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Original Paper

The Associations between 6-*n*-Propylthiouracil (PROP) Intensity and Taste Intensities Differ by *TAS2R38* Haplotype

Mary E. Fischer[a] Karen J. Cruickshanks[a, b] James S. Pankow[c]
Nathan Pankratz[d] Carla R. Schubert[a] Guan-Hua Huang[e]
Barbara E.K. Klein[a] Ronald Klein[a] Alex Pinto[a]

Departments of [a]Ophthalmology and Visual Sciences and [b]Population Health Sciences, University of Wisconsin, Madison, Wis., [c]Division of Epidemiology and Community Health, and [d]Department of Lab Medicine and Pathology, University of Minnesota, Minneapolis, Minn., USA; [e]Institute of Statistics, National Chiao Tung University, Hsinchu City, Taiwan, ROC

Key Words
Taste · Propylthiouracil · Population association study

Abstract
Background/Aims: The influence of *TAS2R38* haplotype on the relationship between the perceived intensity of propylthiouracil (PROP) and the basic tastes of salt, sweet, sour, and bitter (quinine) was evaluated in the Beaver Dam Offspring Study. ***Methods:*** Genotyping was performed on 1,670 participants aged ≥45 years (mean age = 54.4; range = 45–84), and suprathreshold taste intensity was measured using filter paper disks and a general labeled magnitude scale (0–100). ***Results:*** Among those with taste intensity data and the PAV or AVI haplotype (n = 1,258), the mean perceived intensity of PROP was 37.3 (SD = 30.0), but it varied significantly ($p < 0.0001$) by diplotype (PAV/PAV = 60.1; PAV/AVI = 46.5; AVI/AVI = 14.4). PROP intensity was correlated with the basic taste intensities (salt: $r = 0.22$; sweet: $r = 0.25$; sour: $r = 0.21$; quinine bitterness: $r = 0.38$; $p < 0.001$ for all tastes); however, a significant effect modification of the PROP-taste intensity relationships by *TAS2R38* diplotype was observed. There was a stronger association between PROP and each of the basic tastes in the PAV/PAV diplotype group than in the other groups. ***Conclusions:*** Directly measuring the perceived intensity of the 4 tastes, rather than using PROP intensity as an indicator of taste responsiveness, is recommended for studies of taste perception.

Mary E. Fischer
Department of Ophthalmology and Visual Sciences
University of Wisconsin
610 N Walnut Street, Madison, WI 53726 (USA)
E-Mail fischer@episense.wisc.edu

Introduction

Taste may relate to health through food preferences and selection [1, 2], and sensitivity to bitter compounds is important in the avoidance of toxic substances [3]. Variation in the ability to taste the bitterness of phenylthiocarbamide (PTC), a thiourea compound, has a strong genetic component [4] with the *TAS2R38* gene encoding a bitter taste receptor for PTC [5]. There are 3 common nonsynonymous SNPs within *TAS2R38* (rs713598, rs1726866, and rs10246939), and amino acid substitutions of alanine for proline, valine for alanine, and isoleucine for valine occur as a result of base pair substitutions at the 3 sites. These substitutions give rise to the common haplotypes of PAV (PTC sensitive) and AVI (PTC insensitive).

In recent years, work has indicated that the *TAS2R38* gene also plays a role in the genetic component of variability in responsiveness and sensitivity to 6-*n*-propylthiouracil (PROP), another thiourea compound [6, 7]. In addition, it has been proposed that there may be other genes contributing to PROP taste response [8, 9]. The phenotypic variation in the perceived intensity of suprathreshold concentrations of PROP has also been widely investigated, and it has been suggested that there are 3 distinct groups of individuals: (1) those with high perceived PROP intensity, termed 'supertasters', (2) those with low perceived PROP intensity, termed 'nontasters', and (3) those with moderate perceived PROP intensity, termed 'medium tasters' [10].

It has been hypothesized that PROP supertasters also experience other oral sensations, such as the intensity of the 4 basic tastes (bitterness, salt, sour, and sweet), more intensely, and the term supertasting was broadened to imply a generally heightened level of oral perception of all the tastes [11]. Subsequently, positive associations between PROP intensity and the intensity of bitter [12–15], sweet [14–16], salty [11, 14, 15, 17], and sour [14, 15] stimuli as well as the oral sensation of fat or creaminess [18, 19] were observed. However, not all studies found that PROP intensity was predictive of other oral responses [13, 20–22].

