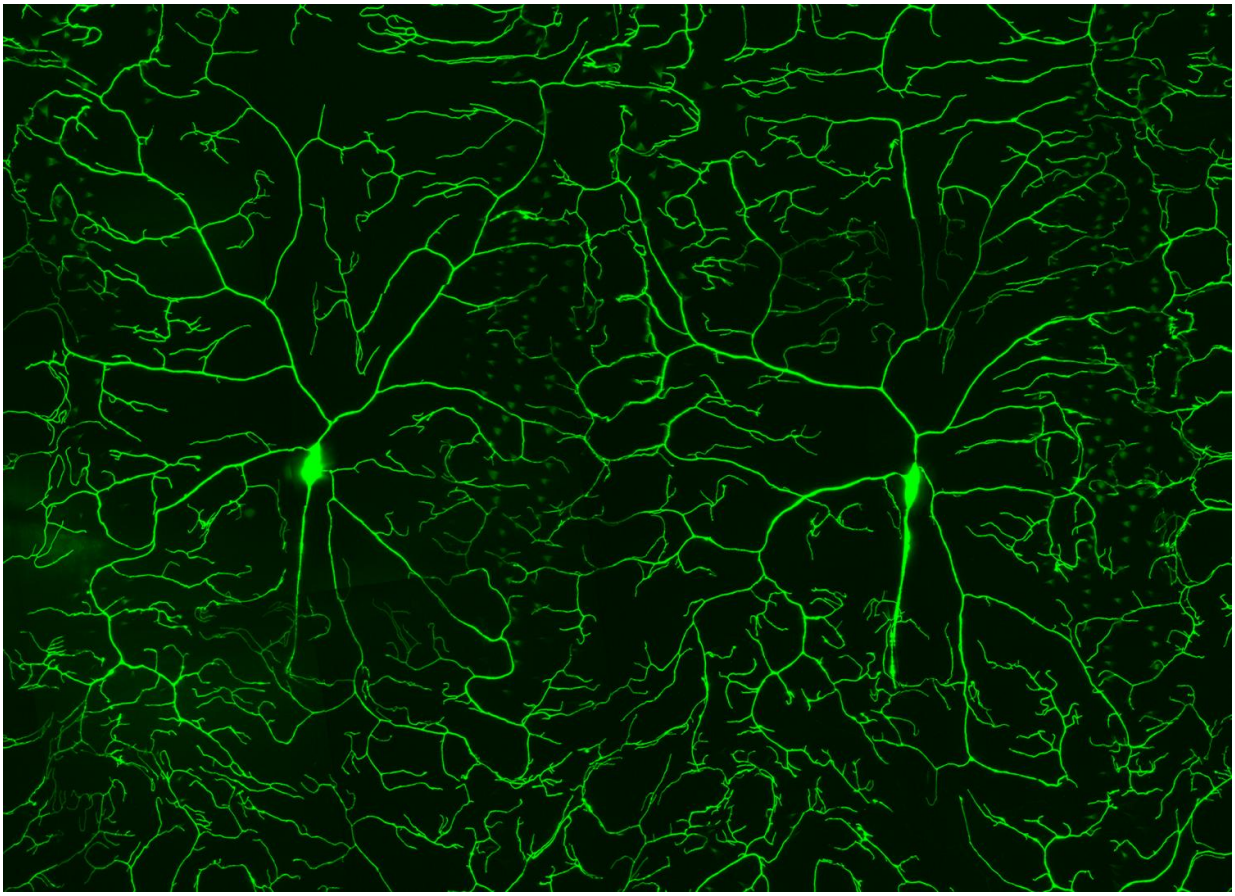
'Smoke alarm' one of 36 genes newly found to play role in pain sensation

June 23 2016



This image, captured with a high-powered confocal laser microscope, shows pain-sensing neurons in the skin of a larval fruit fly. Credit: Stephanie E. Mauthner

Indiana University researchers have that found a suite of genes in both

fruit flies and humans—including one dubbed "smoke alarm"—plays a role in nerve sensitivity. The study could help lead to new drug targets in pain management.

