Craniofacial and dental anomalies in Van der Woude and Blepharocheilodontic syndromes

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To my lovely family,
my wife Noura and my sons,
and to my exceptional supervisor,
I couldn't have done these studies without you.
Thanks for your support along the way.

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1. LIST OF THE ORGINAL PUBLICATIONS

This doctoral thesis based on the following original studies:

I. **Awadh W.,** Kiukkonen A., Nieminen P., Arte, S., Hurmerinta K., Rice, D. P. 2017. Blepharocheilodontic (BCD) syndrome: New insights on craniofacial and dental features. *American Journal of Medical Genetics*. Part A, 173(4), 905–913. doi: 10.1002/ajmg.a.38088.

II. **Awadh W.**, Pegelow M., Heliövaara A., Rice, D. P. 2021. Taurodontism in the first permanent molars in Van der Woude syndrome compared to isolated cleft palate. *European Journal of Orthodontics.* 43(1), 29–35, doi.org/10.1093/ejo/cjaa014.

III. **Awadh W.,** Pegelow M., Heliövaara A., Rice, D. P. 2021. Dental age, agenesis, and morphological anomalies in individuals with Van der Woude syndrome and isolated cleft palate. *European Journal of Orthodontics.* 43(4), 387–393. doi: 10.1093/ejo/cjaa082.

2. ABBREVIATIONS

AEC	Ankyloblepharon-Ectodermal defects–cleft lip/palate
ANOVA	Analysis of variance (a statistical test model utilized to check the mean values for several groups)
AXIN2	Axis inhibition protein 2
BCDS	Blepharocheilodontic syndrome
BCLP	Bilateral cleft lip and palate
CA	Chronological age (the age from the date the person was born, measured in years, months, and days)
CDH1	Cadherin 1, E-cadherin ~~gene~~
CTNND1	Catenin delta-1
CL	Cleft lip only
CL/P	Cleft lip and/or palate (congenital orofacial malformation including cleft lip, cleft palate, or a combination of both)
CLP	Cleft lip and palate
CP	Cleft palate only
DA	Dental age (estimate of the developmental age according to tooth development - eruption and mineralization)
DPT	Dental panoramic tomography
EEC	Ectrodactyly-Ectodermal dysplasia–cleft lip/palate
FAP	Familial adenomatous polyposis
ICC	Intraclass correlation coefficient
KTS	Klippel–Trénaunay syndrome
LADD	Lacrimo-auriculo-dento-digital syndrome
MRI	Magnetic resonance imaging
MSX1	Msh Homeobox 1 gene
NSBCLP	Non-syndromic bilateral cleft lip and palate
NSCLP	Non-syndromic cleft lip and palate
NSCP	Non-syndromic cleft palate
NSUCLP	Non-syndromic unilateral cleft lip and palate

OFCs	Orofacial clefts
OFD2	Orofaciodigital syndrome type 2
OMIM	Online Mendelian Inheritance in Man
PAX9	Paired Box 9
PCR	Polymerase chain reaction
P-value	Probability value (the probability of finding the observed results when the null hypothesis of a study question is true and the probability of the occurrence of a given event)
SCLP	Syndromic cleft lip and palate
SD	Standard deviation
SMCP	Submucous cleft palate
SNPs	Single nucleotide polymorphisms
TMJ	Temporomandibular joint
UCLP	Unilateral cleft lip and palate
VWS	Van der Woude Syndrome
$\bar{x}$	Mean

3. ABSTRACT

Background and objectives: Cleft lip and/or palate (CL/P) is the most common orofacial birth defect, which may either be associated with other abnormalities or occur as an isolated condition. The most common syndromic form of orofacial clefting is the Van der Woude Syndrome (VWS), Blepharocheilodontic (BCD) syndrome is a rare condition characterised by eye, lip and dental developmental orofacial clefting abnormalities. **The aim of this thesis** was to analyse BCD syndrome phenotypes and the associated dental and craniofacial anomalies and compare it with non-syndromic bilateral cleft lip and palate (NSBCLP) and non-cleft) (**study I**), the prevalence, pattern and severity of taurodontism (**study II**), as well as the dental maturity (DM) and anomalies in individuals with VWS exhibiting cleft palate, were analyzed and compared with non-syndromic cleft palate (NSCP) and non-cleft controls (**study III**).

Materials and methods: In **study I**, cephalometric radiographs of BCD syndrome patients, 20 NSBCLP and 20 non-cleft, were analysed. The clinical records, photographs, dental study casts and dental radiographs were also assessed to determine the tooth agenesis extent and pattern, dental morphology and malocclusion. For **study II**, one hundred and seventy-eight dental panoramic tomographs (DPTs) consisting of 42 VWS patients, 42 NSCP patients and 94 normative non-cleft children were assessed, and their first permanent molars evaluated. Measurement 3 of the taurodontism index. Prevalence, pattern, and severity were compared between groups. For **study III**, 204 dental panoramic tomographs (DPTs) consisted of 51 VWS patients, 51 NSCP patients and 102 normative non-cleft children were collected. Dental stages were assessed by Demirjian's method, with the Finnish dental maturity reference values. Dental anomalies included tooth agenesis and taurodontism.

Results: The results of **study I** revealed that BCD syndrome patients had a maxillary–mandibular sagittal discrepancy (very severe skeletal III malocclusion) and decreased anterior lower face height compared to NSBCLP and non-cleft controls ($P = 0.001$, $P = 0.027$). All patients had oligodontia (mean number of missing permanent teeth 13.7). All patients exhibited missing upper central and lateral incisors, upper canine and premolar teeth. In **study II**, the prevalence of taurodontic molars in children with VWS was higher than in the other groups (59.5% compared to 45.2% in the NSCP group, and 26.6% in non-cleft controls). The prevalence and severity of taurodontism in VWS and NSCP were significantly higher than in non-cleft children in all first permanent molars, while the difference between VWS and NSCP groups was not significant. Children in VWS group were approximately twice more likely to have taurodontism compared to NSCP group.

Hypotaurodontism was the most frequent type in taurodontic molars. In **study III**, the differences between dental age (DA) and chronological age (CA) of VWS group and NSCP group were significantly lower than the difference in the non-cleft group (P= 0.002). There was no significant difference between VWS and NSCP groups (P= 0.817). Hypodontia prevalence in the non-cleft group (5.88 %) was significantly lower than both VWS group (37.25 %) (P= 0.0001) and NSCP group (19.6 %) (P= 0.035).

Conclusions: The craniofacial skeletal defects in the BCD syndrome group were more severe than in patients with NSBCLP. The pattern of tooth agenesis is unusual as it included teeth that are normally highly resistant to agenesis. In VWS and NSCP we observed a high prevalence of taurodontism. Most taurodontic molars are hypotaurodontic. Dental maturity was delayed in both the VWS and NSCP groups compared to the non-cleft control. Hypodontia prevalence was significantly high in both VWS and NSCP groups compared to the non-cleft control. This thesis will provide an insight into these diseases and help clinicians develop a proper guideline for treatment protocol.

4. INTRODUCTION

The most common orofacial defect is a cleft lip and/or palate (CL/P) (Kirschner and LaRossa, 2000). Cleft lip and/or palate (CL/P) prevalence is 1/700. The rates are different between countries; in European countries, it affects 1/1000, while the rate of CL/P is less in African countries and higher in Asian countries (Christensen and Mitchell, 1996; Mossey et al., 2009; Dixon et al., 2011). The prevalence of CL/P is greater in males than in females (Hagberg et al., 1998). Types of clefts include cleft palate (CP), cleft lip (CL), unilateral cleft lip and palate (UCLP) and bilateral cleft lip and palate (BCLP). The aetiology of CL/P is still being investigated; however, both genetic and environmental factors play essential roles in causation, with many genes identified as causative (Dixon et al., 2011).

Orofacial clefts may be associated with other abnormalities in addition to the cleft (syndromic clefting) or, alternatively, may be an isolated condition not associated with other anomalies (non-syndromic clefting). The prevalence of syndromic clefts are around 20–30% of CL/P patients (Cohen, 1978). About 50% of CP cases are associated with another malformation syndromes, compared with less than 15% of CL/P cases (Shprintzen et al., 1985). In the syndromic cleft, associated abnormalities in other parts of the body include skeletal deformations, congenital heart defects, hydrocephaly, urinary tract defects and polydactyly (Burg et al., 2016). There are many examples of syndromic orofacial clefts such as Van der Woude Syndrome (VWS; Rintala and Ranta, 1981), Down syndrome, Stickler's syndrome, Treacher Collins syndrome (Willems et al., 2001), and Blepharocheilodontic (BCD) syndrome (Allanson and McGillivray, 1985a).

Genetic studies and the sequencing of genes have improved, which can help to diagnose syndrome patients when there is a genetic cause (Reiter et al., 2012; Watkins et al., 2014). However, it has been shown that some genetic mutations related to specific syndromes may also occur in non-syndromic individuals (Stanier and Moore, 2004).

VWS, an autosomal dominant disorder, is the most common orofacial clefting syndrome (Burdick et al., 1985). VWS is characterised by pits on the lower lip, CL/P and hypodontia (Ranta and Rintala, 1983). BCD syndrome is an autosomal dominant condition characterised by eye, lip and dental developmental abnormalities (Gorlin et al., 1996; Korula et al., 1995; Allanson and McGillivray, 1985).

5. LITERATURE REVIEW

5.1. Normal craniofacial development

5.1.1 Facial development

Understanding craniofacial development is essential for any dental practitioner who frequently treats patients with common anomalies such as cleft patients and the associated dental anomalies. Development of the human face starts with the migration of cranial neural crest cells from the dorsal region of the anterior neural tube into the facial region (Le Douarin et al., 2007), followed by a complex series of embryonic events. Features of the human face can be recognized beginning around week 4 of gestation (Marcucio et al., 2015). Fusion of the facial processes occurs at different times; 6 weeks for the maxilla, 8 weeks for the upper lip and 12 weeks for the palate (Danescu et al., 2015; O'Rahilly and Müller, 2007; O'Rahilly, 1972). This fusion depends on a series of events involving cell migration, growth, adhesion, differentiation and apoptosis. Studies at the molecular level have shown a series of complicated interactions of many factors, including growth factors, in the structural pattern of the facial primordia (Parsons et al., 2015; Marcucio et al., 2015; Mossey et al., 2009). Additional details of the facial developmental component processes are described in **Table 1**.

The prechordal plate, which originates from axial mesoderm migrating through the primitive node, acts as the organiser of facial development. The ectodermal placodes invaginate to form nasal pits and the tissue surrounding them enlarges into a horseshoe-shaped protrusion, which on the lateral side is called the lateral nasal process and on the medial side is called the medial nasal process (Asaumi et al., 2019; Som and Naidich, 2013). Two main processes are involved in facial development (Andre et al., 2015). The process where the groove between the two facial processes is abolished is called merging. Examples include merging of the two mandibular processes (the former mandibular arch) in the midline, merging of the two processes of the medial nasal on the midline, integrate of lateral nasal and maxillary processes and the integrate of maxillary and mandibular processes. Fusion is the process defined as two facial processes that were initially separated by a space unite to become one pattern. The formation of the secondary palate is an example of fusion, where both processes grow toward the other one, touch each other and then fuse in the midline. In the fusion, unlike merging, the epithelium is broken down where the two processes meet. Lip pits form from the vestigial remnants of the lateral sulci of the mandible, and these remnants can form a labial gland duct and develop congenital lip fistula (Chigurupati et al., 2010; Meikle, 2007; Rizos and Spyropoulos, 2004).

The tissue between the nasal and oral cavities is called the palate. The primary palate is formed during week 6 in the uterine life by the two maxillary and two medial nasal processes, and thus separates the developing oral and nasal cavities from each other. Later, between weeks 6 and 8, two palatal extensions from the maxillary process start to grow and form the secondary palate. Together, the primary and secondary palates form the definitive palate. After birth, the human face tends to follow a general somatic growth with periods of steady increments in size intermixed with periods of rapid growth, with the peak growth occurring at puberty (Richmond et al., 2018; Kau and Richmond, 2008). Time duration, and pattern of facial growth tend to be different between males and females and across populations, leading to either the overall well-known facial process or variations (Richmond et al., 2018; Hopman et al., 2014; Kau et al., 2010). Failure at any of these connection points will cause cleft lip and/or palate, as shown in Figure 1.

Table 1: Facial process and associated facial features.

Facial process	**Facial features**
Frontonasal process	Forehead, upper eyelids, conjunctiva
Medial nasal process	Premaxilla, upper incisor teeth, upper lip/philtrum and Nose.
Lateral nasal process	Alae and base of the nose
Maxillary process	Premolar and molar teeth, canine, secondary palate, lower eyelids, cheeks, lateral parts of the upper lip, maxilla.
Mandibular process	Whole lower lip, lower jaw (mandible, including teeth)

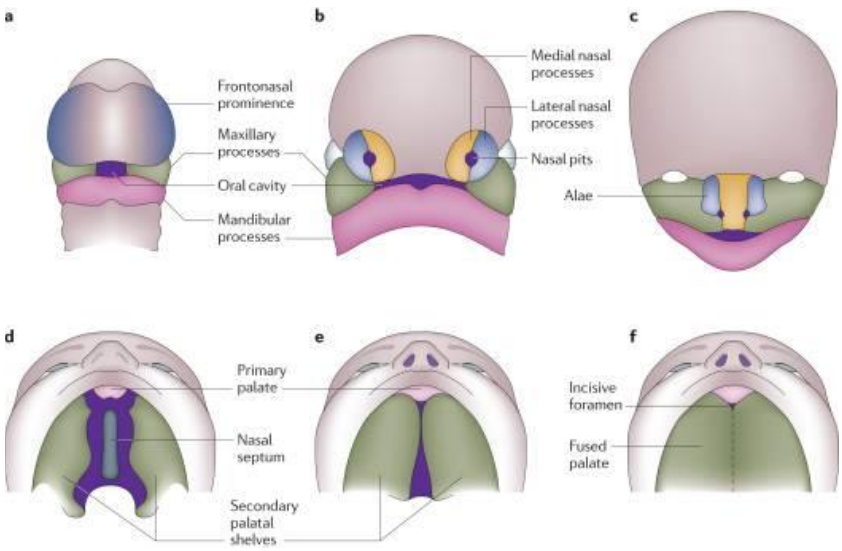

Figure 1: Normal development of the lip and palate in humans.

a. Frontonasal prominence develops as the maxillary and mandibular processes surround the oral cavity (week 4 of human embryonic development).
b. The medial and lateral nasal processes are developing and the nasal pits have formed (week 5 of human embryonic development).
c. Formation of the upper lip and primary palate based on developing and merging of the medial nasal processes with the maxillary processes. Formation of the nasal alae based on the lateral nasal processes. Formation of the lower jaw based on the mandibular processes fusing (all at the end of week 6).
d. The maxillary processes grow down along the side of the tongue in a vertical direction. The secondary palate develops bilaterally (week 6 of human embryonic development).
e. Elevation of the palatal shelves horizontally above the tongue; they then contact each other and will subsequently begin fusing.
f. Fusion of the palatal shelves and separation of the nasal and oral cavities.
 (Dixon et al., 2011).

5.1.2 Tooth development

Teeth develop from an interaction between the oral ectoderm and the neural crest-derived from the mesenchyme. The first sign of tooth development is a thickening of the oral epithelium (Koch and Thesleff, 2001). This thickening then buds into the mesenchyme, which responds by forming a condensation of cells adjacent to the epithelial bud. After rapid growth and epithelium folding, the cap stage is reached. The mesenchyme forms the dental papilla, the dental follicle, the odontoblasts and ultimately the dentine and dental pulp of the tooth. Cementoblasts, which deposit dental

cementum, and the periodontal membrane arise from the follicle that connects the tooth roots to the alveolar bone in periodontium tissue. The enamel knot, which is a functional part of the dental epithelium, is responsible for cusp formation in the teeth. The cusp morphology is established and the tooth crown is determined during the bell stage. The epithelial-derived ameloblasts and the mesenchymal-derived odontoblasts differentiate, then enamel formation begins. Mineralisation begins at the tips of the cusps. Development of the root follows crown development. In advanced levels, the regulation of tooth development occurs through the interaction between epithelium and underlying mesenchymal tissues (Weiss et al., 1998; Thesleff and Sharpe, 1997) (Figure 2).

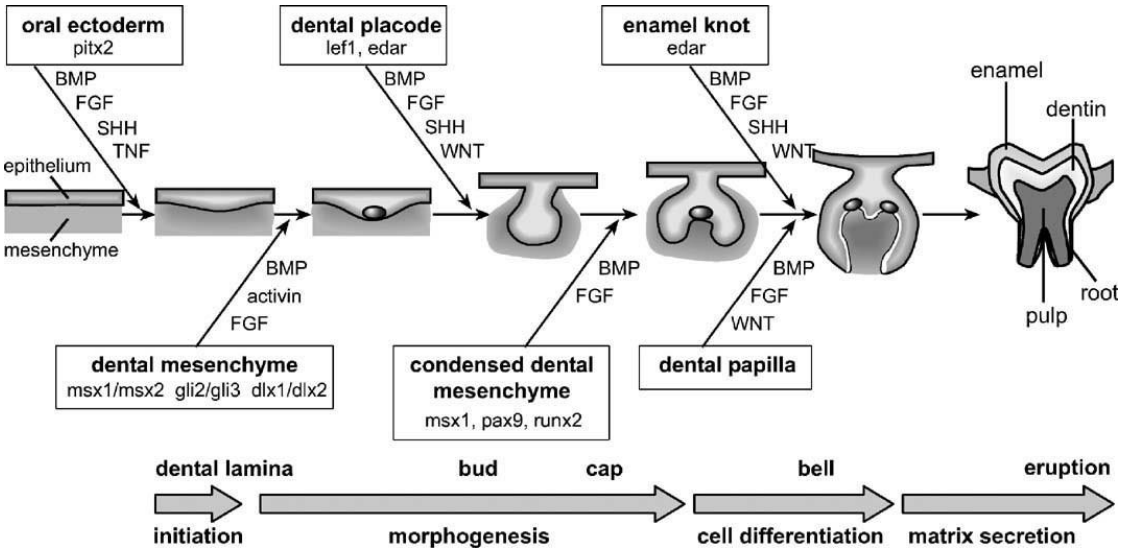

Figure 2: Schematic showing the development of a tooth and most of the essential molecular signals regulating interactions between the oral epithelium and mesenchyme as well as the key transcription factors. Figure is reproduced with permission from Wiley-Liss, Inc. (Thesleff, 2006).

5.1.2.1 Tooth group families

Tooth groups are divided into families according to the specific location of each group in the jaws. The differences between teeth families, according to the typical shape, are incisors, canines, premolars and molars. Each tooth group develops from one epithelial thickening, the dental lamina, and development starts from the anterior to the posterior tooth (Thesleff and Sharpe, 1997).

Control of tooth patterning such as the morphology, location and number is poorly understood. In comparison, knowledge of the processes in the development of individual teeth has expanded. It has been suggested that both jaws' maxilla and mandible develop differently and are patterned by a process that occurs before the neural crest migration (Weiss et al., 1998).

Two different theories for regulation of the shape difference between teeth and patterning have been suggested. The clone theory suggests that stem cells initially differ from each other in each tooth family, the identity of the position of the neural crest cells have before their final migration into the region of tooth development (Osborne, 1978). The field theory proposes that chemical morphogen concentrations regulate different types of teeth (Butler, 1995).

The genes expressed in the neural crest-derived jaw mesenchyme have been suggested to regulate tooth shape and position (Sharpe, 1995). For instance, several genes are expressed in specific patterns in the jaws before tooth development (Tissier-Seta et al., 1995).

5.1.2.2 Timing of dental development

Tooth development begins in weeks 5–6 of human embryonic development. During weeks 14–18, calcification of the teeth begins; at birth, the crowns of the primary teeth are approximately halfway mineralised. Between 1.5–3 years after birth, the root formation of the primary dentation is completed (Koch and Thesleff, 2001). The first teeth to develop are the central upper and lower incisors, followed by the first molars, lateral incisors, canines and second molars. The first tooth erupting in the oral cavity is the lower incisor, with a mean eruption time around 7 months of age. Eruption of the other primary teeth occurs during the following 22 months (Pirinen and Thesleff, 1995).

The development of permanent teeth also begins with the primary teeth. In humans, 32 permanent tooth germs normally form. At birth, the cusps of the first permanent molars have started their mineralisation. The lower incisors, upper central incisors and upper and lower canines start to calcify at 2–3 months of age. The first and second premolars and the second molars start to calcify between 2–3 years after birth. Between 5–7 years of age, the crowns of the permanent teeth, except the third molars, are completed. Then root development takes around 6–7 years (Koch and Thesleff, 2001). The third molars have a very large variation in development patterns and time. They start to mineralise between 8–11 years after birth. However, sometimes third molar development appears very late, at 14–18 years of age.

The lower incisors or the first molars are the first permanent teeth to erupt in the oral cavity, with the mean age of their eruptions at 6–7 years. The second premolars erupt at the age of 11–12 years, and the second molars at 11.5–12.5 years. The third molar erupts at around age 23 years old in females and age 21years old in males as the last permanent teeth to erupt into the oral cavity (Pirinen and Thesleff, 1995).

