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The influence of TAS2R38 bitter taste gene polymorphisms on obesity risk in three racially diverse groups

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Abstract

Objectives: Bitter taste perception affects food preference, eating behavior, and nutrient intake. The purpose of this study was to investigate the contribution of bitter taste gene polymorphisms to body fatness as measured by percentage of body fat.

Method: Three common single nucleotide polymorphisms (SNPs) of the TAS2R38 gene which result in amino acid changes in the protein (A49P, V262A, and I296V), were studied in three racially diverse groups: European Americans n = 313, African Americans n = 109, and Asians n = 234.

Results: The allele frequencies of the three SNPs were similar to previous studies. The rare haplotypes, AAI and AAV, were found in high prevalence in the African American subgroup (22.94%) and European American subgroup (6.07%). The PROP non taster; AVI/AVI diplotype was associated with a higher risk of obesity in European American and Asian but not African American subjects after age adjustment.

Conclusions: TAS2R38 polymorphisms could be associated with obesity development. In addition to taste perception, nutrient sensing and energy metabolism should be studied in relation to bitter taste receptors to confirm the association between genetic polymorphisms and body fatness. Genetic polymorphisms, race, gender, and environmental factors such as dietary patterns could all contribute to body fat.

Keywords: Genetic polymorphism, TAS2R38, Bitter taste receptor, Obesity, Body fat

1. Introduction

Humans taste food and other substances by taste receptors that are located in taste buds on the tongue. Taste perception might affect food preference, eating behavior, and nutrient intake, and therefore possibly also contribute to obesity development [1,2]. In humans, bitter taste receptors belong to the class of G-protein coupled receptors (GPCRs) and they are mediated by 25 different gene families; one of them being the TAS2R38 gene located on chromosome 7q that has been strongly associated with 6-n-propylthiouracil (PROP) sensitivity [3–5]. Three common single nucleotide polymorphisms of TAS2R38 have been described, all of which result in amino acid changes in the protein alanine to proline at position 49 (A49P), valine to alanine at position 262 (V262A), and isoleucine to valine at position 296 (I296V) [4]. These polymorphisms result in two
main haplotypes that are commonly found in the human population: the taster haplotype (PAV), and the non-taster haplotype (AVI) [6]. Other rare haplotypes such as AAV and AAI have been found in the population worldwide [7–9].

Genetic variation in taste sensitivity to PROP has been associated with differences in preference for and selection of bitter tasting fruits and vegetables, sweet tasting foods, added fats, spicy foods, and consumption of alcoholic beverages [2,10–12]. Non-tasters may like a greater variety of foods than tasters; therefore, non-tasters might consume more energy and acquire higher body fatness than tasters [13]. Because taste perception influences eating behavior, taste has been broadly studied as a possible influencing factor for obesity development [14]. In addition to the oral expression of bitter taste receptors for taste sensation, bitter taste receptors are also expressed in other locations such as the human gastrointestinal tract and lungs where they might have a role in nutrient metabolism, the endocrine system, or the immune system [15–17].

It has been shown that PROP tasting and TAS2R38 diplotypes have been associated with perception of other taste stimuli [10,18–21], food preference and choice [22–25] as well as body mass index [26,27]. Additionally, there are associations with metabolic changes with impact on body composition [28–31], antioxidant status [31], risk of colonic cancer [32], smoking behavior [33], infections of the respiratory system [34–36], taste impairments [37], attainment of exceptional longevity [38] and even neurodegenerative diseases [39–41].

Only a few studies have been conducted to observe the effect of TAS2R38 genetic polymorphisms in relation to body fatness among diverse ethnicities. Therefore, the present study aimed to investigate the association between TAS2R38 bitter taste gene polymorphisms and body composition such as body fatness among three ethnic groups.

2. Materials and methods

2.1. Subjects

This was a cross-sectional study with 656 adults age 18–35 years from three ethnic groups: European Americans, African Americans, and Asians. European American and African American subjects were recruited from Mississippi State University, located in the United States (IRB-17-025), and Asian subjects were recruited from a university located in Thailand (COA NO.2018/072.2903). All subjects provided informed consent prior to participation in the study.

