ACTA ODONTOLOGICA SCANDINAVICA
2021, VOL. 79, NO. 2, 147–155
https://doi.org/10.1080/00016357.2020.1832253

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REVIEW ARTICLE

Single nucleotide polymorphisms of taste genes and caries: a systematic review and meta-analysis

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ABSTRACT

Objective: The aim of the present study was to systematically review the literature investigating the single nucleotide polymorphisms (SNP) related to taste genes and their influence on caries.

Material and methods: Search was performed in five databases to respond to the question: 'Are the polymorphisms of taste genes associated with dental caries?'. Studies in humans were included. Assessment of quality of studies, meta-analysis and sensitivity analysis were performed.

Results: Seven studies were included in the systematic review and two in meta-analysis. Most of studies (71.4%) presented cohort design with low-level of evidence. A total of 4,032 individuals were evaluated. Four different taste genes (*TAS1R2, TAS2R38, TAS1R3* and *GLUT2*) and 12 SNPs were reported. Most SNPs of taste genes showed a protective effect of the minor allele against dental caries. Meta-analysis included the SNP rs713598 placed in the *TAS2R38* gene. The results suggest an effect of the heterozygote genotype (CG), which was associate with low caries experience (OR = 0.35 CI95% [0.17–0.75]). However, the genotype GG was not associated (OR = 0.17 CI95% [0.03–1.04]). Sensitivity analysis showed an important influence of one study in the results.

Conclusions: SNP of taste genes seems to be associated with caries experience. Causal inferences should be interpreted with caution and the results must be replicated in different populations.

ARTICLE HISTORY
Received 17 March 2020
Revised 22 September 2020
Accepted 28 September 2020

KEYWORDS
Polymorphisms; dental caries; taste genes; single nucleotide polymorphism

Introduction

Dental caries is one of the most common chronic diseases, affecting the population of all ages worldwide [1,2]. It is the main cause of the need for dental treatments as well as the main reason for treatment failures in both primary [3] and permanent dentition [4]. When the disease is not treated, caries lesions can lead to numerous complications, from pain and abscess, progressing to swelling and orofacial cellulitis, which can be life-threatening to the individual [1].

Dental caries is a complex disease strongly linked to biological, socioeconomic, behavioural and cultural components. In this way, treatments not addressing this multifactorial and amplified approach tend to fail [5–7]. Biological components are mainly linked with low hygiene habits, low exposure to fluoride and high consumption of fermentable carbohydrates [5,6]. In this way, some studies have directed efforts to understand possible factors that may influence dietary preferences among individuals [8,9]. They have indicated a biological plausibility to a predisposition of genetic and non-genetic eating behaviours, which determine a different taste perception for each individual [10–12]. Authors suggest the existence of some taste genes that influence the gustative perception as well as some factors (such as life stage, physical activity, and gum microbiota) which can co-exist for the determination of gustatory perception.

In this way, single nucleotide polymorphisms (SNPs) presented in taste genes seem to modify the taste sensitivity influencing the preference and choice for sweet foods, leading individuals to present a higher sweet food intake [8,9]. Consequently, these individuals could present an increased risk for several diseases, including obesity and dental caries. Changes in the perception of sugar gustatory sensitivity have been associated with genetic variations influencing dental caries susceptibility [13–15].

Therefore, the better comprehension of the genetic contributions in gustatory perception may be valuable information to help to personalize and amplify the strategies to prevent dental caries and other sugar-related diseases. In this way, the aim of the present study was to systematically review the literature investigating the SNPs related to taste genes and their influence on dental caries experience.

Methods

This study was registered in PROSPERO (International Prospective Register of Systematic Reviews) under protocol

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number CRD42019121484. This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [16].

Review question and searches

A structured search was performed in five databases (Pubmed/Medline, Scopus, Web of Science, BIREME – BVS Virtual health library and Scielo) up to January of 2019. Keywords were selected based on the research question, which was structured following PICO model [17]: 'Are the polymorphism of taste genes associated with dental caries?'

- Participants/population: adults and children
- Intervention/exposure: the effect allele in this study was standardized as the minor allele reported in the studies. When the minor allele frequency varied across the studies, the effect allele was referred to as the minor allele in most studies. Likewise, to do the estimates stratifying by genotypes, we opted for choosing the minor homozygote and heterozygotes as effect genotypes.
- Comparator/control: the effect allele was compared to reference allele, defined as that most frequent in the population. To perform genotype analysis, the major homozygote was chosen as the reference.
- Outcome: Dental caries experience. Dental caries was the main outcome of this review, which was considered by the following criteria: International Caries Detection and Assessment System (ICDAS) or DMF/dmf (Decayed, Missing, Filled) teeth/surface. It was preferentially considered groups caries-free versus caries experience. When more than one criteria to investigate dental caries was displayed, DMFT/dmft $= 0$ (caries-free) versus DMFT/dmft ≥ 1 was chosen.

