

Research shines light on Rett Syndrome

Manipulation of gene in mice ends symptoms

By Carey Goldberg, Globe Staff | February 9, 2007

boston.com

The Boston Globe

It almost always strikes girls in infancy. It can leave them unable to walk, talk, or use their hands, racked by seizures, or gasping for irregular breaths with little prospect of improvement. But now the devastating symptoms of Rett Syndrome, a rare genetic disease related to autism, have been dramatically reversed in mice, raising a great wave of hope for families that previously had little.

Researchers reported yesterday that when they reversed the genetic defect involved in Rett Syndrome, they brought on a stunning recovery in mice just days from death: irregular breathing returned to normal and mobility was restored. Brain activity, too, appeared to improve and tremors abated. Scientists caution that it is a long way from mice to humans, that the experiments must be replicated by others, and that the genetic manipulation that restored the brains of the mice is not currently feasible in people. But they also point out that the new findings raise hope not only for people with Rett, but for those with autism and other "developmental" brain diseases that strike after birth, because the dramatic recovery of the mice suggests that the brain is far more fixable than many have thought.

"Everyone assumes that autism, schizophrenia, all these things are done deals once the symptoms are there," said Adrian Bird, senior author of the findings published on line yesterday in the journal *Science*. "But we have to ask ourselves, 'Why do we believe the brain is so fixed and non plastic?' " said Bird, a professor of genetics at Edinburgh University who found the gene that, when mutated, causes Rett. "Maybe we should look more carefully at what else can be reversed."

Rett Syndrome affects an estimated 1 in every 10,000 girls, and occasionally boys. Like autism, it often involves a regression early in life. For example, Lori McTernan of Needham had seemed a fairly normal baby at first, but at nine months she was still not crawling, and over the next few months, she made no progress with language and lost the ability to pick up food between two fingers, said her mother, Maria. Lori is now almost 15, and Maria McTernan said the *Science* paper's findings restore hope that had long since waned. "If Lori could even nod her head yes or no, that would be just unbelievable," she said.

For doctors as well as researchers, the *Science* paper provides a boost broader than Rett Syndrome, said Dr. Omar Khwaja, director of the new Rett Syndrome program at Children's Hospital Boston. "There are very few if any childhood neurological diseases that are curable," he said, but the paper provides "proof of principle" that, in an animal model at least, the symptoms of such a disease can be reversed. So what will Khwaja tell families now about potential help for humans? He does not think it can come within five years, he said, but "It's very unpredictable."

Bird's team worked on a mouse model engineered to have Rett Syndrome that could effectively be turned on and off. The researchers put a "Stop cassette," a kind of chemical roadblock, on the key gene involved in Rett. When the Stop cassette was in place, the gene did not work in brain cells and the mice had all the symptoms of the mouse version of Rett. For example, when a cage lid is lifted, normal mice scurry about but Rett mice sit still. When the mice were a few weeks old, the researchers gave them a drug that would remove the cassette, and the gene began to function. Nine of the 17 mice died, perhaps because the gene came back on too strongly, and the remaining eight showed an amazing recovery. "The first thing we thought was: 'This can't be true! These mice are completely cured! So we'd better do it again,'" said Bird, the senior author, whose research was funded in part by the Rett Syndrome Research Foundation. "The next time we got the drug dose just right, and nearly all mice were cured." The same key gene has been implicated recently in autism, learning disabilities, and some forms of mental retardation.

There are three possible ways that the *Science* experiment may eventually be translated to humans, Bird said, all just beyond the realm of what is currently possible: Gene therapy aimed at somehow producing the same effect as what was done in the mice; a drug that would imitate the effect of turning the gene back on; and a method that would somehow activate the "good," nonmutated copy of the gene that is present along with the "bad" copy in people with Rett.

Neuroscientists not involved in the *Science* paper welcomed the findings, though with the usual scientific caution. Mark Bear, director of the Picower Institute for Learning and Memory at MIT, said that the paper provided "welcome good news" with its suggestion that "it is never too late to try a new treatment for a developmental brain disorder." Of course, he added in an e-mail, "the less interesting aspect of the study is that the rescue was achieved by re-expressing the same gene. I do not think anyone expects that it will be possible, in the near future anyway, to replace a disease gene throughout the nervous system in humans like what they did here in mice."

Local parents of children with Rett said they are realistic and know that a cure remains far away. Still, news that the symptoms could be reversed in animals "seems like a miracle," said Jennifer Endres of South Yarmouth, whose 3-year-old daughter, Jillian, has Rett. Asked what improvement in Jillian they hope for most, Jennifer and her husband, Justin, said they would most love to hear Jillian speak some day. "It would be nice to hear her say, 'Mommy,' 'Daddy,' 'I love you,'" Justin Endres said. "Or to reach up to give you a hug. She doesn't have the use of her arms to do even that, to make any sign of definite communication."