



# Is Lateral Incisor Agenesis Associated with an Increased Occurrence of Tooth Agenesis Outside of the Cleft Region in Complete Bilateral Cleft Lip and Palate Patients?

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## Abstract

**Aim:** This study compared the prevalence of tooth agenesis out of the cleft area in patients with complete bilateral cleft lip and palate (BCLP) with and without agenesis of maxillary permanent lateral incisors.

**Methods:** Tooth agenesis was evaluated in panoramic radiographs taken between 7 and 11 years of age. Intergroup comparison of tooth agenesis frequency was performed using the chi-square test ( $P < 0.05$ ) and the odds ratio. A sample of 130 patients (87 male, 43 female) with non-syndromic bilateral cleft lip and palate was selected. Group P ( $n = 44$ ) consisted of individuals with the presence of maxillary lateral incisors on the right and left sides; group UA ( $n = 40$ ) comprised patients with unilateral agenesis of lateral incisors; group BA ( $n = 46$ ) comprised patients with bilateral agenesis of lateral incisors. Intergroup comparison for frequency of tooth agenesis outside the cleft area was performed using Chi-square test ( $p$ -value  $< 0.05$  was considered significant) and the odds ratio ( $p < 0.016$ ).

**Results:** The prevalence of dental agenesis out of the cleft area in groups P, UA, and BA was 31.8%, 32.5%, and 60.8%, respectively. Group BA showed a significantly greater prevalence of tooth agenesis compared with the UA and P groups. There was no significant difference in the odds ratio between any groups. The most common absent teeth were the maxillary second premolars followed by the mandibular second premolars for all groups.

**Conclusion:** Patients with BCLP and bilateral agenesis of maxillary lateral incisors show an increased prevalence of other permanent teeth. This association demonstrates a genetic background of maxillary lateral incisor agenesis at the cleft area.

**Keywords:** Cleft Lip and Palate, Hypodontia, Tooth Agenesis.

## 1. Background

Individuals with cleft lip and palate (CLP) have a higher prevalence of dental anomalies, even outside the cleft region, when compared to the general population (1-3). Tooth agenesis and microdontia are the most frequent dental anomalies in CLP (3-6). In patients with complete bilateral cleft lip and palate (BCLP), the maxillary lateral incisor (MxI2) is the most commonly absent tooth (5,7,8). Tooth agenesis was

found in 59.8% of patients with BCLP and MxI2 and maxillary and mandibular second premolars were the most frequently absent teeth (1).

Disruption related to cleft proximity including inadequate blood supply and lack of mesenchymal support is the environmental hypotheses that explain the high frequency of number, shape, and size of tooth anomalies involving MxI2 in cleft lip and palate (9,10). Additionally, the MxI2 has a complex embryonic origin, deriving from both medial nasal and

maxillary processes (11,12). On the other hand, both tooth agenesis and cleft lip and palate have a genetic basis (13-15). The simultaneous occurrence of oral clefts and dental anomalies might be a strong indication that a common genetic origin is involved and that a single contribution of the gene should not be ruled out (16,17). Tooth agenesis has also been identified as a potentially useful clinical marker to define the development of subphenotypes of isolated cleft without syndromes (16). Patterns of dental anomalies have been proposed within the cleft individual phenotypes (16). The authors indicated the need for a more sophisticated classification of subphenotypes of clefts based on the occurrence of different patterns of tooth development (16,18). A previous study (17) observed that patients with unilateral complete cleft lip and palate and agenesis of MxI2 on the cleft side have an increased prevalence of agenesis of other permanent teeth. The authors found agenesis of other permanent teeth in 58.5% of the individuals with absent MxI2 on the cleft side in contrast to 29.5% in individuals with the MxI2 at the cleft side (17). This evidence pointed out that cleft-side agenesis of MxI2 seems to be predominantly a genetically controlled anomaly associated with the developmental origin of oral clefts (17). No previous studies evaluated this same association in patients with bilateral complete cleft lip and palate (BCLP).

Therefore, this study aimed to compare the prevalence of tooth agenesis out of the cleft area in patients with BCLP with and without agenesis of maxillary lateral permanent incisors. The null hypothesis was that patients with BCLP and agenesis of MxI2 have a similar frequency of agenesis of other permanent teeth compared to patients with BCLP without agenesis of MxI2.

## 2. Methods

This study was evaluated and approved by the Ethics in Research Committee of Bauru Dental School, University of São Paulo. Considering a power of 80%, an alpha of 5%, and a minimum difference between groups of 30% (effect size, Cohen  $h = 0.61$ ), the minimum sample size required was 42.

