Chapter

Dental Development and Anomalies in Cleft Lip and Palate

Elaine Li Yen Tan and Mimi Yow

Abstract

Cleft lip and/or palate is a birth defect with heterogeneous clinical presentations. Prevalence and cleft-types differ by gender, ethnic groups and geographic locations. Published literature indicates high frequencies of cleft-associated dental anomalies, commonly variations in tooth-number, shape and size. Delayed dental development is also reported with catch-up growth at a later age. In the unilateral cleft phenotype, delayed development can occur on the cleft-side of the maxilla. Dental anomalies present frequently in the spectrum of cleft defects. Heterogeneity of defects is wide-ranging and may represent different aetiological origins of cleft phenotypes and sub-types due to: genetic mutations with altered ectomesenchymal growth; iatrogenesis from disrupted blood supply during early postnatal surgery; and maldevelopment or mistimed development. Orofacial clefting and odontogenesis may share critical pathways.

Keywords: dental anomalies, dental development, cleft lip, cleft palate

1. Introduction

Cleft lip and/or palate (CLP) is a birth defect with heterogeneous clinical presentations [1]. Prevalence and cleft-types differ by gender, ethnic groups and geographic locations [2]. It has been widely reported that dental anomalies (delayed dental development and eruption, hypodontia, supernumeraries, hypoplasia and abnormalities in tooth size and shape) in CLP are commonly associated with the presence of the cleft [3].

2. Dental development and eruption in CLP patients

2.1 Methods in assessing dental development

There are several methods that have been devised for assessing dental development or calculating dental age [4–12]. Essentially, tooth development is observed from radiographs and compared with the formation stages in each system. Some systems allow dental age to be calculated after ascertaining the teeth formation stages.

Of the various systems available, the method proposed by Demirjian et al. [9] and Demirjian and Goldstein [12] has been well researched and was found to be highly accurate and precise for estimation of dental age, particularly during early childhood [13, 14]. For any method of age estimation, it is best established within population-specific groups to reduce confounders [15].

2.1.1 Demirjian's method

According to the criteria, the maturity of the seven mandibular teeth on the left side (excluding the third molar) was determined by comparing their radiographic appearances with a sequence of reference radiographs and diagrams, and description of formation stages. If any of the mandibular left teeth was missing, or its image was unclear, the contra-lateral tooth was used [9].

Each tooth was divided into eight formative stages (A to H), and each stage was allocated a score depending on the gender. The scores for all seven teeth were then added to give the maturity score which can be converted directly into dental age by reading off a percentile curve the age at which the 50th centile attains the maturity score value, or by using a table which had been constructed.

2.2 Delayed dental development

Several investigators reported on delayed formation of the permanent teeth in CLP patients and the delay was observed to vary from 0.3 to 0.9 year [16–22].

Bailit and coworkers found that tooth formation in 39 children with cleft palate was significantly retarded by about 0.7 year when compared with 36 normal controls [16]. Ranta in his earlier study compared 258 CLP Finnish children with 1162 non-cleft children and reported a delay in tooth formation of 0.5 year in the maxilla and 0.4 year in the mandible, but the difference was not statistically significant [18].

2.2.1 Cleft severity and delayed dental development

Ranta went on further to conduct other investigations and revealed that the delay in tooth formation increased from 0.3 to 0.7 year with increasing severity of the cleft deformity. No significant difference was found in the tooth formation of subgroups with and without hypodontia [23]. However, in his later study on children with isolated CP only, he found that the dental development was delayed longer in the cleft subgroup with hypodontia (0.7 year) than in the subgroup without hypodontia (0.4 year), and a somewhat longer delay in tooth formation was observed with increasing number of missing teeth per child [24].

2.2.2 Age and delayed dental development

Harris and Hullings studied 54 CLP children and reported an overall delay in dental development of 0.9 year. They also noted that teeth formed during the early postnatal period were most affected, while the later forming teeth were less delayed [19].

Other authors [25–28] found that the delay in dental development begins to decrease from the age of 8 to 9.5 years old, suggestive of some form of catch-up growth [29, 30]. This is in contrast to the findings of Ranta who noted that the delay in dental development was significantly longer in the older age group of 9 to 12 years old (1.1 years) than in the younger age group of 6–9 years old (0.6 year) [3].

A study by Borodkin et al. found an overall delay in dental development of 0.52 year, but was found to be statistically significant only in male cleft subjects [21]. The most commonly delayed permanent teeth were the maxillary first and second premolars and maxillary second molars. No statistically significant differences in dental development were found between the various cleft types and severity of cleft deformities.

In another investigation, Lai et al. based their study on 231 southern Chinese CLP children from Hong Kong and compared them with a non-CLP control sample of the same size [20]. Similarly, they found an overall delay in tooth formation of Chinese CLP children (0.4 year) with the earlier formed permanent teeth being more delayed in development than those formed later. In accordance to the findings of Ranta [23], CLP children with more severe hypodontia were also more delayed in dental development.

