Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(5) 2084–2096

DOI: 10.1177/0300060519832165
journals.sagepub.com/home/imr
SAGE

Enamel defects in permanent teeth of patients with cleft lip and palate: a cross-sectional study

Chia-An Shen, Runzhi Guo and Weiran Li

Abstract

Objective: This study investigated the prevalence, type, and location of enamel defects in the permanent teeth of patients with complete unilateral or bilateral cleft lip and palate (CLP), and compared the prevalence and characteristics of defects between CLP patients and non-CLP individuals.

Methods: We examined completely erupted permanent dentition, except for third molars, of CLP patients and non-CLP individuals of both sexes, 9–36 years of age, and analyzed corresponding panoramic radiographs. Two independent examiners performed clinical examinations in accordance with the Modified Developmental Defects of Enamel index.

Results: A total of 210 (87.9%) CLP patients and 194 (41.4%) non-CLP individuals had at least one enamel defect; these were more prevalent in the CLP group than in the non-CLP group. Upper teeth were primarily affected by enamel defects associated with the cleft; defects were most prevalent on the cleft side in CLP patients, followed by the non-cleft side in CLP patients, and then by non-CLP individuals.

Conclusion: Enamel defects were more common in CLP patients than in non-CLP individuals. Among CLP patients, enamel defects were more prevalent in the cleft side of the maxilla; the central incisor was the most commonly affected tooth in this quadrant.

Keywords

Cleft lip and palate, enamel defects, dentition, maxilla, central incisor, opacity, hypoplasia, mineralization

Date received: 17 September 2018; accepted: 29 January 2019

Department of Orthodontics, Peking University School and Hospital of Stomatology, Beijing, P.R. China

Corresponding author:
Weiran Li, Department of Orthodontics, Peking University School and Hospital of Stomatology, 22 Zhongguancun Avenue South, Haidian District, Beijing 100081, P.R. China.
Email: weiranli2003@163.com

Introduction

Cleft lip and palate (CLP) is a common birth defect due to abnormal orofacial development, which exhibits both ethnic and geographical variation.[1] The prevalence rates of nonsyndromic, syndromic, and overall CLP in China are 14.23, 2.40, and 16.63 per 10000 live births, respectively.[2] Dental anomalies may comprise enamel defects, hypodontia, supernumerary teeth, and/or microdontia;[3] these anomalies are more common in CLP patients than in the general non-CLP population, and are more frequent in permanent teeth than in primary teeth.[4]

Enamel defects are frequently observed in CLP patients. Maciel et al.[5] reported a higher incidence of enamel defects on the cleft side for both deciduous and permanent dentition, compared with the non-cleft side, in children with complete unilateral CLP. Ruiz et al.[6] reported a significant increase in the incidence of enamel defects in the upper anterior teeth of patients with complete CLP. Nevertheless, previous studies regarding enamel defects in CLP patients have primarily recruited CLP patients and mainly explored developmental defects of the enamel on certain teeth.[7–11] There are no available systematic comparisons of enamel defects between CLP patients and non-CLP individuals across the entire dentition, as well as between affected and non-affected sides of CLP patients.

Incidences of dental anomalies may differ between cleft and non-cleft sides in CLP patients. Some studies have shown a higher rate of dental anomalies in the cleft side,[5,8,10–12] while others[13,14] have reported similar prevalence rates between the two sides, or higher incidence on the non-cleft side. Etiological factors underlying dental anomalies in CLP patients are not yet fully understood, and may include both genetic and environmental factors.[15–17]

This cross-sectional study evaluated the prevalence and characteristics of enamel defects in the permanent teeth of patients with complete unilateral and bilateral CLP, and compared the findings with non-CLP individuals as a control group.

Methods

The study population included non-syndromic individuals from two groups (CLP and non-CLP) at Peking University Hospital of Stomatology, Beijing, China, who were recruited during the period from October 2015 to September 2017. The patients were recruited with the approval of the hospital's Ethics and Research Committee, and all patients provided written informed consent to participate in the study.

Male and female individuals who fulfilled the following criteria were eligible for inclusion: individuals were Chinese non-syndromic patients who all had similar socioeconomic and geographic characteristics, thereby reducing risk of bias; complete eruption of permanent teeth was observed; all surfaces of the teeth were accessible for appropriate clinical examination (no restorations, orthodontic appliances, or crowns); complete medical records were available, including dental history and intraoral standardized panoramic photographs. The following criteria were further applied in the CLP group: complete unilateral or bilateral CLP was present; all patients had received lip and hard tissue closure surgery before 3 years of age. The following criteria were further applied in the non-CLP control group: individuals had no history of dental extractions of any permanent teeth, no history of trauma, and no history of previous orthodontic/prosthodontic treatment or maxillofacial surgery. In both groups, third molars, supernumerary teeth, and unerupted teeth were not examined for enamel defects.

