MCPH may play a role in regulating signaling pathways relevant to brain development. "We would like to gain a broader understanding of how disrupted regulation of progenitor proliferation can impact brain development," Tsai said. "Ultimately, we hope to gain insight into how defects in these processes can contribute to diseases characterized by intelligence deficits and poor mental health."

More information: "Cdk5rap2 Interacts with Pericentrin to Maintain the Neural Progenitor Pool in the Developing Neocortex," Joshua J. Buchman, Huan-Chung Tseng, Ying Zhou, Christopher L. Frank, Zhigang Xie, and Li-Huei Tsai, in Neuron, published May 13, 2010.

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