5.2 Orofacial clefting

The development of orofacial structures from fertilised egg to adult is a tightly regulated process requiring coordination of patterning, organogenesis, morphogenesis and differentiation. Deviations from normal development lead to anomalies of structure and function that, when present at birth, are called developmental anomalies (Gilbert, 2000; Kotilainen, 1996). The prevalence of orofacial clefts varies considerably, from 1/500 to 1/2500 births. In addition to genetics, environmental factors are believed to have an important role in the prevalence, such as toxins, geographic origin, racial and ethnic background, and socioeconomic status (Tolarová and Cervenka, 1998; Murray et al., 1997). It has been observed that Asians have the highest risk (14/10000 births) followed by whites (10/10000 births) and African-Americans (4/10000 births) (Das et al., 1995). However, different ratios have been reported from various African populations. Reported prevalence includes 0.3/1000 in Nigeria (Iregbulem, 1982), 0.7/1000 live births in Malawi (Msamati et al., 2000), 0.9/1000 live births in Sudan (Suleiman et al., 2005), 1.65/1000 in Kenya (Khan, 1965) and, in Ghana, the reported prevalence is 5/1000 live births (Agbenorku et al., 2011).

The aetiology of orofacial clefts (OFC) is complex as it includes a combination of effects of multiple genetic and environmental factors (Tettamanti et al., 2017; Schutte and Murray, 1999). Normal development may be affected by genetic factors, which have been suggested to be a cause of orofacial malformations (Gilbert, 2000; Kotilainen, 1996). The malformation may affect only one organ system. However, genetic factors often have pleiotropic effect on many organs (multi-organ malformation syndrome). These may be independent or related to each other, as reflected in the roles of these genetic factors during the development of multiple organs (Gilbert, 2000). The term ‘trait’ has been used to describe inherited disease phenotypes that may either be regarded as the normal variation or in some cases as anomalies (Guttman et al., 2002). Syndromes and some other genetic diseases can also be caused by sequence defects in one gene that may modify others. Chromosomal abnormalities in syndromes may result from events such as translocations or deletions, or from abnormal chromosome numbers (Gilbert, 2000).

External factors may also play a role in causing developmental anomalies; these factors include medications taken during pregnancy, maternal alcohol consumption and smoking, dietary and vitamin deficiencies, diabetes, environmental toxins, altitude, birth order, socioeconomic status and parental age (Yang et al., 2008; Little et al., 2004; Vieira et al., 2002; Spilson et al., 2001; Castilla et al., 1999), as well as infections, teratogenic agents, radiation, hyperthermia and mechanical forces (Kotilainen, 1996). The effects' severity correlates with the time of exposure for these factors (Sadler, 2011). Thalidomide causes ear defects and truncations of hands and feet (Sadler, 2011; Gilbert, 2000). Tooth development occurs from week 6 of embryonic development to adulthood, and effects will depend on the time of exposure and nature of the deleterious agent (Alaluusua et al., 1999).

5.2.1 Types of orofacial clefts

The cleft may be in the palate (CP) only, the lips only (CL), the lip and alveolus, or the lip and the palate combined unilaterally (UCLP) or bilaterally (BCLP), as shown in Table 2 and Figure 3. More rarely, clefts manifest in the mandible, or as an oblique facial cleft.

Table 2: Epidemiology of oral clefts
(Chigurupati et al., 2010).

Distribution of oral clefts	Cleft lip and palate	Cleft palate only
Cleft lip and palate 46%	Average birth prevalence 1/700	Average birth prevalence 1/2000
Cleft palate only 33%	More common in males	More common in females
Cleft lip only 21%	Unilateral > bilateral	Association with other anomalies: 50–60%
	Left side > right side	
	Association with other anomalies: 10%	

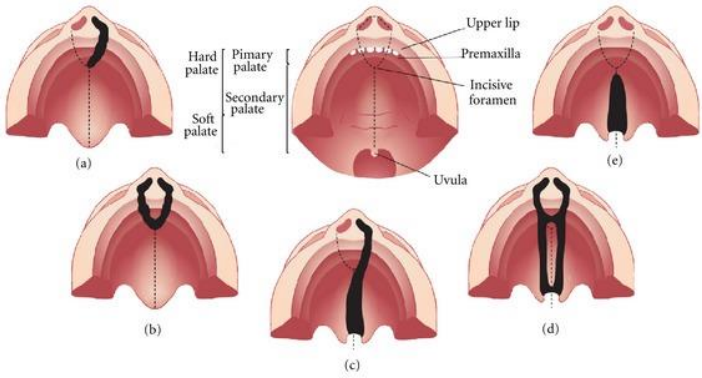

Figure 3: The most common types of cleft lip and palate.
(a) Unilateral cleft lip with alveolar
(b) Bilateral cleft lip with alveolar
(c) Unilateral cleft lip and palate
(d) Bilateral cleft lip and palate;
(e) Cleft palate only.
Figure is reproduced with permission from Luciano Abreu Brito et al. (Brito LA et al.,2012)

Orofacial clefts can be divided into two groups: (1) Syndromic cleft lip and palate (SCLP), associated with other abnormalities occurring in addition to the cleft, with approximately 20–30% of CL/P patients having an associated syndrome (Cohen, 1978), and (2) Non-syndromic cleft lip and palate (NSCLP), an isolated condition not associated with any other anomalies. The proportion of oral clefts with additional anomalies is more frequent for SCLP than for NSCLP (Mossey et al., 2009). About 50% of CP are associated with a malformation syndrome, compared with less than 15% of cleft lip and palate (CLP) (Shprintzen et al., 1985). The most common anomalies with SCLP are congenital heart defects (31.1%), deformations (22.4%), hydrocephaly (11.2%), urinary tract defects (9.7%) and polydactyly (9.2%).

5.2.2 Aetiology of isolated and syndromic orofacial clefts

Both environmental factors and genetic play an essential role in the aetiology of cleft lip and/or palate. Several causative genes have been identified (Dixon et al., 2011). Environmental factors that contribute to the aetiology of facial clefting disorders include cigarette smoking (Little et al., 2004), folic acid deficiency during the periconceptional period (Wilcox et al., 2007), maternal

exposure to alcohol and teratogenic medications such as retinoids and corticosteroids (Eppley et al., 2005). Obesity and maternal diabetes have also been associated to an increased risk of orofacial clefts. Less likely associations have been found between clefts and maternal viral infections such as rubella and varicella (Cohen, 2000). The presence of a cleft in a family member may increase the likelihood of a cleft in other family members. A number of factors play important roles in the recurrence of a cleft, and these factors are often limited to a particular family. These factors include a close relationship between the family members and the cleft patient, the number of family members affected with clefts, race and sex of the cleft-affected member and the type of cleft itself. Once a family has a child with cleft, the probability of the succeeding child having a cleft is about 2–5%. However, this risk increases significantly, up to 10–12%, when there are more close family members with clefts (Lees, 2008; Sivertsen et al., 2008).

5.2.3 Syndromic clefting

A syndromic patient is an individual who has more than one malformation involving more than one developmental region in their body. In other words, the individual has birth defects in more than one organ system (Watkins et al., 2014). Approximately 20–30% of CL/P patients have associated syndromes (Cohen, 1978). The most common of these are VWS, Down syndrome, Stickler's syndrome and Treacher Collins syndrome (Willems et al., 2001). Nearly half of syndromic cleft palate presentations are associated with the triad of micrognathia, glossoptosis and airway obstruction, the Pierre Robin sequence (Watkins et al., 2014).

Cleft lip and /or cleft palate may occur in association with other major birth defects (Watkins et al., 2014). A Cleft palate is more commonly syndromic than a cleft lip with or without cleft palate; about 50% of CP is associated with another malformation, compared with less than 15% of CLP (Shprintzen et al., 1985). As stated previously, the most common anomalies with SCLP are congenital heart defects (31.1%), deformations (22.4%), hydrocephaly (11.2%), urinary tract defects (9.7%) and polydactyly (9.2%) (Burg et al., 2016).

Many syndromic clefts have a known genetic cause; Dixon et al. (2011) showed the various syndrome-related cleft types and which genetic mutations cause those defects (Table 3). More than 400 syndromes have been reported in association with cleft lip, cleft palate or both. Oral clefs may occur in combination with a wide range of chromosomal abnormalities and syndromes, including Meckel syndrome, trisomy 13, Fryns syndrome, Stickler syndrome, Treacher Collins syndrome,

VWS, velocardiofacial syndrome, Pierre Robin sequence, Kabuki syndrome and median facial dysplasia (Patil et al., 2014; Kohli and Kohli, 2012; Maarse et al., 2012; Sárközi et al., 2005).

Table 3: Identified mutated genes causing common clefting syndromes (Ghoumid et al., 2017; Peyrard-Janvid et al., 2014; Dixon et al., 2011).

Cleft Type	**Syndrome**	**Gene**
Cleft lip and cleft palate	Autosomal dominant developmental malformations, deafness and dystonia	*ACTB*
	Familial gastric cancer and CLP Blepharocheilodontic syndrome	*CDH1*
	Craniofrontonasal	*EFNB1*
	Roberts	*ESCO2*
	Oro-facial-digital	*GLI3*
	Hydrolethalus	*HYLS1*
	Van der Woude/popliteal pterygium	*IRF6*
	X-linked mental retardation and CL/P	*PHF8*
	Gorlin	*PTCH1*
	CLP – ectodermal dysplasia	*PVRL1*
	Holoprosencephaly	*SHH*
Cleft palate only	Oculofaciocardiodental	*BCOR*
	Lethal and Escobar multiple pterygium	*CHRNG*
	Oculofaciocardiodental	*BCOR*
	CHARGE	*CHD7*
	Miller	*DHODH*
	Craniofrontonasal	*EFNB1*
	Kallmann	*FGFR1*
	Crouzon	*FGFR2*
	Apert	*FGFR2*
	Otopalatodigital types 1 and 2	*FLNA*
	Larsen syndrome, atelosteogenesis	*FLNB*
	Hereditary lymphedema-distichiasis	*FOXC2*
	Bamforth–Lazarus	*FOXE1*
	Oro-facial-digital	*GLI3*
	Van der Woude/popliteal pterygium	*IRF6* *GRHL3*
	Andersen	*KCNJ2*

	Kabuki	*MLL2*
	Cornelia de Lange	*NIPBL*
	Pierre Robin	*SOX9*
	DiGeorge	*TBX1*
	X-linked cleft palate and ankyloglossia	*TBX22*
	Treacher Collins	*TCOF1*
	Saethre-Chotzen	*TWIST1*
	Miller	*DHODH*
Midline cleft lip	Opitz G/BBB	*MID1*

5.2.4 Cleft patient treatment

The goal of treating the cleft patient is to help the child breathe well, eat well, speak well, grow up in a normal situation, and have good self-esteem. The first surgical correction of CL will be around 3–6 months, to reduce the social effect on the child. In childhood and adolescence, orthodontic treatment and speech improvement therapy are carried out. CP is treated surgically at the age of approximately 1 year. Once the permanent teeth are developing and the child needs bone for tooth eruption, a bone graft is performed at the cleft area of the alveolus. Sometimes lengthening of the palate may be accomplished by surgical correction (velopharyngeal flap), with speech training by a speech therapist at 5 years of age when the palate is too short for good speech. Orthodontic is often needed before bone grafting and when all permanent teeth have erupted. In some patients with the retrognathic maxilla, especially in severe cases or those related to syndromes, orthognathic surgery can correct the occlusion when growth has stopped with a forward movement of the maxilla (Le Fort 1 surgery) (Pegelow, 2012).

5.2.5 Van der Woude Syndrome

VWS was named after the physician Anne Van der Woude, who first (1954) described the genetic disorder as an autosomal dominant condition (OMIM#119500). It is the most common form of syndromic orofacial clefting, accounting for 2% of all cleft lip and palate cases (Burdick et al., 1985; Rintala and Ranta, 1981). Mutations of the genes *IRF6* and *GRHL3* are the primary genetic cause of VWS (Peyrard-Janvid et al., 2014; Kondo et al., 2002). An extrachromosomal locus at *1p34* has also been linked to the development of the syndrome (Peyrard-Janvid et al., 2014; Lacombe et al., 1995; Bocian and Walker, 1987). VWS is believed to affect 1 in 35,000 to 1 in 100,000 individuals (Gorlin et al., 2001), with no significant differences between the sexes;

although some authors believed that the syndrome is more prevalent in females, others have reported more cases in males (Deshmukh et al., 2014; Fullen, 2010; Nopoulos et al., 2007; Tokat et al., 2005). Pits in the lower lip with CL/P are the most common characteristics of VWS. Among individuals with VWS, lower lip pits are found in 80%, hypodontia is found in 25% and CL/P is found in 50% (Ranta and Rintala, 1983) (Figure 4). Cleft lip only and cleft palate only have also been reported among VWS individuals (Altuntaş et al., 2020; Deshmukh et al., 2014; Malik et al., 2010). There are many other associated features of VWS syndrome that may or may not be present such as ankyloglossia, high arched palate, hypoplasia, limb anomalies and congenital heart defects (Deshmukh et al., 2014; Advani et al., 2012; Nopoulos et al., 2007; Rizos and Spyropoulos, 2004; Arangannal et al., 2002). Another unusual feature is the presence of pits in the upper lip (Nakano et al., 2010). The fusion of primary mandibular anterior teeth and mandibular supernumerary incisors has also been reported, as has dental transposition (Goswami, 2017; Ambaldhage and Puttabuddi, 2014; Sarode et al., 2011). The lower lip pits were originally described by Demarquay (1845), while Van der Woude (1954) described the phenotypes of the malformations in detail. It was thought that the pits on the lower lips occured because of mechanical trauma from the upper central incisors. This hypothesis lasted for decades until modern embryologic, histopathological and genetic analysis gave new insights into the formation of the pits. At day 36 of embryonic development the lower pits are formed. However, the lip is formed from day 40 and the cleft formed from day 50. These periods are not fixed and may vary from one individual to another, and the timing of lip and palate development may overlap (Rizos and Spyropoulos, 2004; Kitamura, 1989).

The maxillary permanent second premolars, mandibular permanent second premolars and maxillary permanent lateral incisors are the most commonly missing teeth among VWS patients (Rizos and Spyropoulos, 2004). Other anomalies are associated with VWS and related conditions, such as popliteal pterygium syndrome, which has the same causal gene. Other anomalies include syndactyly, syngnathia, ankyloblepharon, genital deformities, symblepharon and skin webbing (Burdick et al., 1985). The pits located on the lower lip vary from a small depression on the vermilion border to deep fistulas with communication to the underlying minor salivary glands. The lower pits are usually symmetric bilateral paramedian sinuses. Sometimes they present asymmetrically in the midline or unilaterally (Rizos and Spyropoulos, 2004; Ranta and Rintala, 1983; Van der Woude, 1954).

Multiple forms of VWS have been reported. All VWS signs can exist either alone or in combination, or at a level that cannot be detected clinically. When only one sign is present, it is

most often the lower pits without a cleft. Different forms of vertical and horizontal cleft palate have also been reported (Deshmukh et al., 2014; Rizos and Spyropoulos, 2004). After treating the cleft palate for functional reasons, treatment of the pits on the lower lip is considered for aesthetic reasons, although it has been reported that many patients never demand this. However, if the excision of these pits is to be performed, there must be no residual tissue left as it might cause a mucoid cyst (Rizos and Spyropoulos, 2004; Souissi et al., 2004). Soricelli et al. (1966) reported a family case with six members having congenital fistulas of the lower lip and different forms of cleft palate/high arched palate. Although the descriptions of the fistulas among all cases in this report were consistent with VWS, the authors never linked these features with the syndrome.

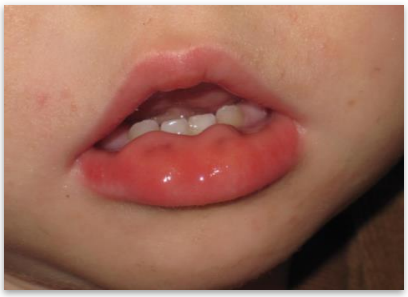

Figure 4: Van der Woude Syndrome phenotypes, pits on the lower lip. Figure is reproduced with permission (Pegelow, 2012).

5.2.6 Blepharocheilodontic Syndrome

Blepharocheilodontic syndrome (OMIM # 119580) is characterised by eye, lip and dental developmental abnormalities (Gorlin et al., 1996; Korula et al., 1995; Allanson and McGillivray, 1985). BCD syndrome is an autosomal dominant condition with eye malformations including a distichiasis on the upper eyelids which is a double row of eyelashes, ectropion of the lower eyelids which means the eyelids turn outwards to reveal the mucosal lining, and euryblepharon which is a widening of the palpebral fissures, lagophthalmia which is mean that the eyes are unable to close completely (Guion-Almeida et al., 1998) (Figure 5). Ocular hypertelorism has also been shown to be associated with BCD (Yen et al., 2001; Allanson and McGillivray, 1985). BCD syndrome patients mostly exhibit bilateral cleft lip and palate (CLP) (Gorlin et al., 1996; Korula et al., 1995). The skeletal class III with a hypoplastic maxilla has been described as the craniofacial skeletal pattern, but this is common to most patients with bilateral CLP (Guion-Almeida et al., 1998). Severe tooth agenesis is another common feature, including 6 or more missing permanent teeth

(oligodontia). The incisors that form may be conical in shape (Gorlin et al., 1996; Falace and Hall, 1989). Other clinical features include abnormalities such as hypothyroidism or thyroid agenesis (Ababneh et al., 2014; Martinhago and Ramos, 2004; Gil da Silva Lopes et al., 2003), sparse hair and nail defects (Gorlin et al., 1996; Korula et al., 1995), imperforate anus (Weaver et al., 2010) and lumbosacral meningomyelocele (Ababneh et al., 2014). Other unusual and very rare features associated with BCD syndrome are incompletely formed arms or legs (limb reduction defects) and spinal cord abnormality (spina bifida). Almost all of the available BCD syndrome studies are case series, with no cross-sectional or longitudinal follow-up studies yet available. Embryogenic development, therefore, has not been clearly described in the literature. However, post-natal growth and development have been reported to be normal except in two cases with delayed development (Ababneh et al., 2014; Adeboye et al., 2009). BCD syndrome has been reported among both sexes and has been detected among different ages ranging from 6 weeks up to 45 years (Ababneh et al., 2014; Retna and Sockalingam, 2013; Adeboye et al., 2009; Iida et al., 2006; Guion-Almeida et al., 1998).

Genetic screening has been used to determine if an autosomally dominant inherited mutation causes BCD syndrome by examining several candidate genes. Candidates were selected based on the phenotypal similarity to orofacial clefting, associated with thyroid agenesis (*FOXE1*), ectodermal dysplasia syndromes (*IRF6, P63*) and orofacial clefting, eye and dental anomalies (*OSR2, TBX10*). Amongst these conditions no mutations have been detected (Weaver et al., 2010; Freitas et al., 2007). However, mutations in E-cadherin gene (*CDH1*) and Catenin delta-1 (*CTNND1*) have been associated with the BCD syndrome phenotype (Ghoumid et al., 2017). Surprisingly, Ghoumid et al. (2020) published an editorial confirming that BCD, particularly BCDS1, families are at a high risk of diffuse gastric or lobular breast cancers, particularly when there is an involvement of *CDH1*.

Selvanathan et al. (2020) analysed the phenotype and molecular data of 280 variants of *CDH1* and their possible correlation with hereditary diffuse gastric cancer (HDGC), lobular breast cancer and both syndromic and non-syndromic cleft lip/palate (CL/P). The authors found that about 245 (88%) mutations caused HDGC and 27 (10%) mutations caused CL/P, while 8 (3%) caused both phenotypes within the same pedigree. LeBlanc et al. (2020) reported a case in which members of a family diagnosed with BCD syndrome, linked to the *CDH1* pathogenic variant, had developed DGC or breast cancer with a lobular component. The authors emphasised the need for appropriate counseling regarding cancer risk in families with BCD. In their analytical study of 13 patients from 9 families, Alharatani et al. (2020) identified novel variants in the *CTNND1* gene associated with human birth defects, including BCD syndrome. In addition to the well-known clinical features,

individuals with BCD syndrome also displayed heart and limb anomalies, neurodevelopmental anomalies, and behavioral disorders. Furthermore, there were multiple participants with auricular anomalies, particularly low-set ears and over-folded helices.