Three complete orofacial CLP categories were analyzed, based on the affected side of the lip, alveolar process, and palate: bilateral CLP (CLPB), left unilateral CLP (CLPL), and right unilateral CLP (CLPR). Patients with unilateral or bilateral lip and alveolus cleft, as well as patients who exhibited only cleft palate or cleft lip, were not included.

Enamel defects in both CLP and non-CLP groups were evaluated and recorded by two independent examiners under artificial light with a dental probe and mouth mirror after drying the teeth for 15 s; examinations were performed in accordance with the Modified Developmental Defects of Enamel Index (Modified DDE Index).[6,18] The Kappa coefficient was used to assess the consistency of enamel examinations between the two examiners.

According to the Modified DDE Index, enamel defects are mainly classified as normal (Code 0), demarcated opacity (Code 1), diffuse opacity (Code 2), or hypoplasia (Code 3). Demarcated opacity and diffuse opacity are characterized by changes in the translucency of enamel to various degrees.[6,19] Hypoplasia is characterized by pits, grooves, and a partial or complete absence of enamel over a considerable area of dentine.[6,20] Combined defects include diffuse opacity or demarcated opacity combined with hypoplasia; however, such defects were not analyzed in this study due to their low incidence rates (<0.8%) in both groups.

The affected surfaces of the teeth (mesial, distal, buccal, or palatal) were recorded, as well as the specific locations of enamel defects along the surfaces of each tooth (incisal, middle, and cervical). Among CLP patients, the prevalence and characteristics of enamel changes on the cleft side were compared with those on the non-cleft side. Moreover, changes in enamel defects were evaluated in non-CLP individuals, as a control group. Chi-squared and Fisher's exact tests were conducted to compare between groups; differences with $p < 0.05$ were considered to be statistically significant.

Results

The study population consisted of 708 non-syndromic individuals, comprising CLP and non-CLP groups. In the CLP group, a total of 239 CLP patients (73 CLPB, 109 CLPL, and 57 CLPR) were thoroughly examined for enamel defects. All patients were between 9 and 34 years of age (mean age, 16 years; 143 male patients, 96 female patients). In the non-CLP group, a total of 469 individuals without CLP (age, 10–36 years; mean age, 20 years; 246 male individuals, 223 female individuals) were also examined as controls. There were no significant differences in sex ratio between the groups. There were also no significant differences in age distribution between the groups. The kappa value for examinations in the CLP group was 0.869 (95% CI: 0.824–0.913, $p < 0.001$), which indicated good consistency between the two examiners. Similarly, the examinations showed good consistency in the non-CLP group, with a kappa value of 0.797 (95% CI: 0.729–0.865, $p < 0.001$).

A total of 210 (87.9%) of 239 CLP patients had enamel defects; 86 (27 CLPB, 37 CLPL, and 22 CLPR) were female, and 124 (37 CLPB, 60 CLPL, and 27 CLPR) were male. There were no significant sex differences in the prevalence of enamel defects across all cleft types, or within the non-CLP group (Table 1). In the non-CLP group, 194 (41.4%) of 469 individuals had enamel defects (89 female individuals, 105 male individuals). There were no significant differences in sex distribution between the CLP and non-CLP groups. However, the prevalence of enamel defects significantly differed between the two groups ($p < 0.0001$).

Table 1. Enamel defects by sex and cleft.

Group	Presence of defect	Total		Male		Female		*p* value*
		N	%	N	%	N	%	
CLPB	No	9	12.3	6	14.0	3	10.0	0.7283
	Yes	64	87.7	37	86.0	27	90.0	
CLPL	No	12	11.0	8	11.8	4	9.8	1
	Yes	97	89.0	60	88.2	37	90.2	
CLPR	No	8	14.0	5	15.6	3	12.0	1
	Yes	49	86.0	27	84.4	22	88.0	
CLP	No	29	12.1	19	14.6	10	9.2	0.5506
	Yes	210	87.9	124	95.4	86	78.9	
Non-CLP	No	275	58.6	141	59.5	134	57.8	0.5738
	Yes	194	41.4	105	44.3	89	38.4	

*Fisher's exact test. CLPB, bilateral cleft lip and palate; CLPL, left unilateral cleft lip and palate; CLPR, right unilateral cleft lip and palate; CLP, cleft lip and palate.

Table 2. Enamel defect incidence and average number of affected teeth.

