Variation in the Ability to Taste Bitter Thiourea Compounds: Implications for Food Acceptance, Dietary Intake, and Obesity Risk in Children

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Abstract

The ability to taste bitter thiourea compounds, such as phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP), is inherited. Polymorphisms in the bitter-taste receptor *TAS2R38* explain the majority of phenotypic variation in the PROP phenotype. It has been hypothesized that the PROP phenotype is a marker for perception of a variety of chemosensory experiences. In this review, we discuss studies that have investigated the relationship between bitter-taste response and dietary behaviors and chronic health in children. Investigators have hypothesized that children who are PROP tasters have lower liking and consumption of bitter foods, such as cruciferous vegetables. Additionally, several studies suggest that children who are unable to taste PROP (i.e., nontasters) like and consume more dietary fat and are prone to obesity. The relationship between the PROP phenotype and obesity is influenced by multiple confounders, including sex, food access, ethnicity, and socioeconomic status. Future studies that adjust for these variables are needed.

Contents

INTRODUCTION

Discovery of Taste Variation in Bitter Thiourea Compounds

The ability of humans to taste bitter compounds varies widely, the most notable example of which is oral sensitivity to a class of compounds containing a thiourea (N–C=S) moiety, including phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP). Variation in the ability to taste these compounds was discovered by chance. Chemist Arthur Fox was developing nonnutritive sweeteners in his DuPont laboratory when crystals of PTC accidentally flew into the air. His lab partner complained about the acrid taste of the chemical, but Fox detected nothing. To make sure, he dipped his finger into the crystals and sampled them, but still he detected nothing. As a result of this discovery, Fox became interested in this striking taste variation. At the 1931 meeting of the British Association for the Advancement of Science, he teamed up with the prominent geneticist Albert F. Blakeslee and tested several thousand participants to determine their ability to taste PTC impregnated on a piece of paper (20). Their tests demonstrated a highly unusual bimodal distribution in the ability to taste PTC, with approximately 70% classified as "tasters" and 30% classified as taste blind, or "nontasters." Additional family-based studies led to the conclusion that taste blindness to the bitterness in PTC was a Mendelian recessive trait (21), although reports of taster offspring coming from two nontaster parents suggest a more complicated inheritance pattern (98, 104). These early studies paved the way for nearly a century of research to understand the inheritance, molecular genetics, dietary implications, and evolutionary significance of this genetic variant. It is the most commonly researched genetic variation in chemosensation, but it is by far not the only example (67).

Since this initial discovery, more than 1,000 papers have examined genetic variation in the ability to taste PTC or, more recently, PROP, which is thought to be less toxic (138). However, until the 1990s, there were sparse reports on the potential importance of bitter-taste variations in the diets of children or adolescents (71, 139). The available literature has grown rapidly over the past two decades, though, perhaps due to increasing interest in the functional significance of PROP taster status in the chemosensation of a broad range of tastes and textures. In this review, we examine the current state of the science on the role of genetic variation in PROP taster status in children's food acceptance, dietary intake, and chronic health. In addition, because children offer

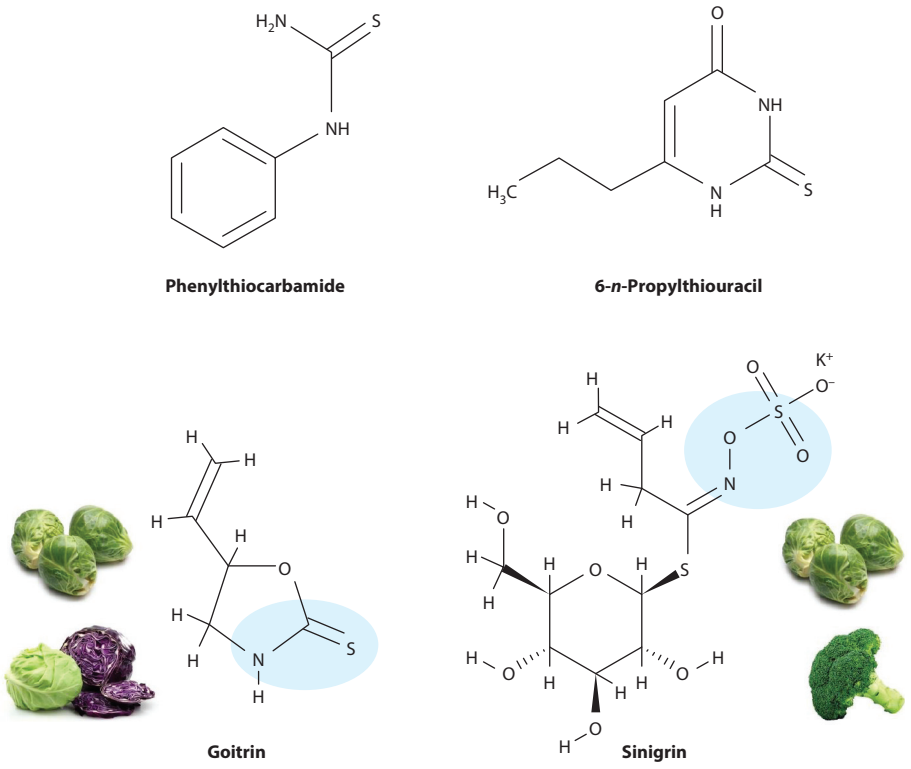

Figure 1

Chemical structures of bitter thiourea compounds phenylthiocarbamide and 6-*n*-propylthiouracil and chemically related structures from food, including goitrin from Brussels sprouts and cabbage and sinigrin from broccoli and Brussels sprouts. All of these compounds contain the characteristic thiourea moiety (N−C=S), which is responsible for their bitter taste.

unique challenges for the field when it comes to measurement of taste response, we discuss the available methodologies to assess taster status in children. We close the review with a discussion of future research questions for experimenters interested in this area.

Phenylthiocarbamide and 6-*n*-Propylthiouracil

PTC, also known as phenylthiourea, is an organosulfur thiourea compound that contains a phenyl ring (see **Figure 1**). It is considered a potent goitrogen that disrupts thyroid metabolism by inhibiting several of the enzymes produced by this gland. It is highly toxic, so in most studies of taste genetics, nontoxic doses of the chemically related compound PROP are used. Both compounds have goitrogenic properties, and at concentrated doses, PROP is used as a medication to treat hyperthyroidism. Although neither PTC nor PROP is present in foods, other thiourea-containing compounds such as glucosinolates are found in cruciferous vegetables. For example, goitrin is a glucosinolate compound found in cabbage and Brussels sprouts, and sinigrin is found in broccoli and Brussels sprouts. All of these compounds contain the characteristic thiourea moiety (N−C=S), which is responsible for their bitter taste.

Genetics Underlying the PROP Phenotype

Phenotypic variation in the ability to taste PROP is in part genetically determined by the *TAS2R38* gene (26, 80). The *TAS2R38* gene found on chromosome 7 is one of a family of approximately 30 bitter-taste receptors (13). *TAS2R38* encodes for a bitter-taste receptor that is specific to perception of thiourea-containing compounds, such as PROP and PTC, as well as compounds such as goitrin (14, 26, 99, 141). Three polymorphisms at amino acid 49 (proline or alanine), 262 (alanine or valine), and 296 (valine or isoleucine) combine to form the taster haplotype PAV and the nontaster haplotype AVI. Other more rare haplotypes (e.g., AAV, PVI) contribute to intermediate PROP/PTC sensitivity (26, 80) and are more common in African Americans than in Caucasians (30, 106). The AVI and PAV haplotypes completely explain the bimodal distribution in the ability to taste PTC and up to 85% of the variability in PTC thresholds (the lowest concentration of PTC that can be distinguished from water) (36), yet these single-nucleotide polymorphisms do not completely explain the PROP phenotype (81). Polymorphisms in *TAS2R38* explain approximately 60% of the variation in suprathreshold (i.e., above-threshold) response to PROP bitterness intensity and only ~40% of variation in PROP thresholds (29). In addition to the *TAS2R38* genotype, expression of messenger RNA in fungiform papillae among PAV heterozygotes correlates with the perceived bitterness of both PROP and broccoli extract (85). Differences in expression of *TAS2R38* on taste cells may therefore explain some of the discordance between genotype and phenotype.

Because prevalence of taste blindness to PTC and PROP is common in both humans and closely related species such as chimpanzees, it has been argued that natural selection maintains variation in the *TAS2R38* gene (55). One theory is that PROP/PTC tasters might be better able to detect potentially deleterious antithyroid compounds in cruciferous vegetables such as cabbage and therefore would avoid consuming these vegetables (24). People who live in geographic regions where iodine is not readily available might be more vulnerable to the effects of antithyroid compounds in foods, which function by limiting iodine availability. Support for the goitrogen-avoidance hypothesis comes from observations that a majority of individuals living in an isolated Andean community in Ecuador are taste blind to PTC (61). This hypothesis could partly explain the large differences in the incidence of PROP/PTC taste blindness globally, which range from as low as 2% in sub-Saharan Africa to 50% in Aboriginal populations of Australia (62). However, because the nontaster allele has remained at high prevalence in humans, more recent theories have suggested that both positive and negative selective pressures act to maintain both the taster and nontaster alleles at high frequency (140).

In addition to variation in *TAS2R38*, other genes and proteins may influence expression of the PROP phenotype (42, 44, 64, 81), and this is presently an active area of research. In an ethnically homogenous cohort of Sardinian adults, Padiglia and colleagues (105) found that polymorphisms in *gustin*, a gene that encodes a zinc-dependent salivary protein thought to function as a taste cell trophic factor, varied with PROP phenotype. PROP nontasters were more likely than supertasters to have a polymorphism in the zinc-binding site of this gene that is required for full functionality of the gustin protein. Nontasters also had higher salivary zinc levels, which were hypothesized to reflect the inability of gustin to effectively bind to zinc in this population. Additional studies in this cohort suggested that the *gustin* gene relates more strongly to density of fungiform papillae (i.e., anatomical mushroom-shaped structures on the tongue that hold taste cells), whereas *TAS2R38* was a better predictor of suprathreshold ratings of PROP intensity (92). Several previous reports have suggested a relationship between PROP taste sensitivity and density of fungiform papillae on the anterior portion of the tongue, with PROP tasters having a greater number of papillae that hold functional taste cells compared to nontasters (3, 6, 47, 120, 142). Higher papillae number and density have been hypothesized to contribute to heightened overall responsiveness to a range

of basic tastes (e.g., bitter, sweet, salty) and textures (e.g., fat texture) in PROP tasters relative to nontasters (47, 110, 113). However, not all studies have demonstrated an association between fungiform papillae density and ratings of PROP bitterness (52, 56), suggesting that this relationship is not straightforward. Moreover, investigations in an ethnically nonhomogeneous cohort from North America did not replicate findings of an association between the polymorphisms in the *gustin* gene and PROP sensitivity or fungiform papillae density (49). Therefore, additional studies are needed to confirm *gustin*'s influence on the PROP phenotype in other populations.