A sample of patients with bilateral clefts born between the years 2000 and 2005, diagnosed by

medical records and registered in a single rehabilitation center was evaluated. The inclusion criterion was the availability of a good quality panoramic radiograph taken in the mixed dentition. The exclusion criterion was the presence of associated syndromes. The panoramic radiograph taken before phase I of orthodontic treatment and before the secondary alveolar bone graft procedure was used.

Considering the variations in MxI2 agenesis phenotype, the patients were divided into three groups: group P ( $n = 44$ ): individuals with the MxI2 on the right and left sides with a mean age of 8.75 y (29 male, 15 female); group UA ( $n = 40$ ): individuals with unilateral agenesis of the MxI2, with a mean age of 8.74 y (33 male, 7 female); group BA ( $n = 46$ ): individuals with bilateral agenesis of the MxI2 with a mean age of 8.97 y (25 male, 21 female). Patients had a mixed multi-ethnic population reflecting the population of the country. MxI2 was considered any tooth located between the maxillary central incisor and the canine, on the mesial or distal sides of the alveolar cleft (17). MxI2 agenesis was considered present when the lateral incisor was absent in the mesial and distal sides of the alveolar cleft.

Tooth agenesis outside the cleft area was considered when there was no evidence of the presence of tooth buds while the contralateral tooth had already reached or passed Nolla's stage 2 (19). Bilateral agenesis of the premolar was considered when both tooth germs were not apparent after age 8, considering delayed appearance is rare after this age. Third molars were not considered in this study.

## Statistical Analyses

Intergroup comparison for frequency of tooth agenesis outside the cleft area was performed using the chi-square test ( $p$ -value  $< 0.05$  was considered significant) and the odds ratio ( $p < 0.016$ ). All tests were performed with Statistica software (Release 7, StatSoft Inc., Tulsa, OK, USA).

## 3. Results

A significantly higher frequency of tooth agenesis outside the cleft area was found in group BA compared to the other groups (Tables 1 and 2).

**Table 1.** Comparison of tooth agenesis frequency outside the cleft region in the three groups

Groups	Tooth agenesis outside the cleft area		X	p
	n	%		
BA (n = 46)	28	60.87%	10.05	0.007*
UA (n = 40)	13	32.50%		
P (n = 44)	14	31.82%		
BA+UA+P (n=130)	55	42.31%		

\* Statistically significant ( $P < 0.05$ )

**Table 2.** Comparison of tooth agenesis frequency outside the cleft region in the three groups

	X <sup>2</sup>	p	OR	IC
BA x UA	6.90	0.009*	3.23	1.33 – 7.85
BA x P	7.63	0.006*	3.33	1.40 – 7.94
UA x P	0.00	0.947	1.03	0.41 – 2.58

\* Statistically significant p<0.016 according to Bonferoni correction

**Table 3.** Frequency of tooth agenesis in the maxilla teeth

	Maxillary Teeth													
	11	12	13	14	15	16	17	21	22	23	24	25	26	27
BA (n=46)	2.17 %(1)	100 %(46)	-(0)	6.52% (3)	36.96 %(17)	-(0)	-(0)	2.17 %(1)	100 %(46)	-(0)	6.52 %(3)	32.61 %(15)	- (0)	- (0)
UA (n=40)	- (0)	45% (18)	-(0)	-(0)	20% (8)	-(0)	-(0)	-(0)	55% (22)	-(0)	-(0)	15% (6)	-(0)	-(0)
P (n=44)	2.27 %(1)	-(0)	-(0)	2.27% (1)	20.45 %(9)	-(0)	-(0)	2.27 %(1)	-(0)	-(0)	-(0)	13.64 %(6)	-(0)	-(0)
Total(n =130)	1.54 %(2)	49.23 %(64)	-(0)	3.08% (4)	26.15 %(34)	-(0)	-(0)	1.54 %(2)	52.30 %(68)	-(0)	2.31 %(3)	20.77 %(27)	-(0)	-(0)

