Received: 29 May 2023 | Revised: 10 August 2023 | Accepted: 31 October 2023

DOI: 10.1002/hsr2.1708

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

The association between *MMP*−13 rs478927 gene polymorphism and dental caries susceptibility in children with mixed dentition from Birjand, Iran: A case-control study

Ebrahim Miri-Moghaddam[1] | **Fatemeh Sadat Mousavi**[2] | **Hamid Salehiniya**[3] | **Farzaneh Vafaeie**[4] | **Hamid Abbaszadeh**[5]

[1]Department of Molecular Medicine, Cardiovascular Diseases Research Center, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran

[2]Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran

[3]Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran

[4]Department of Medical Genetics, Facultyof Medicine, Birjand University of Medical Sciences, Birjand, Iran

[5]Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, Birjand University of Medical Sciences, Birjand, Iran

Correspondence

Hamid Abbaszadeh, Oral and Maxillofacial Pathology Department, Faculty of Dentistry, Birjand University of Medical Sciences, Birjand, Iran.
Email: hamidabbaszade@yahoo.com

Funding information

Birjand University of Medical Sciences, Grant/Award Number: 456582

Abstract

Background and Aims: Gene polymorphisms are responsible for at least part of the variation in caries susceptibility despite similar environmental factors. Genes involved in enamel formation like matrix metalloproteinase-13 (*MMP-13*) may participate in caries process. The aim was to investigate the association between *MMP-13* rs478927 polymorphism and caries susceptibility in 6-years-old children from Birjand, Iran.

Methods: Six-years old children from Birjand, Iran, participated in this study. The total decayed, missing, and filled teeth were calculated and defined as caries index (CI). Based on this CI, two groups of high-caries (case) and low-caries (control) were taken into account. Saliva samples were collected and DNA was extracted. The allele and genotypes of *MMP-13* rs478927 polymorphism were determined by tetra-primer amplification refractory mutation system-polymerase chain reaction (T-ARMS-PCR) method. p Value was significant if $p < 0.05$.

Results: Three hundred sixty-seven children consisted of 186 low-caries children and 181 high-caries children were included in this study. The mean CI was 6.02 ± 0.81. There was no significant association between high and low-caries groups based on socioeconomic status, eating sweet snacks, parents' susceptibility to dental caries, duration of breastfeeding, and the brushing habit ($p > 0.05$). There wasn't any significant association between genotype distribution of *MMP-13* rs478927 polymorphism and CI groups ($p = 0.924$). This polymorphism was associated with increased caries susceptibility under all genetic models but this effect was not significant ($p > 0.05$).

Conclusion: The *MMP-13* rs478927 gene polymorphism was not significantly associated with dental caries susceptibility in Birjandi children with mixed dentition. It is recommended to conduct studies on children of different dentitions to better understand the role of this polymorphism on caries susceptibility in primary and permanent teeth of children.

KEYWORDS
dental caries susceptibility, genetic polymorphism, matrix metalloproteinase 13

1 | INTRODUCTION

Dental caries is considered as one of the most common chronic diseases worldwide[1,2]; bacterial pathogens in the dental plaque start the caries process and their products induce an imbalance between demineralization and remineralization.[3–5] In populations at risk such as children, the decreasing trend of caries index (CI) is not observed so much and dental caries remains one of the most important challenges for children's oral and dental health.[6,7]

A combination of biological, physical, and environmental factors such as dental plaque, inappropriate quantity and quality of saliva, insufficient fluoride, improper oral hygiene habits, carious diet, and improper tooth structure can be among the causes of caries. Evidence have shown that besides these common factors, the host's genetic predisposition can also be effective in the initiation and progression of the caries process.[8,9] The greater susceptibility of some people to dental caries compared to others, despite the existence of relatively similar caries-causing risk factors, is a proof of this claim and indicates the involvement of genetic factors in caries susceptibility.[10–12] Genes involved in enamel formation, immune defense, salivary secretion and composition, taste receptor, and eating behavior are among the most important genes for dental caries susceptibility.[13] An association between genetic variations (such as gene polymorphisms) of enamel formation genes like matrix metalloproteinases (*MMP*s) and caries experience has been reported.[14,15] Gene polymorphism is a change in the DNA strand that occurs in one nucleotide (C, A, T, G) in the genome among individuals of a biological species. The gene polymorphism may influence the expression of mRNA and consequently the amount of protein or protein function. The resulting changes in the proteins of caries susceptibility genes can be effective in caries process. It is noteworthy that the impact of genetic polymorphisms on caries susceptibility varies among different ethnic groups.[16–27]