Group	Demarcated opacity				Diffuse opacity				Hypoplasia			
	Incidence	*p* value*	Affected teeth**	*p* value*	Incidence	*p* value*	Affected teeth**	*p* value*	Incidence	*p* value*	Affected teeth**	*p* value*
CLPB	0.8	n.d	0.74	n.d	2.4	n.d	2.1	n.d	0.4	n.d	0.37	n.d
CLPL	1.3		0.74		4.5		2.66		0.8		0.44	
CLPR	0.5		0.61		1.6		1.82		0.6		0.7	
CLP	2.7	<0.0001	0.71	<0.0001	8.5	0.0153	2.29	0.1734	1.8	<0.0001	0.48	<0.0001
Non-CLP	1.6		0.43		7.5		2.01		0.1		0.02	

*Chi-square test. **Average number. CLPB, bilateral cleft lip and palate; CLPL, left unilateral cleft lip and palate; CLPR, right unilateral cleft lip and palate; CLP, cleft lip and palate; n.d., not determined.

Overall, the incidence rates of all three enamel defects were much higher in the CLP group than in the non-CLP group ($p < 0.0001$, Table 2); there was an increased average number of affected teeth per person in the CLP group, compared with the non-CLP group ($p < 0.0001$). Diffuse opacity was present at a higher rate in the CLP group ($p = 0.0153$), while the average number of affected teeth per person in the CLP group did not significantly differ from that in the non-CLP group. Finally, the rate of demarcated opacity was higher in the CLP group than in the non-CLP group ($p < 0.0001$); the average number of affected teeth per person in the CLP group was greater than that in the non-CLP group ($p < 0.0001$, Table 2).

The prevalence of defects in all quadrants was significantly higher in the CLP group than in the non-CLP group ($p < 0.0001$, Table 3). Furthermore, in the CLP group, the rates of defects were higher in the upper right quadrant (Q1) and upper left quadrant (Q2) than in the mandibular left (Q3) and right (Q4) quadrants; differences in defect distribution among the four quadrants were significant ($p < 0.0001$). Chi-squared analysis revealed

Table 3. Enamel defects by quadrant in maxilla and mandible.

Location	Quadrant	Presence of defect	CLP		Non-CLP		*p* value*
			N	%	N	%	
Maxilla	Q1	No	101	42.3	401	85.5	<0.0001
		Yes	138	57.7	68	14.5	
	Q2	No	76	31.8	404	86.1	<0.0001
		Yes	163	68.2	65	13.9	
Mandible	Q3	No	166	69.5	424	90.4	<0.0001
		Yes	73	30.5	45	9.6	
	Q4	No	171	71.5	418	89.1	<0.0001
		Yes	68	28.5	51	10.9	
p value*			<0.0001		0.0641		

*Chi-squared test. CLP, cleft lip and palate.

Table 4. Enamel defects by quadrant in maxilla and mandible and by cleft type.

Location	Quadrant	Presence of defect	CLPB		CLPL		CLPR		*p* value*
			N	%	N	%	N	%	
Maxilla	Q1	No	21	28.8	58	53.2	22	38.6	0.0039
		Yes	52	71.2	51	46.8	35	61.4	
	Q2	No	19	26	31	28.4	26	45.6	0.035
		Yes	54	74	78	71.6	31	54.4	
Mandible	Q3	No	54	74	71	65.1	41	71.9	0.4016
		Yes	19	26	38	34.9	16	28.1	
	Q4	No	55	75.3	76	69.7	40	70.2	0.6883
		Yes	18	24.7	33	30.3	17	29.8	
p value*			<0.0001		<0.0001		0.0002		

*Fisher's exact test. CLPB, bilateral cleft lip and palate; CLPL, left unilateral cleft lip and palate; CLPR, right unilateral cleft lip and palate.

significant differences in Q1 vs. Q2 ($p = 0.0179$), Q1 vs. Q3 ($p < 0.0001$), Q1 vs. Q4 ($p < 0.0001$), Q2 vs. Q3 ($p < 0.0001$), and Q2 vs. Q4 ($p < 0.0001$). However, there were no significant differences between Q3 and Q4, which suggests that the defects occurred mainly in the maxillary region, rather than the mandibular region. There were no significant differences among the four quadrants in the non-CLP group (Table 3).

With regard to CLP subgroups, similar results regarding differences in defect distributions among the four quadrants were also found in the CLPB group ($p < 0.0001$), CLPL group ($p < 0.0001$), and CLPR group ($p = 0.0002$). The distributions of defects across the three subgroups significantly differed in Q1 ($p = 0.0039$) and Q2 ($p = 0.035$, Table 4); there were no significant associations between defects and teeth located in Q3 and Q4 across the three subgroups (Table 4).

The CLP group showed a much higher incidence of hypoplasia in all upper teeth, with the exception of the second molar, compared with the non-CLP group

(Table 5). Furthermore, the CLP group showed a significantly higher rate of demarcated opacity defects in the central incisors on both sides of the maxilla, as well as in the left maxillary canine and left maxillary first premolar (Table 5). Finally, the right central maxillary incisor and left maxillary canine exhibited higher rates of diffuse opacity defects in the CLP group (Table 5). Overall, the prevalence rates of enamel defects were higher in the CLP group than in the non-CLP group. In addition, the difference in prevalence rate between the two groups was much greater in the left maxilla than in the right maxilla.

