Scandinavian Journal of Clinical & Laboratory Investigation, 2011; 71: 274–279

informa
healthcare

ORIGINAL ARTICLE

Genetic variation in the h*TAS2R38* taste receptor and brassica vegetable intake

NELA GOROVIC[1], SHOAIB AFZAL[1], ANNE TJØNNELAND[2], KIM OVERVAD[3], ULLA VOGEL[4], CHRISTINA ALBRECHTSEN[1] & HENRIK E. POULSEN[1]

[1]*Laboratory of Clinical Pharmacology Q7642, Rigshospitalet, Department of Clinical Pharmacology, Copenhagen University Hospital, Bispebjerg, Copenhagen,* [2]*Institute of Epidemiological Cancer Research, Danish Cancer Society,* [3]*Department of Epidemiology, School of Public Health, Aarhus University, and* [4]*Department for Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark and National Research Centre for the Working Environment, Denmark*

Abstract

The human TAS2R38 receptor is believed to be partly responsible for the ability to taste phenylthiocarbamide (PTC), a bitter compound very similar to the bitter glucosinolates found in brassica vegetables. These vegetables and their active compounds have chemo-protective properties. This study investigated the relationship between genetic variation in the h*TAS2R38* receptor and the actual consumption of brassica vegetables with the hypothesis that taster status was associated with intake of these vegetables. Furthermore, secondary intake information on alcohol, chocolate, coffee, smoking, BMI and waist-circumference was analysed for association with the h*TAS2R38* receptor polymorphisms. The subjects were selected from the Diet, Cancer and Health (DCH) study, which is an ongoing prospective Danish cohort study. Two groups, each consisting of 250 healthy subjects were selected based on their brassica vegetables intake from the upper quartile (≥23 g/day) and the lower quartile (≤7 g/day) daily intake of brassicas from a randomly selected sub-cohort of DCH. DNA was analysed for three functional SNPs in the h*TAS2R38* gene. The h*TAS2R38* bitter taste receptor haplotypes were not associated with the daily intake of brassica vegetables in our study, and no association between the haplotypes and any of the other variables tested was found. We have demonstrated that the h*TAS2R38* haplotypes are not associated with brassica vegetable intake and that results from experimental setups cannot be applied directly to the everyday situation. This indicates that non-genetic factors may have more influence on dietary choice than genetics.

Key Words: *Alcohol, genetics, obesity, smoking, taste, vegetables*

Introduction

The ability to taste bitter substances is believed to have evolved in humans to avoid food that contain toxins, since these often have common chemical properties that can be recognized by taste receptors. Taste is very important in food selection and therefore foods that are perceived as bitter are often excluded from the diet despite their nutritional and disease protective qualities.

An important and well-studied human trait is the sensitivity to the bitterness of the thioureas phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP), a trait that shows large inter-individual differences [1,2]. The underlying gene that is responsible for PTC/PROP taste sensitivity is h*TAS2R38*, a bitter taste receptor that binds the thiourea moiety [3–5]. Although the inheritance pattern for the PTC/PROP trait is not fully determined, polymorphisms in the h*TAS2R38* gene are believed to account for up to 85% of the phenotypic variance of PTC/PROP sensitivity [3,6–8].

The human *TAS2R38* gene has three mis-sense single nucleotide polymorphisms that change the taste receptor's affinity for thioureas. The three corresponding amino acid substitutions are situated at positions 49, 262 and 296, resulting in two major phenotypic forms. The major taster form has proline at position 49, alanine at position 262, and valine at position 296, constituting the PAV haplotype. The major non-taster form contains alanine, valine and

Correspondence: Shoaib Afzal, Laboratory of Clinical Pharmacology Q7642, Rigshospitalet, Tagensvej 20, 2200 Copenhagen N, Denmark. Tel: + 45 3545 7525; Fax + 45 3545 2745. E-mail: shoaib.afzal@rh.regionh.dk

(Received 16 August 2010; accepted 17 January 2011)

ISSN 0036-5513 print/ISSN 1502-7686 online © 2011 Informa Healthcare
DOI: 10.3109/00365513.2011.559553

isoleucine, respectively, at the three positions, giving the AVI haplotype. Possessing one or two of the dominant PAV haplotypes characterizes the 'taster' phenotype while the 'non-taster' phenotype is homozygous for AVI (although some studies have shown intermediate sensitivity to PTC in individuals carrying both haplotypes (PAV/AVI)) [3,4].