The family of *MMP*s includes 23 enzymes, which are divided into six groups, including collagenases, gelatinases, stromelysins, matrilysins, membrane-type *MMP*s, and other nonclassified *MMP*s.[18–20] The activity of *MMP*−2 and *MMP*−9 from the family of gelatinases, *MMP*−8 from the family of collagenases, and *MMP*−3, *MMP*−10, and *MMP*−11 from the family of stromelysins has been shown in caries lesions in recent studies.[18,21–23] Another one of these proteases is *MMP*−13 or collagenase 3, which plays a role in the progress of caries not only by directly destroying the extracellular matrix but also by interfering in the activation of other *MMP*s.[18,21,23] There have been few studies on the association between gene polymorphisms in *MMP-13* gene and caries susceptibility, which have been accompanied by contradictory results in children of different ethnicities from different countries[18,21,27–29]; while in one study a protective role for the *MMP-13* rs2252070 gene polymorphism against caries is mentioned,[18] in two studies it is mentioned as a caries risk factor,[28,29] and in other studies no association between this polymorphism and susceptibility to caries is found.[21,27] Only one study has addressed the role of *MMP-13 rs478927* gene polymorphism in the caries susceptibility,[30] which calls for more studies in this field among different ethnic groups in different countries.

So, due to the rarity of available studies on the association between *MMP-13 rs478927* gene polymorphism and caries susceptibility and the lack of investigation of this association among Iranian children, this study was conducted with the aim of investigating the association between *MMP-13 rs478927* gene polymorphism and caries susceptibility in 6-years old children from Birjand city in east of Iran.

2 | MATERIALS AND METHODS

2.1 | Study participants

Six years old children (who were in mixed dentition stage) from Birjand city, Iran, were included in this case-control study.

If there was a history of genetic disease in the child or his/her family, the child suffered from a chronic disease, the child was using space maintenance or orthodontic appliances, the child had taken antibiotics in the last 3 months, and the child or his/her parents did not want to participate in the study, that child was excluded from the study.[24,25]

2.2 | Ethical statement

This study approved by Ethics Committee of Birjand University of Medical Sciences (ethics code: IR.BUMS.REC.1400.328). The children voluntarily participated in this research. An informed consent form was obtained from the children's parents or guardians.

2.3 | Study design

This case-control study was implemented between July 2021 and March 2022 at Birjand, Iran. The CI was determined by total number of decayed, missing and filled teeth according to world health organization guidelines. The children were divided into two groups: high-caries (if CI > 5) (as case group) and low-caries (if CI ≤ 5) (as control group).[24,26] Also, a questionnaire containing information about some factors affecting susceptibility to caries, such as consumption of sweet snacks, brushing habits, access to dental services, and so forth, was completed by children's parents or their guardians.

2.4 | Saliva collection

The children were asked to brush their teeth 1 h before collecting the saliva sample and avoid eating and drinking afterwards. The children were asked to spit their saliva into the Falcon tube within 5min. In this way, 5 mL of unstimulated children's saliva was collected. It is worth mentioning that Falcon tube contained Tris/Saline/EDTA (TSE) buffer.[27]

2.5 | DNA extraction and polymorphism detection

The saliva samples were stored at −20°C cold room until DNA extraction. DNAs were extracted from saliva by a manual salting-out method. Precipitated DNA was dissolved in TE buffer and stored in a freezer at −20°C until use.