Tan et al. found that UCLP children at 5–9 years old had more delayed dental maturation of 0.55 year when compared to controls [28]. The delay in dental maturation attenuated as they grew older and no difference in dental maturation were found in the UCLP children and controls at 9–13 years old. Several postulations may account for this phenomenon. Firstly, there could be some form of catch-up growth in the patients with CLP as they mature, as described by some authors [27, 29–32]. Secondly, the accuracy and precision of Demirjian's method [9] have been shown to decrease with age [13, 26, 33]. This is because the tooth developmental stages occurring earlier in life are generally of shorter duration than the stages occurring later, and the stages of short duration are more easily discerned with distinctive changes over a shorter period than smaller increments over a longer duration [13]. In addition, at an older age, the assessment of dental age is based on fewer teeth with roots that are not fully formed. For example, at the age of eleven, there may only be two teeth (usually the second premolar and second molar) with incomplete root formation, and the assessment of dental age would be based entirely on these two teeth. Any measurement error will, thus, have a profound effect on the dental age determination. Hence, there is a tendency to overestimate the dental age in the older age group, and this could reduce the discrepancy in dental age delay between the group with UCLP and without CLP. Furthermore, the roots of the teeth in patients with CLP are reported to be shorter than average [34], and this may further complicate the assessment of dental age. Thirdly, only the incisors and first molars are affected by environmental factors during gestation and early prenatal period [35]. As the formation of these teeth plays a big part in determining the dental age in the younger age group, their effects on the length of dental age delay would be significant. Root formation of the incisors and first molars would have been already completed in the older group of subjects; hence, they no longer have an impact on the dental age determination.

2.2.3 Hypodontia and delayed dental development

Tan et al. found that the presence and extent of hypodontia in CLP patients did not influence the dental development [28]. This contrasted with earlier studies [20, 24] that found a bigger delay in dental development in clefts with hypodontia than without hypodontia, and the more severe the hypodontia, the bigger the delay. However, these studies had several confounding factors. Ranta's study only included patients with isolated cleft palate [24], while the study of Lai et al. included various cleft types [20].

2.2.4 Gender and delayed dental development

The evidence for any gender association has been weak, with some studies suggesting that the delay was more pronounced in boys compared to girls [20, 21, 27], and other studies showing no significant gender differences [18, 23, 24, 26, 28, 36].

2.3 Asymmetric tooth formation

2.3.1 Definition

A pair of teeth is regarded as developing asymmetrically when the crown or root development of one of the teeth deviated from that of the antimeric tooth by at least one developmental stage. Ranta was one of the earliest authors to report on asymmetric tooth formation [18]. Studies have found that children with CLP had asymmetrical tooth formation that was 3–4 times more common than those of the control group [20, 21, 23]. The only study that did not report such a finding was by Borodkin et al. [21].

2.3.2 Teeth involved

When considering individual teeth, some teeth seem to display a greater propensity for asymmetric formation. Ranta reported that asymmetric tooth development occurred most frequently in the upper central incisors followed by the upper and lower premolars, without taking into account peg-shaped teeth and third molars [19, 38]. Harris and Hullings found that second premolars and third molars were more likely candidates for asymmetric formation and these teeth were also more likely to be congenitally missing, with the incisors being excluded in their study [19]. Tan et al. found that the most commonly delayed tooth in the maxilla is the cleft-sided lateral incisors (73.3%), followed by the cleft-sided central incisors (37.3%), while the cleft-sided canines and first premolars were the most frequently affected (21.7%) in the mandible [22].

2.3.3 Cleft vs. non-cleft side

Several authors concur that in both the maxilla and mandible, the cleft side has a significantly higher risk of delayed development of teeth than non-cleft side [18, 20, 22].

2.3.4 Maxilla vs. mandible

Ranta also investigated the difference in incidence of asymmetric tooth development between both jaws. In the cleft palate group, asymmetry occurs with equal frequency in both jaws. However in the cleft lip and alveolus group and the CLP group, asymmetry occurs more frequently in the maxilla [18, 37]. Asymmetric development of teeth was also found to decrease as growth of the crowns and roots progresses [38].

2.4 Delayed dental eruption

Tooth eruption occurs at a precise stage of root development and hence, any delay or asymmetric tooth formation would likely affect the timing and pattern of tooth eruption.

Peterka et al. reported that the deciduous and permanent lateral incisors in the maxillary quadrant with cleft showed the greatest retardation [39]. He also noted delayed eruption of the canine, first and second premolars in the maxillary quadrant with cleft. This coincides with the findings of Carrara et al. who found retarded eruption of the maxillary lateral incisor, cuspid and second premolar on the cleft side [40].

2.5 Aetiology of asymmetric tooth formation and eruption

Eerens et al. compared 54 children with cleft, 63 children in the sibling group without cleft as well as 250 normal children in the non-sibling control group and found that the cleft group and sibling group showed a significantly higher frequency of asymmetric tooth formation compared to the control group, hence suggesting some common genetic factors for delayed tooth formation and clefting [41].

Another possible reason for asymmetric tooth formation and delayed eruption in CLP patients has also been proposed. The effects of surgical cleft repair could result in damage to the tooth bud, or fibrosis and reduced blood supply to the cleft area [18]. Other etiological factors include lack of space in the cleft area [39] and growth attenuation due to improper nutrition as a result of feeding problems [18].

3. Dental anomalies in CLP patients

3.1 Lateral incisor in the cleft area

The permanent maxillary lateral incisor in CLP patients is a tooth of much interest and has been widely researched on, due to its proximity to the cleft and hence vulnerability to maldevelopment and injury. Disrupted development at the site of the cleft could also be due to altered neurovascular anatomy that could affect the developing tooth germ [42].