Glucosinolates, also containing thiourea moieties, are present in large quantities in brassica vegetables and are responsible for their bitter taste. In western countries, the primary dietary sources of brassica vegetables come from the species *Brassica oleracea* including broccoli, Brussels sprouts, cabbage and cauliflower. Tasters (PAV haplotype carriers) are believed to perceive bitterness from brassica vegetables and avoid intake, while non-tasters (homozygous AVI haplotype carriers) are believed to consume larger amounts of these vegetables. An inverse relationship between high intake of brassica vegetables and several types of cancer has been observed in some epidemiological studies [9–11]. Experimental studies on brassicas have shown that their active compounds block tumorigenesis in animal models and in humans, even though these studies are small scale [12–15]. The present study was designed to investigate the association of the h*TAS2R38* receptor haplotypes with food preference and dietary intake of brassica vegetables by testing the hypothesis that the intake of brassica vegetables is associated with different h*TAS2R38* haplotypes. We compared two groups of individuals with high (>23 g/day) and low (<7 g/day) daily intake of brassica vegetables in relation to their h*TAS2R38* status in a cohort of healthy Danes. In addition the hypothesis that h*TAS2R38* receptor haplotypes might also be associated with BMI and body type, smoking status, alcohol habits and chocolate and coffee consumption was tested.

Subjects and methods

Study population

The subjects were selected from the prospective Diet, Cancer and Health (DCH) study, which is an ongoing Danish cohort study. Detailed information about the DCH study design is available elsewhere [16]. Briefly, from 1993 to 1997 a random population of 160,725 individuals aged 50–64 years, born in Denmark, living in the greater Copenhagen and Aarhus areas was invited to participate in the study. A total of 57,053 individuals with no previous cancer diagnosis accepted and were examined. At enrolment the participants completed a detailed food-frequency questionnaire containing 192 different food items within 12 categories ranging from never to eight times per day or more. The food-frequency questionnaire has been validated and the results published elsewhere [17,18]. Frequencies of intake of brassica vegetables were assessed from this questionnaire. The category 'brassica' included the following vegetables: broccoli, cauliflower, Brussels sprouts, (white) cabbage, red cabbage and kale. Additional information about lifestyle, height, weight, smoking status, medical treatment and socio-economic relations were registered. Smoking history was collected through self-reported lifestyle questionnaires. Cigarette smoking was defined as current, past or never. Smokers were defined as individuals smoking ≥ one cigarette/day for at least a year. Alcohol intake was recorded as the intake of beer, wine and spirits, respectively in g/day. Body Mass Index was calculated as weight (kg) per height squared (m^2). Blood samples were collected and stored at −150°C.

Ten thousand healthy participants were randomly sampled from the DCH study population. DNA was successfully extracted for 9,423 persons and made available for genetic analysis used for several studies. From this sub-cohort of 9,423, 500 individuals were selected for this study based on their brassica vegetables intake. We identified and included two groups of 250 subjects in each, who had different daily intake of brassicas. Individuals for the high brassica intake group were randomly selected from the upper quartile consisting of 2614 persons with ≥23 g/day intake of these vegetables, while the low intake group was similarly selected from the lower quartile consisting of 2409 persons with ≤7 g/day intake.

Blood samples and PCR

DNA was extracted from frozen blood samples according to the procedure described by Miller et al. [19]. A NanoDrop ND1000 spectrophotometer (Nanodrop Technologies Inc., Rockland, USA) was used to assess DNA quantity. DNA samples were diluted to 10 ng per well and analysed for the h*TAS2R38* Ala49Pro (rs713598), Val262Ala (rs1726866) and Ile296Val (rs10246939) polymorphisms using the fluorogenic 5-nuclease assay (TaqMan® SNP Genotyping Assay Made to Order on an ABI 7900HT, Applied Biosystems, Foster City, USA) Genotypes were determined in a 25µl reaction mix containing 11.25 µl diluted DNA sample and 13.75 µl master mix solution (0.625 µl DNAse/RNAse free water, 0.625 µl TaqMan® SNP Genotyping Assay, and 12.5 µl TaqMan Universal PCR Master mix (Applied Biosystems) according to the manufacturer's instructions). PCR amplification was performed with an initial step of 95°C for 10 min followed by 45 cycles of 92°C for 15 sec and 60°C for 1 min (Applied Biosystems 7900HT Sequence Detection System). The fluorescence profile of each well was measured in an Applied Biosystems 7900HT Sequence Detection System, and the results were analysed with Sequence Detection Software (SDS 2.3, Applied Biosystems). Controls were included on each plate. Reproducibility was checked by re-genotyping 10% of the cases with 100% agreement. The h*TAS2R38* genotyping was unsuccessful for 14 samples.

