Published in final edited form as:

Clin Ther. 2017 October ; 39(10): 2038–2048. doi:10.1016/j.clinthera.2017.08.012.

Use of adult sensory panel to study individual differences in the palatability of a pediatric HIV treatment drug

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Abstract

Purpose—The recommended first-line treatment for young children infected with human immunodeficiency virus (HIV) includes the liquid formulation of the co-formulated protease inhibitors lopinavir/ritonavir (KaletraTM). Clinical reports indicate that some children readily accept the taste of Kaletra, whereas others strongly reject it, which can deter therapeutic adherence and outcomes.

Methods—As a proof-of-concept approach, we used a sensory panel of genotyped adults to document the range of individual differences in the taste and palatability (hedonics) of the liquid formulation of Kaletra and other taste stimuli, including common excipients. Panelists rated taste sensations using generalized labelled magnitude scales to determine genotype-phenotype relationships. Several months later, they were retested to assess response reliability.

Findings—Not all panelists had the same sensory experience when tasting Kaletra. Palatability ratings varied widely, from moderate like to strongest imaginable dislike, and were reliable over time. The more irritating and bitter Kaletra tasted, the more disliked by the panelist. The more they disliked the taste of Kaletra, the more they disliked the taste of its excipient ethanol and the bitter stimulus denatonium. Those who experienced less bitter and sweeter taste sensations had a different genetic signature than the others. Bitterness and irritation ratings of Kaletra varied by the orphaned bitter receptor gene, *TAS2R60*, whereas sweetness ratings of Kaletra varied by the cold receptor gene, *TRPM8* which is activated by menthol, an excipient of Kaletra. Neither genotype related to ratings for ethanol or denatonium, however.

Implications—The use of a sensory panel holds promise as a first step in determining the nature of individual differences in the palatability of existing pediatric drug formulations and sources of

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Clinical Trials Registration: Genetic variability in taste perception study: <https://clinicaltrials.gov/ct2/show/NCT01841710>; registry number NCT01841710, registered 24 October 2013.

Conflicts of interest: none.

variation. In this era of personalized medicine, the need is great to develop psychophysical tools to determine which drugs will show variation in acceptance by children and whether patterns of individual variation in taste as assessed by adults mirror those of young patients.

Keywords

pediatric drug; liquid formulation; taste; hedonics; candidate genes; adult sensory panel

Introduction

The World Health Organization estimates that half of all pediatric patients do not take their medicines correctly¹, in part because of the lack of “child-friendly,” good-tasting formulations^{2,3}. It has been argued that the bitter taste of a drug is a sensory expression of its pharmacological activity⁴. And the more bitter its taste, the more likely children will reject it, especially when they are unable to swallow solid oral dosage forms (e.g., pills, capsules) which have the advantage of encapsulating the taste of the active pharmaceutical ingredients (APIs)¹ and instead are treated with liquid formulations. However, recent discoveries shed light on why solid oral dosage forms do not completely bypass the negative effects of liquid formulations⁵. Beyond conscious taste and smell⁶, G protein-coupled receptors (GPCRs) are located in extraoral tissues, including upper airways^{7,8}, throat⁹, lungs¹⁰, gut¹¹ and skin¹². While we have no conscious access to flavor information arising from these sites, relevant cell types in these tissues sense chemical stimuli leading to common side effects such as nausea, vomiting and skin irritation^{13,14}.

To address the lack of adequate pediatric formulations, legislation was passed in the United States and European Union to create incentives for testing in children^{15,16} and collaborative initiatives highlighted gaps in knowledge, one of which is the lack of palatability assessments^{2,17–19}. Because taste is the key problem in children’s acceptance of medicine^{2,3,20,21}, authorities recommended that “palatability” assessments involve children whenever possible or taste-screening approaches (e.g., adult panels), provided the alternative method is examined for result transferability to children^{2,22–26}.

A fundamental challenge to this global research priority is the lack of validated and universally agreed upon protocols for assessing the taste of medicines, from the earliest Phase 1 clinical trials when human volunteers can taste the medicine for the first time to FDA-approved drug use in clinical care. Furthermore, the expectation that a given medicine or formulation should taste good for an entire population of children fails to recognize the highly personal nature of taste, highlighting the importance of the inherent variation that makes each child a unique patient, commonly referred to as precision medicine^{27,28}. While personal variation among adults exists in the taste of some drugs (e.g., propylthiouracil (PTU)²⁹, quinine^{30,31}, ibuprofen³²), a fundamental challenge remains in assessing individual differences when the patients are newborns or young children, for whom there are no validated methods.

