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Original

Genetic variations in *MMP9* and *MMP13* contribute to tooth agenesis in a Brazilian population

Leonardo S. Antunes[1)], Erika C. Küchler[2)], Patricia N. Tannure[3)], Juliana B. L. Dias[2)], Vanessa N. Ribeiro[2)], Andrea Lips[2)], Marcelo C. Costa[4)], Lívia A. Antunes[1)], and Jose M. Granjeiro[2)]

[1)]Department of Specific Formation, School of Dentistry, Fluminense Federal University, Nova Friburgo, RJ, Brazil
[2)]Cell Therapy Center, Unit of Clinical Research, Fluminense Federal University, Niterói, RJ, Brazil
[3)]Discipline of Pediatric Dentistry, School of Dentistry, Veiga de Almeida University, RJ, Brazil
[4)]Department of Pediatric Dentistry and Orthodontics, School of Dentistry, Federal University of Rio de Janeiro, RJ, Brazil

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Abstract: We investigated the association between polymorphisms in the *MMP2* (rs243865), *MMP9* (rs17576), and *MMP13* (rs2252070) genes with tooth agenesis in humans. Two hundred eighty-five unrelated individuals (202 controls without tooth agenesis and 83 cases with tooth agenesis) were evaluated in a cross-sectional single-center study. The study participants were recruited through the Pediatric Dental Clinics of the Federal University of Rio de Janeiro, Brazil. Genotyping of the selected polymorphisms for *MMPs* was carried out by real-time PCR using the Taqman assay method from genomic DNA isolated from buccal epithelial cells of all the studied individuals. There was no significant association of *MMP2* genotype or allele distribution with tooth agenesis or its absence. For *MMP9*, a significant difference in allele frequency was evident between the two groups ($P = 0.05$). With regard to the affected side, there was a significant difference between unilateral tooth agenesis and the control group in the distribution of *MMP9* ($P = 0.05$). Also, there was a significant difference in *MMP9* distribution between tooth agenesis in the maxilla and control individuals ($P = 0.03$). The genotype distribution of *MMP13* differed significantly between the group with unilateral tooth agenesis and the controls ($P = 0.01$). Our findings provide evidence that *MMP9* and *MMP13* may be involved in tooth agenesis. (J Oral Sci 55, 281-286, 2013)

Keywords: craniofacial abnormality; tooth abnormality; matrix metalloproteinase.

Correspondence to Dr. Leonardo Santos Antunes, Department of Specific Formation, School of Dentistry, Fluminense Federal University, Nova Friburgo, RJ, Brazil
Fax: +55-22-25287168 E-mail: leonardoantunes@id.uff.br

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Introduction

Tooth agenesis is the most common developmental dental anomaly in humans, and is characterized by failure of tooth bud development, causing definitive absence of one or more teeth. It can occur as an isolated trait, or as part of syndromes, essentially reflecting the genetic and phenotypic heterogeneity of the condition (1-3). The prevalence of tooth agenesis ranges from 2.6% to 11.3% depending upon the studied population (4,5). Tooth agenesis may lead to various forms of dysfunction and orthodontic and prosthetic problems (6).

Tooth development is a complex process, including multiple genes involving different interacting molecular pathways. Recent genetic studies have provided information about a number of genes related to tooth agenesis. Several genetic variations and mutations in *AXIN2*

Table 1 Details on the genetic markers gene studied

Gene/base change	Marker ID	Location in the gene	Flanking sequence[a]	Locus	Position	MAF[b]
MMP2 (C/T)	rs243865	promoter	TTCCCCATATTCCCCACCCAGCACTC**[C/T]**ACCTCTTTAGCTCTTCAGGTCTCAG	16q13–q21	chr16:55511806	0.156
MMP9 (A/G)	rs17576	exon 6	CCTCCTCGCCCCAGGACTCTACACCC**[A/G]**GGACGGCAATGCTGATGGGAAACCC	20q1–q13	chr20:44640225	0.450
MMP13 (A/G)	rs2252070	promoter	GTAAGCATGTTTACCTTCAAGTGACT**[A/G]**GGAAGTGGAAACCTATCCATAAGTG	11q22.3	chr11:102826539	0.363

[a] Obtained from ENTREZ SNP database (http://www.ncbi.nlm.nih.gov/snp/); [b] Minor allele frequency

(7), *BMP4* (8), *MMPs* (*MMP1* and *MMP20*) (9), *PAX9* (10,11), *MSX1* (10), *TGFB3* (8), and *WNT10A* (12,13) have been associated with tooth developmental failure.

