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POSSIBLE ASSOCIATION OF TAS2R38 BITTER TASTE RECEPTOR WITH LARYNGEAL CANCER

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ABSTRACT

It is reported that the bitter taste develops to protect people from the consumption of toxic compounds. Genetically, the alleles of the TAS2R38 gene are the main genetic markers of phenotypic variation in 6-n-propylthiouracil (PROP) taste sensitivity used to describe the ability to taste bitter compounds. TAS2R38 mutations and bitter taste responses have been found to be associated with many diseases, including alcoholism, obesity, thyroid function and cancer. Therefore, this study aims to investigate the role of bitter taste receptor genes or polymorphisms in these genes, which can be related to risk factors in head and neck cancers in laryngeal cancer.

Eighty-two individuals, 44 patients diagnosed with laryngeal cancer and 38 patients in control group, were included in this study. DNA isolation was performed from whole blood samples and analysis of TAS2R38 (rs713598, rs1726866, rs10246939) polymorphism from DNA samples was performed on RT-PCR.

While PAV was more common in patients with laryngeal cancer, AVI frequency was similar in both groups. The prevalence of heterozygous individuals was lower in the patient group ($p < 0.005$).

To our knowledge, this is the first study investigating the role of TAS2R38 with laryngeal cancer in the literature. Thus, further studies on the role of TAS2R38 in the diagnosis and treatment of the disease, including taste sensitivity tests shoud be conducted.

KEYWORDS:
Laryngeal cancer, TAS2R38, bitter taste, PAV, AVI

INTRODUCTION

The bitter taste can protect people from the consumption of toxic compounds [1]. Therefore, they have more specific receptors than other tastes, and bitter molecules can be detected at thresholds 1000 times lower than other tastes in some cases [2, 3]. Sensitivity to bitter tastes is variable within the population, and phenotypic and genotypic variability in bitter taste perception has been widely studied [4, 5]. Phenylthiocarbamide (PTC) is a chemical that imitates the bitter taste perception of isothiocyanates obtained from cruciferous vegetable [6]. 6- n-propylthiouracil (PROP) is a derivative of PTC. PROP is generally substituted for PTC in taste studies. The sensitivity spectrum of PTC/PROP is very wide. Some individuals have an intensely bitter taste (supertasters), while others have no taste at all (non-tasters). Most people, on the other hand, are between these two degrees (tasters) [7].

Type 2 taste receptors (T2Rs, TAS2Rs) are a member of the G protein-linked receptor class (GPCRs) involved in signal transduction on the cellular membrane, especially in response to bitter-tasting compounds [1,8,9]. T2R receptors are encoded by members of the TAS2R gene family and they encode approximately 25 different T2R isoforms [10]. Genetically, alleles of the TAS2R38 gene are the main genetic determinants of phenotypic variation in PROP taste sensitivity that is used to describe the ability to taste bitter compounds [11]. In humans, TAS2R genes are known to exist on chromosomes 5, 7 and 12, and TAS2R38 is found on chromosome 7. There are three non-synonymous single nucleotide polymorphisms (SNPs) encountered in the TAS2R38 bitter taste receptor gene, which are: reference SNP (rs) number 713598; rs1726866; rs10246939. Their amino acid substitutions are A49P (A49→P49), A262V (A262 →V262) and I296V (I296 →V296)). These SNPs lead to five haplotypes responsible for varying levels of phenotypic PTC/PROP sensitivity in humans. Due to the high level of linkage disequilibrium between A262V and I296V, the only variation is seen between A49P and A262V in practice. While the PAV haplotype corresponds to a greater sensitivity to certain bitter tastes, the AVI haplotype corresponds to insensitivity to bitter taste [12, 13]. There is also a moderate heterozygous effect. As a group, PAV/AVI heterozygotes have a significantly higher PTC taste threshold than PAV homozygotes. Thus, they are less sensitive to PTC [14].

These receptors are expressed in oral tissues

where the perception of the bitter taste of food or waterborne compounds begins and in other extraoral tissues, including the respiratory, genitourinary, gastro intestinal and nervous systems. T2Rs serve to separate beneficial or harmful exogenous and endogenous molecules and activate subsequent steps, such as the use or elimination of these stimuli. Therefore, in addition to regulating metabolism, it has been reported that they are also associated with disease risk [15, 16]. In addition, studies show that taste genes play a much wider role in human health. Recently, taste receptors have been shown to be expressed in several organs and tissues that are not directly involved in food intake or digestion, such as the lung, airway smooth muscle, nose and testis. Their response to harmful stimuli increases in the airways or they may play a role in spermatogenesis in the testis. These findings suggest that bitter taste perception may have a central role in organisms' homeostasis. Besides, they are only one of the functions performed by this gene cluster [17, 18].