The underlying mechanism for the correlation between PROP responsiveness, the other tastes, and food preferences was thought to be the fact that PROP supertasters had more fungiform papillae (FP; containing taste buds) than nontasters [10, 20, 23, 24]. However, in recent investigations analyzing PROP in a continuous manner and categorically with a number of different grouping schemes, no significant relationship between FP density and PROP intensity was observed [25, 26]. In addition, no significant PROP intensity and FP density association was found within any of the *TAS2R38* haplotype subgroups [25, 26]. In an earlier study, *TAS2R38* haplotype was found to modify the association between FP density and PROP bitterness whereby a significant association between PROP intensity and FP density was observed only in the *TAS2R38* homozygote groups and not among the heterozygotes [15].

The purpose of the present study was to examine the influence of *TAS2R38* genotype on the strength of the phenotypic relationships between the perceived intensity of PROP and the perceived intensities of the other 4 tastes. The suitability of using PROP responsiveness as an indicator of responsiveness to the 4 basic tastes was evaluated. In addition, the distribution of PROP intensity was described and its association with demographic and behavioral factors was assessed.

Materials and Methods

Study Population

The participants in the study were members of the Beaver Dam Offspring Study (BOSS), an investigation of the adult children (ages 21–84 years, predominately non-Hispanic white) of participants in the population-based Epidemiology of Hearing Loss Study (EHLS). The baseline BOSS examination took place in 2005–2008 [27–29]. There were 2,359 BOSS participants who rated the perceived intensity of PROP during the taste testing component of the examination. Approval of the study was granted by the Health Sciences Institutional Review Board of the University of Wisconsin and informed consent was obtained from the participants.

Measurements

TAS2R38 haplotypes were available for participants aged ≥45 years. DNA was extracted from whole blood and was genotyped using the Illumina IBC chip [30]. The IBC chip, also known as the HumanCVD Genotyping BeadChip, is a custom-designed array that interrogates 49,094 SNPs distributed across approximately 2,000 genes and loci previously associated with a range of cardiovascular, metabolic, and inflammatory syndromes. The PLINK tool set with a standard E-M algorithm for making haplotype predictions was used to construct haplotypes from the genotype data for the 3 common nonsynonymous SNPs within *TAS2R38* [31]. Participants with only the common haplotypes of PAV or AVI (92% of genotyped participants) were included in the study resulting in having 3 diplotypes, i.e. PAV/PAV homozygotes, PAV/AVI heterozygotes, and AVI/AVI homozygotes. Ancestry was determined using a self-report and was verified by a principal component analysis as implemented in the Eigensoft package [32, 33]. The principal component analysis included European (CEU), African (YRI), and Asian (CHB/JPT) samples from HapMap2 as anchors in the analysis.

Filter paper disks impregnated with suprathreshold concentrations of 1.0 M PROP, 1.0 M sodium chloride (salt), 1.8 M sucrose (sweet), 0.1 M citric acid (sour), and 0.001 M quinine (bitter) were used to measure taste intensity. Testing was performed in a set order beginning with salt followed by sweet, sour, bitter, and PROP [28].

A general labeled magnitude scale (gLMS) [34] was used for the rating of the perceived intensity. The gLMS was anchored on one end with 0 labeled as 'no sensation' and on the other end with 100 labeled as 'strongest imaginable sensation of any kind'. Taste testing was done only with the participants who successfully completed the training using the gLMS.

Factors included in the descriptive analyses of PROP intensity included the demographic items of age, sex, and education [college graduate (16+ years of education) – yes or no]. The behavioral factors assessed were lifetime smoking history (never, former, current) and alcohol consumption (any in the past year and ever drank 4+ drinks/day on a regular basis). In addition, exercise was measured as the number of times per week the participants engaged in a regular activity long enough to work up a sweat. Responses were grouped into 3 categories: 0, 1–2 and 3+ times per week.