Relevant MeSH terms were considered, even as the relevant entry terms. The complete structure of the search strategy is described in Table S1. All the retrieved records were uploaded into the EndNote™ software (Thomson Reuters, Rochester, New York, NY). Thus, a virtual library was built. Duplicated records were excluded by software. Two independent reviewers (LAC and MCMC) read all reports titles and abstracts, under the following criteria:

a. Inclusion criteria: comprised articles that aim to evaluate the association between genetic taste genes and dental caries in children or adults. Only human studies with cross-sectional, longitudinal and case–control design were included. No restrictions on language or publication period were considered.
b. Exclusion criteria: literature reviews, case reports and case series, abstracts of conferences, letters to the editor as well as qualitative studies were excluded from the present study.

The same reviewers (LAC and MCMC) read the full-text and judged the papers. If any disagreement was found, the reviewers attempted to reach a consensus through discussions. Persistent disagreements were resolved by a third reviewer (MBC), which take the final decision. Grey literature was manually investigated using (Dental caries AND Polymorphism) as keywords in the annals of International Association for Dental Research (IADR) and Researchgate (http://researchgate.net/).

Data collection

Full data extraction was independently executed by both reviewers (LAC and MCMC) in a previously tested and predefined database. The following data were extracted: author, year, country, study design, sample, age, ethnicity of the sample (% for each ethnic group), percentage of both genders sexes of the sample, calculation of statistical power, evaluation and categorization of dental caries, analytical approach, data analysis (crude and adjusted analysis values and their respective 95% confidence intervals [CI]), covariables and main results. Disagreements between the collected data were checked.

Quality of studies

Two instruments were used to assess the quality of studies: first, we used the Appraisal Checklist for Observational Studies (Joanna Briggs Institute) [18]. This tool presents 10 questions assessing different arguments in the study, which must be answered with three possibilities as follows: 'No', 'not clear' or 'Yes'. Each 'Yes' answer corresponds to one point, therefore the tool score can range from 0 to 10. Studies scored between 0 and 3 were considered of low quality; 4–6 were of medium quality; and 7–10 were considered of high quality. To score the studies, two reviewers (LAC and MCMC) performed the evaluation independently. Disagreements were remedied through discussion until consensus was reached. The second instrument was adapted to a 10-point scoring (control group, Hardy–Weinberg equilibrium, case group, primer, reproducibility, blinding, power calculation, Statistics, corrected statistics, independent replication) from a sheet previously used [19,20] in genetic studies. This tool presents two different criteria, ranging from 0 to 10 points (Yes $= 1$) or (no/undetermined $= 0$). The same reviewers performed independently the evaluation. Quality of studies are classified as low quality (up to four points), medium quality (5–7 points) and high quality (more than 7 points).

Strategy for data synthesis

A meta-analysis was adopted to pooling the polymorphisms. Due to the low number of polymorphisms, it was not possible to perform analysis pooling the polymorphisms by respective genes. Only SNPs presented in at least two different studies/populations were considered in meta-analysis. Besides, meta-analysis was performed by genotypic (homozygote and heterozygote). Alle analysis was not performed because alle results were not presented in studies included

in meta-analysis. To perform the analysis, we calculated the estimates for the effect of heterozygote and homozygote genotypes pooling by polymorphism. In studies presenting more than one category for dental caries, we chose the DMF/dmf = 0 versus DMF/dmf ≥ 1.

To avoid inconsistencies in data analysis, we performed the data harmonization for palindromic SNPs. When the palindromic SNP was present in two different studies, we only kept the SNP in the analysis if the study reported the DNA strand. If this information was missing in the papers, the SNP was excluded from further analysis.