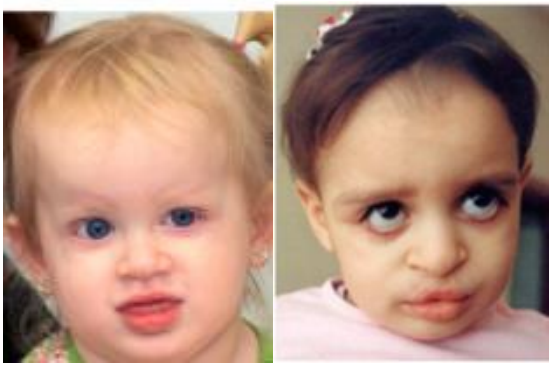

Figure 5: Facial features of Blepharocheilodontic syndrome, showing the phenotype: distichiasis of the upper and lower eyelashes, ectropion of the lower eyelids. Figure is reproduced with permission from European Society of Human Genetics. (Kievit A et al., 2018)

5.3 Tooth development malformations

Developmental anomalies of the teeth include abnormalities in tooth number (supernumerary or agenesis teeth), abnormalities in form and size, delay or failure of tooth eruption and malpositions. There are also external factors affecting tooth formation, such as vitamin D deficiency; many other environmental factors may affect the maturation of teeth (Alaluusua et al., 1999). Moreover, both qualitative and quantitative and any other variations in developmental anomalies have been suggested to be caused by inheritance (Townsend et al., 1998). Several genetic factors are already known to affect tooth development. Defects in regulatory genes lead to a failure of enamel formation, which may result in amelogenesis imperfecta (Hu and Simmer, 2007). The genes defects play a role in the structure of the dentin matrix, collagen I and dentin sialophosphoprote lead to dentinogenesis imperfecta and dentin dysplasia (Kim and Simmer, 2007; MacDougall et al., 2006).

Many studies have reported the variation of tooth sizes (Steigman et al., 1982; Lysell and Myrberg, 1982; Garn and Lewis, 1970) as well as the estimation methods of the developmental timing and eruption or maturation (Demirjian et al., 1973; Haavikko, 1970). Differences between populations and genders in tooth maturation, tooth size and eruption times have also been considered (Bailit, 1975).

Qualitative malformation in tooth number, either as the development of extra teeth or agenesis of one or more teeth, has also been investigated in the literature. Many authors have analysed the morphology of the molar crowns and reduction of cusp number (Lavelle et al., 1970; Davies, 1968; Dahlberg, 1945). Other abnormalities in morphological features include extra cusps in molars, so-called Carabelli's cusp in the medial lingual aspect of the maxillary molars and variations of incisors including peg shape of teeth, talon cusps and densin dente/dens invaginatum in the lingual side of the upper lateral incisors (Tsai and King, 1998; Ooshima et al., 1996). Some of the dental anomalies and variation observed in the size, number and morphology of the teeth will be discussed below in more detail.

5.3.1 Taurodontism

5.3.1.1 Taurodontism in the general population

The first use of the term taurodontism was by Keith (1913); he described it as a short root and large pulp chamber, relative to tooth mass, with the pulpal floor displaced apically. The term taurodont is a Latin/Greek word, consisting of two sections: tauro (Latin), which means 'bull', and dont (Greek), which means 'tooth' (Keith, 1913). In severe cases, molar teeth can have only one root with a large pulp chamber, instead of having many roots. Taurodontism (OMIM #272700), according to the index of severity, can be divided into subgroups by crown and root ratio (Shaw, 1928) (Figure 6). Subgroups include hypotaurodont, mesotaurodont and hypertaurodont. Conical, pyramidal and fused teeth are also classified as taurodontic (Sarr et al., 2000).

The prevalence of taurodontism varies greatly across populations; 0.3% in the Indian population (Gupta and Saxena, 2013), 0.91% among the Yemeni population (Aldhorae et al., 2019) and 2.65% among the Croatian population (Brkić et al., 1992). Even higher rates have been reported in the literature; a prevalence of 5.6% was reported among Israeli dental patients (Shifman and Chanannel, 1978), 5.5% among Iranian dental patients (Bronoosh et al., 2012) and 8% among Jordanian dental patients (Darwazeh et al., 1998). Ruprecht et al. (1987) reported a taurodontism prevalence of 11.3% among Saudi dental patients. Pillai et al. (2007) reported a prevalence of 11.28% among adult Venezuelan dental patients. Yemitan and Adediran reported a prevalence of 33% among Nigerian dental patients (Yemitan and Adediran, 2015). Surprisingly, Toure et al. (2000) reported a prevalence of 48% among young Senegalese individuals, and a prevalence of 46.4% was reported by a study in China (MacDonald-Jankowski and Li, 1993). Moreover, different rates have been reported in the same countries. In another region of India, Shah et al. (2015)

reported a prevalence of 11.8% among Indian dental patients. Most authors claim that they followed the method suggested by Shifman and Chanannel (1978), and differences in the reported rates might be related to factors such as type of teeth examined, genetic factors or ethnicity.

The most frequent subgroup of taurodontism is hypotaurodont, followed by mesotaurodont, then hypertaurodontism, at incident rates of 2.8%, 0.4% and 0.57%, respectively, among American Caucasians (Sood and Sood, 1992). Taurodontism may be found in both premolar and molar teeth, unilaterally and bilaterally, and in both permanent and primary teeth (Simsek et al., 2013; Haskova et al., 2009; Holan and Chosack, 1991). The maxillary second molars, followed by mandibular second molars, were the most common taurodontic teeth, and the maxillary third molars were among the least affected teeth, in a study of the Indian population (Gupta and Saxena, 2013).

The prevalence of taurodontic molars and premolars is significantly higher in females than in males (Bronoosh et al., 2012). Sarr et al. (2000) expected the X chromosome to be related to taurodontism in the Chinese population, having observed a higher prevalence in females (Sarr et al., 2000). However, other studies have found no significant difference between both genders (Burklein et al., 2011; Jafarzadeh et al., 2008; Constant and Grine, 2001). Many studies have stated a higher prevalence of bilateral taurodontism (Shah et al., 2015; Shifman and Chanannel, 1978), while others have reported that unilateral taurodontism is more prevalent (Yemitan and Adediran, 2015; Bronoosh et al., 2012; Pillai et al., 2007).

There are many different theories that have been suggested for the aetiology of taurodontism, including specialized or retrograde character, primitive pattern, Mendelian recessive pattern, atavistic feature and mutation (Dineshshankar et al., 2014; Goldstein and Gottlieb, 1973; Witkop, 1971). Several explanations for the pathogenesis of taurodont formation have been put forward; they include an unusual developmental pattern, a delay in calcification of the pulp chamber floor, an odontoblastic deficiency and an alteration in Hertwig's epithelial root sheath, with an apparent failure of the epithelial diaphragm to invaginate at the normal horizontal levels and a delayed or incomplete union of the horizontal flaps of the epithelial diaphragm. It has also been proposed that taurodontism is a genetically determined trait (Jafarzadeh et al., 2008; Terezhalmy et al., 2001; Witkop et al., 1988).

Taurodontism is commonly seen in permanent dentition. However, it can also be found in the primary dentition. Simsek et al. (2015) reported a prevalence of 2.46% in the primary dentition among Turkish children. Nagaveni et al. (2012) reported a prevalence of 0.4% in the primary dentition among Indian children. Most data from studies are from case reports (Jogendra Sai Sankar

et al., 2017; Panigrahi et al., 2014; Srivathsa, 2014; Bafna et al., 2013; Vashisth et al., 2013; Bhat et al., 2004).

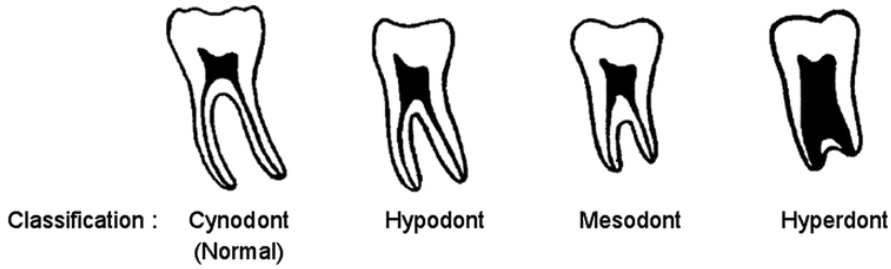

Figure 6: Diagrammatic representation of the three classes of taurodontism as proposed by Shaw. Figure is reproduced with permission from Angle Orthodontist Editor (Nawa et al., 2008)

5.3.1.2 Taurodontism investigation methods

Diagnosis of taurodontism is carried out subjectively from radiographs or from the internal features of the teeth (Ackerman et al., 1973). There are three vertical measurements that can be made using intraoral radiographs of permanent first and second molars described by Shifman and Chanannel (1973). Measurement 1: the height of the pulp chamber vertically, the distance between the floor and roof the pulp chamber. Measurement 2: the distance between the apex of the longest root and the roof of the pulp chamber. Measurement 3: the distance between the highest point of the pulp chamber floor and the connecting line of the cementoenamel junctions (Shifman and Chanannel, 1978). Diagnosis of taurodontism has been made by comparing the ratios of the height of the crown/tooth and pulp (Jorgenson et al., 1982; Shifman and Chanannel, 1978). Tulensalo et al. (1989) modified the taurodontism measurements that were established by Shifman and Chanannel into an index for use on panoramic radiographs, as opposed to the original intraoral periapical radiographs, which have different magnification. If measurement 3 was lower than 3.5 mm, the tooth would be defined as non-taurodontic. They showed that measurement 3 was reliable for assessing taurodontism in the developing dentition and compared it with other variables to investigate how reliable it was for measurement of taurodontism severity (Tulensalo et al., 1989) (Figure 7). The landmarks used for measurement 3 are relatively stable in different age groups (Shifman and Chanannel, 1978; Blumberg et al., 1971). The small range of measurement 3 can be seen as a disadvantage. However, it has been commonly used and validated, and the measurement is still able to distinguish between taurodontic molars in various groups of patients (Arte et al., 2001; Laatikainen and Ranta, 1996b).

Many other investigators have defined taurodontic teeth by performing measurements or calculating the ratios of tooth parameters (Gupta and Saxena, 2013; Bronoosh et al., 2012; Kan et al., 2010; Prakash et al., 2005). Calvano et al. (2008) considered a tooth to be taurodontic if it had more apical furcation area and a larger pulp chamber. Witkop (1971) defined taurodontic teeth according to the distance from the furcation area to the cementoenamel junction, specifically if it was larger than the occluso-cervical height of the tooth. In other studies, taurodontism has been detected using the crown height ratio to the total tooth length (Gomes et al., 2012; Seow and Lai, 1989).

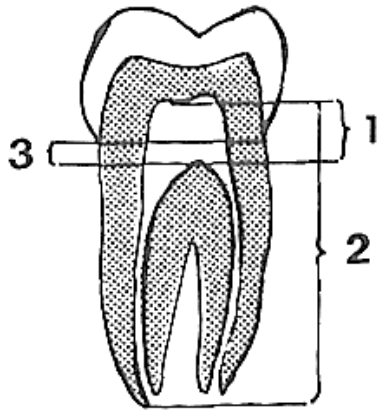

Figure 7 : Three measures used to determine presence of taurodontism. Measure 1 – height of pulp chamber. Measure 2 – roof of pulp chamber to root apex. Measure 3 – connecting line between cementoenamel junctions to floor of pulp chamber. Figure is reproduced with permission from John Wiley and Sons (Tulensalo et al., 1989)

5.3.1.3 Taurodontism in individuals with non-syndromic orofacial clefts

Taurodontism is more common in patients with a cleft compared to non-cleft individuals (Melo Filho et al., 2015; Laatikainen and Ranta, 1996a). The association of taurodontism with non-syndrome cleft patients was reported as 60.4% with cleft lip and palate, 62.4% with cleft lip and 67% with cleft palate, compared to 42.8% of a control population (Weckwerth et al., 2016). Cleft palate seems to have a higher prevalence of associated taurodontism than either cleft lip and palate or cleft lip only (Weckwerth et al., 2016; Laatikainen and Ranta, 1996a). In a case-control study of 88 subjects with non-syndromic cleft lip and/or palate (NSCL/P), 36 patients (40.9%) exhibited taurodontism, compared to 23.3% of the control group. Most teeth were classified as

hypotaurodontic, followed by mesotaurodontic then hypertaurodontic (Melo Filho et al., 2015). These wide variations in taurodontic frequency may reflect the populations sampled and the method used to determine taurodontism. However, they also may be a reflection of the teeth evaluated and of the ages of the patients sampled. For non-cleft and all cleft types, taurodontism is more frequent in second molars than in first molars (Laatikainen and Ranta, 1996b). In general, patients with cleft palate only have a higher prevalence of taurodontism than patients with cleft lip and palate or cleft lip (Weckwerth et al., 2016; Laatikainen and Ranta, 1996a).

5.3.1.4 Taurodontism in individuals with craniofacial developmental anomalies and syndromes

Taurodontism can be found as an isolated dental anomaly in the normal population but it can also be associated with several developmental anomalies and syndromes. Table 4 shows craniofacial syndromes associated with taurodontism (Kantaputra et al., 2020; Jagtap et al., 2019; Desai, 2019; Giambersio et al., 2019; De Souza et al., 2019; Dineshshankar et al., 2014).

Table 4: List of syndromes associated with taurodontism.

Amelogenesis imperfecta	Clouston syndrome
Down syndrome	Rapp–Hodgkin syndrome
Apert syndrome	Dyskeratosis congenital
Focal dermal hypoplasia	Klinefelter syndrome
Ectodermal dysplasia	Tricho-dento-osseous syndrome
Hypophosphatasia	Mohr syndrome
Hyperphosphatasia-oligophrenia-taurodontism	Wolf–Hirschhorn syndrome
Microcephalic dwarfism-taurodontism	Lowe syndrome
Microdontia-taurodontia-dens invaginatus	Smith–Magenis syndrome
Oculo-dento-digital dysplasia	Williams syndrome
Oral-facial-digital, Type II	Al-Awadi–Raas-Rothschild syndrome
McCune–Albright syndrome	Osteogenesis imperfecta
Van der Woude syndrome	Otodental syndrome
Dyke–Davidoff–Masson syndrome	Goldenhar syndrome
Nance–Horan syndrome	

Taurodontism is associated with several other craniofacial developmental conditions, including Amelogenesis imperfecta Types IA and IV (OMIM #104530 and #104510) and tricho-dento-osseous syndrome (OMIM #190320) (Crawford et al., 1988). Taurodontism is also seen in individuals with X-linked hypohidrotic ectodermal dysplasia (OMIM # 305100). These individuals are characterised by sparse hair as well as hypodontia (Crawford et al., 1991). Other conditions

with taurodontism as an associated feature include Down syndrome (OMIM #190685), Williams–Beuren syndrome (OMIM # 194050), Klinefelter syndrome and 47,XXX karyotype (Axelsson, 2005; Varrela and Alvesalo, 1989; Varrela and Alvesalo, 1988). Most taurodontism cases are bilateral (Laatikainen and Ranta, 1996b; Shifman and Chanannel, 1978). However, Seow and Lai (1989) found that nearly half of their cases were unilateral. In a recent case report, Zheng et al. (2019) reported 3 families having 4 individuals that were diagnosed with ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome or ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome. These individuals presented with taurodontism, which was described by the authors as severe.

5.3.1.5 Taurodontism in Van der Woude and blepharocheilodontic syndromes

Taurodontism has been reported in 13 VWS patients, of which 6 were documented as exhibiting taurodontism in at least one tooth (46%) (Nawa et al., 2008). To our knowledge, there are no study has been reported that highlights the prevalence of taurodontism in BCDS patients.

5.3.2 Tooth agenesis

5.3.2.1 Definition and etiology

Tooth agenesis can be defined as the failure of tooth development leading to the absence of one or more teeth in either primary or permanent dentition. In the literature, a variety of descriptive terms that have been used to define this condition including congenitally missing teeth, teeth aplasia, hypodontia, absence of teeth, lack of teeth and teeth agenesis (Brook et al., 2009; Zhu et al., 1996; Brook, 1974; Hunstadbraten, 1973). Hypodontia is a common term used when describing the absence of 1–5 teeth, excluding third molars. In oligodontia, 6 or more teeth are absent, excluding third molars. Anodontia describes the complete absence of teeth according to the severity of agenesis (Arte, 2001) (Figure 8).

A tooth can be confirmed to be missing when the tooth has failed to erupt in the oral cavity clinically and there is no sign of development in radiographs. The cause is usually a disturbance during the early stages of tooth development, either because of genetics or environmental factors. Tooth agenesis is usually observed without any obvious environmental cause (Arte et al., 2017; Pemberton et al., 2005).

Msh Homeobox 1 *(MSX1)* and Paired Box 9 (*PAX9)* were the first identified causative genes for isolated tooth agenesis; they code for transcription factor proteins that play an important role in tooth development (Stockton et al. 2000; Vastardis et al. 1996). In *MSX1* missense mutation in the homeobox, the second premolars, third molars and to an extent other teeth such as first molars, first premolars and incisors may all be affected (Vastardis et al., 1996). In *PAX9* frameshift mutation, all molars, second premolars and some incisors may be affected (Stockton et al. 2000). Wang et al. (2011) reported a family case of a male proband with missing teeth; his maternal grandfather had missing teeth as well. The authors performed a sequence analysis of the *PAX9, MSX1* and Axis inhibition protein 2 (*AXIN2)* genes and concluded that *PAX9* mutation is a risk factor for non-syndromic oligodontia in the Chinese population. There are other mutations that have been identified as a cause of isolated or syndromic tooth agenesis, with the phenotypes of the patients largely confirming the pattern of teeth agenesis (Arte et al., 2013). Liu et al. (2001) have mapped the gene locus for He–Zhao deficiency, which has been characterised in large Chinese kindred as a distinct form of permanent tooth agenesis that is different from previously reported disorders of tooth agenesis, onto the chromosome *l0ql1.2*. Another study demonstrated an association between *rs929387* of *GLI3* and non-syndromic tooth agenesis in Chinese Han individuals (Liu et al., 2013). More details about genetic mutations in non-syndromic and syndromic tooth agenesis are presented in Table 3. Surprisingly, tooth agenesis has been linked to the iatrogenic effect. Tanaka et al. (2015) reported a case of an 11-year-old boy with delayed eruption. After investigation, it was revealed that the boy had undergone high-dose chemotherapy for a hematological malignancy. The panoramic radiograph revealed an absence of 25 permanent teeth accompanying taurodontism of the first molars bilaterally, enamel hypoplasia of erupted incisors and a canine and short roots of the deciduous teeth. Similar results have been found by Kılınç et al. (2019), who concluded that children who received cancer treatment before the age of 7 were a high-risk group for dental anomalies, with more frequencies of microdontia (small peg-shaped teeth) and hypodontia when the patient was treated for cancer before the age of 5.

Table 5: Several genetic mutations associated with tooth agenesis.Tables is reproduced with permission from Springer International Publishing AG (Arte et al., 2017).
Non-syndromic/isolated causes.

Gene mutated / Chromosomal change	**Estimated percentage of non-syndromic oligodontia families**	**Associated non-dental defects**
WNT10A	26–56%	Minor ectodermal features

PAX9	>5%	
MSX1	>3%	Cleft lip/palate, nail dysplasia
AXIN2	>2%	Colorectal cancer
LRP6	>5%	
EDA (ectodysplasin) *EDAR* *EDARADD*	8–10%	Minor ectodermal features

Syndromic causes

Condition	**Gene mutated / Chromosomal change**	**Associated non-dental defects**
Hypohidrotic (anhidrotic) ectodermal dysplasia (HED, ED)	*EDA* (encodes ectodysplasin) *EDAR* *EDARADD*	Ectodermal dysplasia, hypoplastic hair/glands
Ectrodactyly, ectodermal dysplasia and cleft lip/palate syndrome (EEC)	*TP63*	Ectodermal dysplasia, cleft palate, split hands
Odonto-onycho-dermal dysplasia (OODD)	*WNT10A*	Ectodermal dysplasia
Cleft lip/palate-ectodermal dysplasia syndrome (CLPED1)	*PVRL1* (encodes nectin 1)	Ectodermal dysplasia, cleft lip/palate, cutaneous syndactyly
Axenfeld–Rieger syndrome (ARS)	*PITX2* *FOXC1*	Eye defects, umbilical anomalies
Diastrophic dysplasia	*DTDST*	Osteochondrodysplasia
Van der Woude syndrome 1 (VWS1)	*IRF6*	Cleft lip/palate, pits in the lower lip
Van der Woude syndrome 2 (VWS2)	*GRHL3*	Cleft lip/palate, pits in the lower lip
Incontinentia pigmenti (IP)	*NEMO (IKBKG)*	Ectodermal dysplasia, neurological problems
Down syndrome	Trisomy 21	Dysmorphic craniofacial features, mental retardation

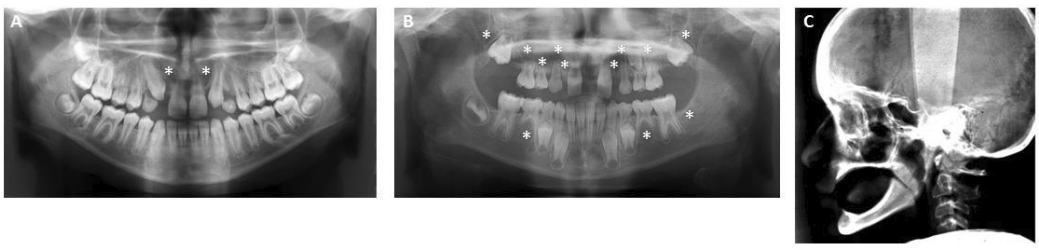

Figure 8: Tooth agenesis severity

A. Dental panoramic tomograph shows hypodontia case, absence of permanent upper laterals.
B. Dental panoramic tomograph shows oligodontia case, absence of 12 permanent teeth.
C. Lateral skull radiograph shows an anodontia case, absent all teeth. Figure is reproduced with permission from Springer International Publishing AG (Arte et al., 2017).

