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Genetic and Developmental Insights into Dental Anomalies in Cleft Lip and Palate

Areesha Rashid[1]*, Muhammad Eesa Akram[2], Sarah Noor[3], Maryam Arshad[4], Mahum Yasin[5], Mahnoor Tahir[6], Nitasha Sabir[7], Areeba Rashid[8]

[1]PhD Scholar: Faculty of Health Sciences, Centre for Applied Molecular Biology (CEMB), Quaid-i-Azam Campus, University of the Punjab, Lahore, 53700, Pakistan,
Email: areesha.rashid@bs.qau.edu.pk ORCID: https://orcid.org/0009-0006-0401-2174

[2-7] Dental Surgeon: Margalla Institute of Health Sciences, Quaid-E-Azam Avenue Gulrez Phase 3, Gulrez Housing Scheme, Rawalpindi, 46000, [2] Email: eesaakram18@gmail.com, [3] Email: sarahnoor0303@gmail.com, [4] Email: maryamarshad.bds@gmail.com, [5] Email: mahum.ya@icloud.com, [6] Email: mahnoort746@gmail.com [7] Email: drnitasha2021@gmail.com

[8] MBBS Scholar (Final Year): D.G. Khan Medical College, Dera Ghazi Khan, 32200, Punjab, Pakistan, ORCID: https://orcid.org/0009-0002-3888-1125, Email: areebar@dgkmc.edu.pk

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Corresponding Author:

Areesha Rashid,

PhD Scholar, Faculty of Health Sciences, Centre for Applied Molecular Biology (CEMB), Quaid-i-Azam Campus, University of the Punjab, Lahore, 53700, Pakistan

Email:
areesha.rashid@bs.qau.edu.pk

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ABSTRACT

Background: Cleft lip (CL), Cleft palate (CP) or cleft lip and palate (CL/P) are among the most widespread craniofacial birth defects, with an occurrence of 1 in 700 live births. In addition to the major facial deformity, individuals with the condition often exhibit dental anomalies that add complexity to functional, cosmetic, and life-long rehabilitation. **Objective**: This review aims to discuss clinical, genetic, and developmental insights about the dental anomalies associated with CL/P and its defining patterns and molecular pathways. **Method**: A narrative review with a semi-structured format was performed through the databases of PubMed, Scopus, and Google Scholar (2000-2024). Inclusion criteria included studies that evaluate dental anomalies in CL/P patients and its genetic or developmental basis. To identify similarities among the identified anomalies and the underlying mechanisms, the data were examined by themes. **Results**: Hypodontia was the most common finding with a prevalence rate of between 28 and 79 % with maxillary lateral incisors being more common on the cleft side. Hyperdontia was seen in as many as 73 % of patients, and enamel defects were present in over 90 % of certain groups, localized to the cleft area in both. Cleft severity and palatal involvement were very strongly associated with malocclusion, especially Class III. The genetic basis highlights MSX1-PAX9, FGFR1 signaling, TP63 variants, and WNT pathway modulators (WNT10A, AXIN2) as key regulators linking fusion and odontogenesis in the craniofacial region. **Conclusion**: The dental anomalies of the CL/P patients are a result of local tissue distraction beside some modal genetic factors. Their prevalence is so high that it prompts the importance of early, multidisciplinary intervention. The improvements in developmental genetics and stem cell biology present new opportunity to revise treatment approaches and enhance living quality of affected individuals.

INTRODUCTION

Cleft lip (CL), with or without palate involvement (CLP) is a result of failed fusion between the maxillary and medial nasal processes between weeks 4-7 of gestation. Its worldwide prevalence is about 1 per 700 live births, and it also occurs differently depending on ethnicity and socioeconomic setting. Dental anomalies are co-morbid with CL/CLP in 80-90 % of cases, compared with 2-10 % of the general population (Ezzeldin et al., 2023).

Dental anomalies in CL/CLP include abnormalities of the number of teeth, tooth shape, and structure, location, and tooth eruption order. The most frequent one is tooth agenesis with the rates of tooth agenesis up to 65 % in the cleft region (Qadeer et al., 2023). Supernumerary teeth also commonly appear in patients, usually located near the site of the cleft (Pradhan et al., 2020) and morphological anomalies like microdontia, peg-shaped lateral incisors, and enamel hypoplasia are also reported mostly in upper incisors (Chang, Chang, Lai, Lin, & Chang, 2022). The position anomalies of incisors and delayed eruption of permanent maxillary incisors complicate the development of occlusion. The occurrence of dental anomalies and their nature are associated with the severity of the cleft. Bilateral CLP and complete clefts have an increased agenesis and supernumerary teeth and are more common on the cleft side suggesting a localized malformation of the morphogenesis (Dias et al., 2018). Beside these dental anomalies, some other complications also lie in cases of CL/P are palatal fistulas after palatoplasty (Rashid et al., 2024)

Genes Implicated in Cleft Lip and Dental Anomalies

Genetic disorders result from variations in genes, DNA, or chromosomal material (Sajid et al., 2025). Genetic causes of CL/CLP and related dental anomalies are mutations or polymorphisms in homeobox genes (MSX1, PAX9), WNT pathway proteins (WNT10A, AXIN2), and transcription factors (IRF6, TBX22). Co-existence of tooth agenesis and orofacial clefts is evidence of common molecular mechanisms during early craniofacial development. Although not always, MSX1 polymorphisms do not correlate with the prevalence of dental anomalies in CLP, and meta-analyses reveal a PAX9 variant to be agenesis-related (Elgali, Abd Rahman, Ahmad, & Ghazali, 2023).

A study examined 45 patients with isolated ankyloglossia in Thailand, 2 atypical CPA pedigrees and 282 patients with non-syndromic CLP in both Thailand and the United Kingdom. Five potential missense mutations were detected of which three were found in T-box binding domain, which influence DNA binding and transcriptional repression. The study broadened the phenotypic spectrum of TBX22-related mutations in the direction of dental anomalies and cleft lip (Kantaputra et al., 2011).