Statistical Analyses

All analyses were performed using SAS, version 9.2 (SAS Institute, Inc., Cary, N.C., USA). Analysis of variance (ANOVA) with unadjusted pairwise comparisons was conducted to test the differences in mean PROP intensity between the *TAS2R38* haplotypes. The coefficient of determination (R^2) from this ANOVA provided the proportion of the phenotypic variance in PROP intensity explained by the *TAS2R38* haplotype. In assessing the relationships between PROP intensity and intensities of the 4 basic tastes, Pearson correlation coefficients were calculated using the CORR procedure in SAS. To determine how these relationships varied by the *TAS2R38* diplotype group, multiple linear regression models were fit with the basic tastes as the dependent variables and the PROP intensity and diplotype group as the independent variables. Indicator variables were created for the diplotype group with the heterozygote (PAV/AVI) group as the reference, and PROP intensity-diplotype group interaction terms were the product of the indicator variables and the PROP intensity score.

To evaluate the error resulting from using the PROP intensity score as an estimate of the intensity of the 4 tastes, the PROP intensity score was subtracted from each of the basic taste intensity scores. Therefore, negative differences indicated an overestimation of the basic taste intensity and positive differences indicated an underestimation. To demonstrate the effect of the estimation errors when making comparisons across populations, the distribution of the errors observed in the study population within each diplotype group was applied to a theoretical population with the same distribution of quinine bitterness intensity but with the homozygote proportions reversed. Thus, in the study population, approximately 18% of the participants with PROP intensity ratings were PAV homozygous and 36% were AVI homozygous, whereas in the theoretical population, 36% were PAV homozygous and 18% were AVI homozygous.

The association between the perceived PROP intensity and the covariates was determined by using general linear modeling (PROC GLM) to estimate the least squares mean PROP intensity for each category of the covariates after adjustment for age and sex, and to test differences for significance. The observed margins (OM) adjustment was used in the calculation of the least squares means so that the weighting scheme was based on the marginal distributions in the study sample. The adjusted means, therefore, reflect the distribution of the covariates among the study participants.