Some primary maxillary lateral incisors were found to be macrodonts whereas the permanent lateral incisors were microdonts or peg-shaped [43]. It has been reported as the most commonly missing tooth in CLP patients with a frequency ranging from 19.2–39.3% [3, 17, 44–47].

3.1.1 Position of cleft-sided lateral incisor

When the permanent maxillary lateral incisor is present in CLP patients, it is usually located on the distal side of the cleft [17, 44, 47–50] and is often reported to be delayed in formation and eruption when compared to the antimeric lateral incisor on the non-cleft side [17, 20, 22, 36, 47, 51].

Tsai et al. reported on the discrepancy in distribution patterns of the cleft-sided maxillary lateral incisors in the primary and permanent dentition [46]. In the primary dentition, the lateral incisor was located most commonly on the distal side of the alveolar cleft (82.4%), followed by missing cleft-sided maxillary lateral incisor (9.9%), one tooth present on each side of the alveolar cleft (5.5%), and lastly, the lateral incisor was located mesial to the alveolar cleft (2.2%). However, in the permanent dentition, the most predominant pattern was the missing cleft-sided maxillary lateral incisor (51.8%), followed by the lateral incisor positioned distal to the alveolar cleft (46%), lateral incisor positioned mesial to the alveolar cleft (1.5%) and the least common finding of one tooth present on each side of the alveolar cleft (0.7%). Due to the difference in the distribution patterns between the primary and permanent dentition, the authors proposed that there may be two odontogenic origins (maxillary and medial nasal process) for the maxillary lateral incisors. Failure of fusion between the two processes could have resulted in unequal mesenchymal mass in each of the segment, hence giving rise to different distribution patterns.

3.1.2 Malformed cleft-sided lateral incisor

The permanent lateral incisor located on the cleft side is also the most malformed tooth in the entire permanent dentition, often presenting with some degree of deformity in size and shape [45, 52]. It is frequently found to be microdontic or peg-shaped [44, 47, 50, 53]. Suzuki et al. found the majority of cleft-sided permanent lateral incisors to be of conical type [49]. Other less common variations include T-shaped lateral incisor or presence of a palatal cusp [44, 53, 54].

Some authors have proposed that malformed or missing lateral incisors are possible microforms of cleft lip and/or palate [55–57] but this proposal has also been disputed by others [58–60] who found the frequency of lateral incisor anomaly to be the same in cleft families and non-cleft families.

3.2 Hypodontia

3.2.1 Teeth involved

Another common dental anomaly found in CLP patients is an increased prevalence of congenitally missing teeth occurring near and away from the cleft area. Apart from the commonly missing lateral incisor as mentioned previously, other teeth frequently involved are the upper and lower second premolars [17, 19, 41, 44–46, 61, 62], with the maxillary second premolar being the more frequently missing tooth [45, 61].

3.2.2 Prevalence

The prevalence of hypodontia in CLP sample has been reported to range from 31.6–77% [50, 62–64]. In addition, the prevalence of hypodontia also increases with severity of the cleft [3, 44, 61, 65].

Ranta found that in complete cleft cases, almost every fourth (24%) of the upper second premolar was found to be missing [61].

However, other authors found that the maxillary lateral incisor was the most commonly missing tooth (41.7%), followed by the maxillary second premolar (18.3%) [50, 62]. Due to its proximity to the cleft defect, the cleft-sided maxillary lateral incisor is the most vulnerable to maldevelopment and iatrogenic injury, hence explaining its high frequency of being missing [66]. It was similarly reported as the most commonly missing tooth in CLP patients with a frequency ranging from 19.2–39.3% [3, 17, 44–47].

In a non-cleft population, Brook (1984) reported that the prevalence of hypodontia in British school children was 4.4%; the most commonly missing tooth was the mandibular second premolar [67]. The lower second premolar was the most commonly missing tooth in 26.1% of the Singapore Chinese orthodontic population with hypodontia. The lower incisor was the next most commonly missing tooth in 21.6%, followed by the upper lateral incisor in 20.5% of the population [68]. In Caucasians, the next most commonly missing tooth would be the maxillary lateral incisors, followed by the maxillary second premolar [69].

3.2.3 Primary vs. permanent dentition

Hypodontia, in contrast to supernumerary teeth, is found to be more prevalent in the permanent dentition than primary dentition in CLP patients [43, 44, 52, 61].

3.2.4 Aetiology

One hypothesis for hypodontia which explains these findings is the Butler's field theory (1939) that postulated teeth were not individual structures but constituted a series of different morphological classes with the most stable tooth at the mesial end. The distal tooth in each class was evolutionarily less stable [70].

Eerens et al. also demonstrated a higher occurrence of hypodontia in the cleft group and sibling group as compared to the normal, non-cleft control group, hence suggesting some relationship between the genetic factors controlling clefting and hypodontia [41].

Among the genetic factors involved in craniofacial development are members of the *Msx* homeobox gene family [71] and till date, *Msx1* has shown good evidence of involvement in human orofacial clefting and tooth agenesis [71–76]. A missense mutation resulting in an arginine to proline substitution within the homeodomain of *Msx1* causes selective tooth agenesis in humans, an autosomal dominant phenotype affecting the second premolars and third molars of the secondary dentition [72].