Interferon Regulatory Factor 6 (IRF6)

Non-coding variants that disrupt enhancer activity in embryonic oral epithelium have been identified by emerging functional genomics near IRF6. Allelic editing of risk alleles in pluripotent-derived oral epithelial cells revealed that risk alleles on two SNPs close to IRF6 increase or decrease IRF6 expression and explain most of the genome-wide association signal at 1q32 in CL/P cohorts. This allele specific control makes IRF6 enhancers a strong candidate as the nodal point between the orofacial cleft liability and the resultant dental phenotypes (Kumari et al., 2025).

MSX1–PAX9 Transcriptional Module

A 2025 meta-analysis of more than 30,000 individuals supported the findings that polymorphisms of PAX9 highly increase the risk of tooth agenesis in non-syndromic CL/CLP patients, which is supplemented by the longstanding evidence that tooth agenesis is a direct result of impaired MSX1-PAX9 protein complexes that coordinate the early tooth germ patterning

and palatal shelf fusion. These evidences strengthen a common MSX1 PAX9 transcriptional axis as a key integrator between odontogenesis and palatogenesis (Zhong, Liu, Liu, Li, & Chen, 2025).

Fibroblast Growth Factor Receptor 1 (FGFR1) Signaling

Whole-exome sequencing of familial tooth agenesis pedigrees has also revealed rare FGFR1 missense mutations (e.g., p.Gly35Arg) that disrupt epithelial-mesenchymal transition, increase proliferation and block apoptosis in dental pulp stem cells by upregulation of SMAD6/7 and down regulation of ID4. These functional studies connect TGF-beta cross-talk mediated by FGFR1 to tooth number determination and midline facial development, and provide evidence implicating FGFR1 in CL/P and dental agenesis (Siyue Yao et al., 2023).

Fibroblast growth factor receptor 1 (FGFR1) is a regulator of cranial neural crest, and intramembranous ossification of the craniofacial skeleton. In early gestation, FGFR1 is expressed highly in head mesenchyme and periosteoidal osteoid, regulating osteoblast differentiation contents and patency of sutures. Normal FGFR1 polymorphisms (such as rs13317, rs6996321) are associated with midface retrusion and overall head size variation in non-diseased populations, and phenocopy milder forms of Pfeiffer syndrome (Adel et al., 2017).

Dental epithelial stem cell migration and differentiation rely on Epithelial Mesenchymal Transition (EMT). FGFR1 Gly35Arg promotes E-cadherin and inhibits N-cadherin and vimentin in hDPSCs, an indication of mesenchymal-to-epithelial skewing. This inhibition of EMT impairs the development of Hertwig epithelial root sheath and consequent odontoblast formation which can lead to tooth anomalies and even supernumerary teeth formation (S. Yao et al., 2023).

Tumor Protein p63 (TP63) in Epithelial Differentiation

In AEC and EEC syndromes caused by heterozygous TP63 mutations the individuals present with enamel hypoplasia, hypodontia, and CL/P. We demonstrate that the pleiotropic TP63 variants impair both keratinocyte differentiation and enamel organ integrity, suggesting that TP63 is a master regulator of both fusion of the facial epithelia and development of the ameloblast lineage (Zheng et al., 2019).

The pathogenic effect of disease-specific mutants resting on the DNA-binding domain (DBD) and sterile alpha motif (SAM) domain differ. R304W mutation in DBD (Pathogenic variant observed in EEC syndrome) also results in a complete lack of p63 association with chromatin and enhanced erg. In contrast, the I537T mutation in the SAM domain (corresponding to AEC syndrome) still has DNA binding capacity, but impaired abilities to open chromatin and become an effective enhancer, which leads to inability to properly upregulate craniofacial genes. These mutations prove that chromatin remodelers have been recruited by the SAM domain to push back the nucleosomes and have established open chromatin (Lin-Shiao, Lan, & Welzenbach, 2019).

TGF-beta signaling and P63 play a complex role in palatogenesis, and craniofacial fusion. TGF-beta signaling is also important to periderm in particular where a third of the Tgfbr1 knockout mice exhibited complete secondary palate clefties upon loss of TGF-beta receptor activity. The periderm also dedifferentiates TGF-b-mediated through a typed transformation to cuboidal morphology that permits medial edge attachment and fusion. Loss of TGF-beta signaling results in medial edge epithelium p63 antagonism to occur unfavourably to facilitate palatal fusion (Saroya et al., 2023). So, cross-Regulation with TGF-β Signaling networks is also crucial.

Recent case reports have also reported intrafamilial variability of TP63-related disorders, with a single pathogenic variant (p.Arg266Gln) producing EEC syndrome in one family member, but ADULT syndrome

in another. This form is associated with angina, narrowing of the nose, the absence of eyebrows and eyebrows, flat and dull nails, anodontia/ hypodontia and micturition disorders, and low rates of cleft palate/lip disturbance pathology occurrence (Corona-Rivera et al., 2024). Such variability highlights the complex genotype-phenotype relationships in TP63-associated disorders.

Evidence has shown that dental pulp stem cells retain the capacity to regenerate dentin-dental pulp complex formation; and TP63-regulated pathways are involved in odontogenic differentiation. The discovery of TP63-regulated enhancers with an enrichment in SNPs associated with cleft lip/palate informs the pathogenome of clefts and possible therapeutics (Enrique Lin-Shiao et al., 2019). Understanding TP63's role in dental pulp stem cell regulation opens therapeutic avenues for regenerative dentistry.

WNT Pathway Modulators

The WNT10A and AXIN2 coding variants have been repeatedly related to agenesis of maxillary lateral incisor in cohorts with CL/P. The co- segregation of mutations that disrupt the impact of the Wnt agonist WNT10A on tooth number and those which affect AXIN2, a direct modulator of canonical Wnt signaling, informs about the critical role of this pathway in cranio-odontogenic patterning both of tooth germ initiation and palatal shelf outgrowth (Mostowska, Biedziak, Zadurska, Matuszewska-Trojan, & Jagodziński, 2015).

