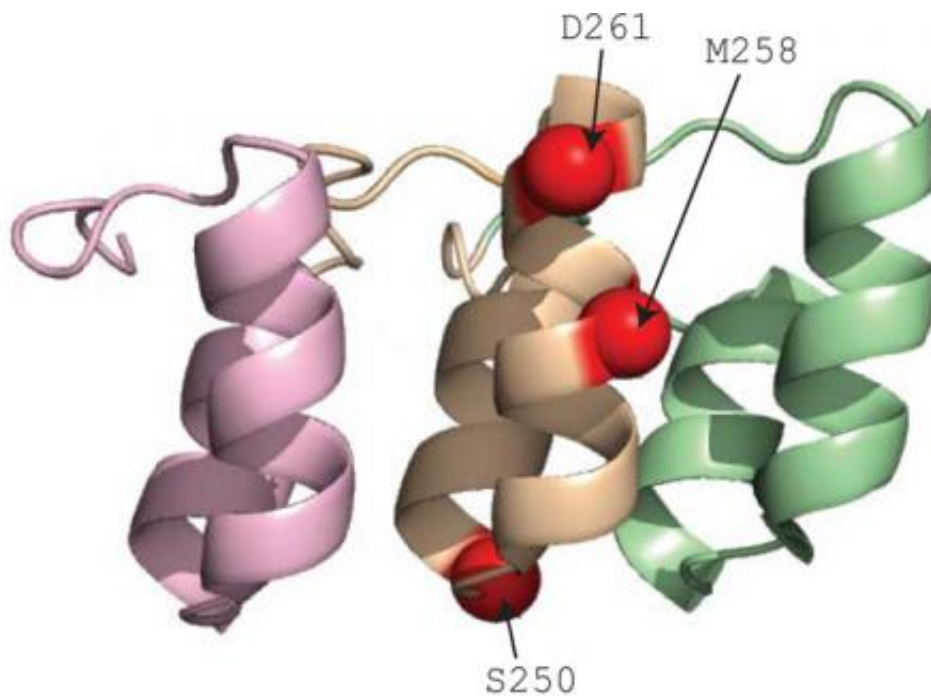


Small mutation changes brain freeze to hot foot

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This ribbon diagram shows three ankyrin repeats, a common structure found in receptor proteins that sense either cold or hot temperatures. A Duke team has identified three single-point mutations that can invert temperature-sensitivity, turning a cold-sensor into a heat-sensor. All three of these mutations are located in on a single ankyrin repeat. Credit: Grandl Lab, Duke University

Ice cream lovers and hot tea drinkers with sensitive teeth could one day have a reason to celebrate a new finding from Duke University

researchers. The scientists have found a very small change in a single protein that turns a cold-sensitive receptor into one that senses heat.

Understanding sensation and pain at this level could lead to more specific pain relievers that wouldn't affect the central nervous system, likely producing less severe side effects than existing medications, said Jörg Grandl, Ph.D., an assistant professor of neurobiology in Duke's School of Medicine who led the research team.

Temperature-induced pain, also called thermal pain, occurs when the body's sensory neurons come in contact with temperatures above or below a certain threshold, such as plunging a limb into freezing water.

"We want to understand how either hot or cold temperatures can activate the sensors of hot and [cold temperatures](#) in the body," Grandl said.

Previous research has identified transient receptor potential (TRP) ion channels as being highly sensitive to either cold or hot temperatures. TRP ion channels are porous proteins that play a role in initiating electrical signals by controlling the flow of charged ions across the cell membrane.

It's still unclear how temperatures make this happen, but the Grandl team's research reveals that single-letter changes in DNA, called point mutations, are sufficient to make cold-sensitive TRP ion channels become sensitive to hot temperatures instead.

"There is strong interest in understanding temperature-sensitive molecules from a functional perspective because they are promising targets for developing analgesic compounds to treat chronic pain," said Grandl, who is also a member of the Duke Institute for Brain Sciences. "It is something we currently do not treat well. So, one promising strategy is to stop pain where it is initially sensed—at that first molecule

that functions as a sensor of pain."

In a study appearing online early May 8 in the journal *Neuron*, Grandl's team focused on TRPA1, an ion channel best known as a sensor for pain caused by environmental irritants and pungent chemicals, such as mustard oil, the active compound found in wasabi.

Grandl's colleagues, postdoctoral fellow Sairam Jabba and research technician Raman Goyal, investigated whether single-point mutations could change cold-activated mouse TRPA1 into heat-activated. They formed this hypothesis because, in some other animals, including *Drosophila* fruit-flies and rattlesnakes, TRPA1 is naturally heat-activated.

To identify these structures, the team created a library of 12,000 mutant clones of the cold-activated mouse TRPA1 ion channel and randomly inserted one or two point mutations into each clone. After placing single clones into the individual slots of a 384-well plate and heating it from 25 degrees Celsius to 45 C in a matter of seconds, they were able to measure the thermal sensitivity of each mutant protein.

This screening pinpointed seven clones that showed strong activation when exposed to heat. Gene sequencing of these clones revealed 12 mutations that could potentially be responsible for changing the mouse TRPA1 from cold-activated to heat-activated. Out of these 12 mutations, Jabba and Goyal identified three mutations powerful enough to individually make that switch in TRPA1.

The mutations all turned out to be located within a single small domain of the ion channel protein known as ankyrin repeat six, indicating this domain plays a role in determining cold or heat activation. Ankyrin repeats are often responsible for managing protein-to-protein interactions, but their precise function in TRPA1 had not been

previously known.

Interestingly, these single-point mutations didn't change the ion channels' responses to chemicals, such as mustard oil.

"This was very surprising and it demonstrates that making a single-point mutation produced a profound change in the temperature sensitivity of the protein, but it did not affect the chemical sensitivity," Grandl said. "It shows these mechanisms are to some degree distinct."

Grandl said that taken together, the findings also suggest that the effectiveness of such a small mutation might have been key to a single ancestral ion channel evolving into the wide diversity of temperature-activated [ion channels](#) we see today.

More information: "Directionality of temperature-activation in mouse TRPA1 ion channel can be inverted by single-point mutations in ankyrin repeat six," Sairam Jabba, Jörg Grandl et al. *Neuron*, June 4, 2014.

Provided by Duke University

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