Prevalence of tooth agenesis and supernumerary teeth related to different Thai cleft lip and cleft palate populations

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Abstract

Background Pattern of dental anomalies encountered in cleft patients shows subtle signs of genetic involvement. This study aimed to evaluate the prevalence and pattern of tooth agenesis and supernumerary teeth in Thai cleft population according to the cleft type.

Methods Data collected from patients with cleft lip and palate, who had been treated at Tawanchai Cleft Center, Khon Kaen University, Thailand, available during year 2012–2022, were investigated. Records from 194 patients with non-syndromic clefts met the inclusion criteria. Standard dental records, and at least either orthopantomogram (OPG) or cone beam computed tomography (CBCT), were examined. Statistical analysis was performed using chi-square and binominal test ($p \leq 0.05$).

Results Prevalence of tooth agenesis was higher (77.3%) than that of supernumerary teeth (5.7%) and was more common in bilateral cleft lip and palate (BCLP) (88.1%) than in unilateral cleft lip and palate (UCLP) (72.6%) ($p = 0.017$). The upper lateral incisor was more frequently affected (46.4%), followed by the upper second premolar. The number of missing teeth observed on the left side was significantly higher. Patients with left UCLP (ULCLP) had the highest prevalence of tooth agenesis. A total of 41 tooth agenesis code (TAC) patterns was found. The prevalence of supernumerary teeth was comparable with 6.6% of ULCLP, 5.1% of BCLP, and 4.5% of URCLP. Tooth-number anomalies were observed more often in the BCLP and were most likely to occur on the left side of the maxilla. Both types of anomalies could be featured in a small proportion of cleft patients.

Conclusions More than half of the patients with non-syndromic cleft lip and palate in this study, presented with tooth-number anomalies. Tooth agenesis was approximately 10-time more prevalent than supernumerary teeth. Tooth agenesis was likely to appear on the left-side of the maxilla regardless of the laterality of the cleft.

Keywords Cleft lip and cleft palate, Tooth agenesis code (TAC), Supernumerary teeth, Cleft sidedness, Dentofacial deformity

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Background

Orofacial cleft is one of the most common congenital defects. Cleft lip with or without cleft palate, and cleft palate alone, are collectively referred to as orofacial cleft. According to the recent meta-analysis, the prevalence of orofacial clefts is 0.3–0.45 in 1,000 live births, globally [1]. In Thailand, the prevalence is relatively high at 2.14 per 1,000 live births, according to a nation-wide registry-based study [2].

Various types of dental anomalies, mainly number, size, shape, structure, and eruption, could be found in patients with orofacial cleft as well as in the unaffected family member of the cleft patient [3–5]. In orofacial deformities, the prevalence of dental anomalies appears to be higher than non-cleft population [3–5]. Among these anomalies, tooth agenesis, supernumerary teeth, developmental enamel defects, microdontia/peg-shaped anterior teeth, and taurodontism are listed as the common dental anomalies in patients with orofacial clefts [3, 6]. Recent meta-analysis showed that tooth agenesis and supernumerary teeth [3] in orofacial cleft population were found to be much higher than in a healthy Asian population. Speculation has arisen from these findings as to whether factors underlying cleft formation might also be associated with dental development.

During embryogenesis, the formation of maxillary permanent incisors could be affected by failure of palate development, as they are derived from common primordium. Various molecular pathways and gene-environment interactions have been shown to be involved in common processes underlying palate and tooth development [7]. Disturbances in palate development might also interfere with the regulation of tooth development, and vice versa. Division of tooth primordia or proliferation of the dental lamina can lead to additional tooth while malformation or incapable growing tooth bud can result in micro-size or even non-formation of the tooth [4, 8]. Tooth-number anomalies do not arise randomly but according to certain patterns linked to their genetic etiology, and this is also seen in some syndromes with clefts [9]. External factors, such as, surgical repairs that usually performed under general anesthesia during early childhood, could disturb the developing permanent tooth buds adjacent to the surgical or the intubation sites, which leads to arrest of tooth development [4, 10]. In view of craniofacial development, reasonable number of teeth in the arch ensures that the maxillary growth could maximize to its potential, and subsequently contribute to normal relationship of the intermaxillary arch [11].

Data on the occurrence of dental anomalies and exposure to associated factors, could be pooled from patients with orofacial clefts, from various genetic/geographic backgrounds who might also receive different treatment protocols. Recent genomic research on cranial neural crest cells, crucial for craniofacial development, has unveiled a molecular profile linked to tooth formation [12]. Systematic analysis of these epidemiological data could illuminate connections between tooth development and palate formation, advancing precision diagnosis for syndromic clefts.

The aim of this retrospective study was to evaluate the prevalence and pattern of tooth agenesis and supernumerary tooth in association with cleft side, and cleft type in non-syndromic cleft lip and palate population of the North-eastern part of Thailand.

