A Case Study on the Association of Variation of Bitter-Taste Receptor Gene *TAS2R38* with the Height, Weight and Energy Intake in Japanese Female College Students

Hiroko INOUE^{1,*}, Kimiko YAMAKAWA-KOBAYASHI^{2,*}, Yuichi SUZUKI^{3,**}, Teruyo NAKANO³, Hisayoshi HAYASHI³ and Toshiko KUWANO¹

¹Laboratory of Nutrition Education, ²Laboratory of Human Genetics and ³Laboratory of Physiology, School of Food and Nutritional Sciences, University of Shizuoka, Yada 52–1, Suruga-ku, Shizuoka 422–8526, Japan

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Summary One of the critical factors that determines individual differences in dietary behavior and nutritional status is the sensory-affecting quality of food, in particular its taste. Variation of one bitter taste receptor gene, *TAS2R38*, which is associated with the differential sensitivity to phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP), has been demonstrated to affect the dietary intake pattern. A case study was performed to examine the association of the *TAS2R38* genotypes/haplotypes with the body size (height, weight and BMI) and with the food and nutrient intake. Eighty-four college students, all females, with an age range of 18–21 y were recruited from the University of Shizuoka. The genotypes of two common single nucleotide polymorphisms in *TAS2R38* (A49P and I296V) were determined by PCR-restriction fragment length polymorphism (RFLP) method. The height, weight and body mass index (BMI), and (in a subgroup of 47 subjects) food and nutrition intake estimated from 3 d of food recording, were compared between homozygotes for the PTC/PROP-nontaster haplotype (AI haplotype) and carriers with the PTC/PROP-taster haplotype (PV haplotype). The results show that the homozygotes with AI haplotype were taller and heavier than the carriers of PV haplotype, while BMI values were similar between them. The former group also had higher energy and carbohydrate intakes than the latter group. Neither vegetable nor dairy product intake was different between the homozygotes with AI haplotype and the carriers of PV haplotype. In conclusion, the PTC/PROP-nontaster *TAS2R38* genotype/haplotype was associated with height and weight but not with BMI, which may in turn have influenced the energy and carbohydrate intakes.

Key Words food intake, BMI, PROP, dietary behavior

Food choice and dietary practice affect the growth and composition of the body, and have important implications for nutrition-related chronic diseases (1–3). One of the critical factors that determine dietary behavior is the sensory-affecting quality of food, in particular taste. Data have been presented that variation of the genes involved in taste perception may account for some of the individual differences in food selection, nutritional status, and nutrition-related disease susceptibility (4–6).

The human bitter taste receptor gene family (hTAS2R) comprises about 25 members belonging to G protein-coupled receptors (7–11). These are expressed in the taste receptor cells of taste buds in the oral cavity, and also in the mucosa of the gastrointestinal tract (12–14). *TAS2R38* is probably best-studied member of the *TAS2R* family, since its variation has predicted to a considerable but not perfectly, traits related to differing sensitivity to the synthetic compounds phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP), i.e., the PTC/PROP tasters and nontasters (15–20). There are three com-

mon single nucleotide polymorphisms in the *TAS2R38* gene that result in amino acid substitutions in the protein (A49P, V262A and I296V). These show strong linkage disequilibrium, giving rise to the two common haplotypes, A(V)I and P(A)V. The PTC/PROP-taster individuals generally possess one or two P(A)V haplotypes, whereas nontaster individuals are homozygous for the A(V)I haplotype (15–20). Such individual difference in the PTC/PROP taste status or *TAS2R38* variation has been demonstrated to result in differences in liking for such foods as some vegetables, fatty foods, spicy foods and alcoholic beverages (5). Such differences have also been suggested to affect the body mass index (BMI) or obesity, but with some controversial results (5, 21); for example, the PROP-taster phenotype has been reported to be associated with larger BMI under certain circumstances (22–26) but not in other cases (27–29). On the other hand, no association between the *TAS2R38* genotype/haplotype and BMI has been reported (30–33). In contrast to BMI and obesity, relatively little information is available for the effect on height of variation in the PTC/PROP sensitivity or *TAS2R38* genotype/haplotype.

The purpose of this study was, therefore, to further

^{**}To whom correspondence should be addressed.

E-mail: yuichi@smail.u-shizuoka-ken.ac.jp

investigate the influence of variation in the *TAS2R38* genotype/haplotype on individual differences in nutritional status and dietary behavior. As a case study, we examined the relationship of the *TAS2R38* genotype/haplotype with the body size (height, weight and BMI) and food and nutrient intakes of a group of female students at our university.