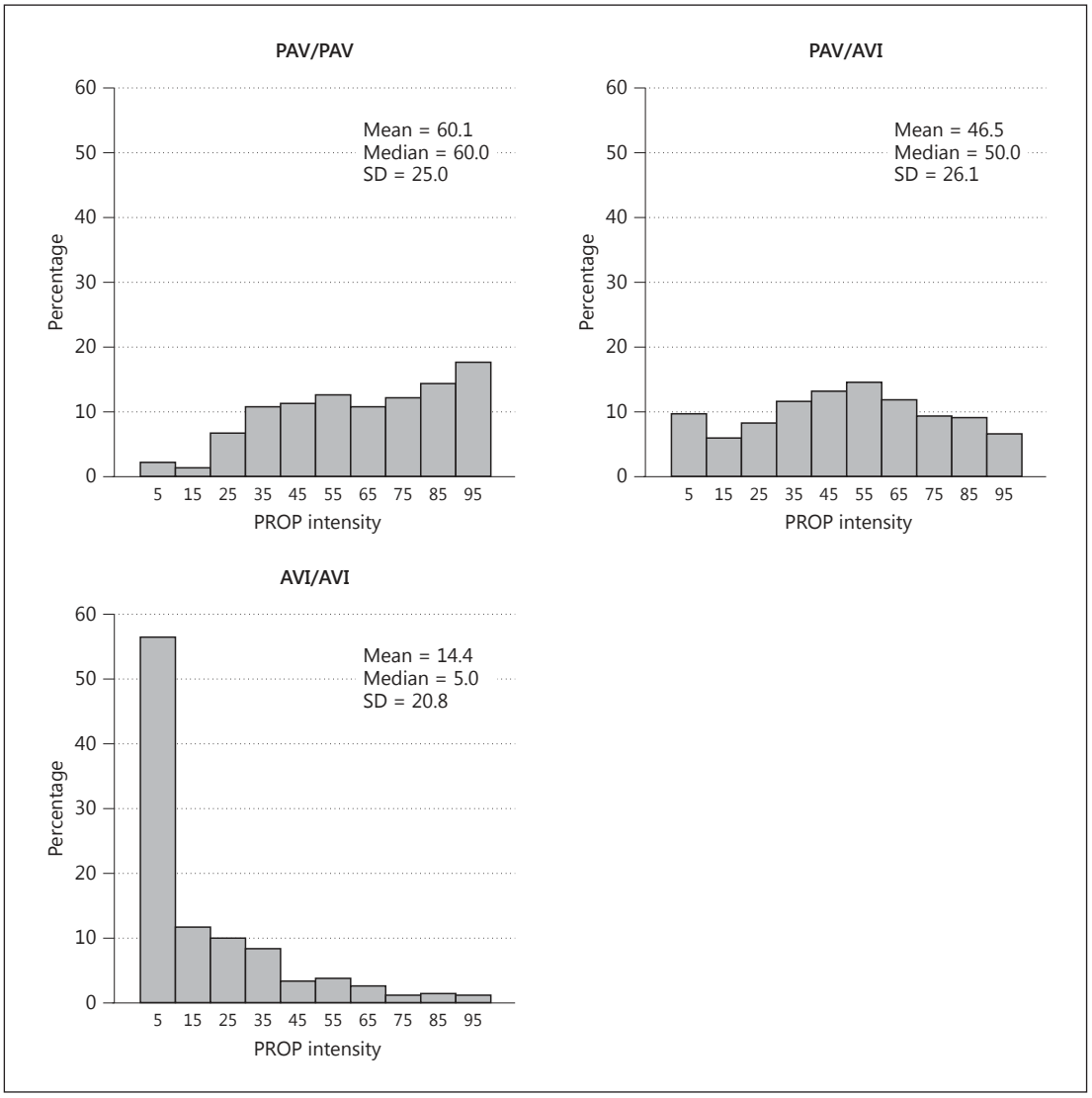

Fig. 1. Distribution of the PROP intensity by *TAS2R38* diplotype.

Results

Of the 1,670 participants aged ≥45 years with *TAS2R38* haplotype identification, 1,258 had only the common haplotypes of PAV and AVI and rated the PROP intensity. There were 222 PAV homozygotes (PAV/PAV), 583 heterozygotes (PAV/AVI), and 453 AVI homozygotes (AVI/AVI).

The mean PROP intensity among this subgroup was 37.3 units on the gLMS (SD = 30.0), and it varied significantly ($p < 0.0001$ for all pairwise comparisons) across *TAS2R38* diplotypes (fig. 1). The mean ranged from 60.1 among the PAV homozygotes to 14.4 among the AVI homozygotes, and the mean PROP intensity was 46.5 for the heterozygotes. The *TAS2R38* haplotype explained 35.6% of the total phenotypic variance in PROP intensity. There were PAV homozygotes reporting very low PROP intensities as well as AVI homozygotes reporting very high PROP intensities. There was considerable overlap of PROP intensities between the PAV homozygotes and the heterozygotes.