¹Abbreviations: API, active pharmaceutical ingredient; gLMS, general Labeled Magnitude Scale; GPCRs, G protein-coupled receptors; GRAS, generally recognized as safe; HIV, human immunodeficiency virus; HWE, Hardy-Weinberg equilibrium; LPV/r, lopinavir/ritonavir; PTU, propylthiouracil; SEM, standard error of the mean; TRP, transient receptor potential

We conducted a proof-of-principle study to establish whether the taste of a pediatric medicine varied among a sensory panel of genotyped adults. To represent the ‘gestalt’ experience of pediatric patients, the medicine evaluated was the liquid formulation of the co-formulated protease inhibitors lopinavir/ritonavir (LPV/r, Kaletra) which is part of the first-line HIV treatment for children under three years of age³³—the first dose can be delivered as early as two weeks of life³⁴. We chose this drug because clinically experienced pediatric HIV care providers report that some, but not all, infants accept or tolerate the taste of LPV/r³⁵, as evidenced by their refusal to take the medicine or by involuntary reactions such as gagging, nausea, and vomiting³⁶. Likewise, some of their older pediatric (and adult) patients claim to like the taste of LPV/r, while others strongly dislike its taste³⁴. To probe individual differences further, we genotyped for selected candidate genes involved in taste, chemical irritation and temperature perception.

Methods

Panelists

We recruited unrelated women (N=84) who were enrolled as adult sensory panelists in a research study on bitter taste perception and the efficacy of classic bitter blockers. We clarify that the use of a sensory panel in academic research can differ from its application in the food industry³⁷. Like in other academic research^{32,38,39}, the sensory panel in the present study is comprised of individuals who are trained in the use of psychophysical tools (gLMS, hedonic gLMS) that allow for valid across-group comparisons^{40,41}. The sensory evaluation of the product, in this case a pediatric medicine, focuses on various dimensions of taste (e.g., bitterness) as well as palatability, and the output is the perception of the individual panelist. The Office of Regulatory Affairs at the University of Pennsylvania and the Institutional Review Board of the Children’s Hospital of Philadelphia approved all procedures and consent forms and the study complies with the Declaration of Helsinki for Medical Research involving Human Subjects. Each panelist gave written informed consent⁴² and we registered the trial at clinicaltrials.gov (NCT01407939).

Taste Stimuli

Stimuli, presented at room temperature when evaluated by panelists, included the currently available liquid formulation of Kaletra (Abbott Laboratories, USA) which contains the following excipients: ethanol, high fructose corn syrup, saccharin, sodium chloride, citric acid, menthol, peppermint oil, cotton candy, vanilla, and other flavors. Panelists also evaluated a battery of generally recognized as safe (GRAS) taste stimuli: common excipients (0.6 M sucrose, 0.3 M sodium chloride, 20% v/v ethanol) and bitter-tasting stimuli commonly used in taste research (but not contained in Kaletra): 0.008 M caffeine, 0.5 M urea, 4.92×10^{-7} M denatonium, 560 μ M propylthiouracil (PTU), and 1.19×10^{-4} M quinine. We included PTU and quinine because they are medications used historically to treat thyroid disorders^{43,44} and malaria⁴⁵, respectively. We also included PTU as a control stimulus since the association between its taste and *TAS2R38* genotype is one of the most studied and robust traits in human genetics^{29,42,46–49} and is now regarded as a benchmark in genotype-taste phenotype and genome wide association studies⁵⁰.

Psychophysical Procedures

Panelists rated the taste sensations (i.e., bitterness, sweetness, saltiness, sourness, savoriness), and irritation using the general Labeled Magnitude Scale (gLMS) and palatability using the hedonic gLMS. Both scales have been validated and shown to be superior to other rating scales (e.g., 9-point scales) when comparing taste sensations among individuals^{40,41,51,52}. The gLMS⁵³ rates taste sensation in terms of no sensation (0), barely detectable (1.4), weak (5.8), moderate (16), strong (35), very strong (53), and strongest imaginable (100). The hedonic gLMS scale⁴⁰ rates affective experiences using the same anchors in terms of the strongest imaginable liking (100) to strongest imaginable disliking (−100) of any kind, with zero equal indicating no preference. Both scales allow for the rating of perceived intensity along a vertical axis lined with adjectives that are spaced quasi-logarithmically to yield ratio-quality data^{52,53}.