METHODS

Subjects. Eighty-seven female college students in the age range of 18–22 y were recruited from the university community. Their birth dates were in the years 1987–1991. The ethics committee of the University of Shizuoka approved the study protocol (no. 21-9), according to principles of the Declaration of Helsinki and all participants provided written informed consent.

Anthropometric measurements. The body height and weight of each subject were measured at 9:00–11:00 a.m. Each subject was allowed to eat breakfast and drink water freely before the measurements. The height was measured in the upright position with a stadiometer. The body weight was measured while wearing light clothes, and 1.0 kg was subtracted from the measured value to give the body weight value to be used. The body mass index (BMI) is defined as the weight in kilograms divided by the square of the height in meters.

Genetic analysis of the *TAS2R38* gene. Genomic DNA was isolated from buccal mucosa cells by using a High-pure PCR template preparation kit (Roche Diagnostics, Tokyo, Japan). We determined the genotypes of A48P and I296V polymorphisms for each subject by the PCR restriction fragment length polymorphism (PCR-RELP) method. We unfortunately were unable to determine the genotype of V262A. The haplotypes and their frequencies were estimated by the maximum-likelihood method with an EM-based algorithm, using the SNPalyze program (Dynacom, Yokohama, Japan). We regarded the PV haplotype as a PTC/PROP-taster type, and the AI haplotype as a PTC/PROP-nontaster type.

Dietary assessment. A subset of subjects, who had registered for the nutrition education classes (by T. Kuwano), was recruited for the dietary assessment. They completed food records of each meal, including weights, for three consecutive weekdays in June (within 1 mo after the anthropometric measurements). The food record for each subject was processed by Excel Eiyokun

software (version 4.5; Kenpakusha, Tokyo) without knowing her *TAS2R38* genotype.

Statistical analysis. A comparison among three groups was analyzed by using ANOVA and the Tukey-Kramer test, and a two-group comparison was made by using an unpaired *t*-test. The statistical analyses were performed with the 18.0J software version (SPSS, Tokyo, Japan), the significance criterion for all tests being set at $p < 0.05$.

RESULTS

TAS2R38 variation

The distribution of *TAS2R28* genotypes and haplotypes in the subjects is summarized in Table 1. The frequency of the AI haplotype was 0.43, suggesting that this haplotype was slightly less frequent than the PV haplotype, agreeing with the previously reported figures for those of Asian descent (15, 17).

Effect of *TAS2R38* variation on the height, weight and BMI

We first compared the body size, i.e., height, weight and BMI, among the three groups with different *TAS2R38* diplotypes (Fig. 1). The homozygotes for the AI haplotype were significantly taller and heavier than the heterozygotes for the PV and AI haplotypes, although not different from the homozygotes for the PV haplotype. On the other hand, there was no difference in BMI among the three groups. We then pooled the data for homozygotes of the PV haplotype and that for heterozygotes of the PV and AI haplotypes into a single group (PTC/PROP-taster group), and compared these with the data for the homozygotes of the AI haplotype

Table 1. Distribution of *TAS2R38* genotypes and haplotypes in Japanese female college students.

Genotype		Haplotype	Number of subjects (n=87)	Subject subset involved in food intake measurement (n=47)
A49P	I296V			
PP	VV	PV/PV	26	14
PA	VI	PV/AI	43	25
AA	II	AI/AI	16	8
PA	VV	PV/AV	1	0
PP	VI	PV/PI	1	0

Fig. 1. Comparison of body size among the three major *TAS2R38* diplotypes. A, Height; B, Weight; C, Body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meters. Unfilled bars ($n=26$), hatched bars ($n=42$) and filled bars ($n=16$) show subjects with respective diplotypes PV/PV, PV/AI, and AI/AI. One PV/AI diplotype, who had an eating disorder, and two minor diplotypes (Table 1) were excluded. Each value is the mean $\pm$ SD. Means with different letters are different at $p < 0.05$ by the Tukey-Kramer test.

(PTC/PROP-nontaster group). As shown in Table 2, the homozygotes of the AI haplotype were significantly taller (by about 4 cm) and heavier (by 4 kg) than carriers of the PV haplotype, while BMI was not different between these two groups.

Effect of TAS2R38 variations on the dietary intake

We next examined the relationships between the TAS2R38 variations and the daily energy and nutrient intake. The subset of subjects recruited for dietary assessment showed that the homozygotes for the AI haplotype were significantly taller and probably heavier

than the carriers of the PV haplotype (Table 3). BMI did not differ between these two groups.