In comparison of the incidence of maxillary enamel defects between cleft and non-cleft sides within the CLP group, the central incisor was the most commonly affected tooth, such that the central incisor on the cleft side had a significantly higher prevalence of defects than the corresponding tooth on the non-cleft side ($p < 0.0001$, Table 6). This was primarily because of increased prevalence of hypoplasia on the

Table 5. Statistical significance of comparisons of different types of enamel defects between CLP and Non-CLP groups.

Tooth No.	Group	Demarcated opacity			Diffuse opacity			Hypoplasia			Overall		
		No	Yes	*p* value*	No	Yes	*p* value*	No	Yes	*p* value*	No	Yes	*p* value*
11	CLP	197	27	0.0043	191	33	0.0188	202	22	<0.0001	142	82	<0.0001
	Non-CLP	438	27		424	41		465	0		397	68	
12	CLP	148	6	0.2527	143	11	0.8142	151	3	0.0028	134	20	0.1582
	Non-CLP	445	10		425	30		455	0		415	40	
13	CLP	199	3	0.6845	184	18	0.627	197	5	0.0062	176	26	0.1586
	Non-CLP	433	4		403	34		436	1		398	39	
14	CLP	193	1	0.2881	175	19	0.1625	191	3	0.009	171	23	0.1865
	Non-CLP	431	8		410	29		439	0		402	37	
15	CLP	187	2	1	171	18	0.5595	187	2	0.0322	167	22	0.3091
	Non-CLP	428	4		397	35		432	0		393	39	
16	CLP	232	7	1	201	38	0.2245	235	4	0.0282	190	49	0.1417
	Non-CLP	455	14		410	59		468	1		395	74	
17	CLP	186	0	N/A	179	7	0.269	185	1	0.1321	178	8	0.5604
	Non-CLP	421	0		396	25		421	0		396	25	
21	CLP	193	28	0.0043	192	29	0.1437	198	23	<0.0001	141	80	<0.0001
	Non-CLP	438	28		422	44		464	2		392	74	
22	CLP	145	8	0.3263	137	16	0.2105	148	5	0.0001	124	29	0.0109
	Non-CLP	439	15		421	33		454	0		406	48	
23	CLP	180	14	0.001	167	27	0.0113	188	6	0.0015	147	47	<0.0001
	Non-CLP	432	7		406	33		438	1		398	41	
24	CLP	183	13	0.0099	173	23	0.0951	194	2	0.033	158	38	0.0013
	Non-CLP	434	10		410	34		444	0		400	44	
25	CLP	180	6	0.0974	162	24	0.0833	184	2	0.0315	154	32	0.0096
	Non-CLP	424	5		393	36		429	0		388	41	
26	CLP	232	6	1	187	51	0.059	235	3	0.0148	178	60	0.0009
	Non-CLP	456	13		413	56		469	0		400	69	
27	CLP	189	0	N/A	182	7	0.2475	188	1	0.1363	181	8	0.4439
	Non-CLP	419	0		394	25		419	0		394	25	

*Fisher's exact test. CLP, cleft lip and palate.

Table 6. Statistical significance of comparisons on different types of enamel defects between Cleft and Non-Cleft sides.

		Demarcated opacity			Diffuse opacity			Hypoplasia			Overall		
Tooth	Side	No	Yes	*p* value*	No	Yes	*p* value*	No	Yes	*p* value*	No	Yes	*p* value*
Central incisor	Cleft	242	11	0.2685	242	44	0.2561	250	36	0.0214	162	124	<0.0001
	Non-Cleft	148	11		141	18		150	9		121	38	
Lateral incisor	Cleft	155	6	1	147	16	0.5495	159	4	1	135	28	0.6398
	Non-Cleft	138	6		133	11		140	4		123	21	
Canines	Cleft	236	5	0.5145	218	30	0.6251	240	8	0.5479	198	50	0.285
	Non-Cleft	143	5		133	15		145	3		125	23	
First premolar	Cleft	239	3	0.6736	223	27	1	247	3	1	209	41	0.6636
	Non-Cleft	138	3		126	15		139	2		121	20	
Second premolar	Cleft	237	4	0.4637	212	29	0.6087	239	2	0.6193	206	35	1
	Non-Cleft	130	4		121	13		132	2		115	19	
First molar	Cleft	304	6	0.3574	256	55	0.4613	307	4	0.6986	245	66	0.2541
	Non-Cleft	160	6		132	34		163	3		123	43	
Second molar	Cleft	241	0	N/A	231	10	0.7777	240	1	1	230	11	0.7952
	Non-Cleft	134	0		130	4		133	1		129	5	

*Fisher's exact test.

Table 7. Percent distribution of types of enamel defects, based on the Modified Developmental Defects of Enamel Index.