After abstaining from eating for at least 1 hour, panelists tasted but did not swallow, in randomized order, 5 mL of each taste stimulus. After tasting each sample for 5 sec via a swish-and-spit protocol, panelists rated its taste and palatability on a computer with Compusense five Plus software (Compusense Inc., Guelph, Canada). One minute separated the presentation of each stimulus, during which panelists rinsed their mouths with water. Several months later, panelists were retested using identical methodologies to establish reliability of Kaletra ratings over time. While Kaletra was tasted without nose clips (to mimic the patient's experience) during both test days, the other taste stimuli were tasted without nose clips on the second day only.

Genotype Procedures

Participants provided DNA samples extracted from saliva (BuccalAmp, Epicenter, Madison, WI, or Genotek, Kanata, Canada). Samples were diluted to a concentration of 5 ng μL^{-1} , which was used as templates in Taqman assays and assayed in duplicate for single-nucleotide polymorphisms (Applied Biosystems, Foster City, CA) using previously established methods⁵⁴. We selected candidate genes that encode for: 1) bitter taste receptors *TAS2R38* Ala49Pro rs713598⁵⁵; *TAS2R60* rs4595035^{56,57}, *TAS2R44* rs10845294; *TAS2R4* rs2234002 because ritonavir is often described as bitter⁵⁸; 2) the sweet taste receptor *TAS1R3* rs35744813⁵⁹ because high fructose corn syrup and saccharin are excipients; and 3) transient receptor potential [TRP] cation channel subfamily M member 5, *TRPM5* rs230169, the final step in the sweet taste receptor transduction cascade that leads to receptor depolarization⁶⁰; and 4) *TRPM8* rs7593557, one of the main cold temperature sensors since menthol and peppermint oil are excipients⁶¹.

Statistical Analyses

We computed descriptive statistics, including tests for normality in the taste ratings of Kaletra, and Pearson correlations to assess test-retest reliability and relationships among psychophysical ratings of different taste stimuli. Analyses of variance were used to probe whether taste ratings of Kaletra differed by candidate genotype. Data were analyzed using Statistica (version 13.1, StatSoft, Tulsa, OK) and Stata/IC (version 14.2, College Station, TX) and data are expressed as mean $\pm$ standard error of the mean (SEM). For all analyses, the statistical significance level was set at $p = 0.05$ (two tailed).

Results

Panelists

Panelists averaged 36.4 ± 0.9 (range, 23–58) years of age and represented the ethnic diversity of the city in which they reside, Philadelphia, PA, USA⁶² (67% African-American, 15% White, 2% Asian, 16% more than one race). Most panelists ($n=73$, 87%) returned several months later (10.7 ± 0.3 months) for the second (retest) session.

Psychophysics

As expected, ratings of saltiness, sourness and savoriness were rarely given so the analyses focused on variation in ratings of bitterness and palatability (primary outcomes) and then sweetness and irritation, each of which was normally distributed (Shapiro-Wilk normality test: bitterness, $W=0.90$; irritation, $W=0.93$; sweetness, $W=0.80$; all p -values < 0.001). Upon first presentation of Kaletra, bitterness ratings averaged $17 (\pm 2)$ and ranged from 0 (no sensation) to 57 (very strong), sweetness ratings averaged $13 (\pm 2)$ and ranged from 0 (no sensation) to 53 (very strong), whereas irritation ratings averaged $27 (\pm 2)$ and ranged from 0 (no sensation) to 96 (very strong to strongest imaginable). Likewise, hedonic ratings of its taste varied widely, ranging from +35 (moderate like) to -92 (very strong to strongest imaginable dislike). The average rating was -28 ± 2 , in the range of “moderate to strong dislike” sensation. Hedonic ratings for the taste of Kaletra were negatively related to ratings of bitterness [$r(82df) = -0.64$, $p < 0.001$] and irritation [$r(82df) = -0.73$, $p < 0.001$] but not sweetness ($p = 0.42$). The higher the ratings of bitterness, the higher the ratings of irritation [$r(82df) = 0.70$, $p < 0.001$]; multiple regression revealed both were significant predictors of hedonic ratings of Kaletra (p 's < 0.001).