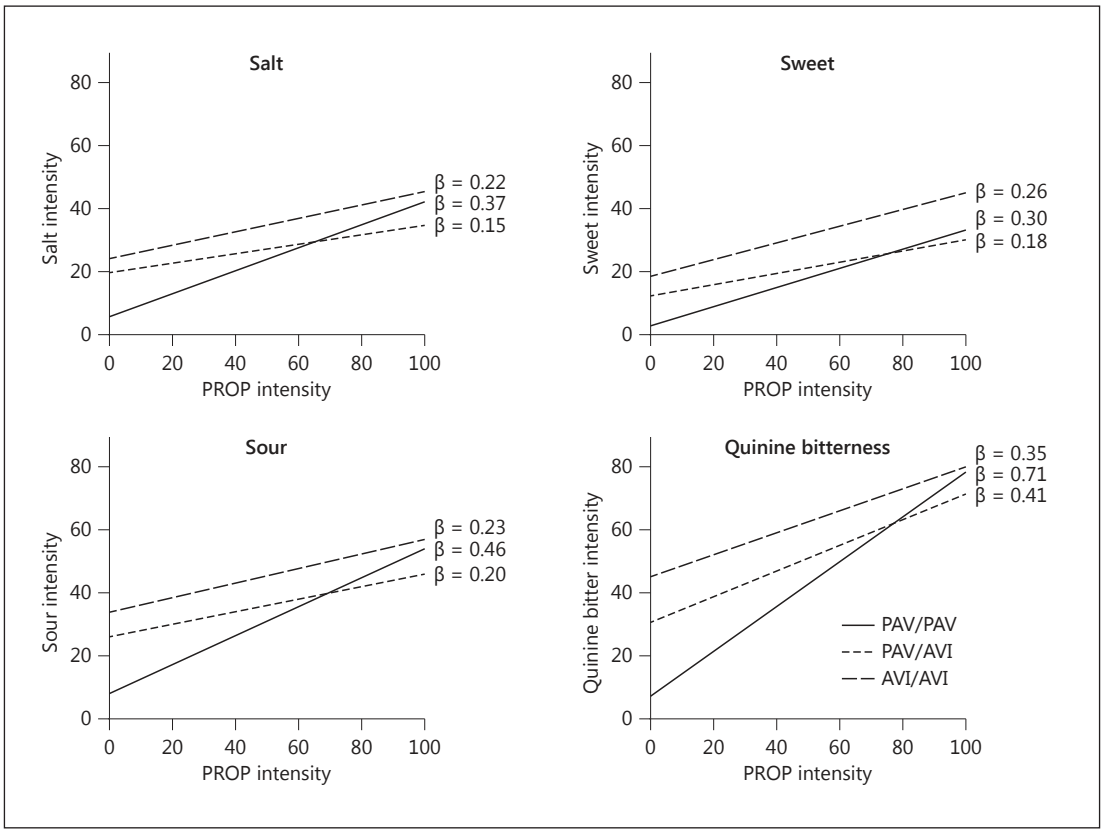

Fig. 2. PROP intensity and taste intensity. Least squares regression fitted lines (β = regression coefficient).

The correlations between PROP intensity and the 4 basic taste intensities were each significant ($p < 0.001$) but weak (salt: $r = 0.22$, sweet: $r = 0.25$, sour: $r = 0.21$, quinine bitterness: $r = 0.38$). The relationships between the intensities of PROP and the basic tastes varied significantly by diplotype group indicating the presence of effect modification (fig. 2). The relationships were stronger among the PAV homozygotes than among the heterozygotes and AVI homozygotes.

Due to the observed effect modification, the magnitude and direction of the error resulting from using PROP intensity to estimate the intensities of the 4 tastes varied by diplotype. For the PAV homozygotes, there was overestimation of the intensities, with quinine bitterness having the least degree of overestimation and sweet having the greatest. Conversely, for the AVI homozygotes, there was underestimation, with sweet having the least amount and quinine bitterness having the greatest. For the heterozygotes, there was also substantial overestimation of salt and sweet intensities.

The extent of the error in the estimation of the 4 tastes varies across populations if the populations have differing distributions of *TAS2R38* diplotype groups. For example, in a population where the distribution of quinine bitterness is the same as in this study population (mean = 50.0) and where there are twice as many AVI homozygotes as PAV homozygotes (also similar to this study population), using PROP intensity to estimate quinine bitterness would result in an average underestimation of approximately 12.7 units (fig. 3). If another population with the same distribution of quinine bitterness had a *TAS2R38* distribution with twice as many PAV homozygotes as AVI homozygotes, the underestimation of quinine bitterness would be approximately 4.4 units.