**Table 4.** Frequency of tooth agenesis in the mandible teeth

	Mandibular Teeth													
	31	32	33	34	35	36	37	41	42	43	44	45	46	47
BA (n=46)	-(0)	-(0)	-(0)	-(0)	10.87% (5)	-(0)	-(0)	-(0)	-(0)	-(0)	-(0)	8.7% (4)	-(0)	-(0)
UA (n=40)	-(0)	-(0)	-(0)	-(0)	5% (2)	-(0)	-(0)	-(0)	-(0)	-(0)	-(0)	10% (4)	-(0)	-(0)
P (n=44)	-(0)	-(0)	-(0)	-(0)	2.27% (1)	-(0)	-(0)	-(0)	-(0)	-(0)	-(0)	4.55 %(2)	-(0)	-(0)
Total (n=130)	-(0)	-(0)	-(0)	-(0)	6.15% (8)	-(0)	-(0)	-(0)	-(0)	-(0)	-(0)	7.69 %(10)	-(0)	-(0)

The odds ratio was approximately 3 for both comparisons (Table 2). No significant difference was found between groups UA and P for the prevalence of tooth agenesis (Table 3). The maxillary second premolars were the most frequently absent teeth in all the groups followed by mandibular second premolars (Tables 3 and 4).

#### 4. Discussion

The sample size collected for this study in a single center allowed stratification of the sample into three subgroups according to the presence/absence of the Mx12 at the cleft region. The Mx12 presents a complex origin and represents the most frequently absent tooth in patients with cleft lip and palate (7,9,10,12). There are two possible explanations for the developmental vulnerability for tooth agenesis in CLP: the environmental origin and the genetic origin (20,21). According to the environmental origin theory, the Mx12 agenesis at the cleft area could be a local effect of the cleft disturbance due to inadequate blood supply, lack of mesenchymal support, or other local disruptions related to cleft proximity (7,9,10). On the other hand, the genetic

theory advocates that some gene mutations might determine both CLP and tooth agenesis (17). A common background between CLP and tooth agenesis is supported by the high prevalence of tooth agenesis outside the cleft area in CLP (5). Additionally, non-cleft siblings of patients with CLP have an increased prevalence of tooth agenesis compared to the general population (1,22).

Our findings contribute additional evidence to the genetic theory. According to the results, patients with BCLP and bilateral agenesis of Mx12 demonstrate a two-fold higher prevalence of tooth agenesis outside the cleft region (Table 1). These results corroborate the findings by Dentino et al. (17) that found a two-fold greater prevalence of permanent tooth agenesis in patients with UCLP and cleft-side Mx12 compared to patients with UCLP without Mx12 agenesis. According to the authors, significant increase in overall tooth agenesis in a subsample with cleft-side Mx12 agenesis supported the inference that cleft-side Mx12 agenesis in CLP subjects is largely a genetically mediated anomaly associated with the genetics of CLP development (17). In addition, these results demonstrate that both UCLP and

BCLP have similar patterns of association between MxI2 agenesis and other permanent tooth agenesis. Additionally, this similarity between UCLP and BCLP provides further support for the evidence that both types of clefts have similar genetic backgrounds (23).

Recent molecular studies identified mutations of genes influencing tooth development in individuals with cleft lip and palate (15,24). PAX9 and MSX1 genes have been identified as candidates for the main causes of hypodontia and oligodontia (15,24). PAX9 is responsible for BMP4 which also regulates expression of MSX1 (15). Mutation of MSX1 is associated with missing premolars and certain conditions such as CLP (25,26). In human studies, an association between genetic disturbances of MSX1 and PAX9 genes and tooth agenesis within and outside the cleft area were revealed (27).

This study showed higher prevalence of ageneses of maxillary and mandibular second premolars in patients with BCLP and MxI2 agenesis (Tables III and IV). Rizell et al. (28) also found that the maxillary second premolar is the most absent tooth outside the cleft site. A previous study evaluating the prevalence of tooth agenesis in a sample of patients with BCLP reported that the lateral incisor was the most affected tooth, followed by the maxillary second premolar and the mandibular second premolar (5).

The limitation of this study was the inclusion of patients from a single center with multiple ethnic backgrounds. These results should be applied with caution to patients with other ethnic backgrounds. Therefore, further studies should evaluate patients with BCLP in different populations.

Our findings allow us to infer that MxI2 agenesis in CLP subjects is largely a genetically mediated anomaly associated with the genetics of CLP development and not directly related to disruptive bony defects or surgical procedures at birth. The disadvantages of these outcomes is that the agenesis of the lateral incisor cannot be prevented because it is a result of genetic background.

## Conclusion

The absence of maxillary lateral incisor in patients with bilateral complete cleft lip and palate is associated with an increased prevalence of agenesis of other permanent teeth.

These findings support the evidence that tooth absence in the cleft area has some genetic background besides being influenced by local factors related to the presence of the alveolar cleft.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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