5.3.2.2 Tooth agenesis of primary teeth in the general population

The tooth agenesis prevalence in the primary dentition is rare, from 0.1–0.9% in the European population (Jarvinen and Lehtinen, 1981), but is reported to be higher, at 2.4%, in Japan (Yonezu et al., 1997). One or two primary incisor teeth are the most commonly missing. In the primary teeth, tooth agenesis of the maxillary lateral incisors was observed in more than 50% of cases, and cases of both maxillary lateral incisors with mandibular incisor agenesis were observed in more than 90% of all agenesis teeth (Daugaard-Jensen et al., 1997a; Whittington and Durward, 1996). In the majority of cases, only one primary tooth is missing (Daugaard-Jensen et al., 1997a). No difference in frequency of tooth agenesis has been observed between the right and left sides, but tooth agenesis is more common in the maxilla (Daugaard-Jensen et al., 1997a). Prevalence in the primary dentition is not influenced by gender as there is no significant difference between males and females in hypodontia (Nunn et al., 2003; Dhanrajani, 2002). Hypodontia in the primary dentition is often associated with hypodontia in the permanent dentition. It can be used as a sign for early diagnosis and management (Daugaard-Jensen et al., 1997b).

5.3.2.3 Tooth agenesis of permanent teeth in the general population

The prevalence of tooth agenesis in the permanent teeth varies from 3–10%, excluding third molars. It is the most common developmental dental anomaly; hypodontia has been observed in 83% of subjects with agenesis (Arte et al., 2017; Polder et al., 2004; Haavikko, 1971) (Figure 9). The prevalence of hypodontia in permanent dentition varies significantly based on factors such as geographical location, race and gender (Polder et al., 2004). In a meta-analysis (Polder et al., 2004) of hypodontia considering a total of 33 studies and approximately 127,000 participants, the authors reported a different prevalence among various racial groups including white Europeans (4.6–6.3%), white North Americans (3.2–4.6%), African-Americans (3.2–4.6%), white Australians (5.5–7.6%), Arabs (2.2–2.7%) and Chinese people (6.1–7.7%). In contrast to the primary dentition, the hypodontia prevalence in the permanent dentition is significantly different between genders with a higher prevalence in females (Flores-Mir, 2005; Polder et al., 2004). The ratio of male: female

varies considerably among different ethnic groups (Table 6). Furthermore, other dental anomalies have been shown to be associated with hypodontia: taurodontism (Seow and Lai, 1989), small tooth size (Garn and Lewis, 1970), delayed formation and eruption of permanent teeth, peg-shaped upper lateral incisors (Alvesalo and Portin, 1969), short root anomaly (Apajalahti et al., 1999), misaligned canines (Pirinen et al., 1996) and ectopic eruption or malposition of first permanent molars (Bjerklin et al., 1992). Bilateral agenesis is found for most teeth in almost half of the possible occurrences when at least two teeth are affected (Polder et al., 2004). Bilateral maxillary lateral incisors agenesis may be more common than bilateral premolars agenesis in either jaw (Polder et al., 2004).

Table 6: Prevalence of hypodontia by gender in different ethnic groups and male to female ratios in each ethnic group. Table adopted from Polder et al. (2004).

Racial group	% Males	% Females	Ratio
European (white)	4.6	6.3	1:1.4
North American (white)	3.2	4.6	1:1.4
North American (African-American)	3.2	4.6	1:1.4
Australian (white)	5.5	7.6	1:1.4
Saudi Arabian (white)	2.7	2.2	1:0.8
Chinese (Mongoloid)	6.1	7.7	1:1.3

The most frequently missing teeth are the lower second premolars, followed by upper second premolars and upper lateral incisors, though some studies have found that upper lateral incisors are most often affected (Khalaf et al., 2014; Polder et al., 2004). These differences may reflect population differences; for instance, agenesis of lower central incisors is more common in Asian populations compared to Caucasian (Yonezu et al., 1997). The third molars may be observed for about 75% of all agenesis teeth (Haavikko, 1971). If they are not considered, tooth agenesis of second premolars and upper lateral incisors is estimated to be 85% of all teeth agenesis in Caucasian populations (Polder et al., 2004). The most stable teeth are the maxillary central incisors (prevalence of agenesis 0.016 %) and the mandibular first molars and canines (prevalences of agenesis about 0.03%) (Polder et al., 2004).

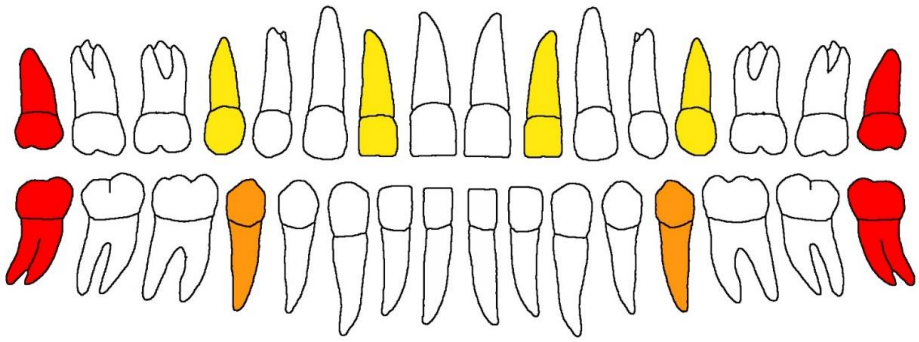

Figure 9: Schematic of most frequently missing permanent teeth in Caucasian populations.
- Red: the most common missing teeth are the 3rd molars
- Orange: the second most common missing teeth are the mandibular 2nd premolars
- Yellow: the third most common missing teeth are the maxillary lateral incisors and maxillary 2nd premolars. Figure is reproduced with permission from Springer International Publishing AG. (Arte et al., 2017).

5.3.2.4 Tooth agenesis in individuals with non-syndromic orofacial clefts

Tooth agenesis is commonly observed in cleft patients in both non-syndromic and syndromic forms (Phan et al., 2016). This prevalence is higher in cleft patients than in non-cleft individuals. In a comparative study, Wong et al. (2012) investigated the prevalence of hypodontia among Southern Chinese children with and without CLP. It found that 57.6% of CLP children had hypodontia, a significantly higher percentage than in those without CLP. In another study by Lai et al. (2009), among Chinese children with complete cleft lip and palate, the authors found a significantly higher prevalence of hypodontia with the maxillary lateral incisor the most frequently missing tooth {19.2% in Unilateral cleft lip and palate (UCLP) and 20.5% in Bilateral cleft lip and palate (BCLP)}. In a similar comparative study in Jordan, hypodontia was observed in 66.7% of CLP patients compared to normal individuals with the maxillary lateral incisor the most frequently missing tooth (Al Jamal et al., 2010). Among Saudi individuals with CLP, Al-Kharboush et al. (2015) found that hypodontia was the most common anomaly among patients, with a prevalence of 66.8% and no significant difference between genders. Among 205 patients with complete bilateral cleft lip and palate, Tereza et al. (2010) found that 144 patients (70.2%) had hypodontia, with the maxillary lateral incisor being the most commonly missing tooth. As in the normal population, the

prevalence of hypodontia in CLP patients is higher in the permanent dentition than in the primary dentition (Pegelow et al., 2012; Vichi and Franchi, 1995). There is a correlation between the prevalence of agenesis and the type of the cleft and, which has been shown to be 49% in unilateral, 68% in bilateral cleft lip and palate, 33% in cleft palate, 16% in submucous cleft and 10% in cleft lip (Jamilian et al., 2015; Heliövaara et al., 2004). The most common tooth agenesis area when a patient has a cleft is around the cleft area, but it is possible to observe it outside the cleft region (Klein et al., 2013). The maxillary lateral incisors and maxillary second premolars are the most commonly missing teeth in CLP patients (Tan et al., 2018; Al Jamal et al., 2010). According to Tan et al. (2017), the presence and extent of hypodontia in CLP patients may not affect the dental development. In contrast, Ranta (1984) and Lai et al. (2008) found a noticeable delay in dental development in cleft patients with hypodontia compared to cleft patients without hypodontia. These differences might be related to the type of cleft patients included in the studies.

5.3.2.5 Tooth agenesis in individuals with syndromic orofacial clefts

A pattern of tooth agenesis in syndromic patients is sometimes more severe when compared to non-syndromic patients (Phan et al., 2016; Klein et al., 2013). Tooth agenesis has been associated with syndromic clefting in VWS (Rizos and Spyropoulos, 2004), Axenfeld–Rieger (Rieger) syndrome (Klein et al., 2013), ectodermal dysplasias (Lexner et al., 2007), odonto-onycho-dermal dysplasia (Adaimy et al., 2007), oral-facial-digital syndrome Type I (Kırzıoglu and Oz, 2018) and Type II (Havle et al., 2015), Down syndrome (Källén et al., 1996) and holoprosencephaly (Frazier-Bowers et al., 2003; Simon and Roberts, 1993). Some syndromes may result from a single-gene mutation that can cause both clefting and hypodontia, as typical phenotypic findings suggest in VWS, ectrodactyly-ectodermal dysplasia-clefting syndrome and Kallmann's syndrome (Mølsted et al., 1997; King et al., 1994; Ranta and Rintala, 1983). Stavropoulos et al. (2011) investigated hypodontia among 23 patients with Apert syndrome. Excluding the third molar, the prevalence of hypodontia with at least one missing tooth was 34.8%, with the maxillary lateral incisor and mandibular second premolar the most frequently missing teeth. The authors also found a symmetrical pattern in the missing teeth. Selvaag (2000) reported a case of hair-tooth ectodermal dysplasia in a Norwegian family. In addition to the structural hair abnormalities, tooth agenesis was also reported in one member of this family with two missing mandibular premolars. Ozdemir et al. (2010) reported a case of a 12-year-old boy diagnosed with Klippel–Trénaunay syndrome (KTS), a genetic syndrome with rare manifestations in the head and neck region. It is sometimes associated

with cleft palate and presents with gingival hyperplasia and teeth agenesis. The authors concluded that oral manifestations of the syndrome are generally related to the severity of the disease.

5.3.2.6 Tooth agenesis in Van der Woude Syndrome

The incidence of tooth agenesis in patients with VWS, compared to non-syndromic cleft controls, has been reported to be 69% and 43%, respectively (Ranta, 1986; Ranta and Rintala, 1982). Another study found that 50% of VWS patients with CP had hypodontia (Oberoi and Vargervik, 2005). Hypodontia in individuals with VWS has been reported in studies with small samples (Oberoi and Vargervik, 2005; Ranta and Rintala, 1982). Most of these reported cases exhibit cleft lip and palate, and most of the missing teeth were in the cleft line. In both VWS and non-syndromic CL/P, it has been noticed that there is a relatively high incidence of tooth agenesis in the non-cleft region compared to non-cleft individuals. Hypodontia in VWS individuals has been reported in the literature, along with other usual or unusual manifestations of the syndrome. Soni et al. (2012) reported a case of a ten-year-old boy with characteristic VWS orofacial features, including central incisors hanging down and missing maxillary lateral incisors. Tripathi et al. (2014) reported a VWS individual with the classical features of the syndrome, including hypodontia, and some rare features such as undescended small testes and syndactyly of the second and third toes. More et al. (2013) reported a VWS case with hypodontia and an unusual additional finding of bilateral commissural pits. Richardson and Khandeparker (2017) reported a VWS case with hypodontia and a single median lower lip pit with associated limb deformities.

5.3.2.7 Tooth agenesis in blepharocheilodontic syndrome (BCDS)

Tooth agenesis is a common feature of BCDS, and may include more than six missing permanent teeth (oligodontia). The incisors form may be conical in shape (Gorlin et al., 1996; Falace and Hall, 1989). Tooth agenesis has been observed in BCD syndrome patients; however, it has been mostly reported in early infancy before the primary dentition has fully erupted and prior to the eruption of the permanent dentition. Therefore, this abnormality may go underreported, and the descriptions of the oligodontia may be inaccurate. In addition, there has been mention of the severity or pattern of tooth agenesis, but it is just a little. Regardless of the generally young age of the samples and lack of detail in reporting, there are many instances where severe oligodontia has been shown, with several cases having teeth agenesis in both the primary and permanent dentitions (Ababneh et al.,

2014; Gil da Silva Lopes et al., 2003; Guion-Almeida et al., 1998). One report described a case of extremely severe oligodontia with only 3 permanent teeth developing at the age of 5 years. Adeboye et al. (2009) described a patient in whom 2 primary and 11 permanent teeth failed to develop. These included an upper central incisor tooth, upper lateral incisor, upper canine, a lower lateral incisor and 7 out of 8 premolar teeth (11, 12, 13, 14, 15, 25, 35, 34, 32, 44 and 45).

5.3.3 Delayed tooth formation and dental age assessment

Growth and maturity can delayed in organs as a result of genetic or environmental factors; there are often differences between developmental age and chronological age (Green, 1961). Estimating dental age (DA) assists in determining the appropriate period for orthodontic time, planning orthodontic treatment and can aid in estimating age even without the birth record in forensic anthropology (Cunha et al., 2009; Maber et al., 2006). Tooth mineralisation is a more accurate indicator for estimating the DA than tooth emergence (Fanning, 1961). DA estimation will be more accurate in a young child than in an adult. There are gender differences in DA estimations (Ritz-Timme et al., 2000).

5.3.3.1 Dental age assessment methods

Many methods have been used to estimate and calculate DA, including the Haavikko method (Haavikko, 1970), Demirjian method (Demirjian et al., 1973), Nolla method (Nolla, 1960), Cameriere method (Cameriere et al., 2006), Nyström method (Nyström et al., 1986) and Willems method (Willems et al., 2001). All of these methods use dental radiographs to measure the DA according to dental development stages. Dental maturity of the seven left permanent mandibular teeth (excluding third molars) were analysed for French-Canadian children. Then, they predicted the dental age according to the maturity scores of each 7-tooth (Demirjian et al., 1973) (Figure 10). This method is used widely for two reasons, it is acceptable to use it in different populations and it is easy (Cunha et al., 2009; Nykänen et al., 1998; Mornstad et al., 1995). However, the DA predicted using the Demirjian method was an overestimation in many populations (Esan et al., 2017; Baghdadi and Pani, 2012), and even across the same population. In central regions of India, the Demirjian method was used as a method for estimating the chronological age of children (Warhekar et al., 2011). However, in South India Prabhakar et al. (2002) concluded in their study that the Demirjian method is not applicable for the estimation of chronological age. In Saudi Arabia,

Alshihri et al. (2016) investigated the dental age of 198 Western Saudi children using the Demirjian method and found that this method yielded a significant overestimation compared to chronological age. Another study, among Saudi children aged 9–14, showed that dental age was significantly higher in both boys and girls, by 0.3 and 0.4 years, respectively (Al-Emran, 2008). The results of Nour El-Deen et al.'s study using the Demirjian method also showed statistically significant differences between dental and chronological ages. However, this method was recommended by the authors because the differences were minimal in both sexes (Nour El Deen et al., 2016). Another study among Saudi children found that the Demirjian method is applicable for age estimation of Saudi boys (Al-Hadlaq et al., 2008). Willems et al. (2001) improved the maturity values by applying some mathematical corrections to the Demirjian method to be more accurate estimation age for other populations. However, for the highest accuracy population-specific estimation standards are recommended (Esan et al., 2017). In the most recent systematic review and meta-analysis, Franco et al. (2020) assessed the applicability of different dental age estimation methods including the Demirjian, Nolla, Cameriere and Willems methods among Brazilian children. It was concluded that these methods are valid and applicable among Brazilian children.

Nyström created specific scores for estimating the dental maturity of the Finnish population, improving the prediction of DA for Finnish children (boys and girls) using the Demirjian 7-teeth method (Nyström et al., 2000). The original Demirjian method without this correction overestimates age. The boys' overestimations were seen at the age of 5–10, and the girls' at the age of 4–12 (Nyström et al., 1986). The mandibular second premolar one of the most frequently missing tooth (excluding third molars) (Haavikko, 1971). However, there are mathematical models for estimating the dental maturity stages of the target teeth for use when they are congenitally missing bilaterally (Nyström et al., 2000). Furthermore, they improved the Finnish dental maturity scores, and compared the differences to the original Demirijian dental maturity scores after changing the weighted scores and polynomial regression according to the Finnish population. They suggested that dental clinicians use the Demirjian method with Finnish weighted scores (Chaillet et al., 2004).

5.3.3.2 Dental age assessment in the general population

Dental age assessment has been studied in the general population of different ethnic groups because of inter-ethnic variations. Many studies using the Demirjian method on other populations reported patterns of advanced or delayed tooth development (Celikoglu et al., 2011; Chaillet et al., 2005; Haavikko, 1974). This led many authors to study the validity of the Demirjian method in other

populations and to discuss specific standards of age estimation for each population (Baghdadi and Pani, 2012; Chaillet et al., 2005; Chaillet and Willems, 2004). Dental maturity in the Finnish population was studied by considering 2,213 dental panoramic radiographs from healthy Finnish children aged 2–19; girls presented a greater maturity than boys in all age groups (Chaillet et al., 2004). Use of the Demirjian method with specific Finnish weighted scores was very accurate (±1.95 years on average between 2–18 years of age) (Chaillet et al., 2004).

Another study estimated the dental age in the population of normal French children, aged 4–15, examined between 2004–2010 in the southwest of France. Dental age was evaluated by three different methods (Willems et al., 2001; Demirjian and Goldstein, 1973; Moorrees et al., 1963). The Demirjian and Goldstein (1973) methods provided an overestimation of dental age (mean difference +0.51 ± 0.91 years), whereas the method described by Willems et al. (2001) gave a more accurate dental estimation (mean difference 0.00 ± 0.96 years). For the Moorrees et al. (1963) method, utilisation of the second mandibular molar was more accurate and reliable than utilisation of the first mandibular molar. It seems that the differences observed in estimated dental age may be explained by secular changes in populations. The Willems et al. (2001) method is reliable and accurate and appears to be suitable for dental age estimation in the population of normal French children (Urzel and Bruzek, 2013). Although the findings of Alqadi and Abuaffan's study (2019) showed a significant delay in dental development among Yemeni children, the authors concluded that the Demirjian method is acceptable for predicting the chronological age (CA) of Yemeni children with no birth certificate for legal, civil and forensic purposes.

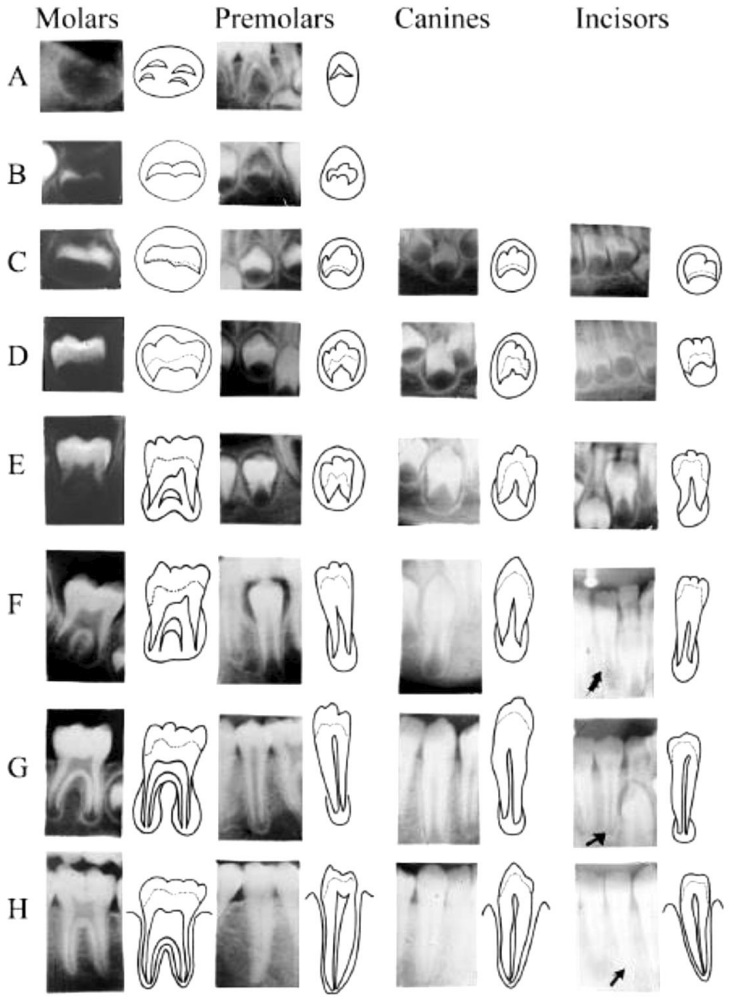

Figure 10 : An illustration of permanent teeth developmental stages according to Demirjian et al. Figure is reproduced with permission from Wayne State University Press (Demirjian et al., 1973)

5.3.3.3 Dental age assessment in individuals with non-syndromic orofacial clefting

It is well known that teeth in cleft patients show delays in development compared to those in healthy subjects. Moreover, the teeth near the cleft generally offer a greater delay than the teeth further away (Van Dyck et al., 2019). The difference between DA and CA in specific groups has also been analysed in the literature. In a recent case-control study, Van Dyck et al. (2020) evaluated dental age among patients with unilateral non-syndromic cleft lip and palate (UCLP), in comparison to

non-cleft patients, using the Demirjian method. It was observed that DA was lower in cleft patients, though not always significantly; the highest difference was −1.4 for females at 13 years old and −0.8 for males at 12 years old. Bindayel and co-workers compared the DA and CA of 51 Saudi CLP patients using the Demirjian method. They concluded that patients with CLP had a delayed dental age by 8.4 months compared to their recorded chronological age (Bindayel et al., 2014). DA/CA differences in non-syndromic unilateral cleft lip and palate children (NSUCLP) were smaller than in the healthy children group (Almotairy and Pegelow, 2018). DA/CA differences in children born with soft palate clefts (CPs) were smaller than in children born with submucous cleft palate (SMCP) (Heliövaara and Nyström, 2009). In a recent systematic review by Franco et al. (2020) of 36 articles assessing tooth development and eruption in CLP patients, it was found that in 32 of the included publications there was a delay in tooth development or eruption in CLP patients; the mean of the delay was 0.56 years (0.20 to 0.90 years) for all types of clefts. Ozturk et al. (2020), in their retrospective case-control study, tested the correlation between dental age obtained using the Demirjian method, chronological age and skeletal age (SA) among individuals with and without CLP. Their results revealed significant correlation between DA and CA and also between DA and SA in both groups and both sexes. The authors concluded that DA can be used for accurate age estimation among patients with CLP (Ozturk et al., 2020). The lateral incisor at the cleft side is generally the most delayed. Conflicting results are seen related to the influence of sex and age. It has therefore been suggested to examine males and females separately and also to segregate samples into subgroups based on chronological age (Ozturk et al., 2020; Bindayel et al., 2014; Beunen et al., 2006; Harris and Hullings, 1990; Demirjian et al., 1985; Harris et al., 1980).