Materials and methods

This retrospective study was carried out in the Pediatric Dentistry Clinic, Department of Preventive Dentistry, Faculty of Dentistry, Khon Kaen University, Thailand and approved by the ethical review committee, Khon Kaen University Ethic Committee, Thailand (HE661161).

Data was obtained from the dental records of the northeastern Thai cleft patients, which had been registered, treated, and followed up at Tawanchai Cleft Center, Khon Kaen University, Thailand between January 2012 to August 2022. Patient's data was collected at the age range of 3 years to 12 years and 11 months old, at the time when tooth-chart was recorded, and radiographs taken. Either analyzable orthopantomogram (OPG) or cone beam computed tomography (CBCT) were available. All OPGs and CBCTs for cleft patients have been performed and interpreted by radiologists.

The exclusion criteria were patients with; (1) any severe associated medical conditions, which might affect odontogenesis such as, coexisting syndrome, congenital heart disease, severe developmental impairment; (2) isolated cleft palate, cleft of the lip and alveolus without cleft palate, and those with atypical clefts; (3) already started orthodontic treatment at the time of radiographic examination.

To elicit the pattern of tooth agenesis, we employed the system devised by van Wijk and Tan (2006). The system was classified into two categories: 0 for the presence of a tooth and the absence of specific tooth types, each assigned a distinct value. 1 for central incisor, 2 for lateral incisor, 4 for canine, 8 for first premolar, 16 for second premolar, 32 for first molar, 64 for second molar, and 128 for third molar were each associated with their respective values. The cumulative score was derived from the sum of these values corresponding to the missing tooth types in each quadrant, yielding a unique numeric representation for each pattern of tooth agenesis. This numerical code denoting the pattern of tooth agenesis was termed the tooth agenesis code (TAC) [13]. This TAC method facilitates data analysis and research into pattern of missing teeth and may contribute to point towards a genetic etiology [13]. For a tooth agenesis code (TAC)

Table 1 Sample recruitment according to the cleft type

Cleft Patients (*n* = 235)	*n* (%)
Included samples in this study (*n* = 194)	
UCLP	135 (69.6)
BCLP	59 (30.4)
Excluded samples from this study (*n* = 41)	
Isolated CL	19 (46.3)
Isolated CP	12 (29.3)
Bilateral CL and alveolar	0 (0)
Unilateral CL and alveolar	10 (24.4)
Atypical cleft	0 (0)

UCLP, Unilateral cleft lip and palate; BCLP, Bilateral cleft lip and palate; CL, cleft lip; CP, cleft palate

of 000.099.026.130, for example, digits signify specific quadrants i.e., 000 corresponds to the first quadrant, 099 to the second quadrant, 026 to the third quadrant, and 130 to the fourth quadrant. The number 099 (representing the second quadrant) is derived from the cumulative values of 1 (missing central incisor), 2 (missing lateral incisor), 32 (missing first molar), and 64 (missing second molar).

For each patient, numbers of permanent teeth were screened, excluding the third molars, using dental records and in the radiographs, at least either OPG or CBCT, by one investigator (WPA). If available, occlusal tomograph and intraoral radiographs were additionally checked, to eliminate ambiguity and ensure reliable results. All radiographic examinations were chosen at the first-time examined to abstain tooth missing from extraction. In patients under 6 years of age, the presence of tooth buds, especially of the 2nd premolars was affirmed in other radiographs taken at the age of 6 and above. Data was re-examined by SM and further compared to the available intraoral photographs. In case of inconsistency, difficulty of interpretation or unclear findings, the observers (WPA-SM) resolved the issue through face-to-face discussion. If no agreement could be reached, the patient was excluded from the study.

The prevalence of each dental anomaly in different cleft types and the combination of various anomalies were calculated. The chi-square test was used to test the significance of differences in the proportions of dental anomalies in different types. Statistical significance for all tests was set at $p < 0.05$. Statistical analysis was performed using the program Statistical Package for the Social Sciences version 28 (IBM SPSS, Inc., Chicago, IL).