3.3 Supernumerary teeth

3.3.1 Prevalence

CLP patients present with a higher prevalence of supernumeraries, more commonly found at the lateral incisor region adjacent to the cleft [17, 44, 46, 50, 54, 77–79]. The prevalence of a supernumerary lateral incisor in CLP patients ranged from 5.1% – 22.1% [47, 50, 52, 61, 62].

In contrast, a lower prevalence of supernumeraries is found in normal children, ranging from 0.46–3.4% across all nationalities [80–82]. In a local study carried out on 408 normal Singaporean Chinese patients, the prevalence of hyperdontia was found to be 7.1%, with most of the supernumeraries found in the premaxilla area [83].

3.3.2 Primary vs. permanent dentition

It has also been reported that supernumeraries occur more frequently in the primary dentition than in the permanent dentition in CLP patients [44, 46, 47, 49, 61]. However, this finding was disputed in the study by Vichi and Franchi which noted a higher prevalence of supernumerary lateral incisors in the permanent dentition (22.1%) than in the primary dentition (19.5%) [52].

3.3.3 Aetiology

Some authors attribute this finding of higher prevalence of supernumerary lateral incisor in CLP patients to the close proximity of the lateral incisor tooth bud to the cleft, hence a higher susceptibility to division or modification of the tooth bud or separation of the epithelial remnants, resulting in a supernumerary tooth forming [76, 77].

Tsai et al. proposed that there could be two odontogenic origins for the maxillary lateral incisors, one from the maxillary process and one from medial nasal process. The two processes are unable to fuse due to the cleft, resulting in two separate odontogenic regions having the potential to develop lateral incisors [46].

3.4 Enamel hypoplasia

A high incidence of enamel hypoplasia is found to occur more frequently in CLP patients compared with non-cleft populations, especially involving the maxillary incisors [1, 52, 62].

Dixon suggested that lip repair could cause enamel hypoplasia in deciduous incisors and tips of permanent incisor crowns related to the surgical area; whereas the palatal repair could cause some defects in the crowns of the permanent incisors [1].

3.5 Abnormalities in shape and size of permanent teeth

3.5.1 Crown abnormalities

CLP patients commonly present with anomalies in shape and size of permanent teeth, especially at the maxillary anterior region. The malformations frequently exhibit as microdontia or macrodontia [47, 50, 52, 62].

Other dental anomalies associated with CLP patients include thick curved maxillary central incisors [53, 54], addition of paralabial tubercles on the central incisor and canine, missing cusp or altered cusp patterns of the maxillary molars and mandibular bicuspids [53] and smaller mesial-distal width of central incisors on the cleft side [44, 84]. Interactive compensations with dental variations in size have been reported to occur within tooth classes [85]. In non-cleft oligodontia with multiple missing teeth, the dentition was found to be reduced in size. However, in dentition with isolated tooth agenesis, tooth-size was larger compared to those of fully dentate individuals without hypodontia [86]. The premise of an odontogenic interactive compensatory mechanism was suggested in that a size reduction of a lateral incisor was a localised response to a large adjacent central incisor [87].

3.5.2 Root abnormalities

Taurodontism [65, 88], root dilacerations [62], fusion, germination and concrescence [81] have also been associated with CLP patients.

3.6 Abnormalities in position of permanent teeth

3.6.1 Rotated cleft-sided central incisors

Cleft sided central incisors are often found to be rotated, with a prevalence of 68.6% to 86.17 [48, 50, 89] reported. This has been attributed to the lack of space at the end of the alveolar segment [90].

3.6.2 Impacted canines

The canines on the cleft side are often palatally impacted. It has been suggested that the impaction may be due to the palatal collapse of the maxillary lateral segment [89] or related to the genetic factor responsible for CLP [91].

Lai et al. suggested that when the lateral incisor is located distal to the cleft, it can provide guidance for the eruption of the adjacent canine [47].

3.6.3 Ectopic eruption

Ectopic eruption of teeth, including transposition has also been reported in patients with CLP [62, 90, 92, 93].

3.7 Aetiology of dental anomalies

3.7.1 Cleft defect and surgical trauma

Since a high prevalence of dental anomalies was found at the region of the cleft, these anomalies may be attributed to the cleft itself or to the early surgical correction of the defects. The severity of these anomalies also appears to be related to the severity of the cleft.

3.7.2 Genetic factors

As the increased prevalence of dental anomalies was also found in the non-cleft region, it was postulated that dental anomalies in CLP patients were affected by common developmental mechanisms that involved non-fusion of orofacial processes and the persistence of orofacial clefts during embryonic and foetal formation. Extensive studies on orofacial clefting have linked genetic susceptibility, signalling pathways and transcription factors in the regulation of -lip, palate and dentition development [94–97].

Multiple disruptions in development of a number of body tissues including the dental lamina result in frequent occurrences of dental anomalies together with and several other visceral and skeletal anomalies in CLP children [41, 98, 99].

This has led to several studies investigating the presence of dental anomalies in parents and siblings of CLP children, of which, the results have been conflicting to date. Both Jordan et al. [53] and Schroeder and Green [54] reported a higher than normal frequency of occurrence of dental anomalies in the siblings of affected CLP individuals than in the general population. More recently, Eerens et al. reported significantly higher frequency of hypodontia and asymmetric tooth formation in both cleft and unaffected sibling groups compared with normal controls [41].