The matrix metalloproteinases (*MMP*) constitute a multigene family of proteolytic enzymes that are capable of remodeling and degrading different extracellular matrix substrates (14). In this sense, extracellular matrix molecules may play an important role in the mechanisms involved in tissue interactions that regulate development of the dentition (15). Functional polymorphisms in *MMPs* located in promoter regions may influence the expression of the proteins and thus contribute to individual differences in susceptibility to tooth agenesis. A study of the developing tooth germ of Wistar rats showed that *MMPs* 1, 2, 3, and 9 were expressed during early tooth development, suggesting that they have a key role during this important developmental period (16). In humans, only a few studies have evaluated the association between genetic variation in *MMPs* and tooth agenesis (9,17).

Although several lines of evidence based on a polygenic model support a genetic etiology for tooth agenesis, the genes that are involved in this dental anomaly have yet to be elucidated. Genes implicated in epithelial-mesenchymal interactions could be potential candidates. Therefore, we tested the hypothesis that single nucleotide polymorphisms in *MMP2* (rs243865), *MMP9* (rs17576), and *MMP13* (rs2252070) were associated with tooth agenesis in a population dataset from Rio de Janeiro, Brazil.

Materials and Methods

Subjects

Ethical approval was obtained from the local Human Ethics Committee of the Health Department of the City of Rio de Janeiro, Brazil (#113/09). All participating individuals or parents/legal guardians provided signed informed consent.

Eligible unrelated individuals were enrolled in this cross-sectional single-center study conducted at the Pediatric Dental Clinics of Federal University of Rio de Janeiro, Brazil. Individuals with oral clefts and syndromes based on the International Classification of Diseases, Ninth Revision (ICD-9) were excluded. We attempted to select cases and controls with similar ethnicity and socio-cultural backgrounds. A total of 285 individuals were included in this study: 202 controls and 83 with tooth agenesis. The decision was made to assess a larger numbers of controls per case in order to improve the study's statistical power.

Diagnostic criteria for tooth agenesis

Tooth agenesis was considered to have occurred when at least one permanent tooth had failed to erupt during development (excluding third molars). All cases were confirmed by radiographic examination. Tooth agenesis was defined based on the age of the individuals and when initial tooth formation was visible in the radiographs (second premolar agenesis was only considered in individuals older than 8 years of age) (5).

DNA samples and genotyping

Genomic DNA for molecular analysis was extracted from oral cells based on a modification of a previously reported method (18). Genetic polymorphisms in the *MMP2* gene (rs243865), *MMP9* gene (rs17576), and *MMP13* gene (rs2252070) were genotyped by real-time polymerase chain reaction using the Taqman method (19) by Agilent Technologies (Stratagene Mx3005P; Santa Clara, CA, USA). Assays and reagents were supplied by Applied Biosystems (Foster City, CA, USA).

Two single nucleotide polymorphisms (SNPs) in the promoters of the genes encoding *MMP2* and *MMP13* (20), and one SNP in a coding region in *MMP9* (21), were selected for this study (Table 1). Markers were chosen based on allele frequency, position on the gene, and linkage disequilibrium relationships to maximize the information content.