Figure 2 shows that the daily energy intake by the homozygotes of the AI haplotype was significantly greater than those by either the homozygotes of the PV haplotype or heterozygotes of the PV and AI haplotypes. In addition, the daily carbohydrate, protein and fat intakes tended to be higher by homozygotes of the AI haplotype, although only the difference between the carbohydrate intake by homozygotes of the AI haplotype and by heterozygotes of the PV and AI haplotypes was significant. We again pooled the data for the homozygotes of the PV haplotype with those for the heterozygotes of the PV and AI haplotypes into one group, and compared these with the data for homozygotes of the AI haplotype (Table 4). The result shows that the homozygotes of the AI haplotype had significantly higher energy and carbohydrate intakes. The mean daily intake values of protein, fat and carbohydrate by homozygotes of the AI haplotype were greater by 14.0%, 14.0% and 17.2%, respectively, these values agreeing well with the 15.2% greater daily energy intake by this group. When the individual energy intake was divided by each basal metabolic rate (calculated from the height, weight, age and sex for each subject) (34), the value of homozygotes of the AI haplotype was no longer significantly higher than that of carriers of the PV haplotype (Table 4). The higher energy intake by homozygotes of the AI haplotype may therefore be explained, if not totally, by their greater body size. Neither the sodium intake nor sodium/energy intake ratio was associated with the TAS2R38 haplotypes (Fig. 2 and Table 4), in agreement with previous reports (31, 35).

We then examined the relationships between the TAS2R38 haplotype and intake of vegetable and dairy products (Table 5), as it has been shown that TAS2R38 variations or sensitivity to PROP might influence the consumption of vegetables (30, 36–39). However,

Table 2. Body size and TAS2R38 haplotype.

Variable	PV/PV and PV/AI (n=68)	AI/AI (n=16)	<i>p</i>
Height (cm)	157.8±5.8	161.5±3.9*	0.02
Weight (kg)	50.5±6.9	54.9±8.5*	0.03
BMI (kg/m ²)	20.4±2.3	21.2±4.3	0.60

Each value is the mean±SD.

Differences were compared by Student's unpaired *t*-test.

**p*<0.05.

Table 3. Body size and TAS2R38 haplotype in the subject subset involved in food intake measurement.

Variable	PV/PV and PV/AI (n=39)	AI/AI (n=8)	<i>p</i>
Height (cm)	158.8±5.67	163.8±3.35*	0.02
Weight (g)	51.4±5.9	55.7±11.3	0.13
BMI (kg/m ²)	20.4±2.3	20.8±4.4	0.74

Each value is the mean±SD.

Differences were compared by Student's unpaired *t*-test.

**p*<0.05.

Fig. 2. Comparison of daily nutrient intake among the TAS2R38 diplotypes. A, Energy; B, Protein; C, Fat; D, Carbohydrate; E, Sodium. Unfilled bars (*n*=14), hatched bars (*n*=25) and filled bars (*n*=8) show respective subjects with diplotypes PV/PV, PV/AI, and AI/AI. Each value is the mean±SD. Means with different letters are different at *p*<0.05 by the Tukey-Kramer test.

Table 4. Nutrient intake and *TAS2R38* haplotype.

Nutrient intake	PV/PV and PV/AI (n=39)	AI/AI (n=8)	p
Energy (kcal/d)	1,512±259	1,742±216*	0.02
Energy/BMR ¹	1.284±0.222	1.396±0.213	0.20
Protein (g/d)	54.2±11.0	61.8±13.5	0.10
Fat (g/d)	44.4±14.7	50.6±12.5	0.30
Carbohydrate (g/d)	217.3±37.4	254.7±34.4*	0.01
Sodium (mg/d)	2,356±781	2,256±566	0.73
Sodium/energy ²	1.56±0.51	1.31±0.35	0.18

Each value is the mean±S.D.

Differences were compared by Student's unpaired *t*-test.

**p*<0.05.

¹ BMR: basal metabolic rate calculated by the equation proposed by Ganpule et al. (34), BMR (kcal/d)=(0.1238+0.0481×weight+0.0234×height−0.0138×age−0.5473×2)×1,000/4.186.

² Sodium intake divided by each energy intake.

Table 5. Vegetable and dairy product intake for *TAS2R38* haplotypes.

Food group	PV/PV and PV/AI (n=39)	AI/AI (n=8)	p
Total vegetables (g/d)	207.8±114.6	220.5±113.9	0.78
Brassicaceae vegetables (g/d)	49.0±55.2	49.7±55.8	0.97
Total dairy products (g/d)	153.1±111.3	182.4±121.3	0.51
Milk (g/d) ¹	81.3±95.7	78.5±94.2	0.94

Each value is the mean±SD.

Differences were compared by Student's unpaired *t*-test.

