There's a gene for detecting that fishy smell, olfactory GWAS shows

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A child smelling fish. Credit: Jón Gústafsson, deCODE Genetics - Amgen Inc

For many people, the smell of fish is rather strong and unpleasant. But some people carry a mutation in a particular gene that makes that fish odor less intense, reports a paper publishing October 8 in the journal *Current Biology*. The study, which is the largest genome-wide association study (GWAS) of olfactory genes in humans involving a sniff test and looked at over 9,000 people from Iceland, also shows that people vary in their ability to discern the smell of licorice and cinnamon.

"We discovered sequence variants that influence how we perceive and describe fish, licorice, and cinnamon odors," said Rosa Gisladottir of deCODE Genetics in Reykjavik, Iceland. "Since our sense of smell is very important for the perception of flavor, these variants likely influence whether we like food containing these odors."

Researchers have known that people perceive odors based on olfactory receptors encoded by 855 olfactory genes. But about half of those genes in people are thought to lack function, leaving us with a relatively small repertoire of about 400 olfactory genes. The reason humans have lost so many olfactory genes has remained mysterious. It is also not well understood how variation in these genes might influence differences among people in their sense of smell.

To explore this in the new study, Gisladottir and her colleagues including Kari Stefansson, also of deCODE, enlisted 9,122 Icelanders in a GWAS in search of variants that influence odor perception. To do it, they asked study participants to smell odors presented to them in pen-like devices that released a particular scent when uncapped. After sniffing each odor "pen," the researchers asked them to name the smell. Participants also rated the intensity and pleasantness of the smell. Those odors included key ingredients found in licorice, cinnamon, fish, lemon, peppermint, and banana.

A participant in the smell test. Credit: Jón Gústafsson, deCODE Genetics - Amgen Inc

Their search turned up variants in three genes or genetic loci of interest, which they were able to confirm in a separate sample of 2,204 Icelanders. One of them is in a non-canonical olfactory receptor gene called trace amine-associated receptor 5

(TAAR5). The TAAR5 variant affects perception of fish odor containing trimethylamine, a compound found in rotten and fermented fish, as well as other animal odors and various bodily secretions. In the smell tests, people with a particular variant of this gene were more likely to not smell anything when presented with the fish odor or to use descriptors for it that were neutral or positive and not seafood related, such as "potatoes," "caramel," and "rose." The findings are the first to show an important role for this gene in people, the researchers say.

"Carriers of the variant find the fish odor less intense, less unpleasant, and are less likely to name it accurately," Gisladottir said. "There is a lot of animal research on TAAR5 in relation to its role in hard-wired aversive responses to trimethylamine. Our findings extend the implications of this research to human odor perception and behavior."

The other two discoveries were found in more typical and common olfactory gene variants. They influenced an individual's ability to name licorice and cinnamon odors. They also influenced the intensity and pleasantness associated with those odors.

"We discovered a common variant in a cluster of olfactory receptors which is associated with increased sensitivity to trans-anethole, found in black licorice products but also in spices and plants such as anise seed, star anise, and fennel," Gisladottir said. "Carriers of the variant find the licorice odor more intense, more pleasant, and can name it more accurately. Interestingly, the variant is much more common in East Asia than in Europe."

The scent pens used in the smell test. Credit: Jón Gústafsson, deCODE Genetics - Amgen Inc

The cinnamon variant influenced the perception of trans-cinnamaldehyde, the major ingredient in both Chinese and Ceylon cinnamon. Carriers of the variant can name the cinnamon odor more accurately, they report. They also find it more intense.

Overall, the findings show that variation in olfactory genes influences odor perception in humans. They also show that, while humans have fewer olfactory genes compared to other species, some of the genetic variation that people do carry makes them more sensitive to particular smells such as licorice or cinnamon, not less.

"When coupled with evidence for geographical differences in allele frequencies, this raises the possibility that the portion of the extensive sequence diversity found in human olfactory receptor genes that affects our sense of smell is still being honed by natural selection," the researchers wrote.

The researchers say they will continue to collect data on odor perception in people. They also plan to use the same olfactory tasks to investigate smell deficits in the context of COVID-19.

More information: *Current Biology*, Gisladottir et al.: "Sequence variants in TAAR5 and other loci affect human odor perception and naming" www.cell.com/current-biology/f … 0960-9822(20)31343-9 , DOI: 10.1016/j.cub.2020.09.012

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