On the other hand, Woolf et al. observed that the incidence of maxillary lateral incisor abnormalities in parents' dentition was similar to non-cleft controls [58]. Mills et al. demonstrated no significant differences in the oral and facial defects between cleft and non-cleft families [59].

Anderson and Moss similarly found no evidence to suggest that parents of CLP children have a higher incidence of dental abnormalities than the general population and suggested that the genes carried by the non-cleft parents of CLP cases do not produce dental manifestations [60]. This could be because the genetics of odontogenesis is complex and is influenced by many factors, genes, epigenetics, and environmental factors [60, 100, 101].

4. Conclusion

It has been well-documented in the literature that CLP patients often present with delayed dental development and tooth eruption, asymmetric tooth formation and dental anomalies like hypodontia, supernumerary teeth, malformed or missing lateral incisor at the cleft region. However, there are minor controversies regarding gender differences, teeth most commonly affected, and differences in the development of maxillary and mandibular teeth.

The coming together of genetic, epigenetic and environmental factors seem to play an important role in the sequential pathway of orofacial and dental formation. Cell differentiation, proliferation and migration, as well as timing and fusion impact on the development of the lip, palate and dentition. Perturbations in the highly orchestrated mechanisms result in orofacial, dental and systemic organ defects.

Further studies are needed to link the dental characteristics of relatives of CLP patients as well as the molecular network that define and regulate orofacial and dental development. With new knowledge from research to bridge these gaps, effective strategies can be derived to prevent or rescue cleft defects and associated multi-system maldevelopment.

Acknowledgements

National Dental Centre of Singapore for the financial support in open access publication fees.

Conflict of interest

There is no conflict of interest related to individual authors' commitments and any project support.

Author details

Elaine Li Yen Tan* and Mimi Yow
Department of Orthodontics, National Dental Centre, Singapore

*Address all correspondence to: elaine.tan.l.y@singhealth.com.sg

References

[1] Dixon MJ, Marazita ML, Beaty TH, Murray JC. Cleft lip and palate: Synthesizing genetic and environmental influences. Nature Reviews Genetics. 2011;**12**:167-178

[2] IPDTOC Working Group. Prevalence at birth of cleft lip with or without cleft palate: Data from the international perinatal database of typical oral clefts (IPDTOC). The Cleft Palate-Craniofacial Journal. 2011;**48**:66-81

[3] Ranta R. A review of tooth formation in children with cleft lip/palate. American Journal of Orthodontics and Dentofacial Orthopedics. 1986;**90**:11-18

[4] Gleiser I, Hunt EE Jr. The permanent mandibular first molar: Its calcification, eruption and decay. American Journal of Physical Anthropology. 1955;**13**:253-283

[5] Hayes RL, Mantel N. Procedures for computing the mean age of eruption of human teeth. Journal of Dental Research. 1958;**37**:938-947

[6] Nolla C. The development of the permanent teeth. Journal of Dentistry for Children. 1960;**49**:197-199

[7] Moorrees CF, Fanning EA, Hunt EE Jr. Age variation of formation stages for ten permanent teeth. Journal of Dental Research. 1963;**42**:1490-1502

[8] Liliequist B, Lundberg M. Skeletal and tooth development. A methodologic investigation. Acta Radiologica: Diagnosis. 1971;**11**:97-112

[9] Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Human Biology. 1973;**45**:211-227

[10] Gustafson G, Koch G. Age estimation up to 16 years of age based on dental development. Odontologisk Revy. 1974;**25**:297-306

[11] Haavikko K. Tooth formation age estimated on a few selected teeth. A simple method for clinical use. Proceedings of the Finnish Dental Society. 1974;**70**:15-19

[12] Demirjian A, Goldstein H. New systems for dental maturity based on seven and four teeth. Annals of Human Biology. 1976;**3**:411-421

[13] Hagg U, Matsson L. Dental maturity as an indicator of chronological age: The accuracy and precision of three methods. European Journal of Orthodontics. 1985;**7**:25-34

[14] Maber M, Liversidge HM, Hector MP. Accuracy of age estimation of radiographic methods using developing teeth. Forensic Science International. 2006;**159**(Suppl. 1):S68-S73

[15] Esan TA, Yengopal V, Schepartz LA. The Demirjian versus the Willems method for dental age estimation in different populations: A meta-analysis of published studies. PLoS One. 2017;**12**(11):e0186682. DOI: 10.1371/journal.pone.0186682

[16] Bailit H, Doykos JD, Swanson LT. Dental development in children with cleft palates. Journal of Dental Research. 1968;**47**:664

[17] Fishman LS. Factors related to tooth number, eruption time, and tooth position in cleft palate individuals. ASDC Journal of Dentistry for Children. 1970;**37**:303-306

[18] Ranta R. A comparative study of tooth formation in the permanent dentition of Finnish children with cleft lip and palate. An orthopantomographic study. Proceedings of the Finnish Dental Society. 1972;**68**:58-66

[19] Harris EF, Hullings JG. Delayed dental development in children with

isolated cleft lip and palate. Archives of Oral Biology. 1990;**35**:469-473

[20] Lai MC, King NM, Wong HM. Dental development of Chinese children with cleft lip and palate. The Cleft Palate-Craniofacial Journal. 2008;**45**:289-296

[21] Borodkin AF, Feigal RJ, Beiraghi S, Moller KT, Hodges JS. Permanent tooth development in children with cleft lip and palate. Pediatric Dentistry. 2008;**30**:408-413