5.3.3.4 Dental age assessment in patients with syndromic orofacial clefts

There are few studies evaluating the dental age of individuals with cleft syndromes. One study that evaluated dental age in 102 patients with Down syndrome using panoramic radiographs determined that, while 18.87% of the males and 10.21% of the females presented with dental ages outside normal standards, the majority of patients with Down syndrome were considered to be within the normal range of mineralisation chronology (Moraes et al., 2007). In another study, the DA of individuals with Down syndrome was compared with a control group of 191 non syndromic individuals of the same age group based on chronological mineralisation. It was found that while DA was lower than CA, it was only significant for females, and the difference between DA and CA was not significant between the Down syndrome and control groups (Pinchi et al., 2018). Halse et al. (1979) investigated dental age among individuals with Aarskog syndrome (a rare X-linked

recessive syndrome sometimes associated with cleft lip/palate). Ten patients aged 7–21 were considered. Estimated dental age was calculated using a method developed by the authors. The results showed delayed dental development in some of the participants; while the dental age of individuals with Aarskog syndrome was inconsistently delayed, the delay was generally less pronounced than skeletal age. In a comparative study carried out by Diz et al. (2010) the correlation between DA and CA was tested among 3 different groups, including individuals with cerebral palsy, mental retardation and no associated syndromes or systemic conditions and Down syndrome of both sexes. Dental age was estimated using Demirjian's and Noll's methods. The results showed no significant differences between dental and chronological age in boys from the three groups. However, a significant delay in dental age was observed in girls with cerebral palsy or Down syndrome (Diz et al., 2011). Among individuals with Apert syndrome, Kaloust et al. (1997) compared dental age with chronological age using the Demirjian method. It was stated that 31 out of 36 patients with Apert syndrome had a significant delay in dental age, by 0.96 years, and the range was 0.5–2.9 years.

5.3.3.5 Dental age assessment in Van der Woude and blepharocheilodontic syndromes

Although VWS and BCD syndromes are associated with obvious dental abnormalities, so far as we are aware, no studies have been reported about the dental age of individuals with these syndromes.

5.3.4 Tooth morphology anomalies

5.3.4.1 Peg-shaped tooth form in the general population

The term peg-shaped tooth refers to a type of microdontia in which the abnormally small tooth has a conical form, that is, a tooth whose sides converge or taper together incisally (MedGen UID: 82730; Concept ID: C0266037). Thus, the incisal mesiodistal width of the tooth crown is shorter than the cervical width (Grahnen, 1956). Both environmental factors and inheritance play a role in development of conical teeth. This form can be found in a single tooth or in a multiple teeth. The maxillary permanent lateral incisor is the tooth most commonly affected with a peg-shaped form, leading to aesthetic, orthodontic and periodontal problems for affected individuals (Figure 11). The following maxillary lateral incisor and maxillary third molar can also have a peg-shaped form (Neville et al., 2019; Scott and Irish, 2017). Peg-shaped mandibular incisors have also been reported in the literature (Devasya and Sarpangala, 2016; Malleshi et al., 2014; Ramachandra et

al., 2009). Sometimes the peg-shaped tooth occurs as a supernumerary tooth, as seen in mesiodens. The prevalence of peg-laterals in the general population worldwide is 1.8%, ranging from 0.6–5.1% (Hua et al., 2013; Wu and Feng, 2005). Their analysis indicated that peg-lateral teeth were significantly more common in the Mongoloid population (3.1%) than in the black (1.5%) and white (1.3%) populations. Peg-shaped lateral is more common in girls than in boys, while unilateral and bilateral are equally common. In unilateral cases, peg-shaped laterals are twice as frequent on the left side compared to the right side (Hua et al., 2013). Patients with unilateral peg-shaped maxillary permanent lateral incisors have a 55% chance of having lateral incisor hypodontia on the contralateral side. Variations across nations could be attributed to differences in ethnicity and geographical locations (Hua et al., 2013).

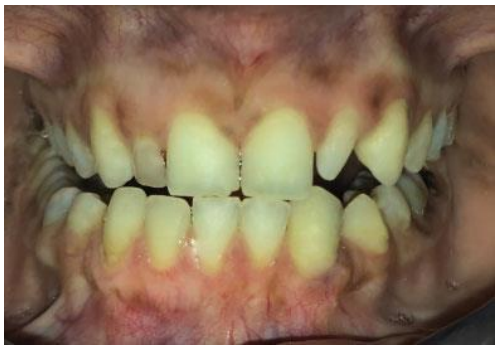

Figure 11 : An intraoral photograph of a patient with congenitally missing 32 associated with a peg-shaped 22. Figure is reproduced with permission from Georg Thieme Verlag KG Stuttgart • New York (Khalaf, K. and El-Kishawi, M 2022)

5.3.4.2 Peg-shaped tooth form in non-syndromic (isolated) orofacial clefting

Non-syndromic cleft lip and/or cleft palate has been reported to be associated with a high prevalence of dental anomalies such as hypodontia, supernumeraries and abnormalities in tooth size, shape and position. Although the peg-shape form has been found more in lateral incisors, these teeth are commonly absent in about 39–66% of reported cleft patients (Haque and Alam, 2015; Wu et al., 2011; Tereza et al., 2010) or are removed during alveolar bone graft surgery (Tan et al., 2018). In a study by Costa et al. (2012) in Brazil, dental anomalies of 76 cleft patients were

investigated, 102 teeth with dental anomolies, 27 (26.5%) presented with a conical shape. Of these, 17 teeth were found in unilateral cleft patients, and 10 teeth were found in bilateral cleft patients. In another study by Wu et al. (2011), 196 patients with different types of clefts were investigated for dental anomalies. The frequency of peg-shaped laterals was highest in the unilateral cleft lip and alveolus (UCLA) group (61.3%), followed by the bilateral cleft lip and palate (BCLP) group (58%), the unilateral cleft lip and palate (UCLP) group (48.2%), the unilateral cleft lip (UCL) group (45%) and the cleft palate (CP) group (10%). Most of these conical teeth were found on the same side; while on the contralateral side in the UCLP and UCLA groups, patients with UCL had no conical teeth on the contralateral side.

5.3.4.3 Peg-shaped tooth form in syndromic orofacial clefting

Peg-shaped (conical) teeth have been reported in many syndromes associated with orofacial anomalies. Chromosome *2q32-q33* deletion syndrome (Glass syndrome), or *SATB2*-associated syndrome (SAS), is a genetic disorder characterised by significant neurodevelopmental compromise and some craniofacial anomalies including palatal abnormalities (cleft or high-arched palate) and abnormal shape and size (conical shape) of the upper central incisors (Zarate and Fish, 2017; Rainger et al., 2014; Van Buggenhout et al., 2005). Weyers acrofacial dysostosis (Curry-Hall syndrome) is caused by heterozygous mutation in the *EVC2* gene and affects tooth development, with cleft lip and/or cleft in the mandible symphysis also reported (Ruiz-Perez et al., 2007; Curry and Hall, 1979; Weyers, 1953). Dental anomalies include hypodontia and microdontia (Goswami, 2018). A mutation in the *MSX1* gene is a possible mechanism for selective tooth agenesis and hypodontia. Mice haplo-insufficient for *MSX1* has a cleft palate and abnormalities in tooth development. In addition to missing teeth, individuals may have small or conical teeth (Hu et al., 1998). In case reports by Chitty et al. (1996), the authors reported two families with Witkop syndrome (tooth and nail syndrome) where the patients presented with cleft palate and multiple conical upper and lower teeth. Levy–Hollister syndrome, or lacrimo-auriculo-dento-digital syndrome (LADD), is caused by mutations in genes involved in the FGF signalling pathway. Individuals with the syndrome display many craniofacial abnormalities, including cleft lip and palate and peg-shaped incisors (Guven et al., 2008; Klein et al., 2006; Ramirez and Lammer, 2004).

5.3.4.4 Peg-shaped tooth form in Van der Woude and blepharocheilodontic syndromes

Peg-shaped teeth are not as common among VWS individuals as hypodontia, which is considered a cardinal feature with occurrence in up to 80% of VWS individuals. The prevalence of peg-shaped teeth in VWS varies according to the severity of the cleft type (Rizos and Spyropoulos, 2004). However, in *IRF6* mutant mice, Chu et al. (2016) reported a different model of VWS; they were able to identify some dental anomalies, including variable hypodontia, supernumerary incisors and molars, peg-shaped first molars and C-shaped mandibular second molars. In a clinical case report, Advani et al. (2012) stated that peg-shaped teeth are considered one of the common dental anomalies among VWS individuals.

In contrast, the prevalence of peg-shaped teeth in BCD individuals has been reported frequently in the literature. Among 35 reported cases, conical teeth were found in 11 cases (31.4%), making it the second most-common dental anomaly after oligodontia, which accounted for 74.3% of the reported cases (Ababneh et al., 2014; Iida et al., 2006; Gorlin et al., 1996; Allanson and McGillivray, 1985). Conical form is observed mostly in incisor teeth and can be found in primary and permanent dentitions (Adeboye et al., 2009; Guion-Almeida et al., 1998).

5.3.5 Supernumerary teeth

5.3.5.1 Supernumerary teeth in the general population

Supernumerary teeth occur in the permanent teeth in 2–3.5% of the normal population. The prevalence is slightly higher in Asians than in Caucasians; it is also more common in males than females (Backman and Wahlin, 2001; Zhu et al., 1996). The rate of incidence is five times higher in the permanent dentition compared to the deciduous dentition (Zhu et al., 1996; Jarvinen and Lehtinen, 1981; Haavikko, 1970). Supernumerary teeth are classified according to their time emergence, place and morphology (Zhu et al., 1996). They may be found with normal size and morphology; malformed supernumerary teeth may be molariform, conical or tuberculate (Figure 12). The incisor region is the most common place for supernumerary teeth to appear (Russell and Folwarczna, 2003). The mesiodens and the tuberculate supernumerary are some examples of supernumerary teeth common in this area. The mesiodens can interfere with the upper central incisors, preventing the eruption of these teeth, which results in the development of a diastema. Sometimes the mesiodens erupt, resulting in occlusal or aesthetic problems. The tuberculate supernumerary also prevents the eruption of the central incisors, as it lies directly over the cingulum of the tooth. In both cases, these supernumerary teeth should be extracted.

The aetiology of supernumerary teeth has been considered from genetic, evolutionary and developmental perspectives; one proposed mechanism is genetic overactivation of pathways which may have been reduced during evolution. Support for this view is the common association of supernumerary teeth with other teeth that are larger than normal (Khalaf et al., 2005). Mutant studies in mice have shown that increased quantitative level of signalling (tumor necrotin factor signalling) may lead to supernumerary teeth (Klein et al., 2006; Mustonen et al., 2004). This is based on the idea that dentition normally suppressed during human development becomes activated. Another suggestion for supernumerary teeth is that they develop from local overactivity of the dental lamina or tooth bud. A third suggestion considers supernumerary teeth as an expression of a quantitative variation; this leads to agenesis or a size reduction of teeth (Brook, 1984).

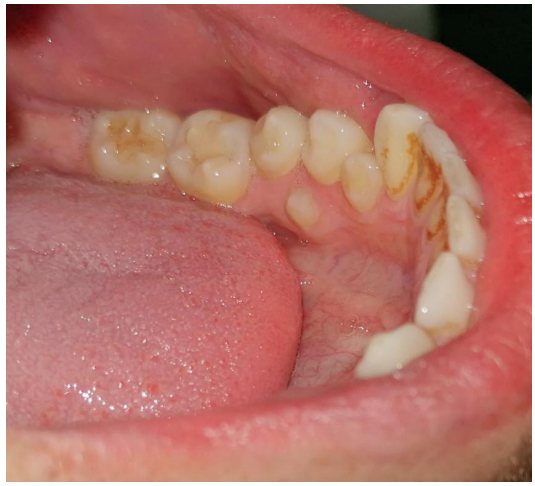

Figure 12: Supernumerary lower left premolar with supernumerary lower left canine. Figure is reproduced with permission from Nermin Suljkanovic, Dženan Balic, Nadina Begic. (Suljkanovic et al 2021)

5.3.5.2 Supernumerary teeth in individuals with non-syndromic (isolated) orofacial clefts

It has been reported that teeth close to the cleft area are more likely to have anomalies or to be missing (Rawashdeh and Abu Sirdaneh, 2009; Ranta, 1986). Supernumerary teeth have also been reported in some studies of isolated clefts (Tannure et al., 2012). Articles on supernumerary teeth among individuals with non-syndromic clefts are rare and differ in their findings. In some studies, supernumerary teeth were considered the second most frequent dental anomaly, with a prevalence of 7.94% (Lourenço Ribeiro et al., 2003). The frequency of supernumerary teeth has been found to

have a range of values; 7.3% in a study by Tortora et al. (2008), 12.5% in a study by Al-Kharboush et al. (2015), 13.3% in a study by Premkumar and Mohan (2015), 25.6% in a study by Jordan et al. (1966) and up to 30% in a study by Rullo et al. (2015). Anterior and posterior supernumerary teeth have also been reported in individuals with isolated clefts (Schwartz et al., 2014). These variations might be related to differences in study designs or between populations.

5.3.5.3 Supernumerary teeth in individuals with craniofacial syndromes

Dental anomalies become more obvious in syndromes affecting the ectodermal derivatives such as ectodermal dysplasias. The development of supernumerary teeth is also associated with some syndromes, for example adenomatous polyposis coli (APC) and cleidocranial dysplasia (Jensen and Kreiborg, 1990; Wolf et al., 1986). *RUNX2* gene mutations are responsible for cleidocranial dysplasia, and APC gene mutations are responsible for familial adenomatous polyposis (FAP) (Jarvinen and Peltomaki, 2004; Mundlos et al., 1997). Expression of both genes is required for normal tooth development (Aberg et al., 2004; Otto et al., 1997). Another syndromic cleft associated with supernumerary teeth is Papillon–Léage–Psaume syndrome, which results from mutations in the *CXORF5* gene that are dominant and limited to women, as they are lethal in heterozygous men (Macca and Franco, 2009). In orofaciodigital syndrome type 2 (OFD2), malposition of teeth and supernumerary canines as well as hypoplastic lateral maxillary incisors are found in about 20% of patients and are thought to be associated with the abnormal frenula (Romero et al., 2007; Feather et al., 1997).

5.3.5.4 Supernumerary teeth in Van der Woude and blepharocheilodontic syndromes

Although individuals with VWS present with some dental anomalies such as hypodontia, hypoplasia and dental malformations, the presence of supernumerary teeth in such individuals is very rare. The most common dental anomaly is hypodontia, which is seen in 10–81% of all VWS cases (Lam et al., 2010; Möhrenschlager et al., 1998). In the dental literature, a single VWS case has been reported with a supernumerary mandibular incisor (Goswami, 2017). In addition, a study on *IRF6* mutant mice by Chu et al. (2016) reported that 2 out of 20 mice had supernumerary teeth, one an extra mandibular incisor and the other as mesiodens.

Regarding BCD syndrome, among all reported cases, none have directly mentioned supernumerary teeth. The most common dental anomalies reported were oligodontia and conical teeth in both

primary and permanent dentitions (Ababneh et al., 2014; Gorlin et al., 1996; Gorlin and Wiedemann, 1996). However, in their case report, Adeboye et al. (2009) claimed that the dental history of the presented patient included extraction of supernumerary teeth in the line of the cleft palate (Adeboye et al., 2009).

5.4 Facial growth

5.4.1 Facial growth in the general population

Growth of the face is a gradual maturational process that takes several years and requires different changes in regional proportions and relationships of various parts of the facial skeleton. An understanding of the mechanisms of growth and development of the face is necessary for dentistry, particularly in orthodontics. Facial growth is considered a differential process in which some parts of the facial skeleton grow more or less than other parts. This growth can occur in different directions (Enlow and Dale, 1989).

Most of the longitudinal studies carried out to understand facial growth focused on the changes from 5–18 years of age, and the observations from these studies have led to a significant understanding of facial growth from infancy to adulthood. Most studies were carried out using lateral and posterior–anterior cephalometric radiographs, with the Bolton study and Fels study using lateral cephalograms in infants (Bishara, 2000; Hans et al., 1994; Hunter et al., 1993; Lewis et al., 1985; Adams, 1972).

In the prenatal stage, the formation of the face starts around day 24 in utero when the maxillary and mandibular processes can first be identified. Later, around day 38, the maxillary and mandibular processes fuse and complete the face outlines (Nanci, 2017). At about day 90 of intrauterine life, the head takes up almost half of the total body length, and the cranium comprises more than half of the total volume of the head. However, after birth, the limbs and trunk grow faster than the head and face such that the proportion of the head to the entire body decreases to about 30%.

The head of a newborn infant, compared to that of an adult, shows a significantly larger cranium and smaller face. The face of the young child or an infant is characterised by a round and wide appearance because horizontal/lateral facial growth occurs earlier than vertical growth. The profile view of a baby's face appears to be flat as the nose is small relative to the broad face. The upright and bulbous forehead can be seen because forward growth of the face has not yet occurred. At this stage, the mandibular ramus is short because it is linked with the maturing of the nasal and dental

regions. The body keeps growing throughout childhood and adolescence, and dental and other oral components approach approximately adult sizes (Enlow and Hans, 1996). The mandible also tends to grow more than the maxilla, and the face shows a pubertal growth (Nanda, 1955). The growth of the face continues from late adolescence to adulthood (West and McNamara, 1999). This growth, as described by Hellman (1932), is greatest in the anteroposterior direction between the ages 3–22, while being less in the vertical direction and least in the transverse dimension.

5.4.2 Facial growth patterns

It has been thoroughly documented that facial growth can be categorised into horizontal and vertical growth patterns (Creekmore, 1967; Schudy, 1964; Scott, 1958). Schudy (1964) investigated the interaction between these patterns and described horizontal and vertical growth as opposing forces, with the final vector of the face a result of the combined effects of these components. The term 'facial divergence' was used by Schudy to describe facial types based on several indicators (Schudy, 1964), and was then divided into 'hyperdivergent' and 'hypodivergent' subtypes. Other terms, including high and low angle or long or short, were also used to describe the degree of facial divergence and different vertical facial types. Individuals with a vertical growth pattern have short posterior and long anterior facial heights, a high mandibular plane angle and a tendency to open bite. Individuals with a horizontal growth pattern may present with long posterior and short anterior facial heights, a low angle of the mandibular plane and a tendency to deep bite. A longitudinal study by Popovich and Thompson (1977) analysed the records of 120 males and 90 females to assess the cephalometric changes during different intervals between the ages of 4–20. Based on the growth direction they identified, observations were divided into vertical, horizontal and average growth patterns to be used as a practical analysis approach to craniofacial growth.