The quantity and quality (purity) of isolated DNA were measured by a spectrophotometer (Epoch). DNA concentration was estimated at a wavelength of 260 nm, and its purity was estimated by measuring the ratio of absorbance at 260 and 280 nm. The tetra-primer amplification refractory mutation system-polymerase chain reaction (T-ARMS-PCR) technique was used for genotyping the *MMP-13* rs478927 polymorphism.[31] Primer3 software (http://frodo.wi.mit.edu/cgi-bin/primer3/primer38www.cgi) was used for designing the primers. Tetra ARMS PCR is a technique used to detect specific mutations or genetic variations in DNA samples. It involves the design of primers with a mismatch at the 3′ end to selectively amplify the wild-type or mutant allele. This technique is useful in genetic research and diagnostic applications. It does not directly involve the use of restriction enzymes. The sequence of the primers and length of the amplified fragments have been presented in Table 1 (Table 1). The conditions for performing PCR were as follows: Each 25 mL of PCR mixture contains genomic DNA (50 ng), 1 mL of each primer, 12.5 mL of Taq polymerase master mix red (Aura Biotech), and the final volume reached 25 mL by adding distilled water. PCR reaction was performed at the following temperatures in order: initial phase of denaturation at 95°C for 5 min, followed by 30 cycles at 95°C for 1 min, 58°C for 30 s, 72°C for 45 s. Then, at the end of the reaction, a temperature of 72°C was applied for 5 min. Finally, the PCR product was electrophoresed on a 2% agarose gel and the genotype of the individuals was determined (Figure 1). Using a ladder of 100 kb in size can be helpful for detecting the tetra arms PCR bonds to accurately determine the presence and size of the amplified DNA fragments.

2.6 | Statistical analysis

SPSS software (version 22; SPSS Inc.) was used for analyzing the data. The χ^2 test and student *t*-test were used for this purpose. The tests were two-sided. $p < 0.05$ was considered significant.

TABLE 1 Sequence of the primers and length of the amplified fragments.

Primers' sequence		Product size
Forward inner allele A	GTTATTAGATTAGACAGTGAACACAATA (FI478927)	For I & Rev O product Length: 192 bp For O & Rev I product Length: 257 bp For O & Rev O product Length: 396 bp
Reverse inner allele G	CTTTTATGTGTTTTAACTTCATCCC (RI478927)	
Forward outer	GTACTCCTGGATGTGATAAGACT (FO478927)	
Forward outer	AGCCACAGTGACAGATTAAGTAGAT (RO478927)	

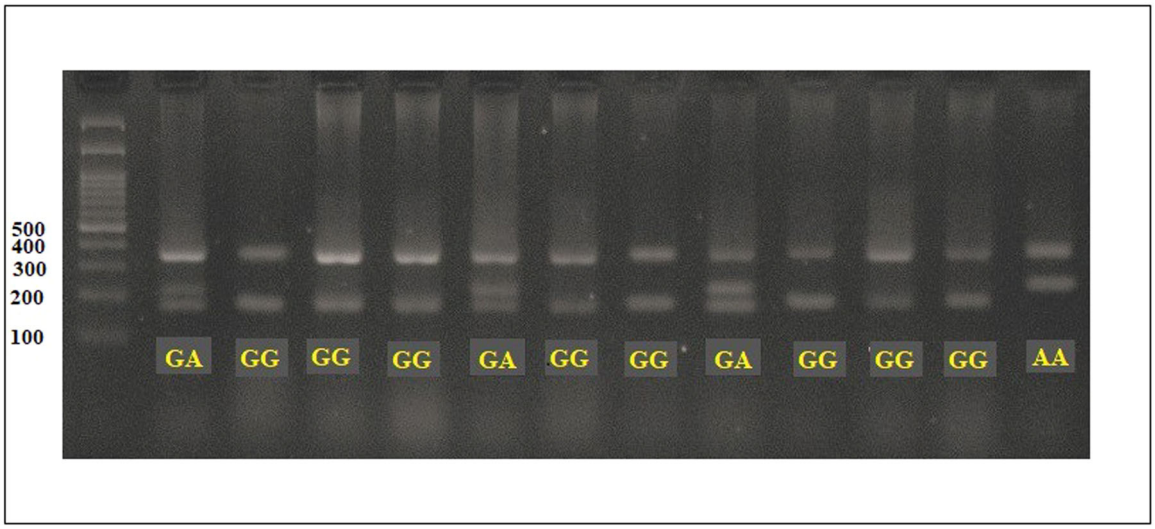

FIGURE 1 Representative agarose gels for *MMP-13* rs478927 polymorphism.

TABLE 2 The association of socioeconomic factors and oral hygiene habits with caries susceptibility.