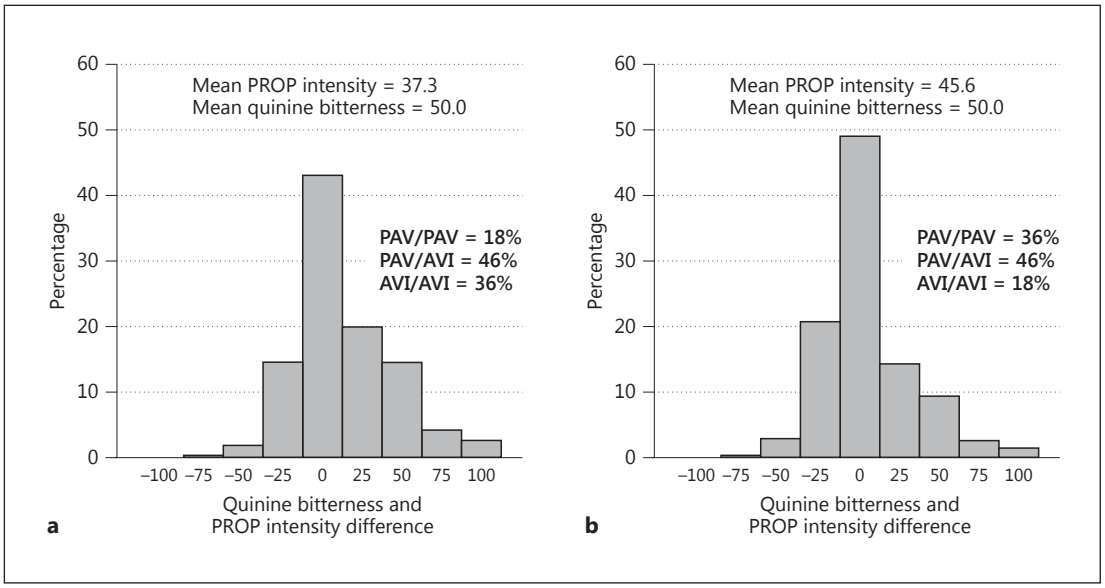

Fig. 3. Difference between quinine bitterness and PROP intensity (error) for two populations (**a, b**) with varying *TAS2R38* diplotype distributions.

With respect to the distribution and nongenetic determinants of PROP intensity, there were a total of 2,359 participants (mean age = 48.8 years) in the entire cohort who rated the intensity of the PROP stimulus. The average perceived intensity was 37.4 (SD = 30.2, median = 34, range = 0–100) (table 1). With age and sex adjustment, middle-aged groups had the highest mean PROP intensities (35–44 years = 37.8; 45–54 years = 39.5), and females demonstrated a significantly greater mean PROP intensity (40.1) than males (34.3). In addition, college graduates had a significantly lower mean PROP intensity (35.7) than participants with less education (38.4). There were no significant differences in mean PROP intensity for any of the behavioral factors. In the sample with *TAS2R38* haplotype information, similar relationships of PROP intensity with age and gender were observed. College graduates again had a lower mean intensity (36.1) than those with less education (38.0), but the difference was no longer significant.

Discussion

As expected, a significant relationship between the perceived intensity of PROP presented at a suprathreshold concentration and *TAS2R38* diplotype was observed in this large cohort of middle- to late-aged individuals. Participants with the PAV haplotype had a higher mean PROP intensity than participants with the AVI haplotype, but there was considerable overlap in intensity ratings across the groups.

The perceived intensity of PROP and the 4 basic tastes were found to be positively correlated, which is consistent with previous reports [11, 13, 15, 16]. However, the strength of the relationships differed by *TAS2R38* haplotype; the relationships were significantly stronger in the PAV homozygotes. A previous study with 198 participants, substantially fewer than in the present study, did not find significant effect modification of the PROP-basic taste relationships by *TAS2R38* diplotypes [15], while other prior investigations [11, 13, 16] did not assess

Table 1. Mean PROP intensity by participant characteristics, adjusted for age group and sex

Characteristic	All participants			Participants with *TAS2R38* diplotype[a]		
	n	PROP least squares, mean ± SE[b]	p value	n	PROP least squares, mean ± SE[b]	p value
Overall	2,359	37.4±30.2[c]	–	1,258	37.3±30.0[c]	
Demographic						
Age group			0.02			0.04
21–34	131	35.0±2.6		–	–	
35–44	714	37.8±1.1		–	–	
45–54	881	39.5±1.0		730	39.1±1.1	
55–64	483	34.0±1.4		407	34.4±1.5	
65–84	150	36.1±2.4		121	36.9±2.7	
Gender			<0.0001			<0.001
Male	1,105	34.3±0.9		518	34.5±1.2	
Female	1,254	40.1±0.8		640	40.1±1.2	
Education (college graduate)			0.04			0.28
Yes	838	35.7±1.0		398	36.1±1.5	
No	1,509	38.4±0.8		852	38.0±1.0	
Behavioral						
Smoking			0.31			0.66
Current	390	38.6±1.5		195	37.6±2.1	
Former	689	38.3±1.2		438	38.3±1.4	
Never	1,279	36.5±0.8		624	36.6±1.2	
Any alcohol in the past year			0.63			0.09
Yes	2,128	37.5±0.7		1,123	37.8±0.9	
No	229	36.5±2.0		134	33.2±2.6	
Ever drank 4+ drinks/day			0.20			0.67
Yes	412	39.2±1.5		237	38.1±2.0	
No	1,946	37.0±0.7		1,021	37.2±0.9	
Exercise (times/week)			0.97			0.82
0	892	37.3±1.0		502	36.8±1.3	
1–2	548	37.7±1.3		275	37.4±1.8	
3+	914	37.3±1.0		478	38.0±1.4	