[22] Tan EL, Yow M, Kuek MC, Wong HC. Dental maturation of unilateral cleft lip and palate. Annals of Maxillofacial Surgery. 2012;**2**:158-162

[23] Ranta R. Comparison of tooth formation in noncleft and cleft-affected children with and without hypodontia. ASDC Journal of Dentistry for Children. 1982;**49**:197-199

[24] Ranta R. Associations of some variables to tooth formation in children with isolated cleft palate. Scandinavian Journal of Dental Research. 1984;**92**(6):496-502

[25] Prahl-Andersen B. The dental development in patients with cleft lip and palate. Transactions of European Orthodontic Society. 1976;**52**:155-160

[26] Poyry M, Nystrom M, Ranta R. Tooth development in children with cleft lip and palate: A longitudinal study from birth to adolescence. European Journal of Orthodontics. 1989;**11**:125-130

[27] Heidbuchel KL, Kuijpers-Jagtman AM, Ophof R, van Hooft RJ. Dental maturity in children with a complete bilateral cleft lip and palate. The Cleft Palate-Craniofacial Journal. 2002;**39**:509-512

[28] Tan ELY, Kuek MC, Wong HC, Yow M. Longitudinal dental maturation of children with complete unilateral cleft lip and palate: A case-control cohort study. Orthodontics & Craniofacial Research. 2017;**20**:189-195

[29] Tanner JM. The regulation of human growth. Child Development. 1963;**34**:817-847

[30] Krogman WM, Mazaheri M, Harding RL, Ishiguro K, Bariana G, Meier J, et al. A longitudinal study of the craniofacial growth pattern in children with clefts as compared to normal, birth to six years. The Cleft Palate Journal. 1975;**12**:59-84

[31] Seow WK. A study of the development of the permanent dentition in very low birthweight children. Pediatric Dentistry. 1996;**18**:379-384

[32] Solis A, Figueroa AA, Cohen M, Polley JW, Evans CA. Maxillary dental development in complete unilateral alveolar clefts. The Cleft Palate-Craniofacial Journal. 1998;**35**:320-328

[33] Davis PJ, Hagg U. The accuracy and precision of the "Demirjian system" when used for age determination in Chinese children. Swedish Dental Journal. 1994;**18**(3):113-116

[34] Hunter WS. The effects of clefting on crown-root length, eruption, height and weight in twins discordant for cleft of lip and/or palate. The Cleft Palate Journal. 1975;**12**:222-228

[35] Heikkinen T, Alvesalo L, Osborne RH, Tienari J. Maternal smoking and tooth formation in the foetus. II. Tooth crown size in the permanent dentition. Early Human Development. 1994;**40**:73-86

[36] Pioto NR, Costa B, Gomide M. Dental development of the permanent lateral incisor in patients with incomplete and complete unilateral

cleft lip. The Cleft Palate-Craniofacial Journal. 2005;**42**:517-520

[37] Ranta R. Asymmetric tooth formation in the permanent dentition of cleft-affected children. An orthopantomographic study. Scandinavian Journal of Plastic and Reconstructive Surgery. 1973;**7**:59-63

[38] Ranta R. Development of asymmetric tooth pairs in the permanent dentition of cleft-affected children. Proceedings of the Finnish Dental Society. 1973;**69**:71-75

[39] Peterka M, Tvrdek M, Mullerova Z. Tooth eruption in patients with cleft lip and palate. Acta Chirurgiae Plasticae. 1993;**35**:154-158

[40] Carrara CFC, Lima JEO, Carrara CE, Gonzalez VB. Chronology and sequence of eruption of the permanent teeth in patients with complete unilateral cleft lip and palate. The Cleft Palate-Craniofacial Journal. 2004;**41**:642-645

[41] Eerens K, Vlietinck R, Heidbuchel K, Van Olmen A, Derom C, Willems G, et al. Hypodontia and tooth formation in groups of children with cleft, siblings without cleft, and nonrelated controls. The Cleft Palate-Craniofacial Journal. 2001;**38**:374-378

[42] Kjaer I, Kocsis G, Nodal M, Christensen LR. Aetiological aspects of mandibular tooth agenesis — focusing on the role of nerve, oral mucosa, and supporting tissues. European Journal of Orthodontics. 1994;**16**:371-375

[43] Pegelow M, Alqadi N, Karsten A. The prevalence of various dental characteristics in the primary and mixed dentition in patients born with non-syndromic unilateral cleft lip with or without cleft palate. The European Journal of Orthodontics. 2012;**34**(5):561-570

[44] Boehn A. Dental anomalies in harelip and cleft palate. Acta Odontologica Scandinavica. 1963;**21**(Suppl. 38):1-109

[45] Olin WH. Dental anomalies in cleft lip and palate patients. The Angle Orthodontist. 1964;**34**:119-123

[46] Tsai TP, Huang CS, Huang CC, See LC. Distribution patterns of primary and permanent dentition in children with unilateral complete cleft lip and palate. The Cleft Palate-Craniofacial Journal. 1998;**35**:154-160

[47] Lai MC, King NM, Wong H. Abnormalities of maxillary anterior teeth in Chinese children with cleft lip and palate. The Cleft Palate-Craniofacial Journal. 2009;**46**:58-64

