# Stumbling fruit flies lead scientists to discover gene essential to sensing joint position

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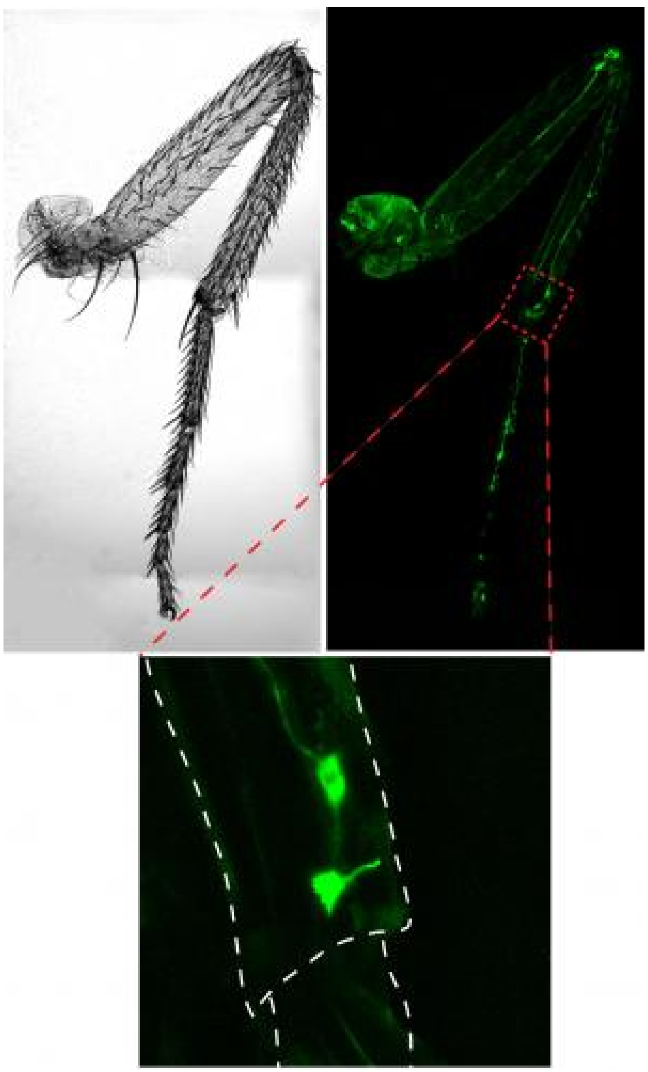

The new study identified a new gene and a type of nerve cell required for detection of leg position. This image shows a stum-expressing sensory neuron in a leg joint. Credit: Image from the Cook lab, The Scripps Research Institute.

Scientists at The Scripps Research Institute (TSRI) have discovered an important mechanism underlying sensory feedback that guides balance and limb movements.

The finding, which the TSRI team uncovered in fruit flies, centers on a gene and a type of nerve cell required for detection of leg-joint angles. "These cells resemble human nerve cells that innervate joints," said team leader Professor Boaz Cook, who is an assistant professor at TSRI, "and they encode joint-angle information in the same way."

If the findings can be fully replicated in humans, they could lead to a better understanding of, as well as treatments for, disorders arising from faulty proprioception, the detection of body position.

A report of the findings appears in the March 14, 2014 issue of the journal *Science*.

## A Mystery of Sensation

The proprioceptive sense of how the limbs are positioned is what enables a person, even with eyes closed, to touch the tip of the nose with the tip of a finger—an ability easily impaired by alcohol, which is why traffic police often test suspected drunk drivers this way.

Scientists have known that proprioceptive signals originate from so-called mechanosensory neurons, whose nerve ends are embedded in muscles, skin and other tissues. The stretching or compression of these tissues opens ion channels in the nerve membrane, which results in a signal to the brain.

What hasn't been clear is how such a neuron can specialize in sensing just one type of membrane-distorting stimulus—such as the angle of a limb joint—yet exclude others, such as impact pressures.

In the new study, Cook and two members of his laboratory, first author Bela S. Desai, a postdoctoral fellow, and graduate student Abhishek Chadha, sought to shed some light on this mystery with a study of Drosophila fruit flies. Quickly maturing and easily studied, *Drosophila* often are analyzed for clues to the genetic underpinnings of basic animal behaviors.

## Following the Trail

Cook and his colleagues began with a special collection of *Drosophila* containing a variety of uncatalogued mutations. The scientists sifted through the collection looking for mutant flies with walking impairments and soon zeroed in on several impaired walkers that turned out to have mutations in the same gene.

The scientists named the gene stumble (stum for short) for the abnormality caused by its absence.

Using a fluorescent tracer, they then localized the expression of stum in normal flies to neurons that lay close to the three main leg joints. Each neuron's input-sensing tendril (dendrite) grew right up to the joints—a sign that its evolved function is to detect joint angle.

The researchers also found that the protein specified by the stum gene normally migrates to the tip of each dendrite. With high-resolution microscopy, they imaged each of these tips and observed an extra length branching more or less sideways at the joint.

At ordinary, at-rest joint angles, the relative positions of the main dendrite tip and its side branch stayed more or less the same; however, at extreme joint angles, the pair stretched out. As they did, the level of calcium ions in the neuron rose sharply, suggesting that ion channels had opened and the neuron was becoming active.

Cook noted the results show how a seemingly general mechanosensory, membrane-stretch-sensitive neuron can evolve a specificity for a particular type of proprioceptive signal. "It's a nice example of how you can create that specificity from something that only stretches mechanically," he said.

The team is now trying to nail down the specific role of stum proteins in *Drosophila* and to determine whether the human version of stum—which has never been characterized—also works in joint angle sensing. Some sensory role for the human version of stum is likely, as the stum gene has been remarkably well conserved throughout animal evolution. Cook and his colleagues were even able to restore some normal walking ability to stum-mutant flies by adding the mouse version of the stum gene. "Stum is probably doing the same thing in all animals," he said.

The title of the *Science* study is "The stum Gene Is Essential for Mechanical Sensing in Proprioceptive Neurons."

**More information:** "The stum Gene Is Essential for Mechanical Sensing in Proprioceptive Neurons," by B.S. Desai; A. Chadha; B. Cook, *Science*, 2014.

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