Ethics

The Diet, Cancer and Health study and this substudy was approved by the Danish Data Protection Agency, and by the regional Ethics Committees of Human studies in Copenhagen and Aarhus (File: H-KF-01-345/93, notification number: 19739).

Statistical methods

The primary endpoint was haplotype frequency difference between brassica high-intake vs. low-intake.

Our study had 250 case patients and 250 control patients. Prior data indicate that the proportion of non-tasters among controls is around 30%. We will be able to detect true odds ratios for low brassica intake of 1.719 in non-tasters relative to tasters with probability (power) 80%. The Type I error probability associated with this test of the null hypothesis that this odds ratio equals 1 is 0.05.

Secondary end-points were alcohol intake, coffee intake, chocolate intake, smoking, BMI and waist-circumference. The Cochrane-Armitage trend test was used to detect possible gene-dose effects. Logistic regression was used for obtaining unadjusted and adjusted estimates of haplotype effects on brassica intake and secondary end-points.

The continuous variables were changed to dichotomous variables by using median as cut-off. Haplotypes and haplotype frequencies were inferred by using Phase v.2.1.1. Software [20,21]. Hardy-Weinberg equilibrium was assessed using Haploview v4.1 (www.broad.mit.edu/mpg/haploview/). All reported *p* values are two sided. The analyses were performed using the SAS Statistical Package Version 9.1.3 (SAS Institute Inc, Cary, NC).

Results

Genotype and haplotype distribution

Genotype data and demographic data are summarized in Table I. All genotypes were in Hardy-Weinberg equilibrium. Genotyping was successful in 98% of the samples. Taster haplotypes are defined in the introduction and presented in Table II along with the distribution. Fourteen persons out of the 500 persons had incomplete genotyping data and they were excluded from the analysis. As expected the three polymorphisms were tightly linked with r^2 values ranging from 0.82–1.00 (Figure 1).

Haplotype associations

Associations between haplotypes and intake of brassica vegetables and secondary diet intakes were analysed using the non-taster (AVI/AVI) and taster (PAV/AVI or PAV/PAV) classification. All other haplotypes were excluded from the initial analysis since their taster status has not been conclusively determined [3,4,22,23]. There was no association between taster status and brassica intake (see Table III). The absolute difference in non-taster proportions between the low and high brassica intake groups was $(p_{low}–p_{high}) \pm 1.96 \times se((p_{low}–p_{high}) = 1.3\% \pm 9.1\%$, indicating that the real difference lies between –8 and 10% in non-taster haplotype distribution.

Our population was selected on the basis of brassica intake information, so analysis were only carried out on those secondary intake or demographic variables that showed the same degree of associations in the two intake groups separately or to rephrase where brassica intake was not an effect modifier of the association of taster status with secondary endpoints. All of the secondary endpoints fulfilled this assumption and could be analysed. Logistic regression analysis showed similar results both unadjusted and adjusted for sex and age (Table III).

These analyses were repeated using 3-group classification into taster (PAV/PAV), intermediate taster

Table I. Demographic data and h*TAS2R38* genotype distribution.

	Brassica vegetables intake	
	Low: ≤ 7 g/day (n = 250)	High: ≥ 23 g/day (n = 250)
Median age (range)	56 (50–65)	57 (50–65)
Sex		
Male	128 (51%)	122 (49%)
Female	122 (49%)	128 (51%)
Ala49Pro (rs713598)		
Ala/Ala	97 (39%)	104 (42%)
Pro/Ala	110 (44%)	115 (46%)
Pro/Pro	36 (14%)	28 (11%)
Missing	7 (3%)	3 (1%)
Val262Ala (rs1726866)		
Val/Val	87 (35%)	93 (37%)
Ala/Val	114 (46%)	116 (46%)
Ala/Ala	43 (17%)	38 (15%)
Missing	6 (2%)	3 (1%)
Ile296Val (rs10246939)		
Ile/Ile	87 (35%)	92 (37%)
Val/Ile	113 (45%)	115 (46%)
Val/Val	43 (17%)	38 (15%)
Missing	7 (3%)	5 (2%)

Table II. h*TAS2R38* haplotype distribution in groups with high and low brassica vegetables intake.

