Research Article

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Association of bitter and sweet taste gene receptor polymorphisms with dental caries formation

[Farklı Acı ve Tatlı Tat Gen Reseptör Polimorfizmlerinin Diş Çürüğü Oluşumu ile İlişkisi]

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Abstract

Objectives: The aim of the study is to analyze the association of different bitter and sweet gene receptor polymorphisms and bitter and sweet food consumption on formation of dental caries in Turkish adult population.

Methods: This study included 205 adults whose detailed intraoral health examination was completed and decayed, missing, filled teeth (DMFT) index values were recorded. A mini questionnaire was applied to assess the consumption of bitter and sweet food. A venous blood sample from each participant was collected in Ethylenediamine tetraacetic acid (EDTA) tubes. Further, DNA samples were isolated from the blood samples by utilizing a DNA isolation kit,

which were stored at +4 °C prior to the analysis. Taste receptor type 2 member 38 (*TAS2R38*; rs10246939, rs713598, rs1726866), Taste receptor type 1 member 2 (*TAS1R2*; rs35874116, rs9701796), and Taste receptor type 1 member 3 (*TAS1R3*; rs307355) gene polymorphisms were detected using real-time polymerase chain reaction (PCR).

Results: There was no statistically significant association between the *TAS2R38*, *TAS1R2*, and *TAS1R3* gene polymorphism and the DMFT index ($p>0.05$). No significant difference was found between the consumption of bitter and sweet food and the DMFT index ($p>0.05$).

Conclusions: *TAS2R38* (rs10246939, rs713598, rs1726866), *TAS1R2* (rs35874116, rs9701796), and *TAS1R3* (rs307355) gene polymorphism may not be associated with the formation of dental caries in the Turkish adult population.

Keywords: bitter taste; dental caries; gene polymorphisms; sweet taste; *TAS1R2*; *TAS1R3*; *TAS2R38*.

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Öz

Amaç: Bu çalışmanın amacı, farklı acı ve tatlı gen reseptör polimorfizmleri ile acı ve tatlı gıda tüketiminin diş çürüğü oluşumu üzerindeki ilişkisini değerlendirmektir.

Yöntem: Çalışmaya detaylı ağız-diş sağlığı muayenesi yapılmış ve çürük, eksik, dolgulu dişler (DMFT) indeksi değerleri not edilen 205 yetişkin dahil edildi. Acı ve tatlı yiyeceklerin tüketimini değerlendirmek için mini bir anket uygulandı. Katılımcılardan EDTA tüplerine venöz kan örneği alındı. DNA izolasyon kiti ile kan örneklerinden DNA örnekleri izole edildi ve analiz gününe kadar + 4 °C'de saklandı. Tip 2 tat reseptörü üye 38 (*TAS2R38*; rs10246939, rs713598, rs1726866), Tip 1 tat reseptörü üye 2 (*TAS1R2*; rs35874116, rs9701796) ve Tip 1 tat reseptörü üye

3 (*TAS1R3*; rs307355) gen polimorfizmleri Real-Time PCR kullanılarak tespit edildi.

Bulgular: *TAS2R38*, *TAS1R2* ve *TAS1R3* gen polimorfizmi ile DMFT indeksi arasında istatistiksel olarak anlamlı bir ilişki yoktu ($p>0.05$). Acı ve tatlı gıda tüketimi ile DMFT indeksi arasında anlamlı bir fark bulunmadı ($p>0.05$).

Sonuç: *TAS2R38* (rs10246939, rs713598, rs1726866), *TAS1R2* (rs35874116, rs9701796) ve *TAS1R3* (rs307355) gen polimorfizmleri, Türk yetişkin popülasyonunda diş çürüğü oluşumu ile ilişkili olmayabilir.

Anahtar Kelimeler: acı tat; diş çürüğü; gen polimorfizmleri; tatlı tat; *TAS1R2*; *TAS1R3*; *TAS2R38*.

Introduction

Complex environmental and numerous genetic factors are known to influence the occurrence and progression of dental caries [1]. The importance of genetic factors in the formation of caries is supported by twin studies. It is estimated that 40–60% of caries susceptibility is genetically determined [1–6]. Animal studies also strongly support the genetic contribution to the risk of developing caries [7–10]. Studies have demonstrated the importance of dietary habits, nutritional status, and chemically determined taste sensitivity in determining this risk [1, 4].