Results

In this retrospective study, tooth numbers could be accurately obtained from existing radiographs or CBCT. These anomalies were differentiated according to the cleft type and laterality. We further analyzed the distribution of tooth agenesis and mapping the percentage found in each tooth, onto the maxilla arch. 194 samples out of 235

Table 2 Distribution of samples according to genders, cleft types, and cleft sides

Gender	Cleft type (*n* = 194)				
	UCLP (*n* = 135)			BCLP (*n* = 59)	Total Cleft
	Right	Left	Total UCLP		
Male	31 (70.5%)	38 (41.8%)	69 (51.1%)	39 (66.1%)	108 (55.7%)
Female	13 (29.5%)	53 (58.2%)	66 (48.9%)	20 (33.9%)	86 (44.3%)
Total	44 (100%)	91 (100%)	135 (100%)	59 (100%)	194 (100%)
(% by side of cleft)	(32.6)	(67.4)	(100.0)	-	-
% by Cleft type	69.6			30.4	100.0

UCLP, Unilateral cleft lip and palate; BCLP, Bilateral cleft lip and palate

Table 3 Comparison of samples with TA between UCLP and BCLP groups

Dental anomalies	Cleft type (*n* = 194)			
	UCLP (*n* = 135)	BCLP (*n* = 59)	Total	*P*value[a]
	n (%)	n (%)	n (%)	
Tooth Agenesis				0.017*
Yes	98 (50.5)	52 (26.8)	150 (77.3)	
No	37 (19.1)	7 (3.6)	44 (22.7)	
Number of missing teeth	UCLP (*n* = 98)	BCLP (*n* = 52)	Total	-
1 tooth	45 (45.9)	20 (38.5)	65 (43.3)	
2 teeth	31 (31.6)	20 (38.5)	51 (34.0)	
3 teeth	15 (15.3)	5 (9.6)	20 (13.3)	
4 teeth	5 (5.1)	6 (11.5)	11 (7.3)	
5 teeth	1 (1.0)	1 (1.9)	2 (1.3)	
> 5 teeth	1 (1.0)	0 (0)	1 (0.7)	

TA, Tooth agenesis; UCLP, Unilateral cleft lip and palate; BCLP, Bilateral cleft lip and palate; n, absolute number of samples; (%), percentage of sample; [a] Chi square test; * Statistically significant at < 0.05

cleft lip and/or palate patients met the inclusion criteria (Table 1), comprising of 108 males and 86 females (1.3:1 male to female ratio) (Table 2). Based on cleft types, 135 patients were classified as unilateral clefts (UCLP), of which 44 were on the right side and 91 were on the left side (Table 2).

Tooth agenesis
Tooth agenesis was observed in 150 out of 194 individuals (77.3%) (Table 3), with equal distribution between 78 in male (72.2%) and 72 in female (83.7%). Tooth agenesis affected 88.1% of BCLP patients (Table 3), while the occurrence was 73.6% and 70.5% among unilateral right cleft lip and palate (URCLP), and unilateral left cleft lip and palate (ULCLP) patients, respectively (Table 4). The prevalence of tooth agenesis in BCLP group was statistically higher when compared to that of UCLP ($p = 0.017$).

Table 4 Comparison of samples with TA in UCLP group between left and right sides

Dental anomalies	Cleft type (*n* = 135)			
	URCLP (*n* = 44)	ULCLP (*n* = 91)	Total	*P*val-ue[a]
	n (%)	n (%)	n (%)	
Tooth Agenesis				0.699
Yes	31 (23.0)	67 (49.6)	98 (72.6)	
No	13 (9.6)	24 (17.8)	37 (27.4)	
Number of missing teeth	URCLP (*n* = 31)	ULCLP (*n* = 67)	Total	-
1 tooth	16 (51.6)	29 (43.3)	45 (45.9)	
2 teeth	7 (22.6)	24 (35.8)	31 (31.6)	
3 teeth	2 (6.5)	13 (19.4)	15 (15.3)	
4 teeth	5 (16.1)	0 (0)	5 (5.1)	
5 teeth	1 (3.2)	0 (0)	1 (1.0)	
>5 teeth	0 (0)	1 (1.5)	1 (1.0)	

TA, tooth agenesis; URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; n, absolute number of samples; %, percentage of sample, [a] Chi square test;

In UCLP samples, the prevalence of tooth agenesis between ULCLP and URCLP was not statistically different ($p = 0.699$) (Table 4). The frequency of missing teeth per patient is also presented in Tables 3 and 4.

For tooth agenesis characterization, a total of 287 teeth were missing (Table 5). Figure 1 also shows distribution of the missing teeth. The upper lateral incisor was the most commonly missing tooth (46.4%, 180 of 388 missing teeth), followed by the maxillary second premolar (18.8%). Two patients with single-canine agenesis were members of the UCLP groups (TAC 000.006.000.000 and 030.018.000.000). In UCLP samples, there was no missing central incisor at the contralateral side. In BCLP samples, the right central incisor was always present (0%). None of maxillary permanent molars were missing (0%). The average of missing teeth per patient was 1.47 teeth that could subdivide into 1.76, 1.39, and 1.34 missing teeth per patient in the BCLP, URCLP, and ULCLP groups, respectively.

We further analyzed the laterality of tooth agenesis in patients with UCLP (Table 6) with a higher proportion of missing teeth in the left-sided cleft. The disparity in the side of tooth agenesis was obvious in this left side group ($p = 0.008$). Notably, the ULCLP group exhibited a greater prevalence of tooth agenesis on both sides compared to the URCLP group (72.7% and 27.3%, respectively).