		Brassica vegetables intake	
Haplotypes	Classification [3]	Low: ≤ 7 g/day	High: ≥ 23 g/day
AVI/AVI	Non-taster	86 (34%)	91 (36%)
PAV/AVI	Taster/Intermediate	100 (40%)	105 (42%)
PAV/PAV	Taster	33 (13%)	28 (11%)
PAV/AAV	Unknown	8 (3%)	9 (4%)
PAV/PVI	Unknown	2 (1%)	0
PVI/AVI	Unknown	1	1
AAV/AAV	Unknown	0	1
AAV/AVI	Unknown	11 (4%)	10 (4%)

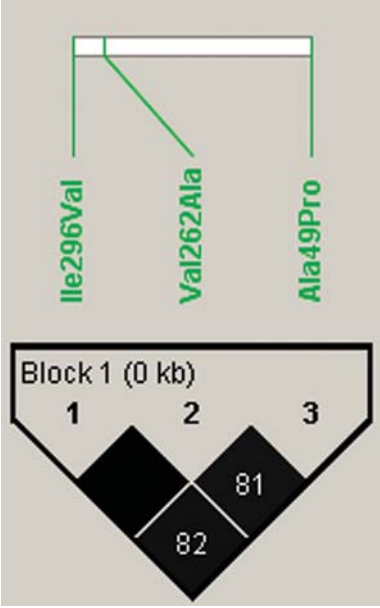

Figure 1. LD-plot of the three SNPs showing r^2 as the measures linkage disequilibrium.

(PAV/AVI) and non-taster (AVI/AVI) as well as excluding/including the unknown haplotypes. The results remained the same without change in associations. Trend-tests did not reveal any significant gene-dose effects (data not shown).

Discussion

The results of our study clearly show that the h*TAS2R38* haplotypes were not associated with brassica intake in the Danish diet in a design where subjects from a high intake and a low intake group were compared. Our results indicate that the difference in non-taster-haplotypes is around 1% (–10 to 10%) between high and low brassica intake groups making them unlikely determinants of brassica vegetable intake. Furthermore no association was found between h*TAS2R38* receptor haplotypes and any other variable tested in the two brassica vegetables intake groups. Our study is a cross-sectional study based on a healthy prospective cohort where the present study population was chosen based on brassica intake balanced with regards to age and sex. Out of the total 500 individuals in our study group 14 were excluded due to incomplete genotyping. The association between intake of different brassica vegetables and the phenotypic PTC/PROP taster status has been studied earlier with inconclusive results [24–26]. Taster status, tested by genetic variation in PROP/PTC or h*TAS2R38*, has been associated with higher bitterness and lower acceptance scores for brassica vegetables when compared to non-tasters, although these studies were also inconclusive [5,27–29]. However, only two studies in the past few years have examined the brassica intake in relation to the h*TAS2R38* haplotypes. One study of 3383 British women found no association with the h*TAS2R38* receptor when testing the cumulative green vegetable intake [30]. They did not examine the brassica vegetables independently, making their results incomparable with ours. Another study was performed on the Italian population from the European Prospective Investigation into Cancer and Nutrition (EPIC) including 634 subjects. They found a significant association between intake of brassicas and the h*TAS2R38* haplotypes [22]. Our study differs from this study in that we carried out a full genotyping whereas only Ala49Pro (rs713598) and Val262Ala (rs1726866) were genotyped in the Italian study. The intake amounts seem to be different as well so the studies are not completely comparable, opening the possibility that the genetic effects may only be relevant depending on average population intake amount. Our results do not support these findings that the h*TAS2R38* haplotypes are associated with brassica vegetable intake. The present lack of association between taster status and brassica intake indicates that bitterness perception results found in the laboratory setting do not modify intake in population studies.