¹ Includes milk consumed only as a drink but not as a food ingredient.

the vegetable intake was no different as a function of *TAS2R38* haplotype. We then specifically examined the intake of vegetables belonging to Brassicaceae family which contain bitter compounds, glucosinolates, as previous studies have reported that PTC/PROP-tasters had a lower consumption of glucosinolate-containing vegetables than non-tasters (40–42). However, no association between the *TAS2R38* haplotype and Brassicaceae vegetable intake was evident, in agreement with a recent report (43). We finally analyzed the dairy product intake, because previous studies have reported that the PTC/PROP-taste status was implicated in the liking for dairy products (35, 44, 45). However, we found no association between the *TAS2R38* haplotype and the intake of total dairy products by the present subjects (Table 5). In addition, the cow's milk intake was not associated with the *TAS2R38* haplotype; cow's milk intake during childhood is believed to be associated with growth and height in adulthood (46–50).

DISCUSSION

A significant finding of the present study based on a

group of female college students is that the homozygotes for the AI haplotype (PTC/PROP-nontaster haplotype) were greater in height and weight than the carriers with the PV haplotype (PTC/PROP-taster haplotype). Our result demonstrates, probably for the first time, that the *TAS2R38* variation is associated with height: previous studies on females have demonstrated no difference in the height or weight as a function of the PROP-taste status (31) or of the *TAS2R38* variation (30). Yackinous and Guinard (51) have also reported that the PROP-taster status determined by PROP sensitivity did not significantly affect either the height or weight in either young adult men or women. However, the results of their report show the mean value for height being greater by 4–8 cm and that for weight by 0.1–3.6 kg for the PROP-nontasters than for the PROP-tasters (cf. Table 1 in their report), these differences being similar to those observed with our *TAS2R38* haplotype study on young adult women (Tables 2 and 3).

One possible mediator that may link the *TAS2R38* haplotype to higher stature is cow's milk consumption during childhood. There is evidence that cow's milk consumption was associated with a high growth rate and height in adulthood, although the exact mechanism and health implications for this remain to be understood (46–50). Previous studies on children have shown the acceptance rating for cow's milk to be higher for PROP-nontasters than -tasters, whether it was examined as a function of PROP sensitivity (45) or of variations in the *TAS2R38* gene (35, 44). Contrary to our expectations, however, we could not detect in the present study any difference in the cow's milk intake or dairy food intake between homozygotes of the AI haplotype and carriers of the PV haplotype (Table 5).

Our results show that BMI was no different among the *TAS2R38* haplotypes (Table 2). The relationship examined as a function of the *TAS2R38* variations has shown BMI to be no different between the PTC/PROP-taster and -nontaster haplotype groups (30–33), in agreement with the present result. The relationship examined as a function of the PTC/PROP-sensitivity phenotypes has also shown BMI not to be associated with the sensitivity in most studies (27–29). However, the results of several studies have shown the PROP-sensitivity status to be negatively associated with BMI (22–26). Disparity between the influence of the *TAS2R38* variations and PTC/PROP-taster phenotype on BMI may be explained by hypothesis that phenotypic PTC/PROP-tasters and -nontasters capture additional taste information that is not provided by the *TAS2R38* variations.

Our results demonstrate that the homozygotes of the AI haplotype had a higher dietary energy intake than the carriers of the PV haplotype (Fig. 2, Table 4). This appears to have resulted from the greater intake of all three macronutrients, although significance was only evident for the carbohydrate intake. The higher energy intake by homozygotes of the AI haplotype in our study was probably the result, rather than the cause, of the increased height (and weight) in this group, since the difference in energy intake between the two *TAS2R38*

haplotype groups was weakened when the individual energy intake was divided by individual predictive basal metabolic rate i.e. normalized by body size (Table 4) (34). Previous studies have shown that pre-adolescent children and adult women with the PROP-nontaster phenotype consumed more energy than the PROP tasters (29, 31) without any noticeable change in the intake ratio among the three macronutrients (i.e. a greater intake of all three macronutrients), in agreement with our results (Table 4), although the influence of body size on energy consumption has not been examined.

In summary, the present results obtained from a group of female college students show that the homozygotes of the AI haplotype (PTC/PROP-nontaster haplotype) were taller and heavier (although having similar BMI), and had a greater energy intake, than the carriers of the PV haplotype (PTC/PROP-taster haplotype). It remains to be determined whether there is a similar association of the TAS2R38 variations with height and weight, first in other Japanese young female groups and then in other populations of different races, generations and sexes. Our findings reinforce the notion that variation in taste receptor genes influences individual differences in food intake and nutritional status (4–6). Elucidation of the precise mechanisms underlying an association between the TAS2R38 variations and body size may be important not only for understanding the nutritional role of taste receptors, but may also be relevant to nutrition education, particularly for children, because the impact of taste gene variations on dietary preference would be stronger in children than in adults (35, 52, 53).

Statement of potential conflict of interest

No potential conflict of interest was reported by the authors.

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