MEASUREMENT OF PROP STATUS IN CHILDREN

Even though experimenters have classified individuals into groups with respect to the ability to taste PROP (i.e., tasters and nontasters), within these groups oral sensitivity lies along a continuum. Studies in adults have classified individuals as nontasters, medium-tasters, or supertasters at approximate breakdowns of 25%, 50%, and 25%, respectively. The discovery of a group of tasters with extremely high suprathreshold intensity ratings for PROP (i.e., supertasters) was made by Bartoshuk (7). The gold standard for determining these classifications is to use an adjective-labeled scale with ratio properties, such as the labeled magnitude scale (LMS) or the general labeled magnitude scale (gLMS) (8, 10). Categorical scales, such as the nine-point Likert scale, are unreliable for these classifications because they are susceptible to ceiling effects; moreover, because they do not have ratio properties, it is not possible to compare ratings across individuals (i.e., one person's rating of 6 cannot be assumed to be twice as intense as another person's rating of 3). In addition to the appropriate scale, it is necessary to have a standard that does not vary with taster status that can be used to compare responses to PROP across individuals. Several laboratories have had success using NaCl solutions as a standard (130), although Bartoshuk and colleagues reported that salt taste also varied with taster status (9) and therefore recommended use of the gLMS anchored with "the strongest imaginable sensation of any kind" or use of a nontaste standard such as sound.

Young children lack the cognitive skills necessary to rate the intensity of sensations on analog scales such as the gLMS, so for participants age 7 years and under, most investigators have used simple forced-choice screening methods to classify children as tasters or nontasters. Two exceptions are Anliker and colleagues (2) and Turnbull & Matisoo-Smith (135), who both assessed PROP status in children under age 7 by measuring PROP thresholds and suprathreshold responses on simple categorical scales. Although these procedures are more sensitive than the two-group classification method, they involve tasting multiple solutions and are not feasible for a field-based test with a large cohort. The most common method for classifying children into tasters or nontasters is to use some variation on a forced-choice procedure. In younger children (ages 3 to 4 years), Keller and colleagues (77) used a variation of a forced-choice procedure developed by Lawless (82) to assess children's ability to taste a 0.56 mM screening solution of PROP in spring water. After they taste the solution, children are asked if they detect anything, and following this question, children are asked to describe the drink's taste. Verbal responses are coded, and those who indicate an unpleasant taste or rejection (e.g., bad, bitter, yucky) are classified as tasters; those who report a pleasant taste or use descriptors such as plain, water, or nothing are classified as nontasters. Children with incongruous responses (e.g., "tastes yucky, like water") are typically retested at a later date. High test-retest reliability ($\rho = 0.92$) for this procedure was reported in a follow-up study (76).

Mennella and colleagues (95) have pointed out that children often answer in the affirmative, so asking them "yes" or "no" questions such as "Do you taste anything?" can result in false positives. To avoid this, these investigators use a variation of a procedure developed by Birch & Sullivan (19) to assess food preference. Children are presented with a PROP solution and asked to taste it

and give it to Big Bird (a likeable, well-known character from the children's show *Sesame Street*) if it tastes like water or to Oscar the Grouch (a well-known curmudgeonly character from the same show) if it does not so he can throw it in his trash can (95). This procedure is appropriate for preschool-aged children and eliminates the need for asking "yes" or "no" questions, and to improve compliance, it adds an element of fun to the testing that children enjoy. However, this procedure may be less effective with diverse participants who are unfamiliar with these characters. This forced-choice procedure can be used to classify children into tasters or nontasters on the basis of whether or not they can taste the solution. In addition, both Mennella and colleagues (95) and later our own group (75) used the procedure to classify children into several groups by having them taste a series of three solutions in ascending order of concentration and determining the lowest concentration of the three they are able to taste. This method yields more information than the simple two-group classification, but it is important to note that it cannot be used to determine which children are "supertasters" according to the way this term has been used in the adult literature. Although procedures have been used to classify children as young as age 7 (102) as supertasters, there have been no validation or reproducibility studies to determine whether children this age can actually understand and reliably use the LMS or gLMS.

PROP PHENOTYPE AS A MARKER FOR EATING BEHAVIORS

Observations in adults that PROP tasters perceive greater oral intensity from a wide range of compounds, including bitter (39, 64), sweet (65, 142), and fat (46, 65, 110, 131), provoked the possibility that the PROP phenotype might serve as a marker of dietary intake with important nutritional implications. Interest in the potential association between taste sensitivity to bitter thiourea compounds like PROP and dietary patterns grew from data from surveys conducted in adult populations by Fischer and colleagues (53) and Glanville & Kaplan (57). These early studies noted that in comparison with nontasters, PROP/PTC tasters tended to dislike pungent, strong-tasting foods. The notion that PROP status might serve as a simple, noninvasive screening method to predict dietary choices and, potentially, chronic disease risk is attractive for public health researchers as well as those who work in the food industry. However, food choice and dietary intake are complex phenotypes influenced by a broad range of factors, including social cues, peers, socioeconomic status (SES), culture, and education, as well as by individual characteristics, such as sex, ethnicity, body weight, and health status. As a result of these multiple influences, elucidation of the pathway linking the PTC genotype and PROP taster status to diet and health is not straightforward.

To guide our discussion in this section, we have modified the theoretical pathway presented previously by other groups (46, 129) (**Figure 2**). This pathway makes several assumptions that we use to guide our examination of the literature relating PROP status to diet and health. First, the PROP phenotype is in part genetically determined, with *TAS2R38* variation explaining ratings of PROP bitterness, whereas other genes (e.g., *gustin*) reportedly explain a higher amount of variance in fungiform papillae density (at least in some populations) (29, 92, 105). Other factors, including salivary proteins (28) and expression of *TAS2R38* on taste cells, may also influence expression of the PROP phenotype. Next, evidence supports a relationship between the PROP phenotype and taste and textural responses to a range of compounds, including the bitterness of quinine (64), sweetness of sucrose (142), perceived oral irritation from capsaicin and alcohol (44, 111), and perceived fat content (46, 65, 132). PROP tasters generally have heightened responses to these stimuli in comparison with nontasters, although not all studies support this (40). The next assumption is that perception of food taste and texture impacts food acceptance. In the case of bitter taste, this assumption may be partly true, as bitterness is the primary reported reason for

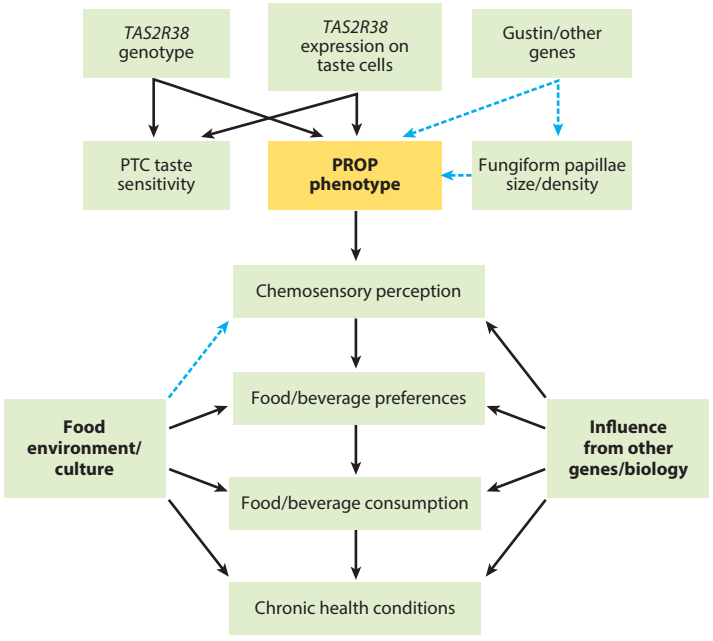

Figure 2

Theoretical pathway linking PTC genotype (*TAS2R38*) and PROP phenotype to chronic health. Blue dashed lines represent pathways for which less evidence exists. Variations in both the PTC genotype and other genes (e.g., *gustin*) are thought to influence variation in the ability to taste PROP. The PROP phenotype is a marker for a variety of chemosensory experiences and may also impact food and beverage preferences. Moreover, a link has been identified between food and beverage preference and dietary consumption. Finally, consumption patterns influence chronic health conditions. Other influences on taste perception, food preference, diet, and chronic disease risk include lifestyle and environmental factors as well as other genes.

avoiding fruits and vegetables (28). For example, children who have higher bitter sensitivity to quinine consume less grapefruit juice when given ad libitum access in the laboratory (63). Evidence in children also indicates that sourness perception is inversely related to acceptance of sour-tasting foods (32, 79). For sweet and fatty taste, however, the relationship between perception and intake is more complicated and likely is an inverse U-shaped curve, where the optimally preferred concentration varies depending on age and developmental and genetic factors (93).

The next step in the pathway relates dietary acceptance to intake, and because children tend to eat what they like (18), the relationship between liking and intake is probably tighter in children than in adults. In the final step, dietary intake influences chronic health problems, such as cancer, cardiovascular disease, and obesity. The associations between dietary patterns and chronic disease are well accepted, although diet is only one putative cause, and factors such as genetic susceptibility, age, and environmental exposures also impact this relationship. Given the complexity of this pathway and the multiple influences that affect each of its steps, it is likely that PROP taster status explains only a small amount of variance in both dietary patterns and chronic health conditions. Unless studies are sufficiently powered and/or attempt to explain the variance by controlling for multiple confounders, they are unlikely to identify a clear relationship.

The research on PROP status and eating behaviors in children has been influenced by a number of factors that distinguish this literature from adult studies. In the initial reports from Glanville & Kaplan (57), adults with higher PROP thresholds (i.e., lower ability to detect the taste of

PROP) reported liking stronger-tasting foods such as blue cheese, grapefruit juice, sauerkraut, and horseradish. These foods are not commonly consumed by children, and thus the majority of studies in younger age groups have focused on nutritionally relevant foods, such as fruits and vegetables, that are not as bitter or strong tasting (e.g., broccoli, grapefruit-orange juice blends). A second consideration with children is the measurement of PROP status. Given that young children lack the cognitive ability to perform the sophisticated scaling procedures used in adult studies, the classification of PROP status in this population is not as sensitive. As a result, studies in children cannot capture differences related to PROP taster status that may be driven by the phenotypic extremes. Another potential consideration is the impact that growth and development have on taste sensitivity, which could change the relationship between PROP status and dietary behaviors. In comparison with adults, children are more sensitive to the taste of PROP (2), and age modifies the relationship between PROP phenotype and *TAS2R38* genotype, with heterozygous (e.g., PAV/AVI) children able to perceive PROP bitterness at lower concentrations than heterozygous adults (94). A final factor that has impacted the research in children relates to the chronic health problems most relevant to this population. The continuing high rates of obesity among children in the United States (103) and globally (1, 136) have fueled interest in developing field-appropriate screening methods for determining risk for future weight problems, with PROP status being an obvious candidate. These factors have uniquely shaped the direction of studies examining the influence of PROP status on food acceptance, dietary intake, and chronic health in children.