The results of the adjusted models were preferably included. In cases where the adjusted results were not reported, the unadjusted estimates were considered or calculated. In cases where results were only showed by stratified analysis, we included the group with the highest number of individuals. Odds ratio (OR) was used to measure effect size with 95% confidence interval. The prevalence ratio measures were converted to OR using the formula proposed by Zhang and Yu: PR = odds ratio/1− risk0 + risk0 × odds ratio, where risk0 is the prevalence of the disease among non-exposed individuals [21,22]. When high heterogeneity (I^2 statistic >50%) was observed, random models were performed while when heterogeneity was less than 50%, analysis was performed with fixed models. Moreover, to assess the effect of each study on the pooled estimate, a sensitivity analysis was used. Analyzes were performed using Stata 12.0 software (StataCorp, College Station, TX).

Results

Study selection

The search resulted in 1200 initial records, which 985 remained after the removal of duplicated papers. After the evaluation of abstracts, 10 papers were selected to full-text assessment, from which seven were included in the systematic review [15,23–28] and two in the meta-analysis [26,28]. Three studies were excluded in full-text evaluation [8,29,30]. The reasons for exclusion are justified in the flowchart of Figure 1.

Study characteristics

From the 7 included studies, 71.4% ($n = 5$) presented cohort design and 28.6% were case–control studies ($n = 2$). These studies were carried out mainly in Turkey (28.6%) [23,28] and North America (28.6%) [15,27]. Other studies were performed in the Czech Republic [24], Italy [25] and Japan [26]. Most of the studies (57.1%) included only Caucasian individuals while others have not reported the ethnicity of the investigated population. All Studies used DMF/dmf to assess dental caries

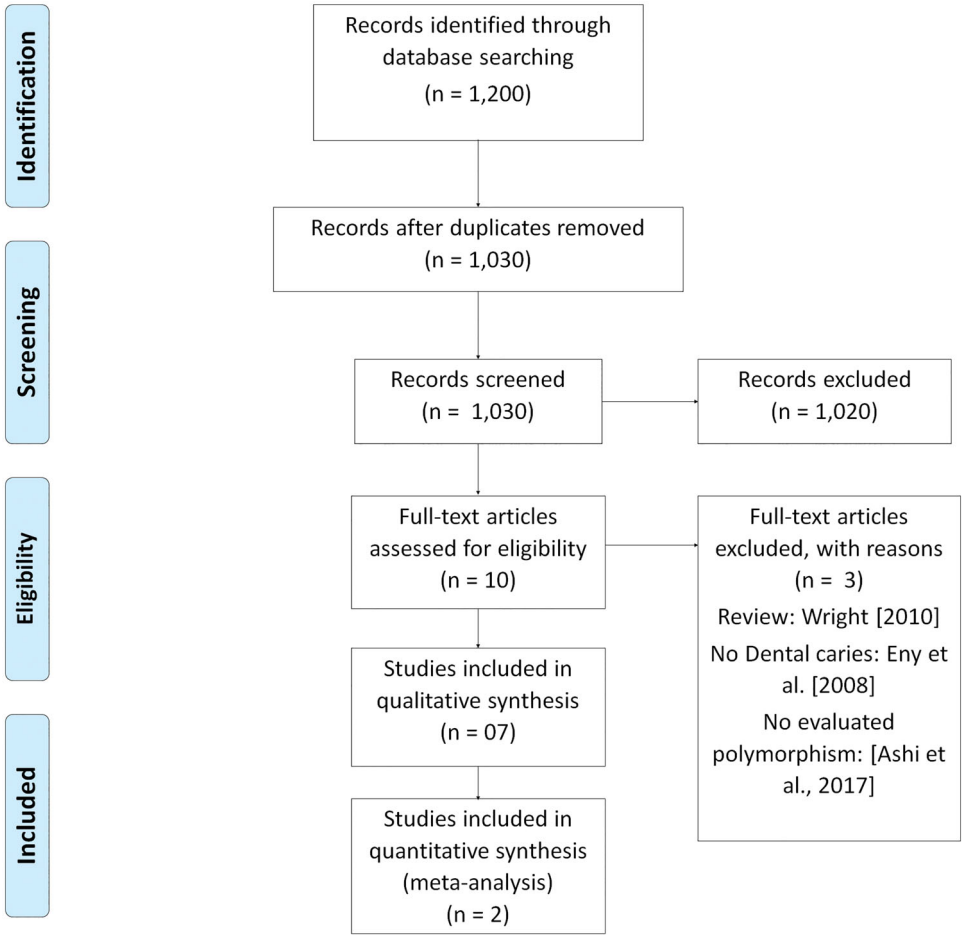

Figure 1. Prisma flow diagram.

Table 1. Critical Appraisal Checklist for observational studies (Joanna Briggs Institute) in the systematic review according to the 10-items.