[48] Keith A. Three demonstrations ON CONGENITAL MALFORMATIONS OF PALATE, FACE, AND NECK: Given at the royal college of surgeons, England. British Medical Journal. 1909;**2**:438-441

[49] Suzuki A, Watanabe M, Nakano M, Takahama Y. Maxillary lateral incisors of subjects with cleft lip and/or palate: Part 2. The Cleft Palate-Craniofacial Journal. 1992;**29**:380-384

[50] Tan ELY, Kuek MC, Wong HC, Ong SAK, Yow M. Secondary dentition characteristics in children with nonsyndromic unilateral cleft lip and palate: A retrospective study. The Cleft Palate-Craniofacial Journal. 2018;**55**:582-589

[51] Ribeiro LL, das Neves LT, Costa B, Gomide M. Dental development of permanent lateral incisor in complete unilateral cleft lip and palate. The Cleft Palate-Craniofacial Journal. 2002;**39**:193-196

[52] Vichi M, Franchi L. Abnormalities of the maxillary incisors in children with cleft lip and palate. ASDC

Journal of Dentistry for Children. 1995;**62**:412-417

[53] Jordan RE, Kraus BS, Neptune CM. Dental abnormalities associated with cleft lip and/or palate. The Cleft Palate Journal. 1966;**3**:22-55

[54] Schroeder DC, Green L. Frequency of dental trait anomalies in cleft, sibling, and noncleft groups. Journal of Dental Research. 1975;**54**:802-807

[55] Fukuhara T, Saito S. Possible carrier status of hereditary cleft palate with cleft lip; report of cases. The Bulletin of Tokyo Medical and Dental University. 1963;**10**:333-345

[56] Meskin LH, Gorlin RJ, Isaacson RJ. Abnormal morphology of the soft palate. Ii. The genetics of cleft uvula. The Cleft Palate Journal. 1965;**45**:40-45

[57] Tolarova M. Microforms of cleft lip and-or cleft palate. Acta Chirurgiae Plasticae. 1969;**11**:96-107

[58] Woolf CM, Woolf RM, Broadbent TR. Lateral incisor anomalies. Microforms of cleft lip and palate? Plastic and Reconstructive Surgery. 1965;**35**:543-547

[59] Mills LF, Niswander JD, Mazaheri M, Brunelle JA. Minor oral and facial defects in relatives of oral cleft patients. The Angle Orthodontist. 1968;**38**:199-204

[60] Anderson PJ, Moss AL. Dental findings in parents of children with cleft lip and palate. The Cleft Palate-Craniofacial Journal. 1996;**33**:436-439

[61] Ranta R. The development of the permanent teeth in children with complete cleft lip and palate. Proceedings of the Finnish Dental Society. 1972;**68**(Supl. III):6-27

[62] Al Jamal GA, Hazza'a AM, Rawashdeh MA. Prevalence of dental anomalies in a population of cleft lip and palate patients. The Cleft Palate-Craniofacial Journal. 2010;**47**:413-420

[63] Da Silva AP, Costa B, de Carvalho Carrara CF. Dental anomalies of number in the permanent dentition of patients with bilateral cleft lip: Radiographic study. The Cleft Palate-Craniofacial Journal. 2008;**45**:473-476

[64] Shapira Y, Lubit E, Kuftinec MM. Hypodontia in children with various types of clefts. The Angle Orthodontist. 2000;**70**:16-21

[65] Ranta R, Stegars T, Rintala AE. Correlations of hypodontia in children with iolated cleft palate. The Cleft Palate Journal. 1983;**20**:163-165

[66] Dixon DA. Defects of structure and formation of the teeth in persons with cleft palate and the effect of reparative surgery on the dental tissues. Oral Surgery, Oral Medicine, and Oral Pathology. 1968;**25**:435-446

[67] Brook AH. A unifying aetiological explanation for anomalies of human tooth number and size. Archives of Oral Biology. 1984;**29**:373-378

[68] Qian L, Chew MT, Yow M, Wong HC, Foong WCK. Anomalies in tooth number in the permanent dentition of three Asian ethnicities. Australian Orthodontic Journal. 2017;**33**:212-219

[69] Polder BJ, Van't Hof MA, Van der Linden FP, Kuijpers-Jagtman AM. A meta-analysis of the prevalence of dental agenesis of permanent teeth. Community Dentistry and Oral Epidemiology. 2004;**32**:217-226

[70] Butler PM. Studies of the mammalian dentition - differentiation of the postcanine dentition. Proceedings of the Zoological Society of London. 1939;**B109**:1-36

[71] Alappat S, Zhang ZY, Chen YP. Msx homeobox gene family and craniofacial

development. Cell Research. 2003;**13**:429-442

[72] Vastardis H, Karimbux N, Guthua SW, Seidman JG, Seidman CE. A human MSX1 homeodomain missense mutation causes selective tooth agenesis. Nature Genetics. 1996;**13**:417-421

[73] Lidral AC, Romitti PA, Basart AM, Doetschman T, Leysens NJ, Daack-Hirsch S, et al. Association of MSX1 and TGFB3 with nonsyndromic clefting in humans. American Journal of Human Genetics. 1998;**63**:557-568

[74] van den Boogaard MJ, Dorland M, Beemer FA, van Amstel HK. MSX1 mutation is associated with orofacial clefting and tooth agenesis in humans. Nature Genetics. 2000;**24**:342-343