As shown in Figure 1, the bitterness [$r(71df) = 0.36$, $p = 0.002$], irritation [$r(71df) = 0.54$, $p < 0.001$], and hedonic [$r(71df) = 0.66$; $p < 0.001$] ratings for Kaletra overall were reliable over time. Panelists who did not return ($n = 11$) did not rate the taste of the drug as more unpleasant during the first session than those who came back for retesting ($p = 0.69$). Palatability ratings for the taste of Kaletra were significantly related to palatability ratings for the excipient ethanol [$r(71df) = 0.31$, $p = 0.007$] and for the bitter stimulus denatonium [$r(71df) = 0.23$, $p = 0.045$] but not for quinine, urea, caffeine, PTU, sodium chloride, sucrose, or citric acid (all p -values > 0.18).

Genotyping

As shown in Table 1, the genotype call rates for the candidate genes were high (94–100%) and met Hardy-Weinberg equilibrium. Bitterness and irritation ratings for Kaletra varied by *TAS2R60* genotype, with CC individuals rating the bitterness of Kaletra lower than CT or TT individuals (Figure 2). However, this genotype did not account for variation in the bitterness ratings for ethanol or denatonium (Table 1). For the *TRPM8* genotype (but not *TRPM5*), individuals with an A allele perceived Kaletra to taste less sweet. The expected pattern was observed for PTU ratings and *TAS2R38* genotype. The association displayed a heterozygote effect: the bitter-sensitive (P) form such that two copies of the bitter sensitive form (P) conferred higher bitterness and irritation and lower pleasantness ratings than did a single copy (AP), and results for both the PP and AP genotypes were different from those

for the bitter-insensitive AA genotype (Figure 2). We tested for specificity of response by examining the effects of *TAS2R60* on bitter response to PTU and *TAS2R38* on response to Kaletra but found no relationships (*TAS2R60* on PTU: $p=0.22$, *TAS2R38* on Kaletra: $p=0.71$).

Discussion

Not all adult panelists had the same sensory experience when tasting the liquid formulation of the HIV treatment drug Kaletra (LPV/r), a finding consistent with clinical reports on pediatric HIV patients^{2,5,63}. This individual variation was consistent over time and related to how bitter and irritating the liquid formulation tasted. These individual differences were genetic in origin. That the genotype-phenotype association between the *TAS2R38* genotype and bitterness ratings of PTU was observed as expected^{29,42,46–49} provides internal validity for the following genotype-phenotype findings.

Those who perceived Kaletra as tasting less bitter possessed nonfunctional receptors of the *TAS2R60* gene, albeit to date considered an orphan receptor⁵⁷. While variation in perceived sweetness did not associate with sweet receptor gene *TAS1R3*, it did associate with gene related to variation in the *TRPM8* gene, also known as the cold and menthol receptor 1. Indeed Kaletra contains the excipients saccharin and high fructose corn syrup and all panelists perceived sweetness, albeit at varying levels. Although taste stimuli were presented at room temperature, we hypothesized that individuals with functional *TRPM8* genotypes perceived greater cooling sensation due to activation of receptor by menthol and in turn perceived less sweetness (or greater sweetness adaptation). We based this hypothesis on the following lines of evidence. First, the cold-receptor *TRPM8* is activated by low levels of menthol⁶¹, an excipient of Kaletra. Second, while no research to date has determined whether menthol-containing solutions in the oral cavity changes how cool the solution tastes, we know that direct application of menthol to the skin leads to perceptions of coolness⁶⁴. Third, actual cooling of the oral cavity leads to reductions in the perceived intensity of some sweeteners, including saccharin, an excipient in Kaletra⁶⁵. Clearly more research is needed to determine the contribution of the taste-mixture interactions of the excipients⁶⁶ to variation in how the patient perceives the formulation¹⁶.