2.2. Anthropometric measurements

Height was measured using a calibrated touchless stadiometer (SONARIS; Cardinal/Detecto, Webb City, Mo, USA) in European American and African American subjects and measured using a 235-Heightronic Digital stadiometer in Asian subjects. A bioelectrical impedance analysis scale (TBF-300; Tanita Corp., Tokyo, Japan) was used to estimate body fat percentage and weight in European American and African American subjects, and an Omron body composition monitor (HBF375, Omron Health Care, Tokyo, Japan) was used in Asian subjects. Body fat percentage was classified into categories according to the study of Gallagher, et al. (2000) [42] which for standard adults ages 20–39 years are: underfat (BF% < 20% in females, <10% in males), healthy (BF% 20%–34% in females, 10%–21% in males), and overfat/obese (BF% > 34% in females, BF% > 21% in males). Body mass index (BMI) values were calculated using the standard BMI equation (kg/m²).

2.3. Genotyping

Three non-synonymous single nucleotide polymorphisms in TAS2R38 were genotyped for: rs713598 (A49P), rs1726866 (A262V), and rs10246939 (V296I). TaqMan allelic discrimination assays (ThermoFisher, USA) were used for the study at Mississippi State University, USA. DNA sequencing methods (Macrogen, South Korea) were used for rs1726866 (A262V) and rs10246939 (V296I) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) with HaeIII (Cat. number: ER0151, ThermoFisher, USA) were used for rs713598 (A49P) genotyping in the Asian study. The primers were described elsewhere [11,20]. To ensure accurate recording of TAS2R38 diplotypes from the sequencing method, the professional staff imported all sequences into the BioEdit program (USA) and aligned them to the human reference sequences from NCBI. Second, professional staff used the program to locate and highlight the variations in the aligned sequences. Any samples that showed either a discrepancy between the chromatograph and the computer assignment or a potential rare diplotype were flagged for retesting. Common and rare diplotypes were confirmed in this way.
2.4. Statistical analysis

Means and standard deviations were used for quantitative parameters. Frequencies and percentages were used to describe genotype variation among groups. The allele frequencies were calculated to evaluate the differences among populations. Hardy Weinberg equilibrium was also calculated, and statistical analyses were performed using the software GENEPOP [43]. One-way ANOVA with Tukey post-hoc testing was used to describe the differences among genotypes and body composition parameters. Logistic regression was used for odds ratio calculations. P-values < 0.05 were considered statistically significant. The statistical software program SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for analysis.

3. Results

3.1. Subject characteristics

The characteristics of study participants are reported in Table 1. Six hundred and fifty-six adults with mean age of 21.5 years of age were included in the study. Subjects were comprised of 314 European Americans (48%), 109 African Americans (17%), and 234 Asians (35%). Male subjects represented 15% of European Americans, 17% of African Americans and 30% of Asian participants. BMI and body fat percentage in African Americans were the highest (266 (84.7) 91 (83.5) 165 (70.5)) and statistical analysis for adjusted odds ratio is shown in Table 5. Interestingly, obesity risk (from the body fat percentage categories) significantly decreased for PAV/PAV (odds ratio; 0.180, 80%) and PAV/AVI (odds ratio; 0.294, 70.6%) when compared to PROP non taster diplotype (AVI/AVI) with odds ratio; 0.333 (66.7%) and 0.223 (77.7%), respectively. However, no significant associations between TAS2R38 diplotypes and obesity risk were observed in African American subjects.

3.2. TAS2R38 genotype distribution

Genotyping and allelic distributions were analyzed and are described in Table 2. All SNPs were in Hardy-Weinberg Equilibrium with p-values greater than 0.05. The combination of three non-synonymous SNPs caused variation in phenotypes. Eight haplotypes and 20 diplotypes with various frequencies were observed among different races (Table 3). The distribution of TAS2R38 haplotypes were assessed in study participants. The primary haplotypes observed were PAV (48.78%) and AVI (41.92%), followed by AAI (4.04%) and AAV (3.58%). The rare haplotype AAI had a higher frequency in the African American group (22.94%), and the AAV rare haplotype was found in the European American group (6.07%). These results were similar to previously published studies that described the global diversity in TAS2R38 [7,9]. Major diplotypes found in the European American group were AVI/AVI, AVI/PAV, and PAV/PAV; in the Asian group AVI/PAV, PAV/PAV, and AAV/AVI, and in the African American group PAV/AAI (Table 4).