Data about tooth agenesis was encoded using Tooth Agenesis Code (TAC), which is a valuable tooth agenesis

Table 5 Distribution of sample with TA and number of TA according to cleft types and tooth types

Cleft Type	Type of Tooth									Missing teeth per person
	12	22	14	24	15	25	O.Max	Mand	total	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
URCLP										1.39
No. of patient	20 (45.5)	17 (38.6)	3 (6.8)	0 (0)	8 (18.2)	10 (22.7)	2 (4.6)	1 (2.3)	44 (100.0)	
No. of missing teeth	20 (32.8)	17 (27.9)	3 (4.9)	0 (0)	8 (13.1)	10 (16.4)	2 (3.3)	1 (1.6)	61 (100.0)	
ULCLP										1.35
No. of patient	23 (25.3)	55 (60.4)	1 (1.1)	6 (6.6)	17 (18.7)	13 (14.3)	3 (3.3)	5 (5.5)	91 (100.0)	
No. of missing teeth	23 (18.9)	55 (45.1)	1 (0.8)	6 (4.9)	17 (13.9)	13 (10.7)	3 (2.5)	5 (4.1)	123 (100.0)	
UCLP										1.36
No. of patient	43 (31.9)	72 (53.3)	4 (3.0)	6 (4.4)	25 (18.5)	23 (17.0)	5 (3.7)	6 (4.4)	135 (100)	
No. of missing teeth	43 (23.5)	72 (39.3)	4 (2.2)	6 (3.3)	25 (13.7)	23 (12.6)	5 (2.7)	6 (3.3)	183 (100)	
BCLP										1.76
No. of patient	29 (49.2)	36 (61.0)	1 (1.7)	2 (3.4)	14 (23.7)	13 (22.0)	1 (1.7)	7 (11.9)	59 (100)	
No. of missing teeth	29 (27.9)	36 (34.6)	1 (1.0)	2 (1.9)	14 (13.5)	13 (12.5)	1 (1.0)	7 (6.7)	104 (100)	
All Cleft patients										1.48
No. of patient	72 (37.1)	108 (55.7)	5 (2.6)	8 (5.9)	39 (20.1)	36 (18.6)	6 (3.1)	13 (6.7)	194 (100)	
No. of missing teeth	72 (25)	108 (37.5)	5 (1.7)	8 (2.8)	39 (13.5)	36 (12.5)	6 (2.1)	13 (4.5)	288 (100)	

URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; UCLP, Unilateral cleft lip and palate; BCLP, Bilateral cleft lip and palate; n, absolute number of samples with TA; (%), percentage value of the samples with TA, O. Max, other maxillary teeth; Mand, any teeth in mandible

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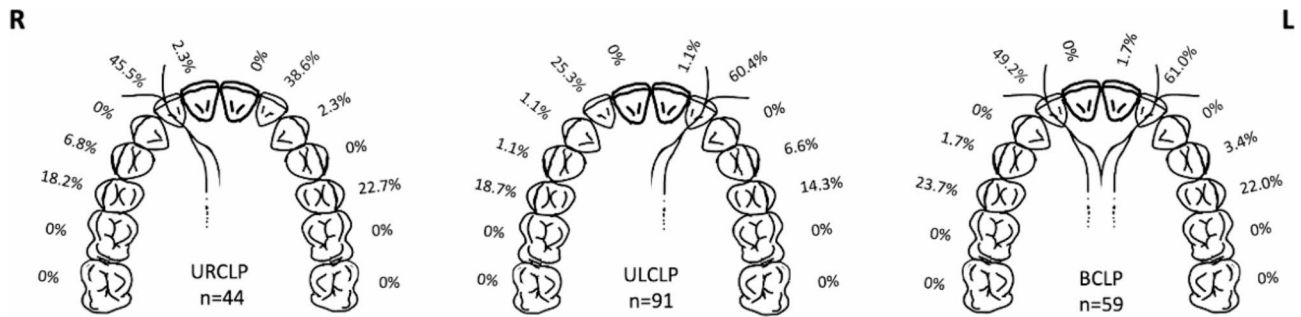
Fig. 1 Percentage of samples with TA according to each specific tooth in different cleft types. URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; BCLP, Bilateral cleft lip and palate; TA, Tooth agenesis

Table 6 Laterality of TA according to cleft sides in UCLP groups

Laterality	URCLP n (%)	ULCLP n (%)	Total n (%)	P value[a]
Left-sided TA	9 (24.3)	28 (75.7)	37 (100)	0.008*
Right-sided TA	9 (69.2)	4 (30.8)	13 (100)	
Both-sided TA	12 (27.3)	32 (72.7)	44 (100)	
Total	30 (31.9)	64 (68.1)	94 (100)	