[a] Participants with *TAS2R38* diplotypes of PAV/PAV, PAV/AVI, or AVI/AVI.
[b] Adjusted for age group and sex.
[c] Unadjusted overall mean and SD.

the influence of *TAS2R38*. This study's observation that the relationships between the intensities of PROP and the other tastes were weaker in the nontasters (AVI/AVI diplotype) may be a result of the lower level of variability in PROP intensity in that group. Although the range of PROP intensity in the AVI/AVI group was 0–100, the standard deviation was lower than in the other groups. It is possible that participants with the PAV/PAV diplotype show a stronger relationship between the perceived intensities of the 4 basic tastes and PROP simply because they are able to taste the bitterness of PROP, and there is variation in the perceived intensity of the PROP bitterness.

The observed difference in the relationship between the perceived intensities of PROP and the 4 tastes by *TAS2R38* diplotype has important implications when considering PROP intensity as a possible marker for the tastes. The current study demonstrated that there is less misclas-

sification of taste status when using PROP as a surrogate in people with the PAV/PAV diplotype. In the participants with the PAV/AVI or AVI/AVI diplotypes, there was substantial underestimation of perceived intensity of the 4 tastes and therefore, subjects were more likely to be erroneously classified as weak tasters of the 4 basic tastes. The nontasters or weak tasters of PROP (AVI/AVI diplotype) are not necessarily weak tasters of salt, sweet, sour, and quinine bitter since the *TAS2R38* gene encodes bitter taste receptors for compounds containing the thiourea moiety [5].

Differential misclassification of taste status for the 4 tastes will possibly lead to biased findings within studies. In addition, comparisons across populations will be difficult if the *TAS2R38* haplotype distribution differs in the populations. This is more likely to occur when the populations being compared have small numbers of participants or are different with respect to ancestry. Previous investigations of PROP responsiveness were primarily conducted in small, selected convenience samples of healthy volunteers and many studies did not include *TAS2R38* genotype information [11, 13, 14, 16, 18]. For these reasons, inconsistencies in findings across studies may be partially explained by reliance on PROP intensity to represent the other taste intensities.

Regarding our secondary objective, age, sex, and education were found to be related to the perceived intensity of PROP but no behavioral factors were associated with PROP suprathreshold perception. These results are consistent with reported studies suggesting that females are more likely to be PROP supertasters [10, 35]. Previous work in the BOSS cohort found that females also had significantly greater mean intensities for salt, sour, sweet, and bitter presented at suprathreshold concentrations [36]. College graduates demonstrated significantly lower mean intensities for all 4 tastes [36]. The observed sex differences in the perceived intensity may be related to hormonal fluctuations in females [37] or to cognitive assessment differences between males and females, as observed in an investigation of intranasal irritation and odorousness [38]. The present study's findings did not agree with previous work suggesting that variability in PROP bitterness is related to alcohol consumption [39].

Strengths of the present study include the fact that the measurement of the perceived intensity of PROP and the 4 tastes was done using a standard protocol employing the gLMS to ensure valid comparisons across the diplotype groups [34]. Although taste testing was done using filter paper disks, previous studies have shown that the perceived intensity of PROP delivered through filter paper disks is correlated with the perceived intensity of PROP delivered through solutions [40–42]. In addition, test-retest reliability using filter paper disks has been high (r = 0.9) [42]. Tastants were presented only once but in a set order with PROP as the final taste to minimize context effects [43].

PROP bitterness has served as a marker of orosensory response in many previous investigations over the past two decades. Because of the observed relationship of the perceived intensity of PROP with the other tastes and with oral somatosensation (irritation, temperature, pain), the concept of PROP supertasting was broadened to imply heightened oral sensation in general [44]. The results of this study suggest that this broadening of the concept of supertasting may lead to difficulties, particularly when comparing or integrating results across studies. The value of using PROP intensity as a marker for the 4 basic taste intensities depends on the underlying distribution of the *TAS2R38* haplotype. When the distribution varies across studies, as it likely does, it is difficult, if not impossible (when *TAS2R38* genotyping is not available), to determine the impact of the difference in distributions. In agreement with Lim et al. [22], the present study suggests that at this time, it may be important to directly measure responses to the 4 basic tastes when studying the relationship between taste perception, food preferences and choices, and ultimately health.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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