A spectrum of new mutation variants in WNT10A in diverse populations has been widely reported, which has expanded the genotype phenotype correlation of NSTA. A broad cohort study has identified the WNT10A gene as a hotspot in NSTA, thereby identifying new and already known variants (e.g., A135S) which destabilize WNT10A expression or the formation of the dental lamina position, corresponding with maxillary lateral loss dentition (Wu, Lai, Chen, Li, & Hou, 2024). In vitro functional experiments with a Tyr118Cys missense variant demonstrated impaired proliferation and osteogenic differentiation in alveolar bone mesenchymal stem cells, indicating that WNT10A plays another role in the homeostasis of the jawbone other than early odontogenesis (Lin et al., 2025). Hypodontia was exacerbated by compound heterozygous missense variants in WNT10A (c.511C>T, c.637G>A) in hypohidrotic ectodermal dysplasia, alterations that were predicted to change the structure of the protein and disrupt binding of FZD5, in a possible example of digenic interactions (Liu et al., 2024). A study of the next-generation sequencing of Korean NSTA patients identified the exonic and intronic variants of WNT10A and it is noted that non-coding regions also play an important role in regulating WNT10A and contributing to the risk of tooth agenesis (Ju et al., 2025).

The dynamic epithelial-to-mesenchymal expression of NT10A during tooth morphogenesis involves precise epithelial-mesenchymal communications and interplay with modulators such as Dkk1 and Sost that help refine tooth morphogenesis involving cusp patterning and enamel organ differentiation (Raju et al., 2024). Other types of pathogenic mutations in the WNT family that cause oligodontia colorectal cancer syndrome are described in XIN2 mutations, which likewise lead to altering Wnt/beta-catenin equilibrium in not only craniofacial but also gastrointestinal epithelia (Roht et al., 2023). In vitro palate fusion assays show that AXIN2 upregulation induced by retinoic acid has a negative effect on palatal shelf fusion, thus providing the connection of environmental teratogens to Wnt pathway involvement in CL/P development (Roa Fuentes, Bloemen, & Carels, 2022). Signaling downstream of Pax9, canonical Wnt-signaling plays a central role in palatal morphogenesis, where Axin2 expression in palatal mesenchyme is strongly perturbed in Pax9-null palates and fusion can be rescued by Wnt agonist treatment, implicating AXIN2 as a direct downstream target in palatal development

(Li, Lan, Krumlauf, & Jiang, 2017). These results highlight Wnt pathway components, specifically WNT10A and AXIN2, as central molecular effectors in the dynamic relationships between tooth morphogenesis and palate development, where its deregulation combines both genetic and environmental factors in the pathophysiology of CL/P with dental dysmorphology. **Figure 1** reflects the genetic pathways linking cleft lip/palate to dental anomalies.

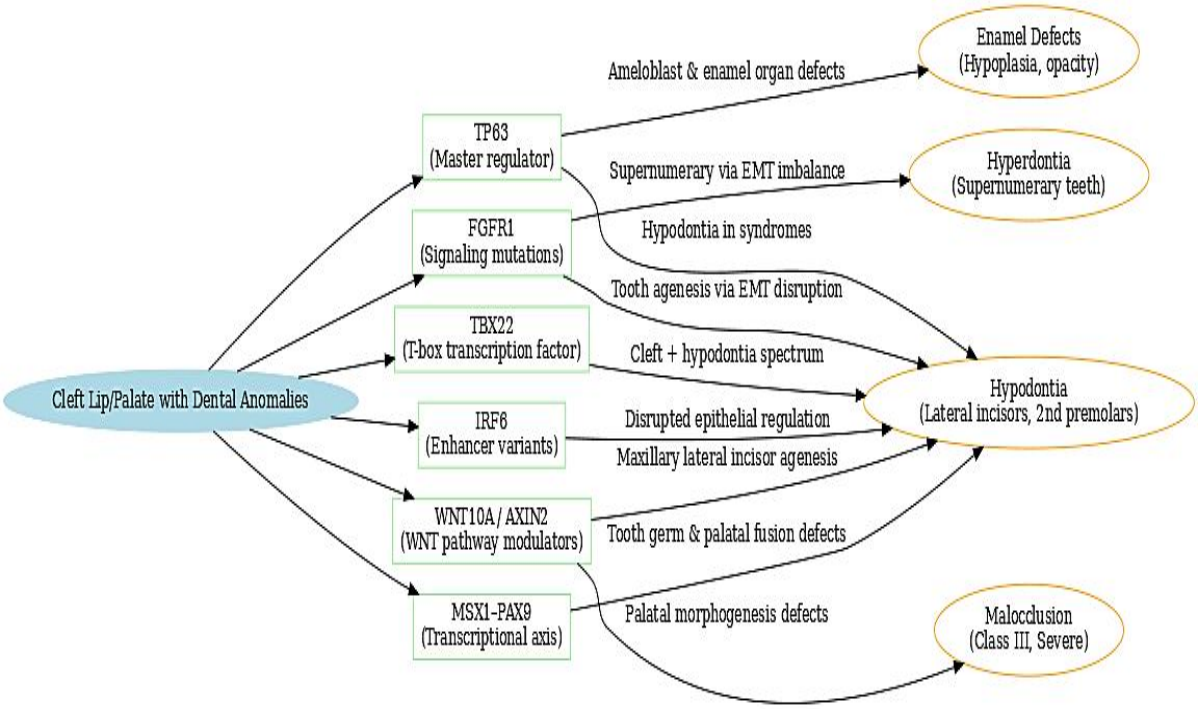

Figure 1: Genetic Pathways Linking Cleft Lip/Palate To Dental Anomalies

Shared genetic pathways link cleft lip/palate (CL/P) with dental anomalies. Genes like TP63, FGFR1, TBX22, IRF6, WNT10A/AXIN2, and MSX1-PAX9 impact craniofacial and dental development, contributing to enamel defects, hypodontia, hyperdontia, and malocclusion. These genes influence processes such as EMT, epithelial regulation, and palatal morphogenesis.

