# Schizophrenia gene's role may be broader, more potent, than thought

November 19 2009

(PhysOrg.com) -- UCSF scientists studying nerve cells in fruit flies have uncovered a new function for a gene whose human equivalent may play a critical role in schizophrenia.

Scientists have known that the mutated form of the human gene - one of three consistently associated with schizophrenia - mildly disrupts the transmission of chemical signals between nerve cells in the brain.

The new study focuses on genes involved in "adaptive plasticity," the capacity of nerve cells to compensate for a wide range of perturbations and continue to function normally.

Studies ranging from fruit flies to human have shown that if a nerve cell is functionally impaired then the surrounding cells can compensate and restore normal cell-to-cell communication. This type of "adaptive plasticity" stabilizes brain function, but the molecules involved remain largely unknown.

In the current study, the team screened 276 mutated, or disabled, fly genes to determine if their absence revealed a role in adaptive plasticity in the fruit fly nervous system. While absence of most of the genes had no impact on adaptive plasticity, the absence of the gene known as dysbindin did.

The finding, reported in the November 20, 2009 issue of *Science*, was dramatic, says the senior author of the study, Graeme Davis, PhD,

Albert Bowers Endowed Professor and Chair of the Department of Biochemistry and Biophysics at UCSF.

"Mutation of the gene completely prevented the capacity of the neural circuitry to respond to an experimental perturbation, to be adaptive. The dysbindin mutation was one of very few gene mutations that had this effect," he says. "The gene's unique function suggests to us that impaired adaptive plasticity may have particular relevance to the cause or progression of schizophrenia."

Schizophrenia generally emerges in people in their late teens or early adulthood. It's possible, says Davis, that normal developmental changes at this stage of life represent a significant stress to ongoing, stable neural function. If so, he says, the capacity of the nervous system to respond to these normal developmental changes - which in a sense are perturbations - may be impaired in people who become schizophrenic.

The next question the researchers will ask," he says, "is whether absence of the dysbindin gene causes a blockade of adaptive plasticity in mice and whether other genes linked to schizophrenia cause a similar block of adaptive plasticity."

The study, led by Dion K. Dickman, PhD, a postdoctoral fellow in the Davis lab, also revealed a more general insight into the mechanisms of adaptive plasticity because they were able to rule out the involvement of numerous genes that were previously considered as candidate players.

"We tested numerous mutations that alter neural function, and most showed perfectly fine adaptive plasticity." he says, "This suggests that there are distinct roles for genes at the synapse, some support normal neural function while a small subset control adaptive plasticity."

The phenomenon of adaptive plasticity, a burgeoning area of inquiry in

the neurosciences, was first recognized more than a decade ago. Early studies by Davis, a pioneer of the field, showed that when genes functioning in the fruit fly nervous system were mutated, the nervous system would compensate and the animals appeared remarkably normal.

Davis has explored this and related phenomena at the neuromuscular junction in the fruit fly, or Drosophila melanogaster. He's been asking how neural function is stabilized but also how the physical connections between nerve cells are stabilized and maintained throughout life. He would like to understand how this process sometimes fails, leading to neurodegeneration, such as occurs in amyotrophic lateral sclerosis, or ALS.

"It's become clear that the nervous system is remarkably stable, but not as one might suspect," says Davis. "It is continuously responsive to a changing environment, which allows us to learn and remember and to respond to environmental change. There probably are many processes that are sensing the environment, continually updating neural function and neural structure in order to keep the brain stable. If we can understand how stability is maintained in the nervous system, perhaps we could understand what happens when stability is lost and disease ensues."

"These are big questions that reach far beyond our current understanding of brain function," he says. "This is the power and importance of basic science. By studying fundamental questions, you can discover unexpected phenomenon and also create new perspectives for understanding existing diseases, even if the human genes are known." The new finding, he says, "may add a new dimension to the conversation about the origins of schizophrenia."

Provided by University of California - San Francisco