	NIH criteria										
References	1	2	3	4	5	6	7	8	9	10	Final score
Wendell et al. [27]	–	/	/	–	+	+	+	–	/	/	Low Quality (3)
Kulkarni et al. [15]	–	–	–	–	–	+	+	–	–	/	Low Quality (2)
Haznedaroglu et al. [23]	–	–	–	+	+	+	+	–	/	/	Low Quality (3)
Holla et al. [24]	+	+	+	+	+	+	+	–	+	/	High Quality (8)
Robino et al. [25]	+	+	/	+	+	+	+	–	/	/	Medium Quality (6)
Yildiz et al. [28]	–	–	+	–	–	+	+	+	–	–	Medium Quality (4)
Shimomura-Kuroki et al. [26]	–	–	/	–	–	+	+	–	/	/	Low Quality (2)

+ Yes; – No; /: Unclear.

investigating only permanent (57.1%) and permanent/primary teeth (42.9%). Therefore, 4032 individuals were evaluated.

Risk of bias within studies

Regarding the quality assessment through the Critical Appraisal Checklist for observational studies (Joanna Briggs Institute), most studies (57.1%) were considered of low quality and 28% of medium quality (Table 1). Similarly, considering methodological scoring protocol based on quality assessment for genetic studies, it was observed that 71.4% of the studies were classified as low level of evidence and the remained as a medium level of evidence (Table 2).

Overview of SNPs

Twelve SNPs were found investigating possible associations between SNPs of taste genes and dental caries experience. These SNPs were present in four genes. Most SNPs were missense (58.3%), followed by intronic (33.3%). Moreover, 91.7% of SNPs are related to possible functional impact in protein. More details of SNPs and their functional impact on protein are available in Table 3. One SNP was included in the meta-analysis and presented a palindromic sequence. However, studies reported the evaluated sequence, therefore, it was possible to perform the meta-analysis.

Results of individual studies

Four different taste genes – taste 1 receptor member 2 (*TAS1R2*), taste 2 receptor member 38 (*TAS2R38*), taste 1 receptor member 3 (*TAS1R3*), and glucose transporter 2 (*GLUT2*) – and 12 polymorphisms were cited in the literature investigating possible associations with dental caries experience. The summarized results according to gene and polymorphism in the studies are displayed in Table 4. In general, it was possible to observe that most of allele and genotype effects of taste genes SNPs presented a protective factor against dental caries.

In Table S2, the main characteristics of included studies are shown. Wendell et al. [27] observed different results between permanent/mixed and primary teeth related to taste genes (*TAS2R38* [rs713598, rs1726866, and rs10246939] and *TAS1R2* [rs4920566]). While both SNPs were associated

Table 2. Methodological scoring protocol based on quality assessment for genetic studies.

	Genetic criteria										
References	Control group	Hardy–Weinberg equilibrium	Case group	Primer	Reproducibility	Blinding	Power calculation	Statistics	Corrected statistics	Independent replication	Score	Evidence*
Wendell et al. [27]	0	1	0	1	1	0	0	0	0	0	3	Low
Kulkarni et al. [15]	0	0	1	0	1	0	0	0	0	0	2	Low
Haznedaroglu et al. [23]	0	0	1	0	1	0	0	0	0	0	2	Low
Holla et al. [24]	1	1	1	1	1	0	1	0	0	0	6	Medium
Robino et al. [25]	1	0	1	0	1	0	0	0	0	0	3	Low
Yildiz et al. [28]	1	0	1	1	1	0	1	0	0	0	4	Medium
Shimomura-Kuroki et al. [26]	0	0	1	1	1	0	0	0	0	0	3	Low

*For the quantification of criteria: «1» means present, and «0» absent.

Table 3. Description of single nucleotide polymorphism investigated in the present systematic review according genes[a].