5.4.3 Facial growth in individuals with non-syndromic (isolated) orofacial clefts

The facial growth of individuals with clefts (either unoperated or operated) differs from that of those without clefts. Many studies have been checked out to assess facial growth among individuals with unoperated or operated clefts. Almost all of them found some deviations from normal growth. These deviations might be related directly to the primary defect or the result of surgical interventions and the ensuing scarring affecting the growth of the facial bones (Friede and Enemark, 2001; Sandham and Foong, 1997; Capelozza Filho et al., 1996; Tomanová and Müllerová, 1994;

Friede and Morgan, 1976; Bishara and Olin, 1972). The intrinsic factors, iatrogenic factors or functional factors responsible for facial growth are still unclear. This might be related to knowledge of craniofacial growth and development among cleft newborns and infants based on large and well-controlled samples with a long-term follow-up design is very limited. This is because surgical treatment of these defects (clefts) is performed soon after birth, particularly in developed countries; thus, the period to follow the unoperated site is very short, and there are also some methodological problems. In contrast, in developing countries, unoperated individuals with clefts can be found and followed where surgery is not readily available, but such studies lack a local matched group for comparison, affecting the validity of the results (Mars, 1993). The main deviations in the embryonic development of the non-syndromic (isolated) cleft palate are both maxilla and mandible presenting with retrognathia, reduced length of the posterior height of the maxilla and increase in width of the maxilla nasal cavity. However, the relationship between the jaws in the sagittal view is normal. The dimensions of the upper airway are reduced. Unoperated children, as well as adults, may also exhibit bimaxillary retrognathia and a short mandible (Bishara, 1973; Dahl, 1970). The scar from surgical repair of the cleft can affect the long-term growth of the orofacial complex, particularly the maxilla, resulting in skeletal jaw disharmony. Subsequently, aesthetic as well as functional problems will occur that are complex to treat and can be a challenge for the patient, the family and the clinicians involved as well as the surrounding society. Effective cooperation between well-trained specialists is necessary to approach such cases. Maxillofacial surgeon, a plastic surgeon, an otolaryngologist, a speech therapist, a psychologist and an orthodontist are all necessary members of the cleft team (Mossey and Little, 2009).

5.4.4 Facial growth in syndromic orofacial clefting

Facial growth in individuals with orofacial cleft syndromes differs from syndrome to syndrome, with each syndrome having its own specific characteristics and anomalies. Furthermore, it is difficult to longitudinally follow craniofacial growth in all syndromes as some syndromes are very rare and others have life-threatening effects which result in the death of the syndromic individuals at an early age. In general, facial growth in syndromic individuals with a cleft is different from that in normal individuals. Many syndromes are associated with cleft palate; in this section, I will present a short review of the most common findings associated with some well-known syndromes. In individuals with 22q11.2 deletion syndrome, the face appears asymmetric and long with hypotonic muscles and microcephaly (Wu et al., 2013; Nugent et al., 2010; Toka et al., 2010). Other craniofacial features include a short cranial base, large cranial base angle, micrognathia,

retrognathia, steep mandibular plane angle, retruded chin, retruded mandible and open bite (Lewyllie et al., 2017; Oberoi et al., 2011). Furthermore, function impairment may result from craniospinal growth disorders (Leveau-Geffroy et al., 2011). An orofacial cleft is common in individuals with EEC syndrome (Roelfsema and Cobben, 1996; Buss et al., 1995). Hypoplasia can also be seen in zygomatic, maxillary and mandibular bones. Those individuals may also present with microcephaly and premaxilla protrusion (Roelfsema and Cobben, 1996). Individuals with Pierre Robin sequence have a variable morphology and position of the mandible depending on the type of associated syndrome (Rogers et al., 2009). However, smaller mandibular length, a higher ratio between ramus height and mandibular body and higher gonial angle are common findings (Boyce et al., 2012; Suri et al., 2010).

5.4.5 Facial growth in Van der Woude Syndrome

Comparative studies that assessed craniofacial growth in VWS individuals revealed deficient growth of the maxilla compared with matched controls (Heliövaara et al., 2015; Oberoi and Vargervik, 2005; Kane et al., 2002). These studies included patients of different ages and with different cleft types. In a longitudinal study by Kane et al. (2002), a total of 17 cephalometric radiographs of individuals with VWS were compared with controls at different ages. The authors found that the anteroposterior length of the maxilla was shorter in the oldest VWS individuals. Longitudinal analysis of the growth showed that the B point was in a more inferior vertical position in the control groups. Measurements of the soft tissue in VWS individuals revealed that the lower lip had significantly greater protrusion over several age periods. In a study by Oberoi and Vargervik (2005), 15 VWS individuals (aged 9–10) were matched with 15 non-syndromic individuals with cleft lip and/or palate. More hypoplasia in the maxilla, particularly in the more severe cleft types, was observed in the VWS individuals. In addition, a smaller jaw relationship in the sagittal view and steeper mandibular plane angles were found in the VWS individuals compared to the matched groups. At 6 years of age, as the children still have almost all deciduous teeth, the craniofacial morphology of VWS individuals is similar to non-syndromic individuals with cleft palate (Heliövaara et al., 2015). However, with increasing age, the high number of congenitally missing permanent teeth in VWS individuals may contribute to the constriction of dental arches, especially in the maxilla.

5.4.6 Facial growth in blepharocheilodontic syndrome

As BCD syndrome is very rare, there is to date a lack of longitudinal studies that evaluate facial growth in such individuals. Generally, patients with this syndrome have many manifestations, including eye, dental, and limb anomalies. Cleft lip and palate is always found and most often present bilaterally. Dental anomalies include conical teeth, hypodontia or oligodontia and microdontia. Oligodontia may vary from a mild form to anodontia. In mild oligodontia, the missing teeth are usually located adjacent to the cleft of the alveolus (Retna and Sockalingam, 2013; Guion-Almeida et al., 1998). However, in severe oligodontia, all teeth except permanent molars were found to be symmetrically missing (Iida et al., 2006; Guion-Almeida et al., 1998; Martínez et al., 1987). With these craniofacial phenotypes, it is reasonable to suspect associated abnormalities in craniofacial growth.

6. AIMS OF THE STUDY

The dental and craniofacial anomalies of VWS and BCD syndromes are poorly characterised due to both the rarity of cases and difficulties with collecting the patients' materials. The aim of this thesis was to analyse and describe VWS and BCD syndrome phenotypes, including dental and craniofacial anomalies.

The specific aims of this thesis were:

1. To analyse and compare the dental and craniofacial skeletal abnormalities in a cohort of patients with BCD syndrome with age-matched patients born with NSBCLP and age-matched non-cleft controls.

2. To analyse and compare the prevalence, pattern and severity of taurodontic molars in cohort patients born with VWS with age-matched patients born with NSCP and age-matched non-cleft controls.

3. To analyse and compare the dental maturity and anomalies in patients born with VWS with aged-matched patients born with NSCP and age-matched non-cleft controls.

7. SUBJECTS, MATERIALS AND METHODS

7.1 Ethical issues

Ethical approval for conducting the research was obtained from the Ethics Committee of Helsinki and the Uusimaa Hospital District, which approved the protocol of the studies. The ethical permission number for study I was DOC10092014135002 and the ethical permission number for studies II and III was HUS/358/2018. Every participant in the BCD syndrome study and/or their parents were given written information describing the research plan and signed a consent form for participation in study.

7.2. Subjects

All the patients included in studies I–III of this thesis were treated at the Cleft Palate and Craniofacial Centre (HUSUKE) of the Helsinki University Hospital in Finland. The research was conducted at HUSUKE and at the Faculty of Medicine of the University of Helsinki. There was a research collaboration with the Karolinska Institute of Sweden for studies II and III.

In **study I**, 44 patients were analysed: 4 BCD syndrome patients from two families (see the pedigrees of the families in Figure 13), 20 NSBCLP patients and 20 non-cleft individual controls selected randomly (all radiographs were taken at the age of 8 years).

Our criteria were as follows: include all patients in the syndrome group that had BCD syndrome only. In the non-syndromic cleft group, include only bilateral cleft lip and palate. Select only radiographs that were taken at the age of 8 years and were of good quality. Bad quality radiographs resulted in the patient being excluded, as were patients in the non-syndromic cleft group diagnosed with another cleft type in addition to the bilateral cleft lip and palate.

Dental panoramic tomographs (DPTs) of the NSCP group in study II and III and cephalometric radiographs of the NSBCLP group in study I were randomly selected from patients age-matched with syndrome groups in each study and collected from the cleft centre archive using ‘Pick Me!’ the free random selection program (By Donation Coder forum, 2009). The non-cleft groups in studies I-III were from the normative Finnish database. This collection consists of DPTs and cephalometric radiographs taken of 1,017 children between 2–19 years of age. The material was collected from children's schools in Helsinki, Finland (Haavikko and Helle, 1974).

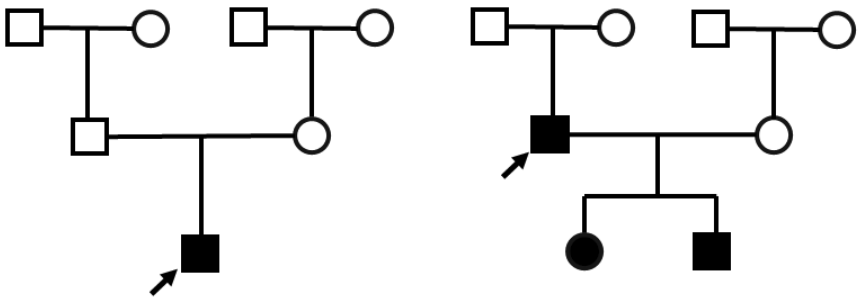

Figure 13: Pedigrees of the families. Arrow indicates proband. Figure is reproduced with permission from Wiley Periodicals, Inc (Awadh W et al., 2017).

In **studies II and III**, 204 children were analysed, 86 male and 118 female, consisting of 51 VWS patients (age 8.17 ±1.34 years), 51 NSCP patients (age 8.09 ±1.41 years) and 102 non-cleft controls (age 8.62 ±1.24 years). The NSCP and VWS groups had the same subtypes of cleft palate (70.5% cleft of the hard palate, 13.7% cleft of the soft palate and 15.6% cleft of the submucous palate).

Our criteria were the following: include all patients in the syndrome group with VWS with cleft palate only. Include patients with cleft palate only in the non-syndromic group. Select only the DPTs of patients between the ages of 6–10 years with good quality radiographs. Exclude bad quality radiographs and patients with another cleft type with the cleft palate or another syndrome with VWS. A specific exclusion criteria applied in **study II** was if any patient had half of the roots not developed, one or more first permanent molars had been extracted or a large restoration had been performed.

In **study II**, after these specific exclusion criteria were applied, the remaining sample pool consisted of 178 DPTs from 105 girls and 73 boys. There were 42 DPTs from individuals with VWS (age 8.55 ±1.02 years), 42 DPTs from individuals with NSCP (age 8.59 ±1.02 years) and 94 DPTs from non-cleft controls (age 8.79 ±1.16 years).

7.3. Methods

7.3.1 Craniofacial analysis of blepharocheilodontic syndrome patients

In **study I**, we analysed lateral cephalogram radiographs of the BCD syndrome patients. We considered the following parameters: SNA, SNB, ANB, Frankfort horizontal line (FH) angle–mandibular line, SN-mandibular line, gonial angle and percentages of the anterior facial height (ANS-ME and N-ME). We used Dolphin Imaging software version 11.7 (Dolphin Imaging and Management Solutions). Only the angles and percentages were measured due to the differences in radiographic magnification.

7.3.2 Dental features analysis of blepharocheilodontic syndrome patients

Study models, clinical photographs and DPTs were used to describe the pattern of dental agenesis and other dental morphology as well as eruption of the primary and permanent teeth. The third molars were excluded from our analysis of all studied groups as our patients were too young during the period of study to allow evaluation of their third molars.

7.3.3 Taurodontism prevalence pattern and severity

In **study II**, both the prevalence and severity of taurodontism in the first permanent molars were evaluated. We used 'measurement 3' from the taurodontism index as described by Shifman and Chananel (1978) and modified by Tulensalo et al. (1989). Tracing paper and a 0.5 mm pencil were used to draw the tooth outlines on the radiographs. The gender, age and group were blinded during the examination.

The tooth was classified as a non-taurodontic molar if the the distance between the connecting line of the cemento-enamel junctions and the highest point of the pulp chamber floor was less than 3.5 mm. The tooth was classified as hypotaurodontic if the distance was 3.5–5.0 mm, as mesotaurodontic if the distance 5.5–7.0 mm and as hypertaurodontic if the distance was >7.5 mm (Tulensalo et al., 1989). The second permanent molars were not included in this study because they were still immature in our patients. We calculated the prevalence of taurodontism in each first permanent molar.

7.3.4 Tooth agenesis and prevalence of peg-shaped teeth

In **study III**, we analyse the prevalence of missing teeth and crown anomalies by diagnosing the DPTs (excluding the third molars). A tooth was diagnosed as congenitally missing when there was no mineralisation visible in the expected area. The patterns of missing teeth were registered in each group. Peg-shaped incisor teeth were identified on a panoramic radiograph when the mesiodistal width of the incisal edge of the tooth was smaller than the cervical width.

7.3.5 Dental age assesment

In **study III,** we analysed DPTs by evaluating the developmental stages of the seven left mandibular teeth, excluding third molars, matching each tooth to one of the eight developmental stages using the Demirjian method (Demirjian et al., 1973). The sum of the weighted scores of Finnish girls or boys, specifically for left mandibular teeth as described by Chaillet et al. (2004), were measured. Then, using the Finnish references values, we converted the dental maturity scores to DA. The difference between dental age (DA) and chronological age (CA) was calculated (Chaillet et al., 2004). In the case of an unclear tooth in the x-ray or unilateral missing tooth the contralateral tooth was used. If the teeth were missing bilaterally we used a specific mathematical formula suggested by Nyström et al. (2000).

7.4 Statistics

The statistical software SPSS was used (version 22.0, SPSS Inc., Chicago IL, USA). In **study I**, one-way ANOVA was used to analyse the statistical significance of craniofacial skeletal abnormalities between patients born with BCD syndrome, patients born with NSBCLP and non-cleft controls. For the reliability test, we re-digitised SNA, SNB and ANB angles of the 24 cephalograms twice (4 cephalograms from the BCD syndrome group, 10 cephalograms from the NSBCLP group and 10 cephalograms from the normal children group). The interval period was 2 weeks between two measurements. An intra-class correlation test (ICC) and 95% confidence interval (95% CI) were used. To indicate significant difference we considered $p < 0.05$ as the significant *p*-value.

In **studies II and III**, one-way ANOVA tests were used to analyse the statistical significance of DA/CA differences and taurodontism severity between the VWS and NSCP groups compared to the non-cleft reference control group. The regression test was used to analyse the interaction between groups and between genders. The prevalence of taurodontism was analysed by the Fisher test. The prevalence of tooth agenesis and morphological anomalies were described as a percentage and the interaction between groups and between genders was analysed using logistic regression. For the repeatability test, a total of 45 DPTs, 15 from each group, were reanalysed twice. The interval period between the two measurements was two days. The dental stages were revaluated again in the selected subject using the same method as the first measurement. An intra-class correlation test (ICC) and 95% confidence interval (95% CI) were used.

8. RESULTS

Study I.

8.1 Craniofacial analysis of blepharocheilodontic syndrome

BCD syndrome patients showed reduced vertical dimension of both angles, the mandibular line–FH angle and mandibular line–SN plane angle, compared to patients with NSBCLP and normal individuals. The anterior lower facial height in BCD syndrome patients was significantly reduced compared to normal individuals ($p = 0.027$). This reduction was compatible with both reduced angles (Figure 14).

The ANB angle, as representative of the anterior-posterior dimension, was significantly smaller in BCD syndrome patients than in NSBCLP ($p = 0.001$) and healthy individuals. Moreover, the SNA angles were clearly smaller in BCD syndrome patients compared to both NSBCLP patients and normal individuals, and the SNB angles were clearly larger in BCD syndrome patients compared to NSBCLP patients, but these differences were not significant (Figure 14). The mean superimposition of the cephalometrics of BCD syndrome patients and NSBCLP patients showed these differences. In BCD syndrome patients, the occlusal and mandibular lines (ML) are more horizontal than in control NSBCLP patients (mean SN/ML angle 31.2° in BCDS patients compared to 36.3° in controls). The maxilla is more retrognathic in BCD syndrome patients than NSBCLP patients (mean SNA is 78.3° BCDS patients and 81.8° in controls). The mandible is more prominent in BCD syndrome patients than NSBCLP patients (the mean SNB angle is 77.8° in BCDS patients and 73.4° in controls). In profile, BCD syndrome patients had more retrusive and shorter upper lip and prominent chin point than control NSBCLP patients (Figure 14).

Inter-observer repeatability by ICC and 95% CI agreement was excellent. ICC and 95% CI of SNA were 0.995 (0.989, 0.998), for SNB 0.995 (0.989, 0.998) and for ANB 0.996 (0.990, 0.998).

Taken together, BCD syndrome patients showed very severe skeletal III malocclusion with reduced anterior face height.

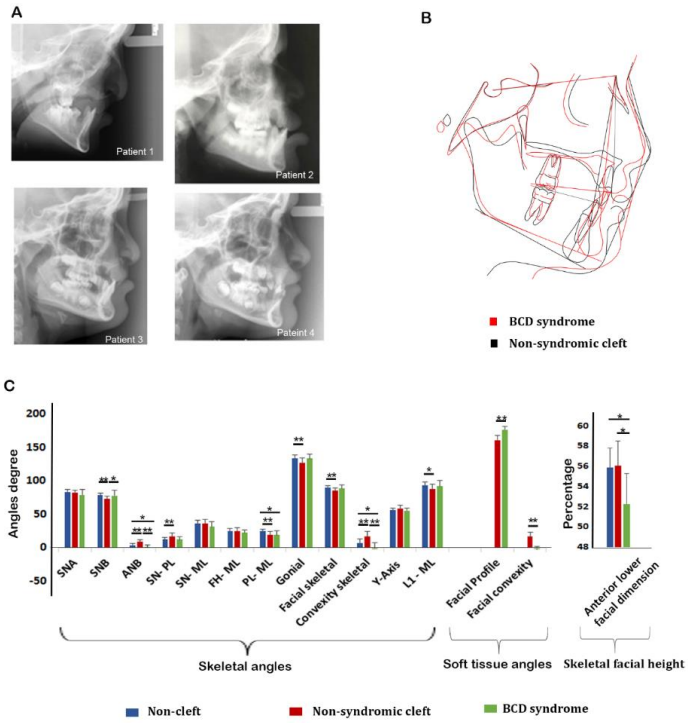

Figure 14: Craniofacial analysis.
(A) Cephalometric radiographs of BCD syndrome patients at 8 years.
(B) Mean cephalometric analyses of BCD syndrome patients (red) and NSBCLP patients (black) superimposed on the S-Nasion line (SN). In BCD syndrome patients the occlusal and mandibular lines (ML) were more horizontal, the maxilla was more retrognathic and the mandible was more prognathic, compared to NSBCLP patients.
(C) Comparison of the cephalometric analysis between BCD syndrome patients (green), NSBCLP patients (red) and non-cleft children (blue). The ANB angle of BCD syndrome patients was significantly reduced compared to NSBCLP and non-cleft controls. BCD syndrome patients have shown decreased anterior lower face height compared to controls. * $p < 0.05$; ** $p < 0.00$. Figure is reproduced with permission from Wiley Periodicals, Inc. (Awadh W et al., 2017).

8.2 Dental features of blepharocheilodontic syndrome

Abnormalities in oral and dental morphology were seen in all four BCD syndrome patients, including severe oligodontia. The mean prevelance of missing permanent teeth in the BCD patients was 13.7 ±4.7. The most common missing permanent teeth in the maxilla were 14, 13, 12, 11, 21, 22, 23, 24 and 25. The most common missing permanent teeth in the mandible were 33, 34, 43 and 44. Abnormalities in tooth forms were found in all BCD syndrome patients, including notched

teeth, conical teeth, taurodontic molars and grooved teeth. Other dental variations included anterior and lateral crossbite and enamel hypoplasia (Figure 15).

In summary, all individuals with BCD syndrome exhibited severe dental abnormalities, including tooth agenesis of upper central incisor teeth and upper and lower canine teeth, which were a highly resistant to agenesis.