Bitter- and Strong-Tasting Foods

Humans and other species have an inborn rejection of bitter taste (123, 124) that is presumably protective, to prevent ingestion of toxins. It follows that a heightened sensitivity to bitter taste, such as that observed in PROP tasters, could adversely impact the acceptance of bitter-tasting foods, such as some vegetables. Plant foods are the most common source of bitter-tasting compounds in the diet, and the majority of plants are capable of synthesizing bitter compounds for protection against predators (25, 51). Tasters have been hypothesized to have lower acceptance and intake of bitter-tasting fruits and vegetables (e.g., grapefruit juice, cruciferous vegetables) on the basis of early studies demonstrating a positive association between PROP taste sensitivity and perceived bitterness in compounds, such as caffeine (90), quinine (64), and naringin (the bitter compound in grapefruit) (39). These findings could have important health implications because many of the bitter-tasting compounds in foods (e.g., flavonoids, phenols, glucosinolates) are anticarcinogenic. Several studies in adults have also shown that PROP tasters consume fewer vegetables (45), and evidence in adults indicates higher incidence of colonic neoplasms in PROP tasters (11).

Vegetable intake among children, particularly intake of dark green leafy vegetables, is lower than recommended, and this is a concern because of the proposed health benefits of these foods (137). Some research in children suggests that the PROP/PTC phenotype and/or genotype may partially explain this dietary pattern. We conducted taste tests with 67 children ages 4 to 5 and found that taster children gave lower liking scores to raw broccoli compared with nontasters, but no differences were observed for liking of cooked broccoli (77). Raw broccoli contains bitter-tasting flavonoids and isothiocyanates that are degraded during the cooking process (17). However, in this same study, PROP tasters did not report lower liking for a mixture of orange-grapefruit juice (a 2:1 mixture of orange juice to grapefruit juice). We suspected that this juice blend was not sufficiently bitter to warrant lower liking ratings among PROP taster children, as had previously been observed in adults (39). This notion was supported in a follow-up study in which we increased the bitter content of the juice by using a 1:1 ratio of orange to grapefruit juice. The majority of nontaster children rated the orange-grapefruit juice blend as a 4 (“good”) or 5 (“super good”) on

a 5-point facial hedonic scale, whereas the majority of tasters gave the juice a rating of 1 ("super bad") (chi-square = 29.2; $p \leq 0.001$). Additionally, although Turnbull & Matisoo-Smith (135) did not replicate findings with raw broccoli, they did show that 3- to 6-year-old children who had higher taste sensitivity to PROP had lower acceptance of the taste of raw spinach. Moreover, in 525 Irish 7- to 13-year-olds, PROP phenotype, age, and sex were significant predictors of children's liking of bitter, glucosinolate-containing vegetables (101). Finally, Sharma & Kaur (121) studied 210 adolescent girls living in the Kangra Valley in India and showed that PTC tasters reported lower preference of raw cruciferous vegetables and bitter gourd.

Few studies in children have examined the relationship between PROP taster status and vegetable intake. One exception is Bell & Tepper (15), who measured preschool children's ad libitum intake of bitter and nonbitter vegetables served raw at snack time. In comparison with tasters, nontaster children consumed more total vegetables as well as more vegetables classified as bitter. Additionally, when vegetables were analyzed separately, intake of raw broccoli was higher among nontasters than tasters. In another study in a low-income Hispanic population of 3- to 5-year-olds, Fisher and colleagues (54) found that children who were PROP tasters consumed 80% more raw broccoli when it was offered with a dip or sauce (presumably because it masked the bitterness) than when it was served plain. Nontasters ate just as much broccoli when it was served plain as they did when it was offered with a full-fat dip. Other studies have assessed children's intake by parental self-report on food diaries or questionnaires. These methods have well-known biases but are often the only practical means of estimating intake, particularly for large populations. In 323 children ages 4 to 6 from Japan, nontaster boys reported higher intake of soy-containing foods on a three-day food record compared with taster boys, but only food neophobia, and not PROP status, predicted vegetable intake in this cohort (134). In the Irish cohort from Feeney and colleagues (50), children who had the AVI/AVI nontaster genotype reported higher intake of folate, a nutrient found in green leafy vegetables, compared to children who had taster haplotypes. Moreover, Sharma & Kaur (121) also reported a negative association between PTC taste sensitivity and intake of raw cabbage and bitter foods (e.g., bitter gourd).

Not all studies in children support a relationship between PROP taster status or *TAS2R38* genotype and acceptance or intake of bitter-tasting vegetables. For example, in one of the first studies reported in children, Anliker et al. (2) found no differences as a function of PROP status among 5- to 7-year-olds for their rated liking of raw or cooked broccoli. In addition, we did not replicate our initial findings with raw broccoli in a subsequent study with preschool children (78). Moreover, in a follow-up study of nearly 500 Irish school-age children, no differences were found in reported dietary intake of fruits and/or vegetables as a function of PROP phenotype or *TAS2R38* genotype (101). Other studies in ethnically diverse populations of lower-SES children have also not reported associations between PROP status and liking or intake of cruciferous and/or bitter-tasting vegetables (5, 89). Some of these inconsistencies could be due to the method of recording dietary information via self-report. Both O'Brien and colleagues (101) and Baranowski's group (5) used three-day diet records in children, and given the low intake of dark green leafy vegetables in this population, it is possible that assessing intake over three days was not sufficient to examine the relationship to PROP phenotype. For example, in O'Brien et al. (101), only 0.4% and 0.6% of children reported consuming bitter citrus fruits and bitter fruit juices, respectively, and no children reported intake of bitter salad vegetables. An additional possibility is that differences in SES and ethnicity of the cohorts explain some differences across studies. Further research is needed to determine the impact of SES and ethnicity on the relationship between the PROP phenotype and children's diets.

The food environment plays a key role in driving food selection and dietary patterns, but most studies have not systematically investigated how differences in food access and availability might

impact the relationship between PROP status and eating behaviors. To address this question, we conducted a secondary analysis with data from 120 children ages 4 to 6 who had participated in studies at our feeding lab in New York City. We characterized the food environment by using a geographical information system to determine the number of fruit and vegetable vendors as well as stores selling high-energy-dense, low-nutrient foods within walking distance (defined by a 0.5-mile radius) of where children lived. We used this information to create an index of the number of healthy food establishments relative to the number of unhealthy food establishments and then classified children's food environments as primarily healthy or unhealthy based on a median split. Children who were nontasters reported liking nearly twice as many vegetables as tasters, but this was only true for children who lived in healthy food environments and presumably had greater access and exposure to vegetables. PROP status did not impact vegetable liking for children who lived in primarily unhealthy food environments with less access to vegetables (27). These findings demonstrate the importance of the food environment in moderating the impact of PROP status on eating behaviors, but additional research is needed to replicate these findings in other geographical regions.

Bitter-Tasting Medications

Although not related to diet, several studies have looked at the impact of the PROP phenotype and/or *TAS2R38* genotype on the willingness to try and the rated acceptability of liquid medications. To facilitate ingestion, children are often given liquid forms of medication, but the palatability of these formulations can be adversely impacted by their bitter taste. Lipchock and colleagues (86) hypothesized that bitter-taste sensitivity might impact children's willingness to accept liquid forms of medications. Children who had at least one bitter-sensitive allele at *TAS2R38* reported being more likely to reject liquid medications (97) and were more likely to have consumed solid medication forms (i.e., pills or capsules) (86) compared to children with bitter-insensitive genotypes. Determining the most effective methods of blocking bitter taste in children's medications to improve palatability and compliance is a public health priority. Mennella and colleagues (96) showed evidence to suggest that sucrose was the best method of blocking bitter taste in children who were the most sensitive to PROP, although the effects did not reach significance. As this research becomes more established, it is conceivable that different versions of medications might be formulated to optimize palatability in tasters and nontasters.

Fat-Containing Foods

Excess consumption of dietary fat has been associated with the development of obesity (26), and certain genetic variants may make some individuals more vulnerable to overconsuming this nutrient than others (12, 33, 73, 114). The hypothesis that PROP status might be associated with the perception and intake of dietary fat originated from studies by Tepper & Nurse (131), who showed that adult nontasters were unable to accurately distinguish fat content in high- and low-fat Italian salad dressings. Other studies in adults showed that relative to PROP tasters, nontasters perceived less fat content and creaminess from a variety of foods (46, 65, 66, 110, 131, 132) despite the fact that they reported liking higher-fat foods (65, 66, 132). The relationship between PROP taster status and fat perception is thought to be mediated through fungiform papillae density. PROP supertasters have a higher density of fungiform papillae on the anterior surface of the tongue than do nontasters (47, 65, 92, 131). The fungiform papillae hold active taste cells and are densely innervated by trigeminal (somatosensory) nerves that function to relay information to the brain about textural sensations of food, including the oiliness, creaminess, and mouth-feel

of fats. Polymorphisms in the *gustin* gene that are more commonly observed in PROP nontasters (105) might provide a mechanistic link for the reduced papillae density and size observed in this population (92). Regardless of PROP status, other studies have reported that reduced ability to perceive dietary fat is associated with increased acceptance and intake of higher-fat foods (83, 125, 126). We have speculated that nontasters might compensate for reduced fat perception by consuming higher-fat foods in the diet that provide additional oral stimulation and sensory input (74). An alternative mechanism is also possible. Many fat-containing foods, such as dairy products, also contain small amounts of free fatty acids that are unpleasant and pungent (31), and PROP tasters are able to detect ice creams adulterated with linoleic acid whereas nontasters cannot (100). Therefore, it is also possible that nontasters are better able to tolerate higher-fat foods compared to tasters because they are less sensitive to the unpleasant chemosensory effects imparted by free fatty acids.

Several studies have reported associations between PROP status and liking and/or intake of fat-containing foods in children. Anliker and colleagues (2) reported that nontaster children liked cheddar cheese more than did tasters, yet they liked full-fat milk less. We reported that nontaster 4- to 5-year-olds gave higher liking ratings to American cheese than did tasters (77). In addition, when we stratified children by sex, we found that in comparison with taster girls, nontaster girls reported liking full-fat milk more, but no difference was found in boys. We also assessed intake using a parentally reported food frequency questionnaire and found that nontasters reported greater consumption of discretionary fats (i.e., butters, salad dressings, spreads); however, this relationship was again driven by nontaster girls, who reported consuming two additional servings per day of discretionary fats compared to taster girls (77). We speculated that these sex differences could be due in part to differences in home environmental or parental feeding practices between boys and girls that resulted in differences in how the PROP phenotype was expressed in the two populations. In a follow-up study in a similar population, nontasters (both boys and girls) reported higher consumption of high-fat meats, eggs, and nut butters compared to tasters (78). However, in an ethnically diverse cohort of 4- to 6-year-olds from New York City, we did not find that nontasters consumed more fat or fat-containing foods at an ad libitum test meal (76). In addition, although nontaster preadolescents reported consuming almost 300 more kcal per day than supertasters, no differences in fat intake or macronutrient selection were reported (60). Other studies in children also have not found a relationship between the PROP phenotype and intake of high-fat foods (89, 101, 102), suggesting that factors other than bitter-taste genetics might be more influential at mediating intake of dietary fat in children.