Studies in the last 15 years have allowed for the identification of proteins that act as taste receptors. There are five basic tastes that are consciously perceived as sweet, sour, salty, bitter, and umami [11].

Human sweet taste perception is mediated by the heterodimeric G-protein coupled receptor complex encoded by the *TAS1R2* (taste receptor, type-1, member 2) and *TAS1R3* (taste receptor, type-1, member 3) genes [1, 7, 12–15]. The *TAS1R* gene family is mainly effective in sweet taste perception sensitization. *TAS1R* gene subunits are located on chromosome 1 as *TAS1R1*, *TAS1R2*, and *TAS1R3* [7, 12]. The perception of bitter taste appears to be largely mediated by the *TAS2R38* gene [13–15]. The *TAS2R38* gene located on chromosome 7q36 is a member of the bitter unpleasant and pleasant sensations from alcohol [15]. All these three genes are of the protein coding kind and

among their related pathways are taste transduction and peptide ligand-binding receptors [16]. Detailed information on taste receptor gene polymorphisms that were analyzed in this study has been outlined in Table 1.

Sugar intake was found to be associated with sweet taste receptor (*TAS1R2*) alleles in humans [17]. In addition, the genetic variation of the bitter taste receptor *TAS2R38* is found to be associated with the intake of vegetables, fat, and sweets [17], as dietary habits, nutritional status, and chemically determined taste sensitivity has been associated with the risk of caries [1, 4]. The different polymorphisms of *TAS1R2*, *TAS2R38*, and *TAS1R3* and their possible associations with dental caries have been evaluated in the literature [18–20].

In the literature, there are few studies that have profoundly covered the association of taste genes and dental caries formation across different age ranges: *TAS1R2* (ages 7–12) [7]; (ages 21–32) [21]; *TAS1R2*, *TAS2R38*, *GNAT3* (guanine nucleotide binding protein, alpha transducing-3) (ages 1–42) [1]; *CA6*, *TAS1R1*, *TAS1R3*, *TLR2*, and *TLR4* (ages 25–55) [19]; *AMELX*, *CA6*, *DEFB1*, and *TAS2R38* (ages 20–60) [20]; *TAS1R2* and *GLUT2* (glucose transporter genes) (ages 18–65) [22]; *TAS1R2* and *GLUT2* (ages 11–13) [23]; and *TAS1R1*, *TAS1R2*, *TAS1R3*, *TAS2R16*, *TAS2R38*, *TAS2R50*, *SLC2A2*, *SLC2A4*, *GNAT3*, *SCN1B*, and *TRPV1* (ages 18–23) [24].

There is no study in the literature that has evaluated the association between dental caries formation with three taste genes simultaneously in the Turkish population: a bitter gene with three polymorphisms (*TAS2R38* (rs10246939, rs713598, rs1726866)) and two sweet taste genes with three polymorphisms (*TAS1R2* (rs35874116, rs9701796) and *TAS1R3* (rs307355)). In this study, we aim to investigate the possible effect of bitter and sweet food consumption and different bitter and sweet gene receptor polymorphisms on the formation of dental caries.

Materials and methods

The study protocol was approved by the local Ethical Committee of Mersin University (date: 13/04/2017; number: 102), and the written informed consent was obtained from all participants prior to data collection.

This study included 205 adults (18–45 years old; 91 men, 114 women), who attended the Faculty of Dentistry clinic at Mersin

Table 1: Detailed information on the taste receptor gene polymorphisms.

Gene		Position	SO term	Alleles	MAF*
TAS1R2	rs35874116	chr1:18854899 (GRCh38.p13)	Missense variant	T>C	C=0.319942
	rs9701796	chr1:18859635 (GRCh38.p13)	Missense variant	G>C	C=0.780938
TAS1R3	rs307355	chr1:1329774 (GRCh38.p12)	2 KB upstream variant	T>C	C=0.86580
TAS2R38	rs713598	chr7:141973545 (GRCh38.p13)	Missense variant	C>G	G=0.422175
	rs10246939	chr7:141972804 (GRCh38.p13)	Missense variant	T>C	C=0.464881
	rs1726866	chr7:141972905 (GRCh38.p13)	Missense variant	G>A	A=0.528597

*Global minor allele frequency data from dbSNP.