Table 1. Descriptive characteristics of study participants.

| Characteristic          | European-American | African-American | Asian          |
|-------------------------|--------------------|------------------|---------------|
|                         | (N = 314)          | (N = 109)        | (N = 234)     |
| Mean age (years)        | 20.2 ± 2.4a        | 20.0 ± 1.5a      | 24.2 ± 7.0b   |
| Sex (N, %)              |                    |                  |               |
| Male                    | 48 (15.3)          | 18 (16.5)        | 69 (29.5)     |
| Female                  | 266 (84.7)         | 91 (83.5)        | 165 (70.5)    |
| BMI                     | 23.79 ± 4.83a      | 26.26 ± 7.32b    | 22.94 ± 4.73a |
| Fat%                    | 25.99 ± 8.54a      | 29.66 ± 11.29b   | 25.07 ± 7.25a |
| Body fat % category     |                    |                  |               |
| Underfat                | 52 (16.6)          | 14 (12.8)        | 67 (28.8)     |
| Normal fat              | 200 (63.9)         | 51 (46.8)        | 128 (54.9)    |
| Overfat                 | 61 (19.5)          | 44 (40.4)        | 38 (16.3)     |

Different letters show statistical significance among race groups. ANOVA with Tukey post-hoc tests were used and p values less than 0.05 were considered statistically significant. Body fat % categories for adults ages 20-39 years are underfat (BF% < 20% in females, <10% in males), healthy (BF% 20%-34% in females, 10%-21% in males), and overfat/obese (BF%>34% in females, BF% >21% in males).

4. Discussion

The present study analyzed TAS2R38 genetic polymorphisms among European American, African American, and Asian subjects. Three major
single nucleotide polymorphisms of the TAS2R38 gene were genotyped for in the present study. The minor allele types and frequencies differed among races; however, frequencies were similar to those described in previous studies \([7,9,11]\) and in the dbSNP database (NCBI). Race was an important variable because rare haplotypes were observed in some racial groups. In European American and African American subjects, rare haplotypes including AAV and AAI were found, respectively. The present study showed similar results to a previous study \([8]\), in which the African American group had greater genetic diversity in TAS2R38 than other races. Thus, the role of bitter taste gene polymorphisms and bitter taste sensitivity to health status is more complex in the African American population than previously known. This could be because the African American population is genetically a very diverse group. However, the Asian population had the lowest prevalence of rare haplotypes in TAS2R38 that similar with previous studies \([44,45]\).

As was hypothesized in previous studies, bitter taste gene polymorphisms might affect taste perception, alter eating behavior, and may be a contributing factor for the development of obesity or other metabolic diseases \([2,10–12,26–31]\). The PAV and AVI haplotypes of TAS2R38 represent the PROP taster and non-taster phenotypes, respectively. Other haplotypes including rare haplotypes have been reported as intermediate or supertaster phenotypes \([7,20,46]\). As was observed in the present study, the homozygous AVI/AVI diplotype (non-taster diplotype), was associated with a higher risk for obesity than the heterozygous AVI/PAV and homozygous PAV/PAV diplotypes in European American and Asian subjects after adjustment for age. This might be explained by previous studies that reported PROP non-tasters have reported to have higher reported food intakes, higher intake of fruit, vegetables, and spicy food, and also higher