	Code				
Group/Side	0	1	2	3	*p* value
CLP group	81.1% (2242)	4.4% (121)	11.6% (321)	3.0% (82)	<0.0001
Non-CLP group	89.4% (5574)	2.3% (145)	8.2% (514)	0.1% (5)	
p value*	<0.0001	<0.0001	<0.0001	<0.0001	
Cleft side	79.6% (1385)	4.9% (86)	12.1% (211)	3.3% (58)	<0.0001
Non-Cleft side	83.5% (857)	3.4% (35)	10.7% (110)	2.3% (24)	
p value*	0.0108	0.0572	0.265	0.1365	

*Chi-squared test. CLP, cleft lip and palate.

cleft side in CLP patients ($p = 0.0214$, Table 6).

The incidence rates of defects in the maxilla in both CLP and non-CLP groups were evaluated in accordance with the Modified DDE Index. The distributions of DDE codes significantly differed between CLP and non-CLP groups ($p < 0.0001$; Table 7). The prevalence rates of all three enamel defects in the maxilla were significantly higher on the cleft side than on the non-cleft side in the CLP group ($p < 0.0001$, Table 7). When enamel defect codes were combined (Codes 1–3) for the CLP and non-CLP maxilla, the prevalence of defects in the maxilla was also significantly higher in the CLP group than in the non-CLP group ($p < 0.0001$). Similarly, the prevalence was higher on the cleft side than on the non-cleft side within the CLP group ($p = 0.0125$). Interestingly, the cleft side in the CLP group showed the highest prevalence rate for all three enamel defect codes, followed by the non-cleft side in the CLP group, and finally by the non-CLP group.

The color and location of defects in both groups were also examined. Although the predominant colors in both groups were yellow in teeth with hypoplasia (63.6% in CLP and 66.7% in non-CLP) and white in teeth with diffuse opacity (56.5% in CLP and 56.8% in non-CLP) and demarcated opacity (61.8% in CLP and 75.4% in non-CLP), there were significant differences in demarcated opacity distribution ($p = 0.0046$) and overall color analyses ($p = 0.024$). Clinical examination of the affected teeth indicated that the locations of hypoplasia significantly differed between the two groups ($p = 0.0227$). In the CLP group, the highest prevalence rate of hypoplasia was observed in the cervical one-third of the tooth (34.8%); in contrast, the non-CLP group showed an even distribution of hypoplasia between the cervical, middle, and incisal portions of the tooth. However, there were no significant differences in locations of opacities between the two groups. In the CLP group, the highest prevalence of diffuse opacity was observed in the cervical one-third of the tooth (38.6%), whereas that of demarcated opacity was observed in the middle one-third of the tooth (38.2%). In the non-CLP group, the highest prevalence of diffuse opacity defects was observed in the middle one-third of the tooth (38.5%), whereas that of demarcated opacity was observed in the incisal one-third of the tooth (38.4%).

Discussion

Previous studies have demonstrated no significant differences in the prevalence of dental anomalies between male and female individuals.[4,21,22] Although there were no significant differences in sex proportion between the groups in the present cross-sectional study, the majority of the individuals recruited for the CLP group were male (59.8%). This characteristic was consistent with previous findings that CLP patients are predominantly male.[17,23] Furthermore, patients with enamel defects in the CLP group were also predominantly male (59%). In comparison, while a sex disproportion was observed within the non-CLP group (54% male, 46% female), it was less obvious than that in the CLP group.

We also found a higher prevalence of unilateral clefts than bilateral clefts. Moreover, unilateral clefts were often on the left side (45.6%, CLPL; 23.8%, CLPR; and 30.5%, CLPB), which is consistent with the findings of previous studies involving CLP patients. These trends may be related to the anatomy and direction of human blood vessels, which lead to increased blood pressure in the right internal carotid artery; during prenatal growth, this anatomical feature may cause a greater amount of blood flow to the right side of the face, compared with the blood flow from arteries on the left side of the face.[24–26]

Bartzela et al.[27] found that left-side clefts were more common than right-side clefts, and the rate of tooth agenesis was greater on the left side of the maxilla. Thus, the disproportionate incidence of left-side clefts and tooth agenesis may be due to a connection between clefts and congenital defects in organs located on the same side of the body. The BCL-6 corepressor (*BCOR*) gene, which contributes to asymmetric organ development in oculofaciocardiodental syndrome, could also be associated with clefting genes, resulting in increased prevalence of left-side clefts. However, further studies are necessary to explore the underlying genetic etiology.[27–29]

The etiology of the high prevalence rate of enamel changes in CLP individuals, along with the increased incidence of such changes on the left side of the maxilla, remains unclear. In a case-control study, Carpentier et al.[7] revealed that surgical techniques typically used for soft palate closure may lead to enamel defects involving

maxillary premolars in CLP patients, because such surgeries interfere with blood supply to the developing premolars at a critical stage for tooth enamel development. This conclusion is consistent with previous hypotheses that surgical interventions for cleft repair could result in nutritional and metabolic disturbances in patients, which could lead to increased enamel defects and other dental anomalies.[30,31] In the present study, we found that differences in prevalence rates between the two groups for different kinds of enamel defects were also more striking on the left side of the maxilla (Table 5). This finding supported the data of the previous reports, and may also be related to the implementation of soft palate surgeries and their effects on blood supply during tooth enamel development.