Statistical analysis

Data were processed and analyzed using the SPSS 16.0

Table 2 Characteristics of the population studied

	Cases (n = 83)	Controls (n = 202)	P value
Mean age ± SD, years	18.1 ± 10.1	10.4 ± 2.4	***P* < 0.01****
Sex (%)			
Female	51 (61.4)	90 (44.6)	**0.01***
Male	32 (38.6)	112 (55.4)	
Ethnic background (%)			
Caucasian	55 (66.3)	122 (60.4)	0.35*
African descent	28 (33.7)	80 (39.6)	

* Chi-square test; ** *t*-test; bold emphasis indicates statistical significance ($P \leq 0.05$)

Table 3 Frequency of *MMP2* allele and genotype in tooth agenesis and control subjects

Subjects	n	Alleles, n (%)			Genotypes, n (%)			
		C	T	*P**	CC	CT	TT	*P**
Controls	202	283 (70.0)	121 (30)	-	107 (53.0)	69 (34.1)	26 (12.9)	-
Tooth agenesis								
All tooth agenesis	76	115 (75.7)	37 (24.3)	0.19	47 (61.9)	21 (27.6)	8 (10.5)	0.41
Upper lateral incisor	31	47 (75.8)	15 (24.2)	0.35	19 (61.3)	9 (29.0)	3 (9.7)	0.68
Premolar	34	54 (79.4)	14 (20.6)	0.11	23 (67.7)	8 (23.5)	3 (8.8)	0.28
Others	13	16 (61.5)	10 (38.5)	0.36	6 (46.1)	4 (30.8)	3 (23.1)	0.58
Affected side								
Unilateral	39	59 (75.6)	19 (24.4)	0.32	26 (66.7)	7 (17.9)	6 (15.4)	0.14
Bilateral	37	56 (75.7)	18 (24.3)	0.33	21 (56.8)	14 (37.8)	2 (5.4)	0.43
Dental arch								
Maxilla	36	54 (75.0)	18 (25.0)	0.39	22 (61.1)	10 (27.8)	4 (11.1)	0.66
Mandible	28	43 (76.8)	13 (23.2)	0.30	18 (64.3)	7 (25.0)	3 (10.7)	0.52
Both	12	18 (75.0)	6 (25.0)	0.61	7 (58.3)	4 (33.3)	1 (8.3)	0.88

* Chi-Square test and Fisher's exact tests; control group was used as a reference

statistical software package. The level of statistical significance was set at $P < 0.05$.

Frequencies of alleles and genotypes were analyzed statistically by using chi-squared or Fisher's exact test. Tooth agenesis was analyzed not only in the total subjects, but also in stratified subgroups: tooth agenesis type (all tooth agenesis, upper lateral incisor, premolar, others), affected side (unilateral, bilateral) and dental arch (maxilla, mandible, both). The tests determined if tooth agenesis or its subgroups were preferentially associated with *MMP2*, *MMP9* or *MMP13* genotypes and alleles.

Moreover, the standard chi-squared test was used to test for deviation from a Hardy-Weinberg equilibrium.

Results

The analysis showed that there were no significant differences in ethnicity between the groups ($P > 0.05$). A significant difference for factors such age and sex among the tooth agenesis and control groups was observed. The demographic characteristics of the studied population are summarized in Table 2.

Among the individuals with tooth agenesis, four had oligodontia (agenesis of six or more teeth), one had four congenitally missing teeth, five had three missing teeth, 29 had two missing teeth, and the remaining 44 subjects had just one missing tooth.

No significant association in relation to genotype or allele distribution for *MMP2* SNP was found between the tooth agenesis subgroups (tooth agenesis type, affected side and dental arch) and the controls; the results are shown in Table 3.

For *MMP9* polymorphism, there was a significant difference in the allele frequencies between the tooth agenesis and control groups ($P = 0.05$). The A allele frequency was 0.60 among the tooth agenesis group and 0.68 among the controls, while the G allele frequencies were 0.40 and 0.31, respectively. The frequency of the G allele was higher in the case group than in the control group. Regarding the affected side, there was a significant difference between individuals with unilateral tooth agenesis and the controls ($P = 0.05$). Also, there was a significant difference between tooth agenesis in the maxilla and the control group ($P = 0.03$) (Table 4).