Variable	Group	Control *n* (%)	Case *n* (%)	*p* Value
Father's education	Illiterate	2 (1.1)	3 (1.7)	0.49
	Literacy	2 (1.1)	3 (1.7)	
	Primary school	21 (11.3)	25 (13.8)	
	Secondary school	24 (12.9)	35 (19.3)	
	High school	62 (33.3)	50 (27.6)	
	Associate degree	26 (14)	15 (8.3)	
	bachelor degree	35 (18.8)	32 (17.7)	
	Master degree	12 (6.5)	15 (8.3)	
	PhD degree and above	2 (1.1)	2 (1.1)	
	Don't want to answer	0 (0)	1 (0.6)	
Mother's education	Illiterate	7 (3.8)	8 (4.4)	0.75
	Literacy	2 (1.1)	1 (0.6)	
	Primary school	28 (15.1)	27 (14.9)	
	Secondary school	18 (9.7)	26 (14.4)	
	High school	61 (32.8)	53 (29.3)	
	Associate degree	11 (5.9)	14 (7.7)	
	bachelor degree	52 (28)	46 (25.4)	
	Master degree	7 (3.8)	4 (2.2)	
	PhD degree and above	0 (0)	1 (0.6)	
	Don't want to answer	0 (0)	1 (0.6)	
Family income level	<35,000,000 rials	74 (39.8)	81 (44.8)	0.62
	35,000,000–80,000,000 rials	57 (30.6)	43 (23.8)	
	80,000,000–200,000,000 rials	12 (6.5)	15 (8.3)	
	200,000,000–300,000,000 rials	41 (22)	41 (22.7)	
	>300,000,000 rials	1 (0.5)	0 (0)	
	Don't want to answer	1 (0.5)	1 (0.6)	
Number of times receiving dental services	Never	122 (65.6)	112 (61.9)	0.32
	Once	36 (19.4)	29 (16)	
	Twice	13 (7)	21 (11.6)	
	Three times and more	15 (8.1)	19 (10.5)	
Access to dental services	No	63 (33.9)	123 (66.1)	0.94
	Yes	62 (34.3)	119 (65.7)	
Eating sweet snacks	No	31 (16.7)	155 (83.3)	0.80
	Yes	32 (17.7)	149 (82.3)	
Parents' susceptibility to dental caries	Low	43 (23.1)	143 (76.9)	0.62
	High	38 (21)	143 (79)	
Duration of breastfeeding (month)	Never	5 (2.7)	7 (3.9)	0.69
	1–6	9 (4.8)	9 (5)	

TABLE 2 (Continued)

Variable	Group	Control *n* (%)	Case *n* (%)	*p* Value
	7–12	11 (5.9)	7 (3.9)	
	13–18	27 (14.5)	25 (13.8)	
	19–24	134 (72.1)	133 (73.4)	
Number of times of brushing	Never	5 (2.7)	16 (8.8)	0.11
	Once a day	103 (55.4)	87 (48.1)	
	Twice a day	33 (17.7)	28 (15.5)	
	Three times a day	9 (4.8)	7 (3.9)	
	Once a month	3 (1.6)	7 (3.9)	
	A few per month (2–3 times)	5 (2.7)	11 (6.1)	
	Once a week	13 (7)	11 (6.1)	
	A few per week (2–6 times)	15 (8.1)	14 (7.7)	

3 | RESULTS

Three hundred and sixty-seven children were enrolled in this case-control study. The control group comprised of 186 children and the case group of 186 children. The boys comprised 41.9% of the control group and 46.4% of the case group. There was no significant difference between case and control groups based on gender ($p = 0.388$). The mean CI of total children was 6.02 ± 0.81. Both studied groups were in the Hardy–Weinberg equilibrium.

Table 2 summarizes association of studied risk factors with caries susceptibility in studied children (Table 2).

There was not any significant association between case and control groups based on the father's ($p = 0.491$) and mother's ($p = 0.749$) educational level.

There was not any significant association between case and control groups based on the family income ($p = 0.617$).

There was not any significant association between case and control groups based on the number of dental visit ($p = 0.325$).

There was not any significant association between case and control groups based on access to dental services ($p = 0.938$).

There was not any significant association between case and control groups based on eating sweet snacks ($p = 0.797$).

There was not any significant association between case and control groups based on the degree of parents' susceptibility to dental caries ($p = 0.624$).