TA, Tooth agenesis; URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; [a] Chi square test; * Statistically significant at <0.05

pattern used to classify the dental subphenotypes of non-syndromic orofacial cleft patients. Tooth agenesis patterns were coded using TAC (Table 7). Out of the 39 different TAC patterns found in the study; "no tooth agenesis" was the most seen code. 23 patterns were unique and individually observed in one single patient. We categorized TACs based on cleft diagnoses; URCLP with 16 patterns, ULCLP with 19 patterns, and BCLP with 23 patterns. TAC pattern for no tooth agenesis was found in 44 samples (out of 194 samples). Among 44 URCLP samples, the most prevalent pattern was no tooth agenesis (13 samples), followed by the absence of the maxillary right lateral incisor (TAC 002.000.000.000; 8 samples), which was the ipsilateral side missing tooth. The code for missing maxillary left lateral incisor at contralateral cleft side; TAC 000.002.000.000, was the third most common pattern, being found in 6 samples.

In the ULCLP group, the highest frequency occurred with the TAC pattern for no tooth agenesis (24 samples), followed by the pattern for missing maxillary left lateral incisor, ipsilateral side, (TAC 000.002.000.000; 21 samples), both maxillary lateral incisors being absent (TAC 002.002.000.000; 9 samples), and the combination of the missing maxillary right second premolar and left lateral incisor (TAC 016.002.000.000; 8 samples). In the BCLP group, the predominant pattern consisted of both maxillary lateral incisors being absent (12 samples), followed by the single absence of the maxillary left lateral incisor, 22, (9 samples), and the pattern for no tooth agenesis (7 samples).

Among the ULCLP samples, the frequency of the code for missing maxillary left lateral incisor and right

second premolar (22, 15 TAC 016.002.000.000; 4.4%) was double the number of patients with the code for maxillary left lateral incisor and left second premolar (22, 25 TAC 000.018.000.000; 8.9%). Similar patterning was also observed in URCLP samples. More samples with missing ipsilateral lateral incisor along with contralateral second premolar (12, 25 TAC 002.016.000.000) than samples with missing ipsilateral lateral incisor along with contralateral second premolar (12, 15 TAC 018.000.000.000) in URCLP.

Supernumerary tooth
Among 194 samples studied, there were 11 patients (5.7%) with 12 supernumerary teeth. When considering this proportion by gender, supernumerary teeth could be found in 5 (5.8%) out of 85 female and 6 (5.6%) out of 108 male patients. Table 8 showed distribution of supernumerary teeth according to genders and cleft types. In this study, supernumerary teeth tend to appear in the anterior region of the maxilla. Notably, only one sample of supernumerary tooth was identified in the mandible of a BCLP patient (Table 9).

Regarding the cleft type, individuals with ULCLP (6.6%) tended to show a higher occurrence of supernumerary teeth higher occurrence of supernumerary teeth compared to those with BCLP (5.1%) and URCLP (4.5%). Furthermore, among the 9 supernumerary teeth identified in patients with unilateral clefts, 7 were situated within the cleft area, with only 2 located on the contralateral side (data not shown).

Both tooth agenesis and supernumerary teeth
In our study, simultaneous occurrence of tooth agenesis and supernumerary teeth was observed only in BCLP and ULCLP groups (Table 9).

Discussion
Syndromic orofacial clefts have often been underdiagnosed. For dental professionals, tooth anomalies are easily recognizable and may be considered as dysmorphic developmental signs participating in syndrome clinical