University for a routine dental examination. Clinical observations were made by two experienced dentists who had no knowledge of the individuals' genotype. The patients were subjected to a detailed intraoral examination, and their decayed, missing and filled teeth (DMFT) scores were recorded after their teeth cleaning were performed with a brush and low abrasive polishing paste.

The DMFT index is used in accordance with the World Health Organization's tooth decay evaluation criteria, and it evaluates the oral dental health of the population. It is used for permanent teeth. Further, a similar index used for primary teeth is expressed in small letters and referred to as the dmft index. The sample was surveyed through this mini questionnaire regarding their bitter or sweet taste preferences at the same appointment:

- (1) If you consider your food consumption, which one do you prefer—bitter or sweet?
- (2) When you are hungry, which food do you prefer to consume—bitter or sweet?
- (3) If you consider your family's food consumption, which one do you prefer—bitter or sweet?

Venous blood samples from each participant were drawn into EDTA tubes in the Medical Biochemistry Department. Furthermore, DNA samples were isolated from blood samples using a DNA isolation kit (Roche Diagnostics, GmbH, Germany), which were stored at +4 °C prior to the analysis. *TAS2R38* (rs10246939, rs713598, rs1726866), *TAS1R2* (rs35874116, rs9701796), and *TAS1R3* (rs307355) gene polymorphisms were detected using real-time polymerase chain reaction (PCR) (LightCycler® 480 Instrument II – Diagnostics Roche GmbH, Germany) with a single nucleotide polymorphisms detection kit.

The inclusion and exclusion criteria for patient selection

This study included individuals aged between 18 and 45 years who visited Mersin University for a routine dental examination. Patients with general health problems such as anemia, diabetes mellitus, or any heart diseases; patients with amelogenesis imperfecta and dentinogenesis imperfecta; patients who do not have tooth brushing habits (those who brush less than twice a day); and patients with obesity were excluded from the study group.

Statistical analysis

Descriptive analyses were summarized as the mean $\pm$ standard deviation (SD). Additionally, categorical variables were summarized as counts and percentages. The chi-square test was used for categorical endpoints. An exact test was used when the probability of an expected count less than five was more than 25%. The Hardy-Weinberg equilibrium (HWE) of groups on account of genotypes was checked by the chi-square test and the frequencies of polymorphism were in HWE ($p > 0.05$). A p -value of less than 0.05 was considered statistically significant.

Results

The DMFT index values of 205 adults (aged 18–45 years (mean age 31.36 ± 8.25); 91 men, 114 women) were evaluated in the permanent dentition.

The basic description of participants is shown in Table 2. The education level of the samples is as follows: 47 participants (23%) had completed primary level, 79 of them (39.1%) secondary, and 76 of them (37.6%) graduate. The income level of the participants can be outlined as follows: 81 participants (39.5%) earn less than the minimum wage, 108 of them (52.7%) earn minimum wage, and 16 of them (7.8%) earn more than the minimum wage. There was no significant difference between the samples' basic description. When the relationship between education or income and dental caries risk was analyzed, no statistically significant association was found.

In addition, according to the data obtained from the questionnaire completed by the participants, no significant association was found between the consumption of bitter and sweet food and DMFT index values ($p > 0.05$).

Moreover, the taste gene receptor polymorphisms and DMFT index values were compared, and no statistically significant association was found between the individuals with *TAS2R38*, *TAS1R2*, and *TAS1R3* gene polymorphisms and the DMFT index values ($p > 0.05$) (Table 2).

The distribution of the major–minor allele in the population at stake is displayed in Table 3 and minor allele distribution is seen as *TAS1R2* (rs35874116) C 31.5%, *TAS1R2* (rs9701796) G 20%, *TAS1R3* (rs307355) C 88.05%, *TAS2R38* (rs713598) G 48.29%, *TAS2R38* (rs10246939) C 52.68%, *TAS2R38* (rs1726866) A 47.56%.