METHOD

This review follows a semi-structured narrative approach to synthesize existing literature on dental anomalies associated with cleft lip, with a specific focus on genetic and developmental perspectives. The aim was to identify and summarize key patterns, anomalies, and molecular mechanisms reported in clinical and biomedical studies.

A comprehensive literature search was conducted using the electronic databases PubMed, Scopus, and Google Scholar. The search included English-language articles published between 2000 and 2024. The following keywords and their combinations were used: “cleft lip,” “dental anomalies,” “hypodontia,” “supernumerary teeth,” “genetic factors,” “developmental biology,” and “craniofacial development.” Relevant Medical Subject Headings (MeSH) terms were also incorporated to ensure broader coverage.

Included studies were limited to human-based clinical, genetic, and developmental research that specifically discussed dental anomalies in individuals with cleft lip (with or without cleft palate). Review articles, case reports, and animal studies were excluded, except where foundational developmental mechanisms were discussed. Priority was given to studies reporting genetic associations, molecular pathways, or

developmental timing related to dental abnormalities.

After screening titles and abstracts for relevance, full-text articles were reviewed for detailed extraction. The data were organized thematically to identify recurrent dental anomalies, commonly implicated genes, and developmental disruptions. The findings are presented in a descriptive format to allow for comprehensive understanding while highlighting emerging trends and research gaps.

Table 1: Common Dental Anomalies in Cleft Lip Patients

Dental Anomaly	Prevalence in Cleft Lip (%)	Location (Cleft Side / Bilateral / Midline)	Clinical Significance	Ref.
Hypodontia (Congenital absence of one or more teeth)	Overall in CLP group: 68.68% • Upper lateral incisors: 37.34–48.07% • 2nd premolars (upper & lower): 5.58–8.58%	Maxilla more affected due to cleft • Mandibular 2nd premolar agenesis also high, not due to cleft	Suggests both cleft-related and non-cleft (genetic/environmental) influences; critical for orthodontic treatment	(De Stefani et al., 2019)
	64.1% overall in cleft patients 63.7% in unilateral CLP 71.9% in bilateral CLP	Mostly on cleft side (ipsilateral) Significantly higher on cleft side than non-cleft side	Affects function, aesthetics, requires prosthodontic/orthodontic management	(Jamilian et al., 2015)
	49.8% missing cleft-side lateral incisor 10.9% missing contralateral incisor Most common outside-cleft missing tooth: maxillary 2nd premolar	Mostly on cleft side; also affects non-cleft side but less frequently	Significant for aesthetic and orthodontic planning; cleft area impacts local tooth development	(Lourenço Ribeiro, Teixeira das Neves, Costa, & Ribeiro Gomide, 2003)
	Overall: 50% • CLA: 34.5% • UCLP: 51.6% • BCLP: 70.6% • Most commonly missing tooth: maxillary lateral incisor (23.1%)	• 81.5% in maxilla only • Mostly on cleft side in unilateral clefts ($p << 0.001$) • Left-sided clefts more affected	Increases with cleft severity; impacts aesthetics, speech, and treatment planning (e.g., timing of bone grafting)	(Möller, Pradel, Winnie Gedrange, Tomasz Botzenhart, & Ulrike, 2021)
	Overall: 63% CL: 33% CLA: Not specified CLP: 79% CP: 54% Most common: maxillary latera	Left-sided hypodontia more common ($p < .01$), regardless of cleft sidedness	Severity of cleft correlates with higher hypodontia; particularly impacts anterior esthetics and occlusion	(Matern et al., 2012)
	28%–66% overall More in permanent (52.7%) than primary (16.2%) dentition	Most commonly cleft-side lateral incisor Increases with cleft severity	Common and significant; affects aesthetics, eruption patterns, and orthodontic planning	(Lasota, 2020)
	69% overall in Hungarian CLP Patients UCLP right: 60.87% UCLP left: 66.22% BCLP: 90% Total teeth missing: 235	Most common in maxilla (172 teeth) • Cleft-side upper lateral incisor most affected • Also affects second premolars (upper & lower)	Correlates with cleft severity; impacts treatment planning, especially if multiple teeth are missing	(Berniczei-Roykó et al., 2016)
	Second premolar hypodontia in 19.3% overall Polish population	Maxilla (8.7%) > Mandible (5.7%) • More frequent on cleft	Indicates increased severity with cleft extent; requires early diagnosis for	(Mikulewicz, Ogiński,