Variation in the ratings of the taste of Kaletra was strongly tied to individual differences in the taste of ethanol, one of its excipients, and denatonium, a bitter agent once added to detergents, paints, and antifreeze to deter pediatric poisoning but children varied in how effective it was in deterrence^{67,68}. That personal variation in either ethanol, as previously reported by Nolden and colleagues⁶⁹, or denatonium ratings was not explained by *TAS2R60* or *TRPM8* genotypes suggests that some other ingredients in this liquid formulation, most likely the APIs, are driving the genotype-phenotype relationships.

Our experimental approach was to test not a liquid formulation in development but one currently used by millions of children in treatment. Studying the liquid formulation as a whole was chosen because our primary aim was to establish whether there was wide variation in adults, as has been reported clinically for children^{35,36}. But by having the panelists taste the liquid formulation, we cannot determine whether the distaste was due

solely to the active ingredients (LPV/r) or to the taste-mixture interaction among the wide range of excipients needed to dissolve the APIs (e.g., ethanol⁶⁹) and/or to mask bitterness of the drug (e.g., sweeteners)⁶⁶.

These data provide proof of principle that a genotyped adult sensory panel can be used to assess whether individual variation exists in the taste of pediatric formulations (see also ref³²). Panelists used validated psychophysical tools that allow for the comparisons across individual adults⁵³ but tools that are more cognitively demanding than that typically used to assess taste perception and hedonics in children⁷⁰. We genotyped the panel for a few known candidate genes and related variation in genotype to variation in ratings since we were aware clinically of its importance in medication acceptance. However, we emphasize the preliminary nature of our findings and that the number of comparisons made increases the possibility of an alpha error highlighting the need and importance for replication in a larger cohort.

These findings provide the necessary tools and foundation for the next steps which in addition to replication will include evaluating the contribution of additional known genes regulating multiple points along the taste transduction pathway, in the periphery and along the central pathway⁷¹. That many bitter compounds do not act through known taste receptors⁷², suggests other receptor families and pathways exist^{7,72}. This research also lays the foundation for objectively measuring individual differences—the hallmark of human perception—by not only panelists but also patients. Direct assessments of the variability in taste acceptance/palatability of LPV/r among pediatric patients is critical⁷¹, especially because such human variation cannot be measured by sensors such as the electronic tongue in its current form.⁷¹ The approach of converging information from genotyped adult panels and pediatric patients should not be limited to LPV/r but should extend to other drugs and therapeutics and their excipients including flavor volatiles.

Taste-testing standards for pediatric formulations are past due. To meet these goals, we need nonproprietary and validated psychophysical methodologies to assess personal variation in the taste of a medicine among children⁷¹. In developing such methods, we need to take the special needs of pediatric populations into consideration,² including their sense of taste, which sometimes differs from that of adults⁷³. These methods should determine initial responses to both the taste of the drug and tolerance after swallowing, to capture the full range of individual differences in sensory response, including the impact of the full range of receptors along the throat, gastrointestinal tract and other parts of the body⁷. Factors that impact taste perception may relate to side effects of the drug (e.g., vomiting, nausea, abdominal distress¹⁴). Of interest, side effects were evident in the initial phase of treatment of Kaletra, whether children were given either liquid or “sprinkles” formulations mixed with food, perhaps due in part to the dissolved API binds to these downstream “taste” receptors⁵. In some cases, these aversive side effects conditioned future responses—merely smelling the drug after prior exposures resulted in gagging and vomiting in some infants, making adherence challenging for some^{5,63}.

Caregivers view improving the taste of a drug as the most needed intervention to increase antiretroviral therapy adherence in their children.³⁵ This point is particularly important for

children in sub-Saharan Africa, where more than 200,000 children are born each year infected with HIV, many of whom are prescribed LPV/r. Without treatment, more than 50% of HIV-infected infants die before their second birthday⁷⁴. The time is ripe to focus on personal variation to the taste of their medicine⁷⁵ since a drug, no matter how powerful, is ineffective when the child rejects it⁷¹. By taking the perspective of precision medicine that “nobody is average”, a greater understanding of the genetic and phenotypic variation underlying the flavor of a given medicine may inform the clinical care of the patient and lead to molecular targets to improve palatability.

Acknowledgments

We acknowledge the expert technical assistance of Kristi Roberts, Loma Inamdar, Ashley Reiter, and Jennifer Chapman; the valuable discussions with Drs. Alissa Nolden and Danielle Reed; and the genotyping by Dr. Danielle Reed. All authors participated in the research, data analyses, and JM and EL wrote the manuscript. All authors have approved the final version of the manuscript.