| Table 2. Genotype and allele distribution of TAS2R38 in the study group. |
|--------------------------|-------------------|-----------------|---------------|
| SNP Race Genotype N (%)  | MAF P value       |
|--------------------------|-------------------|-----------------|---------------|
| rs713598 European American 109 (34.7) | 147 (46.8) | 58 (18.5) | P = 0.42 0.233 |
| African American 34 (31.2) | 57 (52.3) | 18 (16.5) | P = 0.43 0.800 |
| Asian 31 (13.2) | 103 (44.0) | 100 (42.7) | A = 0.35 0.337 |
| rs1726866 European American 88 (28.0) | 151 (48.1) | 75 (23.9) | A = 0.48 0.317 |
| African American 13 (11.9) | 50 (45.9) | 46 (42.2) | V = 0.35 0.596 |
| Asian 34 (14.5) | 98 (41.9) | 102 (43.6) | V = 0.35 0.116 |
| rs10246939 European American 75 (23.9) | 149 (47.5) | 90 (28.7) | I = 0.48 0.226 |
| African American 34 (31.2) | 57 (52.3) | 18 (16.5) | V = 0.43 0.813 |
| Asian 35 (15.0) | 97 (41.5) | 102 (43.6) | I = 0.36 0.087 |

MAF; minor allele frequency, P value for Hardy Weinberg Equilibrium, Homozygous allele; AA (alanine), VV (valine), II (isoleucine), PP (proline), Heterozygous allele; AP, VA, IV.

| Table 3. Haplotype percentage distributions of TAS2R38 in the study group. |
|--------------------------|-------------------|-----------------|---------------|
| Population PAV AVI AAV AVV PAI PVI AAI PVV |
| Total 48.78 41.92 3.58 0.23 0.30 0.91 4.04 0.23 |
| European-American 40.73 51.12 6.07 0.48 0.32 0.48 0.48 0.32 |
| African-American 42.20 33.94 0.92 0.00 0.00 0.00 22.94 0.00 |
| Asian 62.61 33.33 1.50 0.00 0.43 1.92 0.00 0.21 |
| Haplotype: subset of allele from multiple loci on a single chromosome. |

| Table 4. Distribution of TAS2R38 diplotype by race. |
|--------------------------|-------------------|-----------------|---------------|
| Diplotype European American African American Asian |
| AVI/AVI 85 (27.16) | 12 (11.01) | 30 (12.82) |
| AVI/PAV 128 (40.89) | 33 (30.28) | 91 (38.89) |
| PAV/PAV 55 (17.57) | 18 (16.51) | 95 (40.60) |
| AAV/AAV 2 (0.64) | - | - |
| PVI/PVI 1 (0.32) | - | 1 (0.43) |
| AAV/AVI 18 (5.75) | 2 (1.83) | - |
| AVI/AVV 1 (0.32) | - | - |
| PAV/AAV 15 (4.79) | - | 7 (2.99) |
| PAV/AVV 1 (0.32) | - | - |
| PAV/PAI 1 (0.32) | - | - |
| AAV/AAI 1 (0.32) | - | - |
| PVI/AVI 1 (0.32) | - | 2 (0.85) |
| PAV/PVV 1 (0.32) | - | - |
| AAI/AAI 2 (0.64) | 14 (12.84) | - |
| PVV/AVI 1 (0.32) | - | 1 (0.43) |
| PAV/AAI - | 22 (20.18) | - |
| PAV/AVI - | 1 (0.92) | - |
| AAI/AAI - | 7 (6.42) | - |
| PAV/PVI - | - | 2.14 |
| AVI/PAI - | - | 0.85 |

Diplotypes; a variant of all possible combined haplotypes in a population.
alcohol consumption [13,22–25,33,46]. PROP tasters might be sensitive to foods with a bitter aftertaste, sweet and fatty foods, spicy foods, and have scored higher overall on food disliking [47,48]. PAV allele carrier might potentially demonstrate more selective eating behavior pattern [49]. In this study, there was no association between non taster and other rare diplotypes. Few studies have reported on associations between common and rare haplotypes with obesity markers such as body fat percentage or BMI because they did not have large enough frequencies for statistical analysis [49,50]. Moreover, body fat percentage was used as obesity risk factor instead of body mass index which could make the study difference or more accurate [42,52]. However, it is difficult to conclude the effect of these genetic polymorphisms on obesity development among African American subjects.

