UT SOUTHWESTERN MEDICAL CENTER NEWS

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New findings help pinpoint autism's genetic roots

DALLAS – May 3, 2006 – By deleting a gene in certain parts of the brain, UT Southwestern Medical Center researchers have created mice that show deficits in social interaction that are reminiscent of humans with autism spectrum disorders.

The investigators also found physical abnormalities in the brains that mimic some cases of autism, showing that the research animals can be useful in studying the mysterious condition.

The finding – to be published in the May 4 issue of the journal *Neuron* – confirms recent indications that a mutation in this particular gene could cause at least some forms of autism, said Dr. Luis F. Parada, director of the Center for Developmental Biology and the study's senior author. Dr. Parada also directs the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration.

"The exciting thing about this mouse is it helps us to zero in on at least one anatomic location of abnormality, because we targeted the gene to very circumscribed regions of the brain," he said. "In diseases where virtually nothing is known, any inroad that gets into at least the right cell or the right biochemical pathway is very important."

Autism is a brain disorder in which people have trouble with communication and social interaction and engage in repetitive movements. Usually manifesting in childhood, it affects about one in every 250 people, primarily males.

The researchers focused on a gene called *Pten*, which is also known to suppress cancers in humans. Some people with autism have mutations in *Pten*, but it has been unclear if that's what causes the disease, Dr. Parada said. To test that hypothesis, the researchers deleted the gene in the front of the mouse brain and in areas of the hippocampus, a structure involved in memory and other functions.

Mice, which are social animals, are a good model for studying the disease, Dr. Parada said. Their behavior can be studied when they are exposed to other mice, when they are provided with inanimate objects and material for making nests, and when they are placed in unfamiliar environments.

In each of those conditions, the mutant mice were distinctly different from normal mice that came from the same litter.

Mice lacking the *Pten* gene were generally uninterested in unfamiliar mice, while normal mice approached the strangers. When mutant mice were exposed to both an inanimate object and another mouse, they showed about equal interest in each – echoing the way children with autism prefer toys to people – while the normal mice preferred the other mouse. When given raw material for nesting, the

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mutants ignored it, while the normal mice teamed up to build nests. And the pups of mutant females often died from lack of maternal care.

The genetically altered mice were also hypersensitive to stressful stimuli, such as being picked up, being subjected to a sudden noise, or being put in a lighted or open area. People with autism are similarly overly sensitive to sensory stimuli.

The mutant mice's brains were also noticeably altered in the areas where the gene was deleted. The nerve cells were thicker than normal and had a higher-than-normal number of connections to other nerve cells. This may lead to the sensory overload that people with autism experience, Dr. Parada said.

The next step in the research, Dr. Parada said, is to treat the mice with drugs to see whether it's possible to reverse the condition.

Autism-like syndromes are being studied at UT Southwestern from another angle through the work of Dr. Lisa Monteggia, assistant professor of psychiatry.

Her investigation of the role of a gene called *MeCP2* in mediating autistic-like behavior has been published recently in the journals *Biological Psychiatry* and *Current Biology*. Mutations in *MeCP2* occur in a pervasive developmental disorder called Rett syndrome, a human disease that shares many clinical features with autism. Mutations in *MeCP2* also have been identified in autism patients.

In *Biological Psychiatry*, she described how the selective deletion of *MeCP2* in the brains of mice – in similar areas as those targeted by Dr. Parada – creates many of the features of Rett syndrome that are also observed in autism patients, including reduced social interaction, abnormal repetitive behavior and increased anxiety.

Current Biology reported her collaborative study with Dr. Ege Kavalali, associate professor in the Center for Basic Neuroscience, in which recorded signals from nerve cells in the mouse brain showed that in those lacking *MeCP2*, there was an imbalance between signals that excite nerve cells and those that inhibit neural activity. Such an imbalance in nerve transmission has been hypothesized as a feature of human autistic disorders; however, this is the first report demonstrating such an imbalance.

Lead authors in the *Pten* study from the Center for Developmental Biology were Dr. Chang-Hyuk Kwon, postdoctoral researcher; former graduate student Bryan Luikart, now at Oregon Health & Science University; and Dr. Craig Powell, assistant professor of neurology and psychiatry. The work was supported by the American and Lebanese Associated Charities, the National Institutes of Health and the American Cancer Society.

UT Southwestern scientists participating in the *MeCP2* research were Erika Nelson, student research assistant in psychiatry, and Terry Gemelli, former research associate in psychiatry. Dr. Monteggia's research is supported in part by the National Alliance for Autism Research, Once Upon A Time …, and the Rett Syndrome Research Foundation.