There was not any significant association between case and control group based on the duration of breastfeeding ($p = 0.689$).

There was not any significant association between case and control group based on the number of times of brushing ($p = 0.109$).

Table 3 shows the genotype distribution of *MMP-13* rs478927 gene polymorphism (Table 3). There was not any significant association between cased and control group based on the genotype distribution of *MMP-13* rs478927 gene polymorphism ($p = 0.283$).

Table 4 presents the association between *MMP-13* rs478927 polymorphism and caries susceptibility under different genetic models (Table 4); this polymorphism was associated with increased caries susceptibility under all genetic models but this effect was not significant ($p > 0.05$).

4 | DISCUSSION

This research was conducted to assess the association between *MMP-13* rs478927 gene polymorphism and dental caries susceptibility in Birjandi children, Iran. There was no significant association between case and control groups based on some studied variables such as socioeconomic status, parents' susceptibility to dental caries, oral hygiene habits, and so forth. There was not also any significant association between case and control groups based on genotype distribution of *MMP-13* rs478927 polymorphism.

Formation of dental caries is a complex and multifactorial process which may result from action of bacterial products in dental plaques in combination with the effects of other factors like saliva, diet, oral hygiene habits, and fluoride intake.[17,32] Genetic may also alter the caries susceptibility as evidenced by multiple research.[33]

MMPs have important effects in the formation process of enamel and dentin and also in caries progression. Expression of *MMP-13* has been documented during the bud stage of tooth development. Altered expression of *MMP-13* as a result of polymorphic alleles with reduced gene function may form an enamel that is more susceptible to caries process; this susceptibility may be due to alteration in enamel structure which lead to porosity of the enamel, a decrease in mineral content and higher amounts of mineral loss under acidic circumstances; it can also help to more dental plaque attachment.[30]

TABLE 3 Genotype distribution of *MMP-13* rs478927 gene polymorphism within studied group.

	Genotype			
Group	**GG *n* (%)**	**GA *n* (%)**	**AA *n* (%)**	***p* Value**
Control	92 (49.5)	73 (39.2)	21 (11.3)	0.92
Case	86 (47.5)	73 (40.3)	22 (12.2)	

TABLE 4 Association of *MMP-13* rs478927 gene polymorphism with caries susceptibility under different genetic model.

	Distribution				
Genetic model	**Allele/ genotype**	**Group**	***N***	**Odd ratio (95% confidence interval)**	***p* Value**
Allelic A versus G	G	Control	257	1.07 (0.78–1.46)	0.68
		Case	245		
	A	Control	115		
		Case	117		
Homozygous AA versus GG	GG	Control	92	1.12 (0.57–2.18)	0.74
		Case	86		
	AA	Control	21		
		Case	22		
Heterozygous GA versus GG	GG	Control	92	1.07 (0.69–1.66)	0.76
		Case	86		
	GA	Control	73		
		Case	73		
Dominant GA+AA versus GG	GG	Control	92	1.08 (0.72–1.63)	0.71
		Case	86		
	GA+AA	Control	94		
		Case	95		
Recessive AA versus GG+GA	GG+GA	Control	165	1.09 (0.58–2.05)	0.79
		Case	159		
	AA	Control	21		
		Case	22		

Since the studied factors and polymorphisms (*MMP-13* rs478927) in the current research did not significantly affect the caries susceptibility in Birjandi children, to identify the factors affecting caries susceptibility, it is necessary to focus on other possible factors such as salivary flow rate, the amount of different defense enzymes and proteins in saliva, the pH of saliva, the amount of calcium and phosphorus in saliva, the buffering properties of saliva, the amount of fluoride in drinking water, the amount of fluoride received from sources other than water, the presence of hereditary diseases, and tooth structure of children. Also, the possible effect of polymorphisms in other caries-susceptibility genes in Birjandi children should be investigated. These polymorphisms can include genes like amelogenin, enamelin, other *MMP*s,[14,15] lactotransferrin,[17,25] carbonic anhydrase VI,[34] vitamin D receptor,[35] and sweet taste receptor genes.[36] It has been suggested that the effects of a large number of gene polymorphisms combine together to provide circumstance for caries process.[37,38] This means that although a gene polymorphism (such as *MMP-13* rs478927 gene polymorphism) alone may not have a significant association with caries susceptibility it may increase the risk of caries in combination with other gene polymorphisms. Therefore, it is recommended to investigate the combined effects of gene polymorphisms and haplotypes in future studies. Also, it has been documented that the effect of gene polymorphisms on caries susceptibility varies in different ethnicities.[17,18] Therefore, the

nonsignificance of the association between *MMP-13* rs478927 gene polymorphism and caries susceptibility in Birjandi children is not surprising.