					Allele Frequencies by populations (%)[a]							
Gene	*Polymorphism*	Chromosomic position	Variation	Biotype/impact functional	African	American	East Asian	Europe	South Asia	All	Allele Reference/ allele Effect used	Ancestral allele
TAS1R2	rs3935570 (G/T)	1:19167371	Intron	Protein coding	G:66% T:34%	G:83% T:17%	G:88% T:12%	G:74% T:26%	G:69% T:31%	G:75% T:25%	G/T	T
	rs4920566 (G/A)	1:19179824	Intron	Protein coding	A:20% G:80%	A:64% G:36%	A:40% G:60%	A:64% G:36%	A:45% G:55%	A:44% G:56%	G/A	G
	rs9701796 (G/C)	1:19186129	Missense	Protein coding	G:18% C:82%	G:16% C:84%	G:23% C:77%	G:22% C:78%	G:22% C:78%	G:20% C:80%	G/C	C
	rs35874116 (T/C)	1:19181393	Missense	Protein coding	T:66% C:34%	T:73% C:27%	T:90% C:10%	T:68% C:32%	T:72% C:28%	T:73% C:27%	T/C	C
TAS2R38	rs713598 (C/G)	7:141673345	Missense	Protein coding	C:52% G:48%	C:34% G:66%	C:32% G:68%	C:58% G:42%	C;66% G:34%	C:50% G:50%	C/G	G
	rs1726866 (G/A)	7:141672705	Missense	Protein coding	G:67% A:33%	G:71% A:29%	G:68% A:32%	G:46% A:54%	G:36% A:64%	G:57% A:43%	G/A	G
	rs10246939 (C/T)	7:141672604	Missense	Protein coding	T:52% C:48%	T:31% C:69%	T:32% C:68%	T:54% C:46%	T:64% C:36%	T:48% C:52%	C/T	C
TAS1R3	rs307355 (C/T)	1:1265154	Regulatory	TF binding site C	T:52% C:48%	T:12% C:88%	T:17% C:83%	T:8% C:92%	T:17% C:83%	T:24% C:48%	C/T	C
GLUT2	rs1499821 (NR)	3:170724729	Intron	Protein coding	C:88% T:12%	C:87% T:13%	C:81% T:19%	C:85% T:15%	C:90% T:10%	C:86% T:14%	NR	C
	rs5398 (NR)	3:170715830	Missense	Protein coding	G:36% A:64%	G:69% A:31%	G:76% A:24%	G:71% A:29%	G:72% A:28%	G:63% A:37%	NR	A
	rs5400 (G/A)	3:170732300	Missense	Protein coding	G:51% A:49%	G:83% A:17%	G:98% A:2%	G:86% A:14%	G:84% A:16%	G:78% A:22%	G/A	A
	rs11924032 (NR)	3:170735099	Intron	Protein coding	G:59% A:41%	G:74% A:26%	G:79% A:21%	G:74% A:26%	G:77% A:23%	G:72% A:28%	NR	G

[a]Based on human (GRCh37.p13), available on: http://grch37.ensembl.org/Homo_sapiens. NR: not reported.

Table 4. Summarization results according to gene and polymorphism in the studies.

Gene	Polymorphism (reference allele/ effect allele)	Study, Year: Wendell et al. [27]	Kulkarni et al. [15]	Haznedaroglu et al. [23]	Holla et al. [24]	Robino et al. [25]	Yildiz et al. [28]	Shimomura-Kuroki et al. [26]
	rs3935570 (G/T)					–#		
TAS1R2	rs4920566 (G/A)	–# [a]						
	rs9701796 (G/C)	–# [a]		NA				
	rs35874116 (T/C)		–#	–#	+# [b]			
TAS2R38	rs713598 (C/G)	–# [a]					–#	NA
	rs1726866 (G/A)	–# [a]						
	rs10246939 (C/T)	–# [a]						
TAS1R3	rs307355 (C/T)			–#				
	rs1499821 (NR)					–#		
GLUT2	rs5398 (NR)					NA		
	rs5400 (G/A)		+#		+# [b]	NA		
	rs5400 (C/T)							NA
	rs11924032 (NR)					NA		

–: Protector factor; +: risk factor; #: statistically associated; NA: not associated.
[a]Statistical difference only in deciduous/mixed dentition; NA: not associated, direction of effect not showed.
[b]Statistical difference only in DMFT = 0 versus component $D \geq 1$.