[75] Blanco R, Chakraborty R, Barton SA, Carreno H, Paredes M, Jara L, et al. Evidence of a sex-dependent association between the MSX1 locus and nonsyndromic cleft lip with or without cleft palate in the Chilean population. Human Biology. 2001;**73**:81-89

[76] Lidral AC, Reising BC. The role of MSX1 in human tooth agenesis. Journal of Dental Research. 2002;**81**:274-278

[77] Millhon J, Stafne EC. Incidence of supernumerary and congenitally missing incisor teeth in eighty-one cases of harelip and cleft palate. American Journal of Orthodontics and Oral Surgery. 1941;**27**:599-604

[78] Nagai I, Fujiki Y, Fuchihata H, Yoshimoto T. Supernumerary tooth associated with cleft lip and palate. Journal of the American Dental Association (1939). 1965;**70**:642-647

[79] Schulze C. Anomalies of the deciduous teeth with special reference to anomalies associated with cleft palate. Stoma. 1953;**6**:201-221

[80] Niswander JD, Sujaku C. Congenital anomalies of teeth in Japanese children. American Journal of Physical Anthropology. 1963;**21**:569-574

[81] Buenviaje TM, Rapp R. Dental anomalies in children: A clinical and radiographic survey. ASDC Journal of Dentistry for Children. 1984;**51**:42-46

[82] Davis P. Hypodontia and hyperdontia of permanent teeth in Hong Kong schoolchildren. Community Dentistry and Oral Epidemiology. 1987;**15**:218-220

[83] Ho KK, Mok YY. Hypodontia and hyperdontia of permanent teeth in 12-14 year old Singaporean Chinese: A preliminary study. Singapore Dental Journal. 1991;**16**:16-19

[84] Zilberman Y. Observations on the dentition and face in clefts of the alveolar process. The Cleft Palate Journal. 1973;**10**:230-238

[85] Bishara SE, Jakobsen JR. Compensatory developmental interactions in the size of permanent teeth in three contemporary populations from Egypt, Mexico, and the United States. Angle Orthodontist. 1989;**59**(2):107-112

[86] Yamada H, Kondo S, Hanamura H. Tooth size in individuals with congenitally missing teeth: A study of Japanese males. Anthropological Science. 2010;**118**(2):87-93

[87] Kondo S, Hanamura H. Does a maxillary lateral incisor reduce to compensate for a large central incisor? Aichi Gakuin Journal of Dental Science. 2010;**48**(3):215-227

[88] Laatikainen T, Ranta R. Taurodontism in twins with cleft lip and/or palate. European Journal of Oral Sciences. 1996;**104**:82-86

[89] Ranta R. On the development of central incisors and canines situated adjacent to the cleft in unilateral total

cleft cases. An orthopantomographic and clinical study. Suomen Hammaslääkäriseuran Toimituksia. 1971;**67**:345-349

[90] Smahel Z, Tomanova M, Mullerova Z. Position of upper permanent central incisors prior to eruption in unilateral cleft lip and palate. The Cleft Palate-Craniofacial Journal. 1996;**33**:219-224

[91] Takahama Y, Aiyama Y. Maxillary canine impaction as a possible microform of cleft lip and palate. European Journal of Orthodontics. 1982;**4**:275-277

[92] Larson M, Hellquist R, Jakobsson OP. Dental abnormalities and ectopic eruption in patients with isolated cleft palate. Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery. 1998;**32**:203-212

[93] Ranta R. Tooth germ transposition: Report of cases. ASDC Journal of Dentistry for Children. 1989;**56**:366-370

[94] Menezes R, Letra A, Kim AH, Küchler EC, Day A, Tannure PN, et al. Studies with Wnt genes and nonsyndromic cleft lip and palate. Birth Defects Research. Part A, Clinical and Molecular Teratology. 2010;**88**(11):995-1000

[95] Lan Y, Jia S, Jiang R. Molecular patterning of the mammalian dentition. Seminars in Cell & Developmental Biology. 2014;**25-26**:61-70

[96] Kwon HE, Jia S, Lan Y, Liu H, Jiang R. Activin and Bmp4 signaling converge on Wnt activation during odontogenesis. Journal of Dental Research. 2017;**96**(10):1145-1152

[97] Reynolds K, Kumari P, Sepulveda Rincon L, Gu R, Ji Y, Kumar S, et al. Wnt signaling in orofacial clefts: Crosstalk, pathogenesis and models. Disease Models & Mechanisms. 2019;**12**(2):dmm037051

[98] Kraus BS, Kitamura H, Ooe T. Malformations associated with cleft lip and palate in human embryos and fetuses. American Journal of Obstetrics and Gynecology. 1963;**86**:321-328

[99] Kitamura H, Kraus BS. Visceral variations and defects associated with cleft lip and palate in human fetusess macroscopic description. The Cleft Palate Journal. 1964;**16**:99-115

[100] Sperber GH. Genetic mechanisms and anomalies in odontogenesis. Journal of the Canadian Dental Association. 1967;**33**:433-442

[101] Howe LJ, Richardson TG, Arathimos R, Alvizi L, Passos-Bueno MR, Stanier P, et al. Evidence for DNA methylation mediating genetic liability to non-syndromic cleft lip/palate. Epigenomics. 2019 Feb;**11**(2):133-145