However, in another cross-sectional study regarding enamel defects of central incisors in children with CLP, Maciel et al.,[5] found that the prevalence of defects was higher on the cleft side than on the non-cleft side, and higher in permanent teeth than in deciduous teeth. These findings may have been related to the pathological processes responsible for clefts, as well as the exposure of permanent teeth to potential prenatal and postnatal etiological factors for longer periods than deciduous teeth.[5,32] The present study supports the hypothesis that the same factors underlying the incidence of clefts may also be responsible for the increased prevalence of enamel defects in these individuals.[30,32–34]

Recent studies have suggested that both genetic and environmental factors contribute to the etiology of clefting.[15,35,36] Genetics-based studies have shown that amelogenin (encoded by the *AMELX* gene), which is involved in the formation of dental enamel, is also a candidate gene for involvement in CLP, which suggests a genetic association (or shared genetic background) linking enamel defects and clefts.[37] Thus, the inclusion of information related to dental anomalies in genetic analyses of CLP may provide new opportunities to map the susceptibility loci associated with the production of clefts.

We analyzed the presence of enamel defects across all quadrants in both CLP and non-CLP groups, as well as their presence across different cleft types within the CLP group. The results indicated a significant increase in the prevalence of enamel defects in the CLP group across all quadrants ($p < 0.0001$). This suggests that clefts are associated with an increased incidence of enamel defects in all permanent dentition. However, it is important to note that, within the CLP group, only the Q1 and Q2 quadrants showed significant differences in prevalence of enamel defects. This indicates that clefts mainly affect the maxilla (rather than the mandible) with regard to enamel development in CLP individuals.

These findings were reinforced in further analyses of enamel codes in the present study. All three types of defects were more prevalent in the CLP group than in the non-CLP group. Moreover, the cleft side of CLP patients showed the highest prevalence of defects, followed by the non-cleft side of CLP patients, and then by non-CLP individuals. Notably, incisors and canines were disproportionately affected in the CLP group. Finally, the central incisor was the most affected tooth on the cleft side in CLP patients.

A potential etiological explanation for our results is that disturbances during embryogenesis, along with genetic interactive pathways, could have contributed to increased prevalence of enamel defects in CLP patients, relative to non-CLP individuals, even outside the cleft area in the CLP group. Moreover, surgical interventions during the critical stage of tooth formation and development may have contributed to the increased prevalence of enamel defects on the cleft side in CLP patients, compared with their non-cleft side. A potential

explanation for these trends is that genetic factors causing clefts may also be responsible for the presence of enamel defects, as variation in enamel defects between the cleft and non-cleft sides in the CLP group was less striking than variation in enamel defects between the CLP and non-CLP groups.

Although the predominant colors in both groups were yellow in teeth with hypoplasia and white in teeth with diffuse opacity or demarcated opacity, there were significant differences in demarcated opacity distribution ($p = 0.0046$) and overall color analyses ($p = 0.024$). This is consistent with the findings of Malanczuk et al.[32] and Maciel et al.,[5] in which white opacities were more prevalent than yellow opacities on the cleft side in CLP patients. However, the differences in the prior studies were not statistically significant, and those authors suggested that the finding may have been due to chance. However, in the present study, there was a significant difference in the color distribution of demarcated opacity between the two groups ($p = 0.0046$). Moreover, we found that hypoplasia was mostly present in the cervical one-third of the tooth (34.8%) in the CLP group, while there was an even distribution of hypoplasia between the cervical, middle, and incisal portions of the tooth in the non-CLP group. We speculate that this may have been associated with soft palate surgeries, the timing of which overlapped with the occurrence of enamel mineralization of the cervical one-third of the tooth.

However, because we sought to explore the relationship between CLP and enamel defects, we did not focus on etiological factors underlying such correlations. Therefore, further studies are needed to confirm our findings, as well as to test existing hypotheses regarding whether genes and surgical disruption clearly contribute to the development of cleft and enamel defects.

A number of recent studies have sought to define sub-phenotypes of oral clefts based on dental development. Most of these studies focused on dental anomalies, including tooth agenesis, supernumerary teeth, taurodontism, and microdontia.[4,14,38] However, enamel defects, which can cause esthetic problems and increase the risk of dental caries development,[39,40] have rarely been investigated. Our results indicate that enamel changes can also serve as clinical markers to define sub-phenotypes of oral clefts. Moreover, central incisors, which are the teeth most commonly affected by enamel defects, should be examined carefully prior to orthodontic treatment.