	CLA: 11.8% UCLP: 15.8% BCLP: 21.6% CP: 35.7%	side (e.g., in UCLP, many missing teeth were ipsilateral)	orthodontic and prosthetic planning	Gedrange, Berniczei-Royko, & Prussak, 2014)
Hyperdontia/ Supernumerary Teeth (Extra teeth)	4.97% overall 6.9% in unilateral cleft lip & alveolus 8.3% in bilateral cleft lip & alveolus 5.5% in unilateral CLP 1.7% in bilateral CLP	All cases occurred in maxilla, usually near cleft site	May hinder eruption of adjacent teeth, cause crowding, or require extraction	(Jamilian et al., 2015)
	Overall: 33.3% • CLA: 51.7% • UCLP: 29.0% • BCLP: 17.6% • Most affected: maxillary lateral incisor (17.6%)	Maxillary anterior region • Mostly on cleft side (85.4% in unilateral clefts) • More in right-sided UCLP clefts	May hinder eruption, crowd teeth, or alter occlusion; usually needs extraction or surgical correction	(Möller et al., 2021)
	17.7% in primary maxillary dentition 5.7% in permanent maxillary dentition	Anterior maxilla, both inside and outside cleft area	May hinder eruption, cause crowding, and require surgical or orthodontic intervention	(Lasota, 2020)
	73% (22 out of 30 patients)	Cleft Side	May cause crowding, delay in eruption, or displacement of adjacent teeth; significant in cleft management and planning.	(Hansen & Mehdinia, 2002)
	26.55%	Cleft Side (mainly left side, 62.83%)	More common in males; may complicate eruption and alignment. Early detection aids in proper dental and orthodontic management.	(Lasota, Siebieszuk, Pastuszak, & Mostowska, 2022)
	15.4% (19.8% in males, 9.1% in females)	97% located on the cleft side (40.9% right, 39.4% left, 19.7% bilateral)	Can cause crowding, delayed eruption, displacement, root resorption, and complicate orthodontic treatment.	(Gómez, Villavicencio, & Vilchis, 2015)
Enamel defects	92.5% of patients 50.8% of teeth 50.7% hypoplasia 23.1% diffuse opacity 18.4% Demarcated opacity	Mostly on cleft side Hypoplasia: Middle third (40%), incisal third (33%)	Compromises enamel strength; higher caries risk; requires monitoring or restorative treatment.	(Ruiz, Maya, D'alpino, Atta, & Da Rocha Svizero, 2013)
	Enamel Hypoplasia (Deciduous Canines) 43.8% in unilateral clefts 39% in bilateral clefts	Similar in maxillary/mandibular arches, both genders, and cleft vs. noncleft sides	Mild to moderate esthetic and structural concerns; no clear influence of cleft presence on hypoplasia in deciduous canines.	(Mary Baaclini Galante, Costa, Felício de Carvalho Carrara, & Marcia, 2005)
	42.6% overall; 11.8% hypoplasia	Primarily on the cleft side in terms of both frequency and severity	May affect esthetics and early tooth function; early defects suggest local developmental disruption from the cleft.	(Gomes, Neves, & Gomide, 2009)

	Permanent Dentition: 87.9% of CLP patients (vs. 41.4% in non-CLP)	Most prevalent on the cleft side of the maxilla; central incisors most affected	Higher prevalence than in non-cleft individuals; primarily affects aesthetics and may suggest developmental disturbances near the cleft.	(Shen, Guo, & Li, 2019)
Malocclusion	Class-III dental malocclusion in Korean cleft patients 72.7% • CLP: 5.5x higher risk • CP: 3.9x higher risk than CL	More frequent in bilateral clefts; severity increases with palatal involvement	Strongly associated with cleft type, especially palate involvement; requires complex orthodontic and sometimes surgical management.	(Baek, Moon, & Yang, 2002)
	Class-I Malocclusion 73.1% overall Class-II Malocclusion 11.5% overall Class-III 15.4% overall, 100% with hard palate cleft	Class-I occurs broadly; no specific side preference noted Class-II associated with hard palate involvement	Class I, II, and III malocclusions in cleft patients contribute to functional, aesthetic, and speech issues and often require early, multidisciplinary orthodontic and surgical management.	(Okoye, Onah, Ekwueme, & Agu, 2020)

RESULTS

Analysis of the included studies highlights a consistently high prevalence of dental anomalies in cleft lip and palate (CLP) patients, with hypodontia, hyperdontia, enamel defects, and malocclusion emerging as the most frequent findings.

Hypodontia was the most common anomaly, with prevalence ranging from 28% to 79%, depending on cleft type and population. Maxillary lateral incisors were most frequently absent, particularly on the cleft side, and prevalence increased with cleft severity. Bilateral CLP patients demonstrated the highest rates (up to 90%), and mandibular second premolar agenesis was also noted, reflecting both cleft-related and non-cleft genetic influences.

Hyperdontia (supernumerary teeth) was reported in 5%–73% of cases, predominantly in the maxilla and near the cleft site. These supernumerary teeth frequently interfered with eruption, contributed to crowding, or required extraction, with higher prevalence in unilateral clefts.

Enamel defects were also highly prevalent, affecting up to 92.5% of patients and approximately half of all teeth examined. Defects, including hypoplasia and opacities, were more common and severe on the cleft side, particularly in maxillary central incisors, increasing susceptibility to caries and posing aesthetic concerns.

Malocclusion was strongly associated with cleft type and severity. Class III malocclusion was especially common in CLP patients, with prevalence rates exceeding 70% in some populations and risks several times higher than in non-cleft groups. Bilateral clefts and those involving the palate were most affected, often necessitating combined orthodontic and surgical interventions.

Overall, the results confirm that dental anomalies are intrinsic to CLP pathology, with both local (cleft-site) and systemic (genetic/environmental) factors contributing. Their high prevalence and functional impact underscore the importance of early detection and multidisciplinary management in cleft care.

DISCUSSION

The findings of this study highlight the extensive burden of dental anomalies in individuals with cleft lip and palate, emphasizing their clinical relevance and the complexity they add to cleft management. Hypodontia emerged as the most prevalent anomaly, particularly affecting maxillary lateral incisors on the cleft side. Its

association with cleft severity suggests that disruption of local morphogenetic fields plays a critical role in tooth germ development. The frequent absence of mandibular second premolars, however, points toward the influence of broader genetic or environmental mechanisms beyond the direct effect of the cleft.

