**'Master Gene' Makes Mouse Brain Look More Human**

*by*[*Emily Underwood*](http://news.sciencemag.org/sciencenow/author/emily-underwood/index.html) on 25 April 2013

**[Previous Article](http://news.sciencemag.org/sciencenow/2013/04/podcast-radioactive-bacteria-the.html)**[**Next Article**](http://news.sciencemag.org/sciencenow/2013/04/scienceshot-solving-the-mystery-.html)

[**Enlarge Image**](http://news.sciencemag.org/sciencenow/assets/2013/04/25/sn-brainfolding.jpg)



**Brain origami.** Tweaking gene's activity alters how the developing brain folds.

Credit: Stockbyte/Thinkstock

In the cartoon series named after them, *Pinky and the Brain*, two laboratory mice genetically enhanced to increase their intelligence plot to take over the world—and fail each time. Perhaps their creators hadn't tweaked the correct gene. Researchers have now found a genetic mutation that causes mammalian neural tissue to expand and fold. The discovery may help explain why humans evolved more elaborate brains than mice, and it could suggest ways to treat disorders such as autism and epilepsy that arise from abnormal neural development.

In mice and humans alike, the cerebral cortex—the outermost layer of brain tissue associated with high-level functions such as memory and decision-making—starts out as a spherical sheet of tissue made up of only neural stem cells. As these stem cells divide, the cortex increases its surface area, expanding like an inflating balloon, says neuroscientist Victor Borrell of the Institute of Neurosciences of Alicante in Spain. Unlike the small, smooth mouse brain, however, the uppermost layers of tissue in the human brain cram millions of neurons into specialized folds and furrows responsible for complex tasks such as language and thought. Because the human cerebral cortex is generally considered "special," some scientists have hypothesized that the genes that govern its development of cortical folds and furrows are also unique to humans, Borrell says.

In 2012, scientists got their first hint that a gene called *TRNP1* might influence brain development in both mice and humans. The discovery came from a dissertation by Ronny Stahl, who conducted his doctoral research in the lab of co-author Magdalena Götz at Ludwig Maximilian University in Munich, Germany. In studies of neural development in mice, Stahl found that *TRNP1* produces a protein that determines whether neural stem cells self-replicate, leading to a balloonlike expansion of cortical surface area, or whether they differentiate into a plethora of intermediate stem cell types and neurons, thickening the cortex and forming more complex brain structures. Based on that discovery, the team hypothesized that varying levels of the gene's expression in mice and humans might account for the varying levels of cortical thickness and different shapes between the two species.

To test their theory, the researchers investigated what would happen to fetal mouse brains if they interfered with *Trnp1* expression using synthetic sequences of genetic material that silenced the gene, a technique called RNA interference. [The tiny fetal mouse brains developed cortical folds](http://www.cell.com/abstract/S0092-8674%2813%2900349-8), the authors report today in *Cell*. The "most exciting" part of the discovery was that "just by varying how much of this gene is expressed, we are able to have folds in the cortex," Borrell says.

The researchers also analyzed samples of human neural tissue from embryos that had been stored by a hospital pathologist. . The team found lower levels of *TRNP1* in areas that were destined to form folds, and higher levels in areas that would not have developed them, suggesting that the protein produced by the gene inhibits more complex brain development in humans as well as in mice. Although the developmental stages they analyzed in the human embryos—gestation weeks 8 to 9 and 17 to 18—occur before the folds begin to appear, Borrell says, the varying levels of gene expression provide an "instruction for something to occur."

The findings go against a common conception that "dumber species will have different genes" for brain development than more intelligent species, Borrell says. He adds that the mechanism could help explain how New World monkeys, with their small, smooth brains, could have evolved from an ancestor with a bigger and more folded brain. "It's not a linear evolution from small, simple, smooth brains to large, gyrated brains," he says. The research could also lead to better diagnosis and treatment of diseases such as microcephaly and autism, which arise from a misfolded cortex, he says.

"These are surprising and interesting findings," says Arnold Kriegstein, a neuroscientist at the University of California, San Francisco. "Clearly this is a model for both human as well as mouse development." The next step, he says, is to investigate how embryonic mouse brains with induced folds develop as they mature past the fetal stages of development and to look across species to see if the gene has similar effects in other mammals. "It is important to pursue this further," he says.