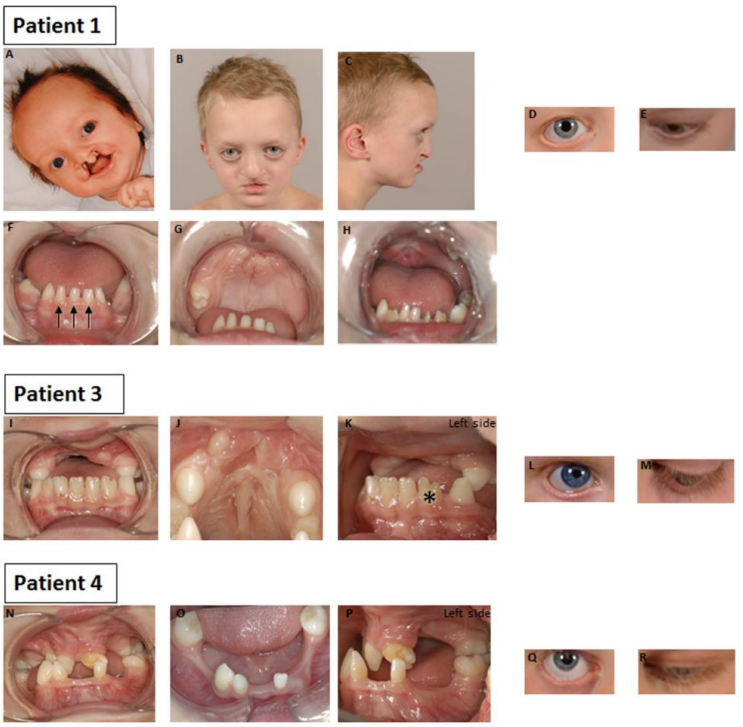

Figure 15: Dental and facial photographs of BCD syndrome patients.
(A–H) Patient number 1. (A–E) Facial photographs, (A) at 6 months, (B–E) at 8 years of age exhibiting retrognathic maxilla, bilateral cleft lip and palate, distichiasis of the upper and lower eyelashes and ectropion of the lower eyelids. (F–H) Intraoral photographs at 5 years (F, G) and at 8 years (H) showing severe oligodontia, notched permanent teeth and conical primary teeth (arrows). (I–M) Patient number 3. (I–K) Photographs taken intraorally at 13 years showing severe oligodontia, notched lower permanent incisor teeth and the repaired cleft alveolus and palate (asterisk showed the notched incisor), (L, M) eye photographs at 8 years showing distichiasis of the upper eyelashes and ectropion of the lower eyelids. (N–R) Patient number 4. (N–P) Photographs taken intraorally (N, O) at 8 years and (P) at 10 years showing severe oligodontia, conical teeth and anterior and bilateral buccal crossbites, (Q, R) eye photographs at 8 years showing ectropion of the lower eyelids and distichiasis of the upper eyelashes. Figure is reproduced with permission from Wiley Periodicals, Inc (Awadh W et al., 2017).

Study II.

8.3 Prevalence of taurodontism in Van der Woude Syndrome

The prevalence of taurodontism in the first permanent molars was significantly higher in both VWS (59.5%) and NSCP (45.2%) individuals compared to non-cleft controls (26.6 %); the *p*-values for each tooth are given in (Table 7, Figure 16). The prevalence of taurodontism was not significantly different between the VWS and NSCP groups. The VWS group had a 4.06 times higher probability of having taurodontism than the non-cleft group ($p = 0.000$). The NSCP group had a 2.28 times higher probability of having taurodontism than the non-cleft group ($p = 0.030$). There was no significant difference between the genders ($p = 0.595$) (Table 8).

In VWS patients, the permanent mandibular left first molars (50%) were most commonly affected by taurodontism, followed by the permanent maxillary first molars (42.9%) and the permanent mandibular right first molars (40.5%).

In NSCP patients, the permanent mandibular left first molars (38.1%) showed the highest prevalence of taurodontism, followed by the permanent maxillary first molars and the permanent mandibular right first molars at the same level (31%).

In non-cleft individuals, the permanent maxillary left first molars (22.3%) showed the highest prevalence of taurodontism, followed sequentially by the permanent maxillary right first molars (17%), the permanent mandibular right first molars (9.6%) and the permanent mandibular left first molars (7.4%) (Table 7 and Figure 17).

8.4 Severity of taurodontism in Van der Woude Syndrome

The non-cleft control group displayed less severe taurodontism in all first maxillary and mandibular permanent molars compared to both the VWS and NSCP groups (Table 9). There was no difference between VWS and NSCP groups in severity for each of the first permanent molars (Table 10). The taurodontic molars from all groups were hypotaurodontic, with four exceptions that were mesotaurodontic.

Inter-observer repeatability as quantified by Cohen's kappa was excellent for all molars, with a range of kappa values from 0.81–0.93.

In summary, VWS and NSCP individuals displayed a high incidence of taurodontism compared to non-cleft controls. Taurodontic molars in VWS individuals were hypotaurodontic, and most occurred bilaterally.

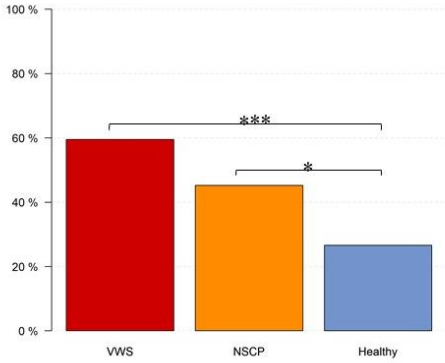

Figure 16: Taurodontism prevalence comparisons between groups. Figure is reproduced with permission from Oxford University Press (Awadh W et al., 2020)

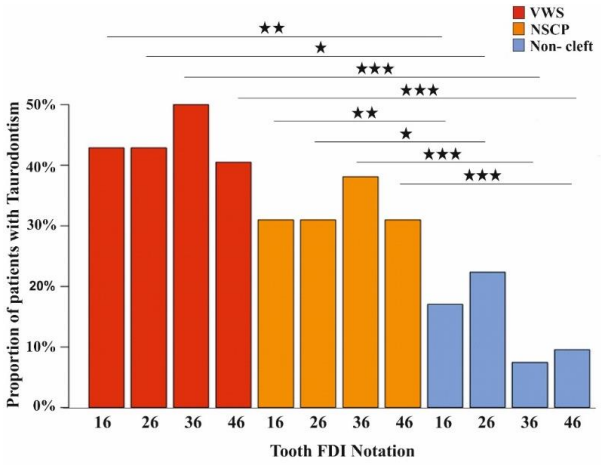

Figure 17: Taurodontism prevalence comparisons between groups for each tooth studied.
* $p < 0.05$ - ** $p < 0.01$ - *** $p < 0.001$. Figure is reproduced with permission from Oxford University Press (Awadh W et al., 2020)

Table 7: Taurodontism prevalence comparisons between groups in each tooth studied. Table is reproduced with permission from Oxford University Press (Awadh W et al., 2020)

Tooth FDI Notation	**Non-cleft (Ref.) (n= 94) n (%)**	**VWS (n = 42) n (%)**	**NSCP (n = 42) n (%)**	***p*-value**		**Test**
16	16 (17.0)	18 (42.9)	13 (31.0)	0.005	**	Fishers
26	21 (22.3)	18 (42.9)	13 (31.0)	0.050	*	Fishers
36	7 (7.4)	21 (50.0)	16 (38.1)	<0.001	***	Fishers
46	9 (9.6)	17 (40.5)	13 (31.0)	<0.001	***	Fishers

n = patient sample size

Table 8: Taurodontism prevalence comparisons using univariable logistic regression between groups and genders in each tooth studied. Table is reproduced with permission from Oxford University Press (Awadh W et al., 2020)

Source	**Odds ratio**	**Lower 95% CI**	**Upper 95% CI**	***p*-value**
Group				
Non- cleft (Ref.)				
VWS	4.06	1.90	8.89	0.000***
NSCP	2.28	1.06	4.90	0.034*
VWS (Ref.)				
NSCP	1.81	0.90	3.62	0.186
Gender				
Female (Ref.)				
Male	1.18	0.64	2.18	0.595

* $p < 0.05$ - ** $p < 0.01$ - *** $p < 0.001$.

Table 9: Comparison of the severity of taurodontism between groups. Table is reproduced with permission from Oxford University Press (Awadh W et al., 2020)

FDI Tooth Notation		Severity of Taurodontism	Non- cleft (n= 94) (Ref.)	VWS (n= 42)	NSCP (n= 42)	Total (n= 178)	p-value	test
16	Mean (SD) mm		2.63(0.72)	3.17 (0.76)	2.98 (0.85)		<0.001 ***	t-test
	n (%)	Hypo	16 (17)	18 (42.9)	13 (31)	47 (26.4)		
		Meso	-	-	-	-		
		Hyper	-	-	-	-		
26	Mean (SD) mm		2.74 (0.71)	3.11 (0.84)	3.02 (0.93)		0.024 *	t-test
	n (%)	Hypo	21 (22.3)	18 (42.9)	13 (31.0)	52(29.2)		
		Meso	-	-	-	-		
		Hyper	-	-	-	-		
36	Mean (SD) mm		2.59 (0.52)	3.32 (0.97)	3.31 (1.02)		<0.001 ***	t-test
	n (%)	Hypo	7 (7.4)	21 (50.0)	15 (15.9)	43 (24.1)		
		Meso	-	-	1(1)	1(0.5)		
		Hyper	-	-	-	-		
46	Mean (SD) mm		2.63 (0.57)	3.29 (0.92)	3.24 (0.96)		<0.001 ***	t-test
	n (%)	Hypo	9 (9.6)	16 (38)	11(11.7)	36 (20.2)		
		Meso	-	1 (2.3)	2(2.1)	3 (1.6)		
		Hyper	-	-	-	-		

*P < 0.05. **P < 0.01. ***P < 0.001. n, sample size; SD, standard deviation

Table 10: Comparison of the severity of taurodontism between VWS and NSCP. Table is reproduced with permission from Oxford University Press (Awadh W et al., 2020)

Tooth FDI Notation	VWS (n= 42) mm	NSCP (n= 42) mm	p-value	test

16	Mean (SD)	3.17 (0.76)	2.98 (0.85)	0.762	t-test
26	Mean (SD)	3.11 (0.84)	3.02 (0.93)	0.951	t-test
36	Mean (SD)	3.32 (0.97)	3.31 (1.02)	0.966	t-test
46	Mean (SD)	3.29 (0.92)	3.24 (0.96)	0.960	t-test

Study III.

8.5 Dental age compared to chronological age

The DA and CA difference in the non-cleft group was significantly higher than in both the VWS and NSCP groups ($p = 0.001$). However, there was no significant difference between the VWS and NSCP groups ($p = 0.885$) (Table 11 and Figure 18a). The difference between DA and CA in the non-cleft group was overestimated for both younger and older children, while the difference between DA and CA was overestimated for younger children and underestimated for older children in the NSCP and VWS groups. No significant difference was found between the sexes ($p = 0.074$) (Table 11 and Figure 18b).

Table 11: Differences between DA and CA between groups and sexes. Table is reproduced with permission from Oxford University Press (Awadh W et al., 2021)

	Estimate	Std. Error	*p*-value
VWS- Non cleft	0.346	0.087	0.001 ***
NSCP- Non cleft	0.392	0.088	0.001 ***
VWS - NSCP	0.047	0.100	0.885
Female- Male	0.13	0.07	0.074

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

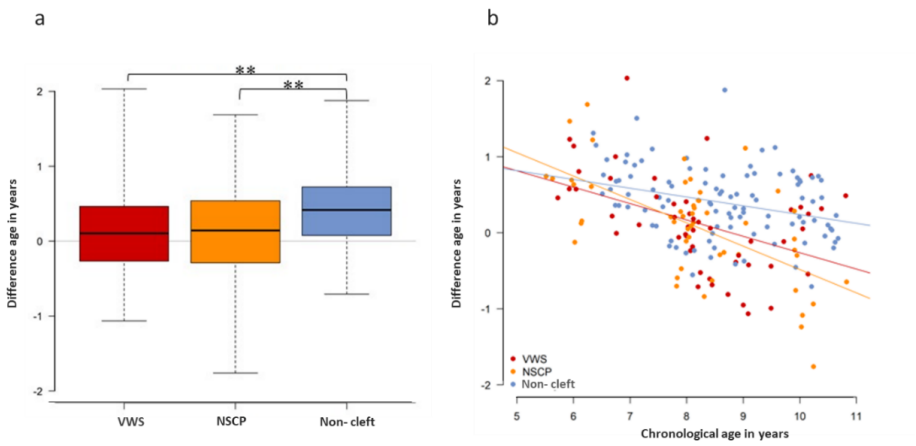

Figure 18 : (a) Differences of dental (DA) age and chronological age (CA) between groups (b) Relationship between CA and DA for individuals in each group. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. Figure is reproduced with permission from Oxford University Press (Awadh W et al., 2021)

8.6 Tooth agenesis and crown morphology of Van der Woude Syndrome

The prevalence of tooth agenesis in the non-cleft group (5.88%) was significantly lower than in both the VWS (37.25%) and NSCP (19.6%) groups, excluding the 3rd molars (Table 12 and 13). VWS patients had a 9.5 times higher probability of having tooth agenesis than the non-cleft control group ($p < 0.001$). NSCP patients had an almost 4 times higher probability of having tooth agenesis than inidividuals in the non-cleft group ($p = 0.035$). There was no significant difference between genders ($p = 0.161$) (Table 13).

In VWS patients, the missing permanent teeth were 15, 14, 12, 22, 24, 25, 35, 42 and 45. The missing permanent teeth in NSCP patients were 15, 12, 22, 25, 42 and 45. The missing permanent teeth in the non-cleft control group were 15, 12, 22, 35 and 45 (Figure 19). The most prevalent missing teeth in VWS patients were the maxillary and mandibular permanent second premolars and the maxillary permanent lateral incisors. Tooth agenesis was found more often in the maxilla than in mandible in both NSCP and VWS patients. In VWS patients, peg-shaped teeth were found in 13.7% of patients and occurred mostly in the maxillary permanent lateral incisors on both sides (Table 12). Inter-observer repeatability as measured by ICC and 95% CI agreement was excellent, with ICC = 0.98 (0.97–0.99).

In summary, the incidence of hypodontia in VWS and NSCP individuals was high. The probability of having hypodontia in the VWS group was approximately double compared to that in the NSCP group. A high incidence of peg-shaped teeth was also noted in individuals with VWS.

Table 12: Tooth agenesis and peg shape crown prevalence per patient in VWS, NSCP and non-cleft control groups. Table is reproduced with permission from Oxford University Press (Awadh W et al., 2021)

		VWS (n = 51)	NSCP (n = 51)	Non-cleft (n = 102)
Tooth agenesis	Male n (%)	6 (11.7%)	4 (7.84%)	1 (0.98%)
	Female n (%)	13 (25.5%)	6 (11.76%)	5 (4.9%)
	Prevalence per patients n (%)	19 (37.25%)	10 (19.6%)	6 (5.88%)
Peg shape crown	Prevalence per patients n (%)	7 (13.7%)	0	0

n = patient sample size

Table 13: Tooth agenesis prevalence between groups and genders using logistic regression test. Table is reproduced with permission from Oxford University Press (Awadh W et al., 2021)

	Estimate	Std. Error	*p*-value	Odds ratio
VWS - Non cleft	2.25	0.51	0.001 ***	9.50
NSCP - Non cleft	1.36	0.55	0.035 *	3.90
VWS - NSCP	-0.89	0.46	0.124	0.41
Female - Male	0.55	0.4	0.161	1.74

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

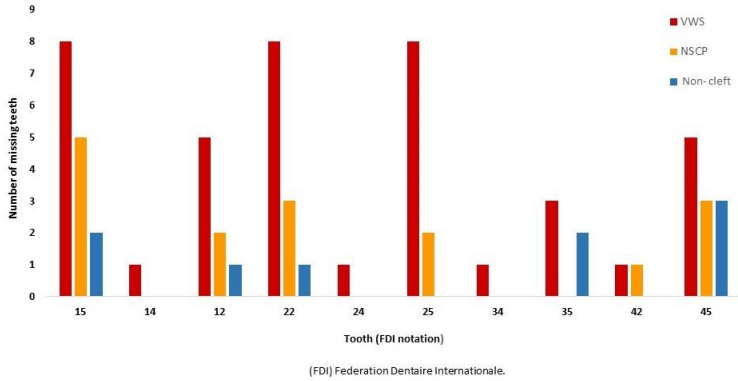

Figure 19: Tooth agenesis prevalence per tooth in all groups. Figure is reproduced with permission from Oxford University Press (Awadh W et al., 2021)

9. Discussion

The etiology of cleft lip and palate is associated with both environmental and genetic factors, with several known causative genes having been discovered (Dixon et al., 2011). Contibutary environmental factors include cigarette smoking (Little et al., 2004), folic acid deficiency during the periconceptional period (Wilcox et al., 2007), maternal alcohol exposure, and teratogenic medications such as retinoids and corticosteroids (Eppley et al., 2005). Orofacial clefts have also been linked to obesity and maternal diabetes.

Studies have reported that cleft lip and/or palate is associated with major congenital anomalies like congenital heart failure (31.1%), deformation (22.4%) and hydrocephaly (11.2%). (Shprintzen et al., 1985; Watkins et al., 2014; Burg et al., 2016). The majority of cleft lip and/or palate cases are non-syndromic, whereas a significant percentage of these clefts are associated with both syndromic and non-syndromic anomalies.

Many syndromic clefts have a known genetic origin; (Dixon et al., 2011). Meckel syndrome, trisomy 13, Fryns syndrome, Stickler syndrome, Treacher Collins syndrome, Van der Woude Syndrome, velocardiofacial syndrome, Pierre Robin sequence, Kabuki syndrome, and median facial dysplasia are only a few of the chromosomal abnormalities and syndromes that can arise with oral clefts as a central feature (Patil et al., 2014; Kohli and Kohli, 2012; Maarse et al., 2012; Sárközi et al., 2005).

The most common chromosomal syndromic anomaly associated with cleft lip/palate is Van der Woude Syndrome (VWS), which accounts for 2% of CL/P cases (Burdick et al., 1985; Rintala and Ranta, 1981). The primary genetic cause of this aforementioned syndrome is genetic mutations in *IRF6* and *GRHL3* genes (Peyrard-Janvid et al., 2014; Kondo et al., 2002). A featured dental anomaly reported with this disease is a single or bilateral cleft lip or palate with a prominent pit in the lower lip. The maxillary permanent second premolars, mandibular permanent second premolars, and maxillary permanent lateral incisors are the most commonly missing teeth among VWS patients (Rizos and Spyropoulos, 2004).

Blepharocheilodontic (BCD) syndrome is an autosomal dominant condition that occurs due to missense mutation of genes in the E-cadherin gene (*CDH1*) and Catenin delta-1 (*CTNND1*). Bilateral cleft lip and palate is one of the major craniofacial disorders characterized in blepharocheilodontic syndrome (BCD), along with dental anomalies like conical teeth and tooth agenesis (Ghoumid et al. 2017). The craniofacial skeletal pattern has been defined as skeletal class III with a hypoplastic maxilla. However, this is prevalent in most individuals with bilateral CLP

(Guion-Almeida et al., 1998). Another typical trait is severe tooth agenesis, which includes the loss of six or more permanent teeth (oligodontia). It's possible that the incisors develop will be conical in shape (Gorlin et al., 1996; Falace and Hall, 1989). Although orofacial clefting and oligodontia are prominent symptoms, studies reporting this disease's dental and craniofacial characteristics are rare. Hence, this study focused on the dental and craniofacial attributes of BCD syndrome sample.

The dental and craniofacial anomalies associated with Van der Woude Syndrome (VWS) and blepharocheilodontic (BCD) syndromes are poorly characterized due to rare cases reported as well as difficulties encountered while collecting patient's data. This study analyzed and described VWS and BCD syndrome phenotypes and included dental and craniofacial anomalies associated with these syndromes.

9.1.Craniofacial morphology of Blepharocheilodontic syndrome

Records of blepharocheilodontic (BCD) syndrome reveal that more than 30 cases of this disease have been reported worldwide (Iida et al., 2006), yet to date no a systematic cephalometric study of the craniofacial skeleton with age-matched controls has been performed. The paucity of information regarding this disease could be due to the lack of follow-up of patients. From the literature review, it was found that there was no gender predilection related to this syndrome (Iida et al., 2006). However, the pattern of family cases suggested this disease could be of autosomal dominant inheritance (Gil da Silva Lopes et al., 2003).

In **study I**, a group of BCD syndrome patients had a prominent skeletal III phenotype with bilateral posterior crossbite and diminished proportions of the lower anterior face height at 8 years. Delay of dental eruption, oligodontia, or bony structural abnormalities is caused by the decrease in mandibular line–Sella-Nasion line angles, mandibular line–Frankfurt horizontal line angles, percentages of lower facial height, and increase in Sella Nasion B point angles in BCD syndrome patients compared to both non-syndromic bilateral cleft lip and palate (NSBCLP) patients (class III) and healthy individuals. The midface is often in a more anterior position in bilateral cleft lip/palate (BCLP) patients in early childhood, and their ANB angle is also prominent. This is probably because the anterior maxillary segment is still in an advanced position. The distinctive skeletal III phenotype with a retruded maxilla is manifested only after replacing the primary teeth (6–14 years) (Semb, 1991). Other discovered skeletal anomalies were retrognathic maxilla and

large mandibles with the interior inclined horizontal angle.