Hyperdontia was also commonly observed, with supernumerary teeth clustering near the cleft site. These additional teeth can hinder eruption of adjacent dentition, alter occlusion, and complicate orthodontic planning. Their occurrence underscores the developmental instability in the cleft region, where both tooth loss and excess can coexist. A recent cross-sectional analysis of 312 Thai patients with various cleft types reported that overall tooth agenesis affected 78.2% of individuals, with the highest rate in bilateral cleft lip and palate (BCLP) (83.9%) and the lowest in cleft palate only (CPO) (69.4%). Supernumerary teeth were observed in 22.1% of cases, predominantly adjacent to the cleft margins. Unilateral cleft lip and palate (UCLP) patients exhibited a significantly higher prevalence of lateral incisor agenesis (71.3%) compared to other cleft types ($p < 0.001$), while supernumerary premolars clustered near the alveolar cleft gap ($p = 0.02$) (Aung, Pungchanchaikul, Pisek, Bloch-Zupan, & Morkmued, 2024). Möller's study demonstrates that cleft severity differentially influences dental anomalies, with greater palatal involvement shifting the pattern from supernumerary teeth toward higher rates of hypodontia, reflecting distinct morphogenetic disruptions across cleft phenotypes. (Möller et al., 2021).

Enamel defects were strikingly frequent, with more than half of the examined teeth showing structural compromise. The predominance of hypoplasia and opacities on the cleft side reinforces the concept of localized developmental disturbances. Clinically, such defects not only pose aesthetic challenges but also increase the risk of caries, further complicating long-term dental health in cleft patients (Paradowska-Stolarz, Mikulewicz, & Duś-Ilnicka, 2022). A service evaluation at a cleft centre in South Thames (UK) assessed 162 five-year-old CL/P patients. Developmental enamel defects on maxillary incisors were diagnosed in 65% of children, with 32% exhibiting hypomineralisation. Regular fluoride varnish application (64–81%) and high-fluoride toothpaste use (72–91%) were noted, yet caries risk remained elevated. The localized predominance of hypoplasia on the cleft side reinforces the impact of surgical timing and local tissue disruption on amelogenesis (Agel, Vaidyanathan, & Bhujel, 2022). These findings suggest that dental anomalies in cleft patients are not isolated features but part of a broader craniofacial dysmorphology that requires integrated management strategies.

Collectively, the presence of hypodontia, hyperdontia, enamel defects, and malocclusion in cleft populations illustrates the convergence of local developmental disruption at the cleft site and systemic genetic influences. These anomalies significantly affect aesthetics, function, and psychosocial well-being, underscoring the need for early diagnosis and comprehensive, multidisciplinary care involving surgeons, orthodontists, prosthodontists, and pediatric dentists.

CONCLUSION

This study reveals that dental anomalies in cleft lip and palate patients are not isolated occurrences but integral manifestations of broader craniofacial dysmorphology. Hypodontia, enamel defects, and malocclusion reflect a convergence of localized morphogenetic disruption at the cleft site and systemic genetic influences, particularly involving pathways such as MSX1-PAX9, FGFR1, TP63, and WNT signaling. These anomalies significantly affect aesthetics, oral function, and psychosocial well-being, while also complicating surgical and orthodontic management. Early detection and multidisciplinary care are therefore essential

to improve treatment outcomes. Future research integrating genomics, stem cell biology, and developmental modeling holds promise for unravelling genotype-phenotype correlations and informing precision approaches in cleft and dental anomaly management.

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REFERENCES

Adel, M., Yamaguchi, T., Tomita, D., Nakawaki, T., Kim, Y. I., Hikita, Y., et al. (2017). Contribution of FGFR1 Variants to Craniofacial Variations in East Asians. *PLoS One, 12*(1), e0170645. doi: 10.1371/journal.pone.0170645

Agel, M., Vaidyanathan, M., & Bhujel, N. (2022). Developmental defects of enamel and dental anomalies in five-year-old cleft patients. *Faculty Dental Journal, 13*(1), 6-11. doi: 10.1308/rcsfdj.2022.3

Aung, W. P., Pungchanchaikul, P., Pisek, A., Bloch-Zupan, A., & Morkmued, S. (2024). Prevalence of tooth agenesis and supernumerary teeth related to different Thai cleft lip and cleft palate populations. *BMC Oral Health, 24*(1), 960. doi: 10.1186/s12903-024-04719-3

Baek, S. H., Moon, H. S., & Yang, W. S. (2002). Cleft type and Angle's classification of malocclusion in Korean cleft patients. *European Journal of Orthodontics, 24*(6), 647-653. doi: 10.1093/ejo/24.6.647

Berniczei-Roykó, Á., Tappe, J. H., Krinner, A., Gredes, T., Végh, A., Gábor, K., et al. (2016). Radiographic Study of the Prevalence and Distribution of Hypodontia Associated with Unilateral and Bilateral Clef Lip and Palate in a Hungarian Population. *Med Sci Monit, 22*, 3868-3885. doi: 10.12659/msm.897957

Chang, C.-H., Chang, C.-H., Lai, J.-P., Lin, S.-S., & Chang, Y.-J. (2022). Prevalence of dental anomalies in Taiwanese children with cleft lip and cleft palate. *Journal of Personalized Medicine, 12*(10), 1708.

Corona-Rivera, J. R., Rios-Flores, I. M., Zenteno, J. C., Peña-Padilla, C., Castillo-Reyes, K., Bobadilla-Morales, L., et al. (2024). A Family with EEC Syndrome in the Son and ADULT Syndrome in His Father Caused by the c.797G>A (p.Arg266Gln) Pathogenic Variant in the TP63 Gene. *Mol Syndromol, 15*(1), 51-57. doi: 10.1159/000531934

De Stefani, A., Bruno, G., Balasso, P., Mazzoleni, S., Baciliero, U., & Gracco, A. (2019). Prevalence of hypodontia in unilateral and bilateral cleft lip and palate patients inside and outside cleft area: a case-control study. *Journal of Clinical Pediatric Dentistry, 43*(2), 126-130.

Dias, V. O., Vieira, M. L., Gonçalves, E. F., Santos, M. L., Oliveira Swerts, M. S., Martelii Júnior, H., et al. (2018). Dental Anomalies in Patients with Cleft Lip and/or Palate in the Brazilian Population: A Systematic Review. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 126*(3), e161. doi: 10.1016/j.oooo.2018.02.641

Elgali, A. E. B., Abd Rahman, N., Ahmad, A., & Ghazali, N. (2023). Dental Anomalies and Muscle Segment Homeobox1 Gene Polymorphism in Non-syndromic Cleft Lip with or without Palate Children. *Annals of Dentistry University of Malaya, 30*, 22-28.