The limitations of this study primarily comprise the general limitation of cross-sectional studies, in that all enamel defects in all individuals in both groups were evaluated at a single, specific time. Other developmental risk factors (e.g., malnutrition and birth weight) that might influence enamel formation were not controlled in this study. Furthermore, no corresponding mechanism studies were performed to investigate reasons underlying the association between cleft presence and occurrence of enamel defects.

In conclusion, the most common enamel defects in both groups were (in descending order): diffuse opacity, demarcated opacity, and hypoplasia. However, the CLP group was disproportionately affected by (in descending order) hypoplasia, demarcated opacity, and diffuse opacity. Both groups showed a similar predominant color distribution in all three types of defects. However, there were significant differences between the two groups with regard to the location of hypoplasia on the surface of the tooth. The rate of defects was significantly higher in the CLP group across all quadrants. Within the CLP group, only Q1 and Q2 quadrants showed significant differences in defects across all cleft types. The cleft side of the CLP group showed the highest

rates of all three types of defects, followed by the non-cleft side of the CLP group. The maxilla of the non-CLP group exhibited the lowest prevalence of defects. Incisors and canines of CLP individuals had higher rates of defects, compared with those of non-CLP individuals. The central incisor was the most commonly affected tooth within the CLP group; central incisors on the cleft side exhibited comparatively higher prevalence of defects than those on the non-cleft side.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Weiran Li http://orcid.org/0000-0002-5126-647X

References

1. Mossey PA, Little J, Munger RG, et al. Cleft lip and palate. *Lancet* 2009; 374: 1773–1785.
2. Dai L, Zhu J, Mao M, et al. Time trends in oral clefts in Chinese newborns: data from the Chinese National Birth Defects Monitoring Network. *Birth Defects Res A Clin Mol Teratol* 2010; 88: 41–47.
3. Jahanimoghadam F. Dental anomalies: an update. *Adv Hum Biol* 2016; 6: 112–118.
4. Konstantonis D, Alexandropoulos A, Konstantoni N, et al. A cross-sectional analysis of the prevalence of tooth agenesis and structural dental anomalies in association with cleft type in non-syndromic oral cleft patients. *Prog Orthod* 2017; 18: 20.
5. Maciel SP, Costa B and Gomide MR. Difference in the prevalence of enamel alterations affecting central incisors of children with complete unilateral cleft lip and palate. *Cleft Palate Craniofac J* 2005; 42: 392–395.
6. Ruiz LA, Maya RR, D'Alpino PH, et al. Prevalence of enamel defects in permanent teeth of patients with complete cleft lip and palate. *Cleft Palate Craniofac J* 2013; 50: 394–399.
7. Carpentier S, Ghijselings E, Schoenaers J, et al. Enamel defects on the maxillary premolars in patients with cleft lip and/or palate: a retrospective case-control study. *Eur Arch Paediatr Dent* 2014; 15: 159–165.
8. Ribeiro LL, DasNeves LT, Costa B, et al. Dental anomalies of the permanent lateral incisors and prevalence of hypodontia outside the cleft area in complete unilateral cleft lip and palate. *Cleft Palate Craniofac J* 2003; 40: 172–175.
9. Galante JM, Costa B, de Carvalho Carrara CF, et al. Prevalence of enamel hypoplasia in deciduous canines of patients with complete cleft lip and palate. *Cleft Palate Craniofac J* 2005; 42: 675–678.
10. Gomes AC, Neves LT and Gomide MR. Enamel defects in maxillary central incisors of infants with unilateral cleft lip. *Cleft Palate Craniofac J* 2009; 46: 420–424.
11. Celikoglu M, Buyuk SK, Sekerci AE, et al. Maxillary dental anomalies in patients with cleft lip and palate: a cone beam computed tomography study. *J Clin Pediatr Dent* 2015; 39: 183–186.
12. Eslami N, Majidi MR, Aliakbarian M, et al. Prevalence of dental anomalies in patients with cleft lip and palate. *J Craniofac Surg* 2013; 24: 1695–1698.
13. Mangione F, Nguyen L, Foumou N, et al. Cleft palate with/without cleft lip in French children: radiographic evaluation of prevalence, location and coexistence of dental anomalies inside and outside cleft region. *Clin Oral Investig* 2018; 22: 689–695.
14. Letra A, Menezes R, Granjeiro JM, et al. Defining subphenotypes for oral clefts based on dental development. *J Dent Res* 2007; 86: 986–991.
15. Dixon MJ, Marazita ML, Beaty TH, et al. Cleft lip and palate: understanding genetic and environmental influences. *Nat Rev Genet* 2011; 12: 167–178.

