SOUTHWESTERN NEWS

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Mouse study shows NPAS3 and NPAS1 genes may be linked to psychosis

DALLAS – Aug. 30, 2004 – Mice with specific genetic mutations exhibit behavior similar to human psychosis, report UT Southwestern Medical Center at Dallas researchers, providing further support to the notion of a genetic link to schizophrenia.

The researchers genetically engineered mice with a mutation in the gene *NPAS3*, a mutation in the gene *NPAS1* or a mutation in both genes. Both genes encode proteins that switch other genes on and off in brain cells.

"These mice display certain deficits that are potentially consistent with schizophrenia," said Dr. Steven McKnight, chairman of biochemistry at UT Southwestern and senior author of the study that will appear in an upcoming issue of the *Proceedings of the National Academy of Sciences* and is to be posted online this week.

"It's too early to tell whether the abnormal behavior we observed in these mutated mice can be directly connected with human disease. On the other hand, we find it intriguing that members of a Canadian family carrying a mutation in the human *NPAS3* gene have been reported to suffer from schizophrenia."

Normal mice in a pen will climb over each other and interact, but the mice with the genetic mutations fail to socialize in this way. Instead, the mutants dart about wildly, avoiding interaction with their normal siblings.

In addition, the mutant mice do not have a normal startle response, and have a distinct reduction of a protein called reelin in their brains. Other researchers have shown in postmortem examinations of the brain tissue of schizophrenics that these patients have a reduction in reelin, said Dr. McKnight.

Schizophrenics also have problems socializing and often have enhanced physical activity, similar to that of the mutant mice. An impaired startle response, Dr. McKnight said, also may lead to a schizophrenia diagnosis.

More than 2 million Americans are affected by schizophrenia, according to the National Institute of Mental Health. The illness may impair a person's ability to manage emotions, interact with

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others and think clearly. Symptoms include hallucinations, delusions, disordered thinking and social withdrawal. Most schizophrenia patients suffer chronically or episodically throughout their lives, and one of every 10 people with schizophrenia eventually commits suicide.

"We recognize that the connection of our study to human psychosis or schizophrenia is very tenuous," Dr. McKnight said. "It's difficult to draw direct parallels between the simple behavioral abnormalities observed in the mutant mice and the complex, delusional cognitive defects that characterize human schizophrenia. Our results may turn out to have nothing to do with schizophrenia, or they could point to something more substantial."

Little is known about the *NPAS1* and *NPAS3* genes. Both genes are expressed in brain cells called inhibitory interneurons. These neurons are smaller than the typical excitatory neurons, which pass electrical signals amongst themselves and act as the brain's wiring. The role of inhibitory interneurons, on the other hand, is to dampen the activity of excitatory neurons.

The NPAS1 and NPAS3 proteins are transcription factors that can activate or deactivate other genes. Just which genes they may control is unclear, Dr. McKnight said.

Dr. McKnight and his research team are currently investigating what genes and what kind of brain cells the NPAS1 and NPAS3 proteins are acting upon. Information about this particular chemical pathway could provide further clues to a genetic link with human psychosis.

Other UT Southwestern biochemistry researchers involved in the study were first authors Drs. Claudia Erbel-Sieler and Xinle Wu, both postdoctoral researchers, and Carol Dudley, senior research scientist; Sandi Jo Estill, research assistant, and Tina Han, research technician. Dr. Ramon Diaz-Arrastia, associate professor of neurology at UT Southwestern and researchers from the University of Mississippi, the University of Cincinnati Medical School and the Children's Medical Center in Cincinnati also participated.

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