Scientists identify new gene for memory

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A team led by a Scripps Research Institute scientist has for the first time identified a new gene that is required for memory formation in *Drosophila*, the common fruit fly. The gene may have similar functions in humans, shedding light on neurological disorders such as Alzheimer's disease or human learning disabilities.

The study was published in the September 9, 2010 edition (Vol. 67, No. 5) of the journal *Neuron*.

"This is the first time we have a new memory and learning gene that lies outside what has been considered the most fundamental signaling pathway that underlies learning in the fruit fly," said Ron Davis, chair of Scripps Research Department of Neuroscience who led the study. "Since many of the learning and memory genes originally identified in the fruit fly are clearly involved in human neurological or psychiatric diseases, this discovery may offer significant new insights into multiple neurological disorders. We're definitely in the right ballpark."

The study shows that different alleles or mutant forms of the gene, known as gilgamesh (gish), are required for short-term memory formation in *Drosophila* olfactory associative learning - learning that links a specific odor with a negative or positive reinforcer.

Because *Drosophila* learning genes are known to be conserved in higher organisms including humans, they often provide new insights into human brain disorders. For example, the *Drosophila* gene known as dunce, which Davis helped identify several years ago, provided clues to the

genetics of the devastating psychiatric condition of schizophrenia. Recent studies have revealed that the human version of the dunce gene is a susceptibility determinant for schizophrenia. In a similar way, any new learning gene identified in *Drosophila*, including gilgamesh, may provide new clues to genes involved in human neurological or psychiatric disorders.

"We're still early in the process of making connections between *Drosophila* memory and learning genes and the pathology of human disease," Davis said, "but it's already clear that many of these genes will provide important conceptual information and potential insights into human brain disorders. In addition, there is every reason to believe that their gene products will be one day become the target of new drugs to enhance cognition. Uncovering this new gene and its signaling pathway helps bring us that much closer to this goal."

New Gene, New Pathway

To identify the new gene, Davis and his colleagues used a novel screen for new memory mutants, looking for lines that showed abnormal learning when only one of two copies of the gene was mutant.

"We used a dominant screen because we realized that behavior such as learning and memory are very sensitive to gene dosage," Davis said. "That is, the mutation of just one copy of a gene involved in behavior is often sufficient to produce an abnormality."

The formation of new memories occurs, in part, through the activation of molecular signaling pathways within neurons that comprise the neural circuitry for learning, and for storing and retrieving those memories.

One of the things that makes the function of gish so interesting, Davis noted, is the fact that it is independent of mutations of the rutabaga gene,

a *Drosophila* memory-learning pathway that is known to be essential for memory formation. The rutabaga mutants convert ATP, the energy chip of cells, into cyclic AMP or cAMP, which plays a critical role in olfactory learning in *Drosophila*.

"The cAMP pathway is the major signaling pathway used by *Drosophila* neurons to turn on other enzymes and genes that are necessary for memories to form," Davis said. "In fruit flies, memory and learning revolves around mutants of this pathway. It is fundamental to the process."

In the new study, gish provided an answer to a longstanding problem in *Drosophila* learning and memory research - the unexplained residual memory performance of flies carrying rutabaga mutations, which indicated the existence of an independent signaling pathway for memory formation. While other memory mutants have been identified, until the discovery of gish none have been shown to reduce the residual learning of mutant rutabaga flies.

Interestingly, the study found that the gish gene encodes a kind of casein kinase (which help regulate signal pathways in cells) called Iγ (CKIγ). This is the first time that this specific kinase has been cited as having a role in memory formation.

The identification of all signaling pathways that are engaged in specific neurons during memory formation and how they interact with one another to encode memories is an issue of great importance, Davis said, one that needs more exploration for a deeper understanding of memory formation and memory failure in humans.

"The truth is that we have an extremely sketchy understanding of what causes diseases like Alzheimer's," Davis said. "We need to understand a lot more than we do now about normal brain functions like memory and

learning before we have a high probability of succeeding in the development of a cure."

More information: "Gilgamesh is required for Rutabaga-independent Olfactory Learning in Drosophila," Ying Tan et al. *Neuron*.

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