The research, published today in the journal *Cell Reports*, was led by W. Daniel Tracey Jr., a professor in the IU Bloomington College of Arts and Sciences' Linda and Jack Gill Center for Biomolecular Science and the Department of Biology.

"Our study is the first to thoroughly assess the function of a large set of genes expressed at high levels in nociceptive neurons, the nerves responsible for the sensation of pain in humans," Tracey said. "It represents a significant step forward in the field of nociception and pain research."

First author on the paper is Ken Honjo of the University of Tsukuba in Japan. Honjo conducted work on the project as a member of Tracey's lab at Duke University, where Tracey was previously on faculty. Also an author is Stephanie E. Mauthner, an assistant scientist at IU Bloomington.

A total of 36 genes were identified as having a role in either hypersensitivity or lack of sensation to stimuli, 20 of which are found in both humans and fruit flies, or Drosophila. Approximately 70 percent of genes in humans are also found in flies, originating in a common ancestor.

The 36 "genes of interest" in the study were screened from a total of 275 genes previously identified by Tracey's lab to express at higher-than-average levels in nociceptors, the nerves that send signals to the brain in response to strong external stimuli.

The human brain can interpret signals from these nerves as pain. In flies,

they may be triggered by mechanical stimuli or high heat. Of the 36 genes under investigation, 22 genes were found to play a role in hypersensitivity to heat; 14 were found to play a role in insensitivity.

"This first group appears to activate a function that inhibits the nociceptors," Tracey said. "These are interesting because you can imagine that if you could make a drug that was able to activate an inhibitor, then you could block pain."

Although nociceptors can trigger pain sensation based on sensory input, Tracey said the nerves can also play a role in other forms of pain not triggered by external stimulation, including chronic or neuropathic pain, estimated to affect 1.5 billion people and up to 4.5 percent of the global population, respectively, according to the American Academy of Pain Medicine.

As the first researchers to ascribe a function to the majority of these genes, Tracey's team had the right to name them. The genes implicated in heat hypersensitivity were named after objects that burn at high temperatures, including "black match," "eucalyptus," "firelighter," "primacord" (a detonating cord used in explosives), "jet fuel," "detonator," "gasoline," "smoke alarm" and "jetboil" (a campsite cooking system).

Genes implicated in heat-resistance were similarly named. They included "boilerman," "bunker gear," "fire dancer," "oven mitt," "trivet" and "thawb" (a traditional, ankle-length garment worn in the desert).

To identify these genes, Tracey's team bred multiple strains of fruit flies, each with one of the 275 genes under investigation suppressed through RNA interference—in which RNA molecules are used to inhibit the expression of a specific gene. The flies were then exposed to two temperatures—42 and 46 degrees Celsius—as larvae, which normally

react to the higher of these temperatures by rolling slowly. If they rolled more quickly at 42 degrees, it indicated hypersensitivity. If they did not roll at 46 degrees, it indicated insensitivity.

Moreover, Tracey said nine of the genes related to insensitivity caused the flies to grow a lower-than-average number of the nerve branches, or "dendrites," connecting nociceptors to the surface of the body. Two of the genes related to hypersensitivity, including "smoke alarm," caused the flies to grow extra dendrites.

The specific reason for this branching behavior is one of the new questions posed by this research. More broadly, Tracey aims to conduct further studies that examine the exact chemical pathways these genes activate in nerve cells in order to understand precisely why they result in changes in sensitivity.

More information: *Cell Reports*, DOI: 10.1016/j.celrep.2016.06.003 , www.cell.com/cell-reports/full … 2211-1247(16)30722-7 , On biorxiv: biorxiv.org/content/early/2016/05/18/053413

Provided by Indiana University