The pattern of oligodontia may explain some of the skeletal alterations seen in BCD syndrome patients. The lack of upper anterior teeth will affect the A point's anterior-posterior location, causing the skeletal III phenotype to be more prominent. Although it should be noted that the 1st permanent molar teeth had emerged by the time the cephalograms were obtained at the age of 8 years, oligodontia can alter vertical dimensions of facial height as well. Furthermore, the gonial angle (the angle formed by the ramus and the mandible's body) was comparable to that of non-cleft children. Non-syndromic BCLP instances, on the other hand, frequently have an increased gonial angle, a larger anterior vertical facial dimension, and a lower posterior face height (Smahel, 1984; Semb, 1991). There is an inter-relation of the vertical and the sagittal craniofacial dimension. A reduced vertical dimension might result in forwarding positioning of the mandible, and skeletal III features becoming more pronounced. According to literature, adults with non-syndromic BCLP increased lower anterior face height, but upper and lower jaw retrusion is measured relative to the cranial base (Smahel, 1984; Semb, 1996).

These findings have a profound clinical impact. Orthognathic surgery is more complex and time-consuming for cleft individuals with flatter profiles, reduce lower anterior facial heights, and reduce ANB angles. Identifying these patients early in age is important to tailor treatment to enhance therapeutic success while minimizing patient and family distress. Patients who are "at-risk" can be recognized as early as the age of 6 years if their ANB angle is less than seven degrees (Heliövaara et al., 2013). In our study group, patients with BCD syndrome had a mean ANB angle of 0.7 degrees, which indicates a great need for prolonged and lengthy treatment.

9.2. Severity of oligodontia in Blepharocheilodontic syndrome

All patients in the study group of blepharocheilodontic syndrome had oligodontia, and in some cases, it was severe. Tooth agenesis affecting a few teeth (hypodontia) is one of the most prevalent developmental abnormalities in general populations (3–10 percent of the population, excluding third molar teeth). However, oligodontia (the loss of six or more permanent teeth) is uncommon, with an incidence of less than 0.1% (Polder et al., 2004).

The teeth most typically impacted in cleft lip and palate are those in the cleft region (upper permanent lateral incisors); however, tooth agenesis is more common beyond the cleft area than in the general population (Klein et al., 2013). The prevalence of hypodontia is reported to be 10–68%,

depending on the severity of the cleft. The patterns and severity of hypodontia vary depending on the type of clefts. Patients with isolated cleft lips had the least tooth agenesis. In contrast, those with BCLP have the highest (cleft lip 10%, submucous cleft 16%, cleft palate 33%, unilateral cleft lip and palate 49%, bilateral cleft lip and palate 60–68%) (Ranta, 1986; Heliövaara et al., 2004; Bartzela et al., 2010; Bartzela et al., 2013; Klein et al., 2013; Riis et al., 2014). In a study of 240 BCLP patients, 3.8 percent had oligodontia, with upper laterals and upper and lower second premolars being the most often missing teeth. It's also worth noting that patients with isolated cleft lip and some BCLP patients have a significantly higher rate of supernumerary teeth (Riis et al. 2014, Sa et al., 2016).

As almost every case of BCD syndrome is reported during infancy, that is to say, before primary dentition is fully erupted and before the mineralization and eruption of permanent dentition, tooth agenesis may be underreported, and descriptions of oligodontia may be inaccurate. In addition, the degree and pattern of tooth agenesis have received little attention. Despite the patients' often young age and lack of detail in reporting, several cases of severe oligodontia have been recorded, including agenesis in both the primary and permanent dentitions in some cases.

In this study, the number of lost permanent teeth in BCD syndrome patients ranged from 7 to 18, excluding the third molars. All BCD patients were missing upper incisors, canines, and first premolars. Oligodontia is the absence of six or more permanent teeth from birth. The maxillary and mandibular premolars and the maxillary lateral incisors are the most commonly inherited absent teeth. Patients with BCD syndrome have severe oligodontia and do not have enough teeth to use an eight-stage approach (Demirjian et al., 1973) or a twelve-stage system to examine the delay of dental eruption (Haavikko, 1970). Although detailed records are very rare, it would appear that other cases of BCD syndrome show a similar pattern of tooth agenesis (Guion-Almeida et al., 1998; Adeboye et al., 2009).

Tooth agenesis pattern of BCD syndrome patients is unusual. It includes teeth generally resistant to agenesis, such as the upper central incisors and upper and lower canines. Agenesis impacts teeth, not in the cleft area; therefore, it is not only a direct effect of clefting. Moreover, because both teeth and the palate originate through epithelial-mesenchymal interactions throughout development, it is logical that mutations in many genes disrupt both processes. Clefting and tooth agenesis result from fundamental problems in the facial procedures and teeth (Rice et al., 2004; Veistinen et al., 2009). Lopes et al., 2003 proposed the possibility of involvement of p63 and interferon regulatory factor

6 gene that controls the development of the palate, teeth, skin, and other ectodermal organs. However, further research found no involvement of IRF6, which causes Van der Woude Syndrome, nor p63 which causes ectrodactyly ectodermal dysplasia (EEC) syndrome in BCD syndrome patients (Gil da Silva Lopes et al., 2003; Weaver et al. 2010). The negative findings are consistent with the unusual pattern of tooth agenesis seen in BCD syndrome, suggesting that the disease is caused by mutations in a gene that functions differently during craniofacial development.

9.3. Dental structural anomalies in Blepharocheilodontic syndrome

Dental anomalies were reported in all cases of BCD patients examined. The anomalies reported were conically shaped teeth, notching the incisal edge, taurodontism, tooth rotations, minor cusp irregularities, and enamel hypoplasia. Tooth agenesis is typically associated with dental abnormalities, and the more severe of the tooth agenesis, the more dental malformations are likely to arise (Alvesalo and Portin, 1969; Baccetti, 1998; Apajalahti et al., 1999). It is essential to be aware that these anomalies are common in BCD syndrome patients since they might significantly influence treatment planning and prognosis.

The small number of the patient sample group in the BCD syndrome investigation was a major limitation. Furthermore, three of the patients have a first-degree link, which means they share sections of their genome other than the underlying mutation. This may enhance the phenotypic resemblance between them. Nonetheless, because BCD syndrome is a rare condition, we believe that this description of patients' various craniofacial and dental aspects is a valuable record of this condition.

9.4. Taurodontism in Van der Woude Syndrome and non-syndromic cleft palate

Results of **study II** report a high prevalence of taurodontism in both the Van der Woude Syndrome and non-syndromic cleft palate syndrome patients. Nawa et al., 2008 reported the prevalence of taurodontism in 6 patients (46%) out of 13 patients with VWS syndrome. The present study reported a high prevalence of taurodontism (59.5%) in VWS patients. This study documented the pattern of taurodontism, reporting that in VWS patients, maximum taurodontism is present in the first permanent molar and is commonly bilateral. Most studies have observed taurodontism bilaterally in VWS patients (Laatikainen and Ranta, 1996b; Shifman and Chanannel, 1978). However, Seow and Lai, in 1989 found that half of their patients with VWS had unilateral

taurodontism. Almost all of the taurodontic molars in the present study were hypotaurodontic in form. Similar findings were reported by Marques Fernandes et al., 2018 that nearly all VWS patients had hypotaurodontic molar.

45.2% of non-syndromic cleft palate (NSCP) patients in study II displayed taurodontism. Similarly, the survey of a cohort of 224 adult patients with NSCP by Weckwerth et al., 2016 reported a taurodontic frequency in 67.0% of patients with NSCP. This study has also recorded taurodontism in 60.4 % of patients with unilateral cleft lip and palate, 62.4% of patients with unilateral cleft lip, and 42.8% of patients without clefts. The aforementioned study also reported that the upper second permanent molar teeth were the most commonly impacted in the entire cleft group. In a case-control study of 88 NSCP patients, 40.9% exhibited taurodontism compared to 23.3% of the healthy control group. Most teeth in this study were identified in different forms as hypotaurodontism, mesotaurodontism, and then hypertaurodontism (Melo Filho et al., 2015). These variations in the frequency of taurodontism amongst the studies could be attributed to the sample size of the population, age, method to determine taurodontism, and teeth evaluated. A case report by Laatikainen and Ranta, (1996a) reported the prevalence of taurodontism amongst the cases of non-cleft and all cleft types in permanent second molar than in first. As the second molar erupts after the first, the increase in age chances of having taurodontic molar increases. In our study, we only investigated first molars as the age of all the participants was 8 years, and chances of developing a second molar at this age are rare.

In the available literature the influence of gender on taurodontism is contentious. Some studies have reported high prevalence amongst the females (Bronoosh et al., 2012; Sarr et al., 2000), while findings of this study and some other studies argue that there is no significant difference noted between gender (Burklein et al., 2011; Jafarzadeh et al., 2008; Constant and Grine, 2001). However, taurodontism has been related to X-linked hypohidrotic ectodermal dysplasia and an extra X chromosome in the 47, XXY, and 47, XXX karyotypes (Crawford et al., 1991; Varrela et al., 1988).

The method to identify taurodontism used in this study was originally described by Blumberg et al. (1971) and adapted by Shifman and Chanannel (1978) and Tulensalo et al. (1989). The Tulensalo modification accounted for the difference in magnification between DPT and intraoral radiographs. This strategy is reliable in determining the presence of taurodontism in the developing dentition (Tulensalo et al., 1989). However, there are many different methods to record taurodontism (Gupta and Saxena, 2013; Bronoosh et al., 2012; Kan et al., 2010; Calvano Kuchler et al., 2008; Witkop, 1971). These methods measure the crown height to compare the total tooth length ratio. To get

accurate results root of the teeth should be fully developed. Moreover, in the present study, the patient's age was 8 years; hence, to get accurate results, Tulensalo modification was applied.

9.5. Dental maturity in Van der Woude Syndrome and non-syndromic cleft palate

To the best of our knowledge, our **study III** is the only research that has analyzed the dental age of children born with Van der Woude Syndrome. The discrepancy between dental age and chronological age was considerably lower in the VWS and NSCP groups than in the non-cleft control group. In children born with VWS or NSCP, there were no significant differences between dental age and chronological age. In the control cases (non-cleft patients) of this study, it was observed that dental age was advanced when compared with chronological age (0.40years, $P<0.01$). However, delay in maturity of dental and chronological age was reported in VWS and NSCP patients. This finding is in line with other studies that reported delays in maxillary and mandibular teeth development in cleft lip and palate (Almotairy and Pegelow, 2018; Brouwers and Kuijpers-Jagtman, 1991; Ranta, 1986). In the study by Heliövaara and Nyström, 2009, a dental maturity age was made between two different types of cleft. They reported that the dental age of children with a submucous cleft was not delayed, whereas maturity in children with a soft palate cleft was reported a slight delay.

The inclusion criteria of this study were comprehensive in regards to patients with VWS, and NSCP patients with the cleft palate of equal severity subgroups were included. This was considered because a handful of studies have compared and found severity and type of cleft correlate with the delay in tooth development (Hazza'a et al., 2009; Heliövaara and Nyström, 2009). However, some studies have considered isolated cleft concluded dental maturity delaying in cleft patients independent of severity and type (Van Dyck et al., 2019).

Underestimation of dental age was recorded for patients of the older age group. In contrast, the overestimation of dental age maturity was reported for younger age groups in this study group of VWS and NSCP patients. However, an overestimation of dental age was recorded in both young and old patients in the non-cleft group. Several genetic and environmental factors may account for the delay in dental maturity age in VWS and NSCP patients (Jamilian et al., 2015). According to our findings and the method we employed to estimate dental age, the Demirijian approach for predicting dental age by utilizing particular Finnish reference values was more accurate in the VWS and NSCP groups than in the non-cleft group. In the non-cleft population, there is a lot of diversity in each sex when calculating dental age. According to several researches, the Demirjian approach overestimates more for girls than boys (Kirzioglu and Ceyhan, 2012; Willems et al., 2001), whereas

other studies do not conclude the same (Maber et al. 2006). This study resulted in no significant difference in the comparison between dental and chronological age in all age groups. These results were in line with findings of other studies (Heliövaara and Nyström, 2009; de Carvalho Carrara et al., 2004; Ranta, 1986). Our findings reveal that boys in both the non-cleft and NSCP groups, however, had a propensity to overestimate dental age. This contrasts with the results of earlier research, which revealed that Demirjian's technique overestimates dental maturity age in females more than in boys (Kirzioglu and Ceyhan, 2012; Willems et al., 2001). The Demirjian technique for measuring dental age with particular Finnish reference values, as reported by Chaillet et al (2004) and recommended for a dental clinician in the Finnish population, was used to assess dental maturity in this thesis. If teeth are missing bilaterally, the Demirijian technique cannot be employed (Smith, 1991). If teeth were missing bilaterally in this study, we applied a mathematical procedure to determine the developing tooth stage based on the other teeth developmental stages, age, and gender (Nyström et al., 2000).

When developing a treatment protocol, differences in dental maturity must be considered. Assessing dental age aids in determining the best time for orthodontic and orofacial surgical therapy, hence reducing treatment time and expense. A complete understanding of dental development in cleft individuals is essential to make the best judgments. Orthodontists, pediatricians, and forensic dentists all benefit from dental age estimation. In forensic applications, dental age estimation, together with other maturity markers, can be used to estimate the age of children whose birth information is unknown (Van Dyck et al., 2019; Demirjian et al., 1973).

9.6. Tooth agenesis in Van der Woude Syndrome and non-syndromic cleft palate

Hypodontia is considered a classical phenotype amongst the clinical features of the Van der Woude Syndrome (Ranta and Rintala, 1982). Multiple factors have been linked with the development of hypodontia in cleft patients, including genetic and environmental factors, altered mesenchymal differentiation, and the direct effect of the cleft on odontogenesis. Tooth agenesis may contribute to arches atresia, particularly in the maxilla, resulting in dental malocclusion and skeletal discrepancies that may require orthodontic and/or orthopedic surgery (Lam et al., 2010). In both VWS and non-syndromic CL/P, tooth agenesis in the cleft region occurs at a higher incidence rate when compared with non-cleft healthy individuals (Klein et al., 2013; Shapira et al., 1999). **Study III** also recorded the prevalence of agenesis higher in a cohort of VWS patients (37.25%) and non-syndromic cleft lip cohort (19.60%) than in non-cleft (5.88%) group.

In the clinical study by Lam et al. (2010), evaluation of dental agenesis was done by radiographical examination on twenty-two patients with VWS syndrome, reported prevalence of 86% agenesis amongst these patients. The teeth most affected by this phenotype were the upper lateral incisors and second premolar. Similarly, agenesis was mainly noted in the maxillary and mandibular second premolar and maxillary lateral incisors in this study. Moreover, authors of different studies on types of clefts like unilateral cleft lip, bilateral cleft lip, cleft palate, and syndromic cleft palate reported agenesis associated with at least one tooth (Lam et al., 2010; Oberoi and Vargervik, 2005)

A retrospective clinical study conducted by Oberoi and Vargervik, in 2005 reported the prevalence of tooth agenesis of VWS patients with cleft lip/palate 50%. Their studies reported a higher prevalence of this phenotype in mandibular second premolar bilaterally in VWS patients. In contrast, in the control group with non-syndromic cleft lip and palate, there was the predominance of agenesis in the mandibular left second premolar. These studies support the findings of the present study.

In the findings of this study, hypodontia was recorded amongst the patients with VWS. Similarly, another study showed that 50% of VWS patients with cleft lip/palate had hypodontia (Oberoi and Vargervik, 2005). The high prevalence of hypodontia and taurodontism in VWS patients may have a genetic origin, leading to the notion that the disease and these two abnormalities share a genetic mechanism that causes their occurrence. Taurodontism is also an important trait since it might increase the danger of pulpal exposure during restorative operations and the risk of root resorption during orthodontic therapy due to the small size of roots. As a result, it is indispensable for the dental surgeon to be aware of the likelihood of this dental phenotype in VWS patients.

The radiographs' substantial 'drop out' rate in the non-cleft control group was a serious constraint in our taurodontism, dental maturity and tooth agenesis analyses (**studies II and III)**. Additionally, despite the historical periods in which the radiographs were collected overlapped, there were variances across the groups' time spans. The huge sample size of patients with this uncommon condition, collected data with standardized records over 42 years, with control samples gathered from the same population and location with the correct age and gender matching, was a strong point of this research.

9.7. Aetiology of the orofacial abnormalities in Van der Woude Syndrome

Classical features associated with Van der Woude Syndrome are orofacial clefting and hypodontia, and in general there is a strong association of these phenotypes with taurodontism (Arte et al., 2001; Schalk-van der Weide et al., 1993; Seow and Lai, 1989). Moreover, incisor-premolar hypodontia

and oligodontia have been reported in patients with taurodontism (Schalk-van der Weide et al., 1993). Dental maturity is delayed due to environmental and genetic developmental factors (Green, 1961).

IRF6 gene mutations that induce loss of function is one of the important causes of VWS (Kondo et al., 2002). Mutant mice with a homolog of the gene mutated in human VWS that die perinatally show impaired palate development and extensive epithelial abnormalities, including intraoral adhesions, similar to gene mutation observed in VWS patients (Richardson et al., 2006). IRF6 is essential for the appropriate development and function of the periderm. The periderm, or outermost layer of the oral epithelium, plays a vital role in preventing pathological adhesions and modulating palatal adhesion and fusion competence (Hammond et al., 2019). IRF6 mutant mice with hypodontia, a reduction in crown size and altered crown morphology, as well as peg-shaped teeth and severe taurodontism, have a phenotype similar to that seen in VWS patients in **study II and III** and described in previous reports, namely hypodontia, a reduction in crown size and altered crown morphology, as well as peg-shaped teeth and severe taurodontism (Awadh, 2020; Oberoi and Vargervik, 2005; Ranta and Rintala, 1982; Schneider, 1973). In addition, Pitx2; Irf6 mice have supplementary incisors and hypodontia. *IRF6* is expressed in the developing oral/palatal epithelium, dental epithelium, and ameloblasts. It has a definite functional role during palate and tooth morphogenesis and dental hard tissue creation, which may help to explain the many craniofacial phenotypes reported in VWS patients (Chu et al., 2016; Washbourne and Cox, 2006; Knight et al., 2006).

9.8. Strength, weakness, and future research

The main strength of this study is the evaluation of the clinical manifestation of the rare conditions blepharocheilodontic syndrome and Van der Woude Syndrome. Secondly, this study has collected standardized data of over 42 years in VWS patients and helped develop the standardized protocol for diagnosis and treatment for BCD and VWS patients. Finally, appropriate control groups, taken from the same general population and the geographical region as the test sample, are well matched for age and gender. Moreover, this data and protocols can be utilized for further clinical research to provide in-depth knowledge of these aforementioned syndromes. They can help reduce the burden of these diseases.

The small number of BCD patients analyzed in this study is a drawback of this research. Furthermore, the first-degree relationship of three BCD patients means that they share the same

causative mutation genes and other parts of their genome. This shows that similar family traits may be reduced in the phenotypic variability amongst these patients. Another point of concern is the rate of radiographic 'drop out' in the samples of the Non-cleft control group. Also, the overlap in the historical periods over which the radiographs were taken is still the difference in the time period between the groups.

This novel study has evaluated the clinical manifestation of BCD and VWS patients and tried to provide an insight into these aforementioned anomalies. However, information regarding the pattern of inheritance, the range of clinical manifestations, and the consequence of these phenotypes should be emphasized amongst a larger sample size in future studies. This will provide an insight into these diseases and help clinicians develop a proper guideline for treatment protocol, which will hopefully reduce the burden of care for these conditions.

10. CONCLUSIONS

Craniofacial skeletal defects are more severe in patients with BCD syndrome than in non-syndromic bilateral cleft lip and palate patients. BCD syndrome patients showed reduced anterior lower face height, a severe sagittal discrepancy in the maxilla–mandible, severe tooth agenesis and multiple dental anomalies. The pattern of tooth agenesis, which includes the upper central incisors and upper and lower canine teeth, is unusual as it encompasses teeth that are usually highly resistant to agenesis. These findings expand the description of BCD syndrome and can assist in the diagnosis, treatment planning, treatment efficacy and prognosis of BCD syndrome patients.

The prevalence and severity of taurodontism in all first permanent molars of VWS and NSCP patients were significantly higher than in non-cleft individuals. Individuals in the VWS group have a higher probability of taurodontism compared to the NSCP group. Most of the taurodontic molars showed hypotaurodontism and taurodontism was more frequently bilateral rather than unilateral. This information will be of use when planning orthodontic and routine dental care for patients with VWS and NSCP, particularly individuals with a high caries risk who may need invasive dental treatment and extractions. DM was significantly delayed in both VWS and NSCP patients compared to non-cleft individuals. However, there was no significant difference in DM between the VWS and NSCP groups. There was no significant difference in DM between genders. Regarding dental abnormalities, both hypodontia and peg-shaped teeth were prevalent in the VWS group. The prevalence of hypodontia was significantly higher in both the VWS and NSCP groups than the non-cleft controls. There was no significant difference in prevalence of hypodontia between the VWS and NSCP groups; however, the prevalence of hypodontia in the VWS group was approximately double that in the NSCP group. The teeth with the highest prevalence of agenesis in VWS patients were the maxillary and mandibular permanent second premolars and the maxillary permanent lateral incisors.

In summary, this thesis investigated and described two rare syndromes related to cleft patients and compared them with normal populations, which will help health practitioners to gain knowledge about these syndromes and their differences that will help them in treatment planning and treatment strategies. The knowledge contained in this thesis will also help guide further study of these syndromes.

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