According to the results of present study, the A allele of *MMP-13* rs478927 polymorphism (compared to G allele under allelic model), the AA variant compared to GG genotype (under homozygous model), the GA variant (compared to GG genotype under heterozygous model), the GA+AA variant (compared to GG genotype under dominant model), and the AA variant compared to GG+GA genotype (under recessive model) played as a risk factor for caries development in Birjandi children but these effects were insignificant. The insignificant results show that *MMP-13* rs478927 polymorphism is not associated with caries susceptibility in Birjandi children although large-scale population-based studies with caries-free control group are needed to better reveal such an effect under these genetic models.

In a study by Tannure et al., the *MMP-13* rs2252070 was significantly associated with decrease in dental caries[18]; in two studies by Çağırır Dindaroğlu et al. and Dk et al., this polymorphism significantly increased the caries risk in Turkey and Nepal children[28,29]; in contrast in Borilova Linhartova et al. and Hu et al. studies, this polymorphism was not significantly associated with dental caries susceptibility in Czech and Chinese children as was the *MMP-13* rs597315 polymorphism.[21,27] The result of present study is inconsistent with the result of Vasconcelos et al. study; their results showed that TT genotype of *MMP13* rs478927 gene polymorphism was significantly associated with the simultaneous occurrence of caries and developmental defects of enamel (DDE) in children from the Amazon region of Brazil.[30] The reason for this inconsistency may be related to different ethnic groups, limitation of their participants to children with enamel developmental defects, different control group (caries-free and DDE-free children in their study), different age groups of study participants (children of 10–12 years of age in their study vs. 6-years-old children in our study), different dentition groups of study participants (mixed and permanent dentitions in their study vs. mixed dentition in our study), and different methods for detection of polymorphisms (TaqMan method in their study vs. T-ARMS-PCR in our study). Assessing the national data on the association of gene polymorphisms and dental caries susceptibility revealed four studies which have been conducted in Iranian adults (>18 years old). In two studies, there are significant associations between *MBL2* rs11003125[39] and AMELX *rs946252*[40] gene polymorphisms and increased dental caries (conducted both studies in Shiraz city) and on other two studies, there are no significant associations between *ENAM* rs3796704[7] (conducted in Shiraz city), *ENAM* rs2609428 and *AMELX* rs17878486[41] (conducted on students of Tehran University of Medical Sciences) gene polymorphisms and caries susceptibility.

4.1 | Limitation

One of the limitations of the present study was that the study population was limited to children with mixed dentition and children from Birjand city. Another limitation of the study is the use of salting out method for DNA purification, instead of using commercial kits due to its high costs.

5 | CONCLUSION

There was no significant association between selected risk factor and *MMP-13* rs478927 gene polymorphism with caries experience in Birjandi children from east of Iran. Investigation of other enamel formation genes polymorphisms and also haplotypes are recommended to understand the genetic background of dental caries in Birjandi children.

AUTHOR CONTRIBUTIONS

Ebrahim Miri-Moghaddam: Conceptualization; supervision; writing—review and editing. **Fatemeh Sadat Mousavi**: Investigation; writing—original draft. **Hamid Salehiniya**: Formal analysis; methodology; writing—review and editing. **Farzaneh Vafaeie**: Investigation; supervision; writing—review and editing. **Hamid Abbaszadeh**: Conceptualization; investigation; methodology; project administration; supervision; validation; writing—original draft; writing—review and editing. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

We thank research vice chancellor of Birjand University of Medical Sciences for their support of this study (grant number: 456582). This study was funded by Research Vice Chancellor of Birjand University of Medical Sciences (grant number: 456582).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data related to this study have been included in the text. Corresponding author or manuscript guarantor had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. All data related to this study have been included in the text.