Sweet Foods

Both the PROP phenotype and PTC genotype have also been associated with liking and intake of sweet foods. Bitter and sweet taste perception share similarities in that the taste receptors for these compounds are both G protein–coupled receptors (115). Early studies in this area suggested that PROP tasters tended to dislike intensely sweet solutions (87, 88, 107). Yet, more recent studies by Duffy & Bartoshuk (43) showed that adult women who were PROP tasters had higher liking for sweet-fats (e.g., brownies, cookies, cakes), honey, and fruits, whereas the opposite pattern was seen in men. Therefore, studies in adults have shown contradictory findings with respect to PROP status and liking for sweets.

There is reason to think that the relationship between PROP status and sweet liking might differ between children and adults. Liking for sweet taste is highest in childhood and declines over time (34), and sweetness is a strong driver of palatability and food acceptance in children. Because children are so attracted to sweets, we hypothesized that those who were PROP tasters might

actually have higher liking for sweet foods simply because the sweetness is more pronounced. Several lines of evidence support this. First, we found that 4- to 5-year-old PROP tasters reported greater intake of sweet-fats and total dietary sugars compared to nontasters (78). In a doctoral thesis published from this same cohort, PROP tasters also reported higher intake of sweetened cereals (72). Additionally, in an ethnically diverse sample of 4- to 6-year-olds, we observed that PROP tasters consumed more energy from sweet foods (e.g., juices, fruit candies) at an ad libitum palatable buffet (75). Also, Sharma & Kaur (121) reported a positive relationship between taste sensitivity to PTC and reported intake of sweet-tasting foods among adolescent girls from India.

In addition to relationships between bitter-taste phenotypes and intake and liking of sweets, relationships have also been reported with *TAS2R38* genotype. Mennella and colleagues (95) showed in an ethnically diverse cohort that children who were homozygous for bitter-sensitive alleles preferred sweeter sucrose solutions and reported liking beverages and cereals with higher sugar content compared to children who were genetically bitter insensitive. A similar relationship between *TAS2R38* genotype and sucrose preference was reported in a follow-up study (96). Given the health implications of consuming excess dietary sugars, additional studies are warranted to understand the relationships between PROP phenotype, *TAS2R38* genotype, and dietary sugar consumption.

Somewhat contradictory to observations that PROP tasters consume a sweeter diet, several studies have found that there is an inverse correlation between PROP sensitivity and incidence of dental caries (68, 84, 108, 119, 122). In addition, 3- to 6-year-old PROP nontasters from India had higher levels of salivary *Streptococcus mutans*, the primary microbe that contributes to tooth decay, compared to tasters (109). Higher *S. mutans* could be due to higher carbohydrate intake among PROP nontasters but could also be attributed to biological or genetic differences associated with variants of *TAS2R38*. Studies are needed to determine whether these relationships are generalizable across populations.

PROP STATUS, *TAS2R38*, AND BODY WEIGHT

PROP/PTC sensitivity has also been hypothesized to play a role in growth and the regulation of body size. Several theories support this relationship. Thyroid hormones are necessary for growth, and because PROP/PTC sensitivity is thought to be involved in avoidance of antithyroid compounds in the diet, one hypothesis is that PROP status is associated with body size through thyroid function as a mediator. One could speculate that tasters might be taller than nontasters because they avoid consumption of dietary goitrogens that might impair thyroid function. Limited evidence for this notion can be found in early studies that related PTC taste sensitivity to growth. For example, Johnson and colleagues (71) found that PTC tasters tended to be taller and to have more mature skeletons, but no relationships were found with body weight. Others showed that PTC sensitivity was correlated with visual-motor maturation in children (61).

In addition to growth patterns, more recent studies have hypothesized a link between PROP taste sensitivity and body weight (128). Because of reported links between PROP status and liking of high-fat foods (132), Tepper first suggested that PROP taste blindness might be a marker for higher body weights (127, 128). In adults, these relationships have been more pronounced in Caucasian women, with some studies suggesting that nontasters had average body mass indices (BMIs) over six units higher than those of supertasters (59). Additionally, Stewart and colleagues (125, 126) and our own group (83) have also found that adults who have reduced oral sensitivity to fatty acids or dietary triglycerides reported higher dietary fat intake and had higher BMIs. These studies suggest that PROP status might be a marker of obesity mediated by its associations with fat perception, liking, and intake. Notably, not all studies are in support of these findings (37, 38, 41).

A third, more speculative, mechanism linking PROP status to body weight could be through the expression of *TAS2R38* receptors in the gastrointestinal tract. Taste receptors for bitter and sweet compounds are expressed in the gut of humans and other mammals (16, 69, 91, 116, 117). These receptors likely play critical roles in nutrient detection. For example, bitter-taste receptors have been found to mediate glucose homeostasis (35) and secretion of the appetite-stimulating hormone ghrelin (70). Therefore, it is possible that variants in *TAS2R* genes could modulate appetite, food intake, and body weight through their functional roles in the gut.

Following reports of a relationship between the PROP phenotype and body weight status in adult women (59, 133), we also found a relationship between PROP status and BMI-for-age percentiles in 4- to 5-year-old children (78). Sex moderated the relationship, with nontaster boys having higher BMI-for-age percentiles than taster boys. Unexpectedly, the opposite pattern was observed in girls (i.e., taster girls had higher BMIs than nontaster girls). When these same children were tested at a six-year follow-up (ages 7 to 13 years), the interaction between PROP status and gender explained a significant amount of variance in children's BMI percentile, and a trend suggested an inverse relationship between PROP taste sensitivity and weight status again in boys but not in girls (102). We found a similar interaction between PROP status and sex on weight status in a follow-up study with ethnically diverse 4- to 6-year-olds (76). However, when we included children's *TAS2R38* genotype in the analyses, we observed a three-way interaction between PROP phenotype, PTC genotype, and sex. Overall, PROP nontasters who were also homozygous for the bitter-insensitive allele at *TAS2R38* (i.e., who genetically were nontasters) had average BMI-for-age percentiles over the 95th percentile (i.e., in the obese range), and this was greater than BMI percentiles for tasters who had the same genotype. These findings suggest that the PROP phenotype and PTC genotype interact to influence child body weight status, with children who are nontasters by both phenotype and genotype carrying the highest risk for obesity. These findings should be interpreted with caution, however, because small cohorts were tested in the aforementioned studies, and future investigations should be adequately powered to detect interactions among PROP status, PTC genotype, and sex.

Not all studies support a relationship between bitter-taste insensitivity and BMI. Goldstein and colleagues (60) did not find a relationship between PROP status and BMI percentile in preadolescent children, even though nontasters in this study reported consuming more daily energy compared with supertasters. In addition, no relationship was found between PROP taster status and BMI in a sample of 120 Filipino adolescents ages 13 to 17 (22), but null results may be due to ethnic and cultural differences. Other studies conducted in ethnically and socioeconomically diverse cohorts also dispute the notion that PROP insensitivity is a marker for higher body weights in children. Baranowski and colleagues (4) reported an interaction between PROP status and SES in a sample of 813 children ages 9 to 10 and 17 to 18 in which supertasters in the highest SES category actually had higher BMI z-scores than did nontasters. However, the effects in this study were small, with the interaction of PROP status and SES explaining only 1% of the variance in the model predicting child BMI z-score. In addition, Lumeng and colleagues (89) reported higher BMI percentiles among PROP tasters compared to nontasters in a sample of low-income Mexican American children ages 3 to 6. These results suggest that factors such as SES and ethnicity may influence the relationship between bitter-taste insensitivity and obesity, and additional studies are needed to understand these complex associations.

Two recent studies have advanced our understanding of the relationship between bitter-taste sensitivity and body weight in children and may provide some insight for the design of future studies. First, Burd and colleagues (27) found that nontaster children living in unhealthy food environments, with ready access to high-energy-dense, low-nutrient foods, had higher BMI z-scores in comparison with nontasters living in healthy food environments and taster children regardless

of environment. This difference was significant even after adjusting for income, ethnicity, and measures of fruit and vegetable acceptance. Nontaster children living in unhealthy food environments had average BMIs that were above the 95th percentile, which places them in the obese range. These results suggest that healthier food environments may act as a protective factor for nontaster children. However, children's food intake and home food environment were not reported in this study; therefore, future studies should include these measures to determine the extent to which they mediate the relationships between PROP status and obesity.

Second, Bouthoorn and colleagues (23) used Mendelian randomization to test a potential causal pathway linking PROP status to body weight. In this design, randomly assorted genes are used as instrumental variables between phenotype and outcome based on the assumption that genes are not as susceptible to confounding from factors such as lifestyle, ethnicity, and demographics. This type of design also eliminates the potential of reverse causation, which is particularly important in this case because obesity has been reported to impact taste perception. They tested 3,778 six-year-olds from a prospective birth cohort study from the Netherlands and found that nontaster girls had higher BMI z-scores and percent body fat than taster girls. No PROP-related differences were found in boys. These results remained after adjusting for parental BMI, SES, ethnicity, and reported hours of outside play.

It is likely that taste blindness to PROP serves as a marker for obesity in some populations but not in others. Differences in ethnicity and SES across cohorts may explain some of the discrepancies across studies. Findings from primarily lower-SES, ethnically diverse cohorts either have suggested no relationship (4) or have found higher weight status in tasters but not in nontasters (89). It is possible that the influence of SES on body weight overwhelms any potential effect of PROP status. Alternatively, as suggested by Bouthoorn and colleagues (23), the impact of PROP status on body weight could be mediated by the diet of the population tested. Perhaps the effects across population are truly heterogeneous. The findings from Burd and colleagues (27) are in support of this, as the interaction between PROP status and the food environment had a greater influence on food acceptance and weight status than either measure did when tested alone. Future studies in this area should systematically consider the dietary environment of the population tested to clarify the associations between PROP status and chronic health.

CONCLUSIONS AND DIRECTIONS FOR FUTURE STUDIES

We have summarized outcomes from the pertinent studies we discuss in this review in **Tables 1, 2**, and **3**. Across studies, some themes in the literature emerge. In the case of food acceptance and intake, the most common foods to show a relationship with PROP status in children are mildly bitter cruciferous vegetables (e.g., raw spinach and broccoli) and fat-containing foods such as cheese and milk. Only one study has reported associations between PROP status and intake of highly bitter foods, and this was conducted with adolescent girls from India who were presumably consuming diets that were substantially different from most Northern European, primarily Caucasian, samples (121). The majority of studies that have shown effects of PROP phenotype on liking and intake have been conducted with higher-SES cohorts of primarily Caucasian background. An exception was the study by Fisher and colleagues (54), who reported that PROP-sensitive Hispanic children from Head Start consumed more raw broccoli when it was paired with a dip or sauce, whereas PROP-insensitive children consumed similar amounts of broccoli with or without dip. These findings suggest important differences in the relationship among PROP status, ethnicity, and customary diet that need to be addressed in future studies.