Ezzeldin, M., Gee, S., Curtis, J., Clark, V. J., Smallridge, J., & Collard, M. (2023). Dental anomalies in cleft lip and/or palate children at age 10-a retrospective review across three cleft centres: Part 1. *British Dental Journal, 234*(12), 926-930.

Gomes, A. C., Neves, L. T. d., & Gomide, M. R. (2009). Enamel Defects in Maxillary Central Incisors of Infants with Unilateral Cleft Lip. *The Cleft Palate Craniofacial Journal, 46*(4), 420-424. doi: 10.1597/08-044.1

Gómez, O. V., Villavicencio, M. Á. F., & Vilchis, M. d. C. V. (2015). Prevalence of supernumerary teeth in children with cleft lip and/or palate. *Revista Odontológica Mexicana Órgano Oficial de la Facultad de Odontología UNAM, 19*(2), 81-88.

Hansen, K., & Mehdinia, M. (2002). Isolated Soft Tissue Cleft Lip: The Influence on the Nasal Cavity and Supernumerary Laterals. *The Cleft Palate Craniofacial Journal, 39*(3), 322-326. doi: 10.1597/1545-1569_2002_039_0322_istclt_2.0.co_2

Jamilian, A., Jamilian, M., Darnahal, A., Hamedi, R., Mollaei, M., & Toopchi, S. (2015). Hypodontia and supernumerary and impacted teeth in children with various types of clefts. *American Journal of Orthodontics and Dentofacial Orthopedics, 147*(2), 221-225. doi: https://doi.org/10.1016/j.ajodo.2014.10.024

Ju, Y., Lee, J. Y., Hwang, W., Shin, J., Kim, H.-S., Hur, J. K., et al. (2025). Exonic and Intronic WNT10A Variants Isolated from Korean Children with Non-Syndromic Tooth Agenesis. *Diagnostics, 15*(3), 310.

Kantaputra, P. N., Paramee, M., Kaewkhampa, A., Hoshino, A., Lees, M., McEntagart, M., et al. (2011). Cleft Lip with Cleft Palate, Ankyloglossia, and Hypodontia are Associated with TBX22 Mutations. *Journal of Dental Research, 90*(4), 450-455. doi: 10.1177/0022034510391052

Kumari, P., Friedman, R. Z., Curtis, S. W., Pi, L., Paraiso, K., Visel, A., et al. (2025). Identification of functional non-coding variants associated with orofacial cleft. *Nature communications, 16*(1), 6545.

Lasota, A. (2020). Dental abnormalities in children with cleft lip with or without cleft palate. *Journal of Pre-Clinical and Clinical Research, 15*(1), 46-49.

Lasota, A., Siebieszuk, W., Pastuszak, P., & Mostowska, A. (2022). The Prevalence and Morphology of Supernumerary Teeth in Children With Nonsyndromic Cleft Lip and Palate. *The Cleft Palate Craniofacial Journal, 59*(7), 867-872. doi: 10.1177/10556656211027750

Li, C., Lan, Y., Krumlauf, R., & Jiang, R. (2017). Modulating Wnt Signaling Rescues Palate Morphogenesis in Pax9 Mutant Mice. *J Dent Res, 96*(11), 1273-1281. doi: 10.1177/0022034517719865

Lin-Shiao, E., Lan, Y., & Welzenbach, J. (2019). p63 establishes epithelial enhancers at critical craniofacial development genes. *5*(5), eaaw0946. doi: 10.1126/sciadv.aaw0946

Lin-Shiao, E., Lan, Y., Welzenbach, J., Alexander, K. A., Zhang, Z., Knapp, M., et al. (2019). p63 establishes epithelial enhancers at critical craniofacial development genes. *Science Advances, 5*(5), eaaw0946. doi: doi:10.1126/sciadv.aaw0946

Lin, B., Liu, H., Liu, H., Su, L., Sun, K., Feng, H., et al. (2025). A novel WNT10A variant impairs the homeostasis of alveolar bone mesenchymal stem cells. *Oral Diseases, 31*(1), 168-180. doi: https://doi.org/10.1111/odi.15032

Liu, Y., Sun, J., Zhang, C., Wu, Y., Ma, S., Li, X., et al. (2024). Compound heterozygous WNT10A missense variations exacerbated the tooth agenesis caused by hypohidrotic ectodermal dysplasia. *BMC Oral Health, 24*(1), 136. doi: 10.1186/s12903-024-03888-5

Lourenço Ribeiro, L., Teixeira das Neves, L., Costa, B., & Ribeiro Gomide, M.

(2003). Dental Anomalies of the Permanent Lateral Incisors and Prevalence of Hypodontia outside the Cleft Area in Complete Unilateral Cleft Lip and Palate. *The Cleft Palate Craniofacial Journal, 40*(2), 172-175. doi: 10.1597/1545-1569_2003_040_0172_daotpl_2.0.co_2

Mary Baaclini Galante, J., Costa, B., Felício de Carvalho Carrara, C., & Marcia, R. G. (2005). Prevalence of Enamel Hypoplasia in Deciduous Canines of Patients with Complete Cleft Lip and Palate. *The Cleft Palate Craniofacial Journal, 42*(6), 675-678. doi: 10.1597/04-068r.1

Matern, Olivier Sauleau, Erik-André Tschill, Pascal Perrin-Schmitt, Fabienne Grollemund, & Bruno. (2012). Left-Sided Predominance of Hypodontia Irrespective of Cleft Sidedness in a French Population. *The Cleft Palate Craniofacial Journal, 49*(3), 1-5. doi: 10.1597/11-025

Mikulewicz, M., Ogiński, T., Gedrange, T., Berniczei-Royko, A., & Prussak, E. (2014). Prevalence of second premolar hypodontia in the Polish cleft lip and palate population. *Med Sci Monit, 20*, 355-360. doi: 10.12659/msm.890386

Möller, L. H., Pradel, Winnie Gedrange, Tomasz Botzenhart, & Ulrike, U. (2021). Prevalence of hypodontia and supernumerary teeth in a German cleft lip with/without palate population. *BMC Oral Health, 21*(1), 60. doi: 10.1186/s12903-021-01420-7

Mostowska, A., Biedziak, B., Zadurska, M., Matuszewska-Trojan, S., & Jagodziński, P. P. (2015). WNT10A coding variants and maxillary lateral incisor agenesis with associated dental anomalies. *European journal of oral sciences, 123*(1), 1-8.