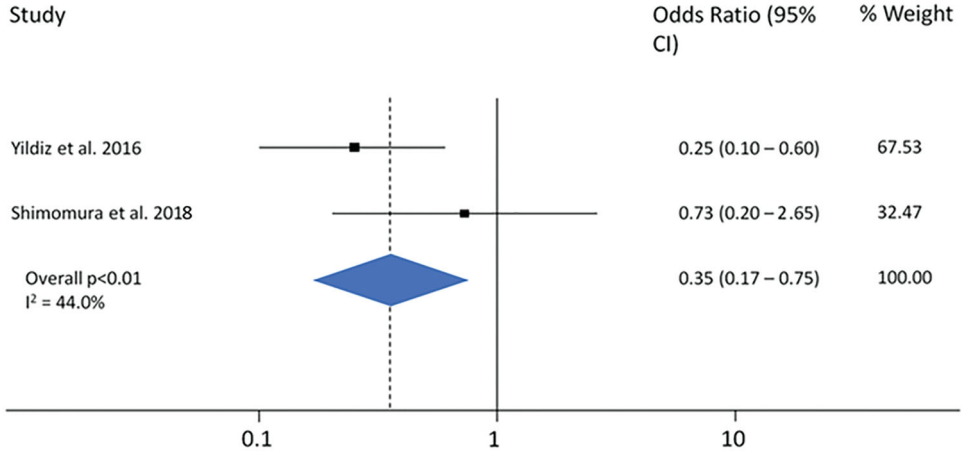

Figure 2. Pooled effect of *TAS2R38* rs713598 in genotype heterozygote. Data are presented as odds ratio for each study (boxes), 95% CIs (horizontal lines) and summary as odds ratio with 95% CI (diamond). Fixed model was performed.

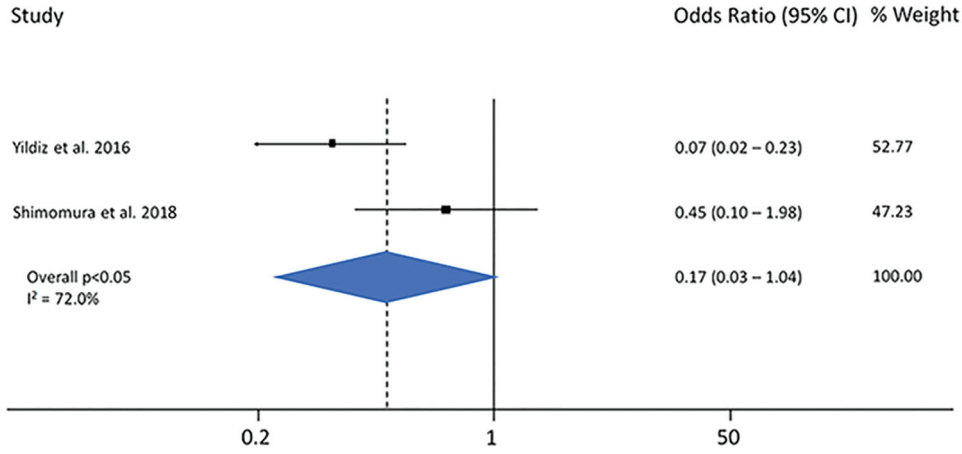

Figure 3. Pooled effect of *TAS2R38* rs713598 in genotype homozygote. Data are presented as odds ratio for each study (boxes), 95% CIs (horizontal lines) and summary as odds ratio with 95% CI (diamond). Randomic model was performed.

with dental caries in primary teeth, no associations were observed in permanent teeth. Moreover, the SNP rs9701796 (*TAS1R2*) was only associated with primary teeth [27]. Holla et al. [24] presented different approaches to categorize dental caries, observing different results. When DMFT = 0 versus DMFT ≥1 were compared, no statistical differences were observed for s35874116 (*TAS1R2*) and rs5400 (*GLUT2*). However, when considered DMFT = 0 versus decayed teeth ≥1, statistical difference was observed in these SNPs.