Table III. Logistic regression analysis of h*TAS2R38* taster status association with outcome variables.

	Taster status (taster = reference)	
	OR (95% CI, *p*-value)	
Outcome variables	Unadjusted	Adjusted[#]
Brassica intake	*0.95 (0.65 – 1.38, 0.77)*	*0.92 (0.62 – 1.34, 0.65)*
Beer	0.92 (0.63 – 13.4, 0.66)	0.79 (0.52 – 1.22, 0.29)
Spirits	1.21 (0.83 – 1.78, 0.32)	1.17 (0.79 – 1.73, 0.44)
Wine	1.26 (0.86 – 1.85, 0.24)	1.23 (0.83 – 1.80, 0.30)
Total alcohol	0.89 (0.61 – 1.38, 0.55)	0.80 (0.54 – 1.20, 0.29)
Coffee	1.09 (0.72 – 1.63, 0.70)	1.06 (0.70 – 1.60, 0.80)
Smoking[*]	1.06 (0.75 – 1.51, 0.74)	1.05 (0.74 – 1.50, 0.79)
Chocolate	0.94 (0.63 – 1.40, 0.75)	0.92 (0.61 – 1.38, 0.68)
BMI	1.02 (0.70 – 1.50, 0.92)	0.98 (0.66 – 1.44, 0.90)
Waist-circumference	1.14 (0.78 – 1.67, 0.50)	1.05 (0.67 – 1.66, 0.83)

[*]Results from ordinal logistic regression.
[#]Sex and age.

The reasons for this might seem evident when considering the complexity of determinants for food preferences. In the everyday situation other factors like economy, sex, age, cultural heritage, deviating taste preferences, prior experience, sociocultural variables and health-awareness influence human food selection [31,32]. Furthermore, laboratory testing is done using pure bitter compounds while in real life the mixing of foods (and beverages) may mask bitter compounds and produce additional taste nuances that are not present in the laboratory setting.

An association between bitter taste, defined by taste thresholds for PROP/PTC), and alcohol consumption, dependence and family history has been investigated in several studies. The results from these studies are contradictory showing general associations [33–35], associations for subgroups only [36,37] or no associations at all [30,38,39] with alcoholism or alcohol intake. Studies specifically studying the association of h*TAS2R38* with alcohol intake have also been contradictory, but in the largest study including more than 3000 women no association was found. We found that the PTC taster status, determined by the h*TAS2R38* haplotypes, was not associated to total alcohol intake.

We also investigated the possible relation between PTC perception and BMI in our sample. Positive results have been shown in phenotype studies with mainly small population samples [40,41]. It has been suggested that the underlying reason for differences in BMI measures for the taster and non-taster individuals is the different perception of fat in the diet and thus their intake of fat-containing foods, but this theory is questionable [42,43]. More studies point in the opposite direction, reporting no influence of PTC taste ability on BMI-measure, waist-hip ratio and waist-circumference when testing for an association with either PTC/PROP sensitivity or the h*TAS2R38* receptor haplotypes [7,8,43,44]. Our results are in accordance with these negative studies rejecting the theory that the h*TAS2R38* receptor should have any influence on BMI or waist circumference.

Because PTC perception has been linked to several bitter compounds, a relation between the bitterness of chocolate and taster status has been suggested. Ly and Drenowski examined the sensory response to three kinds of chocolate (white/milk/dark) and their intake, but found no significant difference between the phenotypic taster and non-taster groups [45]. We examined chocolate consumption in our sample with the hypothesis that non-tasters would consume more chocolate because they would not be able to detect its bitterness but did not find any correlation between the h*TAS2R38* haplotypes and chocolate intake.

Conclusions

Our results do not support previous findings of an association between brassica intake and h*TAS2R38* haplotypes, indicating that non-genetic factors may be of greater importance than genetics in determining food selection. In conclusion, our study indicates that the determinants of bitter food intake, specifically brassica vegetables, may be principally independent of genetic profiles of the hTAS2R38 bitter taste receptor. Additionally h*TAS2R38* haplotypes were not associated with intake of alcohol, chocolate or body type measured by BMI and waist circumference.

Acknowledgments

Sources of support: Danish Cancer Society (AT) and Rigshospitalets Forskningsudvalg (HEP).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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