TRANSPARENCY STATEMENT

The lead author Hamid Abbaszadeh affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Hamid Salehiniya http://orcid.org/0000-0001-7642-5214
Hamid Abbaszadeh http://orcid.org/0000-0002-7443-0607

REFERENCES

1. Selwitz RH, Ismail AI, Pitts NB. Dental caries. *Lancet*. 2007;369(9555):51-59.
2. Watt RG. Strategies and approaches in oral disease prevention and health promotion. *Bull World Health Organ*. 2005;83:711-718.
3. Featherstone J. Dental caries: a dynamic disease process. *Aust Dent J*. 2008;53(3):286-291.
4. Kidd EA, Fejerskov O. *Essentials of Dental Caries*. 4th ed. Oxford University Press; 2016.
5. Nicoline NI, Partakusuma FB, Joenoes H, et al. Association of ENAM C2452T polymorphism with high rates of caries occurrence in an Indonesian population. *Int J Appl Pharm*. 2020;12(1):1-4.
6. Petersen PE. Sociobehavioural risk factors in dental caries–international perspectives. *Community Dent Oral Epidemiol*. 2005;33(4):274-279.
7. Koohpeima F, Hashemi-Gorji F, Mokhtari MJ. Evaluation of caries experience in two genders and ENAM polymorphism in Iranian adults. *Meta Gene*. 2018;17:78-81.
8. Wang X, Shaffer JR, Zeng Z, et al. Genome-wide association scan of dental caries in the permanent dentition. *BMC Oral Health*. 2012;12(1):57.
9. Wang X, Shaffer JR, Weyant RJ, et al. Genes and their effects on dental caries may differ between primary and permanent dentitions. *Caries Res*. 2010;44(3):277-284.
10. Yildiz G, Ermis RB, Calapoglu NS, Celik EU, Türel GY. Gene-environment interactions in the etiology of dental caries. *J Dent Res*. 2016;95(1):74-79.
11. Werneck R, Mira M, Trevilatto P. A critical review: an overview of genetic influence on dental caries. *Oral Dis*. 2010;16(7):613-623.
12. Renuka P, Pushpanjali K, Sangeetha R. Review on "influence of host genes on dental caries". *MIOSR J Dent Med Sci*. 2013;4(3):86-92.
13. Vieira AR, Modesto A, Marazita ML. Caries: review of human genetics research. *Caries Res*. 2014;48(5):491-506.
14. Deeley K, Letra A, Rose EK, et al. Possible association of amelogenin to high caries experience in a Guatemalan-Mayan population. *Caries Res*. 2008;42(1):8-13.
15. Patir A, Seymen F, Yildirim M, et al. Enamel formation genes are associated with high caries experience in Turkish children. *Caries Res*. 2008;42(5):394-400.
16. Nireeksha N, Hegde MN, Shetty SS, Kumari SN. FOK I vitamin D receptor gene polymorphism and risk of dental caries: a case-control study. *Int J Dent*. 2022;2022:1-7.
17. Li X, Su Y, Liu D, Yang J. The association between genetic variants in lactotransferrin and dental caries: a meta-and gene-based analysis. *BMC Med Genet*. 2020;21(1):114.
18. Tannure PN, Küchler EC, Falagan-Lotsch P, et al. MMP13 polymorphism decreases risk for dental caries. *Caries Res*. 2012;46(4):401-407.
19. Hannas AR, Pereira JC, Granjeiro JM, Tjäderhane L. The role of matrix metalloproteinases in the oral environment. *Acta Odontol Scand*. 2007;65(1):1-13.
20. Lewis DD, Shaffer JR, Feingold E, et al. Genetic association of MMP10, MMP14, and MMP16 with dental caries. *Int J Dent*. 2017;2017:1-7.
21. Borilova Linhartova P, Deissova T, Kukletova M, Izakovicova Holla L. Matrix metalloproteinases gene variants and dental caries in Czech children. *BMC Oral Health*. 2020;20(1):138.
22. Sulkala M, Pääkkönen V, Larmas M, Salo T, Tjäderhane L. Matrix metalloproteinase-13 (MMP-13, collagenase-3) is highly expressed in human tooth pulp. *Connect Tissue Res*. 2004;45(4-5):231-237.
23. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res*. 2003;92(8):827-839.