Table 2: Basic description of participants.

	n	%
Age, mean $\pm$ standard deviation, years	31.36 $\pm$ 8.25	
Sex		
Male	91	44.4
Female	114	55.6
Education		
Primary	47	23.3
Secondary	79	39.1
Licentiate	76	37.6
Income		
<minimum wage	81	39.5
=minimum wage	108	52.7
>minimum wage	16	7.8
If you consider your food consumption, which one do you prefer, bitter or sweet?		
Equal	73	35.6
Bitter	60	29.3
Sweet	72	35.1
When you are hungry which food do you prefer to consume, bitter or sweet?		
Bitter	43	21.0
Sweet	75	36.6
Not matter	87	42.4
If you consider your family's food consumption, which one do you prefer, bitter or sweet?		
Equal	86	42.0
Bitter	61	29.8
Sweet	58	28.3

Table 3: Association of taste gene receptor polymorphisms and caries risk groups within DMFT values and allele distribution.

		DMFT			p-Value
		Low risk (0–3) n, %	Moderate risk (4–7) n, %	High risk (>8) n, %	
TAS1R3 (rs307355)	CC	43 (26.7%)	56 (34.8%)	62 (38.5%)	0.548
	CT	9 (23.1%)	13 (33.3%)	17 (43.6%)	
	TT	2 (40.0%)	0 (0.0%)	3 (60.0%)	
	Total	54 (100.0%)	69 (100.0%)	82 (100%)	
	C	95 (87.9%)	125 (90.6%)	141 (85.9%)	
	T	13 (12.1%)	13 (9.4%)	23 (14.1%)	
TAS1R2 (rs35874116)	CC	2 (9.1%)	11 (50.0%)	9 (40.9%)	0.055
	CT	20 (24.7%)	32 (39.5%)	29 (35.8%)	
	TT	31 (31.0%)	25 (25.0%)	44 (44.0%)	
	Total	53 (100.0%)	68 (100.0%)	82 (100.0%)	
	C	24 (22.6%)	54 (39.7%)	47 (28.6%)	
	T	82 (77.4%)	82 (60.3%)	117 (71.3%)	
TAS1R2 (rs9701796)	CC	36 (27.5%)	44 (33.6%)	51 (38.9%)	0.986
	CG	16 (24.2%)	22 (33.3%)	28 (42.4%)	
	GG	2 (25.0%)	3 (37.5%)	3 (37.5%)	
	Total	54 (100.0%)	69 (100.0%)	72 (100.0%)	
	C	88 (81.4%)	110 (79.7%)	130 (79.3%)	
	G	20 (18.6%)	28 (20.3%)	34 (20.7%)	
TAS2R38 (rs713598)	CC	15 (27.8%)	15 (27.8%)	24 (44.4%)	0.661
	CG	28 (26.9%)	39 (37.5%)	37 (35.6%)	
	GG	11 (23.9%)	14 (30.4%)	21 (45.7%)	
	Total	54 (100.0%)	68 (100.0%)	82 (100.0%)	
	C	58 (53.7%)	69 (50.7%)	85 (51.8%)	
	G	50 (46.3%)	67 (49.3%)	79 (48.2%)	
TAS2R38 (rs10246939)	CC	14 (25.9%)	17 (31.5%)	23 (42.6%)	0.987
	CT	29 (26.9%)	38 (35.2%)	41 (38.0%)	
	TT	11 (26.2%)	14 (33.3%)	17 (40.5%)	
	Total	54 (100.0%)	69 (100.0%)	81 (100.0%)	
	C	57 (52.7%)	72 (52.2%)	87 (53.7%)	
	T	51 (47.3%)	66 (47.8%)	75 (46.3%)	
TAS2R38 (rs1726866)	AA	11 (25.6%)	14 (32.6%)	18 (41.9%)	0.879
	AG	29 (27.1%)	39 (36.4%)	39 (36.4%)	
	GG	14 (25.9%)	16 (29.6%)	24 (44.4%)	
	Total	54 (100.0%)	69 (100.0%)	81 (100.0%)	
	A	51 (47.2%)	67 (48.5%)	75 (46.3%)	
	G	57 (52.8%)	71 (51.4%)	87 (53.7%)	

The chi-square test was used for categorical endpoints. An exact test was used when the probability of an expected count less than five was more than 25%. Hardy-Weinberg equilibrium (HWE) of groups on account of genotypes was checked by chi-square test and the frequencies of polymorphism were in HWE ($p > 0.05$).