TAS2R38 mutations and bitter taste responses are associated with alcoholism, smoking and many diseases, including obesity, thyroid function, colon polyps and types of cancer [3]. Moreover, in the study conducted by Mirza et al. [19], taste abnormalities were observed in patients with head and neck cancer, and it was suggested that these defects were caused by radiation exposure based on treatment. Laryngeal cancer, which constitutes 25% of head and neck region malignancies, constitutes 2-5% of all malignant tumors [20]. Although the incidence of laryngeal cancers in men is higher, increased smoking habits in women caused a decrease in the male/female ratio similar to lung cancer [21]. Many factors may play a role in the development of laryngeal cancer. These factors may be effective alone in cancer formation, or they may have a synergistic effect with other factors [22]. Studies have shown that the effects of these genes or the variability in these genes are quite extensive, apart from protection from toxic compounds. Therefore, this study aimed to investigate the role of bitter taste receptor genes or polymorphisms in these genes in laryngeal cancer.

MATERIALS AND METHODS

This study consisted of individuals with the larynx (patient group, n=44) and healthy (control group, n=38). Participants were selected from patients with a similar age range between the groups who applied to Mersin University Medical Faculty Hospital ENT Department. While determining the inclusion criteria of the participants in the patient group, attention was paid to that there was no other cancer history other than larynx ca and that treatment was not initiated and newly diagnosed. Apart from this, the pediatric group, patients diagnosed with any cancer other than laryngeal cancer and any systemic disease, patients with obesity or any substance addiction were excluded from this study. After DNA isolation from blood samples taken from individuals belonging to the patient and control groups to the tubes with EDTA and stored at +4°C, analysis of TAS2R38 (ThermoFisher, rs713598, rs1726866, rs10246939) polymorphism was performed on RT-PCR device (RocheLightCycler480) to investigate its role in laryngeal cancer. As a result of the data obtained, allele frequency, genotype distribution and risk ratio were calculated. In addition, disease risk was evaluated according to haplotype types. Whether the groups were in Hardy-Weinberg balance concerning genotype distribution was investigated. A chi-square test was used to investigate the relationship between two categorical variables. The exact test was used as the frequency percentage that was expected lower than 5 was greater than 20%. If a significant relationship was found, a pairwise ratio comparison was made. An independent sample t-test was used to compare the means of two independent groups. $p < 0.05$ was accepted as the statistical significance level. Analyses were made in Statistica v.13.3.1 program.

Before conducting this study, ethical approval was obtained from the ethics committee of the university (Decision No: 12/275, Date: 26.06.2019).

RESULTS

The study group consisted of 44 patients (average age: 58) and 38 controls (average age: 57). Of those included in this study, 67.1% were men, 32.9% were women. 84.1% of the patient group were male, while 15.9% of the control group were male and a statistically significant relationship was found between the gender and the group ($p<0.001$). The findings obtained in this study showed that the rate of males in the patient group was significantly higher than in the control group.

In this study, 3 SNPs of TAS2R38 taste receptor gene polymorphisms were studied to investigate their role in laryngeal cancer in the patient and control groups (Table 1). As shown in Table 2, no statistically significant difference was found between the groups concerning distribution of genotype and allele frequencies (rs102469; p=0.412, p=0.797), (rs713598; p=0.105, p=0.205), (rs1726866; p=0.727, p=0.917).

The importance of TAS2R38 for bitter taste perception was first shown by Kim et al. (12), and it was named PAV and AVI, which defined two common alleles with extremely different functional characteristics associated with threshold detection of PTC.