Funding

The research was supported by the National Institute of Deafness and Other Communication Disorders (NIDCD), National Institutes of Health (NIH), grant R01 DC011287. Genotyping was performed at the Genotyping and DNA/RNA Analysis Core (NIH-NIDCD core grant P30DC011735) under the supervision of Dr. Reed. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIDCD or NIH. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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A. Bitterness, Kaletra

B. Irritation, Kaletra

C. Hedonics, Kaletra

Figure 1.

A. Kaletta and *TAS2R60* **B. Kaletta and *TRPM8*** **C. PTU and *TAS2R38*** **Figure 2.**

Table 1

Genotype associations with taste ratings of Kaletra™ and PTU (control drug)

Chromosome	Gene	Variant Name	Call Rate (%)	HWE ^a p-Value	Taste Quality, Drug	p-Value
7	TAS2R60	rs4595035	94.0	0.8928	Bitterness, Kaletra	p=0.017
					Irritation, Kaletra	p=0.054
					Hedonics, Kaletra	p=0.073
7	TAS2R38	rs713598	100.0	0.5436	Bitterness, Kaletra	p=0.594
					Irritation, Kaletra	p=0.504
					Hedonics, Kaletra	p=0.907
12	TAS2R44	rs10845293	96.4	0.3247	Bitterness, Kaletra	p=0.252
					Irritation, Kaletra	p=0.914
					Hedonics, Kaletra	p=0.277
7	TAS2R4	rs2234002	97.6	0.2202	Bitterness, Kaletra	p=0.769
					Irritation, Kaletra	p=0.694
					Hedonics, Kaletra	p=0.837
1	TAS1R3	rs35744813	97.6	0.9057	Bitterness, Kaletra	p=0.780
					Irritation, Kaletra	p=0.388
					Sweetness, Kaletra	p=0.670
2	TRPM8	rs7593557	96.4	0.3542	Hedonics, Kaletra	p=0.572
					Bitterness, Kaletra	p=0.344
					Irritation, Kaletra	p=0.424
11	TRPM5	rs2301699	98.8	0.7780	Sweetness, Kaletra	p=0.008
					Hedonics, Kaletra	p=0.893
					Bitterness, Kaletra	p=0.830
7	TAS2R60	rs4595035	94.0	0.8928	Irritation, Kaletra	p=0.597
					Sweetness, Kaletra	p=0.367
					Hedonics, Kaletra	p=0.206
					Bitterness, PTU	p=0.218

Chromosome	Gene	Variant Name	Call Rate (%)	HWE ^a p-Value	Taste Quality, Drug	p-Value
7	<i>TAS2R38</i>	rs713598	100.0	0.5436	Irritation, PTU	p=0.527
					Hedonics, PTU	p=0.420
					Bitterness, PTU	p=0.00008
12	<i>TAS2R44</i>	rs10845293	96.4	0.3247	Irritation, PTU	p=0.00068
					Hedonics, PTU	p=0.00000
					Bitterness, PTU	p=0.972
7	<i>TAS2R4</i>	rs2234002	97.6	0.2202	Irritation, PTU	p=0.355
					Hedonics, PTU	p=0.925
					Bitterness, PTU	p=0.0164
1	<i>TAS1R3</i>	rs35744813	97.6	0.9057	Irritation, PTU	p=0.0451
					Hedonics, PTU	p=0.067
					Bitterness, PTU	p=0.919
2	<i>TRPM8</i>	rs7593557	96.4	0.3542	Irritation, PTU	p=0.897
					Sweetness, PTU	p=0.256
					Hedonics, PTU	p=0.948
11	<i>TRPM5</i>	rs2301699	98.8	0.7780	Bitterness, PTU	p=0.353
					Irritation, PTU	p=0.430
					Sweetness, PTU	p=0.682
11	<i>TRPM5</i>	rs2301699	98.8	0.7780	Hedonics, PTU	p=0.743
					Bitterness, PTU	p=0.939
					Irritation, PTU	p=0.620
11	<i>TRPM5</i>	rs2301699	98.8	0.7780	Sweetness, PTU	p=0.863
					Hedonics, PTU	p=0.709

^aHWE, Hardy-Weinberg equilibrium. Bold indicates significant at p<0.05.