Table 7 Distribution of TA by TAC according to cleft types and cleft sides

TAC	Tooth/Teeth missing	*n* of teeth	*n* of samples			
			URCLP	ULCLP	BCLP	Overall
000.000.000.000	None	**0**	13	24	7	**44**
000.002.000.000	22	**1**	6	**21**	9	**36**
002.002.000.000	12, 22	**2**	2	9	**12**	**23**
002.000.000.000	12	**1**	**8**	3	6	**17**
016.002.000.000	15, 22	**2**	-	8	1	**9**
000.018.000.000	22, 25	**2**	2	4	1	**7**
002.018.000.000	12, 22, 25	**3**	1	3	1	**5**
018.018.000.000	15, 12, 22, 25	**4**	2	-	3	**5**
016.000.000.000	15	**1**	1	-	3	**4**
018.002.000.000	15, 12, 22	**3**	-	2	2	**4**
000.016.000.000	25	**1**	-	2	1	**3**
000.000.000.016	45	**1**	-	3	-	**3**
002.016.000.000	12, 25	**2**	2	-	1	**3**
016.018.000.000	15, 22, 25	**3**	-	2	1	**3**
016.016.000.000	15, 25	**2**	-	-	2	**2**
002.010.000.000	12, 22, 24	**3**	-	2	-	**2**
000.000.002.000	32	**1**	1	-	-	**1**
000.006.000.000	22, 23	**2**	1	-	-	**1**
018.016.000.000	15, 12, 25	**3**	1	-	-	**1**
026.002.000.000	15, 14, 12, 22	**4**	1	-	-	**1**
026.016.000.000	15, 14, 12, 25	**4**	1	-	-	**1**
019.002.000.000	15, 12, 11, 22	**4**	1	-	-	**1**
026.018.000.000	15, 14, 12, 22, 25	**5**	1	-	-	**1**
018.000.000.000	15, 12	**2**	-	1	-	**1**
000.002.016.000	22, 35	**2**	-	1	-	**1**
016.024.000.000	15, 24, 25	**3**	-	1	-	**1**
016.010.000.000	15, 22, 24	**3**	-	1	-	**1**
003.002.000.000	12, 11, 22	**3**	-	1	-	**1**
002.002.016.000	12, 22, 35	**3**	-	1	-	**1**
030.018.000.000	15, 14, 13, 12, 22, 25	**6**	-	1	-	**1**
000.000.016.000	35	**1**	-	-	1	**1**
016.000.000.002	15, 42	**2**	-	-	1	**1**
002.000.016.000	12, 35	**2**	-	-	1	**1**
008.002.000.000	14, 22	**2**	-	-	1	**1**
000.018.016.000	22, 25, 35	**3**	-	-	1	**1**
018.002.016.000	15, 12, 22, 35	**4**	-	-	1	**1**
002.026.000.000	12, 22, 24, 25	**4**	-	-	1	**1**
002.002.016.016	12, 22, 35, 45	**4**	-	-	1	**1**
002.026.000.016	12, 22, 24, 25, 45	**5**	-	-	1	**1**

TA, Tooth agenesis; TAC, Tooth agenesis code; CLP, cleft lip and palate; n, number; URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; UCLP, Unilateral cleft lip and palate; BCLP, Bilateral cleft lip and palate

Table 8 Distribution of samples with supernumerary teeth according to cleft types, and genders

Supernumerary teeth	URCLP			ULCLP			BCLP		
	M *n* (%)	F *n* (%)	Total *n* (%)	M *n* (%)	F *n* (%)	Total *n* (%)	M *n* (%)	F *n* (%)	Total *n* (%)
Yes	1 (3.2)	1 (7.7)	2 (4.5)	4 (10.5)	2 (3.8)	6 (6.6)	1 (2.6)	2 (10.0)	3 (5.1)
No	30 (96.8)	12 (92.3)	42 (95.5)	34 (89.5)	51 (96.2)	85 (93.4)	38 (97.4)	18 (90.0)	56 (94.9)
Total	31 (100)	13 (100)	44 (100)	38 (100)	53 (100)	91 (100)	39 (100)	20 (100)	59 (100)

URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; UCLP, Unilateral cleft lip and palate; BCLP, Bilateral cleft lip and palate; M, male; F, female; n, absolute number; (%), percentage

Table 9 Distribution of samples who has both tooth agenesis and supernumerary tooth

Cleft type	Gender	Tooth agenesis (tooth number)	Supernumerary tooth (in the closest proximity to)
BCLP	F	15, 12, 22	42
BCLP	M	22	11
BCLP	F	12, 25	22
ULCLP	F	15, 22, 25	22
ULCLP	F	12, 22	21

BCLP, Bilateral cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; M, male; F, female

synopsis and diagnosis [14]. Due to dental anomalies, these patients often experience dental caries and malocclusion, resulting in poorer oral health-related quality of life [15]. Early detection and appropriate treatment are therefore crucial for improving outcomes in these patients. However, patterns of dental anomalies like hypodontia in syndromic clefts are not well-documented. Would the association of a cleft and tooth agenesis especially outside the cleft area be considered as two independent traits defining a genetically/syndromic related disorder, rather than environmental factors? Our retrospective study examined the prevalence of tooth number anomalies, namely tooth agenesis and supernumerary teeth, in permanent dentition of children with cleft lip and palate.

In the general population, the prevalence of tooth-number anomalies, both tooth agenesis and supernumerary teeth, were not as high as those reported in the cleft population. According to the recent meta-analysis and systemic review in mainstream Asian population, 6.3% of individuals had tooth agenesis excluding the wisdom tooth [16] and around 0–3% had supernumerary teeth [17]. In this study, the prevalence of tooth agenesis in an orofacial cleft population was found approximately 13 times higher.