However, recent studies have revealed that TAS2R38 contains a wide range of genetic variation beyond the PAV and AVI alleles and contains 19 amino acid variants cataloged in populations worldwide up to date, which may underlie unrecognized

TABLE 1
SNP genotyping of TAS2R38 taste receptor gene

SNP ID	SNP Location	Polymorphism	Major/minor allele	MAF	SNP Type	Observed Codons	Observed Amino Acid
rs713598	229	C/G, Transversion Substitution	C/G	0.42	Missense Mutation	CCA, GCA	P,A 49
rs1726866	869	A/G, Transition Substitution	T/C	0.46	Missense Mutation	GCT, GTT	A,V 262
rs10246939		C/T, Transition Substitution	T/C	0.46	Missense Mutation	ATC, GTC	I,V 296

TABLE 2
Allele frequency and genotype data in groups

SNP ID	Genotype	Patient n (%)	Control n (%)	P Value
rs102469	**CC**	15 (34.1)	9 (23.7)	0.412
	CT	18 (40.9)	21 (55.3)	
	TT	11 (25.0)	8 (21.1)	
	Allele frequency			
	C	48 (54.5)	39 (51.3)	0.797
	T	40 (45.5)	37 (48.7)	
rs713598	**CC**	**10 (22.7)**	**9 (23.7)**	**0.105**
	CG	**12 (27.3)**	**18 (47.4)**	
	GG	**22 (50.0)**	**11 (28.9)**	
	Allele frequency			
	C	**32 (36.4)**	**36 (47.4)**	**0.205**
	G	**56 (63.7)**	**40 (52.6)**	
rs1726866	**AA**	11 (25.0)	8 (21.1)	0.727
	AG	17 (38.6)	18 (47.4)	
	GG	16 (36.4)	12 (31.6)	
	Allele frequency			
	A	39 (44.3)	34 (44.7)	0.917
	G	49 (55.7)	42 (55.3)	

functional and phenotypic diversity [23,24]. In this study, the PAV rate was 54.54%, the AVI rate was 32.95% and the rate of PAV/AVI presence was 20.5% in the patient group. In all individuals included in this study, the rate of presence of PAV was 53.05%, and the rate of AVI was 36.59%. There was no statistically significant relationship between haplotype and groups (p=0.3110). PAV/PAV was detected as 29.3% in all individuals, and PAV/AVI rate was 30.5%. When the pairwise ratio comparison was made between the groups, while the percentage of PAV/AVI presence was 20.5 in the patients, it was found as 42.1 in the control group, and the percentage of PAV/PVI presence was 2.6 in the patients and 18.2 in the control group, and a statistically significant difference was found between both rates ($p<0.05$) (Table 3).

DISCUSSION

To our knowledge, this is the first study with laryngeal cancer for the role of TAS2R38 in the literature. Bitter taste sensitivity, polymorphisms in the TAS2R38 gene and its association with many diseases, including alcoholism, obesity, COPD, asthma, coronary artery diseases, head and neck cancers, ovarian, prostate cancers and colon polyps, were investigated [25-27]. The underlying reason for its association with diseases is that the increased sensitivity to bitter taste, the change caused by preference and unwillingness, also affects dietary choices. The underlying reason for its association with diseases is that changes in preference and reluctance caused by the increased sensitivity to bitter taste also affect dietary choices. In addition, developing nutritional habits may affect the nutritional status later and increase the risk of long-term health and chronic diseases.

However, the interactions between taste and other dietary effects are complex, and the exact nature of the interactions cannot yet be fully explained [3]. It has been reported that individuals with increased sensitivity to bitter taste tend to avoid foods rich in antioxidants and nutrients with a bitter taste and maybe less healthy due to this. It is even assumed that the risk of many diseases, especially cardiovascular diseases, will increase, as there will be an increase in the consumption of sweet, fatty and low-nutritional foods instead of a bitter taste. It is also argued that those with very high sensitivity to bitter taste generally increase their taste acuity, which may cause a parallel decrease in sugar and fat intake. While the possible interactions between bitter taste and health remain complex, it is seen that non-

TABLE 3
Haplotype and diplotype distributions

		Control	Patient	Total
Haplotype				
PAV	n (%)	39 (51.32)	48 (54.54)	87 (53.05)
AVI	n (%)	31 (40.79)	29 (32.95)	60 (36.59)
AAV	n (%)	2 (2.63)	3 (3.41)	5 (3.04)
AVV	n (%)	1 (1.32)	--	1 (0.61)
PAI	n (%)	1 (1.32)	--	1 (0.61)
PVI	n (%)	2 (2.63)	8 (9.1)	10 (6.1)
	Total	76	88	164
Diplotype				
PAV/PAV	n (%)	10 (26.3)	14 (31.8)	24 (29.3)
AVI/AVI	n (%)	6 (15.8)	10 (22.7)	16 (19.5)
PAV/AVI*	**n (%)**	**16 (42.1)**	**9 (20.5)**	**25 (30.5)**
PAV/PVI*	**n (%)**	**1 (2.6)**	**8 (18.2)**	**9 (11.0)**
AAV/AVI	n (%)	1 (2.6)	0 (0.0)	1 (1.2)
AVI/AVV	n (%)	1 (2.6)	0 (0.0)	1 (1.2)
PAV/AAV	n (%)	1 (2.6)	3 (6.8)	4 (4.9)
PAV/PAI	n (%)	1 (2.6)	0 (0.0)	1 (1.2)
PVI/AVI	n (%)	1 (2.6)	0 (0.0)	1 (1.2)
	Total	38	44	82