Discussion

Dental caries is a complex disease that is related to dietary habits, taste sensitivity, genetic factors, and teeth brushing habits [1–4, 25]. The evaluated literature states that 40–60% cases of dental caries are affected by genetic factors [1–6].

Evaluations of the relationships of dental caries, varying ages and genetic polymorphisms in different genes, such as *TAS1R1*, *TAS1R2*, *TAS1R3*, *TAS2R16*, *TAS2R8*, *CA6*, *TLR2*, *TLR4*, *TAS2R50*, *AMELX*, *DEFB*, *SLC2A2*, *SLC2A4*, *GNAT3*, *SCN1B*, *TRPV1*, and *GLUT2*, have been analyzed in various studies [1, 7, 19–24].

This study is the first to evaluate the relationship between dental caries formation and both *TAS1R2* and *TAS1R3* sweet taste genes and the *TAS2R38* bitter taste gene with six polymorphisms and food consumption in a sample group of the Turkish adult population.

The perception of sweet, umami, and bitter tastes is mediated via G-coupled protein receptors encoded by the *TAS1R1* and *TAS1R2* taste receptor gene families. The area of bitterness sensitivity is the most extensively researched of all taste qualities. The bitter compounds phenylthiocarbamide (PTC) and propylthiouracil (PROP) were first noted in the early 1930s. The *TAS2R38* gene was found to be responsible for the majority of the variation in bitter taste sensitivity [25] and included the study with three polymorphisms.

The sweet taste was found to be mediated by two genes, *TAS1R3* [25] and *TAS1R2* [25, 26]. The *TAS2R38* bitter taste gene has three common SNPs (rs10246939, rs713598, rs17268663), and all of them were included in the study plan. Further, *TAS1R2* (rs35874116, rs9701796) and *TAS1R3* (rs307355) gene polymorphisms were selected, similar to Haznedaroğlu et al.'s study, which evaluated the same population with different age groups [7].

There is no analysis encountered in the literature that has explored allele and minor allele distribution gene polymorphisms in the Turkish population but the frequency of global minor allele distribution has been known (Table 1). When the minor allele distribution frequency of this study and frequency of global minor allele distribution were evaluated together, our findings appeared to be similar to the *TAS1R2* (rs35874116) C allele, *TAS1R3* (rs307355) C allele, and all polymorphisms that have been explored of *TAS2R38* gene (rs713598 G allele, rs10246939 C allele, rs1726866 A allele); yet, they are lower than the *TAS1R2* (rs9701796) C allele.

In the literature, there is no caries risk classification for adults that performs its evaluation with DMFT caries scores. On the contrary, with reference to children, there is caries risk group classification with DMFT/dmft scores [7]. In the studies that investigate adults, the results were analyzed among gene polymorphisms by median and standard deviation [21, 22]. We analyzed the results of both DMFT caries risk groups and median–standard deviation and found no significant results again (data not shown).

In a family study, Wendell et al. evaluated the relationship between *TAS2R38* (rs10246939, rs713598, rs17268663) as a bitter taste gene and *TAS1R2* (rs4920566, rs9701796) as a sweet taste gene in caries formation. No statistically significant results were found between

the DMFT index values of the *TAS2R38* (rs10246939, rs713598, rs17268663) and *TAS1R2* (rs9701796) genes in the permanent dentition group, although a statistically significant difference was found in the mixed dentition group [1]. Our study, on the other hand, was different from this study as it included the evaluation of *TAS1R2* (rs35874116) and *TAS1R3* (rs307355) polymorphisms. This is also true since the *TAS1R2* (rs4920566) polymorphism was not included in our study design. However, in permanent dentition, our results and Wendell et al.'s results were similar with regard to the *TAS2R38* (rs10246939, rs713598, rs17268663) and *TAS1R2* (rs9701796) gene polymorphisms.