With respect to the studies that have looked at intake (**Table 2**), some inconsistencies across studies might be explained by the methodology used to capture diet. The majority of studies that

Table 1 Influence of PROP phenotype and/or PTC genotype on food liking and preference

Reference (year published)	Cohort sample size, age, and primary ethnicity or place of residence	Methods	BMI	Bitter-taste assessment	Outcomes
2 (1991)	$n = 30$ 5–7 years Ethnicity not reported	Preference ranking of 8 sampled foods Liking ratings of 60 foods from survey	Yes	PROP thresholds	NT ranked cheddar cheese higher than T NT ranked full-fat milk lower than T No difference in cooked/raw broccoli and spinach
73 (2002)	$n = 67$ 4–5 years 97% Caucasian	Liking ratings of 10 tasted foods	Yes	PROP forced-choice screening	NT liked American cheese and raw broccoli more than T No effect for cooked broccoli, orange-grapefruit mixture NT girls liked full-fat milk more than T girls
135 (2002)	$n = 42$ 3–6 years Ethnicity not reported	Preference ranking and liking of 7 sampled foods Liking of 30 foods from a questionnaire	No	PROP thresholds and suprathresholds	NT more likely to like the taste of raw spinach than T
96 (2005)	$n = 143$ 5–10 years African American, Caucasian	Optimally preferred sucrose concentration Child self-report of favorite cereals	No	PROP forced-choice screening and *TAS2R38*	Children with bitter-sensitive alleles preferred higher-sucrose concentrations and sweetened cereals compared to NT
15 (2006)	$n = 65$ 3–4 years Majority Caucasian	Liking ratings for 5 sampled vegetables	Yes	PROP forced-choice screening	NT gave higher liking ratings to raw broccoli than T
49 (2014)	$n = 525$ 7–13 years Irish	Liking ratings of foods from pictures	Yes	Perceived intensity of PROP filter paper and *TAS2R38*	PROP status, age, and sex explained 1% of children's vegetable liking *TAS2R38* did not influence vegetable liking
22 (2012)	$n = 120$ 13–17 years Filipino	Liking ratings of 88 foods on checklist	Yes	Perceived intensity of PROP solutions on LMS	T rated liking of umami-rich condiments higher than NT
54 (2012)	$n = 15$ 23–5 years Hispanic	Liking ratings of 6 vegetables	Yes	PROP forced-choice screening	Children's rated liking of broccoli increased following repeated exposure but did not vary by taster status
27 (2013)	$n = 120$ 4–6 years African American, Hispanic, Caucasian, Asian	Liking/disliking ratings of 36 common foods from pictures	Yes	PROP forced-choice screening	NT living in healthy food environments liked more vegetables than T living in healthy food environments

(*Continued*)

Table 1 (*Continued*)

Reference (year published)	Cohort sample size, age, and primary ethnicity or place of residence	Methods	BMI	Bitter-taste assessment	Outcomes
121 (2014)	$n = 210$ 11–18 years (girls) Kangra Valley, India	Liking ratings of foods on questionnaire	Yes	PTC thresholds	T had lower liking of bitter gourd, raw cruciferous vegetables, and sweets than NT

Abbreviations: BMI, body mass index; LMS, labeled magnitude scale; NT, nontasters; PROP, 6-*n*-propylthiouracil; PTC, phenylthiocarbamide; T, tasters.

Table 2 Influence of PROP phenotype and/or PTC genotype on food intake

Reference (year published)	Cohort sample size, age, and primary ethnicity	Methods	BMI	Bitter-taste assessment	Outcomes
73 (2002)	$n = 67$ 4–5 years 97% Caucasian	Parental report food frequency	Yes	PROP forced-choice screening	NT report greater intake of discretionary fats than T Driven by NT girls
74 (2004)	$n = 53$ 4–5 years Majority Caucasian	Parental report food frequency	Yes	PROP forced-choice screening	NT report higher intake from protein (high-fat meats) T report higher intake of sweet-fats and total dietary sugars
15 (2006)	$n = 65$ 3–4 years Majority Caucasian	Ad libitum intake of 5 vegetables	Yes	PROP forced-choice screening	NT ate more bitter and total vegetables than T NT ate more raw broccoli than T
60 (2007)	$n = 65$ 7–11 years Majority Caucasian	Food diary for 3 days	Yes	Perceived intensity of PROP filter paper on LMS	NT report higher total daily intake (~300 kcal) than T No difference in macronutrient selection
89 (2008)	$n = 81$ 3–6 years Hispanic, low income	Maternal report on food frequency	Yes	PROP forced-choice screening	No difference in dietary intake between groups
78 (2010)	$n = 72$ 4–6 years African American, Hispanic, Caucasian, Asian	Ad libitum intake of multi-item test meal	Yes	PROP forced-choice screening and *TAS2R38*	No difference in test-meal intake by PROP or *TAS2R38*
5 (2011)	$n = 665$ 9–10 years and 17–18 years African American, Hispanic, Caucasian	Self-report 3-day dietary recall	Yes	Perceived intensity of PROP filter paper on LMS	No difference in intake by PROP

(*Continued*)

Table 2 (*Continued*)

Reference (year published)	Cohort sample size, age, and primary ethnicity	Methods	BMI	Bitter-taste assessment	Outcomes
49 (2014)	$n = 525$ 7–13 years Irish	Self-report 3-day diet history	Yes	Perceived intensity of PROP filter paper; *TAS2R38*	AVI/AVI females had higher intake of thiamine, vitamin B_6, and folate compared to bitter-sensitive genotypes
22 (2012)	$n = 120$ 13–17 years Filipino	Self-report 3-day food record	Yes	Perceived intensity of PROP solutions on LMS	No difference in intake by PROP
54 (2012)	$n = 152$ 3–5 years Majority Hispanic, low income	Ad libitum intake of broccoli plain, with dip, or sauce across 7 weeks	Yes	PROP forced-choice screening	T ate more raw broccoli when it was served with dip or sauce
134 (2012)	$n = 323$ 4–6 years Japanese	Self-report 3-day diet history BMI assessed by parental report	Yes	PROP forced-choice screening	NT boys reported higher soy intake than T (except for those who had low food neophobia)
101 (2013)	$n = 483$ 7–13 years Irish	Self-report 3-day diet history	Yes	Perceived intensity of PROP filter paper on gLMS; *TAS2R38*	No difference in intake of fruits and vegetables
102 (2013)	$n = 73$ 7–13 years Majority Caucasian	Three 24-hour dietary recalls	Yes	Perceived intensity of PROP filter paper on LMS; *TAS2R38*	No difference in energy or macronutrient intake
77 (2014)	$n = 79$ 4–6 years African American, Hispanic, Caucasian, Asian	Ad libitum intake of palatable buffet of sweets, sweet-fats, and savory-fats	Yes	PROP forced-choice screening and *TAS2R38*	T consumed more sweets than NT No difference in intake by *TAS2R38* Weight status but not taster status influenced intake of savory-fats

Abbreviations: BMI, body mass index; gLMS, general labeled magnitude scale; LMS, labeled magnitude scale; NT, nontaster; PROP, 6-*n*-propylthiouracil; PTC, phenylthiocarbamide; T, taster.

have found differences between dietary intake as a function of PROP status have utilized food frequency questionnaires (77, 78) or measured ad libitum intake (15, 54, 75). Most studies that have used self-report diet recalls or food diaries have not seen any relationship with PROP status (5, 22, 50, 101, 102, 134). The biases inherent in methods for dietary reporting have been thoroughly discussed, and all methods have obvious strengths and limitations. Although food diaries and 24-hour dietary recalls are considered more accurate for assessing total energy intake, they may not capture sufficient variability in the foods that are likely to be influenced by PROP phenotypic variation (especially in children). In addition, although test meals are limited in the foods they can assess, they offer greater control over environmental conditions and can be designed to test specific hypotheses about how PROP status influences ad libitum intake. For example, by offering a highly palatable meal of sweets, sweet-fats, and savory-fats, we were able to detect differences related to PROP status that might be difficult to capture with other methods (e.g., food frequency

Table 3 Influence of PROP phenotype and/or PTC genotype on body weight status

Reference (year published)	Cohort sample size, age, and primary ethnicity or country of residence	Methods	BMI	Bitter-taste assessment	Outcomes
73 (2002)	*n* = 67 4–5 years 97% Caucasian	Measured BMI	Yes	PROP forced-choice screening	No relationship with BMI
74 (2004)	*n* = 53 4–5 years Majority Caucasian	Measured BMI	Yes	PROP forced-choice screening	NT boys had higher BMIz than T boys T girls had higher BMIz than NT girls
15 (2006)	*n* = 65 3–4 years Majority Caucasian	Measured BMI	Yes	PROP forced-choice screening	No relationship with BMI
60 (2007)	*n* = 65 7–11 years Majority Caucasian	Measured BMI	Yes	Perceived intensity of PROP filter paper on LMS	No relationship with BMI
58 (2009)	*n* = 5,294 10–11 years Southwest England	Measured BMI	Yes	Perceived intensity of PROP filter paper on 10 cm line	No relationship with BMI
89 (2008)	*n* = 81 3–6 years Hispanic, low-income	Measured BMI	Yes	PROP forced-choice screening	T had higher BMIz than NT
78 (2010)	*n* = 72 4–6 years African American, Hispanic, Caucasian, Asian	Measured BMI	Yes	PROP forced-choice screening; *TAS2R38*	NT boys had higher BMIz than T boys NT (boys and girls) with AVI genotypes had higher BMIz than T with AVI
4 (2009)	*n* = 1,551 9–10 years and 17–18 years African American, Hispanic, Caucasian	Measured BMI	Yes	Perceived intensity of PROP filter paper on LMS	T in highest SES had higher BMIz than NT
22 (2012)	*n* = 120 13–17 years Filipino	Measured BMI	Yes	Perceived intensity of PROP solutions on LMS	No relationship with BMI
101 (2013)	*n* = 483 7–13 years Irish	Measured BMI	Yes	Perceived intensity of PROP filter paper on gLMS; *TAS2R38*	No relationship with BMI
102 (2013)	*n* = 73 7–13 years Majority Caucasian	Measured BMI	Yes	Perceived intensity of PROP filter paper on LMS; *TAS2R38*	No relationship with BMI Trend for boy NT to have higher BMI% than T

(*Continued*)

Table 3 (*Continued*)

Reference (year published)	Cohort sample size, age, and primary ethnicity or country of residence	Methods	BMI	Bitter-taste assessment	Outcomes
27 (2013)	$n = 120$ 4–6 years African American, Hispanic, Caucasian	Measured BMI	Yes	PROP forced-choice screening	NT living in unhealthy food environments had higher BMIz
121 (2014)	$n = 210$ 11–18 years (female) Kangra Valley India	Measured BMI and skinfolds to assess body fat and basal metabolic rate	Yes	PTC thresholds	NT had higher stature T had higher skinfolds and body fat (age 14–16 years)
23 (2014)	$n = 3{,}773$ 6 years From Rotterdam	Measured BMI and DXA; Mendelian randomization	Yes	PROP forced-choice screening	NT girls had higher BMIz and body fat than T girls Evidence of a causal relationship No relationship in boys
77 (2014)	$n = 79$ 4–6 years African American, Hispanic, Caucasian, Asian	Measured BMI	Yes	PROP forced-choice screening and *TAS2R38*	No relationship with BMI and PROP or *TAS2R38*

Abbreviations: BMI, body mass index; BMIz, body mass index z-score; DXA, dual-energy X-ray absorptiometry; gLMS, general labeled magnitude scale; LMS, labeled magnitude scale; NT, nontasters; PROP, 6-*n*-propylthiouracil; PTC, phenylthiocarbamide; T, tasters.

questionnaire, food diary) because these foods are all highly palatable and therefore usual intake may not show much variance across children (75).