For *MMP13* polymorphism, a significant differ-

Table 4 Frequency of *MMP9* allele and genotype in tooth agenesis and control subjects

Subjects	*n*	Alleles, *n* (%)			Genotypes, *n* (%)			
		A	G	*P**	AA	AG	GG	*P**
Controls	201	276 (68.7)	126 (31.3)	-	106 (52.7)	64 (31.9)	31 (15.4)	-
Tooth agenesis								
All tooth agenesis	83	100 (60.2)	66 (39.8)	**0.05**	35 (42.2)	30 (36.1)	18 (21.7)	0.22
Upper lateral incisor	34	43 (63.2)	25 (36.8)	0.38	14 (41.2)	15 (44.1)	5 (14.7)	0.35
Premolar	36	44 (61.1)	28 (38.9)	0.21	16 (44.5)	12 (33.3)	8 (22.2)	0.53
Others	18	20 (55.6)	16 (44.4)	0.11	7 (38.9)	6 (33.3)	5 (27.8)	0.34
Affected side								
Unilateral	45	52 (57.8)	38 (42.2)	**0.05**	18 (40.0)	16 (35.6)	11 (24.4)	0.21
Bilateral	38	48 (63.2)	28 (36.8)	0.35	17 (44.7)	14 (36.9)	7 (18.4)	0.66
Dental arch								
Maxilla	40	45 (56.3)	35 (43.7)	**0.03**	14 (35.0)	17 (42.5)	9 (22.5)	0.12
Mandible	31	39 (62.9)	23 (37.1)	0.37	16 (51.6)	7 (22.6)	8 (25.8)	0.29
Both	12	16 (66.7)	8 (33.3)	0.84	5 (41.7)	6 (50.0)	1 (8.3)	0.41

* Chi-Square test and Fisher's exact tests; control group was used as a reference; bold emphasis indicates statistical significance ($P \leq 0.05$)

Table 5 Frequency of *MMP13* allele and genotype in tooth agenesis and control subjects

Subjects	*n*	Alleles, *n* (%)			Genotypes, *n* (%)			
		A	G	*P**	AA	AG	GG	*P**
Controls	202	269 (66.6)	135 (33.4)	-	95 (47.0)	79 (39.1)	28 (13.9)	-
Tooth agenesis								
All tooth agenesis	81	108 (66.7)	54 (33.3)	0.98	42 (51.9)	24 (29.6)	15 (18.5)	0.28
Upper lateral incisor	34	47 (69.1)	21 (30.9)	0.68	19 (55.9)	9 (26.5)	6 (17.6)	0.36
Premolar	35	44 (62.9)	26 (37.1)	0.54	16 (45.7)	12 (34.3)	7 (20.0)	0.62
Others	17	22 (64.7)	12 (35.3)	0.82	9 (53.0)	4 (23.5)	4 (23.5)	0.35
Affected side								
Unilateral	42	57 (67.9)	27 (32.1)	0.82	25 (59.5)	7 (16.7)	10 (23.8)	**0.01**
Bilateral	39	51 (65.4)	27 (34.6)	0.84	17 (43.6)	17 (43.6)	5 (12.8)	0.87
Dental arch								
Maxilla	40	56 (70.0)	24 (30.0)	0.55	23 (57.5)	10 (25)	7 (17.5)	0.23
Mandible	29	38 (65.5)	20 (34.5)	0.87	15 (51.7)	8 (27.6)	6 (20.7)	0.40
Both	12	14 (58.3)	10 (41.7)	0.41	4 (33.3)	6 (50.0)	2 (16.7)	0.65

* Chi-Square test and Fisher's exact tests; control group was used as a reference; bold emphasis indicates statistical significance ($P \leq 0.05$)

ence was found for genotype frequencies between the unilateral tooth agenesis group and the control group ($P = 0.01$). Allele and genotype frequency comparisons between subgroups are summarized in Table 5.

Discussion

One of the challenges of studying a developmental dental anomaly such as tooth agenesis is the likely genetic factors that underlie inherited contributions to this disease. We believe that tooth agenesis subgroups may be used as an additional tool for clarifying the genetic etiology of this dental anomaly. Broadening the tooth agenesis phenotype would improve our understanding of the etiology of this condition by allowing affected individuals to be placed into more etiologically homogeneous categories. These more sophisticated clinical definitions would help to identify the genes involved in tooth agenesis.