TAS2R38 haplotype predicts the majority (55–85%) of phenotypic variance in PROP sensitivity [51–54]. These genetic polymorphisms might regulate the receptor function which differs from taste perception function. Bitter taste receptors are G protein coupled receptors, and in addition to being present in taste buds, are also present in the gastrointestinal system, respiratory system, and brain, although their function in these locations is not well understood [53–56]. Taste receptors could also function in nutrient sensing [17], endocrine regulation, or energy metabolism such glucose homeostasis [1,15,30]. The expression of TAS2R38 in the intestines might influence energy balance and intraluminal changes occurring in obesity [17,57]. Moreover, three candidate genetic polymorphism could change the gut TAS2R38 receptor by the alteration of ligand binding site. These data suggested that the extra oral of TAS2R38 could modulate the release of gut peptides and possibly caused in metabolic effects [58]. Therefore, the genetic polymorphism of TAS2R38 might associate with obesity risk as in this present study.

We identified several limitations to our study. We did not measure PROP sensitivity in study participants therefore we lack the association between genotype and taste perception phenotype. We did not measure other bitter and non-bitter taste gene polymorphisms which could be functioning together with TAS2R38 [59].

### Table 5. The risk of TAS2R38 diplotype to obesity in each race group.

| Parameters | Number (%) | Adjusted Odds ratio | 95% CI | P value |
|------------|------------|---------------------|--------|---------|
|            | Normal | Obese |         |          |         |
| European American | | | | | |
| Gender | | | | | |
| Female | 164 (79) | 44 (21) | 1.294 | 0.619-2.704 | 0.494 |
| Male | 29 (67) | 14 (33) | - | - | - |
| Diploype | | | | | |
| AVI/AVI (reference) | 46 (72) | 18 (28) | - | - | - |
| PAV/AVI | 37 (84) | 7 (16) | 0.180 | 0.079-0.410 | <0.001 |
| PAV/AVI | 87 (76) | 27 (23) | 0.294 | 0.185-0.467 | <0.001 |
| AAV/AVI | 9 (60) | 6 (40) | 0.611 | 0.211-1.773 | 0.365 |
| PAV/AAV | 14 (100) | 0 (0) | - | - | - |
| African American | | | | | |
| Gender | | | | | |
| Male | 8 (17) | 38 (83) | 0.612 | 0.186-2.006 | 0.417 |
| Female | 38 (53) | 34 (47) | - | - | - |
| Diploype | | | | | |
| AVI/AVI (reference) | 7 (70) | 3 (30) | - | - | - |
| PAV/AVI | 18 (67) | 9 (33) | 0.526 | 0.234-1.181 | 0.120 |
| PAV/AVI | 8 (50) | 8 (50) | 1.063 | 0.393-2.869 | 0.905 |
| PAV/AVI | 8 (40) | 12 (60) | 1.618 | 0.647-4.050 | 0.304 |
| AAV/AVI | 5 (42) | 7 (58) | 1.460 | 0.460-4.633 | 0.521 |
| Asian | | | | | |
| Gender | | | | | |
| Female | 86 (83) | 17 (17) | 1.454 | 0.711-2.974 | 0.305 |
| Male | 33 (66) | 17 (34) | - | - | - |
| Diploype | | | | | |
| AVI/AVI (reference) | 20 (87) | 3 (13) | - | - | - |
| PAV/AVI | 51 (80) | 13 (20) | 0.223 | 0.115-0.435 | <0.001 |
| PAV/AVI | 48 (73) | 18 (27) | 0.333 | 0.183-0.603 | <0.001 |

Normal and obese criteria characterized by normal and overfat cut-off. Under-fat was excluded from this analysis. Logistic regression analyzed with Enter method. P value less than 0.05 was statistical significant.
5. Conclusion

The PROP non-taster diplotype was associated with a higher risk for obesity in European Americans and Asians after adjustment for sex. These diplotypes relate to bitter taste perception and to eating behavior which affects food choice but not energy intake, or they might affect extra-oral functions such as gastrointestinal function. The mechanisms could not be clarified in the present study. Race, sex, and environmental factors cannot be excluded from the complex relationship between genetic polymorphisms and obesity.

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