24. Devang Divakar D, Alanazi SAS, Assiri MYA, et al. Association between ENAM polymorphisms and dental caries in children. *Saudi J Biol Sci*. 2019;26(4):730-735.
25. Brancher JA, Pecharki GD, Doetzer AD, et al. Analysis of polymorphisms in the lactotransferrin gene promoter and dental caries. *Int J Dent*. 2011;2011:1-9.
26. Olszowski T, Milona M, Janiszewska-Olszowska J, et al. The lack of association between FCN2 gene promoter region polymorphisms and dental caries in Polish children. *Caries Res*. 2017;51(1):79-84.
27. Hu XP, Song TZ, Zhu YY, et al. Association of ENAM, TUFT1, MMP13, IL1B, IL10 and IL1RN gene polymorphism and dental caries susceptibility in Chinese children. *J Int Med Res*. 2019;47(4):1696-1704.
28. Çağırır Dindaroğlu F, Eronat N, Durmaz A, Çoğulu D, Durmaz B, Çoğulu Ö. The association between genetic polymorphisms in matrix metalloproteinases and caries experience. *Clin Oral Investig*. 2021;25(9):5403-5410.
29. Dk R, Cohen S, Vikram M, et al. Role of single nucleotide polymorphism of matrix metalloproteinase (MMP-13 rs2252070) in the etiology of dental caries: a PCR based. *Am J Biomed Sci*. 2022;14(2):47-57.
30. Vasconcelos KR, Arid J, Evangelista S, et al. MMP13 contributes to dental caries associated with developmental defects of enamel. *Caries Res*. 2019;53(4):441-446.
31. Medrano RF, de Oliveira CA. Guidelines for the tetra-primer ARMS–PCR technique development. *Mol Biotechnol*. 2014;56(7):599-608.
32. Harris R, Nicoll AD, Adair PM, Pine CM. Risk factors for dental caries in young children: a systematic review of the literature. *Community Dent Health*. 2004;21(1):71-85.
33. Piekoszewska-Ziętek P, Turska-Szybka A, Olczak-Kowalczyk D. Single nucleotide polymorphism in the aetiology of caries: systematic literature review. *Caries Res*. 2017;51(4):425-435.
34. Hatipoglu O, Saydam F. Effects of the carbonic anhydrase VI gene polymorphisms on dental caries: a meta-analysis. *Dental Med Problems*. 2019;56(4):395-400.
35. Kong Y, Zheng J, Zhang W, et al. The relationship between vitamin D receptor gene polymorphism and deciduous tooth decay in Chinese children. *BMC Oral Health*. 2017;17(1):111.
36. Haznedaroğlu E, Koldemir-Gündüz M, Bakır-Coşkun N, et al. Association of sweet taste receptor gene polymorphisms with dental caries experience in school children. *Caries Res*. 2015;49(3):275-281.
37. Karayasheva D, Glushkova M, Boteva E, Mitev V, Kadiyska T. Association study for the role of matrix metalloproteinases 2 and 3 gene polymorphisms in dental caries susceptibility. *Arch Oral Biol*. 2016;68:9-12.
38. Li X, Liu D, Sun Y, Yang J, Yu Y. Association of genetic variants in enamel-formation genes with dental caries: a meta-and gene-cluster analysis. *Saudi J Biol Sci*. 2021;28(3):1645-1653.
39. Mokhtari MJ, Koohpeima F, Hashemi-Gorji F. Association of the risk of dental caries and polymorphism of MBL2 rs11003125 gene in Iranian adults. *Caries Res*. 2019;53(1):60-64.
40. Koohpeima F, Derakhshan M, Mokhtari MJ. AMELX gene association with dental caries in Iranian adults. *Int J Mol Cell Med*. 2019;8(4):294-300.
41. Reza Khami M, Asgari S, Valizadeh S, Karami J, Rezaei A, Rezaei N. AMELX and ENAM polymorphisms and dental CariesAMELX and ENAM polymorphisms and dental caries. *Int J Dent*. 2022;2022(1):1-6.

How to cite this article: Miri-Moghaddam E, Mousavi FS, Salehiniya H, Vafaeie F, Abbaszadeh H. The association between *MMP*–13 rs478927 gene polymorphism and dental caries susceptibility in children with mixed dentition from Birjand, Iran: A case-control study. *Health Sci Rep*. 2023;6:e1708. doi:10.1002/hsr2.1708