In general, fewer studies have included assessments of both PROP phenotype and PTC genotype, and for those studies that have assessed *TAS2R38*, the majority have not found it to be related to eating behaviors or body weight. A notable exception is Mennella and colleagues (95), who found that children who were homozygous for bitter-sensitive alleles at the PTC taste receptor preferred higher-concentration sucrose solutions and reported liking sweeter cereals compared with children who had bitter-insensitive genotypes. In Irish school children, Feeney and colleagues (50) also reported higher intake of some nutrients commonly found in cruciferous vegetables in the diets of those homozygous for bitter-insensitive alleles (i.e., AVI/AVI). In addition, a study by Keller and colleagues (76) suggested an interaction between PROP phenotype and PTC genotype on body weight, such that children who were nontasters both by phenotype and genotype might be at higher risk for obesity. Future studies are needed that include measures of both PROP phenotype and PTC genotype, particularly because of recent studies that have pointed out potential relationships between PROP status and other genes, such as *gustin* (29). PROP status is clearly not just a phenotypic marker of the PTC genotype, and therefore one might expect associations with eating behavior and chronic health to differ depending on what measure is included.

The relationship between PROP phenotype and body weight is highly discrepant across studies and depends on the population examined and the confounders accounted for in the analysis. This discrepancy is not surprising given that diet likely mediates the relationship between PROP

phenotype and body weight. Types of foods consumed, as well as the culturally acceptable ways of preparing those foods, vary widely across different ethnicities and geographical regions. Most cultures have developed preparation techniques intended to mask or dampen bitter and/or pungent flavors (e.g., preparing bitter greens with fatback, preparing broccoli with cheese and/or butter, frying green tomatoes). In Asian and Indian cuisine, bitter flavors are often balanced in dishes with sweet, sour, salty, and umami flavors. Culture is thought to be the most important influence on what people eat (118), and therefore to predict how PROP status will influence body weight it is critical to account for the customary cuisine of the population. In the case of children, parents also employ different methods to make bitter foods acceptable, such as the "stealth" approach of mixing them with other foods or by adding sauces and dips to bitter vegetables. The success of these methods may vary depending upon children's PROP status (54), and additional insight is needed to understand how to tailor feeding practices to children who vary by bitter-taste sensitivity.

Studies are also needed that account for variation in food access and availability to determine how these factors mediate relationships among PROP status, diet, and health. Although access to food in the environment is only a proxy for consumption, systematically measuring this variable may clarify the relationship between PROP status and body weight. For example, Burd and colleagues (27) found that nontaster children who had greater access to unhealthy foods in the environment were at the greatest risk for obesity. Future studies in this area should include measures of food accessibility and availability, as they are likely to interact with bitter-taste phenotype to influence body weight.

In addition to accounting for the customary diet of a population, future investigations should also include other genetic markers of chemosensation to understand how they interact with PROP status to influence eating behaviors. *TAS2R38* and PROP status are well studied, but numerous other polymorphisms impact taste perception, with potential implications for dietary intake (67). Additional studies are needed to understand how these polymorphisms interact with *TAS2R38* variation and the PROP phenotype to influence eating behaviors and chronic health.

In conclusion, genetic variation in the ability to taste bitter thiourea compounds may have important implications as a marker for dietary patterns and chronic health in children. The available literature suggests that some children who are sensitive to bitter taste may require additional strategies to accept and consume bitter-tasting fruits and vegetables (e.g., using dips and sauces, offering milder juice blends, and providing greater access to these foods in the environment). Additionally, children who are insensitive to bitter thiourea may have greater intakes of high-fat foods and excess body weight, but it is likely that this relationship is affected by factors such as sex, age, culture, and access to foods in the environment. Future studies are needed to provide insight on the relationships among PROP taster status, PTC genotype, and liking and intake of sweet-tasting foods across childhood. In addition, future studies should include measures of the food environment, cultural methods of food preparation, and other genetic markers of chemosensation to understand the complex pathway linking bitter-taste variation to dietary patterns and chronic health.

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LITERATURE CITED

1. Adair LS. 2008. Child and adolescent obesity: epidemiology and developmental perspectives. *Physiol. Behav.* 94:8–16
2. Anliker J, Bartoshuk L, Ferris A, Hooks L. 1991. Children's food preferences and genetic sensitivity to the bitter taste of 6-n-propylthiouracil (PROP). *Appetite* 54:316–20
3. Bajec M, Pickering G. 2008. Thermal taste, PROP responsiveness, and perception of oral sensations. *Physiol. Behav.* 95:581–90
4. Baranowski J, Baranowski T, Beltran A, Watson K, Jago R, et al. 2009. 6-n-Propylthiouracil sensitivity and obesity status among ethnically diverse children. *Public Health Nutr.* 13:1587–92
5. Baranowski T, Baranowski J, Watson K, Jago R, Islam N, et al. 2011. 6-n-Propylthiouracil taster status not related to reported cruciferous vegetable intake among ethnically diverse children. *Nutr. Res.* 31:594–600
6. Bartoshuk LM. 1994. PTC/PROP tasting: anatomy, psychophysics, and sex effects. *Physiol. Behav.* 56:1165–71
7. Bartoshuk LM. 1996. Supertasting, earaches and head injury: Genetics and pathology alter our taste worlds. *Neurosci. Biobehav. Rev.* 20:79–87
8. Bartoshuk LM. 2000. Comparing sensory experiences across individuals: recent psychophysical advances illuminate genetic variation in taste perception. *Chem. Senses* 25:447–60
9. Bartoshuk LM, Duffy V, Lucchina L, Prutkin J, Fast K. 1998. PROP (6-*n*-propylthiouracil) supertasters and the saltiness of NaCl. *Ann. N. Y. Acad. Sci.* 855:793–96
10. Bartoshuk LM, Duffy VB, Green BG, Hoffman HJ, Ko CW, et al. 2004. Valid across-group comparisons with labeled scales: the gLMS versus magnitude matching. *Physiol. Behav.* 82:109–14
11. Basson M, Bartoshuk L, Dichello S, Panzini L, Weiffenbach J, Duffy V. 2005. Association between 6-*n*-propylthiouracil (PROP) bitterness and colonic neoplasms. *Digest. Dis. Sci.* 50:483–89
12. Bauer F, Elbers CC, Adan RAH, Loos RJF, Onland-Moret NC, et al. 2009. Obesity genes identified in genome-wide association studies are associated with adiposity measures and potentially with nutrient-specific food preference. *Am. J. Clin. Nutr.* 90:951–59
13. Behrens M, Foerster S, Staehler F, Raguse J, Meyerhof W. 2007. Gustatory expression pattern of the human TAS2R bitter receptor gene family reveals a heterogeneous population of bitter responsive taste receptor cells. *J. Neurosci.* 27:12630–40
14. Behrens M, Gunn H, Ramos P, Meyerhof W, Wooding S. 2013. Genetic, functional, and phenotypic diversity in TAS2R38-mediated bitter taste perception. *Chem. Senses* 38:475–84
15. Bell K, Tepper B. 2006. Short-term vegetable intake by young children classified by 6-*n*-propylthiouracil bitter-taste phenotype. *Am. J. Clin. Nutr.* 84:245–51
16. Benzencon C, Le Coutre J, Damak S. 2007. Taste-signaling proteins are coexpressed in solitary intestinal epithelial cells. *Chem. Senses* 32:41–49
17. Betz J, Fox W. 1994. High-performance liquid chromatographic determination of glucosinolates in *Brassica* vegetables. *Am. Chem. Soc.* 546:181–96
18. Birch LL. 1979. Preschool children's food preferences and consumption patterns. *J. Nutr. Educ.* 11:189–92
19. Birch LL, Sullivan S. 1991. Measuring children's food preferences. *J. School Health* 61:1245–51
20. Blakeslee A, Fox A. 1932. Our different taste worlds. *J. Heredity* 23:97–107
21. Blakeslee A, Salmon M. 1931. Odor and taste blindness. *Eugen. News* 16:105–10
22. Borazon E, Villarino B, Magbuhat R, Sabandal M. 2012. Relationship of PROP (6-*n*-propylthiouracil) taster status with body mass index, food preferences, and consumption of Filipino adolescents. *Food Res. Int.* 47:229–35
23. Bouthoorn S, van Lenthe F, Kiefte-de Jong J, Taal H, Wijtzes A, et al. 2014. Genetic taste blindness to bitter and body composition in childhood: a Mendelian randomization design. *Int. J. Obes.* 38:1005–10
24. Boyd W. 1950. Taste reactions to antithyroid substances. *Science* 112:153
25. Bravo L. 1998. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutr. Rev.* 56:317–33