Haznedaroğlu et al. found no correlation between the DMFT index and *TAS1R2* (rs35874116, rs9701796) and *TAS1R3* (rs307355) gene polymorphisms in permanent dentition but found significant results between *TAS1R2* (rs35874116) when compared with DMFT + dmft in mixed dentition and, in different age groups, in C/C in the high caries risk group [7]. This data is similar to our study results within the same population in permanent dentition. In addition, Holla et al. showed that the same polymorphism in *TAS1R2* (rs35874116) was associated with the risk of dental caries formation, defined as DMFT scores ≥ 4 in permanent dentition (11–13 years) with children in their study, which evaluated the *TAS1R2* gene (rs35874116) and the *GLUT2* gene [23]. The study conducted by Kulkanie et al. reported a direct effect of *TAS1R2* (rs35874116) and *GLUT2* taste genes on caries formation in adults. Kulkanie's results were different from those of Haznedaroğlu et al. and Holla et al., which showed the lowest caries scores in the *TAS1R2* (rs35874116) group and our study as finding *TAS1R2* (rs35874116) ineffective on caries formation [21]. In another study, Robino et al. evaluated the relationship between *TAS1R2* (rs3935570) and *GLUT2* in dental caries formation. They found that both *TAS1R2* and *GLUT2* were associated with dental caries risk or protection in adults [22].

In addition, no significant difference was found between the consumption of bitter and sweet food and DMFT index values ($p > 0.05$) in this study. In the literature, another study evaluated bitter and sweet food preferences or intake and dental caries formation and similarly found no correlation with caries status and bitter and sweet food intake. However, it has also been reported that allelic variations in the *GNAT3*, *SLC2A2*, *SLC2A4*, *TAS1R1*, and *TAS1R2* genes are associated with caries status [24].

In conclusion, we found that *TAS2R38* (rs10246939, rs713598, rs17268663), *TAS1R2* (rs9701796) and *TAS1R3*

(rs307355) gene polymorphisms have no effect on dental caries formation and bitter and sweet food consumption in the Turkish population.

It is known that candidate gene association studies have undergone various setbacks including false positives and poor control of population stratification [27]. Thus, the sample size was determined by power analysis where more participants were included in the study to overcome such a setback. The reasons for finding no association among polymorphisms as an outcome of the study might stem from the fact that this analysis was previously planned as a preliminary population study. It, thus, failed to impose control on all segments of the population, just like all genome-wide association studies (GWAS). Other reasons could be related with the fact that there is a lack of equal sampling on dental caries risk groups and that the patients involved have lower DMFT scores.

The results of this study show similarities and differences in the literature regarding the polymorphic changes by geographical region. The aim of this research was to investigate the taste receptors that have not been investigated in the Turkish population previously as a preliminary study. In the future, we aim to contribute to the literature with studies of different caries risk groups and different taste gene receptors and a more detailed analysis of the taste pathway mechanisms in relation with smoking and alcohol consumption.

