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RESEARCH NEWS

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Left- or Right-Brain? Genes May Tell the Story

Subtle differences in how a single gene behaves on opposite sides of the growing brain may explain how various intellectual talents - language, math skills, imagination - arise in specific sides of the brain in most people, according to new studies by Howard Hughes Medical Institute (HHMI) researchers.

According to HHMI investigator Christopher A. Walsh, postdoctoral fellow Tao Sun, and their colleagues at Beth Israel Deaconess Medical Center and Harvard Medical School, their discovery that a gene called *LM04* is expressed differently in the cerebral cortex in the left brain, compared to the right brain, may help understand how in most people one side of the brain achieves dominance over the other. It is well known that, in most people, the "left brain" has a larger role in languages and math, while the "right brain" is more essential for spatial tasks and abstract reasoning.

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> **— Christopher A. Walsh**

Walsh said the simple goal of the study "is to understand what makes our left brain different from our right brain. As far as we know, most other animals don't show this right/left specialization of brain function."

A detailed report on their findings is published in the May 12, 2005, edition of *Science Express* , which provides rapid online publication of select articles from *Science* magazine.

"This left/right asymmetry (in the brain) is an essential part of our humanness," Walsh said, "and learning how it comes about is important for understanding where our human abilities came from. So it speaks about evolution; it's part of the system that makes our brains so different from the brains of other animals."

Perhaps more important, this normal asymmetry of the brain is disrupted “in a host of human neurological diseases, including dyslexia, schizophrenia and other disorders,” he said. “So this may offer us entry into how such problems relate to the development of the human brain.”

The new research is based on earlier studies showing that certain genes do act differently in various areas of the brain. It was also well known that specific patterns of gene expression are involved in laying out the body's basic architecture, ensuring the heart is on the left, for example, while the liver and pancreas also grow where they're supposed to. “So we know that patterns of gene expression create the various body patterns,” Walsh explained.

Some researchers “have wondered if there are specific genes for right and left brain,” he added, “but we didn't think so. One thing we did know about gene expression patterns in the frontal cortex is that there are higher levels of gene expression in the front of the brain compared to the back. This is well known in animals.”

Years of brain research has shown, in fact, that distinct functional “maps” exist in the cerebral cortex. “There are places where visual input from the eyes goes, a different part where input from the skin goes, and another place where hearing goes. These are well-mapped areas in animals, and the same rules seem to apply to humans,” Walsh said.

This led to the hypothesis that differences in gene expression—that is, amounts and patterns of gene—ather than gene identity, might be responsible for human right brain/left brain dominance. To find out, Walsh and his colleagues obtained samples of human fetal brain tissue from the National Institutes of Health for study. They dissected specific regions of the fetal brains to prepare the brain tissue samples for study.

“We compared the future language area of the left brain with the corresponding region of the right brain,” he said. “We found a lot of genes behaving differently, but we focused mostly on one called *LMO4* .”

By studying mice with engineered mutations of *Lmo4* —prepared in the laboratory of Stuart Orkin, an HHMI investigator at Dana-Farber Cancer Institute and Children's Hospita—they showed that Lmo4 is essential for normal cortical development. Walsh said what they found in humans was a surprise: “In some areas, the amounts of *LMO4* (expression) are equal on both sides. But the level (of *LMO4* activity) in the brain's future language area - on the left - is much lower than in the right cerebral cortex. We didn't know whether there would be differences in expression or not, so we were pleasantly surprised to find differences in expression of *LMO4* .”

In contrast to humans, mice showed more subtle differences in *LMO4* gene expression, without consistent right-left bias. This is interesting because mice do develop “handedness,” preferring left paw to right paw, or vice-versa. But unlike in humans, no systematic right-left bias is seen in mice.

Walsh said this difference between animals and humans may represent “an evolutionary change, some sort of entrainment, or consistent biasing” seen only in humans, while in animals it's still a random system.

The HHMI team used new genome-wide methods to monitor the activity of thousands of genes at a time, watching for genes that were active under specific conditions.