Research team elucidates evolution of bitter taste sensitivity

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Researchers from the University of Pennsylvania asked 296 Africans from a variety of groups -- here, a group of Yaaku people in Kenya -- to perform "taste tests" of progressively more concentrated solutions of salicin and report when they could detect a bitter taste. They matched the participants' genotypes onto their phenotypes, and found one genetic variant, prevalent in East African people, correlated with a high sensitivity to salicin's bitterness. Credit: University of Pennsylvania

It's no coincidence that the expression "to leave a bitter taste in one's mouth" has a double meaning; people often have strong negative reactions to bitter substances, which, though found in healthful foods like vegetables, can also signify toxicity. For this reason, the ability to sense bitterness likely played an important role in human evolution.

A new study by University of Pennsylvania scientists provides new evidence underlining the significance of bitter taste perception. Their work suggests that a genetic mutation that makes certain people sensitive to the taste of a bitter compound appears to have been advantageous for certain human populations in Africa. Yet the reason why this trait was selected may not have to do with just taste. Instead, the molecular receptor under study may also play important roles in immune response or metabolism.

"We're starting to understand that these taste receptors are involved in so many functions other than just oral sensory perception," said Michael Campbell, lead author on the study and a postdoctoral fellow in Penn's Perelman School of Medicine's Department of Genetics.

The study, published in the journal *Molecular Biology and Evolution*, represents the first time that this bitter-taste sensing gene, TAS2R16, was studied in a large set of ethnically and culturally diverse African populations.

"Because Africa is the site of origin of all modern humans," said Sarah Tishkoff, the study's senior author and a Penn Integrates Knowledge Professor with appointments in the School of Arts and Sciences' Department of Biology and Penn Medicine's Department of Genetics. "Africans are going to have a large amount of diversity and non-Africans are going to have a subset of that diversity. In Africa, you get an opportunity to observe how these genetic variants are influencing phenotypes that you wouldn't have if you were only studying non-

Africans."

Campbell, Tishkoff and other Penn researchers collaborated with Paul Breslin of Rutgers University and Monell Chemical Senses Center, as well as scientists from Addis Ababa University, France's Musée de L'Homme, Integral Molecular Inc., the Kenya Medical Research Institutes, Cameroon's Ministry of Scientific Research and Innovation, Tanzania's Muhimbili University of Health and Allied Sciences and the National institute on Deafness and Other Communication Disorders.

The work builds on a previous study by the group, which explored the evolutionary history of a gene called TAS2R38, responsible for the ability to perceive the bitter tasting compound PTC. In that research, published in Molecular Biology and Evolution in 2011, the geneticists discovered that something other than taste perception must have driven the selection of that gene.

The current work examines the related gene TAS2R16, which codes for a molecular receptor that binds salicin. Salicin is a chemical found naturally in willow bark, the source of aspirin. It acts as an anti-inflammatory but in large doses can be toxic. It is also found in many nuts, fruits and vegetables.

To understand the patterns of variation at TAS2R16 in humans globally, the researchers collected DNA from 595 people in 74 populations across Africa with diverse lifestyles, such as pastoralism, hunting-gathering and agriculture. They sequenced the stretch of DNA encompassing the TAS2R16 gene in all of these individuals and also examined previously collected DNA from 94 non-Africans from the Middle East, Europe, East Asia and the Americas and found 15 variants total, most of which were only found in Africa.

In addition, the researchers asked 296 of the Africans sampled to

perform "taste tests" of progressively more concentrated solutions of salicin and report when they could detect a bitter taste. The team also performed a cellular analysis, led by Integral Molecular scientists, to see the molecular effects of different TAS2R16 mutations.

The taste testing shows that the mutations in TAS2R16 had functional significance for the bitter taste perception system," Breslin said. "In this case, the mutation caused a gain of taste function.

When the researchers "mapped" individuals' genetic profiles onto their tasting ability, they found a strong correlation between one of the 15 variants and an increased sensitivity to salicin. The cell-based analysis offered an explanation for this sensitivity: cells with this genetic mutation had nearly twice as many receptors for salicin on their membranes as did cells with other forms of the TAS2R16 gene.

On a population level, the researchers found that the "high-sensitivity" variant for salicin was more prevalent in individuals from East Africa than in those from West Central or Central Africa, and non-Africans possessed only the "high-sensitivity" version of the gene. What's more, in East Africans this high-sensitivity variant, which arose roughly 1.1 million years ago, showed signs of being under a force of natural selection in humans, suggesting it conferred an evolutionary advantage at some point during our past.

"That's another sign that this variant must be tremendously important for human survival because it evolved in our human ancestors so long ago and carried over to us," Campbell said.

The geographic structure of TAS2R16 variants contrasts with the previous work on TAS2R38, variants of which did not appear to fall into any clear geographic pattern. These differences between two genes that both relate to bitter taste perception offer more support to the idea that

taste was not the only force driving the evolution of this gene.

"The types of populations we're studying are diverse and they have diverse diets," Tishkoff said, "suggesting that there is likely something else going on here. By getting a handle on how much variation is in these populations, where it is located and what are the particular signatures of selection, it might start giving us clues as to what we should be looking at in terms of the biomedical or physiological significance of these genes."

Provided by University of Pennsylvania