26. Bufe B, Kuhn C, Reed D, Tharp C, Slack J, et al. 2005. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. *Curr. Biol.* 15:1–20
27. Burd C, Senerat A, Chambers E, Keller K. 2013. PROP taster status interacts with the built environment to influence children's food acceptance and body weight status. *Obesity* 21:786–94
28. Cabras T, Melis M, Castagnola M, Padiglia A, Tepper BJ, et al. 2012. Responsiveness to 6-*n*-propylthiouracil (PROP) is associated with salivary levels of two specific basic proline-rich proteins in humans. *PLOS ONE* 7:e30962
29. Calo C, Padiglia A, Zonza A, Corrias L, Contu P, et al. 2011. Polymorphisms in TAS2R38 and the taste bud trophic factor, *gustin* gene co-operate in modulating PROP taste phenotype. *Physiol. Behav.* 104:1065–71
30. Campbell MC, Ranciaro A, Froment A, Hirbo J, Omar S, et al. 2011. Evolution of functionally diverse alleles associated with PTC bitter taste sensitivity in Africa. *Mol. Biol. Evol.* 29:1141–53
31. Chale-Rush A, Burgess JR, Mattes RD. 2007. Evidence for human orosensory (taste?) sensitivity to free fatty acids. *Chem. Senses* 32:423–31
32. Chauhan J, Hawrysh Z. 1988. Suprathreshold sour taste intensity and pleasantness perception with age. *Physiol. Behav.* 43:601–7
33. Collaku A, Rankinen T, Rice T, Leon AS, Rao DC, et al. 2004. A genome-wide linkage scan for dietary energy and nutrient intakes: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study. *Am. J. Clin. Nutr.* 79:881–86
34. Desor JA, Beauchamp GK. 1987. Longitudinal changes in sweet preferences in humans. *Physiol. Behav.* 39:639–41
35. Dotson C, Zhang LH, Xu H, Shin YV, Vigues S, et al. 2008. Bitter taste receptors influence glucose homeostasis. *PLOS ONE* 3:e3974
36. Drayna D, Coon H, Kim U-K, Elsner T, Cromer K, et al. 2003. Genetic analysis of a complex trait in the Utah Genetic Reference Project: a major locus for PTC taste ability on chromosome 7q and a secondary locus on chromosome 16p. *Hum. Genet.* 112:567–72
37. Drewnowski A, Henderson S, Cockroft J. 2007. Genetic sensitivity to 6-*n*-propylthiouracil has no influence on dietary patterns, body mass indexes, or plasma lipid profiles of women. *J. Am. Diet. Assoc.* 107:1340–48
38. Drewnowski A, Henderson S, Hann C, Berg W, Ruffin M. 2000. Genetic taste markers and preferences for vegetables and fruit of female breast cancer patients. *J. Am. Diet. Assoc.* 100:191–97
39. Drewnowski A, Henderson S, Shore A. 1997. Taste responses to naringin, a flavonoid, and the acceptance of grapefruit juice area related to genetic sensitivity to 6-*n*-propylthiouracil. *Am. J. Clin. Nutr.* 66:391–97
40. Drewnowski A, Henderson SA, Shore AB, Barratt-Fornell A. 1997. Nontasters, tasters, and supertasters of 6-*n*-propylthiouracil (PROP) and hedonic response to sweet. *Physiol. Behav.* 62:649–55
41. Drewnowski A, Kristal A, Cohen J. 2001. Genetic taste responses to 6-*n*-propylthiouracil among adults: a screening tool for epidemiological studies. *Chem. Senses* 26:483–89
42. Duffy B, Peterson J, Bartoshuk L. 2004. Associations between taste genetics, oral sensation and alcohol intake. *Physiol. Behav.* 82:435–45
43. Duffy V, Bartoshuk LM. 2000. Food acceptance and genetic variation in taste. *J. Am. Diet. Assoc.* 100:47–55
44. Duffy V, Davidson A, Kidd J, Kidd K, Speed W. 2004. Bitter receptor gene (*TAS2R38*), 6-*n*-propylthiouracil (PROP) bitterness and alcohol intake. *Alcohol. Clin. Exp. Res.* 28:1629–37
45. Duffy V, Hayes J, Davidson A, Kidd J, Kidd K, Bartoshuk L. 2010. Vegetable intake in college-aged adults is explained by oral sensory phenotypes and *TAS2R38* genotype. *Chemosens. Percept.* 3:137–48
46. Duffy V, Lucchina L, Bartoshuk L. 2004. Genetic variation in taste: potential biomarker for cardiovascular disease? See Ref. 112, pp. 195–228
47. Essick G, Chopra A, Guest S, McGlone F. 2003. Lingual tactile acuity, taste perception, and the density and diameter of fungiform papillae in female subjects. *Physiol. Behav.* 80:289–302
48. Febbraio M, Abumrad NA, Hajjar DP, Sharma K, Cheng W, et al. 1999. A null mutation in murine CD36 reveals an important role in fatty acid and lipoprotein metabolism. *J. Biol. Chem.* 274:19055–62
49. Feeney E, Hayes J. 2014. Exploring associations between taste perception, oral anatomy and polymorphisms in the carbonic anhydrase (*gustin*) gene *CA6*. *Physiol. Behav.* 128:148–54

50. Feeney E, O'Brien S, Scannell A, Markey A, Gibney ER. 2011. Genetic variation in taste perception: Does it have a role in healthy eating? *Proc. Nutr. Soc.* 70:135–43
51. Fenwick G, Heaney R, Mullin W. 1983. Glucosinolates and their breakdown products in food and food plants. *Crit. Rev. Food. Sci. Nutr.* 18:123–201
52. Fischer M, Cruickshanks K, Schubert C, Pinto A, Klein R, et al. 2013. Factors related to fungiform papillae density: the Beaver Dam Offspring Study. *Chem. Senses* 38:669–77
53. Fischer R, Griffin F, England S, Garn S. 1961. Taste thresholds and food dislikes. *Nature* 191:1328
54. Fisher JO, Mennella JA, Hughes SO, Yan L, Mendoza PM, Patrick H. 2012. Offering "dip" promotes intake of a moderately-liked raw vegetable among preschoolers with genetic sensitivity to bitterness. *J. Am. Diet. Assoc.* 112:235–45
55. Fisher R, Ford E, Huxley J. 1939. Taste-testing the anthropoid apes. *Nature* 144:750
56. Garneau N, Nuessle T, Sloan M, Santorico S, Coughlin B, Hayes J. 2014. Crowdsourcing taste research: genetic and phenotypic predictors of bitter taste perception as a model. *Front. Integr. Neurosci.* 8:33
57. Glanville E, Kaplan A. 1965. Food preference and sensitivity of taste for bitter compounds. *Nature* 205:851–52
58. Golding J, Steer C, Emmett P, Bartoshuk LM, Horwood J, Smith GD. 2009. Associations between the ability to detect a bitter taste, dietary behavior, and growth: a preliminary report. *Ann. N. Y. Acad. Sci.* 1170:553–57
59. Goldstein G, Daun H, Tepper B. 2005. Adiposity in middle-aged women is associated with genetic taste blindness to 6-*n*-propylthiouracil. *Obes. Res.* 13:1017–23
60. Goldstein G, Daun H, Tepper B. 2007. Influence of PROP taster status and maternal variables on energy intake and body weight of pre-adolescents. *Physiol. Behav.* 90:809–17
61. Greene L. 1973. Physical growth and development, neurological maturation and behavioral functioning in two Ecuadorian Andean communities in which goiter is endemic. *Am. J. Phys. Anthropol.* 38:119–34
62. Guo SW. 2001. The genetics of phenylthiocarbamide perception. *Ann. Hum. Biol.* 28:111–42
63. Hartvig D, Hausner H, Wendin K, Bredie W. 2014. Quinine sensitivity influences the acceptance of sea-buckthorn and grapefruit juices in 9- to 11-year-old children. *Appetite* 74:70–78
64. Hayes J, Bartoshuk L, Kidd J, Duffy V. 2008. Supertasting and PROP bitterness depends on more than the *TAS2R38* gene. *Chem. Senses* 33:255–65
65. Hayes J, Duffy V. 2007. Revisiting sugar-fat mixtures: Sweetness and creaminess vary with phenotypic markers of oral sensation. *Chem. Senses* 32:225–36
66. Hayes J, Duffy V. 2008. Oral sensory phenotype identifies level of fat and sugar required for maximal liking. *Physiol. Behav.* 95:77–87
67. Hayes J, Feeney E, Allen A. 2013. Do polymorphisms in chemosensory genes matter for human ingestive behavior? *Food Qual. Pref.* 30:202–16
68. Hedge AM. 2008. Genetic sensitivity to 6-*n*-propylthiouracil (PROP) as a screening tool for obesity and dental caries in children. *J. Clin. Pediatr. Dent.* 33:107–11
69. Jang H, Kokrashvili Z, Theodorakis M, Carlson O, Kim B, et al. 2007. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *PNAS* 104:15069–74
70. Jannsen S, Laermans J, Verhulst P, Thijs T, Tack J, et al. 2011. Bitter taste receptors and α-gustducin regulate the secretion of ghrelin with functional effects on food intake and gastric emptying. *PNAS* 108:2094–99
71. Johnson FE, Hertzog KP, Malina RM. 1966. Phenylthiocarbamide taste sensitivity and its relationship to growth variation. *Am. J. Phys. Anthropol.* 24:253–56
72. Keller KL. 2002. *Genetic sensitivity to 6-n-propylthiouracil (PROP): associations with food acceptance, intake, and body weight in preschool children*. PhD Thesis, Rutgers Univ., New Brunswick, NJ
73. Keller KL. 2012. Common variants in the CD36 gene are associated with oral fat perception, fat preferences, and obesity in African Americans. *Obesity* 20:1066–73
74. Keller KL. 2012. Genetic influences on oral fat perception and preference. Presented at the symposium "The Taste for Fat: New Discoveries on the Role of Fat in Sensory Perception, Metabolism, Sensory Pleasure and Beyond" held at the Institute of Food Technologists 2011 Annual Meeting, New Orleans, La., June 12, 2011. *J. Food Sci.* 77:S143–47

75. Keller KL, Olsen A, Cravener TL, Bloom R, Chung WK, et al. 2014. Bitter taste phenotype and body weight predict children's selection of sweet and savory foods at a palatable test-meal. *Appetite* 77:115–23
76. Keller KL, Reid A, MacDougall MC, Cassano H, Song JL, et al. 2010. Sex differences in the effects of bitter thiourea sensitivity on body weight in 4–6-year-old children. *Obesity* 18:1194–200
77. Keller KL, Steinmann L, Nurse RJ, Tepper BJ. 2002. Genetic taste sensitivity to 6-*n*-propylthiouracil influences food preference and reported intake in preschool children. *Appetite* 38:3–12
78. Keller KL, Tepper BJ. 2004. Inherited taste sensitivity to 6-*n*-propylthiouracil in diet and body weight in children. *Obes. Res.* 12:904–12
79. Kildegaard H, Tonning E, Thybo A. 2011. Preference, liking and wanting for beverages in children aged 9–14 years. Role of sourness perception, chemical composition and background variables. *Food Qual. Pref.* 22:620–27
80. Kim U, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. 2003. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science* 299:1221–24
81. Kim U, Wooding S, Ricci D, Jorde L, Drayna D. 2005. Worldwide haplotype diversity and coding sequence variation at human bitter taste receptor loci. *Hum. Mutat.* 26:199–204
82. Lawless H. 1980. A comparison of different methods used to assess sensitivity to the taste of phenylthiocarbamide (PTC). *Chem. Senses* 5:247–56
83. Liang L, Sakimura J, May D, Breen C, Driggin E, et al. 2012. Fat discrimination: a phenotype with potential implications for studying fat intake behaviors and obesity. *Physiol. Behav.* 105:470–75
84. Lin B. 2003. Caries experience in children with various genetic sensitivity levels to the bitter taste of 6-*n*-propylthiouracil (PROP): a pilot study. *Pediatr. Dent.* 25:37–42
85. Lipchock S, Mennella J, Spielman A, Reed D. 2013. Human bitter perception correlates with bitter receptor messenger RNA expression in taste cells. *Am. J. Clin. Nutr.* 98:1136–43
86. Lipchock S, Reed D, Mennella J. 2012. Relationship between bitter-taste receptor genotype and solid medication formulation usage among young children: a retrospective analysis. *Clin. Ther.* 34:728–33
87. Looy H. 1992. Hedonic response of sucrose likers and dislikers to other gustatory stimuli. *Physiol. Behav.* 52:219–25
88. Looy H, Weingarten HP. 1992. Facial expressions and genetic sensitivity to 6-*n*-propylthiouracil predict hedonic response to sweet. *Physiol. Behav.* 52:75–82
89. Lumeng J, Cardinal T, Sitto J, Kannan S. 2008. Ability to taste 6-*n*-propylthiouracil and BMI in low-income preschool-aged children. *Obesity* 16:1522–28
90. Ly A, Drewnowski A. 2001. PROP (6-*n*-propylthiouracil) tasting and sensory responses to caffeine, sucrose, neohesperidin dihydrochalcone and chocolate. *Chem. Senses* 26:41–47
91. Mace O, Affleck J, Patel N, Kellett G. 2007. Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. *J. Physiol.* 582:379–92
92. Melis M, Atzori E, Cabras S, Zonza A, Calò C, et al. 2013. The *gustin* (CA6) gene polymorphism, rs2274333 (A/G), as a mechanistic link between PROP tasting and fungiform taste papilla density and maintenance. *PLOS ONE* 8:e74151
93. Mennella JA, Bobowski NK. 2015. The sweetness and bitterness of childhood: Insights from basic research on taste preferences. *Physiol. Behav.* 152 (Part B):502–7
94. Mennella JA, Pepino MY, Duke FF, Reed DR. 2010. Age modifies the genotype-phenotype relationship for the bitter receptor *TAS2R38*. *BMC Genet.* 11:60–69
95. Mennella JA, Pepino MY, Reed DR. 2005. Genetic and environmental determinants of bitter perception and sweet preferences. *Pediatrics* 115:216–22
96. Mennella JA, Reed DR, Mathew PS, Roberts KM, Mansfield CJ. 2014. "A spoonful of sugar helps the medicine go down": bitter masking by sucrose among children and adults. *Chem. Senses* 40:17–25
97. Mennella JA, Roberts KM, Mathew PS, Reed DR. 2015. Children's perceptions about medicines: individual differences and taste. *BMC Pediatr.* 15:130–36
98. Merton B. 1958. Taste sensitivity to PTC in 60 Norwegian families with 176 children; confirmation of the hypothesis of single gene inheritance. *Acta Genet. Stat. Med.* 8:114–28
99. Meyerhof W, Batram C, Kuhn C, Brockhoff A, Chudoba E, et al. 2010. The molecular receptive ranges of human TAS2R bitter taste receptors. *Chem. Senses* 35:157–70