*$p<0.05$

tasters who are less sensitive to bitter vegetables may consume more vegetables but also prefer more sweet and high-fat foods. Thus, the finding suggests that increased taste acuity can prevent excessive consumption in all food groups [27].

TAS2Rs are G protein-like receptors. GPCRs bind to taste receptors to which specific intracellular G proteins are coupled, and G α-gustducin is involved in sweet and bitter taste transduction. When stimulated with PROP or PTC, phosphodiesterase (PDE) is stimulated via the activated a-gustducin and cAMP is hydrolyzed. Decreased levels of cAMP may also raise intracellular Ca^{2+} and consequently promote neurotransmitter release. While this path is still uncertain, a second way is as follows. It activates the phospholipase C isoform β2 via the β and γ subunits of gustducin (described as Gβ3 and Gγ13). When inositol trisphosphate (IP3) is released, it binds to IP3 receptor type III and causes Ca^{2+} release. High Ca^{2+} levels activate transient receptor potential proteins (TRP) in the taste receptor and TRPM5, which is abundantly expressed in taste receptor cells involved in taste sensing. TAS2R38, which mediates taste responses of thioamides, including PTC and PROP, is the most extensively studied bitter receptor concerning both functional and epidemiological relationships [26].

In many diseases, the course of the disease can be completely different in patients with the same risk factors of the same age and same gender. In such cases, we encounter genetic differences. One of the genetic factors in diseases that develop in the upper respiratory tract is the bitter taste receptors. The ability to regulate congenital immunity, especially in the respiratory system, is increasingly dependent on bitter taste receptors, specifically TAS2R38 [28, 29]. When stimulated with known agonists of TAS2R38, such as PTC, low-level calcium responses occur in epithelial cells, which activate nitric oxide (NO) synthase and lead to strong intracellular NO production [30]. The effectiveness of this innate immune defense in the nasal and sinus mucosa differs due to the three most common polymorphisms in TAS2R38. Studies suggest that people affected by chronic rhinosinusitis are much less likely to have PAV/PAV homozygotes [31]. The expression of TAS2Rs in human airway smooth muscle (ASM) has recently been described. Stimulation with TAS2R agonists has been shown to cause relaxation of ASM. The dysfunction of ASM cells plays a crucial role in promoting the progression of diseases, such as asthma and COPD and contributing to the symptoms of these diseases [32].

In oncology, genetic factors come to the fore in following the course of the disease and the search for new treatments and new possibilities. Singh et al. examined the expression levels of TAS2Rs in high and low metastatic breast epithelial cells and non-cancerous cell lines. It is reported that the increase in expression levels may be functional because there is anincrease in intracellular calcium mobilization of bitter agonist kin after administration of dextromethorphan and phenylthiocarbamide. They found that the expression patterns of TAS2R 4 and TAS2R 14, in particular, were different in these cells, and there were decreased TAS2R4 levels and increased TAS2R14 levels in breast cancer clinical samples than non-cancerous controls. While activation of TAS2Rs with their relevant agonists causes physiological responses in metastatic breast cancer cells, it has been argued that this response is absent in non-

tumorigenic breast epithelial cells. The agonist activation of TAS2Rs induces anti-proliferative, pro-apoptotic, and anti-migration responses in highly metastatic breast cancer cells, and the signal network of the chemosensor TAS2R plays a role in inducing physiological responses in the metastatic breast cancer cell line [33].

In studies conducted in ovarian and prostate cancers, it has been reported that some TAS2R receptors are expressed in ovarian cancer and that the transcriptional regulation of these receptor genes differs in high-grade serous and low-grade serous ovarian cancer cell lines. It was found that the expression of TAS2R14 and TAS2R38 decreased in almost all ovarian cell lines, while TAS2R4 and TAS2R10 increased compared to control tissue samples. In prostate cancer cells, it was found that the expression of TAS2Rs, except TAS2R38, significantly reduced in PC3 cells [34].