Individuals recruited in this study were derived from non-syndromic, homogenous ethnicity of the northeastern Thai population who had undergone calibrated treatments under the Khon Kaen University Cleft Protocol [18]. Almost all data were obtained from digital Orthopantomograms and CBCTs. The majority of malformations were unilateral cleft, where the left side was more affected. Bilateral cleft lips were observed predominantly in male, whereas the gender ratio in unilateral clefts was comparable. The distribution of demographic data in this study e.g., more proportion of UCLP than BCLP, resembles other reports in the cleft populations [19, 20]. Besides atypical clefts, this study further excluded the cleft of the lip/alveolar and isolated cleft palate, because cleft lip and palate is a more severe form of malformation, and the diagnosis of this cleft type is undoubtful.

Tooth agenesis

Tooth agenesis is regarded as the most frequently seen dental anomaly in cleft population [3, 5]. In this study, 77.3% of the cleft patients analyzed, had congenital missing teeth. This is slightly larger than the 52.7–73.5% reported in comparable studies in Asian population, [21–23] though is close to the prevalence found in the Nepalese population (77.9%) [24]. Generally, the percentage of tooth agenesis in our and other Asian studies is higher than those reported in the European and Australian populations [3, 5, 6], with the exception of 83.8%, reported in a 2018 French study [20].

Most tooth agenesis cases found in this study were mild with 1 to 2 missing teeth. Further analysis showed that the most frequently absent tooth is the maxillary lateral incisor, followed by the maxillary second premolar, which is similarly found in other studies [6, 19–22, 24]. The most common missing tooth, the upper lateral incisor, was observed in 37% cases on the right, and more often on the left side at 55.7%. These figures appeared to be higher than the one reported in other studies with percentages ranging from 21.9 to 24% on the right side, and 32.5–33.2% on the left side [21, 24]. Notably, the prevalence of missing upper lateral incisors was always higher on the left side in our and other studies.

This study also highlights a higher prevalence of missing upper second premolars at approximately 20%, compared to 7.8–14.4% previously reported in both Asian and European studies [6, 21, 24]. However, mandibular second premolars were missing at a rate of 5.7%, which was in the range of the prevalence described in other studies (3–11%) [6, 20, 21].

Regardless of tooth types, percentage of tooth agenesis was higher in the BCLP patients. In UCLP patients, the prevalence was higher on the cleft side, compared to the unaffected side of the maxilla, observation which was also described in previous studies [6, 20, 21]. In both unilateral and bilateral CLP, tooth agenesis was significantly higher on the left side. TACs involving only the maxillary lateral incisor, either single or bilaterally, were representing a large subgroup of 39%, as expected. The pattern of missing lateral incisors on ipsilateral cleft-side was the most common pattern of tooth agenesis in all cleft groups, similar to the patterns reported by other studies in cleft populations [25, 26]. Previous studies did not describe the TAC pattern in association to the cleft types [25, 26].

When cleft laterality was accounted for, the pattern for missing of ipsilateral lateral incisor along with contralateral second premolar was more frequently observed than the pattern for missing ipsilateral lateral incisor with ipsilateral second premolar. These findings suggested that the influence of genetic regulation underlying premolar development, in the contralateral (unaffected cleft side),

might be unrelated to the formation of cleft, rather than the environmental "mechanistic" factors like limited arch space of the segment on the affected side. It has been showed that tooth missing outside the cleft and its laterality was likely to correlate to genetic influences as in the non-cleft population [27].

A hypothesis of dual embryonic origin of maxillary lateral incisor proposes that this tooth forms from two distinct primordia. The mesial portion of the lateral incisor is probably derived from the medial nasal process arising from the frontonasal process while the distal portion of the incisor might originate from the maxillary process [7]. Even though there is no correspondence with the cleft location and the suture distal to the lateral incisor, clefting could affect the partial portion of each process resulting in the maxillary lateral incisor (1) agenesis, (2) mesial to the cleft, (3) distal to the cleft, or (4) duplication.

Supernumerary teeth

Supernumerary teeth were observed less frequently (5.7%) of the cleft samples, within the range previously reported for CLP samples with 5.7–6.1% in cleft Asian population [21, 22, 24]. This percentage was, however, two times higher than the one observed in the healthy Asian population [17] but lower than the percentage described in the European cleft populations, ranging from 17.8 to 33.3% [6, 28, 29]. According to previous systematic review and meta-analysis [5], almost all supernumerary teeth found in the cohort were located in the maxillary anterior region, except for one individual with a mandibular supernumerary tooth in the BCLP group. In the anterior region of the maxilla, the supernumerary tooth was mostly located close to the upper lateral incisor. This is consistent with many other investigations [6, 22]. Regarding the cleft type, the prevalence of supernumerary teeth was comparable among URCLP, ULCLP and BCLP samples, resembling the pattern seen in the Polish cleft patients [29].