100. Nasser JA, Kissileff HR, Boozer CN, Chou CJ, Pi-Sunyer FX. 2001. PROP taster status and oral fatty acid perception. *Eat. Behav.* 2:237–45
101. O'Brien S, Feeney E, Scannell A, Markey A, Gibney E. 2013. Bitter taste perception and dietary intake patterns in Irish children. *J. Nutrigenetics Nutrigenomics* 6:43–58
102. Oftedal KN, Tepper BJ. 2013. Influence of the PROP bitter taste phenotype and eating attitudes on energy intake and weight status in pre-adolescents: a 6-year follow-up study. *Physiol. Behav.* 118:103–11
103. Ogden CL. 2012. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA* 307:483–90
104. Olson JM, Boehnke M, Neiswanger K, Roche AF, Siervogel RM, MacCluer JW. 1989. Alternative genetic models for the inheritance of the phenylthiocarbamide taste deficiency. *Genet. Epidemiol.* 6:423–34
105. Padiglia A, Zonza A, Atzori E, Chillotti C, Calo MC, et al. 2010. Sensitivity to 6-*n*-propylthiouracil (PROP) is associated with *gustin* (carbonic anhydrase VI) gene polymorphism, salivary zinc, and body mass index in humans. *Am. J. Clin. Nutr.* 92:539–45
106. Pepino MY. 2005. Factors contributing to individual differences in sucrose preference. *Chem. Senses* 30(Suppl. 1):i319–20
107. Peterson JM, Bartoshuk LM, Duffy VB. 1999. Intensity and preference for sweetness is influenced by genetic taste variation. *J. Am. Diet. Assoc.* 99(Suppl.):A28
108. Pidamale R, Sowmya B, Thomas A, Jose T. 2012. Genetic sensitivity to bitter taste of 6-*n* propylthiouracil: a useful diagnostic aid to detect early childhood caries in pre-school children. *Indian J. Hum. Genet.* 18:101–5
109. Pidamale R, Sowmya B, Thomas A, Jose T, Madhusudan KK, Prasad G. 2012. Association between early childhood caries, *Streptococcus mutans* level and genetic sensitivity levels to the bitter taste of, 6-N propylthiouracil among the children below 71 months of age. *Dent. Res. J.* 9:730–34
110. Prescott J, Bartoshuk L, Prutkin J. 2004. 6-*n*-Propylthiouracil tasting and the perception of nontaste oral sensations. See Ref. 112, pp. 89–104
111. Prescott J, Swain-Campbell N. 2000. Responses to repeated oral irritation by capsaicin, cinnamaldehyde and ethanol in PROP tasters and non-tasters. *Chem. Senses* 25:239–46
112. Prescott J, Tepper B, eds. 2004. *Genetic Variation in Taste Sensitivity*. New York: Marcel Dekker
113. Prutkin J, Duffy V, Etter L, Fast K, Gardner E, et al. 2000. Genetic variation and inferences about perceived taste intensity in mice and men. *Physiol. Behav.* 69:161–73
114. Reed DR, Bachmanov AA, Beachamp GK, Tordoff MG, Price RA. 1997. Heritable variation in food preferences and their contribution to obesity. *Behav. Genet.* 27:373–87
115. Reed DR, Tanaka T, McDaniel AH. 2006. Diverse tastes: genetics of sweet and bitter perception. *Physiol. Behav.* 88:215–26
116. Rozengurt E. 2006. Taste receptors in the gastrointestinal tract. I. Bitter taste receptors and α-gustducin in the mammalian gut. *Am. J. Physiol. Gastrointest. Liver Physiol.* 291:G171–77
117. Rozengurt E, Sternini C. 2007. Taste receptor signaling in the mammalian gut. *Curr. Opin. Pharmacol.* 7:557–62
118. Rozin P. 1976. Psychobiological and cultural determinants of food choice. In *Dahleon Workshop on Appetite and Food Intake*, ed. T Silverstone, pp. 285–312. Berlin: Dahleon Konferenzen
119. Rupesh SS. 2006. Genetic sensitivity to the bitter taste of 6-n propylthiouracil: a new risk determinant for dental caries in children. *J. Indian Soc. Pedod. Prev. Dent.* 24:63–68
120. Shahbake M, Hutchinson I, Laing D, Jinks A. 2005. Rapid quantitative assessment of fungiform papillae density in the human tongue. *Brain Res.* 1052:196–201
121. Sharma K, Kaur G. 2014. PTC bitter taste genetic polymorphism, food choices, physical growth in body height and body fat related traits among adolescent girls from Kangra Valley, Himachal Pradesh (India). *Ann. Hum. Biol.* 41:29–39
122. Shetty V, Pooja B, Hegde AM. 2014. PROP test: prediction of caries risk by genetic taste perception among the visually impaired children. *Spec. Care Dent.* 34:34–40
123. Steiner JE. 1977. Facial expressions of the neonate infant indicating the hedonics of food-related chemical stimuli. In *Taste and Development: The Genesis of Sweet Preference*, ed. JM Weiffenbach, pp. 173–88. Bethesda, MD: US Dep. Health Educ. Welf., Public Health Serv., Natl. Inst. Health

124. Steiner JE, Glaser D, Hawilo ME, Berridge KC. 2001. Comparative expression of hedonic impact: affective reactions to taste by human infants and other primates. *Neurosci. Biobehav. Rev.* 25:53–74
125. Stewart JE, Feinle-Bisset C, Golding M, Delahunty C, Clifton PM, Keast RSJ. 2010. Oral sensitivity to fatty acids, food consumption and BMI in human subjects. *Br. J. Nutr.* 104:145–52
126. Stewart JE, Seimon RV, Otto B, Keast RSJ, Clifton PM, Feinle-Bisset C. 2011. Marked differences in gustatory and gastrointestinal sensitivity to oleic acid between lean and obese men. *Am. J. Clin. Nutr.* 93:703–11
127. Tepper BJ. 1998. 6-*n*-Propylthiouracil: a genetic marker for taste, with implications for food preference and dietary habits. *Am. J. Hum. Genet.* 63:1271–76
128. Tepper BJ. 1999. Does genetic taste sensitivity to PROP influence food preferences and body weight? *Appetite* 32:422
129. Tepper BJ, Banni S, Melis M, Crnjar R, Tomassini Barbarossa I. 2014. Genetic sensitivity to the bitter taste of 6-*n*-propylthiouracil (PROP) and its association with physiological mechanisms controlling body mass index (BMI). *Nutrients* 6:3363–81
130. Tepper BJ, Christensen CM, Cao J. 2001. Development of brief methods to classify individuals by PROP taster status. *Physiol. Behav.* 73:571–77
131. Tepper BJ, Nurse RJ. 1997. Fat perception is related to PROP taster status. *Physiol. Behav.* 61:949–54
132. Tepper BJ, Nurse RJ. 1998. PROP taster status is related to fat perception and preference. *Ann. N. Y. Acad. Sci.* 30:802–4
133. Tepper BJ, Ullrich NV. 2002. Influence of genetic taste sensitivity to 6-*n*-propylthiouracil (PROP), dietary restraint and disinhibition on body mass index in middle-aged women. *Physiol. Behav.* 75:305–12
134. Tsuji M, Nakamura K, Tamai Y, Wada K, Sahashi Y, et al. 2012. Relationship of intake of plant-based foods with 6-*n*-propylthiouracil sensitivity and food neophobia in Japanese preschool children. *Eur. J. Clin. Nutr.* 66:47–52
135. Turnbull B, Matisoo-Smith E. 2002. Taste sensitivity to 6-*n*-propylthiouracil predicts acceptance of bitter-tasting spinach in 3–6-y-old children. *Am. J. Clin. Nutr.* 6:1101–5
136. Tzioumis E, Adair LS. 2014. Childhood dual burden of under- and overnutrition in low- and middle-income countries: a critical review. *Food Nutr. Bull.* 35:230–43
137. Verhoeven D, Verhagen H, Goldbolm R, van den Brandt P, van Poppel G. 1997. A review of mechanisms underlying anti-carcinogenicity by brassica vegetables. *Chem. Biol. Interact.* 103:79–129
138. Wheatcraft P. 1972. Toxicity of the taste testing compound phenylthiocarbamide. *Nature* 235:93–94
139. Whissell-Buechy D, Wills C. 1989. Male and female correlations for taster (P.T.C.) phenotypes and rate of adolescent development. *Ann. Hum. Biol.* 16:131–46
140. Wooding S. 2006. Phenylthiocarbamide: a 75-year adventure in genetics and natural selection. *Genetics* 172:2015–23
141. Wooding S, Gunn H, Ramos P, Thalmann S, Xing C, Meyerhof W. 2010. Genetics and bitter taste responses to goitrin, a plant toxin found in vegetables. *Chem. Senses* 35:685–92
142. Yeomans MR, Tepper BJ, Rietzschel J, Prescott J. 2007. Human hedonic responses to sweetness: role of taste genetics and anatomy. *Physiol. Behav.* 91:264–73