The role of the TAS2R38 in pancreatic cancer has been studied in the literature. TAS2R38 has been reported to be expressed and localized in lipid droplets of tumor cells from pancreatic cancer patients and cell lines. Stimulation with N-acetyl-dodecanoyl homoserine and phenylthiourea leads to TAS2R38-mediated activation of key transcription factors. These results have shown the potential role of TAS2R38 in pancreatic cancer progression [35].

Yamaki et al. [36] conducted a genotyping study of TAS2R38 and TAS2R46 in hepato-pancreatic-biliary system cancers, with patients diagnosed with colorectal and gastric cancer. They reported that non-taster homozygotes (AVI/AVI) for TAS2R38 were more common in Japanese cancer patients, with cancer risk not associated with any TAS2R46 genotype. They reported that non-taster homozygotes (AVI/AVI) for TAS2R38 were more common in Japanese cancer patients, and cancer risk was not associated with any TAS2R46 genotype [36].

Some studies have hypothesized that individuals with the PAV/PAV diplotype may have a greater risk for cancer than the AVI/AVI group. However, some studies have also reported a trend towards an increased risk for colorectal cancer independent of dietary food intake in the AVI/AVI group and not in the PAV/PAV group. While the exact mechanism of this phenomenon has not yet been confirmed, it is attributed to the variable protein's less ability to neutralize and excrete potentially harmful chemicals from the gastrointestinal tract [37].

A49P, V262A, I296V and diplotypes were genotyped for determining the relationship between TAS2R38 polymorphism and gastric cancer and it was found that the AVI/AVI was not associated with consumption of food, alcohol or cigarettes, regardless of or dependent on gastric cancer phenotype, whereas the PAV/AVI diplotype significantly increased the risk of gastric cancer regardless of dietary intake. The TAS2R38 receptor encoded by the PAV/PAV variant is activated by bitter compounds containing only one thiourea moiety; the response to other bitter flavors is rather low. It has been reported that the TAS2R38 protein encoded by the AVI/AVI variant rarely responds to PTC and PROP, even to other bitter tastes as well as individuals with PAV/PAV. These data suggest that AVI carriers mediate a reaction to unknown bitter chemicals rather than impaired receptor activity. That is, both PAV/PAV and AVI/AVI can fully respond to each agonist and therefore have a greater ability to initiate protective mechanisms against potentially toxic chemicals in the gastrointestinal tract. However, the PAV/AVI heterozygous protein may be less active in detecting agonist molecules, resulting in longer exposure to carcinogenic chemicals. The findings suggest that TAS2R38 may be associated with stomach cancer risk in Koreans but that TAS2R38 diplotype does not affect dietary intake [38].

In the study involving laryngeal, hypopharyngeal, and pharyngeal tumor types, Tsutsumi et al. [39] examined the effects of chemotherapy and radiotherapy on the expression of the taste receptors in lingual mucosa samples. Although the bitter taste perception threshold remained unchanged, the lingual mRNA levels of TAS2R5 increased significantly after chemotherapy. In another study evaluating the differences in PTC response between the patient and healthy controls, genotyping has been performed for the TAS2R38 gene. It has been reported that there is no difference in genotype distribution and haplotype frequencies in healthy and patient groups; however, the frequency of subjects with the PAV/AVI diplotype in the patient cohort is lower than expected [40].

In this study, when evaluations were made in all of the included participants, similar to the studies conducted, the findings showed that 53.05% had PAV and 36.59% had AVI. While PAV was more common in the patient group, the frequency of AVI was similar in both groups. Although there was no significant difference between the groups due to the similarity in allele frequency and haplotype distribution in the groups, the frequency of heterozygous (PAV/AVI) individuals was lower in the patient group ($p<0.005$).

It has been determined that bitter taste receptors are in the mouth and in many tissues. Studies show that its stimuli and responses differ according to the tissue and cell it is located in. In particular, variations in TAS2R38 genes cause different responses even in diseases. Looking at the relationship between bitter taste and diseases, it is seen that different results are obtained due to reasons, such as geographical, population and race differences, whether nutrition is a risk for the disease. To our knowledge, these findings, which need to be confirmed in a larger population, are the first study for the role of TAS2R38 in laryngeal cancer. The data obtained through further studies, in which taste sensitivity test is added, can make a significant contribution to the literature.

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