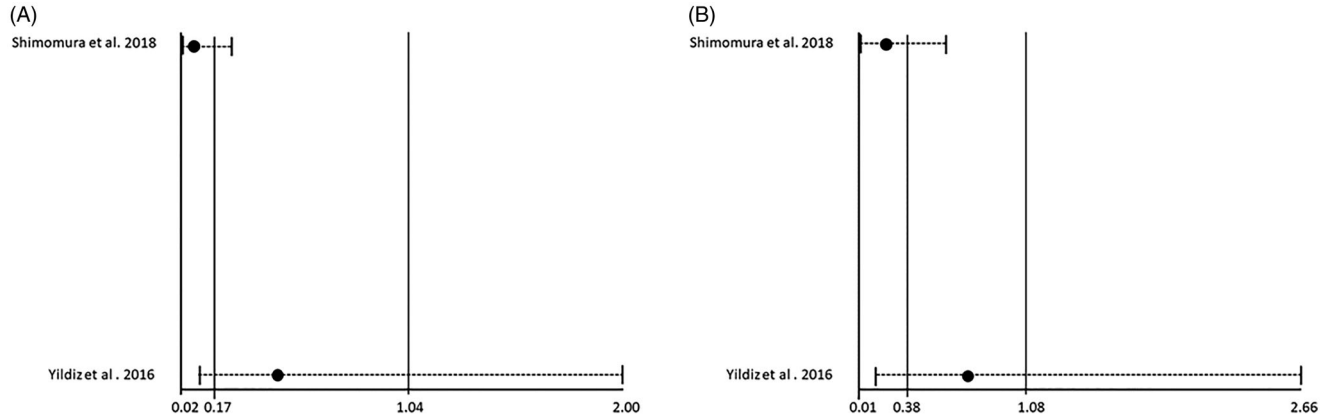

Figure 4. Sensibility analysis of included studies. In (A) heterozygote genotype and (B) homozygote genotype.

Although some SNPs have been reported in several papers, not all studies displayed the effects measures or presented the data in a way to make it possible to calculate the Odds Ratio and be included in the meta-analysis.

Synthesis of results (meta-analysis)

Two studies were included in the meta-analysis [26,28] evaluating the SNP rs713598 in *TAS2R38* gene. For this analysis, the genotype heterozygote (Figure 2) and the homozygote (Figure 3) were considered. Considering the heterozygote, a low heterogenicity was observed ($I^2 = 44\%$) and a fixed model was used in the analysis. The pooled effect in the heterozygote analysis showed that genotype CG was associate with low caries experience (OR 0.35 [0.17–0.75]).

On the other hand, considering homozygote analysis, high heterogenicity was observed ($I^2 = 72.0\%$ and OR 0.15 [0.06–0.38]). So, a random model was performed, presenting no significant association considering the genotype GG (OR 0.17 [0.03–1.04]). Sensibility analysis showed an important influence of Yildiz et al. [28] in the results (Figure 4).

Risk of bias across studies

Due to the low number of studies included in the meta-analysis (less than 7), it was not possible to perform the Funnel Plot and Egger's test.

Discussion

Twelve SNP presented in four different genes (*TAS1R2, TAS2R38, TAS1R3* and *GLUT2*) were identified suggesting an impact in eating behaviour and influencing on dental caries experience. Most of these SNPs showed a protective effect for the minor allele, suggesting that these genetic variations may be involved in taste sensibility. The meta-analysis results suggested that the SNP rs713598 presents in TAS2R38 may play an important role in dental caries susceptibility.

While polymorphism in *CD36* suggests a possible influence in the fast taste perceptions, decreasing the attraction to these foods in mice [31], *TAS2R38* gene – taste receptor gene cluster on chromosome 12p13/taste receptor, type-2, member 38 – is responsible to sensitivity to the bitter compound of propylthiouracilis. They are a member of the G-protein-coupled receptor superfamily. These proteins are expressed mainly in the epithelial cells of tongue and palate. In special, the SNP rs713598 lead a change of amino acid alanine to proline at position 49. Besides, it is a candidate gene to sweet taste perception [32–34]. Homozygote to Alanine (AA) individuals are referred as 'nontasters', while allele heterozygote (Alanine and Proline) are referred as 'medium-tasters' and allele homozygote to Proline (PP) are referred as 'supertasters' individuals to bitter [9,32]. Thus, it seems that medium and supertasters individuals can be more taste sensitive to the high diversity of substances and, therefore, more prone to decrease sugar intake in detriment to different flavours when are compared with individuals considered 'nontasters' [9,32]. Therefore, a gradual intensity of phenotype change is expected, since 'supertasters' homozygote to mutant allele should present the less sugar intake and, consequently, a decrease of dental caries experience. In this study, the genotype CG of SNP rs713598 showed an odds 75% lower of presenting dental caries. Genotype GG of the same SNP presented a borderline result (OR 0.17 [0.03–1.04]), revealing a tendency of protection against dental caries, although it was not statistically significant. The lack of significance for the CC homozygote can be explained due to elevate heterogenicity between the methodological approaches observed in the included studies even as to the significant weight of Shimomura-Kuroki et al. [26] on result observed in the sensibility analysis. Despite the results have presented similar tendencies in both studies, the study of Shimomura-Kuroki et al. [26] was decisive in the final result.

