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COMMENTARY

Gustation Genetics: Sweet Gustducin!

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Abstract

Two recent studies, the second of which is reported herein, provide evidence that genetic variation in the sweet receptor subunit, *TAS1R3*, and the second messenger, gustducin (*GNAT3*), affect the ability of people to correctly sort ascending concentrations of sucrose. These findings raise questions about how variation in the *TAS1R3* and *GNAT3* gene shape the human sweet tooth and its unwelcome consequences, diabetes and obesity.

Key words: genotype, phenotype, sweet

Sugar is an economic as well as a biological stimulus. The activation of the sweet receptor causes pleasure that people will pay for, recently spending $70.1 billion on sweetened soda drinks in the United States alone (Fletcher et al. 2009). Sugar is also important to the health-care debate because it is believed to contribute to obesity and diabetes (Bray et al. 2004). Sin taxes for popular products with added sweeteners (like soda) are under serious consideration by lawmakers in the United States (Adamy 2009). But rarely do we ask why humans like sugar so much, even less rarely to do we consider why some people like it more than others (Reed et al. 2006).

Fushan et al. (2009) make a step toward addressing this complex issue by discovering how people might differ genetically in sweet sensitivity. They report in this issue of *Chemical Senses* that there is a statistical association between the sucrose sensitivity of human subjects and the genotype of alleles near the α-gustducin gene. α-Gustducin is a G-protein subunit that is selectively expressed in taste cells (McLaughlin et al. 1992) and has been implicated in the intracellular signaling cascades underlying taste transduction. Knockout mice lacking α-gustducin have an impaired ability to taste sugars and other sweeteners (as well as bitter and umami compounds but not sour or salty ones) (Wong et al. 1996; He et al. 2004). Individual differences in human sweet perception are probably determined by multiple genes, and with this discovery the list has now grown, starting with the original discovery by these authors of the effects of upstream alleles of the sweet receptor subunit *TAS1R3* (Fushan et al. 2009), to encompass a second gene involved in intracellular signaling.

The authors discovered this association by comparing subjects' alleles of "taste genes" (identified in earlier work as important in taste perception) with their results on a psychophysical test, which involved ranking a series of sucrose concentrations in the correct order. The authors infer that this test measures sweetness sensitivity, but the term "sensitivity" is imprecise and it is unclear what exactly is measured when sucrose solutions are ranked. We might wonder why this test is better than, say, another fast threshold method that was successfully used by the authors to identify the famous dimorphism in bitter tasting ability (Kim et al. 2003).

Having mentioned the limitations of the phenotyping measure, it is important to mention its strengths. This is a fast, fun, and reliable metric of taste, and it is thus important for investigators conducting epidemiological and genetic studies of taste to know about; experts are currently debating about the best methods to use for these large-scale studies (Toolbox 2009). Although it may be unfamiliar to some readers of *Chemical Senses*, the success of the test here may lure taste and smell psychophysicists to use it in futures studies. Also, the ability to judge the relative taste intensity at different concentrations is of practical and evolutionary importance.

Ranking apples by how sweet they are is a task as relevant today as it was to our ancestors (Pollan 2001).

A strength of this study was the control of false-positive results: they dealt firmly with the 3 main culprits of spurious association: 1) by reducing the number of tests, focusing on candidate genes, 2) when positive results were obtained, expanding the genotyping to rule out the influence of flanking genes, and 3) demonstrating that the allele has the same direction and magnitude of effect regardless of racial group, ruling out ethnic stratification as an explanation for the association. (Ethnic stratification occurs when a trait varies between 2 ethnic groups; when this happens, any allele that also varies between the groups will appear to be related to the trait.) However the authors may have missed links between perception and rare variants in genes like *TAS1R2* (Kim et al. 2006) because too few people were studied. The power to detect an association might also be diminished because rare variants may not be in linkage disequilibrium with common nearby alleles chosen for genotyping. One solution would be to group people by those with or without any rare variant, focusing on alleles that change the amino acid sequence. (This type of rare variant is often deleterious [Kryukov et al. 2007].) Therefore, allelic variation in the *TAS1R2* gene (or others with this pattern of genetic variation) may be more influential than the results reported here suggest.

One of the frustrations of genetic association studies is that associations between alleles and traits, no matter how statistically compelling, do not unequivocally identify the exact allele (or even the exact gene). Gustducin is near another gene with a proposed role in taste, CD36 (Laugerette et al. 2005), and the association may have arisen through linkage disequilibrium, when alleles hitchhike together during meioses, making it difficult to distinguish the causal from "ride-along" allele. The issue of gene specificity could have been resolved if the authors had provided a mechanistic explanation for how the associated alleles in the vicinity of the gustducin gene might affect gustducin messenger RNA expression or otherwise affect gustducin gene function. As it stands, like many genetic association studies, the satisfaction of finding the missing link to causality has been, at least temporarily, frustrated. Regardless, this research has laid a firm foundation, demonstrating that genetic variation is important in human taste perception: there may be other genes which influence sweet perception in mice and rats which might also be important in humans (Bachmanov et al. 2002; Tordoff 2010) and genome-wide studies to find them lie ahead.

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