The *MMP* family consists of more than 23 enzymes that can be classified into subfamilies such as collagenases, stromelysins, gelatinases, and membrane-type *MMPs* (22). *MMP2* and *MMP9* are gelatinases that can degrade denatured collagens (gelatins) and type IV collagen, which is the major structural component of the ECM (23). *MMP13*, also called collagenase-3, can degrade ECM components such as collagens, gelatin, aggrecan, perlecan, and fibronectin (24). *MMP13* is expressed in hypertrophic chondrocytes and osteoblasts during embryogenesis (25). It has been demonstrated

that *MMPs* play a critical role controlling remodeling of the extracellular matrix during development (26). Alterations of tissue remodeling during odontogenesis may explain the association between *MMP9*, *MMP13* and tooth agenesis.

To our knowledge this is the first reported study to have investigated *MMP2* polymorphism and its association with tooth agenesis. In mice, the distribution of *Mmp2* has been studied during early craniofacial morphogenesis, being particularly localized to outgrowth regions of the primary palate, mandible, and second branchial arch (27). It is well established that *MMP2* is also expressed in developing tooth tissues and plays an important role during the biomineralization processes responsible for the formation of enamel and dentin (28). Despite this participation, our present results did not show a significant association between tooth agenesis and controls in terms of genotype or allele distributions. Indeed, several genetic factors probably play different roles in tooth development. Moreover, experimental studies using distinct models and populations may also help to confirm or refute the present findings.

A study using animal models has demonstrated that Mmp9 is expressed by mesenchymal cells at the tip of the growing tooth bud (29). Its expression decreases progressively and no transcripts can be detected in dental mesenchyme after the cap stage. The present study indicated that *MMP9* polymorphism was associated with tooth agenesis, although Peres and Line (17) were unable to detect evidence of any association between the allele and genotype frequencies for polymorphism in this gene promoter and hypodontia (the most common form of tooth agenesis). Several hypotheses can explain this apparent discrepancy. First, Peres and Line (17) included in their study tooth agenesis of third molars. Second, their study involved only Caucasian individuals, whereas ours included individuals with various ethnicities. Third, Peres and Line (17) analyzed the risk in 52 cases and 48 controls, though this sample size was too small to yield a significant association. In *MMP9* analysis, we noted differences for maxillary tooth agenesis but not for mandible tooth agenesis. One possible reason for the difference between the arches may be that *MMPs* have a role in palatogenesis, and disruption of its activity can result in cleft palate (30). In some instances, oral clefts and tooth agenesis may share the same genetic background (2,31).

We also investigated promoter polymorphism in *MMP13* and found evidence for an association with unilateral tooth agenesis. Although a previous study has demonstrated that genetic variations in *MMP13* might contribute to caries susceptibility (32), the exact role of *MMP13* in tooth development cannot be explained by current knowledge. The extent to which this polymorphism may actually contribute to tooth formation status still remains to be clarified. It is reasonable to hypothesize that *MMP13* may be involved in regulating early tooth formation, and that tooth mineralization may also be affected. Thus, functional studies aiming to define the specific roles of matrix metalloproteinases in the development of dental alterations in humans are necessary to confirm our findings.

One additional worthwhile observation is that subtle random deviations from perfect bilateral symmetry, known as "fluctuating asymmetry", have been previously observed in tooth agenesis. In a Brazilian population, unilateral cases of tooth agenesis were more common than bilateral cases (33). We have recently proposed that distinctive genes could influence tooth agenesis laterality (33), and in the light of the results presented here, *MMP9* and *MMP13* appear to be associated only with unilateral forms of tooth agenesis.

In summary, our present findings have demonstrated that *MMP9* and *MMP13* contribute to tooth agenesis and will help to clarify the development and prevention of dental alterations in humans. The approach adopted in this study was limited in that only one genetic variant in each *MMP* gene was evaluated. To properly assess the association between the *MMP* genes and tooth agenesis, it would be preferable to take a tagging variant approach. Thus, further investigations of other polymorphisms in these genes, as well as a larger number of samples, would be necessary to confirm the involvement of *MMP9* and *MMP13* with tooth agenesis in different populations. Also, functional studies may lead to a better understanding of the effect of this polymorphism during odontogenesis.

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