The nomenclature system like TAC is unavailable for supernumerary teeth [13]. We also observed individuals presenting both with dental agenesis and supernumerary tooth. Although the number of individuals presenting the two anomalies was not high enough to describe a pattern in relation to the cleft type, they could represent an interesting group of patients for genetic diagnosis.

Left and right asymmetry of tooth number anomalies

Our results showed a higher percentage of tooth agenesis and supernumerary teeth on the left side. This finding correlates to another study showing the dominance of left unilateral cleft lip and palate and left upper lateral incisors agenesis [30]. Similarly, previous studies showed that the upper left incisor was prone to being undifferentiated [19, 21]. The molecular differences observed

between the developing left and right sides could influence cleft formation and tooth development. The analysis of the transcriptome of murine right and left maxilla-mandible complex pointed towards significant upregulated or downregulated genes reported to be associated with a cleft-palate phenotype (*Ap2b1*, *Gbx2*, *Chrd*, *Eya1*, *Inpp5e*, *Mllt10*, *Ncor2*, *Pnn* and *Snx3* at E14.5; *Ptch1*, *Satb2*, *Acan*, *Cdkn1c*, *Ctnnb1 and Hand2* at E18.5) [31]. Among them *Ap2b1*, *Gbx2*, *Chrd*, *Eya1*, *Inpp5e*, *Mllt10*, *Ncor2*, *Pnn*, *Snx*, *Ptch1*, *Satb2*, *Acan*, *Cdkn1c*, *Ctnnb1and Hand2* are also expressed during tooth development at E14.5 [32].

It has been suggested that some molecules, acting as the left-right organizers, controlling laterality, may be both involved during palatogenesis and odontogenesis [33]. Some genetic susceptibility loci involved in left–right patterning contribute to facial asymmetry of the CLP spectrum [34]. For example, *PITX2* contributes to tooth initiation, maxillary hypoplasia, laterality, and is causing Axenfeld-Rieger syndrome [33, 35]. These results shed light on the molecular genetic relationships between tooth, face, and left-right patterning.

Further investigation

In this study, the number of patients with complete records meeting the inclusion criteria was limited and the distribution of the sample size between UCLP and BCLP, and between URCLP and ULCLP was unequal. Further studies are compulsory to provide, not only additional insight into the factors dually involved in palatal fusion and tooth anomalies, but also, the effect on treatment outcomes. Presence of the tooth affects the size of maxilla [11]. We purpose that the TAC patterning in children with clefts could provide a useful prediction in the comprehensive multidisciplinary planning. We urge the professionals providing care for children with clefts to report the epidemiological data, on tooth development in these patients and unaffected family members, potentially using a standard data collection system. The evaluation of the prevalence of tooth agenesis and supernumerary tooth in cleft population requires a joint multi-centered data collection effort in the Southeast Asia as well as across the regions. These data could be beneficial to approach the variability of ethnicities and genetic background that is involved in tooth development and cleft formation.

Conclusion

Our study reveals that cleft lip and cleft palate constitute the largest subgroup of orofacial clefts and are frequently linked to tooth-number anomalies. BCLP showed the highest incidence of tooth agenesis, particularly in the upper permanent lateral incisors on the left side. ULCLP exhibited the highest occurrence of supernumerary teeth

and a higher rate of tooth agenesis compared to other unilateral CLP cases. In BCLP and ULCLP individuals, both tooth agenesis and supernumerary teeth can coexist. These findings underscore the need for targeted dental care in individuals with cleft conditions, focusing on the prevalence of dental anomalies.

Abbreviations

BCLP	Bilateral cleft lip and palate
CBCT	Cone beam computed tomography
CLP	Cleft lip and palate
OPG	Orthopantomogram
PITX-2	Paired-like homeodomain transcription factor 2
TAC	Tooth agenesis code patterning
UCLP	Unilateral cleft lip and palate
ULCLP	Unilateral left cleft lip and palate
URCLP	Unilateral right cleft lip and palate

Author contributions
WPA contributed to the design of the work, acquired, analyzed, and interpreted the patient data on tooth-number anomalies, drafted and revised the article. SM contributed to the concept and design of the work, analyzed, and interpreted patient data, and revised the article critically. PP contributed to the concept and design of the work, the analysis, and major revision of the article. AP contributed to the design of the work, draft results of the manuscript and analyzed. ABZ reviewed the article. All authors read and approved the final version of the manuscript.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All methods were performed in accordance with the relevant guidelines and regulations of the World Medical Association Declaration of Helsinki and approved by the ethical review committee, Khon Kaen University, Thailand with the Number: HE661161, registered on 10th April 2023. A need for informed consent of the patients and/or its legal guardian was waived off by the ethics committee, due to the retrospective character of the study, the use of pseudonymous data and all investigations performed in accordance with the standards of care.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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