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References

- Wendell S, Wang X, Brown M, Cooper M, DeSensi RS, Weyant RJ, et al. Taste genes associated with dental caries. *J Dent Res* 2010; 89:1198–202.
- Boraas JC, Messer LB, Till MJ. A genetic contribution to dental caries, occlusion, and morphology as demonstrated by twins reared apart. *J Dent Res* 1988;67:1150–5.
- Conry JP, Messer LB, Boraas JC, Aeppli DP, Bouchard TJ Jr. Dental caries and treatment characteristics in human twins reared apart. *Arch Oral Biol* 1993;38:937–43.
- Bretz WA, Corby PM, Melo MR, Coelho MQ, Costa SM, Robinson M, et al. Heritability estimates for dental caries and sucrose sweetness preference. *Arch Oral Biol* 2006;51:1156–60.
- Bretz WA, Corby PM, Schork NJ, Robinson MT, Coelho M, Costa S, et al. Longitudinal analysis of heritability for dental caries traits. *J Dent Res* 2005;84:1047–51.
- Wang X, Shaffer JR, Weyant RJ, Cuenco KT, DeSensi RS, Crout R, et al. Genes and their effects on dental caries may differ between primary and permanent dentitions. *Caries Res* 2010;44:277–84.
- Haznedaroğlu E, Koldemir-Gündüz M, Bakır-Coşkun N, Bozkuş HM, Çağatay P, Süsleyici-Duman B, et al. Association of sweet taste receptor gene polymorphisms with dental caries experience in school children. *Caries Res* 2015;49:275–81.
- Liu H, Deng H, Cao CF, Ono H. Genetic analysis of dental traits in 82 pairs of female-female twins. *Chin J Dent Res* 1998;1:12–6.
- Shuler CF. Inherited risks for susceptibility to dental caries. *J Dent Educ* 2001;65:1038–45.
- Nariyama M, Shimizu K, Uematsu T, Maeda T. Identification of chromosomes associated with dental caries susceptibility using quantitative trait locus analysis in mice. *Caries Res* 2004;38: 79–84.
- San Gabriel AM. Taste receptors in the gastrointestinal system. *Flavour* 2015;4:14.
- Kim UK, Wooding S, Riaz N, Jorde LB, Drayna D. Variation in the human TAS1R taste receptor genes. *Chem Senses* 2006;31: 599–611.
- Opal S, Garg S, Jain J, Walia I. Genetic factors affecting dental caries risk. *Aust Dent J* 2015;60:2–11.
- Fushan AA, Simons CT, Slack JP, Manichaikul A, Drayna D. Allelic polymorphism within the TAS1R3 promoter is associated with human taste sensitivity to sucrose. *Curr Biol* 2009;19:1288–93.
- Duffy VB, Davidson AC, Kidd JR, Kidd KK, Speed WC, Pakstis AJ, et al. Bitter receptor gene (TAS2R38), 6-n-propylthiouracil (PROP) bitterness and alcohol intake. *Alcohol Clin Exp Res* 2004;28: 1629–37.
- Alelyani AA, Azar PS, Khan AA, Chrepa V, Diogenes A. Quantitative assessment of mechanical allodynia and central sensitization in endodontic patients. *J Endod* 2020;46:1841–8.
- Han P, Keast R, Roura E. TAS1R1 and TAS1R3 polymorphisms relate to energy and protein-rich food choices from a buffet meal respectively. *Nutrients* 2018;10:1906.
- Chisini LA, Cademartori MG, Conde MCM, Costa FDS, Salvi LC, Tovo-Rodrigues L, et al. Single nucleotide polymorphisms of taste genes and caries: a systematic review and meta-analysis. *Acta Odontol Scand* 2021;79:147–55.
- Yıldız Telatar G, Saydam F, Güzel Aİ, Telatar BC. Variants in taste genes on caries risk and caries activity status. *Med Mol Morphol* 2020;53:244–51.
- Yıldız G, Ermis RB, Calapoglu NS, Celik EU, Türel GY. Gene-environment interactions in the etiology of dental caries. *J Dent Res* 2016;95:74–9.
- Kulkarni GV, Chng T, Eny KM, Nielsen D, Wessman C, El-Sohemy A. Association of GLUT2 and TAS1R2 genotypes with risk for dental caries. *Caries Res* 2013;47:219–25.
- Robino A, Bevilacqua L, Pirastu N, Situlin R, Di Lenarda R, Gasparini P, et al. Polymorphisms in sweet taste genes (TAS1R2 and GLUT2), sweet liking, and dental caries prevalence in an adult Italian population. *Genes Nutr* 2015;10:485.
- Izakovicova Holla L, Borilova Linhartova P, Lucanova S, Kastovsky J, Musilova K, Bartosova M, et al. GLUT2 and TAS1R2 polymorphisms and susceptibility to dental caries. *Caries Res* 2015;49:417–24.

24. Eriksson L, Esberg A, Haworth S, Holgerson PL, Johansson I. Allelic variation in taste genes is associated with taste and diet preferences and dental caries. *Nutrients* 2019; 11:1491.
25. Feeney E, O'Brien S, Scannell A, Markey A, Gibney ER. Genetic variation in taste perception: does it have a role in healthy eating? *Proc Nutr Soc* 2011;70:135–43.
26. Eny KM, Wolever TM, Fontaine-Bisson B, El-Sohemy A. Genetic variant in the glucose transporter type 2 is associated with higher intakes of sugars in two distinct populations. *Physiol Genom* 2008;33:355–60.
27. Duncan LE, Ostacher M, Ballon J. How genome-wide association studies (GWAS) made traditional candidate gene studies obsolete. *Neuropsychopharmacology* 2019;44:1518–23.