Okoye, L., Onah, I., Ekwueme, O., & Agu, K. (2020). Pattern of Malocclusion and Caries Experience in Unrepaired Cleft Lip and Palate Patients in Enugu. *Nigerian Journal of Clinical Practice, 23*(1), 59-64. doi: 10.4103/njcp.njcp_249_19

Paradowska-Stolarz, A., Mikulewicz, M., & Duś-Ilnicka, I. (2022). Current concepts and challenges in the treatment of cleft lip and palate patients—A comprehensive review. *Journal of Personalized Medicine, 12*(12), 2089.

Pradhan, L., Shakya, P., Thapa, S., Nakarmi, K. K., Maharjan, A., Sagtani, R. A., et al. (2020). Prevalence of dental anomalies in the patient with cleft lip and palate visiting a tertiary care hospital. *JNMA: Journal of the Nepal Medical Association, 58*(228), 591.

Qadeer, M., Jaafar, S., Khamis, M. F., Alam, M. K., Arshad, A. I., Saeed, M. Q., et al. (2023). A systematic scoping review of dental anomalies associated with cleft lip and palate patients. *Bangladesh Journal of Medical Science, 22*(1), 22-31.

Raju, R., Piña, J. O., Roth, D. M., Chattaraj, P., Kidwai, F. K., Faucz, F. R., et al. (2024). Profiles of Wnt pathway gene expression during tooth morphogenesis. *Frontiers in Physiology, 14*, 1316635.

Rashid, A., Rashid, A., Ali, A., Rubab, R., Ali, R., & Ullah, H. (2024). RISK FACTORS, PREVALENCE, AND SURGICAL OUTCOMES OF PALATAL FISTULAS: A GLOBAL AND PAKISTANI PERSPECTIVE. *The Research of Medical Science Review, 2*(3), 438-451. doi: https://medscireview.net/index.php/Journal/article/view/111

Roa Fuentes, L. A., Bloemen, M., & Carels, C. E. (2022). Retinoic acid effects on in vitro palatal fusion and WNT signaling. *130*(6), e12899. doi: 10.1111/eos.12899

Roht, L., Hyldebrandt, H. K., Stormorken, A. T., Nordgarden, H., Sijmons, R. H., Bos, D. K., et al. (2023). AXIN2-related oligodontia-colorectal cancer syndrome with cleft palate as a possible new feature. *11*(6), e2157. doi: 10.1002/mgg3.2157

Ruiz, L. A., Maya, R. R., D'alpino, P. H. P., Atta, M. T., & Da Rocha Svizero, N. (2013). Prevalence of Enamel Defects

in Permanent Teeth of Patients with Complete Cleft Lip and Palate. *The Cleft Palate Craniofacial Journal, 50*(4), 394-399. doi: 10.1597/11-200

Sajid, S., Laraib, F., Rashid, A., Arshad, A., Ahmad, N., & Rashid, A. (2025). Exploring Pakistani Doctors' Perspectives on Genetic Counseling: Challenges and Opportunities. *Journal of Medical & Health Sciences Review, 2*(1), 2012-2024. doi: https://doi.org/10.62019/nzbf4q93

Saroya, G., Hu, J., Hu, M., Panaretos, C., Mann, J., Kim, S., et al. (2023). Periderm Fate during Palatogenesis: TGF-β and Periderm Dedifferentiation. *102*(4), 459-466. doi: 10.1177/00220345221146454

Shen, C.-A., Guo, R., & Li, W. (2019). Enamel defects in permanent teeth of patients with cleft lip and palate: a cross-sectional study. *Journal of International Medical Research, 47*(5), 2084-2096. doi: 10.1177/0300060519832165

Wu, Y., Lai, L., Chen, J., Li, X., & Hou, J. (2024). Genotypic and phenotypic correlations in tooth agenesis: insights from WNT10A and EDA mutations in syndromic and non-syndromic forms. *Human Genetics, 143*(11), 1253-1264. doi: 10.1007/s00439-024-02705-x

Yao, S., Zhou, X., Gu, M., Zhang, C., Bartsch, O., Vona, B., et al. (2023). FGFR1 variants contributed to families with tooth agenesis. *Hum Genomics, 17*(1), 93. doi: 10.1186/s40246-023-00539-8

Yao, S., Zhou, X., Gu, M., Zhang, C., Bartsch, O., Vona, B., et al. (2023). FGFR1 variants contributed to families with tooth agenesis. *Human Genomics, 17*(1), 93.

Zheng, J., Liu, H., Zhan, Y., Liu, Y., Wong, S. W., Cai, T., et al. (2019). Tooth defects of EEC and AEC syndrome caused by heterozygous TP63 mutations in three Chinese families and genotype-phenotype correlation analyses of TP63-related disorders. *Molecular Genetics & Genomic Medicine, 7*(6), e704.

Zhong, X., Liu, K., Liu, Z., Li, C., & Chen, W. (2025). Association between PAX9 or MSX1 gene polymorphism and tooth agenesis risk: A meta-analysis. *Open Life Sciences, 20*(1), 20220987.