Moreover, the *TAS1R2* – taste receptor, type-1, member 2 – was also associated with a low intake of sugar consumption [35]. A high number of studies have found an association of *TAS1R2* and dietary behaviours, such as sucrose/carbohydrate preference [36,37]. In this way, it seems that *TAS1R2* can contribute to sensitivity to sweet taste and influence sugar consumption. Based on this pathway, it was proposed the hypothesis that *TAS1R2* could also influence the caries experience. Thus, while effect SNPs of rs3935570, rs4920566 and rs9701796 (presents in *TAS1R2*) minor alleles were associated with a decrease of dental caries [25,27], rs35874116 showed contrasting results across the studies

[15,23,24]. *TAS1R3* have analogous mechanisms and is involved in sweet perception, which is determined *via* a G-protein-linked [23]. Only one study investigated the influence of TAS1R3 on caries, showing also a protective effect [23]. In this context, glucose transporter type 2 (*GLUT2*) facilitates the first step in glucose-induced insulin secretion, brain detection of glucose [38], as well as facilitative glucose transporter in the plasma membrane of the intestinal and provide metabolites stimulating the transcription of glucose-sensitive genes [39]. Henceforth, this polymorphism seems to be associated with higher habitual consumption of sugar [8], and some studies have detected possible associations with dental caries experience [15,24].

Moreover, another important point must be discussed. In the Wendell et al. [27] study, significant differences between (*TA1R2* and *TAS2R38*) were observed when primary/mixed dentition were considered. However, when permanent teeth were investigated, these statistical differences were not observed, although the direction of effect has been preserved [27]. These can be explained due to other non-genetic factors, which can be more expressed in adulthood [9,40,41]. Thus, studies have supposed that genetic taste influence would be more correlated in childhood. Over time, cultural and environmental contributions could influence more significantly [9,40,41], explaining the observed results.

It is important to highlight that less than half of the included studies investigated primary teeth, and this high heterogenicity can be the main limitation to be considered in the interpretation of present results, contributing to being classified as 'low quality' in the assessments of quality of studies. Moreover, in the meta-analysis, only crude estimative were included. In addition, despite 4032 individuals were included in the studies, the results were based mainly on the Caucasian population distributed basically in North America and Europe. Therefore, we must emphasize the ethnicity of samples investigated and population stratification. The absence of control for populations diversity can introduce important bias in genetic studies, leading to problems in association estimates. A limited part of the included studies adjusted the results for any type of ancestry information. Fundamental differences between allele frequencies and population ethnicity have been identified when investigated SNPs were analyzed in a complementary database. This point highlights the need to perform a control for this variable to decrease possible bias of studies. Therefore, the conclusion and interpretations of the results should take in account these limitations. Besides, most of the studies presented low quality of evidence in both instruments used to investigate this point as well as we only include candidate-gene studies in the present study. Thus, other genes or pathways related to taste genes can be important to explain the relationship between taste gene and dental caries experience. A recent study has explored *TLR2 [*rs121917864*] and TLR4 [rs4986790]* polymorphism (Toll-like receptors: expressed in the tongue gustatory papillae where they might initiate immune responses to pathogens) and no observed associations with caries in Turkish adults [42]. On the other hand, genotype CC and allele C of Carbonic Anhydrase 6 (*CA6*) [rs17032907] were less frequent in the advanced caries lesion group [42]. Thus, these genes can be explored in further studies. The low number of studies addressing this topic reinforces the need for new investigations with different genetic methods. Studies at genomic scales are more robust for the identification of genetic component since they are not based on previous knowledge of pathophysiology and should be used to detect new routes and identify new candidate genes. However, the available literature on caries experience and genomic is limited [43].

We have also to emphasize that was performed an analysis with quality control filters aiming to decrease possible biases in our estimates. We investigate SNPs in linkage disequilibrium as well as palindromic SNPs. Moreover, we performed a sensitivity analysis to observe the weight of studies in meta-analysis. Our findings highlight that studies focussing on the relationship between taste genetic SNPs and dental caries experience are relatively new, needing support of high evidence studies to be confirmed. Preferably, future studies should include representative and wide samples (presenting power calculation) with populations of different ethnic groups. Epigenetic issues, genome wide-associations studies and interactions between genetic and environmental factors have been encouraged since they are necessary to complement the findings observed in gene-candidate studies.

Therefore, SNPs of taste genes seem to be associated with the experience of dental caries. The genotype CG of SNP rs713598 present in *TAS2R38*-gene presented a reduction of 75% on the odds for dental caries. Present findings were mostly based in studies with low evidence, performed in Caucasian individuals; Henceforth, interpretations should be taken with caution and the results must be replicated in different populations with a high-quality level of evidence. Further studies should also consider epigenetic issues, interactions between genetic and environmental factors.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was conducted in a Graduate Program supported by CAPES, Brazil.

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