16. Vieira AR, McHenry TG, Daack-Hirsch S, et al. Candidate gene/loci studies in cleft lip/palate and dental anomalies finds novel susceptibility genes for clefts. *Genet Med* 2008; 10: 668–674.
17. Ajami S, Pakshir H and Samady H. Prevalence and characteristics of developmental dental anomalies in Iranian orofacial cleft patients. *J Dent (Shiraz)* 2017; 18: 193–200.
18. Clarkson J, O'Mullane D. A modified DDE index for use in epidemiological studies of enamel defects. *J Dent Res* 1989; 68; 445–450.
19. Suckling GW, Nelson DG and Patel MJ. Macroscopic and scanning electron microscopic appearance and hardness values of developmental defects in human permanent tooth enamel. *Adv Dent Res* 1989; 3; 219–233.
20. Suckling GW. Developmental defects of enamel—historical and present-day perspectives of their pathogenesis. *Adv Dent Res* 1989; 3: 87–94.
21. Wangsrimongkol T, Manosudprasit M, Pisek P, et al. Prevalence and types of dental anomaly in a Thai non-syndromic oral cleft sample. *J Med Assoc Thai* 2013; 96: S25–S35.
22. Al Jamal GA, Hazza'a AM and Rawashdeh MA. Prevalence of dental anomalies in a population of cleft lip and palate patients. *Cleft Palate Craniofac J* 2010; 47: 413–420.
23. Rajabian MH and Aghaei S. Cleft lip and palate in south-western Iran: an epidemiologic study of live births. *Ann Saudi Med* 2005; 25: 385–388.
24. Shapira Y, Haklai Z, Blum I, et al. Prevalence of non-syndromic orofacial clefts among Jews and Arabs, by type, site, gender and geography: a multi-center study in Israel. *Isr Med Assoc J* 2014; 16: 759–763.
25. Gundlach KK and Maus C. Epidemiological studies on the frequency of clefts in Europe and worldwide. *J Craniomaxillofac Surg* 2006; 34: 1–2.
26. Shapira Y, Lubit E, Kuftinec MM, et al. The distribution of clefts of the primary and secondary palates by sex, type and location. *Angle Orthod* 1999; 69: 523–528.
27. Bartzela TN, Carels CE, Bronkhorst EM, et al. Tooth agenesis patterns in unilateral cleft lip and palate in humans. *Arch Oral Biol* 2013; 58: 596–602.
28. Hilton E, Johnston J, Whalen S, et al. BCOR analysis in patients with OFCD and Lenz microphthalmia syndromes, mental retardation with ocular anomalies, and cardiac laterality defects. *Eur J Hum Genet* 2009; 17: 1325–1335.
29. Hilton EN, Manson FD, Urquhart JE, et al. Left-sided embryonic expression of the BCL-6 corepressor. BCOR, is required for vertebrate laterality determination. *Hum Mol Genet* 2007; 16: 1773–1782.
30. Ranta R. A review of tooth formation in children with cleft lip/palate. *Am J Orthod Dentofacial Orthop* 1986; 90: 11–18.
31. Tortora C, Meazzini MC, Garattini G, et al. Prevalence of abnormalities in dental structure, position, and eruption pattern in a population of unilateral and bilateral cleft lip and palate patients. *Cleft Palate Craniofac J* 2008; 45: 154–162.
32. Malanczuk T, Opitz C and Retzlaff R. Structural changes of dental enamel in both dentitions of cleft lip and palate patients. *J Orofac Orthop* 1999; 60: 259–268.
33. Olin WH. Dental anomalies in cleft lip and palate patients. *Angle Orthod* 1964; 34: 119–123.
34. Vichi M and Franchi L. Abnormalities of the maxillary incisors in children with cleft lip and palate. *ASDC J Dent Child* 1995; 62: 412–417.
35. Shaw GM, Wasserman CR, Lammer EJ, et al. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. *Am J Hum Genet* 1996; 58: 551–561.
36. Romitti PA, Lidral AC, Munger RG, et al. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts. *Teratology* 1999; 59: 39–50.
37. Oliveira FV, Dionísio TJ, Neves LT, et al. Amelogenin gene influence on enamel defects of cleft lip and palate patients.

Braz Oral Res 2014; 28: pii: S1806-83242014000100245.
38. Küchler EC, da Motta LG, Vieira AR, et al. Side of dental anomalies and taurodontism as potential clinical markers for cleft subphenotypes. *Cleft Palate Craniofac J* 2011; 48: 103–108.
39. Sujak SL, Abdul Kadir R and Dom TN. Esthetic perception and psychosocial impact of developmental enamel defects among Malaysian adolescents. *J Oral Sci* 2004; 46: 221–226.
40. Vargas-Ferreira F, Salas MM, Nascimento GG, et al. Association between developmental defects of enamel and dental caries: a systematic review and meta-analysis. *J Dent* 2015; 43: 619–628.